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

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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.

Table of Contents

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.

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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.

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Grad school is long and it wouldn't have been enjoyable without some friends. Just to mention a few, I'd like to thank Greg for his friendship. I've really enjoyed talking about all

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

t	tert
TBAF	tetra-n-butylammonium fluoride
TBME	methyl tert-butyl ether
TCDI	1,1'-Thiocarbonyldiimidazole
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl

Chapter 1

β-Selective Glycosylation Reactions Catalyzed by

Macrocyclic Bis-Thiourea Catalysts[1]

1.1 Introduction

Carbohydrates are essential to the fundamental processes of life, providing energy, constituting structural components, and modulating signaling pathways.[2] 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.[3] The primary technological gap in sugar synthesis is predominantly associated with controlling the stereochemistry (α or β) of glycosidic bonds.[4] 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*.

[2] Varki, A., Cummings, R. D., Esko, J. D., Freeze, H. H., Stanley, P., Bertozzi, C. R., Hart, G. W., Etzler, M. E., Eds. *Essentials of Glycobiology*, 2nd ed.; Cold Spring Harbor Laboratory Press; Cold Spring Harbor, NY, **2009**.

[3] Seeberger, P. H. *Acc. Chem. Res.* **2015**, *48*, 1450 and references therein.

[4] (a) Werz, D. B., Vidal, S., Eds., *Modern Synthetic Methods in Carbohydrate Chemistry*: *From Monosaccharides to Complex Glycoconjugates*; Wiley-VCH: Weinheim, **2014**. (b) Zhu, X.; Schmidt R. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900.

Stereocontrol in glycosylation has largely been achieved by utilizing substituents and protecting groups.[5] 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.[6] Alternatively, diastereocontrol can be addressed by using a chiral catalyst to direct the nucleophilic addition to a specific face of the oxocarbenium intermediate.[7] 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).[8] This precedent, combined with the recent uses of achiral hydrogen bond donors in glycosylation reactions,[9] led us to examine the effect of chiral thioureas on the diastereoselectivity of glycosylation processes.

[5] Demchenko, A. V., Ed., *Handbook of Chemical Glycosylation*: *Advances in Stereoselectivity and Therapeutic Relevance*; Wiley-VCH: Weinheim, **2008**.

[6] Danisehfsky, S. J.; Shue, Y.-K.; Chang, M. N.; Wong, C.-H. *Acc. Chem. Res.* **2015**, *48*, 643 and references therein.

[7] (a) Cox, D. J.; Smith, M. D.; Fairbanks, A. J. *Org. Lett.* **2010**, *12*, 1452. (b) Gould, N. D.; Allen, C. L.; Nam, B. C.; Schepartz, A.; Miller, S. J. *Carbohydr. Res.* **2013**, *382*, 36.

[8] Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198

[9] (a) Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M. *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 9152. (b) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Angew. Chem.*, *Int. Ed.* **2013**, *52*, 10089. (c) Sun, L.; Wu, X.; Xiong, D.-C.; Ye, X.-S. *Angew. Chem.*, *Int. Ed.* **2016**, *55*, 8041. (d) Kimura, T.; Eto, T.; Takahashi, D.; Toshima, K. *Org. Lett.*, **2016**, *18*, 3190.
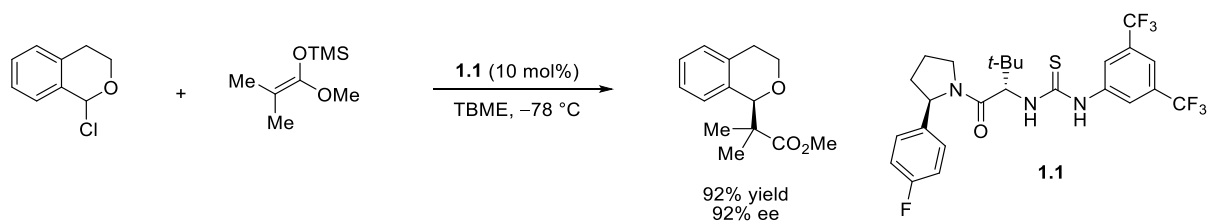
Scheme 1.1. Asymmetric alkylation of α-chloroisochroman with silyl ketene acetal

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

[10] Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687.
[11] Lehnherr, D.; Rajapaksa, N. S.; Ford, D. D.; Kennedy, C. R.; Jacobsen, E. N. *Manuscript in preparation*.

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 C_2-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 indoline 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
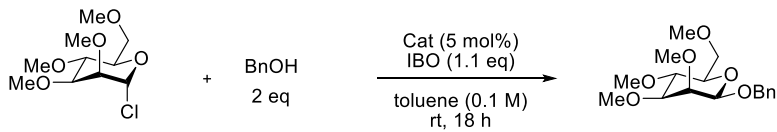
Entry	catalyst	yield	α:β
1	none	0.1	84:16
2[b]	**1.1**	1	52:48
3[c]	**1.1**	5	40:60
4	**1.2**	15	20:80
5	**1.3**	1	46:54
6	**1.4**	10	18:82
7	**1.5**	2	15:85
8	**1.6**	1	67:33
9	**1.7**	68	18:82
10	(*S,S*)-**1.8**	79	9:91
11	(*R,R*)-**1.8**	88	8:92

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.
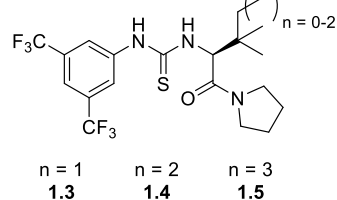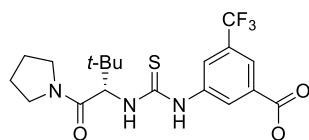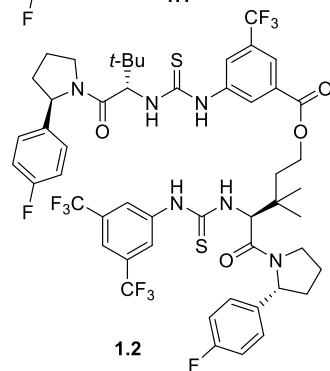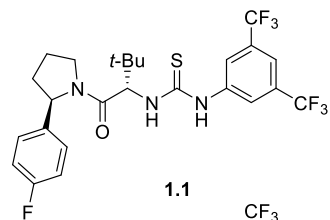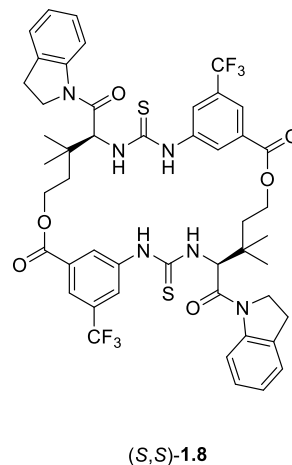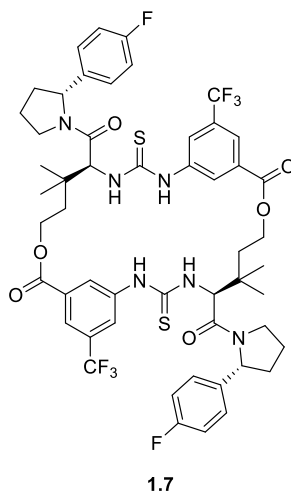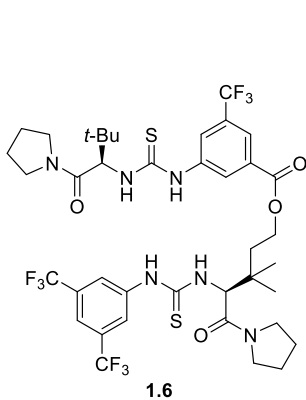
1.3 Substrate Scope

Next, catalytic glycosylation was applied to the construction of significantly more challenging 1,2-cis-β-D-mannosides. Using **(*R,R*)-1.8**, both β(1,6)- and β(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.
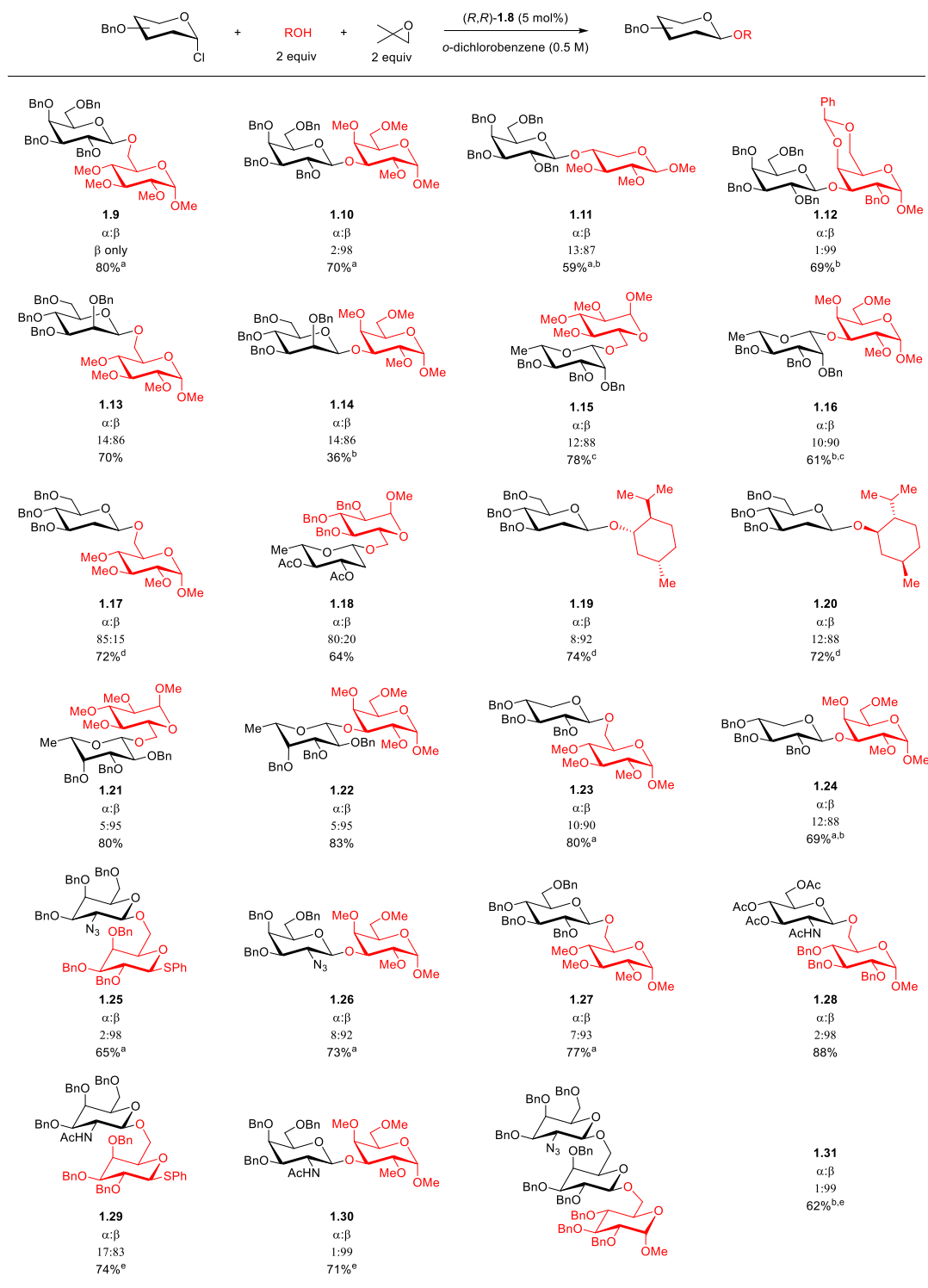
Figure 1.1. Substrate scope.

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).[13] 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.[14]
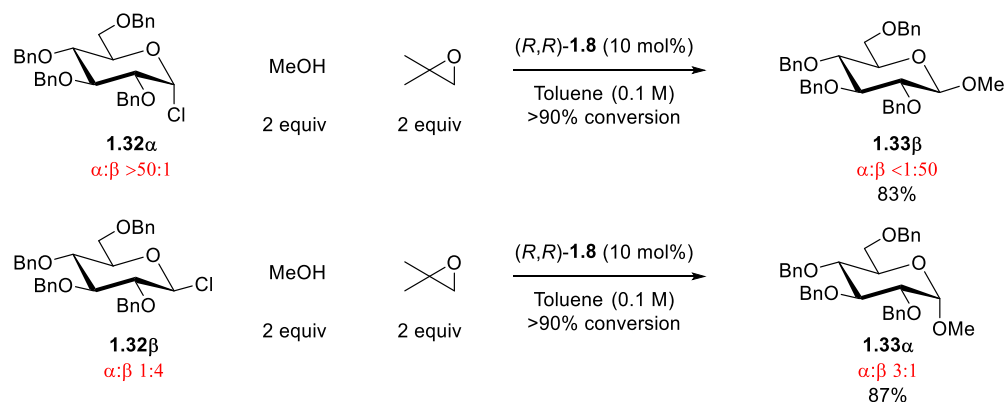
Scheme 1.2. Stereospecificity experiments.

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 S_N1 and S_N2 mechanistic spectrum.[15] Since glycosyl acceptors

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[13] See Section 1.6.4 for details

[14] Recent examples of invertive glycosylation reactions: (a) Pelletier, G.; Zwicker, A.; Allen, C. L.; Schepartz, A.; Miller, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 3175. (b) Peng, P.; Schmidt, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 12653. (c) Kaneko, M.; Herzon, S. B. Org. Lett. **2014**, *16*, 2776. (d) Beale, T. M.; Moon, P. J.; Taylor, M. S. *Org. Lett.* **2014**, 16, 3604. (e) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926. (f) Kumar, A.; Kumar, V.; Dere, R. T.; Schmidt, R. R. *Org. Lett.* **2011**, *13*, 3612

[15] (a) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907. (b) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144. (c) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D.

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 Brönsted 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.
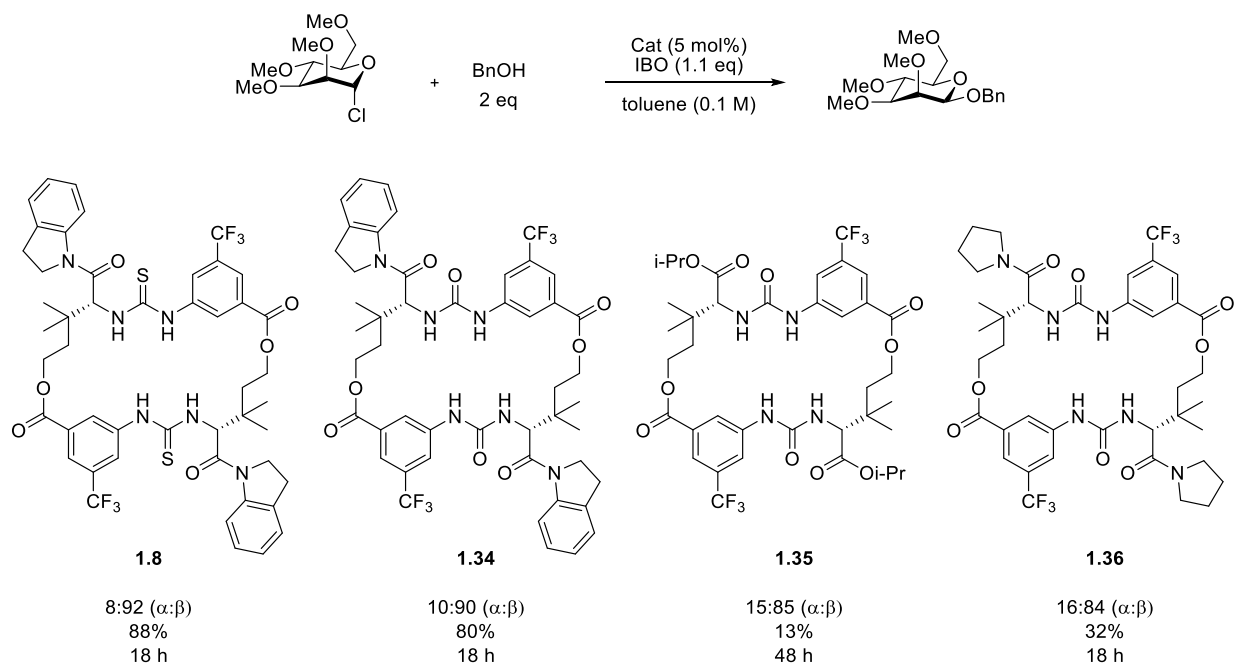

Figure 1.2. Evaluation of the Lewis basic sites on the catalyst.

E.; Crich, D. *Nat. Chem.* **2012**, *4*, 663. (d) Chan, J.; Sannikova, N.; Tang, A.; Bennet, A. J. T. *J. Am. Chem. Soc.* **2014**, *136*, 12225.
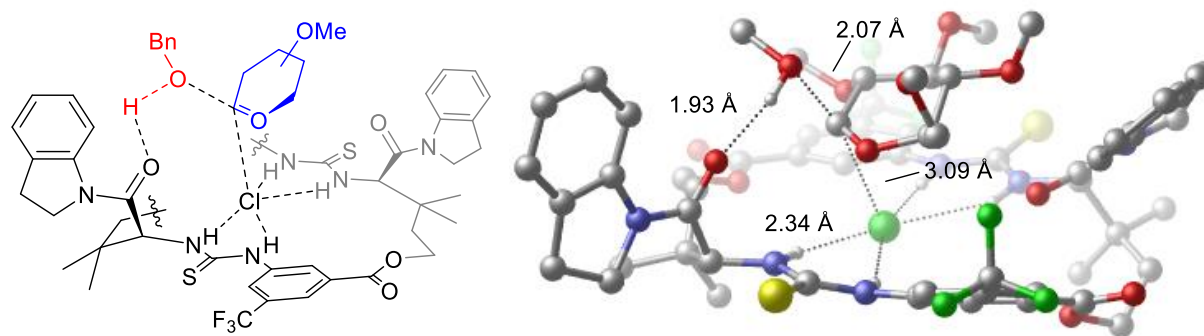
Figure 1.3. M06-2X/6-31g(d)/PCM transition structure for glycosylation (distances in Å).

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).[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.[17] The amide can also participate as a nucleophilic catalyst generating the α-diastereomer through a doubly invertive process.[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. [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

[16] The reaction outcome was not sensitive to *p*-substituents of indoline.

[17] Ford, D. D.; Lehnherr, D.; Kennedy, C. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 7860.

[18] Mulani, S. K.; Hung, W.-C.; Ingle, A. B.; Shiau, K.-S.; Mong, K.-K. T. *Org. Biomol. Chem.* **2014**, *12*, 1184–1197.

[19] (a) Melander, L.; Saunders, W. H., Jr. *Reactions Rates* of *Isotopic Molecules;* Wiley: New York, **1980**. (b) Wolfsberg, M.; Van Hook, W.A.; Paneth, P. Rebelo, L.P.N. *Isotope Effects in the Chemical, Geological, and Bio Sciences*; Springer: Dordrecht, **2010.**

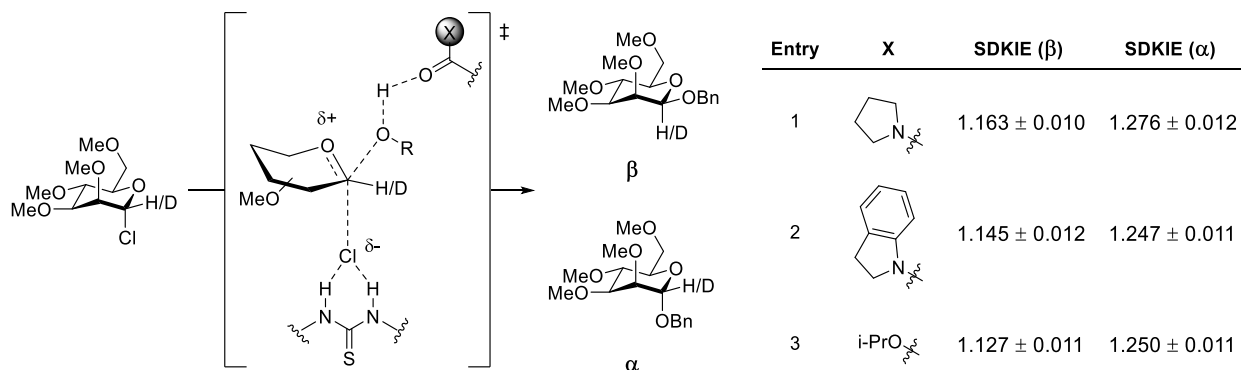freely in the transition state than in the ground state, they would lie lower in energy and give a more positive KIE value. [20]

Figure 1.4. Secondary deuterium KIE experiments.

Entry	X	SDKIE (β)	SDKIE (α)
1		1.163 ± 0.010	1.276 ± 0.012
2		1.145 ± 0.012	1.247 ± 0.011
3	i-PrO	1.127 ± 0.011	1.250 ± 0.011

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.

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[20] For reviews on the KIEs in substitution reactions, see: (a) Matsson, O.; Westaway, K. *Adv. Phys. Org. Chem.* **1998**, *31*, 143 and references therein. (b) Westaway, K. C. *J. Label Compd. Radiopharm.* **2007**, *50*, 989 and references therein.
[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).[22] 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.
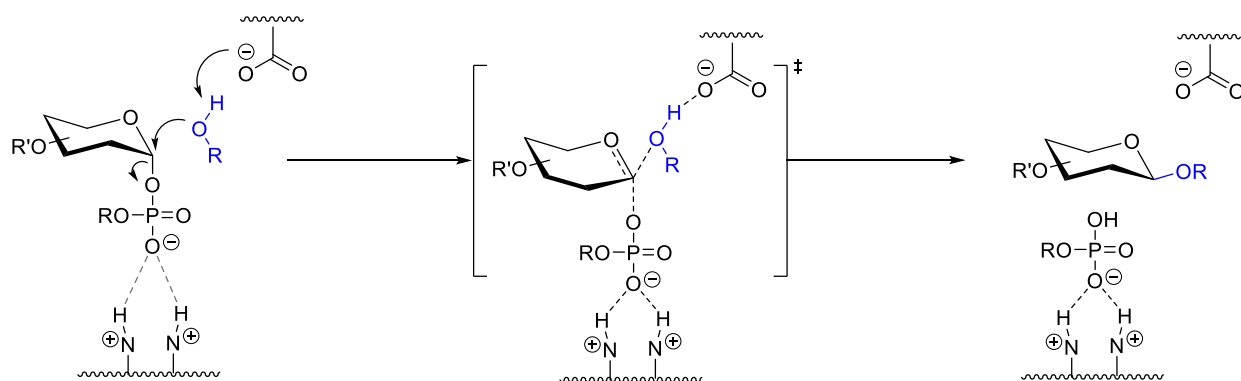

Figure 1.5. Mechanism of catalysis by inverting GT-B fold glycosyl transferases.

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[22] Lairson, L. L.; Henrissat, B.; Davies, G. J.; Withers, S. G. *Annu. Rev. Biochem.* **2008**, *77*, 521.

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 $NaSO_4$.

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 (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C 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 ^{1}H and ^{13}C{^{1}H} NMR spectra were calibrated based on residual solvent signals (CDCl$_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm; CD$_2$Cl$_2$: $\delta_H = 5.30$ ppm, $\delta_C = 53.84$ ppm; DMSO-d$_6$: $\delta_H = 2.50$ ppm, $\delta_C = 39.52$ ppm; acetone-d$_6$: $\delta_H = 2.05$ ppm, $\delta_C = 29.84$ 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.[23] The hemiacetals were prepared from the corresponding hexoses using a modified procedure by Kishi et al. (Dowex®50WX8 instead of Sc(OTf)$_3$)[24] to install the allyl protecting group at the anomeric position. Global protection of the remaining hydroxyl groups followed by deprotection[25] at the anomeric center yielded the hemiacetal intermediates.

3,4,6-tri-*O*-benzyl-2-azido-2-deoxy-galactosyl chloride[26] and 3,4,6-tri-*O*-benzyl-2-acetamido-2-deoxy-galactosyl chloride[27] were prepared in five/six steps from galactal following standard literature procedures.[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[29] and methyl 2,3,4,6-terta-*O*-benzyl-α-D-glucopyranoside were prepared as described by McGarrigle et al.[30]

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[23] Matwiejuk, M; Thiem, J.; *Eur. J. Org. Chem.* **2011**, 5860.
[24] Hsu, M. C.; Lee, J.; Kishi, Y; *J. Org. Chem.* **2007**, *72*, 1931.
[25] Zeng, J.;, Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42.
[26] Plattner, C.; Höfener, M.; Sewald, N.; *Org. Lett.* **2011**, *13*, 545.
[27] Burkhart, F.; Kessler, H.; *Tetrahedron Lett.* **1998**, *39*, 255.
[28] Lemieux, R. U.; Ratcliffe, R. M.; *Can. J. Chem.* **1979**, *57*, 1244; Garegg, P. J.; Haraldsson, M.; *Tetrahedron* **1990**, *46*, 13; Briner, K.; Vasella, A.; *Helv. Chim. Acta.* **1987**, *70*, 1341.
[29] Boultadakis-Arapinis, M.; Prost, E.; Gandon, V.; Lemoine, P.; Turcaud, S.; Micouin, L.; Lecourt, T.; *Chem. Eur. J.* **2013**, *19*, 6052.
[30] Balmond, E. I.; Coe, D. M.; Galan, M. C.; Mc Garrigle, E. M.; *Angew. Chem. Int. Ed.* **2012**, *51*, 9152.

Procedures reported by Pei et al.[31] and Thiem et al.[32] were used for the synthesis of methyl 2,4,6-tri-*O*-methyl-α-D-galactopyranoside.

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside was prepared as described by Gilmour et al.[33]

Methyl 2,3-di-*O*-methyl-β-D-xylopyranoside was prepared through selective benzoylation of methyl β-D-xylopyranoside[34] followed by standard protection and deprotection procedures.

Phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside was prepared as previously described.[35]

3,4-Di-O-acetyl-2-deoxy-α-L-rhamnopyranosyl chloride was prepared as described.[36]

1.6.2   Catalyst Synthesis

tert-Butyl (_R_)-(1-(indolin-1-yl)-3,3-dimethyl-1-oxopent-4-en-2-yl)carbamate (1.8a):
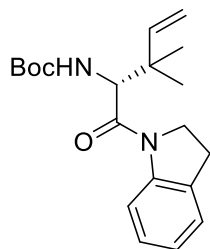
To a cooled (0 °C) solution of (_R_)-2-(2,2-dimethyl-propionylamino)-3,3-dimethyl-pent-4-enoic acid[37] (1.715 g, 7.048 mmol) in CH_2Cl_2 (35 mL, 0.2 M) was added indoline (0.87 mL, 7.753

[31] Xu, H.; Lu, Y.; Zhou, Y.; Ren, B.; Pei, Y.; Dong, H.; Pei, Z.; *Adv. Synth. Catal.* **2014**, 356, 1735.

[32] Matwiejuk, M.; Thiem, J.; Eur. *J. Org. Chem.* **2012**, 2180.

[33] Durantie, E.; Bucher, C.; Gilmour, R.; *Chem. Eur. J.* **2012**, *18*, 8208.

[34] Demizu, Y.; Kubo, Y.; Miyoshi, H.; Maki, T.; Matsumura, Y.; Moriyama, N.; Onomura, O.; *Org. Lett.* **2008**, *10*, 5075.

[35] Ren, C.-T.; Tsai, Y.-H.; Yang, Y.-L.; Zou, W.; Wu, S.-H.; *J. Org. Chem.* **2007**, *72*, 5427.

[36] Beale, T. M.; Moon, P. J.; Taylor, M. S. *Org. Lett.* **2014**, *16*, 3604.

[37] Rossi, F.; Corcella, F.; Caldarelli, F. S.; Heidempergher, F.; Marchionni, C.; Auguadro, M.; Cattaneo, M.; Ceriani, L.; Visentin, G.; Ventrella, G.; Pinciroli, V.; Ramella, G.; Candiani, I.; Bedeschi, A.; Tomasi, A.; Kline, B. J.; Martinez, C. A.; Yazbeck, D.; Kucera, D. J.; *Organic Process Research & Development* **2008,** *12,* 322.

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_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_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%).

$[\alpha]^{22}_D = +6.6$ (*c* 1.0, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 1H), 7.19–21 (m, 2H), 7.04 (dd, *J* = 7.2, 7.8 Hz, 1H), 6.03 (dd, *J* = 10.8, 18.0 Hz, 1H), 5.28 (d, *J* = 9.6 Hz, 1H), 5.09–5.12 (m, 2H), 4.44 (d, *J* = 10.2 Hz, 1H), 4.38 (dt, *J* = 6.6, 10.2 Hz, 1H), 4.19 (dt, *J* = 6.6, 10.2 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, $CDCl_3$) δ 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 $C_{20}H_{28}N_2NaO_3$ (M+Na) 367.1998]

tert-Butyl (*R*)-(5-hydroxy-1-(indolin-1-yl)-3,3-dimethyl-1-oxopentan-2-yl)carbamate (1.8b):
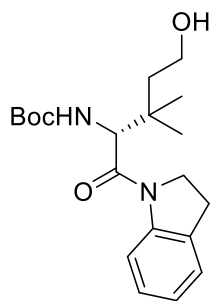
To a cooled (0 °C) solution of olefin **1.8a** (2.015 g, 5.850 mmol, 1.0 equiv.) in THF (60 mL, 0.1 M) was added 9-BBN (2.141 g, 17.55 mmol, 3 equiv.). The resulting mixture was allowed to warm to rt and was stirred for 3 hours. The reaction was cooled to 0 °C, and 2 M aqueous NaOH (30 mL) was added dropwise followed by 30% H_2O_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_4Cl solution, sat. aqueous $Na_2S_2O_3$ solution and brine, dried over anhydrous Na_2SO_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%).

$[\alpha]^{23}_D = +4.8$ (*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 $C_{20}H_{30}N_2NaO_4$ (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):
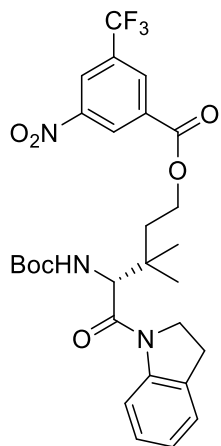
To a stirred solution of alcohol **1.8b** (1.802 g, 4.974 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL, 0.2 M) was added 3-nitro-5-(trifluoromethyl)benzoic acid (1.286 g, 5.471 mmol, 1.1 equiv.), EDC·HCl (1.049 g, 5.471 mmol, 1.1 equiv.), Et_3N (0.76 mL, 5.471 mmol, 1.1 equiv.) and DMAP (66.8 mg, 0.547 mmol, 0.1 eq) at room temperature. The resulting mixture was stirred for 1 h, and quenched with sat. aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 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%).

$[\alpha]^{23}_D = +3.0$ (*c* 1.0, $CHCl_3$);

^1H NMR (600 MHz, $CDCl_3$) 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);

^{13}C NMR (126 MHz, $CDCl_3$) 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 C$_{28}$H$_{32}$F$_3$N$_3$NaO$_7$ (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):
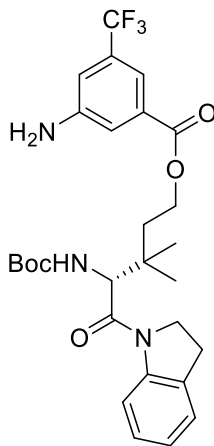
To a stirred solution of alcohol **1.8c** (2.536 g, 4.377 mmol, 1.0 equiv.) in EtOH (22 mL, 0.2 M) was added Pd/C (254 mg, 10 wt%) at room temperature. The resulting mixture was stirred under atmospheric pressure of H$_2$ overnight, concentrated and filtered through a pad of celite with ethyl acetate. 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, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) 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}C NMR (126 MHz, CDCl$_3$) δ 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-((*Tert*-butoxycarbonyl)amino)-5-(indolin-1-yl)-3,3-dimethyl-5-oxopentyl 3-isothiocyanato-5-(trifluoromethyl)benzoate (1.8e):
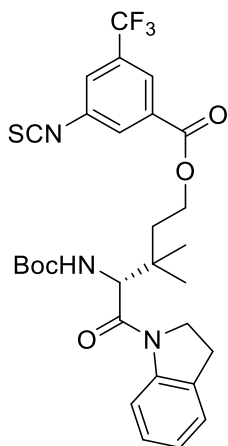
To a stirred solution of aniline **1.8d** (2.564 g, 4.666 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (23 mL, 0.2 M) was added TCDI (1.663 g, 9.332 mmol, 2 equiv.) and imidazole (158.8 mg, 2.333 mmol, 0.5 equiv.) at room temperature. The resulting mixture was stirred for 4 h, and quenched with aqueous NH$_4$Cl 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%).

$[α]^{23}_D$ = +1.0 (*c* 1.0, CHCl$_3$);

¹H NMR (600 MHz, CDCl₃) δ 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);

¹³C NMR (126 MHz, CDCl₃) δ 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, 1168, 1132, 755, 689;

HRMS (ESI) found 614.1908 [calcd for C₂₉H₃₂F₃N₃NaO₅S (M+Na) 614.1912].

(5R,15R)-5,15-Di(indoline-1-carbonyl)-6,6,16,16-tetramethyl-3,13-dithioxo-15,115-bis(trifluoromethyl)-9,19-dioxa-2,4,12,14-tetraaza-1,11(1,3)-dibenzenacycloicosaphane-10,20-dione (1.8):
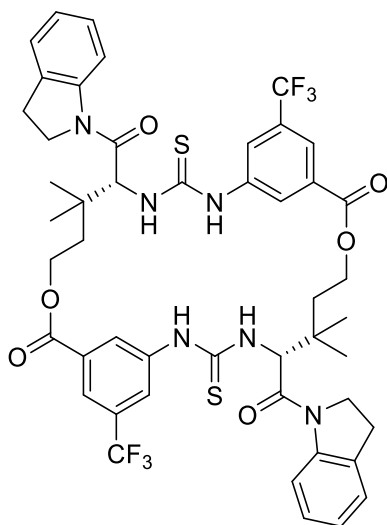
To a stirred solution of carbamate **1.8e** (2.512 g, 4.246 mmol, 1.0 equiv) in CH₂Cl₂ (6.5 mL) was added TFA (1.6 mL, 21.23 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 4 h, concentrated *in vacuo* and re-dissolved in CH₂Cl₂ (42 mL, 0.1 M). The solution

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%).

$[\alpha]^{23}_D = +168$ (*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):
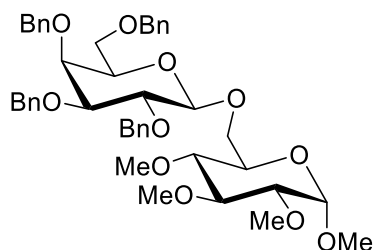
The general procedure was conducted on a 0.25 mmol scale. After stirring for 7 h at 40 ˚C, **1.9** was obtained as a single isomer (crude ¹H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded **β-1.9** as a white solid (152 mg, 0.20 mmol, 80%).

$[\alpha]^{23}_{D}$ = +48 (*c* 1.0, CHCl$_3$);

¹H NMR (600 MHz, CDCl$_3$) 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);

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.8, 138.7, 138.5, 138.0, 128.5, 128.4, 128.3, 128.2, 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^{-1}) 3063, 3030, 2928, 1497, 1454, 1363, 1157, 1100, 1068, 1028, 996, 905, 733, 698;

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-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-D-galactopyranoside (1.10):
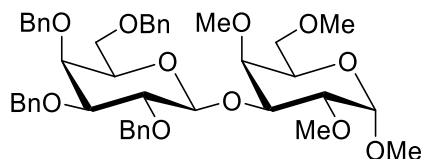
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at 40 ˚C, **1.10** was obtained as the major isomer (α:β = 2:98, crude ^{1}H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded **1.10** (α:β = 2:98) as a white solid (133 mg, 0.17 mmol, 70%).

$[\alpha]^{23}{}_D$ = +47.7 (*c* 1.2, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) 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$_3$) δ 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, 3030, 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$_{58}$NO$_{11}$ (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%).

[α]^{22}$_D$ = –20 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 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$_{54}$NO$_{10}$ (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):
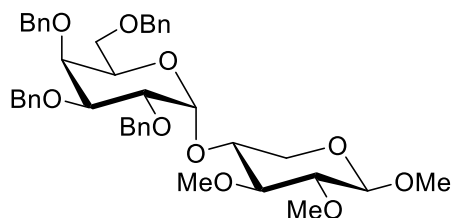
White solid;

[α]^{23}$_D$ = +23.4 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 138.8, 138.7, 138.6, 138.0, 128.5, 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 C$_{42}$H$_{54}$NO$_{10}$ (M+NH$_4$)$^{+}$ 732.3742].

Methyl (2,3,4,6-Tetra-*O*-benzyl-β-ᴅ-galactopyranosyl)-(1→3)-2-*O*-benzyl-4,6-benzylidene-α-ᴅ-galactopyranoside (1.12):
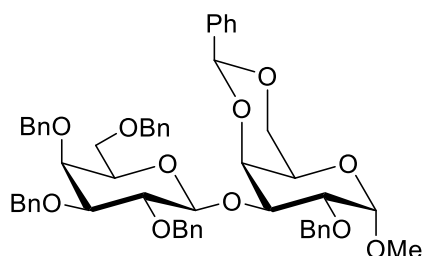
The general procedure was conducted on a 0.25 mmol scale using 10 mol% catalyst. After stirring for 48 h at rt, **1.12** was obtained as the major isomer (α:β = 1:99, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.12** (α:β = 1:99) as a white solid (153 mg, 69%).

[α]^{22}$_{D}$ = +15 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) 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);

^{13}C NMR (126 MHz, CDCl$_3$) 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, 1027, 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):
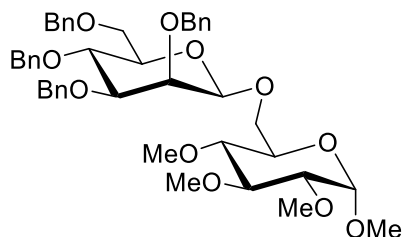
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at rt **1.13** was obtained as the major isomer (α:β = 14:86, crude ^{1}H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded **1.13** (α:β = 14:86) as a white solid (133 mg, 0.17 mmol, 70%). The anomers were separated for further characterization.

White solid;

[α]^{24}$_D$ = +8.2 (*c* 1.0, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43–7.47 (m, 2H), 7.33–7.36 (m, 2H), 7.24–7.32 (m, 14H), 7.18–7.21 (m, 2H), 5.00 (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$_3$) δ 138.8, 138.5, 138.4, 138.2, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 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$_{58}$NO$_{11}$ (M+NH$_4$)$^+$ 776.4010].

