Activation of Weak Nucleophiles in Anion-Binding Catalysis

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ACTIVATION OF WEAK NUCLEOPHILES IN ANION-BINDING CATALYSIS

A dissertation presented

by

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to

The Department of Chemistry and Chemical Biology

In partial fulfillment of the requirements

for the degree of

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Chemistry

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Activation of Weak Nucleophiles in Anion-Binding Catalysis

Abstract

Anion-binding catalysis has emerged as a powerful principle for the development of highly enantioselective transformations. This strategy relies on the ability of dual hydrogen-bond donors to promote anion abstraction from neutral substrates to generate cationic electrophiles such as iminium ions and oxocarbenium ions. Activation of nucleophiles in anion-binding reactions can further expand the scope of both electrophiles and nucleophiles in this mode of catalysis. The research described in this dissertation explores the use of thiourea catalysts to activate weak nucleophiles in two distinct reactions.

In Chapter 1, a diastereoselective glycosylation reaction of glycosyl halides is reported. The transformation is catalyzed by macrocyclic bis-thiourea catalysts to afford β-glycosides. Experimental and computational evidence indicate a stereospecific, invertive mechanism in which thiourea moieties facilitate leaving group departure and the amide carbonyl group of the catalyst activates alcohol nucleophiles via general base catalysis.

In Chapter 2, an enantioselective aza-Sakurai cyclization of chlorolactams is described. The reaction is effected by an electron-rich thiourea catalyst to provide an efficient entry into indolizidine and quinolizidine frameworks. Structure-enantioselectivity relationship studies and mechanistic analysis point to a dual role of the catalyst wherein the thiourea moiety of the catalyst is engaged in both generation of electrophile and Lewis base activation of allylsilane.
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Acknowledgements

First and foremost, I would like to thank Eric. For the past six years, he has been a wonderful mentor and a great friend. I am grateful for the opportunity to be a part of his lab where he always tries to set high standards and cultivate a professional environment. I am thankful for the independence he has granted me which allowed me to pursue my own research in ways that interest me (but often times wouldn’t interest him) and the trust he had in me. I have appreciated his patience and honesty for all these years and I always will. Despite all the ups and downs we’ve had over the years, it’s been a great journey and it saddens me greatly that my time here is coming to an end.

I’d also like to thank Nicole who makes our job so much easier. There’s a lot of work behind the scenes that we take for granted, but it’s only made possible for her hard work.

I’d like to express my gratitude towards Matt and Tobias who served on my GAC. Even though it was difficult for me at times to see immediately where they were coming from, looking back at this moment, their questions and advice have been invaluable for my professional development. Also thanks to Emily and Christina for serving on my thesis committee at the last minute.

One of the perks of working in the Jacobsen lab is working with the best chemists from all over the world, and I’ve been fortunate enough to have fruitful collaboration with some of those. I’d like to thank Corinna for taking me under her wing. I’ve always been impressed by her unwavering optimism, which I still lack to this day, and relentless and fearless approach to solving problems. Working with Kaid was probably the best experience during my stay here. He’s shown me what it’s really like to work in a phys org lab, and I’ve learned so much from
him. Aside from all the bickering over $S_N1$ and $S_N2$, it was awesome to just shoot the shit all the time from if the Cubs would ever win it all (hey, maybe 2016 is the year. I’m still hoping for the jays cubs series) to what the best Ozzy song is. Working with Nadine was also great. She’s always brought the smile and positive energy to the glycosylation team. She’s made a great progress toward developing the small molecule version of retentive glycosyltransferase, and I hope to see that work reaching its full potential one day. Richard is one of the most talented undergrads I’ve met here, and I have no doubt he will continue to produce great work in the Buchwald group. Sam and Alison joined the glycosylation project near the end of my time here and I wish them the best of luck in advancing the project beyond everything I could’ve hoped for. It’s been a great pleasure working with Eugene on the KIE project. It’s good to know there’s another skeptic, and I’ve learned more NMR and computational chemistry from him than I was ever willing to. I also had an opportunity of collaborating outside of the lab with Seungjun. Although it was brief and we didn’t really get anything done, it’s been refreshing to learn how to look at things from an inorganic perspective.

Two postdocs, Charles and Pam, have had a significant impact on me in a lot of ways. Charles is one of those special individuals who don’t seem to have any negative thought yet provide a realistic perspective. Since we worked in the end of the main lab, we were just stuck with each other all day in our bay, but working next him for three years was really awesome. I couldn’t have asked for a better baymate. Pam also has been a great mentor. She’d know which experiments would be the best to test a hypothesis, and wouldn’t let me talk myself out of an experiment (dtfe).

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kinds of things over lunch from some obscure chemical reactions to heavy metal. I’d also like acknowledge Amanda; we are two snarky peas in a pod. I appreciate all the support and friendship, especially in my last year. Thanks to Heejun for all the “chimek” runs and baseball talks that made some late nights more enjoyable. Last but not least, friends and family outside the department have been a great source of support and inspiration. I hesitate listing them here for fear of leaving anyone out, but you know who you are. Thank all of you again for everything.
List of Abbreviations

α alpha
Ac acetyl
Alloc allyloxycarbonyl
aq aqueous
β beta
9-BBN 9-Borabicyclo[3.3.1]nonane
Bn benzyl
Bu butyl
Boc tert-butyloxycarbonyl
°C degree Celcius
calcd. calculated
DCM dichloromethane
DFT density functional theory
DIAD diisopropyl azodicarboxylate
DMSO dimethyl sulfoxide
d.r. diastereomeric ratio
EDC·HCl 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee enantiomeric excess
equiv equivalents
Et ethyl
EtOAc ethyl acetate
g gram
GC  gas chromatography
h  hour
HOBT  1-Hydroxybenzotriazole
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry
Hz  hertz
i  iso
IBO  isobutylene oxide
IR  infrared
KIE  kinetic isotope effects
LAH  lithium aluminum hydride
m  milli
M  molar
M06-2X  Minnesota 2006 hybrid meta density functional theory
Me  methyl
min  minute
mol  mole
µ  micro
NMR  nuclear magnetic resonance
Ph  phenyl
Pr  propyl
PyAOP  (7-Azabenzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate
rt  room temperature
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$</td>
<td>tert</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBME</td>
<td>methyl tert-butyl ether</td>
</tr>
<tr>
<td>TCDI</td>
<td>1,1'-Thiocarbonyldiimidazole</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TMS</td>
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Chapter 1

β-Selective Glycosylation Reactions Catalyzed by
Macroyclic Bis-Thiourea Catalysts

1.1 Introduction

Carbohydrates are essential to the fundamental processes of life, providing energy, constituting structural components, and modulating signaling pathways. Despite their biological significance, the synthesis of oligosaccharides has not reached the level of generality and practicality as has been achieved with proteins and nucleic acids, which has helped to transform our understanding of these biomolecules. The primary technological gap in sugar synthesis is predominantly associated with controlling the stereochemistry (α or β) of glycosidic bonds. A general solution to the stereoselective synthesis of either diastereomer remains elusive.

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1 Portions of this chapter have been prepared for publication: Park, Y.; Harper, K. C.; Kuhl, N.; Liu, R. Y.; Jacobsen, E. N. Manuscript in preparation.
Stereocontrol in glycosylation has largely been achieved by utilizing substituents and protecting groups. Since the stereochemistry of the substituents and the electronic properties of the protecting groups can strongly influence the stereochemical outcome, the synthesis of a specific linkage pattern requires a tailored approach using a unique combination of substrates and reaction conditions. While this strategy has enabled chemists to access numerous carbohydrates, its substrate-dependent nature has resulted in a plethora of substrate-specific methods, requiring a high level of specialized training in organic and/or enzymatic synthesis to determine the most suitable approach to a specific target. Alternatively, diastereocntrol can be addressed by using a chiral catalyst to direct the nucleophilic addition to a specific face of the oxocarbenium intermediate. This strategy has been shown feasible in a study in which the asymmetric alkylation of α-chloroisochroman with silyl ketene acetal nucleophiles is accomplished by the use of a chiral thiourea catalyst (Scheme 1.1). This precedent, combined with the recent uses of achiral hydrogen bond donors in glycosylation reactions, led us to examine the effect of chiral thioureas on the diastereoselectivity of glycosylation processes.

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Scheme 1.1. Asymmetric alkylation of α-chloroisochroman with silyl ketene acetal

### 1.2 Catalyst Optimization

Our initial investigations were carried out in a model O-mannosylation reaction, where the formation of the β-diastereomer is disfavored sterically and stereoelectronically (Table 1.1).\(^{10}\) A mixture of diastereomers (52:48 d.r.) was obtained in small quantities using monomeric thiourea catalyst 1.1 (Table 1.1, entry 2). The low reactivity of 1.1 prompted us to explore a dimeric catalyst (1.2) that was specifically designed to promote anion-binding by mimicking the chloride binding behavior of its two monomeric subunits (Table 1.1, entry 3).\(^{11}\) As expected, an improvement in yield is observed, but the enhanced β-selectivity observed (80:20 d.r.) implies that 1.2 catalyzes a reaction mechanism that is difficult to access with the monomer. Indeed, increasing the catalyst loading of 1.1 affords diastereoselectivity more similar to that obtained with 1.2, suggesting the cooperativity between the two monomers is important for the observed β-selectivity (Table 1.1, entry 3).

Structure-selectivity-relationship studies of the dimeric catalyst were carried out to determine the structural features responsible for the cooperativity observed in our catalytic glycosylation reaction. A similar level of diastereoselectivity is obtained with truncated dimer 1.4, which shows that the two chiral arylpyrrolidine fragments are not essential (Table 1.1, entry

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\(^{10}\) Nigudkar, S. S.; Demchenko, A. V. Chem. Sci. 2015, 6, 2687.

6). However, the relative position of the two thioureas is critical. For example, adding or removing a single methylene group in the linker results in less efficient catalysis (Table 1.1, entry 5 and 7). Switching the stereochemistry of one of the amino acid subunits also proves detrimental (Table 1.1, entry 8). Based on these observations, we pursued C₂-symmetric macrocyclic bisthiourea catalysts, linked as in 1.2, with the aim of further rigidifying the overall structure. The macrocyclic variant of 1.2 displays a significantly enhanced reactivity (Table 1.1, entry 9), and further optimization identified indole as the optimal amide substituent (Table 1.1, entry 10). Enantiomeric catalyst (R,R)-1.8 slightly improves the selectivity (9:91 vs 8:92), indicating subtle catalyst-substrate matching effects (Table 1.1, entry 11). Several compatible solvents were identified with o-dichlorobenzene providing the best reactivity and selectivity at a relatively high concentration (0.5 M).¹²

With optimal catalyst 1.8, we examined the scope of glycosyl donors (Figure 1.1). Galactosyl chloride was coupled to a variety of glycosyl acceptors to afford β(1,6)-, β(1,3)-, and β(1,4)-linkages (1.9-1.11) in moderate-to-good yields and synthetically useful selectivities. In each of these cases, methyl-protected nucleophiles were employed to facilitate the analysis of crude NMR spectra; however, the reaction is also amenable to larger and more easily cleavable protecting groups. Disaccharide 1.12, which contains only benzylidene acetal and benzyl protecting groups, was obtained in good yield and selectivity. However, more hindered alcohol nucleophiles fail to react with galactosyl chloride, presumably due to steric clash between the substrate and catalyst.

¹² See Section 1.6.6 for details
Table 1.1. Catalyst Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield</th>
<th>α:β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0.1</td>
<td>84:16</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.1</td>
<td>1</td>
<td>52:48</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.1</td>
<td>5</td>
<td>40:60</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>15</td>
<td>20:80</td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>1</td>
<td>46:54</td>
</tr>
<tr>
<td>6</td>
<td>1.4</td>
<td>10</td>
<td>18:82</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>2</td>
<td>15:85</td>
</tr>
<tr>
<td>8</td>
<td>1.6</td>
<td>1</td>
<td>67:33</td>
</tr>
<tr>
<td>9</td>
<td>1.7</td>
<td>68</td>
<td>18:82</td>
</tr>
<tr>
<td>10</td>
<td>(S,S)-1.8</td>
<td>79</td>
<td>9.91</td>
</tr>
<tr>
<td>11</td>
<td>(R,R)-1.8</td>
<td>88</td>
<td>8.92</td>
</tr>
</tbody>
</table>

a. Reactions run on a 0.1 mmol scale. Diastereomeric ratio determined by GC analysis on commercial chiral columns. Yields determined by GC analysis relative to undecane as an internal standard. b. 10 mol% catalyst loading. c. 50 mol% catalyst loading.
1.3 Substrate Scope

Next, catalytic glycosylation was applied to the construction of significantly more challenging 1,2-cis-β-D-mannosides. Using \((R,R)-1.8\), both \(\beta(1,6)\)- and \(\beta(1,3)\)-mannosides (1.13 and 1.14) are obtained, albeit with slightly decreased but synthetically useful levels of β-selectivity. Similarly challenging β-L-rhamnosides (1.15 and 1.6) are also obtained in good yield and selectivity using \((S,S)-1.8\). Furthermore, 2-deoxy-β-linkages (1.17 and 1.18) are obtained using the same protocol. Products 1.19 and 1.20 are both afforded in high selectivity and yield, indicating that the chiral catalyst indiscriminately interacts with each enantiomer of the nucleophile.

Other glycosyl chlorides derived from simple carbohydrates were also evaluated. In all systems derived from fucose (1.21 and 1.22), xylose (1.23 and 1.24), 2-azidogalactose (1.25 and 1.26), glucose (1.27), 2-acetamidoglucose (1.28), and 2-acetamidogalactose (1.29 and 1.30), good to excellent β-selectivities are observed, highlighting the general applicability of the system. No oxazolidine formation is observed in the preparation of 1.28-1.30, allowing direct access to β-N-acyl disaccharides without the use of a nitrogen protecting group. Disaccharide 1.25 is converted into the corresponding chloride, and trisaccharide 1.31 is obtained in excellent diastereoselectivity through the same reaction conditions. Overall, the reactivity across the different pyranoses correlates strongly with the stability of the oxocarbenium intermediates, and disarmed glycosyl chlorides are unreactive in the current system. Although the 1,2-cis-β-glycosides are obtained in slightly decreased selectivity, the breadth of glycosidic linkages that can be constructed by 1.8 presents a general solution towards β-selective glycosylation.
Figure 1.1. Substrate scope.
1.4 Mechanistic Studies

The broadly observed β-selectivity with 1.8 prompted us to study the mechanism of this reaction in greater detail. Since both enantiomers of the catalyst are found to induce similar levels of β-selectivity from α-glycosyl chloride, we examined whether the reaction is stereospecific or stereoselective (Scheme 1.2). Starting with purely α-configured glucosyl chloride 1.32α, only the β-product 1.33β is obtained. Likewise, the α-enriched product 1.33α is obtained from the same reaction conditions when β-enriched glucosyl chloride 1.32β is used. These results indicate that 1.8 catalyzes a stereospecific, invertive substitution.

![Scheme 1.2. Stereospecificity experiments.](image)

The observed stereospecificity offers further insight into the nature of the substitution process. Due to the short lifetime of the oxocarbenium intermediate, glycosylation reactions typically fall in the middle of the SN1 and SN2 mechanistic spectrum. Since glycosyl acceptors

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13 See Section 1.6.4 for details
are weak nucleophiles, the observed stereospecificity strongly suggests nucleophile activation by the Lewis basic sites on the catalyst. The bis-urea analogue of 1.8 showed very comparable reactivity and β-selectivity to 1.8 (Figure 1.2). Given the significant difference in Brønsted basicity and nucleophilicity between ureas and thioureas, the similarity in the catalytic properties of the bis-urea and bis-thiourea catalyst appears to rule out the direct involvement of thiourea as a general base. In contrast, the amide-to-ester perturbation results in a much less reactive and selective catalyst, suggesting the amide carbonyl is engaged in the activation of the nucleophile. In addition, DFT modeling of the putative mechanism located a transition state structure supporting simultaneous activation of the glycosyl chloride and the alcohol nucleophile through hydrogen bonding (Figure 1.3). The computed structure is characterized by a significant amount of C–Cl bond cleavage, and consistent with a loose S_N2 transition state.

Figure 1.2. Evaluation of the Lewis basic sites on the catalyst.

The proposed model predicts that reactivity would increase with the Lewis basicity of the carbonyl group. However, replacing indoline with pyrrolidine gave a more ineffective catalyst despite the substantial increase in basicity (Figure 1.2).\textsuperscript{16} Due to the increased Lewis basicity and decreased steric demand, the pyrrolidine-amide could be more prone to an off-cycle catalyst aggregation, which has been shown to have detrimental effects on the overall reaction.\textsuperscript{17} The amide can also participate as a nucleophilic catalyst generating the \( \alpha \)-diastereomer through a doubly invertive process.\textsuperscript{18}

Because of these scenarios that could complicate the reaction kinetics, we turned to secondary deuterium kinetic isotope effects (KIEs) to probe the general base mechanism.\textsuperscript{19} Although a multitude of factors affect the KIE, its magnitude is primarily determined by changes in the out-of-plane bending vibrations of the C–H(D). If the C–H(D) bonds were to bend more

\textsuperscript{16} The reaction outcome was not sensitive to \( p \)-substituents of indoline.


freely in the transition state than in the ground state, they would lie lower in energy and give a more positive KIE value.20

![Figure 1.4. Secondary deuterium KIE experiments.](image_url)

For the β-products, the KIE values increased with the Lewis basicity of the carbonyl group.21 This trend is consistent with the general base model, in which a more Lewis basic catalyst induces an earlier transition state with a greater distance between the anomeric carbon and the nucleophile oxygen. As a result, the C–H(D) out-of-plane bending vibrations are less restricted, and a larger secondary deuterium KIE is obtained. In contrast, no such trend is observed in the case of the α-diastereomers. Instead, much looser transition states are observed in all cases as evidenced by relatively large KIEs (>1.20). A competitive S_N1 process due to insufficient activation of the nucleophile could be responsible for the generation of the α-product. Also, the high α-bias of the mannose oxocarbenium intermediate is stereochemically consistent with the S_N1 mechanism. However, we cannot currently rule out epimerization of α-chloride to β-chloride followed by a stereospecific substitution.


21 See Section 1.6.4 for details.
1.5 Conclusions

In nature, many glycosyltransferases control the anomeric stereochemistry through a stereospecific mechanism in which both the glycosyl donor and the acceptor are activated via a network of hydrogen bonds (Figure 1.4). Similarly, diastereoselective chemical glycosylation reactions can be more reliably attained by a bifunctional catalyst that promotes the $S_N2$ pathway over the inherently more variable $S_N1$, as demonstrated by the application of 1.8 to the synthesis of 1,2-trans-, 1,2-cis-, and 2-deoxy-β-glycosides. This strategy is highly attractive because its generality and predictability can simplify carbohydrate synthesis, obviating the need for specific protecting groups or reaction conditions. We anticipate this mode of activation will be further generalized to other types of glycosyl donors and acceptors.

![Figure 1.5. Mechanism of catalysis by inverting GT-B fold glycosyl transferases.](image)

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1.6 Experimental Details

1.6.1 General Information

All reactions were performed in flame-dried vials or round-bottom flasks unless otherwise noted. The vials and flasks were fitted with rubber septa, and reactions were conducted under an atmosphere of nitrogen. Solvents and solutions were transferred by syringes or cannulae using standard inert atmosphere techniques.

Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, Matrix Scientific, TCI and CarboSynth and were used as received with the following exceptions: dichloromethane, benzene, tetrahydrofuran, tert-butyl methyl ether, diethyl ether and toluene were dried by passing through columns of activated alumina; isobutylene oxide was distilled at atmosphere pressure and stored over NaSO₄.

Column chromatography was carried out as flash chromatography or with a Biotage Isolera Four automated purification system using silica gel 60 (230-400 mesh) from EM Science.

Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on an Agilent DD2-600 (600 MHz) and on Varian Inova-500 (500 MHz) spectrometers. Fluorine nuclear magnetic resonance (¹⁹F NMR) were recorded on a Varian Inova-500 (500 MHz) or a Varian 400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane (TMS). The ¹H and ¹³C{¹H} NMR spectra were calibrated based on residual solvent signals (CDCl₃: δₜₐₖ₉ = 7.26 ppm, δₜₐ₉ = 77.16 ppm; CD₂Cl₂: δₜₐ₉ = 5.30 ppm, δₜₐ₉ = 53.84 ppm; DMSO-d₆: δₜₐ₉ = 2.50 ppm, δₜₐ₉ = 39.52 ppm; acetone-d₆: δₜₐ₉ = 2.05 ppm, δₜₐ₉ = 29.84 ppm).

Infrared (IR) spectra were obtained using a Bruker Alpha FTIR spectrometer with ATR sample module.
Optical rotations were measured using a 1 mL cell with a 0.5 dm path length on a Jasco DIP 370 digital polarimeter. Concentrations are given in mg/mL.

High Resolution Mass (HRMS) spectroscopic data were recorded on an ESI-TOF mass spectrometer.

If not stated otherwise, glycosyl chlorides were prepared from the corresponding hemiacetal following a procedure described by Thiem et al.\textsuperscript{23} The hemiacetals were prepared from the corresponding hexoses using a modified procedure by Kishi et al. (Dowex®50WX8 instead of Sc(OTf)\textsubscript{3})\textsuperscript{24} to install the allyl protecting group at the anomeric position. Global protection of the remaining hydroxyl groups followed by deprotection\textsuperscript{25} at the anomeric center yielded the hemiacetal intermediates.

3,4,6-tri-O-benzyl-2-azido-2-deoxy-galactosyl chloride\textsuperscript{26} and 3,4,6-tri-O-benzyl-2-acetamido-2-deoxy-galactosyl chloride\textsuperscript{27} were prepared in five/six steps from galactal following standard literature procedures.\textsuperscript{28} 3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-glucosyl chloride was purchased from TCI and used as received.

Methyl 2,3,4,6-terta-O-methyl-α-D-glucopyranoside\textsuperscript{29} and methyl 2,3,4,6-terta-O-benzyl-α-D-glucopyranoside were prepared as described by McGarrigle et al.\textsuperscript{30}

\textsuperscript{24} Hsu, M. C.; Lee, J.; Kishi, Y; J. Org. Chem. 2007, 72, 1931.
\textsuperscript{26} Plattner, C.; Höfener, M.; Sewald, N.; Org. Lett. 2011, 13, 545.
Procedures reported by Pei et al.\textsuperscript{31} and Thiem et al.\textsuperscript{32} were used for the synthesis of methyl 2,4,6-tri-\textit{O}-methyl-\textalpha{-D-galactopyranoside.

Methyl 2-\textit{O}-benzyl-4,6-\textit{O}-benzylidene-\textalpha{-D-glucopyranoside was prepared as described by Gilmour et al.\textsuperscript{33}

Methyl 2,3-di-\textit{O}-methyl-\textbeta{-D-xylopyranoside was prepared through selective benzoylation of methyl \textbeta{-D-xylopyranoside\textsuperscript{34}} followed by standard protection and deprotection procedures.

Phenyl 2,3,4-tri-\textit{O}-benzyl-1-thio-\textbeta{-D-galactopyranoside was prepared as previously described.\textsuperscript{35}

3,4-Di-\textit{O}-acetyl-2-deoxy-\textalpha{-L-rhamnopyranosyl chloride was prepared as described.\textsuperscript{36}

1.6.2 Catalyst Synthesis

\textit{tert-Butyl (R)-(1-(indolin-1-yl)-3,3-dimethyl-1-oxopent-4-en-2-yl)carbamate (1.8a):

\begin{center}
\includegraphics[width=0.5\textwidth]{catalyst}
\end{center}

To a cooled (0 °C) solution of (\textit{R})-2-(2,2-dimethyl-propionylamino)-3,3-dimethyl-pent-4-enoic acid\textsuperscript{37} (1.715 g, 7.048 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (35 mL, 0.2 M) was added indoline (0.87 mL, 7.753

\begin{thebibliography}{99}
\footnotesize
\setlength{\itemsep}{-0.5pt}
\end{thebibliography}
mmol, 1.1 equiv.), PyAOP (4.042 g, 7.753 mmol, 1.1 equiv.), and \( N,N \)-diisopropylethylamine (1.35 mL, 7.753 mmol, 1.1 equiv.). The resulting mixture was stirred at room temperature for 24 h, and quenched with water. The layers were separated, and the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/ethyl acetate, 6:1) to afford amide 1.8a as a white solid (2.015 g, 5.850 mmol, 83%).

\([\alpha]^{22}_D = +6.6 \text{ (c 1.0, CHCl}_3\text{)}\);

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 8.23 (d, \( J = 8.4 \text{ Hz, 1H} \)), 7.19–21 (m, 2H), 7.04 (dd, \( J = 7.2, 7.8 \text{ Hz, 1H} \)), 6.03 (dd, \( J = 10.8, 18.0 \text{ Hz, 1H} \)), 5.28 (d, \( J = 9.6 \text{ Hz, 1H} \)), 5.09–5.12 (m, 2H), 4.44 (d, \( J = 10.2 \text{ Hz, 1H} \)), 4.38 (dt, \( J = 6.6, 10.2 \text{ Hz, 1H} \)), 4.19 (dt, \( J = 6.6, 10.2 \text{ Hz, 1H} \)), 3.12–3.24 (m, 2H), 1.42 (s, 9H), 1.164 (s, 3H), 1.158 (s, 3H) ppm;

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 170.1, 155.8, 143.4, 142.6, 132.1, 127.5, 124.8, 124.3, 117.7, 114.0, 79.8, 58.7, 49.1, 41.1, 28.5, 28.1, 24.3, 23.2;

IR (neat, cm\(^{-1}\)) 1707, 1647, 1480, 1414, 1154, 754;

HRMS (ESI) found 367.1997 [calcd for C\(_{20}\)H\(_{28}\)N\(_2\)NaO\(_3\) (M+Na) 367.1998]

**tert-Butyl (R)-(5-hydroxy-1-(indolin-1-yl)-3,3-dimethyl-1-oxopentan-2-yl)carbamate (1.8b):**

![tert-Butyl (R)-(5-hydroxy-1-(indolin-1-yl)-3,3-dimethyl-1-oxopentan-2-yl)carbamate (1.8b)
To a cooled (0 °C) solution of olefin 1.8a (2.015 g, 5.850 mmol, 1.0 equiv.) in THF (60 mL, 0.1 M) was added 9-BBN (2.141 g, 17.55 mmol, 3 equiv.). The resulting mixture was allowed to warm to rt and was stirred for 3 hours. The reaction was cooled to 0 °C, and 2 M aqueous NaOH (30 mL) was added dropwise followed by 30% H$_2$O$_2$ (10 mL). The mixture was stirred vigorously for 30 minutes at room temperature and diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sat. aqueous NH$_4$Cl solution, sat. aqueous Na$_2$S$_2$O$_3$ solution and brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/ ethyl acetate, 3:1) to afford alcohol 1.8b as a white solid (1.802 g, 4.974 mmol, 85%).

