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2004

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New Chemistry of Donor-Acceptor Cyclopropanes

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New Chemistry of Donor-Acceptor Cyclopropanes

by

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Dissertation

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Dedication

This dissertation is dedicated to my loving wife, Qiaoyin, whose encouragement and support have helped me tremendously in all of life struggles. I would also dedicate this to my parents, my brothers and sisters, and friends who have given me so much love and support.

Acknowledgements

It has been a difficult road getting my current stage of life, but I would not have made it without the love and support from my family and friends.

First of all, I would like to acknowledge my loving wife, Qiaoyin for her consistent support and love. You are just so wonderful. Very importantly, I would also like to acknowledge my Mom and Dad, the parents of six children. It was not easy for my admirable parents, poor Chinese farmers, to support the education of six children (mostly college and graduate school). Thank you for your endless love and encouragement. It is from you that I learned a strong work ethic, self-discipline and self-motivation. Also my life footsteps have been fulfilled with rich love, encouragements and financial support from my brothers and sisters. Thank you. I am grateful for my family.

Finally, special thanks to my graduate research advisor, Dr. Brian L. Pagenkopf, for his guidance and support.

New Chemistry of Donor-Acceptor Cyclopropanes

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Supervisor: Brian L. Pagenkopf

Donor-Acceptor (DA) cyclopropanes are considered to be well-understood compounds with predictable chemistry. This dissertation focuses on our recent advances and synthetic applications of DA cyclopropanes principally involving 1,3-dipole intermediates revealed by reactions with Lewis acids. Particular emphasis is placed on reactions involving sugar-derived substrates.

Chapter one is an overview of the literature preparations and synthetic applications of DA cyclopropanes. It begins with general DA cyclopropanes but is mostly focused on carbohydrate-derived cyclopropanes.

Chapter two describes our intramolecular glucal cyclopropanation approach toward lactonized cyclopropanes **2.5a-c**, their transformations under mild conditions, and their application to the quasi formal synthesis of the natural product xylobovide **2.34a**.

Chapter three investigates the different chemical behaviors of glucal-derived lactonized cyclopropane **2.5a** under the influence of a variety of different Lewis acids. Use of boron trifluoride etherate (BF_3•OEt_2) leads to regioselective mono-desilylation of the di-*tert*-butylsilylene ether to **2.27**; trimethylsilyl trifluoromethanesulfonate (TMSOTf)

results in anhydro-sugar **3.8** formation; and titanium tetrachloride (TiC_4) facilitates stereoselective allylation and glycosidation.

Chapter four discuses our recently discovered formal [3+2] dipolar cycloaddition reactions of DA cyclopropanes with a wide variety of dipolarophiles including silyl enol ethers, imines, aldehydes and nitriles. The extension of nitrile cyclization to general non-carbohydrate derived DA cyclopropanes leads to the discovery of a novel synthetic methodology toward pyrroles, bipyrroles and thienylpyrroles. Finally, the [3+2] cycloaddition has also been extended to heterocycles including pyridines, quinolines and indoles.

Chapter five summarizes the investigation of regio-selective mono-desilylation of di-*tert*-butylsilylene ethers as a new protocol for selective hydroxy protection. Under optimized conditions, the reaction demonstrates high regioselectivity as well as strong functional group compatibility, and proves promising as a new protocol for selectively manipulating 1,3-diols.

Chapter six provides the experimental procedures and characterization of all the new compounds.

Table of Contents

List of Tables

List of Figures

List of Schemes

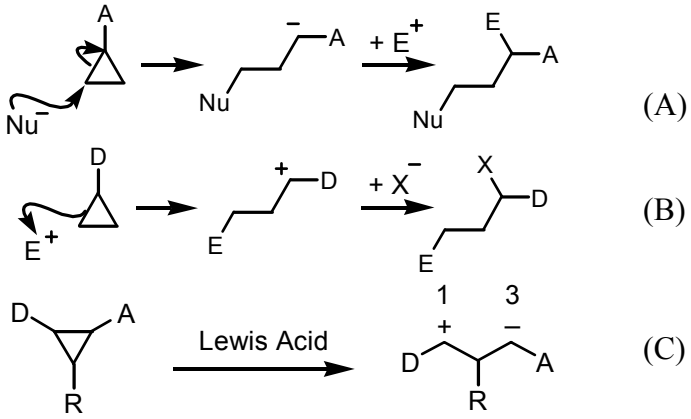
Chapter 1: History of DA cyclopropanes

Synthetic preparation methods and reactivity of donor-acceptor (DA) cyclopropanes have been widely documented and thoroughly reviewed.[1] This chapter is a brief survey of the new advances and synthetic applications of DA cyclopropanes principally involving 1,3-dipole intermediates revealed by reaction with Lewis acids. Particular emphasis is placed on reactions involving sugar-derived substrates.

1.1 General DA cyclopropanes

The high degree of reactivity presented in cyclopropanes makes them versatile building blocks in modern organic synthesis.[2] While unactivated cyclopropanes have been directly employed for certain useful chemical transformations,[3] most of the cyclopropane based synthetic methodologies have relied on activation from additional functional groups. Cyclopropanes substituted with electron accepting groups can react as homo Michael acceptors in nucleophilic ring openings (**Figure 1.1**, Eq A). On the other hand, donor substituted cyclopropanes can be cleaved by electrophiles to afford cation equivalents for further transformations (**Figure 1.1**, Eq B).[4]

Vicinal donor–acceptor (DA) cyclopropanes are particularly useful synthetic building blocks because the reactivity imparted to the cyclopropane by the substituents is amplified by a synergistic electron "push-pull" relationship. Under Lewis acidic conditions, the doubly activated cyclopropanes undergo formal retro-aldol rearrangement to 1,3-zwitterionic intermediates that can be considered as 1,3-dipole equivalents (**Figure 1.1**, Eq C).

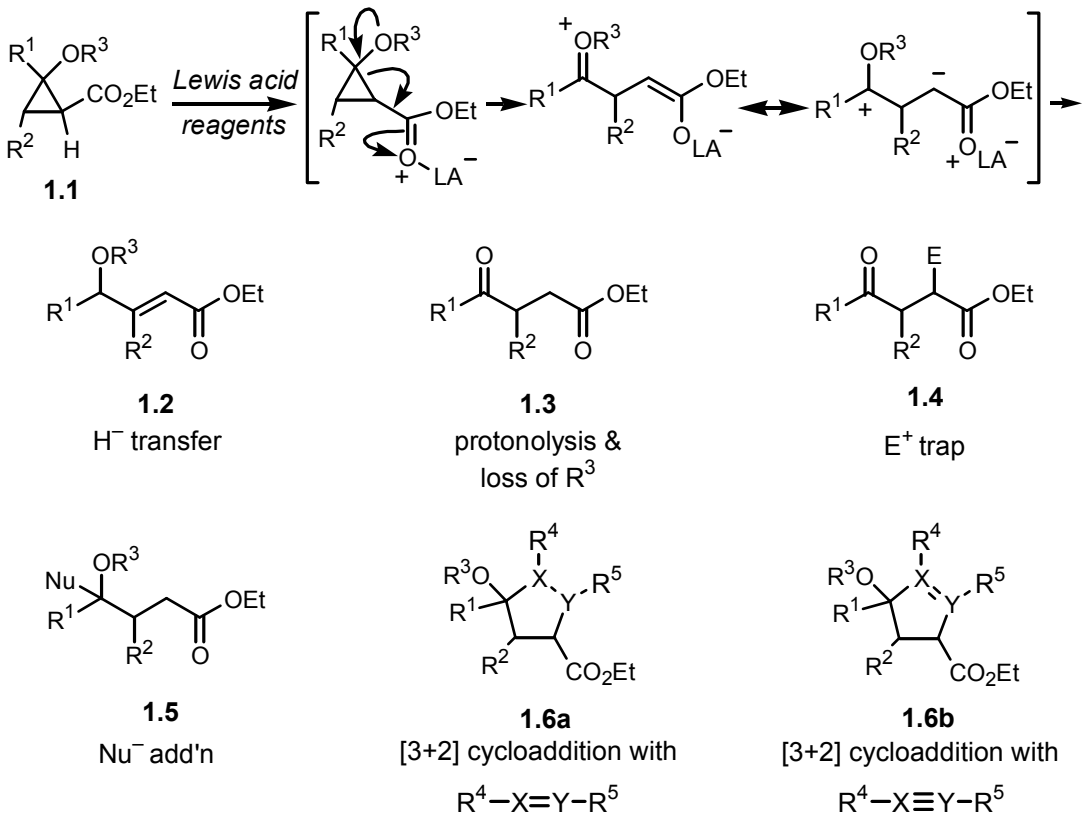


A = Electron Acceptor: CO_2R, C(O)R, CN, etc

D = Electron Donor: OR, $OSiR_3$, NR^1R^2, SR, etc

Figure 1.1: Substituent activated cyclopropanes

The ultimate fate of the 1,3- zwitterion is highly dependent on the nature of the reaction conditions, and the intermediates can react in an intramolecular fashion by hydride or proton transfers to give γ-alkoxy α,β-unsaturated esters **1.2** or saturated γ-oxoesters **1.3** (**Scheme 1.1**).[5] Siloloxy substituted DA cyclopropanes are particularly susceptible to give the simple protonolysis products **1.3**.[6] Intermolecular reactions can occur at just one or both sites of the dipole.[1] Examples of α addition from electrophilic trapping of enolates to afford **1.4**,[7] and nucleophilic addition to the intermediate oxocarbenium ions to give **1.5** are both known.[8] Combining the dual reactivity of the 1,3-dipole results in formal [3+2] cycloadditions to furnish highly functionalized carbon or heterocyclopentane derivatives **1.6a,b**.[9] These latter transformations involving DA cyclopropanes are powerful synthetic transformation for accessing products often not readily available through traditional routes.



Scheme 1.1: Diverse transformations of DA cyclopropanes 1.1

1.2 CARBOHYDRATE-DERIVED DONOR CYCLOPROPANES

Carbohydrates are an indispensable source of materials for asymmetric synthesis supported by a history of well-documented functional group transformations.[10] One challenge in carbohydrate chemistry includes developing economical and stereoselective methods for the introduction of new carbon-carbon bonds bearing suitable functional handles.[11] Carbon-branched sugars[12] are found in numerous natural products and have been used as starting materials for indole alkaloid syntheses,[13] commonly occur in the glycon portion of many antibiotics,[14] and have been studied during the elucidation of biochemical pathways.[15] Additionally, naturally occurring macrolides often contain branched polyol sequences, a structural motif that portends an origin from a *C*-branched sugar.[16]

One of the most important advances in cyclopropane chemistry over the last decade has been the integration of cyclopropanes and carbohydrates.[17] Carbohydrates have an exciting history in organic and medicinal chemistry.[18] Not only are they ubiquitous natural products occurring throughout the biosphere, but also they provide key functional subunits for rational drug designs.[19] They are inexpensive yet powerful members of the chiral pool, which makes them irresistible platforms for asymmetric synthesis.[20,21,22] The cyclopropanation of glycals affords unique bicyclic structures combining the high reactivity of cyclopropanes together with the extreme optical purity and functional density associated with sugars.[17] The electron donating effect from the pyran ring oxygen conveniently helps one predict cyclopropane reactivity for accessing C(2) carbon branched glycosides as well as the C(1) functionalized carbohydrate scaffolds.

1.2.1 Preparation of carbohydrate-derived donor cyclopropanes

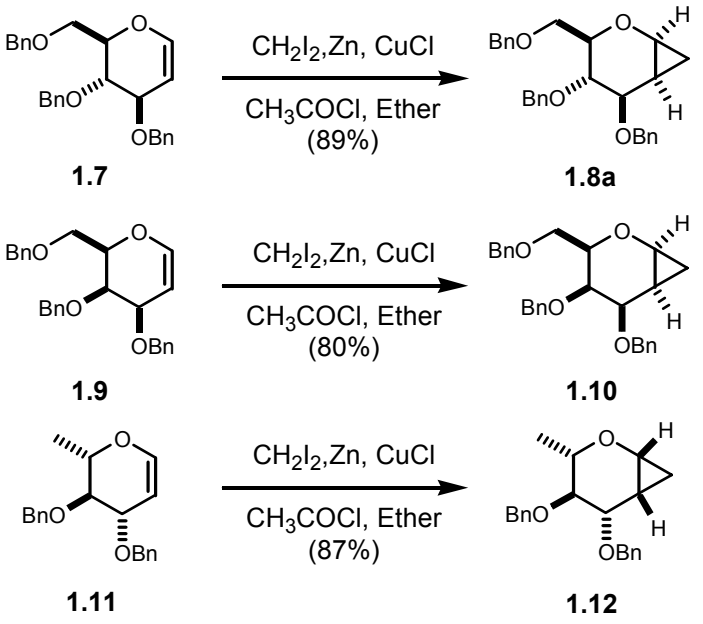
Despite the considerable synthetic potential of cyclopropanated carbohydrates, the area remained dormant until the last two decades, when efficient and reliable procedures for carbohydrate cyclopropanation were established. Vasella has pioneered this area with an effective synthetic approach toward monosaccharide-derived spirocyclic cyclopropylamines through diazo ester cyclopropanation of C(1) exocyclic methylene glycals or cycloaddition of glycal-derived C(1) diazirine with acrylates.[23] The spirocyclopropanes from this method display activity as glycosidase inhibitors. Most of the work in carbohydrate cyclopropanation has, however, been focused on cyclopropanation of the C(1)-C(2) enol ether component of glycal scaffolds. These methods can be classified into three main categories according the cyclopropanation reagents: Simmons-Smith reaction (**Section 1.2.1.1**); dihalocarbene cycloaddition (**Section 1.2.1.2**) and diazo ester cyclopropanation (**Section 1.2.1.3**).

1.2.1.1 Simmons-Smith cyclopropanation

The classic Simmons-Smith reaction is an efficient method for facially selective conversion of alkenes to cyclopropanes. The reaction is believed to proceed through a "butterfly-type" transition state that involves partial delivery of a methylene group between $IZnCH_2I$ and the double bond.[24] When faced with allylic alcohols/ethers, the organozinc species stereoselectively adds to the double bond on the face *syn* to the allylic hydroxy/alkoxyl group, presumably due to the strong chelating effect of the allylic oxygen to the dimeric organozinc reagents.

An early example of Simmons-Smith glycal cyclopropanation was reported by Nagarajan and coworkers in 1995.[25] In his study, the cyclopropanation of benzyl

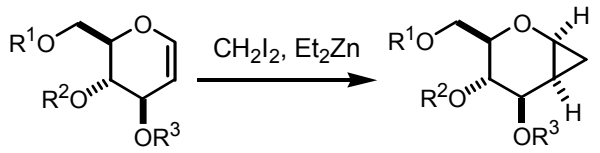
protected glycals **1.7**, **1.9**, **1.11** was achieved by treatment with CH_2I_2/Zn/CuCl activated by acetyl chloride (**Scheme 1.2**). This process proved efficient both in terms of reaction yield (> 80%) and facial selectivity. In the examples reported the C(3) substituent appeared responsible for complete control over facial selectivity to provide exclusively the *syn* diastereoisomer. The directing effect of the allylic oxygen overrode potential steric discouragement from the C(4) and/or C(6) substituents.



Scheme 1.2: Glycal cyclopropanation employing CH_2I_2/Zn/CuCl

The Furukawa modification[26] of the Simmons-Smith reaction employing diethyl zinc instead of Zn(Cu), and provides more reproducible results under milder reaction conditions. This reagent combination displayed high compatibility with different protecting groups (**Table 1.1**), and demonstrated the same level of facial selectivity even on substrates essentially flattened by the cyclic 4,6-di-*tert*-butylsilylene ether (entry 4).[27]

The cyclopropanated glycals were mostly received in 88 – 96% yield, but when faced with steric challenges, the reaction provided only a moderate yield (33%, entry 5). When the steric effect became extreme such as in tri-*tert*-butyldimethylsilyl glycal, the cyclopropane **1.8f** formation process was completely shut down.[27a]

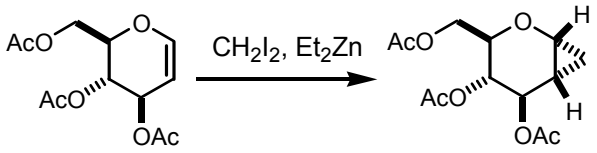


1.8a-f

Entry	R^1	R^2	R^3	Product	Yield
1	Bn	Bn	Bn	**1.8a**	92%
2	Me	Me	Me	**1.8b**	94%
3	TBS	H	H	**1.8c**	88%
4	-Si(^{t}Bu)$_2$-		H	**1.8d**	96%
5	-C(Me)$_2$-		H	**1.8f**	33%
6	TBS	TBS	TBS	-	0%

Table 1.1: Glucal cyclopropanation employing CH_2I_2/Et_2Zn

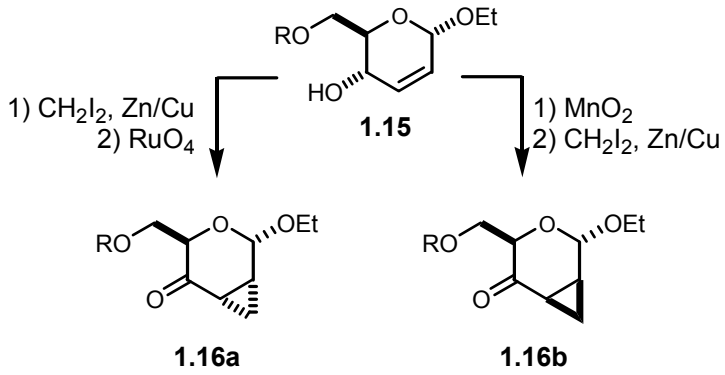
An unexpected *trans* selective example was observed by Lorica and co-workers on 3,4,6-triacetyl glycal **1.13** under classic Simmons-Smith conditions (**Scheme 1.3**).[28] The opposite diastereoselectivity was attributed to the steric hindrance of the upper face from the acetate groups.



1.13 **1.14**

Scheme 1.3: *Trans* glucal cyclopropanation

In addition to glycal substrates, allylic alcohol directed cyclopropanation was investigated with 2,3- and 4,5-unsaturated carbohydrate derivatives (**Scheme 1.4**).[29] Fraser-Reid and coworkers developed a strategy to access both facial diastereomers in the cyclopropanation of Ferrier rearrangement products **1.15**.[30] Reaction with **1.15** provided the expected directed addition product **1.16a**, but the directing effect of the C(4) hydroxyl group was circumvented by prior oxidation. Note that the acetal ethoxy group does not direct the cyclopropanation.

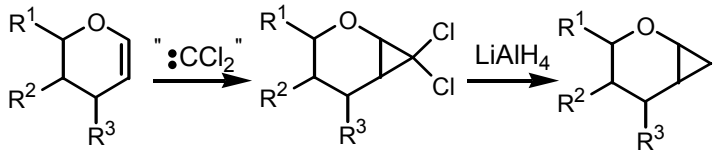


1.16a **1.16b**

Scheme 1.4: Cyclopropanation toward dual stereochemistry

1.2.1.2 Dihalocarbene cyclopropanation

Another strategy for *trans* cyclopropanation of allylic hydroxy/alkoxyl substituted carbohydrates was realized through dihalocarbene cycloaddition. In 1967, Brimacombe and co-workers reported the first carbohydrate cyclopropanation of a trimethyl glycal (**Table 1.2**, entry 1) through dichlorocarbene-glycal cycloaddition.[31] However, only recently was a general methodology developed by Nagarajan for *trans* cyclopropanation, as illustrated by reaction with a series of protected glycal substrates: galactal, rhamnal and xylal (entries 2-5).[32] The glycals were converted to the corresponding dichlorocyclopropanes **1.17** generally in > 80% yield by treatment with $CHCl_3$ in the presence of sodium hydroxide. Similar selectivity has been observed with furanose substrates.[33]



1.17 **1.18**

Entry	R^1	R^2	R^3	Yield
1[a]	$MeOCH_2$ (β)	MeO (α)	MeO (β)	82%
2[b]	$BnOCH_2$ (β)	BnO (α)	BnO (β)	84%
3[b]	$BnOCH_2$ (β)	BnO (β)	BnO (β)	92%
4[b]	Me (α)	BnO (β)	BnO (α)	95%
5[b]	H	BnO (α)	BnO (β)	55%

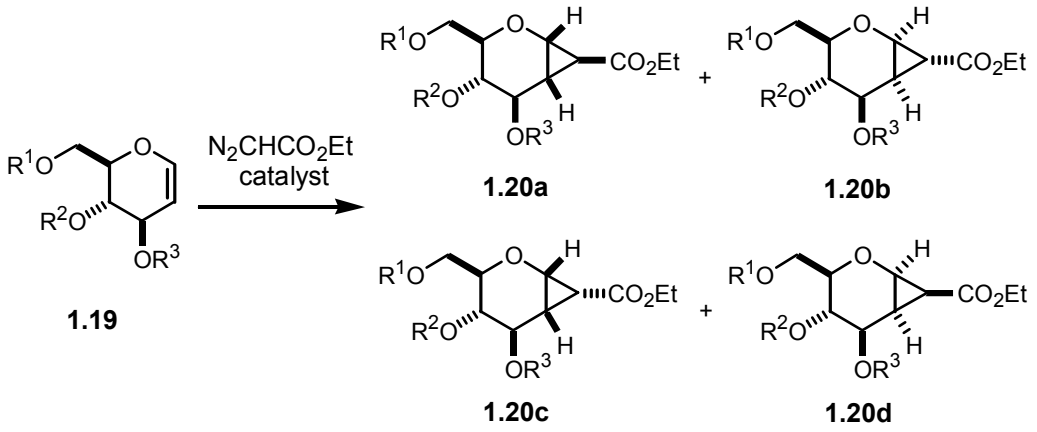
[a] see reference 31; [b] see reference 32.

Table 1.2: Dihalocarbene glycal cyclopropanation

Like other olefin-dihalocarbene cycloadditions, the stereochemistry in this process is governed by steric approach control, with the substituent at C(3) being of primary importance. An important aspect of this chemistry is the ease with which reductive dehalogenation can be achieved to afford products **1.18** with stereochemistry complementary to that obtained by Simmons-Smith and related processes.

1.2.1.3 Diazo ester cyclopropanation

Transition metal catalyzed diazo ester cyclopropanation has also been investigated on carbohydrate substrates.[34,35,36] The lack of cyclopropane functionality in the products prepared through Simmons-Smith or dihalocarbene cycloadditions limits opportunities for subsequent synthetic elaboration. In this regard, the products from reaction with diazoesters are doubly activated DA cyclopropanes, and the ester provides a well-situated functional handle suitable for further modification. The first literature example of carbohydrate-diazo ester cyclopropanation was reported in 1981,[34] but detailed studies of transition metal catalyzed diazoester carbohydrate cyclopropanations were not reported until over a decade later by Henry and Fraser-Reid.[35] They found that the cyclopropanation of tri-*O*-*tert*-butyldimethylsilyl-D-glucal with copper powder provided exclusive β facial selectivity giving the *cis* cyclopropane product in 92% yield (**Table 1.3**, entry 1). The cyclopropanation of the tri-benzyl protected analog was also completely selective, but the stereochemistry was unassigned and the yield was only 34%.

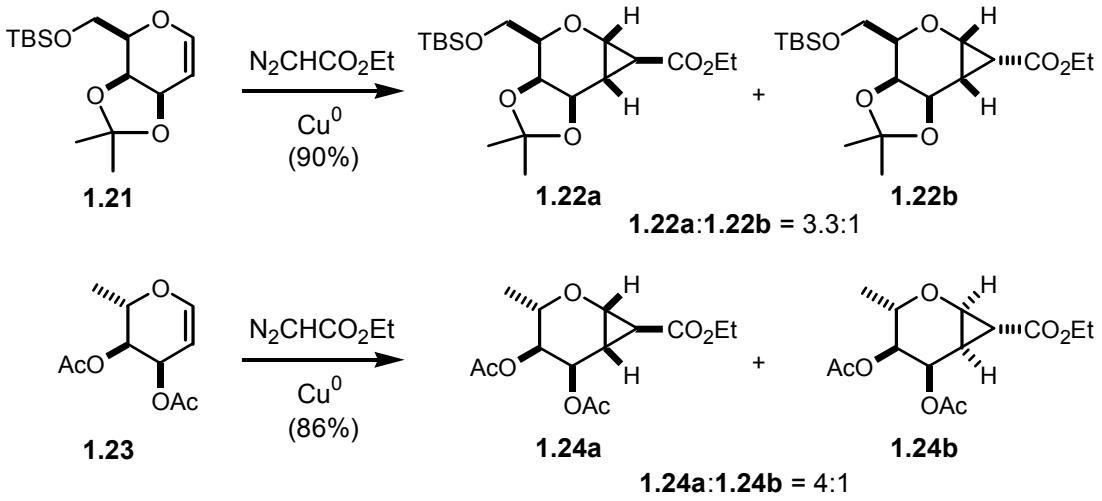


Entry	Protecting Groups			Catalyst	Yield	Product Ratio			
	R^1	R^2	R^3			1.20a	1.20b	1.20c	1.20d
1[a]	TBS	TBS	TBS	Cu^0	92%	0	100	0	0
2[b]	TBS	TBS	TBS	$Rh_2(OAc)_4$	81%	97	3	0	0
3[b]	TBS	Ac	Ac	$Rh_2(OAc)_4$	93%	94	2	2	3
4[b]	TIPS	TIPS	TIPS	$Rh_2(OAc)_4$	66%	91	3	3	3
5[b]	Bn	Bn	Bn	$Rh_2(OAc)_4$	44%	76	8	8	8
6[b]	Ac	Ac	Ac	$Rh_2(OAc)_4$	73%	81	6	4	9
7[b]	Ac	Ac	Ac	$Cu(acac)_2$	4%	70	12	6	12

[a] see reference 35; [b] see reference 36.

Table 1.3: Intermolecular diazo ester glucal cyclopropanation

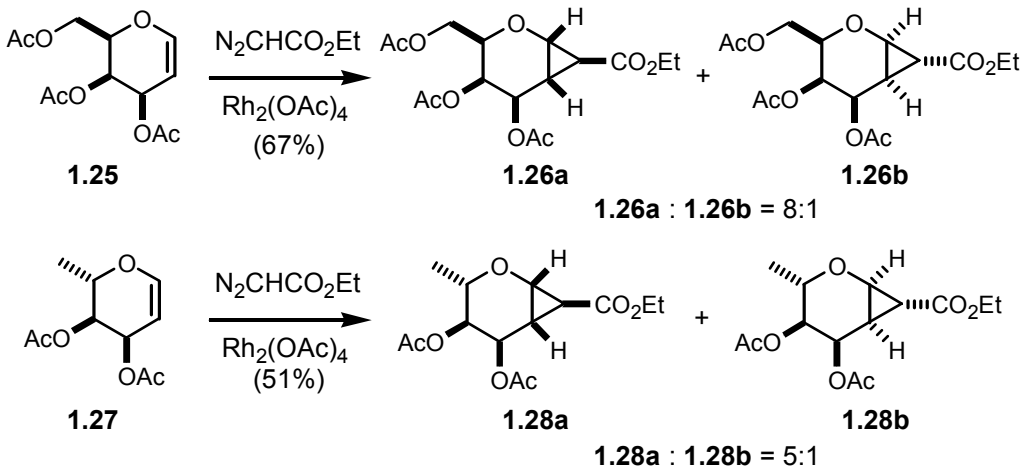
When applied to galactal **1.21** and L-rhamnal **1.23** derivatives (**Scheme 1.5**), the cyclopropanation products **1.22** and **1.24** were obtained with α facial selectivity predominating. While yields were consistently excellent with these substrates (> 85%), the diastereoselectivities were modest 3.3~4:1 (α:β).



Scheme 1.5: Diazo ester cyclopropanation of galactal and L-rhamnal

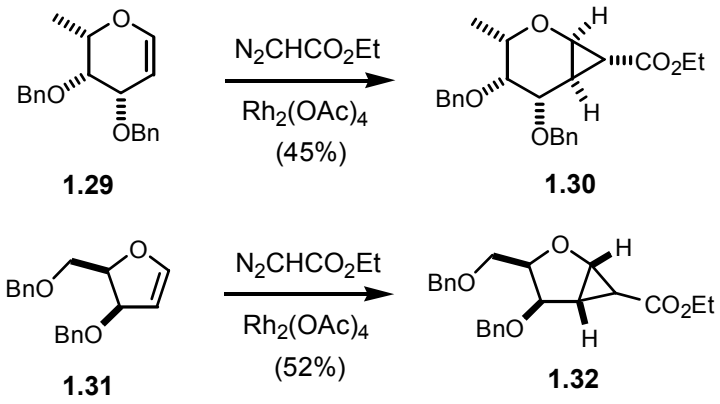
Shortly thereafter, Hoberg and Claffey reported their results from an independent investigation of this reaction using other carbohydrate substrates and transition metal catalysts.[36] As illustrated in **Table 1.3** (entries 2 – 7), many commonly used protecting groups such as TBS, TIPS, benzyl ether, acetyl and acetonide were found compatible with the cyclopropanation conditions. However, unlike Fraser-Reid's results in which β-facial selectivity predominated (**Table 1.3**, entry 1), in Hoberg's examples the α diastereomers were obtained (in good to excellent yield as well). The similar α-facial selectivity was also observed in the cyclopropanation of tri-acetyl galactal **1.25** and L-rhamnal **1.27** (**Scheme 1.6**), but these reactions were less selective. Hoberg attributed the

observed facial selectivity to a steric control process,[17] and the blocking effect from larger protecting groups (especially the C(3) protection) was believed to enforce *trans* addition (**Table 1.3**, e.g., entries 2, 3, 4 versus entries 5,6).



Scheme 1.6: Hoberg's diazoester glucal cyclopropanation

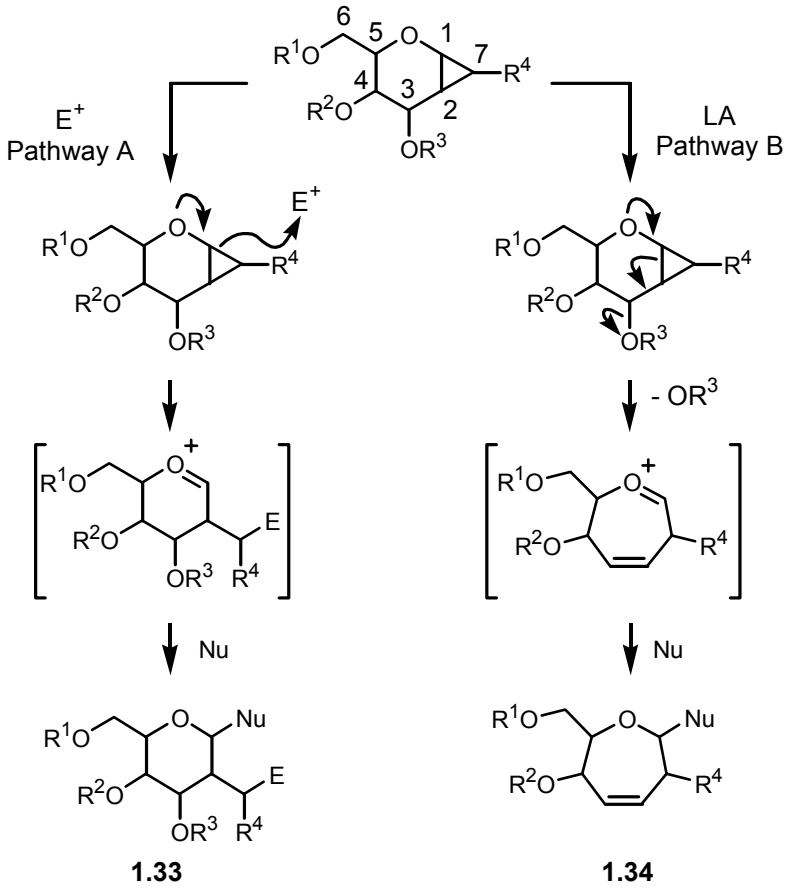
These studies and work by van Boon[37] and coworkers on the cyclopropanation of furanose and pyranose ring systems (**Scheme 1.7**) revealed that among the homogeneous catalysts examined $Rh_2(OAc)_4$ resulted in the highest efficiency. Judicious employment of either $Rh_2(OAc)_4$ or Cu(0) catalysts in the cyclopropanation of glycals with ethyl diazoacetate provides convenient access to products with complementary stereochemistry.



Scheme 1.7: Diazo ester cyclopropanation of furanose and pyranose

1.2.2 Important reactions of carbohydrate-derived cyclopropanes and related compounds

The potential reactivity and high optical purity of carbohydrate-derived cyclopropanes makes this class of compounds stand out as attractive and economical materials for developing new asymmetric synthetic methodologies. In pioneering efforts, several groups have persistently sought strategies to exploit 1,2-cyclopropanated carbohydrates, and a consistent theme emerging from those works is the need for general and predictable cyclopropane ring opening processes. The primary synthetic strategies thus far have invoked two types of cyclopropane ruptures (**Scheme 1.8**): electrophilic cyclopropane ring opening at the C(1)-C(7) position (pathway A) or Lewis acid assisted pyran ring expansion (a process that has been called a σ-Ferrier rearrangement), (pathway B).

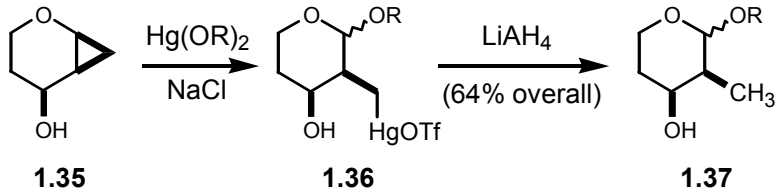


Scheme 1.8: Two main transformations of glycal-derived DA cyclopropanes

1.2.2.1 Electrophilic C(1)-C(7) cyclopropane ring cleavage

The ring opening of carbohydrate derived cyclopropanes along pathway A provides C(2) branched glycosides **1.33** (**Scheme 1.8**). The reaction normally proceeds through electrophilic cyclopropane methylene activation by an electron deficient species that leads directly to formation of the oxonium ion intermediate. An example of electrophilic cyclopropane ring-opening was achieved on the pyran derived substrate **1.35**

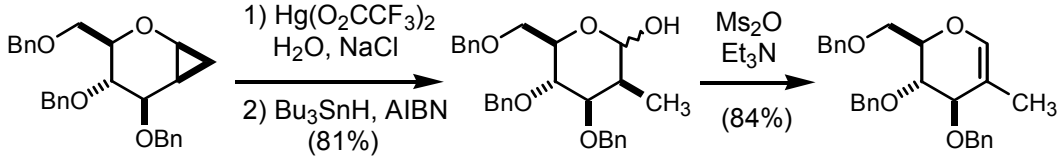
via mercury(II) salt activation (**Scheme 1.9**).[38] This regioselectivity was thought to originate from partial cation charge stabilization by the pyran oxygen.



1.35 **1.36** **1.37**

Scheme 1.9: Mercury (II) activation of pyran-derived cyclopropane

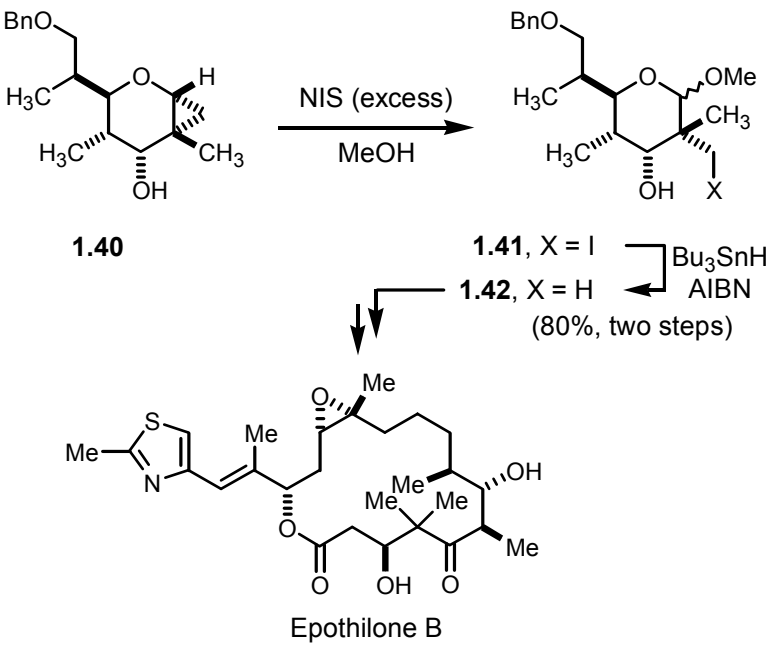
This strategy was later adapted by Heathcock to access C(2) methyl glucal **1.39** (**Scheme 1.10**).[39] Treatment of **1.8a** with mercury(II) trifluoroacetate in presence of water afforded hemiacetal **1.38**, which after subsequent Bu_3SnH reduction and elimination provided glucal **1.39**.



1.8a **1.38** **1.39**

Scheme 1.10: Mercury (II) mediated C(2) glucal preparation

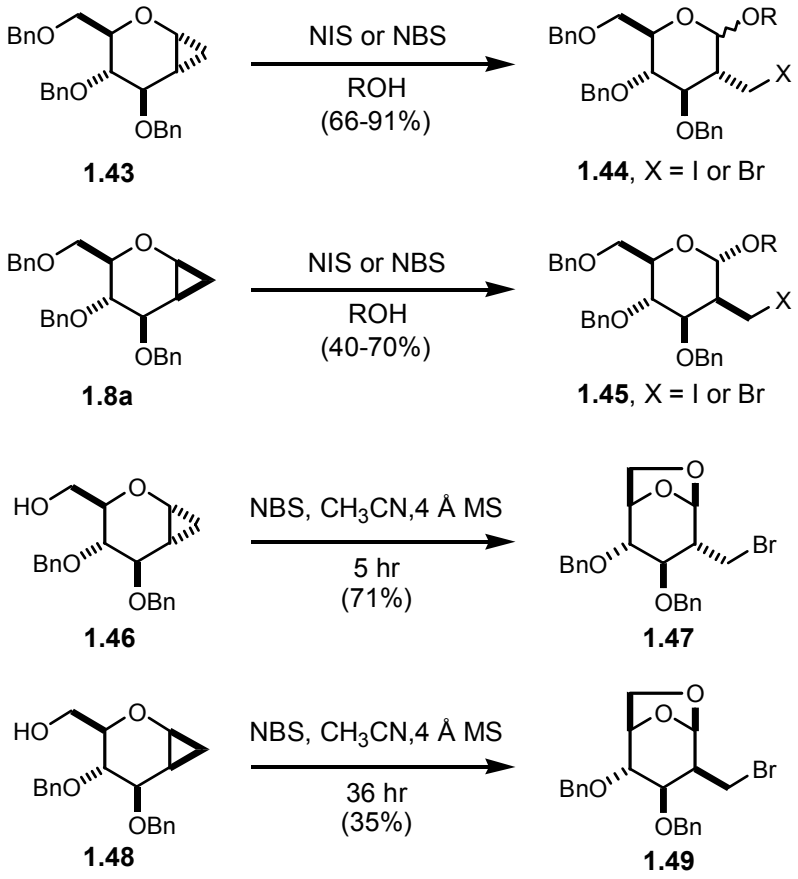
A conceptually equivalent transformation has been recently developed by Danishefsky and coworkers using *N*-iodosuccinimide (NIS) to access the geminal methyl groups in the synthesis of cytotoxic agents epothilone B (**Scheme 1.11**).[40, 41] Importantly, the high efficiency observed in the preparation of the intermediate **1.41** using NIS activation eradicated the need for highly toxic mercury salts.



Scheme 1.11: NIS mediated application in epothilone synthesis

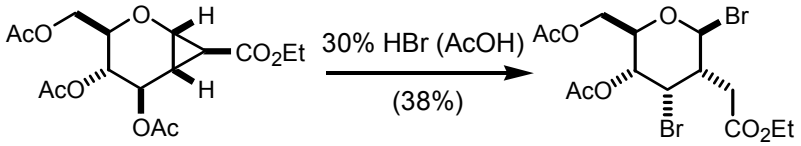
Fascinated by these results, several applications of and modifications to the NIS strategy have been reported.[42,43,44] Compared with the organomercury intermediate **1.36**, the iodomethene appendage obtained directly from the NIS protocol opened a window for more environmentally responsible C(2) elaboration. Nagarajan and coworkers[43] discovered sharply different cyclopropane reactivity between the diastereomers **1.43** and **1.8a** (**Scheme 1.12**). Reaction of the α cyclopropane **1.43** with either NIS or NBS occurred rapidly and provided an anomeric mixture of **1.44** in ~90% yield. In contrast, reaction under otherwise identical conditions with the β cyclopropane **1.8a** results in slower formation of **1.45** with pronounced anomeric selectivity. The same trend in reactivity was also observed on diastereomeric substrates **1.46** and **1.48** in which the free C(6) hydroxy is available to participate in an intramolecular nucleophilic attack. The

differences in reactivity were accredited to steric hindrance on the β-cyclopropanes **1.8a** and **1.48** toward the approaching electrophilic activator. The most reactive α cyclopropane **1.46** not only has the advantage of the least C(3) steric hindrance, but is equipped with a free hydroxy ideally positioned for "S_N2-like" participation. The β-cyclopropane **1.48** is not disposed for direct substitution and is blocked from the electrophilic activators.



Scheme 1.12: NIS mediated acetal formation

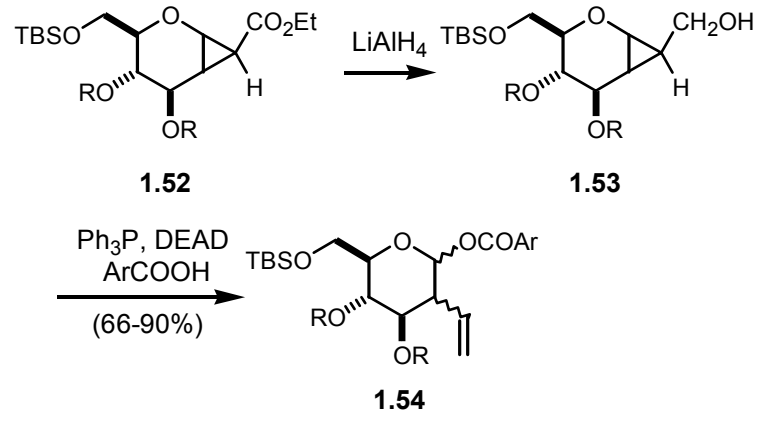
In addition to investigations on 1,2-disubstituted cyclopropanes as shown in **Scheme 1.12**, the electrophilic ring cleavage strategy was applied to substrates prepared through diazo ester cyclopropanation. In an early example reported by Hoberg,[36] the 1-bromopyran derivative **1.51** was prepared in moderate yield (38%) by treating **1.50** with 30% HBr in acetic acid, but the reaction was inevitably accompanied with C(3) "S_N2-like" substitution by bromide (**Scheme 1.13**).



1.50 **1.51**

Scheme 1.13: Bromo-acetal formation

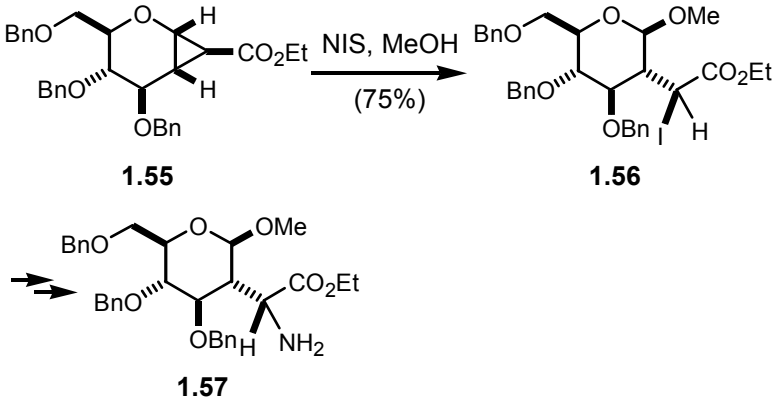
In similar example, Fraser-Reid used the carboxylate substitution on **1.52** to his advantage in a highly selective cyclopropylcarbinyl-homoallyl rearrangement (**Scheme 1.14**).[34] Ester reduction by lithium aluminum hydride ($LiAlH_4$) followed by standard Mitsunobu manipulation employing benzoic acid as the nucleophile gave 66-90% yield of 2-deoxy-2-vinyl glycals **1.54** as anomeric mixtures.



1.52 **1.53** **1.54**

Scheme 1.14: Cyclopropane ring opening via Mitsunobu activation

Very recently an efficient method for the synthesis of C(2) branched glycol-amino acids **1.57** has been developed by Chandrasekaran thorough direct NIS mediated ring opening in methanol (**Scheme 1.15**).[45]



1.55 **1.56** **1.57**

Scheme 1.15: Application in glycol-amino acid preparation

Although electrophilic ring opening reactions of carbohydrate-derived cyclopropanes provide access to C(2) branched glycosides, literature examples have unfortunately been restricted mainly to simple Brønstead nucleophiles (alcohol/water) as

glycosyl acceptors. The resulting acetals or hemiacetals offer a transitional intermediate for further C(1) transformations, but direct formation of C(1) *C*-branched glycosides remained elusive. Moreover, due to the limited assortment of electrophilic activators (e.g., Hg(II), or NIS/NBS), the resultant C(2) moieties were susceptible to few synthetic transformations.

1.2.2.2 Pyran ring expansion

Another transformation of 1,2-cyclopropanated carbohydrates that has been actively investigated is pyran ring enlargement, a process driven primarily by release of cyclopropyl ring strain. The logistics of the σ-Ferrier rearrangement can be rationalized based on conformation models (**Figure 1.2**). In the glycal-derived bicyclic substrate, the fused cyclopropane distorts the pyran skeleton and prevents it from adapting an ideal chair conformation. The pseudo equatorial C(3) substituent will retain an orientation reasonably anti-parallel to the C(1)-C(2) bond. This bonding alignment therefore accommodates a manifold for smooth elimination facilitated by Lewis acid activation of the C(3) oxygen.

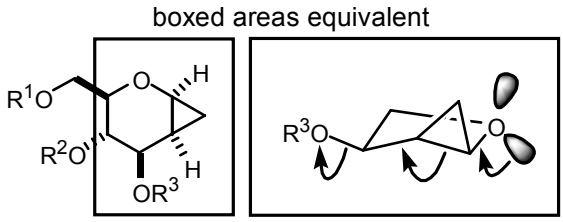
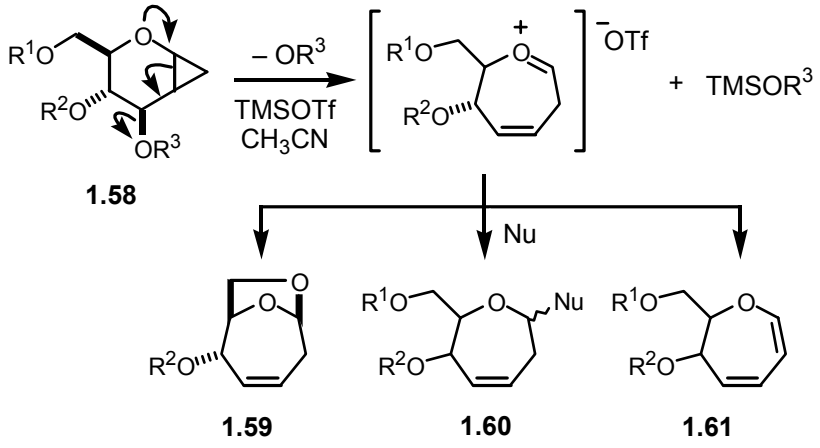


Figure 1.2: Rationale for pyran ring expansion

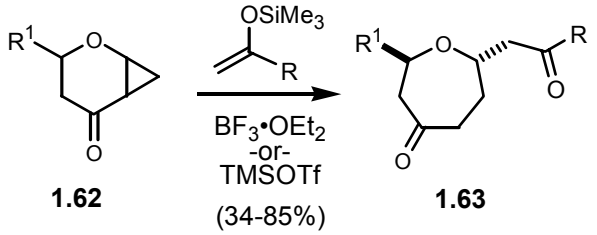
Hoberg has carried out detailed investigations on this variant of the σ-Ferrier rearrangement (**Scheme 1.16**).[27] Upon treatment with TMSOTf, the cyclopropanes **1.58**

cleaved exclusively at the C(1)-C(2) bond as a result of collaboration between the "donating" pyran oxygen and the quasi "accepting" effect from the departing C(3) substituent. Depending on substrate protective groups and reaction conditions, the intermediate oxonium ion can be converted preferentially into one of three oxapenes: **1.59**, **1.60** or **1.61**. In examples where labile C(6) silyloxy protecting groups were present, intramolecular ring closure occurred faster than external nucleophilic substitution to provide anhydro-sugars **1.59** in up to 78% yield. To facilitate intermolecular attack at the C(1) oxonium ion, C(6) deoxygenation or more robust protection (e.g., $R^1 = R^2 = {}^tBu_2Si$) was required. Successful exogenous nucleophiles capable of C(1) functionalization include allylsilanes, silyl ketene acetals and silylthiazole. The reactions offered products **1.60** with moderate facial selectivity (2:1) in 67-93% yield (elimination to **1.61** was competitive). In the examples with sufficient suppression of intramolecular nucleophilic addition, the absence of external nucleophiles lured the oxocarbenium ion intermediate preferentially into a C(2) deprotonation pathway, which led to the oxacycloheptadiene **1.61** ($R^1 = R^2 = {}^tBu_2Si$) in 81% yield.



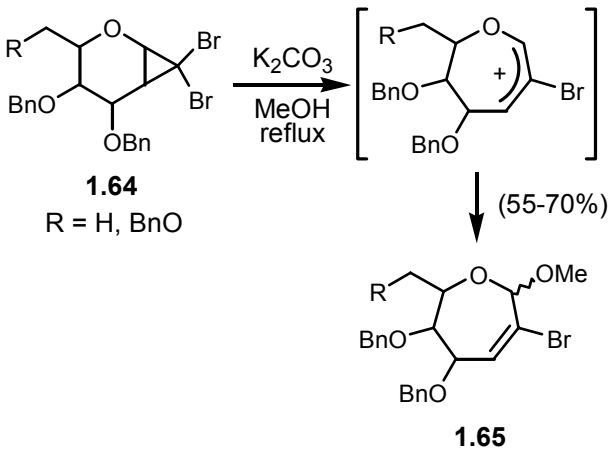
Scheme 1.16: Ring expansion of glucal-derived cyclopropanes

Similar ring expansion-nucleophilic addition sequences have been reported,[46] and Sugita and coworkers described an interesting reaction of cyclopropanated pyranones **1.62** with a variety of silyl enol ethers and silyl ketene acetals (**Scheme 1.17**).[47] Compared with the more rigid planar 4,6-di-*tert*-butylsilylene ether on substrate **1.58** ($R^1 = R^2 = {}^tBu_2Si$), the unfettered C(6) substituent induced excellent *trans* stereochemistry.



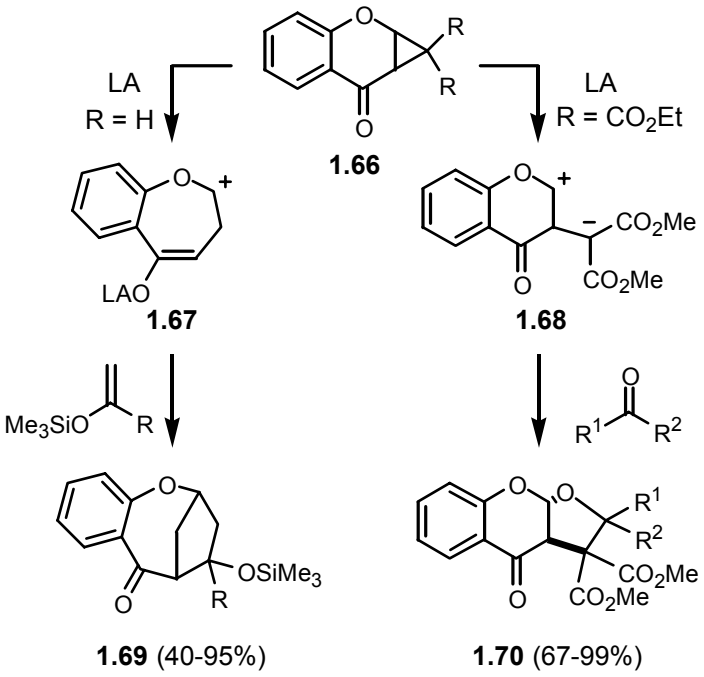
Scheme 1.17: C(1) Functionalization of cyclopropanated pyranones

A mechanistically distinct transformation has been explored by Nagarajan for solvolytic ring-expansion of dihalocyclopropanated sugars to prepare the corresponding halogen substituted anomeric oxepane product **1.65 (Scheme 1.18)**.[32b] A significant difference in this process is that conversion to the 2-halo allylic cationic intermediate is initiated by base. The addition regiochemistry was attributed to the preferential delocalization of the allylic cation adjacent to the stabilizing pyran oxygen.



Scheme 1.18: Application in anomeric oxepane preparation

Glucal-derived DA cyclopropanes prepared through diazo ester cyclopropanation reportedly refuse to participate in the pyran ring expansion (c.f., **Scheme 1.13**).[36] The different reactivity of those cyclopropanes was believed to originate from deactivation of the cyclopropane by the ester group,[36] a postulate that is entirely consistent with Sugita's observation on 2,3-methamochromanones **1.66** (**Scheme 1.19**).[48] These studies elegantly compared the electron withdrawing ability of the ketone vs. a geminal ester substituent under Lewis acidic conditions (BF_3•OEt_2, TMSOTf or $SnCl_4$). The unsubstituted cyclopropane expanded to the 6,7 bicyclic intermediate **1.67**, which after formal dipolar cycloaddition with silyl enol ethers afforded the oxepanone derivatives **1.69** in 40-95% yield. In contrast, the dicarboxylate substituted cyclopropane maintained the methanochromanone core and underwent exo ring cleavage to a zwitterionic intermediate **1.68**. A subsequent cyclization with carbonyl compounds provided mainly the *trans* fused tricyclic products **1.70** in 67~99% yield.



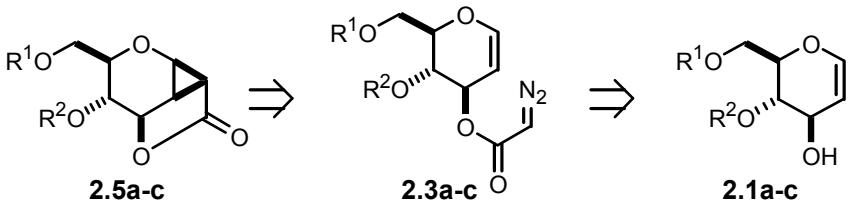
Scheme 1.19: Lewis acid mediated reactions of 2,3-methamochromanones 1.66

Chapter 2: Intramolecular Glycal Cyclopropanation

2.1 INTRODUCTION

A recurring objective of carbohydrate cyclopropanation investigations has been development of new ways for accessing highly functionalized C(1) and C(2) branched glycosides. Glycal-derived cyclopropanes bearing an ester electron withdrawing group are poised for more elaborate transformations (e.g., **Scheme 1.15**) compared to their unsubstituted counterparts. In this regard, the reported methods to control the facial and endo/exo selectivity of diazoester glycal cyclopropanation through catalyst selection (e.g., **Section 1.2.1.3**) is an important accomplishment. However, in our experience, achieving stereo-complementary results with a variety of protected glucal substrates proved elusive.

To circumvent potential difficulties in stereochemical control endemic to glycal cyclopropanation, we recently established an intramolecular version of this reaction as depicted in **Scheme 2.1**.[49] This strategy takes advantage of a molecular tether for obtaining absolute control over cyclopropanation facial selectivity. The unique conformation and strain inherent to the products results in new cyclopropane reactivity, which will be described in subsequent sections. Due to the ease of substrate preparation and complete diastereoselectivity, this method is a more reliable approach to access carbohydrate-derived DA cyclopropanes with stereochemistry complementary to those of steric controlled literature examples.[36]



Scheme 2.1: Reaction design

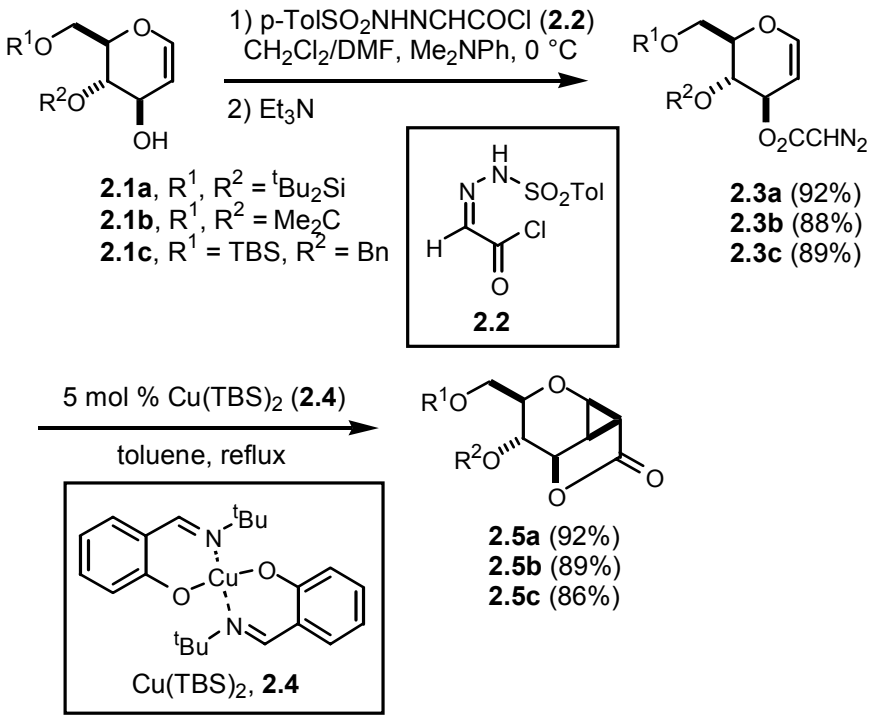
2.2 SUBSTRATE PREPARATION

The hallmarks of standard intramolecular diazo ester cyclopropanation are efficiency and a remarkable ability to rapidly increase molecular complexity.[50,51,52] Generally, excellent stereocontrol is observed in the intramolecular cyclopropanation of allylic alcohols. In pioneering investigations, Corey and Myers[51] developed glyoxylic acid chloride *p*-toluenesulfonylhydrazone **2.2**[53] as a versatile and practical reagent for efficient preparation of diazoacetic esters from allylic alcohols. However, despite ample precedence on various substrates, there were surprisingly no literature reports on intramolecular glycal cyclopropanation.

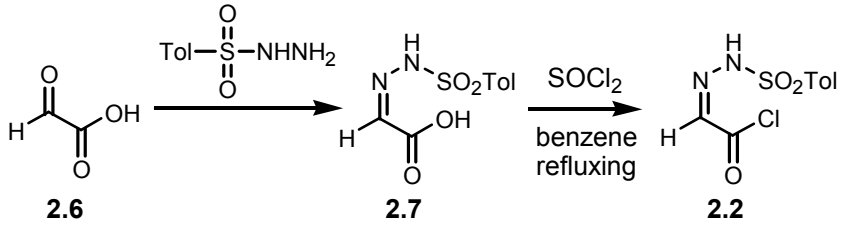
As summarized in **Scheme 2.2**, the lactonized cyclopropanes **2.5a-c** were prepared through intramolecular cyclopropanation of the corresponding diazo esters **2.3a-c**. The glycals **2.1a**,[54] **2.1b**,[55] and **2.1c**[56] were accessible from tri-acetyl D-glucose according to literature procedures. In the first example attempted, the D-glycal was protected as the di-*tert*-butylsilylene ether **2.1a** following Hoberg procedure[54]. The simple hydroxy manipulation together with the high stability of resulting silylene ether make this protecting protocol an excellent choice for this case, especially in consideration of strong Lewis acidic conditions that would be applied during the further exploration of this substrate (see chapter 3 and 4).

As general examples (**Scheme 2.2**), the 4,6-*O*-protected glycals **2.1a-c** were converted to their diazoacetates **2.3a-c** in excellent yields using a slightly modified version of the Corey-Myers procedure. Treating the dichloromethane/*N*,*N*-dimethylformamide (CH_2Cl_2-DMF) solution of the allylic alcohol and **2.2**[57] sequentially with *N*,*N*-dimethylaniline (DMA) and triethylamine at 0 °C afforded the diazoacetates in excellent yields (88-92%). Specifically, small amounts (5-10%) of DMF as co-solvent proved critical for this transformation, and initial attempts using either pure CH_2Cl_2 or DMF solvent resulted in consistent decomposition of starting material and the desired diazoester products were obtained in less than 5% yield.

As a brief aside, in the preparation of glyoxylic acid chloride p-toluenesulfonylhydrazone **2.2**, we note that reaction of **2.7** with thionyl chloride occasionally proved fickle, frequently giving unstable oily product (**Scheme 2.3**). However, the acid chloride **2.2** could be reliably prepared if the intermediate carboxylic acid **2.7** was recrystallized from carbon tetrachloride-ethyl acetate (CCl_4-EtOAc). Alternative diazoacetic esterification methods, such as Doyle's diketene approach,[58] were unsuccessful with glycals **2.1a-c**.



Scheme 2.2: Intramolecular glucal cyclopropanation



Scheme 2.3: Preparation of 2.2

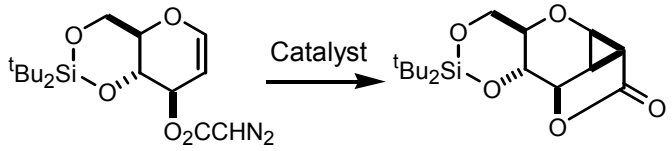
The cyclopropanation was achieved by slow addition of the diazoester **2.3a-c** (8-12 h via syringe pump) to a refluxing toluene solution of 5 mol % pre-catalyst bis(*N-tert*-butylsalicylaldiminato)copper(II) [$Cu(TBS)_2$] **2.4**.[59] The slow addition rate proved crucial for maintaining good reaction yields and minimizing the formation of dimeric fumarates

and maleates. During this reaction, the C(3) stereochemistry of the starting glycal has demonstrated an absolute control on the facial selectivity of intermediate carbenoid species. On all the substrates investigated, the *cis* diastereomers proved to be the only products as detected both by TLC analysis and inspection of ^{1}H NMR spectra of crude product mixtures. The examples in **Scheme 2.2** also indicated that this intramolecular strategy is highly compatible with different protecting groups, including cyclic silylene ether (**2.3a**), acetonide (**2.3b**), as well as acyclic protecting groups such as benzyl and TBS (**2.3c**). It is noteworthy that the limited flexibility of cyclic 4,6-protection did not prevent effective formation of the highly strained cyclopropane products

The intramolecular cyclopropanation process seemed to involve high activation energy, and lowered reaction temperatures led mainly to dimerization of the intermediate carbenoids. Among the solvents screened, toluene proved very efficient, but other common cyclopropanation solvents such as benzene or CH_2Cl_2 led mostly to substrate decomposition and/or dimerization.

Besides the copper Shiff base $Cu(TBS)_2$ complex **2.4**, a wide variety of transition metal catalysts have been screened for this reaction and the results are briefly summarized in **Table 2.1**. The $Cu(TBS)_2$ precatalyst **2.4** performed admirably on the cyclopropanation reaction under study; other common transition metal complexes however proved less than ideal after consistent attempts under different conditions. Among them, rhodium (II) acetate ($Rh_2(OAc_4)$), the widely utilized cyclopropanation catalyst, provided less than 30% desired product. Other catalysts including copper complexes $CuPF_6•(CH_3CN)_4$, $CuBF_4•(CH_3CN)_2$, $Cu(OTf)_2$, $CuClO_4•(CH_3CN)_4$, cobalt complexes ($Co(acac)_2$) and zirconium chloride ($ZrCl_4$) led to either dimerization of the carbenoid intermediate or decomposition of the starting diazo acetate. It is noteworthy

that cyclopropanation was not accompanied by C-H insertion, even with rhodium(II) catalysts. It is likely that the limited conformational freedom of the intermediate carbenoid precludes the necessary perpendicular orientation at either C(2) or C(4).[60]

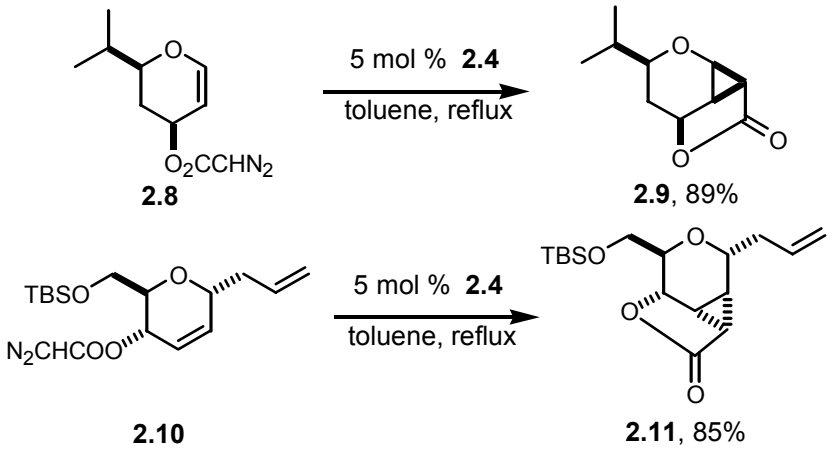


2.3a **2.5a**

Entry	Catalyst	Solvent	Temperature	Yield
1	$Cu(TBS)_2$	toluene	120 °C	92%
2	$Cu(TBS)_2$	CH_2Cl_2	39 °C	Dimerization
3	$Rh_2(OAc)_4$	CH_2Cl_2	39 °C	28%
4	$Rh_2(OAc)_4$	toluene	120 °C	< 25%
5	$CuPF_6•(CH_3CN)_4$	toluene	120 °C	8%
6	$CuBF_4•(CH_3CN)_2$	CH_2Cl_2	39 °C	Dimerization
7	$CuClO_4•(CH_3CN)_4$	toluene	120 °C	Dimerization
8	$Cu(OTf)_2$	CH_2Cl_2	39 °C	Dimerization
9	$Co(acac)_2$	CH_2Cl_2	39 °C	No Reaction
10	$ZrCl_4$	CH_2Cl_2	39 °C	No Reaction

Table 2.1: Screening on different transition metal catalysts

In addition to the inherent complete facial selectivity, as expected, this intramolecular cyclopropanation strategy was not limited to carbohydrate-derived substrates, and the reaction of diazo ester **2.8** prepared from other readily available γ-hydroxy dihydropyrans[61] provided the pyran-derived cyclopropane **2.9** in 89% yield (**Scheme 2.4**). Moreover, besides the electron-rich olefins, the cyclopropanation of isolated olefin **2.10**[62] also proceeded with the same level of efficiency.



