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Total Syntheses of Isomeric Spiroacetal Marine Natural Products Attenols A and B

Vemula Praveen Kumar,[a] Nerella Kavitha,[a] and Srivari Chandrasekhar*[a]

Dedicated to Prof. Goverdhan Mehta on the occasion of his 70th birthday

Keywords: Natural products / Spiro compounds / Total synthesis / Olefination

The convergent total synthesis of two marine natural products, attenols A and B is achieved with excellent stereocontrol. The synthetic route is based on an enantio- and regioselective Sharpless dihydroxylation, palladium(0)-catalyzed reduction to form δ-hydroxy-1-enoates, stereoselective *m*CPBA-mediated epoxidation, and Julia–Kocienski olefination.

Introduction

Marine organisms, particularly invertebrates such as algae, sponges, and coelenterates, are rich sources of biologically promising compounds that are structurally unique and comprise a wide variety of chemical classes with pronounced pharmacological activities.[1] Natural products isolated from these marine extracts are usually scarce and are typically not available in sufficient amounts to allow their complete biological profile to be established. The unique structural features and biological activities of these natural products have always attracted the attention of synthetic organic chemists. Attenols A and B (**1** and **2**; Figure 1) are two isomeric spiroketals that were isolated from Chinese bivalve *Pinna attenuata* by Uemura and co-workers.[2] These two spiro compounds exhibit cytotoxicity against P388 cells at IC_{50} = 24 and 12 μg/mL, respectively. Attenols A and B possess the same empirical formula, but are differentiated by the hydroxy groups that participate in the spiroketal linkage.

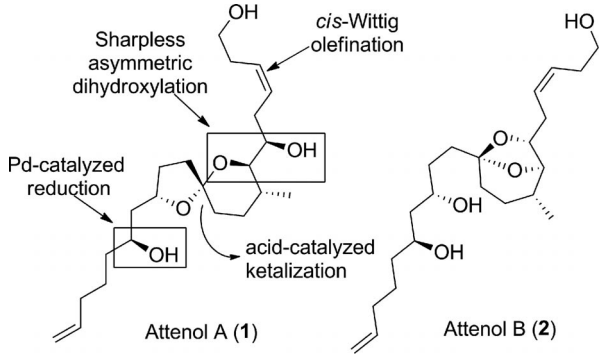

Figure 1. Structures of attenols A and B.

To date, the research groups of Suenaga,[3] Enders,[4a] and Sasaki[4b] have reported the total synthesis of attenols A and B. Eustache et al.[5a] and Rychnosky et al.[5b] published syntheses of attenol A. We have initiated a programme to synthesize marine natural products having cytotoxic properties,[6] and herein we report the total synthesis of attenols A and B.

Results and Discussion

The retrosynthetic strategy is delineated in Scheme 1. The advanced acyclic ketone **3** could be constructed from alkynone **4**, which, in turn, may be built from alkyne **5** and aldehyde **6**. The fragments **5** and **6** could be obtained from known aldehyde **7** and amide **8**, respectively. En route, this Sharpless asymmetric dihydroxylation, palladium(0)-catalyzed reduction, *m*CPBA-mediated epoxidation of allylic alcohol, and acid-catalyzed ketalization of oxo bis(ketal) **3** were planned as key reactions.

Synthesis of terminal alkyne **5** commenced from aldehyde **7** (prepared in three steps from 1,6-hexanediol as reported earlier[7]) in 11 steps as illustrated in Scheme 2. Treatment of ethyl propiolate with LiHMDS at –78 °C effected clean lithiation, and quenching of this anion with aldehyde **7** afforded propargylic alcohol **9** (95% yield). Exposure of γ-hydroxy ynoate **9** to the Lu protocol[8] (Ph_3P/benzene) provided dienoate **10** in 92% yield with 97% dia-

[a] Natural Products Chemistry Division, CSIR – Indian Institute of Chemical Technology,
Hyderabad 500007, India
E-mail: srivaric@iict.res.in
Homepage: www.iictindia.org

