Total Synthesis of (+)-Mycotrienol and (+)-Mycotrienin I: Application of Asymmetric Crotylsilane Bond Constructions

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Abstract: A highly convergent asymmetric synthesis of the ansamycin antibiotics (+)-mycotrienin I (**1c**) and (+)-mycotrienol (**1d**) has been achieved through the synthesis and coupling of the C9−C16 subunit **3b** and the aromatic subunit **4b**, respectively. This article describes the complete details of that work as it illustrates the utility of our developing chiral (*E*)-crotylsilane bond construction methodology in total synthesis. All four stereogenic centers were introduced using chiral allylsilane bond construction methodology. In the synthesis of subunit **3b**, the C12 and C13 stereocenters were installed using an asymmetric crotylsilylation reaction to α-keto dibenzyl acetal **5**. The C11 stereocenter was subsequently installed via a chelate-controlled addition of allyltrimethylsilane to establish the *anti*-1,3-diol system. The C14−C15 trisubstituted double bond was then installed via a reductive opening of α,*β*-unsaturated lactone **10b**. Aromatic subunit **4b** was chosen on the basis of its synthon equivalency to the amidobenzoquinone system of (+)-**1c** and (+)-**1d**. Subunit **4b** was constructed in a concise six-step sequence which incorporates the C3 stereogenic center of the C1−C5 side chain. The C3 stereogenic center was established using a Weinreb amidation of aniline **18** with lactone (+)-**16**, whose absolute stereochemistry was derived using the crotylsilane methodology. The union of subunit **3b** with aromatic subunit **4b** was accomplished using a sulfone-based coupling strategy. Coupling product **21** was transformed through a sequence of steps to triene **24**. Divergence from this advanced intermediate allows access to both natural products. The successful completion of the synthesis included the incorporation of the (*E*,*E*,*E*)-triene unit with simultaneous macrocyclization through a palladium (0)-catalyzed (Stille-type) coupling macrocyclization.

Introduction

A little more than a decade ago, Umezawa and co-workers reported the isolation of five novel ansamycin antibiotics, trienomycins A−E, from the culture broth of *Streptomyces* sp. No. 83-16.[1] These molecules exhibited strong cytotoxicity in vitro against HeLa S_3 cells.[2] The most potent molecule, (+)-trienomycin A (**1a**, Figure 1), along with (+)-mycotrienin I (**1c**) and II (**1e**) and the mycotrienols II (**1d**,**f**) have previously been isolated from the fermentation broth of the *Streptomyces rishirensis.* Their relative and absolute stereochemistries have been determined by Smith and co-workers through careful degradative and spectroscopic methods.[3] A stereoview of a minimized (+)-mycotrienin I (**1c**) illustrating its various structural elements is shown in Figure 2.[4] The (+)-mycotrienins I and II have displayed potent antifungal activity.[5] The structural similarities between trienomycin A, (+)-mycotrienins I and II,

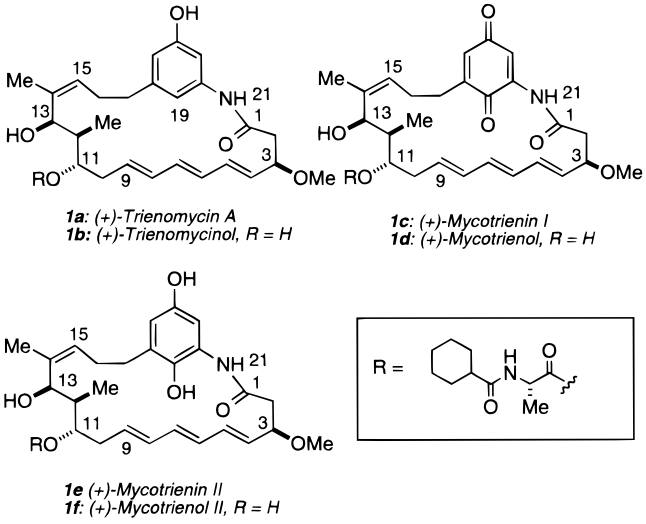

Figure 1.

and the mycotrienols provide circumstantial evidence for a common absolute stereochemistry. This prediction has been confirmed by stereochemical correlation studies where the trienomycin stereochemistry assignments were extended to (+)-mycotrienins I and II and, therefore, to the mycotrienols.[6] An intriguing aspect of the correlation studies is illustrated by the dramatic differences in biological activity of the trienomycins (antitumor activity) and mycotrienins (antifungal) derived from modification of the aromatic portion. Those structure determination−stereochemical correlation studies have laid the

(1) (a) Funyama, S.; Okada, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1107−1109. (b) Funyama, S.; Okada, K.; Iwasaki, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1677−1683. (c) Katasumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Omura, S. *J. Antibiot.* **1989**, *24*, 479−481.

(2) Umezawa, I.; Funayama, S.; Okada, K.; Iwasaki. K.; Satoh, J.; Masuda, K.; Komiyama, K. *J. Antibiot.* **1985**, *38*, 699−705.

(3) () Smith, A. B.; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 7425−7426.

(4) Three-dimensional modeling was carried out with Chem 3-D Pro using MM2 minimization techniques.

(5) (a) Sugita, M.; Natori, Y.; Sasaki, T.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1460−1466. (b) Sugita, M.; Sasaki, T.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1467−1473. For (+)-mycotrienol see: (c) Sugita, M.; Natori, Y.; Sueda, N.; Kazuo, F.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1474−1479.

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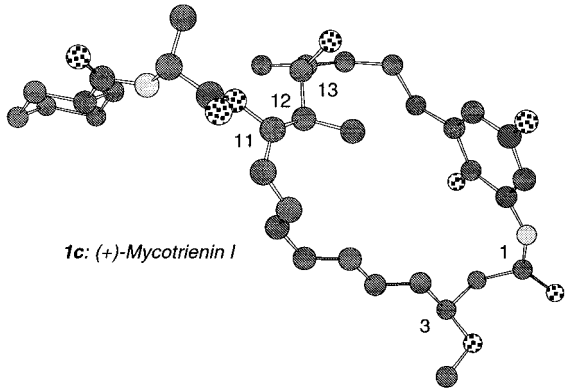


Figure 2. (+)-Mycotrienin I (3-D minimized view).

groundwork for future synthetic and biological studies. To date, Smith and co-workers have reported the only total syntheses of this class of compounds, specifically the synthesis of trienomycins A−F.[7] These structurally related molecules belong to an emerging class of ansa-bridged macrocyclic lactams that possess potent biological activity ranging from antitumor to antifungal activity. Thus, they are of particular interest because of the fact that seemingly simple modifications of the aromatic portion produces dramatic changes in the biological activity. The facts that these natural products have useful antitumor activity and are not readily available from natural sources make them excellent targets for synthesis. Biological evaluation has been limited by the lack of availability of these agents, and only modifications of the aromatic portion of the macrocyclic lactams have been addressed.

In addition, it was found that (+)-mycotrienol (**1d**) is eight times less potent than (+)-mycotrienin I (**1c**), which bears the cyclohexylcarbonyl-*δ*-alanine unit, indicating that this functionalized amino acid moiety is crucial for the biological activity of these agents. (+)-Mycotrienin I is a unique entry into this class of ansamycin antibiotics, consisting of a quinone-centered 21-membered macrocyclic lactam ring bearing a cyclohexylcarbonyl-*δ*-alanine ester functionality. Its four resident stereogenic centers and the (*Z*)-trisubstituted C14−C15 double bond render (+) mycotrienin I a difficult challenge as a target for synthesis.

Analysis of the Synthetic Plan. The synthetic plans developed for (+)-mycotrienin I were guided by the structural constraints of the molecule as well as by our intention to employ asymmetric allylsilane-based bond constructions for the installation of each of the stereogenic centers. For completeness, two retrosynthetic analyses are described in Scheme 1. The original retrosynthetic analysis of the (+)-mycotrienol skeleton is shown on the left side of Scheme 1, and the final analysis is shown on the right side. The reasoning behind the modified analysis will be discussed in the following sections. With respect to the order of fragment coupling, we intended to design flexibility into the synthetic pathways for the assemblage of the individual components of the molecule. In this regard, disconnection of the C8−C9 and N21−C1 bonds affords two fragments of complexity comparable with that of the C9−N21 section (**2a**) serving as our initial synthetic target. A phosphorus-based intermolecular Horner−Emmons olefination reaction appeared attractive in the C8−C9 bond construction due to the relatively mild conditions and the literature precedence for an (*E*)-selective olefination. The final macrolactamization step to form the N21−C1 bond may be achieved with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) which is also based on literature precedent.[8] In the interest of convergency, the C9−N21 synthon was further simplified. The decision was made to section this portion of the molecule at the C16−C17 bond which corresponds to the addition of a benzylic anion to an allylic halide. Collectively, these transformations provided a convergent approach utilizing the three illustrated subunits. It is important to emphasize that this synthetic planning was intended to illustrate the utility of chiral (*E*)-crotylsilanes[9] for the synthesis of complex molecules. As a result of close structural similarities, the synthetic analyses presented are readily applicable to other members of this class of molecules.

Synthesis of the C9−C16 Fragment. It was anticipated that the relative and absolute stereochemical relationships in this subunit might be controlled through the use of chiral (*E*)-crotylsilane bond construction methodology to establish the C12 and C13 centers of (+)-mycotrienin I. From these stereogenic centers, the adjacent center at C11 would be constructed through chelate-controlled addition of allyltrimethylsilane (Hosomi−Sakurai reaction).[10] Earlier reports by Reetz[11] and Keck[12] had established precedence for the stereochemical outcome of such a Lewis acid-promoted allylation reaction. With that in mind, the construction of the C9−C16 subunit **3a** was initiated by an asymmetric crotylation between the α-keto dibenzyl acetal **5** and silane reagent (*S*)-**6** to establish the C12−C13 centers (Scheme 2). This first addition proceeds through an antiperiplanar transition state where the observed syn stereochemistry is consistent with an anti-S_E' mode of addition (see Scheme 2). Two carbon homologation of the homoallylic ether **7** by treatment with the ester enolate of benzyl acetate gave a *β*-tertiary alcohol which was immediately converted to the tertiary acetate under standard DMAP-catalyzed acetylation conditions. Oxidative cleavage of the (*E*)-olefin by ozonolysis furnished the α-methyl aldehyde **8**. This was followed by the chelation-controlled asymmetric allylsilane addition reaction to install the C11 hydroxyl stereocenter (diastereoselection = 28:1 anti/syn). The 1,3-anti relationship is believed to arise from nucleophilic addition to a titanium chelate between the C13 benzyloxy group and the aldehyde carbonyl. Elaboration of the C14−C15 (*Z*)-double bond was initiated by cleavage of the terminal olefin to give the *β*-silyloxy aldehyde which was masked as the ethylene acetal **9a**. Cleavage of the benzyl groups via hydrogenation and simultaneous cyclization of the derived hydroxy acid gives the lactone which upon elimination of the tertiary *β*-acetoxy group with DBU gave the α,*β*-unsaturated lactone **10a**. Subsequently, the lactone was reductively opened using $LiAlH_4$ to give the (*Z*)-olefinic diol. NOE measurements on this compound supported the assignment of the olefin configuration as the (*Z*)-isomer (Scheme 3). Reduction of lactone **10a** to the corresponding diol presented a series of

(6) Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **1996**, *118*, 8308−8315. For other synthetic approaches to the trienomycins and related mycotrienins, see: (a) Yadav, J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2965−2968. (b) Fürstner, A.; Baumgartner, J. *Tetrahedron* **1993**, *49*, 8541−8560. For preliminary work conducted in our laboratories, see: Panek, J. S.; Yang, M. Y.; Solomon, J. *Tetrahedron Lett.* **1995**, *36*, 1003−1006.

(7) Smith, A. B.; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316−8328.

(8) Evans, A. D.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067−1069.

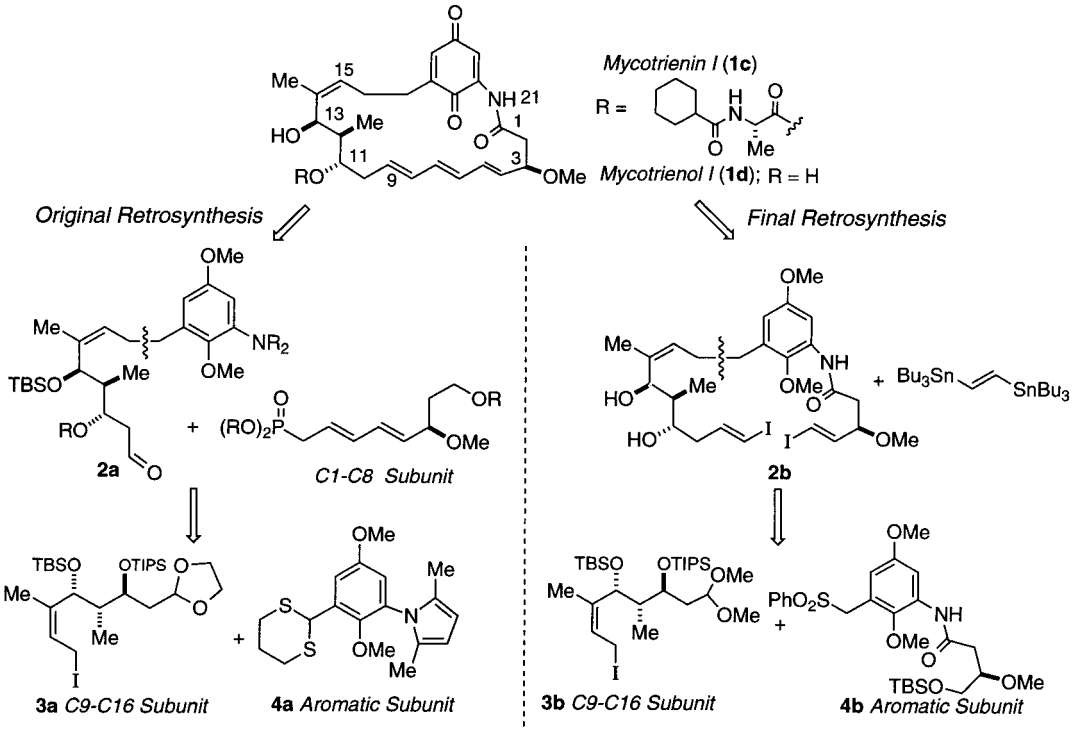
(9) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78−88.