$[\alpha]^{23}_{\text{D}} = +4.8$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) δ 8.23 (d, $J = 8.4$ Hz, 1H), 7.19–7.22 (m, 2H), 7.06 (dd, $J = 6.6, 7.8$ Hz, 1H), 6.23 (d, $J = 9.6$ Hz, 1H), 4.76 (d, $J = 10.2$ Hz, 1H), 4.44 (ddd, $J = 6.6, 10.2, 10.8$ Hz, 1H), 4.24 (td, $J = 7.2, 10.2$ Hz, 1H), 3.72–3.84 (m, 3H), 3.14–3.26 (m, 2H), 1.94 (ddd, $J = 4.2, 8.4, 14.4$ Hz, 1H), 1.43 (s, 9H), 1.11 (s, 3H), 1.09 (s, 3H) ppm;

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.0, 156.4, 142.4, 132.3, 127.5, 124.8, 124.5, 117.8, 79.9, 59.2, 58.1, 49.3, 41.3, 37.5, 28.5, 28.0, 26.1, 23.7 ppm;

IR (neat, cm$^{-1}$) 3350, 1702, 1657, 1479, 1240, 1162, 1047, 754;

HRMS (ESI) found 385.2105 [calcd for C$_{20}$H$_{30}$N$_2$NaO$_4$ (M+Na) 385.2103].

(R)-4-((Tert-butoxycarbonyl)amino)-5-(indolin-1-yl)-3,3-dimethyl-5-oxopentyl 3-nitro-5-(trifluoromethyl)benzoate (1.8c):
To a stirred solution of alcohol 1.8b (1.802 g, 4.974 mmol, 1.0 equiv.) in CH₂Cl₂ (25 mL, 0.2 M) was added 3-nitro-5-(trifluoromethyl)benzoic acid (1.286 g, 5.471 mmol, 1.1 equiv.), EDC·HCl (1.049 g, 5.471 mmol, 1.1 equiv.), Et₃N (0.76 mL, 5.471 mmol, 1.1 equiv.) and DMAP (66.8 mg, 0.547 mmol, 0.1 eq) at room temperature. The resulting mixture was stirred for 1 h, and quenched with sat. aqueous NH₄Cl solution. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/ethyl acetate, 8:1) to afford ester 1.8c as a white solid (2.536 g, 4.377 mmol, 88%).

[α]²³_D = +3.0 (c 1.0, CHCl₃);

¹H NMR (600 MHz, CDCl₃) δ 9.02 (s, 1H), 8.67 (s, 1H), 8.61 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.19–7.22 (m, 2H), 7.06 (dd, J = 6.6, 7.8 Hz, 1H), 5.38 (d, J = 9.6 Hz, 1H), 4.53–4.58 (m, 3H), 4.42 (ddd, J = 5.4, 9.6, 10.2 Hz, 1H), 4.20 (ddd, J = 7.2, 9.6, 10.2 Hz, 1H), 3.16–3.28 (m, 2H), 1.94–2.04 (m, 2H), 1.42 (s, 9H), 1.18 (s, 3H), 1.17 (s, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 170.1, 163.3, 155.9, 148.6, 142.5, 133.5, 132.9 (q, J = 35 Hz), 132.1, 132.0 (q, J = 4 Hz), 127.6, 124.9, 124.6, 124.5, 122.5 (q, J = 272 Hz), 117.7, 80.3, 77.4, 63.6, 58.5, 49.3, 37.7, 36.9, 28.4, 28.1, 23.7, 23.4;
IR (neat, cm⁻¹) 1733, 1654, 1239, 1138, 1045, 757, 688;

HRMS (ESI) found 602.2091 [calcd for C₂₈H₃₂F₃N₃O₇ (M+Na) 602.2090].

(R)-4-((Tert-butoxycarbonyl)amino)-5-(indolin-1-yl)-3,3-dimethyl-5-oxopentyl 3-amino-5-(trifluoromethyl)benzoate (1.8d):

To a stirred solution of alcohol 1.8c (2.536 g, 4.377 mmol, 1.0 equiv.) in EtOH (22 mL, 0.2 M) was added Pd/C (254 mg, 10 wt%) at room temperature. The resulting mixture was stirred under atmospheric pressure of H₂ overnight, concentrated and filtered through a pad of celite with ethyl acetate. The crude mixture was purified by column chromatography (hexanes/ethyl acetate, 4:1) to afford aniline 1.8d as a white solid (2.564 g, 4.666 mmol, 98%).

[α]²³_D = +4.8 (c 1.0, CHCl₃);

¹H NMR (600 MHz, CDCl₃) δ 8.23 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.54 (s, 1H), 7.19–7.22 (m, 2H), 7.04–7.06 (m, 2H), 5.37 (d, J = 9.6 Hz, 1H), 4.58 (d, J = 10.2 Hz, 1H), 4.38–4.46 (m, 3H), 4.16 (ddd, J = 7.2, 9.6, 10.2 Hz, 1H), 4.03 (br s, 2H), 3.11–3.24 (m, 2H), 1.93–1.95 (m, 2H), 1.43 (s, 9H), 1.16 (s, 3H), 1.14 (s, 3H);
\(^{13}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.3, 165.7, 155.9, 147.4, 142.5, 132.08, 132.05, 131.9 (q, \(J = 33\) Hz), 128.4, 127.5, 124.8, 124.4, 123.8 (q, \(J = 271\) Hz), 118.7, 117.7, 115.8 (q, \(J = 4\) Hz), 115.1 (q, \(J = 4\) Hz), 80.1, 77.4, 62.4, 58.5, 49.2, 37.5, 36.9, 28.4, 28.0, 23.5, 23.4; IR (neat, cm\(^{-1}\)) 3368, 1707, 1647, 1236, 1163, 1123, 755; HRMS (ESI) found 572.2347 [calcd for C\(_{28}\)H\(_{34}\)F\(_3\)N\(_3\)NaO\(_5\) (M+Na) 572.2348].

\((R)-4-((\text{Tert-butoxycarbonyl})\text{amino})-5-(\text{indolin-1-yl})-3,3-\text{dimethyl-5-oxopentyl}3-\text{isothiocyanato-5-(trifluoromethyl)benzoate} (1.8e):\)

\[
\begin{align*}
\text{CF}_3 \\
\text{SCN} \\
\text{O} \\
\text{BocHN} \\
\text{O} \\
\text{NH}_2
\end{align*}
\]

To a stirred solution of aniline 1.8d (2.564 g, 4.666 mmol, 1.0 equiv.) in CH\(_2\)Cl\(_2\) (23 mL, 0.2 M) was added TCDI (1.663 g, 9.332 mmol, 2 equiv.) and imidazole (158.8 mg, 2.333 mmol, 0.5 equiv.) at room temperature. The resulting mixture was stirred for 4 h, and quenched with aqueous NH\(_4\)Cl solution. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/ethyl acetate, 8:1) to afford ester 1.8e as a white solid (2.512 g, 4.246 mmol, 91%).

\([\alpha]^{23}_{D} = +1.0\) (c 1.0, CHCl\(_3\));
\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.22 (d, \(J = 8.4\) Hz, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.62 (s, 1H), 7.20–7.22 (m, 2H), 7.06 (dd, \(J = 6.6, 7.8\) Hz, 1H), 5.36 (d, \(J = 9.6\) Hz, 1H), 4.40–4.55 (m, 4H), 4.19 (ddd, \(J = 6.6, 9.6, 10.2\) Hz, 1H), 3.15–3.27 (m, 2H), 1.99 (ddd, \(J = 6.6, 7.2, 14.4\) Hz, 1H), 1.93 (ddd, \(J = 6.0, 7.8, 13.8\) Hz, 1H), 1.43 (s, 9H), 1.16 (s, 3H), 1.15 (s, 3H);

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.1, 164.0, 155.9, 142.4, 139.6, 133.3, 133.1, 132.7 (q, \(J = 34\) Hz), 132.0, 129.8, 127.5, 126.4 (q, \(J = 4\) Hz), 124.8, 124.7 (q, \(J = 4\) Hz), 124.4, 122.8 (q, \(J = 271\) Hz), 117.7, 80.1, 77.4, 63.1, 58.5, 49.2, 37.7, 36.9, 28.4, 28.0, 23.6, 23.4;

IR (neat, cm\(^{-1}\)) 2049, 1707, 1648, 1251, 1132, 755, 689;

HRMS (ESI) found 614.1908 [calcd for C\(_{29}\)H\(_{32}\)F\(_3\)N\(_3\)NaO\(_5\)S (M+Na) 614.1912].

\((5R,15R)-5,15\)-Di(indoline-1-carbonyl)-6,6,16,16-tetramethyl-3,13-dithiao xo-15,115-bis(trifluoromethyl)-9,19-diox a-2,4,12,14-tetraaza-1,11(1,3)-dibenzenacycloicosaphane-10,20-dione (1.8):

To a stirred solution of carbamate 1.8e (2.512 g, 4.246 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (6.5 mL) was added TFA (1.6 mL, 21.23 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 4 h, concentrated in vacuo and re-dissolved in CH\(_2\)Cl\(_2\) (42 mL, 0.1 M). The solution
was cooled to 0 °C and Et₃N (3.0 mL, 21.23 mmol, 5 equiv.) was added. After 1 h at room temperature, the reaction was quenched with aqueous NH₄Cl solution and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/ethyl acetate, 2:1) to afford bisthiourea 1.8 as a white solid (1.578 g, 1.605 mmol, 75%).

[α]²³_D = +168 (c 1.0, CHCl₃);

¹H NMR (600 MHz, CD₃OD) δ 8.64 (s, 1H), 8.11–8.13 (m, 2H), 7.99 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.05 (dd, J = 7.2, 7.8 Hz, 1H), 5.51 (s, 1H), 4.84–4.88 (m, 1H), 4.58 (dd, J = 6.0, 7.2 Hz, 2H), 4.24 (ddd, J = 6.6, 9.0, 10.8 Hz, 1H), 3.21 (ddd, J = 6.6, 8.4, 16.8 Hz, 1H), 3.10 (ddd, J = 6.0, 10.8, 16.8 Hz, 1H), 2.22 (ddd, J = 7.2, 7.8, 15.0 Hz, 1H), 1.90 (ddd, J = 5.4, 6.0, 15.0 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H);

¹³C NMR (126 MHz, (CD₃)₂CO) δ 183.1, 170.7, 165.5, 143.4, 142.0, 133.6, 132.6, 131.4 (q, J = 33 Hz), 128.9, 127.8, 125.7, 125.1, 124.9 (q, J = 4 Hz), 124.5 (q, J = 270 Hz), 122.3 (q, J = 4 Hz), 118.0, 63.3, 62.5, 50.1, 38.6, 38.2, 28.4, 24.1, 23.7;

¹⁹F NMR (375 MHz, (CD₃)₂CO) δ –61.77;

IR (neat, cm⁻¹) 1723, 1629, 1523, 1249, 1127, 755, 692;

HRMS (ESI) found 1005.2866 [calcd for C₄₈H₄₈F₆N₆NaO₆S₂ (M+Na) 1005.2879].
1.6.3 Thiourea-Catalyzed Glycosylation Reactions

Representation procedure

A round bottom flask was charged with glycosyl acceptor (232 mg, 0.50 mmol, 2 equiv) and catalyst (25 mg, 0.025 mmol, 5 mol%). Then the mixture was azeotroped with benzene three times, and placed under vacuum (<1 torr) for an hour. The flask was refilled with nitrogen, and a solution of glycosyl donor (63 mg, 0.25 mmol, 1 equiv) in o-dichlorobenzene was added via syringe. Isobutylene oxide (44 μL, 0.50 mmol, 2 equiv) was added, and the resulting mixture was stirred at room temperature for 48 h. The crude material was analyzed by HPLC to determine the diastereomeric ratio (α:β = 20:80). The reaction was then purified by column chromatography (silica gel, hexanes/ethyl acetate) to afford 1.18 (108 mg, 64%) as a white solid.

Methyl (2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (1.9):

The general procedure was conducted on a 0.25 mmol scale. After stirring for 7 h at 40 °C, 1.9 was obtained as a single isomer (crude 1H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded β-1.9 as a white solid (152 mg, 0.20 mmol, 80%).

[α]^{23}_D = +48 (c 1.0, CHCl₃);

1H NMR (600 MHz, CDCl₃) δ 7.24–7.38 (m, 20H), 4.97 (d, J = 10.6 Hz, 1H) 4.93 (d, J = 11.2 Hz, 1 H), 4.78–4.79 (m, 1H), 4.78 (d, J = 10.6 Hz, 1H), 4.74 (d, J = 11.7 Hz, 1H), 4.71 (d, J =
11.7 Hz, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 11.2 Hz, 1H)
4.41 (d, J = 7.6 Hz, 1H) 4.14–4.16 (m, 1H), 3.90 (br s, 1H), 3.84–3.88 (m, 1H), 3.69–3.74 (m,
1H), 3.61–3.66 (m, 3H), 3.60 (s, 3H), 3.48–3.57 (m, 3H), 3.49 (s, 3H), 3.44 (s, 3H) 3.32 (s, 3H)
3.16–3.20 (m, 1H) 3.06–3.09 (m, 1H);

^1^C NMR (126 MHz, CDCl\textsubscript{3}) δ 138.8, 138.7, 138.5, 138.0, 128.5, 128.4, 128.3,
128.2, 128.2, 127.9, 127.8, 127.6, 127.6, 127.5, 127.5, 104.6, 97.2, 83.5, 82.4, 81.8, 79.9,
79.4, 75.2, 74.5, 73.6 (2C), 73.5, 73.0, 69.9, 68.9, 68.8, 60.8, 60.4, 58.9, 55.2;

IR (neat, cm\textsuperscript{-1}) 3063, 3030, 2928, 1497, 1454, 1363, 1157, 1100, 1068, 1028,
996, 905, 733, 698;

HRMS (ESI) found 776.4025 [calcd for C\textsubscript{44}H\textsubscript{58}N\textsubscript{11}(M+NH\textsubscript{4})\textsuperscript{+} 776.4010].

Methyl (2,3,4,6-Tetra-O-benzyl-\(\beta\)-\(\delta\)-galactopyranosyl)-(1→3)-2,4,6-tri-O-methyl-\(\alpha\)-\(\delta\)-galactopyranoside (1.10):

\[ \text{BnO} \text{MeO} \text{OMe} \]
\[ \text{Bn} \text{MeO} \text{OMe} \text{OMe} \]
\[ \text{BnO} \text{O} \text{Bn} \]
\[ \text{MeO} \text{OMe} \text{OMe} \]

The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at 40 °C, 1.10
was obtained as the major isomer (\(\alpha\):\(\beta\) = 2:98, crude \(^1^H\)NMR). Purification by column
chromatography (hexanes/diethyl ether) yielded 1.10 (\(\alpha\):\(\beta\) = 2:98) as a white solid (133 mg,
0.17 mmol, 70%).

\([\alpha]_{D}^{23} = +47.7 (c 1.2, \text{CHCl}_3);\)

\(^1^H\)NMR (500 MHz, CDCl\textsubscript{3}) δ 7.21–7.42 (m, 20H), 5.01 (d, J = 11.2 Hz, 1H), 4.95 (d, J = 11.7
Hz, 1H), 4.90 (d, J = 3.4 Hz, 1H), 4.78 (d, J = 11.2 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.75 (d, J
= 7.3 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.44 (s, 2H), 4.11 (dd, J = 2.9, 10.2 Hz, 1H), 3.92 (d, J
= 2.9 Hz, 1H) 3.88 (t, J = 6.3 Hz, 1H), 3.79 (dd, J = 7.8, 9.8 Hz, 1H), 3.75 (dd, J = 3.9, 10.2 Hz, 1H), 3.70 (d, J = 2.4 Hz, 1H), 3.60–3.63 (m, 1H), 3.61 (s, 3H), 3.48–3.59 (m, 5H), 3.42 (s, 3H), 3.38 (s, 6H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 139.1, 139.0, 138.7, 138.1, 128.5, 128.4, 128.2, 128.2, 128.1, 128.0, 127.8, 127.8, 127.5, 127.5, 127.4, 104.2, 97.7, 82.3, 80.0, 79.5, 78.8, 76.0, 74.9, 74.5, 73.8, 73.5, 73.2, 73.0, 71.7, 69.2, 68.6, 61.6, 59.3, 58.7, 55.3;

IR (neat, cm$^{-1}$) 3087, 3062, 3032, 2981, 2909, 2839, 1497, 1454, 1360, 1204, 1146, 1097, 1053, 991, 957, 913, 735, 697;

HRMS (ESI) found 776.4027 [calcd for C$_{44}$H$_{58}$N$_{11}$O$_{11}$ (M+NH$_4$)$^+$ 776.4010].

Methyl (2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl)-(1→4)-2,3-di-O-methyl-β-D-xylopyranoside (1.11):

The general procedure was conducted on a 0.19 mmol scale using 10 mol% catalyst. After stirring for 48 h at 40 °C 1.11 was obtained as the major isomer (α:β = 13:87, crude $^1$H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded β-1.11 as a colorless oil (80 mg, 59%).

$[\alpha]_{D}^{22} = -20$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.33–7.26 (m, 20 H), 4.95 (d, J = 13.8 Hz, 1H), 4.83 (d, J = 12.6 Hz, 1H), 4.78 (d, J = 13.2 Hz, 1H), 4.71 (s, 2H), 4.61 (d, J = 13.8 Hz, 1H), 4.1–4.47 (m, 3H),
4.16 (d, J = 8.4 Hz, 1H), 3.96 (dd, J = 6.0, 14.4 Hz, 1H), 3.93 (d, J = 3.6 Hz, 1H), 3.75–3.83 (m, 2H), 3.50–3.67 (m, 13 H), 3.20–3.27 (m, 2H), 2.98 (dd, J = 8.4, 10.2 Hz, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 139.0, 138.8, 138.6, 138.0, 128.6, 128.50, 128.46, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.6, 104.7, 103.0, 84.2, 83.0, 82.6, 79.7, 77.0, 75.4, 74.6, 73.65, 73.63, 73.5, 73.0, 68.6, 63.3, 60.68, 60.66, 60.5, 56.9 ppm;

IR (neat, cm$^{-1}$) 2929, 2863, 1497, 1454, 1363, 1067, 990, 748, 733, 696, 666;

HRMS (ESI) found 732.3770 [calcd for C$_{42}$H$_{54}$N$_{10}$ (M+NH$_4$)$^+$ 732.3742].

**Methyl (2,3,4,6-Tetra-O-benzyl-α-D-galactopyranosyl)-(1→4)-2,3-di-O-methyl-β-D-xylopyranoside (α-1.11):**

![Structural diagram](image)

White solid;

$[\alpha]^{23}_{D} = +23.4$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.19–7.42 (m, 20H), 5.19 (d, J = 3.5 Hz, 1H), 4.94 (d, J = 11.2 Hz, 1H), 4.84 (d, J = 11.7 Hz, 1H), 4.79 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 4.09 (d, J = 7.6 Hz, 1H), 4.04–4.08 (m, 2H) 3.97–3.98 (m, 1H), 3.86–3.90 (m, 2H), 3.63–3.67 (m, 1H), 3.57 (m, 3H), 3.57 (s, 3H), 3.55 (s, 3H), 3.51 (s, 3H), 3.19–3.25 (m, 2H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 138.8, 138.7, 138.6, 138.0, 128.5, 128.4, 128.3, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 104.9, 99.4, 85.1, 83.7, 78.8, 77.5, 76.2, 74.9, 74.8, 73.7, 73.1, 73.0, 69.9, 69.2, 64.7, 61.2, 60.6, 57.0;
IR (neat, cm⁻¹) 3088, 3063, 3029, 2912, 2863, 2838, 1496, 1453, 1351, 1322, 1153, 1134, 1085, 1062, 1038, 1028, 970, 910, 891, 733, 696;

HRMS (ESI) found 732.3770 [calcd for C₄₂H₅₄NO₁₀ (M+NH₄)⁺ 732.3742].

**Methyl (2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl)-(1→3)-2-O-benzyl-4,6-benzylidene-α-D-galactopyranoside (1.12):**

The general procedure was conducted on a 0.25 mmol scale using 10 mol% catalyst. After stirring for 48 h at rt, 1.12 was obtained as the major isomer (α:β = 1:99, crude ¹H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded β-1.12 (α:β = 1:99) as a white solid (153 mg, 69%).

[α]ᵢ²ᵈ = +15 (c 1.0, CHCl₃);

¹H NMR (600 MHz, CDCl₃) δ 7.18–7.58 (m, 30H), 5.56 (s, 1H), 5.05 (d, J = 11.4 Hz, 1H), 4.89–4.94 (m, 3H), 4.83 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.58–4.64 (m, 3H), 4.43 (d, J = 11.4 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 3.0 Hz, 1H), 4.27–4.30 (m, 2H), 4.21 (d, J = 12.6 Hz, 1H), 4.00–4.04 (m, 2H), 3.92 (d, J = 2.4 Hz, 1H), 3.87 (dd, J = 7.8, 9.6 Hz, 1H), 3.58–3.62 (m, 2H), 3.51–3.55 (m, 2H), 3.49 (dd, J = 3.0, 10.2 Hz, 1H), 3.35 (s, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 139.2, 138.8, 138.5, 138.3, 138.1, 128.7, 128.6, 128.51, 128.46, 128.44, 128.32, 128.28, 128.2, 128.1, 127.9, 127.81, 127.79, 127.7, 127.57, 127.55, 127.3, 126.2, 103.8, 100.5, 99.2, 82.2, 79.6, 77.4, 76.6, 75.0, 74.8, 74.0, 73.7, 72.5, 73.19, 73.16, 72.2, 69.3, 68.5, 62.9, 55.6;
IR (neat, cm\(^{-1}\)) 3009, 2911, 1453, 1363, 1195, 1093, 1049, 990, 744, 695, 666;

HRMS (ESI) found 917.3870 [calcd for C\(_{55}H_{58}NaO_{11}\) (M+NH\(_4\))\(^+\) 917.3877].

**Methyl (2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (1.13):**

![Molecular structure of the compound]

The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at rt 1.13 was obtained as the major isomer (α:β = 14:86, crude \(^1\)H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded 1.13 (α:β = 14:86) as a white solid (133 mg, 0.17 mmol, 70%). The anomers were separated for further characterization.

White solid;

\([\alpha]^{24}_D = +8.2 \text{ (c 1.0, CHCl}_3)\);

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.43–7.47 \text{ (m, 2H), 7.33–7.36 (m, 2H), 7.24–7.32 (m, 14H), 7.18–7.21 (m, 2H), 5.50 (d, J = 12.2 Hz, 1H), 4.90 (d, J = 10.7 Hz, 1H), 4.83 (d, J = 12.2 Hz, 1H), 4.79 (d, J = 3.7 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 10.7 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.46 (s, 1H), 4.24 (dd, J = 2.0, 10.7 Hz, 1H), 3.92 (d, J = 2.9 Hz, 1H), 3.87 (t, J = 9.5 Hz, 1H), 3.83 (dd, J = 2.0, 10.7 Hz, 1H), 3.71–3.78 (m, 2H), 3.63 (s, 3H), 3.57 (dd, J = 6.6, 10.5 Hz, 1H), 3.45–3.55 (m, 3H), 3.51 (s, 3H), 3.48 (s, 3H), 3.35 (s, 3H), 3.16 (dd, J = 3.7, 9.5 Hz, 1H), 3.00 (dd, J = 8.8, 10.2 Hz, 1H);
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.8, 138.5, 138.4, 138.2, 128.4, 128.3, 128.2, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 101.9, 97.2, 83.4, 82.2, 81.9, 80.3, 76.1, 75.2, 75.0, 74.0, 73.9, 73.5, 71.5, 70.0, 69.7, 69.0, 60.9, 60.4, 59.0, 55.0;

IR (neat, cm$^{-1}$) 3063, 3031, 2907, 2834, 1497, 1453, 1361, 1146, 1100, 1073, 1057, 1026, 990, 903, 738, 695, 564;

HRMS (ESI) found 776.4031 [calcd for C$_{44}$H$_{58}$N$_{11}$ (M+NH$_4$)$^+$ 776.4010].

Methyl (2,3,4,6-Tetra-O-benzyl-$\alpha$-D-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-$\alpha$-D-glucopyranoside ($\alpha$-1.13):

Colorless oil;

$[^{22}]_{D}^{\alpha} = +82.6$ (c 1.1, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.24–7.43 (m, 18H), 7.17–7.18 (m, 2H), 5.00 (d, $J = 1.8$ Hz, 1H), 4.90 (d, $J = 10.6$ Hz, 1H), 4.77 (d, $J = 12.9$ Hz, 1H), 4.73 (d, $J = 12.9$ Hz, 1H), 4.72 (d, $J = 3.5$ Hz, 1H), 4.68 (d, $J = 12.3$ Hz, 1H), 4.64 (s, 2H), 4.55 (d, $J = 12.3$ Hz, 1H), 4.53 (d, $J = 10.6$ Hz, 1H), 3.98–4.04 (m, 1H), 3.89 (dd, $J = 3.5$, 9.4 Hz, 1H), 3.77–3.85 (m, 4H), 3.74 (dd, $J = 1.8$, 10.6 Hz, 1H), 3.61–3.66 (m, 1H) 3.63 (s, 3H), 3.53–3.57 (m, 1H), 3.52 (s, 3H), 3.46–3.51 (m, 1H), 3.49 (s, 3H), 3.32 (s, 3 H), 3.10 (dd, $J = 3.5$, 9.4 Hz, 1H), 3.02 (dd, $J = 8.8$, 10.0 Hz, 1H);
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.7, 138.5, 138.5, 138.5, 128.5, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 98.3, 97.3, 83.8, 81.9, 80.0, 79.5, 75.2, 75.0, 74.6, 73.4, 72.5, 72.2, 72.0, 69.9, 69.4, 65.8, 61.0, 60.7, 59.1, 55.1;

IR (neat, cm$^{-1}$) 3088, 3062, 3030, 2911, 2836, 1497, 1454, 1362, 1198, 1097, 1050, 1027, 910, 735, 697;

HRMS (ESI) found 776.4025 [calcd for C$_{44}$H$_{58}$NO$_{11}$ (M+NH$_4$)$^+$ 776.4010].

**Methyl (2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside (1.14):**

![Methyl (2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside](image)

The general procedure was conducted on a 0.2 mmol scale using 10 mol% catalyst. After stirring for 72 h at rt 1.14 was obtained as the major isomer ($\alpha$:β = 14:86, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded 1.14 ($\alpha$:β = 10:90) as a colorless oil (54.4 mg, 36%). The anomers were separated for further characterization.

