Part I. Enantioselective Synthesis of (+)-Zaragozic Acid C

Part II. Nitridomanganese(V) Complexes: Design, Preparation, and Use as Novel Nitrogen Atom-Transfer Reagents

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Abstract

An enantioselective synthesis of the potent squalene synthase inhibitor (+)-zaragozic acid C is described. Zaragozic acid C constitutes one member of a family of natural products which possess a unique, highly functionalized 2,8-dioxa-bicyclo[3.2.1]octane core. An efficient route has been delineated which allows for the preparation of multigram quantities of this structural unit. Conversion of the bicyclooctane to the target molecule requires installing three carboxylic acids at C(8), C(9), and C(10), which has been accomplished by simultaneous oxidation of the corresponding tri-aldehyde. Additional highlights and supporting studies from this work include: (1) the use of [Cr(OAc)]₂·H₂O for the stereoselective reduction of ynones to trans enones; (2) an investigation of the diastereoselective dihydroxylation of γ-alkoxy-α,β-unsaturated ketones; (3) the effect of amine cosolvents on the nucleophilic addition of TMSC≡CLi to a key dioxabicyclooctanone intermediate; and (4) stereospecific formation of the C(5) quaternary center by a chelation-controlled ketone addition reaction. The chemical transformations which have been developed should prove useful for the preparation of synthetic and semi-synthetic analogues of this important class of molecules.

The design and preparation of novel nitridomanganese(V) Schiff base-derived complexes which function as nitrogen atom-transfer reagents for olefin amination has been described. X-ray crystallography has been employed to establish the structures of these unique MnV≡N complexes, ORTEP figures of which are presented. The utility of these reagents has been demonstrated in reactions with silyl enol ethers and carbohydrate glycals to give α-amino ketones and 2-amino saccharides, respectively. Yields for these processes typically range from 60–80%, and, in all cases, the olefin starting material is
employed as the limiting reagent. Moreover, the amine products isolated are conveniently protected as their $N$-trifluoroacetyl derivatives. Efforts to prepare additional reagents which display nitrogen transfer activity with unfunctionalized alkenes have led to the development of mild, efficient, and general protocols for the preparation of Mn≡N systems. These complexes function competently as nitrogen transfer agents with styrene.
Acknowledgments

There is an overwhelming sense of finality associated with the writing of this acknowledgments page, and it has caused me to spend much time reflecting on the events in my life over the past several years. There are so many individuals that I am grateful to for their tutelage, their guidance and their support, but no two deserve more credit and more thanks than my parents. They have served as my inspiration; their love and support has been unfailing and their patience without compromise. My older brother, although perhaps unknowingly, has guided me through the past 27 years. I have tried to emulate his idealism and zest for life, and, most importantly, his ability to find humor in all situations. To them, and my entire collection of relatives, I am beholden for always reminding me of the truly important things in life.

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To my family

and

in memory of a

wonderful grandfather
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Part I. Enantioselective Synthesis of (+)-Zaragozic Acid C

Introduction

The zaragozic acids and the squalestatins constitute a class of recently isolated fungal metabolites which are important targets for chemical synthesis as a consequence of their complex molecular structure and potent biological activity. These natural products share a common 2,8-dioxabicyclo[3.2.1]octane core, and differ exclusively at the C(1) alkyl and C(6) O-acyl side chains. All members of this family display picomolar inhibition of mammalian squalene synthase, the enzyme responsible for mediating the first committed step in sterol biosynthesis. Thus, these compounds have potential application as therapeutically useful serum cholesterol-lowering agents. The following


2. Additional squalestatins containing different alkyl and O-acyl side chains as well as the first report of five related structures containing the 6-deoxy, 7-deoxy, or 6,7-dideoxydioxabicyclooctane core have been described, see: (a) Dufresne, C.; Jones, E. T. T.; Omstead, M. N.; Bergstrom, J. D.; Wilson, K. E. J. Nat. Prod. 1996, 59, 52. (b) Blows, W. M.; Foster, G.; Lane, S. J.; Noble, D.; Piercy, J. E.; Sidebottom, P. J.; Webb, G. J. Antibiot. 1994, 47, 740.

provides a detailed account of the first completed synthesis of one of these natural products, (+)-zaragozic acid C 1 (Figure 1).4

**Background.** The zaragozic acids and squalestatins were first isolated in 1991 by research teams working independently at Merck and Glaxo (Figure 2). Zaragozic acid A was extracted from the sterile fungal culture *Sporormiella intermedia*, while zaragozic acids B and C were isolated from a fungal strain identified as *Leptodontium elatius*. The three squalestatins were extracted from the fungus *Phoma* sp. C2932. The structures of these natural products were determined by a combination of chemical degradation and NMR spectroscopy.1,5 X-ray crystallographic analysis and exciton-coupled circular dichroism studies on various derivatives confirmed the structural assignments and established the absolute stereochemistry. These molecules are characterized by a novel 2,8-dioxabicyclo[3.2.1]octane-4,6,7-trihydroxyl-3,4,5-tricarboxylic acid core which has been shown to be biosynthetically derived from succinate and acetate precursors.6

**Figure 1.** (+)-Zaragozic Acid C.

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Syntheses of partially functionalized model systems of the bicyclic core as well as the

Figure 2. Selection of other known zaragozic acids and squalestatins.

preparation of both side chains have been described.\textsuperscript{7,8,9} Additionally, the asymmetric synthesis of zaragozic acid A/squalestatin S1, a relay synthesis of zaragozic acid A, and a

\begin{itemize}
second synthesis of (+)-zaragozic acid C have been accomplished by Nicolaou, Heathcock, and Evans respectively.\textsuperscript{10,11}

Zaragozic acids A, B, and C exhibit potent inhibitory activity toward rat liver squalene synthase with apparent K\textsubscript{i} values from 29–78 pM. In addition, these fungal metabolites have been shown to effect a decrease in cholesterol synthesis in whole cells (Hep G2) and in mice.\textsuperscript{1b,12} The squalestatins display similar efficacy towards both mammalian (rat liver) and microsomal (\textit{Candida albicans}) squalene synthase. This enzyme is responsible for catalyzing a two-step reaction sequence in which farnesyl


pyrophosphate (FPP) is dimerized in a head-to-head manner to form pre-squalene pyrophosphate (PSPP). This cyclopropylcarbinyl pyrophosphate undergoes a series of enzyme-mediated cationic rearrangements followed by reduction with NADPH to furnish squalene.\textsuperscript{13,14} It has been shown that both biosynthetic steps (dimerization and reductive rearrangement) are inhibited by the zaragozic acids and the squalestatins. The structural

![Structural comparison of presqualene pyrophosphate and zaragozic acid C.](image)

**Figure 3.** Structural comparison of presqualene pyrophosphate and zaragozic acid C.

homology between these compounds and pre-squalene pyrophosphate has led to the suggestion that they act by effectively mimicking the binding of PSPP to the enzyme (Figure 3).\textsuperscript{3d,15}


\textsuperscript{15} A number of analogs have been prepared for structure-activity relationship studies, see: (a) Burk, R. M.; Berger, G. D.; Bugianesi, R. L.; Girotra, N. N.; Parsons, W. H.; Ponpipom, M. M. *Tetrahedron Lett.* \textbf{1993}, \textit{34}, 975.  (b) Lester, M. G.; Gilbin, G. M. P.; Inglis, G. G. A.; Procopiou, P. A.; Ross, B.
Analysis. The retrosynthetic disconnections which formed the basis of our plan for the preparation of zaragozic acid C are illustrated in Scheme 1. Removal of the C(6) O-acyl side chain would provide the C(6)/C(7) diol 6; subsequent unraveling of the dioxabicyclic ketal would give a functionalized acyclic precursor. As a consequence of these disconnections, the stereochemical complexity of the dioxabicyclooctane is...
redefined as a problem in acyclic asymmetric synthesis. At the outset, however, we were concerned that cyclization of a highly functionalized acyclic intermediate (e.g., 5) to the appropriate bicyclic ketal might be complicated by side reactions such as δ- and γ-lactonization as well as formation of undesired ketal products.\textsuperscript{16} A synthetic route was developed which we hoped would avoid such competing processes.\textsuperscript{17}

With these considerations in mind, a plan was developed in which the quaternary center at C(4) would be established following the formation of the dioxabicyclooctane framework. Installation of the C(4) hydroxy acid would require either oxidative functionalization of olefin 6 or nucleophilic addition to ketone 7. On the basis of molecular models, we anticipated that dihydroxylation of dioxabicyclooctane 6 would

\begin{figure}[h]
    \centering
    \includegraphics[width=\textwidth]{figure4.png}
    \caption{Functionalization of the dioxabicyclooctane core.}
    \end{figure}

\textsuperscript{16} For alternative strategies in which differently functionalized acyclic precursors are cyclized to the dioxabicyclooctane core intermediates, see refs. 10a-d and 11.

\textsuperscript{17} Early structure–determination studies by $^1$H NMR spectroscopy on the zaragozic acids excluded the other possible [3.2.1]–bicyclic ketal ring system i. Evans and co–workers have performed molecular mechanics calculations on both [3.2.1]–dioxabicyclooctanes and concluded that the unnatural isomer i is more stable (ref. 11). No data is available on the kinetics of formation of each of the two bicyclic ketals from acyclic precursors.
occur preferentially from the convex face to provide the desired C(4) carbinol. Analysis of ketone 7 suggested a similar preference for addition to the convex face to give the undesired stereochemistry at C(4) (Figure 4). Therefore, we initially expected to install the desired C(4) hydroxy acid functionality via the alkene intermediate 6, which would be prepared from ketone 7. Disconnection of ketone 7 led to the acyclic fragment 8 in which a hydroxy group at C(4) would serve as the latent carbonyl (Scheme 1). Fragmentation of the C(1)–C(7) bond in 8 afforded two subunits: 9, which includes most of the stereochemical information present in the dioxabicyclooctane skeleton, and 10, which encompasses the C(1') alkyl side chain with its attendant stereogenic centers.

Results and Discussion

Synthesis of Alkyne 22. The synthesis of zaragozic acid C commenced with the preparation of alkyne 22 (Scheme 2) from D-erythronic γ-lactone 13, which is readily available from D-araboascorbic acid (H₂O₂/K₂CO₃, then H₃O⁺). Condensation of 13 with dimethylamine (MeOH, 0 °C) afforded the derived 2,3,4-trihydroxybutyramide which was selectively ketalized (Et₂C(OMe)₂, cat. TsOH) to give 14. Protection of the secondary alcohol as its corresponding benzyl ether (BnBr, NaH) furnished amide 15.

Installation of the C(5) quaternary center was effected starting with amide 15 through two sequential carbonium additions. Treatment of 15 with ethoxyvinyl lithium (ethyl vinyl ether, nBuLi) yielded an intermediate α-ethoxy-α,β-unsaturated ketone 16. Subsequent addition of TMSC≡CMgBr to 16 afforded a 20:1 mixture of diastereomeric products 17/18 as determined by 1H NMR spectroscopy.


19. The stereochemistry of the major product was assumed to be as shown on the basis of a chelation-controlled addition. This was established unambiguously by 1H NMR NOE difference experiments following cyclization to the dioxabicyclooctane core, see Scheme 5 and Figure 9.
Nucleophilic addition to the intermediate ketone 16 was conducted under reaction conditions which favored a chelation–controlled process. In principle, this ketone can

Scheme 2

(a) Me₂NH, MeOH, 0 °C, 97%; (b) (MeO)₂CeT₂, cat. TsOH, 90%; (c) NaH, BnBr, THF, 96%; (d) ethoxyvinyl lithium, THF, −78 °C; (e) TMSC≡CMgBr, THF, −78 °C, 84%; (f) O₂, CH₂Cl₂/EtOH, −78 °C, 84%; (g) NaBH₄, MeOH; (h) K₂CO₃, MeOH, 78% in two steps; (i) t-BuMe₂SiCl, Et₃N, 4–DMAP, then Me₂SiCl, 88%.

form three different magnesium chelates A, B, and C (Figure 5). The observed stereochemical outcome of the reaction is consistent with the addition of TMSC≡CMgBr occurring through the intermediacy of a 5-membered chelate formed by the α-benzyloxy and ketone–carbonyl oxygens (A, Figure 5). Ketone addition proceeding through a 1,3-chelate B was expected to favor formation of the product bearing the undesired stereochemistry at the newly installed quaternary center (18). Similarly, addition


21. Evans and co-workers have made a related observation in which a 1,2-chelate is assumed to be preferred over a 1,3-chelate, see ref. 11.
proceeding through chelate C was anticipated to give the unwanted Felkin–Ahn product 18.22

**Figure 5.** Stereoselective addition of TMSC≡CMgBr to 16.

Subsequent elaboration to diol 20 was accomplished through ozonolysis of hydroxy vinyl ether 17 under carefully controlled conditions (Scheme 2).23 Treatment of 17 with a dilute stream of ozone (ca. 1 equiv, −78 °C) effected oxidation of the vinyl ether in reproducibly high yields (84%). Mild reduction of α-hydroxy ester 19 with NaBH₄ in MeOH (23 °C) furnished diol 20 along with a small amount (5-10%) of 21, the product of alkyne desilylation. In practice, the unpurified product from this reduction was reacted directly with anhydrous K₂CO₃ in MeOH to effect complete conversion to the desired terminal acetylene 21. Differential protection of the primary and tertiary carbinols in 21 was accomplished using a one-pot procedure involving silylation with tBuMe₂SiCl (TBSCl) and Me₃SiCl (TMSCl), respectively. A solution of the diol, 4-DMAP, and Et₃N was initially treated with TBSCl and, upon consumption of 21 (as indicated by thin-layer chromatography), the reaction mixture was subsequently treated


with TMSCl to furnish 22. The nine-step sequence of reactions described has been routinely conducted to prepare 22 on a 30–40 g scale.

**Synthesis of the Alkyl Side Chain Aldehyde (32).** Preparation of the alkyl side chain was achieved via a seven-step reaction sequence employing Evans’ asymmetric aldol addition chemistry to install both the C(4’) and C(5’) stereogenic centers (Scheme 3). Treatment of 5-benzylxopentanal (24) with the di-n-butylboryl enolate of N-propionyl (S)-benzoxazolidinone gave the aldol adduct 25 in 97% diastereomeric excess (de), as determined by 1H NMR spectroscopy. Hydrolysis of the auxiliary (LiOH, H2O)25 and reduction of the resulting acid 26 with LiAlH4 furnished diol 27 as a white, crystalline solid (92% two steps).

**Scheme 3**

![Scheme 3](image)

(a) 9-BBNOT1, i–Pr2NEt, then H2O2, MeOH, 84%; (b) LiOH, H2O2, aq. THF; (c) LiAlH4, THF, 92%; (d) TsCl, C5H5N, 0 °C, 89%; (e) PhLi, BF3·OEt2, 91%; (f) t-BuCOCl, 4–DMAP, CH2Cl2, 90%; (g) H2, Pd/C, EtOAc, 99%; (h) (COCl)2, DMSO, Et3N, CH2Cl2, 96%.

Replacement of the primary hydroxyl in 27 with the requisite phenyl substituent was effected following a two-step protocol that involved: (1) selective tosylation of the 1° carbinol (TsCl, C5H5N, 0 °C) to give 28; and (2) *in situ* closure to oxetane 29 followed

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by BF$_3$•OEt$_2$-promoted ring opening with phenyllithium (eq 1). Nucleophilic opening of the intermediate oxetane occurred with complete regioselectivity to provide 30 in 80% yield for the overall sequence. The resulting alcohol 30 was protected as the trimethylacetyl (Piv) ester. Utilization of this hindered protecting group ensured that the C(4') carbinol would remain masked under the strongly acidic conditions subsequently developed for the cyclization reaction (vide infra). Hydrogenolytic removal of the benzyl ether (H$_2$, Pd–C) followed by Swern oxidation of the resulting alcohol 31 provided the zaragozic acid C side chain precursor, aldehyde 32.

**Synthesis of the Dioxabicyclooctane Core.** We next proceeded to investigate the coupling of acetylene 22 with aldehyde 32 (Scheme 4). Addition of a solution of

**Scheme 4**

![Scheme 4 Diagram](image)

(a) n-BuLi, THF, −45 °C; (b) 32, LiBr, THF, 93%; (c) Dess-Martin periodinane, CH$_2$Cl$_2$, 93%; (d) [Cr(OAc)$_2$]$_2$H$_2$O$_2$, THF/H$_2$O, 60%; (e) n-Bu$_4$NF, THF, 93%.


aldehyde 32 to a solution of acetylide 33 in either THF or Et₂O at −78 °C yielded a mixture of both desired product 34 and recovered starting materials. We speculated that proton transfer between acetylide 33 and aldehyde 32 was responsible for the reduced yields of 34. Attempts to attenuate the basicity of the lithium acetylide by transmetalation with either MgBr₂ or CeCl₃ had little effect in preventing the proton-transfer side reaction.²⁸ In related model studies, addition of either the lithium, magnesium or cerium acetylide to hexanoyl chloride (used as a model for the side chain acid chloride) was also unsuccessful.²⁹ Efficient coupling of the two subunits, 32 and 33, was accomplished following a protocol described by Brandsma for the addition of lithium acetylides to readily enolizable ketones.³⁰ Addition of 0.5 equiv of anhydrous LiBr to a solution of lithium acetylide 33 prior to the addition of a solution of aldehyde 32 provided the desired adduct 34 as a mixture of epimeric alcohols in 93% yield. The mixture of propargylic alcohols 34 was oxidized with Dess-Martin periodinane to furnish ynone 35.³¹

²⁸ For a review on organolanthanide chemistry, see: Molander, G. A. Chem. Rev. 1992, 92, 29.


Reduction of 35 to the corresponding *trans* enone would provide the intermediate needed for installation of the remaining hydroxyl stereocenters at C(6) and C(7). Thus, we investigated methods for the stereoselective reduction of yrones to *trans* enones. Reagents known to effect this transformation include metal hydride species (e.g. Red-Al), dissolving metal reductions (Li/NH₃), and low-valent chromium salts (CrSO₄, CrCl₂).³² Additionally, semireduction with H₂ over Pd/C followed by photochemical isomerization of the resulting *cis* enone would afford the desired *trans* product. With the exception of the Cr(II) salts, all other methods screened gave poor isolated yields of ketone 36 and led to extensive decomposition of the starting material. Reactions involving either CrSO₄ or CrCl₂ were highly capricious, however, and gave variable yields of 36 (10-30%). We suspected that the air sensitivity of the Cr(II) reagents, which necessitated rigorous exclusion of oxygen during their preparation and in the course of a reaction, was the source of the difficulties.³³ A solution to this problem was discovered in our laboratories when the commercially available chromium(II) acetate monohydrate dimer, [Cr(OAc)₂•H₂O]₂ was used in place of either CrSO₄ or CrCl₂.³⁴ The use of [Cr(OAc)₂•H₂O]₂ gave highly reproducible results and provided 36 in yields more than twice as high (60%) as any of the methods previously examined.

Dihydroxylation of enone 36 with OsO₄ under catalytic conditions (NMO, acetone/H₂O) proceeded very slowly (ca. 10% after 48 h at 23 °C).³⁵ The small amount


³³ (a) A procedure for *in situ* preparation of CrSO₄ is described in reference 32a. (b) For the preparation and isolation of solid CrSO₄, see: Lux, H.; Illmann, G. *Chem. Ber.* 1958, 91, 2143.

³⁴ [Cr(OAc)₂•H₂O]₂ has been used to reduce α-halo ketones and α-halo ketoximes, see: (a) Williamson, K. L.; Johnson, W. S. *J. Org. Chem.* 1961, 26, 4563. (b) Corey, E. J.; Richman, J. E. *J. Am. Chem. Soc.* 1970, 92, 5276. [Cr(OAc)₂•H₂O]₂ is currently sold by Aldrich Chemical Co.

of product isolated proved to be a 1:1 mixture of syn C(6)/C(7) alcohol diastereomers 37:38 as determined by $^1$H NMR spectroscopy (Figure 6). Selective deprotection of the

\[
\begin{align*}
\text{Substrate} & \quad R^1 \quad R^2 \quad \text{Desired : Undesired} \\
36 & \quad \text{TBS} \quad \text{TMS} \quad 1 : 1 (37,38) \\
39 & \quad \text{TBS} \quad \text{H} \quad 1 : 9 (40,41) \\
42 & \quad \text{H} \quad \text{TMS} \quad 1 : 9 (43,44) \\
45 & \quad \text{H} \quad \text{H} \quad 1.1 : 1 (46,47) \\
45^a & \quad \text{H} \quad \text{H} \quad 1.7 : 1 (46,47)
\end{align*}
\]

(a) Reaction conducted with added (DHQ)$_2$PHAL or (DHQD)$_2$PHAL.

**Figure 6.** Summary of results for enone dihydroxylation reactions.

trimethylsilyl ether at C(5) (ClCH$_2$CO$_2$H, MeOH) and treatment of the resulting enone 39 with 10 mol% OsO$_4$ (NMO, acetone/H$_2$O) afforded the product as a 1:9 mixture of diastereomers 40 and 41. The major product 41 isolated in the dihydroxylation reaction, however, was shown to possess the incorrect C(6)/C(7) diol stereochemistry.\(^{36}\) In an analogous experiment, treatment of enone 42 with catalytic OsO$_4$ provided a 1:9 mixture of products with the undesired diol diastereomer 44 predominating. Removal of both the TBS– and TMS– ethers in 36 gave diol 45. Dihydroxylation of 45 furnished a 1.1:1 mixture of 46 and 47. Fortunately, 45 could be osmylated in the presence of either Sharpless ligand (DHQ)$_2$PHAL or (DHQD)$_2$PHAL with NMO as the reoxidant to give a 1.7:1 mixture of desired/undesired products 46:47 in yields greater than 95%.\(^{37,38}\)

36. In each of the dihydroxylations examined, the products were cyclized to the dioxabicyclooctane ketal by treatment with 0.5% HCl/MeOH and the ratio of diastereomers determined by $^1$H NMR spectroscopy of the unpurified ketal products (yield 85–95%).


38. (a) Sharpless has described a protocol for the dihydroxylation of $\alpha,\beta$-unsaturated ketones with either (DHQD)$_2$PHAL or (DHQ)$_2$PHAL and K$_3$Fe(CN)$_6$ as the reoxidant, see: Walsh, P. J.; Sharpless, K. B. *Synlett*, 1993, 605. When 45 was subjected to these conditions, no reaction was observed.
interesting to note that the use of either of these ligands afforded the diol with the desired C(6)/C(7) stereochemistry preferentially.

Additional enones were examined as a means for potentially improving the dihydroxylation diastereoselectivity (Figure 7). Selective benzylation of the 1° alcohol in 45 with either 4-methoxybenzoyl chloride (4–DMAP, Et₃N, CH₂Cl₂) or 2-nitrobenzoic acid (DCC, DMAP) gave the corresponding esters 48 and 49, respectively.³⁹ Subjection

![Chemical structures](image)

**Figure 7.** Alternative enone substrates for dihydroxylation.

of either of these compounds to standard dihydroxylation conditions (OsO₄, NMO, acetone/H₂O/⁻BuOH) furnished mixtures of carbinol products (1.3–1.8:1 by ¹H NMR spectroscopy) favoring the desired 6R,7R diol. Use of either (DHQ)₂PHAL or (DHQD)₂PHAL in the dihydroxylation reaction of substrates 48 and 49 offered no improvement on the reaction diastereoselectivity. Additionally, the derived picolinic ester 50 (prepared in an analogous fashion to 49), when treated with OsO₄, afforded a similar ratio of products.

following one month of stirring. (b) We are grateful to Professor K. Barry Sharpless (Scripps Research Institute) for helpful discussions, and for providing additional ligands for study.

Treatment of 45 with 2-methoxypropene (PPTS, CH₂Cl₂) cleanly provided the isopropylidene ketal 51. Reaction of 51 with OsO₄ yielded a 1:2.2 mixture of desired/undesired diol products (6R, 7R)/(6S, 7S). In contrast, dihydroxylation of the cyclic carbonate 52, derived from treatment of 45 with triphosgene (C₅H₅N, 0–25 °C), gave a 2.2:1 mixture of diols favoring the desired (6R,7R) diastereomer.

Formulation of a useful model that accounts for the observed selectivities in the dihydroxylation reactions of the derivatized enones 36, 45, and 48–52 is difficult. The data does suggest that placement of an electron withdrawing group at C(10) promotes the formation of the desired (6R,7R) product. We speculate that changes to the electronic structure of the enone system may be altering the mechanism and, consequently, the stereochemical outcome of the dihydroxylation reaction.

**Stereochemical Proof.** The two diastereomers 46 and 47 isolated from the dihydroxylation reaction could not be separated by chromatography on silica gel. Cyclization of the mixture of unpurified 46 and 47 with 0.5% HCl in MeOH afforded the corresponding 2,8-dioxabicyclooctanes 53 and 56 (86% combined yield for two steps) which were separated by chromatography on silica gel (Scheme 5). In practice, however,
separation of the mixture was most easily effected following selective protection of both 1° hydroxyls as TBS– ethers (Scheme 5, 53→54 and 56→57). This two-step sequence (cyclization–protection) cleanly provided the desired bicyclic ketal 54. Treatment of either diastereomer with 2 equiv of benzoic anhydride (4–DMAP, CH₂Cl₂) afforded the bis(benzoate) esters 55 and 58, respectively. ¹H NMR difference nOe experiments on both 55 and 58 unambiguously established the proper stereochemical assignment for each diastereomer.

**Synthesis and Functionalization of the 2,8-Dioxabicyclooctan-4-one (61).**

Selective protection of tetraol 53 (TBSCl, Et₃N, 4–DMAP) furnished diol 54 (Scheme 6).

**Scheme 6**

![Scheme 6 Diagram]

(a) t-BuMe₂SiCl, 4–DMAP, Et₃N, CH₂Cl₂, 74%; (b) t-BuCOCl, 4–DMAP, ClCH₂CH₂Cl, 97%; (c) H₂, Pd(OH)₂/C, Pd/CaCO₃, EtOH, 99%; (d) [COCl]₂, DMSO, Et₃N, CH₂Cl₂, 96%; (e) Me₃SiCH₂Li, LiBr, THF/HMPA, −78 °C; (f) 18–crown–6, KN(SiMe₃)₂, THF, −78→20 °C; (g) t-BuMe₂SiOTf, 2,6–lutidine, <35% in three steps.

Reaction of 54 with trimethylacetyl chloride (4–DMAP, ClCH₂CH₂Cl) gave triester 59 which was then subjected to hydrogenolysis (H₂, 1 atm, Pd(OH)₂–C, Pd–CaCO₃) to effect cleavage of the benzylic ether at C(4).⁴⁰ Swern oxidation of the resulting

⁴⁰. Pd/CaCO₃ was a necessary additive; in its absence, the TBS protecting groups were cleaved under the reaction conditions.
secondary alcohol 60 provided ketone 61, a key advanced intermediate in the synthesis.

Our initial plan for conversion of ketone 61 to the requisite α-hydroxy carboxylic acid involved dihydroxylation of olefin 62 and oxidation of the resulting diol. Methylenation of ketone 61 was accomplished through a two-step Peterson olefination sequence to give 62.41 Prior to developing these reaction conditions, a number of other C=O methylenation methods were screened which included: (1) Wittig olefination with Ph3PCH2;42 (2) reaction with both Tebbe (Cp2TiCl2, Me3Al)43 and Nozaki (CH2Br2, Zn, TiCl4) reagents;44 and (3) addition of MeMgBr followed by dehydration of the resulting 3° alcohol.45 Under a variety of conditions, these approaches (eg. 1, 2) either returned unreacted ketone 61 or gave the enone product arising from β-elimination of the C(8)-OTBS group. The addition of MeMgBr was effected in good yield (>80%), however, successful dehydration conditions could not be found. Preparation of the desired exocyclic olefin was accomplished when trimethylsilylmethyllithium (TMSCH2Li) was added to 61 in the presence of 0.5 equiv of LiBr (THF, −78 °C) followed by subsequent elimination of the resulting vicinal hydroxysilane (KN(TMS)2, 18-crown-6, THF/HMPA,−78 °C→−20 °C).46 Although alkene 62 was prepared using this


protocol, the yields for both reactions were highly variable (5–35%) and were sensitive to the source and age of both the TMSCH$_2$Li and the KN(TMS)$_2$ base.

Upon treatment of 62 with catalytic OsO$_4$ (NMO, acetone/iBuOH) a single diol diastereomer 63 possessing the undesired stereochemistry at C(4) was isolated (Figure 8). $^1$H NMR nOe difference experiments on 62 indicated that the 1,3-dioxane ring was in the chair conformation illustrated; moreover, analysis of molecular models suggested that distortions leading to a half-chair arrangement would result in further blocking of the concave face of the exo–methylene. Additionally, dihydroxylation of exocyclic olefins in related ring systems has been shown to favor attack by OsO$_4$ from the convex face.$^{47}$ In light of these observations, the stereochemical outcome of this transformation was surprising.

We proceeded to investigate additions to ketone 61 with nucleophiles that could be subsequently converted to the desired C(4) carboxylate.$^{48}$ This decision was based on

Figure 8. Dihydroxylation of olefin 62.

46. Under the conditions of the elimination, cleavage of both the C(10)–OTBS and C(6)–OPiv protecting groups was observed. The reason for the selective cleavage of these protecting groups is unclear at present. Reprotection with TBSOTf afforded 62.


48. Preliminary results of this work have been previously communicated, see: Carreira, E. M.; Du Bois, J. Tetrahedron Lett. 1995, 36, 1209.
an earlier finding that TMSCH$_2$Li added to 61 to give an approximately equal mixture of epimeric $\beta$-hydroxysilanes (vide supra). In further studies it was demonstrated that lithium trimethylsilyl acetylide (TMSC≡CLi) could be added to ketone 61 in THF to give a 1.5:1 mixture of carbinol adducts 65 and 66 (Table 1, Entry 1). This diastereomeric mixture could be readily separated by chromatography on silica gel, following alkyne desilylation (AgNO$_3$), to furnish the corresponding desired acetylenic alcohol 67 (Scheme 7).$^{49}$

The effect of both co-solvents and additives on the diastereocchemical outcome of the lithium acetylide reaction was investigated (Table 1).$^{50}$ When 61 was added to a

Table 1. Summary of results from TMSC≡CLi addition to ketone 61.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions$^a$</th>
<th>65:66$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>2</td>
<td>THF/TMEDA</td>
<td>1 : 2</td>
</tr>
<tr>
<td>3</td>
<td>Et$_2$O/150 equiv LiBr</td>
<td>1 : 1.7</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$O/diglyme</td>
<td>2.2 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Et$_2$O/pyridine</td>
<td>2.1 : 1</td>
</tr>
<tr>
<td>6</td>
<td>Et$_2$O/1equiv LiBr</td>
<td>3.1 : 1</td>
</tr>
<tr>
<td>7</td>
<td>Et$_2$O</td>
<td>3.5 : 1</td>
</tr>
<tr>
<td>8</td>
<td>Et$_2$O/-Pr$_2$NEt</td>
<td>3.8 : 1</td>
</tr>
<tr>
<td>9</td>
<td>Et$_2$O/Pr$_3$N</td>
<td>4.3 : 1</td>
</tr>
<tr>
<td>10</td>
<td>Et$_2$O/Me$_3$N</td>
<td>6.1 : 1</td>
</tr>
</tbody>
</table>

(a) Reactions were conducted at $-78 \degree C$ with slow warming to $0 \degree C$ in a 1:1 mixture of cosolvents with the exception of entry 5 (3:1 Et$_2$O/C$_6$H$_5$N). (b) The diastereoselectivity was determined by integration of the $^1$H NMR C(6) methine resonances for 65 and 66 at 5.51 and 5.72 ppm, respectively.


50. Addition of either TMSC≡CMgBr or the alkynyl metal reagents derived by transmetalation of the lithium acetylide with CeCl$_3$, Me$_3$Al, BF$_3$•OEt$_2$, YbCl$_3$, or Ti(OiPr)$_4$ resulted in extensive decomposition of the starting material 61.
THF/TMEDA solution of TMSC≡CLi the diastereoselectivity reversed, and a 1:2 mixture of propargylic alcohol diastereomers 65 and 66 was isolated (Entry 2). The use of Et₂O as solvent had a beneficial effect on the reaction diastereoselection (Entry 7, 65:66 = 3.5:1). The same reaction, when conducted with added LiBr (1 equiv), led to a slight attenuation in the product diastereoselectivity (Entry 6, 65:66 = 3.1:1); in the presence of excess LiBr (150 equiv) a reversal in the product distribution resulted as 66 was formed preferentially (Entry 3, 65:66 = 1:1.7). These results suggested that the reaction diastereoselection might be influenced by changes to the aggregation state of the lithium acetylide. Solution studies on lithium acetylides indicate that their aggregation equilibria can be shifted in the presence of added tertiary amines (vide infra). On this basis, we investigated the effect of amine co-solvents on the diastereomical outcome of this reaction. When an ethereal solution of ketone 61 was added to a suspension of TMSC≡CLi in 1:1 Et₂O/Me₃N at −78 °C, a significant improvement in the product ratio of 65:66 (6.1:1) was observed favoring the desired C(4) tertiary alcohol (Entry 10). In the presence of other tertiary amines (Et₃N, iPr₂NEt) similar positive effects on the reaction diastereoselection were noted (65:66 ≥ 3.8:1, see Entries 8, 9).

The structures of lithium acetylides have been studied in the solid-state and in solution. X-ray crystallographic analysis of PhC≡CLi shows a dimeric structure in which two phenylethynyl units bridge two cationic lithium centers. Cryoscopic measurements and ⁶Li and ¹³C NMR studies reveal that in solution this dimer is in equilibrium with other tetrameric aggregates. Further work by Fraenkel has established qualitatively the


52. The effect of Et₃N and TMEDA on diastereoselective Grignard additions to chiral keto oxazolines has been documented, see: Meyers, A. I.; Slade, J. J. Org. Chem. 1980, 45, 2785.


effect of solvent and additives on the \([\text{BuC}=\text{CLi} \cdot \text{L}_x]_2 \rightarrow [\text{BuC}=\text{CLi} \cdot \text{L}_y]_4\) equilibrium (eq 2). These studies demonstrate that diamine ligands such as TMEDA and donating solvents like THF promote dimer formation, whereas tetrameric aggregation states prevail when simple ethers (Et_2O) and tertiary amines are employed. Our findings, in conjunction with these previous investigations, suggest that the observed reaction diastereoselection in the addition of TMSC=CLi to ketone 61 responds in a dramatic fashion to the aggregation state of the acetylide.

\[
\begin{align*}
\text{(BuC}=\text{C-2L)}_2 & \quad \text{K_{eq}} \quad \text{(BuC}=\text{C-2L)}_4 \\
\text{Me_2C=CC=CMe_3} & \quad \text{Me_2C-CC=CMe_3} \\
\end{align*}
\]

In combination with these studies, we also became interested in developing conditions for stereoselective formation of the cyanohydrin derived from ketone 61 (Figure 9). When 61 was treated with TMSCN in the presence of BF_3\cdot OEt_2 (toluene, 0°-25°C), a ≈1:1 mixture of cyanohydrin products was isolated. Under these conditions, the Lewis acid and prolonged reaction times (ca. 13 h) led to cleavage of the C(8)-OTBS ether. A change in the product ratio (67:68 = 1:3.2) favoring attack from the convex ketone face was observed when 61 was treated with gaseous HCN (toluene, 0°-25°C). A reversal in the reaction diastereoselectivity was observed when a toluene solution of ketone 61 was added to a mixture of TMSCN and anhydrous CsF (-78°-0°C). Under


56. It is unclear whether TBS-cleavage occurred prior to or subsequent to cyanide attack.

57. The configuration at C(4) was established by 1H NMR nOe experiments. For 68, irradiation of the C(6) methine resulted in a 2.8% enhancement of the signal corresponding to the alcohol OH proton.
these conditions, cyanohydrin 67 was isolated as the major product (4.5:1). In principle, cyanohydrin 67 could be converted to the requisite α–hydroxy acid at some later stage in the synthesis.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>67:68</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCN</td>
<td>1:3.2</td>
</tr>
<tr>
<td>TMSCN–CsF</td>
<td>4.5:1</td>
</tr>
</tbody>
</table>

Figure 9. Stereoselective formation of the C(4) cyanohydrin.

**Stereochemical Assignment of the C(4) Center.** The initial stereochemical assignment of the acetylenic adducts 65 and 66 was based on a small coupling constant ($J < 2$ Hz) between the C(3)-H methine and the C(4)-OH that was only observed in the $^1$H NMR spectrum (500 MHz) of the desired diastereomer 65. $^1$H NMR difference nOe data for the minor diastereomer 66 provided tentative support of this conclusion. Similar experiments performed on intermediate 76 (Scheme 7) allowed for definitive assignment of the stereochemistry at C(3), C(4), C(6) and C(7). Irradiation of the C(6)-H methine resulted in strong enhancement of both the C(3)–H methine (11%) and the C(9)–H vinylic proton (12%). Similarly, nOe enhancement of both C(6)–H (9%) and C(9)–H (3%) was observed upon irradiation of the C(3)–H methine. Irradiation of the signals corresponding to the side chain C(1')–H$_2$ methylene protons resulted in an enhancement (3%) of the methine signal at C(7)–H (Figure 10). These results secured the configuration of the stereocenter at C(4) and provided additional support for the

58. A small nOe was observed (<3%) from the C(6)–H methine to the 3°–OH in the undesired diastereomer 66.
stereochemical assignment of the dihydroxylation reaction (45 → 46 + 47). Moreover, the nOe data accumulated paralleled that reported for the natural product itself.5

\[
\text{Figure 10. } \text{H NMR difference nOe data for 76.}
\]

**Synthesis of the tris(t-Butyl) Ester (78).** Completion of the synthesis of (+)-zaragozic acid C required installation of the C(4') acetate, oxidation at C(8), C(9) and C(10), and coupling of the C(6) O-acyl side chain. Treatment of 69 with Dibal–H (CH₂Cl₂/toluene) effected removal of all three trimethylacetyl esters (Scheme 7).59 Subsequent exposure of the resulting tetraol 70 to excess Ac₂O (4–DMAP, CH₂Cl₂) furnished 71 and installed the requisite acetate at C(4').

In our first synthesis of zaragozic acid C, the oxidations at C(8), C(9), and C(10) were performed in a stepwise manner to give the dioxabicyclooctane-tricarboxylate ester 78. To this end, intermediate 71 was exposed to mildly acidic conditions (Cl₂CHCO₂H, MeOH) to effect selective cleavage of the C(8)–OTBS ether. Semihydrogenation of the terminal acetylene (H₂, Pd–C, pyridine) provided olefin 72. Oxidation of the primary alcohol in 72 to the corresponding carboxylic acid was accomplished using the Dess–Martin periodinane followed by treatment of the intermediate aldehyde with buffered NaClO₂ solution (NaH₂PO₄, β–isoamylene, THF/H₂O).60 Esterification of the unpurified acid with N,N-diisopropyl-0-tert-butylisourea 73 afforded the tert-butyl

---

59. The use of Dibal–H in CH₂Cl₂/toluene proved to be critical for the successful cleavage of the pivaloate esters. Reactions in either THF or Et₂O failed to remove all three pivaloates.

ester 74. Following a similar sequence of steps, the TBS-ether at C(10) was cleaved (HF•pyridine, THF/pyridine) to give alcohol 75 which was oxidized, and subsequently esterified to give the bis(tert-butyl) ester 76.

Scheme 7

Deprotection of the C(10)-OTBS ether was best accomplished with HF•pyridine buffered in a THF/pyridine solution and gave the desired product 75 in 90% yield. Attempts to cleave this silyl ether under acidic conditions with either aqueous HF in CH$_3$CN or Cl$_2$CO$_2$H in MeOH gave some of 75 (60%) along with the product arising from acyl transfer of the C(6)-OAc to the C(10)-OH 79 (Figure 11). Desilylation conditions such as Et$_3$N•3HF (CH$_3$CN) and n-Bu$_4$NF•2H$_2$O/HF (aqueous CH$_3$CN) were examined and yielded similar mixtures of 75 and 79. Deprotection under basic conditions was not successful.

61. For a review on the synthetic application of isoureas, see: Mathias, L. J. Synthesis 1979, 11, 561.
conditions with n-Bu_4NF (THF) or n-Bu_4NF·2H_2O (CH_3CN) also resulted in the formation of 79 and, additionally, led to extensive product decomposition.

Figure 11. Reagents which promote C(6)–OAc to C(10)–OH acyl migration.

The remaining carboxylate at C(9) was installed following ozonolysis of 76 and oxidation of the resulting aldehyde 77 with buffered NaClO_2 (Scheme 7). Esterification with N,N-diisopropyl- O-tert-butylisourea furnished the desired tris(tert-butyl) ester 78.

A more expeditious route to 78 from 71 was subsequently developed (Scheme 8).