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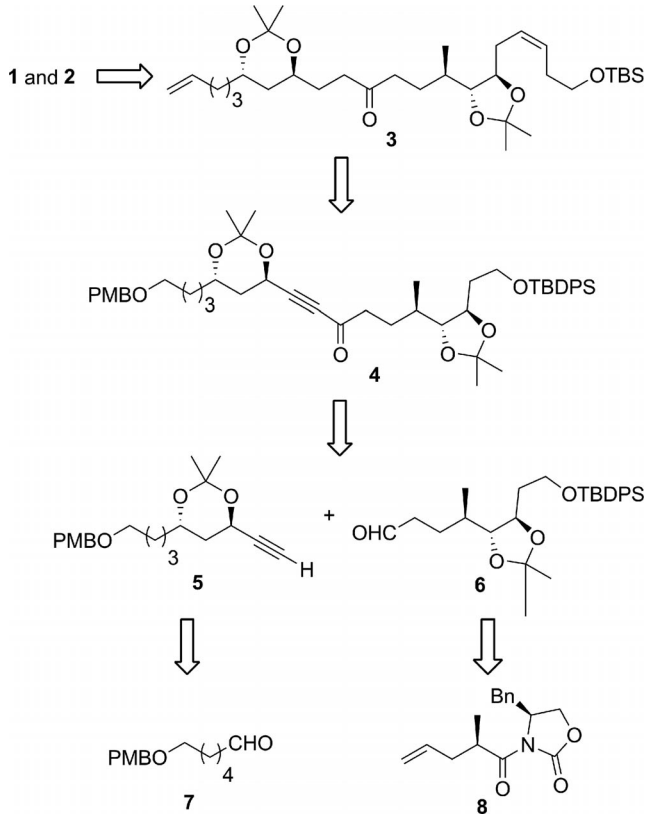
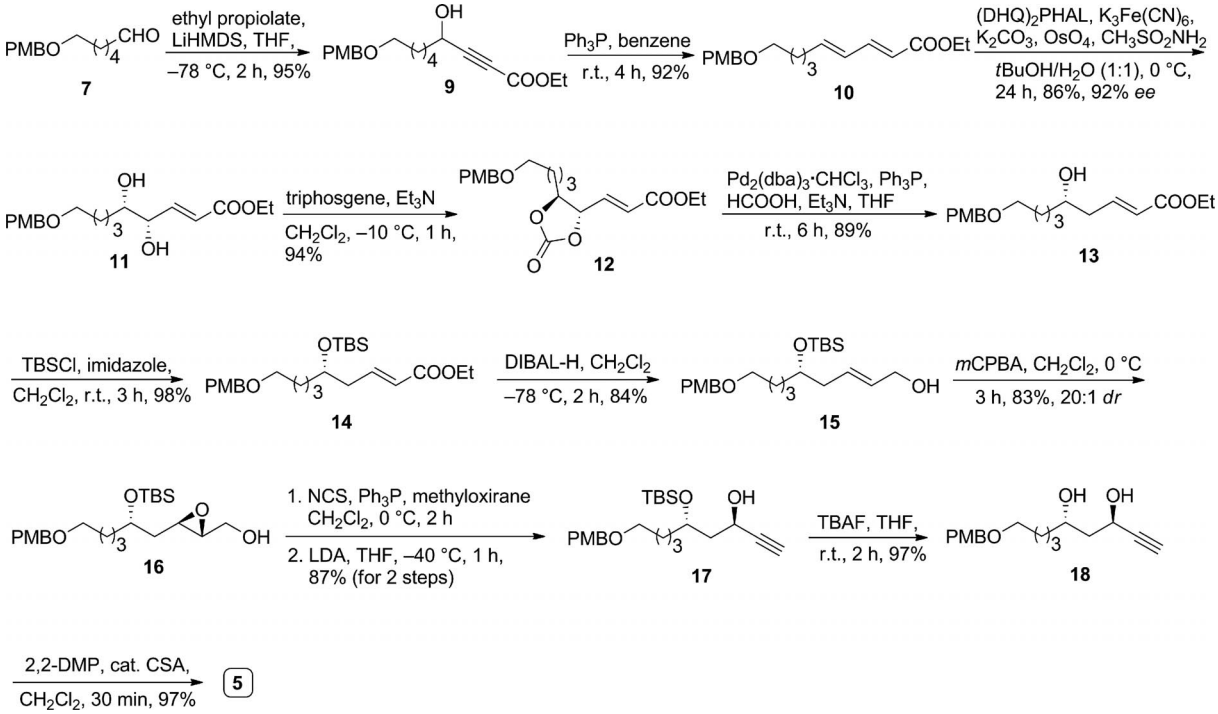


