I. Total Synthesis of Galbulimima Alkaloids

II. Resin-bound Glycosyl Phosphates As Glycosyl Donors

III. A Modular Synthesis of FGF-2 Binding Heparin Pentasaccharide

by

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ARCHIVES
This doctoral thesis has been examined by a committee in the Department of Chemistry as follows:

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To my parents, Ann and Tom Hunt,

to my sisters, JenniferAnn and Susan Elizabeth Hunt

and in memory of my brother,

David Spencer Hunt.
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Preface

Portions of this work have been adapted from the following articles that were co-written by the author and are reproduced in part with permission from:


I. Total Synthesis of Galbulimima Alkaloids

The total synthesis of enantiomerically enriched (+)- and (-)-galbulimima alkaloid 13 is outlined. Sequential use of catalytic cross-coupling and cross-metathesis reactions followed by an intramolecular Diels-Alder reaction provided the required trans-decalin AB ring system and masked the C16-carbonyl as an N-vinyl carbamate for late stage oxidative unveilng as the corresponding C16-enone. Completely diastereoselective introduction of the C-ring via radical cyclization chemistry followed by an enamine-ketone addition for construction of the CDE-ring system allowed rapid entry to the pentacyclic core of these alkaloids. The absolute stereochemistry of natural (-)-galbulimima alkaloid 13 is now unambiguously revised to 2S.

Thesis Supervisor: Mohammad Movassaghi
Title: Firmenich Assistant Professor of Chemistry

II. Resin-bound Glycosyl Phosphates As Glycosyl Donors

Resin-bound glycosyl phosphates were readily accessed on solid support via a three step procedure from support-bound glycals. These resin-bound glycosyl phosphates were successfully used as glycosylating agents for coupling with a series of solution based nucleophiles. The stereochemical outcome of disaccharide formation was dependent on the nature of the linker connecting the saccharide to the polymer. Interestingly, other glycosyl donors such as thioglycosides and trichloroacetimidates did not exhibit this dependence, indicating a different reaction mechanism for glycosylation.

III. A Modular Synthesis of FGF-2 Binding Heparin Pentasaccharide

A modular synthesis of FGF-2 binding heparin pentasaccharide is outlined. The synthetic strategy utilizes a disaccharide trichloroacetimidate donor and a uronic acid acceptor as building blocks designed for later application to a fully automated synthesis.

Thesis Supervisor: Peter H. Seeberger
Title: Firmenich Assistant Professor of Chemistry (2003)
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Abbreviations

Ac acetyl
All allyl
Bn benzyl
Bu butyl
Bz benzoyl
Cy cyclohexyl
DIPC N,N’diisopropylcarbodiimide
DMAP dimethylaminopyridine
DMDO dimethyldioxirane
DMF dimethylformamide
DTBMP 2,6-di-tert-butyl-4-methylpyridine
Et ethyl
g grams
h hours
IBX 2-iodoxybenzoic acid
’Pr isopropyl
Lev levulinoyl
Me methyl
Mes mesityl
mg milligram
MOM methoxymethyl
NBS N-bromosuccinimide
NIS N-iodosuccinimide
nOe nuclear Overhauser effect
Piv pivaloyl
TBS tert-butyldimethyisilyl
TDS dimethylthexylsilyl
TBAF tetrabutylammonium fluoride
Z benzylcarbamate
Chapter 1

Total Synthesis of Galbulimima Alkaloids

Thesis Advisor: Mohammad Movassaghi
Introduction and Background

Organic synthesis has long provided access to biologically relevant but naturally scarce polycyclic alkaloids, facilitating the development of new therapeutic agents and improving our understanding of their essential activity. In addition, consideration of the biogenesis of structurally related alkaloids often suggests biomimetic approaches to their synthesis, frequently simplifying the construction of complex structural motifs. The challenges presented by these synthetic targets also provide an excellent arena for the application of emergent chemical transformations.

In 1956, Ritchie and Taylor reported the isolation of a group of fascinating alkaloids from the bark of *Galbulimima belgraveana*, a tree native to northern Australia and Papua New Guinea. Isolation of 28 distinct components followed, resulting in the identification of three discrete classes, exemplified by himbacine (1), galbulimima alkaloid 13 (GB 13, 2), himgaline (3) and himandrine (4) (Figure 1). The tetracyclic lactones such as himbacine (1) represent the major isolates, while the pentacyclic and hexacyclic bases such as GB 13 (2) and amine himgaline (3), and the highly oxygenated ester alkaloids such as himandrine (4) are found in varying amounts depending on the source. Relative stereochemistry for each member was determined using elegant chemical modification studies and via analysis of their UV, IR, and $^1$H NMR spectra. Initial X-ray crystal data for himbacine hydrobromide indicated the absolute stereochemistry of 1 as depicted in Figure 1, including a 2S configuration of the stereocenter at C2. This original assignment was later confirmed by stereoselective total synthesis. Early structural analyses and X-ray data of the more complex polycycles indicated absolute configurations enantiomeric to those shown in Figure 1.
however recent X-ray data for himandrine hydrogen bromide has suggested a reversal of this original assignment.\textsuperscript{4,7}

Early biochemical evaluation of himbacine 1 indicated anti-spasmodic activity,\textsuperscript{8} while recent studies have demonstrated its potential as a selective muscarinic antagonist in the cholergic treatment of Alzheimer’s disease.\textsuperscript{9} Pharmacological data on the remaining galbulimima alkaloids, particularly the penta- and hexacyclic compounds, remains sparse, although spasmylytic activity and central and peripheral cardiovascular effects have been observed.\textsuperscript{10} *Galbulimima* bark has also been reported to have psychoactive properties on ingestion.\textsuperscript{10}

**Biogenetic analysis of the *Galbulimima* alkaloids.**

A compelling hypothesis by Mander, Ritchie and Taylor in 1967 linked various galbulimima alkaloids to a common polyacetate derived precursor.\textsuperscript{3c} Atom mapping suggests a combination of nine acetate units and one pyruvate unit, with incorporation of ammonia to provide the necessary amine (Figure 2). Presumably the core skeletal structure of the Class I lactones would arise from AB ring bicycle formation followed by lactonization involving the incorporated pyruvate unit, and subsequent piperidine formation. For the more complex penta- and hexacyclic alkaloids, backbone construction would require

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Mander, Ritchie and Taylor’s biogenetic analysis of the galbulimima alkaloids.\textsuperscript{3c}}
\end{figure}
connection of the C20-acetate unit to both C8 and the nascent piperidine ring. Subsequent decarboxylation of C18 would provide access to the Class III bases such as GB 13 (2), while N-C9 bond formation and oxidation at C13 would afford the skeleton of the highly oxygenated ester alkaloids of Class II.

Building on this initial analysis, in 2003 we developed a biogenetic proposal for the penta- and hexacyclic galbulimima alkaloids (Figure 3), particularly the captivating

![Biogenetic proposal diagram](image)

**Figure 3.** Our biogenetic analysis of the penta- and hexacyclic galbulimima alkaloids. In particular we sought a strategy that would obviate the need for late-stage oxidation state adjustment. A combination of the acetate, pyruvate, and ammonia building blocks may give rise to an unsaturated linear structure such as 5. Iminium formation at C6 would provide the E ring and an intramolecular Diels-Alder cycloaddition of the resulting activated α,β-unsaturated iminium 6 would provide the AB ring system common to all members of the family. Stereocontrol of this cyclization to provide the required absolute stereochemistry and the trans-decalin may be substrate-derived or rely on enzymatic catalysis. We hypothesized that the bicyclic framework thus installed would afford the structure necessary to direct subsequent
transformations in a diastereoselective manner. In examining the remaining framework, we envisioned that C-ring construction would result from conjugate addition of the C20-C21 enol of tricycle 7 to C8 of the α,β-unsaturated piperidine imine; tautomerization to the enamine would then provide tetracyclic ketone 8. Addition at the C20-ketone of the C5-C6 enamine and subsequent diastereoselective reduction of the resulting imine would complete construction of the bridged CDE ring system and provide the tertiary alcohol at C20 (9). With this major framework established, conversion to the various alkaloids would be straightforward. For example, GB 13 (2) would result from decarboxylation of pentacycle 9. Similarly, himandrine (4) would result from an amine addition to a conjugated enol at C9, followed by reduction at C16 and benzoylation. Conversion of GB 13 (2) to hexacyclic himgaline (3) would result from the conjugate addition of the amine onto the enone at C19 and subsequent C16-ketone reduction to provide the secondary alcohol (Scheme 1). This hypothesis is supported by the conjugate addition observed during Ritchie and Taylor's initial structure determination studies, where treatment with mild protic acid produced oxohimgaline (10), although initial reduction attempts provided the undesired C16-epimer of himgaline (11). It is noteworthy that several years after we began this work, Baldwin reported an interesting and biomimetically relevant synthesis of tetracyclic (+)-himbacine utilizing an iminium mediated transformation for diastereoselective formation of the AB ring system. This work supports the viability of our independent proposal for substrate-directed formation of the AB bicycle en route to the more complex penta- and hexacyclic Galbulimima alkaloids.

![Scheme 1. Interconversion of GB 13 (2) and himgaline (3).](image-url)
Prior Synthetic Studies

The demonstrated biological activity of himbacine (1) has prompted a number of total syntheses of the tetracyclic lactone \(^{14}\) as well as various derivatives for biological testing.\(^ {15}\) To date, construction of the AB-ring trans-decalin fragment has relied on a Diels-Alder reaction of various diene-dienophile pairs as outlined in Figure 4. In most cases subsequent coupling with the piperidine ring fragment has completed the total synthesis.

Despite the considerable interest shown in the galbulimima alkaloids and their intriguingly unique molecular framework, when we initiated our studies only a single report existed concerning synthesis of the more complex members of the family containing the CDE bridged tricyclic moiety. Work by Mander and McLachlan in 2003 outlined the first total synthesis of (±)-GB 13 (2).\(^ {16}\) Key steps in this original report include cycloaddition for construction of the AB decalin and subsequent elaboration of the benzenoid moiety of 17 to provide the piperidine E ring of the target structure (Scheme 2). In the event, acid-catalyzed cyclization of 2-(3-methoxybenzyl)-1,3-dienol ether 12 produced tricycle 13, which on protection, diazoketone formation, and Wolff ring contraction afforded amide 14 as a mixture of endo:exo products with the desired endo compound as the major component (Scheme 2). Amide conversion to the nitrile and dehydrogenation using a \(\alpha\)-selenation, oxidation, elimination sequence provided dienophile 15, which smoothly underwent cycloaddition with
diene 16 in the presence of ytterbium tris(2,2,6,6-tetramethyl-3,5-heptane-dionate) (Yb(thd)_3) at 110 °C to produce the desired endo-adduct 17 in excellent yield. Reduction of the unmasked C16 ketone and protection as the corresponding methoxymethyl ether and subsequent decyanation and Birch reduction of the benzenoid afforded enone 18. Formation of the epoxy ketone 19 via a three step procedure was followed by Eschenmoser fragmentation to provide alkyne 20. Condensation to the bis-oxime, reductive cyclization, further reduction of the resulting hydroxylamine and protection provided the trifluoroacetamide 21 as the major product. Reconstitution of the C16 ketone, installation of the required enone via silyl enol ether formation and Saegusa dehydrosilylation followed by final deprotection completed the synthesis of (±)-GB13 (2).

Scheme 2. Mander's synthesis of (±)-GB13 (2).

Subsequent work out of the Mander group outlined construction of the hexacyclic himandrine skeleton 30 utilizing a similar strategy to that for GB 13. Inclusion of methanol during the photo-Wolff rearrangement sequence and dehydrogenation provided unsaturated
ester 22 for the cycloaddition with diene 16 (Scheme 3). Conversion of the Diels-Alder adduct to the carboxylic acid and isomerization to the trans-decalone was followed by acyl azide formation. Methyl carbamate 24 was accessed via methanolation of the isocyanate obtained from thermal rearrangement of acyl azide 23. Birch reduction of the aromatic ring

Scheme 3. Mander's synthesis of model himandrine skeleton (+)-30.17

also reduced the decalone to provide the enone 25 on isomerization of the anisole-derived methyl enol ether. Fragmentation of the enone to keto-aldehyde 27 required a multistep sequence via triol 26. Subsequent conversion of the aldehyde to the alkyne and dissolving metal reduction provided β-carbinol 28 as a single diastereomer with concomitant reduction to the alkene. Pyrrolidine ring closure was effected by mesylation and carbamate cleavage with subsequent nucleophilic displacement by the unmasked amine. Final ring closure was achieved via an oxidative amination with subsequent hydrogenation and deprotection to provide the desired model system 30 of the himandrine skeleton.
Intrigued by the unique structure of these alkaloids and the paucity of studies directed at complex members possessing the fused CDE-ring system (i.e., 2–4, Figure 1), we initiated our studies in this area. In particular we sought to design a synthetic strategy that would capitalize on our biogenetic analysis of the galbulimima alkaloids and hence allow access to multiple members of the family while minimizing the number of protecting group and oxidation state manipulations required. The resulting synthetic strategy has culminated in the first total synthesis of both (+)- and (−)-galbulimima alkaloid 13 (2), allowing the unambiguous absolute stereochemical assignment of the natural isomer.11

Retrosynthetic Analysis
Motivated by our biogenetic analysis of these interesting alkaloids, we composed a synthetic strategy for galbulimima alkaloid 13 (2) that incorporated several biomimetically inspired key steps. We envisioned a strategic C5-C20 bond disconnection to greatly simplify the structure of 2 to the tetracyclic precursor 31 (Scheme 4). As proposed in our initial biosynthetic analysis, addition of a C5-C6 enamine at the C20 ketone would provide the required bridged CDE ring system. In turn, imino-ketone 31 was expected from conjugate addition to α,β-unsaturated imine 32 of the C20 enol tautomer. In practice, we discovered that incorporation of a silyl enol ether at C20 in 32 was advantageous for effective C-ring closure, AB bicycle generation, and provided an appropriately masked ketone during fragment condensation. Ultimately, application of this endgame strategy to a tricycle
obtained from a linear precursor related to 5 (Figure 3) would allow examination of the practicality of our biomimetic hypothesis. Alternatively, fragment coupling to produce tricycle 32 was envisioned via condensation of aldehyde 33 with iminium chloride salt 34 (Scheme 4). Given the uncertainty concerning the absolute stereochemistry of naturally occurring 2, incorporation of either hand of the readily available optically active iminium salt with a racemic bicycle 33 would provide an expedient route to both enantiomers of advanced intermediates and the target compound. Rapid access to the tricycle 32 would also allow timely exploration of the unique CDE ring system and implementation of our biomimetic proposal for its formation. To this end, construction of the linear tetraene 35 for an endo-selective intramolecular Type I Diels-Alder cycloaddition was anticipated via sequential cross-coupling and cross-metathesis reactions. Introduction of a vinyl oxazolidinone to linear tetraene 35 installed the desired C16 oxidation state, effectively masked the C16-carbonyl during subsequent transformations and was readily removed for late-stage conversion to the required enone of the target compound. Incorporation of the vinyl amide also provided a reactive N-acyl-2-aminodiene for the intramolecular cycloaddition.

Results and Discussion

Synthesis of the AB ring bicycle.

Our first challenge in implementing our synthetic strategy toward galbulimima alkaloid 13 (2) lay in preparing the required substituted AB ring system. Construction of the trans-decalin framework and installation of four new stereocenters was envisioned via an intramolecular Diels-Alder reaction of linear precursor 35 (Figure 5). Elaboration

![Figure 5. Retrosynthetic analysis of tetraene 35.](image-url)
of dibromoalkene 36 via sequential cross-coupling would provide the required diene. Installation of a vinyl oxazolidinone was proposed for introduction of a masked C16-carbonyl. The vinyl enamide should be stable to base and mild acid treatment, fluoride ion, and hydride, yet reactive toward oxidative functionalization or hydrolysis with strong acid for late-stage unveiling of the C16-ketone and conversion to the required α,β-enone of 2. Following diene formation, the dienophile may be installed via olefin cross-metathesis with acrolein as the coupling partner (Figure 5).

Synthesis of tetraene 35 began with dibromoalkene 36, readily prepared from commercially available 7-octene-1,2-diol via oxidation to known 6-heptenal followed by dibromomethylenation (Scheme 5). Elaboration of the dihaloalkene to the

![Scheme 5. Synthesis of dibromoalkene 36.](image)

Z,E-bromodiene was then undertaken. A number of palladium-catalyzed cross coupling strategies have taken advantage of the steric and electronic difference between the cis- and trans-bromide of dibromoalkenes such as 36 to effect stereoselective coupling with the more accessible trans-carbon-bromide bond, among them selective Suzuki, Stille, and Sonogashira, and Heck reactions. Our initial efforts focused on the use of palladium-catalyzed Heck and Stille conditions as outlined in Scheme 6. Early work with

![Scheme 6. Strategy for selective Heck or Stille cross-coupling with dibromoalkene 36.](image)

a C9-C10 acetonide model system exhibited adequate reactivity only at elevated temperatures and was accompanied by dehydrobromination to produce undesired alkyne 38 (Figure 6). The desired vinyl bromide 37 was not observed, suggesting initial
dehydrobromination to the bromoalkyne at elevated temperature with subsequent cross-coupling, a pathway that may result from a slow rate of transmetalation.\textsuperscript{22}

In preparation for Suzuki cross-coupling,\textsuperscript{26} boronate \textsuperscript{40} and boronic acid \textsuperscript{41} were prepared from silyl ether alkyne \textsuperscript{39} via hydroboration\textsuperscript{27} and subsequent hydrolysis\textsuperscript{28} (Scheme 7). Use of the silyl ether allowed straightforward modification at C20 for optimization of diene reactivity in the planned Diels-Alder cyclization. A variety of basic additives including potassium carbonate, potassium hydroxide, and thallium ethoxide were screened for a related model system, however these conditions generally required a large excess of the boronic acid and only produced moderate yields (15-50\%). Ultimately, the Suzuki coupling of dihalide \textsuperscript{36} with boronic acid \textsuperscript{41} (1.1 equiv) utilizing tetrakis(triphenylphosphine) palladium with thallium carbonate (2 equiv) as the base in tetrahydrofuran-water smoothly provided desired vinyl bromide \textsuperscript{42} in 75\% yield (Scheme 8).\textsuperscript{29,30} Later work performed by Meiliana Tjandra, in an effort to reduce the amount of

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**Figure 6.** Dehydrobrominated alkyne product x.\textsuperscript{25}

**Scheme 7.** Synthesis of boronate (±)-\textsuperscript{40} and boronic acid \textsuperscript{41}.

**Scheme 8.** Synthesis of bromodiene \textsuperscript{42} via thallium carbonate mediated Suzuki cross-coupling.
thallium reagent required in favor of the less toxic potassium hydroxide, provided no overall improvement in reaction yield and also produced unwanted dimerization of the boronate (Table 1). Use of the highly reactive catalyst system recently reported by Buchwald employing the SPhos ligand and palladium acetate likewise produced a 1:1 mixture of the desired vinyl bromide 42 and dimer 43.

With vinylhalide 42 in hand, installation of the desired N-acyl group to the diene was addressed. While there is precedent for successful Diels-Alder cycloaddition in the presence of 2-bromo-1,3-dienes, early Diels-Alder studies utilizing this functional group resulted in decomposition of the starting triene. In the event, successful introduction of a vinyl carbamate served a critical role in not only providing a robust N-acyl 2-aminodiene for the planned intramolecular type I Diels-Alder reaction, but also proved a highly effective strategy for masking the C16-carbonyl during subsequent manipulations. Recent work by Buchwald has outlined an efficient method for copper-catalyzed coupling of vinyl halides with various amide derivatives as outlined in Scheme 9. Amination of vinyl bromides was optimal with cyclic amides, catalytic copper iodide with N,N-dimethylethlenediamine
as the ligand at high concentration and elevated temperature. Our examination of the amidation of bromodiene 42 with excess oxazolidin-2-one is outlined in Table 2. Early work indicated that lower levels of copper iodide (20 mol%) provided low conversion, even at high concentration (Table 2, entries 1-3). Stoichiometric amounts of copper iodide improved the reactivity of the system, however extended reaction times produced only moderate yields (12-52%, Table 2, entries 4-6). Performing the reaction at higher concentration resulted in dehydrobromination to form the corresponding alkyne (Table 2, entry 7). Ultimately, use of 50 mol% of copper iodide with 250 mol% of the diamine ligand and potassium carbonate as the base was found to produce the desired product in reasonable yield (Table 2, entry 8).
Given the heterogeneous nature of the reaction mixture, slightly more dilute conditions were found to be optimal, allowing for better mixing and preventing unwanted alkyne formation to afford the desired N-acyl 2-aminodiene 44 in 95% yield (Table 2, entry 9).

Successful installation of the N-acyl group was followed by modification of the functional group at C20 moiety in order to optimize diene reactivity for trans-decalin formation via an intramolecular Diels-Alder cyclization. Incorporation of the dieneophile would then allow access to various Diels-Alder precursors, where the desired oxidation state at C20 would be obtained via conversion of the cyclized products. Desilylation of C20-silyl ether 44 to the corresponding C20-alcohol and subsequent conversion to the C20-ketone and C20-silyl enol ether proceeded in excellent yield to produce N-acyl 2-aminodienes

![Chemical Structures]

Scheme 10. Synthesis and thermal Diels-Alder cycloaddition of trienes 48-50 and tetraene 51.
45, 46, and 47, respectively (Scheme 10). Generation of the activated dienophile was achieved via olefin cross-metathesis of the terminal C9-C10 alkene with acrolein. External activation of the dienophile should selectively provide the desired trans-fused decalin system on cycloaddition. The recent development of well-defined, air-stable, highly reactive ruthenium catalysts such as 55, 56, and 57 has provided an expedient route to functionalized alkenes from simple alkenes via cross-metathesis (Figure 7). Recent work by Grubbs has demonstrated the successful, E-selective installation of α,β-unsaturated carbonyl compounds via cross metathesis with terminal alkenes. Of the metathesis catalysts examined for the cross metathesis of terminal alkenes 44-47, the Grubbs-Hoveyda G2 catalyst 57 proved the most effective, providing the desired enals 48-51 in good yield with excellent E:Z selectivity (>20:1) (Scheme 10). The exceptional reactivity of catalyst 57 allowed the metathesis to proceed rapidly at ambient temperature, a feature vital for successful formation of the highly air- and temperature-sensitive silyl enol ether tetraene product 51.

In approaching the planned intramolecular Diels-Alder cycloaddition, we initially envisioned eventual application of chiral catalysis for enantioselective formation of the desired bicycle. Thus far, efforts for Lewis acid catalysis of triene 48 cycloaddition with lanthanide triflates (scandium (Sc(OTf)3 and ytterbium (Yb(OTf)3)) have resulted in low yields of the desired products and decomposition of the precursor. Fortunately, heating the C20-silyl ether and C20-alcohol trienes 48 and 49 in benzene at 90 °C cleanly effected the desired cyclization in moderate to good yield (Scheme 10). In each case the desired endo cyclization was observed exclusively to provide the required trans-decalin system as a 1:1 mixture of diastereomers at C20. The slower reaction rate of silyl ether diene 48, compared to that of alcohol 49, likely results from steric congestion due to the bulky silyl alkyl substituents. Cyclization of triene 49 directly afforded the corresponding tricyclic hemiacetal.
53 formed from the proximal C20-alcohol and C8-aldehyde. Deprotection of bicycle 52 en route to keto-aldehyde 54 via subsequent oxidation also produced acetal 53. High diastereoselectivity for acetal formation was observed in both cases, providing (8R,9S) relative stereochemistry about the acetal center (Scheme 10), however further conversion to the keto-aldehyde 54 failed. Direct access to the keto-aldehyde bicycle was then envisioned via cyclization of the trienal 50. Monitoring of the thermal Diels-Alder cyclization of ketodiene 50 by $^1$H NMR suggested initial cycloaddition accompanied by further reaction, possibly due to internal aldol condensation with the C8-aldehyde. Extended exposure to the reaction conditions resulted in the decomposition, and neither the keto-aldehyde nor the putative tricyclic aldol product could be successfully isolated. Alternatively, analysis of triene 50 suggested the use of an organocatalyst such as MacMillan’s imidazolidinone 58 for formation of an intermediate chiral iminium ion and subsequent diastereoselective synthesis of the desired ketone bicycle 54 (Figure 8). Unfortunately, use of organocatalyst 58 as well as the achiral lanthanide scandium triflate resulted in decomposition and polymerization of triene 50.

![Figure 8. MacMillan's imidazolidinone organocatalyst 58.](image)

Ultimately, a silyl enol ether at C20 was found to provide the required diene reactivity for the cycloaddition and prevent undesired interaction with the neighboring C8-aldehyde. Heating a solution of tetraenal 51 in toluene at 90 °C afforded the desired trans-decalin aldehyde 33 with high endo-selectivity (>20:1 endo:exo), providing gram-quantities of this key building block in racemic form. The relative stereochemistry of the bicycle was indicated by nOe correlations between the C10-C8 and C9-C19 methines (Scheme 10), and later confirmed by X-ray crystal analysis of an advanced derivative, vide infra. Additionally, the silyl enol ether thus installed effectively masked the ketone from undesired reactivity during fragment coupling and provided a reactive handle for later formation of the C ring.
Access to optically active bicycle 33 was envisioned via asymmetric catalysis, however the sensitivity of the butyl dimethylsilyl enol ether tetraenal 51 to polymerization and decomposition has thus far precluded the use of chiral catalysts. Preparation of the more bulky triisopropyl silyl enol ether at C20 was undertaken in an attempt to circumvent this sensitivity by providing a more stable tetraenal (Scheme 11). Interestingly, olefin cross-

\[ \text{Me} \quad \begin{array}{c}
\text{O} \\
\text{N-)}
\end{array} \quad \begin{array}{c}
\text{OHC} \\
\text{1:1 mixture of diastereomers}
\end{array} \]

(a) TIPSOTf, NEt3, CH2Cl2, -78 °C, 83%. (b) acrolein, 4,5-DihydrolMesCl2Ru=CH(o-PrO)Ph (10 mol%), CH2Cl2, 23 °C, 70% 61, 5% 60. (c) 90 °C, toluene, 25%, (>20:1 endo:exo).


metathesis of precursor tetraene 59 also resulted in an unexpected Diels–Alder cycloaddition of the silyl enol ether diene with acrolein to produce the substituted cyclohexene 60 as a mixture of diastereomers. Unfortunately, the triisopropylsilyl enol ether tetrenal 61 did not provide the desired decalin with the same level of efficiency as the butyl dimethylsilyl enol ether 51 (Scheme 11).

Further efforts to produce optically active bicycle 33 were focused on the incorporation of chiral auxiliaries. Examination of the synthetic strategy immediately suggests incorporation of a chiral oxazolidinone during diene construction. Amination of bromodiene 42 with (R)-(+)−benzyloxazolidin-2-one according to our developed protocol provided the desired N-acyl diene 63 as a mixture of diastereomers at C20, albeit in low yield (Scheme 12). While access to C20-ketone 64 from this triene was straightforward,
formation of the required C20-silyl enol ether 65 returned primarily unreacted ketone. Examination of ketone 64 suggests that the steric bulk of the benzyl substituent may force the oxazolidinone carbonyl out of diene conjugation, resulting in competing reactivity during formation of the silyl enol ether. Installation of a chiral oxazolidinone at C8 was also undertaken by Meiliana Tjandra in an effort to provide enantioenriched bicycle (Scheme 13). Unfortunately, catalysis of the cycloaddition was unsuccessful, while heating tetraene 66 at 90 °C in toluene produced a mixture of exo- and endo-products, with the undesired exo-product 67 predominating. Although an optically active bicycle would allow direct access to a single enantiomer of future intermediates, ultimately future work focused on the fragment coupling of the readily prepared racemic bicycle 33 with an optically active chiral E ring. Subsequent diastereomer separation provided the optically active target compound, while use of either hand of the chiral fragment proved an expedient route to both enantiomers of advanced intermediates and target alkaloid 2.
Exploration of CDE ring synthesis: A C2 desmethyl model system.

With racemic bicycle 33 in hand, fragment coupling with the piperidine E ring was addressed. Inspired by possible biomimetic transformations, we envisioned a potential cascade cyclization for formation of the pentacyclic ring system as described in Scheme 14.

Scheme 14. Our proposed cascade mechanism for the condensation of bicycle 33 and metalloenamine 68 and acid-catalyzed formation of pentacyle 72.

Addition of chiral metalloenamine 68 to the bicycle would provide β-hydroxyimine 69, which would then undergo acid-catalyzed elimination to provide the α,β-unsaturated iminium 70. Conjugate addition of the reactive C21-silyl enol ether at C8 of the iminium 70 would then provide the tetracyclic ketone 71, which would provide the desired pentacyle 72 and its C2-epi enantiomer via C5-C6 enamine addition to the C20-ketone as proposed in the biogenetic analysis of the CDE ring system.

Although our final synthetic strategy involved incorporation of an optically active piperidine ring fragment, initial reaction optimization utilized a system lacking the C1 methyl group in order to simplify reaction monitoring and data analysis by avoiding mixtures of diastereomers at intermediate stages. 6-Methyl-2,3,4,5-tetrahydropyridine 74 was prepared according to literature procedure from 2-methyl-1-piperidine 73 via dehydrohalogenation of the corresponding N-chloropiperidine with potassium hydroxide in methanol at reflux.
While bulb-to-bulb distillation provided the pure imine 74, polymerization and decomposition was observed on storage. Dr. Bin Chen in our laboratory has successfully prepared the more robust chloride salt 75 on multi-gram scale by treatment of the free imine with hydrochloric acid, followed by trituration from tetrahydrofuran and rigorous drying. Iminium chloride 75 was highly hygroscopic and required handling under inert atmosphere for optimal results.

Fragment coupling with bicycle 33 was achieved via condensation of the C8-aldehyde with the metalloenamine of imine salt 75. Although lithiation and transmetalation routes involving cerium and magnesium were explored, direct use of the lithiated imine at low temperature provided optimal results, affording the desired β-hydroxyimine 76 in 74% as a mixture of diastereomers at C8 (Scheme 16). Careful control of reaction temperature was required to avoid undesired addition to the vinyl oxazolidinone carbonyl. With β-hydroxyimine 76 in hand, implementation of our proposed cascade cyclization for formation of the CDE ring system was undertaken. As outlined in Scheme 14, exposure of the β-hydroxyimine 76 to acidic conditions was expected to provide the α,β-unsaturated iminium ion, followed by cascade cyclization to provide the pentacyclic skeleton. Surprisingly,
exposure of the diastereomeric mixture 76 to a mixture of trifluoroacetic acid and pyridine in benzene resulted in rapid cyclization of the C8-hydroxyl onto C21 of the silyl enol ether to give a single diastereomer of imine-acetal 77 (Scheme 17). The relative stereochemistry at C20 was obtained via nOe correlation of the C21 methyl protons and the C19 methine (Scheme 17). Subsequent reduction of imine-acetal 77 with sodium borohydride in ethanol at low temperature provided the corresponding amino-acetal 78 as a mixture of diastereomers at C6 (2:1, relative stereochemistry: (6R,8R):(6S,8R), diastereomeric mixture, Scheme 17). X-ray crystallographic analysis of the major diastereomer established the relative stereochemistry of the acetal as shown and confirmed the endo-configuration of the trans-decalin system formed in the earlier Diels-Alder cyclization (Figure 9).

Figure 9. Chem3D representation of the X-ray crystal structure of amine acetal (±)-78. Silyl alkyl groups and methylene hydrogens have been omitted for clarity.
Subsequent efforts to obtain the \( \alpha,\beta \)-unsaturated imine utilized chemical methods for the dehydration. While use of Burgess reagent\(^{45} \) required elevated temperatures incompatible with the sensitive conjugated product, introduction of a benzene solution of Martin sulfurane\(^{46} \) to the diastereomeric mixture of \( \beta \)-hydroxyimines 76 in benzene provided the desired \( E \)-alkene 79 cleanly in twenty minutes at ambient temperature (Scheme 18). Protonation of imine 79 was readily achieved with trifluoroacetic acid and pyridine in benzene,\(^{47} \) however further reactivity was not observed, and heating of the mixture resulted in decomposition of the sensitive silyl enol ether. Subsequently, activation the silyl enol ether via nucleophilic catalysis was explored.\(^{48} \) Where possible, deuterated solvent was used and reaction progress was monitored directly by \(^1\)H NMR spectral analysis of the reaction mixture. Electrophilic activation of the imine by protonation with either trifluoroacetic acid or nonafluoro \( \text{t-butyl alcohol} \) was followed by addition of a fluoride source to effect the Mukaiyama aldol-Michael addition (Table 3). Work by Carriera has demonstrated the use of tetrabutylammonium triphenyldifluorosilicate (TBAT) for nucleophilic catalysis of Mukaiyama aldol reactions.\(^{49} \) Unfortunately, exposure of silyl enol ether 79 to TBAT in the presence of either proton source resulted in decomposition of the substrate (Table 3, entries 1, 2). Surprisingly, silyl enol ether activation with triethylamine trihydrofluoride effected conjugate addition of the unmasked C20-oxygen, which was followed by C5-C6-enamine addition to the resulting C20-oxonium of intermediate 83 to

![Scheme 18. Dehydrogenation of \( \beta \)-hydroxyimine 76 with Martin sulfurane.](image-url)
Table 3. Attempted electrophilic/nucleophilic activation of imine 79 for Mukaiyama-Michael reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>proton source/solvent</th>
<th>fluoride source</th>
<th>yield (±)-82</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA, pyridine-d&lt;sub&gt;5&lt;/sub&gt; THF</td>
<td>TBAT* decomposition</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(CF&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;COH benzene</td>
<td>TBAT* decomposition</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TFA, pyridine-d&lt;sub&gt;5&lt;/sub&gt; benzene-d&lt;sub&gt;6&lt;/sub&gt;</td>
<td>3HF·NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>4</td>
<td>TFA, pyridine-d&lt;sub&gt;5&lt;/sub&gt; THF</td>
<td>3HF·NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>none/THF</td>
<td>3HF·NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>73%</td>
</tr>
</tbody>
</table>

provide the air-sensitive ether imine 82 as a single diastereomer (Scheme 19; Table 3, entries 3-5). The presence of the methyl substituent was confirmed by <sup>13</sup>C DEPT-135 NMR and 2D-HSQC correlation spectra. The relative stereochemistry about the tetrohydrofuran ring was determined via nOe correlations for the C8-C9 and C21-C17 protons (Scheme 19).

Scheme 19. Formation of pentacyclic ether 82 from tricycle 79.

This rapid cascade cyclization was observed with and without imine activation via an added proton source (Table 3, Entry 5). The preferred reactivity of the C20-oxygen to form
oxonium 83 is likely due to a non-optimal orientation of the bulky C20-\textsuperscript{b}utyldimethylsilyl enol ether for conjugate addition (see 70, Scheme 14). While disappointed at the failure to produce the desired carbocyclic C-ring, we were encouraged by the high diastereoselectivity of the transformation and the demonstrated reactivity of the enamine toward cyclization. These observations supported our proposal that the \textit{trans}-decalin framework was capable of exerting stereocontrol in construction of the unique CDE ring system of the complex galbulimima alkaloids.

An alternative route for C ring formation via a radical cyclization strategy was then explored. We envisioned exploitation of the silyl enol ether of 79 to produce the corresponding \(\alpha\)-halo ketone,\textsuperscript{50} with subsequent free-radical cyclization onto the \(\alpha,\beta\)-unsaturated imine to provide the desired five-membered carbocyclic C ring. Initial treatment of silyl enol ether 79 with \(N\)-iodosuccinimide (NIS) and sodium carbonate in tetrahydrofuran\textsuperscript{51} resulted in \(N\)-iodination of the piperidine imine,\textsuperscript{52} a process readily reversed by treatment with tributyltin hydride. Subsequent halogenation conditions relied on protonation of the imine with either nonafluoro-\textsuperscript{b}utyl alcohol or trifluoroacetic acid in the presence of pyridine to engage the imine prior to addition of either NIS or \(N\)-bromosuccinimide (NBS), respectively at 0 °C in toluene (Scheme 20). Interestingly, halogenation did not produce the corresponding \(\alpha\)-halo ketone,\textsuperscript{53} providing the silyl enol ether vinyl halides 84 and 85 as mixtures of regioisomers (~1.5:1). Excess halogenation, ostensibly at the imine nitrogen, occurred to a lesser extent. Reversion of the dihalo compounds to the C21-halogenated products was observed on exposure to a sodium thiosulfate workup or tributyltin hydride and gentle heating.\textsuperscript{54} As attempted purification, extended storage, or exposure to light resulted in decomposition of the sensitive vinyl

![Scheme 20. Formation of silyl enol ether vinyl halides 84 and 85.](image)

thiosulfate workup or tributyltin hydride and gentle heating.\textsuperscript{54} As attempted purification, extended storage, or exposure to light resulted in decomposition of the sensitive vinyl
halides, crude iodide 84 and bromide 85 were treated to either a sodium thiosulfate workup or rapid filtration through silica gel to remove excess halosuccinimide and used immediately in the subsequent radical cyclization.

Despite a lack of precedent for the use of silyl enol ether vinyl halides for radical cyclization, we envisioned that successful generation of a free-radical at C21 would result in rapid intramolecular 5-exo-trig vinyl-radical cyclization onto C8 of the α,β-unsaturated imine (Scheme 21). Exposure of crude iodide 84 to tributyltin hydride with catalytic 2,2'-azobis(2-methylpropionitrile) (AIBN, 0.05-0.1 equiv) as the radical initiator and subsequent heating from 60 to 90 °C provided a single tetracyclic product 87, albeit in low overall yield (two steps, Table 4, entries 1-3). Deuterated solvent was used to facilitate direct monitoring of the reaction mixture by $^1$H NMR spectral analysis. NOESY experiments performed by my co-worker Meiliana Tjandra indicated key correlations between the C7-C9 and C8-C10 methines, indicating the desired 8R,9S relative stereochemistry about the newly formed C8 stereocenter (Table 4). Use of higher levels of initiator in an effort to improve the overall yield produced an inseparable and unidentified impurity (Table 4, entries 4, 5). Application of these catalytic conditions to vinyl bromide 85 failed to effect the radical cyclization (Table 4, entry 6,7). After some experimentation it was discovered that sequential addition of stoichiometric AIBN was required for effective cyclization of substrate 85 (Table 4, entries 8-10), while the quality of the crude vinyl halide influenced the overall yield. Ultimately, revisititation of the halogenation conditions revealed that bromination in the presence of excess sodium bicarbonate with freshly purified NBS, followed by exposure to tributyltin hydride (4.5 equiv) with portionwise addition of an excess of AIBN (1.5 equiv)
Table 4. Intramolecular vinyl radical cyclization with vinyl iodide 84 and vinyl bromide 85.

<table>
<thead>
<tr>
<th>Entry</th>
<th>equiv AIBN</th>
<th>yield (two steps)</th>
<th>Entry</th>
<th>equiv AIBN</th>
<th>yield (two steps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1 (x2)</td>
<td>23%</td>
<td>6</td>
<td>0.1</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>40%</td>
<td>7</td>
<td>0.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>30%</td>
<td>8</td>
<td>1.0</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>~33%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
<td>1.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35%</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>~50%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>1.0&lt;sup&gt;e&lt;/sup&gt;</td>
<td>44%</td>
</tr>
</tbody>
</table>

<sup>a</sup> 3:1 87:unidentified diastereomer  
<sup>b</sup> 8:1 87:unidentified diastereomer  
<sup>c</sup> sequential addition, 2 portions.  
<sup>d</sup> sequential addition, 4 portions.  
<sup>e</sup> sequential addition, 2 portions.

and heating at 90 °C over 1.5 hours provided a single diastereomer of tetracycle 87 in good yield over the two steps (Scheme 22).

Scheme 22. Optimized conditions for vinyl bromide formation and vinyl radical cyclization for construction of tetracycle 87 from tricycle 79.

With successful diastereoselective introduction of the C-ring, final construction of the CDE-ring framework was undertaken. Earlier formation of pentacyclic ether 82 suggested that unmasking of the ketone at C20 of tetracycle 87 would result in the desired C5-C6 enamine addition, consistent with our proposed biosynthesis (Scheme 14). Treatment of silyl
enol ether 87 with acetic acid in benzene or gentle heating with scandium triflate in methanol resulted in decomposition (Table 5, entries 1,2). Exposure to trifluoroacetic acid in benzene-d$_6$ produced the silyl enol ether tautomer 88 as observed by direct $^1$H NMR spectral analysis of the reaction mixture (Table 5, entry 3). These data indicated the disappearance of the C21-vinyl methine resonance and a downfield shift of the C17-vinyl methine peak, consistent with the conjugated diene of 88. Gratifyingly, we discovered that treatment of silyl enol ether 87 with either tetrabutylammonium fluoride or triethylamine-trihydrofluoride in tetrahydrofuran at ambient temperature smoothly effected the deprotection and addition, directly providing the pentacycle 81 as a single diastereomer (Table 5, entries 4,5). Isolation of compound 81 was hampered by the extreme air-sensitivity of the strained cyclic imine. Direct diastereoselective reduction of the imine was then effected on the crude mixture with sodium borohydride in ethanol at 0 °C following removal of the volatiles from the cyclization reaction. While the resulting amine was air-stable, successful purification of the highly polar amino-alcohol was problematic. Ultimately, a four-step, one-pot synthesis was developed, wherein following reduction of the C6-imine the excess hydride was quenched with ethanolic hydrochloric acid, the mixture was neutralized with triethylamine,

Table 5. Attempted formation of pentacycle 81.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>temp, time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetic acid-d$_4$, benzene-d$_6$</td>
<td>23 °C, 24h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OAc)$_3$ (0.2 equiv) MeOH</td>
<td>23-50 °C, 21h</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>TFA, benzene-d$_6$</td>
<td>23 °C, 1h</td>
<td>(±)-88, 67%</td>
</tr>
<tr>
<td>4</td>
<td>TBAF, THF</td>
<td>0-23 °C, 20min</td>
<td>(±)-81 observed$^a$</td>
</tr>
<tr>
<td>5</td>
<td>3HF+NEt$_3$ THF</td>
<td>23 °C, 3h</td>
<td>(±)-81 observed$^a$</td>
</tr>
</tbody>
</table>

$^a$ Decomposed on attempted purification.
the volatiles were removed, and the crude amine exposed to benzylchloroformate in methylene chloride to provide the benzyl carbamate 89 as a single diastereomer in 46% overall yield (Scheme 23). A key nOe correlation between the C5 and C6 methines indicated that the required cis-stereochemistry at the piperidine ring juncture was achieved.

With a robust route to pentacycle 89 in hand, final conversion of N-acyl alkene to the desired enone was addressed. Initial work exploited the reactivity of the C16-vinyl oxazolidinone to produce an α-hydroxy ketone, where subsequent dehydrogenation would provide the desired unsaturated carbonyl. Dihydroxylation of pentacycle 89 with osmium tetroxide\(^{57}\) provided α-hydroxy ketone 90 as a single diastereomer, \(^{58}\) however the yield was poor (Scheme 24). Alternatively, epoxidation with dimethyldioxirane(DMDO)\(^ {59}\) provided ketone 90 in moderate yield as a mixture of diastereomers following acid hydrolysis of the intermediate epoxide 91 (Scheme 25). Unfortunately, attempted dehydration of α-hydroxy
ketone 90 with either Martin sulfurane or via mesylation and elimination was unsuccessful. Subsequently, functionalization of the unmasked ketone was explored.