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):
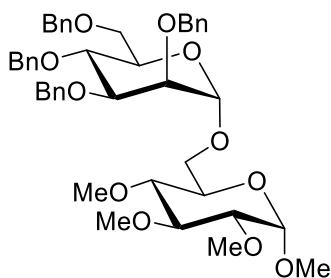
Colorless oil;

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

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 138.7, 138.5, 138.5, 138.5, 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):
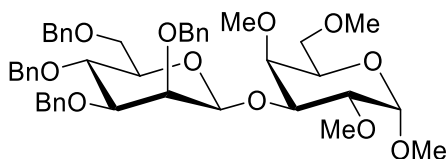
The general procedure was conducted on a 0.2 mmol scale using 10 mol% catalyst. After stirring for 72 h at rt **1.14** was obtained as the major isomer (α:β = 14:86, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **1.14** (α:β = 10:90) as a colorless oil (54.4 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;

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

^{1}H NMR (600 MHz, CDCl$_3$) δ 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, 128.4, 128.2, 128.2, 127.8, 127.7, 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$_{58}$NO$_{11}$ (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):
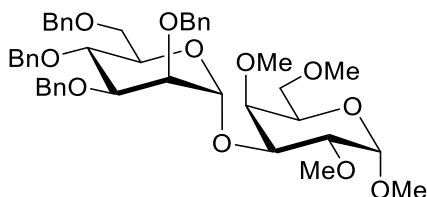
Colorless oil;

[α]$^{23}_{D}$ = +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, $J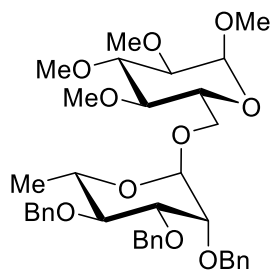$ = 12.9 Hz, 1H), 4.81 (d, J = 3.5 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.70 (d, J = 12.9 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.10–4.14 (m, 1H), 4.04 (dd, J = 2.9, 10.6 Hz, 1H), 3.97–4.02 (m, 1H), 3.91 (dd, J = 2.9, 9.4 Hz, 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$_3$) δ 139.0, 138.6, 138.4, 128.4, 128.4, 128.3, 128.2, 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-*O*-benzyl-6-deoxy-β-L-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (1.15):
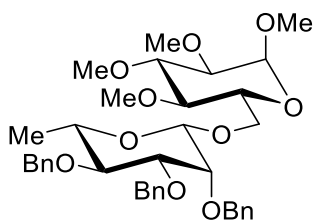
The general procedure was conducted on a 0.27 mmol scale using (*S*,*S*)-**1.8** catalyst. After stirring for 48 h at 0 ˚C **β-1.15** was obtained as the major isomer (α:β = 12:88, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **1.15** (α:β = 14:86) as a colorless oil (135 mg, 0.21 mmol, 78%). The anomers were separated for further characterization.

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

Colorless oil;

[α]^{22}$_D$ = +87 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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* =

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$_3$) δ 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, 72.1, 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$_{52}$NO$_{10}$ (M+NH$_4$)$^+$ 670.3586].

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

Colorless oil;

[α]$^{23}_D$ = +14.8 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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-ʟ-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-ᴅ-galactopyranoside (1.16):
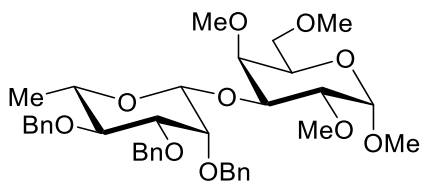
The general procedure was conducted on a 0.22 mmol scale using 10 mol% (*S,S*)-**1.8** catalyst. After stirring for 80 h at 0 ˚C **β-1.16** was obtained as the major isomer (α:β = 10:90, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.16** as a white solid (89 mg, 0.13mmol, 61%).

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

White solid

[α]^{22}$_D$ = +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, 3H), 4.08 (dd, *J* = 2.9, 10.0 Hz, 1H), 3.80–3.89 (m, 2H), 3.69 (dd, *J* = 3.7, 10.0 Hz, 1H), 3.60–3.66 (m, 1H), 3.53–3.59 (m, 2H), 3.55 (s, 3H), 3.49–3.52 (m, 1H), 3.43–3.48 (m, 1H), 3.45 (s, 3H), 3.40 (s, 6H), 3.28–3.33 (m, 1H), 1.38 (d, *J* = 6.5 Hz, 3H);

^{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-α-ʟ-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-ᴅ-galactopyranoside (α-1.16):
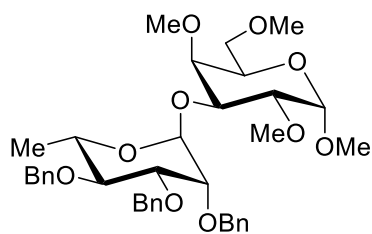
Colorless oil;

[α]^{22}$_D$ = +118.4 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.17–7.45 (m, 15H) 5.16 (d, *J* = 1.8 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.87 (d, *J* = 3.5 Hz, 1H), 4.78 (d, *J* = 12.9 Hz, 1H), 4.68 (d, *J* = 12.9 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.62 (s, 2 H), 4.00 (dd, *J* = 2.9, 10.6 Hz, 1H), 3.87 (t, *J* = 6.7 Hz, 1H), 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$_{52}$NO$_{10}$ (M+NH$_4$)$^+$ 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):
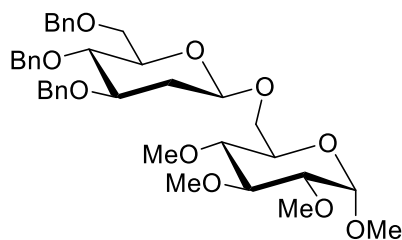
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at −40 ˚C in toluene (0.1 M) **β-1.17** was obtained as the major isomer (α:β = 15:85, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.17** as a white solid (117 mg, 72%).

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):

[α]^{22}$_D$ = +54 (*c* 1.0, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 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$_3$) δ 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-α-D-glucosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (α-1.17):
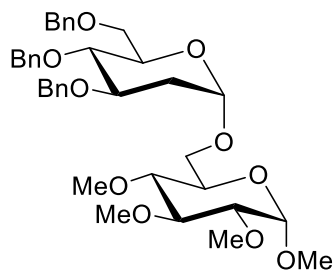
$[α]^{22}_D$ = +44 (*c* 1.0, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 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);

¹³C NMR (126 MHz, CDCl₃) δ 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-β-L-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (1.18):
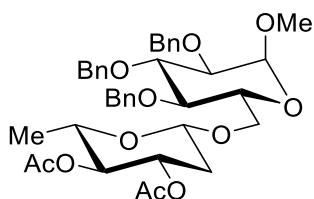
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at rt, **β-1.18** was obtained as the major isomer (α:β = 20:80, crude HPLC). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.18** as a colorless liquid (108 mg, 64%).

$[\alpha]^{22}_{D}$ = +21 (*c* 1.0, CHCl₃);

¹H NMR (600 MHz, CDCl₃) δ 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, 1029, 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):
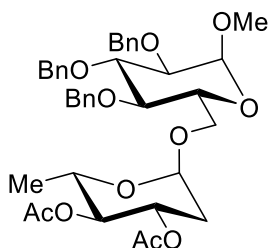
[α]^{22}$_D$ = –25 (*c* 1.0, CHCl$_3$);

^{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 (ddd, *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 $C_{38}H_{46}NaO_{11}$ (M+Na)$^+$ 701.2938]

(+)-Menthoyl (3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (1.19):
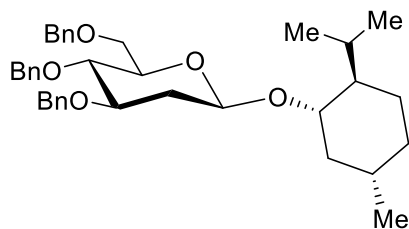
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at −40 ˚C in toluene (0.1 M) **β-1.19** was obtained as the major isomer (α:β = 8:92, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.19** as a white solid (104 mg, 74%).

(+)-Menthoyl (3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (β-1.19):


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

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.24–7.35 (m, 15H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.59–4.63 (m, 3H), 4.53–4.56 (m, 2H), 3.72 (d, *J* = 3.6 Hz, 2H), 3.67 (ddd, *J* = 4.8, 6.4, 11.4 Hz, 1H), 3.50–3.56 (m, 2H), 3.38 (dt, *J* = 3.0, 6.6 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 Hz, 1H), 0.81–0.92 (m, 11H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.7, 128.53, 128.49, 128.45, 128.3, 127.8, 127.7, 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^{-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]

(+)-Menthoyl (3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (α-1.19):
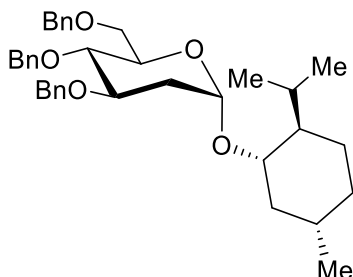
$[\alpha]^{22}_D = +41$ (*c* 1.0, CHCl$_3$);

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

^{13}C NMR (126 MHz, CDCl$_3$) δ 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]

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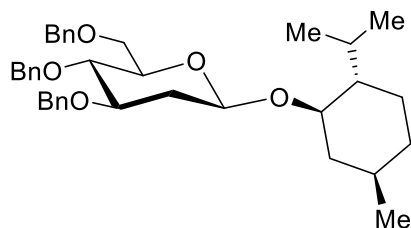
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at −40 ˚C in toluene (0.1 M) **β-1.20** was obtained as the major isomer (α:β = 12:88, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.20** as a white solid (103 mg, 72%).

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

$[\alpha]^{23}_D$ = +9 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) 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);

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.7, 138.6, 128.6, 128.49, 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 C$_{37}$H$_{48}$NaO$_5$ (M+Na)$^+$ 595.3399]

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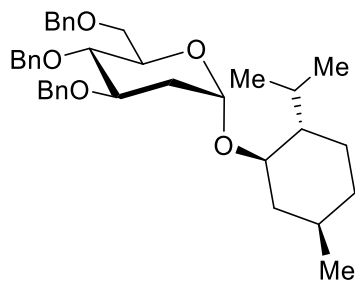
$[\alpha]^{22}{}_D = +77$ (c 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 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):
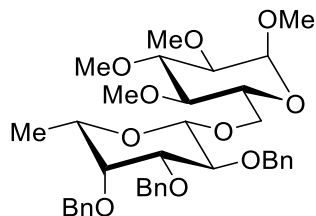
43

The general procedure was conducted on a 0.20 mmol scale. After stirring for 18 h at rt **β-1.21** was obtained as the major isomer (α:β = 5:95, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **1.21** (α:β = 4:96) as a colorless oil (105 mg, 0.16 mmol, 80%).

$[\alpha]^{22}_D = +63.4$ (c 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 139.0, 138.7, 138.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 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-β-L-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-D-galactopyranoside (1.22)
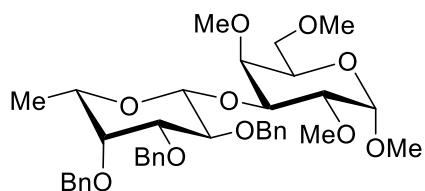
The general procedure was conducted on a 0.25 mmol scale. After stirring for 18 h at rt **β-1.22** was obtained as the major isomer (α:β = 5:95, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.22** as a white solid (135 mg, 0.21 mmol, 83%).

$[\alpha]^{23}_D = +49.8$ (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 141.7, 141.4, 141.1, 131.0, 130.9, 130.8, 130.7, 130.2, 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-*O*-benzyl-β-D-xylopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (1.23):
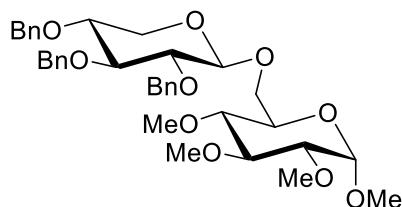
The general procedure was conducted on a 0.20 mmol scale. After stirring for 48 h at 40 ˚C **β-1.23** was obtained as the major isomer (α:β = 10:90, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **1.23** (α:β = 13:87) as a white solid (102 mg, 0.16 mmol, 80%).

$[α]^{23}_D$ = +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-β-D-xylopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-D-galactopyranoside (1.24):
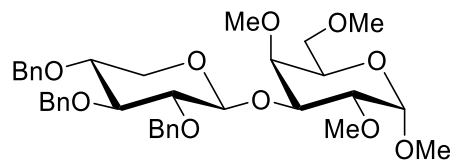
The general procedure was conducted on a 0.20 mmol scale using 10 mol% catalyst. After stirring for 48 h at 40 ˚C **β-1.24** was obtained as the major isomer (α:β = 12:88, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.24** as a white solid (89 mg, 0.14 mmol, 69%).

$[\alpha]^{22}_D$ = +59.4 (*c* 1.0, CHCl$_3$);

^{1}H 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, 1 H), 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, 3 H), 3.34 (s, 3H), 3.33 (s, 3H), 3.27–3.33 (m, 1H), 3.12–3.19 (m, 1H);

^{13}C 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, 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):
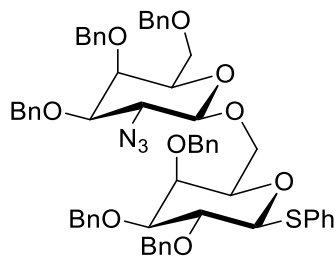
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at 40 ˚C **β-1.25** was obtained as the major isomer (α:β = 2:98, crude ¹H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.25** as a white solid (162 mg, 65%).

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):

$[\alpha]^{22}_D = -5.2$ (*c* 1.0, CHCl₃);

¹H NMR (600 MHz, CDCl₃) δ 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);

¹³C NMR (126 MHz, CDCl₃) δ 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 $C_{60}H_{61}N_3NaO_9S$ (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):
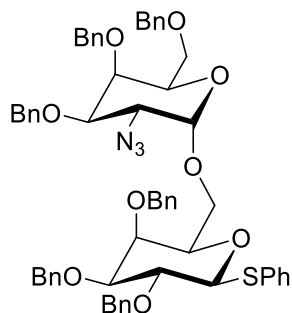
$[\alpha]^{22}_{D}$ = +7.4 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) 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);

^{13}C NMR (126 MHz, CDCl$_3$) 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 C$_{60}$H$_{61}$N$_3$NaO$_9$S (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):
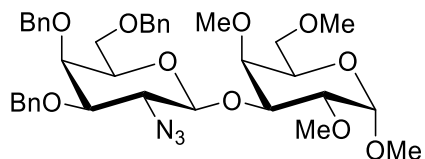
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at 40 ˚C **β-1.26** was obtained as the major isomer (α:β = 8:92, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.26** as a white solid (126 mg, 73%).

$[\alpha]^{22}_D = +60$ (c 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) 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);

^{13}C NMR (126 MHz, CDCl$_3$) 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 C$_{37}$H$_{47}$N$_3$NaO$_{10}$ (M+Na)$^+$ 716.3159]

Methyl (3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl- β -D-galactopyranoside (α-1.26):
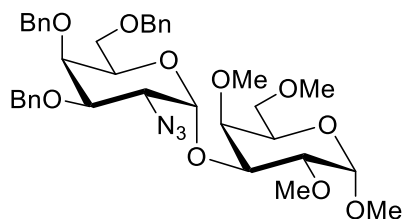
$[\alpha]^{22}_D = +120$ (c 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 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):
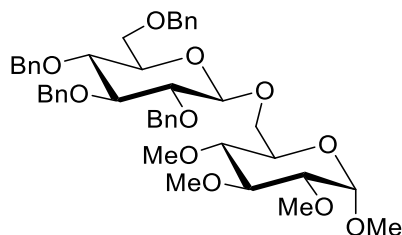
The general procedure was conducted on a 0.25 mmol scale. After stirring for 48 h at 40 ˚C **β-1.27** was obtained as the major isomer (α:β = 7:93, crude ^{1}H NMR). Purification by column chromatography (hexanes/diethyl ether) yielded **1.27** (α:β = 5:95) as a white solid (146 mg, 0.19 mmol, 77%).

[α]$^{23}_D$ = +57 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) 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);

^{13}C NMR (126 MHz, CDCl$_3$) 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, 1155, 1098, 1067, 1028, 999, 736, 698;

HRMS (ESI) found 776.4026 [calcd for C$_{44}$H$_{58}$NO$_{11}$ (M+NH$_4$) 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):
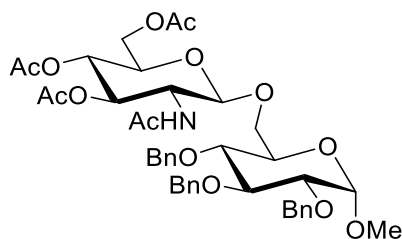
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at 50 ˚C **β-1.28** was obtained as the major isomer (α:β = 2:98, crude HPLC). Purification by column chromatography (ethyl acetate/methanol) yielded **β-1.28** (α:β = 2:98) as a white solid (173 mg, 88%). The spectral data was in agreement with those reported in literature.[38]

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[38] Bongat, A. F. G.; Kamat, M. N.; Demchenko, A. V. *J. Org. Chem*. **2007**, *72*, 1480.

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

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):
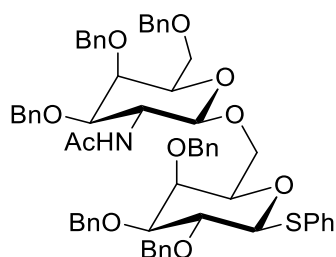
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at rt in dichloromethane (0.5 M) **β-1.29** was obtained as the major isomer (α:β = 17:83, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **β-1.29** as a white solid (187 mg, 74%).

$[\alpha]^{22}_{D} = +15$ (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CD$_3$CN) δ 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$_3$) δ 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, 75.4, 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):
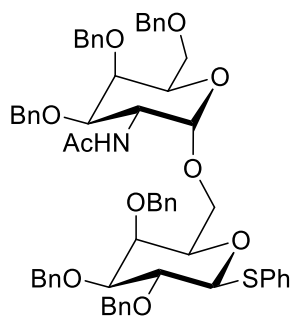
$[\alpha]^{22}_{D} = +55$ (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CDCl$_3$) δ 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$_3$) δ 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, 74.4, 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$_{10}$S (M+Na)$^+$ 1038.4227].

Methyl (3,4,6-Tri-*O*-benzyl-2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl- β -D-galactopyranoside (1.30):
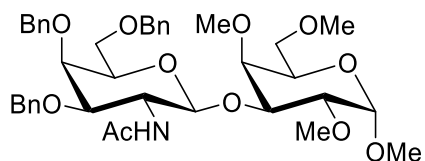
The general procedure was conducted on a 0.25 mmol scale. After stirring for 24 h at rt in dichloromethane (0.5 M) **β-1.30** was obtained as the major isomer (α:β = 1:99, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **1.30** as a white solid (125 mg, 71%).

[α]^{22}$_D$ = +46 (*c* 1.0, CHCl$_3$);

^{1}H NMR (600 MHz, CD$_3$CN) δ 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);

<superscript>13</superscript>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):
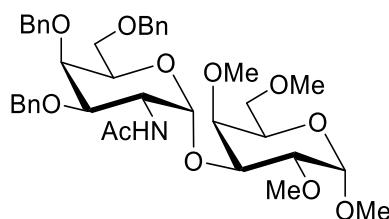
[α]^{22}$_D$ = +157 (*c* 1.0, CHCl$_3$);

^{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].

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 (1.31):
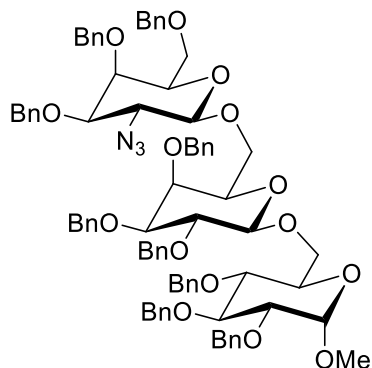
Disaccharide **β-1.25** was converted to the corresponding chloride by Ph$_2$SO and (COCl)$_2$.[39] The crude glycosyl chloride was used in the glycosylation reaction without further purification. The general procedure was conducted on a 0.05 mmol scale using 10 mol% catalyst. After stirring for 48 h at rt in dichloromethane (0.5 M) **β-1.31** was obtained as the major isomer (α:β = 1:99, crude ^{1}H NMR). Purification by column chromatography (hexanes/ethyl acetate) yielded **1.31** (α:β = 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$_3$) δ 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);

[39] Sugiyama, S.; Diakur, J. M. *Org. Lett*. **2000**, *2*, 2713.

^{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
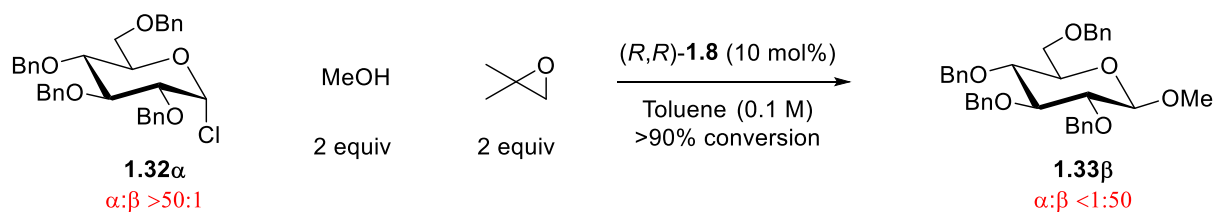
The general procedure was conducted with **1.32α** (0.1 mmol) and (*R,R*)-**1.8** (10 mol%). After stirring for 48 h at rt in toluene (0.1 M) **1.33β** was obtained as the major isomer (83%, β:α: >50:1, HPLC analysis).

58
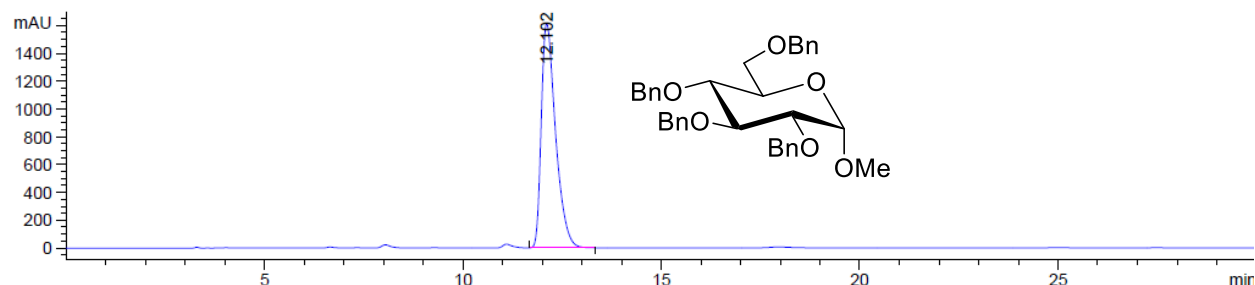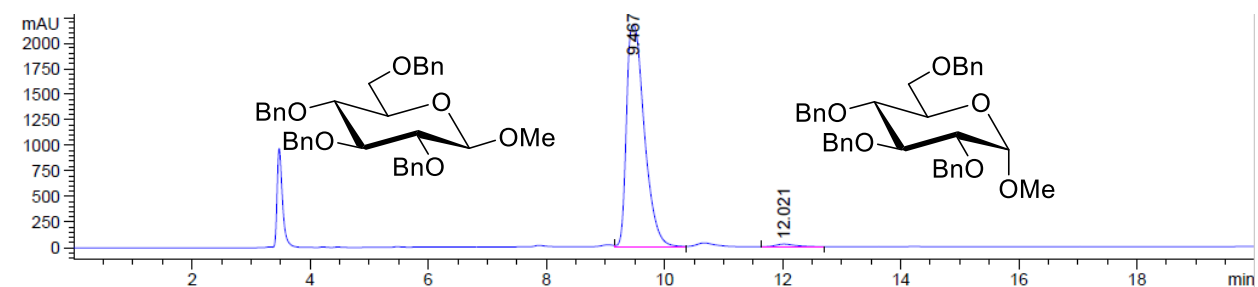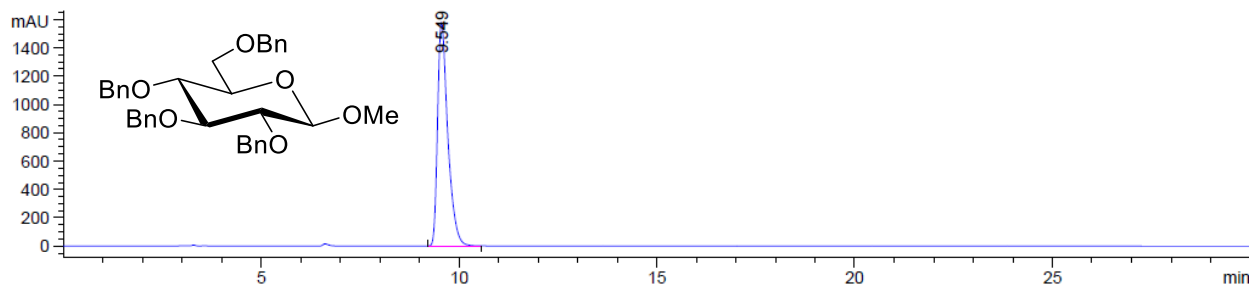
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.467	VV	0.3219	4.53791e4	2170.99536	98.7223
2	12.021	BB	0.3397	587.32153	25.59933	1.2777
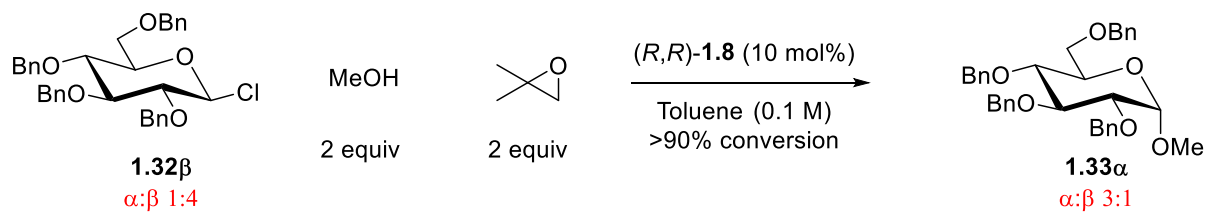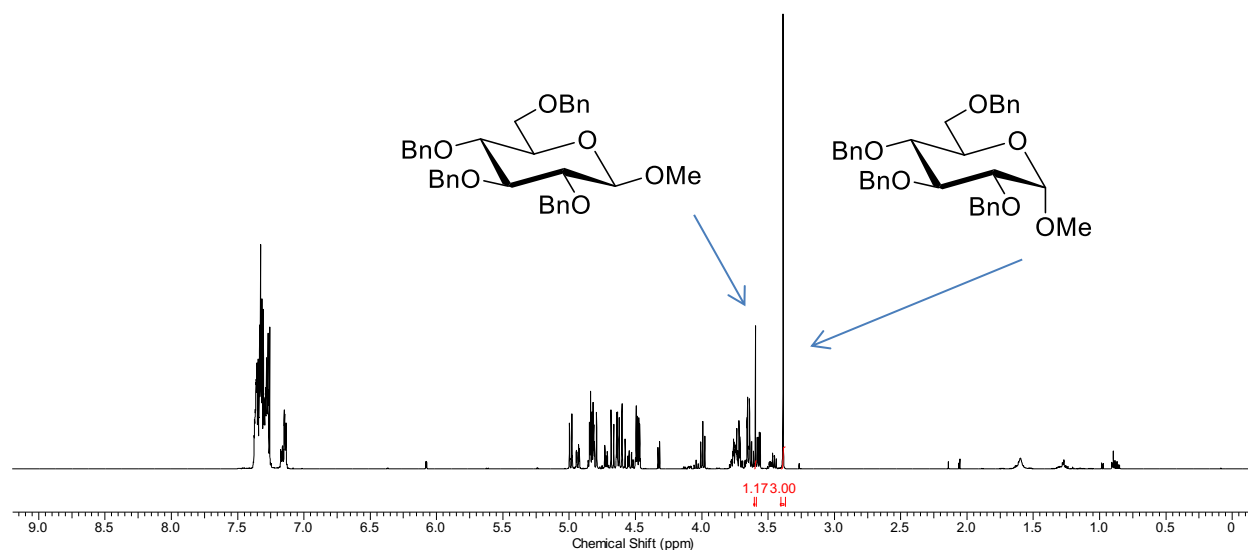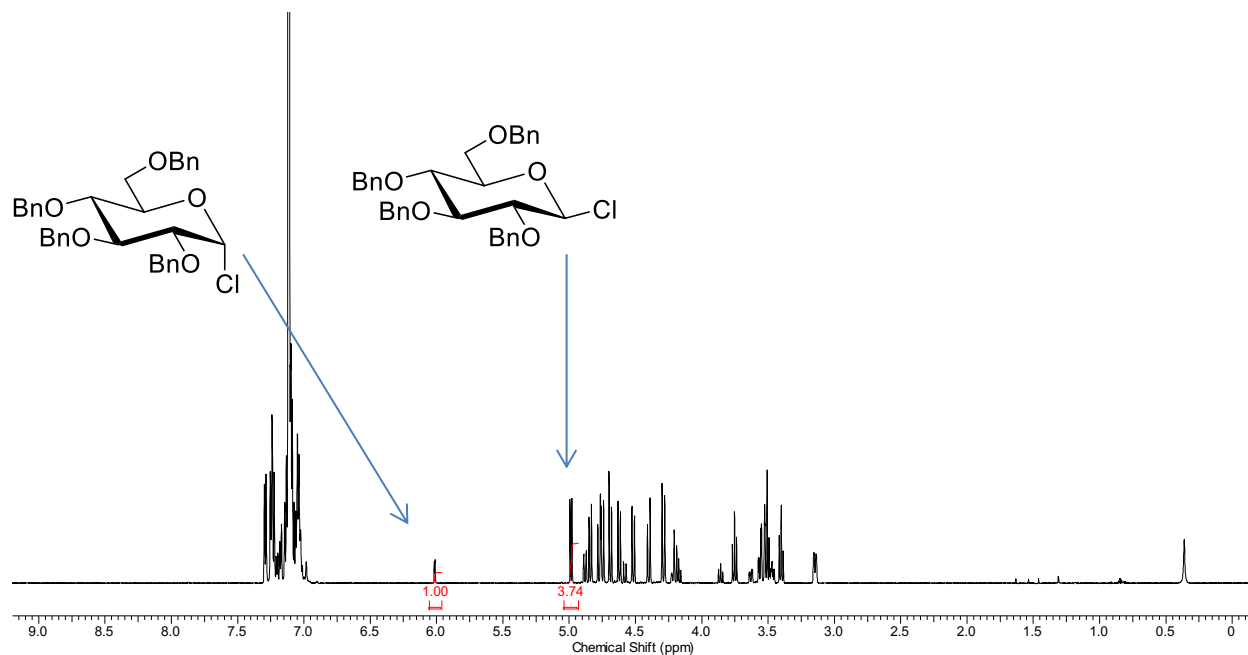
The general procedure was conducted with **1.32β**[40] (0.1 mmol, β:α = 4:1 by NMR) and (*R*,*R*)-**1.8**

(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).

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[40] Ford, M. J.; Ley, S. V. *Synlett*, **1990**, 255.

KIE Experiments

Entry	X	SDKIE (β)	SDKIE (α)
1	(pyrrolidine)	1.163 ± 0.010	1.276 ± 0.012
2	(indoline)	1.145 ± 0.012	1.247 ± 0.011
3	i-PrO	1.127 ± 0.011	1.250 ± 0.011

1.36   **1.34**   **1.35**
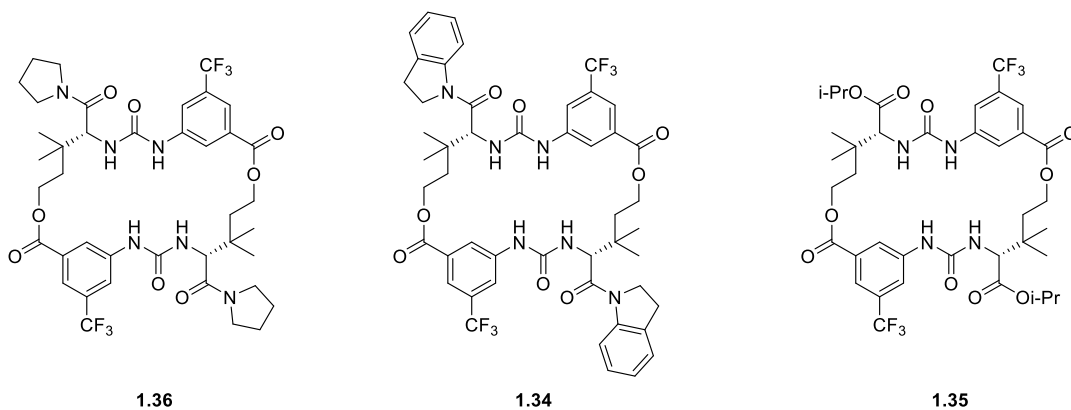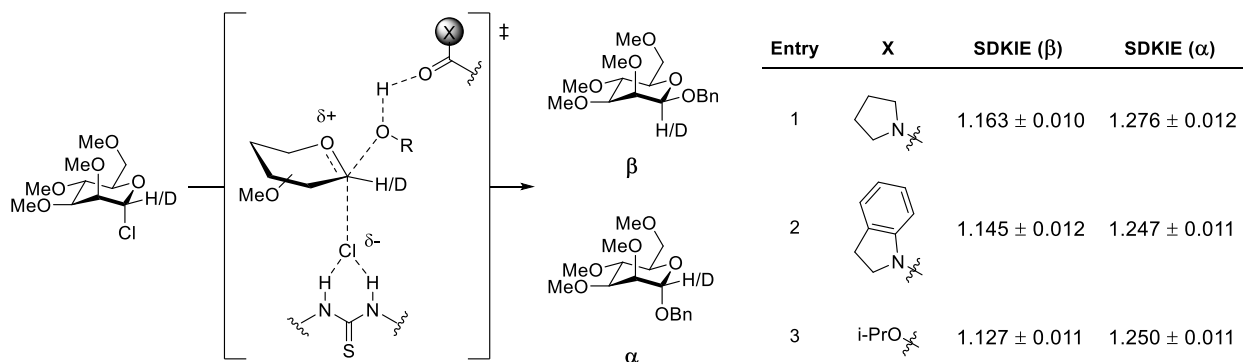
A mixture of partially deuterated mannosyl chloride was prepared and the R_0 was measured by NMR (d1 = 60 s). To a stirred solution of the above mixture (102 mg, 0.400 mmol), **1.34** (19 mg, 5 mol%), and isobutylene oxide (1.1 equiv) in toluene (4 mL, 0.1 M) was added BnOH (2 equiv). After 1 h, the 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] $\Delta F = 0.007$

