SYNTHESIS OF A STRUCTURALLY AND STEREOCHEMICALLY DIVERSE SPIROKETAL LIBRARY USING NOVEL STEREOSELECTIVE SPIROCYCLIZATIONS OF *C*1-SUBSTITUTED GLYCAL EPOXIDES

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by

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Sirkka B. Moilanen, Ph.D.

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A chemical genetic approach that uses small organic molecules to modulate protein function has the potential to overcome the limitations of classical genetic techniques for the study of biological processes. However, acquiring the features of broad applicability and specificity that are inherent to traditional genetics is still a challenge in chemical genetics. The impact that chemical genetics will have on our understanding of biological systems depends on a steady supply of biologically active small molecules with novel targets or improved specificity for known targets.

Diversity-oriented synthesis (DOS) of small molecule libraries is an emerging method to identify new probes for biological studies and potential therapeutic lead compounds. We have explored the use of an approach that employs structural features commonly found in natural products as starting points for library design. Our library incorporates spiroketal motifs, but is otherwise stereochemically and structurally diverse to address a wide range of biological targets. Although many efforts have been made to synthesize members of the spiroketal class of natural products, traditional methods are not suitable for generating stereochemical diversity in DOS. Therefore, we have developed a strategy to create stereochemical diversity by using novel stereocontrolled spiroketalization reactions that provide access to both spiroketal stereoisomers from a common *C*1-substituted glycal epoxide precursor. Our route has allowed the synthesis of a library of diastereomeric spiroketals in which we control the stereochemical configuration not only at the quaternary spiroketal carbon, but also at

multiple ring carbons. The library will ultimately be screened against a number of biological targets to evaluate the effectiveness of the design strategy, and potentially identify new biological probes or lead compounds for drug development.

BIOGRAPHICAL SKETCH

Sirkka Moilanen was born in 1979 and grew up in Dearborn, Michigan. At an early age, she began to develop her chemistry skills by investigating the reactivity of household cleaning supplies. In 2001, she graduated *summa cum laude* with a B.S. in Chemistry from Case Western Reserve University. Later that year, she began her graduate education at Cornell University as part of the Tri-Institutional Training Program in Chemical Biology. Since 2003, she has been developing methodology for spiroketal synthesis in the lab of Dr. Derek Tan at Memorial Sloan–Kettering Cancer Center.

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LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
Å	Ångstrom
Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
anhyd	anhydrous
aq	aqueous
BINOL	1,1'-Bi(2-naphthol)
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
c	concentration
COSY	Correlated spectroscopy
CSA	10-Camphorsulfonic acid
d	days
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4 benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMEM	Dulbecco's Modified Eagle's Medium
DMF	*N,N*-Dimethylformamide

DMSO	Dimethyl sulfoxide
DPPA	Diphenyl phosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalents
Et	Ethyl
h	hours
HMPA	Hexamethylphosphoramide
HPLC	High pressure liquid chromatography
IC_{50}	half maximal inhibitory concentration
im	Imidazole
IR	Infrared
J	Coupling constant
LiDBB	Lithium di-*tert*-butylbiphenylide
M	molar
m-CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
min	minutes
mol	mole
MS	molecular sieves
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
OD	Optical density

Ph	Phenyl
Piv	Pivaloyl
PMB	4-Methoxybenzyl
PMP	4-Methoxyphenyl
PPTS	Pyridinium 4-toluenesulfonate
Pr	Propyl
RCM	Ring-closing metathesis
rt	room temperature
sat'd	saturated
SEM	2-(Trimethylsilyl)ethoxymethyl
TBAF	Tetrabutylammonium fluoride
TBDAS	*tert*-Butyldiarylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMOF	Trimethyl orthoformate
TMS	Trimethylsilyl
Tr	Triphenylmethyl
Ts	4-Toluenesulfonyl
UV	Ultraviolet

CHAPTER 1

INTRODUCTION TO SPIROKETALS

1.1. Genetic and Chemical Genetic Approaches to Studying Biological Processes

Developing an understanding of biological processes is a monumental task, requiring the functions of multiple participating components with complex regulation and interactions to be unraveled. Historically, genetic approaches have proven to be extremely useful for dissecting biological systems. Forward genetic techniques involve mutating the genome of a particular organism, followed by identification of the gene mutation that produces a desired phenotype. Conversely, reverse genetic techniques help to elucidate the function of a protein through analysis of the resulting phenotype when the corresponding gene is mutated. Although these complementary genetic approaches have had a powerful impact on the progress of molecular biology, there are inherent limitations. One problem is that it is difficult to perform forward genetic analyses in mammalian systems because of the complexity of mammalian genomes and the slow rate of mammalian reproduction. In addition, genetic mutations are usually constitutive, so the activity of the protein cannot be easily turned on and off. Constitutive mutations may result in embryonic lethality or the effects may be obscured by compensatory changes in related genes and proteins. Although techniques for conditional activation have been developed (e.g. temperature-sensitive mutations or control by inducible promoters), the time required for initiation limits the potential for studying dynamic processes.

RNA interference (RNAi) has recently become a valuable tool for modulating protein function. When a small interfering RNA (siRNA) is introduced into a cell, it can knock down a cognate mRNA by targeting it for degradation. In this way, siRNA may be used to suppress the expression of specific genes of interest, but it does not

provide the possibility of direct functional activation. RNAi offers improved temporal control over protein function relative to most genetic approaches, but the timescale is still significantly slower than many dynamic biological processes. In contrast to the specificity that can be obtained using genetic mutations, off-target effects are common with the use of RNAi techniques.

A chemical genetic approach that uses small organic molecules to modulate protein function has the potential to overcome the limitations of classical genetic and RNAi techniques. In chemical genetics, small molecules are used to directly alter protein function by binding to a target and either inhibiting or activating its function. In analogy to traditional genetics, both forward and reverse chemical genetic techniques are used. In forward chemical genetics, a biological system is treated with various small molecules, and then the target of a molecule that causes a particular phenotype is identified. In reverse chemical genetics, small molecules are identified that modulate the function of a particular protein; the effect of the small molecule in a biological system is then analyzed. There are several advantages of chemical genetics compared to traditional genetics. The compounds can be added in variable amounts or removed at any time, so the effects are conditional, potentially reversible, and often tunable based on dosage. Furthermore, the rapid action of small molecules makes them useful for dissecting dynamic cellular processes. Small molecules can also be used to modulate individual functions of multifunctional proteins, which is not possible with either genetic or RNAi techniques. Additionally, small molecules that are found to modulate a target of therapeutic interest can then serve as leads for drug development. However, while traditional genetic approaches to modulating protein function are broadly applicable and completely specific, attaining these features in chemical genetics is still a challenge.

1.2. Sources of Small Molecules for Chemical Genetics

The effectiveness of chemical genetics in understanding biological systems and identifying therapeutic leads depends on a steady supply of biologically active small molecules with novel targets or improved specificity for known targets. Traditionally, natural products have been a valuable source of chemical probes for biological studies, in addition to playing an important role in drug discovery. Natural products are extremely diverse and their biological activities are often highly specific. However, isolation of natural products is frequently problematic, and useful amounts cannot always be obtained from natural sources. Although many efficient synthetic routes to natural products have been developed in response to this problem, difficulties with scale-up are still common. Therefore, alternative sources that provide molecules for biological screening in an efficient and practical way are needed.

The development of combinatorial chemistry has led to the production of a large number of small molecules available for high-throughput screening. The initial expectation was that the synthesis and screening of millions of compounds would lead to large numbers of biological hits. However, these early efforts have mainly resulted in disappointment. The underlying problem in this approach is that the number of small molecules that could potentially be synthesized is essentially infinite, and most of those molecules are not biologically relevant. More recently, the focus of library synthesis has shifted from quantity to quality; the present goal is to design smaller libraries that permit hit or lead compounds to be found with increased probability. One common approach has been to synthesize libraries of molecules with properties typical of known drugs. Although commercial libraries of “drug-like” molecules are now readily accessible for biological screening, these libraries consist of molecules comprising a focused region of chemical structure space. As a result, the range of biological targets that they are able to address may be limited. The finding that drug-

like molecules have significantly different structural properties from those of natural products lends credibility to this concern. Natural products are comparatively rigid, and they tend to have higher molecular weights, more stereogenic centers, fewer rotatable bonds, more complex ring systems, fewer nitrogen and sulfur atoms, and more hydrogen bond donors and acceptors than drug-like molecules.[1]

An alternate approach to designing biologically relevant libraries uses nature as inspiration. Natural products are selected by evolution to bind to specific protein domains; accordingly, they are a logical starting point for library design. Basing a library on natural products increases the likelihood that the molecules will be biologically compatible and therefore useful for applications in chemical genetics. In addition, creation of libraries with properties distinct from drug-like molecules allows relatively untapped regions of chemical structure space to be explored, and potentially, novel biological targets to be identified. A common strategy is to build a library around the core scaffold of a natural product; the goal is normally to improve the properties of the natural compound in relation to its original biological target. However, the minimal diversity of this type of library is not likely to lead to the identification of novel targets. Importantly, it has been found that substructures or fragments of natural products sometimes maintain biological activity, and this activity is often distinct from that of the parent natural product. Additionally, there are a number of structural motifs commonly found in natural products that are capable of interacting with multiple unrelated biological targets, referred to as privileged structures.[2,3] Therefore, there has been an increasing interest in the synthesis of small-molecule libraries based on natural product motifs for use in discovery screening. We wanted to explore the effectiveness of this approach, and we chose the spiroketal motif for our studies.

1.3. Bioactive Spiroketals in Nature

The spiroketal substructure is found in a wide variety of biologically active natural products with diverse biological activities (Figure 1.1).[4]

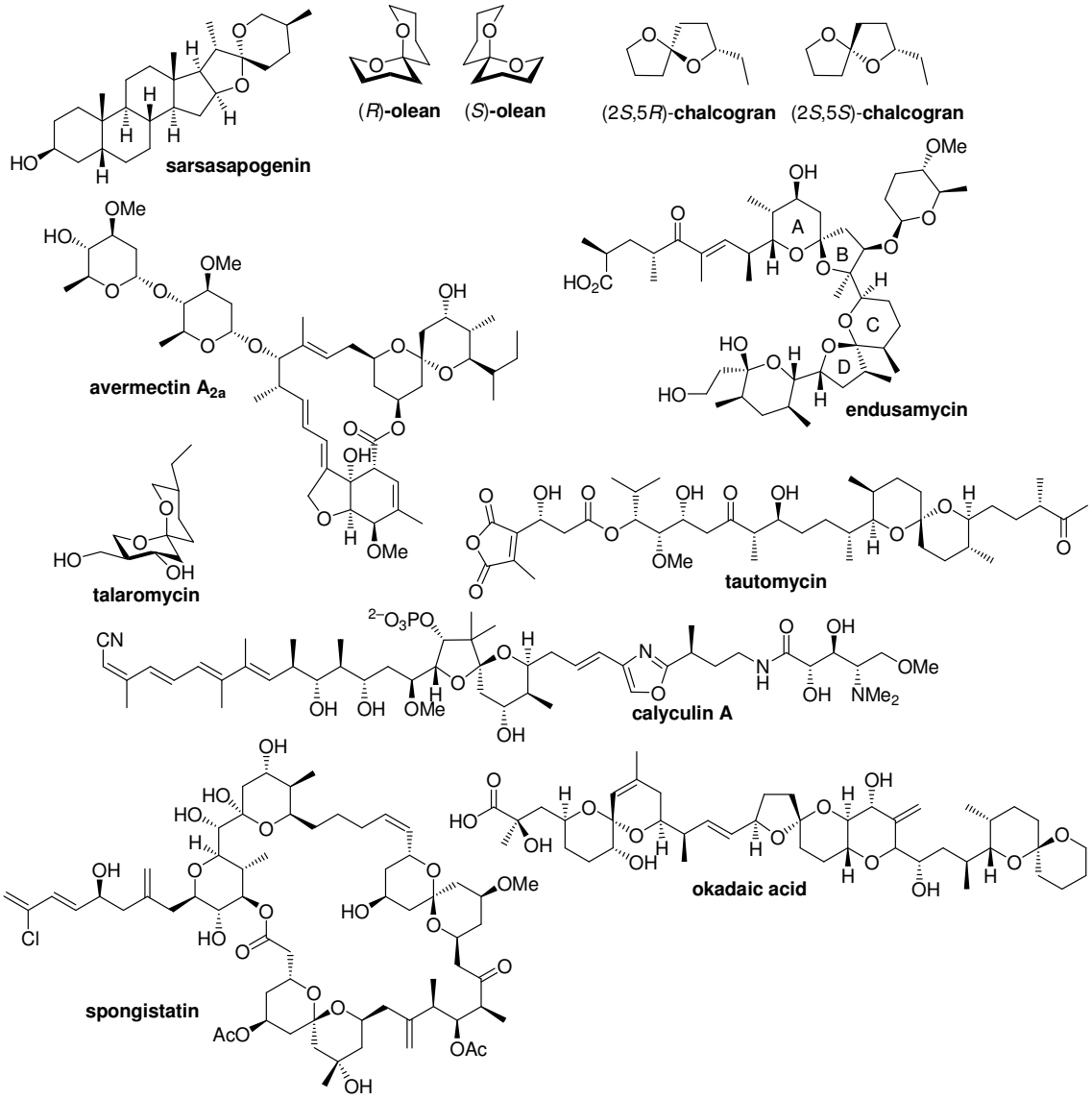

Figure 1.1. Structures of various natural products containing a spiroketal substructure

The steroidal sapogenins, originally discovered in the 1930s and 1940s, are the first known spiroketal-containing molecules that were isolated from natural sources. This class of compounds consists of a steroidal nucleus possessing a spiroketal fused

to the D-ring (e.g. sarsasapogenin), and is often glycosylated on the A-ring (referred to as a saponin). Over 200 saponins have been isolated, although variation in the spiroketal portion is rare. Saponins have shown hypocholesterolemic, immunostimulant, antiviral, antifungal, and anticancer properties. The biological activity of these molecules is likely due to their interaction with membrane sterols, which disrupts membrane function.[5,6]

Insect pheromones constitute another major class of spiroketals, and are some of the most structurally simple spiroketal natural products. Because they lack additional functionality, insect pheromones demonstrate that the spiroketal itself is capable of binding to biological receptors.[7] Although the structural variation and complexity found in these compounds is limited, stereochemical diversity is often displayed. In fact, stereoisomers are often found in the same organism and exhibit stereospecific biological activities. For example, both enantiomers of olean are produced by the female olive fly, but the (*R*)-enantiomer only attracts males, while the (*S*)-enantiomer is only active on females. Similarly, the European spruce bark beetle produces both (2*S*,5*R*)- and (2*S*,5*S*)-chalcogran, but only the (2*S*,5*R*)-epimer is active. This phenomenon illustrates the importance of stereochemistry for recognition of biological targets.

Other natural products also demonstrate the ability of the spiroketal to bind directly to biological targets. Talaromycin, a potent mycotoxin, is one example.[8] Other examples include the milbemycin and related avermectin antibiotics (e.g. avermectin A_{2a}), which are spiroketal-containing 16-membered macrolides that have potent anti-parasitic activity and low mammalian toxicity. They are widely used in human and veterinary medicine to combat infections, as well as in agriculture for the control of pests.[9] The spiroketal portion in the avermectins exhibits a narrow structure–activity

profile, suggesting that it is directly involved in binding to the target.[10] Molecules in this class are thought to target glutamate-gated chloride channels.[11]

There are many other larger, more complex natural products that also contain the spiroketal motif. However, the main role of the spiroketal in these cases is likely to act as a rigid scaffold to present sidechains in orientations that allow binding to specific sites on the biological targets.[12] Examples include the polyketide polyether antibiotics (e.g. endusamycin), which have ionophoric properties,[13] the spongistatins, which inhibit tubulin protein–protein interactions, and tautomycin, calyculin A, and okadaic acid, which are serine/threonine phosphatase inhibitors. Interestingly, some simple spiroketal analogs of these complex natural products have been shown to exhibit biological activity of their own.[14-16]

Spiroketals are an attractive starting point for library design because of their proven ability to bind directly to multiple classes of biological targets, along with their capability of serving as rigid scaffolds to present functional groups in three dimensions. Since the appropriate stereochemistry is often crucial for recognition of a particular biological target, incorporating stereochemical diversity in a compound library should improve the probability of identifying biologically active molecules. Importantly, spiroketal-based libraries can exploit stereochemical diversity at the spiroketal carbon, in addition to the more typically-used sidechain stereodiversity.

1.4. Synthetic Approaches to Spiroketals

The wealth of biological activity displayed by spiroketals in nature has inspired the development of numerous strategies for spiroketal synthesis. Although these syntheses have traditionally focused on natural product targets with known biological activity, a number of unnatural spiroketals have been synthesized and found to be biologically active.[14–16] The most frequently used strategy is acid-catalyzed spiroketalization of a dihydroxyketone precursor or an equivalent. Under equilibrating

conditions, the more thermodynamically stable isomer will be generated as the major product. For example, Merifield showed that acid-catalyzed spirocyclization of dithiane **1** yielded the spiroketal isomer **2**, which is found in the natural product milbemycin.[17]

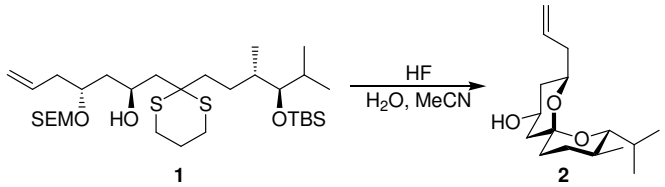

Figure 1.2. Thermodynamically controlled acid-catalyzed spiroketalization

Since many spirocyclizations in target-oriented syntheses are carried out under equilibrating conditions, the ability to predict thermodynamic stability is important. Thermodynamic stability of spiroketals is influenced by steric interactions, anomeric effects,[18] chelation effects, and intramolecular hydrogen bonding. The typical preference for substituents to occupy an equatorial orientation must be considered in addition to the stabilization provided by the anomeric effect. The anomeric effect has been estimated to lower the total energy of the molecule by 1.4–2.4 kcal/mol per interaction;[19] accordingly, it plays a major role in determining the relative stabilities of spiroketal structures. When the two factors are reinforcing (i.e. the contribution of anomeric stabilizations is maximized and unfavorable steric interactions are minimized), the preferred structure can be predicted.

For example, each of the 6,5-spiroketal isomers **3** and **4** can exist in an anomeric conformation (**3a** or **4b**, Figure 1.3). However, unfavorable steric interactions in **4b** will cause **3a** to predominate in an equilibrating mixture of **3** and **4**. Similarly, each of the two 6,6-spiroketal isomers **5** and **6** can exist as four chair–chair conformers (Figure 1.3). While spiroketals **5** and **6** can both exist as conformers

having two anomeric stabilizations (**5a** or **6a**), **5a** will predominate due to steric strain in **6a**. Therefore, **5** would be the major isomer in an equilibrating mixture of **5** and **6**.

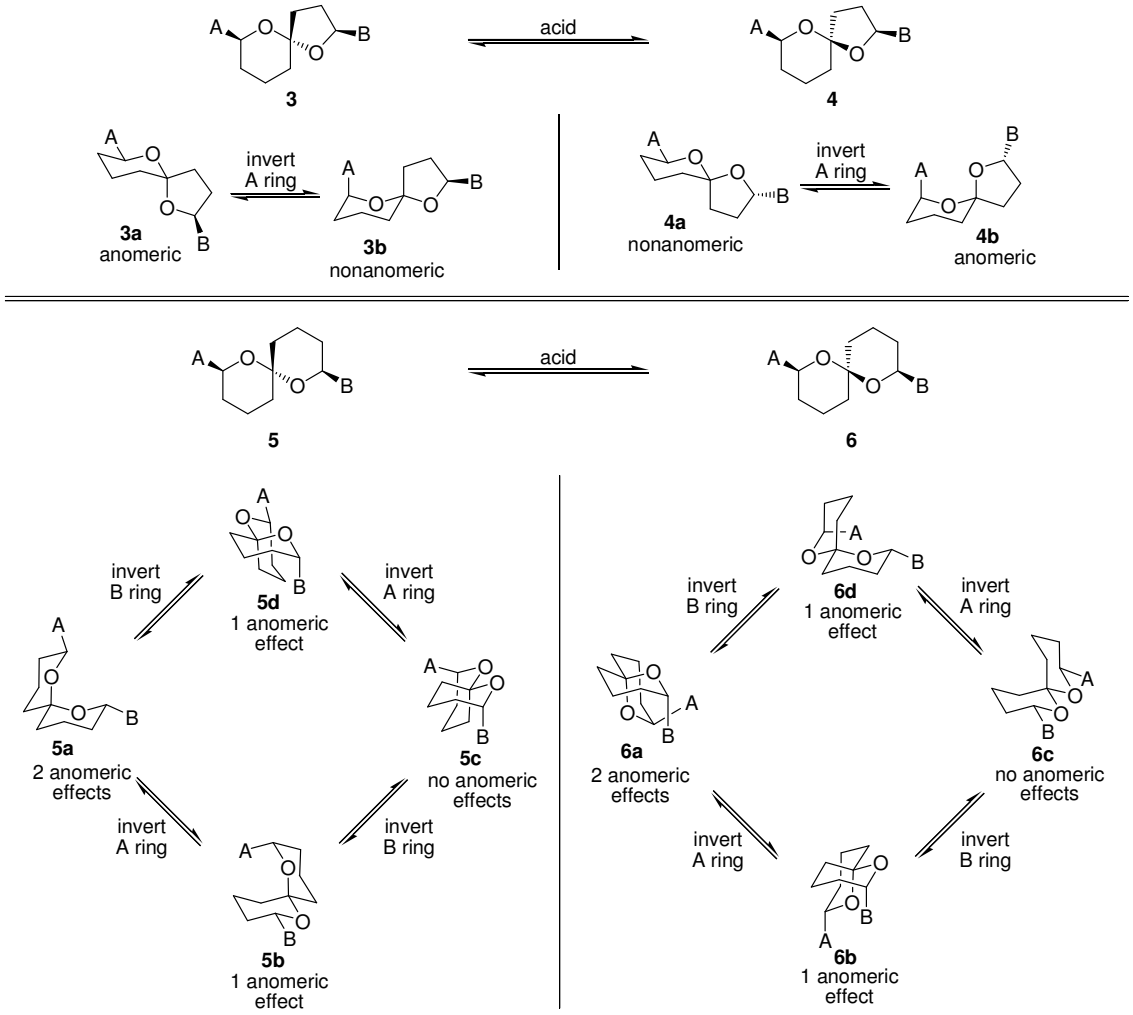

Figure 1.3. Anomeric relationships in 6,5- (**3** and **4**) and 6,6-spiroketal (**5** and **6**) systems

Although spiroketals are most commonly synthesized using internal ketalization strategies, other methods have also been developed. One conceptually unique approach developed by Paul utilizes a hetero-Diels–Alder cycloaddition.[20] The effectiveness of this strategy was demonstrated by Ireland in the synthesis of racemic chalcogran (Figure 1.4).[21] The condensation between vinyl ether **7** and

α,β-unsaturated ketone **8** proceeded in the presence of hydroquinone to yield spiroketal **9** in high yield.

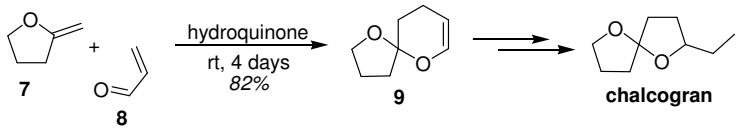

Figure 1.4. Hetero-Diels–Alder approach to spiroketals

Another unconventional approach to spiroketals made use of ketal-tethered ring-closing metathesis to construct a range of spiroketal structures.[22] In one case, the insect pheromone **12** was synthesized via a Grubbs' I-catalyzed RCM, followed by hydrogenation. The RCM precursor **11** was formed via addition of the lithiated analog of **10** to crotyl bromide, followed by stereoelectronically favored axial addition of allyl alcohol.

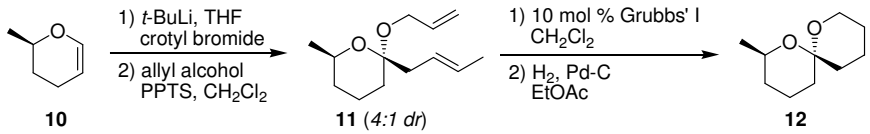

Figure 1.5. Ketal-tethered ring-closing metathesis

1.5. Synthetic Approaches to Nonanomeric Spiroketals: Thermodynamic Control

Although most known spiroketal natural products have two anomeric stabilizations, there are a number of naturally occurring compounds that do not.[23] These "nonanomeric" spiroketals may be favored due to steric effects or macrocyclic constraints, or may be stabilized by intramolecular hydrogen bonding. Alternatively, they could be formed kinetically and exist as contrathermodynamic spiroketals. Chemical synthesis of nonanomeric spiroketals has generally relied on methods that stabilize the nonanomeric product under thermodynamic, equilibrating conditions.

These methods often use steric constraints, intramolecular hydrogen bonding, or a chelating metal to drive the equilibrium in the desired direction.

For example, Ireland has taken advantage of steric strain in an acid-catalyzed equilibration to generate the spiroketal segment of 3-deoxyaplysiatoxin (Figure 1.6).[24] The enol ether **15** was formed via a hetero-Diels–Alder reaction between **13** and **14**, then converted to the bis-anomeric spiroketal **16** through hydroboration and benzoate protection. The desired spiroketal **17** was formed as a 70:30 equilibrium mixture with **16** upon treatment with HCl. This equilibrium ratio is likely due to the 1,3-diaxial interactions in **16**, which counteract the two anomeric stabilizations.

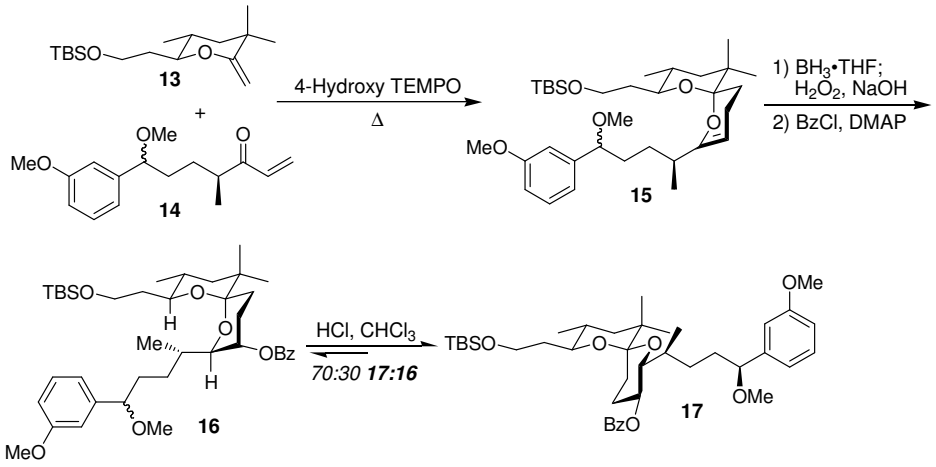

Figure 1.6. Thermodynamic equilibration using imposed steric constraints

Another common approach, demonstrated by Evans in the synthesis of the CD spiroketal segment of spongistatin, involves equilibration in the presence of a chelating metal (Figure 1.7).[25] Removal of the protecting groups in **18** resulted in spontaneous spirocyclization to yield an 85:15 mixture of the spiroketal **19** and its anomer **20**. The amount of the desired isomer **20** was increased (80:20 with **19**) when the mixture was equilibrated with a stoichiometric amount of $ZnCl_2$, presumably due

to an internal chelate between the hydroxyl groups, metal cation, and the anomeric oxygens (**21**), which stabilizes this isomer during equilibration.

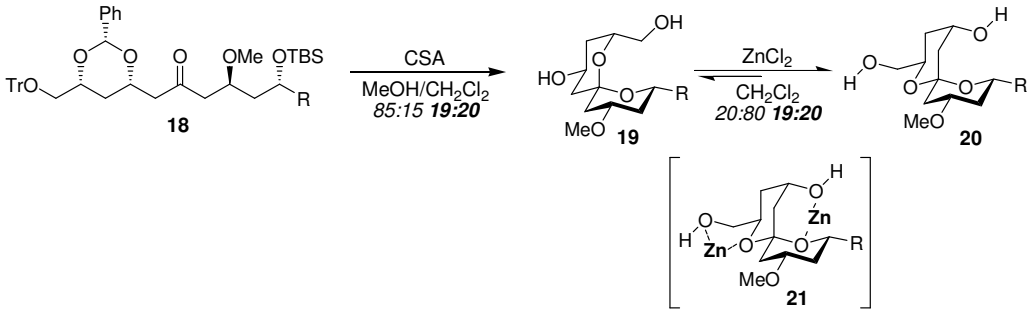

Figure 1.7. Thermodynamic equilibration with chelation by a metal

1.6. Synthetic Approaches to Nonanomeric Spiroketals: Kinetic Control

Although the equilibrative strategies described in Section 1.5 are often successful in producing nonanomeric spiroketals, in some cases the inherent stability of the bis-anomeric isomer is difficult to overcome. The selectivity complications arising from thermodynamically controlled reactions have inspired the development of several kinetically controlled methods for spirocyclization that allow formation of the desired product independent of thermodynamic considerations. While acid-catalyzed spiroketalizations are typically under thermodynamic control, Deslongchamps has shown that certain acidic conditions can provide access to kinetically controlled cyclization products.[18] However, more recent approaches toward contrathermodynamic products have completely avoided acid-catalyzed cyclization. These reactions usually take advantage of stereoelectronically preferred axial attack of an oxygen nucleophile at the anomeric position. For example, to construct the CD spiroketal subunit of spongistatin, Paterson subjected the alcohol intermediate **22** to a base-induced hetero-Michael reaction (Figure 1.8).[26,27] Favored axial attack provided the desired isomer **23** as the major product, although a significant amount of the thermodynamically favored anomer **24** was also formed. Similarly, the CD spiroketal

segment of spongistatin was obtained by Roush via activation of glycal **25** with *N*-iodosuccinimide to form the activated oxonium species **26**.[28] Axial attack by the *C*19 hydroxyl group formed the desired isomer (**27**) as the major product.

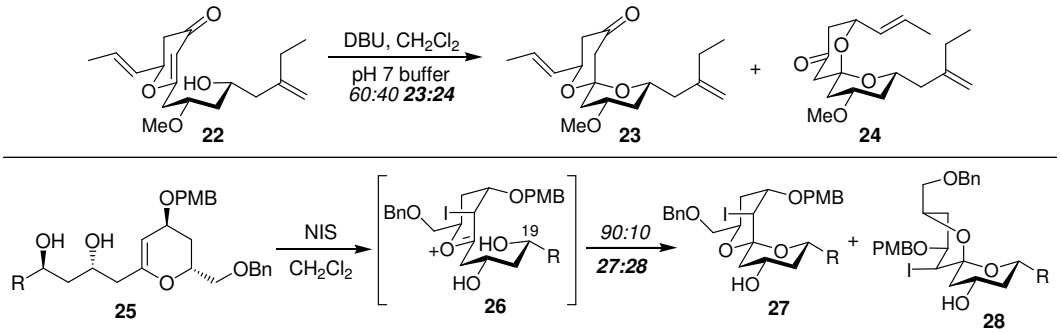

Figure 1.8. Kinetically controlled approaches to the CD spiroketal segment of spongistatin

One kinetic approach that is not limited by dependence on spirocyclization of an oxygen nucleophile along an axial trajectory was developed by Rychnovsky for the synthesis of the spiroketal portion of the polyketide antibiotic spirofungin B (Figure 1.9).[29] This method reverses the usual roles of the nucleophile and electrophile in spiroketal synthesis, avoiding the preference for formation of an axially-oriented oxygen. Lithium di-*tert*-butylbiphenylide is used to convert the cyanide **30** to the axial lithium species **31**. The lithiated acetal then displaces the chloride on the sidechain to form the desired spiroketal **32** as a single diastereomer.

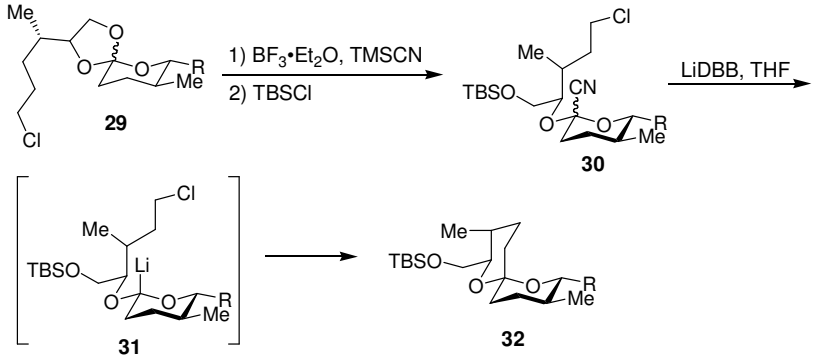

Figure 1.9. Reductive cyclization approach to the spiroketal segment in spirofungin B

1.7. Previous Approaches to Spiroketal Libraries

As described above, the spiroketal motif is an attractive starting point for library design. The syntheses of several spiroketal-based libraries have been described recently. The first of these, reported by Porco in 2002,[30] consisted of a single spiroketal scaffold containing three independently addressable functional groups that were used for elaboration of the scaffold (Figure 1.10). The spiroketal scaffold (**34**), which has two anomeric stabilizations, was synthesized by deprotection and cyclization of **33** under acidic conditions. After cyclization, diversity was introduced at positions R^1, R^2, and R^3 (**35**) by systematic introduction of sidechains at each position using solution-phase parallel synthesis techniques. No biological screening of the resulting library has been reported.

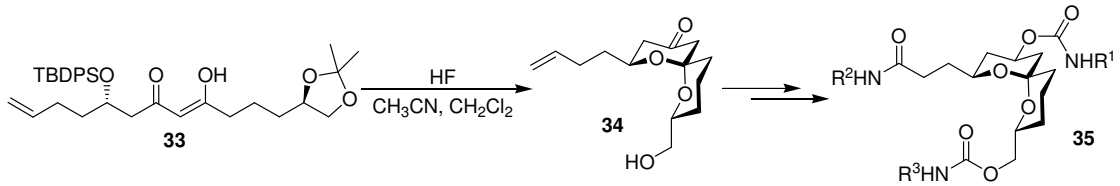

Figure 1.10. Porco's synthesis of a library based on a single spiroketal scaffold

In 2005, a spiroketal library based on a single spiroketal scaffold was reported by Waldmann (Figure 1.11).[31] A series of immobilized spirocyclization substrates **36** was synthesized using asymmetric boron enolate aldol reactions. Spontaneous spirocyclization of these substrates occurred upon deprotection with DDQ to form spiroketals **37**, usually providing the isomer with two anomeric stabilizations as the major product. In cases where mixtures were produced, only the doubly anomeric product was included in the library. Therefore, stereochemical diversity was achieved only through decoration of the spiroketal skeleton with stereogenic centers, not through variations in spiroketal stereochemistry. The library was found to contain several phosphatase inhibitors and modulators of microtubule formation. Importantly,

changes in the stereochemistry of the substituents were shown to affect biological activity. For example, spiroketal **38** inhibited the phosphatase VHR with an IC_{50} of 6 ± 4 μM, while **39** was a less potent inhibitor (IC_{50} = 31 ± 17 μM).

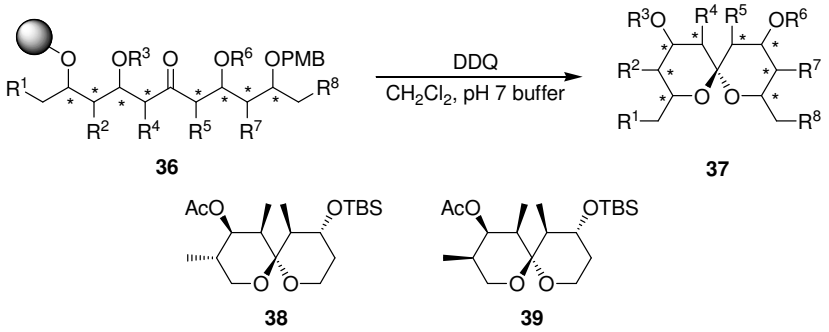

Figure 1.11. Waldmann's synthesis of a library based on a single spiroketal scaffold

The synthesis of a library encompassing multiple spiroketal scaffolds was reported in 2006 by Ley (Figure 1.12).[32] This approach was the first to make use of stereochemical diversity at the spiroketal carbon for library synthesis. When treated with acid, the *β*-keto-1,3-dithiane derivatives **40** cyclized to form the 6,6- (**41**) or 6,5-spiroketals (**42**) as mixtures of isomers. In addition to these structural and stereochemical skeletal variations, removal of the dithiane and elaboration of R^1 and R^2 provided functional group and sidechain diversity. Biological screening was not reported for this library.

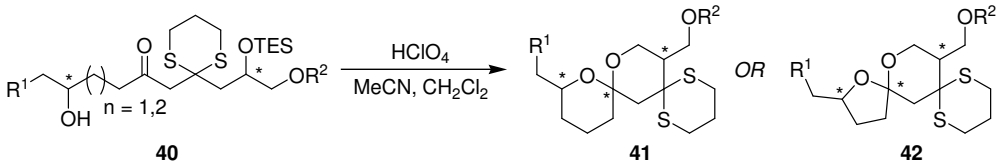

Figure 1.12. Ley's synthesis of a library based on multiple spiroketal scaffolds

1.8. Synthesis of a Structurally and Stereochemically Diverse Spiroketal Library Using Stereoselective Spirocyclizations of C1-Substituted Glycal Epoxides

While previous approaches to spiroketal libraries have focused primarily on structural diversity, we wanted to take advantage of the potential for stereochemical diversity presented by spiroketals. However, existing methods for synthesizing spiroketals had mainly been developed in the context of target-oriented synthesis, and were not suitable for the stereodiversified library that we envisioned. In order to synthesize systematically stereodiversified spiroketals, we needed to develop a general method allowing control of anomeric stereochemistry independent of thermodynamic stabilization or stereoelectronically favored axial attack.

We envisioned a stereoselective route to spiroketals using *C*1-substituted glycal epoxides (Figure 1.13). This approach would use the *C*3-substituent as a directing element for a stereoselective epoxidation reaction (**45**→**46**). The epoxide could then be used to invoke stereochemical control in two discrete kinetic spirocyclization reactions, providing access to both spiroketal stereoisomers (**47** or **48**) from a common intermediate.

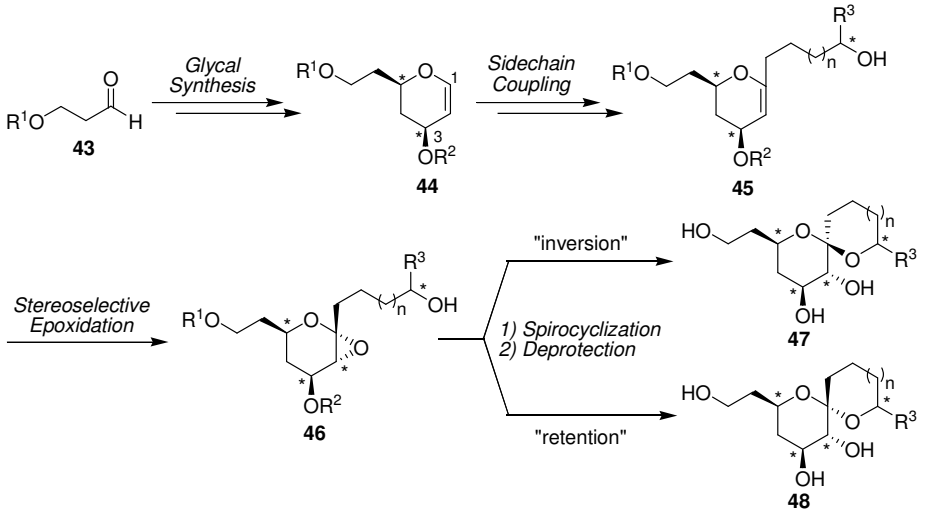

Figure 1.13. Stereoselective route to spiroketals (*site of stereochemical diversity)

Via this route, we would be able to generate stereochemical and structural diversity by: 1) using all four stereoisomers of 4-deoxyglycal substrates **44**; 2) attaching sidechains of different lengths at the *C*1-position (**45**), which would result in multiple spiroketal ring sizes; 3) varying the R^3 substituent; 4) carrying out spirocyclization reactions with either inversion or retention of configuration at *C*1 (**47** and **48**); and 5) derivatizing the spiroketals at the *C*2- or *C*7-position (not shown).

As will be described in Chapters 2–3, we have developed the synthetic methodology required to complete this route, providing access to eight spiroketal stereoisomers (four pairs of enantiomers) for each combination of R^3 and n = 0–1. As discussed in Chapter 4, we have used our novel methodology to synthesize a small library of stereochemically and structurally diverse spiroketals, which will be subjected to a range of biological assays. Comparison of the results of these screens to other types of libraries will allow us to evaluate the effectiveness of our library design strategy. We have also explored ways to increase the diversity and utility of our first-generation library, as illustrated in Chapter 5. Chapter 6 describes efforts to adapt our spiroketal synthetic methodology to a related problem in intermolecular glycosylation reactions.

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CHAPTER 2

ENANTIOSELECTIVE SYNTHESIS OF *C*1-SUBSTITUTED *THREO*- AND *ERYTHRO*-4-DEOXYGLYCALS

2.1. Introduction

Our plan for spiroketal library synthesis (Figure 1.13) required access to *C*1-substituted analogs (**6**) of all four stereoisomeric 4-deoxyglycals **2**–**5** (Figure 2.1). We designed these substrates to maintain the spacing of oxygen functionalities found in polyketide natural products. We also envisioned that an orthogonally protected *C*7-hydroxyl (OR^1) might provide an attachment point for future application in solid phase synthesis. This chapter is based in part on a previous publication.[1]

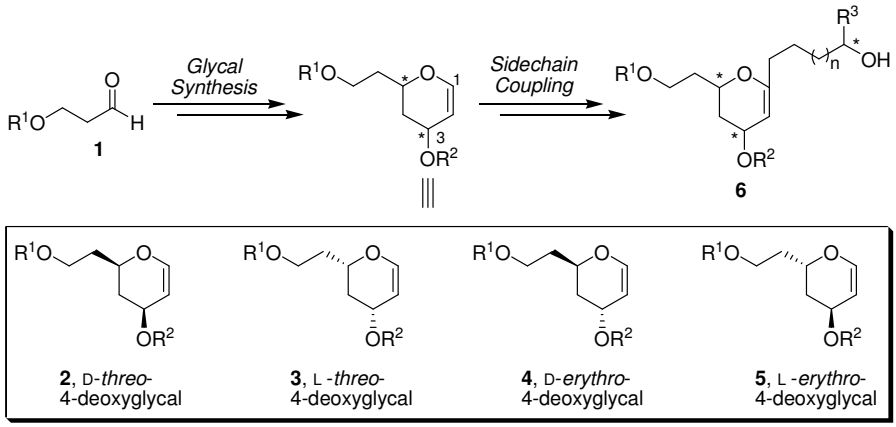


Figure 2.1. 4 stereoisomeric *C*1-substituted 4-deoxyglycal scaffolds required for spiroketal synthesis

2.2. Synthesis of the threo-4-Deoxyglycals

A synthesis of the *threo*-4-deoxyglycals (**2** and **3**) was developed by Justin Potuzak (Figure 2.2). An enantioselective cyclocondensation[2] of aldehyde **7** and the Danishefsky diene (**8**) to a dihydropyrone (**10**) is accomplished using a catalyst developed by Jacobsen[3] (**9**). Substrate-controlled stereoselective Luche reduction[4] of

the dihydropyrone followed by protection of the *C*3-hydroxyl of **11** produces the D-*threo*-glycal **12**. The corresponding L-*threo*-glycal is synthesized by using the enantiomer of the Jacobsen catalyst **9**.

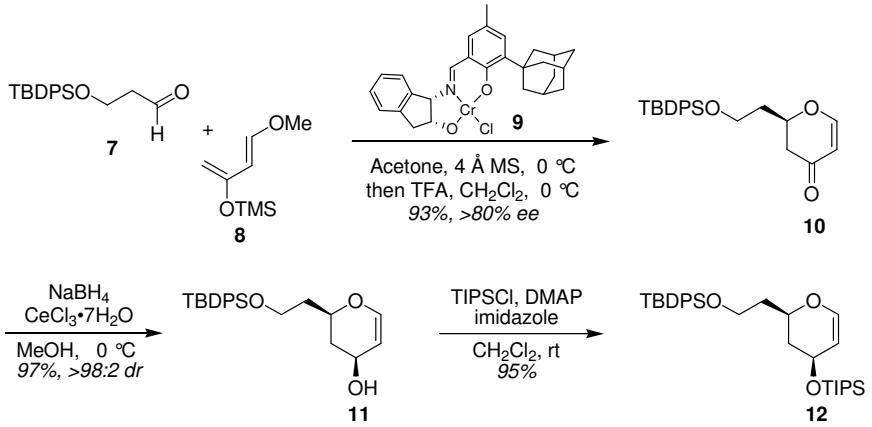


Figure 2.2. Enantioselective synthesis of the *threo*-4-deoxyglycals **12**

2.3. Synthesis of the erythro-4-Deoxyglycals

To expand the stereochemical diversity of the library, a route was needed to the *erythro*-4-deoxyglycals **4** and **5**. Attempts to synthesize the *erythro*-glycal **15** by 1,2-reduction of the dihydropyrone **13** using sterically demanding hydride reagents were based on the expectation that equatorial attack would occur to produce the desired product. However, treatment of **13** with a variety of bulky hydride reagents (Figure 2.3) resulted in exclusive formation of the *threo* stereoisomer **14**. Although these results contrast with stereoselectivity trends observed with bulky hydride reductions of cyclohexanones,[5] they can be rationalized by the reduced steric conflict along the axial trajectory,[6] increased torsional strain associated with the transition state for equatorial attack,[7] stereoelectronic effects involving the ring oxygen,[8] or the availability of a competing reactive conformation in which the *C*5-substituent is oriented axially.

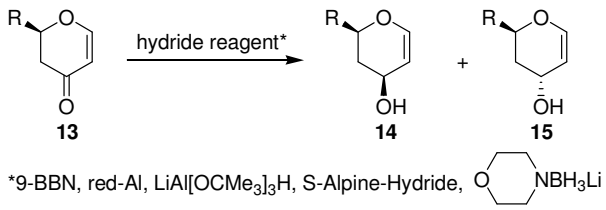


Figure 2.3. Reduction of the dihydropyrone **13** with bulky hydride reagents. R = Ph or *n*-Pr

Subsequent efforts to synthesize the *erythro* glycals were focused on inversion of the *C*3-hydroxyl group of the *threo*-glycal **14**. Attempts at Mitsunobu inversion were unsuccessful due to competing S_N2' displacement to form **16** (Figure 2.4). This result was not surprising due to the known propensity of glycals to undergo nucleophilic attack at the *C*1 position.[9]

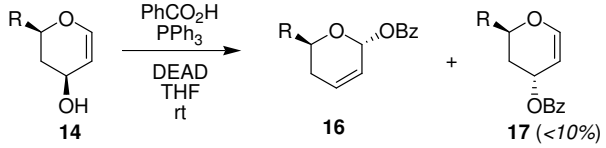


Figure 2.4. Attempted Mitsunobu inversion using the *threo*-glycal substrate **14**. R = Me or *n*-Pr

The susceptibility of glycals to S_N2' displacement has been exploited by Danishefsky in an indirect approach to *C*3 inversion. This approach converted the glucal substrate **18** to the allal product **22** using a thiophenol Ferrier/sigmatropic rearrangement sequence[10] (Figure 2.5). Unfortunately, substrate **24** was unstable to the reported thiophenol Ferrier conditions ($BF_3 \bullet OEt_2$) and the use of $SnCl_4$ resulted in direct substitution at the *C*3 position by thiophenol to provide glycal **25**. Interestingly, treatment with 4-methoxyphenol in the presence of $SnCl_4$ resulted in allylic substitution (**23**).

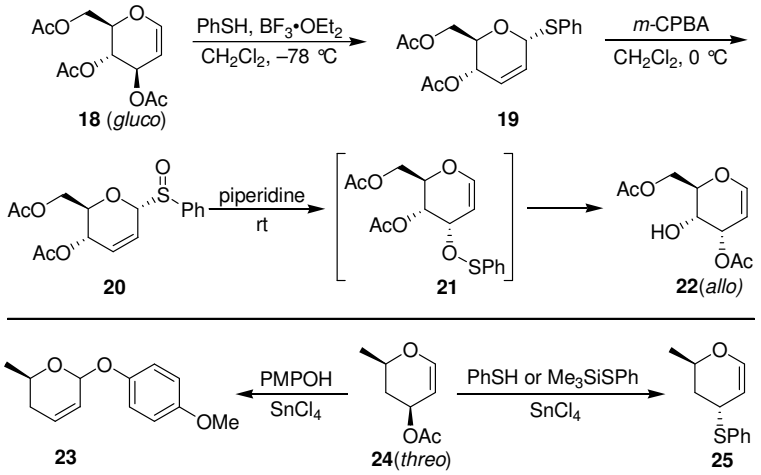


Figure 2.5. Net *C*3-inversion of 3,4,6-tri-*O*-acetyl-D-glucal **18** and related reactions of *threo*-4-deoxyglycal **24**

This regioselectivity can be rationalized by the hard-soft acid-base principle, in which soft nucleophiles tend to attack at the *C*3 position, and hard nucleophiles favor the *C*1 position.[11] With this idea in mind, the harder nucleophile *S*-trimethylsilyl thiophenol was tested since it favors *C*1 attack on other glycal substrates.[12] However, attack still occurred at the *C*3-position (**25**). This surprising regioselectivity may be due to the absence of a *C*4-substituent in our 4-deoxyglycal substrate, which reduces the steric conflict for attack at the *C*3-position.

Having explored the classical approaches, an alternative strategy involving *endo*-cycloisomerization of a linear alkynol precursor was evaluated. This class of reaction has been explored extensively by McDonald and Trost and is generally driven by molybdenum,[13] tungsten,[14-17] rhodium,[18] or ruthenium[19] catalysts. McDonald has reported a series of reactions catalyzed by $W(CO)_6$ that form glycals with various stereochemical configurations[17] (**27**) in high yield (Figure 2.6). The conditions were effective regardless of substrate stereochemistry, but no examples using 4-deoxy substrates were reported. While our work was in progress, Wipf reported a strong influence of stereochemistry, substitution patterns, and protecting groups on the

regiochemical outcome of the reaction (**29** (*endo*-glycal) *vs* **30** (*exo*-glycal) formation).[20] Discouragingly, cycloisomerization of substrates with our required substitution pattern and stereochemical configuration (**28a–e**) were reported to lead to low yields (3–15%) of the desired *erythro*-4-deoxyglycal products (**29a–e**). When a coordinating substituent was present at the propargylic position, the low yield was due to competing *exo*-cycloisomerization. Although the *endo*-glycal was the major product when the propargylic substituent was non-coordinating (**28e**), the yield was still low (15% **29e**, unreported byproducts).