Recent work by Nicolau outlined a mild, efficient, one-pot conversion of unfunctionalized alcohols, aldehydes, and ketones to their α,β-unsaturated carbonyl counterparts with 2-iodoxybenzoic acid (IBX). Addition of acid accelerated the process, supporting the hypothesis that the dehydrogenation proceeds through enolization followed by single electron transfer to IBX and subsequent rearrangement of the radical cation to provide the desired enone. Initial enone formation therefore takes place at the more enolizable site, although further unsaturation may be obtained through the use of excess reagent and extended reaction times. Hydrolysis of vinyl oxazolidinone 89 to the corresponding C16-ketone 92 was effected by gentle heating in the presence of p-toluenesulfonic acid (Scheme 26). While dehydrogenation of ketone 92 with IBX (2 equiv) in dimethylsulfoxide at 85°C was sluggish, we were ultimately pleased to discover that direct conversion of the vinyl oxazolidinone 89 to enone 93 could be effected with a large excess of IBX (10-20 equiv) and p-toluenesulfonic acid (4 equiv) in a mixture of benzene and dimethylsulfoxide (3:4, [89] = 0.06 M) (Scheme 27). Direct 1H NMR monitoring of the reaction in deuterated solvent indicated acid-assisted hydrolysis to the C16-ketone 92, followed by oxidation to the desired enone.
Synthesis of optically active (+)- and (−)-galbulimima alkaloid 13.

Having established a rapid and efficient route to racemic desmethyl pentacyclic model system 93, application to the natural system was executed. Enantiomerically pure imine salts (R)- and (S)-34 were prepared on multi-gram scale by Meiliana Tjandra from D- and L-alanine, respectively, via a five step procedure (Scheme 28). Reduction of the acid and protection of the primary amine was followed by iodination to provide known alkyl halide 94. Radical addition of methyl vinyl ketone introduced the remaining four carbon chain. Deprotection of linear ketone 95 to the primary amine with aqueous hydrochloric acid resulted in cyclization to produce the optically active piperidine imine salt (−)-(S)-34 after trituration from tetrahydrofuran and rigorous drying. The optical activity of (−)-34 was measured to be >99% ee by chiral HPLC analysis of the corresponding benzylated derivative. Use of either salt ((−)-(S)-34 or (+)-(R)-34) in subsequent reaction sequences provided access to both enantiomers of the intermediates and target compounds.

Following our optimized protocol, deprotonation of the iminium chloride (−)-(S)-34 with "butyl lithium gave the corresponding lithiated enamine, which upon addition to a cold solution of racemic aldehyde 33 provided the corresponding β-hydroxy imine 69 in 85% yield as an inconsequential mixture of 4 diastereomers (Scheme 29). Dehydration using the Martin sulfurane reagent afforded the desired (7E)-α,β-unsaturated imine 32 and the
Scheme 29. Synthesis of pentacycles (-)-98 and (+)-99 from bicycle (±)-33 and imine salt (-)-(S)-34. 

The corresponding 2-epi-enantiomer as an equal mixture of inseparable diastereomers in 81% yield. These diastereomers were carried forward together in the next two steps prior to their chromatographic separation. Conversion of the imines 32 and 2-epi-ent-32 to the corresponding silyl enol ether vinyl bromides (Scheme 29, ~1:1.5 mixture of C20-olefin isomers) was followed by heating of the crude vinyl bromides with excess tributyltin hydride and sequential addition of AIBN to provide the desired tetracycle 97 along with the C2-epi-enantiomer in 55% yield over the two steps. Treatment of the enol ethers with triethylamine–trihydrofluoride, subsequent removal of the volatiles under reduced pressure, and introduction of sodium borohydride in ethanol resulted in the desired enamine-to-ketone addition and diastereoselective C6-imine reduction, cleanly affording the desired stable
pentacyclic amines in a one-pot process (Scheme 29). At this stage the optically active
diptacyclic amine (−)-98 (36%) and the corresponding 2-epi-enantiomer, amine (+)-99
(34%), were readily separated by flash column chromatography (Scheme 29). Formation of
the corresponding benzyl carbamates (−)-100 and (+)-101 and detailed 2D-NMR analysis
indicated that formation of the C8 stereocenter during the radical cyclization as well as the
introduction of the three contiguous stereocenters (C20, C5, and C6) occurred with a high
level of diastereoselection (Scheme 30). For (−)-100, NOESY correlations between H5-H6
and H9-H19 confirmed the cis-BC- and cis-DE-ring systems, respectively, while a
correlation between H6-H21 was consistent with the correct relative stereochemistry for the
CDE-ring system (Scheme 30). Observation of a NOESY correlation between C1-C6 for

(+)-101 identified this compound as the C2-epimer of the target intermediate (−)-100.
Synthesis from (−)-98 of an advanced intermediate from Mander’s synthesis of (±)-GB 13
confirmed this assignment (Scheme 31).16 Protection of the amine with trifluoroacetic acid
and pyridine in methylene chloride occurred with concomitant acetylation of the tertiary
hydroxyl at C20. Selective cleavage of this ester with lithium hydroxide in water-THF
provided the desired trifluoroacetamide 102 in 23% yield over the two steps (unoptimized).
Subsequent hydrolysis of the vinyl oxazolidinone by gentle heating in benzene with p-
toluenesulfonic acid provided the corresponding ketone in excellent yield.

Scheme 30. Formation of benzyl carbamates (−)-100 and (+)-101. NOESY correlations are indicated with
curved arrows (Diana K. Hunt, Meiliana Tjandra).18
Scheme 31. Synthesis of advanced intermediate 104 from pentacycle (-)-98. Ketone 103 was converted to the desired enone via formation of the trimethylsilyl enol ether followed by Saegusa dehydrosilylation. Spectra for the trifluoroacetamide 104 matched published spectra.

Direct conversion of N-vinyl carbamate (-)-100 to the desired N-Cbz galbulimima alkaloid 13 (105) with IBX and p-toluenesulfonic acid proceeded smoothly in 80% yield (Scheme 32). We were pleased to discover that deprotection of N-Cbz 105 with trimethylsilyl iodide (TMSI) followed by hydrolysis (1N HCl) and basic (1N NaOH) treatment provided synthetic galbulimima alkaloid 13 (2) in 89% yield (Scheme 32). It is of note that in the absence of base treatment trace C16-oxohimgaline (10) resulting from conjugate addition of the secondary amine at C19 was observed, as proposed for the biogenetic synthesis of these alkaloids (Scheme 1). All spectroscopic data for our enantiomerically enriched (-)-galbulimima alkaloid 13 matched those reported for the natural compound. Detailed analysis of 2D-NMR data identified key NOESY correlations between
the protons at C2-C6 and C6-C5, indicating the all-cis configuration of these methines (Figure 10). Correlations between the C6 and C5 methines and one of the C21 methylene protons indicated the correct configuration of the bridged CDE ring system, while a correlation between the C9-C15 methines indicated the relative stereochemistry about the AB trans-decalin. Significantly, the sign of rotation for our synthetic 2 ([α]$_{22}^D$ = −64 (c 0.06, CHCl$_3$)), was consistent with that reported for the natural galbulimima alkaloid 13 (2, Figure 1, [α] = −84 (CHCl$_3$)$_3$ d), unambiguously securing the absolute stereochemistry. Furthermore, synthesis of (+)-galbulimima alkaloid 13 (ent-2, [α]$_{22}^D$ = +66 (c 0.07, CHCl$_3$)) using (+)-(R)-34 (>99% ee) via the route described above with intermediacy of key pentacycle (+)-ent-98 confirmed our absolute stereochemical assignment. Consideration of these data require that the previously reported absolute stereochemistry for natural GB 13 (2) be revised as shown in Figure 1.$^4,7$

Figure 10. Key NOESY correlations for (−)-galbulimima alkaloid 13 2.

Synthesis of C2-epi-C16-oxohimgaline: Insight into the biogenesis of himgaline.

With access to pentacyclic amine (+)-101 and (−)-ent-101 via incorporation of either (S)- or (R)-34 (Scheme 33), we attempted the synthesis of optically active 2-epi-galbulimima alkaloid 13 (i.e., 107, Scheme 33). Interestingly, removal of the nitrogen-protective group of 2-epi-N-Cbz galbulimima alkaloid 13 (106, Scheme 33), under identical conditions to those described for compound 105 led to exclusive isolation of (−)-2-epi-16-oxohimgaline (108, Scheme 33, [α]$_{22}^D$ = −24 (c 0.085, CH$_2$Cl$_2$)). Formation of hexacyclic 108 was indicated by the disappearance of the $^1$H NMR C17 vinylic methine resonance and an upfield shift in the $^{13}$C NMR ketone resonance consistent with a saturated carbonyl. Detailed analysis of 2D-
NMR data identified key NOESY correlations between the protons at C5-C21b and C21a-C10, indicating the correct relative stereochemistry for the bridged CDE-ring system (Figure 11). Correlations between the C9 and C15 methines indicated the correct stereochemistry for the AB *trans*-decalin system. The corresponding enantiomer (+)-2-epi-ent-16-oxohimgaline was also prepared ([α]$_D$$^22$ = +24 (c 0.070, CH$_2$Cl$_2$), using the same procedure and starting with (+)-101. As previously noted, the amine-C19 conjugate addition was observed to a lesser extent for galbulimima alkaloid 13 (2), and was found to be subject to basic hydrolysis. The exclusive isolation of the cyclized product for the 2-epi-compounds is likely due to decreased steric interactions between the C2-methyl and the C17 methine. Significantly, this facile conjugate addition further supports the hypothesis for the biosynthesis of himgaline (3) via sequential conjugate addition and carbonyl reduction of galbulimima alkaloid 13 (2).
Conclusion

We describe the first total synthesis of (-)- and (+)-galbulimima alkaloid 13 (2 and ent-2, respectively, Figure 1). The previously reported absolute stereochemistry of natural (-)-galbulimima alkaloid 13 is now unambiguously revised to 2S. The diastereoselective introduction of the C-ring via radical cyclization chemistry followed by successful execution of our strategy for construction of the CDE-ring system of 98 (33→98, Scheme 29) allowed a rapid entry to the pentacyclic core of these alkaloids, while masking the C16-carbonyl as an N-vinyl carbamate enabled its late stage oxidative unveiling as the corresponding C16-enone. The completely diastereoselective conversion of tetracycle 97 to pentacycle 98 and the conjugate addition seen for both galbulimima alkaloid 13 (2) and 2-epi-galbulimima alkaloid 13 (107) provide strong experimental support for the hypothesis that the more complex galbulimima alkaloids derive from a common precursor. Indeed, many of the biosynthetic steps may rely on highly diastereoselective, non-enzymatically catalyzed transformations. Ongoing work in our laboratory is focused on the synthesis of other members of this intriguing family of alkaloids.

4 The structures for 2-4 shown in Figure 1 are antipodal to the originally described structures. Movassaghi, M.; Hunt, D. K.; Tjandra, M. submitted.
7 Unpublished X-ray data of himandrine (4)-hydrogen bromide has suggested a reversal of the originally assigned absolute stereochemistry of 3; see reference 2 in O’Connor, P. D.; Mander, L. N.; McLachlan, M. M. W. Org Lett. 2004, 6, 703.
12 Further substitution on the AB ring system for certain intermediates in the biogenetic proposal (e.g., in himandrine 4) has been omitted for clarity.


Dr. Bin Chen, Movassaghi Group, Massachusetts Institute of Technology, Cambridge, MA, 2005, personal communication.


Protonation was observed by direct 1H NMR spectral analysis of the reaction mixture.


A downfield shift of the C7, C8 vinyl proton spectra consistent with N-halogenation was observed in the 1H NMR spectrum. For an example of imine N-halogenation, see: Barluenga, J.; Tomás, M.; López-Ortiz, J. F.; Gotor, V. Synthesis 1984, 935.


Kolb, H. C.; VanNieuwenhze, M. S.; Sharples, K. B. Chem. Rev. 1994, 94, 2483. The stereochemistry of the C17-hydroxyl group was not determined.

Adam, W.; Hadjiarapoglou, L. Topics in Current Chemistry 1993, 145. 5


Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies).1 Where necessary (so noted), silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing 1% triethylamine. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Where necessary (so noted), silica gel plates were neutralized by treatment with a solution of 5% triethylamine in dichloromethane followed by heating on a hot plate (~250 °C). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic phosphomolybdic acid (PMA), an acidic solution of p-anisaldehyde (anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate (KMnO₄) or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr at 25–35 °C, then at ~1 Torr unless otherwise indicated.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, and toluene were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.2 Triethylamine, diisopropylethylamine, and benzene were distilled over calcium hydride immediately before use. Acrolein was distilled over calcium sulfate immediately before use. Methyl vinyl ketone was distilled over potassium carbonate and calcium chloride immediately prior to use. Martin sulfurane was purchased from Aldrich and stored in a glove box under nitrogen atmosphere. N-Bromosuccinimide (NBS) was recrystallized from boiling water prior to use. 2-Iodoxybenzoic acid (IBX) was prepared according to literature procedure.3 Activated γ-manganese dioxide (MnO₂) was prepared according to literature procedure.4 The molarity of n-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).5 Ammonia saturated dichloromethane was obtained by agitation of dichloromethane in the presence of ammonium hydroxide followed by drying over anhydrous sodium sulfate. Where necessary (so noted) solutions were deoxygenated by alternate freeze (liquid nitrogen)/evacuation/argon-flush/thaw cycles (FPT, three iterations) or degassed by purging with argon for several minutes.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded with a Varian 300 Mercury or a Varian inverse probe 500 INOVA spectrometer or a Bruker inverse probe 600 Avance spectrometer. Chemical shifts are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the

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NMR solvent (CHCl₃: δ 7.27, C₆D₅H: δ 7.16). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded with a Varian 500 INOVA spectrometer or a Bruker 400 spectrometer with a Magnex Scientific superconducting magnet and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent (CDCl₃: δ 77.2, benzene-d₆: δ 128.4). Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Gas chromatography was performed on an Agilent Technologies 6890N Network GC System with a HP-5 5% Phenyl Methyl Siloxane column (50 °C, 6 min; 25 °C/min to 250 °C; 250 °C, 6 min). We acknowledge the assistance of Dr. Peter Mueller and Mr. Michael Schmidt in obtaining the X-ray crystal structure of compound 78. We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry’s Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electrospray ion source (ESI) or electrospray (ES).

**Compound Numbering.** For compound 2 and compounds ≥ 52, the atom numbering system used is consistent with correlated atoms in the final product as numbered in the isolation papers of the natural alkaloids.⁶

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(±)-trans-2-[3-(tert-Butyl-dimethyl-silyloxy)-but-1-enyll-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (40):

Terminal alkyne 39\(^7\) (4.70 g, 25.5 mmol, 1 equiv) was added dropwise via syringe to a solution of freshly prepared pinacolborane\(^8\) in dichloromethane (5 M, 10 mL, 50.2 mmol, 2.00 equiv) at 0°C. The solution was stirred and allowed to warm to ambient temperature. After 24 h, the solution was partitioned between diethyl ether (300 mL) and saturated aqueous ammonium chloride solution (150 mL). The aqueous phase was extracted with diethyl ether (2 x 150 mL) and the combined organic phases were washed with saturated aqueous ammonium chloride solution (100 mL), were washed with brine (80 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting oil by flash column chromatography (silica gel: diam. 9 cm, ht. 10 cm; eluent: hexanes:EtOAc [95:5] to hexanes:EtOAc [80:20]) provided boronate (±)-40 (5.40 g, 68%) as a colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\), 20°C): 6.60 (dd, \(J = 18, 4.0 \text{ Hz}, 1\text{H}, \text{CH}=\text{CHB}), 5.63 (dd, \(J = 18, 1.7 \text{ Hz}, 1\text{H}, \text{CH}=\text{CHB}), 4.37-4.32 (m, 1\text{H}, \text{CH}_3\text{CHCH}=\text{CH}), 1.28 (s, 6\text{H}, \text{BOC(CH}_3\text{)CH}_3), 1.28 (s, 6\text{H}, \text{BOC(CH}_3\text{)CH}_3), 1.22 (d, \(J = 6.7 \text{ Hz}, 3\text{H}, \text{CHCH}_3), 0.91 (s, 9\text{H}, \text{SiC(CH}_3\text{)}_3), 0.05 (s, 6\text{H}, \text{Si(CH}_3\text{)}_2).

\(^13\)C NMR (125 MHz, CDCl\(_3\), 20°C): 157.2 (BC=C), 83.3 (BC=C), 70.0 ((Me)_2C), 26.1, 25.0, 24.9, 23.9, 18.5, -4.5 (SiCH\(_3\)), -4.6 (SiCH\(_3\)).

FTIR (thin film) \text{cm}^{-1}: 2929 (m), 1996 (w), 1611 (w), 1370 (w), 1337 (w), 1146 (w).

HRMS (ESI) calcd for C\(_{16}\)H\(_{33}\)BNaO\(_3\)Si [M+Na]\(^+\): 335.2184, found: 335.2177.

GC, \(t_R\): 11.73 min

TLC (20% EtOAc in hexanes), \(R_f\): 40, 0.63 (KMnO\(_4\))


\(^8\) Pinacolborane was prepared according to Tucker, C. E.; Davidson, J.; Knochel, P. J. Org. Chem. 1992, 57, 3482.
1,1-Dibromo-octa-1,7-diene (9):

Triphenylphosphine (6.34 g, 24.2 mmol, 2.40 equiv) was added in three portions to a solution of carbon tetrabromide (4.00 g, 12.1 mmol, 1.20 equiv) in dichloromethane (30 mL) at 0°C in an ice bath to produce a yellow-orange solution. The solution was stirred at 0°C for 10 min. A solution of 6-heptenal 9 (1.12 g, 10.0 mmol, 1 equiv) in dichloromethane (6 mL) was introduced via cannula to the cold reaction mixture. The transfer was completed using a second 4-mL portion of dichloromethane and the mixture was vigorously stirred at 0°C. The solution became dark orange and white solid precipitated. After 1 h, excess dibromophosphorane was quenched by sequential addition of triethylamine (3.4 mL, 24 mmol, 2.4 equiv) and methanol (1.0 mL, 25 mmol, 2.5 equiv). The solution was allowed to warm to room temperature, transferred to a separatory funnel and added dropwise to a solution of pentane-diethyl ether (5:1, 300 mL), resulting in precipitation of triphenylphosphine oxide. The resulting light brown solid was removed by filtration and washed with pentane (100 mL). The combined organic filtrate was concentrated and purified by flash column chromatography (silica gel: diam. 5 cm, ht. 10 cm; eluent: hexanes:EtoAc [90:10]) to yield dibromide 36 as a colorless oil (2.21 g, 82%).

\[^{1}H\] NMR (500 MHz, CDCl\textsubscript{3}, 20°C):

6.40 (t, \(J = 7.4\) Hz, 1H, Br\textsubscript{2}C=CH), 5.85-5.76 (m, 1H, HC=CH\textsubscript{2}), 5.02 (app-dq, \(J = 17, 1.5\) Hz, 1H, trans-HC=CH\textsubscript{2}), 4.97 (m, 1H, cis-HC=CH\textsubscript{2}), 2.14-2.05 (m, 4H, Br\textsubscript{2}C=CHCH\textsubscript{2}, H\textsubscript{2}C=CHCH\textsubscript{2}), 1.47-1.41 (m, 4H, CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{2}CH\textsubscript{2}).

\[^{13}C\] NMR (125 MHz, CDCl\textsubscript{3}, 20°C):

138.9, 138.7, 114.9 (HC=CH\textsubscript{2}), 88.9 (Br\textsubscript{2}C=CH), 33.6, 33.0, 28.4, 27.4.

FTIR (thin film) cm\textsuperscript{-1}:

2928 (s), 2857 (m), 1641 (m), 911 (s), 804 (m), 780 (m).

HRMS–EI (m/z):

calcd for C\textsubscript{8}H\textsubscript{13}Br\textsubscript{2}[M+H]\textsuperscript{+}: 265.9300, found: 265.9324.

GC, \(t_{R}\):

10.16 min

TLC (40% EtOAc in hexanes), \(R_{f}\):

6-heptenal, 0.64 (KMnO\textsubscript{4})

36, 0.75 (UV, KMnO\textsubscript{4})

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\textsuperscript{9} 6-Heptenal was prepared from 7-octene-1,2-diol (commercially available), sodium metaperiodate, diethyl ether, water, 1h, 93%. Spectroscopic data matched published data; see: Taylor, R. E.; Galvin, G. M.; Hilfiker, K. A.; Chen, Y. J. Org. Chem. 1998, 63, 9580.
(±)-(2E,4Z)-(4-Bromo-1-methyl-undeca-2,4,10-trienyloxy)-tert-butyl-dimethyl-silane (42):

To a solution of boronate (±)-40 (0.94 g, 3.0 mmol, 1 equiv) in acetone and water (30 mL, 2:1) was added sodium periodate (2.0 g, 9.4 mmol, 3.1 equiv) and ammonium acetate (0.71 g, 9.2 mmol, 3.0 equiv). The resulting cloudy solution was stirred at ambient temperature. After 48 h, the reaction mixture was placed under reduced pressure to remove acetone, was diluted with ethyl acetate (100 mL) and the phases separated. The aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic layers were washed with brine (50 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide boronic acid (±)-41 as a light brown oil (0.66 g, 95%). Dibromide 36 (150 mg, 0.56 mmol, 1 equiv) and crude boronic acid (±)-41 (160 mg, 0.69 mmol, 1.2 equiv) were combined, dissolved in THF-water (3:1, 11 mL), and the solution was degassed thoroughly (FPT). Tetrakis(triphenylphosphine)palladium (33 mg, 0.028 mmol, 0.050 equiv) was added as a solid, light was excluded, and the resulting clear yellow solution was stirred for 5 min. Thallium carbonate (0.53 g, 1.1 mmol, 2.0 equiv) was added as a solid, and the resulting heterogeneous yellow-white mixture was stirred in the dark. After 25 h, the light tan reaction mixture was diluted with ethyl acetate and passed through a silica plug and the clear solution was concentrated. The resulting brown oil was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 4 cm; eluent: hexanes:EtOAc [98:2] to hexanes:EtOAc [96:4]) to provide triene (±)-42 as a yellow oil (156 mg, 75%).

\[\text{H NMR (500 MHz, CDCl}_3, 20^\circ\text{C):} \]

\[
\begin{align*}
6.19 & (d, J = 14.6 \text{ Hz}, 1\text{H, BrCCH=CH}), 
6.03 & (dd, J = 14.6, 4.8 \text{ Hz}, 1\text{H, BrCCH=CH}),
5.91-5.75 & (m, 2\text{H, BrC=CH; CH}_2=\text{CH}),
5.06-4.93 & (m, 2\text{H, CH}_2=\text{CH}),
4.44 & (m, 1\text{H, TBSOCHCH}_3),
2.35-2.28 & (m, 2\text{H, BrC=CHCH}_2),
2.10-2.06 & (m, 2\text{H, CH}_2=\text{CHCH}_2),
1.49-1.43 & (m, 4\text{H, (CH}_2)_2),
1.25 & (d, J = 6.4 \text{ Hz}, 3\text{H, CH}_3),
0.92 & (s, 9\text{H, SiC(CH}_3)_3),
0.08 & (s, 3\text{H, SiCH}_3),
0.07 & (s, 3\text{H, SiCH}_3).
\end{align*}
\]

\[\text{C NMR (125 MHz, CDCl}_3, 20^\circ\text{C):} \]

\[
\begin{align*}
138.9, & 138.3, 133.7, 127.5, 125.2, 114.7, 68.5 \\
(\text{TBSOCH}), & 33.8, 31.6, 28.7, 28.1, 26.1
\end{align*}
\]
FTIR (thin film) cm$^{-1}$: 2955 (s), 2929 (s), 2857 (s), 1472 (w), 1462 (w), 1255 (m), 1149 (m), 1089 (m), 835 (s), 776 (s).


TLC (40% EtOAc in hexanes), $R_f$: 41, 0.26 (KMnO$_4$) 42, 0.83 (UV, KMnO$_4$)
Vinyl bromide (±)-42 (3.10 g, 8.30 mmol, 1 equiv) was transferred in dry toluene to a flame-dried Schlenk pressure vessel, the solvent was removed under reduced pressure, and the vessel filled with argon. Oxazolidin-2-one (869 mg, 9.96 mmol, 1.20 equiv), copper iodide (790 mg, 4.15 mmol, 0.500 equiv), and potassium carbonate (2.29 g, 16.6 mmol, 2.00 equiv) were added under argon, and the vessel was evacuated and back-filled with argon three times. Dimethylethlenediamine (2.23 mL, 20.8 mmol, 2.50 equiv) and toluene (33 mL) were added. The reaction vessel was sealed under argon atmosphere and the green-gray heterogeneous mixture was heated to 110 °C. The solution turned slate-blue after five minutes, then light yellow-green. After 21 h, the solution was cooled to ambient temperature and partitioned between ethyl acetate (200 mL) and water (100 mL). The blue aqueous layer was extracted with ethyl acetate (3 × 150 mL), and the combined yellow organic layers were washed with brine (50 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography (silica gel: diam. 7 cm, ht. 10 cm; eluent: CH₂Cl₂:acetone [99:1] to CH₂Cl₂:acetone [96:4] to CH₂Cl₂:acetone [85:15]) to provide triene (±)-44 as a light yellow oil (2.98 g, 95%).

**1H NMR (500 MHz, C₆D₆, 20°C):**

- 6.09 (dd, \( J = 15.4, 1.0 \) Hz, 1H, \( \text{CH}=\text{CH}_2 \))
- 5.77-5.69 (m, 1H, \( \text{CH}=\text{CH}_2 \))
- 5.63 (dd, \( J = 15.6, 5.5 \) Hz, 1H, \( \text{TBSO}\text{CHCH}=\text{CH} \))
- 5.46 (t, \( J = 7.4 \) Hz, 1H, \( \text{N}\text{C}=\text{CH} \))
- 5.04-4.97 (m, 2H, \( \text{CH}=\text{CH}_2 \))
- 4.27 (app-p, \( J = 6.1 \) Hz, 1H, \( \text{TBSO}\text{CH} \))
- 3.55-3.51 (m, 2H, \( \text{OCH}_2\text{CH}_2\text{N} \))
- 3.02-2.91 (m, 2H, \( \text{OCH}_2\text{CH}_2\text{N} \))
- 2.04-1.98 (m, 2H, \( \text{CH}_2\text{CH}=\text{CH}_2 \))
- 1.94-1.90 (m, 2H, \( \text{N}\text{C}=\text{CHCH}_2 \))
- 1.28-1.24 (m, 4H, \( \text{CH}_2\text{CH}_2\text{N} \))
- 1.21 (d, \( J = 6.3 \) Hz, 3H, \( \text{TBSOCHCH}_3 \))
- 0.11 (s, 9H, \( \text{Si(CH}_3)_3 \))
- 0.10 (s, 3H, \( \text{Si(CH}_3)_2 \))

**13C NMR (125 MHz, C₆D₆, 20°C):**

- 156.2 (O=C)
- 139.2, 134.5, 134.1, 134.0, 125.6, 115.1, 69.5, 61.9, 46.2, 34.3, 29.3, 28.8, 28.3, 26.5 (C(CH₃)₃)
- 25.2, 18.8, -4.0 (Si(CH₃))
- -4.2 (Si(CH₃))

**FTIR (thin film) cm⁻¹:**

- 2928 (w), 2856 (w), 1758 (s), 1414 (m), 1251 (w), 834 (m).
HRMS (ESI): calcd for C\textsubscript{21}H\textsubscript{37}NaNO\textsubscript{3}Si [M+Na]\textsuperscript{+}: 402.2435, found: 402.2444.

TLC (3% acetone in CH\textsubscript{2}Cl\textsubscript{2}), \textit{Rf}: 42, 0.89 (UV, CAM) 
44, 0.54 (UV, CAM)
(±)-3-[(1Z)-1-((E)-3-Hydroxy-but-1-enyl)-octa-1,7-dienyl]-oxazolidin-2-one (45):

A solution of tetrabutylammonium fluoride in THF (1M, 1.9 mL, 1.9 mmol, 1.5 equiv) was added to a solution of silyl ether (±)-44 (487 mg, 1.28 mmol, 1 equiv) in THF (10 mL) at 0 °C. The resulting light yellow solution was vigorously stirred and allowed to warm to ambient temperature. After 3.5 h, the reaction mixture was diluted with ethyl acetate (50 mL), water (5 mL), and saturated aqueous ammonium chloride solution (25 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 ml), and the combined organic layers were washed with brine (25 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 6.5 cm; eluent: CH₂Cl₂:acetone [95:5] to CH₂Cl₂:acetone [80:20] to CH₂Cl₂:acetone [50:50]) to provide the alcohol (±)-45 as a clear oil (321 mg, 95%).

¹H NMR (500 MHz, C₆D₆, 20°C):
5.99 (d, J = 15.6 Hz, 1H, MeC(OH)CH=CH), 5.81-5.71 (m, 1H, CH=CH₂), 5.64 (dd, J = 15.6, 5.5 Hz, 1H, MeC(OH)CH=CH), 5.41 (t, J = 7.4 Hz, 1H, (N)C=CH), 5.07-4.97 (m, 2H, CH=CH₂), 4.24 (br-s, 1H, CHOCH), 3.67-3.57 (m, 2H, OCH₂CH₂N), 2.97 (t, J = 8.0 Hz, 2H, OCH₂CH₂N), 2.36-2.18 (br-s, OH), 2.03-1.91 (m, 4H, (allylic CH₂), 1.32-1.25 (m, 4H, (CH₂)₂), 1.23 (d, J = 6.3 Hz, 3H, CH₃).

¹³C NMR (125 MHz, C₆D₆, 20°C):
156.7 (O=C), 139.2 (C=CN), 134.5, 134.1, 128.7, 126.1, 115.1 (HC=CH₂), 68.3, 62.2, 46.2, 34.3, 29.3, 28.9, 28.2, 24.0.

FTIR (thin film) cm⁻¹:
3421 (br-m, OH), 2973 (w), 2927 (m), 2857 (w), 1741 (s, C=O), 1419 (s), 1247 (m), 1037 (m).

HRMS (ESI):

TLC (10% acetone in CH₂Cl₂), Rf:
44, 0.75 (UV, CAM)
45, 0.16 (UV, CAM)
(±)-3-[(1Z)-1-((E)-3-Oxo-but-1-enyl)-octa-1,7-dienyl]-oxazolidin-2-one (46):

γ-Manganese dioxide (1.21 g, 13.9 mmol, 11.7 equiv) was added under an argon atmosphere in one portion to a solution of alcohol (±)-45 (317 mg, 1.20 mmol, 1 equiv) in dichloromethane (6 mL) and the mixture was stirred at ambient temperature. After 19.5 h, the reaction mixture was diluted with dichloromethane and passed through celite. The resulting solution was concentrated under reduced pressure to provide spectroscopically clean ketone 46 as a clear oil (289 mg, 92%). If desired, purification of ketone 46 could be achieved via flash column chromatography (silica gel, eluent: CH$_2$Cl$_2$:acetone [98:2] to CH$_2$Cl$_2$:acetone [90:10]).

$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C):

6.77 (d, $J = 15.8$ Hz, 1H, MeCOCH=CH), 6.00 (d, $J = 15.8$ Hz, 1H, MeCOCH=CH), 5.78-5.70 (m, 1H, CH=CH$_2$), 5.52 (t, $J = 7.6$ Hz, 1H, (N)C=CH), 5.06-4.99 (m, 2H, CH=CH$_2$), 3.47 (app-t, $J = 7.8$ Hz, 2H, OCH$_2$CH$_2$N), 2.73 (app-t, $J = 7.8$ Hz, 2H, OCH$_2$CH$_2$N), 1.94-1.90 (m, 7H, allylic-CH$_2$, allylic-CH$_2$, Me), 1.21-1.20 (m, 4H, (CH$_2$)$_2$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C):

196.6 (ketone-C=O), 156.1 (carbamate-C=O), 143.7, 140.2, 139.0, 134.1, 126.6, 115.3, 62.2 (OCH$_2$CH$_2$N), 46.0 (OCH$_2$CH$_2$N), 34.2, 29.3, 28.8, 28.3, 27.9.

FTIR (thin film) cm$^{-1}$:

2924 (m), 1754 (s, C=O), 1746 (s, C=O), 1666 (m), 1631 (m), 1599 (m), 1414 (s), 1251 (m).

HRMS (ESI):

calcd for C$_{13}$H$_{21}$NaNO$_3$ [M+Na$^+$]: 286.1414, found: 286.1421.

TLC (10% acetone in CH$_2$Cl$_2$), $R_f$:

45, 0.16 (UV, CAM) 46, 0.42 (UV, CAM)
3-[(1Z)-1-[(Z)-3-(tert-Butyl-dimethyl-silanyloxy)-but-1,3-dienyl]-octa-1,7-dienyl]-oxazolidin-2-one (47):

Triethylamine (860 μL, 6.12 mmol, 1.50 equiv) was added to a solution of ketone 46 (1.07 g, 4.08 mmol, 1 equiv) in dichloromethane (20 mL) at -78 °C, followed by dropwise addition of TBSOTf (1.12 mL, 4.89 mmol, 1.20 equiv). After 15 min, the excess silylating agent was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL) and allowed to warm to ambient temperature. The reaction mixture was diluted with ethyl acetate (80 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL). The aqueous phase was extracted with ethyl acetate (4 × 75 mL), and the combined organic layers were washed with brine (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 5 cm, ht. 9 cm; eluent: CH₂Cl₂:acetone [97:3]) to provide the silyl enol ether 47 as a white solid (1.44 g, 93%).

¹H NMR (500 MHz, C₆D₆, 20°C):

6.80 (d, J = 15.3 Hz, 1H, HC=CHCOTBS), 6.06 (d, J = 15.3 Hz, 1H, HC=CHCOTBS), 5.76-5.68 (m, 1H, CH=CH₂), 5.60 (t, J = 7.4 Hz, 1H, (N)C=CH), 5.03-4.96 (m, 2H, CH=CH₂), 4.42 (s, 1H, CH₂=CHOTBS), 4.33 (s, 1H, CH₂=CHOTBS), 3.51 (app-t, J = 7.6 Hz, 2H, OCH₂CH₂N), 2.89 (app-t, J = 8.0 Hz, 2H, OCH₂CH₂N), 2.03-1.99 (m, 2H, CH₂CH=CH₂), 1.95-1.85 (m, 2H, (N)C=CHCH₂), 1.24-1.21 (m, 4H, (CH₃)₂), 1.02 (s, 9H, SiC(CH₃)₃), 0.18 (s, 6H, Si(CH₃)₂).

¹³C NMR (125 MHz, C₆D₆, 20°C):

156.3, 155.6, 139.2, 136.1, 134.8, 127.3, 126.5, 115.1, 97.4, 62.1, 46.3, 34.2, 29.3, 28.7, 28.6, 26.4, 18.9, -4.2.

FTIR (thin film) cm⁻¹:

2930 (s), 2858 (s), 1759 (s, C=O), 1415 (m), 1316 (m), 1254 (m), 1030 (m), 840 (m).

HRMS (ESI):

called for C₂₁H₃₆NO₃Si [M+H]⁺: 378.2459, found: 378.2465.

TLC, Rf:

(10% acetone in CH₂Cl₂, neutralized plates): 46, 0.58 (UV, CAM) 47, 0.79 (UV, CAM)
12-(tert-Butyl-dimethyl-silyloxy)-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (48):

To a solution of silyl ether (±)-44 (47.6 mg, 0.125 mmol, 1 equiv) in dichloromethane (625 µL) was added freshly distilled acrolein (34 µL, 0.50 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydrolMES)-(PCy3)Cl2Ru=CH(o-iPrO)Ph), 8.5 mg, 0.014 mmol, 0.110 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH2Cl2:acetone [99:1] to CH2Cl2:acetone [98:2] to CH2Cl2:acetone [90:10]) to provide the triene (±)-48 as a tan oil (40.1 mg, 78%). Additionally, the starting silyl ether (±)-44 was recovered (6.5 mg, 14%).

\[ \text{CHCl}_2, 23 \degree \text{C}, 78\% \]

\[ \text{Me} \]

\[ \text{TBSO} \]

\[ \text{acrolein,} \]

\[ \text{4,5-DihydrolMES-Cl}_2 \text{Ru=CH(o-OiPr)Ph} \]

(10 mol%) 

\[ \text{CHCl}_2 \]

\[ \text{Me} \]

\[ \text{TBSO} \]

\[ \text{CH} \]

\[ \text{23 \degree \text{C}} \]

\[ 78\% \]

\[ \text{OHC} \]

\[ \text{Me} \]

\[ \text{TBSO} \]

\[ (\pm)-48 \]

\[ \text{O-} \]

\[ \text{12-(tert-Butyl-dimethyl-silyloxy)-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (48):} \]

\[ \text{To a solution of silyl ether (±)-44 (47.6 mg, 0.125 mmol, 1 equiv) in dichloromethane (625 µL) was added freshly distilled acrolein (34 µL, 0.50 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydrolMES)-(PCy3)Cl2Ru=CH(o-iPrO)Ph), 8.5 mg, 0.014 mmol, 0.110 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH2Cl2:acetone [99:1] to CH2Cl2:acetone [98:2] to CH2Cl2:acetone [90:10]) to provide the triene (±)-48 as a tan oil (40.1 mg, 78%). Additionally, the starting silyl ether (±)-44 was recovered (6.5 mg, 14%).} \]

\[ \text{H} \text{NMR (500 MHz, C6D6, 20 °C):} \]

\[ 9.34 \ (d, J = 7.6 \ Hz, 1H, CHO), 6.12 \ (dd, J = 15.4, 1.2 \ Hz, 1H, (TBSO)CHCH=CH), 6.04 \ (dt, J = 15.5, 6.8 \ Hz, 1H, CHOCH=CH), 5.91 \ (ddt, J = 15.6, 7.6, 1.2 \ Hz, 1H, CHOCH=CH), 5.63 \ (dd, J = 15.6, 5.5 \ Hz, 1H, (TBSO)CHCH=CH), 5.42 \ (t, J = 7.3 \ Hz, 1H, (N)C=CH), 4.28 \ (app-p, J = 6.1 \ Hz, 1H, (TBSO)CHH), 3.58-3.54 \ (m, 2H, OCH2CH2N), 3.03-2.91 \ (m, 2H, OCH2CH2N), 1.95-1.90 \ (m, 2H, CH2CH=CHCHO), 1.71-1.67 \ (m, 2H, (N)C=CHCH2), 1.20 \ (d, J = 6.3 \ Hz, 3H, TBSOCHCH3), 1.15-1.03 \ (m, 4H, (CH2)2), 0.10 \ (s, 9H, Si(CH3)3), 0.10 \ (s, 3H, Si(CH3)2), 0.10 \ (s, 3H, Si(CH3)2). \]

\[ \text{C} \text{NMR (125 MHz, C6D6, 20 °C):} \]

\[ 193.1 \ (CHO), 157.3, 156.2, 134.7, 134.5, 133.7, 133.3, 125.4, 69.4 \ (C(OSi), 62.0 \ (OCH2CH2N), 46.2 \ (OCH2CH2N), 32.6, 28.6, 28.1, 27.9, 26.5 \ (SiC(CH3)3), 25.2, 18.8, -4.0 \ (Si(CH3)2), -4.2 \ (Si(CH3)2). \]

\[ \text{FTIR (neat) cm}^{-1}: \]

\[ 2929 \ (m), 1759 \ (s), 1690 \ (s), 1416 \ (m), 1251 \ (m), 836 \ (m). \]

\[ \text{HRMS (ESI)} \]

\[ \text{calcd for C22H37NNaO4Si [M+Na]+: 430.2384, found: 430.2374.} \]

\[ \text{TLC (3% acetone in hexanes), Rf:} \]

\[ 44, 0.42 \ (UV, CAM) \]

\[ 48, 0.24 \ (UV, CAM) \]

\[ \text{-----} \]

\[ \text{10 Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2000, 122, 8168.} \]
12-Hydroxy-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (49):

To a solution of alcohol (±)-49 (43.0 mg, 0.162 mmol, 1 equiv) in dichloromethane (800 μL) was added freshly distilled acrolein (43 μL, 0.65 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydropIMES)Cl2Ru=CH(o-iPr)Ph)((4,5-DihydropIMES)-(PCy3)Cl2Ru=CHPh, 10.5 mg, 0.0168 mmol, 0.10 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH2Cl2:acetone [85:15] to CH2Cl2:acetone [75:25] to CH2Cl2:acetone [70:30]) to provide the triene (±)-49 as a tan oil (37.6 mg, 79%). Additionally, the starting alcohol (±)-45 was recovered (2.8 mg, 7%).

1H NMR (500 MHz, C6D6, 20 °C):

- 9.38 (d, J = 7.7 Hz, 1H, CHO)
- 6.20 (dt, J = 15.6, 6.7 Hz, 1H, CHOCH=CH)
- 6.11 (d, J = 15.7 Hz, 1H, (HO)CHCH=CH)
- 5.98 (ddt, J = 15.6, 7.7, 1.0 Hz, 1H, CHOCH=CH)
- 5.73 (dd, J = 15.6, 5.8 Hz, 1H, (HO)CHCH=CH)
- 5.44 (t, J = 7.4 Hz, 1H, (N)C=CH)
- 4.40-4.33 (m, 1H, (HO)CH)
- 3.78 (td, J = 7.8, 2.1 Hz, 2H, OCH2CH2N)
- 3.19-3.14 (m, 1H, OH)
- 3.09 (app-t, J = 8.0 Hz, 2H, OCH2CH2N)
- 1.94 (app-q, J = 7.0 Hz, 2H, CH2CH=CHCHO)
- 1.80 (app-q, J = 6.4 Hz, 2H, (N)C=CHCH2)
- 1.31 (d, J = 6.4 Hz, 3H, HOCHCH3)
- 1.21-1.09 (m, 4H, (CH2)2).

13C NMR (125 MHz, C6D6, 20°C):

- 193.6 (CHO), 157.9, 156.9, 134.6, 134.6, 133.7, 133.6, 125.8, 68.2 (C(OH)), 62.5 (OCH2CH2N), 46.3 (OCH2CH2N), 32.7, 28.7, 28.0, 27.8, 24.1.

FTIR (neat) cm⁻¹:

- 3427 (br-m, OH), 2926 (m), 1750 (s), 1686 (s), 1418 (m), 1243 (br-w), 1036 (w), 972 (w).

HRMS (ESI)


TLC (15% acetone in hexanes), Rf:

- 45, 0.24 (UV, CAM)
- 49, 0.12 (UV, CAM)
12-Oxo-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (50):  
To a solution of ketone alcohol 46 (37.3 mg, 0.142 mmol, 1 equiv) in dichloromethane (710 µL) was added freshly distilled acrolein (38 µL, 0.56 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydroIMES)Cl₂Ru=CH(o-iPr)Ph)((4,5-DihydroIMES)-(PCy₃)Cl₂Ru=CHPh,¹⁰ 9.1 mg, 0.0145 mmol, 0.10 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH₂Cl₂:acetone [96:4] to CH₂Cl₂:acetone [94:6] to CH₂Cl₂:acetone [89:11] to CH₂Cl₂:acetone [80:20]) to provide the triene 50 as a tan oil (36.0 mg, 87%). Additionally, the starting ketone 46 was recovered (4.1 mg, 11%).