Scheme 8

(a) H_2, Pd/C, C_6H_6 N; (b) HF•pyr, THF/C_6H_6 N, 64% in two steps; (c) Dess-Martin periodinane, CH_2Cl_2/C_6H_6 N, 93%; (d) O_3, CH_2Cl_2/Methanol, -78 °C; (e) NaClO_2, NaH_2PO_4, β-isopropylene, THF/H_2O; (f) N,N-diisopropyl-O-tert-butylisourea (73), CH_2Cl_2, 72% in three steps; (g) K_2CO_3, Methanol, 90%.
Semi-hydrogenation of 71 (H$_2$, Pd–C, pyridine) furnished olefin 80; exposure of 80 to HF•pyridine (THF/pyridine) provided triol 81. Longer reaction times (ca. 4h) were necessary to effect cleavage of both the C(8) and C(10) silyl ethers. As a result, a small percentage (ca. 10–15%) of the product arising from acyl migration of the C(6)–OAc formed (vide supra). Fortunately, separation of this material from the desired compound 81 was possible by chromatography on silica gel. Simultaneous oxidation of both 1° carbinols at C(8) and C(10) gave dialdehyde 82. Treatment of a solution of 82 with a dilute stream of ozone (CH$_2$Cl$_2$/MeOH, –78 °C) followed by reductive workup with Ph$_3$P provided 83. The unpurified trialdehyde was then treated with a buffered NaClO$_2$ solution and the resulting triacid esterified to give the tris(tert-butyl) ester 78 (72%, three steps). Selective hydrolysis of the C(6) and C(7) acetates with 0.2% K$_2$CO$_3$ in MeOH (0.5 h) yielded 84.\(^1\)

**Synthesis of C(6) O–Acyl Side Chain.** Preparation of the C(6) O–acyl side chain was achieved using a Claisen rearrangement-based strategy for the construction of the derived γ,δ-unsaturated carboxylic acid 92 (Scheme 9). Treatment of a suspension of para-formaldehyde in THF with alkynyl lithium 86 afforded a propargylic alcohol which was reduced with LiAlH$_4$ to give trans allylic alcohol 87.\(^6\)\(^5\) Sharpless asymmetric epoxidation of 87 provided the epoxy alcohol 88 in > 95% ee, as determined by analysis of the $^1$H NMR spectrum of the corresponding Mosher (S)–MTPA ester.\(^6\)\(^6\),\(^6\)\(^7\) Regioselective epoxide opening with Me$_3$Al using conditions described by Roush and

\(^{64.}\) The $^1$H NMR spectrum of 83 shows a mixture of at least three products presumed to be hydrated forms of the trialdehyde.


Nozaki for related epoxy alcohols, followed by NaIO₄ cleavage of the resulting 1,2-diol yielded 89. Aldehyde 89 was treated with vinyl magnesium bromide to give a 60:40 mixture of alcohol diastereomers 90. Upon heating a solution of 90 in triethyl orthoacetate (cat. diglycolic acid), the trans ester 91 was formed exclusively, as determined by ¹H NMR spectroscopy. Saponification of the ethyl ester provided the corresponding carboxylic acid 92, suitable for coupling to the zaragozic acid core 84.

**Scheme 9**

![Chemical Reaction Diagram](attachment:image.png)

(a) n-BuLi, (CH₂O)n, THF, 92%; (b) LiAlH₄, Et₂O, 79%; (c) t-BuOOH, Ti(OPr)₄, L-(-)-DIPT, 4Å MS, CH₂Cl₂, 98%; (d) Me₂Al then NaIO₄, aq. THF; (e) vinylmagnesium bromide, THF, 62% in three steps; (f) (EtO)₂CMe, H⁺, 89%; (g) NaOH, THF/H₂O, 100%; (h) (COCl)₂, cat. DMF, CH₂Cl₂.

**Model Studies with Zaragozic Acid A.** Previously, it was shown that treatment of 84 (4-DMAP, CH₂Cl₂) with acid chloride 93 prepared from 92 afforded a 1:3 mixture of desired C(6) to undesired C(7) regioisomers, respectively. Thus, we initiated an investigation of reaction conditions that would favor formation of desired C(6) O-acylated compound. As a model substrate we chose to examine the acylation chemistry of zaragozic acid A (94), which was available in multi-gram quantities. In addition, hexanoyl chloride was employed as a surrogate acyl side chain (Scheme 10).

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69. We are grateful to Drs. Gregory Berger and Albert Robichaud (Merck Reasearch Laboratories) for generously providing the tris(tert-butyl)ester of zaragozic acid A.
Condensation of 95 with hexanoyl chloride (4–DMAP, CH₃CN) led to the formation of products 96 and 97 in a similar ratio to that observed in our original studies (ca. 1:3). Acylation procedures which utilized either bis(tributyltin) oxide or dibutyltin oxide and hexanoyl chloride did not provide either 96 or 97. Hexanoyl chloride was found to couple to 95 in the presence of excess 2–*tert*-butyl–2–diethylamino–1,3–dimethylperhydro–1,3,2–diazaphosphorine.⁷⁰ In the event, it was discovered that the undesired product 97 had formed predominantly (96:97, ca. 1:10 by ¹H NMR spectroscopy).

The development of a strategy which involved *in situ* protection of the C(7)–OH and subsequent acylation of the C(6) carbinol was then investigated and ultimately realized. Upon treatment of 95 with di–*tert*–butyl dicarbonate (Et₃N, CH₂Cl₂, 0 °C) and catalytic 4–DMAP, a ca. 1:3 mixture of C(6)/C(7)–carbonates 98 and 99 was isolated (52% combined) along with recovered starting material 95 (ca. 25%) and a small amount

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(≤15%) of the bis-protected material.\(^7\) Alternatively, when 4-pyrrolidinopyridine was used instead of 4–DMAP, the reaction yielded C(7)O–Boc intermediate 99 as the exclusive product (80–85%).\(^7\) This highly regioselective transformation made it possible to perform the subsequent coupling of hexanoyl chloride (4–DMAP, Et\(_3\)N) to the C(6)–OH in a single operation.\(^7\)

\textbf{(+-)–Zaragozic Acid C.} Completion of the zaragozic acid C synthesis was accomplished following a strategy similar to that developed with the zaragozic acid A model (Scheme 11). Treatment of 84 with di–tert–butyl dicarbonate and catalytic 4–pyrrolidinopyridine (Et\(_3\)N, CH\(_2\)Cl\(_2\)) gave 100 as the exclusive product (82%).

\textbf{Scheme 11}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {84};
\node (b) at (3,0) {100};
\node (c) at (6,0) {101};
\node (d) at (0,-2) {(+)-Zaragozic Acid C};
\node (e) at (0,-4) {R = \text{Ph}};
\end{tikzpicture}
\end{center}

(a) (Boc)\(_2\)O, 4–pyrrolidinopyridine, CH\(_2\)Cl\(_2\), 82%; (b) 92, DCC, 4–DMAP, CH\(_2\)Cl\(_2\), 78%; (c) CF\(_3\)CO\(_2\)H, CH\(_2\)Cl\(_2\), 100%.

Subsequent addition of a solution of carboxylic acid 92 and 1,3-dicyclohexyl carbodiimide (4–DMAP, CH\(_2\)Cl\(_2\)) furnished 101 (78%). Complete deprotection of 101 was effected with a 25% solution of trifluoroacetic acid in CH\(_2\)Cl\(_2\) (16h) to afford the

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71. The ratio of 98:99 was dependent on the extent of conversion of 95.

72. We speculated that the bulkier acylating agent generated with 4–pyrrolidinopyridine would be more selective for the less sterically hindered secondary alcohol at C(7).

73. In practice a higher yield of the desired product was isolated when the reaction was performed in a two–step sequence.
target compound, (+)-zaragozic acid C. Zaragozic acid C, prepared via the synthetic route described, was identical in all respects (¹H NMR, ¹³C NMR, IR, HRMS, TLC, HPLC co-injection, optical rotation) to an authentic sample of the natural product.⁷⁴

Conclusion

We have described an enantioselective synthesis of the potent squalene synthase inhibitor, (+)-zaragozic acid C. This route is highlighted by: (1) a highly diastereoselective addition of TMSC≡CMgBr to an α,β-unsaturated ketone to establish the quaternary center at C(5); (2) the use of [Cr(OAc)₂•H₂O]₂ for the stereoselective reduction of α,β-ynones to trans enones; (3) an investigation of the effect of amine co-solvents on the nucleophilic addition of TMSC≡CLi to a key dioxabicyclooctanone intermediate; and (4) a solution to the problem of coupling the acyl side chain to the C(6)–OH by regioselective protection of the C(7) carbinol. Additionally, we have outlined a protocol for installing the three carboxylic acids at C(8), C(9), and C(10) by simultaneous oxidation of the corresponding tris-aldehyde, which represents a more efficient strategy than that which we have previously reported.⁴ This work has resulted in the development of a synthesis which allows for rapid assembly of the dioxabicyclooctane skeleton common to all of the zaragozic acids and squalestatins. Moreover, a number of synthetic transformations on the bicyclic core have been delineated which may find use in the preparation of synthetic and semisynthetic analogs.

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⁷⁴. We thank Dr. Conrad Santini (Merck Research Laboratories) for generously providing us with an authentic sample of zaragozic acid C.
Experimental

**General methods.** All reagents were commercially obtained and purified prior to use. All non–aqueous reactions were performed using flame-dried glassware under an atmosphere of dry nitrogen. Air and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at ca. 25 mm Hg (water aspirator). Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl prior to use. N,N–diisopropylethylamine, dichloromethane, pyridine, triethylamine and boron trifluoride etherate were distilled from calcium hydride prior to use. Dimethylsulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Methanol was distilled from magnesium methoxide prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on Baker 7024–R silica gel according to the method of Still. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60F plates (230–400 mesh). Visualization of the developed chromatogram was performed by either fluorescence quenching, aqueous ceric ammonium molybdate (CAM) stain, or an ethanolic p-anisaldehyde spray.

NMR spectra were recorded on a Bruker AM–500 operating at 500 and 125 MHz for ¹H and ¹³C, respectively, and are referenced internally to residual protio solvent signals. Data for ¹H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), integration, coupling constant (Hz), and assignment (when indicated, numbered protons refer to zaragozic acid C numbering¹c). Data for ¹³C are reported in terms of chemical shift. ¹H NMR nOe difference spectra were recorded on degassed samples and were quantitated by

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integrating the difference spectra. IR spectra were recorded on a Perkin–Elmer 1600 Series spectrometer using NaCl salt plates, and reported in terms of frequency of absorption (cm\(^{-1}\)). Melting points were determined on a Mel-Temp apparatus and are uncorrected. Combustion analysis was performed by Galbraith Laboratories, Inc. (Knoxville, TN). High resolution mass spectra were obtained from the UC Irvine Mass Spectral facility. Optical rotations were determined on a JASCO DIP–181 polarimeter operating at either the sodium D line or Hg\(_{365}\) and are reported as follows: \([\alpha]\)^{23}, concentration (g/100 mL), and solvent.

![Chemical Structure](image)

\(N, N\)-Dimethyl-2,3,4-trihydroxybutyramide. Gaseous Me\(_2\)NH (ca. 40 mL, 83 mmol, 1.2 equiv) was condensed directly into a reaction flask containing a suspension of 81.3 g (68.8 mmol) of d-erythronic \(\gamma\)-lactone\(^{18}\) 13 in 240 mL of reagent–grade methanol at 0 °C. The resulting homogeneous solution was stirred at 0 °C for 15 min and then warmed to 23 °C. Consumption of the starting lactone (\(R_f = 0.80\)) was monitored by TLC with 1% H\(_2\)O–CH\(_3\)CN as eluent. After stirring at 23 °C for 30 min, the solvent was evaporated under reduced pressure to afford a white solid. Recrystallization of the unpurified product from hot/cold methanol yielded 112.3 g (97%) of a white crystalline solid. mp 108-110 °C; \([\alpha]_\text{Hg} -117.4^\circ (c = 0.15, \text{CH}_3\text{OH}); \) \(^1\)H NMR (CD\(_3\)OD, 500 MHz) \(\delta\) 4.49 (d, 1H, \(J = 7.1\) Hz, H\(_4\)), 3.74-3.65 (m, 3H, H\(_3\) and H\(_8\)), 3.13 (s, 3H, -NCH\(_3\)), 2.97 (s, 3H, -NCH\(_3\)) ppm; \(^{13}\)C NMR (CD\(_3\)OD, 125 MHz) \(\delta\) 174.9, 74.8, 69.5, 64.2, 37.7, 36.2 ppm; IR (thin film) \(\nu\) 3356 (br), 2936, 1629, 1508, 1401, 1257, 1064 cm\(^{-1}\); Anal. Calcd for C\(_6\)H\(_{13}\)NO\(_4\): C, 44.16; H, 8.03. Found: C, 44.12; H, 8.09.
α-Hydroxyamide (14). To a solution of 3,3-dimethoxypentane (107 g, 809 mmol, 1.2 equiv) and anhydrous p-toluenesulfonic acid (5.5 g, 29 mmol, 0.04 equiv) in 1 L of THF was added N,N-dimethyl-2,3,4-trihydroxybutyramide (110 g, 674 mmol) portionwise. The pale yellow solution was heated at reflux for 4 h before being cooled to 23 °C. The reaction was made basic with 20.0 mL Et$_3$N and concentrated in vacuo to afford a pale yellow oil. The unpurified material was filtered through silica gel (gradient elution: 3:1→1:2 hexanes/EtOAc) to give 140 g (90%) of 14 as a clear, colorless oil. TLC $R_f = 0.56$ (1:1 CH$_2$Cl$_2$/EtOAc); $[\alpha]_{\text{Hg}}$ -27.8° ($c = 0.18$, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 4.38 (d, 1H, $J = 7.4$ Hz, H$_4$), 4.10 (dd, 1H, $J = 8.2$, 6.2 Hz, H$_8$), 3.99-3.95 (m, 1H, H$_3$), 3.90 (dd, 1H, $J = 8.2$, 7.4 Hz, H$_8$), 3.53 (br s, 1H, -OH$_2$), 3.07 (s, 3H, -NCH$_3$), 2.99 (s, 3H, -NCH$_3$), 1.69-1.59 (m, 2H, -CH$_2$CH$_3$), 1.54 (q, 2H, $J = 7.4$ Hz, -CH$_2$CH$_3$), 0.88 (t, 3H, $J = 7.5$ Hz, -CH$_2$CH$_3$), 0.81 (t, 3H, $J = 7.4$ Hz, -CH$_2$CH$_3$) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 172.2, 113.8, 77.6, 68.99, 68.97, 67.8, 36.9, 36.0, 29.4, 28.5, 8.1, 8.0 ppm; IR (thin film) ν 3417 (br), 2972, 2940, 2883, 1789, 1644, 1504, 1463, 1392, 1172, 1078, 919 cm$^{-1}$; Anal. Calcd for C$_{11}$H$_{21}$NO$_4$: C, 57.12; H, 9.15. Found: C, 56.81; H, 9.17.

α-Benzylxoyamide (15). A 60% dispersion of NaH in mineral oil (4.4 g, 110 mmol) was washed under a stream of N$_2$ three times with dry pentane and dried briefly under vacuum. THF was added (125 mL) and the suspension was cooled to 0 °C. A
solution of amide 14 (25.0 g, 108 mmol) in 200 mL of THF was added dropwise over a 30 min period. The mixture was stirred until H₂ gas evolution subsided, at which time benzyl bromide (16 mL, 135 mmol) was added via syringe. The reaction was held at 0 °C for 15 min before being warmed to 23 °C. After 3 h at 23 °C the reaction was quenched with 200 mL 1.0 M K₂HPO₄, and the product extracted with Et₂O (3 x 200 mL). The combined organic extracts were washed with sat. aqueous NaCl (1 x 250 mL), dried over Na₂SO₄ and evaporated under reduced pressure. Purification by silica gel chromatography (gradient elution: 5:1→1:1 hexanes/EtOAc) gave 33.4 g (96%) of 15 as a colorless oil which solidified in vacuo. TLC Rₚ= 0.38 (1:1 hexanes/EtOAc); mp 55-56 °C; [α]Na +136.8° (c = 0.23, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.35-7.27 (m, 5H, H aromatic), 4.62 (d, 1H, J = 11.8 Hz, -CH₂Ph), 4.46 (d, 1H, J = 11.8 Hz, -CH₂Ph), 4.35 (dd, 1H, J = 13.1, 6.5 Hz, H₃), 4.28 (d, 1H, J = 6.4 Hz, H₄), 4.15 (dd, 1H, J = 8.4, 6.3 Hz, H₅), 3.93 (dd, 1H, J = 8.4, 7.0 Hz, H₆), 2.99 (s, 3H, -NCH₃), 2.97 (s, 3H, -NCH₃), 1.66-1.56 (m, 4H, both -CH₂CH₃), 0.85 (m, 6H, both -CH₂CH₃) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 169.5, 137.2, 128.4, 127.97, 127.94, 113.4, 76.8, 76.3, 71.8, 67.4, 36.9, 36.05, 36.03, 29.5, 28.4, 8.1 ppm; IR (thin film) ν 3030, 2971, 2939, 2881, 1650, 1497, 1455, 1172, 1129, 1083, 1058, 919, 699 cm⁻¹; HRMS (EI) calcd for C₁₈H₂₇NO₄ 321.2120, found 321.1971; Anal. Calcd for C₁₈H₂₇NO₄: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.09; H, 8.47; N, 4.12.

Propargylic alcohol (17). A 1.7 M solution of t-BuLi in pentane (182 mL, 310 mmol, 3.0 equiv) was added to a solution of ethyl vinyl ether (59 mL, 620 mmol, 6.0 equiv) in 125 mL of THF at −78 °C. After 1 h the yellow suspension was warmed to 0 °C
and stirred for an additional 2 h. The resulting colorless solution was re-cooled to −78 °C before a cold solution (0 °C) of amide 15 (33.2 g, 103 mmol) in 150 mL of THF was added dropwise. The mixture was then stirred at −78 °C for 10 min and then transferred via cannula into 500 mL of a vigorously stirred solution of 1:1 Et₂O/0.2 M aqueous Na₂CO₃ at 0 °C. The organic phase was separated and the aqueous layer extracted additionally with Et₂O (2 x 300 mL). The combined organic extracts were washed with sat. aqueous NaCl (1 x 400 mL), dried over Na₂SO₄ and concentrated to afford 36.0 g of an unpurified yellow oil 16. TLC Rf = 0.57 (4:1 hexanes/EtOAc).

The unpurified product 16 (36.0 g, 103.3 mmol) was dissolved in 200 mL of THF, cooled to −78 °C, and added via cannula to a cold suspension (−78 °C) of the Grignard reagent derived from trimethylsilyl acetylene and ethyl magnesium bromide (359 mL of a 0.86 M solution in THF/Et₂O, 3.0 equiv). Following addition, the reaction was warmed to 0 °C and stirred for 15 min before being quenched with 300 mL sat. aqueous NH₄Cl. The organic phase was collected and the aqueous layer was extracted with 2 x 300 mL Et₂O. The organic extracts were combined, washed with sat. aqueous NaCl (1 x 500 mL), dried over Na₂SO₄ and concentrated in vacuo to a yellow oil. Purification by chromatography on silica gel (gradient elution: 10:1→9:1 hexanes/EtOAc) afforded propargyl alcohol 17 as a single diastereomer (38.7 g, 84%, colorless oil). TLC Rf = 0.59 (4:1 hexanes/EtOAc); mp 37-40 °C; [α]Na + 71.9° (c = 0.41, CH₂Cl₂); ¹H NMR (C₆D₆, 500 MHz) δ 7.44 (d, 2H, J = 7.2 Hz, H aromatic), 7.18 (t, 2H, J = 7.6 Hz, H aromatic), 7.10 (t, 1H, J = 7.4 Hz, H aromatic), 4.98 (d, 1H, J = 2.3 Hz, -C=CH₂), 4.93 (d, 1H, J = 10.8 Hz, -OCH₂Ph), 4.88 (d, 1H, J = 10.8 Hz, -OCH₂Ph), 5.70 (ddd, 1H, J = 9.0, 5.7, 2.9 Hz, H₃), 4.47 (d, 1H, J = 3.3 Hz, H₄), 4.18 (dd, 1H, J = 8.1, 6.2 Hz, H₈), 4.09 (t, 1H, J =8.3 Hz, H₈), 3.98 (d, 1H, J = 2.3 Hz, -C=CH₂), 3.39-3.34 (m, 2H, -OCH₂CH₃), 3.20 (s, 1H, -OH₃), 1.74-1.62 (m, 4H, both -CH₂CH₃), 1.00 (t, 3H, J = 7.0 Hz, -OCH₂CH₃), 0.94 (t, 6H, J = 7.5 Hz, both -CH₂CH₃), 0.10 (s, 9H, H TMS) ppm; ¹³C NMR (CD₂Cl₂, 125 MHz) δ 160.3, 139.1, 128.8, 128.5, 128.2, 112.7, 106.0, 90.8, 84.6, 82.1, 77.0, 76.1, 74.5,
Alkynyl Ester (19). A solution of vinyl ether 17 (43.2 g, 96.7 mmol) in 450 mL of CH₂Cl₂ and 50 mL of absolute EtOH was cooled to −78 °C before being treated with a dilute stream of ozone in oxygen (0.8 mmol/min). Careful monitoring by TLC showed the reaction to be complete after 2.5 h (ca. 1 equiv O₃). Triphenylphosphine (26.2 g, 100 mmol) was then added to the reaction, and the mixture was slowly warmed to 23 °C. Concentration of the reaction mixture yielded an orange oil. Purification by chromatography on silica gel (gradient elution: 12:1→6:1 hexanes/EtOAc) gave 36.4 (84%) of a clear, viscous oil 19. TLC R_f = 0.42 (4:1 hexanes/EtOAc). [α]_Hg +92.3° (c = 0.17, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.38-7.27 (m, 5H, H arom), 5.03 (d, 1H, J = 11.1 Hz, -CH₂Ph), 4.77 (d, 1H, J = 11.1 Hz, -CH₂Ph), 4.41-4.36 (m, 1H, -OCH₂CH₃), 4.27 (m, 1H, H₃), 4.17 (m, 1H, -OCH₂CH₃), 4.09 (d, 1H, J = 5.9 Hz, H₄), 4.03 (dd, 1H, J = 8.2, 6.3 Hz, H₈), 3.73 (t, 1H, J = 8.1 Hz, H₈), 3.69 (s, 1H, -OH½), 1.61-1.54 (m, 4H, both -CH₂CH₃), 1.32 (t, 3H, J = 7.1 Hz, -OCH₂CH₃), 0.85 (m, 6H, both -CH₂CH₃), 0.16 (s, 9H, H TMS) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 169.7, 137.8, 128.3, 127.84, 127.78, 112.88, 102.1, 91.3, 83.7, 76.0, 74.7, 73.1, 67.0, 62.9, 29.4, 28.7, 13.8, 8.1, -0.49, -0.52 ppm; IR (thin film) ν 3482 (br), 2970, 2941, 2883, 1743, 1498, 1464, 1295, 1251, 1127, 1094, 1077, 1060, 1028, 845, 698 cm⁻¹; HRMS (EI) calcd for C₂₅H₃₈SiO₅ 448.2550, found 448.2271.
Core Fragment (21). A solution of the alkynyl ester 19 (36.2 g, 80.7 mmol) in 200 mL of CH$_3$OH was cooled to 0 °C, and NaBH$_4$ (9.1 g, 240 mmol, 3.0 equiv) was cautiously added portionwise. Once gas evolution had subsided, the mixture was warmed to 23 °C. After 2 h the reaction was re-cooled to 0 °C, diluted with 100 mL Et$_2$O and acidified to pH 2 with aqueous 1.0 M NaHSO$_4$. The ethereal layer was collected, and the aqueous layer was extracted with 3 x 300 mL CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$, then concentrated to a colorless, viscous oil (32.8 g). The product 20 was used without further purification. TLC $R_f = 0.52$ (2:1 hexanes/EtOAc).

To a solution of 20 (32.8 g, 80.7 mmol) in 200 mL of CH$_3$OH was added solid K$_2$CO$_3$ (11.2 g, 80.7 mmol). The reaction was stirred for 8 h at 23 °C before 300 mL of Et$_2$O was added. The resulting precipitate was removed via filtration through Celite. Evaporation of the filtrate under reduced pressure afforded a pale brown oil which was purified by chromatography on silica gel (gradient elution: 9:1→1:1 hexanes/EtOAc) to furnish 21.0 g (78%) of diol 21 as a clear, colorless oil. TLC $R_f = 0.27$ (2:1 hexanes/EtOAc); [α]$_{Na}$ +68.5° (c = 0.43, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.38-7.32 (m, 5H, H$_{aromatic}$), 4.85 (d, 1H, J = 11.4 Hz, -CH$_2$Ph), 4.65 (d, 1H, J = 11.4 Hz, -CH$_2$Ph), 4.52-4.47 (m, 1H, H$_3$), 4.43 (s, 1H, -OH$_3$), 4.10 (dd, 1H, J = 8.4, 6.2 Hz, H$_8$), 3.84-3.80 (m, 2H, H$_{10}$), 3.65 (d, 1H, J = 8.4 Hz, H$_4$), 3.59 (t, 1H, J = 7.9 Hz, H$_8$), 2.54 (s, 1H, -C≡CH), 2.35 (dd, 1H, J = 9.9, 4.4 Hz, -OH$_2$), 1.67-1.60 (m, 4H, both -CH$_2$CH$_3$), 0.89 (t, 6H, J = 7.4 Hz, both -CH$_2$CH$_3$) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 137.5, 128.5 (2), 128.2, 114.1, 82.8, 78.5, 76.3, 74.76, 74.72, 73.9, 68.4, 66.1, 29.8, 28.9, 8.1, 8.0 ppm; IR (thin film) ν 3446 (br), 3283, 2972, 2939, 1456, 1355, 1200, 1077, 917 cm$^{-1}$; Anal. Calcd for C$_{19}$H$_{26}$O$_5$: C, 68.24; H, 7.84. Found: C, 67.89; H, 7.91.
Core Fragment (22). To a solution of diol 21 (18.9 g, 56.5 mmol) in 250 mL of CH₂Cl₂ was added Et₃N (23.6 mL, 169.0 mmol, 3.0 equiv), iBuMe₂SiCl (12.8 g, 84.8 mmol, 1.5 equiv), and 4–DMAP (696 mg, 5.7 mmol, 0.1 equiv). The reaction mixture was stirred at 23 °C for 12 h before an additional 3.0 equiv of Et₃N (23.6 ml) was added along with 700 mg of 4–DMAP and Me₃SiCl (10.7 ml, 84.8 mmol, 1.5 equiv). A precipitate formed immediately following addition of Me₃SiCl. After 30 min the pale red mixture was poured onto 200 mL of a 1.0 M K₂HPO₄ solution. The product was extracted into CH₂Cl₂ (3 x 100 ml), the combined extracts dried over Na₂SO₄ and concentrated to a red-brown oil. Purification by chromatography on silica gel (gradient elution: 30:1→20:1 hexanes/Et₂O) afforded 26.0 g (88%) of 22 as a colorless oil. TLC Rₐ = 0.65 (8:1 hexanes/EtOAc); [α]_Hg +150.0° (c = 0.17, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.36 (dd, 2H, J = 7.4, 1.5 Hz, H_arámatico), 7.34-7.31 (m, 2H, H_arámatico), 7.28-7.26 (m, 1H, H_arámatico), 4.87 (d, 1H, J = 11.1 Hz, -CH₂Ph), 4.80 (d, 1H, J = 11.1 Hz, -CH₂Ph), 4.47 (ddd, J = 8.5, 6.6, 1.7 Hz, 1H, H₃), 4.13-4.06 (m, 3H, H₄, H₅), 3.78 (d, 1H, J = 10.3 Hz, H₁₀), 3.60 (d, 1H, J = 10.3 Hz, H₁₀), 2.47 (s, 1H, -C≡CH), 1.69-1.55 (m, 4H, both -CH₂CH₃), 0.94-0.87 (m, 6H, both -CH₂CH₃), 0.92 (s, 9H, H_TBS-₄Bu), 0.19 (s, 9H, H_TMS), 0.09 (s, 3H, H_TBS-Me), 0.07 (s, 3H, H_TBS-Me) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 139.0, 128.1, 127.5, 127.2, 111.0, 83.8, 80.1, 76.6, 76.0, 75.5, 74.3, 68.4, 65.0, 29.8, 28.7, 25.9, 18.3, 8.4, 8.1, 1.9, -5.2, -5.3 ppm; IR (thin film) ν 2930, 2857, 1463, 1359, 1251, 1129, 1102, 984, 924, 840, 778 cm⁻¹; HRMS (EI) calcd for C₂₈H₄₈Si₂O₅ 520.3265, found 520.3045.
**Aldol Adduct (25).** To a solution of (S)-benzyloxazolidinone\(^\text{24}\) (20.0 g, 85.7 mmol) in 400 mL of CH\(_2\)Cl\(_2\) at \(-78^\circ\)C was added a solution of 25.5 g of 9-BBNOTf (94.3 mmol, 1.1 equiv) in 50.0 mL of CH\(_2\)Cl\(_2\), followed by neat \(\text{Pr}_2\)NEt (20.9 mL, 120.0 mmol, 1.4 equiv). The mixture was allowed to stir for 30 min at \(-78^\circ\)C and was then warmed to 0 \(^\circ\)C, where it was held for an additional 3 h. Upon re-cooling the contents to \(-78^\circ\)C, a cold solution (-78 \(^\circ\)C) of aldehyde 24 (18.1 g, 94.3 mmol, 1.1 equiv) in 100 mL of CH\(_2\)Cl\(_2\), was transferred via cannula to the reaction flask. The solution was allowed to warm slowly to 23 \(^\circ\)C over 12 h. After cooling to 0 \(^\circ\)C the reaction was diluted with 400 mL of MeOH and 90 mL of a 1.0 M aqueous K\(_2\)HPO\(_4\)–H\(_3\)PO\(_4\) solution (pH 7). Careful addition of 180 mL of a 1:1 MeOH/30% H\(_2\)O\(_2\) solution resulted in the formation of a milky white suspension which was stirred vigorously at 0 \(^\circ\)C for 2 h. The mixture was partitioned between 400 mL of H\(_2\)O and 400 mL of CH\(_2\)Cl\(_2\), the organic phase was collected and the aqueous layer extracted additionally with 2 x 400 mL CH\(_2\)Cl\(_2\). The combined extracts were dried over Na\(_2\)SO\(_4\) and concentrated *in vacuo* to a yellow oil. Purification by chromatography on silica gel (gradient elution: 5:1→1:1 hexanes/EtOAc) gave 25 (30.4 g, 84%) as a single diastereomer. TLC R\(_f\) = 0.12 (2:1 hexanes/EtOAc); [\(\alpha\)]\(_\text{Na}^+\) +101.9\(^\circ\) (c = 0.41, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.35-7.33 (m, 6H, H\(_{\text{aromatic}}\)), 7.30-7.26 (m, 2H, H\(_{\text{aromatic}}\)), 7.20 (d, 2H, J = 7.2 Hz, H\(_{\text{aromatic}}\)), 4.72-4.68 (m, 1H, -OCH\(_2\)CH(N-))Bn), 4.50 (s, 2H, -OCH\(_2\)Ph), 4.24-4.18 (m, 2H, -OCH\(_2\)CH(N-))Bn), 3.96-3.95 (m, 1H, H\(_5\)), 3.76 (dd, 1H, J = 14.1, 7.0, 2.6 Hz, H\(_4\)), 3.48 (t, 2H, J = 6.5 Hz, -CH\(_2\)OCH\(_2\)Ph), 3.25 (dd, 1H, J = 13.4, 3.3 Hz, -OCH\(_2\)CH(N-))CH\(_2\)Ph), 2.89 (d, 1H, J = 3.0 Hz, -OH\(_2\)), 2.79 (dd, 1H, J = 13.4, 9.5 Hz, -OCH\(_2\)CH(N-))CH\(_2\)Ph), 1.68-1.55 (m, 4H, H\(_1\), H\(_3\)), 1.47-1.41 (m, 2H, H\(_2\)), 1.25 (d, 3H, J = 7.0 Hz, H\(_{13}\)) ppm; \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 177.5, 153.0, 138.6, 135.0, 129.4, 129.0, 128.3, 127.6, 127.45, 127.43, 72.9,
71.4, 70.2, 66.2, 55.1, 42.1, 37.8, 33.6, 29.6, 22.7, 10.4 ppm; IR (thin film) ν 3512 (br), 2938, 2861, 1779, 1695, 1496, 1454, 1385, 1210, 1109, 738 cm⁻¹; HRMS (FAB⁺) calc'd for C_{25}H_{31}NO_{5} 425.2202, found 426.2287 (MH⁺).

**Diol (27).** 30% H₂O₂ (26.4 mL, 264 mmol, 4.0 equiv) was added dropwise to a solution of aldol adduct 25 (28.0 g, 65.8 mmol) in 1 L of a 3:1 THF/H₂O mixture at 0 °C. LiOH·H₂O (5.5 g, 132 mmol, 2.0 equiv) was transferred in five equal portions to the reaction flask. Stirring continued at 0 °C for 3 h before 200 mL of a 1.5 M aqueous Na₂SO₃ solution (4.5 equiv) was carefully added. The mixture was made alkaline by the addition of 250 mL of a 10% v/v HCl solution. The organic phase was collected, and the aqueous layer was extracted with 4 x 750 mL CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and concentrated to a pale orange, viscous oil (17.5 g). The product was used without further purification.

A solution of the unpurified acid (17.5 g, 65.8 mmol) in 500 mL THF was cooled to 0 °C, and solid LiAlH₄ (11.4 g, 300.0 mmol) was cautiously added portionwise. Following addition, the gray suspension was heated to reflux. After 8 h at reflux the mixture was cooled to 0 °C, diluted with 250 mL Et₂O, and quenched by the dropwise addition of 500 mL of a 10% v/v HCl solution. The ethereal layer was collected and the aqueous phase extracted additionally with 3 x 400 mL Et₂O. The combined organic extracts were dried over Na₂SO₄ and the solvent removed under reduced pressure to afford a pale orange oil. Purification of the residue by chromatography on silica gel (gradient elution: 2:1→1:3 CH₂Cl₂/EtOAc) furnished the diol 27 as a white solid (15.2 g, 92%). TLC Rᶠ = 0.30 (1:1 CH₂Cl₂/EtOAc); mp 43-44 °C; [α]_Na +40.8 (c = 0.42,
CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.35-7.34 (m, 1H, Hᵦaromatic), 7.33-7.28 (m, 1H, Hᵦaromatic), 4.50 (s, 2H, -OCH₂Ph), 3.82 (m, 1H, H₄'), 3.69 (m, 2H, H₆'), 3.49 (dt, 2H, J = 6.3, 1.6 Hz, -CH₂OCH₂Ph), 2.47 (br s, 2H, -OH₁⁻ and -OH₂⁻), 1.78-1.74 (m, 1H, H₅'), 1.68-1.51 (m, 4H, H₁', H₃'), 1.49-1.41 (m, 2H, H₂'), 0.90 (d, 3H, J = 7.1 Hz, H₁₃'). ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 138.5, 128.4, 127.7, 127.6, 74.5, 73.0, 70.3, 67.2, 39.1, 33.7, 29.6, 22.9, 10.1 ppm; IR (thin film) ν 3367 (br), 2935, 1361, 1099, 1027, 734, 696 cm⁻¹; Anal. Caled for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.51.

**Tosylate (28).** To an ice cold solution of diol 27 (15.0 g, 59.5 mmol) in 300 mL of pyridine was added solid p-TsCl (11.3 g, 59.5 mmol, 1.0 equiv). The solution was stirred at 0 °C for 42 h and then partitioned between 300 mL of a 10% v/v HCl solution and 400 mL of Et₂O. The ethereal layer was collected and washed additionally with 300 mL of 10% v/v HCl. The combined aqueous portions were extracted with 3 x 300 mL Et₂O. The ethereal extracts were washed successively with 1 x 400 mL 10% v/v HCl, 1 x 400 mL 0.2 M aqueous CuSO₄, and 1 x 400 mL sat. aqueous NaCl, then dried over Na₂SO₄. Evaporation of the Et₂O under reduced pressure yielded a pale brown residue which was purified by chromatography on silica gel (gradient elution: 5:1→1:1 hexanes/EtOAc) to give the product 28 as a colorless oil (21.5 g, 89%). TLC Rₜ = 0.62 (1:1 hexanes/EtOAc); [α]Na +45.8° (c = 0.38, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.79 (d, 2H, Hᵦaromatic), 7.36-7.32 (m, 6H, Hᵦaromatic), 7.31-7.27 (m, 1H, Hᵦaromatic), 4.50 (s, 1H, -OCH₂Ph), 4.06 (dd, 1H, J = 9.7, 7.9 Hz, H₆'), 3.88 (dd, 1H, J =9.7, 6.0 Hz, H₆'), 3.70 (m, 1H, H₄'), 3.49-3.45 (m, 2H, -CH₂OCH₂Ph), 2.45 (s, 3H, -SO₂ArCH₃), 1.91-1.86 (m, 1H, H₅'), 1.67-1.34 (m, 6H, H₁', H₂', H₃'), 0.84 (d, 3H, J = 7.0 Hz, H₁₃') ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 144.8, 138.6, 133.1, 129.9, 128.4, 127.9, 127.7, 127.5, 72.9,
72.7, 70.5, 70.2, 37.8, 34.1, 29.6, 22.9, 21.6, 9.5 ppm; IR (thin film) ν 3433 (br), 2938, 2861, 1598, 1495, 1454, 1357, 1188, 1176, 1097, 963, 814, 737 cm⁻¹; Anal. Calcd for C₂₂H₃₀SO₅: C, 65.00; H, 7.44. Found: C, 64.94; H, 7.53.

**Alcohol (30).** A 1.3 M solution of PhLi (64.5 mL, 83.8 mmol, 1.5 equiv) in 70:30 cyclohexane/Et₂O was added dropwise to a solution of 28 (22.7 g, 55.8 mmol) in 500 mL of THF at 0 °C. The mixture was warmed to 23 °C and stirred for 30 min, then transferred via cannula over a 1 h period to a solution of PhLi (1.3 M c-hex/Et₂O, 129.0 mL, 167.6 mmol, 3.0 equiv) and BF₃•OEt₂ (21.0 ml, 167.6 mmol, 3.0 equiv) in 250 ml of THF at −78 °C. Following addition, the reaction was warmed to 0 °C over 1 h, then quenched by the addition of 600 ml sat. aqueous NaHCO₃. The aqueous phase was collected and extracted additionally with 3 x 300 mL Et₂O. The combined organic extracts were washed once with sat. aqueous NaCl (500 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the isolated brown residue by chromatography on silica gel (gradient elution: 7:1→3:1 hexanes/EtOAc) afforded 15.8 g (91%) of 30 as a clear, colorless oil. TLC Rf = 0.23 (4:1 hexanes/EtOAc); [α]_Na +4.5° (c = 0.43, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.36-7.34 (m, 4H, Haryl), 7.31-7.27 (m, 3H, Haryl), 7.21-7.17 (m, 3H, Haryl), 4.50 (s, 2H, -OCH₂Ph), 3.55-3.51 (m, 1H, H₄), 3.48 (t, 2H, J = 6.4 Hz, -CH₂OCH₂Ph), 2.78 (dd, 1H, J = 13.4, 6.3 Hz, H₆), 2.46 (dd, 1H, J = 13.4, 8.6 Hz, H₆), 1.85-1.82 (m, 1H, H₅), 1.83-1.34 (m, 6H, H₁, H₂, H₃), 0.85 (d, 3H, J = 6.9 Hz, H₁₃) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 141.2, 138.6, 129.1, 128.33, 128.25, 127.6, 127.5, 125.8, 74.1, 72.9, 70.3, 40.3, 39.9, 34.5, 29.7, 23.0, 13.1 ppm; IR (thin film) ν 3419 (br), 2935, 1494, 1452, 1359, 1099, 735 cm⁻¹; HRMS (FAB⁺) calc'd for C₂₁H₂₈O₂ 312.2089, found 313.2167 (MH⁺).
C(1) Alkyl Side Chain Alcohol (31). To a solution of alcohol 30 (4.80 g, 15.4 mmol) in 150 mL of CH₂Cl₂ was added 4–DMAP (2.40 g, 20.0 mmol, 1.3 equiv) followed by 1BuCOCl (2.50 mL, 20.0 mmol, 1.3 equiv). The reaction was heated at reflux for 16 h. After cooling to 23 °C, the mixture was poured onto 200 mL of sat. aqueous NaHCO₃. The aqueous phase was collected and extracted additionally with 2 x 200 mL CH₂Cl₂. The combined organic extracts were washed with 1 x 250 mL sat. aqueous NaCl, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the product by chromatography on silica gel (gradient elution: 20:1→15:1 hexanes/Et₂O) gave 5.5 g (90%) of the pivaloate ester 30' as a colorless oil. TLC Rᵣ = 0.71 (hexanes/EtOAc); [α]Na +70.8° (c = 0.25, CH₂Cl₂) ¹H NMR (CDCl₃, 500 MHz) δ 7.36-7.33 (m, 5H, H₉aromatic), 7.32-7.26 (m, 2H, H₉aromatic), 7.18 (t, 1H, J = 7.3 Hz, H₉aromatic), 7.11 (d, 2H, J = 7.2 Hz, H₉aromatic), 4.89 (dt, 1H, J = 8.4, 4.2 Hz, H₄'), 4.49 (s, 2H, -OCH₂Ph), 3.46 (t, 2H, J = 6.5 Hz, -CH₂OCH₂Ph), 2.75 (dd, 1H, J = 13.4, 5.0 Hz, H₆'), 2.30 (dd, 1H, J = 13.4, 9.6 Hz, H₆'), 1.99-1.94 (m, 1H, H₅'), 1.72-1.54 (m, 4H, H₁', H₃'), 1.40-1.28 (m, 2H, H₂'), 1.25 (s, 9H, H-Piv-Bu), 0.86 (d, 3H, J = 6.8 Hz, H₁₃') ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 178.0, 140.7, 138.7, 129.1, 128.33, 128.26, 127.6, 127.5, 125.9, 76.2, 72.9, 70.1, 39.51, 39.49, 38.7, 31.1, 29.6, 27.3, 22.4, 13.9 ppm; IR (thin film) ν 2935, 2866, 1724, 1603, 1496, 1479, 1454, 1396, 1362, 1283, 1163, 1102, 1029, 736 cm⁻¹; HRMS (FAB⁺) calc'd for C₂₆H₃₆O₃ 396.2664, found 397.2729 (MH⁺).