(10) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295−1298.

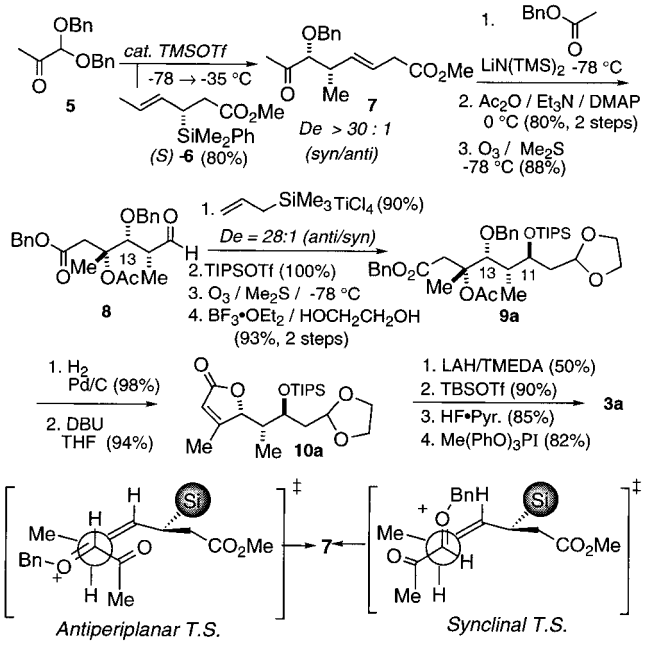
(11) For a discussion of chelation-controlled carbonyl addition, see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

(12) (a) Keck, G. E.; Murry, A. J. *J. Org. Chem.* **1991**, *56*, 6606−6611. (b) Keck, G. E.; Abbot, D. E.; Boden, E. P. *J. Org. Chem.* **1986**, *51*, 5478−5480.

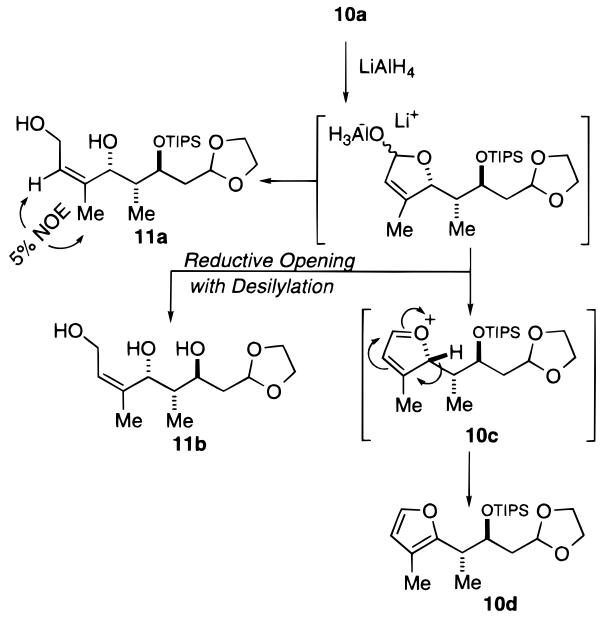
Scheme 1



Scheme 2



Scheme 3



problems with the different reducing agents that were employed. Attempts to open the lactone using both DIBAL-H and $LiAlH_4$/$AlCl_3$ repeatedly gave mixtures of unidentifiable products including desilylated materials at a variety of temperatures (−78 °C → room temperature (rt)). Lithium trialkoxyaluminum hydrides provided only starting lactone even with gentle warming. Reduction with $LiAlH_4$/TMEDA proved to be the most successful at providing **11a** as the major product. Two side products have been isolated from this reaction and fully characterized. They have been identified as triol **11b** and furan **10d** as shown in Scheme 3. We tentatively conclude that the oxocarbenium ion **10c** is one of the intermediates leading to furan formation. In an effort to optimize the reaction conditions for the $LiAlH_4$ reduction of **10a**, four different sets of reaction conditions were surveyed. A summary of these experiments is given in Table 1. After an extensive screening of reaction variables, a $LiAlH_4$/TMEDA combination provided the highest yield (70%) of **11a** with minimal amounts of furan **10d** produced. Table 1 summarizes the lactone opening experiments.

Finally, protection of the primary and secondary hydroxyl groups of **11a** as their TBS ethers, selective deprotection of the primary TBS ether with HF·pyridine, and conversion to the allylic iodide completes the construction of **3a** containing the cyclic ethylene acetal.

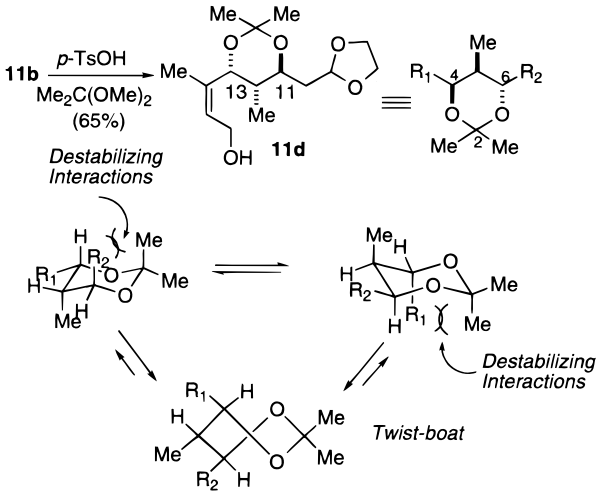
In view of our need to confirm the stereochemical assignment of the newly generated C11 stereocenter, triol **11b** was converted to the diastereomerically pure acetonide **11d** in 65% yield (Scheme 4). At this juncture, the stereochemistry of the allylsilane−aldehyde condensation reaction was determined. The

Table 1. Lithium Aluminum Hydride Reduction of the Lactone **10a**[a]

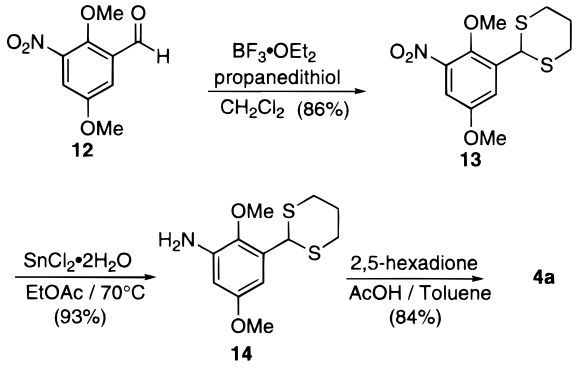
entry	solvent	temp (°C)	% yield[b] of **11a**	% yield[b] of **11b**	% yield[b] of **10d**
1	Et_2O	−15	10	10	45
2	Et_2O/5 equiv of TMEDA	0	50	15	30
3	*Et_2O/20 equiv of TMEDA*	*0*	*70*	*20*	*10*
4	Et_2O	24	15	35	40

[a] Two equivalents of $LiAlH_4$ were used for all reactions. [b] All yields are based on pure materials isolated by chromatography on SiO_2.

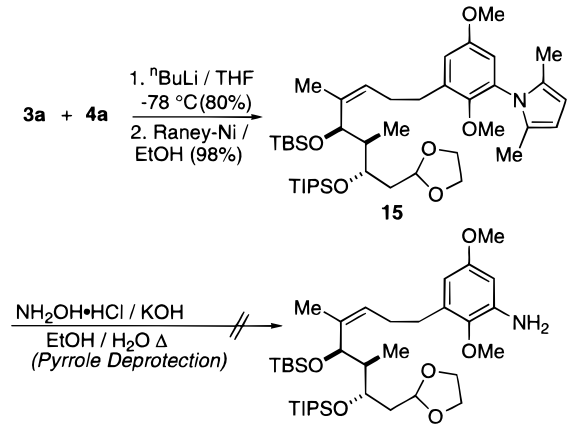
Scheme 4



Scheme 5



Scheme 6



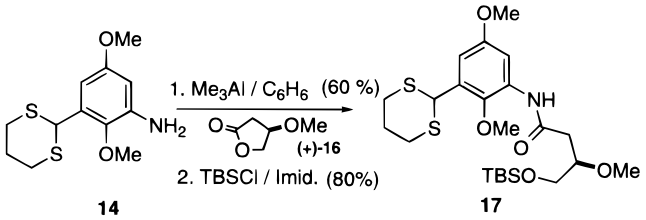
^{13}C NMR method for the stereochemical identification of 1,3-diols relies on the conformational properties of the derived 1,3-diol acetonides and has been developed and utilized by Rychnovsky and Evans research groups.[13] The C(2)-acetal ^{13}C chemical shift of compound **11d** was 101.1 ppm, and the chemical shifts of the two acetonide methyl groups were observed to be 24.6 and 24.0 ppm, in excellent agreement with the values commonly observed for an *anti*-1,3-diol acetonide. No resonances were observed in the regions expected for a *syn*-1,3-diol acetonide. The stereochemical correlation is only reliable where the *syn*- and *anti*-1,3-diol acetonides adopt different conformations. Virtually any syn acetonide will adopt a chair conformation,[14] but the anti acetonide will only adopt the twist-boat conformation when the chair conformation is strongly destabilized. When R_1 and R_2 are large (e.g., R_1, R_2 = CH_2R) the 1,3-diaxial interaction with the appropriate C(2)-methyl destabilizes both of the possible chair conformations and forces the acetonide to adopt a twist-boat conformation.[15]

Synthesis of the Aromatic Core. The design of the aromatic core was centered around generating an intermediate that would couple with the C9−C16 fragment while maintaining adequate functionalization for its conversion to the amido-quinone. To implement this idea, the primary allylic iodide of C9−C16 synthon was installed with the intention of displacing it with a strong nucleophile, thus effecting a useful one-step alkylation procedure. The aromatic core was constructed from 2,5-dimethoxy-3-nitrobenzaldehyde (**12**)[16] (Scheme 5). This aromatic substitution pattern was chosen for its synthon equivalency and ease of conversion to the amido−benzoquinone system of mycotrienol. On the basis of literature precedent,[17] we chose to employ the six-membered cyclic dithioacetal **4a** as the precursor nucleophile. The three-step synthesis of **4a** (Scheme 5) begins with the boron trifluoride etherate ($BF_3{\cdot}OEt_2$)-promoted thioacetal formation with 1,3-propanedithiol from the known 2,5-dimethoxy-3-nitrobenzaldehyde[16] to give the cyclic 1,3-dithiane **13** in good yield. The coupling reaction with allylic iodide **3a** would require the use of a strong base and precludes the presence of the nitro functionality, which was therefore reduced to the corresponding amine **14** via $SnCl_2{\cdot}2H_2O$ in EtOAc at 70 °C.[18] The final step in the construction of this synthon was the protection of the arylamine as a 2,5-dimethylpyrrole,[19] which was accomplished by refluxing **14** with excess 2,4-hexadione and a catalytic amount of acetic acid in toluene. This sequence provided the functionalized aromatic subunit **4a** in 68% overall yield.

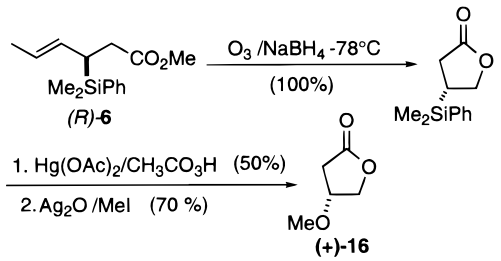
Initial Coupling Strategy for the C9−C16 and Aromatic Fragments. With the allylic iodide **3a** and aromatic synthon **4a** available, the two subunits were assembled according to the alkylation procedure outlined in Scheme 6.[20] The coupling procedure consisted of low-temperature deprotonation of the dithioacetal **4a** with ^{n}BuLi to form the lithiodithiane anion which was alkylated with allylic iodide **3a**. The coupling reaction proceeded cleanly at −78 °C in 1.5 h to give the desired dithioketal in 80% yield. The dithioketal was then cleaved by treatment with a 50% slurry of W-7 Raney nickel in ethanol under a hydrogen atmosphere, giving rise to the coupling product

(13) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948.
(14) Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 2931−2971.
(15) Pihlaja, K.; Nurmi, T. *Isr. J. Chem.* **1980**, *20*, 160−167.
(16) For the preparation of **12** as well as its conversion to the quinone core, see: Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587−10588.
(17) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231−237.
(18) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839−842.
(19) Bruekelman, S. P.; Leach, S. E.; Mealkins, G. D.; Tirel, M. D. *J. Chem. Soc., Perkins Trans. 1* **1984**, 2801−2805.
(20) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231−237.