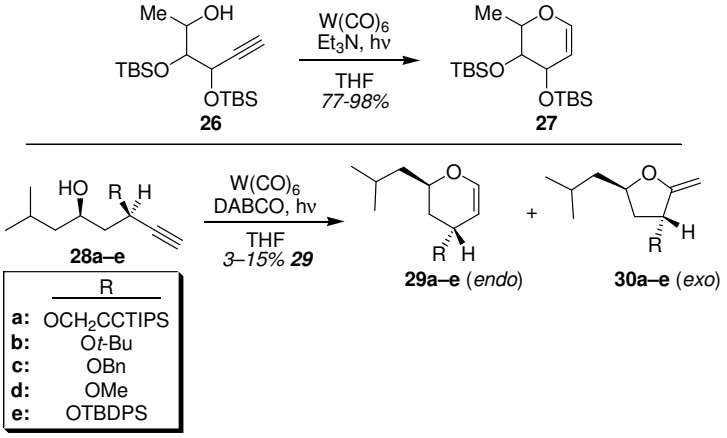


Figure 2.6. Tungsten-catalyzed cycloisomerizations of alkynol substrates **26** and **28**

To determine if higher yields of the desired *erythro*-4-deoxyglycal could be achieved by a cycloisomerization route, we synthesized a series of alkynol precursors using methodologies that have been developed in the context of polyketide synthesis. Enantioselective allylation of aldehyde **7** with Leighton's allylsilane reagent[21] (**31**) provided homoallylic alcohol **32** with high optical purity (96% e.e.) The homoallylic alcohol was protected as the triethylsilyl ether then converted to aldehyde **33**. At this point, several recently developed diastereoselective alkyne addition reactions were evaluated. Unfortunately, attempted couplings of **33** with trimethylsilylacetylene using $Zn(OTf)_2$/*N*-methylephedrine[22] led to recovered starting material, consistent with a

report involving related substrates.[23] Reactions at higher temperatures or with $Et_2Zn/Ti(O\textit{i}\text{-}Pr)_4$/BINOL[18,24] led to β-elimination of **33** to the corresponding α,β-enone. Direct addition of lithium trimethylsilylacetylide resulted in a mixture of propargylic alcohol diastereomers (52:39 **34**:**35**), however, the minor diastereomer **35** was readily separated chromatographically from **34** and carried on to alkynol **36** using standard Mitsunobu inversion protocols. Protecting group manipulations of **36** provided cycloisomerization substrates **37a–g**.

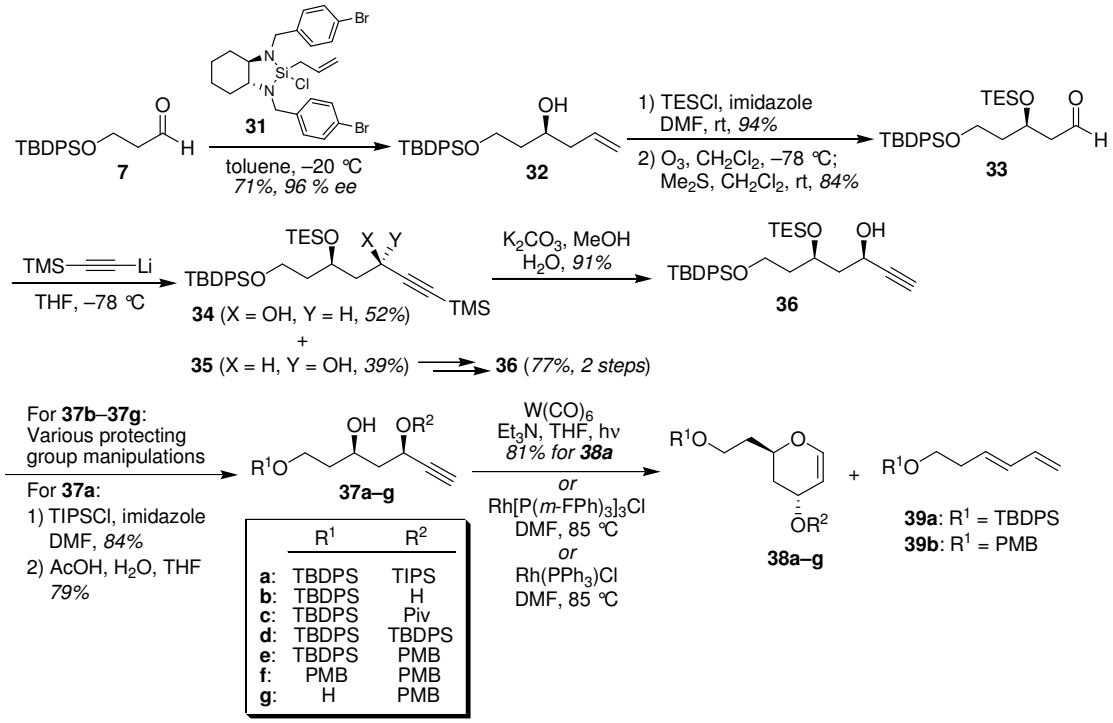


Figure 2.7. Enantioselective synthesis of protected alkynol substrates **37a–g** and *endo*-cycloisomerization reactions to form *erythro*-4-deoxyglycals **38a–g**

We were then in a position to carry out a series of alkynol cycloisomerization reactions. Unfortunately, attempted cycloisomerizations of **37a,e–g** using conditions developed by Trost (catalysis by $Rh[P(m\text{-}FPh)_3]_3Cl$ or $Rh(PPh_3)_3Cl$)[18] yielded only trace amounts of the corresponding glycals **38a,e–g**. Interestingly, $W(CO)_6$-catalyzed[17] cycloisomerizations of **37b** and **37c** resulted in the formation of truncated diene **39a** as

the only product. This diene was a major product for **37d** (50:50 with **38d**) and **37e** (45:2:53 with **38e** and the corresponding *exo*-glycal). Similarly, reaction of the doubly PMB-protected alkynol **37f** yielded the corresponding diene **39b** (54:23:23 with **38f** and the corresponding *exo*-glycal).

The appearance of the diene and *exo*-glycal[20] products can be rationalized by the mechanisms shown in Figure 2.8. When an alkynol **37** is exposed to the $W(CO)_6/Et_3N/h\nu$ cycloisomerization conditions, coordination of tungsten to the alkyne (**40** or **41**) can be followed by direct cyclization to the *exo*-glycal (**44**). However, if hydride transfer is faster than *exo*-cyclization, *endo*-cyclization can then occur, yielding the *endo*-glycal (**38**) after protonation.

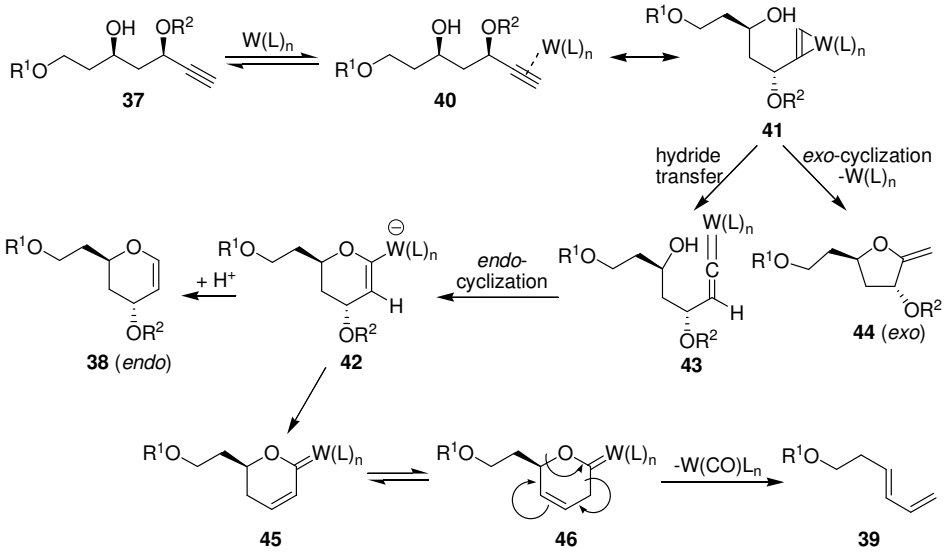


Figure 2.8. Proposed mechanisms of formation of *endo*-glycal **38**, *exo*-glycal **44**, and diene **39** from alkynol **37**

Since the *C*3-substituent of our *erythro* glycal substrates is in an axial orientation, the intermediate following *endo*-cyclization (**42**) is stereoelectronically predisposed to undergo elimination to **45**. Alkene isomerization to **46** followed by [4+2] cycloreversion leads to the observed diene (**39**). Analogous diene products had

not been reported previously, however, the proposed diene formation pathway may not be relevant for *threo* stereoisomers (due to the decreased propensity for elimination), or substrates having a substituent at the *C*4 position (due to decreased acidity). Furthermore, the low isolated yields reported by Wipf for *erythro*-4-deoxy substrates[20] could be partially due to volatility of dienes lacking our bulky sidechains.

After extensive experimentation with alkynol substrates **37a**–**f**, it was found that exposure of **37a** to $W(CO)_6/Et_3N/h\nu$ provided the desired *erythro*-4-deoxyglycal **38a** in good yield with no evidence of competing *exo*-cycloisomerization and only trace amounts of the diene byproduct (Figure 2.7). Replacement of Et_3N with DABCO, which is now more commonly used as the base,[16,17] resulted in distinctly slower reaction rates and incomplete conversion to the desired glycal. This route provided access to gram quantities of the critical *erythro*-4-deoxyglycal (approximately 30% overall yield of glycal **38a** from aldehyde **7** when carried out on a multigram scale) that provided the first basis for stereochemical diversity in our library. Importantly, synthesis of the glycal enantiomer (**3**) was equally successful when the enantiomer of the allylation reagent **31** was used, providing even greater stereochemical diversity.

2.4. Reactivity of the erythro-4-Deoxyglycals

Access to the *erythro*-4-deoxyglycals also provided the opportunity to explore their reactivity, and to determine the feasibility of stereoselective reactions of the glycal double bond that are complementary to those available using the corresponding *threo* stereoisomer. Reactions were expected to occur selectively at the β-face of the double bond due to a favored reactive conformation in which the *C*3-OTIPS substituent is axially disposed (**47**, Figure 2.9).

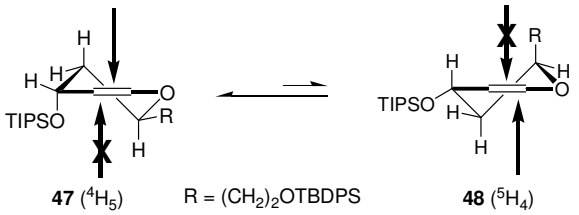


Figure 2.9. Half-chair conformations of the *erythro*-4-deoxyglycal **38a** and steric influences upon double bond reactivity

As anticipated, epoxidation of **38a** with dimethyldioxirane[25] afforded the β-epoxide **53** (Figure 2.10). Methanolysis of the epoxide proceeded stereoselectively to the α-D-*arabino*-4-deoxyglycoside **49**. Similarly, allylation of **53** with allylmagnesium chloride provided the corresponding α-allyl *C*-glycoside **55**. Hydroboration–oxidation of **38a** using BH_3 led to a 2:1 ratio of **50** and its α-C2-epimer while 9-BBN and dicyclohexylborane were unreactive. However, the use of thexylborane led to highly stereoselective formation of the β-*C*2-alcohol **50**.

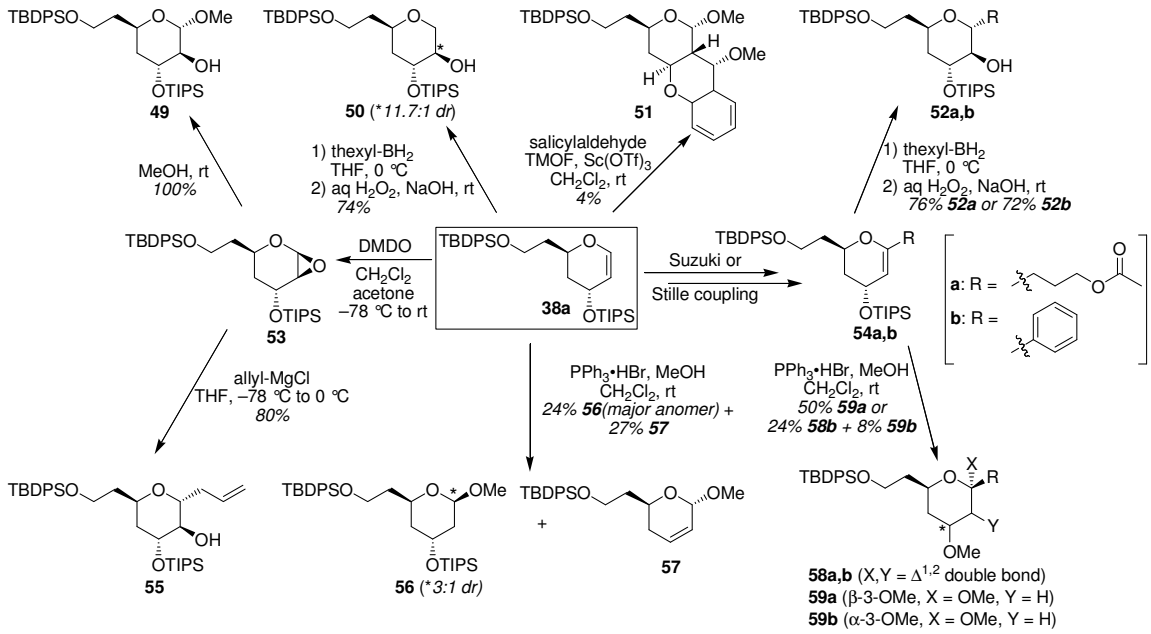


Figure 2.10. Stereoselective reactions of the *erythro*-4-deoxyglycal **38a**

Interestingly, attempted direct methanolysis of the glycal double bond under mild acidic conditions (PPh_3•HBr) led to a 41:14:45 mixture of β-methyl *erythro*-2,4-dideoxyglycoside **56**, its α-anomer (not shown), and the α-glycoside Ferrier rearrangement product **57**. Notably, exposure of the corresponding *threo*-4-deoxyglycal to identical conditions did not result in any Ferrier rearrangement. These results are consistent with axial orientation of the *C*3-OTIPS substituent in the *erythro*-glycal, which would be stereoelectronically predisposed to Ferrier-type elimination. Similarly, $Sc(OTf)_3$-catalyzed condensation of **38a** with salicylaldehyde[26] resulted in the formation of tricycle **51** instead of the expected Diels–Alder reaction product. Although the isolated yield of the tricycle was low, the reaction proceeded with high regio- and stereoselectivity, which can be rationalized by the mechanism shown in Figure 2.11.

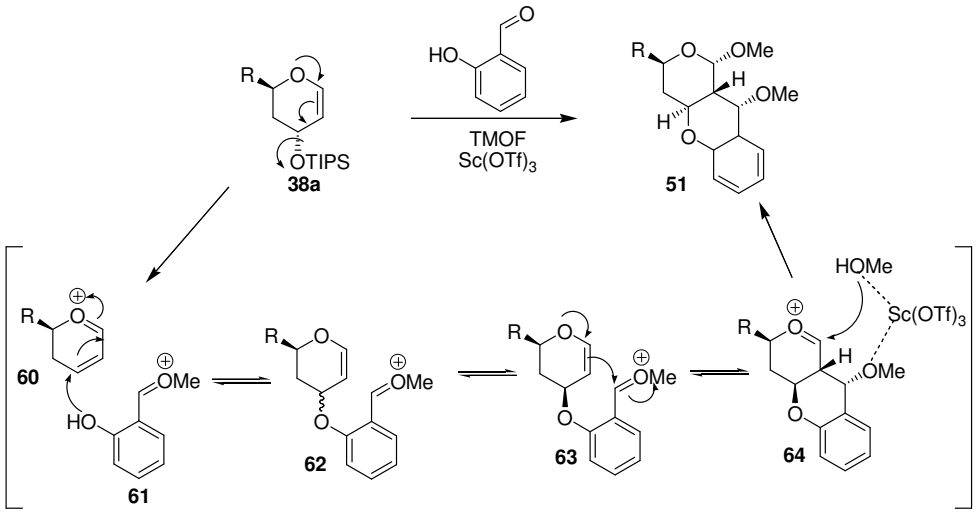


Figure 2.11. Proposed mechanism for formation of tricycle **51** through $Sc(OTf)_3$-catalyzed condensation of **38a** with salicylaldehyde. R = $(CH_2)_2$OTBDPS

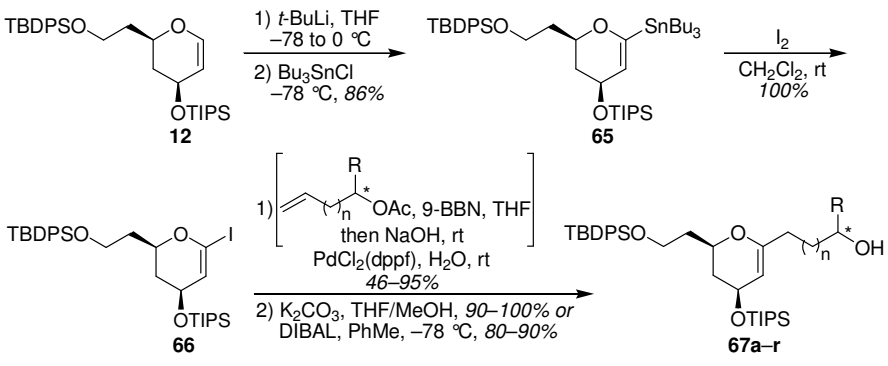
After exposure of glycal **38a** to $Sc(OTf)_3$, a Ferrier-type reaction leads to **60**, which then undergoes reaction with **61** to form **62**. Although this addition reaction is probably not stereoselective, facile Ferrier-type elimination of the α-*C*3-substituent in

intermediate **62** would cause the β-*C*3-substituted **63** to become the major stereoisomer. Reversible cyclization then occurs to produce the thermodynamically-favored **64**, which is then quenched by MeOH. The observed stereochemistry at the anomeric position may be due to positioning of the incoming MeOH by $Sc(OTf)_3$ through coordination with the α-OMe-substituent.

The *erythro*-4-deoxyglycal **38a** was also converted to *C*1-substituted glycals **54a,b** via Suzuki[27] or Stille[28] coupling, respectively (Figure 2.10). Hydroboration–oxidation with thexylborane proceeded from the β-face of the glycal double bond with complete stereoselectivity to provide the corresponding α-D-*arabino*-4-deoxy-*C*-glycosides **52a,b.** Interestingly, acid-catalyzed alcoholysis of the *C*1-substituted glycals **54a,b** provided α-methyl ketoglycosides **59a,b**, corresponding to a double substitution at both the *C*1 and *C*3 positions. It is likely that steric factors in these *C*1-substituted glycals cause MeOH to attack at the *C*3 position following an initial Ferrier-type elimination, leading to the 3-methoxyglycal intermediates **58a,b**. In the *C*1-phenylglycal series, **58b** was observed as a reaction intermediate in equilibrium with **59b**, supporting the proposed mechanism.

2.5. Synthesis of C1-Substituted Glycals

An efficient and flexible method for attaching sidechains to the *C*1 position of the *threo*-4-deoxyglycal (**12**) was developed by Justin Potuzak. The *C*1-iodoglycal **66** is prepared via the corresponding glycal stannane **65** according to Friesen's protocol.[29] The iodide can then be coupled to a range of olefins using an optimized *B*-alkyl Suzuki–Miyaura cross-coupling reaction to yield *C*1-alkylglycals **67a–r**.[27] This route also allows efficient formation of the analogous *erythro*-*C*1-alkylglycals (not shown).



glycal	n	R	glycal	n	R	glycal	n	R
a: *threo*	1	H	**h**: *erythro*	1	H	**o**: *threo*	1	*R*-CH_2Cl
b: *threo*	1	*R*-Me	**i**: *erythro*	1	*R*-Me	**p**: *threo*	1	*S*-CH_2Cl
c: *threo*	1	*S*-Me	**j**: *erythro*	1	*S*-Me	**q**: *threo*	0	*R*-CH_2Cl
d: *threo*	0	H	**k**: *erythro*	0	H	**r**: *threo*	0	*S*-CH_2Cl
e: *threo*	0	*R*-Me	**l**: *erythro*	0	*R*-Me			
f: *threo*	0	*S*-Me	**m**: *erythro*	0	*S*-Me			
g: *threo*	2	H	**n**: *erythro*	2	H			

Figure 2.12. Synthesis of *C*1-alkyl glycals **67**

2.6. Experimental Section

Materials and Methods:

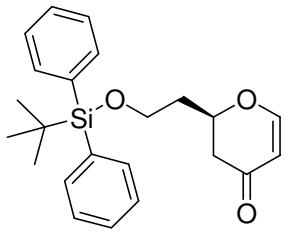
Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) or Acros Organics (www.fishersci.com) and used without further purification. 1-Methoxy-3-trimethylsiloxy-1,3-butadiene was obtained from Alfa Aesar. Optima grade solvents were obtained from Fisher Scientific (www.fishersci.com), degassed with Ar, and purified on a solvent drying system as described in Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996,** *15*, 1518–1520 unless otherwise indicated. Triethylamine was distilled from CaH under N_2. Reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring unless otherwise indicated. Cold baths were generated as follows: 0 °C, wet ice/water; –78 °C, dry ice/acetone; –63 °C dry ice/chloroform. Photolysis reactions were carried out in a Rayonet photoreactor at 300 nm. Flash chromatography was performed on E. Merck 60 230–400 mesh silica gel. Chiral HPLC analysis was carried out on a Varian analytical HPLC with a Chiracel OD-H

column using a flow rate of 0.7 mL/min of 2% isopropanol in hexanes, with UV detection at 252 nm. Optical rotations were recorded on a JASCO model DIP-370 digital polarimeter. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by using potassium permanganate or cerium ammonium molybdenate stains. IR spectra were recorded neat on NaCl plates with a Perkin–Elmer model 1600 FTIR spectrometer with peaks reported in cm^{-1}. NMR spectra were recorded on Bruker DRX500 or AMX400 instruments at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to TMS (^1H, 0 ppm) or solvent signals: $CDCl_3$ (^{13}C, 77.0 ppm), C_6D_6 (^1H, 7.16 ppm; ^{13}C, 128.0 ppm) or acetone-d_6 (^{13}C, 206.2 ppm). Coupling constants are expressed in Hz. Mass spectra were obtained at the MSKCC Analytical Core Facility on a PE SCIEX API 100 mass spectrometer by electrospray (ESI) ionization.

Atom numbering in IUPAC compound names herein does not correspond to conventional carbohydrate nomenclature and is used for naming purposes only. Atom numbering in the text corresponds to conventional carbohydrate nomenclature. Compounds not cited in the previous sections of this chapter are numbered herein **E1–E9**.

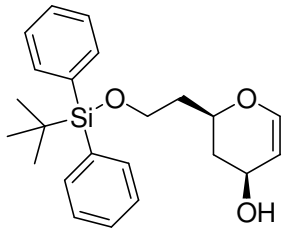
*Synthesis of threo-4-deoxyglycal **12:***

Compounds **10–12** were characterized by Justin Potuzak.



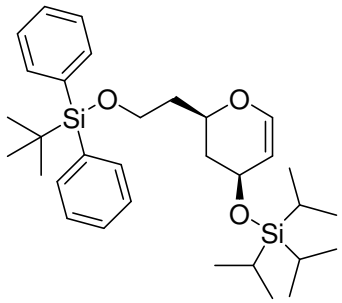
(6*R*)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2,3-dihydropyran-4-one (10). A solution of catalyst **9**[3] (310 mg, 0.64 mmol, 0.050 equiv) in anhyd acetone (2.5 mL)

was stirred over 4 Å molecular sieves (2.5 g) for 30 min then cooled to 0 ºC. Aldehyde **7**[30,31] (4.0 g, 0.013 mol, 1.0 equiv) was added and the reaction was stirred 10 min. 1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (3.7 mL, 0.019 mol, 1.5 equiv) was added slowly then the reaction was warmed to rt. After 3 h, the reaction was cooled to 0 ºC then CH_2Cl_2 (25 mL) was added. After 10 min, TFA (1.5 mL, 0.019 mol, 1.5 equiv) was added slowly then the reaction was warmed to rt. The mixture was filtered through Celite/silica and the filtrate was concentrated. The residue was purified by flash chromatography (elution with 5:1 hexanes/EtOAc) to yield dihydropyrone **10** as a yellow oil (3.4 g, 70%). The e.e. of **10** was determined to be 88% by chiral HPLC analysis. **TLC**: R_f 0.51 (2:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +46º (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3071, 2953, 2930, 2884, 2856, 1679, 1594, 1469, 1429, 1403, 1272, 1212, 1107, 1031, 739, 703, 613, 503. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.46–7.37 (m, 6H), 7.28 (d, 1H, *J* = 6.0), 5.40 (dd, 1H, *J* = 0.7, 5.8), 4.68 (m, 1H), 3.89–3.76 (m, 2H), 2.57–2.43 (m, 2H), 2.03 (m, 1H), 1.88 (m, 1H), 1.05 (s, 9H). **^{13}C-NMR** (125 MHz): δ 192.6, 163.1, 135.5, 133.4, 129.8, 127.7, 107.1, 76.4, 59.2, 42.0, 37.2, 26.8, 19.2. **ESI-MS** *m/z*: pos 403.0 $[M+Na]^+$; neg 379.2 $[M–H]^–$, 415.3 $[M+Cl]^–$.



(4*S*,6*R*)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-3,4-dihydro-2*H*-pyran-4-ol (11). $CeCl_3$•$7H_2O$ was added to a solution of dihydropyrone **10** (3.4 g, 9.0 mmol, 1.0 equiv) in anhyd MeOH (40 mL) at rt then the mixture was cooled to –78 ºC. $NaBH_4$ (510 mg, 13 mmol, 1.5 equiv) was added in one portion. After 30 min at –78 ºC, the reaction was warmed to rt then quenched by slow addition of sat'd aq NaOAc. The aqueous

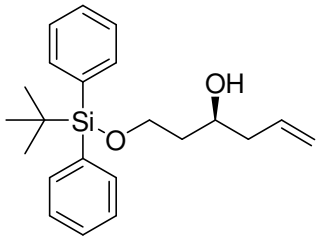
layer was extracted 3x with EtOAc then the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 3:1 hexanes/EtOAc) to yield glycal **11** as a clear oil (3.1 g, 90%). **TLC**: R_f 0.38 (2:1 hexanes/EtOAc). $[\alpha]_D^{25} = -3.4°$ (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3335, 3066, 2951, 2931, 2880, 2858, 1642, 1469, 1427, 1389, 1234, 1105, 1059, 1030, 953, 822, 739, 702, 612, 502. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.44–7.36 (m, 6H), 6.33 (d, 1H, *J* = 6.0), 4.73 (dt, 1H, *J* = 6.2, 1.8), 4.41 (m, 1H), 4.18 (m, 1H), 3.86–3.73 (m, 2H), 2.17 (m, 1H), 1.91–1.78 (m, 2H), 1.64–1.55 (m, 1H), 1.35 (d, 1H, *J* = 7.1), 1.05 (s, 9H). **^{13}C-NMR** (125 MHz): δ 145.2, 135.5, 133.8, 129.6, 127.7, 105.3, 71.7, 63.1, 59.9, 38.2, 37.8, 26.9, 19.2. **ESI-MS** *m/z*: pos 405.2 $[M+Na]^+$.



(4*S*,6*R*)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (12). Imidazole (1.1 g, 16 mmol, 2.0 equiv) then TIPSCl (2.6 mL, 12. mmol, 1.5 equiv) was added to a solution of glycal **11** (3.1 g, 8.1 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at rt. After stirring at rt 2 h, the reaction was quenched with sat'd aq $NaHCO_3$. The aqueous layer was extracted 3x with Et_2O then the combined organic layers were washed with H_2O then brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (elution with 99:1 hexanes/EtOAc) to yield *threo*-4-deoxyglycal **12** as a clear oil (3.6 g, 82%). **TLC**: R_f 0.70 (4:1 hexanes/EtOAc). $[\alpha]_D^{25} = -19°$ (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3067, 2941, 2863,

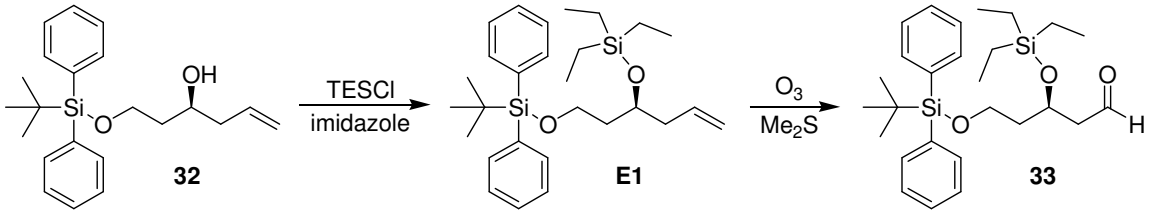
1643, 1465, 1428, 1388, 1237, 1104, 1005, 883, 822, 738, 702, 502. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.44–7.35 (m, 6H), 6.28 (d, 1H, *J* = 6.27), 4.71 (dt, 1H, *J* = 6.2, 1.7), 4.53 (dd, 1H, 8.2, 6.7), 4.18 (m, 1H), 3.85-3.73 (m, 2H), 2.08 (m, 1H), 1.92 (m, 1H), 1.82–1.69 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 144.1, 135.5, 133.8, 129.6, 127.6, 106.2, 71.6, 63.3, 60.1, 38.2, 37.8, 36.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z*: pos 561.5 $[M+Na]^+$; neg 573.4 $[M+Cl]^-$.

*Synthesis of erythro-4-deoxyglycal **38a**:*



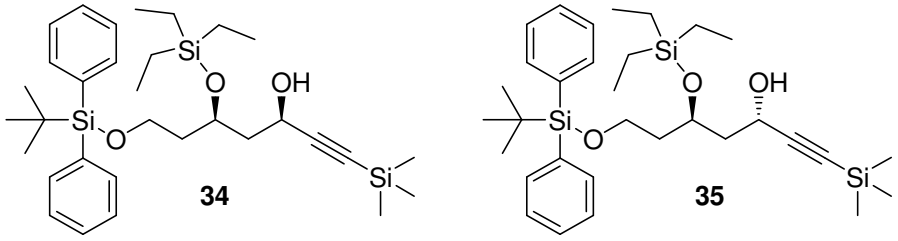
(3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-hex-5-en-3-ol (32). A solution of aldehyde **7**[30,31] (3.0 g, 9.7 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (40 mL) was transferred by cannula to a cooled (–78 ºC) solution of (3a*R*,7a*R*)-2-allyl-1,3-bis-(4-bromobenzyl)-2-chlorooctahydrobenzo[1,3,2]diazasilole[32] (8.1 g, 15 mmol, 1.5 equiv) in anhyd CH_2Cl_2 (40 mL). The reaction was transferred to a freezer (–10 ºC) then allowed to stand for 21 h. The cold reaction mixture was quenched with sat'd aq $NaHCO_3$ then warmed to rt and stirred 15 min. The aqueous layer was extracted 2x with EtOAc then the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 9:1 hexanes/EtOAc) to yield alcohol **32** as a clear oil (2.5 g, 71%). The e.e. of **32** was determined to be 96% by analysis of its Mosher ester. **TLC**: R_f 0.13 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 3441, 3058, 2926, 2854, 1463, 1428, 1104, 1080, 823, 739, 703, 613, 506. **^{1}H-NMR** (400 MHz): δ 7.71 (d, 4H, *J* = 7.1), 7.45 (m, 6H), 5.86 (m, 1H), 5.11 (m, 2H), 3.96 (m,

1H), 3.89 (m, 2H), 3.19 (d, 1H, J = 2.6), 2.25 (m, 2H), 1.70 (m, 2H), 1.21 (s, 9H). **^{13}C-NMR** (125 MHz): δ 135.7, 133.2, 128.8, 127.7, 117.5, 70.9, 63.4, 41.7, 37.9, 26.6, 19.0. **ESI-MS** *m/z*: (pos) 377.1 $[M+Na]^+$; (neg) 389.2 $[M+Cl]^-$.



32 **E1** **33**

The homoallylic alcohol **32** was converted to aldehyde **33** in two steps as described.[33] For analytical scale synthesis, olefin **E1** and aldehyde **33** were purified by flash chromatography as usual. For preparative scale synthesis, 14 g of alcohol **32** was converted to 19 g of crude aldehyde **33** (84% overall yield based on NMR analysis of the crude product) that was carried on to **34** without further purification (see below).



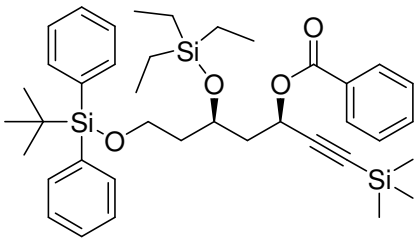
34 **35**

(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)-hept-1-yn-3-ol (34) and **(3*S*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)-hept-1-yn-3-ol (35).** *n*-BuLi (2.5 M in hexane, 2.0 mmol, 1.3 equiv) was added dropwise to a cooled (–78 °C) solution of TMS acetylene (270 μL, 2.0 mmol, 1.3 equiv) in anhyd THF (4.5 mL). The reaction mixture was stirred at –78 °C for 1 h then treated over 5 min with a solution of the aldehyde **33** (720 mg, 1.5 mmol, 1.0 equiv) in anhyd THF (3.5 mL). After an additional 20 min at –78 °C, the reaction

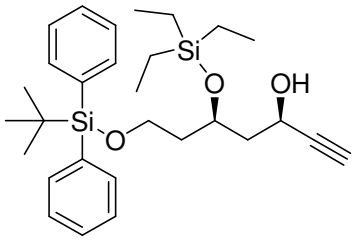
was quenched with H_2O. The aqueous layer was extracted 3x with Et_2O and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford a 59:41 mixture of **34** and **35**. The crude material was purified by flash chromatography (elution with 93:7 hexanes/EtOAc) to yield propargylic alcohols **34** (450 mg, 52%) and **35** (340 mg, 39%) as clear oils. For preparative scale synthesis, 18.7 g of crude aldehyde **33** (see above) was converted to alcohol **34**, which was purified by flash chromatography (10 g, 46% overall yield over 3 steps **32** → **34**).

34: TLC: R_f 0.11 (9:1 hexanes/EtOAc). $[\alpha]_D^{25} = -8.7°$ (*c* 0.5, $CHCl_3$). **IR** (NaCl, film): 2955, 2871, 1422, 1249, 1111, 1087, 1009, 841, 739, 703, 613, 505. **^{1}H-NMR** (400 MHz): δ 7.63 (m, 4H), 7.39 (m, 6H), 4.52 (m, 1H), 4.14 (m, 1H), 3.69 (m, 2H), 2.80 (d, 1H, *J* = 3.9), 1.89-1.70 (m, 4H), 1.04 (s, 9H), 0.95 (t, 9H, *J* = 7.9), 0.50 (q, 6H, *J* = 7.9), 0.16 (s, 9H). **^{13}C-NMR** (100 MHz): δ135.8, 135.0, 133.9, 129.9, 127.9, 106.9, 89.3, 69.2, 62.0, 60.6, 44.2, 40.9, 27.1, 19.3, 7.1, 5.3. **ESI-MS** *m/z*: (pos) 569.4 $[M+H]^+$, 591.3 $[M+Na]^+$; (neg) 567.3 $[M-H]^-$.

35: TLC: R_f 0.34 (9:1 hexanes/EtOAc). $[\alpha]_D^{25} = -6.4°$ (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 3436, 2955, 2872, 1467, 1420, 1384, 1249, 1096, 1008, 844, 738, 697, 615, 503. **^{1}H-NMR** (400 MHz): δ 7.64 (m, 4H), 7.40 (m, 6H), 4.59 (m, 1H), 4.37 (m, 1H), 3.68 (m, 2H), 3.41 (d, 1H, *J* = 5.5), 1.92-1.63 (m, 4H), 1.06 (s, 9H), 0.95 (t, 9H, *J* = 7.9), 0.61 (q, 6H, *J* = 8.0), 0.15 (s, 9H). **^{13}C-NMR** (100 MHz): δ136.3, 135.6, 133.6, 127.8, 127.5, 127.0, 106.7, 88.8. 60.4, 27.1, 26.8, 26.6, 19.1, 5.0. **ESI-MS** *m/z*: (pos) 569.2 $[M+H]^+$, 591.3 $[M+Na]^+$; (neg) 567.3 $[M-H]^-$, 603.3 $[M+Cl]^-$.



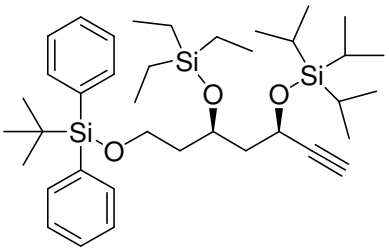
(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)-hept-1-yn-3-yl benzoate (E2). Benzoic acid (1.9 g, 0.015 mol, 1.2 equiv) then PPh_3 (4.0 g, 0.015 mol, 1.2 equiv) were added sequentially to a solution of alcohol **35** (7.3 g, 0.013 mol, 1.0 equiv) in benzene (32 mL). The mixture was stirred until a clear solution was obtained, then cooled to 0 °C. DEAD (2.4 mL, 0.015 mol, 1.2 equiv) was added dropwise. The mixture was stirred at 0 °C for 15 min then quenched with brine. The aqueous layer was extracted 3x with Et_2O then the combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography (elution with 95:5 hexanes/EtOAc) to yield benzoate **E2** (7.7 g, 90%) as a clear oil. **TLC**: R_f 0.30 (9:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): δ 8.06 (d, 2H, *J* = 8.1), 7.66 (m, 4H), 7.54 (m, 1H), 7.40 (m, 8H), 5.79 (t, 1H, *J* = 7.3), 4.22 (m, 1H), 3.73 (t, 2H, *J* = 6.1), 2.05 (m, 2H), 1.77 (m, 2H), 1.03 (m, 9H), 0.98 (m, 9H), 0.64 (m, 6H), 0.15 (s, 9H).



(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-hept-1-yn-3-ol (36). Method A: A cooled (0 °C) solution of **34** (10 g, 18 mmol) in MeOH (180 mL, Optima grade) was treated with H_2O (9.8 mL) and K_2CO_3 (5.0 g, 36 mmol). The mixture was stirred at 0 °C for 10.5 h then the MeOH was evaporated to afford a white solid. The solid was dissolved in Et_2O, washed 3x with H_2O, washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield propargylic alcohol **36** as a white solid (9.4 g, 91% based on NMR analysis of the crude product) that was carried on without further purification. The reaction was also carried out on analytical scale with

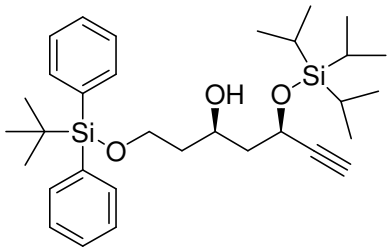
purification by flash chromatography to provide 110 mg of **36**.

Method B: H_2O (6 mL) was added to a solution of benzoate **E2** (7.7 g, 0.011 mol, 1.0 equiv) in MeOH (120 mL) then the solution was cooled to 0 °C. K_2CO_3 (4.7 g, 0.034 mol, 3.0 equiv) was added then the mixture was stirred at 0 °C for 7h. The majority of the solvent was removed by rotary evaporation then the mixture was diluted with ether. The organic layer was washed 2x with H_2O, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography (elution with 9:1 hexanes/EtOAc) to yield propargylic alcohol **36** (4.9 g, 86%) as a white solid. **TLC**: R_f: 0.24 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3307, 2950, 2881, 1461, 1427, 1104, 1006, 816, 735, 695, 505. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.40 (m, 6H), 4.52 (m, 1H), 4.20 (m, 1H), 3.70 (m, 2H), 2.81 (d, 1H, J = 4.0), 2.44 (d, 1H, J = 2.1), 1.91-1.68 (m, 4H), 1.03 (s, 9H), 0.92 (t, 9H, J = 7.9), 0.60 (q, 6H, J = 7.9). **^{13}C-NMR** (100 MHz): δ135.8, 135.0, 133.8, 129.9, 127.9, 85.0, 73.1, 69.0, 61.3, 60.6, 44.2, 40.8, 27.1, 19.4, 7.1, 5.3. **ESI-MS** *m/z*: (pos) 497.3 $[M+H]^+$, 519.3 $[M+Na]^+$; (neg) 495.3 $[M–H]^–$, 531.0 $[M+Cl]^–$.



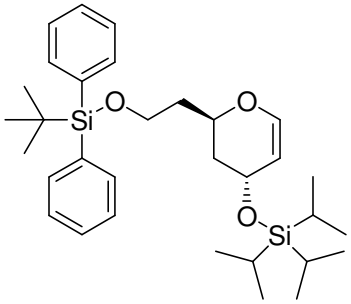
(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-3-(triisopropylsilyloxy)-hept-1-yne (E3). Triisopropylsilyl chloride (73 μL, 0.34 mmol, 1.5 equiv) was added dropwise to a solution of the propargylic alcohol **36** (110 mg, 0.23 mmol, 1.0 equiv) and imidazole (31 mg, 0.46 mmol, 2.0 equiv) in anhyd DMF (2.3 mL, sureseal bottle). After 22 h at rt the reaction mixture was quenched with sat'd aq $NaHCO_3$. The

aqueous layer was extracted 3x with Et_2O and the combined extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 98:2 hexanes/EtOAc) to yield alkyne **E3** a clear oil (130 mg, 84%). For preparative scale synthesis, 9.4 g of crude alcohol **36** was converted to 14 g of crude alkyne **E3** that was carried on without further purification (see below). **TLC**: R_f 0.59 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 3296, 2950, 2869, 1461, 1427, 1237, 1104, 1058, 1006, 885, 822, 735, 695. **^{1}H-NMR** (400 MHz): δ 7.67 (d, 4H, *J* = 6.9), 7.40 (m, 6H), 4.61 (m, 1H), 4.19 (m, 1H), 3.70 (m, 2H), 2.40 (d, 1H, *J* = 1.8), 1.91-1.69 (m, 4H), 1.13-1.02 (m, 30H), 0.92 (t, 9H, *J* = 7.9), 0.59 (q, 6H, *J* = 7.9). **^{13}C-NMR** (100 MHz): δ135.8, 134.1, 129.7, 127.8, 85.7, 73.2, 67.1, 61.3, 60.6, 46.5, 41.1, 27.0, 19.3, 18.2, 12.4, 7.2, 5.3. **ESI-MS** *m/z*: (pos) 653.6 $[M+H]^+$, 675.3 $[M+Na]^+$; (neg) 687.4 $[M+Cl]^-$.



(3*R*,5*R*)-1-(*tert*-Butyldiphenylsilyloxy)-5-(triisopropylsilyloxy)-hept-6-yn-3-ol (37a). Acetic acid (1.1 mL) was added to a solution of alkyne **E3** (120 mg, 0.19 mmol) in THF (0.4 mL, Optima grade) and water (0.4 mL). After 1.5 h at rt the mixture was quenched with sat'd aq $NaHCO_3$. The aqueous layer was extracted 3x with Et_2O and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (elution with 95:5 hexanes:EtOAc) to yield alcohol **37a** as a clear oil (80 mg, 79%). For preparative scale synthesis, 14 g of crude alkyne **E3** (see above) was converted to alcohol **37a**,

which was purified by flash chromatography (8.0 g, 81% overall yield over 3 steps; **34** → **37a**). **TLC**: R_f 0.35 (9:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +4.2° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 2934, 2862, 1462, 1426, 1105, 881, 820, 736, 699, 506. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.41 (m, 6H), 4.72 (m, 1H), 4.18 (m, 1H), 3.85 (m, 2H), 3.27 (d, 1H, *J* = 2.7), 2.45 (d, 1H, *J* = 2.0), 1.97 (m, 1H), 1.82 (m, 1H), 1.72 (m, 2H), 1.20-1.13 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.8, 133.5, 130.0, 128.0, 85.4, 73.2, 68.7, 62.6, 61.8, 46.1, 39.3, 27.0, 19.3, 18.2, 12.5. **ESI-MS** *m/z*: (pos) 561.4 $[M+Na]^+$; (neg) 537.3 $[M-H]^-$.

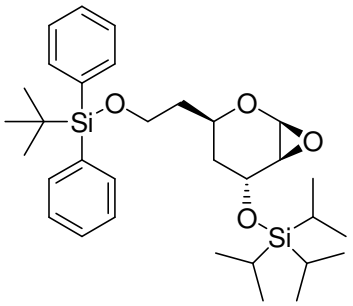


(2*R*,4*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (38a). A solution of the alkynol **37a** (120 mg, 0.22 mmol, 1.0 equiv) in anhyd THF (0.6 mL) was added to $W(CO)_6$ (19 mg, 0.054 mmol, 0.25 equiv) and the mixture was treated with distilled Et_3N (140 μL, 0.97 mmol, 4.5 equiv). The mixture was irradiated without cooling for 8 h. The solvent was evaporated to give a yellow mixture of oil and solid. The crude material was purified by flash chromatography (elution with 99:1 hexanes:EtOAc) to yield *erythro*-4-deoxyglycal **38a** as a clear oil (95 mg, 81%). For preparative scale synthesis, the reaction was carried out in three parallel batches of alkynol **37a** (160, 200, and 250 mg), which were then combined and purified to afford 480 mg of glycal **38a** (79%). **TLC**: R_f 0.33 (9:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +70° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 2941, 2864, 2360, 1636, 1241, 1111, 1088, 997, 882, 735, 701, 614, 504. **^{1}H-NMR** (400 MHz): δ 7.64

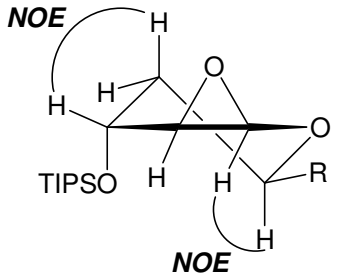
(d, 4H, J = 6.8), 7.39 (m, 6H), 6.39 (d, 1H, J = 6.1), 4.88 (t, 1H, J = 4.9), 4.28–4.17 (m, 2H), 3.81 (m, 2H), 1.81 (m, 3H), 1.60 (m, 1H), 1.03 (m, 30H). **^{13}C-NMR** (100 MHz): δ145.9, 135.8, 134.3, 134.1, 129.8, 127.8, 104.1, 68.4, 60.6, 60.3, 38.7, 38.5, 27.1, 19.4, 18.4, 12.6. **ESI-MS** *m/z*: (pos) 539.3 $[M+H]^+$, 561.4 $[M+Na]^+$; (neg) 573.5 $[M+Cl]^-$.

*Reactions of erythro-4-deoxyglycal **38a**:*

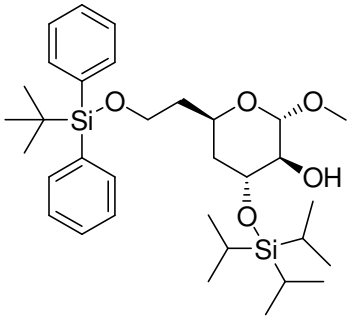
The following reactions were carried out with **(±)-38a**. Treatment of aldehyde **7** with allylmagnesium chloride provided **(±)-32**, which was converted to **(±)-38a** as described above. Yields of the following reactions are unoptimized.



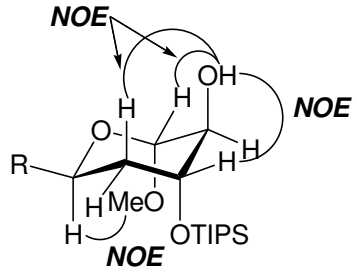
(2*R,4*R**,5*S**,6*S**)-2[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran-5,6-oxide (53).** A solution of dimethyldioxirane (0.030 M in acetone, 1.9 mL, 0.056 mmol, 1.5 equiv) was added dropwise to a cooled (–78 ºC) solution of glycal **38a** (20 mg, 0.037 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (1.9 mL). After 15 min the reaction was allowed to warm to rt and the solvent was removed with a stream of Ar. The crude glycal epoxide **53** was carried on without further purification, but was stable enough to characterize by NMR, which indicated a single diastereomer. The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.



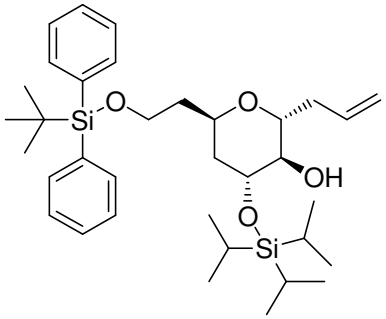
^{1}H-NMR (500 MHz, C_6D_6): δ 7.80 (m, 4H), 7.27 (m, 6H), 4.74 (d, 1H, *J* = 2.4), 4.41 (m, 2H), 3.98 (m, 1H), 3.78 (m, 1H), 2.95 (bs, 1H), 1.96 (m, 1H), 1.68-1.53 (m, 2H), 1.45 (d, 1H, *J* = 13.6), 1.16 (s, 9H), 1.02-0.95 (m, 21H). **^{13}C-NMR** (125 MHz, C_6D_6): δ136.0, 134.3, 134.2, 129.9, 77.8, 66.2, 64.9, 60.2, 54.6, 39.1, 36.7, 30.1, 27.1, 19.5, 18.2, 12.4.



(2*S,3*R**,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-methoxy-4-(triisopropylsilyloxy)-tetrahydropyran-3-ol (49).** Epoxide **53** formed from glycal **38a** (10 mg, 0.019 mmol, 1.0 equiv) was dissolved in anhyd MeOH (1.0 mL, Sureseal™ bottle). After 10 min at rt the solvent was evaporated to yield methylglycoside **49** as a clear oil (11 mg, 100%). NMR analysis indicated a single diastereomer. The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.

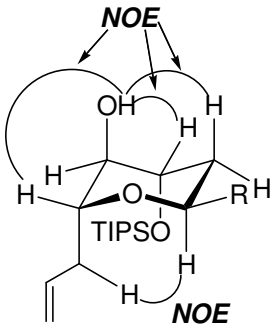


TLC: R_f: 0.61 (2:1 hexanes/EtOAc). **IR** (NaCl, film): 2943, 2864, 2345, 1462, 1428, 1101, 881, 700. **^{1}H-NMR** (400 MHz): δ 7.67 (m, 4H), 7.40 (m, 6H), 4.50 (d, 1H, *J* = 3.4), 4.39 (m, 1H), 4.00 (m, 1H), 3.82 (m, 1H), 3.71 (m, 1H), 3.50 (m, 1H),3.31 (s, 3H),2.00 (d, 1H, *J* = 5.7), 1.82-1.53 (m, 4H), 1.02 (m, 30H). **^{13}C-NMR** (125 MHz): δ135.5, 133.9, 129.5, 127.6, 101.5, 72.1, 69.0, 62.6, 60.2, 55.3, 3.7, 35.9, 26.8, 19.2, 18.0, 12.3. **ESI-MS** *m/z*: (pos) 609.3 $[M+Na]^+$; (neg) 585.3 $[M–H]^–$, 621.3 $[M+Cl]^–$.