5% Palladium on carbon (2.0 g, 25 wt.%) was suspended in a 200 mL EtOAc solution of 30' (8.50 g, 21.4 mmol). The slurry was stirred at 23 °C under 1 atm of H₂ for 12 h. Removal of the palladium catalyst by filtration through Celite followed by evaporation of the filtrate under reduced pressure afforded 6.5 g (99%) of a colorless oil. The alcohol 31 was used without further purification. TLC Rᵣ = 0.17 (4:1
hexanes/EtOAc); [α]_Na +68.5° (c = 0.31, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.27 (t, 2H, J = 7.4 Hz, H_{aromatic}), 7.19 (t, 1H, J = 7.4 Hz, H_{aromatic}), 7.11 (d, 2H, J = 7.11 Hz, H_{aromatic}), 4.89 (dt, 1H, J = 8.3, 4.2 Hz, H₄'), 3.62 (t, 2H, J = 6.5 Hz, -CH₂OH), 2.74 (dd, 1H, J = 13.4, 5.2 Hz, H₆'), 2.31 (dd, 1H, J = 13.4, 9.4 Hz, H₆'), 1.99-1.94 (m, 1H, H₅'), 1.70-1.50 (m, 4H, H₁', H₃'), 1.41-1.29 (m, 3H, H₂' and -OH₁'), 1.25 (s, 9H, H_{Piv-Bu}), 0.87 (d, 3H, J = 6.8 Hz, H₁₃') ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 178.2, 140.7, 129.1, 128.3, 125.9, 76.0, 62.9, 39.6, 39.1, 38.7, 32.5, 31.1, 27.3, 21.8, 13.9 ppm; IR (thin film) ν 3428 (br), 3026, 2935, 2871, 1724, 1602, 1495, 1480, 1457, 1396, 1284, 1164, 1058, 963, 744 cm⁻¹; Anal. Calcd for C₁₉H₃₀O₃: C, 74.46; H, 9.87. Found: C, 74.05; H, 10.16.

![Diagram](image)

**C(1) Alkyl Side Chain Aldehyde (32).** Dimethyl sulfoxide (6.00 mL, 84.0 mmol, 4.0 equiv) was added dropwise to a solution of oxaly chloride (3.70 mL, 42.0 mmol, 2.0 equiv) in 100 mL of CH₂Cl₂ at −78 °C. Following gas evolution, the mixture stirred for 10 min before a solution of alcohol 31 (6.30 g, 20.6 mmol) in 75.0 mL of CH₂Cl₂ was added dropwise over 45 min. The resulting white suspension stirred at −78 °C for an additional 30 min. Triethylamine (16.7 mL, 120 mmol, ca. 6.0 equiv) was then added dropwise causing the solution to clear. The solution was stirred at −78 °C for 15-20 min before warming to 0 °C. The reaction was quenched at 0 °C with 200 mL of a 1.0 M aqueous KH₂PO₄ solution. The organic layer was collected, and the aqueous phase was extracted with 3 x 100 mL CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated _in vacuo_. Purification of the yellow residue by chromatography on silica gel (gradient elution: 8:1→6:1 hexanes/EtOAc) gave 32 as a colorless oil (6.0 g, 96%). TLC Rₐ = 0.48 (4:1 hexanes/EtOAc); [α]_Na +60.2° (c = 0.34,
CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 9.74 (t, 1H, J = 1.4 Hz, -CHO), 7.27 (t, 2H, J = 7.5 Hz, H aromatic), 7.19 (t, 1H, J = 7.4 Hz, H aromatic), 7.11 (d, 2H, J = 7.3 Hz, H aromatic), 4.88 (dt, 1H, J = 8.2, 3.9 Hz, H₄), 2.74 (dd, 1H, J = 13.4, 5.3 Hz, H₆), 2.46-2.41 (m, 2H, -CH₂CHO), 2.31 (dd, 1H, J = 13.4, 9.3 Hz, H₆), 1.99-1.94 (m, 1H, H₅), 1.70-1.52 (m, 4H, H₂, H₃), 1.26 (s, 9H, H Piv-Bu), 0.87 (d, 3H, J = 6.8 Hz, H₁₃) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 201.9, 178.1, 140.5, 129.0, 128.3, 125.9, 75.4, 43.4, 39.4, 39.0, 38.7, 30.7, 27.3, 18.1, 13.9 ppm; IR (thin film) ν 3026, 2968, 2873, 2719, 1724, 1495, 1480, 1455, 1396, 1283, 1163, 1031, 961, 743 cm⁻¹; Anal. Calcd for C₁₉H₂₈O₃: C, 74.96; H, 9.27. Found: C, 74.49; H, 9.56.

### Propargylic alcohol (34).
To a solution of alkyne 22 (15.4 g, 29.6 mmol, 1.5 equiv) in 150 mL of THF at −45 °C was slowly added a 1.6 M solution of nBuLi in hexanes (16.0 ml, 25.6 mmol, 1.3 equiv). The mixture was held at −45 °C for 45 min, then a 4.0 M solution of LiBr in THF (2.5 mL, 9.9 mmol, 0.5 equiv) was added. After stirring for 10 min, a cold solution (−45 °C) of 32 (6.0 g, 19.7 mmol) in 34.0 mL of THF was added via cannula over 40 min. Following addition, the reaction was stirred for 10 min and then quenched with 200 mL sat. aqueous NH₄Cl. The mixture was partitioned with Et₂O (100 mL), the organic phase was collected and the aqueous phase was extracted additionally with 3 x 150 mL Et₂O. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to a pale yellow oil. Purification by chromatography on silica gel (gradient elution: 10:1→2:1 hexanes/Et₂O) afforded 15.2 g (93%) of 34 as a clear, colorless oil. Recovery of excess starting acetylene 22 was essentially quantitative (5.0 g). The product was isolated as a mixture of C(1) alcohol
epimers: TLC R_f = 0.49 (4:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 500 MHz) δ 7.36-7.25 (m, 7H, H_{aromatic}), 7.18 (t, 1H, J = 7.4 Hz, H_{aromatic}), 7.10 (d, 2H, J = 7.0 Hz, H_{aromatic}), 4.89 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.85 (m, 1H, H_{4'}), 4.77 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.46 (ddd, J = 8.5, 6.6, 1.9 Hz, H_3), 4.30-4.26 (m, 1H, H_1), 4.12-4.05 (m, 3H, H_4 and H_8), 3.74 (two d, 1H, J = 10.2 Hz, H_{10} + epimer), 3.56 (d, 1H, J = 10.2 Hz, H_{10}), 3.72 (dd, 1H, J = 13.4, 5.0 Hz, H_6'), 2.29 (dd, 1H, J = 13.4, 9.4 Hz, H_6'), 1.99-1.94 (m, 1H, H_8'), 1.69-1.35 (m, 10H, H_{1'}, H_2', H_3' and both -CH_2CH_3), 1.24 (s, 9H, H_{Piv-tBu}), 0.93-0.85 (m, 9H, H_{13'} and both -CH_2CH_3), 0.91 (s, 9H, H_{TBS-tBu}), 0.18 (s, 9H, H_{TMS}), 0.08 (s, 3H, H_{TBS-Me}), 0.06 (s, 3H, H_{TBS-Me}) ppm; ^13C NMR (CDCl_3, 125 MHz) δ 178.02, 178.00, 140.6, 139.1, 129.1, 128.3, 128.1, 127.3, 127.2, 125.9, 111.1, 110.4, 88.37, 88.35, 84.5, 80.44, 80.35, 76.6, 75.86, 75.82, 75.4, 74.3, 68.3, 65.0, 62.1, 39.5, 39.0, 38.66, 38.62, 37.31, 37.27, 30.82, 30.77, 29.7, 28.6, 27.3, 25.9, 21.41, 21.37, 18.3, 13.9, 8.3, 8.1, 1.98, 1.93, -5.2, -5.3 ppm; IR (thin film) ν 3464 (br) 2956, 1726, 1462, 1361, 1284, 1250, 1159, 1131, 1100, 984, 842, 778 cm⁻¹; Anal. Calcd for C_{47}H_{76}Si_{2}O_{8}: C, 68.40; H, 9.28. Found: C, 68.40; H, 8.92.

Ynone (35). To a solution of alcohol 34 (15.1 g, 18.3 mmol) in 150 mL of CH_2Cl_2 was added 15.5 g (36.6 mmol, 2.0 equiv) of the Dess–Martin periodinane. The resulting white suspension was stirred at 23 °C for 5 h. To the reaction mixture was then added 300 mL of pentane. The resulting precipitates were removed by filtration through Celite. The filtrate was concentrated in vacuo and the isolated pale yellow residue purified by chromatography on silica gel (gradient elution: 15:1→10:1 hexanes/Et_2O) to afford 14.0 g (93%) of 35. TLC R_f = 0.54 (6:1 hexanes/EtOAc); [α]_Na +57.8° (c = 0.38,
CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.36-7.25 (m, 7H, H₆ arom), 7.18 (t, 1H, J = 7.4 Hz, H₇ arom), 7.10 (d, 1H, J = 7.1 Hz, H₈ arom), 4.89 (d, 1H, J = 11.2 Hz, -OCH₂Ph), 4.85-4.83 (m, 1H, H₄), 4.76 (d, 1H, J = 11.2 Hz, -OCH₂H₄), 4.42 (ddd, J = 8.4, 6.5, 2.0 Hz, H₃), 4.11 (d, 1H, J = 2.0 Hz, H₄), 4.08-4.01 (m, 2H, H₆), 3.73 (d, 1H, J = 10.2 Hz, H₁₀), 3.65 (d, 1H, J = 10.2 Hz, H₅), 2.73 (dd, 1H, J = 13.4, 5.0 Hz, H₆'), 2.49 (t, 2H, J = 6.8 Hz, H₁'), 2.27 (dd, 1H, J = 13.4, 9.6 Hz, H₆'), 1.99-1.94 (m, 1H, H₅'), 1.67-1.49 (m, 8H, H₂', H₃' and both -CH₂CH₃), 1.24 (s, 9H, H₃Piv-Bu), 0.93-0.88 (m, 6H, both -CH₂CH₃), 0.92 (s, 9H, H₃TBS-Bu), 0.84 (d, 3H, J = 6.8 Hz, H₁₃'), 0.20 (s, 9H, H₂TMS), 0.09 (s, 3H, H₃TBS-Me), 0.07 (s, 3H, H₂TBS-Me) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 185.8, 177.9, 140.5, 138.6, 129.1, 128.3, 128.2, 127.46, 127.36, 125.95, 111.4, 91.0, 85.9, 80.4, 76.2, 75.7, 75.1, 67.9, 65.1, 44.8, 39.4, 39.0, 38.6, 30.4, 29.7, 28.6, 27.3, 25.8, 19.5, 18.3, 13.9, 8.3, 8.1, 1.8, -5.32, -5.37 ppm; IR (thin film) ν 2957, 2933, 2212, 1726, 1680, 1462, 1360, 1282, 1252, 1159, 1104, 921, 843, 778, 699 cm⁻¹; HRMS (FAB⁺) calc'd for C₄₇H₇₄Si₂O₈ 822.4922, found 823.5022 (MH⁺).

**trans Enone (36).** To a suspension of [Cr(OAc)₂·H₂O]₂ (31.7 g, 84.4 mmol, 5.0 equiv) in 50.0 mL of degassed THF was added a solution of ynone 35 (13.9 g, 16.9 mmol) in 310 mL of degassed THF, followed by 36.0 mL of deoxygenated H₂O. The reaction was warmed to 65 °C and stirred for two weeks. Filtration of the reaction mixture through Celite removed most of the insoluble salts. The filter cake was rinsed thoroughly with Et₂O (3 x 100 mL) and the combined filtrates concentrated to a pale blue oil. Purification by chromatography on silica gel (gradient elution: 12:1→8:1 hexanes/Et₂O) furnished 36 (8.3 g, 60%) as a colorless oil. TLC Rf = 0.51 (6:1
hexanes/EtOAc): $[\alpha]_{\text{Na}}^+319.5^\circ$ (c = 0.25, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.36-7.25 (m, 7H, H$_{\text{aromatic}}$), 7.18 (t, 1H, $J$ = 7.4 Hz, H$_{\text{aromatic}}$), 7.12 (d, 2H, $J$ = 7.0 Hz, H$_{\text{aromatic}}$), 6.80 (d, 1H, $J$ = 15.9 Hz, H$_6$), 6.29 (d, 1H, $J$ = 15.9 Hz, H$_7$), 4.96 (d, 1H, $J$ = 11.5 Hz, -OCH$_2$Ph), 4.87-4.85 (m, 1H, H$_4'$), 4.61 (d, 1H, $J$ = 11.5 Hz, -OCH$_2$Ph), 4.38 (ddd, $J$ = 8.5, 6.6, 1.8 Hz, H$_3$), 4.09 (d, 1H, $J$ = 1.7 Hz, H$_4$), 3.79 (t, 1H, $J$ = 8.3 Hz, H$_8$), 3.73 (t, 1H, $J$ = 6.6 Hz, H$_8$), 3.71 (d, 1H, $J$ = 10.5 Hz, H$_{10}$), 3.57 (d, 1H, $J$ = 10.5 Hz, H$_{10}$), 2.75 (dd, 1H, $J$ = 13.4, 5.0 Hz, H$_6'$), 2.51 (t, 1H, $J$ = 6.7 Hz, H$_1'$), 2.28 (dd, 1H, $J$ = 13.4, 9.6 Hz, H$_6'$), 1.99-1.94 (m, 1H, H$_5'$), 1.67-1.55 (m, 8H, H$_2'$, H$_3'$ and both -CH$_2$CH$_3$), 1.25 (s, 9H, H$_{\text{Piv-tBu}}$), 0.91-0.87 (m, 6H, both -CH$_2$CH$_3$), 0.89 (s, 9H, H$_{\text{TBS-tBu}}$), 0.86 (d, 3H, $J$ = 6.9 Hz, H$_{13'}$), 0.18 (s, 9H, H$_{\text{TMS}}$), 0.02 (s, 3H, H$_{\text{TBS-Me}}$), 0.01 (s, 3H, H$_{\text{TBS-Me}}$) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 199.3, 178.0, 146.3, 140.6, 138.7, 130.2, 129.1, 128.32, 128.26, 127.5, 127.4, 125.9, 111.3, 80.7, 80.5, 76.4, 75.9, 74.9, 66.5, 64.9, 40.0, 39.5, 38.6, 30.7, 29.6, 28.2, 27.3, 26.0, 19.8, 18.4, 13.8, 8.3, 8.1, 2.4, -5.36, -5.41 ppm; IR (thin film) $\nu$ 2956, 1725, 1676, 1636, 1459, 1361, 1283, 1251, 1161, 1108, 991, 925, 838, 777, 699 cm$^{-1}$; Anal. Calcd for C$_{47}$H$_{76}$Si$_2$O$_8$: C, 68.40; H, 9.28. Found: C, 68.47; H, 8.98.

trans Enone-Diol (45). A solution of enone 36 (2.50 g, 3.03 mmol) in 60.0 mL of THF at 0 °C was treated with 6.7 mL of a 1.0 M THF solution of n-Bu$_4$NF (6.7 mmol, 2.2 equiv). The resulting yellow solution was stirred for 45 min and then partitioned between 75 mL of sat. aqueous NH$_4$Cl and 50 mL of Et$_2$O. The organic phase was collected, and the aqueous layer was extracted with 3 x 75 mL Et$_2$O. The combined organic extracts were washed with 1 x 100 mL of sat. aqueous NaCl, dried over Na$_2$SO$_4$,
and evaporated under reduced pressure. Purification of the product chromatography on silica gel (gradient elution: 2:1→1:1 hexanes/EtOAc) afforded the product 45 as a colorless oil (1.8 g, 93%). TLC Rf = 0.19 (2:1 hexanes/EtOAc); [α]Na +104.4° (c = 0.27, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.39-7.25 (m, 7H, H aromatic), 7.18 (t, 1H, J = 7.4 Hz, H aromatic), 7.11 (d, 2H, J = 7.0 Hz, H aromatic), 6.95 (d, 1H, J = 15.9 Hz, H₆), 6.53 (d, 1H, J = 15.9 Hz, H₇), 4.88-4.85 (m, 1H, H₄), 4.79 (d, 1H, J = 11.3 Hz, -OCH₂Ph), 4.63 (d, 1H, J = 11.3 Hz, -OCH₂Ph), 4.13 (d, 1H, J = 1.7 Hz, -OH₃), 4.07-4.02 (m, 2H, H₄ and H₈), 3.80-3.73 (m, 2H, H₁₀), 3.64-3.60 (m, 1H, H₃), 3.43 (dd, 1H, J = 11.6, 3.5 Hz, H₈), 2.74 (dd, 1H, J = 13.4, 5.0 Hz, H₆), 2.58-2.54 (m, 2H, H₁), 2.31-2.27 (m, 2H, H₆ and -OH₃), 1.98-1.96 (m, 1H, H₅), 1.68-1.55 (m, 8H, H₂, H₃ and both -CH₂CH₃), 1.24 (s, 9H, H piv-Bu), 0.91 (t, 3H, J = 7.5 Hz, -CH₂CH₃), 0.85 (d, 3H, J = 6.8 Hz, H₁₃), 0.82 (t, 3H, J = 7.4 Hz, -CH₂CH₃) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 199.3, 178.1, 144.9, 140.6, 137.5, 130.4, 129.1, 128.5, 128.3, 128.2, 128.0, 125.9, 114.0, 79.3, 78.8, 76.3, 75.7, 74.9, 68.6, 65.6, 40.4, 39.5, 39.1, 38.6, 30.7, 29.7, 28.8, 27.3, 19.9, 13.8, 8.1, 8.0 ppm; IR (thin film) ν 3470 (br), 3028, 2971, 2937, 2880, 1723, 1632, 1480, 1455, 1397, 1379, 1284, 1164, 1078, 1058, 990, 918, 735, 700 cm⁻¹; Anal. Calcd for C₃₈H₅₄O₈: C, 71.44; H, 8.52. Found: C, 71.39; H, 8.63.

**Dimethyl acetonide-enone (51).** A solution of enone 45 (8.0 mg, 12.5 μmol) in 1.5 mL of CH₂Cl₂ was treated with 12 μL of 2-methoxypropene (125 μmol, 10 equiv) and a catalytic amount of anhydrous p-toluenesulfonic acid (1 mg, 4 μmol, 0.3 equiv). After 1 h the mixture was poured onto 4 mL of a 1:1 CH₂Cl₂/sat. aqueous NaHCO₃ solution. The organic phase was isolated and the aqueous layer was extracted with 2 x 3
mL CH$_2$Cl$_2$. The combined extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo to an oily residue. Purification by chromatography on silica (9:1 hexanes/EtOAc) afforded 8 mg (94%) of 51 as a colorless oil. TLC $R_f = 0.46$ (4:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.38-7.31 (m, 5H, H$_{aromatic}$), 7.30-7.25 (m, 2H, H$_{aromatic}$), 7.18 (t, 1H, $J = 7.5$ Hz, H$_{aromatic}$), 7.11 (d, 2H, $J = 7.1$ Hz, H$_{aromatic}$), 6.87 (d, 1H, $J = 15.9$ Hz, H$_6$), 6.39 (d, 1H, $J = 15.9$ Hz, H$_7$), 4.98 (d, 1H, $J = 11.5$ Hz, -OCH$_2$Ph), 4.87-4.86 (m, 1H, H$_4$), 4.67 (d, 1H, $J = 11.4$ Hz, -OCH$_2$Ph), 4.35-4.30 (m, 1H, H$_3$), 4.05 (d, 1H, $J = 9.0$ Hz, H$_{10}$), 3.96 (d, 1H, $J = 1.9$ Hz, H$_4$), 3.78 (t, 1H, $J = 8.1$ Hz, H$_8$), 3.73 (d, 1H, $J = 9.0$ Hz, H$_8$), 3.74-3.71 (m, 1H, H$_8$), 2.75 (dd, 1H, $J = 13.3$, 5.0 Hz, H$_6$), 2.53 (t, 2H, $J = 6.8$ Hz, H$_1$), 2.29 (dd, 1H, $J = 13.5$, 9.7 Hz, H$_6$), 1.99-1.94 (m, 1H, H$_5$), 1.71-1.54 (m, 8H, H$_2$, H$_3$ and both -CH$_2$CH$_3$), 1.46 (s, 3H, -CH$_3$), 1.39 (s, 3H, -CH$_3$), 1.25 (s, 9H, H$_{Piv-tBu}$), 0.92-0.86 (m, 9H, H$_{13}$ and both -CH$_2$CH$_3$) ppm; IR (thin film) ν 2970, 1723, 1636, 1458, 1371, 1282, 1162, 1075, 700 cm$^{-1}$; HRMS (Cl$^+$) calc'd for C$_{41}$H$_{58}$O$_8$ 678.4131, found 679.4208 (MH$^+$).

Carbonate-enone (52). To a solution of enone 45 (20.0 mg, 31.3 μmol) in 2.0 mL of pyridine at 0 °C was added solid triphosgene (13.0 mg, 45.0 μmol, 1.5 equiv) in a single portion. A white precipitate formed instantaneously upon addition. The resulting mixture was stirred at 0 °C for 10 min, then allowed to warm over a 2 h period to 23 °C during which time the solution became homogenous. The volatiles were removed in vacuo to leave a pale yellow residue which was purified by chromatography on silica gel (5:1 hexanes/EtOAc) The product 52 was isolated as a clear, colorless oil (20 mg, 96%). TLC $R_f = 0.34$ (4:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.40-7.27 (m, 7H,
H_{aromatic}, 7.19 (t, 1H, J = 7.3 Hz, H_{aromatic}), 7.11 (d, 2H, J = 7.1 Hz, H_{aromatic}), 6.91 (d, 1H, J = 15.7 Hz, H_6), 6.48 (d, 1H, J = 15.8 Hz, H_7), 4.88-4.85 (m, 1H, H_4'), 4.79 (d, 1H, J = 11.1 Hz, -OCH_2Ph), 4.74 (d, 1H, J = 11.1 Hz, -OCH_2Ph), 4.49 (d, 1H, J = 8.6 Hz, H_10), 4.17 (d, 1H, J = 8.5 Hz, H_10), 4.10 (ddd, 1H, J = 6.8, 5.6 Hz, H_3), 3.94 (dd, 1H, J = 8.2, 6.4 Hz, H_8), 3.84 (d, 1H, J = 5.4 Hz, H_4), 3.71 (t, 1H, J = 7.9 Hz, H_8), 2.74 (dd, 1H, J = 13.3, 5.0 Hz, H_6'), 2.56-2.54 (m, 2H, H_1'), 2.30 (dd, 1H, J = 13.3, 9.5 Hz, H_6'), 1.99-1.94 (m, 1H, H_5'), 1.67-1.56 (m, 8H, H_2', H_3' and both -CH_2CH_3), 1.25 (s, 9H, H_{Piv-Bu}), 0.89-0.85 (m, 9H, H_{13'} and both -CH_2CH_3) ppm; IR (thin film) ν 2968, 2936, 1812, 1718, 1458, 1282, 1166, 1067 cm^{-1}; HRMS (FAB^+) calc'd for C_{39}H_{52}O_9 664.3611, found 687.3309 (MNa^+).

**Carbonate-Diols from 52.** To a solution of enone 52 (18.0 mg, 27.1 μmol) in 2.5 mL of acetone and 0.1 mL tBuOH was added 4-methylmorpholine-N-oxide (2 mg, 17 μmol) and CH_3SO_2NH_2 (2 mg, 21 μmol). A 0.16 M aqueous solution of OsO_4 (10 μL, 1.6 μmol) was added to the mixture via micropipette. The pale yellow solution was stirred for 18 h after which time the reaction was quenched by the addition of 5.0 mL 10 wt.% aqueous Na_2SO_3. The mixture was stirred vigorously for 20 min and then extracted with 4 x 5 mL Et_2O. The ethereal extracts were washed once with sat. aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a milky white oil. Analysis of the ^1H NMR spectrum of the unpurified material showed two major products in a 2.2:1 ratio. Purification by chromatography on silica gel (gradient elution: 7:2→3:1 hexanes/EtOAc) afforded both the desired 6R,7R (11 mg) and the undesired 6S,7S (5 mg) diols as colorless oils (85% combined yield). Physical data for the 6R,7R diol: TLC R_f =
0.41 (2:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.38-7.28 (m, 7H, H$_{aromatic}$), 7.20 (t, 1H, $J = 7.3$ Hz, H$_{aromatic}$), 7.11 (d, 2H, $J = 7.2$ Hz, H$_{aromatic}$), 4.93 (d, 1H, $J = 8.0$ Hz, H$_{10}$), 4.93 (d, 1H, $J = 10.8$ Hz, -OCH$_2$Ph), 4.87-4.83 (m, 1H, H$_4'$), 4.60 (d, 1H, $J = 10.6$ Hz, -OCH$_2$Ph), 4.55 (d, 1H, $J = 4.8$ Hz, H$_7$), 4.43 (dd, 1H, $J = 5.6$, 1.6 Hz, H$_6$), 4.36 (d, 1H, $J = 8.0$ Hz, H$_{10}$), 4.20 (dd, 1H, $J = 8.6$, 6.0 Hz, H$_8$), 4.04-3.96 (m, 2H, H$_3$, H$_4$), 3.78-3.72 (m, 3H, H$_8$ and both -OH$_2$), 2.73 (dd, 1H, $J = 13.4$, 5.1 Hz, H$_6'$), 2.59-2.47 (m, 2H, H$_1'$), 2.31 (dd, 1H, $J = 13.4$, 9.4 Hz, H$_6'$), 1.96-1.94 (m, 1H, H$_5'$), 1.71-1.53 (m, 8H, H$_2'$, H$_3'$ and both -CH$_2$CH$_3$), 1.26 (s, 9H, H$_{Piv-tBu}$), 0.90 (t, 3H, $J = 7.5$ Hz, -CH$_2$CH$_3$), 0.87 (d, 3H, $J = 6.8$ Hz, H$_{13'}$), 0.83 (t, 3H, $J = 7.4$ Hz, -CH$_2$CH$_3$) ppm; IR (thin film) v 3446 (br), 2971, 1804, 1719, 1458, 1362, 1284, 1166, 1078, 911, 741, 700 cm$^{-1}$; HRMS (FAB$^+$) calc'd for C$_{39}$H$_{54}$O$_{11}$ 698.3666, found 699.3756 (MH$^+$).

Physical data for the 6S,7S diol: TLC R$_f$ = 0.50 (2:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.35-7.26 (m, 7H, H$_{aromatic}$), 7.22 (t, 1H, $J = 7.2$ Hz, H$_{aromatic}$), 7.11 (d, 2H, $J = 7.3$ Hz, H$_{aromatic}$), 4.93 (d, 1H, $J = 11.3$ Hz, -OCH$_2$Ph), 4.80-4.76 (m, 2H, H$_{10}$, H$_{4'}$), 4.58 (d, 1H, $J = 11.4$ Hz, -OCH$_2$Ph), 4.45 (d, 1H, $J = 8.1$ Hz, H$_7$), 4.39 (d, 1H, $J = 9.2$ Hz, H$_{10}$), 4.28 (dd, 1H, $J = 12.8$, 6.3 Hz, H$_3$), 4.20 (d, 1H, $J = 5.0$ Hz, H$_4$), 4.19-4.16 (m, 2H, H$_6$, H$_8$), 4.03 (t, 1H, $J = 8.1$ Hz, H$_8$), 3.82 (d, 1H, $J = 8.0$ Hz, -OH$_2$), 3.68 (d, 1H, $J = 5.0$ Hz, -OH$_2$), 2.67 (dd, 1H, $J = 13.5$, 6.2 Hz, H$_6'$), 2.49 (ddd, 1H, $J = 13.9$, 8.6, 5.6 Hz, H$_1'$), 2.37 (dd, 1H, $J = 13.4$, 8.5 Hz, H$_6'$), 1.93-1.88 (m, 1H, H$_5'$), 1.83-1.74 (m, 1H, H$_1'$), 1.73-1.34 (m, 8H, H$_2'$, H$_3'$ and both -CH$_2$CH$_3$), 1.22 (s, 9H, H$_{Piv-tBu}$), 0.94 (t, 3H, $J = 7.5$ Hz, -CH$_2$CH$_3$), 0.91 (d, 3H, $J = 7.0$ Hz, H$_{13'}$), 0.89 (t, 3H, $J = 7.5$ Hz, -CH$_2$CH$_3$) ppm; IR (thin film) v 3432 (br), 2970, 1802, 1719, 1458, 1363, 1284, 1168, 1063, 700 cm$^{-1}$; HRMS (FAB$^+$) calc'd for C$_{39}$H$_{54}$O$_{11}$ 698.3666, found 699.3745 (MH$^+$).
TBS-Protected Bicyclic Ketal (54). To a solution of 45 (1.40 g, 2.19 mmol) in 85.0 mL of acetone was added (DHQD)$_2$PHAL (1.0 g, 1.32 mmol), 4-methylmorpholine-$N$-oxide (513 mg, 4.38 mmol), and CH$_3$SO$_2$NH$_2$ (210 mg, 2.2 mmol). The pale yellow solution was cooled to 0 °C before 4.1 mL of an aqueous solution of OsO$_4$ (0.66 mmol, 0.16 M) was added dropwise via pipette. 5.0 mL of tBuOH was then added to the slightly turbid mixture. The reaction was warmed to 23 °C and stirred for 12 h, after which time 20 mL of a buffered 1.5 M NaHSO$_3$/Na$_2$SO$_4$ solution (pH 7) was poured into the reaction mixture. The resulting slurry was stirred vigorously for 2 h before being partitioned between 20 mL of sat. NaCl and 50 mL of 20% MeOH/CH$_2$Cl$_2$. The organic layer was collected and the aqueous phase was extracted with 4 x 50 mL 20% MeOH/CH$_2$Cl$_2$. The extracts were combined and dried over Na$_2$SO$_4$. Evaporation of the solvent under reduced pressure yielded 1.8 g of a pale brown foam. The desired product was isolated as a 1.7:1 mixture of epimeric diols 46/47 (as shown by $^1$H NMR of the unpurified material) and used without further purification.

The unpurified mixture of tetraols 46/47 (1.50 g, 2.19 mmol) was dissolved in 200 mL of MeOH, cooled to 0 °C, and 1.0 mL of 12 N HCl was added. The solution was warmed to 23 °C and stirred for 2 h. Quenching the reaction at 0 °C with iPr$_2$NEt (ca. 2 mL) followed by evaporation of the solvent under reduced pressure gave a pale yellow viscous oil. Purification by chromatography on silica gel (3:2 CH$_2$Cl$_2$/EtOAc) yielded the product as a white foam (1.1 g, 86%). The bicyclic ketal was isolated as a 1.7:1 mixture of C(6)/C(7) anti diol diastereomers 53/56 as shown by $^1$H NMR. TLC $R_f$ = 0.49 (1:1 CH$_2$Cl$_2$/EtOAc).
To a solution of 53/56 (684 mg, 1.17 mmol) in 10.0 mL of CH$_2$Cl$_2$ was added Et$_3$N (1.6 mL, 11.7 mmol, 10.0 equiv), $t$BuMe$_2$SiCl (369 mg, 2.45 mmol, 2.1 equiv) and 4–DMAP (14.0 mg, 0.12 mmol, 10 mol%) successively. The mixture was stirred at 23 °C for 46 h and then poured onto 20 mL of a 1.0 M aqueous KH$_2$PO$_4$ solution. The two phases were separated and the aqueous phase extracted additionally with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo to a yellow oil. Purification by chromatography on silica gel (gradient elution: 4:1→2:1 hexanes/EtOAc) provided both 54 (460 mg, 74%) and 57 (270 mg, 81%) as colorless oils. TLC R$_f$(54) = 0.43, R$_f$(57) = 0.61 (2:1 hexanes/EtOAc); physical data for 54: [α]$_{Na}$$^+$384.7º (c = 0.27, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.36-7.23 (m, 7H, H$_{aromatic}$), 7.18 (t, 1H, J = 7.4 Hz, H$_{aromatic}$), 7.11 (d, 2H, J = 7.2 Hz, H$_{aromatic}$), 4.86-4.84 (m, 1H, H$_4'$), 4.64 (d, 1H, J = 11.3 Hz, -OCH$_2$Ph), 4.59 (d, 1H, J = 11.3 Hz, -OCH$_2$Ph), 4.33 (dd, 1H, J = 6.6, 2.6, H$_6$), 3.95 (d, 1H, J = 11.8 Hz, H$_5$), 3.95-3.93 (m, 1H, H$_7$), 3.80 (d, 1H, J = 9.5 Hz, H$_4$), 3.80-3.77 (m, 2H, H$_8$), 3.71 (d, 1H, J = 11.8 Hz, H$_8$), 3.66-3.63 (m, 1H, H$_3$), 3.29 (d, 1H, J = 6.6 Hz, -OH$_2^-$), 2.75 (dd, 1H, J = 13.3, 5.0 Hz, H$_6'$), 2.29 (dd, 1H, J = 13.4, 9.6 Hz, H$_6'$), 2.07 (d, 1H, J = 5.7 Hz, -OH$_2^-$), 2.00-1.94 (m, 1H, H$_5'$), 1.78-1.45 (m, 6H, H$_{1'}$, H$_{2'}$, H$_{3'}$), 1.24 (s, 9H, H$_{TBS-tBu}$), 0.89 (s, 9H, H$_{TBS-tBu}$), 0.85 (d, 3H, J = 6.8 Hz, H$_{13'}$), 0.08 (s, 3H, H$_{TMS-Me}$), 0.062 (s, 6H, H$_{TMS-Me}$), 0.056 (s, 3H, H$_{TMS-Me}$) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 178.0, 140.7, 138.3, 129.1, 128.4, 128.3, 128.0, 127.8, 125.9, 103.6, 86.3, 83.9, 79.3, 76.2, 74.8, 74.1, 71.0, 63.3, 62.7, 39.5, 39.0, 38.3, 35.6, 31.4, 27.3, 25.9, 25.8, 19.3, 18.3, 18.2, 13.7, -4.9, -5.2, -5.32, -5.37 ppm; IR (thin film) ν 3447 (br), 2956, 2929, 2856, 1726, 1702, 1496, 1461, 1397, 1360, 1285, 1252, 1162, 1087, 1004, 971, 837, 777, 738, 699 cm$^{-1}$; Anal Calcd for C$_{45}$H$_{74}$Si$_2$O$_9$: C, 66.30; H, 9.15. Found: C, 65.98; H, 8.84.
**Pivaloate Ester (59).** To a solution of diol 54 (710 mg, 0.87 mmol) in 15.0 mL of 1,2-dichloroethane was added 4-DMAP (635 mg, 5.20 mmol, 6.0 equiv) and tBuCOCl (320 µL, 2.60 mmol, 3.0 equiv). The contents were warmed to 55 °C and stirred for 8 h. After allowing the solution to cool to 23 °C, 30 mL of pentane was added. The resulting white precipitate was removed by filtration through Celite. The filter cake was rinsed with pentane (3 x 20 mL) and the combined filtrates were concentrated under reduced pressure to give an oily yellow residue. Purification by chromatography on silica gel (20:1 hexanes/EtOAc) provided 830 mg of 59 (97%) as a clear, colorless oil. TLC R = 0.54 (8:1 hexanes/EtOAc); [α]_D +78.1° (c = 0.27, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.35-7.26 (m, 7H, Hromatic), 7.18 (t, 1H, J = 7.3 Hz), 7.10 (d, 2H, J = 7.1 Hz), 5.38 (d, 1H, J = 2.7 Hz, H₆), 4.98 (d, 1H, J = 2.7 Hz, H₇), 4.85-4.82 (m, 1H, H₄), 4.82 (d, 1H, J = 11.7 Hz, -OCH₂Ph), 4.60 (d, 1H, J = 11.7 Hz, -OCH₃Ph), 4.07 (d, 1H, J = 10.0 Hz, H₄), 3.80-3.75 (m, 3H, H₃, H₁₀), 3.71-3.68 (m, 2H, H₈), 2.75 (dd, 1H, J = 13.3, 4.7 Hz, H₆), 2.27 (dd, 1H, J = 13.3, 9.8 Hz, H₆), 1.99-1.94 (m, 1H, H₅), 1.69-1.35 (m, 6H, H₁', H₂', H₃'), 1.24 (s, 9H, H₄Bu), 1.21 (s, 9H, H₄Bu), 1.20 (s, 9H, H₄Bu), 0.92 (s, 9H, H₄Bu), 0.89 (s, 9H, H₄Bu), 0.84 (d, 3H, J = 6.8 Hz, H₁₃), 0.11 (s, 3H, H₃Me), 0.07 (s, 3H, H₃Me), 0.05 (s, 3H, H₃Me), 0.02 (s, 3H, H₃Me) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 177.8, 176.9, 176.8, 140.8, 138.7, 129.1, 128.29, 128.23, 127.5, 125.9, 103.9, 84.8, 81.3, 77.5, 76.3, 74.8, 73.9, 69.4, 62.9, 61.5, 39.5, 39.0, 38.8, 38.7, 38.4, 36.1, 31.3, 27.3, 27.0, 25.9, 19.2, 18.36, 18.34, 13.7, -4.9, -5.1, -5.3, -5.5 ppm; IR (thin film) ν 3028, 2957, 2930, 2857, 1740, 1479, 1460, 1396, 1362, 1282, 1252, 1159, 1098, 1006, 837, 699 cm⁻¹; Anal. Calcd for C₅₅H₉₀Si₂O₁₁: C, 67.17; H, 9.22. Found: C, 66.80; H, 8.81.
Ketone (61). 20% Pd(OH)$_2$ on carbon (400 mg) and 5% palladium on calcium carbonate (400 mg) were suspended in 15.0 mL of an absolute EtOH solution of 59 (830 mg, 0.84 mmol). The slurry was stirred vigorously at 23 °C under 1 atm of H$_2$ for 168 h. Removal of the palladium catalysts by filtration through Celite followed by evaporation of the filtrate under reduced pressure afforded 730 mg (99%) of 60 as a colorless oil. The product 60 was used without further purification. TLC R$_f$ = 0.38 (8:1 hexanes/EtOAc). [α]$_{Na}$ +81.4° (c = 0.25, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.27-7.24 (m, 2H, H$_{aromatic}$), 7.18 (t, 1H, J = 7.3 Hz, H$_{aromatic}$), 7.10 (d, 1H, J = 7.1, H$_{aromatic}$), 5.48 (d, 1H, J = 2.6 Hz, H$_6$), 5.00 (d, 1H, J = 2.6 Hz, H$_7$), 4.86-4.83 (m, 1H, H$_4^-$), 3.99 (dd, 1H, J = 9.0, 1.5 Hz, H$_4$), 3.88 (d, 1H, J = 11.2 Hz, H$_{10}$), 3.87-3.81 (m, 2H, H$_3$, H$_8$), 3.78-3.74 (m, 1H, H$_8$), 3.74 (d, 1H, J = 11.3 Hz, H$_{10}$), 3.13 (d, 1H, J = 1.5 Hz, -OH$_3^-$), 2.75 (dd, 1H, J = 13.3, 4.7 Hz, H$_6^-$), 2.55 (dd, 1H, J = 13.3, 9.8 Hz, H$_6^-$), 1.96-1.93 (m, 1H, H$_5^+$), 1.69-1.26 (m, 6H, H$_1^+$, H$_2^+$, H$_3^+$), 1.234 (s, 9H, H$_{Piv-rBu}$), 1.229 (s, 9H, H$_{Piv-rBu}$), 1.21 (s, 9H, H$_{Piv-rBu}$), 0.91 (s, 9H, H$_{TBS-rBu}$), 0.90 (s, 9H, H$_{TBS-rBu}$), 0.83 (d, 3H, J = 6.8 Hz, H$_{13^+}$), 0.092 (s, 6H, H$_{TBS-Me}$), 0.085 (s, 3H, H$_{TBS-Me}$), 0.07 (s, 3H, H$_{TBS-Me}$) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 177.9, 176.85, 176.81, 140.8, 129.1, 128.2, 125.9, 104.0, 83.4, 81.1, 76.42, 76.40, 76.2, 73.5, 66.5, 65.2, 62.2, 39.4, 39.0, 38.8, 38.7, 35.8, 31.1, 27.3, 27.01, 26.99, 25.89, 25.86, 19.2, 18.3, 13.8, -5.4 ppm; IR (thin film) ν 3027 (br), 2958, 2931, 2857, 1740, 1480, 1462, 1397, 1363, 1283, 1255, 1160, 1036, 1006, 939, 837, 778, 700 cm$^{-1}$; HRMS (FAB+) calcd for C$_{48}$H$_{84}$Si$_2$O$_{11}$ 892.6046, found 893.5645 (MH$^+$); Anal. Calcd for C$_{48}$H$_{84}$Si$_2$O$_{11}$: C, 64.53; H, 9.48. Found: C, 64.34; H, 9.32.

