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Studies toward the Asymmetric Synthesis of the Right Part of the Mycalamides

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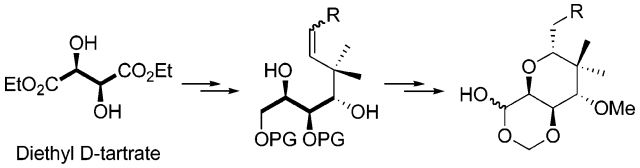

Described herein is the asymmetric synthesis of a functionalized, trioxadecalin unit that comprises the right-hand part of the mycalamides and related natural products. The synthetic route involves a 16-step sequence that accomplishes the formation of two heterocyclic rings and the generation of five stereocenters. The synthesis commenced with a C2-symmetric starting material, diethyl D-tartrate, and took advantage of a relay of diastereoselective reactions to extend this four-carbon chain and introduce new chiral centers. Subsequent electrophile-mediated cyclization afforded the desired pyran ring, which was then transformed into the desired, functionalized trioxadecalin skeleton.

Introduction

Mycalamides A−D,[1,2] onnamides A−F,[3] and theopederins A−L[4] are structurally related natural products isolated from marine sponge of the genera *Mycale* and *Theonella*, collected from New Zealand and Okinawan waters. These compounds all exhibit potent cytotoxicity, subnanomolar in many cases, against various tumor cell lines. Mycalamide A (**1**) (Figure 1), in particular, has been evaluated as an anti-tumor agent based on its in vivo activity against P388 murine leukemia and a variety of solid tumor model systems, including Lewis lung, M5076, Burkitt's lymphoma, and MX-1 and CX-1 human tumor xenografts.[5] Mycalamide A also displays significant anti-viral activity as well as immunosuppressive action against T-cell activation in mice.[6] Interestingly, the structures of these sponge derived compounds are strikingly similar to that of pederin, a strong insect poison isolated from the terrestrial beetle, *Paederus fuscipes*.[7]

These structurally challenging and potently bioactive compounds have stimulated considerable attention from the organic synthesis community. Kishi's pioneering total synthesis of mycalamide A and B was followed by reports from many other research groups, including Nakata, Roush, Kocienski, Trost, and Toyota, on the total syntheses or formal syntheses of several members of this class.[8−11] Studies toward the synthesis of

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(1) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Am. Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.

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(3) (a) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851. (b) Matsunaga, S.; Fusetani, N.; Nakao, Y. *Tetrahedron* **1992**, *48*, 8369. (c) Kobayashi, J.; Itagaki, F.; Shigemori, H.; Sasaki, T. *J. Nat. Prod.* **1993**, *56*, 976. (d) Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *J. Nat. Prod.* **2001**, *64*, 640.

(4) (a) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1992**, *57*, 3828. (b) Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A. *Tetrahedron* **1999**, *55*, 13697. (c) Paul, G. K.; Gunasekera, S. P.; Longley, R. E.; Pomponi, S. A. *J. Nat. Prod.* **2002**, *65*, 59.

(5) Burres, N. S.; Clement, J. J. *Cancer Res.* **1989**, *49*, 2935.

(6) Glavine, F.; Freeman, G. J.; Razi-Wolf, Z.; Bennacerraf, B.; Nadler, L.; Reiser, H. *Eur. J. Immunol.* **1993**, *23*, 283.

(7) (a) Furusaki, A.; Watanabe, T.; Matsumoto, T.; Yanagiya, M. *Tetrahedron Lett.* **1968**, 6301. (b) Corradi, A. B.; Mangia, A.; Nardelli, N.; Pelizzi, G. *Gazz. Chim. Ital.* **1971**, *101*, 591.

(8) Mycalamide A: (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (b) Nakata, T.; Fukui, H.; Nakawara, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159. (c) Roush, W. R.; Pfeifer, L. A. *Org. Lett.* **2000**, *2*, 859. (d) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290. (e) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875. Formal synthesese: (f) Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett.* **1994**, *35*, 8229. (g) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48.

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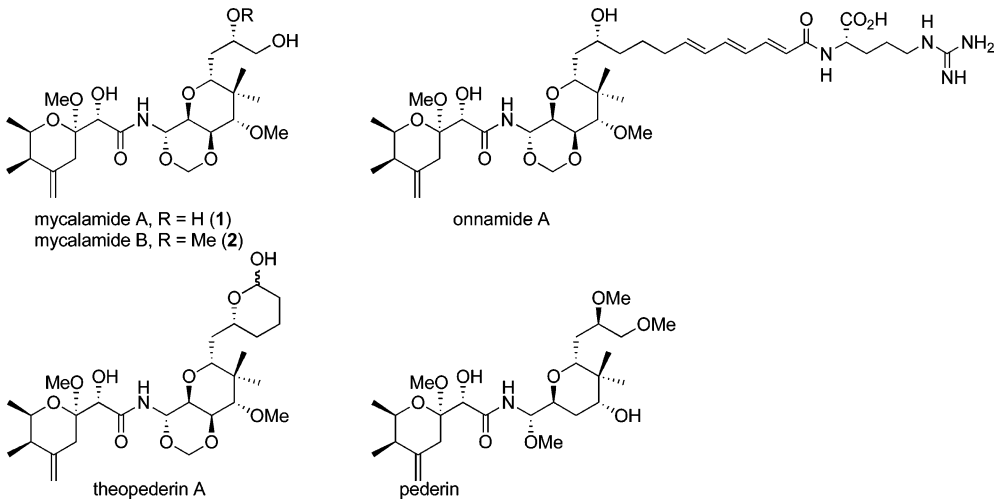


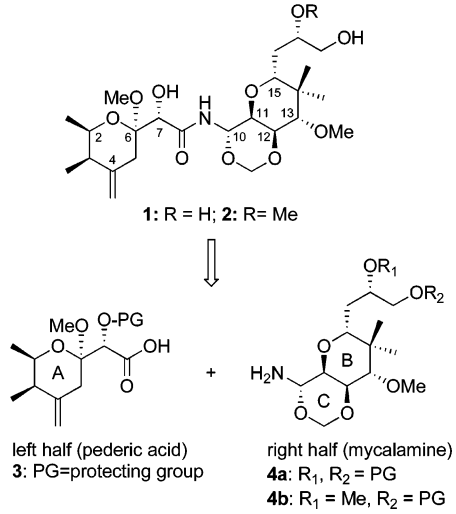
FIGURE 1. Structures of mycalamides A and B, onnamide A pederin, theopederin A.

analogues of these natural products[12] and SAR study of derivatives prepared from naturally occurring mycalamides have also been reported.[13] The published synthetic studies were accomplished, for the most part, through a strategy that entailed the coupling of the left half (**3**) portion with the right half (**4**), often through an amide bond formation. The left half of mycalamide A is identical to the left half of pederin, and this portion is commonly referred to as pederic acid. Over the years, there has been extensive work on the synthesis of pederin, and this effort has resulted in several solutions to the synthesis of the pederic acid unit. Consequently, in 1993, when we began our work in this area, we focused first on the synthesis of right part of the mycalamides, known as mycalamine (**4**). With six stereogenic centers decorating an array of nine contiguous carbons, mycalamine presents a formidable synthetic challenge. Our analysis revealed that the core of mycalamine could potentially be fashioned from the C2-symmetric chiral pool compound, tartaric acid. We report here the results of our efforts to transform diethyl tartrate into the tetrahydropyran-containing, trioxadecalin skeleton of mycalamine.

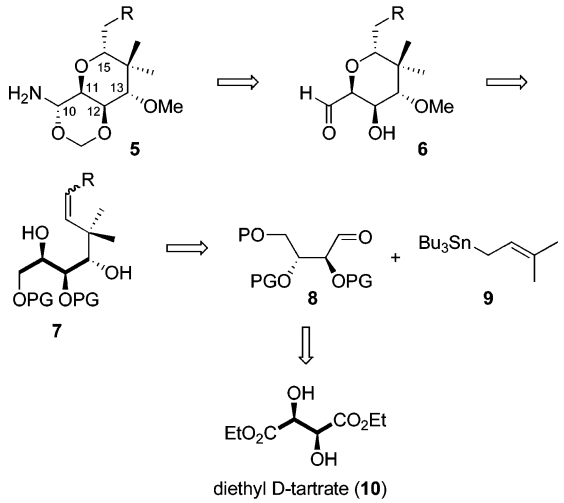
Retrosynthetic Analysis. When these studies were initiated, the only work on the synthesis of the mycalamides was the work of Hong and Kishi.[8a,10] These authors had reported the successful coupling of pederic acid (**3**) with mycalamine (**4**) to yield mycalamide A (Scheme 1). In light of this accomplishment, our goal was to develop a strategy that would enable us to synthesize mycalamine more efficiently and by a route that controlled all newly created stereocenters.

The essence of our strategy to mycalamine is depicted in

SCHEME 1. Hong−Kishi Disconnection of Mycalamides to Pederic Acid and Mycalamine Units



SCHEME 2. Retrosynthetic Analysis of the Right Part of Mycalamides



Scheme 2. The densely functionalized trioxadecalin framework (**5**), which also contains a labile aminal linkage, was expected to be derived from hydroxyaldehyde **6**. Pyran **6** could, in turn,

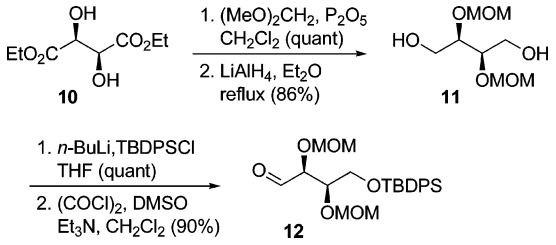
(9) Mycalamide B and theopederin D: Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357 and references therein. See also ref 8a for mycalamide B.

(10) Onnamide, A.; Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

(11) Mycalamine unit and model study: (a) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495. (b) Gardiner, J. M.; Mills, R.; Fessard, T. *Tetrahedron Lett.* **2004**, 1215. (c) Toyota, M.; Hirota, M.; Hirano, H.; Ihara, M. *Org. Lett.* **2000**, *2*, 2031. (d) Breitfelder, S.; Schlapbach, A.; Hoffmann, R. W. *Synthesis* **1998**, 468 and references therein. (e) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421.