**¹H NMR (500 MHz, C₆D₆, 20 °C):**

9.39 (d, 8.7 Hz, 1H, CHO), 6.87 (d, 15.8 Hz, 1H, CH₃(O)CCH=CH), 6.17 (dt, 15.6, 6.7 Hz, 1H, CHOCH=CH), 6.06 (d, 15.8 Hz, 1H, CH₃(O)CCH=CH), 5.98 (ddt, 15.7, 7.8, 1.3 Hz, 1H, CHOCH=CH), 5.61 (t, 7.5 Hz, 1H, (N)C=CH), 3.68 (dd, 8.9, 7.7 Hz, 2H, OCH₂CH₂N), 2.89 (dd, 8.0, 6.9 Hz, 2H, OCH₂CH₂N), 1.89 (app-q, 7.2 Hz, 2H, CH₂CH=CHCHO), 1.77 (app-q, 6.3 Hz, 2H, (N)C=CHCH₂), 1.97 (s, 3H, CH₃), 1.15-1.03 (m, 4H, (CH₂)₂).

**¹³C NMR (125 MHz, C₆D₆, 20°C):**

196.8 (CO(CH₃)), 193.3 (CHO), 157.4, 156.3, 143.3, 140.1, 134.2, 133.7, 126.7, 62.4 (OCH₂CH₂N), 46.0 (OCH₂CH₂N), 32.5, 28.6, 28.1, 28.0, 27.8.

**FTIR (neat) cm⁻¹:**

2928 (w), 1755 (s), 1687 (s), 1418 (s), 1254 (brm), 1037 (w), 977 (w).

**HRMS (ESI)**


**TLC (10% acetone in hexanes), Rf:**

46, 0.34 (UV, CAM)  
50, 0.16 (UV, CAM)
(2E,8Z,10E)-12-(tert-Butyl-dimethyl-silyl oxy)-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10,12-tetraen-1-yl (51):

To a solution of silyl enol ether 47 (500 mg, 1.32 mmol, 1 equiv) in dichloromethane (6.6 mL) was added freshly distilled acrolein (354 µL, 5.30 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda-Grubbs G2 cat (4,5-DihydroIMES(Cl₂Ru=CH(o-O'Pr)Ph, 82 mg, 0.13 mmol, 0.10 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 5 cm, ht. 8 cm; eluent: CH₂Cl₂:acetone:NEt₃ [98:1:1]) to provide the tetraene 51 as a tan solid (455 mg, 85%).

**¹H NMR (500 MHz, C₆D₆, 20°C):**

9.34 (d, J = 7.6 Hz, 1H, CHO), 6.71 (d, J = 15.3 Hz, 1H, HC=CHOTBS), 6.07 (d, J = 15.3 Hz, 1H, HC=CHOTBS), 6.01 (dd, J = 15.6, 6.6 Hz, 1H, CH=CHCHO), 5.90 (dd, J = 15.6, 7.6 Hz, 1H, CH=CHCHO), 5.55 (t, J = 7.4 Hz, 1H, (N)C=CH), 4.43 (s, 1H, CH₂=CHOTBS), 4.34 (s, 1H, CH₂=CHOTBS), 3.55 (app-t, J = 7.9 Hz, 2H, OCH₂CH₂N), 2.90 (app-t, J = 7.4 Hz, 2H, OCH₂CH₂N), 1.93 (app-q, J = 7.2 Hz, 2H, CH₂CH=CH₂), 1.67 (app-q, J = 6.9 Hz, 2H, (N)C=CHCH₂), 1.11-0.94 (m, 13H, (CH₂)₂, SiC(CH₃)₃), 0.18 (s, 6H, Si(CH₃)₂).

**¹³C NMR (125 MHz, C₆D₆, 20°C):**

193.2 (CHO), 157.5, 156.4, 155.5, 135.5, 135.0, 133.6, 127.0, 126.8, 97.5, 62.2, 46.3, 32.6, 28.5, 28.3, 27.9, 26.3, 18.8, -4.2.

**FTIR (thin film) cm⁻¹:**

2951 (s), 2930 (s), 2858 (m), 1753 (s), 1689 (s), 1414 (m), 1253 (m), 840 (m).

**HRMS (ESI):**


**TLC, Rf:**
(3% acetone in CH₂Cl₂, neutralized plates) 47, 0.63 (UV, CAM) 51, 0.30 (UV, CAM)

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¹¹ Concentration of the reaction mixture of extended reaction times resulted in decomposition of the sensitive tetraene 51.
Silv ether bicycle 52:

Triene (+)-48 (24.5 mg, 0.064 mmol, 1 equiv) was dissolved in benzene (750 μL) under argon atmosphere and the vessel was heated to 90 °C. After 23 h, the solvent was removed under reduced pressure and the resulting oil purified by flash column chromatography (silica gel: diam. 1 cm, ht. 5 cm; eluent: hexanes:acetone [85:15]) to provide the (+)-trans-decalin aldehyde 52 as a yellow oil (14.1 mg, 58%, 1:1 mixture of diastereomers).

$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C, mixture of two diastereomers, 52:20-epi-52, 1:1): 9.85 (d, $J = 4.3$ Hz, 1H, CHO), 9.74 (d, $J = 3.6$ Hz, 1H, CHO), 5.21 (dd, $J = 5.2, 2.2$ Hz, 1H, NC=CH), 5.04 (dd, $J = 4.7, 2.1$ Hz, 1H, NC=CH), 3.95-3.87 (m, 2H, CHO), 3.46-3.36 (m, 4H, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N), 2.86 (app-p, $J = 8.7$ Hz, 2H), 2.61-2.54 (m, 2H), 2.50-2.41 (m, 2H), 2.37-2.25 (m, 2H), 2.25-2.16 (m, 2H), 2.09-1.93 (m, 4H), 1.84-1.78 (m, 1H), 1.76-1.56 (5H), 1.38-1.16 (m, 4H), 1.13 (d, $J = 6.1$ Hz, 3H, CH$_3$), 1.08 (d, $J = 6.5$ Hz, 3H, CH$_3$), 1.05-0.87 (m, 2H), 0.98 (s, 9H, SiC(CH$_3$)$_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), 0.78 (app-dq, $J = 13.0, 5.1$ Hz, 2H), 0.08 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$), 0.01 (s, 3H, SiCH$_3$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C mixture of two diastereomers, 52:20-epi-52, 1:1): 203.6 (CHO), 202.8 (CHO), 156.0 (carbamate-C=O), 155.9 (carbamate-C=O), 140.7, 140.3, 117.3, 117.3, 70.5, 70.3, 61.8, 61.8, 54.8, 53.6, 47.0, 46.7, 45.5, 44.4, 43.0, 42.7, 38.3, 38.3, 31.2, 30.8, 30.6, 30.3, 27.1, 27.0, 27.0, 27.0, 26.5, 26.5, 22.9, 22.7, 18.6, 18.6, -3.6 (SiCH$_3$), -3.7 (SiCH$_3$), -3.9(SiCH$_3$), -4.2 (SiCH$_3$).

FTIR (thin film) cm$^{-1}$: 3411 (br-w), 2929 (s), 2856 (m), 1754 (br-s), 1410 (m), 1254 (m), 836 (m).

HRMS (ESI): calcd for C$_{22}$H$_{37}$NNaO$_4$Si [M+Na]$^+$: 430.2384, found: 430.2399.
TLC (40% acetone in hexanes), $R_f$: 

48, 0.53 (UV, CAM, KMnO$_4$)  
52, 0.55 (UV, CAM, KMnO$_4$)
Hemiacetal bicycle 53:

Triene (±)-49 (33.0 mg, 0.112 mmol, 1 equiv) was dissolved in benzene (750 µL) under argon atmosphere and the vessel was heated to 90 °C. After 13 h, the solvent was removed under reduced pressure and the resulting oil purified by flash column chromatography (silica gel: diam. 1 cm, ht. 5 cm; eluent: hexanes:acetone [70:30]) to provide the (±)-trans-decalin acetal 53 as a white solid (29.6 mg, 90%, 1:1 mixture of diastereomers).

\[ \text{1H NMR (500 MHz, C}_6\text{D}_6, 20°C, mixture of two diastereomers, 53:20-epi-53, ~1:1): 5.47 (d, } \]
\[ J = 2.6 \text{ Hz, 1H, HOCH)}, 5.43 (d, } \]
\[ J = 3.3 \text{ Hz, 1H, HOCH)}, 5.13 (dd, } \]
\[ J = 4.9, 2.2 \text{ Hz, 1H, NC=CH)}, 5.13 (dd, } \]
\[ J = 4.7, 2.2 \text{ Hz, 1H, NC=CH)}, 4.56 (ddd, } \]
\[ J = 13.1, 9.1, 6.1 \text{ Hz, 1H, CHCH}_{3}), 3.88 (ddd, } \]
\[ J = 12.1, 9.3, 6.1 \text{ Hz, 1H, CHCH}_{3}), 3.66 (d, } \]
\[ J = 3.5 \text{ Hz, 1H, OH)}, 3.52-3.45 (m, 5H, OH, OCH}_{2}\text{CH}_{2}N, OCH}_{2}\text{CH}_{2}N)}, 3.23 (ddd, } \]
\[ J = 10.1, 4.7, 2.5 \text{ Hz, 1H, C=CHCH)}, 2.88 (qd, } \]
\[ J = 8.7, 3.6 \text{ Hz, 2H, OCH}_{2}\text{CH}_{2}N, OCH}_{2}\text{CH}_{2}N)}, 2.68 (tdd, } \]
\[ J = 9.3, 5.1, 2.2 \text{ Hz, 1H, C=CHCH)}, 2.55-2.48 (m, 2H, OCH}_{2}\text{CH}_{2}N, OCH}_{2}\text{CH}_{2}N)}, 2.38-2.31 (m, 1H, NCCH)}, 2.30-2.23 (m, 1H, NCCH)}, 2.08-1.99 (m, 4H, HOCHCH, HOCHCH)}, 1.80 (app-td, } \]
\[ J = 12.9, 2.3 \text{ Hz, 2H)}, 1.71-1.57 (m, 4H), 1.40 (d, } \]
\[ J = 6.0 \text{ Hz, 3H, CH}_{3}), 1.34-1.22 (m, 3H), 1.22-1.01 (m, 3H), 1.14 (d, } \]
\[ J = 6.6 \text{ Hz, 3H, CH}_{3}), 0.94-0.79 (m, 4H). \]

\[ \text{13C NMR (125 MHz, C}_6\text{D}_6, 20°C mixture of two diastereomers, 53:20-epi-53, ~1:1): 156.4 (carbamate-C=O)}, 156.3 (carbamate-C=O)}, 140.1, 139.8, 117.2, 116.7, 100.9, 99.5, 81.7, 75.8, 62.0, 62.0, 51.0, 50.0, 47.2, 47.0, 44.8, 41.8, 41.3, 40.9, 39.8, 38.8, 32.1, 31.1, 30.4, 30.3, 27.0 26.9, 26.9, 26.9, 22.5, 20.6. \]
nOe data (500 MHz, C₆D₆, 20°C):

FTIR (thin film) cm⁻¹:
3406 (br-s, OH), 2926 (s), 2855 (m), 1747 (br-s), 1415 (s), 1279 (m), 1236 (m), 1082 (m), 994 (m).

HRMS (ESI):
calcd for C₁₆H₂₃NNaO₄ [M+Na]⁺: 316.1519,
found: 316.1513.

TLC, Rf:
(40% acetone in hexanes) 49, 0.18 (UV, CAM, KMnO₄)
53, 0.24 (UV, CAM, KMnO₄)
(±)-(9S, 10R, 15R, 19S)-trans-Decalin aldehyde 33:

A flame-dried Schlenk flask was charged with tetraene 51 (279 mg, 0.688 mmol, 1 equiv) and toluene (34 mL) and sealed under argon atmosphere. The vessel was heated to 90 °C. After 13 h, the solvent was removed under reduced pressure and the resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH₂Cl₂:acetone:NEt₃ [94:5:1]) to provide the (±)-trans-decalin aldehyde 33 as a yellow oil (228 mg, 82%).

¹H NMR (500 MHz, C₆D₆, 20°C):

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¹³C NMR (125 MHz, C₆D₆, 20°C):

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nOe data (500 MHz, C₆D₆, 20°C):

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FTIR (thin film) cm⁻¹:

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<td>1220</td>
<td>(m)</td>
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<td>837</td>
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HRMS (ESI): calcd for C_{22}H_{36}NO_4Si [M+H]^+: 406.2408, found: 406.2403.

TLC, $R_f$: (30% acetone in hexanes, pretreat NEt_3) 51, 0.26 (UV, CAM) 33, 0.33 (CAM)
**β-hydroxy imine 76 and α,β-unsaturated imine (±)-79:**

To a suspension of iminium chloride 75 (68 mg, 0.51 mmol, 2.0 equiv) in THF (600 μL) at -78 °C and sealed under argon was added a solution of n-butyllithium in hexanes (2.53 M, 380 μL, 1.9 mmol, 3.9 equiv). The resulting brown solution was maintained at -78 °C for 30 min, was warmed to 0 °C for 10 min, then cooled to -78 °C. A sample of aldehyde (±)-33 (101 mg, 0.25 mmol, 1 equiv) in a round-bottomed flask was azeotropically dried from toluene (2 × 2 mL), the flask was evacuated and backfilled with argon three times, charged with THF (600 μL), and cooled to -78 °C. The lithiated enamine solution was transferred cold via cannula to the cold aldehyde solution. After ten minutes excess anion was quenched at -78 °C by the addition of saturated aqueous ammonium chloride solution (1 mL) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate (65 mL) and saturated aqueous ammonium chloride solution (25 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 × 60 mL) and the combined organic layers were washed with brine (25 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 6.5 cm; eluent: hexanes:acetone:NEt₃ [89:10:1] to hexanes:acetone:NEt₃ [74:25:1] to provide β-hydroxyimine (±)-76 (92 mg, 74%, mixture of diastereomers) as a yellow foam. Additionally, the starting aldehyde (±)-33 was recovered (9.5 mg, 9%).

To a solution of β-hydroxyimine (±)-76 (92 mg, 0.18 mmol, 1 equiv, equal mixture of two diastereomers) in benzene (8 mL) at 23 °C was added a solution of Martin sulfurane (170 mg, 0.25 mmol, 1.4 equiv) in benzene (1 mL) via syringe. After 1 h the solution was concentrated under reduced pressure and the resulting orange residue purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 5 cm; eluent: acetone:hexanes:NEt₃ [79:10:1] to acetone:hexanes:NEt₃ [69:30:1] to acetone:hexanes:NEt₃ [64:35:1]) to provide the α,β-unsaturated imine (±)-79 (78 mg, 88%) as a clear solid.

**¹H NMR (500 MHz, C₆D₆, 20 °C):**

- 6.43 (d, J = 16.1 Hz, 1H, C7-H), 6.08 (dd, J = 16.2, 10.3 Hz, 1H, C8-H), 5.14 (dd, J = 5.1, 2.1 Hz, 1H, C17-H), 4.29 (s, 1H, C21-H), 4.25 (s, 1H, C21-H), 3.75 (br-t, 2H, C2-H), 3.46-3.42

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12 Rigorous inert atmosphere and anhydrous conditions were required for optimal results.
13C NMR (125 MHz, C6D6, 20 °C):

(m, 2H, OCH2CH2N), 2.94 (app-q, J = 8.8 Hz, 1H, OCH2CH2N), 2.77 (m, 1H, C19-H), 2.64 (dt, J = 8.3, 5.1 Hz, 1H, OCH2CH2N), 2.42 (m, 1H, C15-H), 2.27 (br-dt, J = 11.5, 6.3 Hz, 1H, C5-H), 2.15 (td, J = 10.9, 6.3 Hz, 1H, C9-H), 2.12-2.03 (m, 2H, C14-H, C5-H), 1.84 (m, 1H, C10-H), 1.80-1.68 (m, 2H, C11-H, C12-H), 1.44-1.20 (m, 6H, C3-H, C3-H, C4-H, C4-H, C12-H, C13-H), 1.06 (app-dq, J = 12.3, 3.2 Hz, 1H, C14-H), 1.00-0.92 (m, 10H, SiC(CH3)3, C13-H), 0.81 (aqd, J = 3.2, 12.6 Hz, 1H, C11-H), 0.18 (s, 3H, SiCH3), 0.17 (s, 3H, SiCH3).

164.9, 159.0, 140.5, 137.6 (C8), 136.3 (C7), 119.3 (C17), 94.3 (C21), 61.8 (Ca), 50.4 (C19), 48.0 (C2), 46.8 (Cb), 46.6 (C9), 43.2 (C15), 40.3 (C10), 31.7 (C11), 30.6 (C14), 27.4 (C12), 27.1 (C13), 26.3 (SiC(CH3)3), 26.2 (C5), 23.0 (C3), 20.2 (C4), 18.7 (SiC(CH3)3), -4.1 (SiCH3), -4.2 (SiCH3).

FTIR (thin film) cm⁻¹:

2929 (s), 2856 (m), 1757 (s, C=O), 1619 (w), 1406 (m), 1216 (br-m), 836 (m).

TLC, Rf:
(50% acetone in hexanes, neutralized plates) 33, 0.64 (UV, CAM)
76, 0.55 (ninhydrin, green)
79, 0.45 (UV, ninhydrin, yellow)

79, calcd for C29H47N2O3Si [M+H]⁺: 485.3171, found: 485.3198
Imine-acetal (±)-77:

To a solution of β-hydroxyimine 76 (65.1 mg, 0.129 mmol, 1 equiv, equal mixture of two diastereomers) in benzene (12.9 mL) at 23 °C was added pyridine (36.5 μL, 0.451 mmol, 3.5 equiv), followed by dropwise addition of trifluoroacetic acid (30 μL, 0.388, 3.0 equiv). After 4 h the solution was concentrated under reduced pressure and the resulting oil purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 9 cm; eluent: hexanes:acetone:NEt$_3$ [79:20:1] to hexanes:acetone:NEt$_3$ [69:30:1]) to provide the acetal (±)-77 as an orange solid (51.4 mg, 81%).

$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C):

5.15 (dd, J = 4.2, 2.5 Hz, 1H, C17-H), 4.48-4.43 (m, 1H, C8-H), 3.60 (br-s, 2H, C2-H), 3.50-3.44 (m, 2H, OCH$_2$CH$_2$N), 3.07 (app-q, J = 8.6 Hz, 1H, OCH$_2$CH$_2$N), 2.89-2.83 (m, 1H, OCH$_2$CH$_2$N), 2.49-2.42 (m, 1H, C15-H), 2.42-2.37 (m, 1H, C7-H), 2.37-2.32 (m, 1H, C19-H), 2.23-2.17 (m, 1H, C10-H), 2.03-1.81 (m, 4H), 1.77-1.60 (m, 4H, C9-H), 1.43 (s, 3H, C21-H), 1.42-1.15 (m, 6H), 1.02-0.89 (m, 1H), 0.95 (s, 9H, SiC(CH$_3$)$_3$), 0.77 (qd, J = 12.8, 3.4 Hz, 1H), 0.26 (s, 3H, SiCH$_3$), 0.22 (s, 3H, SiCH$_3$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C):

167.2 (N=C), 156.0 (carbamate-C=O), 140.2 (NC=CH), 116.5, 106.5 (CCH$_3$), 81.1, 61.6 (OCH$_3$CH$_2$N), 50.2, 49.3, 47.9, 47.3, 46.3, 42.3, 41.3, 31.4, 30.6, 29.6, 27.0, 26.9, 26.8, 26.2 (SiC(CH$_3$)$_3$), 22.3, 20.0, 18.3, -2.6 (SiCH$_3$), -2.7 (SiCH$_3$).
nOe data (500 MHz, C₆D₆, 20°C):

![Chemical structure](image)

FTIR (thin film) cm⁻¹: 3424 (br-s), 2927 (m), 2854 (w), 1757 (m), 1659 (br-w), 1408 (w), 992 (m).


TLC, Rf:
(30% acetone in hexanes, neutralized plates) 76, 0.14 (ninhydrin, CAM)
77, 0.44 (ninhydrin, CAM)
Amine acetal tetracycle 78:
To a solution of imine acetal (±)-77 (1.9 mg, 3.9 µmol, 1 equiv) in ethanol (1 mL) at -78 °C was added a solution of sodium borohydride in ethanol (0.07M, 80 µL, 59 µmol, 1.5 equiv). After 1 h excess hydride was quenched at -78 °C by the addition of saturated aqueous ammonium chloride (1 mL) and the solution was allowed to warm to ambient temperature. The resulting heterogeneous solution was diluted with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (5 mL) and the combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 0.5 cm, ht. 1.2 cm; eluent: hexanes:acetone:NEt 3 [54:45:1]) to provide the amine acetal tetracycles (±)-78 (major) and (±)-6-epi-78 (minor) as a mixture of diastereomers (1.5 mg, 79%, 2:1 78:6-epi-78).

1H NMR (500 MHz, C6D6, 20°C): (major diastereomer 78): 5.16 (dd, J = 4.0, 2.3 Hz, 1H, C17-H), 4.16 (dt, J = 9.9, 3.8 Hz, 1H), 3.53-3.45 (m, 2H, OCH₂CH₂N), 3.11 (app-q, J = 8.6 Hz, OCH₂CH₂N), 3.04 (br-d, J = 11.8 Hz, 1H), 2.90-2.84 (m, 1H, OCH₂CH₂N), 2.77-2.70 (m, 1H), 2.52 (td, J = 12.0, 3.1 Hz, 1H), 2.47-2.39 (m, 1H, C15-H), 2.36-2.31 (m, 1H, C19-H), 2.25-2.19 (m, 1H, C10-H), 1.85-1.65 (m, 5H), 1.65-1.56 (m, 1H), 1.56-1.17 (m, ?H), 1.46 (s, 3H, C21-H), 1.01-0.90 (m, 1H), 0.93 (s, 9H, SiC(CH₃)₃), 0.82-0.72 (m, 1H), 0.21 (s, 3H, SiCH₃), 0.19 (s, 3H, SiCH₃).

TLC, Rf:
(70% acetone in hexanes, neutralized plates) 77, 0.58 (CAM)
6-epi-78 (minor), 0.22 (CAM)
78 (major), 0.19 (CAM)
Pentacyclic ether (±)-82:

To a solution of α,β-unsaturated imine (±)-79 (3.0 mg, 6.1 µmol, 1 equiv) in THF (610 µL) at 23 °C was added triethylamine trihydrogen fluoride (6 µL, 0.037 mmol, 6.0 equiv). After 15 hours, the reaction mixture was concentrated under reduced pressure\(^\text{13}\) and purified by flash column chromatography (neutralized silica gel: diam. 0.5 cm, ht. 2.5 cm; eluent: hexanes:acetone:NEt\(_3\) [69:30:1] to provide ether (±)-82 (1.6 mg, 73%) as a yellow oil.

\(^\text{13}\) The ether product was highly air-sensitive and must be handled under rigorous air-free conditions.

\(^{1}\)H NMR (500 MHz, C\(_{6}\)D\(_{6}\), 20 °C) δ:

5.74 (d, \(J = 2.1\) Hz, 1H, C17-H), 4.75 (ddd, \(J = 10.5, 8.0, 3.8\) Hz, 1H, C8-H), 3.61 (br-t, 2H, C2-H), 3.45-3.42 (m, 2H, OCH\(_2\)CH\(_2\)N), 2.89 (app-q, \(J = 8.6\) Hz, 1H, OCH\(_2\)CH\(_2\)N), 2.69 (m, 1H, C15-H), 2.59-2.52 (m, 3H, OCH\(_2\)CH\(_2\)N, C7-H, C19-H), 2.04 (dtt, \(J = 18.5, 5.6, 2.1\) Hz 1H), 1.91 (dtt, \(J = 18.5, 5.6, 2.1\) Hz 1H), 1.72 (app-d, \(J = 1.7\) Hz, 3H, C21-H), 1.70-1.66 (m, 2H), 1.57 (m, 1H), 1.36-1.26 (m, 6H), 1.05 (app-qt, \(J = 13.2, 4.0\) Hz, 1H), 0.93 (app-qd, \(J = 12.4, 3.4\) Hz, 1H), 0.83 (app-qd, \(J = 12.2, 3.8\) Hz, 1H).

\(^{13}\)C NMR (100 MHz, C\(_{6}\)D\(_{6}\), 20 °C) δ:

167.3, 156.1, 148.4, 135.3, 112.1, 110.2 (C17), 85.0 (C8), 61.8 (OCH\(_2\)CH\(_2\)N), 52.3 (C19), 49.7 (C19), 48.1 (C7), 47.0 (C9), 46.9 (OCH\(_2\)CH\(_2\)N), 43.5 (C15), 30.9 (C11), 30.8 (C13), 30.6 (C14), 27.3 (C12), 26.7, 22.6 (C3), 20.4 (C4), 12.1 (C21).

FTIR (neat) cm\(^{-1}\):

2923 (s), 2852 (m), 1750 (s), 1411 (m), 1216 (m).
nOe data (500 MHz, C₆D₆, 20°C): Additional data: H8-H7 (5.8%).

FTIR (neat) cm⁻¹: 2923 (s), 2852 (m), 1750 (s, C=O), 1411 (m), 1216 (br-m), 1038 (w).

TLC, Rf:
(50% acetone in hexanes, neutralized plates) 79, 0.45 (UV, ninhydrin, yellow)
82, 0.38 (ninhydrin)
Tetracycle (±)-87:
A solution of $\alpha,\beta$-unsaturated imine (±)-79 (37.8 mg, 0.0780 mmol, 1 equiv) in THF (4 mL) was degassed via an argon purge. To this solution was added solid sodium bicarbonate (35.0 mg, 0.417 mmol, 5.34 equiv) under argon. The reaction mixture was cooled to 0 °C, light was excluded, and NBS (17.5 mg, 0.098 mmol, 1.3 equiv) was added as a solid. The reaction mixture was maintained at 0 °C for ten minutes, then diluted with hexanes:acetone:NEt$_3$ ([50:50:1], 10 mL), was filtered cold through a silica plug (diam. 0.5 cm, ht. 2.5 cm) and the filtrate was concentrated under reduced pressure to produce an orange-brown foam. This residue was dissolved in benzene and filtered to remove excess insoluble succinimide, and the solution was then concentrated and placed under reduced pressure (~ 0.5 Torr) for 1 h. The resulting brominated product was used crude for the cyclization step.

The crude vinyl bromide was dissolved in benzene-$_d_6^{14}$ (1.2 mL), was degassed via an argon purge, and was charged with tributyltin hydride (62 μL, 0.23 mmol, 3.00 equiv). A solution of AIBN in benzene-$_d_6$ (0.30M) was prepared in a flame-dried flask, degassed via bubbling argon, and a portion$^{15}$ (66 μL, 0.0195 mmol, 0.25 equiv) was transferred to the reaction mixture. The reaction solution was placed in a pre-heated 60 °C oil bath and heated to 90 °C over 20 min. After 30 min, the reaction mixture was cooled, an additional portion of AIBN was added (66 μL, 0.0195 mmol, 0.25 equiv), and the mixture was returned to 90 °C. After a subsequent 20 min, the solution was cooled, additional tributyltin hydride (32 μL, 0.12 mmol, 1.5 equiv) and AIBN (132 μL, 0.039 mmol, 0.50 equiv) were added, and the reaction was returned to 90 °C. After 30 min, the reaction was cooled, a final portion of AIBN was added (132 μL, 0.039 mmol, 0.50 equiv), and the mixture was returned to 90 °C. After an additional 30 min at 90 °C, the reaction appeared complete by direct $^1$H NMR spectral analysis. The reaction solution was cooled, triethylamine (300 μL) was added to neutralize adventitious hydrobromic acid, and the solution was concentrated to ~200 μL under reduced pressure. The resulting brown oil was purified via flash column chromatography (neutralized silica gel: diam. 1.0 cm, ht. 10 cm; eluent: hexanes:acetone:NEt$_3$ [97:2:1] to acetone:hexanes:NEt$_3$ [94:5:1] to acetone:hexanes:NEt$_3$ [91:8:1] to acetone:hexanes:NEt$_3$ [89:10:1]) to provide a tetracycle (±)-87 as a tan foam (26.3 mg, 70% (two steps)).

$^{14}$ Deuterated solvent was used to facilitate evaluation of reaction progress by direct $^1$H NMR monitoring.
$^{15}$ Sequential addition of the reagents was necessary for optimal results.
$^1$H NMR (500 MHz, C$_6$D$_6$, 20 °C):

5.65 (dd, $J = 4.3, 2.4$ Hz, 1H, C17-H), 4.75 (app-t, $J = 2.7$ Hz, 1H, C21-H), 3.61 (br-t, 2H, C2-H), 3.45-3.35 (m, 3H, OCH$_2$CH$_2$N, C19-H), 3.08 (app-q, $J = 8.5$ Hz, 1H, OCH$_2$CH$_2$N), 2.96 (m, 1H, C8-H), 2.71 (dt, $J = 8.5, 4.9$ Hz, 1H, OCH$_2$CH$_2$N), 2.47 (m, 1H, C15-H), 2.17 (m, 3H, C7-H), 2.06 (m, 1H), 1.82-1.72 (m, 4H, C9-H), 1.42-1.25 (m, 6H), 1.17 (m, 1H C10-H), 1.00-0.92 (m, 10H, SiC(CH$_3$)$_3$), 0.90 (m, 1H), 0.20 (s, 3H, SiCH$_3$), 0.18 (s, 3H, SiCH$_3$).

TLC, $R_f$:

(50% acetone in hexanes, neutralized plates) 87, 0.63 (ninhydrin)

NOESY correlations (600 MHz, C$_6$D$_6$, 20 °C): H7-H9, H8-H10.
To a solution of tetracycle (+)-87 (45.9 mg, 0.095 mmol, 1 equiv) in THF (5 mL) at 23 °C was added triethylamine trihydrogen fluoride (77 µL, 0.47 mmol, 5.0 equiv). After 3 h, the solution was cooled to 0 °C and the volatiles were removed under reduced pressure on a manifold and allowed to warm to ambient temperature (3 h). The crude reaction mixture was dissolved in ethanol (3.5 mL) and cooled to 0 °C. A suspension of sodium borohydride (5.5 mg, 0.14 mmol, 1.5 equiv) in ethanol (1.5 mL) was added dropwise to the cold reaction mixture under an argon atmosphere. The resulting solution was stirred at 0 °C for ten minutes, then excess hydride was quenched at 0 °C by the addition of ethanolic hydrochloric acid (0.5 M, 200 µL) and the solution was vigorously stirred for five minutes. The reaction mixture was neutralized by the addition of triethylamine (300 µL), was stirred for five minutes, and the volatiles were removed under reduced pressure on a manifold (2 h). The resulting white solid was dissolved in CH₂Cl₂ (1.9 mL), followed by the addition of triethylamine (66 µL, 0.48 mmol, 5.0 equiv), 4-dimethylaminopyridine (18 mg, 0.14 mmol, 1.5 equiv), and benzylchloroformate (27 µL, 0.19 mmol, 2.0 equiv). After 2 h, an additional portion of benzylchloroformate (27 µL, 0.19 mmol, 2 equiv) was added. After an additional 13 h, the reaction was diluted with ethyl acetate (25 mL), hexanes (25 mL), and saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (silica gel: diam. 1 cm, ht. 10 cm; eluent: hexanes:acetone [85:15] to hexanes:acetone [80:20] to hexanes:acetone [70:30]) afforded pentacycle (+)-89 (22.1 mg, 46%, three steps) as a clear oil.

¹H NMR (500 MHz, C₆D₆, 20 °C):

7.33-7.29 (m, 2H, ArH), 7.20-7.12 (m, 2H, ArH), 7.09-7.04 (m, 1H, ArH), 5.85 (br-s, 1H, C17-H), 5.25 (d, J = 12.4 Hz, 1H, CH₂Ph), 5.19 (d, J = 12.4 Hz, 1H, CH₂Ph), 4.70-4.62 (m, 1H, C6-H), 4.17 (br-d, J = 12.5 Hz, 1H, C2-H), 3.49-3.39 (m, 2H, OCH₂CH₂N), 2.94 (app-q, J = 8.6 Hz, 1H, OCH₂CH₂N), 2.70 (dt, J = 8.6, 5.9 Hz, 1H, OCH₂CH₂N), 2.66 (br-s, 1H, OH), 2.51-2.47 (m, 1H, C15-H), 2.44 (dt, J = 12.8, 2.3 Hz, 1H, C2-H), 2.12-1.91 (m, 2H, C10-H, C7-H), 1.81-1.52 (m, 4H, C4-H, C5-H, C8-H, C21-H), 1.38-1.28 (m, 2H, C3-H), 1.28-1.17 (m, 2H, C21-H), 1.15-0.89 (m, 4H, C3-H, C7-H, C19-H), 0.87-0.77 (m, 1H), 0.68 (app-q, J = 11.7 Hz, 1H, C9-H).
$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20 °C):
157.2, 155.7, 139.7 (C16), 138.2, 129.1, 128.9, 123.5 (C17), 80.3 (C20), 67.5 (BnCH$_2$), 61.9 (Ca), 52.6 (C19), 48.0 (C6), 48.0 (Cb), 47.7 (C5), 46.2 (C9), 40.8 (C10), 40.5 (C2), 39.5 (C15), 34.6, 34.0 (C8), 33.3, 30.0 (C7), 29.4, 27.1, 27.0 (C21), 25.8 (C3), 23.5 (C4).

nOe data (500 MHz, C$_6$D$_6$, 20°C):

FTIR (neat) cm$^{-1}$:
3428 (br-m, OH), 2926 (s), 1735 (s), 1691 (s), 1424 (s), 1267 (s), 1169 (w), 1097 (m), 735 (w).

HRMS (ESI):
calcd for C$_{30}$H$_{38}$NaN$_2$O$_5$ [M+Na]$^+$: 529.2673, found: 529.2671.

TLC (40% acetone in hexanes), $R_f$: 89: 0.27 (KMnO$_4$)

*A silyl enol ether tautomer was also obtained using acid treatment:

**Silyl tetracycle (±)-88:**
To a solution of tetracycle (±)-87 (1.0 mg, 2.0 μmol, 1 equiv) in benzene-$d_6$ (700 μL) was added a solution of trifluoroacetic acid in benzene-$d_6$ (0.13M, 38.5 μL, 5.0 μmol, 2.5 equiv) at 23 °C. After 1.5 h, excess acid was quenched by the addition of triethylamine (15 μL), the solution was concentrated under reduced pressure to 200 μL, and purified immediately by flash column chromatography (neutralized silica gel: diam. 0.5 cm, ht. 1.2 cm; eluent: hexanes:acetone:NEt$_3$ [84:15:1]) to provide the tetracycle (±)-88 as a clear film (0.5 mg, 67%). $^1$H NMR (500 MHz, C$_6$D$_6$, 20°C): 6.11 (d, $J = 1.6$ Hz, 1H, C17-H), 3.57 (m, 2H, C2-H), 3.37 (app-q, $J = 8.4$ Hz, 1H, OCH$_2$CH$_2$N), 3.29 (td, $J = 8.8$ Hz, 4.1 Hz, 1H, OCH$_2$CH$_2$N), 3.05 (app-q, $J = 8.8$ Hz, 1H, OCH$_2$CH$_2$N), 2.96-2.86 (m, 1H, C15-H), 2.61-2.53 (m, 1H, OCH$_2$CH$_2$N), 2.49-2.40 (m, 1H), 2.27-2.22 (m, 1H), 2.17-2.06 (m, 1H), 1.94-1.88 (m, 1H), 1.78-1.60 (m, 4H), 1.51-1.40 (m, 1H), 1.40-1.28 (m, 6H), 1.28-1.20 (m, 2H), 1.07-0.87 (m, 4H), 1.04 (s, 9H, Si(CH$_3$)$_3$), 0.18 (s, 3H, Si(CH$_3$)$_3$), 0.17 (s, 3H, Si(CH$_3$)$_3$). TLC, $R_f$: (50% acetone in hexanes, neutralized plates): 87, 0.52 (CAM); 88, 0.54 (UV, CAM).
3-[[3-[[tert-Butyl-dimethyl-silyloxy]-vinyl]-4-[2-(6-methyl-3,4,5,6-tetrahydro-pyridin-2-yl)-vinyl]-3,4,4a,5,6,8,8a-octahydro-naphthalene-1-yl]-oxazolidin-2-one (32):

To a suspension of iminium chloride (−)-(2S)-34 (101 mg, 0.68 mmol, 2.00 equiv) in THF at −78 °C and sealed under argon was added a solution of n-butyllithium in hexanes (2.53 M, 520 µL, 1.32 mmol, 3.87 equiv). The resulting brown solution was maintained at −78 °C for 30 min, was warmed to 0 °C for 10 min, then cooled to −78 °C. A sample of aldehyde (+)-33 (137 mg, 0.34 mmol, 1 equiv) in a round-bottomed flask was azeotropically dried from toluene (2 × 4 mL), the flask was evacuated and backfilled with argon three times, charged with THF (700 µL), and cooled to −78 °C. The lithiated enamine solution was transferred cold via cannula to the cold aldehyde solution. After ten minutes excess anion was quenched at −78 °C by the addition of saturated aqueous ammonium chloride solution (2 mL) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate (40 mL) and saturated aqueous ammonium chloride solution (15 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 40 mL) and the combined organic layers were washed with brine (15 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 10 cm; eluent: CH$_2$Cl$_2$:acetone:NEt$_3$ [98:1:1] to CH$_2$Cl$_2$:acetone:NEt$_3$ [97:2:1] to CH$_2$Cl$_2$:acetone:NEt$_3$ [96:3:1]) to provide β-hydroxyimine 69 (168 mg, 85%, equal mixture of 4 diastereomers) as a light yellow oil. Additionally, the starting aldehyde (±)-33 was recovered (8.1 mg, 6%).

A solution of Martin sulfurane (219 mg, 0.326 mmol, 1.18 equiv) in benzene (2 mL) under argon atmosphere was transferred via cannula to a solution of β-hydroxyimine 69 (153 mg, 0.276 mmol, 1 equiv) in benzene (4 mL) at 23 °C. After 25 min, the reaction mixture was concentrated under reduced pressure and the resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 5 cm, ht. 18 cm; eluent: hexanes:acetone:NEt$_3$ [89:10:1] to acetone:hexanes:NEt$_3$ [84:15:1] to acetone:hexanes:NEt$_3$ [74:25:1] to acetone:hexanes:NEt$_3$ [64:35:1]) to provide the α,β-unsaturated imines (119 mg, 81%, **32**:ent-2-epi-**32**, ∼1:1) as a yellow oil. The corresponding enantiomers of the β-hydroxyimine (203 mg, 70%, equal mixture of 4 diastereomers) and the α,β-unsaturated imine (167 mg, 85%, **ent-32**:2-epi-**32**, ∼1:1) were prepared using the same procedure and the imine salt (+)-(2R)-34.

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16 Meiliana Tjandra, Movassaghi group, Massachusetts Institute of Technology, Cambridge, MA, 2005, personal communication.

17 Rigorous inert atmosphere and anhydrous conditions were required for optimal results.
$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C, equal mixture of two diastereomers, 32:ent-2-epi-32, ~1:1):
6.46 (d, $J = 4.6$ Hz, 1H, C7-H), 6.43 (d, $J = 4.6$ Hz, 1H, C7-H), 6.13-6.05 (m, 2H, C8-H, C8-H), 5.14-5.11 (m, 2H, C17-H, C17-H), 4.29 (br-s, 2H, C21-H, C21-H), 3.62-3.52 (m, 2H, C2-H, C2-H), 3.46-3.41 (m, 4H, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N), 2.95-2.89 (m, 2H, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N), 2.79-2.75 (m, 2H, C19-H, C19-H), 2.65-2.60 (m, 2H, C19-H, C19-H), 2.40-2.31 (m, 4H, C15-H, C15-H, C9-H, C9-H), 2.19-2.07 (m, 2H, C10-H, C10-H), 1.86-1.71 (m, 8H, CH$_2$, CH$_2$), 1.57-1.49 (m, 8H, CH$_2$, CH$_2$), 1.39 (br-s, 3H, C1-H), 1.38 (br-s, 3H, C1-H), 1.36-1.21 (m, 6H, CH$_2$, CH$_2$), 0.97 (br-s, 18H, Si(C(CH$_3$)$_3$)), 0.19 (br-s, 3H, Si(C(CH$_3$)$_3$), 0.18 (br-s, 3H, Si(C(CH$_3$)$_3$), 0.17 (br-s, 3H, Si(C(CH$_3$)$_3$), 0.17 (br-s, 3H, Si(C(CH$_3$)$_3$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C, equal mixture of two diastereomers, 32:ent-2-epi-32, ~1:1): 163.99, 163.98, 159.64, 159.63, 156.01, 155.99, 140.46 (br-s, 2 carbons), 137.99 (C8), 137.95 (C8), 136.26 (C7), 136.19 (C7), 119.44 (C17), 119.25 (C17), 94.39 (C21), 94.34 (C21), 61.80 (br-s, 2 carbons, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N), 54.53, 54.41, 48.05 (C19), 48.04 (C19), 46.82 (OCH$_2$CH$_2$N), 46.78 (OCH$_2$CH$_2$N), 46.63 (C9), 46.60 (C9), 43.21 (C15), 43.16 (C15), 40.39 (C10), 40.36 (C10), 31.74 (C11), 31.67 (C11), 30.65 (C14), 30.61 (C14), 30.42, 30.37, 27.39, 27.36, 27.11 (br-s, 2 carbons), 26.31, 26.29, 25.88, 25.85, 24.30, 24.26, 19.66, 19.47, 18.69 (Si(C(CH$_3$)$_3$), –4.03 (Si(CH$_3$)$_2$), –4.05 (Si(CH$_3$)$_2$), –4.17 (Si(CH$_3$)$_2$), –4.23 (Si(CH$_3$)$_2$).

FTIR (thin film, equal mixture of two diastereomers, 32:ent-2-epi-32, ~1:1) cm$^{-1}$: 2929 (s), 2856 (m), 1756 (s), 1615 (m), 1406 (m), 1259 (m), 1215 (m), 839 (s).

HRMS (ESI, 15):
calcd for C$_{29}$H$_{47}$N$_2$O$_4$Si [M+H]$^+$: 517.3456,  
found: 517.3464.

HRMS (ESI, 6:ent-2-epi-6, ~1:1):
calcd for C$_{29}$H$_{46}$N$_2$O$_3$Si [M]$^+$: 499.3351,
found: 499.3354.

TLC Rf (neutralized plates):
(CH$_2$Cl$_2$:acetone:NEt$_3$ [96:3:1])

33, 0.59 (CAM)  
69, 0.21 (CAM)

(hexanes:acetone:NEt$_3$ [69:30:1])

69, 0.40 (UV, CAM)  
32 and ent-2-epi-32, 0.44 (UV, CAM)
3-[(tert-Butyl-dimethyl-silyloxy)-1-(6-methyl-3,4,5,6-tetrahydro-pyridin-2-ylmethyl)-3a,5a,6,7,8,9,9a,9b-octahydro-1H-cyclopent[a]naphthalen-5-yl]-oxazolidin-2-one (97 and ent-2-epi-97).

A solution of α,β-unsaturated imine 32 (119 mg, 0.238 mmol, 1 equiv, equal mixture of 32 and ent-2-epi-32) in THF (12 mL) was degassed via an argon purge. To this solution was added solid sodium bicarbonate (106 mg, 1.26 mmol, 5.29 equiv) under argon. The reaction mixture was cooled to 0 °C, light was excluded, and NBS (50.5 mg, 0.284 mmol, 1.19 equiv) was added as a solid. The reaction mixture was maintained at 0 °C for ten minutes, then diluted with hexanes:acetone:NEt₃ ([50:50:1], 10 mL), was filtered cold through a silica plug (diam. 1 cm, ht. 2.5 cm) and the filtrate was concentrated under reduced pressure to produce an orange-brown foam. This residue was dissolved in benzene and filtered to remove excess insoluble succinimide. It was then concentrated and placed under reduced pressure (~ 0.5 Torr) for 1 h. The resulting brominated product was used crude for the cyclization step.

