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

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

A dissertation presented by

Justin Du Bois

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1997

(Submitted March 7, 1997)

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 $[Cr(OAc)_2 \bullet H_2O]_2$ 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 $Mn^{V} \equiv N$ 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.

My arrival at Caltech more than four and one-half years ago seems so distant, and yet much of the "early days" remains quite vivid in my memory. As I sprinted through the halls of Church trying to keep pace with a tremendously spirited assistant professor, I can remember being both exhilarated and exhausted. I will always recall these times fondly and am forever grateful to my research advisor, Professor Erick Carreira, for instilling in me his passion and emotion. He has been a teacher, a support staff, a motivator, and a friend. He has given me the opportunity to express myself and the freedom to explore and learn from experience, all the while providing expert advice and encouragement. I am also grateful to his wife, Andrea, for her continuous support, encouragement, and friendship. The Carreira group is fortunate to have such a wonderful "group mom."

I have incredibly fond memories of my undergraduate experience at Berkeley. It was there that I first became excited about chemistry. Much of the credit for this belongs to my benevolent undergraduate advisor, Professor Ken Raymond, and members of his

group, Drs. Torin Dewey, Andrew Borovik, Dan Stack, and Tim Karpishin. Their guidance, patience, friendship and confidence in me will always be remembered. At Berkeley, I met my good friend and roommate of many years, Norma Tom. I am grateful to her for so much, but most of all for inspiring me with her work ethic and her tenacity.

I have been extremely fortunate to have worked with many talented people while at Caltech. Mike, Curtis, Jason, Craig, Mary, Jay, Tehshik, Drs. Don, Guido, Gavin, Yuntae, and Wheeseong have been wonderful friends and colleagues and have provided most of the memories I will carry with me forever. I owe special thanks to Craig for reinvigorating me with a first-year's excitement for chemistry. I cannot thank him enough for his supreme efforts on the nitrido project, his good-nature, and his sense of humor. My time at Caltech has been extremely rewarding because of my interaction and my friendship with Jason. He is an extraordinarily gifted individual whose excitement and wonderful inquisitiveness will no doubt take him to great heights. I would also like to thank Mary, Don, Mike, and Jay for their help with the preparation and careful proofing of this thesis.

My experience at Caltech would not have been the same had it not been for the stimulating (and often hilarious) interactions with Professor Harry Gray and members of his group, in particular Don Low and Chris Chang. Also to be included is Shannon Stahl (like me, another honorary Gray group member). I have been greatly rewarded by the friendship that I have shared with these individuals.

I cannot, of course, finish without expressing my sincerest appreciation to Daisy Joe, my confidant of many years. Her support of me has been unwavering; she has been my strength when times were hard, the voice of reason when I was irrational, and the greatest fan when I had success. From the days past at Berkeley through the long commute from Irvine to Pasadena, I have always been able to count on her for her laughter, her sensibility, and most of all her friendship.

To my family

and

in memory of a

wonderful grandfather

Table of Contents

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

List of Figures for Part I

List of Schemes and Tables for Part I

List of Figures for Part II

Chapter 1

Chapter 2

Chapter 3

List of Schemes and Tables for Part II

Chapter 1

Chapter 2

Chapter 3

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.[1] 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.[2] All members of this family display picomolar inhibition of mammalian squalene synthase, the enzyme responsible for mediating the first committed step in sterol biosynthesis.[3] Thus, these compounds have potential application as therapeutically useful serum cholesterol-lowering agents. The following

---

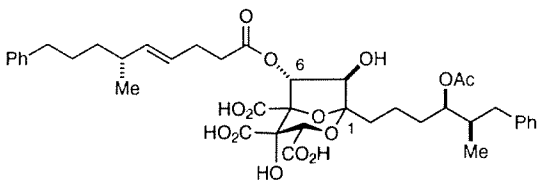
1. For leading references on the recent isolation, see: (a) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151. (b) Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P. A.; Watson, N. S. *J. Antibiot.* **1992**, *45*, 648. (c) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48* , 10221. (d) Dufresne, C.; Wilson, K. E.; Singh, S. B.; Zink, D. L.; Bergstrom, J. D.; Rew, D.; Polishook, J. D.; Meinz, M.; Huang, L. Y.; Silverman, K. C.; Lingham, R. B.; Mojena, M.; Cascales, C.; Pelaez, F.; Gibbs, J. B. *J. Nat. Prod.* **1993**, *56*, 1923.

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-dideoxy dioxabicyclooctane 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.

3. (a) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neil, M. J.; Shuttleworth, A.; Stylli, C.; Tait, M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639. (b) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. *J. Biol. Chem.* **1992**, *267*, 11705. (c) Hasumi, K.; Tachikawa, K.; Sakai, K.; Murakawa, S.; Yoshikawa, N.; Kumazawa, S.; Endo, A. *J. Antibiot.* **1993**, *46*, 689. (d) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Nallin-Omstead, M.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. *Proc. Nat. Acad. Sci. USA* **1993**, *90*, 80. (e) Lindsey, S.; Harwood, H. J., Jr. *J. Biol. Chem.* **1995**, *270*, 9083.

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



(+)–Zaragozic Acid C

1

Figure 1. (+)–Zaragozic Acid C.

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]

---

4. (a) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106. (b) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825. (c) For a recent, comprehesive review on both the chemistry and biology of the zaragozic acids, see: Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622.

5. Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. *Tetrahedron Lett.* **1993**, *34*, 399.

6. Byrne, K. M.; Arison, B. H.; Nallin–Omstead, M.; Kaplan, L. *J. Org. Chem.* **1993**, *58*, 1019.

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

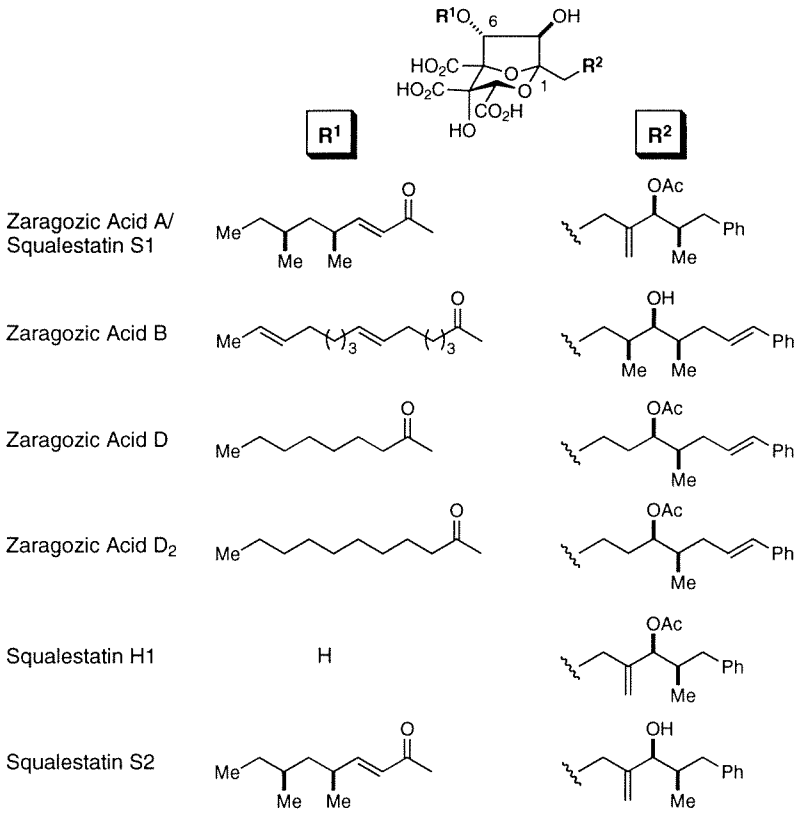


Figure 2. Selection of other known zaragozic acids and squalestatins.

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

---

7. Reports of model studies directed towards the total synthesis of the zaragozic acids/squalestatins include: (a) Paterson, I.; Feßner, K.; Finlay, M. R. V.; Jacobs, M. F. *Tetrahedron Lett.* **1996**, *37*, 8803. (b) Maezaki, N.; Gijsen, H. J. M.; Sun, L. Q.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 6685. (c) Caron, S.; McDonald, A. I.; Heathcock, C. H. *J. Org. Chem.* **1995**, *60*, 2780. (d) Kraus, G. A.; Maeda, H. *J. Org. Chem.* **1995**, *60*, 2. (e) Gujar, M. K.; Das, S. K.; Sadalapur, K. S. *Tetrahedron Lett.* **1995**, *36*, 1933. (f) Gujar, M. K.; Das, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **1995**, *36*, 1937. (g) Gurjar, M. K.; Das, S. K.; Saha, U. K. *Tetrahedron Lett.* **1994**, *35*, 2241. (h) Brzezinski, L. J.; Levy, D. D.; Leahy, J. W. *Tetrahedron Lett.* **1994**, *35*, 7601. (i) Abdel–Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelley, M. J.; Lamont, R. B. Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1259. (j) McVinish, L. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 923. (k) Aggarwal, V. K.; Wang, M. F.; Zaparucha, A. *J. Chem. Soc. Chem. Comm.* **1994**, 87. (l) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Lamont, R. B.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc. Perkin*

second synthesis of (+)–zaragozic acid C have been accomplished by Nicolaou, Heathcock, and Evans respectively.[10,11]

Zaragozic acids A, B, and C exhibit potent inhibitory activity toward rat liver squalene synthase with apparent K_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.[1b,12] The squalestatins display similar efficacy towards both mammalian (rat liver) and microsomal (*Candida albicans*) squalene synthase. This enzyme is responsible for catalyzing a two-step reaction sequence in which farnesyl

---

Trans. 1 **1994**, 1259. (m) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc. Chem. Comm.* **1993**, 1839. (n) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Sidebottom, P. J.; Sik, V.; Slee, D. H.; Watson, N. S. *J. Chem. Soc. Chem. Comm.* **1993**, 1841.

8. For the preparation of analogs by directed biosynthesis, see: (a) Chen, T. S.; Petuch, B. ; MacConnell, J.; White, R.; Dezeny, G.; Arison, B.; Bergstrom, J. D.; Colwell, L.; Huang, L.; Monaghan, R. L. *J. Antibiotics* **1994**, *47*, 1290. (b) Cannell, R. J. P.; Dawson, M. J.; Hale, R. S.; Hall, R. M.; Noble, D.; Lynn, S.; Taylor, N. L. *J. Antibiotics* **1994**, *47*, 247.

9. For reports on the synthesis of the zaragozic acid sidechains, see: (a) Robichaud, A. J.; Berger, G. D.; Evans, D. A. *Tetrahedron Lett.* **1993**, *34*, 8403. (b) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261. (c) Parsons, J. G.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 8263.

10. Zaragozic acid A/Squalestatin S1, see: (a) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467. (b) Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; De Riccardis, F.; Nadin, A.; Leresche, J. E.; La Greca, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2184. (c) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; La Greca, S.; Tsuri, T.; Yue, E. W.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2187. (d) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2190. (e) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115. (f) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126.

11. Zaragozic acid C, see: Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 12111.

12. The zaragozic acids have also been investigated as inhibitors of farnesyl-protein transferase, see: (a) Gibbs, J. B.; Pompliano, D. L.; Mosser, S. D.; Rands, E.; Lingham, R. B.; Singh, S. B.; Scolnick, E. M.; Kohl, N. E.; Oliff, A. *J. Biol. Chem.* **1993**, *268*, 7617. (b) Tamanoi, F. *Trends Biol. Sci.* **1993**, *18*, 349.

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.[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

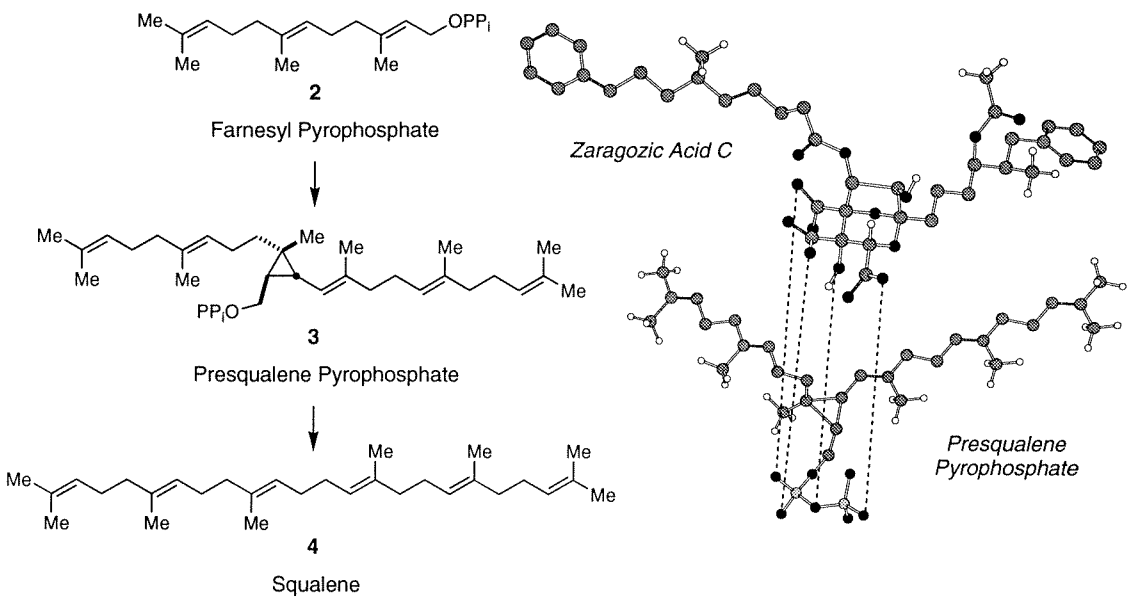


Figure 3. Structural comparison of presqualene pyrophosphate and zaragozic acid C.

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).[3d,15]

---

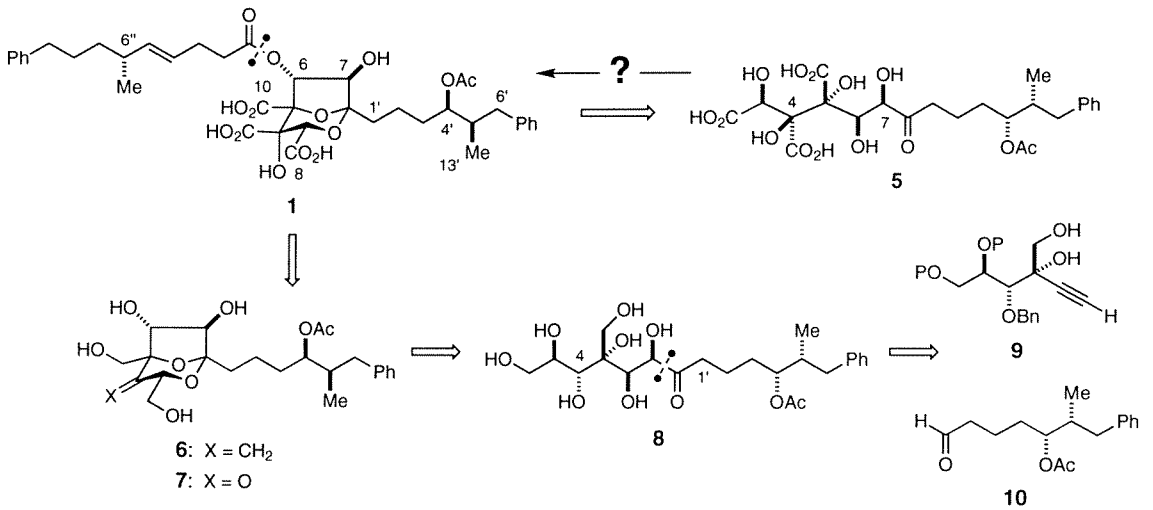
13. (a) Jarstfer, M. B.; Blagg, B. S. J.; Rogers, D. H.; Poulter, C. D. *J. Am. Chem. Soc.* **1996**, *118*, 13089. (b) Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70. (c) Poulter, C. D.; Rilling, H. C. *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L., Eds.; Wiley, New York, 1981, Vol. 1, Chapter 8.

14. For a recent investigation of non–head–to–tail isoprenoid biosynthesis by recombinant yeast squalene synthase, see: Zhang, D.; Poulter, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 1641.

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.* **1993**, *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

Scheme 1



dioxabicyclic ketal would give a functionalized acyclic precursor. As a consequence of these disconnections, the stereochemical complexity of the dioxabicyclooctane is

---

C.; Watson, N. S. *Tetrahedron Lett.* **1993**, *34*, 4357. (c) Chiang, Y. P.; Biftu, T.; Doss, G. A.; Plevyak, S. P.; Marquis, R. W.; Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Berger, G. D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2029. (d) Kuo, C. H.; Plevyak, S. P.; Biftu, T.; Parsons, W. H.; Berger, G. D. *Tetrahedron Lett.* **1993**, *34*, 6863. (e) Lester, M. G.; Evans, G. L.; Henson, R. A.; Procopiou, T. A.; Sareen, M.; Snowden, M. A.; Spooner, S. J.; Srikantha, A. A. P.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2683. (f) Shaw, R. E.; Burgess, C.; Cousins, R. P. C.; Giblin, G. M. P.; Livermore, D. G. H.; Shingler, A. H.; Smith, C.; Youds, P. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2155. (g) Cox, B.; Hudson, J. L.; Keeling, S. E.; Kirk, B. E.; Srikantha, A. R. P.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1931. (h) Kuo, C. H.; Robichaud, A. J.; Rew, D. J.; Bergstrom, J. D.; Berger, J. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1591. (i) Andreotti, D.; Procopiou, P. A.; Watson, N. S. *Tetrahedron Lett.* **1994**, *35*, 1789. (j) Sharratt, P. J.; Hutson, J. L.; Inglis, G. G. A.; Lester, M. G.; Procopiou, P. A.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 661. (k) Biftu, T.; Acton, J. J.; Berger, G. D.; Bergstrom, J. D.; Dufresne, C.; Kurtz, M. M.; Marquis, R. W.; Parsons, W. H.; Rew, D. R.; Wilson, K. E. *J. Med. Chem.* **1994**, *37*, 421. (l) Pompipom, M. M.; Girotra, N. N.; Bugianesi, R. L.; Roberts, C. D.; Berger, G. D.; Burk, R. M.; Marquis, R. W.; Parsons, W. H.; Bartizal, K. F.; Bergstrom, J. D.; Kurtz, M. M.; Onishi, J. C.; Rew, D. J. *J. Med. Chem.* **1994**, *37*, 4031. (m) Additional citations to this literature can be found in the references above.

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.[16] A synthetic route was developed which we hoped would avoid such competing processes.[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

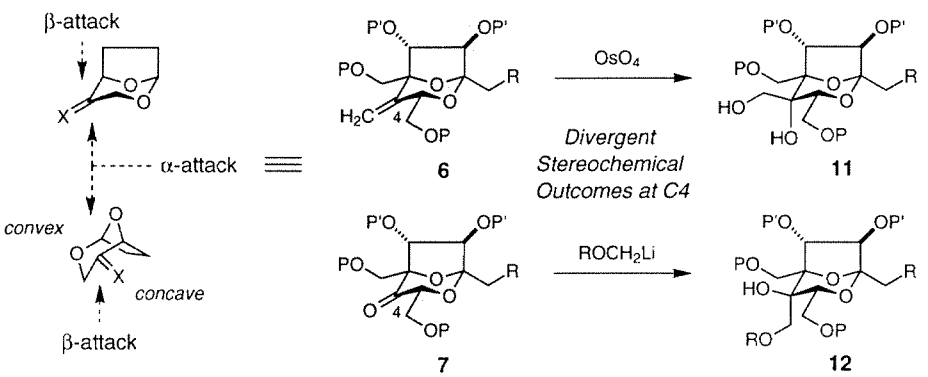


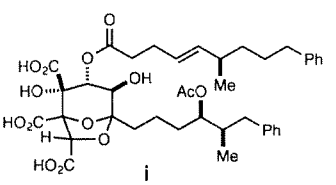
Figure 4. Functionalization of the dioxabicyclooctane core.

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

---

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

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–*arabo*ascorbic acid (H_2O_2/K_2CO_3, then H_3O^+).[18] Condensation of **13** with dimethylamine (MeOH, 0 °C) afforded the derived 2,3,4–trihydroxybutyramide which was selectively ketalized ($Et_2C(OMe)_2$, 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 carbanion additions. Treatment of **15** with ethoxyvinyl lithium (ethyl vinyl ether, ^{t}BuLi) 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 ^{1}H NMR spectroscopy.[19]

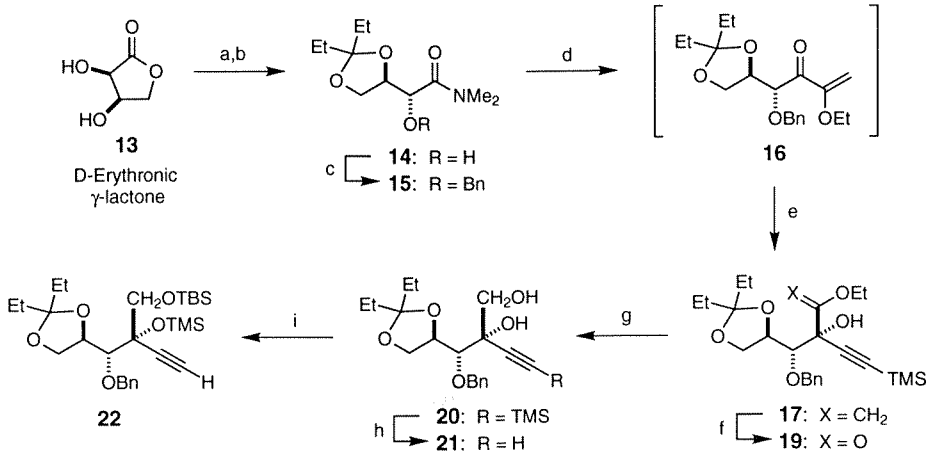
---

18. Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y.–Y.; Thom, E.; Liebmann, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661. D-*arabo*ascorbic acid is available from Aldrich Chemical Co.

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 ^{1}H 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) Me_2NH, MeOH, 0 °C, 97%; (b) $(MeO)_2CEt_2$, cat. TsOH, 90%; (c) NaH, BnBr, THF, 96%; (d) ethoxyvinyllithium, THF, –78 °C; (e) TMSC≡CMgBr, THF, –78 °C, 84%; (f) O_3, CH_2Cl_2/EtOH, –78 °C, 84%; (g) $NaBH_4$, MeOH; (h) K_2CO_3, MeOH, 78% in two steps; (j) *t*–$BuMe_2SiCl$, Et_3N, 4–DMAP, then Me_3SiCl, 88%.

form three different magnesium chelates **A**, **B**, and **C** (Figure 5).[20] 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).[21] 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

20. (a) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) For recent review of chelation-controlled additions to carbonyl compounds, see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (c) The preference for 1,2-chelates over 1,3-chelates has been noted, see: Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769; and Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.

21. Evans and co-wokers 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]

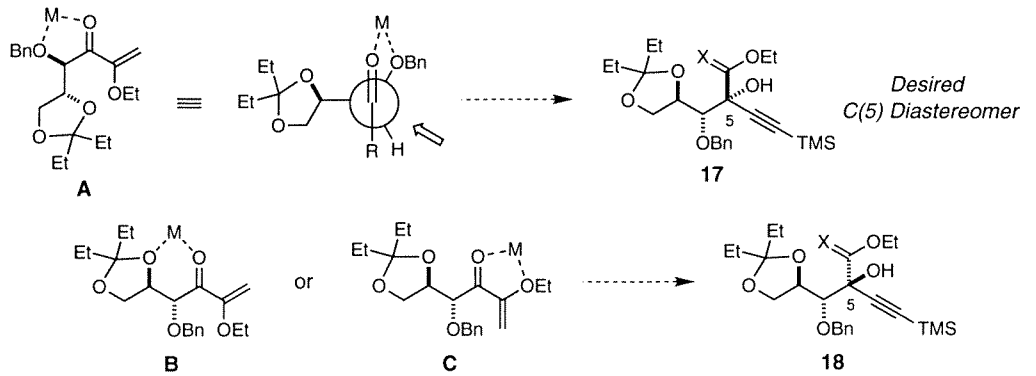


Figure 5. Stereoselective addition of TMSC≡CMgBr to **16**.

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 $NaBH_4$ 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 K_2CO_3 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 ^{t}BuMe$_2$SiCl (TBSCl) and Me$_3$SiCl (TMSCl), respectively. A solution of the diol, 4–DMAP, and Et_3N was initially treated with TBSCl and, upon consumption of **21** (as indicated by thin-layer chromatography), the reaction mixture was subsequently treated

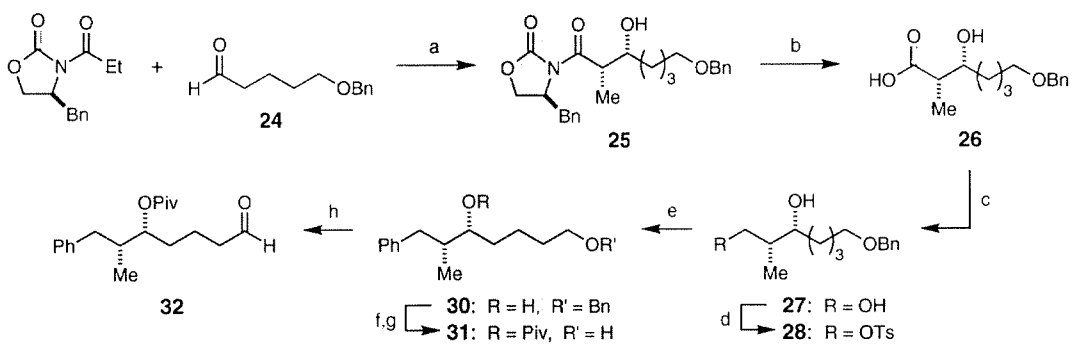
22. (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Reetz, M. T.; Hullman, M.; Setitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477.

23. For selective ozonolysis of vinyl ethers over other alkenes or alkynes, see: (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *46*, 1396. (b) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

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).[24] Treatment of 5-benzyloxypentanal (**24**) with the di–*n*–butylboryl enolate of *N*–propionyl (S)–benzyloxazolidinone gave the aldol adduct **25** in 97% diastereomeric excess (de), as determined by ^{1}H NMR spectroscopy. Hydrolysis of the auxiliary (LiOH, H_2O_2)[25] and reduction of the resulting acid **26** with $LiAlH_4$ furnished diol **27** as a white, crystalline solid (92% two steps).

Scheme 3



(a) 9–BBNOTf, *i*–Pr_2NEt, then H_2O_2, MeOH, 84%; (b) LiOH, H_2O_2, aq. THF; (c) $LiAlH_4$, THF, 92%; (d) TsCl, C_5H_5N, 0 °C, 89%; (e) PhLi, BF_3•OEt_2, 91%; (f) *t*–BuCOCl, 4–DMAP, CH_2Cl_2, 90%; (g) H_2, Pd/C, EtOAc, 99%; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%.

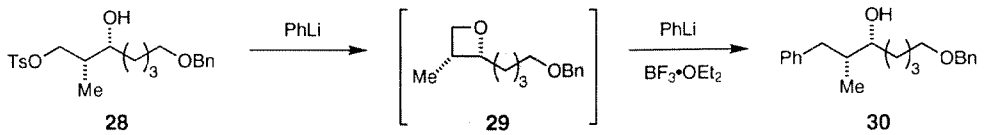
Replacement of the primary hydroxyl in **27** with the requisite phenyl substituent was effected following a two–step protocol that involved: (1) selective tosylation of the 1° carbinol (TsCl, C_5H_5N, 0 °C) to give **28**; and (2) *in situ* closure to oxetane **29** followed

---

24. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

25. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

by BF_3•OEt_2–promoted ring opening with phenyllithium (eq 1).[26] 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

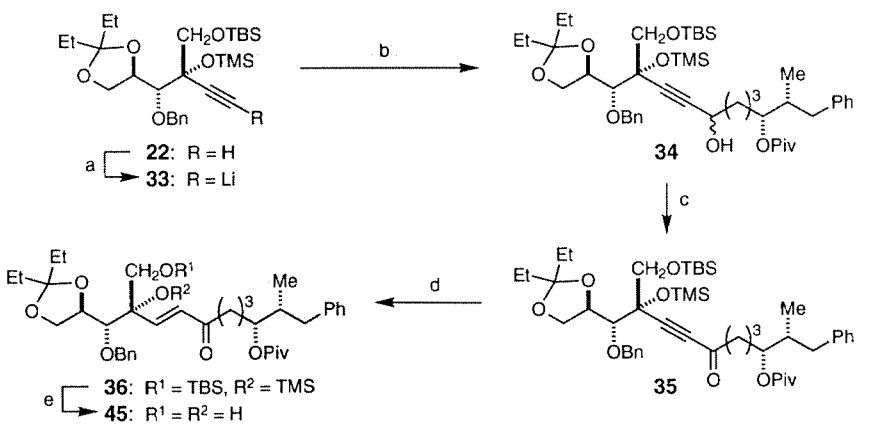


(1)

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**.[27]

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



(a) *n*–BuLi, THF, –45 °C; (b) **32**, LiBr, THF, 93%; (c) Dess-Martin periodinane, CH_2Cl_2; 93%; (d) $[Cr(OAc)_2•H_2O]_2$, THF/H_2O, 60%; (e) *n*–Bu_4NF, THF, 93%.

26. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

27. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

aldehyde **32** to a solution of acetylide **33** in either THF or Et_2O 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 $MgBr_2$ or $CeCl_3$ 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.

29. Attempts to couple an aldehyde or an acid chloride with the alkenyl metal species derived from hydrostannylation, hydrozirconation, or hydrozincation of acetylene **22** did not provide any of the allylic alcohol or enone product, respectively. For reports of palladium catalyzed hydrostannylation and alkenyl stannane coupling to acid chlorides, see: (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. For reports of additions of alkenyl zirconocene reagents to aldehydes catalyzed by $AgClO_4$, see: (c) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965. Transmetalations of alkenyl zirconocenes with either $CuBr{\bullet}SMe_2$ or $AlCl_3$ and subsequent coupling to acid chlorides have been documented, see: (d) Wipf, P.; Xu, W. *Synlett* **1992**, 718. (e) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. Addition of alkenylzinc reagents (derived by transmetalation of alkenyl boranes) to aldehydes has been reported, see: (f) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (g) Screbnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449.

30. van Rijn, P. E.; Mommers, S.; Visser, R. G.; Verkruijsse, H. D.; Brandsma, L. *Synthesis* **1981**, 459.

31. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) For an excellent procedure for the preparation of multi–gram quantities of the Dess–Martin reagent see: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

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 ynones to *trans* enones. Reagents known to effect this transformation include metal hydride species (e.g. Red-Al), dissolving metal reductions (Li/NH_3), and low–valent chromium salts ($CrSO_4$, $CrCl_2$).[32] Additionally, semireduction with H_2 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 $CrSO_4$ or $CrCl_2$ 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, $[Cr(OAc)_2{\bullet}H_2O]_2$ was used in place of either $CrSO_4$ or $CrCl_2$.[34] The use of $[Cr(OAc)_2{\bullet}H_2O]_2$ 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 OsO_4 under catalytic conditions (NMO, acetone/H_2O) proceeded very slowly (ca. 10% after 48 h at 23 °C).[35] The small amount

---

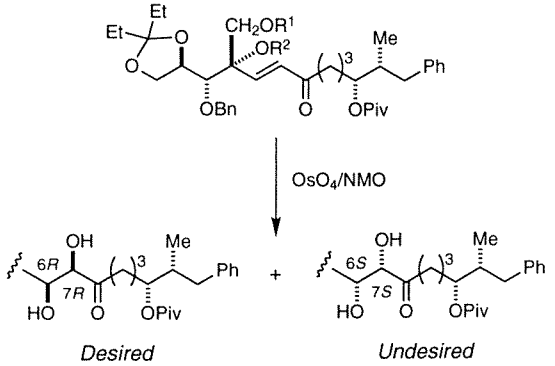
32. For the reduction of ynones with $CrSO_4$ and $CrCl_2$, see: (a) Smith, A. B., III; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184. Reduction of alkynols with Cr(II), see: (b) Castro, C. E.; Stephens, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 4358.

33. (a) A procedure for *in situ* preparation of $CrSO_4$ is described in reference 32a. (b) For the preparation and isolation of solid $CrSO_4$, see: Lux, H.; Illmann, G. *Chem. Ber.* **1958**, *91*, 2143.

34. $[Cr(OAc)_2{\bullet}H_2O]_2$ has been used to reduce α–haloketones and α–haloketoximines, 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. $[Cr(OAc)_2{\bullet}H_2O]_2$ is currently sold by Aldrich Chemical Co.

35. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

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



Substrate	R^1	R^2	Desired : Undesired
36	TBS	TMS	1 : 1 (**37**,**38**)
39	TBS	H	1 : 9 (**40**,**41**)
42	H	TMS	1 : 9 (**43**,**44**)
45	H	H	1.1 : 1 (**46**,**47**)
45[a]	H	H	1.7 : 1 (**46**,**47**)

(a) Reaction conducted with added $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$.

Figure 6. Summary of results for enone dihydroxylation reactions.

trimethylsilyl ether at C(5) ($ClCH_2CO_2H$, MeOH) and treatment of the resulting enone **39** with 10 mol% OsO_4 (NMO, acetone/H_2O) 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 $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ 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] It is

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%).

37. For a recent discussion of the asymmetric dihydroxylation reaction, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 243, and references therein.

38. (a) Sharpless has described a protocol for the dihydroxylation of α,β-unsaturated ketones with either $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ and $K_3Fe(CN)_6$ 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 benzoylation of the 1° alcohol in **45** with either 4-methoxybenzoyl chloride (4–DMAP, Et_3N, CH_2Cl_2) or 2-nitrobenzoic acid (DCC, DMAP) gave the corresponding esters **48** and **49**, respectively.[39] Subjection

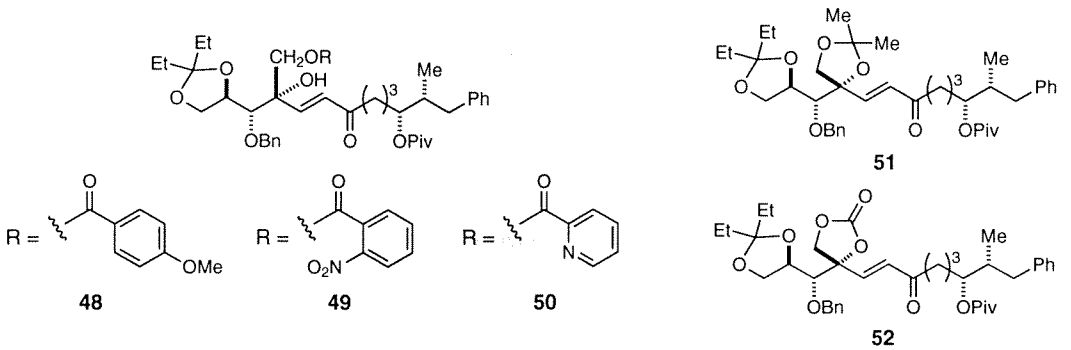


Figure 7. Alternative enone substrates for dihydroxylation.

of either of these compounds to standard dihydroxylation conditions (OsO_4, NMO, acetone/H_2O/^{t}BuOH) furnished mixtures of carbinol products (1.3–1.8:1 by ^{1}H NMR spectroscopy) favoring the desired 6*R*,7*R* 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 OsO_4, 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.

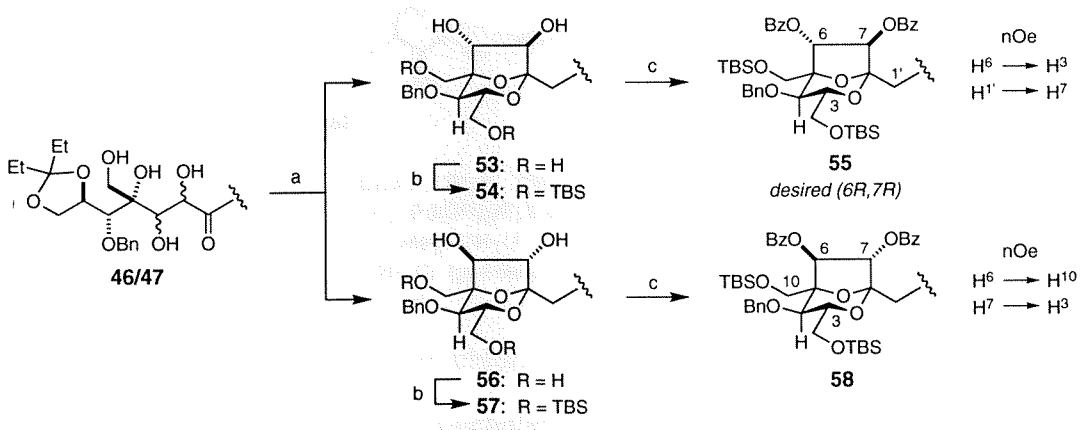
39. The dramatic effect of an allylic *p*–methoxybenzoyl ester on the enantioselectivity of olefin dihydroxylation by OsO_4 has been reported, see: Corey, E. J.; Guzman–Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109.

Treatment of **45** with 2-methoxypropene (PPTS, CH_2Cl_2) cleanly provided the isopropylidene ketal **51**. Reaction of **51** with OsO_4 yielded a 1:2.2 mixture of desired/undesired diol products (6*R*, 7*R*)/(6*S*, 7*S*). In contrast, dihydroxylation of the cyclic carbonate **52**, derived from treatment of **45** with triphosgene (C_5H_5N, 0–25 °C), gave a 2.2:1 mixture of diols favoring the desired (6*R*,7*R*) 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 (6*R*,7*R*) 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

Scheme 5



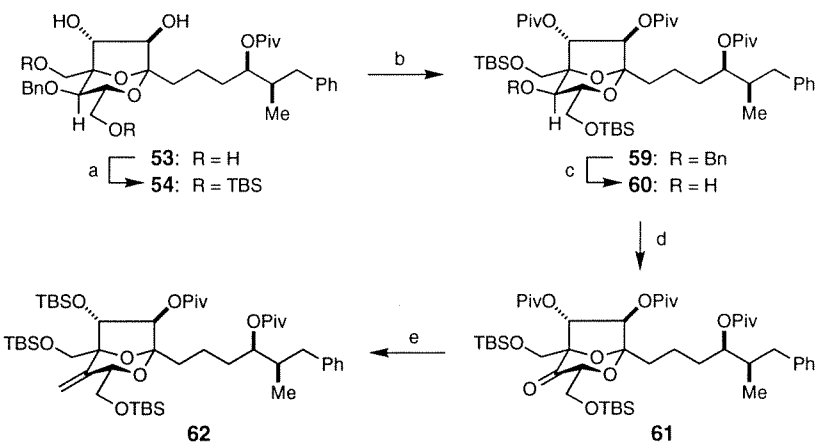
(a) HCl, MeOH; (b) *t*-$BuMe_2SiCl$, 4–DMAP, Et_3N, 86% in two steps; (c) $(PhCO)_2O$, 4–DMAP, 90%.