(12) (a) Fukui, H.; Tsuchiya, Y.; Fujita, K.; Nakagawa, T.; Koshino, H.; Nakata, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2081. (b) Abell, A. D.; Blunt, J. W.; Foulds, G. J.; Munro, M. H. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1647. (c) Takahashi, S.; Okada, A.; Nakata, T. *Heterocycles* **2004**, *63*, 2111.

SCHEME 3. Preparation of Aldehyde 12 from Diethyl D-Tartrate



be formed from an acyclic precursor such as **7**, through either electrophile or nucleophile promoted cyclization. Further analysis revealed that embedded in **7** was a four-carbon piece that was derivable from the C2-symmetric compound, tartaric acid, readily available in both antipodes. The required starting material, diethyl D-tartrate (**10**), would not only provide two of the stereocenters, C-11 and C-12, but also offer handles for the introduction of additional stereocenters. After transformation of **10** into a properly protected aldehyde (**8**), the third stereocenter (C-13) as well as the geminal dimethyl groups could be introduced by a chelation-controlled addition of tributylprenylstannane (**9**).

Results and Discussion

Tartrate Desymmetrization and Diastereoselective Prenylstannane Addition. Central to the strategy to mycalamine was the use of a tartrate-derived four-carbon piece, to which would be grafted the additional carbons through diastereoselective reactions. In preparation for this, the hydroxyl groups of diethyl D-tartrate needed to be protected. The methoxy methyl ether (MOM) protecting group was selected over a silyl group because it was expected to be stable to the basic conditions present in the next few steps, yet removable under milk condition when necessary and compatible with the required chelation-controlled addition of the prenyl unit. Importantly, the hope was to parlay the methylene of the MOM group into the $-CH_2-$ of the C-ring acetal. Treatment of tartrate **10** with P_2O_5 in dimethoxymethane and dichloromethane afforded the bis-MOM protected tartrate in quantitative yield (Scheme 3).[14] Attempted reduction of the bis-MOM ester with DIBAL-H to yield a mono-aldehyde directly proved unsatisfactory due to competing over reduction of the aldehyde as well as reduction of the second ester. Consequently, the bis-MOM ester was reduced down to diol **11**[15a] using an excess amount of $LiAlH_4$. The high water solubility of diol **11** made it difficult to isolate by standard extraction. Good results were obtained, however, when the reaction was quenched with a minimum amount of water, and the gelatinous, crude reaction product was subjected to Soxhlet extraction with THF for 48 h. Alternatively, the diol was isolated in good yield upon quenching the reaction by successive addition of water (1 mL/1 g of LAH), 15% NaOH (1 mL/1 g of LAH), and water (3 mL/1 g of LAH), followed by filtration.[15b] The two hydroxyls in **11** are chemically equivalent because of C2 symmetry, so protection of one renders the molecule unsymmetrical. The desymmetrization was accomplished in quantitative yield by treating **11** with 1.2 equiv of *n*-BuLi and 1 equiv of *t*-butyldiphenylsilyl chloride (TBDPSCl) in THF solution. Swern oxidation of the free alcohol gave the desired aldehyde (**12**), which was poised for a key C−C bond-forming step, the addition of tributylprenylstannane.

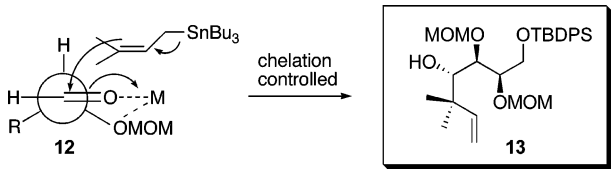
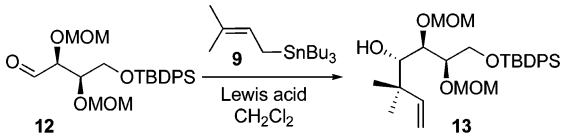


FIGURE 2. Chelation-controlled addition of aldehyde **12**.

TABLE 1. Diastereoselective Tributylprenylstannane Addition to Aldehyde 12



entry	Lewis acid	temp (time)	yield	dr
1	$TiCl_4$	−78 °C (25 min)	65%	14:1
2	$BF_3{\cdot}OEt_2$	−78 °C (25 min)	messy	
3	$ZnBr_2$	−78 °C	very slow	
4	$ZnBr_2$	rt (8 h)	77%	2:1
5	$ZnBr_2$	−10 °C (2 d)	81%	>12:1
6	$ZnBr_2$	−78 to 0 °C (6 h) then 0 °C (2 h)	90%	>50:1

The plan for the introduction of the gem-dimethyl group entailed reaction of stannane **9** with aldehyde **12** in the presence of a suitable Lewis acid.[11d,16] Diastereoselective addition was expected on the basis of the chelation-Cram model (Figure 2), wherein the prenyl unit would add to the less hindered face of the conformationally locked carbonyl. Several conditions were examined for this addition reaction, and the results are summarized in Table 1. The addition product **13** was obtained with high diastereoselectivity (14:1), but in modest and variable yields (up to 65%) with $TiCl_4$ as the Lewis acid at −78 °C. Decomposition products usually accompanied the desired product. In one instance, the major side-product was the expected addition product in which the MOM group on the adjacent alcohol had been removed. Although not sought at the time, this regioselectively deprotected diol could prove quite useful in an improved synthesis of the trioxadecalin skeleton. A messy reaction was observed with $BF_3{\cdot}Et_2O$ as the Lewis acid. The best results were obtained using the weak Lewis acid, $ZnBr_2$. The reaction rate and diastereoselectivity were found to vary significantly with temperature. Whereas a very slow reaction took place at −78 °C, it progressed quickly at room temperature (8 h, 77%), albeit with poor diastereoselectivity (2:1). The reaction proceeded well at −10 °C and afforded alcohol **13** in 81% yield and with >12:1 diastereoselectivity. The conditions were fine-tuned, such that the major product was obtained in 90% yield with essentially none of the minor diastereomer.

(13) (a) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B.; Pannel, L. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1335. (b) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Clark, B. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1025. (c) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1223.

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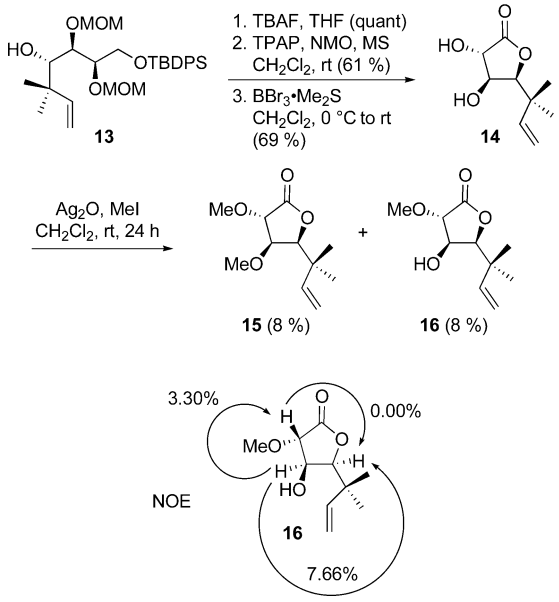
(15) (a) Dulphy, H.; Gras, J.-L.; Lejon, T. *Tetrahedron* **1996**, *52*, 8517. (b) Fieser, L. F.; Fieser, M. *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, 1967; Vol. 1, pp 583−584.

(16) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. (c) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927. (d) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 2183. (e) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1991**, *56*, 483 and references therein.

SCHEME 4. Determination of Stereochemistry of Addition Product 13

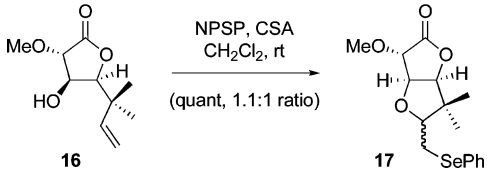


To determine the stereochemistry of the newly formed chiral center, alcohol **13** was converted into a cyclic form, such that NOE analysis would reveal the relative position of different substituents (Scheme 4). Removal of the TBDPS group with TBAF followed by treatment of the resulting diol with NMO/TPAP combination provided a lactone in 61% yield.[17] Unfortunately, the relative stereochemistry of the substituents in the lactone could not be determined, because the critical signals in its ^{1}H NMR spectrum were not cleanly separated. The same problem was encountered with diol **14**, obtained upon the removal of both MOM groups with BBr_3•Me_2S.[18] A suitable NOE sample was finally obtained by converting diol **14** into a monomethoxy derivative. Treatment of **14** with Ag_2O and MeI in CH_2Cl_2 gave, in low yield, a 1:1 mixture of the mono- and dimethylated products. The yield of this reaction was not optimized because enough material was obtained for the purpose of NMR analysis. All protons in the NMR spectrum of **16** were nicely separated, and NOE analysis indicated that the stereochemistry of the newly formed center was as shown (*S* configuration), as expected for chelation-controlled addition of the prenylstannane.

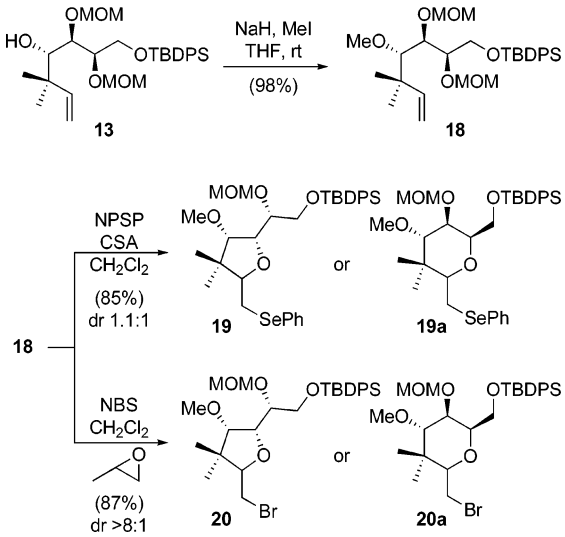
A chemical transformation corroborated the above assigned stereochemistry. Lactone-alcohol **16** readily underwent a facile selenoetherification reaction to afford bicyclic compound **17** in quantitative yield, as a 1:1 mixture of diastereomers (Scheme 5).[19] If the prenyl unit were oriented trans to the free hydroxyl, then the cyclization would be expected to proceed with difficulty, if at all, as it would produce the strained *trans*-[5,5]-bicyclic lactone. These results confirmed that $ZnBr_2$-promoted addition of tributylprenylstannane (**9**) onto aldehyde **12** was chelation controlled and that it introduced the desired stereochemistry at the C-13 carbon center.