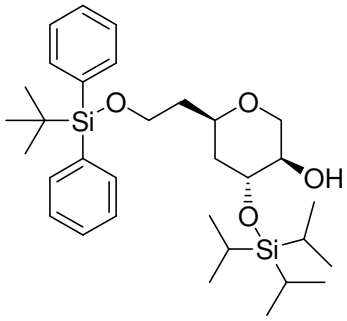


(2*R,3*R**,4*R**,6*R**)-2-Allyl-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-triisopropylsilyloxy)-tetrahydropyran-3-ol (55).** Epoxide **53** formed from glycal **38a** (10 mg, 0.019 mmol, 1.0 equiv) was dissolved in anhyd THF (0.2 mL) and cooled to –78 ºC. Allylmagnesium chloride (2.0 M in THF, 19 µL, 0.037 mmol, 2.0 equiv) was added and the reaction mixture was stirred at –78 ºC for 20 min then warmed to 0 ºC. After 45 min at 0 ºC the reaction was quenched with sat'd aq NH_4Cl. The aqueous layer was extracted 3x with Et_2O and the combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 9:1 hexanes/EtOAc) to yield **55** as

a clear oil (8.9 mg, 80%). NMR analysis of the crude product indicated a single diastereomer. The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.

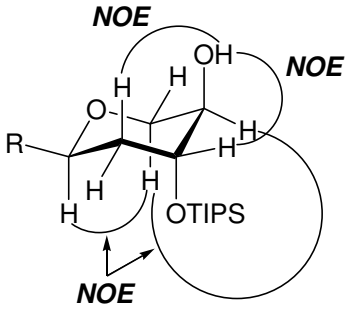


TLC: R_f 0.67 (2:1 hexanes/EtOAc). **IR** (NaCl, film): 3448, 2931, 2861, 2355, 1467, 1425, 1108, 873, 820, 738, 697, 509. **^{1}H-NMR** (400 MHz): δ 7.65 (t, 4H, *J* = 7.8), 7.40 (m, 6H), 5.79 (m, 1H), 5.10-4.93 (m, 2H), 4.22 (m, 1H), 3.92 (m, 1H), 3.78 (m, 1H), 3.65 (m, 1H), 3.41 (td, 1H, *J* = 7.8, 3.6), 3.23 (td, 1H, *J* = 7.4, 3.4), 2.51 (m, 1H), 2.40 (m, 1H), 2.29 (d, 1H, *J* = 3.4), 1.99 (m, 1H), 1.80 (m, 2H), 1.61 (m, 1H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ135.9, 135.6, 134.3, 130.0, 128.0, 117.0, 75.6, 73.8, 71.5, 66.2, 60.9, 37.2, 36.3, 35.2, 27.2, 19.6, 18.5, 15.7, 12.9. **ESI-MS** *m/z*: (pos) 619.4 $[M+Na]^+$; (neg) 595.4 $[M–H]^–$, 631.3 $[M+Cl]^–$.

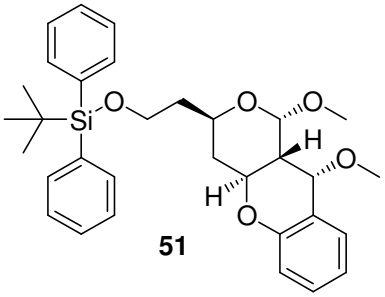


(3*R,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-tetrahydropyran-3-ol (50).** Thexylborane[34] (0.50 M in THF, 94 µL, 0.047 mmol, 2.0 equiv) was added dropwise to a cooled (0 ºC) solution of glycal **38a** (13 mg, 0.023

mmol, 1.0 equiv) in anhyd THF (0.3 mL). After 2 h at 0 ºC, aq NaOH (1.0 M, 0.15 mL, 0.15 mmol, 6.6 equiv) was added slowly, followed by H_2O_2 (30 wt % in H_2O, 18 µL, 0.15 mmol, 6.6 equiv). The reaction mixture was warmed to rt, stirred 1 h, then diluted with Et_2O. The aqueous layer was extracted 3x with Et_2O then the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 9:1 hexanes/EtOAc) to yield alcohol **50** as a clear oil (9.6 mg, 74%). NMR analysis of the crude product indicated an 11.7:1.0 diastereomeric ratio. The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.



TLC: R_f 0.38 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3401, 2943, 2861, 2355, 1467, 1096, 885, 738, 703, 679, 503. **^{1}H-NMR** (400 MHz): δ 7.68 (m, 4H), 7.40 (m, 6H), 4.00 (m, 3H), 3.81 (m, 1H), 3.70 (m, 2H), 3.48 (m, 1H), 2.20 (d, 1H, J = 8.8), 1.75 (m, 1H), 1.62 (m, 3H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ135.6, 129.5, 127.6, 68.8, 67.99, 67.6, 59.9, 39.0, 35.4, 26.8, 18.1, 12.2. **ESI-MS** *m/z*: (pos) 579.2 $[M+Na]^+$; (neg) 555.3 $[M–H]^–$, 591.5 $[M+Cl]^–$.



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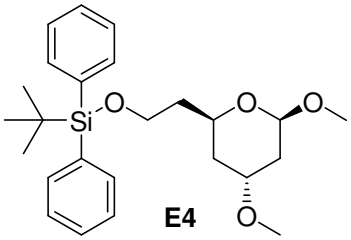
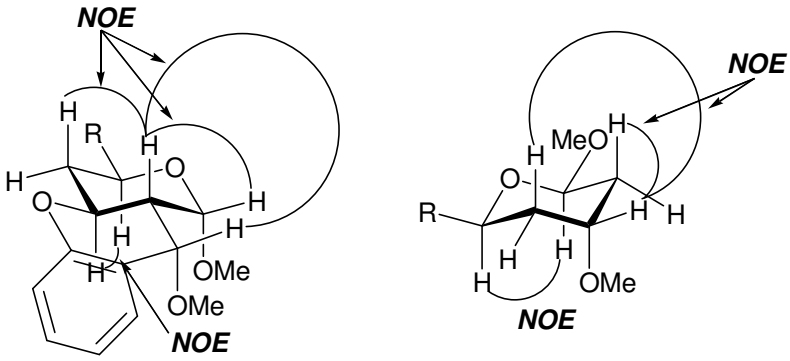


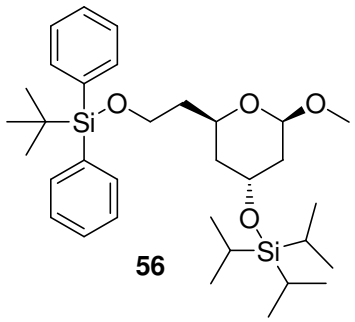
E4

(1*S,3*R**,5*S**,6*S**,10*S**)-1,10-Dimethoxy-3-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4,4a,10,10a-tetrahydro-1*H*,3*H*-pyrano[4,3-*b*]chromene (51)** and **(2*R**,4*R**,6*R**)-2,4-Dimethoxy-6-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-tetrahydropyran (E4).** A mixture of salicylaldehyde (23 µL, 0.22 mmol, 1.2 equiv), TMOF (24 µL, 0.22 mmol, 1.2 equiv), and $Sc(OTf)_3$ (2.7 mg, 5.6 µmol, 0.030 equiv) in anhyd CH_2Cl_2 (1.7 mL) was stirred at rt for 20 min. The reaction mixture was cooled to 0 ºC then treated with a solution of glycal **38a** (100 mg, 0.19 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (1.0 mL). The reaction mixture was warmed to rt, stirred for 30 min, then quenched with H_2O. The aqueous layer was extracted 3x with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated. NMR analysis of the crude product indicated a 1.0:3.5:1.3 ratio of **51**, **E4**, and Ferrier rearrangement product **57**. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc) to yield a 2.5:1.0 mixture of **51** and **E4** (4.7 mg, 3.6% yield of **51**) as a clear oil. The stereochemical configurations were assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.



TLC: R_f: 0.11 (9:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): **51**: δ 7.72-7.61 (m, 4H), 7.51 (d, 1H, *J* = 7.6), 7.40 (m, 6H), 7.18 (t, 1H, *J* = 7.6), 6.96 (t, 1H, *J* = 7.3), 6.78 (d, 1H, *J* = 7.3), 5.59 (d, 1H, *J* = 3.2), 4.71 (d, 1H, *J* = 4.7), 4.27 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.59 (s, 3H), 3.30 (m, 1H), 3.21 (s, 3H), 2.50 (m, 1H), 2.08 (ddd, 1H, *J* = 14.2. 5.0, 2.1), 1.82-1.70 (m, 2H), 1.25 (m, 1H), 1.07 (s, 9H). **E4**: 7.65 (m, 4H), 7.38

(m, 6H), 4.56 (dd, 1H, J = 9.8, 2.1), 3.99 (m, 1H), 3.89-3.70 (m, 2H), 3.69 (m, 1H), 3.40 (s, 3H), 3.31 (s, 3H), 2.01 (m, 1H), 1.84-1.68 (m, 3H), 1.44 (m, 1H), 1.34 (m, 1H), 1.04 (s, 9H). **ESI-MS** *m/z*: **51**: (pos) 555.2 $[M+Na]^+$; (neg) 531.2 $[M–H]^–$, 567.3 $[M+Cl]^–$. **E4**: 451.1 $[M+Na]^+$.



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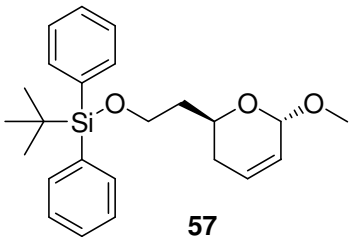
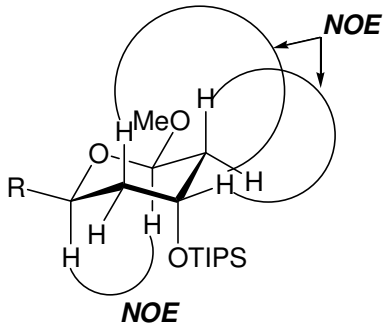
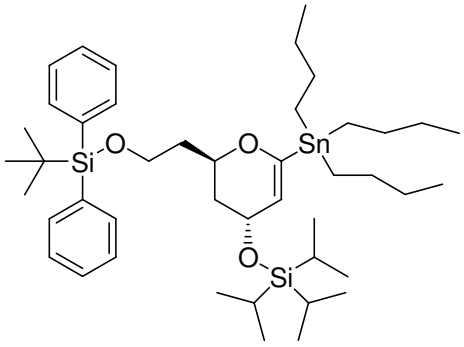


57

(2*R,4*R**,6*R**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-methoxy-4-(triisopropylsilyloxy)-tetrahydropyran (56)** and **(2*R**,6*S**)-6-Methoxy-2-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-3,6-dihydro-2*H*-pyran (57).** Anhyd methanol (2.3 µL, 0.057 mmol, 3.0 equiv, sureseal bottle) then Ph_3P•HBr (0.30 mg, 0.95 µmol, 0.050 equiv) was added to a solution of **38a** (10 mg, 0.019 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (0.2 mL). After 20 min at rt the reaction mixture was diluted with CH_2Cl_2, washed 2x with sat'd aq $NaHCO_3$, once with brine, dried ($MgSO_4$), filtered, and concentrated. NMR analysis of the crude product indicated a 3.0:1.0:3.3 ratio of **56**, its α-anomer, and **57**. Purification by flash chromatography (elution with 95:5 hexanes/EtOAc) yielded a 1.0:1.1 mixture of **56** and **57 (**4.5 mg, 24% yield of **56**, 27% yield of **57**) as a clear oil. The stereochemical configurations were assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs for **56** are shown below. The stereochemical configuration of **57** was tentatively assigned based on the absence of an NOE between the anomeric *C*1-H and *C*5-H.

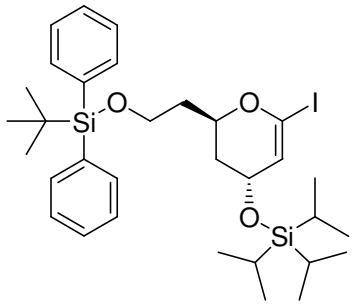


TLC: R_f 0.31 (9:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): **56**: δ 7.66 (m, 4H), 7.40 (m, 6H), 4.71 (dd, 1H, *J* = 1.9, 9.6), 4.38 (m, 1H), 4.22 (m, 1H), 3.93-3.69 (m, 2H), 3.42 (s, 3H), 1.90 (m, 1H), 1.76 (m, 2H), 1.63 (m, 1H), 1.54-1.39 (m, 2H). **57**: 7.65 (m, 4H), 7.38 (m, 6H), 6.00 (m, 1H), 5.72 (m, 1H), 4.80 (s, 1H), 4.11 (m, 1H), 3.92-3.72 (m, 2H), 3.32 (s, 3H), 1.96 (m, 2H), 1.78 (m, 2H), 1.02 (s, 9H). **ESI-MS** *m/z*: **56**: (pos) 593.4 $[M+Na]^+$; (neg) 605.2 $[M+Cl]^-$. **57**: (pos) 419.1 $[M+Na]^+$.



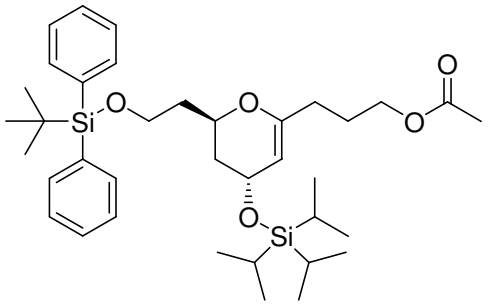
(2*R,4*R**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(tributylstannanyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E5).** *t*-BuLi (1.5 M in pentane, 2.1 mL, 3.2 mmol, 4.0 equiv) was added slowly to a cooled (–78 ºC) solution of glycal **38a** (430 mg, 0.80 mmol, 1.0 equiv) in anhyd THF (4.0 mL). After 15 min at –78 ºC, the reaction was warmed to 0 ºC, maintained at that temperature 1 h, then cooled to –78 ºC. Tributyltin chloride (540 µL, 2.0 mmol, 2.5 equiv) was added, the reaction was stirred at –78 ºC 30 min, then quenched with sat'd aq $NaHCO_3$. The aqueous layer was extracted 3x with Et_2O then the combined organic layers were washed with H_2O

and brine, dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (elution with 7:1 hexanes/CH_2Cl_2+ 0.5% Et_3N) to yield glycal stannane **E5** as a clear oil (490 mg, 74 %). **TLC**: R_f 0.67 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2959, 2923, 2864, 1590, 1460, 1087, 1063, 998, 879, 737, 695, 506. **^{1}H-NMR** (400 MHz): δ 7.63 (dt, 4H, *J* = 1.8, 7.7), 7.39 (m, 6H), 4.90 (d, 1H, *J* = 4.2), 4.09 (m, 2H), 3.81 (m, 2H), 1.82-1.71 (m, 3H), 1.60-1.40 (m, 7H), 1.23 (m, 6H), 1.02 (m, 30H), 0.82 (m, 15H). **^{13}C-NMR** (125 MHz): δ135.6, 134.1, 129.5, 127.6, 114.9, 68.2, 60.7, 60.6, 38.7, 38.6, 29.0, 27.2, 26.9, 19.2, 18.2, 13.7, 12.5, 9.6. **ESI-MS** *m/z*: (pos) 851.3 $[M+Na]^+$; (neg) 863.4 $[M+Cl]^-$.



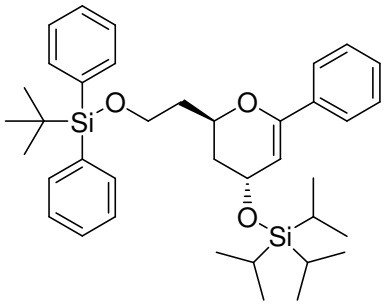
(2*R,4*R**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-iodo-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E6).** A solution of iodine (0.20 M in CH_2Cl_2, 620 µL, 0.12 mmol, 1.0 equiv) was added dropwise to a solution of glycal stannane **E5** (100 mg, 0.12 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (2.4 mL) in the dark. As soon as a purple color persisted in the reaction mixture, the reaction was quenched with 10% aq $Na_2S_2O_3$. The aqueous layer was extracted 3x with CH_2Cl_2, then the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (elution with 4:1 hexanes/CH_2Cl_2 + 0.5% Et_3N) to yield glycal iodide **E6** as a clear oil (80 mg, 98%). **TLC**: R_f 0.70 (4:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz, C_6D_6): δ 7.77 (m, 4H), 7.40-7.22 (m, 6H), 5.58

(d, 1H, J = 4.0), 4.75 (m, 1H), 3.91 (m, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 1.79-1.52 (m, 3H), 1.40 (m, 1H), 1.14 (s, 9H), 1.08-0.92 (m, 21H).

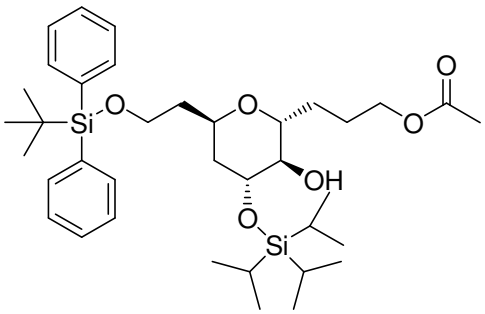


(2*R,4*R**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3-acetoxypropyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (54a).** 9-BBN (0.50 M in THF, 1.4 mL, 0.72 mmol, 3.0 equiv) was added dropwise to a cooled (0 ºC) solution of allyl acetate (39 µL, 0.36 mmol, 1.5 equiv) in anhyd THF (3.6 mL). The mixture was stirred at 0 ºC for 5 min then warmed to rt. After 4 h, aq NaOH (1.0 N, 730 µL, 0.72 mmol, 3.0 equiv) was added and the mixture was stirred an additional 30 min. The hydroboration reaction was then added to a mixture of glycal iodide **E6** (160 mg, 0.24 mmol, 1.0 equiv), $PdCl_2$(dppf) (20 mg, 0.024 mmol, 0.10 equiv), and H_2O (0.7 mL) in THF (2.4 mL, Optima grade). After 20 min at rt the reaction mixture was diluted with pentane and the solid was filtered off. The filtrate was washed with 1 N NaOH, H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (elution with 95:5 hexanes/EtOAc) to yield 1-alkylglycal **54a** as a clear oil (110 mg, 68%). **TLC**: R_f 0.32 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2935, 2864, 1739, 1661, 1460, 1241, 1093, 695, 506. **^{1}H-NMR** (500 MHz): δ 7.68 (d, 4H, J = 7.3), 7.40 (m, 6H), 4.69 (d, 1H, J = 5.0), 4.29-4.19 (m, 2H), 4.02 (t, 2H, J = 6.6), 3.90-3.70 (m, 2H), 2.05 (t, 2H, J = 7.3), 2.02 (s, 3H), 1.82-1.71 (m, 5H), 1.51 (m, 1H), 1.03 (m, 30H). **^{13}C NMR** (125 MHz): δ155.3, 135.6, 133.9, 129.5, 127.6, 99.5,

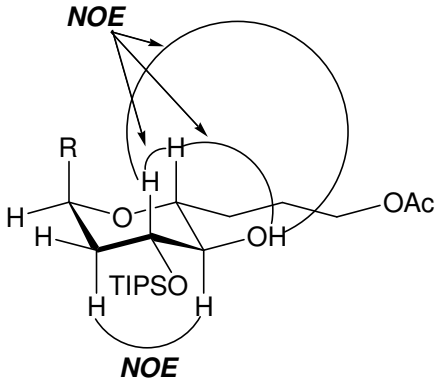
68.4, 63.9, 61.2, 60.1, 38.2, 38.1, 30.6, 26.8, 25.9, 21.0, 19.2, 18.2, 12.4. **ESI-MS** *m/z*: (pos) 661.3 $[M+Na]^+$.



(2*R,4*R**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-phenyl-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (54b).** A mixture of glycal stannane **E5** (80 mg, 0.097 mmol, 1.0 equiv), bromobenzene (15 µL, 0.15 mmol, 1.5 equiv), and $Pd(PPh_3)_4$ (5.6 mg, 4.9 µmol, 0.050 equiv) in anhyd THF (1.9 mL) was refluxed 7 h. The solvent was evaporated and the residue was purified by flash chromatography (elution with 98:2 hexanes/EtOAc) to yield 1-phenylglycal **54b** as a clear oil (58 mg, 96%). **TLC**: R_f 0.54 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2935, 2864, 1644, 1466, 1424, 1282, 1093, 1004, 873, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.69 (m, 4H), 7.51 (m, 2H), 7.42-7.27 (m, 9H), 5.49 (d, 1H, *J* = 4.8), 4.45 (m, 2H), 4.02 (m, 1H), 3.90 (m, 1H), 2.00-1.86 (m, 3H), 1.69 (m, 1H), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ135.6, 129.5, 128.3, 128.1, 127.6, 125.1, 99.7, 68.7, 61.6, 60.2, 38.4, 38.2, 26.8, 19.2, 18.2, 12.4. **ESI-MS** *m/z*: (pos) 615.5 $[M+H]^+$, 637.2 $[M+Na]^+$; (neg) 649.2 $[M+Cl]^-$.

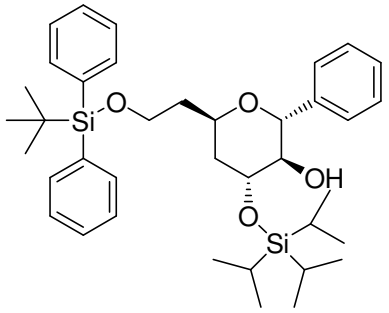


(2*R,3*R**,4*R**,6*R**)-2-(3-Acetoxypropyl)-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)tetrahydropyran-3-ol (52a).** Thexylborane[34] (0.50 M in THF, 65 µL, 0.033 mmol, 2.0 equiv) was added dropwise to a cooled (0 ºC) solution of 1-alkylglycal **54a** (10 mg, 0.016 mmol, 1.0 equiv) in anhyd THF (0.2 mL). The reaction mixture was stirred for 1.5 h at 0 ºC then warmed to rt. After 1.5 h at rt, aq NaOH (1.0 M, 0.11 mL, 0.11 mmol, 6.6 equiv) was added slowly, followed by H_2O_2 (30 wt % in H_2O, 12 µL, 0.11 mmol, 6.6 equiv). The reaction mixture was stirred for 1 h then diluted with Et_2O. The organic layer was washed with sat'd aq NH_4Cl, H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 4:1 hexanes/EtOAc) to yield alcohol **52a** as a clear oil (8.1 mg, 76%). NMR analysis of the crude product indicated a single diastereomer. The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.

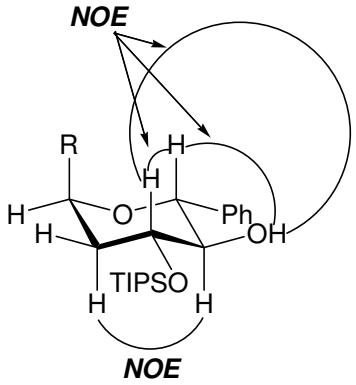


TLC: R_f 0.40 (9:1 CH_2Cl_2/Et_2O). **IR** (NaCl, film): 3460, 2943, 2861, 1731, 1425, 1361, 1243, 1108, 703. **^{1}H-NMR** (400 MHz): δ 7.64 (m, 4H), 7.39 (m, 6H), 4.22 (m, 1H), 4.01 (m, 2H), 3.90 (m, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 3.32 (m, 1H), 3.19 (td, 1H, *J* = 3.3, 7.3), 2.29 (d, 1H, *J* = 3.3), 2.01 (s, 3H), 1.95 (m, 1H), 1.81-1.48 (m, 7H), 1.03 (m, 30H). **^{13}C NMR** (125 MHz): δ135.5, 129.6, 127.6, 73.2, 71.1, 64.6, 41.0,

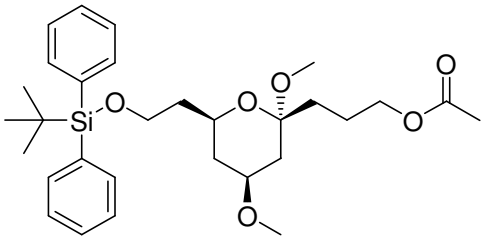
36.8, 34.8, 26.8, 24.9, 18.1, 12.4. **ESI-MS** *m/z*: (pos) 679.5 $[M+Na]^+$; (neg) 655.4 $[M+H]^-$, 691.3 $[M+Cl]^-$.



(2*R,3*R**,4*R**,6*R**)-2-Phenyl-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)tetrahydropyran-3-ol (52b).** Thexylborane[34] (0.50 M in THF, 140 µL, 68 µmol, 10 equiv) was added dropwise to a cooled (0 ºC) solution of 1-phenylglycal **54b** (4.2 mg, 6.8 µmol, 1.0 equiv) in anhyd THF (0.2 mL). The reaction mixture was stirred for 1 h at 0 ºC then warmed to rt and stirred for 20 h. At this time, the reaction was approximately 50% complete (TLC). Additional freshly prepared thexylborane (0.50 M in THF, 140 µL, 68 µmol, 10 equiv) was added and the reaction mixture was stirred an additional 4 h at rt. Aq NaOH (1.0 N, 0.45 mL, 0.45 mmol, 66 equiv) was added slowly, followed by H_2O_2 (30 wt % in H_2O, 51 µL, 0.45 mmol, 66 equiv). The reaction mixture was stirred 2 h then diluted with Et_2O. The organic layer was washed with sat aq NH_4Cl, brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 9:1 hexanes/EtOAc) to yield alcohol **52b** as a clear oil (3.1 mg, 72%). NMR analysis of the crude product indicated a single diastereomer. The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.

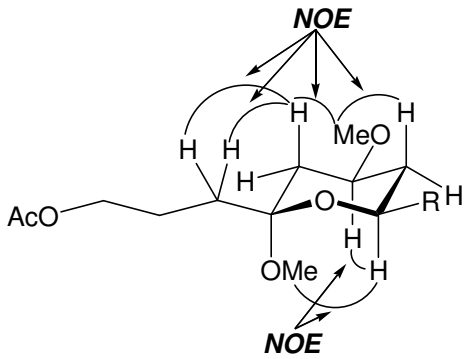


TLC: R_f 0.21 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2931, 2861, 1462, 1428, 1111, 882, 738, 700. **^{1}H-NMR** (400 MHz): δ 7.62 (m, 4H), 7.40-7.21 (m, 11H), 4.40 (m, 1H), 4.22 (d, 1H, J = 9.2), 4.05 (m, 1H), 3.80 (m, 1H), 3.69 (m, 1H), 3.49 (m, 1H), 2.18 (m, 2H), 1.98 (m, 2H), 1.75 (m, 1H), 1.02 (m, 30H). **^{13}C-NMR** (125 MHz): δ139.5, 135.5, 129.6, 129.5, 128.3, 128.0, 127.6, 127.5, 77.7, 75.3, 71.2, 70.0, 60.7, 37.3, 33.8, 26.8, 19.2, 18.1, 18.0, 12.5, 12.3. **ESI-MS** *m/z*: (pos) 655.4 $[M+Na]^+$; (neg) 631.4 $[M–H]^–$, 667.4 $[M+Cl]^–$.

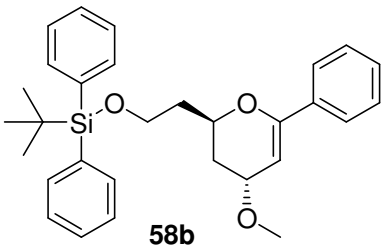


(2*R,3*R**,4*R**,6*R**)-2-(3-Acetoxypropyl)-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-2,4-dimethoxytetrahydropyran (59a).** Anhyd MeOH (2.3 µL, 0.058 mmol, 3.0 equiv, sureseal bottle) then Ph_3P•HBr (0.30 mg, 0.96 µmol, 0.050 equiv) were added to a solution of 1-alkylglycal **54a** (12 mg, 0.019 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (0.2 mL). The reaction was stirred at rt for 1 h then diluted with CH_2Cl_2, washed with sat'd aq $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 4:1 hexanes/EtOAc) to yield methyl

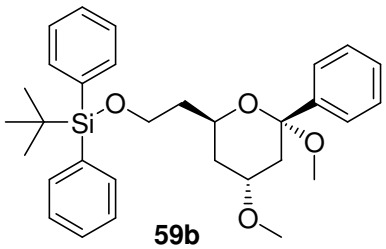
glycoside **59a** as a clear oil (5.1 mg, 50%). The stereochemical configuration was assigned by multidimensional NMR analysis (COSY, NOESY). Diagnostic NOEs are shown below.



TLC: R_f 0.14 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2935, 2864, 1739, 1466, 1424, 1359, 1235, 1093, 701, 506. **^{1}H-NMR** (500 MHz): δ 7.65 (m, 4H), 7.42 (m, 6H), 4.06 (t, 2H, *J* = 6.4), 3.87-3.79 (m, 2H), 3.75 (m, 1H), 3.60 (m, 1H), 3.32 (s, 3H), 3.08 (s, 3H), 2.15 (dd, 1H, *J* = 3.5, 12.1), 2.04 (s, 3H), 1.98 (dt, 1H, *J* = 12.3, 2.1), 1.77-1.53 (m, 6H), 1.17 (t, 1H, *J* = 12.1), 1.05 (s, 10H). **^{13}C NMR** (125 MHz): δ135.5, 129.6, 127.6, 100.7, 73.5, 65.6, 64.4, 60.2, 55.5, 47.2, 38.8, 37.2, 32.5, 26.9, 22.9, 21.0. **ESI-MS** *m/z*: (pos) 551.2 $[M+Na]^+$; (neg) 563.3 $[M+Cl]^-$.



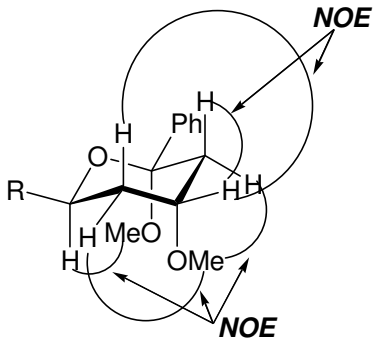
58b



59b

(2*R,4*R**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-methoxy-6-phenyl-3,4-dihydro-2*H*-pyran (58b)** and **(2*R**,3*R**,4*R**,6*R**)-2-Phenyl-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-2,4-dimethoxytetrahydropyran (59b).** Anhyd MeOH (3.4 µL, 0.084 mmol, 3.0 equiv, Sureseal™ bottle) then Ph_3P•HBr (0.50 mg, 1.4 µmol,

0.050 equiv) were added to a solution of 1-phenylglycal **54b** (15 mg, 0.028 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (0.3 mL). The reaction was stirred at rt for 1 h then diluted with CH_2Cl_2, washed 2x with sat aq $NaHCO_3$, once with brine, dried ($MgSO_4$), filtered, and concentrated to afford a 3.4:1 mixture of **58b** and **59b**. The residue was purified by flash chromatography (elution with 98:2 hexanes/EtOAc then 9:1 hexanes/EtOAc) to yield methyl ether **58b** (2.8 mg, 24%) and methyl glycoside **59b** (1.0 mg, 8.1%) as clear oils. The stereochemical configuration of **58b** was tentatively assigned based on comparison of chemical shifts with other *C*1-substituted glycals. The stereochemical configuration of **59b** was assigned by multidimensional NMR analysis (COSY, NOESY). Formation of the axially oriented *C*3-OMe (in contrast to the equatorial orientation in **59a**) may result from stereoelectronic effects of the *C*1-phenyl substituent. Diagnostic NOEs are shown below.



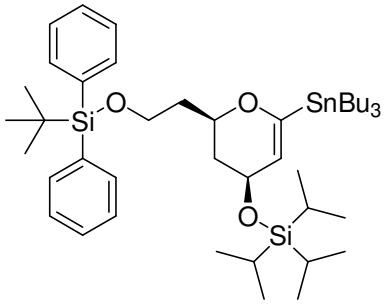
58b: TLC: R_f 0.18 (9:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): δ 7.68 (m, 4H), 7.52 (m, 2H), 7.41-7.22 (m, 9H), 5.59 (dd, 1H, *J* = 1.2, 5.2), 4.28 (m, 1H), 3.94 (m, 2H), 3.82 (m, 1H), 3.40 (s, 3H), 2.04-1.89 (m, 3H), 1.61 (m, 1H), 1.02 (s, 9H). **ESI-MS** *m/z*: (pos) 495.3 $[M+Na]^+$; (neg) 507.2 $[M+Cl^-]$.

59b: TLC: R_f 0.17 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 2926, 2863, 1427, 1109, 1087, 742, 700. **^{1}H-NMR** (500 MHz): δ 7.68 (m, 4H), 7.46-7.26 (m, 11H), 4.30 (m, 1H), 3.90 (m, 2H), 3.57 (m, 1H), 3.38 (s, 3H), 2.92.(s, 3H), 2.28 (dt, 1H, *J* = 2.1,

14.9), 1.93-1.74 (m, 3H), 1.58 (obs, 1H), 1.45 (m, 1H), 1.05 (s, 9H). **ESI-MS** *m/z*: (pos) 527.2 $[M+Na]^+$.

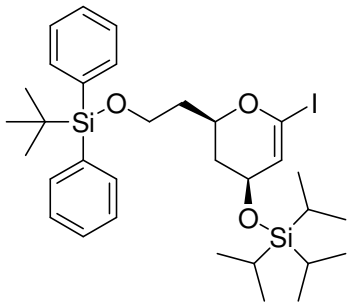
Synthesis of C1-substituted glycals:

Compounds **E9a–g** and **67a–g** were synthesized and characterized by Justin Potuzak.



(–)-(2*R*,4*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(tributylstannyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (65). To a 50 mL roundbottom flask was added *threo*-glycal **12** (2.3 g, 4.2 mmol, 1.0 equiv) and anhyd THF (21 mL). The mixture was cooled to –78 °C, and *t*-BuLi (1.5 M in pentane, 11 mL, 17 mmol, 4.0 equiv) was added slowly via syringe. The reaction was stirred at –78 °C for 15 min, then warmed to 0 °C, stirred for 1 h, then recooled to –78 °C. Tributyltin chloride (2.8 mL, 10 mmol, 2.5 equiv) was added slowly via syringe, and the reaction was stirred for 30 min, warmed to rt, quenched with sat'd aq $NaHCO_3$, and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O and brine, then dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Silica flash chromatography (elution with 7:1 hexanes/CH_2Cl_2 + 0.5% Et_3N) afforded stannane **65** as a clear oil (2.7 g, 77%). **TLC**: R_f 0.26 (4:1 hexanes/CH_2Cl_2). $[\alpha]_D^{25}$: –9.0° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2951, 2926, 2862, 1598, 1463, 1103, 1067, 1008, 882, 737, 700. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.43–7.34 (m, 6H), 4.75 (m, 1H), 4.47 (m, 1H), 4.05 (m, 1H), 3.78 (m, 2H), 2.00 (m, 1H), 1.89 (m, 1H), 1.71 (m, 2H), 1.47 (m,

6H), 1.28 (m, 6H), 1.05 (m, 30H), 0.86 (m, 15 H). **^{13}C-NMR** (125 MHz): δ 162.9, 135.5, 134.0, 129.5, 127.6, 117.2, 71.7, 64.0, 60.6, 38.4, 38.3, 28.9, 27.2, 26.9, 19.2, 18.1, 13.7, 12.3, 9.6. **ESI-MS** *m/z* (rel int): (pos) 851.5 ($[M+Na]^+$, 100); (neg) 863.7 ($[M+Cl]^-$, 100).

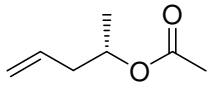


(2*R*,4*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-iodo-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (66). To a 100 mL roundbottom flask was added *threo*-glycal stannane **65** (2.5 g, 3.0 mmol, 1.0 equiv) and CH_2Cl_2 (30 mL). In a separate 100 mL flask, iodine (1.5 g, 6.0 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (60 mL). The iodine solution was then added via syringe to the glycal until a purple color persisted. The reaction was immediately quenched with the addition of 10 mL 10% aq $Na_2S_2O_3$ with vigorous stirring. The mixture was then poured into 20 mL 10% aq $Na_2S_2O_3$, and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Silica flash chromatography (elution with 4:1 hexanes/CH_2Cl_2 + 0.5% Et_3N) afforded iodide **66** as a clear oil (2.0 g, 100%), which was used immediately in subsequent cross coupling reactions. **TLC**: R_f 0.19 (4:1 hexanes/CH_2Cl_2). **IR** (NaCl, film): 2942, 2863, 1622, 1465, 1427, 1321, 1106, 1038, 882, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.36 (m, 6H), 5.32 (d, 1H, J = 1.9), 4.49 (m, 2H), 3.82 (m, 1H), 3.72 (m, 1H), 2.19 (m, 1H), 2.00 (m, 1H), 1.86–1.76 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.5, 133.7, 129.6, 127.7, 116.8, 107.1, 76.5, 65.3, 59.8, 37.3, 37.1, 26.9, 19.2,

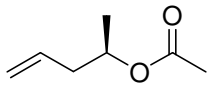
18.0, 12.2. **ESI-MS** *m/z* (rel int): (pos) 687.3 ($[M+Na]^+$, 100); (neg) 699.4 ($[M+Cl]^-$, 100).

Synthesis of sidechain precursors:

Allyl acetate was obtained commercially. But-3-enyl acetate and pent-4-enyl acetate were prepared as previously described.[35] (*R*)- and (*S*)-But-3-en-2-yl acetate, (*R*)- and (*S*)-1-chlorobut-3-en-2-yl acetate, and (*R*)- and (*S*)-1-chloropent-4-en-2-yl acetate were prepared by Justin Potuzak as previously described. [36,37]



(–)-(*S*)-Pent-4-en-2-yl acetate (E7). To a 10 mL roundbottom flask was added (*S*)-pent-4-en-2-ol (1.0 g, 12 mmol, 1.0 equiv), acetic anhydride (2.2 mL, 23 mmol, 2.0 equiv), and pyridine (25 μL). The reaction was heated to 100 ºC, and stirred for 16 h. The solution was cooled to rt, then quenched with H_2O, and extracted with pentane. The combined organic extracts were washed with sat'd aq $NaHCO_3$, 1 M aq $CuSO_4$, and brine, then dried ($MgSO_4$) and filtered. Evaporation of the solvent provided **E7** (650 mg, 44%) as a clear liquid. $[\alpha]_D^{25}$ –23° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3080, 2980, 1737, 1643, 1435, 1373, 1244, 1126, 1062, 1024, 995, 959, 919. **^{1}H-NMR** (500 MHz): δ 5.75 (m, 1H), 5.08 (m, 2H), 4.96 (m, 1H), 2.36–2.25 (m, 2H), 2.03 (s, 3H), 1.22 (d, 3H, *J* = 6.3). **^{13}C-NMR** (125 MHz): δ 170.6, 117.7, 70.0, 54.9, 40.3, 21.3, 19.5.

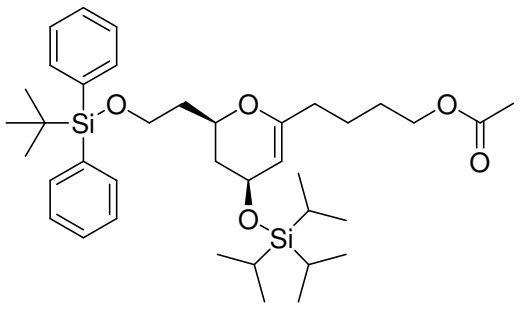


(+)-(*R*)-Pent-4-en-2-yl acetate (E8). Prepared from (*R*)-pent-4-en-2-ol as above. Clear liquid (660 mg, 44%). $[\alpha]_D^{25}$ +26° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3080, 2980,

1737, 1643, 1435, 1373, 1244, 1126, 1062, 1024, 995, 959, 919. **^{1}H-NMR** (500 MHz): δ 5.75 (m, 1H), 5.08 (m, 2H), 4.96 (m, 1H), 2.36–2.25 (m, 2H), 2.03 (s, 3H), 1.22 (d, 3H, J = 6.3). **^{13}C-NMR** (125 MHz): δ 170.6, 117.7, 70.0, 54.9, 40.3, 21.3, 19.5.

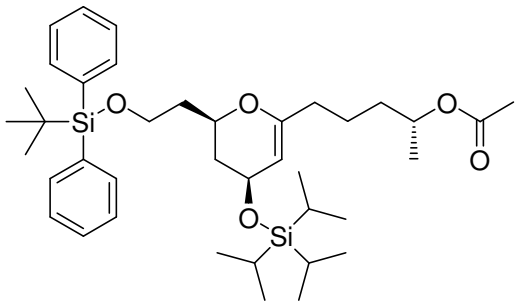
General procedure for sidechain coupling:

The appropriate sidechain precursor (1.5 equiv) was dissolved in anhyd THF (0.1 M). A freshly prepared solution of 9-BBN (0.50 M in THF, 3.0 equiv) was added dropwise at rt. After 3 h, aq NaOH (1.0 N, 3.0 equiv) was added, and the reaction was stirred for an additional 30 min at rt. In a separate flask, the *C*1-iodoglycal (*threo*-**66** or *erythro*-**E5**, 1.0 equiv) was dissolved in THF and water (3:1, 0.10 M). Solid $Pd(dppf)Cl_2$ (0.20 equiv) was then added. The hydroboration reaction mixture was then added to the mixture via syringe. The reaction was stirred for 1 h at rt, then diluted with pentane, filtered through Celite/silica (1:1), washed with 1 N aq NaOH, H_2O, and brine, then dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Silica flash chromatography yielded the *C*1-alkylated glycals **E9a–r**.

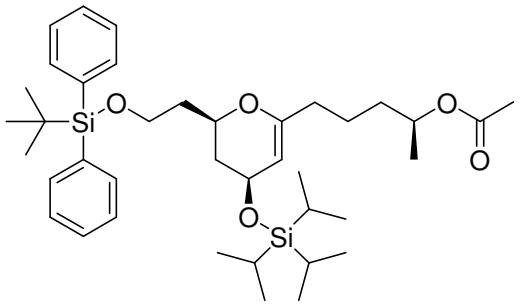


(–)-(2*R*,4*S*)-6-(4-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9a). Clear oil (130 mg, 85%). **TLC**: R_f 0.59 (4:1 hexanes/EtOAc). **[α]$_D^{25}$**: –7.5° (c 1.0, $CDCl_3$). **IR** (NaCl, film): 2943, 2863, 1741, 1668, 1465, 1428, 1385, 1364, 1239, 1087, 1010, 884, 820, 738,

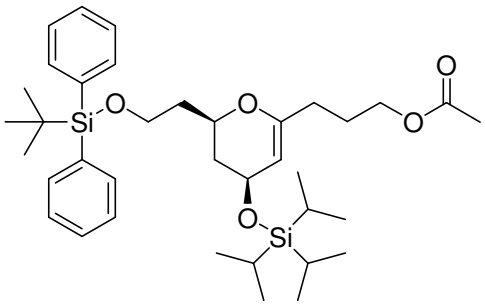
702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.50 (m, 2H), 4.16 (m, 1H), 4.03 (t, 2H, *J* = 6.6), 3.86–3.73 (m, 2H), 2.07–1.92 (m, 7H), 1.81 (m, 1H), 1.68–1.58 (m, 3H), 1.49 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 171.2, 154.5, 135.5, 133.9, 129.6, 127.6, 101.2, 71.4, 64.4, 63.9, 60.2, 37.8 (br, 2C), 33.5, 28.1, 26.8, 23.2, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 675.5 ([M+Na]$^+$, 100); (neg) 687.5 ([M+Cl]$^-$, 100).



(–)-(2*R*,4*S*,4′*R*)-6-(4′-Acetoxypentyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9b). Clear oil (170 mg, 86%). **TLC**: R_f 0.63 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –5.9° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2940, 2863, 1736, 1668, 1464, 1428, 1371, 1244, 1087, 1014, 959, 884, 821, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.87 (m, 1H), 4.50 (m, 2H), 4.15 (m, 1H), 3.85–3.73 (m, 2H), 2.05–1.92 (m, 7H), 1.79 (m, 1H), 1.64 (m 1H), 1.60–1.40 (m, 4H), 1.17 (d, 3H, *J* = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 170.7, 154.6, 135.5, 133.9, 129.6, 127.6, 101.1, 71.4, 70.8, 63.9, 60.3, 37.7 (br, 2C), 35.3, 33.7, 26.8, 22.6, 21.4, 19.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 689.5 ([M+Na]$^+$, 100); (neg) 701.4 ([M+Cl]$^-$, 100).

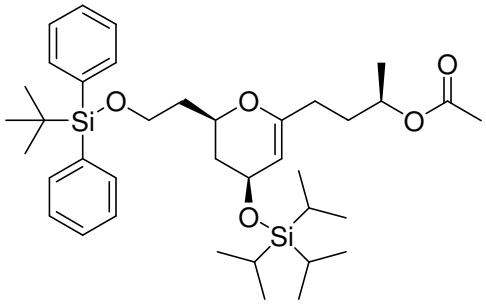


(–)-(2*R*,4*S*,4′*S*)-6-(4′-Acetoxypentyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9c). Clear oil (180 mg, 90%). **TLC**: R_f 0.63 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –8.5° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2941, 2863, 1736, 1668, 1464, 1428, 1371, 1244, 1088, 1014, 959, 884, 821, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.86 (m, 1H), 4.49 (m, 2H), 4.16 (m, 1H), 3.85–3.73 (m, 2H), 2.06–1.92 (m, 7H), 1.80 (m, 1H), 1.64 (m 1H), 1.57–1.40 (m, 4H), 1.17 (d, 3H, *J* = 6.3), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 170.7, 154.5, 135.5, 133.8, 129.6, 127.6, 101.1, 71.3, 70.8, 63.9, 60.3, 37.7 (br, 2C), 35.3, 33.7, 26.9, 22.6, 21.4, 19.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 689.5 ($[M+Na]^+$, 100); (neg) 701.4 ($[M+Cl]^-$, 100).

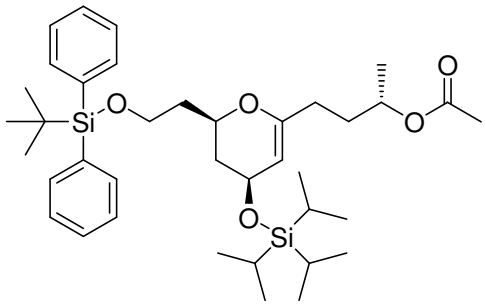


(–)-(2*R*,4*S*)-6-(3-Acetoxypropyl)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9d). Clear oil (160 mg, 85%). **TLC**: R_f 0.58 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –6.7° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2942, 2864, 1742, 1670, 1468, 1428, 1388, 1364, 1240, 1110, 1086, 1011, 998, 961, 918, 882, 822, 737, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H),

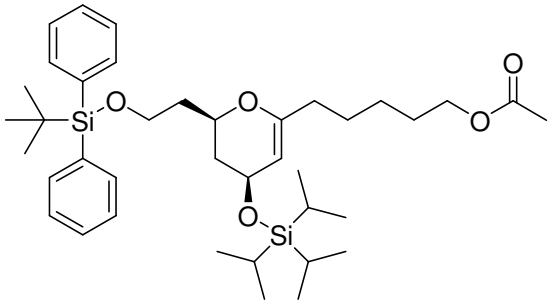
4.51 (m, 2H), 4.16 (m, 1H), 4.04 (t, 2H, J = 6.6), 3.86–3.73 (m, 2H), 2.06–1.90 (m, 7H), 1.82–1.73 (m, 3H), 1.65 (m, 1H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 171.1, 153.9, 135.5, 133.9, 129.6, 127.6, 101.5, 71.5, 64.0, 63.9, 60.2, 37.8, 37.7, 30.5, 26.9, 25.8, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 661.5 ([M+Na]$^+$, 100); (neg) 637.4 ([M–H]$^-$, 90), 673.7 ([M+Cl]$^-$, 100).



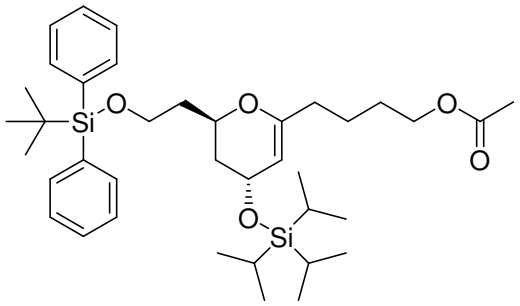
(–)-(2*R*,4*S*,3′*R*)-6-(3′-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9e). Clear oil (170 mg, 86%). **TLC**: R_f 0.65 (4:1 hexanes/EtOAc). **[α]$_D^{25}$**: –3.7° (c 1.0, $CDCl_3$). **IR** (NaCl, film): 2942, 2864, 1738, 1669, 1463, 1428, 1371, 1241, 1110, 1088, 1066, 1012, 961, 882, 822, 737, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.86 (m, 1H), 4.50 (m, 2H), 4.15 (m, 1H), 3.86–3.73 (m, 2H), 2.05–1.92 (m, 6H), 1.85–1.60 (m, 4H), 1.18 (d, 3H, J = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.7, 154.2, 135.5, 133.9, 129.6, 127.6, 101.2, 71.5, 70.5, 64.0, 60.2, 37.8, 37.7, 32.9, 30.0, 26.9, 21.4, 20.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 675.6 ([M+Na]$^+$, 100); (neg) 651.5 ([M–H]$^-$, 100), 687.4 ([M+Cl]$^-$, 10).



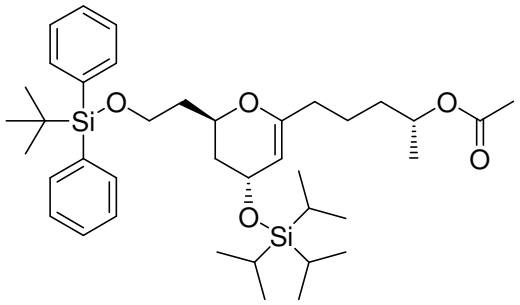
(–)-(2*R*,4*S*,3′*S*)-6-(3′-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9f). Clear oil (160 mg, 84%). **TLC**: R_f 0.65 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –7.2° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2941, 2864, 1738, 1669, 1462, 1428, 1370, 1241, 1110, 1087, 1066, 1012, 961, 882, 822, 737, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.87 (m, 1H), 4.50 (m, 2H), 4.16 (m, 1H), 3.86–3.73 (m, 2H), 2.05–1.91 (m, 6H), 1.85–1.60 (m, 4H), 1.19 (d, 3H, *J* = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.6, 154.3, 135.5, 133.9, 129.6, 127.6, 101.0, 71.5, 70.7, 64.0, 60.2, 37.8, 37.7, 33.0, 30.1, 26.9, 21.4, 19.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 675.6 ($[M+Na]^+$, 100); (neg) 651.5 ($[M–H]^–$, 40), 687.4 ($[M+Cl]^–$, 100).