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, CH_2Cl_2) 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, Et_3N, 4–DMAP) furnished diol **54** (Scheme 6).

Scheme 6



(a) *t*–$BuMe_2SiCl$, 4–DMAP, Et_3N, CH_2Cl_2, 74%; (b) *t*–BuCOCl, 4–DMAP, $ClCH_2CH_2Cl$, 97%; (c) H_2, $Pd(OH)_2/C$, $Pd/CaCO_3$, EtOH, 99%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%; (e) Me_3SiCH_2Li, LiBr, THF/HMPA, –78 °C; (f) 18–crown–6, $KN(SiMe_3)_2$, THF, –78→20 °C; (g) *t*–$BuMe_2SiOTf$, 2,6–lutidine, <35% in three steps.

Reaction of **54** with trimethylacetyl chloride (4–DMAP, $ClCH_2CH_2Cl$) gave triester **59** which was then subjected to hydrogenolysis (H_2, 1 atm, $Pd(OH)_2$–C, Pd–$CaCO_3$) to effect cleavage of the benzylic ether at C(4).[40] Swern oxidation of the resulting

40. $Pd/CaCO_3$ 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 Ph_3PCH_2;[42] (2) reaction with both Tebbe (Cp_2TiCl_2, Me_3Al)[43] and Nozaki (CH_2Br_2, Zn, $TiCl_4$) 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 ($TMSCH_2Li$) 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 °→–20 °C).[46] Although alkene **62** was prepared using this

---

41. (a) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, *15*, 1133. (b) Magnus, P. *Tetrahedron* **1983**, *39*, 867.

42. (a) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. (c) Corey, E. J.; Smith, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1038. (d) Still, W. C.; Tsai, M.–Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. (e) Fitjer, L.; Quabeck, U. *Syn. Commun.* **1985**, *15*, 855.

43. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Pettit, R. J.; Guibe, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.

44. (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *18*, 2417. (b) Lombardo, L. *Org. Syn.* **1987**, *65*, 81.

45. (a) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478. (b) Paquette, L. A.; Poupart, M. A. *J. Org. Chem.* **1993**, *58*, 4245.

protocol, the yields for both reactions were highly variable (5–35%) and were sensitive to the source and age of both the $TMSCH_2Li$ and the $KN(TMS)_2$ base.

Upon treatment of **62** with catalytic OsO_4 (NMO, acetone/^{t}BuOH) 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

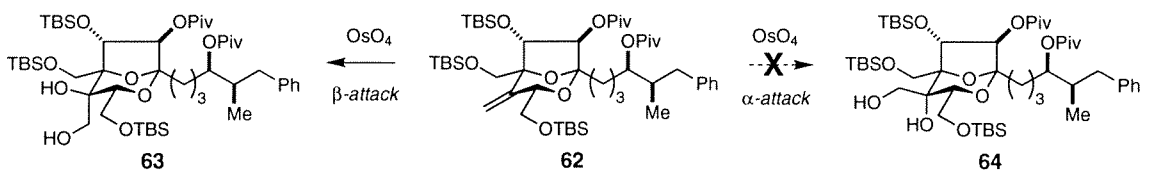


Figure 8. Dihydroxylation of olefin **62**.

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

---

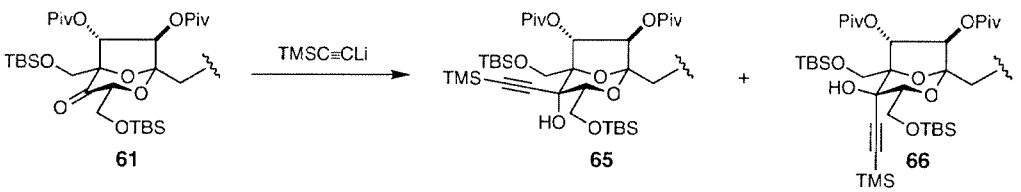
46. Under the conditions of the elimination, cleavage of both the C(10)–OTBS and C(6)–OPiv protecting groups was observed. The reason for the selective cleavage of these protecting groups is unclear at present. Reprotection with TBSOTf afforded **62**.

47. (a) Chiu, C. K-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311. (b) Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217. (c) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Grass, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. (d) Cross, E. B. *J. Chem. Soc. C* **1966**, 501. Dihydroxylation of a related, all–carbon [3.2.1]–ring system was reported to give the product arising exclusively from osmylation of the concave face, similar to our observations, see: Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 100.

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 $TMSCH_2Li$ added to **61** to give an approximately equal mixture of epimeric β–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

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



Entry	Conditions[a]	65:66[b]
1	THF	1.5 : 1
2	THF/TMEDA	1 : 2
3	Et_2O/150 equiv LiBr	1 : 1.7
4	Et_2O/diglyme	2.2 : 1
5	Et_2O/pyridine	2.1 : 1
6	Et_2O/1equiv LiBr	3.1 : 1
7	Et_2O	3.5 : 1
8	Et_2O/*i*-Pr_2NEt	3.8 : 1
9	Et_2O/Et_3N	4.3 : 1
10	Et_2O/Me_3N	6.1 : 1

(a) Reactions were conducted at –78 °C with slow warming to 0 °C in a 1:1 mixture of cosolvents with the exception of entry 5 (3:1 Et_2O/C_5H_5N). (b) The diastereoselectivity was determined by intergration of the ^1H NMR C(6) methine resonances for **65** and **66** at δ 5.51 and 5.72 ppm, respectively.

desilylation ($AgNO_3$), to furnish the corresponding desired acetylenic alcohol **67** (Scheme 7).[49]

The effect of both co-solvents and additives on the diastereochemical outcome of the lithium acetylide reaction was investigated (Table 1).[50] When **61** was added to a

49. For the use of $AgNO_3$ in the deprotection of silylacetylenes, see: Schimdt, H. M.; Arens, J. F. *Recl. Trav. Chim. Pays–Bas.* **1967**, *86*, 1138.

50. Addition of either TMSC≡CMgBr or the alkynyl metal reagents derived by transmetallation of the lithium acetylide with $CeCl_3$, Me_3Al, $BF_3{\cdot}OEt_2$, $YbCl_3$, or $Ti(O^iPr)_4$ 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 Et_2O 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.[51] 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 diastereochemical outcome of this reaction.[52] When an ethereal solution of ketone **61** was added to a suspension of TMSC≡CLi in 1:1 Et_2O/Me_3N 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 (Et_3N, $^iPr_2NEt$) 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.[53] Cryoscopic measurements and ^6Li and ^{13}C NMR studies reveal that in solution this dimer is in equilibrium with other tetrameric aggregates.[54] Further work by Fraenkel has established qualitatively the

---

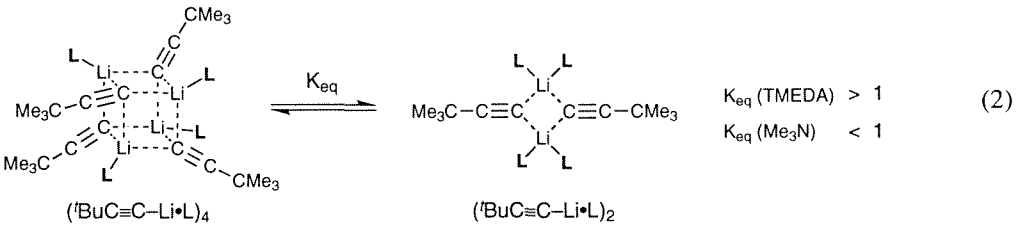
51. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

52. The effect of Et_3N 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.

53. (a) Schubert, B.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 496. (b) Schubert, B.; Weiss, E. *Chem. Ber.* **1983**, *116*, 3212. (c) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta.* **1983**, *66*, 308.

54. (a) Hässig, R.; Seebach, D. *Helv. Chim. Acta.* **1983**, *66*, 2269. (b) Bauer, W.; Seebach, D. *Helv. Chim. Acta.* **1984**, *67*, 1972.

effect of solvent and additives on the $[^tBuC{\equiv}CLi{\bullet}L_x]_2 \rightarrow [^tBuC{\equiv}CLi{\bullet}L_y]_4$ equilibrium (eq 2).[55] 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.



(2)

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 $BF_3{\bullet}OEt_2$ (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.[56] 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).[57] 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

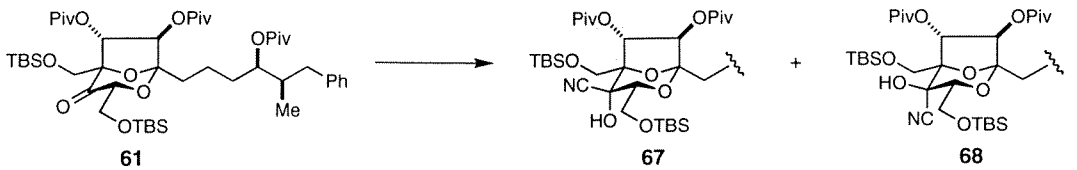
---

55. (a) Fraenkel, G.; Pramanik, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1527. (b) Fraenkel, G. *Polym. Prep., Am. Chem. Soc. Div. Polym. Chem.* **1986**, *27*, 132. (c) The crystal structure of $[^tBuC{\equiv}CLi{\bullet}THF]_4$ has been reported, see: Geissler, M.; Kopf, J.; Schubert, B.; Weiss, E.; Neugebauer, W.; von Rague Schleyer, P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 587.

56. It is unclear whether TBS–cleavage occured 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.



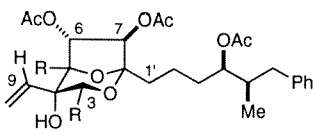
Conditions	67:68
HCN	1:3.2
TMSCN–CsF	4.5:1

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.[58] 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]



76: R = $CO_2{}^tBu$

nOe:

$H^3 \rightarrow H^6 = 9.7\%$ $H^6 \rightarrow H^9 = 12.2\%$

$H^3 \rightarrow H^9 = 3.1\%$ $H^{1'} \rightarrow H^7 = 3.3\%$

$H^6 \rightarrow H^3 = 11.0\%$

Figure 10. ^1H 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 (CH_2Cl_2/toluene) effected removal of all three trimethylacetyl esters (Scheme 7).[59] Subsequent exposure of the resulting tetraol **70** to excess Ac_2O (4–DMAP, CH_2Cl_2) furnished **71** and installed the requisite acetate at C(4').

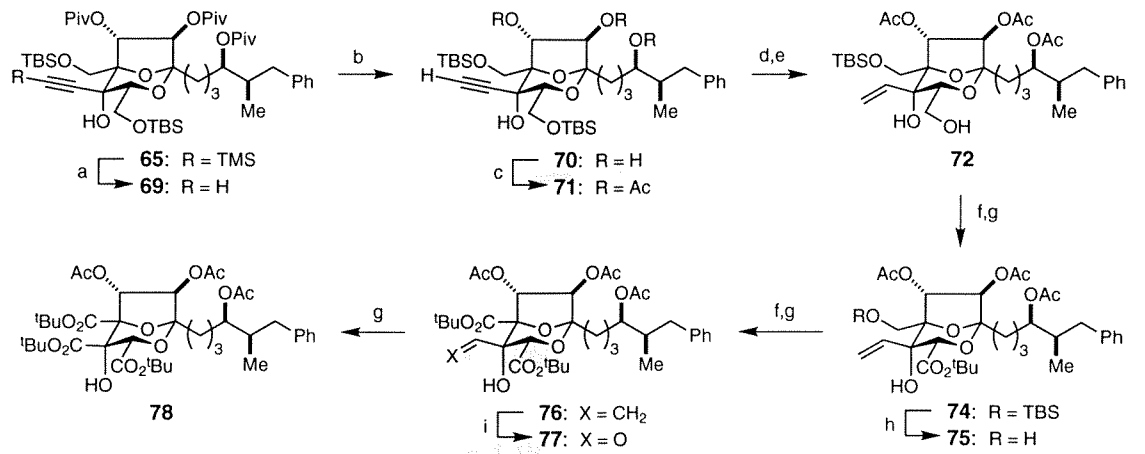
In our first synthesis of zaragozic acid C, the oxidations at C(8), C(9), and C(10) were performed in a stepwise manner to give the dioxabicyclooctane-tricarboxylate ester **78**. To this end, intermediate **71** was exposed to mildly acidic conditions (Cl_2CHCO_2H, MeOH) to effect selective cleavage of the C(8)–OTBS ether. Semihydrogenation of the terminal acetylene (H_2, 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 $NaClO_2$ solution (NaH_2PO_4, β–isoamylene, THF/H_2O).[60] Esterification of the unpurified acid with *N,N'*–diisopropyl–*O*–*tert*-butylisourea **73** afforded the *tert*-butyl

59. The use of Dibal–H in CH_2Cl_2/toluene proved to be critical for the successful cleavage of the pivaloate esters. Reactions in either THF or Et_2O failed to remove all three pivaloates.

60. (a) Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (c) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.

ester **74**.[61] Following a similar sequence of steps, the TBS– ether at C(10) was cleaved (HF•pyridine, THF/pyridine)[62] to give alcohol **75** which was oxidized, and subsequently esterified to give the bis(*tert*-butyl) ester **76**.

Scheme 7



(a) $AgNO_3$, 2,6–lutidine, 90%; (b) Dibal–H, CH_2Cl_2/toluene, 84%; (c) Ac_2O, 4–DMAP, CH_2Cl_2, 94%; (d) Cl_2CHCO_2H, MeOH, 90%; (e) H_2, Pd/C, C_5H_5N, 99%; (f) Dess-Martin periodinane, CH_2Cl_2, 80–95%; (g) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF/H_2O then *N,N'*–diisopropyl–*O*–*tert*–butylisourea (**73**), CH_2Cl_2, 70–85%; (h) HF•pyr, THF/C_5H_5N, 90%; (i) O_3, CH_2Cl_2/MeOH, 97%.

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_3CN or Cl_3CCO_2H 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_3N•3HF (CH_3CN) and *n*-Bu_4NF•$2H_2O$/HF (aqueous CH_3CN)[63] were examined and yielded similar mixtures of **75** and **79**. Deprotection under basic

61. For a review on the synthetic application of isoureas, see: Mathias, L. J. *Synthesis* **1979**, *11*, 561.

62. For the preparation of HF•pyridine buffered with excess pyridine in THF, see: Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

63. Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400.

conditions with *n*-Bu_4NF (THF) or *n*-$Bu_4NF{\bullet}2H_2O$ (CH_3CN) also resulted in the formation of **79** and, additionally, led to extensive product decomposition.

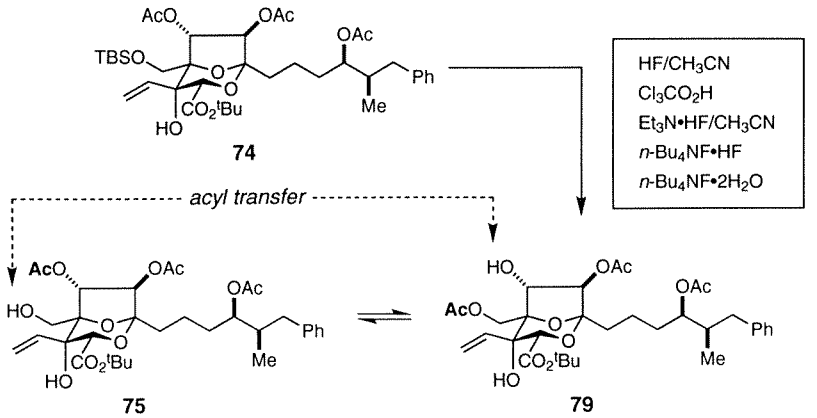
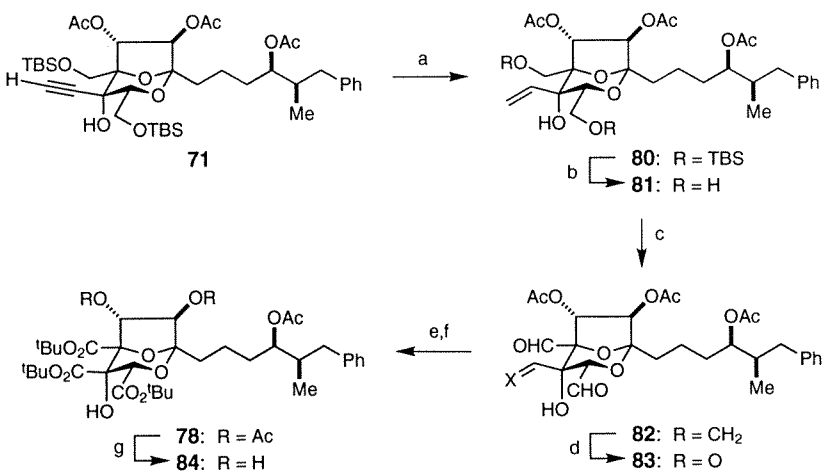


Figure 11. Reagents which promote C(6)–OAc to C(10)–OH acyl migration.

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_5H_5N; (b) HF•pyr, THF/C_5H_5N, 64% in two steps; (c) Dess-Martin periodinane, CH_2Cl_2/C_5H_5N, 93%; (d) O_3, CH_2Cl_2/MeOH, –78 °C; (e) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF/H_2O; (f) *N,N'*–diisopropyl–*O*–*tert*–butylisourea (**73**), CH_2Cl_2, 72% in three steps; (g) K_2CO_3, MeOH, 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_2Cl_2/MeOH, –78 °C) followed by reductive workup with Ph_3P provided **83**.[64] 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_2CO_3 in MeOH (0.5 h) yielded **84**.[1a]

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**.[65] Sharpless asymmetric epoxidation of **87** provided the epoxy alcohol **88** in > 95% ee, as determined by analysis of the ^1H NMR spectrum of the corresponding Mosher (S)–MTPA ester.[66,67] Regioselective epoxide opening with Me_3Al using conditions described by Roush and

---

64. The ^1H NMR spectrum of **83** shows a mixture of at least three products presumed to be hydrated forms of the trialdehyde.

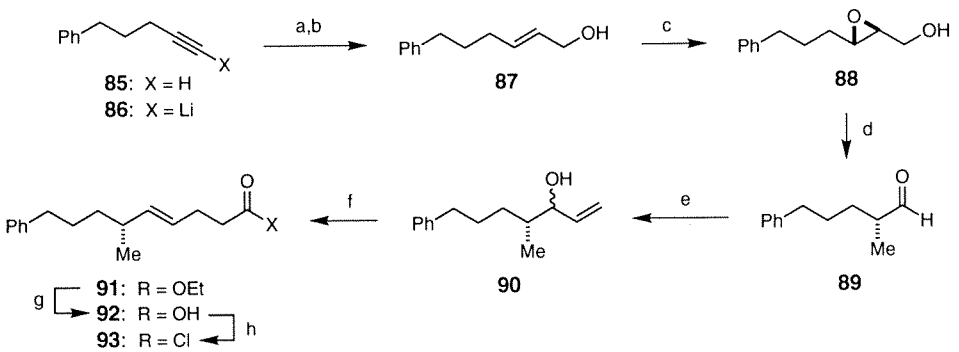
65. Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.

66. Gao, R.; Hanson, J.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

67. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Nozaki for related epoxy alcohols, followed by $NaIO_4$ cleavage of the resulting 1,2–diol yielded **89**.[68] 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



(a) *n*–BuLi, $(CH_2O)_n$, THF, 92%; (b) $LiAlH_4$, Et_2O, 79%; (c) *t*–BuOOH, $Ti(O^iPr)_4$, L–(+)–DIPT, 4Å MS, CH_2Cl_2, 98%; (d) Me_3Al then $NaIO_4$, aq. THF; (e) vinylmagnesium bromide, THF, 62% in three steps; (f) $(EtO)_3CMe$, H^+, 89%; (g) NaOH, THF/H_2O, 100%; (h) $(COCl)_2$, cat. DMF, CH_2Cl_2.

Model Studies with Zaragozic Acid A. Previously, it was shown that treatment of **84** (4–DMAP, CH_2Cl_2) with acid chloride **93** prepared from **92** afforded a 1:3 mixture of desired C(6) to undesired C(7) regioisomers, respectively.[4] 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.[69] In addition, hexanoyl chloride was employed as a surrogate acyl side chain (Scheme 10).

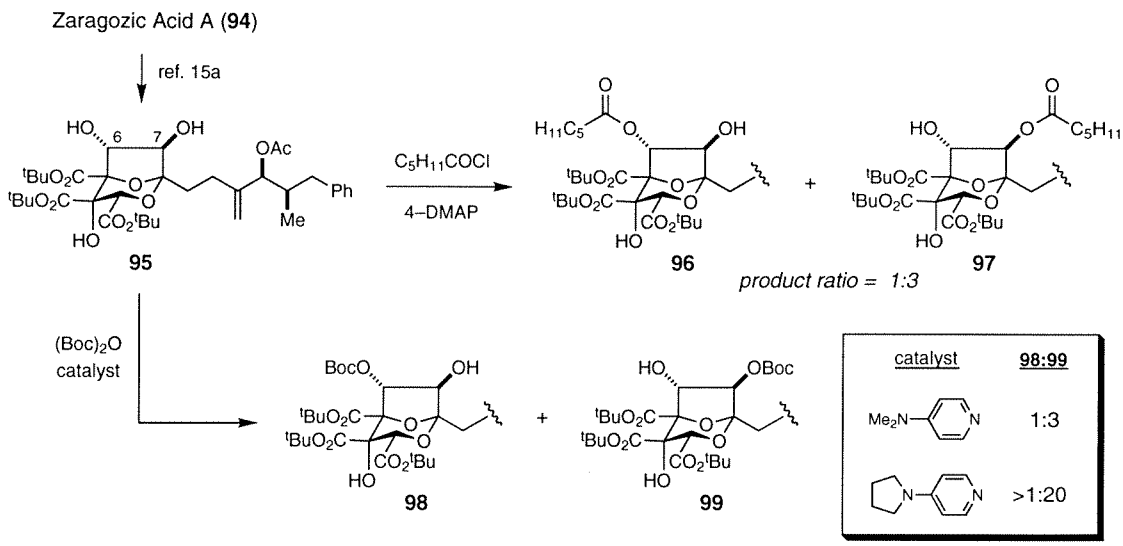
---

68. (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597. (b) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377.

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, CH_3CN) 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

Scheme 10



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).

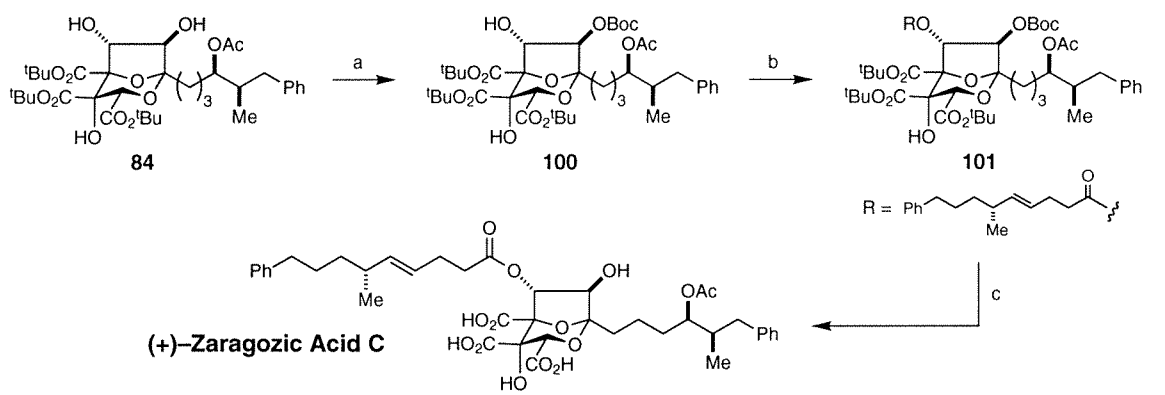
The development of a strategy which involved *in situ* protection of the C(7)–OH and subsequent acylation of the C(6) carbinol was then investigated and ultimately realized. Upon treatment of **95** with di–*tert*–butyl dicarbonate (Et_3N, CH_2Cl_2, 0 °C) and catalytic 4–DMAP, a ca. 1:3 mixture of C(6)/C(7)–carbonates **98** and **99** was isolated (52% combined) along with recovered starting material **95** (ca. 25%) and a small amount

70. Schwesinger, R.; Schlemper, H. *Angew. Chem., Ind. Ed. Engl.* **1987**, *26*, 1167.

(≤15%) of the bis-protected material.[71] 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%).[72] This highly regioselective transformation made it possible to perform the subsequent coupling of hexanoyl chloride (4–DMAP, Et_3N) to the C(6)–OH in a single operation.[73]

(+)–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_3N, CH_2Cl_2) gave **100** as the exclusive product (82%).

Scheme 11



(a) $(Boc)_2O$, 4–pyrrolidinopyridine, CH_2Cl_2, 82%; (b) **92**, DCC, 4–DMAP, CH_2Cl_2, 78%; (c) CF_3CO_2H, CH_2Cl_2, 100%.

Subsequent addition of a solution of carboxylic acid **92** and 1,3-dicyclohexyl carbodiimide (4–DMAP, CH_2Cl_2) furnished **101** (78%). Complete deprotection of **101** was effected with a 25% solution of trifluoroacetic acid in CH_2Cl_2 (16h) to afford the

---

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.[1c] Zaragozic acid C, prepared via the synthetic route described, was identical in all respects (^{1}H NMR, ^{13}C 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 $[Cr(OAc)_2 \cdot H_2O]_2$ 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.

---

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

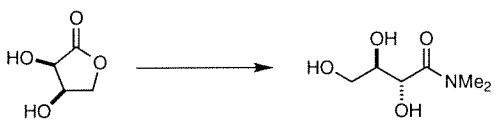
Experimental

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.[75] 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 ^{1}H and ^{13}C, respectively, and 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, coupling constant (Hz), and assignment (when indicated, numbered protons refer to zaragozic acid C numbering[1c]). Data for ^{13}C are reported in terms of chemical shift. ^{1}H NMR nOe difference spectra were recorded on degassed samples and were quantitated by

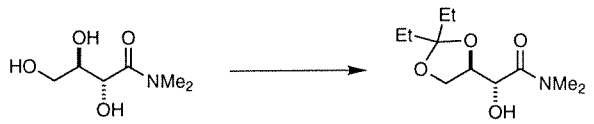
75. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

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.



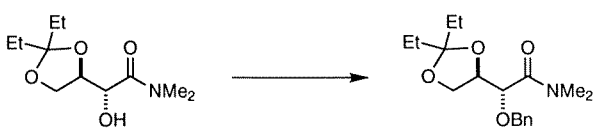
13

***N, N*-Dimethyl-2,3,4-trihydroxybutyramide.** Gaseous Me_2NH (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 γ-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_2O–CH_3CN 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; $[\alpha]_{Hg}$ -117.4° (*c* = 0.15, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 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, -NC*H*$_3$), 2.97 (s, 3H, -NC*H*$_3$) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 174.9, 74.8, 69.5, 64.2, 37.7, 36.2 ppm; IR (thin film) ν 3356 (br), 2936, 1629, 1508, 1401, 1257, 1064 cm^{-1}; Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03. Found: C, 44.12; H, 8.09.



14

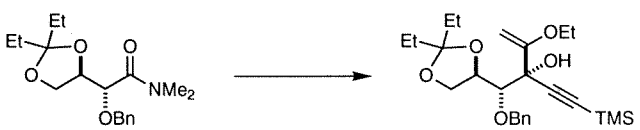
α–Hydroxyamide (14). To a solution of 3,3–dimethoxypentane (107 g, 809 mmol, 1.2 equiv) and anhydrous *p*-toluenesulfonic acid (5.5 g, 29 mmol, 0.04 equiv) in 1 L of THF was added *N,N*-dimethyl-2,3,4-trihydroxybutyramide (110 g, 674 mmol) portionwise. The pale yellow solution was heated at reflux for 4 h before being cooled to 23 °C. The reaction was made basic with 20.0 mL Et_3N 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_2Cl_2/EtOAc); $[\alpha]_{Hg}$ -27.8° (*c* = 0.18, CH_2Cl_2); ^1H 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, -NC*H*$_3$), 2.99 (s, 3H, -NC*H*$_3$), 1.69-1.59 (m, 2H, -C*H*$_2$CH$_3$), 1.54 (q, 2H, *J* = 7.4 Hz, -C*H*$_2$CH$_3$), 0.88 (t, 3H, *J* = 7.5 Hz, -CH$_2$C*H*$_3$), 0.81 (t, 3H, *J* = 7.4 Hz, -CH$_2$C*H*$_3$) 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.



14 15

α–Benzyloxyamide (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 H_2 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 K_2HPO_4, and the product extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with sat. aqueous NaCl (1 x 250 mL), dried over Na_2SO_4 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 R_f= 0.38 (1:1 hexanes/EtOAc); mp 55-56 °C; $[\alpha]_{Na}$ +136.8° (*c* = 0.23, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.27 (m, 5H, $H_{aromatic}$), 4.62 (d, 1H, *J* = 11.8 Hz, -C*H*$_2$Ph), 4.46 (d, 1H, *J* = 11.8 Hz, -C*H*$_2$Ph), 4.35 (dd, 1H, *J* = 13.1, 6.5 Hz, H_3), 4.28 (d, 1H, *J* = 6.4 Hz, H_4), 4.15 (dd, 1H, *J* = 8.4, 6.3 Hz, H_8), 3.93 (dd, 1H, *J* = 8.4, 7.0 Hz, H_8), 2.99 (s, 3H, -NC*H*$_3$), 2.97 (s, 3H, -NC*H*$_3$), 1.66-1.56 (m, 4H, both -C*H*$_2$CH$_3$), 0.85 (m, 6H, both -CH$_2$C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{27}NO_4$ 321.2120, found 321.1971; Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.09; H, 8.47; N, 4.12.



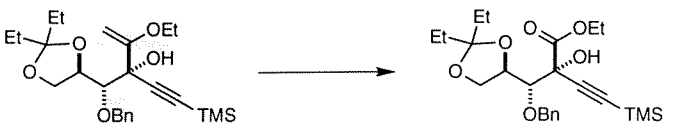
15 **17**

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

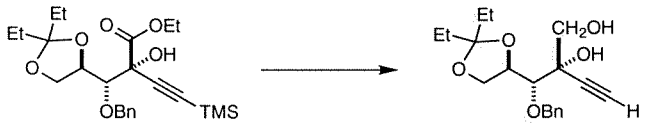
and stirred for an additional 2 h. The resulting colorless solution was re-cooled to –78 °C before a cold solution (0 °C) of amide **15** (33.2 g, 103 mmol) in 150 mL of THF was added dropwise. The mixture was then stirred at –78 °C for 10 min and then transferred via cannula into 500 mL of a vigorously stirred solution of 1:1 Et_2O/0.2 M aqueous Na_2CO_3 at 0 °C. The organic phase was separated and the aqueous layer extracted additionally with Et_2O (2 x 300 mL). The combined organic extracts were washed with sat. aqueous NaCl (1 x 400 mL), dried over Na_2SO_4 and concentrated to afford 36.0 g of an unpurified yellow oil **16**. TLC R_f = 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/Et_2O, 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 NH_4Cl. The organic phase was collected and the aqueous layer was extracted with 2 x 300 mL Et_2O. The organic extracts were combined, washed with sat. aqueous NaCl (1 x 500 mL), dried over Na_2SO_4 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 R_f = 0.59 (4:1 hexanes/EtOAc); mp 37-40 °C; $[\alpha]_{Na}$ + 71.9° (*c* = 0.41, CH_2Cl_2); ^1H NMR (C_6D_6, 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=CH_2), 4.93 (d, 1H, *J* = 10.8 Hz, -OCH_2Ph), 4.88 (d, 1H, *J* = 10.8 Hz, -OCH_2Ph), 5.70 (ddd, 1H, *J* = 9.0, 5.7, 2.9 Hz, H_3), 4.47 (d, 1H, *J* = 3.3 Hz, H_4), 4.18 (dd, 1H, *J* = 8.1, 6.2 Hz, H_8), 4.09 (t, 1H, *J* =8.3 Hz, H_8), 3.98 (d, 1H, *J* = 2.3 Hz, -C=CH_2), 3.39-3.34 (m, 2H, -OC$H_2$$CH_3$), 3.20 (s, 1H, -$OH_3$°), 1.74-1.62 (m, 4H, both -C$H_2$$CH_3$), 1.00 (t, 3H, *J* = 7.0 Hz, -OCH_2CH_3), 0.94 (t, 6H, *J* = 7.5 Hz, both -CH_2CH_3), 0.10 (s, 9H, H_{TMS}) ppm; ^{13}C NMR (CD_2Cl_2, 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,

66.7, 64.4, 30.3, 29.4, 14.8, 8.7, 8.5, 0.01 ppm; 3421 (br), 2973, 2940, 2170, 1654, 1628, 1498, 1458, 1376, 1251, 1130, 1072, 1058, 843, 759, 698 cm^{-1}; Anal. Calcd for $C_{25}H_{38}SiO_5$: C, 67.23; H, 8.57. Found: C, 67.32; H, 8.15.

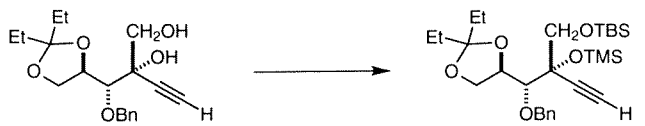


Alkynyl Ester (19). A solution of vinyl ether **17** (43.2 g, 96.7 mmol) in 450 mL of CH_2Cl_2 and 50 mL of absolute EtOH was cooled to –78 °C before being treated with a dilute stream of ozone in oxygen (0.8 mmol/min). Careful monitoring by TLC showed the reaction to be complete after 2.5 h (ca. 1 equiv O_3). 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). $[\alpha]_{Hg}$ +92.3° (*c* = 0.17, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.27 (m, 5H, $H_{aromatic}$), 5.03 (d, 1H, *J* = 11.1 Hz, -C*H*$_2$Ph), 4.77 (d, 1H, *J* = 11.1 Hz, -C*H*$_2$Ph), 4.41-4.36 (m, 1H, -OC*H*$_2$CH$_3$), 4.27 (m, 1H, H_3), 4.17 (m, 1H, -OC*H*$_2$CH$_3$), 4.09 (d, 1H, *J* = 5.9 Hz, H_4), 4.03 (dd, 1H, *J* = 8.2, 6.3 Hz, H_8), 3.73 (t, 1H, *J* = 8.1 Hz, H_8), 3.69 (s, 1H, -OH$_3$◦), 1.61-1.54 (m, 4H, both -C*H*$_2$CH$_3$), 1.32 (t, 3H, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 0.85 (m, 6H, both -CH$_2$C*H*$_3$), 0.16 (s, 9H, H_{TMS}) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{24}H_{36}SiO_6$ 448.2550, found 448.2271.



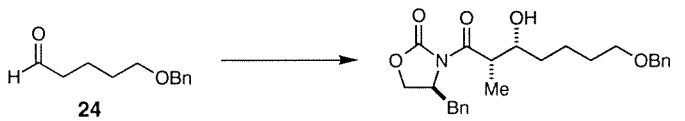
Core Fragment (21). A solution of the alkynyl ester **19** (36.2 g, 80.7 mmol) in 200 mL of CH_3OH was cooled to 0 °C, and $NaBH_4$ (9.1 g, 240 mmol, 3.0 equiv) was cautiously added portionwise. Once gas evolution had subsided, the mixture was warmed to 23 °C. After 2 h the reaction was re-cooled to 0 °C, diluted with 100 mL Et_2O 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_2Cl_2. The combined organic extracts were dried over Na_2SO_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_3OH was added solid K_2CO_3 (11.2 g, 80.7 mmol). The reaction was stirred for 8 h at 23 °C before 300 mL of Et_2O 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); $[\alpha]_{Na}$ +68.5° (c = 0.43, CH_2Cl_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_2Ph), 4.65 (d, 1H, J = 11.4 Hz, -CH_2Ph), 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≡C*H*), 2.35 (dd, 1H, J = 9.9, 4.4 Hz, -OH$_2$°), 1.67-1.60 (m, 4H, both -CH_2CH$_3$), 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.



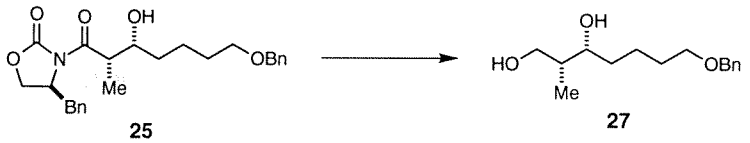
21 22

Core Fragment (22). To a solution of diol **21** (18.9 g, 56.5 mmol) in 250 mL of CH_2Cl_2 was added Et_3N (23.6 mL, 169.0 mmol, 3.0 equiv), $^tBuMe_2SiCl$ (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 Et_3N (23.6 ml) was added along with 700 mg of 4–DMAP and Me_3SiCl (10.7 ml, 84.8 mmol, 1.5 equiv). A precipitate formed immediately following addition of Me_3SiCl. After 30 min the pale red mixture was poured onto 200 mL of a 1.0 M K_2HPO_4 solution. The product was extracted into CH_2Cl_2 (3 x 100 ml), the combined extracts dried over Na_2SO_4 and concentrated to a red-brown oil. Purification by chromatography on silica gel (gradient elution: 30:1→20:1 hexanes/Et_2O) afforded 26.0 g (88%) of **22** as a colorless oil. TLC R_f = 0.65 (8:1 hexanes/EtOAc); $[\alpha]_{Hg}$ +150.0° (*c* = 0.17, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36 (dd, 2H, *J* = 7.4, 1.5 Hz, $H_{aromatic}$), 7.34-7.31 (m, 2H, $H_{aromatic}$), 7.28-7.26 (m, 1H, $H_{aromatic}$), 4.87 (d, 1H, *J* = 11.1 Hz, -C*H*$_2$Ph), 4.80 (d, 1H, *J* = 11.1 Hz, -C*H*$_2$Ph), 4.47 (ddd, *J* = 8.5, 6.6, 1.7 Hz, 1H, H_3), 4.13-4.06 (m, 3H, H_4, H_8), 3.78 (d, 1H, *J* = 10.3 Hz, H_{10}), 3.60 (d, 1H, *J* = 10.3 Hz, H_{10}), 2.47 (s, 1H, -C≡C*H*), 1.69-1.55 (m, 4H, both -C*H*$_2$CH$_3$), 0.94-0.87 (m, 6H, both -CH$_2$C*H*$_3$), 0.92 (s, 9H, $H_{TBS\text{-}tBu}$), 0.19 (s, 9H, H_{TMS}), 0.09 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{28}H_{48}Si_2O_5$ 520.3265, found 520.3045.



