Diastereoselective 6-*exo* Radical Cyclizations of Oxime Ethers: Total Synthesis of 7-Deoxypancratistatin

Gary E. Keck,* Stanton F. McHardy, and Jerry A. Murry

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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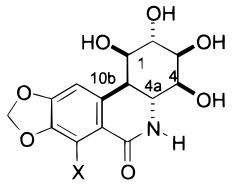
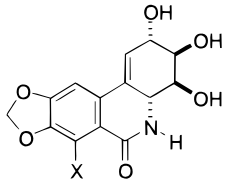
The development of an approach leading to the total synthesis of 7-deoxypancratistatin is described. The key features of the approach include a 6-*exo* radical cyclization reaction between a benzylic radical and an *O*-benzyloxime ether to establish the $C_{4a}-C_{10b}$ bond. The stereochemistry of this reaction was examined in both acyclic radical precursors and ones in which the aryl moiety was tethered to the C_1 oxygen substituent. It was found that the use of such a tether was essential to obtain the stereochemical result required for the synthesis. The correct absolute and relative configurations at the hydroxylated carbons C_1-C_4 were obtained using D-gulonolactone as the source of $C_{10b}-C_{4a}$.

Introduction

The use of *Amaryllidaceous* plant extracts for medicinal purposes dates back to at least the fourth century;[1] in recent times a large number of alkaloids which possess a wide spectrum of biological activities have been isolated from these species. Pancratistatin (**1**), isolated by Pettit and co-workers,[2] displays promising antineoplastic and antiviral activity. The 7-deoxy compound (**2**), isolated by Ghosal and co-workers,[3] has been shown in in vitro antiviral assays to exhibit a better therapeutic index than **1** due to decreased toxicity.[4] The biologically active alkaloids narciclasine (**3**) and lycoricidine (**4**) are also isolated from this plant species.[5] The unique structural characteristics and promising biological activities of this group of alkaloids have made them attractive synthetic targets.



1 X = OH Pancratistatin
2 X = H 7-Deoxypancratistatin



3 X = OH Narciclasine
4 X = H Lycoricidine

A considerable body of work directed toward the synthetic reconstruction of these materials has been reported. The first total synthesis of pancratistatin (as the racemate) was reported by Danishefsky and Lee in 1989.[6] More recently, Hudlicky and co-workers reported[7] an asymmetric synthesis of **1** which relied on an S_N2 opening of a vinyl aziridine with an aryl cyanocuprate reagent and have applied their approach to the synthesis of **2** as well. Shortly after that, we[8] reported an asymmetric synthesis of **2** utilizing a diastereoselective 6-*exo* radical cycliation to an oxime ether to construct the highly functionalized cyclohexane nucleus found in **1**,[9] **2**, and related substances. Later that year, Trost reported the synthesis of **1** based on a palladium-catalyzed desymmetrization,[10] and Magnus has also recently reported a total synthesis of **1**.[11] Sometimes overlooked is a synthesis of **2** by Paulsen and co-workers, who synthesized 7-deoxypancratistatin en route to lycoricidine, prior to the isolation of **2** from natural sources.[12] Described herein is an account of our studies on diastereoselective 6-*exo* radical cyclizations to oxime ethers,[8,13] which has led to the total synthesis of **2**.

(1) Hartwell, J. L. *Lloydia* **1967**, *30*, 379.
(2) (a) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018. (b) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693.
(3) Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.
(4) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kefauver, D. F.; Pettit, G. R.; Groszek, G.; Hollingshead, M.; Kirsi, J. J.; Shannon, W. M.; Schubert, E. M.; Dare, J.; Ugarkar, B.; Ussery, M. A.; Phelan, M. J. *J. Nat. Prod.* **1992**, *55*, 1569.
(5) For total syntheses of (and leading references to) lycoricidine, see: (a) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108. (b) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823. (c) Martin, S. F.; Tso, H. *Heterocycles* **1993**, *35*, 85. (d) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525.
(6) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.
(7) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.
(8) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289.
(9) For previous synthetic studies on **1** and **2**, see: (a) Rigby, J. H.; Gupta, V. *Synlett* **1995**, 547. (b) Park, T. K.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 195. (c) Doyle, T. J.; VanDerveer, D.; Haseltine, J. *Tetrahedron Lett.* **1995**, *36*, 6197. (d) Doyle, T. J.; Hendrix, M.; Haseltine, J. *Tetrahedron Lett.* **1994**, *35*, 8295. (e) Lopes, R. S. C.; Lopes, C. C.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 6775. (f) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1993**, *34*, 4751. (g) Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6076.
(10) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
(11) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341.
(12) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535.
(13) For previous work on both inter- and intramolecular free radical additions to oxime ethers, see: (a) Chiara, J. L.; Marco-Contelles, J.; Khair, N.; Gallego, P.; Destabel, C.; Bernabe, M. *J. Org. Chem.* **1995**, *60*, 6010. (b) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron Lett.* **1995**, *36*, 253. (c) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205. (d) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B.; *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499. (e) Parker, K.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3927. (f) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559. (g) Pattenden, G.; Schulz, D. J. *Tetrahedron Lett.* **1993**, *34*, 6787. (h) Hatem, J.; Henriet-Bernard, C.; Grimaldi, J.; Maurin, R. *Tetrahedron Lett.* **1992**, *33*, 1057. (i) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625. (j) Marco-Contelles, J.; Ruiz, P.; Sanchez, B.; Jimeno, M. L. *Tetrahedron Lett.* **1992**, *33*, 5261. (k) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688. (l) Marco-Contelles, J.; Martinez, L.; Martinez-Grau, A.; Pozuelo, C.; Jimeno, M. L. *Tetrahedron Lett.* **1991**, *32*, 6437. (m) Booth, S. E.; Jenkins, P. R.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1248. (n) Marco-Contelles, J.; Martinez, L.; Martinez-Grau, A. *Tetrahedron: Asymmetry* **1991**, *2*, 961. (o) Enholm, E. J.; Burnoff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727. (p) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. (q) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (r) Hart, D. J.; Seely, F. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (s) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.

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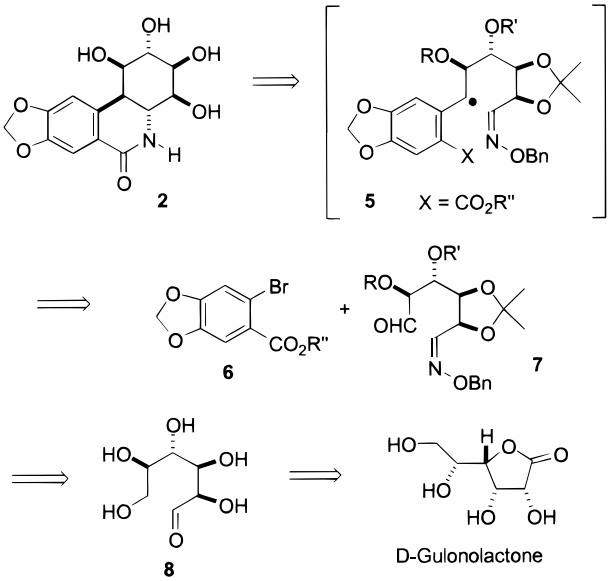
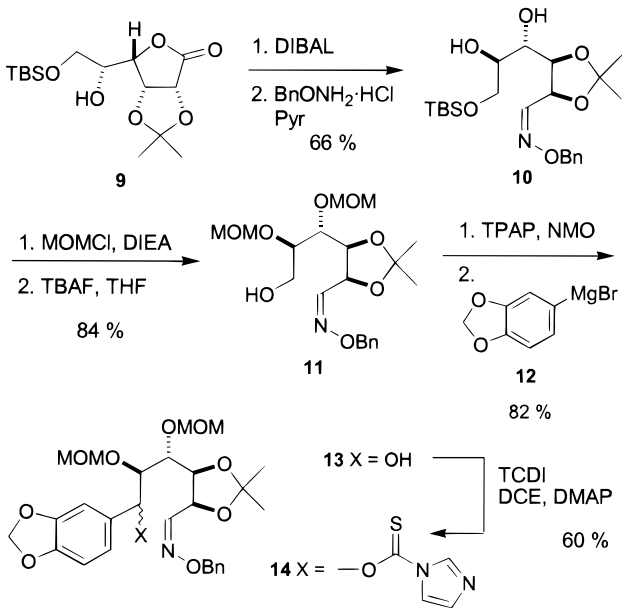
Retrosynthetic Analysis

Our retrosynthetic analysis of 7-deoxypancratistatin is outlined below. The critical aspect of interest to us was the viability and stereochemistry of an approach which relied upon a very late construction of the desired *trans* phenanthridone ring nucleus via a 6-*exo* cyclization of a radical intermediate of type **5**. The radical intermediate **5** would ultimately be generated from some derivative of the corresponding benzylic alcohol, which was envisioned to arise from the coupling of an aryl bromide **6** and the oxime−aldehyde **7**. A functionalized aryl bromide such as **6** should be readily prepared from piperonal. The oxime−aldehyde **7**, which possesses the desired absolute configurations for the oxygen substituents at C_1−C_4, should be accessible from a hydroxy−aldehyde of type **8**. The structure of hydroxy−aldehyde **8**, in turn, suggests a carbohydrate approach to this subunit. We chose to approach this material from commercially available D-gulonolactone. Although the choices of protecting groups for the C_1 and C_2 hydroxyls (pancratistatin numbering) are in principle not critical, use of the acetonide moiety for the C_3 and C_4 hydroxyls was an integral part of the strategy, since the appendages involved in the radical cyclization would be held *cis* to one another on the 1,3-dioxolane using this approach. This would clearly be more favorable for the cyclization process we required than if acyclic protecting groups were employed. The two main questions in such an approach were whether a benzylic radical would be sufficiently reactive in such a 6-*exo* radical cyclization and, if so, if such an approach could be utilized for the synthesis of the *trans* phenanthridone ring system. The construction of this subunit of the structure is considerably more difficult than might be apparent and has proven to be particularly problematic.[14]



Construction of a Radical Precursor

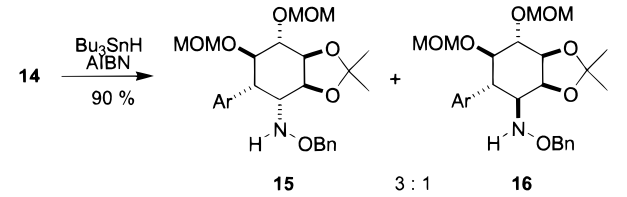
Our studies on such radical cyclization to oxime ethers began with the D-gulonolactone derivative **9**.[15] Treatment of lactone **9** with DIBAL at −78 °C gave the corresponding lactol. Oxime formation was carried out by treatment of the lactol with *O*-benzylhydroxylamine·HCl in the presence of pyridine,[13b] which gave the desired diol **10** in 66% yield and as a 2:1 mixture of oxime isomers. (See Experimental Section. For convenience, only one oxime isomer will be depicted throughout.) Protection of the diol



with chloromethyl methyl ether and *N*,*N*-diisopropylethylamine afforded the corresponding bis-MOM ether. Deprotection of the TBS group (TBAF/THF) gave the desired alcohol **11**, which was oxidized using the method of Ley[16] to afford the corresponding aldehyde. Immediate treatment of the aldehyde so produced with the Grignard reagent **12** (prepared from commercially available 4-bromo-1,2-methylenedioxybenzene) gave the desired alcohol **13** in 82% yield. Radical precursor **14** was prepared in 60% yield (as a mixture of diastereomers which were not separated) by treatment of alcohol **13** with 1,1′-thiocarbonyldiimidazole in 1,2-dichloroethane.[17] With the desired radical precursor in hand, studies on the radical cyclization process were commenced.

Radical Cyclization Results

Slow addition of a solution of Bu_3SnH and AIBN in toluene to a solution of thionocarbamate **14** at 90 °C over 12 h afforded the two cyclized products **15** and **16** in a 3:1 ratio and in 90% isolated yield.