Formation of Tetrahydropyran Ring by Electrophilic Cyclization. After the stereoselective installation of the prenyl group, the next objective en route to mycalamine was formation

SCHEME 5. Corroboration of the Assigned Stereochemistry of C-13



SCHEME 6. Electrophilic Cyclization of Bis-MOM Alkene 18



of the tetrahydropyran ring through an electrophile-mediated cyclization reaction. An important requirement for this process was that the cyclization produce the tetrahydropyran ring with the 2 and 6 position substituents in a trans arrangement. In preparation for the cyclization, the hydroxyl group of **13** was converted into a methyl ether (**18**), as required for the natural product (Scheme 6). Treatment of **13** with NaH and MeI in THF at room temperature gave the methyl ether in excellent yield (>90%). Although there was no precedent for the direct electrophilic cyclization of MOM-protected alcohols (e.g., **18**) onto an alkene, it was investigated as it represented the most concise route to the desired pyran.[20] When MOM ether **18** was treated with either *N*-phenylselenophthalimide (NPSP) or *N*-bromosuccinimide (NBS), a facile cyclization took place. Whereas the reaction with NPSP was unselective, the reaction with NBS proceeded with high diastereoselectivity. From the NMR spectra of the products, however, it was not clear if the cyclizations had given the five- or six-membered ring products.

Because it was not possible to unambiguously distinguish between the different products in the above reaction, several derivatives of the cyclization products were prepared for NMR study as well as X-ray crystallographic analysis. Ultimately, successful structural assignment was possible with diol **21** (or, potentially, **22**), which was obtained by deprotection of bromide **20** (or **20a**). All of the protons in **21** were sufficiently separated so as to allow a detailed proton−proton decoupling study (Figure 3). Proton **a**, which appeared most downfield among such protons, was coupled to proton **b**, the only one in the group that can give a unique doublet. This coupling pattern can only

(17) Bloch, R.; Brillet, C. *Synlett* **1991**, 829.
(18) Williard, P. G.; Fryhle, G. B. *Tetrahedron Lett.* 1**980**, 3731.
(19) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835.
(20) (a) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (b) Bartlett, P. A. *Asymmetric Synthesis* 1984; Vol. 4, pp 411−454 and references therein.

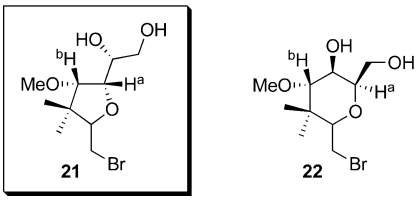
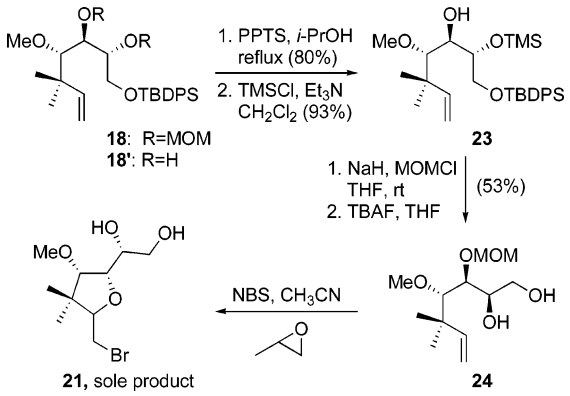


FIGURE 3. Determination of the structure of cyclization product by ^{1}H NMR decoupling pattern of the derivative of **21** or **22**.

SCHEME 7. Differentiation of the Two Hydroxyl Groups and Cyclization



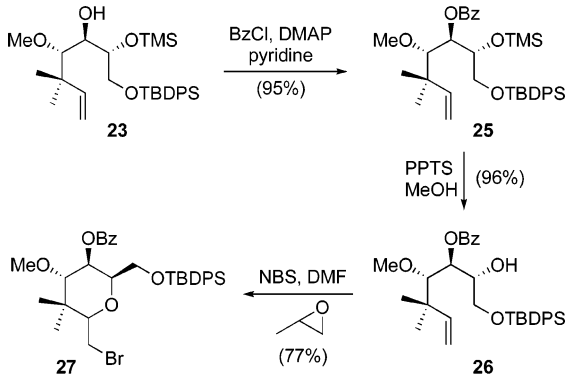
occur in the five-membered ring compound **21**. Indeed, no coupling would be expected between protons **a** and **b** in the six-membered ring compound **22**. The five-membered ring product was also produced upon electrophilic cyclization of **18′** (vide infra), the free diol that results from removal of the two MOM groups of **18**.

On the basis of the above results, it was clear that we would need to manipulate the protecting groups on the oxygens to differentiate them and thereby overcome the kinetic preference for five-membered ring formation. The two MOM groups of **18** were removed in refluxing *i*-PrOH with a catalytic amount of PPTS to give the corresponding diol (**18′**) in 80% yield (Scheme 7).[21] Treatment of diol **18′** with 1.2 equiv of TMSCl and an excess amount of triethylamine in CH_2Cl_2 promoted the selective, but slow, formation of the monoprotected silyl ether **23**. The reaction proceeded well with 2 equiv of TMSCl and yielded only the mono-silyl product in 93% yield. This result illustrates the significant differences that exist in the chemical and steric environments of these two hydroxyl groups. To prevent the formation of a five-membered compound by electrophilic cyclization, the free alcohol was protected with the MOM group using NaH followed by MOMCl. Subsequent removal of the TMS and TBDPS groups using TBAF gave diol **24** in 53% overall yield.

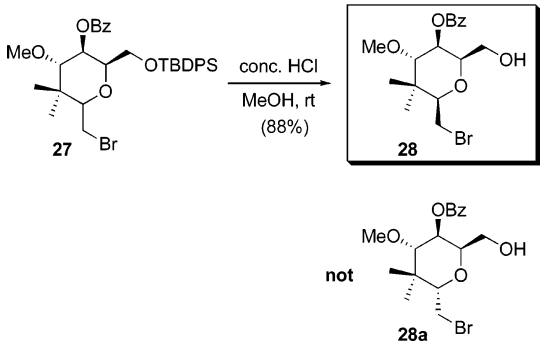
Surprisingly, the electrophilic cyclization of **24** with NBS again gave the five-membered diol **21** as the sole product (Scheme 7). These results highlight in an emphatic way the strong kinetic preference for the formation of the five-membered ring product. Despite the presence of a free hydroxyl group available for the formation of the six-membered ring, the MOM protected hydroxyl participated instead and produced the kinetically preferred five-membered ring product.

It was clear from the above results that the C-12 hydroxyl had to be blocked by a more effective protecting group. The benzoyl group was chosen as it was expected to resist the electrophilic cyclization conditions and, more importantly, to reduce the nucleophilic capability of the C-12 oxygen. Introduction of this group on **23** was found to be difficult under conventional conditions due to the greater steric hindrance of the C-12 hydroxyl group. Under forcing conditions, the major product resulted from a desilylative benzoylation of the C-11 alcohol. The desired benzoyl product (**25**) was eventually obtained in excellent yield when the reaction was carried out using pyridine as the solvent for the reaction. Selective removal of the TMS group using PPTS in MeOH gave alcohol **26**, which was expected to give only the six-membered ring product. Indeed, upon treatment of alcohol **26** with NBS, a smooth cyclization took place to form desired tetrahydropyran derivative **27** in 77% yield, as a single diastereomer (Scheme 8).

SCHEME 8. Electrophilic Cyclization of Benzoyl Alcohol 26 To Give Six-Membered Product 27



SCHEME 9. Establishment of Absolute Stereochemistry of Cyclization Product

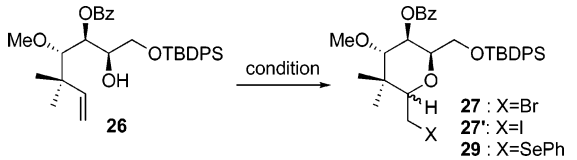


With the six-membered product in hand, the next issue was determination of the stereochemistry at the newly formed chiral center. The relative stereochemistry in pyran **27** could not be established unambiguously even after extensive NMR studies. Because a definitive answer was available by X-ray crystallographic analysis, several derivatives of **27** were prepared with the hope of getting one that was nicely crystalline. A suitable crystal was finally obtained from alcohol **28**, prepared by treatment of **27** with concentrated HCl in MeOH (Scheme 9). Unfortunately, the result of X-ray analysis[22a] of **28** indicated that the newly formed chiral center had the *R* configuration, epimeric to that found in the natural products. In other words,

(21) Monti, H.; Leandri, G.; Klos-Ringquet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.

(22) (a) The ORTEP diagram and X-ray crystallographic data of **28** are in the Supporting Information. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (c) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, III, R. *J. Org. Chem.* **1987**, *52*, 4191.