Aldol Adduct (25). To a solution of (*S*)–benzyloxazolidinone[24] (20.0 g, 85.7 mmol) in 400 mL of CH_2Cl_2 at –78 °C was added a solution of 25.5 g of 9-BBNOTf (94.3 mmol, 1.1 equiv) in 50.0 mL of CH_2Cl_2, followed by neat $^iPr_2NEt$ (20.9 mL, 120.0 mmol, 1.4 equiv). The mixture was allowed to stir for 30 min at –78 °C and was then warmed to 0 °C, where it was held for an additional 3 h. Upon re-cooling the contents to –78 °C, a cold solution (–78 °C) of aldehyde **24** (18.1 g, 94.3 mmol, 1.1 equiv) in 100 mL of CH_2Cl_2, was transferred via cannula to the reaction flask. The solution was allowed to warm slowly to 23 °C over 12 h. After cooling to 0 °C the reaction was diluted with 400 mL of MeOH and 90 mL of a 1.0 M aqueous K_2HPO_4–H_3PO_4 solution (pH 7). Careful addition of 180 mL of a 1:1 MeOH/30% H_2O_2 solution resulted in the formation of a milky white suspension which was stirred vigorously at 0 °C for 2 h. The mixture was partitioned between 400 mL of H_2O and 400 mL of CH_2Cl_2, the organic phase was collected and the aqueous layer extracted additionally with 2 x 400 mL CH_2Cl_2. The combined extracts were dried over Na_2SO_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); $[\alpha]_{Na}$ +101.9° (*c* = 0.41, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.33 (m, 6H, $H_{aromatic}$), 7.30-7.26 (m, 2H, $H_{aromatic}$), 7.20 (d, 2H, *J* = 7.2 Hz, $H_{aromatic}$), 4.72-4.68 (m, 1H, -OCH_2CH(N-)Bn), 4.50 (s, 2H, -OCH_2Ph), 4.24-4.18 (m, 2H, -OCH_2CH(N-)Bn), 3.96-3.95 (m, 1H, $H_{5'}$), 3.76 (ddd, 1H, *J* = 14.1, 7.0, 2.6 Hz, $H_{4'}$), 3.48 (t, 2H, *J* = 6.5 Hz, -CH_2OCH_2Ph), 3.25 (dd, 1H, *J* = 13.4, 3.3 Hz, -OCH_2CH(N-)CH_2Ph), 2.89 (d, 1H, *J* = 3.0 Hz, -$OH_{2'}$), 2.79 (dd, 1H, *J* = 13.4, 9.5 Hz, -OCH_2CH(N-)CH_2Ph), 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; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 153.0, 138.6, 135.0, 129.4, 129.0, 128.3, 127.6, 127.45, 127.43, 72.9,

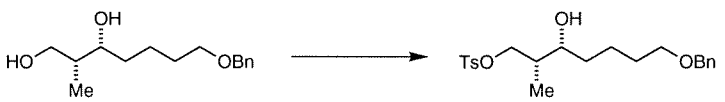
71.4, 70.2, 66.2, 55.1, 42.1, 37.8, 33.6, 29.6, 22.7, 10.4 ppm; IR (thin film) ν 3512 (br), 2938, 2861, 1779, 1695, 1496, 1454, 1385, 1210, 1109, 738 cm^{-1}; HRMS (FAB+) calc'd for $C_{25}H_{31}NO_5$ 425.2202, found 426.2287 (MH^+).



Diol (27). 30% H_2O_2 (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/H_2O mixture at 0 °C. $LiOH•H_2O$ (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 Na_2SO_3 solution (4.5 equiv) was carefully added. The mixture was made alkaline by the addition of 250 mL sat. aqueous $NaHCO_3$, then acidified to pH = 1 with ca. 500 ml of a 10% v/v HCl solution. The organic phase was collected, and the aqueous layer was extracted with 4 x 750 ml CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 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 $LiAlH_4$ (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 Et_2O, 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 Et_2O. The combined organic extracts were dried over Na_2SO_4 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 CH_2Cl_2/EtOAc) furnished the diol **27** as a white solid (15.2 g, 92%). TLC R_f = 0.30 (1:1 CH_2Cl_2/EtOAc); mp 43-44 °C; $[\alpha]_{Na}$ +40.8 (*c* = 0.42,

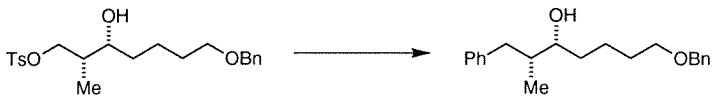
CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.34 (m, 1H, $H_{aromatic}$), 7.33-7.28 (m, 1H, $H_{aromatic}$), 4.50 (s, 2H, -OCH_2Ph), 3.82 (m, 1H, $H_{4'}$), 3.69 (m, 2H, $H_{6'}$), 3.49 (dt, 2H, J = 6.3, 1.6 Hz, -CH_2OCH_2Ph), 2.47 (br s, 2H, -$OH_{1°}$ and -$OH_{2°}$), 1.78-1.74 (m, 1H, $H_{5'}$), 1.68-1.51 (m, 4H, $H_{1'}$, $H_{3'}$), 1.49-1.41 (m, 2H, $H_{2'}$), 0.90 (d, 3H, J = 7.1 Hz, $H_{13'}$).ppm; ^{13}C NMR ($CDCl_3$, 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. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.51.



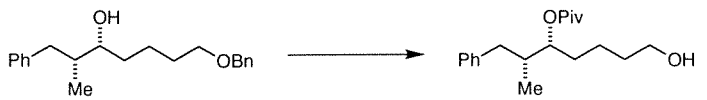
27 28

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 Et_2O. 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 Et_2O. The ethereal extracts were washed successively with 1 x 400 mL 10% v/v HCl, 1 x 400 mL 0.2 M aqueous $CuSO_4$, and 1 x 400 mL sat. aqueous NaCl, then dried over Na_2SO_4. Evaporation of the Et_2O 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 R_f = 0.62 (1:1 hexanes/EtOAc); $[\alpha]_{Na}$ +45.8° (c = 0.38, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, 2H, $H_{aromatic}$), 7.36-7.32 (m, 6H, $H_{aromatic}$), 7.31-7.27 (m, 1H, $H_{aromatic}$), 4.50 (s, 1H, -OCH_2Ph), 4.06 (dd, 1H, J = 9.7, 7.9 Hz, $H_{6'}$), 3.88 (dd, 1H, J =9.7, 6.0 Hz, $H_{6'}$), 3.70 (m, 1H, $H_{4'}$), 3.49-3.45 (m, 2H, -CH_2OCH_2Ph), 2.45 (s, 3H, -SO_2ArCH_3), 1.91-1.86 (m, 1H, $H_{5'}$), 1.67-1.34 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.84 (d, 3H, J = 7.0 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{30}SO_5$: 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/Et_2O 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/Et_2O, 129.0 mL, 167.6 mmol, 3.0 equiv) and BF_3•OEt_2 (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 $NaHCO_3$. The aqueous phase was collected and extracted additionally with 3 x 300 mL Et_2O. The combined organic extracts were washed once with sat. aqueous NaCl (500 mL), dried over Na_2SO_4, 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 R_f = 0.23 (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +4.5° (*c* = 0.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.34 (m, 4H, $H_{aromatic}$), 7.31-7.27 (m, 3H, $H_{aromatic}$), 7.21-7.17 (m, 3H, $H_{aromatic}$), 4.50 (s, 2H, -OC*H*$_2$Ph), 3.55-3.51 (m, 1H, $H_{4'}$), 3.48 (t, 2H, *J* = 6.4 Hz, -C*H*$_2$OCH$_2$Ph), 2.78 (dd, 1H, *J* = 13.4, 6.3 Hz, $H_{6'}$), 2.46 (dd, 1H, *J* = 13.4, 8.6 Hz, $H_{6'}$), 1.85-1.82 (m, 1H, $H_{5'}$), 1.83-1.34 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.85 (d, 3H, *J* = 6.9 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{28}O_2$ 312.2089, found 313.2167 (MH^+).

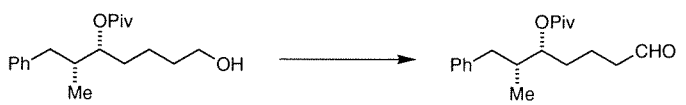


30 31

C(1) Alkyl Side Chain Alcohol (31). To a solution of alcohol **30** (4.80 g, 15.4 mmol) in 150 mL of CH_2Cl_2 was added 4–DMAP (2.40 g, 20.0 mmol, 1.3 equiv) followed by ^{t}BuCOCl (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 $NaHCO_3$. The aqueous phase was collected and extracted additionally with 2 x 200 mL CH_2Cl_2. The combined organic extracts were washed with 1 x 250 mL sat. aqueous NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the product by chromatography on silica gel (gradient elution: 20:1→15:1 hexanes/Et_2O) gave 5.5 g (90%) of the pivaloate ester **30'** as a colorless oil. TLC R_f = 0.71 (hexanes/EtOAc); $[\alpha]_{Na}$ +70.8° (*c* = 0.25, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.33 (m, 5H, $H_{aromatic}$), 7.32-7.26 (m, 2H, $H_{aromatic}$), 7.18 (t, 1H, *J* = 7.3 Hz, $H_{aromatic}$), 7.11 (d, 2H, *J* = 7.2 Hz, $H_{aromatic}$), 4.89 (dt, 1H, *J* = 8.4, 4.2 Hz, $H_{4'}$), 4.49 (s, 2H, -OC*H*$_2$Ph), 3.46 (t, 2H, J = 6.5 Hz, -C*H*$_2$OCH$_2$Ph), 2.75 (dd, 1H, *J* = 13.4, 5.0 Hz, $H_{6'}$), 2.30 (dd, 1H, *J* = 13.4, 9.6 Hz, $H_{6'}$), 1.99-1.94 (m, 1H, $H_{5'}$), 1.72-1.54 (m, 4H, $H_{1'}$, $H_{3'}$), 1.40-1.28 (m, 2H, $H_{2'}$), 1.25 (s, 9H, $H_{Piv\text{-}tBu}$), 0.86 (d, 3H, *J* = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{26}H_{36}O_3$ 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 H_2 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 R_f = 0.17 (4:1

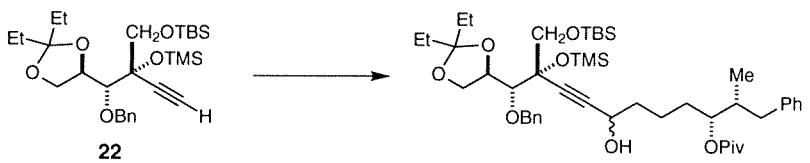
hexanes/EtOAc); $[\alpha]_{Na}$ +68.5° (*c* = 0.31, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (t, 2H, *J* = 7.4 Hz, $H_{aromatic}$), 7.19 (t, 1H, *J* = 7.4 Hz, $H_{aromatic}$), 7.11 (d, 2H, *J* = 7.11 Hz, $H_{aromatic}$), 4.89 (dt, 1H, *J* =8.3, 4.2 Hz, $H_{4'}$), 3.62 (t, 2H, *J* = 6.5 Hz, -CH_2OH), 2.74 (dd, 1H, *J* = 13.4, 5.2 Hz, $H_{6'}$), 2.31 (dd, 1H, *J* = 13.4, 9.4 Hz, $H_{6'}$), 1.99-1.94 (m, 1H, $H_{5'}$), 1.70-1.50 (m, 4H, $H_{1'}$, $H_{3'}$), 1.41-1.29 (m, 3H, $H_{2'}$ and -$OH_{1'}$), 1.25 (s, 9H, $H_{Piv\text{-}tBu}$), 0.87 (d, 3H, *J* = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{19}H_{30}O_3$: C, 74.46; H, 9.87. Found: C, 74.05; H, 10.16.



31 **32**

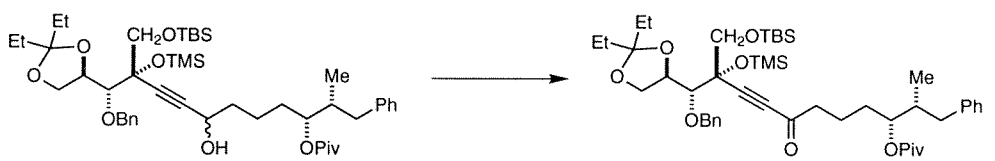
C(1) Alkyl Side Chain Aldehyde (32). Dimethyl sulfoxide (6.00 mL, 84.0 mmol, 4.0 equiv) was added dropwise to a solution of oxalyl chloride (3.70 mL, 42.0 mmol, 2.0 equiv) in 100 mL of CH_2Cl_2 at –78 °C. Following gas evolution, the mixture stirred for 10 min before a solution of alcohol **31** (6.30 g, 20.6 mmol) in 75.0 mL of CH_2Cl_2 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 KH_2PO_4 solution. The organic layer was collected, and the aqueous phase was extracted with 3 x 100 mL CH_2Cl_2. The combined extracts were dried over Na_2SO_4 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 R_f = 0.48 (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +60.2° (*c* = 0.34,

CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.74 (t, 1H, J = 1.4 Hz, -C*H*O), 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, $H_{4'}$), 2.74 (dd, 1H, J = 13.4, 5.3 Hz, $H_{6'}$), 2.46-2.41 (m, 2H, -C*H*$_2$CHO), 2.31 (dd, 1H, J = 13.4, 9.3 Hz, $H_{6'}$), 1.99-1.94 (m, 1H, $H_{5'}$), 1.70-1.52 (m, 4H, $H_{2'}$, $H_{3'}$), 1.26 (s, 9H, $H_{Piv\text{-}tBu}$), 0.87 (d, 3H, J = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.49; H, 9.56.



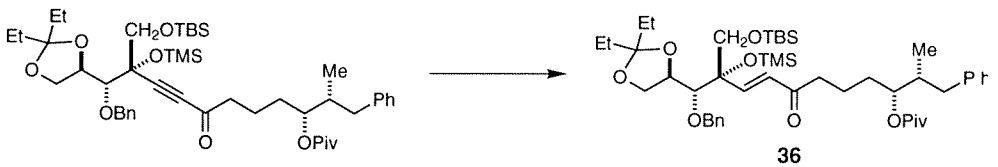
Propargylic alcohol (34). To a solution of alkyne **22** (15.4 g, 29.6 mmol, 1.5 equiv) in 150 mL of THF at –45 °C was slowly added a 1.6 M solution of ^{n}BuLi in hexanes (16.0 ml, 25.6 mmol, 1.3 equiv). The mixture was held at –45 °C for 45 min, then a 4.0 M solution of LiBr in THF (2.5 mL, 9.9 mmol, 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 NH_4Cl. The mixture was partitioned with Et_2O (100 mL), the organic phase was collected and the aqueous phase was extracted additionally with 3 x 150 mL Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a pale yellow oil. Purification by chromatography on silica gel (gradient elution: 10:1→2:1 hexanes/Et_2O) 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); ^{1}H 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}), 2.72 (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, $H_{5'}$), 1.69-1.35 (m, 10H, $H_{1'}$, $H_{2'}$, $H_{3'}$ and both -CH_2CH$_3$), 1.24 (s, 9H, $H_{Piv\text{-}tBu}$), 0.93-0.85 (m, 9H, $H_{13'}$ and both -CH$_2$CH_3), 0.91 (s, 9H, $H_{TBS\text{-}tBu}$), 0.18 (s, 9H, H_{TMS}), 0.08 (s, 3H, $H_{TBS\text{-}Me}$), 0.06 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C 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 $C_{47}H_{76}Si_2O_8$: C, 68.40; H, 9.28. Found: C, 68.40; H, 8.92.



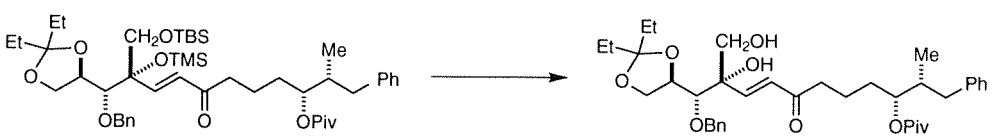
Ynone (35). To a solution of alcohol **34** (15.1 g, 18.3 mmol) in 150 mL of CH_2Cl_2 was added 15.5 g (36.6 mmol, 2.0 equiv) of the Dess–Martin periodinane.[31] The resulting white suspension was stirred at 23 °C for 5 h. To the reaction mixture was then added 300 mL of pentane. The resulting precipitates 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); $[\alpha]_{Na}$ +57.8° (c = 0.38,

CH_2Cl_2); ^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, 1H, J = 7.1 Hz, $H_{aromatic}$), 4.89 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.85-4.83 (m, 1H, $H_{4'}$), 4.76 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.42 (ddd, J = 8.4, 6.5, 2.0 Hz, H_3), 4.11 (d, 1H, J = 2.0 Hz, H_4), 4.08-4.01 (m, 2H, H_8), 3.73 (d, 1H, J = 10.2 Hz, H_{10}), 3.65 (d, 1H, J = 10.2 Hz, H_5), 2.73 (dd, 1H, J = 13.4, 5.0 Hz, $H_{6'}$), 2.49 (t, 2H, J = 6.8 Hz, $H_{1'}$), 2.27 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 1.99-1.94 (m, 1H, $H_{5'}$), 1.67-1.49 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH$_3$), 1.24 (s, 9H, $H_{Piv\text{-}tBu}$), 0.93-0.88 (m, 6H, both -CH$_2$CH_3), 0.92 (s, 9H, $H_{TBS\text{-}tBu}$), 0.84 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.20 (s, 9H, H_{TMS}), 0.09 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{47}H_{74}Si_2O_8$ 822.4922, found 823.5022 (MH$^+$).



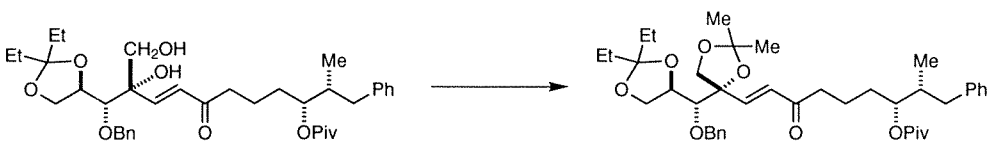
***trans* Enone (36).** To a suspension of $[Cr(OAc)_2{\bullet}H_2O]_2$ (31.7 g, 84.4 mmol, 5.0 equiv) in 50.0 mL of degassed THF was added a solution of ynone **35** (13.9 g, 16.9 mmol) in 310 mL of degassed THF, followed by 36.0 mL of deoxygenated H_2O. The reaction was warmed to 65 °C and stirred for two weeks. Filtration of the reaction mixture through Celite removed most of the insoluble salts. The filter cake was rinsed thoroughly with Et_2O (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/Et_2O) furnished **36** (8.3 g, 60%) as a colorless oil. TLC R_f = 0.51 (6:1

hexanes/EtOAc); $[\alpha]_{Na}$ +319.5° (c = 0.25, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.25 (m, 7H, $H_{aromatic}$), 7.18 (t, 1H, J = 7.4 Hz, $H_{aromatic}$), 7.12 (d, 2H, J = 7.0 Hz, $H_{aromatic}$), 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_2Ph), 4.87-4.85 (m, 1H, $H_{4'}$), 4.61 (d, 1H, J = 11.5 Hz, -OCH_2Ph), 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_2CH$_3$), 1.25 (s, 9H, $H_{Piv\text{-}tBu}$), 0.91-0.87 (m, 6H, both -CH$_2$CH_3), 0.89 (s, 9H, $H_{TBS\text{-}tBu}$), 0.86 (d, 3H, J = 6.9 Hz, $H_{13'}$), 0.18 (s, 9H, H_{TMS}), 0.02 (s, 3H, $H_{TBS\text{-}Me}$), 0.01 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 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) ν 2956, 1725, 1676, 1636, 1459, 1361, 1283, 1251, 1161, 1108, 991, 925, 838, 777, 699 cm^{-1}; Anal. Calcd for $C_{47}H_{76}Si_2O_8$: 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_4Cl and 50 mL of Et_2O. The organic phase was collected, and the aqueous layer was extracted with 3 x 75 mL Et_2O. The combined organic extracts were washed with 1 x 100 mL of sat. aqueous NaCl, dried over Na_2SO_4,

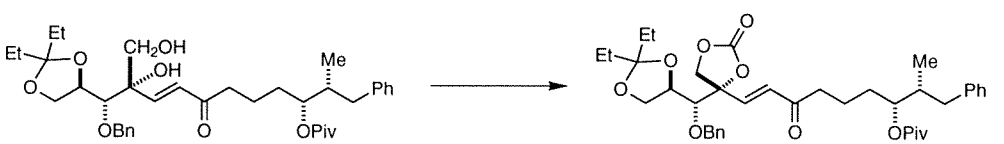
and evaporated under reduced pressure. Purification of the product chromatography on silica gel (gradient elution: 2:1→1:1 hexanes/EtOAc) afforded the product **45** as a colorless oil (1.8 g, 93%). TLC $R_f = 0.19$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +104.4° ($c = 0.27$, CH_2Cl_2); ^1H NMR ($CDCl_3$, 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, H_6), 6.53 (d, 1H, J = 15.9 Hz, H_7), 4.88-4.85 (m, 1H, $H_{4'}$), 4.79 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.63 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.13 (d, 1H, J = 1.7 Hz, -OH_3°), 4.07-4.02 (m, 2H, H_4 and H_8), 3.80-3.73 (m, 2H, H_{10}), 3.64-3.60 (m, 1H, H_3), 3.43 (dd, 1H, J =11.6, 3.5 Hz, H_8), 2.74 (dd, 1H, J =13.4, 5.0 Hz, $H_{6'}$), 2.58-2.54 (m, 2H, $H_{1'}$), 2.31-2.27 (m, 2H, $H_{6'}$ and -OH_1°), 1.98-1.96 (m, 1H, $H_{5'}$), 1.68-1.55 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH$_3$), 1.24 (s, 9H, $H_{Piv\text{-}tBu}$), 0.91 (t, 3H, J = 7.5 Hz, -CH$_2$CH_3), 0.85 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.82 (t, 3H, J = 7.4 Hz, -CH$_2$CH_3) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{38}H_{54}O_8$: C, 71.44; H, 8.52. Found: C, 71.39; H, 8.63.



45 **51**

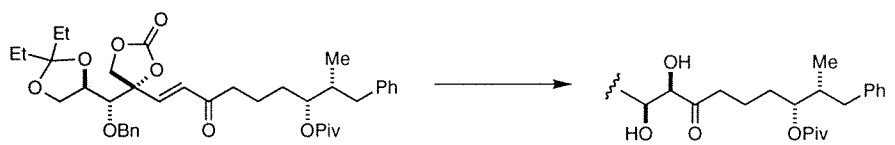
Dimethyl acetonide-enone (51). A solution of enone **45** (8.0 mg, 12.5 μmol) in 1.5 mL of CH_2Cl_2 was treated with 12 μL of 2-methoxypropene (125 μmol, 10 equiv) and a catalytic amount of anhydrous *p*- toluenesulfonic acid (1 mg, 4 μmol, 0.3 equiv). After 1 h the mixture was poured onto 4 mL of a 1:1 CH_2Cl_2/sat. aqueous $NaHCO_3$ solution. The organic phase was isolated and the aqueous layer was extracted with 2 x 3

mL CH_2Cl_2. The combined extracts were dried over Na_2SO_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); ^1H 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_2Ph), 4.87-4.86 (m, 1H, $H_{4'}$), 4.67 (d, 1H, J = 11.4 Hz, -OCH_2Ph), 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_2CH$_3$), 1.46 (s, 3H, -CH_3), 1.39 (s, 3H, -CH_3), 1.25 (s, 9H, $H_{Piv\text{-}tBu}$), 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 (CI$^+$) 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); ^1H NMR ($CDCl_3$, 500 MHz) δ7.40-7.27 (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, $H_{Piv\text{-}tBu}$), 0.89-0.85 (m, 9H, $H_{13'}$ and both -CH$_2$CH_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$^+$).

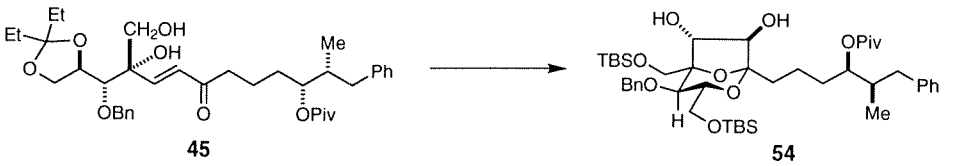


52

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 ^{t}BuOH 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 ^{1}H 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) δ 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, -OC*H*$_2$Ph), 4.87-4.83 (m, 1H, $H_{4'}$), 4.60 (d, 1H, *J* = 10.6 Hz, -OC*H*$_2$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 -C*H*$_2$CH$_3$), 1.26 (s, 9H, $H_{Piv\text{-}tBu}$), 0.90 (t, 3H, *J* = 7.5 Hz, -CH$_2$C*H*$_3$), 0.87 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.83 (t, 3H, *J* = 7.4 Hz, -CH$_2$C*H*$_3$) ppm; IR (thin film) ν 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) δ 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, -OC*H*$_2$Ph), 4.80-4.76 (m, 2H, H_{10}, $H_{4'}$), 4.58 (d, 1H, *J* = 11.4 Hz, -OC*H*$_2$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 -C*H*$_2$CH$_3$), 1.22 (s, 9H, $H_{Piv\text{-}tBu}$), 0.94 (t, 3H, *J* = 7.5 Hz, -CH$_2$C*H*$_3$), 0.91 (d, 3H, *J* = 7.0 Hz, $H_{13'}$), 0.89 (t, 3H, *J* = 7.5 Hz, -CH$_2$C*H*$_3$) ppm; IR (thin film) ν 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$^+$).

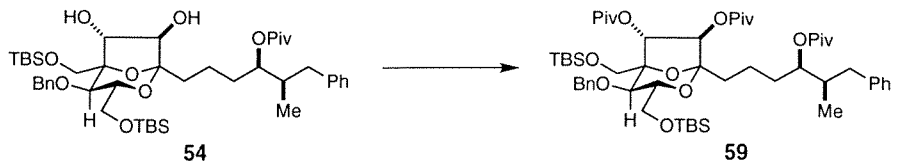


45 54

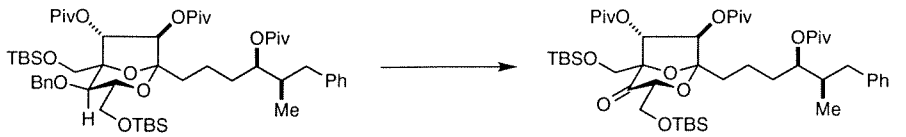
TBS–Protected Bicyclic Ketal (54). To a solution of **45** (1.40 g, 2.19 mmol) in 85.0 mL of acetone was added $(DHQD)_2PHAL$ (1.0 g, 1.32 mmol), 4-methylmorpholine-*N*-oxide (513 mg, 4.38 mmol), and $CH_3SO_2NH_2$ (210 mg, 2.2 mmol). The pale yellow solution was cooled to 0 °C before 4.1 mL of an aqueous solution of OsO_4 (0.66 mmol, 0.16 M) was added dropwise via pipette. 5.0 mL of ^{t}BuOH 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 $NaHSO_3/Na_2SO_4$ 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_2Cl_2. The organic layer was collected and the aqueous phase was extracted with 4 x 50 mL 20% MeOH/CH_2Cl_2. The extracts were combined and dried over Na_2SO_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 ^{i}Pr$_2$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_2Cl_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_2Cl_2/EtOAc).

To a solution of **53/56** (684 mg, 1.17 mmol) in 10.0 mL of CH_2Cl_2 was added Et_3N (1.6 mL, 11.7 mmol, 10.0 equiv), $^tBuMe_2SiCl$ (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_2PO_4 solution. The two phases were separated and the aqueous phase extracted additionally with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over Na_2SO_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**: $[\alpha]_{Na}$ +384.7° (*c* = 0.27, CH_2Cl_2); ^1H 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, -OC*H*$_2$Ph), 4.59 (d, 1H, *J* = 11.3 Hz, -OC*H*$_2$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_5), 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, $H_{Piv\text{-}tBu}$), 0.91 (s, 9H, $H_{TBS\text{-}tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}tBu}$), 0.85 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.08 (s, 3H, $H_{TMS\text{-}Me}$), 0.062 (s, 6H, $H_{TMS\text{-}Me}$), 0.056 (s, 3H, $H_{TMS\text{-}Me}$) 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 $C_{45}H_{74}Si_2O_9$: 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 ^{t}BuCOCl (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_f = 0.54 (8:1 hexanes/EtOAc); $[\alpha]_{Na}$ +78.1° (*c* = 0.27, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.26 (m, 7H, $H_{aromatic}$), 7.18 (t, 1H, *J* = 7.3 Hz), 7.10 (d, 2H, *J* = 7.1 Hz), 5.38 (d, 1H, *J* = 2.7 Hz, H_6), 4.98 (d, 1H, *J* = 2.7 Hz, H_7), 4.85-4.82 (m, 1H, $H_{4'}$), 4.82 (d, 1H, *J* = 11.7 Hz, -OCH_2Ph), 4.60 (d, 1H, *J* = 11.7 Hz, -OCH_2Ph), 4.07 (d, 1H, *J* = 10.0 Hz, H_4), 3.80-3.75 (m, 3H, H_3, H_{10}), 3.71-3.68 (m, 2H, H_8), 2.75 (dd, 1H, *J* = 13.3, 4.7 Hz, $H_{6'}$), 2.27 (dd, 1H, *J* = 13.3, 9.8 Hz, $H_{6'}$), 1.99-1.94 (m, 1H, $H_{5'}$), 1.69-1.35 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 1.24 (s, 9H, $H_{Piv\text{-}tBu}$), 1.21 (s, 9H, $H_{Piv\text{-}tBu}$), 1.20 (s, 9H, $H_{Piv\text{-}tBu}$), 0.92 (s, 9H, $H_{TBS\text{-}tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}tBu}$), 0.84 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.11 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$), 0.05 (s, 3H, $H_{TBS\text{-}Me}$), 0.02 (s, 3H, $H_{TBS\text{-}Me}$) ppm. ^{13}C NMR ($CDCl_3$, 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 $C_{55}H_{90}Si_2O_{11}$: C, 67.17; H, 9.22. Found: C, 66.80; H, 8.81.

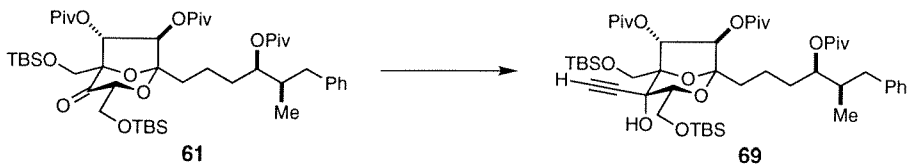


59 **61**

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). $[\alpha]_{Na}$ +81.4° (*c* = 0.25, CH_2Cl_2); ^1H 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, $H_{Piv\text{-}tBu}$), 1.229 (s, 9H, $H_{Piv\text{-}tBu}$), 1.21 (s, 9H, $H_{Piv\text{-}tBu}$), 0.91 (s, 9H, $H_{TBS\text{-}tBu}$), 0.90 (s, 9H, $H_{TBS\text{-}tBu}$), 0.83 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.092 (s, 6H, $H_{TBS\text{-}Me}$), 0.085 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$) 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 $C_{48}H_{84}Si_2O_{11}$ 892.6046, found 893.5645 (MH^+); Anal. Calcd for $C_{48}H_{84}Si_2O_{11}$: 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_2Cl_2 at –78

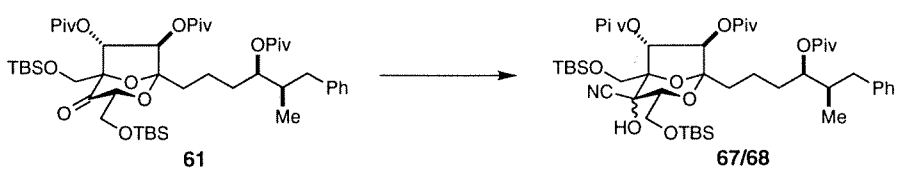
°C. Following gas evolution, the mixture stirred for 10 min before a solution of alcohol **60** (725 mg, 0.81 mmol) in 2.0 mL of CH_2Cl_2 was added dropwise over 10 min. The resulting white suspension was stirred at –78 °C for an additional 1 h; Et_3N (2.90 mL, 20.5 mmol, 25 equiv) was then added dropwise 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 KH_2PO_4 solution. The organic layer was collected, and the aqueous phase was extracted with 4 x 25 mL CH_2Cl_2. The combine extracts were dried over Na_2SO_4 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 $R_f \approx 0.50$ (8:1 hexanes/EtOAc); $[\alpha]_{Na}$ +42.9° (*c* = 0.42, CH_2Cl_2); ^1H NMR (C_6D_6, 500 MHz) δ 7.23-7.11 (m, 3H, $H_{aromatic}$), 7.08-7.04 (m, 3H, $H_{aromatic}$), 5.40 (d, 2H, *J* = 1.8 Hz, H_6, H_7), 5.08-5.04 (m, 1H, $H_{4'}$), 4.61 (dd, 1H, *J* = 6.4, 4.1 Hz, H_3), 4.32 (d, 1H, *J* = 10.8 Hz, H_{10}), 4.15 (dd, 1H, *J* = 10.9, 6.4 Hz, H_8), 4.12 (dd, 1H, *J* = 11.0, 4.2 Hz, H_8), 4.05 (d, 1H, *J* = 10.8 Hz, H_{10}), 2.74 (dd, 1H, *J* = 13.4, 4.8 Hz, $H_{6'}$), 2.22-2.16 (m, 2H, $H_{1'}$, $H_{6'}$), 2.08-2.02 (m, 1H, $H_{1'}$), 1.89-1.83 (m, 1H, $H_{5'}$), 1.81-1.77 (m, 1H, $H_{3'}$), 1.68-1.64 (m, 1H, $H_{3'}$), 1.62-1.56 (m, 1H, $H_{2'}$), 1.39-1.29 (m, 1H, $H_{2'}$), 1.27 (s, 9H, $H_{Piv\text{-}tBu}$), 1.16 (s, 9H, $H_{Piv\text{-}tBu}$), 1.10 (s, 9H, $H_{Piv\text{-}tBu}$), 1.00 (s, 9H, $H_{TBS\text{-}tBu}$), 0.97 (s, 9H, $H_{TBS\text{-}tBu}$), 0.78 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.154 (s, 3H, $H_{TBS\text{-}Me}$), 0.150 (s, 3H, $H_{TBS\text{-}Me}$), 0.14 (s, 3H, $H_{TBS\text{-}Me}$), 0.11 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR (C_6D_6, 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 $C_{48}H_{82}Si_2O_{11}$: 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 Et_2O/Me_3N 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 Et_2O was added dropwise via cannula over a 3 min period. The transfer of **61** was made quantitative with an additional 500 μL of Et_2O. 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 NH_4Cl. The resulting frozen mixture was warmed to 23 °C. The solution was extracted with 3 x 5 ml Et_2O; the organic extracts were combined, washed once with sat. aqueous NaCl (10 mL), and dried over Na_2SO_4. 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 R_f = 0.52 (8:1 hexanes/EtOAc).

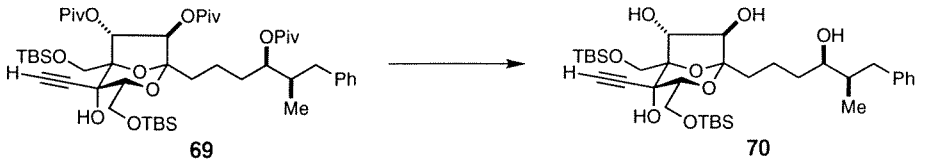
To a solution of trimethylsilyl acetylene **65/66** (172 mg, 0.17 mmol) in 8.0 mL of a 1:1:1:0.1 mixture of $THF/H_2O/EtOH$/2,6-lutidine was added solid $AgNO_3$ (295 mg, 1.70 mmol, 10 equiv). The white suspension was stirred vigorously for 3.5 h, then 5 mL of a 1.0 M aqueous KH_2PO_4 solution was added. 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 Et_2O (3 x 10 mL), the combined

organic extracts were washed once with sat. aqueous NaCl (1 x 20 mL) and dried over Na_2SO_4. 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 ^{1}H NMR. TLC R_f = 0.36 (10:1 hexanes/EtOAc); $[\alpha]_{Na}$ +10.8° (*c* = 0.45, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.24 (m, 2H, $H_{aromatic}$), 7.17 (t, 1H, *J* = 7.4 Hz, $H_{aromatic}$), 7.11 (d, 2H, *J* = 7.1 Hz, $H_{aromatic}$), 5.52 (d, 1H, *J* = 1.9 Hz, -OH_3◦), 5.43 (d, 1H, *J* = 2.8 Hz, H_6), 4.99 (d, 1H, *J* = 2.8 Hz, H_7), 4.88-4.84 (m, 1H, $H_{4'}$), 4.18 (d, 1H, *J* = 11.5 Hz, H_{10}), 4.11 (dd, 1H, *J* = 11.5, 1.7 Hz, H_8), 4.03 (ddd, 1H, *J* = 7.1, 1.7, 1.6 Hz, H_3) 3.92 (d, 1H, *J* = 11.5 Hz, H_{10}), 3.89 (dd, 1H, *J* = 11.5, 7.1 Hz, H_8), 2.76 (dd, 1H, *J* = 13.3, 4.7 Hz, $H_{6'}$), 2.61 (s, 1H, -C≡C*H*), 2.26 (dd, 1H, *J* = 13.3, 9.9 Hz, $H_{6'}$), 2.00-1.96 (m, 1H, $H_{5'}$), 1.80-1.25 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 1.23 (s, 9H, $H_{Piv\text{-}tBu}$), 1.228 (s, 9H, $H_{Piv\text{-}tBu}$), 1.226 (s, 9H, $H_{Piv\text{-}tBu}$), 0.91 (s, 9H, $H_{TBS\text{-}tBu}$), 0.90 (s, 9H, $H_{TBS\text{-}tBu}$), 0.83 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.120 (s, 3H, $H_{TBS\text{-}Me}$), 0.116 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$), 0.06 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{50}H_{84}Si_2O_{11}$ 916.5552, found 917.5637 (MH^+).