$$\text{KIE} = \frac{\ln(1-F)}{\ln(1-F*R_P/R_0)}$$

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

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

$$\Delta\text{KIE} = |\Delta\text{KIE}_F| + |\Delta\text{KIE}_{R/R_0}|$$
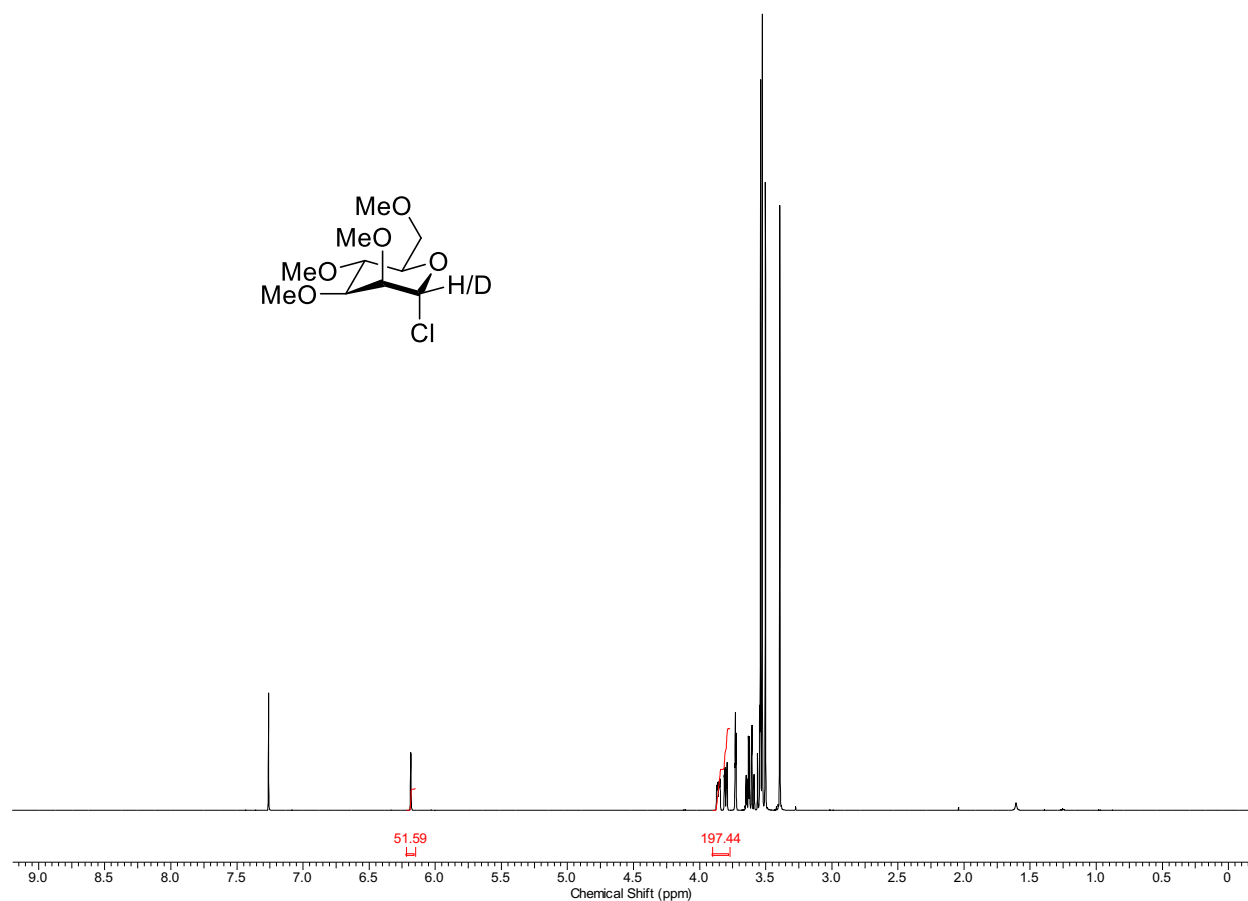
[41] Huang, M.; Garrett, G. E.; Birlirakis, N.; Boh, L.; Pratt, D. A.; Crich, D. *Nat*. *Chem*. **2012**, *4*, 663.
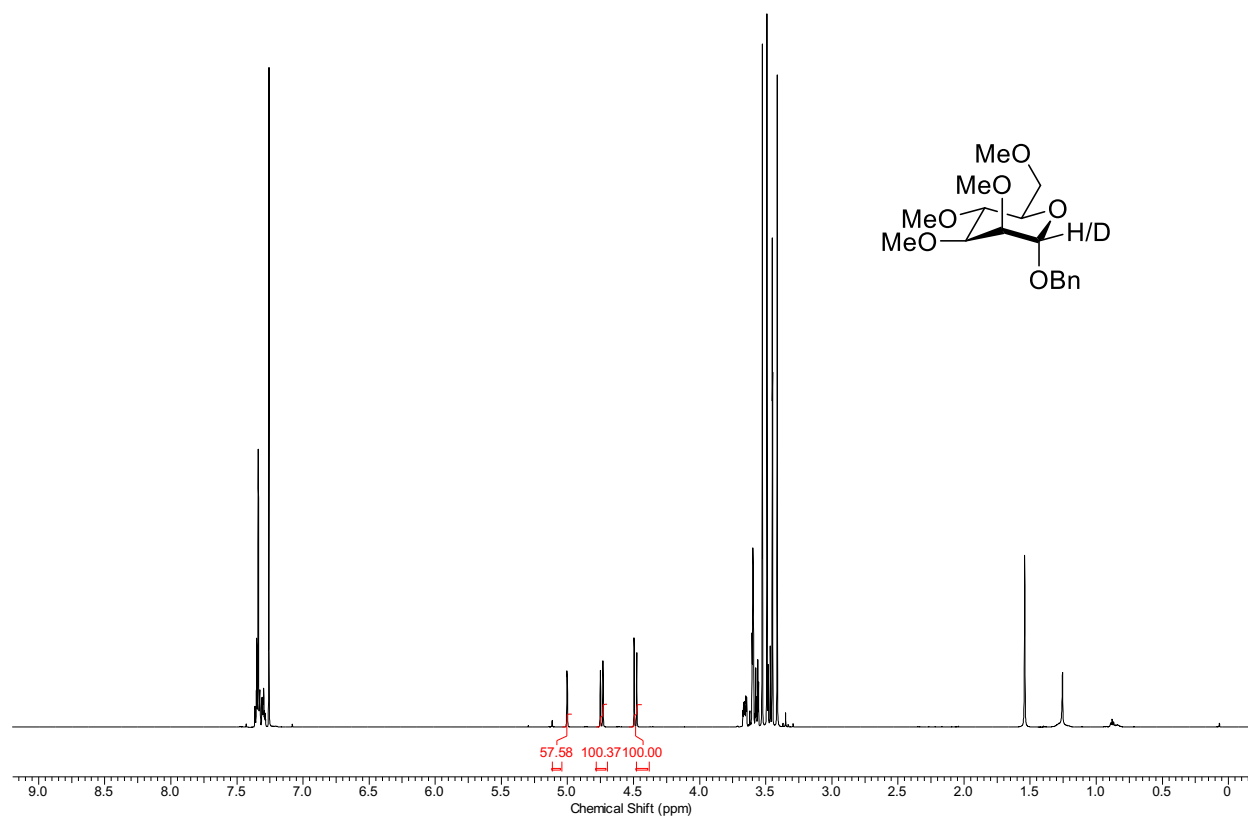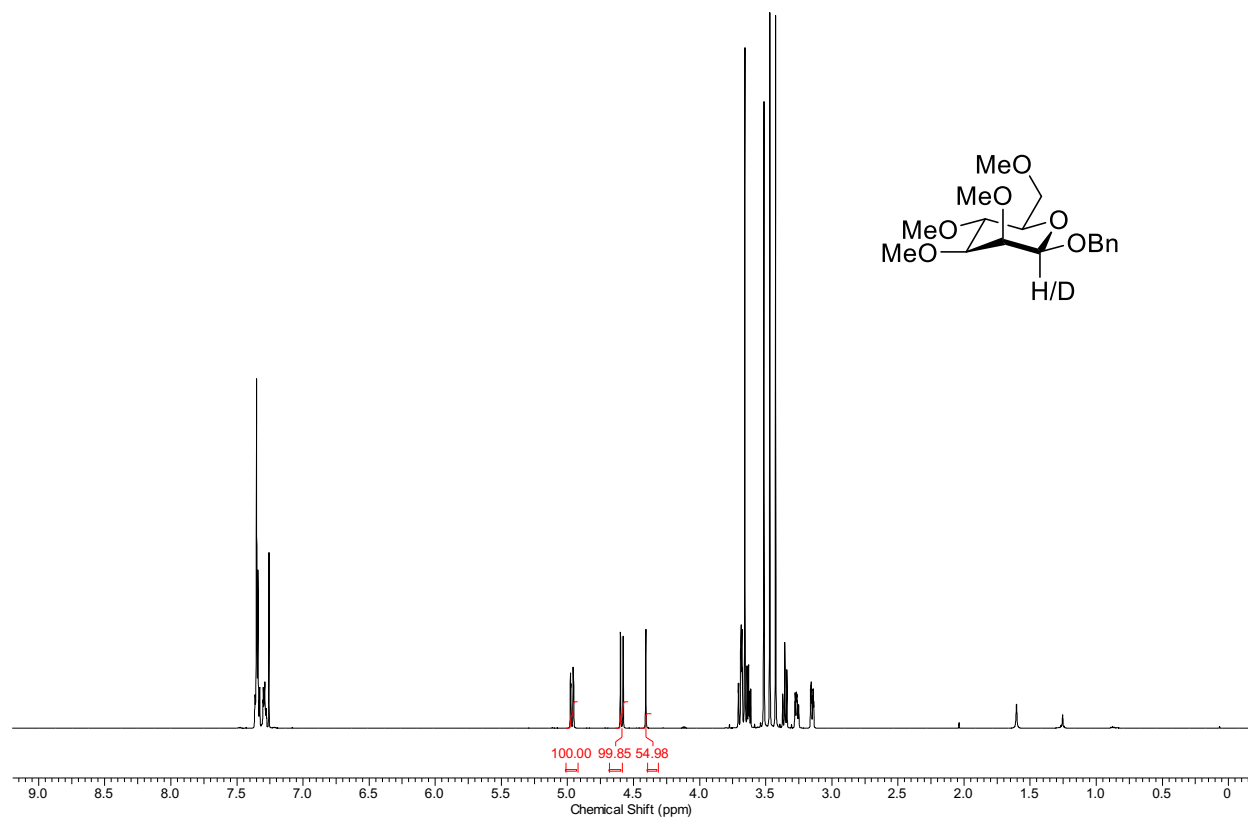
Starting material

Run	6.19 ppm (labeled)	3.80 ppm (ref 1)	3.86 ppm (ref 2)	R_0
1	51.59	99.19	98.25	0.913549
2	51.43	99.38	98.32	0.922030
3	51.46	99.03	98.41	0.918383
4	51.31	99.17	98.26	0.923894
5	51.10	99.32	97.83	0.929061
average				0.921383
stdev				0.005832

1.36 and **1.34β** (F = 0.24 after 1 hour)

Run	4.41 ppm (labeled)	4.59 ppm (ref 1)	4.97 ppm (ref 2)	R_P
1	54.98	99.85	100	0.817479
2	54.85	99.87	100	0.821969
3	55.01	99.87	100	0.81667
4	55.11	99.98	100	0.814371
5	55	100.31	100	0.821
average				0.818298
stdev				0.003143

1.36 and **1.34α** (F = 0.02 after 1 hour)

Run	5.00 ppm (labeled)	4.74 ppm (ref 1)	4.49 ppm (ref 2)	R_P
1	57.58	100.37	100	0.739927
2	57.53	100.23	100	0.740222
3	57.59	100.15	100	0.737715
4	57.46	100.15	100	0.741646
5	57.45	100.12	100	0.741688
average				0.74024
stdev				0.001624

1.35 and **1.34β** (F = 0.10 after 6 hours)

Run	4.41 ppm (labeled)	4.59 ppm (ref 1)	4.97 ppm (ref 2)	R_P
1	55.68	100	100.23	0.798042
2	55.73	100	100.32	0.797237
3	55.56	100	99.99	0.799766
4	55.56	100	99.82	0.798236
5	55.56	100	99.71	0.797246
average				0.798105
stdev				0.001033

1.35 and **1.34α** (F = 0.02 after 6 hours)

Run	5.00 ppm (labeled)	4.74 ppm (ref 1)	4.49 ppm (ref 2)	R_P
1	58.07	100.12	100	0.723093
2	58.09	100.31	100	0.724135
3	58.03	100.14	100	0.724453
4	58.18	100.31	100	0.721468
5	57.99	100.21	100	0.726246
average				0.723879
stdev				0.001763

1.37 and **1.34β** (F = 0.11 after 48 hours)

Run	4.41 ppm (labeled)	4.59 ppm (ref 1)	4.97 ppm (ref 2)	R_P
1	54.96	100.05	100	0.81996
2	54.81	100	99.8	0.82266
3	54.73	100	99.89	0.826147
4	54.9	100	99.96	0.821129
5	54.8	100	100.04	0.825182
average				0.823016
stdev				0.002623

1.37 and **1.34α** (F = 0.02 after 48 hours)

Run	5.00 ppm (labeled)	4.74 ppm (ref 1)	4.49 ppm (ref 2)	R_P
1	57.55	100.07	100	0.738228
2	57.51	100.06	100	0.73935
3	57.57	100.09	100	0.737797
4	57.57	100.14	100	0.738232
5	57.51	99.96	100	0.73848
average				0.738417
stdev				0.000576

	beta		alpha	
	KIE	ΔKIE	KIE	ΔKIE
Indoline	1.145	0.012	1.247	0.011
Amide	1.163	0.010	1.276	0.012
ester	1.127	0.011	1.250	0.011

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

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[42] MacroModel, version 10.4, Schrödinger, LLC, New York, NY, **2014**.

[43] Jorgensen, W.L.; Maxwell, D.S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225.

[44] Zhao, Y.; Truhlar, D.G. *Theor. Chem. Account.* **2008**, *120*, 215.

[45] Cossi et al. *J. Comput. Chem.* **2003**, *24*, 669.

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:

C	0.86855600	-4.73422500	-1.97711500
C	1.37101400	-3.48706500	-2.35363700
C	0.52754500	-2.39469800	-2.47436500
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

C	-2.85374800	-0.99165900	-2.00188900
N	-3.00315700	0.33767400	-1.77868400
C	-4.29090800	0.99285900	-1.71858300
C	-4.13725200	2.55264000	-1.79423400
C	-5.51844000	3.14541800	-2.10467300
C	-3.17738600	2.90571700	-2.94207300
C	-3.62108600	3.13842200	-0.46169000
C	-3.23085600	4.61824300	-0.48872700
O	-1.81427000	4.67243600	-0.69094300
C	-1.20546200	5.84654700	-0.44862600
O	-1.80068100	6.88236600	-0.26674400
C	0.27543900	5.68206800	-0.36580500
C	0.82243300	4.41111600	-0.43499400
C	2.19825200	4.20017600	-0.26973900
C	3.02716500	5.30178800	-0.04310100
C	2.45375500	6.57559500	0.01424500
C	1.09086700	6.79127600	-0.13840800
N	2.56990400	2.85610300	-0.38691400
C	3.73699900	2.17755200	-0.23752300
N	3.59576600	0.87320400	-0.57055800
C	4.61672700	-0.14584200	-0.45323900
C	5.52780000	-0.31679200	-1.75622400
C	6.97503500	0.01515100	-1.34566400

C	5.10662100	0.70006800	-2.82278900
C	5.54319800	-1.74991800	-2.36257300
C	4.58380800	-2.09496500	-3.49647600
C	3.85969900	-1.41713900	-0.03508900
C	-5.01427700	0.54095900	-0.43457700
O	-4.37130700	0.46985600	0.61695500
N	-6.34884400	0.32169200	-0.48890100
C	-7.11308600	0.11074500	-1.74445200
C	-8.57241000	-0.06455500	-1.29258100
C	-8.44787600	-0.34709400	0.18192300
C	-7.14515700	-0.08682900	0.61551800
C	-9.41699500	-0.76434500	1.07913500
C	-9.07818700	-0.92003000	2.42438700
C	-7.78095300	-0.64904900	2.84944000
C	-6.79486200	-0.22743100	1.95610000
O	2.69399900	-1.56978200	-0.39132300
N	4.51869100	-2.32942200	0.72480400
C	5.92464700	-2.24025300	1.17069900
C	6.03289300	-3.26576900	2.31187700
C	4.85740100	-4.17420000	2.05583600
C	3.98113700	-3.57286600	1.15123200
C	4.54555000	-5.39978200	2.62620000
C	3.34752500	-6.02589300	2.27819400

C	2.47954200	-5.41588900	1.37248600
C	2.78112300	-4.18161100	0.79821800
C	3.34080700	7.74808600	0.32663100
F	4.59694300	7.56084300	-0.10056900
F	3.40946800	7.97586900	1.64969200
F	2.88613000	8.87773700	-0.23690900
C	-1.03669800	-6.13940500	-1.20242100
F	-1.05410300	-6.10515200	0.15115700
F	-0.29118900	-7.19612800	-1.54734800
F	-2.29378100	-6.37603800	-1.59417300
Cl	0.14931500	1.07817500	-1.34669600
H	1.54556900	-5.57286500	-1.85252100
H	0.94634200	-1.42094100	-2.71157000
H	-2.42956300	-3.90316600	-1.71697400
H	-0.92833700	-0.51818800	-2.29496300
H	-2.15820100	0.90465100	-1.70905200
H	-4.86226900	0.67788600	-2.59775000
H	-5.47046800	4.23798100	-2.13528300
H	-5.87361500	2.81129700	-3.08573600
H	-6.25837100	2.86642400	-1.34589300
H	-3.44239200	2.35634000	-3.85160500
H	-3.24330400	3.97522600	-3.16624000
H	-2.13093700	2.69464600	-2.69811800

H	-2.72125800	2.59786900	-0.14117300
H	-4.37929200	2.98594900	0.31371800
H	-3.45723500	5.10550900	0.46450500
H	-3.73066100	5.19237800	-1.27495500
H	0.17563300	3.55663600	-0.60011600
H	4.09371300	5.17470300	0.08308500
H	0.66058400	7.78514500	-0.07789200
H	1.77335700	2.27524400	-0.66631300
H	2.69131700	0.53477400	-0.90619900
H	5.27217500	0.17952800	0.35793300
H	7.61985800	0.02976200	-2.23088900
H	7.02027400	0.99618600	-0.86523800
H	7.38355500	-0.72889200	-0.65343500
H	5.74014500	0.57810300	-3.70898600
H	4.06228000	0.57502400	-3.12505600
H	5.24004800	1.72078900	-2.45371100
H	5.45906300	-2.52283500	-1.59126900
H	6.53834700	-1.88708400	-2.80629100
H	4.88825800	-3.05190000	-3.92757100
H	4.59543000	-1.33500600	-4.27834500
H	-6.99637800	0.95944500	-2.41630600
H	-6.72120400	-0.78842000	-2.23010700
H	-9.06491100	-0.87277900	-1.83827200

H	-9.15101000	0.85047200	-1.46089800
H	-10.42718200	-0.96803700	0.73547700
H	-9.82556500	-1.25266400	3.13736000
H	-7.52143900	-0.77080400	3.89664200
H	-5.79103700	-0.02342700	2.29363600
H	6.58383600	-2.51958900	0.34107800
H	6.17121300	-1.22772100	1.49122700
H	5.93209600	-2.77758200	3.28802800
H	6.99396000	-3.78451200	2.29426200
H	5.22733600	-5.86188100	3.33468600
H	3.09310600	-6.98815500	2.71087600
H	1.54696500	-5.90476800	1.09928200
H	2.10099000	-3.69953400	0.11258700
C	-3.41357100	1.00983500	3.39039300
H	-2.64958500	1.51682700	3.98331800
H	-4.17879200	0.62282500	4.07007000
H	-3.86898300	1.71044400	2.68289500
O	-2.78377600	-0.07000000	2.70530100
H	-3.43299700	-0.41444500	2.05868900
C	-0.34152000	1.07371400	2.09969500
C	0.97643900	0.31234200	2.15457800
C	0.64475900	-1.15537800	2.36908900
C	-0.13144900	-1.70494600	1.17243000

C	-1.37504500	0.35862400	1.24608200
H	1.52420500	0.43948900	1.20991300
H	-0.72044800	1.08416400	3.13155200
H	0.51888000	-1.70809000	0.28994500
H	-2.14694100	0.93006000	0.73579800
H	0.02615000	-1.24806100	3.27329000
O	-1.25158300	-0.82747200	0.80338300
O	-0.14707000	2.37700700	1.63062100
O	1.70944900	0.78519300	3.25376200
O	1.82705700	-1.89872600	2.49321500
C	-0.70883900	-3.07935900	1.41500100
H	-1.38253600	-3.34859200	0.59028300
H	0.12583600	-3.79860600	1.42340900
O	-1.39489700	-3.08540200	2.64082900
C	-0.93948800	3.35261100	2.28046900
H	-0.61445100	4.32196600	1.90112400
H	-2.00928500	3.22105400	2.06205900
H	-0.78615900	3.31671100	3.36667400
C	2.95277700	1.36514500	2.90271000
H	3.57823900	0.64900000	2.35162300
H	2.81024800	2.26484600	2.29264400
H	3.45171500	1.63514700	3.83490600
C	1.86651000	-2.71724200	3.64926000

H	1.00894200	-3.40211800	3.68014500
H	2.78897300	-3.29904800	3.59452500
H	1.86808000	-2.09944000	4.55565300
C	-1.92317400	-4.36254400	2.92621800
H	-2.43517000	-4.29404100	3.88696100
H	-2.63460700	-4.67917900	2.15192800
H	-1.12203200	-5.11316100	2.99058600
S	5.17901400	2.83749800	0.33793800
S	-4.16089400	-2.05410100	-1.97571500

1.6.6   Additional Optimization Data
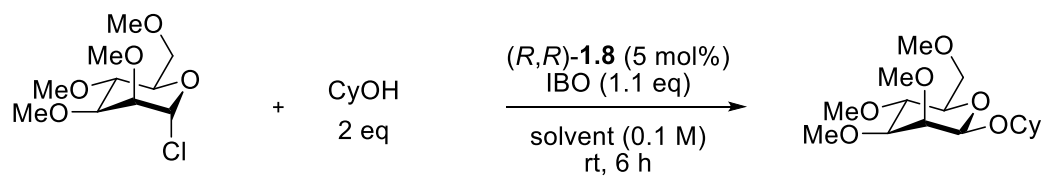
solvent	$\alpha : \beta$	yield
DMF	59 : 41	6
THF	41 : 59	12
CH$_2$Cl$_2$	14 : 86	38
Et$_2$O	9 : 91	43
TBME	9 : 91	40
CPME	7 : 93	46
toluene	5 : 95	63
o-dichlorobenzene	4 : 96	89
o-dichlorobenzene (0.5 M)	5 : 95	87
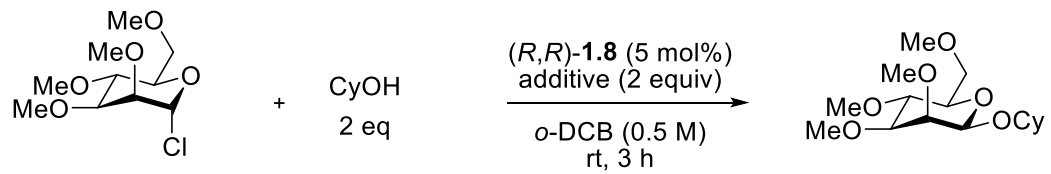
additive	α : β	yield
none	7 : 93	7
IBO	5 : 95	53
NaHCO$_3$	5 : 95	38
K$_2$CO$_3$	5 : 95	40
Et$_3$N	22 : 78	3
pyridine	25 : 75	2
Na$_2$HPO$_4$	5 : 95	42
4A sieves	5 : 95	43

1.6.7 Spectral Data

Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside 1.9:
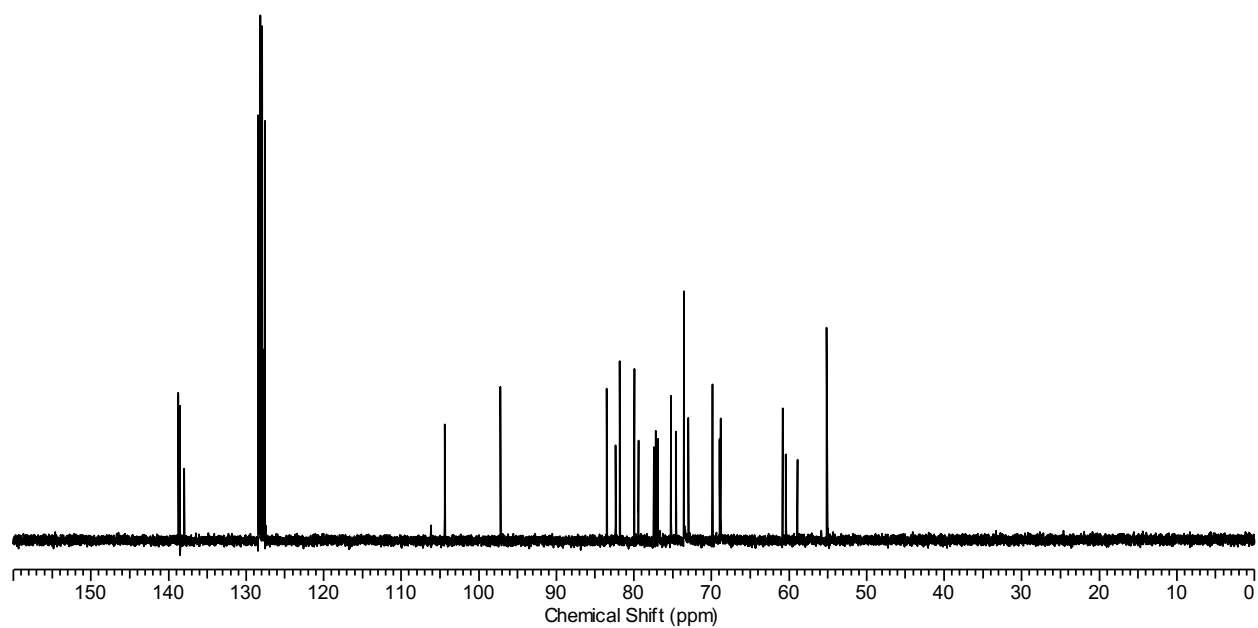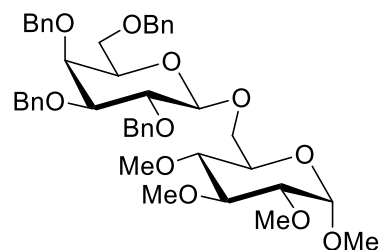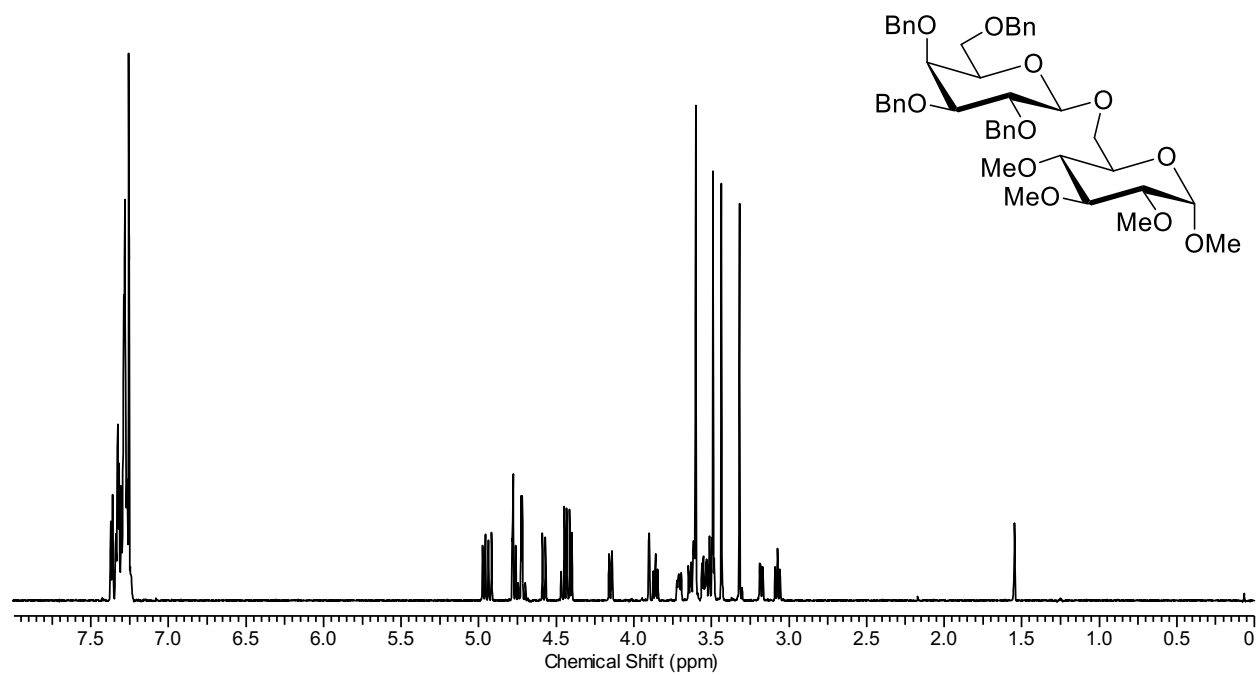
Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-D-galactopyranoside 1.10:
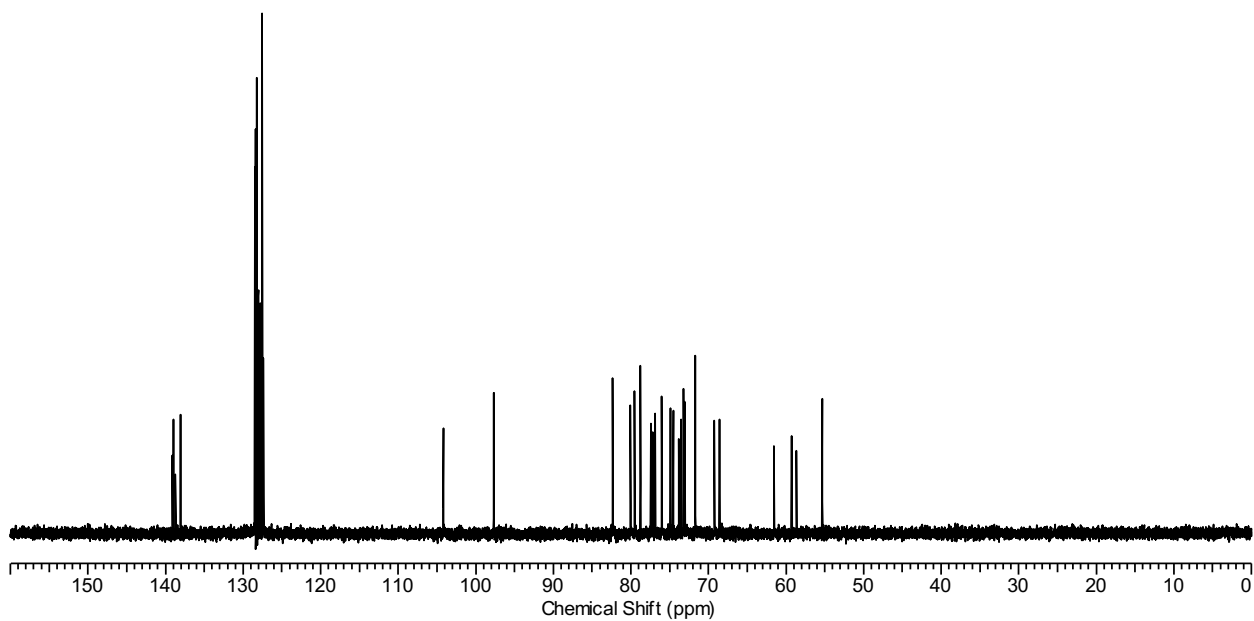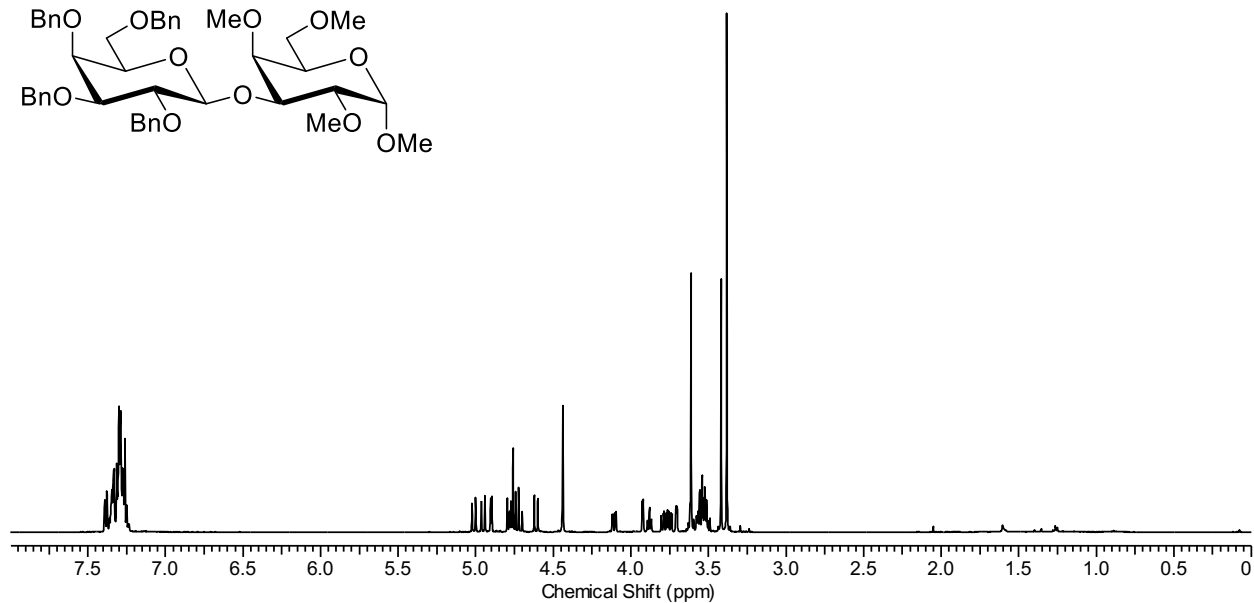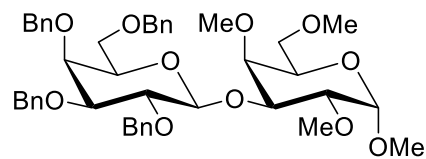
Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3-di-*O*-methyl-β-D-xylopyranoside β-1.11:
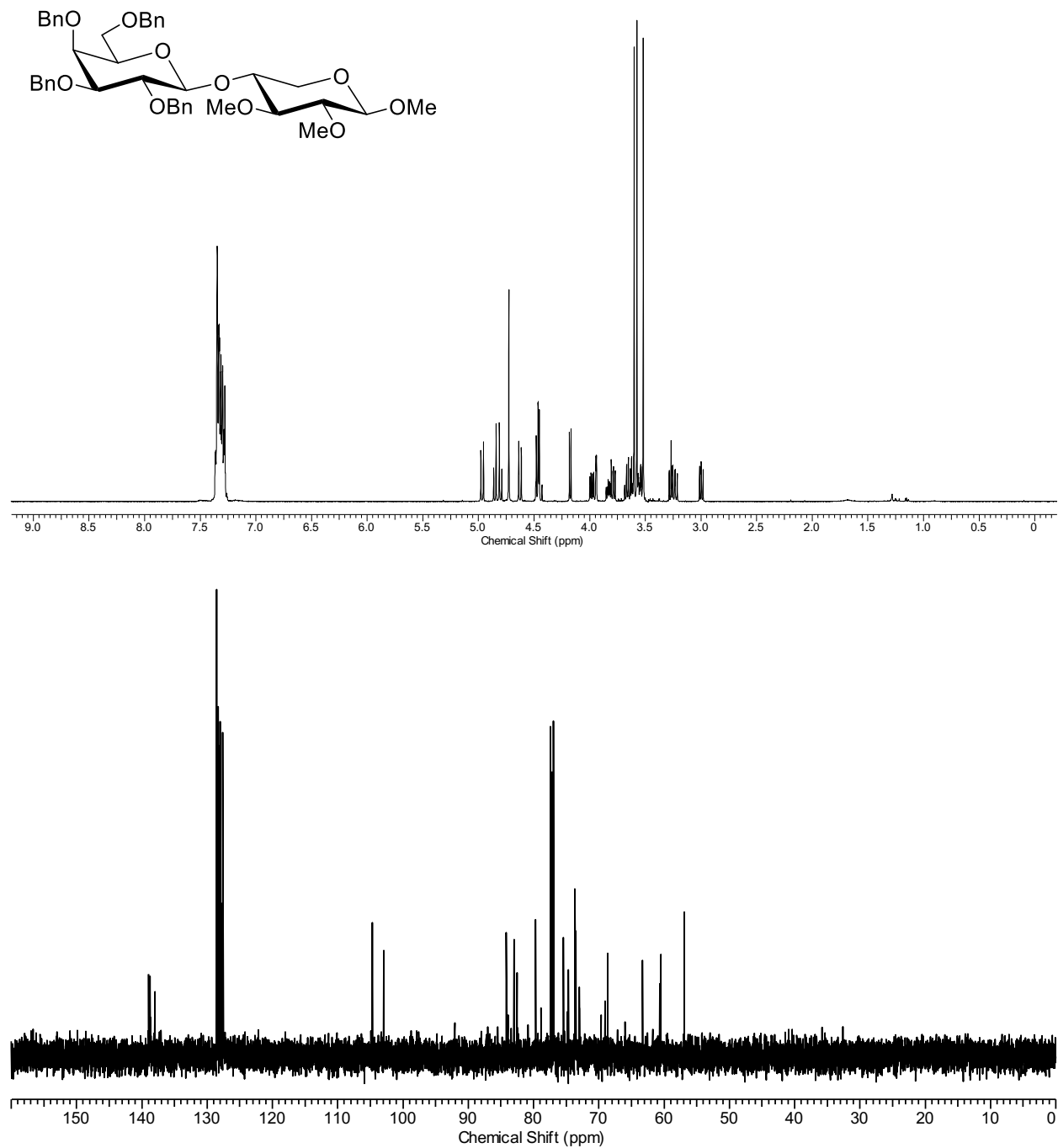
Methyl (2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→4)-2,3-di-*O*-methyl-β-D-xylopyranoside α-1.11:
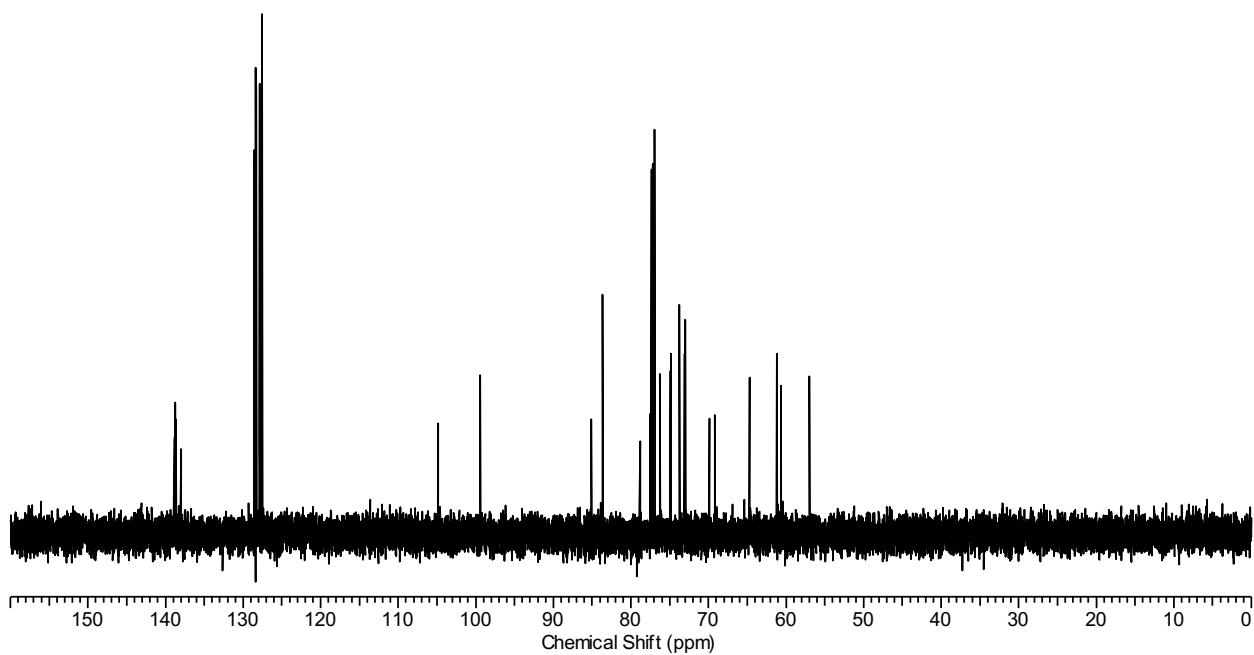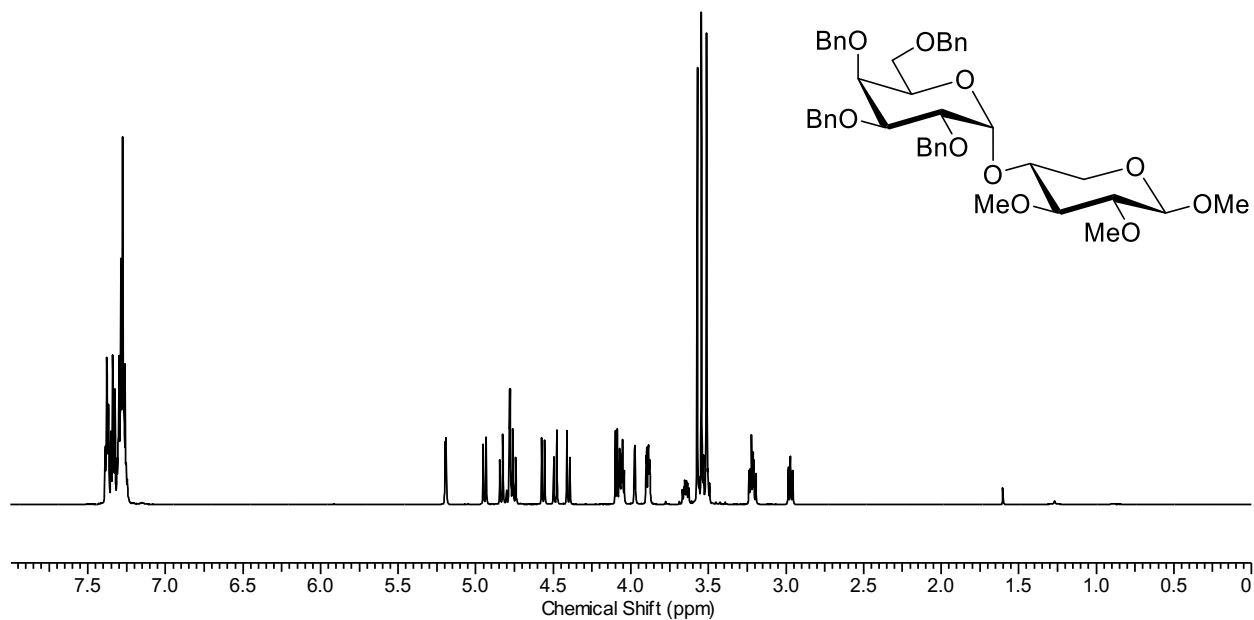
Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2-*O*-benzyl-4,6-benzylidene-α-D-galactopyranoside 1.23:
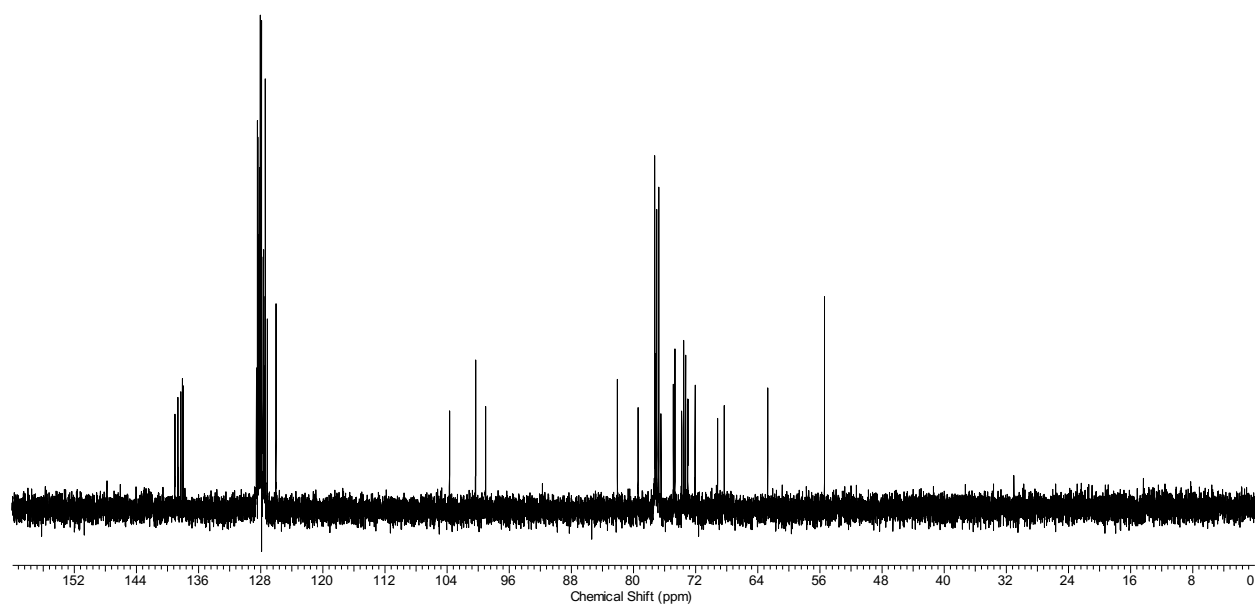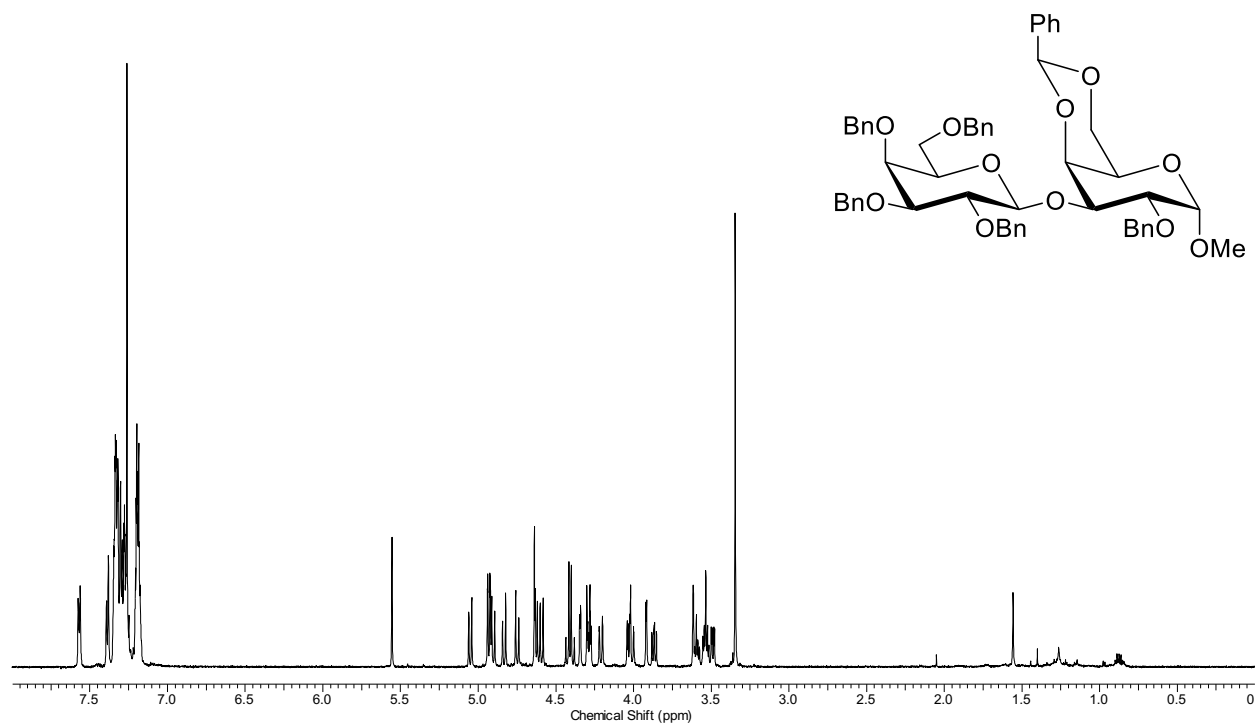
Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside β-1.13:
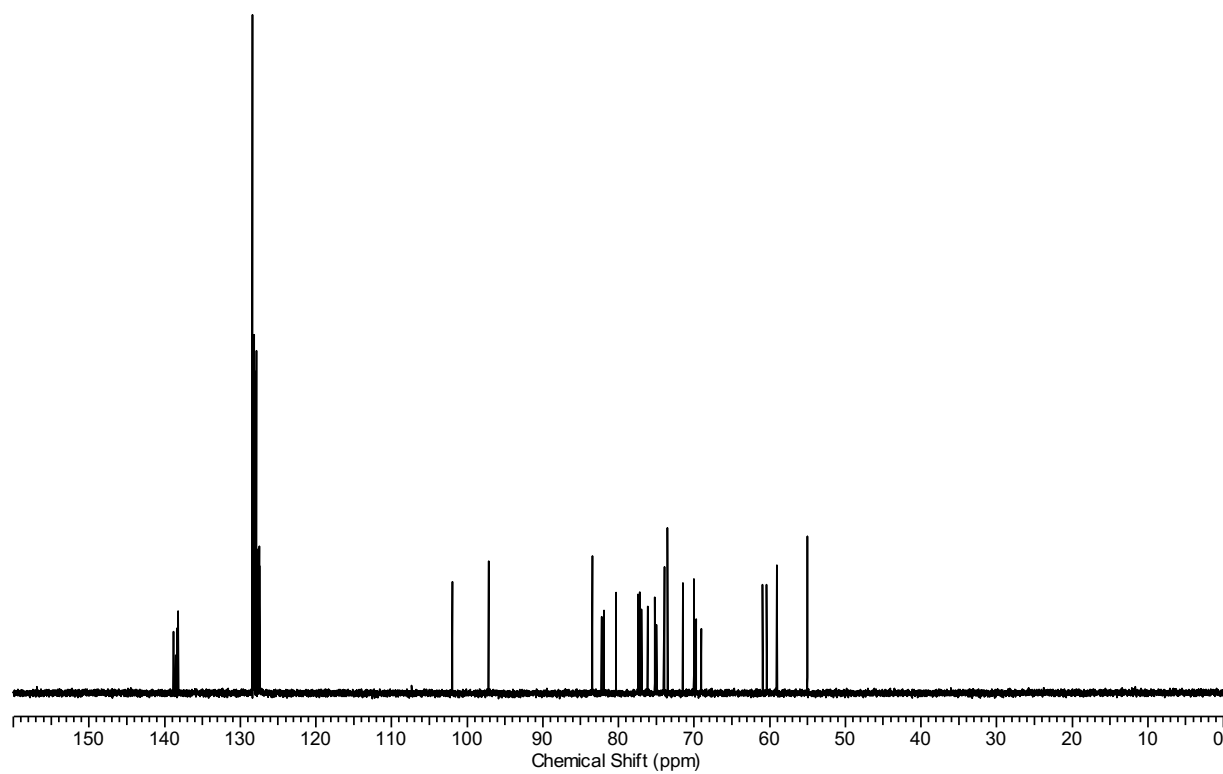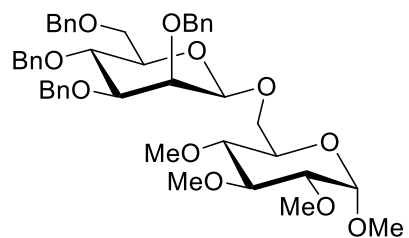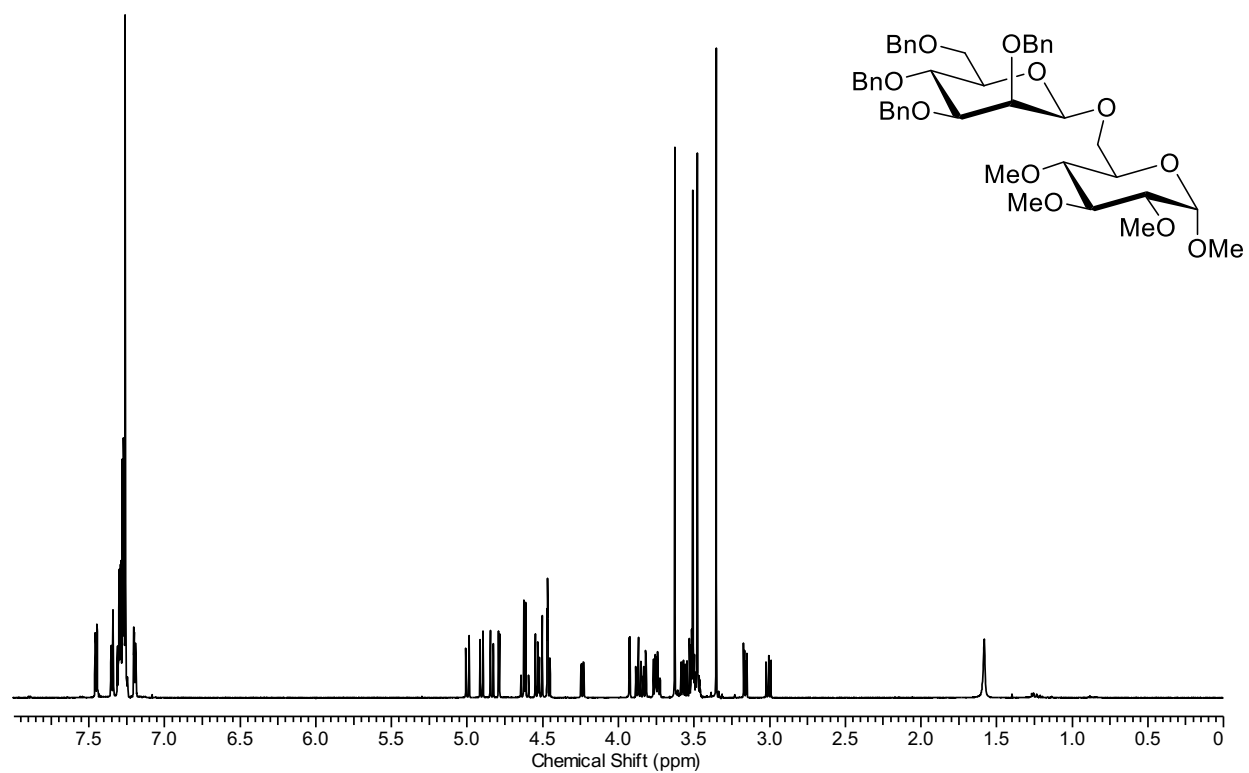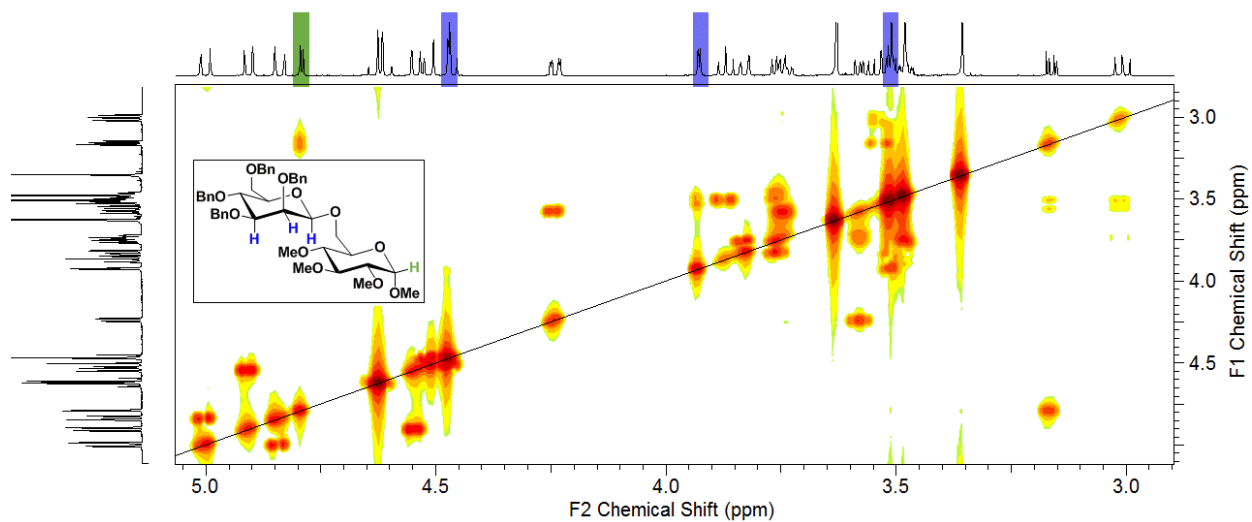
gCOSY at 600 MHz of β-1.13.
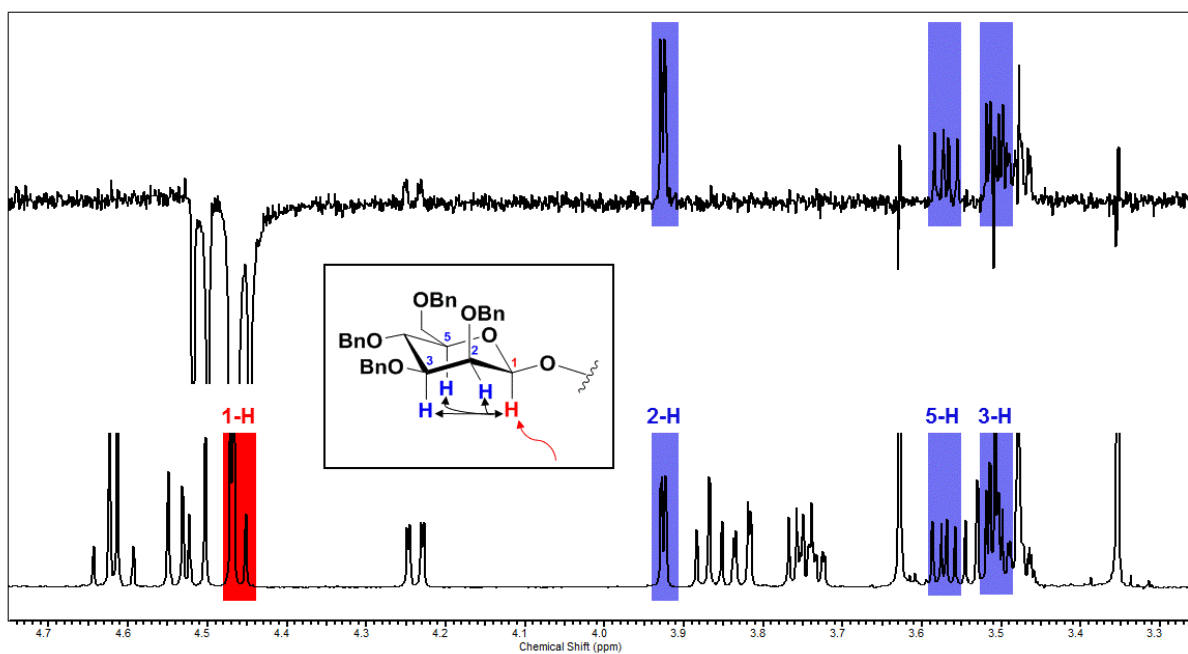
1D-NOE at 600 MHz of β-1.13. Irradiation at 4.46-4.52 ppm (1-H).