**Methyl (2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside (β-1.14):**

Colorless oil;

$[\alpha]_{D}^{23} = +27.7$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.46–7.48 (m, 2H), 7.21–7.36 (m, 18H), 4.99 (d, $J = 12.3$ Hz, 1H), 4.87–4.93 (m, 3H), 4.68 (d, $J = 11.7$ Hz, 1H), 4.52–4.62 (m, 5H), 3.86–3.93 (m, 4H), 3.76–3.78
(m, 3H), 3.65 (dd, J = 3.8, 10.3 Hz, 1H), 3.59 (s, 3H), 3.42–3.56 (m, 4H), 3.41 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.9, 138.7, 138.5, 138.3, 128.4, 128.2, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 103.5, 97.9, 82.4, 79.7, 79.6, 78.0, 75.8, 75.3, 74.9, 74.6, 74.0, 73.5, 71.9, 71.7, 69.7, 69.2, 61.5, 59.4, 59.2, 55.3;

IR (neat, cm$^{-1}$) 3088, 3064, 3030, 2926, 2833, 1496, 1453, 1359, 1330, 1314, 1276, 1203, 1130, 1097, 1076, 1050, 1027, 990, 957, 909, 844, 807, 731, 697, 647, 620, 606, 483, 465;

HRMS (ESI) found 776.4034 [calcd for C$_{44}$H$_{58}$N$_{11}$O$_{11}$ (M+NH$_4$)$^+$ 776.4010].

**Methyl (2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside (α-1.14):**

![Methyl (2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside (α-1.14):](image)

Colorless oil;

[$\alpha$]$^{23}$$^D = +118.4$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.20–7.40 (m, 18H), 7.15–7.19 (m, 2H), 5.01 (d, J = 1.8 Hz, 1H), 4.88 (d, J = 11.7 Hz, 1H), 4.82 (d, J = 12.9 Hz, 1H), 4.81 (d, J = 3.5 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.70 (d, J = 12.9 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.10–4.14 (m, 1H), 4.04 (dd, J = 2.9, 10.6 Hz, 1H), 3.97–4.02 (m, 1H), 3.91 (dd, J = 2.9, 9.4 Hz, 1H), 3.82 (dd, J = 4.1, 11.2 Hz, 1H), 3.79 (t, J = 6.7 Hz, 1H), 3.68–3.74 (m, 2H), 3.44–3.52 (m, 4H), 3.40 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.17 (s, 3H);
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 139.0, 138.6, 128.4, 128.4, 128.3, 128.2, 128.0, 127.8, 127.8, 127.6, 127.4, 127.4, 98.1, 94.5, 80.0, 77.1, 75.4, 74.9, 74.8, 74.5, 73.3, 73.0, 72.9, 72.6, 71.6, 71.2, 69.1, 68.5, 61.2, 59.8, 59.3, 55.3; 
IR (neat, cm$^{-1}$) 3088, 3063, 3030, 2925, 2904, 2874, 2839, 1497, 1454, 1362, 1313, 1203, 1098, 1066, 1028, 990, 957, 903, 795, 733, 699, 649; 
HRMS (ESI) found 776.4038 [calcd for C$_{44}$H$_{58}$NO$_{11}$ (M+NH$_4$)$^+$ 776.4010].

**Methyl (2,3,4-Tri-0-benzyl-6-deoxy-$\beta$-l-mannopyranosyl)-(1→6)-2,3,4-tri-0-methyl-$\alpha$-D-glucopyranoside (1.15):**

The general procedure was conducted on a 0.27 mmol scale using $(S,S)$-1.8 catalyst. After stirring for 48 h at 0°C $\beta$-1.15 was obtained as the major isomer ($\alpha$:$\beta$ = 12:88, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded 1.15 ($\alpha$:$\beta$ = 14:86) as a colorless oil (135 mg, 0.21 mmol, 78%). The anomers were separated for further characterization.

**Methyl (2,3,4-Tri-O-benzyl-6-deoxy-$\beta$-l-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-$\alpha$-D-glucopyranoside ($\beta$-1.15):**

Colorless oil;  
$[\alpha]_{D}^{22} = +87$ ($c$ 1.0, CHCl$_3$);  
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.47–7.48 (m, 2H), 7.25–7.38 (m, 13H), 5.01 (d, $J = 12.3$ Hz, 1H), 4.97 (d, $J = 11.2$ Hz, 1H), 4.87 (d, $J = 12.3$ Hz, 1H), 4.81 (d, $J = 3.5$ Hz, 1H), 4.65 (d, $J = 4.5$ Hz, 1H).
11.2 Hz, 1H), 4.52 (d, \( J = 11.7 \) Hz, 1H), 4.46 (d, \( J = 11.7 \) Hz, 1H), 4.44 (s, 1H), 4.18 (dd, \( J = 3.5, 11.2 \) Hz, 1H), 3.96 (d, \( J = 2.9 \) Hz, 1H), 3.64 (s, 3H), 3.59–3.66 (m, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.50–3.53 (m, 1H), 3.45–3.48 (m, 1H), 3.39 (s, 3H), 3.32–3.34 (m, 1H), 3.25 (dd, \( J = 8.8, 10.0 \) Hz, 1H), 3.16 (dd, \( J = 3.5, 9.4 \) Hz, 1H), 1.38 (d, \( J = 5.9 \) Hz, 3H);

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 138.9, 138.6, 138.3, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 101.8, 97.6, 83.6, 82.1, 81.8, 80.3, 79.6, 75.5, 74.4, 74.1, 71.4, 70.2, 67.7, 61.0, 60.9, 59.2, 55.3, 18.1;

IR (neat, cm\(^{-1}\)) 3088, 3063, 3030, 2976, 2931, 2909, 2836, 1497, 1454, 1362, 1187, 1158, 1098, 1066, 1048, 1026, 1001, 907, 735, 696;

HRMS (ESI) found 670.3616 [calcd for C\(_{37}\)H\(_{52}\)N\(_{10}\)(M+NH\(_4\))^+] 670.3586.

**Methyl (2,3,4-Tri-O-benzyl-6-deoxy-\( \alpha \)-L-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-\( \alpha \)-D-glucopyranoside (\( \alpha \)-1.15):**

Colorless oil;

\([\alpha]_{D}^{23} = +14.8 \) (c 1.0, CHCl\(_3\));

\(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.23–7.39 (m, 15H), 4.96 (d, \( J = 11.2 \) Hz, 1H), 4.78 (d, \( J = 12.9 \) Hz, 1H), 4.76 (d, \( J = 1.8 \) Hz, 1H), 4.73 (d, \( J = 3.5 \) Hz, 1H), 4.71 (d, \( J = 12.9 \) Hz, 1H), 4.67 (d, \( J = 11.7 \) Hz, 1H), 4.66 (d, \( J = 11.2 \) Hz, 1H), 4.63 (d, \( J = 11.7 \) Hz, 1H), 3.85 (dd, \( J = 2.9, 9.4 \) Hz, 1H), 3.82 (dd, \( J = 1.5, 10.9 \) Hz, 1H), 3.71–3.77 (m, 2H), 3.62–3.65 (m, 1H), 3.62 (s, 3H), 3.52–
3.56 (m, 1H), 3.51 (s, 3H), 3.43–3.49 (m, 2H), 3.38 (s, 3H), 3.30 (s, 3H), 3.14 (dd, J = 3.5, 9.4 Hz, 1H), 2.95–3.01 (m, 1H), 1.35 (d, J = 6.5 Hz, 3H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.6, 138.6, 138.3, 128.4, 128.4, 128.1, 128.0, 127.8, 127.7, 127.6, 98.5, 97.2, 83.5, 81.8, 80.6, 79.9, 79.7, 75.5, 74.8, 72.8, 72.4, 69.8, 68.1, 66.2, 60.9, 60.4, 59.0, 55.0, 18.0;

IR (neat, cm$^{-1}$) 3088, 3063, 3030, 2975, 2926, 2833, 1497, 1454, 1363, 1324, 1283, 1198, 1098, 1084, 1047, 1027, 996, 973, 911, 735, 697;

HRMS (ESI) found 670.3595 [calcd for C$_{37}$H$_{52}$NO$_{10}$ (M+NH$_4$)$^+$ 670.3586].

**Methyl (2,3,4-Tri-O-benzyl-2-deoxy-β-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside (1.16):**

![Methyl (2,3,4-Tri-O-benzyl-2-deoxy-β-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside](image)

The general procedure was conducted on a 0.22 mmol scale using 10 mol% (S,S)-1.8 catalyst. After stirring for 80 h at 0 °C β-1.16 was obtained as the major isomer (α: β = 10:90, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded β-1.16 as a white solid (89 mg, 0.13mmol, 61%).

**Methyl (2,3,4-Tri-O-benzyl-2-deoxy-β-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside (β-1.16):**

White solid

$[^{22}]{\alpha} = +82.4$ (c 1.0, CHCl$_3$);
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.45–7.46 (m, 2 H), 7.21–7.37 (m, 13 H), 4.97 (d, $J = 12.3$ Hz, 1H), 4.94 (d, $J = 11.2$ Hz, 1H), 4.89 (d, $J = 12.3$ Hz, 1H), 4.86 (d, $J = 3.7$ Hz, 1H), 4.64 (d, $J = 11.2$ Hz, 1H), 4.53–4.58 (m, 3 H), 4.08 (dd, $J = 2.9$, 10.0 Hz, 1H), 3.80–3.89 (m, 2 H), 3.69 (dd, $J = 3.7$, 10.0 Hz, 1H), 3.60–3.66 (m, 1H), 3.53–3.59 (m, 2 H), 3.55 (s, 3 H), 3.49–3.52 (m, 1 H), 3.43–3.48 (m, 1 H), 3.45 (s, 3 H), 3.40 (s, 6 H), 3.28–3.33 (m, 1 H), 1.38 (d, $J = 6.5$ Hz, 3 H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 139.0, 138.7, 138.4, 128.5, 128.5, 128.3, 128.3, 128.2, 127.8, 127.8, 127.7, 127.5, 99.1, 98.6, 82.7, 80.3, 76.5, 75.6, 75.2, 74.1, 72.3, 71.9, 71.1, 68.7, 61.8, 60.0, 59.4, 55.5, 18.1;

IR (neat, cm$^{-1}$) 3058, 3028, 2917, 2869, 2836, 1497, 1453, 1396, 1362, 1206, 1189, 1110, 1097, 1072, 1052, 1025, 986, 953, 927, 910, 890, 862, 787, 763, 736, 697, 634, 596, 552, 543, 511, 464;

HRMS (ESI) found 656.3606 [calcd for C$_{36}$H$_{50}$NO$_{10}$ (M+NH$_4$)$^+$ 670.3586].

**Methyl (2,3,4-Tri-O-benzyl-2-deoxy-$\alpha$-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-$\alpha$-D-galactopyranoside ($\alpha$-1.16):**

![Methyl (2,3,4-Tri-O-benzyl-2-deoxy-$\alpha$-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-$\alpha$-D-galactopyranoside ($\alpha$-1.16)](image)

Colorless oil;

$\left[\alpha\right]_{D}^{22} = +118.4$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.17–7.45 (m, 15 H) 5.16 (d, $J = 1.8$ Hz, 1 H), 4.96 (d, $J = 11.2$ Hz, 1 H), 4.87 (d, $J = 3.5$ Hz, 1 H), 4.78 (d, $J = 12.9$ Hz, 1 H), 4.68 (d, $J = 12.9$ Hz, 1 H), 4.65 (d, $J = 11.2$ Hz, 1 H), 4.62 (s, 2 H), 4.00 (dd, $J = 2.9$, 10.6 Hz, 1 H), 3.87 (t, $J = 6.7$ Hz, 1 H), 3.83–3.84
(m, 1H), 3.75–3.82 (m, 2H), 3.64–3.68 (m, 1H), 3.55–3.60 (m, 1H), 3.48–3.51 (m, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 3.38 (s, 3H), 3.32 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 138.8, 138.6, 138.5, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 99.5, 97.6, 80.5, 79.7, 79.4, 79.1, 75.5, 75.4, 74.5, 72.2, 72.1, 71.3, 69.3, 69.0, 61.7, 59.4, 58.9, 55.4, 18.3;

IR (neat, cm$^{-1}$) 3088, 3062, 3030, 2976, 2909, 2835, 1497, 1454, 1360, 1203, 1093, 1072, 1041, 1027, 990, 955, 914, 886, 840, 804, 736, 697, 620, 479;

HRMS (ESI) found 670.3615 [calcd for C$_{37}$H$_{52}$N$_{10}$ (M+NH$_4$)$_{10}$] 670.3586].

**Methyl (3,4,6-Tri-O-benzyl-2-deoxy-β-D-glucosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (1.17):**

![Methyl (3,4,6-Tri-O-benzyl-2-deoxy-β-D-glucosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside](image)

The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at −40 °C in toluene (0.1 M) β-1.17 was obtained as the major isomer (α:β = 15:85, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded β-1.17 as a white solid (117 mg, 72%).

**Methyl (3,4,6-Tri-O-benzyl-2-deoxy-β-D-glucosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (β-1.17):**

$[\alpha]^{22}_D = +54$ (c 1.0, CHCl$_3$);
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21–7.36 (m, 15H), 4.90 (d, $J$ = 11.0 Hz, 1H), 4.82 (d, $J$ = 3.0 Hz, 1H), 4.68 (d, $J$ = 12.0 Hz, 1H), 4.55–4.63 (m, 4H), 4.49 (dd, $J$ = 2.0, 4.5 Hz, 1H), 4.13 (dd, $J$ = 1.5, 10.5 Hz, 1H), 3.78 (dd, $J$ = 1.5, 10.5 Hz, 1H), 3.60–3.72 (m, 7H), 3.42–3.53 (m, 9H), 3.39 (s, 3H), 3.21 (dd, $J$ = 3.5, 9.5 Hz, 1H), 3.12 (t, $J$ = 9.0 Hz, 1H), 2.33 (ddd, $J$ = 1.5, 5.0, 12.0 Hz, 1H), 1.71 (td, $J$ = 9.5, 12.5 Hz, 1H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.52, 138.48, 138.4, 128.6, 128.51, 128.46, 128.2, 127.8, 127.7, 100.4, 97.4, 83.6, 81.9, 79.7, 79.6, 78.3, 75.5, 75.1, 73.6, 71.6, 69.9, 69.6, 68.2, 61.0, 60.5, 59.1, 55.2, 36.7;

IR (neat, cm$^{-1}$) 2929, 2835, 1454, 1364, 1187, 1098, 1048, 738, 698;

HRMS (ESI) found 675.3146 [calcd for C$_{37}$H$_{48}$NaO$_{10}$ (M+Na)$^+$ 675.3145]

Methyl (3,4,6-Tri-O-benzyl-2-deoxy-$\alpha$-D-glucosyl)-(1→6)-2,3,4-tri-O-methyl-$\alpha$-D-glucopyranoside (α-1.17):

![Chemical Structure](image-url)

$[\alpha]^{22}_D$ = +44 (c 1.0, CHCl$_3$);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.17–7.36 (m, 15H), 5.03 (d, $J$ = 2.0 Hz, 1H), 4.89 (d, $J$ = 11.0 Hz, 1H), 4.78 (d, $J$ = 3.5 Hz, 1H), 4.61–4.68 (m, 3H), 4.50–4.54 (m, 2H), 3.96 (ddd, $J$ = 5.0, 9.0, 11.5 Hz, 1H), 3.76–3.81 (m, 3H), 3.48–3.69 (m, 14H), 3.36 (s, 3H) 3.18 (dd, $J$ = 4.0, 10.0 Hz, 1H), 3.11 (dd, $J$ = 8.5, 9.5 Hz, 1H), 2.32 (dd, $J$ = 5.5, 12.5 Hz, 1H), 1.72 (ddd, $J$ = 3.5, 12.0, 13.0 Hz, 1H);
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 138.8, 138.7, 138.3, 128.50, 128.45, 128.4, 128.0, 127.9, 127.8, 127.74, 127.69, 127.65, 97.8, 97.4, 83.9, 82.0, 79.6, 78.3, 77.5, 75.0, 73.6, 71.9, 71.0, 69.9, 69.0, 65.8, 61.0, 60.6, 59.1, 55.2, 35.5;

IR (neat, cm\(^{-1}\)) 2931, 1453, 1363, 1199, 1157, 1098, 1050, 1028, 1007, 748, 698;

HRMS (ESI) found 675.3142 [calcd for C\(_{37}\)H\(_{48}\)NaO\(_{10}\) (M+Na)\(^+\) 675.3145]

Methyl (3,4-Di-O-acetyl-2,6-dideoxy-\(\beta\)-l-mannopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-\(\alpha\)-D-glucopyranoside (1.18):

The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at rt, \(\beta\)-1.18 was obtained as the major isomer (\(\alpha\):\(\beta\) = 20:80, crude HPLC). Purification by column chromatography (hexanes/ethyl acetate) yielded \(\beta\)-1.18 as a colorless liquid (108 mg, 64%).

\([\alpha]\)\(_{D}^{22}\) = +21 (c 1.0, CHCl\(_3\));

\(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.27–7.37 (m, 15H), 4.94–4.98 (m, 2H), 4.84 (m, 2H), 4.80 (d, \(J = 12.0\) Hz, 1H), 4.71 (m, 2H), 4.70 (d, \(J = 12.6\) Hz, 1H), 4.59–4.61 (m, 2H), 4.20 (dd, \(J = 3.6, 10.8\) Hz, 1H), 3.97 (t, \(J = 10.8\) Hz, 1H), 3.71 (dq, \(J = 1.8, 10.2\) Hz, 1H), 3.66 (dd, \(J = 1.8, 11.4\) Hz, 1H), 3.61 (t, \(J = 9.0\) Hz, 1H), 3.52 (dd, \(J = 4.2, 9.6\) Hz, 1H), 3.45 (qd, \(J = 12.0, 15.6\) Hz, 1H), 3.36 (s, 3H), 2.35 (ddd, \(J = 2.4, 6.0, 13.2\) Hz, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.70 (td, \(J = 12.6, 10.2\) Hz, 1H), 1.17 (d, \(J = 6.6\) Hz, 3H);
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.5, 170.2, 138.9, 138.6, 138.3, 128.6, 128.52, 128.45, 128.2, 128.13, 128.09, 128.0, 127.8, 99.2, 98.4, 82.1, 80.1, 77.6, 75.9, 75.2, 74.4, 73.6, 70.8, 70.1, 70.0, 67.0, 55.3, 36.6, 21.1, 21.0, 17.7;

IR (neat, cm$^{-1}$) 2936, 1746, 1368, 1244, 1224, 1163, 1086, 1070, 1047, 914, 749, 698;

HRMS (ESI) found 701.2939 [calcd for C$_{38}$H$_{46}$NaO$_{11}$ (M+Na)$^+$ 701.2938]

**Methyl (3,4-Di-O-acetyl-2,6-dideoxy-α-L-mannopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (α-1.18):**

![Chemical Structure](image)

[$\alpha$]$^{22}_D$ = −25 (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.25–7.39 (m, 15H), 5.25 (ddd, $J = 5.4, 9.6, 12.0$ Hz, 1H), 5.00 (d, $J = 10.8$ Hz, 1H), 4.90 (d, $J = 11.4$ Hz, 1H), 4.82 (d, $J = 11.4$ Hz, 1H), 4.81 (d, $J = 12.0$ Hz, 1H), 4.74 (d, $J = 3.0$ Hz, 1H), 4.71 (t, $J = 9.6$ Hz, 1H), 4.68 (d, $J = 12.6$ Hz, 1H), 4.59 (d, $J = 3.6$ Hz, 1H), 4.55 (d, $J = 10.8$ Hz, 1H), 4.00 (t, $J = 10.8$ Hz, 1H), 3.84 (dq, $J = 6.6, 9.6$ Hz, 1H), 3.81 (dd, $J = 1.8, 10.8$ Hz, 1H), 3.76 (dd, $J = 1.8, 6.0, 10.2$ Hz, 1H), 3.56 (dd, $J = 3.6, 9.6$ Hz, 1H), 3.46–3.49 (m, 2H), 3.39 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.13 (d, $J = 6.0$ Hz, 3H) 2.18 (dd, $J = 4.8, 12.6$ Hz, 1H), 1.74 (td, $J = 4.2, 13.2$ Hz, 1H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.3, 138.8, 138.4, 138.3, 128.6, 128.54, 128.50, 128.2, 128.1, 128.0, 127.92, 127.87, 127.7, 98.1, 97.1, 82.3, 80.3, 77.9, 75.9, 75.1, 74.9, 73.6, 70.1, 69.1, 66.4, 65.7, 55.2, 35.3, 21.1, 21.0, 17.6;

IR (neat, cm$^{-1}$) 2935, 1741, 1367, 1243, 1224, 1087, 1028, 741, 698;
HRMS (ESI) found 701.2948 [calcd for C\text{38}H\text{46}NaO\text{11} (M+Na)^+ 701.2938]

(+)−Menthoyl (3,4,6−Tri-\textit{O}-benzyl-2-deoxy-\textit{β}-\textit{D}-glucopyranoside) (1.19):

![Image of the structural formula]

The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at −40 °C in toluene (0.1 M) \( \beta-1.19 \) was obtained as the major isomer (\( \alpha:\beta = 8:92 \), crude \( ^1\text{H} \) NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded \( \beta-1.19 \) as a white solid (104 mg, 74%).

(+)−Menthoyl (3,4,6−Tri-\textit{O}-benzyl-2-deoxy-\textit{β}-\textit{D}-glucopyranoside) (\( \beta-1.19 \)):

\[ [\alpha]^{22}_D = -44 \text{ (c 1.0, CHCl}_3) \; \]

\( ^1\text{H} \) NMR (600 MHz, CDCl\textsubscript{3}) \( \delta \) 7.24−7.35 (m, 15H), 4.91 (d, \( J = 10.8 \text{ Hz, 1H} \)), 4.69 (d, \( J = 11.4 \text{ Hz, 1H} \)), 4.59−4.63 (m, 3H), 4.53−4.56 (m, 2H), 3.72 (d, \( J = 3.6 \text{ Hz, 2H} \)), 3.67 (ddd, \( J = 4.8, 6.4, 11.4 \text{ Hz, 1H} \)), 3.50−3.56 (m, 2H), 3.38 (dt, \( J = 3.0, 6.6 \text{ Hz, 1H} \)), 2.25−2.34 (m, 2H), 1.98−2.01 (m, 1H), 1.62−1.68 (m, 3H), 1.32−1.38 (m, 1H), 1.19−1.23 (m, 1H), 0.98 (qd, \( J = 3.0, 12.6 \text{ Hz, 1H} \)), 0.81−0.92 (m, 11H);

\( ^{13}\text{C} \) NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) 138.7, 128.53, 128.49, 128.45, 128.3, 127.8, 127.7, 127.6, 110.1, 96.4, 79.9, 78.4, 76.4, 75.3, 75.1, 73.8, 71.3, 69.9, 48.0, 40.8, 37.5, 34.6, 31.6, 25.3, 23.3, 22.5, 21.2, 16.0;

IR (neat, cm\textsuperscript{-1}) 2951, 2922, 2866, 1454, 1362, 1092, 988, 734, 697;
HRMS (ESI) found 595.3402 [calcd for C_{37}H_{48}NaO_{5} (M+Na)^+ 595.3399]

(+)-Mentholyl (3,4,6-Tri-O-benzyl-2-deoxy-\(\alpha\)-D-glucopyranoside) (\(\alpha\)-1.19):

\[
\begin{align*}
\text{BnO} & \quad O \quad \text{Me} \\
\text{BnO} & \quad O \quad \text{Me}
\end{align*}
\]

\(\left[\alpha\right]_{D}^{22} = +41 \ (c 1.0, \text{CHCl}_3);\)

\(^1\text{H} \text{NMR} (600 \text{ MHz, CDCl}_3) \delta 7.25–7.36 (m, 13\text{H}), 7.17–7.18 (m, 2\text{H}), 5.10 (d, J = 2.4 \text{ Hz, 1H}), 4.90 (d, J = 11.4 \text{ Hz, 1H}), 4.64–4.69 (m, 3\text{H}), 4.50 (d, J = 12.0 \text{ Hz, 1H}), 3.99 (ddd, J = 4.8, 6.4, 11.4 \text{ Hz, 1H}), 3.94 (dq, J = 1.8, 4.2 \text{ Hz, 1H}), 3.79 (dd, J = 4.2, 10.8 \text{ Hz, 1H}), 3.66 (dd, J = 1.8, 9.0 \text{ Hz, 1H}), 3.59 (t, J = 9.0 \text{ Hz, 1H}), 3.30 (td, J = 4.8, 9.0 \text{ Hz, 1H}), 2.26 (dd, J = 4.8, 12.0 \text{ Hz, 1H}), 2.09–2.11 (m, 1\text{H}), 2.02 (quintd, J = 2.4, 7.2 \text{ Hz, 1H}), 1.68 (td, J = 3.0, 12.0 \text{ Hz, 1H}), 1.56–1.62 (m, 2\text{H}), 1.33–1.39 (m, 1\text{H}), 1.14–1.19 (m, 1\text{H}), 0.90–0.98 (m, 5\text{H}), 0.74–0.84 (m, 7\text{H});\)

\(^{13}\text{C} \text{NMR} (126 \text{ MHz, CDCl}_3) \delta 138.9, 138.7, 138.4, 128.49, 128.45, 128.4, 128.1, 128.0, 127.8, 127.69, 127.65, 99.6, 80.7, 78.6, 77.9, 75.1, 73.6, 71.9, 71.0, 69.2, 48.9, 43.1, 36.2, 34.5, 31.8, 25.9, 23.5, 22.4, 21.3, 16.5;\)

IR (neat, cm\(^{-1}\)) 2953, 2920, 2866, 1453, 1364, 1091, 1023, 999, 732, 695;

HRMS (ESI) found 595.3390 [calcd for C_{37}H_{48}NaO_{5} (M+Na)^+ 595.3399]

(\(-\))-Menthoxy (3,4,6-Tri-O-benzyl-2-deoxy-\(\beta\)-D-glucopyranoside) (1.20):
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at −40 °C in toluene (0.1 M) **β-1.20** was obtained as the major isomer (α:β = 12:88, crude **1H NMR**). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.20** as a white solid (103 mg, 72%).