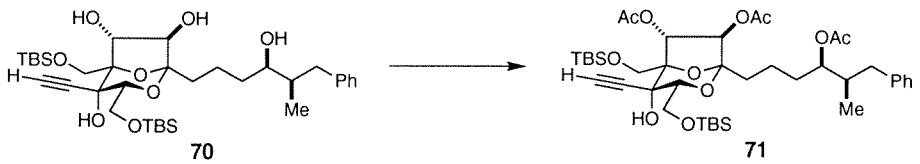


C(4) Cyanohydrin(67/68). Finely pulverized CsF (3 mg, 20 μmol, 10 equiv) was dried under vacuum (1 mm Hg) at 120 °C for 15 h prior to being suspended in 0.5 mL of

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 KH_2PO_4. The mixture was extracted with 4 x 2 mL Et_2O; the extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a pale yellow oil. TLC R_f = 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 ($CDCl_3$, 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, –$OH_{3\circ}$–**67**), 5.61 (d, 1H, J = 2.7 Hz, H_6–**68**), 5.31 (d, 1H, J = 2.7 Hz, H_6–**67**), 5.24 (s, 1H, –$OH_{3\circ}$–**68**), 5.02 (d, 2H, J = 2.8 Hz, H_7), 4.86–4.84 (m, 2H, $H_{4'}$), 4.18 (d, 1H, J = 11.7 Hz, H_{10}–**67**), 4.13 (ddd, 1H, J = 5.1, 4.4, 1.3 Hz, H_3–**67**), 4.10–4.02 (m, 6H, H_8, H_{10}–**67**, H_3, H_8, both H_{10}–**68**), 3.91–3.87 (m, 1H, H_8–**68**), 3.85 (dd, 1H, J = 10.9, 5.8 Hz, H_8–**67**), 2.76 (dd, 2H, J = 13.3, 4.6 Hz, $H_{6'}$), 2.26 (dd, 2H, J = 13.3, 9.9 Hz, $H_{6'}$), 1.99–1.91 (m, 2H, $H_{5'}$), 1.78–1.50 (m, 8H, $H_{1'}$, $H_{3'}$), 1.39–1.22 (m, 4H, $H_{2'}$), 1.233 (s, 9H, $H_{Piv\text{-}tBu}$–**67**), 1.225 (s, 9H, $H_{Piv\text{-}tBu}$–**68**), 0.93 (s, 9H, $H_{TBS\text{-}tBu}$–**67**), 0.92 (s, 9H, $H_{TBS\text{-}tBu}$–**67**), 0.904 (s, 9H, $H_{TBS\text{-}tBu}$–**68**), 0.896 (s, 9H, $H_{TBS\text{-}tBu}$–**68**), 0.84 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.16 (s, 3H, $H_{TBS\text{-}Me}$–**67**), 0.15 (s, 3H, $H_{TBS\text{-}Me}$–**67**), 0.11 (s, 3H, $H_{TBS\text{-}Me}$–**68**), 0.10 (s, 3H, $H_{TBS\text{-}Me}$–**67**), 0.093 (s, 3H, $H_{TBS\text{-}Me}$–**67**), 0.85 (s, 3H, $H_{TBS\text{-}Me}$–**68**), 0.07 (s, 6H, $H_{TBS\text{-}Me}$–**68**) ppm.

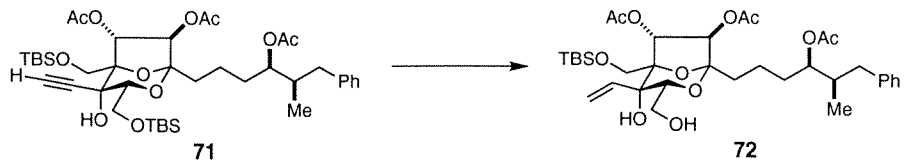


Tetraol (70). A 1.5 M solution of Dibal-H in toluene (3.2 mL, 4.7 mmol, 15 equiv) was added to a solution of **69** (290 mg, 0.316 mmol) in 30.0 mL of a 1:1 CH_2Cl_2/toluene mixture at –78 °C. The reaction was stirred at –78 °C for 30 min and then warmed over a 5 h period to ca. -5 °C before being quenched 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 Na_2SO_4 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 R_f = 0.20 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +18.1° (*c* = 0.24, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.26 (m, 3H, $H_{aromatic}$), 7.20-7.16 (m, 3H, $H_{aromatic}$), 4.70 (d, 1H, *J* = 1.1 Hz, $-OH_{3°}$), 4.68 (dd, 1H, *J* = 5.8, 2.7 Hz, H_6), 4.39 (dd, 1H, *J* = 5.6, 2.6 Hz, H_7), 4.29 (d, 1H, *J* = 11.3 Hz, H_{10}), 4.09-4.05 (m, 3H, H_8 and H_{10}), 3.95 (dd, 1H, *J* = 3.4, 3.2 Hz, H_3), 3.51 (br s, 1H, $H_{4'}$), 2.78 (dd, 1H, *J* = 13.4, 6.3 Hz), 2.74 (br s, 1H, $-OH_{2°}$), 2.54 (d, 1H, *J* = 0.7 Hz, -C≡C*H*), 2.45 (dd, 1H, *J* =13.3, 8.6 Hz), 1.83-1.46 (m, 7H, $H_{1'}$, $H_{2'}$, $H_{3'}$, $H_{5'}$), 0.90 (s, 9H, $H_{TBS\text{-}tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}tBu}$), 0.84 (d, 1H, *J* = 6.8 Hz, $H_{13'}$), 0.11 (s, 6H, $H_{TBS\text{-}Me}$), 0.09 (s, 6H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{35}H_{60}Si_2O_8$ 664.4186, found 665.3903 (MH^+).



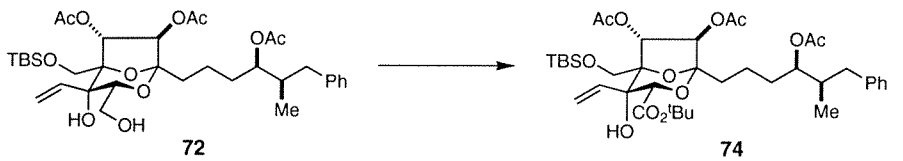
70 71

Tris-Acetate (71). To a solution of polylol **70** (130 mg, 0.195 mmol) in 5.0 mL of CH_2Cl_2 was added 4–DMAP (490 mg, 4.0 mmol, 20 equiv) followed by Ac_2O (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 KH_2PO_4 solution. The organic phase was collected and the aqueous layer was extracted with 3 x 5 mL CH_2Cl_2. The combined extracts were dried over Na_2SO_4 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 R_f = 0.16 (6:1 hexanes/EtOAc); $[\alpha]_{Na}$ + 37.0° (*c* = 0.56, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.25 (m, 2H, $H_{aromatic}$), 7.18 (t, 1H, *J* = 7.4 Hz, $H_{aromatic}$), 7.12 (d, 2H, *J* = 7.3 Hz, $H_{aromatic}$), 5.50 (d, 1H, *J* = 2.9 Hz, H_6), 5.42 (d, 1H, *J* = 1.6 Hz, -$OH_{3°}$), 5.06 (d, 1H, *J* = 2.9 Hz, H_7), 4.88-4.84 (m, 1H, $H_{4'}$), 4.17 (d, 1H, *J* = 11.5 Hz, H_{10}), 4.13 (dd, 1H, *J* = 11.6, 1.7 Hz, H_8), 4.03 (ddd, 1H, *J* = 6.9, 1.7, 1.6 Hz, H_3) 3.93 (d, 1H, *J* = 11.4 Hz, H_{10}), 3.90 (dd, 1H, *J* = 11.7, 6.9 Hz, H_8), 2.76 (dd, 1H, *J* = 13.5, 5.0 Hz, $H_{6'}$), 2.60 (s, 1H, -C≡C*H*), 2.28 (dd, 1H, *J* = 13.4, 9.7 Hz, $H_{6'}$), 2.11 (s, 6H, two -COCH_3), 2.06 (s, 3H, -COCH_3), 2.00-1.96 (m, 1H, $H_{5'}$), 1.85-1.25 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.91 (s, 9H, $H_{TBS\text{-}tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}tBu}$), 0.83 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.13 (s, 3H, $H_{TBS\text{-}Me}$), 0.12 (s, 3H, $H_{TBS\text{-}Me}$), 0.08 (s, 6H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{41}H_{66}Si_2O_{11}$ 790.4143, found 791.4204 (MH^+).



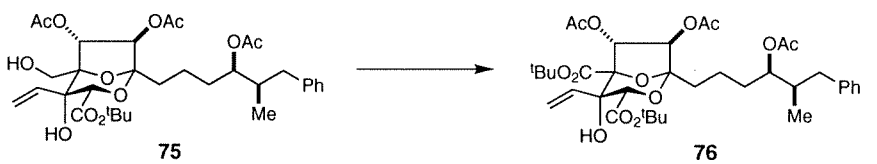
C(8) Alcohol (72). A solution of **71** (104 mg, 0.131 mmol) in 20.0 mL of MeOH was treated with 95 μL (1.2 mmol, 9 equiv) of Cl_2CHCO_2H and stirred for 7 h. The mixture was then diluted with 20 mL of Et_2O and poured onto 20 mL of sat. aqueous NH_4Cl. The organic phase was isolated and the aqueous layer extracted with 3 x 20 mL Et_2O. The combined ethereal extracts were washed with 1 x 40 mL sat. aqueous NaCl, dried over Na_2SO_4, 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 R_f = 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 H_2 and stirred vigorously for 2 h. The mixture was filtered through Celite, the filter cake rinsed with Et_2O (10 mL), and the filtrate concentrated *in vacuo* to a pale yellow oil. The product **72** was used without further purification. TLC R_f = 0.17 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ -165.2° (*c* = 0.26, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.25 (m, 2H, $H_{aromatic}$), 7.18 (dt, 1H, *J* = 7.3, 1.2 Hz, $H_{aromatic}$), 7.13 (dd, 1H, *J* = 6.9, 1.2 Hz, $H_{aromatic}$), 5.98 (dd, 1H, *J* = 16.8, 10.7 Hz, -C*H*=CH_2), 5.69 (dd, 1H, *J* = 16.8, 1.7 Hz, -CH=CH_2), 5.44 (d, 1H, *J* = 3.0 Hz, H_6), 5.42 (dd, 1H, *J* =10.7, 1.7 Hz, -CH=CH_2), 5.10 (d, 1H, *J* = 3.0 Hz, H_7), 4.90-4.86 (m, 1H, $H_{4'}$), 4.71 (br s, 1H, -OH_3°), 3.88 (dd, 1H, *J* = 5.3, 3.4 Hz, H_3), 3.80 (dd, 1H, *J* = 12.0, 5.4 Hz, H_8), 3.79 (d, 1H, *J* = 11.2 Hz, H_{10}), 3.71 (d, 1H, *J* = 11.0 Hz, H_{10}), 3.70 (dd, 1H, *J* = 12.0, 3.3 Hz, H_8), 2.75 (dd, 1H, *J* = 13.4, 5.0 Hz, $H_{6'}$), 2.29 (dd, 1H, *J* = 13.4, 9.5 Hz, $H_{6'}$), 2.12 (s, 3H, -COCH_3), 2.10 (s, 3H, -COCH_3), 2.07 (s, 3H, -COCH_3), 2.00-1.95 (m, 1H, $H_{5'}$), 1.87-1.47 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.87 (s, 9H, $H_{TBS\text{-}tBu}$), 0.84 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.06 (s, 3H, $H_{TBS\text{-}Me}$), 0.04 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR

($CDCl_3$, 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 $CDCl_3$), 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 $C_{35}H_{54}SiO_{11}$ 678.3929, found 679.3501 (MH^+).



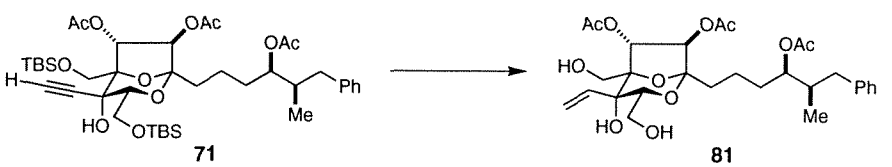
C(8) *tert*-Butyl Ester (74). To a solution of alcohol **72** (15.0 mg, 22.1 μmol) in 3.0 mL of CH_2Cl_2 was added 21 mg (50 mmol) of freshly prepared Dess-Martin periodinane.[31] The white suspension was stirred at 23 °C for 2 h. Et_2O (5 mL) was then added to the reaction mixture and the resulting 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 $R_f \approx 0.37$ (2:1 hexanes/EtOAc). The intermediate aldehyde (11.0 mg, 16.3 μmol) was dissolved in 6.0 mL of a 5:1.2 ^{t}BuOH/2-methyl-2-butene solution and cooled to ca. 10 °C. An ice-cold buffered 1.1 M aqueous solution of $NaClO_2$ (150 μL, 165 μmol, 10 equiv) was added dropwise.[58] The resulting pale yellow solution was stirred for 3 h and then quenched with 5.0 mL of a pH 2 KH_2PO_4-HCl buffer. The solution was extracted with 6 x 3 mL EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified product was re-dissolved in 3.0 mL of CH_2Cl_2 and *N,N'*-diisopropyl-*O-tert*-butylisourea (**73**)[59] (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 R_f = 0.24 (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +11.4° (*c* = 0.25, 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* = 7.4 Hz, $H_{aromatic}$), 6.03 (dd, 1H, *J* = 16.7, 10.8 Hz, -C*H*=CH_2), 5.62 (dd, 1H, *J* = 16.7, 1.5 Hz, -CH=CH_2), 5.47 (d, 1H, *J* = 2.9 Hz, H_6), 5.35 (dd, 1H, *J* = 10.7, 1.5 Hz, -CH=CH_2), 5.11 (d, 1H, *J* = 2.9 Hz, H_7), 4.87-4.85 (m, 1H, $H_{4'}$), 4.38 (s, 1H, H_3), 4.34 (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* = 13.4, 4.9 Hz, $H_{6'}$), 2.29 (dd, 1H, *J* = 13.4, 9.6 Hz, $H_{6'}$), 2.12 (s, 3H, -COCH_3), 2.10 (s, 3H, -COCH_3), 2.06 (s, 3H, -COCH_3), 2.03-1.93 (m, 1H, $H_{5'}$), 1.91-1.74 (m, 2H, $H_{1'}$), 1.68-1.48 (m, 4H, $H_{2'}$, $H_{3'}$), 1.43 (s, 9H, H_{tBu}), 0.86 (s, 9H, $H_{TBS\text{-}tBu}$), 0.83 (d, 3H, *J* = 6.8 Hz, $H_{13'}$), 0.03 (s, 3H, $H_{TBS\text{-}Me}$), 0.03 (s, 3H, $H_{TBS\text{-}Me}$) ppm; ^{13}C NMR ($CDCl_3$, 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) ν 3452, 2956, 2931, 1753, 1643, 1603, 1495, 1462, 1416, 1370, 1240, 1153, 1099, 1041, 930, 838, 701 cm^{-1}; HRMS (FAB^+) calc'd for $C_{39}H_{60}SiO_{12}$ 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 CH_2Cl_2 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 Et_2O (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

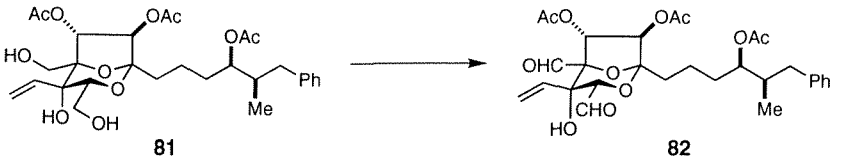
chromatography on silica gel (gradient elution: 7:2→2:1 hexanes/EtOAc) yielded the desired aldehyde as a colorless oil (32 mg, 84%). TLC R_f = 0.43 (2:1 hexanes/EtOAc). Oxidation and *tert*-butyl esterification was accomplished following a procedure outlined for the preparation of compound **74**. The 3,5-bis-*tert*-butyl ester **76** was isolated a colorless oil (27 mg, 76%). TLC R_f = 0.45 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +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, -C*H*=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; ^{13}C 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^+).



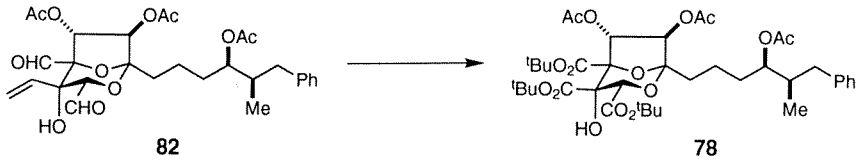
Olefin (81). 5% palladium on carbon (112 mg, 100 wt.%) was suspended in 5.0 mL of a pyridine solution of **71** (112 mg, 0.142 mmol). The slurry was stirred at 23 °C under 1 atm of H_2 for 4.5 h. Removal of the palladium catalysts by filtration through

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 R_f = 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 KH_2PO_4 solution. The mixture was extracted with 4 x 5 ml Et_2O, the combined organic extracts were washed once with sat. aqueous NaCl (5 ml), dried over Na_2SO_4 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 R_f = 0.13 (1:1 hexanes/EtOAc); $[\alpha]_{Na}$ +33.3° (*c* = 0.86, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 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, H_9), 5.79 (dd, 1H, *J* = 16.9, 0.9 Hz, -CH=C*H*$_2$), 5.51-5.48 (m, 2H, H_6 and -CH=C*H*$_2$), 5.17 (d, 1H, *J* = 3.0 Hz, H_7), 4.91-4.88 (m, 1H, $H_{4'}$), 3.98 (dd, 1H, *J* = 4.4, 4.1 Hz, H_3), 3.91 (s, 1H, -OH$_{3°}$), 3.80-3.71 (m, 4H, H_8, H_{10}), 2.74 (dd, 1H, *J* = 13.5, 5.0 Hz, $H_{6'}$), 2.33 (dd, 1H, *J* = 13.5, 9.4 Hz, $H_{6'}$), 2.30-2.26 (m, 1H, -OH$_{1°}$), 2.23 (dd, 1H, *J* = 6.4, 2.8 Hz, -OH$_{1°}$), 2.14 (s, 3H, -COC*H*$_3$), 2.13 (s, 3H, -COC*H*$_3$), 2.09 (s, 3H, -COC*H*$_3$), 2.01-1.97 (m, 1H, $H_{5'}$), 1.90-1.43 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.86 (d, 3H, *J* = 6.9 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{29}H_{40}O_{11}$ 564.2570, found 565.2634 (MH$^+$).

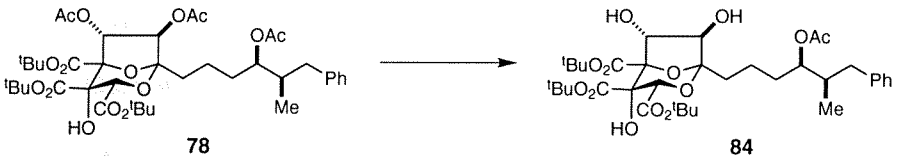


Dialdehyde (82). To a solution of **81** (40.0 mg, 70.8 μmol) in 4.0 mL of CH_2Cl_2 was added 72 μL of pyridine (0.9 mmol, 12.5 equiv) followed by 150 mg (0.35 mmol, 5 equiv) of the Dess–Martin periodinane.[31] The resulting white suspension was stirred at 23 °C for 2.5 h. To the reaction mixture was then added 5.0 mL of Et_2O, 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 R_f = 0.16 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +33.1° (*c* = 0.39, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.47 (s, 1H, -C*H*O), 9.36 (s, 1H, -C*H*O), 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, H_9), 5.73 (d, 1H, *J* = 16.7 Hz, -CH=CH_2), 5.65 (d, 1H, *J* = 11.5 Hz, -CH=CH_2), 5.56 (d, 1H, *J* = 2.6 Hz, H_6), 5.24 (d, 1H, *J* = 2.6 Hz, H_7), 4.91-4.89 (m, 1H, $H_{4'}$), 4.40 (s, 1H, H_3), 3.62 (d, 1H, *J* = 1.6 Hz, -$OH_{3'}$), 2.75 (dd, 1H, *J* = 13.5, 5.2 Hz, $H_{6'}$), 2.33 (dd, 1H, *J* = 13.4, 9.3 Hz, $H_{6'}$), 2.15 (s, 3H, -COCH_3), 2.09 (s, 3H, -COCH_3), 2.07 (s, 3H, -COCH_3), 2.01-1.97 (m, 1H, $H_{5'}$), 1.90-1.52 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.86 (d, 3H, *J* = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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) ν 3459, 2966, 1743, 1420, 1373, 1237, 1036, 959, 740, 702 cm^{-1}; HRMS (FAB^+) calc'd for $C_{29}H_{36}O_{11}$ 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-CH_2Cl_2 solution was cooled to –78 °C and treated with a dilute stream of ozone in oxygen (0.8 mmol/min). After 30 min, PPh_3 (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 ^{t}BuOH/2–methyl–2–butene solution and cooled to ca. 10 °C. An ice-cold buffered 1.1 M aqueous solution of $NaClO_2$ (370 μL, ca. 410 μmol, 10 equiv) was added dropwise.[58] The resulting pale yellow solution was stirred for 3 h before being quenched with 5.0 mL of a pH 2 KH_2PO_4-HCl buffer. The solution was extracted with 6 x 5 mL EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified product was redissolved in 3.0 mL of CH_2Cl_2 and *N,N'*-diisopropyl-*O-tert*-butylisourea (**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); $[\alpha]_{Na}$ +69.9° (*c* = 0.29, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.25 (m, 2H, $H_{aromatic}$), 7.16 (t, 1H, *J* = 7.3 Hz, $H_{aromatic}$), 7.11 (d, 2H, *J* = 7.4 Hz, $H_{aromatic}$), 6.33 (d, 1H, *J* = 1.9 Hz, H_6), 5.08 (d, 1H, *J* = 1.9 Hz, H_7), 4.88 (s, 1H, H_3), 4.88-4.86 (m, 1H, $H_{4'}$), 4.06 (s, 1H, -$OH_{3°}$), 2.75 (dd, 1H, *J* = 13.4, 4.9 Hz, $H_{6'}$), 2.29 (dd, 1H, *J* = 13.4, 9.6 Hz, $H_{6'}$), 2.14 (s, 3H, -COCH_3), 2.06 (s, 3H, -COCH_3), 2.05 (s, 3H, -COCH_3), 2.05-1.91 (m, 3H, $H_{1'}$, $H_{5'}$), 1.67-1.50 (m, 4H, $H_{2'}$, $H_{3'}$), 1.61 (s, 9H, H_{tBu}), 1.46 (s, 9H, H_{tBu}), 1.45 (s, 9H, H_{tBu}),

0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR (CD_3OD, 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 $C_{40}H_{58}O_{15}$ 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_2CO_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_2PO_4 solution. The mixture was extracted with 5 x 3 mL Et_2O; the combined organic extracts were dried over Na_2SO_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); ^1H NMR (CD_3OD, 500 MHz) δ 7.26-7.22 (m, 2H, $H_{aromatic}$), 7.16-7.13 (m, 3H, $H_{aromatic}$), 4.97 (s, 1H, H_3), 4.95 (d, 1H, J = 2.0 Hz, H_6), 4.90-4.86 (m, 1H, $H_{4'}$), 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, -COC*H*$_3$), 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_{tBu}), 1.46 (s, 9H, H_{tBu}), 1.45 (s, 9H, H_{tBu}), 0.87 (d, 3H, $H_{13'}$) ppm; ^{13}C NMR (CD_3OD, 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^+).

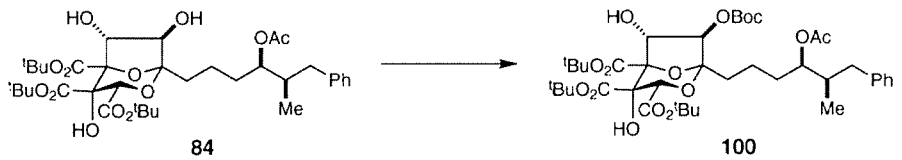
87

Allylic alcohol (87). To a suspension of $LiAlH_4$ (3.6 g, 95 mmol, 2.5 equiv) in 200 mL of Et_2O 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_2O, 3.6 mL 15% aqueous NaOH, and 10.8 mL H_2O, 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_2O. The colorless filtrate was dried over Na_2SO_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); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.26 (m, 2H, $H_{aromatic}$), 7.20-7.18 (m, 3H, $H_{aromatic}$), 5.75-5.63 (m, 2H, -C*H*=C*H*CH_2OH), 4.09 (d, 2H, *J* = 5.6 Hz, -C*H*$_2$OH), 2.64 (t, 2H, *J* = 7.7 Hz, PhC*H*$_2$$CH_2$-), 2.10 (dt, 2H, *J* = 7.1, 6.8 Hz, -C*H*$_2$CH=CHCH_2OH), 1.74 (tt, 2H, *J* = 7.6 Hz, $PhCH_2$C*H*$_2$$CH_2$-), 1.38 (br s, 1H, -$OH_1$°) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.3, 132.8, 129.4, 128.4, 128.3, 125.7, 63.7, 35.3, 31.7, 30.7 ppm; IR (thin film) ν 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.

87 88

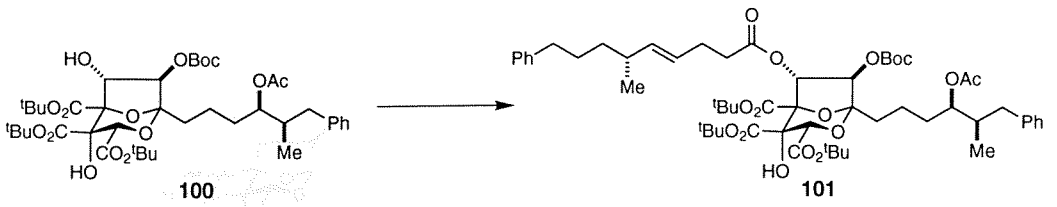
Epoxy Alcohol (88). A flask containing 1.0 g of freshly activated 4Å molecular sieves was charged with 140 mL of CH_2Cl_2 and 268 μL of L-(+)-diisopropyl tartrate (1.28 mmol, 0.075 equiv). The mixture was cooled to -30 °C (2:3 ethylene glycol/H_2O-dry ice) before $Ti(O^iPr)_4$ (250 μL, 0.85 mmol, 0.05 equiv) and a 4.0 M CH_2Cl_2 solution of ^{t}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 CH_2Cl_2 was added dropwise via cannula. Transfer of **87** was made quantitative with an additional 2.0 mL of CH_2Cl_2. 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 Et_2O. 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 $MgSO_4$, the slurry was warmed to 23 °C and the mixture was filtered through Celite. The solids collected were rinsed with Et_2O (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 R_f = 0.20 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +18.9° (*c* = 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.26 (m, 2H, $H_{aromatic}$), 7.21-7.18 (m, 3H, $H_{aromatic}$), 3.89 (ddd, 1H, *J* = 12.5, 5.1, 2.5 Hz, -OC*H*CH_2OH), 3.61 (ddd, 1H, *J* = 12.5, 7.1, 4.8 Hz, $PhCH_2CH_2CH_2HCO$-), 3.00-2.96 (m, 1H, -C*H*$_2$OH), 2.92-2.90 (m, 1H, -C*H*$_2$OH), 2.68 (t, 2H, *J* = 7.7 Hz, PhC*H*$_2$$CH_2$-), 1.90 (br s, 1H, -OH), 1.85-1.73 (m, 2H, $PhCH_2CH_2CH_2$CH-), 1.68-1.57 (m, 2H, $PhCH_2CH_2CH_2$-) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{12}H_{16}O_2$: 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).



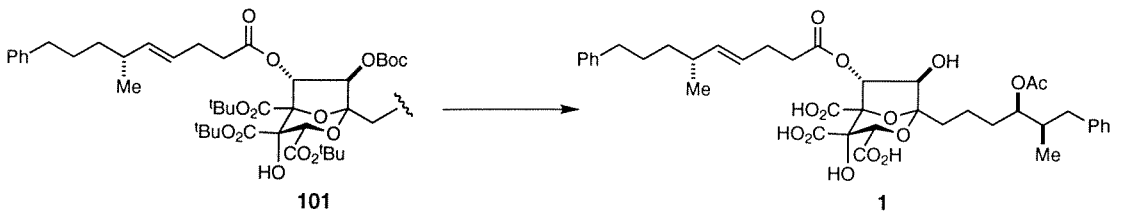
C(7)-OBoc (100). To a cold solution (0 °C) of **84** (8.5 mg, 12.2 μmol) and 4-pyrrolidinopyridine (1.5 mg, 10.1 μmol, 0.8 equiv) in 1.0 mL of CH_2Cl_2 was added Et_3N (7 μL, 49.4 μmol, 4.0 equiv) followed by 140 μL of a 0.10 M CH_2Cl_2 solution of di-*tert*-butyl dicarbonate (14.0 μmol, 1.15 equiv). 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_2HPO_4 and extracted with 5 x 2 mL Et_2O. The combined ethereal extracts were washed once with sat. aqueous NaCl (5 mL), dried over Na_2SO_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); $[\alpha]_{Na}$ +43.3° (*c* = 0.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.24 (m, 2H, $H_{aromatic}$), 7.17 (t, 1H, *J* = 7.3 Hz, $H_{aromatic}$), 7.12 (d, 2H, *J* = 7.1 Hz, $H_{aromatic}$), 5.11 (br. s, 1H, H_6), 4.88-4.86 (m, 1H, $H_{4'}$), 4.72 (s, 1H, H_3), 4.64 (d, 1H, *J* = 2.1 Hz, H_7), 3.93 (br. s, 1H, -$OH_{3'}$), 2.80 (br. s, 1H, -$OH_{2'}$), 2.75 (dd, 1H, *J* = 13.5, 5.1 Hz, $H_{6'}$), 2.30 (dd, 1H, *J* = 13.5, 9.7 Hz, $H_{6'}$), 2.05 (s, 3H, -COCH_3), 2.05-1.91 (m, 3H, $H_{1'}$, $H_{5'}$), 1.68-1.26 (m, 4H, $H_{2'}$, $H_{3'}$), 1.58 (s, 9H, $H_{Boc\text{-}tBu}$), 1.50 (s, 9H, H_{tBu}), 1.49 (s, 9H, H_{tBu}), 1.45 (s, 9H, H_{tBu}), 0.84 (d, 3H, *J* = 6.8 Hz, $H_{13'}$) 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,

964, 843, 733 cm^{-1}; HRMS (FAB^+) calc'd for $C_{41}H_{62}O_{15}$ 794.4088, found 817.3986 (MNa^+).



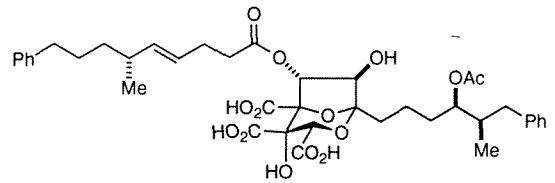
C(7)-OBoc Zaragozic Acid C, 3,4,5-tris-*tert*-Butyl Ester (101). To a solution of acyl side chain acid **92** (9.0 mg, 36.5 μmol) in 365 μL of CH_2Cl_2 was added 7.5 mg of 1,3-dicyclohexylcarbodiimide (36.5 μmol). The resulting suspension was stirred for 15 min before use. A solution of **100** (4.0 mg, 5.0 μmol) and 4–DMAP (2 mg, 16 μmol) in 1.0 mL of CH_2Cl_2 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 $NaHCO_3$. The mixture was extracted with 4 x 2 mL Et_2O; the organic extracts were dried over Na_2SO_4 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 R_f = 0.37 (3:1 hexanes/EtOAc); $[\alpha]_{Na}$ +8.5° (*c* = 0.27, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.22 (m, 4H, $H_{aromatic}$), 7.18-7.12 (m, 6H, $H_{aromatic}$), 6.40 (d, 1H, *J* = 1.9 Hz, H_6), 5.38-5.29 (m, 2H, $H_{4''}$, $H_{5''}$), 4.91 (s, 1H, H_3), 4.89-4.86 (m, 2H, H_7, $H_{4'}$), 4.05 (br s, 1H, $-OH_{3^\circ}$), 2.76 (dd, 1H, *J* = 13.4, 4.7 Hz, $H_{6'}$), 2. 57 (t, 2H, *J* = 7.7 Hz, $H_{9''}$), 2.39-2.27 (m, 3H, $H_{6'}$, $H_{2''}$), 2.12-1.84 (m, 6H, $H_{1'}$, $H_{5'}$, $H_{3''}$, $H_{6''}$), 2.05 (s, 3H, -COCH_3), 1.68-1.26 (m, 8H, $H_{2'}$, $H_{3'}$, $H_{7''}$, $H_{8''}$), 1.62 (s, 9H, $H_{Boc\text{-}tBu}$), 1.47 (s, 9H, H_{tBu}), 1.452 (s, 9H, H_{tBu}), 1.446 (s, 9H, H_{tBu}), 0.93 (d, 3H, *J* = 6.7 Hz, $H_{16''}$), 0.83 (d, 3H, *J* = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR ($CDCl_3$, 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 $CDCl_3$), 76.2, 75.3, 74.0, 39.4, 38.0, 36.6, 36.5, 36.1, 35.8, 34.2, 30.9, 29.2, 28.1 (2 lines), 28.0,

27.9, 27.7, 21.2, 20.6, 18.9, 13.9 ppm; IR (thin film) ν 3480, 2933, 1746, 1458, 1370, 1279, 1254, 1158, 1118, 700 cm^{-1}; HRMS (FAB$^+$) calc'd for $C_{57}H_{82}O_{16}$ 1022.5602, found 1045.5501 (MNa^+).



Zaragozic Acid C (1). To a solution of **101** (3.0 mg, 2.9 μmol) in 1.5 mL of CH_2Cl_2 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 R_f = 0.34 (6:1 CH_3CN/H_2O); HPLC: t_R = 12.03 ± 0.5 min (reverse phase, 20% CH_3CN in 0.1% aqueous H_3PO_4 initially, graded to 95% CH_3CN over 20 min); $[\alpha]_{Na}$ +9.0° (*c* = 0.23, EtOH); ^1H NMR (CD_3OD, 500 MHz) δ 7.25-7.21 (m, 4H, $H_{aromatic}$), 7.15-7.10 (m, 6H, $H_{aromatic}$), 6.23 (d, 1H, *J* = 1.8 Hz, H_6), 5.37 (dt, 1H, *J* = 15.3, 6.1 Hz, $H_{4''}$), 5.30 (dd, 1H, *J* = 15.4, 7.5 Hz, $H_{5''}$), 5.23 (s, 1H, H_3), 4.90-4.86 (m, 1H, $H_{4'}$ masked by CD_3OH signal), 4.01 (d, 1H, *J* = 1.8 Hz, H_7), 2.73 (dd, 1H, *J* = 13.3, 5.6 Hz, $H_{6'}$), 2.58-2.54 (m, 2H, $H_{9''}$), 2.37-2.32 (m, 3H, $H_{6'}$, $H_{2''}$), 2.28-2.25 (m, 2H, $H_{3''}$), 2.09-2.01 (m, 3H, $H_{5'}$, $H_{6''}$), 2.05 (s, 3H, -COC*H*$_3$), 1.91-1.86 (m, 2H, $H_{1'}$), 1.69-1.66 (m, 2H, $H_{3'}$), 1.61-1.53 (m, 4H, $H_{2'}$, $H_{8''}$), 1.31-1.24 (m, 2H, $H_{7''}$), 0.93 (d, 3H, *J* = 6.9 Hz, $H_{16''}$), 0.86 (d, 3H, *J* = 6.8 Hz, $H_{13'}$) ppm; ^{13}C NMR (CD_3OD, 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^+).



(+)–Zaragozic Acid C

(d_4–MeOH)

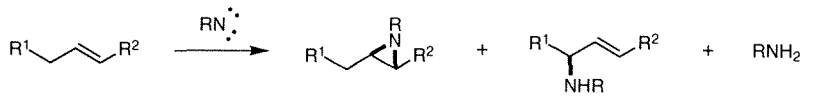
Part II. Nitridomanganese(V) Complexes: Design, Preparation and Use as Novel Nitrogen Atom-Transfer Reagents

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



(1)

---

1. (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidation of Organic Compounds,* Academic: New York, 1981. (b) Mijs, W. J.; de Jonge, C. R. H. I. (Eds.)*Organic Synthesis by Oxidation with Metal Compounds*, Plenum: New York, 1986. (c) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*, Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995, Vol. 12, 1097. (d) Murahashi, S.-I.; Naota, T. In *Comprehensive Organometallic Chemistry II*, Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995, Vol. 12, 1177.

2. (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993, p. 159. (b) Jorgensen, K. A., *Chem. Rev.* **1989**, *89*, 431. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 243, and references therein. (d) Johnson, R. A.; Sharpless, K. B. In *Catalytic Aysmmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993, p 103. (e) Doyle, M. P. *Aldrichimica Acta* **1996**, *29*, 1996. (f) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

3. For leading references on olefin aziridination methodology, see (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (c) Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. *Tetrahedron* **1989**, *45*, 2875. (d) Atkinson, R. S. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984, 247.

to an olefin are often low yielding and complicated by product mixtures resulting from competing hydrogen abstraction and insertion reactions (eq 1).[4] 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).[5]

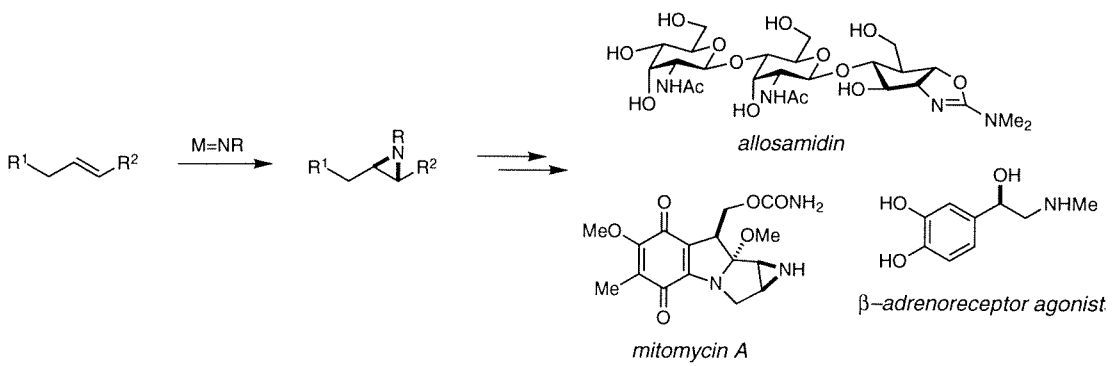
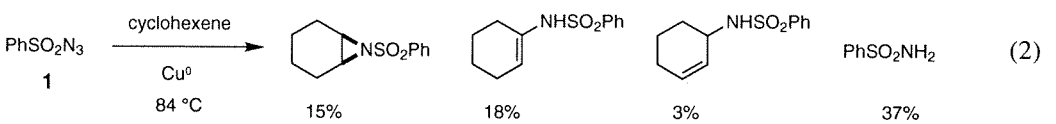


Figure 1. Olefin amination: a valuable method for chemical synthesis.