TABLE 2. Electrophilic Cyclization of 26 under Different Reagents and Conditions



reagent	solvent	temp	time (h)	yield	ratio[a]
NBS	DMF	rt	20	77%	α-H only
NIS	CH_2Cl_2	rt	4		1:2.3
$I(collidine)_2ClO_4$	CH_2Cl_2	rt	1	73%	1:2.8
I_2, prop. oxide	CH_2Cl_2	rt	1		1:4.2
$Hg(OAc)_2$; Br_2	THF	rt	12	71%	α-H only
NPSP, CSA	DMF	rt	4	87%	1.1:1
NPSP, CSA	DMF	80 °C	1	82%	1:1.1
NPSP, CSA	DMF	−20 °C to rt	8	66%	1:1.3
NPSP, CSA	DMF	rt	4	87%	1.1:1
NPSP, CSA	DMF	80 °C	1	82%	1:1.1
NPSP, CSA	**CH_2Cl_2**	**rt**	**8**	**78%**	**1.8:1**
NPSP, CSA	CH_2Cl_2	−78 °C	6	no rxn	
NPSP, CSA	$(ClCH_2)_2$	reflux	1		1.5:1
NPSP, CSA	CCl_4	rt	48	66%	1.6:1
PhSeBr	DMF	−30 °C	4		1:2.3
PhSeBr	CH_2Cl_2	rt	5		1:1

[a] β-H/α-H.

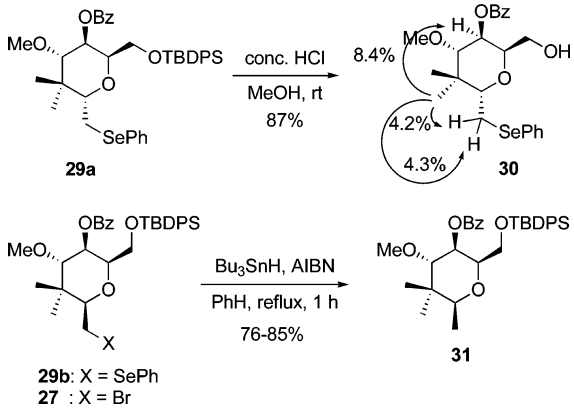
rather than the desired 2,6-*trans*-pyran, the product obtained was the 2,6-*cis*-pyran. This outcome was puzzling because our analysis of the problem, as well as literature precedent with simpler systems,[22b] had suggested that the major product would be the desired *trans*-pyran, **28a**.

Two different avenues were investigated to address the diastereoselectivity issue. One approach was to improve the desired diastereoselectivity by varying the reagents and the reaction conditions. The other was to control the available conformations for the transition state in the electrophilic cyclization by chemically modifying and restricting the flexibility of the cyclization precursors. To evaluate the first tactic, the cyclization of precursor **26** was carried out using a wide variety of reagents and conditions. Some of these results are summarized in Table 2.[20b,22]

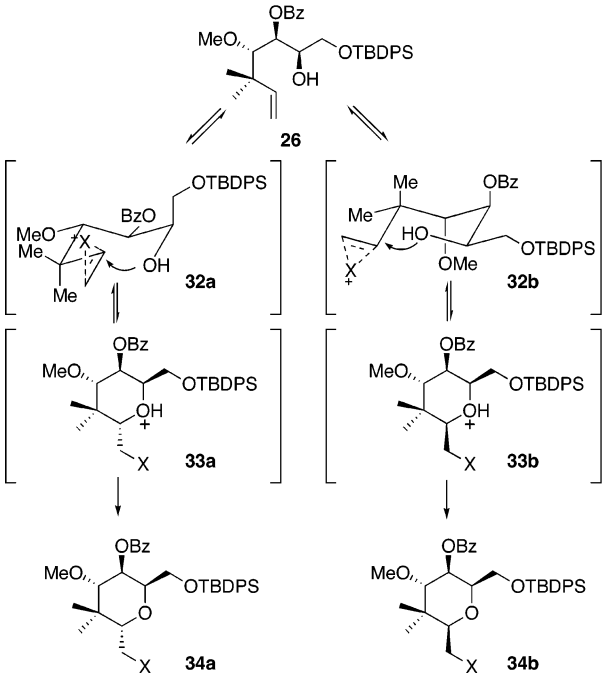
As can be seen from the results, NBS in DMF promoted the most selective cyclization, albeit to produce the undesired pyran derivative. Most of the other electrophiles afforded modest selectivity, producing more-or-less equal amounts of the two diastereomeric products. The reaction temperature did not affect diastereoselectivity significantly. The most promising result was with *N*-phenylselenophthalimide (NPSP), which gave the two diastereomers in approximately a 1:1 ratio in DMF. A study of solvent effects showed that the desired product predominated in less polar solvents. Under the best conditions found, using a combination of NPSP and CSA in CH_2Cl_2, the cyclization proceeded to afford the desired diastereomer in a 1.8/1 ratio.

The structures of the two cyclization products were assigned by correlation to **28**, whose structure was established through X-ray crystallography. The diastereomeric mixture of the NPSP cyclization products (X = PhSe, **29a** and **29b**) was separable by flash column chromatography. Treatment of **29a** with concentrated HCl in MeOH gave alcohol **30**, whose NMR spectrum had all oxygen-substituted protons nicely separated. NOE experiments convincingly showed that the cyclization had taken place to position the selenomethyl unit trans to the benzoyl group. A chemical correlation provided further support to the

SCHEME 10. Stereochemistry Determination of 29a and 29b



SCHEME 11. Mechanistic Pathway for Cyclization of 26

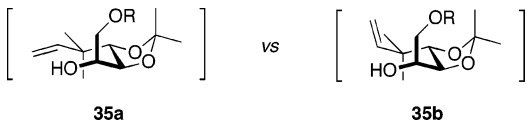


assigned structures. Reduction of **29b**, the minor diastereomer from NPSP cyclization, with Bu_3SnH gave pyran **31**,[23] identical to the product obtained from the reduction of bromide **27**. The relative stereochemistry of the latter had been established by X-ray crystallographic analysis, as described earlier (Scheme 10).

The differing stereochemical outcome of the NBS- and NPSP-mediated cyclizations is difficult to understand. The reaction outcome is expected to depend on the kinetic selectivity for the cyclic onium ion formation as well as equilibration between two possible onium ions (**32a**/**32b**) prior to cyclization.[22b] In the case of NBS cyclization, formation of the three-centered bromonium species is generally believed to be freely reversible,[24] so the observed diastereoselectivity may reflect the greater

(23) (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (b) Neumann, W. P. *Synthesis* **1987**, 665.

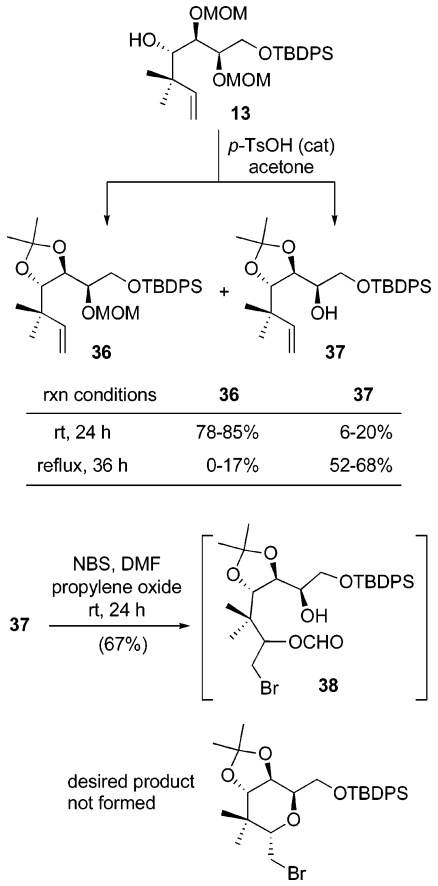
(24) (a) Brown, R. S.; Gedye, R.; Slebocka-Tilk, H.; Buschek, J. M.; Kopecky, K. R. *J. Am. Chem. Soc.* **1984**, *106*, 4515. (b) Slebocka-Tilk, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4504. (c) Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1985**, *107*, 2464. (d) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Am. Chem. Soc.* **1987**, *109*, 515.



35a 35b

FIGURE 4. Two possible transition states of **35** in electrophilic cyclization.

SCHEME 12. Synthesis and Attempted Cyclization of Acetonide 37

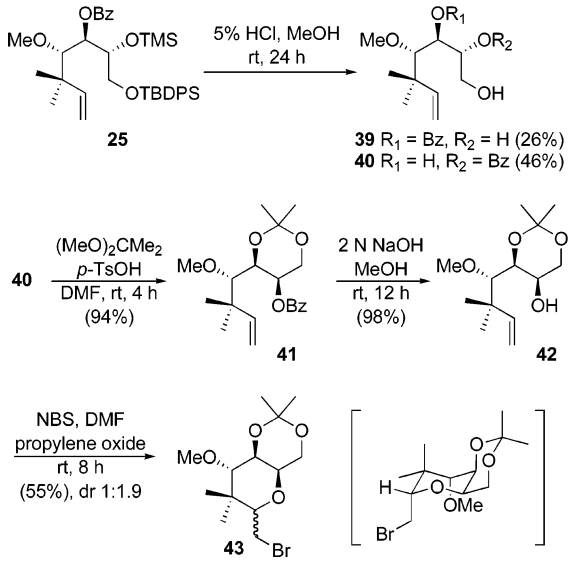


thermodynamic stability of the cyclized intermediate, tetrahydropyranonium ion **33b**. In other words, reversible formation of the two bromonium ions is followed by ring closure to give the more stable final product, **34b**. In the case of NPSP cyclization, the three-centered selenonium intermediate from the first step is expected to be relatively stable. The stereochemistry of the product is determined upon coordination of the olefin with the electrophile, which is then followed by the stereospecific ring closure step. The low diastereoselectivity for the NPSP-mediated cyclization reflects the modest kinetic selectivity expected for complexation of the electrophilic selenium species to the diastereomeric faces of the alkene (Scheme 11).

Control of Cyclization Diastereoselectivity. In addition to the investigation of reagents and the reaction conditions, numerous other means were explored to improve the cyclization diastereoselectivity, such as modification of the cyclization precursor. The general idea was to introduce an additional ring, the conformation of which would bias the conformation of the transition state leading to the key cyclization.