**(-)-Menthoylethyl (3,4,6-Tri-O-benzyl-2-deoxy-β-D-glucopyranoside) (β-1.20):**

[α]^{23}_D = +9 (c 1.0, CHCl₃);

**1H NMR** (600 MHz, CDCl₃) δ 7.24–7.36 (m, 15H), 4.91 (d, J = 10.8 Hz, 1H), 4.70 (d, J = 11.4 Hz, 1H), 4.58–4.64 (m, 4H), 4.48 (dd, J = 1.8, 10.2 Hz, 1H), 3.87 (d, J = 10.8 Hz, 1H), 3.65–3.69 (m, 2H), 3.42–3.47 (m, 2H), 3.34 (td, J = 4.8, 10.8 Hz, 1H), 2.35 (ddd, J = 1.8, 4.8, 11.4 Hz, 1H), 2.27–2.30 (m, 1H), 2.10 (quintd, J = 2.4, 7.2 Hz, 1H), 1.60–1.69 (m, 3H), 1.34–1.40 (m, 1H), 1.23–1.28 (m, 1H), 1.09 (q, J = 10.8 Hz, 1H), 0.80–0.99 (m, 8H), 0.77 (d, J = 6.6 Hz, 3H);

**13C NMR** (126 MHz, CDCl₃) δ 138.7, 138.6, 128.6, 128.49, 128.45, 128.45, 128.2, 127.79, 127.76, 127.7, 127.6, 101.5, 81.5, 79.9, 78.4, 75.3, 75.1, 73.6, 71.6, 69.9, 48.6, 43.6, 37.2, 34.5, 31.9, 25.8, 23.4, 22.4, 21.3, 16.5;

IR (neat, cm⁻¹) 2953, 2924, 2867, 1725, 1453, 1363, 1271, 1093, 1077, 734, 697;

HRMS (ESI) found 595.3388 [calcd for C₃₇H₄₈NaO₅ (M+Na)⁺ 595.3399]

**(-)-Menthoylethyl (3,4,6-Tri-O-benzyl-2-deoxy-α-D-glucopyranoside) (α-1.20):**
\([\alpha]^{22}_D = +77 \ (c 1.0, \text{CHCl}_3)\);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.25–7.36 (m, 13H), 7.16–7.18 (m, 2H), 5.21 (d, $J = 3.6$ Hz, 1H), 4.88 (d, $J = 10.2$ Hz, 1H), 4.65–4.70 (m, 3H), 4.53 (d, $J = 10.8$ Hz, 1H), 4.49 (d, $J = 12.6$ Hz, 1H), 3.98 (ddd, $J = 5.4$, 9.0, 12.0 Hz, 1H), 3.84 (dd, $J = 3.0$, 10.8 Hz, 1H), 3.78–3.80 (m, 1H), 3.63–3.68 (m, 2H), 3.46 (td, $J = 4.2$, 10.2 Hz, 1H), 2.19–2.23 (m, 2H), 2.08–2.10 (m, 1H), 1.79 (ddd, $J = 4.2$, 6.0, 7.2 Hz, 1H), 1.62–1.67 (m, 2H), 1.32–1.38 (m, 1H), 1.21–1.26 (m, 1H), 0.72–1.00 (m, 12H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 139.0, 138.3, 128.5, 128.4, 128.3, 128.0, 127.8, 127.71, 127.66, 127.6, 93.3, 78.7, 78.0, 75.3, 74.5, 73.7, 71.9, 71.5, 69.0, 48.1, 39.9, 36.4, 34.7, 31.5, 25.2, 23.0, 22.5, 21.4, 15.6;

IR (neat, cm$^{-1}$) 2953, 2921, 2868, 1453, 1090, 1018, 995, 748, 695;

HRMS (ESI) found 595.3404 [calcd for C$_{37}$H$_{48}$NaO$_{5}$ (M+Na)$^+$ 595.3399]

**Methyl (2,3,4-Tri-O-benzyl-6-deoxy-β-L-galactopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (1.21):**
The general procedure was conducted on a 0.20 mmol scale. After stirring for 18 h at rt \(\beta\)-1.21 was obtained as the major isomer (\(\alpha:\beta = 5:95\), crude \(^1\)H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded 1.21 (\(\alpha:\beta = 4:96\)) as a colorless oil (105 mg, 0.16 mmol, 80%).

\[\text{[\alpha]_{22}^D = +63.4 (c 1.0, CHCl}_3)\];

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.43–7.44 (m, 2H), 7.25–7.40 (m, 13H), 4.98–5.06 (m, 2H), 4.77–4.83 (m, 2H), 4.70–4.75 (m, 3H), 4.43 (d, \(J = 7.6\) Hz, 1H), 4.13 (dd, \(J = 4.1, 11.5\) Hz, 1H), 3.84 (dd, \(J = 7.9, 9.7\) Hz, 1H), 3.77 (dd, \(J = 1.8, 11.2\) Hz, 1H), 4.57–4.64 (m, 2H), 3.63 (s, 3H), 3.59 (s, 3H), 3.46–3.56 (m, 3H), 3.45 (s, 3H), 3.37 (s, 3H), 3.26 (dd, \(J = 9.0, 10.2\) Hz, 1H) 3.07 (dd, \(J = 3.5, 9.4\) Hz, 1H), 1.20 (d, \(J = 6.5\) Hz, 3H);

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 139.0, 138.7, 138.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.6, 127.5, 104.3, 97.4, 83.6, 82.6, 81.7, 79.6, 79.5, 76.5, 75.0, 74.6, 73.2, 70.4, 70.2, 68.0, 60.8, 60.7, 59.0, 55.1, 16.9;

IR (neat, cm\(^{-1}\)) 3063, 3029, 2978, 2932, 2902, 2835, 1497, 1454, 1360, 1159, 1140, 1064, 1045, 1027, 1000, 900, 731, 670, 632;

HRMS (ESI) found 670.3617 [calcd for C\(_{37}\)H\(_{52}\)NO\(_{10}\) (M+NH\(_4^+\)) \(+\) 670.3586].

**Methyl (2,3,4-Tri-O-benzyl-6-deoxy-\(\beta\)-1-galactopyranosyl)-(1\(\rightarrow\)3)-2,4,6-tri-O-methyl-\(\alpha\)-\(\delta\)-galactopyranoside (1.22)**

![Image of the compound structure]
The general procedure was conducted on a 0.25 mmol scale. After stirring for 18 h at rt \( \beta-1.22 \) was obtained as the major isomer (\( \alpha:\beta = 5:95 \), crude \(^1\)H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded \( \beta-1.22 \) as a white solid (135 mg, 0.21 mmol, 83%).

\[ [\alpha]^{23}_{D} = +49.8 \ (c\ 1.0, \text{CHCl}_3) \];

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.22–7.41 (m, 15H), 4.99 (d, \( J = 11.7 \) Hz, 1H), 4.95 (d, \( J = 11.7 \) Hz, 1H), 4.92 (d, \( J = 11.2 \) Hz 1H), 4.86 (d, \( J = 3.5 \) Hz, 1H), 4.74 (s, 2H), 4.68 (d, \( J = 12.3 \) Hz, 1H), 4.54 (d, \( J = 7.6 \) Hz, 1H), 4.14 (dd, \( J = 2.3, 10.0 \) Hz, 1H), 3.83 (dd, \( J = 7.9, 9.1 \) Hz, 1H), 3.78 (t, \( J = 6.5 \) Hz, 1H), 3.71 (dd, \( J = 3.5, 10.0 \) Hz, 1H), 3.55–3.62 (m, 3H), 3.54 (s, 3H), 3.46–3.51 (m, 2H), 3.50 (s, 3H), 3.42–3.46 (m, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 1.22 (d, \( J = 6.5 \) Hz, 3H);

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 141.7, 141.4, 141.1, 131.0, 130.9, 130.8, 130.7, 130.2, 130.1, 130.0, 105.2, 101.0, 86.0, 82.8, 80.7, 80.4, 79.9, 79.1, 77.8, 77.2, 75.5, 73.9, 73.4, 71.6, 64.2, 62.5, 61.8, 58.0, 19.7;

IR (neat, cm\(^{-1}\)) 3063, 3032, 2990, 2967, 2930, 2915, 2882, 2856, 2821, 1455, 1359, 1207, 1139, 1093, 1052, 1015, 993, 957, 918, 822, 760, 731, 695, 658, 591 cm\(^{-1}\); HRMS (ESI) found 670.3633 [calcd for C\(_{37}\)H\(_{52}\)NO\(_{10}\) (M+NH\(_4^+\)) 670.3586].

**Methyl (2,3,4-Tri-\(\text{O}\)-benzyl-\(\beta\)-\(\text{D}\)-xylopyranosyl)-(1\(\rightarrow\)6)-2,3,4-tri-\(\text{O}\)-methyl-\(\alpha\)-\(\text{D}\)-glucopyranoside (1.23):**
The general procedure was conducted on a 0.20 mmol scale. After stirring for 48 h at 40 °C β-1.23 was obtained as the major isomer (α:β = 10:90, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded 1.23 (α:β = 13:87) as a white solid (102 mg, 0.16 mmol, 80%).

$[^\alpha]^D_{23} = +64.6$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.22–7.41 (m, 15H), 4.96 (d, $J = 11.2$ Hz, 1H), 4.86 (s, 2 H), 4.83 (d, $J = 3.5$ Hz, 1H), 4.76 (d, $J = 11.2$ Hz, 1H), 4.74 (d, $J = 11.7$ Hz, 1H), 4.63 (d, $J = 11.7$ Hz, 1H), 4.41 (d, $J = 7.6$ Hz, 1H), 4.10 (dd, $J = 1.8$, 10.6 Hz, 1H), 3.95 (dd, $J = 5.3$, 11.7 Hz, 1H), 3.74 (dd, $J = 4.7$, 10.6 Hz, 1H), 3.57–3.70 (m, 4H), 3.62 (s, 3H), 3.51 (s, 3H), 3.46 (s, 3H), 3.42–3.48 (m, 1H), 3.36 (s, 3H), 3.14–3.27 (m, 3H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 138.7, 138.5, 138.3, 128.6, 128.4, 128.1, 128.0, 127.7, 127.7, 104.3, 97.5, 84.1, 83.6, 81.9, 81.8, 79.6, 77.9, 75.7, 75.1, 73.5, 69.8, 68.6, 64.1, 60.9, 60.5, 59.0, 55.3;

IR (neat, cm$^{-1}$) 3087, 3064, 3031, 3004, 2963, 2929, 2908, 2865, 2826 1496, 1452, 1387, 1355, 1327, 1257, 1197, 1147, 1080, 1066, 1045, 1027, 965, 895, 752, 728, 691, 629, 575, 542, 462;

HRMS (ESI) found 656.3458 [calcd for C$_{36}$H$_{50}$NO$_{10}$ (M+NH$_4$)$^+$ 656.3429].

Methyl (2,3,4-Tri-$O$-benzyl-$\beta$-$D$-xylopyranosyl)-(1→3)-2,4,6-tri-$O$-methyl-$\alpha$-$D$-galactopyranoside (1.24):
The general procedure was conducted on a 0.20 mmol scale using 10 mol% catalyst. After stirring for 48 h at 40 °C δ-1.24 was obtained as the major isomer (α:β = 12:88, crude 1H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded δ-1.24 as a white solid (89 mg, 0.14 mmol, 69%).

\[ \alpha \]_D = +59.4 (c 1.0, CHCl_3);

1H NMR (600 MHz, CDCl_3) δ 7.31–7.32 (m, 2H), 7.18–7.29 (m, 13H), 4.95 (d, J = 11.2 Hz, 1H), 4.86 (d, J = 3.5 Hz, 1H), 4.83 (d, J = 11.2 Hz, 1H), 4.79 (d, J = 10.6 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.67 (d, J = 11.7 Hz, 2H), 4.65 (d, J = 7.6 Hz, 1H), 4.57 (d, J = 11.7 Hz, 1H), 4.02 (dd, J = 2.9, 10.0 Hz, 1H), 3.80–3.89 (m, 2H), 3.67 (dd, J = 3.5, 10.0 Hz, 1H), 3.53 (s, 3H), 3.44–3.61 (m, 5H), 3.38 (s, 3H), 3.34 (s, 3H), 3.33 (s, 3H), 3.27–3.33 (m, 1H), 3.12–3.19 (m, 1H);

13C NMR (151 MHz, CDCl_3) δ 138.9, 138.8, 138.3, 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.6, 104.6, 97.6, 83.9, 82.4, 79.8, 78.6, 78.1, 76.3, 75.8, 74.6, 73.4, 71.6, 69.1, 63.8, 61.6, 59.4, 58.6, 55.5;

IR (neat, cm⁻¹) 3065, 3027, 2986, 2935, 2916, 2900, 2862, 1496, 1452, 1360, 1210, 1190, 1165, 1146, 1107, 1073, 1053, 1021, 967, 949, 884, 749, 698, 656. 593, 500, 451;

HRMS (ESI) found 656.3455 [calcd for C_{36}H_{50}NO_{10} (M+NH_4)^+ 656.3429].

Thiophenyl (3,4,6-Tri-O-benzyl-2-azido-2-deoxy-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl- β -D-galactopyranoside (1.25):
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at 40 °C $\beta$-1.25 was obtained as the major isomer ($\alpha:\beta = 2:98$, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded $\beta$-1.25 as a white solid (162 mg, 65%).

**Thiophenyl (3,4,6-Tri-$O$-benzyl-2-azido-2-deoxy-$\beta$-$D$-galactopyranosyl)-(1→6)-2,3,4-tri-$O$-benzyl-$\beta$-$D$-galactopyranoside ($\beta$-1.25):**

$[\alpha]^{22}_D = -5.2$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.16–7.56 (m, 35H), 4.93 (d, $J = 12.0$ Hz, 1H), 4.88 (d, $J = 10.8$ Hz, 1H), 4.80 (d, $J = 10.2$ Hz, 1H), 4.76 (d, $J = 10.8$ Hz, 1H), 4.64–4.73 (m, 6H), 4.56 (d, $J = 10.8$ Hz, 1H), 4.40 (d, $J = 12.0$ Hz, 1H), 4.37 (d, $J = 11.4$ Hz, 1H), 4.25 (d, $J = 7.8$ Hz, 1H), 3.88–3.97 (m, 4H), 3.75–3.82 (m, 2H), 3.64 (t, $J = 6.0$ Hz, 1H), 3.60 (dd, $J = 2.4$, 8.4 Hz, 1H), 3.57 (t, $J = 8.4$ Hz, 1H), 3.43–3.48 (m, 2H), 3.26 (dd, $J = 2.4$, 10.8 Hz, 1H);

$^1$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.8, 138.5, 138.3, 137.7, 134.3, 131.6, 129.0, 128.64, 128.61, 128.56, 128.45, 128.42, 128.39, 128.31, 128.28, 128.07, 128.05, 128.03, 127.9, 127.83, 127.81, 127.7, 127.6, 127.5, 127.2, 102.2, 87.9, 84.1, 80.7, 77.5, 75.8, 74.9, 74.4, 73.7, 73.4, 73.2, 72.7, 72.6, 72.3, 68.2, 67.9, 63.3;

IR (neat, cm$^{-1}$) 2111, 1264, 1050, 732, 669;

HRMS (ESI) found 1022.4000 [calcd for C$_{60}$H$_{61}$N$_3$NaO$_9$S (M+Na)$^+$ 1022.4026].
Thiophenyl (3,4,6-Tri-O-benzyl-2-azido-2-deoxy-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside (α-1.25):

\[
\begin{align*}
 & \text{BnO} \quad \text{BnO} \quad \text{O} \\
 & \text{BnO} \quad \text{N}_3 \quad \text{O} \\
 & \text{BnO} \quad \text{OBn} \quad \text{O} \\
 & \text{BnO} \quad \text{SPh}
\end{align*}
\]

\[
[\alpha]^{22}_D = +7.4 \ (c \ 1.0, \ \text{CHCl}_3);
\]

1H NMR (600 MHz, CDCl₃) δ 7.18–7.57 (m, 35H), 5.02 (d, \( J = 11.4 \) Hz, 1H), 4.85 (d, \( J = 11.4 \) Hz, 1H), 4.79 (d, \( J = 9.6 \) Hz, 1H), 4.71–4.75 (m, 5H), 4.63–4.66 (m, 3H), 4.53 (d, \( J = 11.4 \) Hz, 1H), 4.46 (d, \( J = 11.4 \) Hz, 1H), 4.39 (d, \( J = 12.0 \) Hz, 1H), 4.02 (s, 1H), 3.91–3.96 (m, 3H), 3.81–3.87 (m, 3H), 3.57–3.63 (m, 3H), 3.47–3.54 (m, 2H);

13C NMR (126 MHz, CDCl₃) δ 138.7, 138.5, 138.4, 137.9, 131.7, 128.9, 128.6, 128.4, 128.2, 128.1, 128.0, 127.2, 98.6, 87.6, 84.2, 77.4, 77.2, 77.0, 75.8, 75.0, 74.5, 73.8, 73.7, 73.2, 72.9, 72.2, 69.5, 68.5, 67.2, 59.9;

IR (neat, cm⁻¹) 2108, 1264, 1096, 1049, 734, 699;

HRMS (ESI) found 1022.4034 [calcd for C₆₀H₆₁N₃NaO₉S (M+Na)⁺ 1022.4026].

Methyl (3,4,6-Tri-O-benzyl-2-azido-2-deoxy-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-O-methyl-β-D-galactopyranoside (1.26):

\[
\begin{align*}
 & \text{BnO} \quad \text{OBn} \quad \text{MeO} \\
 & \text{BnO} \quad \text{N}_3 \quad \text{OMe} \\
 & \text{BnO} \quad \text{OMe}
\end{align*}
\]
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at 40 °C β-1.26 was obtained as the major isomer (α:β = 8:92, crude ¹H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded β-1.26 as a white solid (126 mg, 73%).

\([\alpha]_{D}^{22} = +60 \text{ (c 1.0, CHCl}_3\text{)};\)

¹H NMR (600 MHz, CDCl₃) δ 7.25–7.39 (m, 15H), 4.91 (d, J = 3.6 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 11.4 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 7.2 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.44 (s, 2H), 4.04 (dd, J = 3.0, 10.2 Hz, 1H), 3.88 (d, J = 3.0 Hz, 1H), 3.85 (t, J = 6.0 Hz, 1H), 3.76–3.79 (m, 2H), 3.65 (d, J = 2.4 Hz, 1H), 3.62 (t, J = 6.4 Hz, 1H), 3.48–3.56 (m, 10H), 3.42 (s, 3H), 3.37 (s, 3H), 3.28 (dd, J = 3.0, 9.6 Hz, 1H);

¹³C NMR (126 MHz, CDCl₃) δ 138.7, 138.0, 137.9, 128.6, 128.3, 128.1, 127.94, 127.93, 127.8, 127.7, 103.2, 97.7, 80.7, 79.3, 78.7, 77.0, 74.7, 73.6, 73.3, 72.9, 72.6, 71.7, 69.4, 68.4, 63.8, 61.5, 59.4, 58.8, 55.5;

IR (neat, cm⁻¹) 2111, 1454, 1264, 1068, 734, 698;

HRMS (ESI) found 716.3158 [calcd for C₃₇H₄₇N₃NaO₁₀ (M+Na)⁺ 716.3159]

Methyl (3,4,6-Tri-Ø-Benzyl-2-azido-2-deoxy-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-Ø-methyl- β-D-galactopyranoside (α-1.26):

\([\alpha]_{D}^{22} = +120 \text{ (c 1.0, CHCl}_3\text{)};\)
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.25–7.40 (m, 15H), 5.10 (d, $J = 3.0$ Hz, 1H), 4.87–4.89 (m, 2H), 4.76 (d, $J = 12.0$ Hz, 1H), 4.66 (d, $J = 11.4$ Hz, 1H), 4.57 (d, $J = 11.4$ Hz, 1H), 4.50 (d, $J = 11.4$ Hz, 1H), 4.45 (d, $J = 11.4$ Hz, 1H), 4.26 (t, $J = 7.2$ Hz, 1H), 4.11 (br s, 1H), 4.00–4.03 (m, 2H), 3.95 (dd, $J = 3.6$, 10.8 Hz, 1H), 3.83 (t, $J = 6.0$ Hz, 1H), 3.63–3.66 (m, 3H), 3.50–3.60 (m, 6H), 3.41 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.6, 138.1, 137.6, 128.6, 128.5, 128.4, 128.2, 128.13, 128.11, 128.05, 127.81, 127.77, 97.9, 95.3, 77.3, 77.1, 75.8, 75.0, 74.5, 73.4, 71.9, 71.2, 69.3, 68.9, 68.3, 61.4, 60.0, 59.32, 59.29, 55.4;

IR (neat, cm$^{-1}$) 2107, 1453, 1264, 1050, 731, 696;

HRMS (ESI) found 716.3165 [calcd for C$_{37}$H$_{47}$N$_3$NaO$_{10}$ (M+Na)$^+$ 716.3159]

Methyl (2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (1.27):

The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at 40 °C β-1.27 was obtained as the major isomer ($\alpha$:$\beta = 7:93$, crude $^1$H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded 1.27 ($\alpha$:$\beta = 5:95$) as a white solid (146 mg, 0.19 mmol, 77%).

$[\alpha]_{D}^{23} = +57$ (c 1.0, CHCl$_3$);
^1H NMR (600 MHz, CDCl₃) δ 7.15–7.34 (m, 18H), 7.07–7.13 (m, 2H), 4.96 (d, J = 11.2 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.72–4.76 (m, 3H), 4.70 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 7.6 Hz, 1H), 4.13–4.16 (m, 1H), 3.58–3.73 (m, 5H), 3.50–3.56 (m, 1H), 3.54 (s, 3H), 3.42–3.49 (m, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 3.28 (s, 3H), 3.13 (dd, J = 3.8, 9.7 Hz, 1H), 3.08 (t, J = 9.4 Hz, 1H);

^13C NMR (126 MHz, CDCl₃) δ 138.5, 138.4, 138.2, 138.0, 128.3, 128.3, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 103.8, 97.3, 84.8, 83.4, 82.1, 81.7, 79.7, 77.9, 75.7, 75.0, 75.0, 74.8, 73.3, 69.8, 68.9, 68.8, 60.8, 60.3, 58.9, 55.1;

IR (neat, cm⁻¹) 3063, 3030, 2904, 2836, 1467, 1454, 1360, 1454, 1360, 1155, 1098, 1067, 1028, 999, 736, 698;

HRMS (ESI) found 776.4026 [calcd for C₄₄H₅₈NO₁₁ (M+NH₄) 776.4010].

Methyl (3,4,6-Tetra-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside (1.28):

The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at 50 °C β-1.28 was obtained as the major isomer (α:β = 2:98, crude HPLC). Purification by column chromatography (ethyl acetate/methanol) yielded β-1.28 (α:β = 2:98) as a white solid (173 mg, 88%). The spectral data was in agreement with those reported in literature.³⁸

\[ ^1H\text{NMR (500 MHz, }\text{CDCl}_3\text{)} \delta 7.27 - 7.36 (m, 15), 5.35 (d, }J = 8.0\text{ Hz, 1H}), 5.27 (dd, }J = 9.5, 10.5\text{ Hz, 1H}), 5.04 (dd, }J = 9.0, 10.0\text{ Hz, 1H}), 4.98 (d, }J = 11.0\text{ Hz, 1H}), 4.84 (d, }J = 11.0\text{ Hz, 1H}), 4.80 (d, }J = 11.0\text{ Hz, 1H}), 4.78 (d, }J = 12.0\text{ Hz, 1H}), 4.64 - 4.68\text{ (m, 2H}), 4.59 (d, }J = 3.5\text{ Hz, 1H}), 4.57 (d, }J = 11.0\text{ Hz, 1H}), 4.21 (dd, }J = 4.0, 12.5\text{ Hz, 1H}), 4.10 (dd, }J = 2.0, 13.0\text{ Hz, 1H}), 4.05 (dd, }J = 1.5, 10.5\text{ Hz, 1H}), 3.98 (dd, }J = 9.0, 9.5\text{ Hz, 1H}), 3.84 (dt, }J = 8.0, 11.0\text{ Hz, 1H}), 3.75 - 3.77\text{ (m, 1H}), 3.71 (dd, }J = 4.0, 11.0\text{ Hz, 1H}), 3.66 (dq, }J = 2.0, 10.0\text{ Hz, 1H}), 3.52 (dd, }J = 4.0, 10.0\text{ Hz, 1H}), 3.47 (t, }J = 10.0\text{ Hz, 1H}), 3.36\text{ (s, 3H}), 2.01 - 2.02\text{ (m, 9H)}, 1.82\text{ (s, 3H)};\]

HRMS (ESI) found 816.3224 [calcd for C\(_{42}\)H\(_{51}\)NNaO\(_{14}\) (M+Na\(^+\)) 816.3207].

**Thiophenyl (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside (1.29):**

![Structure of Thiophenyl (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside (1.29).](image)

The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at rt in dichloromethane (0.5 M) \textbf{β-1.29} was obtained as the major isomer (α:β = 17:83, crude \(^1\text{H NMR}).

Purification by column chromatography (hexanes/ethyl acetate) yielded \textbf{β-1.29} as a white solid (187 mg, 74%).
$[\alpha]_{22}^{22} = +15$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CD$_3$CN) $\delta$ 7.15–7.52 (m, 35H), 6.20 (d, $J$ = 9.6 Hz, 1H), 4.82 (d, $J$ = 10.8 Hz, 1H), 4.81 (d, $J$ = 10.8 Hz, 1H), 4.66–4.75 (m, 5H), 4.62 (d, $J$ = 12.0 Hz, 1H), 4.59 (d, $J$ = 10.8 Hz, 1H), 4.54 (d, $J$ = 10.8 Hz, 1H), 4.52 (d, $J$ = 12.0 Hz, 1H), 4.47 (d, $J$ = 12.0 Hz, 1H), 4.41–4.43 (m, 2H), 3.96–4.01 (m, 3H), 3.80–3.83 (m, 1H), 3.68–3.74 (m, 3H), 3.54–3.64 (m, 5H), 1.83 (s, 3H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.7, 140.0, 139.9, 139.7, 139.5, 139.4, 135.3, 131.7, 130.0, 129.3, 129.21, 129.19, 129.1, 129.0, 128.9, 128.82, 128.79, 128.69, 128.58, 128.56, 128.54, 128.52, 128.49, 128.4, 127.9, 102.8, 87.8, 84.5, 80.8, 78.1, 77.9, 75.9, 75.5, 74.9, 74.1, 74.0, 73.8, 72.8, 72.7, 69.9, 68.9, 52.8, 23.7;

IR (neat, cm$^{-1}$) 2866, 1658, 1454, 1362, 1216, 1064, 745, 695, 666;

HRMS (ESI) found 1038.4207 [calcd for C$_{62}$H$_{65}$NNaO$_{10}$S (M+Na)$^+$ 1038.4227].