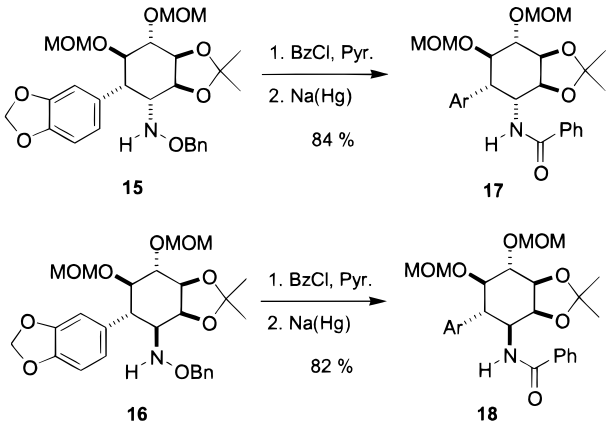
The major isomer **15** was ultimately shown to have the aryl group and the amine group in a *cis* orientation, with the nitrogen substituent at C_{4a} *trans* disposed with respect to the adjacent oxygen at C_3. Thus, in this isomer, the stereochemistry at the nitrogen-bearing center C_{4a} is as required for the synthesis of **2**, but the configuration at the aryl-bearing carbon C_{10b} is incorrect. Literature precedent for a *trans* relationship between the nitrogen and oxygen centers in such a cyclization was available in a previous report by Marco-Contelles and co-workers.[13a]

(14) For a review of synthetic work in this area, see: Polt, R. In *Organic Synthesis: Theory and Application*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1996; Vol. 3, p 109.

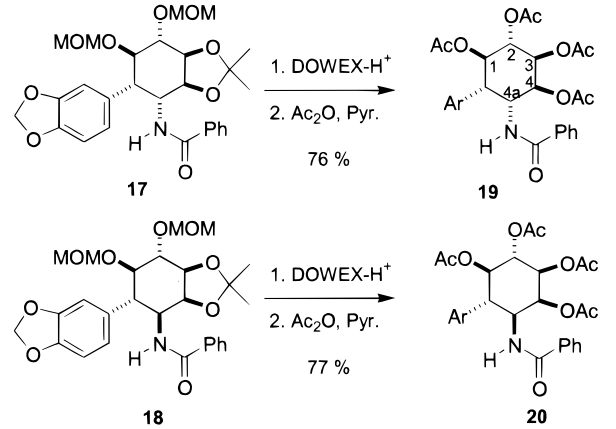
(15) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.

The minor isomer **16** contained the aryl and amine groups in a *trans* orientation; however, the configurations at *both* centers were epimeric with respect to those needed for the synthesis of **2**.

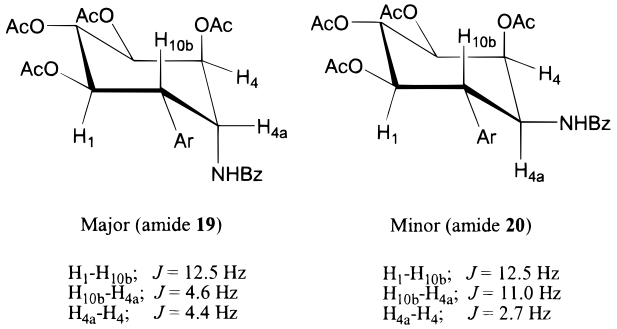
When amines **15** and **16** were first isolated, the ^{1}H NMR data did not allow for an unambiguous assignment of stereochemistry, presumably due to distortions away from idealized chair structures by the presence of the fused five-membered ring. Therefore, both **15** and **16** were converted to the tetraacetate derivatives **19** and **20**. For amine **15**, this sequence commenced by treatment with benzoyl chloride/pyridine, followed by reductive N−O bond cleavage[18] using 6% Na(Hg) in EtOH, which cleanly afforded the benzamide **17** in 84% yield. The same sequence was performed with the minor amine isomer **16**, which gave the amide **18** in 82% yield.



Treatment of amide **17** with DOWEX-H$^+$ resin in MeOH cleanly removed both the acetonide and MOM ether protecting groups to afford the corresponding tetraol, which was then peracetylated with Ac_2O/pyridine to give the tetraacetate **19** in 76% yield. Again, the same steps were performed on the amide **18**, which gave the tetraacetate **20** in 77% yield. These derivatives gave very richly detailed and clean NMR spectra in which all resonances were easily observable and assigned by decoupling experiments; in these materials, the expected chair conformations were evident. In the major isomer



(amide **19**), the small coupling constant ($J_{H10b}-J_{H4a}$) of 4.6 Hz was indicative of a *cis* relationship. In the minor isomer (amide **20**), a large coupling ($J_{H10b}-J_{H4a}$) of 11.0 Hz was observed, indicative of a *trans*-diaxial relationship.



Encouraged by the results of the radical cyclization of **14**, we next considered means by which the stereochemistry of the aryl group at C_{10b} might be controlled. We envisioned that the desired stereochemistry at C_{10b} could arise by conducting the key radical cyclization using a precursor in which the aryl group was tethered to the C_1 oxygen substituent as indicated generically in structure **21**. The net effect of this change would be to hold the aryl group in the desired β orientation during the radical cyclization. Since an additional carbon, in the form of an aryl carbonyl substituent, would eventually be required for the synthesis of 7-deoxypancratistatin, the most natural way to incorporate the proposed tether would be in the form of an ester linkage as in lactone **22**. Thus, with such a lactone moiety incorporated as a means to link the aryl unit to the hydroxyl group at C_1, it can be readily seen that the desired stereochemical outcome translates simply into a requirement that the 6-*exo* cyclization process occur so as to produce a *cis* ring fusion. Said another way, this requires radical addition onto the same face of the lactone ring that the tether terminating in the *O*-benzyloxime originates from. Clearly, this would be expected to be strongly preferred in this system.

One final stereochemical consideration is the disposition of the nitrogen substituent at C_{4a} using this approach. It becomes clear upon inspection of molecular models for the proposed cyclization that only two possible dispositions of the oxime ether with respect to the adjacent oxygen substituent allow the requisite trajectory for radical addition in a 6-*exo* manner: either essentially synperiplanar or essentially antiperiplanar. Of these, it would reasonably be expected that the antiperiplanar arrangement would be preferred to minimize nonbonded interactions in the transition state. With these considerations in mind, we set out to synthesize such a "cyclic" radical precursor (**23**) in hopes of obtaining the correct stereochemistry in the radical cyclization step.

Construction of the Cyclic Radical Precursor

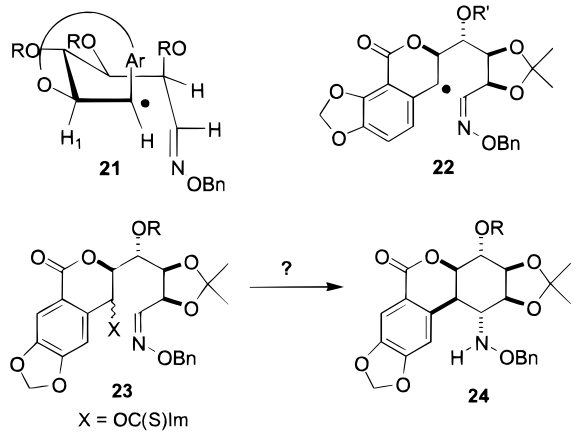
Starting from the D-gulonolactone derivative **25**, DIBAL reduction, followed by oxime formation (*O*-benzylhydroxylamine·HCl, pyr) gave the alcohol **26** in 89% yield (2:1 mixture of oxime isomers). Protection of **26** with MOMCl/

(16) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

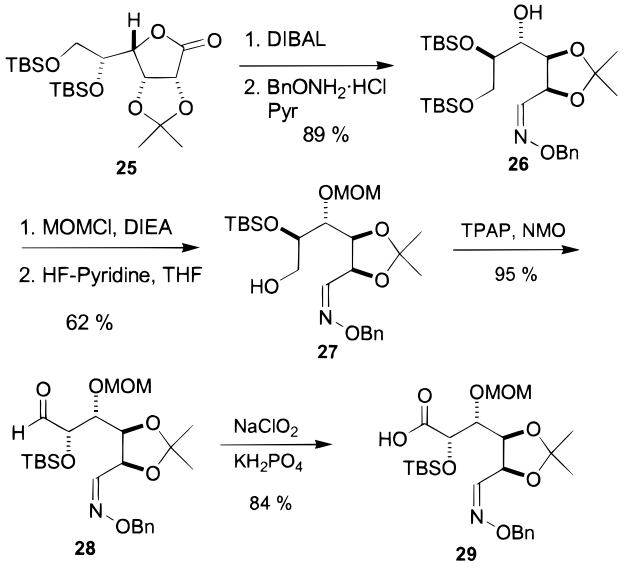
(17) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(18) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.

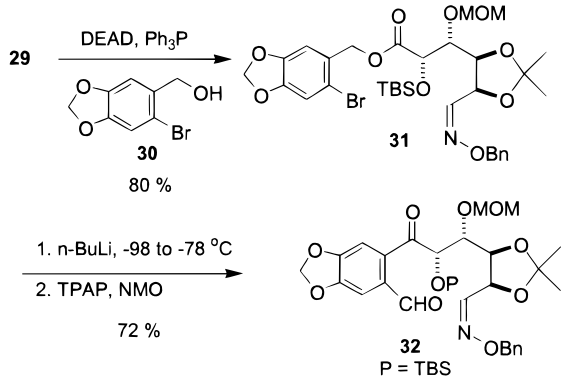
(19) Evans, D. A.; Gage, J. R.; Leighton, J. *J. Am. Chem. Soc.* **1992**, *114*, 9434.



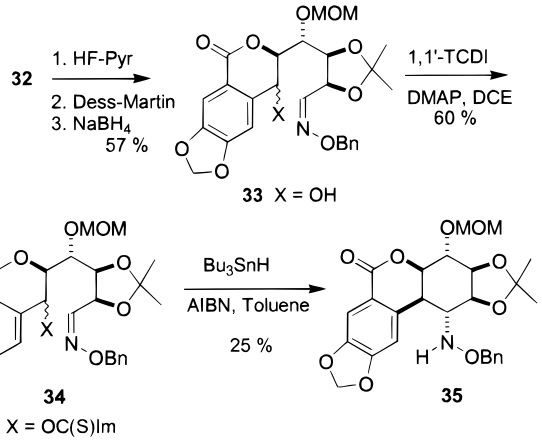
DIEA, followed by selective deprotection[19] of the primary TBS group (HF·Pyr) afforded the desired primary alcohol **27** in 62% yield. Oxidation (TPAP, NMO) of **27** to aldehyde **28** was straightforward; however, additions of various lithiated aromatic subunits to **28** proved to be problematic. Further oxidation[20] to acid **29** also occurred readily, but attempts to add lithiated aromatic subunits to the corresponding Weinreb amide[21] again failed, yielding only recovered starting material.



Due to the unexpected problems encountered with these intermolecular reactions, we next investigated the use of an intramolecular variant of the same basic bond construction.[22] Mitsunobu esterification[23] of acid **29** with alcohol **30** cleanly afforded ester **31** in 80% yield. Treatment of **31** with *n*-butyllithium at −98 °C, followed by gradual warming to −78 °C, afforded the corresponding rearranged benzylic alcohol. This alcohol unexpectedly proved to be very unstable and thus was immediately oxidized (TPAP, NMO) to the keto−aldehyde **32**. The keto−aldehyde **32** was not labile and was obtained in 72% overall yield from ester **31** after purification by column chromatography.



The keto−aldehyde **32** was converted to alcohol **33** by a three-step sequence, which began by removal of the TBS group using HF·pyridine. This afforded a hydroxy−aldehyde corresponding to **32** which existed almost exclusively as the cyclic lactol structure. Dess−Martin oxidation[24] of this material then provided the lactone moiety, and finally, reduction of the keto carbonyl group using $NaBH_4$ afforded alcohol **33**. Treatment of alcohol **33** with 1,1′-TCDI as previously described afforded the desired "cyclic" radical precursor **34**.