The crude vinyl bromide was dissolved in benzene-d₆ (4.8 mL), was degassed via an argon purge, and was charged with tributyltin hydride (192 μL, 0.722 mmol, 3.00 equiv). A solution of AIBN in benzene-d₆ (0.30M) was prepared in a flame-dried flask, degassed via bubbling argon, and a portion (200 μL, 0.060 mmol, 0.25 equiv) was transferred to the reaction mixture. The reaction solution was placed in a pre-heated 60 °C oil bath and heated to 90 °C over 20 min. After 30 min, the reaction mixture was cooled, an additional portion of AIBN was added (200 μL, 0.060 mmol, 0.25 equiv), and the mixture was returned to 90 °C. After a subsequent 20 min, the solution was cooled, additional tributyltin hydride (96 μL, 0.36 mmol, 1.5 equiv) and AIBN (400 μL, 0.030 mmol, 0.50 equiv) were added, and the reaction was returned to 90 °C. After 30 min, the reaction was cooled, a final portion of AIBN was added (400 μL, 0.030 mmol, 0.50 equiv), and the mixture was returned to 90 °C.

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18 Deuterated solvent was used to facilitate evaluation of reaction progress by direct ¹H NMR monitoring.
19 Sequential addition of the reagents was necessary for optimal results.
After an additional 30 min at 90 °C, the reaction appeared complete by direct $^1$H NMR spectral analysis. The reaction solution was cooled, triethylamine (1 mL) was added to neutralize adventitious hydrobromic acid, and the solution was concentrated to ~400 μL under reduced pressure. The resulting brown oil was purified via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 10 cm; eluent: hexanes:acetone:NEt$_3$ [97:2:1] to acetone:hexanes:NEt$_3$ [95:4:1] to acetone:hexanes:NEt$_3$ [92:7:1] to acetone:hexanes:NEt$_3$ [84:15:1]) to provide an equal mixture of two diastereomeric 97 and ent-2-epi-97 as a tan foam (65.7 mg, 55% (two steps)).

The corresponding enantiomers, tetracycles ent-97 and 2-epi-97 (90 mg, 54% (two steps), (~1:1)) were prepared using the same procedure and starting with α,β-unsaturated imines ent-32:2-epi-32, (~1:1)).

$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C, equal mixture of two diastereomers, 97:ent-2-epi-97, ~1:1): 5.66-5.63 (m, 2H, C17-H, C17-H), 4.83 (app-t, $J = 2.9$ Hz, 1H, C21-H), 4.70 (app-t, $J = 2.9$ Hz, 1H, C21-H), 3.46-3.35 (m, 8H, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N, C2-H, C2-H, C19-H, C19-H), 3.11-3.05 (m, 2H, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N), 2.99-2.94 (m, 1H, C8-H), 2.94-2.88 (m, 1H, C8-H), 2.74-2.69 (m, 2H, OCH$_2$CH$_2$N, OCH$_2$CH$_2$N), 2.50-2.44 (m, 2H, C15-H, C15-H), 2.21-2.15 (m, 4H, C7-H, C7-H, CH$_2$, CH$_2$), 2.15-2.09 (m, 2H, CH$_2$, CH$_2$), 2.09-2.02 (m, 2H, CH$_2$, CH$_2$), 1.79-1.65 (m, 8H, C9-H, C9-H, CH$_2$, CH$_2$), 1.56-1.43 (m, 4H, CH$_2$, CH$_2$), 1.43-1.26 (m, 4H, C10-H, C10-H, CH$_2$, CH$_2$), 1.36 (d, $J = 6.7$ Hz, 3H, C1-H), 1.35 (d, $J = 6.7$ Hz, 3H, C1-H), 1.24-1.11 (m, 4H, CH$_2$, CH$_2$), 1.01 (br-s, 18H, SiC(CH$_3$)$_3$), 0.99-0.83 (m, 8H, CH$_2$, CH$_2$), 0.21 (s, 3H, SiCH$_3$)$_2$), 0.20 (s, 3H, SiCH$_3$)$_2$), 0.19 (s, 3H, SiCH$_3$)$_2$), 0.18 (s, 3H, SiCH$_3$)$_2$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C, equal mixture of two diastereomers, 97:ent-2-epi-97, ~1:1): 167.31, 167.16, 156.35 (br-s, 2 carbons), 155.48, 155.24, 139.62 (br-s, 2 carbons), 128.93 (br-s, 2 carbons), 118.02, 117.96, 105.25, 104.82, 61.89 (br-s, 2 carbons), 53.97, 53.84, 47.27, 47.24, 46.95, 46.82, 44.87, 44.76, 43.99, 43.95, 43.63 (br-s, 2 carbons), 32.10, 32.01, 30.36 (br-s, 2 carbons), 30.29, 30.24, 30.14, 30.05, 27.38 (br-s, 2 carbons), 27.36, 27.34, 26.34, 26.32, 24.42, 24.38, 19.84, 19.67, 18.76, 18.73, -4.17, -4.18, -4.20, -4.21.
FTIR (thin film, equal mixture of two diastereomers, 97:ent-2-epi-97, ~1:1) cm$^{-1}$: 3397 (br-w), 2928 (s), 2856 (m), 1758 (s, C=O), 1650 (m), 1408 (m), 1254 (m), 1212 (w), 865 (m), 841 (m), 782 (w).

HRMS (ESI): calcd for C$_{29}$H$_{47}$N$_2$O$_3$Si [M+H]$^+$: 499.3351, found: 499.3357.

TLC, $R_f$:
(30% acetone in hexanes, neutralized plates) 32, 0.44 (UV, CAM)
ent-2-epi-97, 0.51 (UV, CAM)
Pentacyclic amines (-)-98 and (+)-99:

To a solution of tetracycle 97 (65.7 mg, 0.132 mmol, 1 equiv, equal mixture of 97 and ent-2-epi-97) in THF (13 mL) at 23 °C was added triethylamine trihydrogen fluoride (107 μL, 0.660 mmol, 5.00 equiv). After 3 h, the solution was cooled to 0 °C and the volatiles were removed under reduced pressure on a manifold and allowed to warm to ambient temperature (3 h). The crude reaction mixture was dissolved in ethanol (10 mL) and cooled to 0 °C. A suspension of sodium borohydride (10 mg, 0.26 mmol, 2.0 equiv) in ethanol (2 mL) was added dropwise to the cold reaction mixture under an argon atmosphere. The resulting solution was stirred at 0 °C for ten minutes, then excess hydride was quenched at 0 °C by the addition of ethanolic hydrochloric acid (0.5 M, 1.5 mL) and the solution was vigorously stirred for five minutes. The reaction mixture was neutralized by the addition of triethylamine (2 mL), was stirred for five minutes, and the volatiles were removed under reduced pressure on a manifold (1 h). The resulting white solid was dissolved in ethyl acetate (50 mL), saturated aqueous sodium bicarbonate solution (25 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (10 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (neutralized silica gel: diam. 1 cm, ht. 10 cm; eluent: CH₂Cl₂:methanol [95:5] to ammonia saturated CH₂Cl₂:methanol [92:8]) afforded the readily separable pentacyclic amines (-)-98 (18.4 mg, 36%, [α]²²D = -29 (c 0.44, CH₂Cl₂)) and (+)-99 (17.3 mg, 34%, [α]²²D = +65 (c 0.43, CH₂Cl₂)).

The corresponding enantiomeric amines, (+)-98 and (-)-99 (20.0 mg and 25.0 mg, respectively, 66%), were obtained using the same procedure and starting with a mixture of ent-97 and 2-epi-97 (~1:1).

¹H NMR (500 MHz, C₆D₆, 20°C):

Pentacyclic amine (-)-98: 6.09 (br-s, 1H, C17-H), 3.85-3.80 (m, 1H, C19-H), 3.50 (app-q, J = 7.4 Hz, 1H, OCH₂CH₂N), 3.44 (app-q, J = 6.6 Hz, 1H, OCH₂CH₂N), 3.02-2.91 (m, 2H, OCH₂CH₂N), 2.79-2.71 (m, 2H, OCH₂CH₂N), 2.42-2.33 (m, 1H), 2.13 (t, J = 9.8 Hz, 1H), 2.00-1.94 (m, 1H), 1.90-1.84 (m, 2H), 1.74 (ddd, J = 14.0, 6.2, 3.6 Hz, 1H), 1.71-1.61 (m, 2H), 1.56-1.46 (m, 3H), 1.44-1.31 (m, 3H), 1.23-1.09 (m, 6H), 0.98-0.88 (m, 2H) 0.85 (d, J = 6.2 Hz, 3H, C1-H).
**$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C):**

Pentacyclic amine (+)-99: 6.00 (br-s, 1H, C17-H), 3.70-3.65 (m, 1H, C19-H), 3.56-3.46 (m, 2H, OCH$_2$CH$_2$N), 3.26 (t, $J = 6.1$ Hz, 1H, C6-H), 3.07 (app-q, $J = 6.3$ Hz, 1H, C2-H), 3.04-2.96 (m, 1H, OCH$_2$CH$_2$N), 2.77 (app-q, $J = 6.5$ Hz, 1H, OCH$_2$CH$_2$N), 2.07-1.67 (m, 11H), 1.30-1.09 (m, 6H), 1.09-1.02 (m, 2H), 1.00-0.98 (m, 2H), 0.93 (d, $J = 6.5$ Hz, 3H, C1-H).

**$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C):**

Pentacyclic amine (-)-98: 157.4 (carbamate C=O), 137.5 (C16), 128.9 (C17), 80.6 (C20), 61.7 (OCH$_2$CH$_2$N), 56.2, 53.8, 47.8, 47.6, 46.3, 45.8, 45.1, 42.1, 40.6, 40.1, 38.1, 33.8, 31.6, 29.4, 27.1, 26.9, 24.0, 23.4.

Pentacyclic amine (+)-99: 157.5 (carbamate C=O), 138.0 (C16), 128.9 (C17), 81.1 (C20), 61.9 (OCH$_2$CH$_2$N), 48.6, 48.0, 47.3, 46.2, 44.0 (br), 40.9, 40.6, 40.0 (br), 37.6, 33.9, 29.7, 28.2, 27.3, 27.1, 21.1, 20.6.

**FTIR (thin film) cm$^{-1}$:**

Pentacyclic amine (-)-98: 3430 (br-s, OH), 2926 (s), 2855 (m), 1748 (s), 1662 (m), 1481 (w), 1447 (w), 1413 (m), 1279 (w), 1101 (m), 735 (m).

Pentacyclic amine (+)-99: 3424 (br-s, OH), 2926 (s), 2856 (m), 1743 (s), 1666 (w), 1482 (w), 1446 (w), 1416 (m), 1280 (w), 1101 (w), 734 (m).

**HRMS (ESI):**


**TLC, $R_f$:**

(10% MeOH:NH$_3$ satd CH$_2$Cl$_2$) 98, 0.63 (KMnO$_4$) 99, 0.26 (KMnO$_4$)
Carbamate (-)-100:

A solution of sodium carbonate (21 mg, 0.19 mmol, 10 equiv) in water (475 μL) was added to a solution of amine (-)-98 (7.5 mg, 0.019 mmol, 1 equiv) in dichloromethane (600 μL) at 23 °C. The heterogeneous mixture was stirred vigorously and cooled to 0 °C. Benzylchloroformate (8.2 μL, 0.057 mmol, 3.0 equiv) was added dropwise and the resulting mixture was warmed to room temperature for 15 minutes. Two additional portions of benzylchloroformate (8.2 μL, 0.057 mmol, 3.0 equiv each) were added over 30 minutes, followed by dilution of the reaction mixture with dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (silica gel: diam. 1 cm, ht. 2.5 cm; eluent: hexanes:acetone [90:10] to hexanes:acetone [70:30]) provided the carbamate (-)-100 ([α]22D = −62 (c 0.6, CH2Cl2)) as a clear film (6.6 mg, 65%).

The corresponding enantiomer, carbamate (+)-98 (17.0 mg, 63%), was obtained using the same procedure and starting with amine (+)-100.

1H NMR (500 MHz, C6D6, 20°C):

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.32 (d, J = 7.2 Hz, 2H, ArH)</td>
<td>7.18 (m, 2H, ArH)</td>
</tr>
<tr>
<td>7.07 (t, J = 7.4 Hz, 1H, ArH)</td>
<td>5.86 (bs, 1H, C17-H)</td>
</tr>
<tr>
<td>5.27-5.19 (m, 2H, PhCH2OC(O)N)</td>
<td>4.66-4.57 (m, 1H, C6-H)</td>
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<tr>
<td>4.39 (br-s, 1H, C2-H)</td>
<td>3.55-3.43 (m, 2H, OCH2CH2N)</td>
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<tr>
<td>3.01 (app-q, J = 8.3 Hz, 1H, OCH2CH2N)</td>
<td>2.75 (td, J = 8.6, 5.9 Hz, 1H, OCH2CH2N)</td>
</tr>
<tr>
<td>2.66-2.61 (m, 1H, C19-H)</td>
<td>2.45-2.37 (m, 2H, OH, C7-H)</td>
</tr>
<tr>
<td>2.09-2.01 (m, 3H, C5-H, C15-H)</td>
<td>1.78-1.65 (m, 3H, C8-H)</td>
</tr>
<tr>
<td>1.56-1.43 (m, 3H, C4-H, C4-H, C3-H)</td>
<td>1.37-1.28 (m, 2H, C3-H, C21-H)</td>
</tr>
<tr>
<td>1.26 (dt, J = 13.2, 3.2 Hz, 1H)</td>
<td>1.20 (app-t, J = 9.7 Hz, 1H, C9-H)</td>
</tr>
<tr>
<td>1.13 (m, 1H)</td>
<td>1.12 (d, J = 6.9 Hz, 3H, C1-H)</td>
</tr>
<tr>
<td>1.04-0.95 (m, 2H, C7-H)</td>
<td>0.83-0.74 (m, 2H, C10-H).</td>
</tr>
</tbody>
</table>

13C NMR (125 MHz, C6D6, 20°C):

<table>
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<tr>
<th>Chemical Shift</th>
<th>Description</th>
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<tbody>
<tr>
<td>157.3 (carbamate-C=O)</td>
<td>156.0 (PhCH2OC(O)N)</td>
</tr>
<tr>
<td>139.3 (C16)</td>
<td>138.3 (HC=CCCH2OC(O)N)</td>
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<tr>
<td>129.1 (Ar-C)</td>
<td>128.9 (Ar-C)</td>
</tr>
<tr>
<td>128.6 (Ar-C)</td>
<td>127.9 (Ar-C)</td>
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<tr>
<td>123.6 (br, C17)</td>
<td>80.5 (C20)</td>
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<tr>
<td>67.4 (PhCH2OC(O)N)</td>
<td>62.0</td>
</tr>
</tbody>
</table>
(OCH₂CH₂N), 52.9 (C9), 48.1 (C5), 48.0
(OCH₂CH₂N), 47.9 (C6), 46.8 (C2), 45.0 (C10),
40.8 (C15), 39.4 (C19), 34.7 (C21), 34.4 (C4),
33.5 (C8), 33.0, 30.2 (C3), 29.6, 27.1, 27.0, 20.7
(C1), 17.8 (C4).

FTIR (thin film) cm⁻¹:
3427 (br-s, OH), 2928 (s), 2855 (w), 1733 (s),
1688 (s), 1415 (s), 1316 (s), 1093 (s).

HRMS (ESI):
calcd for C₃₁H₄₀NaN₂O₅ [M+Na]^+: 543.2829,
found: 543.2808.

TLC, Rf:
(50% acetone:hexanes) 98, <0.05 (KMnO₄)
100, 0.31 (KMnO₄)

NOESY correlations (600 MHz, C₆D₆, 20°C): Additional data: H2-H3, H3-H4, H4-H5, H4-
H19, H3-H5, H₅-H₆, H6-H7a, H6-H21a, H7a-
H8, H7b-H9, H₉-H₁₉, H17-H19, H19-H4a,b.
Key correlations are shown in bold.
**Carbamate (+)-101:**

A solution of sodium carbonate (62 mg, 0.58 mmol, 10 equiv) in water (1 mL) was added to a solution of pentacyclic amine (+)-99 (22.50 mg, 0.0580 mmol, 1 equiv) in dichloromethane (1.2 mL) at 23 °C. The heterogeneous mixture was stirred vigorously and cooled to 0 °C. Benzylchloroformate (25 µL, 0.18 mmol, 3.0 equiv) was added dropwise and the resulting solution was warmed to room temperature for 15 minutes. The reaction mixture was diluted with dichloromethane (15 mL) and saturated aqueous sodium bicarbonate solution (10 mL), and water (3 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 15 mL). The combined organic layers were washed with brine (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (silica gel: diam. 1 cm, ht. 7.5 cm; eluent: hexanes:acetone [90:10] to hexanes:acetone [75:25] to hexanes:acetone [70:30]) provided the carbamate (+)-101 ([α]_D^22 = +63 (c 0.7, CH₂Cl₂)) as a clear film (22.4 mg, 74%).

The corresponding enantiomer, carbamate (−)-99 (18.2 mg, 54%), was obtained using the same procedure and starting with amine (−)-101.

**¹H NMR (500 MHz, C₆D₆, 20°C):**

7.28 (d, J = 7.6 Hz, 2H, ArH), 7.08 (app-t, J = 8.1 Hz, ArH), 5.69 (br-s, 1H, C17-H), 5.21 (d, J = 12.4 Hz, 1H, PhCH₂OC(O)N), 5.11 (d, J = 12.4 Hz, 1H, PhCH₂OC(O)N), 4.13 (app-q, J = 8.2 Hz, 1H, C6-H), 4.05 (app-q, J = 6.0 Hz, 1H, C2-H), 3.53-3.43 (m, 2H, OCH₂CH₂N), 2.96 (app-q, J = 8.5 Hz, 1H, OCH₂CH₂N), 2.85-2.80 (m, 1H, C19-H), 2.73-2.67 (m, 1H, OCH₂CH₂N), 2.30-2.21 (m, 2H, C15-H, C5-H), 2.01-1.97 (m, 3H, C8-H, C10-H), 1.87-1.85 (m, 2H, C9-H, C4-H), 1.79 (br-d, J = 12.6 Hz, 1H, C7-H), 1.68-1.61 (m, 3H, C3-H), 1.58-1.53 (m, 2H, C4-H, C21-H), 1.38 (d, J = 11.4 Hz, 1H, C21-H), 1.27-1.24 (m, 2H), 1.16-1.14 (m, 2H), 1.15-1.13 (m, 3H, C1-H), 1.09 (m, 2H, C3-H), 0.86-0.85 (m, 2H, C7-H).

**¹³C NMR (125 MHz, C₆D₆, 20°C):**

157.3 (carbamate-C=O), 156.4 (PhCH₂OC(O)N), 139.2 (C16), 138.3 (HC=CCCH₂OC(O)N), 129.1 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 123.3 (br, C17), 81.3 (C20), 67.1 (PhCH₂OC(O)N), 62.0 (OCH₂CH₂N), 49.2 (C2), 49.1 (C9), 48.8 (C6), 47.6 (OCH₂CH₂N), 40.3 (C12), 36.1 (C19), 28.8 (C3), 27.0 (C22), 25.7 (C15), 21.4 (C14), 19.0 (C1), 18.7 (C4), 15.4 (C10), 11.8 (C18), 11.2 (C13), 10.7 (C11), 10.5 (C7), 10.4 (C8), 10.2 (C16), 10.1 (C23), 9.3 (C17), 5.1 (C21), 3.9 (C20).
FTIR (thin film) cm$^{-1}$: 3423 (br-s, OH), 2927 (s), 2855 (w), 1734 (s), 1691 (s), 1407 (m), 1297 (m), 1095 (w), 1039 (w).

HRMS (ESI): calcd for C$_{31}$H$_{40}$NaN$_2$O$_5$ [M+Na]$^+$: 543.2829, found: 543.2817.

TLC, $R_f$: 99, <0.05 (KMnO$_4$)
(50% acetone:hexanes) 101, 0.31 (KMnO$_4$)

NOESY correlations (600 MHz, C$_6$D$_6$, 20°C): Additional data: H1-H6, H5-H6, H9-H19, H17-Hb, H17-H19, H19-H4, H15-H9, H4-H2, H4-H6. Key correlations are shown in bold.
(--)-N-Cbz-Galbulimima alkaloid 13 (105):
p-Toluenesulfonic acid monohydrate (12 mg, 60 µmol, 4.0 equiv) and IBX (47 mg, 0.16 mmol, 11 equiv) were added to a solution of vinyl oxazolidinone (--)-100 (8.0 mg, 15 µmol, 1 equiv) in benzene-d$_6$ (300 µL) and DMSO-d$_6$ (400 µL) at 23 °C. The resulting suspension was sonicated (1.5 h) until it became homogeneous, then heated to 65 °C. $^1$H NMR spectral analysis of the reaction mixture was used to monitor conversion to product. After 10 h, the solution was diluted with ethyl acetate (10 mL), saturated aqueous sodium bicarbonate solution (5 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow residue via flash column chromatography (silica gel: diam. 0.5 cm, ht. 3.5 cm; eluent: hexanes:acetone [85:15] to hexanes:acetone [70:30]) provided enone 105 (5.5 mg, 80%).

The corresponding enantiomer, enone ent-105 (3.5 mg, 67%) was obtained using the same procedure and starting with vinyl oxazolidinone (+)-100.

$^1$H NMR (500 MHz, C$_6$D$_6$, 20°C): 7.32 (d, $J$ = 7.2 Hz, 2H, ArH), 7.20-7.15 (m, 2H, ArH 7.09 (t, $J$ = 7.2 Hz, 1H, ArH), 5.99 (d, $J$ = 2.1 Hz, 1H, C17-H), 5.23 (m, 2H, PhCH$_2$OC(O)N), 4.69 (app-q, $J$ = 8.5 Hz, C6-H), 4.46-4.39 (m, 1H, C2-H), 2.67-2.52 (m, 2H), 1.97-1.90 (m, 1H), 1.75-1.64 (m, 4H), 1.55-1.44 (m, 3H), 1.38-1.24 (m, 3H), 1.21-1.13 (m, 2H), 1.12-1.04 (m, 5H, Cl-H), 1.04-0.85 (m, 3H), 0.84 (dd, $J$ = 11.6, 5.2 Hz, 1H), 0.61 (app-dq, $J$ = 12.2, 3.3 Hz, 1H).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C): 199.0 (C16), 172.5 (C19), 155.8 (PhCH$_2$OC(O)N), 138.1 (HC=CH$_2$OC(O)N), 129.1 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 119.3 (C17), 81.1 (C20), 67.5 (PhCH$_2$OC(O)N), 56.7, 52.6, 47.4, 47.3, 46.2, 45.2, 36.1, 35.7, 31.7, 30.3, 30.2, 26.9, 26.5, 25.9, 20.4, 19.3.

FTIR (thin film) cm$^{-1}$: 3428 (br-s, OH), 2924 (s), 2852 (m), 1687 (m), 1666 (s), 1412 (w), 1314 (w).

HRMS (ESI): calcd for C$_{28}$H$_{37}$N$_{10}$O$_4$ [M+H]$^+$: 450.2639,

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Deuterated solvent was used to facilitate evaluation of reaction progress by direct $^1$H NMR monitoring.
found: 450.2639.

TLC, *Rf*:
(50% acetone:hexanes)

100, 0.31 (KMnO₄)
105, 0.57 (UV, CAM)
**N-Cbz-2-epi-Galbulimima alkaloid 13 (106):**

\( p \)-Toluenesulfonic acid monohydrate (8.0 mg, 42 \( \mu \)mol, 4.6 equiv) and IBX (31 mg, 0.11 mmol, 12 equiv) were added to a solution of vinyl oxazolidinone (+)-101 (4.8 mg, 9.2 \( \mu \)mol, 1 equiv) in benzene-\( d_6 \) (300 \( \mu \)L) and DMSO-\( d_6 \) (450 \( \mu \)L) at 23 °C. The suspension was sonicated (1 h) until it became homogeneous, then heated to 65 °C. \( ^1 \)H NMR analysis of the reaction mixture was used to monitor conversion to product. After 10 h, the solution was diluted with ethyl acetate (8 mL), saturated aqueous sodium bicarbonate solution (8 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 \( \times \) 8 mL). The combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow residue via flash column chromatography (silica gel: diam. 1 cm, ht. 2 cm; eluent: hexanes:acetone [85:15] to hexanes:acetone [80:20]) provided enone ent-106 (2.3 mg, 56%).

The corresponding enantiomer, enone 106 (4.8 mg, 59%) was obtained using the same procedure and starting with vinyl oxazolidinone (−)-101.

\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\), 20°C):

7.30-7.27 (m, 2H, ArH), 7.15-7.12 (m, 2H, ArH), 7.09-7.05 (m, 1H, ArH), 5.99-5.96 (m, 1H, C17-H), 5.18 (d, \( J = 12.4 \) Hz, PhCH\(_2\)OC(O)N), 5.14 (d, \( J = 12.4 \) Hz, PhCH\(_2\)OC(O)N), 4.50 (app-q, \( J = 9.2 \) Hz, 1H, C6-H), 3.71-3.64 (m, 1H, C2-H), 2.64-2.59 (m, 1H), 2.30 (dt, \( J = 13.8, 8.0 \) Hz, 1H), 2.23-2.16 (m, 1H), 1.77-1.65 (m, 3H), 1.64-1.43 (m, 6H), 1.36-1.27 (m, 2H), 1.22 (d, \( J = 6.5 \) Hz, 3H, C1H), 1.18-1.04 (m, 4H), 1.04-0.96 (m, 1H), 0.96-0.86 (m, 2H), 0.74-0.65 (m, 1H).

\(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\), 20°C):

199.0 (C16), 173.3 (C19), 156.6 (PhCH\(_2\)OC(O)N), 138.1 (HC=CH\(_2\)OC(O)N), 129.1 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 119.6 (C17), 82.0 (C20), 67.3 (OCH\(_2\)CH\(_2\)N), 54.4, 52.4, 49.1, 48.5, 47.4, 43.1, 39.3, 35.6, 31.8, 30.6, 29.9, 27.0, 26.5, 26.0, 21.1, 21.0.

FTIR (thin film) cm\(^{-1}\):

3423 (br-s, OH), 2929 (m), 2857 (w), 1687 (m), 1662 (s), 1300 (m), 1154 (w).

HRMS (ESI):

calcd for C\(_{28}\)H\(_{37}\)N\(_3\)O\(_4\) [M+H]\(^+\): 450.2639.

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\(^{21}\) Deuterated solvent was used to facilitate evaluation of reaction progress by direct \(^1\)H NMR monitoring.
found: 450.2644.

TLC, $R_f$:
(50% acetone:hexanes)  
101, 0.31 (KMnO₄)  
106, 0.57 (UV, CAM)
(−)-Galbulimima alkaloid 13 (2):22

N-Cbz enone 105 (2.7 mg, 6.0 μmol, 1 equiv) was azeotropically dried from toluene (3 × 1 mL), was dissolved in dichloromethane (1.0 mL), and was cooled to 0 °C. Trimethylsilyliodide (TMSI, 1.2 μL, 9.0 μmol, 1.5 equiv) was added to the cooled solution, and the resulting yellow solution was stirred at 0 °C. Additional portions of TMSI were added at 20 minute intervals until complete consumption of 105 was observed by TLC analysis (70 min). The reaction mixture on completion was a cloudy yellow solution, with a brown residue. Excess silylated products were quenched at 0 °C by the addition of aqueous hydrochloric acid solution (1N, 1.5 mL) and the mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with hexanes (10 mL) and aqueous hydrochloric acid solution (1N, 2 mL) and the layers were separated. The organic layer was extracted with aqueous hydrochloric acid solution (1N, 4 mL). The combined acidic aqueous layers were washed sequentially with hexanes (2 × 10 mL), dichloromethane (10 mL), and hexanes (10 mL). The aqueous layer was then basified to pH 13 with aqueous sodium hydroxide solution (1N, 10 mL). The resulting solution was stirred at ambient temperature for 1 h. The aqueous solution was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed sequentially with water (18 mL) and brine (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide (−)-galbulimima alkaloid 13 (2, [α]22D = −34 (c 0.045, CH2Cl2)23) as a white film (1.7 mg, 89%).

The corresponding enantiomer, (±)-ent-galbulimima alkaloid 13 (2, 1.4 mg, 58%, [α]22D = +34 (c 0.090, CH2Cl2)23), was obtained using the same procedure and starting with N-Cbz amine ent-105.

1H NMR (500 MHz, C6D6, 20°C):

6.07 (d, J = 2.2 Hz, 1H, C17-H), 3.28 (dt, J = 11.4, 2.3 Hz, 1H, C9-H), 2.88 (app-t, J = 5.1 Hz, 1H, C6-H), 2.72-2.66 (m, 1H), 2.60-2.55 (m, 1H), 2.15 (app-qq, J = 6.1, 2.3 Hz, 1H, C2-H), 1.98 (m, 1H, OH), 1.91 (app-t, J = 4.4 Hz, 1H, C5-H), 1.84-1.81 (m, 1H, C8-H), 1.78 (dd,


23 Literature value: [α] = −84 (CHCl3); see reference 22b. We have also measured the rotation of (−)-2 in chloroform (2 sources): a) chloroform passed through basic alumina (Grade I) and dried over 4Å-MS, [α]22D = −51 (c 0.06, CHCl3), and b) chloroform passed through basic alumina (Grade I) and distilled from P2O5, [α]22D = −64 (c 0.06, CHCl3). Additionally, we have measured the rotation of (±)-2 in chloroform: a) chloroform passed through basic alumina (Grade I) and dried over 4Å-MS, [α]22D = +51 (c 0.07, CHCl3), and b) chloroform passed through basic alumina (Grade I) and distilled from P2O5, [α]22D = +66 (c 0.07, CHCl3).
J = 11.2, 3.6 Hz, 1H, C15-H), 1.75-1.69 (m, 1H), 1.67-1.60 (m, 1H), 1.55 (app-dq, J = 13.9, 2.9 Hz, 1H, C7-Ha), 1.53-1.47 (m, 1H), 1.40 (ddd, J = 10.8, 5.6, 2.1 Hz, 1H, C21-Ha), 1.26 (dd, J = 5.6, 2.4 Hz, 1H, C21-Hb), 1.23-0.90 (m, 8H, C10-H, C7-Hb), 0.77 (m, 1H), 0.75 (d, J = 6.1 Hz, 3H, C1-H).

$^{13}$C NMR (125 MHz, C$_6$D$_6$, 20°C):

199.4 (C16), 178.9 (C19), 119.2 (C17), 79.7 (C20), 55.4 (C6), 53.3 (C15), 53.2 (C2), 51.2 (C9), 48.2 (C21), 47.6 (C10), 46.6 (C5), 41.0 (C7), 33.1 (C8), 31.9, 30.6, 27.3 (C3 or C4), 26.7, 26.1, 25.0 (C3 or C4), 23.6 (C1).

FTIR (thin film) cm$^{-1}$:

3403 (br-s, OH), 2921 (s), 2851 (m), 1708 (w), 1646 (s), 1447 (m), 1261 (m). (Literature values: 3406, 2929, 2854, 1705, 1646, 1446).$^{22}$

HRMS (ESI):

calcd for C$_{20}$H$_{30}$N$_{10}$O$_2$ [M+H]$^+$: 316.2271, found: 316.2280.

NOESY correlations (600 MHz, C$_6$D$_6$, 20°C): Additional data: H1-H2, H2-H6, H5-H6, H5-H21b, H6-H7a, H6-H21b, H7a-H8, H7a-H6, H8-H21a, H9-H15. Key correlations are shown in bold.

Comparison of our (−)-GB 13 (2) assignments with prior assignments for (±)-2:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Mander’s report$^{22a}$ (±)-GB-13 (2) ($^1$H, 300 MHz, CDCl$_3$)</th>
<th>This work (−)-GB 13 (2) ($^1$H, 500 MHz, CDCl$_3$)</th>
<th>This work (−)-GB 13 (2) ($^1$H, 500 MHz, C$_6$D$_6$)</th>
<th>This work (−)-GB 13 (2) $^{13}$C (125 MHz, C$_6$D$_6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.89, (d, J = 6.2 Hz)</td>
<td>0.89, (d, J = 6.1 Hz)</td>
<td>0.75, (d, J = 6.1 Hz)</td>
<td>23.6</td>
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<tr>
<td>C2</td>
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<td>2.15, (app-qd, J = 6.1, 2.3 Hz)</td>
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<td>C3,C4</td>
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<td>2.72-2.66 (m); 2.60-2.55 (m)</td>
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<td>27.3, 25.0</td>
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<tr>
<td>C5</td>
<td></td>
<td>1.91 (app-t, J = 4.4 Hz)</td>
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<td>46.6</td>
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<tr>
<td>C6</td>
<td>3.34, (t, J = 5.1 Hz)</td>
<td>3.34, (t, J = 5.1 Hz)</td>
<td>2.88, (app-t, J = 5.1 Hz)</td>
<td>55.4</td>
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<tr>
<td>C7</td>
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<td>1.55 (app-dq, J = 13.9, 2.9); 1.02 (m)</td>
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<td>41.0</td>
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<td>C8</td>
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<td>Chemical Shifts and Couplings</td>
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<tr>
<td>C9</td>
<td>3.47, (dt, $J = 11.3$, 2.2 Hz)</td>
<td>3.47, (dt, $J = 11.2$, 2.1 Hz)</td>
<td>3.28, (dt, $J = 11.4$, 2.3 Hz)</td>
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<td>C10</td>
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<td>47.6</td>
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<td>C11-C14</td>
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<td>31.9, 30.6, 26.7, 26.1</td>
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<tr>
<td>C15</td>
<td></td>
<td></td>
<td>1.78, dd, $J = 11.2$, 3.6 Hz</td>
<td>53.3</td>
</tr>
<tr>
<td>C16</td>
<td>~</td>
<td>~</td>
<td>~</td>
<td>199.4</td>
</tr>
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<td>C17</td>
<td>5.92, (d, $J = 2.0$ Hz)</td>
<td>5.93 (d, $J = 2.1$ Hz)</td>
<td>6.07, (d, $J = 2.2$ Hz)</td>
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<td>C19</td>
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<td>~</td>
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<td>C20</td>
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<tr>
<td>C21</td>
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<td></td>
<td>1.40 (ddd, $J = 10.8$, 5.6, 2.1 Hz); 1.26 (dd, $J = 5.6$, 2.4 Hz)</td>
<td>48.2</td>
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</tbody>
</table>
(+)-ent-108:

N-Cbz enone ent-106 (2.1 mg, 4.7 μmol, 1 equiv) was azeotropically dried from toluene (3 x 1 mL), was dissolved in dichloromethane (800 μL), and was cooled to 0 °C. Trimethylsilyliodide (TMSI, 1.5 μL, 11 μmol, 2.2 equiv) was added to the cooled solution, and the resulting yellow solution was stirred at 0 °C. Additional portions of TMSI were added at 20 minute intervals until complete consumption of ent-106 was observed by TLC analysis (50 min). The reaction mixture on completion was a cloudy yellow solution, with a brown residue. Excess silylated products were quenched at 0 °C by the addition of aqueous hydrochloric acid solution (1 N, 1.5 mL) and the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with hexanes (10 mL) and aqueous hydrochloric acid solution (1 N, 3 mL) and the layers were separated. The organic layer was extracted with aqueous hydrochloric acid solution (1 N, 4 mL). The combined acidic aqueous layers were washed sequentially with hexanes (2 x 10 mL), dichloromethane (10 mL), and hexanes (10 mL). The aqueous layer was then basified to pH 13 with aqueous sodium hydroxide solution (1 N, 11 mL). The resulting solution was stirred at ambient temperature for 1 h. The aqueous solution was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were washed sequentially with water (18 mL) and brine (10 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide (+)-ent-108, [α]22 D = +24 (c 0.070, CH₂Cl₂) as a white film (1.4 mg, 93%).

The corresponding enantiomer, (-)-108, 2.8 mg, 82%, [α]22 D = -24 (c 0.085, CH₂Cl₂), was obtained using the same procedure and starting with N-Cbz enone 106.

1H NMR (500 MHz, C₆D₆, 20°C):

3.08-3.02 (m, 2H, C₂-H, C₆-H), 3.02 (d, J = 13.5 Hz, 1H, C₁₇-Ha), 2.55 (br-d, J = 12.9 Hz, 1H, C₁₇-Hb), 1.99-1.91 (m, 2H, C₉-H, OH), 1.91-1.88 (m, 1H, C₈-H), 1.87-1.81 (m, 1H), 1.80-1.72 (m, 2H, C₁₅-H, C₂₁-Ha), 1.68-1.48 (m, 7H, C₅-H, C₁₁-H, C₂₁-Hb, C₇-Ha), 1.43-1.30 (m, 3H), 1.26 (br-d, J = 12.7 Hz, 1H, C₇-Hb), 1.14 (qd, J = 11.4, 3.4 Hz, 1H, C₁₀-H), 1.06 (d, J = 7.0 Hz, 3H, C₁-H), 1.02-0.89 (m, 3H), 0.79 (dd, J = 13.6, 6.5 Hz, 1H), 0.73-0.63 (m, 1H).

13C NMR (125 MHz, C₆D₆, 20°C):

212.3 (C₁₆), 87.4 (C₂₀), 75.7 (C₁₉), 60.5 (C₉), 57.3 (C₆), 55.0 (C₅), 52.8 (C₁₅), 50.6 (C₂), 47.9 (C₂₁), 44.4 (C₁₀), 40.9 (C₁₇), 37.1 (C₇), 36.2 (C₈), 32.5, 30.3, 26.4, 25.7, 24.1, 22.4, 20.7 (C₁).
FTIR (thin film) cm\(^{-1}\):
3302 (br-m, OH), 2929 (s), 2853 (w), 1706 (m, C=O), 1314 (w), 1300 (w), 1182 (w).

HRMS (ESI):
calcd for C\(_{20}\)H\(_{30}\)N\(_{1}\)O\(_{2}\) [M+H]\(^{+}\): 316.2271, found: 316.2270.

NOESY correlations (600 MHz, C\(_{6}\)D\(_{6}\), 20°C): H\(_6\)-H\(_7\)b, H\(_8\)-H\(_7\)a, H\(_8\)-H\(_7\)b, **H\(_9\)-H\(_{15}\)**, **H\(_5\)-H\(_{21}\)b**, H\(_5\)-H\(_7\)b, H\(_{10}\)-H\(_{21}\)a. Key correlation shown in bold.
Crystal data and structure refinement for imine acetal 78:

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<td>b</td>
<td>19.7724(16) Å</td>
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<td>Refinement method</td>
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Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for imine acetal 78. U(eq) is defined as one third of the trace of the orthogonalized $U^0$ tensor.

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| O(4)-C(20)-C(21) | 104.38(12) |
| O(4)-C(20)-N(1) | 108.42(12) |
| C(21)-C(20)-C(19) | 113.86(13) |
| C(16)-C(15)-C(14) | 113.83(12) |
| C(16)-C(15)-C(10) | 110.32(12) |
| C(14)-C(15)-C(10) | 108.28(12) |
| C(28)-C(27)-C(29) | 124.36(14) |
| C(28)-C(27)-C(30) | 109.02(13) |
| C(29)-C(27)-C(30) | 109.04(14) |
| C(29)-C(27)-Si(1) | 108.78(14) |
| C(28)-C(27)-Si(1) | 111.50(13) |
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| C(30)-C(27)-Si(1) | 109.03(11) |
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| N(1)-C(6)-C(7) | 109.05(12) |
| C(5)-C(6)-C(7) | 113.54(13) |
| C(11)-C(10)-C(9) | 111.87(13) |
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Chapter 2

Resin-bound Glycosyl Phosphates As Glycosyl Donors

Thesis Advisor: Peter H. Seeberger
Introduction and Background

While the significance of oligosaccharides and glycoconjugates in biological signaling pathways and cell adhesion is generally appreciated, the difficulty associated with their isolation and identification has hindered detailed investigations. Unlike nucleic acid and protein biopolymers, which are biosynthesized under genetic control, complex carbohydrates are enzymatically generated, resulting in microheterogeneous mixtures that are difficult to characterize and purify. Synthetic methodologies must take into consideration the specific challenges posed by oligosaccharides, particularly hydroxyl group differentiation, the generation of highly branched structures, and the stereospecific formation of each glycosidic linkage. Both enzymatic and chemical methods have been applied to these issues, each offering unique advantages.

The application of natural glycosyltransferases and glycosidases to oligosaccharide construction offers the benefit of excellent stereo- and regiocontrol and eliminates the need for extensive protecting group manipulations. The diversity of carbohydrates available by this method is limited, however, by enzyme specificity, precluding the use of non-natural substrates. Where unusual linkages or unnatural sugars would be advantageous for biological study or therapeutic application, chemical synthesis remains an invaluable tool.

Synthetic oligosaccharide formation requires a glycosyl donor which forms an electrophilic species on activation and couples with a nucleophilic acceptor hydroxyl (Scheme 1). Since the first report by Koenigs and Knorr involving glycosyl halides (1),

Scheme 1. The general strategy for chemical synthesis of oligosaccharides.
numerous glycosyl donors have been developed, among them 1,2-anhydrosugars (glycals, 2),
glycosyl trichloroacetimidates (3), thioglycosides (4), glycosyl sulfoxides (5),
and glycosyl phosphates (6). Although α-glycosidic linkages are favored due to the anomeric
effect, stereoselectivity can depend on a number of factors, including leaving group identity,
the electronic and steric nature of donor and acceptor substituents, the activator, the solvent,
and the temperature. These variables are thought to affect the stability and conformation of
the putative oxonium ion formed following the departure of the leaving group during
activation (Scheme 2). Though the mechanisms of several donor types, such as sulfoxides,
trichloroacetimidates,' and phosphites,' have been investigated, a detailed general
mechanism remains elusive and is often a matter of debate. 12

Various techniques have been developed to enhance the stereoselectivity of
glycosylation reactions, particularly the formation of energetically-disfavored β-glucosidic
linkages, which are prevalent in biological systems. Numerous methods have been employed
to produce β-linked sugars, including the use of participating solvents,' intramolecular
aglycone delivery, and glycal donors. A common and general method for producing β-
linked glucosyl sugars utilizes anchimeric assistance from an ester or amide protecting group
installed at C2. For a wide range of donor types and sugars, interaction of a C2-ester with the
intermediate oxonium species formed on activation effectively blocks the cis-face such that
the trans-product is formed exclusively (Scheme 3).16
Advances in the chemical synthesis of oligonucleotides and oligopeptides over the last several decades, particularly the exploitation of solid phase strategies,\textsuperscript{17} have facilitated widespread exploration of their structure and function. As a result of this success, interest in the application of the solid phase paradigm to the construction of complex carbohydrates has intensified. Attractive features of the solid-phase approach include the elimination of intermediate purification steps, which allows the use of excess reagent to drive reactions to high conversion. Recent work has also demonstrated the applicability of the solid-phase paradigm to the automated synthesis of oligosaccharides.\textsuperscript{18}

Solid-phase oligosaccharide synthesis may be approached from two different directions, through linker attachment at either a reducing or non-reducing site on the sugar, resulting in immobilized acceptor or donor, respectively (Scheme 4).\textsuperscript{19} In the acceptor-bound paradigm, following glycosylation an orthogonal temporary protecting group is removed and the process repeated, while in the donor-bound strategy, a new donor is regenerated and the process repeated. A number of syntheses have employed the acceptor-
bound method and a variety of donors to produce diverse and complex structures such as the phytoalexin elicitor (7),\textsuperscript{18} Lewis blood determinants (8),\textsuperscript{20} and heparin sulfate-like oligomers (9), as well as carbohydrate libraries (Figure 1).\textsuperscript{19} In addition, a variety of polymer-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Representative structures synthesized using acceptor-bound solid-phase oligosaccharide synthesis: protected phytoalexin elicitor (7), protected Lewis Y (8), and a heparin sulfate-like oligomer 9.}
\end{figure}

supported glycosyl donors, attached to the solid phase at each of the four non-reducing positions, have been explored. While acceptor-bound methods often lead to inert anomeric moieties, efficient donor-bound synthesis may allow straight-forward access to peptide or lipid containing glycoconjugates by direct ligation on solid support at the available reducing sugar.\textsuperscript{19} Effective glycosylations with resin-bound glycosyl fluorides, trichloroacetimidates, thioglycosides and glycals have been demonstrated, with the latter two methods providing the best yields and purity.\textsuperscript{15,21} Several examples of oligosaccharides synthesized utilizing the donor-bound method are shown in Figure 2.\textsuperscript{15,21c}
Figure 2. Representative structures synthesized using donor-bound solid-phase oligosaccharide synthesis.