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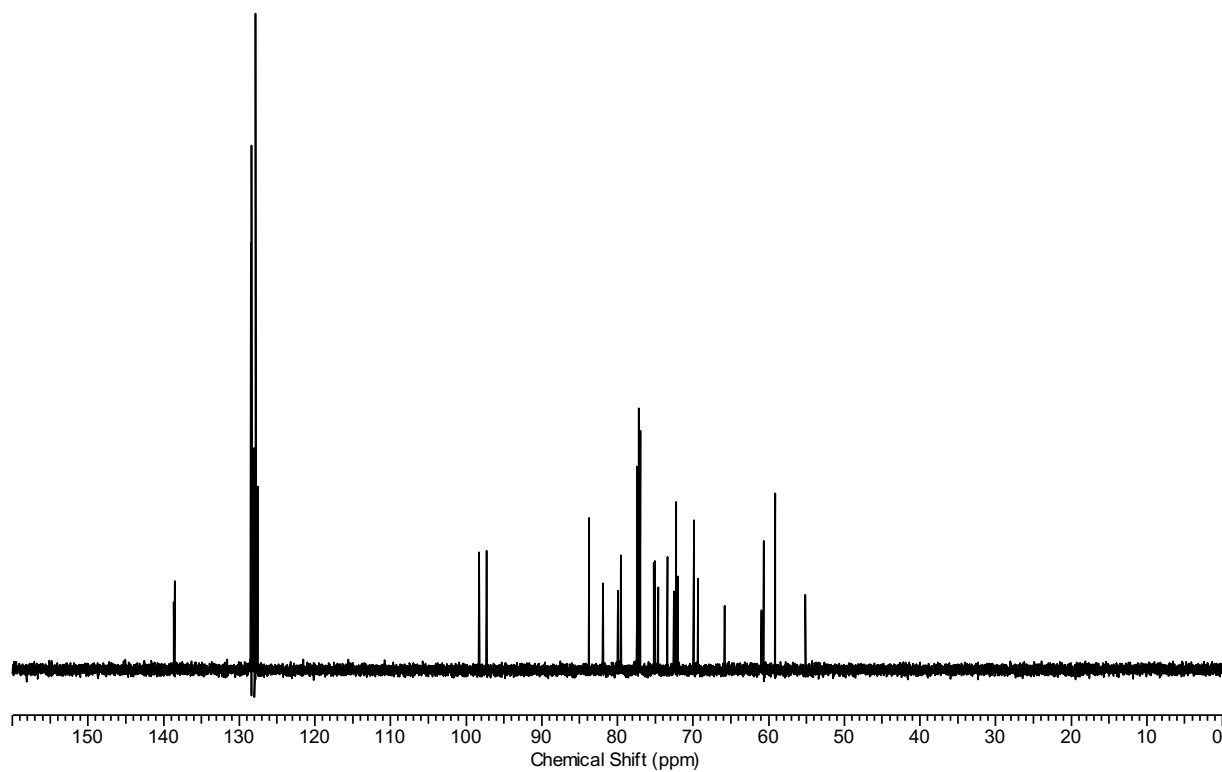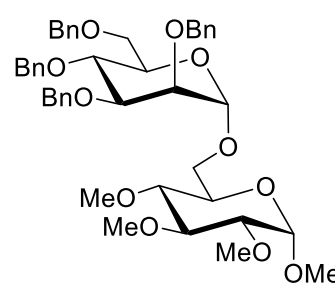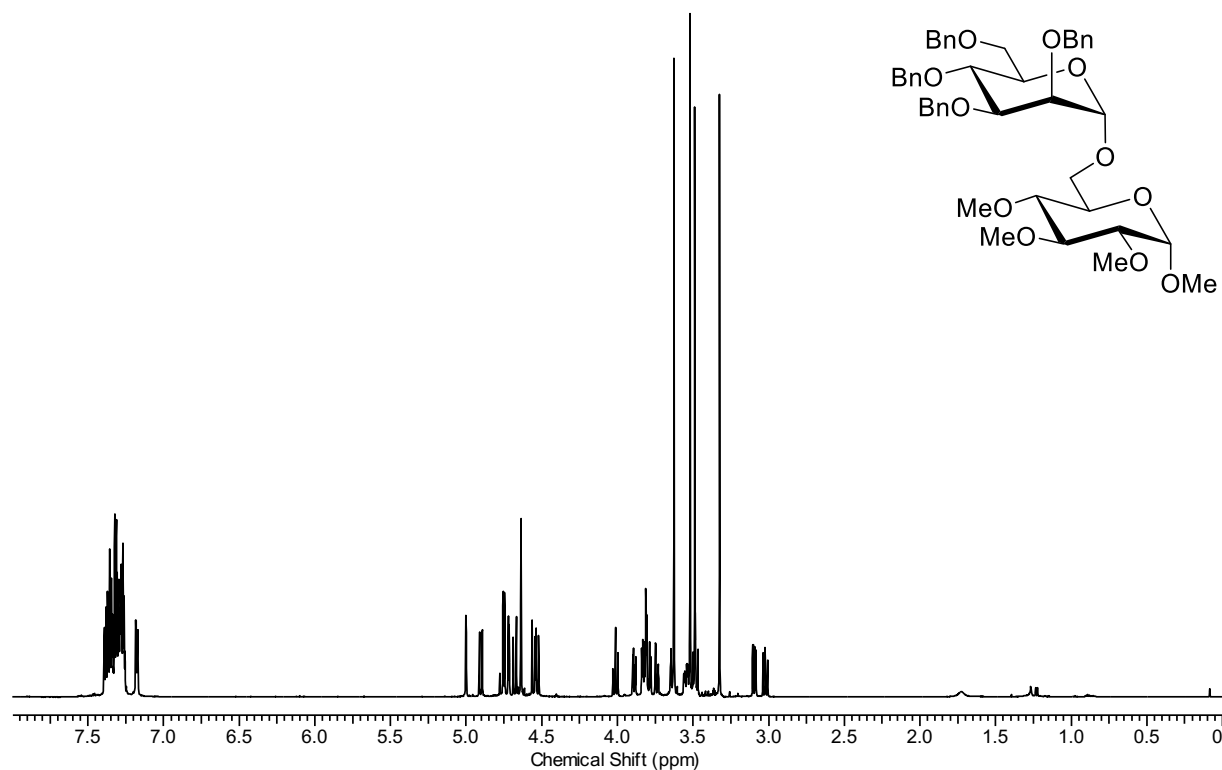
Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-D-galactopyranoside β-1.14:

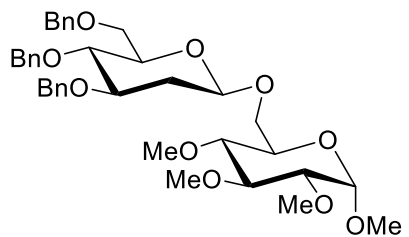**Methyl (2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-D-galactopyranoside α-1.14:**

Methyl (2,3,4-Tri-*O*-benzyl-6-deoxy-β-ʟ-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-ᴅ-glucopyranoside β-1.15:

Methyl (2,3,4-Tri-*O*-benzyl-6-deoxy-α-ʟ-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-ᴅ-glucopyranoside α-1.15:

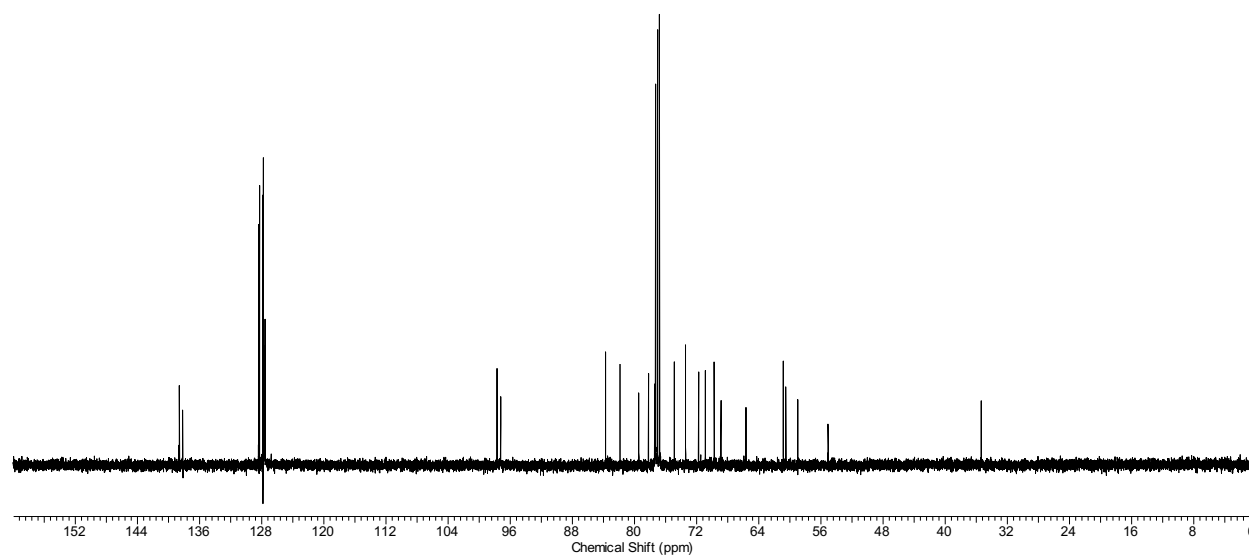**Methyl (2,3,4-Tri-*O*-benzyl-2-deoxy-β-ʟ-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-ᴅ-galactopyranoside β-1.16:**

gCOSY at 600 MHz of β-1.16.
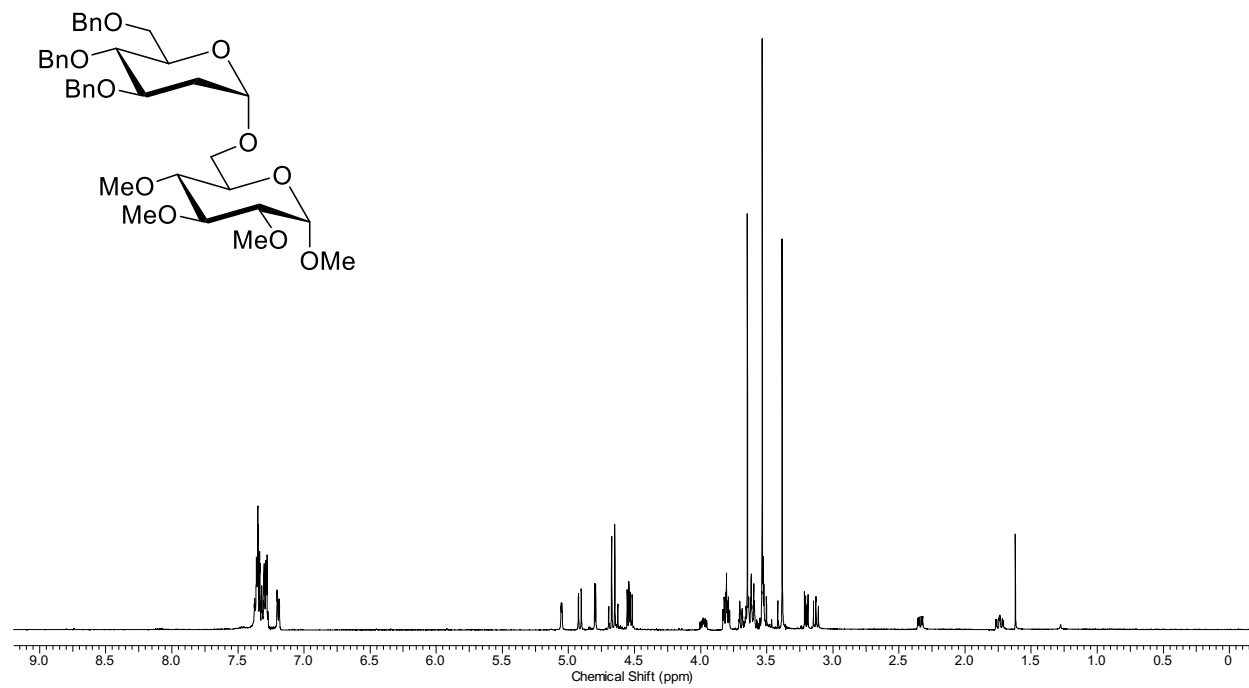

1D-NOE at 600 MHz of β-1.16. Irradiation at 4.52-4.58 ppm (1-H).
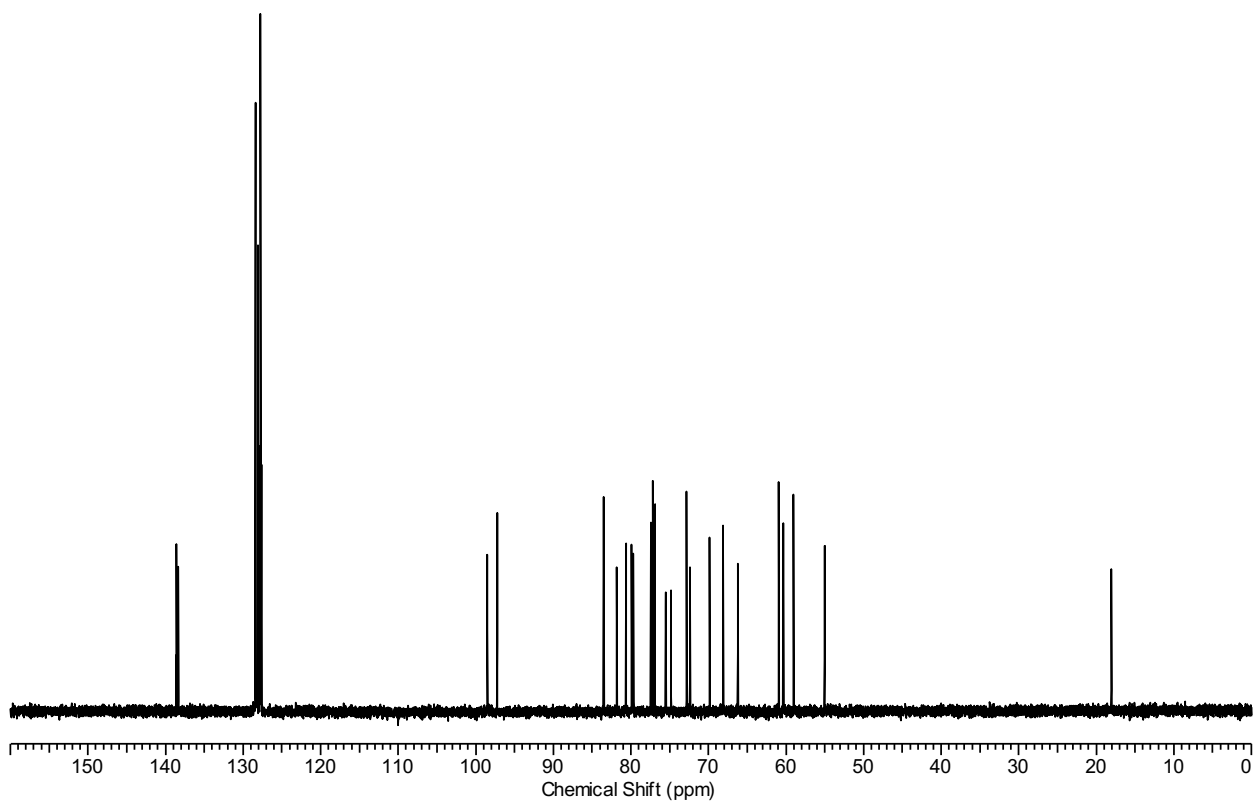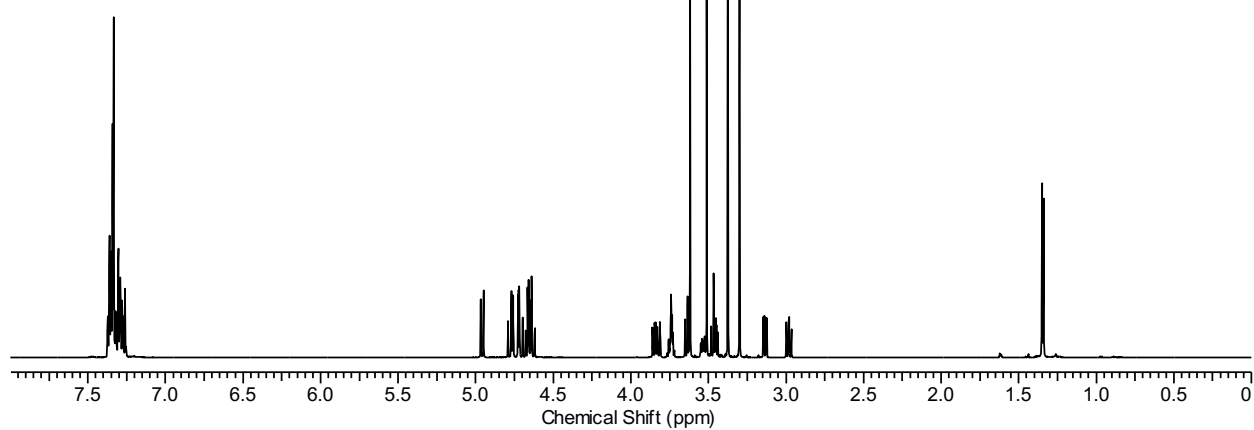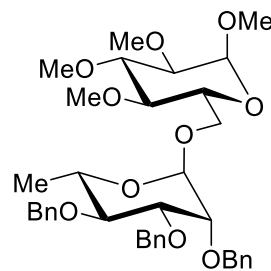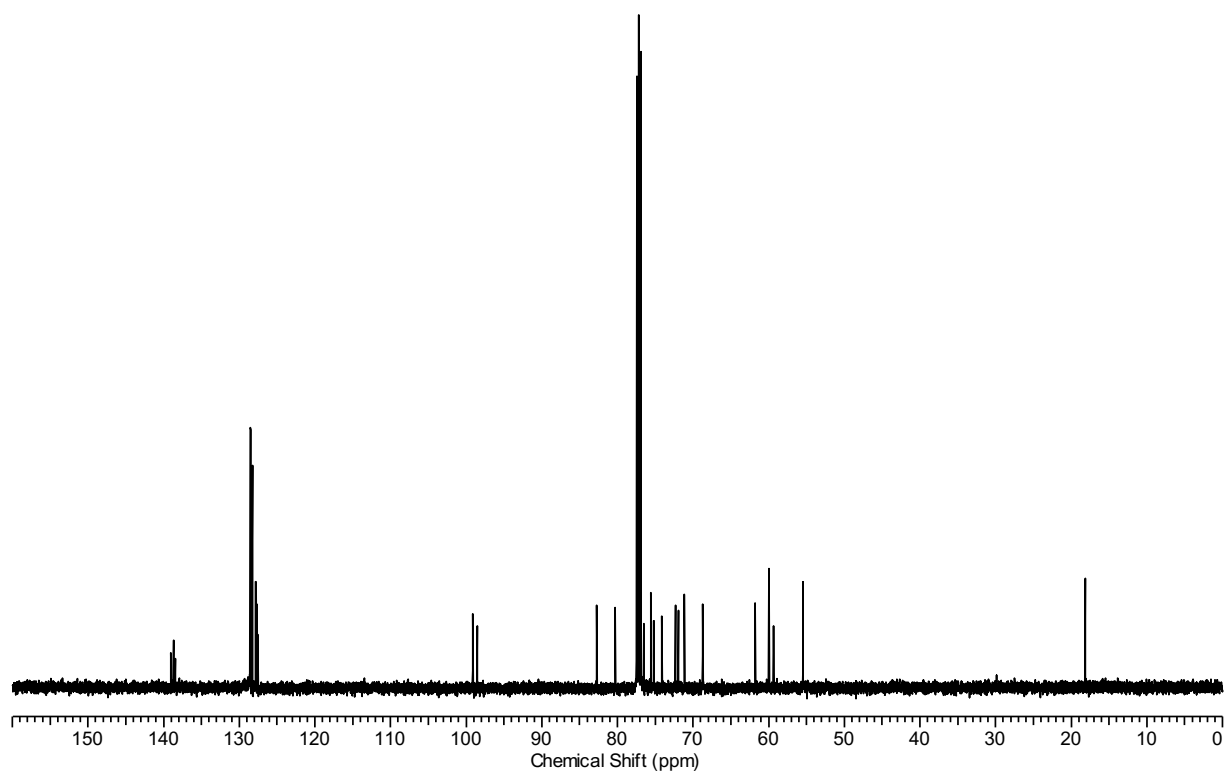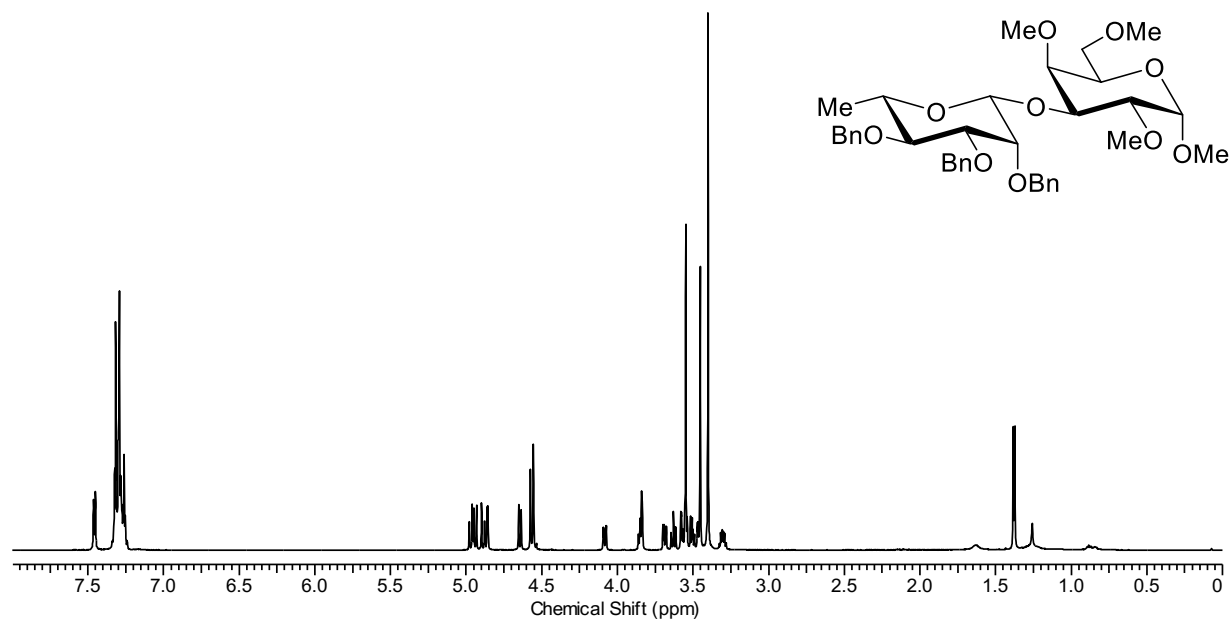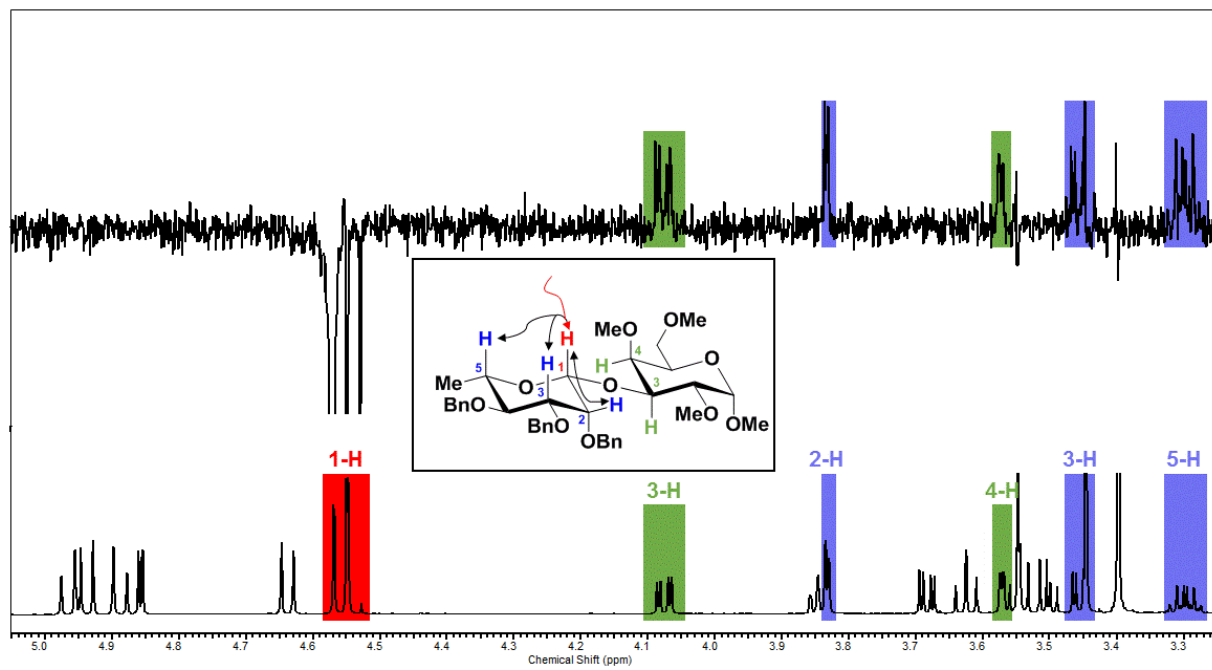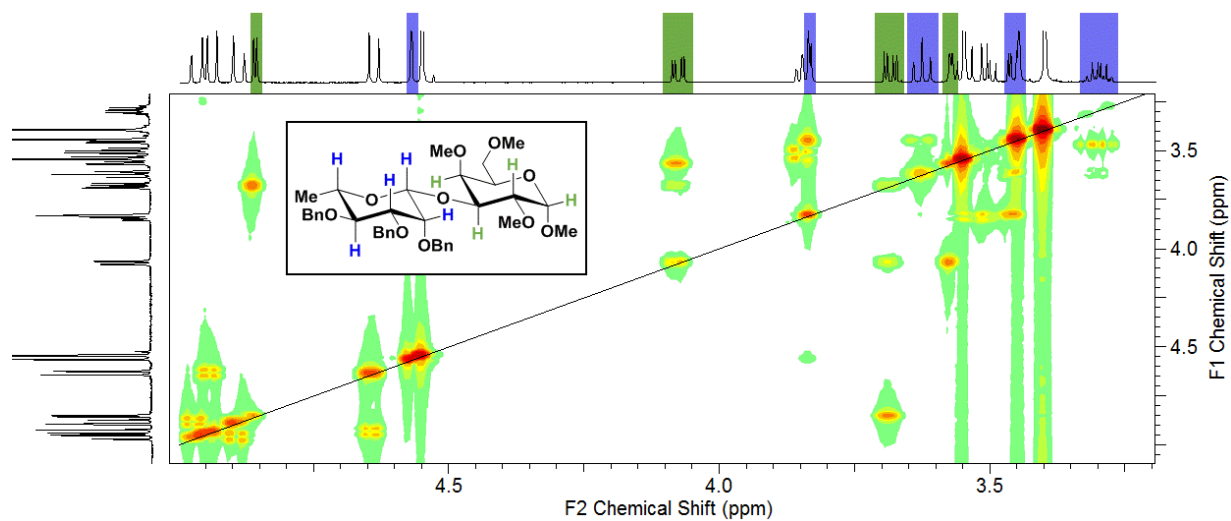
Methyl (2,3,4-Tri-*O*-benzyl-2-deoxy-α-ʟ-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-ᴅ-galactopyranoside α-1.16:

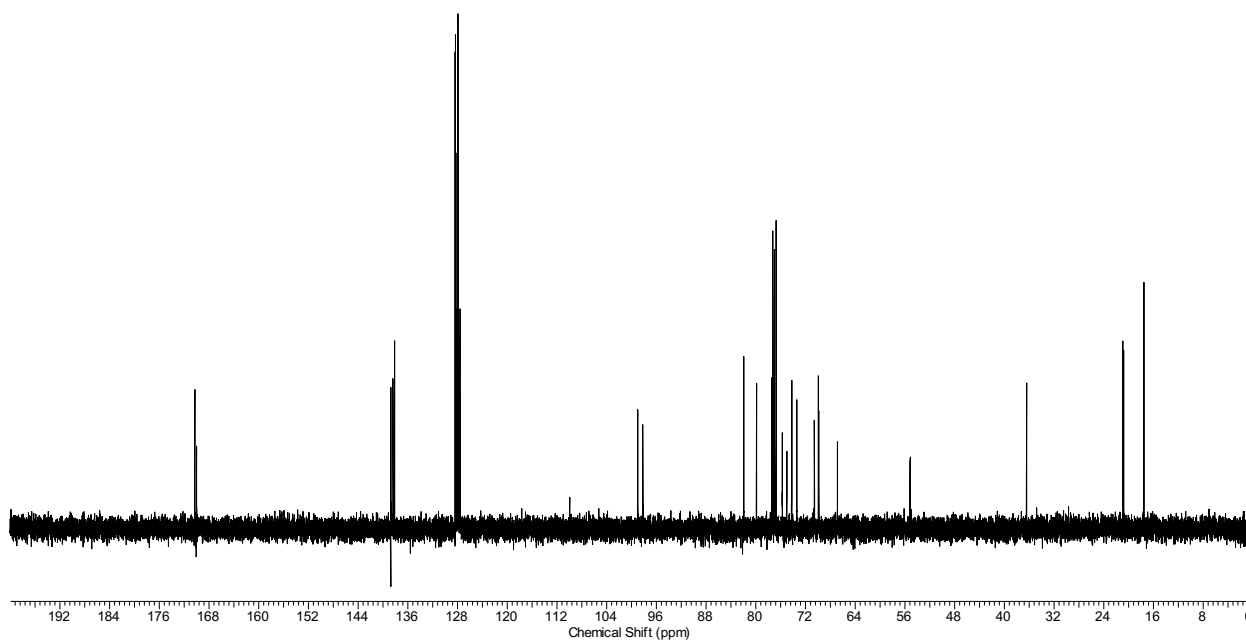**Methyl (3,4,6-Tri-*O*-benzyl-2-deoxy-β-ᴅ-glucosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-ᴅ-glucopyranoside β-1.17:**

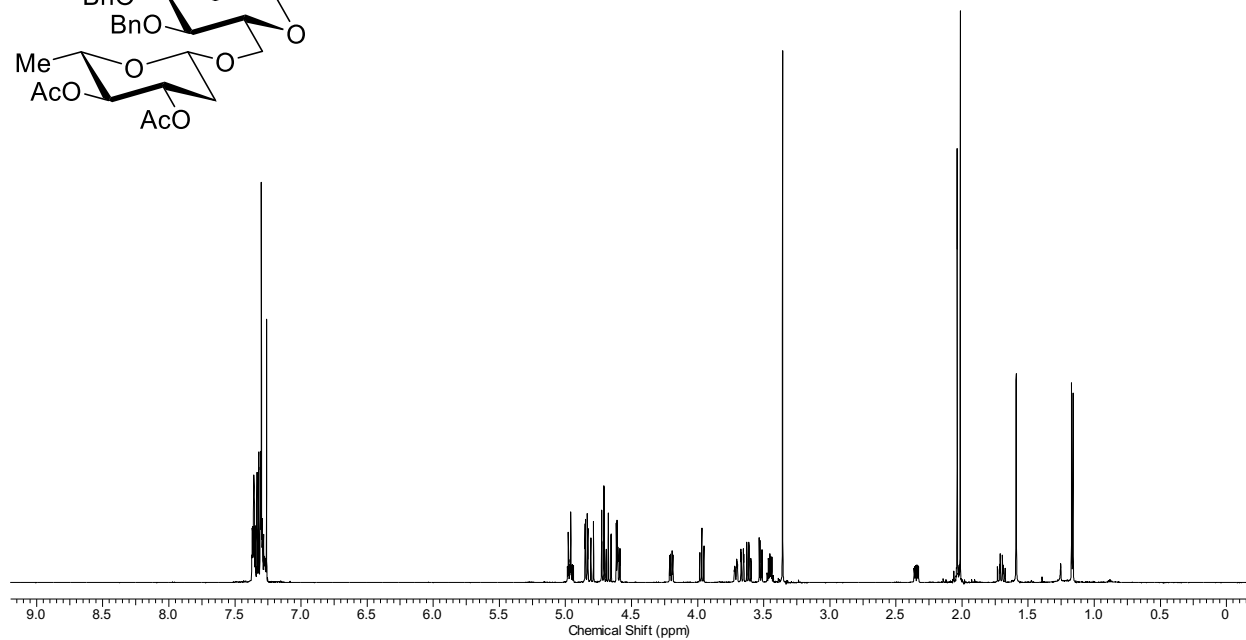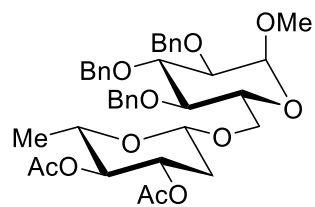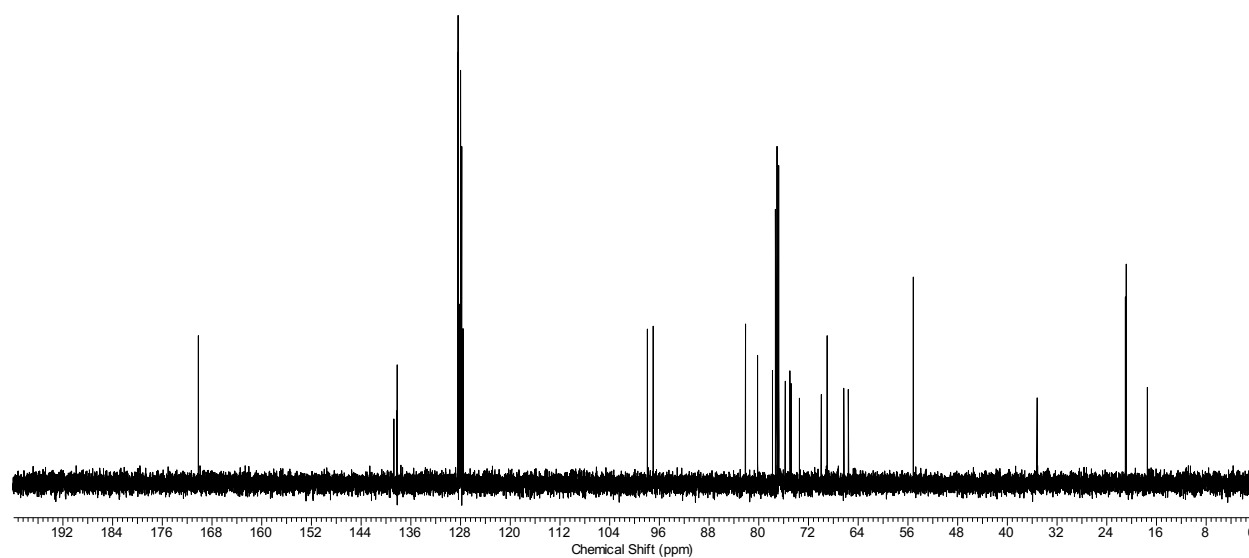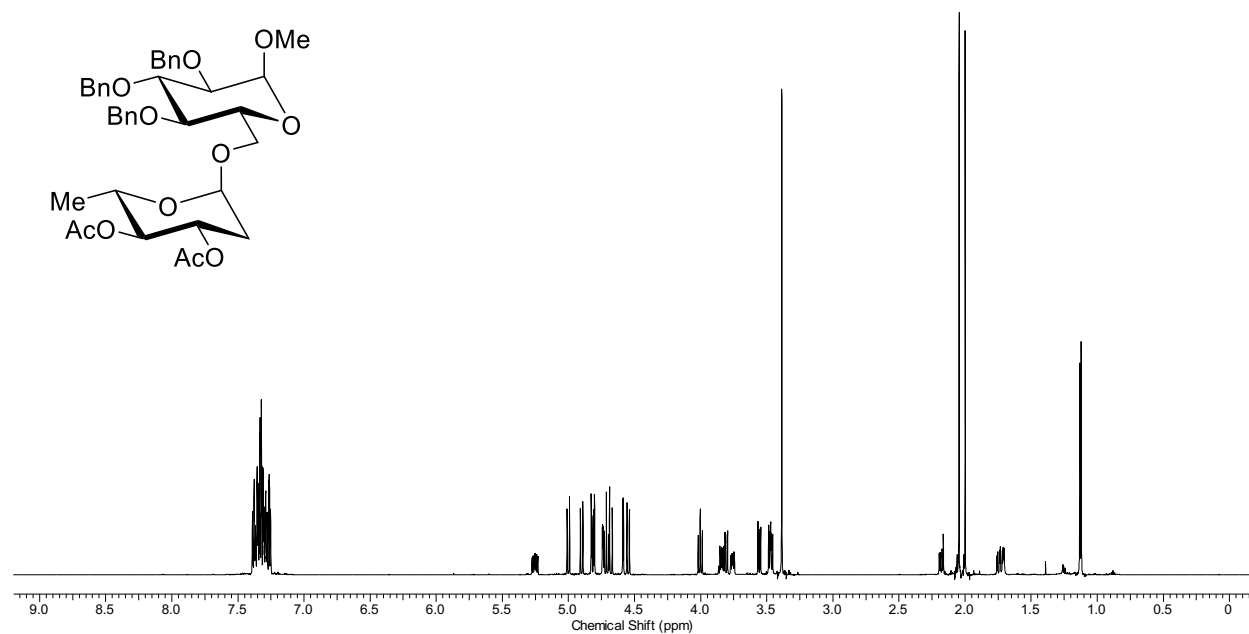**Methyl (3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-glucosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside α-1.17:**

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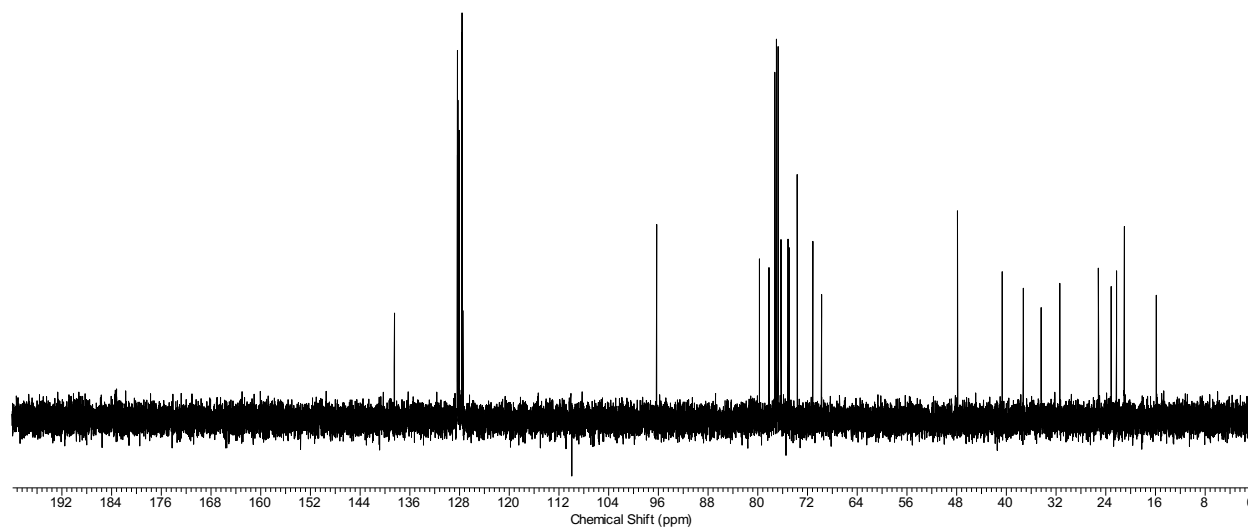
Methyl   (3,4-Di-*O*-acetyl-2,6-dideoxy-α-ʟ-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-ᴅ-glucopyranoside α-1.18:

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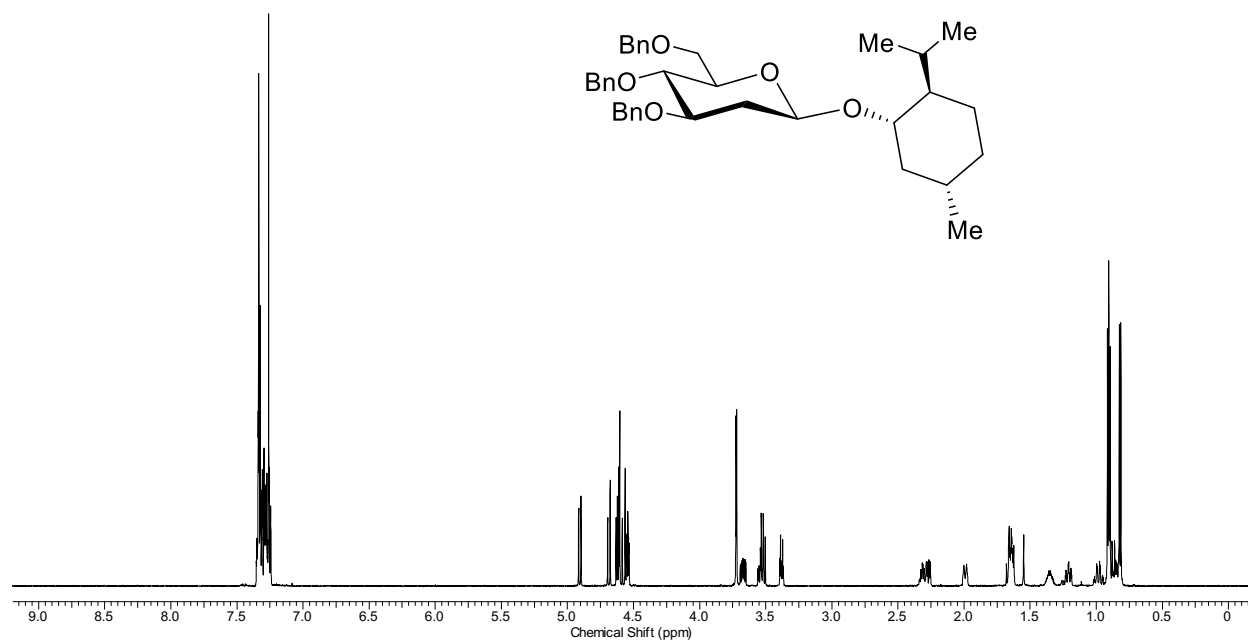
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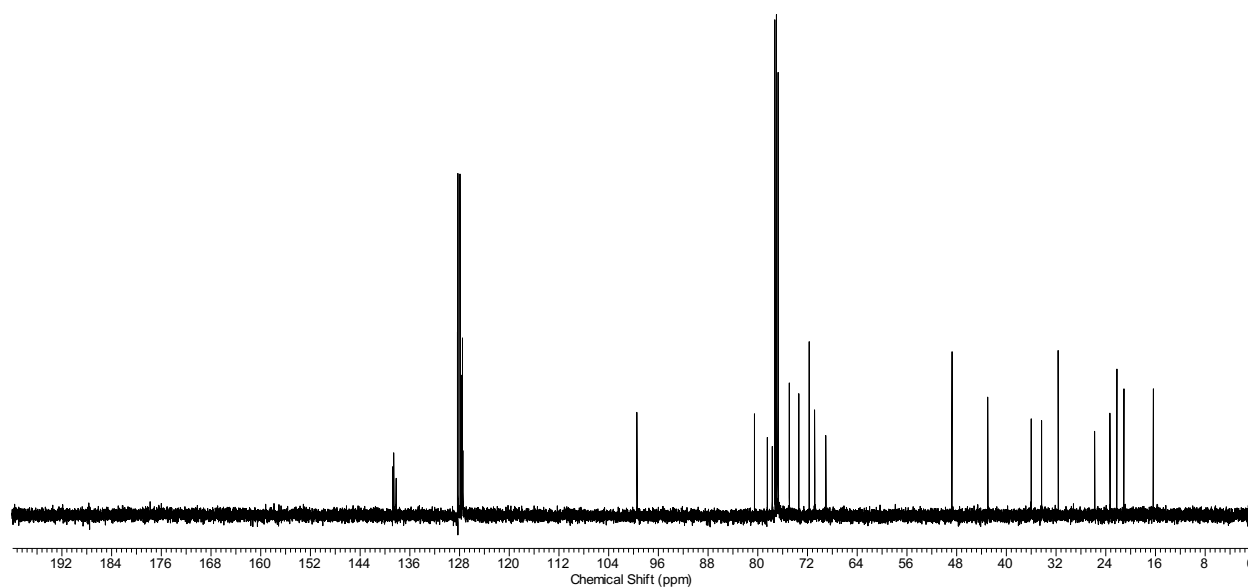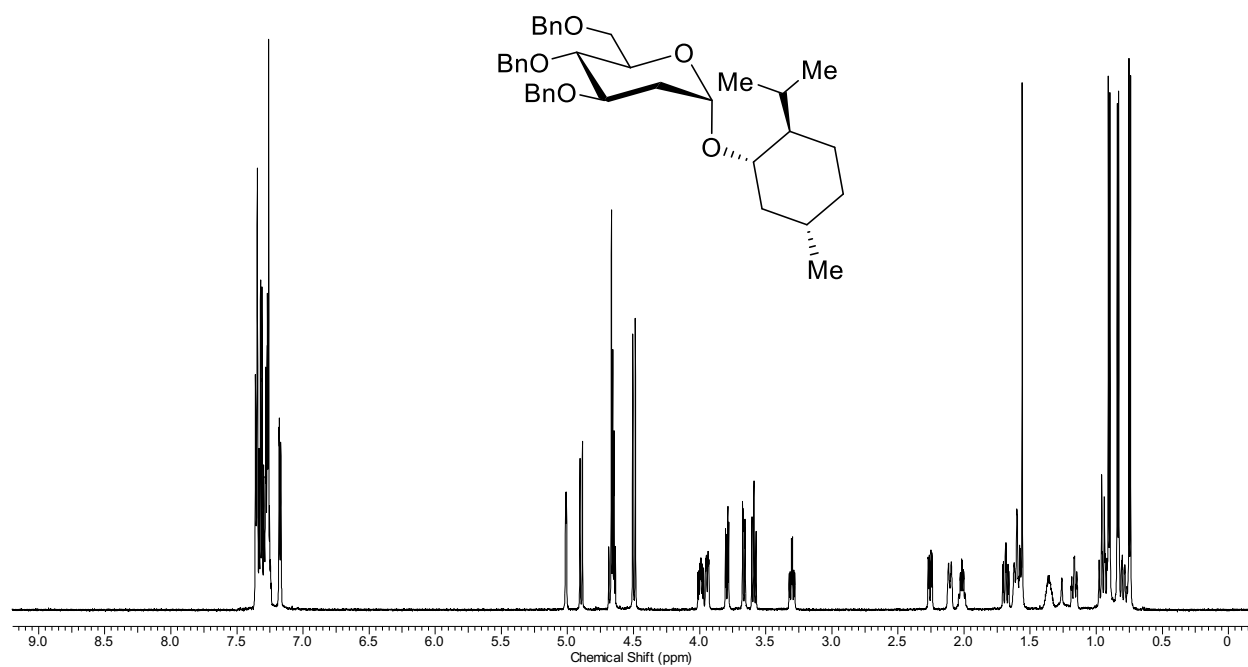
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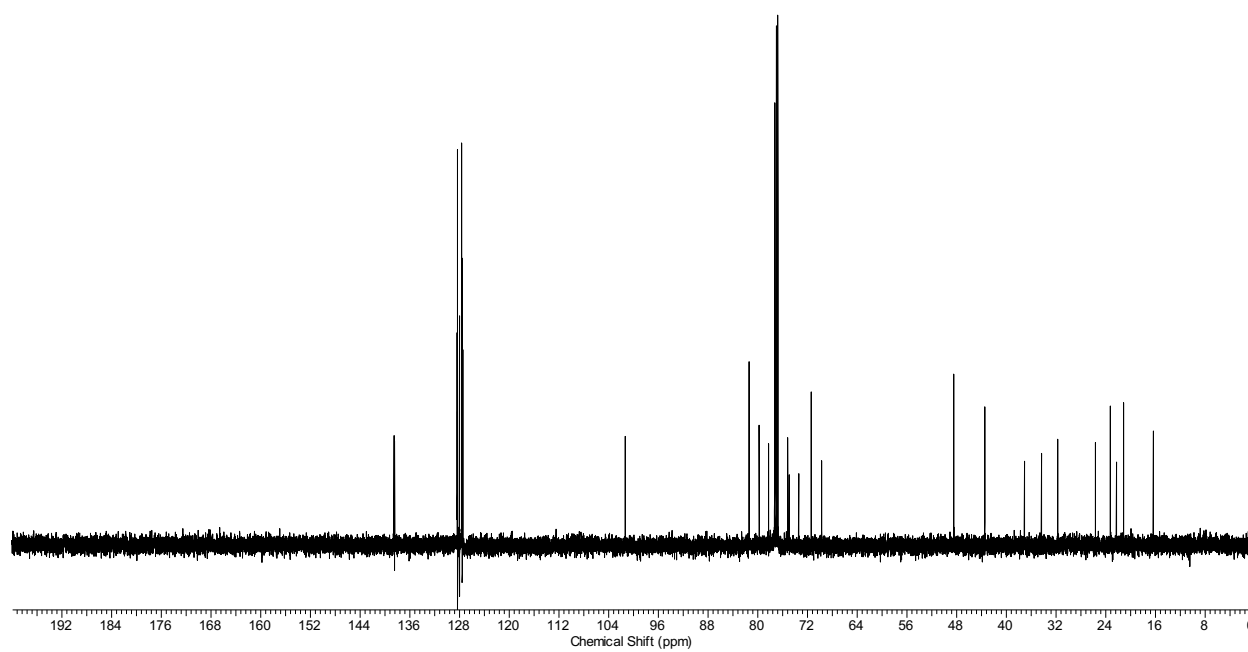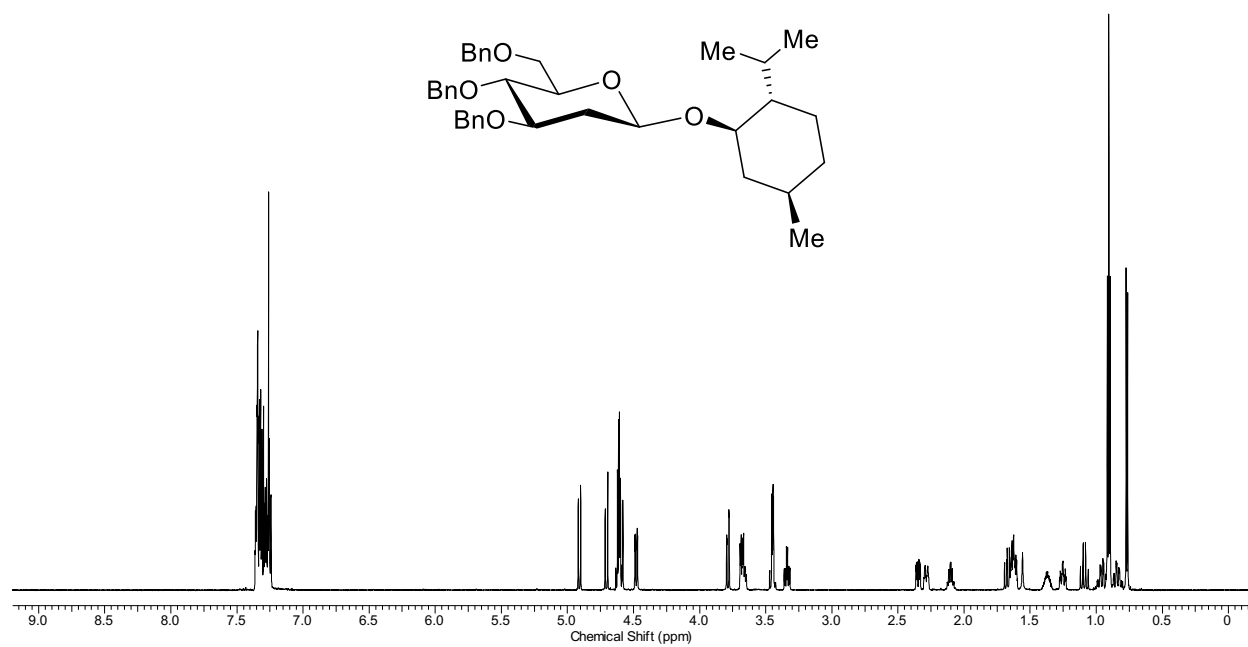
(-)-Menthoyl (3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-glucopyranoside) α-1.20:
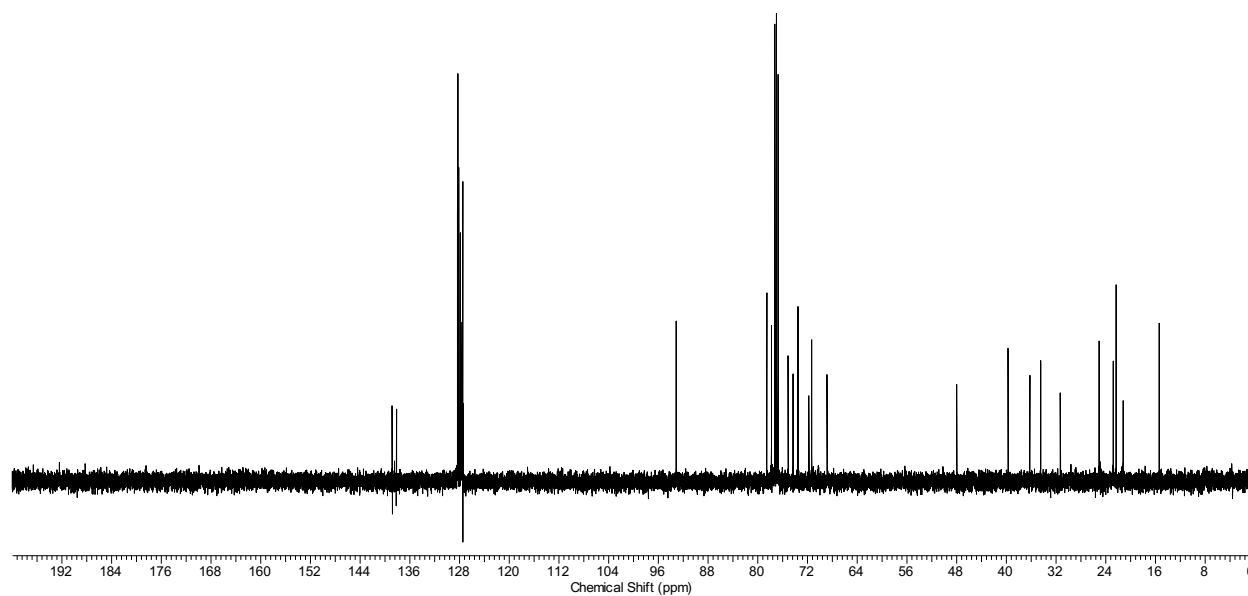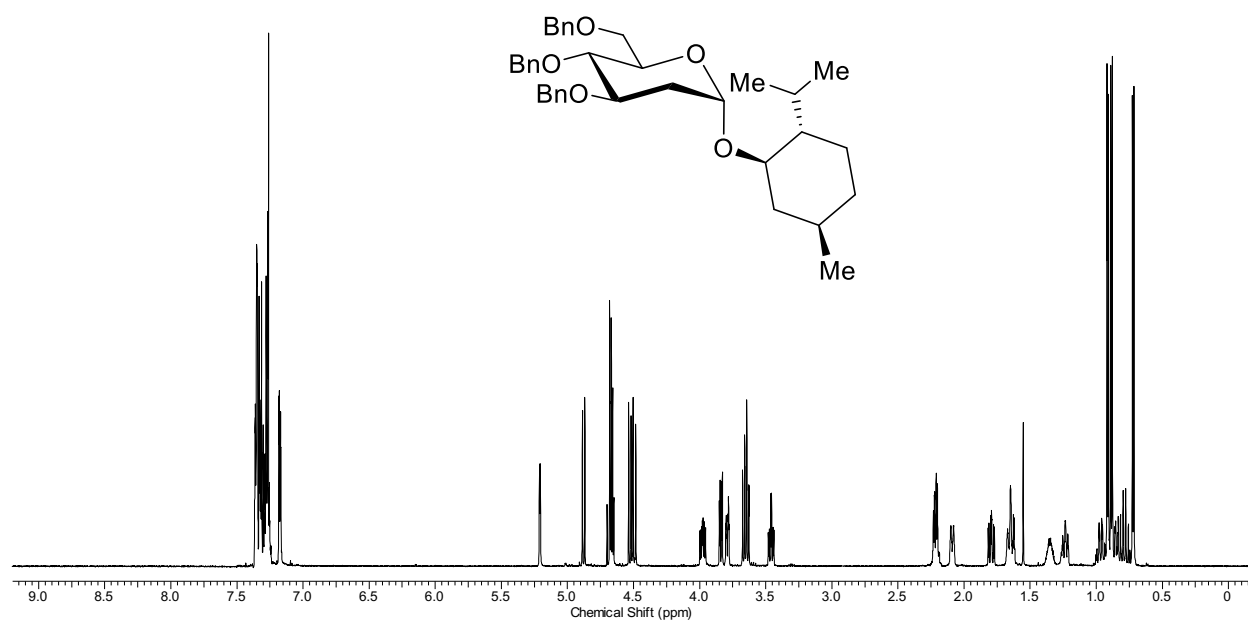
Methyl   (2,3,4-Tri-*O*-benzyl-6-deoxy-β-L-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside β-1.21:

Methyl (2,3,4-Tri-*O*-benzyl-6-deoxy-β-ʟ-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-α-ᴅ-galactopyranoside β-1.22
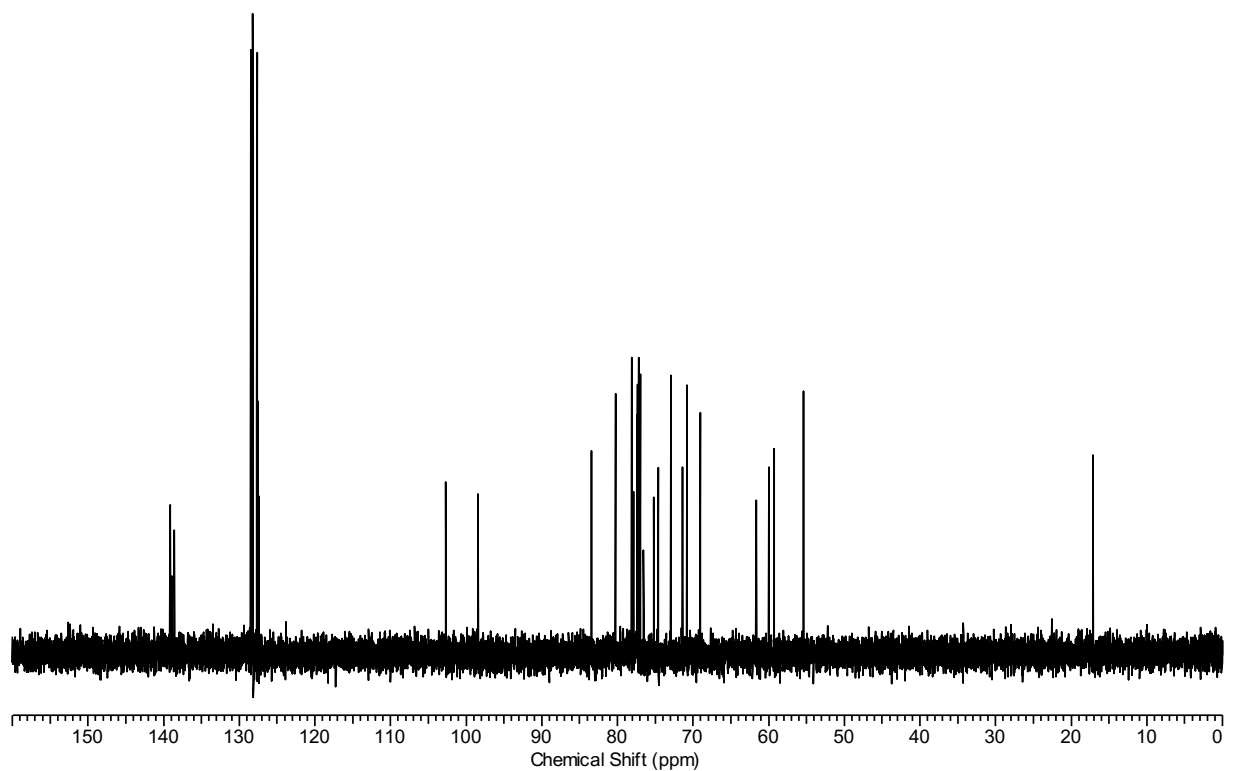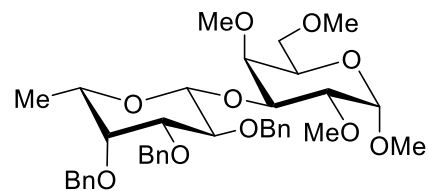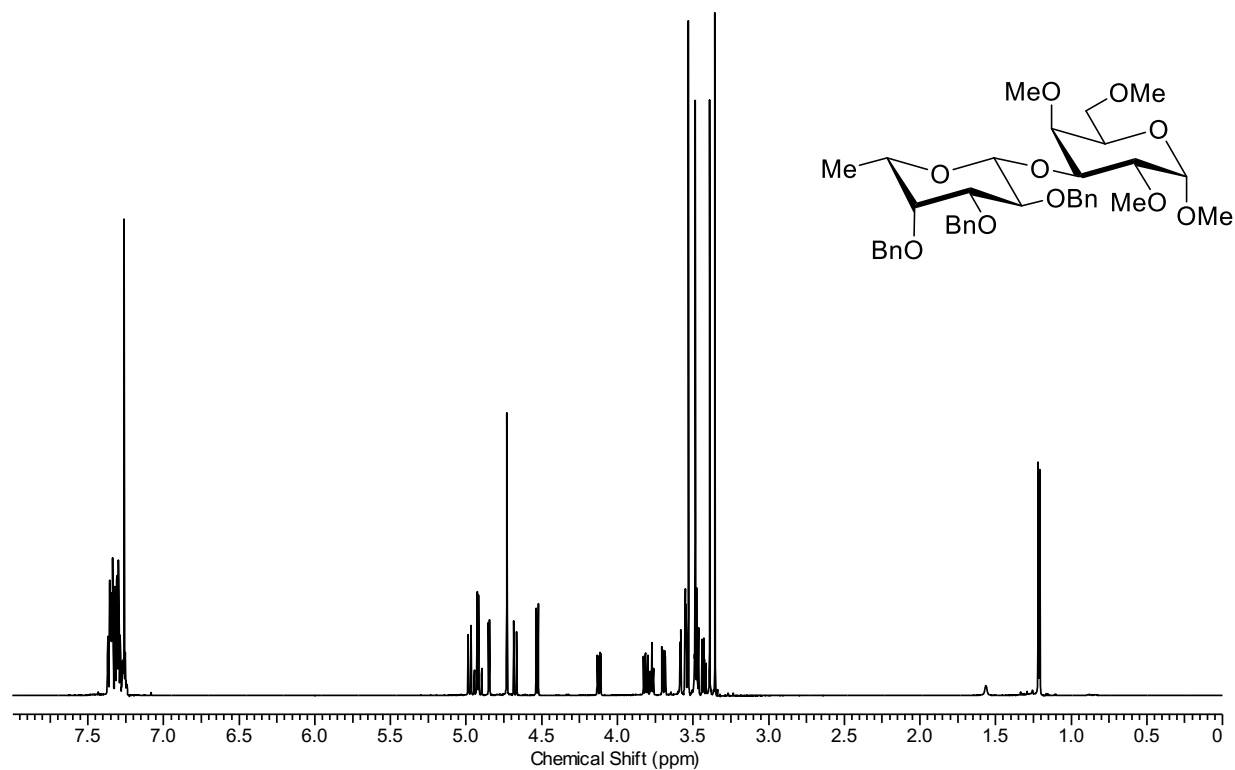
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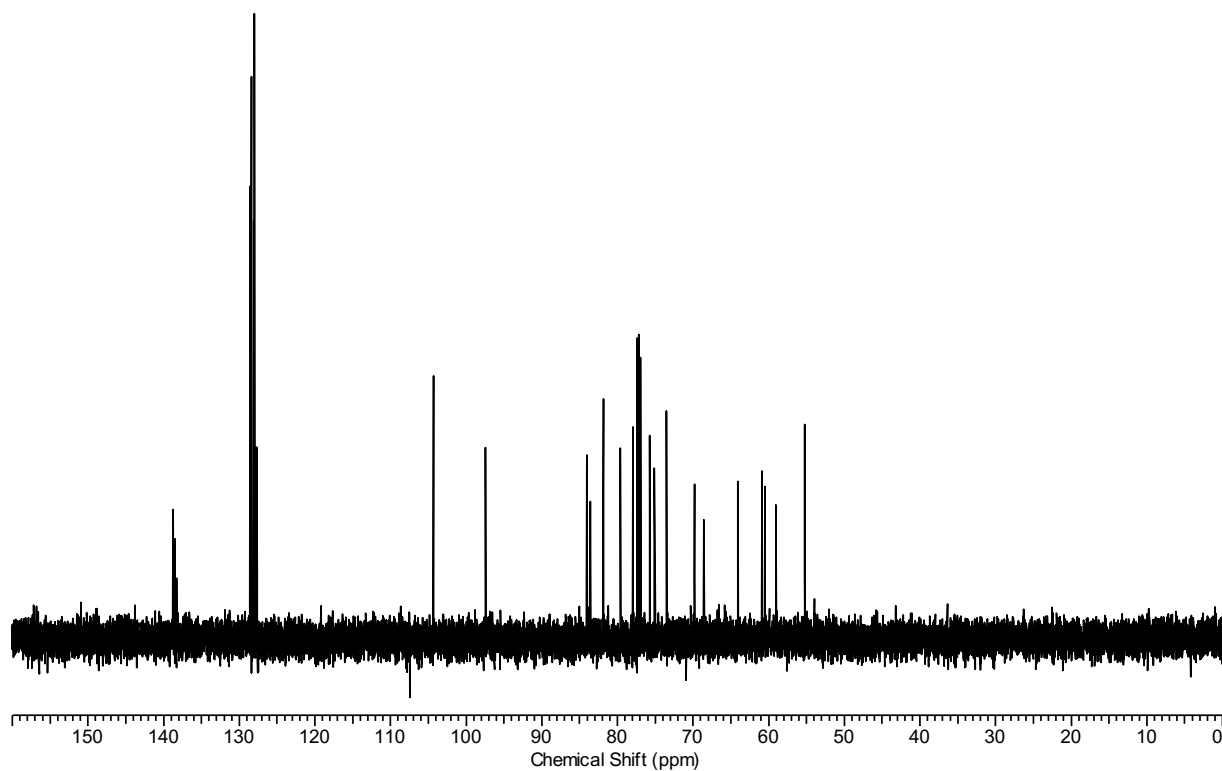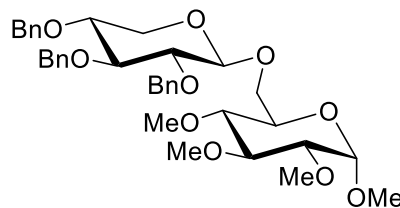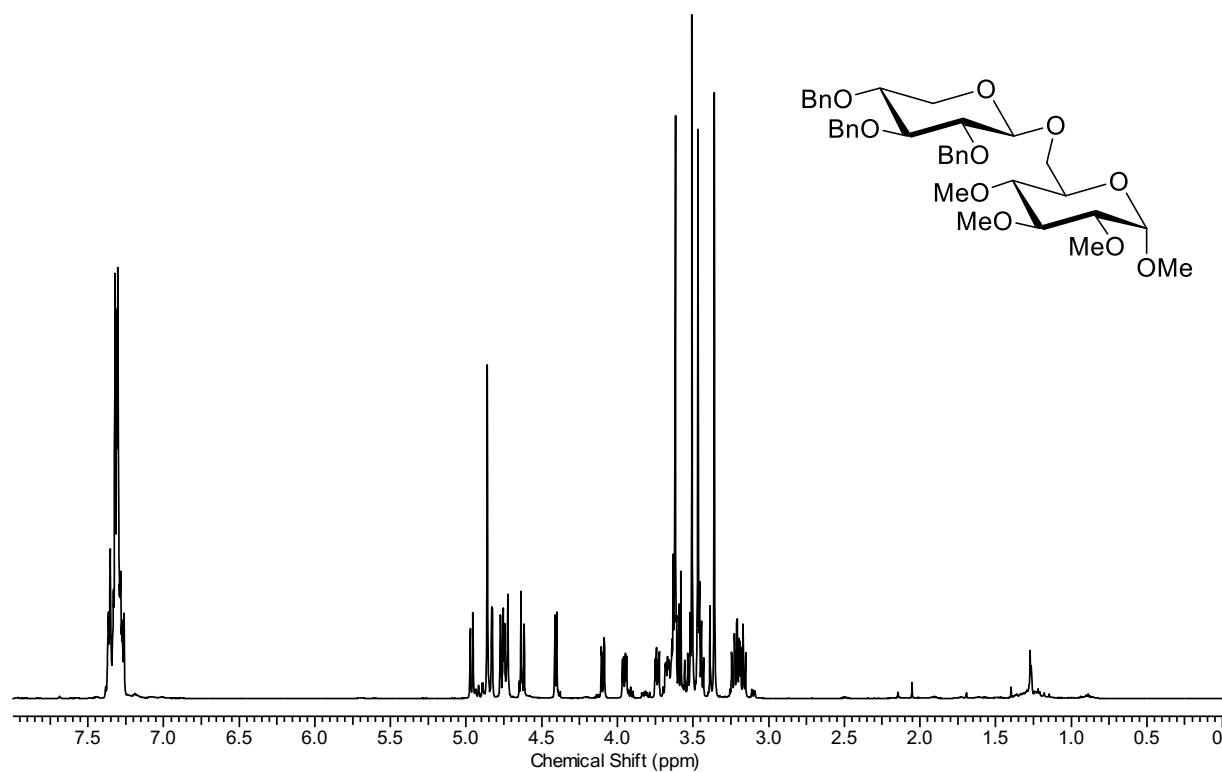
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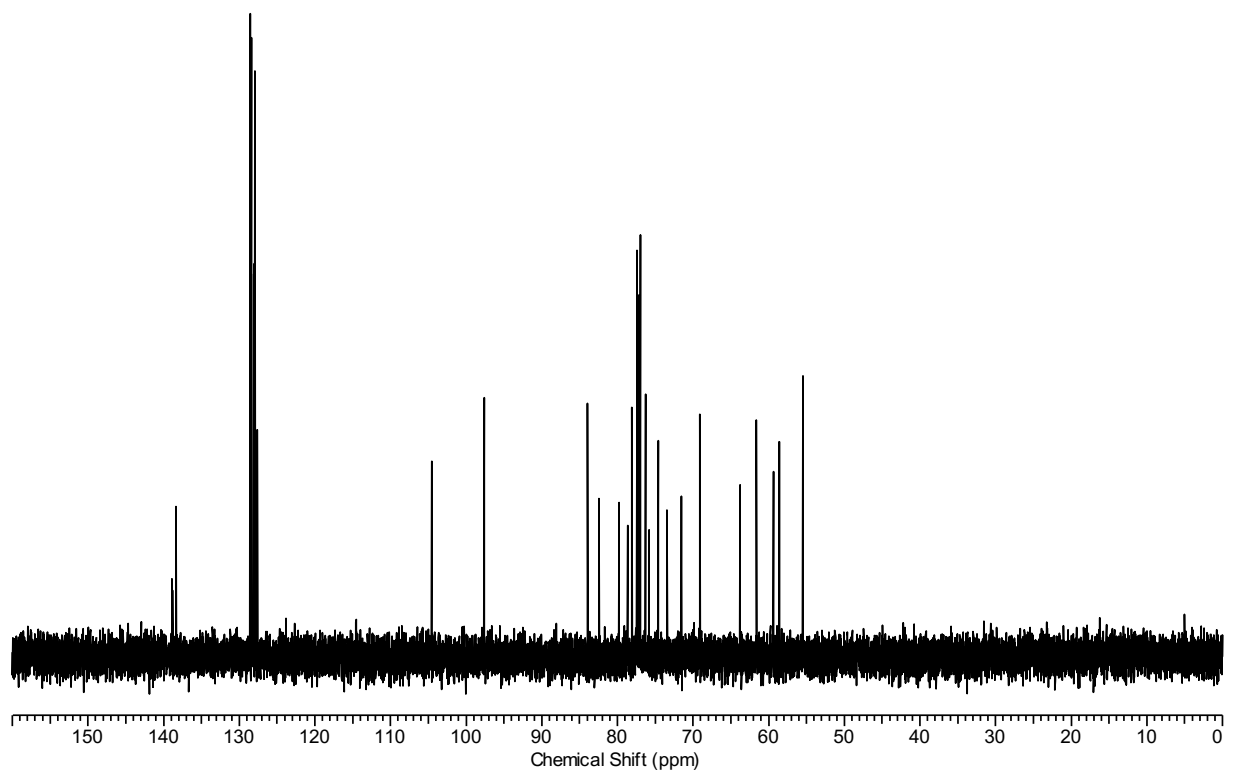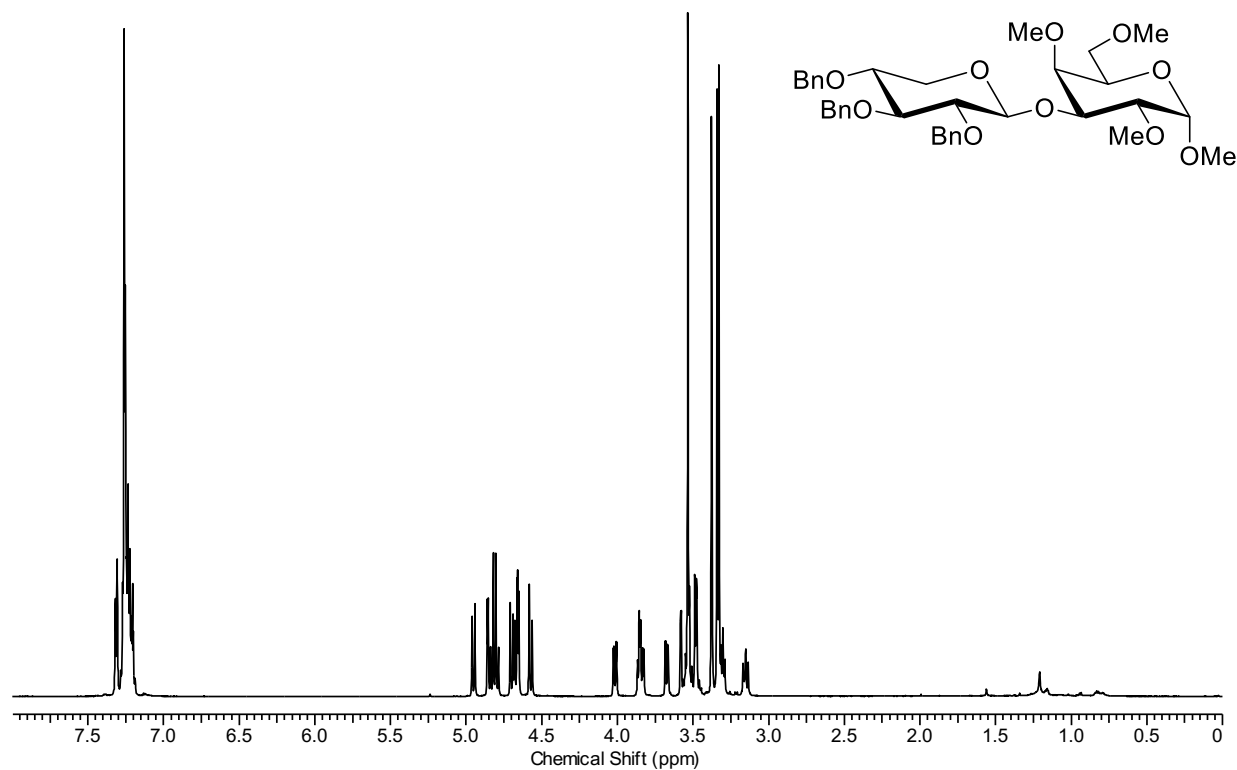
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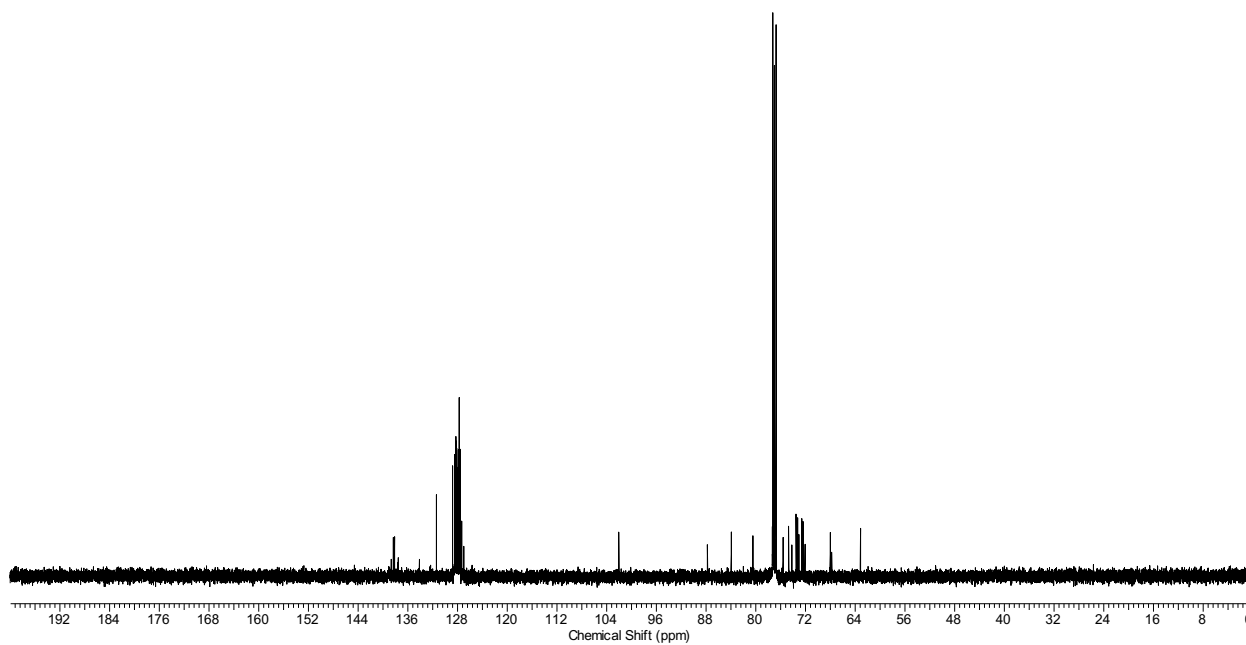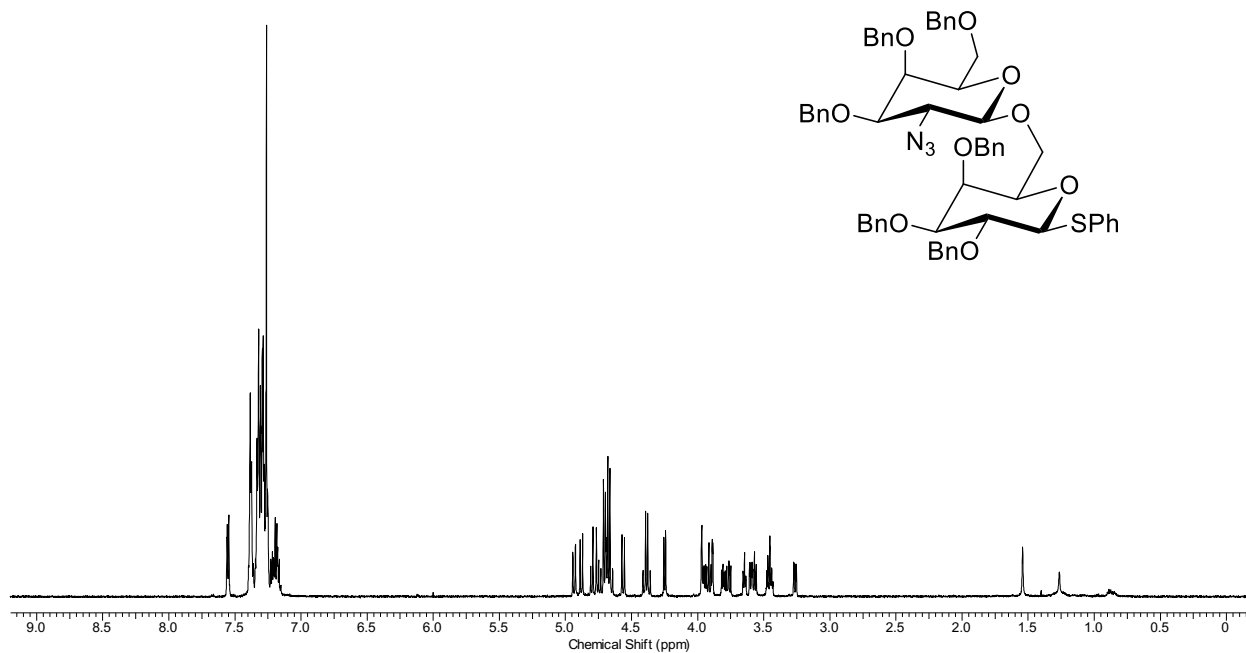
Thiophenyl (3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl- β -D-galactopyranoside α-1.25:
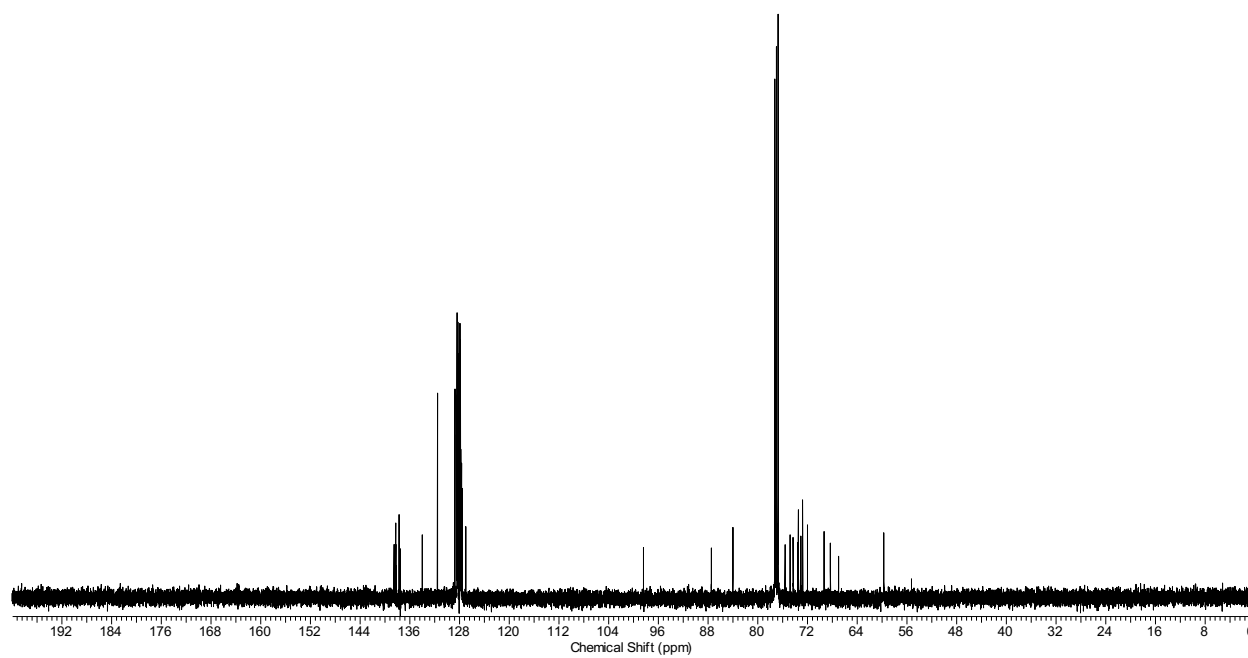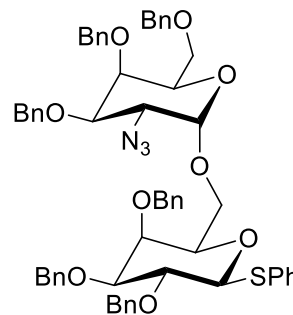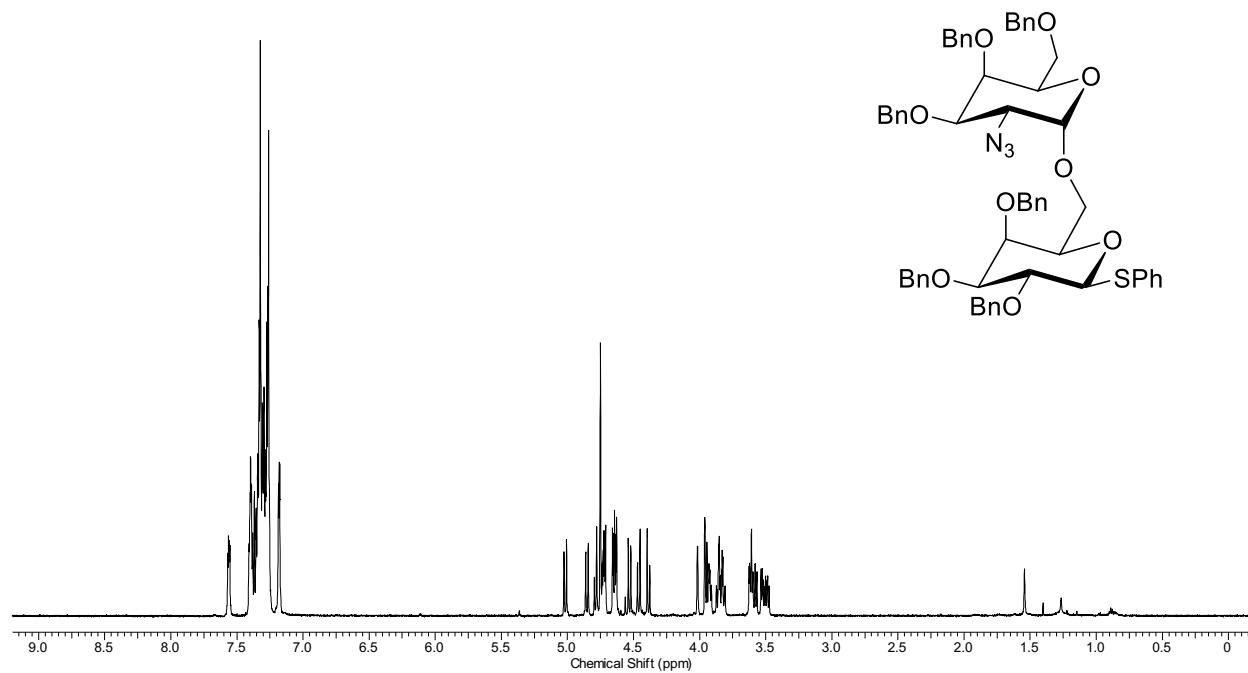
Methyl **(3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-**

methyl- β -D-galactopyranoside β-1.26:
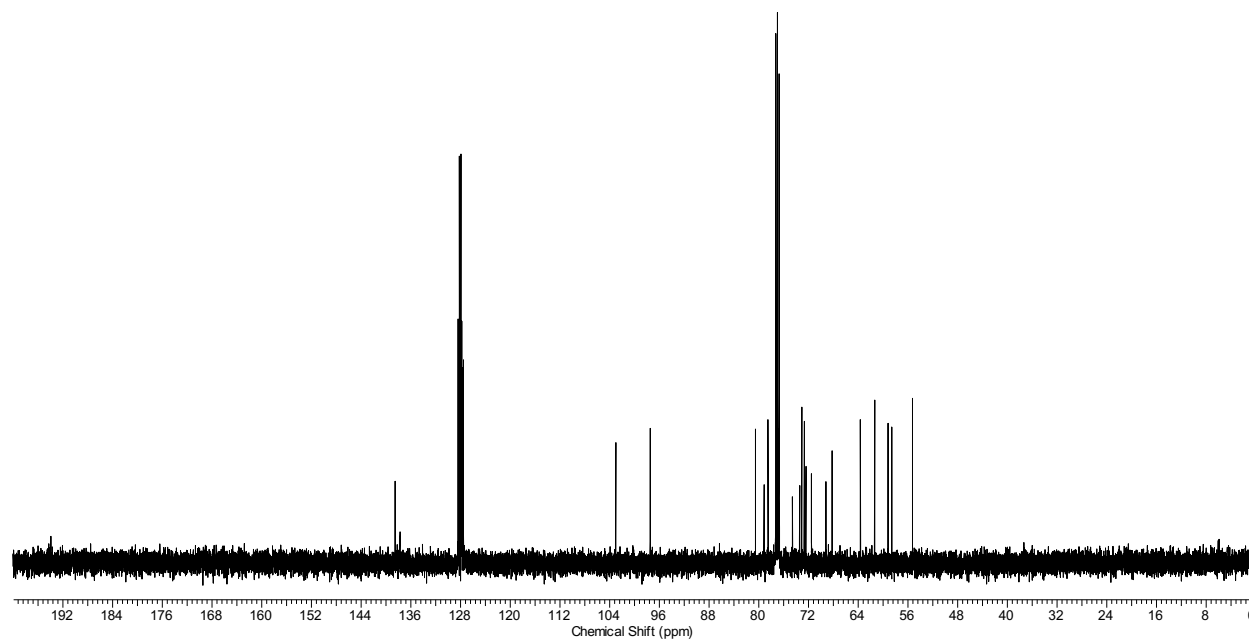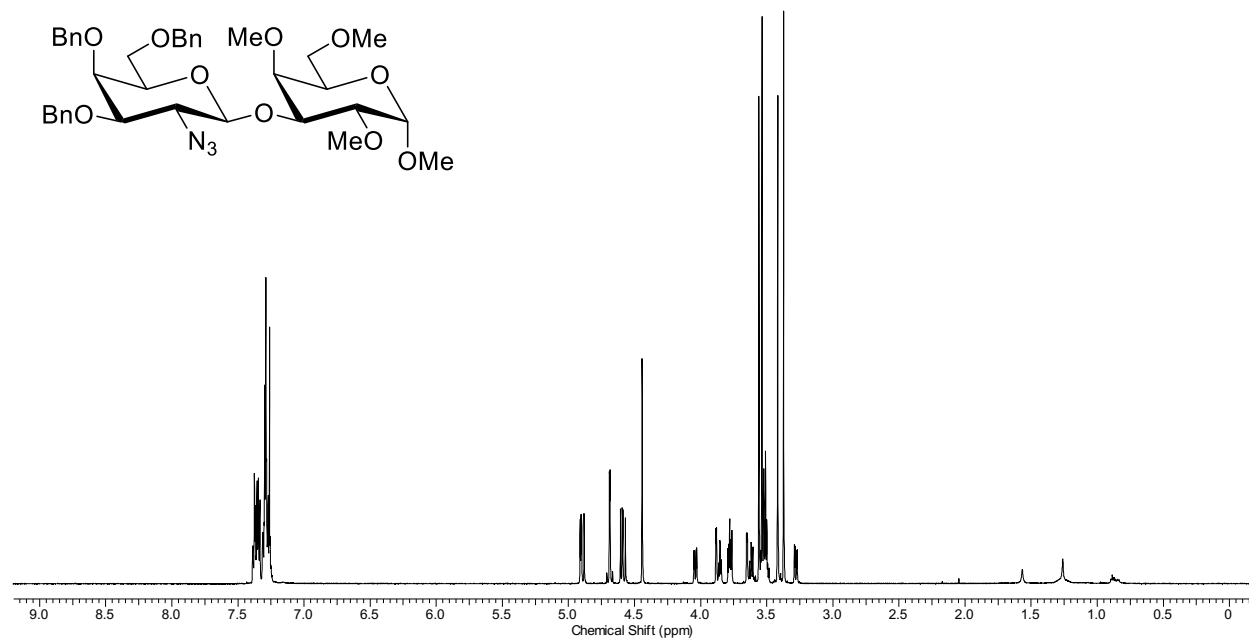
Methyl (3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl-β-D-galactopyranoside α-1.26:
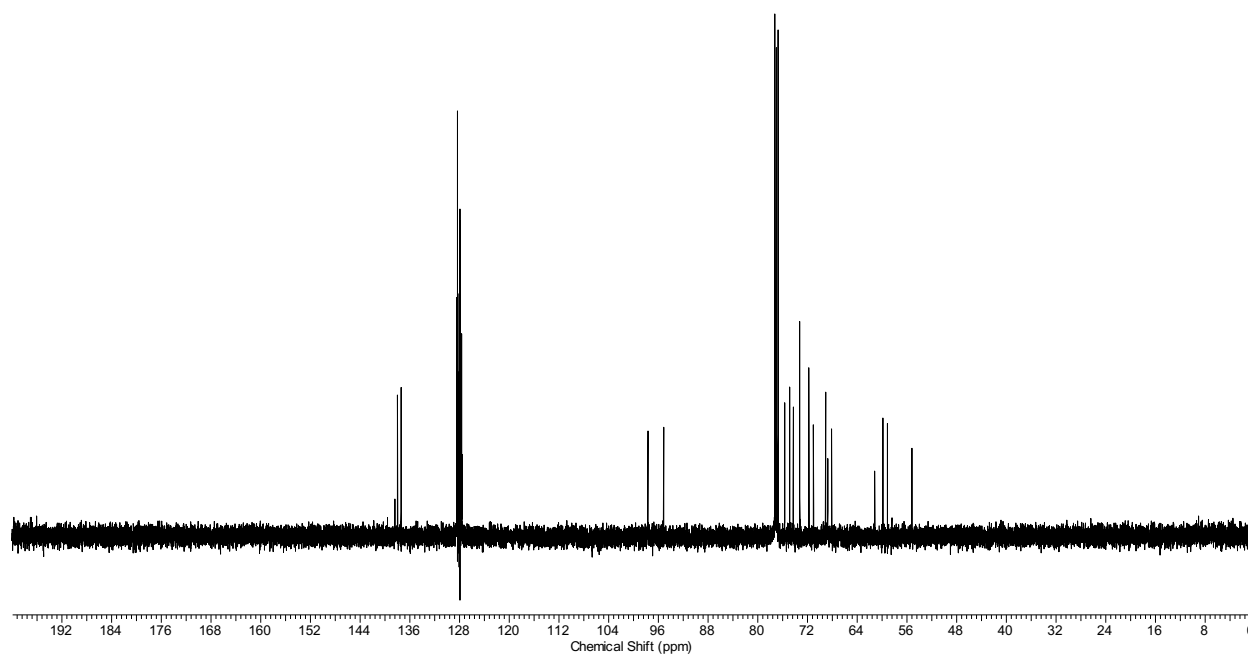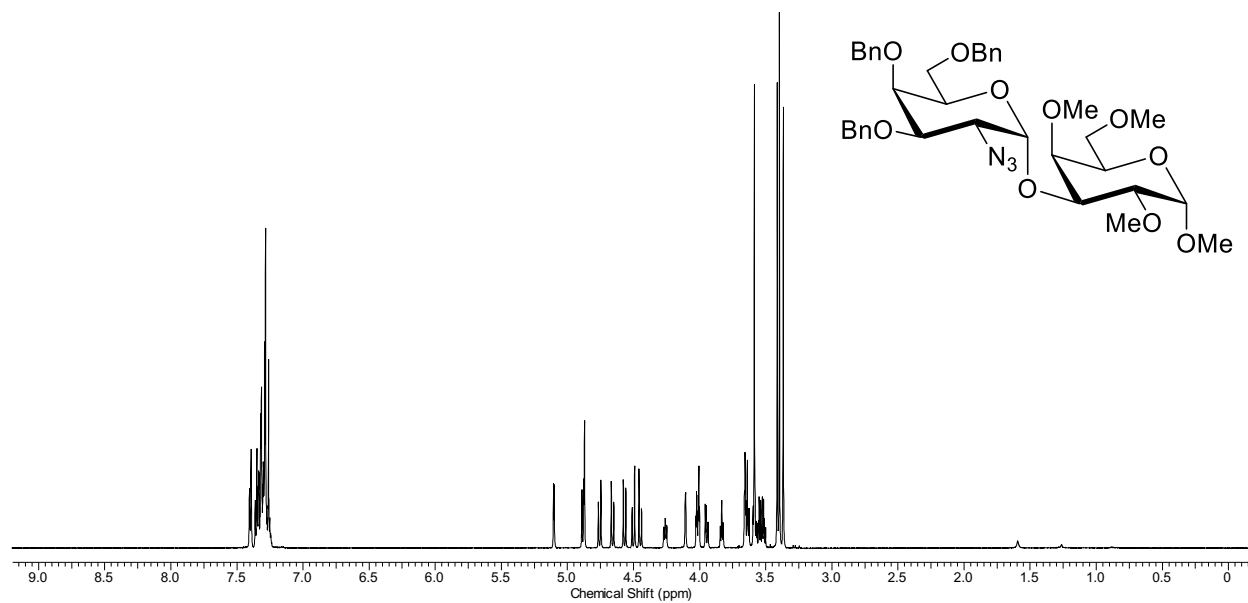
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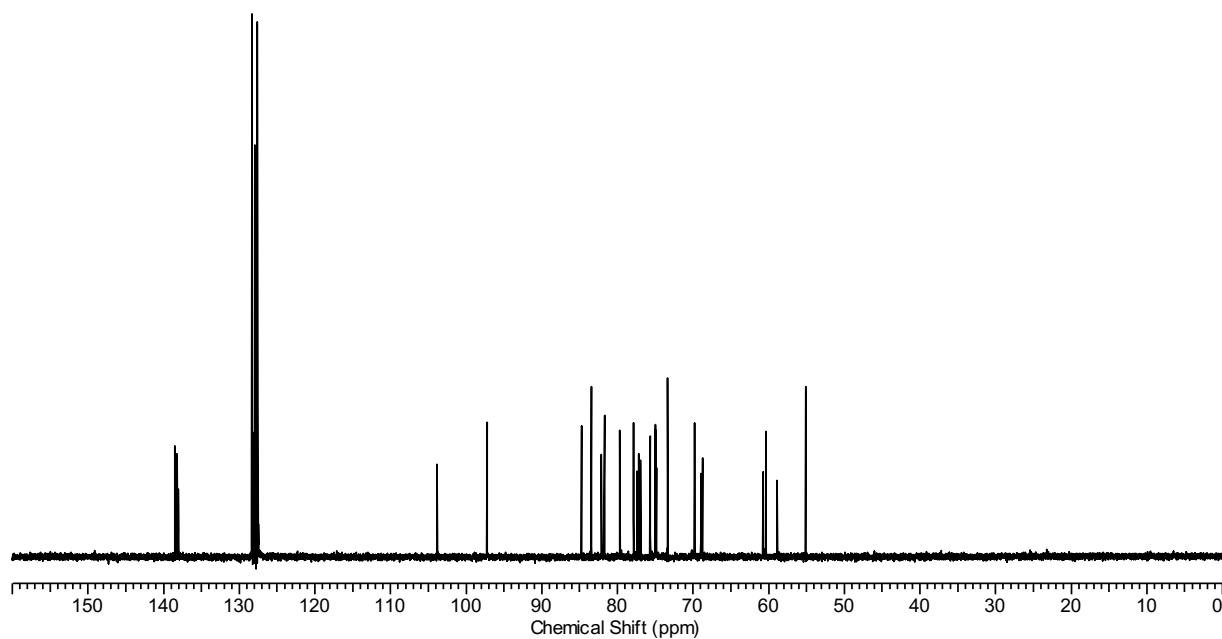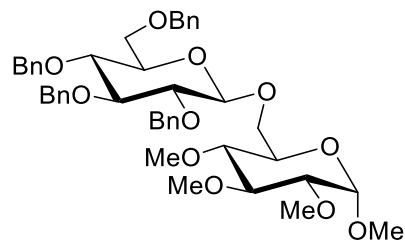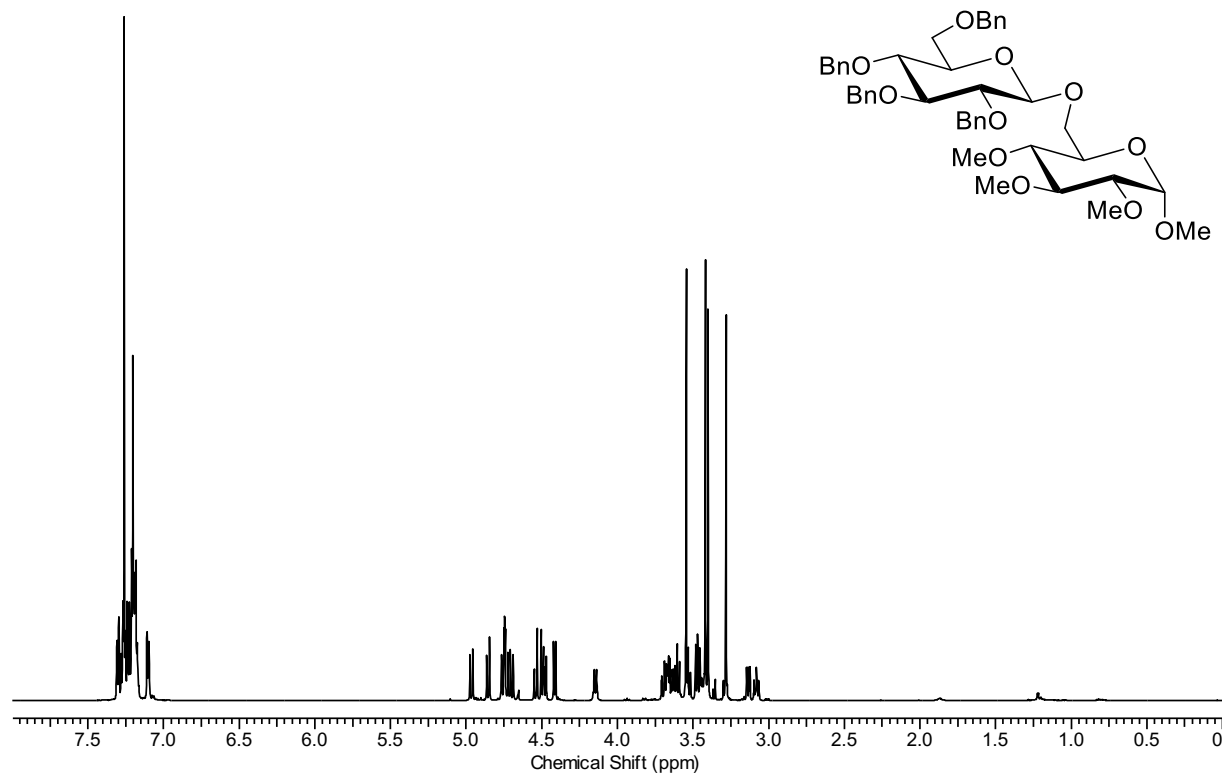
Methyl (3,4,6-Tetra-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside β-1.28:

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:
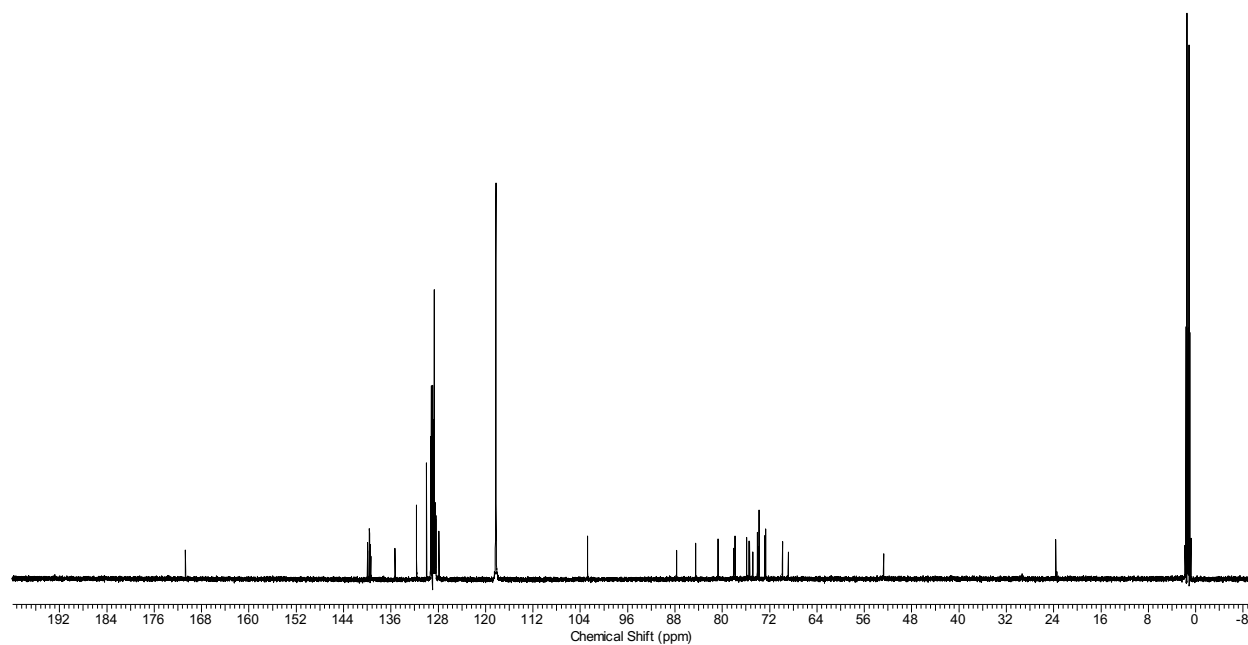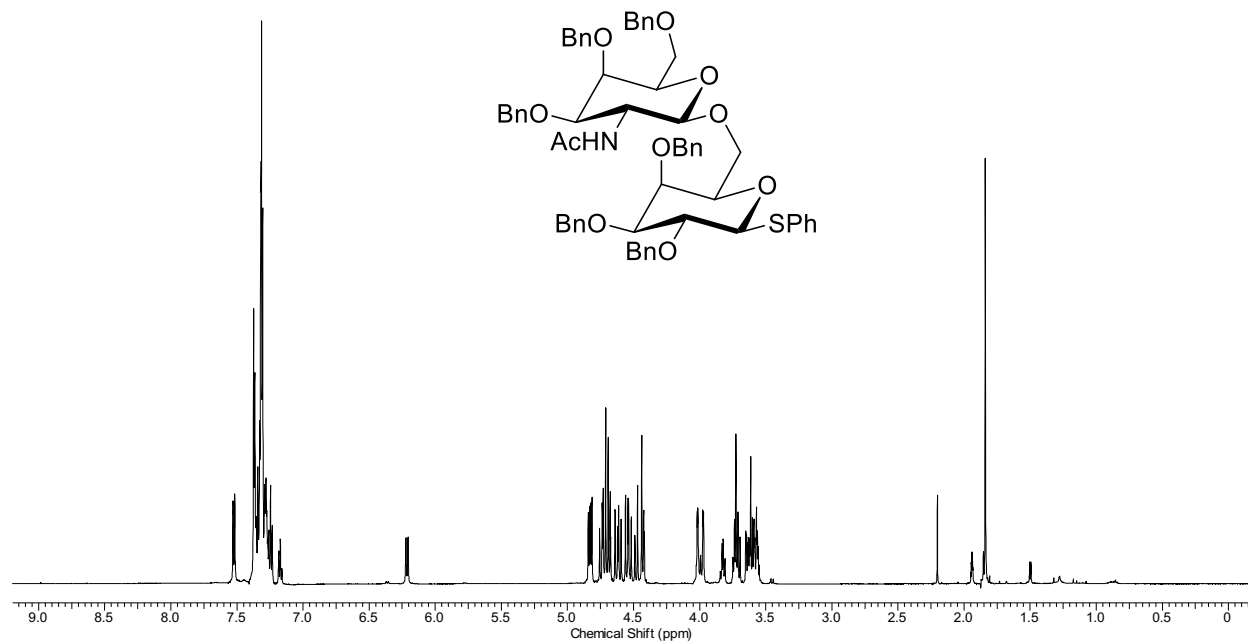
Thiophenyl (3,4,6-Tri-*O*-benzyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl- β -D-galactopyranoside α-1.29:
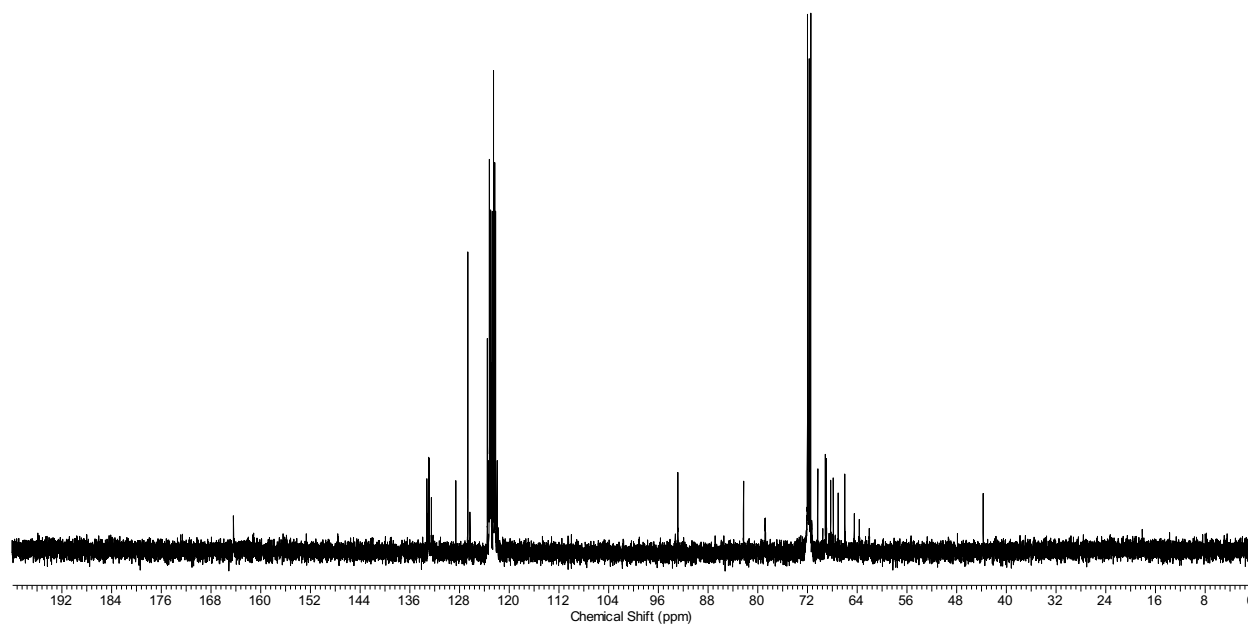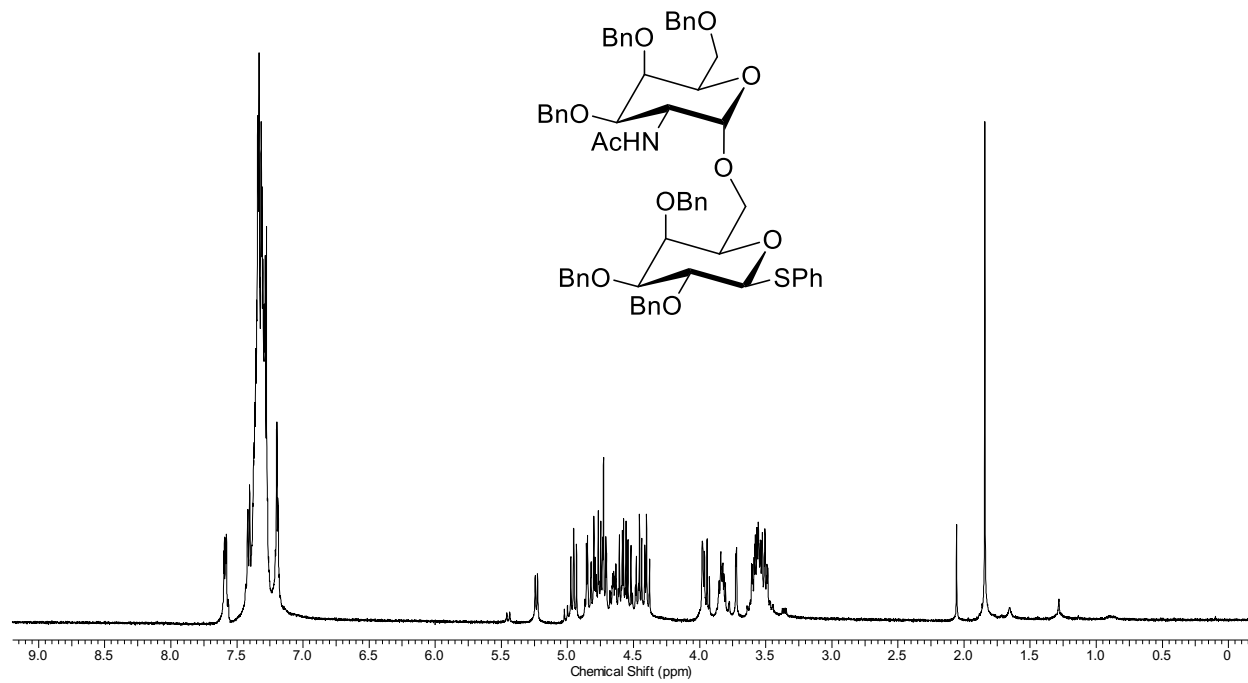
Methyl (3,4,6-Tri-*O*-benzyl-2-acetamido-2-deoxy-β-ᴅ-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl- β -ᴅ-galactopyranoside β-1.30:
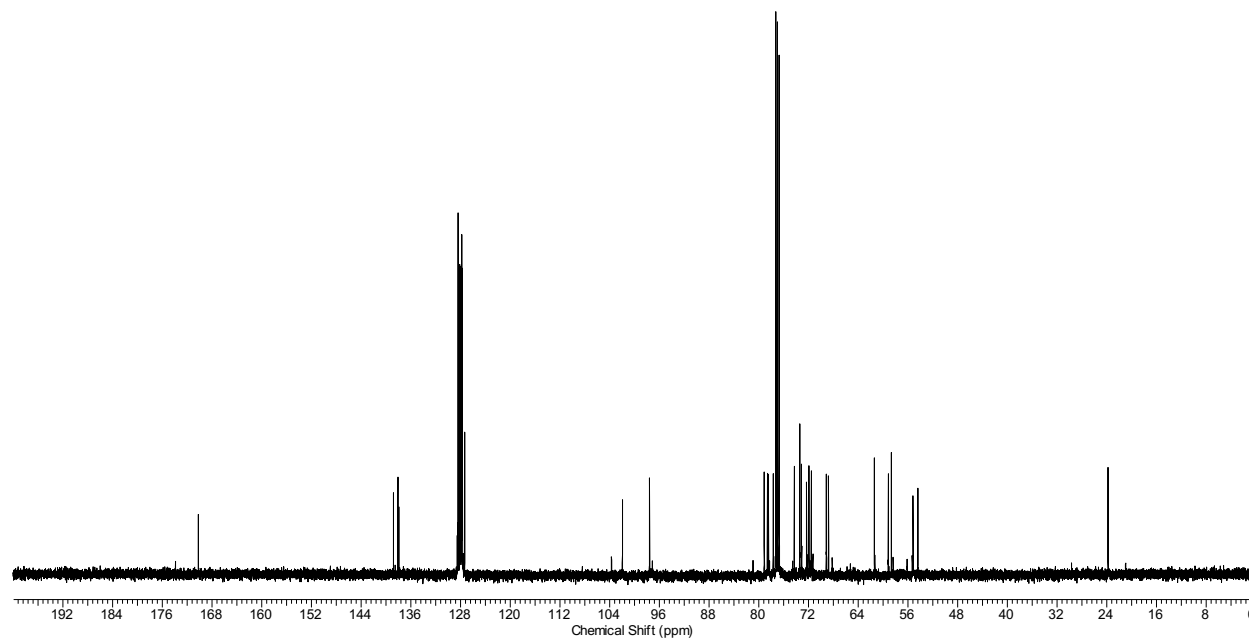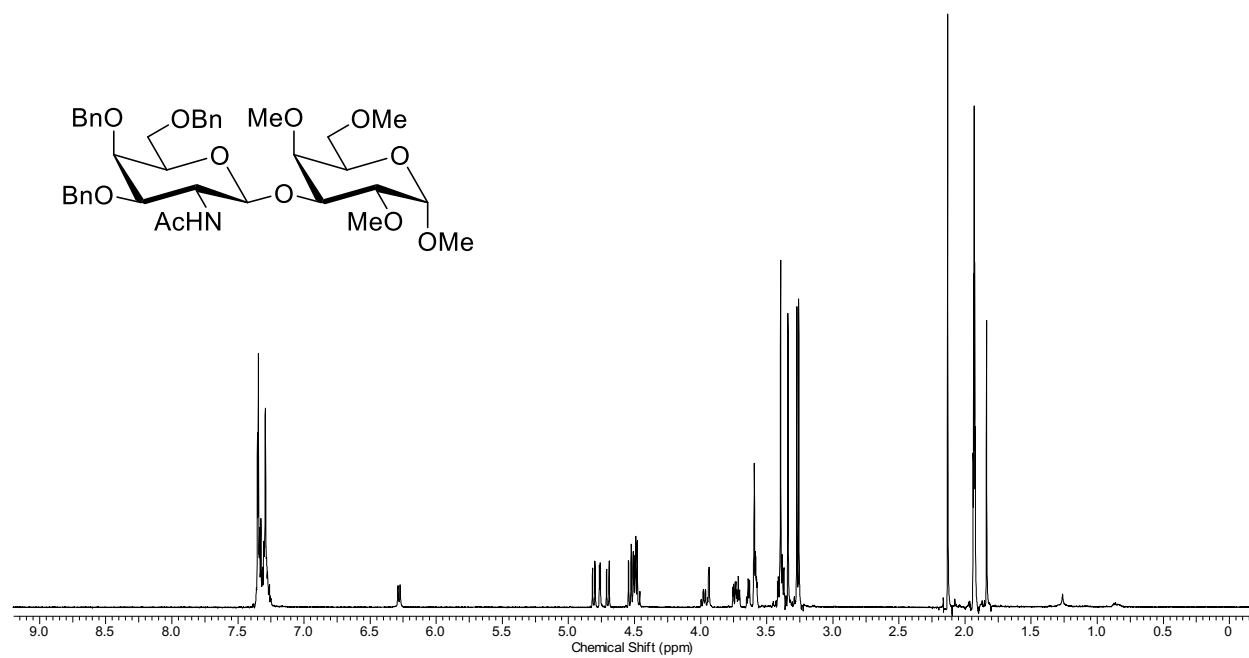
Methyl (3,4,6-Tri-*O*-benzyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-methyl- β -D-galactopyranoside α-1.30:

Thiophenyl (3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-β-ᴅ-galactopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl- β -ᴅ-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-methyl-α-ᴅ-glucopyranoside β-1.31:
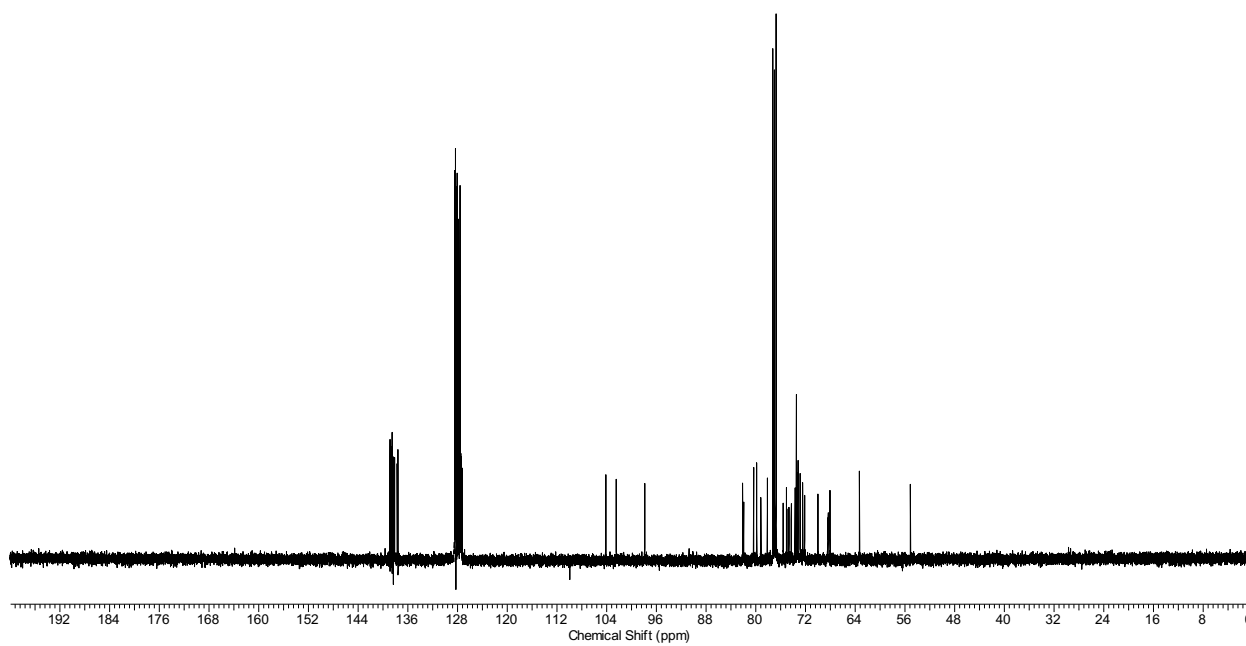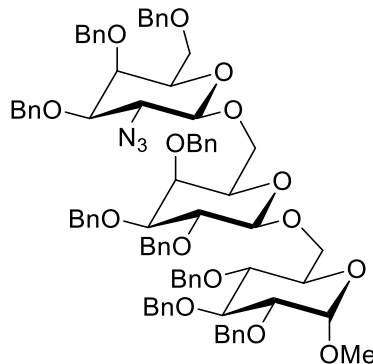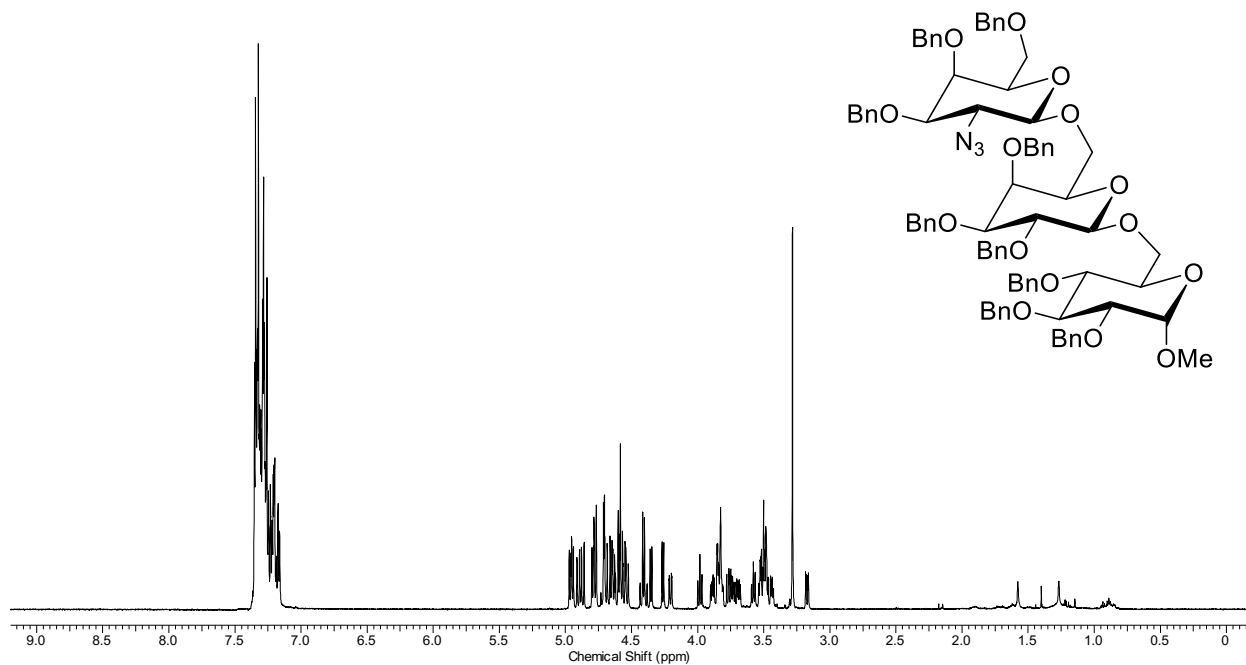
Enantioselective Aza-Sakurai Cyclizations: a Dual Role of Thiourea as H-bond Donor and Lewis Base[1]

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. [2] The aza-Sakurai cyclization, which involves the intramolecular reaction of an iminium ion with an allylsilane, represents a powerful method for constructing these heterocycles, [3] and diastereoselective variants of this transformation have enabled the efficient synthesis of naturally occurring compounds in this class (Figure 2.1). [4,5] 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*.

[2] (a) Roughley, S. D.; Jordan, A, M. *J. Med. Chem.* **2011**, *54*, 3451. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139.

[3] Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.

[4] Selected total syntheses using the aza-Sakurai cyclization: (a) Grieco, P. A.; Fobare, W. F. *J. Chem. Soc*., *Chem. Commun.* **1987**, 185. (b) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (c) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (d) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (e) Wang, Y.; Zhu, L.; Hong, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 2787. (f) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237.

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-Cl** would generate a chiral ion pair that could undergo an enantioselective aza-Sakurai cyclization to give bicyclic lactam **2.2** (Scheme 2.1).
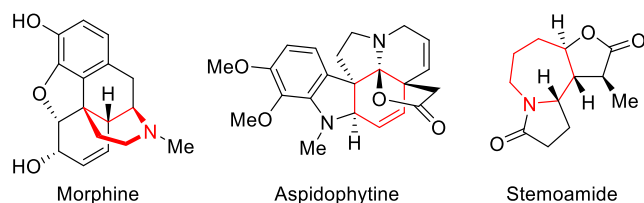
Figure 2.1. Natural products synthesized using the aza-Sakurai cyclization reaction.
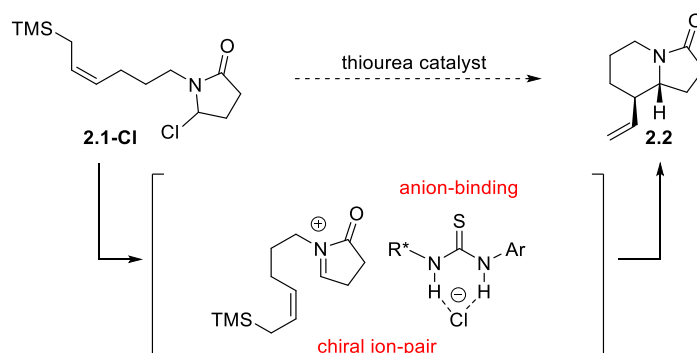
Scheme 2.1. Reaction design.

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[5] For reviews on the use of allylsilanes and related nucleophiles in, see: (a) Yus, M.; Gonzáles-Gómez, J. C.; Foubelo, F. Chem. Rev. **2011**, *111*, 7774. (b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173. (c) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (d) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293-1316.

[6] For reviews on reactions involving N-acyliminium intermediates, see: (a) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

[7] (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126,* 10558. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44,* 6700. (c) Raheem, I. T.; Thiara, P. V.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (d) Raheem, I. T.; Thiara, P. V.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (e) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6446. (f) Knowles, R. R.; Lin, S.: Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

[8] Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534.

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).[9] 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).[10] 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.[11] 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.[12]

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[9] An unactivated alkene showed no signs of reactivity.

[10] See Section 2.6.7 for details

[11] (a) Zhang, H.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 16485. (b) Yeung, C. S.; Ziegler, R. E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2014**, *136*, 13614. (c) Lin, S.; Jacobsen, E. N. *Nature Chem.* **2012**, *4*, 817. (d) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564. (e) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872.

[12] UV/Vis experiments with benzhydryl chloride show **2.3d** is more Lewis basic than **2.3c**, but **2.3e** and **2.3f** are equally Lewis basic. Obtained by Andreas Rötheli.

Table 2.1. Catalyst optimization[a]
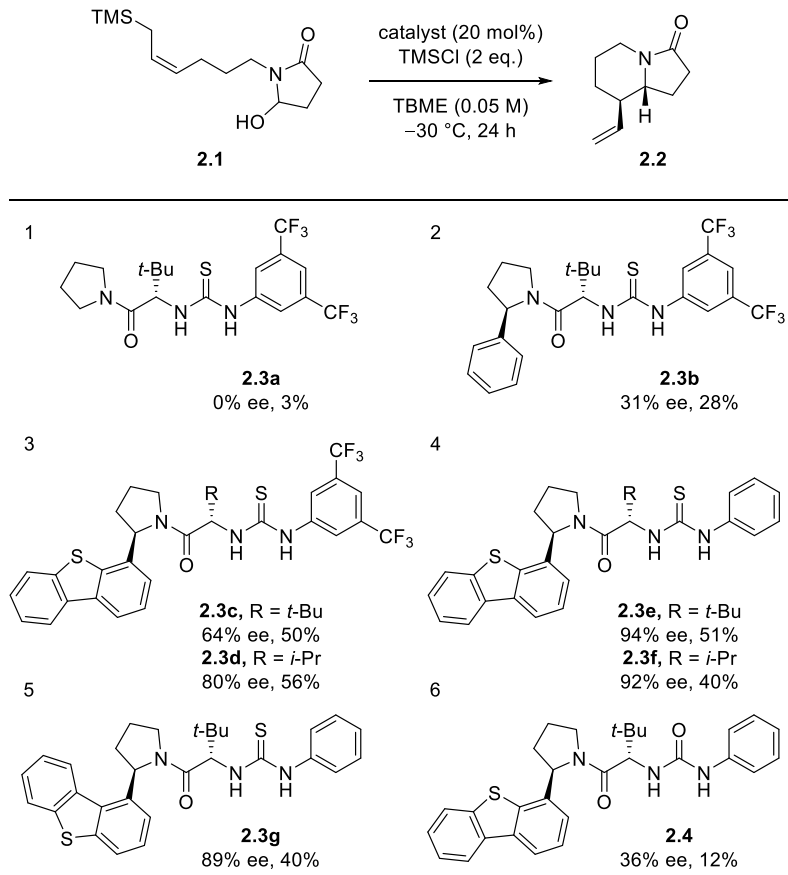
a. Reactions run on a 0.05 mmol scale. Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns. Yields determined by GC analysis relative to dodecane as an internal standard.

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[13] of **ent-2.2**,[14] followed by a global reduction gave (–)-tashiromine in 90% yield over two steps.[15] The same two-step sequence from **2.10** afforded (+)-epi-lupinine in 72% yield.[16]
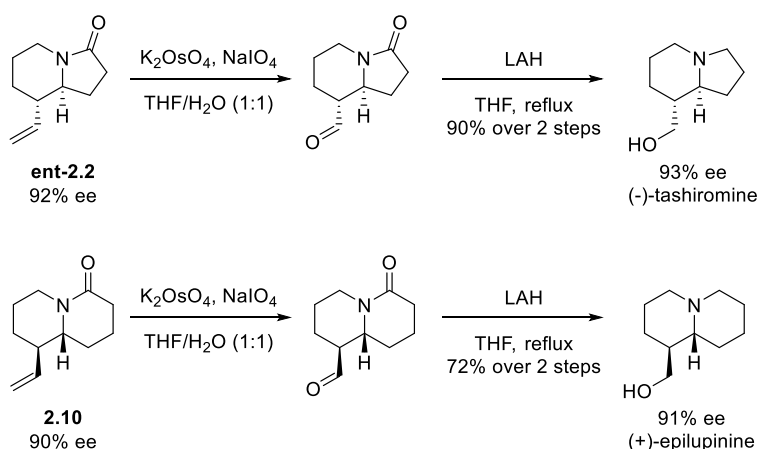
Scheme 2.2. Total synthesis of (–)-tashiromine and (+)-epilupinine

[13] Poppo, R.; Allen, Jr., D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem*. **1956**, *21*, 478.
[14] Ent-2.**2** was obtained using ent-2.**3e**.
[15] Cutter, A. C.; Miller, I. R.; Kelly, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett*. **2011**, *13*, 3988.
[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[a]

entry	substrate	product	yield[b]	ee[c]
1	**2.1**	**2.2**	85	91
2[d]	**2.5**	**2.6**	72	90
3[e]	**2.7**	**2.8**	82	94
4[d,f]	**2.9**	**2.10**	90	90
5[g]	**2.11**	**2.12**	93	94
6[g]	**2.13**	**2.14**	83	92
7[h]	**2.15**	**2.16**	85	88

a. Reactions run on a 0.2 mmol scale. b. Isolated yields. c. Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns. d. Reaction run using 20 mol % thiourea catalyst. e. Reaction run for 3 days. f. Reaction run for 1 day. g. Reactions run at −30 °C. 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**).[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**.[18]

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 β-silyl cation.

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[17] (a) Mayr, H.; Hagen, G. *J. Chem. Soc.*, *Chem. Commun.* **1989**, 91-92. (b) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.

[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.
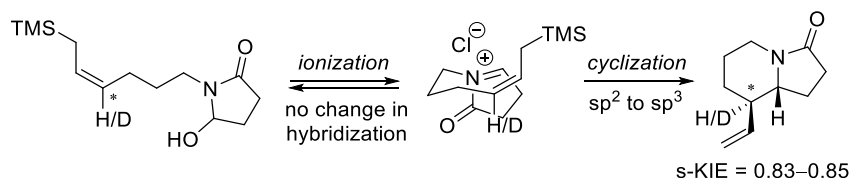
Table 2.3. Effect of silicon Lewis acidity on reaction rate[a]
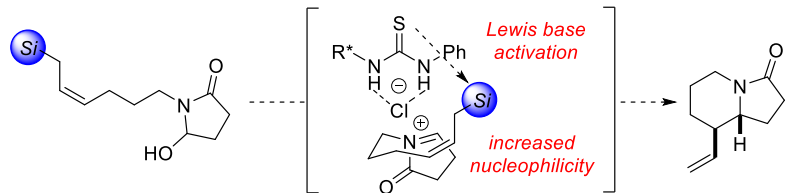
Relative rates of consumption

entry	substrate	thiourea (**2.3e**)	urea (**2.4**)
1	**2.1** (Me₃Si)	1 (defined) 92% ee	0.13 28% ee
2	**2.17** (i-Pr₃Si)	0.14 33% ee	0.27 41% ee
3	**2.18** (HMe₂Si)	1.79 89% ee	0.09 26% ee

a. Relative rates were assigned by comparing the initial rates of each system. See the Supporting Information for details.
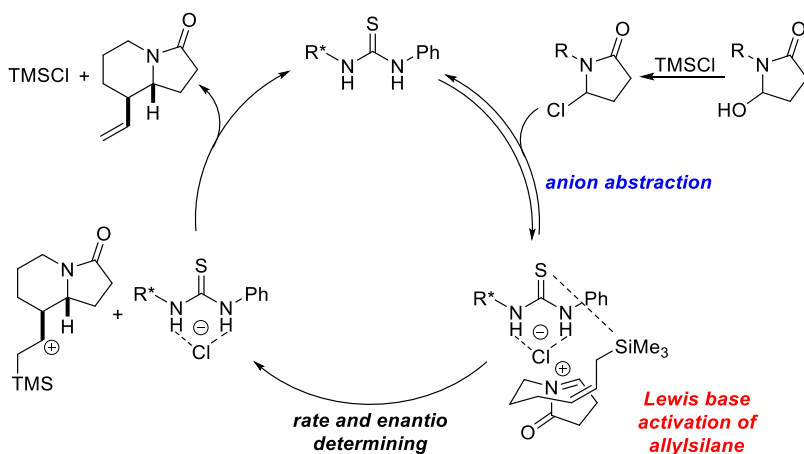
Scheme 2.3. Proposed Catalytic Cycle

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_6D_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, C6D6: 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:
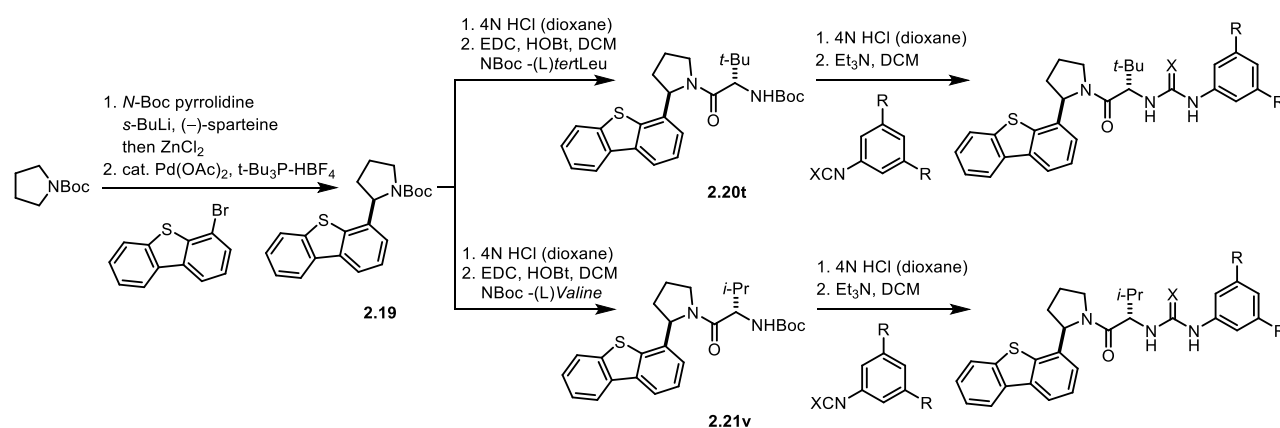
Scheme 2.4. Synthesis of catalysts **2.3** and **2.4**.