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



(2)

4. (a) Kemp, J. E. G. In *Comprehensive Organic Synthesis*, Ley, S. V., Ed.; Pergamon: Oxford, U.K., 1991, Vol. 7, p. 469. (b) Lwowski, W. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984, 205.

5. For a recent review on the applications of azirdines, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

decomposition.[6] 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).[7] In this work, *p*–tolylsulfonyl 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.

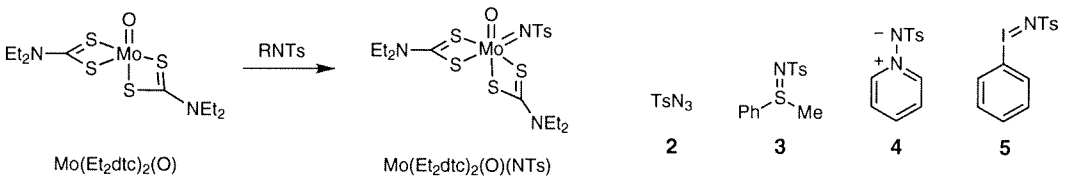
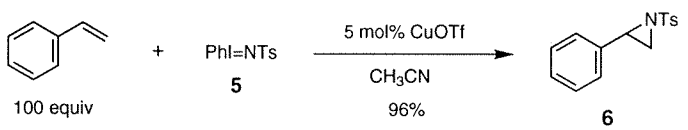


Figure 2. Imido group transfer reactions with nitrene equivalents **2–5**.

Evans has reported the use of compounds **2–5** as nitrogen atom sources for olefin aziridination reactions.[3a] In these studies, **2–5** were screened for their efficacy in the aziridination of styrene (100 equiv) with catalytic CuOTf (5 mol%). (*N*–(*p*–tolylsulfonyl)imino)phenyliodinane (PhI=NTs) **5** was found to be the most effective



(3)

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

---

6. Kwart, H.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951.

7. (a) Harlan, E. W.; Holm, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 186, and references therein. Also, see: Chou, C. Y.; Devore, D. D.; Huckett, S. C.; Maata, E. A.; Huffman, J. C.; Takasugawa, F. *Polyhedron* **1986**, *5*, 301, and references therein.

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

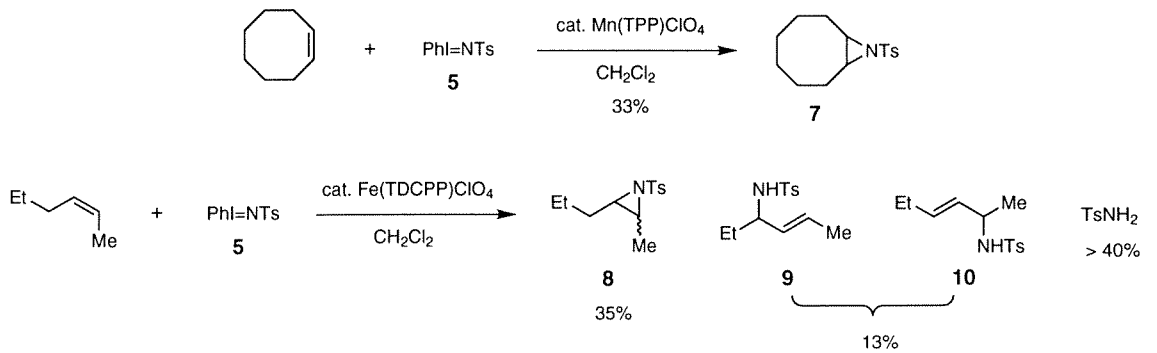
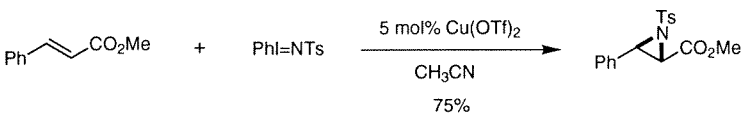


Figure 3. Aziridination and allylic amination of alkenes with PhI=NTs.

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



(4)

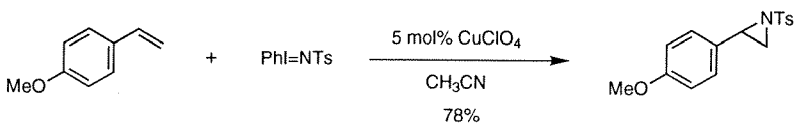
process.[8,9] However, the subsequent finding by Evans that both Cu(I) and Cu(II) salts were significantly more effective as catalysts for transfer of NTs from PhI=NTs to an

---

8. (a) Mansuy, D.; Mahy, J.-P. In *Metalloporphyrins Catalyzed Oxidations*; Montanari, F. and Casella, L., Eds.; Kluwer Academic Publishers: Dordrecht, 1994, 175. (b) Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *New J. Chem.* **13**, *651*, 1989. (c) Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1517. (d) Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927. (e) Mansuy, D.; Mahy, J.-P.; Duréault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161.

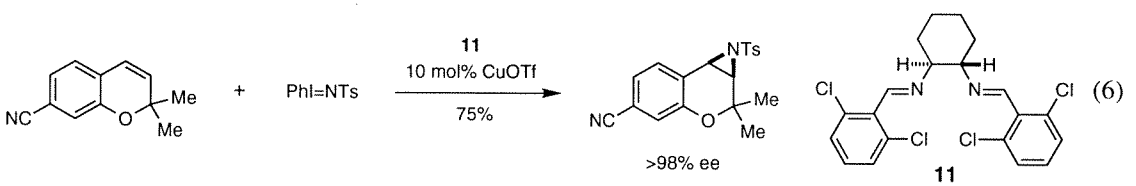
9. (a) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728. (b) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400.

olefin has greatly extended the scope and utility of this methodology.[3a,3b,10] Using



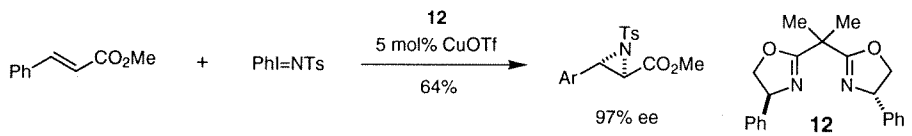
(5)

$CuClO_4$, $Cu(acac)_2$, 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



(6)

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]



(7)

---

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

11. Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

12. Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

13. For additional reports of metal-catalyzed, asymmetric aziridination, see: (a) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245. (b) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469. (c) O'Connor, K. J.; Wey, S.-J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001.

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

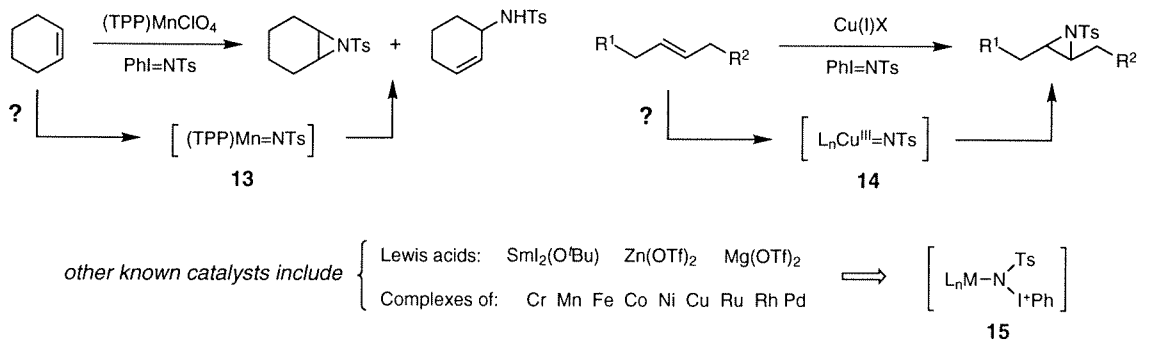


Figure 4. Possible pathways in the nitrene transfer reaction with PhI=NTs and metal catalysts.

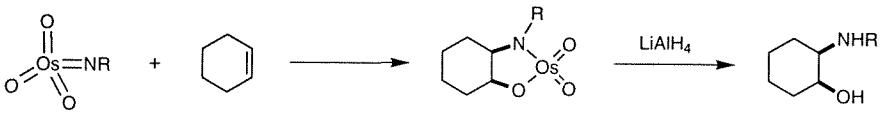
follows from the isolation of allylic insertion products with simple olefins (e.g., 2-hexene), compounds typically identified in reactions involving nitrene species.[8a,8c,14] Additionally, Jacobsen has reported evidence for the involvement of a discrete, monomeric Cu(III)–nitrene **14** in the Cu(I)/PhI=NTs olefin aziridination process.[15] Unlike the Mn and Fe systems, however, copper salts exhibit an exceedingly low propensity to catalyze C–H insertion of NTs.[3a] This, coupled with the fact that Lewis acids ($SmI_2(O^tBu)$, $Zn(OTf)_2$, $Mg(OTf)_2$) 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

14. (a) Mahy, J.-P.; Battioni, P.; Bedi, G.; Mansuy, D.; Fisher, J.; Weiss, R.; Morgenstern-Badarau, I. *Inorg. Chem.* **1988**, *27*, 353. (b) Mahy, J.-P.; Battioni, P.; Mansuy, D. *J. Am. Chem. Soc.* **1986**, *108*, 1079.

15. Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.

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

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



(8)

reaction of an olefin with stoichiometric amounts of trioxo(*tert*–alkylimido)osmium(VIII) (derived from OsO_4), followed by reductive cleavage of the resulting osmate ester with $LiAlH_4$ (eq 8).[20] Subsequently, it was discovered that *N*–toluenesulfonyl amino alcohols could be generated with catalytic amounts of OsO_4 when Chloramine–T trihydrate ($TsNClNa•3H_2O$) was utilized as the nitrene source.[21,22] This method offered significant

---

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.

17. (a) $Rh_2(OAc)_4$ catalyzed aziridination, see: Muller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543. (b) Ru(bbpc)(PPh_3)Cl catalyzed aziridination, see: Ko, P.-H.; Chen, T.-Y.; Zhu, J.; Cheng, K.-F.; Peng, S.-M.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1995**, 2215.

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.

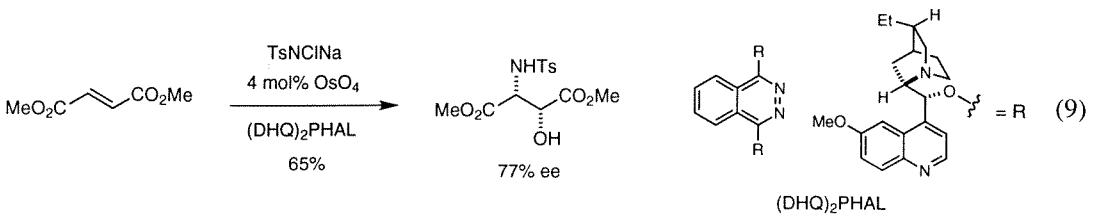
19. This work has been highlighted in a short review, see: Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1308.

20. Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305. Also, see: (a) Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628. (b) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420.

21. (a) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177. (b) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544.

22. *N*–Chloro–*N*–metallocarbamates may also be employed as nitrene equivalents, see: (a) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2710. (b) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3596.

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



(9)

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) **17** which, when reacted with trifluoroacetic anhydride (TFAA), transferred a CF_3CON unit to *cis*–cyclooctene to furnish the *N*–trifluoroacetyl-protected aziridine, **18** (Figure 5).[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.[4,8] Additionally, the mechanism for CF_3CON transfer parallels that of well-known manganese and iron-catalyzed epoxidation reactions (*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.[1a,25] In this regard, particular

---

23. Guigen, L.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.

24. (a) Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073. (b) Groves, J. T.; Takahashi, T.; Butler, W. M. *Inorg. Chem.* **1983**, *22*, 884.

25. (a) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science*, **1993**, *261*, 1404. (b) Ostovic, D.; Bruice, T. C. *Acc. Chem. Res.* **1992**, *25*, 314, and references therein. (c) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497. (d) Mansuy, D.; Battioni, P.; Battioni, J.-P. *Eur. J. Biochem.* **1989**, *184*, 267. (e) Holm, R. H. *Chem. Rev.* **1987**,

attention was paid to the numerous examples of olefin epoxidation catalyzed by non-porphyrin Mn and Fe complexes.[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.[24,27,28]

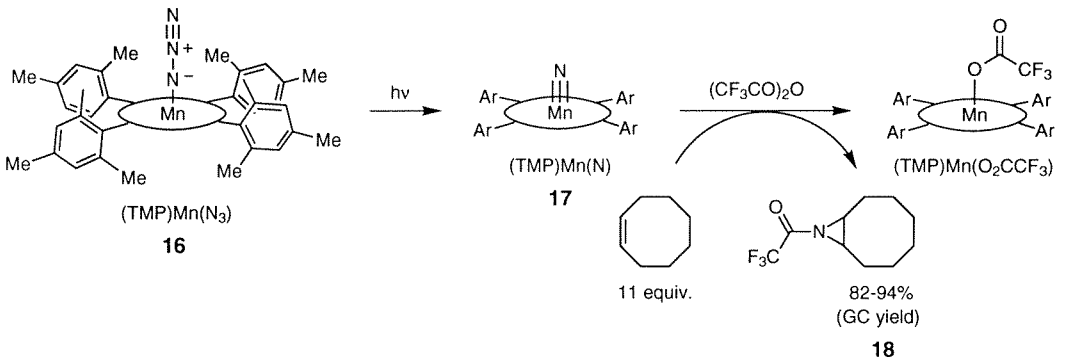


Figure 5. Aziridination of cyclooctene with nitrido[*meso*-tetrakis(2,4,6–trimethyl-phenyl)porphyrinato]manganese(V), (TMP)Mn(N).

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.

87, 1401, and references therein. (f) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375.

26. (a) Bottcher, A.; Grinstaff, M. W.; Labinger, J. A.; Gray, H. B. *J. Mol. Cat. A* **1996**, *113*, 191. (b) Katsuki, T. *J. Mol. Cat. A* **1996**, *113*, 87. (c) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (d) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

27. (a) Buchler, J. W.; Dreher, C.; Lay, K.-L. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, *37B*, 1155. (b) Hill, C. L.; Hollander, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 7318. (c) Buchler, J. W.; Dreher, C.; Lay, K.-L.; Lee, Y. J. A.; Scheidt, W. R. *Inorg. Chem.* **1983**, *22*, 888.

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 ($\lambda \geq 290$ 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.[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.[30] Thus, alternative Mn complexes with inexpensive, readily derivatizable ligand systems were considered.

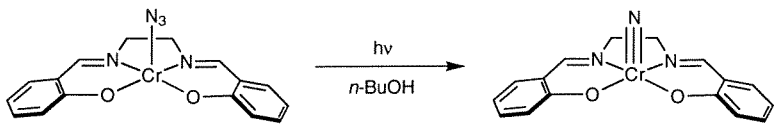
In an effort to find non-porphyrin ligands suitable for the formation of a highly oxidized Mn(V) nitrido species, we became interested in a report by Arshankow and Poznjak of a salen Cr(V) nitride **20** which had been prepared photolytically from the (salen)$Cr^{III}(N_3)$ **19** (eq 10).[31] Assignment of this complex as (salen)$Cr^{V}(N)$, in the absence of X–ray crystallographic data, was based on electron paramagnetic resonance (EPR) spectroscopy which supported a d^1 valence configuration, and infrared (IR) spectroscopy which established the presence of a Cr–nitrogen triple bond ($\nu_{Cr\equiv N}$ = 1012 cm^{-1}). Subsequently, Che had described a second non-porphyrin nitrido chromium

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

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

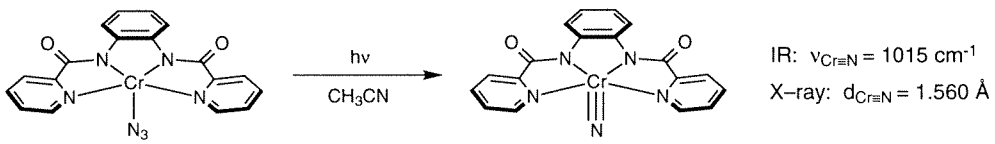
31. Arshankow, S. I.; Poznjak, A. L. *Z. Anorg. Allg. Chem.* **1981**, *481*, 201. (Salen)Cr(N) has also been prepared by intermetal nitrogen atom-transfer from an (octaethylporphyrinato)chromium nitride to (salen)CrCl, see: Neely, F. L.; Bottomley, L. A. *Inorg. Chim. Acta* **1992**, *192*, 147.

compound, (bpb)Cr^{V}(N) **22**, derived from the tetradentate 1,2–bis(2–pyridinecarboxamido)benzene (bpb) ligand (eq 11).[32] This was prepared in an analogous fashion to the (salen)Cr(N) complex, and had been characterized by single crystal X–ray



(salen)Cr(N_3) **19** (salen)Cr(N) **20** (10)

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.



(bpb)Cr(N_3) **21** (bpb)Cr(N) **22** (11)

Results

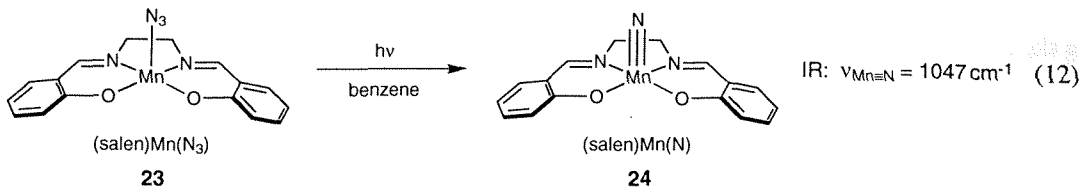
Synthesis. Following the protocol delineated by Arshankow and Poznjak, (salen)Mn^{V}(N) **24** was successfully prepared upon irradiation of the corresponding (salen)$Mn^{III}(N_3)$ **23** (eq 12). Although formation of **24** was possible under these conditions, isolated yields of this compound were 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 NH_4OH had been reported to yield the corresponding Cr(V) and

---

32. Che, C.-M.; Ma, J.-X.; Wong, W.-T.; Lai, T.-F.; Poon, C.-K. *Inorg. Chem.* **1988**, *27*, 2547. Also, see: Azuma, N.; Ozawa, T.; Tsuboyama, S. *J. Chem. Soc., Dalton Trans.* **1994**, 2609.

Mn(V) nitrides.[27] 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.[33] These concerns were assuaged when, upon treatment of a dark brown, methanolic suspension of (salen)Mn^{III}OAc with NH_4OH (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 (CH_2Cl_2, EtOAc, CH_3CN, Et_2O) 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.[34] Condensation of this diamine with salicylaldehyde (2 equiv) furnished the H_2saltmen ligand as a yellow crystalline solid (96%). The nitrido Mn(V) complex (**26**) derived from H_2saltmen was prepared in a single operation by first reacting $Mn(OAc)_2 \cdot 4H_2O$ with a solution of the ligand in methanol to give an air-oxidized (saltmen)Mn(III) intermediate **25**.[35] Subsequent

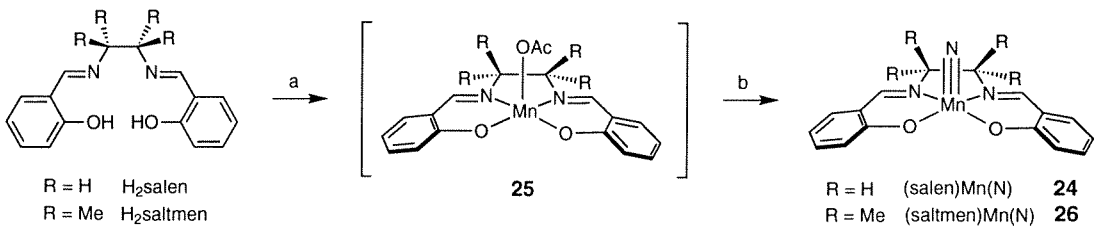
33. Collins, T. J. *Acc. Chem. Res.* **1994**, *27*, 279.

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 NH_4OH 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) $Mn(OAc)_2 \cdot 4H_2O$, MeOH; (b) 15 M NH_4OH, 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 H_2O. ^1H and ^{13}C 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 d^2 configuration. Infrared spectroscopic analysis established the Mn≡N stretching frequency at 1047 cm^{-1} for **24** and **26**, similar to that

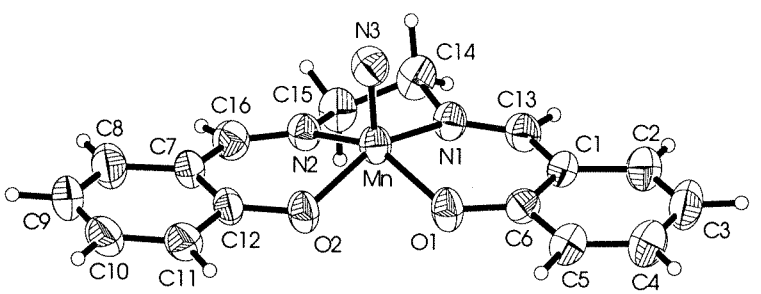


Figure 6. ORTEP diagram of (salen)Mn(N) **24** displaying 50% probability ellipsoids.

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

a Mn–N bond length of 1.51 Å, consistent with the assignment of a formal Mn≡N triple bond.[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.[38] Treatment of a solution of **26** (2 equiv), one equivalent of a Me_3Si–enol ether, and pyridine (3 equiv) in CH_2Cl_2 with trifluoroacetic anhydride (2.4 equiv) at reduced temperature (ca. –30 °C) led to rapid consumption of the starting materials and provided the corresponding *N*–trifluoroacetylated α–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_3CO_2H 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 °C does not occur.[39]

---

36. Crystal data for (salen)Mn(N) **1**: emerald green crystals were deposited by slow evaporation of a CH_2Cl_2 solution of **1**. Space group $P2_1/c$; cell constants: a = 9.496(3), b = 12.313(3), c = 12.857(4) Å; β = 103.61°; V = 1461.1(7) Å^3, Z = 4. A total of 4023 observations were collected ($Mo_{K\alpha}$, $2\theta_{max}$ = 44°, $-9 \leq h \leq 9$, $0 \leq k \leq 12$, $-13 \leq l \leq 13$) and merged to 1781 unique reflections (R_{merge} = 0.038, GOF_{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.

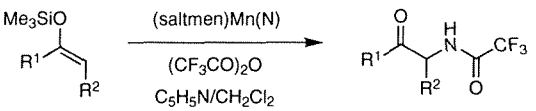
37. Mn≡N distances of 1.51 Å have been reported for (TpMPP)Mn(N) and (OEP)Mn(N), see ref. 27b and 27c, respectively.

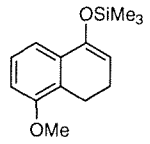
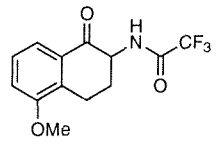
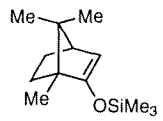
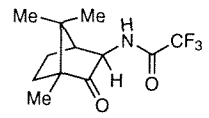
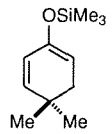
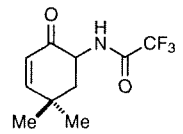
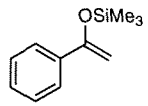
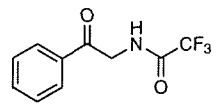
38. Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915.

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 α–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).



entry[a]	substrate	product	temperature (°C)	yield
1	 **27**	 **31**	–78→23	78%
2	 **28**	 **32**	–78→23	55%
3	 **29**	 **33**	–78→23	50%
4[b]	 **30**	 **34**	–30→23	69%

(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.

40. The *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. 353–354.

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*–trifluoroacetylimido manganese species **35** (Figure 7).[24a,29,41] Subsequent transfer of the CF_3CON 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

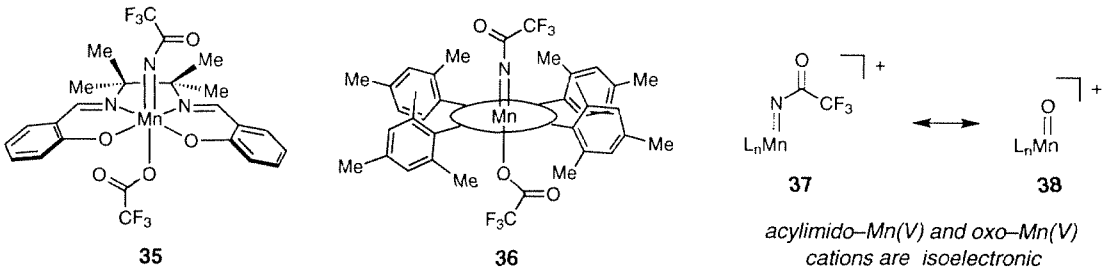


Figure 7. Electronic equivalence between reactive intermediates in manganese-mediated nitrogen and oxygen atom-transfer processes.

Mn–salen catalyzed reactions.[1a,25f,26d,35,42] Because of this relationship, it has been speculated that the mechanism for CF_3CON and oxygen-atom transfer to an olefin in

41. For mechanistic studies on the reaction of TFAA with nitrido Cr and Mn porphyrin complexes, see: (a) Bottomley, L. A.; Neely, F. L. *Inorg. Chem.* **1990**, *29*, 1860. (b) Bottomley, L. A.; Neely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 6748.

42. (a) Popisil, P.; Carsten, D. H.; Jacobsen, E. N. *Chem. Eur. J.* **1996**, *2*, 974. (b) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323. (c) Stern, M. K.; Groves, J. T. *J. Am. Chem. Soc.* **1988**, *110*, 8628, and references therein. (d) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606.

these processes are analogous.[8a,8c,24a,29,43] It is worth noting, however, that the $Mn{=}NCOCF_3^+$ and $Mn{=}O^+$ cations possess different reactivity and stability profiles, despite their electronic equivalence.[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.[45] Importantly, the t_{2g} metal orbitals together with the N^{3-} p_x and p_y MO's form a set of doubly degenerate π bonding and π* antibonding orbitals (d_{xz}, d_{yz}), and a singly degenerate nonbonding orbital (d_{xy}). The d^2 valence configuration for

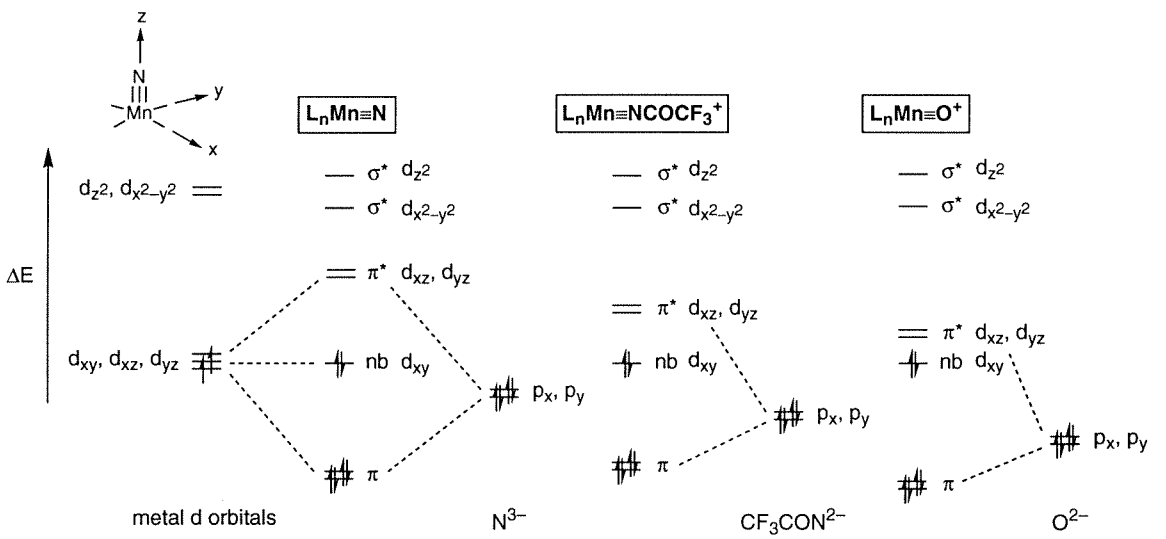


Figure 8. Molecular orbital diagrams for nitrido, imido, and oxo manganese species.

---

43. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.

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 double bond.

45. (a) Ballhausen, C. J.; Gray, H. B. *Inorg. Chem.* **1962**, *1*, 111. (b) Cowman, C. D.; Trogler, W. C.; Mann, K. R.; Poon, C. K.; Gray, H. B. *Inorg. Chem.* **1976**, *15*, 1747. (c) Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley Interscience: New York, 1988.

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

(1) The ability of metal imido compounds like **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 π^* 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 π^* 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.[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.[24a,29,38]

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

---

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* **1988**, *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.[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).[48,49] The intermediate aziridine **39** is expected to be quite labile, and, as a consequence, has not been observed

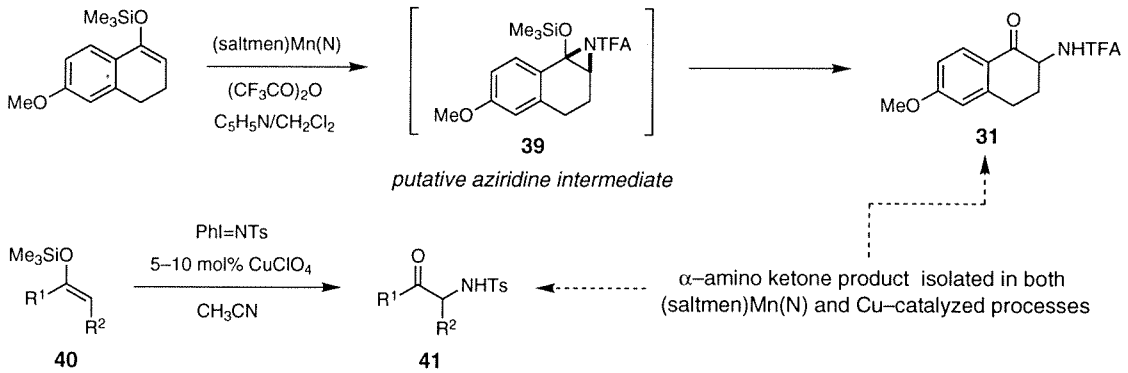


Figure 9. Proposed mechanism for silyl enol ether amination reactions.

in any of the reactions recorded.[50] Evans has reported reactions of enol silanes with PhI=NTs and catalytic $CuClO_4$. This reagent combination has been shown to furnish aziridine products in reactions with unfunctionalized olefins (*vide supra*). However, in

47. (a) Mansuy, D. *Coord. Chem. Rev.* **1993**, *125*, 129. (b) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462.

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. *Tetrahedron Lett.* **1983**, *24*, 593.

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. *Tetrahedron Lett.* **1974**, 4319.

50. A product which has been assigned as the *N*–trifluoracetylated aziridine was isolated from the reaction of (saltmen)Mn(N) **26** with TFAA and *p*–methoxystyrene.

accord with our observations, when silyl enol ethers **40** were reacted with $CuClO_4$ and PhI=NTs, *N*–(*p*–tolylsulfonyl) α–amino ketone products **41** were generated exclusively.[3a,3b]

Development of (salen)Mn(N) Derivatives. Although (saltmen)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 (saltmen)Mn(N) was employed under otherwise identical conditions. We speculated that the saltmen-derived Mn nitride was, for reasons unclear to us, intrinsically less reactive towards unfunctionalized, unsaturated

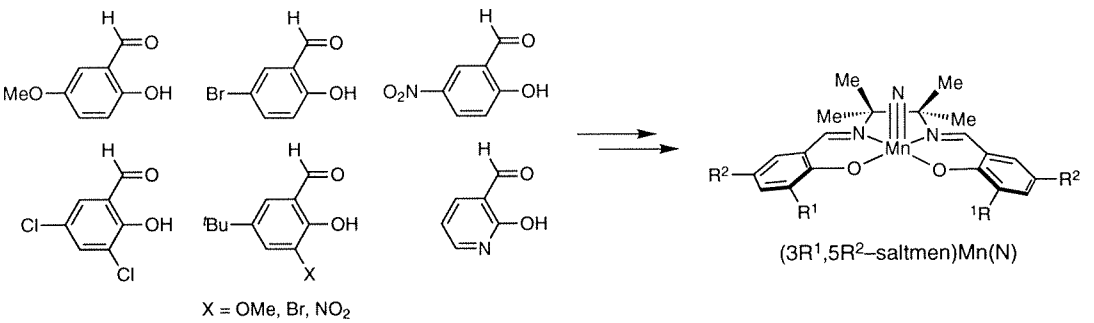


Figure 10. Generation of saltmen-based nitridomanganese reagents from substituted salicylaldehydes.

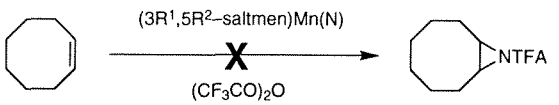
hydrocarbons than the nitrido porphyrin complex. To this end, derivatives of H_2saltmen with both electron withdrawing and electron donating groups were prepared in an effort to generate more reactive aminating agents.[26d,51]

---

51. 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.[52] Following the protocol outlined for the synthesis of H_2saltmen, 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 $Mn(OAc)_2 \cdot 4H_2O$ (1 equiv), and subsequently adding NH_4OH (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_2Cl_2 or CH_3CN 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



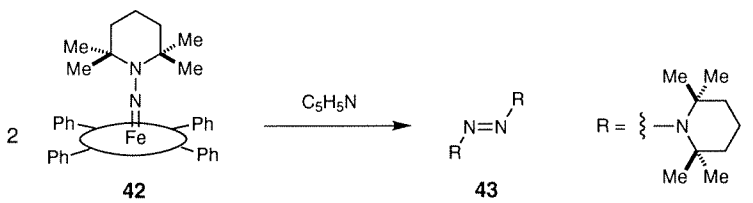
(13)

surprise, transfer of CF_3CON 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.

---

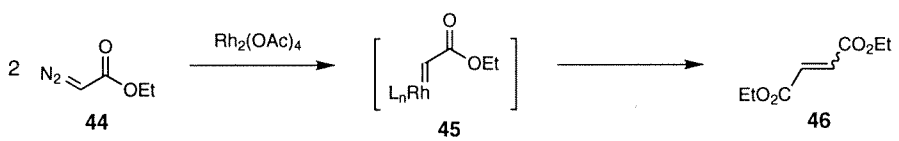
52. For an excellent method for the formylation of subsituted phenols, see: Aldred, R.; Johnston, R.; Levin, D.; Nieland, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1823.

Mechanistic Hypothesis – "The Cyclooctene Problem". The inability of (saltmen)Mn(N) **26** to transfer CF_3CON 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 $Mn{=}NCOCF_3$ 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).[53] Similarly, competitive



42 43 (14)

dimerization of carbenoid equivalents **45** to give olefins **46** is a common occurrence in metal-catalyzed cyclopropanation reactions from diazo precursors **44** (eq 15).[54] With



44 45 46 (15)

---

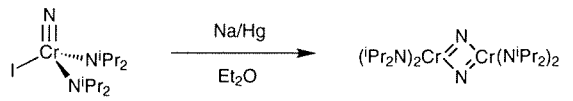
53. Mansuy, D.; Battioni, P.; Mahy, J.-P. *J. Am. Chem. Soc.* **1982**, *104*, 4487. Also, see: Mahy, J.-P.; Battioni, P.; Mansuy, D.; Fisher, J.; Weiss, R.; Mispelter, J.; Morgenstern-Badarau, I.; Gans, P. *J. Am. Chem. Soc.* **1984**, *106*, 1699.

54. (a) Maxwell, J. L.; Brown, K. C.; Bartley, D. W.; Kodadek, T. *Science* **1992**, *256*, 1544. (b) Doyle, M. P.; Griffith, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53. (c) Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787, and references therein.

reactive metal-oxo species **47**, the formation of oxo-bridged products **48** is well-precedented and is often a highly favorable process (eq 16).[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).[57] Thus, it appeared eminently reasonable that trifluoroacetylated

47 48 (16)

(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



49 50 (17)

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_3CON from nitridomanganese systems to unfunctionalized alkenes.[58] The first approach involved the construction of nitrido complexes with ligand systems designed to

---

55. (a) Chin, D.-H.; La Mar, G. N.; Balch, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 4344, and references therein. The X–ray structure of [(salen)Fe]$_2$(μ–O) has been solved, see: Davies, J. E.; Gatehouse, B. M. *Acta Cryst.* **1973**, *B29*, 1934, and references therein. An anlogous μ-aza bridged diiron complex, [(salen)Fe]$_2$(μ–NTol) has also been crystallographically characterized, see: Nichols, P. J.; Fallow, G. D.; Murray, K. S.; West, B. O. *Inorg. Chem.* **1988**, *27*, 2795.

56. μ–Oxo bridged Mn dimers have been characterized in reactions with PhI=O, see: (a) Smegal, J. A.; Schardt, B. C.; Hill, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 3510. (b) Smegal, J. A.; Hill, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 3515.

57. Odom, A. L.; Cummins, C. C. *Organometallics* **1996**, *15*, 898.

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

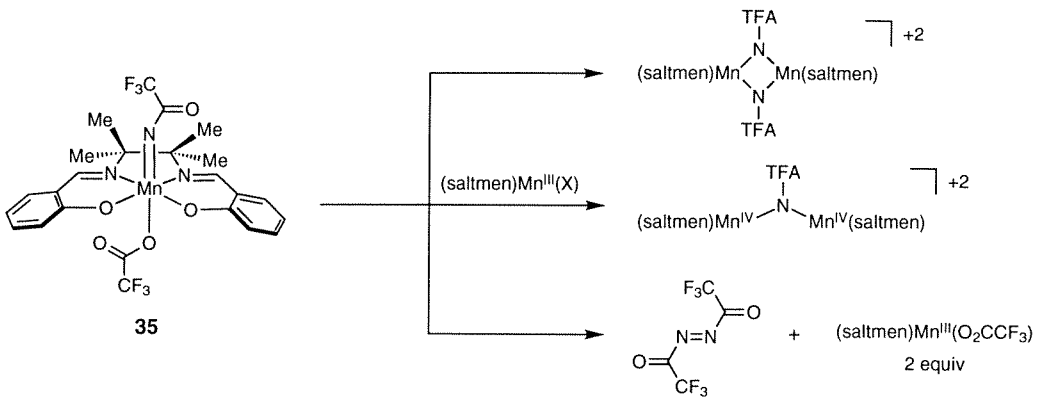


Figure 11. Possible bimolecular processes involving intermediate **35**.