The use of glycals as synthetic intermediates is particularly attractive as they simplify the manipulations required for hydroxyl differentiation. Glycals have been used both as donors and as precursors to thioglycosides and glycosyl phosphates (Scheme 5). Use of a C2-ester in thiodonor and phosphate formation generally insures β-linkages in the final products. Resin-bound glycals have been used to produce extended structures as well as resin-bound thioglycosides and thioethyl 2-amidoglucosyl donors (Scheme 6). The high-

Scheme 5. Glycals as donors (path a) and precursors to thioglycosides (path b) or glycosyl phosphates (path c).
yielding one-pot synthesis of glycosyl phosphates from glycals and the high reactivity of these donors suggest they would be an attractive addition to donor-bound oligosaccharide synthesis.

Linker choice is an important consideration in any solid-phase synthesis. The linker should be inert to all required manipulations, yet easily installed and readily cleaved to release the desired product. Donor-bound strategies have employed assorted chemical anchors for resin attachment, including various trialkylsilyl and p-alkoxybenzyl groups, as well as base-labile succinate and succinamyl linkers. Linkers are chosen with the overall protecting scheme and chemical pathway in mind and are designed for generalized use. The work discussed in this chapter describes the synthesis and use of resin-bound glycosyl phosphates, where the succinate linker chosen was observed to influence the stereochemical outcome of the glycosylation reaction.

**Results and Discussion**

**Preparation of resin-bound glycosyl phosphates.**

Recent work has demonstrated the utility of anomeric phosphate donors, which couple rapidly and in high yield in both solution phase and acceptor-bound glycosylations.
upon activation with stoichiometric trimethylsilyl trifluoromethanesulfonate (TMSOTf). Successful application of glycals to the solution phase one-pot synthesis of glycosyl phosphates suggested an efficient route to their resin-bound counterparts analogous to Danishefsky's synthesis of polymer supported thioglycosides (Scheme 6).

Preparation of resin-bound glycosyl phosphates began with the selection of an appropriate support and linker system. Polystyrene resin was chosen for its excellent swelling properties in methylene chloride, the primary solvent for our planned resin-bound operations. An aminomethyl-functionalized resin coupled to succinate would provide a succinamyl linker that could be readily cleaved through basic hydrolysis.

Attachment to the resin was undertaken at the readily differentiated C6-hydroxyl of dibenzyl glycal 10. Exposure of 10 to succinic anhydride and dimethylaminopyridine (DMAP) in pyridine and methylene chloride provided the C6-succinate 11 in excellent yield (Scheme 7). Immobilization of glycal 11 onto the aminomethyl resin via amide formation with diisopropylcarbodiimide provided resin-bound glycal 12. In order to facilitate reaction analysis a solution-phase model system of the resin-bound donor system was also prepared. Analogous coupling of glycal 11 with benzylamine provided model system 13.

Application of our previously developed solution-phase three-step, one-pot procedure for access to glycosyl phosphates from glycals provided resin-bound glycosyl phosphate 14 and model glycosyl phosphate 15 from glycals 12 and 13, respectively. Initial epoxidation of each glycal was achieved by exposure to an acetone solution of dimethyldioxirane (DMDO) (Scheme 7). Removal of the volatiles was followed by epoxide opening with...
dibutylphosphate to provide the desired anomeric phosphate. Finally, installation of a pivaloyl ester at C2 provided the desired participating group, which was expected to ensure the desired β-selectivity for the glycosylation reaction. Epoxidation with dimethyldioxirane (DMDO) was performed twice for the resin-bound conversion as outlined for Danishefsky’s thioglycoside preparation from the 1,2-anhydrosugar. Comparative analysis of $^{31}$P NMR and high resolution magic angle spinning (HR-MAS) $^{31}$P NMR for compounds 15 and 14, respectively, indicated a 1:1 mixture of α and β glycosyl phosphates was obtained in both cases.

**Disaccharide synthesis with resin-bound glycosyl phosphates.**

With glycosyl phosphates 14 and 15 in hand, activation of the support-bound donor for union with a series of nucleophiles was explored. Glycosyl acceptors displaying C6 (16), C2 (17), and C4 (18) hydroxyl groups were investigated in glycosylations with both the resin-bound donor 14 and model system 15 (Figure 3). Acceptor 18 was synthesized from glycal 19 via epoxidation and ring opening with methanol to provide methyl glycoside 20, subsequent pivaloyl protection at C2 (21), and fluoride-mediated silyl deprotection to reveal the desired C4-hydroxyl of 18 in good yield (Scheme 8).

Glycosylation was effected by swelling of resin 14 in methylene chloride, followed by phosphate activation with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at low temperature in the presence of acceptor 16, 17, or 18 (Table 1). Cleavage of the disaccharides from the resin was achieved by exposure to sodium methoxide in a mixture of methanol and methylene chloride to provide glycosides 22, 24 and 26. The reported yields in Table 1 reflect the total yield over the four solid-phase operations. In several cases double glycosylations or excess activator were required for full conversion of the resin bound donor.
Table 1. Disaccharide synthesis using resin-bound phosphate 14 and solution-phase model 15.

<table>
<thead>
<tr>
<th>entry</th>
<th>donor</th>
<th>R’OH</th>
<th>product</th>
<th>R</th>
<th>yield (%, α:β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td></td>
<td>22</td>
<td>H</td>
<td>58%, α:β 1:2:2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td></td>
<td>23</td>
<td>Succ-NHBn</td>
<td>85%, α:β 1:1.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td></td>
<td>24</td>
<td>H</td>
<td>28%, α:β 1:2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td></td>
<td>25</td>
<td>Succ-NHBn</td>
<td>98%, α:β 1:1.1&lt;sup&gt;c&lt;/sup&gt; (38%, α:β 1:1.4)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td></td>
<td>26</td>
<td>H</td>
<td>27%, α:β 1:1.7&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td></td>
<td>27</td>
<td>Succ-NHBn</td>
<td>80%, α:β 1:1:1&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Resin-bound phosphate 14 (1.0 equiv) was swelled in CH₂Cl₂, R’OH (2.5-6.5 equiv) was added, followed by TMSOTf (1.1 equiv) at -15 °C, and the reaction shaken for 2 h; the procedure was repeated twice.  
<sup>b</sup> Phosphate 6 (1.1 equiv) and R’OH (1.0 equiv) were dissolved in CH₂Cl₂, TMSOTf (1.3 equiv) added at -78 °C, and the reaction warmed to -10 °C over 2 h.  
<sup>c</sup> Phosphate 6 (1.1 equiv) and R’OH (1.0 equiv) were dissolved in CH₂Cl₂, TMSOTf (1.3 equiv) added at -78 °C, followed by another 1.3 equiv activator after warming to -30 °C over 1 h.  
<sup>d</sup> Resin-bound phosphate 5 (1.0 equiv) was swelled in CH₂Cl₂, R’OH (2.0 equiv) added, followed by slow warming from -78 °C with addition of 3 x 1.1 equiv of TMSOTf added on one hour delays at -78 °C, -30 °C, and -10 °C.

Surprisingly, despite the presence of a participating pivaloyl ester at C2 for the resin-bound donor 14, the resulting disaccharides were obtained as anomeric mixtures that only
slightly favored the expected β-anomer (Table 1, entries 1, 3, and 5). Analogous solution phase glycosylation reactions employing glycosyl phosphate 15 also produced anomic mixtures, suggesting the nature of the linker, rather than the solid-phase protocol, was responsible for these unexpected results (Table 1, entries 2, 4, and 6).

**Investigation of C6-linker effects on reactions with glycosyl phosphates.**

Previous work in our laboratory, including couplings with glycosyl phosphates containing a C6-levulinate ester, had not indicated any interference of the C6-hydroxyl protecting group with anomeric selectivity.8,18 On the basis of these considerations, we reasoned that a levulinate-type linker would not affect glycosylation stereoselectivity, while hydrazine cleavage should allow rapid removal of the products from the resin under neutral conditions. A 3-benzoxypropionate ester linker, previously utilized at the anomeric position in an acceptor-bound strategy for the assembly of di-, tri-, and tetrasaccharides,27 was selected to replace the succinamyl linker.

Investigations into the use of this new linker were performed on a solution-phase model system for expedient analysis of the chosen route. Glycosyl phosphate formation, subsequent glycosylations, and linker cleavage therefore utilized C6-3-benzoxypropionate ester 30 (Scheme 9). Union of glycal 10 and 3-benzoxypropionic acid 28 afforded protected glycal 30 that was readily converted to the corresponding glycosyl phosphate 32 as described above. Subsequent coupling with acceptor 16 produced exclusively the β-disaccharide 34, consistent with effective participation of the C2-pivaloate ester (Scheme 10). Unfortunately,
cleavage of the 3-benzoylpropionic ester with either excess hydrazine or hydrazine acetate proved very slow, requiring prolonged reaction times (18 h) to produce 50-80% conversion even at elevated temperature (80°C). We hypothesized that addition of a methylene group to the linker would alter the electrophilicity of the benzylic carbonyl, alleviate steric crowding, and facilitate its removal with hydrazine. To assess this strategy, a 4-oxo-5-phenyl-valerate ester\textsuperscript{28} model linker was installed at C6 of galactose 16. We were pleased to find the linker was efficiently cleaved at ambient temperature in the presence of hydrazine (2 equiv) in 90 minutes. Encouraged by these initial observations, we investigated the use of this linker for glycosyl phosphate formation and glycosylation with acceptor 16. Glycal 10 was equipped with the 4-oxo-5-phenyl-valeric ester at C6 and converted to the corresponding glycosyl phosphate 33 (Scheme 9). Surprisingly, subsequent coupling with the acceptors 16, 17, and 18 produced an anomeric mixture of disaccharides 35-37 as previously observed for the succinamyl glycosyl phosphates 14 and 15 (Table 2).
Table 2. Disaccharide synthesis using 4-oxo-5-phenylvaleric ester linker model phosphate 33.

<table>
<thead>
<tr>
<th>acceptor</th>
<th>product</th>
<th>yield (%; α:β)</th>
</tr>
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<tbody>
<tr>
<td>16</td>
<td>OR Bn O PivO Bn O PivO</td>
<td>88% (α:β 1:1.6)</td>
</tr>
<tr>
<td>17</td>
<td>OR Bn O PivO Bn O OMe</td>
<td>94% (α:β 1:2.2)</td>
</tr>
<tr>
<td>18</td>
<td>OR Bn O PivO Bn O OMe</td>
<td>53% (α:β 1:1.8)</td>
</tr>
</tbody>
</table>

Exploring linker effects with thioglycosides and trichloroacetimidates.

In light of the observed erosion of glycosylation stereoselectivity for glycosyl phosphates 15 and 33, we decided to explore the generality of the observed linker effect for different anomeric leaving groups. To this end, the corresponding thioglycoside and glycosyl trichloroacetimidate donors, each containing a C2-pivaloate ester and one of the three C6 model linkers, were prepared. 3-Benzoylpropioanoate and 4-oxo-5-valerate ester glycals 30 and 31 were subjected to epoxidation and ring opening with ethanethiol to produce the corresponding phenyl and benzyl ketone thioglycosides, where installation of the C-2 pivaloate ester then provided thioglycosides 38 and 39 (Scheme 11). Application of this sequence to succinamyl glycal 13 failed to provide the desired thioglycoside 45, and an

Alternate route was employed (Scheme 12). The C6-acetate thioglycoside 41 was obtained from glycal 40, followed by pivaloate formation to provide C2-pivaloyl thioglycoside 42.

Scheme 12. Synthesis of C6-succinamyl thioglycoside 45.

Basic hydrolysis of the acetate was then followed by introduction of the succinate at C6 and amide coupling with benzylamine to provide the desired succinamyl thioglycoside 45. The required trichloroacetimidates 46-48 were synthesized from thioglycosides 38, 39, and 45 via the corresponding lactols (Scheme 13).

Scheme 13. Formation of C6-model linker trichloroacetimidates 46-48 from thioglycosides 38, 39, and 45.

Thioglycosides 38, 39, and 45 and trichloroacetimidates 46-48 were then coupled with galactose acceptor 16 (Table 3). Both donor types exhibited complete β-selectivity for
Table 3. Glycosylations with thioglycosides and glycosyl trichloroacetimidates with various C6-linkers.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>X</th>
<th>activator</th>
<th>donor</th>
<th>R</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>-SEt</td>
<td>NIS</td>
<td>38</td>
<td>Ph</td>
<td>34</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>TMSOTf (cat)</td>
<td>39</td>
<td>Bn</td>
<td>35</td>
<td>79%</td>
</tr>
<tr>
<td>-0CCl3</td>
<td>TMSOTf (cat)</td>
<td>45</td>
<td>NH-Bn</td>
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<td></td>
<td>46</td>
<td>Ph</td>
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<td>70%</td>
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<td></td>
<td>47</td>
<td>Bn</td>
<td>35</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>NH-Bn</td>
<td>23</td>
<td>69%</td>
</tr>
</tbody>
</table>

each of the three model linkers. The influence of a C6 linker on glycosylation stereoselectivity for glycosyl phosphates and the absence of a dependence for thioglycosides and glycosyl trichloroacetimidates suggest the presence of different intermediates along the reaction pathway. The exact nature of the linker interference during glycosylation is not understood at this time, but must be taken into consideration in the development of new linkers for the donor-bound approach to the synthesis of oligosaccharides and carbohydrate libraries on solid support.

Conclusion

We have demonstrated the preparation of glycosyl phosphates from support-bound glycals using a one-pot, three-step procedure. These glycosyl phosphates were used as resin-bound glycosyl donors in the formation several disaccharides with a variety of acceptors. The nature of the succinic-like linker connecting the C6 hydroxyl group to the support was found to fundamentally influence the stereoselectivity of glycosylations involving these donors, but not that of similar thioglycoside or trichloroacetimidate donors. These results suggest that protecting-group influence on glycosylation with glycosyl phosphates must be considered during synthetic planning, and illuminate the difficulty in proposing a general mechanism for chemical glycosylations.
26 Glycosyl acceptor x is commercially available (Aldrich).
Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 400 mesh, Silicycle). ¹ Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and by exposure an aqueous solution of ceric ammonium molybdate (CAM), followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr at 25–35 °C, then at ~1 Torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, and tetrahydrofuran were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.² Trimethylsilyl trifluoromethanesulfonate (TMSOTf) purchased from Acros Chemicals. All solid-phase resin was purchased from Novabiochem and was prewashed six times with each of the following: tetrahydrofuran, tetrahydrofuran:methanol (95:5), and dichloromethane. Pyridine was distilled over calcium hydride immediately before use. N-Bromosuccinimide (NBS) was recrystallized from boiling water prior to use.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded with a Bruker-400 NMR spectrometer (400 MHz) or a Varian VXR-500 spectrometer (500 MHz). Chemical shifts are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent (CHCl₃: δ 7.27). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded with a Varian 500 INOVA spectrometer or a Bruker 400 spectrometer with a Magnex Scientific superconducting magnet and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent (CDCl₃: δ 77.2). Phosphorus-31 nuclear magnetic resonance spectra (³¹P NMR) spectra were obtained on a Varian VXR-300 (120 MHz) or a Varian VXR-500 (200 MHz) and are reported in δ relative to H₃PO₄ (0.0 ppm) as an external reference. Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 24 °C using a sodium lamp (589 λ). We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry’s Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electrospray ion source (ESI) or electrospray (ES).

Solution phase phosphate synthesis. General Procedure A. The protected glycal (1.0 equiv) was azeotropically dried with toluene (3 x 10 mL), dried under reduced pressure (~1 Torr) for 2 h. To a solution of the glycal in methylene chloride (1.5 mL/0.1 mmol glycal) at 0 °C was added a solution of dimethyldioxirane in acetone (0.08 M, 1.5 equiv) After 15 min, the volatiles were removed under reduced pressure (~1 Torr), the residue was dissolved in methylene chloride (2 mL/0.1 mmol glycal), and the solution cooled to -78 °C. Dibutylphosphate (1.1 equiv) was added drop wise to this solution, and the reaction stirred at -78 °C for 30 min. The solution was warmed to 0 °C and dimethylaminopyridine (4.0 equiv) was added, followed by pivaloyl chloride (2.0 equiv) and the reaction was warmed to room temperature. After 1 h, the mixture was concentrated under reduced pressure and the resulting white solid purified by flash column chromatography to provide the desired phosphate.

Solid phase phosphate coupling and disaccharide cleavage from the resin. General Procedure B. The acceptor (2.5-6.5 equiv) was azeotropically dried with toluene (3 x 5 mL) and dried under reduced pressure (~1 Torr) for 2 h. A solution of this acceptor in methylene chloride was transferred via cannula to the resin bound glycosyl phosphate (1.0 equiv) swelled in methylene chloride (10 mL/1.0 g resin). The reaction was cooled to -10 °C, trimethylsilyl trifluoromethane sulfonate was added, and the reaction shaken at -10 °C for 2 h. The solution phase was decanted, the resin was washed three times with methylene chloride (5 mL/g resin), and the reaction sequence repeated. Excess activator was quenched at -10 °C with methanol (10 mL/1.0 g resin), the resin as washed six times with each of tetrahydrofuran, tetrahydrofuran:methanol (95:5), and methylene chloride, then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentoxide. The resin (1.0 equiv) was swelled in CH$_2$Cl$_2$:methanol (10:1, 1.0 mL/g resin) and a solution of sodium methoxide in methanol (25% by weight, 2.0 equiv) was added and the reaction was shaken for 30 min at ambient temperature. The resin was washed with methylene chloride and the solution decanted six times. The solution phase was washed with dilute aqueous hydrochloric acid, water and brine, and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification was accomplished by flash column chromatography on silica gel to provide the desired disaccharides.

Solution phase phosphate coupling. General Procedure C. Glycosyl phosphate (1.1 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 x 5 mL) and dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in methylene chloride (1 mL/0.1 mmol phosphate) at -78 °C was added trimethylsilyl trifluoromethane sulfonate (TMSOTf, 1.3 equiv), and the reaction was warmed to -30 °C. After 1 h, a second portion of TMSOTf (1.3 equiv) was added, and the reaction stirred for an additional 1 h. Excess activator was quenched at -30 °C with triethylamine (1 mL/0.1 mmol

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phosphate), the volatiles were removed under reduced pressure, and the resulting oil purified by flash column chromatography on silica gel to give the desired disaccharide.

**Solution phase phosphate coupling. General Procedure D.** Glycosyl phosphate (1.1 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 x 5 mL), and dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in dichloromethane (1 mL/0.1 mmol phosphate) at -78 °C was added trimethylsilyl trifluoromethane sulfonate (1.5 equiv), and the reaction mixture was warmed to -40 °C. After 45 min, the reaction mixture was warmed to -10 °C. After an additional 45 min, excess activator was quenched with triethylamine (1 mL/1 mL phosphate), the volatiles were removed under reduced pressure, and the resulting oil was purified by flash column chromatography on silica gel to give the desired disaccharide.

**Solution phase thioglycoside coupling. General Procedure E.** Thioglycoside (1.1-1.2 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 x 5 mL), and dried under reduced pressure for 2 h. To a solution of this mixture in methylene chloride (3 mL/0.1 mmol donor), was added freshly activated 4 Å molecular sieves (1:1 sieves:donor, acceptor by weight). The reaction mixture was cooled to 0 °C, N-iodosuccinimide (NIS) (1.6 equiv) was added, light was excluded, and trimethylsilyl trifluoromethane sulfonate (0.5 equiv) was added dropwise. After 10 minutes, the reaction mixture was warmed to ambient temperature until the reaction appeared complete by analytical thin layer chromatography (0.5-12 h). The red reaction mixture was diluted with ethyl acetate, was filtered through celite, and was washed sequentially with aqueous sodium thiosulfate solution and brine. The clear organic layer was then dried over anhydrous magnesium sulfate, was filtered, was concentrated under reduced pressure, and was purified via flash column chromatography on silica gel to provide the disaccharide.

**Solution phase trichloroacetimidate coupling. General Procedure F.** Trichloroacetimidate (1.1-1.2 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 x 5 mL), and dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in methylene chloride (3 mL/0.1 mmol donor) at 0 °C was added trimethylsilyl trifluoromethane sulfonate (TMSOTf, 0.1 equiv). After 1 h, excess activator was quenched by addition of triethylamine (1:1 NEt₃:TMSOTf by volume). The volatiles were removed under reduced pressure and the residue was purified via flash column chromatography on silica gel to provide the disaccharide.

**Thioglycoside formation from protected glycalcs. General Procedure G.** The glucal (1.0 equiv) was azeotropically dried toluene (3 x 5 mL), dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in dichloromethane (0.5 mL/0.1 mmol glycal) at 0 °C was added a solution of dimethyldioxirane in acetone (0.08 M, 1.2-1.5 equiv) was added dropwise to this solution, followed by a few drops of TFAA. The

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reaction was stirred at −78 °C for 30 minutes and then allowed to warm to ambient temperature until the reaction appeared complete by analytical thin layer chromatography (0.5-12 h). The volatiles were removed by evaporation under a nitrogen stream, and the resulting oil purified by flash column chromatography on silica gel. To a solution of this thioglycoside in dichloromethane (0.5 mL/0.1 mmol glycal) and dimethylaminopyridine (4 equiv) and pivaloyl chloride (2 equiv) were added. When the reaction appeared complete by analytical thin layer chromatographyn (3-12 h), the reaction solution was diluted with ethyl acetate:hexanes (1:1), was filtered through a silica plug, was concentrated under reduced pressure, and was purified via flash column chromatography on silica gel to give the desired thioglycoside.

Glycosyl trichloroacetimidate synthesis from protected thioglycosides. General Procedure H. To a solution of the thioglycoside (1.0 equiv) in acetone:water (4:1, 2.5 mL/0.2 mmol thiodonor) was added N-bromosuccinimide (NBS) (4.0 equiv). After 1-3 h, the solution was concentrated under reduced pressure and the resulting residue purified by flash column chromatography on silica gel. The resulting oil was azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 1 h. To a solution of this lactol in dichloromethane:trichloroacetonitrile (1:1, 1.0 ml/0.04 mmol thioglycoside) at 0 °C was added DBU (0.1 equiv) and the reaction warmed to ambient temperature. After 12 h, the solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel to give the desired glycosyl trichloroacetimidate.

3,4-Di-O-benzyl-D-glucal (10):

To a solution of 6-O-Triisopropylsilyl-D-glucal\(^8\) (8.07 g, 26.8 mmol) in dimethylformamide (DMF, 80 mL) was added benzylbromide (7.00 mL, 58.9 mmol), followed by slow addition of sodium hydride (60% suspension in oil, 2.36 g, 58.9 mmol). After 12 h, excess hydride was quenched by slow addition of methanol (10 mL). The resulting solution was diluted with water and extracted with ethyl acetate (3 x 100 mL). The organic layers were washed with saturated aqueous sodium bicarbonate solution and water, were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. The crude oil was then dissolved in THF (80 mL) and acetic acid (1.53 mL, 26.8 mmol) and a solution of tetrabutylammonium fluoride in THF (1M, 40 mL, 40 mmol) were added. After 4 h, the reaction mixture was diluted with ethyl acetate (300 mL) and washed sequentially with water (100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash silica column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) to afford glycal 10 as a clear oil (5.73 g, 66%). Characterization data were consistent with previously reported data.\(^3\)

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3,4-Di-O-benzyl-6-O-succinoyl-D-glucal (11):

To a solution of glycal 10 (1.91 g, 5.84 mmol) in pyridine:methylene chloride (1:1, 40 mL) was added dimethylaminopyridine (1.21 g, 9.92 mmol) and succinic anhydride (0.88 g, 8.76 mmol). After 18 h, the reaction mixture was diluted with diethyl ether (500 ml) and washed with dilute aqueous acetic acid (pH 3), water, and brine. The combined organic phases were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash silica column chromatography (silica gel: eluent: hexanes:ethyl acetate [40:60]) to afford glucal 11 as a yellow oil (2.48 g, 98%).

^1H NMR (500 MHz, CDCl₃, 20°C):

- 8.56 (br-s, 1H), 7.71 (m, 1H), 7.28-7.18 (m, 8H), 6.31 (app-d, J = 6.5 Hz, 1H), 5.07 (s, 1H), 4.85-4.82 (m, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.37-4.31 (m, 2H), 4.15-4.14 (m, 1H), 4.03-4.00 (m, 1H), 3.55 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 2.61-2.52 (m, 4H).

^13C NMR (125 MHz, CDCl₃, 20°C):

- 177.4, 171.8, 144.3, 138.0, 127.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 100.0, 75.4, 74.9, 73.8, 73.6, 70.5, 62.9, 28.8, 28.7

FTIR (thin film) cm⁻¹:

- 3432 (br-m), 1735 (s), 1718 (s), 1648 (w), 1166 (m), 1098 (m).

HRMS–ESI (m/z):


[α]D²⁴:

- -1.5 (c 1.00, CH₂Cl₂).
Resin-bound glycal 12:

To a solution of glucal 11 (1.55 g, 3.64 mmol) in dichloromethane (10 mL) at 0 °C was added dimethylaminopyridine (0.142 g, 1.17 mmol) and diisopropylcarbodiimide (DIPC, 0.506 mL, 4.01 mmol). After 10 min, this solution was transferred via cannula to aminomethyl polystyrene resin (1.43 g, 1.46 mmol) swelled in pyridine (10 mL), and the reaction was shaken at room temperature for 20 h. Unreacted resin was capped by the addition of acetic anhydride (1.5 mL) and the suspension shaken for an additional 2 h. The solution decanted, and the resin was rinsed six times with each of tetrahydrofuran, tetrahydrofuran:methanol (95:5), and methylene chloride, then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide. HR-MAS $^1$H NMR indicated successful resin loading, with a theoretical resin loading 0.711 mmol/g (calculated from resin weight gain).
3,4-Di-O-benzyl-6-O-N-benzyl-succinamyl-D-glucal (13):

To a solution of glucal 11 (0.603 g, 1.41 mmol) in methylene chloride (20 mL) at 0 °C was added dimethylaminopyridine (0.190 g, 1.55 mmol) and diisopropylcarbodiimide (0.243 mL, 1.55 mmol). After 10 min, benzylamine (0.309 mL, 2.83 mmol) was added and the reaction warmed to ambient temperature. After 19 h, the reaction mixture was diluted with ethyl acetate (200 mL) and run through a silica plug to remove excess urea. The resulting solution was concentrated under reduced pressure and purified by flash silica column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40]) to afford 13 as a white solid (0.55 g, 75%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

$^1$H NMR (500 MHz, CDCl$_3$, 20°C): 7.28-7.18 (m, 11H), 6.29 (d, $J$ = 6.0 Hz, 1H), 5.86 (br-s, 1H), 4.85-4.83 (m, 1H), 4.78 (d, $J$ = 11.0 Hz, 1H), 4.59 (dd, $J$ = 11.5, 5.5 Hz, 2H), 4.48 (d, $J$ = 4.0 Hz, 1H), 4.35-4.29 (m, 4H), 4.15-4.13 (m, 1H), 4.04-4.00 (m, 1H), 3.69 (dd, $J$ = 8.5, 6.0, Hz, 1H), 2.64 (t, $J$ = 6.5 Hz, 2H), 2.42 (t, $J$ = 6.5 Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C): 172.6, 171.0, 144.3, 138.1, 138.0, 137.8, 128.7, 128.4, 128.0, 127.9, 127.7, 127.5, 100.0, 75.3, 74.9, 73.8, 73.6, 70.5, 62.9, 43.7, 31.0, 29.5

FTIR (thin film) cm$^{-1}$:

FTIR (thin film) cm$^{-1}$: 3408 (br-s), 1735 (m), 1652 (s), 1237 (w), 1099 (m), 737 (m).

HRMS–ESI (m/z):

HRMS–ESI (m/z): calcd for C$_{31}$H$_{33}$NNaO$_6$ [M+Na]$^+$: 538.2200, found: 538.2200.

$[\alpha]^{24}_D$:

$[\alpha]^{24}_D$: $-3.13$ (c 0.99, CH$_2$Cl$_2$).
Resin-bound phosphate 14:

To resin-bound glucal 12 (0.728 mmol/g, 1.80 g, 1.30 mmol) swelled in methylene chloride (30 mL) at 0 °C was added a solution of dimethyldioxirane in acetone (0.08 M, 24.3 mL, 1.95 mmol) the mixture was shaken at 0 °C for 30 min. The solution was decanted and the process repeated once. The solution was decanted and the resin rinsed three times with methylene chloride (10 mL each), then swelled in methylene chloride (30 mL) and the mixture cooled to -78 °C. Dibutyl phosphate (0.281 mL, 1.43 mmol) was added dropwise to this mixture and the vessel was shaken at -78 °C. After 30 min, the mixture was warmed to 0 °C, dimethylaminopyridine (0.633 g, 5.19 mmol) and pivaloyl chloride (0.320 mL, 2.60 mmol) were added, and the reaction was warmed to ambient temperature. The solution was decanted, and the resin was rinsed six times with each of tetrahydrofuran, tetrahydrofuran:methanol (95:5), and methylene chloride, then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide to afford a tan resin with a theoretical loading of 0.585 mmol/g (calculated by resin weight gain). $^{31}$P and $^{1}$H HR-MAS NMR of the tan resin indicated phosphate formation.
Dibutyl 6-O-N-benzyl-succinamyl-3,4-di-O-benzyl-2-O-pivaloyl-α-D glucopyranoside phosphate (15):

General Procedure A using glucal 13 (0.232 g, 0.449 mmol), dimethyldioxirane (8.4 mL, 0.67 mmol), dibutylphosphate (97 μL, 0.49 mmol), pivaloyl chloride (0.193 mL, 0.898 mmol), and dimethylaminopyridine (0.219 g, 1.80 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [40:60]) afforded phosphate 15 as a colorless oil (0.311 g, 84%, 1:1 α:β).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C, equal mixture of diastereomers (α:β)): 7.37-7.25 (m, 30H), 6.30 (app-s, 1H), 5.56 (dd, $J = 6.1, 2.1$ Hz, 0.8H), 5.40 (t, $J = 2.7$ Hz, 0.8H), 5.13 (s, 0.4H), 5.04 (dd, $J = 9.2, 7.9$ Hz, 1H), 4.87 (d, $J = 11.0$ Hz, 1H), 4.78-4.59 (m, 6.1H), 4.52 (dd, $J = 11.0, 3.7$ Hz, 1.8H), 4.45-4.42 (m, 2H), 4.29 (dd, $J = 7.6, 2.8$ Hz, 2H), 4.26 (d, $J = 2.1$ Hz, 1H), 4.21 (dd, $J = 14.7, 4.9$ Hz, 1H), 4.09-3.93 (m, 8.4H), 3.75 (t, $J = 9.8$ Hz, 1H), 3.54 (t, $J = 9.2, 1.1$H), 3.46 (t, $J = 10.1, 1$H), 3.31-3.27 (m, 1.1H), 2.95-2.89 (m, 1.1H), 2.78 (t, $J = 6.7$ Hz, 0.6H), 2.66 (t, $J = 6.7$ Hz, 1.8H), 2.60-2.42 (m, 1.8H), 1.69-1.57 (m, 6.5H), 1.43-1.32 (m, 5.6H), 1.27-1.16 (m, 13.8H), 0.96-0.89 (m, 7.5H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C): 177.3, 172.7, 172.2, 171.6, 171.3, 139.4, 138.5, 137.8, 137.5, 128.9, 128.8, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.6, 127.6, 127.7, 127.7, 103.3, 96.5, 95.6, 82.7, 77.6, 77.6, 77.5, 75.3, 75.1, 73.8, 72.9, 72.8, 71.8, 71.5, 68.3, 68.2, 68.1, 63.3, 63.0, 43.8, 43.8, 39.2, 39.0, 32.3, 32.3, 32.2, 32.1, 31.3, 31.2, 30.2, 29.8, 27.3, 27.3, 18.8, 18.8, 13.8, 13.8.

$^{31}$P NMR (120 MHz, CDCl$_3$, 20°C): -2.91, -2.93.

FTIR (thin film) cm$^{-1}$: 2962 (m), 1739 (s), 1673 (m), 1275 (m), 1148 (s), 1029 (s).

HRMS–ESI (m/z): calcd for C$_{43}$H$_{60}$N$_2$NaO$_{12}$P [M+Na]$^+$: 848.3745, found: 848.3719.
Methyl 3,6-di-O-benzyl-3-O-tert-butyldimethylsilyl-β-D-glucopyranoside (20):

Glycal 19 (1.1056 g, 2.509 mmol) was azeotropically dried from toluene (3 × 10 mL) and dried at ~1 Torr for 5 h. The glucal was dissolved in CH₂Cl₂ (15 mL) and cooled to 0 °C. A solution of dimethyldioxirane (DMDO) in acetone (0.08 M, 34.5 mL, 2.750 mmol) was added via cannula and the reaction was stirred for 15 min. The solvent was removed in vacuo, and the residue dissolved in CH₂Cl₂:methanol (3:2, 25 mL) and stirred vigorously. After 2.5 h, the volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) to afford 20 as a clear oil (1.0937 g, 89%).

¹H NMR (500 MHz, CDCl₃, 20°C):
7.30-7.24 (m, 8H), 7.21-7.18 (m, 2H), 4.87 (d, J = 11.6 Hz, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.13 (d, J = 7.6 Hz, 1H), 3.71 (dd, J = 10.3, 1.5 Hz, 1H), 3.52-3.48 (m, 5H), 3.44-3.37 (m, 2H), 3.31 (app-t, J = 8.8 Hz, 1H), 2.18 (d, J = 2.4 Hz, 1H), 0.76 (s, 9H), −0.06 (s, 3H), −0.09 (s, 3H).

¹³C NMR (125 MHz, CDCl₃, 20°C):
139.0, 138.5, 128.5, 128.5, 127.8, 127.7, 127.6, 103.7, 84.8, 76.8, 75.1, 74.8, 73.6, 71.1, 69.7, 57.3, 26.1, 18.2, −3.6, −4.7.

FTIR (thin film) cm⁻¹:
2929 (w), 2856 (w), 1251 (w), 1114 (s), 1064 (s).

HRMS–ESI (m/z):

[α]²⁴D:
−0.73 (c 0.96, CH₂Cl₂).
Methyl 3,6-di-O-benzyl-3-O-tert-butyldimethylsilyl-2-O-pivaloyl-β-D-glucopyranoside (21):

To a solution of methyl glycoside 20 (1.0318 g, 2.111 mmol) in dichloromethane (25 mL) was added dimethylaminopyridine (0.5268 g, 4.318 mmol) and pivaloyl chloride (0.520 mL, 4.222 mmol) and the reaction stirred vigorously at ambient temperature. After 24 h, the volatiles were removed under reduced pressure and the residue purified by flash column chromatography (silica gel: hexanes:ethyl acetate [80:20]) to provide 21 as a clear oil (1.1788 g, 97%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

- 7.26-7.16 (m, 10H)
- 4.99 (dd, $J = 9.2$, 7.9 Hz, 1H)
- 4.63-4.56 (m, 3H)
- 4.46 (d, $J = 12.5$ Hz, 1H)
- 4.26 (d, $J = 7.9$ Hz, 1H)
- 3.70 (dd, $J = 10.7$, 1.8 Hz, 1H)
- 3.59 (dd, $J = 9.5$, 8.6 Hz, 1H)
- 3.53-3.50 (m, 1H)
- 3.45 (app-t, $J = 8.5$ Hz, 1H)
- 3.43-3.40 (m, 1H)
- 3.41 (s, 3H)
- 1.05 (s, 9H)
- 0.74 (s, 9H)
- -0.12 (s, 3H)
- -0.17 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):

- 177.1, 138.5, 138.3, 128.5, 128.3, 127.8, 127.7, 127.4, 127.1, 102.3, 102.3, 83.4, 76.9, 74.7, 73.7, 73.6, 71.2, 69.5, 56.9, 39.0, 27.2, 26.1, 18.2, -3.7, -4.7.

FTIR (thin film) cm$^{-1}$:

- 2930 (m)
- 1740 (s)
- 1455 (w)
- 1135 (s)
- 1105 (s).

HRMS–EI (m/z):

- calcd for C$_{32}$H$_{48}$NaO$_7$Si [M+Na]$^+$: 595.3061
- found: 595.3074.

$[\alpha]^{24}_D$:

- +5.07 (c 0.75, CH$_2$Cl$_2$).
Methyl 3,6-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside (18):

To a solution of glucopyranoside 21 (1.0987 g, 1.918 mmol) in THF (20 mL) was added acetic acid (0.110 mL, 1.918 mmol) and a solution of tetrabutylammonium fluoride in THF (1M, 2.88 mL, 2.877 mmol) and were added and the reaction stirred at ambient temperature (30 °C). After 14 h, an additional portion of TBAF (1M, 1.5 mL, 1.5 mmol) was added. After another 7 h, an additional portion of TBAF (1M, 1.5 mL, 1.5 mmol). After 14 h, the reaction mixture was diluted with ethyl acetate, washed with water, saturated aqueous sodium bicarbonate solution, and brine. The organic layer was dried anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) to afford 18 as a light yellow oil (0.8495 g, 97%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

7.36-7.28 (m, 10H), 5.02 (dd, $J$ = 9.5, 7.9 Hz, 1H), 4.73 (d, $J$ = 11.3 Hz, 1H), 4.68 (d, $J$ = 11.3 Hz, 1H), 4.63 (d, $J$ = 11.9 Hz, 1H), 4.58 (d, $J$ = 11.9 Hz, 1H), 4.32 (d, $J$ = 7.9 Hz, 1H), 3.79-3.72 (m, 3H), 3.56 (app-t, $J$ = 9.2 Hz, 1H), 3.52-3.50 (m, 1H), 3.48 (s, 3H), 2.67 (d, $J$ = 2.4 Hz, 1H), 1.22 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):

177.1, 138.4, 137.9, 128.7, 128.7, 128.0, 128.0, 127.8, 102.5, 82.8, 74.5, 74.3, 73.9, 72.8, 72.0, 70.5, 57.1, 27.3.

FTIR (thin film) cm$^{-1}$:

3485 (br-w, OH), 2969 (m), 1738 (s), 1135 (s), 1076 (s).

HRMS—EI (m/z):

calcd for C$_{26}$H$_{34}$NaO$_7$ [M+Na]$^+$: 481.2197, found: 481.2182.

$[\alpha]_{D}^{24}$:

$-29.8$ (c 1.85, CH$_2$Cl$_2$).
3,4-Di-\(O\)-benzyl-2-\(O\)-pivaloyl-\(D\)-glucopyranosyl-(1→6)-1,2:3,4-di-\(O\)-isopropylidene-\(\alpha\)-\(D\)-galactopyranoside 22.

General Procedure B using resin 14 (0.585 mmol/g, 0.149 g, 0.0872 mmol), acceptor 7 (0.153 g, 0.585 mmol; 0.140 g, 0.536 mmol), and TMSOTf (22 µL, 0.095 mmol, twice), and NaOMe (40 µL, 0.17 mmol), and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded disaccharide 22 (35 mg, 58%, 1:2.2 \(\alpha\):\(\beta\)).

\[^1\text{H} \text{NMR} \text{ (500 MHz, CDCl}_3, 20^\circ\text{C})\]:

\(\alpha\) isomer: 7.34-7.27 (m, 10H), 5.52 (d, \(J = 5.0\) Hz, 1H), 5.41 (m, 1H), 4.88 (d, \(J = 10.5\) Hz, 1H), 4.84 (s, 1H), 4.70 (d, \(J = 11.0\) Hz, 1H), 4.64-4.61 (m, 2H), 4.51 (d, \(J = 10.5\) Hz, 1H), 4.33-4.31 (m, 1H), 4.24 (app-d, \(J = 8.0\) Hz, 1H), 4.00 (app-d, \(J = 3.0\) Hz, 1H), 3.95 (app-s, 1H), 3.83-3.71 (m, 5H), 1.53 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.22 (s, 9H).

\[^1\text{H} \text{NMR} \text{ (500 MHz, CDCl}_3, 20^\circ\text{C})\]:

\(\beta\) isomer: 7.35-7.26 (m, 10H), 5.49 (d, \(J = 4.9\) Hz, 1H), 5.05 (app-t, \(J = 7.9\) Hz, 1H), 4.81-4.70 (m, 3H), 4.62-4.59 (m, 2H), 4.50 (d, \(J = 7.9\) Hz, 1H) 4.30-4.27 (m, 2H), 4.02-3.99 (m, 1H), 3.93-3.86 (m, 2H), 3.73 (t, \(J = 9.2\) Hz, 1H), 3.68-3.61 (m, 3H), 3.46-3.43 (m, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H).

\[^{13}\text{C} \text{NMR} \text{ (125 MHz, CDCl}_3, 20^\circ\text{C})\]:

\(\alpha\) isomer: 177.5, 138.1, 128.4, 128.2, 127.9, 127.8, 127.5, 109.4, 108.6, 98.2, 96.2, 78.2, 75.1, 73.7, 71.9, 71.4, 70.8, 70.6, 70.5, 68.0, 66.5, 65.9, 62.0, 38.9, 27.2, 26.1, 25.9, 24.9, 24.5

\[^{13}\text{C} \text{NMR} \text{ (125 MHz, CDCl}_3, 20^\circ\text{C})\]:

\(\beta\) isomer: 176.8, 138.0, 137.7, 128.5, 128.4, 128.0, 127.9, 127.6, 127.4, 109.3, 108.6, 101.2, 96.3, 83.0, 77.7, 75.3, 75.0, 74.9, 72.9, 70.9, 70.5, 70.5, 68.3, 66.6, 62.1, 38.8, 27.1, 26.1, 25.9, 24.9, 24.3, 14.2.

FTIR (thin film) cm\(^{-1}\): 

\(\alpha\) isomer: 3464 (w), 2979 (m), 1733 (m), 1138 (m), 1072 (s).
FTIR (thin film) cm$^{-1}$: (β isomer): 3464 (m), 2979 (m), 1741 (m), 1383 (m), 1072 (s).

HRMS–ESI (m/z): (α isomer): calcd for C$_{37}$H$_{50}$NaO$_{12}$ [M+Na]$^+$: 709.3194, found: 709.3198.

HRMS–ESI (m/z): (β isomer): calcd for C$_{37}$H$_{50}$NaO$_{12}$ [M+Na]$^+$: 709.3194, found: 709.3204.

[$\alpha$]$^D_2$: (α isomer): −11.9 (c 0.91, CH$_2$Cl$_2$).