(–)-(2*R*,4*S*)-6-(5-Acetoxypentyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9g). Clear oil (160 mg, 82%). **TLC**: R_f 0.58 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –6.7° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2942, 2834, 1741, 1668, 1463, 1428, 1388, 1363, 1237, 1110, 1087, 1012, 961, 882, 822, 737, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.50 (m, 2H), 4.15 (m, 1H), 4.03 (t, 2H, *J* = 6.7), 3.86–3.73 (m, 2H), 2.06–1.92 (m, 7H), 1.80 (m, 1H), 1.66–1.56 (m, 3H), 1.44 (m, 2H), 1.33 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 171.2, 154.8, 135.5, 133.9, 129.6, 127.6, 100.9, 71.4, 64.6, 64.0, 60.3, 37.8, 37.7, 33.8, 28.4, 26.9, 26.4, 25.5, 21.0, 19.3, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 689.6 ($[M+Na]^+$, 100); (neg) 665.5 ($[M–H]^–$, 100), 701.6 ($[M+Cl]^–$, 30).

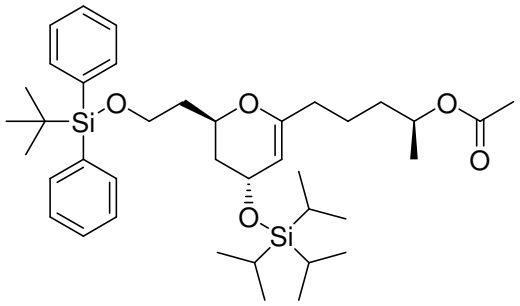


(+)-(2*R*,4*R*)-6-(4-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9h). Clear oil (270 mg, 79%). **TLC**: R_f 0.61 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +7.0° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 2941, 2859, 1737, 1661, 1462, 1426, 1360, 1238, 1095, 881. **^{1}H-NMR** (400 MHz): δ 7.66 (d, 4H, *J* = 7.4), 7.39 (m, 6H), 4.68 (d, 1H, *J* = 5.1), 4.22 (m, 2H), 4.01 (t, 2H, *J* = 6.6), 3.88 (m, 1H), 3.79 (m, 1H), 2.01 (m, 5H), 1.80 (m, 3H), 1.62–1.42 (m, 5H), 1.02 (m, 30H). **^{13}C-NMR** (125 MHz): δ 171.2, 156.0, 135.6, 134.0 (Ph), 133.9 (Ph′), 129.5, 127.6, 99.2, 68.3, 64.4, 61.3, 60.1, 38.2, 38.0, 33.6, 28.0, 26.8, 23.2, 21.0, 19.2, 18.1, 12.2. **ESI-MS** *m/z* (rel int): (pos) 653.7 ($[M+H]^+$, 1), 675.6 ($[M+Na]^+$, 100); (neg) 651.6 ([M–H]-, 100), 687.6 ($[M+Cl]^-$, 10).

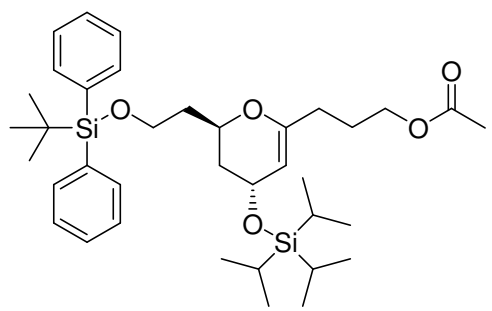


(+)-(2*R*,4*R*,4′*R*)-6-(4′-Acetoxypentyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9i). Clear oil (86 mg, 65%). **TLC**: R_f 0.60 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +59° (*c* 0.84, $CHCl_3$). **IR** (NaCl, film): 2941, 2864, 1737, 1659, 1462, 1427, 1370, 1245, 1092, 1010, 882, 822, 736, 702. **^{1}H-NMR** (400 MHz): δ 7.68 (dd, 4H, *J* = 6.5, 1.3), 7.40 (m, 6H), 4.86 (m, 1H), 4.68 (d, 1H, *J* = 5.1), 4.23 (m, 2H), 3.90–3.72 (m, 2H), 1.99 (m, 5H), 1.83–1.72 (m, 3H), 1.53–1.38

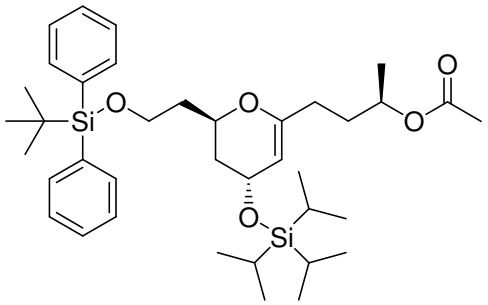
(m, 5H), 1.16 (d, 3H, J = 6.3), 1.08–1.02 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.8, 156.0, 135.5, 134.0, 129.5, 127.6, 99.2, 70.8, 68.3, 61.3, 60.2, 38.3, 38.0, 35.2, 33.8, 26.8, 22.6, 21.4, 19.9, 19.2, 18.2, 12.4. **ESI-MS** *m/z* (rel int): (pos) 689.4 ($[M+Na]^+$, 100); (neg) 665.4 ($[M–H]^–$, 40), 701.5 ($[M+Cl]^–$, 100).



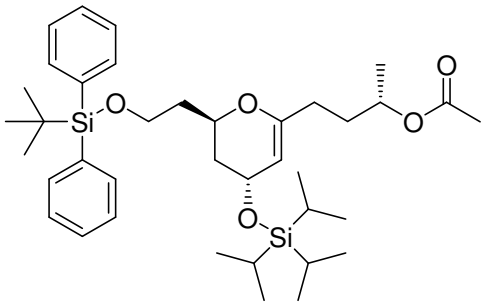
(+)-(2*R*,4*R*,4′*S*)-6-(4′-Acetoxypentyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9j). Clear oil (50 mg, 61%). **TLC**: R_f 0.59 (4:1 hexanes/EtOAc). **$[\alpha]_D^{25}$**: +56° (c 0.53, $CHCl_3$). **IR** (NaCl, film): 2954, 2862, 1737, 1588, 1468, 1442, 1427, 1370, 1244, 1111, 823, 737, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.39 (m, 6H), 4.87 (m, 1H), 4.67 (d, 1H, J = 5.0), 4.28–4.17 (m, 2H), 3.90–3.72 (m, 2H), 2.00 (m, 5H) 1.89–1.73 (m, 3H), 1.57–1.43 (m, 5H) 1.17 (d, 3H, J = 6.3), 1.08–1.01 (m, 30H). **^{13}C-NMR** (100 MHz): δ 170.8, 156.0, 135.5, 134.0, 129.5, 127.6, 96.7, 70.9, 68.3, 61.3. 60.6, 38.4, 38.0, 35.3, 33.8, 27.2, 26.8, 21.4, 19.9, 19.2, 18.2, 12.4. **ESI-MS** *m/z* (rel int): (pos) 689.4 ($[M+Na]^+$, 100); (neg) 665.3 ($[M–H]^–$, 50), 701.3 ($[M+Cl]^–$, 100).



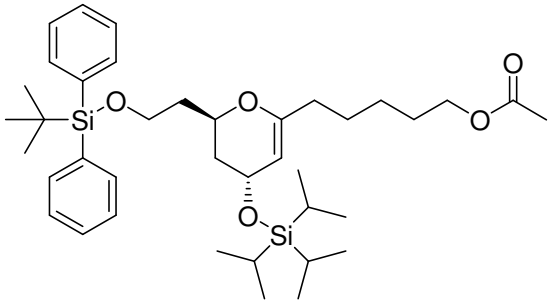
(+)-(2*R*,4*R*)-6-(3-Acetoxypropyl)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9k). Clear oil (100 mg, 68%). **TLC**: R_f 0.32 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +7.6° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 2935, 2864, 1739, 1661, 1460, 1241, 1093. **^{1}H-NMR** (500 MHz): δ 7.68 (d, *J* = 7.3), 7.40 (m, 6H), 4.69 (d, 1H, *J* = 5.0), 4.29–4.19 (m, 2H), 4.02 (t, 2H, *J* = 6.6), 3.90–3.70 (m, 2H), 2.05 (t, 2H, *J* = 7.3), 2.02 (s, 3H), 1.82–1.71 (m, 5H), 1.51 (m, 1H), 1.03 (m, 30H). **^{13}C-NMR** (125 MHz): δ 171.1, 155.3, 135.6, 133.9, 129.5, 127.6, 99.5, 68.4, 63.9, 61.2, 60.1, 38.2, 38.1, 30.6, 26.8, 25.9, 21.0, 19.2, 18.2, 12.4. **ESI-MS** *m/z* (rel int): (pos) 661.3 ([M+Na]$^+$, 100).



(+)-(2*R*,4*R*,3′*R*)-6-(3′-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9l). Clear oil (82 mg, 67%). **TLC**: R_f 0.54 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +63° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 2361, 1736, 1696, 1646, 1556, 1538, 1511, 1241, 1102, 701. **^{1}H-NMR** (500 MHz): δ 7.67 (d, 4H, *J* = 7.7), 7.39 (m, 6H), 4.36 (m, 1H), 4.69 (d, 1H, *J* = 5.3), 4.28–4.20 (m, 2H), 3.89 (m, 1H), 3.79 (m, 1H), 2.09–1.95 (m, 5H), 1.86–1.76 (m, 3H), 1.73–1.62 (m, 2H), 1.52 (m, 1H), 1.20 (d, 3H, *J* = 6.3), 1.01 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.6, 155.8, 135.5, 134.0 (Ph), 133.9 (Ph′), 129.5, 127.6, 99.0, 70.7, 68.3, 61.2, 60.1, 38.2, 38.0, 33.2, 30.2, 26.8, 21.3, 19.9, 19.2, 18.2, 12.4. **ESI-MS** *m/z* (rel int): (pos) 675.6 ([M+Na]$^+$, 100).

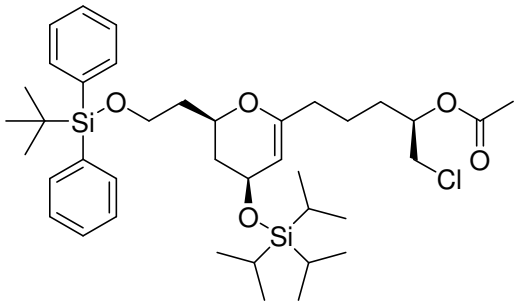


(+)-(2*R*,4*R*,3′*S*)-6-(3′-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9m). Clear oil (62 mg, 46%). **TLC**: R_f 0.54 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +58° (*c* 1.6, $CHCl_3$). **IR** (NaCl, film): 2940, 2862, 1733, 1460, 1368, 1241, 1094, 738. **^{1}H-NMR** (400 MHz): δ 7.65 (d, 4H, *J* = 7.1), 7.37 (m, 6H), 4.85 (m, 1H), 4.66 (d, 1H, *J* = 5.3), 4.28–4.19 (m, 2H), 3.85 (m, 1H), 3.78 (m, 1H), 2.07–1.97 (m, 5H), 1.87–1.59 (m, 5H), 1.52 (m, 1H), 1.18 (d, 3H, *J* = 6.2), 1.01 (m, 30H). **^{13}C-NMR** (100 MHz): δ 170.5, 155.7, 135.6, 134.0 (Ph), 133.9 (Ph′), 129.5, 127.6, 99.1, 70.5, 68.4, 61.2, 60.1, 38.2, 38.0, 33.0, 30.2, 26.8, 21.4, 19.9, 19.2, 18.1, 12.4.

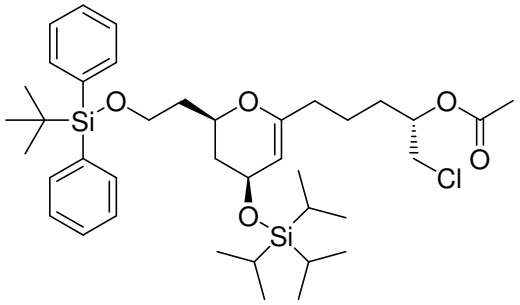


(+)-(2*R*,4*R*)-6-(5-Acetoxypentyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9n). Clear oil (79 mg, 79%). **TLC**: R_f 0.58 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +58° (*c* 1.6, $CHCl_3$). **IR** (NaCl, film): 2930, 2852, 1738, 1363, 1236, 1099, 738. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.36 (m, 6H), 4.67 (d, 1H, *J* = 5.0), 4.28–4.19 (m, 2H), 4.03 (t, 2H, *J* = 6.7), 3.88 (m, 1H), 3.77 (m, 1H), 2.01 (m, 5H), 1.86–1.73 (m, 3H), 1.63–1.53 (m, 2H), 1.52–1.41 (m, 3H), 1.38–1.31 (m, 2H), 1.10–0.97 (m, 30H). **^{13}C-NMR** (100 MHz): δ 171.1, 156.3, 135.5,

134.0 (Ph), 133.9 (Ph′), 129.5, 127.5, 99.0, 68.2, 64.5, 61.3, 60.1, 38.2, 38.1, 33.9, 28.4, 26.8 26.4, 25.4, 21.0, 19.2, 18.1, 12.4. **ESI-MS** *m/z* (rel int): (pos) 689.5 ($[M+Na]^+$, 100); (neg) 665.3 ($[M–H]^–$, 1), 701.4 ($[M+Cl]^–$, 100).

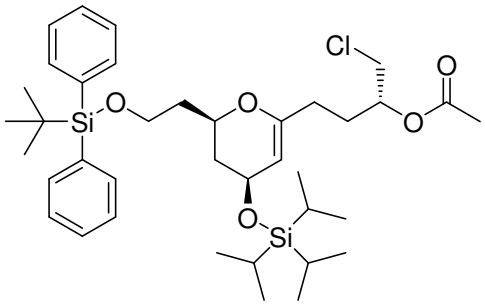


(+)-(2*R*,4*S*,4′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-acetoxy-5-chloropentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9o). Clear oil (330 mg, 74%). **TLC**: R_f 0.53 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +16° (*c* 0.99, $CDCl_3$). **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44-7.35 (m, 6H), 5.00 (m, 1H), 4.49 (m, 2H), 4.15 (m, 1H), 3.85–3.73 (m, 2H), 3.59 (dd, 1H, *J* = 11.7, 4.4), 3.50 (dd, 1H, *J* = 11.7, 5.4), 2.09–1.92 (m, 7H), 1.80 (m, 1H), 1.65 (m, 3H), 1.46 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.5, 154.1, 135.5, 133.9, 129.6, 127.6, 101.4, 72.6, 71.5, 63.9, 60.3, 45.6, 37.7, 33.6, 30.8, 26.9, 22.2, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 723.6 ($[M+Na]^+$, 100); neg 735.6 ($[M+Cl]^–$, 100).

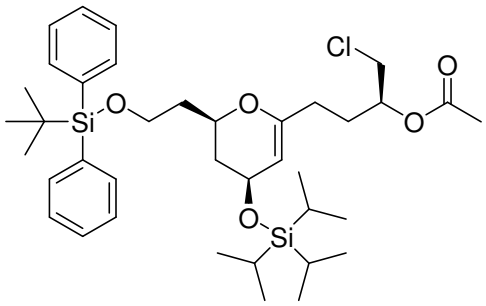


(–)-(2*R*,4*S*,4′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-acetoxy-5-chloropentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9p). Clear oil

(480 mg, 91%). **TLC**: R_f 0.54 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –8.4° (*c* 1.0, $CDCl_3$). **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44-7.35 (m, 6H), 5.00 (m, 1H), 4.49 (m, 2H), 4.15 (m, 1H), 3.85–3.73 (m, 2H), 3.60–3.49 (m, 2H), 2.09–1.92 (m, 7H), 1.80 (m, 1H), 1.65 (m, 3H), 1.46 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.5, 154.2, 135.5, 133.9, 129.6, 127.6, 101.4, 72.7, 71.5, 63.9, 60.3, 45.6, 37.7, 33.6, 30.9, 26.9, 22.2, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 723.5 ($[M+Na]^+$, 100); neg 735.4 ($[M+Cl]^-$, 100).



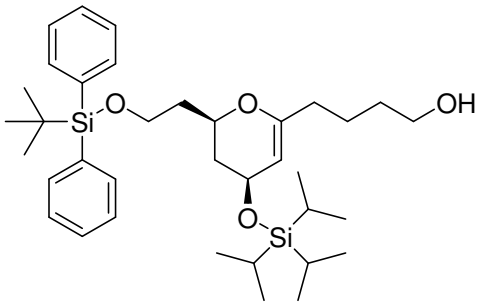
(–)-(2*R*,4*S*,3′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-acetoxy-4-chlorobutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9q). Yellow oil (56 mg, 45%). $[\alpha]_D^{25}$ = –4.1° (*c* 1.1, $CDCl_3$). **IR** (NaCl, film): 2928, 2863, 1744, 1464, 1428, 1374, 1234, 1111, 1091, 882, 823, 737, 702. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.99 (m, 1H), 4.49 (m, 2H), 4.15 (m, 1H), 3.84–3.73 (m, 2H), 3.60 (m, 1H), 3.53 (m, 1H), 2.05–1.91 (m, 7H), 1.83–1.76 (m, 3H), 1.63 (m, 1H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.7, 153.7, 135.7, 134.0, 129.7, 127.8, 101.7, 72.6, 71.8, 64.0, 60.3, 45.6, 37.9, 37.8, 29.8, 28.8, 27.0, 21.1, 19.3, 18.2, 12.4. **ESI-MS** *m/z* (rel int): pos 709.5 ($[M+Na]^+$, 100); neg 721.7 ($[M+Cl]^-$, 100).



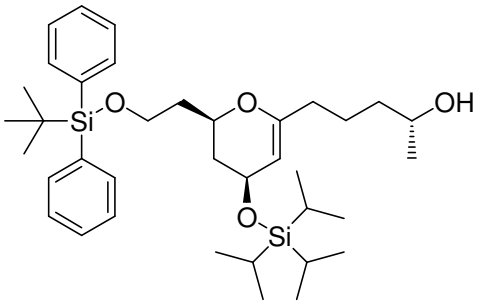
(–)-(2*R*,4*S*,3′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-acetoxy-4-chlorobutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E9r). Yellow oil (61 mg, 49%). $[\alpha]_D^{25}$ = –6.7° (*c* 1.1, $CDCl_3$). **IR** (NaCl, film): 2928, 2863, 1744, 1464, 1428, 1374, 1234, 1111, 1091, 882, 823, 737, 702. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.98 (m, 1H), 4.49 (m, 2H), 4.13 (m, 1H), 3.84–3.73 (m, 2H), 3.58 (m, 1H), 3.52 (m, 1H), 2.05–1.92 (m, 7H), 1.83–1.76 (m, 3H), 1.63 (m, 1H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.5, 153.6, 135.7, 134.0, 129.7, 127.7, 101.9, 72.4, 71.8, 64.0, 60.3, 45.7, 37.9, 37.8, 29.8, 28.7, 27.0, 21.1, 19.3, 18.2, 12.4. **ESI-MS** *m/z* (rel int): pos 709.5 ($[M+Na]^+$, 100); neg 721.7 ($[M+Cl]^-$, 100).

General procedure for acetate deprotection:

The acetate-protected glycal (**E9a–n**, 1.0 equiv) was dissolved in THF/MeOH (1:1, 0.10 M). K_2CO_3 (2.0 equiv) was added, and the mixture was stirred vigorously at rt. After 3 h, the mixture was filtered through Celite/silica (1:1), and the flask was rinsed with Et_2O. The solvent was evaporated, the residue was dissolved in Et_2O, washed with H_2O (3×), dried ($MgSO_4$), and filtered. Evaporation of the solvent provided the alcohol products **67a–n** in sufficient purity (>99%, NMR) for direct use in subsequent epoxidation reactions.

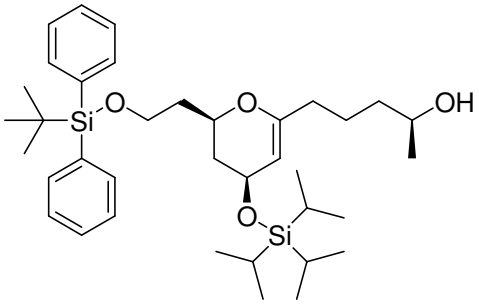


(–)-(2*R*,4*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67a). Clear oil (140 mg, 100%). **TLC**: R_f 0.35 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –6.7° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3332, 2940, 2863, 1668, 1465, 1428, 1385, 1242, 1087, 1007, 883, 820, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.50 (m, 2H), 4.16 (m, 1H), 3.86–3.73 (m, 2H), 3.61 (q, 2H, *J* = 6.0), 2.06–1.92 (m, 4H), 1.80 (m, 1H), 1.64 (m, 1H), 1.57–1.48 (m, 4H), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 154.7, 135.5, 133.9, 129.5, 127.6, 101.1, 71.4, 64.0, 62.8, 60.2, 37.8, 37.7, 33.6, 32.2, 26.8, 22.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 633.4 ($[M+Na]^+$, 100); (neg) 645.3 ($[M+Cl]^-$, 100).

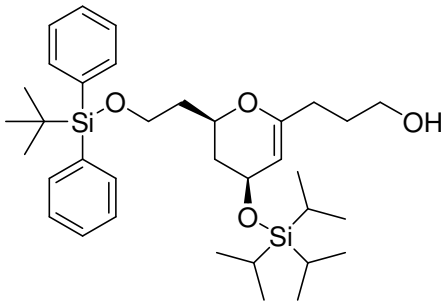


(–)-(2*R*,4*S*,4′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-hydroxypentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67b). Clear oil (140 mg, 98%). **TLC**: R_f 0.35 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –8.2° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3349, 2940, 2863, 1668, 1464, 1428, 1383, 1243, 1088, 1006, 883, 821, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.50 (m, 2H), 4.16 (m, 1H), 3.86–3.73 (m, 3H), 2.06–1.92 (m, 4H), 1.80 (m, 1H), 1.64 (m, 1H), 1.54–1.40 (m,

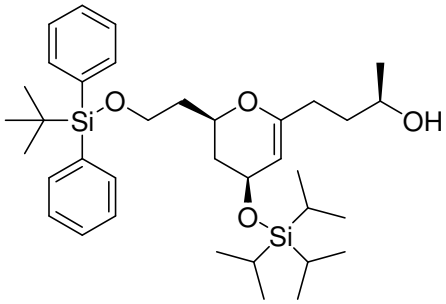
4H), 1.16 (d, 3H, J = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 154.7, 135.5, 133.9, 129.5, 127.6, 101.1, 71.4, 67.9, 64.0, 60.3, 38.8, 37.8, 37.7, 33.8, 26.8, 23.4, 22.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 647.5 ([M+Na]$^+$, 100); (neg) 659.3 ([M+Cl]$^-$, 100).



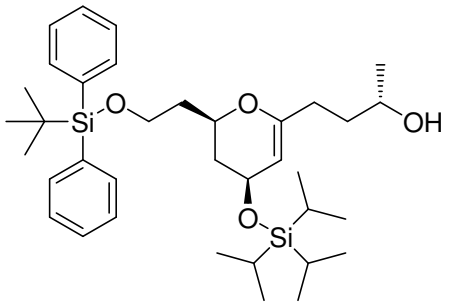
(–)-(2*R*,4*S*,4′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-hydroxypentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67c). Clear oil (150 mg, 98%). **TLC**: R_f 0.35 (4:1 hexanes/EtOAc). **$[\alpha]_D^{25}$**: –5.6° (c 1.0, $CDCl_3$). **IR** (NaCl, film): 3350, 2940, 2863, 1668, 1464, 1428, 1383, 1243, 1088, 1007, 884, 821, 738, 702 **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.50 (m, 2H), 4.16 (m, 1H), 3.86–3.73 (m, 3H), 2.06–1.93 (m, 4H), 1.80 (m, 1H), 1.64 (m, 1H), 1.54–1.40 (m, 4H), 1.17 (d, 3H, J = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 154.8, 135.6, 133.9, 129.6, 127.6, 101.1, 71.4, 67.9, 64.0, 60.3, 38.8, 37.72, 37.71, 33.9, 26.9, 23.5, 22.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 647.5 ([M+Na]$^+$, 100); (neg) 659.3 ([M+Cl]$^-$, 100).



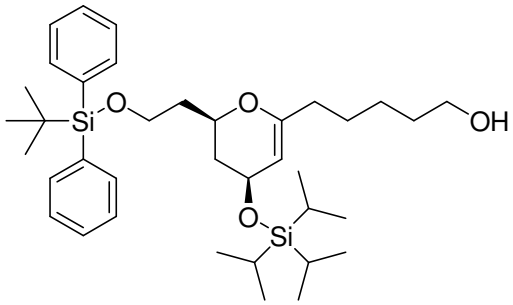
(–)-(2*R*,4*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3-hydroxypropyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67d). Clear oil (130 mg, 95%). **TLC**: R_f 0.25 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –4.3° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3326, 2941, 2864, 1668, 1462, 1428, 1388, 1238, 1111, 1087, 1064, 1011, 882, 822, 737, 701. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.56 (s, 1H), 3.99 (t, 1H, *J* = 6.8), 4.17 (m, 1H), 3.81 (m, 1H), 3.76 (m, 1H), 3.62 (dd, 2H, *J* = 11.9, 5.9), 2.06 (m, 3H), 1.93 (m, 1H), 1.82 (m, 1H), 1.72–1.63 (m, 3H), 1.41 (t, 1H, *J* = 5.5), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.5, 135.5, 133.8, 129.6, 127.6, 101.5, 71.6, 63.9, 62.5, 60.2, 37.8, 37.7, 30.5, 30.1, 26.9, 19.2, 18.3, 12.3. **ESI-MS** *m/z* (rel int): (pos) 619.4 ($[M+Na]^+$, 100); (neg) 631.5 ($[M+Cl]^-$, 100).



(–)-(2*R*,4*S*,3′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67e). Clear oil (100 mg, 75%). **TLC**: R_f 0.39 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –9.5° (*c* 0.50, $CDCl_3$). **IR** (NaCl, film): 3339, 2957, 2941, 2864, 1668, 1462, 1428, 1388, 1110, 1086, 1011, 959, 882, 822, 736, 701. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.56 (s, 1H), 4.50 (t, 1H, *J* = 6.3), 4.17 (m, 1H), 3.91–3.73 (m, 3H), 2.10–2.03 (m, 3H), 1.94 (m, 1H), 1.80 (m, 1H), 1.66–1.57 (m, 3H), 1.16 (d, 3H, *J* = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.7, 135.5, 133.8, 129.6, 127.6, 101.4, 71.6, 67.6, 63.9, 60.2, 37.8, 37.7, 36.4, 30.5, 26.9, 23.3, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 633.4 ($[M+Na]^+$, 100); (neg) 645.4 ($[M+Cl]^-$, 100).

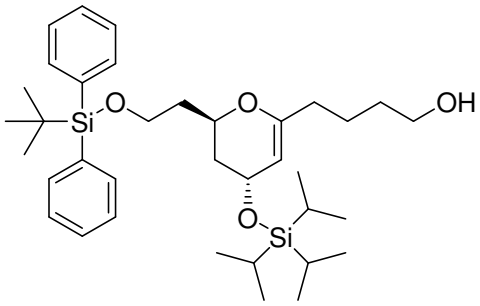


(–)-(2*R*,4*S*,3′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67f). Clear oil (100 mg, 71%). **TLC**: R_f 0.39 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –2.2° (*c* 0.50, $CDCl_3$). **IR** (NaCl, film): 3339, 2958, 2941, 2864, 1668, 1462, 1428, 1388, 1110, 1086, 1011, 959, 882, 822, 737, 701. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.56 (s, 1H), 4.50 (t, 1H, *J* = 6.8), 4.17 (m, 1H), 3.91–3.70 (m, 3H), 2.10–2.03 (m, 3H), 1.94 (m, 1H), 1.80 (m, 1H), 1.66–1.57 (m, 3H), 1.16 (d, 3H, *J* = 6.2), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.7, 135.5, 133.8, 129.6, 127.6, 101.4, 71.6, 67.7, 63.9, 60.2, 37.8, 37.7, 36.6, 30.5, 26.9, 23.3, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 633.4 ($[M+Na]^+$, 100); (neg) 645.5 ($[M+Cl]^-$, 100).

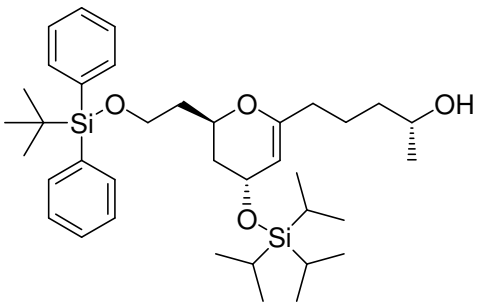


(–)-(2*R*,4*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(5-hydroxypentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67g). Clear oil (140 mg, 100%). **TLC**: R_f 0.33 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –6.2° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3336, 2940, 2863, 1668, 1462, 1428, 1388, 1238, 1111, 1086, 1011, 961, 882, 822, 737, 701. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.50 (m, 2H),

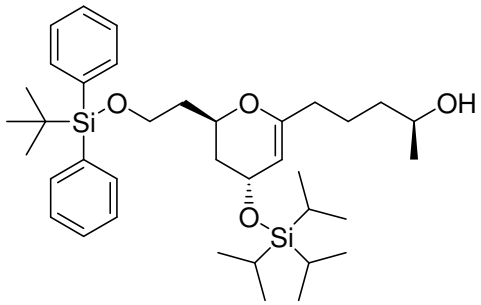
4.15 (m, 1H), 3.86–3.74 (m, 2H), 3.61 (dd, 1H, *J* = 12.3, 6.0), 2.02 (m, 1H), 1.97 (m, 3H), 1.80 (m, 1H), 1.65 (m, 1H), 1.55 (m, 2H), 1.45 (m, 2H), 1.34 (m, 2H), 1.18 (t, 1H, *J* = 5.2), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 155.0, 135.5, 133.9, 129.6, 127.6, 100.9, 71.4, 64.0, 63.0, 60.3, 37.8, 37.7, 33.9, 32.5, 26.9, 26.5, 25.2, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): (pos) 647.6 ([M+Na]$^+$, 100); (neg) 659.3 ([M+Cl]$^-$, 100).



(+)-(2*R*,4*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67h). Clear oil (250 mg, 100%). **TLC**: R_f 0.22 (4:1 hexanes/EtOAc). **[α]$_D^{25}$**: +67° (*c* 0.95, C_6H_6). **IR** (NaCl, film): 3315, 2943, 2859, 1661, 1463, 1421, 1247, 1097, 1001, 737, 701. **^{1}H-NMR** (400 MHz, C_6D_6): δ 7.79 (m, 4H), 7.24 (m, 6H), 4.82 (d, 1H, *J* = 5.0), 4.52 (m, 1H), 4.22 (m, 1H), 4.01 (m, 1H), 3.85 (m, 1H), 3.32 (t, 2H, *J* = 6.3), 2.03 (t, 2H, *J* = 7.4), 1.89–1.78 (m, 3H), 1.57–1.43 (m, 3H), 1.38 (m, 2H), 1.22–1.01 (m, 30H). **^{13}C-NMR** (125 MHz, C_6D_6): δ 157.0, 136.0, 134.4, 134.3, 129.9, 99.3, 68.5, 62.4, 61.9, 60.5, 38.7, 38.5, 34.2, 32.6, 27.1, 23.6, 19.5, 18.4, 12.8. **ESI-MS** *m/z* (rel int): (pos) 633.4 ([M+Na]$^+$, 100); (neg) 609.4 ([M–H]$^-$, 100), 645.4 ([M+Cl]$^-$, 100).

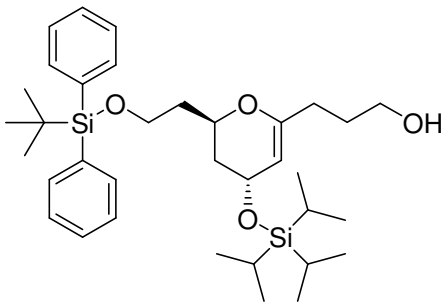


(+)-(2*R*,4*R*,4′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-hydroxypentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67i). Clear oil (81 mg, 100%). **TLC**: R_f 0.26 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +60° (*c* 1.1, C_6H_6). **IR** (NaCl, film): 3345, 2941, 2864, 1663, 1462, 1428, 1247, 1094, 1008, 882, 822, 734, 701. **^{1}H-NMR** (500 MHz, C_6D_6): δ 7.79 (m, 4H), 7.26 (m, 6H), 4.85 (d, 1H, *J* = 5.1), 4.53 (m, 1H), 4.24 (m, 1H), 4.03 (m, 1H), 3.88 (m, 1H), 3.53 (m, 1H), 2.06 (m, 2H), 1.90–1.78 (m, 3H), 1.64 (m, 1H), 1.58–1.47 (m, 2H), 1.32–1.25 (m, 2H), 1.19–1.06 (m, 30H), 0.98 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz, C_6D_6): δ 157.0, 136.0, 134.4 (Ph), 134.3 (Ph′), 129.9, 128.5, 99.4, 68.5, 67.4, 61.9, 60.5, 39.0, 38.8, 38.5, 34.4, 27.1, 23.8, 23.5, 19.5, 18.5, 12.8. **ESI-MS** *m/z* (rel int): (pos) 647.5 ($[M+Na]^+$, 100); (neg) 623.1 ($[M-H]^-$, 10), 659.2 ($[M+Cl]^-$, 100).

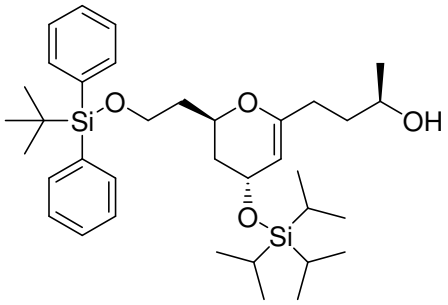


(+)-(2*R*,4*R*,4′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-hydroxypentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67j). Clear oil (65 mg, 99%). **TLC**: R_f 0.26 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +62° (*c* 0.42, C_6H_6). **IR** (NaCl, film): 3344, 2940, 2863, 1663, 1462, 1427, 1247, 1094, 1007, 882, 823, 736, 701. **^{1}H-NMR** (500 MHz, C_6D_6): δ 7.81 (m, 4H), 7.25 (m, 6H), 4.85 (d, 1H, *J* = 5.0), 4.53 (m, 1H), 4.24 (m, 1H), 4.03 (m, 1H), 3.86 (m, 1H), 3.52 (m, 1H), 2.06 (t, 2H, *J* = 7.4), 1.90–1.77 (m, 3H), 1.68–1.45 (m, 3H), 1.32–1.21 (m, 2H), 1.20–1.05 (m, 30H), 0.98 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz, C_6D_6): δ 157.0, 136.0, 134.4 (Ph), 134.3 (Ph′), 129.9, 128.5, 99.4, 68.5, 67.5, 62.0, 60.5, 39.1, 38.8, 38.5, 34.5, 27.1, 23.8, 23.6, 19.5, 18.5, 12.8.

ESI-MS *m/z* (rel int): (pos) 647.5 ($[M+Na]^+$, 100); (neg) 623.2 ($[M–H]^–$, 15), 659.2 ($[M+Cl]^–$, 100).

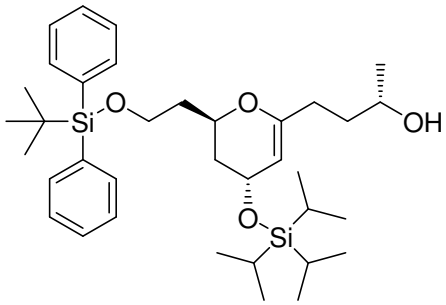


(+)-(2*R*,4*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3-hydroxypropyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67k). Clear oil (35 mg, 95%). **TLC**: R_f 0.27 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +67° (*c* 1.1, C_6H_6). **IR** (NaCl, film): 3339, 2943, 2859, 1661, 1463, 1427, 1241, 1091, 1001, 881, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.68 (m, 4H), 7.39 (m, 6H), 4.72 (d, 1H, *J* = 5.3), 4.30–4.19 (m, 2H), 3.90-3.73 (m, 2H), 3.61 (q, 2H, *J* = 6.1), 2.10 (td, 2H, *J* = 2.8, 7.1), 1.88–1.76 (m, 3H), 1.69 (p, 2H, *J* = 6.6, 6.8), 1.55 (m, 1H), 1.43 (t, 1H, *J* = 5.8), 1.02 (m, 30H). **^{13}C-NMR** (125 MHz, C_6D_6): δ 156.9, 136.0, 134.3, 134.2, 129.9, 99.5, 68.6, 62.2, 61.9, 60.4, 38.7, 38.4, 31.1, 30.6, 27.1, 19.5, 18.5, 12.8. **ESI-MS** *m/z* (rel int): (pos) 619.5 ($[M+Na]^+$, 100); (neg) 595.2 ($[M–H]^–$, 10), 631.4 ($[M+Cl]^–$, 100).

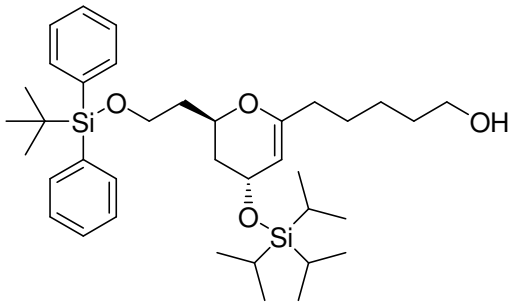


(+)-(2*R*,4*R*,3′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67l). Clear oil (44 mg, 95%). **TLC**: R_f 0.26 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +60° (*c* 0.47, C_6H_6). **IR** (NaCl, film): 3352,

2945, 2862, 1658, 1460, 1423, 1095, 1058, 1001, 881, 734. **^{1}H-NMR** (500 MHz, C_6D_6): δ 7.80 (m, 4H), 7.24 (m, 6H), 4.86 (d, 1H, *J* = 5.2), 4.53 (m, 1H), 4.22 (m, 1H), 4.01 (m, 1H), 3.83 (m, 1H), 3.60 (m, 1H), 2.21–2.08 (m), 1.88–1.78 (m), 1.59 (m, 2H), 1.49 (m, 1H), 1.19 (s, 9H), 1.17–1.02 (m), 0.99 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz, C_6D_6): δ 157.5, 136.4, 134.7, 134.6, 130.1, 99.8, 69.0, 67.6, 62.3, 60.8, 39.1, 38.8, 37.4, 31.5, 27.5, 24.0, 19.8, 18.8, 13.1. **ESI-MS** *m/z* (rel int): (pos) 633.5 ($[M+Na]^+$, 100); (neg) 609.3 ($[M–H]^–$, 10), 645.5 ($[M+Cl]^–$, 100).



(+)-(2*R*,4*R*,3′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67m). Clear oil (51 mg, 98%). **TLC**: R_f 0.26 (4:1 hexanes/EtOAc). **$[\alpha]_D^{25}$**: +70° (*c* 0.37, C_6H_6). **IR** (NaCl, film): 3346, 2940, 2863, 1665, 1462, 1427, 1093, 998, 882, 736, 701. **^{1}H-NMR** (500 MHz, C_6D_6): δ 7.81 (m, 4H), 7.25 (m, 6H), 4.86 (d, 1H, *J* = 5.1), 4.53 (m, 1H), 4.22 (m, 1H), 4.01 (m, 1H), 3.83 (m, 1H), 3.60 (m, 1H), 2.19–2.11 (m, 2H), 1.87–1.78 (m, 3H), 1.59 (m, 2H), 1.49 (m, 1H), 1.21 (s, 9H), 1.13–1.05 (m, 22H), 0.99 (d, 3H, *J* = 3.7). **^{13}C-NMR** (125 MHz, C_6D_6): δ 157.5, 136.4, 134.7, 134.6, 130.3, 99.8, 69.0, 67.6, 62.3, 60.8, 39.1, 38.8, 37.5, 31.5, 27.5, 24.1, 19.8, 18.8, 13.2. **ESI-MS** *m/z* (rel int): (pos) 633.4 ($[M+Na]^+$, 100); (neg) 645.4 ($[M+Cl]^–$, 100).



(+)-(2*R*,4*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(5-hydroxypentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (67n). Clear oil (120 mg, 97%). **TLC**: R_f 0.21 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +38° (*c* 0.85, C_6H_6). **IR** (NaCl, film): 3331, 2935, 2851, 1658, 1465, 1423, 1095, 1058, 1001, 881, 734. **^{1}H-NMR** (500 MHz, C_6D_6): δ 7.79 (m, 4H), 7.23 (m, 6H), 4.84 (d, 1H, *J* = 5.0), 4.53 (m, 1H), 4.25 (m, 1H), 4.02 (m, 1H), 3.87 (m, 1H), 3.33 (t, 2H, *J* = 6.4), 2.05 (t, 2H, *J* = 7.5), 1.90–1.79 (m, 3H), 1.52–1.49 (m, 3H), 1.39–1.34 (m, 3H), 1.26 (m, 2H), 1.19–1.03 (m, 30H). **^{13}C-NMR** (125 MHz, C_6D_6): δ 157.5, 136.4, 134.7, 134.6, 130.3, 128.9, 99.6, 68.9, 63.0, 62.3, 60.9, 39.1, 38.9, 34.9, 33.3, 27.5, 26.0, 19.8, 18.8, 13.2. **ESI-MS** *m/z* (rel int): (pos) 625.6 ($[M+H]^+$, 1), 647.7 ($[M+Na]^+$, 100); (neg) 623.5 ($[M–H]^-$, 15) 659.5 ($[M+Cl]^-$, 100).

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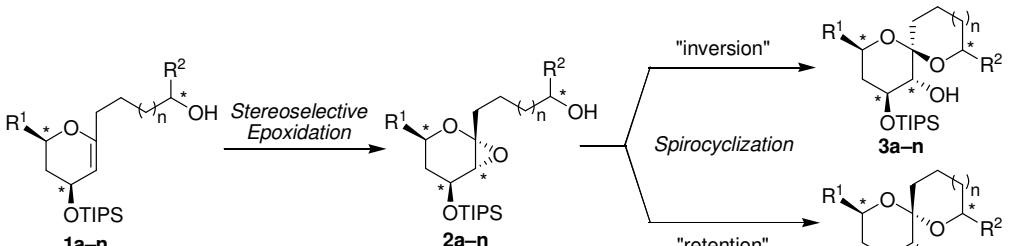
CHAPTER 3

KINETICALLY CONTROLLED STEREOSELECTIVE SPIROCYCLIZATIONS OF *C*1-SUBSTITUTED GLYCAL EPOXIDES WITH INVERSION OR RETENTION OF CONFIGURATION

3.1. Introduction

In order to generate a library of systematically stereodiversified spiroketals, we required kinetically controlled access to both of the two possible stereochemical configurations at the spiroketal carbon (Figure 3.1). We envisioned an approach in which the stereochemical configuration at the anomeric carbon is controlled by an initial stereoselective epoxidation of *C*1-substituted glycals **1a–n**. Further stereodiversification would then be accomplished using kinetic spirocyclization reactions that proceed with either inversion (**3**) or retention (**4**) of configuration at the anomeric carbon, independent of thermodynamic considerations or cyclization trajectory. This chapter is based in part on two previous publications.[1,2]



1a–n **2a–n**

glycal	n	R^2	glycal	n	R^2
a: *threo*	1	H	**h**: *erythro*	1	H
b: *threo*	1	*R*-Me	**i**: *erythro*	1	*R*-Me
c: *threo*	1	*S*-Me	**j**: *erythro*	1	*S*-Me
d: *threo*	0	H	**k**: *erythro*	0	H
e: *threo*	0	*R*-Me	**l**: *erythro*	0	*R*-Me
f: *threo*	0	*S*-Me	**m**: *erythro*	0	*S*-Me
g: *threo*	2	H	**n**: *erythro*	2	H

Figure 3.1. Stereoselective epoxidation of *C*1-substituted glycals **1a–n** and stereoselective spirocyclization of the resulting glycal epoxides **2a–n**.
$R^1 = (CH_2)_2OTBDPS$

3.2. Stereoselective Epoxidation of C1-Substituted Glycals

Epoxidation of the *C*1-substituted glycals **1a–n** with DMDO at –78 °C results in exclusive formation of the *anti*-epoxides **2a–n**. Although epoxidations of glycals with DMDO are well-precedented,[3-6] we were concerned about the stability of our *C*1-substituted glycal epoxides, since it is possible for the epoxide to open prematurely to form an oxonium species. This activated species would then undergo spirocyclization and we would not have an opportunity to control the stereochemistry of the cyclization. Indeed, following treatment of *C*1-alkylglycals **1a–n** with DMDO, we isolated only a mixture of spiroketals (70:30 **3a**:**4a** for **2a**; 75:25 **3h**:**4h** for **2h**), with no remaining epoxide. Fortunately, our later experimental results suggested that the epoxides are stable at low temperature. This was confirmed by variable temperature ^{1}H-NMR experiments, which showed that the epoxide **2a** is stable below –40 °C.

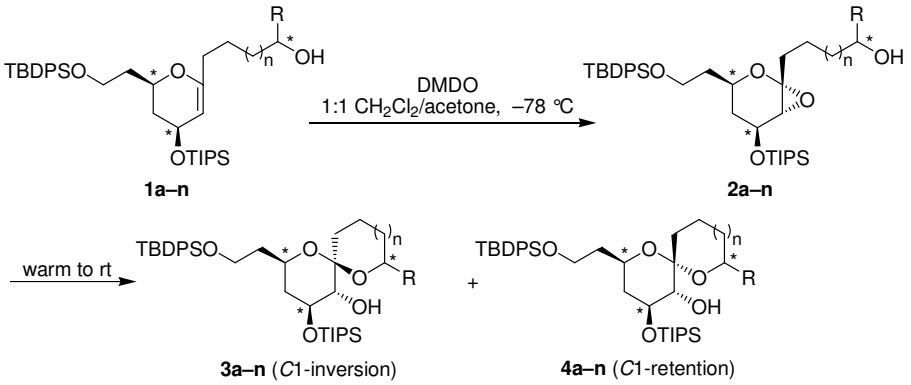


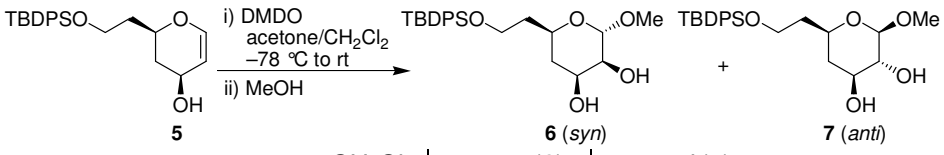
Figure 3.2. Stereoselective epoxidation with DMDO and spontaneous spirocyclization

The possibility of carrying out the corresponding *syn*-epoxidation was also investigated. In the absence of any directing effects, diastereoselectivity of DMDO epoxidations is normally attributed to steric factors,[7,8] which is consistent with the *anti*-epoxidation observed for glycal substrates **1a–n**. Although an early study of allylic alcohol epoxidations with DMDO concluded that hydrogen bonding of the

substrate hydroxyl group to DMDO did not play a significant role in directing epoxidation,[9] later studies showed that hydrogen bonding effects are highly solvent dependent. Danishefsky first reported that decreasing the polarity of the solvent mixture increased the proportion of *syn*-epoxide formed from an allylic alcohol substrate, presumably due to greater opportunity for hydrogen bonding of DMDO with the substrate rather than the solvent.[10] This idea was developed further by Murray, who showed a definite correlation between decreased polarity of the solvent mixture and a greater *syn*:*anti* epoxide ratio.[11]

To explore this concept with a substrate more relevant to our planned spiroketal synthesis, epoxidations of the *C*3-unprotected glycal (**5**) were conducted in various solvent systems. The diastereoselectivity was determined by ^{1}H-NMR analysis after methanolysis of the epoxides. As expected, the use of less polar solvent mixtures resulted in greater amounts of *syn*-epoxidation (Table 3.1).

Table 3.1. Solvent effects on DMDO epoxidation



5 **6** (*syn*) **7** (*anti*)

acetone:CH_2Cl_2	*syn* (**6**)	*anti* (**7**)
80:20	34	66
50:50	36	64
30:70	54	46
10:90	75	25

In order to investigate a similar *syn*-epoxidation with a substrate appropriate for spirocyclization, the *C*1-substituted glycal **9** was synthesized. To allow coordination of DMDO, the *C*3-OH of glycal **8** was selectively desilylated by treatment with TBAF, although the yield was low because of incomplete conversion.

Deprotection of the *C*11-OH afforded a substrate (**9**) suitable for *syn*-epoxidation followed by spirocyclization. Treatment of **9** with DMDO followed by exposure to MeOH resulted in spirocyclization with inversion of configuration instead of the expected methyl glycoside (see Section 3.3). Unfortunately, decreased solvent polarity for epoxidation of this *C*1-substituted glycal did not have as great of an effect as with the *C*1-unsubstituted glycal **5**. Epoxidation in a 5:95 acetone/CH_2Cl_2 solvent mixture only afforded a 1:1 mixture of *syn* and *anti* epoxidation (identified through ^{1}H-NMR analysis of the spiroketal mixture). Use of a 10:90 acetone/CCl_4 solvent mixture improved the ratio slightly (59:41 *syn*:*anti*), but a large amount of an unidentified byproduct was also produced.

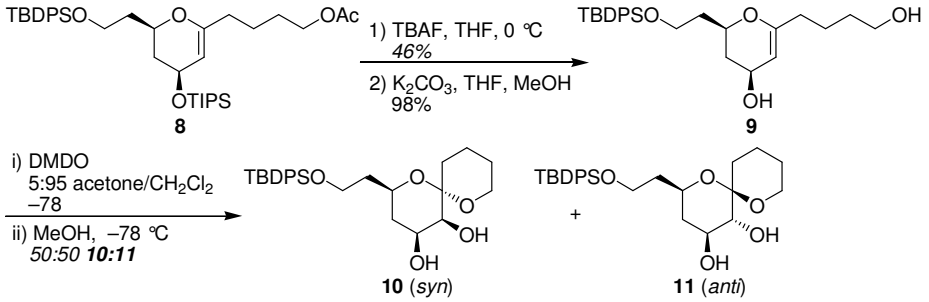


Figure 3.3. *syn*-Epoxidation and spirocyclization of *C*1-alkylglycal **9**

An alternate approach to *syn*-epoxidation developed by Chiappe involves hydroxyl-directed epoxidation via the *m*-CPBA-KF (Camps) complex.[12-14] The presence of KF in the reaction mixture causes precipitation of the *m*-chlorobenzoic acid as it is produced. Although other acid-labile epoxides have been shown to be stable under these conditions,[14] our glycal epoxides were degraded to the corresponding benzoate ester. Due to the problems encountered in attempts at *syn*-epoxidation, we chose to only include *anti*-epoxidation in the synthesis of our primary library.