A promising modification involved the introduction of an acetonide ring from alcohol **13**. On the basis of conformational analysis of the expected transition state, depicted without the electrophile in Figure 4, the acetonide ring was expected to lock the system and allow cyclization by only one of the two possible transition states. Transition state **35a** would lead to the desired diastereomer, as it is expected to be of lower energy than **35b**, which should experience more 1,3-diaxial interactions during the ring closure.

SCHEME 13. Electrophilic Cyclization of Acetonide Alcohol 42

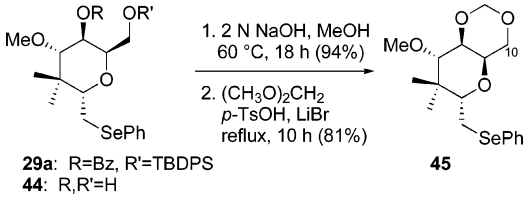


The required "locked" precursors were prepared from alcohol **13**, the prenylstannane addition product.[25] Upon treatment of **13** with *p*-TsOH in acetone, the alcohol was converted to acetonide **36** in good yield (Scheme 12). When the reaction was carried out under more vigorous conditions, the second MOM group was also removed, giving alcohol **37** as the major product. Numerous reagents and reaction conditions were examined for carrying out the electrophilic cyclization of **36** and **37**, but to no avail. In no case were cyclized products obtained. The only time an isolable, electrophile addition product was obtained was when **37** was treated with NBS and propylene oxide in DMF for 24 h at room temperature. These conditions produced in 67% yield a formate-containing product (tentatively assigned as **38**), presumably by addition of DMF to the expected bromonium ion followed by hydrolysis. These results show that the cyclization product, a *trans*-fused 5,6-bicyclic system, is evidently too strained to be formed under the reaction conditions used.

The *cis*-decalin structure present in the right part of mycalamides suggested an alternative synthetic design for closure of the pyran unit. The idea was to start with a six-membered acetonide from which to construct the second ring of the decalin. Assuming that the natural product represented the thermodynamically more stable diastereomer, then the expectation was that the cyclization step would favor formation of the desired *trans*-2,6-substituted pyran ring. The cyclization precursor for this approach was prepared in three steps from one of the earlier intermediates, **25**, as outlined in Scheme 13. One-step deprotection of both silyl groups in **25**, carried out in 5% methanolic HCl solution, gave the expected diol, **39**, along with diol **40**, in

(25) (a) Nishiyama, S.; Ikeda, Y.; Yoshida, S.; Yamamura, S. *Tetreahedron Lett.* **1989**, *30*, 105. (b) Angyal, S. J.; Beveridge, R. J. *Carbohydr. Res.* **1978**, *65*, 229. (c) Grieco, P. A.; Yokoyama, Y. Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178.

SCHEME 14. Construction of Dioxane Ring via Direct Methylene Ketal Formation

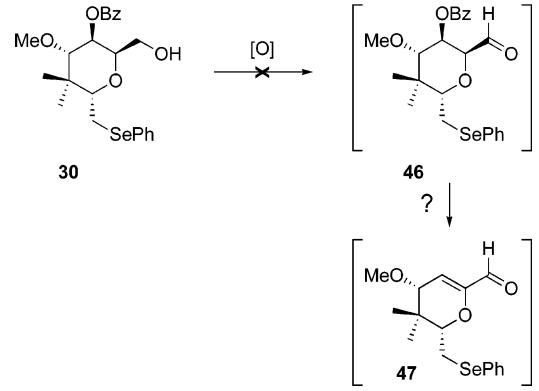


which the benzoyl group had migrated to a less congested location. Without optimization, the benzoyl migration product (**40**) was converted into an acetonide ketal (**41**), which upon basic hydrolysis gave alcohol **42** in high overall yield. Alcohol **42** was subjected to electrophilic cyclization conditions using NBS and gave the expected dioxa-decalin product **43** in 55% yield, favoring the undesired diastereomer by 1.9/1. If one assumes that the steric interactions in the products resemble those present in the transition states, then the observed diastereoselectivity may arise from the presence of more serious 1,3-diaxial interactions in the minor (desired) product, shown in brackets, as compared to the major one.

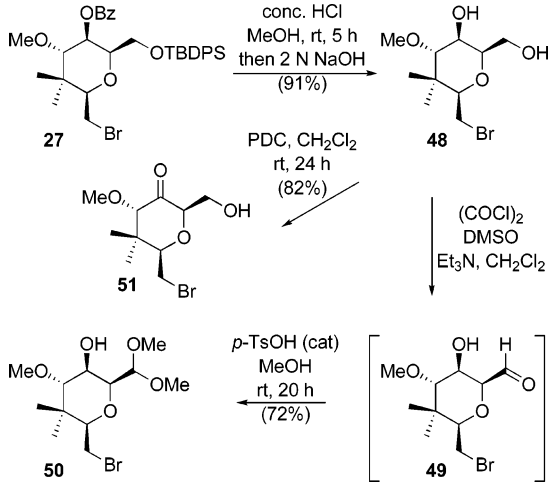
Trioxadecalin Ring Formation: A Functionalized B,C-Ring Skeleton. Given the difficulties encountered in trying to promote an electrophilic cyclization favoring the desired diastereomer, a decision was made to continue the synthetic sequence using the major diastereomer of the selenoetherification (**29a**) and work out the remaining steps to generate the trioxadecalin skeleton of mycalamine. Deprotection of both the benzoyl and the TBDPS groups was achieved in one step by treatment of **29a** with 2 N NaOH in MeOH at 60 °C, which afforded diol **44** in 94% yield. Formation of a simple dioxane ring C was examined at this point using the methodology developed by Gras and his colleagues.[26] A solution of diol **44** in dimethoxymethane was treated with a catalytic amount of LiBr and *p*-TsOH under reflux condition for 10 h to furnish the trioxadecalin system (**45**) in 81% yield (Scheme 14).

While technically a trioxadecalin skeleton, compound **45** lacks a functional group at the C-10 position, necessary for further transformation to an aminal, as required in the natural product. A precursor with the C-10 carbon at the aldehyde oxidation state would be ideal, as it would allow for introduction of both the acetal and the aminal functionalities. Thus, it was necessary to selectively oxidize the primary hydroxyl group of **44** (or a related compound) into an aldehyde without oxidation of the secondary hydroxyl group. This is a problem for which there are no good solutions. The few methods available for such selective oxidations[27] are further hampered in the case at hand by the presence of the easily oxidizable selenophenyl group.[28] Several different protocols were examined for the selective oxidation of the primary hydroxyl group in **44** and related compounds, but none were successful. The oxidation of benzoyl alcohol **30** was also examined, but the expected product (**46**)

SCHEME 15. Unsuccessful Selective Oxidation of Primary Alcohol to Aldehyde



SCHEME 16. Selective Oxidations



was unstable and led to what was tentatively assigned as the β-elimination product **47** (Scheme 15).[29]

Curiously, in contrast to the difficulties encountered above, selective oxidation of the primary alcohol over the secondary alcohol was possible for the undesired diol diastereomer obtained through NBS cyclization (Scheme 16). The benzoyl and TBDPS groups in **27** were removed in high yield through a one-pot procedure. The resulting diol (**48**), when subjected to standard Swern oxidation conditions, produced what was considered to be the desired hydroxyaldehyde **49**. The NMR spectrum of compound **49**, however, lacked the telltale aldehydes peak in 9−10 ppm region, and indicated that it existed as either the hydrate or, possibly, the dimer. Indeed, treatment of the oxidation product with a catalytic amount of *p*-TsOH in MeOH transformed it to the corresponding dimethoxy acetal (**50**), which was isolated in 72% yield. It should be noted that the selective oxidation of a secondary alcohol over a primary one is well precedented, especially with chromium oxidants. Thus, treatment of diol **48** with PDC in CH_2Cl_2 for 24 h at room temperature provided ketone **51** in 82% yield.

After successfully exploring various oxidants on the undesired pyran diastereomer, we directed our efforts to the selective

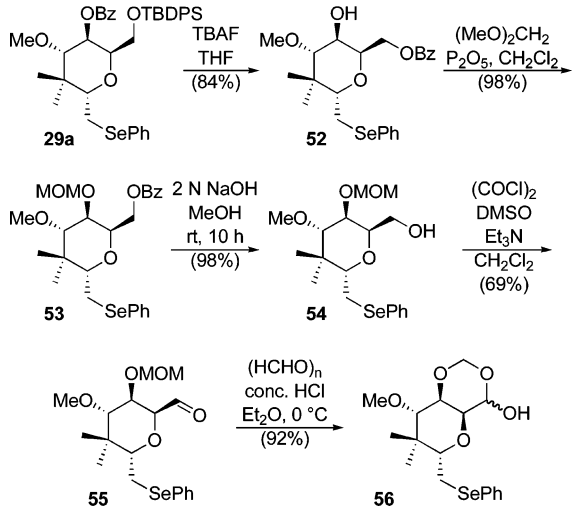
(26) Gras, J.-L.; Nouguier, R.; Mchich, M. *Tetradedron Lett.* **1987**, *28*, 6601.

(27) (a) Tidwell, T. T. *Org. React.* **1990**, *39*, 297. (b) Timioka, K.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605 and references therein.

(28) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: New York, 1986; Chapter 5.

(29) (a) Martin, O. R.; Szarek, W. A. *Carbohydr. Res.* **1984**, *130*, 195. (b) Halmos, T.; Filippi, J.; Bach, J.; Antonakis, K. *Carbohydr. Res.* **1982**, *99*, 180. (c) Cree, G. M.; Mackie, D. W.; Perlin, A. S. *Can. J. Chem.* **1969**, *47*, 511. (d) Graig, G. W.; Sternberg, E. D.; Jones, G. H.; Moffatt, J. G. *J. Org. Chem.* **1986**, *51*, 1258. (e) Vatele, J.-M. *Tertrahedron* **1986**, *42*, 4443.

