Studies on Synthesis of the C-1 to C-18 Fragment of Pamamycins 607 and 621A†

Ren, Guobao(任国宝) Wu, Yikang*(伍贻康)

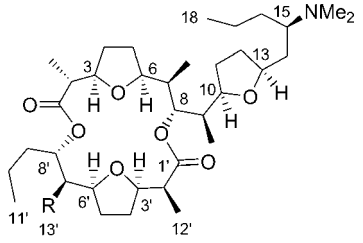
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Some efforts directed towards synthesis of the C-1 to C-18 fragment of natural antibiotic pamamycins 607 and 621A are disclosed. The nine stereogenic centers in the fragment were installed using a chiral auxiliary-induced asymmetric aldol reaction, a chiral building block derived from malic acid, or substrate chirality-induced asymmetric reduction of a ketone carbonyl group.

Keywords aldol reaction, alcohol, antibiotic, cross metathesis, chiron, enantioselective synthesis

Introduction

Pamamycin 621A (**1a**) and pamamycin 607 (**1b**) are the only two members in the pamamycin family with full ^{1}H and ^{13}C NMR data for the natural samples disclosed in the literature to date.[1] Because of their intriguing structures and significant bioactivities,[2] pamamycins have attracted considerable attention from the synthetic community around the world soon after their discovery. Many synthetic efforts,[3] along with eight total syntheses,[4] are subsequently documented.



Pamamycin 621A (**1a**) R = Me

Pamamycin 607 (**1b**) R = H

Figure 1 Structures of pamamycins 621A (**1a**) and 607 (**1b**).

As the structures of the pamamycins are highly similar to each other, clean separation of individual components, especially those minor ones, is extremely difficult. Further biological investigations therefore have to rely mainly on synthetic samples, providing additional stimulus to the synthetic investigations. Herein, we wish to present some of our efforts directed toward synthesis of the C-1 to C-18 fragment of pamamycins 607 and 621A.

Results and discussion

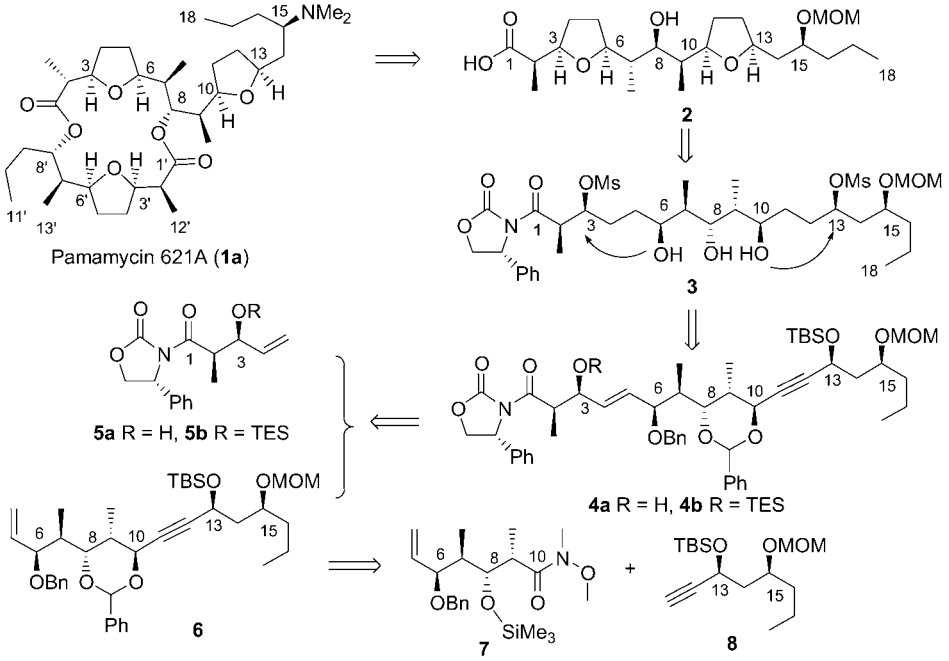
The general feature of our plan for the synthesis of the larger fragment **2** (C-1 to C-18) of pamamysin 621A is shown in Scheme 1. The characteristic THF rings were designed to be built from the linear precursor **3**, which already carried all stereogenic centers of well-defined desired absolute configurations, via intramolecular *O*-alkylations. In an earlier endeavor directed to the synthesis of nonactin,[5] we developed an effective protocol for construction of similar THF rings from the corresponding aldols without suffering otherwise readily occurred side reactions associated with the carbonyl groups β to the leaving groups. Judging from the structural similarity of **2** and nonctin, such a plan appeared to be feasible.

In a retrosynthetic sense, introduction of C-C double and triple bonds between the C-4/C-5 and the C-11/C-12 of **3** should make further disconnections more feasible: The double bond would allow for disconnection of the C-1/C-2 sterogenic centers from the C-5 to C-18 chain, giving smaller fragments **5** and **6**. The triple bond offered another excellent disconnecting point, which divided the **6** into two even smaller fragments, the Weinreb amide **7** and the alkyne **8**.

The fragment **5a**, which corresponds to the C-1 to C-3 part of the target structure, is most readily attainable from the aldol reaction between the *N*-acyl-oxazolidinone **9** and acrolein **10**. As shown in Scheme 2, under the conditions [$TiCl_4$/TMEDA (*N*,*N*′-tetramethylethylenediamine)] originally reported by Crimmins,[6] the desired *syn* aldol was obtained in 73% isolated yield. Further treatment with TESCl (triethylsilyl chloride)/DMAP (4-dimethyl-aminopyridine) delivered the

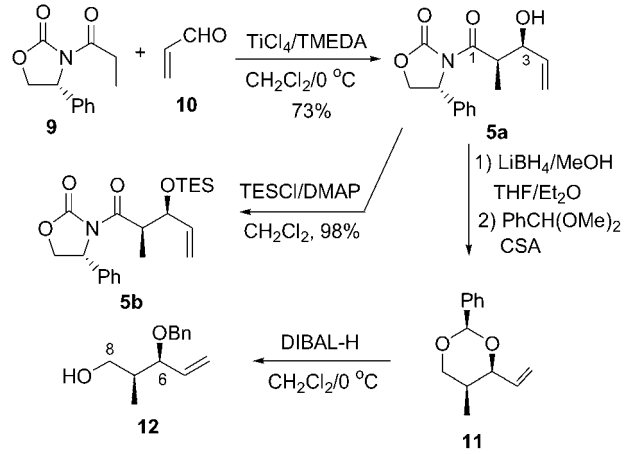
* E-mail: yikangwu@sioc.ac.cn
Received April 26, 2010; received May 21, 2010; accepted June 3, 2010.
Project supported by the National Basic Research Program of China (973 Program) (No. 2010CB833200), the National Natural Science Foundation of China (Nos. 20921091, 20672129, 20621062, 20772143) and the Chinese Academy of Sciences ("Knowledge Innovation", KJCX2.YW.H08).
† Dedicated to the 60th Anniversary of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Scheme 1



TES protected aldol **5b**.