Scheme 2.4: Generality on different substrates

While the intramolecular cyclopropanation has introduced considerable ring and bonding strains on the lactonized products, it does not prevent the cyclopropanes from possessing high stability. In fact, the product formation needs reaction temperature as high as refluxing toluene. In addition, the resultant cyclopropane products were found to be quite stable even under fairly harsh conditions including both strongly acidic (10% H_2SO_4, 10 hours) and basic conditions (saturated aqueous Na_2CO_3, 12 hours).

The stereochemistry of cyclopropane **2.5a** was unambiguously established by X-ray crystallographic analysis of single crystals (mp 199.5-201.5 °C) obtained from EtOAc–hexanes solvent mixture (**Figure 2.1**). As anticipated, in the lactonized cyclopropane **2.5a**, the bonds C(1)-C(2) and C(3)-O(8) are no longer in anti-parallel relationship but a torsion angle of 70.6°, which strongly disfavors the σ Ferrier rearrangement as observed in the intermolecular counterparts.

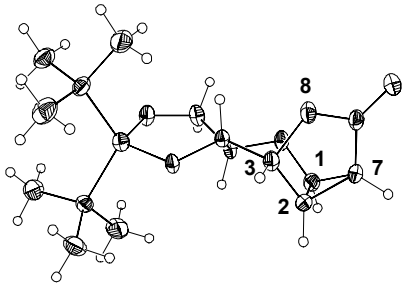


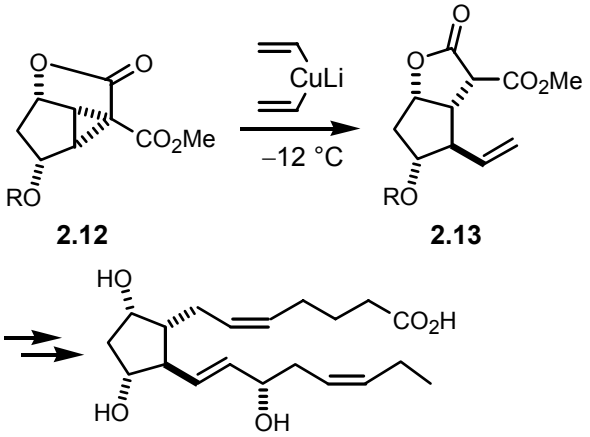
Figure 2.1: X-ray structure of 2.5a

2.3 TRANSFORMATIONS UNDER MILD CONDITIONS

Although DA cyclopropanes enjoy dual activation, reaction conditions to fragment these species are often quite harsh (**Section 1.2.2**). However, the lactonized substrates prepared through the aforementioned intramolecular strategy undergo certain useful transformations under milder conditions, thus opening the doors to new reaction pathways.

2.3.1 Reactions attempted with organocopper reagents

Acceptor substituted cyclopropanes **2.12** are opened by cuprates through what is generally perceived as a S_N2 type reaction.[63] One of the representative examples was demonstrated on Corey's synthesis of prostaglandins,[50] where the *trans* relationship required for the target prostaglandin E3 **2.14** was established through S_N2 like cuprate addition (**Scheme 2.5**).[51,64]

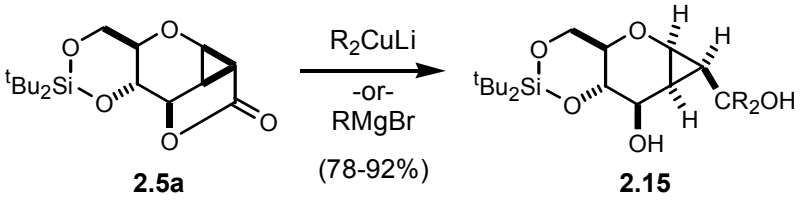


2.12 **2.13**

prostaglandin E3, **2.14**

Scheme 2.5: Cyclopropane ring opening through organocopper reagents

In our glycal lactonized substrates, the analogous reaction did not happen. Upon treatment with a variety of alkyl organic copper reagents, the lactonized cyclopropanes such as **2.5a** failed to react in an analogous fashion. Instead the nucleophilic addition to the lactone carbonyl was observed (**Scheme 2.6**). The ring strain appears to make this lactone more electrophilic than normal, and coupled with cyclopropane deactivation (toward nucleophiles) from the pyran oxygen, reaction at the cyclopropane under nucleophilic conditions has not been observed. When excess Grignard reagents were employed, the reaction generally provided enhanced yields of alcohol **2.15**. Since the resultant product **2.15** possesses *cis* cyclopropane stereochemistry that are opposite to literature examples obtained through intermolecular cyclopropanations (**Table 1.3**),[34,36] this transformation provides a reliable path toward their diastereomers with complementary stereochemistry.



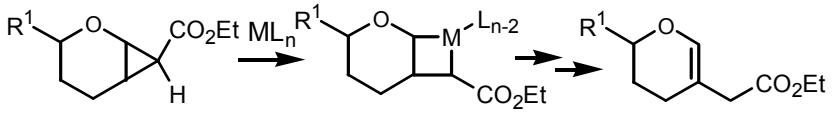
Scheme 2.6: Lactone breakage via cuprates or Grignard reagents

2.3.2 Transition metal mediated cyclopropane ring opening

2.3.2.1 Background

Transition metal catalyzed rearrangements of DA cyclopropanes to give (or regenerate) enol ether products are well established and known as "Puddephatt" transformations (**Scheme 2.7**).[65,66,67] A broad range of transition metals such as

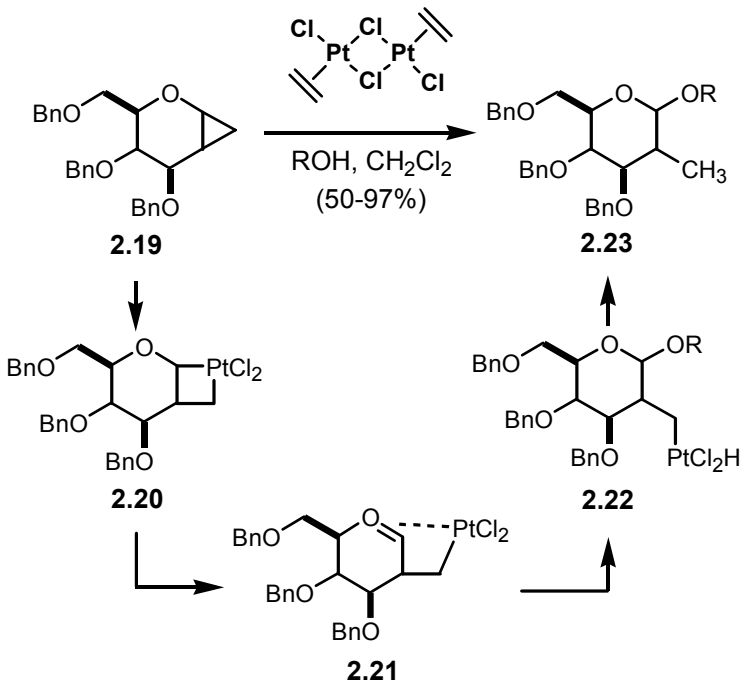
rhodium(I) ($[Rh(CO)_2Cl]_2$), ruthenium(II) ($[Ru(CO)_3Cl_2]_2$), platinum(II) ($PtCl_2$•2PhCN), copper bronze and CuCl were reported to be efficient catalysts for this transformation. The reaction proceeds by a regioselective oxidative addition to generate a metallacyclobutane intermediate. A subsequent reductive β-hydride extraction and reductive elimination affords the vinyl ether products, which have shown little tendency toward C=C bond migration.



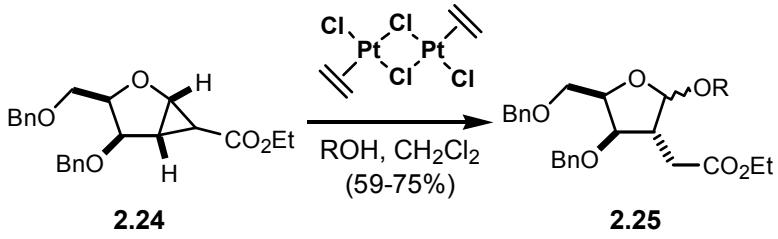
2.16 **2.17** **2.18**

Scheme 2.7: Puddephatt rearrangement of DA cyclopropanes

Using Ziese's dimer in alcoholic solvent, Madsen recently extended this transformation to glycal-derived cyclopropane substrates as a means to access C(2) branched glycosides (**Scheme 2.8**).[68] Interestingly, the platinacyclobutane intermediate gained sufficient lifetime for competitive C(1)-Pt bond dissociation before β-hydride elimination to the glycoside products. Even when challenged with electronic effects from substrates bearing a carboxylate group **2.24**, the C(1)-Pd bond dissociation still overrode the β-hydride elimination, and the same reaction pathway was observed (**Scheme 2.9**).



Scheme 2.8: Ziese's dimer mediated ring cleavage of 2.19

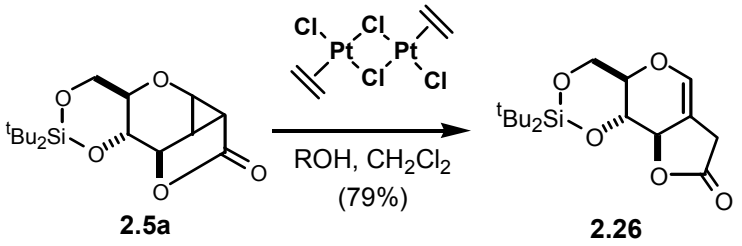


Scheme 2.9: Ziese's dimer mediated ring cleavage of 2.24

2.3.2.2 Results and discussion

In our situation, reaction of the lactonized cyclopropane **2.5a** in the presence of transition metal catalysts (vide infra) failed to give the corresponding acetal product, but

provided the Puddephatt rearranged product **2.26** in 79% yield (**Scheme 2.10**).[69] It is very likely that the conformational restriction of lactonized cyclopropane substantially offsets the stabilizing effect of the pyran oxygen, and the transient metallocyclic intermediate does not possess sufficient freedom to maintain a lifetime for C(1)-Pt bond polarization.



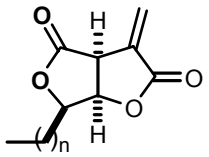
2.5a **2.26**

Scheme 2.10: Puddephatt rearrangement of 2.5a

2.4 APPLICATION IN QUASI FORMAL SYNTHESIS OF XYLOBOVIDE

To demonstrate the potential synthetic utility of this methodology, the cyclopropane **2.5a** was applied to a quasi formal synthesis of bislactone product **2.34a** and its derivatives.

The phytotoxic natural product xylobovide **2.34a**,[70] together with the fungicide canadensolide **2.34b**,[71] and antibacterial agent sporothriolide **2.34c** are closely related natural products that differ simply in the length of their side chain (**Scheme 2.11**). These structures have received considerable attention as synthetic targets. Canadensolide **2.34b** and sporothriolide **2.34c** have been synthesized,[72,73] but the total synthesis of xylobovide **2.34a** has not been reported. Inspection of **2.34a** reveals that, excluding the exocyclic methylene,[74] all of the carbons with the correct stereochemistry necessary for its synthesis are present in cyclopropanes **2.5a**.



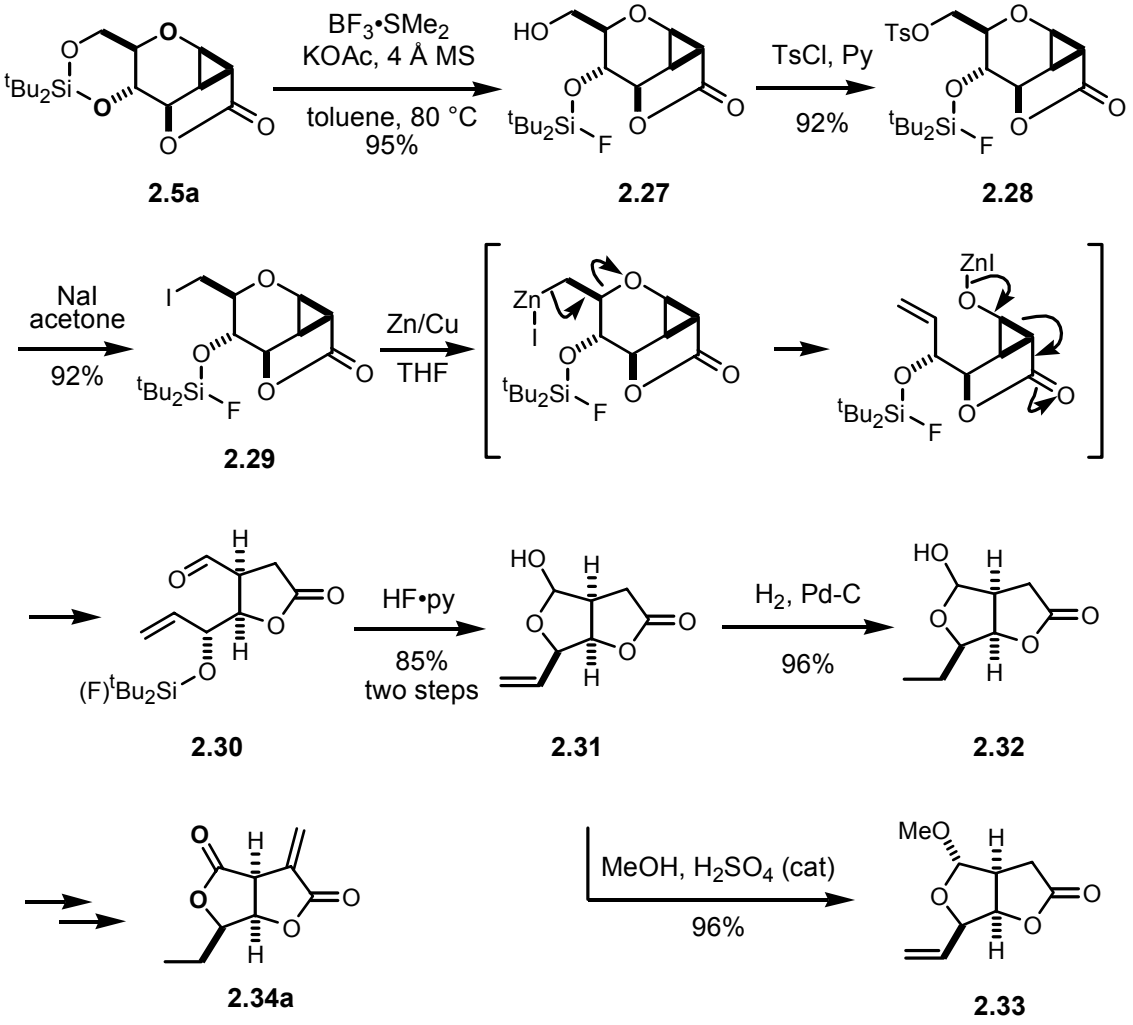
2.34a, xylobovide, n = 1
2.34b, canadensolide n = 3
2.34c, sporothriolide, n = 5

Scheme 2.11: Xylobovide and derivatives

As illustrated in **Scheme 2.12**, cyclopropane **2.5a** was converted into the advanced intermediate **2.32**, which, on the basis of literature precedent,[72g,h] provides access to xylobovide **2.34a**. The first synthetic task was the removal of the di-*tert*-butyl silylene ether. Complete desilylation with TBAF in THF afforded, as expected, the corresponding diol in 93% yield. However, the possibility of achieving a more interesting mono-desilylation of the di-*tert*-butylsilylene ether was explored with this substrate. After some experimentation, it was discovered that treatment of **2.5a** with BF_3•Et_2O in toluene (85 °C, 30 min) in the presence an HF scavenger such as allyltrimethylsilane revealed exclusively the primary alcohol **2.27** in 95% yield.[75,76] (The generality of this selective mono-deprotection protocol is described in Chapter 5.) Conversion of alcohol **2.27** to iodide **2.29** (ca. 90%, two steps) following a Finkelstein transformation set the stage for a zinc-mediated reductive ring opening cascade.[77] Addition of iodide **2.29** to a room-temperature suspension of zinc-copper couple[78] in dry THF resulted in rapid reduction and cleavage of the pyran ether to zinc alkoxide, which spontaneously underwent further ring opening to aldehyde **2.30**. Aldehyde **2.30** was converted without purification to the hemiacetal **2.31** by desilylation of the di-*tert*-butylfluorosilyl ether with HF•pyridine.[79] The di-*tert*-butylfluorosilyl ether protecting group utilized in this

reaction sequence proved to be quite robust in the absence of fluoride ion and was labile only upon exposure for several hours to strongly basic conditions (5% aqueous NaOH).

Reduction of olefin intermediate with hydrogen over palladium on carbon provided hemiacetal **2.32** (96%), which maps nicely onto an advanced intermediate in the Fraser-Reid total synthesis of canadensolide.[72g,h] Additionally, treatment of hemiacetal **2.31** with catalytic H_2SO_4 in refluxing methanol afforded acetal **2.33** in 96% yield. The acetal **2.33** presents a convenient divergence point for the synthesis of canadensolide **2.34b**, sporothriolide **2.34c**, and related structures by oxidative olefin cleavage and Wittig homologation.



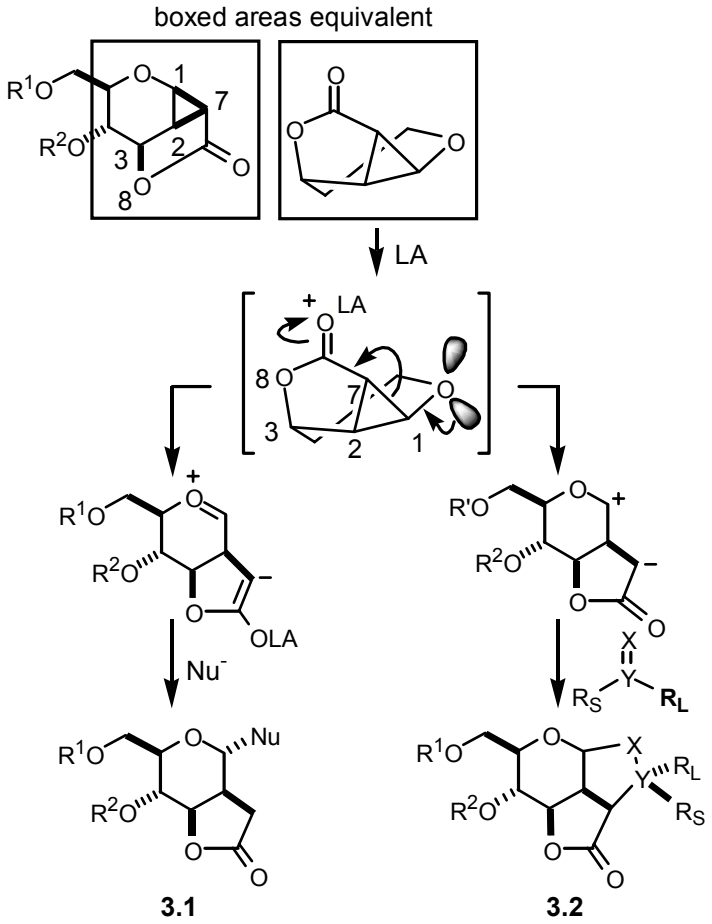
Scheme 2.12: Quasi formal synthesis of xylobovide 2.34a

Chapter 3: Lewis acid mediated reactions of DA cyclopropanes

3.1 INTRODUCTION

Lewis acid (LA) mediated ring opening reactions are among the most important synthetic transformations for DA cyclopropanes (**Section 1.2.2.2**).[1] Lewis acid promoted reactions of DA-cyclopropanes prepared by intermolecular cyclopropanation offer an efficient route to oxapanes through ring expansion.[17] While useful for accessing seven-membered rings, the transformation fails to exploit the difficult-to-establish cyclopropane stereochemistry.

In this regard, the unique bond angles of the lactonized DA cyclopropanes prepared through intramolecular cyclopropanation provided an excellent approach to circumvent the σ-Ferrier rearrangement. Single crystal X-ray crystallographic analysis of tricycle **2.5a** revealed a twisted boat conformation of the pyran scaffold (instead of the chair-like intermolecular counterparts) and a C(1)-C(2)-C(3)-O(8) dihedral angle of 70.6° (**Figure 2.1**), which disfavors the C(3)-O(8) elimination pathway as observed on the intermolecular counterparts. Additionally, unlike the one in the chair like structure **1.58**, the C(1)-C(7) bond alignment is distorted into a position reasonably anti-parallel to the lone pair electrons of the pyran ring oxygen, and therefore suitable for C(1)-C(7) bond cleavage (**Scheme 3.1**).



Scheme 3.1: Lewis acid mediated C(1) cleavage of lactonized DA cyclopropane

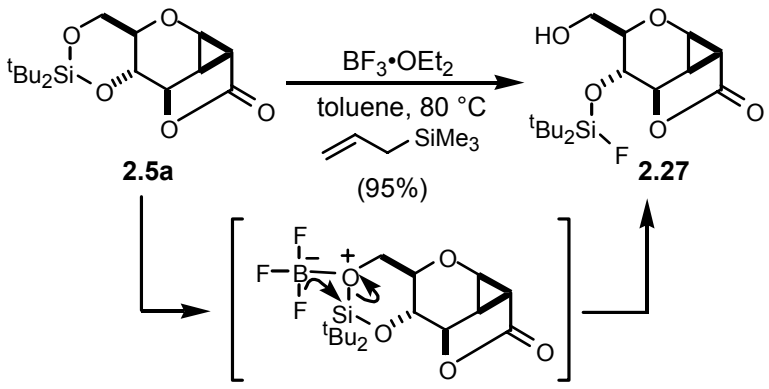
The reactivity of cyclopropane **2.5a** was studied with a variety of Lewis acids including $SnCl_4$, Et_2AlCl, $Ti(^iOpr)_4$, $Cl_2Ti(^iOpr)_2$, $ZnCl_2$, $Sc(OTf)_3$, $ZrCl_4$, $Zr(OTf)_4$. In most cases, Lewis acid treatment under various conditions resulted in either no reaction or substrate decomposition. However, three Lewis acids were identified to be effective for promoting C(1)-C(7) bond cleavage: BF_3•OEt_2 (**Section 3.2**), TMSOTF (**Section 3.3**), and $TiCl_4$ (**Section 3.4** and **3.5**). This chapter summarizes the useful transformations we have recently achieved on lactonized DA cyclopropanes and related substrates. Some of

the newly discovered chemical reactivity of **2.5a** has been expanded to encompass general non-carbohydrate derived DA cyclopropanes (**Chapter 4**).

3.2 REACTIONS MEDIATED BY BORON TRIFLUORIDE ETHERATE

Compared with TMSOTf and $TiCl_4$, the use of BF_3•OEt_2 as an activator of DA cyclopropanes has received less attention. Generally, DA cyclopropanes are quite resilient to this promoter, and application of BF_3•OEt_2 has been mostly restricted to initiating cascade sequences consisting of pyran expansion and nucleophilic addition (**Section** 1.2.2.2).[47,48,49]

The lactonized DA cyclopropane **2.5a** was found to be essentially unreactive toward BF_3•OEt_2. Under conditions attempted for direct allylation, the cyclopropane refused to undergo either retro-aldol rearrangement or pyran ring expansion. Changing the solvent system to include CH_2Cl_2, chloroform, ether, or THF did not appear to have a positive effect. When forcing conditions were applied (e.g., 80 °C, toluene), the cyclopropane nucleus remained intact, but the di-*tert*-butylsilylene ether succumbed to ring cleavage (**Scheme 3.2**), giving the primary alcohol **2.27** in nearly quantitative yield.[49] While there was no noticeable allylation side products observed during this reaction, the trimethyl allylsilane was found to be indispensable for maintaining high efficiency. Control experiments without this reagent normally led to incomplete reaction, poor regioselectivity, and over-deprotection. This apparent difference strongly suggested trimethyl allyl silane as an acid scavenger to minimize side effects from inadvertent water.



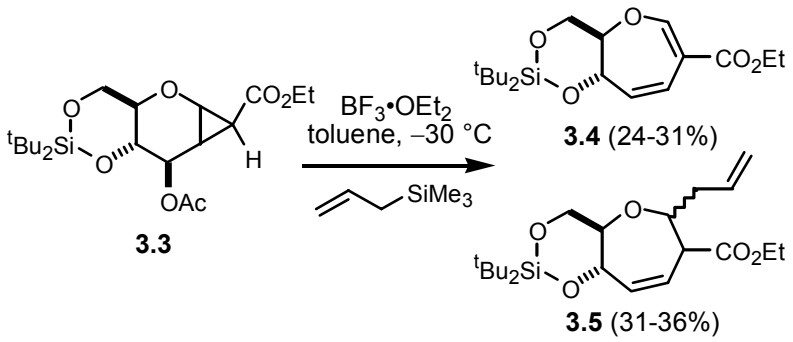
Scheme 3.2: Regioselective desilylation of silylene ether 2.5a

The general reactivity and selectivity of the deprotection, and the stability of the fluorosilane protective group have been systematically explored (**Chapter 5**).[76] A useful observation from those studies is that the stability of the subject di-*tert*-butylsilylene ether falls in between that of the *tert*-butyl-dimethylsilyl ethers (TBDMS) and triisopropylsilyl (TIPS) ethers.

The mono-desilylation of **2.5a** requires relatively high temperatures (80 °C). For example, in refluxing CH_2Cl_2 solution, the reaction was still plagued with incompletion and over-deprotection, which strongly suggests the high stability of the subjective cyclopropane.

The reactivity (or stability) of **2.5a** afforded the opportunity for an important comparison between similar lactonized cyclopropanes and those prepared from intermolecular cyclopropanation. Specifically, the control cyclopropane **3.3** underwent rapid ring expansion at temperatures as low as –30 °C, giving oxacycloheptene products **3.4**, **3.5** (**Scheme 3.3**). The distinctly different reactivity displayed by the structurally

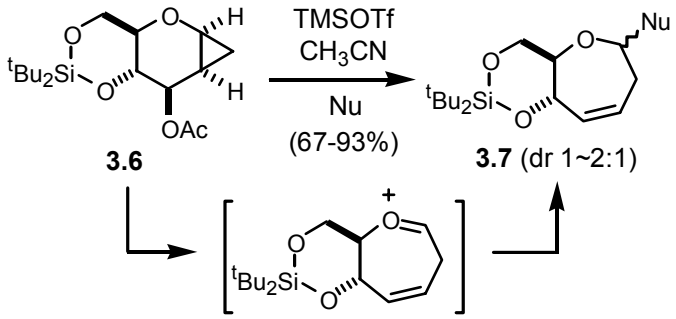
similar substrates in **Scheme 3.2** and **Scheme 3.3** appears to support the hypothesis that a lactone linkage is a viable strategy for suppressing the ring expansion process.



Scheme 3.3: Control reaction: pyran ring expansion

3.3 REACTIONS MEDIATED BY TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE

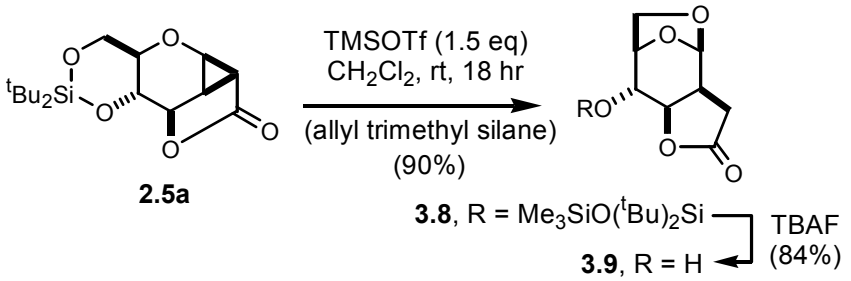
The use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to activate cyclopropanes has seen more frequent literature success, but the application on carbohydrate-derived DA cyclopropanes has been mainly restricted to pyran ring expansion (**Section 1.2.2.2**). For example, Hoberg showed that catalytic TMSOTf generated an oxocarbenium ion intermediate sufficiently long lived that it could be intercepted with a variety of nucleophiles, including allylsilanes, propargylsilanes, sily enol ethers and disulfides (**Scheme 3.4**).[27b] But the conformationally planar di-*tert*-butyl silylene ether protection normally resulted in only moderate facial selectivity.



Scheme 3.4: Pyran ring expansion of glycal derived DA cyclopropane

In stark contrast, under similar conditions employing catalytic TMSOTf, the lactonized DA cyclopropane **2.5a** remained intact even in refluxing CH_2Cl_2 (**Scheme 3.5**). Cyclopropane cleavage at the C(1)-C(7) bond was eventually realized under forcing conditions including stoichiometric Lewis acid loading (1.5 equivalents) and extended reaction time (18 hours). But these conditions also led to destruction of the silylene ether, which after a subsequent intramolecular ring closure provided the anhydro-sugar product

3.8 in up to 90% yield. This anhydro-sugar **3.8** formation process appears to be very favorable, easily out-competing nucleophilic allyl trimethylsilane addition.



Scheme 3.5: Anhydro-sugar 3.8 formation

The amphibious chemical behavior of **2.5a** has stimulated further investigation on lactonized DA cyclopropane reactivity. The unique ring strain and bonding angle of the quartcycle **2.5a** seems to place the intermediate oxocarbenium ion in a self-stabilized conformation which is unmotivated for either C(2) deprotonation or neutralization with external nucleophiles. Further attempts to intercept the oxocarbenium generated from reaction of the lactonized DA cyclopropanes with TMSOTf using other nucleophiles eventually met success, and these results will be described in chapter 4.

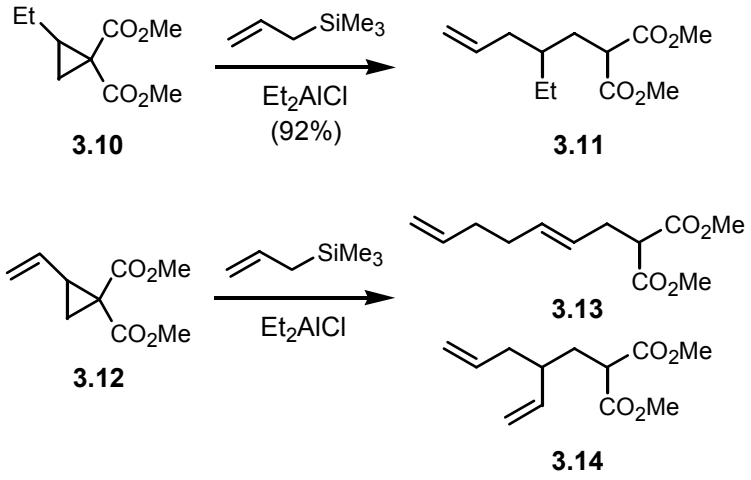
3.4 STEREOSELECTIVE ALLYLATION MEDIATED BY TITANIUM TETRACHLORIDE

We have recently developed Lewis acid promoted direct allylation of glycal-derived DA cyclopropane, and this methodology provided a convenient route toward glycosides with both C(1) and C(2) *C*-branches for future structural modifications.

3.4.1 Brief literature survey

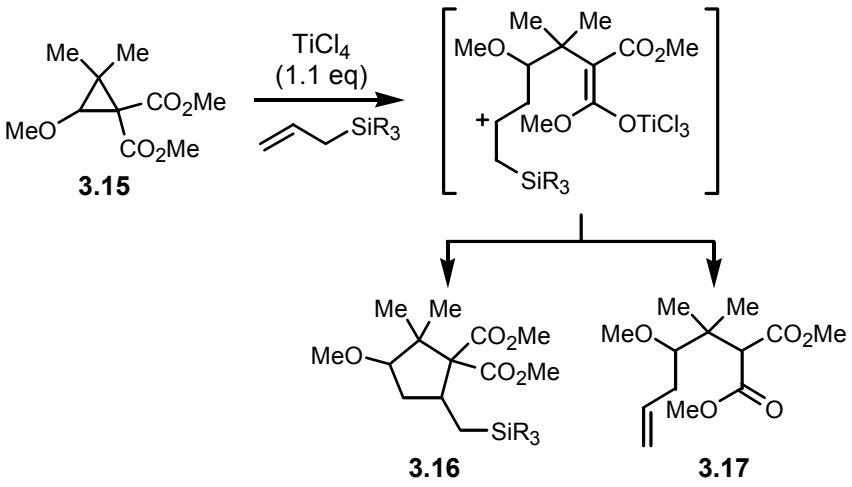
The allylation of activated cyclopropanes is an attractive strategy for increasing molecular diversity. Kemmitt pioneered homoconjugate allyl additions to geminally

activated cyclopropanes (**Scheme 3.6**).[80] The allylation of **3.10** occurred regio-selectively at the substituted position, but in the case of **3.12** addition to the vinyl group was also observed. Hoberg reported the direct allylation of donor activated glycal-derived cyclopropane **3.6**, but the flattened bicycle oxonium intermediate did not show satisfactory facial selectivity toward allylsilane attack.[27b]



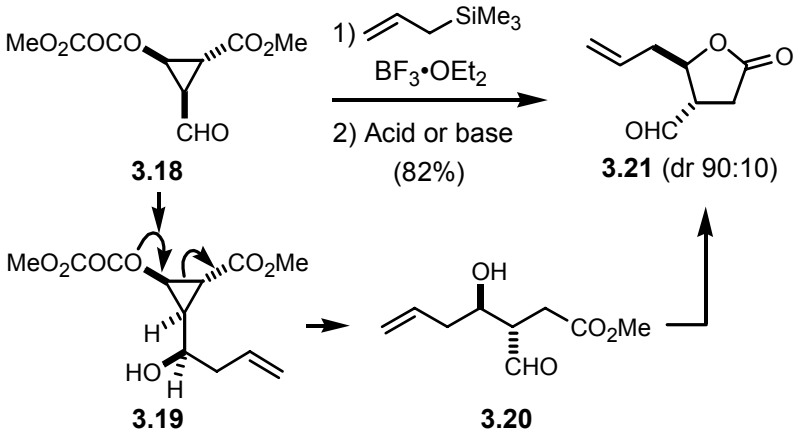
Scheme 3.6: Attempts on direct allylation of cyclopropanes

Direct Lewis acid mediated allylation of DA cyclopropane might be anticipated to be a straightforward process, but throughout the literature there are few examples. Because allylsilanes can also function as both 1,2 and 1,3 dipoles, the allylation of DA cyclopropanes **3.15** is often accompanied, or even dominated by [3+2] cycloaddition (**Scheme 3.7**).[81]

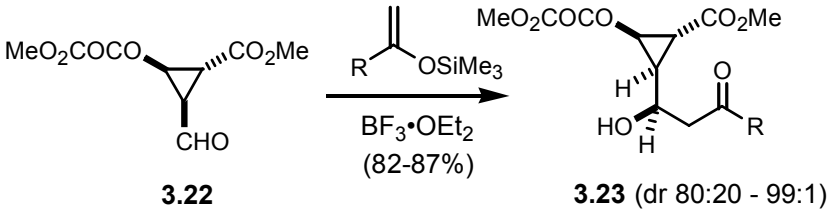


Scheme 3.7: Allylation vs. [3+2] cycloaddition of 3.15

Products derived from the formal allylation of DA cyclopropanes were recently reported by Reiser,[82,83] but that process does not involve authentic allylation of the cyclopropane core (**Scheme 3.8**). Instead, reaction of cyclopropane **3.18** with allyltrimethylsilane in the presence of BF_3•OEt_2 resulted in Sakurai reaction with the pendant aldehyde. The alcohol **3.20** was converted into the lactone **3.12** through treatment with acid or base. Even with two electron withdrawing groups, the remarkable stability of the cyclopropane ring was further demonstrated by its noninvolvement during a Mukaiyama aldol reaction (**Scheme 3.9**).



Scheme 3.8: Pseudo-allylation of 3.18

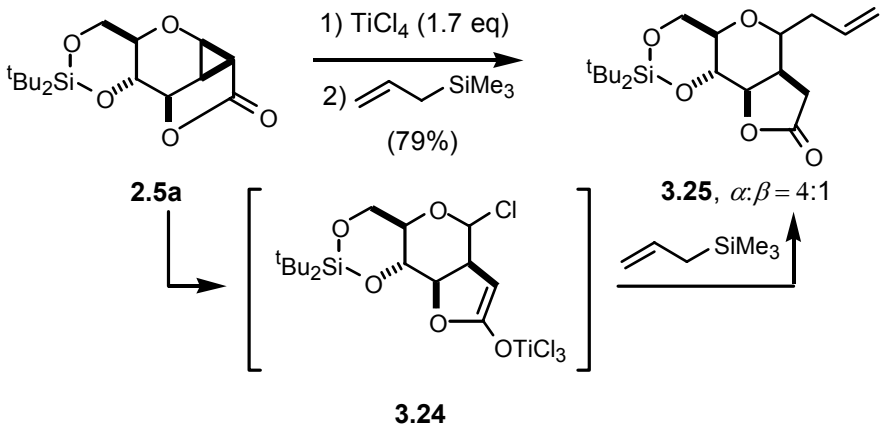


Scheme 3.9: Mukaiyama transformation of 3.22

3.4.2 Direct allylation of lactonized glucal-derived cyclopropanes

A wealth of information is known about glycosyl donors,[84] and this work prompted us to test whether activation of DA cyclopropane **2.5a** with a suitable Lewis acid would generate an oxo-carbenium ion as a compatible glycosyl donor for direct allylation.[85] Toward this end, treating the cyclopropane **2.5a** with a stoichiometric (1.7 equivalents) amount of $TiCl_4$ for two hours at room temperature resulted in complete conversion to a more polar species (TLC), presumably the α-chloropyran intermediate **3.24** that was stable for several hours in the absence of nucleophiles. Subsequent addition

of allyltrimethylsilane led to formation of **3.25** (**Scheme 3.10**) in 79% isolated yield, and the sterically favored α-diastereomer predominated (4:1) in the product mixture.[86] While the similar 2-halopyrans/furanoses were reported isolatable,[87] the 2-chloropyran intermediate **3.24** proved elusive for isolation after careful attempts, and it was finally characterized as the hemiacetal through aqueous $NaHCO_3$ workup (**Section 3.5**).



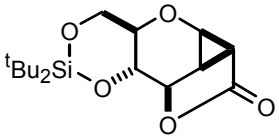
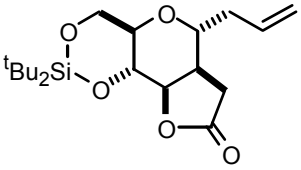
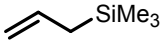
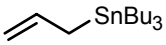
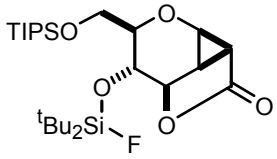
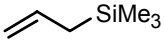
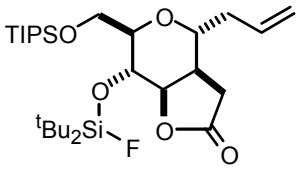
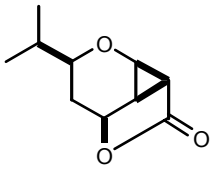
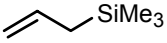
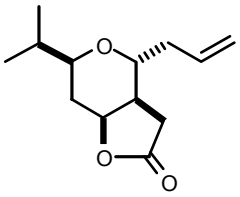
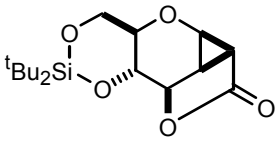
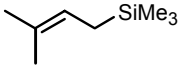
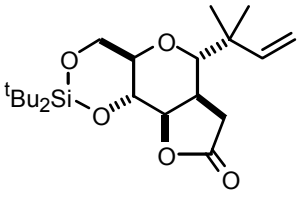
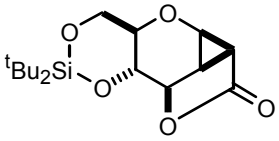
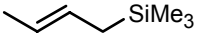
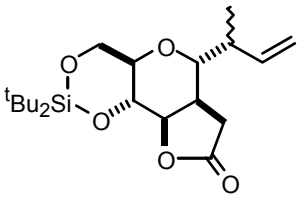
Scheme 3.10: Stereoselective allylation of 2.5a

Lewis acid $TiCl_4$ was found to be the only successful promoter for this reaction. Other Lewis acids (e.g., $BF_3{\cdot}OEt_2$, $SnCl_4$, $Sc(OTf)_3$, $ZrCl_4$ and Et_2AlCl) under standard Sakura allylation conditions[88] resulted in either substrate decomposition or no reaction. Reactions under TMSOTf condition furnished the anhydro-sugar product **3.8** after silylene ether cleavage (**Section 3.3**).

A very curious aspect of this allylation had been the high dependence on reagent addition order, and the above stepwise addition sequence proved critical for success. Initial attempts treating a mixture of the cyclopropane and allylsilane with a Lewis acid,

as typically employed in Sakurai reactions,[88] resulted exclusively substrate decomposition.

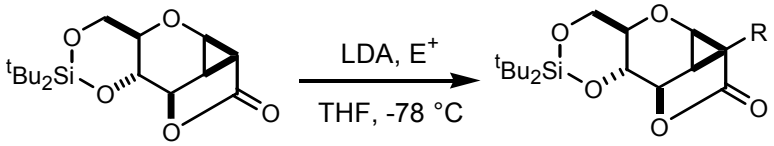
As illustrated in **Table 3.1**, employing allyltributylstannanes improved both reaction yields and facial selectivity (entry 2), but due to high toxicity it was not the primary focus of the study. The subject allylation reaction was found to be quite general and efficient on this classic of lactonized DA cyclopropanes (entry 1-3), as well as the non-sugar-derived substrate **2.9** (entry 4). In entries 3 and 4 the conformationally restricted 4,6-cyclic protecting groups proved unnecessary. A variety of enantiomerically pure dihydropyrans are available from hetero-Diels-Alder cycloadditions,[61] and entry 4 confirms that cyclopropanes derived from these synthetically important substrates participate efficiently in the stereoselective allylation. The more hindered prenylsilane gave the addition product **3.29** in 78% yield with enhanced diastereoselectivity of 10:1 (entry 5). Crotylation resulted in exclusive formation of the α-isomer **3.30**, but no diastereoselectivity was observed at the allylic methyl position (entry 6).

Entry	Substrate	Allylation reagent	Products	Yield[a] (α:β)
				
1	**2.25a**		**3.25**	79% (4:1)
2	**2.25a**		**3.25**	87% (7:1)
3	 **3.26**		 **3.27**	78% (5:1)
4	 **2.9**		 **3.28**	72% (5:1)
5	 **2.25a**		 **3.29**	78% (10:1)
6	 **2.25a**		 **3.30**	79%[b] --

[a] CH_2Cl_2 solvent, isolated yields; [b] 1:1 mixture of diastereomers at the allylic position.

Table 3.1: Allylation of lactonized DA cyclopropanes

To improve the diastereoselectivity of the allylation, steric hindrance was temporarily introduced onto the lactone tether to increase the nonbonding interactions between nucleophilic allylsilane and substrates (**Table 3.2**). In these reactions, premixing **2.25a** and electrophile compatible with strong base before enolate formation is absolutely necessary. Efforts to introduce different activating functionality through other electrophiles such as chloroformate was unsuccessful.

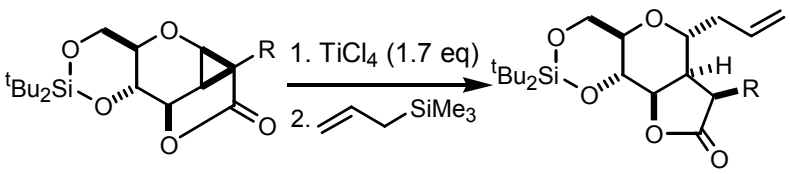


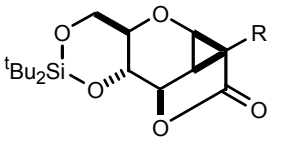
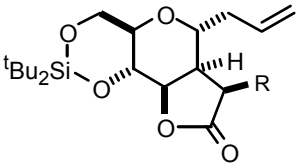
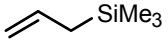
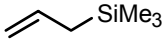
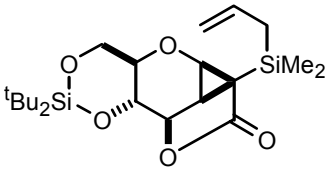
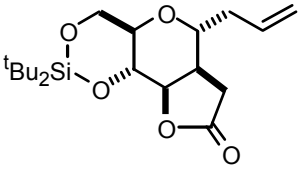
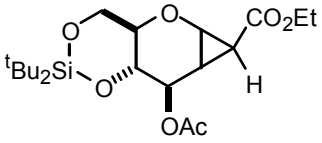
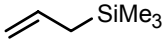
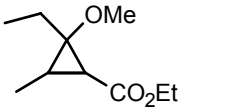
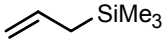
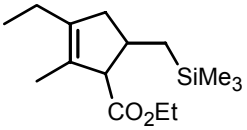
2.5a **3.31a-c**

Entry	Electrophile	R	Product	Yield
1	Me_3SiCl	Me_3Si	**3.31a**	96%
2	$(C_2H_3)Me_2SiCl$	$C_2H_3Me_2Si$	**3.31b**	97%
3	$(C_3H_5)Me_2SiCl$	$(C_3H_5)Me_2Si$	**3.31c**	93%
4	MeO_2CCl	-	-	decomposition

Table 3.2: Temporary silylation of 2.5a

With the temporary steric hindrance, the reaction diastereoselectivity increased to an 8:1 ratio (**Table 3.3**, entry 1). The stereochemical assignment of the major diastereomer **3.32a(α)** (entry 1) was unambiguously confirmed by single-crystal X-ray analysis (**Figure 3.1**), and subsequent desilylation with KF in MeOH/MeCN provided a product identical to the major diastereomer **3.25(α)** (**Table 3.1**, entry 1) obtained from direct allylation (**Scheme 3.11**).



Entry	Substrate	Allylation reagent	Products	Yield[a] (α:β)
				
1	**3.31a**, R = $SiMe_3$		**3.32a**, R = $SiMe_3$	81%[b] (8:1)
2	**3.31b**, R = $Si(C_2H_3)Me_2$		**3.32b**, R = $Si(C_2H_3)Me_2$	79% (8:1)
3	 **3.31c**	No exogenous silane	 **3.25c**	77% (3:1)
4	 **3.33**		-	-
5	 **3.34**		 **3.35**	85%[c]

[a] CH_2Cl_2 solvent, isolated yields; [b] Structure assignment of **3.32a(α)** by X-ray crystallography; [c] Inseparable mixture.

Table 3.3: Diastereoselective allylation of modified DA cyclopropanes

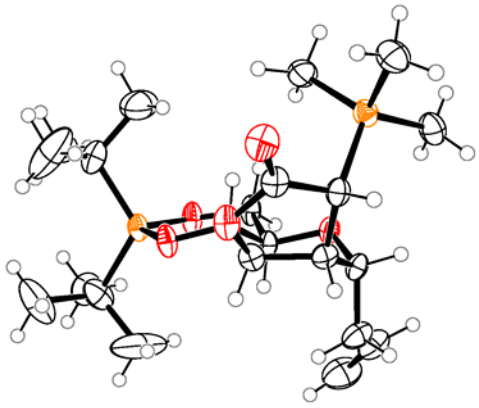
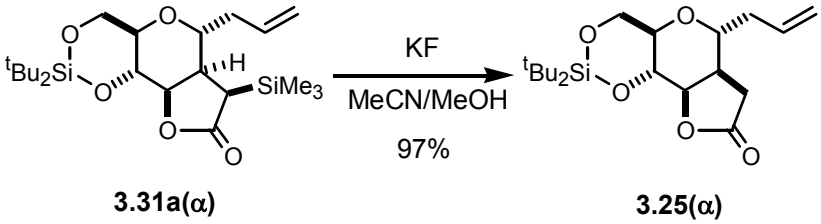


Figure 3.1: X-ray structure of 3.32a(α)



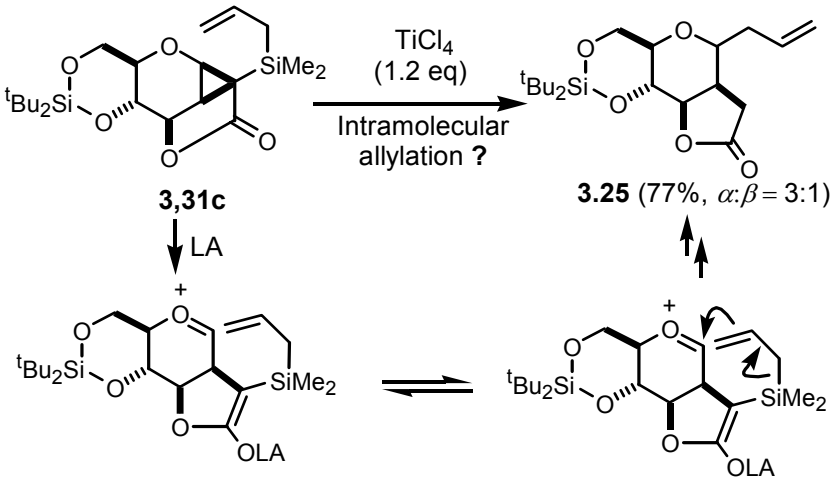
3.31a(α) **3.25(α)**

Scheme 3.11: Selective desilylation of 3.32a(α)

The internal lactone linkage proved to be a necessary structural feature for direct allylation, and control experiments attempted on flexible carbohydrate-derived substrate **3.33** led to exclusive substrate decomposition (**Table 3.3**, entry 4). Application of similar conditions to general DA cyclopropane **3.34** resulted in formation of cyclopentene derivative **3.35** (entry 5).[81]

In an attempt to access the β diastereomer as the major product, a possible intramolecular allylation was attempted on substrate **3.31c**, which was prepared in 93% yield from allyl dimethyl chlorosilane following the similar procedure as described for **3.31a**. The flexibility of the allylsilane tether makes possible an intramolecular delivery

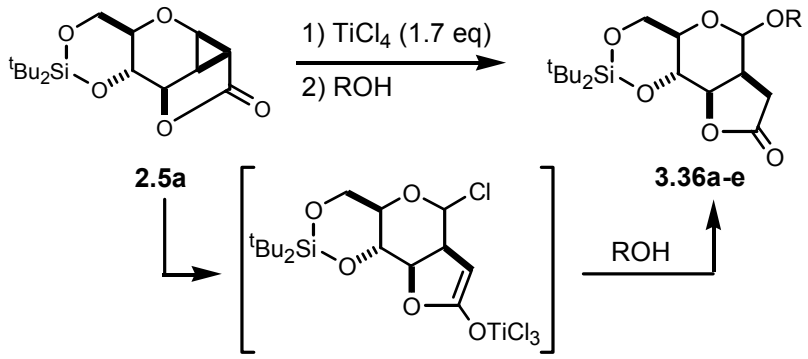
from the β face of the intermediate oxonium ion (**Table 3.3**, entry 3; **Scheme 3.12**), but the change in the diastereomeric ratio was minimal (3:1 vs. 4:1); either in presence or absence of exogenous allylation reagents. Convincing evidence for the reactions mechanism has thus far proved unclear.



Scheme 3.12: Possible intramolecular allylation

3.5 STEREOSELECTIVE GLYCOSYLATION MEDIATED BY TITANIUM TETRACHLORIDE

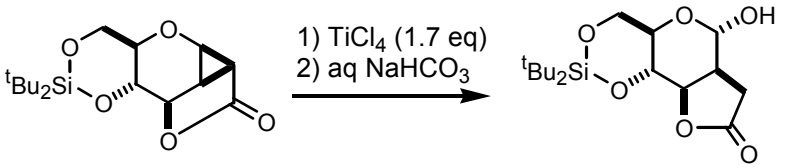
In addition to direct DA cyclopropane allylation, Lewis acid $TiCl_4$ also proved efficient in mediating alcohol solvolysis of lactonized glucal-derived DA cyclopropanes and provided C(2) branched glycoside products (**Scheme 3.13**).[69] Alcohol has been reported to react with functionalized cyclopropane under various reaction conditions including neutral,[89] acidic,[90] electrochemical,[91] photochemical,[92] mercuration,[93] and others as briefly summarized in **Section** 1.2.2.1. However, of these solvolysis reactions, few of the cyclopropanes were dihydropyran-derived, and a scant number of them were prepared from carbohydrates.[94,95] It has been reported that closely related cyclopropanes preferentially undergo ring expansion to seven-membered oxacycles when treated with strong electrophiles (**Section 1.2.2.2**), but this mode of ring opening has not been previously observed with the intermolecular variants (e. g., **1.20**).



Scheme 3.13: Stereoselective glycosidation of 2.5a

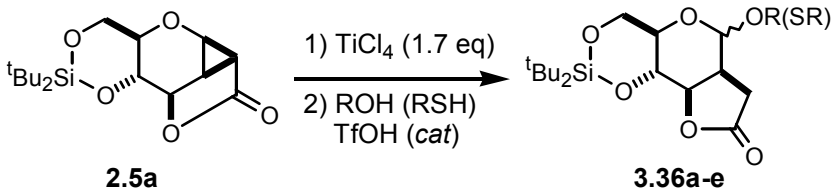
After activation of cyclopropane **2.5a** with stoichiometric amounts of $TiCl_4$, the resulting mixture was worked up with aqueous $NaHCO_3$ solution to afford hemiacetal **3.36a** with 7:3 (α:β) facial selectivity (90%, **Scheme 3.14**). Treatment of the resulting

mixture with excess methanol led to the formation of acetal **3.36b**, but the reaction was plagued with substrate decomposition and low conversion yield (<35%). Mercury or silver salts were added to promote reactivity in the Köenigs–Knoor glycosidation reaction, but both of these additives were less than ideal in the current case. In this regard, it was discovered that the addition of a catalytic amount of strong Brønsted acid, such as trifluoromethanesulfonic acid (TfOH), resulted in clean solvolysis. Under these conditions, a 6:1 mixture of α and β acetals **3.36b** was obtained from the reaction with methanol (91%, **Table 3.4**, entry 2). Both the ^{13}C and ^{1}H NMRs consistently indicated α-diastereomer as the major product. The observed facial selectivity is consistent with the anomeric effect as well as steric directing factor. Under the cooperation of increased alcohol steric hindrance, the reaction generally displayed elevated α-facial selectivity, with a ratio of 8:1 for benzyl alcohol (entry 3), and 15:1 (α:β) for allylic alcohol (entry 4). Phenols worked equally well as glycosyl acceptors, and from the reaction in entry 5 provided a 12:1 acetal mixture in 87% yield.



2.5a **3.36a** (90%, α:β = 7:3)

Scheme 3.14: Hemiacetal formation from 2.5a



2.5a **3.36a-e**

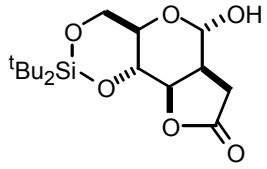
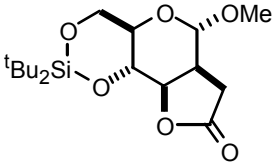
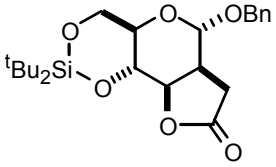
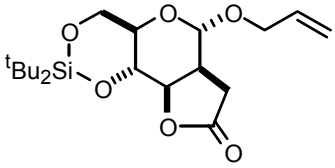
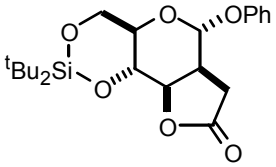
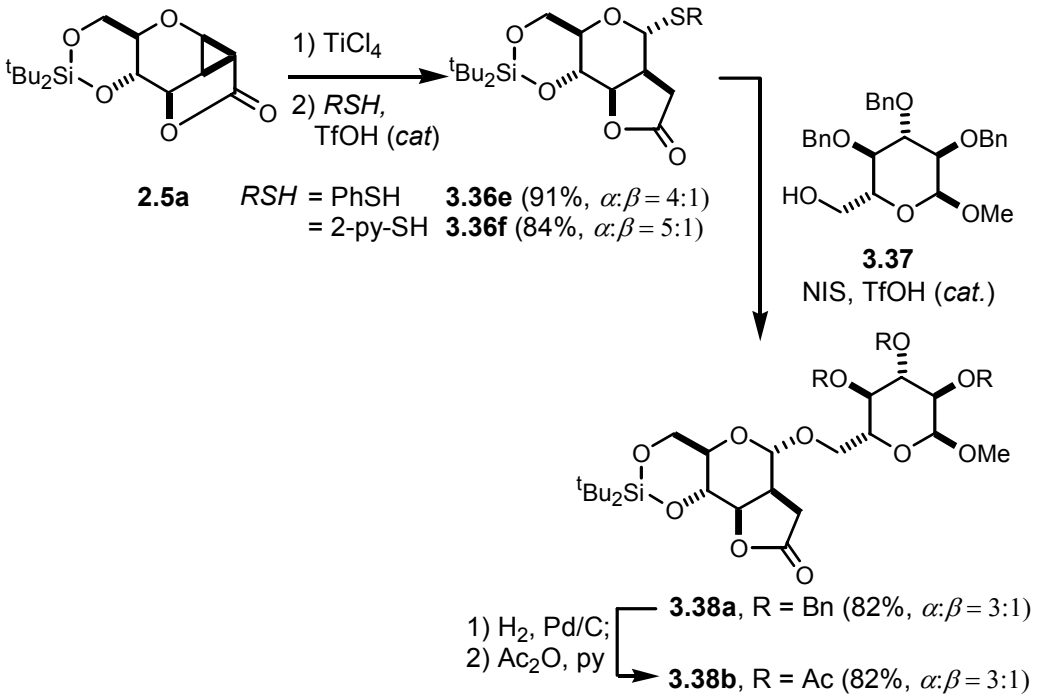
Entry	Nucleophile	Product		Yield	Ratio (α:β)
1	$NaHCO_3/H_2O$		**3.36a**	90%	7:3
2	MeOH		**3.36b**	91%	6:1
3	$PhCH_2OH$		**3.36c**	84%	8:1
4	$CH_2=CHCH_2OH$		**3.36d**	89%	15:1
5	PhOH		**3.36e**	87%	12:1

Table 3.4: Acetal formation from 2.5a

Whereas CH_2Cl_2 has been the most efficient solvent for direct allylation (**Section 3.4**), diethyl ether was more effective for both the $TiCl_4$ activation and the proceeding

alcohol hydrolysis. Glycosidations in CH_2Cl_2 are normally accompanied with many uncharacterized by-products.

A major disincentive for employing the acetal synthesis as outlined above for direct preparation of oligosaccharides is the requirement for excess alcohol to satisfy the electrophilic titanium chloride. However, practical glycosylation can be achieved by a two-step sequence that proceeds through traditional 2-sulfanyl pyran intermediates such as **3.36e**,**f**. The *S*,*O*-acetals **3.36e**,**f** were prepared through $TiCl_4$ activation of **2.5a** followed by thiol trapping (**Table 3.4**, entries 6 and 7).[96,97,98] To demonstrate the glycosylation procedure, treatment of **3.36e** with 2,3,4-tribenzyl methyl pyranoside **3.37**[99] in the presence of *N*-iodosuccinamide and TfOH gave the disaccharide **3.38a** (82%) as a 3:1 mixture of diastereomers.[100] As further structural confirmation, the **3.38a** was subsequently converted to triacetyl oligosaccharide **3.38b** through debenzylation and acylation.



Scheme 3.15: Stereoselective glycosidation

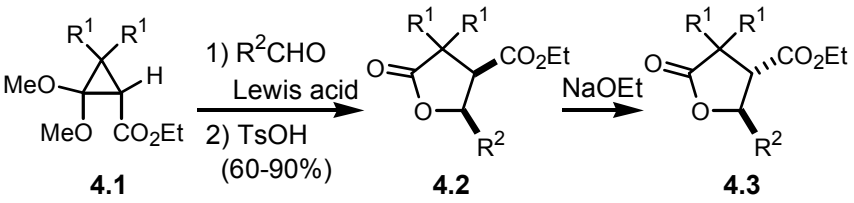
Chapter 4: Formal [3+2] cycloaddition of DA cyclopropanes

One of the most important synthetic applications of DA cyclopropanes has been in the area of (formal) [3+2] dipolar cycloadditions to generate five-membered carbocyclic and heterocyclic structures.[1] Because of the dual electrostatic character of the intermediate 1,3-zwitterion (**Scheme 1.1**), the cyclization can begin with either an electrophilic or nucleophilic reaction with the intermediate 1,3-dipole. The unique chemical behavior of DA cyclopropane **2.5a** prepared through intramolecular glucal cyclopropanation has led to the discovery of several new type of [3+2] dipolar cyclizations.

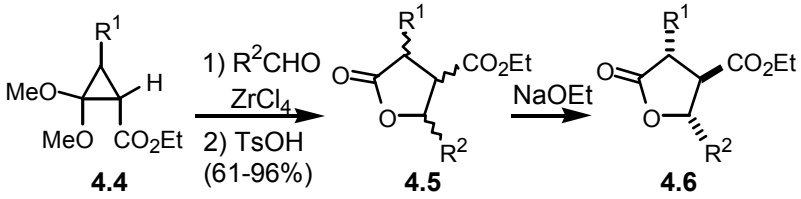
4.1 INTRODUCTION

A wide variety of π-electron systems are efficient dipolarophiles for cyclization with DA cyclopropanes, and aldehydes and ketones were among the first successful dipolarophiles to be identified. However, the majority of successful examples have employed cyclopropanes further activated by incorporation of additional electron donor or acceptor groups. For example, reaction of **4.1** with aldehydes followed by an acidic workup provided γ-lactone products **4.2** (**Scheme 4.1**).[101] The reaction was selective for the diastereomer with a *cis* relationship between the carboxylate and R^2, but a subsequent basic epimerization provided access to the *trans* epimer **4.3**. A similar reaction with a less substituted cyclopropane such as **4.4** resulted in the formation of four diastereomers **4.5** (**Scheme 4.2**), but a single Diastereomer **4.6** was available by base catalyzed equilibration.[102] Excellent stereocontrol was observed in the reaction with symmetric ketones (**Scheme 4.3**),[103] and similar aldehyde and ketone cyclizations have also been

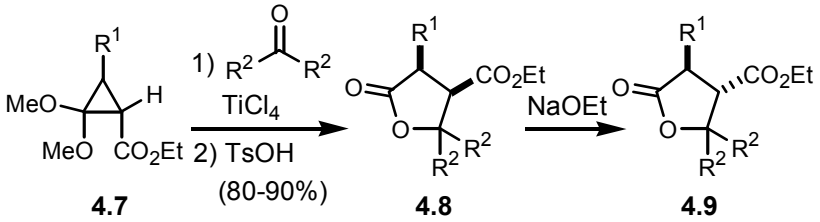
reported on 2,3-carboxylate substituted methanochromanone derived DA cyclopropane **1.66** (**Scheme 1.19**).[48b,c]



Scheme 4.1: γ-lactone formation



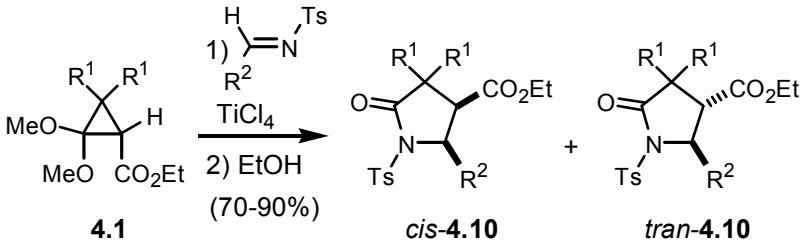
Scheme 4.2: DA cyclopropane-aldehyde cycloaddition



Scheme 4.3: DA cyclopropane-aldehyde/ketone cycloaddition

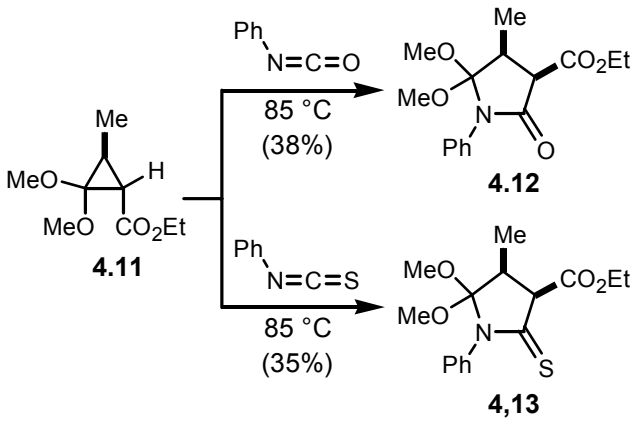
Carbon-nitrogen double bonds in the form of imines,[104] isocyanates,[105] and isothiocyanates[106] also react with DA cyclopropanes to provide lactams **4.10**, **4.12** and thiolactams **4.13** (**Scheme 4.4** and **Scheme 4.5**). Unlike the corresponding lactones (vide

supra), attempts at basic epimerization of **4.12** with NaOEt were plagued with lactam ring opening.