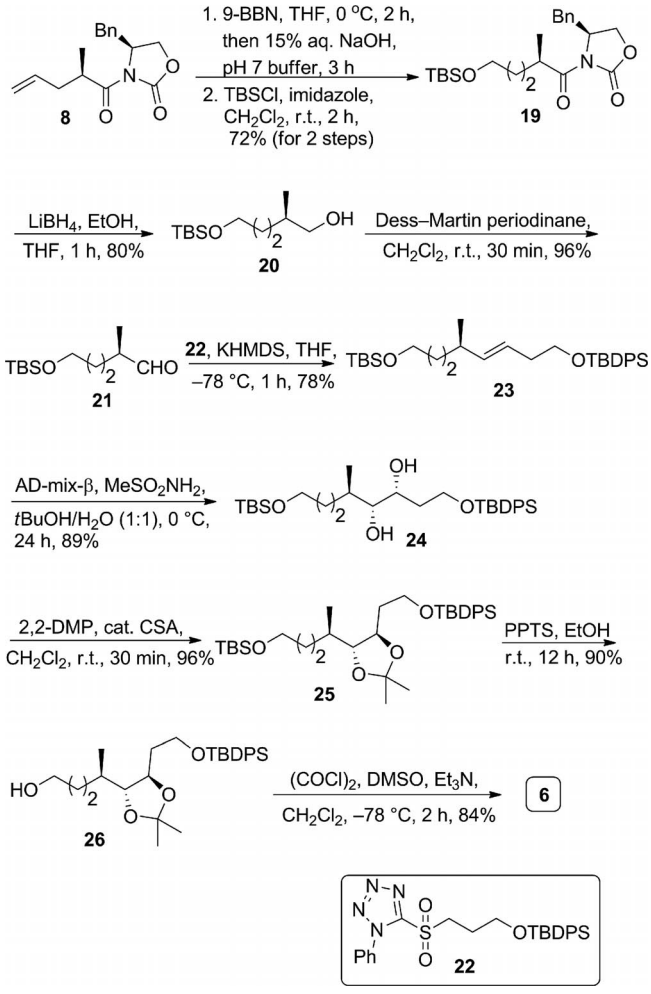
Scheme 1. Retrosynthetic analysis of **1** and **2**.

stereocontrol of the (*E*,*E*) isomer. By using the Sharpless asymmetric dihydroxylation protocol[9] [$(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4 and $CH_3SO_2NH_2$] in *t*BuOH/H_2O (1:1) at 0 °C for 24 h, dienoate **10** proceeded to give diol **11** (86% yield, 92% *ee*). Cyclic carbonate **12** was obtained by treating a solution of diol **11** with triphosgene and Et_3N in CH_2Cl_2 in 94% yield. Treatment of **12** with a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of Ph_3P and a mild hydride source (Et_3N/HCOOH)[10] in tetrahydrofuran (THF) at room temperature afforded the desired δ-hydroxy enoate **13** in 89% yield. Silylation of **13** gave TBS ether **14** by using *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in CH_2Cl_2 in 98% yield, which was followed by reduction of the ester functionality with diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 at –78 °C to give allylic alcohol **15** in 84% yield. Treatment of (*E*)-allylic alcohol **15** with *meta*-chloroperoxybenzoic acid (*m*CPBA)[11] afforded a mixture of the *anti*- and *syn*-epoxides in a 20:1 ratio, from which *anti*-epoxide **16** could be isolated by column chromatography in 83% yield. Chlorination of epoxy alcohol **16** by using *N*-chlorosuccinimide (NCS) and Ph_3P in CH_2Cl_2 gave the epoxy chloride, which was further treated with lithium diisopropylamide (LDA) in THF at –40 °C to form alkynol **17** in 87% yield over two steps. Fluoride-induced deprotection of the TBS ether by using tetrabutylammonium fluoride (TBAF) at room temperature afforded 1,3-*anti*-diol **18** in 97% yield, and the resultant diol was protected as acetonide **5** by using 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of 10-camphorsulfonic acid (CSA) in CH_2Cl_2 in 97% yield.