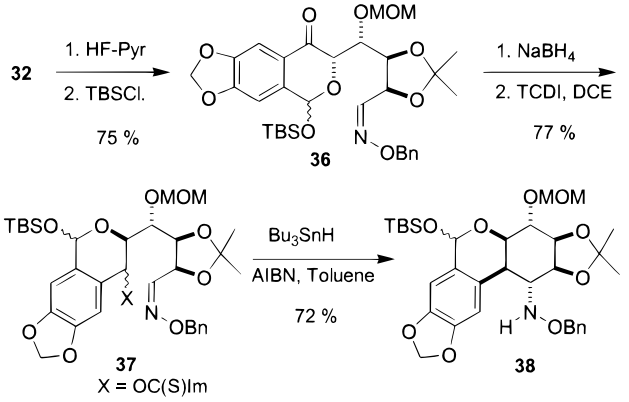


Radical cyclization of **34** (Bu_3SnH, AIBN, toluene, 90 °C) was unexpectedly complicated by competing reduction of the lactone moiety, and afforded amine **35** in only 25% isolated yield. A number of conditions for this transformation were examined in an attempt to improve upon this result, including the use of low-temperature initiators,[25] but in no case could we obtain more than a 30% isolated yield of **35**. Thus, the yield for the radical cyclization process using the lactone substrate **34** was unacceptably low. However, we were extremely gratified to find that **35** was obtained as a *single* diastereomer in which the desired relative and absolute configurations had been established at both C_{10b} and C_{4a}, thus establishing the viability of this aspect of the radical cyclization approach.

(20) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.
(21) (a) Sibi, M. P. *Org. Prep. Proc. Intl.* **1993**, *25*, 15. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (c) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (d) Aidhen, I. S.; Ahuja, J. *Tetrahedron Lett.* **1992**, *33*, 5431. (e) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
(22) (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. (b) Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1992**, 164. (c) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402. (d) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147.
(23) Mitsunobu, O. *Synthesis* **1981**, 1.
(24) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(25) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

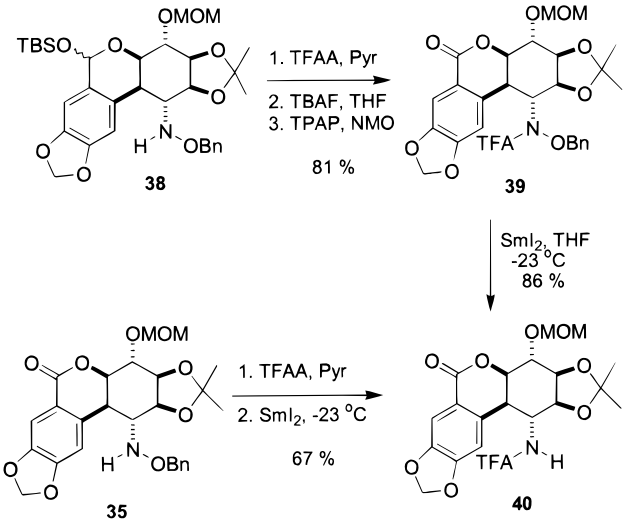
Cyclic Acetal Route

It did not prove practical to attempt to salvage the lactol side products encountered in the cyclization of the lactone substrate; thus, an alternative radical precursor was needed in which this unexpected reduction process was not possible. We chose to investigate the use of a TBS silyl acetal in this context. A radical precursor very similar to **34** was prepared which incorporated a protected lactol as a latent lactone. Keto−aldehyde **32** was converted to the TBS-protected lactol **36** via TBS deprotection as described before, followed by reprotection of the resulting lactol with TBSCl. Ketone reduction ($NaBH_4$ MeOH) and acylation (1,1′-TCDI) as previously described afforded radical precursor **37**, which yielded **38** as a single stereoisomer (ignoring lactol stereoisomers) upon radical cyclization in 72% isolated yield.



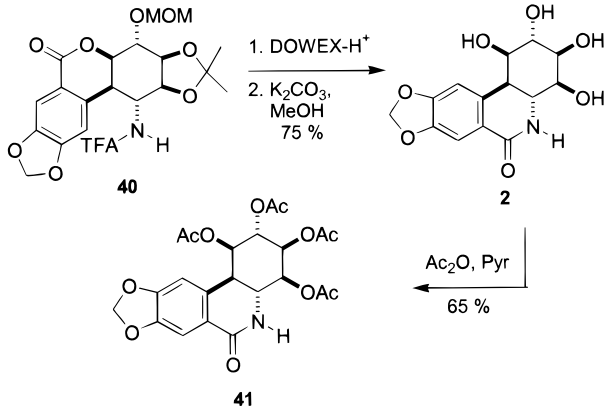
Completion of the Route to 2

Now that a satisfactory result for the critical radical cyclization had been realized, our attention turned to elaborating this substance to afford **2**. All attempts at deprotection of the TBS lactol and oxidation to the lactone (in **38**) in the presence of the free amine were unsuccessful. Therefore, protection of the amine was required, ideally with a group which would not require any additional steps for its removal. This was accomplished by acylation of **38** with TFAA to give the trifluoroacetamide derivative. Removal of the TBS group (TBAF) and oxidation (TPAP, NMO) then gave lactone **39** in 81% overall yield.



Completion of the synthesis from this point required several operations which at first glance would appear to be largely independent of one another: (1) removal of the MOM ether and acetonide moieties under acidic conditions, (2) removal of the TFA group under basic conditions, (3) rearrangement of the amino−lactone structure to a hydroxy−amide, and (4) reductive cleavage of the N−O bond. However, it was ultimately found experimentally that a precise ordering of these steps was required. For example, it did not prove possible to effect the lactone to lactam rearrangement unless the acetonide was removed prior to this step. It was also found that this rearrangement could not be done using the *O*-benzylhydroxylamine; reductive cleavage of the N−O bond was required prior to conducting this rearrangement.

Cleavage of the N−O bond in **39** was not straightforward. Treatment of **39** under hydrogenolysis[26] conditions and aluminum or sodium amalgam[27] conditions was not successful. However, reaction of **39** with SmI_2/THF[28] cleanly afforded amide **40**. We have found this to be a very general and useful reaction for the cleavage of N−O bonds in *O*-alkylhydroxylamines and *O*-alkylhydroxamic acid derivatives.[29] Finally, removal of the acetonide and MOM ether (DOWEX-H^+, MeOH, 65 °C) gave the corresponding triol. The triol was then treated with K_2CO_3 in dry MeOH,[30] which effected trifluoroacetamide removal with concomitant lactone to lactam reorganization, producing the natural product 7-deoxypancratistatin (**2**).



The natural product **2** was peracetylated (Ac_2O, pyridine) to give the corresponding tetraacetate **41**. The tetraacetate was spectroscopically and chromatographically indistinguishable (R_f, ^1H, ^{13}C, and $[\alpha]_D$) from that described by Paulsen.[12]

Reinvestigation of the Lactone Route

To avoid the two extra steps nessessary for transforming the TBS-lactol in **38** back to the desired lactone (i.e., deprotection and oxidation), a number of radical cycliza-

(26) Nikam, S. S.; Kornberg, B. E.; Johnson, D. R.; Doherty, J. A. *Tetrahedron Lett.* **1995**, *36*, 197.

(27) In our original study on the reductive cleavage of N−O bonds, *O*-alkyl trifluorohydroxamate derivatives were not studied, see ref 18.

(28) (a) Molander, G. A. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1994; Vol. 46, pp 211−367. (b) Brandukova, N. E.; Vygodskii, Y. S.; Vinogradova, S. V. *Russ. Chem. Rev.* **1994**, *63*, 345. (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (d) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.

(29) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419.

(30) (a) For a closely related transformation, see ref 12. (b) For a different outcome in a similar transformation using the same reagents, see ref 6.

Table 1. Conditions for the Radical Cyclization of 34

entry	conditions	yield of **35**, %
a	Bu_3SnH, AIBN, 95 °C, toluene, 12 h	25[a]
b	Bu_3SnH, AIBN, 80 °C, benzene, 2 h	25[a]
c	Bu_3Sn-O-$SnBu_3$, PMHS, *p*-dioxane, 95 °C	28[a]
d	Et_3B, Bu_3SnH, 0 °C to room temperature, 26 h	30[b]
e	Ph_3SnH, AIBN, 65 °C toluene, 4.5 h	70[c]
f	Bu_3SnH, AIBN, 65 °C toluene, 5 h	28[d]

[a] Remaining material was over-reduced products. [b] No over-reduced products observed, only remaining starting material. [c] No over-reduced products observed. [d] Remaining material was over-reduced product and starting material.

tion conditions were studied in an attempt to preclude the competing over reduction in the cyclization of **34**. As shown in Table 1, conditions employing Bu_3SnH at high temperatures (entries a, b, and c) gave the desired product in low yield, along with considerable amounts of the over-reduced side products. Using a low-temperature radical initiation method[25] (entry d), the desired product **35** was obtained in only 30% yield; however, none of the over-reduced products were observed, and the remaining material was recovered **34**. Attempts to improve the conversion under the low-temperature Et_3B/Bu_3SnH conditions were unsuccessful. Finally, it was discovered that treatment of **34** with Ph_3SnH/AIBN in toluene at 65 °C gave a 70% yield of **35** (entry e) as a single diastereomer; again, no over-reduced products were observed. To confirm that this was indeed unique to the use of Ph_3SnH and not to some other, possibly overlooked change in experimental conditions, the Bu_3SnH reaction was repeated using the same experimental conditions, but again gave only 28% yield (entry f). This result provides an efficient method for the conversion of **34** to **35** without employing the previously required TBS-lactol linkage. The cyclized product obtained in this way was converted to intermediate **40** by acylation with TFAA, followed by reduction with samarium iodide as previously described.

Conclusions

The chemistry described herein provides an indication of the utility of 6-*exo* radical cyclizations to oxime ethers as a method for construction of the highly functionalized *trans* phenanthridone ring nucleous found in various *Amaryllidacae* alkaloids. The radical precursors are easily prepared from readily available carbohydrate derivatives. The route described herein affords 7-deoxypancratistatin in 7% overall yield over 21 steps. Although the overall synthesis is longer than we envisioned, efforts toward shorter and more convergent approaches using this radical cyclization strategy can now be undertaken with confidence given the results of these studies.

Experimental Section

General. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Reagent grade t-BuOH, pyridine, and 1,2-dichloroethane were purchased and used without further purification. *N*,*N*-Diisopropylethylamine was distilled from CaH_2 and stored over oven-dried 4 Å molecular sieves. MOMCl was freshly prepared by a modification of the Linderman method[31] and distilled prior to use. Bu_3SnH and Ph_3SnH were flushed through a small column of activated alumina prior to use. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-Molybdophosphoric acid or *p*-anisaldehyde. Flash column chromatography was performed with Davisil 62 silica gel, slurry packed with 4% ethyl acetate/hexanes in glass columns, and flushed with hexanes prior to use. HPLC, high-pressure liquid chromatography, was performed with a Rainin HPXL system, utilizing a 21.4 mm × 5 cm preparative silica gel column with UV monitoring. Nuclear magnetic resonance spectra were acquired at 300 MHz for ^1H and 75 MHz for ^{13}C. The abbreviations s, d, t, q, brs, and brt stand for the resonance multiplicities singlet, doublet, triplet, quartet, broad singlet, and broad triplet, respectively. Analytical C and H analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Glassware for all reactions was oven dried at 125 °C and cooled in a desiccator prior to use. Liquid reagents and solvents were introduced by oven-dried syringes through septa-sealed flasks under a nitrogen atmosphere. In the reactions involving oxime ethers, a ca. 2:1 mixture of oxime isomers was used. However, for characterization purposes the major oxime isomer was separated and fully characterized. Oxime isomers were separated by flash chromatography, with the exception of diol **10** and alcohol **11** which were separated by preparative HPLC. Optical rotations were measured at 23 °C unless otherwise indicated.

Preparation of (1*S*,2*R*)-1-{(4*S*,5*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-3-(1,1,2,2-tetramethyl-1-silapropoxy)propane-1,2-diol (10). To a stirring solution of 6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-gulonolactone (2.0 g, 6.0 mmol) in 40 mL of CH_2Cl_2 at −78 °C was added a 1.0 M solution of DIBAL (7.2 mL, 7.2 mmol) over 1 h. After complete addition the reaction was stirred for 45 min and then quenched with 10 mL of MeOH. The solution was warmed to room temperature and stirred with 100 mL of saturated Rochelle salts for 3 h. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure to yield a light yellow oil.