SCHEME 17. Formation of Trioxadecalin 56, the B,C-Ring System of Mycalamides

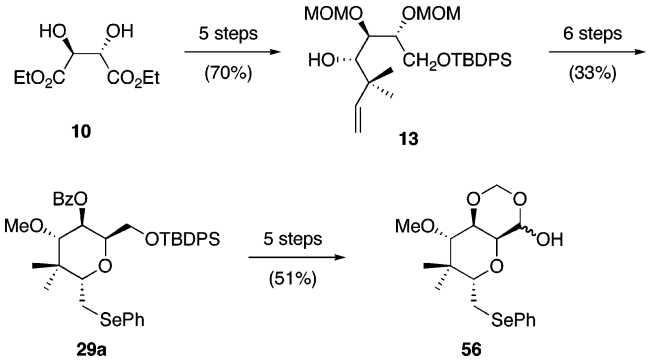


oxidation and further elaboration of the desired diastereomer of the selenocyclization product, **29a** (Scheme 17). Treatment of **29a** with TBAF in THF gave not the expected primary alcohol, but secondary alcohol **52** (84%), which arises from a 1,2-migration of the benzoyl group.[30] In all likelihood, this migration takes place intramolecularly, although this notion was not verified using crossover studies. This was one of several instances in which groups migrated away from the sterically demanding gem-dimethyl groups. The secondary hydroxyl group of **52** was protected as a MOM ether (**53**), and the benzoyl group was removed by saponification to give free alcohol **54** in nearly quantitative yield. The primary hydroxyl group was then oxidized under Swern conditions to afford aldehyde **55**. Finally, upon treatment of MOM-aldehyde **55** with paraformaldehyde and concentrated HCl, it was transformed into the desired trioxadecalin unit (**56**), isolated in 92% yield.[8a] The diastereomeric ratio of **56** was initially 2:1 and slowly became 1:1 upon standing in $CDCl_3$, an acidic environment. The transformation of the lactol hydroxyl into an amino group, which is necessary for coupling to the pederic acid part, has been already been demonstrated in an analogous compound in Kishi's mycalamide synthesis.[8a,b,10] The selenophenyl group obtained through the above sequence is expected to be useful for the introduction of various side chains necessary for the mycalamides and related compounds.

Conclusion

We have described the asymmetric synthesis of trioxadecalin unit **56**, an important intermediate for the synthesis of mycalamides and related natural compounds. The overall synthetic sequence, which required the formation of two heterocycles and the generation of five stereocenters, was executed in 16 steps in 12% overall yield from the C2-symmetric starting material, diethyl D-tartrate (Scheme 18). The strategy took advantage of diastereoselective reactions to extend the four-carbon chain of tartrate. Subsequent electrophile-mediated cyclization afforded

SCHEME 18. Overall Sequence for Synthesis of Trioxadecalin 56 from Diethyl D-Tartrate



the desired 2,6-*trans*-substituted pyran, which was then transformed into a functionalized trioxadecalin skeleton.[31]

Experimental Section

(4*S*,5*R*,6*R*)-5,6-Bis(methoxymethoxy)-3,3-dimethyl-7-[(1,1-dimethylethyl)diphenylsilyl]oxy-4-hydroxy-1-heptene (13). To a solution of aldehyde **12** (8.014 g, 17.94 mmol) and tri(*n*-butyl)-prenyl stannane (6.63 mL, 19.73 mmol) in CH_2Cl_2 (30 mL) was added $ZnBr_2$ (8.890 g, 39.48 mmol) at −78 °C. The resulting mixture was allowed to warm to 0 °C over 6 h, and stir further for 2 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ solution (80 mL) and brine (80 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (70 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude yellow oil was purified by flash column chromatography (EtOAc/hexane, 1:6) to afford hydroxyl alkene **13** (8.345 g, 90%, dr >50:1) as a colorless oil: $[\alpha]^{23}_D$ −20.8° (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.42−7.33 (m, 6H), 5.88 (dd, J = 10.5, 17.9 Hz, 1H), 5.01 (m, 1H), 4.98 (dd, J = 1.1, 4.3 Hz, 1H), 4.79 (d, J = 6.7 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 4.62 (dd, J = 6.6, 10.4 Hz, 2H), 3.91 (dd, J = 8.0, 11.9 Hz, 1H), 3.84 (m, 2H), 3.75 (dd, J = 1.7, 3.9 Hz, 1H), 3.50 (dd, J = 1.7, 8.0 Hz, 1H), 3.35 (s, 3H), 3.26 (s, 3H), 2.59 (d, J = 8.0 Hz, 1H), 1.05 (s, 9H), 1.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 135.6, 135.5, 133.4, 133.3, 129.65, 129.62, 127.63, 127.61, 112.3, 97.9, 97.0, 79.2, 75.5, 74.7, 63.8, 56.4, 55.8, 41.5, 26.8, 24.4, 22.2, 19.1; IR (neat) 3558, 1111, 1034 cm^{-1}; HRMS *m*/*e* calc'd for C $Zn_{26}H_{35}O_3Si$ ($M^+ - C_2H_2O_2$) 423.2355, found 423.2336.

(3*S*,4*R*,5*S*)-3,4-Dihydroxy-5-(1,1-dimethyl-2-propenyl)-2*H*-tetrahydrofuran-2-one (14). A solution of hydroxy alkene **13** (1.034 g, 2.001 mmol) in THF (10 mL) was treated with TBAF (1.0 M in THF, 4.00 mL, 4.00 mmol), and the reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with H_2O (20 mL) and extracted with ether (4 × 20 mL). The combined extract was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford the expected diol (0.557 g, 100%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, J = 18.0, 10.3 Hz, 1H), 5.06 (br s, 1H), 5.01 (dd, J = 5.7, 1.4 Hz, 1H), 4.713 (m, 4H), 3.80 (m, 4H), 3.61 (d, J = 9.2 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 2.75 (d, J = 9.4 Hz, 1H), 1.06 (s, 9H), 1.05 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.6, 112.4, 98.1, 96.5, 79.6, 76.0, 74.2, 61.0, 56.4, 55.7, 41.4, 24.5, 22.5; IR (neat) 3447, 1030 cm^{-1}; HRMS *m*/*e* calc'd for $C_{10}H_{18}O_3$ ($M^+ - C_3H_8O_3$) 186.1256,

(30) Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-h. *J. Am. Chem. Soc.* **1988**, *110*, 3929.

(31) This work was taken in large part from the doctoral dissertation of H. M. Zhong. See: Zhong, H. M. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1995.

found 186.1240. To a stirred mixture of above diol (278 mg, 0.999 mmol), NMO (352 mg, 3.00 mmol), and activated molecular sieves (0.5 g) in CH_2Cl_2 (10 mL) was added a catalytic amount of TPAP (8.0 mg, 0.023 mmol) in one portion at room temperature. The resulting deep blue solution was stirred at room temperature for 18 h. Upon consumption of the starting material, the reaction mixture was filtered through a pad of silica gel, which was then washed with CH_2Cl_2. The filtrate was concentrated in vacuo, and the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:5) to afford bis-MOM lactone (176 mg, 61%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.02 (dd, J = 17.6, 10.1 Hz, 1H), 5.11 (dd, J = 17.6, 1.2 Hz, 1H), 5.06 (dd, J = 10.1, 1.2 Hz, 1H), 4.97 (d, J = 6.7 Hz, 1H), 4.68 (m, 3H), 4.36 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.7, 143.1, 113.3, 96.4, 95.6, 86.6, 78.7, 74.8, 56.3, 55.9, 39.5, 24.6, 23.4; IR (neat) 1787, 1153, 1108 cm^{-1}; HRMS *m*/*e* calc'd for $C_{13}H_{22}O_6$ (M^+) 274.1416, found 274.1416. A stirred solution of the above bis-MOM lactone (235 mg, 0.816 mmol) in CH_2Cl_2 (8 mL) was treated with solid BBr_3·Me_2S (469 mg, 1.50 mmol) in one portion at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with Et_2O (3 × 15 mL). The combined Et_2O phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:2) to afford dihydroxy lactone **14** (102 mg, 69%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (dd, J = 17.7, 10.9 Hz, 1H), 5.18 (dd, J = 17.7, 1.0 Hz, 1H), 5.15 (dd, J = 10.9, 1.0 Hz, 1H), 4.52 (m, 1H), 4.38 (m, 2H), 4.29 (br s, 1H), 3.28 (br s, 1H), 1.24 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.8, 143.0, 114.5, 87.1, 75.2, 73.8, 39.8, 24.7, 23.9; IR (neat) 3430, 1770, 1046 cm^{-1}; HRMS *m*/*e* calc'd for $C_9H_{14}O_4$ (M^+) 186.0892, found 186.0899.

Synthesis of Selenotetrahydrofuran 19. A stirred solution of bis-MOM alkene **18** (1.610 g, 3.033 mmol) in CH_2Cl_2 (2 mL) was treated with NPSP (1.813 g, 5.999 mmol) and CSA (0.139 g, 0.598 mmol) at room temperature, and the reaction was monitored by TLC. Upon consumption of the starting material, the solvent was removed under reduced pressure. The resulting yellow solid was purified by flash column chromatography (EtOAc/hexane, 1:6) to afford the desired product **19** (1.632 g, 85%) as a 1.12:1 mixture of diastereomers: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.47 (m, 2H), 7.39 (m, 6H), 7.21 (m, 3H), 4.80 (m, 2H), 4.10 (dd, J = 8.7, 4.1 Hz, 0.45H), 4.32 (dd, J = 8.1, 4.7 Hz, 0.55H), 3.95−3.67 (m, 4H), 3.41 (s, 1.35H), 3.38 (s, 1.65H), 3.18 (m, 1H), 3.14 (s, 1.35H), 3.13 (s, 1.65H), 3.01−2.89 (m, 2H), 1.06 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.8, 135.7, 133.5, 133.2, 132.3, 132.2, 131.3, 131.2, 129.7, 129.6, 129.0, 128.9, 127.7, 127.60, 126.59, 126.5, 96.4, 96.0, 90.5, 90.1, 86.2, 83.0, 80.1, 79.6, 77.3, 64.1, 64.0, 60.4, 60.2, 55.7, 55.6, 47.3, 46.7, 31.3, 27.8, 27.7, 26.8, 20.2, 19.2, 19.1, 17.8; IR (neat) 1105, 1030 cm^{-1}; HRMS *m*/*e* calc'd for $C_{34}H_{46}O_5SeSi$ (M^+) 642.2279, found 642.2282.