As depicted in Scheme 3, aldehyde **6** was synthesized from known oxazolidinone amide **8**.[12] Hydroboration {9-borabicyclo[3.3.1]nonane (9-BBN-H)/THF, pH 7 buffer, 30% H_2O_2} of the olefin in oxazolidinone amide **8** gave the



Scheme 2. Synthesis of alkyne segment **5**.



Scheme 3. Synthesis of aldehyde segment **6**.

alcohol, which was immediately silylated as TBS ether **19** by using TBDMSCl and imidazole in CH_2Cl_2 in 72% yield for two steps. Reductive cleavage of the chiral auxiliary was achieved with $LiBH_4$ in THF/EtOH to yield alcohol **20** (80% yield). Oxidation of **20** with the Dess–Martin reagent furnished the corresponding aldehyde **21** in 96% yield. Julia–Kocienski olefination[13] of **21** with sulfone **22**[14] in the presence of potassium bis(trimethylsilyl)amide (KHMDS) resulted in the formation of (*E*)-olefin **23** as a single isomer (78% yield). Exposure of **23** to Sharpless asymmetric dihydroxylation conditions with AD-mix-β and methanesulfonamide in *t*BuOH/H_2O (1:1) at 0 °C gave diol **24** in 89% yield with good diastereoselectivity. The diol functionality in **24** was protected as an acetonide by using 2,2-DMP and CSA in CH_2Cl_2 to afford differentially fully protected compound **25** (96% yield). Selective cleavage of the TBS ether of **25** under mild acidic conditions [pyridinium *p*-toluenesulfonate (PPTS) in ethanol][15] afforded primary alcohol **26** in 90% yield. Swern oxidation [$(COCl)_2$, Et_3N in CH_2Cl_2 at –78 °C] of **26** led to the construction of the aldehyde segment **6** in 84% yield.

