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Enantioselective Synthesis of the C1−C11 Fragment of Bafilomycin A_1 Using Non-Wittig and Desymmetrization Strategies

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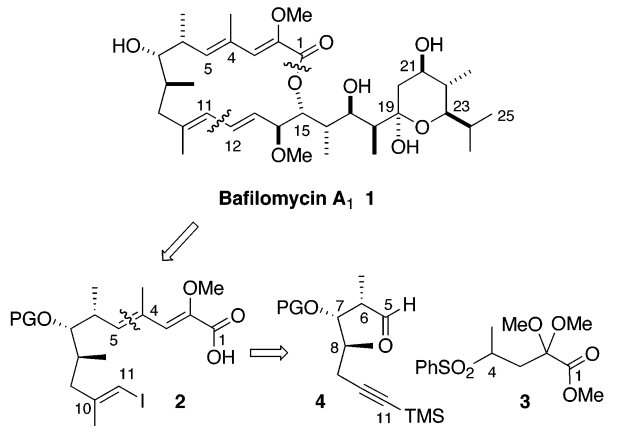
The synthesis of the C1−C11 fragment **33** of bafilomycin A_1 was achieved. Intermediate ketone **16** was prepared in six steps from 4-oxopimelate **13**. Desymmetrization of this ketone using Koga's chiral base followed by TMSCl quench furnished silyl enol ether **17** with excellent enantioselectivity. Further elaboration led to C5−C11 aldehyde **24**, which was coupled with sulfone **3** to give lactone **25** in very good yield. The subsequent reductive elimination created the *E*-trisubstituted C4−C5 olefin with a 13:1 selectivity. The *E* C2−C3 double bond was then installed by methanol elimination, and compound **33** was obtained after a few functional group manipulations and a Negishi methyl zirconation.

Introduction

Bafilomycin A_1 **1** (Scheme 1) was first isolated from the broth of *Streptomyces griseus* in 1984 by Werner et al.[1] It is a 16-membered plecomacrolide with potent biological activities due to its unique specific inhibitory effect on vacuolar-type proton translocating ATP-ases (V-ATPases).[2] Four total syntheses of bafilomycin A_1 **1** and one synthesis of a *seco*-form of the molecule, bafilomycin V_2, which is a methanolysis product of bafilomycin C_2, have been reported so far.[3] Significant partial contributions as well as three total syntheses of the related concanamycin F have also been described.[4] Moreover, extensive chemical studies are devoted to the synthesis of derivatives possessing improved specificity in inhibiting the V-ATPases overexpressed in the bone-resorbing osteoclasts, a major metabolic disorder associated with osteoporosis.[5]

SCHEME 1



The retrosynthesis we envisaged for the synthesis of bafilomycin A_1[6] is shown in Scheme 1. The macrolactone can be opened and then disconnected between C-11 and C-12 via a Stille- or Suzuki-type coupling reaction. The resulting C1−C11 fragment **2** would be synthesized from

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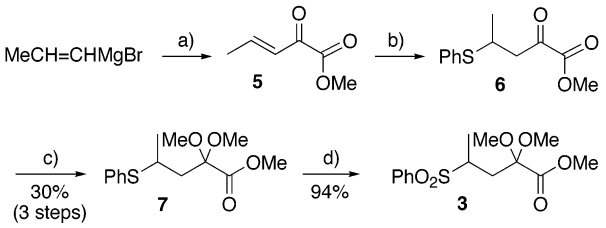
SCHEME 2[a]



[a] Key: (a) $(COOMe)_2$, Et_2O, −40 °C; (b) PhSH, Et_3N, CH_2Cl_2, 0 to 20°C; (c) $HC(OMe)_3$, MeOH, PTSA, reflux; (d) *m*-CPBA, CH_2Cl_2, 0 °C.

sulfone **3** and aldehyde **4** by a convergent Julia−Lythgoe strategy instead of the two consecutive Horner−Wadsworth−Emmons reactions which have been employed in all the published syntheses (except for Hanessian, who chose an aldol reaction to make the C2−C3 bond).

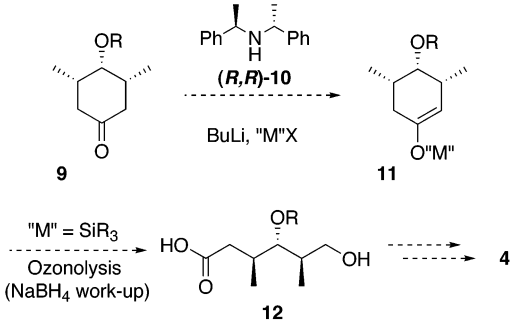
Results and Discussion

Preparation of Sulfone 3. Crystalline sulfone **3** was synthesized on a 10-g scale in four steps from methyl oxalate and 1-bromopropene via the known unsaturated keto ester **5** (Scheme 2).[7] Conjugate addition of thiophenol to **5** gave the corresponding sulfenyl derivative **6**.[8] Transformation of **6** into the corresponding ketal **7** followed by oxidation of the sulfenyl residue with *m*-chloroperbenzoic acid led to the expected ketal **3** in 28% overall yield.

Synthesis of the Aldehyde Partner. The next task to achieve for the construction of **2** was the elaboration of acetylenic aldehyde **4** bearing the required *anti-anti* stereotriad at C6−C8.

Among the four possible diastereoisomers, the construction of the *anti-anti* type of stereotriads is one of the most difficult to achieve, particularly in an enantioselective manner.[9] One of the main reasons for this difficulty is that such a triad formally results from a mismatched attack of a chiral enolate (or allyl analogue)[10] onto a chiral aldehyde under prevailing reagent-controlled conditions. To date, Brown's allyl boranes[11] or Roush's allyl boronates[12] give an efficient access to these triads. The latter author recently succeeded in developing an excellent access to such triads in the case of allylation of α-methyl *β*-hydroxy aldehydes with *Z*-crotyltrifluorosilanes.[13] Allenyltin reactions[14] or silicon-mediated allylation condensations[15] were also shown to give *anti,anti*-stereotriads. Other clever solutions have been developed in the case of aldol reactions.[16] However, most of these approaches requires the prerequisite preparation of both homochiral partners.

SCHEME 3



Other answers to this problem have been developed through non-aldol-type strategies. These methods involve hydroboration of allylic alcohols,[17] 1,3-reduction of *β*-hydroxylated ketones,[18] iodocyclization/radical reduction,[19] or alternative routes involving conjugate additions of cuprates to *γ*-hydroxyl α,*β*-unsaturated esters [20] or even *γ*-hydroxyl α,*β*-unsaturated sulfones.[21]

For the construction of optically active aldehyde **4**, we decided to develop a desymmetrization reaction of meso dimethyl ketone **9** with a chiral base (Scheme 3).[22] This ketone has been previously used for the construction of an acyclic intermediate during a synthesis of racemic tyrandamycin A.[23] Interestingly, the resulting enol ether **11** can be envisioned not only to be a convenient precursor of bafilomycin intermediates but also of numerous other synthetic targets due to the anticipated flexibility of the enol ether function. A second point of importance is that such a strategy would allow synthesis of both *anti,anti*-triad enantiomers, independently of preexisting chiral centers, as it is the case for several routes already developed (see refs 17−21 and also ref 12). Further transformations of **11** into **4** could be reasonably envisaged by ozonolysis of enol ether **11** to give hydroxy acid **12,** which has then to be transformed into **4**.