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=NCOCF$_3$ species **35** would be kept low

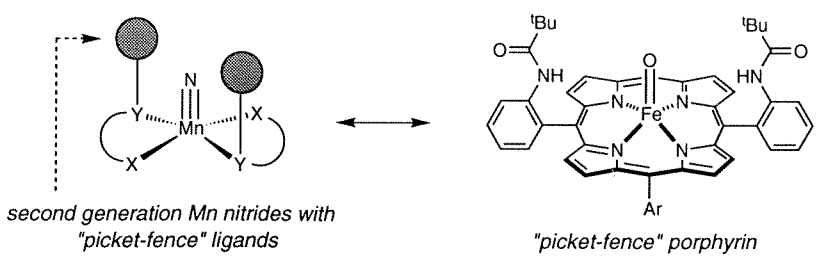


Figure 12. Second generation nitridomanganese reagents.

---

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

60. Collman, J. P.; Gagne, R. R.; Halbert, T. R.; Marchon, J.-C.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 7868. Also, see: Traylor, T. G. *Acc. Chem. Res.* **1981**, *14*, 102.

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

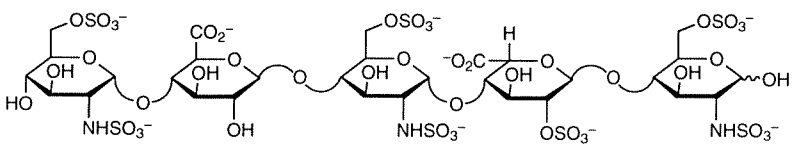
Both the "slow addition" and the "picket-fence" solutions have been investigated. The implementation of a new experimental procedure has made it possible to aminate glycal substrates, an important class of olefins which, in initial studies, had shown no reaction with the (saltmen)Mn(N) reagent. The successful 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

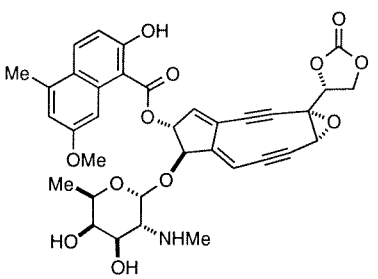
Novel, Stereoselective Synthesis of 2–Amino Saccharides

Introduction

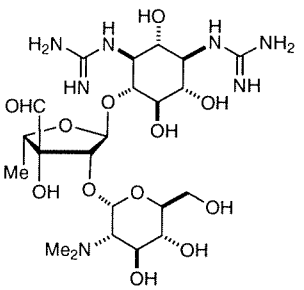
Available methods for the preparation of 2–amino sugars are few in number despite the ubiquity of such structures in nature (Figure 1).[1] Recent work by



Heparin pentasaccharide



Neocarzinostatin Chromophore



Streptomycin

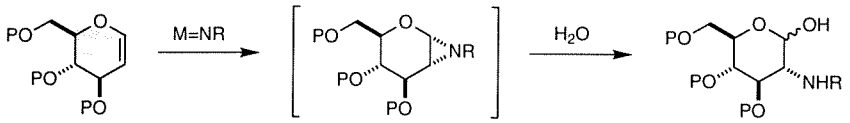
Figure 1. Naturally occurring 2–amino saccharides.

Danishefsky, Fitzsimmons and Leblanc has led to the development of two distinct methodologies for the conversion of carbohydrate glycals to the corresponding 2–amino

---

1. (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (b) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443. (c) Danishefsky, S. J.; Roberge, J. Y. *Pure Appl. Chem.* **1995**, *67*, 1647. (d) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167. (e) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

products.[2,3] These protocols have found widespread use in the construction of complex, amine-containing polysaccharides.[1a,4,5] 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.[1c] 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.



1 2

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

---

2. (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863. (c) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811.

3. (a) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995. (b) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889. (c) Fitzsimmons, B. J.; Leblanc, Y.; Chan, N.; Rokach, J. *J. Am. Chem. Soc.* **1988**, *110*, 5229. (d) Fitzsimmons, B. J.; Leblanc, Y.; Rokach, J. *J. Am. Chem. Soc.* **1987**, *109*, 285.

4. (a) Park, T. K.; Kim, I. J.; Hu, S.; Bilodeau, M. T.; Randolph, J. T.; Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 11488. (b) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Griffith, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 1940. (c) Danishefsky, S. J.; Koeski, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc.* **1992**, *114*, 8331.

5. (a) Leblanc, Y.; Labelle, M. In *ACS Symposium Series: Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; American Chemical Society: Washington, D.C., 1990, v. 494, p. 81. (b) Danishefsky, S. J.; DeNinno, S. L.; Chen, S.-H.; Boisvert, L.; Barbachyn, M. *J. Am. Chem. Soc.* **1989**, *111*, 5810.

azidonitration methods described by Lemieux.[6,7] In the former process, the reaction of glycals **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

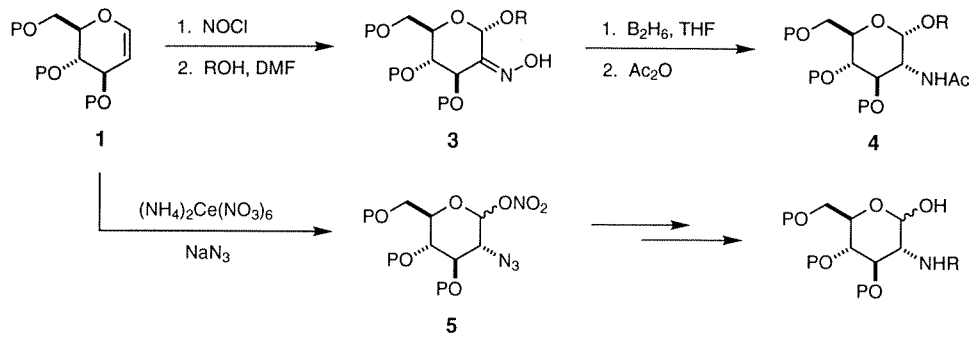


Figure 3. Lemieux's glycal nitrosochlorination and azidonitration methodologies.

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_3) to generate 2–azido products **5** (Figure 3). Facile reduction of the azide and hydrolysis of the anomeric 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 glycals 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).[8] Presumably, these

6. (a) Lemieux, R. U.; James, K.; Nagabhushan, T. L. *Can. J. Chem.* **1973**, *51*, 48. (b) Lemieux, R. U.; Ito, Y.; James, K.; Nagabhushan, T. L. *Can. J. Chem.* **1973**, *51*, 7. (c) Lemieux, R. U.; Nagabhushan, T. L. *Can. J. Chem.* **1968**, *46*, 413.

7. Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. Also, see: Bovin, V.; Zurabyan, S. É.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25.

8. (a) Kozlowska-Gramsz, E.; Descotes, G. *Can. J. Chem.* **1982**, *60*, 558. (b) Kozlowska-Gramsz, E.; Descotes, G. *Tetrahedron Lett.* **1981**, *22*, 563.

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

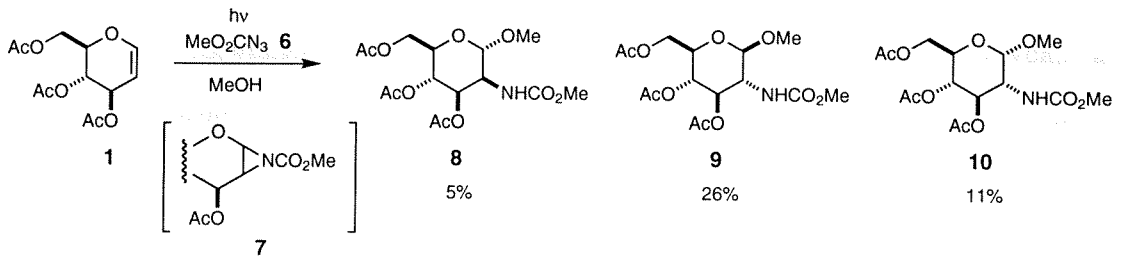
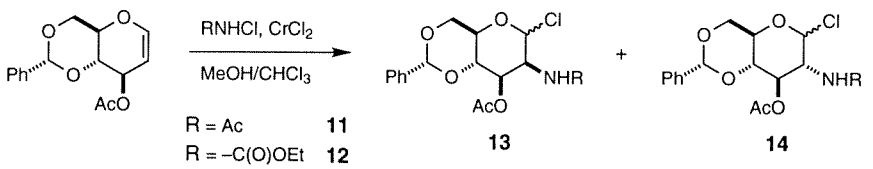


Figure 4. Glycal amination by photolysis of methyl azidoformate **6**.

12 catalyzed by chromous chloride ($CrCl_2$).[9] Like the photolysis reaction, however, this strategy has found limited use in synthesis (eq 1).



(1)

Fitzsimmons and Leblanc have developed one of the more practical and generally employed methodologies for the conversion of glycals to amino sugars.[3,5a] 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

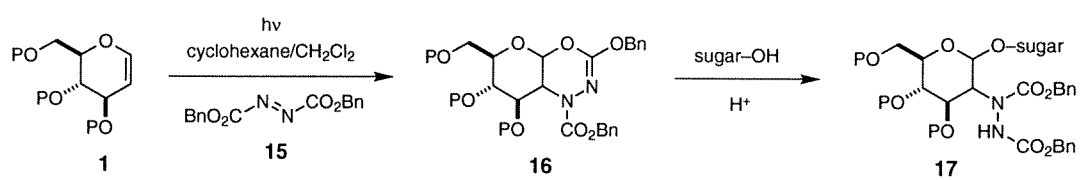


Figure 5. [4 + 2] Cycloaddition strategy for 2–amino sugar synthesis.

9. Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119.

or Lewis acidic conditions, **16** has been shown to function as an effective glycosyl donor.[3c,5] The resulting hydrazodicarboxylate linkage may be reductively cleaved using any one of a number of available reagent combinations (e.g.; Raney–Ni, H_2).

Arguably the most useful method for 2–amino sugar synthesis is the sulfonamidoglycosylation strategy of Danishefsky.[1a,2,4a,4b] As reported, glycals are initially transformed to 2–halo–1–sulfonamidopyranosides **18** under conditions which employ either benzenesulfonamide ($PhSO_2NH_2$) and iodonium di–*sym*–collidinium perchlorate ($I(sym\text{–coll})_2ClO_4$) or *N*,*N*–dibromobenzenesulfonamide. Subsequent

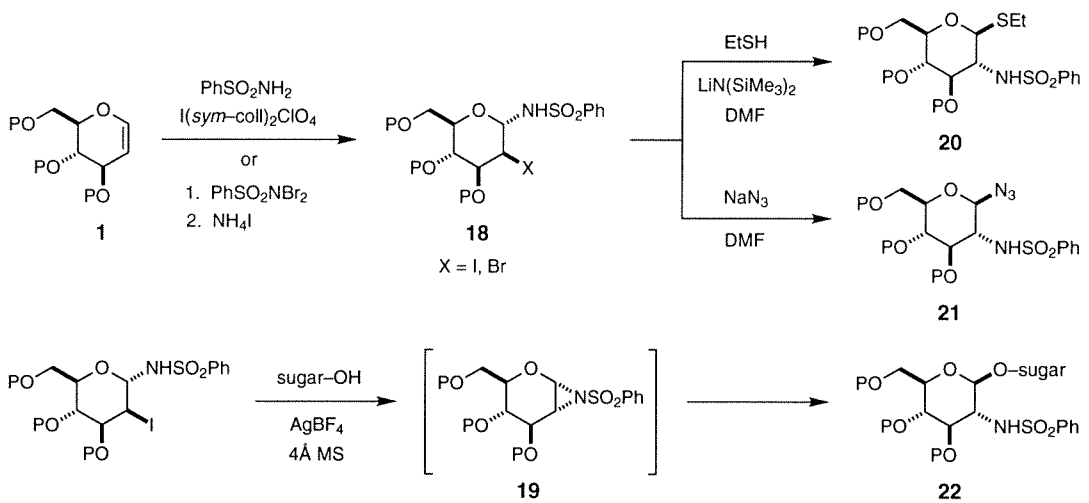


Figure 6. Danishefsky's sulfamidoglycosylation methodology.

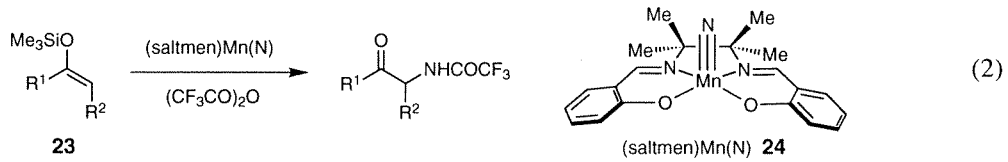
treatment of these materials with various nucleophiles (alkoxides, thiolates, azide), bases ($KN(TMS)_2$), or Ag^+ salts results in the rapid formation of the 2–sulfonamide products **20–22**, presumably via the intermediacy of a 1,2–sulfonylaziridine **19** (Figure 6).[1a,10] This putative aziridine is a highly reactive electrophile and promotes clean attack by nucleophiles at the anomeric position. The Danishefsky methodology offers an efficient

10. (a) Griffith, D. A. Ph.D. Dissertation, Yale University, New Haven, CT, 1993. (b) Takemura, S.; Otsuki, K.; Okamoto, K.; Ueno, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1881.

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).[11] 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.[12] As a result, we speculated that the reactive



(2)

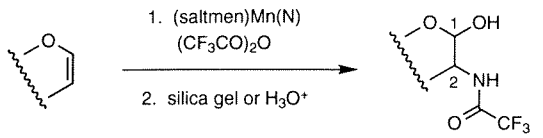
manganese species was being consumed in side-reactions which occurred at a rate faster than the desired alkene amination step. This problem could be circumvented by maintaining a high concentration of the glycal relative to the activated manganese complex, thereby allowing the rate of CF_3CON transfer to effectively compete with other

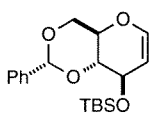
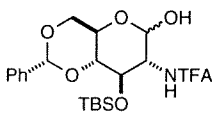
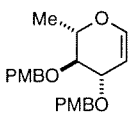
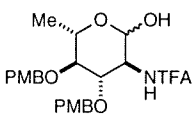
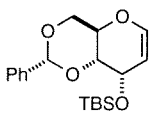
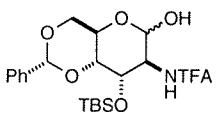
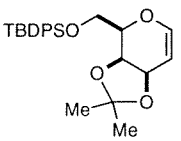
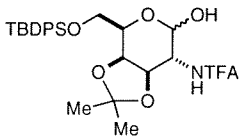
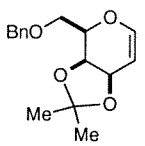
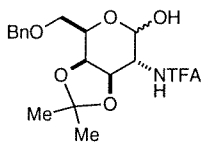
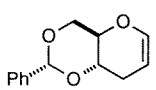
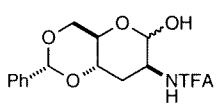
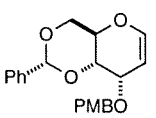
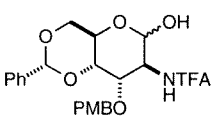
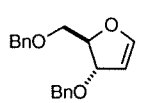
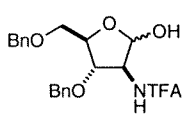
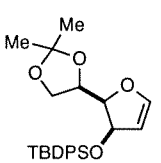
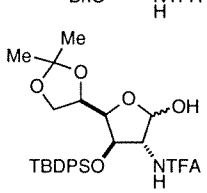
---

11. Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915.

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–2*H*–pyran. We have found that CF_3CON may be transferred to 3,4–dihydro–2*H*–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 glycals **36–44**.



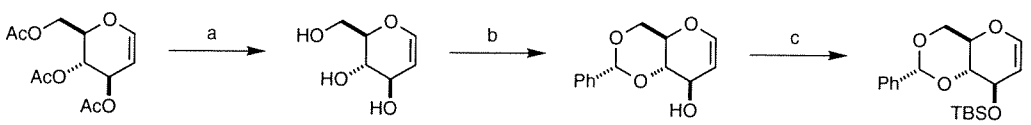
entry	glycal		major product		selectivity(C–2)[a]	yield
1		**36**		**45**	7:1	75%
2		**37**		**46**	7:1	60%
3		**38**		**47**	7:1	68%
4[b]		**39**		**48**	>10:1	64%
5[b]		**40**		**49**	>10:1	62%
6		**41**		**50**	1:1	70%
7		**42**		**51**	6:1	66%
8		**43**		**52**	>10:1	80%
9		**44**		**53**	>10:1	80%

(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, CH_2Cl_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).[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

Scheme 1



25 tri–*O*–acetyl–D–glucal **26** **27** **36**

(a) K_2CO_3, MeOH, 99%; (b) PhCHO, $ZnCl_2$, 11%; (c) TBSOTf, 2,6–lutidine, CH_2Cl_2, 95%.

preparation of these substrates was accomplished using standard carbohydrate methods and is oulined in Schemes 1–4.[14,15,16] Facile synthesis of the protected glycal **36** was

13. An analogous, slow addition procedure is typically used for alkene cyclopropanation reactions with diazo compounds, see: Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787.

14. For general references for the preparation of glycals, see: (a) Collins, P.; Ferrier, R. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*, John Wiley & Sons Ltd.: New York, 1995, p. 316. (b) Roth, W.; Pigman, W. In *Methods in Carbohydrate Chemistry*, Whistler, R. L. and Wolfrom, M. L., Eds.; Academic Press: New York, 1963, v. 2, p. 405. (c) Fraser-Reid, B.; Radatus, B.; Tam, S. Y.-K. In *Methods in Carbohydrate Chemistry*, Whistler, R. L. and BeMiller, J. N., Eds.; Academic Press: New York, 1980, v. 8, p. 219. (d) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825.

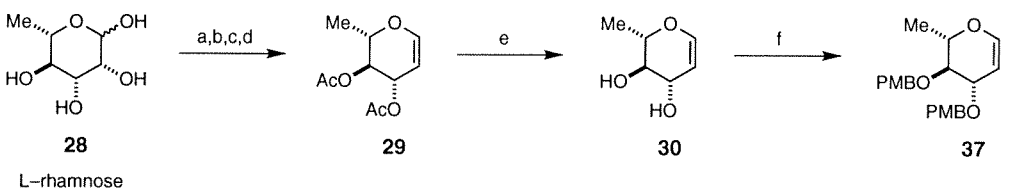
15. For leading references for the preparation of furanoid glycals, see: (a) Yokoyama, M.; Ikuma, T.; Obara, N.; Togo, H. *J. Chem. Soc. Perkin Trans. 1* **1990**, 3243, and references therein. (b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.

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).[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_2O, C_5H_5N) furnished the corresponding tetraacetate, which could be selectively de-esterified at C–1 (piperidine, THF, 80%) to reveal the anomeric –OH.[17] Conversion of this material to the glycosyl bromide was possible with PBr_3 (CH_2Cl_2, 94%). Subsequent reduction of the C–1 bromide using Zn dust (AcOH/Et_2O), with concomitant elimination of the C–2 acetate, installed the glycal bond (71%). Treatment of the resulting bis-acetate

Scheme 2

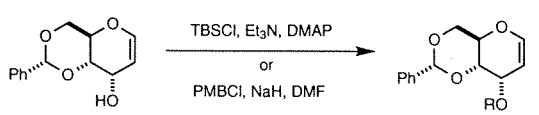


28 L–rhamnose **29** **30** **37**

(a) Ac_2O, C_5H_5N, 100%; (b) piperidine, THF, 80%; (c) PBr_3, CH_2Cl_2, 94%; (d) Zn, Et_2O/AcOH, 71%; (e) K_2CO_3, MeOH, 99%; (f) PMBCl, NaH, DMF, 41%.

---

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**.



4,6–*O*–benzylidene–D–allal **i**

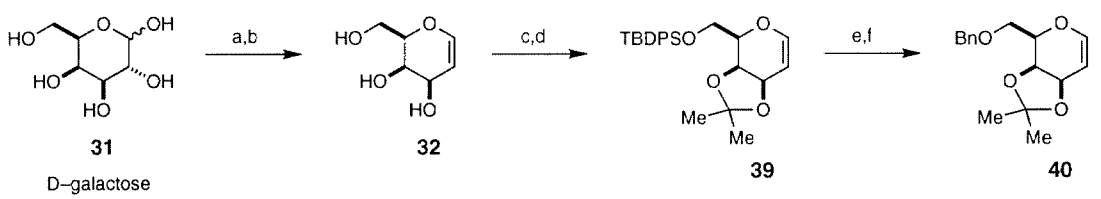
38: R = TBS
42: R = PMB

17. Rowell, R. M.; Feather, M. S. *Carbohyd. Res.* **1967**, *4*, 486.

29 with K_2CO_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 ineffeciency of this process, but may attributable to the insoluabiliy of **37** in standard chromatography solvents (EtOAc, Hexanes, CH_2Cl_2, $CHCl_3$, C_6H_6, Et_2O), 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_2O, $HClO_4$); (2) direct conversion of the pentaacetate to the glycosyl bromide with red phosphorous and Br_2; (3) reduction with Zn ($AcOH/H_2O$).[14b] 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_2CO_3 furnished galactal **32**. In order to block the C–3 and C–4 alcohols as

Scheme 3



31 D–galactose **32** **39** **40**

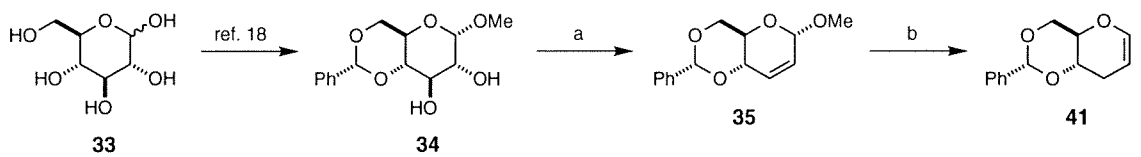
(a) i. Ac_2O, $HClO_4$ ii. red P, Br_2 iii. Zn, NaOAc, $CuSO_4$, $AcOH/H_2O$, 69%; (b) K_2CO_3, MeOH, 96%; (c) TBDPSCl, imidazole, DMF, 78%; (d) $Me_2C(OMe)_2$, PPTS, 92%; (e) *n*–Bu_4NF, THF, 93%; (f) BnCl, NaH, DMF, 97%.

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**.[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_3, PPh_3, imidazole).[19] Treatment of this allylic methyl ether **35** with $LiAlH_4$, as outlined by Fraser-Reid, resulted in exclusive S_n2' reduction to afford the target compound, **41** (57%).[14c] Glycal **41** was found to be only partially soluble in most organic solvents (EtOAc, Et_2O, C_6H_6, CH_2Cl_2) which precluded its purification by chromatography. However, **41** could be easily purified by recrystallization from 95% aq. EtOH.

Scheme 4



33 D–glucose **34** **35** **41**

(a) CHI_3, PPh_3, imidazole, Δ, 76%; (b) $LiAlH_4$, dioxane, 57%.

Amination Reactions. Following a procedure in which (saltmen)Mn(N) (1 equiv) was slowly added (ca. 7 h) to a CH_2Cl_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

---

18. (+)-(4,6–*O*–Benzylidene)methyl–α–D–glucopyranoside **34** may be purchased from Aldrich Chemical Co. or prepared from glucose **33**, see: Richtmyer, N. K. In *Methods in Carbohydrate Chemistry*, Whistler, R. L. and Wolfrom, M. L., Eds.; Academic Press: New York, 1962, v. 1, p. 108.

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).[11,20] In all cases (with the exception of entry 6), the product amino sugars were formed with high

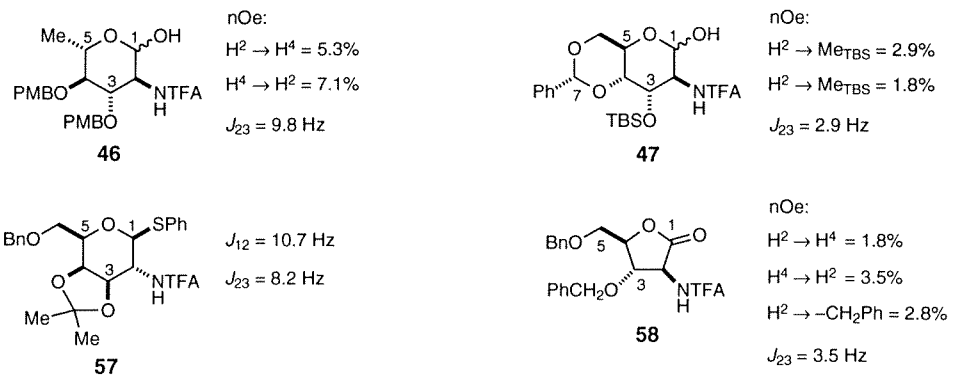


Figure 7. Select ^{1}H NMR difference nOe and coupling constant data.[21]

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).[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–*tert*–butyl–4–methylpyridine (3.0 equiv) was substituted for pyridine proved to be most effective with glycals **43** and **44**, see Experimental.

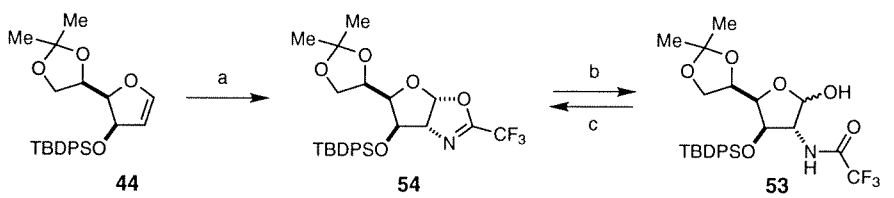
21. Lactone **58** was prepared by PCC oxidation (4 Å MS, CH_2Cl_2) of the corresponding lactol, **52** (C. S. Tomooka).

22. The magnitudes of the observed coupling constants compare favorably with literature values for analogous compounds, see ref. 10a.

derivatives.[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.[24] To this end we have isolated oxazoline **54** (derived from glycal **44**) which, under mildly acidic conditions, could be opened to the *N*–protected amino alcohol **53** (Scheme 5).[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_3N, CH_2Cl_2, 90%). For the six-membered ring glycals, both the putative aziridine and oxazoline products have eluded isolation.

Scheme 5



44 **54** **53**

(a) (saltmen)Mn(N), $(CF_3CO)_2O$, 2,6-di-*tert*-butyl-4-methyl-pyridine; (b) aq. AcOH, THF, 80% (two steps); (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2,90%.

We reasoned if an aziridine or oxazoline was an intermediate on the reaction pathway then it might be possible to trap *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_2Cl_2,

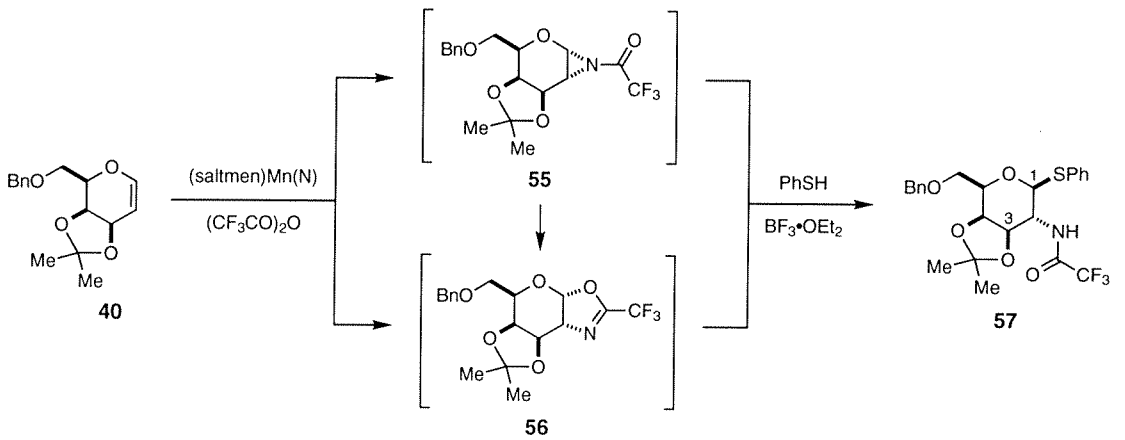
---

23. The *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.

24. *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

Scheme 6



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.

26. (a) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239, and references therein. (b) Kahne, D.; Walker, S.; Cheng, Y.; van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (c) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430. (d) Fukase, K.; Kinoshita, I.; Kanoh, T.; Nakai, Y.; Hasuoka, A.; Kusumoto, S. *Tetrahedron* **1996**, *52*, 3897, and references therein.

27. For a recent, comprehensive review on glycosylation methods, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

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_3CON 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]

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_3CON 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

---

1. Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915.

2. For leading references on metal-catalyzed aziridination with PhI=NTs, see: (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (c) Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1517. For other available aziridination and amination methods, see: Kemp, J. E. G. In *Comprehensive Organic Synthesis*, Ley, S. V., Ed.; Pergamon: Oxford, U.K., 1991, Vol. 7, p. 469, and references therein.

3. The results presented herein have been recently communicated, see: Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M.; Day, M. W. *Angew. Chem., Int. Ed. Engl.* **1997**, submitted for publication.

porphyrin and phthalocyanine derived systems.[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

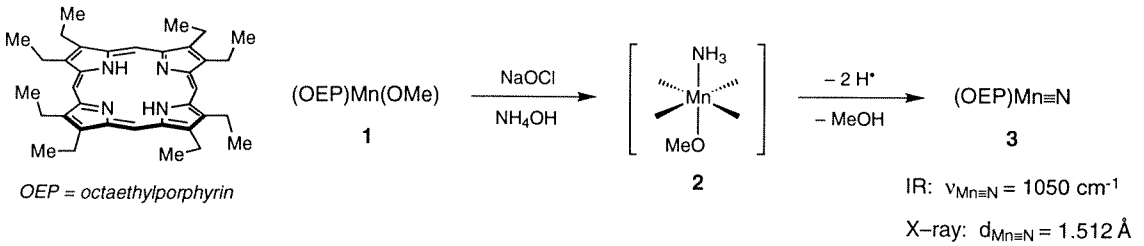


Figure 1. Buchler's preparation of (OEP)Mn≡N with NH_4OH and NaOCl.

corresponding methoxymanganese(III) derivative **1** with NH_4OH and NaOCl (Figure 1).[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.[6] Using a related protocol, Hill was able to construct the porphyrin complex (TpMPP)Mn(N) **7** (TpMPP = tetrakis(*p*–methoxyphenyl)porphyrinate).[4b] In this case, iodosylbenzene (PhIO) was employed as the oxidant, and was added to a CH_2Cl_2/liquid NH_3 solution containing the Mn(III) starting material **4** (Figure 2). Alternatively, condensation of NH_3 with the putative oxo-Mn(V) species **6** (the adduct of PhIO and **4**) yielded nitride **7** as well.[4b,7] More recently, Grunewald and Homborg have shown that a combination of

4. (a) Buchler, J. W.; Dreher, C.; Lay, K.-L. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, *37B*, 1155. (b) Hill, C. L.; Hollander, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 7318. (c) Groves, J. T.; Takahashi, T.; Butler, W. M. *Inorg. Chem.* **1983**, *22*, 884. (d) Buchler, J. W.; Dreher, C.; Lay, K.-L.; Lee, Y. J. A.; Scheidt, W. R. *Inorg. Chem.* **1983**, *22*, 888.

5. (a) Grunewald, H.; Homborg, H. *Z. Anorg. Allg. Chem.* **1992**, *608*, 81. (b) Grunewald, H.; Homborg, H. *Z. Naturforsch.* **1990**, *45B*, 483.

6. (a) Buchler, J. W.; Dreher, C.; Lay, K.-L.; Raap, A.; Gersonde, K. *Inorg. Chem.* **1983**, *22*, 879. (b) Antipas, A.; Buchler, J. W.; Gouterman, M.; Smith, P. D. *J. Am. Chem. Soc.* **1980**, *102*, 198.

7. (a) Hill, C. L.; Schardt, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 6374. (b) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375.

gaseous Cl_2 and NH_3 will oxidize Mn(III) phthalocyanine derivatives to their respective nitrido Mn(V) species.[5]

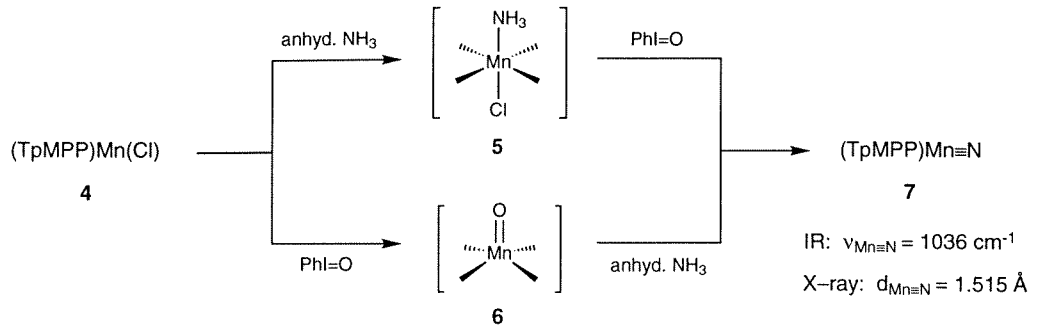


Figure 2. Oxidative formation of Mn≡N bond with PhI=O and NH_3.

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

$$\underset{\mathbf{8}}{L_nMn{-}N_3} \xrightarrow[\text{or } \Delta H]{h\nu} \underset{\mathbf{9}}{L_nMn{\equiv}N} + N_2 \qquad (1)$$

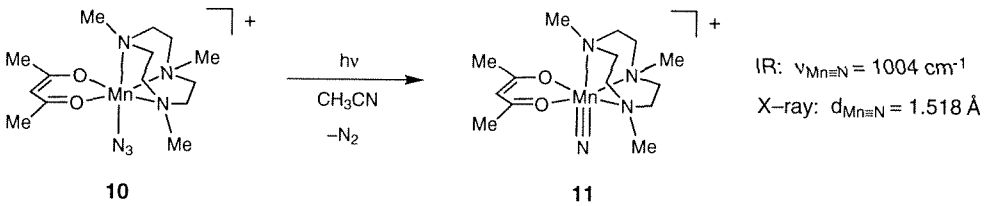
of this procedure have since been used to prepare nitrido complexes of several transition metals which include vanadium, chromium, manganese, and iron.[10] We, too, have

8. For comprehensive reviews on transition-metal nitrido complexes, see: (a) Dehnicke, K.; Strähle, J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 955. (b) Dehnicke, K.; Strähle, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 413. Also, see: Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*, Wiley Interscience: New York, 1988.

9. Arshankow, S. I.; Poznjak, A. L. *Z. Anorg. Allg. Chem.* **1981**, *481*, 201.

10. (a) Niemann, A.; Bossek, U.; Haselhorst, G.; Wieghardt, K.; Nuber, B. *Inorg. Chem.* **1996**, *35*, 906. (b) Jüstel, T.; Weyhermüller, T.; Wieghardt, K.; Bill, E.; Lengen, M.; Trautwein, A. X.; Hildebrandt, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 669. (c) Wagner, W.-D.; Nakamoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 1590, and references therein. (d) Che, C.-M.; Ma, J.-X.; Wong, W.-T.; Lai, T.-F.; Poon, C.-K. *Inorg. Chem.* **1988**, *27*, 2547. (e) Jin, T.; Suzuki, T.; Imamura, T.; Fujimoto, M. *Inorg. Chem.* **1987**, *26*, 1280. (f) Buchler, J. W.; Dreher, C. *Z. Naturforsch.* **1984**, *39B*, 222.

employed this technology to generate nitrido Mn(V) salen reagents (see Chapter 1).[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).[10a] 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]



10 **11** (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

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.

12. For leading references on metal-catalyzed and metal-mediated olefin aziridination methodology, see (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (c) Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. *Tetrahedron* **1989**, *45*, 2875. (d) Atkinson, R. S. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984, p. 247.

13. For a recent review on the applications of azirdines, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

this issue, we considered developing ligands which would provide a pocket (or picket-fence) for the Mn≡N moiety.[14] Bidentate Schiff base ligands, prepared from substituted salicylaldehydes and primary amines, were chosen because of their ready accessibilty and their amenability to numerous structural and electronic modifications (Figure 3).[15] Importantly, molecular models indicated that these ligands would form complexes with the imine donors positioned *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.[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.

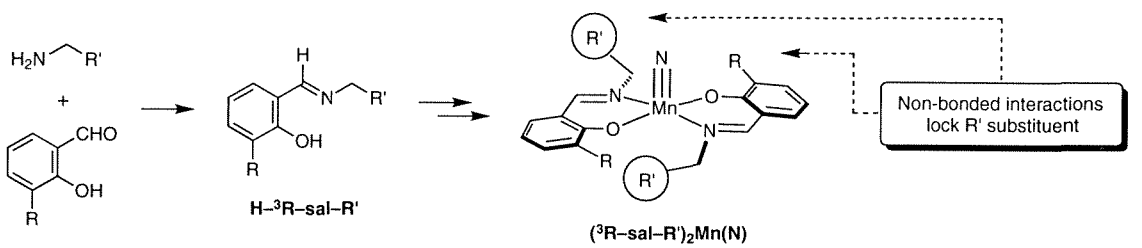


Figure 3. Readily prepared Schiff base ligands with "picket-fence" construction.

---

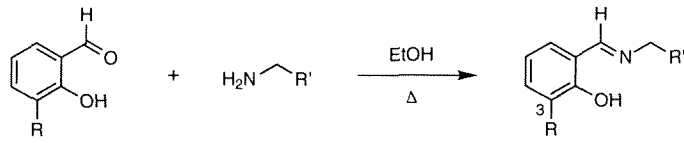
14. Seminal work by Collman, Traylor and others with "picket-fence" porphyrin systems suggested this approach. For a recent, comprehensive review of this subject, see: Momenteau, M.; Reed, C. A. *Chem. Rev.* **1994**, *94*, 659, and references therein.

15. For elegant studies of electronic tuning in metal catalysts, see: (a) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703. (b) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

16. (a) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128. (b) Iimori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439.

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).[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 (*vide supra*).