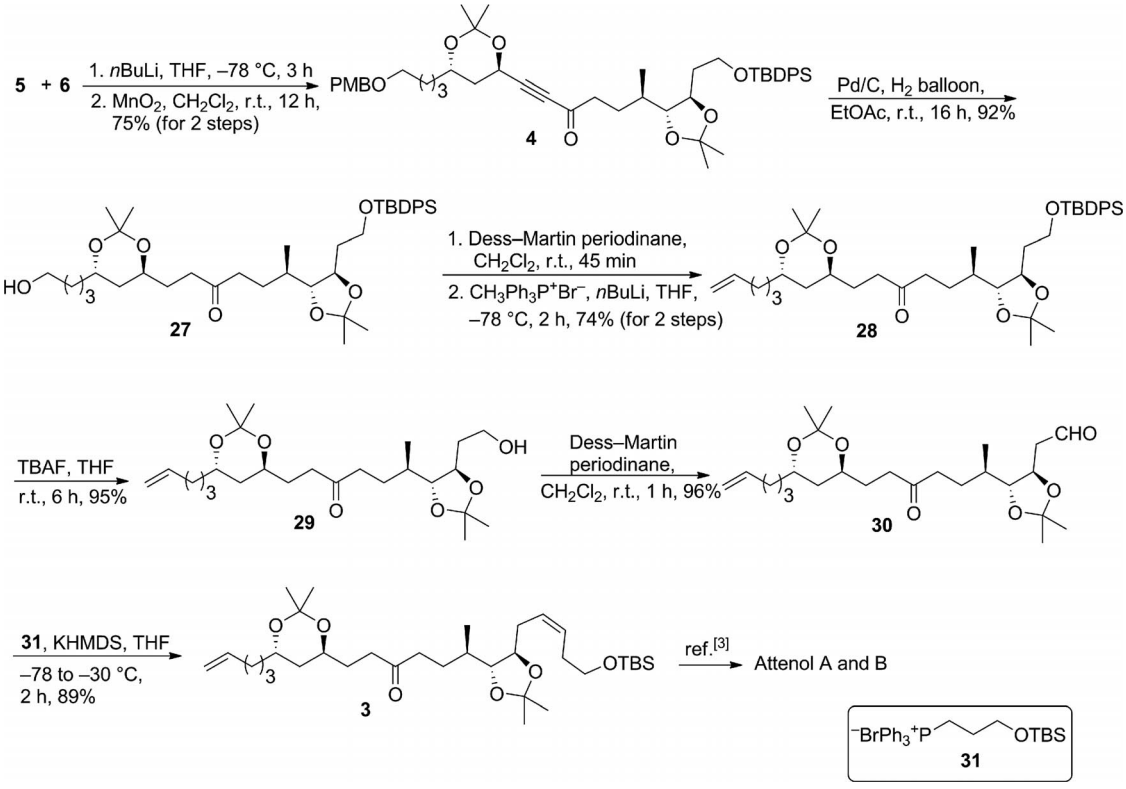
After generating the two key fragments, alkyne **5** and aldehyde **6**, the stage was set to couple these fragments. Coupling of the lithiated alkyne (generated in situ from alkyne **5** and *n*BuLi in THF) and aldehyde **6** gave the diastereomeric alkynol, which, on MnO_2-mediated oxidation, afforded alkynone **4** (75% yield, two steps; Scheme 4). Next, one-pot reduction of the alkyne functionality and deprotection of the *p*-methoxybenzyl (PMB) ether by hydrogenation in the presence of 10% Pd/C in ethyl acetate afforded primary alcohol **27** in 92% yield. One-carbon homologation of **27** through oxidation and Wittig reaction furnished **28** in 74% yield (two steps). Desilylation of the TBS group in **28** with TBAF in THF produced primary alcohol **29** in 95% yield, which was oxidized with Dess–Martin periodinane to aldehyde **30** in 96% yield. Next, aldehyde **30** was subjected to a stereoselective *cis*-Wittig reaction[16] by using [3-(*tert*-butylsilyloxy)propyl]triphenylphosphonium bromide (**31**)[17] in the presence of KHMDS in THF at –30 °C to afford acyclic ketone **3** with fixed (*Z*) stereoselectivity at the newly formed double bond in 89% yield. Finally, one-pot global deprotection followed by spiro ketalization was achieved with *p*TsA in methanol according to a literature procedure[3] to provide the desired spiroketal products attenols A (**1**) and B (**2**) in 52 and 12% yields, respectively (Scheme 4). The final compounds were fully characterized with complete spectral analysis. All spectroscopic data (^1H and ^{13}C NMR, HRMS, IR) of the synthetic compounds **1** and **2** are in perfect accord with those of the natural product[2] as well as those previously published.[3–5] The specific rotations of the synthetic attenols {for **1**: $[\alpha]_D^{20} = -5.2$ ($c = 0.22$, $CHCl_3$); for **2**: $[\alpha]_D^{20} = +25.9$ ($c = 0.09$, $CHCl_3$)} correspond to those of natural attenols {for **1**: $[\alpha]_D^{28} = -8.0$ ($c = 0.38$, $CHCl_3$); for **2**: $[\alpha]_D^{28} = +31$ ($c = 0.065$, $CHCl_3$)}.[2–5]

Conclusions

We have achieved a concise and highly stereoselective synthesis of cytotoxic marine spiroketals attenols A and B from readily available starting materials.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with 300, 400 or 500 MHz spectrometers at ambient temperature. Chemical shifts were measured in ppm and coupling constants in Hertz (Hz); shifts were measured relative to the signals for residual $CHCl_3$ ($\delta = 7.26$ ppm) and $CDCl_3$ ($\delta = 77.0$ ppm). All ^{13}C NMR spectra were proton-decoupled. Optical rotations were measured with an Anton-Paar MCP 200 digital polarimeter operating with the sodium D line by using a 1 mL cell and a 1 dm path length. Infrared (IR) spectra were obtained with a Perkin–Elmer 400 FTIR spectrophotometer by using either thin film (for oils) or KBr matrix (for solids). High-resolution mass spectra (HRMS) were recorded with an Agilent Technologies 6510 Q-TOF spectrometer. Commercially available reagents were used, unless otherwise indicated. THF was distilled under nitrogen from Na/benzophenone prior to use. CH_2Cl_2 was dried with 4 Å molecular sieves. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. Column chromatography was carried out with silica gel (60–120 mesh) packed in glass



Scheme 4. Synthesis of attenols A (**1**) and B (**2**).

columns. All reactions were performed under nitrogen in oven-dried glassware with magnetic stirring.