Construction of the Intermediate Cyclohexanone. Looking for an efficient route for the construction of **9**, we turned to a cyclization−alkylation approach from 4-oxopimelate **13** instead of the apparently more straightforward route starting from 2,6-dimethyphenol.[24] One

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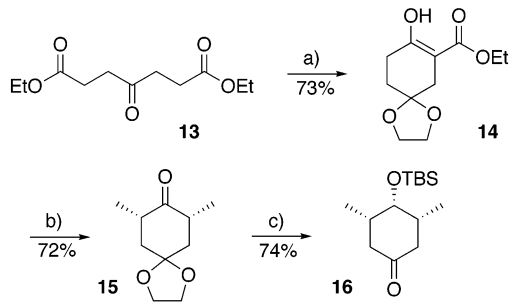
SCHEME 4[a]



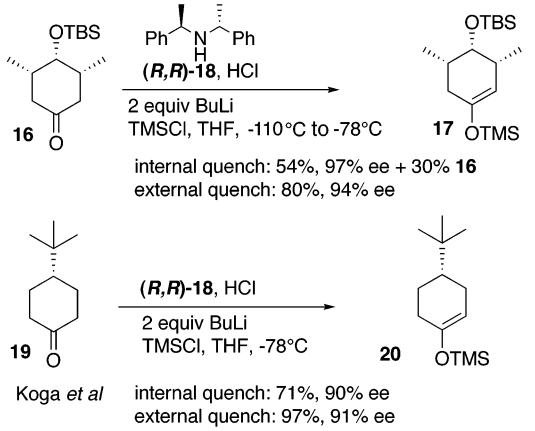
[a] Key: (a) (i) $(CH_2OH)_2$, PTSA, PhH, reflux, (ii) NaH, THF, reflux; (b) (i) NaH, THF, 0 °C; *t*-BuLi, −78 °C, HMPA; MeI, −78 to +25 °C; (ii) NaOH/EtOH, reflux; (c) (i) L-Selectride, THF, −78 °C, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, (iii) PTSA, acetone, reflux.

advantage of the pimelate route is to exhibit more flexibility in allowing formal preparation of the corresponding *syn*,*syn*-triad from an alternative axial reduction of the intermediate **15** to give the corresponding equatorial alcohol. The synthesis of ketone **16** (**9**, R = TBS) is summarized in Scheme 4.

Dieckmann cyclization of the dioxolane derivative of **13** afforded cyclohexenecarboxylic ester **14**.[25] Interestingly, the yield of the reaction was improved from 49% (literature) to 73% from **13** using two modifications: the intermediate acetal was not purified and the Dieckmann reaction was conducted in refluxing tetrahydrofuran instead of diethyl ether. For the subsequent dimethylation reaction, we addressed a one-pot dianion approach[26] which, in our hands, gave better results than the two-step procedure described by Narang and Dutta.[27] The dianion approach required strong basic conditions (1 equiv of NaH, then *t*-BuLi/HMPA in THF at −78 °C), and the reaction was clean on a 1-g scale. When carried out on a 30-g scale, ca. 5% α-monomethylated product was formed together with the expected α,γ-dimethyl derivative (obtained as 9:1 mixture of diastereoisomers). Direct refluxing of the alkylation crude extract in a 10% NaOH ethanolic solution resulted in a decarboxylation reaction together with total equilibration of the diastereomeric mixture of the dimethylated products to the more stable 1,3-*cis* isomer **15,** which was easily separated from the corresponding monomethylated adduct by flash chromatography. The rest of the synthesis of **16**, including L-Selectride reduction of the carbonyl group affording the expected axial hydroxyl group exclusively, was carried out according to Boeckman.[23] Interestingly, reduction of the carbonyl group under $NaBH_4/CeCl_3$ conditions of Luche gave the corresponding equatorial hydroxyl group in a 91:9 ratio (76% yield).[28]

Desymmetrization of the Intermediate Cyclohexanone. Deprotonation of the symmetrical cyclohexanone

SCHEME 5



intermediate **16** using chiral base (*R*,*R*)-**18** could be effected under two sets of conditions, as shown by Koga:[29] internal quench, where the ketone is added to a mixture of base and trimethylchlorosilane,[30] and external quench, where the base is added to the ketone followed by TMSCl. The presence of LiCl is crucial to obtain a good ee in the case of the external quench. The base is thus generated by treating the easily available hydrochloride salt of **18**[31] with 2 equiv of butyllithium.[32] As shown in Scheme 5, ketone **16** smoothly afforded silyl enol ether **17** in 54% yield and 97% ee[33] for the internal quench and 80% yield and 94% ee for the external quench.[34] The absolute stereochemistry of **17** was proved by correlating a later intermediate in the synthesis to a known compound. These results parallel those observed for 4-*tert*-butylcyclohexenol ether **20** obtained by Koga and coworkers from 4-*tert*-butylcyclohexanone **19**,[29] with lower yields but better enantioselectivities.

Molecular calculations (Macromodel) have confirmed unique severe constraints occurring from the ring substituents and particularly from the bulky axial OTBS group (Figure 1). Conformational analysis of **16** reveals a close proximity between the methyl groups of the axial

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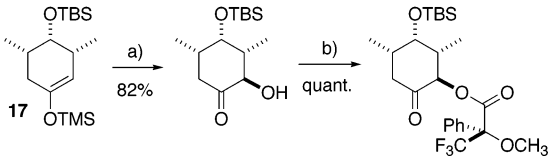
(33) The enantioselectivity analysis (^{1}H NMR and GLC) was carried out by preparing the Mosher ester of the α-hydroxy ketone derived from **17** according to ref 23 (step a) and: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512 (step b).



Reagents and conditions: a) NMO, cat. OsO_4, THF/H_2O 3:1, 20°C b) (+)-MTPA-Cl, Et_3N, DMAP, CH_2Cl_2.

(34) In this case, the enantioselectivity analysis (^{1}H NMR) was carried out by preparing the Mosher ester of the later intermediate hydroxy ester **21** (see Scheme 6).

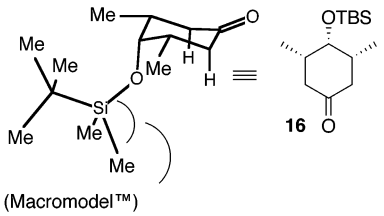
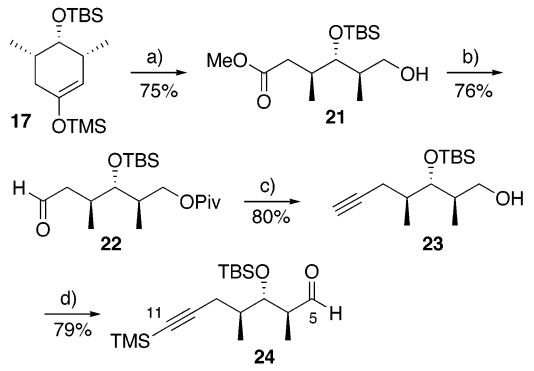


FIGURE 1.