3.3. Spirocyclization of C1-Substituted Glycal Epoxides with Inversion of Configuration

With effective *anti*-epoxidation conditions in hand, we then turned to the development of stereoselective spirocyclization reactions. In the *threo* series, the inversion spiroketal is usually less thermodynamically stable than the corresponding retention spiroketal, due to double anomeric stabilization in the retention product. Therefore, in most cases, spirocyclization of a *C*1-substituted *threo*-glycal epoxide (**2a,b,d–f**) with TsOH results in exclusive formation of the retention product (**4a,b,d–f**). A procedure for spirocyclization with inversion of configuration regardless of thermodynamic stability evolved from an attempt to form the methyl glycoside **12a** in a control experiment. Justin Potuzak found that addition of a large excess of MeOH to glycal epoxide **2a** generated inversion spiroketal **3a** as the major product, instead of the expected methyl glycoside (Figure 3.4).[1]

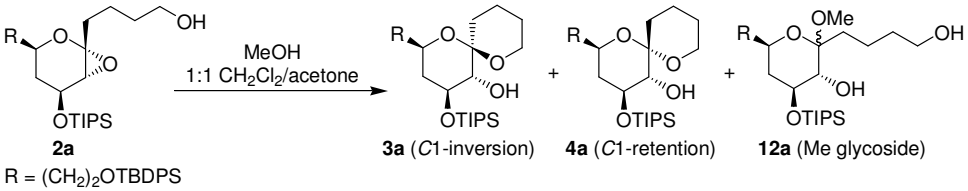


Figure 3.4. MeOH-induced spirocyclization. Optimized conditions yield 92:0:8 **3a**:**4a**:**12a**.

After optimization, we showed that the conditions are also effective for our other glycal epoxide substrates (Figure 3.5). Although most of the *C*1-inversion spiroketals in the *erythro* series can be accessed through thermodynamic equilibration with TsOH (**3h,i,k–m**), the process is accompanied by desilylation of the *C*3-OH. This presumably occurs due to a directing effect of the neighboring diaxial ring oxygen. However, spirocyclization with MeOH leaves the *C*3-OH protecting group intact, and also provides access to the contrathermodynamic **3j**. Attempted spirocyclizations of

2g,**n** to form seven-membered rings produced only the corresponding methyl glycosides.

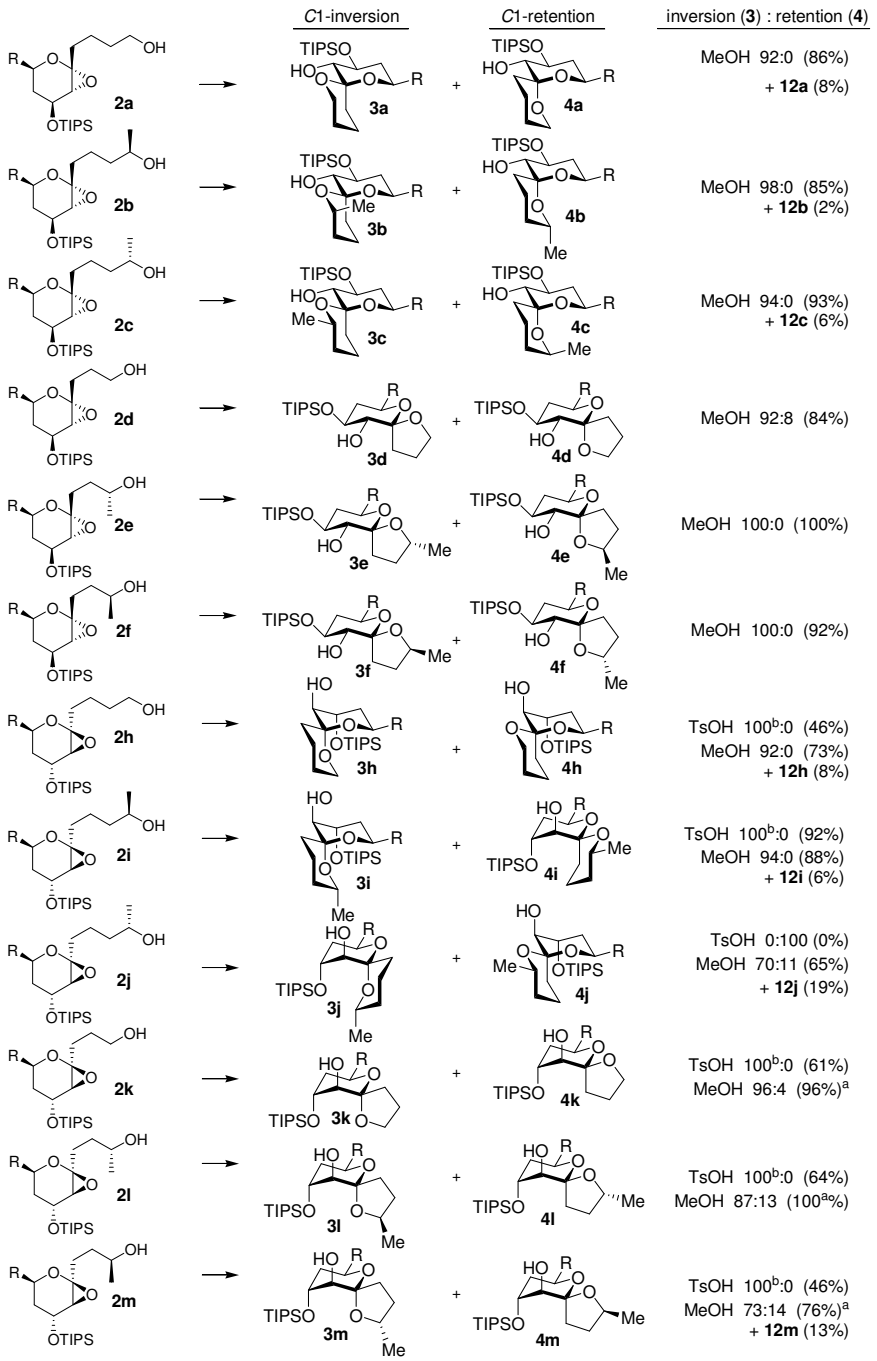


Figure 3.5. MeOH- or TsOH-induced spirocyclization. Isolated yields of the *C*1-inversion products are shown in parentheses. Indicated conformations were determined by NMR or predicted based on conformational analysis. [a] Inseparable mixture of spiroketals **3** and **4**; [b] *C*3-desilylated spiroketal **3**. R = $(CH_2)_2OTBDPS$

3.4. Spirocyclization of C1-Substituted Glycal Epoxides with Retention of Configuration

In the *erythro* series, the retention spiroketal is usually less thermodynamically stable than the corresponding inversion spiroketal, due to double anomeric stabilization in the inversion product. Therefore, in most cases, spirocyclization of a *C*1-substituted *erythro*-glycal epoxide (**2h,i,k–m**) with TsOH results in exclusive formation of the inversion product (**3h,i,k–m**; Figure 3.5).

Although the *erythro*-glycal epoxides should be kinetically predisposed to spirocyclization with inversion of configuration via favorable *trans*-diaxial epoxide opening, we realized that an appropriate multidentate Lewis acid might serve as a tether between the epoxide oxygen and the sidechain hydroxyl of **2h** and drive kinetic epoxide opening with retention of configuration (Figure 3.6). Specifically, coordination of the Lewis acid (**13**) could promote formation of the oxonium intermediate (**14**), then deliver the sidechain hydroxyl to the β-face of the anomeric carbon (**15**). This would lead to the desired end result of epoxide opening with retention of configuration (**4h**), overriding the inherent thermodynamic and kinetic preferences of the system.

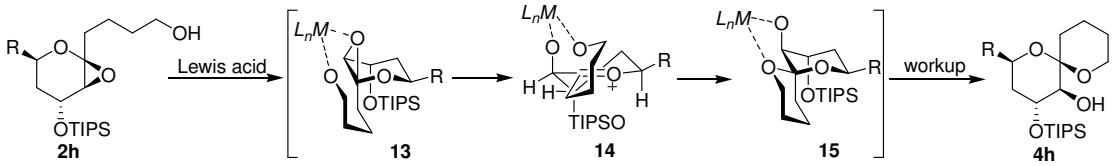
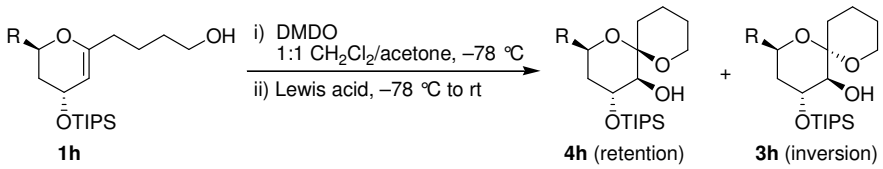


Figure 3.6. Proposed Lewis acid-tethered kinetic spirocyclization of **2h**.
R = $(CH_2)_2$OTBDPS

Therefore, Lewis acid-tethered spirocyclizations were investigated as a means of providing kinetically controlled retention of configuration (Table 3.2). Since isolation of the epoxide formed from *erythro*-glycal **1h** was not possible due to

spontaneous spirocyclization, various multidentate Lewis acids were added directly to the nascent epoxide at –78 °C. After 1 h, the reactions were warmed to rt then quenched immediately to avoid potential equilibration. Although we were concerned that the acetone cosolvent used in the epoxidation reaction might interfere with substrate coordination by the Lewis acids, all of the reagents tested provided an improved ratio of retention (**4h**) to inversion (**3h**). Encouragingly, Ti(O*i*-Pr)$_4$ provided the retention spiroketal **4h** as a single stereoisomer, though large amounts of various overoxidation and glycoside byproducts were also formed.

Table 3.2. Epoxide-opening spirocyclization reactions of **1h** with multidentate Lewis acids



1h **4h** (retention) **3h** (inversion)

Lewis acid	retention (**4h**)	inversion (**3h**)
none	25	75
Yb(OTf)$_3$	43	57
$ZnCl_2$	43	57
$MgCl_2$	60	40
$SnCl_4$	67	33
Ti(O*i*-Pr)$_4$	100	0

Further investigations revealed that warming the reaction to 0 °C immediately after addition of Ti(O*i*-Pr)$_4$ drastically improved the yield (81%). Importantly, exposure of the inversion spiroketal **3h** to the reaction conditions did not result in equilibration to **4h**, demonstrating that Ti(O*i*-Pr)$_4$-mediated spirocyclization is in fact kinetically controlled. Stereoselectivity was reduced when sub-stoichiometric amounts of Ti(O*i*-Pr)$_4$ were used, suggesting that the metal remains coordinated to the product (**15**) until workup.

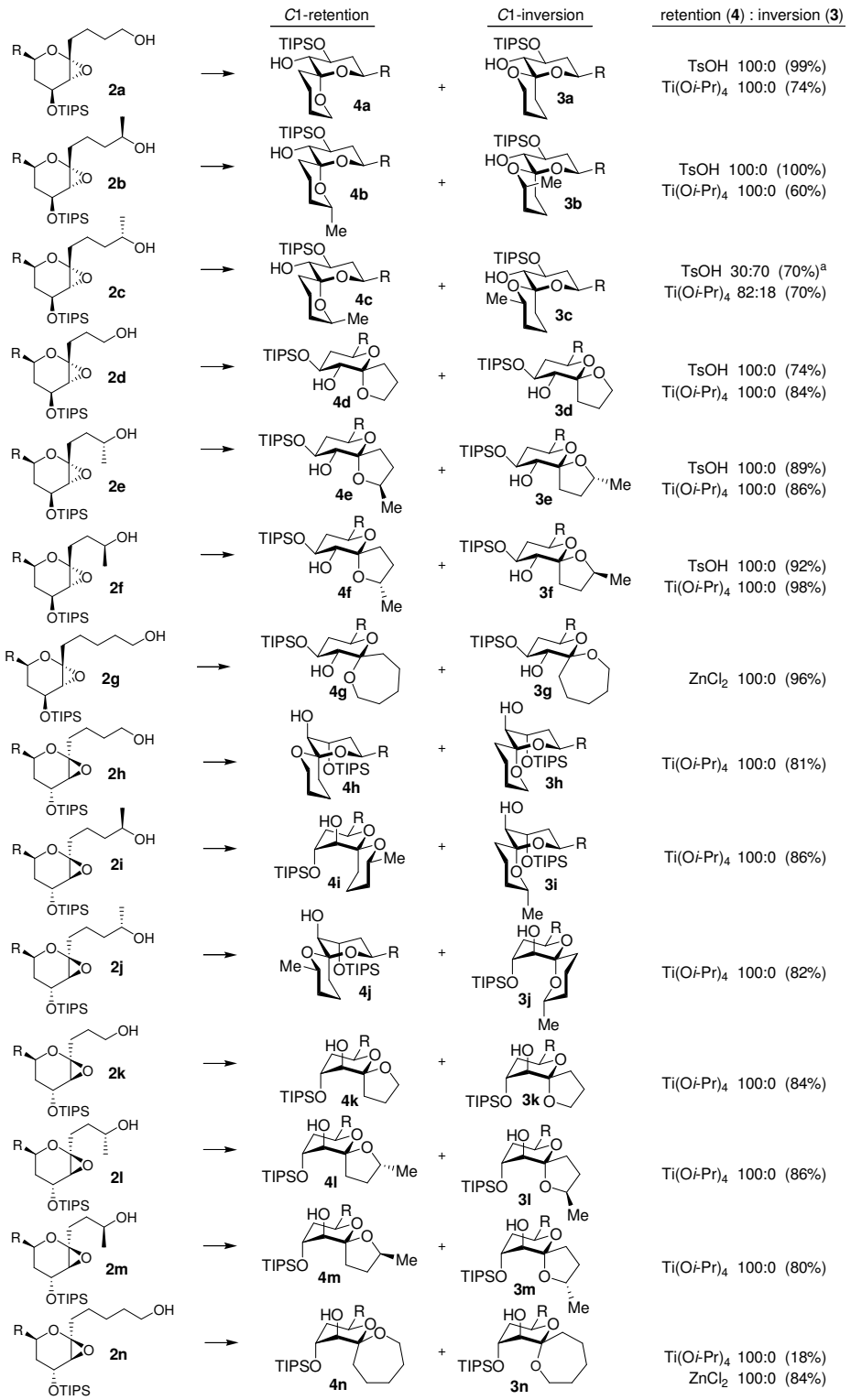


Figure 3.7. Ti(O*i*-Pr)$_4$-, $ZnCl_2$-, or TsOH-induced spirocyclization. Isolated yields of the *C*1-retention products are shown in parentheses. Indicated conformations were determined by NMR or predicted based on conformational analysis. [a] Inseparable mixture of spiroketals **4** and **3**. R = $(CH_2)_2$OTBDPS

The optimized reaction conditions are also effective with our other glycal epoxide substrates, providing five- and six-membered ring retention spiroketals with complete stereocontrol (Figure 3.7). Especially notable is spiroketal **4i**, which has no anomeric stabilizations. These cyclization conditions are also useful for the single *threo*-glycal epoxide substrate (**2c**) for which the retention product is contrathermodynamic. The seven-membered ring retention spiroketals (**4g** and **4n**) can also be accessed using Ti(O*i*-Pr)$_4$ with complete stereocontrol, but yields are low due to competing formation of the isopropyl glycoside **16** (Figure 3.8).

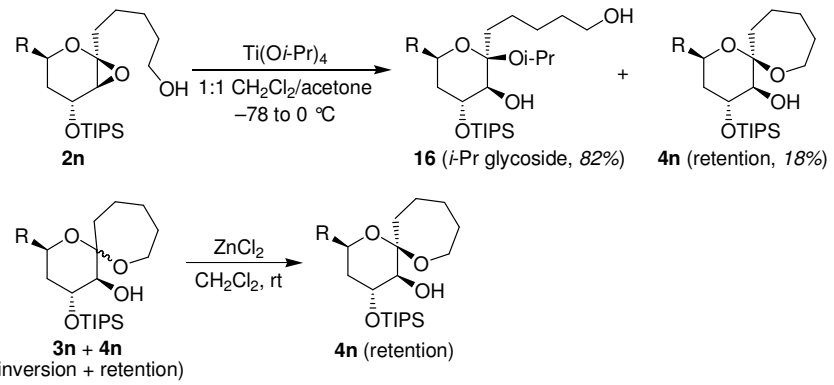


Figure 3.8. Ti(O*i*-Pr)$_4$-mediated reaction of glycal epoxide **2n** and $ZnCl_2$-mediated equilibration of spiroketals **3n + 4n**. R = $(CH_2)_2$OTBDPS

To address this problem, a related reaction using $ZnCl_2$ that provides retention spiroketals through thermodynamic rather than kinetic chelation control was developed. Although the stabilization provided by chelation of the metal is not enough to overcome the inherent thermodynamic stability of all of the inversion spiroketals in the *erythro* series, we have found that the $ZnCl_2$ conditions are particularly useful for forming seven-membered rings. Namely, exposure of inversion/retention spiroketal mixture **3n/4n** to $ZnCl_2$ results in complete equilibration to **4n**. Similar results were obtained for the analogous *threo* spiroketals **3g/4g**. This result is especially valuable

since equilibration of **3g/4g** with TsOH results in the formation of spiroketal **20** instead of the expected retention spiroketal **4g**. A potential mechanism for this reaction is shown in Figure 3.9. After treatment of **3g/4g** with TsOH, the oxonium ion formed (**17**) could be quenched through formation of glycal **18**. This glycal could then undergo elimination at the *C*3 position (**19**), followed by spirocyclization and tautomerization to produce the observed product **20**. This ketone product was only observed in the 6,7-spiroketal series, presumably because, after initial oxonium formation, reclosure of the seven-membered ring is slower than the competing reaction pathway. An analogous product was obtained from TsOH treatment of the *erythro*-6,7-spiroketals **3n/4n**.

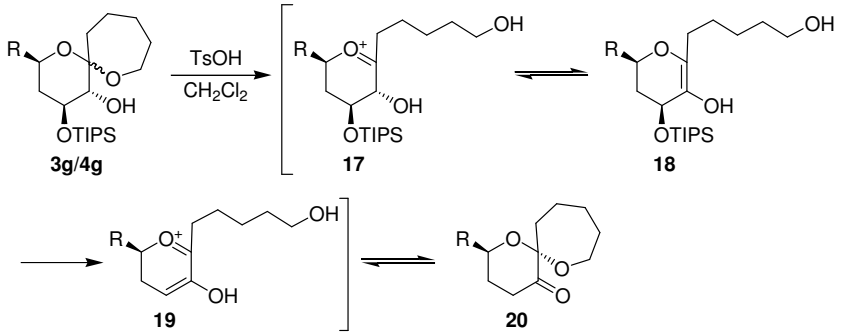


Figure 3.9. Potential mechanism for formation of **20** from TsOH-promoted reaction of 6,7-spiroketal mixture **3g/4g**

3.5. Experimental Section

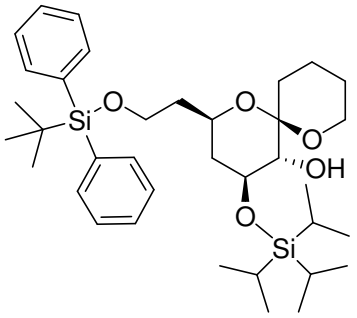
Materials and Methods:

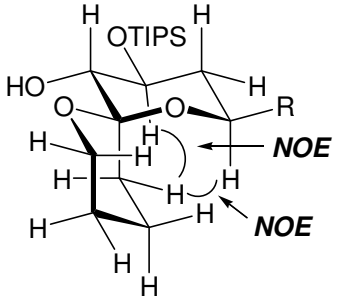
See Section 2.6.

Spirocyclization with inversion of configuration:

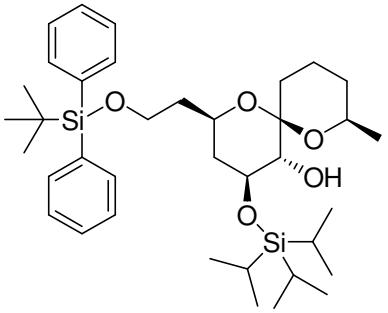
Spiroketals **3a–3f** were synthesized and characterized by Justin Potuzak.

General procedure for epoxidation and methanol-induced spirocyclization:
The glycal alcohol (**1a–n**, 1.0 equiv) was dissolved in CH_2Cl_2 (final ratio 1:1 acetone/CH_2Cl_2) and cooled to –63 °C. DMDO (0.092 M in acetone, 1.2 equiv) was added, and the mixture was stirred at –63 °C. After 20 min, MeOH (5 volumes) was added rapidly via syringe, and stirring continued at –63 °C for 1 h. Warming to rt, evaporation of the solvent by rotary evaporation, and silica flash chromatography provided the "inversion" spiroketals **3a–f**,**h–m**.

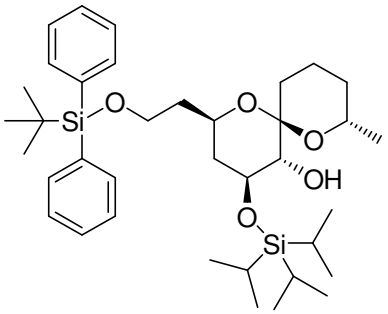




(+)-(2*R*,4*S*,5*R*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (3a). White solid (8.6 mg, 86%). **TLC**: R_f 0.37 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +13° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3486, 2942, 2863, 1465, 1428, 1384, 1361, 1252, 1184, 1093, 999, 883, 821, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 3.97-3.68 (m, 6H), 3.23 (dd, 1H, *J* = 9.2, 1.5), 2.35 (d, 1H, *J* = 1.8), 1.90-1.41 (m, 10H), 1.06 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.5. 133.2, 129.6, 127.6, 99.1, 79.5,70.8, 65.8, 62.1, 60.3, 40.7, 38.7, 26.8, 25.2, 22.6, 19.2, 18.1, 17.5, 12.5. **ESI-MS** *m/z*: (pos) 649.5 $[M+Na]^+$; (neg) 625.4 $[M–H]^-$, 661.5 $[M+Cl]^-$.

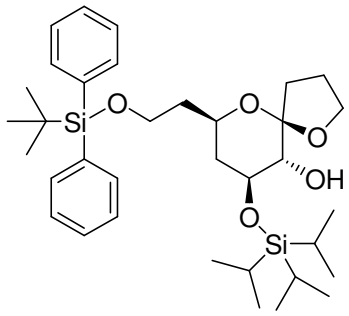


(+)-(2*R*,4*S*,5*R*,6*R*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (3b). Clear oil (8.7 mg, 85%). **TLC**: R_f 0.41 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +28° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3460, 2936, 2863, 1464, 1428, 1381, 1250, 1109, 1014, 967, 883, 822, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.12 (m, 1H), 3.88–3.80 (m, 2H), 3.77–3.70 (m, 2H), 3.29 (dd, 1H, *J* = 9.1, 1.7), 2.37 (d, 1H, *J* = 1.8), 1.93-1.43 (m, 10H), 1.20 (d, 3H, *J* = 6.5), 1.05 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.5, 133.9, 129.6, 127.6, 100.8, 80.1, 71.3, 69.5, 66.1, 60.5, 40.5, 38.7, 29.6, 26.9, 22.4, 21.6, 19.2, 18.1, 14.2, 12.6. **ESI-MS** *m/z*: (pos) 663.5 $[M+Na]^+$; (neg) 639.2 $[M-H]^-$, 675.4 $[M+Cl]^-$.

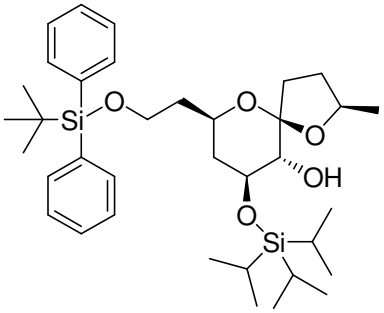


(+)-(2*R*,4*S*,5*R*,6*R*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (3c). Clear oil (9.5 mg, 93%). **TLC**: R_f 0.44 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +11° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3476, 2938, 2864, 1464, 1428, 1383, 1251, 1106, 1090, 1006, 968, 882, 823,

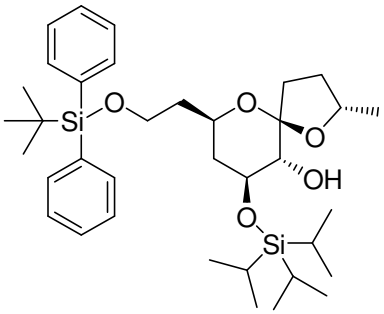
738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.02 (m, 1H), 3.86 (m, 2H), 3.75 (m, 1H), 3.68 (m, 1H), 3.24 (dd, 1H, *J* = 9.2, 1.8), 2.36 (d, 1H, *J* = 1.9), 1.89 (m, 1H), 1.80 (m, 1H), 1.74–1.43 (m, 8H), 1.14 (d, 3H, *J* = 6.3), 1.06 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.5, 133.9, 129.6, 127.6, 99.7, 79.5, 70.8, 67.2, 65.8, 60.3, 40.6, 38.7, 32.8, 30.9, 26.8, 22.1, 19.2, 18.1, 17.7, 12.5. **ESI-MS** *m/z*: (pos) 663.4 $[M+Na]^+$; (neg) 639.3 $[M-H]^-$.



(+)-(2*R*,4*S*,5*R*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (3d). Clear oil (8.6 mg, 84%). **TLC**: R_f 0.39 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ +17° (*c* 0.86, $CDCl_3$). **IR** (NaCl, film): 3479, 2942, 2864, 1463, 1428, 1388, 1248, 1111, 1093, 1068, 998, 883, 822, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 3.99–3.68 (m, 6H), 3.49 (dd, 1H, *J* = 9.3, 1.9), 2.34 (d, 1H, *J* = 2.0), 2.08 (m, 1H), 1.96–1.69 (m, 7H), 1.06 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.5, 133.8, 129.6, 127.6, 109.3, 76.8 (obsc), 72.3, 68.3, 66.7, 60.0, 40.4, 38.4, 27.0, 26.8, 25.0, 19.2, 18.1, 12.5. **ESI-MS** *m/z*: (pos) 635.4 $[M+Na]^+$; (neg) 611.3 $[M-H]^-$, 647.5 $[M+Cl]^-$.

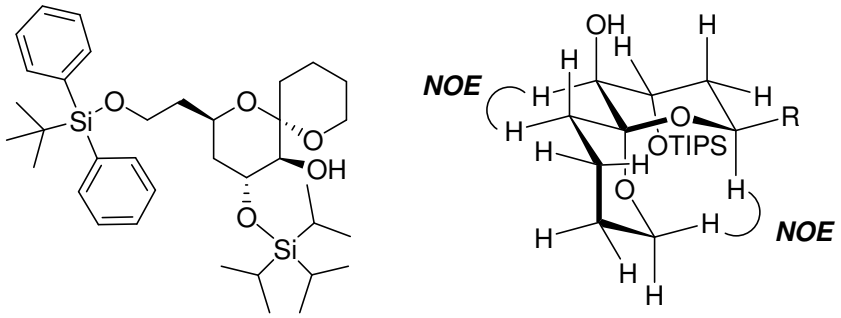


(+)-(2*R*,4*S*,5*R*,6*R*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (3e). Clear oil (10 mg, 100%). **TLC**: R_f 0.47 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +15° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3466, 2942, 2864, 1462, 1428, 1381, 1247, 1112, 1094, 996, 882, 822, 736, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.21 (m, 1H), 3.84 (m, 1H), 3.71 (m, 3H), 3.49 (dd, 1H, *J* = 9.3, 1.5), 2.37 (d, 1H, *J* = 1.9), 2.08–1.43 (m, 8H), 1.28 (d, 3H, *J* = 6.2), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.9, 129.6, 127.6, 109.3, 77.1 (obsc), 76.9 (obsc), 72.2, 66.9, 60.2, 40.4, 38.3, 31.9, 26.8, 26.7, 22.4, 19.2, 18.1, 12.5. **ESI-MS** *m/z*: (pos) 649.5 $[M+Na]^+$; (neg) 625.3 $[M–H]^–$, 661.4 ($[M+Cl]^–$.

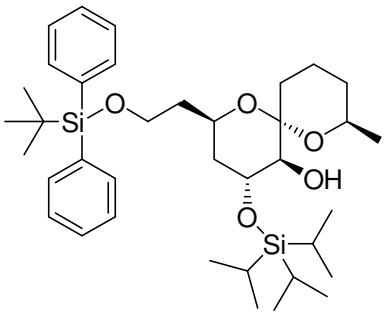


(+)-(2*R*,4*S*,5*R*,6*R*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (3f). Clear oil (9.5 mg, 92%). $[\alpha]_D^{25}$ = +19° (*c* 0.95, $CDCl_3$). **TLC**: R_f 0.53 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3482, 2942, 2864, 1463, 1428, 1388, 1247, 1111, 1081, 1008, 882, 822, 737, 701.

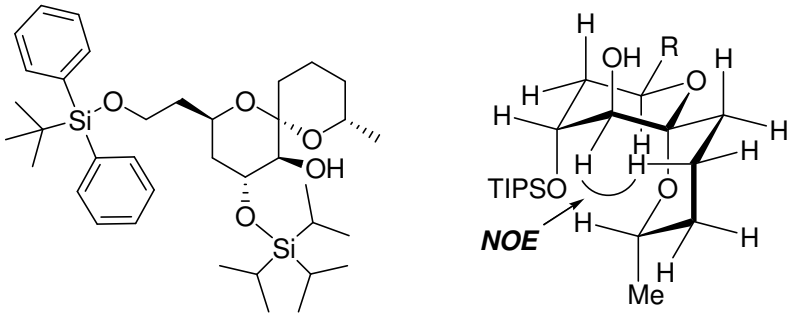
^{1}H-NMR (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.26(m, 1H), 3.85 (m, 1H), 3.71 (m, 3H), 3.43 (dd, 1H, *J* = 9.2, 2.0), 2.32 (d, 1H, *J* = 2.0), 2.18 (m, 1H), 2.02 (m, 1H), 1.89–1.70 (m, 4H), 1.47 (m, 2H), 1.26 (d, 3H, *J* = 6.1), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.8, 129.6, 127.6, 109.4, 76.8 (obsc), 75.2, 72.2, 66.1, 60.0, 40.5, 38.3, 33.1, 28.4, 26.8, 20.5, 19.2, 18.1, 12.5. **ESI-MS** *m/z*: (pos) 649.5 $[M+Na]^+$; (neg) 625.3 $[M–H]^–$, 661.5 $[M+Cl]^–$.



(+)-(2*R*,4*R*,5*S*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (3h). Clear oil (15 mg, 73%). **TLC**: R_f 0.27 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +34 ° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 3409, 2930, 2859, 1462, 1426, 1110, 1080, 998, 886, 703. **^{1}H-NMR** (400 MHz, C_6D_6): δ 7.79 (m, 4H), 7.22 (m, 6H), 4.51 (m, 1H), 4.09 (m, 2H), 3.90–3.43 (m, 2H), 3.58 (dd, 1H, *J* = 11.3, 3.8), 3.49 (dd, 1H, *J* = 7.8, 3.0), 1.90–1.79 (m, 2H), 1.77–1.62 (m, 3H), 1.55 (m, 1H), 1.49–1.33 (m, 3H), 1.23–1.03 (m, 31H). **^{13}C-NMR** (100 MHz, C_6D_6): δ 136.4, 136.3, 134.8, 134.7, 130.3, 98.2, 73.0, 71.0, 60.9, 60.8, 39.8, 35.8, 32.5, 27.5, 25.9, 19.8, 19.3, 18.7, 13.0. **ESI-MS** *m/z*: (pos) 627.6 $[M+H]^+$, 649.4 $[M+Na]^+$; (neg) 661.3 $[M+Cl]^–$.

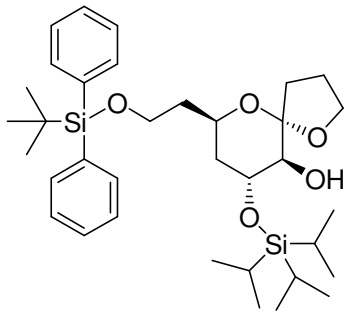


(+)-(2*R*,4*R*,5*S*,6*S*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (3i). Clear oil (14 mg, 88%). **TLC:** R_f 0.35 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +26° (*c* 1.0, $CHCl_3$). **IR** (NaCl, film): 3448, 2931, 2861, 1467, 1425, 1384, 1190, 1108, 997, 732. **^{1}H-NMR** (500 MHz): δ 7.67 (m, 4H), 7.40 (m, 6H), 4.32 (m, 1H), 4.03 (m, 1H), 3.92 (m, 1H), 3.78–3.71(m, 2H), 3.36 (dd, 1H, *J* = 8.0, 3.3), 1.76–1.66 (m, 5H), 1.64 (d, 1H, *J* = 8.0), 1.59 (m, 1H), 1.49 (m, 1H), 1.36 (m, 1H), 1.15 (m, 2H), 1.07–1.02 (m, 33H). **^{13}C-NMR** (125 MHz): δ 135.6 (Ph_a), 135.5 (Ph_a'), 134.1 (Ph_b), 133.9 (Ph_b'), 129.5, 127.6, 98.1, 72.6, 69.9, 65.5, 60.3, 60.1, 39.1, 35.4, 32.6, 31.2, 26.8, 22.1, 19.1, 18.8, 18.1, 12.2. **ESI-MS** *m/z*: (pos) 641.6 $[M+H]^+$, 663.5 $[M+Na]^+$; (neg) 639.5 $[M–H]^–$, 675.5 $[M+Cl]^–$.

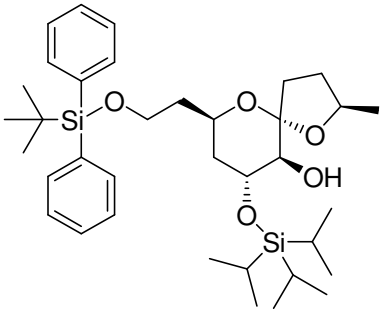


(+)-(2*R*,4*R*,5*S*,6*S*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (3j). Clear oil (7.0 mg, 65%). **TLC:** R_f 0.35 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +6.8° (*c* 0.86, $CHCl_3$). **IR** (NaCl, film): 3462, 2934, 2862, 1465, 1381, 1105, 1003. **^{1}H-NMR** (500 MHz): δ 7.70 (m,

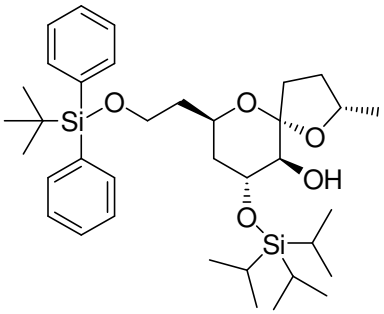
4H), 7.40 (m, 6H), 4.71 (m, 1H), 4.11 (m, 1H), 3.86–3.78 (m, 3H), 3.69 (m, 1H), 1.99 (m, 1H), 1.76–1.60 (m, 8H), 1.32 (m, 2H), 1.15 (d, 3H, J = 6.2), 1.09 (m, 21H), 1.02 (m, 9H). **^{13}C-NMR** (125 MHz): δ 135.8 (Ph_a), 135.6 (Ph_a'), 134.0 (Ph_b), 133.8 (Ph_b'), 129.4, 127.6 (Ph_c), 127.5 (Ph_c'), 98.8, 69.9, 69.2, 66.9, 61.6, 59.8, 38.9, 34.9, 32.1, 31.6, 26.8, 22.0, 18.8, 18.2, 18.1, 12.4. **ESI-MS** *m/z*: (pos) 641.8 $[M+H]^+$, 663.5 $[M+Na]^+$; (neg) 639.4 $[M–H]^–$, 675.4 $[M+Cl]^–$.



(+)-(2*R*,4*R*,5*S*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (3k). MeOH was added before DMDO addition (–78 °C). Clear oil (5.0 mg, 96%, 96:4 **3k/4k**). **TLC:** R_f 0.22 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +27° (*c* 0.49, $CHCl_3$). **IR** (NaCl, film): 3451, 2941, 2864, 1463, 1428, 1112, 1078, 999, 882, 822, 735, 701. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.38 (m, 6H), 4.43 (m, 1H), 4.06 (m, 1H), 3.85 (m, 2H), 3.79 (m, 1H), 3.69 (m, 1H), 3.45 (dd, 1H, J = 8.5, 3.4), 1.91–1.62 (m, 8H), 1.54 (m, 1H), 1.09–1.01 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.1, 129.5, 127.5, 107.4, 72.3, 69.6, 68.0, 61.9, 60.3, 38.7, 36.2, 35.1, 27.0, 22.6, 19.2, 18.0, 12.3. **ESI-MS** *m/z*: (pos) 613.5 $[M+H]^+$, 635.3 $[M+Na]^+$; (neg) 611.2 $[M–H]^–$, 647.2 $[M+Cl]^–$.



(2*R*,4*R*,5*S*,6*S*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (3l). MeOH was added before DMDO addition (–78 °C). Clear oil (5.0 mg, 100%, 87:13 **3l/4l**). **TLC:** R_f 0.24 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3439, 2941, 2864, 1462, 1428, 1112, 1086, 1006, 882, 822, 731, 701. **^{1}H-NMR** (500 MHz): δ 7.67 (m, 4H), 7.39 (m, 6H), 4.48 (m, 1H), 4.20 (m, 1H), 4.06 (m, 1H), 3.79 (m, 1H), 3.69 (m, 1H), 3.42 (dd, 1H, J = 8.8, 3.4), 2.02–1.89 (m, 2H), 1.85 (m, 1H), 1.78–1.60 (m, 5H), 1.30 (m, 1H), 1.15 (d, 1H, J = 6.2), 1.09–1.02 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.1, 129.5, 127.5, 107.4, 75.1, 72.4, 69.6, 61.6, 60.2, 38.7, 36.1, 35.1, 30.2, 26.8, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z*: (pos) 627.6 $[M+H]^+$, 649.4 $[M+Na]^+$; (neg) 625.3 $[M–H]^–$, 661.3 $[M+Cl]^–$.



(2*R*,4*R*,5*S*,6*S*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (3m). MeOH was added before DMDO addition (–78 °C). Clear oil (5.0 mg, 76%, 73:14 **3m/4m**). **TLC:** R_f 0.26 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3450, 2941, 2864, 1462, 1427, 1382, 1245, 112, 1085, 998, 882, 822,

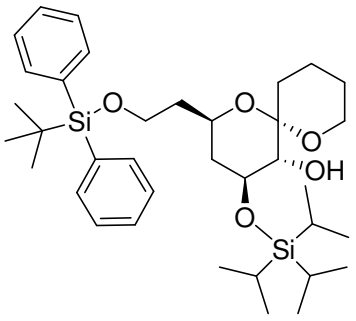
734, 701. **^{1}H-NMR** (500 MHz): δ 7.68 (m, 4H), 7.39 (m, 6H), 4.46 (m, 1H), 4.20 (m, 1H), 4.05 (m, 1H), 3.79–3.66 (m, 2H), 3.38 (dd, 1H, *J* = 8.9, 3.4), 2.02–1.80 (m, 3H), 1.73–1.56 (m, 5H), 1.54 (m, 1H), 1.18 (d, 3H, *J* = 5.1), 1.10–1.01 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 134.1, 129.4, 127.5, 107.2, 77.8, 72.5, 69.6, 61.9, 60.6, 39.0, 37.8, 35.1, 30.9, 26.8, 23.0, 18.1, 18.0, 12.3. **ESI-MS** *m/z*: (pos) 649.5 $[M+Na]^+$; (neg) 625.4 $[M–H]^–$, 661.2 $[M+Cl]^–$.

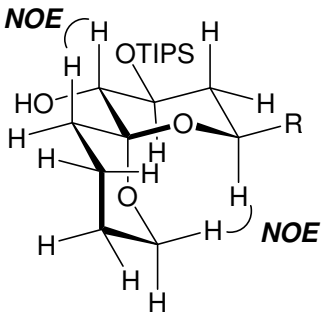
Spirocyclization with retention of configuration:

Spiroketals **4a–f** were synthesized and characterized by Justin Potuzak.

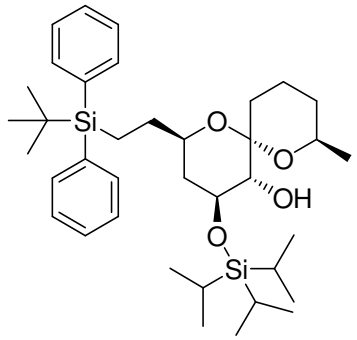
General procedure for epoxidation and Ti(Oi-Pr)$_4$-induced spirocyclization:

The glycal alcohol (**1a–n**, 1.0 equiv) was dissolved in CH_2Cl_2 (final ratio 1:1 acetone/CH_2Cl_2) and cooled to –78 °C. DMDO (0.03 M in acetone, 1.2 equiv) was added, and the mixture was stirred at –78 °C. After 10 min, Ti(O*i*Pr)$_4$ (2.0 equiv) was added via syringe. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The cold reaction mixture was quenched with sat'd aq $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, then the combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated by rotary evaporation. Silica flash chromatography provided the "retention" spiroketals **4a–f, h–m**.



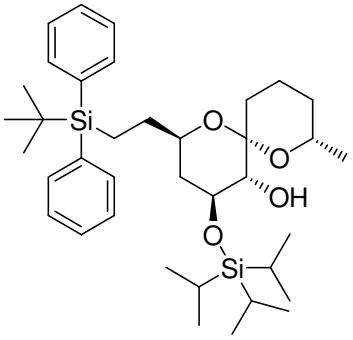


(+)-(2*R*,4*S*,5*R*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (4a). Clear oil (9.9 mg, 74%). **TLC**: R_f 0.44 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +40° (*c* 0.99, $CDCl_3$). **IR** (NaCl, film): 3568, 2939, 2863, 1465, 1429, 1385, 1258, 1106, 1067, 997, 934, 883, 823, 738, 702, 613, 503, 463. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.02 (m, 1H), 3.89 (m, 2H), 3.76 (m, 1H), 3.68 (m, 1H), 3.60 (m, 1H), 3.07 (dd, 1H, *J* = 8.7, 6.3), 2.18 (d, 1H, *J* = 6.3), 2.02 (m, 1H), 1.93 (m, 1H), 1.71 (m, 3H), 1.57 (m, 2H), 1.41 (m, 3H), 1.06 (m, 30H). **^{13}C-NMR** (100 MHz): δ 135.5, 133.9, 129.6, 127.6, 97.7, 78.6, 70.9, 63.6, 60.8, 60.3, 40.8, 38.4, 30.9, 26.9, 24.9, 19.2, 18.3, 18.2, 12.6. **ESI-MS** *m/z* (rel int): (pos) 649.5 ($[M+Na]^+$, 100); (neg) 625.5 ($[M–H]^-$, 100).

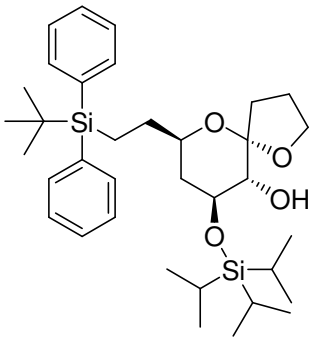


(+)-(2*R*,4*S*,5*R*,6*S*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (4b). Clear oil (11 mg, 60%). **TLC**: R_f 0.44 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +40° (*c* 1.1, $CDCl_3$). **IR** (NaCl, film): 3568, 2936, 2863, 1464, 1429, 1385, 1257, 1187, 1105, 1080, 1002, 941, 882, 820, 737, 702, 613, 503. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.04 (m, 1H), 3.89 (m, 2H), 3.78-3.71 (m, 2H), 3.06 (m, 1H), 2.10 (d, 1H, *J* = 7.7), 1.94 (m, 2H), 1.80–1.68 (m, 4H), 1.57–1.37 (m, 4H), 1.06 (m, 33H). **^{13}C-NMR** (100 MHz): δ 135.5, 133.9, 129.6, 127.6, 98.4, 78.3, 70.9, 65.9, 63.5, 60.2, 40.9, 38.5, 32.4,

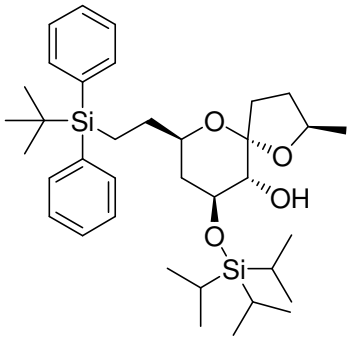
30.2, 26.8, 21.8, 19.2, 18.7, 18.2, 12.6. **ESI-MS** *m/z* (rel int): (pos) 663.5 ($[M+Na]^+$, 100); (neg) 639.3 ($[M–H]^-$, 100).



(+)-(2*R*,4*S*,5*R*,6*S*,8S)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (4c). Clear oil (3.6 mg, 70%). **TLC:** *Rf* 0.44 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +27° (*c* 0.36, $CHCl_3$). **IR** (NaCl, film): 3568, 2936, 2863, 1464, 1429,1385, 1257, 1187, 1105, 1080, 1002, 941, 882, 820, 737, 702, 613, 503. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.12 (m, 1H), 4.04 (m, 1H), 3.96 (m, 1H), 3.73 (m, 2H), 2.99 (dd, 1H, *J* = 8.7, 7.5), 2.11 (d, 1H, *J* = 7.5), 2.05 (m, 1H), 1.95 (m, 1H), 1.90–1.79 (m, 2H), 1.70–1.62 (m, 2H), 1.53–1.44 (m, 3H), 1.38–1.34 (m, 1H), 1.25 (d, 3H, *J* = 6.7), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.9, 129.6, 127.6, 98.8, 79.0, 70.7, 69.4, 64.9, 60.7, 40.5, 38.4, 30.8, 29.4, 26.8, 21.2, 19.2, 18.2, 14.0, 12.6. **ESI-MS** *m/z* (rel int): pos 663.5 ($[M+Na]^+$, 100); neg 639.3 ($[M–H]^-$, 100).

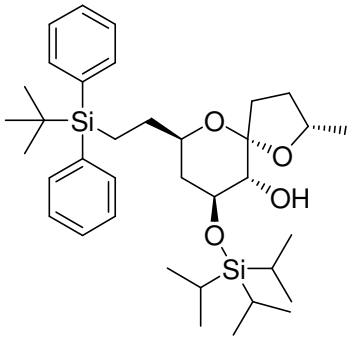


(+)-(2*R*,4*S*,5*R*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (4d). Clear oil (7.6 mg, 84%). **TLC**: R_f 0.57 (4:1 hexanes/EtOAc). **[α]$_D^{25}$**: +39° (*c* 0.76, $CDCl_3$). **IR** (NaCl, film): 3568, 2942, 2864, 1463, 1428, 1389, 1258, 1112, 1092, 1013, 882, 823, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 3.99–3.91 (m, 3H), 3.84 (m, 1H), 3.72 (m, 2H), 3.39 (dd, 1H, *J* = 8.7, 7.4), 2.21 (m, 1H), 1.99 (d, 1H, *J* = 7.2), 1.95–1.65 (m, 6H), 1.42 (m, 1H), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.0, 129.6, 127.6, 107.6, 75.6, 72.0, 68.1, 65.0, 60.5, 40.8, 38.3, 34.0, 26.8, 23.8, 19.2, 18.2, 12.6. **ESI-MS** *m/z* (rel int): (pos) 635.3 ([M+Na]$^+$, 100); (neg) 611.1 ([M–H]$^-$, 20), 647.2 ([M+Cl]$^-$, 100).

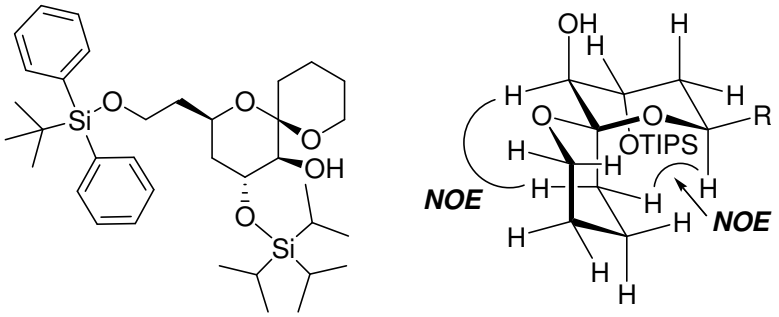


(+)-(2*R*,4*S*,5*R*,6*S*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (4e). Clear oil (9.2 mg, 86%). **TLC**: R_f 0.50 (4:1 hexanes/EtOAc). **[α]$_D^{25}$**: +37° (*c* 0.92, $CDCl_3$). **IR** (NaCl, film): 3565, 2942, 2864, 1463, 1428, 1388, 1259, 1112, 1095, 1071, 1013, 926, 882, 822, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.17 (q, 1H, *J* = 6.5), 4.00–3.87 (m, 2H), 3.78–3.69 (m, 2H), 3.30 (t, 1H, *J* = 8.9), 2.27 (m, 1H), 2.05–1.65 (m, 7H), 1.38 (m, 1H), 1.21 (d, 3H, *J* = 6.1), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.0, 129.5, 127.6, 107.9, 75.7, 75.1, 72.1, 64.9, 60.4, 40.9, 38.3,

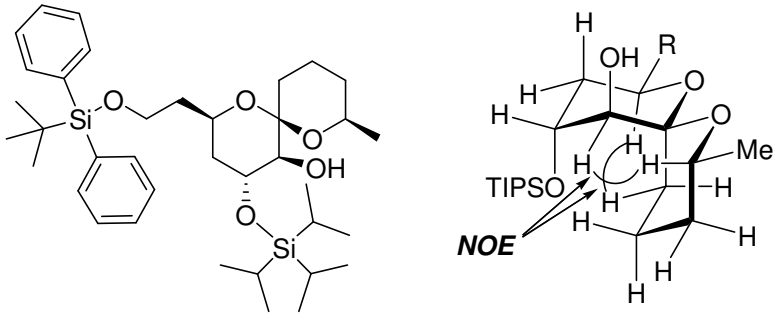
34.5, 31.7, 26.8, 20.7, 19.2, 18.2, 12.6. **ESI-MS** *m/z* (rel int): (pos) 649.4 ($[M+Na]^+$, 100); (neg) 625.2 ($[M–H]^-$, 20), 661.3 ($[M+Cl]^-$, 100).



(+)-(2*R*,4*S*,5*R*,6*S*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (4f). Clear oil (9.5 mg, 98%). **TLC**: R_f 0.57 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +40° (*c* 0.95, $CDCl_3$). **IR** (NaCl, film): 3562, 2942, 2864, 1463, 1428, 1388, 1258, 1112, 1095, 1012, 997, 825, 882, 822, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.28 (m, 1H), 3.98 (m, 1H), 3.91 (m, 1H), 3.73 (t, 2H, *J* = 6.5), 3.31 (dd, 1H, *J* = 8.6, 7.9), 2.25 (m, 1H), 1.99–1.90 (m, 3H), 1.83 (m, 1H), 1.74 (m, 1H), 1.63 (m, 2H), 1.39 (m, 1H), 1.21 (d, 3H, *J* = 6.2), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.8, 134.0, 127.6, 107.7, 78.3, 75.6, 72.1, 64.7, 60.8, 40.7, 38.5, 34.9, 31.5, 26.8, 23.3, 19.2, 18.2, 12.6. **ESI-MS** *m/z* (rel int): (pos) 649.4 ($[M+Na]^+$, 100); (neg) 625.2 ($[M–H]^-$, 20), 661.2 ($[M+Cl]^-$, 100).