To a stirring solution of the crude lactol prepared above in 20 mL of pyridine at room temperature was added *O*-benzylhydroxylamine·HCl (2.9 g, 18 mmol) in one portion. After 12 h, the reaction was diluted with 100 mL of EtOAc and washed with 50 mL each of H_2O, saturated $CuSO_4$, H_2O, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4.5 × 25 cm column, eluting with a solvent gradient of 10%, 15%, 20%, 25%, 30%, and 40% EtOAc/hexanes, collecting 20 mL fractions. The product-containing fractions (26−50) were collected and concentrated to yield 1.8 g (66%) of the diol **10** as a clear colorless oil and as a 2:1 mixture of oxime isomers (major oxime isomer): R_f 0.49 (50% EtOAc/hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.23−7.33 (m, 5H), 5.05 (s, 2H), 4.71 (dd, J = 8.1, 7.0 Hz, 1H), 4.37 (dd, J = 7.0, 4.3 Hz, 1H), 3.55−3.68 (m, 4H), 2.87 (d, J = 6.3 Hz, 1H), 2.72 (d, J = 4.3 Hz, 1H), 1.51 (s, 3H), 1.37 (s, 3H), 0.87 (s, 9H), 0.51 (s, 3H), 0.49 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 148.4, 137.3, 128.4, 128.2, 127.9, 110.1, 79.2, 76.1, 75.0, 71.6, 69.1, 64.9, 27.2, 25.8, 25.0, 18.2, −5.5; IR (neat) 3510 cm^{-1}; HRMS *m*/*z* (EI) calcd $C_{22}H_{37}NO_6Si$ 439.2388, obsd 439.2375. Anal. Calcd for $C_{22}H_{37}NO_6Si$: C, 60.11; H, 8.48; N, 3.19. Found: C, 60.21; H, 8.37; N, 3.29.

(31) Linderman, R. J.; Jaber, M.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6499.

Preparation of (3*S*,2*R*)-3-{(5*S*,4*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-2,3-bis(methoxymethoxy)propan-1-ol (11). To a stirring solution of diol **10** (1.75 g, 3.99 mmol) in 40 mL of CH_2Cl_2 cooled to −5 °C was added *N*,*N*-diisopropylethylamine (28.0 mL, 160 mmol), followed by chloromethyl methyl ether (9.10 mL, 120 mmol). The solution was warmed to room temperature and stirred for 19 h and then quenched by addition of 50 mL of a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was filtered through a silica gel plug, and the plug was washed with 30% EtOAc/hexanes. The solvents were removed under reduced pressure to yield a yellow oil, which was used in the next step without further purification.

To a stirring solution of the crude bis-MOM ether (1.70 g) prepared above in 30 mL of THF at −5 °C was added a 1.0 M solution of tetrabutylammonium fluoride (6.30 mL, 6.30 mmol) dropwise over 5 min. The solution was allowed to slowly warm to room temperature, stirring for a total of 2 h, and then was quenched with 15 mL of a saturated NH_4Cl solution and diluted with 40 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2.3 × 15 cm column, eluting with a solvent gradient of 20%, 40%, and 45% EtOAc/hexanes, collecting 15 mL fractions. The product-containing fractions (13−28) were collected and concentrated to yield 1.20 g (67%) of alcohol **11** as a clear colorless oil and as a 2:1 mixture of oxime isomers (major oxime isomer): R_f 0.15 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 1H), 7.31−7.35 (m, 5H), 5.05 (s, 2H), 4.78 (d, J = 6.9 Hz, 1H), 4.56−4.65 (m, 4H), 4.51 (t, J = 6.4 Hz, 1H), 3.63−3.74 (m, 4H), 3.38 (s, 3H), 3.37 (s, 3H), 2.98 (t, J = 7.6 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 147.9, 137.3, 128.4, 128.0, 109.7, 98.0, 97.3, 79.8, 77.9, 76.2, 75.5, 74.7, 62.0, 56.3, 55.9, 27.9, 25.6; IR (neat) 3500 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_8$: C, 58.10; H, 7.56; N, 3.39. Found: C, 57.93; H, 7.51; N, 3.42.

Preparation of 1-(2*H*-Benzo[3,4-*d*]-1,3-dioxolan-5-yl)-(3*S*,2*R*)-3-{(5*S*,4*R*)-5-[(1*Z*)-2-aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-2,3-bis(methoxymethoxy)-propan-1-ol (13). To a stirring solution of alcohol **11** (960 mg, 2.30 mmol) in 35 mL of CH_2Cl_2 at room temperature were added oven-dried 4 Å molecular sieves (960 mg) and *N*-methylmorpholine *N*-oxide (410 mg, 3.50 mmol), followed by tetrapropylammonium perruthenate (42.0 mg, 0.120 mmol). After 30 min, the reaction was filtered through a $MgSO_4$/silica gel plug with the aid of EtOAc. The resulting solution was concentrated under reduced pressure to yield 826 mg (87%) of the crude aldehyde, which was used in the next step without further purification.

To a stirring solution of the Grignard reagent **12** (16.0 mL of 0.5 M, 8.0 mmol, prepared from 4-bromo-1,2-methylenedioxybenzene) in 15 mL of THF at −78 °C was added the aldehyde prepared above (826 mg, 2.01 mmol) in 8 mL of THF dropwise. The reaction slowly warmed to −10 °C over 3.5 h and was then quenched with 20 mL of a saturated NH_4Cl solution and warmed to room temperature. The solution was diluted with 40 mL of Et_2O, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2.1 × 20 cm column, eluting with a solvent gradient of 10%, 20%, 25%, 30%, 35%, and 40% EtOAc/hexanes, collecting 8 mL fractions. The product-containing fractions (53−87) were collected and concentrated under reduced pressure to give 998 mg (82% yield) of **13** as a light yellow oil and a mixture of diastereomers: one diastereomer, $[\alpha]_D$ −26.9° (*c* 1.8, $CHCl_3$); R_f 0.34 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.28−7.35 (m, 6H), 6.70−6.90 (m, 3H), 5.87 (ABq, ΔAB = 7.3 Hz, J = 1.5 Hz, 2H), 5.09 (s, 2H), 4.90 (t, J = 3.6 Hz, 1H), 4.61−4.71 (m, 4H), 4.57 (d, J = 6.9 Hz, 1H), 4.46 (d, J = 6.9 Hz, 1H), 4.03 (d, J = 3.0 Hz, 1H), 3.80 (t, J = 3.7 Hz, 1H), 3.54 (dd, J = 5.1, 3.4 Hz, 1H), 3.44 (s, 3H), 3.26 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 147.8, 147.6, 146.9, 137.1, 135.1, 128.4, 128.3, 128.0, 119.9, 109.9, 108.0, 107.2, 100.9, 98.5, 98.4, 82.5, 77.2, 76.3, 76.2, 74.9, 71.6, 56.6, 56.1, 27.6, 25.5; IR (neat) 3472 cm^{-1}; HRMS *m*/*z* (EI) calcd $C_{27}H_{35}NO_{10}$ 533.2259, obsd 533.2289.

Preparation of [3-(2*H*-Benzo[3,4-*d*]1,3-dioxolan-5-yl)-(1*S*,3*S*,5*S*,2*R*,4*R*,6*R*)-4,5-bis(methoxymethoxy)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-yl](phenylmethoxy)-amine (15) and [3-(2*H*-Benzo[3,4-*d*]1,3-dioxolan-5-yl)-(1*S*,2*S*,3*S*,5*S*,4*R*,6*R*)-4,5-bis(methoxymethoxy)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-yl](phenylmethoxy)-amine (16). To a stirring solution of alcohol **13** (995 mg, 1.87 mmol) in 25 mL of 1,2-dichloroethane at room temperature was added 4-(dimethylamino)pyridine (115 mg, 0.940 mmol), followed by 1,1′-thiocarbonyldiimidazole (1.70 g, 9.40 mmol). The solution was heated at reflux for 24 h and then cooled to room temperature and poured into a separatory funnel containing 50 mL of a NH_4Cl solution and 50 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow oil was filtered through a silica gel plug, and the plug was washed several times with 75% EtOAc/hexanes. The filtrate was concentrated under reduced pressure to yield 724 mg of the crude thionocarbamate **14** as a light yellow foam.

The thionocarbamate (724 mg, 1.10 mmol) prepared above was dissolved in 19 mL of toluene, and the solution was degassed with N_2 for 20 min. The solution was brought to reflux, and a solution of tri-*n*-butyltin hydride (1.51 mL, 5.70 mmol) and 2,2′-azobis(2-methylpropionitrile) (56.0 mg, 0.340 mmol) in 19 mL of toluene (degassed with N_2) was added over 12 h via syringe pump. After complete addition, the residual syringe contents were added to the reaction. After 30 min, the reaction was cooled to room temperature and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2.1 × 18 cm column, eluting with a solvent gradient of 5%, 10%, 15%, 20%, and 30% EtOAc/hexanes, collecting 8 mL fractions. Fractions 42−53 were collected and concentrated to yield amine **15** (371 mg, 64% yield) as the major product. Fractions 54−61 were collected and concentrated to yield a mixture of amines **15** and **16** (31.0 mg, 5% yield). Fractions 62−80 were collected and concentrated to yield amine **16** (123 mg, 21% yield). Amine **15**: $[\alpha]_D$ +29.7° (*c* 3.22, $CHCl_3$); R_f 0.52 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.22−7.35 (m, 5H), 6.87 (s, 1H), 6.71−6.79 (m, 2H), 5.92 (d, J = 1.4 Hz, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.80 (bs, 1H), 4.90 (d, J = 6.4 Hz, 1H), 4.83 (d, J = 6.9 Hz, 1H), 4.75 (d, J = 6.4 Hz, 1H), 4.60 (ABq, ΔAB = 15.7 Hz, J = 11.9 Hz, 2H), 4.45 (d, J = 6.9 Hz, 1H), 4.33 (dd, J = 5.5, 2.9 Hz, 1H), 4.10−4.18 (m, 2H), 3.83 (dd, J = 8.1, 7.3 Hz, 1H), 3.39 (s, 3H), 3.19−3.26 (m, 2H), 2.81 (s, 3H), 1.55 (s, 3H), 1.33 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 147.7, 146.4, 137.2, 131.9, 128.6, 128.4, 128.1, 127.9, 122.5, 109.8, 108.6, 108.2, 100.9, 97.3, 96.5, 81.2, 79.4, 76.5, 75.8, 61.6, 55.9, 55.5, 46.9, 27.8, 26.1; HRMS *m*/*z* (EI) calcd $C_{27}H_{35}NO_9$ 517.2310, obsd 517.2322.

Amine **16**: $[\alpha]_D$ +50.5° (*c* 1.31, $CHCl_3$); R_f 0.44 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.19−7.31 (m, 5H), 6.68−6.76 (m, 3H), 5.93 (s, 2H), 5.51 (bs, 1H), 4.82 (ABq, ΔAB = 24.5, J = 6.3 Hz, 2H), 4.58−4.70 (m, 4H), 4.20 (d, J = 6.8 Hz, 1H), 4.16 (dd, J = 7.2, 5.1 Hz, 1H), 3.55 (dd, J = 10.7, 8.9 Hz, 1H), 3.40 (s, 3H), 3.33−3.39 (m, 1H), 2.90 (dd, J = 12.0, 10.7 Hz, 1H), 2.70 (s, 3H), 1.63 (s, 3H), 1.44 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 148.1, 146.9, 137.1, 132.0, 128.6, 128.4, 127.9, 122.1, 109.6, 108.5, 108.3, 101.0, 97.2, 96.5, 79.9, 79.1, 78.9, 76.8, 73.2, 60.5, 55.9, 55.4, 45.4, 27.9, 26.3.