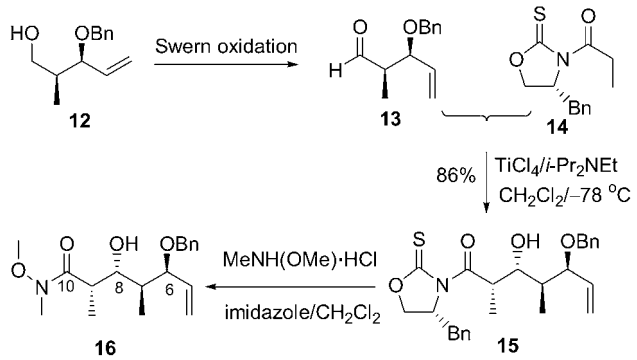
Scheme 2



As the relative as well as the absolute stereochemistry at the C-6/C-7 is the same as at the C-2/C-3 part embedded in **5**, the C-5 to C-8 portion of the carbon chain could be derived from **5** to simplify the synthesis. Thus, removal of the oxazolidinone auxiliary from **5a** with $LiBH_4$ in THF-Et_2O in the presence of MeOH provided an intermediate diol, which on reaction with $PhCH(OMe)_2$ with catalysis of CSA [(±)-camphor-10-sulfonic acid] afforded the known[7] 1,3-dioxane **11**. Reductive cleavage of the benzylidene group in **11** with DIBAL-H (diisobutylaluminium hydride) yielded the desired alcohol **12**, also a previously known[7] compound.

Elaboration of **12** into Weinreb amide **16**, a convenient precursor to the unstable fragment **7**, is depicted in Scheme 3. First, the primary alcohol was oxidized into the corresponding aldehyde **13** by treatment with $(COCl)_2$/DMSO/Et_3N in CH_2Cl_2 (Swern oxidation). The resulting aldehyde was then subjected to a Crimmins aldol reaction with oxazolidinethione **14** to deliver aldol **15**. Finally, the oxazolidinthione chiral auxiliary was replaced by a MeN(OMe) group through an exchange reaction with MeNH(OMe)•HCl in the presence of imidazole to give **16**, showing that oxazolidinethione type auxiliaries like thiazolidinethione type ones[8] also enjoy remarkable advantages at the auxiliary removal stage compared with the more traditional oxazolidinones auxiliaries.

Scheme 3



The other fragment (C-11 to C-18) required for construction of **6** was derived from the alcohol **17**, a known chiral building block readily accessible from (*S*)-malic acid using the literature[9] procedure. Swern oxidation of **17** followed by Grignard reaction with *n*-PrMgBr gave a pair of alcohols **18a** and **18b** (separable on silica gel), which on oxidation with Dess-Martin periodinane afforded the corresponding ketone **19** (Scheme 4, to make full use of the undesired isomer).

The desired stereochemistry at the C-15 was then installed by a 1,3-induced asymmetric reduction[10] with

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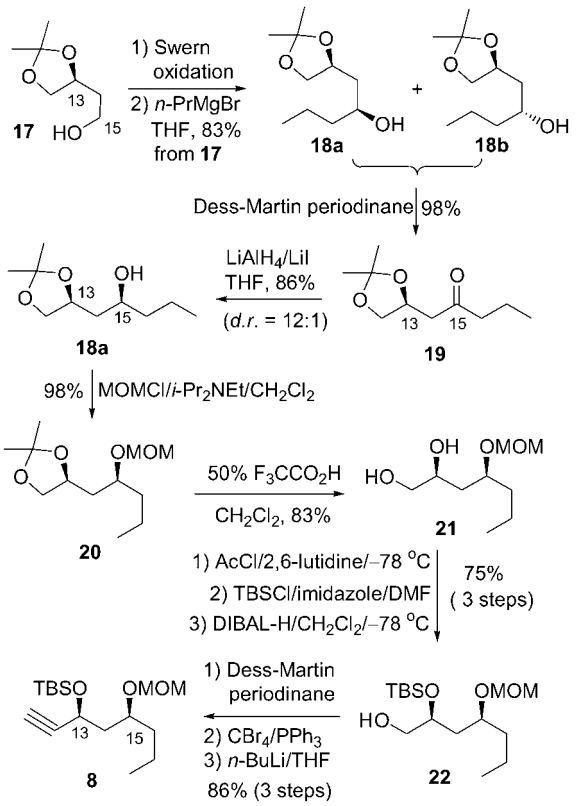
Scheme 4

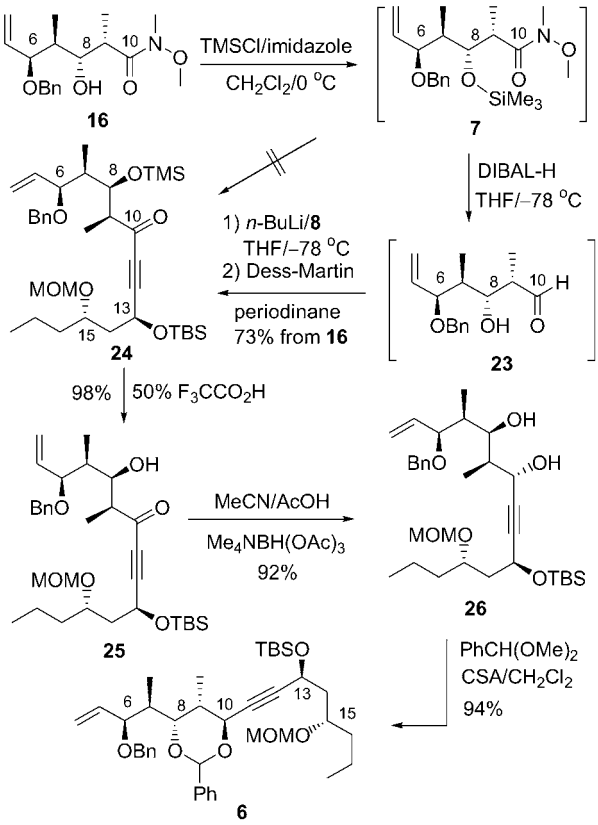


$LiAlH_4$/LiI. It is noteworthy that in this reaction 10 molar equivalent (with respect to ketone **19**) of LiI proved to be necessary for the desired stereoselectivity. Use of less amounts of LiI or with LiCl instead all led to significant loss of the setereoselectivity.