SCHEME 6[a]

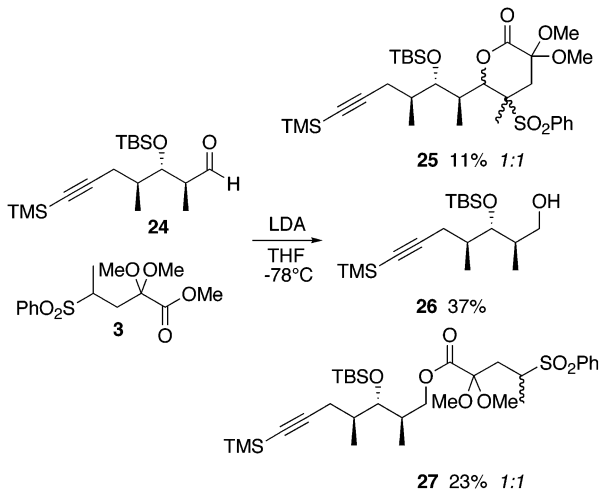


[a] Key: (a) (i) O_3, CH_2Cl_2/MeOH, −78 °C; $NaBH_4$, −78 to +20 °C, (ii) CH_2N_2, Et_2O; (b) (i) PivCl, Py, (ii) DIBAL-H, THF, −78 to −20 °C, (iii) IBX, THF, DMSO; (c) (i) $CH_3C(O)C(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 0 to 20 °C, (ii) DIBAL-H, toluene, −78 °C; (d) (i) BuLi, TMSCl; Et_3N; 2 N HCl, (ii) IBX, THF, DMSO.

tert-butyldimethylsilyloxy substituent and the axial protons susceptible to be removed. These constraints may be responsible for a better discrimination in the deprotonation reaction for **16** than for **19** where the bulky *tert*-butyl group adopts an equatorial position.

Final Elaboration of Aldehyde C5−C11. Ozonolysis of silyl enol ether **17** followed by reductive workup ($NaBH_4$) and treatment with diazomethane gave ester alcohol **21** in 75% yield (Scheme 6). The hydroxyl group was then protected as a pivalate ester and the methyl ester reduced with DIBAL-H in THF. This reduction is totally chemoselective because the reducing agent is deactivated by THF so it does not affect the more hindered ester function.[35] Oxidation with IBX[36] then furnished aldehyde **22**. Homologation to the corresponding acetylenic compound was effected with Ohira's reagent,[37] which is easier to make and to store than Seyferth's phosphonate,[38] and the pivalate ester was reduced with DIBAL-H in toluene in good yield. Alcohol **23** [$[\alpha]_D$ −9.8 (*c* 2.2, CH_2Cl_2) (lit.[3c] −6.7 (*c* 2.39, CH_2Cl_2))] is identical to the compound described by Roush,[3c] therefore establishing that the desymmetrization occurred as shown in Scheme 5. Silylation of the acetylenic moiety followed by IBX oxidation of the primary alcohol provided aldehyde **24** (**4**, PG = TBS) in 79% yield for the two steps. In summary, the C5−C11 fragment of bafilomycin A_1 was synthesized in 16 steps in 11% overall yield.

SCHEME 7



Coupling of Sulfone 3 and Aldehyde 24. Model Julia couplings of sulfone **3** with diverse aldehydes have been reported.[6a] Yields range from 52% to 95% if sulfone **3** is used in excess. The optimized conditions (3 equiv of **3**, 3 equiv of LDA) were applied to aldehyde **24**, and to our surprise, lactone **25**, resulting from cyclization of the alkoxy ester adduct, was obtained in only 11% yield (Scheme 7). Significant amounts of alcohol **26** (resulting from reduction of **24**) and ester **27** (the transesterification product of sulfone **3** with alcohol **26**) were produced.[39] The deprotonation of sulfone **3** is probably incomplete, and the condensation of the anion of this secondary sulfone, which is reversible, does not efficiently compete with the reduction of aldehyde **24** by LDA. No epimerization of aldehyde **24** was observed.

We screened several strong bases to try to improve the yield of this coupling reaction, with unfortunate results.[40] Finally, we decided to test lithium diethyl amide, which has been used by Evans et al.[41] for the key coupling in the total synthesis of cytovaricin because it is more kinetically efficient than LDA. Addition of this base to sulfone **3** resulted in a deep orange color, in opposition to the pale yellow color observed with LDA, and lactone **25** was obtained in 83% yield as a 1:1 mixture of diastereomers (Scheme 8). In addition, 94% of the excess sulfone (4 equiv) was recovered after flash chromatography. Reductive elimination was performed with sodium amalgam in methanol and produced the trisubstituted C4−C5 double bond of **31** with a 13:1 selectivity in favor of the *E* isomer.[6a] Elimination of methanol must

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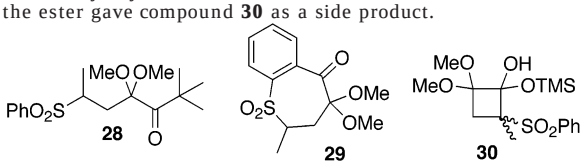
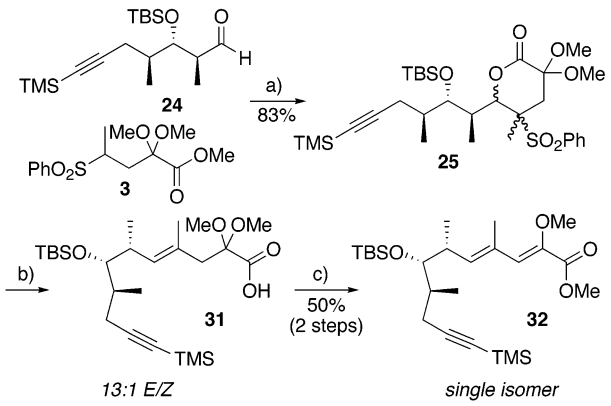
(39) For examples of aldehyde reduction by LDA, see: Leonard, J.; Hussain, N. *J. Chem. Soc., Perkin Trans. 1* **1994**, 49. Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057.

(40) *t*-Buli added to the ester function to give ketone **28** and lithium tetramethylpiperidide deprotonated the ortho aromatic proton, and the resulting anion cyclized to furnish **29**. If the reaction was quenched with trimethylsilyl chloride, intramolecular condensation of the anion on the ester gave compound **30** as a side product.



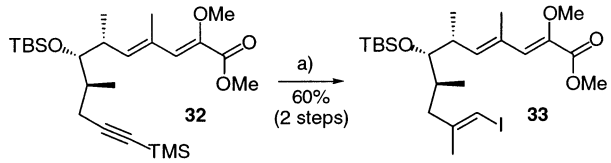
(41) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

SCHEME 8[a]



[a] Key: (a) $LiNEt_2$, THF, −78 to 0 °C; (b) Na/Hg, MeOH, −40 °C; (c) (i) CSA, benzene, reflux, (ii) CH_2N_2, Et_2O.