Table 1. Preparation of Schiff base ligands **12–18**.



ligand		R	R'
H–^{3}Me–sal–^{i}Pr	**12**	Me	^{i}Pr
H–^{3}Me–sal–Ph	**13**	Me	Ph
H–^{3}Ph–sal–Me	**14**	Ph	Me
H–^{3}Ph–sal–^{i}Pr	**15**	Ph	^{i}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

Manganese(III) Complexes. An extensive literature exists on the coordination chemistry of manganese in its divalent and trivalent oxidation states.[18] In a majority of

17. For a convenient method for the formylation of substituted phenols, see: Aldred, R.; Johnston, R.; Levin, D.; Nieland, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1823.

18. (a) Chiswell, B.; McKenzie, E. D.; Lindoy, L. F. In *Comprehensive Coordination Chemistry*, Wilkinson, G., Ed.; Pergamon: Oxford, U.K., 1987, Vol. 4, p. 1. (b) Vites, J. C.; Lynam, M. M. *Coord. Chem. Rev.* **1995**, *146*, 167. (c) Pecoraro, V.; Baldwin, M. J.; Gelasco, A. *Chem. Rev.* **1994**, *94*, 807. (d) Brudvig, G. W.; Crabtree, R. H. *Prog. Inorg. Chem.* **1989**, *37*, 99.

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.[19] Mononuclear Mn^{III}(Schiff base)$_2$X derivatives have, however, been documented in the literature, although reliable structural information on many of these compounds is not available.[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–^{3}R–sal–R' ligands.

Manganese(III) adducts, (^{3}R–sal–R')$_2$Mn(X), could be formed under a variety of conditions from either Mn^{II} or Mn^{III} starting materials. In the former case, reactions were conducted open to air which led to rapid oxidation of the initially formed Mn^{II} species, as witnessed by an immediate solution color change from yellow to dark brown. The effectiveness of Mn(acac)$_2$X (X = Br, N_3), Mn(acac)$_3$, Mn(OAc)$_3$•2H$_2$O, $MnCl_2$•4H$_2$O, and Mn(OAc)$_2$•4H$_2$O as starting materials for the preparation of the desired (^{3}R–sal–R')$_2$Mn(X) complexes was assayed.[21] In a typical experiment, treatment of two equivalents of the Schiff base with one equivalent of Mn(OAc)$_2$•4H$_2$O efficiently provided the (^{3}R–sal–R')$_2$Mn(OAc) complex as a forest green solid which precipitated from the reaction mixture (65–75% yields, eq 3). Alternatively, the acetylacetonate ligands on Mn(acac)$_2N_3$ could be exchanged with two equivalents of H–^{3}R-sal–R' and the volatile acetylacetone removed *in vacuo* to afford the corresponding azido species (eq

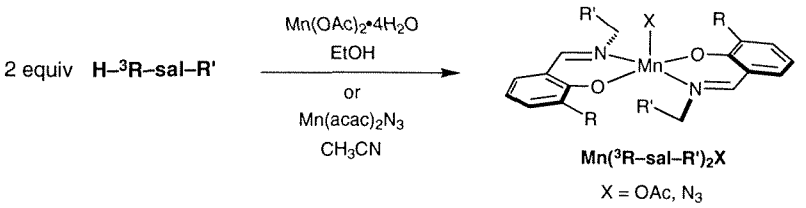
---

19. (a) Boucher, L. J.; Demmer, H.; Koeber, K.; Köttelwesch, H.; Schneider, D. *Gmelin Handbook of Inorganic Chemistry: Mn,* Schleitzer-Rust, E., Ed.; Springer-Verlag: Berlin, 1985, D4, p. 296. (b) Koeber, K.; Schneider, D. *Gmelin Handbook of Inorganic Chemistry: Mn,* Schleitzer-Rust, E., Ed.; Springer-Verlag: Berlin, 1982, D3, p. 77. (c) Dave, B. C.; Czernuszewicz, R. S. *New. J. Chem.* **1994**, *18*, 149. (d) Bardwell, D. A.; Jeffrey, J. C.; Ward, M. D. *Inorg. Chim. Acta* **1995**, *236*, 125.

20. (a) Patel, M. M.; Patel, R. P. *J. Indian Chem. Soc.* **1974**, *51*, 770, and references therein. (b) van den Bergen, A.; Murray, K. S.; O'Connor, M. J.; West, B. O. *Aust. J. Chem.* **1969**, *22*, 39.

21. For the preparation of Mn(acac)$_3$, see: Charles, R. G. *Inorg. Syn.* **1963**, *7*, 183. For Mn(acac)$_2N_3$ and Mn(acac)$_2$Br, see: Stults, B. R.; Marianelli, R. S.; Day, V. W. *Inorg. Chem.* **1975**, *14*, 722.

3). Other reagents and methods employed ($MnCl_2 \cdot 4H_2O$/KOH, $Mn(OAc)_3 \cdot 2H_2O$, $Mn(acac)_3$, $Mn(acac)_2Br$) gave variable results.



(3)

X–ray Crystallographic Analysis. The structure of one of the acetate derivatives, (^{3}Ph–sal–^{i}Pr)$_2$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^{III} center in which the η^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 C_2–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}Ph–sal–^{i}Pr)$_2$OAc represents a rare example of symmetric, bidentate carboxylate chelation to a single metal

22. Crystal data for (^{3}Ph–sal–^{i}Pr)$_2$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; β = 108.62°; V = 3253.3(11) Å^3, Z = 4, ρ_{calc} = 1.263 g/cm^3. A total of 6433 observations were collected (MoKα, $2\theta_{max}$ = 50°, -17≤ h ≤17, -18≤ k ≤18, -17≤ l ≤0) and merged to 2859 unique reflections (R_{merge} = 0.021, GOF_{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.

23. The imine nitrogens occupy the remaining two equatorial sites. A similar coordination geometry has been recently observed in a mono-acetate Mn(III) complex, see: Inamoto, K.; Koikawa, M.; Nakashima, M.; Tokii, T. *Inorg. Chim. Acta* **1996**, *249*, 251.

center.[18,19,23,24,25] Representative bond lengths and angles for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc) are featured in Table 2.

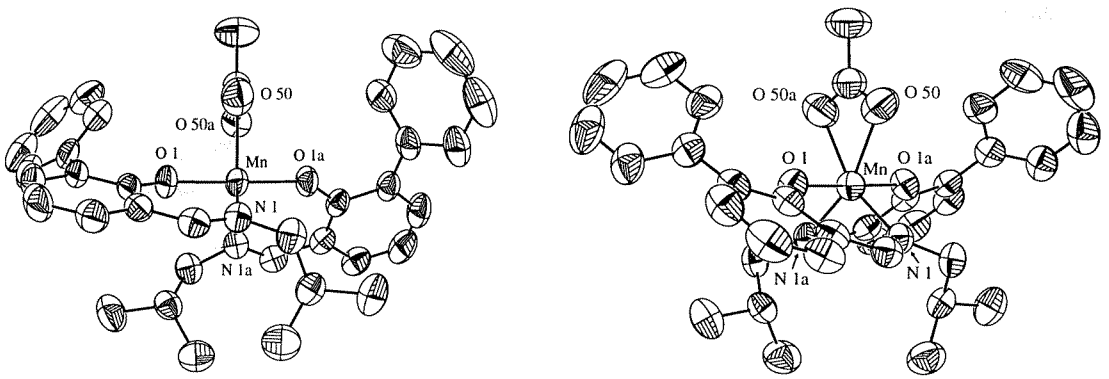


Table 2. Select bond lengths [Å] and angles [°] for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc) **19**.

Mn–O_1	1.842(12)	O_1–Mn–O_{1a}	178.91(8)	N_1–Mn–N_{1a}	104.76(8)
Mn–N_1	2.113(2)	O_1–Mn–N_{1a}	91.15(6)	N_1–Mn–O_{50}	98.41(6)
Mn–O_{50}	2.212(2)	O_1–Mn–N_1	89.51(6)	O_{50}–Mn–N_{50a}	58.43(9)

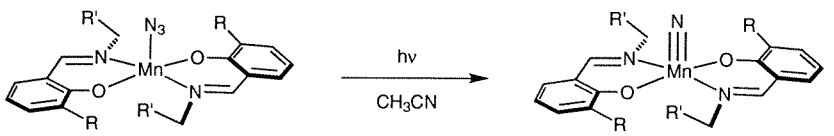
Figure 4. ORTEP diagram of Mn(^{3}Ph–sal–^{i}Pr)$_2$OAc **19** displaying 50% probability ellipsoids. The two perspectives are related by rotation around the C2–axis. Hydrogens not shown for clarity.

Nitridomanganese(V) Complexes. Small quantities (5–10 mg) of the desired nitridomanganese(V) complexes, (^{3}R–sal–R')$_2$Mn(N), could be generated upon prolonged irradiation (>18 h, Hg lamp) of the corresponding $Mn^{III}(N_3)$ (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}R–sal–R')$_2$Mn(X) (X = OAc, Cl, N_3) using an NH_4OH/Clorox bleach

24. For comprehensive reviews on Mn–carboxylate coordination chemistry, see: (a) Wieghardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 725. (b) Wieghardt, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1153. (c) Christou, G. *Acc. Chem. Res.* **1989**, *22*, 328.

25. Poganiuch, P.; Liu, S.; Papaefthymiou, G. C.; Lippard, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 4645, and references therein. For a comprehensive discussion of metal ion–carboxylate interactions, see: Carrell, C. J.; Carrell, H. L.; Erlebacher, J.; Glusker, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 8651.

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.



$Mn(^3R\text{–sal–}R')_2N_3$ $Mn(^3R\text{–sal–}R')_2N$ (4)

Thereafter, it was discovered that the preparation of $(^3R\text{–sal–}R')_2Mn(N)$ from $(^3R\text{–sal–}R')_2Mn(OAc)$ could be effected using gaseous NH_3 and the commodity chemical *N*–bromosuccinimide (NBS). We speculated that this reaction occured through an oxidative dehydrogenation mechanism in which a Mn–coordinated bromamine intermediate was formed, and subsequently reduced (Figure 5).[26] In support of this hypothesis, it was found that other halogenating agents including *t*–butylhypochlorite (*t*–BuOCl) and *N*–bromoacetamide ($CH_3CONHBr$) could also be employed as oxidants in this process.[27]

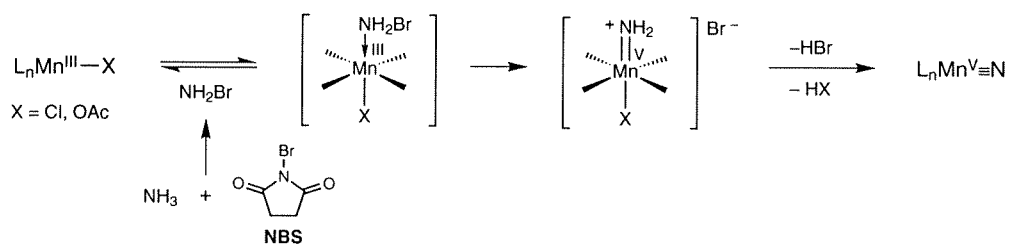


Figure 5. Putative mechanism for Mn≡N formation with NH_3 and *N*–bromosuccinimide.

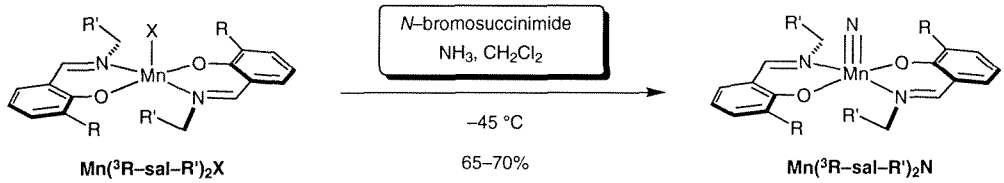
After some optimization, it was determined that the conversion of $(^3R\text{–sal–}R')_2Mn(OAc)$ to $(^3R\text{–sal–}R')_2Mn(N)$ was best performed at reduced temperatures (–45

---

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.

27. For the preparation of *t*–BuOCl, see: Mintz, M. J.; Walling, C. *Org. Synth., Coll. Vol. V* **1973**, 183. For $CH_3CONHBr$, see: Oliveto, E. P.; Gerold, C. *Org. Synth., Coll. Vol. IV* **1963**, 104.

°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 NH_3 to a solution of NBS and a Mn(III) precursor. Aqueous work–up and purification through a small plug of neutral Al_2O_3 (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.



(5)

X–ray Crystallographic Analysis. The structure of (^{3}MeO–sal–Me)$_2$Mn(N) **20** represents one of few crystallographically characterized Mn(V) nitrido complexes (Figure 6, Table 3).[1,4a,4b,4d,10a,28] 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–N_{imine} distances are substantially longer (2.02 Å) than the Mn–$O_{phenolate}$ 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 (^{3}MeO–sal–Me)$_2$Mn(N): pale brown crystals were deposited by diffusing pentane into an Et_2O 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) Å^3, Z = 8, ρ_{calc} = 1.413 g/cm^3. A total of 1533 observations were collected (MoKα, $2\theta_{max}$ = 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]

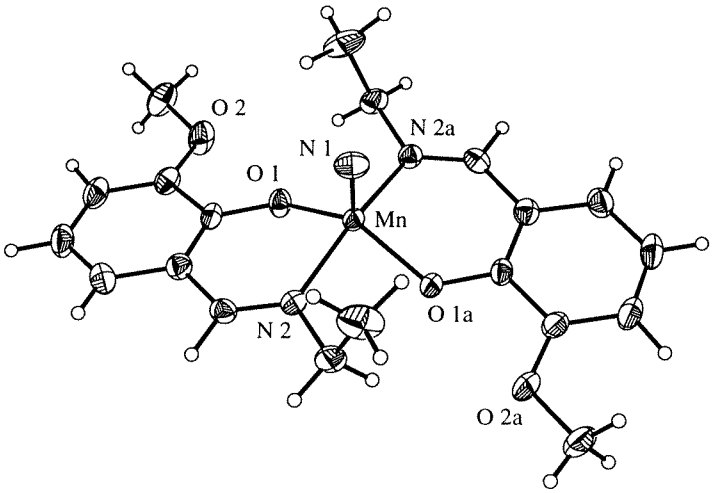


Table 3. Select bond lengths [Å] and angles [°] for (^{3}MeO–sal–Me)$_2$Mn(N) **20**.

Mn–N_1	1.543(4)	O_1–Mn–O_{1a}	134.99(12)	N_1–Mn–N_2	96.45(6)
Mn–O_1	1.868(2)	O_1–Mn–N_2	90.46(8)	O_{1a}–Mn–N_2	84.61(8)
Mn–N_2	2.023(2)	N_1–Mn–O_1	112.51(6)		

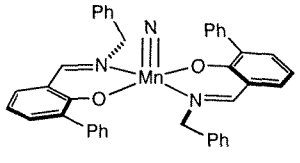
Figure 6. ORTEP diagram of Mn(^{3}MeO–sal–Me)$_2$N **20** displaying 50% probability ellipsoids.

A second nitrido complex, (^{3}Ph–sal–Ph)$_2$Mn(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 (^{3}MeO–sal–Me)$_2$Mn(N) complex. Additional, important information which may be gathered from this figure is that the benzyl groups appended to

29. Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073.

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.



$Mn(^3Ph\text{–}sal\text{–}Ph)_2N$

21

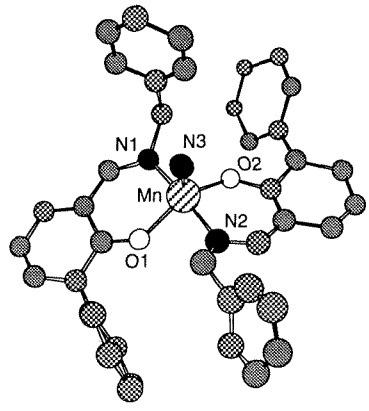
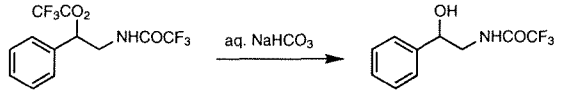


Figure 7. Chem–3D representation of the X–ray structure of **21**.

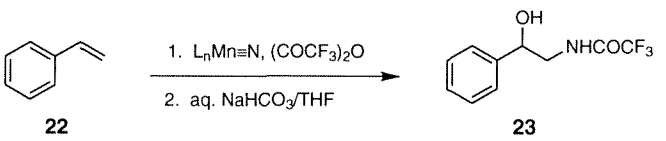
Nitrogen-Atom Transfer Reactions. Having developed preparative methods for the construction of Schiff base derived Mn(V) nitrides, we wished to examine the ability of these systems to function as nitrogen atom–transfer reagents with unfunctionalized alkenes. To this end, we tested the reactivity of $(^3Ph\text{–}sal\text{–}Ph)_2Mn(N)$ **21** with styrene **22** (Figure 8). Addition of **21** (1 equiv) to a solution of TFAA and **22** (5 equiv) in CH_2Cl_2 followed by treatment of the unpurified reaction product with aq. $NaHCO_3$/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 $(^3Ph\text{–}sal\text{–}Ph)_2Mn(N)$ **21** with styrene. Ester **i** is readily hydrolyzed ($NaHCO_3$) to give **23**.



i **23**

reagent.[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}Ph–sal–Ph)$_2$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_3CON to the alkene substrate.[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_3CON transfer to **22**. This reaction is remarkably efficient, providing 70% yield of **23**, using a 1:1 sytrene-to-(saltmen)Mn(N) stoichiometry.[34]



22 **23**

$L_nMn{\equiv}N$	equiv	yield
(^{3}Ph–sal–Ph)$_2$Mn(N) **21**	1.0	64%
(saltmen)Mn(N)	1.0	70%

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

32. Takahashi, T. Ph.D. Dissertation, The University of Michigan, Ann Arbor, MI, 1985.

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* **1981**, 787, and references therein.

34. Optimization of the (^{3}R–sal–R')$_2$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 $Mn{=}NCOCF_3$ 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 $Mn{=}NCOCF_3$ 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.

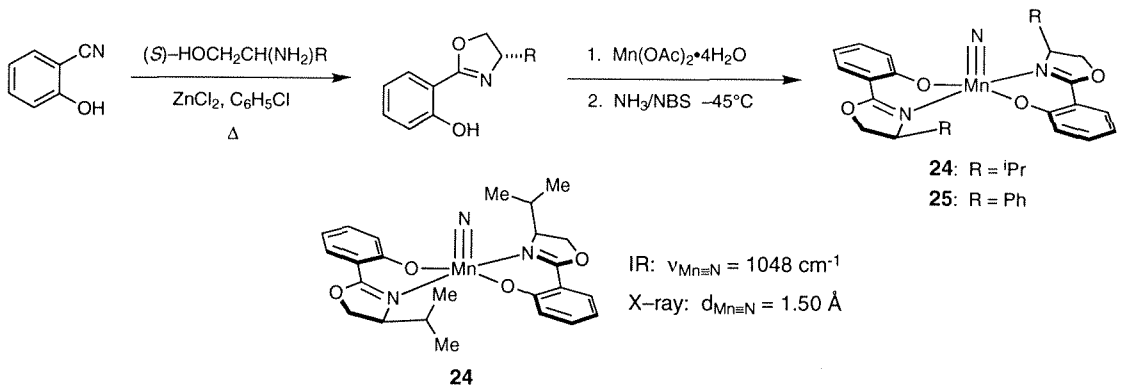


Figure 9. Chiral nitridomanganese complexes derived from bidentate, oxazoline ligands.

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).[35] The X–ray crytal structure of one of these compounds, **24**, has been solved and reveals a number similarities to the structures of both (^{3}MeO–sal–Me)$_2$Mn(N) **20** and (^{3}Ph–sal–Ph)$_2$Mn(N) **21**, which include Mn≡N bond length (1.50 Å) and Mn coordination geometry (distorted trigonal bipyramid).[36] Experiments are currently in progress to determine if these systems will perform the enantioselective transfer of CF_3CON 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.

---

35. For the preparation of these ligands, see: Bolm, C.; Wieckhardt, K.; Zehnder, M.; Glasmacher, D. *Helv. Chim. Acta* **1991**, *74*, 717, and references therein.

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 **H_2saltmen**

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 H_2O 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}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}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 $C_{20}H_{24}N_2O_2$ 324.1838, found 325.1906 (MH^+); Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.63. Found: C, 73.54; H, 7.21; N, 8.41.

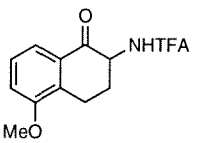
Preparation of **(saltmen)Mn(N)**

H_2saltmen (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 $Mn(OAc)_2{\cdot}4H_2O$ (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_4OH (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 a 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. ^{1}H 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; ^{13}C 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 $MnC_{20}H_{22}N_3O_2$ 391.1092 found 391.1080 (M^+); Anal. Calcd for $MnC_{20}H_{22}N_3O_2 \cdot (0.1\ CH_2Cl_2)$: C, 60.38; H, 5.60; N, 10.51. Found: C, 60.28; H, 5.55; N, 10.50.

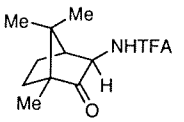
General procedure for the amination of silyl enol ethers: A solution of silyl enol ether (1.0 mmol, 2 equiv) in 3.0 mL of CH_2Cl_2 was cooled to –78 °C. Pyridine (1.5 mmol) was added followed by a solution of the silyl enol ether (0.5 mmol) in 2.0 mL of CH_2Cl_2. Freshly distilled TFAA (1.2 mmol) was 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 Et_2O (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 H_2O/ethylene glycol–dry ice) and only a catalytic amount of pyridine (62 μmol) was employed.

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

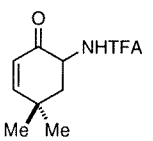


TLC R_f = 0.28 (2:3 hexanes/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, 1H, J = 8.6 Hz), 7.55 (br s, 1H), 7.34 (t, 1H, J = 8.0 Hz), 7.08 (d, 1H, J = 7.6 Hz), 4.63 (dt, 1H, J = 13.9, 4.8 Hz), 3.89 (s, 3H), 3.26-3.22 (m, 1H), 2.95-2.88 (m, 2H), 1.91-1.87 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.1, 157.1 (q, $J_{C\text{-}F}$ = 37.2 Hz), 157.0, 132.5, 131.8, 127.6, 119.1, 115.7 (q, $J_{C\text{-}F}$ = 288.0 Hz), 115.3, 56.3, 55.7, 28.6, 21.9 ppm; IR (thin film) ν 3285, 2947, 1707, 1684, 1557, 1316, 1270, 1209, 1183, 1046, 905, 804

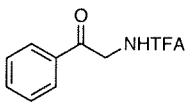
cm^{-1}; HRMS (CI) calcd for $C_{13}H_{12}F_3NO_3$ 287.0769, found 288.0851 (MH^+); Anal. Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.35; H, 4.21; N, 4.88. Found: C, 54.27; H, 4.23; N, 4.74.



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; ^{13}C 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 (CI) 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; ^{13}C 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 (CI) 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.

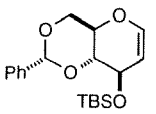


TLC R_f = 0.18 (1:1 hexanes/CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.99 (dd, 2H, J = 8.3, 1.2 Hz), 7.69 (dt, 1H, J = 7.4, 1.2 Hz), 7.54 (dt, 2H, J = 7.9, 1.6 Hz), 7.50 (br s, 1H), 4.83 (d, 2H, 4.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.1, 157.2 (q, $J_{C\text{-}F}$ = 37.8 Hz), 134.7, 133.8, 129.1, 128.0, 115.7 (q, $J_{C\text{-}F}$ = 286.8 Hz), 46.2 ppm; IR (thin film) ν 3314, 1713, 1686, 1560, 1350, 1181, 1153 cm^{-1}; HRMS (CI) calcd for $C_{10}H_8F_3NO_2$ 231.0507, found 232.0585 (MH^+); Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 52.12; H, 3.46; N, 6.03.

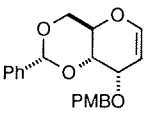
General procedure for the preparation of 2–amino sugars from pyranoid glycals : A 25 mL schlenk flask was flushed with N_2 and charged with glycal (0.40 mmol) and 0.5 mL of CH_2Cl_2. Freshly distilled TFAA (200 μL, 1.4 mmol, 3.5 equiv) was then added. A solution of (saltmen)Mn(N) (0.04 M, 10 mL, 0.40 mmol, 1equiv) in CH_2Cl_2 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 Et_2O (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 CH_2Cl_2 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 Et_2O (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.

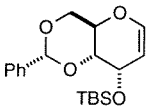
Physical data for glycal starting materials:



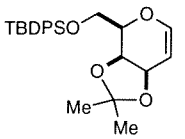
TLC R_f = 0.22 (3:1 hexanes/CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50 (dd, 2H, *J* = 7.5, 1.8 Hz), 7.40-7.34 (m, 3H), 6.30 (dd, 1H, *J* = 6.1, 1.5 Hz), 5.61 (s, 1H), 4.67 (dd, 1H, *J* = 6.1, 2.0 Hz), 4.51 (dt, 1H, *J* = 7.4, 1.8 Hz), 4.36 (dd, 1H, *J* = 10.3, 4.8 Hz), 3.89 (dt, 1H, *J* = 10.1, 4.8 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) δ 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) ν 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.



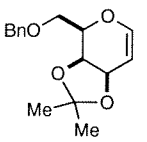
TLC R_f = 0.43 (4:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.53 (dd, 2H, *J* = 7.5, 2.0 Hz), 7.42-7.37 (m, 3H), 7.30 (d, 2H, *J* = 8.5 Hz), 6.86 (d, 2H, *J* = 8.7 Hz), 6.39 (d, 1H, *J* = 6.0 Hz), 5.60 (s, 1H), 4.93 (t, 1H, *J* = 6.0 Hz), 4.86 (d, 1H, *J* = 11.5 Hz), 4.61 (d, 1H, *J* = 11.5 Hz), 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) δ 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) ν 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.



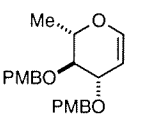
TLC R_f = 0.18 (3:1 hexanes/CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50 (dd, 2H, *J* = 7.2, 2.7 Hz), 7.38-7.34 (m, 3H), 6.34 (d, 1H, *J* = 6.0 Hz), 5.60 (s, 1H), 4.90 (t, 1H, 6.0 Hz), 4.43 (dd, 1H, *J* = 10.5, 5.4 Hz), 4.28-4.22 (m, 2H), 3.82-3.78 (m, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 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.



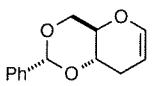
TLC R_f = 0.17 (3:1 hexanes/CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71-7.68 (m, 4H), 7.45-7.37 (m, 6H), 6.33 (d, 1H, *J* = 6.3 Hz), 4.77 (ddd, 1H, *J* = 6.3, 2.7, 1.6 Hz), 4.66 (dd, 1H, 6.0, 2.8 Hz), 4.46 (d, 1H, *J* = 6.0 Hz), 4.03 (t, 1H, *J* = 6.8 Hz), 3.99-3.91 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.07 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 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) δ 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) δ 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$^+$).

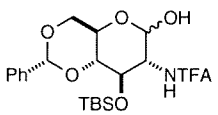


TLC R_f = 0.22 (8:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.24 (m, 4H), 6.90-6.87 (m, 4H), 6.34 (d, 1H, *J* = 6.1 Hz), 4.85-4.79 (m, 2H), 4.62 (d, 1H, *J* = 10.9 Hz), 4.60 (d, 1H, *J* = 11.3 Hz), 4.51 (d, 1H, *J* = 11.3 Hz), 4.17 (dd, 1H, *J* = 6.5, 1.6 Hz), 3.95-3.89 (m, 1H), 3.810 (s, 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) δ 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.



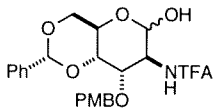
TLC R_f = 0.14 (2:1 hexanes/CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51 (dd, 2H, *J* = 7.8, 1.7 Hz), 7.40-7.34 (m, 3H), 6.34 (dt, 1H, *J* = 6.0, 2.0 Hz), 5.63 (s, 1H), 4.74 (dt, 1H, *J* = 5.8, 2.2 Hz), 4.40 (dd, 1H, *J* = 16.2, 10.7 Hz), 3.94 (dd, 1H, *J* = 16.5, 6.6 Hz), 3.82-3.77 (m, 2H), 2.39-2.33 (m, 1H), 2.30-2.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 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:

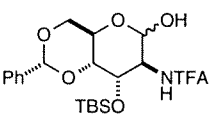


TLC R_f = 0.46–0.28 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49-7.47 (m), 7.38-7.36 (m), 6.45 (d, -NH major, *J* = 9.5 Hz), 5.53 (s, major), 5.52 (s), 5.29 (t, major, *J* = 3.6 Hz), 4.92 (t, *J* = 6.1 Hz), 4.27-4.22 (m), 4.07 (dt, major, *J* = 9.9, 4.9 Hz), 4.02 (t, major, *J* = 9.4 Hz), 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) δ 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 $C_{21}H_{30}SiNO_6F_3$: C, 52.82; H, 6.33; N, 2.93. Found: C, 53.01; H, 6.51; N, 2.81.

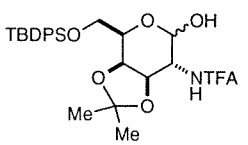


TLC R_f = 0.26 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50-7.47 (m), 7.41-7.38 (m), 7.35-7.29 (m), 6.88-6.86 (m), 6.65 (d, -NH major, J = 5.9 Hz), 6.40 (br s), 5.60 (s), 5.95 (s), 5.57 (s), 5.55 (s, major), 5.47 (s, major), 4.97 (d, J = 11.0 Hz), 4.91 (d, J = 10.9 Hz), 4.83 (d, major, J = 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) δ 159.6, 159.2, 157.7 (q, $J_{C\text{-}F}$ = 37.6 Hz), 156.7 (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 287.8 Hz), 115.4 (q, $J_{C\text{-}F}$ = 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) ν 3419 (br), 3294 (br), 2931, 2868, 1717, 1515, 1249, 1213, 1175, 1103, 1030, 700 cm^{-1}; Anal. Calcd for $C_{23}H_{24}NO_7F_3$: C, 57.14; H, 5.00; N, 2.89. Found: C, 57.21; H, 5.32; N, 2.66.



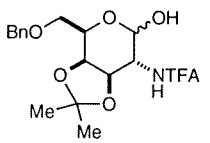
TLC R_f = 0.16 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (dd, J = 7.5, 2.2 Hz), 7.36-7.35 (m), 6.67 (d, -NH major, J = 8.4 Hz), 5.81 (br d, J = 11.1 Hz),

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) δ 157.8 (q, $J_{C\text{-}F}$ = 37.7 Hz), 156.9 (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 287.6 Hz), 115.4 (q, $J_{C\text{-}F}$ = 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) ν 3339 (br), 3239 (br), 2930, 2859, 1715, 1553, 1395, 1214, 1165, 1103, 1004, 830, 780 cm^{-1}; Anal. Calcd for $C_{21}H_{30}SiNO_6F_3$: C, 52.82; H, 6.33; N, 2.93. Found: C, 52.79; H, 6.55; N, 2.82.

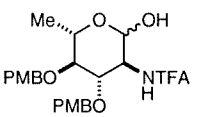


TLC R_f = 0.24–0.12 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73-7.62 (m), 7.47-7.38 (m), 6.47 (d, J = 7.0 Hz), 6.38 (d, -NH major, J = 9.5 Hz), 5.15 (s, major), 4.77-4.73 (m), 4.53-4.51 (m), 4.38-4.30 (m, major), 4.22 (dt, major, J = 9.0, 3.2 Hz), 4.17 (dd, major, J = 8.8, 4.6 Hz), 4.08-4.06 (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) δ 157.4 (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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,

51.7, 31.5, 28.0, 27.9, 26.72, 26.68, 26.3, 26.1, 25.5, 19.2, 19.14, 19.07 ppm; IR (thin film) ν 3326 (br), 2934, 2859, 1716, 1558, 1428, 1381, 1219, 1162, 1114, 1079, 823, 738, 702 cm^{-1}; Anal. Calcd for $C_{27}H_{34}SiNO_6F_3$: C, 58.57; H, 6.19; N, 2.53. Found: C, 58.76; H, 6.32; N, 2.39.

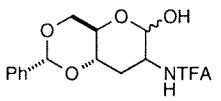


TLC R_f = 0.26–0.17 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.30 (m), 6.37 (d, -NH major, J = 10.0 Hz), 5.23 (s, major), 4.67 (d, major, J = 12.2 Hz), 4.56 (d, major, J = 12.2 Hz), 4.47-4.45 (m, major), 4.25-4.21 (m, major), 4.17-4.13 (m, major), 3.79 (dd, major, J = 10.2, 8.0 Hz), 3.73 (dd, major, J = 10.2, 4.1 Hz), 1.57 (s, major), 1.54 (s), 1.34 (s), 1.33 (s, major) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{22}NO_6F_3$: C, 53.33; H, 5.47; N, 3.46. Found: C, 53.50; H, 5.49; N, 3.16.

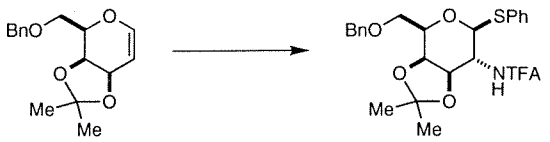


TLC R_f = 0.26–0.08 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.24 (m), 7.22-7.19 (m), 6.91-6.86 (m), 6.23 (d, -NH major, J = 8.9 Hz), 5.23 (s), 5.19 (s, major), 4.88-4.79 (m), 4.80 (d, major, J = 10.6 Hz), 4.78 (d, major, J = 11.2 Hz), 4.74-4.64 (m), 4.61 (d, major, J = 11.3 Hz), 4.59 (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_2Cl_2, 125 MHz) δ 160.0, 159.96, 157.4 (q, $J_{C\text{-}F}$ = 37.0 Hz), 131.0, 130.8, 130.6, 130.5, 130.4, 130.2, 129.9, 116.4 (q, $J_{C\text{-}F}$ = 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) ν 3279 (br), 2911, 1708, 1613, 1562, 1515, 1303, 1251, 1187, 1068, 1035, 820 cm^{-1}; Anal. Calcd for $C_{24}H_{28}NO_7F_3$: C, 57.71; H, 5.65; N, 2.80. Found: C, 57.55; H, 5.90; N, 2.56.



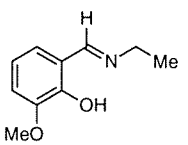
TLC R_f = 0.31–0.21 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49-7.46 (m), 7.39-7.35 (m), 6.72 (br s, -NH), 6.56 (br s, -NH), 6.60 (s), 5.57 (s), 5.56 (s), 5.22 (t, J = 3.5 Hz), 5.14-5.12 (m), 4.38-4.18 (m), 4.12-4.03 (m), 3.84-3.65 (m), 3.58 (dt, J = 9.7, 4.9 Hz), 3.27 (d, J = 4.0 Hz), 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) δ 157.7 (q, $J_{C\text{-}F}$ = 37.6 Hz), 156.8 (q, $J_{C\text{-}F}$ = 37.7 Hz), 136.9, 136.8, 129.3, 128.4, 126.1, 126.0, 115.58 (q, $J_{C\text{-}F}$ = 288.0 Hz), 115.56 (q, $J_{C\text{-}F}$ = 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) ν 3393, 3276 (br), 2860, 1700, 1553, 1169, 1098, 1028, 968, 906, 701 cm^{-1}; Anal. Calcd for $C_{15}H_{16}NO_5F_3$•(0.25 H_2O): C, 51.21; H, 4.72; N, 3.98. Found: C, 51.21; H, 4.87; N, 3.75.



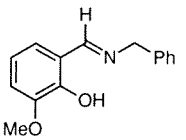
***N*–Trifluoroacetyl–2–galactosamine thioglycoside.** A 10 mL schlenk flask was flushed with N_2 and charged with glycal (28 mg, 0.1 mmol), 2,6–di–*tert*–butyl–4–methylpyridine (39 mg, 0.1 mmol, 1 equiv) and 300 μL of CH_2Cl_2. Freshly distilled TFAA (50 μL, 0.35 mmol, 3.5 equiv) was then added. A solution of (saltmen)Mn(N) (0.04 M, 2.5 mL, 0.1 mmol, 1 equiv) in CH_2Cl_2 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 BF_3•OEt_2 (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 Et_2O (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 R_f = 0.18 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3 (q, $J_{C\text{-}F}$ = 37.5 Hz), 138.0, 132.5, 132.2, 129.0, 128.4, 128.1, 127.7, 127.6, 115.5 (q, $J_{C\text{-}F}$ = 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 $C_{24}H_{26}SNO_5F_3$ 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 Al_2O_3 (Brockmann, activity I) with 4:1 hexanes/EtOAc as eluent typically afforded the product ligand as a yellow solid (60–70%).

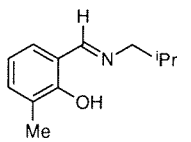
Physical data for select Schiff base ligands:



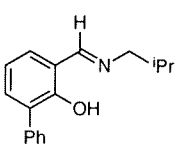
H–^{3}MeO–sal–Me. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (t, 1H, J = 1.0 Hz), 6.90 (dd, 1H, J = 7.9, 1.3 Hz), 6.86 (dd, 1H, J = 7.7, 1.4 Hz), 6.78 (t, 1H, J = 7.8 Hz), 3.90 (s, 3H), 3.63 (dq, 2H, J = 7.3, 1.0 Hz), 1.32 (t, 3H, J = 7.3 Hz) ppm.; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0, 152.7, 148.5, 122.6, 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}.



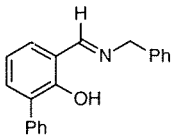
H–^{3}MeO–sal–Ph. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (s, 1H), 7.37-7.32 (m, 4H), 7.31-7.27 (m, 1H), 6.94 (dd, 1H, J = 8.0, 1.3 Hz), 6.92 (dd, 1H, J = 7.9, 1.3 Hz), 6.83 (t, 1H, J = 7.9 Hz), 4.83 (s, 2H), 3.91 (s, 3H) ppm; IR (thin film) ν 2832, 1630, 1464, 1254, 1079, 1028, 736, 697 cm^{-1}.



H–^{3}Me–sal–^{i}Pr. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) ν 2958, 1631, 1458, 1272, 1248, 1086, 1038, 846, 772, 747 cm^{-1}.