The newly introduced hydroxyl group was subsequently masked as a MOM (methoxymethyl) ether by treatment with MOMCl/*i*-Pr_2NEt in CH_2Cl_2. The acetonide group in the resulting **20** was cleaved by treatment with 50% aqueous F_3CCO_2H to yield an intermediate diol, which was transformed into the desired alcohol **22** via a three-step sequence: (1) acetyl protection of the primary hydroxyl group with AcCl in the presence of 2,6-lutidine at −78 ℃, (2) masking the secondary hydroxyl group as a TBS (*tert*-butyldimethylsilyl) ether using TBSCl/imidazole in DMF, and (3) reductive cleavage of the Ac group with DIBAL-H to free the primary hydroxyl group. The **22** was further oxidized with Dess-Martin periodinane to yield the corresponding aldehyde, which on further treatment with CBr_4/PPh_3 followed by *n*-BuLi afforded[4h] alkyne **8**.

The catenation of the C-5 to C-10 and C-11 to C-18 fragments was first attempted (Scheme 5) using direct coupling of the Weinreb amide **7**, which was prepared from **16** via silylation with TMSCl (trimethylsilyl chloride) in the presence of imidazole, with lithiated **8** (generated *in situ* from alkyne **8** by reaction with either *n*-BuLi or LiMe with or without HMPA (hexamethylphosphoramide) at different temperatures even after prolonged reaction time) without success. No reaction seemed to have occurred. However, quenching the reaction with D_2O did give deuteriated alkyne **8**, proving that the anion of **8** was indeed formed. Hence, the failure of further reaction of the acetylide with the amide was most likely to be caused by the steric crowding around the amide carbonyl group.

Scheme 5

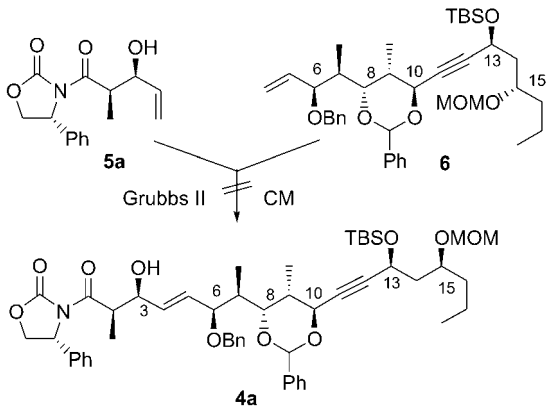


Unable to realize direct coupling mentioned above, we decided to switch to a more feasible alternative—to achieve the same goal via the addition of the acetylide to aldehyde **23** followed by oxidation of the resulting propargyl alcohols. To this end, the amide **7** was reduced to the corresponding aldehyde **23** by reaction with DIBAL-H at −78 ℃ in THF. Subsequent exposure of **23** to the lithiated **8** led to expected propargyl alcohol as a 1∶1 mixture of the two epimers, which were oxidized into a single ketone **24** using Dess-Martin oxidation with an overall yield (from **16**) of 73%.

The TMS protecting group was then removed with 50% aqueous F_3CCO_2H to give the hydroxyketone **25** in 98% yield. With a free hydroxyl group at the carbon β to the carbonyl group, the stage was set for Evans' asymmetric reduction[11] of the ketone. Thus, treatment of **25** with $Me_4NBH(OAc)_3$ at −20 ℃ in MeCN-AcOH afforded the 1,3-*anti* diol **26** in 92% yield. To meet the functional group elaboration requirements at later stages the hydroxyl groups were masked with benzylidene group through an acetal exchange reaction with $PhCH(OMe)_2$ in the presence of a catalytic amount of CSA in CH_2Cl_2.

According to our initial plan, construction of the full linear chain that contains C-1 to C-18 (**4**) relied on a cross metathesis (CM) reaction between fragments **5** and **6**. Although there have been a huge number of ring-closing metathesis reports in the literature, the precedents of cross coupling between two fragments carrying multi-functionalities/stereogenic centers are scant. One of such examples was reported by Crimmins and co-workers,[12] which did not require large excess of any of the two coupling partners as in most known CM reactions, yet still gave reasonably good yield (68%). One of the two substrates in their case bore a free hydroxyl group at the allylic position immediately next to the reaction center, which appeared to be critical to the success. Therefore, we decided to use **5a** rather than more hindered **5b** in our CM attempts (Scheme 6). However, to our disappointment with the Grubbs II catalyst at different temperatures (r.t., refluxing CH_2Cl_2, refluxing toluene, 130 ℃/sealed tube) in different solvents (CH_2Cl_2 or toluene) with different reactant ratios no acceptable results could be obtained. At low temperatures essentially no reactions took place, while at elevated temperatures extensive side products formation occurred, with the desired **4a** formed in ＜4% yield. As this approach did not work out as planned, later we turned to other alternatives, which eventually led to a total synthesis of pamamycin 621A.[4h]

Scheme 6



Conclusion

Attempts directed toward synthesis of the linear precursor to the C-1 to C-18 fragment of pamamycins 607 and 621A are presented. The target chain structure was planned to be built up from three subunits, which contained the C-1 to C-4, C-5 to C-10, and C-11 to C-18, respectively. Among the nine stereogenic centers spread over the 18-carbon chain, the one at the C-13 was derived from (*S*)-malic acid. The C-10 and C-15 stereogenic centers were installed via asymmetric reduction. The remainders were generated using chiral auxiliary-induced asymmetric aldol reactions. Catenation of the C-5 to C-18 portion has been successfully achieved. However, incorporation of the C-1 to C-4 onto the C-5 to C-18 chain via a cross metathesis reaction failed to give expected coupling product in acceptable yields.

Experimental

Dry THF was distilled over Na/Ph_2CO under N_2 prior to use. Dry CH_2Cl_2 was distilled over CaH_2 under N_2 prior to use. Addition of air/moisture sensitive reagents was done using syringe techniques. PE (for chromatography) stands for petroleum ether (b.p. 60—90 ℃). Column chromatography was performed on silica gel (300—400 mesh) under slightly positive pressure. CSA refers to (±)-camphor-10-sulfonic acid. NMR spectra were recorded on a Varian Mercury 300 or a Bruker Avance 300 NMR spectrometer with Me_4Si as the internal standard. IR spectra were measured on a FT-IR 440 or a Nicolet Avatar 360 infrared spectrometer. ESI-MS data were acquired on a HP5989A mass spectrometer. HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 or an Agilent Technologies P-1030 polarimeter. Elemental analysis was performed with an Elementar VarioEL III instrument.