Scheme 7



Scheme 8



15. The desulfurization proceeded cleanly with no apparent reduction of the (*Z*)-olefin.

The next stage in the synthesis required the deprotection of the dimethylpyrrole to expose the masked arylamine functionality for further elaboration. This deprotection was attempted using $NH_2OH{\cdot}HCl/KOH$ in aqueous ethanol according to literature precedent.[21] However, all attempts at this deprotection provided only low yields (<10%) of the desired product. The major side product involved deprotection and subsequent elimination of the C11 TIPS silyl ether. At this point, it was decided to elaborate the C1−C5 side chain at an earlier stage by attaching this subunit to the aromatic core prior to coupling with the C9−C16 fragment. A precedent for this type of bond construction had been reported by Smith and co-workers relative to the synthesis of the trienomycins A and F.[22] The procedure involved a Weinreb amidation of the precursor aniline aromatic core with a γ-lactone containing the C3 stereogenic center. Thus, aniline **14** was subjected to a Weinreb-type amidation[23] with lactone **16** and the resulting amido−alcohol protected as its TBS ether (Scheme 7). Lactone (+)-**16** was also readily prepared using the crotylsilane methodology. Lactone (+)-**16** has also been prepared from D-malic acid in four steps;[22] however, we decided to outline a more concise and cost-effective scheme where its absolute chirality is derived from the (*E*)-crotylsilane reagents. Therefore, ozonolysis of silane (*R*)-**6** and in situ reduction of the derived silyl aldehyde afforded the β-silyl lactone which was subjected to silyl to hydroxyl interconversion[24] and methylation[25] to afford lactone (+)-**16** (Scheme 8). This Lewis acid-promoted lactone opening installed the C1−C5 side chain bearing the C3 stereogenic center of the aromatic core and eliminates the need for arylamine *N*-protection at any stage of the synthesis.

We next turned our attention to the critical union of the C9−C16 iodide **3a** with the newly elaborated aromatic core **17**. Unfortunately, slow addition of 2.2 equiv of ^{n}BuLi to a solution

Scheme 9

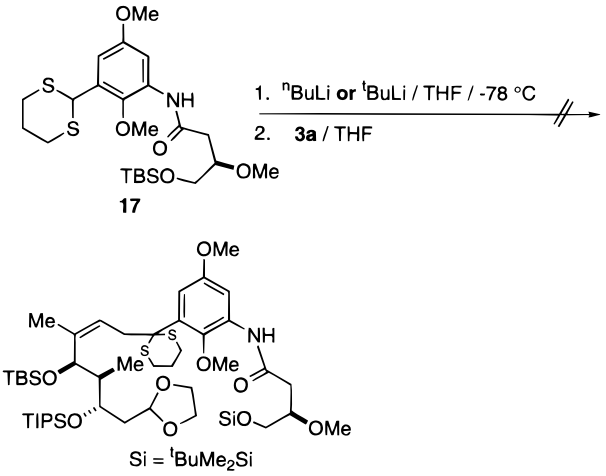
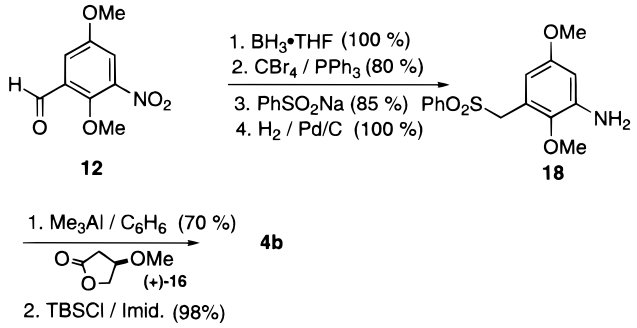


Table 2. Unsuccessful Coupling Attempts with 1,3-Dithiane **17**

entry	deprotection conditions	solvent system	electrophile	result[a]
1	^{n}BuLi/−78 °C	THF	**3a**	NR
2	^{t}BuLi/−78 °C	THF	**3a**	NR
3	^{n}BuLi/−78 °C	THF/10% HMPA	**3a**	NR
4	^{n}BuLi/−78 °C	THF/10% DMPU	**3a**	NR
5	^{n}BuLi/−78 °C	THF	allyl bromide	NR
6	^{n}BuLi/−78 °C	THF	benzyl bromide	NR

[a] NR = starting materials recovered.

Scheme 10



of **17** in THF (−78 °C), followed by slow addition of **3a** failed to provide the required coupling product. Attempts to effect the coupling with ^{t}BuLi, additives such as 10% (v/v) HMPA/DMPU, or other electrophiles (e.g., allylbromide, benzyl bromide) provided none of the desired coupling product (Scheme 9, Table 2).

At this point, we elected to investigate a more reactive and reliable dianion precursor for the coupling procedure. This involved replacement of the dithiane functionality with a phenyl sulfone. The prior work of Smith and co-workers had established that such benzylic sulfones could successfully alkylate allylic halides.[22]

Construction and Coupling of the Sulfone Aromatic Core. The construction of the new aromatic core also originates from 2,5-dimethoxy-3-nitrobenzaldehyde (**12**) (Scheme 10). This aromatic substitution pattern was chosen for its synthon equivalency and ease of conversion to the amido−benzoquinone system of (+)-mycotrienol. Borane reduction of the aldehyde, conversion to the benzylic bromide, displacement with sodium benzenesulfinate, and reduction of the nitro group furnished the benzylic sulfone **18**. Completion of subunit **4b** was achieved

(21) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47−65.

(22) Smith, A. B., III, Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777−10778.

(23) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1988**, *6*, 492−495.

(24) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317−321. (b) For a review, see: Fleming, I. *Chemtracts: Org. Chem.* **1996,** *9*, 1−64.

(25) Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 2003−2005.

Scheme 11

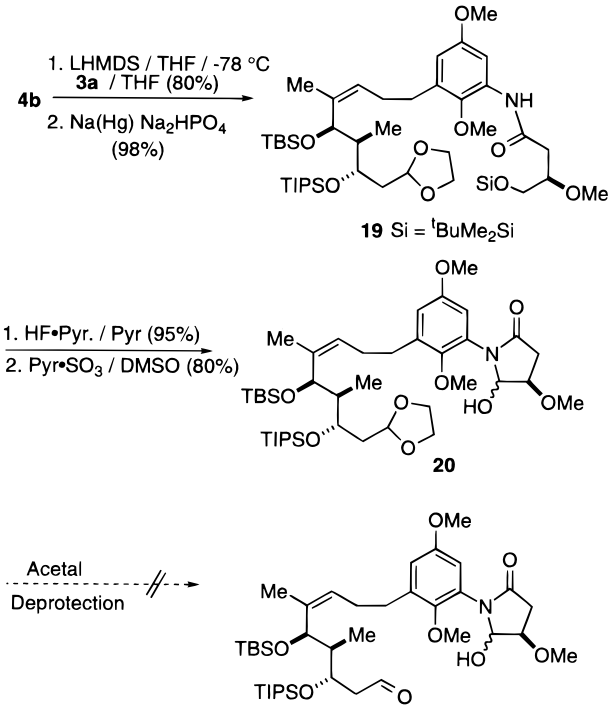


Table 3. Deprotection Attempts of Acetal **20**

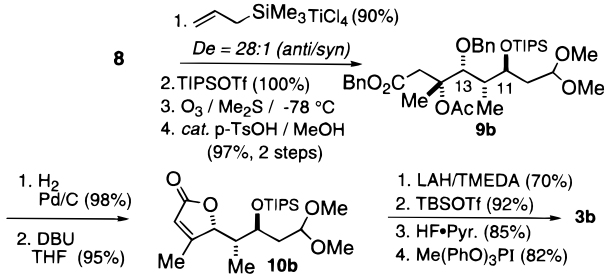
deprotection conditions	result[a]
1. $FeCl_3$•SiO_2, acetone/H_2O (10:1)	NR[b]
2. *cat. p*-TsOH, THF/H_2O (50:1)	2° TIPS deprotection
3. $LiBF_4$/2% wet CH_3CN	NR[b]
4. PPTS wet acetone, reflux	NR[b]
5. H_5IO_6, dioxane/H_2O (10:1)	silyl deprotection (1° and 2°)
6. DMSO/H_2O, 145 °C	decomposition of substrate
7. Dowex-X8, THF/H_2O (1:1)	NR[b]

[a] Based on materials isolated from SiO_2 chromatography. [b] Recovered starting material.

by Weinreb-type amidation[26] of the derived aniline with the chiral lactone **16** and protection of the primary hydroxyl as its TBS ether.

We then redirected our attention to the coupling of the C9−C16 iodide **3a**, with the sulfone aromatic core **4b**. Deprotonation of the latter with LHMDS (2.2 equiv) at −78 °C generated the stable lithium dianion which was efficiently alkylated at the benzylic position by the allylic iodide **3a** (1 equiv); reductive desulfonylation gave adduct **19** (Scheme 11). Selective deprotection of the primary TBS ether of **19** with HF•-pyridine was followed by a Parikh−Doering oxidation[27] of the derived primary alcohol to give the *N*-acyl hemiaminal **20**. We next began to explore the hydrolysis of the ethylene acetal to set the stage for the construction of the (*E*,*E*,*E*)-diene system. However, numerous attempts to deprotect the ethylene acetal under a variety of conditions (see Table 3) failed to provide any of the requisite aldehyde as competing desilylation of the secondary hydroxyl groups at C11 and C13 complicated the acetal deprotection step. Due to the difficulties associated with the selective deprotection of the ethylene acetal, we felt the need to tune the reactivity of the acetal protecting group. We opted to change the ethylene acetal to a more labile dimethyl acetal in an effort to effect a more facile cleavage of the this protecting group. In fact, our expectation that the dimethyl acetal would hydrolyze more readily was supported by a recent work from the Danishefsky group.[28] This protecting group change requires only a minor modification in the synthesis of the C9−C16 subunit. In this modified scheme, aldehyde **8** is elaborated through a similar sequence in which the aldehyde derived from ozonolysis of the terminal olefin is treated with catalytic *p*-TsOH in anhydrous methanol to furnish dimethyl acetal **9b** (Scheme 12). In a sequence analogous to Scheme 3, cleavage of the benzyl groups via hydrogenation and simultaneous cyclization of the derived hydroxy acid gives the lactone which upon elimination of the tertiary β-acetoxy group with DBU gave the α,β-unsaturated lactone **10b**. As described earlier, the lactone was reductively opened using $LiAlH_4$ to give the (*Z*)-olefinic diol. Differentiation of the primary and secondary hydroxyl groups as their TBS ethers and conversion to the allylic iodide completed the construction of allylic iodide **3b**.

Scheme 12



Coupling of Allylic Iodide 3b and Aromatic Sulfone 4b: Completion of the Total Synthesis of (+)-Mycotrienol. Coupling of the final subunits was accomplished by deprotonation of sulfone **4b** with LHMDS to generate a stable lithium dianion which was efficiently alkylated at the benzylic position by allylic iodide **3b** (Scheme 13); reductive desulfonylation gave adduct **21**. At this stage, we chose to explore a "stitching cyclization" to elaborate the (*E*,*E*,*E*)-triene of (+)-mycotrienin I via a Stille-type protocol of a bis(vinyl iodide) and an enedistannane. This type of macrocyclization technique had been successfully utilized in the synthesis of both rapamycin[29] and dynemicin.[30] With the coupling product in hand, we initiated construction of the key bis[(*E*,*E*)-vinyl iodide] (**2b**) for macrocyclization. Selective deprotection of the primary TBS ether was followed by a Parikh−Doering oxidation[27] of the derived primary alcohol to give the *N*-acyl hemiaminal. Gratifyingly, the dimethyl acetal was readily hydrolyzed with PPTS and wet acetone[31] to give the aminal−aldehyde. Homologation of the resulting aldehyde using the Takai protocol[32] furnished the bis[(*E*,*E*)-vinyl iodide] **22** as the key cyclization substrate. An (*E*,*E*) ratio of >10:1 was established in this Takai homologation on the basis of ^{1}H NMR analysis of **22**. This set the stage for the crucial Stille-type "stitching" macrocyclization of **22** with the missing two-carbon enedistannane **23**[33] (C6−C7) to give the (*E*,*E*,*E*)-triene and completing the synthesis of the fully functionalized macrolide of (+)-mycotrienol. Subse-

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(27) Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(28) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801−2803.

(29) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420.