H–^{3}Ph–sal–^{i}Pr. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 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) δ 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) ν 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 ($CDCl_3$, 500 MHz) δ 14.07 (s, 1H, -OH), 8.52 (s, 1H), 7.63 (dd, 2H, J = 8.2, 1.2 Hz), 7.45-7.41 (m, 3H), 7.36-7.28 (m, 7H), 6.98 (t, 1H, J = 7.6 Hz), 4.83 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 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) ν 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^{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 °C was added $Mn(OAc)_2$•$4H_2O$ (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 °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_2Cl_2 solutions of the complex. Alternative methods which included $Mn(acac)_2N_3$ in CH_3CN or $MnCl_2$•$4H_2O$/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(^{3}Ph–sal–Ph)$_2$OAc

IR (KBr) ν 3029, 1631, 1619, 1555, 1452, 1422, 1397, 1316, 1280, 1225, 1104, 1030, 860, 761 cm^{-1}. HRMS (FAB$^+$) calcd for $MnC_{42}H_{35}N_2O_4$ 686.1978, found 627.1843 (M–OAc).

Mn(^{3}Ph–sal–^{i}Pr)$_2$OAc

IR (KBr) ν 2961, 2867, 1620, 1588, 1558, 1423, 1393, 1311, 1285, 1030, 864, 765 cm^{-1}. HRMS (FAB$^+$) calcd for $MnC_{36}H_{39}N_2O_4$ 618.2291, found 559.2160 (M–OAc).

Mn(^{3}MeO–sal–Me)$_2$N$_3$

IR (KBr) ν 2926, 2052 (–N_3), 1620, 1598, 1555, 1472, 1449, 1302, 1253, 1226, 1093, 978, 863, 738 cm^{-1}.

Mn(^{3}MeO–sal–Ph)$_2$N$_3$

IR (thin film) ν 2931, 2046 (–N_3), 1610, 1555, 1470, 1448, 1296, 1251, 1224, 1080, 864, 738 cm^{-1}.

Mn(^{3}Ph–sal–^{i}Pr)$_2$N$_3$

IR (KBr) ν 2958, 2047 (–N_3), 1615, 1588, 1558, 1448, 1423, 1312, 1284, 1227, 1030, 861 cm^{-1}.

General procedure for the preparation of (^{3}R–sal–R')$_2$Mn^V(N) products: A solution of (^{3}R–sal–R)$_2$MnX (X = OAc, Cl or N_3, 1.8 mmol) in 60 mL of CH_2Cl_2 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 NH_3 was bubbled into the reaction mixture. The dark color began to lighten upon addition of NH_3, and, within 30 sec, the flow of NH_3 was ceased. The solution stirred at –45 °C for < 5 min

before 75 mL of a saturated aq. NH_4Cl solution was added. The frozen mixture was warmed to 23 °C and extracted with 2 x 35 mL CH_2Cl_2. The organic extracts were washed with 4 x 75 mL H_2O, dried over Na_2SO_4 and concentrated under reduced pressure to a brown oily residue. Purification through a short plug of neutral Al_2O_3 (Brockmann, activity I) with CH_2Cl_2 as eluent afforded the desired product as a brown foam (60–70%).

Mn(^{3}Ph–sal–Ph)$_2$N

^{1}H NMR ($CDCl_3$, 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 $MnC_{40}H_{32}N_3O_2$ 641.1875, found 641.1875 (M^+).

Mn(^{3}Ph–sal–^{i}Pr)$_2$N

^{1}H NMR ($CDCl_3$, 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 Anistropic Thermal Factors for (salen)Mn(N)

X-Ray Crystallographic Data and Structure Refinement for (salen)Mn(N)

Empirical formula	$MnC_{16}H_{14}N_3O_2$	
Formula weight	335.24	
Crystal color	dark green	
Solvent of crystallization	CH_2Cl_2	
Type of diffractometer	*Enraf-Nonius Cad-4*	
Data collection method	Omega	
Temperature	293(2) K	
Wavelength	0.71073 Å MoKα	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.496(3) Å	α = 90°
	b = 12.313(3) Å	β = 103.61(3)°
	c = 12.857(4) Å	γ = 90°
Volume	1461.1(7) $Å^3$	
Z	4	
Density (calculated)	1.524 g/cm^3	
Absorption coefficient	0.913 mm^{-1}	
F(000)	688	
Crystal Size	0.12 x 0.22 x 0.29 mm	
Theta range for data collection	2.0–22.0°	
Index ranges	$-9 \leq h \leq 9$, $0 \leq k \leq 12$, $-13 \leq l \leq 13$	
Reflections collected	4023	
Independent reflections	1781	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	1781/0/199	
GOF on F^2	1.304	
Final R indices [$I>2\sigma_I$]	R_1 = 0.0409, wR_2 = 0.0697	
R indices (all data)	R_1 = 0.0607, wR_2 = 0.0745	
Largest diff. peak and hole	0.219 and -0.256 e^-/A^{-3}	
Lattice parameter determination	# of reflections = 25, range = $8.6° \leq \theta \leq 10.4°$	

Number of standard reflections	3
Interval (minutes)	60
Coefficients in weighting scheme	a = 0, b = 0, c= 0, d = 0, e = 0
$(\Delta/\sigma)_{max}$ in final least squares cycle	0.001

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_{merge} = 3.8% and GOF_{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.

atom	x	y	z	U(eq)
Mn	-122(1)	1778(1)	5328(1)	38(1)
N(1)	-148(3)	1949(3)	3819(2)	38(1)
O(1)	1937(3)	1781(2)	5689(2)	45(1)
O(2)	152(3)	950(2)	6622(2)	44(1)
N(2)	-1904(3)	985(3)	4736(2)	38(1)
C(7)	-2313(4)	384(3)	6437(3)	40(1)
C(5)	4266(5)	2380(4)	5636(3)	50(1)
C(4)	5218(5)	2803(4)	5087(4)	59(1)
C(10)	-1613(5)	-104(4)	8596(4)	56(1)
C(14)	-1606(4)	1836(4)	3126(3)	50(1)
N(3)	-687(4)	2875(3)	5569(2)	46(1)
C(12)	-887(5)	568(3)	7035(3)	39(1)
C(6)	2796(4)	2205(3)	5134(3)	39(1)
C(11)	-549(5)	294(3)	8135(3)	50(1)
C(1)	2355(4)	2452(3)	4039(3)	38(1)
C(16)	-2686(4)	517(3)	5296(3)	47(1)
C(13)	911(5)	2246(3)	3423(3)	44(1)
C(8)	-3345(5)	-29(4)	6945(4)	56(1)
C(3)	4758(5)	3074(4)	4014(4)	64(1)
C(9)	-3008(5)	-252(4)	8014(4)	61(2)
C(15)	-2384(4)	946(4)	3560(3)	47(1)
C(2)	3344(5)	2892(4)	3497(4)	55(1)

Table 2. Bond lengths (Å) for (salen)Mn(N).

Mn-N(3)	1.512(3)	C(7)-C(16)	1.435(5)
Mn-O(1)	1.900(3)	C(5)-C(4)	1.374(6)
Mn-O(2)	1.916(3)	C(5)-C(6)	1.409(5)
Mn-N(1)	1.946(3)	C(4)-C(3)	1.386(6)
Mn-N(2)	1.946(3)	C(10)-C(9)	1.371(6)
N(1)-C(13)	1.283(5)	C(10)-C(11)	1.377(6)
N(1)-C(14)	1.466(4)	C(14)-C(15)	1.501(5)
O(1)-C(6)	1.312(4)	C(12)-C(11)	1.415(5)

O(2)-C(12)	1.313(4)	C(6)-C(1)	1.405(5)
N(2)-C(16)	1.286(5)	C(1)-C(2)	1.404(5)
N(2)-C(15)	1.474(5)	C(1)-C(13)	1.435(5)
C(7)-C(8)	1.396(5)	C(8)-C(9)	1.364(6)
C(7)-C(12)	1.410(5)	C(3)-C(2)	1.369(5)

Table 3. Bond angles (°) for (salen)Mn(N).

N(3)-Mn-O(1)	110.0(2)	C(4)-C(5)-C(6)	121.6(4)
N(3)-Mn-O(2)	106.2(2)	C(5)-C(4)-C(3)	120.7(4)
O(1)-Mn-O(2)	82.34(12)	C(9)-C(10)-C(11)	121.7(4)
N(3)-Mn-N(1)	100.7(2)	N(1)-C(14)-C(15)	108.7(3)
O(1)-Mn-N(1)	90.80(12)	O(2)-C(12)-C(7)	123.6(4)
O(2)-Mn-N(1)	152.94(13)	O(2)-C(12)-C(11)	118.3(4)
N(3)-Mn-N(2)	102.1(2)	C(7)-C(12)-C(11)	118.0(4)
O(1)-Mn-N(2)	147.79(14)	O(1)-C(6)-C(5)	119.2(4)
O(2)-Mn-N(2)	90.03(13)	O(1)-C(6)-C(1)	123.6(4)
N(1)-Mn-N(2)	81.92(13)	C(5)-C(6)-C(1)	117.0(4)
C(13)-N(1)-C(14)	120.2(3)	C(10)-C(11)-C(12)	119.9(4)
C(13)-N(1)-Mn	126.9(3)	C(2)-C(1)-C(6)	120.3(4)
C(14)-N(1)-Mn	112.6(2)	C(2)-C(1)-C(13)	117.3(4)
C(6)-O(1)-Mn	127.2(2)	C(6)-C(1)-C(13)	122.4(4)
C(12)-O(2)-Mn	125.5(2)	N(2)-C(16)-C(7)	125.9(4)
C(16)-N(2)-C(15)	118.7(3)	N(1)-C(13)-C(1)	124.6(4)
C(16)-N(2)-Mn	124.7(3)	C(9)-C(8)-C(7)	121.4(4)
C(15)-N(2)-Mn	116.6(3)	C(2)-C(3)-C(4)	119.2(4)
C(8)-C(7)-C(12)	119.6(4)	C(8)-C(9)-C(10)	119.4(4)
C(8)-C(7)-C(16)	119.2(4)	N(2)-C(15)-C(14)	107.3(3)
C(12)-C(7)-C(16)	120.9(4)	C(3)-C(2)-C(1)	121.1(4)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for (salen)Mn(N). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U(11) + ... + 2hka^*b^*U(12)]$.

atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
Mn	41(1)	43(1)	29(1)	0(1)	10(1)	-5(1)
N(1)	40(2)	47(2)	29(2)	-1(2)	10(2)	-2(2)
O(1)	43(2)	61(2)	32(2)	7(2)	10(1)	-8(2)
O(2)	44(2)	57(2)	31(2)	7(2)	11(1)	-7(2)
N(2)	42(2)	44(2)	28(2)	2(2)	7(2)	-1(2)
C(7)	42(3)	41(3)	41(3)	6(2)	15(2)	-4(2)
C(5)	42(3)	59(3)	50(3)	-5(2)	14(2)	-1(2)
C(4)	40(3)	69(4)	70(4)	-2(3)	15(3)	-7(3)
C(10)	72(4)	51(3)	49(3)	16(2)	25(3)	6(3)
C(14)	45(3)	70(3)	31(2)	1(3)	4(2)	1(3)
N(3)	57(2)	44(2)	41(2)	-4(2)	18(2)	-1(2)
C(12)	49(3)	33(3)	40(3)	3(2)	22(2)	-3(2)
C(6)	41(3)	38(3)	41(3)	-1(2)	14(2)	2(2)
C(11)	58(3)	49(3)	45(3)	10(3)	16(2)	6(3)
C(1)	37(3)	43(3)	38(3)	3(2)	17(2)	2(2)
C(16)	42(3)	48(3)	49(3)	1(3)	9(2)	-6(2)
C(13)	57(3)	44(3)	33(2)	3(2)	17(2)	3(2)
C(8)	51(3)	60(3)	59(3)	11(3)	17(3)	-8(3)
C(3)	47(3)	78(4)	74(4)	9(3)	30(3)	-7(3)
C(9)	62(4)	65(4)	68(4)	18(3)	38(3)	-1(3)
C(15)	45(3)	60(3)	32(3)	-4(2)	4(2)	-9(3)
C(2)	55(3)	63(4)	52(3)	5(3)	26(3)	1(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (salen)Mn(N).

atom	x	y	z	U(eq)
H(5A)	4599(5)	2206(4)	6355(3)	80
H(4A)	6182(5)	2909(4)	5440(4)	80
H(10A)	-1380(5)	-277(4)	9320(4)	80
H(14A)	-1543(4)	1662(4)	2403(3)	50
H(14B)	-2133(4)	2514(4)	3108(3)	50
H(11A)	391(5)	383(3)	8545(3)	80

H(16A)	-3575(4)	239(3)	4928(3)	80
H(13A)	731(5)	2334(3)	2685(3)	80
H(8A)	-4283(5)	-155(4)	6546(4)	80
H(3A)	5401(5)	3376(4)	3650(4)	80
H(9A)	-3717(5)	-501(4)	8346(4)	80
H(15A)	-3423(4)	1053(4)	3337(3)	50
H(15B)	-2150(4)	246(4)	3297(3)	50
H(2A)	3034(5)	3063(4)	2774(4)	80

Appendix Two:

Tables of Crystallographic Data and Collection Parameters, Positional Parameters, Bond Lengths, Bond Angles, and Anistropic Thermal Factors for $(^{3}Ph–sal–^{i}Pr)_{2}Mn(OAc)$

X-Ray Crystallographic Data and Structure Refinement for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc)

Empirical formula	$MnC_{36}H_{39}N_2O_4$	
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 MoKα	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 14.588(3) Å	α = 90°
	b = 15.996(3) Å	β = 108.62(3)°
	c = 14.712(3) Å	γ = 90°
Volume	3253.3(11) Å^3	
Z	4	
Density (calculated)	1.263 g/cm^3	
Absorption coefficient	0.446 mm^{-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^2	
Data/restraints/parameters	2843/0/270	
GOF on F^2	2.135	
Final R indices [$I>2\sigma_I$]	$R_1 = 0.0334$, $wR_2 = 0.0748$	
R indices (all data)	$R_1 = 0.0443$, $wR_2 = 0.0806$	
Largest diff. peak and hole	0.177 and -0.242 e$^-$/A^{-3}	

Lattice parameter determination	# of reflections = 25
	range = $11.4° \leq \theta \leq 13.3°$
Number of standard reflections	3
Interval (minutes)	60
$(\Delta/\sigma)_{max}$ in final least squares cycle	0.001
Average shift/error	0.000
Absorption correction	None
Variation of standards	none within counting statistics
R_{merge}	2.1%
GOF_{merge}	1.19
Structure solution program	SHELXS-86 (Sheldrick, 1990)
Primary solution method	Patterson method
Secondary solution method	Difference Fourier maps
Hydrogen placement	Difference Fourier maps
Structure refinement program	SHELXL-93 (Sheldrick, 1993)
Treatment of hydrogen atoms	unrestained except for acetate methyl
Disorder present	acetate methyl hydrogens

Table 1. Atomic coordinates (x 10^2) and equivalent isotropic displacement parameters (Å^2 x 10^2) for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc). U(eq) is defined as one third of the trace of the orthogonalized U(ij) tensor.

atom	x	y	z	U(eq)
Mn	5000	5230(1)	7500	47(1)
O(1)	3718(1)	5241(1)	7435(1)	53(1)
N(1)	5309(1)	4424(1)	8698(1)	49(1)
C(1)	6291(2)	4076(2)	9085(2)	60(1)
C(2)	6486(2)	3378(1)	8465(2)	56(1)
C(3)	7576(2)	3271(2)	8682(3)	87(1)
C(4)	6000(2)	2566(2)	8578(3)	83(1)
C(5)	4698(1)	4256(1)	9137(1)	52(1)
C(11)	3263(1)	5016(1)	8044(1)	47(1)
C(12)	3701(1)	4529(1)	8863(1)	50(1)
C(13)	3153(2)	4277(1)	9448(2)	63(1)
C(14)	2201(2)	4502(2)	9223(2)	75(1)
C(15)	1782(2)	4984(2)	8431(2)	69(1)
C(16)	2280(1)	5256(1)	7818(2)	53(1)
C(21)	1797(1)	5778(1)	6969(2)	59(1)
C(22)	872(2)	5590(2)	6374(2)	77(1)
C(23)	398(3)	6095(3)	5615(2)	101(1)
C(24)	831(3)	6802(3)	5432(3)	110(1)
C(25)	1755(3)	7001(2)	5994(2)	94(1)
C(26)	2232(2)	6489(2)	6752(2)	71(1)
O(50)	5197(1)	6436(1)	8272(1)	84(1)
C(50)	5000	6822(2)	7500	72(1)
C(51)	5000	7764(2)	7500	107(2)

Table 2. Bond lengths (Å) for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc).

Mn-O(1a)	1.8420(12)	C(13)-C(14)	1.369(3)
Mn-O(1)	1.8420(12)	C(13)-H(13)	0.93(2)
Mn-N(1a)	2.113(2)	C(14)-C(15)	1.368(3)
Mn-N(1)	2.113(2)	C(14)-H(14)	0.95(2)
Mn-O(50a)	2.212(2)	C(15)-C(16)	1.395(3)
Mn-O(50)	2.212(2)	C(15)-H(15)	0.90(2)
Mn-C(50)	2.547(3)	C(16)-C(21)	1.480(3)

O(1)-C(11)	1.324(2)	C(21)-C(26)	1.388(3)
N(1)-C(5)	1.285(2)	C(21)-C(22)	1.388(3)
N(1)-C(1)	1.473(2)	C(22)-C(23)	1.373(4)
C(1)-C(2)	1.525(3)	C(22)-H(22)	0.93(2)
C(1)-H(1A)	0.96(2)	C(23)-C(24)	1.363(5)
C(1)-H(1B)	0.97(2)	C(23)-H(23)	0.90(3)
C(2)-C(4)	1.515(3)	C(24)-C(25)	1.374(5)
C(2)-C(3)	1.528(3)	C(24)-H(24)	0.83(3)
C(2)-H(2)	0.94(2)	C(25)-C(26)	1.379(4)
C(3)-H(3A)	0.98(3)	C(25)-H(25)	0.94(2)
C(3)-H(3B)	0.96(3)	C(26)-H(26)	0.90(2)
C(3)-H(3C)	0.99(3)	O(50)-C(50)	1.243(2)
C(4)-H(4A)	0.91(3)	C(50)-O(50a)	1.243(2)
C(4)-H(4B)	1.01(3)	C(50)-C(51)	1.506(4)
C(4)-H(4C)	0.98(2)	C(51)-H(51A)	0.99(2)
C(5)-C(12)	1.446(3)	C(51)-H(51B)	0.99(2)
C(5)-H(5)	0.99(2)	C(51)-H(51C)	0.99(2)
C(11)-C(12)	1.405(3)	C(51)-H(51D)	0.99(2)
C(11)-C(16)	1.419(2)	C(51)-H(51E)	0.99(2)
C(12)-C(13)	1.408(3)	C(51)-H(51F)	0.99(2)

Table 3. Bond angles (°) for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc).

O(1a)-Mn-O(1)	178.91(8)	C(14)-C(13)-C(12)	120.5(2)
O(1a)-Mn-N(1a)	89.51(6)	C(14)-C(13)-H(13)	121.6(13)
O(1)-Mn-N(1a)	91.15(6)	C(12)-C(13)-H(13)	117.9(13)
O(1a)-Mn-N(1)	91.15(6)	C(15)-C(14)-C(13)	119.8(2)
O(1)-Mn-N(1)	89.51(6)	C(15)-C(14)-H(14)	121.4(14)
N(1a)-Mn-N(1)	104.76(8)	C(13)-C(14)-H(14)	118.8(14)
O(1a)-Mn-O(50a)	88.95(6)	C(14)-C(15)-C(16)	122.9(2)
O(1)-Mn-O(50a)	90.10(6)	C(14)-C(15)-H(15)	124(2)
N(1a)-Mn-O(50a)	98.41(6)	C(16)-C(15)-H(15)	113(2)
N(1)-Mn-O(50a)	156.84(6)	C(15)-C(16)-C(11)	117.4(2)
O(1a)-Mn-O(50)	90.10(6)	C(15)-C(16)-C(21)	121.0(2)
O(1)-Mn-O(50)	88.95(6)	C(11)-C(16)-C(21)	121.6(2)
N(1a)-Mn-O(50)	156.84(6)	C(26)-C(21)-C(22)	117.2(2)
N(1)-Mn-O(50)	98.41(6)	C(26)-C(21)-C(16)	121.8(2)
O(50a)-Mn-O(50)	58.43(9)	C(22)-C(21)-C(16)	121.0(2)

O(1a)-Mn-C(50)	89.45(4)	C(23)-C(22)-C(21)	121.4(3)
O(1)-Mn-C(50)	89.45(4)	C(23)-C(22)-H(22)	125(2)
N(1a)-Mn-C(50)	127.62(4)	C(21)-C(22)-H(22)	114(2)
N(1)-Mn-C(50)	127.62(4)	C(24)-C(23)-C(22)	120.3(3)
O(50a)-Mn-C(50)	29.22(4)	C(24)-C(23)-H(23)	121(2)
O(50)-Mn-C(50)	29.21(4)	C(22)-C(23)-H(23)	119(2)
C(11)-O(1)-Mn	133.01(12)	C(23)-C(24)-C(25)	120.0(3)
C(5)-N(1)-C(1)	118.2(2)	C(23)-C(24)-H(24)	118(2)
C(5)-N(1)-Mn	123.31(14)	C(25)-C(24)-H(24)	122(2)
C(1)-N(1)-Mn	118.38(13)	C(24)-C(25)-C(26)	119.6(3)
N(1)-C(1)-C(2)	112.9(2)	C(24)-C(25)-H(25)	125(2)
N(1)-C(1)-H(1A)	108.6(12)	C(26)-C(25)-H(25)	115(2)
C(2)-C(1)-H(1A)	109.5(12)	C(25)-C(26)-C(21)	121.5(3)
N(1)-C(1)-H(1B)	106.7(11)	C(25)-C(26)-H(26)	121.0(14)
C(2)-C(1)-H(1B)	109.9(12)	C(21)-C(26)-H(26)	117.2(14)
H(1A)-C(1)-H(1B)	109(2)	C(50)-O(50)-Mn	90.5(2)
C(4)-C(2)-C(1)	112.3(2)	O(50a)-C(50)-O(50)	120.5(3)
C(4)-C(2)-C(3)	111.9(2)	O(50a)-C(50)-C(51)	119.7(2)
C(1)-C(2)-C(3)	109.7(2)	O(50)-C(50)-C(51)	119.7(2)
C(4)-C(2)-H(2)	107.0(11)	O(50a)-C(50)-Mn	60.3(2)
C(1)-C(2)-H(2)	107.5(11)	O(50)-C(50)-Mn	60.3(2)
C(3)-C(2)-H(2)	108.2(11)	C(51)-C(50)-Mn	180.0
C(2)-C(3)-H(3A)	113(2)	C(50)-C(51)-H(51A)	109.471(8)
C(2)-C(3)-H(3B)	112(2)	C(50)-C(51)-H(51B)	109.5(2)
H(3A)-C(3)-H(3B)	118(3)	H(51A)-C(51)-H(51B)	109.5
C(2)-C(3)-H(3C)	107(2)	C(50)-C(51)-H(51C)	109.471(9)
H(3A)-C(3)-H(3C)	102(2)	H(51A)-C(51)-H(51C)	109.5(3)
H(3B)-C(3)-H(3C)	103(2)	H(51B)-C(51)-H(51C)	109.47(5)
C(2)-C(4)-H(4A)	111(2)	C(50)-C(51)-H(51D)	109.47(4)
C(2)-C(4)-H(4B)	112(2)	H(51A)-C(51)-H(51D)	141.1
H(4A)-C(4)-H(4B)	110(2)	H(51B)-C(51)-H(51D)	56.25(8)
C(2)-C(4)-H(4C)	112.2(14)	H(51C)-C(51)-H(51D)	56.25(6)
H(4A)-C(4)-H(4C)	105(2)	C(50)-C(51)-H(51E)	109.47(6)
H(4B)-C(4)-H(4C)	107(2)	H(51A)-C(51)-H(51E)	56.25(9)
N(1)-C(5)-C(12)	126.4(2)	H(51B)-C(51)-H(51E)	141.1
N(1)-C(5)-H(5)	118.7(11)	H(51C)-C(51)-H(51E)	56.3(2)
C(12)-C(5)-H(5)	114.9(11)	H(51D)-C(51)-H(51E)	109.5(2)
O(1)-C(11)-C(12)	122.8(2)	C(50)-C(51)-H(51F)	109.5(2)
O(1)-C(11)-C(16)	117.1(2)	H(51A)-C(51)-H(51F)	56.3
C(12)-C(11)-C(16)	120.0(2)	H(51B)-C(51)-H(51F)	56.25(9)

C(11)-C(12)-C(13)	119.4(2)	H(51C)-C(51)-H(51F)	141.06(12)
C(11)-C(12)-C(5)	123.2(2)	H(51D)-C(51)-H(51F)	109.47(8)
C(13)-C(12)-C(5)	117.4(2)	H(51E)-C(51)-H(51F)	109.5(2)

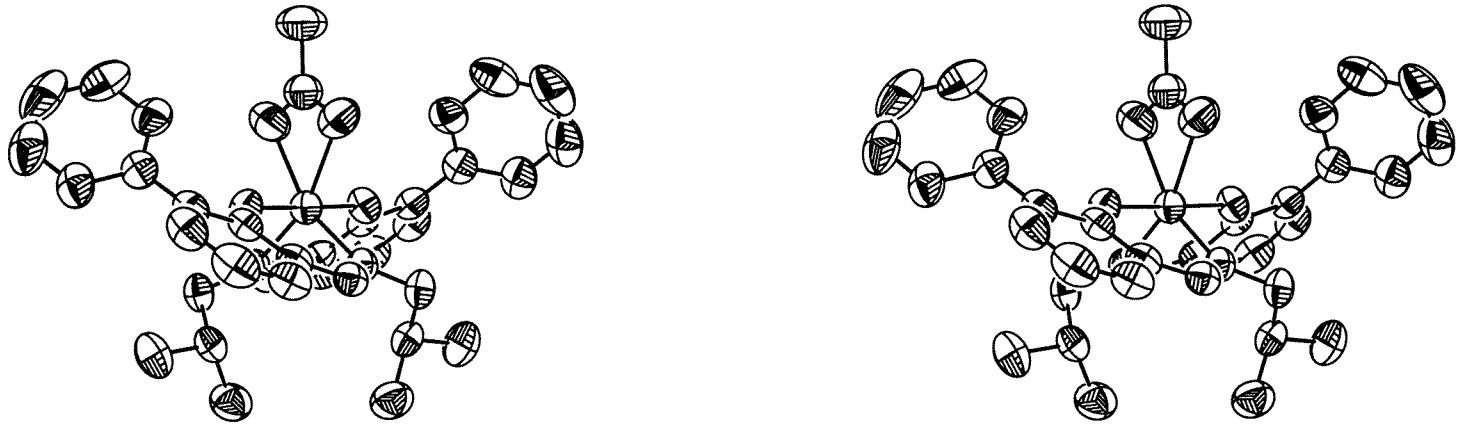
Symmetry transformations used to generate equivalent atoms: -x+1, y, -z+3/2

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U(11) + ... + 2hka^*b^*U(12)]$.

atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
Mn	41(1)	55(1)	52(1)	0	23(1)	0
O(1)	41(1)	68(1)	57(1)	10(1)	25(1)	5(1)
N(1)	47(1)	57(1)	43(1)	-3(1)	14(1)	1(1)
C(1)	53(1)	76(2)	44(1)	3(1)	7(1)	5(1)
C(2)	56(1)	62(1)	49(1)	9(1)	14(1)	11(1)
C(3)	62(2)	101(2)	95(2)	11(2)	19(2)	23(2)
C(4)	95(2)	70(2)	83(2)	16(2)	29(2)	2(2)
C(5)	63(1)	54(1)	39(1)	-4(1)	17(1)	-4(1)
C(11)	46(1)	50(1)	52(1)	-12(1)	25(1)	-8(1)
C(12)	57(1)	50(1)	48(1)	-10(1)	25(1)	-9(1)
C(13)	76(2)	63(1)	59(1)	-6(1)	36(1)	-11(1)
C(14)	78(2)	87(2)	80(2)	-12(1)	54(2)	-22(1)
C(15)	51(1)	85(2)	82(2)	-17(1)	38(1)	-9(1)
C(16)	45(1)	56(1)	67(1)	-15(1)	28(1)	-6(1)
C(21)	46(1)	68(1)	69(1)	-13(1)	29(1)	10(1)
C(22)	51(1)	97(2)	85(2)	-17(2)	25(1)	13(1)
C(23)	69(2)	138(3)	89(2)	-24(2)	15(2)	41(2)
C(24)	118(3)	134(3)	82(2)	6(2)	36(2)	76(3)
C(25)	109(2)	78(2)	106(2)	14(2)	51(2)	36(2)
C(26)	66(2)	68(2)	83(2)	-4(1)	30(1)	13(1)
O(50)	73(1)	80(1)	101(1)	22(1)	30(1)	8(1)
C(50)	60(2)	61(2)	94(3)	0	25(2)	0
C(51)	148(4)	59(2)	110(3)	0	36(3)	0

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc).

atom	x	y	z	U(eq)
H(51A)	5406(149)	7970(6)	8138(60)	161
H(51B)	4328(28)	7970(6)	7363(181)	161
H(51C)	5266(172)	7970(6)	6999(124)	161
H(51D)	4594(149)	7970(6)	6862(60)	161
H(51E)	5672(28)	7970(6)	7637(181)	161
H(51F)	4734(172)	7970(6)	8001(124)	161
H(1A)	6379(13)	3865(12)	9721(15)	65(6)
H(1B)	6738(14)	4536(12)	9124(14)	59(6)
H(2)	218(12)	3544(10)	7819(13)	47(5)
H(3A)	7742(20)	2764(19)	8402(21)	127(12)
H(3B)	7888(22)	3782(20)	8605(23)	140(13)
H(3C)	7854(18)	3163(15)	9376(20)	97(9)
H(4A)	6236(18)	2379(16)	9192(21)	98(9)
H(4B)	6082(18)	2121(17)	8122(20)	105(9)
H(4C)	5304(18)	2636(14)	8459(19)	93(9)
H(5)	4909(13)	3898(12)	9719(14)	62(6)
H(13)	3457(14)	3957(12)	9984(14)	63(6)
H(14)	1839(16)	4303(14)	9613(16)	88(7)
H(15)	1168(15)	5165(13)	8259(16)	77(7)
H(22)	628(16)	5092(15)	6534(17)	86(9)
H(23)	-191(21)	5943(17)	5229(20)	114(11)
H(24)	543(22)	7077(19)	4944(22)	121(13)
H(25)	2109(17)	7465(16)	5901(19)	94(9)
H(26)	2815(15)	6629(12)	7157(15)	65(7)



Stereoview of **(^{3}Ph–sal–^{i}Pr)$_2$Mn(OAc)**

Appendix Three:

Tables of Crystallographic Data and Collection Parameters, Positional Parameters, Bond Lengths, Bond Angles, and Anistropic Thermal Factors for $(^3MeO–sal–Me)_2Mn(N)$

X-Ray Crystallographic Data and Structure Refinement for (^{3}MeO–sal–Me)$_2$Mn(N)

Empirical formula	$MnC_{20}H_{24}N_3O_4$	
Formula weight	425.36	
Crystal color	pale brown	
Crystal shape	prism	
Solvent of crystallization	Et_2O/pentane	
Type of diffractometer	Siemens P4	
Temperature	163 K	
Wavelength	0.71073 Å MoKα	
Crystal system	Orthorhombic	
Space group	Fdd2	
Unit cell dimensions	a = 14.693(2) Å	α = 90°
	b = 23.268(3) Å	β = 90°
	c = 11.6940(10) Å	γ = 90°
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	$0 \leq h \leq 17$, $0 \leq k \leq 27$, $0 \leq l \leq 13$	
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$^-$/A^{-3}	
Lattice parameter determination	# of reflections = 34	

	range = $5.22° \leq \theta \leq 12.48°$
Number of standard reflections	3
Interval (minutes)	97
$(\Delta/\sigma)_{max}$ in final least squares cycle	0.000
Average shift/error	0.000
Absorption correction	None
Decay of standards	< 0.01
Final weighting scheme	$w = 1/[\sigma^2(F^2) + (0.0398P)^2 + 1.313P]$ where $P = (F^2 + 2F^2)/3$
Structure solution program	SHELXTL (version 5.03)
Primary solution method	Direct methods
Structure refinement program	SHELXTL (version 5.03)

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (^{3}MeO–sal–Me)$_2$Mn(N). U(eq) is defined as one third of the trace of the orthogonalized U(ij) tensor.

atom	x	y	z	U(eq)
Mn	0	0	8341(1)	18(1)
N(1)	0	0	9660(3)	30(1)
N(2)	387(1)	-829(1)	8146(2)	22(1)
O(1)	-1143(1)	-170(1)	7729(2)	25(1)
O(2)	-2895(1)	-123(1)	7421(2)	37(1)
C(1)	-168(2)	-1245(1)	7983(2)	24(1)
C(2)	-1143(2)	-1202(1)	7840(2)	25(1)
C(3)	-1653(2)	-1713(1)	7808(3)	31(1)
C(4)	-2579(2)	-1694(1)	7654(3)	34(1)
C(5)	-3017(2)	-1166(1)	7518(3)	32(1)
C(6)	-2529(2)	-659(1)	7543(2)	26(1)
C(7)	-1573(2)	-668(1)	7717(2)	22(1)
C(8)	1363(2)	-985(1)	8258(3)	28(1)
C(9)	1715(2)	-871(2)	9448(3)	45(1)
C(10)	-3858(2)	-78(2)	7361(3)	39(1)

Table 2. Bond lengths (Å) for (^{3}MeO–sal–Me)$_2$Mn(N).

Mn(1)-N(1)	1.543(4)	O(2)-C(10)	1.421(3)
Mn(1)-O(1)	1.868(2)	C(1)-C(2)	1.446(4)
Mn(1)-O(1a)	1.868(2)	C(2)-C(7)	1.401(4)
Mn(1)-N(2)	2.023(2)	C(2)-C(3)	1.407(4)
Mn(1)-N(2a)	2.023(2)	C(3)-C(4)	1.373(4)
N(2)-C(1)	1.282(3)	C(4)-C(5)	1.395(4)
N(2)-C(8)	1.485(3)	C(5)-C(6)	1.380(4)
O(1)-C(7)	1.319(3)	C(6)-C(7)	1.421(4)
O(2)-C(6)	1.365(4)	C(8)-C(9)	1.508(5)

Table 3. Bond angles (°) for (^{3}MeO–sal–Me)$_2$Mn(N).

N(1)-Mn(1)-O(1)	112.51(6)	N(2)-C(1)-C(2)	126.5(2)
N(1)-Mn(1)-O(1a)	112.51(6)	C(7)-C(2)-C(3)	120.5(2)
O(1)-Mn(1)-O(1a)	134.99(12)	C(7)-C(2)-C(1)	121.4(2)
N(1)-Mn(1)-N(2)	96.45(6)	C(3)-C(2)-C(1)	118.2(2)
O(1)-Mn(1)-N(2)	90.46(8)	C(3)-C(2)-C(1)	118.2(2)
O(1a)-Mn(1)-N(2)	84.61(8)	C(4)-C(3)-C(2)	120.2(3)
N(1)-Mn(1)-N(2a)	96.45(6)	C(3)-C(4)-C(5)	120.1(3)
O(1)-Mn(1)-N(2a)	84.61(8)	C(6)-C(5)-C(4)	120.7(2)
O(1a)-Mn(1)-N(2a)	90.46(8)	O(2)-C(6)-C(5)	125.1(2)
N(2)-Mn(1)-N(2a)	167.11(12)	O(2)-C(6)-C(7)	114.6(2)
C(1)-N(2)-C(8)	116.3(2)	C(5)-C(6)-C(7)	120.3(3)
C(1)-N(2)-Mn(1)	124.0(2)	O(1)-C(7)-C(2)	124.2(2)
C(8)-N(2)-Mn(1)	119.7(2)	O(1)-C(7)-C(6)	117.6(2)
C(7)-O(1)-Mn(1)	128.3(2)	C(2)-C(7)-C(6)	118.2(2)
C(6)-O(2)-C(10)	117.7(2)	N(2)-C(8)-C(9)	111.6(2)

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

Table 4. Anisotropic displacement parameters (Å^2 x 10^3) for (^{3}MeO–sal–Me)$_2$Mn(N). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U(11) + ... + 2hka^*b^*U(12)]$.

atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
Mn(1)	14(1)	19(1)	21(1)	0	0	0(1)
N(1)	29(2)	34(2)	27(2)	0	0	10(1)
N(2)	18(1)	24(1)	23(1)	0(1)	1(1)	1(1)
O(1)	17(1)	22(1)	36(1)	3(1)	-4(1)	-2(1)
O(2)	16(1)	37(1)	57(1)	5(1)	-7(1)	-1(1)
C(1)	28(1)	20(1)	23(1)	1(1)	3(1)	2(1)
C(2)	25(1)	26(1)	23(1)	-1(1)	1(1)	-2(1)
C(3)	34(2)	24(1)	33(2)	0(1)	-1(1)	-5(1)
C(4)	33(2)	33(2)	37(2)	-3(1)	0(1)	-16(1)
C(5)	23(1)	42(2)	31(2)	0(1)	-2(1)	-11(1)
C(6)	21(1)	33(2)	25(1)	3(1)	-2(1)	-2(1)
C(7)	21(1)	26(1)	20(1)	2(1)	1(1)	-7(1)

C(8)	19(1)	28(1)	37(2)	-2(1)	-2(1)	7(1)
C(9)	35(2)	53(2)	47(2)	-9(2)	-15(2)	21(2)
C(10)	18(1)	52(2)	47(2)	8(2)	-5(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (^{3}MeO–sal–Me)$_2$Mn(N).

atom	x	y	z	U(eq)
H(1)	51(17)	-1667(13)	7929(26)	24(8)
H(3)	-1374(21)	-2070(13)	914(28)	33(8)
H(4)	-2907(23)	-2050(14)	635(31)	38(8)
H(5)	-3676(26)	-1112(16)	432(30)	42(9)
H(8A)	1710(21)	-770(13)	7752(29)	27(8)
H(8B)	1432(20)	-1381(14)	8058(27)	28(8)
H(9A)	1382(27)	-1119(18)	10097(41)	61(12)
H(9B)	1684(26)	-456(17)	9626(35)	57(11)
H(9C)	2256(31)	-984(18)	9514(41)	62(12)
H(10A)	-4172(24)	-237(14)	8068(33)	43(9)
H(10B)	-4083(22)	-275(13)	6685(30)	31(8)
H(10C)	-4007(22)	324(16)	7356(30)	39(9)