**Thiophenyl (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside (α-1.29):**

\[
\begin{align*}
\text{BnO} & \quad \text{BnO} \\
\text{AcH} & \quad \text{O} \\
\text{BnO} & \quad \text{O} \\
\text{OBn} & \quad \text{O} \\
\text{BnO} & \quad \text{BnO} \\
\text{SPh} &
\end{align*}
\]

$[\alpha]_{22}^{22} = +55$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.17–7.57 (m, 35H), 5.21 (d, $J$ = 7.8 Hz, 1H), 4.91–4.95 (m, 2H), 4.68–4.84 (m, 6H), 4.36–4.65 (m, 7H), 3.91–3.96 (m, 2H), 3.78–3.85 (m, 2H), 3.70 (d, $J$ = 2.4 Hz, 1H), 3.46–3.58 (m, 6H), 1.82 (s, 3H);
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 169.8, 138.7, 138.5, 138.4, 138.3, 138.0, 134.0, 132.1, 131.7, 128.9, 128.7, 128.64, 128.61, 128.60, 128.57, 128.50, 128.48, 128.45, 128.41, 128.37, 128.29, 128.16, 128.0, 127.93, 127.90, 127.78, 127.77, 127.7, 127.6, 127.4, 98.3, 87.7, 84.22, 84.19, 77.3, 76.7, 75.8, 74.5, 74.1, 73.7, 73.3, 72.5, 71.4, 69.9, 69.1, 67.5, 49.1; IR (neat, cm\(^{-1}\)) 2920, 2873, 1651, 1545, 1453, 1354, 1215, 1090, 1051, 1026, 732, 694, 666; HRMS (ESI) found 1038.4221 [calcd for C\(_{62}\)H\(_{65}\)NNaO\(_{10}\) (M+Na)]\(^+\) 1038.4227.

**Methyl (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-\(\beta\)-D-galactopyranosyl)-(1→3)-2,4,6-tri-O-methyl- \(\beta\) -D-galactopyranoside (1.30):**

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} & \quad \text{MeO} & \quad \text{OMe} \\
\text{BnO} & \quad \text{AcHN} & \quad \text{MeO} & \quad \text{OMe}
\end{align*}
\]

The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at rt in dichloromethane (0.5 M) \(\beta\)-1.30 was obtained as the major isomer (\(\alpha:\beta = 1:99\), crude \(^1\)H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded 1.30 as a white solid (125 mg, 71%).

\([\alpha]\)\(^{22}\)_D = +46 (c 1.0, CHCl\(_3\));

\(^1\)H NMR (600 MHz, CD\(_3\)CN) \(\delta\) 7.26–7.36 (m, 15 H), 6.28 (d, \(J = 9.6\) Hz, 1 H), 4.81 (d, \(J = 10.8\) Hz, 1 H), 4.76 (d, \(J = 3.6\) Hz, 1 H), 4.70 (d, \(J = 12.0\) Hz, 1 H), 4.46–4.55 (m, 5 H), 3.97 (q, \(J = 9.6\) Hz, 1 H), 3.94 (d, \(J = 2.4\) Hz, 1 H), 3.74 (dd, \(J = 3.6, 10.4\) Hz, 1 H), 3.72 (dd, \(J = 6.0\) Hz, 1 H), 3.57–3.65 (m, 5 H), 3.37–3.42 (m, 6 H), 3.34 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 1.84 (s, 3 H);
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.4, 139.0, 138.3, 138.1, 128.7, 128.61, 128.56, 128.4, 128.3, 128.2, 128.1, 128.00, 127.97, 127.90, 127.87, 127.5, 102.1, 97.7, 79.3, 78.8, 78.6, 77.9, 74.5, 73.6, 73.3, 72.5, 72.1, 71.7, 69.3, 68.9, 61.6, 59.3, 58.8, 55.3, 54.6;

IR (neat, cm$^{-1}$) 3294, 2923, 1651, 1556, 1453, 1355, 1137, 1107, 1055, 990, 748, 733, 696;

HRMS (ESI) found 732.3344 [calcd for C$_{39}$H$_{51}$NNaO$_{11}$ (M+Na)$^+$ 732.3360].

Methyl (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-O-methyl- β-D-galactopyranoside (α-1.30):

[α]$^{22}_D = +157$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.26–7.38 (m, 15H), 6.31 (d, $J = 8.4$ Hz, 1H), 4.99 (d, $J = 3.6$ Hz, 1H), 4.80–4.82 (m, 2H), 4.74 (d, $J = 11.4$ Hz, 1H), 4.52–4.56 (m, 2H), 4.49 (s, 2H), 4.41 (ddd, $J = 3.6, 9.6, 12.0$, 1H), 4.24 (t, $J = 6.6$ Hz, 1H), 4.05 (d, $J = 1.2$ Hz, 1H), 3.91 (dd, $J = 3.0, 10.2$ Hz, 1H), 3.78 (dd, $J = 2.4, 10.8$, 1H), 3.74 (t, $J = 6.0$ Hz, 1H), 3.61 (dd, $J = 7.2, 11.2$ Hz, 1H), 3.58 (d, $J = 3.0$ Hz, 1H), 3.45–3.50 (m, 3H), 3.38–3.40 (m, 4H), 3.38 (s, 3H), 3.29 (s, 3H), 3.25 (s, 3H), 1.85 (s, 3H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.7, 138.8, 138.3, 128.64, 128.59, 128.51, 128.47, 128.44, 128.35, 128.29, 128.19, 128.17, 128.02, 128.00, 127.8, 127.6, 97.8, 93.8, 77.1, 76.6, 75.5, 74.7, 73.4, 72.60, 72.56, 71.0, 69.3, 68.7, 68.5, 61.1, 59.4, 59.3, 55.4, 49.0, 23.7;

IR (neat, cm$^{-1}$) 3320, 2929, 1645, 1545, 1453, 1348, 1120, 1098, 1052, 721, 695;

HRMS (ESI) found 732.3363 [calcd for C$_{39}$H$_{51}$NNaO$_{11}$ (M+Na)$^+$ 732.3360].
Disaccharide $\beta$-1.25 was converted to the corresponding chloride by Ph$_2$SO and (COCl)$_2$.\textsuperscript{39} The crude glycosyl chloride was used in the glycosylation reaction without further purification. The general procedure was conducted on a 0.05 mmol scale using 10 mol% catalyst. After stirring for 48 h at rt in dichloromethane (0.5 M) $\beta$-1.31 was obtained as the major isomer ($\alpha$:$\beta$ = 1:99, crude $^1$H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded 1.31 ($\alpha$:$\beta$ = 1:99) as a white solid (42 mg, 62%).

$[\alpha]^{22}_D = +6.2$ (c 1.0, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.17–7.36 (m, 45H), 4.97 (d, $J$ = 10.2 Hz, 1H), 4.95 (d, $J$ = 11.4 Hz, 1H), 4.91 (d, $J$ = 12.0 Hz, 1H), 4.87 (d, $J$ = 11.4 Hz, 1H), 4.77- 4.80 (m, 3H), 4.53–4.74 (m, 10H), 4.43 (d, $J$ = 11.4 Hz, 1H), 4.40 (d, $J$ = 12.0 Hz, 1H), 4.36 (d, $J$ = 7.8 Hz, 1H), 4.27 (d, $J$ = 7.8 Hz, 1H), 4.21 (dd, $J$ = 1.8, 11.4 Hz, 1H), 3.99 (t, $J$ = 9.6 Hz, 1H), 3.81–3.91 (m, 5H), 3.68–3.78 (m, 3H), 3.58 (t, $J$ = 9.0 Hz, 1H), 3.43–3.54 (m, 6H), 3.29 (s, 3H), 3.18 (dd, $J$ = 2.4, 10.8 Hz, 1H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 139.1, 138.9, 138.7, 138.58, 138.55, 138.49, 138.3, 137.9, 137.8, 128.61, 128.56, 128.48, 128.45, 128.44, 128.36, 128.33, 128.32, 128.30, 128.26, 128.24, 128.05, 128.02, 128.00, 127.84, 127.79, 127.71, 127.69, 127.66, 127.61, 127.55, 127.45, 104.3, 102.6, 98.0, 82.3, 82.1, 80.5, 80.0, 79.3, 78.3, 75.8, 75.2, 75.0, 74.9, 74.5, 73.9, 73.7, 73.49, 73.47, 73.4, 73.0, 72.6, 72.3, 70.2, 68.6, 68.5, 68.2, 63.5, 55.3;

IR (neat, cm$^{-1}$) 2867, 2110, 1497, 1454, 1361, 1061, 1027, 732, 695;

HRMS (ESI) found 1376.6060 [calcd for C$_{82}$H$_{87}$N$_3$NaO$_{15}$ (M+NH$_4$)$^+$ 1376.6035].

1.6.4 Mechanistic Experiments

Stereospecificity Experiments

The general procedure was conducted with 1.32α (0.1 mmol) and (R,R)-1.8 (10 mol%). After stirring for 48 h at rt in toluene (0.1 M) 1.33β was obtained as the major isomer (83%, β:α: >50:1, HPLC analysis).
Peak | RetTime | Type | Width | Area (mAU*s) | Height (mAU) | Area (%) |
-----|---------|------|-------|--------------|--------------|---------|
1    | 9.467   | VV   | 0.3219| 4.5379e4    | 2170.99536   | 98.7223 |
2    | 12.021  | BB   | 0.3397| 587.32153   | 25.59933     | 1.2777  |

\[ \begin{align*}
&\text{BnO} \quad \text{OBn} \\
&\text{O} \quad \text{BnO} \quad \text{OMe}
\end{align*} \]

\( (R,R)-1.8 \) (10 mol%) 
Toluene (0.1 M) 
>90% conversion

\[ \begin{align*}
&\text{BnO} \quad \text{OBn} \\
&\text{O} \quad \text{BnO} \quad \text{OMe}
\end{align*} \]

\( \alpha: \beta \ 1:4 \)
The general procedure was conducted with 1.32β\(^{40}\) (0.1 mmol, β:α = 4:1 by NMR) and (R,R)-1.8 (10 mol%). After stirring for 48 h at rt in toluene (0.1 M) 1.33α was obtained as the major isomer (87%, β:α: 1:3 by NMR).

\(^{40}\) Ford, M. J.; Ley, S. V. Synlett, 1990, 255.
A mixture of partially deuterated mannosyl chloride was prepared and the $R_0$ was measured by NMR (d1 = 60 s). To a stirred solution of the above mixture (102 mg, 0.400 mmol), 1.34 (19 mg, 5 mol%), and isobutylene oxide (1.1 equiv) in toluene (4 mL, 0.1 M) was added BnOH (2 equiv). After 1 h, the reaction was directly loaded on a short pad of silica to quickly remove the SM from the reaction mixture (silica gel, hex/EA, 4:1 to 1:1). Fractions containing the product were combined, undecane (20 μL, internal standard) was added, and an aliquot was removed for a GC analysis (24% β, 2% α) The mixture was concentrated in vacuo and purified by column (silica gel, 1:1 hex/EA). Then $R_P$ of each diastereomer was measured by NMR (d1 = 60 s). The procedure was repeated with 1.35 and 1.36.
Error was calculated by using the following equations. $^{41} \Delta F = 0.007$

\[
\text{KIE} = \frac{\ln(1 - F)}{\ln(1 - F \cdot R_p/R_0)}
\]

\[
\Delta \text{KIE}_F = \left[ \frac{R/R_0}{1 - F \cdot (R/R_0)} \cdot \frac{\ln(1 - F)}{(\ln(1 - F \cdot (R/R_0))^2 - (1 - F) \cdot \ln(1 - F (R/R_0))} \right] \cdot \Delta F
\]

\[
\Delta \text{KIE}_{R/R_0} = \frac{F}{1 - F \cdot (R/R_0)} \cdot \frac{\ln(1 - F)}{(\ln(1 - F \cdot (R/R_0))^2} \cdot \Delta (R/R_0)
\]

\[
\Delta \text{KIE} = |\Delta \text{KIE}_F| + |\Delta \text{KIE}_{R/R_0}|
\]

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1.36 and 1.34$\beta$ ($F = 0.24$ after 1 hour)

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1.6.5 Transition State Calculations

Theoretical Construction of a Transition State Model

Using Macromodel\(^{42}\), a series of accessible conformations were located for the catalyst using a Monte Carlo search, using the OPLS-AA\(^{43}\) force field in chloroform solvent. The lowest energy structure that was suitable for anion-binding was selected by consideration of the location and direction of the thiourea N-H groups. Excluded structures include thiourea-thiourea or thiourea-amide self-hydrogen-bonded geometries and those in which the thiourea groups are spaced far apart. To the selected conformation was introduced a central chloride anion, in order to simulate anion binding, and the conformation was optimized at \(^{44,45}\) M06-2X/6-31G(d)/PCM(benzene). After removal of the chloride, the glucosyl chloride and methanol were docked into the catalyst and a transition state was located at M06-2X/6-31G*/PCM(benzene).

Using model systems, attempts to locate a transition state was located without a proton transfer to catalyst amide were unsuccessful. Additionally, transition states involving other catalyst functionalities as general base were extremely strained and could not be located. Nevertheless, the possibility of lower energy catalyst conformations in the transition state and the role of addition alcohol molecules in the general base mechanism cannot be conclusively excluded.

Non-polar hydrogens omitted for clarity.

Charge: 0

Multiplicity: 1

---

\(^{42}\) MacroModel, version 10.4, Schrödinger, LLC, New York, NY, 2014.


Geometry: M06-2X/6-31g(d)/PCM(solvent=benzene)

Electronic Energy (M06-2X/6-31g(d)/PCM(solvent=benzene): -5376.24323571 hartree

Imaginary Frequencies: 1,155.00 cm^-1

Zero-point correction = 1.287386 (Hartree/Particle)

Thermal correction to Energy = 1.370367

Thermal correction to Enthalpy = 1.371311

Thermal correction to Gibbs Free Energy = 1.166007

Sum of electronic and zero-point Energies = -5374.955849

Sum of electronic and thermal Energies = -5374.872869

Sum of electronic and thermal Enthalpies = -5374.871925

Sum of electronic and thermal Free Energies = -5375.077229

Geometry:

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C  -0.85039600  -2.52250000  -2.22801300
C  -1.36973300  -3.77550200  -1.89492700
C  -0.49410800  -4.85341000  -1.75293500
N  -1.56426900  -1.31986400  -2.28409800
C  2.84442500  -3.36553500  -2.56810900
O  3.62509100  -4.25203500  -2.30228900
O  3.20284600  -2.19844800  -3.11756000
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1.6.6 Additional Optimization Data

\[ \text{MeO} \quad \text{MeO} \quad \text{O} \quad \text{Cl} \quad + \quad \text{C} \quad \text{H}_2 \text{OH} \quad 2 \text{eq} \quad \xrightarrow{(R,R)-1.8 \text{ (5 mol\%)} \quad \text{IBO (1.1 eq)}} \quad \xrightarrow{\text{solvent (0.1 M) \quad rt, 6 h}} \quad \text{MeO} \quad \text{MeO} \quad \text{O} \quad \text{OCy} \]

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76
$$\begin{align*}
\text{MeO} & \quad \text{MeO} \quad \text{MeO} \\
\text{MeO} & \quad \text{Cl} \\
\text{MeO} & \quad \text{MeO} \quad \text{O} \\
+ & \quad \text{CyOH} \\
2 \text{ eq} & \quad \frac{(R,R)-1.8 (5 \text{ mol} \%) \text{ additive (2 equiv)}}{\text{additive (2 equiv)}} \\
& \quad \frac{\text{o-DCB (0.5 M)}}{\text{o-DCB (0.5 M)}} \\
& \quad \frac{\text{rt, 3 h}}{\text{rt, 3 h}}
\end{align*}$$

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1.6.7 Spectral Data

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Methyl \(\text{2,3,4,6-Tetra-O-benzyl-}\beta-\text{D-galactopyranosyl)-(1→3)2,4,6-tri-O-methyl-}\alpha-\text{D-galactopyranoside}\) 1.10:
Methyl (2,3,4,6-Tetra-\textit{O}-benzyl-\textit{\beta}-\text{\textit{D}}-galactopyranosyl)-(1\rightarrow4)-2,3-di-\textit{O}-methyl-\textit{\beta}-\text{\textit{D}}-xylopyranoside \textit{\beta}-1.11:
Methyl (2,3,4,6-Tetra-\(O\)-benzyl-\(\alpha\)-\(D\)-galactopyranosyl)-(1→4)-2,3-di-\(O\)-methyl-\(\beta\)-\(D\)-xylopyranoside \(\alpha\)-1.11:
Methyl (2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl)-(1→3)-2-O-benzyl-4,6-benzylidene-α-D-galactopyranoside 1.23:
Methyl (2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside β-1.13:
gCOSY at 600 MHz of β-1.13.

1D-NOE at 600 MHz of β-1.13. Irradiation at 4.46-4.52 ppm (1-H).
Methyl (2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside α-1.13:
Methyl (2,3,4,6-Tetra-\textit{O}-benzyl-\textit{\beta}-\textit{D}-mannopyranosyl)-(1→3)-2,4,6-tri-\textit{O}-methyl-\textit{\alpha}-\textit{D}-galactopyranoside \textit{\beta}-1.14:
Methyl (2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside α-1.14:
Methyl (2,3,4-Tri-O-benzyl-6-deoxy-β-L-mannopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside β-1.15:
Methyl (2,3,4-Tri-\(O\)-benzyl-6-deoxy-\(\alpha\)-l-mannopyranosyl)-(1→6)-2,3,4-tri-\(O\)-methyl-\(\alpha\)-D-glucopyranoside \(\alpha\)-1.15:
Methyl (2,3,4-Tri-O-benzyl-2-deoxy-β-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside β-1.16:
gCOSY at 600 MHz of β-1.16.

1D-NOE at 600 MHz of β-1.16. Irradiation at 4.52-4.58 ppm (1-H).
Methyl (2,3,4-Tri-O-benzyl-2-deoxy-α-L-mannopyranosyl)-(1→3)-2,4,6-tri-O-methyl-α-D-galactopyranoside α-1.16:
Methyl (3,4,6-Tri-\(O\)-benzyl-2-deoxy-\(\beta\)-\(\text{D}\)-glucosyl)-(1→6)-2,3,4-tri-\(O\)-methyl-\(\alpha\)-\(\text{D}\)-glucopyranoside \(\beta\)-1.17:
Methyl (3,4,6-Tri-\(O\)-benzyl-2-deoxy-\(\alpha\)-\(D\)-glucosyl)-(1\(\rightarrow\)6)-2,3,4-tri-\(O\)-methyl-\(\alpha\)-\(D\)-glucopyranoside \(\alpha\)-1.17:
Methyl (3,4-Di-O-acetyl-2,6-dideoxy-β-L-mannopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside β-1.18:
Methyl (3,4-Di-O-acetyl-2,6-dideoxy-α-L-mannopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside α-1.18:
(+)-Menthoyl (3,4,6-Tri-O-benzyl-2-deoxy-β-D-glucopyranoside) β-1.19:
(+)-Menthoyl (3,4,6-Tri-O-benzyl-2-deoxy-α-D-glucopyranoside) α-1.19:
(-)-Menthoyl (3,4,6-Tri-O-benzyl-2-deoxy-β-D-glucopyranoside) β-1.20:
(-)-Menthoyl (3,4,6-Tri-O-benzyl-2-deoxy-α-D-glucopyranoside) α-1.20:
Methyl (2,3,4-Tri-O-benzyl-6-deoxy-β-L-galactopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside β-1.21:
Methyl (2,3,4-Tri-\textit{O}-benzyl-6-deoxy-\textit{\beta}-\textit{L}-galactopyranosyl)-(1→3)-2,4,6-tri-\textit{O}-methyl-\textit{\alpha}-\textit{D}-galactopyranoside \textit{\beta}-1.22
Methyl \( (2,3,4\text{-Tri-O-benzyl-}\beta\text{-D-xylopyranosyl})-(1\rightarrow6)\text{-2,3,4-tri-O-methyl-}\alpha\text{-D-}
\text{glucopyranoside } \beta\text{-1.23:} \)
Methyl (2,3,4-Tri-\textit{O}-benzyl-\textit{\beta}-\textit{D}-xylopyranosyl)-(1\text{→}3)-2,4,6-tri-\textit{O}-methyl-\textit{\alpha}-\textit{D}-galactopyranoside \textit{\beta}-1.24:
Thiophenyl (3,4,6-Tri-O-benzyl-2-azido-2-deoxy-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl- β-D-galactopyranoside β-1.25:
Thiophenyl (3,4,6-Tri-O-benzyl-2-azido-2-deoxy-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside α-1.25:
Methyl (3,4,6-Tri-\textit{O}-benzyl-2-azido-2-deoxy-\textit{\beta}-\textit{D}-galactopyranosyl)-(1\textrightarrow{}3)-2,4,6-tri-\textit{O}-methyl- \textit{\beta}-\textit{D}-galactopyranoside \textit{\beta}-1.26:
Methyl \((3,4,6\text{-Tri-}O\text{-benzyl}-2\text{-azido}-2\text{-deoxy-}\alpha\text{-D-galactopyranosyl})\text{-}(1\rightarrow3)\text{-}2,4,6\text{-tri-}O\text{-methyl-} \beta\text{-D-galactopyranoside \(\alpha\)-1.26:} \)
Methyl (2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside β-1.27:
Methyl (3,4,6-Tetra-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside β-1.28:
Thiophenyl  (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside β-1.29:
Thiophenyl (3,4,6-Tri-\(O\)-benzyl-2-acetamido-2-deoxy-\(\alpha\)-\(D\)-galactopyranosyl)-(1→6)-2,3,4-tri-\(O\)-benzyl-\(\beta\)-\(D\)-galactopyranoside \(\alpha\)-1.29:
Methyl (3,4,6-Tri-\(O\)-benzyl-2-acetamido-2-deoxy-\(\beta\)-D-galactopyranosyl)-(1→3)-2,4,6-tri-\(O\)-methyl-\(\beta\)-D-galactopyranoside \(\beta\)-1.30:
Methyl (3,4,6-Tri-O-benzyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-O-methyl-β-D-galactopyranoside α-1.30:
Thiophenyl (3,4,6-Tri-O-benzyl-2-azido-2-deoxy-β-D-galactopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-methyl-α-D-glucopyranoside β-1.31:
Chapter 2

Enantioselective Aza-Sakurai Cyclizations: a Dual Role of Thiourea as H-bond Donor and Lewis Base

2.1 Introduction

Indolizidines and quinolizidines are common N-heterocyclic motifs present in biologically active molecules, and the development of efficient methods for their synthesis has accordingly attracted considerable attention from synthetic chemists. The aza-Sakurai cyclization, which involves the intramolecular reaction of an iminium ion with an allylsilane, represents a powerful method for constructing these heterocycles, and diastereoselective variants of this transformation have enabled the efficient synthesis of naturally occurring compounds in this class (Figure 2.1). Recently, asymmetric anion-binding catalysis has been

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1 Portions of this chapter have been prepared for publication: Park, Y.; Schindler, C. S.; Jacobsen, E. N. Manuscript in preparation.


successfully utilized successfully to achieve catalyst-controlled stereochemical communication between \(N\)-acyliminium ions\(^6\) and a variety of nucleophiles, such as silyl ketene acetals, indoles, and polyenes.\(^7,8\) Drawing from the previous work, we envisioned that the thiourea-assisted ionization of chlorolactam 2.1-CI would generate a chiral ion pair that could undergo an enantioselective aza-Sakurai cyclization to give bicyclic lactam 2.2 (Scheme 2.1).

![Figure 2.1. Natural products synthesized using the aza-Sakurai cyclization reaction.](image)

**Scheme 2.1. Reaction design.**

---


2.2 Catalyst Optimization

Our initial studies focused on model substrate 2.1 which contains a hydroxylactam as a latent N-acyliminium precursor and a pendant allyltrimethylsilane as a potential nucleophile (Table 2.1). Initial catalyst screens revealed that thiourea catalysts containing an arylpyrrolidine moiety were effective for this transformation. A promising level of reactivity and enantioselectivity was obtained with thiourea 2.3b (Table 2.1, entry 2). Investigations into a variety of arylpyrrolidine groups differing in the size and orientation of the arene moiety led to a dibenzothiophene fragment as the optimal arene (2.3c, Table 2.1, entry 3). The best result is obtained with thiourea 2.3e which contains a significantly less acidic N-H proton, in contrast to our experience with a wide range of anion-binding reactions catalyzed by this class of catalysts. In the previously reported systems, the bis(trifluoromethyl) anilide is required to achieve high reactivity and enantioselectivity, but the superiority of the phenyl anilide is noticed throughout the optimization for this study. Furthermore, valine-derived 2.3d is more selective than tert-leucine-derived 2.3c, despite being less rigid. Higher enantioselectivity is typically obtained with less sterically hindered and less acidic thiourea catalysts, indicating that the Lewis basicity of the thiourea is critical in this reaction. The marked difference in reactivity and selectivity between thiourea 2.3e and urea 2.4 (Table 2.1, entry 6), is also consistent with the trend described above.

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9 An unactivated alkene showed no signs of reactivity.
10 See Section 2.6.7 for details
Table 2.1. Catalyst optimization\textsuperscript{a}

\begin{center}
\begin{tabular}{ll}
1 & \begin{equation*}
\text{Catalyst (20 mol\%)}
\end{equation*} \\
& \begin{equation*}
\text{TMSCl (2 eq.)}
\end{equation*} \\
& \begin{equation*}
\text{TBME (0.05 M)}
\end{equation*} \\
& \begin{equation*}
\text{30 °C, 24 h}
\end{equation*} \\
\hline
2.1 & \begin{equation*}
\text{TMS-}
\end{equation*} \\
& \begin{equation*}
\text{NO-}
\end{equation*} \\
& \begin{equation*}
\text{HO-}
\end{equation*} \\
2.2 & \begin{equation*}
\text{N-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
\hline
1 & \begin{equation*}
\text{t-Bu-}
\end{equation*} \\
& \begin{equation*}
\text{S-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
2 & \begin{equation*}
\text{t-Bu-}
\end{equation*} \\
& \begin{equation*}
\text{S-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
3 & \begin{equation*}
\text{R}
\end{equation*} \\
& \begin{equation*}
\text{S-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
4 & \begin{equation*}
\text{R}
\end{equation*} \\
& \begin{equation*}
\text{S-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
5 & \begin{equation*}
\text{t-Bu-}
\end{equation*} \\
& \begin{equation*}
\text{S-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
6 & \begin{equation*}
\text{R}
\end{equation*} \\
& \begin{equation*}
\text{S-}
\end{equation*} \\
& \begin{equation*}
\text{CF}_3
\end{equation*} \\
\hline
2.3a & 0\% ee, 3\% \\
2.3b & 31\% ee, 28\% \\
2.3c, R = t-Bu & 64\% ee, 50\% \\
2.3d, R = i-Pr & 80\% ee, 56\% \\
2.3e, R = t-Bu & 94\% ee, 51\% \\
2.3f, R = i-Pr & 92\% ee, 40\% \\
2.3g & 89\% ee, 40\% \\
2.4 & 36\% ee, 12\%
\end{tabular}
\end{center}

\textsuperscript{a} Reactions run on a 0.05 mmol scale. Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns. Yields determined by GC analysis relative to dodecane as an internal standard.