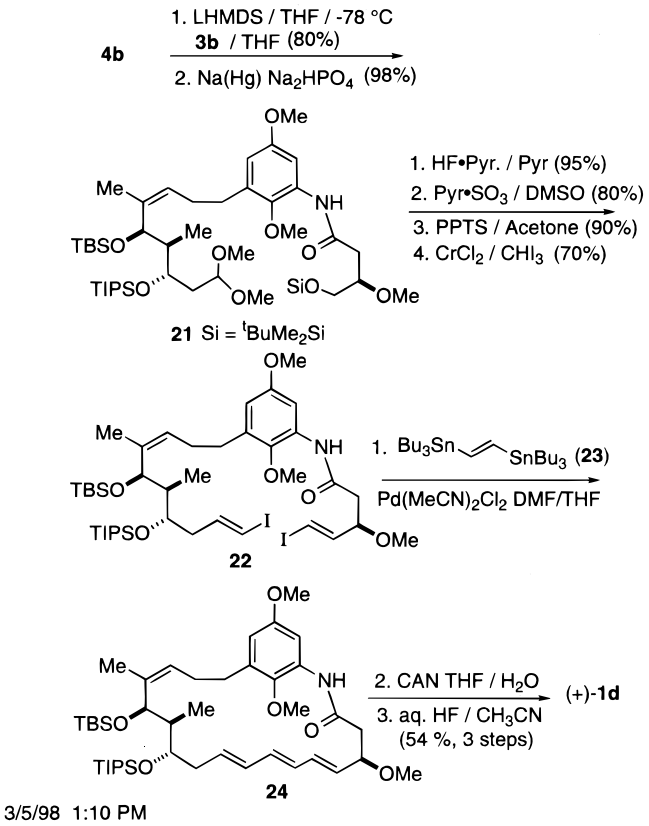
(30) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755−3757.

(31) Sterzycki, R. *Synthesis* **1979**, 724−725.

(32) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(33) For the preparation of enedistannane **23**, see: Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581−5583.

Scheme 13



quent oxidation of the aromatic core with ceric ammonium nitrate (CAN) and removal of the silicon protecting groups with aqueous HF furnished synthetic (+)-mycotrienol (**1d**).

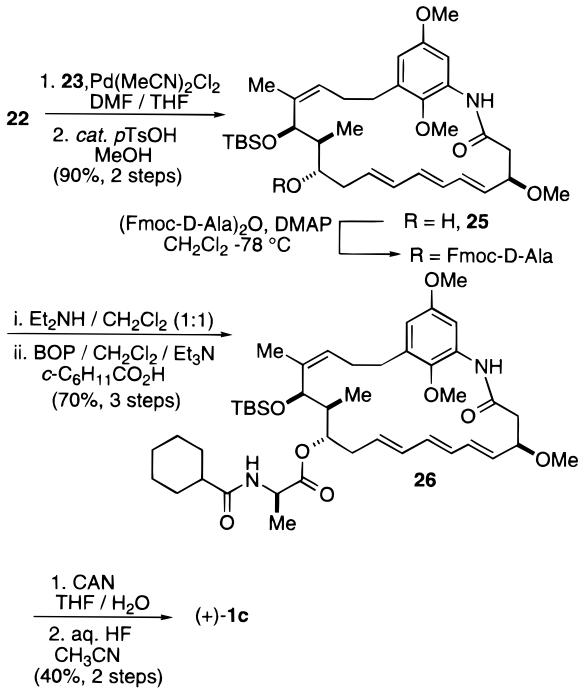
Total Synthesis of (+)-Mycotrienin I. The completion of (+)-mycotrienin would ideally involve selective deprotection of the C11 TIPS group of **24** followed by acylation of the C11 hydroxy with the cyclohexylcarbonyl-*δ*-alanine ester functionality. During the course of the selective deprotection studies for ethylene acetal **20**, we had discovered that the use of cat. *p*-TsOH in methanol cleanly afforded selective deprotection of the secondary TIPS group on C11 without deprotection of the C13 secondary TBS group (entry 2, Table 2). Gratifyingly, exposure of the (*E*,*E*,*E*)-triene to these conditions effected selective deprotection of the C11 TIPS group as expected. Installation of the amino acid side chain according to literature precedent[34] and desilylation gave (+)-mycotrienin I (**1c**) (Scheme 14). Both **1c,d** were identical in all respects with the corresponding natural products (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation, and TLC in two solvent systems).[5]

Conclusion

The asymmetric synthesis of (+)-mycotrienol has been achieved in 32 steps with an overall yield of 3%. The synthesis of (+)-mycotrienin I was achieved in 35 steps with an overall yield of 1.5%. The synthesis plan is noteworthy in that all four resident stereogenic centers were established through the crotylsilane-based bond constructions whereas previous efforts have relied on enolate-based methods and the chiral pool. Additionally, the final macrocyclization was achieved through a tandem Stille coupling procedure affording the macrocycle with a configurationally pure (*E*,*E*,*E*)-triene. The synthetic plan presented here allows access to the remaining members of this class of compounds as well as other potentially biologically active analogues via one centralized intermediate.

(34) Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Omura, S.; Komiyama, K. *Tetrahedron Lett.* **1991**, *32*, 1627−1630.

Scheme 14



Experimental Section

Pyruvate Aldehyde Dibenzyl Acetal (5). To a flask containing pyruvate aldehyde dimethyl acetal (10 g, 84.7 mmol) were added benzyl alcohol (20.1 g, 186 mmol, 2.2 equiv) and *p*-toluenesulfonic acid (380 mg, 4.2 mmol, 0.05 equiv) without solvent. The mixture was heated to 80 °C with stirring in an open flask. Over a 20-h period, the methanol generated was allowed to evaporate into the fume hood. After the reaction was complete, the flask was cooled and the crude oil subject to purification on SiO_2 (2.5 → 5% EtOAc/PE) to afford **5** as a light yellow oil (12.6 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 10H), 4.72 (s, 1H), 4.68 and 4.63 (ABq, 4H, J_{AB} = 11.8 Hz), 2.24 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 136.8, 128.4, 127.9, 100.8, 69.1, 24.9; IR (neat) ν_{max} 3400, 3000, 2850, 1760, 1450, 1350; CIHRMS M + NH_4^+ (calcd for $C_{17}H_{22}NO$) 288.1600, found 288.1600.

(3*E*,5*R*,6*R*)-Methyl-6-(benzyloxy)-5-methyl-7-oxo-3-octenoate (7). A solution of **5** (6.00 g, 22.9 mmol) in 23 mL of CH_2Cl_2 (1.0 **M**) was cooled to −78 °C and treated with TMSOTf (1.30 mL, 6.87 mmol, 0.30 equiv). The light yellow solution was stirred for 5 min and then treated with a solution of (*S*)-**6** (6.20 g, 22.9 mmol) in CH_2Cl_2 (1.0 M). The temperature of the reaction mixture was increased from −78 to −35 °C over a 3-h period. The reaction was then stirred for an additional 20 h at −35 °C and subsequently diluted with saturated $NaHCO_3$ and warmed to rt with stirring. The reaction mixture was extracted with CH_2Cl_2 (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (10% EtOAc/PE) afforded **7** as a light yellow oil (80%, 5.3 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.26 (m, 5H), 5.57−5.53 (m, 1H), 5.43 (dd, 1H, J = 7.6, 11.7 Hz), 4.55 and 4.37 (ABq, 2H, J_{AB} = 11.7 Hz), 3.64 (s, 3H), 3.54 (d, 1H, J = 6.7 Hz), 2.99 (d, 2H, J = 6.8 Hz), 2.58−2.55 (m, 1H), 2.12 (s, 3H), 1.02 (d, 3H, J = 6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.1, 137.3, 134.8, 128.4, 127.9, 127.8, 88.8, 72.9, 51.8, 39.7, 37.8, 37.7, 26.2, 15.9; IR (neat) ν_{max} 2900, 1730, 1500, 1450, 1300, 900; CIHRMS M + NH_4^+ (calcd for $C_{17}H_{26}NO_4$) 308.1900, found 308.1900; $[\alpha]^{23}_D$ = +21.4° (*c* 0.90, CH_2Cl_2).

(5*R*,4*R*,5*S*,6*E*)-Benzyl 3-Acetoxy-4-(benzyloxy)-3,5-dimethyl-8-(methoxycarbonyl)-6-nonenoate. To a solution of HMDS (9.4 mL, 48.48 mmol, 1.2 equiv) in 80 mL of dry THF (0.5 **M**) at 0 °C was added dropwise a solution of ^{n}BuLi (2.5 M in hexanes, 19.4 mL, 48.48

mmol, 1.2 equiv). The reaction was stirred for 30 min at 0 °C then cooled to −78 °C. To the reaction mixture at −78 °C was added benzyl acetate (46.4 mL, 44.44 mmol, 1.1 equiv), and the reaction mixture was stirred for 30 min at −78 °C, after which time a solution of **7** in THF (12 mL, 1.0 M) was added. The reaction mixture was stirred for 1.0 h at −78 °C and subsequently diluted with saturated NH_4Cl and stirred to rt. The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo, leaving the crude alcohol which was immediately dissolved in 40 mL of dry CH_2Cl_2 (1.0 M). In a separate flask, catalytic DMAP (2.5 g, 20.2 mmol, 0.5 equiv) was dissolved in 40 mL of dry CH_2Cl_2 and cooled to 0 °C. To the cooled DMAP solution was added triethylamine (45.3 mL, 0.32 mol, 8.0 equiv) and Ac_2O (22.9 mL, 0.24 mol, 6.0 equiv), and the bright yellow reaction mixture was stirred for 5 min, after which time the solution of the crude alcohol was added via syringe over an 1-h period. The reaction mixture was stirred for 48 h at 0 °C and subsequently diluted with $NaHCO_3$ and warmed to rt with stirring. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the organic extracts were washed with 5% HCl. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford the crude acetate. Purification on SiO_2 (7.5% EtOAc/PE) afforded the tertiary acetate as a light yellow oil (80%, two steps, 15.5 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 10H), 5.56−5.51 (m, 2H), 5.04 (d, 2H, J = 2.4 Hz), 4.57 (d, 2H, J = 4.0 Hz), 3.91 (d, 1H, J = 5.3 Hz), 3.66 (s, 3H), 3.21 and 3.09 (ABq, 2H, J_{AB} = 5.9 Hz), 3.01 (d, 2H, J = 6.3 Hz), 2.62−2.60 (m, 1H), 1.82 (s, 3H), 1.51 (s, 3H), 1.29 (d, 3H, J = 3.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.1, 170.3, 170.1, 139.0, 135.8, 128.4, 128.3, 128.2, 128.1, 127.5, 127.4, 120.1, 83.7, 74.7, 66.1, 51.7, 39.9, 38.0, 37.8, 37.7, 22.0, 16.5; IR (neat) ν_{max} 2900, 1720, 1440, 1360, 1250, 1140, 1100; CIHRMS M + NH_4^+ (calcd for $C_{28}H_{37}NO_7$) 499.2600, found 499.2590; $[\alpha]^{23}_D$ = −8.80° (*c* 0.95, CH_2Cl_2).

(3*R*,4*R*,5*S*)-Benzyl 3-Acetoxy-4-(benzyloxy)-3,5-dimethyl-6-oxohexanoate (8). A dilute solution of the tertiary acetate (11.09 g, 23.0 mmol) in a 1:1 mixture of methanol/methylene chloride (0.1 M, 230 mL) was treated with 5 drops of pyridine to reduce acidity. The solution was then cooled to −78 °C. Ozone was bubbled through the homogeneous solution until a blue color persisted. The solution was then purged with argon to remove any excess ozone. The ozonide was reduced with methyl sulfide (17 mL, 230 mmol, 10.0 equiv) and gradually warmed to rt over a 12-h period. The reaction mixture was concentrated in vacuo to afford the crude aldehyde. Purification on SiO_2 (15% EtOAc/PE) afforded **8** as a colorless oil (88%, 8.3 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, 1H, J = 2.76 Hz), 7.33−7.23 (m, 10H), 5.12 and 5.06 (ABq, 2H, J_{AB} = 3.6 Hz), 4.58 and 4.56 (ABq, 2H, J = 3.6 Hz), 4.29 (d, 1H, J = 6.1 Hz), 3.31 and 3.04 (ABq, 2H, J_{AB} = 14.7 Hz), 2.72−2.65 (m, 1H), 1.79 (s, 3H), 1.51 (s, 3H), 1.20 (d, 3H, J = 7.12 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 202.0, 169.7, 169.6, 137.5, 135.6, 128.5, 128.4, 128.3(2), 127.8, 127.4, 82.6, 78.6, 74.4, 48.8, 34.7, 21.8, 20.1, 10.4; IR (neat) ν_{max} 3400, 1710, 1450, 1370, 1240, 1150, 1090; CIHRMS M^+ (calcd for $C_{24}H_{29}O_6$): 413.1980, found: 413.2000; $[\alpha]^{23}_D$ = +1.50° (*c* 0.65, CH_2Cl_2).