4.1 *cis*-**4.10** *tran*-**4.10**

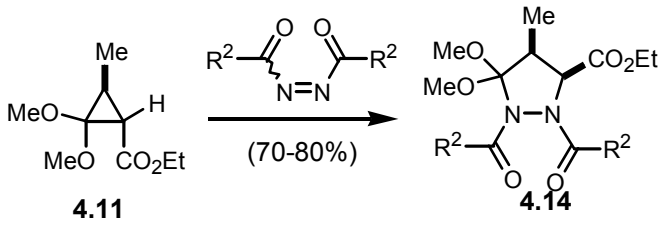
Scheme 4.4: DA cyclopropane-imine cycloaddition



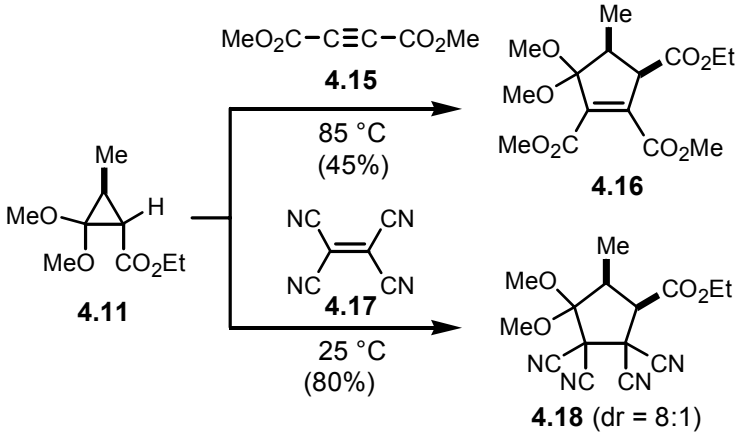
Scheme 4.5: DA cyclopropane-isocyanates cycloaddition

DA cyclopropane **4.11** has also been reported to undergo thermal cyclization with azodicarbonyl compounds in 70–80% yields (**Scheme 4.6**),[107] and the diastereoselectivity is highly dependent on the conformation of **4.11** as well as the polarity of the solvents. In other examples, the cyclization of **4.11** with electron deficient acetylene **4.15**[108] or alkene **4.17**[109] provided the cyclic products **4.16** and **4.18** (**Scheme 4.7**). Both the reactions have

very good diastereoselectivity, but the former was accompanied by considerable formation of acyclic addition product.

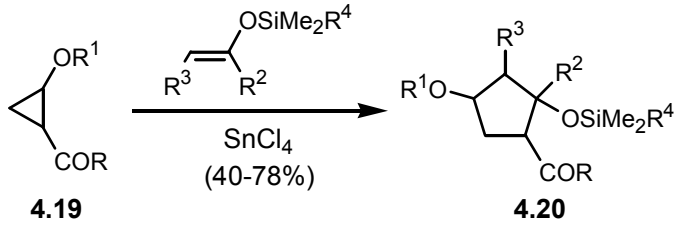


Scheme 4.6: DA cyclopropane-azodicarbonyl compound cycloaddition



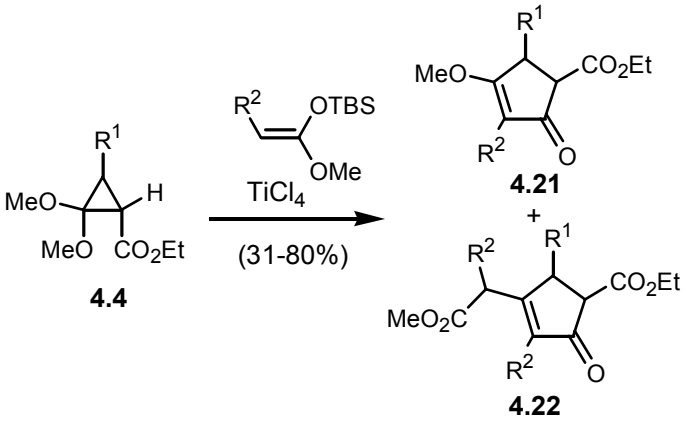
Scheme 4.7: Cyclopentane/cyclopentene preparation from DA cyclopropanes

Compared with the large diversity of electron deficient dipolarophiles, fewer electron rich dipolarophilic components have been reported to participate with DA cyclopropanes. The reaction with electron rich dipolarophiles normally requires catalytic Lewis acid activation. The reaction of cyclopropyl carboxylate or ketone **4.19** with silyl enol ethers under $SnCl_4$ activation afforded the cyclopentane products **4.20** in good yields, but without stereoselectivity (**Scheme 4.8**).[110]



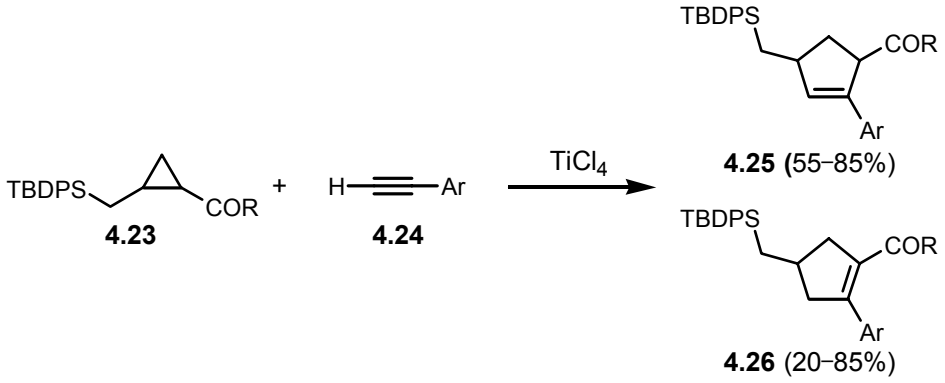
Scheme 4.8: DA cyclopropane-silyl enol ether cycloaddition

The reaction of cyclopropane **4.4** and silyl ketene acetals however did not stop at the cyclopentanes, and spontaneous elimination of MeOH gave the cyclopentenone products **4.21** and **4.22** (**Scheme 4.9**).[111]

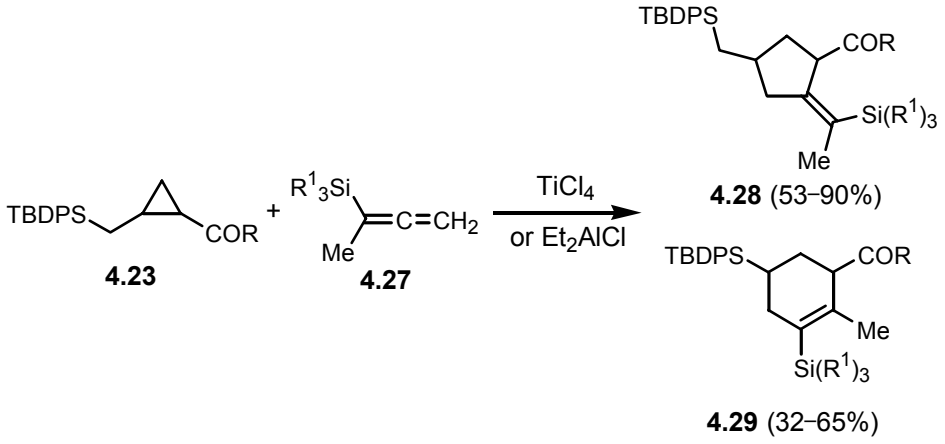


Scheme 4.9: DA cyclopropane-silyl ketene acetals cycloaddition

Recently, Yadav and coworkers have reported formal [3+2] cyclizations of acceptor cyclopropane **4.23** with aryl acetylenes **4.24** (**Scheme 4.10**),[112] and allenylsilanes **4.27** (**Scheme 4.11**).[113] These reactions demonstrated both high regio- and stereocontrol, and provided convenient access to highly functionalized cyclopentane and cyclohexene derivatives.



Scheme 4.10: DA cyclopropane-aryl acetylenes cycloaddition



Scheme 4.11: DA cyclopropane-allenylsilanes cycloaddition

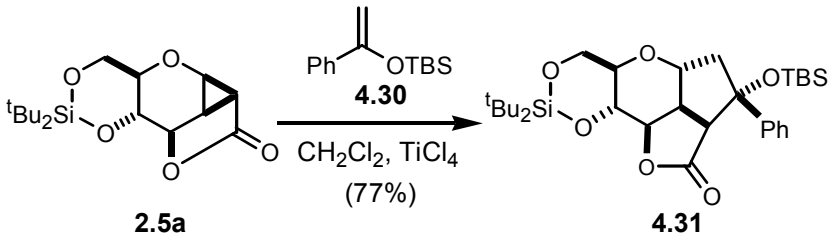
4.2 FORMAL [3+2] CYCLOADDITION OF GLYCAL-DERIVED DA CYCLOPROPANES

Despite the above diverse examples on general DA cyclopropanes, the formal [3+2] dipolar cycloaddition has been unprecedented for carbohydrate-derived cyclopropanes. A likely reason behind the paucity of examples on this class of substrates is their high tendency toward ring expansion (**Section 1.2.2.2**). Glucal–derived DA

cyclopropanes prepared by intramolecular cyclopropanation, in contrary, displayed many improved reactivities. Extension of the Lewis acid activation study on this class of substrates has led to discovery of several highly stereoselective formal [3+2] dipolar cycloadditions. This section summarizes those new cyclization reactions that we recently developed on lactonized cyclopropanes.[114,115, 116]

4.2.1 Cyclization with sily enol ethers

With the assistance of Lewis acid $TiCl_4$ the lactonized cyclopropane **2.5a** cyclizes with silyl enol ether **4.30** to provide the cycloadduct **4.31** as the only isolatable product in 77% yield (**Scheme 4.12**). It is noteworthy that the cycloaddition reaction did not require cyclopropane pre-activation as previously employed for allylation[86] and glycosidation.[69] Compared with substrates **1.58** and **1.62**, the intramolecular lactone linkage seems to be responsible for the lack of ring expansion as previously observed on the flexible substrates (**Scheme 1.16** and **Scheme 1.17**).



Scheme 4.12: Cycloaddition with silyl enol ether

The stereochemistry of the product **4.31** was determined by single crystal X-ray analysis (**Figure 4.1**). The stereochemistry of this reaction is consistent with a steric control process in which the nucleophilic silyl enol ether approaches the oxocarbenium ion intermediate from the more accessible α-face (**Scheme 4.13**). The subsequent

intramolecular ring closure places the larger substituent (TBS) preferentially in a pseudo-equatorial position.

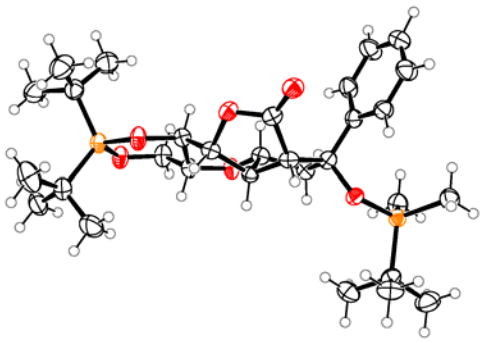
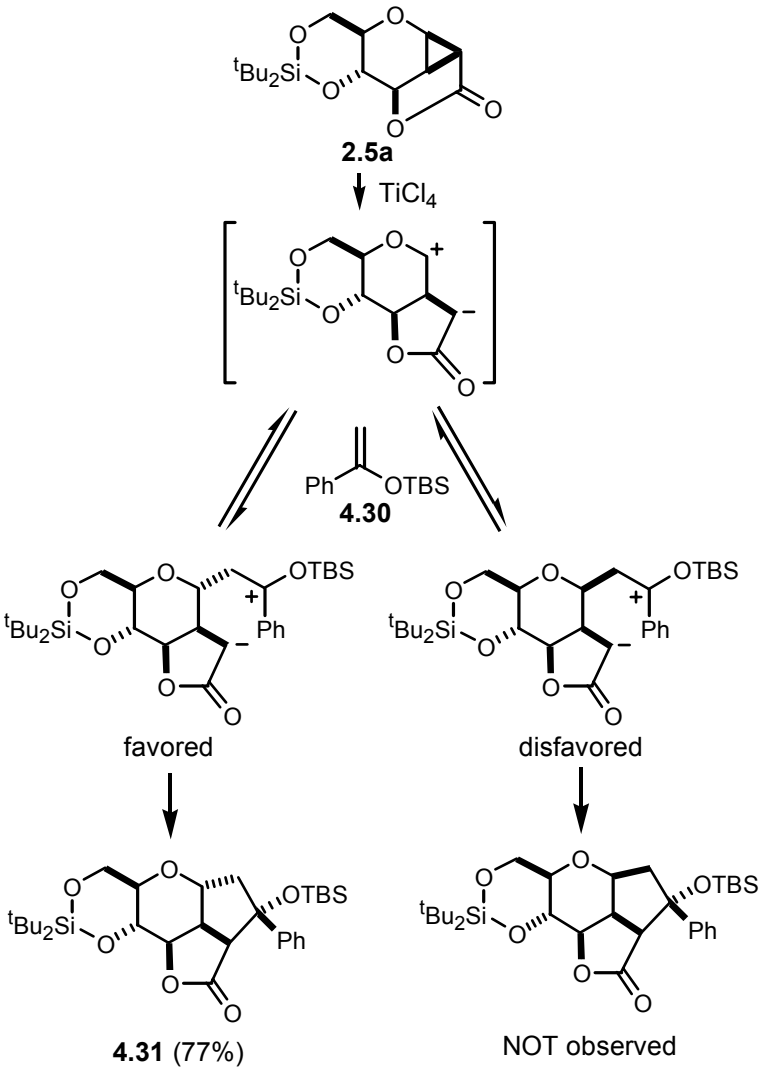


Figure 4.1: X-ray structure of 4.31

This silyl enol ether cyclization displays high dependency on the reaction conditions and the reaction requires promotion by $TiCl_4$. Efforts using Lewis acid promoters other than $TiCl_4$ (e.g., $ZrCl_4$, BF_3•OEt_2, TMSOTf) did not lead to successful transformation. Other reaction conditions such as lower temperatures (e.g., –78 °C), alternative solvents (including toluene, diethyl ether), or substrate pre-activation also led to less efficient reactions. Similar reaction conditions with silyl ketene acetals did not provide the corresponding cyclization products.

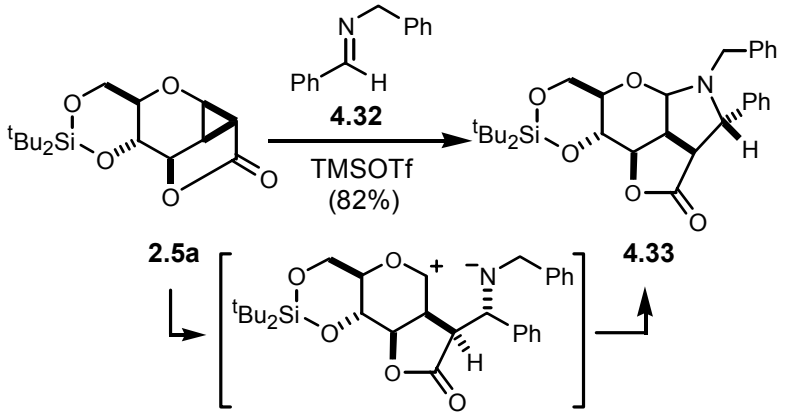


Scheme 4.13: Mechanistic hypothesis for silyl enol ether addition

4.2.2 Cyclization with imines and carbonyl compounds

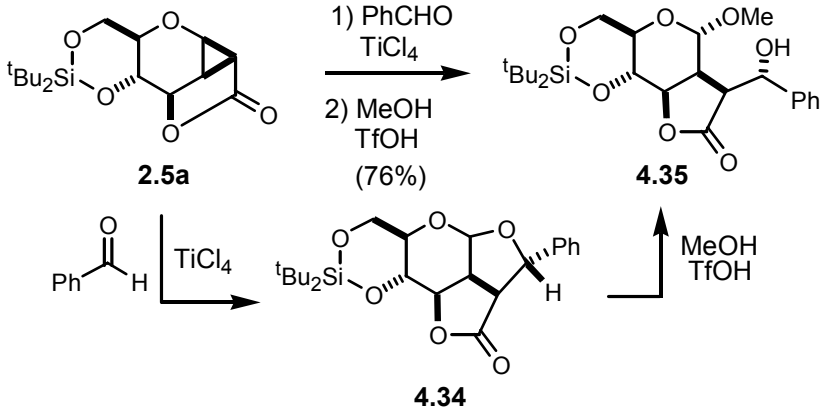
In addition to electron rich π-electron systems, electron deficient dipolarophiles also participate in the cyclizations with lactonized DA cyclopropanes. The TMSOTf mediated cycloaddition of imine **4.32** with **2.5a** furnished the aminal product **4.33** in 82%

yield (**Scheme 4.14**). The reaction displayed excellent stereoselectivity and dependence upon a single Lewis acid (vide supra).



Scheme 4.14: Cycloaddition with imines

Reactions with aldehydes required $TiCl_4$ activation (**Scheme 4.15**). The acetal product **4.34** is highly susceptible to hydrolysis, which complicated isolation. Therefore, the product was characterized as the corresponding methyl acetal **4.35** following acid catalyzed methanolysis.

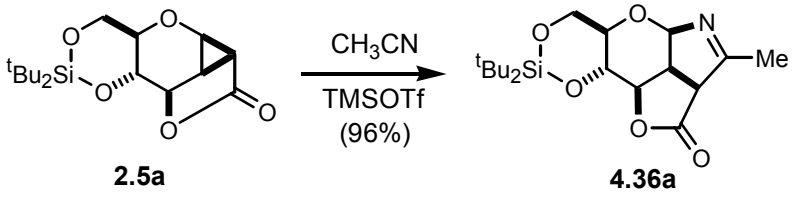


Scheme 4.15: Cycloaddition with aldehydes

4.2.3 Cyclization with nitriles

Acetonitrile is a common solvent for reactions involving charged intermediates, and often becomes incorporated into reaction products, as in the classic Ritter reaction.[117] It is generally a useful and unreactive solvent for ring opening reactions of DA cyclopropanes, even when highly electrophilic oxocarbenium ion intermediates are involved (e.g., **Scheme 1.16**, **Scheme 3.4**). In marked contrast, treating the lactonized DA cyclopropanes **2.5a** under similar reaction conditions using TMSOTf as Lewis acid resulted in clean formation of 2*H*-3,4-dihydropyrrole product **4.36a** in moderate to quantitative yields (**Scheme 4.16**). The same level of efficiency was also observed even in the presence of excess external nucleophilic allyltrimethylsilane,[114] and possible side reactions such as pyran ring expansion were not observed.

The efficient stereoselective assembly of densely functionalized amine-containing heterocycles is an active area of investigation due to the wide occurrence of these species in natural products and synthetic materials. Additionally, the 2*H*-3,4-dihydropyrrole products from the cycloaddition contain an aminal, a functional group that has classically served as a latent iminium ion.[118,119]



Scheme 4.16: Acetonitrile-DA cyclopropane 2.5a cycloaddition

The stereochemistry of the reaction was unambiguously determined by X-ray crystallographic analysis of crystals of benzonitrile cyclization product **4.36b** (**Figure 4.2**).

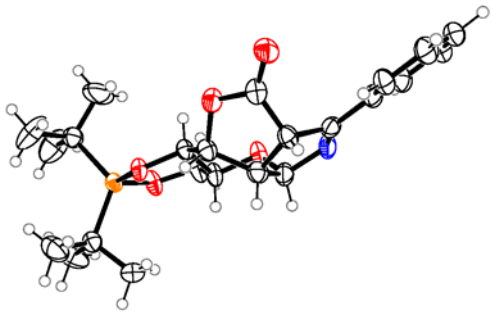
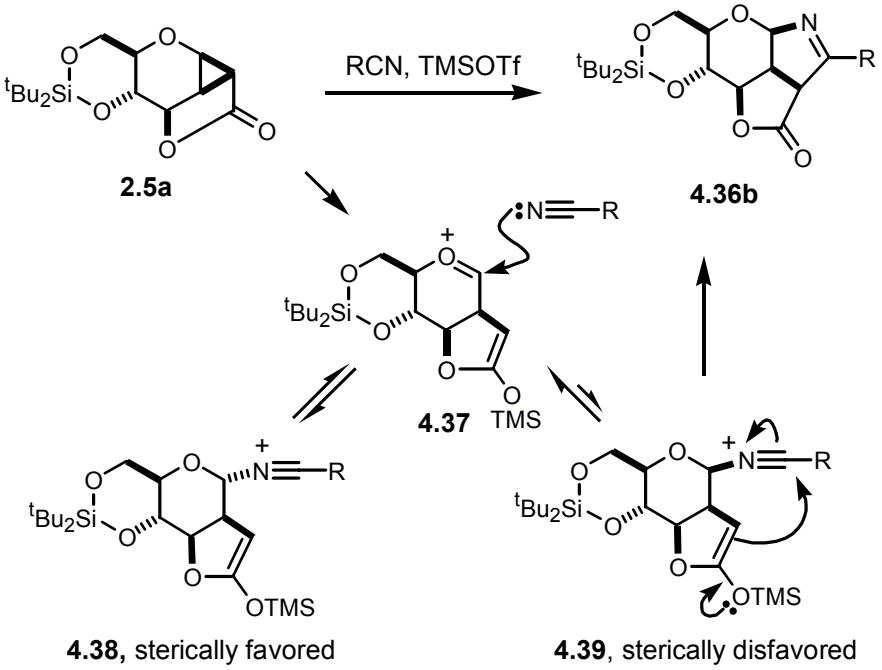


Figure 4.2: X-ray structure of 4.36b

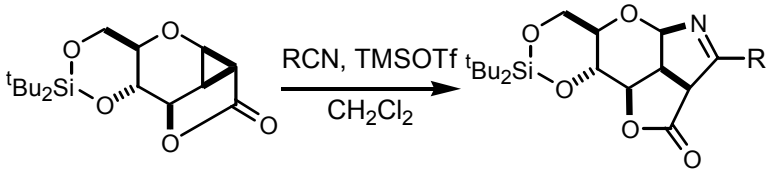
Curiously, the *cis*-like stereochemistry of this cyclization is *opposite of that observed in the cycloaddition with silyl enol ethers* (**Scheme 4.12**, **Figure 4.1**). A mechanistic hypothesis consistent with a Ritter-like transformation starts with nucleophilic nitrile addition onto an intermediate oxonium ion **4.37** (**Scheme 4.17**). Although steric approach control would favor attack at the α-face, but presumably the electrophilic linear nitrilium ion of **4.38** is too distant for enolate attack. In contrast, the sterically less favorable cis-like intermediate **4.39** can be trapped by the enolate giving the observed product.



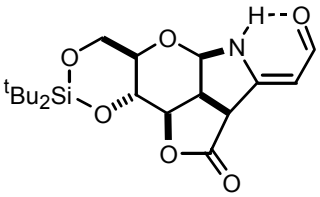
Scheme 4.17: Mechanistic hypothesis for *cis* cycloaddition

This formal dipolar cycloaddition demonstrated excellent reagent compatibility as aliphatic, aromatic and α,*β*-unsaturated nitriles participated (**Table 4.1**). Aliphatic nitriles ranging from MeCN to the much larger ^{t}BuCN all gave the expected imine adducts in high efficiency. The nitrile could be used as solvent (entry 1), and where this was impractical, the use of $MeNO_2$ or CH_2Cl_2 with 5 to 10 equivalents of nitrile also gave excellent yields (entry 2-9). The reaction with *α,β*-unsaturated nitriles in $MeNO_2$ occurs exclusively on the nitrile functional group and no side reaction with C=C has been observed (entries 7-9).[7a] The nitrile components help to introduce diverse functionality such as halides, olefins onto the cyclization products and thus leaves a large window for future structural transformations. Reaction with β-methoxy acrylonitrile proved useful for

introducing an aldehyde functional group (entry 9), and the vinylogous amide **4.36h** was isolated in 78% yield. Among the nitriles screened for this reaction, electron rich nitriles generally provide high efficiency, electron deficient nitriles, however, failed to participate. The retarded reactivity of the latter is probably due to their poor nucleophilicity of those nitriles.



2.5a **4.36a-h**

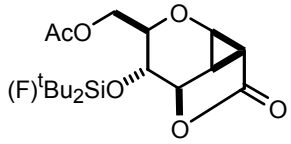
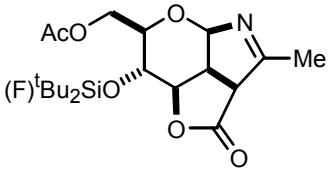
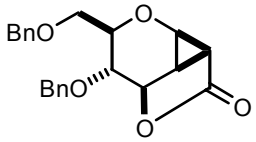
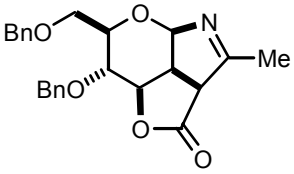
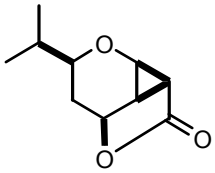
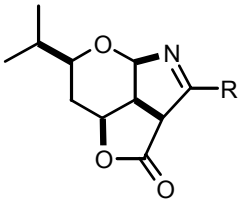
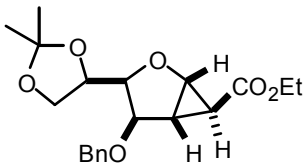
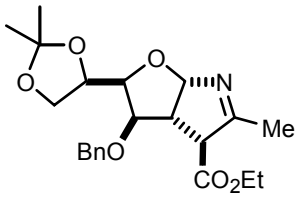
Entry	Nitrile	Solvent	Product	Yield
1	MeCN	MeCN	**4.36a**, R = Me	96%
2	MeCN	CH_2Cl_2	**4.36a**, R = Me	84%
3	PhCN	CH_2Cl_2	**4.36b**, R = Ph	81%
4	PrCN	CH_2Cl_2	**4.36c**, R = Pr	95%
5	^{t}BuCN	CH_2Cl_2	**4.36d**, R = ^{t}Bu	79%
6	$Cl(CH_2)_3CN$	CH_2Cl_2	**4.36e**, R = $(CH_2)_3Cl$	87%
7		$MeNO_2$	**4.36f**, R = CHCHPh	60%
8[a]		$MeNO_2$	**4.36g**, R = CHCHAr	75%
9		CH_2Cl_2	**4.36h**, 	78%

[a] Ar = *m*,*p*-$(MeO)_2C_6H_3$-.

Table 4.1: DA cyclopropane-nitrile [3+2] cycloaddition

In addition to the diversity of suitable nitrile components, the cycloaddition tolerates reasonable diversity on cyclopropane substituents (**Scheme 4.2**). The di-*tert*-butylsilylene protective group is not a necessary structural feature for successful [3 + 2] cycloaddition, and cyclopropanes with distal acetate and benzyl ether protective groups

were equally effective substrates (entries 1 and 2). Moreover, cyclopropane **2.9,** prepared from readily available γ-hydroxy dihydropyran also participates in the cycloaddition reaction (entries 3 and 4). This and related processes offer a new approach to the functionalization and utilization of the growing number of enantiomerically pure dihyropyrans available from hetero-Diels-Alder cycloadditions.[61]

Entry	Substrate	Nitrile	Product		Yield
1[a]	 **4.40**	MeCN		**4.41**	92%
2[b]	 **4.42**	MeCN		**4,.43**	90%
3[b]	 **2.9**	MeCN		**4.44a**	96%
4[a]		PhCN		**4.44b**	92%
5[b]	 **4.45**	MeCN		**4.46**	43%

[a] CH_2Cl_2 solvent; [b] MeCN solvent;

Table 4.2: Generality on DA cyclopropanes

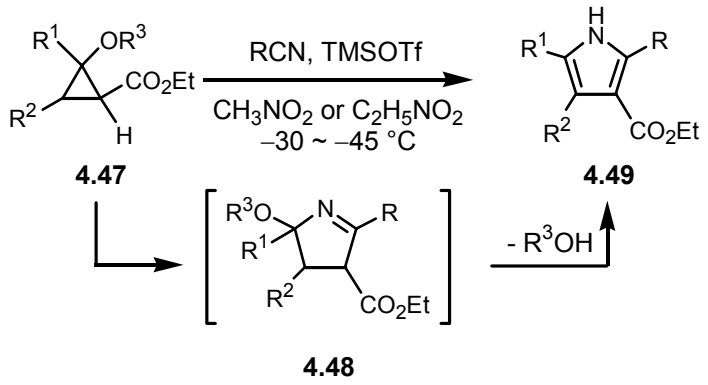
As illustrated on **Table 4.2**, the internal lactone linkage appears to have been an important advance necessary for accessing the 3,4-dihydro-2*H*-pyrrole cycloaddition products. Attempted [3 + 2] cycloaddition reactions between nitriles and various cyclopropane substrates (**Table 4.6**) prepared through intermolecular processes gave multiple products. The ^{1}H NMR spectra of the crude reaction mixtures suggested imine formation, but decomposition occurred before purification was possible. Cyclopropanated furanose substrate **4.45**[120] in entry 5 however offered the imine addition product **4.46** in 43% yield, but it has been the best results from intermolecular variants.

4.3 A NEW POWERFUL PYRROLE SYNTHETIC METHODOLOGY

Pyrroles are important heterocycles that occur in porphyrins,[121] pigments,[122] and natural alkaloids.[123] They have found wide applications in materials science[124] and are common components in molecular recognition and self-assembly ensembles.[125] There are dozens of reported pyrrole syntheses, some of the most reliable of which date from the 19th century, such as the Hantzsch[126] and Paal-Knorr[127] procedures. These classic condensation reactions between activated methylenes and amino ketones can be limited by their efficiency, functional group compatibility, regiospecificity, or the variety of substituents that can be introduced around the pyrrole. More recent pyrrole syntheses typically showcase special methodology or excel at accessing one substitution motif, but an universal strategy for efficiently preparing all combinations of substituted pyrroles from easily handled materials is lacking.

The novelty and the synthetic potential of nitrile-DA cyclopropane cycloaddition prompted further study of the generality of this class of reactions. However, when extended to general non-carbohydrate-derived DA cyclopropane substrates **4.47**, the

reaction did not stop at the stage of the corresponding aminal cycloadduct **4.48** (**Scheme 4.18**). Instead, the intermediate *N*,*O*-acetals were further driven to the aromatic pyrrole products **4.49** after an alcohol elimination and tautomerization. Based on this discovery, a powerful new synthetic method for pyrrole synthesis was developed.[115,116,128]



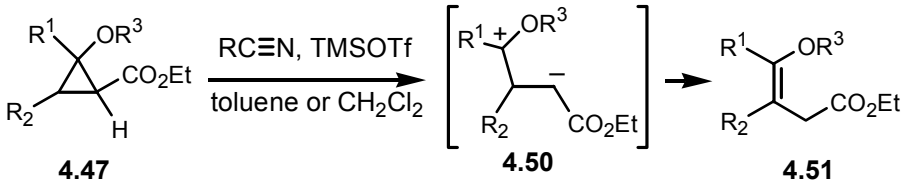
Scheme 4.18: Pyrrole formation through nitrile cycloaddition

Initial studies of nitrile cyclizations with general DA cyclopropanes **4.47** in nonpoloar solvent as benzene, toluene or CH_2Cl_2 (**Table 4.3**) failed to incorporate the nitrile components. Instead, the intermediate 1,3-dipoles display reduced affinity toward the nitrile components and readily rearrange into enol ether **4.51** upon TMSOTf treatment (**Scheme 4.19**). While TMSOTf emerged as ideal Lewis acid for the cyclopropane activation, attempts with other Lewis acids have not met success. For further studies on the pyrrole synthesis the unsubstituted DA cyclopropane **4.52a (Table 4.4)** was chosen as a model substrate. Reaction at room temperature with acetonitrile as solvent led to detectable cyclization, but enol ether formation kept plaguing the reaction and the target pyrrole was obtained in less than 9% isolated yield (entry 1). Employing reactant acetonitrile as solvent at –40 °C provided pyrrole **4.53a** in 80% isolated yield (**Table 4.4**,

entry 2). Inclusion of other polar external solvents generally gave lower yields, but practical considerations required the use of solvent when most other nitriles were employed. In this regard, polar solvents such as nitromethane and nitroethane (CH_3NO_2/$C_2H_5NO_2$, **Table 4.3**) that are capable of stabilizing the intermediate oxocarbenium ion tunneled the reaction back in to the cycloaddition manifold. After these condition modifications, the reaction was effectively directed into pyrrole products in good to excellent isolation yields (entry 3-8). In some difficult examples, reactions were conducted at a lower temperature of −50 °C. The standard conditions were to add 1 to 1.5 equivalents of TMSOTf to a cold (−50 to −25 °C) solution of cyclopropane and 5 to 10 equivalents of nitrile in either nitromethane or nitroethane solvent.

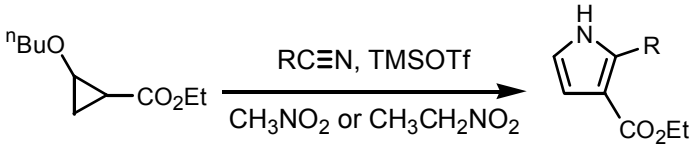
Entry	Solvent	Dielectric Constant (25 °C)
1	Benzene	2.28
2	Toluene	2.36
3	CH_2Cl_2	9.08
4	CH_3NO_2	28.06
5	$C_2H_5NO_2$	35.87
6	CH_3CN	36.6

Table 4.3: Dielectric constants for different solvents

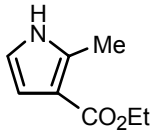
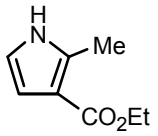
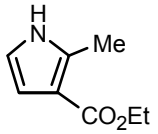
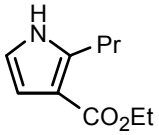
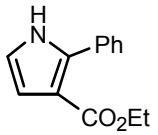
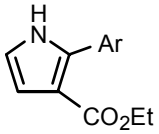
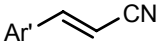
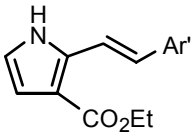
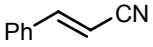
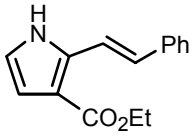


4.47 **4.50** **4.51**

Scheme 4.19: Enol ether formation from DA cyclopropanes



4.52a **4.53a-f**

Entry	Nitrile	Solvent	Temperature	Product		Yield
1	MeCN	MeCN	25°C		**4.53a**	<9%
2	MeCN	MeCN	–40 °C		**4.53a**	80%
3	MeCN	CH_3NO_2	–30 °C		**4.53a**	73%
4	*n*-PrCN	$C_2H_5NO_2$	–40 °C		**4.53b**	77%
5	PhCN	$C_2H_5NO_2$	–50 °C		**4.53c**	35%
6[a]	ArCN	$C_2H_5NO_2$	–40 °C		**4.53d**	55%
7[b]		$C_2H_5NO_2$	–40 °C		**4.53e**	85%
8		$C_2H_5NO_2$	–50°C		**4.53f**	39%

[a] Ar = *p*-$MeOC_6H_4$-; [b] Ar' = *m*,*p*-$(MeO)_2C_6H_3$-.

Table 4.4: Pyrroles from nitrile cycloaddition of 4.52a

As clearly illustrated on **Table 4.4**, the nitrile components efficient for this pyrrole technology are consistent with those previously discovered in the formal [3+2] cyclization reaction on carbohydrate-derived DA cyclopropanes (**Section 4.2.3**). By using the right nitrile substitution, this synthetic approach allows for introduction of diverse C(2) pyrrole substituents (**Table 4.4**). Butyronitrile gives a yield similar to that obtained with acetonitrile (entry 4), and the aromatic nitriles provides reasonable reaction yields (entries 5, 6). When pressed with α,β-unsaturated nitriles, no product from reaction across the double bond of conjugated nitrile was detected (entry 7, 8).

Because of the regiospecific nature of the cycloaddition reaction, product isolation for this preparative method has been very convenient, simply requiring a quick short column flash chromatography, as compared to the tedious separation processes typically involved in literature condensation methods.

In addition to improved reaction efficiencies and simplified isolation, the regiospecificity of the pyrrole synthesis methodology permits an assortment of substitution patterns as summarized in **Table 4.5**. Synthesis of the required DA cyclopropanes by the established methods allows installation of alkyl groups selectively around the pyrrole product at either, both or neither the C(4) and C(5) positions without formation of constitutional diastereomers. Various nitriles are shown to react with pyran and furan derived cyclopropanes (entries 1–9), affording pyrroles with a hydroxy terminated C(4) side chain. Introduction of an alkyl group at C(5) resulted in lower yields for entries 8 and 9, but fortunately reaction efficiency was restored when unnecessary ring strain in the starting materials was avoided (entries 10-14). In entries 15 and 16, mono C(5) methyl pyrroles were obtained in 55-62% isolated yield. Placing the alkoxy leaving group at the bridgehead of the [4.1.0] bicyclic system permitted the synthesis of

4,5,6,7-tetrahydroindoles (entries 17 and 18), which are useful synthetic intermediates in natural product and pharmaceutical chemistry and can be readily oxidized to the indoles.[129, 130]

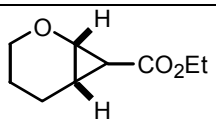
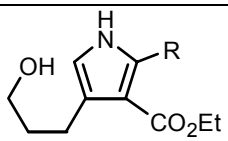
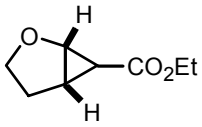
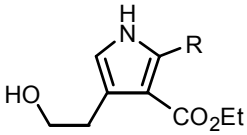
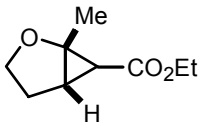
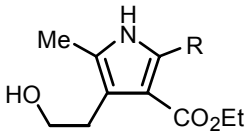
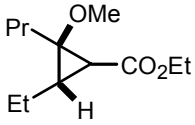
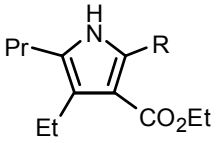
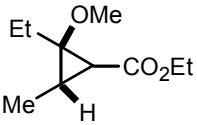
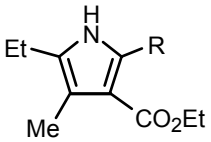
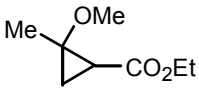
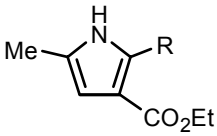
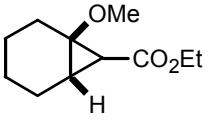
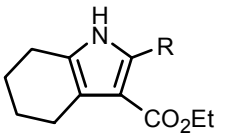
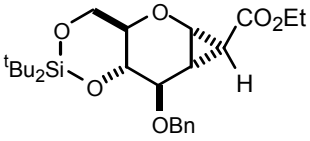
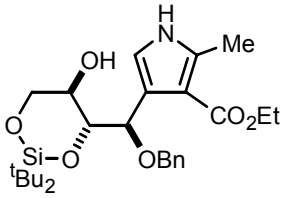
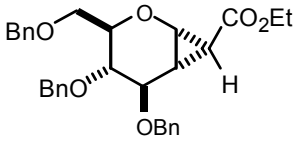
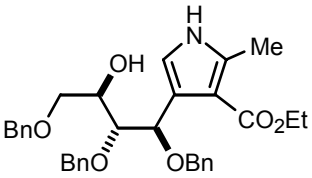
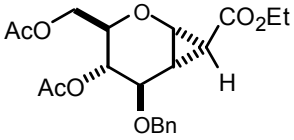
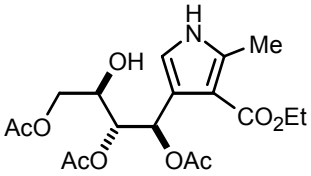
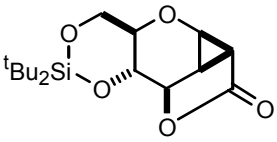
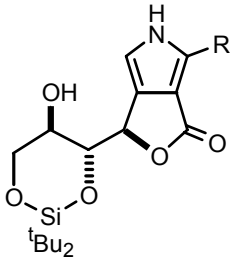
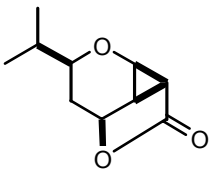
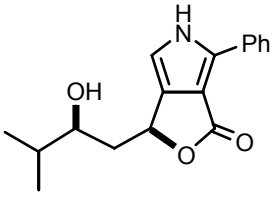
Entry	Substrate	Nitrile	Product		Yield
1		MeCN		**4.54a**	72%
2		PrCN		**4.54b**	78%
3		PhCN		**4.54c**	58%
4	**4.52b**	$Cl(CH_2)_3CN$		**4.54d**	61%
5		MeCN		**4.54e**	52%
6		PrCN		**4.54f**	58%
7	**4.52c**	$MeOC_2H_2CN$		**4.54g**	81%
8		MeCN		**4.54h**	31%
9		PrCN		**4.54i**	25%
	4.52d				
10		MeCN		**4.54j**	93%
11		PrCN		**4.54k**	82%
12		PhCN		**4.54l**	76%
	4.52e				
13		MeCN		**4.54m**	98%
14		PrCN		**4.54n**	85%
	4.52f				
15		MeCN		**4.54o**	62%
16		PrCN		**4.54p**	55%
	4.52g				
17		MeCN		**4.54q**	72%
18		PrCN		**4.54r**	75%
	4.52h				

Table 4.5: Nitrile-DA cyclopropane cycloaddition

The effectiveness of this methodology appeared unaffected by the stereochemistry of the starting cyclopropanes. As for all the examples examined in **Table 4.5**, consistent yields were obtained from cyclopropane substrates with different diastereomeric ratios. Based on the above inherent merits, this methodology is of high potential as a new synthetic approach, especially to prepare pyrroles with substitution patterns less accessible by condensation methods.

The nitrile cyclization attempted with more densely functionalized substrates prepared through intermolecular carbohydrate cyclopropanation provided multiple dihydropyrrole products. Subsequent aqueous acid treatment (e.g., 5% HCl) led to complete conversion to the pyrroles (**Table 4.6**). The substrate and functional group compatibility will be an important asset for preparing pyrroles of increased complexity. In this regard, the examples illustrated in **Table 4.6** testify to the compatibility of the reaction with various functionalities including di-*tert*-butylsilylenes (entry 1, 4-6), benzyl ethers (entry 2) and acetates (entry 3). This reaction is also applicable to non-carbohydrate derived substrates as demonstrated in entry 7.

Entry	Substrate	Nitrile	Product		Yield
1		MeCN		**4.55a**	87%
2		MeCN		**4.55b**	77%
3		MeCN		**4.55c**	58%
4[a]		^{t}BuCN		**4.55d**	87%
5[a]		PhCN		**4.55e**	85%
6[a]		ArCN[b]		**4.55f**	93%
7		PhCN		**4.55g**	82%

[a] Acidic workup (1 M HCl); [b] ArCN = *p*-$MeOC_6H_4CN$.

Table 4.6: Pyrrole from lactonized cyclopropanes

In summary, the domino DA cyclopropane nitrile [3+2] cycloaddition, elimination, and tautomerization strategy is a powerful and efficient new method for pyrrole synthesis that allows precise control over the installation of substituents at three positions around the pyrrole. The method is characterized by operational simplicity,

substrate generality, and mild reaction conditions. The material costs associated with this procedure are generally less than other modern strategies, and the ease of product purification simplifies large-scale reactions. Given the compatibility of this method with various nitrile classes and the great number of nitriles that are commercially available, it is likely that this work will find useful application in diversity-oriented synthesis.

4.4 BIPYRROLE AND THIENYLPYRROLE SYNTHESIS

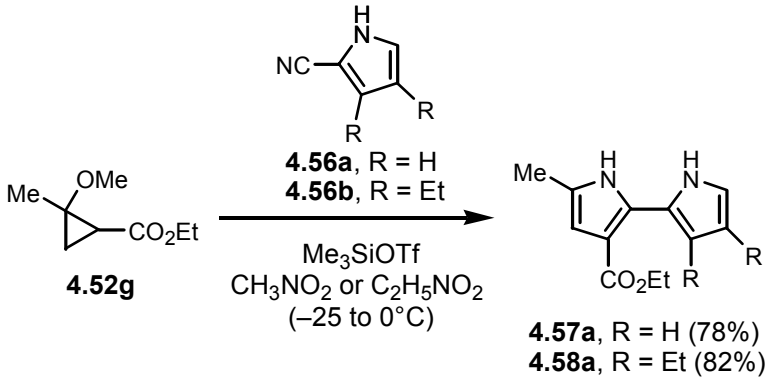
Bipyrroles and thienylpyrrole have been synthetic building blocks for preparing medicinally interesting compounds including anti-tumor agents (e.g., prodigiosins,[131] sapphyrins[132]) and radiation sensitizers for photodynamic therapy.[132] They have also found wide application in preparation of dyes[133] and semi-conducting polymers.[134] Additionally, compounds prepared from bipyrroles have been used as anion binding agents as well as nuclear waste removal agents. [135,136]

Classic bipyrrole syntheses mostly employ oxidative,[137] Ullman-type homocouplings[138] or couplings of pyrrolinones with pyrroles.[139] While these methods are widely employed, they are generally limited to symmetric bipyrrole product preparation. When pressed to create asymmetric products, the pyrrolinone pathway[139] seems to be the favorable option, but still remains limited in substituent diversity. Recent years also brought new advances in Suzuki[140] and Stille[141] couplings, primarily focused on prodigiosin synthesis, for preparing asymmetric bipyrroles; however, a more practical and reliable synthetic method still remains desirable.

The high efficiency of the pyrrole synthesis (**Section 4.3**) has inspired further extension of this technique to the synthesis of asymmetric bipyrroles and thienylpyrroles.[116] During the course of these efforts, an efficient synthetic approach has been developed that employs the previously discussed pyrrole synthetic strategy utilizing

a cyano group extending from a preexisting heterocycle.[142] The required nitriles, 2-cyanopyrroles **4.56a,b** and 2-cyanothiophene **4.59,** each possesses an electron rich aromatic ring and thus are very reactive substrates for the dipolar cyclization with DA cyclopropanes.

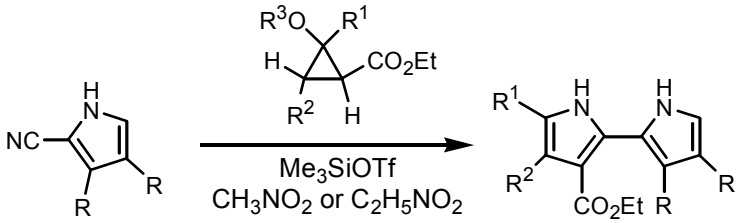
The initial study was directed toward the synthesis of α,α'-bipyrroles from 2-cyanopyrroles that are commercially available (**4.56a**, 1*H*-pyrrole-2-carbonitrile, **Scheme 4.20**) or accessible through a literature procedure (3,4-diethyl-1*H*-pyrrole-2-carbonitrile, **4.56b**).[143] When a cold (–25 to 0 °C) CH_3NO_2 or $C_2H_5NO_2$ solution of DA cyclopropane **4.52g** and pyrrole-2-carbonitrile **4.56a** was treated with a stoichiometric amount of TMSOTf, a cascade cycloaddition, elimination, and tautomerization reaction ensued and provided the targeted bipyrrole product **4.57a** in isolated yield of 78%. The 2-carbonitrile with preexisting electron donating alkyl group (**4.56b)** led to slightly improved reaction yields (82%).



Scheme 4.20: Model reaction for bipyrrole synthesis

Inspired by these results, the generality of the bipyrrole synthesis was further examined on different cyclopropanes as summarized in **Table 4.7**. With various

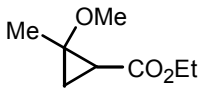
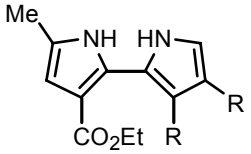
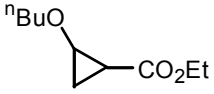
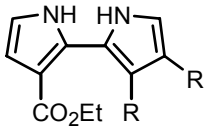
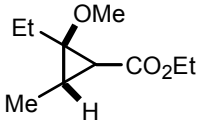
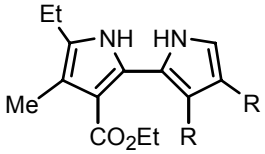
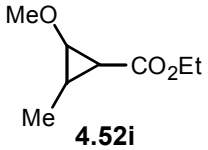
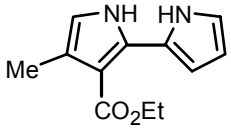
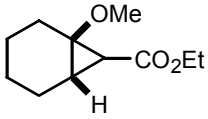
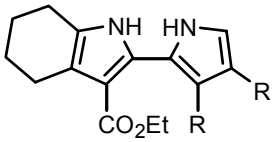
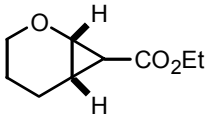
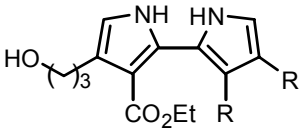
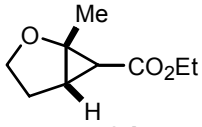
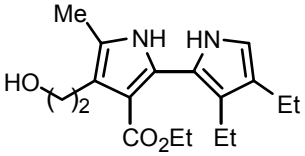
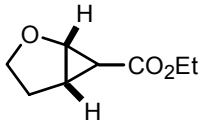
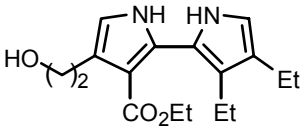
substitution patterns on the starting DA cyclopropanes, this methodology demonstrated complete regiochemical control. The first examples studied gave bipyrroles in excellent yield (78% and 82%) with an alkyl group at the alpha position (entries 1 and 2). The reactions in entries 3 and 4 show that the alpha substitution is unnecessary, but the reaction yields were considerably diminished (41% and 45% respectively). Entries 5 and 6 provided bipyrroles with alkyl substitution at both the alpha and beta positions (82% and 85% respectively), and entry 7 completes the series by a bipyrrole with only beta substitution. The remaining entries explore reactivity with [4.1.0] and [3.1.0] cyclic DA cyclopropanes, including pyran and furan derivatives. These substrates afforded bipyrroles with different substitution patterns, and in entries 10–13, a hydroxy group terminates the alkyl chain at the β position, thereby providing useful synthetic handle.



4.56a, R = H
4.56b, R = Et

4.57a-f, R = H
4.58a-g, R = Et

Scheme 4.21: Bipyrrole synthesis-generality on DA cyclopropanes

Entry	Substrate	Product		Yield
1 2	 **4.52g**		**4.57a** **4.58a**	78%[a] 82%[b]
3 4	 **4.52a**		**4.57b** **4.58b**	41%[a] 45%[b]
5 6	 **4.52f**		**4.57c** **4.58c**	82%[a] 85%[b]
7	 **4.52i**		**4.57d**	48%
8 9	 **4.52h**		**4.57e** **4.58d**	62%[a] 82%[b]
10 11	 **4.52b**		**4.57f** **4.58e**	46%[a] 54%[b]
12	 **4.52d**		**4.58f**	84%
13	 **4.52c**		**4.58g**	42%

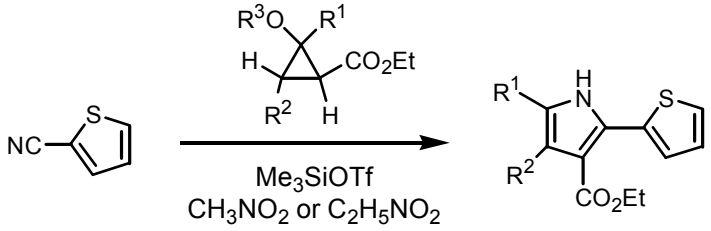
[a] R = H; [b] R = Et.

Table 4.7: Bipyrrole synthesis from pyrrole-2-carbonitrile

Higher yields were generally obtained from reactions with DA cyclopropanes with alkoxy group attachment to a quaternary carbon (e.g., entries 1, 2, 5, 6, 8, 9 and 12). The gradual reactivity parallels the stability of the intermediate oxocarbenium ion generated from Lewis acid mediated cyclopropane ring opening, as observed in the previously discussed pyrrole synthesis (**Section 4.4**). A cursory inspection of the results summarized in **Table 4.7** reveals that the yields for formation of bipyrroles starting from 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** were consistently higher than those obtained from the unsubstituted pyrrole **4.56a**. This observation is consistent with the greater nucleophilicity expected to be endowed to the nitrile by the electron-donating ethyl groups at the pyrrole β-positions.

Remarkably, the current bipyrrole preparation does not require prior protection of the starting pyrroles. The compatibility observed on the starting pyrrole under the strong Lewis acid conditions are likely attributed to the α-cyano group that significantly withdraws electron density from the pyrrole.

With a bipyrrole synthesis established, identical reaction conditions were applied to the synthesis of thienylpyrroles by the combination of thiophene-2-carbonitrile **4.59** and various DA cyclopropanes (**Table 4.8**). While the thienylpyrrole products are generally obtained in reduced yields, this method still remains attractive for its brevity in accessing the asymmetric products.



4.59 **4.60a-f**

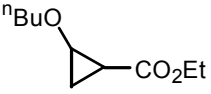
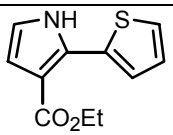
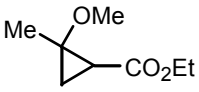
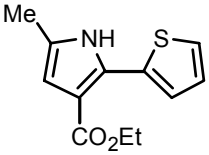
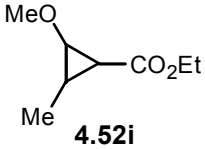
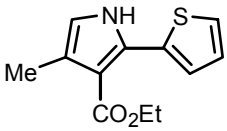
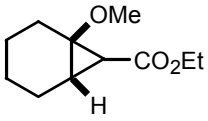
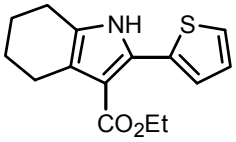
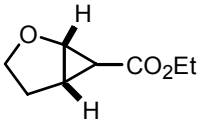
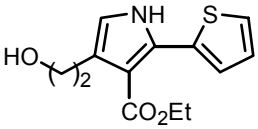
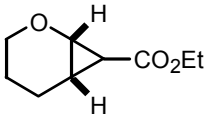
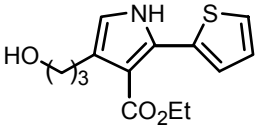
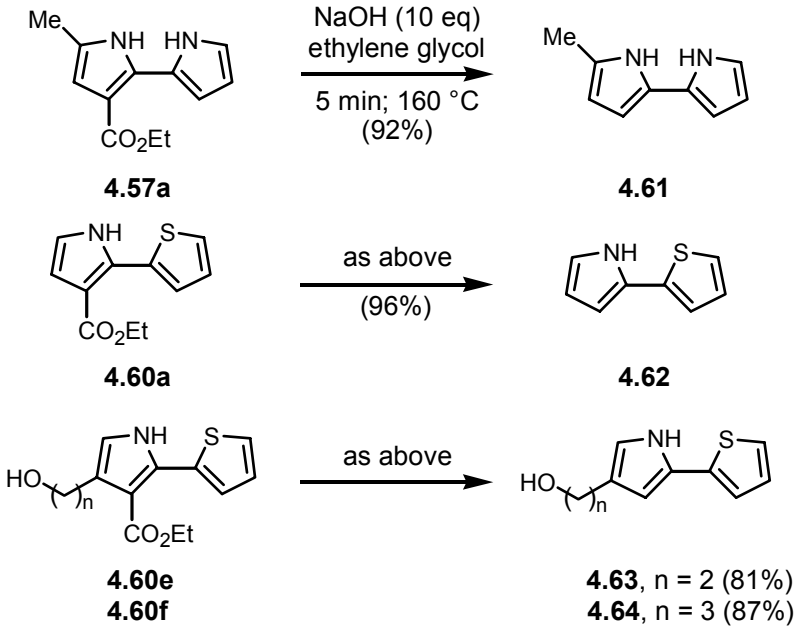
Entry	Substrate	Product		Yield
1	 **4.52a**		**4.60a**	47%
2	 **4.52g**		**4.60b**	69%
3	 **4.52i**		**4.60c**	63%
4	 **4.52h**		**4.60d**	37%
5	 **4.52d**		**4.60e**	41%
6	 **4.52b**		**4.60f**	73%

Table 4.8: Thienyl pyrrole synthesis from 4.59

For some prospective applications, electron rich variant of these bipyrroles and thienylpyrroles will be required. In this regard, the β-ethyl carboxylate can be removed by a convenient decarboxylation in hot alkaline ethylene glycol solution (**Scheme 4.22**). High reaction temperatures and short reaction times (e.g., 160 °C, 2 to 5 minutes) provided the highest yields.



Scheme 4.22: Decarboxylation

Extension of the pyrrole construction method to electron deficient heterocyclic nitriles other than **4.56a,b** and **4.59** did not result in formation of the corresponding bicyclic products. For example, 2-cyanofuran completely decomposed upon treatment with TMSOTf before any evident cyclization.

4.5 CYCLIZATIONS WITH PYRIDINES AND QUINOLINES

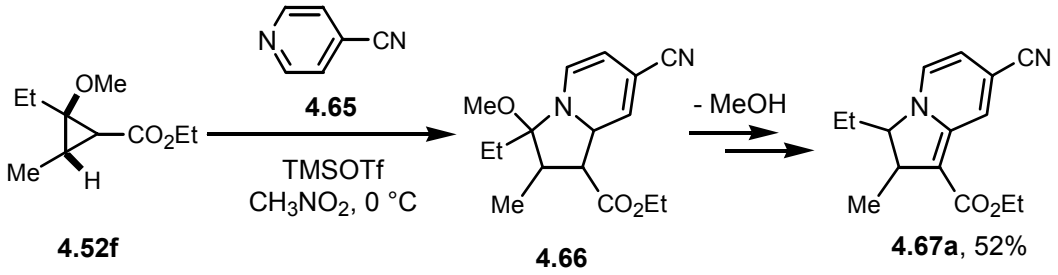
4.5.1 Introduction

Due to the unique chemical behavior of lactonized DA cyclopropanes they are well suited for highly stereoselective [3+2] dipolar cycloaddition with nitriles (**Section 4.2.3**, **4.3** and **4.4**).[114] Extension of this reaction to general DA cyclopropane substrates has led to a synthetic pyrrole methodology with complete regiochemical control of the products.[115,116] The high efficiency observed on the DA cyclopropane-nitrile cyclizations stimulated further exploration of diverse functionalized dipolarophiles for practical synthetic applications. This section summarizes the recently discovered cyclization reactions on heterocyclic dipolarophiles including pyridines and quinolines.

Pyridines and quinolines are ubiquitous in natural compounds. They are also extensively employed in organic reactions. Pyridines have been one of the most widely used chemical reagents, as catalysts and organic bases as well as solvents in both laboratory research and industrial production. Natural and artificial products containing pyridine and quinoline motifs have found wide applications in medicinal chemistry and material science (e.g., dyes, semi-conducting polymers).

The effectiveness of formal [3+2] cycloadditions of DA cyclopropane proved highly dependent on the dipolarophile nucleophilicity. Among the nitrile dipolarophiles screened, the electron rich compounds provided higher affinity toward the 1,3-zwitterionic intermediate (**Table 4.4**, entries 5 vs. 6 and entries 7 vs. 8). However, in the interest of investigating the scope of DA cyclopropane cyclizations, electron poor nitrile **4.65** was also tested. Using conditions similar to the pyrrole methodology, nitrile **4.65** did not afford any detectable pyrrole product. In stark contrast, a curious cyclization was

observed occurring at N(1)=C(2) of the pyridine ring (**Scheme 4.23**). The cycloaddition was also followed subsequently with a elimination and tautomerization to provide dihydro-indolizine product **4.67a** in 52% yield.



Scheme 4.23: Cycloaddition with 4-cyano pyridine 4.65

Artificial and naturally occurring heterocycles indolizines **4.68**, benzoindolizines **4.69** (**Figure 4.3**), and derivatives are some of the most intriguing pyrrole derivatives that demonstrate high pharmacological properties in treating inflammation,[144] cardiovascular disease,[145] as well as the physical problems associated with amplified Ca^{2+} channel.[146] Moreover, due to the high degree of conjugation throughout the systems, these compounds possess unique optical properties that can be translated into ideal materials for spectral sensitizers[147] and dyes.[148]

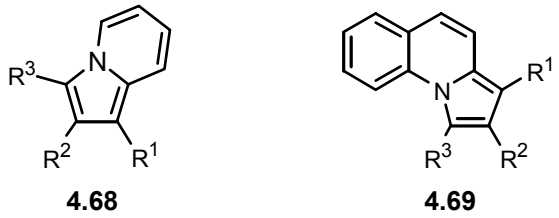


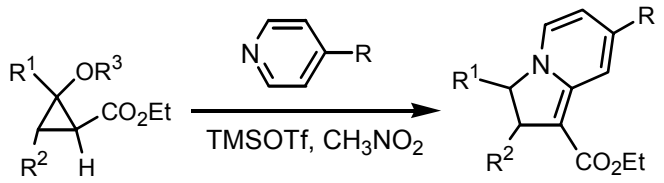
Figure 4.3: Indolizines and benzoindolizines

A wide variety of synthetic methods have been reported for the synthesis of indolizine and benzoindolizine products.[149] Among these methods the 1,3-dipolar cycloaddition of pyridinium *N*-methylidine with π-electron systems such as acetylenedicarboxylate under hydrogenation conditions, or oxidative cyclization with ethylenes, have been well known.[149,150] But, the requirement for prior formation of the pyridinium salt limits this method to electron rich pyridines. Further, due to poor regioselectivity, the reaction is typically applicable only when R^1 and R^2 are equivalent. Cyclization employing pyridines as dipolarophile components has also been an efficient approach,[151] and formal [3+2] dipolar cycloaddition of pyridines and quinolines have been recently reported on certain 1,3-dipoles such as nitrile ylides and nitrile imines.[152,153] But the poor regio-differentiation regarding R^1 and R^2 placement has also prevented these methods from accessing diverse substitution for the products.

4.5.2 Cyclization with pyridines and quinolines

In principle, one of the strengths of the subject DA cyclopropane-pyridine cyclization approach was its complete regiochemical control, which allowed for a wide variety of substituent patterns around the resultant indolizine derivatives. Having the first successful example in hand, attention was turned to the generality of this preparative method. For this, 4-cyano-pyridine **4.65** was screened as a model dipolarophile against a wide variety of DA cyclopropane substrates (**Table 4.9**), but the reaction yields remained poor to moderate even on highly reactive substrates with alkoxyl attachment to a quaternary carbon (entry 1-3). When applied to cyclopropanes without an R^1 substituent (entry 4, 5), the reactions were unsuccessful, and only trace amounts of the desired products were obtained (<1%). Having explored scope in the context of the cyclopropane, an investigation into the effect of pyridine structure was undertaken. In this regard,

several substituted pyridines were tested, showing that reaction efficiency is inversely related to the electron donating ability of the C(4) substituent. In entry 6, the unactivated pyridine provided product **4.67f** in less than 3% isolated yield. When pressed with an electron rich 4-methoxy pyridine, the cyclization was completely depressed (entry 7).



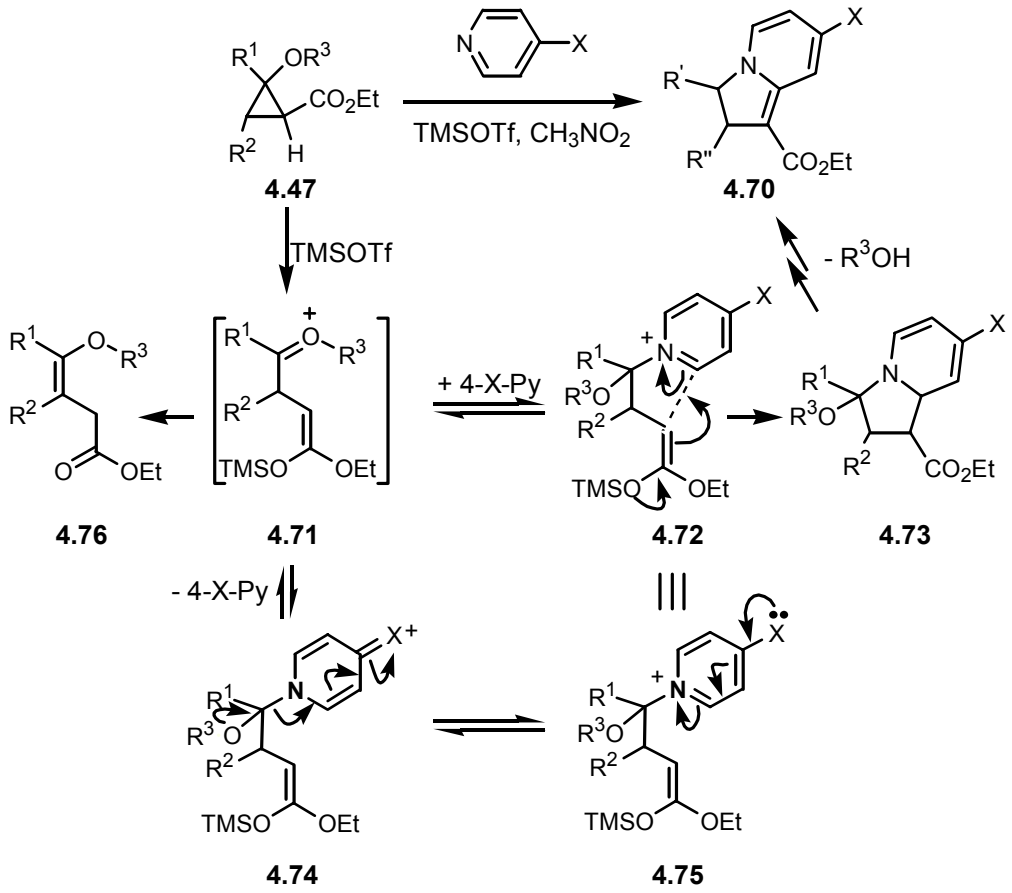
4.67a-f

Entry	R^1	R^2	R^3	R	Product	Yield
1	Et	Me	Me	CN	**4.67a**	52%
2	-$(CH_2)_4$-		Me	CN	**4.67b**	41%
3	Pr	Et	Me	CN	**4.67c**	54%
4	H	Me	Me	CN	**4.67d**	< 1%
5	H	H	^{n}Bu	CN	**4.67e**	< 1%
6	Et	Me	Me	H	**4.67f**	< 3%
7	-$(CH_2)_4$-		Me	OMe	-	-

Table 4.9: DA cyclopropane-pyridine cycloaddition

The observed electronic effect of the current pyridine cycloaddition is opposite to those observed in nitrile cyclizations.[114,115,116] A mechanistic hypothesis that accounts for this inverse relationship is depicted as in **Scheme 4.24**. Upon Lewis acid activation, DA cyclopropanes **4.47** undergo retro-aldol rearrangement forming the corresponding formal 1,3-dipole intermediate **4.71**. The subsequent nucleophilic addition from pyridine nitrogen provides pyridinium ion **4.72** wherein the positive charge sits at a position

conjugated with C(4) substituent. When a C(4) EWG (e.g., X = CN) is present, it enhances the electrophilicity of the pyridinium ring, activating intermediate **4.72** toward

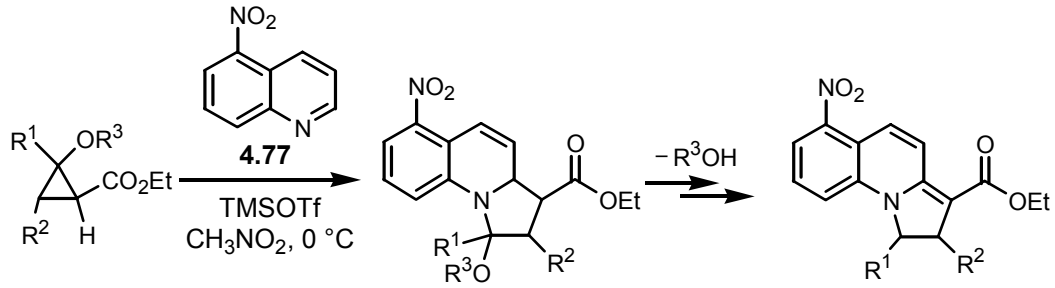


Scheme 4.24: Mechanistic hypothesis for pyridine cycloaddition

intramolecular nucleophilic attack by the TMS enolate. This neutralization tendency remarkably overrides the price of aromaticity and leads to the formation of dihydro-indolizine product **4.70** after R^3OH elimination and tautomerization. Conversely, the electron donating C(4) substituent can sufficiently stabilize the pyridinium ion of intermediate **4.72** through full resonance delocalization, and therefore precludes the ring

closure step. In this case, the resulting formal 1,3-dipole **4.71** will be restricted in the equilibrium circle (**4.71** ↔ **4.72** ↔ **4.75** ↔ **4.74** ↔ **4.71**) before transforming into enol ether by product **4.76**.[154] This mechanistic hypothesis suggests that the RDS is the intramolecular ring closure.