2.3 Substrate Scope

The scope of the cyclization reaction was investigated with optimal catalyst 2.3e (Table 2.2). Carbamate-derivative 2.5 undergoes cyclization with similar enantioselectivity to the structurally analogous lactam 2.2 (Table 2.2, entry 2). From hydantoin-derived 2.7, the cyclization was achieved at a sterically hindered carbon adjacent to a quaternary center in good yield and enantioselectivity (Table 2.2, entry 3). The reaction scope was further extended to access 6,6-fused bicyclic systems (Table 2.2, entries 4–6). Substrates derived from glutarimide (2.9) and dihydrouracils bearing different N-substituents (2.11, 2.13) gave the corresponding
bicycles (2.10, 2.12, 2.14) in excellent yield and enantioselectivity. Use of trisubstituted allylsilane 2.15 allowed enantioselective construction of a quaternary stereocenter (Table 2.2, entry 7). In this instance, thiourea 2.3g afforded improved enantioselectivity relative to 2.3e (88 vs 75% ee).

The absolute stereochemistry of the products was assigned through the synthesis of two alkaloid natural products (Scheme 2.2). Lemieux–Johnson oxidation\textsuperscript{13} of ent-2.2,\textsuperscript{14} followed by a global reduction gave (−)-tashiromine in 90% yield over two steps.\textsuperscript{15} The same two-step sequence from 2.10 afforded (+)-epi-lupinine in 72% yield.\textsuperscript{16}

\textbf{Scheme 2.2.} Total synthesis of (−)-tashiromine and (+)-epilupinine

\textsuperscript{14}Ent-2.2 was obtained using ent-2.3e.
\textsuperscript{16}The absolute stereochemistry of ent-2.2 and 2.10 was assigned by comparing the optical rotation of synthetic tashiromine and epi-lupinine to their values in the literature. The stereochemistry of all other products was assigned by analogy.
Table 2.2. Substrate scope\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield\textsuperscript{b}</th>
<th>ee\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate Image" /></td>
<td><img src="image2" alt="Product Image" /></td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>2\textsuperscript{d}</td>
<td><img src="image3" alt="Substrate Image" /></td>
<td><img src="image4" alt="Product Image" /></td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>3\textsuperscript{e}</td>
<td><img src="image5" alt="Substrate Image" /></td>
<td><img src="image6" alt="Product Image" /></td>
<td>82</td>
<td>94</td>
</tr>
<tr>
<td>4\textsuperscript{d,f}</td>
<td><img src="image7" alt="Substrate Image" /></td>
<td><img src="image8" alt="Product Image" /></td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>5\textsuperscript{g}</td>
<td><img src="image9" alt="Substrate Image" /></td>
<td><img src="image10" alt="Product Image" /></td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>6\textsuperscript{g}</td>
<td><img src="image11" alt="Substrate Image" /></td>
<td><img src="image12" alt="Product Image" /></td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>7\textsuperscript{h}</td>
<td><img src="image13" alt="Substrate Image" /></td>
<td><img src="image14" alt="Product Image" /></td>
<td>85</td>
<td>88</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions run on a 0.2 mmol scale. \textsuperscript{b} Isolated yields. \textsuperscript{c} Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns. \textsuperscript{d} Reaction run using 20 mol % thiourea catalyst. \textsuperscript{e} Reaction run for 3 days. \textsuperscript{f} Reaction run for 1 day. \textsuperscript{g} Reactions run at -30 °C. \textsuperscript{h} Catalyst 2.3g used instead of 2.3e.
2.4 Mechanistic Studies

To investigate the basis for the putative Lewis acid-base interaction on the outcome of the reaction, a series of substrates varying the substitution on the silyl groups were prepared (Table 3). In experiments with thiourea 2.3e, substrates containing a more electron-rich allylsilane were consumed more slowly despite being more inherently nucleophilic ($k_{rel}: 2.18 > 2.1 > 2.17$). With urea 2.4, however, faster rates were observed with intrinsically more nucleophilic substrates ($k_{rel}: 2.17 > 2.1 > 2.18$). The reversal of the relative reactivity due to S vs O substitution in the catalyst is highly indicative of nucleophilic activation of allylsilane by the thiourea moiety in 2.3e.

Based upon these observations, the following catalytic cycle is proposed (Scheme 2.3). A chlorolactam generated in situ from the corresponding hydroxylactam is ionized by thiourea to result in the formation of an $N$-acyliminium thiourea-bound chloride ion pair. The Lewis basicity of the thiourea should be enhanced by anion binding, and this charged moiety can activate the allylsilane to effect the cyclization. The resulting cyclic intermediate would form the lactam product upon elimination of the $\beta$-silyl cation.

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18 Inverse secondary KIE (0.88-0.90) in the following system is consistent with rate-limiting cyclization. Rate-limiting desilylation is unlikely, but cannot be ruled out. See Section 2.6.6 for details.
Table 2.3. Effect of silicon Lewis acidity on reaction rate

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>thiourea (2.3e)</th>
<th>urea (2.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1 [Me_3Si]</td>
<td>0.13 [0.13 (defined) 92% ee]</td>
<td>0.13 [28% ee]</td>
</tr>
<tr>
<td>2</td>
<td>2.17 [i-Pr_3Si]</td>
<td>0.14 [33% ee]</td>
<td>0.27 [41% ee]</td>
</tr>
<tr>
<td>3</td>
<td>2.18 [HMe_2Si]</td>
<td>1.79 [89% ee]</td>
<td>0.09 [26% ee]</td>
</tr>
</tbody>
</table>

a. Relative rates were assigned by comparing the initial rates of each system. See the Supporting information for details.

Scheme 2.3. Proposed Catalytic Cycle
2.5 Conclusions

In summary, we have developed a catalytic enantioselective aza-Sakurai cyclization with N-acyliminium ions as a route to various indolizidine, quinolizidine, and related bicyclic frameworks. The catalyst structure-enantioselectivity relationship and substrate studies suggest a mechanism by which the thiourea catalyst is not only involved in the generation of the reactive cationic electrophile but also engaged in the Lewis base activation of the allylsilane nucleophile. We anticipate this dual activation strategy will be applicable in other transformations.
2.6 Experimental Details

2.6.1 General Information

All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks or glass vials fitted with rubber septa and/or septa equipped screw caps. For reactions run at low temperatures the caps were wrapped with Teflon® tape and parafilm to minimize the introduction of adventitious water. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Flash chromatography was performed using silica gel ZEOprep60 ECO 40-63 micron from American International Chemical, Inc.

All chemicals were purchased from Sigma-Aldrich, VWR or Acros and were used as received unless otherwise stated. Solvents were dried by passing through columns of activated alumina. Triethylamine and N,N-diisopropylethylamine were distilled from CaH$_2$ at 760 Torr. Proton Nuclear Magnetic Resonance NMR (1H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a Varian Inova-600 (600 MHz) or Varian Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million and are referenced to the NMR solvent peak (CDCl$_3$: δ 7.26, C$_6$D$_6$: δ 7.16). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent (CDCl$_3$: δ 77.0, C$_6$D$_6$: δ 128.06). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet), coupling constants in Hertz (Hz), and integration. Mass spectroscopic (MS) data were obtained using an Agilent 6120 Single Quadrupole LC/MS instrument equipped with an ESI-APCI multimode source. Infrared (IR) spectra were obtained using a Bruker Tensor 27 FTIR spectrophotometer. Optical rotation data were obtained using a 1 mL cell with a 0.5 dm path length on a Jasco P-2000 polarimeter. Chiral HPLC analysis was performed using Agilent 1200
series instruments. Chiral GC analysis was performed using an Agilent analytical chromatograph with a commercial chiral column.

2.6.2. Catalyst Synthesis

The catalysts shown in Table 2.1 were synthesized following the general reaction sequence shown below:

Scheme 2.4. Synthesis of catalysts 2.3 and 2.4.

(R)-tert-butyl 2-(dibenzothiophen-4-yl)pyrrolidine-1-carboxylate (2.19).

The preparation follows a procedure described by Campos and coworkers for the Palladium-catalyzed α-arylation of N-Boc-pyrrolidines. To a solution of N-Boc-pyrrolidine (2.0 mL, 11.4 mmol) and (–)-sparteine (2.6 ml, 11.4 mmol) in MTBE (24 mL) at -78°C was added s-BuLi (9.6 mL, 11.4 mmol, 1.2 M in cyclohexane) via syringe pump over the course of 60 minutes. The resulting solution was stirred at -78°C for 3 hours. A solution of ZnCl₂ (6.4 mL, 6.8 mmol, 1.0 M

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in Et₂O) was added to the reaction via syringe pump over the course of one hour. Stirring at -78°C was continued for 30 minutes and the resulting suspension was subsequently warmed to room temperature. 4-Bromodibenzothiophene²⁰ (2.5 g, 9.5 mmol) was subsequently added followed by Pd(OAc)₂ (102 mg, 0.46 mmol) and t-Bu₃P-HBF₄ (164 mg, 0.57 mmol). Stirring at room temperature was continued for 12 hours. NH₄OH solution (1 ml) was then added and stirring was continued for one hour. To this mixture was then added 1M HCl (100 mL) and the aqueous phase was extracted twice with DCM (100 mL). The combined organic phases were washed with brine, dried using Na₂SO₄ filtered and concentrated. The crude material was purified using column chromatography and hexane/EtOAc (4:1) as eluent to yield S1 (2.5 g, 73% yield) as a colorless oil.

Compound 2.19 is characterized as a mixture of rotamers.

[α]D²³ = +43.8° (c = 0.50, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ = 8.16 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.94–7.79 (m, 1H), 7.53–7.36 (m, 3H), 7.25 (m, 1H), 5.05 (s, 1H), 3.89–3.69 (m, 2H), 2.41 (b, 1H), 2.11–1.88 (m, 3H), 1.46 (s, 9H);

¹³C NMR (125 MHz, CDCl₃) δ = 154.80, 139.81, 139.37, 136.36, 135.72, 126.83, 124.77, 124.58, 123.53, 122.81, 121.62, 120.15, 79.58, 79.10, 61.40, 47.36, 46.17, 45.81, 34.16, 28.83, 28.23, 26.04, 25.33, 24.13;

IR (thin film, cm⁻¹) 2976, 2876, 1685, 1390, 1158, 1120, 855, 754;

HRMS (ESI) calculated for C₂₁H₂₃NO₂SNa: 376.1347; found: 376.1356.

tert-butyl \((\text{S})-1-(\text{R})-2-((\text{dibenzothiophen}-4-\text{yl})\text{pyrrolidin}-1-\text{yl})-3,3\text{-dimethyl-1-oxobutan-2-yl})\text{carba-mate (2.20t).}

To a solution of \((\text{R})\text{-tert-butyl 2-((dibenzothiophen-4-yl)pyrrolidine-1-carboxylate (2.19)}\) (2.4 g, 6.74 mmol) in DCM was added HCl (6.75 mL, 27 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH₄OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na₂SO₄, filtered and concentrated. To the resulting oil in DCM was then added EDC hydrochloride (1.36 g, 7.08 mmol) and HOBr (1.08 g, 7.08 mmol) together with Boc-L-\(\text{tert-leucine (1.73 g, 7.08 mmol)}\) and stirring at room temperature was continued for 12 hours. The reaction was quenched by the addition of 50 mL of water and the aqueous phase was extracted with DCM (100 mL, 3 times). The combined organic phases were dried using Na₂SO₄, filtered and concentrated. The crude reaction mixture was purified using column chromatography with hexanes/EtOAc (4:1) as eluent to yield the desired product as a yellow foam (2.89 g, 89% yield).

Compound 2.20t is characterized as a mixture of rotamers.

\[
\left[\alpha\right]_{D}^{22} = +18.5^\circ \quad (c = 0.50, \text{CHCl}_3);
\]

\(^1\)H NMR (500 MHz, CDCl₃) δ 8.17–8.09 (m, 1H), 8.01 (d, \(J = 7.8 \text{ Hz, 1H}\)), 7.90–7.75 (m, 1H), 7.50–7.39 (m, 2H), 7.34 (t, \(J = 7.6 \text{ Hz, 1H}\)), 7.14 (d, \(J = 7.3 \text{ Hz, 1H}\)), 5.44 (dd, \(J = 2.0, 7.8 \text{ Hz, 1H}\),...
1H), 5.14 (d, J = 10.3 Hz, 1H), 4.44 (d, J = 10.3 Hz, 1H), 4.38–4.22 (m, 1H), 3.87–3.70 (m, 1H), 2.42–2.26 (m, 1H), 2.16–1.93 (m, 3H), 1.67–1.51 (m, 2H), 1.51–1.40 (m, 10H), 1.16–0.95 (m, 11H), 0.93–0.78 (m, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.1, 156.5, 139.5, 137.1, 136.5, 136.1, 136.0, 126.8, 124.9, 124.6, 123.0, 122.9, 121.9, 120.3, 79.8, 60.4, 59.0, 48.6, 34.8, 32.2, 28.6, 28.6, 26.8, 26.7, 26.5, 24.4;

IR (thin film, cm$^{-1}$) 2954, 2870, 1700, 1646, 1506, 1420, 1365, 124, 751;

HRMS (ESI) calculated for C$_{27}$H$_{34}$N$_2$O$_3$SNa: 489.2188; found: 489.2194.

tert-butyI ((S)-1-((R)-2-(dibenzothiophen-4-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl) (2.20v).

To a solution of (R)-tert-butyl 2-(dibenzothiophen-4-yl)pyrrolidine-1-carboxylate (2.19) (2.4 g, 6.74 mmol) in DCM was added HCl (6.75 mL, 27 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH$_4$OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na$_2$SO$_4$, filtered and concentrated. To the resulting oil in DCM was then added EDC hydrochloride (1.36 g, 7.08 mmol) and HOBT (1.08 g, 7.08 mmol) together with Boc-L-valine (1.53 g, 7.08 mmol) and stirring at room temperature was continued for 12 hours.
The reaction was quenched by the addition of 50 mL of water and the aqueous phase was extracted with DCM (100 mL, 3 times). The combined organic phases were dried using Na$_2$SO$_4$, filtered and concentrated. The crude reaction mixture was purified using column chromatography with hexanes/EtOAc (4:1) as eluent to yield the desired product as a yellow foam (2.71 g, 89% yield).

Compound 2.20v is characterized as a mixture of rotamers.

$\left[\alpha\right]_D^{23} = +36.4^\circ$ (c = 0.50, CHCl$_3$);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.22–8.07 (m, 2H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.96–7.77 (m, 1H), 7.54–7.41 (m, 3H), 7.41–7.29 (m, 1H), 7.18 (d, $J = 7.3$ Hz, 1H), 5.44 (dd, $J = 2.2$, 8.1 Hz, 1H), 5.07 (d, $J = 9.8$ Hz, 1H), 4.41–4.33 (m, 1H), 4.33–4.23 (m, 1H), 3.86 (s, 1H), 3.82–3.68 (m, 1H), 2.52–2.30 (m, 2H), 2.14–1.95 (m, 5H), 1.58 (br. s., 1H), 1.49–1.38 (m, 14H), 1.09–0.95 (m, 6H), 0.63 (d, $J = 6.8$ Hz, 2H), 0.28 (d, $J = 6.8$ Hz, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.5, 156.4, 139.5, 137.7, 137.0, 136.5, 136.1, 136.0, 127.2, 126.9, 125.0, 124.9, 124.8, 124.6, 123.2, 123.1, 122.9, 122.0, 121.9, 121.1, 120.4, 79.7, 61.3, 60.4, 57.9, 56.9, 47.9, 47.7, 34.0, 32.2, 31.1, 30.5, 28.6, 24.4, 23.0, 19.8, 19.7, 18.5, 17.0;

IR (thin film, cm$^{-1}$) 2970, 2872, 1702, 1642, 1496, 1424, 1365, 1251, 1162, 751;

HRMS (ESI) calculated for C$_{26}$H$_{32}$N$_2$O$_3$SNa: 475.2031; found: 475.2026.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(dibenzo[b,d]thiophen-4-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (2.3c).
To a solution of amide (2.20t) (2.82 g, 6.05 mmol) in DCM was added HCl (6.05 mL, 24.21 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH₄OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na₂SO₄, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et₃N (1.7 mL, 12.1 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.1 mL, 6.05 mmol) was added. Stirring at room temperature was continued for 12 hours. The mixture was then concentrated under reduced pressure and the resulting crude product was purified using column chromatography with hexane/EtOAc (4:1) as eluent to form the desired product 2.3c (2.69 g, 70% yield) as a colorless foam.

Compound 2.3c is characterized as a mixture of rotamers.

[α]D²⁴ = −13.1° (c = 0.50, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 8.71 (br. s., 1H), 8.02 (d, J = 7.3 Hz, 1H), 7.79 (d, J = 6.3 Hz, 2H), 7.58 (br. s., 2H), 7.52–7.34 (m, 4H), 7.11 (br. s., 2H), 5.59 (d, J = 9.3 Hz, 1H), 5.37–5.17 (m, 1H), 4.56 (t, J = 10.7 Hz, 1H), 3.93 (d, J = 10.3 Hz, 1H), 2.35 (br. s., 1H), 2.05 (dd, J = 4.2, 6.6 Hz, 2H), 1.19–1.09 (m, 9H), 0.62 (s, 2H);
\[^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\text{) } \delta 181.7, 171.1, 139.5, 139.2, 136.3, 135.4, 135.3, 132.2, 132.0, 127.3, 127.0, 124.8, 124.7, 124.7, 124.2, 124.1, 123.6, 123.5, 123.0, 122.8, 122.0, 121.9, 121.8, 120.2, 118.7, 63.3, 61.1, 49.1, 36.1, 35.9, 32.8, 27.2, 27.1, 26.7, 24.4;\]

IR (thin film, cm\(^{-1}\)) 1614, 1528, 1443, 1382, 1276, 1175, 1128, 884, 752, 702, 681;

HRMS (ESI) calculated for C\(_{31}\)H\(_{29}\)F\(_6\)N\(_3\)OS\(_2\)Na: 660.1554; found: 660.1557.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(dibenzothiophen-4-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (2.3d)

![Chemical Structure](image)

To a solution of amide (2.20v) (2.73 g, 6.05 mmol) in DCM was added HCl (6.05 mL, 24.21 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH\(_4\)OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na\(_2\)SO\(_4\), filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et\(_3\)N (1.7 mL, 12.1 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.1 mL, 6.05 mmol) was added. Stirring at room temperature was continued for 12 hours. The mixture was then concentrated under reduced pressure and the resulting crude product was purified using column chromatography with hexane/EtOAc (4:1) as eluent to form the desired product 2.3d (3.01 g, 80% yield) as a colorless foam.
Compound 2.3d is characterized as a mixture of rotamers.

\[ \left[ \alpha \right]_{D}^{23} = -106^\circ \quad (c = 1.0, \text{CHCl}_3) \]

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.00 (br s, 1H), 7.87 (d, $J = 7.0$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.3 –7.56 (m, 7 H), 7.29 (d, $J = 7.5$ Hz, 1H), 7.20 (d, $J = 7.0$ Hz, 1H), 6.62 (t, $J = 7.5$ Hz, 1H), 5.38 (d, $J = 7.0$ Hz, 1H), 5.00 (br s, 1H), 4.56 (t, $J = 3.0$ Hz, 1H), 3.81–3.88 (m, 1H), 2.03–2.35 (m, 4 H), 1.16 –1.18 (m, 6H), 0.87 – 0.95 (m, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 182.2, 173.3, 140.3, 139.6, 139.2, 138.7, 136.9, 136.5, 136.2, 136.1, 135.6, 135.4, 135.3, 130.6, 130.3, 127.0, 126.8, 126.4, 124.6, 124.50, 124.46, 124.2, 122.9, 122.4, 122.0, 121.7, 121.6, 120.9, 119.9, 119.4, 118.3, 62.7, 61.1, 48.4, 47.9, 33.4, 32.1, 31.6, 31.3, 30.9, 23.8, 22.6, 19.7, 19.3, 18.4, 14.1;

IR (thin film, cm$^{-1}$) 3302, 2969, 1618, 1541, 1381, 1277, 1178, 1127, 752;

HRMS (ESI) calculated for C$_{30}$H$_{27}$F$_6$N$_3$OS$_2$Na: 646.1397; found: 646.1416.

1-((S)-1-((R)-2-(dibenzothiophen-4-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-phenylthio-urea (2.3e)

To a solution of amide (2.20t) (2.82 g, 6.05 mmol) in DCM was added HCl (6.05 mL, 24.21 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH$_4$OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL)
and the combined organic phases were dried using Na$_2$SO$_4$, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et$_3$N (1.7 mL, 12.1 mmol) and phenyl isothiocyanate (723 μL, 6.05 mmol) was added. Stirring at room temperature was continued for 12 hours. The mixture was then concentrated under reduced pressure and the resulting crude product was purified using column chromatography with hexane/EtOAc (4:1) as eluent to form the desired product 2.3e (2.30 g, 76% yield) as a colorless foam.

Compound 2.3e is characterized as a mixture of rotamers.

$[\alpha]_D^{23} = +43.8^\circ$ (c = 0.50, CHCl$_3$);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.20–8.07 (m, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.97–7.83 (m, 1H), 7.70 (br. s., 1H), 7.55–7.36 (m, 4H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.22 (t, $J = 7.8$ Hz, 2H), 7.14 (d, $J = 7.3$ Hz, 1H), 6.92 (d, $J = 7.8$ Hz, 1H), 6.61 (br. s., 1H), 5.50 (d, $J = 9.3$ Hz, 1H), 5.38 (dd, $J = 2.2$, 8.1 Hz, 1H), 4.73–4.59 (m, 1H), 3.94–3.72 (m, 1H), 2.49–2.26 (m, 1H), 2.19–1.96 (m, 4H), 1.58 (br. s., 2H), 1.08 - 0.94 (m, 9H), 0.56 (s, 2H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 181.1, 170.2, 139.5, 136.7, 136.4, 135.9, 135.8, 130.2, 129.9, 127.1, 126.9, 126.9, 125.1, 125.0, 124.7, 124.7, 124.6, 123.7, 123.0, 121.8, 120.3, 63.4, 60.7, 48.9, 35.8, 32.4, 26.9, 26.8, 24.4;

IR (thin film, cm$^{-1}$) 3222, 2957, 1625, 1525, 1441, 1297, 1237, 750;

HRMS (ESI) calculated for C$_{29}$H$_{31}$N$_3$OS$_2$Na: 524.1806; found: 524.1791.

1-((S)-1-((R)-2-(dibenzothiophen-4-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)-3-phenylthiourea (2.3f)
To a solution of amide (2.20v) (2.73 g, 6.05 mmol) in DCM was added HCl (6.05 mL, 24.21 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH₄OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na₂SO₄, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et₃N (1.7 mL, 12.1 mmol) and phenyl isothiocyanate (722 μL, 6.05 mmol) was added. Stirring at room temperature was continued for 12 hours. The mixture was then concentrated under reduced pressure and the resulting crude product was purified using column chromatography with hexane/EtOAc (4:1) as eluent to form the desired product 2.3f (2.35 g, 80% yield) as a colorless foam.

Compound 2.3f is characterized as a mixture of rotamers.

\[[\alpha]_{D}^{23} = +39.6^\circ\ (c = 0.50, \text{CHCl}_3)\];

\[^1H\] NMR (500 MHz, CDCl₃) δ 8.16–8.07 (m, 1H), 7.95–7.83 (m, 1H), 7.54–7.36 (m, 5H), 7.32 (d, \(J = 7.3\) Hz, 1H), 7.26–7.09 (m, 2H), 7.00 (d, \(J = 7.8\) Hz, 1H), 5.41 (dd, \(J = 2.4, 7.8\) Hz, 1H), 4.58 (br. s., 1H), 3.99–3.89 (m, 1H), 3.87–3.73 (m, 1H), 2.36 (br. s., 1H), 2.20–1.97 (m, 4H), 1.07 (d, \(J = 6.8\) Hz, 2H), 1.01 (d, \(J = 6.8\) Hz, 3H), 0.60 (d, \(J = 6.8\) Hz, 2H), 0.23 (d, \(J = 6.8\) Hz, 2H);

\[^{13}C\] NMR (125 MHz, CDCl₃) δ 181.9, 181.5, 173.3, 172.2, 139.7, 139.4, 137.8, 137.7, 137.4, 136.8, 136.5, 136.2, 136.1, 136.0, 135.9, 135.6, 129.5, 129.1, 127.2, 126.9, 126.6, 126.2, 125.6,
125.4, 125.1, 124.8, 124.7, 124.6, 123.4, 123.1, 122.9, 121.9, 121.1, 120.3, 62.4, 61.8, 61.2, 60.6, 48.3, 47.9, 33.9, 32.2, 31.8, 31.1, 24.0, 23.0, 19.8, 19.6, 19.3, 17.7;

IR (thin film, cm\(^{-1}\)) 3049, 1622, 1523, 1442, 1297, 1247, 751, 694;

HRMS (ESI) calculated for C\(_{28}\)H\(_{29}\)N\(_3\)OS\(_2\)Na: 510.1650; found: 510.1646.

1-((S)-1-((R)-2-(dibenzothiophen-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-phenyl-thiourea (2.3g).

The thiourea catalyst 2.3g was prepared following the general reaction sequence described above from 1-bromodibenzothiophene.\(^2\)

Compound 2.3g is characterized as a mixture of rotamers.