(4*R*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methyl-pent-4-enoyl]-4-phenyl-oxazolidin-2-one (5a) $TiCl_4$ (4.8 mL, 44.0 mmol) was added (via a syringe) dropwise to a solution of **9** (8.63 g, 140.0 mmol) in dry CH_2Cl_2 (240 mL) stirred at 0 ℃ (ice-water bath) under N_2. After completion of the addition, the mixture was stirred at the same temperature for 10 min before dry TMEDA (16.8 mL, 104.0 mmol) was introduced dropwise. The dark red-brown mixture was stirred at 0 ℃ for another 30 min. A solution of aldehyde **10** (8.39 g, 149.8 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. After completion of the addition, the mixture was stirred at the same temperature for 1 h. Aqueous NH_4Cl (20 mL) was added. The mixture was filtered through Celite (washing with CH_2Cl_2 three times). The filtrate and washings were combined, washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography [*V*(EtOAc)∶*V*(PE)＝1∶45] on silica gel gave enantiopure aldol **5a** as a yellowish oil (8.02 g, 29.1 mmol, 73%). $[\alpha]_D^{26}$ −86.9 (*c* 3.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.41—7.26 (m, 5H), 5.86 (ddd, *J*＝16.4, 10.9, 5.4 Hz, 1H), 5.46 (dd, *J*＝8.8, 3.8 Hz, 1H), 5.30 (d, *J*＝17.2 Hz, 1H), 5.19 (d, *J*＝10.4 Hz, 1H), 4.70 (t, *J*＝8.8 Hz, 1H), 4.49 (m, 1H), 4.26 (dd, *J*＝9.0, 3.8 Hz, 1H), 3.91 (dq, *J*＝3.3, 7.1 Hz, 1H), 2.82 (d, *J*＝3.2 Hz, 1H), 1.15 (d, *J*＝7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 176.1, 153.4, 138.8, 137.3, 129.3, 128.8, 125.5, 116.2, 72.3, 69.9, 57.5, 42.5, 10.8; FT-IR (film) *v*: 3525, 2982, 1773, 1699, 1476, 1418, 1201, 706 cm^{-1}; ESI-MS *m/z*: 298.2 ($[M+Na]^+$); ESI-HRMS calcd for $C_{15}H_{17}NO_4Na$ ($[M+Na]^+$) 298.1050, found 298.1063.

(4*R*)-3-[(2*R*,3*S*)-3-Triethylsilyloxy-2-methyl-pent-4-enoyl]-4-phenyl-oxazolidin-2-one (5b) A solution

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of **5a** (681 mg, 2.48 mmol), imidazole (337 mg, 4.95 mmol), DMAP (15 mg, 0.12 mmol), and TESCl (0.64 mL, 3.72 mmol) in dry CH_2Cl_2 (8 mL) was stirred at ambient temperature for 20 min. Water (10 mL) was added. The mixture was extracted with Et_2O (50 mL×3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶10] on silica gel gave **5b** (947 mg, 2.43 mmol, 98%) as a white solid. m.p. 64—66 ℃; $[\alpha]_D^{26}$ −95.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.41—7.26 (m, 5H), 5.86 (ddd, *J*=17.0, 10.4, 7.0 Hz, 1H), 5.37 (dd, *J*=8.5, 3.3 Hz, 1H), 5.18 (d, *J*=17.0 Hz, 1H), 5.11 (d, *J*=10.4 Hz, 1H), 4.62 (t, *J*=8.4 Hz, 1H), 4.30—4.23 (m, 2H), 4.06 (m, 1H), 1.12 (d, *J*=6.5 Hz, 3H), 0.94 (t, *J*=7.8 Hz, 9H), 0.57 (q, *J*=7.6 Hz, 6H); FT-IR (film) *v*: 2955, 2912, 2877, 1782, 1706, 1457, 1381, 1197, 848, 699 cm^{-1}; ESI-MS *m/z*: 412.1 ($[M+Na]^+$). Anal. calcd for $C_{21}H_{31}NO_4Si$: C 64.75, H 8.02, N 3.60; found C 64.90, H 7.83, N 3.20.

(2*S*,3*S*)-2-Methyl-3-benzyloxy-pent-4-en-1-ol (12) $LiBH_4$ (1.5 mol•L^{-1} in THF, 6.0 mL, 9.0 mmol) was added dropwise to a solution of **5a** (1.658 g, 6.00 mmol) in anhydrous Et_2O (20 mL) and anhydrous MeOH (0.36 mL, 9.0 mmol) stirred at 0 ℃ under N_2 (balloon). After completion of the addition, the mixture was stirred at the same temperature until TLC showed completion of the reaction. Aqueous NaOH (1.0 mol•L^{-1}, 1.0 mL) was added. The mixture was stirred for another hour before the volatiles were removed on a rotary evaporator. The residue was extracted with CH_2Cl_2 (50 mL×5). The combined organic layers were dried over anhydrous $MgSO_4$. Solvents were removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (20 mL). To this solution CSA (130 mg, 0.6 mmol) was added, followed by $PhCH(OMe)_2$ (0.92 mL, 6.6 mmol). The mixture was stirred at ambient temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (50 mL×4). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Solvents were removed by rotary evaporation. To the residue was triturated with Et_2O to dissolve the intermediate **11**. The insoluble white solids (the recovered chiral auxiliary) were filtered off. The filtrate was concentrated on a rotary evaporator to give a yellow oil, which was dissolved in CH_2Cl_2 (10 mL) and stirred at 0 ℃. To the solution DIBAL-H (1.0 mol•L^{-1} in cyclohexane, 10.0 mL, 10.0 mmol) was added dropwise. The mixture was stirred at the same temperature until TLC showed completion of the reaction. MeOH was added to quench the excess hydride, followed by an aqueous solution of sodium potassium tartrate. The mixture was stirred at ambient temperature for 2 h, forming a two-phase system. The phases were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL×3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶6] on silica gel gave the known alcohol **12** (924 mg, 4.49 mmol, 74% from **5a**) as a yellowish oil. $[\alpha]_D^{26}$ +39.4 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.41—7.26 (m, 5H), 5.86 (ddd, *J*=17.7, 10.4, 7.8 Hz, 1H), 5.34 (dd, *J*=10.6, 3.3 Hz), 5.18 (d, *J*=17.6 Hz, 1H), 4.62 (d, *J*=11.8 Hz, 1H), 4.61 (d, *J*=11.8, 1H), 3.90 (dd, *J*=7.2, 4.2 Hz, 1H), 3.70—3.51 (m, 2H), 2.51 (br s, 1H), 2.06—1.99 (m, 1H), 0.91 (d, *J*=7.1 Hz, 1H).