A similar electronic effect was observed on quinoline cyclizations. While unsubstituted quinoline refused to incorporate with LA activated DA cyclopropanes, electron deficient substrates such as 5-nitro quinoline **4.77** readily cyclize with various substrates (**Scheme 4.25**).



Scheme 4.25: Cycloaddition of DA cyclopropane and 5-nitroquinoline 4.77

Compared with 4-cyano-pyridine **4.65**, the reactions with **4.77** seemed to be quite effective even on less reactive cyclopropanes (**Table 4.10**, entry 1-3). But unlike in the pyridine cyclization, the aminal cyclization products **4.78a,b** from this reaction have a reasonable lifetime and partially survived isolation (entry 1 and 2). Subsequent treatment of the crude mixture with aqueous acid (5% aqueous HCl) facilitated complete conversion into dihydro-benzoindolizine **4.79**, which displayed high inclination for auto oxidative aromatization to **4.80** (

Scheme 4.26).

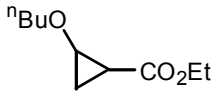
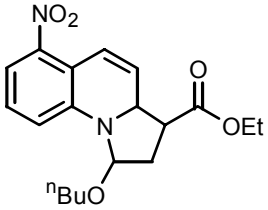
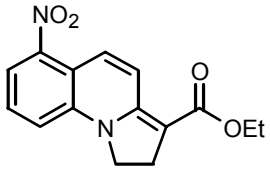
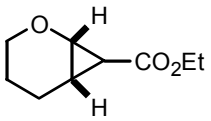
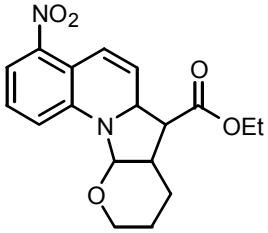
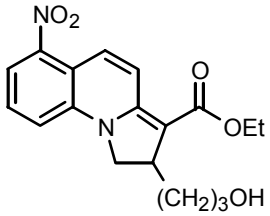
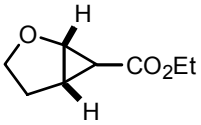
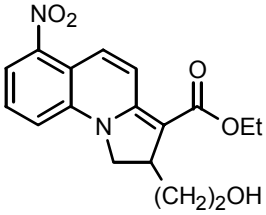
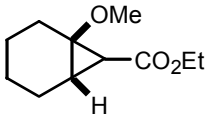
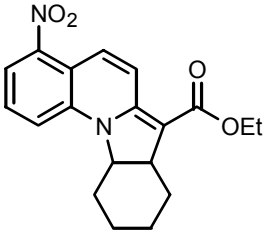
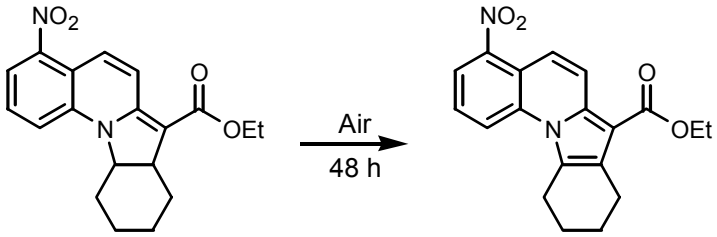
Entry	Cyclopropane	Product	Yield
1	 **4.52a**	 **4.78a**  **4.79a**	31% 52%
2	 **4.53b**	 **4.78b**  **4.79b**	41% 38%
3	 **4.53c**	 **4.79c**	42%
4	 **4.52h**	 **4.79d**	84%

Table 4.10: Cycloaddition with 5-nitroquinoline 4.77



4.79d **4.80** (99%)

Scheme 4.26: Oxidative aromatization of 4.79d

As illustrated in **Figure 4.4**, the X-ray crystallographic analysis of **4.80** strongly suggests new double bond formation (C(1)–C(2) = 1.374 Å). The ease with which the cycloadducts undergo aromatization upon exposure to air made this reaction an attractive approach toward indolizine and benzoindolizine products with absolute regioselectivity.

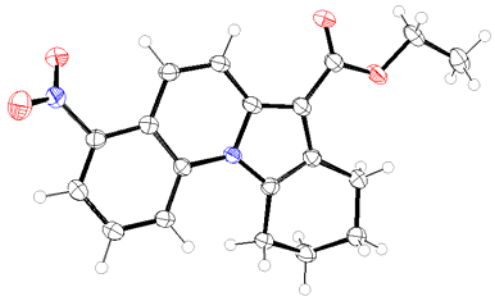
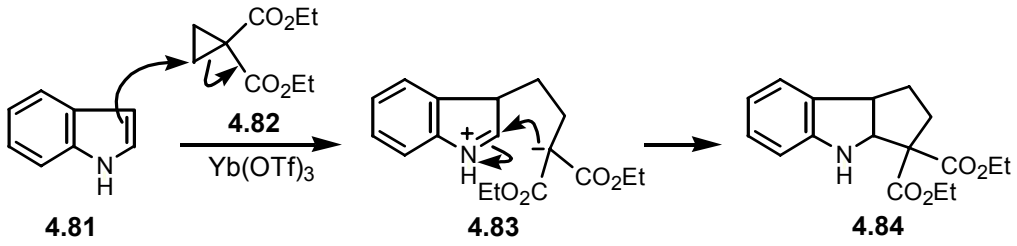


Figure 4.4: X-ray structure of 4.80

In summary, the first formal [3+2] cycloaddition of DA cyclopropane with pyridines and quinolines was recently discovered. Electron poor dipolarophiles display enhanced efficiency for this reaction, and this methodology provided convenient access to indolizine and benzoindolizine compounds that are of wide practical applications.

4.6 FORMAL [3+2] CYCLOADDITION WITH INDOLES

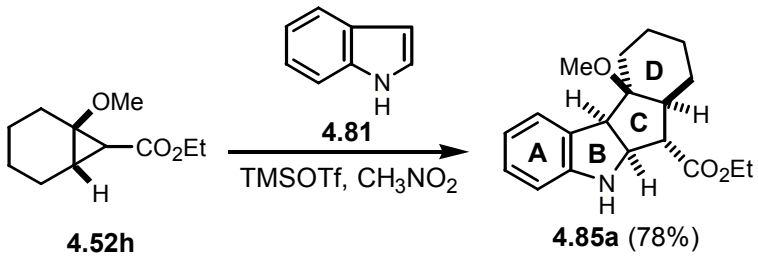
As one of the classic heterocycles, indoles have played a large role in the history of organic chemistry. It is not only because of the frequent presence of this constructional motif in medicinally important and bioactive alkaloids, but also its unique and predictable reactivity. Indole-based synthetic methodologies have been well documented, among them transformations with indole as dienophiles for [4+2] cyclization[155] is well established approaches toward complicated cyclic structures with high atom economy and diastereoselectivity. Recently Kerr and coworkers discovered a [3+2] cycloaddition of unprotected indole **4.81** with doubly activated acceptor cyclopropane **4.82** as a side reaction in C(3) indole alkylation studies (**Scheme 4.27**),[156] and this transformation has been later developed as a general reaction of on different acceptor cyclopropanes.[157] The reaction was believed to proceed through a tandem attack of the putative manolic enolate **4.83** on the intermediate iminium ion **4.84**.



Scheme 4.27: [3+2] cycloaddition of indole and acceptor cyclopropane

Encouraged by the results from cycloadditions of DA cyclopropanes with pyridines and quinolines as described in previous sections, we sought to further extend the strategy to other useful heterocyclic dipolarophiles. During this course a general DA cyclopropane-indole cyclization reaction has been established.

Our study began with a tentative cyclization between a reactive DA cyclopropane **4.52h**. Treating a CH_3NO_2 solution of **4.52h** and indole **4.81** with stoichiometric amounts of TMSOTf (1.3 eq) led to rapid formation of cycloadduct **4.85a** in 78% isolated yield (**Scheme 4.28**). Curiously, ^{1}H NMR studies revealed a significant upfield shift of the auxiliary methoxy group (σ 2.75 ppm). This was good indication of a shielding effect from the benzene ring. Finally single crystal X-ray structure analysis provided unambiguous determination of the stereochemistry of **4.85a**, as well as a solid state explanation for this chemical shift. **Figure 4.5** shows that the tetracyclic product **4.85a** adapts *trans* conjunction between CD rings but a *cis* B-C ring relationship. This structural conformation helps force the methoxy group near to the π system of the benzene ring, producing a strong shielding effect.



Scheme 4.28: Formal [3+2] cyclization of 4.52b and indole

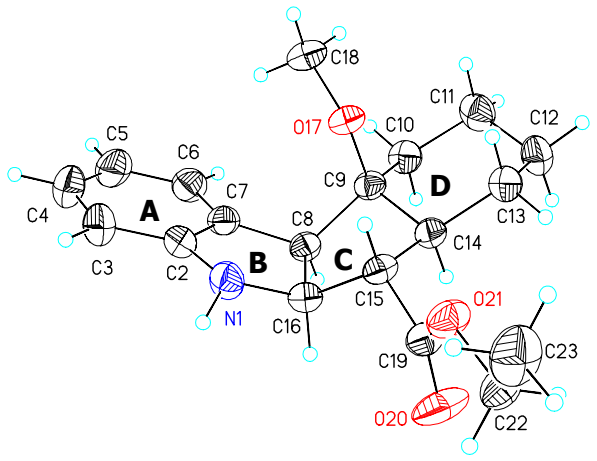
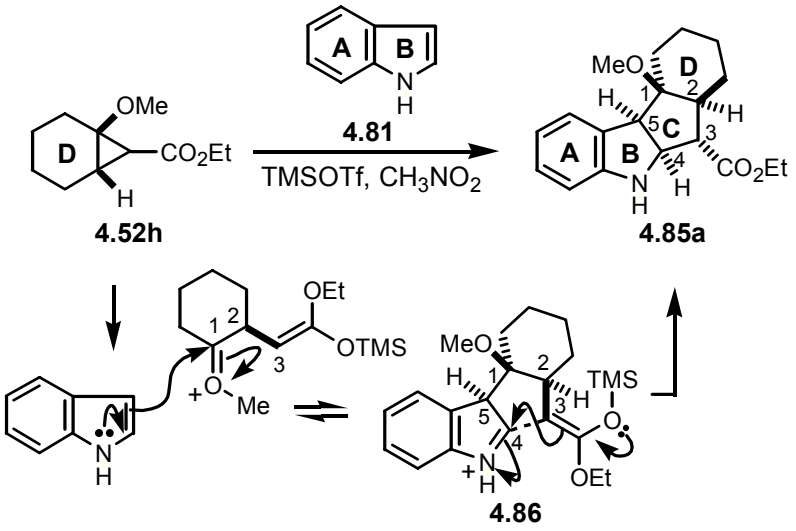


Figure 4.5: X-ray structure of 4.85a

In addition to the high reaction yield, this single step cyclization is also featured with very high stereochemical control, with five relative stereocenters established around the middle C ring. After repeated attempts, the reaction provided **4.85a** as the only isolatable diastereomeric product regardless of stereochemistry on starting cyclopropane **4.52h**. A tentative mechanistic hypothesis for this highly stereoselectivite process is illustrated in **Scheme 4.29**. After TMSOTf activation of the DA, the nucleophilic indole approaches the formal 1,3-zwitterionic intermediate from the more sterically accessible face. This *trans* addition not only leads to the relative stereochemistry between the 1,2 positions, but also places the resulting iminium ion below the enolate, allowing the latter to approach only from the top face leading to the relative configuration at positions 3, 4 and 5. diastereomeric



Scheme 4.29: Mechanistic hypothesis for indole cycloaddition

With the model reaction established, efforts were focused on examining the generality of the reaction on DA cyclopropane components. For this purpose, indole **4.81** was chosen as the model dipolarophile for screening on different DA cyclopropanes. As summarized in **Table 4.11**, this cyclization was highly effective with a variety of cyclopropanes, including those difficult for pyridines reactions (entry 3-5). A quick inspection of **Table 4.11** reveals that that the preliminary D ring in the starting cyclopropanes is essential in achieving the relative stereochemistry (entries 1, 4, and 5). In entries 2 and 3, the conformationally flexibile substrates without D rings resulted in no strong facial selectivity during the indole nucleophilic addition, which makes possible formation of all the diastereomers. This observation is consistent with the mechanistic hypothesis proposed in **Scheme 4.29**.

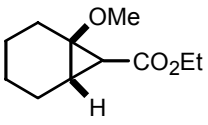
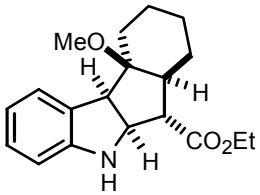
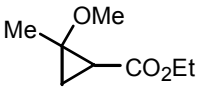
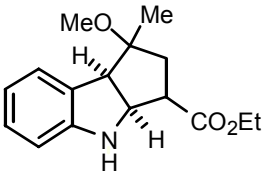
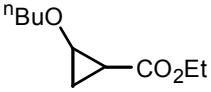
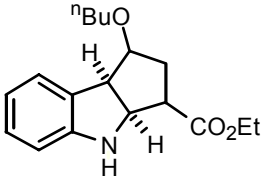
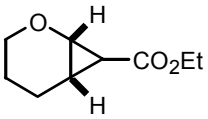
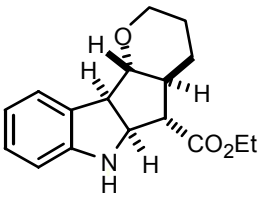
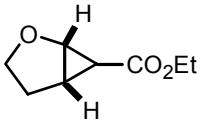
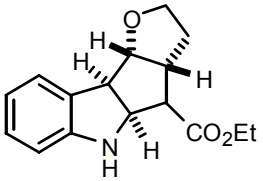
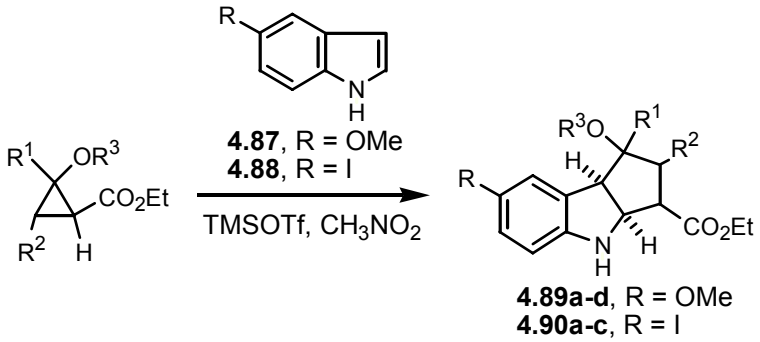
Entry	Substrate	Product		Yield
1	 **4.52h**		**4.85a**	78%
2	 **4.52g**		**4.85b**	64%
3	 **4.52a**		**4.85c**	62%
4	 **4.52b**		**4.85d**	74%
5	 **4.52c**		**4.85e**	58%

Table 4.11: Formal indole-DA cyclopropane [3+2] cycloaddition

One of the key parameters examined for the subject reaction was substituent electronic effects on the indole dipolarophiles. In stark contrast to prior observations on pyridine cyclizations, introduction of strong EWG groups onto the indole significantly limited reactivity. As a comparison, the results from commercially available 5-iodo and 5-methoxy indoles are summarized on **Table 4.12**. While the electron rich 5-methoxy indole **4.87** possesses high reactivity, 5-iodo indole **4.88** demonstrated consistently

diminished efficiency, and indoles with strong EWGs (e.g., 5-fluore) failed to yield any cyclization products.



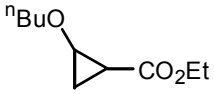
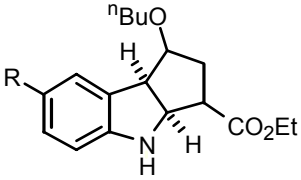
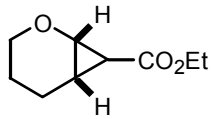
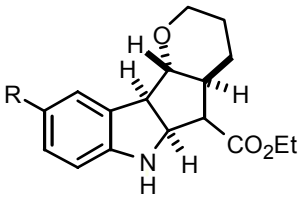
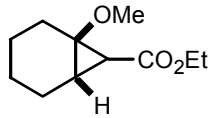
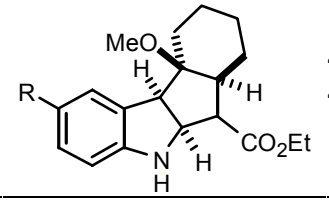
Entry	Cyclopropane	R	Product		Yield
1		OMe		**4.89a**	74%
2	**4.52a**	I		**4.90a**	51%
3		OMe		**4.89b**	68%
4	**4.52b**	I		**4.90b**	61%
5		OMe		**4.89c**	72%
6	**4.52h**	I		**4.90c**	54%

Table 4.12: Substituent electronic effects

The stereochemistry of cycloadduct **4.89b** was determined by single crystal X-ray analysis as shown in **Figure 4.6**. Given the well-documented literature examples of transition metal catalyzed iodoarene transformations, the iodo-substituted products **4.90a-c** offer a convenient handle for future functionalization.

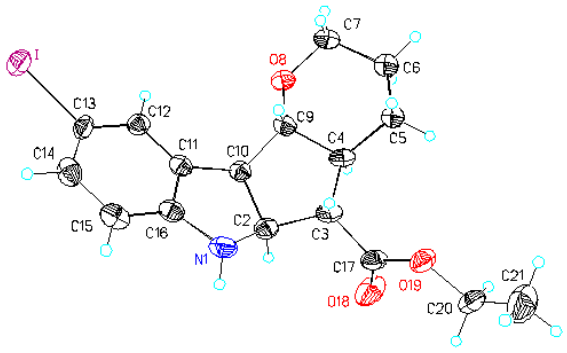
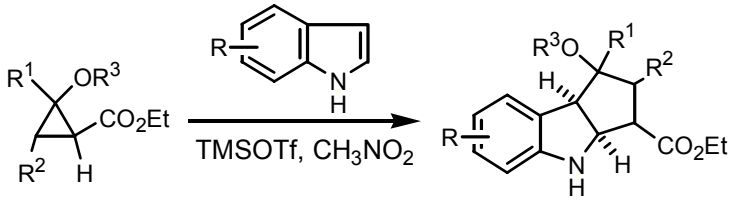


Figure 4.6: X-ray structure of 4.89b

The remainder of the study was centered on determining the scope of the reaction with respect to indole substitution pattern. In this regard, a matrix of reactions between DA cyclopropanes and commercially available methyl indoles was completed as shown in **Table 4.13**. From this table it is clear that the subject cyclization is relatively independent of the location of methyl substitution.



4.91a-l

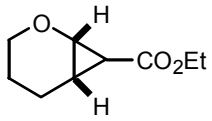
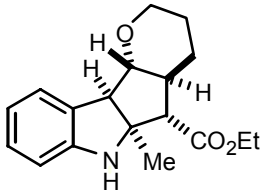
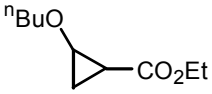
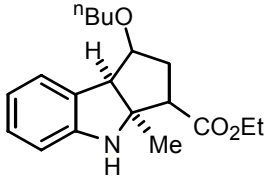
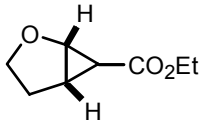
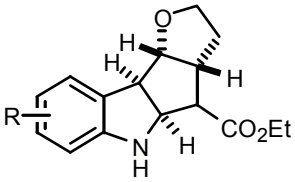
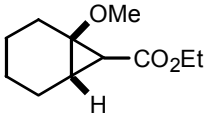
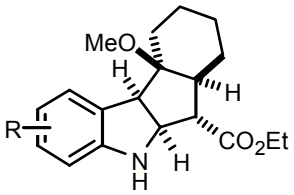
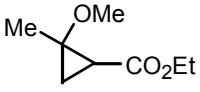
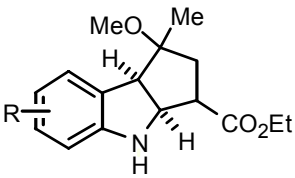
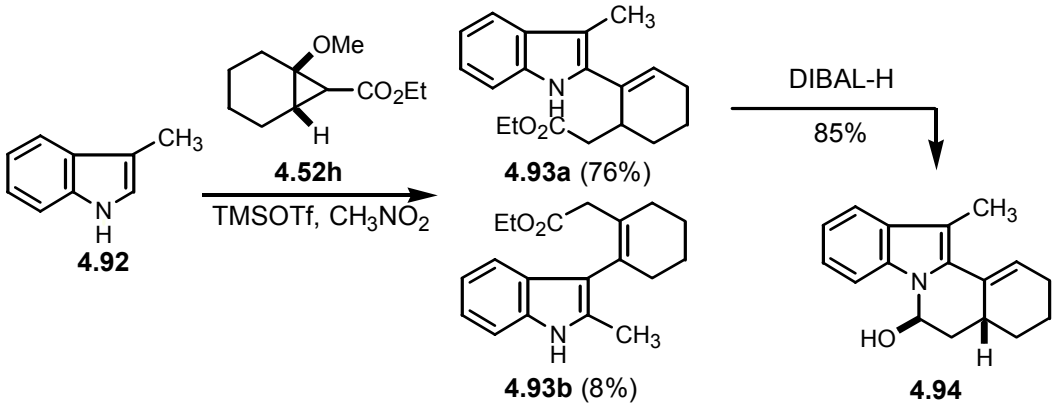
Entry	Cyclopropane	R	Product		Yield
1	 **4.52b**	2-Me		**4.91a**	74%
2	 **4.52a**	2-Me		**4.91b**	69%
3	 **4.52c**	1-Me		**4.91c**	69%
4		2-Me		**4.91d**	72%
5	 **4.52h**	1-Me		**4.91e**	88%
6		2-Me		**4.91f**	89%
7		5-Me		**4.91g**	77%
8		7-Me		**4.91h**	81%
9	 **4.52g**	2-Me		**4.91i**	81%
10		5-Me		**4.91j**	81%
11		7-Me		**4.91k**	72%
12		2-Me, 3-Me		**4.91l**	52%

Table 4.13: DA cyclopropane-methyl indole cycloaddition

While most of the mono-methyl substituted indoles successfully participated in the cycloaddition, it was interesting that 3-methyl indole **4.92** varied from the normal reaction pathway. Employing similar conditions on a mixture of **4.53b** and **4.92** provided a clean mixture of two major products, which were later characterized to be **4.93a** (76%) and **4.93b** (8%) (**Scheme 4.30**). For the purpose of structure determination, the major product **4.93a** was, after DIBAL-H reduction, converted into aminal **4.94**, the structure that determined by X-ray crystallographic study (**Figure 4.7**).



Scheme 4.30: Vinyl migration of 3-methyl indole

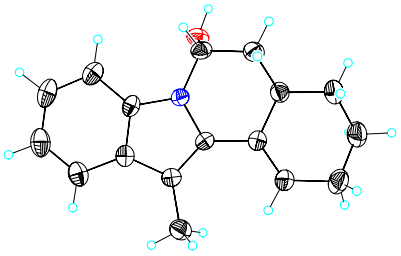
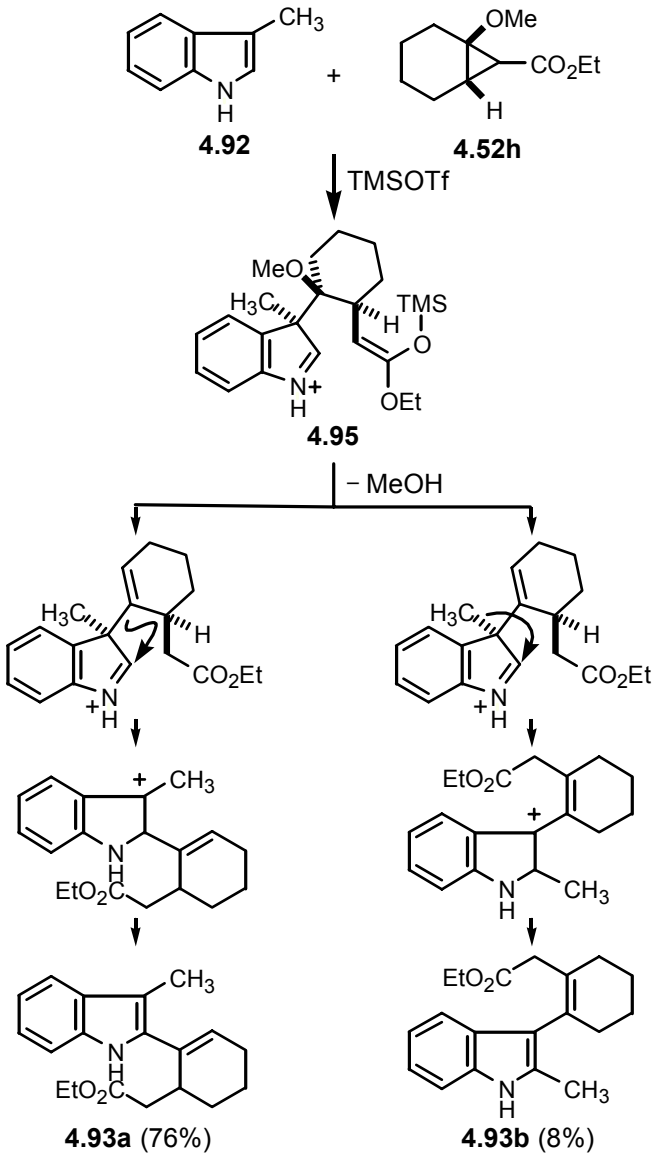


Figure 4.7: X-ray structure of 4.94

It is noteworthy that this rearrangement was not observed on more sterically challenging indoles, specifically 2,3-dimethylindole (**Table 4.13**, entry 12), which provided cyclization product **4.91l** in moderate yield (52%). A possible mechanistic rationale for this reactivity difference is provided in **Scheme 4.31**. It is very likely that increased steric interactions within the first addition intermediate A stimulates a prompt MeOH elimination. Therefore the resulting iminium ion B is aligned for a subsequent 1,2-sigma shift (preferentially for a vinyl migration) and aromatization. While the bulkiness from 2,3-dimethylindole may encourage a stronger tendency for MeOH elimination, the preexisting 2-methyl makes subsequent aromatization impossible, thus providing no driving force for the rearrangement.

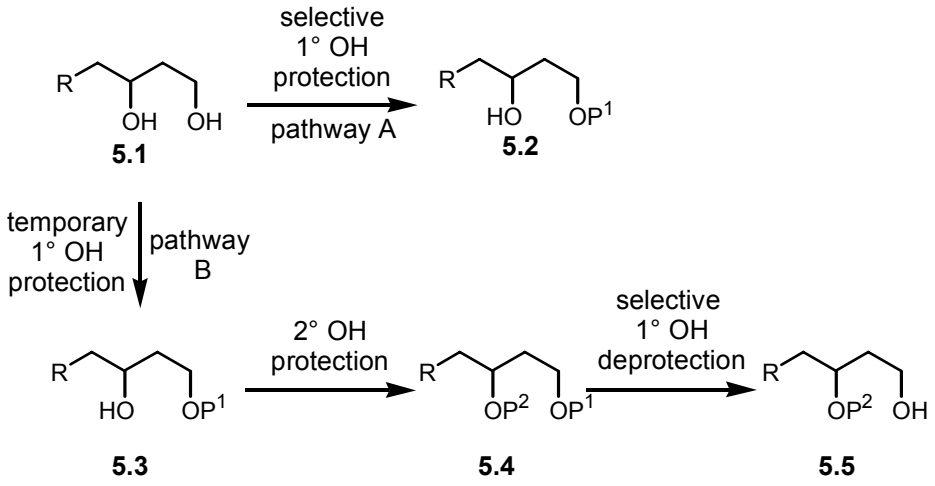


Scheme 4.31: Mechanistic hypothesis for vinyl migration of 4.92

Chapter 5: Mono-deprotection of Di-*tert*-butyl Silylene Ether

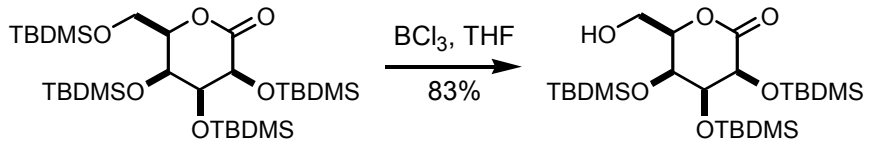
5.1 INTRODUCTION

A frequently encountered challenge in organic synthesis is selective protection and deprotection of alcohols. The regioselectivity of 1,3-diol hydroxy protection is often governed by sterics, and the reactions normally favor the less hindered positions (**Scheme 5.1**, pathway A). When protection of the more hindered hydroxy group is required, it is generally accomplished through multi-step transformations that involve temporary masking of the active hydroxy through labile protecting groups (P^1). For example, the product **5.5** with secondary protection can be prepared from 1,3-diol **5.1** through transitory masking of the primary hydroxy group, protection of secondary hydroxy of the intermediate **5.3**, and primary deprotection of the resultant **5.4** (pathway B).



Scheme 5.1: Steric controlled selectively 1,3-diol protection

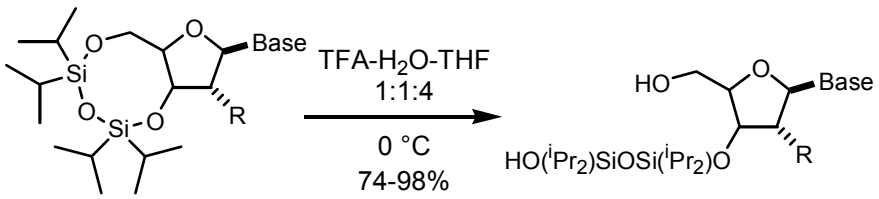
Among the numerous methods that have been developed for selective hydroxy protection, silyl ethers emerged as, undoubtedly, the most widely used protocols for selective alcohol protection.[158] Standard silylation conditions normally result in preferential protection of the less hindered hydroxy group, whereas protection at the more hindered site of 1,3-diol is typically accomplished through a stepwise process. Since the increased reactivity at the more accessible position normally allows selective deprotection at the less hindered site of a persilylated substrate,[159] a roundabout approach toward the "unfavorable" silylation could also be achieved through uniform full protection followed by discriminating desilylation at the less hindered sites. For example, by using BCl_3, Lin and co-workers[160] selectively cleaved the primary 6-*tert*-butyldimethylsilyl ether (TBDMS) of **5.6** in the presence of secondary hydroxy group (**Scheme 5.2**).



5.6 **5.7**

Scheme 5.2: BCl_3 mediated selective deprotection of TBDMS ether

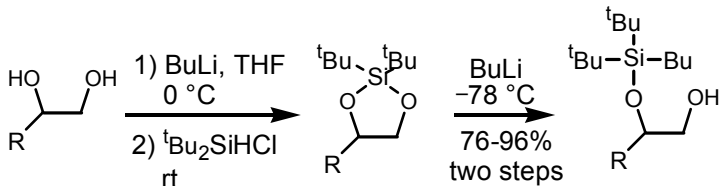
This strategy has also been reported for partial deprotection of cyclic 3,5-tetra-isopropyldisiloxane (TIPDS) at the 5-position of nucleosides **5.8** (**Scheme 5.3**).[161]



5.8 **5.9**

Scheme 5.3 Selective cleavage of tetra-isopropyldisiloxane

Cyclic protection of primary and secondary hydroxys employing di-*tert*-butylsilyl reagent gives the silylene ethers as five or six-membered ring. Since five-membered cyclic silyl ethers easily undergo hydrolysis and do not survive isolation, a recent one-pot protocol was developed for the selective silylation of 1,2-diol **5.10** (**Scheme 5.4**).[162] The selective formation of primary alcohol was attributed to preferential complexation of lithium at the sterically less hindered oxygen.

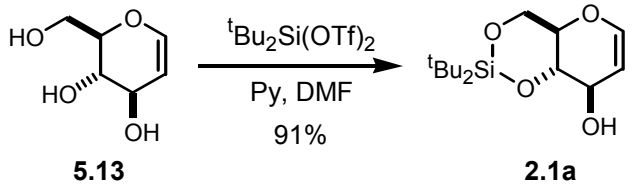


5.10 **5.11** **5.12**

Scheme 5.4: Di-*tert*-butylsilylene ether protection of 1,2-diol

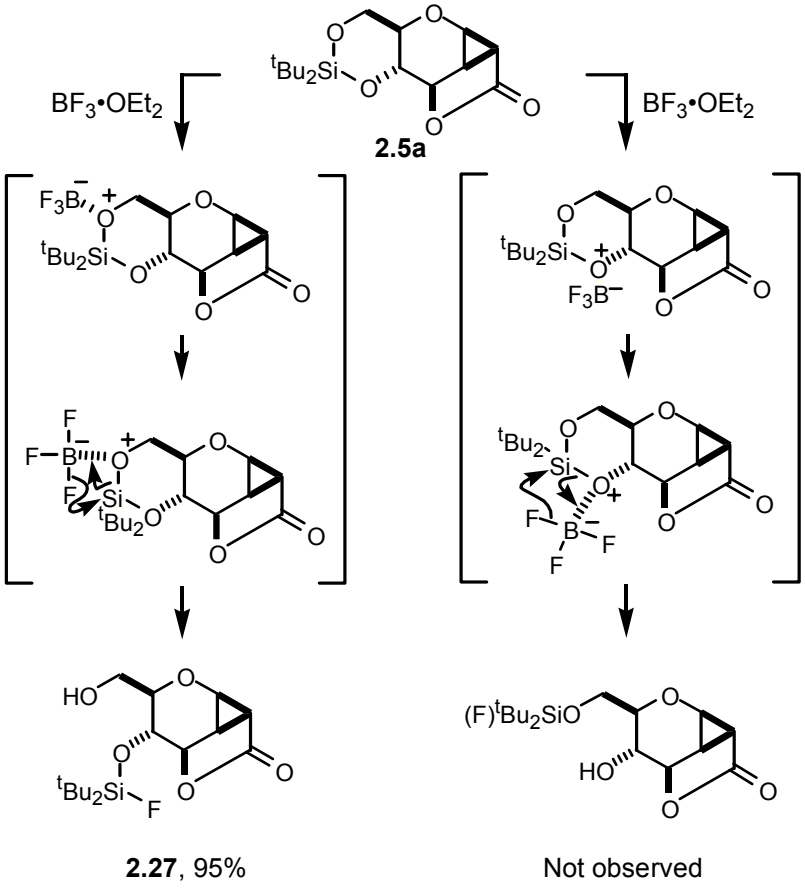
In contrast to **5.10**, the silylene ethers in six-membered rings are typically very stable and therefore more convenient for synthetic applications.[163,164] However no general route to selective mono cleavage of this group exists. Very recently, Hoberg applied this protecting protocol onto glucal **5.13** and successfully prepared the 4, 6-*O*-di-*tert*-butyl-

silylene ether **2.1a** in the presence of 3-hydroxy group (**Scheme 5.5**), but his attempt on differentiating the 4,6-position for a selective O-6-deprotection was unsuccessful.[54]



Scheme 5.5: Di-*tert*-butylsilylene ether protection of Glucal

We recently adapted this protection protocol to the preparation of lactonized glucal-derived DA cyclopropane **2.5a** (**Chapter 2**). The 4,6-di-*tert*-butyl silylene ether **2.5a** turned out to be robust toward several Lewis acidic conditions. While probing the chemical behavior of this cyclopropane, a BF_3•OEt_2 mediated regioselective mono-deprotection of the di-*tert*-butylsilylene ether **2.5a** was discovered. Treating a toluene solution of **2.5a** with BF_3•OEt_2 at 85 °C for 45 minutes resulted in exclusive formation of di-*tert*-butylfluorosilyl ether **2.27** in 95% isolated yield. Further investigation illustrated that small amounts (0.5 eq) of allyl trimethylsilane additive was crucial in inhibiting full deprotection and maintaining primary regioselectivity. The function of allyltrimethylsilane has not been exhaustively investigated, but presumably it serves as a acid scavenger to trap HF. This selective desilylation is consistent with a steric control process starting with regioselective boron coordination to the more accessible primary (C6) position followed by an internal fluoride delivery process (**Scheme 5.6**). The excellent regioselectivity and reaction yield have stimulated further investigation of this mono-desilylation route as a general protocol for selective 1,3-diol protection.[76]

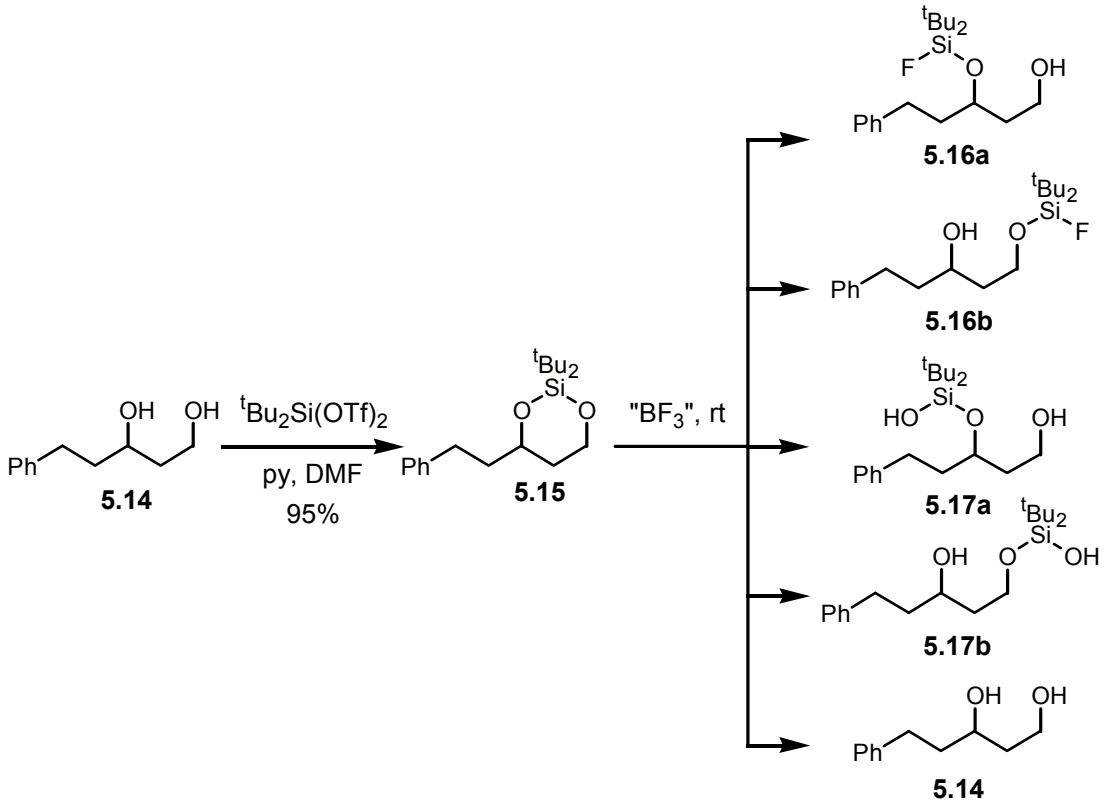


Scheme 5.6: Steric rationale for regioselective deprotection of 2.5a

5.2 REGIOSELECTIVE MONO-DEPROTECTION OF DI-*TERT*-BUTYL SILYLENE ETHER

5.2.1 Reaction condition optimization

To simulate the chemical condition of **2.5a**, a model substrate di-*tert*-butylsilylene ether **5.15**[163] was prepared via the conversion of the simple 1,3-diol **5.14**.[165] Unfortunately, subjecting the model substrate **5.15** to reaction conditions (room temperature) similar to those applied on **2.5a** resulted in formation of the desired fluorosilane **5.16a** (21%) in a disappointing mixture of the unwanted regio-diastereomer **5.16b** (2%), silanols **5.17a** (9%), **5.17b** (3%), diol **5.14** (8%) and starting material **5.15** (36%) (**Scheme 5.7**). This reaction proved to be extremely water sensitive, which induced formation of silanols **5.17a** and **5.17b**, and also plagued the products **5.16** with poor regioselectivity. Substantial reduction of the formation of silanols **5.17a** and **5.17b** was achieved by addition of 3 Å molecular sieves prior to BF_3•OEt_2 addition.

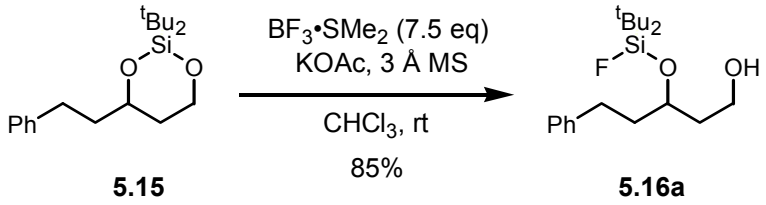


Scheme 5.7: Tentative deprotection of model substrate 5.15

The screening of other commercially available BF_3-Lewis base complexes, including BF_3•THF, BF_3•^{t}BuOMe, and BF_3•MeOH, revealed that BF_3•SMe_2 improved both the conversion and selectivity of the reaction. However, the formation of considerable amounts of diol **5.14** continued to plague the process. The varying reactivity displayed by different BF_3 sources clearly demonstrated the importance of Lewis bases in the reaction, and a survey of assorted additives including esters, ethers, amines, and salts showed that the addition of excess anhydrous potassium acetate (KOAc) to the reaction greatly minimized complete desilylation to diol **5.14**. The role of the KOAc is still unclear, and related salts that proved less effective include NaOAc, CsOAc, $PhCO_2Na$,

$PhCO_2K$, Na_2CO_3, and K_2CO_3. The more soluble salts such as potassium stearate ($CH_3(CH_2)_{16}COO^-K^+$) and sodium 2-ethylhexanoate performed similarly to KOAc.

Unlike the original reaction conditions utilized for substrate **2.5a**, using toluene or benzene as solvent for **5.15** resulted in poor selectivity and incomplete conversion. Replacing toluene with oxygen-containing solvents such as THF, diethyl ether, EtOAc or CH_3CN provided very slow reaction. Surveying multi solvent systems demonstrated that polar solvents such as chloroform, CH_2Cl_2 were superior for this process, especially in minimizing diol **5.14** formation. With these modifications, the regioselective deprotection of **5.15** with BF_3•SMe_2 consistently yielded the fluorosilanes **5.16a**:**5.16b** in over 15:1 ratio and 85% isolated yields (**Scheme 5.8**).

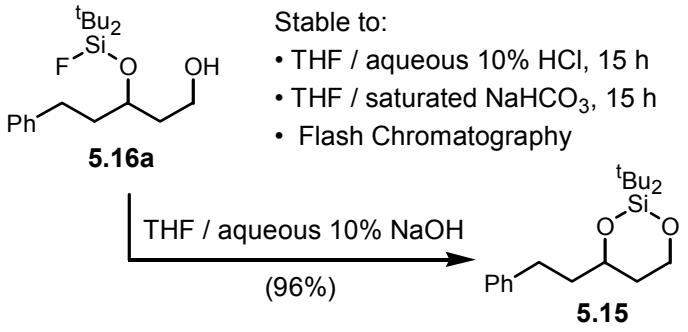


Scheme 5.8: Regioselective deprotection of model substrate 5.15

5.2.2 Stability of the resultant fluorosilane

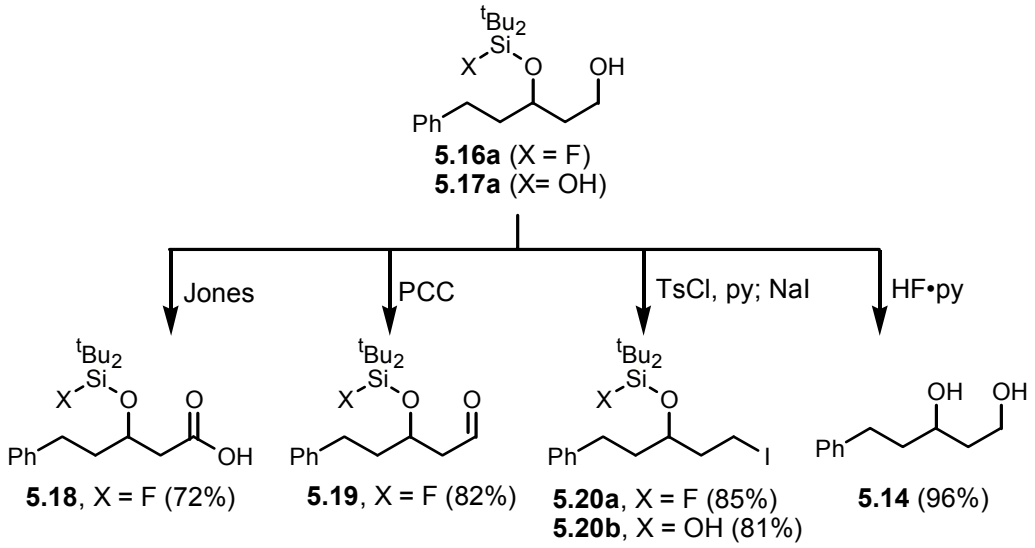
While results from the model substrate **5.15** were encouraging, to make the transformation valuable the fluorosilane products must be sufficiently robust to serve as viable protecting groups in subsequent reactions. In this regard, the fluorosilane **2.27** survived several synthetic steps and flash chromatography.[49] Likewise, the fluorosilane **5.16a** was stable to aqueous acid for 15 h (THF, 10% aqueous HCl) and neutral solutions

(THF, saturated $NaHCO_3$) (**Scheme 5.9**), but strong basic conditions resulted in closure to the silylene ether **5.15** (THF, 10% aqueous NaOH, 15 min, 96%).



Scheme 5.9: Stability of fluorosilane 5.16a

Several transformations at the primary alcohol of the fluorosilane **5.16a** have demonstrated the stability of the (F)^{t}Bu$_2$Si group, including Jones oxidation to **5.18**,[166] PCC oxidation to **5.19**, and Finkelstein transformation to **5.20** (**Scheme 5.10**). A cursory inspection of the ^{1}H NMR and IR spectra of these products proved the primary regiochemistry of mono-deprotection product **5.16a**. The silanol **5.17a** was also reasonably stable, as demonstrated by its conversion to **5.20b** in 81% yield. As for full deprotection, the di-*tert*-butylfluorosilane **5.16a** can be easily cleaved to the diol **5.14** upon HF·pyridine treatment (96%).[167]

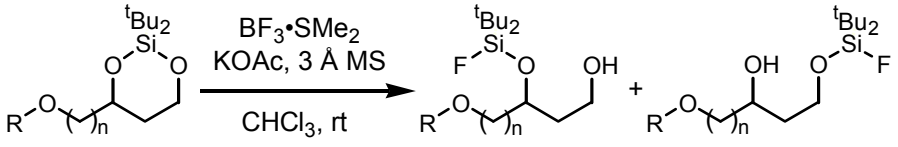


Scheme 5.10: Chemical compatibility of fluorosilane 5.16a

5.2.3 Compatibility with diverse functionality

With the integrity of the di-*tert*-butylfluorosilane ether amply demonstrated, substrate compatibility and availability of orthogonal protective moieties was briefly surveyed. The model substrates shown in **Table 5.1** were used to explore the functional group orthogonality between di-*tert*-butylsilylene ether and several common protective groups. Acetate and benzoate esters **5.21a-d** are highly compatible with the deprotection conditions (entries 1-4), and no diminishment of regioselectivity at the silylene ether was observed, as might have occurred if complicated by neighboring group participation of the ester functionality. An allyl group easily survived the Lewis acid conditions (entry 5), as did benzyl **5.21f** (entry 6), but the reaction with the latter failed to go to completion. The methyl ether substituted substrate **5.21g** was poor (entry 7). The bulky triisopropylsilyl ether **5.21h** was mostly unaffected during the deprotection with

BF_3•SMe_2 as depicted in entry 8, whereas cleavage of the *tert*-butyl dimethylsilyl ether **5.21i** demarcates silicon reactivity (entry 9). The gradient reactivity between these silyl ethers leaves this protecting protocol a broad space for selective hydroxy manipulations.



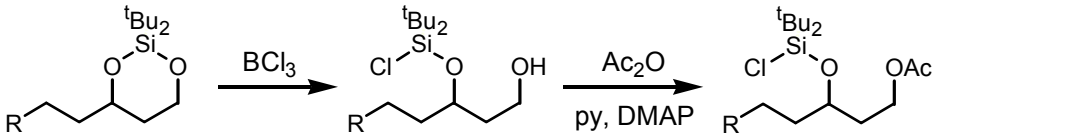
5.21 **5.22** **5.23**

Entry	*n*	R	Product	Yield
1	1	CH_3CO	**5.22a**	91%
2	2	CH_3CO	**5.22b**	87%
3	1	PhCO	**5.22c**	90%
4	2	PhCO	**5.22d**	82%
5	2	Allyl	**5.22e**	78%
6	2	$PhCH_2$	**5.21f**, **5.22f**	57%, 35%
7	2	CH_3	**5.22g**	43%
8	2	iPr_3Si	**5.22h**	78%
9	2	(^{t}Bu)Me_2Si	**5.21i**	97%

Table 5.1: Functional group compatibility

While selective cleavage of silyl ethers with BCl_3 is known,[160] it is interesting to note that selective mono-desilylation of the di-*tert*-butylsilylene ether occurred cleanly with BCl_3 (**Scheme 5.11**). Treatment of **5.15** and **5.21h** with BCl_3 (heptane solution) resulted in immediate formation of clean intermediate which after aqueous $NaHCO_3$ workup provided the primary alcohols **5.24** and **5.25** in excellent yields. However, the

chlorosilane had to be characterized as their acetates **5.26** and **5.27**, as the reactive free alcohols reverted back to starting material (with up to 15% silanol formation) under acidic, basic or even neutral conditions including simply standing in $CHCl_3$ or methanol. The instability displayed by the chlorosilane discouraged further investigation on this class of silylated alcohols.



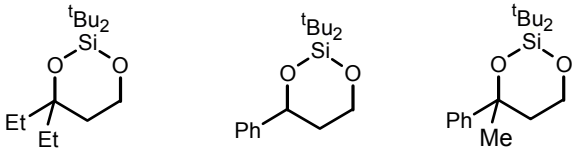
5.15, R = Ph
5.21h, R = OTIPS

5.24, R = Ph
5.25, R = OTIPS

5.26, R = Ph (81%, 2 steps)
5.27, R = OTIPS (80%, 2 steps)

Scheme 5.11: Regioselective desilylation via BCl_3

As anticipated, the Lewis acidic nature of the reaction media precluded the use of substrates with Lewis acid sensitive functionality. For example, at its current stage of development, silylene ethers prepared from tertiary or benzylic alcohols (**Figure 5. 1**) predominately undergo elimination under the deprotection reaction conditions.



5.28 **5.29** **5.30**

Figure 5. 1: Unsuccessful silylene ethers

5.2.4 Differentiation between secondary positions

To ascertain whether deprotection could succeed selectively when challenged with substrates presenting less steric differentiation, silylene ethers derived from internal secondary 1,3-diol were examined (**Table 5.2**). In entries 1 and 2 methyl and *tert*-butyl groups are compared. In both cases, the Si-O cleavage occurred preferentially at the more accessible position, affording exclusively one diastereomeric fluorosilane products **5.32** and **5.34**. The *syn* diastereomer **5.33** required nearly three times as long (2.5 h) for complete consumption of starting material than did the anti diastereomer **5.31**, and a third of the starting material was fully desilylated. Stopping the reaction in entry 2 prematurely before significant amounts of diol formation increased the yield to 79%, based on recovered starting material. Analogous results occurred with the *anti* and *syn* substrates shown in entries 3 and 4. Again, reaction with the *syn* diastereomer **5.37** gave nearly 30% of unwanted diol when allowed to proceed to complete consumption of the starting material. These experiments revealed that stereochemistry greatly influenced the efficiency of the desilylation reaction.

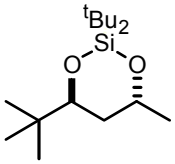
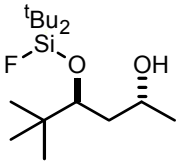
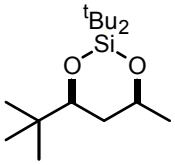
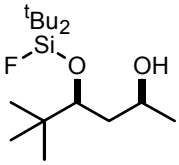
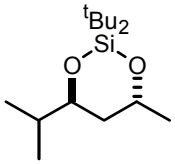
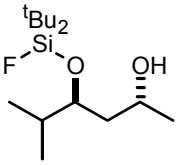
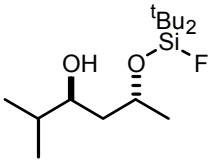
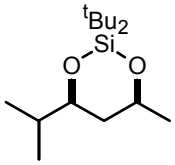
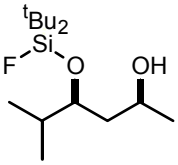
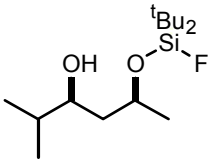
Entry	Substrate	Product(s), (ratio)	Yield
1	 **5.31**	 **5.32**	93%
2	 **5.33**	 **5.34**	64%
3	 **5.35**	 **5.36a** (6:1)  **5.36b**	89%
4	 **5.37**	 **5.38a** (6:1)  **5.38b**	43%

Table 5.2: Selectivity between secondary positions

In summary, parameters influencing the regioselective mono-desilylation of di-*tert*-butylsilylene ethers using BF_3•SMe_2 have been elucidated. The reaction can be efficient, highly selective and provide access to 1,3-diols silylated at the sterically more hindered positions. This new method is likely to see continued application on organic synthetic chemistry.

Conclusion

The first intramolecular glycal cyclopropanation has been developed. The potential utility of this methodology has been demonstrated in the quasi formal synthesis of bislactone natural product xylobovide and derivatives. The unique chemical behavior of the resultant lactonized DA cyclopropane **2.5a** under different Lewis acid promoters has led to the discovery of a wide variety of new reactions including regioselective deprotection of di-*tert*-butyl silylene ethers (BF_3•OEt_2), anhydro-sugar formation (TMSOTf), and stereoselective allylation and glycosidation ($TiCl_4$). Under Lewis acid promotion, DA cyclopropane **2.5a** also participated in formal [3+2] cycloadditions with various dipolarophiles including silyl enol enols, imines, aldehydes, nitriles, pyridines, quinolines and indoles. Extension of the nitrile cyclization reaction to general non-carbohydrate-derived DA cyclopropanes has led to the discovery of a novel synthetic methodology toward pyrroles, bipyrroles and thienyl pyrroles.

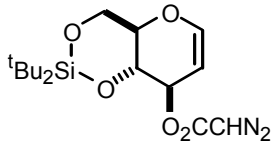
Chapter 6: Experimental Procedures

General Procedures.

All reactions were run under an atmosphere of argon unless otherwise indicated. Reaction vessels were oven or flame-dried and allowed to cool in a dry box or desiccator prior to use. Solvents and reagents were purified by standard methods.[168] Toluene, benzene, $CHCl_3$, CH_2Cl_2, CH_3NO_2, $C_2H_5NO_2$, CH_3CN, THF, Et_2O and pyridine were purified by distillation from CaH_2 under an Ar atmosphere right before use. Powdered KOAc was flame dried as a melt under vacuum (0.1 mm Hg). Thin-layer chromatography (TLC) was performed on EM 250 Kieselgel 60 F254 silica gel plates. The plates were visualized by staining with I_2 on silica, CAM,[169] ninhydrin, or potassium permanganate. Column chromatography was performed with silica gel 60 according to the method of Still.[170]

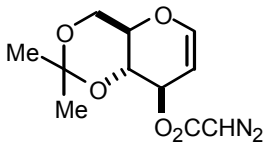
The ^1H, ^{13}C, ^{31}F NMR data was obtained on a General Electric QE-300 spectrometer, a Varian Unity Plus 300 or 400 spectrometer, or a Varian INOVA 500 spectrometer. For ^1H NMR, chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are, in all cases, referenced to the residual proton resonance peaks: δ 7.24 for $CHCl_3$, δ 7.15 for benzene-d_6, δ 2.49 (hept) for DMSO-d_6, and 2.09 (pent) for acetone-d_6. The ^{13}C NMR chemical shifts were reported in ppm relative to the center peak of the multiplet for deuterated solvents: δ 77.0 (t) for $CHCl_3$, 39.5 (pent) for DMSO-d_6, 29.8 (hept) for acetone-d_6, and 28.0 (t) for benzene-d_6. ^{13}C and ^{19}F NMR spectra were routinely run with broadband ^1H decoupling. Chemical shifts for ^{19}F NMR are reported in ppm downfield from $CFCl_3$ as external standard. Coupling constants for all spectra are reported in Hertz (Hz). Infrared spectra were measured on a

NEXUS 470 FT-IR spectrometer as thin films on sodium bromide plates and are recorded in units of cm^{-1}. HRMS were made with a VG analytical ZAB2-E instrument.



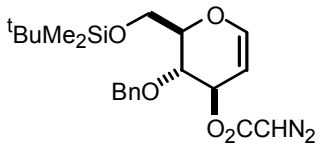
2.3a

Diazo-acetic acid 2,2-di-*tert*-butyl-4,4a,8,8a-tetrahydro-1,3,5-trioxa-2-sila-naphthalen-8-yl ester (2.3a). To a solution of glycal **2.1a** (288 mg, 1.0 mmol)[54] and glyoxylic acid chloride *p*-toluenesulfonylhydrazone **2.2** (340 mg, 1.3 mmol)[53] in CH_2Cl_2 (8 mL) and DMF (2 mL) cooled to 0 °C was added *N*,*N*-dimethylaniline (294 μL, 2.9 mmol) in one portion. The resulting solution was stirred 5 min and treated with Et_3N (750 μL, 5.4 mmol). The reaction mixture was stirred for an additional 10 min and H_2O (30 mL) and CH_2Cl_2 (10 mL) was added. The organic layer was separated and washed with H_2O (3 × 10 mL), saturated Na_2CO_3 solution (10 mL), and dried (Na_2SO_4). After filtration through a pad of celite, the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a light yellow syrup (325 mg, 92%): R_f 0.54 (15% EtOAc/hexanes); IR (thin film) ν 3150, 2105, 1692, 1643 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 6.27 (dd, *J* = 6.1, 1.2 Hz, 1H), 5.41 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.76 (s, 1H), 4.68 (dd, *J* = 6.1, 1.8 Hz, 1H), 4.15-4.00 (m, 2H), 3.93-3.78 (m, 2H), 1.01 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 166.8, 145.3, 101.0, 74.0, 73.2, 73.1, 66.1, 46.6, 27.7, 27.2, 23.0, 20.2; HRMS: m/z calcd for $C_{16}H_{27}N_2O_5Si$ ($M+1^+$): 355.1689, found: 355.1684.



2.3b

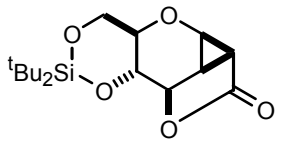
Diazo-acetic acid 2,2-dimethyl-4,4a,8,8a-tetrahydro-pyrano[3,2-*d*]dioxin-8-yl ester (2.3b). The title compound was prepared from **2.1b** (102 mg, 0.54 mmol)[55] according to the general procedure described above for the preparation of **2.3a**. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (122 mg, 88%): R_f 0.45 (25% EtOAc/hexanes); IR (thin film) ν 3106, 2112, 1689, 1623 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 6.32 (dd, *J* = 6.1, 1.5 Hz, 1H), 5.41 (dd, *J* = 6.1, 1.8 Hz, 1 H), 4.79 (s, 1 H), 4.74 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.01-3.90 (m, 2H), 3.86-3.77 (m, 2H), 1.49 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 166.6, 145.7, 101.2, 100.1, 70.2, 70.1, 70.0, 61.8, 46.6, 29.1, 19.2; HRMS: m/z calcd for $C_{11}H_{15}N_2O_5$ ($M+1^+$): 255.0981, found: 255.0971.



2.3c

Diazo-acetic acid 3-benzyloxy-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-3,4-dihydro-2*H*-pyran-4-yl ester (2.3c). The title compound was prepared from **2.1c**[56] (110 mg, 0.31 mmol) according to the general procedure described above for the preparation of **2.3a**. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (117 mg, 89%): R_f 0.65 (EtOAc : hexanes

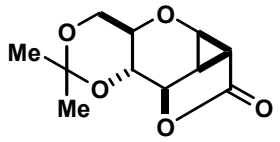
= 1 : 5); IR (thin film) ν 3111, 2109, 1693, 1650 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 7.34-7.25 (m, 5H), 6.40 (dd, *J* = 6.1, 1.4 Hz, 1 H), 5.51-5.47 (m, 1 H), 4.74 (dd, *J* = 6.1, 3.0 Hz, 1H), 4.69 (s, 2H), 4.67 (s, 1H), 3.95-3.81 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 166.3, 145.9, 138.1, 128.4, 127.9, 127.7, 98.8, 78.1, 73.6, 73.0, 71.0, 61.3, 46.3, 25.9, 18.3, -5.2, -5.4; HRMS: m/z calcd for $C_{21}H_{31}N_2O_5Si$ ($M+1^+$): 419.2002, found: 419.1018.



2.5a

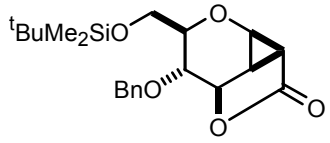
6,6-Di-*tert*-butyl-hexahydro-1,3,5,7-tetraoxa-6-sila-benzo[*g*]cyclopropa[*cd*]inden-2-one (2.5a). To a refluxing solution of $Cu(TBS)_2$ complex **2.4**[59] (7.5 mg, 5 mol %) in 60 mL of toluene was added **2.3a** (1.20 g, 3.38 mmol) in 20 mL of toluene over a period of 12 h via syringe pump. After the addition was complete, the reaction mixture was heated at reflux for additional 2 h, allowed to cool to rt, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 5:1 hexane-EtOAc to 100% EtOAc for gradient elution gave a pale yellow solid (1.01 g, 92%): Recrystallization from EtOAc/hexane afforded the title compound as a colorless needles (81%): mp (ethyl acetate-hexanes) 199.5-201.0 °C; R_f 0.52 (33% EtOAc/hexanes); IR (KBr pellet) ν 3035, 1790, 1466 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 4.91 (*app* d, *J* = 6.1 Hz, 1H), 4.34-4.29 (m, 2H), 3.92 (*app* d, *J* = 9.4 Hz, 1H), 3.79 (dd, *J* = 9.6, 10.8 Hz, 1H), 3.46 (ddd, *J* = 9.4, 5.3, 1.4 Hz, 1H), 2.57 (ddd, *J* = 12.1, 6.2, 6.0 Hz, 1H), 2.32 (dd, *J* = 6.7, 6.7 Hz, 1H), 1.01 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75 MHz,

$CHCl_3$): δ 171.1, 78.6, 76.3, 74.6, 67.2, 60.0, 28.9, 27.8, 27.5, 22.9, 22.8, 20.6; HRMS: m/z calcd for $C_{16}H_{27}O_5Si$ ($M+1^+$): 327.1628, found: 327.1618.