(3*R*,4*R*,5*S*,6*S*)-Benzyl 3-Acetoxy-4-(benzyloxy)-3,5-dimethyl-6-hydroxy-8-nonenoate. To a stirred solution of **8** (8.3 g, 20.2 mmol) in 100 mL of CH_2Cl_2 (0.2 M) at −78 °C was added dropwise freshly distilled $TiCl_4$ (2.7 mL, 24.24 mol, 1.2 equiv). The reaction mixture was stirred for 5 min at −78 °C followed by addition of allyltrimethylsilane (4.2 mL, 26.2 mmol, 1.3 equiv) in one portion. The reaction was stirred for 16 h at −78 °C before dilution with H_2O (100 mL) and warmed to rt with stirring. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (15 → 20% EtOAc/PE) afforded the homoallylic alcohol as a colorless oil (90%, 8.2 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 10H), 5.83−5.79 (m, 1H), 5.19−5.05 (m, 2H), 5.04 (s, 2H), 4.72 and 4.59 (ABq, 2H, J_{AB} = 11.4 Hz), 4.26 (s, 1H), 3.46−3.40 (m, 1H), 3.18 (s, 2H), 2.39−2.16 (m, 1H) 2.16−2.10 (m, 1H), 1.92 (t, 1H, J = 6.8 Hz), 1.87 (s, 3H), 1.54 (s, 3H), 1.03 (d, 3H, J = 6.1 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.3, 170.1, 138.7, 135.7, 134.8, 128.4, 128.3, 128.2, 128.1, 127.4, 127.3, 118.3, 84.1, 79.0, 74.0, 73.7, 66.1, 39.6, 39.5, 38.7, 22.1, 20.2, 12.4; IR (neat) ν_{max} 3400, 2800, 1700, 1450, 1380, 1200; CIHRMS M + NH_4^+ (calcd for $C_{27}H_{37}NO_6$) 471.2600, found 471.2490; $[\alpha]^{23}_D$ = −4.30° (*c* 1.50, CH_2Cl_2).

(3*R*,4*R*,5*R*,6*S*)-Benzyl 3-Acetoxy-4-(benzyloxy)-3,5-dimethyl-6-(triisopropylsiloxy)-8-oxooctanoate. A dilute solution of the above silyl ether (11.1 g, 18.1 mmol) in a 1:1 mixture of methanol/methylene chloride (180 mL, 0.1 M) was treated with 5 drops of pyridine to reduce acidity. The solution was then cooled to −78 °C. Ozone was bubbled through the homogeneous solution until a blue color persisted. The solution was then purged with argon to remove any excess ozone. The ozonide was reduced with methyl sulfide (13.3 mL, 181 mmol, 10.0 equiv) and gradually warmed to rt over a 12-h period. The reaction mixture was concentrated in vacuo to afford the crude aldehyde. Purification on SiO_2 (10% EtOAc/PE) afforded the aldehyde as a colorless oil (100%, 11.1 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.34−7.24 (m, 10H), 5.07 and 5.03 (ABq, 2H, J_{AB} = 12.2 Hz), 4.67 and 4.57 (ABq, 2H, J_{AB} = 11.6 Hz), 4.44 (m, 1H), 3.84 (d, 1H, J = 3.3 Hz), 3.28 and 3.05 (ABq, 2H, J_{AB} = 14.8 Hz), 2.66−2.61 (m, 2H) 2.19−2.18 (m, 1H), 1.82 (s, 3H), 1.53 (s, 3H), 1.10 (d, 3H, J = 6.4 Hz), 1.06 (s, 18H), 1.03−0.98 (m, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.5, 170.2, 170.1, 138.4, 128.5 (2), 128.3, 128.2, 127.3, 127.0, 84.2, 79.6, 73.9, 70.9, 66.2, 48.1, 39.6, 39.2, 22.1, 19.9, 18.2, 18.1, 12.7, 11.3; IR (neat) ν_{max} 2900, 2780, 1750, 1480, 1380; CIHRMS M + NH_4^+ (calcd for $C_{35}H_{55}NSiO_7$) 629.3790, found 629.3800; $[\alpha]^{23}_D$ = −8.90° (*c* 0.55, CH_2Cl_2).

(3*R*,4*R*,5*R*,6*S*)-3-Acetoxy-4-(benzyloxy)-3,5-dimethyl-6-(triisopropylsiloxy)-8-(dimethoxy)-octan-4-olide. A dilute solution of **9b** (11.0 g, 17.5 mmol) in anhydrous EtOH (350 mL, 0.05 **M**) was treated with 10% Pd−C (2.3 g, 20 wt %) and catalytic trifluoroacetic acid (3 drops). The suspension was stirred under 1 atm of hydrogen for 24 h. The resulting suspension was filtered through Celite, washed with EtOH, and concentrated in vacuo. Purification on SiO_2 (20 → 30% EtOAc/PE) afforded the lactone as a colorless oil (98%, 8.6 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (dd, 1H, J = 3.2, 3.6 Hz), 4.53 (d, 1H, J = 3.6 Hz), 4.09−4.05 (m, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.91 and 2.81 (ABq, 2H, J_{AB} = 17.6 Hz), 2.19 (m, 1H), 2.02 (s, 3H), 1.86−1.61 (m, 2H), 1.60 (s, 3H), 1.07 (s, 18H), 1.06−1.03 (m, 3H), 0.96 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.5, 170.0, 102.0, 86.4, 83.6, 71.5, 53.0, 52.2, 42.7, 39.4, 35.6, 21.6, 18.9, 18.2, 12.9, 8.20; IR (neat) ν_{max} 2945, 2894, 2868, 1792, 1744, 1464; CIHRMS M + H^+ (calcd for $C_{23}H_{45}SiO_7$) 461.2935, found 461.2952; $[\alpha]^{23}_D$ = +2.81° (*c* 0.89, $CHCl_3$).

(2*Z*,4*R*,5*R*,6*S*)-3,5-Dimethyl-6-(triisopropylsiloxy)-8-(ethyleneoxy)octen-4-olide (10a). The procedure is the same as that for **10b** below and afforded **10a** as a colorless oil (94%, 1.7 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.12 (s, 1H), 5.077 (t, 1H, J = 5.3 Hz), 4.09−4.06 (m, 1H), 3.92−3.78 (m, 5H), 2.07−2.01 (m, 2H), 1.97 (s, 3H), 1.88−1.83 (m, 1H), 1.04 (s, 18H), 1.04−0.99 (m, 3H), 0.62 (d, 3H, J = 7.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.5, 168.3, 117.4, 101.7, 84.5, 71.6, 64.9, 64.2, 40.1, 38.1, 18.1, 18.0, 13.8, 12.8, 6.60; IR (neat) ν_{max} 2950, 2870, 1760, 1470, 1380; CIHRMS M^+ (calcd for $C_{37}H_{59}NSiO_8$) 399.2500, found 399.2524; $[\alpha]^{23}_D$ = +14.3° (*c* 0.40, CH_2Cl_2).

(2*Z*,4*R*,5*R*,6*S*)-3,5-Dimethyl-6-(triisopropylsiloxy)-8,8-dimethoxyocten-4-olide (10b). A solution of the above lactone (4.8 g, 9.60 mmol) in 96 mL of THF (0.1 M) was cooled to −78 °C and treated with DBU (1.32 mL, 9.60 mmol, 1.0 equiv). The resulting solution was stirred at 0 °C for 30 min and subsequently diluted with H_2O (100 mL). The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification on SiO_2 (20% EtOAc/PE) afforded **10b** as a colorless oil (95%, 4.1 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.07 (s, 1H), 4.67 (t, 1H, J = 4.8 Hz), 4.08−4.06 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 2.07−2.02 (m, 1H), 2.00 (s, 3H), 1.83−1.78 (m, 2H), 1.08 (s, 18H), 1.06−0.99 (m, 3H), 0.65 (d, 3H, J = 7.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.5, 167.9, 117.6, 101.5, 84.8, 72.1, 52.7, 51.9, 40.5, 36.7, 18.2, 13.8, 13.0, 12.9, 6.17; IR (neat) ν_{max} 2944, 2868, 1763, 1646, 1385; CIHRMS M + NH_4^+ (calcd for $C_{21}H_{44}NSiO_5$) 418.2990, found 418.3020; $[\alpha]^{23}_D$ = +9.60° (*c* 1.34, $CHCl_3$).

(3*S*,4*R*,5*R*,6*Z*)-4,6-Dimethyl-5,8-dihydroxy-3-(triisopropylsiloxy)-6-octenal 1,2-Ethanediol Acetal (11a). Lithium aluminum hydride (0.14 g, 3.77 mmol, 2.5 equiv) was added to a stirred solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; 4.6 mL, 30.2 mmol, 20 equiv) in anhydrous Et_2O (8 mL, 0.2 M) at 0 °C. This solution

was stirred for 3 min followed by the addition of a solution of **10a** (0.67 g, 1.51 mmol) in Et_2O (3 mL, 0.5 M). The mixture was stirred for 1 h at 0 °C and subsequently quenched with a quantitative amount of H_2O (0.14 mL), 15% NaOH (0.14 mL), and additional H_2O (0.42 mL). The resulting suspension was filtered through Celite and concentrated in vacuo. Purification on SiO_2 (40% EtOAc/PE) afforded **11a** as a colorless oil (50%, 0.34 g): ^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 5.60 (t, 1H, $J = 7.4$ Hz), 4.86 (dd, 1H, $J_1 = 3.8$ Hz, $J_2 = 6.2$ Hz), 4.81 (t, 1H, $J = 4.9$ Hz), 4.57 (d, 1H, $J = 5.4$ Hz), 4.28−4.08 (m, 3H), 3.99−3.61 (m, 5H), 2.59−1.76 (m, 3H), 1.70 (s, 3H), 1.05 (s, 18H), 0.98 (d, 3H, $J = 6.7$ Hz), 1.04−0.96 (m, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) ***δ* 139.2, 127.4, 102.2, 73.1, 72.7, 64.7, 58.2, 38.2, 20.2, 18.1, 12.7, 11.1;** IR (neat) ν_{max} 3450, 2950, 2880, 1800, 1500, 1420; CIHRMS M^+ (calcd for $C_{21}H_{43}SiO_5$) 403.2800, found 403.2820; $[\alpha]^{23}_D = -9.8°$ (*c* 0.50, CH_2Cl_2).

(3*S*,4*R*,5*R*,6*Z*)-4,6-Dimethyl-5,8-dihydroxy-3-(triisopropylsiloxy)-6-octenal Dimethyl Acetal. Lithium aluminum hydride (0.75 g, 19.83 mmol, 2.5 equiv) was added to a stirred solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; 24 mL, 158.6 mmol, 20 equiv) in anhydrous Et_2O (40 mL, 0.2 **M**) at 0 °C. This solution was stirred for 3 min followed by the addition of a solution of **10b** (3.5 g, 7.93 mmol) in Et_2O (20 mL, 0.5 M). The mixture was stirred for 1 h at 0 °C and subsequently quenched with a quantitative amount of H_2O (0.75 mL), 15% NaOH (0.75 mL), and additional H_2O (2.25 mL). The resulting suspension was filtered through Celite and concentrated in vacuo. Purification on SiO_2 (40% EtOAc/PE) afforded the diol as a colorless oil (70%, 2.5 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (t, 1H, $J = 7.2$ Hz), 4.48−4.45 (m, 2H), 3.99−3.96 (m, 3H), 3.64 (s, br, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 3.28 (s, br, 1H), 1.92−1.73 (m, 3H), 1.71 (s, 3H), 1.06 (s, 18H), 1.05−1.00 (m, 3H), 0.99 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.8, 127.7, 102.6, 74.8, 72.5, 58.1, 54.1, 52.4, 40.6, 37.3, 19.8, 18.2, 12.8, 10.9; IR (neat) ν_{max} 3416, 2972, 2869, 2076, 1653; CIHRMS M^+ (calcd for $C_{21}H_{44}SiO_5$) 404.2958, found 404.2953; $[\alpha]^{23}_D = -16.5°$ (*c* 1.76, $CHCl_3$).

(3*S*,4*R*,5*R*,6*Z*)-4,6-Dimethyl-8-iodo-5-(*tert*-butyldimethylsiloxy)-3-(triisopropylsiloxy)-6-octenal 1,2-Ethanediol Acetal (3a). The intermediate allylic alcohol (0.040 g, 0.08 mmol) was dissolved in anhydrous DMF (0.25 mL, 0.3 M) and cooled to 0 °C. The solution was treated with methyltriphenoxyphosphonium iodide (0.053 g, 0.12 mmol, 1.5 equiv). The ice bath was removed, and the reaction was allowed to warm to rt for 30 min and subsequently diluted with excess H_2O (5 mL). The reaction mixture was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (PE → 2% EtOAc/PE) afforded **3a** as a colorless oil (82%, 0.040 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (dd, 1H, $J = 6.8$, 11.2 Hz), 4.92 (d, 1H, $J = 8.3$ Hz), 4.03−3.74 (m, 7H), 1.92−1.75 (m, 2H), 1.35 (dd, 1H, $J = 8.3$, 13.2 Hz), 1.05−1.02 (m, 3H), 1.02 (s, 18H), 0.96 (d, 3H, $J = 6.8$ Hz), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 140.7, 124.8, 102.7, 69.2, 64.7, 37.3, 25.9, 18.2, 18.0, 12.8, 10.4, −4.40, −5.00; IR (neat) ν_{max} 2940, 2900, 1850, 1500; CIHRMS M^+ (calcd for $C_{27}H_{46}ISi_2O_4$) 617.1900, found 617.1907; $[\alpha]^{23}_D = +62.0$ (*c* 0.35, CH_2Cl_2).