(2*S*,3*R*,4*R*,5*S*)-5-Benzyloxy-1-[(4*R*)-4-benzyl-2-thioxo-oxazolidin-3-yl]-3-hydroxy-2,4-dimethyl-hept-6-en-1-one (16) DMSO (0.58 mL, 8.15 mmol) was added dropwise to a solution of $(COCl)_2$ (0.36 mL, 4.08 mmol) in dry CH_2Cl_2 (15 mL) stirred at −78 ℃. After stirring for 30 min, a solution of alcohol **12** (600 mg, 2.91 mmol) in CH_2Cl_2 (3 mL) was introduced. Stirring was continued at −78 ℃ for another 2 h. Et_3N (2.1 mL, 14.6 mmol) was added dropwise. The cooling bath was allowed to warm naturally to ambient temperature. Aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with Et_2O (100 mL×3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶5] on silica gel gave aldehyde **13** (575 mg, 2.82 mmol, 97% from **12**) as a colorless oil.

In another flask, a solution of **14** (220 mg, 0.88 mmol) in dry CH_2Cl_2 (9 mL) was stirred at −78 ℃ while $TiCl_4$ (0.21 mL, 1.77 mmol) was introduced dropwise. Stirring was continued at the same temperature for 15 min before *i*-Pr_2NEt (0.17 mL, 0.97 mmol) was introduced. The mixture was stirred at −78 ℃ for another 30 min. Then a solution of the above obtained aldehyde **13** (98 mg, 0.48 mmol) in dry CH_2Cl_2 (1 mL) was introduced. Stirring was continued at −78 ℃ until TLC showed completion of the reaction. Aqueous NH_4Cl was added. The mixture was extracted with Et_2O (20 mL×4). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶8] on silica gel gave **15** (186 mg, 0.41 mmol, 85% from **13**, 82% from **12**) as a yellowish oil, from which the following data were acquired. ESI-MS *m/z*: 476.2 ($[M+Na]^+$). ESI-HRMS calcd for $C_{26}H_{31}NO_4SNa$ ($[M+Na]^+$) 476.1866, found 476.1873.

A solution of the above obtained **15** (180 mg, 0.396 mmol), MeNH(OMe)•HCl (48 mg, 0.49 mmol), and imidazole (41 mg, 0.62 mmol) in dry CH_2Cl_2 (4 mL) was stirred at ambient temperature for several hours. Another portion of MeNH(OMe)•HCl (48 mg, 0.49 mmol), and imidazole (121 mg, 1.86 mmol) was added. After that, the mixture was stirred at ambient temperature for 4 d before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4.

Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶7] on silica gel gave **16** (116 mg, 0.361 mmol, 91% from **15**, 75% from **12**) as a colorless oil. $[\alpha]_D^{26}$ +9.2 (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 7.33—7.24 (m, 5H), 5.86 (ddd, *J*=17.3, 10.7, 6.6 Hz, 1H), 5.30 (d, *J*=17.2 Hz, 1H), 5.23 (d, *J*=10.3 Hz, 1H), 4.60 (d, *J*=11.7 Hz, 1H), 4.40—4.36 (m, 2H), 4.15 (d, *J*=2.7 Hz, 1H), 3.90—3.85 (m, 1H), 3.65 (s, 3H), 3.18 (s, 3H), 3.00 (br, 1H), 1.70—1.65 (m, 1H), 1.26 (d, *J*=7.0 Hz, 3H), 0.91 (d, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 138.8, 137.6, 128.3, 127.7, 127.4, 116.8, 79.3, 73.2, 61.5, 40.4, 36.4, 10.4, 9.9; FT-IR (film) *v*: 3470, 2972, 2938, 1637, 1458, 1420, 1389, 1067, 996 cm^{-1}; ESI-MS *m*/*z*: 344.1 ($[M+Na]^+$); ESI-HRMS calcd for $C_{18}H_{27}NO_4Na$ ($[M+Na]^+$) 344.1836, found 344.1832.

1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-pentanone (19) DMSO (0.15 mL, 2.04 mmol) was added dropwise to a solution of $(COCl)_2$ (90 μL, 1.02 mmol) in dry CH_2Cl_2 (6 mL) stirred at −78 ℃. After stirring for 30 min, a solution of alcohol **17** (125 mg, 0.86 mmol) in CH_2Cl_2 (3 mL) was introduced. Stirring was continued at −78 ℃ for another 2 h. Et_3N (0.60 mL, 4.30 mmol) was added dropwise. The cooling bath was allowed to warm naturally to ambient temperature. Aqueous $NaHCO_3$ was added. The mixture was extracted with Et_2O (100 mL×4). The combined organic layers were washed with water and brine before being dried over anhydrous $MgSO_4$. Solvents were removed by rotary evaporation. The residue was dissolved in dry Et_2O (3 mL) and cooled to −78 ℃. A solution of *n*-PrMgBr (1.0 mol•L^{-1} in THF, 2.0 mL, 2.0 mmol) was added dropwise. The mixture was stirred at the same temperature until TLC showed completion of the reaction. Aqueous saturated NH_4Cl was added. The mixture was extracted with Et_2O (20 mL×3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶4] on silica gel gave **18a** and **18b** as colorless oils (135 mg, 0.717 mmol, 83% from **17**, with data for **18a**/**18b** listed in next experiment). The two alcohols were dissolved in dry CH_2Cl_2 (2 mL). To this solution was added Dess-Martin periodinane (609 mg, 1.434 mmol), followed by $NaHCO_3$ (301 mg, 3.585 mmol). The mixture was stirred at ambient temperature until TLC showed completion of the reaction before being diluted with Et_2O (50 mL) and filtered through Celite. The filtrate and ethereal washings were combined and chromatographed [*V*(EtOAc)∶*V*(PE)=1∶5] on silica gel to give ketone **19** (132 mg, 0.701 mmol, 98% from **18a**/**18b**, 82% from **17**) as a colorless oil. $[\alpha]_D^{24}$ +21.7 (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 4.50—4.40 (m, 1H), 4.18 (t, *J*=6.7 Hz, 1H), 3.53 (t, *J*=7.8 Hz, 1H), 2.89 and 2.56 (ABX, J_{AB}=6.7 Hz, J_{AX}=6.1 Hz, J_{BX}=7.2 Hz, 2H), 2.43 (t, *J*=7.0 Hz, 2H), 1.67—1.55 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 0.92 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 208.7, 108.7, 71.7, 69.4, 46.8, 45.3, 26.8, 25.4, 17.0, 13.6; FT-IR (film) *v*: 2986, 2936, 2876, 1712, 1379, 1052, 848 cm^{-1}; ESI-MS *m*/*z*: 209.1 ($[M+Na]^+$); ESI-HRMS calcd for $C_{10}H_{18}ONa$ ($[M+Na]^+$) 209.1148, found 209.1147.