Dimethyl sulfoxide (580 µL, 8.19 mmol, 10.0 equiv) was added dropwise to a solution of oxalyl chloride (360 µL, 4.10 mmol, 2.0 equiv) in 10.0 mL of CH$_2$Cl$_2$ at −78
°C. Following gas evolution, the mixture stirred for 10 min before a solution of alcohol 60 (725 mg, 0.81 mmol) in 2.0 mL of CH₂Cl₂ was added dropwise over 10 min. The resulting white suspension was stirred at −78 °C for an additional 1 h; Et₃N (2.90 mL, 20.5 mmol, 25 equiv) was then added dropwise which caused the solution to clear. The solution was stirred at −78 °C for 15-20 min and then warmed to 0 °C. The reaction was quenched at 0 °C with 30 mL of a 1.0 M aqueous KH₂PO₄ solution. The organic layer was collected, and the aqueous phase was extracted with 4 x 25 mL CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification of the yellow residue by chromatography on silica gel (20:1 hexanes/EtOAc) gave the desired product 61 as a colorless oil (6.0 g, 96%). TLC Rₜ ≈ 0.50 (8:1 hexanes/EtOAc); [α]ₙₐ +42.9° (c = 0.42, CH₂Cl₂); ¹H NMR (CD₆D₆, 500 MHz) δ 7.23-7.11 (m, 3H, H₁-H₇), 7.08-7.04 (m, 3H, H₁-H₇), 5.40 (d, 2H, J = 1.8 Hz, H₆, H₇), 5.08-5.04 (m, 1H, H₄'), 4.61 (dd, 1H, J = 6.4, 4.1 Hz, H₃), 4.32 (d, 1H, J = 10.8 Hz, H₁₀), 4.15 (dd, 1H, J = 10.9, 6.4 Hz, H₈), 4.12 (dd, 1H, J = 11.0, 4.2 Hz, H₈), 4.05 (d, 1H, J = 10.8 Hz, H₁₀), 2.74 (dd, 1H, J = 13.4, 4.8 Hz, H₆'), 2.22-2.16 (m, 2H, H₁-H₆'), 2.08-2.02 (m, 1H, H₁'), 1.89-1.83 (m, 1H, H₅'), 1.81-1.77 (m, 1H, H₃'), 1.68-1.64 (m, 1H, H₃'), 1.62-1.56 (m, 1H, H₂'), 1.39-1.29 (m, 1H, H₂'), 1.27 (s, 9H, H₆-Bu'), 1.16 (s, 9H, H₆-Bu'), 1.10 (s, 9H, H₆-Bu'), 1.00 (s, 9H, H₆-Bu'), 0.97 (s, 9H, H₆-Bu'), 0.78 (d, 3H, J = 6.8 Hz, H₁₃'), 0.154 (s, 3H, H₆-Me), 0.150 (s, 3H, H₆-Me), 0.14 (s, 3H, H₆-Me), 0.11 (s, 3H, H₆-Me) ppm; ¹³C NMR (CD₆D₆, 125 MHz) δ 202.8, 177.6, 177.0, 176.8, 141.5, 129.8, 129.0, 126.6, 106.6, 92.0, 82.6, 81.8, 79.5, 76.2, 65.8, 61.3, 40.3, 39.9, 39.5, 39.4, 39.0, 37.9, 32.3, 27.9, 27.42, 27.35, 26.5 (2 lines), 20.2, 19.01, 18.94, 14.4, -4.6, -4.7, -4.9, -5.0 ppm; IR (thin film) ν 2958, 2931, 2857, 1743, 1480, 1462, 1396, 1363, 1282, 1256, 1159, 1128, 1037, 838, 779 cm⁻¹; Anal. Calcd for C₄₈H₉₂Si₂O₁₁: C, 64.68; H, 9.27. Found: C, 64.57; H, 9.03.
Alkyne (69). Tert-butyl lithium (1.5 mL, 2.5 mmol) was added dropwise to a solution of trimethylsilyl acetylene (360 μL, 2.55 mmol) in 1.0 mL of hexanes at −78 °C. The reaction was stirred at −78 °C for 10 min and then warmed to 0 °C. After reaching 0 °C the white suspension was stirred for an additional 45 min. The suspension of lithium trimethylsilyl acetylide (1.7 mL, 1.7 mmol) was added to 5.0 mL of a 1:1 Et₂O/Me₃N mixture at −78 °C. The resulting homogenous solution was stirred for 5 min before a cold solution (−78 °C) of ketone 61 (155 mg, 0.17 mmol) in 1.5 mL of Et₂O was added dropwise via cannula over a 3 min period. The transfer of 61 was made quantitative with an additional 500 μL of Et₂O. The mixture was stirred at −78 °C for 10 min, then allowed to slowly warm to −20 °C over 2h. Upon reaching this temperature the reaction was quenched by the addition of 5.0 mL sat. aqueous NH₄Cl. The resulting frozen mixture was warmed to 23 °C. The solution was extracted with 3 x 5 ml Et₂O; the organic extracts were combined, washed once with sat. aqueous NaCl (10 mL), and dried over Na₂SO₄. Evaporation of the ethereal solvent in vacuo afforded the product as a 6.1:1 mixture of C(4) carbinol epimers 65/66 as determined by ¹H NMR of the unpurified material. The product was used without prior purification. TLC Rᵣ = 0.52 (8:1 hexanes/EtOAc).

To a solution of trimethylsilyl acetylene 65/66 (172 mg, 0.17 mmol) in 8.0 mL of a 1:1:1:0.1 mixture of THF/H₂O/EtOH/2,6-lutidine was added solid AgNO₃ (295 mg, 1.70 mmol, 10 equiv). The white suspension was stirred vigorously for 3.5 h, then 5 mL of a 1.0 M aqueous KH₂PO₄ solution was added. The resulting yellow slurry was stirred for an additional 30 min. Filtration of the reaction mixture through Celite removed most of the yellow precipitate. The filtrate was extracted with Et₂O (3 x 10 mL), the combined
organic extracts were washed once with sat. aqueous NaCl (1 x 20 mL) and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure afforded a pale yellow oil. Purification by chromatography on silica gel (20:1 hexanes/EtOAc) furnished 97 mg of 69 (61%) as a clear, colorless oil. The product 69 was shown to be a single C(4) carbinol epimer by ¹H NMR. TLC Rf = 0.36 (10:1 hexanes/EtOAc); [α]Na⁺ +10.8° (c = 0.45, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.27-7.24 (m, 2H, Hromatic), 7.17 (t, 1H, J = 7.4 Hz, Hromatic), 7.11 (d, 2H, J = 7.1 Hz, Hromatic), 5.52 (d, 1H, J = 1.9 Hz, -OH₃°), 5.43 (d, 1H, J = 2.8 Hz, H₆), 4.99 (d, 1H, J = 2.8 Hz, H₇), 4.88-4.84 (m, 1H, H₄°), 4.18 (d, 1H, J = 11.5 Hz, H₁₀), 4.11 (dd, 1H, J = 11.5, 1.7 Hz, H₈), 4.03 (ddd, 1H, J = 7.1, 1.7, 1.6 Hz, H₃) 3.92 (d, 1H, J = 11.5 Hz, H₁₀), 3.89 (dd, 1H, J = 11.5, 7.1 Hz, H₈), 2.76 (dd, 1H, J = 13.3, 4.7 Hz, H₆°), 2.61 (s, 1H, -C≡CH), 2.26 (dd, 1H, J = 13.3, 9.9 Hz, H₆°), 2.00-1.96 (m, 1H, H₅°), 1.80-1.25 (m, 6H, H₁°, H₂°, H₃°), 1.23 (s, 9H, H₄°Bu), 1.228 (s, 9H, H₅°Bu), 1.226 (s, 9H, H₆°Bu), 0.91 (s, 9H, H₇°Bu), 0.90 (s, 9H, H₈°Bu), 0.83 (d, 3H, J = 6.8 Hz, H₁₃°), 0.120 (s, 3H, HTBS-Me), 0.116 (s, 3H, HTBS-Me), 0.07 (s, 3H, HTBS-Me), 0.06 (s, 3H, HTBS-Me) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 177.9, 177.0, 176.6, 140.8, 129.1, 128.2, 125.9, 105.0, 83.7, 81.7, 80.0, 78.8, 78.3, 76.2, 76.0, 69.3, 65.1, 63.5, 39.4, 39.0, 38.8, 38.7, 38.5, 35.8, 31.1, 27.3, 27.02, 26.95, 26.1, 25.8, 19.1, 18.5, 18.3, 13.8, -5.0, -5.2, -5.5, -5.8 ppm; IR (thin film) ν 3434, 3258, 2958, 2932, 2858, 1742, 1480, 1462, 1397, 1363, 1282, 1255, 1159, 1033, 973, 837, 780 cm⁻¹; HRMS (FAB⁺) calc'd for C₅₀H₈₄Si₂O₁₁ 916.5552, found 917.5637 (MH⁺).

C(4) Cyanohydrin(67/68). Finely pulverized CsF (3 mg, 20 µmol, 10 equiv) was dried under vacuum (1 mm Hg) at 120 °C for 15 h prior to being suspended in 0.5 mL of
toluene. The suspension was cooled to 0 °C and TMSCN (13 μL, 100 μmol, 50 equiv) was added dropwise. The heterogenous solution was stirred at 0 °C for 5 min, then warmed to 23 °C and stirred for 1 h. Upon re-cooling the mixture to −78 °C, a solution of ketone 61 (2 mg, 2 μmol) in 0.5 mL of toluene was added via cannula. Transfer of 61 was made quantitative with an additional 250 μL of toluene. Stirring continued for 4 h during which time the reaction warmed to 0 °C. The reaction was quenched at 0 °C with 2.0 mL of 1.0 M aqueous KH2PO4. The mixture was extracted with 4 x 2 mL Et2O; the extracts were dried over Na2SO4 and concentrated in vacuo to give a pale yellow oil. TLC Rf = 0.48 (10:1 hexanes/EtOAc). Analysis of the 1H NMR spectrum of the unpurified product showed a 4.5:1 mixture of desired/undesired C(4) cyanohydrins 67/68 in a combined yield of >90%. 1H NMR (CDCl3, 500 MHz) δ 7.28–7.25 (m, 4H, H aromatic), 7.18 (t, 2H, J = 7.3 Hz, H aromatic), 7.10 (d, 4H, J = 7.2 Hz, H aromatic), 6.08 (d, 1H, J = 1.4 Hz, –OH3–67), 5.61 (d, 1H, J = 2.7 Hz, H6–68), 5.31 (d, 1H, J = 2.7 Hz, H6–67), 5.24 (s, 1H, –OH3–68), 5.02 (d, 2H, J = 2.8 Hz, H7), 4.86–4.84 (m, 2H, H4'), 4.18 (d, 1H, J = 11.7 Hz, H10–67), 4.13 (ddd, 1H, J = 5.1, 4.4, 1.3 Hz, H3–67), 4.10–4.02 (m, 6H, H8, H10–67, H3, H8, both H10–68), 3.91–3.87 (m, 1H, H8–68), 3.85 (dd, 1H, J = 10.9, 5.8 Hz, H8–67), 2.76 (dd, 2H, J = 13.3, 4.6 Hz, H6'), 2.26 (dd, 2H, J = 13.3, 9.9 Hz, H6'), 1.99–1.91 (m, 2H, H5'), 1.78–1.50 (m, 8H, H1', H3'), 1.39–1.22 (m, 4H, H2'), 1.233 (s, 9H, HPiv-tBu–67), 1.225 (s, 9H, HPiv-tBu–68), 0.93 (s, 9H, HTBS-tBu–67), 0.92 (s, 9H, HTBS-tBu–67), 0.904 (s, 9H, HTBS-tBu–68), 0.896 (s, 9H, HTBS-tBu–68), 0.84 (d, 3H, J = 6.8 Hz, H13'), 0.16 (s, 3H, HTBS-Me–67), 0.15 (s, 3H, HTBS-Me–67), 0.11 (s, 3H, HTBS-Me–68), 0.10 (s, 3H, HTBS-Me–67), 0.093 (s, 3H, HTBS-Me–67), 0.85 (s, 3H, HTBS-Me–68), 0.07 (s, 6H, HTBS-Me–68) ppm.
**Tetraol (70).** A 1.5 M solution of Dibal-H in toluene (3.2 mL, 4.7 mmol, 15 equiv) was added to a solution of 69 (290 mg, 0.316 mmol) in 30.0 mL of a 1:1 CH₂Cl₂/toluene mixture at -78 °C. The reaction was stirred at -78 °C for 30 min and then warmed over a 5 h period to ca. -5 °C before being quenched by the addition of 10 mL of EtOAc. A 5.0 M aqueous solution of Na/K tartrate was added (30 mL) and the biphasic mixture was stirred for 12 h. The organic phase was collected and the aqueous layer was extracted with 3 x 25 mL EtOAc. The combined extracts were washed once with sat. aqueous NaCl (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography on silica gel (gradient elution: 2:1→3:2 hexanes/EtOAc) provided 176 mg of 70 (84%) as a colorless oil. TLC Rᵣ = 0.20 (2:1 hexanes/EtOAc); [α]Na +18.1° (c = 0.24, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.29-7.26 (m, 3H, Hₐromatic), 7.20-7.16 (m, 3H, Hₐromatic), 4.70 (d, 1H, J = 1.1 Hz, -OH₃), 4.68 (dd, 1H, J = 5.8, 2.7 Hz, H₆), 4.39 (dd, 1H, J = 5.6, 2.6 Hz, H₇), 4.29 (d, 1H, J = 11.3 Hz, H₁₀), 4.09-4.05 (m, 3H, H₈ and H₁₀), 3.95 (dd, 1H, J = 3.4, 3.2 Hz, H₃), 3.51 (br s, 1H, H₄'), 2.78 (dd, 1H, J = 13.4, 6.3 Hz), 2.74 (br s, 1H, -OH₂'), 2.54 (d, 1H, J = 0.7 Hz, -C≡CH), 2.45 (dd, 1H, J =13.3, 8.6 Hz), 1.83-1.46 (m, 7H, H₁', H₂', H₃', H₅'), 0.90 (s, 9H, HTBS₂-tBu), 0.89 (s, 9H, HTBS₂-tBu), 0.84 (d, 1H, J = 6.8 Hz, H₁₃'), 0.11 (s, 6H, HTBS₂-Me), 0.09 (s, 6H, HTBS₂-Me) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 141.1, 129.1, 128.3, 125.8, 105.1, 85.8, 84.8, 81.06, 80.93, 75.98, 75.72, 74.1, 68.5, 63.7, 62.5, 40.4, 39.9, 35.5, 34.5, 25.9, 25.7, 19.9, 18.3, 18.1, 13.2, -5.2, -5.3, -5.5, -5.6 ppm; IR (thin film) ν 3415 (br), 2954, 2930, 2857, 1463, 1362, 1255, 1086, 971, 837, 781, 700 cm⁻¹; HRMS (FAB⁺) calcd for C₃₅H₆₀Si₂O₈ 664.4186, found 665.3903 (MH⁺).
**Tris-Acetate (71).** To a solution of polyol 70 (130 mg, 0.195 mmol) in 5.0 mL of CH₂Cl₂ was added 4–DMAP (490 mg, 4.0 mmol, 20 equiv) followed by Ac₂O (190 µL, 2.0 mmol, 10 equiv). The solution was stirred for 12 h and then poured onto 5 mL of a 1.0 M aqueous KH₂PO₄ solution. The organic phase was collected and the aqueous layer was extracted with 3 x 5 mL CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and evaporated under reduced pressure. Purification of the pale yellow residue by chromatography on silica gel (6:1 hexanes/EtOAc) gave the product 71 (145 mg, 94%) as a clear, colorless oil. TLC Rᵣ = 0.16 (6:1 hexanes/EtOAc); [α]ᵣNa + 37.0° (c = 0.56, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.28-7.25 (m, 2H, Hₐromatic), 7.18 (t, 1H, J = 7.4 Hz, Hₐromatic), 7.12 (d, 2H, J = 7.3 Hz, Hₐromatic), 5.50 (d, 1H, J = 2.9 Hz, H₆), 5.42 (d, 1H, J = 1.6 Hz, -OH₃), 5.06 (d, 1H, J = 2.9 Hz, H₇), 4.88-4.84 (m, 1H, H₄), 4.17 (d, 1H, J = 11.5 Hz, H₁₀), 4.13 (dd, 1H, J = 11.6, 1.7 Hz, H₈), 4.03 (ddd, 1H, J = 6.9, 1.7, 1.6 Hz, H₃) 3.93 (d, 1H, J = 11.4 Hz, H₁₀), 3.90 (dd, 1H, J = 11.7, 6.9 Hz, H₈), 2.76 (dd, 1H, J = 13.5, 5.0 Hz, H₆), 2.60 (s, 1H, -C≡CH), 2.28 (dd, 1H, J = 13.4, 9.7 Hz, H₆), 2.11 (s, 6H, two -COCH₃), 2.06 (s, 3H, -COCH₃), 2.00-1.96 (m, 1H, H₅), 1.85-1.25 (m, 6H, H₁, H₂, H₃), 0.91 (s, 9H, HTBS-Bu), 0.89 (s, 9H, HTBS-Bu), 0.83 (d, 3H, J = 6.8 Hz, H₁, H₁), 0.13 (s, 3H, HTBS-Me), 0.12 (s, 3H, HTBS-Me), 0.08 (s, 6H, HTBS-Me) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 170.7, 169.7, 169.3, 140.6, 129.0, 128.1, 125.8, 104.8, 83.5, 81.5, 80.29, 80.27, 78.4, 78.2, 76.8, 76.1, 69.0, 64.3, 63.2, 39.3, 38.3, 35.5, 31.1, 25.8, 25.7, 21.1, 20.65, 20.61, 19.0, 18.2, 14.0, -5.0, -5.2, -5.5, -5.8 ppm; IR (thin film) ν 3426, 3259, 2955, 2931, 2885, 1753, 1472, 1463, 1372, 1239, 1138, 1088, 1041, 1021, 837, 780 cm⁻¹; HRMS (FAB⁺) calc’d for C₄₁H₆₆Si₂O₁₁ 790.4143, found 791.4204 (MH⁺).
C(8) Alcohol (72). A solution of 71 (104 mg, 0.131 mmol) in 20.0 mL of MeOH was treated with 95 µL (1.2 mmol, 9 equiv) of Cl₂CHCO₂H and stirred for 7 h. The mixture was then diluted with 20 mL of Et₂O and poured onto 20 mL of sat. aqueous NH₄Cl. The organic phase was isolated and the aqueous layer extracted with 3 x 20 mL Et₂O. The combined ethereal extracts were washed with 1 x 40 mL sat. aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by chromatography on silica gel (2:1 hexanes/EtOAc) furnished 80 mg (90%) of the alcohol product as a clear, colorless oil. TLC Rₜ = 0.19 (2:1 hexanes/EtOAc). To a solution of the alcohol (79.0 mg, 0.18 mmol) in 15.0 mL of pyridine was suspended 80 mg of 5% Pd-C. The contents were placed under 1 atm H₂ and stirred vigorously for 2 h. The mixture was filtered through Celite, the filter cake rinsed with Et₂O (10 mL), and the filtrate concentrated in vacuo to a pale yellow oil. The product 72 was used without further purification. TLC Rₜ = 0.17 (2:1 hexanes/EtOAc); [α]Na -165.2° (c = 0.26, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.28-7.25 (m, 2H, Hₐromatic), 7.18 (dt, 1H, J = 7.3, 1.2 Hz, Hₐromatic), 7.13 (dd, 1H, J = 6.9, 1.2 Hz, Hₐromatic), 5.98 (dd, 1H, J = 16.8, 10.7 Hz, -CH=CH₂), 5.69 (dd, 1H, J = 16.8, 1.7 Hz, -CH=CH₂), 5.44 (d, 1H, J = 3.0 Hz, H₆), 5.42 (dd, 1H, J = 10.7, 1.7 Hz, -CH=CH₂), 5.10 (d, 1H, J = 3.0 Hz, H₇), 4.90-4.86 (m, 1H, H₄), 4.71 (br s, 1H, -OH₃), 3.88 (dd, 1H, J = 5.3, 3.4 Hz, H₃), 3.80 (dd, 1H, J = 12.0, 5.4 Hz, H₈), 3.79 (d, 1H, J = 11.2 Hz, H₁₀), 3.71 (d, 1H, J = 11.0 Hz, H₁₀), 3.70 (dd, 1H, J = 12.0, 3.3 Hz, H₈), 2.75 (dd, 1H, J = 13.4, 5.0 Hz, H₆'), 2.29 (dd, 1H, J = 13.4, 9.5 Hz, H₆'), 2.12 (s, 3H, -COCH₃), 2.10 (s, 3H, -COCH₃), 2.07 (s, 3H, -COCH₃), 2.00-1.95 (m, 1H, H₅), 1.87-1.47 (m, 6H, H₁₁', H₂', H₃'), 0.87 (s, 9H, TBS-cBu), 0.84 (d, 3H, J = 6.8 Hz, H₁₃'), 0.06 (s, 3H, HTBS-Me), 0.04 (s, 3H, HTBS-Me) ppm; ¹³C NMR
(CDCl₃, 125 MHz) δ 170.9, 169.9 (2 lines), 140.7, 134.8, 129.1, 128.2, 125.9, 118.9, 104.5, 84.2, 80.5, 77.4, 77.0 (masked by CDCl₃), 75.2, 75.0, 62.9, 61.3, 39.4, 38.4, 35.4, 31.1, 25.7, 21.1, 20.7, 20.6, 19.0, 18.1, 14.0, -5.7, -5.8 ppm; IR (thin film) ν 3450 (br), 3026, 2955, 2931, 1749, 1463, 1432, 1372, 1240, 1179, 1093, 1039, 967, 838, 781, 701 cm⁻¹; HRMS (FAB⁺) calc’d for C₃₅H₅₄SiO₁₁ 678.3929, found 679.3501 (MH⁺).

C(8) tert-Butyl Ester (74). To a solution of alcohol 72 (15.0 mg, 22.1 μmol) in 3.0 mL of CH₂Cl₂ was added 21 mg (50 mmol) of freshly prepared Dess-Martin periodinane. The white suspension was stirred at 23 °C for 2 h. Et₂O (5 mL) was then added to the reaction mixture and the resulting precipitates removed by filtration through Celite. The filtrate was concentrated in vacuo to give a white solid residue. Purification by chromatography on silica gel (2:1 hexanes/EtOAc) afforded the product aldehyde (14 mg, 94%) as a colorless oil. TLC Rf ≈ 0.37 (2:1 hexanes/EtOAc). The intermediate aldehyde (11.0 mg, 16.3 μmol) was dissolved in 6.0 mL of a 5:1.2 4BuOH/2-methyl-2-butene solution and cooled to ca. 10 °C. An ice-cold buffered 1.1 M aqueous solution of NaClO₂ (150 μL, 165 μmol, 10 equiv) was added dropwise. The resulting pale yellow solution was stirred for 3 h and then quenched with 5.0 mL of a pH 2 KH₂PO₄-HCl buffer. The solution was extracted with 6 x 3 mL EtOAc. The combined extracts were dried over Na₂SO₄ and concentrated in vacuo. The unpurified product was re-dissolved in 3.0 mL of CH₂Cl₂ and N,N'-diisopropyl-O-tert-butylisourea (73) (10 mg, 50 μmol, 3 equiv) was added. The solution was stirred for 22 h during which time formation of a white precipitate was observed. The mixture was concentrated under reduced pressure to a pale yellow residue. Purification by chromatography on silica gel (5:1 hexanes/EtOAc)
gave 9 mg (76%) of 74 as a colorless oil. TLC Rf = 0.24 (4:1 hexanes/EtOAc); [α]Na
+11.4° (c = 0.25, CH2Cl2); 1H NMR (CDCl3, 500 MHz) δ 7.27-7.24 (m, 2H, Haromatic),
7.16 (t, 1H, J = 7.3 Hz, Haromatic), 7.12 (d, 1H, J = 7.4 Hz, Haromatic), 6.03 (dd, 1H, J =
16.7, 10.8 Hz, -CH=CH2), 5.62 (dd, 1H, J = 16.7, 1.5 Hz, -CH=CH2), 5.47 (d, 1H, J =
2.9 Hz, H6), 5.35 (dd, 1H, J = 10.7, 1.5 Hz, -CH=CH2), 5.11 (d, 1H, J = 2.9 Hz, H7),
4.87-4.85 (m, 1H, H4'), 4.38 (s, 1H, H3), 4.34 (s, 1H, -OH3'), 3.77 (d, 1H, J = 11.2 Hz,
H10), 3.72 (d, 1H, J = 11.2 Hz, H10), 2.75 (dd, 1H, J = 13.4, 4.9 Hz, H6'), 2.29 (dd, 1H,
J = 13.4, 9.6 Hz, H6'), 2.12 (s, 3H, -COCH3), 2.10 (s, 3H, -COCH3), 2.06 (s, 3H,
-COCH3), 2.03-1.93 (m, 1H, H5'), 1.91-1.74 (m, 2H, H1'), 1.68-1.48 (m, 4H, H2', H3'),
1.43 (s, 9H, fBu), 0.86 (s, 9H, HTBS-fBu), 0.83 (d, 3H, J = 6.8 Hz, H13'), 0.03 (s, 3H,
HTBS-Me), 0.03 (s, 3H, HTBS-Me) ppm; 13C NMR (CDCl3, 125 MHz) δ 170.8, 169.88,
169.73, 165.7, 140.7, 134.3, 129.1, 128.2, 125.8, 117.8, 104.1, 85.1, 82.5, 80.4, 77.1,
76.9, 75.5, 73.9, 62.2, 39.3, 38.2, 35.2, 31.1, 28.2, 25.7, 21.1, 20.8, 20.7, 19.0, 18.1, 13.9,
-5.6, -5.7 ppm; IR (thin film) v 3452, 2956, 2931, 1753, 1643, 1603, 1495, 1462, 1416,
1370, 1240, 1153, 1099, 1041, 930, 838, 701 cm⁻¹; HRMS (FAB⁺) calc'd for
C39H60SiO12 748.4392, found 749.3943 (MH⁺).

3,5-Bis-tert-Butyl Ester (76). To a solution of alcohol 75 (38.0 mg, 60.0 μmol)
in 5.0 mL of CH2Cl2 was added 25 μL (310 μmol, 5 equiv) of pyridine and 51 mg (120 μmol, 2 equiv) of Dess-Martin periodinane sequentially.31 The white suspension was
stirred for 35 min at 23 °C. The reaction mixture was then diluted with Et2O (10 mL)
and the resulting precipitates removed by filtration through Celite. Evaporation of the
filtrate under reduced pressure gave the product as pale yellow oil. Purification by
chromatography on silica gel (gradient elution: 7:2→2:1 hexanes/EtOAc) yielded the desired aldehyde as a colorless oil (32 mg, 84%). TLC R_f = 0.43 (2:1 hexanes/EtOAc). Oxidation and tert-butyl esterification was accomplished following a procedure outlined for the preparation of compound 74. The 3,5-bis-tert-butyl ester 76 was isolated as a colorless oil (27 mg, 76%). TLC R_f = 0.45 (2:1 hexanes/EtOAc); [α]_Na^+ 56.5° (c = 0.26, CH_2Cl_2); 1H NMR (CDCl_3, 500 MHz) δ 7.27-7.24 (m, 2H, H aromatic), 7.16 (t, 1H, J = 7.3 Hz, H aromatic), 7.12 (d, 1H, J = 7.2 Hz, H aromatic), 5.96 (dd, 1H, J = 16.7, 10.9 Hz, -CH=CH_2), 5.60 (d, 1H, J = 2.6 Hz, H_6), 5.55 (dd, 1H, J = 16.7, 1.5 Hz, -CH=CH_2), 5.36 (dd, 1H, J = 10.9, 1.5 Hz, -CH=CH_2), 5.12 (d, 1H, J = 2.6 Hz, H_7), 4.88-4.87 (m, 1H, H_4''), 4.42 (s, 1H, H_3), 3.61 (br s, 1H, -OH_3'), 3.77 (d, 1H, J = 11.2 Hz, H_10), 3.72 (d, 1H, J = 11.2 Hz, H_10), 2.75 (dd, 1H, J = 13.3, 4.9 Hz, H_6''), 2.29 (dd, 1H, J = 13.3, 9.6 Hz, H_6''), 2.14 (s, 3H, -COCH_3), 2.09 (s, 3H, -COCH_3), 2.06 (s, 3H, -COCH_3), 2.03-1.94 (m, 1H, H_5'''), 1.94-1.80 (m, 2H, H_1'''), 1.73-1.47 (m, 4H, H_2'', H_3'''), 1.43 (s, 9H, H_{tBu}), 1.40 (s, 9H, H_{tBu}), 0.83 (d, 3H, J = 6.8 Hz, H_13''') ppm; 13C NMR (CDCl_3, 125 MHz) δ 170.8, 169.4, 169.0, 165.0, 162.9, 140.7, 132.7, 129.1, 128.2, 125.8, 117.8, 104.1, 89.8, 83.5, 83.0, 80.3, 76.0, 75.4, 73.0 (2 lines), 39.3, 38.4, 35.4, 31.0, 28.1, 28.0, 21.1, 20.7 (2 lines), 19.0, 14.0 ppm; IR (thin film) ν 3567, 2978, 2933, 1752, 1603, 1495, 1455, 1415, 1369, 1298, 1240, 1155, 1035, 937, 846, 702 cm⁻¹; HRMS (FAB⁺) calc'd for C_{37}H_{52}O_{13} 704.3991, found 705.3482 (MH⁺).

**Olefin (81).** 5% palladium on carbon (112 mg, 100 wt.%) was suspended in 5.0 mL of a pyridine solution of 71 (112 mg, 0.142 mmol). The slurry was stirred at 23 °C under 1 atm of H_2 for 4.5 h. Removal of the palladium catalysts by filtration through
Celite followed by evaporation of the filtrate under reduced pressure afforded 115 mg of a colorless oil. The product 80 was used without purification. TLC Rf = 0.26 (6:1 Hexanes/EtOAc).

Compound 80 (0.142 mmol) was transferred to a Teflon vial and dissolved in a solution of HF-pyridine in THF/pyridine prepared according to the method of Trost.60 The solution was stirred at 23 °C for 7.5 h before the reaction was quenched by the addition of 5.0 mL of an 1.0 M aqueous KH2PO4 solution. The mixture was extracted with 4 x 5 ml Et2O, the combined organic extracts were washed once with sat. aqueous NaCl (5 ml), dried over Na2SO4 and concentrated in vacuo to give the product as a yellow oil. Purification of the by chromatography on silica gel (2:3 hexanes/EtOAc) furnished 51 mg of olefin 81 (64%) as a white foam. TLC Rf = 0.13 (1:1 hexanes/EtOAc); [α]Na +33.3° (c = 0.86, CH2Cl2); 1H NMR (CDCl3, 500 MHz) δ 7.29-7.26 (m, 2H, H aromatic), 7.19 (t, 1H, J = 7.3 Hz, H aromatic), 7.12 (d, 2H, J = 7.5 Hz, H aromatic), 5.97 (dd, 1H, J = 16.7, 10.9 Hz, H9), 5.79 (dd, 1H, J = 16.9, 0.9 Hz, -CH=CH2), 5.51-5.48 (m, 2H, H6 and -CH=CH2), 5.17 (d, 1H, J = 3.0 Hz, H7), 4.91-4.88 (m, 1H, H4'), 3.98 (dd, 1H, J = 4.4, 4.1 Hz, H3), 3.91 (s, 1H, -OH3'), 3.80-3.71 (m, 4H, H8, H10), 2.74 (dd, 1H, J = 13.5, 5.0 Hz, H6'), 2.33 (dd, 1H, J = 13.5, 9.4 Hz, H6'), 2.30-2.26 (m, 1H, -OH1'), 2.23 (dd, 1H, J = 6.4, 2.8 Hz, -OH1'), 2.14 (s, 3H, -COCH3), 2.13 (s, 3H, -COCH3), 2.09 (s, 3H, -COCH3), 2.01-1.97 (m, 1H, H5'), 1.90-1.43 (m, 6H, H1', H2', H3'), 0.86 (d, 3H, J = 6.9 Hz, H13') ppm; 13C NMR (CDCl3, 125 MHz) δ 171.1, 170.0, 169.7, 140.5, 133.3, 129.0, 128.2, 125.9, 119.6, 104.7, 85.3, 80.1, 76.9, 76.6, 75.2, 74.5, 61.3, 60.9, 39.4, 38.4, 35.1, 31.0, 21.1, 20.7, 20.6, 18.9, 13.9 ppm; IR (thin film) ν 3400 (br), 2936, 1748, 1454, 1373, 1240, 1021, 962, 746, 702 cm⁻¹; HRMS (FAB⁺) calc'd for C29H40O11 564.2570, found 565.2634 (MH⁺).
Dialdehyde (82). To a solution of 81 (40.0 mg, 70.8 µmol) in 4.0 mL of CH₂Cl₂ was added 72 µL of pyridine (0.9 mmol, 12.5 equiv) followed by 150 mg (0.35 mmol, 5 equiv) of the Dess–Martin periodinane. The resulting white suspension was stirred at 23 °C for 2.5 h. To the reaction mixture was then added 5.0 mL of Et₂O, and the resulting precipitates removed by filtration through Celite. The filtrate was concentrated in vacuo and the isolated pale yellow residue purified by chromatography on silica gel (3:2 hexanes/EtOAc) to afford 37 mg of 82 (93%) as a white foam. TLC Rf = 0.16 (2:1 hexanes/EtOAc); [α]_D +33.1° (c = 0.39, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 9.47 (s, 1H, CHO), 9.36 (s, 1H, -CHO), 7.30-7.26 (m, 2H, H_aromatic), 7.19 (t, 1H, J = 7.3 Hz, H_aromatic), 7.14 (d, 2H, J = 7.1 Hz, H_aromatic), 6.20 (ddd, 1H, J = 16.7, 11.5, 1.6 Hz, H₉), 5.73 (d, 1H, J = 16.7 Hz, -CH=CH₂), 5.65 (d, 1H, J = 11.5 Hz, -CH=CH₂), 5.56 (d, 1H, J = 2.6 Hz, H₆), 5.24 (d, 1H, J = 2.6 Hz, H₇), 4.91-4.89 (m, 1H, H₄'), 4.40 (s, 1H, H₃), 3.62 (d, 1H, J = 1.6 Hz, -OH₃'), 2.75 (dd, 1H, J = 13.5, 5.2 Hz, H₆'), 2.33 (dd, 1H, J = 13.4, 9.3 Hz, H₆'), 2.15 (s, 3H, -COCH₃), 2.09 (s, 3H, -COCH₃), 2.07 (s, 3H, -COCH₃), 2.01-1.97 (m, 1H, H₅'), 1.90-1.52 (m, 6H, H₁', H₂', H₃'), 0.86 (d, 3H, J = 6.8 Hz, H₁₃') ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 195.3, 192.7, 170.9, 169.7, 169.2, 140.5, 129.3, 129.0, 128.3, 125.9, 122.0, 105.1, 90.1, 79.5, 79.2, 76.4, 76.1, 73.2, 39.4, 38.5, 35.1, 31.0, 21.1, 20.6, 20.4, 18.9, 14.0 ppm; IR (thin film) v 3459, 2966, 1743, 1420, 1373, 1237, 1036, 959, 740, 702 cm⁻¹; HRMS (FAB⁺) calc'd for C₂₉H₃₆O₁₁ 560.2257, found 561.2356 (MH⁺).
**Tris-tert-Butyl Ester (78).** A solution of dialdehyde 82 (23.0 mg, 41.0 μmol) in 6.0 mL of a 10% v/v MeOH-CH₂Cl₂ solution was cooled to −78 °C and treated with a dilute stream of ozone in oxygen (0.8 mmol/min). After 30 min, PPh₃ (13 mg, 49.2 μmol, 1.2 equiv) was added to the reaction mixture, and resulting suspension slowly warmed to 23 °C. Concentration of the reaction mixture under reduced pressure yielded a white foam (83). The product was dissolved in 6.0 mL of a 5:1.2 ′BuOH/2-methyl-2-butene solution and cooled to ca. 10 °C. An ice-cold buffered 1.1 M aqueous solution of NaClO₂ (370 μL, ca. 410 μmol, 10 equiv) was added dropwise. The resulting pale yellow solution was stirred for 3 h before being quenched with 5.0 mL of a pH 2 KH₂PO₄-HCl buffer. The solution was extracted with 6 x 5 mL EtOAc. The combined extracts were dried over Na₂SO₄ and concentrated in vacuo. The unpurified product was redissolved in 3.0 mL of CH₂Cl₂ and N,N-diisopropyl-O-tert-butyliosourea (73)⁵⁹ (82 mg, 410 μmol) was added dropwise. The solution was stirred for 24 h during which time formation of a white precipitate was observed. The mixture was filtered through Celite to remove the solid material and concentrated under reduced pressure to a pale yellow oil. Purification by chromatography on silica gel (7:2 hexanes/EtOAc) afforded 78 (23 mg, 72%) as a colorless oil. TLC R_f = 0.44 (2:1 hexanes/EtOAc); [α]_Na +69.9° (c = 0.29, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.27-7.25 (m, 2H, H₂aromatic), 7.16 (t, 1H, J = 7.3 Hz, H₂aromatic), 7.11 (d, 2H, J = 7.4 Hz, H₂aromatic), 6.33 (d, 1H, J = 1.9 Hz, H₆), 5.08 (d, 1H, J = 1.9 Hz, H₇), 4.88 (s, 1H, H₃), 4.88-4.86 (m, 1H, H₄), 4.06 (s, 1H, -OH₃), 2.75 (dd, 1H, J = 13.4, 4.9 Hz, H₆), 2.29 (dd, 1H, J = 13.4, 9.6 Hz, H₆), 2.14 (s, 3H, -COCH₃), 2.06 (s, 3H, -COCH₃), 2.05 (s, 3H, -COCH₃), 2.05-1.91 (m, 3H, H₁, H₅), 1.67-1.50 (m, 4H, H₂, H₃), 1.61 (s, 9H, H₄Bu), 1.46 (s, 9H, H₄Bu), 1.45 (s, 9H, H₄Bu),
0.83 (d, 3H, J = 6.8 Hz, H$^{13\text{y}}$) ppm; $^{13}$C NMR (CD$_3$OD, 125 MHz) δ 173.0, 171.2, 170.3, 168.9, 167.5, 165.7, 142.1, 130.3, 129.4, 127.1, 105.7, 91.3, 86.6, 85.5, 85.1, 81.8 (2 lines), 78.1, 77.0, 75.7, 40.7, 39.8, 36.7, 32.5, 28.6 (2 lines), 28.5, 21.2, 20.8, 20.6, 20.3, 14.4 ppm; IR (thin film) ν 3447, 2979, 2935, 1760, 1732, 1477, 1457, 1394, 1370, 1236, 1152, 1118, 1039, 995, 702 cm$^{-1}$; HRMS (FAB$^+$) calc’d for C$_{46}$H$_{58}$O$_{15}$ 778.3775, found 801.3673 (MNa$^+$).