Ethyl 4-Hydroxy-9-(4-methoxybenzyloxy)non-2-ynoate (9): To a stirred solution of ethyl propiolate (5.15 mL, 50.84 mmol) in anhydrous THF (50 mL) was added LiHMDS (1.06 M in hexane, 46.6 mL, 46.60 mmol) at –78 °C, and the whole mixture was stirred at –78 °C for 1 h. Aldehyde **7** (10 g, 42.37 mmol) dissolved in THF (50 mL) was added dropwise to the reaction mixture over 15 min. Stirring was continued for 2 h, then the reaction was quenched by the addition of saturated aq. NH_4Cl (40 mL) before warming to room temperature. The reaction mixture was diluted with water (100 mL), stirred for 30 min and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 15%) to give alkynol **9** (13.45 g, 95%) as a colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 3391, 2927, 2856, 1708, 1511, 1243, 1027, 816, 772 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 4.50–4.44 (m, 1 H), 4.43 (s, 2 H), 4.24 (q, J = 7.2 Hz, 2 H), 3.80 (s, 3 H), 3.44 (t, J = 6.5 Hz, 2 H), 2.16–2.13 (m, 1 H), 1.80–1.73 (m, 2 H), 1.68–1.58 (m, 2 H), 1.53–1.37 (m, 4 H), 1.31 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.9, 153.4, 130.4, 129.2, 113.6, 88.0, 76.2, 72.4, 69.7, 63.5, 61.7, 55.2, 36.6, 29.3, 25.6, 24.6, 13.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{26}NaO_5$ [M + Na^+] 357.1672; found 357.1677.

Ethyl (2*E*,4*E*)-9-(4-Methoxybenzyloxy)nona-2,4-dienoate (10): To a stirred solution of alkynol **9** (12 g, 35.92 mmol) dissolved in anhydrous benzene (100 mL) was added triphenylphosphane (18.82 g, 71.85 mmol) at room temperature, and the mixture was stirred under nitrogen for 4 h. Upon completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified on a silica gel column (EtOAc/hexane, 2%) to afford (*E*,*E*)-dienoate **10** (10.51 g, 92%) as a colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 2954, 2935, 2860, 1715, 1528, 1218, 1068, 1021, 821, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.29–7.20 (m, 3 H), 6.88 (d, J = 8.6 Hz, 2 H), 6.21–6.05 (m, 2 H), 5.77 (d, J = 15.4 Hz, 1 H), 4.42 (s, 2 H), 4.19 (q, J = 6.9 Hz, 2 H), 3.80 (s, 3 H), 3.44 (t, J = 6.2 Hz, 2 H), 2.18 (q, J = 6.6, 13.2 Hz, 2 H), 1.67–1.45 (m, 4 H), 1.28 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.1, 158.9, 144.8, 144.0, 130.4, 129.0, 128.4, 119.1, 113.5, 72.3, 69.5, 60.0, 55.0, 32.5, 29.1, 25.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{26}NaO_4$ [M + Na^+] 341.1723; found 341.1727.