Synthesis of Bromotetrahydrofuran 20. To a stirred solution of bis-MOM alkene **18** (151 mg, 0.284 mmol) and propylene oxide (0.5 mL) in CH_2Cl_2 (3 mL) was added NBS (0.054 g, 0.30 mmol) at room temperature. The resulting mixture was stirred at room temperature in the dark for 8 h. Upon consumption of the starting material, the solvent was removed under reduced pressure, and the crude yellow oil was purified by flash column chromatography (EtOAc/hexane, 1:6) to afford the desired bromide **20** (130 mg, 86%, diastereomeric ratio >8:1) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.40 (m, 6H), 4.78 (dd, J = 9.2, 6.8 Hz, 2H), 4.42 (dd, J = 8.6, 4.0 Hz, 1H), 4.00 (dd, J = 7.2, 5.4 Hz, 1H), 3.92 (m, 1H), 3.85 (m, 1H), 3.66 (d, J = 4.3 Hz, 1H), 3.41 (s, 3H), 3.36 (m, 2H), 3.19 (m, 1H), 3.16 (s, 3H), 1.13 (s, 3H), 1.06 (s, 9H), 0.92 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.7, 135.6, 133.5, 133.1, 129. 7, 129.6, 127.7, 127.6, 95.9, 90.8, 83.8, 79.7, 76.4, 63.9, 60.3, 55.5, 47.4, 31.1, 26.8, 19.9, 19.5, 19.2; IR (neat) 1112, 1039 cm^{-1}; HRMS *m*/*e* calc'd for $C_{28}H_{41}O_5Br$ (M^+) 536.2138, found 536.2186.

(4*S*,5*S*,6*R*)-5-Benzoyloxy-3,3-dimethyl-7-[(1,1-dimethylethyl)-diphenylsilyl]oxy-4-methoxy-6-(trimethylsilyl)oxy-1-heptene (25). To a stirred solution of BzCl (0.618 g, 4.40 mmol) and a catalytic amount of DMAP (30 mg) in pyridine (5 mL) was added a solution of alcohol **23** (1.131 g, 2.197 mmol) in pyridine (5 mL) dropwise at room temperature. The resulting mixture was stirred at room temperature for 6 h, diluted with diethyl ether (30 mL), and quenched with H_2O (30 mL). The separated aqueous layer was extracted with ether (3 × 30 mL). The ether extracts were combined, washed with saturated $CuSO_4$ solution (30 mL), H_2O (2 × 20 mL), brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (EtOAc/hexane, 1:20) to afford ester **25** (1.299 g, 95%) as a colorless viscous oil: $[\alpha]^{23}_D$ −5.5° (*c* 1.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.68 (m, 2H), 7.59 (m, 3H), 7.44 (m, 5H), 7.19 (m, 3H), 5.19 (dd, J = 17.7, 10.8 Hz, 1H), 5.40 (dd, J = 5.5, 10.8 Hz, 1H), 4.91 (m, 2H), 3.97 (dd, J = 11.0, 5.2 Hz, 1H), 3.76 (dd, J = 10.5, 5.2 Hz, 1H), 3.36 (s, 3H), 3.27 (d, J = 3.4 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 12H), 0.06 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 145.09, 135.6, 135.5, 133.4, 133.1, 132.5, 130.7, 129.9, 129.7, 129.6, 129.5, 128.3, 128.2, 127.6, 127.5, 111.8, 84.9, 73.3, 72.5, 65.4, 61.5, 42.0, 26.7, 24.4, 23.3, 19.0, 0.26; IR (neat) 1725, 1112, 1027 cm^{-1}; HRMS *m*/*e* calc'd for $C_{36}H_{51}O_5Si_2$ (MH^+) 619.3274, found 619.3267.

(4*S*,5*S*,6*R*)-5-Benzoyloxy-3,3-dimethyl-7-[(1,1-dimethylethyl)-diphenylsilyl]oxy-6-hydroxy-4-methoxy-1-heptene (26). To a stirred solution of benzoyl alkene **25** (1.088 g, 1.757 mmol) in MeOH (10 mL) was added PPTS (44 mg, 0.18 mmol) at room temperature, and the mixture was stirred at room temperature for 8 h. Upon consumption of the starting material, the reaction was quenched with saturated $NaHCO_3$ solution until gas evolution ceased. The reaction mixture was extracted with ether (3 × 30 mL), and the combined ether extracts were washed with brine (40 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:10) to afford alcohol **26** (0.784 g, 78.5%) as a colorless viscous oil: $[\alpha]^{23}_D$ −14.3° (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.66−7.59 (m, 4H), 7.54 (tt, J = 1.3, 7.4 Hz, 1H), 7.43−7.33 (m, 6H), 7.31−7.27 (m, 2H), 5.94 (dd, J = 10.8, 17.6 Hz, 1H), 5.50 (t, J = 4.2 Hz, 1H), 4.93 (dd, J = 1.2, 17.6 Hz, 1H), 4.85 (dd, J = 1.2, 10.8 Hz, 1H), 3.95 (m, 1H), 3.68 (d, J = 5.5 Hz, 2H), 3.41 (s, 3H), 3.19 (d, J = 4.1 Hz, 1H), 2.58 (br s, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 144.9, 135.6, 135.5, 133.0, 132.82, 132.78, 130.3, 129.9, 129.8, 128.2, 127.74, 127.69, 111.7, 86.9, 72.34, 72.29, 64.6, 61.9, 41.9, 26.8, 24.5, 23.3, 19.1; IR (neat) 3494, 1724 cm^{-1}; HRMS *m*/*e* calc'd for $C_{29}H_{33}O_5Si$ (M^+-C_4H_9) 489.2097, found 489.2101.

(2*R*,3*R*,4*S*,6*R*)-6-(Bromomethyl)-2-((*tert*-butyldiphenylsilyloxy)-methyl)-4-methoxy-5,5-dimethyltetrahydro-2*H*-pyran-3-yl Benzoate (27). A stirred solution of hydroxy alkene **26** (0.594 g, 1.04 mmol) and propylene epoxide (1 mL) in DMF (5 mL) was treated with solid NBS (0.374 g, 2.10 mmol) at room temperature. The flask was shielded from light, and stirring was continued for 20 h. Upon consumption of the starting material, the reaction mixture was diluted with ether (50 mL) and washed with H_2O (3 × 20 mL). The ether layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/hexane, 1:10) to afford, as the major product, bromide **27** (0.518 g, 77%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.70−7.07 (m, 13H), 5.26 (t, J = 2.4 Hz, 1H), 4.13 (m, 1H), 3.89 (m, 1H), 3.80 (m, 1H), 3.57 (s, 3H), 3.48 (dd, J = 10.8, 1.8 Hz, 1H), 3.32 (d, J = 10.1 Hz, 1H), 3.13 (d, J = 2.8 Hz, 1H), 1.04−0.97 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 135.6, 135.5, 133.2, 133.1, 130.0, 129.7, 128.5, 127.7, 127.5, 83.4, 81.2, 75.1, 67.8, 61.9, 59.0, 38.0, 32.2, 26.8, 26.7, 23.3,

19.29, 14.1; IR (neat) 1721, 1097, 1026 cm^{-1}; HRMS *m*/*e* calc'd for $C_{29}H_{32}BrO_5Si$ (M^+-C_4H_9) 569.1186, found 569.1184.

(2*S*,4*S*,5*S*,6*R*)-5-Benzoyloxy-3,3-dimethyl-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl-4-methoxy-2-(phenylselenyl)-methyl-2*H*-tetrahydropyran (29a) and (2*R*,4*S*,5*S*,6*R*)-5-Benzoyloxy-3,3-dimethyl-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl-4-methoxy-2-(phenylselenyl)methyl-2*H*-tetrahydropyran (29b). A stirred solution of hydroxy alkene **26** (0.150 g, 0.263 mmol) in CH_2Cl_2 (3 mL) was treated with solid NPSP (0.119 g, 0.394 mmol) and a catalytic amount of CSA (0.005 g, 0.02 mmol) at room temperature for 8 h. Upon consumption of the starting material, the reaction solution was concentrated in vacuo, and the crude yellow solid was purified by flash column chromatography (EtOAc/hexane, 1:30) to afford the desired separable diastereomer mixtures **29a** and **29b** (0.148 g, 78%, dr 1.8:1). **29a**: $[\alpha]^{23}_D$ +42.0° (*c* 1.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.65 (m, 6H), 7.49 (m, 2H), 7.42 (m, 2H), 7.23 (m, 8H), 5.34 (d, J = 6.6, 4.8 Hz 1H), 4.27 (dd, J = 10.1, 5.2 Hz, 1H), 4.04 (d, J = 10.9 Hz, 1H), 3.89 (m, 2H), 3.57 (s, 3H), 3.49 (d, J = 6.2 Hz, 1H), 3.01 (dd, J = 12.0, 3.1 Hz, 1H), 1.11 (s, 3H), 1.03, (s, 9H), 1.00 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 135.6, 133.0, 132.8, 132.7, 132.3, 130.0, 129.7, 129.62, 129.56, 128.9, 128.4, 127.62, 127.57, 126.5, 83.1, 79.9, 62.9, 60.7, 39.9, 28.4, 26.7, 22.6, 19.0; IR (neat) 1722, 1025 cm^{-1}; HRMS *m*/*e* calc'd for $C_{39}H_{46}O_4SeSi$ (M^+) 702.2279, found 702.2260. **29b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.63 (m, 3H), 7.43 (m, 9H), 7.25 (m, 4H), 7.09 (m, 2H), 5.27 (t, J = 2.4 Hz, 1H), 4.09 (m, 1H), 3.80 (m, 3H), 3.56 (s, 3H), 3.15 (d, J = 2.4 Hz, 1H), 3.06 (dd, J = 12.0, 10.5 Hz, 1H), 2.91 (dd, J = 12.0, 2.4 Hz, 1H), 1.00 (s, 3H), 0.97 (s, 9H), 0.93 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 135.5, 135.4, 133.2, 133.1, 133.0, 132.7, 131.2, 130.1, 129.7, 129.6, 129.5, 128.9, 128.4, 127.6, 127.5, 126.6, 83.4, 80.6, 75.1, 67.8, 61.7, 58.9, 37.9, 28.5, 26.7, 23.2, 19.3, 19.0; IR (neat) 1720, 1025 cm^{-1}; HRMS *m*/*e* calc'd for $C_{39}H_{46}O_4SeSi$ (M^+) 702.2279, found 702.2321.