(*R*)-*tert*-butyl 2-(dibenzothiophen-4-yl)pyrrolidine-1-carboxylate (2.19).
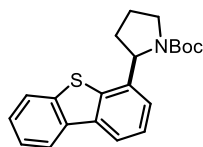
The preparation follows a procedure described by Campos and coworkers for the Palladium-catalyzed α-arylation of *N*-Boc-pyrrolidines.[19] To a solution of *N*-Boc-pyrrolidine (2.0 mL, 11.4 mmol) and (−)-sparteine (2.6 ml, 11.4 mmol) in MTBE (24 mL) at -78˚C was added s-BuLi (9.6 mL, 11.4 mmol, 1.2 M 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 ZnCl$_2$ (6.4 mL, 6.8 mmol, 1.0 M

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[19] Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

in Et$_2$O) 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-Bromodibenzothiophene[20] (2.5 g, 9.5 mmol) was subsequently added followed by Pd(OAc)$_2$ (102 mg, 0.46 mmol) and *t*-Bu$_3$P-HBF$_4$ (164 mg, 0.57 mmol). Stirring at room temperature was continued for 12 hours. NH$_4$OH 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 Na$_2$SO$_4$ 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.

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

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 C$_{21}$H$_{23}$NO$_2$SNa: 376.1347; found: 376.1356.

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[20] Rossi, R.; Bellina, F.; Ciucci, D.; Carpita, A.; Fanelli, C. *Tetrahedron* **1998**, *54*, 7595.

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

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-*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 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 (2.89 g, 89% yield).

Compound **2.20t** is characterized as a mixture of rotamers.

$[\alpha]_D^{22}$ = +18.5° (c = 0.50, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17–8.09 (m, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.90–7.75 (m, 1H), 7.50–7.39 (m, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 5.44 (dd, J = 2.0, 7.8 Hz,

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-butyl ((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_2SO_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.

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

^{1}H NMR (500 MHz, CDCl$_3$) δ 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$_3$) δ 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 NH_4OH 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_2SO_4, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et_3N (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.

$[\alpha]_D^{24} = -13.1°$ (c = 0.50, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) 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, 4H), 1.19–1.09 (m, 9H), 0.62 (s, 2H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 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)

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.

$[\alpha]_D^{23} = -106°$ (c = 1.0, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 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$_3$) δ 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_2SO_4, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et_3N (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° (c = 0.50, CHCl$_3$);

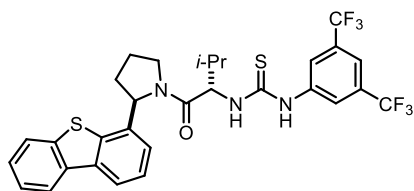^{1}H NMR (500 MHz, CDCl$_3$) δ 8.20–8.07 (m, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.97–7.83 (m, 1H), 7.70 (br. s., 1H), 7.55–7.36 (m, 4H), 7.31 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.8 Hz, 2H), 7.14 (d, J = 7.3 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.61 (br. s., 1H), 5.50 (d, J = 9.3 Hz, 1H), 5.38 (dd, J = 2.2, 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$_3$) δ 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 $C_{29}H_{31}N_3OS_2Na$: 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 NH_4OH 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_2SO_4, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et_3N (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.
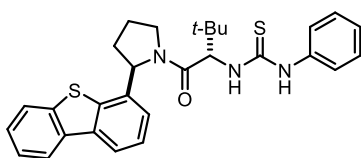
$[\alpha]_D^{23} = +39.6°$ (c = 0.50, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{28}H_{29}N_3OS_2Na$: 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).
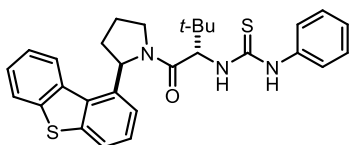
The thiourea catalyst **2.3g** was prepared following the general reaction sequence described above from 1-bromodibenzothiophene.[21]

Compound **2.3g** is characterized as a mixture of rotamers.

$[\alpha]_D^{23}$ = –2.0° (c = 0.50, CHCl$_3$);

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

^{13}C NMR (125 MHz, CDCl$_3$) δ 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,

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[21] Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *J. Org. Chem*. **2006**, *71*, 6291–6294.

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 $C_{29}H_{31}N_3OS_2Na$: 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 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 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.

$[\alpha]_D^{23} = -27.9°$ (c = 0.50, CHCl$_3$);

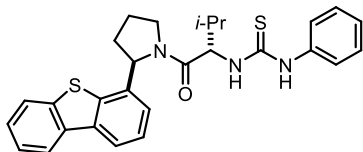137

^{1}H NMR (500MHz, CDCl$_3$) δ 8.07 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.50–7.31 (m, 3H), 7.25–7.22 (m, 1H), 7.22–7.09 (m, 7H), 7.05–6.90 (m, 2H), 6.86 (br. s., 1H), 5.85 (br. s., 1H), 5.44–5.33 (m, 1H), 4.80 (s, 1H), 4.40 (br. s., 1H), 3.92–3.83 (m, 1H), 2.43–2.24 (m, 1H), 2.18–1.96 (m, 4H), 1.15–1.00 (m, 9H), 0.91 (d, J = 14.6 Hz, 1H), 0.58 (s, 2H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 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
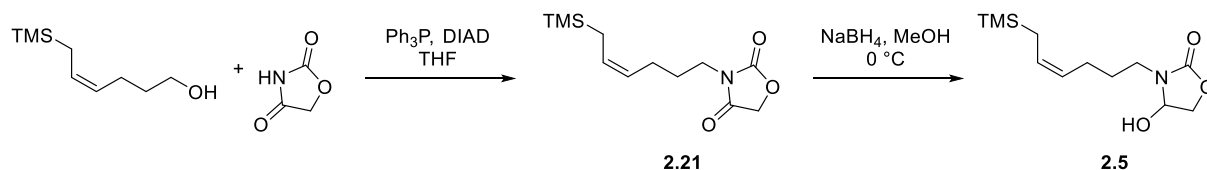
Scheme 2.5. Synthesis of **2.5**.

(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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[22] Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014–4020.

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_2SO_4 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.

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 $C_{12}H_{21}NNaO_3Si$ (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 NaBH$_4$ (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. 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_2SO_4 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$_3$) δ 5.49–5.41 (m, 1H), 5.30–5.21 (m, 2H), 4.39 (dd, J = 6.8, 10.4 Hz, 1H), 4.14 (dd, J = 2.0, 10.4 Hz, 1H), 3.41 (ddd, J = 6.8, 8.8, 14.4 Hz, 1H), 3.31–3.23 (m, 2H), 2.03 (q, J = 7.2 Hz, 2H), 1.73–1.60 (m, 2H), 1.45 (d, J = 8.8 Hz, 2H), 0.00 (s, 9H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 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]
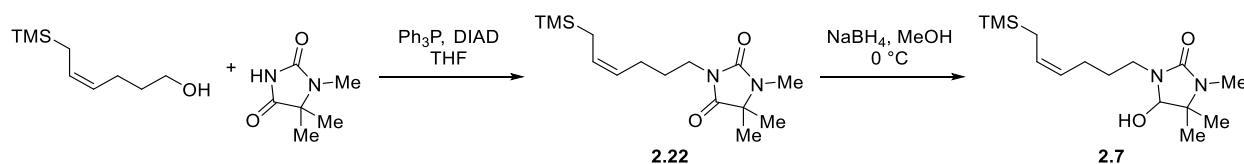
Scheme 2.6. Synthesis of **2.7**.

(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 *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.

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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) 2951, 1770, 1708, 1410, 1384, 1247, 1152, 855 cm^{-1};

HRMS (ESI) found 319.1817 [calcd for C$_{15}$H$_{28}$N$_2$NaO$_2$Si (M+Na) 319.1818]

(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 NaBH$_4$ (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. 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 **2.7** (106 mg, 86%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.44–5.38 (m, 1H), 5.29–5.24 (m, 1H), 4.59 (d, J = 11.5 Hz, 1H), 3.44 (ddd, J = 7.0, 9.0, 14.0 Hz, 1H), 3.13 (ddd, J = 5.5, 8.5, 14.0 Hz, 1H), 2.68 (s, 3H), 2.05–1.97 (m, 2H), 1.67–1.52 (m, 2H), 1.45 (d, J = 9.0 Hz, 2H), 1.26 (s, 3H), 1.13 (s, 3H), 0.00 (s, 9H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 158.5, 126.3, 126.1, 85.7, 59.5, 39.5, 28.2, 24.4, 24.3, 23.0, 19.1, 18.4, –1.9;

IR (neat, cm^{-1}) 3302, 2953, 1672, 839;

HRMS (ESI) found 321.1977 [calcd for $C_{15}H_{30}N_2NaO_2Si$ (M+Na) 321.1974]
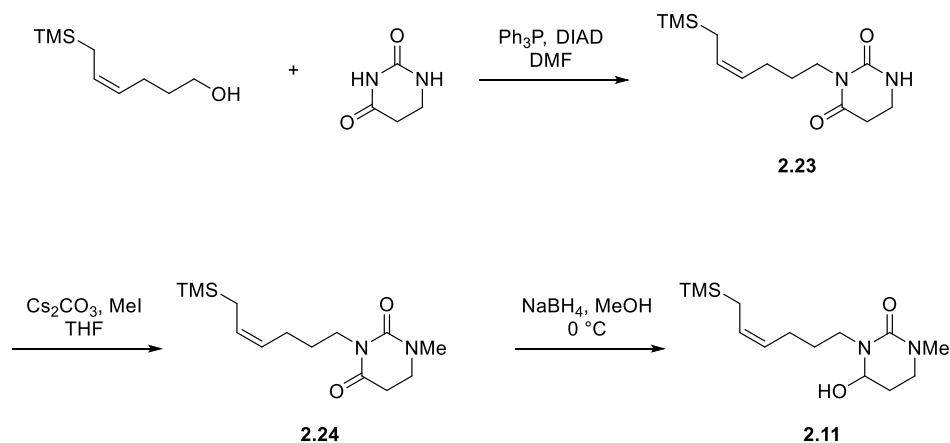
Scheme 2.7. Synthesis of **2.11**.

(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$_2$NaO$_2$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 dihydrouracil (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 NaBH$_4$ (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. 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 (davisil, hexanes/EtOAc, 1:1 to EtOAc only) to afford **X** (91 mg, 73%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 C$_{14}$H$_{28}$N$_2$NaO$_2$Si (M+Na) 307.1818]

Scheme 2.8. Synthesis of **2.13**.

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 NH$_4$Cl(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 Na$_2$SO$_4$ 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.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.01 (ddt, J = 6.0, 11.0, 16.5 Hz, 1H), 5.50–5.41 (m, 2H), 5.34 (dd, J = 1.5, 11.0 Hz, 1H), 5.30–5.25 (m, 1H), 4.81 (ddd, J = 1.0, 1.0, 6.0 Hz, 2H), 3.94 (t, J = 6.0 Hz, 2H), 3.79–3.82 (m, 2H), 2.76 (t, J = 11.5 Hz, 2H), 2.04 (q, J = 7.5 Hz, 2H), 1.65 (quint, J = 7.5 Hz, 2H), 1.47 (d, J = 8.5 Hz, 2H), 0.01 (s, 9H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 168.8, 153.2, 149.9, 131.1, 126.3, 126.1, 119.3, 68.2, 41.2, 39.4, 31.9, 27.8, 24.4, 18.4, –1.8;

IR (neat, cm^{-1}) 2954, 1788, 1723, 1695, 1366, 1309, 1127, 855;

HRMS (ESI) found 375.1717 [calcd for C$_{17}$H$_{28}$N$_2$NaO$_4$Si (M+Na) 375.1716]

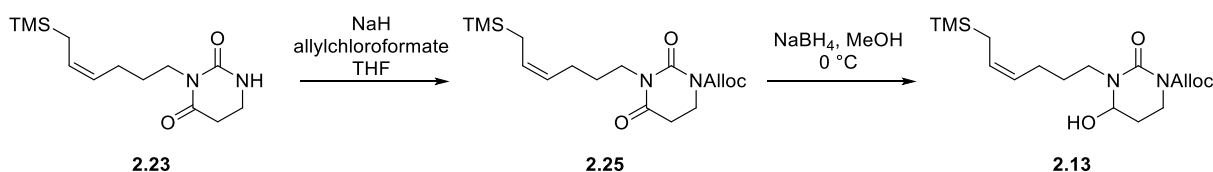**allyl (Z)-4-hydroxy-2-oxo-3-(6-(trimethylsilyl)hex-4-en-1-yl)tetrahydropyrimidine-1(2H)-carboxylate (2.13)**

To a stirred solution of **2.25** (141 mg, 0.399 mmol) in MeOH (4 mL) was added NaBH$_4$ (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. 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_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1 to EtOAc only) to afford **2.13** (124 mg, 88%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 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);

^{13}C NMR (125 MHz, CDCl$_3$) δ 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^{-1}) 3400, 2952, 1757, 1712, 1662, 1308, 1204, 839;

HRMS (ESI) found 377.1877 [calcd for $C_{17}H_{30}N_2NaO_4Si$ (M+H) 377.1873]
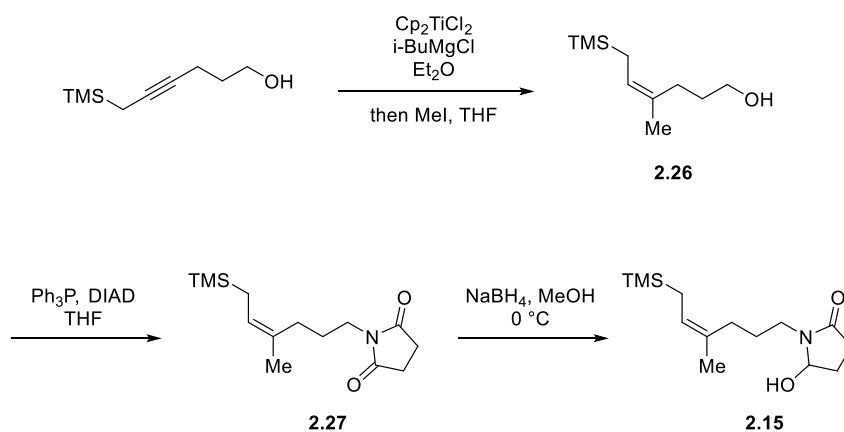
Scheme 2.9. Synthesis of **2.15**

146

(Z)-4-methyl-6-(trimethylsilyl)hex-4-en-1-ol (2.26)

To a cooled (0 °C) solution of Cp_2TiCl_2 (100 mg, 0.400 mmol) in Et_2O (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-ol[23] (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 Na_2SO_4 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.

^{1}H NMR (500 MHz, $CDCl_3$) 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);

^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2, 121.0, 63.1, 30.8, 27.7, 23.3, 18.3, –1.8;

IR (neat, cm[−1]) 3335, 2953, 1247, 834;

HRMS (ESI) found 209.1337 [calcd for $C_{10}H_{22}NaOSi$ (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), Ph_3P (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


23

aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_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$_3$) δ 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$_3$) δ 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 $C_{14}H_{25}NNaO_2Si$ (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_2SO_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$_3$) δ 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 C$_{14}$H$_{27}$NNaO$_2$Si (M+Na) 292.1709]
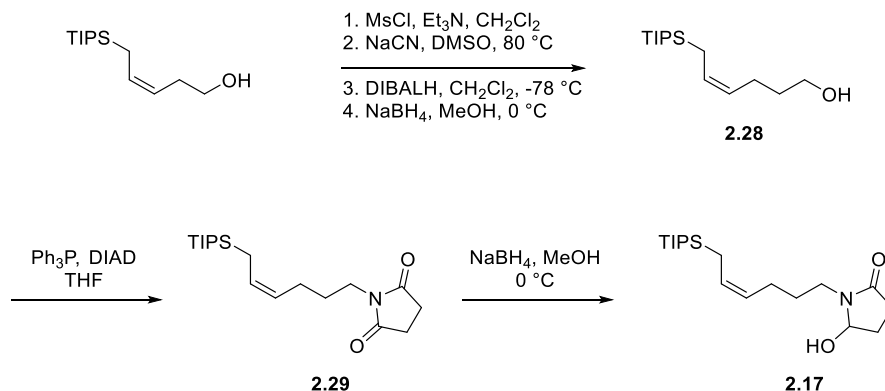
Scheme 2.10. Synthesis of **2.17**.

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

To a stirred solution of primary alcohol[24] (491 mg, 2.03 mmol) in CH$_2$Cl$_2$ (10 mL) was added Et$_3$N (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 NaHCO$_3$(aq). 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 mesylate, which was carried to the next step without further purification.

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[24] Wilkinson, S. C.; Lozano, O.; Schuler, M.; Pacheco, M. C.; Salmon, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 7083.

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_2SO_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_2Cl_2 (5 mL) was added DIBALH (0.66

mL, 1 M in CH_2Cl_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_2Cl_2. The combined organic layers were dried over

anhydrous Na_2SO_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 $NH_4Cl(aq)$. 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_2SO_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).

^{1}H NMR (500 MHz, CDCl$_3$) δ 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$_3$) δ 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 C$_{15}$H$_{32}$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 μL, 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$_3$) δ 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$_3$) δ 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 C$_{19}$H$_{35}$NNaO$_2$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 NaBH$_4$ (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. 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, 3:1 to 1:1) to afford **2.17** (72 mg, 69%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 C$_{19}$H$_{37}$NNaO$_2$Si (M+Na) 362.2491]
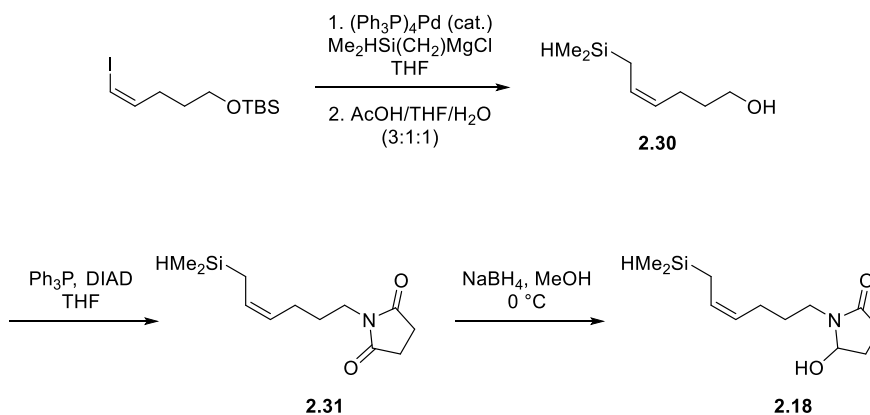
Scheme 2.11. Synthesis of **2.18**.

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

To a cooled (0 °C) solution of (Ph$_3$P)$_4$Pd (168 mg, 0.291 mmol) in THF (5 mL) was added Me$_2$HSi(CH$_2$)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-pyran[25] (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. NH$_4$Cl$_{(aq)}$. 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* to afford the crude cross-coupling product. The crude mixture was dissolved in AcOH/THF/H$_2$O (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 Na$_2$SO$_4$ 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):

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[25] Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, I. Y.; Kampf, J. W. *J. Org. Chem.* **2007**, *72*, 4135.

^{1}H NMR (500 MHz, CDCl$_3$) δ 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);

^{13}C NMR (125 MHz, CDCl$_3$) δ 127.2, 125.7, 62.6, 32.6, 23.4, 15.7, 4.6;

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

HRMS (ESI) found 181.1021 [calcd for C$_8$H$_{18}$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$_3$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 µL, 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$_2$SO$_4$ and concentrated *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.

^{1}H NMR (500 MHz, CDCl$_3$) δ 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);

^{13}C NMR (125 MHz, CDCl$_3$) δ 177.2, 126.4, 126.1, 38.6, 28.1, 27.6, 24.4, 15.8, –4.6;

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

HRMS (ESI) found 262.1244 [calcd for C$_{12}$H$_{21}$NNaO$_2$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 NaBH$_4$ (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. 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 **2.18** (87 mg, 75%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) 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);
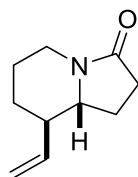
^{13}C NMR (125 MHz, CDCl$_3$) δ 174.6, 126.7, 125.9, 83.3, 39.8, 28.8, 28.4, 27.7, 24.5, 15.8, –4.6;

IR (neat, cm^{-1}) 3316, 2955, 2112, 1659, 1460, 1247, 881, 838, 674;

HRMS (ESI) found 264.1390 [calcd for C$_{12}$H$_{23}$NNaO$_2$Si (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 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 Na$_2$SO$_4$ 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).

$[\alpha]^{24}_D = +54.4$ (*c* 1.00, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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)
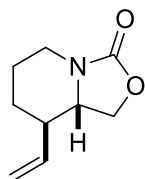
To a stirred solution of **2.5** (52 mg, 0.200 mmol) and **2.3e** (20 mg, 0.040 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol) in an ice bath. Then the reaction was moved to

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, 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, CHCl₃);

¹H NMR (500 MHz, CDCl₃) 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);

¹³C NMR (125 MHz, CDCl₃) 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 C₉H₁₃NNaO₂ (M+ Na) 190.0844]

(8R,8aS)-1,1,2-trimethyl-8-vinylhexahydroimidazo[1,5-a]pyridin-3(2H)-one (2.8)
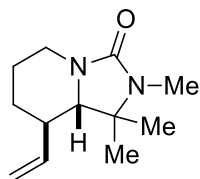
To a stirred solution of **2.7** (60 mg, 0.200 mmol) and **2.3e** (10 mg, 0.020 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol) in an ice bath. Then the reaction was moved to

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$_2$SO$_4$ 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_r(major) = 25.0 min, t_r(minor) = 33.9 min).

$[\alpha]^{24}_D$ = +97.2 (*c* 1.00, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 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);

^{13}C NMR (125 MHz, CDCl$_3$) δ 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^{-1}) 2935, 1697, 1433, 1398, 914, 841;

HRMS (ESI) found 231.1472 [calcd for C$_{12}$H$_{20}$N$_2$NaO (M+ Na) 231.1473]

(9R,9aR)-9-vinyloctahydro-4H-quinolizin-4-one (2.10)
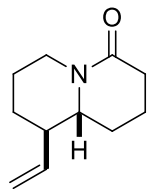
To a stirred solution of **2.9** (54 mg, 0.200 mmol) and **2.3e** (20 mg, 0.040 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol) in an ice bath. Then the reaction was moved to a fridge (4 °C) and stirred for 24 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture 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 Na$_2$SO$_4$ 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, t$_r$(major) = 13.3 min, t$_r$(minor) = 15.2 min).

$[\alpha]^{24}_{D}$ = +52.2 (*c* 1.00, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.59 (ddd, *J* = 9.0, 10.5, 17.5 Hz, 1H), 5.09 (dd, *J* = 1.0, 17.5 Hz, 1H), 5.05 (*J* = 2.0, 10.0 Hz, 1H), 4.82 (dp, *J* = 2.0, 13.5 Hz, 1H), 3.03 (dt, *J* = 7.0, 10.0 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, CDCl$_3$) 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$_{17}$NNaO (M+Na) 202.1208]

(4aR,5R)-2-methyl-5-vinyloctahydro-1H-pyrido[1,2-c]pyrimidin-1-one (2.12)
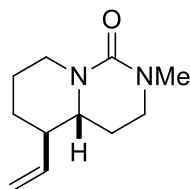
To a cooled (–30 °C) solution of **2.11** (57 mg, 0.200 mmol) and **2.3e** (10 mg, 0.020 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol). Then the reaction was stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na_2SO_4 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, t_r(major) = 29.8 min, t_r(minor) = 19.1 min).

$[\alpha]^{24}_D$ = +10.0 (*c* 1.00, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) 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, 4 H), 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);
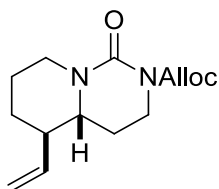
^{13}C NMR (125 MHz, CDCl$_3$) δ 156.6, 139.7, 116.3, 58.0, 47.6, 45.3, 44.0, 35.9, 31.5, 26.7, 24.8;

IR (neat, cm^{-1}) 2930, 2360, 1637, 1501, 1254, 917;

HRMS (ESI) found 217.1315 [calcd for $C_{11}H_{18}N_2NaO$ (M+ Na) 217.1317]

allyl (4aR,5R)-1-oxo-5-vinylhexahydro-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 uL, 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 Na_2SO_4 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, t_r(major) = 33.5 min, t_r(minor) = 29.7 min).

$[\alpha]^{24}_D = +55.4$ (*c* 1.00, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 C$_{14}$H$_{20}$N$_2$NaO$_3$ (M+ Na) 287.1372]

(8R,8aR)-8-methyl-8-vinylhexahydroindolizin-3(2H)-one (2.15)
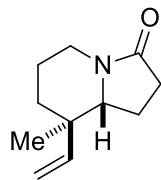
To a stirred solution of **2.15** (54 mg, 0.200 mmol) and **2.3g** (20 mg, 0.040 mmol) in TBME (4 mL, 0.05 M) was added TMSCl (51 uL, 0.400 mmol) in an ice bath. Then the reaction was moved to a fridge (4 °C) and stirred for 48 hours. The reaction was quenched with 2 N NaOH(aq), and the biphasic mixture 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 Na_2SO_4 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, t_r(major) = 21.6 min, t_r(minor) = 25.1 min).
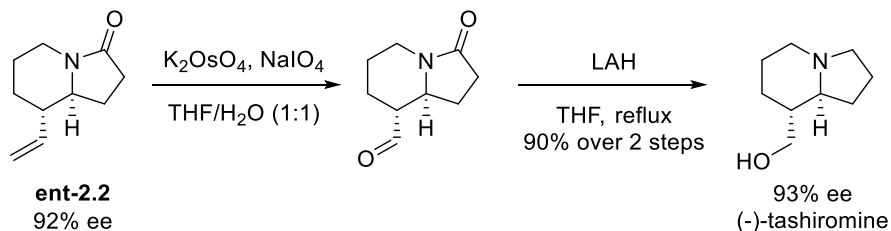
$[\alpha]^{24}_D$ = +42.4 (*c* 1.00, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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 C$_{11}$H$_{17}$NNaO (M+Na) 202.1208]

2.6.5. Natural Product Synthesis

Scheme 2.12. Synthesis of (–)-tashiromine.

(–)-tashiromine

To a stirred solution of **ent-2.2** (50 mg, 0.303 mmol, 92% ee) in 1:1 THF/H$_2$O (3 mL) was added K$_2$OsO$_4$·2H$_2$O (2 mg, 2 mol%) and NaIO$_4$ (324 mg, 1.515 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 (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, CH$_2$Cl$_2$/MeOH/sat. NH$_4$OH(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, t$_r$(major) = 50.1 min, t$_r$(minor) = 49.1 min).
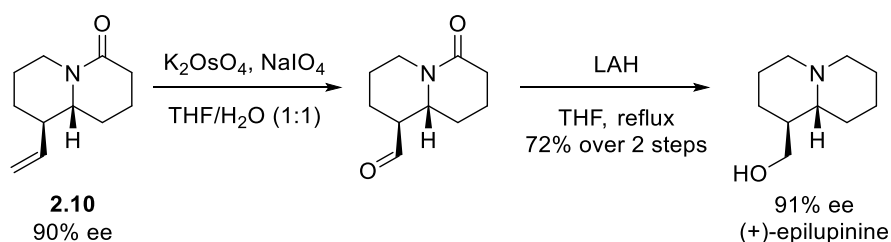
$[\alpha]^{24}{}_D = -41$ (*c* 1.00, EtOH);

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

^{13}C NMR (125 MHz, CDCl$_3$) δ 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, CH_2Cl_2/MeOH/sat. NH_4OH(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, t_r(major) = 53.4 min, t_r(minor) = 51.1 min).

$[\alpha]^{24}_D = +30$ (*c* 1.00, EtOH);

^{1}H NMR (500 MHz, CDCl$_3$) 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);

^{13}C NMR (125 MHz, CDCl$_3$) 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;

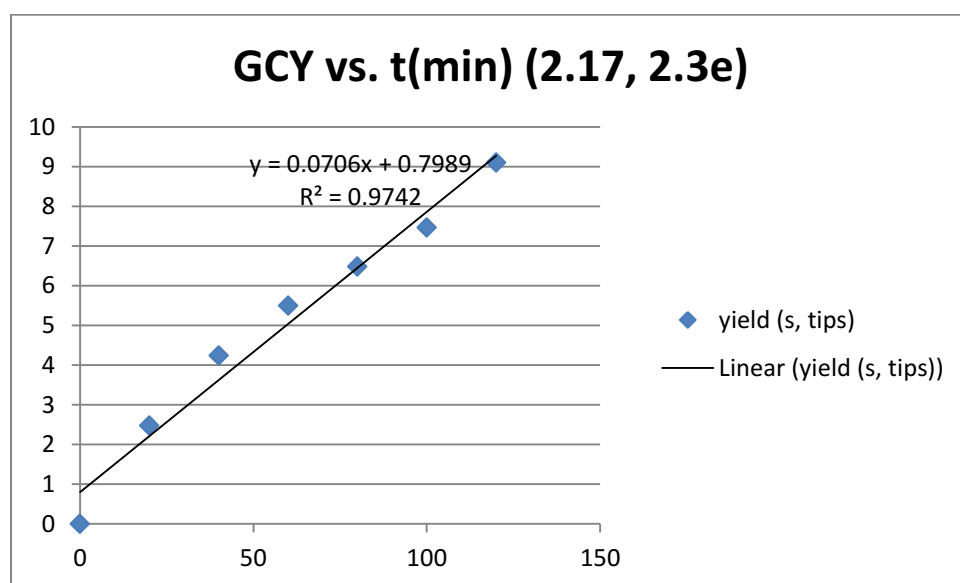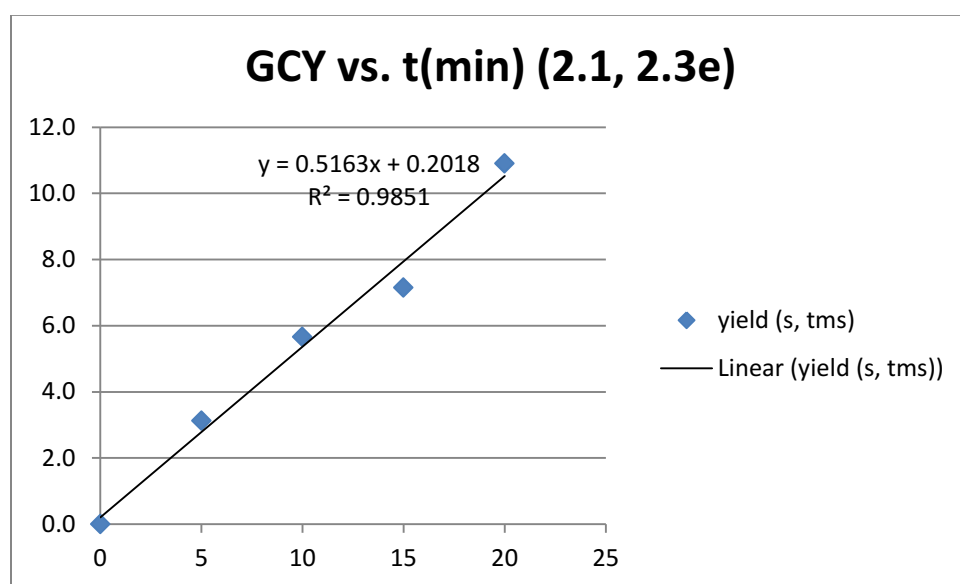HRMS (ESI) found 170.1542 [calcd for $C_{10}H_{20}NO$ (M+H) 170.1545]

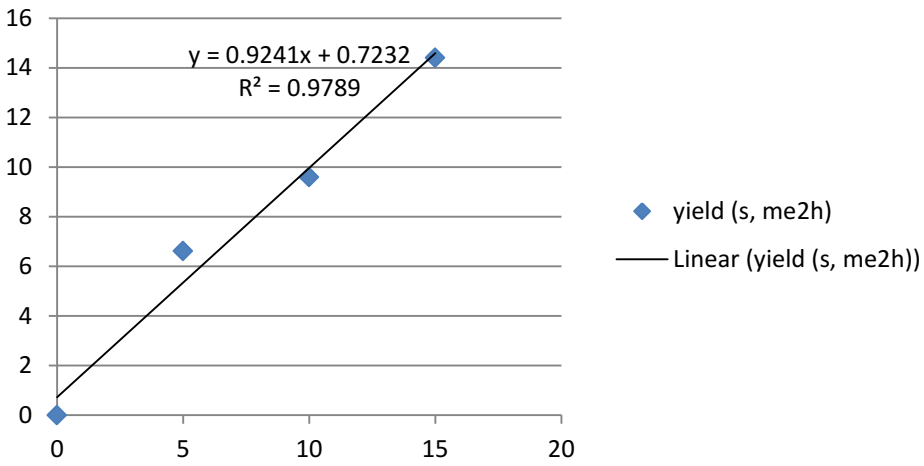## 2.6.6. Mechanistic Experiments

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 uL, 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 $NaHCO_3$(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.

Slope	Catalyst **2.3e**	Catalyst **2.4**
Substrate **2.1**	0.5163	0.0652
Substrate **2.17**	0.0706	0.1375
Substrate **2.18**	0.9241	0.0486

k_{rel}	Catalyst **2.3e**	Catalyst **2.4**
Substrate **2.1**	1 (defined)	0.13
Substrate **2.17**	0.14	0.27
Substrate **2.18**	1.79	0.09

GCY vs. t(min) (2.1, 2.3e)

$y = 0.5163x + 0.2018$
$R^2 = 0.9851$

- yield (s, tms)
- —— Linear (yield (s, tms))

GCY vs. t(min) (2.17, 2.3e)

$y = 0.0706x + 0.7989$
$R^2 = 0.9742$

- yield (s, tips)
- —— Linear (yield (s, tips))

GCY vs. t(min) (2.18, 2.3e)

$y = 0.9241x + 0.7232$
$R^2 = 0.9789$

◆ yield (s, me2h)
── Linear (yield (s, me2h))

GCY vs. t(min) (2.1, 2.4)

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

◆ yield (o, tms)
── Linear (yield (o, tms))

GCY vs. t(min) (2.17, 2.4)

y = 0.1375x + 0.75
R² = 0.94

- ◆ yield (o, tips)
- —— Linear (yield (o, tips))

GCY vs. t(min) (2.18, 2.4)

y = 0.0486x - 0.844
R² = 0.9785

- ◆ yield (o, me2h)
- —— Linear (yield (o, me2h))

KIE Experiments

TMSCl (2 equiv)
2.3e (10 mol%)
TBME (0.05 M)

4 °C

2.1-H/D → **2.2-H/D**

**Scheme 2.14.** Intermolecular competition 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 R_0), **2.3e** (2.5 mg, 10 mol%), dodecane (internal std, 11 µL) in TBME (1 mL, 0.05 M) was added TMSCl (13 uL, 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 Na_2SO_4 and concentrated *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.
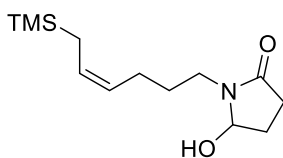
Chemical Formula: $C_{13}H_{25}NO_2Si$
m/z: 255.1655 (100.0%), 256.1688 (14.1%), 256.1650 (5.1%), 257.1623 (3.3%)
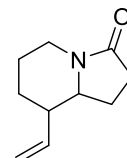
Chemical Formula: $C_{10}H_{15}NO$
m/z: 165.1154 (100.0%), 166.1187 (10.8%)

Run 1	SM (abundance)	P (abundance)	R_0	R_P
$(M+1)^+$	1257629	1136981	1.03532	1.201812
$(M+2)^+$	1543513	1489232		
Run 2				
$(M+1)^+$	1378558	1023626	1.031837	1.202195
$(M+2)^+$	1687130	1341149		
Run 3				
$(M+1)^+$	1126995	879665	1.02716	1.175987
$(M+2)^+$	1373987	1129478		

R_0 = (abundance of M+2 – 0.192 * abundance of M+1) / (abundance of M+1)

R_P = (abundance of M+2 – 0.108 * abundance of M+1) / (abundance of M+1)

Run	R_0	R_P	F	KIE
1	1.035	1.202	0.29	0.83
2	1.032	1.202	0.33	0.83
3	1.027	1.176	0.30	0.85

$$KIE = \frac{\ln(1 - F)}{\ln(1 - F * R_P / R_0)}$$

2.6.7. Additional Optimization Data
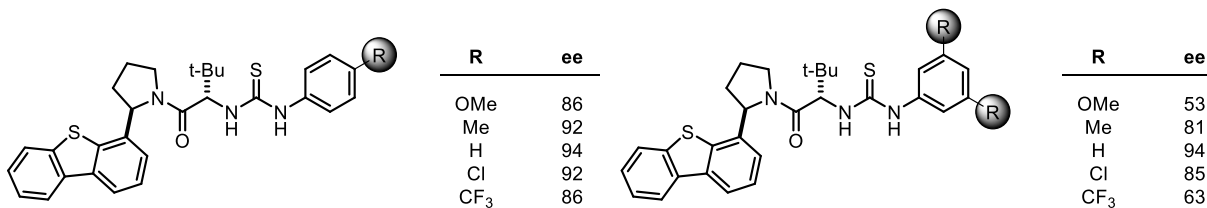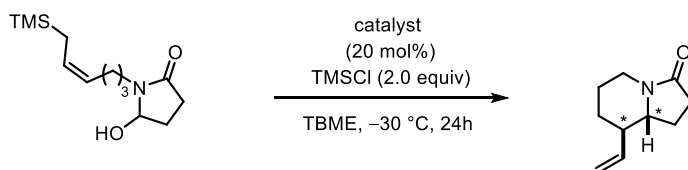
Ar	R = *t*-Bu	R = *i*-Pr	R = *t*-Bu	R = *i*-Pr
phenyl	31% ee	48% ee	55% ee	55% ee
1-naphthyl	18% ee	67% ee	86% ee	87% ee
2-naphthyl	-23% ee	19% ee	56% ee	71% ee
phenanthrenyl	-63% ee	-14% ee	52% ee	77% ee
pyrenyl	54% ee	77% ee	88% ee	87% ee
dibenzofuranyl	52% ee	72% ee	51% ee	86% ee
dibenzothiophenyl	64% ee	80% ee	94% ee	92% ee

171