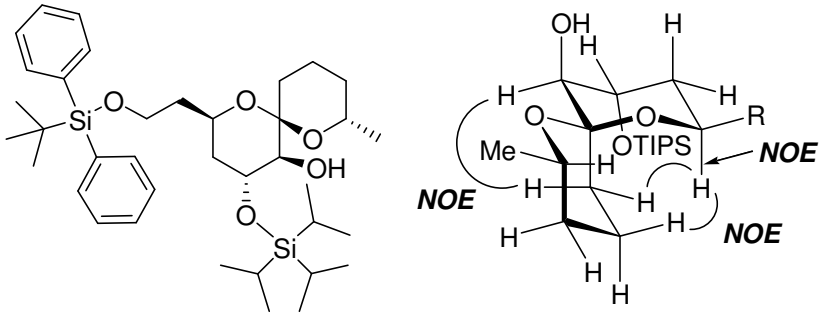


(–)-(2*R*,4*R*,5*S*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (4h). Clear oil (5.0 mg, 81%). **TLC:** R_f 0.45 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –3.9° (*c* 0.60, $CHCl_3$). **IR** (NaCl, film): 2938, 2859, 1463, 1220, 1090, 1005, 886, 734, 705. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.39 (m, 6H), 4.21-4.12 (m, 2H), 4.03-3.92 (m, 2H), 3.77 (m, 1H), 3.68 (m, 1H), 3.40 (d, 1H, *J* = 2.9), 2.98 (d, 1H, *J* = 1.3), 2.51 (m, 1H), 1.85 (m, 1H), 1.77-1.63 (m, C6), 1.59 (m, 1H), 1.52-1.42 (m, 3H), 1.35 (m, 1H), 1.11-1.00 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 134.0 (Ph), 133.9 (Ph′), 129.6, 129.5, 127.6, 96.7, 72.6, 69.3, 64.1, 61.9, 60.1, 38.8, 34.6, 29.2, 26.8, 25.4, 19.2, 18.1, 18.0, 12.1. **ESI-MS** *m/z* (rel int): (pos) 627.5 ($[M+H]^+$, 30), 649.4 ($[M+Na]^+$, 100), 679.7 ($[M+NH_4]^+$, 30); (neg) 661.3 ($[M+Cl]^-$, 100).

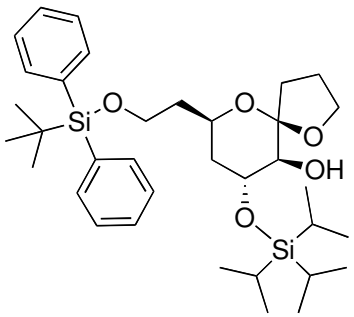


(+)-(2*R*,4*R*,5*S*,6*R*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (4i). Clear oil (8.9 mg, 86%). **TLC**: R_f 0.35 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +11° (*c* 0.52, $CHCl_3$). **IR** (NaCl, film): 2940, 2865, 1462, 1427, 1385, 1227, 1111, 1059, 1047, 1004, 882, 735, 701. **^{1}H-NMR** (500 MHz): δ 7.68 (dd, 2H, *J* = 7.9, 1.4), 7.64 (dd, 2H, *J* = 7.9, 1.4), 7.40 (m, 6H), 4.33–4.26 (m, 2H), 3.91 (m, 1H), 3.83–3.74 (m, 2H), 3.71 (m, 1H), 2.85 (d, 1H, *J* = 2.0), 2.66 (m, 1H), 1.85 (m, 1H), 1.76 (m, 2H), 1.68–1.56 (m, 2H), 1.51 (m, 2H), 1.33–1.25 (m, 2H), 1.24 (d, 3H, *J* = 6.2), 1.15–1.05 (m, 21H), 1.03 (s, 9H). **^{13}C-NMR** (125 MHz): δ 135.6, 134.0, 129.5, 127.6, 99.0, 69.6, 69.4, 66.0, 64.2, 59.9,

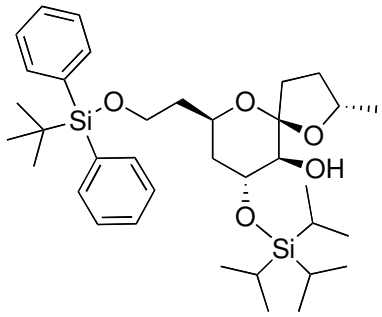
34.0, 31.8, 26.8, 29.8, 22.3, 20.3, 19.2, 18.2, 12.2. **ESI-MS** *m/z* (rel int): (pos) 641.6 ([M+H]$^+$, 5), 663.3 ([M+Na]$^+$, 100); (neg) 639.4 ([M–H]$^-$, 15), 675.3 ([M+Cl]$^-$, 100).



(–)-(2*R*,4*R*,5*S*,6*R*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (4j). Clear oil (4.0 mg, 82%). **TLC:** R_f 0.51 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –4.7° (*c* 0.71, $CHCl_3$). **IR** (NaCl, film): 2934, 2862, 1465, 1384, 1227, 1095, 1007, 881, 737. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.39 (m, 6H), 4.21 (m, 1H), 4.12 (m, 1H), 4.06 (m, 1H), 3.92 (m, 1H), 3.73 (m, 1H), 3.39 (d, 1H, *J* = 3.2), 3.11 (s, 1H), 2.56 (m, 1H), 1.85 (m, 1H), 1.75–1.66 (m, 3H), 1.51–1.43 (m, 2H), 1.24–1.12 (m, 3H), 1.13-1.01 (m, 33H). **^{13}C-NMR** (125 MHz): δ 135.6, 134.1 (Ph), 133.9 (Ph′), 129.5, 127.6, 97.2, 72.7, 69.3, 67.1, 64.0, 60.1, 38.7, 34.6, 33.0, 28.5, 26.8, 22.0, 19.2, 18.3, 18.1, 12.1. **ESI-MS** *m/z* (rel int): (pos) 663.5 ([M+Na]$^+$, 100), 679.7 ([M+K]$^+$, 5); (neg) 639.4 ([M–H]$^-$, 100), 675.4 ([M+Cl]$^-$, 50).

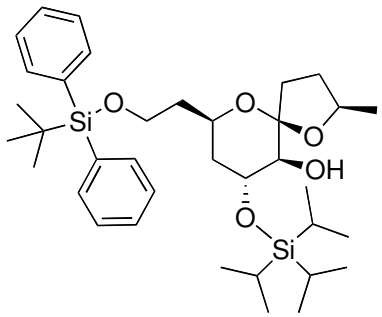


(+)-(2*R*,4*R*,5*S*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.4]decan-5-ol (4k). Clear oil (9.0 mg, 84%). **TLC:** R_f 0.22 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +5.6° (*c* 0.86, $CHCl_3$). **IR** (NaCl, film): 3566, 2942, 2865, 1463, 1427, 1388, 1111, 1083, 998, 823, 736, 701. **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.38 (m, 6H), 4.20 (m, 2H), 3.99 (m, 1H), 3.89-3.78 (m, 2H), 3.69 (m, 1H), 3.50 (m, 1H), 2.63 (d, 1H, *J* = 2.2), 2.32 (m, 1H), 2.03 (m, 1H), 1.90-1.61 (m, 5H), 1.52 (m, 1H), 0.08-1.04 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5 (Ph), 133.9 (Ph′), 129.5, 127.6, 107.0, 73.2, 69.3, 67.5, 65.6, 59.9, 38.6, 34.5, 32.7, 26.8, 25.0, 19.2, 18.1, 12.2. **ESI-MS** *m/z* (rel int): (pos) 635.7 ($[M+Na]^+$, 100); (neg) 611.6 ($[M–H]^-$, 10), 647.7 ($[M+Cl]^-$, 100).



(+)-(2*R*,4*R*,5*S*,6*R*,8*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.4]decan-5-ol (4l). Clear oil (4.0 mg, 80%). **TLC:** R_f 0.39 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +9.2° (*c* 0.41, $CHCl_3$). **IR** (NaCl, film): 2941, 2864, 1463, 1427, 1388, 1111, 1083, 1012, 882, 823, 736, 701. **^{1}H-NMR** (500 MHz): δ 7.68 (m, 4H), 7.39 (m, 6H), 4.29 (m, 1H), 4.20 (m, 2H), 3.89 (m, 1H), 3.69 (m, 1H), 3.47 (m, 1H), 2.70 (d, 1H, *J* = 2.0), 2.21 (m, 1H), 2.09 (m, 1H), 1.84 (m, 1H), 1.76–1.64 (m, 3H), 1.49 (m, 2H), 1.20 (d, 3H, *J* = 6.2), 1.11–0.98 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5 (Ph), 133.9 (Ph′), 129.5, 127.6, 107.0, 74.7, 73.4, 69.3, 64.9, 59.8,

38.5, 34.5, 32.9, 32.6, 26.8, 21.0, 19.1, 18.1, 12.2. **ESI-MS** *m/z* (rel int): (pos) 649.7 ([M+Na]$^+$, 100); (neg) 625.6 ([M–H]$^-$, 20), 661.8 ([M+Cl]$^-$, 100).

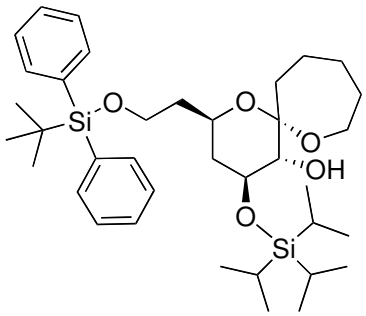


(+)-(2*R*,4*R*,5*S*,6*R*,8*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methyl-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.4]decan-5-ol (4m). Clear oil (4.0 mg, 86%). **TLC:** R_f 0.39 (4:1 hexanes/EtOAc). **[α]$_D^{25}$**: +6.8° (*c* 0.44, $CHCl_3$). **IR** (NaCl, film): 2941, 2865, 1472, 1428, 1388, 1111, 1085, 1005, 954, 882, 823, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.67 (m, 4H), 7.41 (m, 6H), 4.22 (m, 2H), 4.12 (m, 1H), 3.89 (m, 1H), 3.70 (m, 1H), 3.49 (m, 1H), 2.70 (d, 1H, *J* = 1.7), 2.44 (m, 1H), 1.99 (m, 1H), 1.85 (m, 1H), 1.77–1.61 (m, 4H), 1.49 (m, 1H), 1.25 (d, 3H, *J* = 6.1), 1.10–0.97 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.0 (Ph), 133.9 (Ph′), 129.5, 127.6, 106.8, 76.3, 73.3, 69.4, 65.3, 59.9, 38.5, 34.2, 33.3, 32.6, 26.8, 22.5, 19.2, 18.1, 12.2. **ESI-MS** *m/z* (rel int): (pos) 649.7 ([M+Na]$^+$, 100); (neg) 625.7 ([M–H]$^-$, 25), 661.8 ([M+Cl]$^-$, 100).

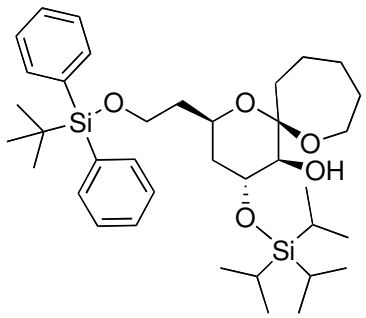
General procedure for epoxidation and $ZnCl_2$-induced spirocyclization and equilibration:

The glycal alcohol (**1g** or **1n**, 1.0 equiv) was dissolved in CH_2Cl_2 (final ratio 1:1 acetone/CH_2Cl_2) and cooled to –78 °C. DMDO (0.030 M in acetone, 1.2 equiv) was added, and the mixture was stirred at –78 °C. After 10 min the reaction was warmed to rt and the solvent was evaporated with a stream of Ar. The residue was dissolved in anhyd CH_2Cl_2 (0.030 M) then $ZnCl_2$ (1.0 M in Et_2O, 1.2 equiv) was added. The

reaction was stirred at rt 2h then quenched with $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, then the combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated by rotary evaporation. Silica flash chromatography provided the "retention" spiroketals **4g,n**.



(+)-(2*R*,4*S*,5*R*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.6]dodecan-5-ol (4g). Clear oil (8.6 mg, 84%). **TLC:** R_f 0.40 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: +43° (*c* 0.86, $CDCl_3$). **IR** (NaCl, film): 3572, 2940, 2864, 1463, 1428, 1389, 1257, 1098, 1053, 966, 883, 822, 738, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 3.99–3.66 (m, 5H), 3.55 (m, 1H), 3.19 (dd, 1H, *J* = 8.5, 7.6), 2.17 (m, 1H), 2.08 (d, 1H, *J* = 7.3), 1.91 (m, 1H), 1.80–1.62 (m, 9H), 1.36 (m, 1H), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.9, 129.6, 127.6, 101.3, 81.5, 71.4, 64.5, 62.1, 60.5, 40.7, 40.6, 38.4, 30.3, 29.5, 26.8, 23.4, 19.2, 18.2, 12.6. **ESI-MS** *m/z*: pos 663.4 $[M+Na]^+$; neg 639.4 $[M–H]^–$, 675.3 $[M+Cl]^–$.



(–)-(2*R*,4*R*,5*S*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.6]dodecan-5-ol (4n). Clear oil (8.7 mg, 84%). **TLC:** R_f 0.38 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$: –4.9° (*c* 0.87, $CHCl_3$). **IR** (NaCl, film): 2928, 2863, 1472, 1428, 1112, 1049, 882, 823, 737, 702. **^{1}H-NMR** (500 MHz): δ 7.67 (ddd, 2H, *J* = 25.1, 8.0, 1.4), 7.42–7.36 (m, 6H), 4.23 (m, 1H), 4.18 (m, 1H), 3.95–3.87 (m, 2H), 3.71 (m, 2H), 3.48 (m, 1H), 3.07 (d, 1H, *J* = 0.85), 2.89 (m, 1H), 1.83–1.72 (m, 3H), 1.71–1.60 (m, 5H), 1.49 (m, 1H), 1.35 (m, 2H), 1.12–1.02 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 134.0 (Ph), 133.9 (Ph′), 129.5, 127.6, 100.9, 70.4, 69.6, 64.1, 63.3, 59.7, 38.8, 34.5, 30.6, 29.9, 26.8, 23.0, 19.2, 18.1, 12.1. **ESI-MS** *m/z*: (pos) 641.5 $[M+H]^+$, 663.3 $[M+Na]^+$; (neg) 639.3 $[M–H]^–$, 675.3 $[M+Cl]^–$.

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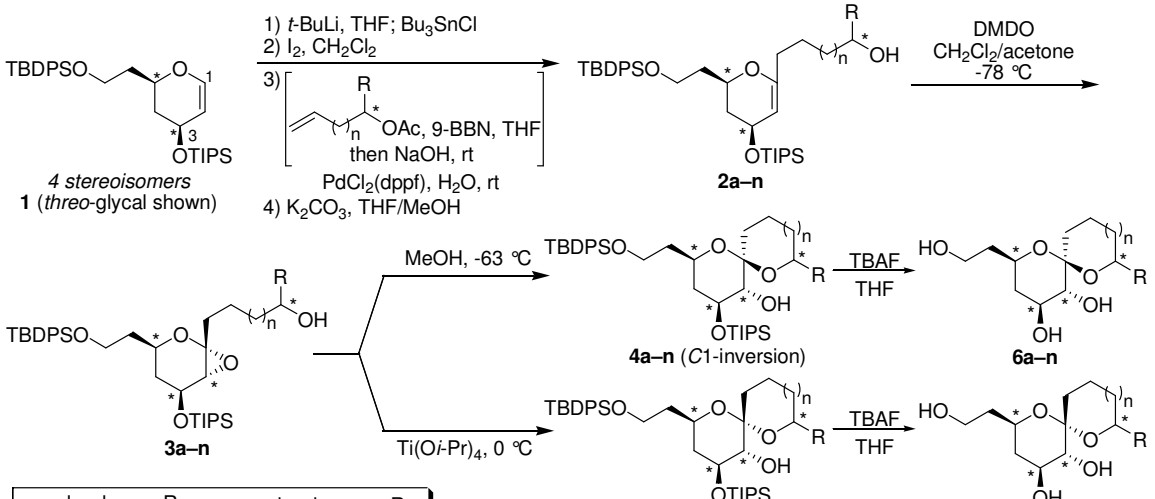
CHAPTER 4

SYNTHESIS AND BIOLOGICAL SCREENING OF A LIBRARY OF STRUCTURALLY AND STEREOCHEMICALLY DIVERSE SPIROKETALS

4.1. Introduction

We used the methodology we developed for *C*1-substituted glycal epoxide synthesis and stereoselective spirocyclization to synthesize a library of 52 stereochemically and structurally diverse spiroketals (Figure 4.1; **6a-f**,**h-m**; **7a–n** plus enantiomers) for evaluation in biological assays. The majority of the spiroketal library was synthesized in solution according to the methods described in Chapters 2–3, then desilylated (**4**→**6** and **5**→**7**) to confer solubility in aqueous media. The remainder of the library was synthesized on solid support, as described in Section 4.2.



glycal	n	R	glycal	n	R
a: *threo*	1	H	**h**: *erythro*	1	H
b: *threo*	1	*R*-Me	**i**: *erythro*	1	*R*-Me
c: *threo*	1	*S*-Me	**j**: *erythro*	1	*S*-Me
d: *threo*	0	H	**k**: *erythro*	0	H
e: *threo*	0	*R*-Me	**l**: *erythro*	0	*R*-Me
f: *threo*	0	*S*-Me	**m**: *erythro*	0	*S*-Me
g: *threo*	2	H	**n**: *erythro*	2	H

Figure 4.1. Synthesis of a library of structurally and stereochemically diverse spiroketals

4.2. Adaptation of Spiroketal Synthesis to Solid Phase

Although the majority of our primary library was synthesized in solution, solid phase conditions that could allow larger spiroketal libraries to be produced more efficiently in the future have been developed (Figure 4.2).

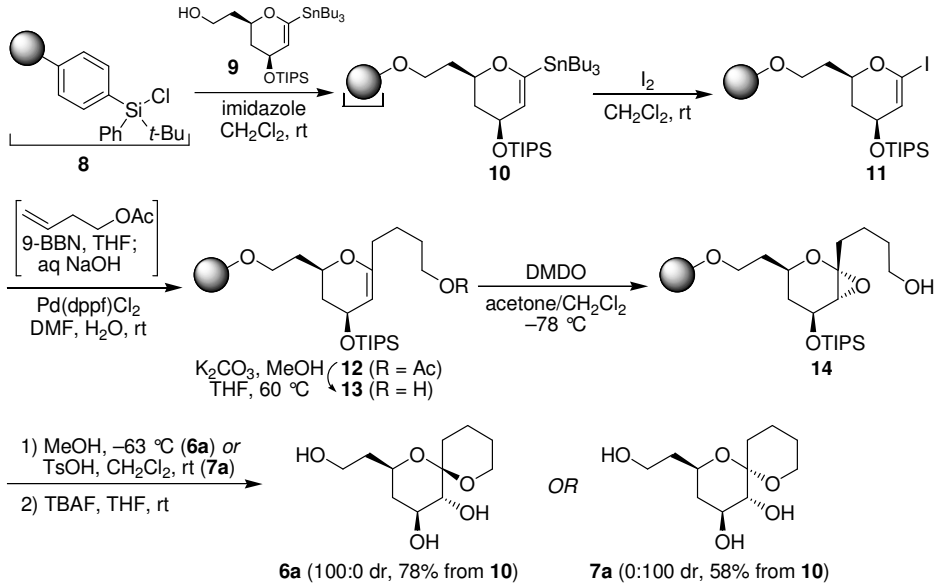


Figure 4.2. Stereoselective solid phase synthesis of spiroketals **6a** and **7a**

The stannane **9** was loaded onto polystyrene resin via the TBDAS linker[1] developed in our lab (**8**). Selection of the analogous *C*7-OTBDPS group for solution phase studies facilitated translation of the subsequent reactions to solid phase synthesis with only minor modifications. Although initial attempts to form the glycal iodide (**11**) on solid support resulted in decomposition, it was found that careful control of stoichiometry and reaction time allowed successful formation of the iodide with little or no decomposition. The *B*-alkyl Suzuki coupling conditions developed in solution provided traces of product when translated to solid support, but conversion was slow and was complicated by decomposition of the iodide starting material. However, use of a THF/DMF solvent mixture and extended reaction times resulted in complete

conversion to the desired *C*1-substituted glycal (**12**). Heating was necessary to drive acetate deprotection (**13**), which was confirmed by acid-promoted cyclization to the *C*2-dehydroxy spiroketal. Treatment with DMDO provided epoxide **14**, which was confirmed by MS analysis of the spiroketals formed upon spontaneous spirocyclization at room temperature. Surprisingly, the solid phase MeOH-induced spirocyclization (**14** → **6a**) proceeded even more effectively than the corresponding solution phase reaction, with no methyl glycosides detected. Moreover, thermodynamic equilibration with TsOH was also readily accomplished (**14** → **7a**). This concise 6-step route provided the spiroketal products **6a** and **7a** in high purity (≥80–90% based on NMR analysis) and overall yields suitable for library synthesis.

4.3. Evaluation of the Spiroketal Library in Multiple Biological Systems

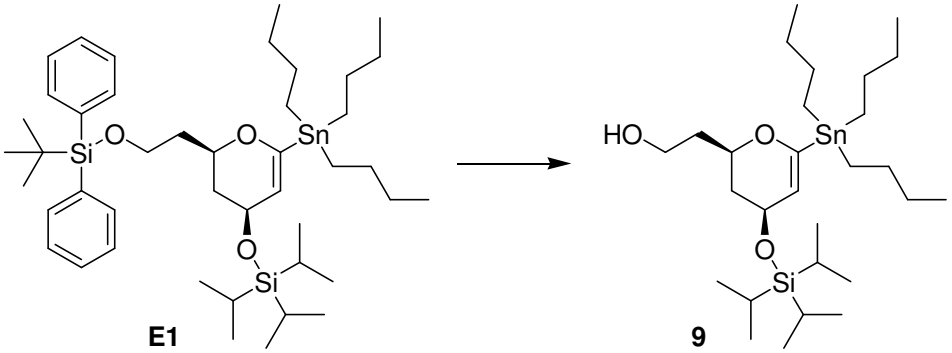
The ultimate goal of this project is to identify compounds that can be used as probes for biological studies, or possibly used as lead compounds for drug development. In order to do this, the spiroketal library will be evaluated in a range of high-throughput screens through the NIH Small Molecule Repository and collaborations with multiple laboratories in the Tri-Institutional Research Program. The results of these screens will allow us to begin analyzing the effectiveness of our library design strategy. In addition, to acquire a general cytotoxicity profile, the library has been screened against HeLa cells and wild-type yeast. None of the compounds were found to be cytotoxic in these assays.

4.4. Experimental Section

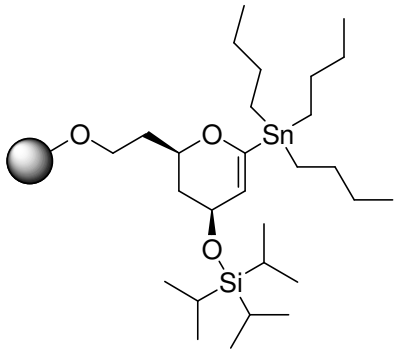
Materials and Methods:

See Section 2.6. The compound not cited in the previous sections of this chapter is numbered herein **E1**.

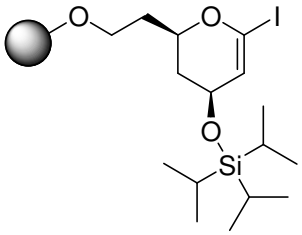
Solid phase synthesis of spiroketals:



(2*R,4*S**)-2-(2-hydroxyethyl)-6-(tributylstannyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (9).** Stannane **E1** (59 mg, 0.071 mmol, 1.0 equiv) was prepared as described in Section 2.6, dissolved in THF (0.6 mL) and HMPA (0.6 mL), then cooled to 0 °C. NaH (60% in oil, 5.7 mg, 0.14 mmol, 2.0 equiv) was added, and the mixture was stirred at 0 °C for 7 h then allowed to stand at –20 °C for 12 h. The mixture was then quenched with H_2O and the aqueous layer was extracted 3x with Et_2O. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated by rotary evaporation. Silica flash chromatography (19:1 hexanes/EtOAc) provided stannane **9** (26 mg, 63%) as a colorless oil. **TLC:** R_f 0.44 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3346, 2955, 2926, 2866, 1601, 1464, 1376, 1321, 1062, 882, 785. **^{1}H-NMR** (400 MHz): δ 4.79 (m, 1H), 4.52 (m, 1H), 4.05 (m, 1H), 3.79 (m, 2H), 2.10 (t, 1H, J = 5.6), 2.02 (m, 1H), 1.89–1.72 (m, 3H), 1.52 (m, 6H), 1.29 (m, 6H), 1.09 (21H), 0.90 (15H). **^{13}C-NMR** (125 MHz): δ 162.4, 118.0, 74.5, 63.9, 60.8, 38.5, 37.6, 28.9, 27.2, 18.0, 13.7, 12.3, 9.6. **ESI-MS** *m/z* (rel int): (pos) 613.7 ($[M+Na]^+$, 100); (neg) 589.7 ($[M–H]^-$, 10), 625.6 ($[M+Cl]^-$, 100).

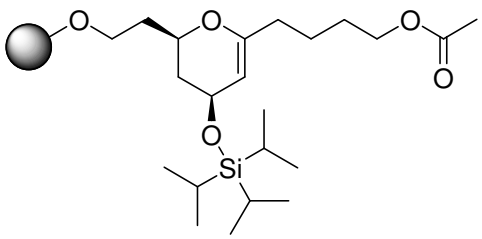


Resin-bound (2*R,4*S**)-2-(2-hydroxyethyl)-6-(tributylstannyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (10).** 1,3-Dichloro-5,5-dimethylhydantoin (1.0 M in CH_2Cl_2, 300 μL, 12 equiv) was added to 150–300 μM polystyrene-TBDAS-H resin[1] (0.94 mequiv/g, 35 mg, 1.0 equiv) in a Bio-Rad column and the mixture was vortexed 30 min. The solution was drained off, then the resin was washed with CH_2Cl_2 (3 x 500 μL). Imidazole (1.0 M in CH_2Cl_2, 400 μL, 12 equiv) was added, followed by a solution of alcohol **9** (0.25 M in CH_2Cl_2, 400 μL, 3.0 equiv). After vortexing the mixture for 16 h, the solution was drained off and the resin was washed 2 x 400 μL each with CH_2Cl_2, THF, 3:1 THF/*i*-PrOH, 3:1 THF/H_2O, 3:1 THF/*i*-PrOH, THF, TMOF, then anhyd THF. Cleavage of a sample of the resin with TBAF (0.2 M in THF) in the presence of a biphenylmethanol internal standard released the corresponding diol stannane (78%, ^{1}H-NMR).

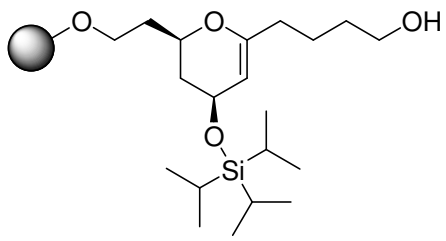


Resin-bound (2*R,4*S**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-iodo-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (11).** ALL STEPS WERE CARRIED OUT IN

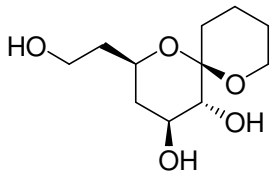
THE DARK. Anhyd CH_2Cl_2 (0.2 mL) then a solution of I_2 (0.20 M in CH_2Cl_2, 29 μL, 5.9 μmol, 1.5 equiv) was added to resin-bound stannane **10** (0.30 mequiv/g, 13 mg, 1.0 equiv) in a Bio-Rad column. The mixture was vortexed for 3 min then the solution was filtered off. The resin was washed with CH_2Cl_2 (3 × 500 μL) then DMF (3 × 500 μL) then used directly in the next reaction.



Resin-bound (2*R,4*R**)-6-(4-Acetoxybutyl)-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (12).** *Hydroboration*: But-3-enyl acetate (30 μL, 0.22 mmol, 1.0 equiv) was dissolved in anhyd THF (2.2 mL). A freshly prepared solution of 9-BBN (0.50 M in THF, 0.86 mL, 0.44 mmol, 2.0 equiv) was added dropwise at rt. After stirring for 3 h, aq NaOH (1.0 N, 430 μL, 0.44 mmol, 2.0 equiv) was added, and the reaction was stirred for an additional 30 min at rt. *Coupling*: ALL STEPS WERE CARRIED OUT IN THE DARK. DMF (0.2 mL) then H_2O (20 μL) were added to resin-bound iodide **11** (3.9 μmol, 1.0 equiv) in a Bio-Rad column. $PdCl_2$(dppf) (3.2 mg, 3.9 μmol, 1.0 equiv) was then added, followed by a portion of the hydroboration reaction mixture (0.50 mL, 31 μmol, 8.0 equiv). After vortexing at rt 40 h, the solution was filtered off. The resin was washed 3 × 500 μL each with DMF, THF, CH_2Cl_2, Ph_3P in CH_2Cl_2, CH_2Cl_2, DMF, 3:1 THF/*i*-PrOH, DMF, THF, then CH_2Cl_2. Cleavage of a sample of the resin with TBAF (0.04 M in THF) in the presence of a biphenylmethanol internal standard released the corresponding diol acetate (>90% over 2 steps, ^{1}H-NMR).

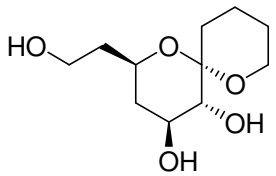


Resin-bound (2*R,4*S**)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4-hydroxybutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (13).** THF (0.8 mL), MeOH (0.2 mL), then K_2CO_3 (5.3 mg, 38 μmol, 5.0 equiv) were added to resin-bound glycal **12** (0.32 mequiv/g, 24 mg, 1.0 equiv) in a 5 mL roundbottom flask. The mixture was heated to 60 °C and stirred 20 h. The solution was then filtered off and the resin was washed with THF (3 × 500 μL), 3:1 THF/H_2O (8 × 1 mL), THF (3 × 500 μL), TMOF (3 × 500 μL) then anhydrous THF (3 × 500 μL). The beads were dried under high vacuum for 1 h then used directly in the next reaction.



(2*R,4*S**,5*R**,6*R**)-2-(2-Hydroxyethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (6a).** DMDO (0.030 M in acetone, 340 μL, 10 μmol, 3.0 equiv) was added to a cooled (−78 °C) mixture of resin-bound alcohol **13** (0.32 mequiv/g, 11 mg, 1.0 equiv) and anhyd CH_2Cl_2 (340 μL) in a 4 mL Wheaton vial. The mixture was stirred at –78 °C for 3 h, then warmed to –63 °C. Anhyd MeOH (450 μL) was added slowly. After stirring at –63 °C for 5 h, the reaction mixture was warmed to rt. The solution was removed by syringe then the resin was washed with CH_2Cl_2 (5 × 1 mL). The resin was cleaved by treatment with TBAF (1.0 M in THF, 34 μL, 10 equiv) in THF (0.4 mL) at rt for 6 h in the presence of a biphenylmethanol internal standard. The solution was removed by

syringe then the resin was extracted further with THF (3 × 500 μL). The combined organic extracts were evaporated, then the residue was dissolved in 0.2 mL MeOH and filtered through a 1-inch plug of normal phase over reverse phase silica gel (4 mL MeOH wash) then evaporated, redissolved in 0.2 mL THF, and passed over a second 1-inch plug of normal phase silica gel (4 mL THF wash). Evaporation of the solvents afforded inversion spiroketal **6a** (≈90% purity, >90% yield over 4 steps, 78% overall yield, ^{1}H-NMR).



(2*R,4*S**,5*R**,6*S**)-2-(2-Hydroxyethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (7a).** DMDO (0.030 M in acetone, 330 μL, 9.8 μmol, 3.0 equiv) was added to a cooled (–78 °C) mixture of resin-bound alcohol **13** (0.32 mequiv/g, 10.2 mg, 1.0 equiv) and anhyd CH_2Cl_2 (330 μL) in a 4 mL Wheaton vial. The mixture was stirred at –78 °C for 3 h then warmed to rt. The solution was removed by syringe then additional CH_2Cl_2 (0.4 mL) was added. The mixture was cooled (–78 °C) then treated with TsOH (0.60 mg, 3.3 μmol, 1.0 equiv). After stirring at –78 °C for 30 min, the mixture was warmed to rt and stirred 12 h. The solution was removed and the resin was washed 2 × 1 mL each with CH_2Cl_2, DMF, 3:1 THF/*i*-PrOH, DMF, THF, CH_2Cl_2, then anhyd THF. The resin was cleaved by treatment with TBAF (1.0 M in THF, 33 μL, 10 equiv) in THF (0.4 mL) at rt for 6 h in the presence of a biphenylmethanol internal standard. The solution was removed by syringe then the resin was extracted further with THF (3 × 500 μL). The combined organic extracts were evaporated, then the residue was dissolved in 0.2 mL MeOH and filtered through a 1-inch plug of normal phase over reverse phase silica gel (4 mL MeOH wash) then evaporated, redissolved in 0.2 mL

THF, and passed over a second 1-inch plug of normal phase silica gel (4 mL THF wash). Evaporation of the solvents afforded retention spiroketal **7a** (≈80% purity, 74% yield over 4 steps, 58% overall yield, ^{1}H-NMR).

Synthesis of the spiroketal library:

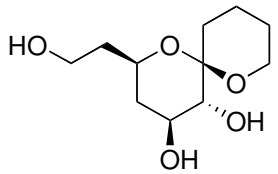
Spiroketals **4a–g** and **5a–g** were synthesized and characterized by Justin Potuzak.

General procedure for desilylation:

The spiroketals **4d–f,h–m** and **5a,c–n** were synthesized in solution according to the procedures in Sections 2.6 and 3.5. These compounds were dissolved in THF (0.1 M) then treated with TBAF (1.0 M in THF, 2.6 equiv) at rt. After the reaction was complete by TLC, the solvent was evaporated by rotary evaporation. The crude material was purified by flash chromatography (elution with 95:5 EtOAc/MeOH) to provide spiroketals **6d–f**,**h–m** and **7a,c–n**.

The spiroketals **6a–c** and **7b** were synthesized on solid support as described above. Solid phase yields are based on **8**.

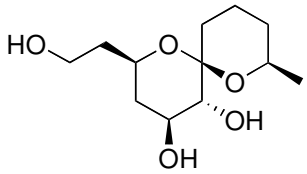
The enantiomers of spiroketals **6a–f, h–m** and **7a–n** were synthesized in solution or solid phase as indicated.



(+)-(2*R*,4*S*,5*R*,6*R*)-2-(2-Hydroxyethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (6a). Clear oil (13 mg, 24%). $[\alpha]_D^{25}$: +14° (*c* 1.3, $CDCl_3$). **IR:** (NaCl, film): 3385, 2945,

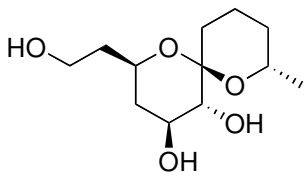
2883, 1444, 1359, 1217, 1073, 1048, 1008, 986, 958, 918, 897. **^{1}H-NMR** (500 MHz): δ 3.94 (m, 1H), 3.91–3.74 (m, 5H), 3.25 (d, 1H, *J* = 9.6), 2.00 (m, 1H), 1.91–1.78 (m, 4H), 1.63 (m, 3H), 1.55 (m, 2H). **^{13}C-NMR** (125 MHz): δ 99.6, 79.3, 69.0, 68.2, 62.4, 60.6, 38.7, 37.9, 25.1, 22.5, 17.4. **ESI-MS** *m/z* (rel int): pos 255.0 ([M+Na]$^+$, 100); neg 230.8 ([M–H]$^-$, 10), 266.9 ([M+Cl]$^-$, 100).

(–)-Enantiomer: Solid phase, 11 mg, 36%. $[\alpha]_D^{25}$: –16° (*c* 1.1, $CDCl_3$).



(+)-(2*R*,4*S*,5*R*,6*R*,8*R*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (6b). Clear oil (22 mg, 40%). $[\alpha]_D^{25}$: +42° (*c* 1.3, $CDCl_3$). **IR:** (NaCl, film): 3382, 2929, 2873, 1446, 1373, 1224, 1126, 1060, 1018, 1010, 953. **^{1}H-NMR** (500 MHz): δ 4.09 (m, 1H), 3.86–3.70 (m, 4H), 3.38 (d, 1H, *J* = 9.5), 2.65 (bs, 2H), 2.18 (bs. 1H), 1.95–1.71 (m, 7H), 1.68–1.52 (m. 3H), 1.27 (d, 3H, *J* = 6.6). **^{13}C-NMR** (125 MHz): δ 101.3, 79.5, 69.6, 68.6, 68.5, 60.3, 38.5, 37.9, 29.2, 22.3, 20.8, 13.3. **ESI-MS** *m/z* (rel int): pos 268.9 ([M+Na]$^+$, 100); neg 245.1 ([M–H]$^-$, 10), 280.9 ([M+Cl]$^-$, 100).

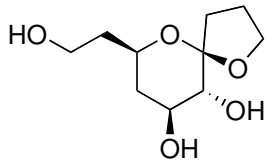
(–)-Enantiomer: Solution phase, 12 mg, 84%. $[\alpha]_D^{25}$: –49° (*c* 1.2, $CDCl_3$).



(+)-(2*R*,4*S*,5*R*,6*R*,8*S*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (6c). Clear oil (14 mg, 24%). $[\alpha]_D^{25}$: +15° (*c* 1.3, $CDCl_3$). **IR:** (NaCl, film):

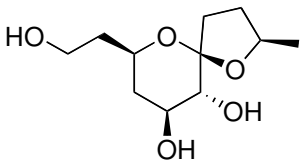
3390, 2932, 2872, 1446, 1384, 1372, 1231, 1202, 1132, 1079, 1056, 1006, 951. **^{1}H-NMR** (500 MHz): δ 4.03 (m, 1H), 3.87–3.71 (m, 4H), 3.26 (d, 1H, *J* = 9.6), 2.85 (bs, 2H), 2.35 (bs, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.83–1.60 (m, 7H), 1.52 (m, 1H), 1.16 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 100.2, 79.3, 69.1, 68.2, 67.8, 60.6, 38.6, 37.8, 32.6, 22.0, 21.9, 17.6. **ESI-MS** *m/z* (rel int): pos 268.8 ($[M+Na]^+$, 100); neg 245.2 ($[M–H]^–$, 25), 280.9 ($[M+Cl]^–$, 100).

(–)-Enantiomer: Solution phase, 24 mg, 100%. $[\alpha]_D^{25}$: –8.4° (*c* 2.4, $CDCl_3$).

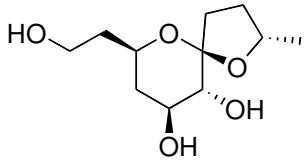


(+)-(5*S*,7*S*,9*S*,10*R*)-7-(2-Hydroxyethyl)-1,6-dioxaspiro[4.5]decane-9,10-diol (6d). Clear oil (15 mg, 100%). $[\alpha]_D^{25}$: +29° (*c* 1.5, $CDCl_3$). **IR:** (NaCl, film): 3368, 2918, 2879, 1363, 1316, 1236, 1173, 1084, 1054, 945, 926, 874, 728. **^{1}H-NMR** (500 MHz): δ 4.02 (m, 1H), 3.93 (m, 1H), 3.81–3.63 (m, 4H), 3.53 (m, 1H), 2.92 (bs, 2H), 2.28 (bs, 1H), 2.10–2.02 (m, 2H), 1.99–1.91 (m, 3H), 1.83 (m, 1H), 1.76 (m, 1H), 1.52 (m, 1H). **^{13}C-NMR** (125 MHz): δ 109.5, 76.2, 69.9, 69.7, 68.3, 60.5, 38.4, 37.5, 26.8, 24.8. **ESI-MS** *m/z* (rel int): pos 241.0 ($[M+Na]^+$, 100); neg 216.8 ($[M–H]^–$, 10), 252.8 ($[M+Cl]^–$, 100).

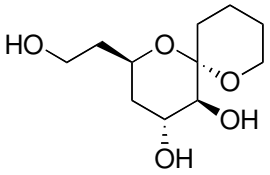
(–)-Enantiomer: Solid phase, 18 mg, 57%. $[\alpha]_D^{25}$: –30° (*c* 1.4, $CDCl_3$).



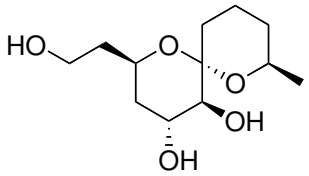
(+)-(2*S*,5*R*,7*S*,9*S*,10*R*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (6e). Clear oil (13 mg, 97%). $[\alpha]_D^{25}$: +29° (*c* 1.3, $CDCl_3$). **IR:** (NaCl, film): 3394, 2966, 2920, 2878, 1442, 1377, 1317, 1212, 1176, 1087, 1060, 888, 955, 944, 895. **^{1}H-NMR** (500 MHz): δ 4.23 (m, 1H), 3.82–3.69 (m, 3H), 3.64 (m, 1H), 3.51 (d, 1H, *J* = 9.7), 2.93 (bs, 2H), 2.38 (bs, 1H), 2.09 (m, 2H), 2.02–1.94 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.32 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 109.5, 77.5, 76.3, 70.1, 69.7, 60.7, 38.5, 37.5, 31.8, 26.7, 22.6. **ESI-MS** *m/z* (rel int): pos 254.7 ($[M+Na]^+$, 100); neg 231.2 ($[M-H]^-$, 20), 266.9 ($[M+Cl]^-$, 100). (–)-Enantiomer: Solution phase, 16 mg, 87%. $[\alpha]_D^{25}$: –28° (*c* 1.6, $CDCl_3$).



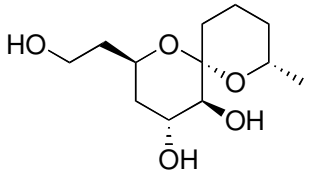
(+)-(2*S*,5*R*,7*S*,9*S*,10*S*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (6f). Clear oil (18 mg, 100%). $[\alpha]_D^{25}$: +37° (*c* 1.8, $CDCl_3$). **IR:** (NaCl, film): 3390, 2966, 2928, 2878, 1446, 1384, 1305, 1246, 1196, 1069, 1012, 957. **^{1}H-NMR** (500 MHz): δ 4.32 (m, 1H), 3.75 (m, 2H), 3.65 (m, 2H), 3.45 (d, 1H, *J* = 9.6), 3.20–2.90 (bm, 2H), 2.40 (bs, 1H), 2.19 (m, 1H), 2.12 (m, 1H), 1.96 (m, 1H), 1.84 (m, 2H), 1.75 (m, 1H), 1.52 (m, 2H), 1.26 (d, 3H, *J* = 6.1). **^{13}C-NMR** (125 MHz): δ 109.6, 76.2, 75.3, 69.8, 69.2, 60.4, 38.4, 37.5, 32.7, 28.0, 20.5. **ESI-MS** *m/z* (rel int): pos 254.7 ($[M+Na]^+$, 100); neg 231.2 ($[M-H]^-$, 20), 266.9 ($[M+Cl]^-$, 100). (–)-Enantiomer: Solution phase, 24 mg, 100%. $[\alpha]_D^{25}$: –45° (*c* 2.4, $CDCl_3$).



(+)-(2*R*,4*R*,5*S*,6*S*)-2-(2-Hydroxyethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (6h). White solid (14 mg, 74%). **TLC:** R_f 0.45 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +77° (*c* 0.70, $CHCl_3$). **IR:** (NaCl, film): 3406, 2940, 1441, 1270, 1996, 1085, 1055, 1002, 945, 889, 732. **^{1}H-NMR** (400 MHz): δ 4.14 (m, 1H), 3.99 (d, 1H, *J* = 10.6), 3.91–3.82 (m, 3H), 3.72 (m, 2H), 3.45 (dd, 1H, *J* = 8.3, 2.8), 2.29 (t, 1H, *J* = 5.3), 1.91–1.71 (m, 5H), 1.69–1.56 (m, 5H), 1.47 (m, 1H). **^{13}C-NMR** (125 MHz): δ 99.0, 69.9, 69.1, 64.6, 61.3, 61.0, 37.6, 33.3, 31.5, 24.6, 17.9. **ESI-MS** *m/z* (rel int): pos 255.2 ($[M+Na]^+$, 100), 487.2 ($[2M+Na]^+$, 40); neg 230.9 ($[M–H]^-$, 40), 267.1 ($[M+Cl]^-$, 100).
(–)-Enantiomer: Solution phase, 25 mg, 84%. $[\alpha]_D^{25}$: –78° (*c* 1.2, $CHCl_3$).

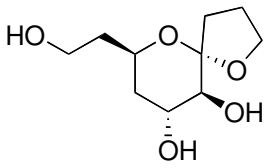


(+)-(2*R*,4*R*,5*S*,6*S*,8*R*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (6i). White solid (31 mg, 88%). **TLC:** R_f 0.32 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +67° (*c* 0.61, $CHCl_3$). **IR:** (NaCl, film): 3400, 2934, 1438, 1386, 1229, 1195, 1072, 992, 887, 729. **^{1}H-NMR** (500 MHz): δ 4.16 (d, 1H, *J* = 10.5), 4.12 (m, 1H), 3.92 (m, 1H), 3.83 (m, 3H), 3.46 (dd, 1H, *J* = 8.4, 3.1), 2.40 (m, 1H), 1.90–1.80 (m, 4H), 1.78–1.61 (m, 5H), 1.42 (m, 1H), 1.28 (m, 1H), 1.19 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 99.8, 69.9, 69.3, 67.2, 64.5, 61.1, 37.5, 33.4, 32.0, 30.9, 21.6, 18.4. **ESI-MS** *m/z* (rel int): pos 269.2 ($[M+Na]^+$, 100); neg 245.2 ($[M–H]^-$, 100), 280.9 ($[M+Cl]^-$, 90).
(–)-Enantiomer: Solution phase, 56 mg, 94%. $[\alpha]_D^{25}$: –66° (*c* 1.1, $CHCl_3$).



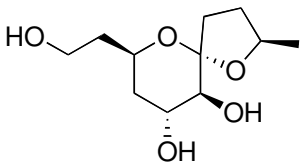
(+)-(2*R*,4*R*,5*S*,6*S*,8*S*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (6j). Clear oil (11 mg, 83%). **TLC:** R_f 0.33 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +48° (*c* 0.56, $CHCl_3$). **IR:** (NaCl, film): 3400, 2934, 1441, 1382, 1205, 1180, 1065, 995, 880. **^{1}H-NMR** (400 MHz): δ 4.45 (m, 1H), 4.02–3.90 (m, 3H), 3.81 (m, 2H), 3.70 (dd, 1H, *J* = 8.8, 2.7), 2.41 (m, 1H), 1.89–1.58 (m, 10H), 1.45 (m, 1H), 1.29 (d, 3H, *J* = 6.4). **^{13}C-NMR** (125 MHz): δ 100.1, 70.5, 69.1, 66.3, 64.9, 60.9, 37.7, 33.1, 31.0, 30.6, 21.5, 16.3. **ESI-MS** *m/z* (rel int): pos 269.2 ($[M+Na]^+$, 100), 515.4 ($[2M+Na]^+$, 75); neg 245.0 ($[M–H]^-$, 100), 281.1 ($[M+Cl]^-$, 10).

(–)-Enantiomer: Solution phase, 18 mg, 88%. $[\alpha]_D^{25}$: –48° (*c* 0.91, $CHCl_3$).



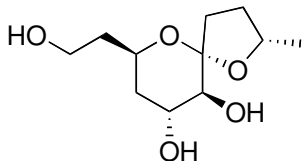
(+)-(5*S*,7*R*,9*R*,10*S*)-7-(2-Hydroxyethyl)-1,6-dioxaspiro[4.5]decane-9,10-diol (6k). White solid (19 mg, 75%). **TLC:** R_f 0.25 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +86° (*c* 0.93, $CHCl_3$). **IR:** (NaCl, film): 3362, 2944, 2888, 1418, 1061, 1000, 862. **^{1}H-NMR** (500 MHz): δ 4.27 (m, 1H), 4.05 (m, 2H), 3.94 (m, 1H), 3.78 (m, 3H), 3.51 (dd, 1H, *J* = 8.1, 2.8), 2.37 (t, 1H, *J* = 4.9), 2.16 (d, 1H, *J* = 8.5), 2.08–1.92 (m, 4H), 1.85–1.81 (m, 2H), 1.72–1.64 (m, 2H). **^{13}C-NMR** (125 MHz): δ 108.0, 70.0, 69.2, 68.9, 65.7, 61.3, 37.4, 36.2, 33.3, 22.6. **ESI-MS** *m/z* (rel int): pos 241.1 ($[M+Na]^+$, 100); neg 217.0 ($[M–H]^-$, 100), 253.0 ($[M+Cl]^-$, 70).

(–)-Enantiomer: Solution phase, 17 mg, 73%. $[\alpha]_D^{25}$: –86° (*c* 0.84, $CHCl_3$).



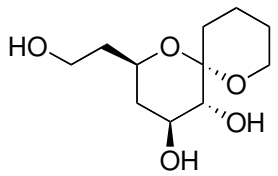
(+)-(2*R*,5*S*,7*R*,9*R*,10*S*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (6l). Clear oil (24 mg, 89%). **TLC:** R_f 0.34 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +83° (*c* 1.2, $CHCl_3$). **IR:** (NaCl, film): 3388, 2928, 1441, 1412, 1384, 1226, 1177, 1062, 1005, 873. **^{1}H-NMR** (500 MHz): δ 4.38 (sx, 1H, *J* = 6.4), 4.29 (m, 1H), 3.94 (m, 1H), 3.82 (d, 1H, *J* = 10.8), 3.78 (m, 2H), 2.52 (dd, 1H, *J* = 8.9, 3.2), 2.34 (m, 1H), 2.11 (m, 2H), 1.98 (m, 2H), 1.82 (m, 2H), 1.72–1.61 (m, 2H), 1.51 (m, 1H), 1.27 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 108.1, 76.9, 70.2, 68.9, 65.8, 61.4, 37.4, 35.9, 33.3, 30.0, 21.1. **ESI-MS** *m/z* (rel int): pos 255.1 ($[M+Na]^+$, 100); neg 231.1 ($[M–H]^–$, 10), 266.9 ($[M+Cl]^–$, 100).

(–)-Enantiomer: Solution phase, 22 mg, 90%. $[\alpha]_D^{25}$: –84° (*c* 1.1, $CHCl_3$).