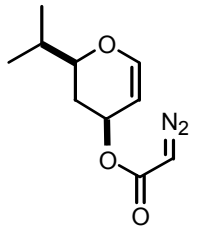
2.5b

6,6-Dimethyl-hexahydro-1,3,5,7-tetraoxa-benzo[*g*]cyclopropa[*cd*]inden-2-one (2.5b). The title compound was prepared from **2.3b** according to the general procedure described above for the preparation of **2.5a**. Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (86 mg, 89%): R_f 0.55 (33% EtOAc/hexanes); IR (thin film) ν 1792 cm^{-1}; ^1H NMR (300 MHz, d_6-benzene): δ 4.39 (*app* d, *J* = 6.4 Hz, 1H), 3.74 (ddd, *J* = 10.1, 4.7, 0.5 Hz, 1H), 3.60 (*app* d, *J* = 10.1 Hz, 1H), 3.43-3.34 (m, 2H), 3.00 (ddd, *J* = 10.3, 10.3, 4.7 Hz, 1H), 1.55 (dd, *J* = 6.7, 6.7 Hz, 1H), 1.40 (ddd, *J* = 13.0, 6.7, 6.7 Hz, 1H), 1.36 (d, *J* = 0.4 Hz, 3H), 1.03 (d, *J* = 0.4 Hz, 3H); ^{13}C NMR (75 MHz, d_6-benzene): δ 169.9, 101.2, 76.2, 74.7, 73.1, 63.6, 62.1, 29.2, 29.1, 23.7, 19.1; HRMS: m/z calcd for $C_{11}H_{15}O_5$ ($M+1^+$): 227.0919, found: 227.0910.



2.5c

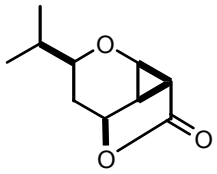
5-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-hexahydro-1,3-dioxa-cyclopropa[*cd*]inden-2-one one (2.5c). The title compound was prepared from **2.3c** according to the general procedure described above for the preparation of **2.5a**. Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a yellow syrup (119 mg, 86%): R_f 0.35 (25% EtOAc/hexanes); IR (thin film) ν 3025, 1779 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 7.38-7.27 (m, 5H), 4.85 (dd, *J* = 6.2, 1.4 Hz, 1H), 4.58 (ddd, *J* = 11.8,11.8, 11.8 Hz, 2H), 4.1 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.60-3.50(m, 4H), 2.51 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.28 (dd, *J* = 6.2, 6.2 Hz, 1H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CHCl_3$): δ171.5, 137.3, 128.6, 128.1, 127.9, 79.5, 73.4, 73.2, 72.4, 64.0, 54.3, 26.6, 25.9, 21.4, 18.3, -5.3; HRMS: m/z calcd for $C_{21}H_{31}O_5Si$ ($M+1^+$): 391.1941, found: 391.1933.



2.8

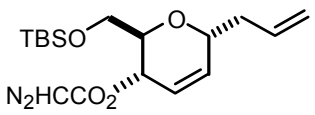
3-**Diazenyl-acetaic acid 2-isopropyl-tetrahydro-pyran-4-yl-ester (2.8).** The title compound was prepared from the corresponding allylic alcohol[61] (136 mg, 0.36 mmol) according to the general procedure described above for the preparation of **2.3a**. Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a light yellow syrup (2.61 g, 83%): R_f 0.67 (25% EtOAc/hexanes); IR (thin film) ν 2110, 1690, 1644 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 6.42 (d, *J* = 2.5 Hz, 1H), 5.49-5.44 (m, 1H), 4.71-4.67 (m, 2H), 3.71 (ddd, *J* = 11.3, 5.8,

2.0 Hz, 1H), 2.19 (dddd, J = 13.0, 6.5, 0.8, 0.8 Hz, 1H), 1.85 (dddd, J = 13.0, 6.5, 6.5, 6.5 Hz, 1H), 1.69 (ddd, J = 11.3, 11.3, 9.6 Hz, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.6, 147.0, 100.8, 79.2, 66.8, 46.3, 31.6, 30.4, 18.0, 17.8; HRMS m/z calcd for $C_{10}H_{15}N_2O_3$ $[M-H]^-$ 211.10831, found: 211.1086.



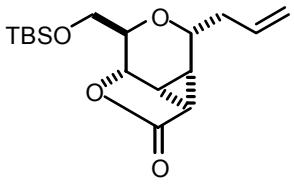
2.9

4-Isopropyl-hexahydro-1,3-dioxa-cyclopropa[*cd*]inden-2-one (2.9). The title compound was prepared from **2.8** according to the general procedure described above for the preparation of **2.5a**. Purification by flash chromatography on silica gel with 10:1 to 3:1 hexanes-EtOAc for gradient elution gave the title compound as a pale yellow solid (1.99 g, 89%): R_f 0.28 (50% EtOAc/hexanes); IR (thin film) ν 1758 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.04 (ddd, J = 5.1, 5.1, 1.5 Hz, 1H), 4.03 (dd, J = 6.0, 6.0 Hz, 1H), 3.53 (ddd, J = 7.5, 7.5, 7.5 Hz, 1H), 2.31 (ddd, J = 6.1, 6.1, 6.1 Hz, 1H), 2.23 (dd, J = 6.4, 6.4 Hz, 1H), 1.87-1.81 (m, 2H), 1.65 (dddd, J = 13.3, 6.6, 6.6, 6.6 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 172.4, 77.5, 72.7, 54.5, 33.0, 29.6, 26.9, 22.4, 17.9, 17.4; HRMS m/z calcd for $C_{10}H_{15}O_3$ $[M+H]^+$ 183.1021, found: 183.1022.



2.10

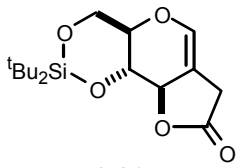
Diazo-acetic acid 6-allyl-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2*H*-pyran-3-yl ester (2.10). The title compound was prepared from the corresponding allylic alcohol[62] according to the general procedure described above for the preparation of **2.5a**. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave title compound as a pale yellow syrup (144 mg, 86%): R_f 0.65 (40% EtOAc/hexanes); IR (thin film) ν 3072, 2110, 1697, 1643 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 5.92-5.76 (m, 3H), 5.18-5.13 (m, 2H), 5.11-5.04 (m, 1H), 4.75 (s, 1H), 4.25-4.17 (m, 1H), 3.78 (ddd, J = 1.0, 5.3, 9.0 Hz, 1H), 3.72 (d, J = 5.3 Hz, 2H), 2.44-2.25 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 166.2, 134.2, 133.3, 123.6, 117.3, 73.3, 70.9, 65.8, 62.8, 46.3, 38.2, 25.9, 18.3, -5.4; HRMS: m/z calcd for $C_{17}H_{28}N_2O_4Si$ ($M+1^+$): 353.1937, found 353.1936.



2.11

3-Allyl-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-hexahydro-1,4-dioxa-cyclopropa[*cd*]inden-2-one (2.11). The title compound was prepared from **2.10** according to the general procedure described above for the preparation of **2.5a**. Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution

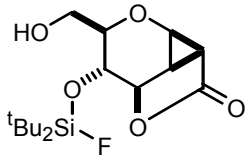
gave the title compound as a pale yellow syrup (99 mg, 85%): R_f 0.35 (25% EtOAc/hexanes); IR (thin film) ν 3073, 1763, 1643 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 5.89-5.75 (m, 1H), 5.19-5.05 (m, 2H), 4.72 (dd, J = 2.3, 4.4 Hz, 1H), 4.13 (dd, J = 6.7, 6.7, 3.4 Hz, 1H), 3.96-3.75 (m, 3H), 2.62 (dd, J = 6.8, 6.8 Hz, 1H), 2.45-2.26 (m, 2H), 2.14 (dd, J = 8.7, 6.7 Hz, 1H), 1.46 (ddd, J = 8.4, 8.4, 3.4 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 174.0, 133.5, 117.9, 72.3, 71.1, 66.1, 60.1, 40.2, 25.8, 22.8, 22.44, 22.40, 18.1, -5.5; HRMS: m/z calcd. for $C_{17}H_{28}O_4Si$ ($M+1^+$): 325.1835, found: 325.1840.



2.26

8,8-Di-*tert*-butyl-5a,6,9a,9b-tetrahydro-3*H*-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalene-2-one (2.26). To a mixture of cyclopropane **2.5a** (75 mg, 0.23 mmol) and ziese's dimmer (14 mg, 0.02 mmol, 0.1 eq) in $ClCH_2CH_2Cl$ (4 mL) was stirred at reflux temperature for 10 h. To the cooled reaction mixture was added CH_2Cl_2 (10 mL). The resulting mixture was washed sequentially with saturated aqueous Na_2CO_3 (2 × 2 mL), H_2O (2 × 2 mL), brine (4 mL) and dried ($MgSO_4$). After filtration through a pad of celite, the solvent was removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (59 mg, 79%): R_f 0.74 (50% EtOAc/hexanes); IR (thin film) ν 1785, 1725, 1698 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 6.28 (s, 1H), 4.88 (dd, J = 7.1, 1.0 Hz, 1H), 4.23 (dd, J = 10.4, 5.0 Hz, 1H), 4.09 (dd, J =

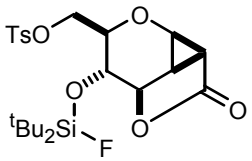
9.9, 7.2 Hz, 1H), 4.00 (dd, J = 10.3, 10.3 Hz, 1H), 3.88 (ddd, J = 10.3, 10.3, 4.8 Hz, 1H), 3.20 (ddd, J = 19.5, 2.2, 2.2 Hz, 1H), 3.05 (d, J = 19.5 Hz, 1H), 1.07 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.4, 138.0, 103.8, 81.1, 73.9, 71.4, 65.8, 31.2, 27.7, 27.2, 23.1, 20.2; HRMS m/z calcd for $C_{16}H_{27}O_5Si$ $[M+H]^+$ 327.1628, found: 327.1616.



2.27

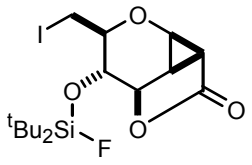
5-(Di-*tert*-butyl-fluoro-silanyloxy)-4-hydroxymethyl-hexahydro-1,3-dioxa-cyclopropa[*cd*]inden-2-one (2.27). To a rt solution of **2.5a** (300 mg, 0.92 mmol) in toluene (11 mL) was added allyltrimethylsilane (306 μL, 1.92 mmol) and BF_3•Et_2O (207 μL, 1.78 mmol) sequentially. The reaction vessel was placed into an 85 °C syrup bath and after 30 min TLC analysis of an aliquot indicated the reaction was complete. The reaction mixture was allowed to cool to rt and was treated with 5% aqueous Na_2CO_3 solution (3 mL). The organic layer was separated and washed with H_2O (3 × 10 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 3:1 of hexanes-EtOAc for elution gave the title compound as a colorless syrup (302 mg, 95%): R_f 0.62 (66% EtOAc/hexanes); IR (thin film) ν 3200-3450 (br), 3092, 1772 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$): δ 4.86 (dd, J = 5.6, 1.6 Hz, 1H), 4.18 (dd, J = 6.1, 6.1 Hz, 1H), 4.13 (dd, J = 6.0, 1.5 Hz, 1H), 3.88-3.81 (m, 1H), 3.65-3.51 (m, 2H), 2.54 (ddd, J = 5.8, 5.8, 5.8 Hz, 1H), 2.35 (dd, J = 6.4, 6.4 Hz, 1H), 2.1 (br s, 1H), 1.03 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CHCl_3$): δ 171.3 (C), 81.4 (CH), 76.1

(CH), 67.3 (CH), 63.0 (CH_2), 54.1 (CH), 26.8 (CH_3), 26.4 (CH), 20.8 (CH), 20.2 (d, J = 14.6 Hz, C), 20.0 (d, J = 14.6 Hz, C); ^{19}F NMR (470 MHz, $CHCl_3$): -159.9; HRMS: m/z calcd for $C_{16}H_{28}O_5FSi$ ($M+1^+$): 347.1690, found: 346.1688.



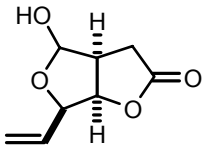
2.28

Toluene-4-sulfonic acid 5-(1-*tert*-butyl-1-fluoro-2,2-silanyloxy)-2-oxo-octahydro-cyclopropa[*cd*]inden-4-ylmethyl ester (2.28). To a rt solution of **2.27** (270 mg, 0.78 mmol) and *p*-toluene sulfonyl chloride (186 mg, 0.98 mmol) in CH_2Cl_2 (6 mL) was added pyridine (2 mL, 24.7 mmol) in one portion. The resulting solution was stirred at rt for 20 h and then volatiles were removed in vacuo. The resulting residue was dissolved in EtOAc (30 mL) and the solution was washed with H_2O (2 × 4 mL), brine (10 mL), and dried ($MgSO_4$). After filtration through a pad of celite, the solvent was removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 4:1 of hexanes-EtOAc for elution gave the title compound as white solid (344 mg, 92%, the tosylate was used immediately in the next reaction): R_f 0.64 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$): 7.74 (dd, J = 6.8, 1.7 Hz, 2H), 7.30 (dd, J = 6.7, 1.7 Hz, 2H), 4.85 (dd, J = 5.7, 1.5 Hz, 1H), 4.27 (dd, J = 11.0, 2.5 Hz, 1H), 4.13 (dd, J = 7.2, 1.5 Hz, 1H), 3.97-3.85 (m, 2H), 3.67 (ddd, J = 9.2, 6.8, 2.5 Hz, 1H), 2.54 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 2.46 (s, 3H), 2.34 (dd, J = 6.4, 6.4 Hz, 1H), 1.07 (s, 9H), 1.12 (s, 9H).



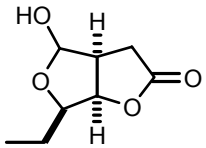
2.29

5-(*tert*-Butyl-hydroxy-isopropyl-silanyloxy)-4-iodomethyl-octahydro-cyclopropa[*cd*]inden-2-one (2.29). A mixture of the tosylate **2.28** (344 mg, 0.71 mmol) and NaI (700 mg, 4.35 mmol, 6.1 equiv) in acetone (3.5 mL) was stirred in the dark at reflux temperature for 30 h. To the cooled reaction mixture solid $NaHCO_3$ (15 mg, 0.21 mmol) was added. After stirring for 10 min, the solvent was removed under reduced pressure. Water (8 mL) and EtOAc (30 mL) were added to residue and the organic layer was separated, washed with H_2O (8 mL) and dried ($MgSO_4$). After filtration through a pad of celite, the solvent was removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 6:1 of hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (300 mg, 92%): R_f 0.74 (50% EtOAc/hexanes); IR (thin film): ν 3115, 1779 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 4.48 (dd, *J* = 5.6, 1.3 Hz, 1H), 4.22 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.00 (dd, *J* = 6.3, 1.1 Hz, 1H), 3.49 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.39 (ddd, *J* = 6.5, 6.5, 2.73 Hz, 1H), 3.13 (dd, *J* = 10.8, 7.8 Hz, 1H), 2.55 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H); 2.35 (dd, *J* = 6.4, 6.4 Hz, 1H), 1.09 (d, *J* = 0.9 Hz, 9H), 1.03 (d, *J* = 0.9 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 171.2 (C), 80.7 (CH), 76.4 (CH), 71.5 (CH), 54.9 (CH), 26.8 (CH_3), 26.7 (CH_3), 26.6 (CH), 20.7(CH), 20.2 (d, *J* = 14.5 Hz, C), 20.0 (d, *J* = 14.5 Hz, C), 4.9 (CH_2); HRMS: m/z calcd for $C_{16}H_{27}O_4FSiI$ ($M+1^+$): 457.0707, found: 457.0700.



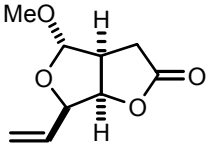
2.31

4-Hydroxy-6-vinyl-tetrahydro-furo[3,4-*b*]furan-2-one (2.31). A 10 mL round-bottomed flask containing a suspension of Zn-Cu couple[171] (400 mg, 6.2 mmol) in THF (1.2 mL) was placed in a 60 °C syrup bath. The reaction mixture was treated sequentially with Me_3SiCl (170 mL, 1.3 mmol) and $BrCH_2CH_2Br$ (150 μL, 1.7 mmol). After ethylene evolution ceased (about 5 min), the reaction mixture was allowed to cool to rt and a solution of iodide **2.29** (40 mg, 0.09 mmol) in 0.8 mL of THF was added. After 20 min the reaction appeared complete as determined by TLC, and the cloudy solution was decanted from the remaining zinc metal and transferred with the aid of additional THF (2 × 2 mL) into a plastic test tube containing HF•pyridine (20% HF, 0.5 mL) and THF (2 mL). After 2 min 10% aqueous H_2SO_4 (2 mL) was added, and the resulting mixture was extracted with EtOAc (4 × 1.5 mL). The combined organic layers were washed with H_2O (2 mL), saturated aqueous $NaHCO_3$ solution (2 × 1 mL), brine (1 mL) and dried ($MgSO_4$). Removal of volatile components under reduced pressure and purification of the resulting residue by flash chromatography on silica gel with 2:1 of hexanes-EtOAc for elution gave the title compound as a colorless syrup (11.4 mg, 76%): R_f 0.45 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$): δ 5.90 (ddd, *J* = 17.3, 10.4, 6.9 Hz, 1H), 5.46-5.41 (m, 2H), 5.28 (*app* s, 1H), 5.00 (dd, *J* = 6.9, 4.0 Hz, 1H), 4.57-4.50 (m, 1H). 3.06-2.90 (m, 1H), 2.83 (dd, *J* = 8.5, 1.2 Hz, 1H), 2.50 (dd, *J* = 8.6, 3.9 Hz, 1H), 2.2 (br s, 1H).



2.32

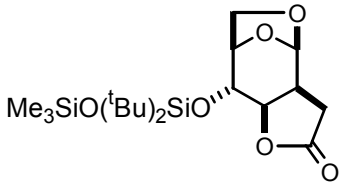
6-Ethyl-4-hydroxyl-tetrahydro-furo[3,4-*b*]furan-2-one (2.32). To a solution of **2.31** (25 mg, 0.145 mmol) in 2.5 mL of ethanol at rt was added 5% Pd-C (ca. 3 mg). The reaction mixture was stirred under hydrogen atmosphere (balloon) for 3 h and then filtrated through a pad of celite. Removal of the solvent under reduced pressure gave the title compound as a colorless oil (24 mg, 96%): The product was used immediately in the following reaction. R_f 0.45 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$): δ 5.32 (s, 1H), 5.00 (dd, *J* = 4.9, 3.7 Hz, 1H), 4.15 (dt, *J* = 7.0, 4.9, Hz, 1H), 3.11-3.02 (m, 1 H), 2.83 (*app* dd, *J* = 18.6, 11.2 Hz, 1H), 2.61 (br s, 1H), 2.48 (dd, 1 H, *J* = 18.6, 3.6 Hz, 1H), 1.76-1.67 (m, 2H), 1.04-0.97 (m, 3H).



2.33

4-methoxy-6-vinyl-tetrahydro-furo[3,4-*b*]furan-2-one (2.33). To a solution of hemiacetal **2.31** (11.4 mg, 66 μmol) in 0.5 mL of MeOH was added 10% aqueous H_2SO_4 (0.1 mL). The reaction mixture was stirred at rt for 6 h and subsequently concentrated under reduced pressure. The residue was dissolved in EtOAc (3 mL), which was then washed with aqueous Na_2CO_3 (2 × 0.5 mL), H_2O (0.5 mL), brine (1 mL) and dried (Na_2SO_4). After filtration through celite, the solvent was removed under reduced pressure

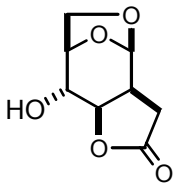
to afford 12.1 mg (96%) of the title compound as a mixture of diastereomers. Separation of the major diastereomer by flash chromatography on silica gel with 4: 1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (10 mg, 82%): R_f 0.75 (50% EtOAc/hexanes); IR (thin film) ν 1771, 1643 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): δ 5.91 (ddd, J = 17.4, 10.4, 7.1 Hz, 1H), 5.55-5.35 (m, 2H), 4.95 (dd, J = 6.9, 3.9 Hz, 1H), 4.85 (*app* s, 1H), 4.51-4.47 (m, 1H), 3.27 (s, 3H), 3.09-3.04 (m, 1H), 2.80 (dd, J = 18.6, 11.2 Hz, 1H), 2.5 (dd, J = 18.5, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 175.4, 131.2, 119.7, 109.2, 84.0, 80.6, 54.8, 45.9, 31.9; HRMS: m/z calcd for $C_8H_{11}O_4$ ($M+1^+$): 185.0814, found: 185.0806.



3.8

7-(Di-*tert*-butyl-trimethylsilyoxy)silyoxy-5,10,11-trioxa-tricyclo[6.2.1.0]undecan-one (3.8). To a solution of cyclopropane **2.5a** (450 mg, 1.4 mmol) in CH_2Cl_2 (10 mL) at rt was added TMSOTf (400 μL, 2.1 mmol, 1.5 eq). After stirring at rt for 10 h saturated aqueous $NaHCO_3$ (5 mL) was added to the reaction solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layer was washed with H_2O (2 × 8 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution afforded the title compound as a colorless syrup (515 mg,

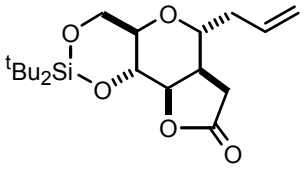
90%): R_f 0.65 (33% EtOAc/hexanes); IR (thin film) ν 1790 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.41 (s, 1 H), 4.57 (dd, *J* = 5.8, 1.3 Hz, 1H), 4.41 (ddd, *J* = 4.8, 1.3, 1.3 Hz, 1H), 4.07 (s, 1H), 3.87 (dd, *J* = 7.5, 1.3 Hz, 1H), 3.68 (dd, *J* = 7.5, 5.8 Hz, 1H), 2.68 (ddd, *J* = 8.5, 6.0, 2.5 Hz, 1H), 2.62 (dd, *J* = 17.0, 8.5 Hz, 1H), 2.45 (d, *J* = 17.0 Hz, 1H), 1.00 (s, 9H), 0.97 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 174.9, 100.7, 79.3, 76.2, 67.5, 64.2, 36.3, 31.2, 27.4, 27.3, 20.6, 20.4, 2.1; HRMS m/z calcd for $C_{19}H_{37}O_6Si_2$ $[M+H]^+$ 417.2129, found: 417.2141.



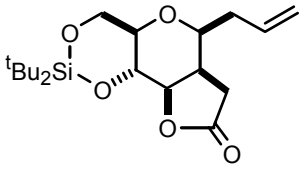
3.9

8,8-Di-*tert*-butyl-4-methoxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.9). To a solution of **3.8** (380 mg, 0.91 mmol) in THF (8 mL) at 0 °C was added Bu_4NF (4.0 mL × 1 M, 4.0 mmol, 4.5 eq). After stirring at rt for 3 h additional THF (10 mL) was added in to the reaction mixture and the resulting solution was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), H_2O (2 × 8 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution afforded the title compound as a colorless syrup (142 mg, 84%): R_f 0.32 (50% EtOAc/hexanes); IR (thin film) ν 3650-3250, 1779, 1760 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.40 (s, 1H), 4.61 (ddd, *J* = 4.4,1.5, 1.5 Hz, 1H), 4.46-4.44 (m, 1H), 3.96 (dd, *J* = 8.0, 1.2 Hz, 2H), 3.75 (dd, *J* = 8.0, 6.0 Hz, 1H),

2.68-2.56 (m, 2H), 2.49-2.45 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.5, 101.0, 78.3, 75.6, 66.5, 64.4, 36.2, 31.2; HRMS m/z calcd for $C_8H_{11}O_5$ $[M+H]^+$ 187.0606, found: 187.0607.



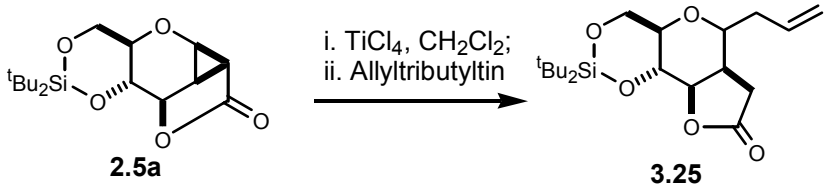
3.25(*α*)



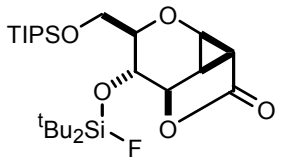
3.25(*β*)

4-Allyl-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalen-2-one (3.25(α) and 3.25(β)). To a solution of the cyclopropane **2.5a** (250 mg, 0.76 mmol) in CH_2Cl_2 (5 mL) at rt was added $TiCl_4$ (82 μL, 1.7 eq). The mixture was stirred at rt for 1.0-1.5 h until TLC indicated complete consumption of starting material. To the dark brown solution was added allyltrimethylsilane (480 μL, 3.05 mmol, 4.0 eq). The resulting mixture was stirred for 2 h and then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic solution was washed with H_2O (2 × 4 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title products as colorless syrups: **3.25(*α*)**(232 mg, 63%): R_f 0.62 (25% EtOAc/hexanes); IR (thin film) ν 1783 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.84-5.70 (m, 1H), 5.19-5.12 (m, 2H), 4.49 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.22 (ddd, *J* = 5.1, 5.1, 5.1 Hz, 1H), 3.90-3.76 (m, 3H), 3.32 (ddd, *J* = 10.2, 10.2, 5.1 Hz, 1H), 2.89-2.78 (m, H), 2.56 (dd, *J* = 16.9, 13.1 Hz, 1H),

2.45-2.37 (m, 2H), 2.10 (ddd, *J* = 14.6, 7.4, 7.4 Hz, 1H), 1.06 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 175.4, 133.1, 118.4, 81.4, 75.9, 72.5, 66.8, 66.6, 38.8, 37.1, 32.0, 27.4, 27.0, 22.7, 19.9; HRMS m/z calcd for $C_{19}H_{33}O_5Si$ $[M+H]^+$ 369.2097, found: 369.2096; **3.25(*β*)**(44 mg, 16 %): R_f 0.69 (25% EtOAc/hexanes); IR (thin film) ν 1779, 1709, 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.84-5.70 (m, 1H), 5.19-5.12 (m, 2H), 4.49 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.22 (ddd, *J* = 5.1, 5.1, 5.1 Hz, 1H), 3.90-3.76 (m, 3H), 3.32 (ddd, *J* = 10.2, 10.2, 5.1 Hz, 1H), 2.89-2.78 (m, H), 2.56 (dd, *J* = 16.9, 13.1 Hz, 1H), 2.45-2.37 (m, 2H), 2.10 (ddd, *J* = 14.6, 7.4, 7.4 Hz, 1H), 1.06 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 175.9, 133.1, 118.5, 82.9, 76.4, 75.7, 74.1, 66.5, 40.9, 37.9, 28.4, 27.6, 27.2, 23.0, 20.2; HRMS m/z calcd for $C_{19}H_{33}O_5Si$ $[M+H]^+$ 369.2097, found: 369.2100.

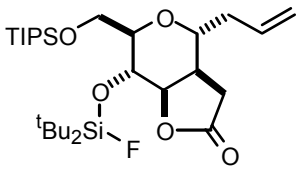


The title compounds were prepared from **2.5a** according to the general procedure described above for the preparation of **3.25,** except that 1.5 equivalents of alltyltributyltin was used (colorless syrups): **3.25(*α*)** (156 mg, 76%); **3.25(*β*)** (20 mg, 11 %).



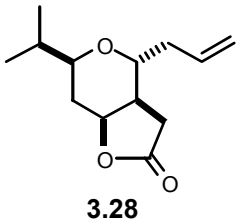
3.26

5-Di-*tert*-butyl-fluoro-silanyloxy)-4-triisopropylsilanyloxymethyl-hexahydro-1,3-dioxa-cyclopropa[*cd*]inden-2-one (3.26). To a rt solution of the alcohol **2.27** (189 mg, 0.54 mmol) in CH_2Cl_2 (3.0 mL) were added pyridine (0.25 mL, 3.1 mmol) and triisopropylsilyl chloride (115 μL, 0.82 mmol, 1.5 eq). The reaction mixture was stirred at rt for 20 h and then poured into saturated aqueous NH_4Cl solution (4 mL) with vigorous stirring. After 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with H_2O (2 × 3 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel using 20:1 hexanes-EtOAc for elution provided the title compound as a foamy solid (240 mg, 88%): R_f 0.75 (50% EtOAc/hexanes); IR (thin film) ν 1783 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.84 (dd, *J* = 6.2, 2.0 Hz, 1H), 4.24 (dd, *J* = 6.2, 2.0 Hz, 1H), 4.14 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.90 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.76 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.44 (ddd, *J* = 6.0, 6.0, 2.4 Hz, 1H), 2.48 (ddd, *J* = 5.8, 5.8, 5.8 Hz, 1H), 2.28 (dd, *J* = 6.2, 6.2 Hz, 1H), 1.04-1.00 (m, 39H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.4,81.8, 76.3, 67.1, 63.5, 54.5, 26.83, 26.80, 26.5, 20.9, 20.05 (d, *J* = 14.5 Hz), 20.02 (d, *J* = 14.5 Hz), 17.8, 11.8; ^{19}F NMR (300 MHz, $CHCl_3$) δ -159.3; HRMS m/z calcd for $C_{25}H_{48}O_5FSi_2$ $[M+H]^+$ 508.3024, found: 508.3014.



3.27

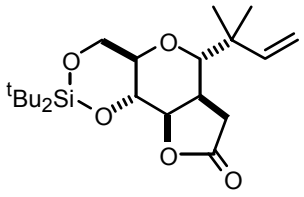
4-Allyl-7-(di-*tert*-butyl-fluoro-silanyloxy)-6-triisopropylsilanyloxymethyl-terahydro-furo[3,2-*c*] pyran-2-one (3.27). The title compounds were prepared from **3.26** according to the general procedure described above for the preparation of **3.25**. Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (142 mg, 65%): R_f 0.74 (25% EtOAc/hexanes); IR (thin film) ν 1716 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 5.87-5.73 (m, 1H), 5.15-5.03 (m, 2H), 4.56 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.38 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.96 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.87 (dd, *J* = 14.4, 6.4 Hz, 1H), 3.75-3.62 (m, 2H), 2.65-2.44 (m, 2H), 2.44-2.23(m, 3H), 1.07-1.02 (m, 39H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.4, 133.5, 118.0, 81.3, 75.8, 71.6, 68.0, 62.3, 37.9, 37.8, 32.5, 27.0, 26.9 (d, *J* = 15.3 Hz), 20.2 (d, *J* = 15.3 Hz), 18.0, 17.9, 11.9; ^{19}F NMR (300 MHz, $CHCl_3$) δ -157.8; HRMS m/z calcd for $C_{28}H_{54}O_5FSi_2$ $[M+H]^+$ 545.3491, found: 545.3494.



3.28

4-Allyl-6-isopropyl-tetrahydro-furo[3,2-*c*]pyran-2-one (3.28). The title compounds were prepared from **2.9** according to the general procedure described above for the

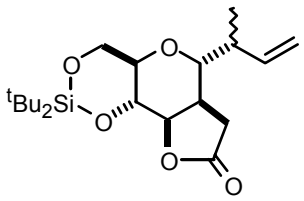
preparation of **3.25**. Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (32 mg, 60%): R_f 0.52 (33% EtOAc/hexanes); IR (thin film) ν 1759 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.85-5.75 (m, 1H), 5.11-5.07 (m, 2H), 4.73 (ddd, *J* = 9.4, 6.4, 6.4 Hz, 1H), 3.70 (ddd, *J* = 8.2, 5.4, 5.4 Hz, 1H), 3.32 (ddd, *J* = 9.6, 7.8, 4.0 Hz, 1H), 2.56-2.42 (m, 2H), 2.38-2.30 (m, 1H), 2.27-2.20 (m, 1H), 2.07 (ddd, *J* = 13.7, 5.8, 4.1 Hz, 1H), 1.78 (dddd, *J* = 6.8, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 1.67-1.51 (m, 2H), 0.86 (dd, *J* = 6.7, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 176.2, 134.0, 117.7, 76.3, 74.1, 71.7, 38.0, 37.9, 31.8, 31.7, 29.7, 18.7, 18.5; HRMS m/z calcd for $C_{13}H_{21}O_3$ $[M+H]^+$ 225.1491, found: 225.1491.



3.29

4-(1,1-Dimethyl-allyl)-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalen-2-one (3.29). The title compounds were prepared from **2.5a** according to the general procedure described above for the preparation of **3.25**, except that 3.0 equivalents of prenyltrimethylsilane was used. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (68 mg, 71%): R_f 0.65 (25% EtOAc/hexanes); IR (thin film) ν 1765 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.86 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.09-5.05 (m, 2H), 4.52 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.09-4.06 (m, 1H), 3.91 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.74-3.70 (m, 2H), 3.45 (d, *J* = 4.8 Hz, 1H), 2.98-2.90 (m, 2H), 1.00 (s, 9H), 0.99 (s,

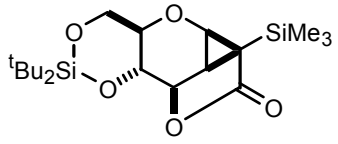
3H), 0.94 (s, 9H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.4, 144.2, 113.9, 82.2, 81.3, 75.1, 68.9, 66.6, 41.8, 35.7, 33.9, 27.3, 26.9, 26.0, 22.7, 22.6, 19.9; HRMS m/z calcd for $C_{21}H_{37}O_5Si$ $[M+H]^+$ 397.2410, found: 397.2394.



3.30

4-(1-Methyl-allyl)-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalen-2-one (3.30). The title compounds were prepared from **2.5a** according to the general procedure described above for the preparation of **3.25**, except that 3.0 equivalents of crotyltrimethylsilane was used. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compounds as a colorless syrup: **Diastereomer A** (41 mg, 40%): R_f 0.60 (15% EtOAc/hexanes); IR (thin film) ν 1761 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.56 (ddddd, *J* = 10.1, 10.1, 10.1, 10.1, 1.4 Hz, 1H), 5.15-5.08 (m, 2H), 4.45 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.10 (ddd, *J* = 10.0, 5.0, 1.8 Hz, 1H), 3.87-3.78 (m, 2H), 3.48 (dd, *J* = 10.0, 1.4 Hz, 1H), 3.44-3.37 (m, 1H), 3.01-2.94 (m, 1H), 2.59-2.43 (m, 3H), 1.02 (d, *J* = 6.3 Hz, 3H), 1.01 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.5, 140.1, 117.1, 81.2, 76.8, 75.7, 66.7, 66.6, 40.0, 37.1, 32.4, 27.4, 26.9, 22.7, 19.9, 16.6; **Diastereomer B** (39 mg, 39%): R_f 0.64 (15% EtOAc/hexanes); IR (thin film) ν 1768 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.75-5.66 (m, 1H), 5.08-5.00 (m, 2H), 4.52 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.03 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.96 (d, *J* = 10.4, 7.8 Hz, 1H), 3.75 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.55-3.47 (m, 2H), 2.86 (dddd, *J* = 9.2, 9.2,

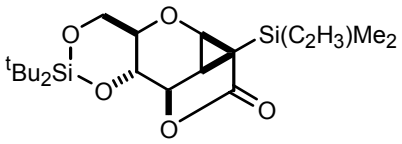
9.2, 4.8 Hz, 1H), 2.57 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.47 (d, *J* = 18.0, 10.0 Hz, 1H), 2.46-2.37 (m, 1H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.01 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.5, 139.0, 115.8, 82.1, 76.5, 75.7, 67.0, 66.6, 40.4, 37.2, 30.9, 27.3, 27.0, 22.6, 19.9, 18.0.



3.31a

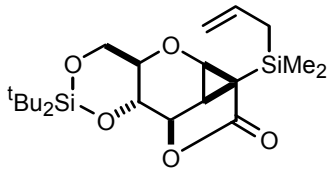
6,6-Di-*tert*-butyl-2a-trimethylsilanyl-hexahydro-1,3,5,7,-tetraoxa-6-silabenzo[*g*] cyclopropa[*cd*]inden-2-one (3.31a). To a solution of cyclopropane **2.5a** (350 mg, 1.1 mmol) in THF (6 mL) at –78 °C was added trimethyl chlorosilane (191 μL, 1.5 mmol, 1.4 eq) followed by LDA (275 μL × 0.8 M, 2.2 mmol, 2.0 eq). After stirring at –78 °C for 5 min saturated aqueous $NaHCO_3$ solution (5 mL) was added to the reaction solution. The resulting mixture was allowed to warm to room temperature and the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 3 mL). The combined organic layers were washed with H_2O (2 × 2 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 50:1 hexanes-EtOAc for elution afforded the title compound as a colorless needles (409 mg, 96%): R_f 0.64 (20% EtOAc/hexanes); IR (thin film) ν 1759, 1713 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.85 (d, *J* = 6.1 Hz, 1H), 4.28 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.17 (d, *J* = 5.4 Hz, 1H), 3.97 (d, *J* = 9.5 Hz, 1H), 3.82 (dd, *J* = 10.8, 9.5 Hz, 1H), 3.51 (ddd, *J* = 9.5, 5.4, 5.4, 5.4 Hz, 1H), 2.44 (dd, *J* = 5.8, 5.8 Hz, 1H), 1.05 (s, 9H), 1.01 (s, 9H), 0.14 (s, 9 H);

^{13}C NMR (75 MHz, $CHCl_3$) δ 173.2, 77.7, 76.3, 74.3, 66.9, 62.5, 28.3, 27.3, 27.1, 26.2, 22.5, 20.1, -3.2; HRMS m/z calcd for $C_{19}H_{35}O_5Si$ $[M+H]^+$ 399.2023, found: 399.2024.



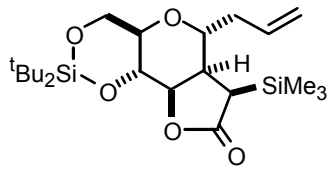
3.31b

6,6-Di-*tert*-butyl-2a-(dimethyl-vinyl-silanyl)-hexahydro-1,3,5,7-tetraoxa-6-sila-benzo[g] cyclopropa[*cd*]inden-2-one (3.31b). The title compound was prepared from **2.5a** according to the procedure described above for the preparation of **3.31a**, except that 1.6 equivalents of vinyldimethylchlorosilane was used. Purification by flash chromatography on silica gel with 50:1 hexanes-EtOAc for elution gave the title compound as an syrup y solid (1.71 g, 97%): R_f 0.55 (25% EtOAc/hexanes); IR (thin film) ν 1761 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 6.10-5.96 (m, 2H), 5.88 (dd, *J* = 18.4, 5.6 Hz, 1H), 4.85 (d, *J* = 5.9 Hz, 1H), 4.28 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.16 (d, *J* = 5.4 Hz, 1H), 3.96 (d, *J* = 9.5 Hz, 1H), 3.81 (dd, *J* = 10.2, 10.2 Hz, 1H), 3.49 (ddd, *J* = 10.2, 10.2, 5.4 Hz, 1H), 2.45 (dd, *J* = 5.6, 5.6 Hz, 1H), 1.04 (s, 9H), 1.00 (s, 9H), 0.27 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 173.4, 135.3, 134.5, 78.0, 76.5, 74.6, 67.2, 62.8, 28.0, 27.6, 27.4, 26.5, 22.8, 20.4, -4.6, -4.7; HRMS m/z calcd for $C_{20}H_{35}O_5Si_2$ $[M+H]^+$ 411.2023, found: 411.2022.



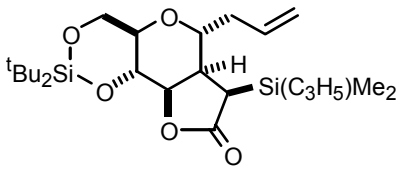
3.31c

2a-(Allyl-dimethyl-silanyl)-6,6-di-*tert*-butyl-hexahydro-1,3,5,7,-tetraoxa-6-sila-benzo[*g*] cyclopropa[*cd*]inden-2-one (3.31c). The title compound was prepared from **2.5a** according to the procedure described above for the preparation of **3.31a**, except that 1.6 equivalents of allyldimethylchlorosilane was used. Purification by flash chromatography on silica gel with 50:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (178 mg, 93%): R_f 0.73 (25% EtOAc/hexanes); IR (thin film) ν 1759, 1627 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 5.85-5.70 (m, 1H), 4.96-4.89 (m, 2H), 4.28 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.17 (d, *J* = 5.4 Hz, 1H), 3.96 (d, *J* = 9.5 Hz, 1H), 3.81 (dd, *J* = 10.8, 9.9 Hz, 1H), 3.50 (ddd, *J* = 10.8, 9.5, 5.4 Hz, 1H), 2.45 (dd, *J* = 5.8, 5.8 Hz, 1H), 1.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 1.04 (s, 9H), 1.00 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 173.4, 133.6, 114.6, 78.0, 76.6, 74.6, 67.2, 62.6, 27.8, 27.6, 27.4, 26.4, 22.7, 21.6, 20.4, -4.8, -4.9; HRMS m/z calcd for $C_{21}H_{37}O_5Si_2$ $[M+H]^+$ 425.2180, found: 425.2178.



3.32a

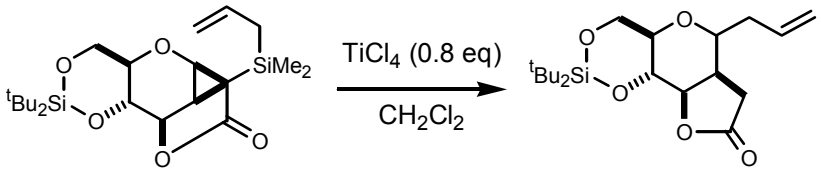
4-Allyl-8,8-di-*tert*-butyl-3-trimethylsilanyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalen-2-one (3.32a). The title compound was prepared from **3.31a** according to the procedure described above for the preparation of **3.25**. Purification by flash chromatography on silica gel with 50:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (68 mg, 72%): R_f 0.52 (25% EtOAc/hexanes); IR (thin film) ν 1751 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 5.83-5.69 (m, 1H), 5.18 (s, 1H), 5.13 (dd, *J* = 7.4, 1.5 Hz, 1H), 4.52 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.18-4.08 (m, 2H), 3.88 (ddd, *J* = 11.2, 11.2, 8.2 Hz, 1H), 3.55 (ddd, *J* = 10.2, 10.2, 5.1 Hz, 1H), 3.09 (dd, *J* = 11.0, 8.5 Hz, 1H), 2.58 (ddd, *J* = 14.8, 7.4, 7.4 Hz, 1H), 2.37 (d, *J* = 11.0 Hz, 1H), 2.35 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 1.05 (s, 9H), 1.02 (s, 9H), 0.28 (s, 9 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 178.5, 133.8, 118.4, 79.9, 75.8, 71.8, 67.0, 66.1, 42.3, 37.4, 35.7, 27.6, 27.2, 22.7, 20.2, 0.0; HRMS m/z calcd for $C_{22}H_{41}O_5Si_2$ $[M+H]^+$ 441.2493, found: 441.2493.



3.32b

4-Allyl-8,8-di-*tert*-butyl-3-(dimethyl-vinyl-silanyl)-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalen-2-one (3.32b). The title compound was prepared from **3.31b**

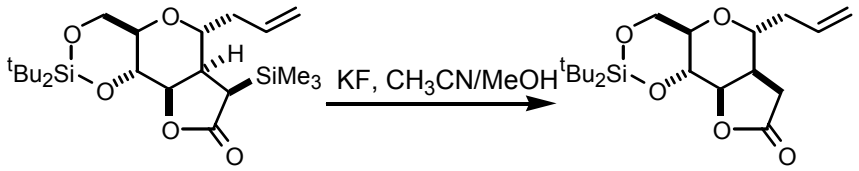
according to the procedure described above for the preparation of **3.25**. Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title compound as white solid (156 mg, 70%): R_f 0.50 (25% EtOAc/hexanes); IR (thin film) ν 1758 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 6.25 (dd, *J* = 20.0, 14.6 Hz, 1H), 6.07 (dd, *J* = 14.6, 3.8 Hz, 1H), 5.82 (dd, *J* = 20.0, 3.8 Hz, 1H), 5.81-5.67 (m, 1H), 5.16 (s, 1H), 5.12 (d, *J* = 8.2 Hz, 1H), 4.49 (dd, *J* = 8.2, 8.2 Hz, 1H), 4.16 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.07 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.95 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.84 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.52 (ddd, *J* = 10.0, 10.0, 5.1 Hz, 1H), 3.06 (dd, *J* = 10.7, 8.6 Hz, 1H), 2.55 (ddd, *J* = 14.7, 7.7, 7.7 Hz, 1H), 2.40 (d, *J* = 11.0 Hz, 1H), 2.31 (ddd, *J* = 14.3, 7.0, 7.0 Hz, 1H), 1.04 (s, 9H), 1.00 (s, 9H), 0.37 (s, 3 H), 0.35 (s, 3 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 178.2, 136.5, 135.0, 133.8, 118.4, 80.1, 75.6, 71.6, 66.9, 66.2, 42.2, 37.4, 35.5, 27.6, 27.3, 22.7, 20.2, -1.7, -2.4; HRMS m/z calcd for $C_{23}H_{41}O_5Si_2$ $[M+H]^+$ 453.2493, found: 453.2498.



3.31c **3.25**

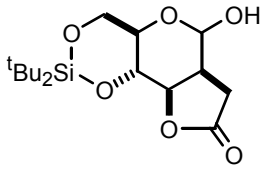
To a solution of starting cyclopropane **3.31c** (130 mg, 0.31 mmol) in CH_2Cl_2 (7 mL) at rt was added $TiCl_4$ (27 μL, 0.25 mmol, 0.8 eq). The mixture was stirred at rt for 3.5 h until TLC indicated complete consumption of starting material. The reaction solution was then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL). The combined organic solution was washed with H_2O (2 × 4 mL), brine (5 mL) and dried

($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title products as colorless syrups: **3.25(*α*)**(65 mg, 58%); **3.25(*β*)**(22 mg, 19 %).



3.32a(*α*) **3.25**(*α*)

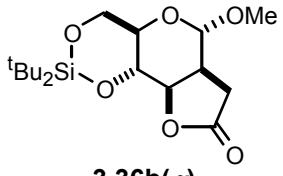
To a solution of **3.32(*α*)**(310 mg, 0.70 mmol) in CH_3CN (4 mL) and MeOH (2 mL) was added KF (204 mg, 3.5 mmol, 5.0 eq). The mixture was stirred at rt for 30 min. The organic solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL). The resulting solution was washed with H_2O (2 × 2 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution afforded the title compound as a colorless syrup (251 mg, 97%).



3.36a

8,8-Di-*tert*-butyl-4-hydroxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36a). To a solution of cyclopropane **2.5a** (250 mg, 0.77 mmol) in Et_2O (13 mL) at rt was added $TiCl_4$ (138 μL, 1.27 mmol, 1.7 eq). The mixture was stirred at rt for 2.5-3.0 h until TLC indicated complete consumption of starting material. The dark brown solution was then quickly poured into saturated aqueous $NaHCO_3$ (5 mL). After stirring for 20 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 8 mL). The combined organic solution was washed with H_2O (2 × 8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution afforded the title compound as an inseparable mixture of two diastereomers (colorless syrup, 237 mg, 90%): R_f 0.51 (50% EtOAc/hexanes); IR (thin film) ν 3600-3250, 1763, 1709 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.26 (d, *J* = 3.0 Hz, 1H), 5.17 (dd, *J* = 3.8, 3.8 Hz, 0.44H), 4.64 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.53 (dd, *J* = 7.7, 7.7 Hz, 0.44H), 4.16 (dd, *J* = 10.2, 4.8 Hz, 0.44H), 4.15-4.09 (m, 2H), 4.07 (d, *J* = 3.1 Hz, 0.44H), 4.01 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.89-3.86 (m, 0.44H), 3.73 (d, *J* = 4.1 Hz, 0.44H), 3.44 (ddd, *J* = 10.2, 10.2, 5.1 Hz, 0.44H), 3.24 (d, *J* = 3.1 Hz, 1H), 3.01 (m, 1H), 2.96 (dd, *J* = 21.9, 8.5 Hz, 1H), 2.67-2.61 (m, 0.88H), 2.60-2.50 (m, 2H), 1.82 (s, 1 H), 1.05 (s, 13.0 H), 1.01 (s, 13.0 H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.3 (minor), 174.5, 93.1 (minor), 91.8, 82.2 (minor), 80.8, 75.7, 75.5 (minor), 69.3 (minor), 66.5 (minor),

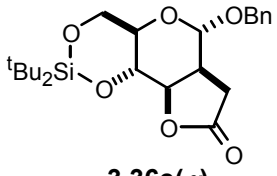
66.4, 64.0, 41.4, 40.7 (minor), 31.3, 28.9 (minor), 27.7, 26.7 (minor), 27.3, 23.1, 20.3; HRMS m/z calcd for $C_{16}H_{29}O_6Si$ $[M+H]^+$ 345.1733, found: 345.1736.



3.36b(*α*)

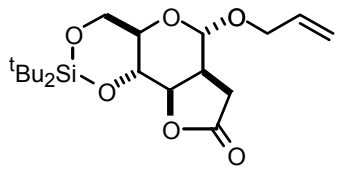
8,8-Di-*tert*-butyl-4-methoxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36b(α)). To a solution of cyclopropane **2.5a** (199 mg, 0.61 mmol) in Et_2O (10 mL) at rt was added $TiCl_4$ (108 μL, 1.7 eq). The mixture was stirred at rt for about 2.5-3.0 h until TLC indicated complete consumption of starting material. To the dark brown solution was then added MeOH (250 μL, 6.1 mmol, 10 eq) immediately followed by triflic acid (100 μL × 3 M in Et_2O, 0.5 eq). The resulting mixture was stirred for 30 min and then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 8 mL). The combined organic solution was washed with H_2O (2 × 8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (173 mg, 78%): R_f 0.71 (50% EtOAc/hexanes); IR (thin film) ν 1783, 1713 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 4.64 (d, *J* = 3.5 Hz, 1H), 4.50 (dd, *J* = 6.8, 6.8 Hz, 1H), 4.18 (dd, *J* = 10.2, 5.1 Hz, 1H), 4.13-4.07 (m, 1H), 3.87 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.48-3.42 (m, 1H), 3.43 (s, 3H), 2.99-2.92 (m, 1H), 2.53 (dd, *J* = 6.8, 3.5 Hz, 2H), 1.06 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.5, 100.3, 82.7, 76.1, 69.6, 67.1, 57.0, 40.3, 29.8,

28.2, 27.8, 23.6, 20.7; HRMS m/z calcd for $C_{17}H_{31}O_6Si$ $[M+H]^+$ 357.1890, found: 359.1890.



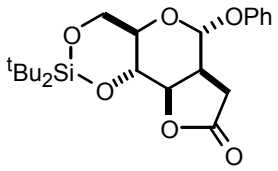
3.36c(*α*)

8,8-Di-*tert*-butyl-4-methoxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36c). The title compound was prepared from **2.5a** according to the procedure described above for the preparation of **3.36b** except that 10 equivalents of benzyl alcohol was used. Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (187 mg, 75%): R_f 0.65 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.36-7.26 (m, 5H), 4.80-4.77 (m, 2H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.50 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.18 (dd, *J* = 12.2, 10.6 Hz, 1H), 4.17 (d, *J* = 10.3 Hz, 1H), 3.83 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.43 (ddd, *J* = 10.2, 10.2, 5.3 Hz, 1H), 2.94 (dddd, *J* = 8.6, 8.6, 8.6, 3.4 Hz, 1H), 2.55 (d, *J* = 8.9 Hz, 2H), 1.02 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.7, 136.9, 128.5, 128.0, 127.8, 97.4, 82.2, 75.5, 70.0, 69.2, 66.6, 39.4, 29.1, 27.4, 26.9, 22.7, 19.8; HRMS m/z calcd for $C_{23}H_{35}O_6Si$ $[M+H]^+$ 435.2203, found: 435.2202.



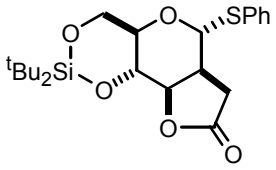
3.36d(*α*)

4-Allyoxy-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36d). The title compound was prepared from **2.5a** according to the procedure described above for the preparation of **3.36b**, except that 15 equivalents of allyl alcohol was used. Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as white solid (310 mg, 84%): R_f 0.61 (50% EtOAc/hexanes); IR (thin film) ν 1775, 1713 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.92-5.82 (m, 1H), 5.29 (dddd, *J* = 17.1, 1.6, 1.6, 1.6 Hz, 1H), 5.22 (dddd, *J* = 10.3, 1.3, 1.3, 1.3 Hz, 1H), 4.82 (s, 1H), 4.59 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.14 (dddd, *J* = 13.0, 5.3, 1.4, 1.4 Hz, 1H), 4.11 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.97 (dddd, *J* = 12.9, 6.2, 1.3, 1.3 Hz, 1H), 3.87 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.80 (dd, *J* = 9.9, 7.8 Hz, 1H), 3.81-3.73 (m, 1H), 2.94 (ddd, *J* = 13.4, 8.6, 8.6 Hz, 1H), 3.53 (dd, *J* = 17.1, 9.0 Hz, 1H), 2.47 (dd, *J* = 17.1, 13.6 Hz, 1H), 1.07 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.1, 132.8, 117.8, 96.2, 80.9, 75.7, 68.2, 66.3, 64.0, 41.4, 31.3, 27.7, 27.3, 23.1, 20.3; HRMS m/z calcd for $C_{19}H_{33}O_6Si$ $[M+H]^+$ 385.2045, found: 385.2046.

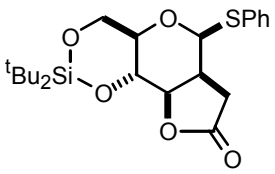


3.36e(*α*)

4-Allyoxy-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36e(α)). The title compound was prepared from **2.5a** according to the procedure described above for the preparation of **3.36b**, except that 8.0 equivalents of phenol solution in 0.5 mL of Et_2O was used. Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (180 mg, 80%): R_f 0.65 (50% EtOAc/hexanes); IR (thin film) ν 1779, 1713, 1661, 1592 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.30-7.26 (m, 2H), 7.04 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 2H), 5.43 (d, *J* = 3.4 Hz, 1H), 4.66 (dd, *J* = 7.4, 7.4 Hz, 1H), 4.38 (dd, *J* = 10.2, 6.8 Hz, 1H), 4.18 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.84 (dd, *J* = 10.1. 10.1 Hz, 1H), 3.66 (ddd, *J* = 10.2, 10.2, 4.8 Hz, 1H), 3.19-3.12 (m, 1H), 2.71(dddd, *J* = 17.0, 17.0, 17.0, 8.5 Hz, 2H), 1.06 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.7, 155.7, 129.2, 122.6, 116.3, 96.9, 81.9, 75.3, 69.4, 66.7, 39.1, 29.9, 27.7, 27.3, 23.1, 20.3; HRMS m/z calcd for $C_{22}H_{33}O_6Si$ $[M+H]^+$ 421.2046, found: 421.2045.



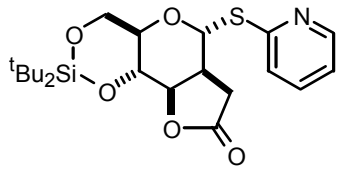
3.36e(α)



3.36e(β)

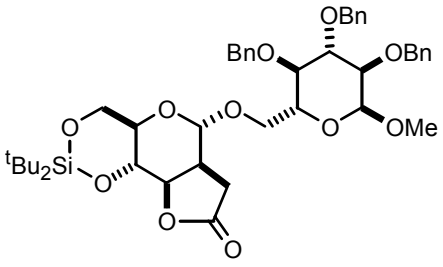
8,8-Di-*tert*-butyl-4-phenylsulfanyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36e(α) and 3.36e(β)). To a solution of cyclopropane **2.5a** (190 mg, 0.58 mmol) in CH_2Cl_2 (6 mL) at rt was added $TiCl_4$ (103 μL, 0.96 mmol, 1.7 eq). The mixture was stirred at rt for 2.0-2.5 h until TLC indicated complete consumption of starting material. To the dark brown solution was added benzenethiol (474 μL, 4.6 mmol, 8.0 eq) immediately followed by triflic acid (100 μL × 3 M in Et_2O, 0.5 eq). The resulting

mixture was stirred for 2.0 h and then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solution was washed with H_2O (2 × 8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title products as colorless syrups: **3.36e(β)** (184 mg, 73%): R_f 0.71 (25% EtOAc/hexanes); IR (thin film) ν 1779, 1732, 1580 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.56-7.41 (m, 2H), 7.36-7.29 (m, 3H), 5.06 (d, *J* = 3.4 Hz, 1H), 4.48 (dd, *J* = 7.8, 7.8, 1H), 4.20 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.95 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.88 (dd, *J* = 9.9, 7.8 Hz, 1H), 3.34 (ddd, *J* = 10.2, 5.1, 5.1 Hz, 1H), 3.24-3.16 (m, 1H), 2.76 (dd, *J* = 7.1, 3.0 Hz, 1H), 2.59 (dd, *J* = 17.1, 8.2 Hz, 1H), 1.06 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.0, 132.6, 131.3, 128.8, 127.8, 84.2, 82.3, 75.5, 73.6, 65.9, 42.0, 29.0, 27.7, 27.3, 23.1, 20.3; HRMS m/z calcd for $C_{22}H_{33}O_5SiS$ $[M+H]^+$ 437.1818, found: 437.1815; **3.36e(*α*)** (46 mg, 18%): R_f 0.60 (25% EtOAc/hexanes); IR (thin film) ν 1783, 1736 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.42-7.38 (m, 2H), 7.34-7.27 (m, 3H), 5.50 (s, 1H), 4.61 (dd, *J* = 7.9, 7.9 Hz, 1 H), 4.33 (ddd, *J* = 10.2, 10.2, 5.1, 1H), 4.00 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.90-3.81 (m, 2H), 3.08 (ddd, *J* = 10.6, 7.9, 0.8 Hz, 1H), 2.63 (d, *J* = 10.6 Hz, 2H), 1.04 (s, 18H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.2, 132.8, 132.2, 129.3, 128.3, 84.1, 81.1, 76.5, 66.5, 65.8, 42.2, 33.2, 28.2, 27.8, 23.6, 20.9; HRMS m/z calcd for $C_{22}H_{33}O_5SiS$ $[M+H]^+$ 437.1818, found: 437.1819.



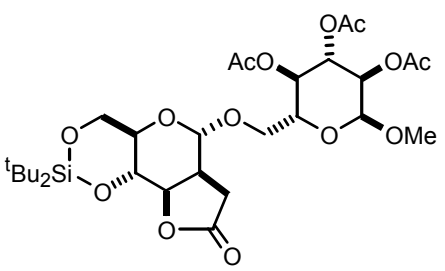
3.36f(α)

8,8-Di-*tert*-butyl-4-phenylsulfanyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (3.36f(α)). The title compound was prepared from **2.5a** according to the procedure described above for the preparation of **3.36e**, except that 6.3 equivalents of 2-mercaptopyridine was used. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as foamy solid (301 mg, 70%): R_f 0.66 (25% EtOAc/hexanes); IR (thin film) ν 1782, 1709, 1577, 1556 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.47 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.55 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 1H), 7.23 (d, *J* = 12.6 Hz, 1H), 7.08 (ddd, *J* = 5.3, 4.8, 1.0 Hz, 1H), 6.40 (s, 1H), 4.61 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.14-4.07 (m, 2H), 4.02 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.94-3.83 (m, 2H), 3.23-3.15 (m, 2H), 1.05 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.8, 154.8, 149.3, 136.4, 123.2, 120.7, 80.7, 80.2, 75.9, 67.0, 66.1, 42.3, 32.8, 27.6, 27.3, 23.1, 20.4; HRMS m/z calcd for $C_{22}H_{32}O_5NSSi$ $[M+H]^+$ 438.1770, found: 438.1762.

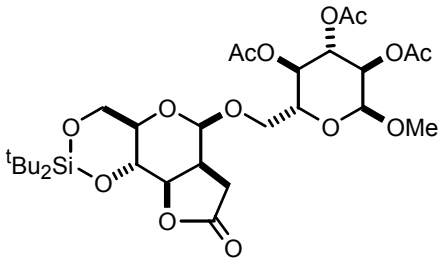


3.38a(α)

8,8-Di-*tert*-butyl-4-(3,4,5-tribenzyloxy-6-methoxyl-tetrahydro-pyran-2-ylmethoxy)-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalene-2-one (3.38a(α)). To a 10-mL round-bottomed flask containing **3.36e(α)** (156 mg, 0.36 mmol) was added N-iodosuccinimide (164 mg, 0.73 mmol, 1.5 eq) and freshly activated molecular sieves (3 Å, 250 mg). The flask was sealed with a rubber septum, flushed with argon and treated with Et_2O (6 mL). After cooled to –35 °C the solution was sequentially treated with **3.37**[99] (288 mg, 0.59 mmol, 1.2 eq, pre-dissolved in 2 mL of Et_2O) and triflic acid (100 μL × 1M in Et_2O, 0.2 eq). After 50 min the glycosylation was complete (TLC) and Et_3N (70 μL, 0.50 mmoL, 1.0 eq) was added. The resulting mixture was stirred for 5 min and poured into saturated aqueous $NaHCO_3$ (5 mL). After 10 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 8 mL). The combined organic solution was washed with H_2O (2 × 8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Flash chromatography on silica gel with 10:1 pentanes-Et_2O for elution afforded the title compound as a colorless syrup (173 mg, 62%): R_f 0.41 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.36-7.23 (m, 15H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.52-4.48 (m, 2H), 4.06 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.98 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.85-3.70 (m, 6H), 3.60 (dd, *J* = 16.0, 4.1 Hz, 1H), 3.48 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.40 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.33 (s, 3H), 2.89 (ddd, *J* = 13.2, 8.3, 8.3 Hz, 1H), 2.55-2.40 (m, 2H), 1.01 (s, 9H), 0.91 (s, 9H); HRMS m/z calcd for $C_{44}H_{57}O_{11}Si$ $[M-H]^+$ 789.3670, found: 789.3666.



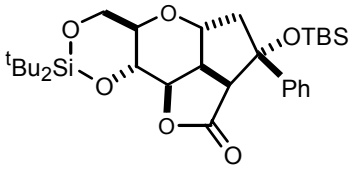
3.38b(α)



3.38b(β)

8,8-Di-*tert*-butyl-4-(3,4,5-triacetoxy-6-methoxyl-tetrahydro-pyran-2-ylmethoxy)-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalene-2-one (3.38b(α) and 3.38b(β)). To a solution of crude **3.38a** (190 mg, 0.24 mmol) in ethanol (2.5 mL) at rt was added 5% Pd-C (ca. 6 mg). The reaction mixture was stirred under hydrogen atmosphere (balloon) for 2 h and then filtered though a pad of celite. Removal of the solvent under reduced pressure gave the debenzylated product as a colorless syrup . The crude product was immediately dissolved in CH_2Cl_2 (5 mL) and the solution was treated sequentially with pyridine (100 μL, 1.1 mmoL) and Ac_2O (250 μL, 2.7 mmol). After 15 h at rt the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL). After stirring for 20 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic solution was washed with NH_4Cl solution (4 mL), H_2O (2 × 8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Flash chromatography on silica gel with 5:1 pentanes-Et_2O for elution afforded the title products as colorless syrups: **3.38b(α)** (95, 61%): R_f 0.36 (50% EtOAc/hexanes); IR (thin film) ν 1775, 1751,1709 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.46 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.98 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.87-4.80 (m, 3H), 4.53 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.10-4.07 (m, 1H), 3.92 (ddd, *J* = 10.2, 5.8, 2.0 Hz, 1H), 3.85-3.75 (m, 3H), 3.68 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.46 (dd, *J* =

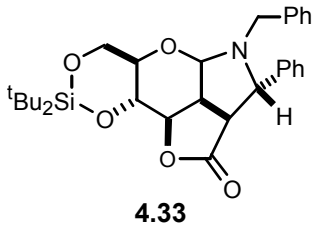
11.0, 2.0 Hz, 1H), 3.37 (s, 3H), 2.92 (ddd, *J* = 16.8, 8.7, 8.7 Hz, 1H), 2.61-2.42 (m, 2H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.02 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.7, 170.2, 170.1, 169.5, 97.7, 96.5, 80.8, 75.6, 70.8, 70.1, 69.1, 67.9, 66.3, 65.6, 63.9, 55.3, 41.0, 30.9, 27.4, 26.9, 22.7, 20.73, 20.69, 20.65, 19.9; HRMS m/z calcd for $C_{29}H_{47}O_{14}Si$ $[M+H]^+$ 647.2735, found: 647.2732; **3.38b(β)** (20 mg, 14%): R_f 0.32 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.45 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.99-4.87 (m, 2H), 4.80 (dd, *J* = 10.2, 3.8 Hz, 1H), 4.73 (d, *J* = 3.1 Hz, 1H), 4.51 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.17-4.11 (m, 2H), 3.90-3.82 (m, 3H), 3.47-3.34 (m, 2H), 3.37 (s, 3H), 2.92 (dddd, *J* = 8.7, 8.7, 8.7, 3.1, Hz, 1H), 2.67-2.60 (m, 1H), 2.53 (dd, *J* = 17.8, 9.3 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.03 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.1, 170.1, 170.0, 169.8, 99.2, 96.5, 81.9, 75.4, 70.9, 69.9, 69.1, 69.0, 68.2, 67.2, 66.5, 55.3, 39.4, 30.3, 29.7, 27.4, 27.0, 22.8, 20.69, 20.68, 19.8; HRMS m/z calcd for $C_{29}H_{47}O_{14}Si$ $[M+H]^+$ 647.2735, found: 647.2727.