Preparation of *N*-[3-(2*H*-Benzo[3,4-*d*]-1,3-dioxolen-5-yl)(1*S*,3*S*,5*S*,2*R*,4*R*,6*R*)-4,5-bis(methoxymethoxy)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-yl]benzamide (17). To a stirring solution of amine **15** (51 mg, 0.10 mmol) in 2 mL of CH_2Cl_2 at room temperature were added *N*,*N*-(dimethylamino)pyridine (6.0 mg, 0.05 mmol) and pyridine (0.08 mL,

1.0 mmol), followed by benzoyl chloride (0.12 mL, 1.0 mmol). After stirring 43 h at room temperature, the reaction was diluted with 2 mL of CH_2Cl_2 and quenched with 10 mL of an aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered through a $MgSO_4$/silica gel plug, and concentrated under reduced pressure. The resulting yellow oil (70 mg) was used in the next step without further purification.

To a stirring solution of the crude benzamide (70 mg) in 2 mL of EtOH at −5 °C was added Na_2HPO_4 (67 mg, 0.47 mmol), followed by finely ground 6% Na(Hg) (900 mg). After 1 h, the reaction was diluted with 2 mL of THF and filtered through a $MgSO_4$/Celite plug, and the plug was washed with THF. The resulting solution was concentrated under reduced pressure to yield an off-white solid. Purification was accomplished by flash chromatography on a 1.3 × 10 cm column, eluting with a solvent gradient of 20%, 30%, and 40% EtOAc/hexanes, collecting 3 mL fractions. The product-containing fractions (13−17) were collected and concentrated to yield amide **17** (43 mg, 84%) as a white foam: $[\alpha]_D$ +64.6° (*c* 0.51, $CHCl_3$); R_f 0.33 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.66−7.69 (m, 2H), 7.38−7.49 (m, 3H), 7.18 (d, J = 10.5 Hz, 1H), 6.67−6.78 (m, 3H), 5.88 (s, 2H), 4.89 (ABq, ΔAB = 9.3 Hz, J = 6.6 Hz, 2H), 4.71 (d, J = 7.1 Hz, 1H), 4.52−4.61 (m, 2H), 4.40 (d, J = 7.1 Hz, 1H), 4.32 (dd, J = 7.0, 3.2 Hz, 1H), 4.29 (dd, J = 3.6, 2.4 Hz, 1H), 4.21 (dd, J = 9.8, 1.2 Hz, 1H), 3.46 (s, 3H), 3.40 (dd, J = 9.6, 3.6 Hz, 1H), 2.96 (s, 3H), 1.63 (s, 3H), 1.37 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.4, 147.6, 146.4, 134.5, 133.8, 131.4, 128.5, 126.7, 121.7, 109.0, 108.8, 108.1, 100.8, 96.2, 95.1, 76.6, 76.1, 75.5, 75.0, 56.2, 55.3, 51.8, 44.0, 26.6, 23.9; HRMS *m/z* (EI) calcd $C_{27}H_{33}NO_9$ 515.2154, obsd 515.2196.

Preparation of *N*-[3-(2*H*-Benzo[3,4-*d*]-1,3-dioxolan-5-yl)(1*S*,2*S*,3*S*,5*S*,4*R*,6*R*)-4,5-bis(methoxymethoxy)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-yl]benzamide (18). To a stirring solution of amine **16** (120 mg, 0.231 mmol) in 3 mL of CH_2Cl_2 at room temperature was added *N*,*N*-(dimethylamino)pyridine (15.0 mg, 0.120 mmol), followed by benzoyl chloride (0.270 mL, 2.30 mmol). A condensor was attached, and the reaction was heated at a gentle reflux for 24 h and then cooled to room temperature and diluted with 5 mL of CH_2Cl_2 and 20 mL of an aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow oil was used in the next step without further purification.

To a stirring solution of the crude benzamide prepared above in 4 mL of EtOH at −5 °C was added Na_2HPO_4 (133 mg, 0.940 mmol), followed by finely ground 6% Na(Hg) (1.90 g). After 1 h, the reaction was diluted with 5 mL of THF and filtered through a $MgSO_4$/Celite plug, and the plug was thoroughly washed with THF. The resulting solution was concentrated under reduced pressure to yield a light yellow solid. Purification was accomplished by flash chromatography on a 1.5 × 13 cm column, eluting with a solvent gradient of 20%, 30%, 40%, and 50% EtOAc/hexanes, collecting 3 mL fractions. The product-containing fractions (16−32) were collected and concentrated under reduced pressure to yield amide **18** (98 mg, 82% yield) as a white foam: $[\alpha]_D$ −15.8° (*c* 5.33, $CHCl_3$); R_f 0.46 (75% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.27−7.46 (m, 5H), 6.67−6.81 (m, 3H), 6.07 (d, J = 9.3 Hz, 1H), 5.83 (ABq, ΔAB = 1.8 Hz, J = 1.4 Hz, 2H), 4.74−4.84 (m, 3H), 4.56 (d, J = 6.9 Hz, 1H), 4.47 (dd, J = 5.7, 3.7 Hz, 1H), 4.29 (t, J = 5.9 Hz, 1H), 4.23 (d, J = 6.7 Hz, 1H), 3.93 (t, J = 6.6 Hz, 1H), 3.73 (dd, J = 10.1, 7.0 Hz, 1H), 3.41 (s, 3H), 3.05 (dd, J = 12.4, 10.1 Hz, 1H), 2.81 (s, 3H), 1.58 (s, 3H), 1.32 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.8, 147.7, 146.6, 134.5, 132.6, 131.3, 128.4, 126.8, 122.2, 109.5, 108.8, 108.0, 100.8, 96.7, 96.2, 79.4, 78.2, 78.0, 75.4, 55.8, 48.8, 47.7, 27.3, 25.6; HRMS *m/z* (EI) calcd $C_{27}H_{33}NO_9$ 515.2154, obsd 515.2187.

Preparation of 3-(2*H*-Benzo[3,4-*d*]-1,3-dioxolan-5-yl)-(1*S*,3*S*,6*S*,2*R*,4*R*,5*R*)-4,5,6-triacetyloxy-2-(phenylcarbonylamino)cyclohexyl Acetate (19). To a stirring solution of amide **17** (16 mg, 0.03 mmol) in 1 mL of MeOH was added 50W-8X Dowex-H$^+$ resin (20 mg). The reaction was sealed and heated in a 65 °C oil bath for 6.5 h and then cooled to room temperature and filtered through a plug of Celite/silica gel (slurry packed in MeOH), and the plug was washed thoroughly with MeOH. The solvent was removed under reduced pressure to yield the crude tetraol as a white solid, which was used in the next step without further purification.

To a stirring solution of the tetraol prepared above (12 mg) in 0.50 mL of pyridine at room temperature was added 4-(dimethylamino)pyridine (3.0 mg), followed by Ac_2O (0.02 mL). After 2 h, the mixture was diluted with 2 mL of CH_2Cl_2 and quenched with an aqueous $NaHCO_3$ solution. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 0.5 × 7 cm column, eluting with a solvent gradient of 20%, 30%, and 50% EtOAc/hexanes, collecting 0.5 mL fractions. The product-containing fractions (21−26) were collected and concentrated under reduced pressure to yield the tetraacetate **19** (13 mg, 76% yield) as a colorless solid: mp 159−161 °C; $[\alpha]_D$ +67.0° (*c* 1.21, $CHCl_3$); R_f 0.59 (75% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.20−7.55 (m, 5H), 7.10 (d, J = 9.1 Hz, 1H), 6.79−6.83 (m, 3H), 6.01 (dd, J = 12.5, 9.3 Hz, 1H), 5.89 (ABq, ΔAB = 13.9 Hz, J = 1.4 Hz, 2H), 5.49−5.56 (m, 2H), 5.31 (dd, J = 10.7, 2.9 Hz, 1H), 4.57−4.63 (m, 1H), 3.67 (dd, J = 12.5, 4.6 Hz, 1H), 2.24 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.64 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.4, 169.9, 169.1, 167.6, 158.0, 148.0, 147.1, 133.9, 131.7, 129.1, 128.4, 127.1, 121.0, 108.7, 108.5, 101.2, 71.7, 70.1, 69.8, 69.1, 52.2, 45.1, 21.0, 20.6, 20.4, 20.3; HRMS (EI) exact mass calcd. for $C_{28}H_{29}NO_{11}$ 555.1739, found 555.1735.

Preparation of 3-(2*H*-Benzo[3,4-*d*]-1,3-dioxolan-5-yl)-(1*S*,2*S*,3*S*,6*S*,4*R*,5*R*)-4,5,6-triacetyloxy-2-(phenylcarbonylamino)cyclohexyl Acetate (20). To a stirring solution of amide **18** (19 mg, 0.04 mmol) in 1 mL of MeOH was added 50W-8X DOWEX-H$^+$ resin (25 mg). The reaction was sealed, heated in a 65 °C oil bath for 5.5 h, then cooled to room temperature, and filtered through a plug of Celite/silica gel (slurry packed in MeOH), and the plug was washed with MeOH. The solvent was removed under reduced pressure to yield the crude tetraol (13 mg) as a white solid.

To a stirring solution of the crude tetraol prepared above in 0.5 mL of pyridine at room temperature was added 4-(dimethylamino)pyridine (4.0 mg), followed by Ac_2O (0.03 mL). After 1.5 h, the solution was diluted with 2 mL of CH_2Cl_2 and quenched with an aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 0.5 × 7 cm column, eluting with a solvent gradient of 30%, 40%, and 50% EtOAc/hexanes, collecting 0.5 mL fractions. The product-containing fractions (17−22) were collected and concentrated to yield the tetraacetate **20** (17 mg, 77% yield) as a colorless solid: mp 173−175 °C; $[\alpha]_D$ +21.6° (*c* 0.64, $CHCl_3$); R_f 0.55 (75% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.28−7.45 (m, 5H), 6.69−6.74 (m, 3H), 5.89 (ABq, ΔAB = 4.2 Hz, J = 1.5 Hz, 2H), 5.74 (t, J = 2.7 Hz, 1H), 5.69 (d, J = 8.3 Hz, 1H), 5.47 (dd, J = 10.5, 9.6 Hz, 1H), 5.20−5.27 (m, 2H), 4.73 (ddd, J = 11.0, 8.3, 2.7 Hz, 1H), 3.19 (dd, J = 12.5, 11.1 Hz, 1H), 2.19 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.79 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.2, 169.6, 169.5, 169.0, 166.8, 148.1, 147.4, 133.9, 131.7, 128.9, 128.6, 126.8, 122.1, 108.2, 101.2, 73.1, 71.1, 70.6, 70.0, 49.2, 47.5, 20.9, 20.6, 20.5, 20.3; HRMS *m/z* (EI) calcd $C_{28}H_{29}NO_{11}$ 555.1739, obsd 555.1771.

Preparation of 4-[(1*S*)-1,2-Bis(1,1,2,2-tetramethyl-1-silapropoxy)ethyl](5*S*,1*R*,4*R*)-7,7-dimethyl-3,6,8-trioxabicyclo[3.3.0]octan-2-one (25). D-Gulonolactone (10.0 g, 56.2 mmol) was suspended in acetone (100 mL), and 2,2-dimethoxypropane (50.0 mL) and *p*-toluenesulfonic acid (50.0 mg) were added. After stirring at room temperature for 24 h, the reaction was neutralized with solid K_2CO_3, filtered, and concentrated under reduced pressure. The resulting slurry was

dissolved in 100 mL of AcOH/ H_2O (7:1), stirred for 12 h at room temperature, and then concentrated and dried by repeated concentration with toluene (3 × 100 mL). The resulting yellow oil was dissolved in *N*,*N*-dimethylformamide (20 mL), and imidazole (15.3 g, 225 mmol) and *tert*-butyldimethylchlorosilane (18.5 g, 123 mmol) were added. The resulting solution was stirred for 20 h and then poured into a separatory funnel containing CH_2Cl_2 (200 mL) and H_2O (200 mL). The layers were separated, and the cloudy organic layer was washed with H_2O (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield a white solid. Purification was accomplished by flash chromatography on a 4.5 × 25 cm column, eluting with a solvent gradient of 5%, 8%, 12%, 15%, and 20% EtOAc/hexanes, collecting 25 mL fractions. The product-containing fraction (22−55) were collected and concentrated to yield lactone **25** (22.6 g, 90%) as a white solid: mp 121 °C; $[\alpha]_D$ −37.8° (*c* 3.63, $CHCl_3$); R_f 0.48 (20% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.89 (m, 2H), 4.61 (dd, J = 3.1, 8.3 Hz, 1H), 4.13 (dt, J = 3.2, 8.3 Hz, 1H), 4.02 (dd, J = 3.4, 11.0 Hz, 1H), 3.82 (dd, J = 3.0, 11.0 Hz, 1H), 1.57 (s, 3H), 1.49 (s, 3H), 1.02 (s, 9H), 1.01 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.19 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 173.7, 113.7, 81.3, 76.5, 76.1, 72.1, 65.4, 26.9, 26.1, 25.9, 25.8, 18.3, 18.2, −4.6, −4.7, −5.3, −5.5; IR (CH_2Cl_2) 1788 cm^{-1}. Anal. Calcd for $C_{21}H_{42}O_6Si_2$: C, 56.50; H, 9.42. Found: C, 56.57; H, 9.40.