Alcohol (84). Tris-tert-butyl ester 78 (15.0 mg, 19.3 μmol) was treated with 3.0 ml of a 0.2% K$_2$CO$_3$ in methanol solution. The solution stirred for 30 min before the reaction was quenched by the addition of 3.0 mL of a 0.3 M aqueous KH$_2$PO$_4$ solution. The mixture was extracted with 5 x 3 mL Et$_2$O; the combined organic extracts were dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give the product as a colorless oil. Purification by chromatography on silica gel (3:2 hexanes/EtOAc) furnished 12 mg (90%) of 84 as a colorless film. TLC R$_f$ = 0.28 (1:1 hexanes/EtOAc); $^1$H NMR (CD$_3$OD, 500 MHz) δ 7.26-7.22 (m, 2H, H$_{\text{aromatic}}$), 7.16-7.13 (m, 3H, H$_{\text{aromatic}}$), 4.97 (s, 1H, H$_3$), 4.95 (d, 1H, J = 2.0 Hz, H$_6$), 4.90-4.86 (m, 1H, H$_{4\text{a}}$), 3.99 (d, 1H, J = 1.9 Hz, H$_7$), 2.74 (dd, 1H, J = 13.4, 5.6 Hz, H$_6'$), 2.35 (dd, 1H, J = 13.4, 9.1 Hz, H$_6'$), 2.05 (s, 3H, -COCH$_3$), 2.05-2.01 (m, 1H, H$_5$'), 1.90-1.79 (m, 2H, H$_1$'), 1.73-1.62 (m, 2H, H$_3$'), 1.60-1.28 (m, 2H, H$_2$'), 1.60 (s, 9H, H$_{t\text{Bu}}$), 1.46 (s, 9H, H$_{t\text{Bu}}$), 1.45 (s, 9H, H$_{t\text{Bu}}$), 0.87 (d, 3H, H$_{13\text{y}}$) ppm; $^{13}$C NMR (CD$_3$OD, 125 MHz) δ 173.0, 169.8, 168.2, 167.4, 142.0, 130.2, 129.3, 126.9, 106.4, 93.2, 85.5, 84.3 (2 lines), 84.2, 79.9, 78.3, 76.8, 76.0, 40.6, 39.5, 36.6, 32.5, 28.7, 28.5 (2 lines), 21.1, 20.2, 14.3 ppm; IR (thin film) ν
3500 (br), 2978, 2933, 1732, 1455, 1394, 1370, 1255, 1153, 1050, 963, 844, 701 cm\(^{-1}\); HRMS (FAB\(^+\)) calc'd for C\(_{36}H_{54}O_{13}\) 694.3564, found 717.3462 (MNa\(^+\)).

![Chemical structure](image)

**Allylic alcohol (87).** To a suspension of LiAlH\(_4\) (3.6 g, 95 mmol, 2.5 equiv) in 200 mL of Et\(_2\)O at 0 °C was added, via addition funnel, 150 mL of an ethereal solution of 5-phenyl-hex-2-yn-1-ol (6.6 g, 38 mmol). The gray suspension was stirred at 0 °C for 10 min. The mixture was warmed to 23 °C and then heated to reflux. After 12 h at reflux the reaction was re-cooled to 0 °C and cautiously quenched with 3.6 mL H\(_2\)O, 3.6 mL 15% aqueous NaOH, and 10.8 mL H\(_2\)O, added sequentially. The resulting viscous suspension was warmed to 23 °C and stirred vigorously for 30 min. The white precipitates were removed by filtration through Celite and the filter cake rinsed with 3 x 150 ml Et\(_2\)O. The colorless filtrate was dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography on silica gel (11:2 hexanes/EtOAc) yielded 5.3 g (79%) of 87 as a clear, colorless oil. TLC R\(_f\) = 0.19 (4:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.30-7.26 (m, 2H, H\(_{\text{aromatic}}\)), 7.20-7.18 (m, 3H, H\(_{\text{aromatic}}\)), 5.75-5.63 (m, 2H, -CH=CHCH\(_2\)OH), 4.09 (d, 2H, \(J = 5.6\) Hz, -CH\(_2\)OH), 2.64 (t, 2H, \(J = 7.7\) Hz, PhCH\(_2\)CH\(_2\)-), 2.10 (dt, 2H, \(J = 7.1, 6.8\) Hz, -CH\(_2\)CH=CHCH\(_2\)OH), 1.74 (tt, 2H, \(J = 7.6\) Hz, PhCH\(_2\)CH\(_2\)CH\(_2\)-), 1.38 (br s, 1H, -OH\(^+\)) ppm; \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 142.3, 132.8, 129.4, 128.4, 128.3, 125.7, 63.7, 35.3, 31.7, 30.7 ppm; IR (thin film) v 3318 (br), 3025, 2928, 1603, 1496, 1452, 1085, 968, 697 cm\(^{-1}\); Anal. Calcd for C\(_{12}\)H\(_{16}\)O: C, 81.77; H, 9.15. Found: C, 81.50; H, 9.18.
Epoxy Alcohol (88). A flask containing 1.0 g of freshly activated 4Å molecular sieves was charged with 140 mL of CH₂Cl₂ and 268 μL of L-(-)-diisopropyl tartrate (1.28 mmol, 0.075 equiv). The mixture was cooled to -30 °C (2:3 ethylene glycol/H₂O-dry ice) before Ti(OiPr)₄ (250 μL, 0.85 mmol, 0.05 equiv) and a 4.0 M CH₂Cl₂ solution of 'BuOOH (8.5 mL, 34 mmol, 2 equiv) were added sequentially. The contents were stirred at -30 °C for 1 h before a solution of alcohol 87 (3.00 g, 17.0 mmol) in 4.0 mL of CH₂Cl₂ was added dropwise via cannula. Transfer of 87 was made quantitative with an additional 2.0 mL of CH₂Cl₂. The reaction was stirred at -30 °C for 20 h after which time 1.0 mL of a 30% aqueous NaOH solution saturated with NaCl was added along with 30.0 mL of Et₂O. The mixture was warmed to -10 °C and stirred for 1 h. Following the addition of 2.5 g of Celite and 1.0 g of MgSO₄, the slurry was warmed to 23 °C and the mixture was filtered through Celite. The solids collected were rinsed with Et₂O (ca. 50 mL) and the combined filtrates concentrated under reduced pressure to give a yellow oil. Purification by chromatography on silica gel (gradient elution: 3:1→2:1 hexanes/EtOAc) furnished 88 as a colorless oil (3.2 g, 98%). TLC Rf = 0.20 (2:1 hexanes/EtOAc); [α]_Na +18.9° (c = 0.42, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.30-7.26 (m, 2H, H_aro), 7.21-7.18 (m, 3H, H_aro), 3.89 (ddd, 1H, J = 12.5, 5.1, 2.5 Hz, -OCH₂CH₂OH), 3.61 (ddd, 1H, J = 12.5, 7.1, 4.8 Hz, PhCH₂CH₂CH₂HCO-), 3.00-2.96 (m, 1H, -CH₂OH), 2.92-2.90 (m, 1H, -CH₂OH), 2.68 (t, 2H, J = 7.7 Hz, PhCH₂CH₂-), 1.90 (br s, 1H, -OH₁), 1.85-1.73 (m, 2H, PhCH₂CH₂CH₂CH-), 1.68-1.57 (m, 2H, PhCH₂CH₂CH₂-), ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 141.8, 128.35, 128.33, 125.9, 61.6, 58.3, 55.7, 35.5, 31.0, 27.6 ppm; IR (thin film) ν 3408 (br), 2933, 1602, 1496, 1452, 1092, 1030, 886, 747, 699 cm⁻¹; Anal. Calcd for C₁₂H₁₆O₂: C, 74.97; H, 8.39. Found: C, 74.61; H, 8.40. The epoxy alcohol 88 was shown to be in >95% ee as determined by analysis of the
$^1$H NMR spectrum of the corresponding Mosher (S)-MTPA ester (prepared as described in ref. 65).

**C(7)-OBoc (100).** To a cold solution (0 °C) of 84 (8.5 mg, 12.2 μmol) and 4-pyrrolidinopyrididine (1.5 mg, 10.1 μmol, 0.8 equiv) in 1.0 mL of CH$_2$Cl$_2$ was added Et$_3$N (7 μL, 49.4 μmol, 4.0 equiv) followed by 140 μL of a 0.10 M CH$_2$Cl$_2$ solution of di–tert–butyl dicarbonate (14.0 μmol, 1.15 equiv). The resulting mixture was stirred at 0 °C for 6 h. The reaction was then poured onto 2.0 mL of 1.0 M aqueous K$_2$HPO$_4$ and extracted with 5 x 2 mL Et$_2$O. The combined ethereal extracts were washed once with sat. aqueous NaCl (5 mL), dried over Na$_2$SO$_4$, and concentrated *in vacuo*. Purification of the white residue by chromatography on silica gel (3:1 hexanes/EtOAc) afforded 100 (8 mg, 82%) as a white foam. TLC R$_f$ = 0.19 (3:1 hexanes/EtOAc); [α]$_{Na}^{25}$ +43.3° (c = 0.25, CH$_2$Cl$_2$);

$^1$H NMR (CDCl$_3$, 500 MHz) δ 7.27-7.24 (m, 2H, H$_{\text{aromatic}}$), 7.17 (t, 1H, $J = 7.3$ Hz, H$_{\text{aromatic}}$), 7.12 (d, 2H, $J = 7.1$ Hz, H$_{\text{aromatic}}$), 5.11 (br. s, 1H, H$_6$), 4.88-4.86 (m, 1H, H$_4^\delta$), 4.72 (s, 1H, H$_3$), 4.64 (d, 1H, $J = 2.1$ Hz, H$_7$), 3.93 (br. s, 1H, -OH$_3^\delta$), 2.80 (br. s, 1H, -OH$_2^\delta$), 2.75 (dd, 1H, $J = 13.5$, 5.1 Hz, H$_6^\delta$), 2.30 (dd, 1H, $J = 13.5$, 9.7 Hz, H$_6^\delta$), 2.05 (s, 3H, -COCH$_3$), 2.05-1.91 (m, 3H, H$_{1^\delta}$, H$_{5^\delta}$), 1.68-1.26 (m, 4H, H$_2^\delta$, H$_3^\delta$), 1.58 (s, 9H, H$_{\text{Boc-fBu}}$), 1.50 (s, 9H, H$_{\text{fBu}}$), 1.49 (s, 9H, H$_{\text{fBu}}$). 1.45 (s, 9H, H$_{\text{fBu}}$). 0.84 (d, 3H, $J = 6.8$ Hz, H$_{13^\delta}$) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 170.8, 168.5, 165.8, 165.2, 153.7, 140.8, 129.1, 128.2, 125.8, 103.9, 90.7, 85.6, 85.0, 83.9, 83.7, 83.2, 76.92, 76.85, 75.3, 74.1, 39.4, 38.0, 35.6, 30.9, 28.2, 28.1, 28.0, 27.7, 21.2, 18.9, 13.8 ppm; IR (thin film) ν 3462 (br), 2980, 2934, 1732, 1456, 1395, 1370, 1278, 1256, 1157, 1119, 1060,
C(7)-OBoc Zaragozic Acid C, 3,4,5-tris-tert-Butyl Ester (101). To a solution of acyl side chain acid 92 (9.0 mg, 36.5 μmol) in 365 μL of CH₂Cl₂ was added 7.5 mg of 1,3-dicyclohexylcarbodiimide (36.5 μmol). The resulting suspension was stirred for 15 min before use. A solution of 100 (4.0 mg, 5.0 μmol) and 4–DMAP (2 mg, 16 μmol) in 1.0 mL of CH₂Cl₂ was treated with 60.0 μL of the 92–DCC mixture (6.0 μmol). The mixture was stirred for 40 h and then quenched with 2.0 mL of 1/2 sat. aqueous NaHCO₃. The mixture was extracted with 4 x 2 mL Et₂O; the organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography on silica gel (5:1 hexanes/EtOAc) gave the product 101 (4 mg, 78%) as a colorless film. TLC Rᵣ = 0.37 (3:1 hexanes/EtOAc); [α]_Na +8.5° (c = 0.27, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.28-7.22 (m, 4H, H₉aromatic), 7.18-7.12 (m, 6H, H₉aromatic), 6.40 (d, 1H, J = 1.9 Hz, H₆), 5.38-5.29 (m, 2H, H₄v, H₅v), 4.91 (s, 1H, H₃), 4.89-4.86 (m, 2H, H₇, H₄'), 4.05 (br s, 1H, -OH₃'), 2.76 (dd, 1H, J = 13.4, 4.7 Hz, H₆'), 2.57 (t, 2H, J = 7.7 Hz, H₉v), 2.39-2.27 (m, 3H, H₁₁, H₂v), 2.12-1.84 (m, 6H, H₁', H₅', H₃v, H₆v'), 2.05 (s, 3H, -COCH₃), 1.68-1.26 (m, 8H, H₂', H₃', H₇v, H₈v'), 1.62 (s, 9H, HBOc-tBu), 1.47 (s, 9H, HfBu), 1.452 (s, 9H, HfBu), 1.446 (s, 9H, HfBu), 0.93 (d, 3H, J = 6.7 Hz, H₁₆v'), 0.83 (d, 3H, J = 6.8 Hz, H₁₃'), ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 170.8, 170.7, 168.6, 165.6, 164.0, 152.4, 142.8, 140.8, 137.6, 129.1, 128.4, 128.23, 128.21, 126.1, 125.8, 125.6, 103.8, 89.8, 86.0, 83.9, 83.4, 83.3, 83.1, 77.0 (masked by CDCl₃), 76.2, 75.3, 74.0, 39.4, 38.0, 36.5, 36.5, 36.1, 35.8, 34.2, 30.9, 29.2, 28.1 (2 lines), 28.0,
Zaragozic Acid C (1). To a solution of 101 (3.0 mg, 2.9 µmol) in 1.5 mL of CH₂Cl₂ was added 500 µL of trifluoroacetic acid. The reaction was stirred for 16 h after which time the volatiles were removed in vacuo. The resulting pale brown residue was dissolved in toluene (5 mL), concentrated in vacuo, and lyophilized from 2 mL of benzene to afford 2.2 mg (100%) of 1 as a white flocculent solid. TLC Rf = 0.34 (6:1 CH₃CN/H₂O); HPLC: tR = 12.03 ± 0.5 min (reverse phase, 20% CH₃CN in 0.1% aqueous H₃PO₄ initially, graded to 95% CH₃CN over 20 min); [α]DNa +9.0° (c = 0.23, EtOH); ¹H NMR (CD₃OD, 500 MHz) δ 7.25-7.21 (m, 4H, H Casual), 7.15-7.10 (m, 6H, H Casual), 6.23 (d, 1H, J = 1.8 Hz, H₆), 5.37 (dt, 1H, J = 15.3, 6.1 Hz, H₄v), 5.30 (dd, 1H, J = 15.4, 7.5 Hz, H₅v), 5.23 (s, 1H, H₃), 4.90-4.86 (m, 1H, H₄' masked by CD₃OH signal), 4.01 (d, 1H, J = 1.8 Hz, H₇), 2.73 (dd, 1H, J = 13.3, 5.6 Hz, H₆'), 2.58-2.54 (m, 2H, H₉v), 2.37-2.32 (m, 3H, H₆', H₂v), 2.28-2.25 (m, 2H, H₃v), 2.09-2.01 (m, 3H, H₅', H₆v), 2.05 (s, 3H, -COCH₃), 1.91-1.86 (m, 2H, H₁'), 1.69-1.66 (m, 2H, H₃'), 1.61-1.53 (m, 4H, H₂', H₈v), 1.31-1.24 (m, 2H, H₇v), 0.93 (d, 3H, J = 6.9 Hz, H₁''v), 0.86 (d, 3H, J = 6.8 Hz, H₁₃''v) ppm; ¹³C NMR (CD₃OD, 125 MHz) δ 173.1, 173.0, 172.6, 170.2, 168.6, 143.9, 142.0, 138.8, 130.2, 129.4, 129.28, 129.26, 127.6, 126.9, 126.6, 107.1, 91.0, 82.3, 81.2, 78.2, 76.7, 75.6, 40.5, 39.7, 37.8, 37.6, 36.9, 36.3, 35.4, 32.5, 30.5, 28.8, 21.2, 21.1, 20.1, 14.3 ppm; IR (thin film) ν 3456 (br), 2928, 1732, 1495, 1454, 1372, 1249,
1148, 1028, 969, 746, 700 cm$^{-1}$; HRMS (FAB$^+$) calc'd for C$_{40}$H$_{50}$O$_{14}$ 754.3198, found 777.3098 (MNa$^+$).
Part II. Nitridomanganese(V) Complexes: Design, Preparation and Use as Novel Nitrogen Atom-Transfer Reagents
Chapter One

Nitrogen Atom-Transfer from Novel Nitridomanganese(V) Complexes

Introduction

Heteroatom-transfer from a reactive transition-metal complex to an olefin substrate is one of the most efficient methods for generating functionalized hydrocarbons.1 Epoxidation, dihydroxylation, and cyclopropanation processes have been extensively refined and have found widespread application in organic synthesis.2 By contrast, methodologies for nitrogen atom-transfer to an olefin are few in number and less developed than their carbon and oxygen analogs.3 Available protocols for aziridine formation which involve the addition of a thermally or photochemically generated nitrene

\[
\begin{align*}
R^1&-\overset{\text{RN}^+}{=}&R^2 \quad \overset{\text{RN}^+}{\longrightarrow} \quad R^1\overset{\text{N}}{=}R^2 + R^1\overset{\text{NHR}}{=}R^2 + \text{RNH}_2
\end{align*}
\]


to an olefin are often low yielding and complicated by product mixtures resulting from competing hydrogen abstraction and insertion reactions (eq 1). Reagents capable of mediating the selective coupling of an intermediate nitrene to an alkene would have tremendous potential utility for the construction of amine-derived natural products, pharmaceuticals, designed molecules, and materials (Figure 1).

![Figure 1. Olefin amination: a valuable method for chemical synthesis.](image)

**Background.** In one of the earliest examples of transition-metal promoted nitrogen atom-transfer, Kwart and Kahn demonstrated that benzenesulfonyl azide 1 could function as a nitrene source for olefin amination when copper was used to initiate its

\[
\begin{align*}
\text{PhSO}_2\text{N}_3 & \overset{\text{cyclohexene}}{\underset{\text{Cu}^2, 84 ^\circ C}{\longrightarrow}} \begin{array}{c}
\text{NSO}_2\text{Ph} \\
15\%
\end{array} & \\
\text{NH}_2\text{SO}_3\text{Ph} & \begin{array}{c}
18\%
\end{array} & \\
\text{NH}_2\text{SO}_3\text{Ph} & \begin{array}{c}
37\%
\end{array}
\end{align*}
\]


decomposition. Upon heating a cyclohexene solution of 1 and copper powder, it was found that a distribution of sulfonamide-containing cyclohexene-derived products was produced (eq 2). The formation of these materials is consistent with the intermediacy of either a nitrene or copper nitrenoid species in this reaction process.

The ability of arenesulfonyl azides to serve as nitrogen atom sources has been further illustrated by Holm (Figure 2). In this work, p-tolysulfonyl azide 2 was shown to function effectively as an imido group donor to complexes of Mo(IV). Other nitrene equivalents 3–5 could also be employed for this reaction.

\[
\text{Mo(ET_{2}dtc)}_{2}(O) \xrightarrow{\text{RNTs}} \text{Mo(ET}_{2}\text{dtc)}_{2}(O)(\text{NTs})
\]

Figure 2. Imido group transfer reactions with nitrene equivalents 2–5.

Evans has reported the use of compounds 2–5 as nitrogen atom sources for olefin aziridination reactions. In these studies, 2–5 were screened for their efficacy in the aziridination of styrene (100 equiv) with catalytic CuOTf (5 mol%). \((N-(p-\text{tolysulfonyl})\text{imino})\text{phenyliodinane (PhI=NTs}) 5\) was found to be the most effective nitrene precursor, providing a 96% yield of the desired \(N\)-tosyl aziridine 6 (eq 3). Prior to this work, Mansuy had disclosed the only investigation of metal-catalyzed nitrogen


atom-transfer to olefins, in which he utilized Mn(III) and Fe(III) porphyrin derivatives as catalysts and PhI=NTs as the nitrone source (Figure 3).\(^8\) In reactions employing 100 equivalents of olefin and 5 mol\% catalyst (based on 1 equiv PhI=NTs), aziridine products

\[
\begin{align*}
\text{Et}-\text{CH=CH-Me} & + \text{PhI}=\text{NTs} & \text{cat. Fe(TDCPP)ClO}_4 \\
& & \text{CH}_2\text{Cl}_2 \\
& & 33\% \\
\text{Et}-\text{CH} & + \text{PhI}=\text{NTs} \\
& \text{cat. Mn(TPP)ClO}_4 \\
& \text{CH}_2\text{Cl}_2 \\
& 35\% \\
\text{Et}-\text{CH=CH-Me} & + \text{PhI}=\text{NTs} & \text{cat. Fe(TDCPP)ClO}_4 \\
& & \text{CH}_2\text{Cl}_2 \\
& & 13\% \\
& & > 40\% \\
\end{align*}
\]

**Figure 3.** Aziridination and allylic amination of alkenes with PhI=NTs.

7 and 8 were generated, but often in only moderate yields (23–43\%). Other problems, including competing allylic insertion to give N-tosyl allylic amines 9 and 10 and non-stereospecific aziridine formation (with cis-disubstituted alkenes), complicated this process.\(^8\)\(^9\) However, the subsequent finding by Evans that both Cu(I) and Cu(II) salts were significantly more effective as catalysts for transfer of NTs from PhI=NTs to an

---


olefin has greatly extended the scope and utility of this methodology. Using

![Chemical Structure](image)

CuClO₄, Cu(acac)₂, or Cu(OTf)₂ as catalyst (5–10 mol%) and either electron-rich or electron-deficient alkenes (5 equiv), aziridine yields typically in the range of 60–90% have been recorded (eq 4 and 5). In contrast to reactions employing Mn and Fe porphyrin complexes, the copper-catalyzed process is highly stereospecific for disubstituted olefins. The versatility of this methodology has been further demonstrated in simultaneous reports by Jacobsen (eq 6) and Evans (eq 7) of a catalytic, enantioselective aziridination process using CuOTf with chiral ligands 11 and 12.¹¹,¹²,¹³

![Chemical Structure](image)

10. For a comprehensive review on the chemistry of polyvalent iodine compounds, see: Stang, P. J.; Zhdankin, V. V. Chem. Rev. 1996, 96, 1123.


Interest in the metal-catalyzed olefin aziridination with PhI=NTs as a potentially valuable synthetic method has raised questions regarding the mechanism of this transformation. Mansuy has suggested the intermediacy of a metal nitrenoid 13 in reactions of PhI=NTs with Mn and Fe porphyrin catalysts (Figure 4). This proposition follows from the isolation of allylic insertion products with simple olefins (e.g., 2-hexene), compounds typically identified in reactions involving nitrene species.\textsuperscript{8a,8c,14} Additionally, Jacobsen has reported evidence for the involvement of a discrete, monomeric Cu(III)–nitrene 14 in the Cu(I)/PhI=NTs olefin aziridination process.\textsuperscript{15} Unlike the Mn and Fe systems, however, copper salts exhibit an exceedingly low propensity to catalyze C–H insertion of NTs.\textsuperscript{3a} This, coupled with the fact that Lewis acids (SmI\textsubscript{2}(O\textsuperscript{3}Bu), Zn(OTf)\textsubscript{2}, Mg(OTf)\textsubscript{2}) as well as coordination complexes of Cr, Mn, Fe, Co, Ni, Cu, Ru, Rh, and Pd have also been shown to promote nitrene transfer from

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Possible pathways in the nitrene transfer reaction with PhI=NTs and metal catalysts.}
\end{figure}


PhI=NTs to olefins, would seem to argue for the availability of more than one operative mechanism for product formation (cf., 15, Figure 4).\textsuperscript{3a,13c,16,17,18}

A separate and distinct methodology for the aminohydroxylation of alkenes has been developed by Sharpless.\textsuperscript{19} As originally reported, the formation of \textit{N}–\textit{tert}–alkyl vicinal amino alcohols was possible following a two-step sequence which involved initial

\[
\begin{align*}
\text{O} &= \text{NR} \\
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} & \rightarrow \\
\text{N} &= \text{R} \\
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} & \rightarrow
\end{align*}
\]

\[
\text{LiAlH}_4 \quad \rightarrow \quad \text{NHR}
\]

reaction of an olefin with stoichiometric amounts of trioxo(\textit{tert}–alkylimido)osmium(VIII) (derived from OsO\textsubscript{4}), followed by reductive cleavage of the resulting osmate ester with LiAlH\textsubscript{4} (eq 8).\textsuperscript{20} Subsequently, it was discovered that \textit{N}–toluenesulfonyl amino alcohols could be generated with catalytic amounts of OsO\textsubscript{4} when Chloramine–T trihydrate (TsNCINa•3H\textsubscript{2}O) was utilized as the nitrene source.\textsuperscript{21,22} This method offered significant

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16. A trispyrazolylborate complex of CuOTf has been shown to catalyze nitrene transfer from PhI=NTs to alkenes, see: Pérez, P. J.; Brookhart, M.; Templeton, J. L. Organometallics 1993, 12, 261.


18. Valentine has shown that Lewis acids will catalyze the epoxidation of olefins with PhI=O, see: Yang, Y.; Diederich, F.; Valentine, J. S. J. Am. Chem. Soc. 1991, 113, 7195.

19. This work has been highlighted in a short review, see: Reiser, O. Angew. Chem., Int. Ed. Engl. 1996, 35, 1308.


improvement over its progenitor, and has since been further optimized and rendered asymmetric by the addition of chiral cinchona alkaloid-based ligands (eq 9).\textsuperscript{23}

\[
\begin{align*}
\text{MeO}_2\text{C} & \xrightarrow{\text{TsNCINa}} \text{NHTs} \\
\text{CO}_2\text{Me} & \xrightarrow{(\text{DHO})_2\text{PHAL}} \text{MeO}_2\text{C} \\
\text{4 mol\% OsO}_4 & \xrightarrow{65\%} \text{R} \\
\text{N} & \xrightarrow{77\% \text{ee}} \text{R} \\
\text{OH} & \xrightarrow{\text{MeO}} \text{Et}
\end{align*}
\]

Our desire to develop novel nitrogen atom–transfer reagents was fueled by the potential application of aziridination and amination technologies for chemical synthesis, together with the paucity of available strategies for effecting such transformations. To this end we became interested in a report by Groves of a nitridomanganese(V) porphyrin system ((TMP)Mn≡N) \textbf{17} which, when reacted with trifluoroacetic anhydride (TFAA), transferred a CF\textsubscript{3}CON unit to cis–cyclooctene to furnish the N–trifluoroacetyl-protected aziridine, \textbf{18} (Figure 5).\textsuperscript{24} This method for the coupling of an acyl nitrene with an olefin is unique, and does not appear to be plagued by competing insertion and C–H abstraction reactions typically observed in processes thought to involve nitrenoid intermediates.\textsuperscript{4,8} Additionally, the mechanism for CF\textsubscript{3}CON transfer parallels that of well-known manganese and iron-catalyzed epoxidation reactions (\textit{vide infra}). We were attracted to the similarities between this novel aziridination reaction and related oxo-transfer processes, and felt that the expansive body of information on metal-catalyzed epoxidation reactions would provide an invaluable guide for our work.\textsuperscript{1a,25} In this regard, particular


attention was paid to the numerous examples of olefin epoxidation catalyzed by non-porphyrin Mn and Fe complexes.\textsuperscript{1a,2a,26} Thus, by analogy, it seemed reasonable that manganese nitrides other than porphyrin-based systems like (TMP)Mn(N) 17 could be utilized as nitrogen transfer reagents. At the time we became involved with this project, however, only nitrido Mn(V) porphyrin complexes had been prepared.\textsuperscript{24,27,28}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Aziridination of cyclooctene with nitrido[meso-tetrakis(2,4,6-trimethyl-phenyl)porphyrinato]manganese(V), (TMP)Mn(N).}
\end{figure}

Although inspired by Groves’ elegant application of (TMP)Mn(N) for the aziridination of cis-cyclooctene, we were cognizant of certain features which would diminish the utility of such nitrogen-transfer technology as a general, practical method.


28. The synthesis of two nitridomanganese phthalocyanine complexes had also been described but their structures were not definitely established by X-ray crystallography, see: (a) Grunewald, H.; Homborg, H. Z. Anorg. Allg. Chem. 1992, 608, 81. (b) Grunewald, H.; Homborg, H. Z. Naturforsch. 1990, 45B, 483.
First, the aziridination of cyclooctene involved using a large excess of the starting olefin (11 equiv) with one equivalent of (TMP)Mn(N). For an inexpensive olefin such as cyclooctene, this does not represent a limitation, but for more complex, less available alkenes, a process in which the olefin substrate serves as the limiting reagent is desirable. Secondly, the formation of (TMP)Mn(N) had been accomplished by irradiation (λ ≥ 290 nm) of the corresponding Mn(III) azide 16 (Figure 5). This photolysis reaction afforded good yields of the Mn(V) nitride (77–82%), but was limited to small scale production (ca. 500 mg) of this compound.\textsuperscript{24,29} A method amenable to large scale synthesis (10–20 g) of the nitrido complex would be necessary, however, because of its requirement as a stoichiometric reagent in the aziridination reaction. Finally, the difficulties associated with the preparation and functionalization of porphyrin ligands, coupled with the prohibitive cost of these materials, rendered the porphyrin-based compounds impractical for our purposes.\textsuperscript{30} Thus, alternative Mn complexes with inexpensive, readily derivatizable ligand systems were considered.

In an effort to find non-porphyrin ligands suitable for the formation of a highly oxidized Mn(V) nitrido species, we became interested in a report by Arshankow and Poznjak of a salen Cr(V) nitride 20 which had been prepared photolytically from the (salen)Cr\textsuperscript{III}(N\textsubscript{3}) 19 (eq 10).\textsuperscript{31} Assignment of this complex as (salen)Cr\textsuperscript{V}(N), in the absence of X-ray crystallographic data, was based on electron paramagnetic resonance (EPR) spectroscopy which supported a d\textsuperscript{1} valence configuration, and infrared (IR) spectroscopy which established the presence of a Cr–nitrogen triple bond (ν\textsubscript{Cr≡N} = 1012 cm\textsuperscript{-1}). Subsequently, Che had described a second non-porphyrin nitrido chromium

\textsuperscript{29} Takahashi, T. Ph.D. Dissertation, The University of Michigan, Ann Arbor, MI, 1985.

\textsuperscript{30} 2,3,7,8,12,13,17,18-Octaethylporphyrin manganese(III) chloride may be purchased for $566/gram from Aldrich Chem. Co.

compound, (bpb)CrV(N) 22, derived from the tetradentate 1,2–bis(2–pyridinecarboxamido)benzene (bpb) ligand (eq 11). This was prepared in an analogous fashion to the (salen)Cr(N) complex, and had been characterized by single crystal X–ray analysis. Noteworthy was the fact that both the (salen)Cr(N) and the (bpb)Cr(N) were stable to air and moisture and could be handled on the benchtop. Aware of these findings, we speculated that analogous nitridomanganese systems could be constructed.

Results

Synthesis. Following the protocol delineated by Arshankow and Poznjak, (salen)MnV(N) 24 was successfully prepared upon irradiation of the corresponding (salen)MnII(N3) 23 (eq 12). Although formation of 24 was possible under these conditions, isolated yields of this compound were low (<35%). This, together with the need for large quantities of manganese nitride, required the development of an alternative method for the synthesis of (salen)Mn(N).

Oxidation of both Cr(III) and Mn(III) porphyrin complexes with either NaOCl or PhIO in the presence of NH4OH had been reported to yield the corresponding Cr(V) and

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Mn(V) nitrides. This method for M=N bond formation possessed two salient features which were ideal for our purposes: (1) experimental simplicity; and (2) amenability to large scale synthesis. However, it was unclear as to whether the salen ligand could withstand such strongly alkaline (pH = 14), oxidizing reaction conditions. These concerns were assuaged when, upon treatment of a dark brown, methanolic suspension of (salen)MnIIIOAc with NH4OH (15 M, 15 equiv) and aqueous NaOCl (Clorox bleach, 6 equiv), nitride 24 was provided as an emerald green solid (Scheme 1). Following this procedure, multigram quantities of 24 could be prepared; however, the low solubility of this compound in most organic solvents (CH2Cl2, EtOAc, CH3CN, Et2O) made its isolation and purification difficult. It was possible to circumvent such problems by synthesizing the ligand in which the ethylenediamine backbone of salen was replaced with 2,3-diamino-2,3-dimethylbutane. Condensation of this diamine with salicylaldehyde (2 equiv) furnished the H2saltmen ligand as a yellow crystalline solid (96%). The nitrido Mn(V) complex (26) derived from H2saltmen was prepared in a single operation by first reacting Mn(OAc)2•4H2O with a solution of the ligand in methanol to give an air-oxidized (saltmen)Mn(III) intermediate 25. Subsequent

34. For the preparation of 2,3-diamino-2,3-dimethylbutane, see: Sayre, R. J. Am. Chem. Soc. 1955, 77, 6689.
35. The nature of this dark brown Mn(III) species has not been established, and is drawn as such for convenience. For an analogous reaction in which the resulting Mn(III)–salen complex was isolated and characterized following treatment with LiCl, see: Zhang, W.; Jacobsen, E. N. J. Org. Chem. 1991, 56, 2296.
treatment of the resulting dark brown solution with NH₄OH and Clorox bleach afforded the desired Mn(V) nitride 26. Following purification by chromatography on basic alumina (activity IV), 26 was isolated as a dark green microcrystalline solid (in up to 20 g scale) in overall yields which consistently ranged from 80–85%.

Scheme 1

(a) Mn(OAc)_2•4H₂O, MeOH; (b) 15 M NH₄OH, Clorox bleach, 80–85%.

Physical Data. The (saltmen)Mn(N) complex 26, like the parent (salen)Mn(N) 24, is remarkably stable to both air and H₂O. ¹H and ¹³C NMR spectra recorded for the two complexes show sharp resonances in the usual range for chemical shifts consistent with a diamagnetic complex of low spin d² configuration. Infrared spectroscopic analysis established the Mn≡N stretching frequency at 1047 cm⁻¹ for 24 and 26, similar to that reported for the analogous nitridomanganese porphyrin species (ca. 1050 cm⁻¹).²⁴a,²⁷a,²⁹

The structures of 24 and 26 were confirmed by single crystal X−ray analysis (ORTEP for 24 shown in Figure 6). X−ray data shows both compounds to be monomeric, each having

Figure 6. ORTEP diagram of (salen)Mn(N) 24 displaying 50% probability ellipsoids.
a Mn–N bond length of 1.51 Å, consistent with the assignment of a formal Mn≡N triple bond.\textsuperscript{36,37} At the time of their preparation, 24 and 26 represented the first non-porphyrin nitridomanganese(V) complexes to be synthesized and crystallographically characterized (see Chapter 3).

**Nitrogen Atom-Transfer Reactions.** Preliminary investigations into the use of (saltmen)Mn(N) 26 as a nitrogen transfer reagent suggested that electron-rich alkenes, such as ketone silyl enol ethers 27–30, would serve as optimal substrates for amination.\textsuperscript{38} Treatment of a solution of 26 (2 equiv), one equivalent of a Me\textsubscript{3}Si–enol ether, and pyridine (3 equiv) in CH\textsubscript{2}Cl\textsubscript{2} with trifluoroacetic anhydride (2.4 equiv) at reduced temperature (ca. \(-30^\circ\text{C}\)) led to rapid consumption of the starting materials and provided the corresponding N-trifluoroacetylated \(\alpha\)-amino ketone (Table 1). In one case (entry 4), a higher yield of the desired product was obtained if only a catalytic amount of pyridine (6 mol\%) was employed. The role of pyridine in these reactions is two-fold, the first being as a base to scavenge adventitious CF\textsubscript{3}CO\textsubscript{2}H which would cause decomposition of the starting enol ethers, and the second as a catalyst which promotes the nitrogen transfer reaction at low temperature. In its absence, product formation at \(-30^\circ\text{C}\) does not occur.\textsuperscript{39}

\textsuperscript{36} Crystal data for (salen)Mn(N) 1: emerald green crystals were deposited by slow evaporation of a CH\textsubscript{2}Cl\textsubscript{2} solution of 1. Space group P2\textsubscript{1}/c; cell constants: \(a = 9.496(3), b = 12.313(3), c = 12.857(4)\) Å; \(B = 103.61^\circ\); \(V = 1461.1(7)\) Å\(^3\), \(Z = 4\). A total of 4023 observations were collected (MoK\textsubscript{α}, 2\(\theta\)\(_{\text{max}}\) = 44\(^\circ\), \(-9\leq h \leq 9, 0\leq k \leq 12, -13\leq l \leq 13\)) and merged to 1781 unique reflections (\(R_{\text{merge}} = 0.038\), GOF\(_{\text{merge}} = 1.05\)). The structure was solved by direct methods (SHELXS-86) and refined anisotropically (SHELXL-93) to an \(R = 0.061\) with a GOF = 1.304. Additional information is given in appendix 1.

\textsuperscript{37} Mn≡N distances of 1.51 Å have been reported for (TpMPP)Mn(N) and (OEP)Mn(N), see ref. 27b and 27c, respectively.


\textsuperscript{39} In the absence of pyridine, no change in the color of the green solution was observed, thus suggesting that acylation of the nitrido does not occur at this temperature.
As a general strategy for the preparation of \( \alpha \)-amino ketones 31–34, the amination method described has several appealing features. These include: (1) the facile preparation of large quantities of the starting Mn-nitrido reagent 26; (2) the use of the silyl enol ether substrate as the limiting reagent (1 equiv); and (3) mild reaction conditions. Additionally, the trifluoroacetyl residue serves as a convenient amine protecting group which may be readily cleaved.\(^{40}\)

Table 1. Amination of silyl enol ethers 27–30 with (saltmen)Mn(N).

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>substrate</th>
<th>product</th>
<th>temperature (°C)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Image" /></td>
<td><img src="" alt="Image" /></td>
<td>-78→23</td>
<td>78%</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Image" /></td>
<td><img src="" alt="Image" /></td>
<td>-78→23</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td><img src="" alt="Image" /></td>
<td><img src="" alt="Image" /></td>
<td>-78→23</td>
<td>50%</td>
</tr>
<tr>
<td>4(^b)</td>
<td><img src="" alt="Image" /></td>
<td><img src="" alt="Image" /></td>
<td>-30→23</td>
<td>69%</td>
</tr>
</tbody>
</table>

(a) Reactions performed with 1 equiv silyl enol ether, 2.0 equiv (saltmen)Mn(N), 2.4 equiv TFAA, and 3 equiv pyridine. (b) A higher yield of the product 34 was obtained if only 0.06 equiv of pyridine was employed.

Discussion

**Mechanism.** The amination of silyl enol ethers with (saltmen)Mn(N), like the analogous reaction of cyclooctene with (TMP)Mn(N) and TFAA (*vide supra*), is presumed to proceed via initial formation of a reactive $N$–trifluoroacetyl imido manganese species **35** (Figure 7).$^{24a,29,41}$ Subsequent transfer of the CF$_3$CON group to the olefin substrate with concomitant generation of a reduced, Mn(III) complex completes this process (see Figure 5). Groves has provided spectroscopic evidence (IR, UV–visible) which supports the formulation of an $N$–acylimido complex **36** as the first-formed product upon reaction of a solution of (TMP)Mn(N) with TFAA.$^{24a}$ The intermediate Mn=NCOCF$_3^+$ **37** is isoelectronic with the putative Mn(V)–oxo cation **38**, a highly reactive species thought to be responsible for olefin epoxidation in Mn–porphyrin and Mn–salen catalyzed reactions.$^{1a,25f,26d,35,42}$ Because of this relationship, it has been speculated that the mechanism for CF$_3$CON and oxygen-atom transfer to an olefin in

![Diagram of molecular structures](image)

**Figure 7.** Electronic equivalence between reactive intermediates in manganese-mediated nitrogen and oxygen atom-transfer processes.