SCHEME 9[a]



[a] Key: (a) (i) K_2CO_3, MeOH; (ii) Cp_2ZrCl_2, $AlMe_3$, H_2O, CH_2Cl_2; I_2, THF, −78 °C to 0 °C.

be conducted under rigorously anhydrous conditions to prevent methyl ketal hydrolysis. After diazomethane treatment, diene **32** was isolated as a single isomer in 50% yield from **25**.[42]

The final steps are described in Scheme 9. Removal of the trimethylsilyl group followed by Negishi's methyl zirconation[43] in the presence of 2 equiv of water[3e] led to the C1−C11 fragment **33** (**2**, PG = TBS), which proved to be identical to the compounds reported by Marshall[3e] and Roush.[3c]

Conclusion

We have synthesized the C1−C11 portion of bafilomycin A_1 in 21 steps and 3.3% overall yield (85% average yield per step). The key steps of this approach are a desymmetrization of a substituted cyclohexanone with Koga's amide base to install the *anti-anti* stereotriad at C6−C8 and a Julia coupling leading to the C4−C5 trisubstituted double bond in a highly selective manner.

Experimental Section

For general methods, see ref 6b.

Methyl 2,2-Dimethoxy-4-phenylsulfanylpentanoate (7). To a solution of 20 g (0.13 mol) of methyl 2-oxopent-3-enoate[7] and thiophenol (11 mL, 0.10 mol, 0.8 equiv) in 150 mL of CH_2Cl_2 at 0 °C was added 1 mL (7.2 mmol, 0.05 equiv) of Et_3N. After the cooling bath was removed, the solution was stirred at room temperature for 2 h, diluted with Et_2O, washed three times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give **6** as a yellow oil which was unstable over silica gel and used in the next reaction without further purification.

A mixture of crude **6** (0.104 mol), trimethyl orthoformate (15 mL, 0.14 mol, 1.3 equiv), and a catalytic amount of *p*-TSA in 200 mL of dry MeOH was refluxed for 72 h and then cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and partitioned between water and Et_2O. The layers were separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed five times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give after flash chromatography on silica gel (petroleum ether/AcOEt, 9:1−3:1) 8.64 g (30% for three steps) of **7** as a yellow oil: IR (film) 2949, 1745, 1637, 1584, 1476, 1374, 1202, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.32 (m, 5H), 3.79 (s, 3H), 3.25, 3.21 (2s, 6H), 3.16 (m, 1H), 2.22 (dd, 1H, J = 15.0, 5.7 Hz), 2.10 (dd, 1H, J = 15.0, 7.0 Hz), 1.28 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 134.4, 133.3, 129.0, 127.6, 101.4, 52.6, 49.9, 49.8, 40.4, 38.8, 22.0; MS (CI, NH_3) m/z 302 ($M + NH_4^+$), 285 ($M + H^+$).

Methyl 4-Benzenesulfonyl-2,2-dimethoxypentanoate (3). To a solution of 3.1 g (10.8 mmol) of **7** in 100 mL of CH_2Cl_2 at 0 °C was added 5.8 g (23.7 mmol, 2.2 equiv) of *m*-CPBA (80% in *m*-chlorobenzoic acid). The resulting mixture was stirred at this temperature for 3 h and quenched with saturated aqueous $NaHCO_3$ and 37% aqueous $NaHSO_3$. The biphasic mixture was stirred for 1 h, the layers were separated, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed three times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give after purification by flash chromatography on silica gel (petroleum ether/AcOEt, 80:20) 3.2 g (94%) of sulfone **3** as a white solid: mp 65−67 °C; IR (film) 2956, 1749, 1447, 1305, 1223, 1148, 1085, 1049, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.32 (m, 5H), 3.72 (s, 3H), 3.23, 3.20 (2s, 6H), 3.13 (m, 1H), 2.60 (dd, 1H, J = 14.6, 1.5 Hz), 1.94 (dd, 1H, J = 14.6, 10.0 Hz), 1.24 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 136.9, 133.9, 129.3, 129.2, 101.0, 55.8, 52.8, 50.6, 49.0, 33.3, 14.3; MS (CI, NH_3) m/z 302 ($M + NH_4^+ -$ MeOH). Anal. Calcd for $C_{14}H_{20}O_6S$: C, 53.15; H, 6.37. Found: C, 53.25; H, 6.34.

Ethyl 8-Hydroxy-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (14).[25] A mixture of diethyl 4-oxopimelate **13** (31 g, 0.20 mol), distilled ethylene glycol (18 mL, 0.32 mol, 1.6 equiv), and a catalytic amount of *p*-TSA (250 mg, 1.3 mmol, 0.007 equiv) in 400 mL of toluene was heated in a flask fitted with a Dean−Stark apparatus with a reflux condenser. After 12 h, the mixture was cooled to room temperature, and 20 mL of saturated aqueous $NaHCO_3$ was added. The toluene was removed in vacuo and the residue treated with Et_2O and H_2O. The layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed three times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired ketal as a yellow oil that was used without purification in the next reaction.

To a suspension of NaH (80% dispersion in mineral oil, 7.2 g, 0.24 mol, 1.2 equiv) in 500 mL of dry THF at 0 °C was added via cannula a solution of the previous crude ketal in 300 mL of dry THF. The resulting solution was refluxed for 5 h and cooled to 0 °C, and glacial acetic acid (15 mL, 0.26 mol, 1.3 equiv) was added with rapid stirring. The resulting solution was diluted with Et_2O, washed three times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give after distillation 33 g (73% for two steps) of product **14** as a colorless oil: bp 120 °C/0.01 mmHg; IR (film) 2958, 2888, 1728, 1654, 1616, 1477, 1366, 1354, 1298, 1197, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, 2H, J = 7.3 Hz), 4.02 (m, 4H), 2.50 (t, 2H, J = 6.8 Hz), 2.48 (s, 2H), 1.84 (t, 2H, J = 6.8 Hz), 1.28 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.1, 107.5, 95.4, 64.6, 60.4, 32.8, 30.4, 28.0, 14.3; MS (CI, NH_3) m/z 229 ($M + H^+$). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.06. Found: C, 57.77; H, 7.18.

(42) The geometry of both double bonds was assigned by NOE experiments performed on the primary alcohol obtained by DIBAL-H reduction of a model compound of **33**.

(43) Negishi, E.-I.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2252.

(7*R,9*S**)-7,9-Dimethyl-1,4-dioxaspiro[4.5]decan-8-one (15).** To a suspension of NaH (80% dispersion in mineral oil, 4.8 g, 0.16 mol, 1.1 equiv) in 500 mL of dry THF at 0 °C was added via cannula under nitrogen a solution of 33 g (0.14 mol) of **14** in 500 mL of dry THF. After 10 min, the solution was cooled to −78 °C, and *t*-BuLi (1.7 M solution in pentane, 112 mL, 0.19 mol, 1.3 equiv) was slowly added via cannula. The resulting red mixture was stirred at −78 °C for 15 min, and HMPA (65 mL, 0.37 mol, 2.6 equiv) was added slowly via syringe. After the resulting mixture was stirred for 10 min, MeI (45 mL, 0.72 mol, 5 equiv) was rapidly added. The color faded immediately. After 5 min, the cold bath was removed and the pale yellow solution was stirred at room temperature for 5 h. Then 30 mL of 1 N aqueous HCl was added, followed by 200 mL of brine and 500 mL of Et_2O. The layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed five times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the dimethylated keto ester which was used without purification in the next reaction.