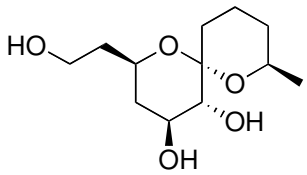
(+)-(2*S*,5*S*,7*R*,9*R*,10*S*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (6m). White solid (22 mg, 88%). **TLC:** R_f 0.21 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +83° (*c* 1.1, $CHCl_3$). **IR:** (NaCl, film): 3470, 3308, 2972, 2949, 2914, 1435, 1411, 1236, 1098, 1068, 996, 864. **^{1}H-NMR** (400 MHz): δ 4.36 (m, 2H), 3.92 (m, 2H), 3.79 (m, 2H), 3.48 (dd, 1H, *J* = 8.7, 2.6), 2.46 (m, 1H), 2.21 (d, 1H, *J* = 8.7), 2.13 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.82 (m, 2H), 1.71–1.58 (m, 3H), 1.36 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 107.9, 79.5, 70.3, 69.0, 65.6, 61.4, 37.7, 37.5, 33.5, 30.7, 22.6. **ESI-MS** *m/z* (rel int): pos 255.2 ($[M+Na]^+$, 100); neg 231.2 ($[M–H]^–$, 100), 267.0 ($[M+Cl]^–$, 20).

(–)-Enantiomer: Solution phase, 9.0 mg, 88%. $[\alpha]_D^{25}$: –83° (*c* 0.45, $CHCl_3$).



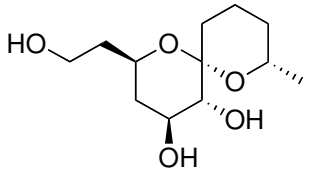
(+)-(2*R*,4*S*,5*R*,6*S*)-2-(2-Hydroxyethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (7a). Clear oil (21 mg, 94%). $[\alpha]_D^{25}$: +77° (*c* 2.1, $CDCl_3$). **IR:** (NaCl, film): 3363, 2939, 2871, 1441, 1386, 1222, 1177, 1090, 1049, 988, 956, 920. **^{1}H-NMR** (500 MHz): δ 3.93 (m, 1H), 3.84 (m, 3H), 3.70 (m, 1H), 3.02 (m, 1H), 2.46 (bs, 1H), 2.05–1.96 (m, 1H), 1.88–1.65 (m, 5H), 1.61–1.47 (m, 4H). **^{13}C-NMR** (125 MHz): δ 98.0, 78.1, 69.3, 67.7, 61.1, 61.0, 38.4, 37.3, 30.4, 24.7, 18.4. **ESI-MS** *m/z* (rel int): pos 255.1 ($[M+Na]^+$, 100); neg 230.9 ($[M–H]^-$, 20), 266.9 ($[M+Cl]^-$, 100).

(–)-Enantiomer: Solid phase, 20 mg, 64%. $[\alpha]_D^{25}$: –81° (*c* 1.5, $CDCl_3$).



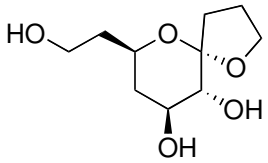
(+)-(2*R*,4*S*,5*R*,6*S*,8*R*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (7b). Clear oil (38 mg, 69%). $[\alpha]_D^{25}$: +61° (*c* 4.5, $CDCl_3$). **IR:** (NaCl, film): 3352, 2935, 2871, 1444, 1385, 1230, 1134, 1090, 1056, 1002, 964, 919. **^{1}H-NMR** (500 MHz): δ 3.89 (m, 2H), 3.79 (m, 3H), 3.02 (m, 1H), 2.60 (bs, 1H), 2.50 (bs, 1H), 2.08–1.90 (m, 3H), 1.82–1.60 (m, 7H), 1.48 (m, 1H), 1.14 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 98.6, 78.0, 69.5, 67.8, 66.5, 61.1, 38.4, 37.3, 32.2, 29.8, 21.7, 18.7. **ESI-MS** *m/z* (rel int): pos 269.0 ($[M+Na]^+$, 100); neg 245 ($[M–H]^-$, 10), 281.0 ($[M+Cl]^-$, 100).

(–)-Enantiomer: Solution phase, 17 mg, 92%. $[\alpha]_D^{25}$: –82° (*c* 1.7, $CDCl_3$).



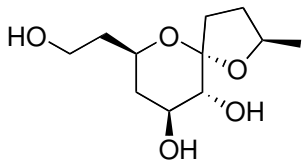
(+)-(2*R*,4*S*,5*R*,6*S*,8*S*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (7c). Clear oil (26 mg, 90%). $[\alpha]_D^{25}$: +49° (*c* 2.6, $CDCl_3$). **IR:** (NaCl, film): 3369, 2943, 1444, 1392, 1225, 1132, 1087, 1060, 1006, 968, 923. **^{1}H-NMR** (500 MHz): δ 4.13 (m, 2H), 3.81 (m, 3H), 2.97 (bm, 1H), 2.68 (bs, 1H), 2.49 (bs, 1H), 2.05 (m, 2H), 1.96 (m, 1H), 1.86 (m, 1H), 1.80–1.71 (m, 3H), 1.62–1.53 (m, 3H), 1.48 (m, 1H), 1.35 (d, 1H, *J* = 6.8). **^{13}C-NMR** (125 MHz): δ 98.9, 78.4, 69.7, 69.1, 68.0, 60.7, 38.3, 37.4, 30.1, 29.0, 21.1, 13.5. **ESI-MS** *m/z* (rel int): pos 247.0 ($[M+H]^+$, 20), 269.1 ($[M+Na]^+$, 100); neg 245.0 ($[M–H]^–$, 10), 281.1 ($[M+Cl]^–$, 100).

(–)-Enantiomer: Solution phase, 22 mg, 96%. $[\alpha]_D^{25}$: –46° (*c* 2.2, $CDCl_3$).



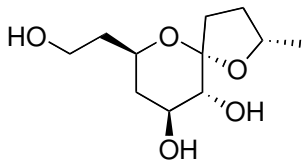
(+)-(5*R*,7*S*,9*S*,10*R*)-7-(2-Hydroxyethyl)-1,6-dioxaspiro[4.5]decane-9,10-diol (7d). Clear oil (16 mg, 47%). $[\alpha]_D^{25}$: +80° (*c* 1.6, $CHCl_3$). **IR:** (NaCl, film): 3368, 2946, 2883, 1441, 1391, 1192, 1163, 1086, 1006, 979, 921, 731. **^{1}H-NMR** (500 MHz): δ 4.00 (m, 3H), 3.81 (m, 1H), 3.75 (m, 2H), 3.36 (m, 1H), 2.70 (bs, 1H), 2.43 (bs, 1H), 2.34 (m, 1H), 2.05–1.96 (m, 3H), 1.94–1.85 (m, 2H), 1.82–1.70 (m, 2H), 1.49 (m, 1H). **^{13}C-NMR** (125 MHz): δ 107.7, 75.2, 70.6, 68.8, 68.6, 61.3, 38.4, 37.1, 34.0, 23.9. **ESI-MS** *m/z* (rel int): pos 241.1 ([M+Na]+, 100); neg 252.9 ([M+Cl]–, 100).

(–)-Enantiomer: Solid phase, 13 mg, 64%. $[\alpha]_D^{25}$: –86° (*c* 1.3, $CDCl_3$).



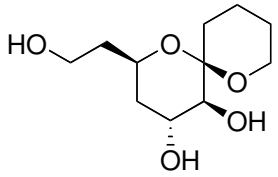
(+)-(2*S*,5*S*,7*S*,9*S*,10*R*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (7e). White solid (14 mg, 94%). $[\alpha]_D^{25}$: +88° (*c* 1.4, $CDCl_3$). **IR:** (NaCl, film): 3356, 2948, 2883, 1444, 1384, 1202, 1161, 1080, 1058, 1010, 925, 883. **^{1}H-NMR** (500 MHz): δ 4.27 (m, 1H), 4.03 (m, 1H), 3.76 (m, 3H), 3.30 (m, 1H), 2.59 (bs, 1H), 2.42 (m, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 1.96 (m, 1H), 1.88–1.68 (m, 4H), 1.48 (m, 2H), 1.26 (d, 3H, *J* = 6.1). **^{13}C-NMR** (125 MHz): δ 108.3, 76.0, 75.7, 71.0, 69.3, 61.7, 38.7, 37.5, 34.8, 31.9, 21.2. **ESI-MS** *m/z* (rel int): pos 255.0 ([M+Na]+, 100); neg 231.1 ([M–H]$^-$, 30), 266.9 ([M+Cl]$^-$, 100).

(–)-Enantiomer: Solution phase, 12 mg, 97%. $[\alpha]_D^{25}$: –86° (*c* 1.2, $CDCl_3$).



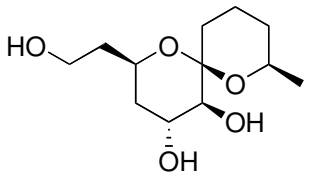
(+)-(2*S*,5*S*,7*S*,9*S*,10*S*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (7f). Clear oil (10 mg, 94%). $[\alpha]_D^{25}$: +94° (*c* 1.0, $CDCl_3$). **IR:** (NaCl, film): 3354, 2966, 2945, 1445, 1378, 1331, 1207, 1169, 1086, 1048, 979, 924, 881, 730. **^{1}H-NMR** (500 MHz): δ 4.31 (m, 1H), 4.07 (m, 1H), 3.78 (m, 3H), 3.28 (m, 1H), 2.60 (bs, 1H), 2.45 (bs, 1H), 2.29 (m, 1H), 2.08 (m, 1H), 1.96 (m, 1H), 1.89 (m, 2H), 1.80–1.69 (m, 3H), 1.48 (m, 1H), 1.33 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 108.2, 79.3, 75.6, 71.1, 68.8, 61.7, 38.9, 37.6, 35.2, 32.0, 23.4. **ESI-MS** *m/z* (rel int): pos 254.9 ([M+Na]+, 100); neg 267.1 ([M+Cl]$^-$, 100).

(–)-Enantiomer: Solution phase, 12 mg, 86%. $[\alpha]_D^{25}$: –99° (*c* 1.2, $CDCl_3$).



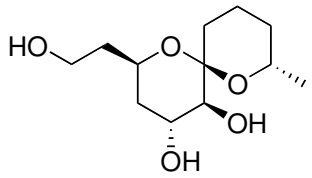
(–)-(2*R*,4*R*,5*S*,6*R*)-2-(2-Hydroxyethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (7h). Clear oil (21 mg, 82%). **TLC:** R_f 0.22 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: –24° (*c* 1.0, $CHCl_3$). **IR:** (NaCl, film): 3388, 2940, 2882, 1441, 1381, 1221, 1078, 1050, 1001, 920, 731. **^{1}H-NMR** (500 MHz): δ 4.12 (m, 1H), 4.05 (m, 1H), 3.89 (td, 1H, *J* = 11.4, 3.5), 3.81 (m, 2H), 3.71 (m, 1H), 3.23 (t, 1H, *J* = 5.9), 2.63 (d, 1H, *J* = 6.1), 2.26 (bs, 1H), 2.02 (m, 4H), 1.83 (m, 1H), 1.72–1.53 (m, 6H). **^{13}C-NMR** (125 MHz): δ 97.9, 75.6, 69.0, 67.1, 61.9, 60.9, 37.7, 34.5, 30.5, 25.1, 18.1. **ESI-MS** *m/z* (rel int): pos 255.1 ($[M+Na]^+$, 100), 487.1 ($[2M+Na]^+$, 80); neg 231.0 ($[M–H]^-$, 10), 267.0 ($[M+Cl]^-$, 100).

(+)-Enantiomer: Solution phase, 26 mg, 99%. $[\alpha]_D^{25}$: +26° (*c* 1.3, $CHCl_3$).



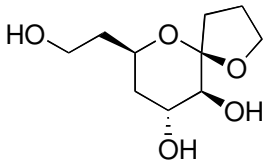
(+)-(2*R*,4*R*,5*S*,6*R*,8*R*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (7i). Clear oil (31 mg, 86%). **TLC:** R_f 0.26 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: +48° (*c* 1.6, $CHCl_3$). **IR:** (NaCl, film): 3410, 2933, 1445, 1383, 1220, 1044, 1006, 924, 731. **^{1}H-NMR** (500 MHz): δ 4.19 (m, 2H), 3.80 (m, 3H), 3.72 (bs, 1H), 2.85 (d, 1H, *J* = 2.0), 2.56 (m, 1H), 2.44 (bs, 1H), 2.36 (bs, 1H), 1.98–1.81 (m, 3H), 1.71–1.49 (m, 5H), 1.37 (m, 1H), 1.24 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 99.0, 69.7, 68.1, 67.1, 66.9, 60.4, 37.9, 33.4, 31.4, 29.8, 22.2, 19.4. **ESI-MS** *m/z* (rel int): pos 269.2 ($[M+Na]^+$, 100), 515.3 ($[2M+Na]^+$, 70); neg 245.0 ($[M–H]^-$, 25), 281.0 ($[M+Cl]^-$, 100).

(–)-Enantiomer: Solution phase, 25 mg, 81%. $[\alpha]_D^{25}$: –47° (*c* 1.2, $CHCl_3$).



(–)-(2*R*,4*R*,5*S*,6*R*,8*S*)-2-(2-Hydroxyethyl)-8-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol (7j). White solid (17 mg, 82%). **TLC:** R_f 0.30 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: –18° (*c* 0.84, $CHCl_3$). **IR:** (NaCl, film): 3381, 2933, 1445, 1384, 1228, 1195, 1056, 1002, 965, 916. **^{1}H-NMR** (400 MHz): δ 4.11 (m, 2H), 3.98 (m, 1H), 3.79 (m, 2H), 3.22 (t, 1H, *J* = 6.2), 2.68 (d, 1H, *J* = 6.2), 2.18 (d, 1H, *J* = 2.3), 2.02–1.95 (m, 4H), 1.82–1.53 (m, 6H), 1.18 (m, 1H), 1.13 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 98.4, 75.4, 69.0, 67.4, 67.2, 61.0, 37.5, 34.4, 32.6, 29.8, 21.8, 18.4. **ESI-MS** *m/z* (rel int): pos 269.2 ($[M+Na]^+$, 100), 515.3 ($[2M+Na]^+$, 90); neg 245.1 ($[M–H]^–$, 40), 491.1 ($[2M–H]^–$, 100).

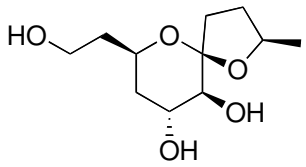
(+)-Enantiomer: Solution phase, 27 mg, 95%. $[\alpha]_D^{25}$: +19° (*c* 0.53, $CHCl_3$).



(–)-(5*R*,7*R*,9*R*,10*S*)-7-(2-Hydroxyethyl)-1,6-dioxaspiro[4.5]decane-9,10-diol (7k). Clear oil (22 mg, 64%). **TLC:** R_f 0.17 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: –27° (*c* 1.1, $CHCl_3$). **IR:** (NaCl, film): 3371, 2932, 2883, 1439, 1379, 1188, 1161, 1067, 1002, 922, 861, 776, 729. **^{1}H-NMR** (500 MHz): δ 4.13 (m, 1H), 4.03 (m, 2H), 3.90 (m, 1H), 3.76 (m, 2H), 3.42 (t, 1H, *J* = 7.0), 2.54 (bs, 1H), 2.33 (d, 1H, *J* = 7.5), 2.14–1.98 (m, 6H), 1.91 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H). **^{13}C-NMR** (125 MHz): δ 108.4,74.8,

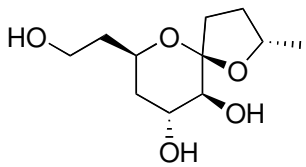
70.2, 68.8, 67.5, 60.8, 37.6, 35.1, 34.5, 24.5. **ESI-MS** *m/z* (rel int): pos 219.2 ($[M+H]^+$, 10), 241.1 ($[M+Na]^+$, 100); neg 217.0 ($[M-H]^-$, 100), 253.0 ($[M+Cl]^-$, 100).

(+)-Enantiomer: Solution phase, 18 mg, 73%. $[\alpha]_D^{25}$: +28° (*c* 0.88, $CHCl_3$).



(–)-(2*R*,5*R*,7*R*,9*R*,10*S*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (7l). Clear oil (17 mg, 75%). **TLC:** R_f 0.23 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: –22° (*c* 0.83, $CHCl_3$). **IR:** (NaCl, film): 3381, 2967, 2930, 1446, 1380, 1208, 1176, 1097, 1063, 1001, 927, 879, 819, 731. **^{1}H-NMR** (500 MHz): δ 4.14 (m, 2H), 4.04 (m, 1H), 3.79 (m, 2H), 3.39 (d, 1H, *J* = 6.5), 2.19 (m, 3H), 2.13–1.96 (m, 5H), 1.75–1.66 (m, 3H), 1.33 (d, 3H, *J* = 6.2). **^{13}C-NMR** (125 MHz): δ 107.9, 78.3, 74.5, 69.9, 67.8, 61.0, 37.6, 34.8, 34.5, 32.3, 22.0. **ESI-MS** *m/z* (rel int): pos 255.0 ($[M+Na]^+$, 100); neg 230.9 ($[M-H]^-$, 40), 266.9 ($[M+Cl]^-$, 100).

(+)-Enantiomer: Solution phase, 17 mg, 87%. $[\alpha]_D^{25}$: +21° (*c* 0.84, $CHCl_3$).



(–)-(2*S*,5*R*,7*R*,9*R*,10*S*)-7-(2-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane-9,10-diol (7m). Clear oil (12 mg, 76%). **TLC:** R_f 0.26 (9:1 CH_2Cl_2/MeOH). $[\alpha]_D^{25}$: –18° (*c* 0.59, $CHCl_3$). **IR:** (NaCl, film): 3365, 2929, 2359, 1456, 1199, 1069, 1007, 926, 879. **^{1}H-NMR** (400 MHz): δ 4.33 (m, 1H), 4.14 (m, 1H), 3.99 (m, 1H), 3.76 (m, 2H), 3.35 (t, 1H, *J* = 7.9), 2.30–2.11 (m, 5H), 2.00 (m, 2H), 1.84–1.62 (m, 3H), 1.46

(m, 1H), 1.21 (d, 3H, J = 6.2). **^{13}C-NMR** (125 MHz): δ 108.5, 75.7, 74.9, 70.2, 67.6, 60.9, 37.6, 35.0, 34.8, 32.0, 21.1. **ESI-MS** *m/z* (rel int): pos 255.2 ($[M+Na]^+$, 100), 487.3 ($[2M+Na]^+$, 20); neg 231.0 ($[M–H]^-$, 70), 463.2 ($[2M–H]^-$, 100).
(+)-Enantiomer: Solution phase, 9.8 mg, 82%. $[\alpha]_D^{25}$: +18° (*c* 0.45, $CHCl_3$).

Cytotoxicity assays:

Stock solutions (10, 5, 1, or 0.25 mM) of 52 spiroketals (**6a–f**,**h–m** and **7a–n** plus enantiomers) were prepared in DMSO then used in the following assays.

Assay for cytotoxicity in yeast:

Yeast (Y384 strain) was grown at 30 °C in rich media to an OD value of 0.05 then transferred to 384 well plates (40 μL culture per well). Aliquots (100 nL) of spiroketal stock solutions or DMSO were transferred to individual wells using an automated pin-transfer system. Cycloheximide (500 nL, 0.35 M in DMSO) was added manually to control wells. The plates were agitated at ambient temperature for 24 h prior to OD measurement in a plate reader set to 590 nm.

Assay for cytotoxicity in HeLa cells:

HeLa cells were grown to confluence in DMEM media then transferred to 384 well plates (15 μL culture per well). Aliquots (100 nL) of spiroketal stock solutions or DMSO were transferred to individual wells using an automated pin-transfer system. Staurosporine (500 nL, 0.5 mM in DMSO) was added manually to control wells. The plates were incubated at 37 °C for 24 h then treated with Alamar Blue (5 μL per well of a 1:1 solution of Alamar Blue in media). The plates were incubated at 37 °C for an additional 24 h prior to fluorescence measurement.

REFERENCES

(1) DiBlasi, C. M.; Macks, D. E.; Tan, D. S. "An acid-stable *tert*-butyldiarylsilyl (TBDAS) linker for solid-phase organic synthesis." *Org. Lett.* **2005,** *7*, 1777-1780.

CHAPTER 5

FURTHER DIVERSIFICATION OF THE SPIROKETAL LIBRARY

5.1. Introduction

Following the synthesis of our primary library (**1**), methods to expand upon the diversity and utility of the library were explored. We envisioned further diversification through modification of the *C*2-hydroxyl (**2**). Increased diversity and utility could also be achieved by incorporating an azide functionality on either ring of the spiroketals (**3** or **5**). The azide would provide a handle enabling simple and versatile coupling of other small molecules, including reporter tags or biasing elements.

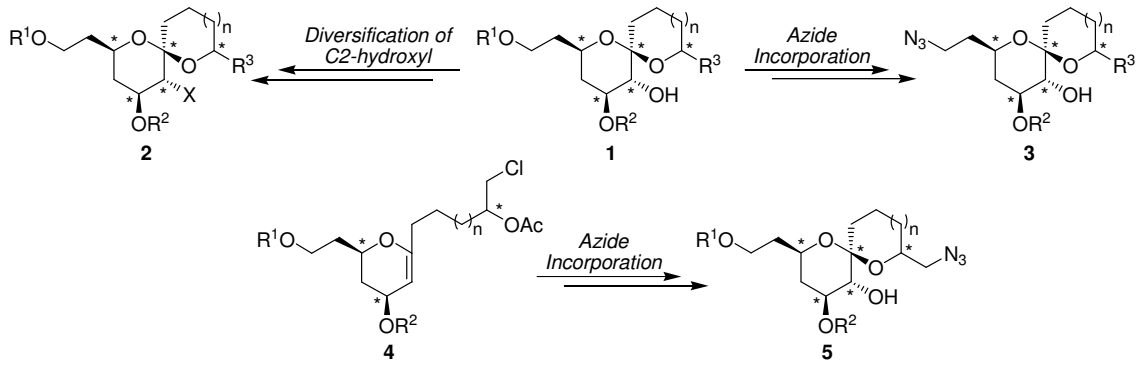


Figure 5.1. Expansion of the diversity and utility of the spiroketal library

5.2. Derivatization of the C2-hydroxyl

In anticipation of future library expansion, we wanted to determine if the spiroketal end products can be diversified further through derivatization of the *C*2-hydroxyl (Figure 5.2). In addition to increasing the diversity of our library, modifications such as acylation and deoxygenation may also increase cell permeability. It was demonstrated that acylation (**9**), deoxygenation (**8**), and oxidation (**11**) are all possible in the *erythro*-series of spiroketals. Oxidation has also been successfully followed by hydride reduction, resulting in an equatorially-oriented

hydroxyl (**12**). This sequence provides access to the stereochemical configuration that would arise from a *syn*-epoxidation reaction, thereby increasing the stereochemical diversity of the library. Unfortunately, Justin Potuzak found that analogous *C*2-hydroxyl acylation reactions are not possible in the *threo*-spiroketal series, likely due to *syn*-pentane-like interactions with the *C*3-substituent.

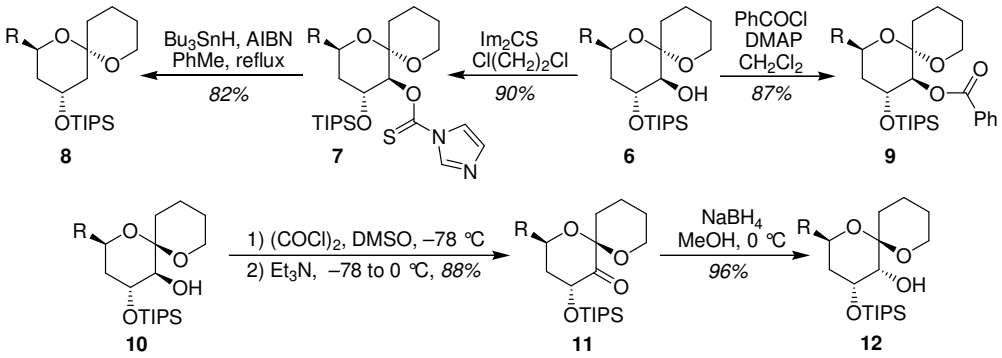


Figure 5.2. Derivatization of *C*2-hydroxyl groups of *erythro*-series spiroketals. R = $(CH_2)_2$OTBDPS

5.3. Incorporation of Azide Tags

It may be useful to incorporate biasing elements into future libraries to target individual proteins for which some structural or mechanistic information is available. Due to the array of reactions that are available using azides, we recognized that azide functionalization of the spiroketals (**3** or **5**) would provide a handle enabling simple and versatile coupling of other small molecules and also provide a means for further diversification and addition of complexity. For example, reduction to the amine **13** using a polymer-supported triaryl phosphine would enable coupling of various biasing elements (e.g. **16**) or complex small molecules (e.g. **17** or **18**) using standard amide bond forming conditions. Direct coupling of the azide with a thioacid to form an amide bond[1] (e.g. **20**) is another possibility. Azide labels would also permit the coupling of a variety of reporter tags to the library compounds either before or after

biological screening[2-4] in aqueous media. Potential methods for generating tagged compounds via an azide include Staudinger ligation with an intramolecular phosphine[3,5] (**19**), Cu(I)-catalyzed Huisgen cycloaddition with an alkyne[6] (**14**), or strain-promoted [3+2] cycloaddition with a cyclooctyne[7] (**15**).

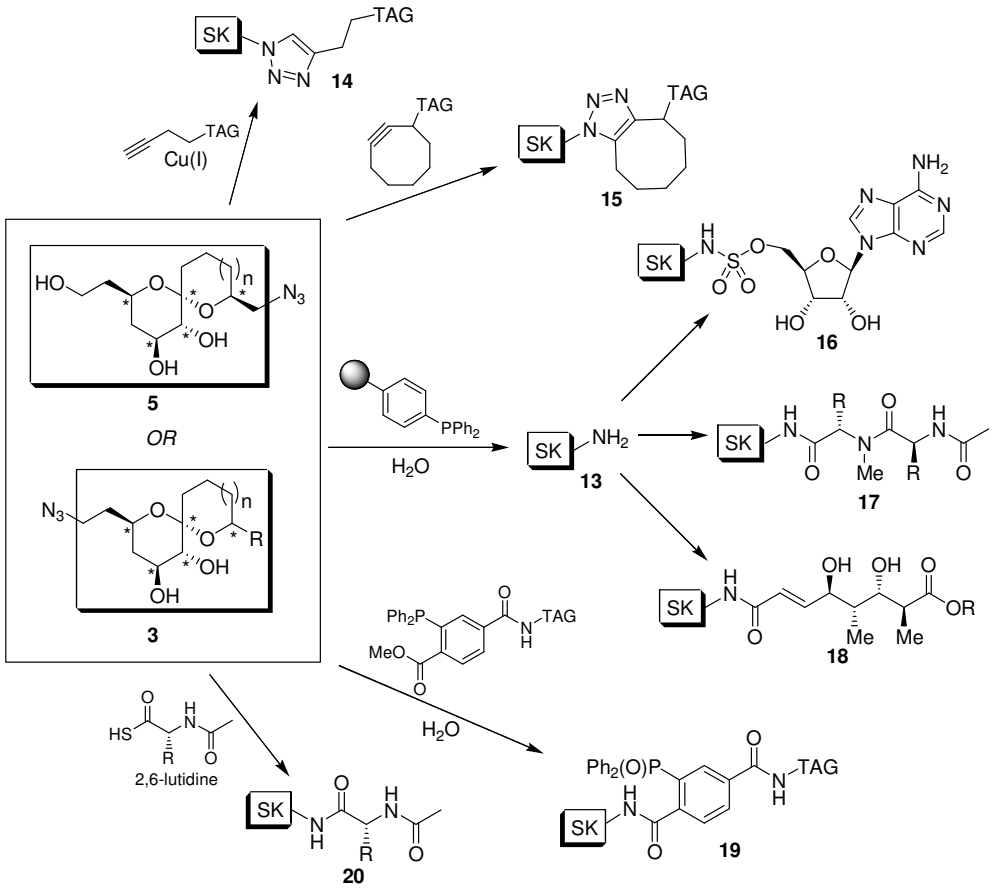
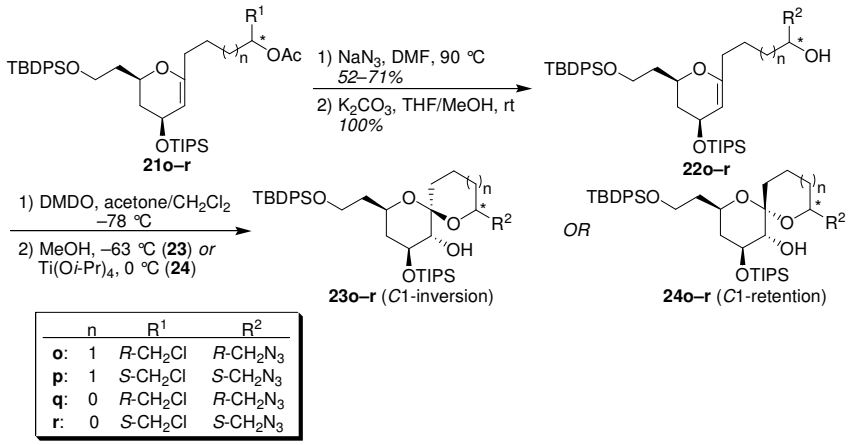


Figure 5.3. Diversification and tagging of azide-labeled library members (*site of stereochemical diversity). SK = boxed portion of spiroketal **3** or **5**

One potential location for an azide tag is on the second ring of the spiroketals (**5**). The optimized *B*-alkyl Suzuki conditions that Justin Potuzak developed allow coupling of chloromethyl-substituted sidechains to the glycals (Figure 2.12). After displacement of the chloride by azide, Justin found that the substrate can be deacetylated (**22o–r**) and epoxidized using the same conditions as our other substrates (Figure 5.4). We then evaluated our kinetic spirocyclization reactions in the

production of azidomethyl-functionalized spiroketals with inversion (**23o–r**) or retention (**24o–r**) of configuration.



	n	R^1	R^2
o:	1	*R*-CH_2Cl	*R*-CH_2N_3
p:	1	*S*-CH_2Cl	*S*-CH_2N_3
q:	0	*R*-CH_2Cl	*R*-CH_2N_3
r:	0	*S*-CH_2Cl	*S*-CH_2N_3

Figure 5.4. Synthesis of azidomethyl-functionalized spiroketals **23** and **24**

While our Ti(O*i*-Pr)$_4$-promoted spirocyclization with retention of configuration was effective with these substrates, achieving inversion of configuration was more problematic (Figure 5.5).

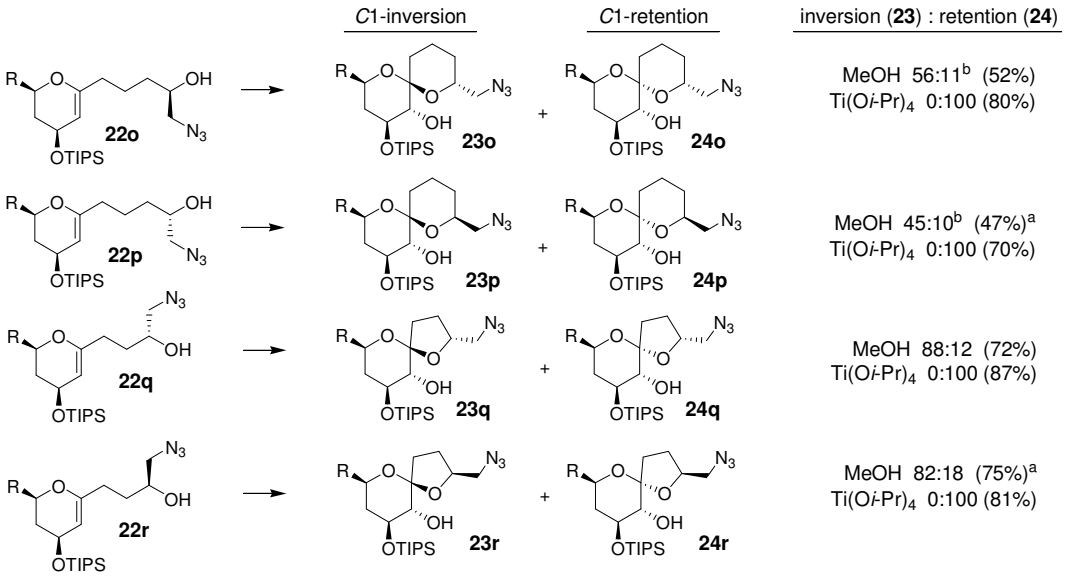
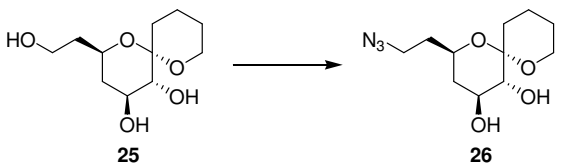


Figure 5.5. MeOH- or Ti(O*i*-Pr)$_4$-induced spirocyclization with inversion or retention of configuration at *C*1. Isolated yields of the major products are shown in parentheses. [a] Inseparable mixture of spiroketals **23** and **24**; [b] Remainder is the corresponding methyl glycoside. R = $(CH_2)_2$OTBDPS

MeOH-promoted spirocyclization was complicated by competing formation of the retention products (**24o–r**) for all substrates. In addition, epoxidation of substrates **22o** and **22p** followed by treatment with MeOH resulted in the formation of significant amounts of methyl glycoside. Since separation of the spiroketal mixtures is not always possible, alternate conditions that selectively form these azidomethyl-substituted inversion spiroketals would be useful.

We also expected that the desilylated spiroketals could be derivatized at the *C*7-position through selective modification of the primary alcohol (**1**→**3**, R^1=R^2=H; Figure 5.1). The possibility of incorporating an azide functionality at this position was explored. Since these tags would be added after synthesis and purification of the library members, an efficient and simple route leading to highly pure final compounds was required. Therefore, initial attempts were focused on one-step approaches to synthesize the azide (**26**) from the primary alcohol in spiroketal **25**. Although several methods have been developed to directly replace primary hydroxyl groups by azide, none of the conditions tested were effective for the spiroketal substrate **25**. Conditions for Mitsunobu-type azide substitution using PPh_3/DIAD/DPPA[8] resulted in low conversion, while only starting material was recovered after treatment with $PPh_3/CBr_4/NaN_3$[9] or PPh_3/DDQ/*n*-Bu_4NN_3.[10] Another related method using *p*-NO_2DPPA in the presence of DBU[11] produced the phosphate intermediate regioselectively, but the majority of this intermediate did not undergo displacement by the azide anion and was isolated after workup.



25 **26**

Figure 5.6. Selective conversion of primary alcohol in spiroketal **25** to azide in **26**

Standard protocols involving sulfonylation followed by displacement with azide anion were also evaluated. A range of sulfonating agents was tested, including tosyl chloride, N-methyltosylimidazolium triflate,[12] mesitylenesulfonyl chloride, and 2,4,6-triisopropylbenzenesulfonyl chloride. Although the more hindered reagents did provide satisfactory regioselectivity, these reactions were difficult to drive to completion, requiring extended reaction times and large excesses of reagent. Interestingly, treatment of bis-tosylated products with Bu_4NN_3 provided only primary azide product, while the secondary tosylate did not react. This tendency could potentially be exploited through use of a sulfonyl chloride resin[13] to form a polymer-bound sulfonate. Treatment with azide ion may then cause selective release of the primary azide product from the resin. However, this possibility was not explored.

Activation of the *C*7 position with halides was also investigated. It has been shown that primary alcohols can be selectively replaced by chloride in the presence of PPh_3 and CCl_4,[14] however, treatment of the spiroketal substrate with these conditions resulted in no reaction. Conversely, similar conditions involving nucleophilic displacement of a phosphonium by iodide anion (PPh_3/I_2/imidazole)[15,16] were very effective, resulting in complete and regioselective conversion to the *C*7-iodide (**28**). Since removal of the triphenylphosphine oxide byproduct was difficult, the possibility of using polymer-supported or fluorous triphenylphosphine was explored. Reactions run in the presence of polymer-supported triphenylphosphine[17] were regioselective, but large excesses of all reagents were required to drive the reaction to completion. Fortunately, replacement of triphenylphosphine with the analogous fluorous reagent[18] **27** did not compromise the regioselectivity or efficiency of the reaction, and all of the byproducts and excess reagents were readily removed by filtration through fluorous silica.[19]

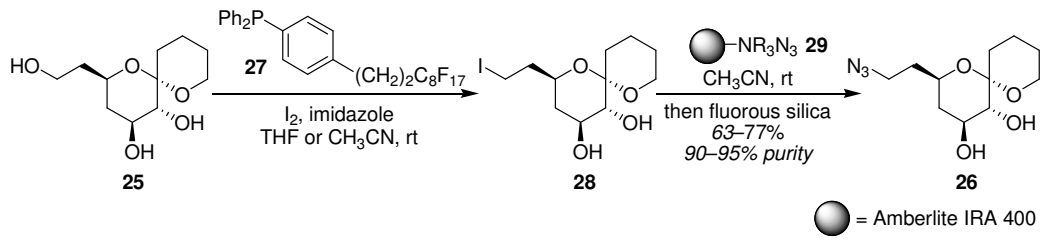


Figure 5.7. Incorporation of azide handle via alkyl iodide

Although treatment of the iodide **28** with a large excess of NaN_3 at high temperature resulted in successful conversion to the azide (**26**), efficient and complete removal of the excess reagent and NaI byproduct was not feasible without an aqueous workup. Azide formation using tetrabutylammonium azide also proceeded smoothly, but complete removal of the tetrabutylammonium iodide byproduct was difficult without chromatography. Fortunately, the azide also formed readily when the iodide was exposed to polymer-supported tetraalkylammonium azide[20] **29**, and the product was easily purified through filtration of the reaction mixture.

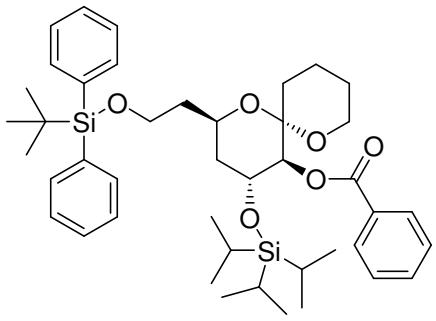
Once these reaction conditions were developed, sequential execution of the two steps was attempted in one pot. Initial efforts using THF as the solvent resulted in efficient formation of the iodide, but no conversion to the azide. Interestingly, when the THF was evaporated after the iodination and the crude iodide was redissolved in CH_3CN, the azidation proceeded as usual. Fortunately, the iodination conditions were also effective in CH_3CN, allowing the two-step sequence to be completed in one pot. After azidation, direct filtration of the reaction mixture through fluorous silica resulted in reasonable yield of a highly pure azide product. Preliminary results suggest that this reaction sequence may also be effective for converting primary hydroxyl groups to azides in other small molecule libraries.

5.4. Experimental Section

Materials and Methods:

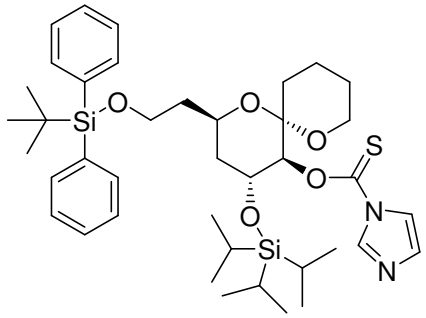
See Section 2.6. Compounds not cited in the previous sections of this chapter are numbered herein **E1o–r**.

Derivatization of the C2-hydroxyl:

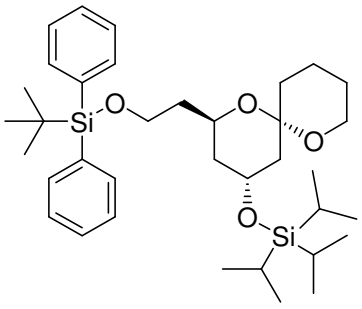


(2*R*,4*R*,5*S*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-yl benzoate (9). DMAP (4.7 mg, 0.038 mmol, 2.5 equiv) then benzoyl chloride (4.0 μL, 0.031 mmol, 2.0 equiv) was added to a solution of spiroketal **6** (9.6 mg, 0.015 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL). The reaction was stirred at rt 45 min then quenched with sat'd aq $NaHCO_3$. The aqueous layer was extracted 3x with Et_2O then the combined organic layers were washed with H_2O then brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography (elution with 95:5 hexanes/EtOAc) to yield **9** as a clear oil (9.7 mg, 87%). **TLC**: R_f 0.60 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2941, 2865, 1724, 1270, 1112, 709. **^{1}H-NMR** (400 MHz): δ 8.06 (d, 2H, J = 8.2), 7.69 (t, 4H, J = 7.9), 7.56 (m, 1H), 7.40 (m, 8H), 4.89 (d, 1H, J = 2.7), 4.49 (m, 1H), 4.11 (m, 1H), 4.02 (m, 1H), 3.82–3.69 (m, 2H), 3.51 (m, 1H), 1.80–1.69 (m, 5H), 1.63–1.49 (m, 3H), 1.35 (m, 2H), 1.15–1.00 (m, 30H). **^{13}C-NMR** (125 MHz): δ 165.2, 135.6, 134.1, 134.0, 133.1, 130.0, 129.8, 129.5, 128.4, 127.6, 96.6, 72.5, 67.7, 60.1, 60.0, 38.8, 35.8, 31.8,

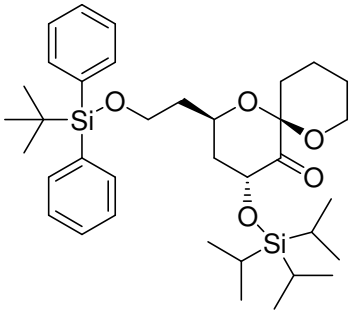
26.8, 25.0, 19.2, 18.4, 18.1, 18.0, 12.3. **ESI-MS** *m/z*: pos 753.5 $[M+Na]^+$; neg 765.3 $[M+Cl]^-$.



(2*R*,4*R*,5*S*,6*S*)-Imidazole-1-carbothioic acid *O*-[2-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undec-5-yl] ester (7). Im_2CS (51 mg, 0.29 mmol, 3.0 equiv) was added to a solution of spiroketal **6** (60 mg, 0.096 mmol, 1.0 equiv) in 1,2-dichloroethane (1.0 mL). The reaction was heated to 80 °C for 6.5 h then the solvent was evaporated. The crude material was purified by flash chromatography (elution with 4:1 hexanes/EtOAc) to provide **7** as a clear oil (63 mg, 90%). **TLC**: R_f 0.21 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2943, 2861, 1461, 1385, 1232, 1103, 1079, 997. **^{1}H-NMR** (400 MHz): δ 8.34 (s, 1H), 7.68 (t, 4H, *J* = 8.4), 7.62 (s, 1H), 7.40 (m, 6H), 7.02 (s, 1H), 5.34 (d, 1H, *J* = 2.7), 4.50 (m, 1H), 4.19 (m, 1H), 3.99 (m, 1H), 3.80-3.69 (m, 2H), 3.52 (dd, 1H, *J* = 11.9, 1.6), 1.77-1.48 (m, 8H), 1.40 (dd, 2H, *J* = 12.9, 3.9), 1.12-0.99 (m, 30H). **^{13}C-NMR** (125 MHz): δ 183.1, 137.0, 135.6, 135.5, 134.0, 133.9, 131.0, 129.6, 127.6, 117.9, 96.2, 80.1, 66.6, 60.3, 60.1, 59.8, 38.7, 35.9, 31.8, 26.8, 24.8, 19.2, 18.2, 18.1, 12.3. **ESI-MS** *m/z*: 737.6 $[M+H]^+$, 759.6 $[M+Na]^+$; neg 771.5 $[M+Cl]^-$.

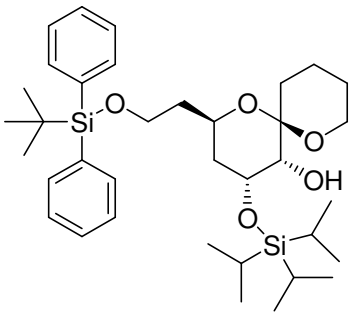


(2*R*,4*R*,6*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecane (8). AIBN (2.1 mg, 0.013 mmol, 0.3 equiv) then Bu_3SnH (15 μL, 0.057 mmol, 2.2 equiv) was added to a solution of spiroketal **7** (19 mg, 0.026 mmol, 1.0 equiv) in anhyd, degassed toluene (0.4 mL). The reaction was heated to reflux and stirred for 1h. The solvent was evaporated and the crude material was purified by flash chromatography (elution with 98:2 hexanes/EtOAc) to yield *C*2-deoxy spiroketal **8** as a clear oil (13 mg, 82%). **TLC**: R_f 0.65 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2941, 2864, 1428, 1113, 1082, 994. **^{1}H-NMR** (400 MHz): δ 7.58 (m, 4H), 7.39 (m, 6H), 4.34 (m, 1H), 4.19 (m, 1H), 3.95 (m, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.45 (dd, 1H, J = 11.6, 4.3), 1.81–1.58 (m, 5H), 1.57–1.41 (m, 5H), 1.33 (m, 2H), 1.11–1.00 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 135.5, 134.2, 134.1, 129.5, 127.5, 95.7, 64.9, 60.3, 60.1, 42.4, 39.6, 39.1, 36.2, 26.8, 25.1, 19.2, 18.8, 18.1, 18.0, 12.3. **ESI-MS** *m/z*: pos 633.3 $[M+Na]^+$; neg 645.5 $[M+Cl]^-$.



(2*R*,4*R*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-one (11). DMSO (110 μL, 1.6 mmol, 25 equiv) was added

dropwise to a cooled (–78 °C) solution of oxalyl chloride (28 μL, 0.32 mmol, 5.0 equiv) in anhyd CH_2Cl_2 (0.3 mL). After 30 min, a solution of spiroketal **10** (40 mg, 0.064 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (0.3 mL) was added dropwise and the reaction was stirred at –78 °C for 15 min. Freshly distilled Et_3N (220 μL, 1.6 mmol, 25 equiv) was then added. The reaction was stirred at –78 °C for 1h then 0 °C for 30 min then quenched with sat'd aq $NaHCO_3$. The aqueous layer was extracted 3x with Et_2O then the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography (elution with 95:5 hexanes/EtOAc) to yield **11** as a clear oil (35 mg, 88%). **TLC**: R_f 0.67 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2942, 2865, 1753, 1464, 1111, 1004. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.45–7.32 (m, 6H), 4.68 (m, 1H), 4.34 (m, 1H), 3.92 (m, 1H), 3.85 (td, 1H, J = 11.4, 2.5), 3.77 (m, 1H), 3.67 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 2.01 (m, 1H), 1.90–1.80 (m, 1H), 1.73–1.57 (m, 3H), 1.44 (m, 1H), 1.11–1.00 (m, 30H). **^{13}C-NMR** (125 MHz): δ 203.3, 135.6, 135.5, 133.7, 129.6, 127.6, 98.7, 70.1, 67.1, 62.2, 60.6, 41.1, 38.3, 28.6, 26.8, 24.8, 19.2, 18.0, 17.9, 12.2. **ESI-MS** *m/z*: pos 647.4 $[M+Na]^+$; neg 623.5 $[M-H]^-$, 659.3 $[M+Cl]^-$.



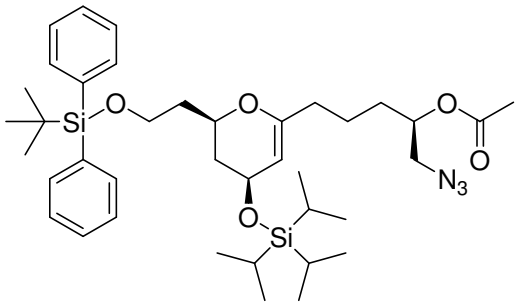
(2*R*,4*R*,5*R*,6*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (12). $NaBH_4$ (2.4 mg, 0.064 mmol, 5.0 equiv) was added in one portion to a cooled (0 °C) solution of spiroketal **11** (8.0 mg, 0.013 mmol,

1.0 equiv) in anhyd MeOH (0.2 mL). After 2 h at 0 °C, the reaction was quenched with sat'd aq NaOAc. The aqueous layer was extracted 3x with Et_2O, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography (elution with 4:1 hexanes/EtOAc) to yield **12** as a clear oil (7.7 mg, 96%). **TLC**: R_f 0.35 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3459, 2942, 2868, 1463, 1111, 999. **^{1}H-NMR** (500 MHz): δ 7.66 (m,4H), 7.38 (m, 6H), 4.32 (m, 1H), 4.18 (m, 1H), 3.93 (m, 2H), 3.76 (m, 1H), 3.62 (m, 1H), 3.37 (dd, 1H, J = 6.9, 3.7), 2.36 (d, 1H, J = 6.9), 2.19 (m, 1H), 1.82 (m, 2H), 1.72 (m, 2H), 1.62 (m, 3H), 1.53 (m, 1H), 1.39 (m, 1H), 1.10–1.00 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 133.9, 129.6, 127.6, 99.1, 74.5, 68.5, 64.9, 61.5, 60.5, 38.5, 37.2, 26.8, 25.2, 19.2, 18.1, 18.0, 12.4. **ESI-MS** *m/z*: pos 649.4 $[M+Na]^+$; neg 625.4 $[M-H]^-$, 661.4 $[M+Cl]^-$.

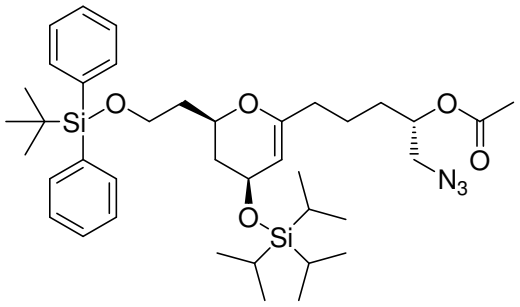
Incorporation of azide tags:

General procedure for conversion of chloro-functionalized glycals to azido-functionalized glycals:

NaN_3 (20 equiv) was added to a solution of chloro-functionalized glycals 2**1o–r** (1.0 equiv) in anhyd DMF (0.020 M final concentration) then the reaction was heated to 90 °C. After 20 h, the reaction was diluted with Et_2O. The organic Et_2O solution was washed 3x with H_2O then the combined aqueous washes were extracted 2x with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. If conversion to the azide was not complete (NMR), the above procedure was repeated. The crude material was purified by flash chromatography (elution with 95:5 pentane/Et_2O) to provide azide-functionalized glycals **E1o–r**. Glycals **E1o–r** were characterized by Justin Potuzak.