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these processes are analogous.\textsuperscript{8a,8c,24a,29,43} It is worth noting, however, that the Mn=NCOCF\textsubscript{3}\textsuperscript{+} and Mn=O\textsuperscript{+} cations possess different reactivity and stability profiles, despite their electronic equivalence.\textsuperscript{1a,26d,29,41,42,44}

The ability of Mn≡N complexes to effect nitrogen-atom transfer when activated with TFAA may be understood from simple, qualitative molecular orbital (MO) arguments. To a first approximation, the MO schemes for 26, 37, and 38 are arranged as shown in Figure 8.\textsuperscript{45} Importantly, the t\textsubscript{2g} metal orbitals together with the N\textsuperscript{3−} p\textsubscript{x} and p\textsubscript{y} MO’s form a set of doubly degenerate π bonding and π* antibonding orbitals (d\textsubscript{xz}, d\textsubscript{yz}), and a singly degenerate nonbonding orbital (d\textsubscript{xy}). The d\textsuperscript{2} valence configuration for

**Figure 8.** Molecular orbital diagrams for nitrido, imido, and oxo manganese species.


\textsuperscript{44} The formal Mn–X bond order in both 37 and 38 is 3 (one σ and two π bonds) as seen from their molecular orbital depiction (Figure 8). As is generally the case, however, these cationic species are drawn with a Mn=X multiple bond.

Mn(V) requires filling the nonbonding $d_{xy}$ MO, leaving the $\pi^*$ as the lowest unoccupied MO (LUMO). $N$-acylation of the nitrido ligand ($N^{3-}$) is expected to weaken its $\pi$-donor strength and to result in a lowering of the $\pi^*$ manifold.\textsuperscript{24a,29} This shift in the MO energies results in an increase in the oxidizing potential of the acylimido species \textbf{35} relative to the parent nitrido. Thus, an olefin with an appropriate reduction potential would be capable of injecting an electron into the unoccupied $\pi^*$ level, necessarily causing Mn=NCOCF$_3$ bond rupture and concomitant CF$_3$CON transfer.\textsuperscript{46} Three significant conclusions may be drawn from this proposed MO diagram:

(1) The ability of metal imido compounds like \textbf{35} to perform alkene amination is correlated with the number of metal $d$-electrons. The $d^2$ valence of Mn(V) ensures that the Mn≡N $\pi^*$ is established as the system’s LUMO. This primes the CF$_3$CON group to become extremely reactive upon oxidation of the substrate and electron addition into the $\pi^*$ MO. In support of this, it has been shown that porphyrin-derived, d$^1$ Cr(V) nitrides do not effect nitrogen–atom transfer to olefins.\textsuperscript{29}

(2) Only alkenes with an appropriate reduction potential will function as suitable substrates for CF$_3$CON transfer, as demonstrated by the fact that electron-rich, nucleophilic silyl enol ethers and reactive olefins like cyclooctene are efficiently aminated under the reaction conditions, whereas cyclohexene is not.\textsuperscript{24a,29,38}

(3) The disparate reactivity of \textbf{37} compared to its isoelectronic analog, \textbf{38}, may be understood in terms of electronegativity differences between CF$_3$CON and O. The more electronegative oxo ligand is a poorer $\pi$ donor than the CF$_3$CON unit. In MO terms, this is reflected by the lower energy of the Mn=O $\pi^*$ orbitals relative to Mn=NCOCF$_3$ $\pi^*$, the

\textsuperscript{46} The generally excepted mechanism for metal-oxo transfer reactions is a stepwise process involving charge transfer (radical) intermediates, see: Bruice, T. C. Aldrichimica Acta \textbf{1988}, \textit{21}, 87, and references therein. A similar mechanism has been postulated for nitrene transfer reactions, see ref. 8a and 8c.
result being that the Mn=O cation is a more potent oxidant which may be reduced by less reactive olefins like cyclohexene.\textsuperscript{1a,26d,29,41,42,47}

**Generation of α–Amino Ketones.** N–Trifluoroacetylated α–amino ketones 31–34 were isolated as products from the reaction of silyl enol ethers 27–30 with (saltmen)Mn(N) and TFAA (Table 1). The generation of these materials is not inconsistent with a mechanism which formally involves aziridination of the enol ether followed by ring opening and loss of the silyl group (Figure 9).\textsuperscript{48,49} The intermediate aziridine 39 is expected to be quite labile, and, as a consequence, has not been observed in any of the reactions recorded.\textsuperscript{50} Evans has reported reactions of enol silanes with PhI=NTs and catalytic CuClO\textsubscript{4}. This reagent combination has been shown to furnish aziridine products in reactions with unfunctionalized olefins (\textit{vide supra}). However, in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Proposed mechanism for silyl enol ether amination reactions.}
\end{figure}


\textsuperscript{48.} Direct amination of silyl enol ethers by thermolysis or photolysis of azidoformates to produce N–protected α–amino ketones is presumed to occur through the intermediacy of an unstable aziridine, see: Lociuro, S.; Pellacani, L.; Tardella, P. A. \textit{Tetrahedron Lett.} \textbf{1983}, \textit{24}, 593.

\textsuperscript{49.} This reaction is analogous to the epoxidation of silyl enol ethers to give α–ketols (Rubottom oxidation), see: Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. \textit{Tetrahedron Lett.} \textbf{1974}, \textit{4319}.

\textsuperscript{50.} A product which has been assigned as the N–trifluoroacetylated aziridine was isolated from the reaction of (saltmen)Mn(N) 26 with TFAA and \(\rho\)–methoxystyrene.
accord with our observations, when silyl enol ethers 40 were reacted with CuClO₄ and PhI=NTs, N-(p-tolylsulfonyl) α-amino ketone products 41 were generated exclusively.³₃ᵃ,³₃ᵇ

**Development of (salen)Mn(N) Derivatives.** Although (salmen)Mn(N) proved an effective reagent for nitrogen atom-transfer to silyl enol ethers, our early investigations suggested that reactions with this complex were limited to only such electron-rich alkenes. Aziridination of cyclooctene was possible with the (TMP)Mn(N) system, but no reaction with this olefin was observed when (salmen)Mn(N) was employed under otherwise identical conditions. We speculated that the salmen-derived Mn nitride was, for reasons unclear to us, intrinsically less reactive towards unfunctionalized, unsaturated

![Chemical structures](image)

**Figure 10.** Generation of salmen-based nitridomanganese reagents from substituted salicylaldehydes.

hydrocarbons than the nitrido porphyrin complex. To this end, derivatives of H₂salmen with both electron withdrawing and electron donating groups were prepared in an effort to generate more reactive aminating agents.²⁶ᵈ,⁵¹

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²⁶ᵈ. Electronic tuning in metal catalysts has been described, see: (a) Jacobsen, E. N.; Zhang, W.; Güler, M. L. J. Am. Chem. Soc. 1991, 113, 6703.
Substituted salicylaldehydes were available from either commercial sources or by formylation of the appropriate phenol. Following the protocol outlined for the synthesis of H$_2$saltmen, a collection of functionalized saltmen ligands was prepared (Figure 10). In general, formation of the corresponding nitrido Mn(V) complexes was possible in a single operation by first reacting the ligand (1 equiv) with Mn(OAc)$_2$·4H$_2$O (1 equiv), and subsequently adding NH$_4$OH (15 equiv) and Clorox bleach (~0.7 M aq. NaOCl, 6 equiv). Like the parent (saltmen)Mn(N) complex, (3R$^1$,5R$^2$–saltmen)Mn nitrides were purified by chromatography on basic alumina (Brockmann, activity IV) and isolated as green microcrystalline solids. The ease with which these nitrido derivatives could be generated highlights one of the most important virtues of the saltmen system over other ligands such as porphyrin.

Having prepared this family of nitridomanganese complexes, efforts to determine which, if any, of these compounds would serve as aminating agents for unfunctionalized alkenes were undertaken. In a typical experiment, TFAA was added to either CH$_2$Cl$_2$ or CH$_3$CN solutions containing both olefin (e.g., cyclooctene) and nitrido reagent. Reactions were performed at different temperatures (-78→23 °C) and with varying equivalents and concentrations of either nitride or olefin starting materials. To our surprise, transfer of CF$_3$CON to cyclooctene (or other unfunctionalized alkenes) was never observed with any of these derivatives (eq 13). In fact, none of these complexes seemed to display reactivity patterns which were different from one another or from the parent (saltmen)Mn(N) system.

Mechanistic Hypothesis – "The Cyclooctene Problem". The inability of (saltmen)Mn(N) 26 to transfer CF₃CON to cyclooctene, together with the inexplicable finding that substituted saltmen nitrido reagents were equally ineffective at performing this reaction, was particularly unsettling in light of Groves' result with (TMP)Mn(N). Although we had assumed initially that the deficiencies in our system were attributable to the insufficient reactivity of 35 versus 36, an explanation to account for this conclusion was not forthcoming. It occurred to us that the active Mn=NCOCF₃ intermediate might be participating in reactions other than olefin amination. Such speculation is not without foundation and, in hindsight, seemed obvious after considering several pieces of information. In this regard, Mansuy has reported the bimolecular decomposition of an Fe(II) nitrene 42 to give a diazene product 43 (eq 14).  

\[ \text{(14)} \]

\[
\begin{array}{c}
\text{Me} \\
\text{Ph} \\
\text{N} \\
\text{Ph} \\
\text{Fe} \\
\text{Ph}
\end{array}
\xrightarrow{\text{C}_3\text{H}_5\text{N}}
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{N} = \text{N} \\
\text{R} \\
\text{Me} \\
\text{Me}
\end{array}
\]

Similarly, competitive dimerization of carbenoid equivalents 45 to give olefins 46 is a common occurrence in metal-catalyzed cyclopropanation reactions from diazo precursors 44 (eq 15).  

\[ \text{(15)} \]

\[
\begin{array}{c}
\text{N} \\
\text{=O} \\
\text{OEt}
\end{array}
\xrightarrow{\text{Rh}(\text{OAc})_4}
\begin{array}{c}
\text{O} \\
\text{OEt}
\end{array}
\xrightarrow{\text{L}_2\text{Rh}}
\begin{array}{c}
\text{EtO}_2\text{C}
\end{array}
\]


reactive metal-oxo species 47, the formation of oxo-bridged products 48 is well-precedented and is often a highly favorable process (eq 16).\textsuperscript{1a,55,56} Finally, Cummins has described the reductive dimerization of a Cr(VI) nitride 49 to give a Cr(V) μ-nitrido complex 50 (eq 17).\textsuperscript{57} Thus, it appeared eminently reasonable that trifluoroacetylated (saltmen)Mn(N) 35 could be susceptible to these types of bimolecular reactions (Figure 11). If the rates of these processes were faster than the rate of the desired alkene amination step (as with weakly nucleophilic olefins like cyclooctene), no olefin-derived products would be expected to form.

Two possible solutions were considered which would allow for the transfer of CF\textsubscript{3}CON from nitridomanganese systems to unfunctionalized alkenes.\textsuperscript{58} The first approach involved the construction of nitrido complexes with ligand systems designed to

\begin{equation}
\text{L}_{n}\text{Fe}^{\text{IV}=\text{O}} + \text{L}_{n}\text{Fe}^{\text{II}} \rightarrow \text{L}_{n}\text{Fe}^{\text{III}}\overset{\text{O}}{\text{Fe}^{\text{II}}}\text{L}_{n}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{P} \text{Pr}_2 \text{N} \text{Pr}_2 \\
\text{N} \text{Pr}_2 \text{N} \text{Pr}_2 \\
\text{N} \text{Pr}_2 \text{N} \text{Pr}_2 \\
\end{array}
\rightarrow \text{Na/Hg}
\text{Et}_2\text{O}
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \text{r} \text{N} \text{Pr}_2 \text{N} \text{Pr}_2 \\
\text{N} \text{Pr}_2 \text{N} \text{Pr}_2 \\
\text{N} \text{Pr}_2 \text{N} \text{Pr}_2 \\
\end{array}
\end{equation}


\textsuperscript{58} Both strategies are based on the assumption that decomposition of the acylated nitrido species 35 does not occur through intramolecular processes. An intramolecular reaction of a putative Fe nitrene-porphyrin complex has, however, been observed, see ref. 14b.
create a steric “pocket” around the Mn≡N center (Figure 12). Such a pocket would protect the reactive intermediate 35 from undesirable, bimolecular processes. A similar

![chemical structure](image)

**Figure 11.** Possible bimolecular processes involving intermediate 35.

strategy has been successfully employed to inhibit the dimerization reaction of metal-oxo species.\(^{59,60}\) The second approach entailed a modification of the experimental protocol which had been employed for silyl enol ether amination. Originally, TFAA had been the final reagent added to a solution containing both the olefin and nitride. If this order was simply reversed so that (saltmen)Mn(N) 26 was slowly transferred to a solution of TFAA and olefin, the concentration of the reactive Mn≡NCOCF₃ species 35 would be kept low

![chemical structure](image)

**Figure 12.** Second generation nitridomanganese reagents.

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59. For an extensive review on this subject, see: Momenteau, M.; Reed, C. A. *Chem. Rev.* 1994, 94, 659.

while the concentration of olefin remained high. This concentration difference might allow the rate of olefin amination to effectively compete with the rates of other deleterious pathways. An analogous slow addition procedure is commonly employed in carbene addition reactions with diazo compounds for similar reasons (cf., eq 15).54c

Conclusion

Both the “slow addition” and the “picket-fence” solutions have been investigated. The implementation of a new experimental procedure has made it possible to aminate glycal substrates, an important class of olefins which, in initial studies, had shown no reaction with the (saltnen)Mn(N) reagent. The successful development of this methodology will be discussed in detail in Chapter 2. The design, synthesis, and characterization of new Mn nitrides and the demonstration of their use as potential nitrogen-atom transfer reagents with unfunctionalized olefins is the subject of Chapter 3.
Chapter Two

Novel, Stereoselective Synthesis of 2–Amino Saccharides

Introduction

Available methods for the preparation of 2–amino sugars are few in number despite the ubiquity of such structures in nature (Figure 1). Recent work by Danishefsky, Fitzsimmons and Leblanc has led to the development of two distinct methodologies for the conversion of carbohydrate glycals to the corresponding 2–amino

![Heparin pentasaccharide](image1)

![Streptomycin](image2)

![Neocarzinostatin Chromophore](image3)

**Figure 1.** Naturally occurring 2–amino saccharides.

products. These protocols have found widespread use in the construction of complex, amine-containing polysaccharides. Both methods, however, require more than a single synthetic operation for the installation of the 2-amino moiety. Transition-metal promoted nitrogen atom-transfer to glycal substrates (Figure 2) would provide a more direct method for the preparation of this important class of carbohydrates. Given our interest in metal-mediated N-atom transfer chemistry and the potential value of a general glycal amination methodology, efforts were undertaken to develop such a process.

![Chemical structure diagram](image)

**Figure 2.** Transition-metal promoted amination of glycals for the preparation of 2-amino sugars.

**Background.** Among the first reported strategies for the construction of 2-amino-2-deoxy sugars from glycal precursors were the nitrosochlorination and


azidonitration methods described by Lemieux.\textsuperscript{6,7} In the former process, the reaction of glycols 1 with nitrosyl chloride (NOCl) provided 2–oximino products 3. These oxime-derived materials could be subsequently reduced and acylated to afford the protected amines 4 (Figure 3). Difficulties with the conversion of the oxime products to the target structures, however, limited the utility of this process. A more efficient method was later developed using a combination of ceric ammonium nitrate (CAN) and sodium azide (NaN\textsubscript{3}) to generate 2–azido products 5 (Figure 3). Facile reduction of the azide and hydrolysis of the anomic nitrate provided the desired amino alcohol.

The direct insertion of a nitrene species into the glycal bond has been illustrated, though this reaction has not been employed as a general method for the preparation of 2–amino saccharides. Photolysis of methyl azidoformate 6 in the presence of glycols was shown to provide only modest yields (ca. 40\%) and poor selectivities of glycosides 8–10 bearing a methyl carbamate moiety at the 2–position (Figure 4).\textsuperscript{8} Presumably, these

\begin{itemize}
\end{itemize}
methyl glycosides 8–10 form via solvolytic opening of an intermediate aziridine 7 with MeOH. In a related process, N–protected 2–amino glycosyl chlorides 13 and 14 have been isolated from reactions of glycals with N–chloroamides 11 and N–chlorocarbamates.

**Figure 4.** Glycal amination by photolysis of methyl azidoformate 6.

12 catalyzed by chromous chloride (CrCl₂). Like the photolysis reaction, however, this strategy has found limited use in synthesis (eq 1).

\[
\begin{align*}
\text{RNHCl, CrCl}_2 & \quad \text{MeOH/CHCl}_3 \\
\text{Cl} & \quad \text{Cl} \quad + \quad \text{Cl} \\
R = \text{Ac} \quad & \quad 11 \quad 13 \quad \text{14} \quad R = -\text{C(O)OEt} \quad 12
\end{align*}
\]

Fitzsimmons and Leblanc have developed one of the more practical and generally employed methodologies for the conversion of glycals to amino sugars. Following this protocol, glycals 1 are reacted with an azodicarboxylate 15 to furnish products 16, formally resulting from a [4 + 2] cycloaddition process (Figure 5). Under either Brønsted

**Figure 5.** [4 + 2] Cycloaddition strategy for 2–amino sugar synthesis.

or Lewis acidic conditions, 16 has been shown to function as an effective glycosyl donor. The resulting hydrazodicarboxylate linkage may be reductively cleaved using any one of a number of available reagent combinations (e.g.; Raney–Ni, H₂).

Arguably the most useful method for 2-amino sugar synthesis is the sulfonamidoglycosylation strategy of Danishefsky. As reported, glycals are initially transformed to 2-halo-1-sulfonamidopyranosides 18 under conditions which employ either benzenesulfonamide (PhSO₂NH₂) and iodonium di-sym-collidinium perchlorate (I(sym-coll)₂ClO₄) or N,N-dibromobenzenesulfonamide. Subsequent

Figure 6. Danishefsky’s sulfamidoglycosylation methodology.

treatment of these materials with various nucleophiles (alkoxides, thiolates, azide), bases (KN(TMS)₂), or Ag⁺ salts results in the rapid formation of the 2-sulfonamide products 20–22, presumably via the intermediacy of a 1,2-sulfonylaziridine 19 (Figure 6). This putative aziridine is a highly reactive electrophile and promotes clean attack by nucleophiles at the anomeric position. The Danishefsky methodology offers an efficient

two-step protocol, starting from a glycal, for the installation of a C2 amine residue with concomitant glycosyl bond construction.

Results and Discussion

We had found previously that easily accessible, salen-derived nitridomanganese complexes could be employed as nitrogen atom-transfer reagents with electron-rich, silyl enol ethers 23 (eq 2, see Chapter 1). Our interest in further exploring the chemistry of these novel Mn compounds, and in finding practical applications for these reagents, provided impetus to begin testing the reactivity of the Mn≡N systems with glycal substrates. Initial attempts to aminate tri–O–benzylglucal using (saltmen)Mn(N) 24 were, however, entirely unsuccessful. The failure of this reaction was attributed to the greatly diminished reactivity of this carbohydrate-derived olefin compared to unfunctionalized vinyl ethers. As a result, we speculated that the reactive manganese species was being consumed in side-reactions which occurred at a rate faster than the desired alkene amination step. This problem could be circumvented by maintaining a high concentration of the glycal relative to the activated manganese complex, thereby allowing the rate of CF₃CON transfer to effectively compete with other

\[ \text{Me₂SiO} \quad \text{(saltmen)Mn(N)} \quad \rightarrow \quad \text{R¹} \quad \text{R²} \quad \text{NHCOCF₃} \]

\[ \text{(saltmen)Mn(N)} \quad 24 \]


12. AM1 calculations performed with the SPARTAN program package (Wavefunction, Inc., Irvine, CA) show that the HOMO of tri–O–benzylglucal is lower in energy than that of 3,4-dihydro–2H–pyran. We have found that CF₃CON may be transferred to 3,4-dihydro–2H–pyran (45–50% yield) following a previously described protocol (see ref. 11). Under identical conditions, no reaction was observed when tri–O–benzylglucal was employed as the substrate.
Table 1. Nitrogen atom-transfer reactions with glycols 36–44.

<table>
<thead>
<tr>
<th>entry</th>
<th>glycal</th>
<th>major product</th>
<th>selectivity(C–2)(a)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Glycal 36" /></td>
<td><img src="image2" alt="Glycol 45" /></td>
<td>7:1</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Glycal 37" /></td>
<td><img src="image4" alt="Glycol 46" /></td>
<td>7:1</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Glycal 38" /></td>
<td><img src="image6" alt="Glycol 47" /></td>
<td>7:1</td>
<td>68%</td>
</tr>
<tr>
<td>4(b)</td>
<td><img src="image7" alt="Glycal 39" /></td>
<td><img src="image8" alt="Glycol 48" /></td>
<td>&gt;10:1</td>
<td>64%</td>
</tr>
<tr>
<td>5(b)</td>
<td><img src="image9" alt="Glycal 40" /></td>
<td><img src="image10" alt="Glycol 49" /></td>
<td>&gt;10:1</td>
<td>62%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Glycal 41" /></td>
<td><img src="image12" alt="Glycol 50" /></td>
<td>1:1</td>
<td>70%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Glycal 42" /></td>
<td><img src="image14" alt="Glycol 51" /></td>
<td>6:1</td>
<td>66%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Glycal 43" /></td>
<td><img src="image16" alt="Glycol 52" /></td>
<td>&gt;10:1</td>
<td>80%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Glycal 44" /></td>
<td><img src="image18" alt="Glycol 53" /></td>
<td>&gt;10:1</td>
<td>80%</td>
</tr>
</tbody>
</table>

\(a\) stereoselectivity at C–2 determined by \(^1\)H and \(^{19}\)F NMR spectroscopy of both the lactol product and the corresponding lactone obtained upon oxidation (PCC, \(\text{CH}_2\text{Cl}_2\)). \(b\) a higher yield of the desired product was obtained if 1 equiv of 2,6-di-tert-butyl-4-methylpyridine was utilized.
deleterious reaction pathways. In practice this was accomplished by slowly adding the (saltmen)Mn(N) reagent to a solution containing both glycal and trifluoroacetic anhydride (TFAA).\textsuperscript{13} As shown in Table 1, application of these conditions with (saltmen)Mn(N) and various glycals 36–44 successfully afforded $N$-trifluoroacetylated 2- amino sugars 45–53.

**Synthesis of Glycals.** The requisite glycal starting materials 36–44 were constructed to incorporate a variety of commonly employed carbohydrate protecting groups, each of which proved tolerant to the mild conditions of the reaction. The preparation of these substrates was accomplished using standard carbohydrate methods and is outlined in Schemes 1–4.\textsuperscript{14,15,16} Facile synthesis of the protected glycal 36 was

![Scheme 1](image)

(a) K$_2$CO$_3$, MeOH, 99%; (b) PhCHO, ZnCl$_2$, 11%; (c) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 95%.


16. Furanoid glycals 43 and 44 were prepared by Craig S. Tomooka and will be described elsewhere. L-Rhamnal 37 was synthesized by Jason Hong. Reactions employing these starting materials were
possible following the method described by Sharma and Brown for the preparation of 4,6–O–benzylidene–D–glucal 27 (Scheme 1).\textsuperscript{14d} Subsequent silylation of the C–3 alcohol in 27 with tert–butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) afforded glycal 36 (10%, 3 steps). Although the ketalization of D–glucal 26 with PhCHO and ZnCl\(_2\) to furnish 27 was low yielding in our hands (11%), it provided the most direct means for accessing this protected sugar.

A synthesis of the L–rhamnose-derived glycal 37 was developed which commenced from L–rhamnose 28 (Scheme 2). To this end, a five step procedure was employed for the conversion of 28 to L–rhamnal 30. Initial acetylation of 28 (Ac\(_2\)O, C\(_5\)H\(_5\)N) furnished the corresponding tetraacetate, which could be selectively de-esterified at C–1 (piperidine, THF, 80%) to reveal the anomeric –OH.\textsuperscript{17} Conversion of this material to the glycosyl bromide was possible with PBr\(_3\) (CH\(_2\)Cl\(_2\), 94%). Subsequent reduction of the C–1 bromide using Zn dust (AcOH/Et\(_2\)O), with concomitant elimination of the C–2 acetate, installed the glycal bond (71%). Treatment of the resulting bis-acetate

\textbf{Scheme 2}

\[
\begin{align*}
\text{Me}_2\text{C}=\text{O} & \quad \text{Ac}_2\text{O}, \text{C}_5\text{H}_5\text{N}, 100\%; \quad \text{b) piperidine, THF, 80\%;}\quad \text{c) PBr}_3, \text{CH}_2\text{Cl}_2, 94\%; \quad \text{d) Zn, Et}_2\text{O}/\text{AcOH, 71\%;} \quad \text{e) K}_2\text{CO}_3, \text{MeOH, 99\%;} \quad \text{f) PMBCl, NaH, DMF, 41\%}. \\
\text{28} & \quad \text{a,b,c,d} \quad \Rightarrow \quad \text{29} & \quad \Rightarrow \quad \text{30} & \quad \Rightarrow \quad \text{37} \\
\text{L–rhamnose} & \quad \text{AcO} & \quad \text{PMB} & \quad \text{PMB} \\
\end{align*}
\]

conducted by C. S. Tomooka and J. Hong, as well. D–Allose-derived glycals 38 and 42 were prepared from 4,6–O–benzylidene–D–allal i. We kindly thank Prof. A. G. Myers for the generous gift of i.

29 with K$_2$CO$_3$ in MeOH cleanly afforded 30 (99%). Lastly, protection of diol 30 with PMBCl (NaH, DMF, 41%) furnished the desired glycal substrate, 37. The reduced yields in this final etherification step are not necessarily reflective of the inefficiency of this process, but may attributable to the insolubility of 37 in standard chromatography solvents (EtOAc, Hexanes, CH$_2$Cl$_2$, CHCl$_3$, C$_6$H$_6$, Et$_2$O), which made purification of this compound difficult.

A similar approach to that of 37 was taken for the preparation of galactose-derived glycals 39 and 40 (Scheme 3). In this case, a “one-pot” procedure was used for the conversion of D-galactose 31 to galactal 32, which involved: (1) acylation of 31 to give the pentaacetate (Ac$_2$O, HClO$_4$); (2) direct conversion of the pentaacetate to the glycosyl bromide with red phosphorous and Br$_2$; (3) reduction with Zn (AcOH/H$_2$O). Following this procedure, multigram quantities (>20 g) of tri-O-acetyl galactal could be synthesized in exceptionally high yield (69%). Saponification of the triacetate with methanolic K$_2$CO$_3$ furnished galactal 32. In order to block the C-3 and C-4 alcohols as

Scheme 3

(a) i. Ac$_2$O, HClO$_4$ ii. red P, Br$_2$ iii. Zn, NaOAc, CuSO$_4$, AcOH/H$_2$O, 69%; (b) K$_2$CO$_3$, MeOH, 96%; (c) TBDPSI, imidazole, DMF, 78%; (d) Me$_2$C(O)Me)$_2$, PPTS, 92%; (e) n-Bu$_4$NF, THF, 93%; (f) BnCl, NaH, DMF, 97%.

the corresponding dimethylacetonide, prior protection of the primary –OH at C-6 was found to be necessary. Selective protection of 32 was possible, however, with tert–butyldiphenylsilyl chloride (imidazole, DMF, 78%). Using 2,2–dimethoxypropane as solvent and catalytic pyridinium p–toluenesulfonate (PPTS), ketal 39 was furnished in 92% yield. This material (39) was readily converted to the benzyl-protected glycal 40 by
removal of the C-6 silyl group (n-Bu_4NF, 93%) and etherification of the resulting 1° -OH (BnCl, NaH, DMF, 97%).

A convenient protocol starting from the available methyl glycoside 34 was employed for the generation of the C-3 deoxy glycal 41.\textsuperscript{18} Simultaneous deoxygenation of the C-2 and C-3 alcohols in 34 was performed in 76% yield following a method described by Garegg and Samuelsson (CHI\textsubscript{3}, PPh\textsubscript{3}, imidazole).\textsuperscript{19} Treatment of this allylic methyl ether 35 with LiAlH\textsubscript{4}, as outlined by Fraser-Reid, resulted in exclusive S_n\textsubscript{2'} reduction to afford the target compound, 41 (57%).\textsuperscript{14c} Glycal 41 was found to be only partially soluble in most organic solvents (EtOAc, Et\textsubscript{2}O, C\textsubscript{6}H\textsubscript{6}, CH\textsubscript{2}Cl\textsubscript{2}) which precluded its purification by chromatography. However, 41 could be easily purified by recrystallization from 95% aq. EtOH.

**Scheme 4**

![Scheme 4](image)

(a) CHI\textsubscript{3}, PPh\textsubscript{3}, imidazole, Δ, 76%; (b) LiAlH\textsubscript{4}, dioxane, 57%.

**Amination Reactions.** Following a procedure in which (saltmen)Mn(N) (1 equiv) was slowly added (ca. 7 h) to a CH\textsubscript{2}Cl\textsubscript{2} solution of TFAA (3.5 equiv) and glycal (1 equiv), pyranoids 36–42 could be converted to their corresponding N-trifluoroacetyl 2-amino alcohols 45–51 in yields consistently ranging from 60–75% (entries 1–7, Table 1). With the more reactive furanoid glycals 43 and 44, use of this slow addition protocol


\textsuperscript{19} Garegg, P. J.; Samuelsson, B. *Synthesis* 1979, 469.
was found to be unnecessary, as these materials could be efficiently aminated in 80% yields (entries 8 and 9) under our previously reported conditions (see Chapter 1).\cite{11,20} In all cases (with the exception of entry 6), the product amino sugars were formed with high levels of diastereoselectivity at C–2. The stereochemical outcome at C–2 in this reaction process was established by a combination of \(^1\)H coupling constant analysis and difference nOe experiments, the corresponding values for which are shown in Figure 7. From this data, it appears that the stereochemistry at C–2 is controlled by the proximal stereocenter at C–3 (cf., entries 1, 3, 6).\cite{22}

This methodology for the preparation of 2–amino monosaccharides offers two attractive and important features: (1) the glycal is used as the limiting reagent, and (2) the products isolated are conveniently protected as the \(N\)–trifluoroacetyl amide.

20. A slight modification of the procedure for the amination of silyl enol ethers in which 2,6-di–\textit{tert}–butyl–4–methylpyridine (3.0 equiv) was substituted for pyridine proved to be most effective with glycals \textbf{43} and \textbf{44}, see Experimental.

21. Lactone \textbf{58} was prepared by PCC oxidation (4 Å MS, CH\(_2\)Cl\(_2\)) of the corresponding lactol, \textbf{52} (C. S. Tomooka).

22. The magnitudes of the observed coupling constants compare favorably with literature values for analogous compounds, see ref. 10a.
derivatives.\textsuperscript{23} In addition, it represents the first example of a metal-mediated glycal amination reaction.

**Mechanism.** We speculated that the product amino alcohols resulted from hydrolytic opening in the work-up of either a labile intermediate aziridine or oxazoline generated under the reaction conditions.\textsuperscript{24} To this end we have isolated oxazoline 54 (derived from glycal 44) which, under mildly acidic conditions, could be opened to the \textit{N}-protected amino alcohol 53 (Scheme 5).\textsuperscript{1d} As confirmation of our structural assignment of 54, we have demonstrated that 53 may be converted back to the oxazoline upon treatment with methanesulfonyl chloride (Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 90\%). For the six-membered ring glycals, both the putative aziridine and oxazoline products have eluded isolation.

**Scheme 5**

![Scheme 5 Diagram](image)

(a) (saltmen)Mn(N), (CF\textsubscript{3}CO)\textsubscript{2}O, 2,6-di-\textit{tert}-butyl-4-methyl-pyridine; (b) aq. AcOH, THF, 80\% (two steps); (c) CH\textsubscript{3}SO\textsubscript{2}Cl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 90\%.

We reasoned if an aziridine or oxazoline was an intermediate on the reaction pathway then it might be possible to trap \textit{in situ} either of these electrophilic species with an appropriate nucleophile. This was demonstrated using galactal 40 (Scheme 6). In the event, a solution of (saltmen)Mn(N) was added to a mixture of TFAA and 40 (CH\textsubscript{2}Cl\textsubscript{2},

\textsuperscript{23} The \textit{N}-trifluoroacetyl protecting group may be cleaved under either mild hydrolytic or reductive conditions, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley & Sons Ltd.: New York, 1991, 2nd Ed., p. 353.

\textsuperscript{24} \textit{N}-Carbomethoxy aziridines generated from glycals have been shown to react with alcohols to give methyl glycoside products, see ref. 8.
23 °C) followed by cooling to −78 °C and sequential treatment with thiophenol and BF$_3$·OEt$_2$. Under these conditions, thioglycoside 57 was isolated solely as the β-epimer with *trans* 1,2 stereochemistry in 36% yield (unoptimized).$^{21}$ Generation of the *trans* product 57 supports the intermediacy of either aziridine 55 or oxazoline 56 in this reaction sequence. The isolation of 54 (described above) would seem to suggest that oxazoline 56 is serving as the glycosyl donor in this coupling reaction with PhSH, but does not, however, preclude formation of aziridine 55.$^{25}$ The single-step preparation of 57 from 40 allows immediate access to 2-amino thioglycosides, whose versatility and importance in glycosidation reactions has been repeatedly displayed.$^{26,27}$

---

25. In reactions with *p*-methoxystyrene and cyclooctene, we have isolated and characterized *N*-trifluoroacetyl aziridine products.


Conclusion

Methodology for the construction of 2-amino-2-deoxy monosaccharides from glycal precursors has been described. This work represents the first example of a metal-mediated amination reaction of this important class of alkene substrates. Activation of (saltmen)Mn(N) with TFAA and transfer of the CF$_3$CON group to give N-trifluoroacetyl protected amine products is efficient in both chemical yield (60–80%) and product stereoselectivity. Moreover, it has been demonstrated that an intermediate in this reaction process can be coupled in situ with PhSH to give a functionalized 2-amino sugar suitable for subsequent glycosidation reactions. Successful extension of this latter reaction to include other coupling partners should provide direct methods for the synthesis of complex 2-amino carbohydrate-derived natural products.$^{28}$

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$^{28}$ The results presented herein are the subject of a recent communication, see: Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. J. Am. Chem. Soc. 1997, accepted for publication.
Chapter Three

Preparation and X-Ray Crystallographic Characterization of Novel Manganese Complexes: Development of a New, Mild Method for Mn≡N Bond Formation

Introduction

Investigations focused on the development of reagents for olefin amination revealed that a novel manganese complex, (saltmen)Mn(N), when activated with trifluoroacetic anhydride, would transfer a CF$_3$CON unit to electron-rich silyl enol ethers.$^1$ This work has been described in detail in Chapter 1. In an effort to explore and to expand the chemistry these complexes, and to generate more reactive and versatile reagents which effect nitrogen atom-transfer to unfunctionalized olefins, new nitridomanganese compounds were desired.$^{2,3}$

Background. Complexes of manganese(V) containing a terminal nitrido ligand had been described prior to the outset of our work, but appeared to be exclusive to

---


porphyrin and phthalocyanine derived systems.\textsuperscript{4,5} Among the first of these to be isolated and characterized was an octaethylporphyrin Mn(V) nitride 3, the synthesis of which was outlined by Buchler. The formation of 3 was possible upon treatment of the

![Chemical structure](image)

\[ \text{OEP} = \text{octaethylporphyrin} \]

\[ \text{(OEP)}\text{Mn(OMe)} \rightarrow \text{NaOCl} \rightarrow \text{NH}_4\text{OH} \rightarrow \text{2} \rightarrow \text{H}^+ \rightarrow \text{MeOH} \rightarrow \text{(OEP)}\text{Mn=N} \]

**Figure 1.** Buchler’s preparation of (OEP)Mn≡N with NH\textsubscript{4}OH and NaOCl.

corresponding methoxymanganese(III) derivative 1 with NH\textsubscript{4}OH and NaOCl (Figure 1).\textsuperscript{4a} Successful installation of the nitrido unit under these conditions was ascribed to the oxidative dehydrogenation of an ammonia–Mn(III) adduct 2 by hypochlorite.\textsuperscript{6} Using a related protocol, Hill was able to construct the porphyrin complex (TpMPP)Mn(N) 7 (TpMPP = tetrakis(p–methoxyphenyl)porphyrinate).\textsuperscript{4b} In this case, iodosylbenzene (PhIO) was employed as the oxidant, and was added to a CH\textsubscript{2}Cl\textsubscript{2}/liquid NH\textsubscript{3} solution containing the Mn(III) starting material 4 (Figure 2). Alternatively, condensation of NH\textsubscript{3} with the putative oxo-Mn(V) species 6 (the adduct of PhIO and 4) yielded nitride 7 as well.\textsuperscript{4b,7} More recently, Grunewald and Homborg have shown that a combination of


gaseous Cl₂ and NH₃ will oxidize Mn(III) phthalocyanine derivatives to their respective nitrido Mn(V) species.⁵

\[
\begin{align*}
\text{(TpMPP)Mn(Cl)} & \quad \xrightarrow{\text{anhyd. NH₃}} \quad \begin{array}{c}
\text{Mn-Cl} \\
\text{NH₃}
\end{array} \\
\text{PhI=O} & \quad \xrightarrow{\text{anhyd. NH₃}} \quad \begin{array}{c}
\text{Mn=O} \\
\text{NH₃}
\end{array} \\
4 & \quad \xrightarrow{\text{PhI=O}} \quad 5 \quad \xrightarrow{\text{anhyd. NH₃}} \quad \begin{array}{c}
\text{Mn=O} \\
\text{NH₃}
\end{array} \\
\xrightarrow{\text{IR: } ν_{Mn=N} = 1036 \text{ cm}^{-1}} \quad \text{(TpMPP)Mn=N 7} \quad \xrightarrow{\text{X-ray: } d_{Mn=N} = 1.515 \text{ Å}} \quad 6
\end{align*}
\]

Figure 2. Oxidative formation of Mn≡N bond with PhI=O and NH₃.

A frequently employed method for the generation of metal nitrides 9 is based on the photochemical or thermal extrusion of molecular nitrogen from lower valent azido complexes 8 (eq 1).⁸ The photolytic conversion of a Cr(III) azide to the nitrido species was described initially by Arshankow and Poznyak (see Chapter 1).⁹ Variants of this procedure have since been used to prepare nitrido complexes of several transition metals which include vanadium, chromium, manganese, and iron.¹⁰ We, too, have


employed this technology to generate nitrido Mn(V) salen reagents (see Chapter 1). In addition, Wieghardt has recently described the preparation and X-ray crystallographic characterization of a six-coordinate, triazacyclonane-derived Mn nitride 11 which was synthesized by photolysis of the corresponding Mn(III) azide 10 (eq 2). This work appeared concurrently with our initial report of salen-based Mn≡N systems, and, at that time, represented the only other example of a non-porphyrin (or non-phthalocyanine) nitrido Mn(V) complex.\(^{11}\)

\[
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{N} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \quad \text{O} \\
\text{N}_3 \quad \text{N}_3 \quad \text{N}_3
\]

\[\text{hv} \quad \text{CH}_3\text{CN} \quad \text{N}_2\]

\[
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{N} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \quad \text{O} \\
\text{N} \quad \text{N} \quad \text{N}
\]

\[\text{IR}: \nu_{\text{Mn-N}} = 1004 \text{ cm}^{-1}\]

\[\text{X-ray}: \quad d_{\text{Mn-N}} = 1.518 \text{ Å}\]

(2)

Results and Discussion

**Ligand Design and Synthesis.** Our interest in constructing new nitridomanganese complexes was fueled by a desire to find systems capable of performing nitrogen atom-transfer to unfunctionalized olefins such as cyclooctene.\(^{12,13}\) Ideally, these new complexes would be unable to participate in deleterious bimolecular reactions, which we speculated were directly responsible for problems we had experienced with the (saltmen)Mn(N) reagent (see Chapter 1). As a means of addressing

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11. To the best of our knowledge, the only other crystallographically characterized non-porphyrin Mn(V) complex is that of a stable Mn(V)-oxo, see: (a) Collins, T. J.; Powell, R. D.; Slebodnick, C.; Uffelman, E. S. *J. Am. Chem. Soc.* 1990, 112, 899. (b) Collins, T. J.; Gordon Wylie, S. W. *J. Am. Chem. Soc.* 1989, 111, 4511.


this issue, we considered developing ligands which would provide a pocket (or picket-fence) for the Mn≡N moiety.\textsuperscript{14} Bidentate Schiff base ligands, prepared from substituted salicylaldehydes and primary amines, were chosen because of their ready accessibililty and their amenability to numerous structural and electronic modifications (Figure 3).\textsuperscript{15} Importantly, molecular models indicated that these ligands would form complexes with the imine donors positioned \textit{trans} to one another to avoid an unfavorable steric interaction. The conformational freedom of the imine appendages could be restricted by placing a substituent adjacent to the phenol on each aryl ring. It was hoped that such interligand, steric interactions would serve as a conformational lock to define a “picket-fence” type arrangement around the nitrido unit (Figure 3). This approach was based largely on the exquisite work of Still, who demonstrated the use of intramolecular steric “ratcheting” to reduce conformational heterogeneity in acyclic receptor molecules.\textsuperscript{16} A particularly attractive feature of this strategy was that it avoided lengthy ligand syntheses which would likely be needed to generate preorganized “picket-fence” ligand systems.

\textbf{Figure 3.} Readily prepared Schiff base ligands with “picket-fence” construction.