A solution of the crude keto ester in 320 mL of 10% aqueous KOH and 80 mL of EtOH was refluxed for 8 h. The solution was cooled to room temperature, and 500 mL of Et_2O was added. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give after flash chromatography on silica gel (petroleum ether/AcOEt, 95:5−60:40) 19.5 g (72% for two steps) of **15** as a pale yellow solid that was identical to the ketone reported by Boeckman.[23]

(3*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsiloxy)-3,5-dimethyl-1-trimethylsiloxycyclohexene (17), External Quench Procedure. To a solution of (*R*,*R*)-(+)-bis(α-methylbenzyl)amine hydrochloride (4.6 g, 17 mmol, 1.5 equiv) in 55 mL of THF at −78 °C was added 19.3 mL (1.7 M in hexane, 33 mmol, 2.8 equiv) of BuLi. After 15 min, the resulting mixture was warmed to 0 °C for 15 min. The resulting solution was warmed to room temperature for 30 min and then cooled to −78 °C. To a solution of **16** (3.0 g, 12 mmol) in 90 mL of THF at −110 °C was added (via cannula on the side of the flask) the cold solution of chiral amide. The resulting solution was stirred at this temperature for 5 min and then treated dropwise with freshly distilled TMSCl (5.9 mL, 47 mmol, 4.0 equiv). After 15 min at −110 °C, the solution was warmed to −78 °C for another 15 min, and then freshly distilled Et_3N (8.1 mL, 59 mmol, 5.0 equiv) was added. After 20 min, the solution was removed from the cold bath and 200 mL of satured aqueous $NaHCO_3$ was added followed by 200 mL of Et_2O. The mixture was warmed to room temperature, and the layers were separated. The aqueous phase was extracted twice with petroleum ether. The combined organic layers were washed twice with water and then with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude material that was purified (important) by a quick flash chromatography (5% Et_2O, 93% petroleum ether, 2% Et_3N) to give 3.1 g (80%) of **17** as a pale yellow oil: $[\alpha]_D$ −18.8 (*c* 2.9, CH_2Cl_2); IR (film) 2957, 2928, 2856, 1668, 1472, 1371, 1251, 1190, 1175, 1105, 1081, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (d, 1H, J = 1.8 Hz), 3.60 (d, 1H, J = 3.1 Hz), 2.37 (m, 1H), 1.95 (m, 1H), 1.83 (m, 2H), 0.97 (d, 3H, J = 2.6 Hz), 0.95 (d, 3H, J = 3.6 Hz), 0.91 (s, 9H), 0.18 (s, 9H), 0.06, 0.05 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 107.4, 73.7, 36.6, 35.6, 33.8, 26.3, 19.1, 18.9, 18.6, 0.4, −3.3; MS (CI, NH_3) m/z 329 ($M + H^+$).

Methyl (3*R*,4*R*,5*S*)-4-(*tert*-Butyldimethylsiloxy)-6-hydroxy-3,5-dimethylhexanoate (21). A stream of O_3/O_2 was passed through a solution of **17** (3.1 g, 9.4 mmol) and 2 mg of Sudan red in 120 mL of CH_2Cl_2 and 30 mL of MeOH at −78 °C until the color of the solution turned from pink to pale yellow. After the resulting solution was purged with oxygen and then with argon, sodium borohydride (1.3 g, 38 mmol, 4.0 equiv) was added and the resulting suspension was stirred at −78 °C for 1 h then warmed to 0 °C, stirred for 90 min, quenched with 50 mL of saturated aqueous NH_4Cl, and diluted with 300 mL of Et_2O. The layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic phases were washed five times with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the desired hydroxy acid (2.9 g) as a yellow solid that was used in the next reaction without further purification.

The preceding crude hydroxy acid (2.9 g) was dissolved in 50 mL of Et_2O in an Erlenmeyer flask, and a freshly distilled solution of diazomethane was added until no more nitrogen evolved. Several drops of acetic acid were added until the solution became colorless and the resulting mixture was concentrated in vacuo. Then 20 mL of pentane was added to remove the acetic acid by azeotropic distillation. Flash chromatography on silica gel (Et_2O/petroleum ether, 5:95−40:60) gave 2.2 g (75% for two steps) of **21** as a colorless oil: $[\alpha]_D$ +2.4 (*c* 2.0, CH_2Cl_2); IR (film) 3452, 2955, 2884, 2857, 1740, 1462, 1436, 1360, 1255, 1171, 1084, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.62 (t, 2H, J = 5.6 Hz), 3.53 (dd, 1H, J = 4.9, 4.4 Hz), 2.53 (dd, 1H, J = 14.6, 3.9 Hz), 2.43 (t, 1H, J = 5.6 Hz), 2.22 (m, 1H), 2.10 (dd, 1H, J = 14.6, 9.2 Hz), 1.84 (m, 1H), 1.00 (d, 3H, J = 6.6 Hz), 0.96 (d, 3H, J = 7.1 Hz), 0.92 (s, 9H), 0.12, 0.10 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 80.3, 65.9, 51.6, 38.1, 37.3, 35.2, 26.2, 18.4, 17.2, 16.0, −3.9; MS (CI, NH_3) m/z 305 ($M + H^+$). Anal. Calcd for $C_{15}H_{32}O_4Si$: C, 59.16, H, 10.59. Found: C, 58.87, H, 10.63.

To 104 mg of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.44 mmol, 3 equiv) in 1 mL of CH_2Cl_2 was added 58 μL (0.66 mmol, 4.5 equiv) of oxalyl chloride and a drop of DMF. After 2 h, the solvent was removed under the vacuum of a pump, and 1 mL of CH_2Cl_2 was added. A solution of **21** (45 mg, 0.15 mmol, and Et_3N (84 μL, 0.60 mmol, 4.0 equiv) in 500 μL of CH_2Cl_2 was added followed by a crystal of DMAP. After 1 night, the solution was diluted with Et_2O and then washed with saturated aqueous NH_4Cl. The aqueous layer was extracted twice with Et_2O. The combined organic phases were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The ^1H NMR spectrum showed 94% ee by integrating the peaks at 4.46 ppm (major diastereomer) and at 4.05 ppm (minor diastereomer).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-6-oxohexyl 2,2-Dimethylpropionate (22). To 1.8 g (5.9 mmol) of **21** in 20 mL of freshly distilled pyridine at 0 °C was added 870 μL (7.1 mmol, 1.2 equiv) of pivaloyl chloride. After 1.5 h at room temperature, 200 mL of Et_2O and 200 mL of 1 N aqueous $KHSO_4$ were added. The organic phase was washed with 100 mL of 1 N aqueous $KHSO_4$. The combined aqueous phases were extracted five times with 100 mL of Et_2O. The combined organic phases were washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/petroleum ether, 0:100−30:70) gave 2.0 g (87%) of the pivalate ester as a colorless oil: $[\alpha]_D$ +11.0 (*c* 2.0, CH_2Cl_2); IR (film) 2958, 1734, 1283, 1160, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (dd, 1H, J = 10.9, 5.1 Hz), 3.87 (dd, 1H, J = 10.9, 6.9 Hz), 3.66 (s, 3H), 3.49 (t, 1H, J = 5.3 Hz), 2.52 (dd, 1H, J = 15.2, 3.7 Hz), 2.25−2.18 (m, 1H), 2.09 (dd, 1H, J = 15.2, 9.9 Hz), 1.99−1.93 (m, 1H), 1.20 (s, 9H), 0.99, 0.96 (2d, 6H, J = 6.8, 7.0 Hz), 0.90 (s, 9H), 0.06, 0.05 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 173.7, 77.7, 66.5, 51.3, 38.8, 37.0, 36.9, 33.8, 27.2, 26.1, 18.3, 17.9, 14.6, -4.0, −4.1; MS (CI, NH_3) m/z 406 ($M + NH_4^+$), 389 ($M + H^+$). Anal. Calcd for $C_{20}H_{40}O_5Si$: C, 61.81; H, 10.37. Found: C, 61.94; H, 10.41.