Preparation of (1*R*,2*R*)-1-{(4*S*,5*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-2,3-bis(1,1,2,2-tetramethyl-1-silapropoxy)propan-1-ol (26). To a stirring solution of lactone **25** (10.0 g, 22.4 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride (25.0 mL, 24.6 mmol) over 1 h. After complete addition, the reaction was stirred for 0.5 h and then quenched by slow addition of MeOH (20 mL) over 0.5 h. The mixture was warmed to room temperature and stirred with saturated aqueous Rochelle salts (300 mL) for 5 h. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting crude oil was dissolved in pyridine (80 mL), and *O*-benzylhydroxylamine·HCl (5.40 g, 33.6 mmol) was added in one portion. After stirring 23 h at room temperature, the reaction was diluted with EtOAc (200 mL) and washed with 100 mL each of H_2O, a saturated $CuSO_4$ solution, H_2O, and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography on a 4.5 × 35 cm column, eluting with a solvent gradient of 5%, 10%, 15%, 20%, and 25% EtOAc/hexanes, collecting 20 mL fractions. The product-containing fractions (28−75) were collected and concentrated to yield **26** (11.0 g, 89%) as a 2:1 mixture of oxime isomers and as a clear colorless oil: major oxime isomer, $[\alpha]_D$ + 13.4° (*c* 3.09, $CHCl_3$); R_f 0.32 (20% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 1H), 7.44−7.39 (m, 5H), 5.21 (s, 2H), 4.80 (dd, J = 7.1, 8.4 Hz, 1H), 4.47 (dd, J = 7.1, 3.3 Hz, 1H), 3.82 (m, 3H), 3.63 (dd, J = 9.5, 4.7 Hz, 1H), 2.62 (d, J = 9.2 Hz, 1H), 1.64 (s, 3H), 1.50 (s, 3H), 1.03 (s, 9H), 1.02 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H), 0.19 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 148.3, 136.9, 127.9, 127.8, 127.6, 127.3, 109.3, 76.2, 75.5, 74.9, 72.4, 68.4, 63.9, 26.9, 25.5, 24.7, −4.6, −5.4, −5.8, −5.9; IR (neat) 3562 cm^{-1}. Anal. Calcd for $C_{28}H_{51}NO_6Si_2$: C, 60.76; H, 9.22; N, 2.53. Found: C, 60.69; H, 9.27; N, 2.54.

Preparation of (2*R*,3*R*)-3-{(4*S*,5*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-3-(methoxymethoxy)-2-(1,1,2,2-tetramethyl-1-silapropoxy)-propan-1-ol (27). To a stirring solution of alcohol **26** (4.5 g, 8.1 mmol) in 41 mL of CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (10 mL, 51 mmol), LiI (5.5 g, 41 mmol), and chloromethyl methyl ether (3.1 mL, 41 mmol), and the solution was heated at 55−60 °C for 15 h. The resulting orange solution was cooled to room temperature, quenched by addition of 50 mL of a saturated $NaHCO_3$ solution, and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through a $MgSO_4$/silica gel plug, and concentrated under reduced pressure. The resulting yellow oil was used in the next step without further purification.

To a solution of the crude oil prepared above in 200 mL of THF was added a pre-prepared solution consisting of HF·pyridine (47 g), pyridine (71 mL), and 200 mL of THF. The solution was allowed to stand at room temperature for 3 h, at which time it was diluted with 200 mL of EtOAc and slowly quenched with a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3.1 × 25 cm column, eluting with a solvent gradient of 10%, 15%, 18%, 20%, and 25% EtOAc/hexanes, collecting 15 mL fractions. The product-containing fractions (50−83) were collected and concentrated to give alcohol **27** (2.43 g, 62%), as a 2:1 mixture of oxime isomers, and as a clear colorless oil: major oxime isomer, $[\alpha]_D$ −40.9° (*c* 5.5, $CHCl_3$); R_f 0.40 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 8.1 Hz, 1 H), 7.32−7.36 (m, 5 H), 5.07 (s, 2H), 4.54−4.70 (m, 4 H), 3.89 (ddd, J = 5.6, 3.4, 1.2 Hz, 1H), 3.51−3.71 (m, 3H), 3.41 (s, 3H), 2.68 (dd, J = 7.8, 6.4 Hz, 1H), 1.50 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.057 (s, 3H), 0.034 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 148.7, 137.7, 128.8, 128.6, 128.3, 110.0, 98.7, 77.7, 77.2, 76.5, 75.2, 71.8, 63.5, 56.5, 28.1, 26.2, 25.8, 18.4, −3.90, −4.50; IR (neat) 3566, 3547, 3421 cm^{-1}. Anal. Calcd for $C_{24}H_{41}NO_7Si$: C, 59.60; H, 8.54; N, 2.89. Found: C, 59.56; H, 8.56; N, 2.84.

Preparation of (2*S*,3*R*)-3-{(4*S*,5*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-3-(methoxymethoxy)-2-(1,1,2,2-tetramethyl-1-silapropoxy)-propanoic Acid (29). To a stirring solution of alcohol **27** (2.10 g, 4.40 mmol) in 45 mL of CH_2Cl_2 at room temperature were added oven-dried 4 Å molecular sieves (2.10 g), 4-methylmorpholine *N*-oxide (772 mg, 6.60 mmol), and tetrapropylammonium perruthenate (75.0 mg, 0.220 mmol). After 1 h, the solution was filtered through a plug of silica gel (slurry packed in EtOAc) and concentrated under reduced pressure to yield 2.01 g (95% yield) of aldehyde **28** as a clear colorless oil.

The crude aldehyde was immediately dissolved in a mixture of *tert*-butyl alcohol (18.0 mL) and 2-methyl-2-butene (18.0 mL) and cooled to −5 °C. To this solution was added a 1.25 M solution of KH_2PO_4 (21.1 mL, 26.4 mmol), followed by sodium chlorite (2.00 g, 22.0 mmol). After 50 min, the reaction was quenched with 20 mL of pH = 4 buffer solution and diluted with CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2.3 × 25 cm column, eluting with a solvent gradient of 8%, 15%, 20%, and 25% EtOAc/hexanes, collecting 8 mL fractions. The product-containing fractions (24−70) were collected and concentrated under reduced pressure to yield acid **29** (1.83 g, 84%), as a 2:1 mixture of oxime isomers, and as a clear colorless oil: major oxime isomer, $[\alpha]_D$ −14.3 (*c* 6.6, $CHCl_3$); R_f 0.21 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 8.2 Hz, 1H), 7.23−7.32 (m, 5H), 5.05 (ABq, ΔAB = 17.3 Hz, J = 12.3 Hz, 2H), 4.70 (ABq, ΔAB = 24.9 Hz, J = 6.9 Hz, 2H), 4.60 (dd, J = 8.2, 6.3 Hz, 1H), 4.51 (t, J = 6.3 Hz, 1H), 4.35 (d, J = 3.4 Hz, 1H), 3.86 (dd, J = 6.4, 3.4 Hz, 1H), 3.36 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 174.5, 147.9, 137.4, 128.4, 128.1, 127.9, 109.9, 97.5, 77.4, 76.4, 76.1, 74.5, 71.8, 56.3, 27.7, 25.8, 25.4, 18.2, −4.7, −5.3; IR (neat) 3350 1759 cm^{-1}. Anal. Calcd for $C_{24}H_{39}NO_8Si$: C, 57.92; H, 7.90; N, 2.82. Found: C, 58.03; H, 7.97; N, 2.81.

Preparation of (6-Bromo-2*H*-benzo[3,4-*d*]-1,3-dioxolan-5-yl)methyl (2*S*,3*R*)-3-{(4*S*,5*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-3-(methoxymethoxy)-2-(1,1,2,2-tetramethyl-1-silapropoxy)propanoate (31). To a stirring solution of acid **29** (715 mg, 1.44 mmol), 4-bromo-5-hydroxymethyl-1,2-meth-

ylenedioxybenzene **30** (499 mg, 2.16 mmol), and triphenylphosphine (566 mg, 2.16 mmol) in 32 mL of THF at room temperature was added diethyl azodicarboxylate (0.360 mL, 2.16 mmol) dropwise. After 42 h, the solution was concentrated under reduced pressure to yield a yellow oil, which was purified by flash chromatography on a 2.1 × 20 cm column, eluting with a solvent gradient of 5%, 8%, 11%, and 15% EtOAc/hexanes, and collecting 8 mL fractions. The product-containing fractions (35−61) were collected and concentrated to yield the bromo ester **31** (810 mg, 80% yield), as a 1.5:1 mixture of oxime isomers, and as a clear colorless oil: major oxime isomer, $[\alpha]_D$ −11.9 (*c* 8.30, $CHCl_3$); R_f 0.53 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 8.2 Hz, 1H), 7.24−7.29 (m, 5H), 6.97 (s, 1H), 6.95 (s, 1H), 5.93 (s, 2H), 5.11 (ABq, ΔAB = 29.2 Hz, J = 13.0 Hz, 2H), 5.00 (ABq, ΔAB = 16.4 Hz, J = 12.0 Hz, 2H), 4.68 (ABq, ΔAB = 28.5 Hz, J = 6.9 Hz, 2H), 4.60 (dd, J = 8.2, 6.0 Hz, 1H), 4.52 (dd, J = 6.7, 6.0 Hz, 1H), 4.33 (d, J = 3.1 Hz, 1H), 3.88 (dd, J = 6.7, 3.1 Hz, 1H), 3.31 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.00 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.7, 148.2, 148.0, 147.4, 137.2, 128.3, 128.2, 128.0, 127.9, 113.9, 112.7, 110.0, 109.8, 101.8, 97.6, 77.4, 77.2, 76.1, 74.6, 72.0, 66.2, 56.2, 27.8, 25.8, 25.4, 18.3, −4.5, −5.3; IR (neat) 1761 cm^{-1}. Anal. Calcd for $C_{32}H_{44}NO_{10}SiBr$: C, 54.08; H, 6.24; N, 1.97. Found: C, 54.19; H, 6.31; N, 1.91.

Preparation of 6-((2*S*,3*R*)-3-{(5*S*,4*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-3-(methoxymethoxy)-2-(1,1,2,2-tetramethyl-1-silapropoxy)-propanoyl)-2*H*-benzo[*d*]-1,3-dioxolane-5-carbaldehyde (32). To a stirring solution of bromo ester **31** (478 mg, 0.670 mmol) in 17 mL of THF at −98 °C was added a 2.40 M solution of *n*-BuLi (0.335 mL, 0.804 mmol) dropwise over 5 min. After 15 min, the reaction was transferred to a −78 °C bath and was stirred for 1.5 h. The reaction was quenched at −78 °C by addition of a saturated solution of NH_4Cl (10 mL), and upon warming to 0 °C the solution was poured into a separatory funnel containing CH_2Cl_2 (30 mL) and H_2O (30 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solution was filtered, concentrated under reduced pressure to a volume of approximately 2 mL, and used immediately in the next reaction.