4.31

8,8-Di-*tert*-butyl-3-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-octahydro-1,5,7,9-tetraoxa-8-sila-pentaleno[1,6-*ab*]naphthalene-2-one (4.31). To a solution of **2.5a** (92 mg, 0.28 mmol) in CH_2Cl_2 (3.5 mL) at rt was added $TiCl_4$ (45 μL, 0.40 mmol, 1.5 eq). The mixture was stirred at rt for 2.0-2.5 h until TLC indicated complete consumption of starting material. To the dark brown solution was added 1-phenyl-vinyl-*tert*-butyl-dimethylsilyl ether **4.30**[172] (248 mg, 0.99 mmol, 3.5 eq). The resulting solution was

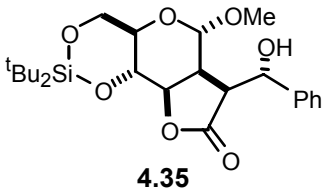
stirred for 2 min and then poured into saturated aqueous $NaHCO_3$ (2 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic solution was washed with H_2O (2 × 3 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 100:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (123 mg, 77%): R_f 0.72 (20% EtOAc/hexanes); IR (thin film) ν 1775 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.39-7.26 (m, 5H), 4.54-4.45 (m, 2H), 4.20-4.17 (m, 1H), 3.99-3.91 (m, 3H), 3.33 (ddd, *J* = 13.7, 8.2, 5.5 Hz, 1H), 3.22 (d, *J* = 8.2 Hz, 1H), 2.96 (dd, *J* = 12.0, 5.8 Hz, 1H), 2.20 (dd, *J* = 12.5, 12.5 Hz, 1H), 1.05 (s, 9H), 1.00 (s, 9 H), 0.94 (s, 9H), -0.01 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 172.0, 141.2, 127.6, 127.3, 125.8, 85.2, 80.6, 78.0, 73.4, 71.7, 67.0, 55.9, 47.0, 45.5, 27.7, 27.3, 26.4, 23.1, 20.2, 18.6, -1.8, -2.2; HRMS m/z calcd for $C_{30}H_{49}NO_5Si_2$ $[M+H]^+$ 561.3068, found: 561.3058.



4.33

4-Benzyl-8,8-di-tert-butyl-3-phenyl-octahydro-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalen-2-one (4.33). To a solution of **2.5a** (155 mg, 0.48 mmol) and the imine **4.32** (329 mg, 1.68 mmol, 3.5 eq) in CH_2Cl_2 (8.0 mL) at rt was added TMSOTf (230 μL, 1.20 mmol, 2.5 eq). The mixture was stirred at rt for 4.5 h until TLC

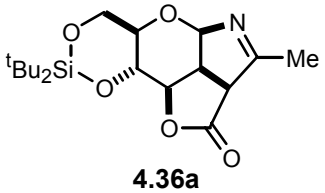
indicated complete consumption of starting material. The resulting dark solution was poured into a vigorously stirred saturated aqueous $NaHCO_3$ (15 mL). After 3 min the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 5 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 8:1 hexanes-EtOAc for elution gave the title product as a pale yellow syrup (201 mg, 82%): R_f 0.53 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.25-7.23 (m, 4H), 7.14-7.12 (m, 2H), 6.99-6.96 (m, 4H), 4.92 (d, *J* = 8.7 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 1H), 4.74 (d, *J* = 3.6 Hz, 1H), 4.67 (d, *J* = 9.3 Hz, 1H), 4.64 (t, *J* = 3.9 Hz, 1H), 4.23 (dd, *J* = 6.9, 4.2 Hz, 1H), 4.16-4.07 (m, 2H), 4.01 (t, *J* = 9.9 Hz, 1H), 3.79 (d, *J* = 14.1 Hz, 1H), 3.65 (d, *J* = 14.1 Hz, 1H), 3.40-3.29 (m, 2H), 1.07 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 194.0, 137.9, 135.4, 129.0, 128.3, 127.9, 127.7, 126.7, 88.1, 81.4, 77.7, 72.7, 68.0, 67.0, 49.9, 44.9, 43.4, 27.4, 27.0, 22.7, 19.8; HRMS m/z calcd for $C_{30}H_{40}NO_5Si$ $[M+H]^+$ 522.2676, found: 522.2660.



4.35

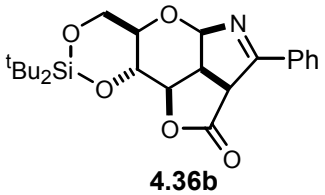
8,8-Di-tert-butyl-3-(hydroxy-phenyl-methyl)-4-methoxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[a]naphthalen-2-one (4.35). To a solution of cyclopropane **2.5a** (226 mg, 0.69 mmol) in Et_2O (10 mL) at rt was added $TiCl_4$ (121 μL, 1.7 eq). The mixture was stirred at rt for about 2.5-3.0 h until TLC indicated complete consumption of starting material. To the dark brown solution was then added benzaldehyde (700 μL, 6.9 mmol, 10 eq)

immediately. The resulting mixture was stirred for 30 min and then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic solution was washed with H_2O (2 × 8 mL), brine (8 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. To the resulting residue was added MeOH (10 mL) followed with triflic acid (114 μL × 3 M in Et_2O, 0.5 eq). After stirring at rt for 2.0 h, the resulting solution was poured into saturated aqueous $NaHCO_3$ (8 mL). The mixture was extracted with Et_2O (3× 12 mL) and the combined organic solution was washed with H_2O (2 × 8 mL), brine (8 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (173 mg, 76%): R_f 0.62 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.36-7.30 (m, 4H), 7.30-7.27 (m, 1H), 5.36 (dd, *J* = 5.5, 3.5 Hz, 1H), 4.46 (d, *J* = 7.2, 6.8 Hz, 1H), 4.37 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.10 (t, *J* = 4.8 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 1H), 3.78 (t, *J* = 10.0 Hz, 1H), 3.52 (ddd, *J* = 10.0, 10.0, 4.8 Hz, 1H), 3.23 (s, 3H), 3.01-2.95 (m, 2H), 2.81 (ddd, *J* = 8.4, 5.2, 3.6 Hz, 1H), 1.03 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 177.6, 141.1, 129.0, 128.2, 125.7, 99.7, 82.1, 74.9, 72.7, 69.4, 67.4, 55.7, 50.0, 39.4, 27.7, 27.2, 22.9, 20.0; HRMS m/z calcd for $C_{24}H_{37}O_7Si$ $[M+H]^+$ 465.2309, found: 465.2316.



4.36a

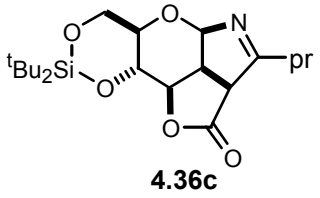
8,8-Di-*tert*-butyl-3-methyl-4a,5a,6,9a,9b,9c-hexahydro-2*aH*-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalen-2-one (4.36a). To a solution of **2.5a** (184 mg, 0.57 mmol) in CH_2Cl_2 (4 mL) at rt was added acetonitrile (370 μL, 3.7 mmol, 5.0 eq) and TMSOTf (110 μL, 0.74 mmol, 1.0 eq) sequentially. The resulting solution was stirred at rt for about 5 min and then poured into a vigorously stirred saturated aqueous $NaHCO_3$ (8 mL). After 3 min the mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (2 × 3 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification by flash chromatography on silica gel with 1:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (174 mg, 84%): R_f 0.48 (67% EtOAc/hexanes); IR (thin film) ν 1767, 1654 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.81 (dd, *J* = 3.2, 1.0 Hz, 1H), 4.68 (dd, *J* = 9.9, 6.1 Hz, 1H), 4.19 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.92 (ddd, *J* = 10.2, 10.2, 6.2 Hz, 2H), 3.88-3.83 (m, 1H), 3.54 (ddd, *J* = 10.2, 10.2, 5.2 Hz, 2H), 2.23 (d, *J* = 1.4 Hz, 3H), 1.02 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.4, 169.8, 100.2, 82.3, 75.5, 69.8, 66.5, 59.4, 38.9, 27.7, 27.2, 23.0, 20.2, 18.2; HRMS m/z calcd for $C_{18}H_{30}NO_5Si$ $[M+H]^+$ 368.1893, found: 368.1891.



4.36b

8,8-Di-*tert*-butyl-3-phenyl-4a,5a,6,9a,9b,9c-hexahydro-2*aH*-1,5,7,9-tetraoxa-4-aza-8-sila-pentalen-2-one (4.36b). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that 5.0

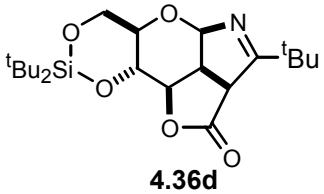
equivalents of benzonitrile were used. Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (258 mg, 81%): R_f 0.55 (50% EtOAc/hexanes); IR (thin film) ν 1763, 1705, 1612, 1577 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.15 (d, *J* = 7.2, 2H), 7.52-7.41 (m, 3H), 6.02 (d, *J* = 7.0 Hz, 1H), 4.75 (dd, *J* = 10.1, 5.6 Hz, 1H), 4.53 (d, *J* = 10.2 Hz, 1H), 4.27 (dd, *J* = 10.2, 5.0, 1H), 4.03 (dd *J* = 10.1, 5.6 Hz, 1H), 3.95 (dd, *J* = 10.1 Hz, 1H), 3.76-3.58 (m, 2H), 1.00 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 185.1, 171.0, 132.2, 129.9, 128.5, 99.9, 81.8, 75.4, 70.4, 66.7, 55.9, 39.6, 27.3, 26.9, 22.6, 19.8; HRMS m/z calcd for $C_{23}H_{32}NO_5Si$ $[M+H]^+$ 430.2050, found: 430.2057.



4.36c

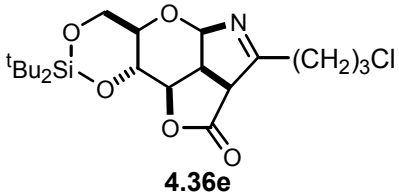
8,8-Di-*tert*-butyl-3-propyl-4a,5a,6,9a,9b,9c-hexahydro-2*aH*-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalene-2-one (4.36c). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that 10 equivalents of *n*-butyronitrile was used. Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (188 mg, 95%): R_f 0.45 (50% EtOAc/hexanes); IR (thin film) ν 1767, 1644 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.81 (dd, *J* = 6.9, 0.7 Hz, 1H), 4.65 (dd, *J* = 10.3, 6.4 Hz, 1H), 4.18 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.93-3.84 (m, 3H), 3.57-3.50 (m, 2H), 2.62-2.54 (m, 1H), 2.46-2.38 (m, 1H), 1.76-1.59 (m, 3H), 0.99 (s, 9H), 0.94 (s, 9H), 0.93 (dd, *J* = 7.2, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 172.7, 171.5,

100.2, 82.1, 75.4, 70.0, 66.6, 58.3, 38.5, 33.1, 27.3, 26.9, 22.6, 19.8, 19.2, 13.7; HRMS m/z calcd for $C_{20}H_{34}NO_5Si$ $[M+H]^+$ 396.2206, found: 396.2205.



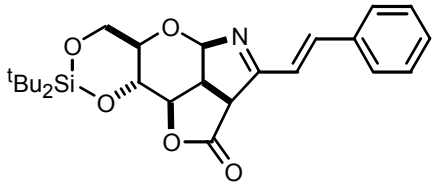
4.36d

3,8,8-Di-*tert*-butyl-4a,5a,6,9a,9b,9c-hexahydro-2*aH*-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalene-2-one 4.36d). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that 5.0 equivalents of trimethylacetonitrile was used. Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (175 mg, 79%): R_f 0.48 (50% EtOAc/hexanes); IR (thin film) ν 1767, 1629 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.76 (d, *J* = 3.5 Hz, 1H), 4.56 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.18 (dd, *J* = 10.2, 5.0 Hz, 1H), 4.00 (d, *J* = 9.6 Hz, 1H), 3.94-3.85 (m, 2H), 3.64-3.56 (m, 2H), 1.28 (s, 9H), 0.99 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 178.6, 172.1, 98.9, 80.4, 74.9, 71.0, 67.0, 56.0, 40.1, 37.2, 28.4, 27.3, 26.9, 22.6, 19.8; HRMS m/z calcd for $C_{21}H_{36}NO_5Si$ $[M+H]^+$ 410.2363, found: 410.2361.



4.36e

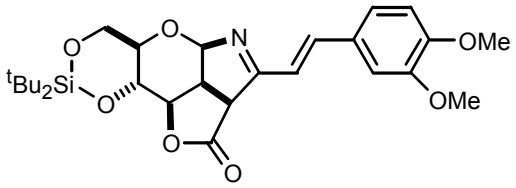
8,8-Di-*tert*-butyl-3-(3-chloro-propyl)-4a,5a,6,9a,9b,9c-hexahydro-2a*H*-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalen-2-one (4.36e). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that 7.0 equivalents of 4-chlorobutyronitrile was used. Purification by flash chromatography on silica gel with 1:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (137 mg, 87%): R_f 0.31 (50% EtOAc/hexanes); IR (thin film) ν 1770, 1649 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.84 (d, *J* = 7.2 Hz, 1H), 4.71 (dd, *J* = 10.3, 5.8 Hz, 1H), 4.20 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.93 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.89 (dd, *J* = 16.0, 10.2 Hz, 2H), 3.66-3.50 (m, 4H), 2.83 (ddd, *J* = 17.5, 7.2, 7.2 Hz, 1H), 2.66-2.57 (m, 1H), 2.27-2.08 (m, 2H), 1.01 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.8, 171.4, 100.4, 82.5, 75.5, 70.0, 66.6, 58.8, 44.1, 38.4, 28.4, 28.2, 27.3, 26.9, 22.6, 19.8; HRMS m/z calcd for $C_{20}H_{33}NO_5SiCl$ $[M+H]^+$ 430.1817, found: 430.1819.



4.36f

8,8-Di-*tert*-butyl-3-styryl-4a,5a,6,9a,9b,9c-hexahydro-2a*H*-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalen-2-one (4.36f). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that nitromethane was used as solvent and 8.0 equivalents of cinnamonitrile was employed. Purification of the residue by flash chromatography on silica gel with 4:1 to

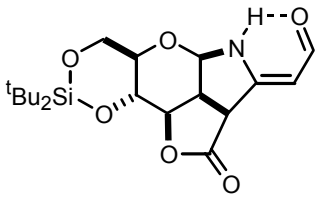
2:1 hexanes-EtOAc for elution gave the title product as a white solid (199 mg, 60%): R_f 0.63(50% EtOAc/hexanes); IR (thin film) ν 1767, 1708, 1639 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.77 (d, *J* = 16.8 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.53 (s, 1H), 7.39-7.32 (m, 3H), 7.00 (d, *J* = 16.8 Hz, 1H), 5.92 (d, *J* = 7.2 Hz, 1H), 4.71 (dd, *J* = 10.0, 6.4 Hz, 1H), 4.26 (d, *J* = 9.6 Hz, 1H), 4.23 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.99 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.92 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.69-3.58 (m, 2H), 1.00 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.5, 166.6, 144.4, 135.1, 130.0, 128.9, 127.9, 120.1, 99.6, 81.8, 75.4, 70.2, 66.7, 56.0, 39.1, 27.3, 26.9, 22.6, 19.8; HRMS m/z calcd for $C_{25}H_{34}NO_5Si$ $[M+H]^+$ 456.2206 found: 456.2206.



4.36g

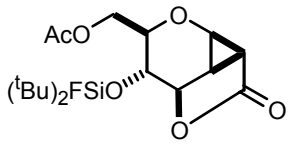
8,8-Di-*tert*-butyl-3-[2-(3,4-dimethoxy-phenyl)-vinyl]-4a,5a,6,9a,9b,9c-hexahydro-2a*H*-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalen-2-one (4.36g). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that nitromethane was used as solvent and 6.0 equivalents of 3,4-dimethoxycinnamonitrile was employed. Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (141 mg, 75%): R_f 0.36(66% EtOAc/hexanes); IR (thin film) ν 1766, 1735, 1712, 1629 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.71 (d, *J* = 16.5 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.06 (s, 1H), 6.87 (d, *J* = 16.5 Hz, 1H), 6.84 (d, *J* =

8.1 Hz, 1H), 5.90 (d, *J* = 6.6 Hz, 1H), 4.70 (dd, *J* = 9.9, 6.6 Hz, 1H), 4.26-4.20 (m, 2H), 4.10-3.91 (m, 2H), 3.89 (s, 6H), 3.70-3.56 (m, 2H), 1.00 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.6, 150.9, 149.2, 144.3, 128.2, 122.3, 118.1, 111.0, 109.4, 99.5, 81.8, 75.3, 70.3, 66.7, 55.94, 55.86, 39.2, 29.7, 29.2, 27.3, 26.9, 22.6, 19.8; HRMS m/z calcd for $C_{27}H_{38}NO_7Si$ $[M+H]^+$ 516.2418.2363, found: 516.2428.



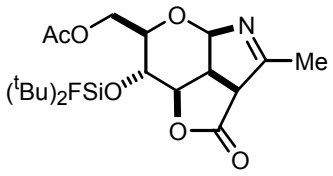
4.36h

(8,8-Di-*tert*-butyl-2-oxo-2,2a,4a,5a,6,9a,9b,9c-octahydro-1,5,7,9-tetraoxa-4-aza-8-sila-pentaleno[1,6-*ab*]naphthalen-3-yl)-acetaldehyde (4.36h). The title compound was prepared from **2.5a** according to the general procedure described above for the preparation of **4.36a**, except that 9.0 equivalents of 3-methoxyacryloitrile was used. Purification by flash chromatography on silica gel with 2:1 to 1:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (151 mg, 78%): R_f 0.37 (50% EtOAc/hexanes); IR (thin film) ν 1774, 1711, 1649, 1618 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.70 (s, br, 1H), 9.24 (d, *J* = 2.1 Hz, 1H), 5.63 (d, *J* = 6.6 Hz, 1H), 5.54 (s, 1H), 4.78 (dd, *J* = 9.9, 5.6 Hz, 1H), 4.14 (ddd, *J* = 9.9, 9.9, 5.1 Hz, 2H), 3.85 (ddd, *J* = 10.2, 10.2, 10.2 Hz, 2H), 3.59-3.47 (m, 2H), 1.01 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 189.0, 171.4, 156.2, 93.2, 88.4, 82.1, 74.8, 70.0, 66.7, 49.2, 37.5, 27.3, 26.9, 22.6, 19.9; HRMS m/z calcd for $C_{19}H_{30}NO_6Si$ $[M+H]^+$ 396.1842, found: 396.1836.



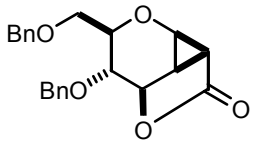
4.40

Acetic acid 5-(di-*tert*-butyl-fluoro-silanyloxy)-2-oxo-hexahydro-1,3-dioxa-cyclopropa [*cd*] inden-4-ylmethyl ester (4.40). To a solution of the **2.27** (2.70 g, 7.8 mmol) in CH_2Cl_2 (12 mL) was added pyridine (1.65 mL, 19.5 mmol) and Ac_2O (2.97 mL, 31.5 mmol). After 15 h at rt the mixture was poured into a vigorously stirred saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic solution was washed with saturated NH_4Cl (15 mL), H_2O (2 × 8 mL), brine (5 mL), dried ($MgSO_4$) and filtered through celite. Volatile components were removed under reduced pressure, and the residual syrup was purified by flash chromatography on silica gel using 10:1 hexanes-EtOAc for elution to provide the title compound as a pale yellow syrup (2.69 g, 89%): R_f 0.38 (33% EtOAc/hexanes); IR (thin film) ν 1766, 1747 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 4.86 (dd, J = 5.7, 1.5 Hz, 1H), 4.38 (dd, J = 12.3, 2.7 Hz, 1H), 4.18 (dd, J = 6.2, 6.2 Hz, 1H), 4.13 (dd, J = 6.5, 1.4 Hz, 1H), 4.02 (dd, J = 12.3, 6.8 Hz, 1H), 3.64 (ddd, J = 6.5, 6.5, 2.7 Hz, 1H), 2.53 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 2.34 (dd, J = 6.2, 6.2 Hz, 1H), 2.06 (s, 3H), 1.04 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.8, 170.7, 78.7, 75.8, 67.7, 63.8, 54.2, 26.8, 26.4, 20.8, 20.7, 20.1 (J = 16.8 Hz), 19.9 (J = 16.8 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ–159.8; HRMS m/z calcd for $C_{18}H_{30}O_6FSi$ $[M+H]^+$ 389.1796, found: 389.1792.



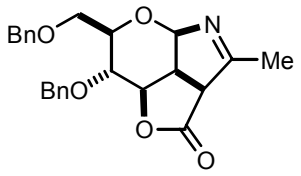
4.41

Acetic acid 7-(di-*tert*-butyl-fluoro-silanyloxy)-3-methyl-2-oxo-2a,4a,6,7,7a,7b-hexahydro-1,5-dioxa-4-aza-cyclopenta[*cd*]inden-6-ylmethyl ester (4.41). The title compound was prepared from **4.40** according to the general procedure described above for the preparation of **4.36a**, except that 10.0 equivalents of acetonitrile was used and the reaction mixture was stirred for 10 h before quenched with saturated aqueous $NaHCO_3$ solution. Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (217 mg, 92%): R_f 0.42 (66% EtOAc/hexanes); IR (thin film) ν 1774, 1747, 1645 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 5.69 (dd, *J* = 5.6, 0.8 Hz, 1H), 4.84 (dd, *J* = 7.6, 2.8 Hz, 1H), 4.39 (dd, *J* = 5.4, 2.8 Hz, 1H), 4.26 (dd, *J* = 12.1, 4.2 Hz, 1H), 4.18 (dd, *J* = 11.8, 5.9 Hz, 1H), 3.80 (dd, *J* = 9.4, 4.7 Hz, 2H), 3.24 (ddd, *J* = 7.6, 7.2, 5.6 Hz, 1H), 2.32 (s, 3H), 2.05 (s, 3H), 1.04 (s, 18H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 175.8, 170.8, 170.7, 98.6, 79.2, 77.2, 66.9, 64.0, 57.6, 39.7, 26.9, 26.8, 20.8, 20.2 (*J* = 14.2 Hz), 20.0 (*J* = 16.8 Hz), 19.0; ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.8; HRMS m/z calcd for $C_{20}H_{33}NO_6FSi$ $[M+H]^+$ 430.2061, found: 430.2054.



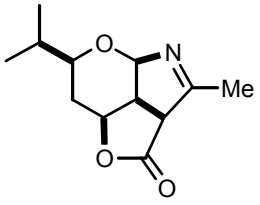
4.42

5-Benzyloxy-4-benzyloxymethyl-hexahydro-1,3-dioxa-cyclopropa[*cd*]inden-2-one (4.42). To a rt solution of **2.5a** (1.85 g, 5.7 mmol) in THF (11 mL) was added 20% HF-py (2.2 mL, 4.0 mmol). The resulting mixture was stirred for 10 min and the resulting solution was filtered through a small pad of silica gel and celite sequentially. Removal of the volatiles under reduced pressure afforded a pale yellow syrup. The crude product was dissolved in DMF (10 mL) and the solution was slowly added over 20 min to a mixture of NaH (680 mg, 17.1 mmol), tetrabutylammonium iodide (420 mg, 1.1 mmol) and benzyl bromide (2.05 mL, 17.1 mmol) in DMF (25 mL) maintained at 0 °C. The resulting mixture was allowed to warm to rt and after 30 min the reaction mixture was poured into a saturated aqueous NH_4Cl solution (25 mL). The resulting mixture was extracted with Et_2O (4 × 20 mL), the combined organic layer was washed with H_2O (3 × 20 mL), brine (15 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (1.70 g, 82%): R_f 0.65 (33% EtOAc/hexanes); IR (thin film) ν 1774 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.37-7.24 (m, 10H), 4.88 (dd, *J* = 5.4, 1.4 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.50 (dd, *J* = 11.8, 2.2 Hz, 2H), 4.17 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.71 (ddd, *J* = 6.4, 6.4, 4.4 Hz, 1H), 3.51 (dd, *J* = 7.0, 1.0 Hz, 1H), 3.46 (d, *J* = 2.2 Hz, 1H), 3.44 (s, 1H), 2.54 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 2.33 (dd, *J* = 6.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.5, 137.8, 137.0, 128.6, 128.4, 128.2, 128.0, 127.8, 127.7, 78.1, 73.4, 73.3, 73.2, 72.4, 70.6, 54.5, 26.6, 21.3; HRMS m/z calcd for $C_{22}H_{23}O_5$ $[M+H]^+$ 367.1545, found: 367.1535.



4.43

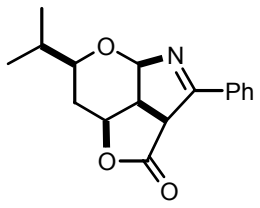
7-Benzyloxy-6-benzyloxymethyl-3-methyl-2a,4a,6,7,7a,7b-hexahydro-1,5-dioxa-4-aza-cyclopenta[*cd*]inden-2-one (4.43). The title compound was prepared from **4.42** according to the general procedure described above for the preparation of **4.36a**, except that acetonitrile was used as solvent. Purification by flash chromatography on silica gel with 1:1 hexanes-EtOAc for elution gave the title product as a colorless syrup (225 mg, 90%): R_f 0.24 (50% EtOAc/hexanes); IR (thin film) ν 1770, 1635 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.34-7.22 (m, 10H), 5.72 (d, *J* = 5.6 Hz, 1H), 4.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.53-4.50 (m, 3H), 3.82-2.73 (m, 3H), 3.59 (d, *J* = 4.4 Hz, 2H), 3.27 (ddd, *J* = 8.4, 8.4, 6.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 174.4, 171.2, 138.0, 137.0, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 99.4, 78.8, 76.1, 73.5, 72.6, 72.2, 70.2, 58.1, 39.5, 18.7; HRMS m/z calcd for $C_{24}H_{26}NO_5$ $[M+H]^+$: 408.1811, found: 408.1817.



4.44a

6-Isopropyl-3-methyl-2a,4a,6,7,7a,7b-hexahydro-1,5-dioxa-4-aza-cyclopenta[*cd*]inden-2-one (4.44a). The title compound was prepared from **2.9**

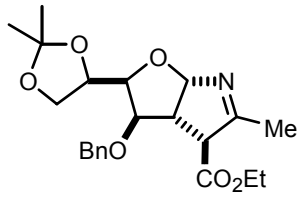
according to the general procedure described above for the preparation of **4.36a**, except that acetonitrile was used as solvent. Purification by flash chromatography on silica gel with 2:1 to 1:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (151 mg, 96%): R_f 0.25(66% EtOAc/hexanes); IR (thin film) ν 1758, 1649 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 5.63 (dd, *J* = 6.1, 1.0 Hz, 1H), 4.89 (ddd, *J* = 8.1, 7.1, 5.5 Hz, 1H), 3.77 (d, *J* = 9.0 Hz, 1H), 3.35 (ddd, *J* = 10.2, 6.1, 5.1 Hz, 1H), 3.13 (ddd, *J* = 8.6, 8.6, 6.4 Hz, 1H), 2.25 (d, *J* = 0.8 Hz, 3H), 2.00 (ddd, *J* = 12.1, 6.9, 5.1 Hz, 1H), 1.80-1.68 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 172.0, 171.9, 99.9, 76.7, 75.2, 58.6, 39.1, 33.5, 28.7, 18.5, 18.1, 17.7; HRMS m/z calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287, found: 224.1277.



4.44b

6-Isopropyl-3-phenyl-2a,4a,6,7,7a,7b-hexahydro-1,5-dioxa-4-aza-cyclopenta[*cd*]inden-2-one (4.44b). The title compound was prepared from **2.9** according to the general procedure described above for the preparation of **4.36a**, except that 9.5 equivalents of benzonitrile was used. Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as white solid (180 mg, 92%): R_f 0.59(50% EtOAc/hexanes); IR (thin film) ν 1743, 1610 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.16-8.13 (m, 2H), 7.48-7.40 (m, 3H), 5.76 (d, *J* = 6.3 Hz, 1H), 4.95 (ddd, *J* = 7.5, 6.0, 4.8 Hz, 1H), 4.42 (d, *J* = 9.0 Hz, 1H), 3.48 (ddd, *J* = 9.0, 6.3, 6.3 Hz,

1H), 3.24 (ddd, *J* = 14.7, 7.5, 6.0 Hz, 1H), 2.01-1.86 (m, 2H), 1.79 (dddd, *J* = 12.6, 6.3, 6.3, 6.3 Hz, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91(d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.7, 170.5, 132.0, 131.4, 129.8, 128.4, 99.1, 77.0, 74.8, 55.1, 40.3, 33.5, 27.7, 18.0, 17.6; HRMS m/z calcd for $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1443, found: 286.1441.



4.46

3-Benzyloxy-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-5-methyl-3,3a,4,6a-tetrahydro-2*H*-furo[2,3-*b*]pyrrole-4-carboxylic acid ethyl ester (4.46). The title compound was prepared from **4.45**[120] according to the general procedure described above for the preparation of **4.36a**, except acetonitrile was used as solvent and the reaction mixture was stirred for 1 min before washing with saturated aqueous $NaHCO_3$ solution. Purification by flash chromatography on silica gel with 1:15:100 Et_3N-Et_2O-hexanes for elution gave the title compound as a pale yellow syrup (191 mg, 43%): R_f 0.35 (20% EtOAc/hexanes); IR (thin film) ν 1735, 1665, 1599 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.36-7.25 (m, 5H), 5.74 (d, *J* = 7.6 Hz, 1H), 4.92 (s, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.39 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.17-4.11 (m, 3H), 4.05 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.96 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.85 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.80 (dd, *J* = 7.2, 0.8 Hz, 1H), 2.18 (d, *J* = 0.8 Hz, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.26 (dd, *J* = 6.8, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.1, 160.3, 138.6, 128.3, 1274, 127.3, 108.5, 95.4,

90.9, 83.4, 80.8, 73.3, 71.2, 66.8, 58.9, 53.6, 26.6, 25.2, 14.6, 14.1; HRMS m/z calcd for $C_{22}H_{29}NO_6$ M^+ 403.1995, found: 403.1995.

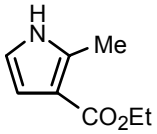
General Procedure for DA Cyclopropane Preparation (4.52a -i). To a solution of the corresponding enol ether (10 mmol) and bis(*N*-*tert*-butylsalicylaldiminato)copper(II) Cu(TBS)$_2$ **2.4** (0.5 mmol) in CH_2Cl_2 (10 mL) at reflux was slowly added a CH_2Cl_2 (20 mL) solution of ethyl diazoacetate (1.5 g, 13 mmol) via syringe pump over 8 hours. After the addition the resulting mixture was stirred for 3 h and the volatiles were removed under reduced pressure. The crude products were purified by chromatography on silica using appropriate combination of hexanes-EtOAc for elution.

General Procedure A for Pyrrole Synthesis (Nitrile as solvent) To a solution of the DA cyclopropane (1.0 mmol) in the nitrile (2.5 mL) at –40 °C was added TMSOTf (1.0 mmol). The resulting solution was stirred at –40 °C for 10 h and then poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (10 mL). The heterogeneous mixture was extracted with Et_2O (3 × 6 mL), and the combined organic extracts were washed with H_2O (2 × 2 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. The product was purified by chromatography on silica using appropriate combination hexanes-EtOAc for elution.

General Procedure B for Pyrrole Synthesis. To a solution of the cyclopropane (1.0 mmol) and the nitrile (10 mmol, 10 eq) in CH_3NO_2 or $C_2H_5NO_2$ (2 mL) at –30 °C were added TMSOTf (1.0 mmol). The resulting solution was stirred at -30 °C for 15 h, poured

into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (10 mL) and worked up as described in procedure A.

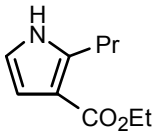
General Procedure C for Pyrrole Synthesis. To a solution of the cyclopropane (1.0 mmol) and the nitrile (10 mmol) in CH_2Cl_2 (2.0 mL) at rt was added TMSOTf (1.0 mmol). The resulting mixture was stirred at rt for 5 h and then poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (10 mL). After 2 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL). The combined organic solution was washed with H_2O (2 × 3 mL) and the volatiles were removed under reduced pressure. The residue was dissolved in THF (6 mL) and treated with 5% aqueous HCl (1 mL) until complete consumption of the [3+2] cycloaddition intermediate (TLC). After extraction with CH_2Cl_2 (8 mL), the aqueous layer was treated with $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (2 × 4 mL). The combined organic extracts were washed with H_2O (2 × 3 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with appropriate combination of hexanes-EtOAc for elution gave the product.



4.53a

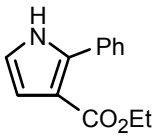
2-Methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.53a). The title compound was prepared from **4.52a** and acetonitrile according to general procedure A for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 15:1

hexanes-EtOAc for elution gave the title compound as a colorless syrup (245 mg, 80%):[173] R_f 0.47 (20% EtOAc/hexanes); IR (thin film) ν 3286, 1674 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.51 (s, br, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 165.8, 135.2, 115.8, 111.7, 110.4, 59.4, 14.5, 13.2.



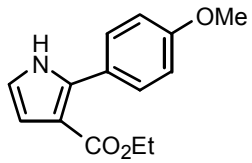
4.53b

2-Propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.53b). The title compound was prepared from **4.52a** and *n*-butyronitrile (8.0 eq) according to general procedure A for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (279 mg, 77%):[174] R_f 0.52 (20% EtOAc/hexanes); IR (thin film) ν 3310, 1674 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.57 (s, br, 1H), 6.55 (s, 1H), 6.54 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 1.65 (qt, *J* = 7.6, 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.7, 139.8, 115.8, 111.2, 110.4, 59.3, 29.2, 22.7, 14.4, 13.8.



4.53c

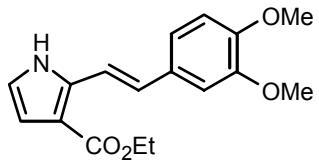
2-Phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.53c). The title compound was prepared from **4.52a** and benzonitrile (5.0 eq) in $C_2H_5NO_2$ according to general procedure B for pyrrole synthesis (–55 °C, 8 h). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (150 mg, 35%):[175] R_f 0.35 (20% EtOAc/hexanes); IR (thin film) ν 3306, 1682 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.56 (s, br, 1H), 7.56-7.53 (m, 2H), 7.39-7.33 (m, 3H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.0, 137.0, 132.1, 128.9, 128.2, 128.1, 117.7, 112.2, 112.1, 59.6, 14.2.



4.53d

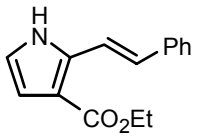
2-(4-methoxy-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.53d). The title compound was prepared from **4.52a** and 4-methoxybenzonitrile (5.0 eq) according to general procedure B for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (271 mg, 55%): R_f 0.35 (20% EtOAc/hexanes); IR (thin film) ν 3309, 1682, 1615 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.67 (s, br, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.68 (dd, *J* = 3.0, 3.0 Hz, 1H), 6.37 (dd, *J* =3.0, 3.0 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 165.2, 159.4, 137.1,

130.2, 124.5, 117.3, 113.4, 111.8, 111.4, 59.5, 55.2, 14.2; HRMS m/z calcd for $C_{14}H_{16}NO_3[M+H]^+$ 246.1130, found: 246.1117.



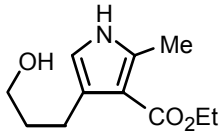
4.53e

2-[2-(3,4-Dimethoxy-phenyl)-vinyl]-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.53e). The title compound was prepared from **4.52a** and 3,4-dimethoxycinnamonitrile (5.0 eq) according to general procedure B for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (512 mg, 85%): R_f 0.65 (50% EtOAc/hexanes); IR (thin film) ν 3340, 1693, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 9.10 (s, br, 1H), 7.70 (d, *J* = 16.8 Hz, 1H), 6.99 (d, *J* = 1.6 Hz, 1H), 6.93 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.74 (d, *J* = 14.4 Hz, 1H), 6.68 (dd, *J* = 2.8, 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.841 (s, 3H), 3.838 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.4, 149.03, 148.99, 135.1, 129.9, 127.3, 120.1, 118.4, 116.0, 113.2, 111.6, 111.1, 108.3, 59.7, 55.8, 55.7, 14.4; HRMS m/z calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1392, found: 302.1381.



4.53f

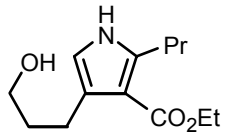
2-Styryl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.53f). The title compound was prepared from **4.52a** and cinnamonitrile (5.0 eq) according to general procedure B for pyrrole synthesis (–50 °C, 8 h). Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (188 mg, 39%): R_f 0.52 (50% EtOAc/hexanes); IR (thin film) ν 3324, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.89 (s, br, 1H), 7.87 (d, *J* = 17.2 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.33 (ddd, *J* = 7.2, 7.2, 1.6 Hz, 2H), 7.25 (tdd, *J* = 7.2, 1.6, 1.6 Hz, 1H), 6.80 (d, *J* = 17.2 Hz, 1H), 6.73 (dd, *J* = 2.8, 2.8 Hz, 1H), 6.67 (dd, *J* = 2.8, 2.8 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.1, 136.8, 134.7, 128.7, 127.8, 127.2, 126.4, 118.5, 118.0, 113.8, 111.8, 59.8, 14.5; HRMS m/z calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1181, found: 242.1176.



4.54a

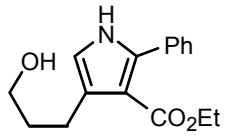
4-(2-Hydroxy-ethyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54a). The title compound was prepared from **4.52b** and acetonitrile according to general procedure A for pyrrole synthesis (–40 °C, 12 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (121 mg, 72%): R_f 0.55 (66% EtOAc/hexanes); IR (thin film) ν 3450-3100, 1666 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.60 (s, br, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 4.25 (q, *J* = 6.9 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.58 (s, br, 1H), 2.44 (s, 3H), 1.79 (tt, *J* = 6.6, 6.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.9,

136.2, 126.1, 114.5, 110.3, 62.2, 59.6, 34.3, 22.6, 14.7, 14.6; HRMS m/z calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$ 212.1287, found: 212.1282.



4.54b

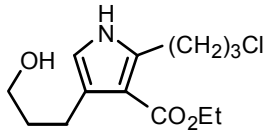
4-(3-Hydroxy-propyl)-2-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54b). The title compound was prepared from **4.52b** and *n*-butyronitrile (8.0 eq) according to general procedure B for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 10:1 to 1:3 hexanes-EtOAc for elution gave the title compound as a colorless solid (272 mg, 78%): R_f 0.50 (66% EtOAc/hexanes); IR (thin film) ν 3380-3100, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.64 (s, br, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.67 (s, br, 1H), 1.80 (tt, *J* = 6.8, 6.8 Hz, 2H), 1.60 (qt, *J* = 7.6, 7.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.5, 140.4, 125.7, 114.3, 109.5, 61.8, 59.2, 33.9, 30.2, 22.8, 22.3, 14.3, 13.9; HRMS m/z calcd for $C_{13}H_{22}NO_3$ $[M+H]^+$ 240.1600, found: 240.1594.



4.54c

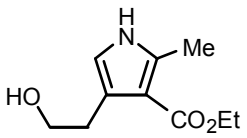
4-(3-Hydroxy-propyl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54c). The title compound was prepared from **4.52b** and benzonitrile (15 eq) according to general

procedure B for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (207 mg, 58%): R_f 0.34 (50% EtOAc/hexanes); IR (thin film) ν 3305, 1678 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.50 (s, br, 1H), 7.46-7.44 (m, 2H), 7.39-7.33 (m, 3H), 6.59 (d, *J* = 1.6 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.44 (s, br, 1H), 1.86 (tt, *J* = 6.8, 6.8 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.0, 137.5, 133.1, 129.1, 127.94, 127.89, 126.7, 116.4, 110.8, 61.8, 59.6, 34.0, 22.1, 13.9; HRMS m/z calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1443, found: 274.1454.



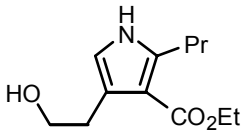
4.54d

2-(3-Chloro-propyl)-4-(3-hydroxy-propyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54d). The title compound was prepared from **4.52b** and 4-chlorobutyronitrile (15 eq) according to general procedure B for pyrrole synthesis (–40 °C, 8 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (204 mg, 61%): R_f 0.31 (50% EtOAc/hexanes); IR (thin film) ν 3332, 1666 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.28 (s, br, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.08 (tt, *J* = 6.6, 6.6 Hz, 2H), 1.81 (tt, *J* = 6.6, 6.6 Hz, 2H), 1.66 (s, br, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.0, 138.2, 126.1, 114.7, 110.1, 62.0, 59.4, 44.6, 33.9, 32.0, 25.3, 22.4, 14.4; HRMS m/z calcd for $C_{13}H_{21}NO_3Cl$ $[M+H]^+$ 274.1210, found: 274.1218.



4.54e

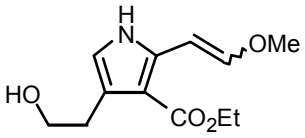
4-(2-Hydroxy-ethyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54e). The title compound was prepared from **4.52c** and acetonitrile according to general procedure A (–40 °C, 10 h). Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (167 mg, 52%): (167 mg, 52%): R_f 0.41 (50% EtOAc/hexanes); IR (thin film) ν 3440-3200, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.67 (s, br, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.79 (t, *J* = 6.1 Hz, 2H), 2.94 (t, *J* = 6.1 Hz, 2H), 2.45 (s, 3H), 2.32 (s, br, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.6, 136.4, 122.4, 115.3, 110.1, 63.6, 59.3, 29.8, 14.4, 14.2; HRMS m/z calcd for $C_{10}H_{16}NO_3$ $[M+H]^+$ 198.1130, found: 198.1126.



4.54f

4-(2-Hydroxy-ethyl)-2-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54f). The title compound was prepared from **4.52c** and *n*-butyronitrile (15 eq) in nitroethane according to general procedure B for pyrrole synthesis (–40 °C, 10 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title

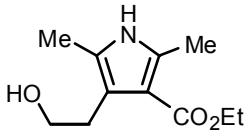
compound as white solid (189 mg, 58%): R_f 0.55 (50% EtOAc/hexanes); IR (thin film) ν 3380-3150, 1666 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.47 (s, br, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.77 (t, *J* = 6.0 Hz, 2H), 2.93 (t, *J* = 5.6 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.44 (s, br, 1H), 1.61 (tq, *J* = 7.6, 7.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.4, 140.9, 122.5, 115.3, 109.7, 63.6, 59.4, 30.2, 29.9, 22.7, 14.3, 13.9; HRMS m/z calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.1443, found: 226.1438.



4.54g

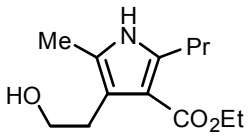
4-(2-Hydroxy-ethyl)-2-(2-methoxy-vinyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54g). The title compound was prepared from **4.52c** and 3-methoxyacrylonitrile (5.0 eq) in nitroethane according to general procedure B for pyrrole synthesis (–40 °C, 10 h). Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (482 mg, 81%): R_f 0.35 (50% EtOAc/hexanes); IR (thin film) ν 3420-3250, 1647 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 9.56 (s, br, 0.5H), 9.20 (s, br, 0.5H), 6.94 (d, *J* = 12.0 Hz, 0.5H), 6.52 (d, *J* = 2.4 Hz, 0.5H), 6.41 (d, *J* = 13.2 Hz, 0.5H), 6.30 (d, *J* = 2.0 Hz, 0.5H), 6.19 (d, *J* = 6.8 Hz, 0.5H), 6.12 (d, *J* = 6.8 Hz, 0.5H), 4.23 (q, *J* = 7.2 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 1H), 3.77 (s, 1.5H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.61 (s, 1.5H), 2.92 (t, *J* = 6.4 Hz, 1H), 2.88 (t, *J* = 6.4 Hz, 1H), 2.56 (s, br, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 1.5H); NMR (100 MHz, $CHCl_3$) δ 166.3, 166.1, 148.7, 147.1, 135.1, 134.6, 122.3, 122.0, 116.7, 116.5,

109.3, 109.2, 96.8, 63.4, 63.3, 60.8, 59.4, 59.5, 56.0, 29.94, 29.89, 14.3, 14.1; HRMS m/z calcd for $C_{12}H_{18}NO_4$ $[M+H]^+$ 240.1236, found: 240.1233.



4.54h

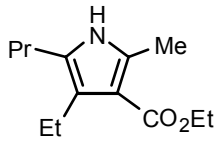
4-(2-Hydroxy-ethyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54h). The title compound was prepared from **4.52d** and acetonitrile according to general procedure A for pyrrole synthesis (–15 °C, 6 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (87 mg, 31%): R_f 0.22 (50% EtOAc/hexanes); IR (thin film) ν 3380-3240, 1654 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.96 (s, br, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.74 (t, J = 6.3 Hz, 2H), 2.87 (t, J = 6.3 Hz, 2H), 2.41 (s, 3H), 2.12 (s, 3H), 2.10 (s, br, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.9, 134.0, 123.5, 117.2, 110.5, 63.8, 59.4, 28.2, 14.4, 14.1, 10.5; HRMS m/z calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$ 212.1287, found: 212.1281.



4.54i

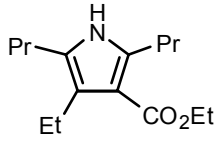
4-(2-Hydroxy-ethyl)-5-methyl-2-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54i). The title compound was prepared from **4.52d** and *n*-butylronitrile (5.0 eq) in nitromethane according to general procedure B for pyrrole synthesis (–15 °C, 6 h).

Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (77 mg, 25%): R_f 0.25 (50% EtOAc/hexanes); IR (thin film) ν 3400-3280, 1666 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.98 (s, br, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.73 (t, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.62 (s, br, 1H), 2.12 (s, 3H), 1.60 (qt, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H), 0.93 (dd, *J* = 7.6, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.7, 138.5, 123.5, 117.2, 110.0, 63.8, 59.3, 30.1, 28.3, 23.0, 14.3, 14.0, 10.7; HRMS m/z calcd for $C_{13}H_{22}NO_3$ $[M+H]^+$ 240.1600, found: 240.1594.



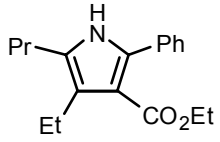
4.54j

4-Ethyl-2-methyl-5-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54j). The title compound was prepared from **4.52e** and acetonitrile according to general procedure A for pyrrole synthesis (rt, 10 min). Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (415 mg, 93%): R_f 0.45 (25% EtOAc/hexanes); IR (thin film) ν 3320, 1666 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.79 (s, br, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.60 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 2H), 2.44 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.53 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.08 (t *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.2, 133.8, 126.4, 122.8, 109.8, 58.9, 27.2, 23.5, 18.5, 16.3, 14.4, 14.0, 13.8; HRMS m/z calcd for $C_{13}H_{22}NO_2[M+H]^+$ 224.1651, found: 224.1639.



4.54k

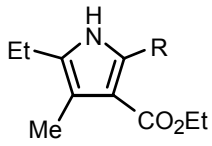
4-Ethyl-2, 5-dipropyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54k). The title compound was prepared from **4.52e** and *n*-butyronitrile (10 eq) in nitromethane according to general procedure B for pyrrole synthesis (–10 °C, 10 h).). Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (411 mg, 82%): R_f 0.52 (25% EtOAc/hexanes); IR (thin film) ν 3327, 1662 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.93 (s, br, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.61 (q, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.61 (qt, *J* = 7.6, 7.6 Hz, 2H), 1.53 (qt, *J* = 7.6, 7.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.1, 138.4, 126.4, 122.7, 109.2, 58.8, 30.0, 27.2, 23.5, 22.9, 18.5, 16.5, 14.3, 13.9, 13.8; HRMS m/z calcd for $C_{15}H_{26}NO_2[M+H]^+$ 252.1964, found: 252.1949.



4.54l

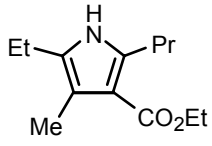
4-Ethyl-2-phenyl-5-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54l). The title compound was prepared from **4.52e** and benzonitrile (10 eq) in nitromethane according to general procedure B for pyrrole synthesis (–10 °C, 10 h). Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title

compound as a colorless solid (469 mg, 76%): R_f 0.45 (25% EtOAc/hexanes); IR (thin film) ν 3312, 1674, 1608 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.22 (s, br, 1H), 7.47-7.45 (m, 2H), 7.36-7.26 (m, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.71 (q, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 1.61 (qt, *J* = 7.2, 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.8, 135.2, 133.2, 129.0, 128.8, 127.8, 127.4, 123.9, 110.5, 59.2, 27.2, 23.3, 18.4, 16.3, 13.9, 13.8; HRMS m/z calcd for $C_{18}H_{24}NO_{2F}$ $[M+H]^+$ 286.1807, found: 286.1795.



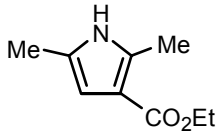
4.54m

5-Ethyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54m). The title compound was prepared from **4.52f** and acetonitrile according to general procedure A for pyrrole synthesis (rt, 2 h). Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (360 mg, 98%): R_f 0.48 (25% EtOAc/hexanes); IR (thin film) ν 3317, 1666 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.52 (s, br, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.50 (q, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 2.17 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.6, 133.7, 128.4, 114.9, 110.3, 58.8, 18.3, 14.38, 14.32, 13.7, 10.7.



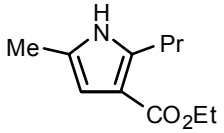
4.54n

5-Ethyl-4-methyl-2-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54n). The title compound was prepared from **4.52f** and *n*-butyronitrile (10 eq) in nitromethane according to general procedure B for pyrrole synthesis (–10 °C, 10 h). Purification by flash chromatography on silica gel with 30:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (436 mg, 85%): R_f 0.53 (25% EtOAc/hexanes); IR (thin film) ν 3328, 1662 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.86 (s, br, 1H), 4.23 (q, J = 7.2 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 2.49 (q, J = 7.6 Hz, 2H), 2.14 (s, 3H), 1.61 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.6 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.3, 138.1, 128.1, 115.2, 110.2, 58.9, 30.0, 23.0, 18.5, 14.4, 14.3, 14.0, 10.8; HRMS m/z calcd for $C_{13}H_{22}NO_2$ $[M+H]^+$ 224.1651, found: 224.1641.



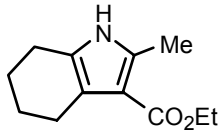
4.54o

2,5-Dimethyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54o). The title compound was prepared from **4.52g** and acetonitrile (10 eq) in nitroethane according to general procedure B for pyrrole synthesis (–10 °C, 9 h). Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (162 mg, 62%): R_f 0.71 (50% EtOAc/hexanes); IR (thin film) ν 3297, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.00 (s, br, 1H), 6.18 (dd, J = 1.2, 1.2 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 2.17 (s, 3H), 1.30 (t, J =7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.8, 134.2, 125.5, 111.6, 107.4, 59.2, 14.5, 13.1, 12.6.



4.54p

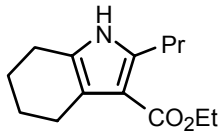
5-Methyl-2-propyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.54p). The title compound was prepared from **4.52g** and *n*-butyronitrile (10 eq) in nitroethane according to general procedure B for pyrrole synthesis (–10 °C, 9 h). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (171 mg, 55%): R_f 0.56 (30% EtOAc/hexanes); IR (thin film) ν 3309, 1674 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.27 (s, br, 1H), 6.18 (dd, *J* = 1.0, 1.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.61 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.7, 139.0, 125.6, 111.0, 107.4, 59.1, 29.2, 22.9, 14.4, 13.8, 12.6.



4.54q

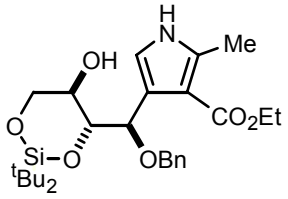
2-Methyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester (4.54q). The title compound was prepared from **4.52h** with acetonitrile according to general procedure A for pyrrole synthesis (–40 °C, 10 h). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (166 mg, 72%):[176] R_f 0.60 (20% EtOAc/hexanes); IR (thin film) ν 3340, 1662 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.87 (s, br, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 6.0, Hz, 2H),

2.46 (s, 3H), 2.46 (t, J = 6.0 Hz, 2H), 1.76-1.69 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.4, 134.1, 125.3, 118.6, 109.5, 58.9, 23.5, 23.3, 22.9, 22.4, 14.5, 13.6.



4.54r

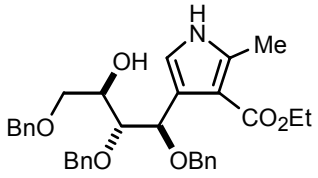
2-Propyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester (4.54r). The title compound was prepared from **4.52h** with *n*-butyronitrile according to general procedure A for pyrrole synthesis (–40 °C, 10 h). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (98 mg, 75%): R_f 0.65 (20% EtOAc/hexanes); IR (thin film) ν 3330, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.78 (s, br, 1H), 4.22 (q, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.68 (td, *J* = 6.0, 1.4 Hz, 2H), 2.47 (td, *J* = 6.0, 1.4 Hz, 2H), 1.79-1.68 (m, 4H), 1.61 (qt, *J* = 7.5, 7.5 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ166.2, 138.8, 129.7, 125.4, 118.5, 58.8, 29.6, 23.4, 23.2, 23.0, 22.9, 22.4, 14.4, 13.9; HRMS m/z calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1651, found: 236.1654.



4.55a

4-[Benzyloxy-(2,2-di-tert-butyl-5-hydroxy-[1,3,2]dioxasilinan-4-yl)-methyl]-2-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (4.55a). The title compound was prepared from the corresponding cyclopropane and acetonitrile according to general procedure C for pyrrole synthesis (rt, 1.5 h). Purification by flash chromatography on

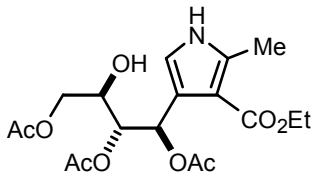
silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (165 mg, 87%): R_f 0.53 (25% EtOAc/hexanes); IR (thin film) ν 3420-3260, 1666 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.25 (s, br, 1H), 7.31-7.25 (m, 5H), 6.75 (d, *J* = 2.4 Hz, 1H), 5.57 (d, *J* = 3.6 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.19 (tt, *J* = 6.8, 6.8 Hz, 2H), 4.05 (ddd, *J* = 12.4, 8.8, 3.6 Hz, 1H), 3.95-3.89 (m, 1H), 3.77 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.09 (d, *J* = 3.2 Hz, 1H), 2.50 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.94 (s, 9H), 0.79 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ165.9, 138.5, 135.5, 128.3, 127.7, 127.6, 122.1, 116.0, 111.4, 78.6, 75.3, 71.0, 68.2, 67.0, 59.3, 27.5, 26.6, 22.7, 20.0, 14.3, 14.0; HRMS m/z calcd for $C_{27}H_{41}NO_6Si$ $[M]^+$ 503.2703, found: 503.2690.



4.55b

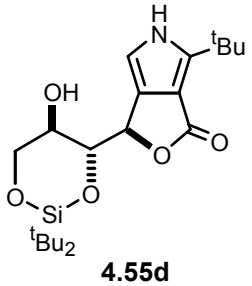
2-Methyl-4-(1,2,4-tris-benzyloxy-3-hydroxy-butyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.55b). The title compound was prepared from the corresponding cyclopropane and acetonitrile according to general procedure C for pyrrole synthesis (rt, 3 h). Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (184 mg, 77%): R_f 0.53 (25% EtOAc/hexanes); IR (thin film) ν 3450-3180, 1662 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.25 (s, br, 1H), 7.24-7.02 (m, 15H), 6.73 (d, *J* = 2.4 Hz, 1H), 5.38 (d, *J* = 2.8 Hz, 1H), 4.61 (t, *J* = 11.6 Hz, 1H), 4.45 (s, 2H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.21 (s, 2H), 4.17 (q, *J*

= 7.2 Hz, 2H), 4.02 (s, br, 1H), 3.90 (dd, *J* = 6.0, 2.8 Hz, 1H), 3.62 (dd, *J* = 7.2, 2.8 Hz, 1H), 3.50 (dd, *J* = 7.2, 3.2 Hz, 1H), 2.68 (s, br, 1H), 2.49 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); HRMS m/z calcd for $C_{33}H_{37}NO_6$ $[M]^+$ 543.2621, found: 543.2618.



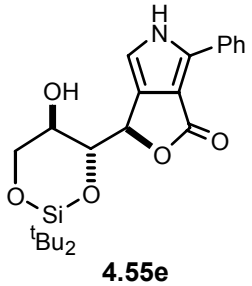
4.55c

2-Methyl-4-(1,2,4-triacetoxy-3-hydroxy-butyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (4.55c). The title compound was prepared from the corresponding cyclopropane and acetonitrile according to general procedure C for pyrrole synthesis (rt, 4 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (97 mg, 58%): R_f 0.45 (66% EtOAc/hexanes); IR (thin film) ν 3550-3180, 1740, 1715, 1705, 1673 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.71 (s, br, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.52 (d, *J* = 1.6 Hz, 1H), 5.37 (dd, *J* = 7.6, 3.2 Hz, 1H), 4.31-4.21 (m, 2H), 4.14-4.03 (m, 2H), 3.87 (s, br, 1H), 3.49 (d, *J* = 6.0 Hz, 1H), 2.39 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.93 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ171.2, 171.0, 169.7, 165.3, 136.3, 121.2, 115.1, 109.2, 73.4, 68.8, 68.5, 65.2, 59.7, 21.0, 20.8, 20.6, 14.4, 13.7; HRMS m/z calcd for $C_{18}H_{25}NO_9$ $[M]^+$ 399.1529, found: 399.1525.



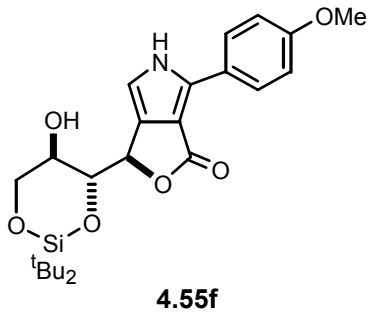
4.55d

6-*tert*-Butyl-3-(2,2-di-*tert*-butyl-5-hydroxy-[1,3,2]dioxasilinan-4-yl)-3,5-dihydro-furo[3,4-c]pyrrol-1-one (4.55d). The title compound was prepared from the corresponding cyclopropane and *tert*-butyronitrile (10 eq) in CH_2Cl_2 (3.0 mL) according to general procedure C for pyrrole synthesis (rt, 2 h). Purification by flash chromatography on silica gel with 4:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (96 mg, 87%): R_f 0.35 (50% EtOAc/hexanes); IR (thin film) ν 3650-3300, 1716 cm^{-1}; ^1H NMR (400 MHz, DMSO-$_{D6}$) δ 11.17 (s, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 5.55-5.27 (m, 2H), 3.96 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.77-3.70 (m, 1H), 3.64 (dd, *J* = 10.1, 10.1 Hz, 1H), 1.31 (s, 9H), 0.82 (s, 18 H); ^{13}C NMR (100 MHz, DMSO-$_{D6}$) δ 167.4, 141.2, 134.0, 111.3, 106.2, 79.8, 75.6, 69.2, 66.4, 33.1, 30.3, 27.8, 27.2, 23.0, 20.4; HRMS m/z calcd for $C_{21}H_{36}NO_5Si$ $[M+H]^+$ 410.2363, found: 410.2360.



4.55e

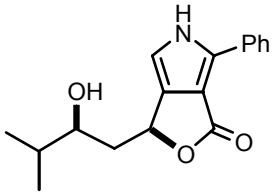
3-(2-Hydroxy-3-methyl-butyl)-6-phenyl-3,5-dihydro-furo[3,4-c]pyrrol-1-one (4.55e). The title compound was prepared from the corresponding cyclopropane and benzonitrile (10 eq) in CH_2Cl_2 (3.0 mL) according to general procedure C for pyrrole synthesis (rt, 2.5 h). Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (119 mg, 85%): IR (thin film) ν 3550-3080, 1717 cm^{-1}; R_f 0.42 (50% EtOAc/hexanes); ^1H NMR (400 MHz, $CHCl_3$) δ 9.50 (s, br, 1H), 7.97 (d, *J* = 7.0, 2H), 7.41 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.33-7.28 (m, 1H), 6.61 (s, 1H), 5.82 (s, 1H), 4.18-4.09 (m, 3H), 3.91-3.78 (m, 2H), 0.94 (s, 9H), 0.90 (s, 9H); HRMS m/z calcd for $C_{23}H_{31}NO_5Si$ $[M]^+$ 429.1972, found: 429.1975.



4.55f

3-(2,2-Di-*tert*-butyl-5-hydroxy-[1,3,2]dioxasilinan-4-yl)-6-(4-methoxy-phenyl)-3,5-dihydro-furo[3,4-*c*]pyrrol-1-one (**4.55f).** The title compound was prepared from the corresponding cyclopropane and *p*-methoxybenzonitrile (5 eq) in CH_2Cl_2 (4.0 mL) according to general procedure C for pyrrole synthesis (rt, 2.5 h). Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a pale yellow syrup (141 mg, 93%): R_f 0.24 (50% EtOAc/hexanes); IR (thin film) ν 3580-3200, 1619 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 9.53 (s, br, 1H), 7.89 (dd, *J* = 8.6, 8.6 Hz, 2H), 6.88 (dd, *J* = 8.6, 8.6 Hz, 2H), 6.51 (s, 1H), 5.82 (s, 1H), 4.21-4.02

(m, 4H), 3.85 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.75 (s, 3H), 0.90 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ169.0, 159.5, 134.9, 130.9, 127.0, 122.7, 114.4, 111.8, 107.3, 78.8, 68.7, 65.9, 55.3, 27.4, 27.3, 26.6, 22.7, 20.0; HRMS m/z calcd for $C_{24}H_{34}NO_6Si$ $[M+H]^+$ 460.2155, found: 460.2144.



4.55g

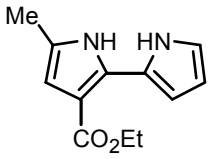
3-(2-Hydroxy-3-methyl-butyl)-6-phenyl-3,5-dihydro-furo[3,4-c]pyrrol-1-one (4.55g). The title compound was prepared from **2.9** and benzonitrile (10 eq) in CH_2Cl_2 (3.0 mL) according to general procedure C for pyrrole synthesis (rt, 3 h). Purification by flash chromatography on silica gel with 1:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (127 mg, 82%): R_f 0.35 (66% EtOAc/hexanes); IR (thin film) ν 3600-3220, 1713 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.4 (s, br, 1H), 8.18 (dd, *J* = 6.8, 1.2 Hz, 2H), 7.43 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H), 7.30 (tt, *J* = 7.2, 1.2 Hz, 1H), 6.84 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.62 (ddd, *J* = 9.6, 3.6, 1.2 Hz, 1H), 3.91 (d, *J* = 5.6 Hz, 1H), 3.72 (qdd, *J* = 5.6, 5.6, 2.0 Hz, 1H), 1.90 (ddd, *J* = 14.0, 10.4, 4.8 Hz, 1H), 1.76 (ddd, *J* = 14.0, 9.6, 2.4 Hz, 1H), 1.67 (ddqq, *J* = 1.6, 1.6, 6.8, 6.8 Hz, 1H), 0.93 (d, *J* = 1.2 Hz, 3H), 0.92 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ167.4, 139.5, 131.4, 130.5, 129.6, 128.5, 126.2, 113.1, 110.0, 76.2, 72.9, 42.1, 35.0, 30.5, 18.9, 17.6; HRMS m/z calcd for $C_{17}H_{19}NO_3$ $[M]^+$ 285.1365, found: 285.1352.

Bipyrrole synthesis: General procedure A

To a solution of cyclopropane (2.0 mmol) and 2-cyano-pyrrole (1.0 mmol) in CH_3NO_2 (4.0 mL) at –25 0°C was added TMSOTf (1.5 mmol). The mixture was stirred at –25 °C for 0.5-4.0 h until TLC indicated complete consumption of starting 2-cyano-pyrrole. The resulting mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) with vigorous stirring. After 2 min the mixture was extracted with EtOAc (3 × 8 mL). The combined organic solution was washed with H_2O (8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. The product was purified by chromatography on silica gel using appropriate combination of hexanes-EtOAc for elution.

Thienylpyrrole synthesis: General procedure B

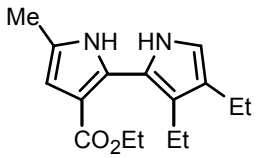
To a solution of cyclopropane (2.0 mmol) and 2-thiophenecarbonitrile (1.0 mmol) in $C_2H_5NO_2$ (4.0 mL) at –25 °C was added TMSOTf (1.5 mmol). The mixture was stirred at –25 °C for 0.5-1.5 h until TLC indicated complete consumption of starting 2-cyano-thiophene and poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (10 mL) and worked up as described in general procedure A for bipyrrole synthesis.



4.57a

5-Methyl-1*H*,1'*H*-[2,2']bipyrrolyl-3-caboxylic acid ethyl ester (4.57a). The title compound was prepared from cyclopropane **4.52g** and 1*H*-pyrrole-2-carbonitrile **4.56a**

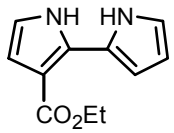
according to the general procedure A for bipyrrole synthesis (0 °C, CH_3NO_2, 25 min). Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (231 mg, 78%): R_f 0.61 (25% EtOAc/hexanes); IR (thin film) ν 3610-3130, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 12.11 (s, br, 1H), 8.39 (s, br, 1H), 6.85 (t, *J* = 2.0 Hz, 1H), 6.40 (td, *J* = 1.3, 1.3 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 6.27-6.24 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.22 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.0, 130.6, 126.6, 124.1, 118.4, 108.9, 108.6, 108.5, 104.2, 60.1, 14.3, 12.5; HRMS m/z calcd for $C_{12}H_{15}N_2O_2$ $[M+H]^+$ 219.1134, found: 219.1139.



4.58a

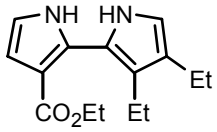
3',4'-Diethyl-5-methyl-1*H*,1'*H*-[2,2']bipyrrolyl-3-caboxylic acid ethyl ester (4.58a). The title compound was prepared from cyclopropane **4.52g** and 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (–10 °C, CH_3NO_2, 45 min). Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (112 mg, 82%): R_f 0.56 (15% EtOAc/hexanes); IR (thin film) ν 3450-3210, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 11.83 (s, br, 1H), 8.28 (s, br, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.34 (dd, *J* = 1.0, 1.0 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.71 (q, *J* = 7.5 Hz, 2H), 2.50 (q, *J* = 7.5 Hz, 2H), 2.28 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.5 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.9, 131.6, 125.9, 125.6, 120.8, 119.7, 114.8, 109.0,

108.8, 60.0, 18.7, 18.1, 15.4, 14.9, 14.4, 12.8; HRMS m/z calcd for $C_{16}H_{23}N_2O_2$ $[M+H]^+$ 275.1760, found: 275.1757.