(2*S*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-pentan-2-ol (18a) via reduction of 19 LiI (540 mg, 4.03 mmol) was added to a solution of **19** (75 mg, 0.403 mmol) in dry Et_2O (8 mL) stirred at −40 ℃. The mixture was stirred for 10 min to result in a yellow solution. The temperature of the cooling bath was lowered to −78 ℃. $LiAlH_4$ (78 mg, 2.02 mmol) was added in one portion. The mixture was stirred at the same temperature until TLC showed completion of the reaction. MeOH (5 mL) was added (still at −78 ℃) to destroy excess hydride, followed by an aqueous solution of sodium potassium tartrate. The mixture was stirred while the bath temperature was allowed to warm to ambient temperature. The mixture was extracted with EtOAc (20 mL×3). The phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶3] on silica gel gave **18a** (60 mg, 0.319 mmol, 79%) and **18b** (5 mg, 0.027 mmol, 6.7%) as colorless oils.

Data for **18a**. $[\alpha]_D^{24}$ +6.4 (*c* 2.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 4.32—4.24 (m, 1H), 4.10 (t, *J*=7.1 Hz, 1H), 3.86—3.78 (m, 1H), 3.56 (t, *J*=7.4 Hz, 1H), 3.12 (br, 1H), 1.72—1.60 (m, 2H), 1.60—1.22 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 0.93 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 109.2, 75.8, 70.6, 69.7, 40.3, 39.6, 26.8, 25.7, 18.5, 14.0; FT-IR (film) *v*: 3443, 2985, 2873, 1060, 870, 826 cm^{-1}; EI-MS *m*/*z* (%): 173 ($[M-CH_3]^+$), 43 (100); EI-HRMS calcd for $C_9H_{17}O_3$ ($[M-CH_3]^+$) 173.1178, found 173.1180.

Data for **18b**. $[\alpha]_D^{24}$ −2.03 (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 4.40—4.30 (m, 1H), 4.09 (br t, *J*=7.1 Hz, 1H), 3.85—3.77 (m, 1H), 3.58 (dt, *J*=1.7, 8.0 Hz, 1H), 2.35 (br, 1H), 1.80—1.58 (m, 2H), 1.52—1.30 (m, 4H), 1.44 (s, 3H), 1.36 (s, 3H), 0.93 (t, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 108.7, 73.6, 69.5, 68.6, 39.9, 39.8, 26.9, 25.6, 18.8, 14.0; FT-IR (film) *v*: 3443, 2985, 2873, 1060, 870, 826 cm^{-1}; EI-MS *m*/*z* (%): 173 ($[M-CH_3]^+$), 43 (100), 95 (81); EI-HRMS calcd for $C_{10}H_{20}O_3$ 188.1412, found 188.1414.

(2*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-met-hoxymethyl-pentane (20) *i*-Pr_2NEt (0.78 mL, 4.52 mmol) was added to a solution of **18a** (85 mg, 0.452 mmol) and DMAP (28 mg, 0.23 mmol) in dry CH_2Cl_2 (5 mL) stirred at ambient temperature. The mixture was stirred for 30 min before MOMCl (0.17 mL, 2.26 mmol) was introduced (with cooling in a 0 ℃ bath). The mixture was stirred at ambient temperature until TLC showed completion of the reaction. Aqueous $NaHCO_3$ was added. The mixture was extracted with Et_2O (50 mL×3). The organic phases were combined, washed with water and brine, and dried over anhydrous

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Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶10] on silica gel gave **20** (87 mg, 0.375 mmol, 83%) as a colorless oil. $[\alpha]_D^{24}$ +17.7 (*c* 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 4.61 (s, 2H), 4.18 (quint, *J*=6.4 Hz, 1H), 4.05 (dd, *J*=6.0, 7.9 Hz, 1H), 3.62 (quint, *J*=5.9 Hz, 1H), 3.50 (t, *J*=7.6 Hz, 1H), 3.36 (s, 3H), 1.95—1.88 (m, 1H), 1.71—1.60 (m, 1H), 1.54—1.47 (m, 2H), 1.40—1.32 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H), 0.90 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 108.5, 95.3, 74.7, 73.1, 69.7, 55.6, 38.0, 36.5, 26.9, 25.7, 18.5, 14.1; FT-IR (film) *v*: 2985, 2935, 2875, 1040 cm^{-1}; ESI-MS *m/z*: 255.1 ($[M+Na]^+$); ESI-HRMS calcd for $C_{12}H_{24}O_4Na$ ($[M+Na]^+$) 255.1567, found 255.1575.

(2*S*,4*S*)-4-Methoxymethoxy-heptane-1,2-diol (21) A solution of **20** (53 mg, 0.229 mmol) and aqueous F_3CCO_2H (50%, 0.2 mL) in CH_2Cl_2 (8 mL) was stirred at ambient temperature until TLC showed completion of the reaction. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with EtOAc (30 mL×4). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶1] on silica gel gave diol **21** (39 mg, 0.203 mmol, 89%) as a colorless oil. $[\alpha]_D^{24}$ +52.1 (*c* 1.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 4.69 (d, *J*=6.7 Hz, 2H), 3.88—3.78 (m, 2H), 3.69 (br, 1H), 3.64—3.45 (m, 2H), 3.40 (s, 3H), 2.92 (br, 1H), 1.80—1.42 (m, 4H), 1.40—1.22 (m, 2H), 0.92 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 95.1, 76.8, 71.0, 66.7, 55.7, 37.4, 36.5, 18.1, 14.1; FT-IR (film) *v*: 3422, 2934, 2874, 1466, 1035 cm^{-1}; ESI-MS *m/z*: 215.0 ($[M+Na]^+$). ESI-HRMS calcd for $C_9H_{20}O_4Na$ ($[M+Na]^+$) 215.1254, found 215.1255.