Ethyl (4*S*,5*S*,*E*)-4,5-Dihydroxy-9-(4-methoxybenzyloxy)non-2-enoate (11): To a stirred solution of a finely ground mixture of $K_3Fe(CN)_6$ (29 g, 90.54 mmol) and K_2CO_3 (12.50 g, 90.54 mmol) in *t*BuOH/H_2O (1:1, 250 mL) at room temperature, was added $CH_3SO_2NH_2$ (4.30 g, 45.27 mmol), $(DHQ)_2PHAL$ (235 mg, 0.301 mmol), and OsO_4 (5 mg/1 mL of toluene solution, 6 mL, 0.120 mmol). The mixture was stirred at room temperature for ca. 30 min and then cooled to 0 °C. To this chilled solution was added dienoate **10** (9.6 g, 30.18 mmol) in *t*BuOH/H_2O (1:1, 50 mL), and the reaction mixture was stirred vigorously at 0 °C for 24 h. The reaction was quenched by the addition of sodium sulfite (35 g), and the reaction mixture was stirred at room temperature for 1 h. All volatile solvents were removed under reduced pressure, and the residue was diluted with EtOAc (100 mL). The layers were separated, the aqueous phase was extracted with EtOAc (3 × 50 mL), and the organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane, 30%) to afford

diol **11** (9.13 g, 86%) as a pale-yellow liquid. $[\alpha]_D^{20}$ = –17.33 (*c* = 1.99, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3440, 2935, 2860, 1709, 1513, 1248, 1091, 1035, 821, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.95–6.84 (m, 3 H), 6.11 (dd, *J* = 1.5, 15.6 Hz, 1 H), 4.41 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.10–4.01 (m, 1 H), 3.79 (s, 3 H), 3.54–3.40 (m, 3 H), 3.34–3.21 (m, 1 H), 3.13–2.99 (m, 1 H), 1.70–1.38 (m, 6 H), 1.28 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.3, 159.0, 147.0, 130.2, 129.2, 122.2, 113.7, 73.9, 73.7, 72.4, 69.8, 60.5, 55.2, 32.6, 29.3, 22.3, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}NaO_6$ [M + Na^+] 375.1778; found 375.1777.

Ethyl (*E*)-3-{(4*S*,5*S*)-5-[4-(4-Methoxybenzyloxy)butyl]-2-oxo-1,3-dioxolan-4-yl}acrylate (12): To a stirred solution of diol **11** (7.9 g, 22.44 mmol) in anhydrous CH_2Cl_2 (50 mL) was added triethylamine (6.25 mL, 44.88 mmol), and the mixture was cooled to –10 °C. Triphosgene (7.99 g, 26.93 mmol) in CH_2Cl_2 (20 mL) was added dropwise by using a syringe over 5 min, and the resulting solution was warmed to 0 °C over 1 h and quenched by the addition of saturated aq. NH_4Cl (40 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were washed with saturated aq. sodium hydrogen carbonate (30 mL), brine (25 mL), dried with anhydrous Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel (EtOAc/hexane, 10%) afforded carbonate **12** (7.97 g, 94%) as a colorless oil. $[\alpha]_D^{20}$ = –61.85 (*c* = 2.67, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2938, 2865, 1805, 1720, 1513, 1250, 1174, 1037, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 6.86–6.77 (dd, *J* = 5.2, 15.8 Hz, 1 H), 6.21–6.13 (dd, *J* = 1.5, 15.8 Hz, 1 H), 4.82–4.76 (m, 1 H), 4.42 (s, 2 H), 4.38–4.31 (m, 1 H), 4.23 (q, *J* = 6.7 Hz, 2 H), 3.80 (s, 3 H), 3.45 (t, *J* = 6.0 Hz, 2 H), 1.85–1.40 (m, 6 H), 1.31 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.7, 159.0, 154.4, 139.1, 130.2, 129.1, 124.7, 113.6, 81.2, 79.6, 72.4, 69.0, 60.9, 55.1, 32.7, 28.9, 21.3, 13.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{26}NaO_7$ [M + Na^+] 401.1570; found 401.1568.