To a stirring solution of the crude alcohol prepared above in 20 mL of CH_2Cl_2 at room temperature were added oven-dried 4 Å molecular sieves (500 mg), 4-methylmorpholine *N*-oxide (118 mg, 1.01 mmol), and tetrapropylammonium perruthenate (11.7 mg, 0.033 mmol). After 45 min, the heterogeneous mixture was filtered through a plug of silica gel (slurry packed in EtOAc) and concentrated under reduced pressure. The crude oil was purified by flash chromatography on a 2.1 × 18 cm column, eluting with a solvent gradient of 5%, 8%, 15%, and 18% EtOAc/hexanes, while collecting 8 mL fractions. The product-containing fractions (34−50) were collected and concentrated to yield 301 mg (72% yield) of keto−aldehyde **32**, as a 1.5:1 mixture of oxime isomers, and as a clear colorless oil: major oxime isomer, $[\alpha]_D$ −1.27° (*c* 4.10, $CHCl_3$); R_f 0.46 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.9 (s, 1H), 7.24−7.54 (m, 7H), 7.38 (d, J = 7.1 Hz, 1H), 6.07 (s, 2H), 5.1 (s, 2H), 4.78 (d, J = 3.2 Hz, 1H), 4.76 (d, J = 6.3 Hz, 1H), 4.59−4.65 (m, 2H), 4.55 (d, J = 6.6 Hz, 1H), 3.93 (dd, J = 7.1, 3.2 Hz, 1H), 3.10 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 0.867 (s, 9H), −0.009 (s, 3H), −0.203 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 199.9, 190.2, 150.6, 150.2, 147.7, 137.2, 135.7, 133.2, 128.5, 128.4, 127.9, 109.9, 109.8, 107.9, 102.5, 97.2, 77.7, 77.4, 76.6, 76.3, 74.4, 56.5, 27.8, 25.8, 25.4, 18.2, −4.2, −5.1; IR (neat) 1683 cm^{-1}. Anal. Calcd for $C_{32}H_{43}NO_{10}Si$: C, 61.03; H, 6.88; N, 2.22. Found: C, 60.87; H, 6.94; N, 2.18.

Preparation of (7*S*)-7-((1*S*){(5*S*,4*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-(methoxymethoxy)methyl)-5-(1,1,2,2-tetramethyl-1-silapropoxy)-2*H* -1,3-dioxoleno[4,5-*g*]isochroman-8-one (36). To a stirring solution of keto−aldehyde **32** (400 mg, 0.640 mmol) in 6 mL of THF was added a solution consisting of HF·pyridine (11.0 mL), pyridine (16.0 mL), and 8 mL of THF. The reaction was allowed to stand at room temperature for 24 h and then diluted with 50 mL of EtOAc and slowly quenched by addition of a saturated $NaHCO_3$ solution. The layers were separated, and the organic layer was washed with 50 mL of saturated $CuSO_4$ followed by 50 mL H_2O and finally dried over anhydrous $MgSO_4$. The solution was filtered through a plug of $MgSO_4$/silica gel (slurry packed in EtOAc) and concentrated under reduced pressure. The resulting white foam was used in the next step without further purification.

To the crude lactol prepared above in 5 mL of *N*,*N*-dimethylformamide was added imidazole (75.0 mg, 1.10 mmol) followed by *tert*-butyldimethylchlorosilane (127 mg, 0.840 mmol). After stirring 19 h at room temperature, the solution was diluted with CH_2Cl_2 (30 mL) and poured into 50 mL of H_2O. The layers were separated, and the organic layer was washed with H_2O (30 mL) and brine (30 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude ketone **36** as a yellow foam. Purification was accomplished by flash chromatography on a 2.5 × 15 cm column, eluting with a solvent gradient of 5%, 10%, 15%, and 20% EtOAc/hexanes, collecting 8 mL fractions. The product-containing fractions (22−41) were collected and concentrated to yield 304 mg (75% yield) of ketone **36** as a white foam and a mixture of diastereomers: one diastereomer, $[\alpha]_D$ + 9.1 (*c* 5.3, $CHCl_3$); R_f 0.52 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 7.24 (d, J = 7.6 Hz, 2H), 7.06 (t, J = 7.8 Hz, 2H), 6.91 (s, 1H), 6.84 (t, J = 7.3 Hz, 1H), 6.09 (d, J = 8.5 Hz, 2H), 5.38 (s, 1H), 5.00 (ABq, ΔAB = 16.1 Hz, J = 12.5 Hz, 2H), 4.87 (d, J = 6.6 Hz, 1H), 4.56−4.62 (m, 3H), 4.38 (br m, 1H), 3.92 (d, J = 0.7 Hz, 1H), 3.23 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H), 1.01 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 190.7, 152.5, 148.2, 147.4, 141.4, 137.8, 128.3, 128.2, 127.5, 125.3, 109.8, 105.3, 104.5, 101.9, 97.0, 93.1, 79.1, 78.8, 75.9, 74.6, 72.9, 56.2, 28.1, 25.7, 25.4, 18.1, −3.86, −5.20; IR ($CHCl_3$) 1695 cm^{-1}; HRMS *m*/*z* (EI) calcd $C_{32}H_{43}NO_{10}Si$ 629.2654, obsd 629.2692.

Preparation of [(4*S*,12*S*,12a*S*,11b*R*,3a*R*,4a*R*)-4-(Methoxymethoxy)-2,2-dimethyl-6-(1,1,2,2-tetramethyl-1-silapropoxy)(4,12,11b,12a,3a,4a-hexahydro-9*H* -1,3-dioxoleno[4′′,5′′-7′,6′]isochromano[4′,3′-5,4]benzo[1,2-*d*]1,3-dioxolan-12-yl)](phenylmethoxy)amine (38). To a stirring solution of ketone **36** (195 mg, 0.310 mmol) in 5 mL of MeOH at room temperature was added $NaBH_4$ (12.0 mg, 0.310 mmol) in one portion. After 2 h, 5 mL of CH_2Cl_2 was added, followed by 5 mL of a saturated NH_4Cl solution. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure to yield the crude alcohol (205 mg) which was used in the next step without further purification.

To a stirring solution of the crude alcohol prepared above in 6 mL of 1,2-dichloroethane were added 4-(dimethylamino)-pyridine (20.0 mg, 0.160 mmol) and 1,1′-thiocarbonyldiimidazole (285 mg, 1.60 mmol) at room temperature. The reaction was then heated at a gentle reflux for 14 h. The mixture was cooled to room temperature, diluted with 10 mL of CH_2Cl_2, and quenched with 15 mL of a saturated NH_4Cl solution. The layers were separated, and the organic layer was washed with 20 mL of H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was dissolved in 30 mL of EtOAc, filtered through a plug of silica gel (slurry packed in EtOAc), and concentrated under reduced pressure to yield 177 mg (77%) of the thionocarbamate **37** as a light yellow foam.

To a solution of the thionocarbamate prepared above (83.0 mg, 0.110 mmol) in 2 mL of toluene (degassed with N_2 for 20 min) at reflux were added 2,2-azobis[2-methylpropionitrile] (10.0 mg, 0.060 mmol) and tri-*n*-butyltin hydride (160 mg, 0.550 mmol) in 2 mL of toluene (degassed with N_2 for 20 min) over 4 h via syringe pump. After complete addition, the residual contents of the syringe and needle were added to the reaction. After an additional 30 min at reflux, the resulting clear solution was cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by

flash chromatography on a 1.3 × 20 cm column, eluting with a solvent gradient of 5%, 10%, 12%, 15%, and 20% EtOAc/hexanes, collecting 5 mL fractions. The product-containing fractions (29−40) were collected and concentrated to yield 49.0 mg (72% yield) of **38** (3:1 mixture of lactol isomers) as a clear colorless oil: major isomer, $[\alpha]_D$ +29.3 (*c* 2.50, $CHCl_3$); R_f 0.49 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.26−7.39 (m, 5 H), 6.95 (s, 1 H), 6.75 (s, 1 H), 5.93 (ABq, ΔAB = 3.4 Hz, J = 1.4 Hz, 2 H), 5.88 (br d, J = 1.7 Hz, 1 H), 5.81 (s, 1 H), 4.75−4.86 (m, 4 H), 4.64 (dd, J = 8.6, 6.4 Hz, 1 H), 4.22 (t, J = 6.1 Hz, 1 H), 3.99−4.06 (m, 2 H), 3.39 (s, 3 H), 3.23 (ddd, J = 11.5, 8.7, 1.5 Hz, 1 H), 2.88 (dd, J = 11.4, 3.2 Hz, 1 H), 1.48 (s, 3 H), 1.38 (s, 3 H), 0.91 (s, 9 H), 0.17 (s, 3 H), 0.13 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 147.1, 146.9, 137.4, 131.6, 128.4, 128.3, 127.8, 126.6, 109.6, 109.5, 106.2, 100.9, 96.1, 95.1, 77.2, 76.8, 76.1, 75.5, 74.1, 62.6, 55.7, 35.9, 28.1, 25.8, 17.5, 13.6, −3.8, −5.0; HRMS *m*/*z* (EI) calcd $C_{32}H_{45}NO_9Si$ 615.2861, obsd 615.2865.

Preparation of *N*-[(12*S*,12a*S*,4*R*,11b*R*,3a*R*,4a*R*)-4-(Methoxymethoxy)-2,2-dimethyl-6-oxo(4,12,11b,12a,3a,4a-hexahydro-9*H*-1,3-dioxoleno[4″,5″-7′,6′]isochromano[4′,3′-5,4]benzo[1,2-*d*]1,3-dioxolan-12-yl)]-2,2,2-trifluoro-*N*-(phenylmethoxy)acetamide (39). To a stirring solution of amine **38** (49 mg, 0.08 mmol) in 2 mL of CH_2Cl_2 at room temperature were added 4-(dimethylamino)pyridine (5.0 mg, 0.04 mmol) and pyridine (0.01 mL, 0.16 mmol), followed by trifluoroacetic anhydride (0.02 mL, 0.12 mmol). After stirring for 0.5 h, the reaction was quenched with 3 mL of a saturated $NaHCO_3$ solution. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solution was filtered through a $MgSO_4$/silica gel plug and concentrated under reduced pressure to yield 51 mg of a white foam.

To a stirring solution of the crude trifluoroacetamide (51 mg, 0.07 mmol) in 2 mL of THF at −5 °C was added a 1.0 M solution of tetrabutylammonium fluoride (0.08 mL, 0.08 mmol). After 1 h, the reaction was quenched by the addition of a saturated NH_4Cl solution and diluted with 5 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield 60 mg of the crude lactol.

To a stirring solution of the crude lactol prepared above in 3 mL of CH_2Cl_2 at room temperature were added oven-dried 4 Å molecular sieves (50 mg) and *N*-methylmorpholine *N*-oxide (13 mg, 0.11 mmol), followed by tetrapropylammonium perruthenate (2.0 mg, 0.004 mmol). After 45 min, the reaction was filtered through a plug of $MgSO_4$/silica gel (slurry packed in EtOAc), the plug was washed with EtOAc, and the filtrate was concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 1.5 × 20 cm column, eluting with a solvent gradient of 10%, 15%, 20%, and 30% EtOAc/hexanes, collecting 4 mL fractions. The product-containing fractions (28−80) were collected and concentrated to yield 39 mg (81% yield from **38**) of the lactone **39** as a white foam: R_f 0.53 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR data was very complex (possibly due to the presence of the tertiary amide); 75 MHz ^{13}C NMR ($CDCl_3$) δ 163.0, 158.0, 152.6, 148.3, 133.0, 129.2, 129.0, 128.7, 121.5, 118.5, 115.7 (q, J_{CF} = 286 Hz), 110.2, 110.0, 107.8, 102.2, 96.7, 78.0, 77.9, 77.2, 72.3, 72.1, 63.4, 56.1, 35.2, 28.3, 25.9; IR ($CHCl_3$) 1722, 1697 cm^{-1}; HRMS *m*/*z* (EI) calcd $C_{28}H_{28}NO_{10}F_3$ 595.1370, obsd 595.1358.