(3*S*,4*R*,5*R*,6*Z*)-4,6-Dimethyl-8-iodo-5-(*tert*-butyldimethylsiloxy)-3-(triisopropylsiloxy)-6-octenal Dimethyl Acetal (3b). A solution of the primary allylic alcohol (0.13 g, 0.25 mmol) in anhydrous DMF (0.3 mL, 1.0 M) was cooled to 0 °C and treated with methyltriphenoxyphosphonium iodide (0.70 g, 0.38 mmol, 1.5 equiv). The ice bath was removed, and the reaction was allowed to warm to rt for 30 min and subsequently diluted with excess H_2O (10 mL). The reaction mixture was extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (PE → 2% EtOAc/PE) afforded **3b** as a colorless oil (82%, 0.13 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (dd, 1H, $J = 5.6$, 4.4 Hz), 4.47 (dd, 1H, $J = 2.0$ Hz), 4.00 (t, 1H, $J = 11.2$ Hz), 3.74 (d, 1H, $J = 9.6$ Hz), 3.30 (s, 3H), 3.29 (s, 3H), 1.90 (m, 2H), 1.70 (s, 3H), 1.67−1.44 (m, 3H), 1.19−1.00 (m, 3H), 1.02 (s, 18H), 0.96 (d, 3H, $J = 6.8$ Hz), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 140.7, 124.8, 103.3, 69.1, 54.5, 52.7, 36.7, 30.3, 29.7, 26.2, 25.9, 25.8, 18.1, 12.9, 12.6, 10.5, −4.34, −5.00; IR (neat) ν_{max} 2945, 2866, 1729, 1649; CIHRMS M^+ (calcd for $C_{27}H_{57}ISi_2O_4$) 628.2840, found 628.2790; $[\alpha]^{23}_D = +63.5$ (*c* 0.95, $CHCl_3$).

3(*R*)-(Dimethylphenylsilyl)butanolide. A solution of (*R*)-**6** (0.5 g, 1.91 mmol) in MeOH (19 mL, 0.1 M) was cooled to −78 °C. Ozone was bubbled through the homogeneous solution until a blue color persisted. The solution was then purged with argon to remove any excess ozone. The reaction was treated with $NaBH_4$ (0.072 g, 1.91 mmol, 1.0 equiv) and gradually warmed to rt over a 12-h period. The reaction mixture was concentrated in vacuo to afford the crude β-silyl lactone. Purification on SiO_2 (20% EtOAc/PE) afforded the β-silyl lactone as a colorless oil (100%, 0.42 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.36 (m, 5H), 4.40 (t, 1H, $J = 9.2$ Hz), 4.09 (dd, 1H, $J = 9.2$ Hz), 2.49 (dd, 1H, $J = 8.8$, 8.4 Hz), 2.27 (dd, 1H, $J = 12.8$ Hz), 2.09−2.00 (m, 1H), 0.35 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 178.0, 135.1, 133.6, 129.9, 128.2, 70.8, 30.3, 23.8, −4.85, −5.13; IR (neat) ν_{max} 3022, 2957, 2900, 1773, 1646; CIHRMS M + NH_4^+ (calcd for $C_{12}H_{20}NSiO_2$) 238.1263, found 238.1295; $[\alpha]^{23}_D = +5.65°$ (*c* 1.77, $CHCl_3$).

3(*R*)-Hydroxybutanolide. A solution of the β-silyl lactone in acetic acid (1.0 mL, 2 **M**) was treated with mercuric acetate (0.91 g, 2.87 mmol, 1.5 equiv) followed by a catalytic amount of concentrated sulfuric acid (1 drop). The resulting white suspension was warmed to rt with stirring for 24 h and subsequently concentrated in vacuo. The crude solid is then diluted with Et_2O, stirred for 1 h, and filtered, and the filtrate is concentrated in vacuo. Purification on SiO_2 (30 → 50% EtOAc/PE) afforded the β-hydroxy lactone as a colorless oil (50%, 0.10 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (m, br, 1H), 4.39 (dd, 1H, $J = 4.8$, 4.4 Hz), 4.27 (d, 1H, $J = 11.6$ Hz), 2.92 (s, br, 1H), 2.72 (dd, 1H, $J = 6.0$ Hz), 2.51 (d, 1H, $J = 18.8$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.5, 76.1, 67.5, 37.8; IR (neat) ν_{max} 3412, 2934, 1773, 1653; CIHRMS M + H^+ (calcd for $C_4H_7NO_3$) 103.0425, found 103.0417; $[\alpha]^{23}_D = +86.0°$ (*c* 2.0, EtOH); $[\alpha]^{23}_D$ (lit.[35] +85.9° (*c* 2.2, EtOH)

3(*R*)-Methoxybutanolide (16). A solution of the β-hydroxy lactone (1.75 g, 17.16 mmol) was dissolved in MeI (30 mL, 0.5 M) and treated with silver(I) oxide (3.98 g, 17.16 mmol, 1.0 equiv). The resulting suspension was refluxed in the dark for 12 h and subsequently concentrated in vacuo. The crude mixture was diluted with Et_2O, filtered through Celite, and concentrated in vacuo to afford a colorless oil. Purification on SiO_2 (20% EtOAc/PE) afforded **11** as a colorless oil (70%, 1.4 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, 2H, $J = 3.6$ Hz), 4.14 (m, 1H), 3.30 (s, 3H), 2.66 (dd, 1H, $J = 6.0$ Hz), 2.53 (dd, 1H, $J = 2.4$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.4, 75.9, 72.7, 56.5, 34.5; IR (neat) ν_{max} 2937, 2833, 1779; CIHRMS M+H^+ (calcd for $C_5H_9O_3$) 117.0552, found 117.0570; $[\alpha]^{23}_D = +34.2°$ (*c* 0.92, $CHCl_3$).

(3*S*,4*R*,5*R*,6*Z*)-9-[2,3-Dimethoxy-4-(2, 5-dimethylpyrrole)benzene]-4,6-dimethyl-5-(*tert*-butyldimethylsiloxy)-3-(triisopropylsiloxy)-6-nonenal 1,2-Ethanediol Acetal (15). A solution of **4a** (0.060 g, 0.1 mmol) in THF (1 mL, 0.1 M) was cooled to −78 °C and treated with ^{n}BuLi (60 μL, 0.1 mmol, 1.25 equiv) and stirred for 30 min to afford a bright yellow colored solution. To the solution of the lithio anion at −78 °C was added a solution of **3a** (0.042 g, 0.08 mmol) in THF (1 mL, 0.08 M) in one portion. The yellow color disappeared immediately and the reaction allowed to stir at −78 °C for 30 min and subsequently diluted with a saturated NH_4Cl solution (5 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude dithiane. The crude dithiane was immediately dissolved in dry EtOH (4 mL, 0.01 M) and treated with W-7 Raney nickel (3 mL of a 50% suspension in EtOH). The reaction was stirred under a hydrogen atmosphere for 10 min and subsequently filtered through SiO_2 and the filtrate concentrated in vacuo. Purification on SiO_2 (5% EtOAc/PE) afforded **15** as a colorless oil (78%, secondeps, 0.030 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, 1H, $J = 3.1$ Hz), 6.53 (d, 1H, $J = 3.1$ Hz), 5.89 (s, 2H),5.25−5.22 (m, 1H), 4.95 (d, 1H, $J = 8.1$ Hz), 4.10−4.08 (m, 1H), 3.95−3.66 (m, 4H), 3.74 (s, 3H), 3.17 (s, 3H), 2.68−2.64 (m, 1H), 2.35−2.29 (m, 1H), 2.02 (s, 6H), 1.98−1.82 (m, 2H), 1.68 (s, 3H), 1.54−1.38 (m, 1H), 1.18−0.98 (m, 3H), 1.02 (s, 18H), 0.95 (d, 3H, $J = 6.7$ Hz), 0.86 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.9, 148.4,

(35) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389−1391.

137.0, 136.3, 131.4, 129.0, 128.8, 126.9, 115.6, 112.2, 105.7, 102.9, 76.5, 71.9, 71.8, 71.7, 69.2, 64.5, 64.4, 59.7, 59.6, 55.5, 43.9, 36.8, 30.4, 29.7, 29.2, 25.9, 25.8, 18.2, 18.1, 12.9, 12.7, 10.6, −4.70, −4.90; IR (neat) ν_{max} 2900, 2890, 1550., 1480; CIHRMS M^+ (calcd for $C_{42}H_{74}Si_2NO_6$) 744.5100, found 744.5120; $[\alpha]^{23}_D = -8.0°$ (*c* 0.15, CH_2Cl_2).

2,5-Dimethoxy-3-(3′(*R*)-methoxy-4-hydroxybutyramido)benzylphenyl sulfone. A sealed flask was purged with argon and charged with benzene (5 mL, 0.5 M) and Me_3Al (1.4 mL, 2.80 mmol, 1.2 equiv) at rt. To this mixture was added a solution of **18** (0.79 g, 2.56 mmol, 1.1 equiv) in benzene (5 mL, 0.5 M) and the reaction stirred at rt for 45 min at which point a solution of **16** (0.27 g, 2.33 mmol) in benzene (4 mL, 0.5 **M**) was added dropwise under stirring. The reaction was stirred at rt for 2 h and subsequently diluted with 5% HCl. The reaction mixture was extracted with EtOAc (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (50 → 100% EtOAc/PE) afforded the hydroxy amide as a white solid (70%, 0.70 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, br, 1H), 7.85 (d, 1H, J = 3.2 Hz), 7.65−7.36 (m, 5H), 6.24 (d, 1H, J = 3.2 Hz), 4.26 (s, 2H), 3.73−3.61 (m, 2H), 3.56 (s, 3H), 3.52−3.49 (m, 1H), 3.50 (s, 3H), 3.34 (s, 3H), 2.56−2.53 (m, 2H), 2.20 (s, br, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.3, 155.8, 142.0, 138.4, 133.8, 132.3, 129.0, 128.6, 121.4, 111.2, 107.6, 78.3, 62.7, 61.8, 57.4, 56.5, 55.5, 39.8; IR (neat) ν_{max} 3441, 2961, 1650, 1543, 1467; CIHRMS M + H^+ (calcd for $C_{20}H_{26}NSO_7$) 424.1430, found 424.1511; $[\alpha]^{23}_D = +6.0°$ (*c* 0.34, $CHCl_3$).

Desulfonylated Arene (19). A solution of **4b** (0.16 g, 0.30 mmol, 1.5 equiv) in THF (2.0 mL, 0.1 M) at −78 °C was treated dropwise with lithium bis(trimethylsilyl) amide (0.5 M in THF, 1.3 mL, 0.66 mmol), and the resultant yellow solution was stirred for 20 min at −78 °C. A solution of iodide **3a** (0.11 g, 0.20 mmol) in THF (1 mL, 0.2 M) was then added. The reaction mixture was stirred for 1 h at −78 °C and subsequently poured onto a 1:1 mixutre of Et_2O/pH 7 buffer at 0 °C and warmed to rt with stirring. The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude 1:1 mixture of sulfones was used without further purification. The mixture of sulfones (0.065 g, 0.07 mmol), Na_2HPO_4 (0.040 g, 0.28 mmol, 4.1 equiv), and anhydrous MeOH (1.5 mL, 0.05 M) was cooled to − 20 °C. Excess Na(Hg) (0.29 g, 4.5 wt equiv) was added to the mixture and the suspension stirred until the starting material was consumed as indicated by TLC analysis (20 min). The crude reaction mixture was filtered through a short plug of silica gel with EtOAc as the eluant, and the filtrate was concentrated in vacuo. The residue was redissolved in EtOAc (25 mL), washed with water and brine (2 × 25 mL each), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (20% EtOAc/PE) afforded **19** as a single isomer: colorless oil (78%, two steps, 0.056 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, br, 1H), 7.85 (d, 1H, J = 3.2 Hz), 6.42 (d, 1H, J = 2.8 Hz), 5.20 (t, 1H), 4.92 (dd, 1H, J = 2.0 Hz), 4.10 (m, 1H), 3.90 (d, 1H, J = 10.4 Hz), 3.75 (s, 3H), 3.74−3.62 (m, 8H), 3.63 (s, 3H), 3.50 (s, 3H), 2.65−2.55 (m, 5H) 2.38−2.22 (m, 2H), 1.68 (s, 3H), 1.40−1.30 (m, 1H), 1.00 (s, 18H), 0.95−0.88 (m, 3H), 0.92 (d, 3H, J = 6.4 Hz), 0.90 (s, 9H), 0.82 (s, 9H), 0.050 (s, 3H), −0.004 (s, 3H), −0.084 (s, 3H), −0.093 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.5, 156.0, 140.8, 136.6, 135.0, 132.2, 126.9, 110.3, 103.2, 102.9, 78.9, 71.7, 69.1, 65.0, 64.5, 63.8, 61.0, 57.7, 55.5, 53.8, 52.1, 44.1, 29.9, 29.6, 28.6, 25.8, 18.8, 18.4, 18.2, 13.4, 12.9, 10.7, −4.76, −4.85, −4.98, −5.44; IR (neat) ν_{max} 2930, 2865, 1691, 1531, 1464; CIHRMS M^+ (calcd for $C_{47}H_{89}NSi_3O_9$) 895.5845, found 895.5840; $[\alpha]^{23}_D = +2.81°$ (*c* 0.89, $CHCl_3$).