To a solution of 2.0 g (5.1 mmol, 1.0 equiv) of the previous pivalate ester in 50 mL of THF at −78 °C was added 12 mL (15 mmol, 1.3 M solution in hexane, 3.0 equiv) of DIBAL-H. The solution was warmed slowly to −20 °C over 1 h and stirred at this temperature until no more starting material remained. Then 0.5 mL of MeOH was added and 10 min later 50 mL of saturated aqueous Rochelle's salt. The mixture was vigorously stirred at room temperature for 1 h, and 100 mL of Et_2O was

added. The aqueous mixture was extracted three times with 100 mL of Et_2O. The aqueous phase was acidified with 12 N aqueous HCl and extracted twice with 50 mL of Et_2O. The last two organic phases were washed twice with water and combined with the other organic phases. The combined organic phases were washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. An aliquot of the crude alcohol was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 5:95−40:60): $[\alpha]_D$ +15.1 (*c* 3.2, CH_2Cl_2); IR (film) 3448, 2959, 1734, 1159, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (dd, 1H, J = 10.9, 4.4 Hz), 3.87 (dd, 1H, J = 10.9, 7.0 Hz), 3.77−3.72 (m, 1H), 3.63−3.57 (m, 1H), 3.50 (dd, 1H, J = 6.5, 3.4 Hz), 2.08−2.01 (m, 1H), 1.89−1.84 (m, 1H), 1.73−1.67 (m, 1H), 1.55−1.47 (m, 1H), 1.20 (s, 9H), 0.99, 0.95 (2d, 6H, J = 7.0 Hz and J = 6.8 Hz), 0.91 (s, 9H), 0.09, 0.07 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 78.5, 66.9, 60.7, 39.0, 36.7, 34.4, 33.6, 27.4, 26.2, 18.5, 17.4, 15.1, −3.6, −4.1; MS (CI, NH_3) *m*/*z* 361 ($M + H^+$). Anal. Calcd for $C_{19}H_{40}O_4Si$: C, 63.28; H, 11.18. Found: C, 62.87; H, 11.11.

The previous crude alcohol was dissolved in 30 mL of THF, and 2.8 g (10 mmol, ca. 2.0 equiv) of IBX predissolved in 25 mL of dry DMSO was added via cannula. After 1 h, 30 mL of water was added. Ten minutes later, 60 mL of Et_2O was added and the white precipitate was filtered (rinse several times with Et_2O). The aqueous phase was extracted three times with 30 mL of Et_2O. The combined organic phases were washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give aldehyde **22**. An aliquot was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 0:100−20:80): IR (film) 2959, 1729, 1157, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 4.21 (dd, 1H, J = 10.9, 5.2 Hz), 3.88 (dd, 1H, J = 10.9, 6.9 Hz), 3.50 (m, 1H), 2.59 (dd, 1H, J = 16.3, 2.5 Hz), 2.35−2.31 (m, 1H), 2.26−2.21 (m, 1H), 1.99−1.93 (m, 1H), 1.20 (s, 9H), 1.01 (d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 7.0 Hz), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 178.4, 78.3, 66.7, 47.0, 39.1, 37.7, 31.8, 27.4, 26.3, 18.6, 18.6, 14.5, −3.7, −3.9; MS (CI, NH_3) *m*/*z* 376 ($M + NH_4^+$), 359 ($M + H^+$).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethylhept-6-yn-1-ol (23). To the crude aldehyde **22** in 25 mL of MeOH at 0 °C was added 2.1 g (15 mmol, ca. 3 equiv) of thinly powdered anhydrous K_2CO_3. A solution of 1.5 g (7.7 mmol, ca. 1.5 equiv) of Ohira's diazophosphonate in 25 mL of MeOH was added (the solution quickly turned milky green). After 1.5 h at 20 °C, 500 mL of Et_2O was added followed by 50 mL of water. The aqueous phase was extracted three times with 50 mL of Et_2O. The combined organic phases were washed three times with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. An aliquot was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 0:100−20:80): $[\alpha]_D$ +4.6 (*c* 2.5, CH_2Cl_2); IR (film) 3313, 2958, 2118, 1731, 1156, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (dd, 1H, J = 10.9, 5.3 Hz), 3.87 (dd, 1H, J = 10.9, 7.3 Hz), 3.58 (dd, 1H, J = 4.9, 4.8 Hz), 2.33 (ddd, 1H, J = 16.9, 4.7, 2.7 Hz), 2.13 (ddd, 1H, J = 16.9, 8.3, 2.6 Hz), 2.04−1.95 (m, 1H), 1.96 (t, 1H, J = 2.6 Hz), 1.92−1.85 (m, 1H), 1.21 (s, 9H), 1.07 (d, J = 6.9 Hz, 3H), 0.99 (d, 3H, J = 6.9 Hz), 0.91 (s, 9H), 0.09, 0.08 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 83.7, 77.7, 69.4, 66.8, 39.0, 37.1, 36.9, 27.5, 26.3, 22.2, 18.6, 17.1, 15.4, −3.9; MS (CI, NH_3) *m*/*z* 355 ($M + H^+$); exact mass calcd for $C_{20}H_{39}O_3Si$ 355.2670, found 355.2668.

To a solution of the previous crude alkyne in 50 mL of toluene at −78 °C was added 12 mL (15 mmol, 1.3 M solution in hexane, ca. 3 equiv) of DIBAL-H. After 2 h, 0.5 mL of MeOH was added and 10 min later 50 mL of saturated aqueous Rochelle's salt. The mixture was vigorously stirred at room temperature for 1 h. Then 100 mL of Et_2O was added. The aqueous mixture was extracted three times with 100 mL of Et_2O. The aqueous mixture was acidified with 12 N aqueous HCl and extracted twice with 50 mL of Et_2O. The last two organic phases were washed twice with water and combined with the other organic phases. The combined organic phases were washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/petroleum ether, 5:95−30:70) gave 0.99 g (70% for four steps) of **23** which is identical to the product described by Roush:[3c] $[\alpha]_D$ −9.8 (*c* 2.2, CH_2Cl_2) (lit.[3c] $[\alpha]_D$ −6.7 (*c* 2.4, CH_2Cl_2)).