4.57b

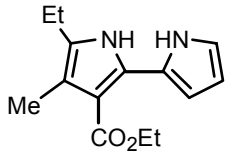
1*H*,1'*H*-[2,2']Bipyrrolyl-3-caboxylic acid ethyl ester (4.57b). The title compound was prepared from cyclopropane **4.52a** and 1*H*-pyrrole-2-carbonitrile **4.56a** according to the general procedure A for bipyrrole synthesis (–45 °C, $C_2H_5NO_2$, 4.5 h). Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (130 mg, 41%): R_f 0.71 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 12.11 (s, br, 1H), 8.52 (s, br, 1H), 6.88-6.86 (m, 1H), 6.63 (t, J = 2.0 Hz, 1H), 6.61 (t, J = 2.0 Hz, 1H), 6.42-6.41 (m, 1H), 6.26 (q, J = 2.0 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.9, 131.5, 123.9, 118.6, 116.6, 111.6, 109.1, 108.8, 104.7, 60.3, 14.4; HRMS m/z calcd for $C_{11}H_{13}N_2O_2$ $[M+H]^+$ 205.0977, found: 205.0967.



4.58b

3',4'-Diethyl-1*H*,1'*H*-[2,2']bipyrrolyl-3-caboxylic acid ethyl ester (4.58b). The title compound was prepared from cyclopropane **4.52a** and 3,4-diethyl-1*H*-pyrrole-2-

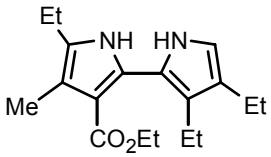
carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (–40 °C, $C_2H_5NO_2$, 3 h). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (147 mg, 45%): R_f 0.56 (15% EtOAc/hexanes); IR (thin film) ν 3580-3050, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 11.85 (s, br, 1H), 8.60 (s, br, 1H), 6.67 (d, *J* = 2.8 Hz, 2H), 6.63 (d, *J* = 2.4 Hz, 1H), 4.30 (q, *J* = 7.5 Hz, 2H), 2.70 (q, *J* = 7.5 Hz, 2H), 2.49 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.9, 132.4, 125.8, 121.3, 119.6, 116.2, 115.1, 111.7, 109.1, 60.2, 18.6, 18.1, 15.6, 14.9, 14.4; HRMS m/z calcd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$ 261.1603, found: 261.1596.



4.57c

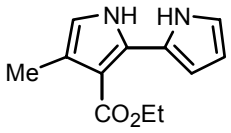
5-Ethyl-4-methyl-1*H*,1'*H*-[2,2']bipyrrolyl-3-caboxylic acid ethyl ester (4.57c). The title compound was prepared from cyclopropane **4.52f** and 1*H*-pyrrole-2-carbonitrile **4.56a** according to the general procedure A for bipyrrole synthesis (–10 °C, CH_3NO_2, 45 min). Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (231 mg, 82%): R_f 0.68 (25% EtOAc/hexanes); ^1H NMR (400 MHz, $CHCl_3$) δ 11.99 (s, br, 1H), 8.13 (s, br, 1H), 6.83 (ddd, *J* = 5.6, 3.2, 3.2 Hz, 1H), 6.36-6.34 (m, 1H), 6.23 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 2.56 (q, *J* = 7.6 Hz, 2H), 2.16 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 168.0, 130.0, 129.6, 124.5, 118.1, 115.7,

108.8, 108.6, 104.2, 60.0, 18.9, 14.4, 14.3, 11.6; HRMS m/z calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$ 247.1447, found: 247.1443.



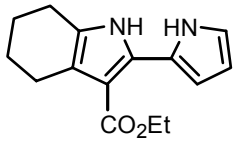
4.58c

5,3',4'-Triethyl-4-methyl-1*H*,1'*H*-[2,2']bipyrrolyl-3-caboxylic acid ethyl ester (4.58c). The title compound was prepared from cyclopropane **4.52f** and 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (0 °C, CH_3NO_2, 45 min). Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (410 mg, 85%): R_f 0.51 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.19 (s, br, 1H), 8.18 (s, br, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.66 (q, *J* = 7.5 Hz, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.49 (q, *J* = 7.5 Hz, 2H), 2.17 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.20 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.8, 130.3, 129.0, 125.5, 120.9, 120.1, 115.3, 114.4, 109.5, 59.9, 18.63, 18.55, 18.2, 15.6, 14.8, 14.4, 13.8, 11.5; HRMS m/z calcd for $C_{18}H_{27}N_2O_2$ $[M+H]^+$ 303.2073, found: 303.2072.



4.57d

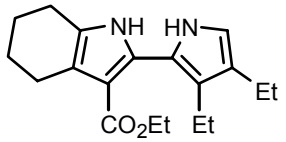
4-Methyl-1*H*,1'*H*-[2,2']bipyrrolyl-3-caboxylic acid ethyl ester (4.57d). The title compound was prepared from cyclopropane **4.52i** and 1*H*-pyrrole-2-carbonitrile **4.56a** according to the general procedure A for bipyrrole synthesis (–25 °C, CH_3NO_2, 45 min). Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (98 mg, 48%): R_f 0.52 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 12.06 (s, br, 1H), 8.34 (s, br, 1H), 6.85 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.42 (d, *J* = 1.2 Hz, 1H), 6.37 (dd, *J* = 3.2, 2.4 Hz, 1H), 6.25 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.9, 132.1, 124.3, 121.9, 118.3, 115.8, 108.9, 108.3, 104.7, 60.2, 14.3, 13.6; HRMS m/z calcd for $C_{12}H_{15}N_2O_2$ $[M+H]^+$ 219.1134, found: 219.1130.



4.57e

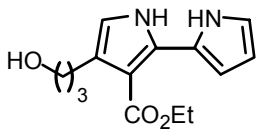
2-(1*H*-Pyrrol-2-yl)-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester (4.57e). The title compound was prepared from cyclopropane **4.52h** and 1*H*-pyrrole-2-carbonitrile **4.56a** according to the general procedure A for bipyrrole synthesis (–10°C, CH_3NO_2, 45 min). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (162 mg, 62%): R_f 0.68 (25% EtOAc/hexanes); IR (thin film) ν 3420-3180, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 12.09 (s, br, 1H), 8.14 (s, br, 1H), 6.82 (dd, *J* = 2.0, 2.0 Hz, 1H), 6.33 (dd, *J* = 2.0, 2.0 Hz, 1H), 6.22 (dd, *J* = 4.0, 2.4 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 5.6

Hz, 2H), 2.53 (t, *J* = 6.4 Hz, 2H), 1.81-1.71 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 168.0, 130.3, 126.8, 124.6, 119.2, 118.2, 108.8, 107.2, 104.2, 60.0, 23.9, 23.5, 22.6, 22.5, 14.4; HRMS m/z calcd for $C_{15}H_{19}N_2O_2$ $[M+H]^+$ 259.1447, found: 259.1449.



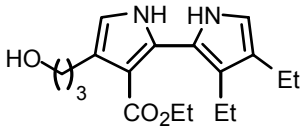
4.58d

2-(3,4-Diethyl-1*H*-pyrrol-2-yl)-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester (4.58d). The title compound was prepared from cyclopropane **4.52h** and 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (–35 °C, $C_2H_5NO_2$, 45 min). Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (171 mg, 82%): R_f 0.68 (25% EtOAc/hexanes); IR (thin film) ν 3520-3180, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.56 (s, br, 1H), 8.13 (s, br, 1H), 6.60 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.75-2.69 (m, 2H), 2.68 (dq, *J* = 2.0, 7.6, Hz, 2H), 2.58-2.54 (m, 2H), 2.49 (dq, *J* = 2.0, 7.6 Hz, 2H), 1.85-1.72 (m, 4H), 1.35 (td, *J* = 7.2, 2.0 Hz, 3H), 1.23 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.8, 130.9, 126.3, 125.5, 120.9, 120.0, 118.9, 114.5, 107.9, 59.8, 23.9, 23.5, 22.7, 22.6, 18.6, 18.2, 15.6, 14.8, 14.4; HRMS m/z calcd for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2073, found: 315.2078.



4.57f

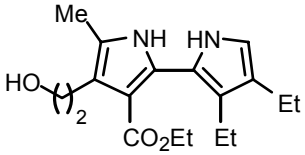
4-(3-Hydroxy-propyl)-1*H*-1'*H*-[2,2']bipyrrolyl-3-carboxylic acid ethyl ester (4.57f). The title compound was prepared from cyclopropane **4.52b** and 1*H*-pyrrole-2-carbonitrile **4.56a** according to the general procedure A for bipyrrole synthesis (–10 °C, CH_3NO_2, 25 min). Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (231 mg, 46%): R_f 0.28 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.94 (s, br, 1H), 8.51 (s, br, 1H), 6.84 (t, *J* = 1.2 Hz, 1H), 6.44 (s, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 6.25-6.23 (m, 1H), 4.32 (qd, *J* = 7.2, 2.0 Hz, 2H), 3.68 (td, *J* = 6.8, 2.0 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.84 (dq, *J* = 6.8, 6.8 Hz, 2H), 1.53 (s, br, 1H), 1.37 (td, *J* = 7.2, 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.6, 132.4, 125.8, 124.2, 118.4, 115.6, 109.0, 107.6, 105.1, 62.6, 60.3, 33.4, 23.7, 14.3; HRMS m/z calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$ 263.1396, found: 263.1392.



4.58e

3',4'-Diethyl-4-(3-hydroxy-propyl)-1*H*-1'*H*-[2,2']bipyrrolyl-3-carboxylic acid ethyl ester (4.58e). The title compound was prepared from cyclopropane **4.52b** and 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (–30 °C, $C_2H_5NO_2$, 45 min). Purification by flash chromatography on

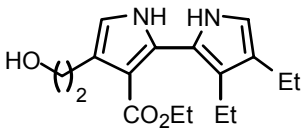
silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (76 mg, 54%): R_f 0.28 (50% EtOAc/hexanes); IR (thin film) ν 3580-3250, 1726 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 11.06 (s, br, 1H), 8.41 (s, br, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.67 (q, *J* = 6.4 Hz, 2H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.48 (q, *J* = 7.2 Hz, 2H), 1.88-1.81 (m, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H), 1.19 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.4, 132.5, 125.64, 125.57, 121.7, 119.7, 115.3, 114.7, 108.8, 62.5, 60.1, 33.5, 23.5, 18.4, 18.1, 15.8, 14.7, 14.2; HRMS m/z calcd for $C_{18}H_{27}N_2O_3$ $[M+H]^+$ 319.2022, found: 319.2019.



4.58f

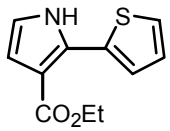
3',4'-Diethyl-4-(2-hydroxy-ethyl)-5-methyl-1*H*-1'*H*-[2,2']bipyrrolyl-3-carboxylic acid ethyl ester (4.58f). The title compound was prepared from cyclopropane **4.52d** and 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (–25 °C, CH_3NO_2, 1.0 h). Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (151 mg, 84%): R_f 0.31 (50% EtOAc/hexanes); IR (thin film) ν 3500-3150, 1670 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 10.82 (s, br, 1H), 8.20 (s, br, 1H), 6.57 (d, *J* = 2.7 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 2.90 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.21 (s, 3H), 2.05 (s, br, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ

167.1, 130.5, 125.5, 124.9, 121.5, 119.6, 116.6, 114.5, 109.3, 63.4, 60.0, 29.1, 18.4, 18.1, 15.7, 14.7, 14.1, 11.0; HRMS m/z calcd for $C_{18}H_{27}N_2O_2$ $[M+H]^+$ 319.2022, found: 319.2025.



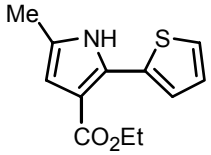
4.58g

3',4'-Diethyl-4-(2-hydroxy-ethyl)-1*H*-1'*H*-[2,2']bipyrrolyl-3-carboxylic acid ethyl ester (4.58g). The title compound was prepared from cyclopropane **4.52c** and 3,4-diethyl-1*H*-pyrrole-2-carbonitrile **4.56b** according to the general procedure A for bipyrrole synthesis (–40 °C, $C_2H_5NO_2$, 1.0 h). Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (86 mg, 42%): R_f 0.45 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.13 (s, br, 1H), 8.41 (s, br, 1H), 6.609 (s, 1H), 6.607 (s, 1H), 4.27 (dq, *J* = 2.0, 7.2 Hz, 2H), 3.81 (t, *J* = 6.2 Hz, 2H), 2.97 (dt, *J* = 2.0, 6.2 Hz, 2H), 2.63 (tq, *J* = 2.0, 7.6 Hz, 2H), 2.47 (dt, *J* = 2.0, 7.6 Hz, 2H), 1.33 (dt, *J* = 2.0, 7.6 Hz, 3H), 1.24-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 167.2, 133.1, 125.7, 122.0, 121.9, 119.5, 116.4, 114.9, 108.8, 63.0, 60.2, 30.9, 18.5, 18.1, 15.8, 14.8, 14.2; HRMS m/z calcd for $C_{17}H_{25}N_2O_3$ $[M+H]^+$ 305.1865, found: 305.1861.



4.60a

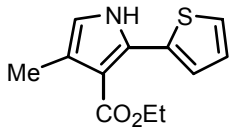
2-Thiophen-2-yl-1*H*-3-carboxylic acid ethyl ester (4.60a). The title compound was prepared from cyclopropane **4.52a** and 2-thiophenecarbonitrile **4.59** according to the general procedure B for thienylpyrrole synthesis (–30 °C, $C_2H_5NO_2$, 3.5 h). Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (136 mg, 47%): R_f 0.51 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.56 (s, br, 1H), 7.50 (dd, *J* = 2.0, 1.2 Hz, 1H), 7.31 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.05 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.72-6.70 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 164.7, 133.0, 130.1, 127.2, 127.1, 125.9, 117.8, 112.6, 112.4, 59.8, 14.4; HRMS m/z calcd for $C_{11}H_{12}NO_2S$ $[M+H]^+$ 222.0589, found: 222.0583.



4.60b

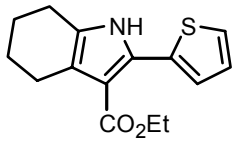
5-Methyl-2-thiophen-2-yl-1*H*-3-carboxylic acid ethyl ester (4.60b). The title compound was prepared from cyclopropane **4.52g** and 2-thiophenecarbonitrile **4.59** according to the general procedure B for thienylpyrrole synthesis (–15 °C, CH_3NO_2, 3.0 h). Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for

elution gave the title compound as a colorless syrup (114 mg, 69%): R_f 0.46 (25% EtOAc/hexanes); IR (thin film) ν 3390-3240, 1675 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.39 (s, br, 1H), 7.46 (dd, *J* = 3.3, 1.0 Hz, 1H), 7.27 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.02 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.36 (dd, *J* = 1.0, 1.0 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 164.8, 133.4, 129.0, 127.9, 127.1, 126.7, 125.4, 112.5, 109.8, 59.7, 14.4, 12.7; HRMS m/z calcd for $C_{12}H_{14}NO_2S$ $[M+H]^+$ 236.0745, found: 236.0743.



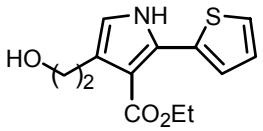
4.60c

4-Methyl-2-thiophen-2-yl-1*H*-3-carboxylic acid ethyl ester (4.60c). The title compound was prepared from cyclopropane **4.52i** and 2-thiophenecarbonitrile **4.59** according to the general procedure B for thienylpyrrole synthesis (–25 °C, CH_3NO_2, 3.0h). Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (119 mg, 63%): R_f 0.37 (25% EtOAc/hexanes); ^1H NMR (400 MHz, $CHCl_3$) δ 8.25 (s, br, 1H), 7.34 (d, *J* = 1.2 Hz, 1H), 7.30 (d, *J* = 5.2, Hz, 1H), 7.03 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.54 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.4, 133.8, 130.3, 127.1, 127.0, 126.8, 122.8, 116.9, 109.7, 59.6, 14.3, 12.7; HRMS m/z calcd for $C_{12}H_{14}NO_2S$ $[M+H]^+$ 236.0745, found: 236.0753.



4.60d

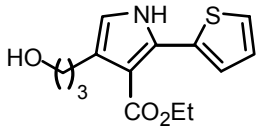
2-Thiophen-2-yl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester (4.60d). The title compound was prepared from cyclopropane **4.52h** and 2-thiophenecarbonitrile **4.59** according to the general procedure B for thienylpyrrole synthesis (–25 °C, CH_3NO_2, 1.5 h). Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (83 mg, 37%): R_f 0.52 (25% EtOAc/hexanes); IR (thin film) ν 3650-3150, 1650 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.14 (s, br, 1H), 7.36 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.25 (dt, *J* = 0.8, 5.2 Hz, 1H), 7.01 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.23 (q, *J* = 7.2 H, 2H), 2.72 (t, *J* = 6.0 H, 2H), 2.53 (t, *J* = 6.0 H, 2H), 1.80-1.73 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.4, 134.0, 128.5, 128.1, 127.0, 126.7, 125.3, 120.4, 110.8, 59.4, 30.9, 23.4, 22.7, 22.5, 14.3; HRMS m/z calcd for $C_{15}H_{18}NO_2S$ $[M+H]^+$ 276.1058, found: 276.1052.



4.60e

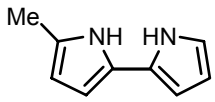
4-(2-Hydroxyl-ethyl-2-thiophen-2-yl-1*H*-3-carboxylic acid ethyl ester (4.60e). The title compound was prepared from cyclopropane **4.52d** and 2-thiophenecarbonitrile **4.59** according to the general procedure B for thienylpyrrole synthesis (–40 °C, $C_2H_5NO_2$, 4.0 h). Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution

gave the title compound as a colorless syrup (114 mg, 41%): R_f 0.31 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.72 (s, br, 1H), 7.31 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.02 (dd, J = 4.8, 3.6 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.81 (t, J = 6.0 Hz, 2H), 2.96 (t, J = 6.0 Hz, 2H), 2.45 (s, br, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.7, 133.6, 130.5, 127.4, 126.8, 126.1, 123.7, 117.8, 111.7, 63.5, 59.9, 29.9, 14.1; HRMS m/z calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 266.0851, found: 266.0851.



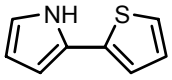
4.60f

4-(3-Hydroxyl-propyl-2-thiophen-2-yl-1*H*-3-carboxylic acid ethyl ester (4.60f). The title compound was prepared from cyclopropane **4.52b** and 2-thiophenecarbonitrile **4.59** according to the general procedure B for thienylpyrrole synthesis (–30 °C, $C_2H_5NO_2$, 2.5 h). Purification by flash chromatography on silica gel with 3:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (187 mg, 73%): R_f 0.25 (50% EtOAc/hexanes); IR (thin film) ν 3620-3175, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.92 (s, br, 1H), 7.31-7.25 (m, 2H), 7.03-7.01 (m, 2H), 6.55 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.65-3.63 (m, 2H), 2.79 (q, J = 7.6 Hz, 2H), 2.54 (s, br, 1H), 1.83-1.82 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.7, 133.8, 130.1, 127.2, 126.8, 126.7, 125.9, 116.9, 111.5, 61.8, 59.8, 33.7, 22.3, 14.1; HRMS m/z calcd for $C_{14}H_{18}NO_3S$ $[M+H]^+$ 280.1007, found: 280.0997.



4.61

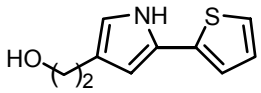
5-Methyl-1H,1'H-[2,2']bipyrrolyl (4.61). To a solution of **4.57a** (143 mg, 0.65 mmol) in ethylene glycol (8.0 mL) was added powdered NaOH (260 mg, 6.5 mmol). After stirring at 160 °C for 5 min, the reaction mixture was treated with 10% aqueous NaCl (15 mL) and resulting solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solution was washed with H_2O (8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as white solid (88, 92%): R_f 0.52 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.12 (s, br, 1H), 7.88 (s, br, 1H), 6.72 (dd, *J* = 4.0, 2.8 Hz, 1H), 6.22 (dd, *J* = 6.4, 2.4 Hz, 1H), 6.15 (dt, *J* = 4.4, 1.6 Hz, 1H), 6.06 (t, *J* = 2.8 Hz, 1H), 5.90-5.88 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 127.7, 126.2, 124.5, 117.2, 109.2, 107.0, 103.6, 102.9, 13.0; HRMS m/z calcd for $C_9H_{11}N_2$ $[M+H]^+$ 147.0922, found: 147.0918.



4.62

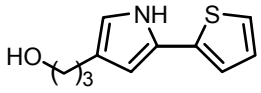
2-Thiophen-2-yl-1H-pyrrole (4.62). The title compound was prepared from **4.60a** according to the decarboxylation procedure described above for preparation of **4.61**. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (81 mg, 96%): R_f 0.41 (33%

EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.28 (s, br, 1H), 7.13 (dt, *J* = 8.0, 3.2 Hz, 1H), 7.02-6.99 (m, 2H), 6.79 (dt, *J* = 8.4, 1.6, 1H), 6.41-6.39 (m, 1H), 6.25 (dt, *J* = 6.0, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 136.2, 127.6, 122.7, 120.9, 118.5, 110.0, 109.7, 106.7; HRMS m/z calcd for C_8H_8NS $[M+H]^+$ 150.0377, found: 150.0378.



4.63

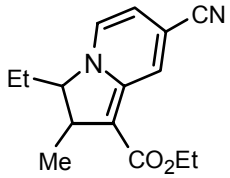
2-(5-Thiophen-2-yl-1*H*-pyrrol-3-yl)-ethanol (4.63). The title compound was prepared from **4.60e** according to the decarboxylation procedure described above for preparation of **4.61**. Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (62 mg, 81%): R_f 0.52 (66% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.17 (s, br, 1H), 7.12 (dd, *J* = 3.6, 2.4 Hz, 1H), 6.99 (s, 1H), 6.98(d, *J* = 0.8 Hz, 1H), 6.65 (dd, *J* = 2.4, 1.6 Hz, 1H), 6.62 (t, *J* = 2.4 Hz, 1H), 3.79 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 6.4 Hz, 2H), 1.57 (s, br, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 136.1, 127.6, 127.1, 122.7, 121.5, 120.8, 116.9, 107.1, 63.3,30.4; HRMS m/z calcd for $C_{10}H_{12}NS$ $[M+H]^+$ 194.0644, found: 194.0640.



4.64

3-(5-Thiophen-2-yl-1H-pyrrol-3-yl)-propan-1-ol (4.64). The title compound was prepared from **4.60f** according to the decarboxylation procedure described above for

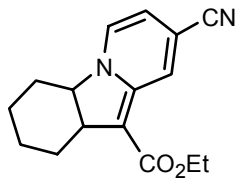
preparation of **4.61**. Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (86 mg, 87%): R_f 0.50 (66% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.16 (s, br, 1H), 7.10 (t, *J* = 3.2 Hz, 1H), 6.98 (d, *J* = 0.4 Hz, 1H),6.97(s, 1H), 6.57 (s, 1H), 6.27 (t, *J* = 2.0 Hz, 1H), 3.70 (t, *J* = 6.4 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.86 (tt, *J* = 6.4, 6.4 Hz, 2H), 1.40 (s, br, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 136.3, 127.6, 126.7, 125.2, 122.5, 120.6, 115.9,106.9, 62.7, 33.7,23.2; HRMS m/z calcd for $C_{11}H_{14}NS$ $[M+H]^+$ 208.0796, found: 208.0802.



4.67a

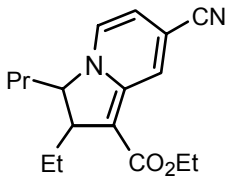
7-Cyano-2,3-diethyl-2,3-dihydro-indolizine-1-carboxylic acid ethyl ester (4.67a) To a solution of the cyclopropane **4.52f** (186 mg, 1.0 mmol) and **4.65** (520 mg, 5.0 mmol, 5.0 eq) in CH_3NO_2 (2.0 mL) at −18 °C was added TMSOTf (1.0 mmol). The resulting mixture was allowed to warm to rt in 2.0 h and then poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (10 mL). After 2 min the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic solution was washed with H_2O (2 × 3 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the product as a solid (78 mg, 52%): R_f 0.38 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.55 (s, 1H), 6.87 (d, *J* = 6.8 Hz, 1H), 5.63 (dd, *J* = 6.8, 1.6 Hz, 1H), 4.19-4.04 (m, 2H), 3.51

(dq, J = 4.0, 4.0 Hz, 1H), 2.88-2.82 (m, 1H), 1.71-1.54 (m, 2H), 1.24 (t, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.9, 135.5, 125.4, 118.7, 116.9, 109.6, 103.3, 95.6, 72.6, 58.6, 39.5, 28.0, 21.4, 14.6, 8.4; HRMS m/z calcd for $C_{15}H_{17}N_2O_2$ $[M-H]^-$ 257.1290, found: 257.1292.



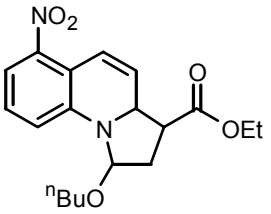
4.67b

8-Cyano-1,2,3,4,4a,10a-hexahydro-pyrido[1,2-a]indole-10-carboxylic acid ethyl ester (4.67b). The title compound was prepared from **4.52h** according to the general procedure described above for the preparation of **4.67a**. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a dark red solid (211 mg, 41%): R_f 0.34 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.61 (s, 1H), 6.96 (d, J = 0.8 Hz, 1H), 5.70 (dd, J = 7.2, 1.6 Hz, 1H), 4.19-4.06 (m, 2H), 3.98 (dt, J = 8.8, 4.0 Hz, 1H), 2.96-2.90 (m, 1H), 1.90-1.76 (m, 2H), 1.60-1.52 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.34-1.14 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.9, 149.8, 133.8, 125.5, 118.4, 117.0, 103.6, 96.8, 63.7, 58.6, 39.7, 26.8, 23.8, 21.5, 19.7, 14.7; HRMS m/z calcd for $C_{16}H_{17}N_2O_2$ $[M-H]^-$ 269.1290, found: 269.1282.

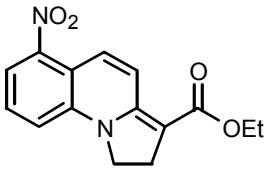


4.67c

7-Cyano-2-ethyl-3-propyl-2,3-dihydro-indolizine-1-carboxylic acid ethyl ester (4.67c). The title compound was prepared from **4.52e** according to the general procedure described above for the preparation of **4.67a**. Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a dark red solid (177 mg, 54%): R_f 0.46 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.58 (s, 1H), 6.87 (dd, *J* = 6.8, 0.4 Hz, 1H), 5.62 (dd, *J* = 6.8, 1.2 Hz, 1H), 4.25-4.15 (m, 2H), 3.70 (dq, *J* = 4.0, 4.0 Hz, 1H), 2.75 (dd, *J* = 9.6, 4.0 Hz, 1H), 1.70-1.57 (m, 3H), 1.53-1.30 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H), ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.0, 135.5, 125.8, 118.7, 116.9, 103.3, 94.0, 68.6, 58.7, 46.5, 37.9, 26.7, 17.5, 14.7, 13.8, 9.8; HRMS m/z calcd for $C_{17}H_{21}N_2O_2$ $[M-H]^-$ 285.1603, found: 285.1614.



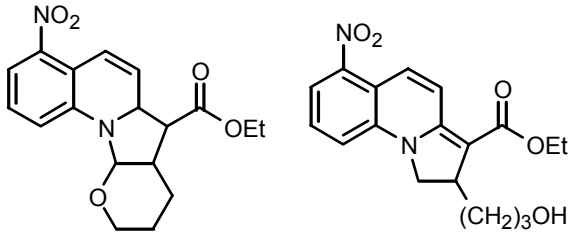
4.78a



4.79a

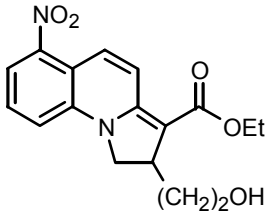
1-Butoxy-6-nitro-1,2,3,3a-tetrahydro-pyrrolo[1,2-*a*]quinoline-3-carboxylic acid ethyl ester (4.78a) and 6-Nitro-1,2-dihydro-pyrrolo[1,2-*a*]quinoline-3-carboxylic acid

ethyl ester (4.79a). The title compounds were prepared from **4.52a** and **4.77** according to the general procedure described above for the preparation of **4.67a**. Purification by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the title compounds: **4.78a**: (81 mg, 31%, pale yellow syrup): R_f 0.65 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (q, *J* = 10.0 Hz, 2H), 7.48 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 5.90 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.41 (dt, *J* = 12.8, 6.4 Hz, 1H), 3.25 (dt, *J* = 12.8, 6.4 Hz, 1H), 3.08 (dd, *J* = 18.0, 9.2 Hz, 1H), 2.90 (dd, *J* = 18.0, 2.4 Hz, 1H), 1.46 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.24-1.22 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.1, 147.2, 139.8, 130.0, 127.9, 122.4, 117.5, 117.4, 116.0, 94.5, 88.1, 62.7, 59.6, 33.3, 31.7, 19.5, 14.9, 13.9; HRMS m/z calcd for $C_{19}H_{23}N_2O_5$ $[M-H]^-$ 359.1607, found: 359.1602; **4.79a**: (108 mg, 52%, dark red solid): R_f 0.51 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 10.0 Hz, 1H), 7.59 (d, *J* = 10.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.01 (t, *J* = 10.0 Hz, 2H), 3.00 (t, *J* = 10.0 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 148.7, 146.8, 140.7, 130.0, 127.5, 122.4, 116.1, 115.8, 115.6, 95.7, 59.1, 48.2, 27.0, 14.7; HRMS m/z calcd for $C_{15}H_{15}N_2O_4$ $[M+H]^+$ 287.1032, found: 287.1039.



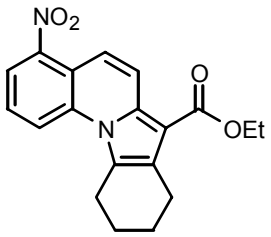
4.78b **4.79b**

4-Nitro-6a,7,7a,9,10,11a-hexahydro-8H-11-oxa-11b-aza-benzo[*c*]fluorene-7-carboxylic acid ethyl ester (4.78b) and 2-(3-Hydroxy-propyl)-6-nitro-1,2-dihydro-pyrrolo[1,2-*a*]quinoline-3-carboxylic acid ethyl ester (4.79b). The title compounds were prepared from **4.52b** and **4.77** according to the general procedure described above for the preparation of **4.67a**. Purification by flash chromatography on silica gel with 10:1 to 2:1 hexanes-EtOAc for elution gave the title compounds: **4.78b** (115 mg, 41%, pale yellow syrup): R_f 0.61 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 10.0, 2.4 Hz, 1H), 5.93 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.43-4.31 (m, 4H), 4.28-4.22 (m, 1H), 3.81 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.97 (dd, *J* = 12.0, 10.0 Hz, 1H), 2.30-2.14 (m, 2H), 1.88-1.80 (m, 2H), 1.63 (dq, *J* = 3.2, 12.0 Hz, 1H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 146.7, 142.8 127.4, 125.1, 122.2, 119.0, 117.4, 114.3, 91.3, 67.3, 61.0, 55.1, 46.5, 45.3, 25.9, 25.4, 14.1; HRMS m/z calcd for $C_{18}H_{21}N_2O_5$ $[M+H]^+$ 345.1450, found: 345.1443; **4.79b** (106.6 mg, 38%): R_f 0.38 (66% EtOAc/hexanes, dark red solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 10.4 Hz, 1H), 7.56 (d, *J* = 10.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.22-4.09 (m, 2H), 4.04 (t, *J* = 11.2 Hz, 1H), 3.71 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.62 (t, *J* = 6.0 Hz, 1H), 3.37-3.31 (m, 1H), 2.35 (s, br, 1H), 1.89-1.81 (m, 1H), 1.64-1.48 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 148.5, 146.6, 140.3, 129.9, 127.8, 122.4, 116.3, 116.1, 115.5, 99.4, 62.4, 59.0, 54.0, 39.1, 30.8, 28.9, 14.5; HRMS m/z calcd for $C_{18}H_{21}N_2O_5$ $[M+H]^+$ 345.1450, found: 345.1445.



4.79c

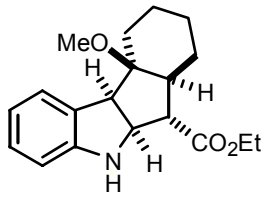
2-(2-Hydroxy-ethyl)-6-nitro-1,2-dihydro-pyrrolo[1,2-*a*]quinoline-3-carboxylic acid ethyl ester (4.79c). The title compound was prepared from **4.52c** and **4.77** according to the general procedure described above for the preparation of **4.6a**. Purification by flash chromatography on silica gel with 2:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (117 mg, 42%): R_f 0.35 (66% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (d, *J* = 10.4 Hz, 1H), 7.61 (d, *J* = 10.4 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.20 (dq, *J* = 1.6, 7.2 Hz, 1H), 4.13 (t, *J* = 11.2 Hz, 1H), 3.84 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.73-3.68 (m, 2H), 3.52-3.45 (m, 1H), 2.88 (s, br, 1H), 1.95-1.87 (m, 1H), 1.79 (dq, *J* = 7.2, 7.2 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.7, 148.8, 146.8, 140.4, 130.0, 128.2, 122.5, 116.6, 116.4, 115.6, 99.0, 60.1, 59.4, 55.3, 38.7, 36.4, 14.6; HRMS m/z calcd for $C_{17}H_{19}N_2O_5$ $[M+H]^+$ 331.1293, found: 331.1304.



4.80

4-Nitro-8,9,10,11-tetrahydro-indolo[1,2-*a*]quinoline-7-carboxylic acid ethyl ester (4.80). To a solution of the cyclopropane **4.52h** (198 mg, 1.0 mmol) and **4.77** (610 mg, 3.5 mmol, 3.5 eq) in CH_3NO_2 (4.0 mL) at −18 °C was added TMSOTf (1.0 mmol). The resulting mixture was allowed to warm to rt in 45 min and then poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (12 mL). After 2 min the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic solution was washed with H_2O (2 × 3 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure and the residue was dissolved in EtOAc (15 mL). The resulting solution was stirred in air for 48 h and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 5:1 hexanes-EtOAc for elution gave the product as a dark red solid (277 mg, 83%): R_f 0.34 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.39 (d, J = 7.6 Hz, 1H), 8.27 (dd, J = 10.0, 2.8 Hz, 1H), 7.85 (dd, J = 7.6, 2.8 Hz, 1H), 7.65 (dd, J = 10.0, 2.8 Hz, 1H), 7.45 (td, J = 7.6, 2.8 Hz, 1H), 4.35 (q, J = 7.6 Hz, 2H), 3.17 (s, 2H), 2.95 (s, 2H), 1.91-1.90 (m, 2H), 1.84-1.83 (m, 2H), 1.41 (td, J = 7.6, 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 165.1, 146.9, 135.1, 133.2, 127.7, 127.1, 125.6, 121.9, 121.5,

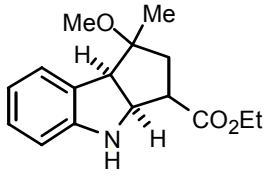
119.9, 118.8, 114.9, 106.0, 59.6, 28.5, 24.3, 23.7, 22.1, 14.5; HRMS m/z calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ 339.1345, found: 339.1352.



4.85a

10a-Methoxy-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-b]indole-6-carboxylic acid ethyl ester (4.85a). To a solution of the cyclopropane **4.52h** (198 mg, 1.0 mmol) and **4.81** (351 mg, 3.0 mmol, 3.0 eq) in CH_3NO_2 (2.5 mL) at −18 °C was added TMSOTf (1.0 mmol). The resulting mixture was stirred for 45 min and then poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (10 mL). After 2 min the resulting mixture was extracted with EtOAc (3 × 6 mL). The combined organic solution was washed with H_2O (2 × 3 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the product as white solid (301 mg, 78%): R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.15 (d, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.64 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 4.53 (dd, *J* = 10.0, 5.2 Hz, 1H), 4.20-4.11 (m, 3H), 3.45 (d, *J* = 10.8 Hz, 1H), 2.99 (dd, *J* = 12.4, 5.6 Hz, 1H), 2.68 (s, 3H), 2.52 (d, *J* = 14.0 Hz, 1H), 1.80-1.69 (m, 2H), 1.62-1.54 (m, 3H), 1.38-1.17 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.8, 152.6, 128.2, 127.3, 125.4, 117.9, 109.9,

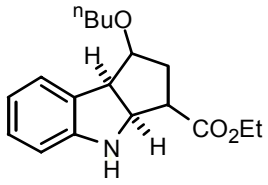
83.6, 67.0, 60.3, 58.0, 55.3, 50.5, 30.5, 25.2, 24.1, 21.4, 14.3; HRMS m/z calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1913, found: 316.1911.



4.85b

1-Methoxy-1-methyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.85b). The title compound was prepared from **4.52g**and **4.81** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound in form of three diastereomers as colorless syrups. **Diastereomer A** (35 mg, 14%): R_f 0.62 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.04 (d, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.23 (td, *J* = 7.2, 1.0 Hz, 1H), 4.77-4.71 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.04 (s, br, 1H), 3.64 (d, *J* = 8.4 Hz, 1H), 3.27-3.21 (m, 1H), 3.22 (s, 3H), 2.18 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.73 (t, *J* = 13.6 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.3, 151.7, 128.0, 127.8, 1276.3, 117.9, 108.7, 86.3, 64.7, 60.4, 56.8, 49.4, 48.5, 36.1, 19.3, 14.3; HRMS m/z calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, found: 276.1601; **Diastereomer B** (20 mg, 8%): R_f 0.58 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.09 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.66 (td, *J* = 7.2, 1.0 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 4.81(dd, *J* = 10.0, 3.6 Hz, 1H), 4.22-4.08 (m, 3H), 3.76 (d, *J* = 7.2 Hz, 1H), 3.21 (s, 3H), 2.75-2.71 (m, 1H), 2.34 (dd, *J* = 13.2, 6.0 Hz,

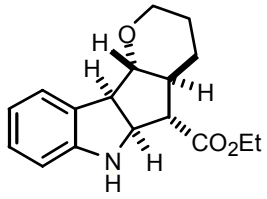
1H), 1.82 (dd, *J* = 13.2, 8.0 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.8, 151.4, 128.0, 127.6, 126.2, 118.1, 109.1, 86.4, 65.0, 60.5, 56.5, 51.9, 50.1, 38.7, 19.3, 14.2; HRMS m/z calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, found: 276.1605; **Diastereomer C** (106 mg, 42%): R_f 0.52 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.13 (d, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.71 (td, *J* = 7.2, 1.0 Hz, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 4.50 (dd, *J* = 13.2, 6.0 Hz, 1H), 4.25 (s, br, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.67 (d, *J* = 10.0 Hz, 1H), 3.09 (s, 3H), 3.02 (dt, *J* = 12.0, 6.4 Hz, 1H), 2.32 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.72 (dd, *J* = 13.2, 12.0 Hz, 1H), 1.45 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.1, 151.6, 127.8, 127.3, 125.3, 118.4, 109.5, 83.9, 66.3, 60.6, 59.0, 51.8, 49.8, 38.7, 21.7, 14.2; HRMS m/z calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, found: 276.1599.



4.85c

1-Butoxy-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.85c). The title compound was prepared from **4.52a** and **4.81** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (132 mg, 62%): R_f 0.63 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.06 (d, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.2

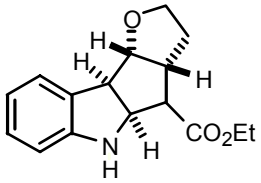
Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 5.67 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.12 (s, br, 1H), 3.79-3.76 (m, 2H), 3.46 (qdd, *J* = 7.2, 9.2, 6.4 Hz, 2H), 3.25 (qd, *J* = 6.0, 12.0 Hz, 1H), 2.10 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.86 (qd, *J* = 9.6, 4.4 Hz, 1H), 1.55 (tt, *J* = 12.8, 6.4, Hz, 2H), 1.39 (qt, *J* = 6.4, 12.8 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.2, 151.1, 128.7, 128.0, 124.5, 118.1, 108.5, 86.8, 68.4, 63.1, 60.4, 54.3, 49.4, 31.9, 31.6, 19.4, 14.3, 13.9; HRMS m/z calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$ 304.1913, found: 304.1916.



4.85d

2,3,4a,4b,9,9a,10,10a-Octahydro-1H-4-oxa-9-aza-indeno[1,2-*a*]indene-10-carboxylic acid ethyl ester (4.85d). The title compound was prepared from **4.52b** and **4.81** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as inseparatable mixture of two diastereomers as colorless syrups (179 mg, 74%): R_f 0.47 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.22 (d, *J* = 7.2 Hz, 0.55H), 7.14 (d, *J* = 7.6 Hz, 0.45H), 7.05 (t, *J* = 7.6 Hz, 0.55H), 6.99 (t, *J* = 7.6 Hz, 0.45H), 6.71 (t, *J* = 7.2 Hz, 0.55H), 6.65 (t, *J* = 7.2 Hz, 0.45H), 6.58 (d, *J* = 7.6 Hz, 0.55H), 6.50 (d, *J* = 7.6 Hz, 0.45H), 4.59-4.50 (m, 1H), 4.29-4.13 (m, 3H), 4.07-4.00 (m, 1.45H), 3.63 (t, *J* = 8.0 Hz, 0.55H), 3.52-3.40 (m, 1H), 3.35 (dd, *J* = 10.4, 7.6 Hz, 0.45 H), 3.18 (t, *J* = 9.6 Hz, 0.55 H), 2.44 (dd, *J* = 12.8, 6.0 Hz, 0.45 H), 2.40 (dd, *J* = 12.0,

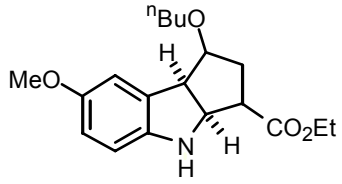
6.4 Hz, 0.55 H), 2.25-2.21 (m, 0.45H), 2.12-2.08 (m, 0.55H), 1.84-1.72 (M, 1H), 1.66-1.56 (m, 1H), 1.53-1.48 (m, 1H), 1.34-1.21 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.8, 171.9, 151.7, 150.0, 129.8, 128.1, 127.8, 126.8, 126.7, 124.5, 118.7, 118.0, 109.4, 108.4, 89.0, 84.4, 69.2, 69.0, 63.8, 61.0, 60.6, 60.3, 55.6, 52.7, 50.8, 47.7, 45.3, 39.2, 28.5, 28.1, 25.5, 25.2, 14.3, 14.2; HRMS m/z calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1600, found: 288.1598.



4.85e

2,3,4a,4b,9,9a,10,10a-Octahydro-1H-4-oxa-9-aza-indeno[1,2-*a*]indene-10-carboxylic acid ethyl ester (4.85e). The title compound was prepared from **4.52c** and **4.81** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups. **Diastereomer A** (53 mg, 25%): R_f 0.55 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.11 (d, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.64 (td, *J* = 7.6, 0.8 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.98-4.92 (m, 1H), 4.34 (td, *J* = 8.0, 1.0 Hz, 1H), 4.26 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.22-4.14 (m, 3H), 3.97-3.92 (m, 2H), 2.65 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.38-2.28 (m, 1H), 1.98-1.92 (m, 1H), 1.70-1.60 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.9, 152.2, 127.9, 126.3, 125.7, 118.1, 108.4, 89.8, 75.6, 69.7, 60.4, 49.1, 46.0, 45.1, 26.4, 14.3; HRMS m/z calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1443, found: 274.1438; **Diastereomer B**

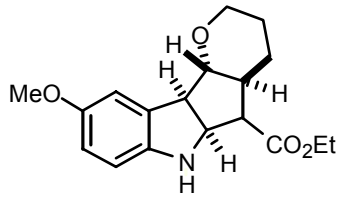
(70 mg, 33%): R_f 0.61 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.20 (d, *J* = 7.6 Hz, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.70 (td, *J* = 7.6, 0.8 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 4.96 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.42-5.29 (m, 2H), 4.30 (s, br, 1H), 4.23-4.15 (M, 2H), 3.75 (t, *J* = 10.2 Hz, 1H), 3.65 (t, *J* = 10.2 Hz, 1H), 2.57 (dd, *J* = 12.4, 5.6 Hz, 1H), 2.38-2.28 (m, 1H), 1.97 (tdd, *J* = 6.4, 11.2, 2.4 Hz, 1H), 1.76-1.65 (m, 1H), 1.29 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.9, 150.4, 128.9, 128.2, 124.7, 118.9, 109.6, 93.9, 75.5, 72.9, 60.8, 51.6, 51.4, 47.6, 26.4, 14.3; HRMS m/z calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1443, found: 274.1446.



4.89a

1-Butoxy-7-methoxy-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.89a). The title compound was prepared from **4.52a** and **4.87** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomer s as a colorless syrup. **Diastereomer A** (89 mg, 31%): R_f 0.42 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.68 (d, *J* = 2.0 Hz, 1H), 6.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.43 (d, *J* = 8.8 Hz, 1H), 4.66 (dd, *J* = 8.4, 5.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.85 (s, br, 1H), 3.77-3.74 (m, 2H), 3.71 (s, 3H), 3.47-3.42 (m, 2H), 3.23 (td, *J* = 6.4, 7.2 Hz, 1H), 2.08 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.87 (dt, *J* = 4.4, 13.2 Hz, 1H), 1.55 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.38 (tq,

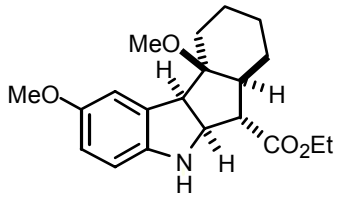
J = 7.2, 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.2, 153.2, 145.2, 130.5, 113.0, 111.3, 109.3, 86.6, 68.4, 63.8, 60.3, 56.0, 54.9, 49.5, 32.0, 31.6, 19.4, 14.3, 13.9; HRMS m/z calcd for $C_{19}H_{28}NO_4$ $[M+H]^+$ 334.2018, found: 334.2021. **Diastereomer B** (123 mg, 43%): R_f 0.38 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.74 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 4.57 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.99-3.95 (m, 2H), 3.88 (s, br, 1H), 3.71 (s, 3H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.78 (td, *J* = 5.6, 13.2 Hz, 1H), 2.20-2.14 (m, 1H), 1.82-1.73 (m, 1H), 1.56 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.37 (tq, *J* = 7.6, 7.6 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 172.3, 152.8, 146.0, 128.6, 113.7, 113.4, 109.1, 81.3, 70.1, 62.8, 60.4, 55.9, 49.2, 47.7, 31.9, 30.5, 19.4, 14.3, 13.9; HRMS m/z calcd for $C_{19}H_{28}NO_4$ $[M+H]^+$ 334.2018, found: 334.2017.



4.89b

6-Methoxy-2,3,4a,4b,9,9a,10,10a-octahydro-1H-4-oxa-9-aza-indeno[1,2-*a*]indene-10-carboxylic acid ethyl ester (4.89b). The title compound was prepared from **4.52b** and **4.87** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as inseparatable mixture of two diastereomers as colorless syrups (129 mg, 68%): R_f 0.35 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz,

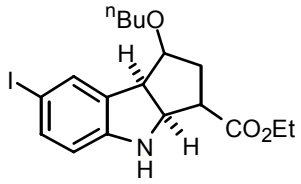
$CHCl_3$) δ 6.83 (d, *J* = 2.4 Hz, 0.55H), 6.77 (d, *J* = 2.4 Hz, 0.45H), 6.63 (dd, *J* = 8.4, 2.8 Hz, 0.55H), 6.56 (dd, *J* = 8.4, 2.8 Hz, 0.45H), 6.52 (d *J* = 8.0 Hz, 0.55H), 6.43 (d, *J* = 8.0 Hz, 0.45H), 4.56-4.49 (m, 1H), 4.20-3.96 (m, 5H), 3.72 (s, 1.65H), 3.70 (s, 1.35H), 3.49-3.39 (m, 1H), 3.32 (dd, *J* = 10.0, 8.0 Hz, 0.55H), 3.16 (t, *J* = 10.0 Hz, 0.45 H), 2.43-2.35 (m, 1H), 2.22-2.05 (m, 1H), 1.81-1.70 (m, 1H), 1.64-1.45 (m, 3H), 1.28-1.21 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.8, 171.9, 153.6, 152.8, 145.7, 143.8, 131.6, 128.6, 113.7, 113.2, 113.1, 110.6, 110.5, 109.2, 89.0, 84.2, 69.2, 69.0, 64.4, 61.6, 60.6, 60.2, 55.9, 55.8, 55.6, 52.7, 51.3, 48.3, 45.4, 39.3, 28.4, 28.1, 25.5, 25.2, 14.3; HRMS m/z calcd for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1705, found: 318.1709.



4.89c

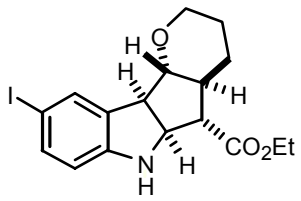
2,10a-Dimethoxy-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.89c). The title compound was prepared from **4.52h** and **4.87** at −18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a pale yellow solid (142 mg, 72%): R_f 0.54 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.77 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 4.51 (dd, *J* = 10.4, 5.6 Hz, 1H), 4.18-4.09 (m, 2H), 3.70 (s, 3H), 3.39 (d, *J* = 10.0 Hz, 1H), 2.96 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.69 (s, 3H), 2.48 (d, *J* = 14.0 Hz, 1H), 1.78-1.65 (m, 2H), 1.60-1.52 (m, 3H), 1.36-1.13 (m, 4H), 1.23

(t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.8, 152.9, 146.6, 129.0, 113.2, 112.2, 110.7, 83.5, 67.5, 60.3, 58.5, 55.9, 55.4, 53.6, 50.5, 30.4, 25.1, 24.0, 21.3, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$ 346.2018, found: 346.2028



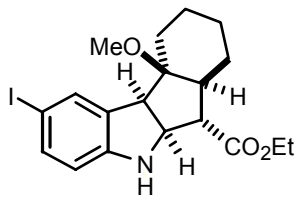
4.90a

1-Butoxy-7-iodo-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.90a). The title compound was prepared from **4.52a** and **4.88** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound as a yellow solid (93 mg, 51%): R_f 0.41 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.30 (s, 1H), 7.22 (dd, J = 8.4, 1.6 Hz, 1H), 6.26 (d, J = 8.0 Hz, 1H), 4.69-4.63 (m, 1H), 4.17 (t, J = 7.2 Hz, 2H), 4.14-4.09 (m, 1H), 3.73 (d, J = 4.8 Hz, 2H), 3.48-3.39 (m, 2H), 3.23 (td, J = 5.6, 12.8 Hz, 1H), 2.11(dd, J = 13.6, 5.6 Hz, 1H), 1.80 (td, J = 13.6, 4.0 Hz, 1H), 1.58-1.50 (m, 3H), 1.38 (dt, J = 7.2, 7.2 Hz, 2H), 1.30-1.23 (m, 4H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.0, 150.8, 136.6, 133.2, 131.7, 112.5, 110.4, 86.6, 68.5, 63.3, 60.4, 53.9, 49.2, 31.9, 31.7, 19.4, 14.3, 13.9; HRMS m/z calcd for $C_{18}H_{25}INO_3$ $[M+H]^+$ 430.0879, found: 430.0875.



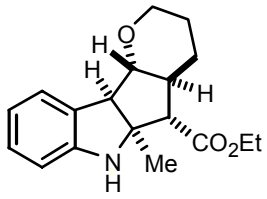
4.90b

6-Iodo-2,3,4a,4b,9,9a,10,10a-octahydro-1H-4-oxa-9-aza-indeno[1,2-*a*]indene-10-carboxylic acid ethyl ester (4.90). The title compound was prepared from **4.52b** and **4.88** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless solid (218 mg, 61%): R_f 0.61 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.46 (s, 1H), 7.30 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.34 (d, *J* = 8.0 Hz, 1H), 4.51 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.26 (s, br, 1H), 4.24-4.14 (m, 2H), 4.06-4.03 (m, 1H), 3.57 (t, *J* = 8.8 Hz, 1H), 3.43 (td, *J* = 11.2, 4.0 Hz, 1H), 3.14 (t, *J* = 9.6 Hz, 1H), 2.36 (dd, *J* = 12.0, 6.4 Hz, 1H), 2.10 (dd, *J* = 12.0, 2.8 Hz, 1H), 1.73 (dq, *J* = 3.2, 12.0 Hz, 1H), 1.63-1.57 (m, 2H), 1.36-1.24 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.6, 149.7, 136.8, 133.2, 132.6, 111.3, 88.8, 79.2, 69.1, 64.0, 60.8, 55.5, 50.4, 45.2, 28.2, 25.5, 14.3; HRMS m/z calcd for $C_{17}H_{21}INO_3$ $[M+H]^+$ 414.0566, found: 414.0558.



4.90c

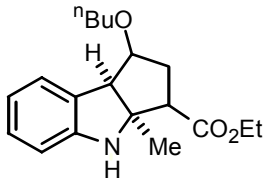
2-Iodo-10a-methoxy-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.90c). The title compound was prepared from **4.52h** and **4.88** at −18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound colorless solid (171 mg, 54%): R_f 0.65 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.40 (s, 1H), 7.28 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.52 (dd, *J* = 10.0, 5.6 Hz, 1H), 4.26 (s, br, 1H), 4.20-4.07 (m, 2H), 3.38 (d, *J* = 10.0 Hz, 1H), 2.95 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.74 (s, 3H), 2.49 (d, *J* = 13.2 Hz, 1H), 1.76-1.69 (m, 2H), 1.58-1.52 (m, 3H), 1.32-1.19 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.5, 152.2, 136.8, 133.9, 130.3, 111.7, 83.8, 78.2, 67.1, 60.4, 57.7, 55.2, 53.4, 50.8, 30.5, 25.1, 24.0 21.4, 14.3; HRMS m/z calcd for $C_{19}H_{25}INO_3$ $[M+H]^+$ 442.0879, found: 442.0855.



4.91a

10a-Methoxy-5-methyl-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.91a). The title compound was prepared from **4.52** and 2-methyl indole at −18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (128 mg, 74%): R_f 0.42 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.12-7.05 (m, 2H), 6.59 (t,

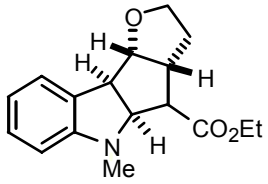
J = 7.2 Hz, 1H), 6.43 (d, J = 8.0 Hz, 1H), 4.25-4.14 (m, 2H), 4.03 (dd, J = 10.2, 5.2 Hz, 1H), 3.38 (d, J = 10.0 Hz, 1H), 2.98 (dd, J = 12.4, 4.8 Hz, 1H), 2.78 (s, 3H), 2.70 (s, 3H), 2.53 (d, J = 10.2 Hz, 1H), 1.90-1.83 (m, 1H), 1.74-1.70 (m, 1H), 1.65-1.55 (m, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.36-1.18 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.9, 154.5, 128.4, 127.3, 125.0, 116.8, 107.4, 83.4, 75.4, 60.4, 56.9, 54.0, 53.7, 50.5, 35.5, 30.5, 25.2, 24.1, 21.3, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2076.



4.91b

1-Butoxy-3a-methyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.91b). The title compound was prepared from **4.52b** and 2-methyl indole at –18 °C according to the general procedure described above for the preparation of **4.85a**. Purification by flash chromatography on silica gel with 20:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups. **Diastereomer A** (33 mg, 12%): R_f 0.52 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.07 (d, J = 7.2 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 6.63 (td, J = 7.2, 0.8 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.98 (ddd, J = 12.4, 9.6, 6.0 Hz, 1H), 3.92 (ddd, J = 3.2, 3.2, 0.8 Hz, 1H), 3.56-3.48 (m, 3H), 2.63 (dd, J = 13.2, 6.0 Hz, 1H), 2.20 (dd, J = 6.0, 6.0 Hz, 1H), 1.83 (q, J = 12.0 Hz, 1H), 1.61-1.51 (m, 5H), 1.38-1.24 (m, 5H), 0.90 (t, J = 7.2 Hz, 3H); HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2063. **Diastereomer B** (152 mg, 57%): R_f 0.61 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz,

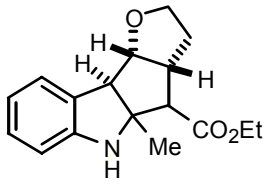
$CHCl_3$) δ 7.05 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 4.18 (qd, *J* = 7.2, 0.8 Hz, 2H), 3.71 (d, *J* = 4.4 Hz, 1H), 3.68 (s, br, 1H), 3.53-3.43 (m, 2H), 3.38 (s, 1H), 3.09 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.12 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.92 (dq, *J* =1.0, 12.4 Hz, 1H), 1.62-1.55 (m, 2H), 1.58 (s, 3H), 1.42 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.28 (dt, *J* = 1.2, 6.4 Hz, 3H), 0.95 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.1, 150.1, 128.0, 127.9, 124.7, 117.9, 108.4, 85.7, 71.1, 68.7, 61.7, 60.2, 53.4, 33.7, 31.9, 27.7, 19.4, 14.3, 13.9; HRMS m/z calcd for $C_{19}H_{28}NO_3$ $[M+H]^+$ 318.2069, found: 318.2077.



4.91c

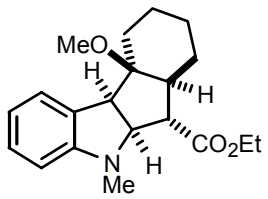
5-methyl-2,3,4a,4b,9,9a,10,10a-Octahydro-1H-4-oxa-9-aza-indeno[1,2-*a*]indene-10-carboxylic acid ethyl ester (4.91c). The title compound was prepared from **4.52c** and 1-methyl indole at −18 °C according to the general procedure described above for the preparation of **4.85a**. Purification by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups (124 mg, 69%): R_f 0.72 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.16 (d, *J* = 7.2 Hz, 1H), 7.10 (dt, *J* = 0.8, 7.6 Hz, 1H), 6.64 (dt, *J* = 0.8, 7.2 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 4.56 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.43-4.31 (m, 2H), 4.26-4.19 (m, 2H), 3.76 (t, *J* = 10.4 Hz, 1H), 3.53 (t, *J* = 10.0 Hz, 1H), 2.80 (s, 3H), 2.62 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.45 (dq, *J* = 6.4, 12.0 Hz, 1H), 2.01-1.94 (m, 1H), 1.71(dddd, *J* =

11.6, 11.6, 9.6, 9.6 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.0, 151.9, 128.6, 128.3, 124.3, 117.5, 106.6, 92.8, 81.0, 75.5, 60.8, 52.6, 49.6, 46.8, 34.2, 26.5, 14.2; HRMS m/z calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1600, found: 288.1602.



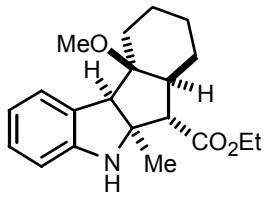
4.91d

6-methyl-2,3,4a,4b,9,9a,10,10a-Octahydro-1H-4-oxa-9-aza-indeno[1,2-*a*]indene-10-carboxylic acid ethyl ester (4.91d). The title compound was prepared from **4.52c** and 2-methyl indole at −18 °C according to the general procedure described above for the preparation of **4.85a**. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (124 mg, 72%): R_f 0.45 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.10 (d, J = 7.2 Hz, 1H), 7.02 (dt, J = 0.8, 7.6 Hz, 1H), 6.66 (dt, J = 1.2, 7.2 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.32 (dt, J = 2.4, 8.8 Hz, 1H), 4.24-4.16 (m, 3H), 4.03 (s, br, 1H), 3.95 (dd, J = 10.8, 8.0 Hz, 1H), 3.53 (d, J = 7.6 Hz, 1H), 2.49 (d, J = 12.1 Hz, 1H), 2.35 (dq, J = 6.4, 12.0 Hz, 1H), 1.98-1.91 (m, 1H), 1.65 (s, 3H), 1.69-1.63 (m, 1H), 1.28 (t, J = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 171.9, 151.2, 128.1, 126.4, 125.5, 117.9, 108.2, 88.5, 78.9, 74.9, 60.4, 54.4, 53.0, 47.5, 29.2, 26.7, 14.3.



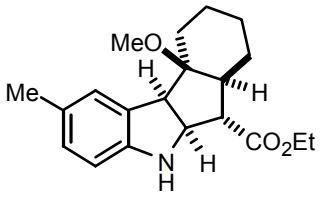
4.91e

10a-Methoxy-5-methyl-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.91e). The title compound was prepared from **4.52h** and 1-methyl indole at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomer as a colorless syrup (175 mg, 88%): R_f 0.42 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.12-7.05 (m, 2H), 6.59 (t, *J* = 7.2 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 4.25-4.14 (m, 2H), 4.03 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.38 (d, *J* = 10.0 Hz, 1H), 2.98 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.78 (s, 3H), 2.70 (s, 3H), 2.53 (d, *J* = 10.2 Hz, 1H), 1.90-1.83 (m, 1H), 1.74-1.70 (m, 1H), 1.65-1.55 (m, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.36-1.18 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.9, 154.5, 128.4, 127.3, 125.0, 116.8, 107.4, 83.4, 75.4, 60.4, 56.9, 54.0, 53.7, 50.5, 35.5, 30.5, 25.2, 24.1, 21.3, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2076.



4.91f

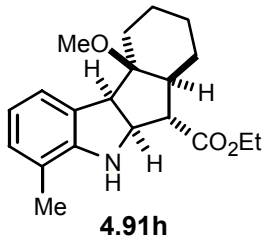
10a-Methoxy-5a-methyl-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.91f). The title compound was prepared from **4.52h** and 2-methyl indole at −18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (166 mg, 89%): R_f 0.67 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.00 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.61 (td, *J* = 7.6, 0.8 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 4.22-4.14 (m, 2H), 3.89 (s, br, 1H), 3.48 (s, 1H), 3.24 (s, 3H), 2.91 (d, *J* = 12.0 Hz, 1H), 2.13 (d, *J* = 14.0 Hz, 1H), 1.81 (td, *J* = 12.0, 4.0 Hz, 1H), 1.71-1.03 (m, 7H), 1.56 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.1, 151.0, 127.9, 126.5, 125.7, 117.3, 108.5, 84.4, 70.7, 59.9, 59.3, 57.7, 48.1, 47.7, 28.9, 28.0, 24.8, 23.8, 20.9, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 30.2070.



4.91g

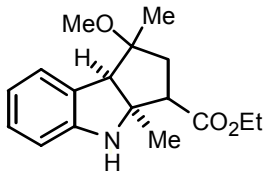
10a-Methoxy-2-methyl-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.91g). The title compound was prepared from **4.52h** and 5-methyl indole at −18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as white solid (185 mg, 77%): R_f 0.74 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.98 (s, 1H), 6.85 (d, *J* = 8.0 Hz,

1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.51 (dd, *J* = 10.0, 5.6 Hz, 2H), 4.19-4.09 (m, 3H), 3.40 (d, *J* = 10.4 Hz, 1H), 2.98 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.69 (s, 3H), 2.52 (d, *J* = 13.2 Hz, 1H), 2.21 (s, 3H), 1.80-1.70 (m, 2H), 1.62-1.54 (m, 3H), 1.34-1.08 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.9, 150.3, 128.6, 127.7, 127.4, 126.1, 110.0, 83.5, 67.3, 60.3, 58.2, 55.4, 53.6, 50.5, 30.5, 25.2, 24.1, 21.4, 20.7, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2063.



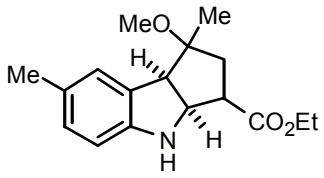
4.91h

10a-Methoxy-4-methyl-5,5a,6,6a,7,8,9,10,10a,10b-decahydro-indeno[2,1-*b*]indole-6-carboxylic acid ethyl ester (4.91h). The title compound was prepared from **4.52h** and 7-methyl indole at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound as a colorless syrup (225 mg, 81%): R_f 0.64 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.02 (d, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.58 (t, *J* = 7.2 Hz, 1H), 4.54 (dd, *J* = 10.8, 5.6 Hz, 1H), 4.23-4.08 (m, 3H), 4.01 (s, br, 1H), 3.46 (d, *J* = 10.8 Hz, 1H), 3.00 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.66 (s, 3H), 2.51 (d, *J* = 14.0 Hz, 1H), 2.11 (s, 3H), 1.81-1.54 (m, 5H), 1.38-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 176.0, 151.4, 129.1, 126.6, 123.0, 119.3, 118.1, 83.7, 67.0, 60.4, 58.4, 55.5, 53.7, 50.5, 30.6, 25.2, 24.1, 21.4, 16.9, 14.4; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2075.