\textsuperscript{14} Seminal work by Collman, Traylor and others with “picket-fence” porphyrin systems suggested this approach. For a recent, comprehensive review of this subject, see: Momenteau, M.; Reed, C. A. \textit{Chem. Rev.} 1994, 94, 659, and references therein.


Substituted salicylaldehydes used to prepare Schiff base ligands 12–18 were obtained from either commercial sources or by formylation of the corresponding phenol (Table 1).\textsuperscript{17} Condensation of any one of these aldehydes with a primary amine afforded the corresponding H–\(^3\)R–sal–R’ product (75–85% yields). Typically, these ligands were isolated as yellow, crystalline solids by simply filtering the reaction mixtures. In all cases, a methyl, methoxy, or phenyl substituent was positioned ortho to the phenol –OH (3–position) to serve as a defining element for the steric “pocket” we wished to create (\textit{vide supra}).

\textbf{Table 1.} Preparation of Schiff base ligands 12–18.

\[
\begin{array}{ccc}
\text{ligand} & R & R' \\
H–\(^3\)Me–sal–Pr & 12 & Me & \text{Pr} \\
H–\(^3\)Me–sal–Ph & 13 & Me & Ph \\
H–\(^3\)Ph–sal–Me & 14 & Ph & Me \\
H–\(^3\)Ph–sal–Pr & 15 & Ph & \text{Pr} \\
H–\(^3\)Ph–sal–Ph & 16 & Ph & Ph \\
H–\(^3\)MeO–sal–Me & 17 & MeO & Me \\
H–\(^3\)MeO–sal–Ph & 18 & MeO & Ph \\
\end{array}
\]

\textbf{Manganese(III) Complexes.} An extensive literature exists on the coordination chemistry of manganese in its divalent and trivalent oxidation states.\textsuperscript{18} In a majority of


cases, the propensity of Mn to form bridged, multinuclear assemblies is often observed. This appears to be particularly true when simple bidentate ligands (e.g., carboxylates, bipyridines, hydroxyquinolines) are used as complexing agents. Mononuclear Mn\textsuperscript{III}(Schiff base)\textsubscript{2}X derivatives have, however, been documented in the literature, although reliable structural information on many of these compounds is not available.\textsuperscript{18a,20} We were interested in examining such complexes as precursors for the generation of Mn(V) nitrides, and thought would be possible to generate these Schiff base systems using the H–\textsuperscript{3}R–sal–R’ ligands.

Manganese(III) adducts, (\textsuperscript{3}R–sal–R’\textsubscript{2}Mn(X), could be formed under a variety of conditions from either Mn\textsuperscript{II} or Mn\textsuperscript{III} starting materials. In the former case, reactions were conducted open to air which led to rapid oxidation of the initially formed Mn\textsuperscript{II} species, as witnessed by an immediate solution color change from yellow to dark brown. The effectiveness of Mn(acac)\textsubscript{2}X (X = Br, N\textsubscript{3}), Mn(acac)\textsubscript{3}, Mn(OAc)\textsubscript{3}•2H\textsubscript{2}O, MnCl\textsubscript{2}•4H\textsubscript{2}O, and Mn(OAc)\textsubscript{2}•4H\textsubscript{2}O as starting materials for the preparation of the desired (\textsuperscript{3}R–sal–R’\textsubscript{2}Mn(X complexes was assayed.\textsuperscript{21} In a typical experiment, treatment of two equivalents of the Schiff base with one equivalent of Mn(OAc)\textsubscript{2}•4H\textsubscript{2}O efficiently provided the (\textsuperscript{3}R–sal–R’\textsubscript{2}Mn(OAc) complex as a forest green solid which precipitated from the reaction mixture (65–75% yields, eq 3). Alternatively, the acetylacetone ligands on Mn(acac)\textsubscript{2}N\textsubscript{3} could be exchanged with two equivalents of H–\textsuperscript{3}R-sal–R’ and the volatile acetylacetone removed \textit{in vacuo} to afford the corresponding azido species (eq


3). Other reagents and methods employed (MnCl₂·4H₂O/KOH, Mn(OAc)₃·2H₂O, Mn(acac)₃, Mn(acac)₂Br) gave variable results.

\[
\begin{align*}
2 \text{ equiv } \text{H}^+ \cdot & \text{R-sal} \cdot \text{R'} \quad \xrightarrow{\text{Mn(OAc)}_2 \cdot 4\text{H}_2\text{O}} \\
\text{or} \quad & \text{Mn(acac)}_2\text{N}_3 \\
& \text{CH}_3\text{CN} \\
\end{align*}
\]

\[\text{Mn}^\text{(R-sal-R')}_2\text{X} \quad X = \text{OAc, N}_3 \]

**X-ray Crystallographic Analysis.** The structure of one of the acetate derivatives, \((^3\text{Ph-sal-}^\text{iPr})_2\text{Mn(OAc)} \) 19, was confirmed by single crystal X-ray analysis (Figure 4).\(^{22}\) Examination of the crystallographic data shows this compound to be monomeric with a six-coordinate Mn\(\text{II} \) center in which the \(\eta^2\)-(OAc) ligand occupies two sites in the equatorial plane of a distorted octahedron.\(^{23}\) The salicylimine chelates are forced to fold towards one another creating a cleft lined by the appended phenyl rings. At the center of this cleft lies the acetate which sits on a crystallographically imposed C₂-axis. On the opposing face, the isopropyl moieties are disposed towards one another and appear to shield the “backside” of the manganese ion. Given the propensity of carboxylate ligands to form bridging complexes, the structure of Mn\((^3\text{Ph-sal-}^\text{iPr})_2\text{OAc} \) represents a rare example of symmetric, bidentate carboxylate chelation to a single metal.

---

22. Crystal data for \((^3\text{Ph-sal-}^\text{iPr})_2\text{Mn(OAc)} \): dark green crystals were deposited by diffusing pentane into an EtOAc solution of the complex. 0.29 x 0.45 x 0.48 mm; monoclinic; space group C2/c; cell constants: \(a = 14.588(3), b = 15.996(3), c = 14.712(3) \) Å; \(\beta = 108.62^\circ, V = 3253.3(11) \) Å³, \(Z = 4, \rho_{\text{calc}} = 1.263 \) g/cm³. A total of 6433 observations were collected (MoKα, \(2\theta_{\text{max}} = 50^\circ, -17 \leq h \leq 17, -18 \leq k \leq 18, -17 \leq l \leq 0\) and merged to 2859 unique reflections (\(R_{\text{merge}} = 0.021, \text{GOF}_{\text{merge}} = 1.19\)). The structure was solved by direct methods (SHELXS-86) and refined anisotropically (SHELXL-93) to an \(R_1 = 0.044, wR_2 = 0.081\) with a GOF = 2.135. Hydrogen positions were determined from the difference Fourier map. Additional information is given in appendix 2.

Representative bond lengths and angles for \((^3\text{Ph–sal–}^3\text{Pr})_2\text{Mn(OAc)}\) are featured in Table 2.

<table>
<thead>
<tr>
<th>Bond Type</th>
<th>Length (Å)</th>
<th>Angle (°)</th>
<th>Length (Å)</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn–O₁</td>
<td>1.842(12)</td>
<td>O₁–Mn–O₁₈</td>
<td>178.91(8)</td>
<td>N₁–Mn–N₁₈</td>
</tr>
<tr>
<td>Mn–N₁</td>
<td>2.113(2)</td>
<td>O₁–Mn–N₁₈</td>
<td>91.15(6)</td>
<td>N₁–Mn–O₅₀</td>
</tr>
<tr>
<td>Mn–O₂₀</td>
<td>2.212(2)</td>
<td>O₁–Mn–N₁</td>
<td>89.51(6)</td>
<td>O₅₀–Mn–N₂₀₈</td>
</tr>
</tbody>
</table>

**Figure 4.** ORTEP diagram of Mn\((^3\text{Ph–sal–}^3\text{Pr})_2\text{OAc}\) 19 displaying 50% probability ellipsoids. The two perspectives are related by rotation around the C2–axis. Hydrogens not shown for clarity.

**Nitridomanganese(V) Complexes.** Small quantities (5–10 mg) of the desired nitridomanganese(V) complexes, \((^3\text{R–sal–}^3\text{R’})_2\text{Mn(N)}\), could be generated upon prolonged irradiation (>18 h, Hg lamp) of the corresponding Mn\(\text{III(N}_3\) (eq 4). Although formation of the nitrido species was possible under these photolysis conditions, a more efficient preparative method was desirable. Initial attempts to form nitrido Mn(V) derivatives of \((^3\text{R–sal–}^3\text{R’})_2\text{Mn(X)}\) (X = OAc, Cl, N₃) using an NH₄OH/Clorox bleach


combination were, however, unsuccessful. We assumed that the labile Mn(III) starting materials were not capable of withstanding the strongly alkaline (pH = 14) and oxidizing reaction conditions, and thus searched for a milder protocol for the synthesis of Mn≡N.

\[
\begin{align*}
\text{Mn}^{\text{III}} & \xrightarrow{\text{hv}} \text{Mn}^{\text{IV}} \\
\end{align*}
\]

Thereafter, it was discovered that the preparation of \((3\text{R}-\text{sal}–\text{R’})_2\text{Mn}(\text{N})\) from \((3\text{R}-\text{sal}–\text{R’})_2\text{Mn}(\text{OAc})\) could be effected using gaseous NH$_3$ and the commodity chemical \(N\)-bromosuccinimide (NBS). We speculated that this reaction occurred through an oxidative dehydrogenation mechanism in which a Mn–coordinated bromamine intermediate was formed, and subsequently reduced (Figure 5). In support of this hypothesis, it was found that other halogenating agents including \(t\)-butylhypochlorite (\(t\)-BuOCl) and \(N\)-bromoacetamide (CH$_3$CONHBr) could also be employed as oxidants in this process.

\[
\begin{align*}
\text{L}_n\text{Mn}^{\text{III}} & \xrightarrow{\text{NH}_3\text{Br}} \text{L}_n\text{Mn}^{\text{IV}} = \text{N} \\
\end{align*}
\]

**Figure 5.** Putative mechanism for Mn≡N formation with NH$_3$ and \(N\)-bromosuccinimide.

After some optimization, it was determined that the conversion of \((3\text{R}-\text{sal}–\text{R’})_2\text{Mn}(\text{OAc})\) to \((3\text{R}-\text{sal}–\text{R’})_2\text{Mn}(\text{N})\) was best performed at reduced temperatures (45

26. The reaction of ammonia with brominating agents has been shown to form bromamine see: Clemens, D. F.; Woodford, W.; Dellinger, E.; Tyndall, Z. *Inorg. Chem.* 1969, 8, 998.

°C) with 5 equivalents of NBS (eq 5). At −45 °C, product formation occurred instantaneously (as noted by a slight color change) upon introduction of NH₃ to a solution of NBS and a Mn(III) precursor. Aqueous work–up and purification through a small plug of neutral Al₂O₃ (activity I) afforded the nitrido complexes as brown foams (65–70%). Crystallization of these nitrides was possible by vapor diffusion of n–pentane into either EtOAc or benzene solutions of the compounds, and in certain cases, X–ray quality single crystals were obtained.

\[
\text{Mn}^{2+} \text{R–sal–R} \_2 \text{X}
\]
\[
\text{N–bromosuccinimide}
\]
\[
\text{NH}_3, \text{CH}_2\text{Cl}_2
\]
\[
\text{–45 °C}
\]
\[
\text{65–70%}
\]
\[
\text{Mn}^{2+} \text{R–sal–R} \_2 \text{N}
\]

**X–ray Crystallographic Analysis.** The structure of \((\text{³MeO–sal–Me})_2\text{Mn(N)}\) 20 represents one of few crystallographically characterized Mn(V) nitrido complexes (Figure 6, Table 3). The coordination geometry of the manganese is best described as trigonal bipyramidal with both phenolate oxygens and the nitrido ligand forming the trigonal plane. The Mn–Nimine distances are substantially longer (2.02 Å) than the Mn–Ophenolate bonds (1.87 Å), and thus define the two apexes of the bipyramid. Formulation of a Mn≡N triple bond is supported by the observed 1.54 Å bond length as well as a recorded Mn≡N infrared stretch at 1047 cm⁻¹, both numbers of which compare favorably

---

28. Crystal data for \((\text{³MeO–sal–Me})_2\text{Mn(N)}\): pale brown crystals were deposited by diffusing pentane into an Et₂O solution of the complex. 0.33 x 0.30 x 0.26 mm; orthorhombic; space group Fdd2; cell constants: \(a = 14.693(2), b = 23.268(3), c = 11.6940(10)\) Å; \(V = 3997.9(7)\) Å³, \(Z = 8\), \(\rho_{\text{calc}} = 1.413\) g/cm³. A total of 1533 observations were collected (MoKα, \(2\theta_{\text{max}} = 50°\), \(0 \leq h \leq 17, 0 \leq k \leq 27, 0 \leq l \leq 13\)) and merged to 931 unique reflections. The structure was solved by direct methods (SHELXTL, version 5.03) and refined anisotropically (SHELXTL, version 5.03) to an \(R_1 = 0.022, wR_2 = 0.054\) with a GOF = 1.062. Hydrogen atoms were included at calculated positions. Additional information is given in appendix 3.
with analogous data collected for known nitridomanganese porphyrin and salen structures.1,4a,4b,4d,29

![Mn-Ni-N2 (3)MeO-sal-3Me2](image)

Table 3. Select bond lengths [Å] and angles [°] for (3MeO-sal-3Me2)2Mn(N) 20.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn–N1</td>
<td>1.543(4)</td>
<td>O1–Mn–O1a</td>
</tr>
<tr>
<td>Mn–O1</td>
<td>1.868(2)</td>
<td>O1–Mn–N2</td>
</tr>
<tr>
<td>Mn–N2</td>
<td>2.023(2)</td>
<td>N1–Mn–O1</td>
</tr>
</tbody>
</table>

Figure 6. ORTEP diagram of Mn(3MeO-sal-3Me)2N 20 displaying 50% probability ellipsoids.

A second nitrido complex, (3Ph-sal-Ph)2Mn(N) 21, has also been crystallographically characterized (Figure 7). Unfortunately, this structure is marred by disorder problems which preclude its refinement.30 It appears, however, that the gross structural features (e.g., ligand configuration and coordination geometry about the Mn center) are similar to that of the (3MeO-sal-3Me)2Mn(N) complex. Additional, important information which may be gathered from this figure is that the benzyl groups appended to

30. The crystals of 21 were of poor quality and produced inferior data which prevented an accurate solution of this structure. However, the presence of a terminal nitrido ligand can be definitely established with the data collected.
the imine donors are not conformationally restricted (this is, in fact, where the disorder in this structure arises). Thus, it would seem that in spite our efforts to create a steric “cleft” around the Mn≡N unit (vide supra), these ligand systems will require additional refinement if this goal is to be realized.

**Figure 7.** Chem–3D representation of the X–ray structure of 21.

**Nitrogen-Atom Transfer Reactions.** Having developed preparative methods for the construction of Schiff base derived Mn(V) nitrides, we wished to examine the ability of these systems to function as nitrogen atom–transfer reagents with unfunctionalized alkenes. To this end, we tested the reactivity of (3Ph–sal–Ph)₂Mn(N) 21 with styrene 22 (Figure 8). Addition of 21 (1 equiv) to a solution of TFAA and 22 (5 equiv) in CH₂Cl₂ followed by treatment of the unpurified reaction product with aq. NaHCO₃/THF afforded the N-trifluoroacetylated amino alcohol 23 in 46% yield.³¹ The generation of 23 was, at the time, the only example of nitrogen atom-transfer to styrene with a nitridomanganese

---

³¹. A mixture of both amino alcohol 23 and trifluoroacetyl ester i are isolated from the reaction of (3Ph–sal–Ph)₂Mn(N) 21 with styrene. Ester i is readily hydrolyzed (NaHCO₃) to give 23.
reagent.\textsuperscript{29,32} This reaction has since been optimized, and may now be performed with a single equivalent of styrene 22 and one equivalent of \((3\text{Ph-sal-Ph})_2\text{Mn(N)}\) to give the desired product 23 in 64\% yield. It is worth noting, however, that syringe-pump addition of the nitrido reagent over a one hour period to a solution of TFAA and 22 is an absolute requirement for the successful transfer of CF\(_3\)CON to the alkene substrate.\textsuperscript{33} If the order in which the reagents were mixed was reversed or if dropwise addition of the solution of 21 was omitted, no products resulting from nitrogen transfer to styrene were formed. Recently, it has also been shown that this syringe-pump addition protocol may be employed with (saltmen)Mn(N) to effect CF\(_3\)CON transfer to 22. This reaction is remarkably efficient, providing 70\% yield of 23, using a 1:1 sytrene-to-(saltmen)Mn(N) stoichiometry.\textsuperscript{34}

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>L(_2)Mn=N</th>
<th>equiv</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>((3\text{Ph-sal-Ph})_2\text{Mn(N)}) 21</td>
<td>1.0</td>
<td>64%</td>
</tr>
<tr>
<td>(saltmen)Mn(N)</td>
<td>1.0</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Figure 8.** Nitrogen atom-transfer to styrene 22 with nitridomanganese reagents.

Having obtained this latter result, it is difficult to conclude that the bidentate Schiff base nitrido complexes possess reactivity which is different from the


\textsuperscript{33} An analogous slow addition procedure is employed in carbene addition reactions with diazo compounds, see: Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. Synthesis \textbf{1981}, 787, and references therein.

\textsuperscript{34} Optimization of the \((3\text{R-sal-R'})_2\text{Mn(N)}\) reaction with styrene as well as the equivalent experiments with (saltmen)Mn(N) were conducted by Craig S. Tomooka.
(saltmen)Mn(N) system. It would appear that the slow addition procedure is essential in order for the reaction of these reagents with unfunctionalized olefins to be at all effective. The design of new complexes with more rigid ligand frameworks which prevent the reactive Mn=NCOCF₃ species from participating in unwanted side-reactions would ideally eliminate any need for prolonged reagent addition times. This is likely, however, to require involved ligand syntheses which would render the resulting complexes impractical for use as stoichiometric reagents. Perhaps not suprisingly then, it seems that the ultimate solution requires developing a catalytic nitrogen atom-transfer process. In a catalytic reaction, a high concentration of olefin relative to the concentration of the Mn=NCOCF₃ intermediate would be maintained until the reaction neared completion. This is an analogous condition to the one established when the slow addition procedure is employed, and is most favorable for promoting olefin amination.

![Chemical Reaction Diagram]

Figure 9. Chiral nitridomanganese complexes derived from bidentate, oxazoline ligands.

**Future Directions.** With the discovery of a new method for Mn≡N bond formation, it has been possible to construct additional nitrido complexes. Recently, bidentate oxazoline-based ligands have been used to prepare first-generation, chiral
nitridomanganese reagents 24 and 25 (Figure 9).\textsuperscript{35} The X-ray crystal structure of one of these compounds, 24, has been solved and reveals a number similarities to the structures of both (\textsuperscript{3}MeO–sal–Me)_2Mn(N) 20 and (\textsuperscript{3}Ph–sal–Ph)_2Mn(N) 21, which include Mn≡N bond length (1.50 Å) and Mn coordination geometry (distorted trigonal bipyramid).\textsuperscript{36} Experiments are currently in progress to determine if these systems will perform the enantioselective transfer of CF\textsubscript{3}CON to olefins.

Conclusion

The synthesis of nitridomanganese(V) complexes which function competently as nitrogen transfer reagents with styrene has been described. Pivotal to the success of this work has been the development of new synthetic protocols for the construction of Mn(III) Schiff base complexes and for the subsequent oxidative conversion of these materials to the desired nitrido Mn(V) products. In conjunction with the Schiff base systems, the application of these protocols has also made possible the preparation of a new class of chiral, oxazoline-derived complexes which have potential use as asymmetric alkene amination reagents. It is hoped that further extension of these methods to incorporate additional, uniquely engineered ligand systems will ultimately furnish a single nitrido Mn reagent capable of performing nitrogen atom-transfer to olefins of all types.


\textsuperscript{36} The preparation and crystallization of the oxazoline-derived complexes 24 and 25 was performed by Craig S. Tomooka.
Experimental

**General methods.** All reagents were commercially obtained and purified prior to use. Air and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C using a water aspirator. Dichloromethane and pyridine were distilled from calcium hydride prior to use. Trifluoroacetic anhydride was distilled at 39.5 °C, 1 atm prior to each use. Chromatographic purification of products was accomplished using forced-flow chromatography on Baker 7024–R silica gel. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60F plates (230-400 mesh). Visualization of the developed chromatogram was performed by either fluorescence quenching, aqueous ceric ammonium molybdate (CAM), ethanolic phosphomolybdic acid (PMA), or an ethanolic p-anisaldehyde stain.

NMR spectra were recorded on either a Bruker AM–500 operating at 500 and 125 MHz or a General Electric–300 operating at 300 and 75 MHz for $^1$H and $^{13}$C, respectively (as indicated). Spectra are referenced internally to residual protio solvent signals. Data for $^1$H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), integration, and coupling constant (Hz). Data for $^{13}$C are reported in terms of chemical shift. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 with samples prepared as either thin films on NaCl salt plates or as a KBr pellet (as indicated) and reported in cm$^{-1}$. Combustion analysis was performed by the analytical laboratory at the California Institute of Technology. High resolution mass spectra were obtained from the UC Irvine Mass Spectral facility. X–ray crystal structures were solved at the Beckman Institute Center for X–ray Crystallography.
Preparation of $\text{H}_2\text{saltmen}$

To a solution of salicylaldehyde (10.8 g, 88.2 mmol, 2.05 equiv) in 150 mL of absolute EtOH was added 2,3-diamino-2,3-dimethylbutane (5.0 g, 43.0 mmol) in a single portion. The resulting yellow solution was heated at reflux for 11 h after which time 40 mL of $\text{H}_2\text{O}$ was added. The mixture was heated at reflux for an additional 5 min before being allowed to cool slowly to 23 °C. The flask, which contained yellow crystals, was then placed in a freezer at −20 °C and the contents were allowed to stand at this temperature for 2 h. The crystalline product was collected upon filtration through a fritted glass funnel, rinsed with ice-cold 80% aqueous EtOH (50 mL), and dried in vacuo at ca. 1 Torr (11.8 g, 85% - 1st crop). The yellow filtrate was concentrated under reduced pressure to a volume of ca. 40 mL and then cooled to −20 °C. Upon filtration an additional 1.6 g of the product was isolated. Combined yield: 13.4 g (96%). $^1\text{H}$ NMR (CDCl$_3$, 500 MHz) δ 14.07 (s, 2H), 8.38 (s, 2H), 7.30 (dt, 2H, $J = 7.8$, 1.9 Hz), 7.26 (dd, 2H, $J = 7.6$, 1.6), 6.94 (d, 2H, $J = 8.2$ Hz), 6.87 (dt, 2H, $J = 7.5$, 0.9 Hz), 1.40 (s, 12H) ppm; $^{13}\text{C}$ NMR (CDCl$_3$, 125 MHz) δ 161.6, 161.5, 132.2, 131.6, 118.8, 118.3, 117.0, 65.1, 23.0 ppm; IR (KBr) ν 2986, 2920, 2587 (br), 1627, 1583, 1499, 1459, 1381, 1280, 1218, 1133, 1111, 947, 892, 831, 754 cm$^{-1}$; HRMS (CI) calcd for C$_{20}$H$_{24}$N$_2$O$_2$ 324.1838, found 325.1906 (MH$^+$); Anal. Calcd for C$_{20}$H$_{24}$N$_2$O$_2$: C, 74.04; H, 7.46; N, 8.63. Found: C, 73.54; H, 7.21; N, 8.41.

Preparation of (saltmen)$\text{Mn}(\text{N})$

$\text{H}_2\text{saltmen}$ (10.0 g, 30.8 mmol) was suspended in 400 mL of MeOH and the mixture was heated to ca. 50–60 °C. To the yellow solution was added Mn(OAc)$_2$·4H$_2$O (7.90 g, 32.4 mmol, 1.05 equiv) portionwise. The resulting dark brown solution was heated at reflux for 1 h after which time the contents were stirred for 30 min at 23 °C. Concentrated NH$_4$OH (15 M, 31.0 mL, 465 mmol, 15 equiv) was then added dropwise
over a 5 min period. To the vigorously stirring mixture was added 280 mL of Clorox bleach (≈0.7 M aq. NaOCl, 196 mmol, 6 equiv) over 40 min. During the addition, the evolution of a white gas was observed. When the addition was complete, the reaction mixture was cooled in an ice-H_2O bath and 400 mL of CH_2Cl_2 was cautiously added. The resulting biphasic mixture was warmed to 23 °C and stirred for 15 min. The contents were then transferred to a separatory funnel with an additional 200 mL of H_2O. The dark green organic phase was isolated and the aqueous layer was extracted with 1 x 200 mL CH_2Cl_2. The combined organic extracts were washed with 6 x 300 mL H_2O and then concentrated under reduced pressure to afford ≈12 g (99%) of a dark green solid. The solid material was dissolved in CH_2Cl_2 (50–75 mL) and filtered through a 70 x 200 mm plug of Brockmann activity IV basic Al_2O_3 using CH_2Cl_2 as eluent. A dark green band was collected as a single fraction and the solvent was removed in vacuo. The resulting green solid was suspended in 150 mL of refluxing EtOAc to which 300 mL of hexanes was then added. The contents were cooled to 23 °C and then placed in a freezer at -20 °C for 10 h. The dark green micro-crystalline precipitate was collected in a fritted glass funnel and rinsed with 3 x 50 mL ice-cold 2:1 hexanes/EtOAc. The product (10.2 g, 85%) was dried in vacuo at ca. 1 Torr for 5 h. ^1H NMR (CDCl_3, 500 MHz) δ 8.06 (s, 2H), 7.36 (dt, 2H, J = 7.7, 1.7 Hz), 7.20 (dd, 2H, J = 7.8, 1.6 Hz), 7.14 (d, 2H, J = 8.7 Hz), 6.68 (t, 2H, J = 7.4 Hz), 1.47 (s, 12H) ppm; ^13C NMR (CDCl_3, 125 MHz) δ 167.7, 162.5, 135.3, 133.8, 121.8, 120.3, 116.0, 72.1, 25.1, 23.5 ppm; IR (KBr) ν 2981, 1620, 1538, 1467, 1445, 1394, 1308, 1205, 1144, 1126, 1053, 1047 (Mn≡N), 906, 850, 800, 765, 741 cm⁻¹; HRMS (FAB⁺) calcd for MnC_{20}H_{22}N_{3}O_{2} 391.1092 found 391.1080 (M⁺); Anal. Calcd for MnC_{20}H_{22}N_{3}O_{2}: C, 60.38; H, 5.60; N, 10.51. Found: C, 60.28; H, 5.55; N, 10.50.
**General procedure for the amination of silyl enol ethers:** A solution of silyl enol ether (1.0 mmol, 2 equiv) in 3.0 mL of CH₂Cl₂ was cooled to −78 °C. Pyridine (1.5 mmol) was added followed by a solution of the silyl enol ether (0.5 mmol) in 2.0 mL of CH₂Cl₂. Freshly distilled TFAA (1.2 mmol) was then added dropwise to the dark green mixture. The solution was allowed to warm slowly from −78 °C to 23 °C over a 3–4 h period. During this time the reaction mixture turned dark brown. Silica gel (800 mg) and Celite (800 mg) were added along with 25 mL of n-pentane. The dark brown slurry was stirred vigorously at 23 °C for 30 min before being filtered through a 20 x 40 mm plug of silica gel using Et₂O (4 x 10 mL) as eluent. Concentration of the filtrate under reduced pressure afforded a pale yellow residue which was purified by chromatography on silica gel. In one case (entry 4; Table 1, Chapter 1) a higher yield of the desired product was obtained if the reaction was initially run at −30 °C (3:2 H₂O/ethylene glycol–dry ice) and only a catalytic amount of pyridine (62 µmol) was employed.

**Physical data for N-trifluoroacetylated amino ketone products:**

![Chemical structure](image)

TLC Rf = 0.28 (2:3 hexanes/CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.62 (d, 1H, J = 8.6 Hz), 7.55 (br s, 1H), 7.34 (t, 1H, J = 8.0 Hz), 7.08 (d, 1H, J = 7.6 Hz), 4.63 (dt, 1H, J = 13.9, 4.8 Hz), 3.89 (s, 3H), 3.26-3.22 (m, 1H), 2.95-2.88 (m, 2H), 1.91-1.87 (m, 1H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 194.1, 157.1 (q, J₃-C = 37.2 Hz), 157.0, 132.5, 131.8, 127.6, 119.1, 115.7 (q, J₃-C = 288.0 Hz), 115.3, 56.3, 55.7, 28.6, 21.9 ppm; IR (thin film) v 3285, 2947, 1707, 1684, 1557, 1316, 1270, 1209, 1183, 1046, 905, 804
cm⁻¹; HRMS (Cl) calcd for C_{13}H_{12}F_3NO_3 287.0769, found 288.0851 (MH⁺); Anal. Calcd for C_{13}H_{12}F_3NO_3: C, 54.35; H, 4.21; N, 4.88. Found: C, 54.27; H, 4.23; N, 4.74.

TLC R_f = 0.09 (3:2 hexanes/CH_2Cl_2); ^1H NMR (CDCl_3, 500 MHz) δ 6.34 (br s, 1H), 3.91 (d, 1H, J = 5.4 Hz), 2.37 (d, 1H, J = 4.4 Hz), 2.14-2.05 (m, 1H), 1.80-1.73 (m, 1H), 1.66-1.58 (m, 2H), 0.99 (s, 3H), 0.97 (s, 3H), 0.85 (s, 3H) ppm; ^13C NMR (CDCl_3, 125 MHz) δ 214.6, 157.4 (q, J_C-F = 37.6 Hz), 115.6 (q, J_C-F = 287.5 Hz), 60.0, 57.2, 48.1, 46.6, 28.0, 26.6, 20.6, 19.9, 8.9 ppm; IR (thin film) ν 3270, 2973, 1726, 1556, 1398, 1328, 1226, 1177, 1156, 1020 cm⁻¹; HRMS (Cl) calcd for C_{12}H_{16}F_3NO_2 263.1133, found 264.1205 (MH⁺); Anal. Calcd for C_{12}H_{16}F_3NO_2: C, 54.75; H, 6.13; N, 5.32. Found: C, 54.78; H, 6.04; N, 5.32.

TLC R_f = 0.21 (6:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 500 MHz) δ 7.27 (br s, 1H), 6.71 (dd, 1H, J = 10.1, 2.1 Hz), 5.94 (d, 1H, J = 10.1 Hz), 4.62 (dt, 1H, J = 13.9, 5.2 Hz), 2.50 (ddd, 1H, J = 12.8, 4.9, 2.0 Hz), 1.74 (t, 1H, J = 13.3 Hz), 1.35 (s, 3H), 1.19 (s, 3H) ppm; ^13C NMR (CDCl_3, 125 MHz) δ 194.4, 160.4, 157.1 (q, J_C-F = 38.7 Hz), 124.2, 115.7 (q, J_C-F = 287.2 Hz), 52.8, 41.7, 34.7, 30.5, 25.0 ppm; IR (thin film) ν 3319, 2964, 1723, 1682, 1554, 1369, 1180, 1159, 821 cm⁻¹; HRMS (Cl) calcd for C_{10}H_{12}F_3NO_2 235.0820, found 236.0897 (MH⁺); Anal. Calcd for C_{10}H_{12}F_3NO_2: C, 51.07; H, 5.14; N, 5.96. Found: C, 51.10; H, 5.17; N, 5.96.
TLC $R_f = 0.18$ (1:1 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.99 (dd, 2H, $J = 8.3, 1.2$ Hz), 7.69 (dt, 1H, $J = 7.4, 1.2$ Hz), 7.54 (dt, 2H, $J = 7.9, 1.6$ Hz), 7.50 (br s, 1H), 4.83 (d, 2H, 4.3 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 192.1, 157.2 (q, $J_{C-F} = 37.8$ Hz), 134.7, 133.8, 129.1, 128.0, 115.7 (q, $J_{C-F} = 286.8$ Hz), 46.2 ppm; IR (thin film) ν 3314, 1713, 1686, 1560, 1350, 1181, 1153 cm$^{-1}$; HRMS (Cl) calcd for C$_{10}$H$_8$F$_3$NO$_2$ 231.0507, found 232.0585 (MH$^+$); Anal. Calcd for C$_{10}$H$_8$F$_3$NO$_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 52.12; H, 3.46; N, 6.03.
General procedure for the preparation of 2–amino sugars from pyranoid glycals: A 25 mL schlenk flask was flushed with N₂ and charged with glycal (0.40 mmol) and 0.5 mL of CH₂Cl₂. Freshly distilled TFAA (200 μL, 1.4 mmol, 3.5 equiv) was then added. A solution of (saltmen)Mn(N) (0.04 M, 10 mL, 0.40 mmol, 1 equiv) in CH₂Cl₂ was drawn into a 10.0 mL gas-tight syringe and transferred dropwise with the aid of a syringe pump to the mixture of TFAA and glycal (7 h addition period). Following the addition of (saltmen)Mn(N), silica gel (500 mg) and Celite (500 mg) were added to the resultant dark brown solution along with 15 mL of n-pentane. The dark brown slurry was stirred vigorously for 30 min before being filtered through a 20 x 50 mm plug of silica gel using Et₂O (2 x 10 mL) as eluent. Concentration of the filtrate under reduced pressure afforded a pale yellow residue which was purified by chromatography on silica gel. In two cases (39 and 40; Table 1, Chapter 2) a higher yield of the desired product was obtained if 1 equiv of 2,6-di-tert-butyl-4-methylpyridine was combined with the solution of glycal prior to the introduction of TFAA.

General procedure for the preparation of 2–amino sugars from furanoid glycals: A solution of glycal (0.40 mmol), (saltmen)Mn(N) (0.80 mmol, 2.0 equiv), and 2,6-di-tert-butyl-4-methylpyridine (1.20 mmol, 3.0 equiv) in 4.0 mL of CH₂Cl₂ was cooled to -78 °C. Freshly distilled TFAA (0.96 mmol, 2.4 equiv) was then added dropwise to the dark green mixture. The solution was allowed to warm slowly from -78 °C to 23 °C over a 5–6 h period. During this time, the reaction mixture turned dark brown. Silica gel (200 mg), Celite (200 mg), and n-pentane (5 mL) were added along with 80% aq. HOAc (0.3 mL). The dark brown slurry was stirred at 23 °C for 5 h before being filtered through a 20 x 100 mm plug of silica gel using Et₂O (60 mL) as eluent. Addition of cyclohexane (10 mL) followed by concentration of the filtrate under reduced pressure afforded a yellow residue, which was purified by chromatography on silica gel.
Physical data for glycal starting materials:

\[
\text{Ph}^\prime \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{TBSO}
\]

TLC $R_f = 0.22$ (3:1 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.50 (dd, 2H, $J = 7.5$, 1.8 Hz), 7.40-7.34 (m, 3H), 6.30 (dd, 1H, $J = 6.1$, 1.5 Hz), 5.61 (s, 1H), 4.67 (dd, 1H, $J = 6.1$, 2.0 Hz), 4.51 (dt, 1H, $J = 7.4$, 1.8 Hz), 4.36 (dd, 1H, $J = 10.3$, 4.8 Hz), 3.89 (dt, 1H, $J = 10.1$, 4.8 Hz), 3.84-3.79 (m, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 143.3, 137.3, 128.9, 128.1, 126.0, 105.4, 101.3, 80.6, 68.8, 68.4, 67.3, 25.8, 18.2, -4.4, -4.8 ppm; IR (thin film) v 2928, 2857, 1640, 1472, 1382, 1233, 1128, 1106, 1072, 1021, 864, 837, 779 cm$^{-1}$; Anal. Calcd for C$_{19}$H$_{28}$SiO$_4$: C, 65.48; H, 8.10. Found: C, 65.11; H, 8.18.

\[
\text{Ph}^\prime \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{PMBO}
\]

TLC $R_f = 0.43$ (4:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.53 (dd, 2H, $J = 7.5$, 2.0 Hz), 7.42-7.37 (m, 3H), 7.30 (d, 2H, $J = 8.5$ Hz), 6.86 (d, 2H, $J = 8.7$ Hz), 6.39 (d, 1H, $J = 6.0$ Hz), 5.60 (s, 1H), 4.93 (t, 1H, $J = 6.0$ Hz), 4.86 (d, 1H, $J = 11.5$ Hz), 4.61 (d, 1H, $J = 11.5$ Hz), 4.47 (dd, 1H, $J = 10.5$, 5.3 Hz), 4.33 (dt, 1H, $J = 10.4$, 5.3 Hz), 4.04 (dd, 1H, $J = 5.9$, 3.6 Hz), 3.97 (dd, 1H, $J = 10.4$, 3.5 Hz), 3.84 (t, 1H, $J = 10.5$ Hz), 3.80 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1, 145.6, 137.5, 131.1, 129.5, 129.1, 128.3, 126.2, 113.7, 102.0, 100.4, 79.6, 72.7, 68.8, 66.7, 64.5, 55.3 ppm; IR (thin film) v 2864, 1637, 1612, 1513, 1456, 1382, 1243, 1140, 1087, 1031, 970, 822, 754, 700 cm$^{-1}$; Anal. Calcd for C$_{21}$H$_{22}$O$_5$: C, 71.17; H, 6.26. Found: C, 71.14; H, 6.37.
TLC $R_f = 0.18$ (3:1 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.50 (dd, 2H, $J = 7.2, 2.7$ Hz), 7.38-7.34 (m, 3H), 6.34 (d, 1H, $J = 6.0$ Hz), 5.60 (s, 1H), 4.90 (t, 1H, 6.0 Hz), 4.43 (dd, 1H, $J = 10.5, 5.4$ Hz), 4.28-4.22 (m, 2H), 3.82-3.78 (m, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 144.5, 137.6, 128.9, 128.1, 126.3, 102.9, 101.7, 78.4, 68.8, 63.7, 61.1, 25.8, 18.3, -4.50, -4.63 ppm; IR (thin film) ν 2856, 1634, 1471, 1388, 1241, 1142, 1119, 1085, 1021, 899, 835, 780, 697 cm$^{-1}$; Anal. Calcd for C$_{19}$H$_{28}$SiO$_4$: C, 65.48; H, 8.10. Found: C, 65.47; H, 8.05.

TLC $R_f = 0.17$ (3:1 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.71-7.68 (m, 4H), 7.45-7.37 (m, 6H), 6.33 (d, 1H, $J = 6.3$ Hz), 4.77 (ddd, 1H, $J = 6.3, 2.7, 1.6$ Hz), 4.66 (dd, 1H, 6.0, 2.8 Hz), 4.46 (d, 1H, $J = 6.0$ Hz), 4.03 (t, 1H, $J = 6.8$ Hz), 3.99-3.91 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.07 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 144.6, 135.62, 135.57, 133.4, 129.7, 127.73, 127.68, 110.2, 102.6, 74.9, 71.8, 68.5, 62.9, 28.2, 26.8, 19.3 ppm; IR (thin film) ν 2932, 2858, 1647, 1472, 1428, 1369, 1239, 1146, 1112, 1031, 824, 702 cm$^{-1}$. HRMS (FAB$^+$) calcd for C$_{25}$H$_{32}$SiO$_4$ 424.2070, found 423.1984 (M--H$^+$).
TLC $R_f = 0.21$ (12:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.37-7.29 (m, 5H), 6.41 (d, 1H, $J = 6.3$ Hz), 4.80 (ddd, 1H, $J = 6.3$, 2.8, 1.4 Hz), 4.69-4.65 (m, 2H), 4.57 (d, 1H, $J = 12.0$ Hz), 4.28 (d, 1H, $J = 6.1$ Hz), 4.12 (t, 1H, $J = 6.2$ Hz), 3.83 (dd, 1H, $J = 10.1$, 7.6 Hz), 3.73 (dd, 1H, $J = 10.1$, 4.9), 1.46 (s, 3H), 1.35 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 144.8, 137.8, 128.4, 127.8, 127.7, 110.5, 102.5, 73.9, 73.5, 72.6, 69.9, 68.6, 28.0, 26.9 ppm; IR (thin film) ν 2984, 2931, 1648, 1454, 1369, 1237, 1147, 1103, 1068, 1027, 866, 735, 698 cm$^{-1}$. HRMS (FAB$^+$) calcd for C$_{16}$H$_{20}$O$_4$ 276.1361, found 275.1285 (M–H$^+$).