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-7-trimethylsilylhept-6-ynal (24). To 1.3 g (4.8 mmol) of alcohol **23** in 90 mL of THF at −78 °C was added 7.0 mL (12 mmol, 1.7 M in hexane, 2.5 equiv) of BuLi. After 15 min, the solution was warmed to −20 °C for 20 min. To the solution cooled to −78 °C was added 3.0 mL (24 mmol, 5.0 equiv) of TMSCl, and the solution was warmed to −50 °C over 30 min. The cold bath was removed, and 100 mL of 2 N aqueous HCl was added. The mixture was vigorously stirred at 0 °C for 15 min, and then 200 mL of Et_2O was added. The organic phase was directly washed with saturated aqueous $NaHCO_3$. The acidic aqueous phase was extracted three times with 50 mL of Et_2O. The combined organic phases were washed with the remaining basic solution, twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel gave 1.4 g (88%) of the desired silyl derivative as a colorless oil: $[\alpha]_D$ −13.3 (*c* 3.2, CH_2Cl_2); IR (film) 3357, 2957, 2175, 1472, 1250, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72−3.66 (m, 1H), 3.62−3.56 (m, 1H), 2.59 (brt, 1H, J = 5.7 Hz), 2.30 (dd, 1H, J = 17.0, 6.6 Hz), 2.19 (dd, 1H, J = 17.0, 7.2 Hz), 1.99−1.84 (m, 2H), 1.06, 1.06 (2d, 6H, J = 7.1, 7.1 Hz), 0.92 (s, 9H), 0.16 (s, 9H), 0.14, 0.14 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.1, 86.3, 79.8, 65.9, 38.0, 36.6, 26.2, 23.7, 18.4, 16.5, 16.0, 0.2, −4.0, −4.1; MS (CI, NH_3) *m*/*z* 343 ($M + H^+$), 324, 271, 211. Anal. Calcd for $C_{18}H_{38}O_2Si_2$: C, 63.09; H, 11.18. Found: C, 63.46; H, 11.31.

The previous alcohol (410 mg, 1.2 mmol) was dissolved in 7 mL of THF, and 680 mg (2.4 mmol, 2.0 equiv) of IBX predissolved in 6 mL of dry DMSO was added via cannula. After 2 h, 7 mL of water was added. Then 10 min later, 20 mL of Et_2O was added and the white precipitate was filtered (rinsed several times with Et_2O). The aqueous phase was extracted three times with 10 mL of Et_2O. The combined organic phases were washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel gave 370 mg (90%) of **24** as a colorless oil: $[\alpha]_D$ +22.8 (*c* 2.1, CH_2Cl_2); IR (film) 2957, 2173, 1726, 1463, 1250, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, 1H, J = 2.0 Hz), 3.99 (dd, 1H, J = 6.2, 3.3 Hz), 2.57 (m, 1H), 2.27 (d, 2H, J = 6.2 Hz), 1.95 (m, 1H), 1.15 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H), 0.90 (s, 9H), 0.16 (s, 9H), 0.13, 0.10 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 105.5, 86.7, 76.7, 49.9, 37.5, 26.0, 23.8, 18.3, 15.8, 11.6, 0.22, −4.3; MS (CI, NH_3) *m*/*z* 358 ($M + NH_4^+$), 341 ($M + H^+$).

(4*RS*,5*RS*,6(1*R*,2*S*,4*S*))-5-Benzenesulfonyl-6-[2-(*tert*-butyldimethylsiloxy)-1,3-dimethyl-6-trimethylsilylhex-5-ynyl]-3,3-dimethoxy-5-methyltetrahydropyran-2-one (25). To a solution of 395 μL (3.8 mmol, 4.9 equiv) of diethylamine in 6.3 mL of THF at −78 °C was added 2.4 mL (3.8 mmol, 1.6 M in hexane, 4.9 equiv) of BuLi. After 5 min, the resulting solution was warmed to −15 °C, and after 10 min, it was warmed to 0 °C for 15 min. To a solution of 1.22 g (3.9 mmol, 5.0 equiv) of sulfone **3** (dried three times by azeotropic distillation with toluene) in 28 mL of THF at −78 °C was added the previous basic solution. After 10 min at −78 °C, the resulting red-orange solution was warmed for 1 h at −55 °C and then recooled to −78 °C. A solution of 260 mg (0.75 mmol) of aldehyde **24** in 4 mL of THF was added dropwise to the cold basic solution (rinse with 1 mL of THF). After 1.2 h at −78 °C, the solution was warmed to 0 °C for 20 min and then quenched with 30 mL of 2 N aqueous $NaHSO_4$ and diluted with 100 mL of Et_2O. The aqueous phase was extracted three times with 50 mL of Et_2O. The combined organic phases were washed once with water and twice with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatog-

raphy on silica gel (Et_2O/petroleum ether, 0:100−40:60) gave 396 mg (83%) of **25** as a 1.2:1 mixture of diasteromers which could be separated for analytical purposes by careful chromatography and 920 mg of recovered sulfone **3** (94% of the excess). **Major isomer**: IR (film) 2955, 2173, 1762, 1447, 1306, 1148, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.72−7.70 (m, 1H), 7.64−7.60 (m, 2H), 5.32 (s, 1H), 3.69−3.67 (m, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 2.90−2.80 (m, 1H), 2.70 (d, 1H, J = 14.0 Hz), 2.43 (dd, 1H, J = 17.0, 4.9 Hz), 2.19 (dd, 1H, J = 17.0, 9.0 Hz), 2.16−1.94 (m, 1H), 1.57 (d, 1H, J = 14.0 Hz), 1.55 (s, 3H), 1.25 (d, 3H, J = 6.9 Hz), 1.20 (d, 3H, J = 6.9 Hz), 0.92 (s, 9H), 0.15 (s, 9H), 0.13, 0.13 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 135.9, 134.6, 130.6, 129.4, 107.1, 94.7, 85.6, 78.3, 77.5, 64.5, 50.4, 49.8, 41.3, 38.2, 36.1, 26.4, 22.8, 18.5, 17.9, 17.7, 11.1, 0.3, −3.8, −4.3; MS (CI, NH_3) m/z 642 ($M + NH_4^+$), 625 ($M + H^+$). **Minor isomer**: IR (film) 2960, 2173, 1773, 1447, 1307, 1147, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.88 (m, 2H), 7.71−7.68 (m, 1H), 7.61−7.58 (m, 2H), 4.95 (d, 1H, J = 1.3 Hz), 3.57 (brt, 1H, J = 5.3 Hz), 3.30 (s, 3H), 3.22 (s, 3H), 2.89−2.81 (m, 1H), 2.68 (d, 1H, J = 15.0 Hz), 2.40 (dd, 1H, J = 17.0, 5.3 Hz), 2.23 (dd, 1H, J = 17.0, 8.3 Hz), 1.95 (d, 1H, J = 15.0 Hz), 1.95−1.89 (m, 1H), 1.49 (s, 3H), 1.31 (d, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.9 Hz), 0.90 (s, 9H), 0.16 (s, 9H), 0.14, 0.14 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 137.1, 134.4, 130.8, 129.3, 106.4, 95.3, 86.2, 80.6, 78.7, 63.7, 51.4, 49.1, 39.4, 36.9, 36.7, 26.3, 23.6, 23.4, 18.5, 16.7, 12.1, 0.3, −3.5, −4.0; MS (CI, NH_3) m/z 642 ($M + NH_4^+$), 625 ($M + H^+$).