Coupled Sulfone. A solution of **4b** (0.16 g, 0.29 mmol, 1.5 equiv) in THF (2.0 mL, 0.1 M) at −78 °C was treated dropwise with lithium bis(trimethylsilyl) amide (0.5 M in THF, 1.3 mL, 0.63 mmol) and the resultant yellow solution was stirred for 20 min at −78 °C. A solution of iodide **3b** (0.12 g, 0.19 mmol) in THF (1 mL, 0.2 M) was then added. The reaction mixture was stirred for 1 h at −78 °C and subsequently poured onto a 1:1 mixutre of Et_2O/pH 7 buffer at 0 °C and warmed to rt with stirring. The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (30% EtOAc/PE) afforded the coupled sulfone as a 1:1 diastereomeric mixture: colorless oil (80%, 0.16 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, br, 1H), 8.02, 7.93 (diastereomers, d, J = 3.2 Hz, 1H), 7.69 (d, 2H), 7.62−7.35 (complex m, 3H), 6.70, 6.62 (diastereomers, d, J = 3.2, 2.8 Hz, 1H), 5.00, 4.91 (diastereomers, apparent t, 1H), 4.55, 4.40 (diastereomers, dd, J = 1.6 Hz, dd, J = 10.0 Hz, 1H), 3.85, 3.80, 3.76, 3.72 (diastereomers, s, s, s, s, 6H), 3.71−3.57 (diastereomers, m, 4 H), 3.55 (s, 3H), 3.53 (s, 3H), 3.44, 3.43, 3.39, 3.38 (diastereomers, s, s, s, s, 6H), 2.65−2.49 (m, 4H), 1.86 (m, 2H), 1.55, 1.53 (diastereomers s, s, 3H), 1.11−1.08 (m, 3H), 1.03, 0.99 (diastereomers, s, s, 18H), 0.87 (d, 3H, J = 1.6 Hz), 0.87, 0.86 (diastereomers, s, s, 9H), 0.81, 0.79 (diastereomers, s, s, 9H), 0.046, 0.039, 0.033, 0.020 (diastereomers, s, s, s, s, 6H), −0.060, −0.078, −0.091, −0.010 (diastereomers, s, s, s, s, 6H) ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.8, 169.6, 169.5, 156.3, 156.1, 142.6, 142.1, 139.8, 139.7, 138.1, 138.0, 137.9, 137.6, 133.4, 133.3, 132.3, 132.2, 129.4, 128.3, 129.0, 128.8, 128.5, 126.4, 125.1, 122.0, 121.8, 120.9, 113.3, 108.7, 107.0, 106.8, 102.8, 102.7, 69.2, 68.8, 63.8, 62.6, 61.5, 61.4, 57.9, 57.7, 55.5, 54.5, 51.8, 44.1, 40.3, 40.2, 29.7, 27.3, 25.8, 25.7, 18.6, 18.5, 18.2, 18.1, 13.6, 13.4, 12.9, 12.8, 10.6, 10.5, −4.93; IR (neat) ν_{max} 2955, 2865, 1614, 1465, 1423; CIHRMS M + H^+ (calcd for $C_{53}H_{96}NO_{11}Si_3S$) 1038.6012, found 1038.6000; $[\alpha]^{23}_D = -2.60°$ (*c* 1.13, $CHCl_3$).

Desulfonylated Arene (21). A mixture of sulfones (0.16 g, 0.15 mmol), Na_2HPO_4 (88 mg, 0.62 mmol, 4.1 equiv), and anhydrous MeOH (3 mL, 0.05 M) was cooled to − 20 °C. Excess Na(Hg) (0.72 g, 4.5 wt equiv) was added to the mixture and the suspension stirred until the starting material was consumed as indicated by TLC analysis (30 min). The crude reaction mixture was filtered through a short plug of silica gel with EtOAc as the eluant, and the filtrate was concentrated in vacuo. The residue was redissolved in EtOAc (25 mL), washed with water and brine (2 × 25 mL each), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (20% EtOAc/PE) afforded **14** as a single isomer: colorless oil (98%, 0.13 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, br, 1H), 7.80 (d, 1H, J = 3.2 Hz), 6.38 (d, 1H, J = 2.8 Hz), 5.10 (t, 1H), 4.42 (dd, 1H, J = 2.0 Hz), 4.00 (m, 1H), 3.72 (d, 1H, J = 10.4 Hz), 3.66 (s, 3H), 3.65−3.57 (m, 4H), 3.58 (s, 3H), 3.42 (s, 3H), 3.13 (s, 3H), 3.10 (s, 3H), 2.57−2.48 (m, 5H) 2.27−2.25 (m, 2H), 1.57 (s, 3H), 1.54−1.51 (m, 1H), 0.93 (s, 18H), 0.95−0.88 (m, 3H), 0.86 (d, 3H, J = 6.4 Hz), 0.79 (s, 9H), 0.76 (s, 9H), −0.039 (s, 3H), −0.044 (s, 3H), −0.084 (s, 3H), −0.093 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.5, 156.0, 140.8, 136.6, 135.0, 132.2, 126.9, 110.3, 103.2, 102.9, 78.9, 71.7, 69.1, 63.8, 61.0, 57.7, 55.5, 53.8, 52.1, 44.1, 40.3, 35.9, 29.9, 29.6, 28.6, 25.8, 18.8, 18.4, 18.2, 13.4, 12.9, 10.7, −4.76, −4.85, −4.98, −5.44; IR (neat) ν_{max} 2930, 2865, 1691, 1531, 1464; CIHRMS M^+ (calcd for $C_{47}H_{91}NSi_3O_9$) 897.6002, found 897.6009; $[\alpha]^{23}_D = -12.9°$ (*c* 2.28, $CHCl_3$).

Hydroxy Arene. A solution of **21** (0.13 g, 0.15 mmol) in anhydrous THF (1.5 mL, 0.1 M) at 0 °C was treated with a stock solution of HF·pyridine (4:1; 0.9 mL, 6.0 equiv). The reaction was stirred at rt over a period of 3 h, at which time the reaction was diluted dropwise with $NaHCO_3$ and warmed to rt with stirring. The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (50% EtOAc/PE) afforded the hydroxy arene as a colorless oil (95%, 0.11 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, br, 1H), 7.86 (d, 1H, J = 3.2 Hz), 6.49 (d, 1H, J = 2.4 Hz), 5.21 (t, 1H, J = 16.8 Hz), 4.50 (d, 1H, J = 6.8 Hz), 4.05 (m, 1H), 3.70 (d, 1H, J = 10.4 Hz), 3.93−3.57 (m, 4H), 3.75 (s, 3H), 3.68 (s, 3H), 3.49 (s, 3H), 3.24 (s, 3H), 3.20 (s, 3H), 2.71−2.60 (m, 5H) 2.35 (d, 2H, J = 6.4 Hz), 1.94 (s, br, 1H), 1.67 (s, 3H), 1.63−1.59 (m, 1H), 1.19−1.03 (m, 3H), 1.03 (s, 18H), 0.94 (d, 3H, J = 6.8 Hz), 0.85 (s, 9H), 0.009 (s, 3H), −0.057 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.1, 156.0, 140.8, 136.6, 135.1, 131.9, 126.9, 110.5, 103.3, 103.1, 78.4, 69.1, 62.9, 61.2, 57.5, 55.5, 53.8, 52.3, 39.8, 36.0, 29.6, 28.6, 25.9, 25.8, 18.4, 18.2, 18.1, 13.4, 12.9, 10.7, −4.75, −4.96; IR (neat) ν_{max} 3450, 2920, 2860, 1690, 1530, 1460; CIHRMS M^+ (calculated for $C_{41}H_{77}NSi_2O_9$) 783.5137, found 783.5130; $[\alpha]^{23}_D = -22.5°$ (*c* 0.20, $CHCl_3$).

Lactam Aminal. A solution of the hydroxy arene (0.11 g, 0.14 mmol) in DMSO (3.0 mL, 0.05 M) was treated with triethylamine (1.0 mL, 7.19 mmol, 50.5 equiv) followed by pyridine·SO_3 (0.33 g, 2.10 mmol, 15 equiv). The resulting mixture was stirred for 45 min at rt and subsequently diluted with excess H_2O (20 mL) and brine (10 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (50 → 75%

EtOAc/PE) afforded the lactam aminal as a light yellow oil (82%, 90 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71, 6.70 (diastereomers, d, J = 3.2 Hz, 1H), 6.63, 6.62 (diastereomers, d, J = 2.8 Hz, 1 H), 5.38, 5.31 (diastereomers, d, J = 2.0 Hz, 1H), 5.20 (t, 1H, J = 6.4 Hz), 4.49 (dd, 1H, J = 2.0 Hz), 4.38 (s, br, 1H), 3.87 (d, 1H, J = 2.0 Hz), 3.80 (d, 1H, J = 10.8 Hz), 3.74 (s, 3H), 3.65, 3.62 (diastereomers, s, s, 3H), 3.49, 3.43 (diastereomers, s, s, 3H), 3.26, 3.25 (diastereomers, s, s, 3 H), 3.24, 3.20 (diastereomers, s, s, 3H), 2.99 (dd, 1H, J = 6.4, 6.0 Hz), 2.66−2.61 (m, 2H), 2.49 (d, 1H, J = 17.2 Hz), 2.33 (s, br, 1H), 1.67, 1.64 (diastereomers, s, s, 3H), 1.42 (dd, 1H, J = 8.8 Hz), 1.31−1.26 (m, 4H), 1.04−0.95 (m, 3H), 1.03 (s, 18H), 0.93 (d, 3H, J = 6.8 Hz), 0.86, 0.85 (diastereomers, s, s, 9H), 0.041, 0.007 (diastereomers, s, s, 3H), −0.014, −0.053 (diastereomers, s, s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.7, 156.3, 147.5, 137.3, 130.3, 126.7, 116.2, 112.1, 103.4, 89.0, 80.0, 69.0, 61.9, 56.9, 55.6, 52.9, 44.1, 36.1, 36.0, 29.9, 29.7, 29.0, 25.9, 25.8, 18.2, 14.1, 13.4, 12.9, 10.7, −4.73, −4.94; IR (neat) ν_{max} 3550, 2980, 2820, 1690, 1530, 1460; CIHRMS M$^+$ (calcd for $C_{41}H_{75}NSi_2O_9$) 781.4980, found 781.5000; $[\alpha]^{23}_D = -20.0°$ (*c* 0.15, $CHCl_3$).

Aminal−Aldehyde. A solution of the lactam−aminal (90 mg, 0.11 mmol) in wet acetone (1.1 mL, 0.1 M) was treated with PPTS (14 mg, 0.06 mmol, 0.5 equiv). The reaction mixture was refluxed for 1 h then cooled to rt and the mixture concentrated in vacuo. The residue was redissolved in Et_2O (25 mL), washed with $NaHCO_3$ and brine (2 × 25 mL each), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (40% EtOAc/PE) afforded the aldehyde as a colorless oil (90%, 73 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (m, 1H), 6.71, 6.70 (diastereomers, d, J = 3.2 Hz, 1H), 6.62, 6.61 (diastereomers, d, J = 2.9 Hz, 1 H), 5.38, 5.31 (diastereomers, d, J = 1.9 Hz, 1H), 5.21 (t, 1H, J = 6.4 Hz), 4.49 (dd, 1H, J = 2.0 Hz), 4.38 (s, 1H), 3.87 (d, 1H, J = 1.9 Hz), 3.80 (d, 1H, J = 10.0 Hz), 3.74 (s, 3H), 3.65, 3.62 (diastereomers, s, s, 3H), 3.50, 3.43 (diastereomers, s, s, 3H), 2.99 (dd, 1H, J = 6.4, 6.2 Hz), 2.66−2.60 (m, 2H), 2.50 (d, 1H, J = 17.0 Hz), 2.33 (s, br, 1H), 1.67, 1.63 (diastereomers, s, s, 3H), 1.41 (dd, 1H, J = 8.6 Hz), 1.31−1.26 (m, 4H), 1.04−0.95 (m, 3H), 1.02 (s, 18H), 0.94 (d, 3H, J = 6.8 Hz), 0.86, 0.85 (diastereomers, s, s, 9H), 0.041, 0.007 (diastereomers, s, s, 3H), −0.014, −0.052 (diastereomers, s, s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.5, 173.8, 147.5, 137.3, 130.2, 126.8, 116.4, 112.0, 103.4, 89.0, 80.0, 69.1, 62.0, 52.9, 44.1, 36.1, 36.0, 29.9, 29.7, 29.0, 26.0, 25.8, 18.2, 14.1, 13.4, 12.9, 10.7, −4.70, −4.95; IR (neat) ν_{max} 3550, 2980, 2800, 1750, 1690, 1460; CIHRMS M$^+$ (calcd for $C_{39}H_{69}NSi_2O_8$) 735.4562, found 735.4560; $[\alpha]^{23}_D = -33.0°$ (*c* 0.10, $CHCl_3$).