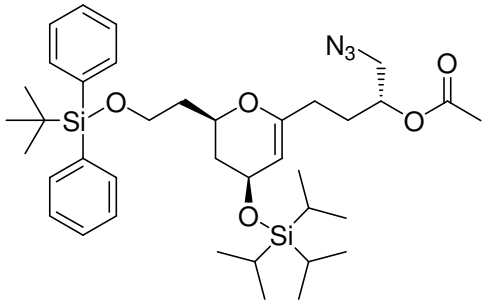


(–)-(2*R*,4*S*,4′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-acetoxy-5-azidopentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E1o). Clear oil (130 mg, 79%) **TLC:** R_f 0.56 (4:1 hexanes/EtOAc). $[\alpha]_D^{25} = -2.7°$ (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2941, 2864, 2100 (N_3), 1744, 1689, 1463, 1428, 1372, 1232, 1110, 1087, 1013, 882, 822, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.97 (m, 1H), 4.49 (m, 2H), 4.15 (m, 1H), 3.85–3.73 (m, 2H), 3.34 (dd, 1H, *J* = 13.1, 3.7), 3.25 (dd, 1H, *J* = 13.1, 6.2), 2.09–1.92 (m, 7H), 1.80 (m, 1H), 1.65 (m, 3H), 1.46 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.5, 154.1, 135.5, 133.9, 129.6, 127.6, 101.4, 72.5, 71.5, 63.9, 60.3, 53.4, 37.7, 33.6, 30.8, 26.9, 22.2, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 730.5 ($[M+Na]^+$, 100); neg 742.4 ($[M+Cl]^-$, 100).

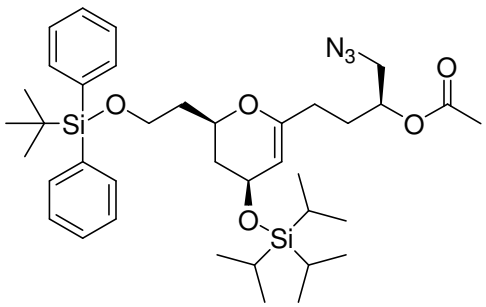


(–)-(2*R*,4*S*,4′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(4′-acetoxy-5-azidopentyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E1p). Clear oil (140 mg, 68%) **TLC**: R_f 0.56 (4:1 hexanes/EtOAc). $[\alpha]_D^{25} = -9.3°$ (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 2941, 2864, 2099 (N_3), 1744, 1668, 1462, 1428, 1372, 1283, 1232, 1110, 1088, 1012, 882, 822, 738, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H),

4.97 (m, 1H), 4.49 (m, 2H), 4.15 (m, 1H), 3.85–3.73 (m, 2H), 3.36–3.23 (m, 2H), 2.09–1.92 (m, 7H), 1.80 (m, 1H), 1.65 (m, 3H), 1.44 (m, 2H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.5, 154.1, 135.5, 133.9, 129.6, 127.6, 101.4, 72.5, 71.5, 63.9, 60.3, 53.4, 37.7, 33.6, 30.9, 26.9, 22.3, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 730.5 ([M+Na]$^+$, 100); neg 742.4 ([M+Cl]$^-$, 100).

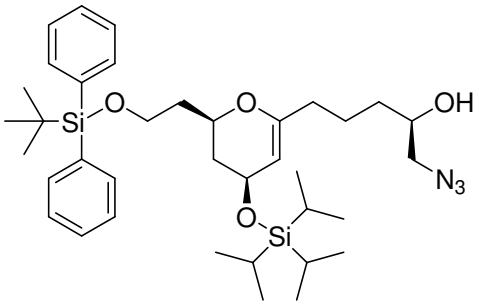


(–)-(2*R*,4*S*,3′*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-acetoxy-4-azidobutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E1q). Yellow oil (35 mg, 83%). $[\alpha]_D^{25} = -7.4°$ (*c* 3.5, $CDCl_3$). **IR** (NaCl, film): 2941, 2864, 2099 (N_3), 1744, 1670, 1463, 1428, 1373, 1230, 1107, 1087, 1064, 882, 823, 738, 702. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.97 (m, 1H), 4.50 (m, 2H), 4.15 (m, 1H), 3.82–3.75 (m, 2H), 3.37 (m, 1H), 3.26 (m, 1H), 2.07–1.92 (m, 7H), 1.82–1.62 (m, 4H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.3, 153.6, 135.5, 133.9, 129.6, 127.6, 101.6, 72.3, 71.7, 63.9, 60.2, 53.3, 37.8, 37.7, 29.8, 28.7, 26.9, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 716.4 ([M+Na]$^+$, 100); neg 728.7 ([M+Cl]$^-$, 100).



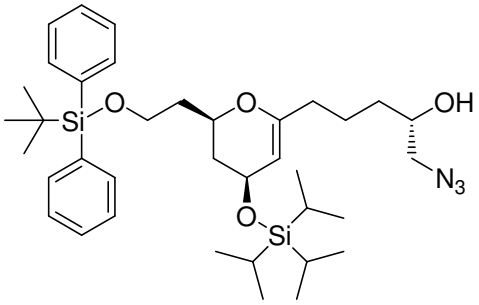
(–)-(2*R*,4*S*,3′*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-(3′-acetoxy-4-azidobutyl)-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran (E1r). Yellow oil (32 mg, 66%). $[\alpha]_D^{25}$ = –7.5° (*c* 3.2, $CDCl_3$). **IR** (NaCl, film): 2942, 2864, 2099 (N_3), 1745, 1670, 1463, 1428, 1373, 1230, 1107, 1086, 1064, 882, 823, 738, 702. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.97 (m, 1H), 4.49 (m, 2H), 4.15 (m, 1H), 3.82–3.74 (m, 2H), 3.36 (m, 1H), 3.25 (m, 1H), 2.07–1.92 (m, 7H), 1.82–1.62 (m, 4H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 170.4, 153.4, 135.5, 133.9, 129.6, 127.6, 101.8, 72.1, 71.7, 63.9, 60.2, 53.4, 37.8, 37.7, 29.8, 28.6, 26.9, 21.0, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 716.4 ($[M+Na]^+$, 100); neg 728.7 ($[M+Cl]^-$, 100).

The glycals **E1o–r** were deacetylated as described in the general procedure (Section 2.6). Glycals **22o–r** were characterized by Justin Potuzak:

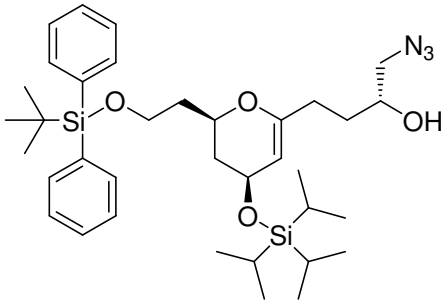


(–)-(2*R*,2′*R*,4*S*)-1-Azido-5-[6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-5,6-dihydro-4*H*-pyran-2-yl]pentan-2′-ol (22o). Clear oil (100 mg, 100%) **TLC**: R_f 0.43 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = –6.0° (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3442, 2941, 2864, 2100 (N_3), 1668, 1462, 1428, 1274, 1106, 1087, 1011, 882, 822, 737, 702. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.49 (m, 2H), 4.15 (m, 1H), 3.83–3.73 (m, 3H), 3.31 (dd, 1H, *J* = 12.4, 3.4), 3.21 (dd, 1H, *J* = 12.4, 7.4), 2.09–1.75 (m, 7H), 1.64 (m, 1H), 1.46 (m, 3H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.1, 135.6, 133.9, 129.6, 127.6, 101.4, 71.5, 70.6, 63.9, 60.3, 57.1,

37.8, 37.7, 33.7, 26.9, 22.6, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 688.5 ($[M+Na]^+$, 100); neg 700.4 ($[M+Cl]^-$, 100).

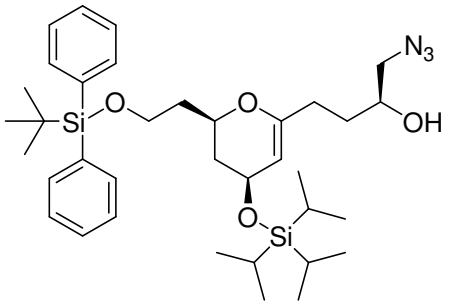


(–)-(2*R*,2′*S*,4*S*)-1-Azido-5-[6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-5,6-dihydro-4*H*-pyran-2-yl]pentan-2′-ol (22p). Clear oil (120 mg, 100%) $[\alpha]_D^{25} = -5.6°$ (*c* 1.0, $CDCl_3$). **IR** (NaCl, film): 3435, 2941, 2863, 2100 (N_3), 1668, 1462, 1427, 1273, 1105, 1087, 1011, 882, 822, 737, 701. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.49 (m, 2H), 4.15 (m, 1H), 3.85–3.70 (m, 3H), 3.31 (dd, 1H, *J* = 12.4, 3.4), 3.21 (dd, 1H, *J* = 12.4, 7.4), 2.09–1.75 (m, 6H), 1.65–1.43 (m, 5H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.1, 135.5, 133.9, 129.6, 127.6, 101.4, 71.5, 70.6, 63.9, 60.3, 57.0, 37.8, 37.7, 33.7, 26.6, 22.6, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 688.4 ($[M+Na]^+$, 100); neg 700.4 ($[M+Cl]^-$, 100).



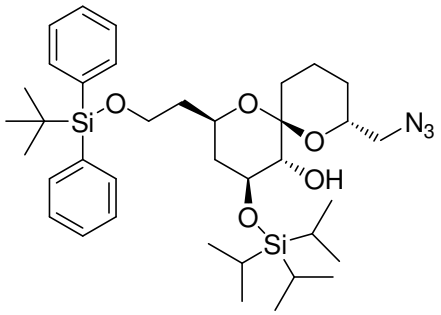
(–)-(2*R*,2′*R*,4*S*)-1-Azido-5-[6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-5,6-dihydro-4*H*-pyran-2-yl]butan-2′-ol (22q). Clear oil (33 mg, 100%). $[\alpha]_D^{25} = -3.5°$ (*c* 2.9, $CDCl_3$). **IR** (NaCl, film): 3428, 2942, 2865, 2101

(N_3), 1670, 1463, 1428, 1277, 1088, 1011, 882, 823, 738, 702. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.58 (s, 1H), 4.49 (m, 1H), 4.17 (m, 1H), 3.82–3.73 (m, 2H), 3.28 (m, 1H), 3.21 (m, 1H), 2.13–2.03 (m, 4H), 1.95 (m, 1H), 1.82 (m, 1H), 1.62 (m, 4H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.0, 135.5, 133.8, 129.6, 127.6, 102.0, 71.8, 70.4, 63.9, 60.2, 56.9, 37.7, 37.6, 31.7, 30.2, 26.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 674.4 ($[M+Na]^+$, 100); neg 686.4 ($[M+Cl]^-$, 100).

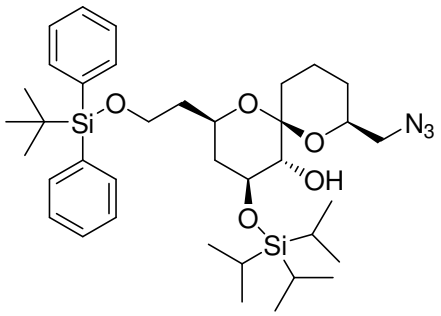


(–)-(2*R*,2′*S*,4*S*)-1-Azido-5-[6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-5,6-dihydro-4*H*-pyran-2-yl]butan-2′-ol (22r). Clear oil (29 mg, 97%). $[\alpha]_D^{25} = -9.1°$ (*c* 2.9, $CDCl_3$). **IR** (NaCl, film): 3460, 2942, 2865, 2101 (N_3), 1670, 1463, 1428, 1274, 1088, 1011, 882, 823, 738, 702. **^{1}H-NMR** (500 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.57 (s, 1H), 4.49 (m, 1H), 4.17 (m, 1H), 3.82–3.73 (m, 2H), 3.28 (m, 1H), 3.21 (m, 1H), 2.13–2.03 (m, 4H), 1.95 (m, 1H), 1.82 (m, 1H), 1.62 (m, 4H), 1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 154.0, 135.5, 133.8, 129.6, 127.6, 101.9, 71.7, 70.3, 63.8, 60.2, 56.9, 37.7, 37.6, 31.6, 30.1, 26.9, 19.2, 18.1, 12.3. **ESI-MS** *m/z* (rel int): pos 674.4 ($[M+Na]^+$, 100); neg 686.6 ($[M+Cl]^-$, 100).

The "inversion" spiroketals **23o–r** were synthesized according to the general procedure for epoxidation and methanol-induced spirocyclization (Section 3.5).

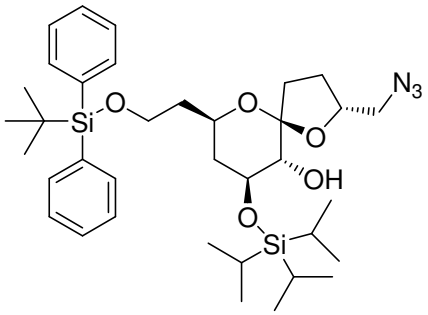


(+)-(2*R*,4*S*,5*R*,6*S*,8*R*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (23o). Clear oil (5.3 mg, 52%). **TLC**: R_f 0.51 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +15º (*c* 0.51, $CHCl_3$). **IR** (NaCl, film): 2940, 2862, 2096 (N_3), 1462, 1261, 1104. **^{1}H-NMR** (500 MHz): δ 7.62 (m, 4H), 7.39 (m, 6H), 4.07 (m, 1H), 3.86 (m, 2H), 3.76 (m, 1H), 3.68 (m, 1H), 3.27 (m, 2H), 3.19 (dd, 1H, J = 12.7, 5.4), 2.32 (d, 1H, J = 2.1), 1.90 (m, 1H), 1.83-1.54 (m, 6H), 1.52-1.35 (m, 3H), 1.08 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.8, 134.1, 129.9, 127.9, 100.2, 79.4, 70.8, 70.6, 66.2, 60.5, 55.4, 40.9, 38.8, 28.0, 27.1, 22.3, 19.4, 18.3, 17.4, 12.8. **ESI-MS** *m/z*: pos 704.1 $[M+Na]^+$; neg 680.1 $[M-H]^-$, 716.2 $[M+Cl]^-$.

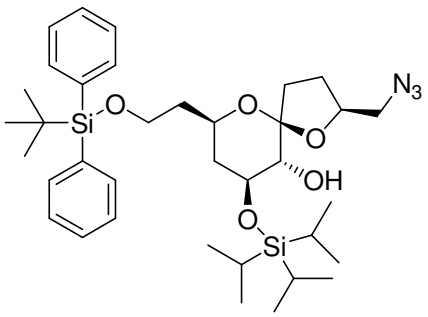


(2*R*,4*S*,5*R*,6*S*,8*S*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (23p). Clear oil (6.8 mg, 47%, 81:19 **23p**:**24p**). **TLC**: R_f 0.43 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2943, 2866, 2095 (N_3), 1465, 1261, 1106. **^{1}H-NMR** (500 MHz): δ 7.64 (m, 4H), 7.43 (m, 6H), 4.06 (m, 1H), 3.79 (m, 3H), 3.69 (m, 1H), 3.63 (m, 1H), 3.32 (dd, 1H, *J* = 9.3, 1.9), 2.80 (dd, 1H, *J* = 12.5, 5.4), 2.37 (d, 1H, *J* = 2.0), 1.88 (m, 2H), 1.77 (m, 4H),

1.62 (m, 1H), 1.48 (m, 3H), 1.07 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 135.5, 129.7, 127.7, 100.8, 79.4, 72.6, 70.7, 66.5, 60.5, 54.6, 40.5, 38.6, 26.9, 25.5, 22.3, 19.2, 18.1, 13.7, 12.6. **ESI-MS** *m/z*: pos 704.2 $[M+Na]^+$; neg 680.2 $[M–H]^–$, 716.3 $[M+Cl]^–$.

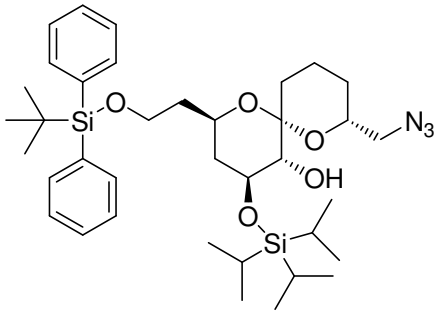


(+)-(2*R*,4*S*,5*R*,6*S*,8*R*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (23q). Clear oil (7.3 mg, 72%). **TLC**: R_f 0.47 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +1.6° (*c* 1.2, $CDCl_3$). **IR** (NaCl, film): 2942, 2864, 2100 (N_3), 1463, 1110. **^{1}H-NMR** (500 MHz): δ 7.62 (m, 4H), 7.44–7.36 (m, 6H), 4.31 (m, 1H), 3.83 (m, 1H), 3.75–3.67 (m, 3H), 3.48 (dd, 1H, *J* = 9.3, 2.3), 3.39 (dd, 1H, *J* = 12.7, 4.4), 3.33 (dd, 1H, *J* = 12.7, 5.3), 2.41 (d, 1H, *J* = 2.3), 2.20 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.85–1.66 (m, 4H), 1.45 (m, 1H), 1.13–1.05 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.8, 129.7, 127.7, 110.0, 77.4, 76.5, 72.1, 66.7, 60.0, 54.0, 40.4, 38.3, 27.8, 27.1, 26.9, 19.2, 18.1, 12.5. **ESI-MS** *m/z*: pos 690.4 $[M+Na]^+$; neg 702.6 $[M+Cl]^–$.



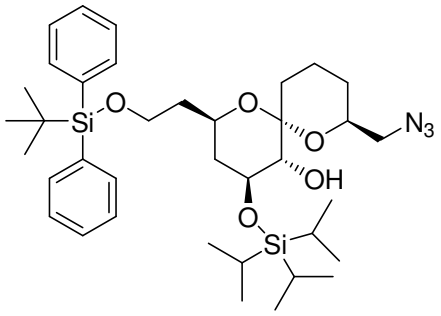
(+)-(2*R*,4*S*,5*R*,6*S*,8*S*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (23r). Clear oil (7.7 mg, 75%, 84:16 **23r**:**24r**). **TLC**: R_f 0.47 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2942, 2865, 2100 (N_3), 1463, 1091. **^{1}H-NMR** (500 MHz): δ 7.62 (m, 4H), 7.41–7.36 (m, 6H), 4.22 (m, 1H), 3.79 (m, 1H), 3.74–3.66 (m, 3H), 3.51 (dd, 1H, *J* = 9.4, 2.1), 3.31 (m, 1H), 3.18 (dd, 1H, *J* = 12.5, 5.0), 2.37 (d, 1H, *J* = 2.1), 2.11 (m, 1H), 2.02 (m, 1H), 1.90 (m, 2H), 1.78–1.62 (m, 3H), 1.49 (m, 1H), 1.08 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.9, 129.7, 127.7, 109.7, 78.7, 76.4, 72.2, 67.1, 60.2, 56.9, 40.3, 38.2, 27.7, 26.9, 26.0, 19.2, 18.1, 12.5. **ESI-MS** *m/z*: pos 690.5 $[M+Na]^+$; neg 702.6 $[M+Cl]^-$.

The "retention" spiroketals **24o–r** were synthesized according to the general procedure for epoxidation and Ti(O*i*-Pr)$_4$-induced spirocyclization (Section 3.5).

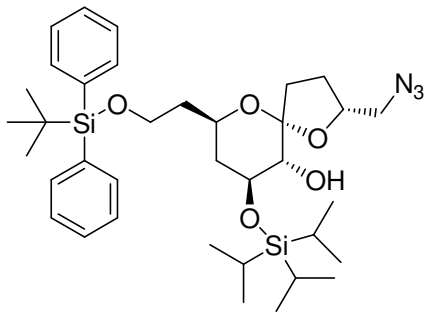


(+)-(2*R*,4*S*,5*R*,6*R*,8*R*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (24o). Clear oil (8.2 mg, 80%). **TLC**: R_f 0.43 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +19º (*c* 0.80, $CHCl_3$). **IR** (NaCl, film): 2941, 2863, 2095 (N_3), 1427, 1259, 1106. **^{1}H-NMR** (500 MHz): δ 7.68 (m, 4H), 7.39 (m, 6H), 4.16 (m, 1H), 4.10–4.01 (m, 2H), 3.74 (m, 2H), 3.38 (dd, 1H, J = 12.4, 7.1), 3.17 (dd, 1H, J = 12.5, 5.9), 3.10 (m, 1H), 2.18 (d, 1H, J = 6.3), 2.10 (m, 1H), 1.98 (m, 1H), 1.79–1.53 (m, 7H), 1.37 (q, 1H, J = 11.9) 1.08 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.8, 129.6, 127.6, 98.9, 79.6, 72.5, 70.5, 65.5, 60.5, 54.6, 40.4, 38.4,

30.8, 26.9, 25.2, 19.2, 18.1, 14.7, 12.5. **ESI-MS** *m/z*: pos 704.5 $[M+Na]^+$; neg 716.4 $[M+Cl]^-$.

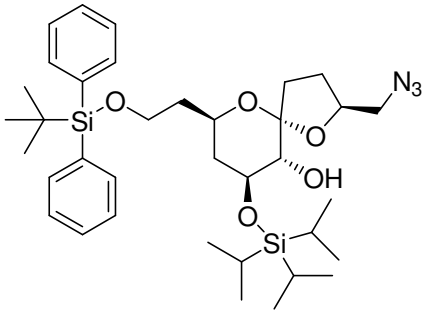


(2*R*,4*S*,5*R*,6*R*,8*S*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[5.5]undecan-5-ol (24p). Clear oil (8.8 mg, 86%). **TLC**: R_f 0.50 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2941, 2864, 2095 (N_3), 1463, 1428, 1388, 1262, 1106. **^{1}H-NMR** (400 MHz): δ 7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.09 (m, 1H), 3.95–3.81 (m, 3H), 3.75 (m, 1H), 3.22 (dd, 1H, *J* = 13.0, 7.5), 3.10 (m, 1H), 2.98 (dd, 1H, *J* = 13.0, 2.7), 2.07–1.96 (m, 3H), 1.78–1.62 (m, 4H), 1.47–1.25 (m, 4H), 1.06 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 133.8, 129.6, 127.6, 98.8, 78.3, 70.6, 70.3, 64.2, 60.3, 55.1, 40.8, 38.5, 30.2, 27.4, 26.8, 19.1, 18.1, 17.9, 12.5. **ESI-MS** *m/z*: pos 682.9 $[M+H]^+$, 704.8 $[M+Na]^+$; neg 680.8 $[M-H]^-$, 716.8 $[M+Cl]^-$.

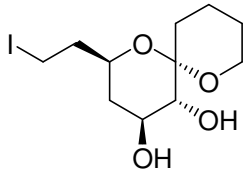


(+)-(2*R*,4*S*,5*R*,6*R*,8*R*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (24q). Clear oil (8.9 mg, 87%).

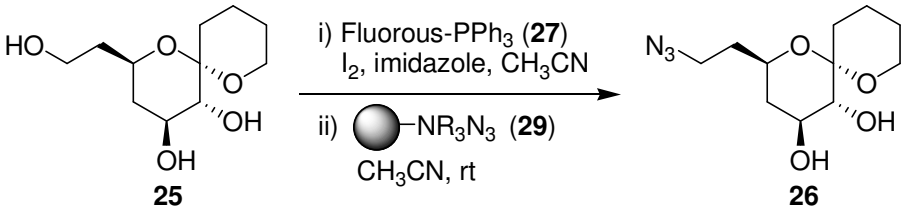
TLC: R_f 0.42 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +41º (*c* 0.93, $CDCl_3$). **IR** (NaCl, film): 2944, 2867, 2096 (N_3), 1465, 1092. **^{1}H-NMR** (500 MHz): δ 7.68 (m, 4H), 7.40 (m, 6H), 4.34 (m, 1H), 3.95 (m, 2H), 3.72 (m, 2H), 3.35–3.25 (m, 2H), 3.0 (m, 1H), 2.28 (m, 1H), 2.02–1.92 (m, 3H), 1.84 (m, 1H), 1.75–1.63 (m, 3H), 1.40 (m, 1H), 1.08 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.6, 133.9, 129.6, 127.6, 108.5, 80.9, 75.4, 71.6, 65.5, 60.7, 56.3, 40.6, 38.4, 34.0, 27.7, 26.9, 19.1, 18.1, 12.6. **ESI-MS** *m/z*: pos 690.4 $[M+Na]^+$; neg 702.6 $[M+Cl]^-$.



(+)-(2*R*,4*S*,5*R*,6*R*,8*S*)-8-Azidomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-1,7-dioxaspiro[4.5]decan-5-ol (24r). Clear oil (8.3 mg, 81%). **TLC**: R_f 0.50 (4:1 hexanes/EtOAc). $[\alpha]_D^{25}$ = +38º (*c* 0.93, $CDCl_3$). **IR** (NaCl, film): 2943, 2865, 2097 (N_3), 1463, 1090. **^{1}H-NMR** (500 MHz): δ 7.64 (m, 4H), 7.44–7.36 (m, 6H), 4.22 (m, 1H), 4.04–3.94 (m, 2H), 3.79–3.70 (m, 2H), 3.36–3.24 (m, 3H), 2.32 (m, 1H), 2.01–1.92 (m, 3H), 1.81 (m, 1H), 1.71–1.63 (m, 3H), 1.42 (m, 1H), 1.12–1.04 (m, 30H). **^{13}C-NMR** (125 MHz): δ 135.5, 134.0, 129.6, 127.6, 108.6, 78.1, 75.9, 71.7, 65.5, 60.3, 54.2, 40.8, 38.2, 33.8, 27.1, 26.8, 19.2, 18.1, 12.6. **ESI-MS** *m/z*: pos 690.4 $[M+Na]^+$; neg 702.6 $[M+Cl]^-$.



(2*S*,4*S*,5*R*,6*S*)-2-(2-Iodoethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (28). A solution of I_2 (33 mg, 0.13 mmol, 1.5 equiv) in anhyd THF (0.8 mL) was added dropwise to a solution of spiroketal **25** (20 mg, 0.086 mmol, 1.0 equiv), diphenyl-[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine **27** (92 mg, 0.13 mmol, 1.5 equiv), and imidazole (12 mg, 0.17 mmol, 2.0 equiv) in anhyd THF (2.0 mL) at reflux. The reaction was refluxed 20 min, cooled to rt, then filtered through a plug of Celite. The filtrate was concentrated, redissolved in a minimal amount of MeCN, then purified by fluorous silica flash chromatography (10 mL fluorous silica, elution with MeCN) to yield iodide **28** as a white foam (25 mg, 83%, ~90% pure). **TLC**: R_f 0.38 (9:1 EtOAc/MeOH). **^{1}H-NMR** (400 MHz): δ 3.86–3.75 (m, 3H), 3.68 (m, 1H), 3.34 (m, 2H), 2.98 (m, 1H), 2.37 (d, 1H, J = 2.0), 2.10–1.90 (m, 5H), 1.79 (m, 1H), 1.65–1.42 (m, 4H), 1.39 (m, 1H). **ESI-MS** *m/z*: pos 365.1 $[M+Na]^+$; neg 377.2 $[M+Cl]^-$.



(2*R*,4*S*,5*R*,6*S*)-2-(2-Azidoethyl)-1,7-dioxaspiro[5.5]undecane-4,5-diol (26). Imidazole (4.1 mg, 0.060 mmol, 1.4 equiv) was added to a solution of diphenyl-[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine **27** (34 mg, 0.047 mmol, 1.1 equiv) and I_2 (12 mg, 0.047 mmol, 1.1 equiv) in anhyd CH_3CN (0.4 mL) in a vial. Spiroketal **25** (10 mg, 0.043 mmol, 1.0 equiv) was added and the reaction was stirred at rt 4 h. The reaction mixture was transferred by syringe to a separate vial containing polymer-supported azide **29**[20] (200 mg). The mixture was vortexed at rt 17 h then additional CH_3CN was added to the vial (2 mL). The solution was removed from the resin by syringe and transferred to a column packed with fluorous silica (20 mL). The resin

was washed with CH_3CN (2 x 2 mL) and the washings were transferred to the silica column. The column was washed with 75 mL CH_3CN then the filtrate was concentrated to provide azide **26** as a clear oil (7.0 mg, 63% from **25**, >95% pure). **TLC**: R_f 0.38 (9:1 EtOAc/MeOH). **^{1}H-NMR** (500 MHz): δ 3.87–3.74 (m, 2H), 3.70–3.61 (m, 2H), 3.52–3.42 (m, 2H), 3.00 (t, 1H, J = 9.5), 2.44 (bs, 1H), 2.01–1.95 (m, 3H), 1.82–1.71 (m, 3H), 1.68–1.47 (m, 4H), 1.39 (m, 1H). **ESI-MS** *m/z*: pos 280.3 $[M+Na]^+$; neg 256.3 $[M–H]^–$, 292.2 $[M+Cl]^–$.

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CHAPTER 6

LEWIS ACID-TETHERED INTERMOLECULAR REACTIONS: CONSTRUCTION OF THE β-1,2-*CIS*-GLYCOSIDIC LINKAGE

6.1. Introduction

Glycoconjugates play important roles in many biological processes such as intercellular communication and adhesion, cell growth, fertilization, immune response, and viral infection.[1] Since homogeneous and chemically defined oligosaccharides are difficult to isolate from biological sources, efficient strategies to chemically synthesize oligosaccharides are essential to explore and manipulate the biological functions of these molecules. In addition, chemical synthesis provides the means to produce non-natural saccharide building blocks or non-natural linkages. Recognition of the significant biological role of oligosaccharides has generated dramatic growth in the field of synthetic carbohydrate chemistry, particularly in the area of glycosylation methods.[2] However, while 1,2-*trans*-glycosides can usually be obtained in pure form by exploiting the neighboring-group effect, there is still no general and straightforward route to 1,2-*cis*-glycosides.[3] The β-1,2-*cis*-glycoside linkage is particularly difficult to construct since the anomeric effect favors the α-linkage.

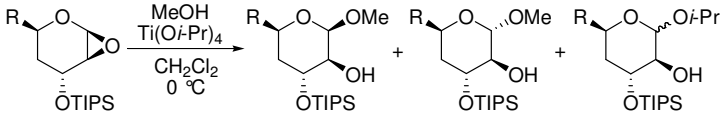
The most common classical methods to synthesize the β-1,2-*cis*-glycoside linkage are the insoluble promoter strategy[4] and oxidation/reduction of the 2-position of a β-glucoside.[5] However, the insoluble promoter strategy is not reliably stereoselective, and the oxidation/reduction strategy is inefficient. More recently, intramolecular delivery strategies that employ a temporary covalent tether between the β-*C*2-hydroxyl group and the nucleophile have been developed that allow synthesis of β-1,2-*cis*-glycosides with complete stereocontrol for some substrates.[6,7] These tethering strategies are similar to our Ti(O*i*-Pr)$_4$-mediated spirocyclization reaction,

and were in fact the inspiration for its development. Therefore, the possibility of using a noncovalent Lewis acid tether to direct intermolecular β-glycosylation of glycal epoxides was explored. While there is some precedent for effective syntheses of *C*-1,2-*cis*-glycosides using Lewis acid tethers,[8-10] the potential of this strategy for *O*-glycosylation[11] has not been thoroughly assessed.

6.2. Studies Toward β-1,2-cis-Glycosidation

In an initial study, the effect of Ti(O*i*-Pr)$_4$ on the stereoselectivity of methanolysis of glycal epoxide **1** was investigated. In the absence of catalyst, methanolysis provides the α-methyl glycoside as a single stereoisomer (Table 6.1, entry 1). Although β-selectivity as high as 10:1 (entry 2) can be achieved in this model system, the reaction is complicated by competing formation of the isopropyl glycosides **4** and **5**. The quantity of isopropyl glycoside formed can be minimized by reducing the amount of Ti(O*i*-Pr)$_4$ used, but the selectivity is then compromised (entry 3).

Table 6.1. Methanolysis of glycal epoxide **1** in the presence of Ti(O*i*-Pr)$_4$.
R = $(CH_2)_2$OTBDPS



1 **2** (β) **3** (α) **4** (β) **5** (α)

entry	Ti(O*i*-Pr)$_4$ (equiv)	MeOH (equiv)	**2** (β) (%)	**3** (α) (%)	**4** + **5** (%)
1	0	1000	0	100	n/a
2	5	2	50	5	45
3	2	5	63	30	7
4	2	2	52	22	26

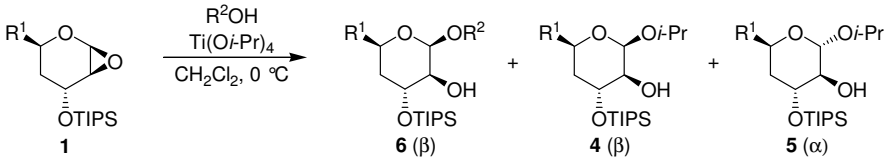
Interestingly, the isopropyl glycoside that was formed in these experiments was found to be a mixture of the α and β anomers. Similarly, when glycal epoxide **1** was treated with Ti(O*i*-Pr)$_4$ alone (Table 6.2, entry 1), selectivity for β- over

α-isopropyl glycoside formation was low. This suggests that "intramolecular" transfer of isopropoxide directly from Ti to the activated oxonium is not necessarily favored over intermolecular addition of free isopropanol to the activated species.

Attempts to suppress unwanted glycoside formation by increasing the steric bulk of the ligands on titanium or reducing their capacity for exchange were unsuccessful. For example, although only a small amount of *t*-butyl glycoside was formed when the Ti(O*i*-Pr)$_4$ catalyst was replaced with Ti(O*t*-Bu)$_4$, the maximum β:α methyl glycoside ratio obtained was 70:30. This poor selectivity may be a result of slow coordination of MeOH to the bulky Ti species. Surprisingly, use of a Ti-BINOL catalyst provided the aryl glycoside as the major product, with only trace amounts of the desired methyl glycosides.

An interesting phenomenon was revealed when a Ti(O*i*-Pr)$_4$-catalyzed glycosylation of **1** with phenol as the nucleophile was carried out, which resulted in complete selectivity for the β-phenyl glycoside (**6**, R^2 = Ph, Table 6.2). This result was not surprising in light of a later experiment showing that even uncatalyzed phenyl glycosylation of the same epoxide **1** occurs exclusively at the β-face. However, there was also a small amount of β-isopropyl glycoside (**4**) produced in the Ti(O*i*-Pr)$_4$-catalyzed version, with no evidence of α-isopropyl glycoside formation (Table 6.2, entry 2). Although the basis of the effect is unclear, coordination of phenol to titanium may facilitate "intramolecular" transfer of isopropoxide, making intermolecular addition of uncoordinated isopropanol to the activated species less competitive. The addition of benzyl alcohol (entry 4) had a similar effect, but the presence of cyclohexanol did not significantly affect the β:α isopropyl glycoside ratio (cf. entries 1 and 3), suggesting the importance of the aryl functionality.

Table 6.2. Ti(O*i*-Pr)$_4$-promoted glycosylations of glycal epoxide **1** with alcohol (R^2OH) additives



1 **6** (β) **4** (β) **5** (α)

entry	Ti(O*i*-Pr)$_4$ (equiv)	R^2OH (equiv)	**6** (%)	**4** (%)	**5** (%)
1	5	none	n/a	56	44
2	5	PhOH (2)	93	7	0
3	5	cyclohexanol (2)	5	45	42
4	5	BnOH (2)	64	29	7
5	5	cyclohexylmethanol (2)	8	50	42
6	5	pentafluorophenol (2)	72	17	11
7	5	2,6-dimethylphenol (2)	31	44	25
8	5	2,6-diphenylphenol (2)	6	80	14
9	2	2,6-diphenylphenol (2)	4	51	45
10	5	2-phenylphenol (2)	73	27	0
11	1.3	2-phenylphenol (1.3)	70	30	0

The outcome of the Ti(O*i*-Pr)$_4$-catalyzed glycosylation reaction in the presence of less nucleophilic aryl alcohols was then explored, with the anticipation that the β-isopropyl glycoside would still be formed selectively, but production of the undesired aryl glycoside would be reduced. Unfortunately, addition of pentafluorophenol or 2,6-dimethylphenol resulted in only moderate selectivity for the β-isopropyl glycoside, and significant amounts of the aryl glycosides **6** were still produced. Encouragingly, the desired effect was achieved in the presence of 2,6-diphenylphenol and 5 equiv Ti(O*i*-Pr)$_4$ (entry 8). However, when only 2 equiv of Ti(O*i*-Pr)$_4$ was used, the outcome was similar to the case where no alcohol additive was employed (cf. entries 1 and 9). Since this trend was not observed with the less-hindered 2-phenylphenol (cf. entries 10 and 11), it is possible that the sterically-encumbered Ti-diphenylphenol complex does not form efficiently unless a large excess of Ti(O*i*-Pr)$_4$ is present. Attempts to pre-form and isolate various Ti-diphenylphenol complexes were not successful.

The use of $TiCl_4$ as a catalyst resulted in decomposition, however, Yamamoto has shown that the Lewis acidity of $TiCl_4$ can be moderated by combination with a Lewis base to generate a $TiCl_4$•XPh_3 complex (X = As, Sb, Bi).[12] This type of complex is thought to generate $TiCl_4$ very slowly *in situ*. The use of $TiCl_4$•$AsPh_3$ as a catalyst for glycosylation of **1** with *i*-PrOH did result in high β-selectivity (94:6 β:α), however, a large amount of hydrolysis product **7** was recovered after aqueous workup. This may be due to incomplete conversion, followed by hydrolysis of the oxonium intermediate. An alternative explanation could be that the chloride adduct is formed during the reaction, then quenched with water upon workup.

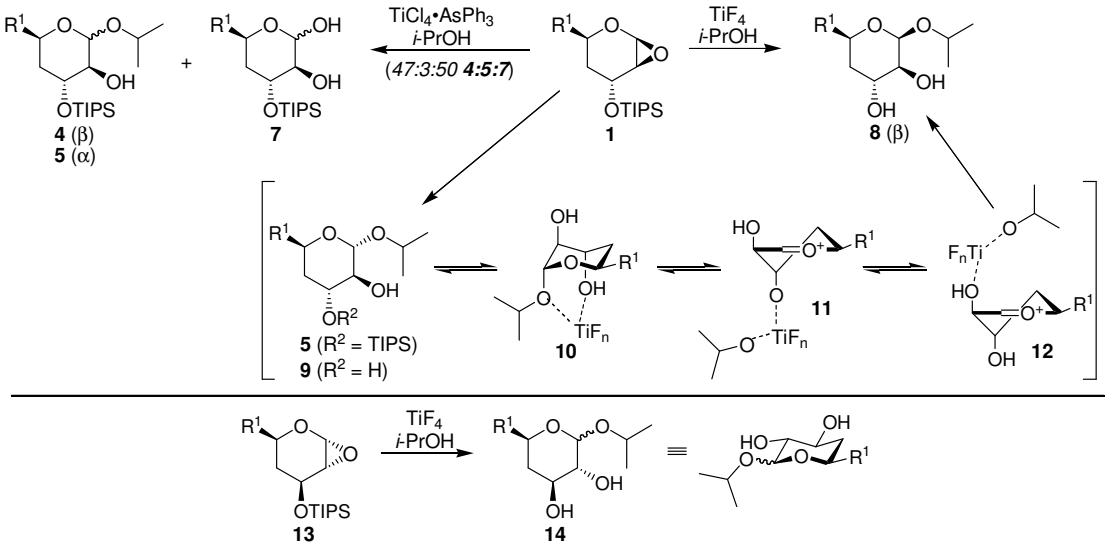


Figure 6.1. $TiCl_4$•$AsPh_3$- and TiF_4-catalyzed glycosylations

The possibility of replacing $TiCl_4$ in this reaction with TiF_4 was then explored, with the expectation that fluoride ion would be less prone to nucleophilic addition. Indeed, use of TiF_4 with or without the $AsPh_3$ additive resulted in exclusive formation of the *C*3-desilylated β-glycoside **8** with no evidence of any hydrolysis products. Later investigations revealed that this reaction is under thermodynamic control. Interestingly, if the reaction is quenched before equilibration to the β-glycoside is

complete, the remaining α-glycoside is still silylated at the *C*3-OH position (**5**). A possible explanation for this observation is that the α-glycoside must be deprotected at the *C*3-OH position before equilibration to the β-glycoside can occur. Once the *C*3-OTIPS group of the α-glycoside has been deprotected (**9**), TiF_4 can coordinate simultaneously to the free *C*3-OH and the oxygen of the isopropyl group (**10**), promoting oxonium formation (**11**). The $TiF_n(O\textit{i}\text{-Pr})$ complex can then coordinate to the *C*2-OH (**12**) and deliver isopropoxide to the β-face of the anomeric position (**8**). Unfortunately, this mechanism is only applicable to substrates with an axial hydroxyl substituent on the α-face. Indeed, exposure of the *threo*-glycal epoxide **13** to the same conditions provided a mixture of α- and β-isopropyl glycosides **14**. Although the substrate scope of this β-glycosylation procedure is limited, these experiments demonstrate the possibility of using TiF_4 for selective TIPS removal in the presence of TBDPS.

6.3. Experimental Section

Materials and Methods:

See Section 2.6. Racemic glycal epoxide **1** was prepared from the corresponding glycal as described in Section 2.4.

*General procedure for methanolysis of glycal epoxide **1** in the presence of Ti(Oi-Pr)$_4$:* $Ti(O\textit{i}\text{-Pr})_4$ then anhyd MeOH were added via syringe to a cooled (0 °C) solution of glycal epoxide **1** (1.0 equiv) in CH_2Cl_2 (0.03 M). The reaction mixture was stirred at 0 °C until all glycal epoxide had reacted (TLC). The cold reaction mixture was quenched with sat'd aq $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, then the combined extracts were washed with H_2O and brine, dried ($MgSO_4$),

filtered and concentrated by rotary evaporation. Glycoside ratios were determined by analysis of the crude material by NMR.

*General procedure for Ti(Oi-Pr)$_4$-promoted glycosylations of glycal epoxide **1** with alcohol (R^{2}OH) additives:*

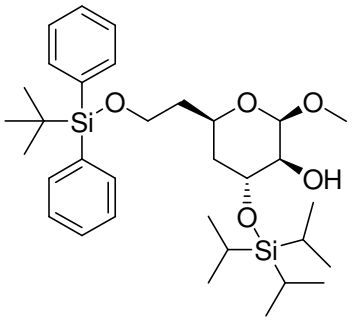
Ti(O*i*-Pr)$_4$ then the alcohol additive (R^{2}OH) were added to a cooled (–78 °C) solution of glycal epoxide **1** (1.0 equiv) in CH_2Cl_2 (0.03 M), then the reaction was warmed to 0 °C. The reaction mixture was stirred at 0 °C until all glycal epoxide had reacted (TLC). The cold reaction mixture was quenched with sat'd aq $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, then the combined extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated by rotary evaporation. Glycoside ratios were determined by analysis of the crude material by NMR.

*Procedure for TiCl$_4$•AsPh$_3$-promoted glycosylation of glycal epoxide **1** with i-PrOH:*

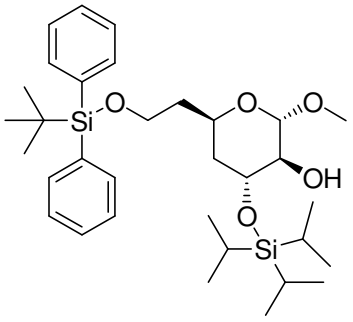
$TiCl_4$ (1.0 M in CH_2Cl_2, 46 μL, 0.046 mmol, 5.0 equiv) was added dropwise to a cooled (–78 °C) solution of $AsPh_3$ (14 mg, 0.046 mmol, 5.0 equiv) in CH_2Cl_2 (0.2 mL). A solution of *i*-PrOH (1.4 μL, 0.019 mmol, 2.0 equiv) in CH_2Cl_2 (0.2 mL) was added dropwise, followed by dropwise addition of a solution of glycal epoxide **1** (0.028 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL). After 30 min at –78 °C and 4 h at rt, the reaction was quenched with sat'd aq $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, then the combined extracts were dried ($MgSO_4$), filtered and concentrated by rotary evaporation to provide a 47:3:50 mixture of β-isopropyl glycoside **4**, α-isopropyl glycoside **5**, and hydrolyzed epoxide **7**. Ratios were determined by analysis of the crude material by NMR.

*Procedure for TiF_4-promoted glycosylation of glycal epoxide **1** with i-PrOH:*

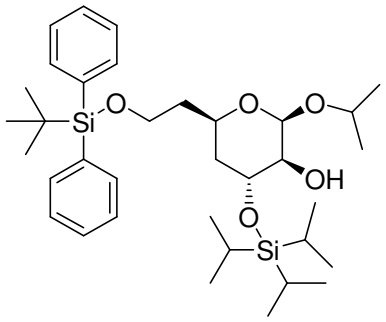
A solution of *i*-PrOH (0.50 μL, 0.0060 mmol, 2.0 equiv) in CH_2Cl_2 (0.1 mL) was added to a solution of glycal epoxide **1** (0.0030 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL), then the combined solutions were transferred to a cooled (–78 °C) solution of TiF_4 (33 μL, 0.016 mmol, 5.0 equiv) in CH_2Cl_2 (0.1 mL). The reaction was stirred at –78 °C for 10 min the quenched with sat'd aq $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, then the combined extracts were dried ($MgSO_4$), filtered and concentrated by rotary evaporation to provide β-isopropyl glycoside **8** as a single isomer (NMR).



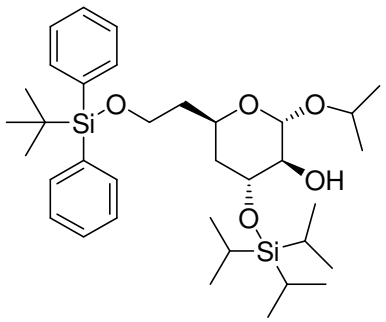
(2*R,3*R**,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-methoxy-4-(triisopropylsilyloxy)-tetrahydropyran-3-ol (2). TLC**: R_f: 0.74 (2:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.40 (m, 6H), 4.65 (s, 1H), 4.19 (m, 2H), 3.91–3.70 (m, 2H), 3.59 (m, 1H), 3.44 (s, 3H), 2.28 (d, 1H, J = 3.5), 1.80–1.60 (m, 4H), 1.12–0.98 (m, 30H).



(2*S,3*R**,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-methoxy-4-(triisopropylsilyloxy)-tetrahydropyran-3-ol (3). TLC**: R_f: 0.61 (2:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): δ 7.67 (m, 4H), 7.40 (m, 6H), 4.50 (d, 1H, *J* = 3.4), 4.39 (m, 1H), 4.00 (m, 1H), 3.82 (m, 1H), 3.71 (m, 1H), 3.50 (m, 1H),3.31 (s, 3H),2.00 (d, 1H, *J* = 5.7), 1.82-1.53 (m, 4H), 1.02 (m, 30H).

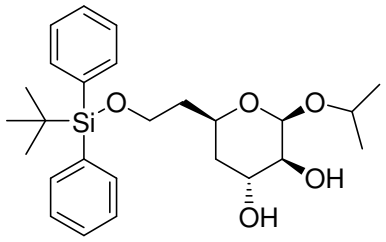


(2*R,3*R**,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-isopropoxy-4-(triisopropylsilyloxy)-tetrahydropyran-3-ol (4). TLC**: R_f: 0.68 (2:1 hexanes/EtOAc). **^{1}H-NMR** (400 MHz): δ 7.65 (m, 4H), 7.39 (m, 6H), 4.86 (s, 1H), 4.19 (m, 2H), 3.96 (m, 1H), 3.88 (m, 1H), 3.73 (m, 1H), 3.52 (m, 1H), 2.37 (d, 1H, *J* = 3.1), 1.81–1.71 (m, 3H), 1.52 (m, 1H, obs), 1.19 (d, 3H, *J* = 6.2), 1.15 (d, 3H, *J* = 6.1), 1.11–1.01 (m, 30H).



(2*S,3*R**,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-isopropoxy-4-(triisopropylsilyloxy)-tetrahydropyran-3-ol (5). TLC**: R_f: 0.63 (2:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.65 (m, 4H), 7.40 (m, 6H), 4.64 (d, 1H, *J* =

3.7), 4.38 (m, 1H), 3.98 (m, 1H), 3.81 (m, 2H), 3.72 (m, 1H), 3.44 (m, 1H), 1.99 (d, 1H, *J* = 5.7), 1.78 (m, 2H), 1.66 (m, 2H), 1.13 (d, 3H, *J* = 5.7), 1.10 (d, 3H, *J* = 5.6), 1.03 (m, 30H).



(2*R,3*S**,4*R**,6*R**)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-isopropoxytetrahydropyran-3,4-diol (8). TLC**: R_f: 0.16 (2:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.64 (m, 4H), 7.39 (m, 6H), 4.87 (bs, 1H), 4.28 (m, 1H), 3.96 (m, 1H), 3.89–3.78 (m, 2H), 3.74–3.67 (m, 2H), 3.58 (m, 1H), 1.86 (d, 1H, *J* = 8.2), 1.80–1.74 (m, 4H), 1.19 (d, 3H, *J* = 6.3), 1.14 (d, 3H, *J* = 6.1), 1.04 (s, 9H).

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CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

As a result of the broader availability of small molecule libraries, the influence of the chemical genetic approach in improving our understanding of biological systems is steadily increasing. The use of small molecules is a powerful complement to gene-based methods for disrupting protein function. However, in order to exhibit the same generality as genetic mutations, small molecules capable of selectively modulating all proteins of interest would need to be identified. Ascertaining the full capabilities of chemical genetics will require the design and synthesis of new libraries that provide chemical structures complementary to those that are already available. In addition to targeting underrepresented regions of chemical structure space, there must be some level of confidence that these newly-designed libraries will be meaningful in biological systems.

One of the standing questions in the field is whether the kinds of chemical structures that are likely to affect protein function can in fact be predicted. Although the strategy of building libraries that are reminiscent of natural products is promising, there are still no generally-accepted guidelines that can be followed for effective library design. In order to determine whether there are a set of rules that govern what types of molecules are likely to modulate specific biological targets, many types of libraries will have to be generated, and their performance assessed in a wide variety of biological assays. Since each protein class will likely require a different type of small molecule modulator, an understanding of what kinds of structures can interact with each class will be necessary.

The availability of more diverse sets of libraries will also allow better determination of the structural features that make a good drug. Although a set of

properties describing “drug-like” molecules has already been established, this description is based on existing drugs and may be biased by the composition of the chemical libraries that have been available for drug identification. Screening of a larger variety of small molecules will also help to determine if all proteins are potential drug targets. Most of the current known drugs bind to proteins that contain receptors for small molecules, but, for example, disrupting protein–protein interactions may require a completely different class of molecules due to the large protein surfaces involved.

The challenge of library synthesis in the context of chemical genetics is twofold: reactions that provide efficient access to a diverse set of molecules must be developed, and these molecules should be limited to structures that are likely to be biologically active. The project described in Chapters 2–5 was designed to address these issues. We have worked out a synthetic strategy that provides access to a specific natural product motif in an efficient and diversified manner. In the process, we have developed methodology that may be useful for other areas of organic chemistry, in addition to library synthesis. The second phase of the project will require evaluation of the library in multiple biological systems to determine how these molecules compare with those in other types of libraries. Although our first-generation library consists of molecules that are relatively small and structurally simple compared to most natural products, we have incorporated functionality that will enable efficient generation of additional complexity for future libraries.