[$\alpha$]$^D_2$: (β isomer): −47.5 (c 1.44, CH$_2$Cl$_2$).
**3,4-di-O-benzyl-6-O-N-benzylsuccinamyl-2-O-pivaloyl-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (23):**

General Procedure C using phosphate 15 (81 mg, 0.098 mmol), acceptor 16 (22 mg, 0.083 mmol) and TMSOTf (24 μL, 0.090 mmol) and purification by flash column chromatography (silica gel: eluent: methylene chloride:acetone [95:5]) afforded 23 as a white solid (62 mg, 85%, 1:4 α:β).

General Procedure E using thiodonor 45 (0.219 g, 0.323 mmol), acceptor 16 (70 mg, 0.27 mmol), NIS (97 mg, 0.43 mmol), and TMSOTf (25 μL, 0.14 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [65:35]) afforded 23 as a white solid (0.161 g, 69%, β).

General Procedure F using trichloroacetimidate 48 (61 mg, 0.079 mmol), acceptor 16 (18 mg, 0.071 mmol), and TMSOTf (2 μL, 0.01 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40]) afforded 23 as a white foam (45 mg, 73%, β).

**1H NMR (500 MHz, CDCl₃, 20°C):**

(α isomer): 7.34-7.25 (m, 10H), 6.14 (app-s, 1H), 5.43 (d, J = 5.0 Hz, 1H), 5.40 (app-d, J = 3.0 Hz, 1H), 4.85 (d, J = 10.5 Hz, 1H), 4.78 (s, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.62-4.59 (m, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.42 (d, J = 6.0 Hz, 1H), 4.34 (app-d, J = 9.5 Hz, 1H), 4.21 (app-d, J = 10.0 Hz, 1H), 3.9 (dd, J = 9.5, 3.0 Hz, 1H), 3.92-3.88 (m, 2H), 3.75-3.62 (m, 3H), 2.69 (t, J = 7.0 Hz, 2H), 2.53-2.46 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.29 (s, 3H), 1.23 (s, 9H).

(β isomer): 7.33-7.24 (m, 15H), 6.27 (br-s, 1H), 5.45 (d, J = 4.9 Hz, 1H), 5.07 (t, J = 9.1 Hz, 1H), 4.81 (d, J = 10.9 Hz, 1H), 4.76-4.72 (m, 2H), 4.57-4.55 (m, 2H), 4.46-4.36 (m, 4H), 4.27-4.18 (m, 3H), 3.97 (dd, J = 10.4, 4.8 Hz, 1H), 3.92 (app-s, 1H), 3.73 (t, J = 9.2 Hz, 1H), 3.62-3.59 (m, 3H), 2.70 (t, J = 6.0 Hz, 2H), 2.49
$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):

\[(\alpha \text{ isomer): 177.4, 172.5, 171.0, 138.2, 137.9, 137.8, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 109.4, 108.6, 97.7, 96.2, 78.4, 74.9, 73.3, 71.4, 70.7, 70.6, 70.5, 69.6, 67.8, 65.9, 63.5, 43.6, 38.9, 31.1, 29.6, 27.1, 26.1, 25.9, 24.8, 24.4.}\]

$^{13}$C NMR (100 MHz, CDCl$_3$, 20°C):

\[(\beta \text{ isomer): 176.9, 172.6, 171.2, 138.5, 138.0, 127.7, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 127.5, 127.5, 109.3, 108.6, 101.4, 96.2, 83.2, 77.4, 75.1, 73.1, 72.9, 71.2, 70.6, 70.5, 67.1, 43.7, 38.9, 31.0, 29.7, 27.2, 26.2, 26.1, 25.1, 24.4.}\]

FTIR (thin film) cm$^{-1}$:

\[(\alpha \text{ isomer): 2918 (w), 1732 (s), 1210 (m), 1138 (s), 1069 (s).}\]

FTIR (thin film) cm$^{-1}$:

\[(\beta \text{ isomer): 2978 (w), 2933 (w), 1739 (s), 1674 (m), 1166 (m), 1071 (s).}\]

HRMS–ESI (m/z):

\[(\alpha \text{ isomer): calcd for C}_{48}\text{H}_{61}\text{NNaO}_{14} [M+Na]^+: 898.3984,}\]

\[\text{found: 898.3968.}\]

HRMS–ESI (m/z):

\[(\beta \text{ isomer): calcd for C}_{48}\text{H}_{61}\text{NNaO}_{14} [M+Na]^+: 898.3984,}\]

\[\text{found: 898.3998.}\]

$[\alpha]^2_{\text{D}}$:

\[(\alpha \text{ isomer): -6.7 (c 0.18, CH}_2\text{Cl}_2).}\]

$[\alpha]^2_{\text{D}}$:

\[(\beta \text{ isomer): -31.2 (c 2.04, CH}_2\text{Cl}_2).}\]
Methyl 3,4-di-O-benzyl-2-O-pivaloyl-d-glucopyranosyl-(1→2)-3,4,6-tri-O-benzyl-d-glucopyranoside (24):

General Procedure B using resin 14 (0.353 mmol/g, 0.327 g, 0.115 mmol), acceptor 17 (0.138 g, 0.309 mmol; 0.130 g, 0.293 mmol), TMSOTf (29 µL, 0.127 mmol, twice), and NaOMe (53 µL, 0.23 mmol), and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded disaccharide 24 as a clear oil (27 mg, 26%, 1:2 α:β).

1H NMR (500 MHz, CDCl3, 20°C):

(α isomer): 7.39-7.10 (m, 25H), 5.42 (dd, J = 3.1, 1.8 Hz, 1H), 5.31 (d, J = 1.8 Hz, 1H), 4.88 (d, J = 11 Hz, 1H), 4.78 (dd, J = 11.0, 7.1 Hz, 2H), 4.73-4.68 (m, 2H), 4.62 (app-t, J = 12.2 Hz, 2H), 4.55 (app-t, J = 12.2 Hz, 3H), 4.26 (d, J = 7.9 Hz, 1H), 3.98 (dd, J = 9.2, 3.1 Hz, 1H), 3.90-3.81 (m, 2H), 3.75 (dd, J = 11.0, 2.1 Hz, 1H), 3.71 (dd, J = 11.0, 4.3 Hz, 1H), 3.67-3.60 (m, 2H), 3.58-3.51 (m, 6H), 3.49-3.45 (m, 1H), 1.23 (s, 9H).

1H NMR (500 MHz, CDCl3, 20°C):

(β isomer): 7.33-7.22 (m, 23H), 7.09-7.07 (m, 2H), 5.07-5.06 (m, 2H), 4.85-4.70 (m, 6H), 4.65-4.59 (m, 2H), 4.51 (at, J = 12.2 Hz, 2H), 4.28 (d, J = 7.6 Hz, 1H), 3.89-3.81 (m, 2H), 3.75-3.65 (m, 4H), 3.61-3.56 (m, 3H), 3.52 (s, 3H), 3.46-3.41 (m, 2H), 1.07 (s, 9H).

13C NMR (125 MHz, CDCl3, 20°C):

(α isomer): 177.8, 138.8, 138.4, 138.3, 138.1, 138.0, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 104.7, 97.5, 83.6, 78.6, 78.0, 77.4, 76.8, 76.2, 75.3, 75.2, 74.0, 73.7, 72.0, 71.4, 68.8, 68.2, 61.8, 57.3, 39.2, 29.9, 27.4.

13C NMR (125 MHz, CDCl3, 20°C):

(β isomer): 177.0, 138.5, 138.3, 138.2, 138.1, 138.0, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.6, 102.8, 99.5, 85.4, 83.4, 78.8, 78.2, 77.0, 75.7, 75.2, 75.2, 75.1, 74.9, 74.1, 73.7, 73.3, 68.7, 61.8, 57.3, 38.9, 27.4, 27.3.
FTIR (thin film) cm$^{-1}$: (α isomer): 3428 (br-m), 2924 (m), 1731 (m), 1142 (s), 1061 (s).

FTIR (thin film) cm$^{-1}$: (β isomer): 3483 (br-m), 2917 (m), 1738 (m), 1362 (w), 1074 (br-s).


$[\alpha]_24^D$: (α isomer): +23.1 (c 0.7, CH$_2$Cl$_2$).

$[\alpha]_24^D$: (β isomer): −8.05 (c 1.23, CH$_2$Cl$_2$).
Methyl 6-O-N-benzylsuccinamyl-3,4-di-O-benzyl-2-O-pivaloyl-D-glucopyranosyl-(1→2)-3,4,6-tri-O-benzyl-β-D-galactopyranoside (25):

General Procedure C using phosphate 15 (0.118 g, 0.143 mmol), acceptor 17 (56 mg, 0.12 mmol), and TMSOTf (36 μL, 0.16 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [60:40]) afforded 25 as a white solid (0.127 g, 98%, 1:1.1 α:β).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

(β isomer): 7.38-7.25 (m, 23H), 7.11-7.09 (m, 2H), 6.09 (br-t, $J = 5.5$ Hz, 1H), 5.13 (app-t, $J = 7.9$ Hz, 1H), 5.02 (d, $J = 7.9$ Hz, 1H), 4.91 (d, $J = 11.6$ Hz, 1H), 4.80-4.75 (m, 2H), 4.70 (d, $J = 11.0$ Hz, 1H), 4.61-4.50 (m, 4H), 4.43-4.40 (m, 3H), 4.34 (d, $J = 7.3$ Hz, 1H), 4.26 (dd, $J = 11.9$, 5.2 Hz, 1H), 3.73-3.59 (m, 2H), 2.74-2.70 (m, 2H), 2.49 (app-t, $J = 6.7$ Hz, 2H), 1.12 (s, 9H).

$^1$C NMR (125 MHz, CDCl$_3$, 20°C):

(α isomer): 177.7, 172.6, 171.3, 138.5, 138.4, 138.2, 138.1, 138.0, 137.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.6, 104.6, 97.1, 83.5, 78.6, 78.2, 77.5, 76.4, 76.1, 75.2, 75.1, 73.7, 73.5, 71.3, 69.7, 68.8, 68.0, 63.4, 57.3, 43.8, 39.2, 31.4, 29.9, 27.4, 27.3.

$^1$C NMR (125 MHz, CDCl$_3$, 20°C):

(β isomer): 176.0, 172.8, 171.3, 138.8, 138.5, 138.2, 138.1, 137.7, 128.9, 128.6, 128.6, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.5, 127.3, 103.1, 103.0, 99.5, 99.3, 85.1, 83.7, 79.7, 77.9, 77.7, 75.8, 75.6, 75.5, 75.2, 75.1, 75.0, 74.8, 73.6, 73.4, 73.0, 68.8, 63.5, 63.4, 60.6, 57.0, 43.7, 39.0, 31.2.

FTIR (thin film) cm$^{-1}$:

(α isomer): 1733 (s), 1677 (w), 1141 (s), 1100 (s), 1059 (s).

FTIR (thin film) cm$^{-1}$:

(β isomer): 2870 (w), 1738 (s), 1659 (w), 1144 (s), 1071 (br-s).

[α]²⁴_d: (α-isomer): +16.6 (c 1.07, CH₂Cl₂).
[α]²⁴_d: (β-isomer): −8.5 (c 0.61, CH₂Cl₂).
Methyl 3,4-di-O-benzyl-2-O-pivaloyl-D-glucopyranosyl-(1→4)-3,6-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside (26):

Acceptor 18 (91 mg, 0.20 mmol) was azeotropically dried with toluene (3 × 5 mL) and dried under reduced pressure for 2 h. A solution of this acceptor in dichloromethane (2 mL) was transferred via cannula to resin 14 (0.353 mmol/g, 0.272 g, 0.096 mmol) swelled in dichloromethane (2 mL). The reaction was cooled to −78 °C, trimethylsilyl trifluoromethane sulfonate (TMSOTf, 24 μL, 0.11 mmol) was added, and the reaction mixture was shaken and warmed slowly to −10 °C over 1 h. The reaction mixture was cooled to −30 °C and an additional portion of TMSOTf (24 μL, 0.11 mmol) was added, followed by warming of the reaction mixture to −15 °C over 45 min. An additional portion of TMSOTf (24 μL, 0.11 mmol) was added and the reaction shaken for 45 min at −15 °C. Excess activator was quenched at −15 °C with methanol (4 mL), the resin was washed six times with each of THF (5 mL ea.), THF:methanol (1:95 mL ea.), and CH₂Cl₂ (5 mL ea.), then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide. The resin was swelled in CH₂Cl₂:MeOH (10:1, 4.2 mL), and a solution of sodium methoxide in methanol (43 μL, 0.19 mmol) was added and the reaction shaken for 30 min. The resin was washed with CH₂Cl₂ (5 × 6 mL), and the solution decanted. The solution phase was washed with dilute aqueous hydrochloric acid, water and brine, and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel; eluent: hexanes:ethyl acetate [80:20]) to afford disaccharide 26 as a clear oil (23 mg, 27%, 1:1.7 α:β).

1H NMR (500 MHz, CDCl₃, 20°C):

(α isomer): 7.33-7.22 (m, 20H), 5.45 (dd, J = 3.1, 1.8 Hz, 1H), 5.35 (d, J = 1.5 Hz, 1H), 5.10 (app-t, J = 7.9 Hz, 1H), 4.85 (d, J = 10.7 Hz, 1H), 4.73-4.66 (m, 3H), 4.60 (s, 2H), 4.58 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.31 (d, J = 7.9 Hz, 1H), 4.00 (app-t, J = 8.9 Hz, 1H), 3.87 (dd, J = 8.9, 3.1 Hz, 1H), 3.80 (app-t, J = 8.9 Hz, 1H), 3.74-3.66 (m, 5H), 3.62-3.58 (m, 2H), 3.51-3.49 (m, 4H), 1.19 (s, 9H), 1.09 (s, 9H).

(β isomer): 7.40-7.21 (m, 10H), 5.02-4.95 (m, 2H), 4.93 (d, J = 11.3 Hz, 1H), 4.80 (d, J = 4.9 Hz, 1H), 4.77 (d, J = 4.3 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.61 (dd, J = 11.0, 6.1 Hz, 2H),
$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):

- (a isomer): 177.3, 177.1, 138.3, 138.3, 138.1, 137.6, 128.6, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.8, 127.6, 102.3, 98.6, 83.4, 78.5, 75.5, 75.0, 74.1, 73.9, 73.6, 73.2, 73.1, 71.6, 68.6, 68.2, 62.1, 57.0, 57.0, 39.0, 39.0, 27.2.
- (p isomer): 177.1, 177.0, 138.8, 138.2, 138.1, 138.0, 128.8, 128.6, 128.6, 128.5, 128.2, 128.0, 127.8, 127.7, 127.4, 126.8, 102.5, 99.6, 83.0, 80.9, 78.1, 77.6, 77.5, 75.5, 75.4, 75.2, 75.0, 74.9, 73.9, 73.5, 72.4, 67.8, 61.6, 57.1, 57.0, 39.0, 39.0, 27.5, 27.3.

FTIR (thin film) cm$^{-1}$:

- (a isomer): 1735 (s), 1640 (m), 1278 (w), 1138 (s), 1075 (s).
- (p isomer): 1739 (s), 1653 (m), 1277 (m), 1140 (s), 1075 (s).

HRMS–ESI (m/z):

- (a isomer): calcd for C$_{51}$H$_{64}$NaO$_{13}$ [M+Na]$^+$: 907.4239, found: 907.4214.
- (p isomer): calcd for C$_{51}$H$_{64}$NaO$_{13}$ [M+Na]$^+$: 907.4239, found: 907.4244.

$[\alpha]_D^{24}$:

- (a isomer): $-2.4$ (c 0.5, CH$_2$Cl$_2$).
- (p isomer): $-26.9$ (c 0.98, CH$_2$Cl$_2$).
Methyl 6-O-N-benzylsuccinamyl-3,4-di-O-benzyl-2-O-pivaloyl-D-glucopyranosyl-(1→4)-3,6-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside (27):

General Procedure C using phosphate 15 (0.138 g, 0.167 mmol), acceptor 18 (69 mg, 0.15 mmol), TMSOTf (42 µL, 0.18 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [60:40]) afforded 27 as a white solid (0.130 g, 80%, 1.1:1 α:β).

1H NMR (500 MHz, CDCl3, 20°C, equal mixture of diastereomers, α:β): 7.36-7.14 (m, 39H), 6.49 (app-s, 1H), 5.97 (br-s, 1H), 5.34 (app-s, 1H), 5.28 (app-s, 1H), 5.08 (s, 1H), 5.02 (t, J = 8.9 Hz, 1H), 4.96-4.90 (m, 2H), 4.83-4.24 (m, 24H), 4.14-4.11 (m, 3H), 4.00 (t, J = 9.2 Hz, 1H), 3.95-3.93 (m, 1H), 3.87-3.83 (m, 2H), 3.75-3.60 (m, 6H), 3.52-3.37 (m, 10H), 3.29-3.27 (m, 1H), 2.72 (t, J = 6.7 Hz, 1H), 2.66 (s, 1H), 2.54-2.28 (m, 9H), 1.14-1.11 (m, 18H), 1.05 (s, 9H), 0.99 (s, 9H).

13C NMR (125 MHz, CDCl3, 20°C, equal mixture of diastereomers, α:β): 177.5, 177.2, 177.1, 176.8, 172.6, 172.5, 171.4, 171.2, 139.1, 138.9, 138.4, 138.1, 138.0, 137.9, 137.7, 137.5, 128.9, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.3, 127.3, 102.3, 99.6, 99.4, 98.2, 83.2, 80.7, 78.7, 78.6, 75.4, 75.2, 75.0, 74.9, 74.6, 74.0, 73.7, 73.6, 73.4, 73.2, 73.0, 72.5, 71.5, 70.6, 69.3, 68.0, 67.8, 66.8, 63.5, 63.2, 57.0, 43.9, 43.7, 43.7, 39.0, 39.0, 38.9, 38.9, 31.3, 31.2, 31.1, 29.9, 29.8, 27.5, 27.3, 27.2, 27.1.

FTIR (thin film) cm⁻¹: 2970 (m), 1737 (s), 1673 (m), 1143 (br-s), 1091 (s).

6-O-3'-benzoylpropionyl-3,4-di-O-benzyl-D-glucal (30):

To a solution of 3-benzoylpropionic acid (74 mg, 0.42 mmol) in dichloromethane (2 mL) at 0 °C was added dicyclohexylcarbodiimie (92 mg, 0.45 mmol) and dimethylaminopyridine (54 mg, 0.44 mmol). After 10 min, a solution of glucal 10 (91 mg, 0.28 mmol) in dichloromethane (2 mL) was transferred via cannula to this solution and the reaction warmed to ambient temperature. After 1.5 h, the solution was diluted with hexanes:ethyl acetate (1:1, 40 mL), filtered through silica gel, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent hexanes:ethyl acetate [75:25]) to afford 30 as a white solid (0.125 g, 92%).

$^1$H NMR (400 MHz, CDCl$_3$, 20°C):

7.99-7.97 (m, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.8$ Hz, 2H), 7.36-7.28 (m, 10H), 6.40 (d, $J = 6.2$ Hz, 1H), 4.92 (dd, $J = 6.2$, 2.7 Hz, 1H), 4.86 (d, $J = 11.3$ Hz, 1H), 4.71-4.65 (m, 2H), 4.57 (d, $J = 11.6$ Hz, 1H), 4.49-4.40 (m, 2H), 4.23-4.22 (m, 1H), 4.15-4.11 (m, 1H), 3.81 (dd, $J = 8.4$, 6.0 Hz, 1H), 3.37-3.27 (m, 2H), 2.80 (t, $J = 6.6$ Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$, 20°C):

198.1, 172.9, 144.6, 138.3, 138.1, 136.7, 133.4, 128.8, 128.7, 128.3, 128.1, 128.0, 127.9, 100.2, 77.4, 75.5, 75.2, 74.1, 73.9, 70.7, 63.1, 33.5, 29.9, 28.3.

FTIR (thin film) cm$^{-1}$: 2918 (w), 1736 (s), 1686 (s), 1215 (m), 1098 (s).


$[\alpha]^{24}_D$: $-2.4$ (c 1.05, CH$_2$Cl$_2$).
**3,4-Di-O-benzyl-6-O-4'-oxo-5'-phenyl-valeryl-D-glucal (31):**

To a solution of 4-Oxo-5-phenylvaleric acid\(^9\) (0.151 g, 0.785 mmol) in dichloromethane (2 mL) at 0 °C was added dicyclohexylcarbodiimide (0.175 g, 0.848 mmol) and dimethylaminopyridine (0.111 g, 0.911 mmol). After 10 min, a solution of glucal 10 (0.123 g, 0.376 mmol) in dichloromethane (2 mL) was transferred via cannula to the reaction mixture, and mixture was allowed to warm to ambient temperature. After 14 h, the solution was diluted with hexanes:ethyl acetate (1:1, 150 mL), was filtered through silica gel, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15]) to afford 31 as a white solid (0.134 g, 71%).

**\(^1\)H NMR (500 MHz, CDCl\(_3\), 20°C):**

7.35-7.20 (m, 15H), 6.39 (dd, \(J = 6.1, 0.9\) Hz, 1H), 4.92 (dd, \(J = 6.1, 2.8\) Hz, 1H), 4.85 (d, \(J = 11.3\) Hz, 1H), 4.67 (d, \(J = 11.8\) Hz, 2H), 4.57 (d, \(J = 11.6\) Hz, 1H), 4.39-4.38 (m, 2H), 4.23-4.21 (m, 1H), 4.10-4.07 (m, 1H), 3.78-3.74 (m, 3H), 2.79-2.73 (m, 2H), 2.58 (t, \(J = 6.7\) Hz, 2H).

**\(^1^3\)C NMR (125 MHz, CDCl\(_3\), 20°C):**

206.4, 172.6, 144.6, 138.3, 138.0, 134.2, 129.7, 129.0, 128.7, 128.7, 128.3, 128.1, 128.0, 127.3, 100.2, 75.6, 75.2, 74.0, 73.8, 70.7, 63.0, 50.2, 36.6, 29.9, 28.1.

**FTIR (thin film) cm\(^{-1}\):**

2922 (m), 1734 (s), 1717 (s), 1099 (br-m), 740 (w).

**HRMS–ESI (m/z):**

Calcd for C\(_{31}\)H\(_{32}\)NaO\(_6\) [M+Na]\(^+\): 523.2091, found: 523.2086.

**\([\alpha]^{24}\)_D:**

+2.22 (c 0.63, CH\(_2\)Cl\(_2\)).

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**Dibutyl 6-O-3'-benzoylpropionyl-3,4-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside phosphate (32):**

General Procedure A using glucal 30 (0.350 g, 0.719 mmol), dimethyldioxirane (13.5 mL, 1.08 mmol), dibutylphosphate (0.156 mL, 0.791 mmol), pivaloyl chloride (0.177 mL, 1.44 mmol), DMAP (0.351 g, 2.88 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 32 as a clear oil (0.340 g, 60%).

**1H NMR (500 MHz, CDCl₃, 20°C):**

- 7.97 (d, J = 8.0 Hz, 2H)
- 7.56 (t, J = 7.5 Hz, 1H)
- 7.47 (t, J = 7.5 Hz, 2H)
- 7.34-7.24 (m, 10H)
- 5.24 (app-t, J = 7.6 Hz, 1H)
- 5.14 (app-t, J = 8.8 Hz, 1H)
- 4.80 (d, J = 11.0 Hz, 2H)
- 4.72 (d, J = 11.0 Hz, 1H)
- 4.60 (d, J = 10.7 Hz, 1H)
- 4.44 (d, J = 12.5 Hz, 1H)
- 4.28 (dd, J = 11.9, 3.7 Hz, 1H)
- 4.07-3.99 (m, 5H)
- 3.75-3.69 (m, 2H)
- 3.33-3.30 (m, 2H)
- 2.78-2.76 (m, 2H)
- 1.68-1.61 (m, 4H)
- 1.41-1.36 (m, 4H)
- 1.21 (s, 9H)
- 0.96-0.89 (m, 6H).

**13C NMR (100 MHz, CDCl₃, 20°C):**

- 197.9, 177.0, 172.7, 137.9, 137.9, 137.6, 137.6, 133.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.5, 96.7, 96.6, 82.9, 76.9, 75.3, 75.3, 73.9, 73.0, 72.9, 68.3, 68.2, 68.1, 68.0, 62.7, 39.1, 33.4, 32.3, 32.3, 28.2, 27.3, 18.8, 18.8, 13.8, 13.8.

**31P (120 MHz, CDCl₃, 20°C):**

- 1.66.

**FTIR (thin film) cm⁻¹:**

- 2961 (m), 1738 (s), 1688 (m), 1151 (s), 1029 (s).

**HRMS–ESI (m/z):**


**[α]₂⁴_D:**

+24.2 (c 1.49, CH₂Cl₂).
Dibutyl 3,4-di-O-benzyl-6-O-4'-oxo-5'-phenyl-valeryl-2-O-pivaloyl-D-glucopyranoside phosphate (33):

General Procedure A using glycal 31 (63 mg, 0.13 mmol), dimethyldioxirane (1.90 mL, 0.151 mmol), dibutylphosphate (0.027 mL, 0.139 mmol), pivaloyl chloride (0.031 mL, 0.252 mmol), DMAP (77 mg, 0.63 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded 33 as a clear oil (56 mg, 54%).

$^1$H NMR (400 MHz, CDCl$_3$, 20°C, mixture of diastereomers, $\alpha:\beta$): 7.53-7.20 (m, 21H), 5.61-5.59 (m, 0.4H), 5.43-5.41 (m, 0.4H), 5.24-5.21 (m, 1H), 5.14 (app-t, $J = 8.0$ Hz, 1H), 4.81-4.70 (m, 4.2H), 4.60-4.51 (m, 2.8H), 4.38-4.32 (m, 1.4H), 4.25-4.12 (m, 2.8H), 4.07-3.96 (m, 5.6H), 3.74 (as, 2.8H), 3.72-3.66 (m, 1.4H), 2.82-2.66 (m, 2.8H), 2.59-2.48 (m, 2.8H), 1.78-1.56 (m, 5.6H), 1.46-1.32 (m, 5.6H), 1.27-1.21 (m, 12.6H), 0.97-0.88 (m, 8.4H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C, mixture of diastereomers, $\alpha:\beta$): 206.2, 206.2, 177.2, 177.0, 172.6, 172.4, 137.9, 137.8, 137.5, 134.1, 134.1, 129.6, 129.6, 129.6, 128.9, 128.7, 128.6, 128.6, 128.5, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.7, 127.6, 127.5, 127.3, 127.3, 96.6, 96.6, 95.6, 95.6, 82.4, 77.6, 77.4, 76.9, 75.3, 75.2, 73.8, 72.9, 72.9, 72.7, 71.7, 71.4, 68.2, 68.2, 68.1, 68.1, 68.0, 68.0, 67.5, 67.4, 63.0, 62.7, 50.1, 50.1, 39.1, 39.0, 36.5, 36.5, 32.4, 32.4, 32.3, 32.3, 32.2, 32.2, 32.2, 29.9, 28.0, 27.8, 27.3, 27.3, 27.2, 27.2, 18.8, 18.8, 18.7, 13.7, 13.7.

$^{31}$P NMR (120 MHz, CDCl$_3$, 20°C, mixture of diastereomers, $\alpha:\beta$): -2.52, -2.58.

FTIR (thin film) cm$^{-1}$: 2961 (m), 1739 (s), 1277 (m), 1144 (s), 1028 (s).

HRMS–EI (m/z): calcd for C$_{44}$H$_{59}$NaO$_{12}$P [M+Na]$^+$: 833.3636, found: 833.3615.
6-O-3′-benzoylpropionyl-3,4-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-β-D-galactopyranoside (34):

Glycosyl phosphate 32 (0.129 g, 0.161 mmol) and acceptor 16 (38 mg, 0.15 mmol) were combined, azeotropically dried with toluene (3 × 5 mL) and dried under reduced pressure for 2 h. To a solution of this mixture in dichloromethane (3 mL) at -78 °C was added trimethylsilyl trifluoromethane sulfonate (40 μL, 0.18 mmol). After 45 min, excess activator was quenched at -78 °C with triethylamine (1 mL), the volatiles were removed under reduced pressure, and the resulting oil purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [60:40]) to afford disaccharide 34 as a white solid (84 mg, 68%).

General Procedure E using thiodonor 38 (0.123 g, 0.189 mmol), acceptor 16 (42 mg, 0.16 mmol), NIS (60 mg, 0.27 mmol), TMSOTf (15 μL, 0.088 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [67:33]) afforded 22 as a white foam (0.113 g, 82%, β).

General Procedure F using trichloroacetimidate 46 (37 mg, 0.049 mmol), acceptor 16 (11 mg, 0.043 mmol), TMSOTf (1 μL, 0.005 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] afforded 34 as a white foam (26 mg, 70%, β).

^1H NMR (500 MHz, CDCl3, 20°C):

7.96 (d, J = 7.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.33-7.25 (m, 10H), 7.48 (d, J = 4.9 Hz, 1H), 5.07 (dd, J = 9.2, 7.9 Hz, 1H), 4.80 (d, J = 10.7 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.60-4.57 (m, 2H), 4.47 (d, J = 7.9 Hz, 1H), 4.41 (dd, J = 11.9, 2.1 Hz, 1H), 4.32-4.27 (m, 2H), 4.23 (dd, J = 7.9, 1.8 Hz, 1H), 4.03 (dd, J = 10.7, 4.9 Hz, 1H), 3.93 (dt, J = 6.4, 1.5 Hz, 1H), 3.73 (t, J = 8.9 Hz, 1H), 3.67 (t, J = 9.4 Hz, 1H), 3.61-3.57 (m, 2H), 3.32 (td, J = 6.7, 1.5 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 1.57 (s, 3H), 1.51 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.23 (s, 9H).
$^{13}$C NMR (100 MHz, CDCl$_3$, 20°C):

198.0, 176.9, 172.8, 138.2, 137.9, 136.6, 133.4, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.6, 109.4, 108.7, 101.7, 96.3, 83.4, 77.5, 75.2, 75.1, 73.3, 73.0, 71.3, 70.7, 70.7, 69.1, 67.3, 63.2, 39.0, 33.5, 28.3, 27.3, 26.3, 26.1, 25.2, 24.5.

FTIR (thin film) cm$^{-1}$:

2977 (w), 1739 (s), 1688 (m), 1382 (m), 1070 (s).

HRMS–ESI (m/z):

calcd for C$_{47}$H$_{58}$NaO$_{14}$ [M+Na]$^+$: 869.3719, found: 869.3754.

$[\alpha]^{24}_D$:

$-29.8$ (c 1.08, CH$_2$Cl$_2$).
3,4-di-O-benzyl-6-O-4'-oxo-5'-phenyl-valeryl-2-O-pivaloyl-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-D-galactopyranoside (35):

General Procedure D using phosphate 33 (80 mg, 0.099 mmol), acceptor 16 (22 mg, 0.085 mmol), TMSOTf (25 μL, 0.14 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 35 as a white solid (64 mg, 88%, 1:1.6 α:β).

General Procedure E using thiodonor 39 (73 mg, 0.11 mmol), acceptor 16 (25 mg, 0.095 mmol), NIS (40 mg, 0.18 mmol), TMSOTf (9 μL, 0.05 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded 35 as a white foam (64 mg, 79%, β).

General Procedure F using trichloroacetimidate 47 (45 mg, 0.058 mmol), acceptor 16 (13 mg, 0.048 mmol), TMSOTf (1 μL, 0.006 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15]) afforded 35 as a clear oil (15 mg, 37%, β).

^1H NMR (400 MHz, CDCl₃, 20°C, mixture of diastereomers, 1:1.6 α:β): 7.37-7.20 (m, 21H), 5.51 (d, J = 5.0 Hz, 0.4H), 5.48 (d, J = 4.9 Hz, 1H), 5.40 (br-s, 0.4H), 5.08 (t, J = 8.2 Hz, 1H), 4.86-4.69 (m, 4.2H), 4.62 (dd, J = 8.0, 2.4 Hz, 0.4H), 4.58-4.49 (m, 4.2H), 4.46 (d, J = 7.9 Hz, 1H), 4.36-4.21 (m, 5.6H), 4.03-4.00 (m, 1.4H), 3.94-3.87 (m, 1.4H), 3.76-3.52 (m, 7H), 2.82-2.67 (m, 2.8H), 2.59-2.52 (m, 2.8H), 1.52 (s, 1.2H), 1.49 (s, 3H), 1.43 (s, 4.2H), 1.35-1.31 (m, 8.4H), 1.21 (s, 12.6H).

^1H NMR (400 MHz, CDCl₃, 20°C): (β isomer) 7.32-7.18 (m, 15H), 5.46 (d, J = 4.9 Hz, 1H), 5.06 (dd, J = 9.2, 8.0 Hz, 1H), 4.79-4.69 (m, 3H), 4.56-4.51 (m, 2H), 4.45 (d, J = 7.9 Hz, 1H), 4.32 (dd, J = 12.0, 2.2 Hz, 1H), 4.27-4.19 (m, 3H), 4.00 (dd, J = 10.5, 4.7 Hz, 1H), 3.93-3.90 (m, 1H), 3.73-3.69 (m, 3H), 3.65-3.50 (m, 3H), 2.76-2.70 (m, 2H), 2.55 (t, J = 6.6 Hz, 2H), 1.48 (s, 3H), 1.42 (s, 3H), 1.30 (s, 6H), 1.20 (s, 9H).
$^{13}$C NMR (100 MHz, CDCl$_3$, 20°C, mixture of diastereomers, 1:1.6 α:β): 206.4, 206.3, 177.6, 177.0, 172.7, 172.6, 138.2, 138.2, 137.8, 134.2, 134.2, 129.6, 129.6, 128.9, 128.9, 128.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 109.6, 109.4, 108.8, 108.7, 101.7, 97.9, 96.4, 96.4, 83.4, 78.5, 77.5, 75.2, 75.2, 73.5, 73.3, 73.0, 71.6, 71.4, 71.0, 70.8, 70.7, 70.7, 69.9, 69.1, 68.1, 67.3, 66.4, 66.1, 63.5, 63.2, 50.2, 50.2, 39.1, 39.0, 36.6, 36.6, 28.1, 27.9, 27.4, 27.3, 27.3, 27.2, 26.3, 26.3, 26.2, 25.2, 25.1, 24.7, 24.5.

$^{13}$C NMR (100 MHz, CDCl$_3$, 20°C): (β isomer): 206.4, 177.0, 172.6, 138.1, 137.8, 134.2, 129.6, 128.9, 128.6, 128.6, 128.3, 128.1, 127.9, 127.6, 127.3, 120.4, 108.7, 101.7, 96.4, 83.4, 77.4, 75.2, 73.2, 73.0, 71.3, 70.7, 70.7, 69.1, 67.3, 63.2, 50.2, 39.1, 39.0, 36.6, 36.6, 28.1, 27.3, 26.3, 26.1, 25.2, 24.5.

FTIR (thin film) cm$^{-1}$: 2978 (m), 1738 (s), 1095 (s), 1071 (s), 1008 (m).

FTIR (thin film) cm$^{-1}$: (β isomer): 2978 (w), 1739 (s), 1139 (m), 1070 (s), 1006 (m).

HRMS–ESI (m/z): calcd for C$_{48}$H$_{60}$NaO$_{14}$ [M+Na]$^+$: 883.3875, found: 883.3881.

HRMS–ESI (m/z): (β isomer): calcd for C$_{48}$H$_{60}$NaO$_{14}$ [M+Na]$^+$: 883.3875, found: 883.3878.

[$\alpha$]$^2$D: (β isomer): −37.0 (c 0.70, CH$_2$Cl$_2$).
Methyl 3,4-di-O-benzyl-6-O-4'-oxo-5'-phenyl-valeryl-2-O-pivaloyl-D-glucopyranosyl-(1→2)-3,4,6-tri-O-benzyl-D-glucopyranoside (36):

General Procedure D using glycosyl phosphate 33 (70 mg, 0.086 mmol), acceptor 17 (36 mg, 0.076 mmol), TMSOTf (22 μL, 0.12 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 36 (76 mg, 94%, 1:2.2 α:β).

$^1$H NMR (400 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β): 7.38-7.07 (m, 46.8H), 5.41 (br-s, 0.6H), 5.31 (br-s, 0.6H), 5.13 (t, $\text{J} = 8.1$ Hz, 1H), 5.02 (d, $\text{J} = 7.8$ Hz, 1H), 4.93 (d, $\text{J} = 11.7$ Hz, 1H), 4.85-4.48 (m, 15.6H), 4.38-4.35 (m, 2.1H), 4.29-4.24 (m, 1.6H), 4.03-3.91 (m, 2H), 3.77-3.42 (m, 19.8H), 2.78-2.68 (m, 3.1H), 2.57 (t, $\text{J} = 6.4$ Hz, 2H), 2.50-2.47 (m, 1.1H), 1.23 (s, 5H), 1.10 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β): 206.4, 206.4, 177.7, 176.7, 172.7, 172.6, 138.9, 138.5, 138.3, 138.2, 138.0, 137.9, 137.8, 134.2, 129.7, 129.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 127.4, 127.3, 104.6, 103.2, 99.6, 97.2, 85.0, 83.8, 83.5, 80.4, 78.6, 78.2, 77.9, 77.4, 76.0, 75.7, 75.1, 75.1, 74.8, 73.7, 73.7, 73.5, 73.1, 71.3, 69.9, 68.9, 68.8, 68.0, 63.6, 63.3, 57.3, 57.0, 50.2, 39.2, 39.0, 36.6, 36.6, 28.1, 27.9, 27.4, 27.3.

FTIR (thin film) cm$^{-1}$: 1736 (s), 1454 (m), 1141 (s), 1094 (s), 1070 (s).

HRMS–ESI ($m/z$): calcd for C$_{64}$H$_{72}$NaO$_{14}$ [M+Na]$^+$: 1087.4814, found: 1087.4819.
Methyl 3,4-di-O-benzyl-6-O-4’-oxo-5’-phenyl-valeryl-2-O-pivaloyl-D-glucopyranosyl-(1→4)-3,6-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside (37):

General Procedure D using glycosyl phosphate 33 (82 mg, 0.10 mmol), acceptor 18 (41 mg, 0.089 mmol), TMSOTf (26 µL, 0.14 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 37 (49 mg, 53%, 1:1.6 α:β).

**1H NMR (400 MHz, CDCl₃, 20°C):**

(β isomer): 7.42-7.17 (m, 25H), 5.03-4.96 (m, 2H), 4.83-4.61 (m, 4H), 4.54-4.47 (m, 3H), 4.28 (d, J = 8.0 Hz, 1H), 4.21-4.04 (m, 3H), 3.85-3.72 (m, 2H), 3.68 (s, 2H), 3.64-3.61 (m, 2H), 3.58-3.44 (m, 3H), 3.39-3.34 (m, 2H), 2.65-2.52 (m, 2H), 2.40-2.30 (m, 1H), 2.24-2.16 (m, 1H), 1.18 (s, 9H), 1.11 (s, 9H).

**13C NMR (100 MHz, CDCl₃, 20°C):**

(β isomer): 206.4, 177.0, 176.8, 172.5, 139.3, 138.1, 138.0, 137.8, 134.3, 129.7, 128.9, 128.6, 128.4, 128.2, 128.1, 128.1, 127.8, 127.3, 127.2, 127.2, 102.5, 99.5, 83.1, 81.0, 78.5, 78.0, 77.4, 75.4, 75.2, 75.1, 75.0, 74.3, 74.1, 73.9, 73.4, 73.0, 72.2, 68.0, 63.1, 57.0, 50.0, 39.0, 38.8, 36.5, 29.9, 27.8, 27.5, 27.1.

**FTIR (thin film) cm⁻¹:**

(β isomer): 2966 (w), 1739 (s), 1277 (w), 1141 (s), 1090 (s).

**HRMS–ESI (m/z):**


**[α]²⁴_D:**

(β isomer): −18.7 (c 1.49, CH₂Cl₂).
Thioethyl 6-\(\beta\)-3'-benzoylpropionyl-3,4-di-\(\beta\)-benzyl-2-pivaloyl-\(\beta\)-glucopyranoside (38):

General Procedure G using glucal 30 (0.340 g, 0.698 mmol), dimethyldioxirane (13 mL, 1.05 mmol), ethanethiol (1.55 mL, 20.9 mmol), DMAP (69 mg, 0.57 mmol), pivaloyl chloride (0.035 mL, 0.29 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 38 as a white solid (79 mg, 44%).

\(^1\)H NMR (400 MHz, CDCl\(_3\), 20°C):

7.96 (app-d, \(J = 7.1\) Hz, 2H), 7.57 (app-t, \(J = 7.4\) Hz, 1H), 7.46 (app-t, \(J = 7.6\) Hz, 2H), 7.34-7.25 (m, 10H), 5.08 (t, \(J = 9.7\) Hz, 1H), 4.83-4.72 (m, 3H), 4.60 (d, \(J = 10.8\) Hz, 1H), 4.44-4.40 (m, 2H), 4.27 (dd, \(J = 12.0, 4.7\) Hz, 1H), 3.75 (t, \(J = 8.9\) Hz, 1H), 3.64-3.59 (m, 2H), 3.31 (t, \(J = 6.5\) Hz, 2H), 2.79 (t, \(J = 6.5\) Hz, 2H), 2.78-2.62 (m, 2H), 1.27-1.17 (m, 12H).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\), 20°C):

198.0, 177.0, 172.7, 138.1, 137.8, 136.6, 133.4, 128.8, 128.7, 128.6, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5, 84.8, 83.8, 77.5, 77.4, 75.4, 75.3, 71.6, 63.4, 38.9, 33.5, 28.3, 27.3, 24.0, 15.1.

FTIR (thin film) cm\(^{-1}\):

2969 (w), 1737 (s), 1687 (m), 1157 (s), 1089 (m).

HRMS–ESI (m/z):

calcld for C\(_{37}\)H\(_{44}\)NaO\(_8\)S [M+Na]\(^+\): 671.2649, found: 671.2635.

\([\alpha]\)\(^{24}\)_D:

\(-16.4\) (c 1.39, CH\(_2\)Cl\(_2\)).
Thioethyl 3,4-di-O-benzyl-6-O-4'-oxo-5'-phenyl-valeryl-2-pivaloyl-β-D-glucopyranoside (39):  
General Procedure G using glucal 31 (0.331 g, 0.661 mmol), dimethyldioxirane (10 mL, 0.79 mmol), ethanethiol (1.50 mL, 19.8 mmol), DMAP (0.186 g, 1.52 mmol), pivaloyl chloride (0.098 mL, 0.800 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 39 as a clear oil (0.215 g, 51%).