Bis[(*E*,*E*)-Vinyl Iodide] (22). Anhydrous $CrCl_2$ (0.12 g, 1.0 mmol, 10.0 equiv) was suspended in THF (1 mL, 0.1 M). A solution of the aminal−aldehyde (73 mg, 0.10 mmol) and iodoform (0.2 g, 0.5 mmol, 5.0 equiv) in THF (1 mL, 0.1 M) was cannulated into the $CrCl_2$ suspension at 0 °C. The mixture was stirred to rt over a 10-h period and subsequently poured into H_2O (10 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (30% EtOAc/PE) afforded **15** as a light yellow oil (70%, 69 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, br, 1H), 6.74, (d, 2H, J = 3.2 Hz), 6.62, (d, 2H, J = 2.9 Hz), 5.40 (d, 1H, J = 1.9 Hz), 5.21 (t, 1H, J = 6.4 Hz), 4.49 (dd, 1H, J = 2.0 Hz), 4.38 (s, 1H), 3.87 (d, 1H, J = 1.9 Hz), 3.80 (d, 1H, J = 10.0 Hz), 3.74 (s, 3H), 3.63 (s, 3H), 3.42 (s, 3H), 2.99 (dd, 1H, J = 6.4, 6.2 Hz), 2.66−2.60 (m, 2H), 2.50 (d, 1H, J = 17.0 Hz), 1.63 (s, 3H), 1.41 (dd, 1H, J = 8.6 Hz), 1.31−1.26 (m, 4H), 1.04−0.95 (m, 3H), 1.02 (s, 18H), 0.93 (d, 3H, J = 6.8 Hz), 0.85 (s, 9H), 0.007 (s, 3H), −0.014, (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.2, 156.0, 150.0, 140.8, 136.8, 135.1, 131.9, 127.0, 120.0, 119.4, 110.5, 103.3, 103.0, 78.4, 69.1, 62.8, 53.8, 52.0, 39.8, 36.0, 29.8, 28.6, 25.9, 25.8, 18.4, 18.2, 18.1, 13.4, 13.0, 10.7, −4.75, −4.96; IR (neat) ν_{max} 2980, 2850, 1700, 1690, 1400; CIHRMS M + H$^+$ (calcd for $C_{41}H_{72}I_2NSi_2O_6$) 984.2988, found 984.3003; $[\alpha]^{23}_D = +21.8°$ (*c* 0.35, $CHCl_3$).

(+)-Mycotrienol (1d). To a flame-dried flask purged with argon was added bis(acetonitrile)palladium(II) dichloride (4.0 mg, 0.014 mmol, 20 mol %) followed by a degassed mixture of 1:1 DMF/THF (0.5 mL). To this mixture was added via cannula a solution of **22** (69 mg, 0.07 mmol) in DMF/THF (1 mL) followed by a solution of the enedistannane **23** (51 mg, 0.084 mmol, 1.2 equiv) in DMF/THF (1 mL) and diisopropylethylamine (18 μL, 0.105 mmol, 1.5 equiv). The reaction mixture was stirred for 24 h at rt and subsequently diluted with 10% NH_4OH (6 mL) and stirred for an additional 5 min. The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude triene. The crude triene was immediately dissolved in a mixture of THF/H_2O (10:1, 20 mL, 0.003 M), cooled to 0 °C, and treated with CAN (1 M in H_2O, 0.35 mL, 5.0 equiv). The bright yellow solution was stirred for 30 min at 0 °C and subsequently poured onto H_2O (20 mL). The reaction mixture was extracted with Et_2O (2 × 25 mL) and CH_2Cl_2 (2 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude quinone as a bright yellow oil. The crude quinone was dissolved in acetonitrile (1.4 mL, 0.05 M) and treated with 40% aqueous HF (10% v/v, 0.14 mL). The reaction mixture was stirred at rt for 48 h and subsequently diluted slowly with $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (25% acetone/benzene) afforded (+)-**1d** as a yellow solid (54%, 3 steps, 17 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, br, 1H), 7.50 (s, 1H), 6.47 (s, 1H), 6.18 (d, 1H, J = 10.5 Hz), 6.10−5.95 (complex m, 4H), 5.59 (m, 2H), 5.05 (apparent t, 1H, J = 6.8 Hz), 4.78 (br d, 1H, J = 4.1 Hz), 4.02 (s, br, 1H), 3.74 (m, 1H), 3.35 (s, 3H), 2.71 (dd, 1H, J = 13.8, 4.0 Hz), 2.62−2.44 (complex m, 4H), 2.29 (m, 3H), 2.02 (m, 1H), 1.78 (s, 3H), 1.75 (m, 1H), 0.98 (d, 3H, J = 6.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 188.3, 182.3, 169.2, 145.4, 138.9, 137.7, 134.0, 133.8, 133.4 (2), 131.8, 130.6, 128.7, 123.4, 114.4, 78.5, 72.4, 69.1, 56.4, 44.6, 40.6, 36.2, 29.7, 25.8, 20.3, 10.7; IR (neat) ν_{max} 3340, 1650, 1503, 1005; CIHRMS M + H$^+$ (calcd for $C_{26}H_{34}NO_6$) 456.2386, found 456.2388; $[\alpha]^{23}_D = +4.7°$ (*c* 0.15, MeOH); $[\alpha]^{23}_D$ (lit.[5c]) = +4.3° (*c* 1.0, MeOH) R_f ($CHCl_3$/EtOH, 15:1) = 0.20; R_f (benzene/$CHCl_3$/MeOH, 3:7:3) = 0.50.

Arene (25). A solution of the silyl triene (50 mg, 0.066 mmol) in methanol (6.0 mL, 0.01 **M**) was treated with catalytic *p*-toluenesulfonic acid (3.0 mg, 0.033 mmol, 0.5 equiv). The reaction mixture was stirred at rt for 30 min and subsequently diluted with $NaHCO_3$ and H_2O (20 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (20 → 30% EtOAc/PE) afforded **25** as a colorless oil (90%, 36 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, br, 1H), 7.84 (d, 1H, J = 3.2 Hz), 6.43 (d, 1H, J = 2.8 Hz), 6.10−5.90 (complex m, 4H), 5.90 (d, 1H, J = 9.5 Hz), 5.59 (m, 2H), 5.05 (apparent t, 1H, J = 6.8 Hz), 4.95 (m, 1H), 4.80 (br d, 1H, J = 4.0 Hz), 4.40 (m, 1H), 4.02 (s, br, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.35 (s, 3H), 2.71 (dd, 1H, J = 13.8, 4.0 Hz), 2.50 (m, 4H), 2.00 (m, 2H), 1.78 (s, 3H), 1.75 (m, 1H), 0.98 (d, 3H, J = 6.0 Hz), 0.82 (s, 9H), −0.033 (s, 3H), −0.044 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.1, 151.0, 141.0, 138.9, 134.0, 133.8, 133.4, 131.8, 131.0, 130.6, 128.7, 128.0, 123.4, 115.5, 107.6, 78.5, 72.4, 69.1, 60.5, 56.4, 56.0, 44.6, 40.6, 36.2, 29.7, 25.8, 25.0, 20.3, 18.3, 10.7, −5.00, −5.50; IR (neat) ν_{max} 3400, 1650, 1500; CIHRMS M + H$^+$ (calcd for $C_{34}H_{54}NSiO_6$) 600.3720, found 600.3755; $[\alpha]^{23}_D = +71.0°$ (*c* 0.10, $CHCl_3$).

Cyclohexylcarbonyl-δ-alanine Arene (26). The symmetrical anhydride of Fmoc-D-alanine was prepared in CH_2Cl_2 (0.1 M) prior to use by the addition of DCC (82 mg, 0.396 mmol) to a solution of Fmoc-D-alanine (250 mg, 0.792 mmol) in CH_2Cl_2. The reaction mixture was cooled to 0 °C and stirred for 30 min, then warmed to rt for 30 min. The reaction mixture was then filtered into a flask and diluted with CH_2Cl_2 to a final volume of 12 mL. A solution of the arene **25** (36 mg, 0.060 mmol) and DMAP (2 mg, 0.0132 mmol, 0.2 equiv) in CH_2Cl_2 (2.6 mL, 0.025 M) was cooled to −78 °C, then treated with the solution of Fmoc-D-alanine anhydride. The suspension was stirred at −78 °C for 1 h, subsequently diluted with pH 7 buffer (10 mL), and allowed to warm to rt. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude Fmoc derivative was redissolved in CH_2Cl_2 (1 mL, 0.06 M) and treated with diethylamine (1 mL). The reaction mixture was stirred at rt for 30 min and subsequently concentrated in vacuo. The crude residue was dissolved in CH_2Cl_2 (10 mL, 0.003 M), and BOP (0.18 g, 0.396 mmol, 6.6 equiv), triethylamine (3.0 mL), and cyclohexanecarboxylic acid (0.1 mL, 0.60 mmol, 10.0 equiv) were added successively. The reaction mixture was stirred at rt for 15 min and subsequently diluted with pH 7 buffer (20 mL). The reaction mixture was extracted

with EtOAc (3 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (30% EtOAc/PE) afforded **26** as a colorless oil (32 mg, 70%, three steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, br, 1H), 7.84 (d, 1H, J = 3.2 Hz), 6.43 (d, 1H, J = 2.8 Hz), 6.10−5.90 (complex m, 4H), 5.90 (d, 1H, J = 9.5 Hz), 5.59 (m, 2H), 5.05 (apparent t, 1H, J = 6.8 Hz), 4.95 (m, 1H), 4.40 (m, 1H), 4.02 (s, br, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.35 (s, 3H), 2.71 (dd, 1H, J = 13.8, 4.0 Hz), 2.52 (m, 3H), 2.41−1.51 (complex m, 16H), 1.78 (s, 3H), 1.75 (m, 1H), 1.39 (d, 3H, J = 5.8 Hz), 0.98 (d, 3H, J = 6.0 Hz), 0.80 (s, 9H), −0.030 (s, 3H), −0.045 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.6, 173.0, 169.5, 152.0, 142.0, 140.0, 138.2 (2), 133.2, 133.0, 131.2, 129.5, 127.8, 122.2, 116.5, 108.0, 79.1, 75.3, 68.0, 60.5, 56.7, 56.0, 48.5, 45.0, 44.8, 40.0, 33.0, 29.4, 29.2 (2), 26.5, 25.7 (2), 25.6 (2), 20.5, 18.2, 17.2, 9.8, −5.00, −5.80; IR (neat) ν_{max} 1730, 1650, 1530, 1210; CIHRMS M + H^+ (calcd for $C_{44}H_{69}N_2SiO_8$) 781.4823, found 781.4861; $[\alpha]^{23}_D$ = +72.7° (*c* 0.11, $CHCl_3$).

(+)-Mycotrienin I (1c). A solution of **18** (32 mg, 0.039 mmol) in a mixture of THF/H_2O (10:1, 10 mL, 0.003 M) was cooled to 0 °C and treated with CAN (1 M in H_2O, 0.20 mL, 5.0 equiv). The bright yellow solution was stirred for 30 min at 0 °C and subsequently poured onto H_2O (20 mL). The reaction mixture was extracted with Et_2O (2 × 25 mL) and CH_2Cl_2 (2 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude quinone as a bright yellow viscous oil. The crude quinone was dissolved in acetonitrile (1.0 mL, 0.05 M) and treated with 40% aqueous HF (10% v/v, 0.10 mL). The reaction mixture was stirred at rt for 24 h and subsequently diluted slowly with $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (2.5% MeOH/CH_2Cl_2) afforded (+)-**1c** as a yellow solid (40%, two steps, 10 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, br, 1H), 7.48 (s, 1H), 6.45 (s, 1H), 6.10−5.90 (complex m, 4H), 5.90 (d, 1H, J = 9.5 Hz), 5.59 (m, 2H), 5.05 (apparent t, 1H, J = 6.8 Hz), 4.95 (m, 1H), 4.80 (br d, 1H, J = 4.0 Hz), 4.40 (m, 1H), 4.02 (s, br, 1H), 3.35 (s, 3H), 2.71 (dd, 1H, J = 13.8, 4.0 Hz), 2.52 (m, 3H), 2.41−1.51 (complex m, 16H), 1.78 (s, 3H), 1.75 (m, 1H), 1.39 (d, 3H, J = 5.8 Hz), 0.98 (d, 3H, J = 6.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 188.1, 182.4, 176.6, 173.0, 169.5, 145.2, 140.0, 137.9, 138.2 (2), 133.2, 133.0, 131.2, 129.5, 122.2, 114.3, 79.1, 75.3, 68.0, 56.7, 48.5, 45.0, 44.8, 40.0, 33.0, 29.4, 29.2 (2), 25.7 (2), 25.6 (2), 20.5, 17.2, 9.8; IR (neat) ν_{max} 3340, 1720, 1650, 1530, 1200, 1004; CIHRMS M + NH_4^+ (calcd for $C_{36}H_{52}N_3O_8$) 654.3754, found 654.3758; $[\alpha]^{23}_D$ = +91.0° (*c* 0.16, MeOH); $[\alpha]^{23}_D$ (lit.[5a]) = +92° (*c* 1.0, MeOH); R_f ($CHCl_3$/EtOH, 15:1) = 0.60; R_f (benzene/$CHCl_3$/MeOH, 3:7:3) = 0.74.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectral data for all intermediates and final products as well as full spectral data for all intermediates not listed in the Experimental Section (109 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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