Preparation of *N*-[(12a*S*,4*R*,12*R*,11b*R*,3a*R*,4a*R*)-4-(Methoxymethoxy)-2,2-dimethyl-6-oxo(4,12,11b,12a,3a,4a-hexahydro-9*H*-1,3-dioxoleno[4″,5″-7′,6′]isochromano[4′,3′-5,4]benzo[1,2-*d*]-1,3-dioxolan-12-yl)]-2,2,2-trifluoroacetamide (40). To a stirring suspension of samarium metal (36 mg, 0.24 mmol) in 4 mL of THF was added iodine (43 mg, 0.17 mmol) in one portion. After 1 h at gentle reflux, the dark blue solution was cooled to −20 °C, and the lactone **39** (34 mg, 0.06 mmol) in 1.5 mL of THF was added via cannula. The solution was allowed to slowly warm to 0 °C over a 2.5 h period. The reaction was quenched with 2 mL of a saturated $Na_2S_2O_3$ solution and diluted with 2 mL of CH_2Cl_2. The layers were separated, the aqueous was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 1.5 × 10 cm column, eluting with a solvent gradient of 10%, 20%, 30%, 40%, and 50% EtOAc/hexanes, collecting 3 mL fractions. The product-containing fractions were collected and concentrated to yield 25 mg (86% yield) of trifluoroacetamide **40** as a colorless solid: mp 118−121 °C; $[\alpha]_D$ +52.7° (*c* 0.11, $CHCl_3$); R_f 0.22 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.61 (s, 1H), 6.05 (s, 2H), 4.79−4.71 (m, 3H), 4.55 (dd, J = 9.0, 5.1 Hz, 1H), 4.42−4.38 (m, 2H), 3.77 (ddd, J = 12.2, 11.7, 8.8 Hz, 1H), 3.47 (dd, J = 12.2, 2.7, 1H), 3.39 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 163.2, 158.0, 152.5, 148.2, 135.3, 131.5, 118.3, 110.2, 109.8, 107.5, 102.3, 96.7, 77.2, 76.1, 74.4, 72.3, 56.1, 53.9, 35.9, 28.3, 25.9; ^{19}F NMR ($CDCl_3$) δ 116.8; IR; HRMS *m*/*z* (EI) calcd $C_{21}H_{22}NO_9F_3$ 489.1245, obsd 449.0929 (C_3H_4).

Preparation of 7-Deoxypancratistatin (2). To a stirring solution of amide **40** (19 mg, 0.04 mmol) in 1 mL of MeOH was added DOWEX-H$^+$ (50W-X8) resin (40 mg), and the mixture was heated at 70 °C for 5.5 h. After cooling to room temperature, the mixture was filtered through a silica gel/Celite pad and the pad was washed with MeOH. The solvent was removed under reduced pressure to yield 13 mg of the triol amide, which was used in the next reaction without further purification.

To a stirring solution of the triol amide prepared above in 1 mL of anhydrous MeOH was added K_2CO_3 (70 mg, 0.51 mmol). The mixture was heated at 70 °C for 19 h and then cooled to room temperature and filtered. The filtrate was acidified with excess DOWEX-H$^+$ resin (50 mg) to a pH = 5 by litmus paper and then filtered and concentrated under reduced pressure. The resulting white solid was purified by flash chromatography on a 0.6 × 4 cm column, eluting with 30%, 50%, and 75% MeOH/$CHCl_3$, collecting 0.5 mL fractions. The product-containing fractions were collected and concentrated to yield 7-deoxypancratistatin (9 mg, 75% yield) as a white film: $[\alpha]_D$ +74.6° (*c* 0.85, DMF); R_f 0.44 (30% MeOH/$CHCl_3$); 300 MHz ^{1}H NMR (DMSO) δ 7.31 (s, 1 H), 6.91 (s, 1 H), 6.87 (br s, 1 H), 6.07 (s, 2 H), 5.41 (d, J = 3.9 Hz, 1 H), 5.05 (d, J = 5.6 Hz, 2 H), 4.82 (d, J = 7.6 Hz, 1 H), 4.32 (m, 1 H), 3.97 (m, 1 H), 3.85 (m, 1 H), 3.69 (m, 2 H), 2.98 (br d, J = 9.8 Hz, 1 H); 75 MHz ^{13}C NMR (DMSO) δ 164.1, 150.6, 145.9, 135.4, 123.8, 106.8, 105.5, 101.6, 73.4, 70.4, 70.2, 68.7, 50.4, 40.3; HRMS *m*/*z* (EI) calcd $C_{14}H_{15}NO_7$ 309.0848, obsd 309.0855

Preparation of Tetraacetate 41. To a stirring solution of 7-deoxypancratistatin (**2**) (9.0 mg, 0.03 mmol) in 1 mL of CH_2Cl_2 at room temperature were added pyridine (0.02 mL, 0.30 mmol), 4-(dimethylamino)pyridine (1.0 mg), and acetic anhydride (0.03 mL, 0.30 mmol). The solution was stirred for 7 h and then diluted with CH_2Cl_2 and quenched with a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude solid was purified by flash chromatography on a 0.6 × 6.5 cm column, eluting with a solvent gradient of 15%, 30%, 50%, and 70% EtOAc/hexanes, collecting 1 mL fractions. The product-containing fractions (29−41) were collected and concentrated to yield **41** (9 mg, 65% yield) as a colorless solid: mp 180−184 °C; $[\alpha]_D$ + 68.4° (*c* 0.5, $CHCl_3$); R_f 0.29 (75% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 6.54 (s, 1H), 6.24 (brs, 1H), 6.02 (ABq, ΔAB = 3.98 Hz, J = 1.3 Hz, 2H), 5.56 (brt, J = 2.9 Hz, 1H), 5.44 (brt, J = 3.0 Hz, 1H), 5.21 (t, J = 2.9 Hz, 1H), 5.16 (dd, J = 10.8, 3.5 Hz, 1H), 4.27 (dd, J = 13.0, 10.8 Hz, 1H), 3.44 (dd, J = 13.0, 2.6 Hz, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 169.9, 169.6, 169.0, 168.3, 164.9, 151.8, 147.3, 131.5, 123.2, 108.5, 103.7, 101.9, 71.7, 67.7, 66.9, 66.3, 48.2, 39.5, 20.8, 20.7, 20.6, 20.5; IR; HRMS *m*/*z* (EI) cacld $C_{22}H_{23}NO_{11}$ 477.1270, obsd 477.1272.

Preparation of (7*R*)-7-((1*R*){(5*S*,4*R*)-5-[(1*Z*)-2-Aza-2-(phenylmethoxy)vinyl]-2,2-dimethyl(1,3-dioxolan-4-yl)}-

(methoxymethoxy)methyl)-8-hydroxy-2*H* -1,3-dioxoleno-[4,5-*g*]isochroman-5-one (33). To a stirring solution of keto−aldehyde **32** (380 mg, 0.602 mmol) in 8 mL of THF was added a solution consisting of HF·pyridine (11.0 mL), pyridine (16.0 mL) and 8 mL of THF. The reaction was allowed to stand at room temperature for 24 h, after which time it was diluted with 50 mL of EtOAc and slowly quenched with saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with 50 mL of a saturated $CuSO_4$ solution followed by 50 mL of H_2O and finally dried over $MgSO_4$. The solution was filtered through a plug of $MgSO_4$/silica gel (slurry packed in EtOAc) and concentrated under reduced pressure. The resulting white foam was used in the next step without further purification.

To a stirring solution of the crude lactol prepared above (228 mg) in 8 mL of CH_2Cl_2 at room temperature was added Dess−Martin reagent (551 mg, 1.31 mmol) in one portion. After 3 h, the reaction was dilulted with EtOAc (20 mL) and quenched with a saturated solution (20 mL) of $NaHCO_3/Na_2S_2O_3$ (1:1). The layers were separated, and the organic layer was washed with brine (10 mL) and then dried over $MgSO_4$ and filtered through a silica gel pad with the aid of EtOAc. The resulting solution was concentrated under reduced pressure to yield the crude keto−lactone as a light yellow foam.

To a stirring solution of the keto−lactone (227 mg) prepared above, in 7 mL of MeOH at −5 °C, was added $NaBH_4$ (29.0 mg, 0.771 mmol) in one portion. The bath was removed, and the reaction was slowly warmed to room temperature over 30 min, then quenched by addition of a saturated NH_4Cl solution (15 mL), and diluted with CH_2Cl_2 (15 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 2.1 × 15 cm column, eluting with a solvent gradient of 10%, 15%, 20%, 25%, and 30% EtOAc/hexanes, collecting 6 mL fractions. The product-containing fractions (36−70) were collected and concentrated to yield the alcohol **33** (130 mg, 42% yield from keto−aldehyde **32**) as a clear colorless oil and a mixture of diastereomers: one diastereomer, $[\alpha]_D$ −13.9° (*c* 2.42, $CHCl_3$); R_f 0.22 (35% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.28−7.34 (m, 5 H), 6.83 (s, 1 H), 6.05 (ABq, ΔAB = 3.6 Hz, J = 1.4 Hz, 2 H), 5.04 (s, 2 H), 4.74−4.77 (m, 3 H), 4.54−4.63 (m, 3 H), 4.45 (d, J = 3.2 Hz, 1 H), 3.93 (dd, J = 5.0, 3.2 Hz, 1 H), 3.31 (s, 3 H), 1.53 (s, 3 H), 1.38 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 163.7, 152.4, 148.6, 148.4, 137.1, 136.9, 128.5, 128.1, 127.8, 118.4, 110.4, 109.7, 107.2, 102.1, 98.8, 78.7, 76.3, 75.9, 75.4, 75.2, 64.4, 56.4, 27.3, 25.4; IR ($CHCl_3$) 3418, 1720 cm^{-1}; HRMS *m*/*z* (EI) calcd $C_{26}H_{29}NO_{10}$ 515.1790, obsd 515.1761.

Preparation of (12a*S*,4*R*,12*R*,11b*R*,3a*R*,4a*R*)-4-(Methoxymethoxy)-2,2-dimethyl-12-[(phenylmethoxy)amino]-4,12,11b,12a,3a,4a-hexahydro-9*H* -1,3-dioxoleno[4″,5″-7′,6′]-isochromano[4′,3′-2,1]benzo[4,5-*d*]-1,3-dioxolan-6-one (35). To a stirring solution of alcohol **33** (44 mg, 0.09 mmol) in 2 mL of 1,2-dichloroethane at room temperature was added 1,1′-thiocarbonyldiimidazole (48 mg, 0.27 mmol). After 4 h, the solution was diluted with 2 mL of CH_2Cl_2 and quenched with 5 mL of a saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a $MgSO_4$/silica gel plug. The solvent was removed under reduced pressure to yield the crude thionocarbamate **34** as a light yellow foam.

To a stirring solution of the crude thionocarbamate in 1.5 mL of toluene (degassed with N_2 for 20 min) at 65 °C was added a solution of triphenyltin hydride (0.07 mL, 0.27 mmol) and 2,2-azobis[2-methylpropionitrile] (5.0 mg, 0.03 mmol) in 1.5 mL of toluene (degassed with N_2 for 20 min) over 3.5 h. After complete addition, the residual syringe contents were added and the solution was stirred at 65 °C for an additional 1 h, then cooled to room temperature, and concentrated under reduced pressure. The resulting clear colorless oil was purified by flash chromatography on a 1.5 × 10 cm column, eluting with a solvent gradient of 10%, 15%, 20%, 25%, and 35% EtOAc/hexanes, collecting 4 mL fractions. The product-containing fractions (48−65) were collected and concentrated to yield amine **35** (30 mg, 70% yield from **33**) as a clear colorless oil: $[\alpha]_D$ +63.1 (*c* 1.0, $CHCl_3$); R_f 0.36 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1H), 7.26−7.38 (m, 5H), 6.92 (s, 1H), 6.04 (ABq, ΔAB = 4.73 Hz, J = 1.2 Hz, 2H), 5.75 (bs, 1H), 4.71−4.84 (m, 5H), 4.56 (dd, J = 8.9, 4.8 Hz, 1H), 4.35−4.38 (m, 2H), 3.38 (s, 3H), 3.28 (dd, J = 11.4, 2.9 Hz, 1H), 2.88 (dd, J = 11.4, 8.9 Hz, 1H), 1.45 (s, 3H), 1.40 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 163.5, 152.2, 147.9, 137.1, 136.3, 128.5, 128.3, 128.0, 118.5, 109.9, 109.3, 108.6, 102.0, 95.5, 78.4, 77.2, 76.7, 76.2, 72.9, 61.6, 55.9, 35.2, 28.3, 25.9; HRMS *m*/*z* (EI) calcd $C_{26}H_{29}NO_9$ 499.1841, obsd 499.1889.

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