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3, 20^\circ\text{C):} & & 7.35-7.20 (m, 15H), 5.09 (t, J = 9.3 Hz, 1H), \\
& & 4.81-4.72 (m, 3H), 4.56 (d, J = 10.0 Hz, 1H), \\
& & 4.40 (d, J = 10.8 Hz, 1H), 4.37-4.34 (m, 1H), \\
& & 4.22 (dd, J = 12.0, 4.8 Hz, 1H), 3.77-3.72 (m, \\
& & 3H), 3.63-3.55 (m, 2H), 2.77-2.65 (m, 4H), 2.56 \\
& & (app-t, J = 6.6 Hz, 2H), 1.26-1.21 (m, 12H).
\end{align*}
\]

\[
\begin{align*}
\text{C NMR (100 MHz, CDCl}_3, 20^\circ\text{C):} & & 206.4, 177.1, 172.6, 138.1, 137.8, 134.2, 129.7, \\
& & 129.0, 128.7, 128.6, 128.3, 128.2, 127.9, 127.6, \\
& & 127.3, 84.9, 83.9, 77.6, 77.4, 75.5, 75.3, 71.6, \\
& & 63.4, 50.2, 39.0, 36.6, 29.9, 28.1, 27.4, 24.2, \\
& & 15.1, 14.4.
\end{align*}
\]

FTIR (thin film) cm⁻¹: 2924 (s), 1736 (s), 1454 (m), 1160 (br-s), 1090 (s).


\[
[\alpha]^{24}_D: -14.0 \text{ (c 0.42, CH}_2\text{Cl}_2).
\]
Thioethyl 6-O-acetyl-3,4-di-O-benzyl-β-D-glucopyranoside (41):

General Procedure G using 6-O-acetyl-3,4-dibenzyl-D-glucal 40\textsuperscript{10} (1.18 g, 3.20 mmol), dimethyldioxirane (48 mL, 3.84 mmol), ethanethiol (7.10 mL, 96 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [75:25]) afforded 41 as a clear oil (0.994 g, 70%).

\[ \text{Thioethyl 6-O-acetyl-3,4-di-O-benzyl-β-D-glucopyranoside (41):} \]

\[ \text{General Procedure G using 6-O-acetyl-3,4-dibenzyl-D-glucal 40}^{10} (1.18 \text{ g, 3.20 mmol), dimethyldioxirane (48 mL, 3.84 mmol), ethanethiol (7.10 mL, 96 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [75:25]) afforded 41 as a clear oil (0.994 g, 70%).} \]

\[ \begin{align*}
\text{1H NMR (400 MHz, CDCl}_3, 20^\circ \text{C):} & \quad 7.36-7.21 (m, 10H), 4.93 (d, J = 11.2 \text{ Hz, 1H}), 4.83 (d, J = 10.3 \text{ Hz, 2H}), 4.53 (d, J = 10.8 \text{ Hz, 1H}), 4.30-4.26 (m, 2H), 4.15 (dd, J = 11.9, 2.2 \text{ Hz, 1H}), 3.57-3.51 (m, 1H), 3.50-3.48 (m, 3H), 2.69-2.66 (m, 2H), 2.41 (br-s, 1H), 1.98 (s, 3H), 1.26 (t, J = 7.4 \text{ Hz, 3H}). \\
\text{13C NMR (100 MHz, CDCl}_3, 20^\circ \text{C):} & \quad 171.0, 138.6, 137.8, 128.7, 128.3, 128.2, 128.0, 86.5, 86.1, 77.3, 77.2, 75.4, 75.3, 73.5, 63.5, 24.8, 21.1, 15.5. \\
\text{FTIR (thin film) cm}^{-1}: & \quad 3453 (\text{br-w}), 2922 (\text{w}), 1742 (\text{s}), 1237 (\text{s}), 1038 (\text{s}). \\
\text{HRMS–ESI (m/z):} & \quad \text{calcd for C}_{24}\text{H}_{30}\text{NaO}_{6}\text{S} [\text{M+Na}^+]: 469.1655, \text{found: 469.1651.} \\
\text{[α]}^{24}_{D}: & \quad -4.3 (c 0.61, \text{CH}_2\text{Cl}_2). \\
\end{align*} \]
**Thioethyl 6-O-acetyl-3,4-di-O-benzyl-2-pivaloyl-β-D-glucopyranoside (42):**

To a solution of thioglycoside 41 (0.994 g, 2.24 mmol) in dichloromethane (20 mL) was added dimethylaminopyridine (1.08 g, 8.85 mmol) and pivaloyl chloride (0.551 mL, 4.47 mmol). After 1 h, the reaction solution was diluted with ethyl acetate:hexanes (1:1), was filtered through silica gel, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent hexanes:ethyl acetate [70:30]) to afford 42 as a clear oil (1.11 g, 93%).

**¹H NMR (400 MHz, CDCl₃, 20°C):**

7.36-7.23 (m, 10H), 5.11 (app-t, \( J = 9.3 \) Hz, 1H), 4.83-4.72 (m, 3H), 4.56 (d, \( J = 10.8 \) Hz, 1H), 4.42 (d, \( J = 10.0 \) Hz, 1H), 4.37 (dd, \( J = 2.0, 12.0 \) Hz, 1H), 4.21 (dd, \( J = 12.0, 4.8 \) Hz, 1H), 3.76 (t, \( J = 8.8 \) Hz, 1H), 3.64 (t, \( J = 9.8 \) Hz, 1H), 3.59-3.56 (m, 1H), 2.74-2.63 (m, 2H), 2.04 (s, 3H), 1.27-1.18 (m, 12H).

**¹³C NMR (100 MHz, CDCl₃, 20°C):**

177.1, 171.0, 138.1, 137.7, 128.7, 128.6, 128.3, 128.3, 127.9, 127.6, 84.9, 83.9, 77.4, 77.3, 75.5, 75.3, 71.6, 63.3, 39.0, 27.4, 24.2, 21.1, 15.1.

**FTIR (thin film) cm⁻¹:**

2970 (w), 2928 (w), 1740 (s), 1233 (m), 1162 (m).

**HRMS–ESI (m/z):**


**[α]²⁴_D:**

-12.1 (c 0.33, CH₂Cl₂).
Thioethyl 3,4-di-O-benzyl-2-pivaloyl-β-D-glucopyranoside (43):

To a solution of thioglycoside 42 (1.11 g, 2.08 mmol) in dichloromethane (20 mL) was added a solution of sodium methoxide in methanol (25% by weight, 0.147 mL, 0.716 mmol). After 2.5 h, the reaction solution was brought to pH 7 by addition of acidic Dowex resin. The solution was decanted and was concentrated under reduced pressure to provide a quantitative yield of 43. Spectral data matched published data.11

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**Thioethyl 3,4-di-O-benzyl-2-pivaloyl-6-O-succinoyl-β-D-glucopyranoside (44):**

To a solution of compound 43 (0.895 g, 1.83 mmol) in pyridine:dichloromethane (1:1, 20 mL) was added dimethylaminopyridine (0.384 g, 3.15 mmol) and succinic anhydride (0.277 g, 2.77 mmol). After 17 h, the solution was diluted with diethyl ether (100 ml) and was washed sequentially with with dilute aqueous acetic acid (pH 3), water, and brine. The combined organic phases were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40] to hexanes:ethyl acetate [40:60]) afforded 44 as a yellow oil (0.876 g, 81%).

**1H NMR (400 MHz, CDCl₃, 20°C):**

7.33-7.22 (m, 10H), 5.08 (t, J = 9.8 Hz, 1H), 4.80-4.76 (m, 2H), 4.72 (d, J = 11.0 Hz, 1H), 4.54 (d, J = 10.8 Hz, 1H), 4.41-4.37 (m, 2H), 4.23 (dd, J = 11.9, 4.7 Hz, 1H), 3.74 (t, J = 8.9 Hz, 1H), 3.60 (t, J = 9.2 Hz, 1H), 3.57-3.53 (m, 1H), 2.71-2.58 (m, 6H), 1.25-1.20 (m, 12H).

**13C NMR (100 MHz, CDCl₃, 20°C):**

178.1, 177.0, 171.9, 138.0, 137.6, 128.7, 128.6, 128.3, 128.2, 127.9, 127.5, 84.8, 83.7, 77.4, 75.4, 75.2, 71.5, 63.5, 38.9, 28.9, 28.8, 27.3, 24.0, 15.1.

**FTIR (thin film) cm⁻¹:**

2970 (w), 1739 (s), 1714 (m), 1160 (s), 1090 (m).

**HRMS–ESI (m/z):**


**[α]D:**

-18.7 (c 1.63, CH₂Cl₂).
Thioethyl 3,4-di-O-benzyl-6-O-benzylsuccinamyl-2-pivaloyl-β-D-glucopyranoside (45):

To a solution of compound 44 (0.685 g, 1.16 mmol) in dichloromethane (20 mL) at 0 °C was added dimethylaminopyridine (0.164 g, 1.35 mmol) and dicyclohexylcarbodiimide (0.265 mL, 1.28 mmol). After 10 min, benzylamine (0.254 mL, 2.33 mmol) was added and the reaction solution was warmed to ambient temperature. After 2 h, the reaction mixture was diluted with hexanes:ethyl acetate (1:1) and filtered through silica gel to remove excess urea. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [50:50]) to afford 45 as a white solid (0.513 g, 65%).

\[ \text{Thioethyl 3,4-di-O-benzyl-6-O-benzylsuccinamyl-2-pivaloyl-β-D-glucopyranoside (45)} \]

**1H NMR (400 MHz, CDCl\textsubscript{3}, 20°C):**

\[ 7.35-7.24 (m, 15H), 5.95 (br-s, 1H), 5.09 (dd, J = 9.8, 9.3 Hz, 1H), 4.83-4.72 (m, 3H), 4.57 (d, J = 10.9 Hz, 1H), 4.43 (d, J = 5.7 Hz, 2H), 4.38 (d, J = 10.1 Hz, 2H), 4.21 (dd, J = 11.9, 4.8 Hz, 1H), 3.74 (t, J = 8.5 Hz, 1H), 3.62-3.56 (m, 2H), 2.73-2.64 (m, 4H), 2.49 (t, J = 6.7 Hz, 2H), 1.27-1.22 (m, 12H). \]

**13C NMR (100 MHz, CDCl\textsubscript{3}, 20°C):**

\[ 176.4, 172.8, 171.2, 138.4, 138.1, 137.7, 128.9, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 84.8, 83.9, 77.6, 75.4, 75.3, 71.6, 63.6, 43.9, 39.0, 31.2, 29.7, 27.4, 24.2, 15.1. \]

**FTIR (thin film) cm\textsuperscript{-1}:**

\[ 2922 (s), 1734 (s), 1456 (m), 1159 (m), 1088 (m). \]

**HRMS–ESI (m/z):**

calcd for C\textsubscript{38}H\textsubscript{47}NNaO\textsubscript{8}S [M+Na]+: 700.2915, found: 700.2921.

\[ [\alpha]^{24}_D: \]

\[ -2.94 (c 0.17, CH\textsubscript{2}Cl\textsubscript{2}). \]
6-O-3'-Benzyloxypivaloyl-3,4-di-O-benzyl-2-pivaloyl-β-D-glucopyranosyl trichloroacetimidate (46):

General Procedure H using thioglycoside 38 (64 mg, 0.099 mmol), NBS (74 mg, 0.41 mmol), DBU (1.5 μL, 0.010 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded 46 (37 mg, 50%, α:β 1:2).

1H NMR (500 MHz, CDCl3, 20°C, mixture of diastereomers, α:β): 8.60-8.59 (m, 1.5H), 7.90 (d, J = 7.3 Hz, 3H), 7.53 (app-t, J = 7.5 Hz, 1.5H), 7.43 (t, J = 7.8 Hz, 3H), 7.35-7.22 (m, 15H), 6.49 (d, J = 3.5 Hz, 0.5H), 5.87 (d, J = 7.5 Hz, 1H), 5.30 (app-t, J = 8.1 Hz, 1H), 5.04 (dd, J = 10.1, 3.7 Hz, 0.5H), 4.84-4.71 (m, 4.5 H), 4.60 (t, J = 9.5 Hz, 1.5H), 4.38-4.27 (m, 3H), 4.15-4.06 (m, 1H), 3.80-3.69 (m, 3.5H), 3.30-3.25 (m, 3H), 2.77-2.73 (m, 3H), 1.15-1.13 (m, 13.5H).

13C NMR (125 MHz, CDCl3, 20°C, mixture of diastereomers, α:β): 198.0, 198.0, 177.7, 176.8, 176.6, 172.7, 172.7, 161.3, 161.0, 138.2, 138.0, 137.7, 137.6, 136.6, 133.5, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.6, 128.4, 128.3, 128.2, 128.2, 128.2, 128.0, 127.9, 127.6, 127.6, 95.9, 93.6, 83.2, 79.9, 77.0, 76.7, 75.7, 75.6, 75.1, 74.8, 73.9, 72.4, 71.8, 71.7, 62.8, 62.6, 39.0, 33.5, 29.9, 28.4, 28.3, 27.3, 27.3, 27.3, 27.3, 27.3.

FTIR (thin film) cm⁻¹: 1735 (s), 1685 (m), 1276 (m), 1145 (m), 750 (m).

3,4-Di-O-benzyl-6-O-4'-oxo-5'-phenyl-valeryl-2-pivaloyl-β-D-glucopyranosyl trichloroacetimidate (47):

General Procedure H using thioglycoside 39 (0.193 g, 0.291 mmol), NBS (0.200 g, 1.12 mmol), DBU (3.8 µL, 0.025 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15]) afforded 47 (70 mg, 31%, α:β 1:1.3).

1H NMR (400 MHz, CDCl3, 20°C, mixture of diastereomers, α:β): 8.64 (s, 1H), 8.63 (s, 0.8H), 7.64-7.61 (m, 0.8H), 7.43-7.20 (m, 25.5H), 6.52 (d, J = 3.5 Hz, 0.8H), 5.90 (dd, J = 7.5, 2.6 Hz, 1H), 5.35 (t, J = 7.6 Hz, 1H), 5.10 (dd, J = 10.1, 3.5 Hz, 0.8H), 4.88-4.76 (m, 7H), 4.60-4.56 (m, 1.8H), 4.36-4.27 (m, 3.5H), 4.17 (app-t, J = 9.6 Hz, 0.8H), 4.09 (td, J = 10.1, 2.6 Hz, 1H), 3.83-3.70 (m, 5.3H), 3.02 (app-q, J = 6.9 Hz, 1H), 2.82-2.70 (m, 2.5H), 2.61-2.52 (m, 3.5H), 1.18 (s, 15.8H).

13C NMR (100 MHz, CDCl3, 20°C, mixture of diastereomers, α:β): 206.4, 206.4, 177.7, 176.6, 172.5, 161.3, 160.9, 138.1, 137.9, 137.6, 137.6, 134.2, 134.2, 130.2, 129.7, 129.6, 129.5, 129.3, 129.0, 128.9, 128.7, 128.7, 128.7, 128.6, 128.6, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.6, 127.6, 127.3, 127.0, 95.9, 93.6, 83.2, 79.9, 76.8, 76.6, 76.4, 75.7, 75.6, 75.0, 75.0, 74.8, 74.8, 73.9, 72.4, 71.8, 71.7, 71.7, 62.9, 62.8, 62.6, 50.2, 50.2, 39.0, 36.6, 31.0, 28.8, 28.1, 28.0, 27.3, 27.3.

FTIR (thin film) cm⁻¹:

2923 (w), 1738 (s), 1675 (w), 1281 (m), 1138 (s), 1066 (s).

HRMS-ESI (m/z):

3,4-Di-O-benzyl-6-O-N-benzylsuccinamyl-2-pivaloyl-β-D-glucopyranosyl trichloroacetimidate 48:

General Procedure H using thioglycoside 45 (0.167 g, 0.246 mmol), NBS (0.186 g, 1.05 mmol), DBU (3.0 μL, 0.019 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 48 (70 mg, 45%, α:β 1:1.4).

\[ \text{General Procedure H using thioglycoside 45 (0.167 g, 0.246 mmol), NBS (0.186 g, 1.05 mmol), DBU (3.0 μL, 0.019 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded 48 (70 mg, 45%, α:β 1:1.4).} \]

\[ \text{1H NMR (500 MHz, CDCl}_3, 20^\circ\text{C, mixture of diastereomers, } \alpha:\beta): 7.41-7.25 \text{ (m, 25.5H), 6.46 (d, } J = 3.8 \text{ Hz, 0.7H), 6.08 (d, } J = 2.9 \text{ Hz, 1H), 6.00-5.90 (m, 1.7H), 5.37 (at, } J = 3.5 \text{ Hz, 1H), 5.08 (dd, } J = 3.5, 9.9 \text{ Hz, 0.7H), 4.96-4.80 (m, 6.8H), 4.63-4.58 (m, 1.7H), 4.46-4.37 (m, 1.7H), 4.34-4.21 (m, 3.4H), 4.20-4.10 (m, 1.7H), 3.91-3.87 (m, 1H), 3.81-3.76 (m, 1H), 3.70-3.67 (m, 0.7H).} \]

\[ \text{13C NMR (125 MHz, CDCl}_3, 20^\circ\text{C, mixture of diastereomers, } \alpha:\beta): 178.1, 177.1, 172.8, 172.7, 171.4, 171.2, 138.4, 138.3, 138.2, 138.0, 137.6, 128.9, 128.9, 128.9, 128.9, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.7, 91.6, 90.4, 82.2, 79.9, 77.9, 75.6, 75.6, 75.5, 75.1, 74.1, 71.8, 71.6, 68.7, 66.8, 63.5, 44.0, 43.9, 39.5, 39.0, 31.3, 31.3, 29.9, 29.8, 29.8, 27.4, 27.3, 27.3, 27.3.} \]

\[ \text{FTIR (thin film) cm}^{-1}: 3352 \text{ (br-w), 1732 (s), 1657 (m), 1161 (s), 1122 (s).} \]

\[ \text{HRMS–EI (m/z): calcd for C}_{38}\text{H}_{43}\text{Cl}_2\text{N}_2\text{NaO}_9 \text{ [M+Na]^{+}: 799.1931, found: 779.1934.} \]
Chapter 3

A Modular Synthesis of FGF-2 Binding Heparin Pentasaccharide

Thesis Advisor: Peter H. Seeberger
Introduction and Background

Glycosaminoglycans (GAGs) are a class of linear, negatively charged, highly functionalized oligosaccharides whose interactions with proteins and other biopolymers are essential to a number of biological processes including anticoagulation\(^1\), cell-cell adhesion\(^2\), and growth factor signaling.\(^3\) Structurally, GAGs are extended polymer chains generally composed of repeating disaccharides of a 2-deoxy-2-amino sugar and an uronic acid. These structures are further elaborated through acetylation, epimerization, and \(N\)- and \(O\)-sulfation by various enzymes to produce a diversely functionalized set of molecules (Figure 1).

![Dermatan sulfate](image1.png)  
![Chondroitin sulfate](image2.png)  

Figure 1. Representative glycosaminoglycan polysaccharides.

Although important for their incredible range of bioactivity, the microheterogeneity of GAGs intensifies the challenge associated with their purification and characterization.

Both heparin and heparan sulfate are biosynthesized as proteoglycans where the carbohydrate chain, consisting of repeating glucosamine and uronic acid disaccharides, is covalently linked to a protein core. They differ in the extent of their sulfation and uronic acid content. Heparin is found in mast cells, generally contains more L-iduronic acid and is more highly sulfated than heparan sulfate, which is produced by nearly all cells.\(^1,4\) Although formed by the same pathway as heparin, heparan sulfate remains attached to its protein core, while heparin is ultimately processed into smaller GAG chains.\(^1\) The differential action of heparin lyases on heparin and heparan sulfate may be used to differentiate the two oligosaccharide types.

While many protein-binding GAGs exist as proteoglycans, in some cases short specific sequences also bind and induce unique biological activity.\(^1,5\) Numerous such heparin...
and heparan sulfate sequences have been identified, largely due to interest generated for possible biomedical applications. Heparin isolated from animal sources has been used medically as an anticoagulant for over sixty years. Heparin and heparan sulfate sequences are also implicated in mast cell regulation, herpes simplex virus infection, and growth factor activation, among other processes.

Commercial heparin is commonly isolated from porcine or bovine tissues containing high levels of mast cells, followed by proteolysis, ion exchange, and fractional precipitation. Fractional precipitation allows isolation of low molecular weight heparin, which is easier to administer clinically than unfractionated heparin and produces fewer undesirable side effects, such as heparin-induced thrombocytopenia. Biochemical studies concerning heparin generally rely on structurally defined sequences prepared by enzymatic degradation of these larger oligomers.

Investigation of heparin conformation has suggested a primarily helical molecule displaying charged sulfate and carboxylate groups in relatively rigid patterns associated with its specificity for protein binding. Protein interaction appears to rely largely on charge orientation in the heparin structure, which in turn results from individual sugar conformation. Computational analysis indicates that configuration and placement of L-iduronic acid in particular may greatly affect this overall charge placement. While D-glucosamine and D-glucoronic acid adopt the $^4C_1$ chair conformation, L-iduronic acid is more flexible and data suggest three possible conformers: $^4C_1$ and $^1C_4$ chairs and the $^2S_0$ skew boat (Figure 2).

![Figure 2](image-url)

Figure 2. Conformations of individual glucosamine and iduronic acid residues found in heparin.
The preferred conformation for iduronic acid depends on substituent identity (sulfation and acetylation) and its position in the chain, with the $^{1}C_{4}$ and $^{2}S_{0}$ preferred for a non-reducing sugar. Interchange between these conformers within larger chains may alter the position of key charged residues, and the low energy barrier between the two suggests that the ring may change conformation on binding to form favorable electrostatic interactions with the protein.\(^1\) The prevalence of L-iduronic acid residues in regions responsible for protein binding supports this observation.\(^2\)

Fibroblast growth factors (FGFs) make up a family of structurally related signaling polypeptides key to a number of developmental processes, including cell proliferation, differentiation, morphogenesis, and angiogenesis.\(^1,3\) Signal transduction involves dimerization of the tyrosine kinase FGF receptors (FGFRs), a process promoted by simultaneous binding of FGF and FGFR to soluble or cell surface-bound heparin and heparan sulfate.\(^1\) Acidic fibroblast growth factor (FGF-1) and basic fibroblast growth factor (FGF-2), have received much attention, resulting in high-resolution X-ray crystallographic data of FGF-FGFR-heparin complexes.\(^10,11\)

The crucial relationship between fibroblast growth factor (FGF) heparin binding and FGF receptor activation offers an entry to promising therapeutic targets for the regulation of cell growth. Heparin-mediated dimer- and oligomerization of both acidic (FGF-1) and basic fibroblast growth factor (FGF-2) with FGF receptors (FGFR) appears critical to receptor activation.\(^12\) Biochemical studies have indicated that small modifications of heparin oligomer length and sulfation pattern affect specificity for distinct FGF polypeptides.\(^13\) In addition to work demonstrating higher FGF-2 affinity for heparin containing L-iduronic acid as the sole uronic acid,\(^14\) preliminary studies suggest 2-0- and 6-O-sulfation of L-iduronic acid and N-sulfation of the D-glucosamine units are essential for binding.\(^1,2\)

Several studies have investigated the minimum required length for heparin-FGF-FGFR binding. Analysis of binding by ultracentrifugation of FGF-2 with heparin oligosaccharides suggest that while a hexasaccharide is sufficient for binding, an octasaccharide is required for receptor activation.\(^1\) Crystallographic work detailing an FGF-2:FGFR complex in the absence of heparin also indicates a minimum octasaccharide to adequately bridge the positively charged "binding canyon" observed between components.\(^16\) Other reports suggest that a hexasaccharide\(^17\) or even a tetrasaccharide\(^18\) are sufficient to
affect FGF-2 binding. In light of this disparity, in approaching a synthesis of FGF-2 binding oligosaccharide, a strategy for rapid access to heparins of varying length would be advantageous for the deconvolution of their biological activity.

**Prior Synthetic Studies**

Inspection of the repeating nature of FGF-2 binding heparin oligosaccharides suggests a disaccharide unit as a key synthetic building block. Use of a disaccharide donor incorporating a removable protecting group at C4 of a non-reducing L-iduronic acid or D-glucosamine would allow iterative synthesis of heparin structures of varying lengths. Possible repeating components may display either an uronic acid or a glucosamine at the disaccharide reducing end (Figure 3).

![Figure 3. FGF-2 binding heparin oligosaccharide retrosynthesis. X=leaving group.](image)

Several syntheses of FGF-2 binding heparin oligosaccharides have been reported, using both uronic acid and glucosamine reducing end strategies. Early work by Sinaý and coworkers utilized disaccharide trichloroacetimidates containing glucosamine moieties at the reducing end. A number of pentasaccharides with both D-glucoronic and L-iduronic acids were synthesized and used in binding studies to determine the optimal uronic acid content for good binding to FGF-2. Subsequent work extended this strategy to the synthesis of related hexa- and octasaccharides (Scheme 1). Iterative glycosylation of a seeding block with an
elongating disaccharide donor was followed by disaccharide capping provided a modular strategy for synthesis of the larger oligomers.\textsuperscript{19}

Scheme 1. Retrosynthesis of FGF-2 binding heparin hexasaccharide synthesized by Sinay and coworkers.

Later reports by Lay and coworkers outlined syntheses of tetra- and hexasaccharides utilizing uronic acid donors (Scheme 2).\textsuperscript{13} Research by Martín-Lomas also employed

Scheme 2. Retrosynthesis of FGF-2 binding heparin tetrasaccharide synthesized by Lay and coworkers.\textsuperscript{2}
reducing end L-iduronic acids in their syntheses of a related hexa- and octasaccharide. In each case, placement of a participating ester at the uronic acid C2 of the trichloroacetimidate donor provided the necessary selectivity on glycosylation.

While these syntheses are impressive, overall they remain lengthy and require numerous purification steps. In addition, coupling yields tend to decrease as oligomer size and complexity increase. Analysis of the repeating heparin polymer suggests iterative synthesis, while the ability to use excess reagents to drive coupling yields and ease of purification recommend a solid-phase strategy. Indeed, after we began this work, the Martín-Lomas group successfully applied their modular approach to a polymer-supported synthesis of heparin-like oligosaccharides (Scheme 3). Triple coupling cycles were used to increase glycosylation efficiency, providing the desired octasaccharide in 10% overall yield. Recent successes concerning the automated syntheses of complex oligosaccharides on solid support indicate the feasibility of a correlated fully automated solid-phase heparin
synthesis. Efforts toward the iterative synthesis of FGF-2 binding heparin oligosaccharides and steps towards the automation of this sequence are discussed in this chapter.

**Retrosynthetic Analysis**

The synthetic work described herein details efforts toward the synthesis of FGF-2 binding heparin of various lengths. Initial solution-phase work was designed with consideration for ultimate application of the sequence to an automated solid-phase synthesis of the desired oligosaccharides. The orthogonal protection required for the sequential unmasking and introduction of the desired sulfation pattern led to the protecting group strategy outlined in Figure 4. Carboxylate moieties in the final structure were protected as methyl esters, O-sulfation sites were masked as acetate or pivaloate esters, N-sulfates were masked as azide groups, and free hydroxyls were protected as benzyl ethers. A levulinic acid ester was used as a temporary protecting group for sequence elongation. A pentenyl alcohol reducing end was used as a linker model and to facilitate spectral comparison with expected cleavage products for an automated solid-phase protocol utilizing an octenediol linker for reducing end immobilization. Reduction of the installed azides was anticipated prior to resin cleavage due to their general incompatibility with the cross-metathesis procedure used to access the free oligosaccharides.

Figure 4. Retrosynthesis of FGF-2 binding heparin protecting group strategy.
Trichloroacetimidates were chosen as the preferred glycosyl donors based on previous success for automated syntheses of complex structures in our laboratory. Prior work in our laboratory indicated a disaccharide donor containing a reducing end glucosamine as the optimal donor for sequence elongation. Early work utilizing alternative uronic acid reducing end disaccharide donor 1 and a pentenyl alcohol acceptor resulted in the loss of the C2 acetate (3) and formation of cyclic lactone 4 along with the desired coupling product 2 (Scheme 4). While in a solid-phase protocol the cyclic lactone would be readily removed during the washing cycle, the free hydroxyl of compound 3 could result in complex mixtures upon structure elongation. Glycosylation of pentenyl alcohol with a glucosamine disaccharide donor produced anomeric mixtures under all solid-phase compatible protocols. Ultimately, reducing end monosaccharide 6 was incorporated, with subsequent elongation utilizing disaccharide trichloroacetimidate 5 (Figure 5). While C2-acetates were used for the disaccharide uronic acids, a C2-pivaloyl ester was chosen for iduronic acid 6 as previous work by India Sietlaff in our group had demonstrated that the corresponding acetate produced the orthoester exclusively on glycosylation with pentenyl alcohol. Additional work showed that disaccharide donor 5 gave the desired α selectivity under conditions amenable to solid-phase work and eventual automation. Synthesis focused on building blocks—disaccharide 5 and monosaccharide 6—and subsequent application of these components to our strategy for the construction of FGF-2 binding heparin oligosaccharides.
**Results and Discussion**

**Iduronic acid donor synthesis.**

The prevalence of L-iduronic acid in many heparin structures, including FGF-2 binding heparin, necessitates concise and efficient access to differentially protected iduronic acid synthons. While itself not commercially available, L-iduronic acid has been synthesized from a variety of starting materials including idose, glucose, glycals, and glucoronic acid. Commercially available L-idose is very costly, rendering it undesirable for large scale synthesis, while syntheses utilizing other starting materials require the inversion of the C-5 stereocenter on a D-gluco sugar. Few methods reported for this inversion have realized full selectivity for the desired configuration.

Previous work by the group and work performed in conjunction with my colleague Greg Lohman outlined a concise, scalable synthetic route to differentially protected iduronic acid from commercially available diacetone glucose (Scheme 5). This sequence relies on selective introduction of the required L-idose-configuration of thioorthoester via addition of trithiophenylmethylithium to aldehyde obtained from diacetone glucose after benzylation, selective acetal cleavage, and diol oxidation (Scheme 5). Cleavage of the thioorthoester to the furanose methyl ester with copper chloride dihydrate and copper...
Scheme 5. Synthesis of differentially protected L-iduronic ester 15 from diacetone glucose. Oxide in methanol followed by acidic removal of the isopropylidene provided crystalline triol 13 in its pyranose form. Installation of a 1,2-isopropylidene onto 13 locked the sugar in the \(^1\)C\(_4\) pyranose form, providing key intermediate 15 after formation of the levulinate ester.

Acidic cleavage of isopropylidene 15 provided diol 16, prepared for differential protection of the C-1 and C-2 hydroxyls (Scheme 6). While selective cleavage of a 1,2-

Scheme 6. Isopropylidene cleavage of acetonide 15 to produce crude diol 16.

diacetate with benzylamine had been shown to provide the desired C2-acetate lactol for a corresponding system, in the presence of the C4-levulinate ester anemic acetate cleavage of 17 proceeded was sluggish and produced low yields of the desired lactol 18 (Scheme 7a).
Undesired reactivity at the C4-levulinate ester may be responsible for this result. As an alternative, differential silyl ether protection was employed. This pathway was additionally attractive as it allowed ready access to both the C2-acetate and C2-pivaloate esters for incorporation into the disaccharide donor and the desired monosaccharide, respectively. While low temperature ether formation for related C4-benzyl ether iduronic acids with tert-butyldimethylsilyl (TBS) chloride produced the desired anomeric silyl ether, the less sterically demanding levulinate ester required the bulkier thexyldimethylsilyl (TDS) species and prolonged reaction at low temperature to achieve the desired selectivity (Scheme 7b). Protection of the C2-hydroxyl of 19 as either the acetate or levulinate ester then provided intermediates 20 and 21. Exposure of TDS ethers 20 and 21 to hydrogen fluoride-pyridine in tetrahydrofuran at ambient temperature provided the desired lactols 18 and 22, respectively, which were smoothly converted to the corresponding trichloracetimidate donors 23 and 24 in high yield with trichloroacetonitrile and catalytic 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU).

**Disaccharide donor and reducing end iduronic acid synthesis.**

With the necessary iduronic acid donors in hand, construction of the disaccharide donor was undertaken. Glucosamine 30 was synthesized in nine steps on multi-gram scale from commercially available D-glucosamine 25 according to the Seeberger group protocol (Scheme 8). Azide formation followed by peracetylation of the crude mixture produced
tetraacetate 26. The anomeric acetate was cleaved selectively with ammonia and the resulting lactol protected as the TBS ether (27). Global deacetylation and protection as the cyclic benzyldiene (28) allowed for selective benzylation of C4, which provided diol 29 on treatment with aqueous trifluoroacetic acid. Selective low-temperature acylation at C6 with acetyl chloride and collidine provided the desired acceptor 30 in excellent overall yield.

Preparation of the required trichloroacetimidate donor began with glycosylation of acceptor 30 with iduronic acid donor 23 in dichloromethane with catalytic trifluoromethanesulfonate (TMSOTf) from −20°C to −10°C to provide disaccharide 31 in excellent yield and selectivity (Scheme 9). Initial orthoester formation was observed followed by rearrangement to the desired α-disaccharide on warming to −10°C. Silyl ether removal in buffered TBAF provided lactol 32, which was readily converted to
trichloroacetimidate 5. In turn, the reducing end monosaccharide 6 was obtained via glycosylation of donor 24 with pentenyl alcohol, followed by levulinate ester cleavage with hydrazine in pyridine-acetic acid (Scheme 10).

Scheme 10. Synthesis of reducing end monosaccharide 6.

Pentasaccharide synthesis.

With access to gram quantities of our two building blocks 5 and 6, our iterative strategy for heparin oligomer construction was implemented. Trisaccharide formation via glycosylation of acceptor 6 with donor 5 was undertaken (Scheme 11). Although activation with catalytic TMSOTf in methylene chloride at -20 °C over activated 4 Å molecular sieves produced trisaccharide 34 in good yield, an additional impurity 35 and several other minor side products were also observed. Impurity 35 was inseparable by standard chromatographic methods on silica gel, and its $^1H$ NMR spectrum was characterized by a pseudo triplet at 5.6 ppm and additional acetate, levulinate, and methyl ester-related peaks. Alternative coupling solvents such as diethyl ether and tetrahydrofuran produced lower product yields and failed
to eliminate this undesired side product. This impurity was also observed during pentasaccharide construction (vide infra) suggesting 35 was associated with the disaccharide donor common to both glycosylations. A sample enriched in by-product 35 was obtained via preparative high pressure liquid chromatographic purification of the trisaccharide glycosylation reaction mixture. $^1$H NMR spectral analysis of this sample and associated mass spectral data identified 35 as the trichloroacetamide shown in Figure 6, probably obtained via reaction of the liberated trichloracetamide following donor activation.

![Figure 6. Trichloroacetamide side product 35 obtained on glycosylation with donor 5.](image)

Ultimately clean trisaccharide 34 was obtained on a small scale via size-exclusion chromatography. Removal of the C4-levulinate ester of 34 with hydrazine then provided trisaccharide acceptor 36 (Scheme 12). Iteration of the glycosylation step with this new acceptor 36 and disaccharide donor 5 then afforded pentasaccharide 37 along with trichloroacetamide 35 (Scheme 12). Although the major impurity resulting from glycosylation had been identified, close examination of the acetate region of the $^1$H NMR spectra for both the tri- and pentasaccharides 34 and 37 between 2-3 ppm indicated apparent peak doubling; further analysis was hindered by the large number of resonances in the acetate region. In order to determine the nature of the doubling, disaccharide donor 38 and iduronic
acid acceptor 40, each containing a benzoate ester at the iduronic acid C2, were synthesized and coupled with acceptor 6 and donor 5, respectively (Scheme 13). The downfield shift of

the benzoate methylene should allow more ready evaluation of the observed impurities. Assessment of the $^{1}H$ NMR spectra of both reaction mixtures indicated multiple products containing the benzoate methylene in the region from 7-8 ppm. Further analysis of mass spectral data of 39 and 41 suggests that these impurities are of the same molecular weight as the desired products and hence may represent the undesired $\beta$-coupled products. While these findings contradict previously published results utilizing donor 5 and similar acceptors,$^{3,7,8}$
Greg Lohman in the Seeberger laboratory also observed the undesired β-coupled product for the glycosylation of tetrasaccharide trichloroacetimidate donor 42 and disaccharide acceptor 43 (Scheme 14). An alternative explanation remains elusive.

Scheme 14. Previous work outlining an unexpected α,β-mixture for coupling of glucosamine donor 42 and uronic acid acceptor 43.39

Early attempts to prepare heparin oligosaccharides via an automated solid-phase protocol were thwarted due to technical difficulties during the initial resin-loading cycle with iduronic acid donor 24. The utility of the general strategy outlined in this chapter has been confirmed, however, by subsequent work by Christian Noti in the Seeberger lab utilizing a modified synthetic strategy with disaccharide donor 5 for the solution phase synthesis of a small library of heparin tetra- and hexasaccharides.40 In addition, microarrays containing these heparin oligosaccharides were prepared.41 Incubation of these carbohydrate microarrays with FGF-2 indicated that both the tetra- and hexasaccharide heparins were sufficient for binding. Ongoing work in the Seeberger laboratory is focused on the automation of these sequences for ready access to heparin libraries for biological testing.
Conclusion

A high-yielding method for the production of differentially protected iduronic acid trichloroacetimidates 23 and 24 via selective silylation was devised. Synthesis of disaccharide 31 and the corresponding trichloroacetimidate 5 was achieved in a manner amenable to large scale preparation. A method for the reduction and acetylation of azides was developed in solution with requirements for solid-phase application taken into account. Trisaccharide 34 and pentasaccharide 37 were synthesized using a solution-phase protocol designed for application to an automated synthesis on solid support. Early analysis of reaction side products suggested the possibility of anomeric mixtures despite contradictory published work regarding donors such as 5.

27 India Sietlaff, Seeberger Group, Massachusetts Institute of Technology, Cambridge, MA, 2002, personal communication.
40 Christian Noti, Seeberger group, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland, 2006, personal communication.
Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 400 mesh, Silicycle). 1 Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and by exposure an aqueous solution of ceric ammonium molybdate (CAM), followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr at 25–35 °C, then at ~1 Torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, and tetrahydrofuran were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.2 Trimethylsilyl trifluoromethanesulfonate (TMSOTf) purchased from Acros Chemicals. All solid-phase resin was purchased from Novabiochem and was prewashed six times with each of the following: tetrahydrofuran, tetrahydrofuran:methanol (95:5), and dichloromethane. Pyridine was distilled over calcium hydride immediately before use. N-Bromosuccinimide (NBS) was recrystallized from boiling water prior to use.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a Bruker-400 NMR spectrometer (400 MHz) or a Varian VXR-500 spectrometer (500 MHz). Chemical shifts are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent (CHCl₃: δ 7.27). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^13C NMR) spectra were recorded with a Varian 500 INOVA spectrometer or a Bruker 400 spectrometer with a Magnex Scientific superconducting magnet and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent (CDCl₃: δ 77.2). Phosphorus-31 nuclear magnetic resonance spectra (^31P NMR) spectra were obtained on a Varian VXR-300 (120 MHz) or a Varian VXR-500 (200 MHz) and are reported in δ relative to H₃PO₄ (0.0 ppm) as an external reference. Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 24 °C using a sodium lamp (589 λ). We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry’s Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electrospray ion source (ESI) or electrospray (ES).

3-O-benzyl-1,2-isopropylidene-α-D-glucofuranoside (9):

Sodium hydride (60% in mineral oil, 3.1 g, 77 mmol) was added portionwise to a solution of commercially-available diacetone glucose 7 (16.6 g, 63.8 mmol) in tetrahydrofuran (160 mL). After evolution of hydrogen ceased, tetrabutylammonium iodide (160 mg, 0.43 mmol) and benzyl bromide (8 mL, 67.2 mmol) were added. After 14 h, excess hydride was quenched by slow addition of water followed by evaporation of the organic layer under reduced pressure. The aqueous phase was extracted with ethyl acetate (3 × 250 mL) and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered through a silica plug, and were concentrated under reduced pressure.

Aqueous acetic acid (66%, 100 mL) was added to the resulting oil (8) and the solution was stirred vigorously at ambient temperature. After 16 h, the volatiles were evaporated under reduced pressure and the residue was partitioned between dichloromethane saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (2 × 250 mL) and the combined organic phases were dried over anhydrous magnesium sulfate and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [90:10] to hexanes:ethyl acetate [1:1]) afforded 9 (17.8 g, 57.4 mmol, 90%). Spectra were consistent with previously reported data.3,4


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**Methyl 3-O-benzyl-1,2-isopropylidene-α-L-idofuranosiduronate (12):**

To a suspension of silica gel (38 g) in dichloromethane (320 mL) was added a solution of sodium metaperiodate (5.25 g, 24.5 mmol) in water (38 mL). The suspension was stirred vigorously for 30 minutes, followed by addition of a solution of 9 (5.87 g, 18.9 mmol) in dichloromethane (30 mL). The reaction was vigorously stirred for 1.5 h, followed by filtration through celite and concentration under reduced pressure. The residue (10) was dried under vacuum over P₂O₅ and used without further purification.

To a flame-dried three-necked flask was added tris(phenylthio)orthoformate (7.74 g, 22.7 mmol), followed by tetrahydrofuran (30 mL). The reaction vessel was cooled to −78 °C and “butyllithium (1.6 M in hexanes, 13.0 mL, 20.8 mmol) was added dropwise. The bright yellow solution was allowed to warm slowly to −50 °C over 1 h, then cooled to −78 °C and stirred for 30 minutes. A solution of the crude aldehyde 10 (5.26 g, 18.9 mmol) in tetrahydrofuran (20 mL) and added dropwise via cannula to the reaction flask at −78 °C over 15 min. After 1 h, the reaction solution was allowed to warm to room temperature over 30 min, when excess anion was quenched by addition of a saturated aqueous ammonium chloride solution (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered, were concentrated under reduced pressure, and were dried under reduced pressure (~1 Torr). The crude thioorthoformate 11 was used without further purification.

To a suspension of copper chloride (1.38 g, 8.08 mmol) and copper oxide (0.263 g, 3.30 mmol) in methanol:water (12:1, 26 mL) was added a solution of crude 11 (1.08 g, 1.63 mmol) in dichloromethane (10 mL). After 5 min, the volatiles were removed under reduced pressure with gentle heat. The resulting green-white solid was dissolved in ethyl acetate (250 mL) and washed with aqueous hydrochloric acid (1 N, 2 × 24 mL), brine (2 × 50 mL), and saturated aqueous sodium bicarbonate solution (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, were filtered, were concentrated under reduced pressure (~1 Torr) for 1 h. The resulting oil was dissolved in dichloromethane (23 mL) and methanol (4 mL) and potassium carbonate (60 mg, 0.43 mmol) was added. After 1.5 h, the reaction solution was filtered through celite and was concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [90:10] to hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [75:25] to hexanes:ethyl acetate [70:30]) afforded 12 as a light yellow oil (437 mg, 83%). Spectra were consistent with reported data.5

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Methyl 3-O-benzyl-1,2-isopropylidene-α-L-idopyranosiduronate (14):

Compound 12 (7.52 g, 22.2 mmol) was dissolved in 90% aqueous trifluoroacetic acid (80 mL) and stirred at ambient temperature for 30 min. The reaction solvent was removed and the residue was azeotropically dried from toluene (5 × 30 mL), and dried under reduced pressure (~1 Torr) over phosphorous pentaoxide for 18 h. The resulting white solid 13 was dissolved in 2-methoxypropene (43 mL) and cooled to 0 ºC. To the cooled reaction mixture was added a solution of (+)-camphorsulfonic acid (529 mg, 2.23 mmol) in dimethylformamide (4.3 mL). After 1 h, the reaction mixture was basified with triethylamine (5 mL) and allowed to warm to ambient temperature. The volatiles were removed under reduced pressure and the reaction mixture was dried under reduced pressure (~1 Torr) for 18 h. The crude product was dissolved in methanol (60 mL), and Dowex acidic resin (50 mg) was added. After 30 min, the resin was filtered off and rinsed with excess dichloromethane. The solution phase was concentrated under reduced pressure and purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [75:25] to hexanes:ethyl acetate [66:33] to hexanes:ethyl acetate [33:66] to ethyl acetate) to afford isopropylidene 14 (4.15 g, 55%) and recovered triol 13 (1.89 g, 28%). Spectra were in agreement with reported data.6

Methyl 3-O-benzyl-1,2-isopropylidene-4-O-levulinyl-α-L-idopyranosiduronate (15):
To a solution of 14 (2.69 g, 7.95 mmol) in dichloromethane (50 mL) at 0 °C were added
levulinic acid (1.34 mL, 12.7 mmol), diisopropylcarbodiimide (DIPC, 1.87 mL, 11.9 mmol),
and dimethylaminopyridine (1.56 g, 12.8 mmol), and light was excluded. The reaction was
allowed to warm to ambient temperature and was stirred vigorously for 11 h. The reaction
mixture was diluted with hexanes:ethyl acetate (1:1) and excess urea removed by filtration
through a silica plug. The resulting solution was concentrated under reduced pressure and
the residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [70:30] to hexanes:ethyl acetate [50:50]) to afford levulinate 15 as a yellow oil (3.44 g, 98%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):
7.39-7.33 (m, 5H), 5.37 (d, $J = 2.61$ Hz, 1H),
5.20 (m, 1H), 4.82 (d, $J = 1.6$ Hz, 1H), 4.68 (d, $J = 1.6$ Hz, 1H), 4.53 (d, $J = 1.5$ Hz, 1H), 4.08
(app-t, $J = 2.1$ Hz, 1H), 3.93 (m, 1H), 3.8 (s, 3H), 2.75 (m, 2H), 2.56 (t, $J = 6.4$ Hz, 2H), 2.18
(s, 3H), 1.62 (s, 3H), 1.38 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):
206.9, 172.5, 168.9, 137.7, 129.3, 128.9, 128.6,
112.7, 97.2, 75.8, 73.5, 72.8, 70.7, 67.8, 38.5,
30.4, 28.7, 28.6, 26.9.