\([\alpha]_D^{23} = -2.0^\circ\ (c = 0.50, \text{CHCl}_3);\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\ 8.59\ (d, J = 8.3\ \text{Hz, 1H}), 8.24\ (d, J = 7.8\ \text{Hz, 1H}), 7.98–7.85\ (m, 2H), 7.73\ (d, J = 7.8\ \text{Hz, 1H}), 7.60–7.29\ (m, 6H), 7.15\ (d, J = 7.3\ \text{Hz, 3H}), 6.75\ (\text{br. s., 1H}), 6.19\ (d, J = 8.3\ \text{Hz, 1H}), 5.47\ (d, J = 9.8\ \text{Hz, 1H}), 5.11\ (d, J = 9.8\ \text{Hz, 1H}), 4.80\ (\text{br. s., 1H}), 3.98–3.69\ (m, 2H), 2.51\ (t, J = 8.8\ \text{Hz, 1H}), 2.18 – 1.95\ (m, 4H), 1.26\ (\text{br. s., 1H}), 1.12–0.99\ (m, 9H), 0.71\ (s, 2H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\ 181.0, 170.3, 140.7, 140.6, 140.0, 138.8, 136.7, 135.5, 135.1, 131.6, 130.2, 129.9, 127.3, 126.9, 126.8, 126.5, 126.0, 125.7, 125.5, 125.1, 124.8, 124.7, 124.5,

123.4, 123.1, 123.0, 122.2, 121.7, 121.6, 63.5, 63.0, 60.7, 59.6, 48.9, 47.9, 35.7, 35.6, 34.0, 32.9, 27.2, 27.0, 23.3, 21.1;

IR (thin film, cm⁻¹) 2955, 1625, 1526, 1435, 1296, 1239, 1193, 734, 694;

HRMS (ESI) calculated for C₂₉H₃₁N₃OS₂Na: 524.1806; found: 524.1799.

1-((S)-1-((R)-2-(dibenzothiophen-4-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-phenylurea (2.4).

To a solution of amide (2.20t) (2.82 g, 6.05 mmol) in DCM was added HCl (6.05 mL, 24.21 mmol, 4 M in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH₄OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na₂SO₄, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et₃N (1.7 mL, 12.1 mmol) and phenyl isocyanate (658 μL, 6.05 mmol) was added. Stirring at room temperature was continued for 12 hours. The mixture was then concentrated under reduced pressure and the resulting crude product was purified using column chromatography with hexane/EtOAc (4:1) as eluent to form the desired product 2.4 (2.17 g, 74% yield) as a colorless foam.

Compound 2.4 is characterized as a mixture of rotamers.

\[ [\alpha]_D^{23} = -27.9^\circ \ (c = 0.50, \text{CHCl}_3); \]
\[ ^1H \text{NMR} \ (500\text{MHz}, \text{CDCl}_3) \delta \ 8.07 \ (d, J = 7.8 \text{ Hz}, 1\text{H}), \ 7.91 \ (d, J = 7.3 \text{ Hz}, 1\text{H}), \ 7.70 \ (d, J = 7.8 \text{ Hz}, 1\text{H}), \ 7.50-7.31 \ (m, 3\text{H}), \ 7.25-7.22 \ (m, 1\text{H}), \ 7.22-7.09 \ (m, 7\text{H}), \ 7.05-6.90 \ (m, 2\text{H}), \ 6.86 \ (\text{br. s., 1H}), \ 5.85 \ (\text{br. s., 1H}), \ 5.44-5.33 \ (m, 1\text{H}), \ 4.80 \ (s, 1\text{H}), \ 4.40 \ (\text{br. s., 1H}), \ 3.92-3.83 \ (m, 1\text{H}), \ 2.43-2.24 \ (m, 1\text{H}), \ 2.18-1.96 \ (m, 4\text{H}), \ 1.15-1.00 \ (m, 9\text{H}), \ 0.91 \ (d, J = 14.6 \text{ Hz}, 1\text{H}), \ 0.58 \ (s, 2\text{H}); \]

\[ ^{13}C \text{NMR} \ (125\text{ MHz}, \text{CDCl}_3) \delta \ 172.0, \ 156.8, \ 156.4, \ 139.4, \ 139.3, \ 138.6, \ 137.7, \ 136.7, \ 136.4, \ 135.9, \ 129.2, \ 129.1, \ 127.2, \ 126.9, \ 124.9, \ 124.7, \ 124.6, \ 124.5, \ 123.7, \ 123.1, \ 123.0, \ 121.8, \ 121.5, \ 121.1, \ 120.9, \ 120.2, \ 120.0, \ 61.3, \ 60.5, \ 58.4, \ 57.4, \ 48.9, \ 47.7, \ 35.1, \ 34.9, \ 33.6, \ 32.4, \ 26.9, \ 26.7, \ 24.3, \ 22.9; \]

IR (thin film, cm\(^{-1}\)) 3338, 2954, 1640, 1545, 1441, 1310, 1229, 749, 692;

HRMS (ESI) calculated for C\(_{29}\)H\(_{31}\)N\(_3\)O\(_2\)SNa: 508.2035; found: 508.2036.

### 2.6.3. Substrate Synthesis

![Scheme 2.5. Synthesis of 2.5.](image)

(Z)-3-(6-(trimethylsilyl)hex-4-en-1-yl)oxazolidine-2,4-dione (2.21)

To a cooled (0 °C) solution of (Z)-6-(trimethylsilyl)hex-4-en-1-ol (243 mg, 1.41 mmol),\(^{22}\) Ph\(_3\)P (1.10 equiv, 407 mg, 1.55 mmol), and oxazolidine-2,4-dione (1.10 equiv, 157 mg, 1.55 mmol) in THF (10 mL) was added DIAD (1.10 equiv, 0.31 mL, 1.55 mmol) dropwise. The ice bath was removed and the mixture was stirred for 2 hours at room temperature. The reaction was diluted

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with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5:1) to afford 2.21 (310 mg, 86%) as a colorless oil.

1H NMR (500 MHz, CDCl₃) δ 5.48–5.42 (m, 1H), 5.25–5.20 (m, 1H), 4.67 (s, 2H), 3.58–3.55 (m, 2H), 2.04 (q, J = 7.5 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.45 (d, J = 9.0 Hz, 2H), −0.01 (s, 9H);

13C NMR (125 MHz, CDCl₃) δ 170.4, 155.8, 127.1, 125.2, 67.7, 40.0, 27.4, 24.1, 18.5, −1.8;

IR (neat, cm⁻¹) 2953, 1816, 1731, 1448, 1416, 1247, 1138, 1049, 839;

HRMS (ESI) found 279.1180 [calcd for C₁₂H₂₁NNaO₃Si (M+Na) 278.1188]

(Z)-4-hydroxy-3-(6-(trimethylsilyl)hex-4-en-1-yl)oxazolidin-2-one (2.5)

To a stirred solution of 2.21 (289 mg, 1.13 mmol) in MeOH (11 mL) was added NaBH₄ (86 mg, 2.26 mmol, 2 equiv) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO₃(aq). The biphasic mixture was stirred vigorously for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:2) to afford hydroxylactam 2.5 (187 mg, 73%) as a colorless oil.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta \) 5.49–5.41 (m, 1H), 5.30–5.21 (m, 2H), 4.39 (dd, \(J = 6.8, 10.4 \text{ Hz}, \) 1H), 4.14 (dd, \(J = 2.0, 10.4 \text{ Hz}, \) 1H), 3.41 (ddd, \(J = 6.8, 8.8, 14.4 \text{ Hz}, \) 1H), 3.31–3.23 (m, 2H), 2.03 (q, \(J = 7.2 \text{ Hz}, \) 2H), 1.73–1.60 (m, 2H), 1.45 (d, \(J = 8.8 \text{ Hz}, \) 2H), 0.00 (s, 9H);

\(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta \) 158.0, 126.5, 125.7, 79.4, 70.8, 40.6, 27.5, 24.2, 18.4, –1.9;

IR (neat, \(cm^{-1}\)) 3355, 2953, 1722, 1431, 1246, 839;

HRMS (ESI) found 280.1343 [calcd for C\(_{12}\)H\(_{23}\)NNaO\(_3\)Si (M+Na) 280.1345]

**Scheme 2.6.** Synthesis of 2.7.

**(Z)-1,5,5-trimethyl-3-(6-(trimethylsilyl)hex-4-en-1-yl)imidazolidine-2,4-dione (2.22)**

To a cooled (0 °C) solution of (Z)-6-(trimethylsilyl)hex-4-en-1-ol (201 mg, 1.17 mmol), Ph\(_3\)P (1.10 eq., 336 mg, 1.28 mmol), and 1,5,5-trimethylhydantoin (1.10 eq., 182 mg, 1.28 mmol) in THF (10 mL) was added DIAD (1.10 eq., 0.25 mL, 1.28 mmol) dropwise. The ice bath was removed and the mixture was stirred for 12 hours at room temperature. The reaction was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford 2.22 (235 mg, 79%) as a colorless oil.
(Z)-5-hydroxy-3,4,4-trimethyl-1-(6-(trimethylsilyl)hex-4-en-1-yl)imidazolidin-2-one (2.7)

To a stirred solution of 2.22 (123 mg, 0.414 mmol) in MeOH (4 mL) was added NaBH₄ (31 mg, 0.828 mmol) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO₃(aq). The biphasic mixture was stirred vigorously for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1 to EtOAc only) to afford 2.7 (106 mg, 86%) as a colorless oil.

1H NMR (500 MHz, CDCl₃) δ 5.44–5.39 (m, 1H), 5.28–5.23 (m, 1H), 3.51 (t, J = 7.5 Hz, 2H), 2.88 (s, 3H), 2.00 (q, J = 7.5 Hz, 2H), 1.66 (quint, J = 7.5 Hz, 2H), 1.45 (d, J = 9.0 Hz, 2H), 1.36 (s, 6H), –0.01 (s, 9H);
13C NMR (125 MHz, CDCl₃) δ 176.6, 155.2, 126.4, 125.8, 60.9, 38.5, 28.1, 24.3, 24.2, 22.0, 18.4, –1.9;
IR (neat, cm⁻¹) 3302, 2953, 1672, 839;
HRMS (ESI) found 321.1977 [calcd for C_{15}H_{30}N_{2}NaO_{2}Si (M+Na) 321.1974]

**Scheme 2.7.** Synthesis of 2.11.

(Z)-3-(6-(trimethylsilyl)hex-4-en-1-yl)dihydropyrimidine-2,4(1H,3H)-dione (2.23)

To a cooled (0 °C) solution of primary alcohol (423 mg, 2.45 mmol), Ph$_3$P (1.10 eq., 708 mg, 2.70 mmol), and dihydrouracil (1.10 eq., 308 mg, 2.70 mmol) in DMF (20 mL) was added DIAD (1.10 eq., 531 μL, 2.70 mmol) dropwise. The resulting mixture was warmed up to room temperature and stirred for 12 h. The reaction was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:2) to afford 2.23 (441 mg, 67%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.41 (dt, $J = 8.5, 10.0$ Hz, 1H), 5.26 (m, 1H), 3.78–3.75 (m, 2H), 3.38 (td, $J = 3.0, 7.0$ Hz, 1H), 2.70 (t, $J = 6.5$ Hz, 2H), 2.01 (q, $J = 7.5$ Hz, 2H), 1.61 (quint, $J = 9.0$ Hz, 2H), 1.46 (d, $J = 8.0$ Hz, 2H), −0.01 (s, 9H);
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.4, 155.3, 126.3, 126.0, 40.0, 35.2, 31.6, 28.3, 24.4, 18.4, −1.9; IR (neat, cm$^{-1}$) 3248, 2954, 1724, 1673, 1385, 1246, 1131, 838; HRMS (ESI) found 291.1501 [calcd for C$_{13}$H$_{24}$N$_2$O$_2$Si (M+Na) 291.1505]

(Z)-1-methyl-3-(6-(trimethylsilyl)hex-4-en-1-yl)dihydropyrimidine-2,4(1H,3H)-dione (2.24)

To a stirred solution of dihydouracil (150 mg, 0.559 mmol) in DMF was added Cs$_2$CO$_3$ (2.00 eq., 364 mg, 1.12 mmol) and MeI (5.00 eq., 174 μL, 2.80 mmol). The reaction mixture was stirred for 12 h, and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford X (160 mg, >99%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.43–5.37 (m, 1H), 5.29–5.24 (m, 1H), 3.78–3.75 (m, 2H), 3.34 (t, $J = 7.0$ Hz, 2H), 3.04 (s, 3H), 2.71 (t, $J = 7.5$ Hz, 2H), 2.01 (q, $J = 7.5$ Hz, 2H), 1.60 (quint, $J = 7.5$ Hz, 2H), 1.45 (d, $J = 8.5$ Hz, 2H), −0.01 (s, 9H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.0, 153.7, 126.4, 125.9, 42.9, 40.6, 35.8, 31.6, 28.3, 24.5, 18.4, −1.8;
IR (neat, cm$^{-1}$) 2953, 1714, 1770, 1492, 1407, 1246, 1201, 1145, 853; HRMS (ESI) found 305.1656 [calcd for C$_{14}$H$_{26}$N$_2$NaO$_2$Si (M+Na) 305.1661]

(Z)-4-hydroxy-1-methyl-3-(6-(trimethylsilyl)hex-4-en-1-yl)tetrahydropyrimidin-2(1H)-one (2.11)
To a stirred solution of dihydrouracil (123 mg, 0.436 mmol) in MeOH (4 mL) was added NaBH₄ (33 mg, 0.872 mmol) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO₃(aq). The biphasic mixture was stirred vigorously for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (davisil, hexanes/EtOAc, 1:1 to EtOAc only) to afford X (91 mg, 73%) as a colorless oil.

₁H NMR (500 MHz, CDCl₃) δ 5.39 (dt, J = 9.0, 10.0 Hz, 1H), 5.25 (dt, J = 7.5, 10.5 Hz, 1H), 4.95–4.93 (m, 1H), 3.62–3.56 (m, 2H), 3.26 (d, J = 5.0 Hz, 1H), 3.16–3.06 (m, 2H), 2.96 (s, 3H), 2.00–1.89 (m, 4H), 1.66–1.56 (m, 2H), 1.44 (d, J = 9.0 Hz, 2H), –0.01 (s, 9H);

¹³C NMR (125 MHz, CDCl₃) δ 155.1, 126.6, 126.0, 78.4, 46.4, 42.6, 35.6, 29.2, 29.0, 24.4, 18.5, –1.8;

IR (neat, cm⁻¹) 3312, 2950, 1614, 1516, 1246, 838;

HRMS (ESI) found 307.1818 [calcd for C₁₄H₂₈N₂NaO₂Si (M+Na) 307.1818]


allyl (Z)-2,4-dioxo-3-(6-(trimethylsilyl)hex-4-en-1-yl)tetrahydropyrimidine-1(2H)-carboxylate (2.25)
To a cooled (0 °C) solution of 2.23 (233 mg, 0.867 mmol) in THF was added NaH (1.50 eq., 60% in mineral oil, 52 mg). The ice-bath was removed and the mixture was stirred for 30 min. Then the reaction was cooled to 0 °C, and allylchloroformate (1.30 eq., 120 μL, 1.13 mmol) was added. The mixture was stirred for 30 min, and quenched with saturated NH₄Cl(aq). The mixture was diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to afford 2.25 (268 mg, 88%) as a colorless oil.

\[ \text{allyl (Z)-4-hydroxy-2-oxo-3-(6-(trimethylsilyl)hex-4-en-1-yl)tetrahydropyrimidine-1(2H)-carboxylate (2.13)} \]

To a stirred solution of 2.25 (141 mg, 0.399 mmol) in MeOH (4 mL) was added NaBH₄ (30 mg, 0.798 mmol) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO₃(aq). The biphasic mixture was stirred vigorously for 30
min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1 to EtOAc only) to afford \textbf{2.13} (124 mg, 88\%) as a colorless oil.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.98 (ddt, \(J = 5.5, 11.0, 17.0\) Hz, 1H), 5.46–5.39 (m, 2H), 5.27–5.22 (m, 2H), 4.98 (dt, \(J = 3.5, 6.0\) Hz, 1H), 4.73 (d, \(J = 5.5\) Hz, 2H), 3.98 (dt, \(J = 4.0, 13.0\) Hz, 1H), 3.76 (ddd, \(J = 5.5, 10.5, 18.0\) Hz, 1H), 3.54 (ddd, \(J = 6.0, 10.0, 14.0\) Hz, 1H), 3.30 (ddd, \(J = 6.0, 9.5, 14.0\) Hz, 1H), 2.54 (d, \(J = 6.0\) Hz, 1H), 2.06–1.99 (m, 4H), 1.75–1.64 (m, 2H), 1.45 (d, \(J = 8.0\) Hz, 2H), −0.01 (s, 9H);

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 153.8, 150.9, 131.8, 126.3, 126.2, 118.6, 77.9, 67.3, 46.4, 39.3, 29.8, 28.1, 24.4, 18.5, −1.8;

IR (neat, cm\textsuperscript{−1}) 3400, 2952, 1757, 1712, 1662, 1308, 1204, 839;

HRMS (ESI) found 377.1877 [calcd for C\textsubscript{17}H\textsubscript{30}N\textsubscript{2}NaO\textsubscript{4}Si (M+H) 377.1873]

\textbf{Scheme 2.9.} Synthesis of \textbf{2.15}
(Z)-4-methyl-6-(trimethylsilyl)hex-4-en-1-ol (2.26)

To a cooled (0 °C) solution of Cp₂TiCl₂ (100 mg, 0.400 mmol) in Et₂O (6 mL) was added isobutylmagnesium chloride (6 mL, 12.0 mmol, 2 M in ether). The mixture was stirred for 5 min at the same temperature. To this solution was added 6-(trimethylsilyl)hex-4-yn-1-ol²³ (681 mg, 4.00 mmol) and the ice-bath was removed. The mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, and then THF (10 mL) and MeI (0.75 mL, 12.0 mmol) were added sequentially at 0 °C. After 30 min, the reaction was quenched with 0.5 M HCl(aq) and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10:1) to afford 2.21 (394 mg, 53%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 5.17 (t, J = 9.0 Hz, 1H), 3.65 (dt, J = 5.5, 6.5 Hz, 2H), 2.06 (t, J = 8.0 Hz, 2H), 1.70–1.62 (m, 5H), 1.40 (d, J = 9.0 Hz, 2H), −0.02 (s, 9H);

¹³C NMR (125 MHz, CDCl₃) δ 132.2, 121.0, 63.1, 30.8, 27.7, 23.3, 18.3, −1.8;

IR (neat, cm⁻¹) 3335, 2953, 2953, 2953, 2953, 2953, 2953, 2953, 2953, 2953;

HRMS (ESI) found 209.1337 [calcd for C₁₀H₂₂NaOSi (M+Na) 209.1338]

(Z)-1-(4-methyl-6-(trimethylsilyl)hex-4-en-1-yl)pyrrolidine-2,5-dione (2.27)

To a cooled (0 °C) solution of 2.21 (197 mg, 1.06 mmol), Ph₃P (1.10 eq., 305 mg, 1.16 mmol), and succinimide (1.10 eq., 115 mg, 1.16 mmol) in THF (10 mL) was added DIAD (1.10 eq., 229 µL, 1.16 mmol) dropwise. The resulting mixture was warmed up to room temperature and stirred for 2 h. The reaction was diluted with EtOAc and water. The layers were separated, and the
aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:2) to afford **2.30** (234 mg, 83%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.19 (td, $J = 1.0$ Hz, 8.0 Hz, 1H), 3.50–3.47 (m, 2H), 2.71 (s, 4H), 2.02 (t, $J = 8.0$, 2H), 1.69–1.63 (m, 5H), 1.38 (d, $J = 8.5$ Hz, 2H), −0.01 (s, 9H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.1, 131.1, 121.4, 38.9, 28.7, 28.1, 25.7, 23.0, 18.4, −1.8;

IR (neat, cm$^{-1}$) 2954, 1700, 1401, 1247, 1153, 836;

HRMS (ESI) found 290.1550 [calcd for C$_{14}$H$_{25}$NNaO$_2$Si (M+Na) 290.1552]

**(Z)-5-hydroxy-1-(4-methyl-6-(trimethylsilyl)hex-4-en-1-yl)pyrrolidin-2-one (2.15)**

To a stirred solution of imide (245 mg, 0.909 mmol) in MeOH (4 mL) was added NaBH$_4$ (69 mg, 1.82 mmol) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO$_3$(aq). The biphasic mixture was stirred vigorously for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1 to EtOAc only) to afford **X** (214 mg, 88%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.20 (ddd, $J = 1.5$ Hz, 6.0 Hz, 8.0 Hz, 1H), 5.14 (t, $J = 8.5$ Hz, 1H), 4.01 (d, $J = 8.5$ Hz, 1H), 3.45 (ddd, $J = 6.5$, 9.5, 13.5 Hz, 1H), 3.11 (ddd, $J = 5.0$, 9.5, 14.0 Hz, 1H), 2.57–2.50 (m, 1H), 2.33–2.24 (m, 2H), 1.98–1.87 (m, 3H), 1.68–1.53 (m, 5H), 1.35 (d, $J = 9.0$ Hz, 2H), −0.04 (s, 9H);
13C NMR (125 MHz, CDCl₃) δ 174.8, 131.5, 121.1, 83.2, 40.0, 28.9, 28.8, 28.3, 25.8, 23.2, 18.4, –1.8;

IR (neat, cm⁻¹) 3326, 2953, 1663, 1462, 1246, 836;

HRMS (ESI) found 292.1710 [calcd for C₁₄H₂₇NNaO₂Si (M+Na) 292.1709]

Scheme 2.10. Synthesis of 2.17.

(Z)-6-(triisopropylsilyl)hex-4-en-1-ol (2.28)

To a stirred solution of primary alcohol²⁴ (491 mg, 2.03 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (0.311 mL, 2.23 mmol, 1.1 eq.) and MsCl (172 µL, 2.23 mmol, 1.1 eq.) at 0 °C. The resulting solution was stirred for 5 min, and the reaction was quenched with NaHCO₃(aq). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude mesylate, which was carried to the next step without further purification.

To a stirred solution of the crude mesylate from the previous step in DMSO (5 mL) was added NaCN (109 mg, 2.22 mmol, 1.1 eq.) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. The reaction was diluted with water and hexanes. The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo, and a half of the crude material was carried to the next step without further purification.

To a cooled (−78 °C) solution of the crude nitrile in CH$_2$Cl$_2$ (5 mL) was added DIBALH (0.66 mL, 1 M in CH$_2$Cl$_2$, 0.66 mmol) dropwise. The reaction was quenched with methanol at the same temperature, and it was warmed to room temperature. An aqueous solution of Rochelle’s salt was added to the mixture, which was stirred overnight. The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to afford the crude aldehyde.

To a cooled (0 °C) solution of the crude aldehyde in MeOH (2 mL) was added NaBH$_4$ (20 mg, 0.529 mmol) in one portion. After 5 minutes, the reaction was quenched with NH$_4$Cl(aq). The mixture was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10:1) to afford 2.28 (94 mg, 18% over 4 steps).
\(^\text{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.55–5.49 (m, 1H), 5.25–5.20 (m, 1H), 3.68 (q, \(J = 6.4\) Hz, 2H), 2.15 (q, \(J = 6.8\) Hz, 2H), 1.65 (quint, \(J = 6.8\) Hz, 2H), 1.56 (d, \(J = 9.8\) Hz, 2H), 1.05–1.03 (m, 21H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 127.0, 126.5, 62.8, 32.6, 23.5, 18.7, 11.1, 10.6;

IR (neat, cm\(^{-1}\)) 3330, 2941, 2866, 2361, 1463, 1155, 918;

HRMS (ESI) found 279.2112 [calcd for \(\text{C}_{15}\text{H}_{32}\text{NaOSi (M+Na)}\) 279.2120]

(Z)-1-(6-(triisopropylsilyl)hex-4-en-1-yl)pyrrolidine-2,5-dione (2.29)

To a cooled (0 °C) solution of 2.28 (94 mg, 0.367 mmol), Ph\(_3\)P (1.10 eq., 106 mg, 0.404 mmol), and succinimide (1.10 eq., 40 mg, 0.404 mmol) in THF (4 mL) was added DIAD (1.1 eq., 80 \(\mu\)L, 0.404 mmol) dropwise. The resulting mixture was warmed up to room temperature and stirred for 2 h. The reaction was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to afford 2.29 (88 mg, 71%) as a colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.54–5.48 (m, 1H), 5.20–5.15 (m, 1H), 3.54–3.51 (m, 2H), 2.69 (s, 4H), 2.07 (q, \(J = 7.0\) Hz, 2H), 1.64 (quint, \(J = 7.6\) Hz, 2H), 1.52 (d, \(J = 9.3\) Hz, 2H), 1.04–1.02 (m, 21H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 177.1, 127.4, 125.6, 38.7, 28.1, 27.5, 24.5, 18.7, 11.1, 10.7;

IR (neat, cm\(^{-1}\)) 2941, 2865, 2360, 1703, 1461, 1402, 1154, 1074, 667;

HRMS (ESI) found 360.2335 [calcd for \(\text{C}_{19}\text{H}_{35}\text{NNaO}_{2}\text{Si (M+Na)}\) 360.2335]
(Z)-5-hydroxy-1-(6-(triisopropylsilyl)hex-4-en-1-yl)pyrrolidin-2-one (2.17)

To a stirred solution of 2.29 (104 mg, 0.309 mmol) in MeOH (3 mL) was added NaBH₄ (23 mg, 0.618 mmol) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO₃(aq). The biphasic mixture was stirred vigorously for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to afford 2.17 (72 mg, 69%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 5.51 (qt, J = 1.5, 10.0 Hz, 1H), 5.25–5.16 (m, 2H), 3.51 (ddd, J = 6.5, 9.0, 13.5 Hz, 1H), 3.17 (ddd, J = 5.0, 8.5, 14.0 Hz, 1H), 2.90 (d, J = 9.0 Hz, 1H), 2.59–2.52 (m, 1H), 2.36–2.28 (m, 2H), 2.07 (q, J = 7.5 Hz, 2H), 1.88–1.82 (m, 1H), 1.71–1.57 (m, 2H), 1.53 (dd, J = 1.0, 8.5 Hz, 2H), 1.04–0.99 (m, 21H);

¹³C NMR (125 MHz, CDCl₃) δ 174.7, 127.2, 126.0, 83.3, 39.8, 28.9, 28.3, 27.6, 24.6, 18.7, 11.1, 10.7;

IR (neat, cm⁻¹) 3233, 2939, 2863, 1659, 1460, 1068, 996, 882, 656;

HRMS (ESI) found 362.2493 [calcd for C₁₉H₃₇NNaO₂Si (M+Na) 362.2491]
Scheme 2.11. Synthesis of 2.18.