TLC $R_f = 0.22$ (8:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.29-7.24 (m, 4H), 6.90-6.87 (m, 4H), 6.34 (d, 1H, $J = 6.1$ Hz), 4.85-4.79 (m, 2H), 4.62 (d, 1H, $J = 10.9$ Hz), 4.60 (d, 1H, $J = 11.3$ Hz), 4.51 (d, 1H, $J = 11.3$ Hz), 4.17 (dd, 1H, $J = 6.5$, 1.6 Hz), 3.95-3.89 (m, 1H), 3.810 (s, 3H), 3.808 (s, 3H), 3.44 (dd, 1H, $J = 9.0$, 6.6 Hz), 1.34 (d, 3H, $J = 6.5$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2, 159.1, 144.7, 130.5, 130.4, 129.6, 129.4, 113.78, 113.76, 100.3, 79.1, 76.2, 74.0, 73.7, 70.28, 70.25, 55.3, 17.5 ppm; IR (thin film) ν 2836, 1646, 1613, 1514, 1464, 1302, 1247, 1173, 1094, 1035, 819 cm$^{-1}$; Anal. Calcd for C$_{22}$H$_{26}$O$_5$: C, 71.33; H, 7.07. Found: C, 71.24; H, 7.37.
TLC $R_f = 0.14$ (2:1 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.51 (dd, 2H, $J = 7.8$, 1.7 Hz), 7.40-7.34 (m, 3H), 6.34 (dt, 1H, $J = 6.0$, 2.0 Hz), 5.63 (s, 1H), 4.74 (dt, 1H, $J = 5.8$, 2.2 Hz), 4.40 (dd, 1H, $J = 16.2$, 10.7 Hz), 3.94 (dd, 1H, $J = 16.5$, 6.6 Hz), 3.82-3.77 (m, 2H), 2.39-2.33 (m, 1H), 2.30-2.23 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 143.1, 137.4, 129.1, 128.3, 126.1, 101.7, 98.7, 75.0, 69.9, 68.9, 26.3 ppm; IR (thin film) ν 2877, 1638, 1402, 1378, 1333, 1241, 1130, 1084, 1003, 974, 756, 696, 650 cm$^{-1}$; Anal. Calcd for C$_{13}$H$_{14}$O$_3$: C, 71.54; H, 6.47. Found: C, 71.52; H, 6.64.

**Physical data for 2-amino sugars:**

TLC $R_f = 0.46$–0.28 (2:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.49-7.47 (m), 7.38-7.36 (m), 6.45 (d, -NH major, $J = 9.5$ Hz), 5.53 (s, major), 5.52 (s), 5.29 (t, major, $J = 3.6$ Hz), 4.92 (t, $J = 6.1$ Hz), 4.27-4.22 (m), 4.07 (dt, major, $J = 9.9$, 4.9 Hz), 4.02 (t, major, $J = 9.4$ Hz), 3.82-3.78 (m), 3.75 (t, major, $J = 10.3$ Hz), 3.63 (d, $J = 8.2$ Hz), 3.56 (t, major, $J = 9.3$ Hz), 3.53-3.51 (m), 2.89 (dd, -OH major, $J = 3.6$, 1.6 Hz), 0.84 (s), 0.81 (s), 0.801 (s), 0.796 (s, major), 0.08 (s), 0.06 (s), 0.02 (s), 0.01 (s, major), -0.03 (s), -0.04 (s, major) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 158.6 (q, $J_{C,F} = 36.9$ Hz), 157.4 (q, $J_{C,F} = 37.2$ Hz), 136.9, 136.83, 136.77, 129.2, 129.1, 128.4, 128.1, 126.3, 126.2, 126.0, 125.9, 115.7 (q, $J_{C,F} = 287.8$ Hz), 102.1, 102.0, 101.9, 101.8, 95.4, 91.8, 91.7, 82.2, 81.8, 71.6, 69.8, 68.7, 68.3, 66.4, 62.7, 62.6, 62.3, 59.6, 55.1, 26.2, 25.5, 25.45, 25.39, 17.94, 17.90, -4.07, -4.13, -4.16, -4.17, -5.19, -5.22, -5.3 ppm; IR (thin film) ν 3428 (br), 3330 (br), 2931, 2856, 1711, 1545, 1384, 1214, 1169, 1087, 839 cm$^{-1}$;
Anal. Calcd for C_{21}H_{30}SiNO_{6}F_{3}: C, 52.82; H, 6.33; N, 2.93. Found: C, 53.01; H, 6.51; N, 2.81.

TLC $R_f = 0.26$ (2:1 hexanes/EtOAc); $^1H$ NMR (CDCl$_3$, 500 MHz) $\delta$ 7.50-7.47 (m), 7.41-7.38 (m), 7.35-7.29 (m), 6.88-6.86 (m), 6.65 (d, -NH major, $J = 5.9$ Hz), 6.40 (br s), 5.60 (s), 5.95 (s), 5.57 (s), 5.55 (s, major), 5.47 (s, major), 4.97 (d, $J = 11.0$ Hz), 4.91 (d, $J = 10.9$ Hz), 4.83 (d, major, $J = 11.2$ Hz), 4.68 (d, $J = 11.0$ Hz), 4.65 (d, major, $J = 11.2$ Hz), 4.50-4.47 (m), 4.40-4.37 (m), 4.34 (dd, major, $J = 10.4$, 5.2 Hz), 4.29-4.25 (m, major), 4.15 (dt, major, $J = 9.9$, 5.0 Hz), 3.85 (s), 3.83 (s), 3.81 (s), 3.80 (s, major), 3.78 (s), 3.76 (s), 3.73 (dd, $J = 9.8$, 2.6 Hz), 3.67 (dd, major, $J = 9.7$, 2.6 Hz), 3.16 (br s, -OH major) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.6, 159.2, 157.7 (q, $J_{C,F} = 37.6$ Hz), 156.7 (q, $J_{C,F} = 38.2$ Hz), 137.0, 136.9, 129.89, 129.86, 129.7, 129.5, 129.25, 129.15, 128.6, 128.3, 128.2, 126.0, 115.5 (q, $J_{C,F} = 287.8$ Hz), 115.4 (q, $J_{C,F} = 287.8$ Hz), 114.2, 113.9, 113.8, 113.7, 102.5, 102.4, 102.2, 102.1, 93.6, 91.2, 91.1, 77.2, 77.1, 76.9, 76.8, 74.4, 74.33, 74.31, 74.26, 73.5, 73.4, 73.3, 73.0, 72.9, 68.9, 68.7, 68.6, 64.5, 64.1, 59.21, 59.15, 55.23, 55.19, 55.17, 55.12, 55.10, 55.0, 53.81, 53.77, 51.6, 51.5 ppm; IR (thin film) v 3419 (br), 3294 (br), 2931, 2868, 1717, 1515, 1249, 1213, 1175, 1103, 1030, 700 cm$^{-1}$; Anal. Calcd for C$_{23}$H$_{24}$NO$_7$F$_3$: C, 57.14; H, 5.00; N, 2.89. Found: C, 57.21; H, 5.32; N, 2.66.

TLC $R_f = 0.16$ (4:1 hexanes/EtOAc); $^1H$ NMR (CDCl$_3$, 500 MHz) $\delta$ 7.45 (dd, $J = 7.5$, 2.2 Hz), 7.36-7.35 (m), 6.67 (d, -NH major, $J = 8.4$ Hz), 5.81 (br d, $J = 11.1$ Hz),
5.61 (s), 5.59 (s), 5.55 (s, major), 5.50 (dd, major, J = 3.8, 1.8 Hz), 5.02 (d, J = 10.9 Hz), 4.45 (t, major, J = 2.9 Hz), 4.43-4.36 (m), 4.32 (dd, major, J = 10.3, 5.2 Hz), 4.26 (dd, J = 7.5, 3.5 Hz), 4.11-4.06 (m, major), 3.82 (t, J = 9.8 Hz), 3.77 (t, major, J = 10.4 Hz), 3.64 (dd, J = 9.5, 2.4 Hz), 3.56 (dd, major, J = 9.5, 2.5 Hz), 3.17 (d, -OH major, J = 4.0 Hz), 0.944 (s), 0.937 (s), 0.92 (s, major), 0.91 (s), 0.19 (s), 0.16 (s, major), 0.12 (s), 0.112 (s), 0.107 (s), 0.08 (s, major) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 157.8 (q, $J_{C,F} = 37.7$ Hz), 156.9 (q, $J_{C,F} = 38.3$ Hz), 137.0, 136.8, 129.2, 129.1, 129.0, 128.13, 128.10, 126.2, 126.14, 126.10, 115.6 (q, $J_{C,F} = 287.6$ Hz), 115.4 (q, $J_{C,F} = 287.8$ Hz), 102.52, 102.48, 102.30, 102.26, 93.9, 91.04, 90.99, 76.69, 76.67, 76.3, 68.9, 68.6, 68.51, 68.47, 67.3, 67.2, 63.7, 58.6, 56.0, 53.1, 53.0, 25.6, 25.5, 18.0, -4.85, -4.87, -5.2, -5.3, -5.46, -5.50 ppm; IR (thin film) $\nu$ 3339 (br), 3239 (br), 2930, 2859, 1715, 1553, 1395, 1214, 1165, 1103, 1004, 830, 780 cm$^{-1}$; Anal. Calcd for C$_{21}$H$_{30}$SiNO$_6$F$_3$: C, 52.82; H, 6.33; N, 2.93. Found: C, 52.79; H, 6.55; N, 2.82.

TLC $R_f$ = 0.24–0.12 (4:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.73-7.62 (m), 7.47-7.38 (m), 6.47 (d, J = 7.0 Hz), 6.38 (d, -NH major, J = 9.5 Hz), 5.15 (s, major), 4.77-4.73 (m), 4.53-4.51 (m), 4.38-4.30 (m, major), 4.22 (dt, major, J = 9.0, 3.2 Hz), 4.17 (dd, major, J = 8.8, 4.6 Hz), 4.08-4.06 (m), 4.00 (dd, major, J = 10.0, 7.2 Hz), 3.98-3.91 (m), 3.87 (dd, major, J = 10.0, 5.9 Hz), 3.76-3.73 (m), 3.65 (d, J = 8.4 Hz), 3.61 (d, J = 8.8 Hz), 3.33 (br s), 2.65 (br s, -OH major), 1.57 (s, major), 1.54 (s), 1.44 (s), 1.40 (s), 1.37 (s), 1.36 (s, major), 1.06 (s, major), 1.05 (s), 1.04 (s) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 157.4 (q, $J_{C,F} = 37.3$ Hz), 135.6, 135.52, 135.49, 135.46, 135.4, 133.3, 133.2, 133.1, 133.0, 129.9, 129.7, 127.84, 127.80, 127.7, 127.6, 124.3, 115.7 (q, $J_{C,F} = 287.9$ Hz), 110.4, 109.8, 91.3, 75.1, 73.6, 73.3, 72.4, 72.21, 72.18, 67.6, 62.8, 62.2,

TLC R_f = 0.26–0.17 (2:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 500 MHz) δ 7.38-7.30 (m), 6.37 (d, -NH major, J = 10.0 Hz), 5.23 (s, major), 4.67 (d, major, J = 12.2 Hz), 4.56 (d, major, J = 12.2 Hz), 4.47-4.45 (m, major), 4.25-4.21 (m, major), 4.17-4.13 (m, major), 3.79 (dd, major, J = 10.2, 8.0 Hz), 3.73 (dd, major, J = 10.2, 4.1 Hz), 1.57 (s, major), 1.54 (s), 1.34 (s), 1.33 (s, major) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 157.3 (q, J_C,F = 37.2 Hz), 137.5, 137.2, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 115.7 (q, J_C,F = 288.0 Hz), 110.5, 110.0, 91.3, 91.2, 75.2, 73.8, 73.4 (t, J = 8.1 Hz), 73.1, 73.0, 72.7, 72.0, 69.7, 69.6, 66.2, 64.4, 51.5, 27.8, 27.7, 26.3, 26.0 ppm; IR (thin film) ν 3326 (br), 2937, 1722, 1552, 1382, 1218, 1160, 1076, 859, 738 cm⁻¹; Anal. Calcd for C₁₈H₂₂NO₆F₃: C, 53.33; H, 5.47; N, 3.46. Found: C, 53.50; H, 5.49; N, 3.16.

TLC R_f = 0.26–0.08 (2:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 500 MHz) δ 7.29-7.24 (m), 7.22-7.19 (m), 6.91-6.86 (m), 6.23 (d, -NH major, J = 8.9 Hz), 5.23 (s), 5.19 (s, major), 4.88-4.79 (m), 4.80 (d, major, J = 10.6 Hz), 4.78 (d, major, J = 11.2 Hz), 4.74-4.64 (m), 4.61 (d, major, J = 11.3 Hz), 4.59 (d, major, J = 11.0 Hz), 4.54-4.45 (m), 4.14 (dt, major, J = 9.8, 3.4 Hz), 4.09-3.95 (m), 3.98 (dd, major, J = 9.5, 3.8 Hz), 3.90-3.86
(m), 3.81 (s, major), 3.80 (s, major), 3.74 (t, major, \(J = 9.7\) Hz), 3.67-3.59 (m), 3.46-3.28 (m), 3.24 (t, major, \(J = 9.2\) Hz), 3.11-3.07 (m), 2.83 (br s, -OH major), 1.34 (d, \(J = 6.2\) Hz), 1.32 (d, \(J = 6.4\) Hz), 1.31 (d, \(J = 6.3\) Hz), 1.27 (d, \(J = 6.5\) Hz), 1.26 (d, major, \(J = 6.3\) Hz) ppm; \(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 125 MHz) \(\delta\) 160.0, 159.96, 157.4 (q, \(J_{C-F} = 37.0\) Hz), 131.0, 130.8, 130.6, 130.5, 130.4, 130.2, 129.9, 116.4 (q, \(J_{C-F} = 287.3\) Hz), 114.5, 114.3, 114.2, 114.1, 95.7, 93.5, 92.8, 92.4, 91.6, 91.4, 84.4, 83.6, 80.2, 79.8, 79.5, 79.0, 77.0, 75.4, 75.3, 75.2, 74.7, 72.6, 72.2, 71.8, 71.5, 68.1, 67.9, 67.6, 58.2, 55.7, 54.9, 52.2, 51.5, 36.3, 30.2, 18.6, 18.4, 18.3, 18.1 ppm; IR (thin film) v 3279 (br), 2911, 1708, 1613, 1562, 1515, 1303, 1251, 1187, 1068, 1035, 820 cm\(^{-1}\); Anal. Calcd for C\(_{24}\)H\(_{28}\)NO\(_7\)F\(_3\): C, 57.71; H, 5.65; N, 2.80. Found: C, 57.55; H, 5.90; N, 2.56.

TLC \(R_f = 0.31-0.21\) (2:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.49-7.46 (m), 7.39-7.35 (m), 6.72 (br s, -NH), 6.56 (br s, -NH), 6.60 (s), 5.57 (s), 5.56 (s), 5.22 (t, \(J = 3.5\) Hz), 5.14-5.12 (m), 4.38-4.18 (m), 4.12-4.03 (m), 3.84-3.65 (m), 3.58 (dt, \(J = 9.7, 4.9\) Hz), 3.27 (d, \(J = 4.0\) Hz), 2.91 (dd, \(J = 3.4, 1.6\) Hz), 2.88 (d, \(J = 3.7\) Hz), 2.59-2.56 (m), 2.35-2.26 (m), 2.17-2.14 (m), 2.03-1.89 (m) ppm; \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 157.7 (q, \(J_{C-F} = 37.6\) Hz), 156.8 (q, \(J_{C-F} = 37.7\) Hz), 136.9, 136.8, 129.3, 128.4, 126.1, 126.0, 115.58 (q, \(J_{C-F} = 288.0\) Hz), 115.56 (q, \(J_{C-F} = 287.8\) Hz), 102.24, 102.15, 102.1, 102.0, 94.2, 92.1, 74.13, 74.07, 73.6, 71.0, 70.0, 68.5, 64.6, 50.3, 50.2, 49.71, 49.65, 31.6, 29.4, 27.9, 27.3 ppm; IR (thin film) v 3393, 3276 (br), 2860, 1700, 1553, 1169, 1098, 1028, 968, 906, 701 cm\(^{-1}\); Anal. Calcd for C\(_{15}\)H\(_{16}\)NO\(_5\)F\(_3\)(0.25 H\(_2\)O): C, 51.21; H, 4.72; N, 3.98. Found: C, 51.21; H, 4.87; N, 3.75.
**N-Trifluoroacetyl-2-galactosamine thioglycoside.** A 10 mL schlenk flask was flushed with N₂ and charged with glycal (28 mg, 0.1 mmol), 2,6-di-tert-butyl-4-methylpyridine (39 mg, 0.1 mmol, 1 equiv) and 300 μL of CH₂Cl₂. Freshly distilled TFAA (50 μL, 0.35 mmol, 3.5 equiv) was then added. A solution of (saltmen)Mn(N) (0.04 M, 2.5 mL, 0.1 mmol, 1 equiv) in CH₂Cl₂ was drawn into a 2.5 mL gas-tight syringe and transferred dropwise with the aid of a syringe pump to the mixture of TFAA and glycal (7 h addition period). The resulting dark brown solution was cooled to −78 °C and thiophenol was added dropwise (50 μL, 0.5 mmol, 5 equiv), followed by BF₃•OEt₂ (50 μL, 0.4 mmol, 4 equiv). The reaction was allowed to warm over a 12 h period to 23 °C, at which time 200 mg of silica gel and 200 mg of Celite were added along with 5 mL of n-pentane. The slurry was stirred vigorously for 15–20 min before being filtered through a 20 x 40 mm plug of silica gel using Et₂O (2 x 10 mL) as eluent. Concentration of the filtrate under reduced pressure afforded a pale yellow which was purified by chromatography on silica gel (gradient elution: 7:1→3:1 hexanes/EtOAc) to give the thioglycoside product as a colorless oil (18 mg, 36%). TLC Rₜ = 0.18 (4:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 500 MHz) δ 7.52 (dd, 2H, J = 7.6, 1.8 Hz), 7.37-7.24 (m, 8H), 6.51 (br s, 1H), 5.06 (d, 1H, J = 10.7 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.43 (dd, 1H, J = 8.2, 5.2 Hz), 4.24 (dd, 1H, J = 5.2, 2.0 Hz), 4.07-4.04 (m, 1H), 3.87-3.79 (m, 2H), 3.62-3.56 (m, 1H), 1.47 (s, 3H), 1.34 (s, 3H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 157.3 (q, Jₛ₋ₐ = 37.5 Hz), 138.0, 132.5, 132.2, 129.0, 128.4, 128.1, 127.7, 127.6, 115.5 (q, Jₛ₋ₐ = 288.4 Hz), 110.5, 84.3, 76.0, 75.4, 73.5 (t, J = 7.3 Hz), 73.2, 69.4, 55.3, 28.1, 26.2 ppm; IR (thin film) ν 3307 (br), 3063, 2872, 1704, 1558, 1374, 1217, 1166, 1080, 1028, 861, 742, 694 cm⁻¹; HRMS (FAB⁺) calcd for C₂₄H₂₆SNO₅F₃ 497.1483, found 520.1376 (MNa⁺).
General procedure for the preparation of Schiff base ligands: To a solution containing 1° amine (12.0 mmol) in 30 mL of absolute EtOH was added salicylaldehyde (12.0 mmol, 1 equiv). The resulting bright yellow solution was heated to reflux for 5 h. Following this time, the reaction was allowed to cool slowly to 23 °C. In certain cases, direct crystallization of the ligand from the reaction mixture was observed, and the desired product could be isolated upon filtration. When crystallization did not occur, the yellow solution was concentrated under reduced pressure to afford a dark, viscous orange oil. Purification through a short plug (40 x 100 mm) of neutral Al₂O₃ (Brockmann, activity I) with 4:1 hexanes/EtOAc as eluent typically afforded the product ligand as a yellow solid (60–70%).

Physical data for select Schiff base ligands:

H–3MeO–sal–Me. ¹H NMR (CDCl₃, 500 MHz) δ 8.32 (t, 1H, J = 1.0 Hz), 6.90 (dd, 1H, J = 7.9, 1.3 Hz), 6.86 (dd, 1H, J = 7.7, 1.4 Hz), 6.78 (t, 1H, J = 7.8 Hz), 3.90 (s, 3H), 3.63 (dq, 2H, J = 7.3, 1.0 Hz), 1.32 (t, 3H, J = 7.3 Hz) ppm.; ¹³C NMR (CDCl₃, 125 MHz) δ 164.0, 152.7, 148.5, 122.6, 118.1, 117.3, 113.5, 55.8 (d, J = 3.4 Hz), 52.9, 16.0 ppm; IR (thin film) ν 2971, 1631, 1469, 1336, 1253, 1091, 968, 736 cm⁻¹.
**H–^3^MeO–sal–Ph.** $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.44 (s, 1H), 7.37-7.32 (m, 4H), 7.31-7.27 (m, 1H), 6.94 (dd, 1H, $J = 8.0, 1.3$ Hz), 6.92 (dd, 1H, $J = 7.9, 1.3$ Hz), 6.83 (t, 1H, $J = 7.9$ Hz), 4.83 (s, 2H), 3.91 (s, 3H) ppm; IR (thin film) $\nu$ 2832, 1630, 1464, 1254, 1079, 1028, 736, 697 cm$^{-1}$.

**H–^3^Me–sal–^3^Pr.** $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.30 (s, 1H), 7.18 (d, 1H, $J = 7.2$ Hz), 7.11 (d, 1H, $J = 6.9$ Hz), 6.79 (t, 1H, $J = 7.5$ Hz), 3.43 (d, 2H, $J = 6.4$ Hz), 2.29 (s, 3H), 2.01-1.94 (m, 1H), 0.99 (d, 6H, $J = 6.6$ Hz) ppm; IR (thin film) $\nu$ 2958, 1631, 1458, 1272, 1248, 1086, 1038, 846, 772, 747 cm$^{-1}$.

**H–^3^Ph–sal–^3^Pr.** $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 14.35 (s, 1H, -OH), 8.37 (s, 1H), 7.63 (dd, 2H, $J = 8.3, 1.0$ Hz), 7.44 (t, 2H, $J = 7.7$ Hz), 7.40 (dd, 1H, $J = 7.6, 1.7$ Hz), 7.35-7.30 (m, 1H), 7.27-7.25 (m, 1H), 6.95 (t, 1H, $J = 7.6$ Hz), 3.44 (dd, 2H, $J = 6.5, 1.0$ Hz), 1.99-1.93 (m, 1H), 0.98 (d, 6H, $J = 6.7$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 164.8, 158.9, 137.8, 133.0, 130.5, 129.7, 129.2, 128.0, 126.9, 118.7, 118.1, 67.1, 29.5, 20.4 ppm; IR (thin film) $\nu$ 3057, 2959, 2871, 2651 (br), 1634, 1609, 1498, 1454, 1435, 1387, 1290, 1098, 1038, 833, 758, 697 cm$^{-1}$.
H–^3^Ph–sal–Ph.  ^1^H NMR (CDCl\textsubscript{3}, 500 MHz) \( \delta \) 14.07 (s, 1H, -OH), 8.52 (s, 1H), 7.63 (dd, 2H, \( J = 8.2, 1.2 \text{ Hz} \)), 7.45-7.41 (m, 3H), 7.36-7.28 (m, 7H), 6.98 (t, 1H, \( J = 7.6 \text{ Hz} \)), 4.83 (s, 2H) ppm; ^1^3C NMR (CDCl\textsubscript{3}, 125 MHz) \( \delta \) 165.6, 158.4, 137.9, 137.6, 133.2, 130.8, 129.7, 129.2, 128.5, 128.0, 127.7, 127.3, 127.0, 118.8, 118.5, 63.0 ppm; IR (thin film) v 3029, 2882, 2651 (br), 1630, 1610, 1496, 1453, 1433, 1378, 1290, 1262, 1101, 1028, 832, 757, 696 cm\(^{-1}\).

**General procedure for the preparation of (\(^3^R–sal–R’\))\(_2\)Mn\textsuperscript{III}(OAc) products:** To a solution of H–\(^3^R–sal–R’\) (8.7 mmol, 2 equiv) in 40 mL of absolute EtOH at \(~75 \text{ °C} \) was added Mn(OAc)\(_2\)\( \cdot 4\text{H}_2\text{O} \) (4.3 mmol). The resulting dark brown solution was heated at reflux for 2.5 h, during which time the solution turned olive green and a precipitate was deposited. The reaction was slowly cooled to \(~-20 \text{ °C} \) and allowed to stand at this temperature for 12 h. The product was collected upon filtration of the cold solution and the green microcrystalline solid rinsed with cold 95% aq. EtOH (yields range from 60–80%). In certain cases, crystals suitable for X-ray diffraction were obtained by diffusing \( n \)-pentane into EtOAc or CH\(_2\)Cl\(_2\) solutions of the complex. Alternative methods which included Mn(acac)\(_2\)N\(_3\) in CH\(_3\)CN or MnCl\(_2\)\( \cdot 4\text{H}_2\text{O}/\text{KOH} \) in EtOH were utilized for the synthesis of (\(^3^R–sal–R’\))\(_2\)Mn(III) azide and chloride complexes, respectively. The effectiveness of either of these protocols, however, was found to vary with each ligand employed.
Mn(3Ph–sal–Ph)2OAc
IR (KBr) v 3029, 1631, 1619, 1555, 1452, 1422, 1397, 1316, 1280, 1225, 1104, 1030, 860, 761 cm⁻¹. HRMS (FAB⁺) calcd for MnC₄₂H₃₅N₂O₄ 686.1978, found 627.1843 (M–OAc).

Mn(3Ph–sal–jPr)2OAc
IR (KBr) v 2961, 2867, 1620, 1588, 1558, 1423, 1393, 1311, 1285, 1030, 864, 765 cm⁻¹. HRMS (FAB⁺) calcd for MnC₃₆H₃₉N₂O₄ 618.2291, found 559.2160 (M–OAc).

Mn(3MeO–sal–Me)₂N₃
IR (KBr) v 2926, 2052 (–N₃), 1620, 1598, 1555, 1472, 1449, 1302, 1253, 1226, 1093, 978, 863, 738 cm⁻¹.

Mn(3MeO–sal–Ph)₂N₃
IR (thin film) v 2931, 2046 (–N₃), 1610, 1555, 1470, 1448, 1296, 1251, 1224, 1080, 864, 738 cm⁻¹.

Mn(3Ph–sal–jPr)₂N₃
IR (KBr) v 2958, 2047 (–N₃), 1615, 1588, 1558, 1448, 1423, 1312, 1284, 1227, 1030, 861 cm⁻¹.

**General procedure for the preparation of (3R–sal–R')₂MnV(N) products:** A solution of (3R–sal–R)₂MnX (X = OAc, Cl or N₃, 1.8 mmol) in 60 mL of CH₂Cl₂ was cooled to −45 °C and N–bromosuccinimide (9.0 mmol, 5 equiv) was added in a single portion. The dark brown solution was stirred at −45 °C for 5 min before anhydrous NH₃ was bubbled into the reaction mixture. The dark color began to lighten upon addition of NH₃, and, within 30 sec, the flow of NH₃ was ceased. The solution stirred at −45 °C for < 5 min
before 75 mL of a saturated aq. NH₄Cl solution was added. The frozen mixture was warmed to 23 °C and extracted with 2 x 35 mL CH₂Cl₂. The organic extracts were washed with 4 x 75 mL H₂O, dried over Na₂SO₄ and concentrated under reduced pressure to a brown oily residue. Purification through a short plug of neutral Al₂O₃ (Brockmann, activity I) with CH₂Cl₂ as eluent afforded the desired product as a brown foam (60–70%).

\textbf{Mn(}³\textbf{Ph–sal–Ph)}₂\textbf{N}

$^{1}$H NMR (CDCl₃, 500 MHz) δ 7.64 (s, 2H), 7.46 (dd, 4H, $J = 8.0$, 1.1 Hz), 7.34-7.30 (m, 6H), 7.29-7.20 (m, 8H), 7.05 (dd, 2H, $J = 7.8$, 1.8 Hz), 6.92 (dd, 4H, $J = 7.5$, 1.6 Hz), 6.74 (t, 2H, 7.5 Hz), 4.06 (d, 2H, $J = 15.0$ Hz), 3.66 (d, 2H, $J = 15.1$ Hz) ppm; IR (thin film) ν 3027, 1627, 1589, 1560, 1495, 1448, 1426, 1402, 1314, 1283, 1229, 1110, 1071, 1045 (Mn≡N), 1029, 860, 756, 698 cm⁻¹. HRMS (FAB⁺) calcd for MnC₄₀H₃₂N₃O₂ 641.1875, found 641.1875 (M⁺).

\textbf{Mn(}³\textbf{Ph–sal–iPr)}₂\textbf{N}

$^{1}$H NMR (CDCl₃, 500 MHz) δ 7.64 (s, 2H), 7.50 (d, 4H, $J = 7.0$ Hz), 7.35-7.30 (m, 6H), 7.26-7.23 (m, 2H), 7.12 (dd, 2H, $J = 7.8$, 1.7 Hz), 6.76 (t, 2H, $J = 7.5$ Hz), 3.10 (dd, 2H, $J = 11.7$, 4.2 Hz), 2.62-2.58 (m, 2H), 1.82 (t, 2H, $J = 11.1$ Hz), 0.78 (d, 6H, $J = 6.5$ Hz), 0.40 (d, 6H, $J = 6.6$ Hz) cm⁻¹; IR (thin film) ν 2956, 1627, 1590, 1561, 1448, 1426, 1313, 1284, 1229, 1045 (Mn≡N), 860, 756 cm⁻¹.
Appendix One:

Tables of Crystallographic Data and Collection Parameters, Positional Parameters, Bond Lengths, Bond Angles, and Anisotropic Thermal Factors for (salen)Mn(N)
**X-Ray Crystallographic Data and Structure Refinement for (salen)Mn(N)**

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<th>Property</th>
<th>Value</th>
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</thead>
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<td>MnC₁₆H₁₄N₃O₂</td>
</tr>
<tr>
<td>Formula weight</td>
<td>335.24</td>
</tr>
<tr>
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<tr>
<td>Solvent of crystallization</td>
<td>CH₂Cl₂</td>
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<tr>
<td>Type of diffractometer</td>
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</tr>
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<td>293(2) K</td>
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<tr>
<td>Wavelength</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>b = 12.313(3) Å, β = 103.61(3)°</td>
</tr>
<tr>
<td></td>
<td>c = 12.857(4) Å, γ = 90°</td>
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<td>Volume</td>
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<tr>
<td>Z</td>
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</tr>
<tr>
<td>Density (calculated)</td>
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<tr>
<td>Absorption coefficient</td>
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<td>Crystal Size</td>
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<td>Data/restraints/parameters</td>
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<tr>
<td>GOF on F²</td>
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<tr>
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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Largest diff. peak and hole</td>
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<td>Lattice parameter determination</td>
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<td>Value</td>
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<td>$(\Delta/\sigma)_{\text{max}}$ in final least squares cycle</td>
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The structure was solved by direct methods with SHELXS-86. The positions of all the non-hydrogen atoms were apparent in the solution. Hydrogen atoms were added at calculated positions and included as riding atoms.

The structure was refined with $1/\sigma^2$ weights. Decay and absorption corrections were not applied. A total of 4023 observations were merged to 1781 unique reflections with $R_{\text{merge}} = 3.8\%$ and $\text{GOF}_{\text{merge}} = 1.05$. 
Table 1. Atomic coordinates (x $10^2$) and equivalent isotropic displacement parameters (Å$^2$ x $10^2$) for (salen)Mn(N). U(eq) is defined as one third of the trace of the orthogonalized U(ij) tensor.

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<th>y</th>
<th>z</th>
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<td>3819(2)</td>
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Table 2. Bond lengths (Å) for (salen)Mn(N).

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<td>Bond</td>
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Table 3. Bond angles (°) for (salen)Mn(N).

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<th>Bond</th>
<th>Angle (°)</th>
<th>Bond</th>
<th>Angle (°)</th>
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Table 4. Anisotropic displacement parameters (Å² x 10³) for (salen)Mn(N). The anisotropic displacement factor exponent takes the form: -2π²[h²a*²U(11) + ... + 2hka*b*U(12)].

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<th>U(33)</th>
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Table 5. Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (Å² x 10³) for (salen)Mn(N).

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<th>atom</th>
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<th>z</th>
<th>U(eq)</th>
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<td>2206(4)</td>
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<td>80</td>
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<td>5440(4)</td>
<td>80</td>
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<td>-277(4)</td>
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<td>80</td>
</tr>
<tr>
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<td>1662(4)</td>
<td>2403(3)</td>
<td>50</td>
</tr>
<tr>
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<td>2514(4)</td>
<td>3108(3)</td>
<td>50</td>
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<tr>
<td>H(11A)</td>
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<td>383(3)</td>
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<td>2334(3)</td>
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<td>H(15B)</td>
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</table>
Appendix Two:

Tables of Crystallographic Data and Collection Parameters, Positional Parameters, Bond Lengths, Bond Angles, and Anisotropic Thermal Factors for (³Ph-sal-³Pr)₂Mn(OAc)
X-Ray Crystallographic Data and Structure Refinement for (\textsuperscript{3}Ph–sal–\textsuperscript{1}Pr\textsubscript{2})Mn(OAc)

Empirical formula: MnC\textsubscript{36}H\textsubscript{39}N\textsubscript{2}O\textsubscript{4}

Formula weight: 618.63

Crystal color: dark green

Crystal shape: bladed

Solvent of crystallization: EtOAc/pentane

Type of diffractometer: Enraf-Nonius Cad-4

Data collection method: Omega

Temperature: 293(2) K

Wavelength: 0.71073 Å MoK\textalpha

Crystal system: Monoclinic

Space group: C2/c

Unit cell dimensions:

\begin{align*}
\text{a} &= 14.588(3) \text{ Å} \quad \alpha = 90^\circ \\
\text{b} &= 15.996(3) \text{ Å} \quad \beta = 108.62(3)^\circ \\
\text{c} &= 14.712(3) \text{ Å} \quad \gamma = 90^\circ \\
\end{align*}

Volume: 3253.3(11) Å\textsuperscript{3}

Z: 4

Density (calculated): 1.263 g/cm\textsuperscript{3}

Absorption coefficient: 0.446 mm\textsuperscript{-1}

F(000): 1304

Crystal size: 0.29 x 0.45 x 0.48 mm

Theta range for data collection: 2.0–25.0°

Index ranges: -17 \leq h \leq 17, -18 \leq k \leq 18, -17 \leq l \leq 0

Reflections collected: 6433

Independent reflections: 2859

Refinement method: Full-matrix least-squares on F\textsuperscript{2}

Data/restraints/parameters: 2843/0/270

GOF on F\textsuperscript{2}: 2.135

Final R indices [I>2\sigma(I)]: R\textsubscript{1} = 0.0334, wR\textsubscript{2} = 0.0748

R indices (all data): R\textsubscript{1} = 0.0443, wR\textsubscript{2} = 0.0806

Largest diff. peak and hole: 0.177 and -0.242 e-/Å\textsuperscript{3}
Lattice parameter determination
Number of standard reflections
Interval (minutes)
$(\Delta/\sigma)_{\text{max}}$ in final least squares cycle
Average shift/error
Absorption correction
Variation of standards
R$_{\text{merge}}$
GOF$_{\text{merge}}$
Structure solution program
Primary solution method
Secondary solution method
Hydrogen placement
Structure refinement program
Treatment of hydrogen atoms
Disorder present

# of reflections = 25
range = $11.4^\circ \leq \theta \leq 13.3^\circ$
3
60
0.001
0.000
None
none within counting statistics
2.1%
1.19
SHELXS-86 (Sheldrick, 1990)
Patterson method
Difference Fourier maps
Difference Fourier maps
SHELXL-93 (Sheldrick, 1993)
unrestrained except for acetate methyl acetate methyl hydrogens
Table 1. Atomic coordinates (x 10^2) and equivalent isotropic displacement parameters (Å^2 x 10^2) for (3Ph-sal-^3Pr)2Mn(OAc). U(eq) is defined as one third of the trace of the orthogonalized U(ij) tensor.

<table>
<thead>
<tr>
<th>atom</th>
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<th>y</th>
<th>z</th>
<th>U(eq)</th>
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</thead>
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<td>7500</td>
<td>47(1)</td>
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<tr>
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<td>5241(1)</td>
<td>7435(1)</td>
<td>53(1)</td>
</tr>
<tr>
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<td>4424(1)</td>
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Table 2. Bond lengths (Å) for (3Ph-sal-^3Pr)2Mn(OAc).

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<tr>
<td>Mn-N(1a)</td>
<td>2.113(2)</td>
</tr>
<tr>
<td>Mn-N(1)</td>
<td>2.113(2)</td>
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<tr>
<td>Mn-O(50a)</td>
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<tr>
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<tr>
<td>Mn-C(50)</td>
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Table 3. Bond angles (°) for \( ^3 \text{Ph-sal-}^i \text{Pr}_2 \text{Mn(OAc)} \).

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<th>Angle (°)</th>
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Table 4. Anisotropic displacement parameters (Å² x 10⁴) for (³Ph-sal-⁻¹Pr)₂Mn(OAc).

The anisotropic displacement factor exponent takes the form:

\[-2\pi²[h²a*²U(11) + ... + 2hka*b*U(12)].\]

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Table 5. Hydrogen coordinates (x \times 10^4) and isotropic displacement parameters (Å^2 x 10^3) for \((^3\text{Ph-sal-}^3\text{Pr})_2\text{Mn(OAc)}\).

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<th>z</th>
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<td>161</td>
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<td>7970(6)</td>
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Appendix Three:

Tables of Crystallographic Data and Collection Parameters, Positional Parameters, Bond Lengths, Bond Angles, and Anisotropic Thermal Factors for ($^3$MeO-sal-Me)$_2$Mn(N)
X-Ray Crystallographic Data and Structure Refinement for (\(3^\text{MeO-sal-Me}\))Mn(N)

Empirical formula: MnC\(_{20}\)H\(_{24}\)N\(_{3}\)O\(_{4}\)

Formula weight: 425.36

Crystal color: pale brown

Crystal shape: prism

Solvent of crystallization: Et\(_2\)O/pentane

Type of diffractometer: Siemens P4

Temperature: 163 K

Wavelength: 0.71073 Å, MoK\(\alpha\)

Crystal system: Orthorhombic

Space group: Fdd2

Unit cell dimensions:
\[ a = 14.693(2) \, \text{Å} \quad \alpha = 90^\circ \]
\[ b = 23.268(3) \, \text{Å} \quad \beta = 90^\circ \]
\[ c = 11.6940(10) \, \text{Å} \quad \gamma = 90^\circ \]

Volume: 3997.9(7) Å\(^3\)

Z: 8

Density (calculated): 1.413 g/cm\(^3\)

Absorption coefficient: 0.691 mm\(^{-1}\)

\(F(000)\): 1776

Crystal size: 0.33 x 0.30 x 0.26 mm

Theta range for data collection: 2.4–25.0°

Index ranges: 0 ≤ h ≤ 17, 0 ≤ k ≤ 27, 0 ≤ l ≤ 13

Reflections collected: 1533

Independent reflections: 931

Refinement method: Full-matrix least-squares on \(F^2\)

Data/restraints/parameters: 931/1/177

GOF on \(F^2\): 1.062

Final R indices [\(I>2\sigma(I)\)]: \(R_1 = 0.0199, \, wR_2 = 0.0523\)

R indices (all data): \(R_1 = 0.0218, \, wR_2 = 0.0536\)

Largest diff. peak and hole: 0.199 and -0.177 e/Å\(^3\)

Lattice parameter determination: # of reflections = 34
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<td>$(\Delta/\sigma)_{\text{max}}$ in final least squares cycle</td>
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<td>Absorption correction</td>
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<tr>
<td>Decay of standards</td>
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<tr>
<td>Final weighting scheme</td>
<td>$w = 1/[\sigma^2(F^2) + (0.0398P)^2 + 1.313P]$ where $P = (F^2 + 2F^2)/3$</td>
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<tr>
<td>Structure solution program</td>
<td>SHELXTL (version 5.03)</td>
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<td>Structure refinement program</td>
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range $= 5.22^\circ \leq \theta \leq 12.48^\circ$
Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for (^3MeO–sal–Me)_2Mn(N). U(eq) is defined as one third of the trace of the orthogonalized U(ij) tensor.

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<th>z</th>
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Table 2. Bond lengths (Å) for (^3MeO–sal–Me)_2Mn(N).

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<td>Mn(1)-O(1a)</td>
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<td>Mn(1)-N(2)</td>
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<td>Mn(1)-N(2a)</td>
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Table 3. Bond angles (°) for \((^3\text{MeO-sal-Me})_2\text{Mn(N)}\).

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Symmetry transformations used to generate equivalent atoms: -x, -y, z

Table 4. Anisotropic displacement parameters (Å² x 10³) for \((^3\text{MeO-sal-Me})_2\text{Mn(N)}\). The anisotropic displacement factor exponent takes the form: \(-2\pi²[h^2a^2*U(11) + ... + 2hka*b*U(12)]\).

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Table 5. Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (Å² x 10³) for (³MeO–sal–Me)₂Mn(N).