(2*R*,4*S*,5*S*,6*R*)-5-Benzoyloxy-2,3,3-trimethyl-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl-4-methoxy-2*H*-tetrahydropyran (31). From **27**: To a solution of bromide **27** (43 mg, 0.066 mmol) in PhH (5 mL) were added Bu_3SnH (29 mg, 0.10 mmol) and a catalytic amount of AIBN (5 mg), and the mixture was heated to reflux for 1 h. After cooling to room temperature, the solution was concentrated in vacuo, and the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:10) to afford the desired reduced product **31** (28 mg, 76%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.64 (m, 3H), 7.44 (m, 3H), 7.34 (m, 4H), 7.07 (m, 3H), 5.29 (dd, J = 2.5, 2.4 Hz, 1H), 4.10 (m, 1H), 3.78 (d, J = 7.4 Hz, 2H), 3.67 (m, 1H), 3.58 (s, 3H), 3.16 (d, J = 2.7 Hz, 1H), 0.95 (m, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 135.5, 135.4, 133.3, 132.94, 132.87, 130.2, 129.7, 129.4, 128.4, 128.3, 127.6, 127.4, 83.3, 75.7, 74.6, 67.9, 62.0, 58.9, 37.0, 26.7, 26.6, 23.2, 19.05, 19.02, 14.7; IR (neat) 1716, 1113 cm^{-1}; HRMS *m*/*e* calc'd for $C_{32}H_{39}O_5Si$ ($M^+ - CH_3$) 531.2567, found 531.2589.

From 29b: To a solution of phenylselenide **29b** (32 mg, 0.044 mmol) in PhH (5 mL) were added Bu_3SnH (29 mg, 0.10 mmol) and a catalytic amount of AIBN (5 mg), and the mixture was heated to reflux for 1 h. After cooling to room temperature, the reaction solution was concentrated in vacuo, and the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:10) to afford the desired reduced product **31** (22 mg, 85%) as a colorless oil. The NMR spectrum of the product of this reaction was identical to compound **31** obtained from the reduction of **27**.

(2*R*,3*R*,4*S*,6*R*)-6-(Bromomethyl)-2-(hydroxymethyl)-4-methoxy-5,5-dimethyltetrahydro-2*H*-pyran-3-ol (48). To the solution of **27** (0.9735 g, 1.5 mmol) in MeOH (10 mL) was added concentrated HCl (1 mL) dropwise, and the reaction mixture was stirred for 5 h at room temperature. To the mixture was added 2 N NaOH solution dropwise until the solution became basic. Upon the completion of the reaction, the mixture was extracted with Et_2O (30 mL × 3). The combined organic layer was washed with H_2O (30 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (hexane/EtOAc = 1/1) to give diol **48** (0.3865 g, 91%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.96 (m, 2H), 3.87 (m, 1H), 3.75 (m, 2H), 3.50 (dd, J = 10.4, 1.9 Hz, 1H), 3.39 (s, 3H), 3.36 (d, J = 10.4 Hz, 1H), 3.16 (d, J = 4.0 Hz, 1H), 2.86 (d, J = 3.0 Hz, 1H), 1.08 (s, 3H), 0.99 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 86.5, 81.8, 75.1, 69.5, 64.3, 59.3, 37.8, 32.6, 23.6, 19.7; IR (neat) 1236, 1012; HRMS *m*/*e* calc'd for $C_{10}H_{19}BrO_4$ (MH^+) 282.0467, found 282.0463.

(2*S*,3*R*,4*S*,6*R*)-6-(Bromomethyl)-2-(dimethoxymethyl)-4-methoxy-5,5-dimethyltetrahydro-2*H*-pyran-3-ol (50). To a stirred solution of $(COCl)_2$ (0.1269 g, 1.0 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.1563 g, 2.0 mmol) in CH_2Cl_2 (2 mL) dropwise at −78 °C. After the mixture was stirred for 15 min, a solution of **48** (0.1182 g, 0.47 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the resulting mixture was stirred for 15 min at −78 °C. Et_3N (0.4047 g, 4.0 mmol) was added, and the mixture was allowed to warm to room temperature over 1 h. After addition of H_2O (10 mL), the mixture was extracted with Et_2O (20 mL × 3), and the combined ether extracts were washed with H_2O (20 mL), brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (hexane/EtOAc = 3/1) to give **50** (0.1139 g, 74%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.61 (d, J = 4.5 Hz, 1H), 3.93 (m, 1H), 3.74 (m, 1H), 3.52 (s, 3H), 3.48 (s, 3H) 3.47 (m, 1H), 3.39 (m, 1H), 3.38 (s, 3H), 3.07 (d, J = 3.6 Hz, 1H), 2.88 (d, J = 3.0 Hz, 1H), 1.09 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 104.5, 86.2, 82.2, 75.7, 66.9, 59.2, 56.1, 54.6, 37.8, 32.5, 23.6, 19.6.

(2*S*,4*S*,5*S*,6*S*)-3,3-Dimethyl-6-carbaldehyde-4-methoxy-5-methoxymethoxy-2-(phenylselenyl)methyl-2*H*-tetrahydrapyran (55). To a solution of $(COCl)_2$ (0.165 g, 1.30 mmol) in CH_2Cl_2 (2 mL) was added a solution of DMSO (0.203 g, 2.60 mmol) in CH_2Cl_2 (0.5 mL) dropwise at −78 °C. After 5 min, a solution of MOM alcohol **54** (0.260 g, 0.645 mmol) in CH_2Cl_2 (2 mL) was added dropwise followed by addition of Et_3N (0.162 g, 1.60 mmol). The resulting cloudy solution was warmed to room temperature and stirred for 45 min. The reaction was quenched by addition of H_2O (30 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined ether phase was washed with H_2O (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude yellow oil was purified by flash column chromatography (EtOAc/hexane, 1:6) to afford aldehyde **55** (0.188 g, 73%) as a pale yellow oil: $[\alpha]^{23}_D$ +128.8° (*c* 1.39, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.45 (m, 2H), 7.24 (m, 3H), 4.77 (dd, J = 16.2, 6.7 Hz, 2H), 4.46 (d J = 6.4 Hz, 1H), 4.00 (dd, J = 8.8, 6.4 Hz, 1H), 3.79 (dd, J = 10.4, 2.7 Hz, 1H), 3.49 (s, 3H), 3.12 (m, 1H), 2.96 (dd, J = 12.2, 2.7 Hz, 1H), 2.84 (d, J = 8.8 Hz, 1H), 0.96 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 201.7, 133.1, 130.7, 127.0, 97.7, 85.7, 80.3, 78.0, 75.6, 61.6, 56.0, 41.2, 28.0, 23.8, 15.2; IR (neat) 1734, 1109 cm^{-1}; HRMS *m*/*e* calc'd for $C_{18}H_{26}O_5Se$ (M^+) 402.0945, found 402.0974.

(4*RS*,4a*S*,6*S*,8*S*,8a*R*)-Hexahydro-8-methoxy-7,7-dimethyl-6-[(phenylselenyl)methyl]pyrano[3,2-*d*]-*m*-dioxin-4-ol (56). A stirred mixture of MOM aldehyde **55** (103 mg, 0.257 mmol) and paraformaldehyde powder (50 mg, excess) in Et_2O (0.5 mL) was cooled to 0 °C and treated dropwise with concentrated HCl (2 mL). The resulting mixture was stirred at 0 °C for 30 min, and then diluted with ether (20 mL). The reaction was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with ether (3 × 15 mL). The combined ether phase was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford **56** (90 mg, 92%) as a colorless oil. The initially formed 2:1 ratio of diastereomers changed

to 1:1 after several hours in $CDCl_3$ solution: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.24 (m, 3H), 5.22 (d, J = 6.0 Hz, 0.5H), 5.11 (d, J = 6.0 Hz, 0.5H), 5.05 (d, J = 1.8 Hz, 0.5H), 4.90 (br d, J = 6.3 Hz, 0.5H), 4.81 (d, J = 6.0 Hz, 0.5H), 4.73 (d, J = 6.0 Hz, 0.5H), 3.95 (dd, J = 3.1, 2.2 Hz, 0.5 Hz), 3.75 (m, 2.5H), 3.58 (m, 1H), 3.40 (s, 3H), 3.07 (d, J = 3.3 Hz, 0.5H), 3.01 (m, 1H), 2.91 (d, J = 5.4 Hz, 0.5H), 1.24 (s, 1.5H), 1.23 (s, 1.5H), 0.98 (s, 1.5H), 0.96 (s, 1.5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.9, 132.7, 130.6, 130.0, 129.0, 128.9, 126.8, 126.6, 93.8, 92.0, 89.9, 84.9, 83.3, 83.2, 80.7, 79.9, 72.3, 69.1, 62.8, 62.0, 59.50, 59.48, 37.71, 37.69, 28.1, 28.0, 27.2, 27.1, 22.3, 22.0; IR (neat) 3418, 1093, 1036 cm^{-1}; HRMS *m*/*e* calc'd for $C_{17}H_{24}O_5Se$ (M^+) 388.0788, found 388.0797.

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Supporting Information Available: Detailed experimental procedures, ORTEP diagram and X-ray crystallographic data of **28**, and copies of the ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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