(Z)-6-(dimethylsilyl)hex-4-en-1-ol (2.30)

To a cooled (0 °C) solution of (Ph₃P)₄Pd (168 mg, 0.291 mmol) in THF (5 mL) was added Me₂HSi(CH₂)MgCl (3.2 mL, 1.0 M in THF, 1.1 equiv). After 10 minutes, a solution of (Z)-2-((5-iodopent-4-en-1-yl)oxy)tetrahydro-2H-pyran²⁵ (950.0 mg, 2.91 mmol) in THF (20 mL) was added, and the ice bath was removed. The mixture was stirred for 4 hours at room temperature before it was quenched with sat. NH₄Cl(aq). The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford the crude cross-coupling product. The crude mixture was dissolved in AcOH/THF/H₂O (3:1:1, 30 mL), stirred overnight at room temperature, and diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and *in vacuo*, and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford 2.30 as a colorless oil (143 mg, 31% for 2 steps):

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 5.49–5.40 (m, 1H), 5.36–5.26 (m, 1H), 3.86 (spt, \( J = 3.4 \) Hz, 1H), 3.67 (q, \( J = 6.4 \), 2H), 2.09 (q, \( J = 7.2 \) Hz, 2H), 1.66–1.56 (m, 5H), 1.29 (t, \( J = 5.4 \) Hz, 1H), 0.09 (d, \( J = 3.4 \) Hz, 6H);

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 127.2, 125.7, 62.6, 32.6, 23.4, 15.7, 4.6;

IR (neat, cm\textsuperscript{-1}) 3337, 2937, 2116, 1249, 881, 838;

HRMS (ESI) found 181.1021 [calcd for C\textsubscript{8}H\textsubscript{18}NaOSi (M+Na) 181.1025]

(Z)-1-(6-(dimethylsilyl)hex-4-en-1-yl)pyrrolidine-2,5-dione (2.31)

To a cooled (0 °C) solution of 2.30 (143 mg, 0.903 mmol), Ph\textsubscript{3}P (1.10 eq., 261 mg, 0.993 mmol), and succinimide (1.10 eq., 92 mg, 0.993 mmol) in THF (10 mL) was added DIAD (1.10 eq., 196 \( \mu L \), 0.993 mmol) dropwise. The resulting mixture was warmed up to room temperature and stirred for 2 h. The reaction was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2:1) to afford 2.31 (115 mg, 53%) as a colorless oil.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 5.47–5.41 (m, 1H), 5.29–5.24 (m, 1H), 3.84 (spt, \( J = 3.4 \) Hz, 1H), 3.53–3.50 (m, 2H), 2.69 (s, 4H), 2.02 (q, \( J = 7.2 \) Hz, 2H), 1.63 (quin, \( J = 7.6 \) Hz, 2H), 1.54 (dd, \( J = 3.2 , 8.5 \) Hz, 2H), 0.07 (d, \( J = 3.9 \) Hz, 6H);

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 177.2, 126.4, 126.1, 38.6, 28.1, 27.6, 24.4, 15.8, −4.6;

IR (neat, cm\textsuperscript{-1}) 2947, 2114, 1696, 1369, 1248, 1141, 663;

HRMS (ESI) found 262.1244 [calcd for C\textsubscript{12}H\textsubscript{21}NNaO\textsubscript{2}Si (M+Na) 262.1239]
(Z)-1-(6-(dimethylsilyl)hex-4-en-1-yl)-5-hydroxypyrrolidin-2-one (2.18)

To a stirred solution of 2.31 (115 mg, 0.478 mmol) in MeOH (5 mL) was added NaBH₄ (36 mg, 0.956 mmol) at 0 °C in one portion. The reaction was stirred for 2 hours at the same temperature, and it was quenched with sat. NaHCO₃(aq). The biphasic mixture was stirred vigorously for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1 to EtOAc only) to afford 2.18 (87 mg, 75%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 5.44 (dt, J = 8.5, 10.5 Hz, 1H), 5.28 (dt, J = 7.5, 10.5 Hz, 1H), 5.22 (td, J = 2.0, 6.0 Hz, 1H), 3.84 (sept, J = 3.5 Hz, 1H), 3.49 (ddd, J = 6.5, 9.0, 13.5 Hz, 1H), 3.16 (ddd, J = 5.5, 9.0, 14.5 Hz, 1H), 3.04 (d, J = 8.0 Hz, 1H), 2.59–2.52 (m, 1H), 2.36–2.27 (m, 2H), 2.01 (q, J = 7.5 Hz, 1H), 1.92–1.85 (m, 1H), 1.68–1.57 (m, 2H), 1.53 (dd, J = 2.0, 9.0 Hz, 2H), 0.08 (d, J = 3.5 Hz, 6H);

¹³C NMR (125 MHz, CDCl₃) δ 174.6, 126.7, 125.9, 83.3, 39.8, 28.8, 28.4, 27.7, 24.5, 15.8, –4.6; IR (neat, cm⁻¹) 3316, 2955, 2112, 1659, 1460, 1247, 881, 838, 674;

HRMS (ESI) found 264.1390 [calcd for C₁₂H₂₃NNaO₂Si (M+Na) 264.1396]

2.6.4. Aza-Sakurai Cyclization Reactions

(8R,8aR)-8-vinylhexahydroindolizin-3(2H)-one (2.2)
To a stirred solution of **2.1** (51 mg, 0.200 mmol) and **2.3e** (10 mg, 0.020 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 μL, 0.400 mmol) in an ice bath. Then the reaction was moved to a fridge (4 °C) and stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc only) to afford **2.2** (28 mg, 85%) as a colorless oil. This material was determined to be 91% ee by chiral GC analysis (β-Cyclosil, 140 °C, *t*_r(major) = 48.0 min, *t*_r(minor) = 46.6 min).

[α]^{24}_D = +54.4 (c 1.00, CHCl₃);

^1^H NMR (500 MHz, CDCl₃) δ 5.66 (ddd, *J* = 8.0, 10.0, 17.5 Hz, 1H), 5.15–5.09 (m, 2H), 4.15 (ddt, *J* = 1.5, 4.5, 13 Hz, 1H), 3.16 (dt, *J* = 7.5, 9.5 Hz, 1H), 2.60 (td, *J* = 3.0, 12.5 Hz, 1H), 2.39–2.35 (m, 2H), 2.21–2.14 (m, 1H), 1.91–1.75 (m, 4H), 1.72–1.64 (m, 2H);

^1^C NMR (125 MHz, CDCl₃) δ 173.6, 138.4, 116.1, 60.6, 48.5, 39.7, 30.2, 30.1, 24.0, 23.6;

IR (neat, cm⁻¹) 2932, 2854, 1684, 1418, 995, 917;

HRMS (ESI) found 188.1052 [calcd for C_{10}H_{15}NNaO (M+ Na) 188.1051]

**(8R,8aS)-8-vinylhexahydro-3H-oxazolo[3,4-a]pyridin-3-one (2.6)**

To a stirred solution of **2.5** (52 mg, 0.200 mmol) and **2.3e** (20 mg, 0.040 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 μL, 0.400 mmol) in an ice bath. Then the reaction was moved to
a fridge (4 °C) and stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2:1) to afford amide (24 mg, 72%) as a colorless oil. This material was determined to be 90% ee by chiral GC analysis (β-Cyclosil, 150 °C, $t_r$(major) = 52.9 min, $t_r$(minor) = 51.0 min).

$[\alpha]^{24}_D = +62.4$ (c 1.00, CHCl$_3$);

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.57 (ddd, $J = 7.5, 10.0, 18.0$ Hz, 1H), 5.14–5.10 (m, 2H), 4.35 (t, $J = 8.5$ Hz, 1H), 3.99 (dd, $J = 5.5, 8.5$ Hz, 1H), 3.89 (ddt, $J = 1.5, 5.0, 13.5$ Hz, 1H), 3.40 (ddd, $J = 6.5, 8.5, 10.0$ Hz, 1H), 2.81 (td, $J = 3.5, 13.5$ Hz, 1H), 2.04–1.98 (m, 1H), 1.93 (ddq, $J = 1.5, 3.5, 13.5$ Hz, 1H), 1.77–1.72 (m, 1H), 1.53 (qdd, $J = 3.5, 5.0, 13.5$ Hz, 1H), 1.39–1.30 (m, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 156.9, 137.4, 117.2, 66.7, 57.8, 46.1, 40.9, 29.6, 23.9;

IR (neat, cm$^{-1}$) 2937, 1748, 1418, 1243, 1006;

HRMS (ESI) found 190.0848 [calcd for C$_9$H$_{13}$NNaO$_2$ (M+ Na) 190.0844]

**(8R,8aS)-1,1,2-trimethyl-8-vinylhexahydroimidazo[1,5-a]pyridin-3(2H)-one (2.8)**

To a stirred solution of 2.7 (60 mg, 0.200 mmol) and 2.3e (10 mg, 0.020 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol) in an ice bath. Then the reaction was moved to
a fridge (4 °C) and stirred for 72 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:2) to afford 2.8 (34 mg, 82%) as a colorless oil. This material was determined to be 94% ee by chiral HPLC analysis (AS-H, 5% IPA/hex, t\textsubscript{r}(major) = 25.0 min, t\textsubscript{r}(minor) = 33.9 min).

\[ \alpha \]\textsuperscript{24}D = +97.2 (c 1.00, CHCl\textsubscript{3});

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 5.66 (ddd, \( J = 9.0, 10.0, 17.0 \) Hz, 1H), 5.14 (dd, \( J = 1.0, 17.0 \) Hz, 1H), 5.07 (dd, \( J = 2.0 \) Hz, 10.5 Hz, 1H), 3.82 (ddt, \( J = 1.5, 4.5, 12.0 \) Hz, 1H), 2.67–2.65 (m, 4H), 2.50 (td, \( J = 3.5, 13.0 \) Hz, 1H), 2.21–2.14 (m, 1H), 1.79–1.69 (m, 2H), 1.47 (qdd, \( J = 3.5, 5.0, 13.0 \) Hz, 1H), 1.30–1.22 (m, 4H), 1.06 (s, 3H);

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 159.7, 139.7, 116.1, 67.6, 59.0, 42.0, 41.4, 32.0, 25.6, 24.1, 24.0, 17.3;

IR (neat, cm\textsuperscript{-1}) 2935, 1697, 1433, 1398, 914, 841;

HRMS (ESI) found 231.1472 [calcd for C\textsubscript{12}H\textsubscript{20}N\textsubscript{2}O (M+ Na) 231.1473]

(9R,9aR)-9-vinyloctahydro-4H-quinolizin-4-one (2.10)
To a stirred solution of 2.9 (54 mg, 0.200 mmol) and 2.3e (20 mg, 0.040 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 μL, 0.400 mmol) in an ice bath. Then the reaction was moved to a fridge (4 °C) and stirred for 24 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc only) to afford 2.10 (32 mg, 90%) as a colorless oil. This material was determined to be 90% ee by chiral HPLC analysis (AD-H, 5% IPA/hex, tᵣ(major) = 13.3 min, tᵣ(minor) = 15.2 min).

\[ [\alpha]^{24}_D = +52.2 \text{ (c 1.00, CHCl}_3) \];

\(^1\)H NMR (500 MHz, CDCl₃) δ 5.59 (ddd, \( J = 9.0, 10.5, 17.5 \text{ Hz, 1H} \)), 5.09 (dd, \( J = 1.0, 17.5 \text{ Hz, 1H} \)), 5.05 (\( J = 2.0, 10.0 \text{ Hz, 1H} \)), 4.82 (dp, \( J = 2.0, 13.5 \text{ Hz, 1H} \)), 3.03 (dt, \( J = 7.0, 10.0 \text{ Hz, 1H} \)), 2.42–2.27 (m, 3H), 2.00–1.93 (m, 2H), 1.83–1.69 (m, 3H), 1.63–1.36 (m, 4H);

\(^{13}\)C NMR (125 MHz, CDCl₃) δ 169.4, 139.7, 116.2, 60.2, 48.6, 42.5, 33.0, 31.9, 27.9, 24.7, 18.7;

IR (neat, cm\(^{-1}\)) 2933, 2856, 1637, 1440, 1269, 916;

HRMS (ESI) found 202.1209 [calcd for C\(_{11}\)H\(_{17}\)N\(\text{NaO} (M+\text{Na}) 202.1208\]

(4aR,5R)-2-methyl-5-vinloctahydro-1H-pyrido[1,2-c]pyrimidin-1-one (2.12)
To a cooled (−30 °C) solution of 2.11 (57 mg, 0.200 mmol) and 2.3e (10 mg, 0.020 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 μL, 0.400 mmol). Then the reaction was stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc only) to afford 2.12 (36 mg, 93%) as a colorless oil. This material was determined to be 94% ee by chiral HPLC analysis (AS-H, 5% IPA/hex, tᵣ(major) = 29.8 min, tᵣ(minor) = 19.1 min).

[α]²⁴_D = +10.0 (c 1.00, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 5.57 (dt, J = 9.5, 17.5 Hz, 1H), 5.08 (dd, J = 1.5, 17.0 Hz, 1H), 5.04 (dd, J = 1.5, 10.5 Hz, 1H), 4.54 (dt, J = 2.0, 13.0 Hz, 1H), 3.16–3.14 (m, 2H), 2.95–2.90 (m, 4H), 2.48 (td, J = 2.5, 13.0 Hz, 1H), 2.07 (dq, J = 5.0, 13.5 Hz, 1H), 1.96–1.89 (m, 1H), 1.83–1.76 (m, 2H), 1.67–1.63 (m, 1H), 1.48 (qt, J = 4.0, 13.0 Hz, 1H), 1.31 (qd, J = 4.0, 13.0 Hz, 1H);

¹³C NMR (125 MHz, CDCl₃) δ 156.6, 139.7, 116.3, 58.0, 47.6, 45.3, 44.0, 35.9, 31.5, 26.7, 24.8;

IR (neat, cm⁻¹) 2930, 2360, 1637, 1501, 1254, 917;

HRMS (ESI) found 217.1315 [calcd for C₁₁H₁₈N₂O (M+ Na) 217.1317]

**allyl (4aR,5R)-1-oxo-5-vinhexahydro-1H-pyrido[1,2-c]pyrimidine-2(3H)-carboxylate (2.14)**
To a cooled (−30 °C) solution of 2.13 (71 mg, 0.200 mmol) and 2.3e (10 mg, 0.020 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 μL, 0.400 mmol). Then the reaction was stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc only) to afford 2.14 (44 mg, 83%) as a colorless oil. This material was determined to be 92% ee by chiral HPLC analysis (OD-H, 2% IPA/hex, tᵣ(major) = 33.5 min, tᵣ(minor) = 29.7 min).

[α]²⁴_D = +55.4 (c 1.00, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 5.97 (ddt, J = 5.0, 10.0, 17.5 Hz, 1H), 5.56 (ddd, J = 9.0, 10.5, 17.0 Hz, 1H), 5.42 (dd, J = 1.5, 17.0 Hz, 1H), 5.25 (dd, J = 1.0, 10.0 Hz, 1H), 5.10 (dd, J = 1.0, 17.5 Hz, 1H), 5.07 (dd, J = 1.0, 10.0 Hz, 1H), 4.76–4.65 (m, 3H), 4.00 (ddd, J = 3.5, 5.5, 12.5 Hz, 1H), 3.40 (ddd, J = 2.5, 10.5, 13.5 Hz, 1H), 3.05 (ddd, J = 6.5, 8.0, 10.0 Hz, 1H), 2.54 (td, J = 2.5, 12.5 Hz, 1H), 2.10 (ddt, J = 2.5, 6.5, 14.5 Hz, 1H), 1.96–1.89 (m, 1H), 1.82–1.87 (m, 1H), 1.78–1.69 (m, 2H), 1.54 (qt, J = 4.0, 13.0 Hz, 1H), 1.37 (qd, J = 4.0, 12.0 Hz, 1H);

¹³C NMR (125 MHz, CDCl₃) δ 154.3, 151.3, 138.7, 131.9, 118.5, 116.9, 67.4, 58.8, 48.4, 44.3, 41.1, 31.4, 28.1, 24.6;

IR (neat, cm⁻¹) 2933, 1761, 1683, 1430, 1228, 1131, 927;

HRMS (ESI) found 287.1377 [calcd for C₁₄H₂₀N₂NaO₃ (M+ Na) 287.1372]

(8R,8aR)-8-methyl-8-vinylhexahydroindolizin-3(2H)-one (2.15)
To a stirred solution of 2.15 (54 mg, 0.200 mmol) and 2.3g (20 mg, 0.040 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol) in an ice bath. Then the reaction was moved to a fridge (4 °C) and stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc only) to afford 2.16 (31 mg, 85%) as a colorless oil. This material was determined to be 88% ee by chiral HPLC analysis (AD-H, 5% IPA/hex, t₁(major) = 21.6 min, t₁(minor) = 25.1 min).

[α]₂₄⁰ = +42.4 (c 1.00, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 5.70 (dd, J = 12.0, 17.5 Hz, 1H), 5.08–5.04 (m, 2H), 4.15 (dd, J = 5.0, 13.5 Hz, 1H), 3.35 (dd, J = 4.5, 8.5 Hz, 1H), 2.61 (td, J = 4.0, 12.5 Hz, 1H), 2.33–2.30 (m, 2H), 1.94 (dq, J = 9.0, 14.0 Hz, 1H), 1.75–1.48 (m, 5H), 0.93 (s, 3H);

¹³C NMR (125 MHz, CDCl₃) δ 173.8, 145.0, 113.2, 63.7, 39.9, 39.7, 36.8, 30.2, 19.8, 18.5, 14.9;

IR (neat, cm⁻¹) 2941, 1679, 1439, 1276, 917;

HRMS (ESI) found 202.1202 [calcd for C₁₁H₁₇NNaO (M+Na) 202.1208]
2.6.5. Natural Product Synthesis


(-)-tashiromine

To a stirred solution of ent-2.2 (50 mg, 0.303 mmol, 92% ee) in 1:1 THF/H₂O (3 mL) was added K₂OsO₄·2H₂O (2 mg, 2 mol%) and NaIO₄ (324 mg, 1.515 mmol, 5 equiv). The mixture was stirred at room temperature for 4 hours. The reaction diluted with water and CH₂Cl₂. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in vacuo, and carried to the next step without further purification.

A solution of the crude material in THF (1 mL) was added to a suspension of LAH (12 mg, 0.303 mmol) in THF (1 mL) at room temperature. The reaction was stirred under refluxing condition for 15 min, and quenched with 12 μL of water, 12 μL of 15% NaOH(aq), and 36 μL of water. The mixture was filtered through a short pad of celite and washed with THF. The filtrate was concentrated and purified by column chromatography (silica gel, CH₂Cl₂/MeOH/sat. NH₄OH(aq), 90:9:1) to afford (-)-tashiromine (42 mg, 90% over 2 steps). This material was determined to be 93% ee by chiral GC analysis (β-Cyclosil, 100 °C, tᵣ(major) = 50.1 min, tᵣ(minor) = 49.1 min).
$[^\alpha]^{24}D = -41 \ (c \ 1.00, \text{EtOH})$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.63 (dd, $J = 4.5, 10.5 \text{ Hz, 1H}$), 3.46 (dd, $J = 7.0, 11.0 \text{ Hz, 1H}$), 3.03–3.10 (m, 2H), 2.05 (q, $J = 9.0 \text{ Hz, 1H}$), 1.43–1.97 (m, 11H), 1.03 (qd, $J = 5.0, 11.5 \text{ Hz, 1H}$);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 64.3, 63.8, 56.7, 56.5, 43.7, 29.5, 28.1, 25.3, 24.8, 24.4;

IR (neat) 3335, 2930, 2798, 2360, 1671, 1444, 1045, 753 cm$^{-1}$;

HRMS (ESI) found 156.1381 [calcd for C$_9$H$_{18}$NO (M+H) 156.1388]

Scheme 2.13. Synthesis of (+)-epilupinine.

(+)-epilupinine

To a stirred solution of X (20 mg, 0.112 mmol, 90% ee) in 1:1 THF/H$_2$O (2 mL) was added K$_2$OsO$_4$•2H$_2$O (1 mg, 2 mol%) and NaIO$_4$ (120 mg, 0.560 mmol, 5 equiv). The mixture was stirred at room temperature for 4 hours. The reaction diluted with water and CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over anhydrous Na$_2$SO$_4$, concentrated in vacuo, and carried to the next step without further purification.

A solution of the crude material in THF (1 mL) was added to a suspension of LAH (4 mg, 0.112 mmol) in THF (1 mL) at room temperature. The reaction was stirred under refluxing condition for 15 min, and quenched with water, 15% NaOH(aq), and water. The mixture was filtered
through a short pad of celite and washed with THF. The filtrate was concentrated and purified by column chromatography (silica gel, CH₂Cl₂/MeOH/sat. NH₄OH(aq), 90:9:1) to afford (+)-epilupinine (14 mg, 72% over 2 steps). This material was determined to be 91% ee by chiral GC analysis (β-Cyclosil, 110 °C, tᵣ(major) = 53.4 min, tᵣ(minor) = 51.1 min).

[α]²⁴
D = +30 (c 1.00, EtOH);

¹H NMR (500 MHz, CDCl₃) δ 3.66 (dd, J = 3.0, 10.5 Hz, 1H), 3.58 (dd, J = 6.0, 10.5 Hz, 1H), 2.85–2.77 (m, 2H), 2.05–1.99 (m, 2H), 1.91–1.88 (m, 1H), 1.86–1.81 (m, 1H), 1.79–1.74 (m, 1H), 1.72–1.64 (m, 3H), 1.62–1.58 (m, 2H), 1.44–1.35 (m, 2H), 1.29–1.14 (m, 3H);

¹³C NMR (125 MHz, CDCl₃) δ 64.3, 63.8, 56.7, 56.5, 43.7, 29.5, 28.1, 25.3, 24.8, 24.4;

IR (neat, cm⁻¹) 3341, 2929, 2361, 1654, 1446, 1249, 1065, 758;

HRMS (ESI) found 170.1542 [calcd for C₁₀H₂₀NO (M+H) 170.1545]

2.6.6. Mechanistic Experiments

Initial Rates

To a stirred solution of 2.1 (51 mg, 0.200 mmol), 2.3e (10 mg, 0.020 mmol), dodecane (internal std, 50 μL) in TBME (4 mL, 0.05 M) was added TMSCl (51 μL, 0.400 mmol) in an ice bath. An aliquot of ~100 μL was removed from the flask every five minute and quenched by adding to a vial containing TBAF (100 μL, 1.0 M, THF). The mixture was diluted with NaHCO₃(aq) and EtOAc, and the reaction was analyzed by GC. The procedure was repeated for 2.17 and 2.18, and with urea catalyst 4 as well.

<table>
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<th>Slope</th>
<th>Catalyst 2.3e</th>
<th>Catalyst 2.4</th>
</tr>
</thead>
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<td>Substrate 2.1</td>
<td>0.5163</td>
<td>0.0652</td>
</tr>
<tr>
<td>Substrate 2.17</td>
<td>0.0706</td>
<td>0.1375</td>
</tr>
<tr>
<td>Substrate 2.18</td>
<td>0.9241</td>
<td>0.0486</td>
</tr>
<tr>
<td>$k_{rel}$</td>
<td>Catalyst 2.3e</td>
<td>Catalyst 2.4</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Substrate 2.1</td>
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</tr>
<tr>
<td>Substrate 2.17</td>
<td>0.14</td>
<td>0.27</td>
</tr>
<tr>
<td>Substrate 2.18</td>
<td>1.79</td>
<td>0.09</td>
</tr>
</tbody>
</table>
y = 0.9241x + 0.7232
$R^2 = 0.9789$

yield (s, me2h)
Linear (yield (s, me2h))

y = 0.0652x + 0.8408
$R^2 = 0.9789$

yield (o, tms)
Linear (yield (o, tms))
KIE Experiments

To a stirred solution of a mixture of 2.1-H and 2.1-D (13 mg, 0.05 mmol total, subjected to MS analysis to calculate R₀), 2.3e (2.5 mg, 10 mol%), dodecane (internal std, 11 μL) in TBME (1 mL, 0.05 M) was added TMSCl (13 μL, 0.400 mmol) in an ice bath. After 1 h, the reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. An aliquot was removed for GC analysis. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated \textit{in vacuo}. The residue was purified by column chromatography (silica gel, EtOAc only) to afford a mixture of 2.2-H and 2.2-D, which was analyzed by MS to calculate R_p.

![Chemical Structures]

### Table 1: Mass Spectral Data

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<th>Mass (M+2)</th>
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<th>R_p</th>
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<tr>
<td></td>
<td>1373987</td>
<td>1129478</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
\[ R_0 = \frac{\text{abundance of M+2} - 0.192 \times \text{abundance of M+1}}{\text{abundance of M+1}} \]

\[ R_P = \frac{\text{abundance of M+2} - 0.108 \times \text{abundance of M+1}}{\text{abundance of M+1}} \]

<table>
<thead>
<tr>
<th>Run</th>
<th>( R_0 )</th>
<th>( R_P )</th>
<th>( F )</th>
<th>KIE</th>
</tr>
</thead>
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<td>0.83</td>
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<tr>
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<tr>
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<td>1.176</td>
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<td>0.85</td>
</tr>
</tbody>
</table>

\[ \text{KIE} = \frac{\ln(1 - F)}{\ln(1 - F \times R_P/R_0)} \]
2.6.7. Additional Optimization Data

```
\[
\text{2.6.7. Additional Optimization Data}
\]

\[
\begin{align*}
\text{TMS} & \quad \text{catalyst} \\
& \quad (20 \text{ mol\%}) \\
& \quad \text{TMSCl (2.0 equiv)} \\
& \quad \text{TBME, \(-30^\circ\text{C}, 24\text{h}\)}
\end{align*}
\]

\[
\begin{array}{ccc}
\text{R} & \text{ee} & \text{R} & \text{ee} \\
\text{OMe} & 86 & \text{OMe} & 53 \\
\text{Me} & 92 & \text{Me} & 81 \\
\text{H} & 94 & \text{H} & 94 \\
\text{Cl} & 92 & \text{Cl} & 85 \\
\text{CF}_3 & 86 & \text{CF}_3 & 63 \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{Ar} & \text{R} = \text{t-Bu} & \text{R} = \text{i-Pr} & \text{R} = \text{t-Bu} & \text{R} = \text{i-Pr} \\
\text{benzene} & 31\% \text{ ee} & 48\% \text{ ee} & 55\% \text{ ee} & 55\% \text{ ee} \\
\text{naphthalene} & 18\% \text{ ee} & 67\% \text{ ee} & 86\% \text{ ee} & 87\% \text{ ee} \\
\text{anthracene} & -23\% \text{ ee} & 19\% \text{ ee} & 56\% \text{ ee} & 71\% \text{ ee} \\
\text{phenanthrene} & -63\% \text{ ee} & -14\% \text{ ee} & 52\% \text{ ee} & 77\% \text{ ee} \\
\text{fluorene} & 54\% \text{ ee} & 77\% \text{ ee} & 88\% \text{ ee} & 87\% \text{ ee} \\
\text{oxyfluorene} & 52\% \text{ ee} & 72\% \text{ ee} & 51\% \text{ ee} & 86\% \text{ ee} \\
\text{benzothiophene} & 64\% \text{ ee} & 80\% \text{ ee} & 94\% \text{ ee} & 92\% \text{ ee} \\
\end{array}
\]