(2*S*,4*S*)-2-*tert*-Butyldimethylsilyloxy-4-methoxymethoxy-heptanol (22) Acetyl chloride (14.6 μL, 0.206 mmol) was added dropwise to a solution of **21** (36 mg, 0.187 mmo) and 2,6-lutidine (46.4 μL, 0.374 mmol) in dry CH_2Cl_2 (2 mL) stirred at −78 ℃. The mixture was stirred until TLC showed completion of the reaction. MeOH (1 mL) was added, followed by aqueous sodium potassium tartrate. Stirring was continued to give a two-phase clear system. The mixture was extracted with Et_2O (30 mL×3). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Solvents were removed by rotary evaporation. The residue was dissolved in dry DMF (1 mL), to which imidazole (64 mg, 0.935 mmol), DMAP (23 mg, 0.187 mmol), and TBSCl (57 mg, 0.374 mmol) were added in turn. The mixture was stirred at ambient temperature until TLC showed completion of the reaction before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was dissolved in dry CH_2Cl_2 (2 mL) and cooled in a −78 ℃ bath. To this solution were added DIBAL-H (1.0 mol•L^{-1} in cyclohenane, 0.37 mL, 0.37 mmol). Stirring was continued at −78 ℃ until TLC showed completion of the reaction. MeOH (1 mL) was added, followed by Et_2O (30 mL) and aqueous sodium potassium tartrate. The mixture was stirred at ambient temperature until a two phase clear system was formed. The product was taken into Et_2O by repeated extraction (30 mL×3). The organic phases were combined, washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶1] on silica gel afforded alcohol **22** (43 mg, 0.141 mmol, 75% from **21**) as a colorless oil. $[\alpha]_D^{24}$ +22.6 (*c* 2.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 4.63 (d, *J*=7.1 Hz, 1H), 4.60 (d, *J*=7.1 Hz, 1H), 3.95—3.88 (m, 1H), 3.67—3.60 (m, 1H), 3.59—3.42 (m, 2H), 3.36 (s, 3H), 2.28 (br, 1H), 1.74—1.69 (m, 2H), 1.58—1.42 (m, 2H), 1.41—1.26 (m, 2H), 0.90 (t, *J*=7.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 95.3, 74.4, 69.9, 65.9, 55.7, 38.8, 36.9, 25.7, 18.4, 18.0, 14.1, −4.7; FT-IR (film) *v*: 3481, 2956, 2930, 2858, 1464, 1039, 836, 776 cm^{-1}; ESI-MS *m/z*: 329.2 ($[M+Na]^+$). ESI-HRMS calcd for $C_{15}H_{34}O_4SiNa$ ($[M+Na]^+$) 329.2119, found 329.2130.

(3*S*,4*R*,5*R*,6*S*,10*S*,12*S*)-3-Benzyloxy-10-(*tert*-butyldimethylsilyloxy)-12-methoxymethoxy-4,6-dimethyl-5-trimethylsilyloxy-pentadec-1-en-8-yn-7-one (24) TMSCl (0.26 mL, 2.037 mmol) was added dropwise to a solution of **16** (218 mg, 0.680 mmol) and imidazole (183 mg, 2.716 mmol) in dry CH_2Cl_2 (7 mL) stirred in an ice-water bath. The mixture was stirred at the same temperature until TLC showed completion of the reaction. Aqueous $NaHCO_3$ was added. The mixture was extracted with Et_2O (100 mL×3). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶6] on silica gel afforded **7** (269 mg, 0.68 mmol, 100%) as a colorless oil. A portion of this oil (119 mg, 0.302 mmol) was dissolved in dry THF (3.0 mL) and cooled in a −78 ℃ bath. To this solution was added DIBAL-H (1.0 mol•L^{-1} in cyclohenane, 0.60 mL, 0.60 mmol). Stirring was continued at −78 ℃ until TLC showed completion of the reaction. MeOH (5 mL) was added, followed by Et_2O (100 mL) and aqueous sodium potassium tartrate. The mixture was stirred at ambient temperature until a two-phase clear system was formed. The product was taken into Et_2O by repeated extraction (20 mL×3). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶15] on silica gel afforded aldehyde **23** (101 mg, 0.302 mmol, 100% from **16** or **7**) as a colorless oil. A portion of this aldehyde (58 mg, 0.173 mmol) was dissolved in dry THF (3.0 mL) and cooled in a −78 ℃ bath. This solution was added via a cannula to a solution of lithiated **8** (prepared by treating a solution of **8** (134 mg, 0.447 mmol) in dry THF (3.0 mL) with *n*-BuLi (1.6 mol•L^{-1} in hexanes, 0.33 mL, 0.526

mmol) at −78 ℃ for 30 min). The mixture was then stirred at the same temperature for 2 h. Water was added to quench the reaction. The mixture was extracted with Et_2O (50 mL×4). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶15] on silica gel afforded the propargyl alcohols (81 mg, 0.128 mmol, 74% from **16**) as a colorless oil.

A portion of the propargyl alcohols (66 mg, 0.104 mmol) was dissolved in dry CH_2Cl_2 (1 mL). To this solution were added Dess-Martin periodinane (132 mg, 0.311 mmol) and $NaHCO_3$ (87 mg, 1.04 mmol). The mixture was stirred at ambient temperature for 20 min. About half of the solvent was removed by rotary evaporation. The residue was chromatographed [*V*(EtOAc)∶*V*(PE)=1∶15] on silica gel to give ketone **24** (61 mg, 0.0964 mmol, 93% from the alcohols, 69% from **16**) as a colorless oil. $[\alpha]_D^{25}$ −4.84 (*c* 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.37—7.25 (m, 5H), 5.89 (ddd, *J*=17.1, 10.7, 6.6 Hz, 1H), 5.30 (d, *J*=16.8 Hz, 1H), 5.28 (d, *J*=11.0 Hz, 1H), 4.70 (t, *J*=6.7 Hz, 1H), 4.62 (s, 2H), 4.61 (d, *J*=11.8 Hz, 1H), 4.34 (d, *J*=11.8 Hz, 1H), 4.50 (d, *J*=8.7 Hz, 1H), 4.13 (d, *J*=7.4 Hz, 1H), 3.75—3.67 (m, 1H), 3.35 (s, 3H), 2.80—2.70 (m, 1H), 2.01—1.80 (m, 1H), 1.72—1.60 (m, 2H), 1.54—1.27 (m, 4H), 1.14 (d, *J*=6.9 Hz, 3H), 0.97—0.91 (m, 15H), 0.13—0.19 (m, 15H); ESI-MS *m/z*: 655.7 ($[M+Na]^+$); ESI-HRMS calcd for $C_{35}H_{60}O_6NaSi$ ($[M+Na]^+$) 655.3821, found 655.3845.