Methyl (6*R*,7*R*,8*S*)-7-(*tert*-Butyldimethylsiloxy)-2-methoxy-4,6,8-trimethyl-11-trimethylsilylundeca-2,4-dien-10-ynoate (32). To freshly prepared and powdered 6% Na/Hg amalgam (1.2 g, ca. 3.3 mmol, 10 equiv) and $NaHCO_3$ (270 mg, 3.3 mmol, 10 equiv) in 3 mL of dry MeOH at −40 °C was added sulfone **25** (204 mg, 0.33 mmol, 1.0 equiv) in 2.5 mL of THF (rinse with 0.5 mL of THF). After 1.5 h, the solution was acidified with 1 N aqueous HCl. After decantation and separation, the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed three times with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude product **31**. To this unpurified product **31** (ca. 0.33 mmol) (dried three times by azeotropic distillation with benzene) diluted in 4 mL of dry benzene was added camphorsulfonic acid (7.5 mg, 0.033 mmol, 0.1 equiv). The solution was heated to reflux for exactly 30 min. After the solution was cooled to 0 °C, freshly distilled CH_2N_2 was added until no more nitrogen evolved. The resulting mixture was concentrated in vacuo. Flash chromatography on silica gel (Et_2O/petroleum ether, 5:95) gave 76 mg (50% for two steps) of **32** as a colorless oil: $[\alpha]_D$ +34.2 (c 1.6, CH_2Cl_2); IR (film) 2956, 2173, 1721, 1249, 1105, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 5.94 (brd, 1H, J = 9.6 Hz), 3.79, 3.66 (2s, 6H), 3.59 (dd, 1H, J = 5.9, 3.0 Hz), 2.76−2.69 (m, 1H), 2.28 (dd, 1H, J = 16.9, 5.9 Hz), 2.17 (dd, 1H, J = 16.9, 7.5 Hz), 1.98 (s, 3H), 1.81−1.75 (m, 1H), 0.99 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 6.9 Hz), 0.90 (s, 9H), 0.15 (s, 9H), 0.10, 0.07 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 142.8, 141.8, 130.2, 106.4, 103.2, 86.1, 78.6, 60.4, 52.1, 37.8, 35.8, 26.3, 23.9, 18.7, 18.6, 16.5, 14.9, 0.3, −3.7, −3.8; MS (CI, NH_3) m/z 484 ($M + NH_4^+$), 467 ($M + H^+$); exact mass calcd for $C_{25}H_{47}O_4Si_2$ 467.3013, found 467.3016.

Methyl (4*S*,5*S*,6*R*)-1-Iodo-5-*tert*-butyldimethylsiloxy-2,4,6,8-tetramethyl-10-methoxy-1,7,9-undecatrienoate (33). To a solution of **32** (76 mg, 0.16 mmol) in 1.5 mL of MeOH was added 500 mg (3.6 mmol, 22 equiv) of thinly powdered anhydrous K_2CO_3. After 3 h, 15 mL of Et_2O was added followed by 1.5 mL of water. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give the desired crude terminal alkyne, which was carried on to the next step without further purification. An aliquot was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 0:100−5:95): $[\alpha]_D$ +24.7 (c 0.75, CH_2Cl_2); IR (thin film) 3312, 2930, 2115, 1720, 1436, 1250, 1105, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 5.93 (d, 1H, J = 9.6 Hz), 3.81, 3.66 (2s, 6H), 3.55 (dd, 1H, J = 6.0, 3.1 Hz), 2.74−2.68 (m, 1H), 2.30 (ddd, 1H, J = 16.7, 5.1, 2.5 Hz), 2.17 (ddd, 1H, J = 16.7, 8.0, 2.5 Hz), 1.99 (s, 3H), 1.97 (t, 1H, J = 2.5 Hz), 1.80−1.77 (m, 1H), 1.00 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.92 (s, 9H), 0.09, 0.07 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 142.8, 141.5, 130.4, 103.1, 88.6, 78.7, 69.6, 60.4, 52.1, 37.6, 36.1, 26.3, 22.4, 18.6, 18.6, 16.5, 14.9, −3.7; MS (CI, NH_3) m/z 412 ($M + NH_4^+$), 395 ($M + H^+$); exact mass calcd for $C_{22}H_{39}O_4Si$ 395.2618, found 395.2614.

To a mixture of Cp_2ZrCl_2 (95 mg, 0.32 mmol, 2.0 equiv) in 1.5 mL of CH_2Cl_2 was added dropwise $AlMe_3$ (490 μL, 0.97 mmol, 2 M solution in hexane, 6.0 equiv). The resulting solution was stirred for 10 min and cooled to −25 °C, and H_2O (6 μL, 0.32 mmol, 2.0 equiv) was added. After 10 min, a solution of the previous crude product (ca. 0.16 mmol) in 250 μL of CH_2Cl_2 (100 μL rinse) was added. The solution was stirred for 18 h at −25 °C, and a solution of I_2 (410 mg, 1.6 mmol, 10 equiv) in 1.5 mL of THF was added dropwise. After 30 min, the solution was allowed to warm to 0 °C, stirred for 10 min, and quenched by addition of 300 μL of saturated aqueous K_2CO_3. The mixture was then stirred for 30 min, 800 mg of $MgSO_4$ was added, and the mixture was filtered through a pad of Celite which was rinsed with Et_2O. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/petroleum ether, 0:100−5:95) gave 52 mg (60% for two steps) of **33** as a colorless oil, which is identical to the product described by Marshall:[3e] $[\alpha]_D$ +32.9 (c 0.59, $CHCl_3$) (lit.[3e] $[\alpha]_D$ +34.9 (c 0.67, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 5.93 (d, 1H, J = 9.7 Hz), 5.84 (s, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.41 (dd, 1H, J = 4.8, 3.4 Hz), 2.72−2.67 (m, 1H), 2.40 (dd, 1H, J = 13.4, 3.9 Hz), 1.98 (s, 3H), 1.95 (dd, 1H, J = 13.4, 10.5 Hz), 1.82−1.73 (m, 1H), 1.79 (s, 3H), 0.98 (d, 3H, J = 6.9 Hz), 0.92 (s, 9H), 0.75 (d, 3H, J = 6.8 Hz), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 147.0, 142.8, 142.1, 130.2, 130.0, 79.9, 75.4, 60.4, 52.1, 43.3, 36.3, 36.1, 26.2, 23.7, 18.9, 18.5, 16.0, 14.9, −3.6, −3.7.

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