4.91i

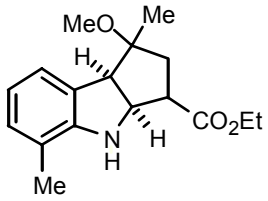
1-Methoxy-1,3a-dimethyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.91i). The title compound was prepared from **4.52g** and 2-methyl indole at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups. **Diastereomer A** (51 mg, 27%): R_f 0.54 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.04-6.98 (m, 2H), 6.62 (t, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.82 (s, br, 1H), 3.24 (s, 1H), 3.23 (s, 3H), 3.04 (dd, *J* =13.2, 5.6 Hz, 1H), 2.18 (ddd, *J* = 13.2, 5.6, 2.4 Hz, 1H), 1.74 (t, *J* = 13.2 Hz, 1H), 1.55 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.1, 150.5, 128.0, 126.7, 126.6, 117.5, 108.7, 85.1, 72.4, 64.2, 60.1, 52.5, 49.2, 38.1, 27.6, 19.3, 14.3; HRMS m/z calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found: 290.1763. **Diastereomer B** (103 mg, 54%): R_f 0.41 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.12 (d, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.65 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.81 (s, br, 1H), 3.14 (t, *J* = 6.0 Hz, 1H), 3.12 (s, 3H), 2.76 (dd, *J* =13.2, 6.4 Hz, 1H), 2.15 (t, *J* = 12.4 Hz, 1H), 1.96 (ddd, *J* = 12.4, 6.0, 0.8 Hz, 1H), 1.54 (s, 3H), 1.39 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 172.4, 150.2, 127.9, 127.8, 127.0, 117.7, 108.5, 81.7, 70.8, 65.2, 60.4, 52.9, 51.5, 37.7, 28.3, 25.8, 14.3; HRMS m/z calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found: 290.1750.



4.91j

1-Methoxy-1,7-dimethyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.91j). The title compound was prepared from **4.52g** and 5-methyl indole at −18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of three diastereomers as colorless syrups. **Diastereomer A** (41 mg, 21%): R_f 0.74 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.98 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.51 (dd, *J* = 10.0, 5.6 Hz, 2H), 4.19-4.09 (m, 3H), 3.40 (d, *J* = 10.4 Hz, 1H), 2.98 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.69 (s, 3H), 2.52 (d, *J* = 13.2 Hz, 1H), 2.21 (s, 3H), 1.80-1.70 (m, 2H), 1.62-1.54 (m, 3H), 1.34-1.08 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.9, 150.3, 128.6, 127.7, 127.4, 126.1, 110.0, 83.5, 67.3, 60.3, 58.2, 55.4, 53.6, 50.5, 30.5, 25.2, 24.1, 21.4, 20.7, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2063; **Diastereomer B** (57 mg, 30%): R_f 0.55 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.86 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 4.72 (dq, *J* = 4.8, 4.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.91 (s, br, 1H), 3.61 (d, *J* = 8.4 Hz, 1H), 3.22 (s, 3H), 3.25-3.19 (m, 1H), 2.21 (s, 3H), 2.19-2.14 (m, 1H), 1.74 (t, *J* = 13.6 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.3, 128.4, 128.2, 127.1, 127.0, 108.7, 86.2, 65.0, 60.3, 56.8, 49.4, 48.5, 36.2, 29.7, 20.8, 19.4, 14.3; HRMS m/z calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found: 290.1754; **Diastereomer C** (39 mg, 20%): R_f 0.48 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz,

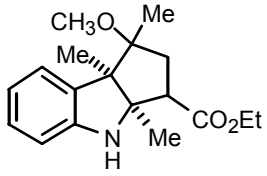
$CHCl_3$) δ 6.92 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 4.79 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.22-4.09 (m, 2H), 3.99 (s, br, 1H), 3.74 (d, *J* = 10.0 Hz, 1H), 3.22 (s, 3H), 2.74 (ddd, *J* = 7.2, 7.2, 3.6 Hz, 1H), 2.33 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.23 (s, 3H), 1.84 (dd, *J* = 12.8, 7.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 174.0, 149.1, 128.4, 128.1, 127.7, 126.9, 109.2, 86.4, 65.3, 60.6, 56.7, 51.9, 50.2, 38.8, 20.8, 19.5, 14.2; HRMS m/z calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found: 290.1749.



4.91k

1-Methoxy-1,5-dimethyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.91k). The title compound was prepared from **4.52g** and 7-methyl indole at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups. **Diastereomer A** (39 mg, 27%): R_f 0.74 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.98 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.51 (dd, *J* = 10.0, 5.6 Hz, 2H), 4.19-4.09 (m, 3H), 3.40 (d, *J* = 10.4 Hz, 1H), 2.98 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.69 (s, 3H), 2.52 (d, *J* = 13.2 Hz, 1H), 2.21 (s, 3H), 1.80-1.70 (m, 2H), 1.62-1.54 (m, 3H), 1.34-1.08 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.9, 150.3, 128.6, 127.7, 127.4, 126.1, 110.0, 83.5, 67.3, 60.3, 58.2, 55.4, 53.6, 50.5,

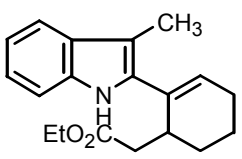
30.5, 25.2, 24.1, 21.4, 20.7, 14.3; HRMS m/z calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2069, found: 330.2063; **Diastereomer B** (65 mg, 45%): R_f 0.60 (25% EtOAc/hexanes); IR (thin film) ν cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.00 (d, *J* =7.6 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 4.50 (dd, *J* = 7.2, 6.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.01 (s, br, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 3.09 (s, 3H), 3.01 (dt, *J* = 13.2, 7.2 Hz, 1H), 2.31 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.10 (s, 3H), 1.70 (dd, *J* = 13.2, 12.0 Hz, 1H), 1.45 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 175.2, 150.4, 128.7, 126.6, 122.9, 118.8, 118.4, 83.8, 66.1, 60.6, 59.3, 52.0, 49.9, 38.8, 22.0, 17.0, 14.3; HRMS m/z calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found: 290.1753.



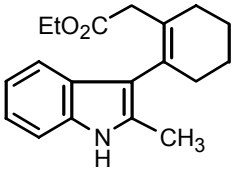
4.91l

1-Methoxy-1,3a,8b-trimethyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole-3-carboxylic acid ethyl ester (4.91l). The title compound was prepared from **4.52g** and 2, 3-dimethyl indole at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups. **Diastereomer A** (21 mg, 15%): R_f 0.46 (20% EtOAc/hexanes); ^1H NMR (400 MHz, $CHCl_3$) δ 7.10 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 7.2 Hz, 1H), 4.23-4.08 (m, 3H), 3.15 (dd *J* = 6.0, 2.8 Hz, 1H), 3.02 (s, 3H), 2.21-2.09 (m, 2H), 1.32 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.13

(s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.8, 148.5, 133.5, 127.5, 125.4, 118.2,109.4, 85.1, 74.2, 62.5, 60.4, 53.8, 49.6, 35.5, 22.6, 20.2, 19.5, 14.4; HRMS m/z calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$ 304.1913, found: 304.1914; **Diastereomer B** (52 mg, 37%): R_f 0.57 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.19 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.97 (dt, *J* = 1.6, 7.2 Hz, 1H), 6.64 (dt, *J* = 0.8, 7.2 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.92 (s, br, 1H), 3.23 (s, 3H), 2.69 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.00 (t, *J* = 7.6 Hz, 1H), 1.94 (q, *J* = 6.8 Hz, 1H), 1.49 (s, 3H), 1.30 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 172.4, 148.9, 134.2, 127.6, 127.4, 117.6, 107.6, 83.6, 71.1, 61.0, 60.3, 54.2, 51.2, 36.8, 25.3, 20.2, 19.0, 14.3; HRMS m/z calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$ 304.1913, found: 304.1912.



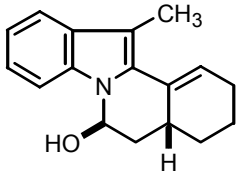
4.93a



4.93b

[2-(3-Methyl-1H-indol-2-yl)-cyclohex-2-enyl]-acetic acid ethyl ester (4.93a) and [6-(2-Methyl-1H-indol-3-yl)-cyclohex-1-enyl]-acetic acid ethyl ester (4.93b). The title compounds were prepared from **4.52h** and 3-dimethyl indole **4.92** at –18 °C according to the general procedure described above for the preparation of 4.85a. Purification by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution gave the title compound in form of two diastereomers as colorless syrups. **4.93a**: (164mg, 76%): R_f 0.45 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.00 (s, br, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.16-7.07 (m, 2H), 6.00 (dt, *J* = 1.6, 4.0 Hz,

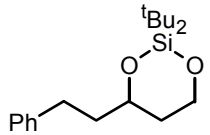
1H), 4.02 (dq, *J* = 3.2, 7.2 Hz, 2H), 3.17-3.10 (m, 1H), 2.34 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.30 (s, 3H), 2.26-2.17 (m, 3H), 1.97-1.87 (m, 1H), 1.73-1.64 (m, 3H), 1.67 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 173.2, 135.1, 134.7, 132.5, 130.3, 129.5, 121.6, 119.1, 118.4, 110.5, 108.3, 60.4, 38.7, 33.6, 27.8, 25.7, 18.6, 14.1, 9.6; **4.93b** (17 mg, 8%): R_f 0.58 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.13 (dt, *J* = 0.8, 8.0 Hz, 1H), 6.93 (d, = 0.8 Hz, 1H), 5.92 (dt, *J* = 0.8, 8.0 Hz, 1H), 3.97 (dq, *J* = 2.0, 7.2 Hz, 2H), 3.28-3.20 (m, 1H), 2.35 (d, *J* = 0.8 Hz, 3H), 2.33-2.17 (m, 3H), 2.10 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.06-1.99 (m, 1H), 1.78-1.74 (m, 3H), 1.14 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 172.3, 137.6, 136.6, 128.8, 124.4, 124.3, 121.7, 119.0, 118.8, 111.3, 110.5, 77.2, 60.2, 37.1, 34.5, 27.9, 24.8, 18.7, 14.0, 9.5.



4.94

12-Methyl-2,3,4,4a,5,6-hexahydro-indolo[2,1-*a*]isoquinolin-6-ol (4.94): To a solution of the cyclopropane **4.93a** (147 mg, 0.49 mmol) in THF (4.0 mL) at –0 °C was added DIBAL-H (20% in toluene, 0.9 mL, 0.9 mmol). The resulting mixture was stirred for 1.5 h and then poured into a vigorously stirred solution of saturated aqueous NH_4Cl (10 mL). After 2 min the resulting mixture was extracted with EtOAc (3 × 6 mL). The combined organic solution was washed with H_2O (2 × 3 mL), brine (5 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced

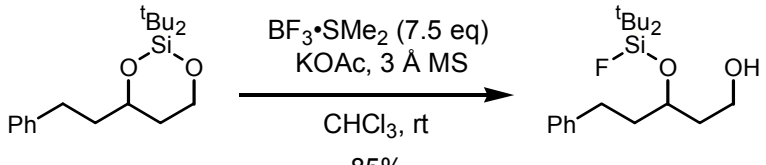
pressure. Purification of the residue by flash chromatography on silica gel with 10:1 hexanes-EtOAc for elution gave the product as white solid (104 mg, 85%): R_f 0.28 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.18 (dt, *J* = 1.4, 8.2 Hz, 1H), 7.13 (dt, *J* = 1.0, 8.5 Hz, 1H), 6.30-6.25 (m, 1H), 5.99 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.86-2.77 (m, 1H), 2.57 (d, *J* = 5.2 Hz, 1H), 2.40 (s, 3H), 2.37-2.28 (m, 2H), 2.20 (dt, *J* = 13.6, 2.8 Hz, 1H), 2.02-1.98 (m, 1H), 1.91-1.87 (m, 1H), 1.80 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.70-1.59 (m, 1H), 1.37-1.26 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 134.3, 131.0, 130.6, 125.7, 121.8, 120.0, 118.5, 108.6, 107.1, 73.8, 37.8, 30.1, 28.6, 26.4, 21.6, 11.2.



5.15

2,2-Di-*tert*-butyl-4-phenethyl-[1,3,2]-dioxasilinane (5.15). To a solution of diol **5.14**[165] (2.59 g, 14.4 mmol) in THF:DMF (2:1, 30 mL) cooled to –30 °C was added ^{t}Bu$_2$Si(OTf)$_2$ (5.80 mL, 15.8 mmol) dropwise over 15 min. After 25 min the reaction mixture was neutralized with pyridine (2.40 mL, 30.0 mmol), allowed to warm to rt and diluted with Et_2O (150 mL). The reaction mixture was washed with saturated $NaHCO_3$ solution, H_2O, brine, dried ($MgSO_4$), and filtered through celite. Volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using 20:1 hexanes-EtOAc for elution to provide the title compound as a colorless syrup (4.01 g, 87%): R_f 0.70 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.35-7.20 (m, 5H), 4.12-4.02 (m, 3H), 2.90-2.71 (m, 2H), 1.93-1.73 (m, 3H), 1.62 (dd, *J* = 14.1, 1.5 Hz, 1H),

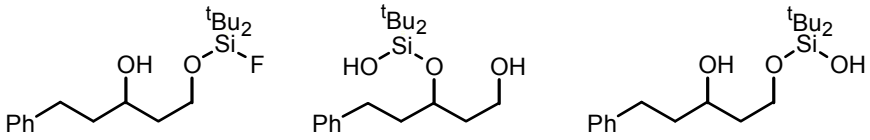
1.08 (d, J = 1.2 Hz, 9H), 1.06 (d, J = 1.2 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.7, 128.8, 128.5, 125.9, 73.0, 64.5, 40.7, 36.8, 31.6, 27.7, 27.4, 22.9, 20.1; HRMS m/z calcd for $C_{19}H_{32}O_2Si$ $[M+H]^+$ 321.1150, found: 321.2248.



5.15 **5.16a**

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-phenyl-pentan-1-ol (5.16a). To a 10-mL round-bottomed flask containing **5.15** (350 mg, 1.09 mmol) was added KOAc (300 mg, 3.0 mmol) and freshly activated molecular sieves (3 Å, 250 mg). The flask was sealed with a rubber septum, flushed with argon and treated sequentially with $CHCl_3$ (2.5 mL), allyl trimethylsilane (35 μL, 0.20 mmol) and BF_3•Me_2S (860 μL, 8.2 mmol, 7.5 eq). After 5.5 h the mono-deprotection was complete (TLC), and the reaction mixture was transferred into a vigorously stirred saturated $NaHCO_3$ solution (10 mL) with the aid of CH_2Cl_2. The heterogeneous solution was filtered through a glass frit and the organic layer was separated and washed with H_2O, brine and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution afforded the title compound as a colorless syrup (316 mg, 85%): R_f 0.61 (33% EtOAc/hexanes); IR (thin film) ν 3450 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.36-7.21 (m, 5H), 4.42-4.38 (dddd, J = 5.3, 5.3, 5.3, 5.3 Hz, 1H), 3.92-3.79 (m, 2H), 2.77-2.72 (m, 2H), 2.36 (br s, 1H), 2.10-1.84 (m, 5H), 1.13 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.4 (C), 128.7 (CH), 128.6 (CH), 126.1 (CH), 72.0 (CH), 59.7 (CH_2),

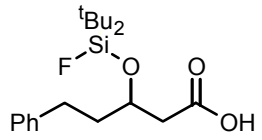
39.1 (CH_2), 38.9 (CH_2), 31.5 (CH_2), 27.4 (CH_3), 20.7 (d, J = 15.1 Hz, C), 20.4 (d, J = 15.1 Hz, C); ^{19}F NMR (300 MHz, $CHCl_3$) δ –158.7; HRMS m/z calcd for $C_{19}H_{33}FO_2Si$ $[M+H]^+$ 341.2312, found: 341.2323.



5.16b **5.17a** **5.17b**

1-(Di-*tert*-butyl-fluoro-silanyloxy)-5-phenyl-pentan-3-ol (5.16b), **3-(Di-*tert*-butyl-hydroxy-silanyloxy)-5-phenyl-pentan-1-ol (5.17a) and 1-(Di-*tert*-butyl-hydroxy-silanyloxy)-5-phenyl-pentan-3-ol (5.17b).** Deprotection of **5.15** with BF_3•Et_2O according to the procedure previously described for preparation of **2.27** except that the reaction was performed at rt, provided a mixture of: **5.14**, 12 mg, 8%; **5.15**, 97 mg, 36%; **5.16a**, 58 mg, 21%; **5.16b**, 6 mg, 2%; **5.17a**, 25 mg, 9%; and **5.17b**, 8 mg, 3%. (**5.16b**): R_f 0.67 (33% EtOAc/ hexanes); IR (thin film) ν 3405 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.34-7.18 (m, 1H), 4.16 (dddd, J = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 4.09-4.02 (m, 1H), 3.98-3.86 (m, 1H), 2.90-2.80 (m, 1H), 2.77-2.67 (m, 1H), 2.62 (d, J = 3.4 Hz, 1H), 1.90-1.73 (m, 4H), 1.06 (s, 18H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.0 (C), 128.7 (CH), 128.6 (CH), 126.0 (CH), 70.4 (CH), 63.2 (CH_2), 39.4 (CH_2), 39.2 (CH_2), 32.2 (CH_2), 27.1 (CH_3), 27.0 (CH_3), 20.2 (d, J = 15.0 Hz, C), 20.1 (d, J = 15.0 Hz, C); ^{19}F NMR (300 MHz, $CHCl_3$) δ –165.3; HRMS m/z calcd for $C_{19}H_{33}FO_2Si$ $[M+H]^+$ 341.2312, found: 341.2312. (**5.17a**): R_f 0.37 (33% EtOAc/ hexanes); IR (thin film) ν 3420 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.34-7.17 (m, 5H), 4.37-4.30 (m, 1H), 4.01-3.92 (ddd, J = 12.1, 6.8, 4.0 Hz, 1H), 3.79-3.72 (ddd, J = 10.1, 4.8, 2.2 Hz, 1H), 3.48 (br s, 1H), 3.06 (br

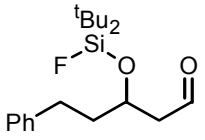
s, 1H), 2.82-2.61 (m, 2H), 2.00-1.88 (m, 3H), 1.81-1.70 (m, 1H), 1.07 (d, J = 1.0 Hz, 9H), 1.05 (d, J = 1.0 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.6 (C), 128.7 (CH), 128.6 (CH), 126.0 (CH), 70.0 (CH), 59.6 (CH_2), 39.5 (CH_2), 38.3 (CH_2), 31.3 (CH_2), 27.9 (CH_3), 27.6 (CH_3), 21.1 (C), 20.8 (C); HRMS m/z calcd for $C_{19}H_{34}O_3Si$ $[M+H]^+$ 339.2355, found: 339.2355. (**5.17b**): R_f 0.32 (33% EtOAc/ hexanes); IR (thin film) ν 3405 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.33-7.17 (m, 5H), 4.18-4.11 (m, 1H), 4.00-3.89 (m, 2H), 3.19 (br s, 1H), 2.88-2.66 (m, 3H), 1.19-1.62 (m, 4H), 1.05 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.4, 128.7, 128.6, 126.0, 70.4, 62.4, 39.4, 39.1, 32.2, 27.8, 27.7, 20.9, 20.6; HRMS m/z calcd for $C_{19}H_{34}O_3Si$ $[M+H]^+$ 339.2355, found: 339.2349.



5.18

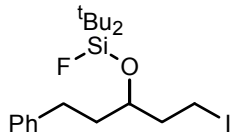
3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-pheny-pentanoic acid (5.18). To a rt solution of **5.16a** (150 mg, 0.44 mmol) in acetone (3.5 mL) was added Jones' reagent[177] drop wise until a brown color persisted. The resulting solution was then treated with *iso*-propanol drop-wise until the solution became green-blue. To the reaction mixture was added H_2O and the organic solvent was removed under reduced pressure. The residue was redissolved in Et_2O and the solution was washed with saturated $NaHCO_3$ solution, H_2O, brine and dried ($MgSO_4$). The solution was filtered through celite and volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution provided the title

compound as a yellow syrup (112 mg, 72%): R_f 0.34 (50% EtOAc/hexanes); IR (thin film) ν 3110 (br), 1738 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.33-7.19 (m, 5H), 4.61 (dddd, *J* = 5.9, 5.9, 5.9, 5.9 Hz, 1H), 2.78-2.63 (m, 4H), 2.03-1.95 (m, 2H), 1.07 (s, 18H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 177.1, 141.9, 128.7, 128.6, 126.2, 70.7, 42.1, 39.1, 31.3, 27.25, 27.21, 20.5 (d, *J* = 15.3 Hz), 20.4 (d, *J* = 15.3 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –158.8; HRMS m/z calcd for $C_{19}H_{31}FO_3Si$ $[M+H]^+$ 355.2105, found: 355.2100.



5.19

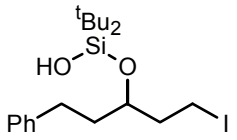
3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-pheny-pentanal (5.19). To a rt suspension of pyridinium chlorochromate (133 mg, 0.62 mmol) in CH_2Cl_2 (3.5 mL) was added a solution of **5. 16a** (60 mg, 0.18 mmol) in CH_2Cl_2 (1.2 mL). After 2.5 h florisil and Et_2O (5 mL) were added to the reaction mixture, which was subsequently filtered through florisil. The volatile components were removed under reduced pressure and purification of the residue by flash chromatography on silica gel (20:1 hexanes-EtOAc for elution) provided the title compound as a colorless syrup (109 mg, 82%): R_f 0.65 (25% EtOAc/hexanes); IR (thin film) ν 1722 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 9.88 (dd, *J* = 2.3, 2.3 Hz, 1H), 7.34-7.20 (m, 5H), 4.66 (dddd, *J* = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 2.78-2.69 (m, 4H), 2.00 (ddd, *J* = 5.8, 2.9, 2.9 Hz, 2H), 1.07 (s, 18H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 201.5, 141.7, 128.7, 128.6, 126.3, 69.6, 50.7, 39.4, 31.5, 27.2, 20.6, 20.4; ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.1; HRMS m/z calcd for $C_{19}H_3F_1O_2Si$ $[M+H]^+$ 339.2156, found: 339.2158.



5.20a

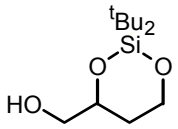
Di-*tert*-butyl-fluoro-(3-iodo-1-phenethyl-propoxy)-silane (5.20a). To a rt solution of **5.16a** (160 mg, 0.47 mmol) and *p*-toluene sulfonyl chloride (106 mg, 0.59 mmol) in CH_2Cl_2 (4.5 mL) was added pyridine (0.5 mL, 6.2 mmol) in one portion. The resulting solution was stirred at rt for 20 h and then volatiles were removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and the solution was washed with saturated $NaHCO_3$ solution, H_2O, brine and dried ($MgSO_4$). After filtration through a pad of celite, volatiles were removed under reduced pressure, and the residue was dissolved in a mixture of acetone (4.5 mL) and NaI (720 mg, 4.8 mmol, 10.0 equiv). After 30 h at reflux, the cooled reaction mixture was treated with saturated $NaHCO_3$ solution, and the acetone was removed under reduced pressure. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O, brine and dried ($MgSO_4$). After filtration through a pad of celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel with 15:1 hexanes-EtOAc for elution provided the title compound as a pale yellow syrup (180 mg, 85%): R_f 0.57 (15% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.34-7.19 (m, 5H), 4.23 (dddd, J = 6.5, 6.5, 6.5, 6.5 Hz, 1H), 3.30 (t, J = 7.2 Hz, 2H), 2.74-2.68 (m, 2H), 2.17 (ddd, J = 7.2, 7.2, 7.2 Hz, 2H), 1.96-1.89 (m, 2H), 1.08 (s, 18H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.1 (C), 128.7 (CH), 128.6 (CH), 126.1 (CH), 74.0 (CH), 41.0 (CH_2), 38.5 (CH_2), 31.3 (CH_2), 27.4 (CH_3), 27.3 (CH_3), 20.6 (C), 20.4

(C), 1.9 (CH_2); ^{19}F NMR (300 MHz, $CHCl_3$) δ –157.9; HRMS m/z calcd for $C_{19}H_{32}FIOSi$ $[M+H]^+$ 451.1330, found: 451.1334.



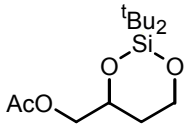
5.20b

Di-*tert*-butyl-3-iodo-1-phenethyl-propoxy)-silanol (5.20b). The title compound was prepared from **5.17a** according to the general procedure described for the preparation of **5.20a** (pale syrup, 81%): R_f 0.47 (15% EtOAc/hexanes); IR (thin film) ν 3590 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.34-7.19 (m, 5H), 4.15 (dddd, *J* = 5.7, 5.7, 5.7, 5.7 Hz, 1H), 3.33 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 2H), 2.70 (dddd, *J* = 7.2, 7.2, 7.2, 5.7 Hz, 2H), 2.20-2.14 (m, 2H), 2.07 (s, 1H), 1.96-1.90 (m, 2H), 1.06 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.3 (C), 128.7 (CH), 128.6 (CH), 126.2 (CH), 72.9 (CH), 41.0 (CH_2), 38.3 (CH_2), 31.3 (CH_2), 27.9 (CH_3), 20.6 (C), 2.8 (CH_2); HRMS m/z calcd for $C_{19}H_{33}IO_2Si$ $[M+H]^+$ 449.1373, found: 449.1368.



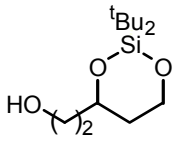
(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-methanol. The title compound was prepared from butane-1,2,4-triol[178] according to the general procedure described for the preparation of **4** (colorless syrup, 82%): R_f 0.35 (50% EtOAc/hexanes); IR (thin film) ν 3400 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.22-4.15 (m, 1H), 4.12 (dd, *J* = 8.4, 2.6

Hz, 2H), 3.58-3.51 (m, 1H), 3.46 (dd, J = 10.1, 7.4 Hz, 1H), 2.37 (br s, 1H), 1.92-1.78 (m, 1H), 1.59 (dddd, J = 14.1, 2.6, 2.6, 2.6 Hz, 1H), 1.04 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 74.6, 67.7, 64.0, 32.5, 27.6, 27.3, 22.9, 20.1; HRMS m/z calcd for $C_{12}H_{26}O_3Si$ $[M+H]^+$ 247.1729, found: 247.1733.

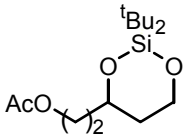


5.21a

Acetic acid 2,2-di-*tert*-butyl-[1,3,2]dioxasilinan-4-ylmethyl ester (5.21a). To a solution of (2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-methanol (2.52 g, 10.2 mmol) in CH_2Cl_2 (22 mL) was added pyridine (2.41 mL, 29.7 mmol) and Ac_2O (4.33 mL, 45.9 mmol). After 15 h at rt the mixture was poured into a vigorously stirred saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and washed with saturated NH_4Cl solution, H_2O, brine, dried ($MgSO_4$) and filtered through celite. Volatile components were removed under reduced pressure, and the residual syrup was purified by flash chromatography on silica gel using 15:1 hexanes-EtOAc for elution to provide the title compound as a pale yellow syrup (2.70 g, 92%): R_f 0.35 (15% EtOAc/hexanes); IR (thin film) ν 1744 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.31-4.27 (m, 1H), 4.13-4.08 (m, 3H), 4.03 (ddd, J = 11.0, 5.2, 1.0 Hz, 1H), 2.06 (s, 3H), 1.95-1.81 (m, 1H), 1.66 (ddd, J = 14.1, 4.1, 1.5 Hz, 1H), 1.01 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.1, 71.9, 68.4, 63.9, 33.1, 27.5, 27.2, 22.8, 21.1, 20.1; HRMS m/z calcd for $C_{14}H_{28}O_4Si$ $[M+H]^+$ 289.1835, found: 289.1833.



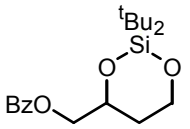
2-(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethanol. The title compound was prepared from 1,3,5-pentane triol[179] according to the general procedure described for the preparation of **4** (colorless syrup, 85%): R_f 0.37 (50% EtOAc/hexanes); IR (thin film) ν 3405 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.36-4.28 (m, 1H), 4.09-4.04 (m, 2H), 3.89-3.77 (m, 2H), 3.03 (br s, 1H), 1.96-1.74 (m, 2H), 1.67-1.53 (m, 2H), 1.00 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 75.6, 64.2, 61.9, 39.7, 36.6, 27.4, 27.0, 22.6, 19.7; HRMS m/z calcd for $C_{13}H_{28}O_3Si$ $[M+H]^+$ 261.1886, found: 261.1878.



5.21b

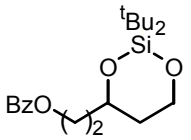
Acetic acid 2-(2,2-di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethyl ester (5.21b). The title compound was prepared from 2-(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethanol according to the general procedure described for the preparation of **5.21a** (pale yellow syrup, 90%): R_f 0.55 (25% EtOAc/ hexanes); IR (thin film) ν 1740 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.24-4.10 (m, 3H), 4.07 (ddd, J = 5.4, 2.6, 2.6 Hz, 2H), 2.01 (s, 3H), 1.83-1.60 (m, 3H), 1.59 (ddd, J = 13.3, 2.3, 2.3 Hz, 1H), 0.98 (s, 9H), 0.94 (s, 9H); ^{13}C

NMR (75 MHz, $CHCl_3$) δ 171.4, 70.9, 64.5, 61.4, 37.6, 36.8, 27.6, 27.3, 22.9, 21.2, 20.0; HRMS m/z calcd for $C_{15}H_{30}O_4Si$ $[M+H]^+$ 303.1992, found: 303.1985.



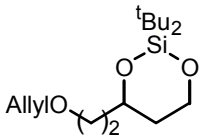
5.21c

Benzoic acid 2,2-di-*tert*-butyl-[1,3,2]dioxasilinan-4-ylmethyl ester (5.21c). To a solution of (2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-methanol (1.76 g, 7.2 mmol) in CH_2Cl_2 (20 mL) was added pyridine (1.00 mL, 12.3 mmol) and benzoyl chloride (2.51 mL, 21.6 mmol). After stirring for 13 h at rt the mixture was worked up as described for **5.12a**. Purification of the residual syrup by flash chromatography on silica gel using 18:1 hexanes-EtOAc for elution provided the title compound as a colorless syrup (2.23 g, 89%): R_f 0.45 (20% EtOAc/hexanes); IR (thin film) ν 1720 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.10-8.06 (m, 2H), 7.62-7.58 (m, 1H), 7.57-7.44 (m, 2H), 4.49-4.38 (m, 2H), 4.33-4.26 (m, 1H), 4.18 (ddd, *J* = 7.8, 2.5, 2.5 Hz, 2H), 2.06-1.94 (m, 1H), 1.79 (ddd, *J* = 13.8, 2.5, 2.5 Hz, 1H), 1.06 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.6, 133.2, 130.4, 129.8, 128.6, 72.0, 68.8, 64.0, 33.2, 27.6, 27.2, 22.9, 20.1; HRMS m/z calcd for $C_{19}H_{30}O_4Si$ $[M+H]^+$ 351.1992, found: 351.1985.



5.21d

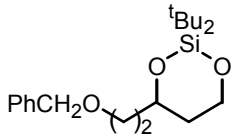
4-(2-Benzyloxy-ethyl)-2,2-di-*tert*-butyl-[1,3,2]-dioxasilinane (5.21d). The title compound was prepared from 5-benzyloxy-pentane-1,3-diol[180] according to the general procedure described for the preparation of **5.15** (colorless syrup, 94%): R_f 0.45 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.39-7.28 (m, 5H), 4.56 (s, 2 H), 4.34-4.26 (m, 1H), 4.14-4.10 (m, 2H), 3.77-3.61 (m, 2H), 1.92-1.72 (m, 3H), 1.70-1.62 (m, 1H), 1.10 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 138.5, 128.3, 127.6, 127.4, 73.1, 70.8, 66.5, 64.3, 38.7, 36.6, 27.4, 27.1, 22.6, 19.7; HRMS m/z calcd for $C_{20}H_{35}O_3Si$ $[M+H]^+$ 351.2355, found: 351.2345.



5.21e

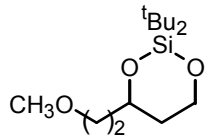
4-(2-Allyloxy-ethyl-2,2-di-*tert*-butyl-[1,3,2]-dioxasilinane (5.21e). To a rt solution of 2-(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethanol (1.22 g, 4.7 mmol) in CH_2Cl_2 (1.4 mL) and cyclohexane (2.8 mL) was added allyl trichloroacetimidate[181] (1.78 g, 8.9 mmol) and catalytic trifluoromethanesulphonic acid (~50 μL). After 3 h the reaction mixture was filtered through florisil and concentrated under reduced pressure. The residue was

dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, H_2O, brine and dried ($MgSO_4$). After filtration through celite, the volatile components were removed under reduced pressure, and the residual syrup was purified by flash chromatography on silica gel using 40:1 hexanes-EtOAc for elution to provide the title compound as a colorless syrup (1.14 g, 81%): R_f 0.68 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.98-5.81 (m, 1H), 5.30-5.14 (m, 2H), 4.27-4.19 (m, 1H), 4.10-4.07 (m, 2H), 3.99-3.96 (m, 2H), 3.66-3.52 (m, 2H), 1.88-1.66 (m, 3H), 1.60 (dddd, J = 14.1, 2.6, 2.6, 2.6 Hz, 1H), 1.02 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 135.2, 117.0, 72.2, 71.1, 66.6, 64.6, 38.9, 36.9, 27.7, 27.3, 22.9, 20.0; HRMS m/z calcd for $C_{16}H_{32}O_3Si$ $[M+H]^+$ 301. 2199, found: 301.2201.



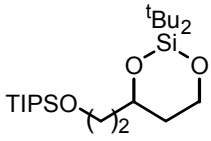
5.21f

4-(2-Benzyloxy-ethyl)-2,2-di-*tert*-butyl-[1,3,2]-dioxasilinane (5.21f). The title compound was prepared from 5-benzyloxy-pentane-1,3-diol[180] according to the general procedure described for the preparation of **5.15** (colorless syrup, 94%): R_f 0.45 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.39-7.28 (m, 5H), 4.56 (s, 2 H), 4.34-4.26 (m, 1H), 4.14-4.10 (m, 2H), 3.77-3.61 (m, 2H), 1.92-1.72 (m, 3H), 1.70-1.62 (m, 1H), 1.10 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 138.5, 128.3, 127.6, 127.4, 73.1, 70.8, 66.5, 64.3, 38.7, 36.6, 27.4, 27.1, 22.6, 19.7; HRMS m/z calcd for $C_{20}H_{35}O_3Si$ $[M+H]^+$ 351.2355, found: 351.2345.



5.21g

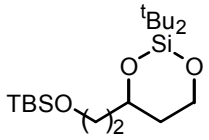
2,2-Di-*tert*-butyl-4-(2-methoxy-ethyl)-[1,3,2]-dioxasilinane (5.21g). The title compound was prepared from 2-(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethanol and methyl trichloroacetimidate (2.0 eq) according to the general procedure described for the preparation of **5.21e** (colorless syrup, 76%): R_f 0.53 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.16 (dddd, *J* = 5.4, 5.4, 5.4, 2.5 Hz, 1H), 4.06 (ddd, *J* = 9.0, 2.5, 2.5 Hz, 2H), 3.49 (m, 2H), 3.31 (s, 3H), 1.81-1.71 (m, 1H), 1.69-1.62 (m, 2H), 1.57 (dddd, *J* = 14.2, 2.5, 2.5, 2.5 Hz, 1H), 0.99 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 71.2, 69.2, 64.6, 59.0, 38.9, 36.9, 27.7, 27.4, 22.9, 20.0; HRMS m/z calcd for $C_{14}H_{30}O_3Si$ $[M+H]^+$ 275.2042, found: 275.2043.



5.21h

2,2-Di-*tert*-butyl-4-(2-triisopropylsilanyloxy-ethyl)-[1,3,2]-dioxasilinane (5.21h). To a rt solution of 2-(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethanol (1.97 g, 7.6 mmol) in CH_2Cl_2 (7.5 mL) were added pyridine (1.22 mL, 15.0 mmol) and triisopropylsilyl chloride (1.58 mL, 11.4 mmol). The reaction mixture was stirred at rt for 20 h and then

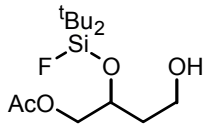
poured into a vigorously stirred saturated NH_4Cl solution (8 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, brine and dried ($MgSO_4$). After filtration through celite, volatiles were removed under reduced pressure. Purification of the residual syrup by flash chromatography on silica gel using 30:1 hexanes-EtOAc for elution provided the title compound as a colorless syrup (1.91 g, 90%): R_f 0.69 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.29 (dddd, J = 12.8, 6.2, 6.2, 2.6 Hz, 1H), 4.13-4.08 (m, 2H), 3.95-3.79 (m, 2H), 1.91-1.77 (m, 1H), 1.73-1.61 (m, 3H), 1.11-0.98 (m, 39H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 70.9, 64.4, 59.7, 42.1, 37.0, 27.6, 27.4, 22.8, 20.0, 18.3, 12.2; HRMS m/z calcd for $C_{22}H_{48}O_3Si$ $[M+H]^+$ 417.3220, found: 417.3220.



5.21i

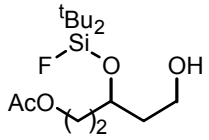
2,2-Di-*tert*-butyl-4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-[1,3,2]-dioxasilinane (5.21i). The title compound was prepared from 2-(2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-yl)-ethanol according to the general procedure described for the preparation of **5.21h** except using *tert*-butyldimethylsilyl chloride (1.7 eq) afforded the product as a colorless syrup (colorless syrup, 90%): R_f 0.57 (5% EtOAc/ hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.20 (dddd, J = 12.9, 10.5, 5.7, 5.7 Hz, 1H), 4.08-4.04 (m, 2H), 3.82-3.66 (m, 2H), 1.85-1.71 (m, 1H), 1.66-1.55 (m, 3H), 0.99 (s, 9H), 0.96 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 70.5, 64.3, 59.2, 41.7, 36.7, 27.4, 27.1, 26.0, 22.6,

19.8, 18.3, –5.4, –5.3; HRMS m/z calcd for $C_{19}H_{43}O_3Si$ $[M+H]^+$ 375.2751 found: 375.2750.



5.22a

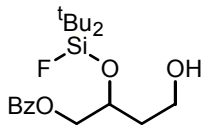
Acetic acid 2-(di-*tert*-butyl-fluoro-silanyloxy)-4-hydroxy-butyl ester (5.22a). The title compound was prepared from **5.21a** according to the general procedure described for the preparation of **5.16a**, except that 2.3 equivalents of BF_3•Me_2S were used (colorless syrup, 91%): R_f 0.48 (33% EtOAc/hexanes); IR (thin film) ν 3450 (br), 1744 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.42 (dddd, *J* = 4.2, 4.2, 4.2, 4.2 Hz, 1H), 4.09 (dddd, *J* = 11.2, 11.2, 11.2, 4.2 Hz, 2H), 3.94-3.71 (m, 2H), 2.39 (br s, 1H), 2.04 (s, 3H), 1.78 (ddd, *J* = 11.2, 3.8, 3.8 Hz, 2H), 1.01 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.3, 68.7, 68.0, 58.8, 37.0, 27.2, 27.1, 21.0, 20.5, 20.3; ^{19}F NMR (300 MHz, $CHCl_3$) δ –160.0; HRMS m/z calcd for $C_{14}H_{29}FO_4Si$ $[M+H]^+$ 309.1897, found: 309.1894.



5.22b

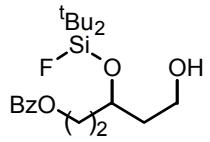
Acetic acid 3-(di-*tert*-butyl-fluoro-silanyloxy)-5-hydroxy-pentyl ester (5.22b). The title compound was prepared from **5.21b** according to the general procedure described for the preparation **5.16a**, except that 4.5 equivalents of BF_3•Me_2S were used (colorless

syrup, 87%): R_f 0.55 (25% EtOAc/hexanes); IR (thin film) ν 3450 (br), 1743 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.38 (dddd, *J* = 6.0, 6.0, 6.0, 6.0 Hz, 1H), 4.15 (t, *J* = 6.5 Hz, 2H), 3.78-3.74 (m, 2H), 2.01 (s, 3H), 2.00-1.73 (m, 5H), 1.01 (d, *J* = 0.8 Hz, 9H), 1.00 (d, *J* = 0.8 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.3, 69.4, 61.2, 59.4, 39.3, 36.0, 27.3, 27.2, 21.2, 20.5 (d, *J* = 14.7 Hz), 20.4 (d, *J* = 14.7 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) –159.1; HRMS m/z calcd for $C_{15}H_{31}FO_4Si$ $[M+H]^+$ 323.2054, found: 323.2054.



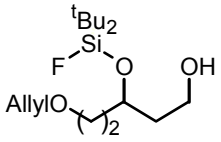
5.22c

Benzoic acid 2-(di-*tert*-butyl-fluoro-silanyloxy)-4-hydroxy-butyl ester (5.22c). The title compound was prepared from **5.21c** according to the general procedure described for the preparation of **5.16a**, except that 4.0 equivalents of BF_3•Me_2S were used (colorless syrup, 90%): R_f 0.69 (20% EtOAc/hexanes); IR (thin film) ν 3460 (br), 1720 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.53-7.50 (m, 1H), 7.41 (dd, *J* = 7.3, 7.3 Hz, 2H), 4.57 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 4.37 (d, *J* = 4.8 Hz, 2H), 3.86-3.78 (m, 2H), 1.99-1.81 (m, 3H), 1.03 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.7, 133.3, 130.2, 129.9, 128.6, 70.0, 68.4, 59.2, 37.2, 27.2, 27.1, 20.5 (d, *J* = 14.0 Hz), 20.3 (d, *J* = 14.0 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –160.0; HRMS m/z calcd for $C_{19}H_{31}FO_4Si$ $[M+H]^+$ 371.2054, found: 371.2049.



5.22d

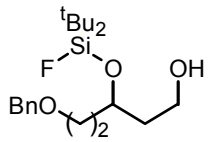
Benzoic acid 3-(di-*tert*-butyl-fluoro-silanyloxy)-5-hydroxy-pentyl ester (5.22d). The title compound was prepared from **5.21d** according to the general procedure described for the preparation of **5.16a**, except that 5.0 equivalents of BF_3•Me_2S were used (colorless syrup, 82%): R_f 0.67 (15% EtOAc/hexanes); IR (thin film) ν 3420 (br), 1720 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.61-7.57 (m, 1H), 7.46 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.48-4.42 (m, 3H), 3.91-3.77 (ddd, *J* = 7.6, 6.4, 6.4 Hz, 2H), 2.11 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 2H), 1.97-1.84 (m, 3H), 1.82 (br s, 1H), 1.08 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.8, 133.2, 130.5, 129.8, 128.6, 69.6, 61.7, 59.5, 39.3, 36.1, 27.6, 27.3, 20.5 (d, *J* = 15.2 Hz), 20.4 (d, *J* = 15.2 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.1; HRMS m/z calcd for $C_{20}H_{33}FO_4Si$ $[M+H]^+$ 385.2210, found: 385.2210.



5.22e

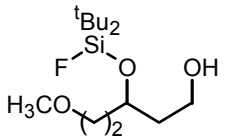
5-Allyloxy-3-(di-*tert*-butyl-fluoro-silanyloxy)-pentan-1-ol (5.22e). The title compound was prepared from **5.21e** according to the general procedure described for the preparation of **5.16a**, except that 6.5 equivalents of BF_3•Me_2S were used (colorless syrup, 78%): R_f

0.59 (20% EtOAc/hexanes); IR (thin film) ν 3395 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 5.98-5.85 (m, 1H), 5.31-5.16 (m, 2H), 4.44 (dddd, *J* = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 3.97 (ddd, *J* = 5.5, 3.1, 1.6 Hz, 2H), 3.94-3.74 (m, 2H), 3.58-3.52 (m, 2H), 2.15 (br s, 1H), 1.96-1.77 (m, 4H), 1.07 (d, *J* = 0.9 Hz, 9H), 1.06 (d, *J* = 0.9 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 135.0, 117.2, 72.2, 70.3, 66.7, 59.7, 39.3, 37.0, 27.3, 27.2, 20.5 (d, *J* = 12.1 Hz), 20.3 (d, *J* = 12.1 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.3; HRMS m/z calcd for $C_{16}H_{33}FO_3Si$ $[M+H]^+$ 321.2261, found: 321.2252.



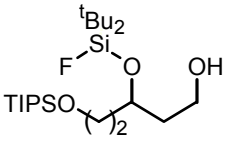
5.22f

5-Benzyloxy 3-(di-*tert*-butyl-fluoro-silanyloxy)-pentan-1-ol (5.22f). The title compound was prepared from **5.21f** according to the general procedure described for the preparation of **5.16a**, except that 6.5 equivalents of BF_3•Me_2S were used (colorless syrup, 35%): R_f 0.62 (15% EtOAc/hexanes); IR (thin film) ν 3405 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.39-7.28 (m, 5H), 4.60-4.45 (m, 3H), 3.84-3.77 (m, 2H), 3.61 (dd, *J* = 6.2, 6.2 Hz, 2H), 2.00-1.84 (m, 4H), 1.69 (br s, 1H), 1.07 (d, *J* = 0.8 Hz, 9H), 1.05 (d, *J* = 0.8 Hz, 9H); ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.3; HRMS m/z calcd for $C_{20}H_{35}FO_3Si$ $[M+H]^+$ 371.2418, found: 371.2419.



5.22g

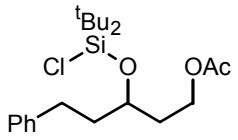
3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-methoxy-pentan-1-ol (5.22g). The title compound was prepared from **5.21g** according to the general procedure described for the preparation of **5.16a**, except that 3.5 equivalents of BF_3•Me_2S were used (colorless syrup, 43%): R_f 0.32 (33% EtOAc/hexanes); IR (thin film) ν 3390 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.43 (dddd, J = 6.1, 6.1, 6.1, 6.1 Hz, 1H), 3.85-3.72 (m, 2H), 3.53-3.45 (m, 2H), 3.35 (s, 3H), 2.04 (br s, 1H), 1.97-1.79 (m, 4H), 1.07 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 70.3, 69.1, 59.7, 58.8, 39.3, 37.0, 27.3, 27.2, 20.6 (d, J = 15.1 Hz), 20.5 (d, J = 15.1 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.4; HRMS m/z calcd for $C_{20}H_{36}FO_3Si$ $[M+H]^+$ 371.2418, found: 371.2419.



5.22h

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-triisopropylsilanyloxy-pentyl-1-ol (5.22h). The title compound was prepared from **5.21h** according to the general procedure described for the preparation of **5.16a**, except that 7.0 equivalents of BF_3•Me_2S were used (colorless syrup, 78%): R_f 0.48 (15% EtOAc/hexanes); IR (thin film) ν 3380 (br) cm^{-1}; ^1H NMR

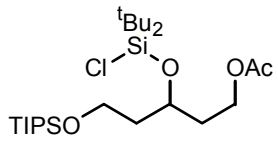
(300 MHz, $CHCl_3$) δ 4.48 (dddd, J = 5.9, 5.9, 5.9, 5.9 Hz, 1H), 3.88-3.76 (m, 3H), 2.03-1.91 (m, 2H), 1.89-1.77 (m, 1H), 1.63 (br s, 1H), 1.09-1.06 (m, 39H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 70.6, 60.1, 59.9, 40.1, 39.0, 27.3, 20.6 (d, J = 12.0 Hz), 20.3 (d, J = 12.0 Hz), 18.2, 12.2; ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.4; HRMS m/z calcd for $C_{22}H_{49}FO_3Si_2$ $[M+H]^+$ 437.3283, found: 437.3282.



5.26

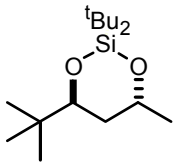
Acetic acid 3-(di-*tert*-butyl-chloro-silanyloxy)-5-phenyl-pentyl ester (5.26). To a rt solution of **5.15** (540 mg, 1.69 mmol) in $CHCl_3$ (5.5 mL) was added BCl_3 (2.1 mL, 1.0 M in heptane, 2.1 mmol). After 25 min TLC analysis of an aliquot indicated the reaction was complete, and the reaction mixture was transferred with the aid of CH_2Cl_2 into a stirring saturated $NaHCO_3$ solution (8 mL). The organic layer was separated and washed with H_2O, brine and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using 10:1 hexanes-EtOAc for elution to provide the alcohol **5.24** as a colorless syrup (534 mg, 89%): R_f 0.38 (33% EtOAc/hexanes); ^1H NMR (300 MHz, $CHCl_3$) δ 7.35-7.20 (m, 5H), 4.36 (dddd, J = 5.7, 5.7, 5.7, 5.7 Hz, 1H), 3.95-3.88 (m, 1H), 3.84-3.76 (m, 1H), 2.75-2.68 (m, 2 H), 2.05-1.85 (m, 4H), 1.75 (br s, 1H), 1.14 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 142.3, 128.7, 128.6, 126.1, 72.3, 59.5, 38.3, 38.2, 31.3, 27.6, 27.5, 23.5, 23.3. The syrup was immediately acylated

according to the general procedure described for the preparation of **5.21a** to afford the product as a colorless syrup (544 mg, 91%): R_f 0.67 (10% EtOAc/hexanes); IR (thin film) ν1739 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.35-7.18 (m, 5H), 4.32-4.20 (m, 3H), 2.72 (dddd, *J* = 13.5, 7.8, 2.7, 2.7 Hz, 2H), 2.08 (s, 3H), 2.03-1.99 (m, 4H), 1.12 (s, 18H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.3, 142.2, 128.7, 128.6, 126.1, 71.5, 61.3, 38.2, 34.7, 31.1, 27.6 23.4, 21.3; HRMS m/z calcd for $C_{21}H_{35}ClO_3Si$ $[M+H]^+$ 399.2122, found: 399.2115.



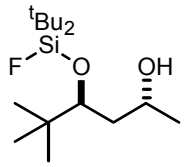
5.27

Acetic acid 3-(di-*tert*-butyl-chloro-silanyloxy)-5-triisopropylsilanyloxy-pentyl ester (5.27). The title compound was prepared from **5.21h** according to the general procedure described for the preparation of **5.26** (80%, two steps). R_f 0.45 (5% EtOAc/hexanes); IR (thin film) ν 1740 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.41 (dddd, *J* = 5.6, 5.6, 5.6, 5.6 Hz, 1H), 4.21 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.82 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.04 (s, 3H), 2.02-1.88 (m, 3H), 1.84-1.69 (m, 1H), 1.10-1.03 (m, 39H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 171.3, 69.7, 61.3, 60.0, 39.6, 35.2, 27.6, 27.5, 23.3, 23.2, 21.2, 18.2, 12.2; HRMS m/z calcd for $C_{24}H_{51}ClO_4Si_2$ $[M+H]^+$ 495.3093, found: 495.3068.



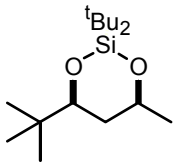
5.31

2,2,4-Tri-*tert*-butyl-6-methyl-[1,3,2]dioxasilinane (5.31). The title compound was prepared from (2*S*, 4*R*)-5,5-dimethyl-hexane-2,4-diol[182] according to the general procedure described for the preparation of **5.15** (colorless syrup, 94%): R_f 0.66 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.46 (dddd, *J* = 6.7, 6.7, 6.7, 6.7 Hz, 1H), 3.78 (dd, *J* = 11.0, 0.6 Hz, 1H), 1.97 (ddd, *J* = 13.8, 11.0, 6.7 Hz, 1H), 1.46 (d, *J* = 13.8 Hz, 1H), 1.32 (d, *J* = 6.7 Hz, 3H), 1.03 (s, 18 H), 0.91 (d, *J* = 0.8 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 75.5, 68.3, 35.1, 34.8, 27.4, 27.3, 25.6, 23.4, 21.7, 20.8; HRMS m/z calcd for $C_{16}H_{34}O_2Si$ $[M-H]^-$ 285.2250, found: 285.2263.



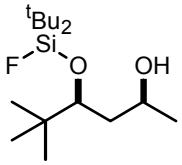
5.32

4-(Di-*tert*-butyl-fluoro-silanyloxy)-5,5-dimethyl-hexan-2-ol (5.32). The title compound was prepared from **5.31** according to the general procedure described for the preparation of **5.16a**, except that 3.0 equivalents of BF_3•Me_2S were used (colorless syrup, 93%): R_f 0.44 (33% EtOAc/hexanes); IR (thin film) ν 3415 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.12 (qdd, *J* = 6.2, 12.2, 2.3 Hz, 1H), 4.02 (dd, *J* = 8.3, 1.8 Hz, 1H), 1.64-1.55 (m, 1H), 1.51 (br s, 1H), 1.45 (ddd, *J* = 14.6, 8.3, 2.5 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H), 1.04 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 80.1, 64.6, 42.8, 35.8, 27.5, 27.3, 26.2, 24.9, 21.1 (d, *J* = 16.0 Hz), 20.3 (d, *J* = 16.0 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –152.0; HRMS m/z calcd for $C_{16}H_{35}FO_2Si$ $[M+H]^+$ 307.2469, found: 307.2453.



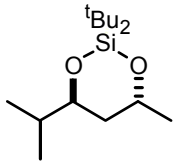
5.33

2,2,4-Tri-*tert*-butyl-6-methyl-[1,3,2]dioxasilinane (5.33). The title compound was prepared from (2*S*, 4*S*)-5,5-dimethyl-hexane-2,4-diol[182] according to the general procedure described for the preparation of **5.15** (colorless syrup, 91%): R_f 0.64 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.16 (qdd, *J* = 6.2, 5.6, 2.3 Hz, 1H), 3.63 (dd, *J* = 11.2, 1.8 Hz, 1H), 1.58 (ddd, *J* = 13.4, 1.6, 1.6 Hz, 1H), 1.32 (ddd, *J* = 13.4, 11.1, 11.1 Hz, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.00 (s, 9H), 0.97 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 81.6, 71.0, 37.9, 35.4, 27.8, 27.3, 25.7, 25.2, 23.0, 19.8; HRMS m/z calcd for $C_{16}H_{34}O_2Si$ $[M+H]^+$ 287.2406, found: 287.2398.



5.34

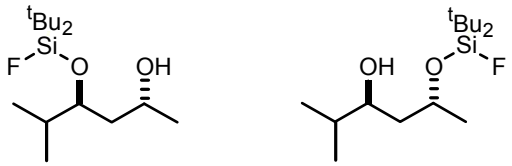
4-(Di-*tert*-butyl-fluoro-silanyloxy)-5,5-dimethyl-hexan-2-ol (5.34). The title compound was prepared from **5.33** according to the general procedure described for the preparation of **5.16a**, except that 5.0 equivalents of BF_3•Me_2S were used (colorless syrup, 64%): R_f 0.42 (40% EtOAc/hexanes); IR (thin film) ν 3365 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.00-3.91 (m, 1H), 3.80 (ddd, *J* = 6.1, 3.6, 1.5 Hz, 1H), 1.77 (ddd, *J* = 14.8, 6.9, 3.6 Hz, 1H), 1.64-1.55 (m, 3H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.04 (d, *J* = 1.0 Hz, 9H), 1.03 (d, *J* = 1.0 Hz, 9H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 80.7, 66.7, 44.2, 36.2, 27.4, 27.1, 25.9, 23.6, 21.1 (d, *J* = 15.0 Hz), 21.0 (d, *J* = 15.0 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –153.2; HRMS m/z calcd for $C_{16}H_{35}FO_2Si$ $[M+H]^+$ 307.2469, found: 307.2461.



5.35

2,2-Di-*tert*-butyl-4-isopropyl-6-methyl-[1,3,2]dioxasilinane (5.35). The title compound was prepared from (2*S*, 4*R*)-5-methyl-hexane-2,4-diol[183] according to the general procedure described for the preparation of **5.15** (colorless syrup, 96%): R_f 0.58 (10%

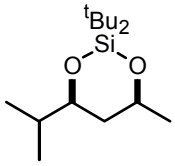
EtOAc/hexanes); ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.47-4.36 (m, 1H), 3.85 (ddd, *J* = 9.0, 5.9, 2.8 Hz, 1H), 1.97 (ddd, *J* = 14.2, 9.1, 5.4 Hz, 1H), 1.73-1.62 (m, 1H), 1.52-1.46 (m, 1H), 1.30 (d, *J* = 10.0 Hz, 3H), 1.02 (s, 18H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 73.7, 67.8, 37.7, 34.5, 27.5, 23.9, 21.5, 21.0, 18.9, 17.9; HRMS m/z calcd for $C_{15}H_{32}O_2Si$ $[M-H]^-$ 271.2093, found: 271.2093.



5.36a **5.36b**

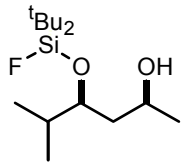
4-(Di-*tert*-butyl-fluoro-silanyloxy)-5-methyl-hexan-2-ol (5.36a) and **5-(Di-*tert*-butyl-fluoro-silanyloxy)-2-methyl-hexan-3-ol (5.36b).** The title compounds were prepared from **5.35** according to the general procedure described for the preparation of **5.16a**, except that 2.5 equivalents of BF_3•Me_2S were used. Purification of the reaction mixture by flash chromatography on silica gel using 10:1 hexanes-EtOAc for elution provided the title compounds **5.36a** and **5.36b** as a colorless syrups. **5.36a (**138 mg, 76%): R_f 0.45 (33% EtOAc/ hexanes); IR (thin film) ν 3365 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.13 (dddd, *J* = 4.1, 4.1, 4.1, 4.1 Hz, 1H), 4.06-3.99 (m, 1H), 2.05-2.00 (br s, 1H), 1.92 (dddd, *J* = 7.6, 4.1, 4.1, 0.4 Hz, 1H), 1.54-1.43 (m, 2H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.01 (s, 18H), 0.87 (dd, *J* = 6.9, 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 75.9, 64.3, 41.2, 33.6, 27.2, 24.4, 20.5, 20.3, 18.1, 16.8; ^{19}F NMR (300 MHz, $CHCl_3$) δ –157.0; HRMS m/z calcd for $C_{15}H_{33}FO_2Si$ $[M+H]^+$: 293.2312, found: 293.2308. **5.36b (**23 mg, 13%): R_f 0.34

(33% EtOAc/hexanes); IR (thin film) ν 3350 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.57-4.48 (m, 1H), 3.70 (ddd, *J* = 9.3, 8.1, 2.7 Hz, 1H), 2.51 (br s, 1H), 1.67-1.47 (m, 3H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.03 (d, *J* = 1.1 Hz, 9H), 1.01 (d, *J* = 1.1 Hz, 9H), 0.89 (dd, *J* = 6.7, 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 72.7, 68.7, 41.7, 33.9, 27.0, 26.9, 23.3, 20.4 (d, *J* = 15.3 Hz), 19.8 (d, *J* = 15.3 Hz), 18.4, 17.6; ^{19}F NMR (300 MHz, $CHCl_3$) δ –162.0; HRMS m/z calcd for $C_{15}H_{33}FO_2Si$ $[M+H]^+$ 293.2312, found: 293.2319.



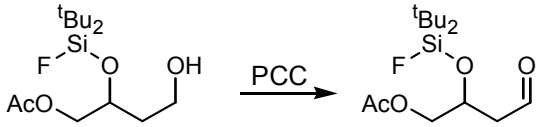
5.37

2,2-Di-*tert*-butyl-4-isopropyl-6-methyl-[1,3,2]dioxasilinane (5.37). The title compound was prepared from (2*S*, 4*S*)-5-methyl-hexane-2,4-diol[183] according to the general procedure described for the preparation of **5.15** (colorless syrup, 92%): R_f 0.61 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CHCl_3$) δ 4.20 (qdd, *J* = 5.9, 11.8, 2.2 Hz, 1H), 3.78 (ddd, *J* = 5.4, 5.4, 2.2 Hz, 1H), 1.68-1.58 (m, 2H), 1.42 (ddd, *J* = 11.1, 11.1, 2.8 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.93 (dd, *J* = 6.4, 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 78.7, 70.6, 40.7, 35.0, 27.7, 27.3, 25.1, 22.8, 20.0, 18.5, 17.6; HRMS m/z calcd for $C_{15}H_{32}O_2Si$ $[M+H]^+$ 273.2250, found: 273.2252.



5.38a

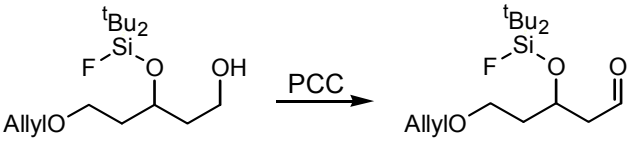
4-(Di-*tert*-butyl-fluoro-silanyloxy)-5-methyl-hexan-2-ol (5.38a). The title compound was prepared from **5.37** according to the general procedure described for the preparation of **5.16a**, except that 2.5 equivalents of BF_3•Me_2S were used (colorless syrup, 37%): R_f 0.48 (33% EtOAc/hexanes); IR (thin film) ν 3330 (br) cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.16 (dddd, *J* = 4.2, 4.2, 4.2, 0.8 Hz, 1H), 3.92-3.86 (m, 1H), 2.39 (br s, 1H), 1.98 (qdd, *J* = 6.8, 6.8, 6.8 Hz, 1H), 1.68-1.47 (m, 3H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.05 (d, *J* = 0.8 Hz, 9H), 1.03 (d, *J* = 0.8 Hz, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 79.1, 67.2, 40.5, 33.4, 27.5, 27.4, 24.1, 20.9, 18.1, 16.8; ^{19}F NMR (300 MHz, $CHCl_3$) δ –156.6; HRMS m/z calcd for $C_{15}H_{33}FO_2Si$ $[M+H]^+$ 293.2312, found: 293.2305.



5.22a

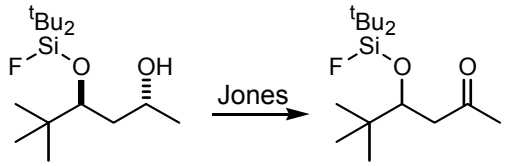
The title compound was prepared from **5.22a** according to the general procedure described for the preparation of **5.19** (pale syrup, 84%): R_f 0.42 (25% EtOAc/hexanes); IR (thin film) ν 1744, 1717 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 9.83 (dd, *J* = 2.0, 2.0 Hz,

1H), 4.76 (dddd, *J* = 5.3, 5.3, 5.3, 5.3 Hz, 1H), 4.15 (ddd, *J* = 5.3, 5.3,5.3 Hz, 2H), 2.71 (dd, *J* = 5.9, 2.0 Hz, 2H), 2.05 (s, 3H), 1.03 (d, *J* = 0.8 Hz, 9H), 1.02 (d, *J* = 0.8 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 200.0, 170.8, 67.5, 67.3, 48.3, 27.1, 27.0, 20.9, 20.5 (d, *J* = 15.1 Hz), 20.3 (d, *J* = 15.1 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –160.8; HRMS m/z calcd for $C_{14}H_{27}FO_4Si$ $[M+H]^+$ 307.1741, found: 307.1751.



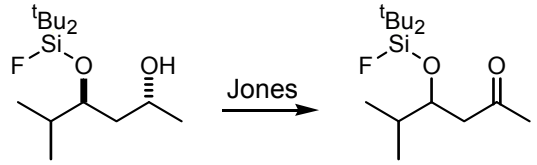
5.22e

The title compound was prepared from **5.22e** according to the general procedure described for the preparation of **5.19** (pale syrup, 85%): R_f 0.50 (20% EtOAc/hexanes); IR (thin film) ν 1728 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.84 (dd, *J* = 2.2, 2.2 Hz, 1H), 5.96-5.83 (m, 1H), 5.30-5.15 (m, 2H), 4.76 (dddd, *J* = 5.9, 5.9, 5.9, 5.9 Hz, 1H), 3.95 (ddd, *J* = 5.6, 3.0, 1.3 Hz, 2H), 3.55 (dd, *J* = 5.9, 5.9 Hz, 2H), 2.75 (ddd, *J* = 16.2, 5.7, 1.9 Hz, 1H), 2.65 (ddd, *J* = 16.2, 5.6, 2.8 Hz, 1H), 1.98-1.86 (m, 2H), 1.04 (d, *J* = 1.0 Hz, 9H), 1.03 (d, *J* = 1.0 Hz, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 201.6, 134.9, 117.2, 72.1, 67.7, 66.2, 51.0, 37.5, 27.2, 27.1, 20.5 (d, *J* = 11.8 Hz), 20.4 (d, *J* = 11.8 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –159.4; HRMS m/z calcd for $C_{16}H_{31}FO_3Si$ $[M+H]^+$ 319.2105, found: 319.2096.



5.32

The title compound was prepared from **5.32** according to the general procedure described for the preparation of **5.18** (pale syrup, 89%): R_f 0.56 (25% EtOAc/hexanes); IR (thin film) ν 1726 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.43 (dd, *J* = 4.9, 4.9 Hz, 1H), 2.60 (dd, *J* = 4.9, 4.9 Hz, 2H), 2.14 (s, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 206.3, 77.2, 47.7, 35.8, 30.8, 27.3, 27.0, 25.7, 21.0 (d, *J* = 15.2 Hz), 21.1 (d, *J* = 15.2 Hz); ^{19}F NMR (300 MHz, $CHCl_3$) δ –155.9; HRMS m/z calcd for $C_{16}H_{33}FO_2Si$ $(M+H)^+$ 305.2312, found: 305.2323.



5.36a

The title compound was prepared from **5.36a** according to the general procedure described for the preparation of **5.18** (pale syrup, 81%): R_f 0.48 (10 % EtOAc/hexanes); IR (thin film) ν 1719 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 4.50 (ddd, *J* = 6.7, 5.2, 3.6 Hz, 1H), 2.68 (dd, *J* = 16.1, 7.0 Hz, 1H), 2.49 (dd, *J* = 16.1, 5.2 Hz, 1H), 2.17 (s, 3H), 1.90-1.81 (m, 1H), 1.03 (d, *J* = 1.0 Hz, 9H), 1.02 (d, *J* = 1.0 Hz, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 207.4, 75.0, 47.4, 33.7, 31.5,

27.4, 27.3, 20.6 (d, J = 15.0 Hz), 20.4 (d, J = 15.0 Hz), 17.9, 17.3; ^{19}F NMR (300 MHz, $CHCl_3$) δ –157.3; HRMS m/z calcd for $C_{15}H_{31}FO_2Si$ $[M+H]^+$ 291.2156, found: 291.2146.

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