(3*S*,4*R*,5*R*,6*S*,10*S*,12*S*)-3-Benzyloxy-10-(*tert*-butyldimethylsilyloxy)-12-methoxymethoxy-4,6-dimethyl-5-hydroxy-pentadec-1-en-8-yn-7-one (25) Aqueous F_3CCO_2H (50%, 0.7 mL) was added dropwise to a solution of **24** (60 mg, 0.095 mmol) in CH_2Cl_2 (3.2 mL) stirred at ambient temperature. Stirring was continued at the same temperature for 5 min. Aqueous saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (10 mL×3). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶8] on silica gel afforded hydroxyketone **25** (52 mg, 0.0932 mmol, 98%) as a colorless oil. $[\alpha]_D^{25}$ −19.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.37—7.27 (m, 5H), 5.91 (ddd, *J*=17.5, 10.4, 7.3 Hz, 1H), 5.37 (d, *J*=9.6 Hz, 1H), 5.29 (d, *J*=17.5 Hz, 1H), 4.71 (t, *J*=6.6 Hz, 1H), 4.65 (s, 2H), 4.65 (d, *J*=11.5 Hz, 1H), 4.34 (d, *J*=11.5 Hz, 1H), 4.24—4.15 (m, 2H), 3.80—3.70 (m, 1H), 3.44 (d, *J*=4.1 Hz, 1H), 3.38 (s, 3H), 2.65—2.55 (m, 1H), 1.97—1.82 (m, 1H), 1.56—1.49 (m, 2H), 1.43—1.26 (m, 4H), 1.20 (d, *J*=7.3 Hz, 3H), 0.97—0.91 (m, 15H), 0.14 (d, *J*=9.4 Hz, 6H); FT-IR (film) *v*: 3496, 3031, 2960, 2208, 1678, 1496, 1463, 836, 779 cm^{-1}; ESI-MS *m/z*: 583.4 ($[M+Na]^+$); MALDI/DHB calcd for $C_{32}H_{52}SiO_6Na$ ($[M+Na]^+$) 583.3425, found 583.3454.

(3*S*,4*R*,5*R*,6*S*,7*S*,10*S*,12*S*)-3-Benzyloxy-10-(*tert*-butyldimethylsilyloxy)-12-methoxymethoxy-4,6-dimethylpentadec-1-en-8-yn-5,7-diol (26) A solution of ketone **25** (52 mg, 0.0932 mmol) in an dry MeCN (1.0 mL) was added to a solution of $Me_4NBH(OAc)_3$ (262 mg, 1.00 mmol) in glacial HOAc (1.0 mL) and dry MeCN (1.0 mL) stirred at −20 ℃. Stirring was then continued at the same temperature for 14 h. Aqueous sodium potassium tartrate (1.0 mol•L^{-1}, 1.0 mL) was added, followed by Et_2O. The pH of the aqueous layer was adjusted to *ca*. 8 with aqueous saturated $NaHCO_3$. The mixture was extracted with Et_2O (20 mL×5). The organic phases were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶8] on silica gel afforded diol **26** (48 mg, 0.086 mmol, 92%) as a colorless oil. $[\alpha]_D^{25}$ −30.7 (*c* 2.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.36—7.25 (m, 5H), 5.95 (ddd, *J*=17.7, 10.2, 7.9 Hz, 1H), 5.37 (d, *J*=10.6 Hz, 1H), 5.28 (d, *J*=17.4 Hz, 1H), 4.67—4.56 (m, 4H), 4.41—4.26 (m, 3H), 4.04 (s, 1H), 3.96 (m, 1H), 3.80—3.74 (m, 2H), 3.36 (s, 3H), 2.04—1.89 (m, 2H), 1.80—1.21 (m, 6H), 1.02 (d, *J*=7.5 Hz, 3H), 0.90 (t, *J*=7.4 Hz, 3H), 0.88 (s, 9H), 0.09 (d, *J*=7.1 Hz, 6H); FT-IR (film) *v*: 3459, 2929, 2857, 1463, 1040, 838, 778 cm^{-1}; ESI-MS *m/z*: 585.5 ($[M+Na]^+$); MALDI/DHB calcd for $C_{32}H_{54}SiO_6Na$ ($[M+Na]^+$) 585.3582, found 583.3553.

(3*S*,5*S*)-1-[(4*S*,5*S*,6*R*)-6-((2*R*,3*S*)-2-Methyl-3-benzyloxy-buta-3-enyl)-2-phenyl-5-methyl-1,3-dioxan-4-yl]-3-*tert*-butyldimethylsilyl-5-methoxymethoxy-1-octyne (6) A solution of **26** (11 mg, 0.0196 mmol), CSA (2 mg), and $PhCH(OMe)_2$ (6 μL, 0.0392 mmol) in dry CH_2Cl_2 (0.5 mL) was stirred at ambient temperature for 1 d. Another portion of $PhCH(OMe)_2$ (12 μL, 0.0784 mmol) was added. Stirring was continued at ambient temperature until TLC showed completion of the reaction. The mixture was diluted with EtOAc (50 mL), washed in turn with aqueous saturated $NaHCO_3$, water, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(EtOAc)∶*V*(PE)=1∶15] on silica gel gave **6** (12 mg, 0.0185 mmol, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.38—7.25 (m, 10H), 5.80 (ddd, *J*=17.7, 10.2, 7.9 Hz, 1H), 5.32—5.24 (m, 3H), 4.72—4.60 (m, 5H), 4.34—4.28 (m, 2H), 3.87 (d, *J*=10.0 Hz, 1H), 3.81—3.75 (m, 1H), 3.35 (s, 3H), 2.04—1.89 (m, 2H), 1.80—1.21 (m, 6H), 1.19 (d, *J*=6.9 Hz, 3H), 0.94—0.82 (m, 15H), 0.12 (d, *J*=10.5 Hz, 6H); ESI-MS *m/z*: 673.6 ($[M+Na]^+$); MALDI/DHB calcd for $C_{39}H_{58}SiO_6Na$ ($[M+Na]^+$) 673.3895, found 673.3897.

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(E1004261 Li, L.)