FTIR (thin film) cm$^{-1}$: 2934, 1766, 1742, 1721

HRMS–EI (m/z): calcd for C$_{22}$H$_{28}$NaO$_9$ [M+Na]$^+$: 459.1626,
found: 459.1617.

$[\alpha]^{24}$D: $-32.0$ (c 1.00, CH$_2$Cl$_2$)
Methyl (dimethylthexylsilyl-3-O-benzyl-4-O-levulinoyl-β-idopyranosid)uronate (19):

Isopropylidene 15 (503 mg, 1.15 mmol) was dissolved in 90% aqueous trifluoroacetic acid (10 mL) and stirred at ambient temperature for 15 min. The volatiles were removed under reduced pressure and the resulting oil azeotropically dried from toluene (5 × 10 mL), and dried under reduced pressure (~1 Torr) for 18 h. The resulting brown oil was dissolved in dichloromethane (1.2 mL) and imidazole (304 mg, 4.4 mmol) was added. The solution was cooled to −20 °C and dimethylthexylsilyl chloride (0.290 mL, 1.5 mmol) was added. After 41 h, saturated aqueous sodium bicarbonate solution (1 mL) was added and the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was partitioned between dichloromethane and brine, and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, were filtered, were concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [66:33] to hexanes:ethyl acetate [50:50]) to afford 19 as a clear oil (500 mg, 80%, α:β 1:2.5).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

(α isomer): 7.39-7.28 (m, 5H, ArH), 5.31 (s, 1H), 5.27 (app-t, $J = 2.8$ Hz, 1H), 4.97 (d, $J = 2.4$ Hz, 1H), 4.67 (dd, $J = 11.6, 14.0$ Hz, 2H), 3.78 (s, 3H), 3.76 (app-t, $J = 2.4$ Hz, 1H), 3.60 (br-d, $J = 10.1$ Hz, 1H), 2.73 (t, $J = 10.0$ Hz, 2H), 2.58-2.48 (m, 3H), 2.17 (s, 3H), 1.60-1.56 (m, 1H), 0.83-0.81 (m, 12H), 0.17 (s, 3H, SiCH$_3$), 0.14 (s, 3H, SiCH$_3$).

(β isomer): 7.38-7.32 (m, 5H, ArH), 5.17 (s, 1H, C4-H), 5.04 (app-s, 1H, C1-H), 4.77 (d, $J = 11.9$ Hz, 1H, ArCH$_2$), 4.63 (d, $J = 11.9$ Hz, 1H, ArCH$_2$), 4.60 (app-s, 1H, C5-H), 3.92-3.91 (m, 1H, C3-H), 3.80 (s, 3H, OCH$_3$), 3.58 (s, 1H, C2-H), 2.74-2.71 (m, 2H), 2.60-2.52 (m, 2H), 2.43 (d, $J = 4.9$ Hz, 1H, OH), 2.18 (s, 3H), 1.67-1.64 (m, 1H), 0.91-0.88 (m, 12H), 0.26 (s, 3H, SiCH$_3$), 0.19 (s, 3H, SiCH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C):

(α isomer): 206.4, 171.4, 169.4, 137.9, 128.4, 127.9, 127.7, 96.0, 75.0, 72.6, 69.3, 69.0, 66.5, 52.6, 38.0, 34.1, 29.8, 28.1, 25.0, 20.2, 20.1, 18.6, 18.6, −2.3, −3.5.

(β isomer): 206.4, 171.9, 168.1, 137.5, 128.7, 128.3, 128.0, 94.3, 75.2, 72.9, 72.7, 68.8, 67.5.
FTIR (thin film) cm\(^{-1}\):

(\(\alpha\) isomer): 1744 (s), 1719 (m), 1364 (w), 1153 (s), 1054 (s).

FTIR (thin film) cm\(^{-1}\):

(\(\beta\) isomer): 1768 (s), 1742 (s), 1721 (s), 1253 (m), 1154 (s), 1048 (s), 836 (m).

HRMS–EI (\(m/z\)):

(\(\alpha\) isomer): calcd for C\(_{27}\)H\(_{42}\)NaO\(_9\)Si[M+Na]\(^+\):
561.2490,
found: 561.2488.

HRMS–EI (\(m/z\)):

(\(\beta\) isomer): calcd for C\(_{27}\)H\(_{42}\)NaO\(_9\)Si[M+Na]\(^+\):
561.2490,
found: 561.2473.

\([\alpha]^{24}_D\):

(\(\alpha\) isomer): –54.9 (c 2.35, CH\(_2\)Cl\(_2\)).

\([\alpha]^{24}_D\):

(\(\beta\) isomer): +8.65 (c 1.90, CH\(_2\)Cl\(_2\)).
Methyl (dimethyldithexylsilyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-L-idopyranosid)uronate (20):

To a solution of silyl ether 19 (345 mg, 0.641 mmol) in dichloromethane (6 mL) were added acetic anhydride (0.120 mL, 1.28 mmol) and dimethylaminopyridine (130 mg, 1.07 mmol). After 2 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [66:33]) to afford 20 as a clear oil (363 mg, 97%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β, 1:2): 7.40-7.28 (m, 7.5H), 5.30 (s, 0.5H), 5.19 (app-s, 0.5H), 5.14 (app-s, 1H), 5.00-4.98 (m, 1.5H), 4.79-4.70 (m, 3.5H), 4.62 (d, $J = 1.8$ Hz, 1H), 3.87 (t, $J = 2.8$ Hz, 1H), 3.80-3.78 (m, 5H), 2.83-2.77 (m, 1.5H), 2.68-2.49 (m, 4.5H), 2.21-2.19 (m, 4.5H), 2.11-2.09 (m, 4.5H), 1.64-1.58 (m, 1.5H), 0.88-0.82 (m, 18H), 0.24-0.15 (m, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β, 1:2): 206.3, 172.1, 172.0, 170.5, 170.2, 169.4, 168.1, 137.7, 137.3, 128.8, 128.5, 128.3, 128.0, 127.9, 127.7, 93.3, 93.2, 77.5, 74.2, 73.1, 72.9, 72.7, 72.6, 68.6, 68.3, 67.7, 67.4, 66.1, 52.7, 52.6, 37.8, 37.8, 34.2, 34.2, 30.0, 30.0, 28.1, 28.1, 25.1, 25.0, 21.2, 21.2, 20.4, 20.2, 20.1, 20.0, 18.8, 18.7, 18.7, 18.6, -1.7, -2.4, -3.4, -3.5.

FTIR (thin film) cm$^{-1}$: 1744 (s), 1720 (w), 1231 (br-m), 1156 (m), 1055 (m).

HRMS–EI (m/z): calcd for C$_{29}$H$_{44}$NaO$_{10}$Si [M+Na]$^+$: 603.2596, found: 603.2600.
Methyl (dimethylthexysilyl 3-O-benzyl-4-O-levulinoyl-2-O-pivaloyl-L-idopyranosid)uronate (21):

To a solution of silyl ether 19 (541 mg, 1.00 mmol) in dichloromethane (10 mL) were added pivaloyl chloride (0.250 mL, 2.01 mmol) and dimethylaminopyridine (227 mg, 1.86 mmol). After 48 h, the reaction mixture was diluted with ethyl acetate:hexanes (1:1) and filtered through a silica plug. The solution phase was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [50:50]) to afford 21 as a clear oil (588 mg, 94%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C, mixture of diastereomers, $\alpha$: $\beta$, 1:0.3): 7.39-7.32 (m, 6.5H), 5.26 (app-s, 0.3H), 5.24 (app-s, 0.3H), 5.07 (m, 1H), 4.99 (d, $J = 2.0$ Hz, 0.3H), 4.98-4.97 (m, 1H), 4.78-4.70 (m, 3.6H), 4.57 (app-s, 1H), 3.80-3.78 (m, 3.9H), 3.71 (app-s, 0.3H), 2.78-2.68 (m, 2.6H), 2.56-2.53 (m, 2.6H), 2.19 (app-s, 3.9H), 1.63-1.59 (m, 1.3H), 1.26-1.21 (m, 11.7H), 0.87-0.82 (m, 15.6H), 0.22-0.15 (m, 7.8H).

$^{13}$C NMR (125 MHz, CDCl$_3$, 20°C, mixture of diastereomers, $\alpha$: $\beta$,): 206.2, 206.2, 177.8, 177.7, 172.2, 172.0, 169.3, 168.0, 137.7, 137.4, 128.7, 128.5, 128.3, 127.9, 127.7, 93.6, 93.4, 75.3, 73.7, 73.1, 72.8, 72.6, 68.5, 68.2, 67.3, 66.1, 52.7, 52.5, 39.1, 37.9, 37.9, 34.2, 34.1, 30.0, 29.9, 28.1, 28.1, 27.4, 27.3, 26.7, 25.1, 25.0, 20.2, 20.1, 18.7, 18.7, 18.7, 18.6, -1.7, -2.4, -3.4, -3.5.

FTIR (thin film) cm$^{-1}$: 1741 (s), 1368 (w), 1152 (s), 1053 (m), 837 (m).

HRMS-EI (m/z): calcd for C$_{32}$H$_{50}$NaO$_{10}$Si [M+Na]$^+$: 645.3065, found: 645.3080.
Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-L-idopyranosiduronate trichloroacetimidate (23):

To a solution of silyl ether 20 (890 mg, 1.53 mmol) in tetrahydrofuran (15 mL) was added HF·pyridine (70% solution, 1.0 mL). After 28 h, the reaction solution was diluted with water and extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [65:35] to hexanes:ethyl acetate [40:60]) provided the deprotected lactol 18. To a solution of this lactol in dichloromethane and trichloroacetonitrile (1:1, 10 mL) at 0°C was added DBU (5 μL) and the reaction mixture was allowed to warm over 30 min. The volatiles were removed under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [50:50]) to afford trichloroacetimidate 23 as a white foam (662 mg, 74%). Spectra corresponded to published data.7

Methyl 3-O-benzyl-4-O-levulinoyl-2-O-pivaloyl-1-idopyranosiduronate trichloroacetimidate (24):

To a solution of silyl ether 21 (588 mg, 0.94 mmol) in tetrahydrofuran (8 mL) was added HF-pyridine (70% solution, 0.7 mL). After 28 h, the reaction solution was diluted with water, was extracted with dichloromethane (3 × 40 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: hexanes:ethyl acetate [50:50]) provided the deprotected lactol 22. To a solution of this lactol in dichloromethane and trichloroacetonitrile (1:1, 7 mL) at 0 °C was added DBU (4 μL) and the reaction was allowed to warm to ambient temperature over 30 min. The volatiles were removed under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: hexanes:ethyl acetate [65:35]) to afford trichloroacetimidate 24 as a white foam (398 mg, 68%, equal mixture of diastereomers, α:β).

H NMR (500 MHz, CDCl₃, 20°C, equal mixture of diastereomers, α:β): 8.72 (s, 1H), 8.70 (s, 1H), 7.38-7.29 (m, 10H), 6.38 (s, 1H), 6.23 (app-s, 1H), 5.32 (s, 1H), 5.28-5.26 (m, 2H), 5.13 (s, 1H), 5.04 (s, 1H), 4.84-4.72 (m, 5H), 3.94 (t, J = 3.0 Hz, 1H), 3.83-3.80 (m, 7H), 2.79-2.68 (m, 4H), 2.57-2.53 (m, 4H), 2.19 (app-s, 6H), 1.25-1.23 (m, 18H).

C NMR (125 MHz, CDCl₃, 20°C, equal mixture of diastereomers, α:β): 206.0, 177.5, 177.2, 171.9, 171.8, 168.1, 167.2, 160.6, 160.0, 137.2, 137.0, 128.7, 128.4, 128.3, 127.9, 127.9, 127.7, 95.1, 94.3, 74.6, 73.3, 73.2, 72.6, 72.3, 67.8, 67.5, 67.5, 65.8, 65.0, 52.8, 52.7, 39.1, 38.9, 37.9, 29.8, 28.0, 27.3, 27.1.

FTIR (thin film) cm⁻¹: 1769 (w), 1741 (s), 1722 (m), 1677 (w), 1144 (s), 1064 (s).

HRMS–EI (m/z): calcd for C₂₆H₃₂Cl₃NNaO₁₆Si [M+Na]⁺: 646.0984, found: 646.0996.
p-Pentenyl methyl 3-O-benzyl-4-O-levulinoyl-2-O-pivaloyl-L-idopyranosiduronate (33):

Iduronic trichloroacetimidate 24 (398 mg, 0.637 mmol, 1 equiv) was azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 3 h. To a solution of this donor in dichloromethane (5 mL) at −25 °C was added 4-pentenol (72 μL, 0.70 mmol, 1.1 equiv), followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, 12 μL, 0.1 equiv). After 10 min, excess acid was quenched at low temperature by addition of triethylamine (100 μL) and the reaction solution was allowed to warm to ambient temperature. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [60:40]) to afford 33 as a clear oil (333 mg, 95%).

\[ \text{Iduronic trichloroacetimidate 24 (398 mg, 0.637 mmol, 1 equiv) was azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 3 h. To a solution of this donor in dichloromethane (5 mL) at −25 °C was added 4-pentenol (72 μL, 0.70 mmol, 1.1 equiv), followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, 12 μL, 0.1 equiv). After 10 min, excess acid was quenched at low temperature by addition of triethylamine (100 μL) and the reaction solution was allowed to warm to ambient temperature. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [60:40]) to afford 33 as a clear oil (333 mg, 95%).} \]

\[ \text{1H NMR (500 MHz, CDCl}_3, 20^\circ\text{C):} \]

\[ \text{7.38-7.28 (m, 5H), 5.81-5.76 (m, 1H), 5.23 (t, } J = 4.5 \text{ Hz, 1H), 5.00 (dd, } J = 3.5, 1.5 \text{ Hz, 1H), 4.97-4.93 (m, 2H), 4.92-4.91 (m, 1H), 4.88 (d, } J = 2.0 \text{ Hz, 1H), 4.80 (d, } J = 11.5 \text{ Hz, 1H), 4.69 (d, } J = 11.5 \text{ Hz, 1H), 3.79 (s, 3H), 3.77-3.74 (m, 1H), 3.71 (dd, } J = 4.0, 2.0 \text{ Hz, 1H), 3.52-3.49 (m, 1H), 2.77-2.70 (m, 2H), 2.55-2.52 (m, 2H), 2.18 (s, 3H), 2.18-2.11 (m, 2H), 1.73-1.67 (m, 2H), 1.20 (s, 9H).} \]

\[ \text{13C NMR (125 MHz, CDCl}_3, 20^\circ\text{C):} \]

\[ \text{206.2, 177.5, 171.9, 169.3, 138.2, 137.8, 128.5, 127.9, 127.7, 115.1, 98.7, 77.5, 77.2, 77.0, 73.3, 72.3, 68.3, 68.2, 66.7, 66.1, 52.7, 38.9, 37.9, 30.4, 29.9, 28.7, 28.1, 27.2.} \]

\[ \text{FTIR (thin film) } \text{cm}^{-1}: \]

\[ \text{2957 (w), 1741 (s), 1366 (w), 1149 (s), 1055 (m).} \]

\[ \text{HRMS–EI (m/z):} \]

\[ \text{calcd for C}_{29}\text{H}_{40}\text{NaO}_{10} [\text{M+Na}^+]: 571.2514,} \]

\[ \text{found: 571.2501.} \]
**n-Pentenyl methyl 3-O-benzyl-2-O-pivaloyl-1-idopyranosiduronate (6):**

To a solution of levulinate ester 33 (333 mg, 0.606 mmol, 1 equiv) in dichloromethane (6 mL) was added a solution of hydrazine in pyridine:acetic acid (0.5 M, 3:2, 2.5 mL, 2 equiv). After 1 h the reaction mixture was diluted with acetone and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [70:30]) to afford acceptor 6 as a yellow oil (266 mg, 97%).

**\(^1\)H NMR (500 MHz, CDCl\(_3\), 20°C):**

7.37-7.24 (m, 5H), 5.84-5.71 (m, 1H), 5.01-4.99 (m, 1H), 4.97-4.93 (m, 2H), 4.86 (d, \(J = 1.8\) Hz, 1H), 4.81 (d, \(J = 11.7\) Hz, 1H), 4.60 (d, \(J = 11.7\) Hz, 1H), 4.05 (d, \(J = 10.2\) Hz, 1H), 3.82 (s, 3H), 3.81-3.74 (m, 1H), 3.70-3.68 (m, 1H), 3.50 (dt, \(J = 9.6, 7.8\) Hz, 1H), 2.67 (d, \(J = 12.0\) Hz, 1H), 2.13 (dd, \(J = 13.5, 6.9\) Hz, 1H), 1.77-1.67 (m, 2H), 1.23 (s, 9H).

**\(^13\)C NMR (125 MHz, CDCl\(_3\), 20°C):**

177.4, 170.7, 138.6, 138.3, 129.1, 128.5, 128.3, 115.7, 99.5, 74.9, 72.4, 68.9, 68.8, 68.2, 67.1, 53.1, 39.5, 30.9, 30.4, 29.3, 27.8, 1.7.

**FTIR (thin film) cm\(^{-1}\):**

3582 (br-w), 2918 (s), 1739 (s), 1141 (s), 1210 (w), 1049 (s)

**HRMS–EI (m/z):**

calcd for C\(_{24}\)H\(_{34}\)NaO\(_8\) [M + Na]\(^+\): 473.2146, found: 473.2146.
**tert-Butyldimethylsilyl (Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosiduronate)-(1→4)-2-azido-6-O-acetyl-4-O-benzyl-2-deoxy-β-D-glucopyranoside (31):**

Trichloroacetimidate 23 (1.390 g, 2.39 mmol, 1.3 equiv) and glucosamine 30 (832 mg, 1.84 mmol, 1 equiv) were combined and azeotropically dried from toluene (3 × 20 mL) and dried under reduced pressure (~1 Torr) over phosphorous pentaoxide for 18 h. To a solution of this mixture in dichloromethane (25 mL) at -20 °C to -10 °C was added trimethylsilyl trifluoromethanesulfonate (TMSOTf, 44 μL, 0.24 mmol, 0.1 equiv), and the reaction mixture was allowed to warm to -10 °C over 30 min. Excess triflic acid was quenched by addition of triethylamine (200 μL), and the reaction was allowed to warm to ambient temperature. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [50:50]) to afford disaccharide 31 as a clear oil (1.548 g, 95%).

**1H NMR (500 MHz, CDCl3, 20°C):**

7.39-7.21 (m, 10H), 5.10 (s, 1H), 5.08 (t, J = 3.0 Hz, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.85 (s, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.53 (d, J = 8.0 Hz, 1H), 4.52 (dd, J = 12.0, 2.5 Hz, 1H), 4.14 (dd, J = 11.5, 5.5 Hz, 1H), 3.85 (t, J = 9.5 Hz, 1H), 3.80 (t, J = 3.0 Hz, 1H), 3.50-3.47 (m, 1H), 3.44 (s, 3H), 3.36 (dd, J = 10.0, 7.5 Hz, 1H), 3.23 (t, J = 9.5 Hz, 1H), 2.81-2.74 (m, 1H), 2.67-2.61 (m, 1H), 2.58-2.52 (m, 1H), 2.49-2.43 (m, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H).

**13C NMR (125 MHz, CDCl3, 20°C):**

206.2, 171.9, 170.7, 170.1, 168.7, 138.1, 137.5, 128.6, 128.4, 128.3, 128.1, 127.6, 97.7, 97.4, 81.0, 74.8, 74.7, 73.6, 72.8, 7.27, 68.9, 68.1, 67.3, 66.8, 62.5, 52.3, 37.7, 30.0, 28.0, 25.8, 21.1, 21.1, 18.2, -4.2, -5.0.

**FTIR (thin film) cm⁻¹:**

2929 (m), 2111 (s), 1743 (s), 1367 (m), 1260 (s), 1231 (s), 1158 (m), 1107 (s), 1071 (s), 1043 (s), 840 (m).

**HRMS–EI (m/z):**

Caled for C_{42}H_{57}N_{3}O_{18}NaSi [M+Na]⁺: 894.3400, found: 894.3462.
Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosiduronate-(1→4)-2-azido-6-O-acetyl-4-O-benzyl-2-deoxy-β-D-glucopyranoside trichloroacetimidate (5):

To a solution of silyl ether 31 (1.663 g, 1.87 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added acetic acid, followed by a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 3.71 mL, 3.7 mmol, 2 equiv). After 3 h, the reaction solution was diluted with ethyl acetate (150 mL) and washed sequentially with aqueous sodium bicarbonate solution (1%) and brine. The combined aqueous layers were extracted with ethyl acetate (2 × 75 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, were concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [65:35] to hexanes:ethyl acetate [25:75]) to afford lactol 32 as a yellow foam (1.256 g, 89%).

To a solution of lactol 32 (88 mg, 0.12 mmol, 1 equiv) in dichloromethane: trichloroacetonitrile (1:1, 3 mL) at 0 °C was added DBU (3 drops). After 10 min, the reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [50:50]) to afford trichlroacetimidate 5 (95 mg, 91%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

8.77 (s, 1H), 7.43-7.19 (m, 10H, ArH), 6.42 (d, $J = 3.7$ Hz, 1H), 5.13 (s, 1H), 5.09-5.06 (m, 1H), 4.95-4.90 (m, 2H), 4.75 (d, $J = 11.0$ Hz, 1H), 4.70 (d, $J = 11$ Hz, 1H), 4.67 (d, $J = 11.0$ Hz, 1H), 4.62 (d, $J = 11.0$ Hz, 1H), 4.49 (app-d, $J = 12.2$ Hz, 1H), 4.22 (dd, $J = 12.5$, 2.8 Hz, 1H), 4.07-4.04 (m, 1H), 3.87-3.81 (m, 2H), 3.73 (dd, $J = 10.4$, 3.7 Hz, 1H), 3.46 (s, 3H, OCH$_3$), 2.77 (ddd, $J = 18.3$, 8.2, 5.2 Hz, 1H), 2.65 (ddd, $J = 18.6$, 6.7, 4.9 Hz, 1H), 2.55 (ddd, $J = 17.4$, 8.2, 4.9 Hz, 1H), 2.47 (ddd, $J = 17.4$, 6.7, 5.2 Hz, 1H), 2.18 (s, 3H), 2.09 (s, 3H), 2.09 (s, 3H).
**n-Pentenyl (Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-O-acetyl-4-O-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) methyl 3-O-benzyl-4-O-levulinoyl-2-O-pivaloyl-L-idopyranosiduronate (34):**

Trichloroacetimidate 5 (125 mg, 0.139 mmol, 1.3 equiv) and iduronic acid 6 (48.9 mg, 0.109 mmol, 1 equiv) were combined and azeotropically dried from toluene (3 x 5 mL) and dried under reduced pressure (~1 Torr) for 18 h. To a solution of this mixture in dichloromethane (1 mL) was added freshly activated 4 Å molecular sieves (100 mg) and the suspension was stirred vigorously. After 30 min, the reaction mixture was cooled to -20 °C. Trimethylsilyl trifluoromethane sulfonate (2.5 μL, 0.013 mmol, 0.1 equiv) was added and the reaction allowed to warm to -10 °C over 30 min. Excess acid was quenched by addition of triethylamine (50 μL) and the reaction was allowed to warm to ambient temperature. The reaction solution was filtered through celite to remove the molecular sieves and the resulting solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [50:50]) to afford trisaccharide 34 as a light yellow oil along with trichloroacetamide impurity 35 (93.7 mg, 73%, 34:35, 4:1).

**1H NMR (500 MHz, CDCl₃, 20°C):**

34: 7.39-7.24 (m, 15H), 5.82-5.76 (m, 1H), 5.16 (d, J = 3 Hz, 1H), 5.10 (t, J = 3.5 Hz, 1H), 5.04 (d, J = 3.5 Hz, 1H), 5.02 (d, J = 1.5 Hz, 1H), 4.99-4.94 (m, 2H), 4.87 (dd, J = 7.0, 3.5 Hz, 2H), 4.80 (dd, J = 10.5, 5.5 Hz, 2H), 4.75 (d, J = 4.0 Hz, 1H), 4.73 (d, J = 2.0 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.66 (d, J = 10.5 Hz, 1H), 4.47 (d, J = 12.5 Hz, 1H), 4.22 (dd, J = 12.5, 3.0 Hz, 1H), 4.12 (t, J = 4.5 Hz, 1H), 3.95-3.92 (m, 2H), 3.81-3.71 (m, 3H), 3.73 (s, 3H, OCH₃), 3.54-3.48 (m, 1H), 3.50 (s, 3H, OCH₃), 3.33 (dd, J = 10, 3.5 Hz, 1H), 2.78-2.71 (m, 1H), 2.70-2.63
^1H NMR (500 MHz, CDCl₃, 20°C):

35: 7.44-7.21 (m, 9H), 7.07-7.04 (m, 1H), 5.63 (app-t, J = 5.8 Hz, 1H), 5.18-5.06 (m, 2H), 4.91 (app-t, J = 2.7 Hz, 1H), 4.87 (d, J = 3.3 Hz, 1H), 4.86-4.84 (m, 1H), 4.82-4.79 (m, 1H), 4.78-4.65 (m, 1H), 4.55 (app-d, J = 3.2 Hz, 1H), 4.47-4.38 (m, 1H), 4.29-4.10 (m, 1H), 4.03-3.98 (m, 1H), 3.95-3.91 (m, 1H), 3.84-3.73 (m, 1H), 3.72-3.69 (m, 1H), 3.59 (s, 3H), 3.60-3.54 (m, 1H), 2.84-2.43 (m, 4H), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H).

HRMS–EI (m/z):

-calcd for 34 \( \text{C}_{60}\text{H}_{75}\text{N}_3\text{NaO}_{22} \) [M+H]^+: 1212.4734,

-found: 1212.4766.
n-Pentenyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-O-acetyl-4-O-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) methyl 3-O-benzyl-2-O-pivaloyl-L-idopyranosiduronate (36):

To a solution of trisaccharide 34 (93.7 mg, 0.078 mmol, 1 equiv) in dichloromethane (500 μL) was added a solution of hydrazine in pyridine:acetic acid (0.5 M, 3:2, 230 μL, 0.117 mmol, 1.5 equiv). After 1.5 h, excess hydrazine was quenched by addition of acetone (1 mL) and the reaction solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40] to hexanes:ethyl acetate [50:50]) to afford acceptor 36 as a clear oil (64.4 mg, 76%).

$^1$H NMR (500 MHz, CDCl$_3$, 20°C):

7.42-7.25 (m, 15H, ArH), 5.84-5.75 (m, 1H), 5.10-4.61 (m, 15H), 4.49-4.43 (m, 2H), 4.24 (dd, $J = 12.2$, 3.4 Hz, 1H), 4.12 (app-t, $J = 4.3$ Hz, 1H), 4.00-3.91 (m, 3H), 3.90-3.82 (m, 1H), 3.80-3.69 (m, 2H), 3.55 (d, $J = 4.0$ Hz, 1H), 3.52 (s, 3H), 3.51-3.48 (m, 1H), 3.33 (dd, $J = 10.4$, 3.7 Hz, 1H), 2.62 (br-s, 1H, OH), 2.15-2.07 (m, 8H), 1.74-1.66 (m, 2H), 1.22 (s, 9H).
n-Pentenyl (Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-O-acetyl-4-O-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) (Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-O-acetyl-4-O-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) methyl 3-O-benzyl-4-O-levulinyl-2-O-pivaloyl-L-idopyranosiduronate (37):

Trichloroacetimidate 5 (70.2 mg, 0.078 mmol, 1.3 equiv) and trisaccharide 36 (64.4 mg, 0.059 mmol, 1 equiv) were combined and azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 18 h. To a solution of this mixture in dichloromethane (1 mL) was added freshly activated 4 Å molecular sieves (70 mg) and the suspension was stirred vigorously. After 30 min, the reaction mixture was cooled to -20 °C. Trimethylsilyl trifluoromethane sulfonate (5.0 μL, 0.027 mmol, 0.45 equiv). After 30 min, excess acid was quenched by addition of triethylamine (50 μL) and the reaction was allowed to warm to ambient temperature. The reaction solution was filtered through celite to remove the molecular sieves and the resulting solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25] to hexanes:ethyl acetate [66:34] to hexanes:ethyl acetate [50:50]) to afford pentasaccharide 37 as a white foam along with trichloroacetamide 35 (75.8 mg, 70% (37:35, 4:1)).

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3, 20^\circ \text{C}):\)

7.42-7.23 (m, 25H), 5.84-5.75 (m, 1H), 5.31 (d, \(J = 4.7 \text{ Hz}, 1\text{H})

5.16 (d, \(J = 2.9 \text{ Hz}, 1\text{H)

5.10-5.07 (m, 1H), 5.06-4.99 (m, 3H), 4.98-4.95 (m, 4H), 4.94-4.89 (m, 1H), 4.88-4.84 (m, 4H), 4.81-4.66 (m, 8H), 4.64-4.59 (m, 1H), 4.52-4.39 (m, 2H), 4.23 (dd, \(J = 12.6, 3.3 \text{ Hz}, 1\text{H})

4.19 (dd, \(J = 12.6, 2.9 \text{ Hz}, 1\text{H})

4.11 (t, \(J = 4.4 \text{ Hz}, 1\text{H})
1H), 4.02-3.99 (m, 1H), 3.97-3.79 (m, 5H), 3.76 (s, 3H, OCHO), 3.63 (dd, J = 10.2, 9.1 Hz, 1H),
3.50 (s, 3H, OCH3), 3.48 (s, 3H, OCH3), 3.34-
3.28 (m, 3H), 2.80-2.62 (m, 3H), 2.57-2.43 (m,
2H), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H),
2.07 (s, 3H), 2.04 (s, 3H), 1.73-1.66 (m, 1H),
1.35-1.18 (m, 12H),

HRMS–EI (m/z):
calcd for C91H110N6NaO34 [M+H]+: 1853.6955,
found: 1853.6989.
Appendix A

Spectra for Chapter 1

Thesis Advisor: Mohammad Movassaghi
1:1 mixture of diastereomers
1:1 mixture of diastereomers
1:1 mixture of diastereomers
STANDARD CARBON PARAMETERS
exp2 2pul

SAMPLE

date Apr 21 2005 dfreq 499.747
solvent Benzene dn M
file /data/export/~ dfwp 34
home/movies/rob/hump dof 9
bulklink/rob-V-1- dm YYY
28_carbon.fid dam w

ACQUISITION
def 100080

sfreq 125.673 dseq 1.0
at 0.888 homo n
np 32480
sw 30234.3 lb 1.00
fb not used wfile ft
bs 4 proc
ss 1 fn 131072
tpw 5.8 math f
pw 7.5
d1 3.000 warr
wex 565.4 wexp
nt 10000 vbc
cx 5116 wnt
alock n

gain not used

FLAGS

sp -2551.9
wp 30233.0
vs 2288
c0 0
wc 250
hzn 120.94
lt 500.00
rr 2052.0
rfp 0
th 66
ins 1.000
al cdc ph

200 180 160 140 120 100 80 60 40 20 0 ppm
Current Data Parameters

EXPNO: 1
PROCNO: 1

F1 - Acquisition Parameters

Date: 20060111
Time: 7.54
INSTRUM: spect
PROBMD: 5mm BB6 NS-1
PULPROG: zpgp10
TD: 65536
SOLVENT: C6D6
NS: 13187
DB: 4
SW: 24875.621 Hz
PDRES: 0.375572 Hz
AQ: 1.3173236 sec
DG: 1.192
DN: 20.100 usec
DE: 6.00 usec
TE: 300.0 K
D1: 2.00000000 sec
d11: 0.03000000 sec
d12: 0.00002000 sec

---------- CHANNEL f1 ----------

NUC1: 13C
F1: 15.25 usec
PL1: 0.010 dB
SFO1: 100.6237959 MHz

---------- CHANNEL f2 ----------

CHFDOE: wait216
NUC2: 1H
PC02: 107.50 usec
PL2: 0.000 dB
PL12: 24.000 dB
PL13: 24.000 dB
SF02: 400.11314005 MHz

F2 - Processing parameters

SI: 12768
SF: 100.6127290 MHz
VWM: 21M
SBB: 0
LB: 1.00 Hz
RB: 0
PC: 1.40

1D NMR plot parameters

CH: 20.00 cm
PF: 233.416 ppm
PH: 23504.7 Hz
PF: -13.625 ppm
F2: -1370.90 Hz
FWCM: 12.36206 ppm/cm
H2CM: 1243.7511 Hz/cm

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
SAMPLE

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dpwr 37
home/advatag/M60/
dof -500.0
rocky/GM-VI-144.c
dm Y
arbon.fld dm Y

ACQUISITION

efreq 125.754
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ln C13
dres 1.0
np 182882
sw 236314.9
fb not used
bs 6
ss 1
spwr 53
pw 6.9
dil 0.763
wexn
nt 1
ct 10184
lock n

gain not used

FLAGS

dl n
dp y
hs n

DISPLAY

sp -825.9
wp 236314.9
v5 117.
sC 0
wc 250
hzmm 85.58
t5 550.00
rf1 16777.7
rf2 18111.4
th 20
in 1.000
ai ph

180 160 140 120 100 80 60 40 20
ppm

(-100)

H
HO

H
H

H

H

H

H

H

H

H

Me

Cbz

O

O
Pulse Sequence: gCOSY
Solvent: Benzene
Ambient temperature

INNOVA-500 "Zippy"
PULSE SEQUENCE: gCOSY
Relax. delay 1.000 sec
Acq. time 0.298 sec
Width 4093.7 Hz
2D Width 4093.7 Hz
28 repetitions
128 increments

DATA PROCESSING
SH. 1, 499.7Hz 815 MHz
F1 DATA PROCESSING
Sq. sine bell 0.118 sec
F1 size 2048 x 2048
Total time 0 min, -1 sec
Pulse Sequence: gCOSY
Solvent: Benzene
Ambient temperature
INDOA-500 "Zippy"
PULSE SEQUENCE: gCOSY
Relax, delay 1.000 sec
Acq. time 0.241 sec
Width 4247.2 Hz
2D Width 4247.2 Hz
24 repetitions
128 Increments
OBSERVE H1 400.7446814 MHz
DATA PROCESSING
Sqw. sine bell 0.120 sec
F1 DATA PROCESSING
Sqw. sine bell 0.030 sec
FT size 2048 x 2048
Total time 0 min, -1 sec
Pulse Sequence: HSQC
Solvent: Benzene
Ambient temperature
User: 1-14-87
INOV-500 "zippy"

PULSE SEQUENCE: HSQC
Relax. delay 1.000 sec
Acq. time 0.005 sec
Width 4444.8 Hz
2D Width 22222.8 Hz
32 repetitions
2 × 256 increments
OBSERVE H1 499.7466817 MHz
DECOUPLE C13 125.6721325 MHz
Power 52 dB
on during acquisition
off during delay
GARP-1 modulated

DATA PROCESSING
Gauss apodization 0.107 sec
F1 DATA PROCESSING
5q sine bell 0.023 sec
Shifted by -0.023 sec
FFT size 2048 × 2048
Total time 6 hr, 52 min, 27 sec
ROESY

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F1 - Acquisition parameters
Date: 20060127
Time: 15:54
INSTROM spect
PROBES: 5 mm CPTX Z-G
PULPROG: roesyph
TO: 1024
SOLVENT: CD6D
NS: 24
DS: 16
SNH: 4807.692 Hz
FIDRES: 4.695012 Hz
AQ: 0.1066500 sec
RG: 128
DM: 104.000 usec
DE: 6.00 usec
TE: 295.0 K
D0: 0.00009431 sec
D1: 0.69999999 sec
D12: 0.00000000 sec
D10: 0.00000000 sec
MCWST: 0.00000000 sec
MCNWX: 0.69999999 sec

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F1 - Acquisition parameters
ND0: 1
TD: 480
SP01: 600.4674 MHz
FIDRES: 10.016026 MHz
SM: 8.007 ppm
PRMODE: T1P1

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F1 - Processing parameters
SI: 3248
SF: 600.4650000 MHz
SW: SINE
SSB: 2
LB: 0.00 Hz
GC: 0
PC: 1.00

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F1 - Processing parameters
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**DISPLAY**

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563.9
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250
115.52
590.80
16187.5
18131.4
26
1.000

**Diagram**

![Chemical Structure](image)
Pulse Sequence: gCOSY

PULSE SEQUENCE: gCOSY
Relax. delay 1.000 sec
Acq. time 0.213 sec
Width 4801.9 Hz
2D Width 4801.9 Hz
16 repetitions
128 increments

OBSEERVE H1 410.7446813 MHz
DATA PROCESSING
Se. sine bell 0.107 sec
F1 DATA PROCESSING
Se. sine bell 0.027 sec
F1 size 2048 x 2048
Total time 0 min, -1 sec
Pulse Sequence: HSQC
Solvent: Benzene
Ambient temperature
Date: 1-14-87

Pulse sequence:

- Relax. delay 1.000 sec
- Acq. time 0.100 sec
- Width 540.4 Hz
- 20 Width 26400.1 Hz
- 10 repetitions
- 2 x 389 increments
- OBSERVE H1, 498.744668 MHz
- DECOUPLE C13, 125.6740715 MHz
- Power 52 dB
- On during acquisition
- Off during delay
- GARP-1 modulated

Data processing:
- Gauss apodization 0.104 sec
- F1 DATA PROCESSING
- "q, sine bell 0.013 sec
- "Shifted by -0.019 sec
- FT size 2048 x 2048
- Total time 9 hr, 2 min, 7 sec

(-)-gaoulimima Alkaloid 13 (2)
natural (−)-galbulimima alkaloid 13

Pulse Sequence: gCOSY
Solvent: Benzene
Ambient temperature

PULSE SEQUENCE: gCOSY
Relax. delay 1.086 sec
Acq. time 8.227 sec
Width 4587.9 Hz
2D Width 4587.9 Hz
64 repetitions
128 Increments
OBSERVE H1: 498.7445840 MHz
DATA PROCESSING
SQ. time bell 0.113 sec
1D DATA PROCESSING
SQ. time bell 0.028 sec
FT size 2048 x 2048
Total time 0 min, -1 sec

(-)-2-epi-16-Oxohimaline
(108)
Pulse Sequence: HSQC
Solvent: Benzene
Ambient temperature

PULSE SEQUENCE: HSQC
Relax. delay 1.000 sec
Acq. time 0.257 sec
Width 4587.6 Hz
2D width 27692.5 Hz
32 repetitions
2 x 256 increments
OBSERVE H1, 499.7443840 MHz
DECOUPLE C13, 125.6746638 MHz
Power 52 dB
on during acquisition
do during delay
QAP-1 modulated
DATA PROCESSING
Gauss apodization 0.105 sec
F1 DATA PROCESSING
Sine, sine bell 0.019 sec
Shifted by -0.018 sec
FT size 2048 x 2048
Total time 7 hr, 27 min, 44 sec

(-)-2-epi-16-Oxohimaline
(108)
Appendix B

Spectra for Chapter 2

Thesis Advisor: Peter H. Seeberger
Appendix C

Spectra for Chapter 3

Thesis Advisor: Peter H. Seeberger
MeO₂C

O

OBn

OTDS

OLev OAc

20
Diana Katharine Hunt  
*Curriculum Vitae*

**Education**

Massachusetts Institute of Technology, Cambridge, MA.  
Ph.D. Organic Chemistry (expected 2006)  

Swarthmore College, Swarthmore, PA.  
BA, major in Chemistry, 1999  
Thesis title: "Enantiopure Eight and Nine-Membered Carbocycle Synthesis via Transition Metal Catalyzed Ring-Closing Metathesis."

**Research Experience**

2003-present  
Graduate Research Associate, Massachussetts Institute of Technology  
Dr. Mohammad Movassaghi, Advisor.  
- Progress toward the total synthesis of galbulimima alkaloid 13 and himgaline.

2000-2003  
Graduate Research Associate, Massachussetts Institute of Technology  
Dr. Peter H. Seeberger, Advisor.  
- Investigated the modular synthesis of FGF-2 binding heparin pentasaccharide in solution for application to automated solid phase synthesis.  
- Investigated linker influence on the stereochemical outcome of glycosylations with resin-bound glycosyl phosphates.

1999-2000  
Research Intern, Pfizer Research and Development (formerly Parke-Davis)  
Dr. Charles Stankovic, Supervisor.  
- Worked on a broad range of synthetic projects including large scale synthesis of intermediates and exploratory work for development of new routes.

1998-1999  
Undergraduate Researcher, Swarthmore College  
Dr. Robert S. Paley, Advisor.  
- Prepared eight and nine-membered carbocycles via ring-closing metathesis of organometallic complexes.

1997  
Undergraduate Researcher, University of Michigan  
Dr. Coleen Pugh, Advisor.  
- Investigated the effect of immiscible components on smectic layer induction in nematic liquid crystals.  
- Preparation and purification of liquid crystals and analysis via differential scanning calorimetry.
Teaching Experience
2004-present Volunteer docent, Museum of Science, Boston.
2003 Teaching assistant for graduate level organic synthesis course (one semester); MIT.
2000-2001 Teaching assistant for introductory organic chemistry (three semesters); MIT, Head TA Fall 2001.
1999 Student tutor, organic chemistry; Swarthmore College.
1997-1999 Laboratory teaching assistant for organic chemistry; Swarthmore College.
1997-1999 Writing Associate; Swarthmore College.

Awards
2004 Wyeth Scholar Travel Award, MIT.
2001 Excellence in Teaching Award, MIT.
1998 Stanley Adamson Award for Excellence in Chemistry, Swarthmore College.

Publications


Small, A. C.; Hunt, D. K.; Pugh, C. “Induction of Smectic Layering in Nematic Liquid Crystals using Immiscible Components. III. The Effect of Lateral \( n \)-Alkanoyl Substituents on the Thermotropic Behaviour of \( 2,5\text{-bis}[4'(n\text{-Perfluoroheptyloxy})\text{benzoyloxy}]\text{toluene} \)” J. of Liquid Crystals 1999, 26, 849-857.

Presentations


Affiliations
American Chemical Society
Sigma Xi Research Society