Ethyl (*S*,*E*)-5-Hydroxy-9-(4-methoxybenzyloxy)non-2-enoate (13): To a solution of carbonate **12** (7.9 g, 20.89 mmol) in THF (50 mL) under nitrogen was added $Pd_2(dba)_3{\cdot}CHCl_3$ (108 mg, 0.104 mmol) and triphenylphosphane (27 mg, 0.104 mmol). A solution of triethylamine (7.27 mL, 52.22 mmol) and formic acid (4.32 mL, 94.0 mmol) in THF (5 mL) was added, and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of saturated $NaHCO_3$ (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3× 25 mL), and the organic layer was washed with brine, dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexane, 30%) to give δ-hydroxy ester **13** (6.25 g, 89%). $[\alpha]_D^{20}$ = +2.35 (*c* = 1.06, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3448, 2932, 2358, 1707, 1514, 1246, 1171, 1034, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 7.03–6.91 (m, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 5.88 (d, *J* = 15.8 Hz, 1 H), 4.42 (s, 2 H), 4.18 (q, *J* = 6.7 Hz, 2 H), 3.80 (s, 3 H), 3.77–3.68 (m, 1 H), 3.44 (t, *J* = 6.0 Hz, 2 H), 2.43–2.12 (m, 3 H), 1.69–1.55 (m, 2 H), 1.55–1.37 (m, 4 H), 1.28 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.28, 159.0, 145.2, 130.5, 129.1, 123.6, 113.6, 72.4, 70.2, 69.7, 60.2, 55.1, 40.0, 36.7, 29.4, 22.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}NaO_5$ [M + Na^+] 359.1829; found 359.1828.

Ethyl (*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-9-(4-methoxybenzyl-oxy)-non-2-enoate (14): To a solution of δ-hydroxy ester **13** (6.2 g, 18.45 mmol) in anhydrous CH_2Cl_2 (50 mL) was added imidazole (2.51 g, 36.9 mmol) and TBSCl (3.32 g, 22.14 mmol) at 0 °C. The resultant mixture was warmed to room temperature and stirred for 3 h, then immersed in an ice bath, and saturated aq. NH_4Cl was added. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2× 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel (EtOAc/hexane, 5%) to give TBS ether **14** (8.14 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ = –3.92 (*c* = 1.63, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2937, 1720, 1513, 1462, 1250, 1098, 1041, 832, 794 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 7.01–6.88 (m, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 5.83 (d, *J* = 15.8 Hz, 1 H), 4.43 (s, 2 H), 4.18 (q, *J* = 7.5 Hz, 2 H), 3.81 (s, 3 H), 3.80–3.71 (m, 1 H), 3.43 (t, *J* = 6.0 Hz, 2 H), 2.40–2.24 (m, 2 H), 1.65–1.54 (m, 2 H), 1.50–1.32 (m, 4 H), 1.28 (t, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.2, 159.0, 145.8, 130.6, 129.1, 123.2, 113.6, 72.4, 71.2, 69.8, 60.0, 55.1, 39.9, 36.9, 29.7, 25.8, 25.7, 21.9, 17.9, 14.2, –4.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{42}NaO_5Si$ [M + Na^+] 473.26937; found 473.26935.

(*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)non-2-en-1-ol (15): To a solution of ester **14** (7.8 g, 17.33 mmol) in anhydrous CH_2Cl_2 (100 mL) at –78 °C was added DIBAL-H (25% in toluene, 19.71 mL, 34.66 mmol) dropwise over 10 min. The resultant mixture was stirred at the same temperature for 2 h, then the reaction was quenched by the addition of aqueous sodium potassium tartrate (50 mL). The reaction mixture was allowed to come to room temperature and stirred for 6 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude product was subjected to silica gel column chromatography (EtOAc/hexane, 30%) to yield allyl alcohol **15** (5.94 g, 84%) as a colorless oil. $[\alpha]_D^{20}$ = –7.12 (*c* = 2.31, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3440, 2934, 2856, 1513, 1247, 1093, 829, 774, 667 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 5.74–5.59 (m, 2 H), 4.43 (s, 2 H), 4.10–4.03 (m, 2 H), 3.80 (s, 3 H), 3.72–3.58 (m, 1 H), 3.43 (t, *J* = 6.7 Hz, 2 H), 2.24–2.16 (m, 2 H), 1.67–1.28 (m, 6 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 131.2, 130.6, 129.2, 129.1, 113.7, 72.4, 71.9, 69.9, 63.6, 55.2, 40.1, 36.6, 29.7, 25.8, 21.9, 18.0, –4.4, –4.5 ppm. HRMS (ESI): calcd. for $C_{23}H_{40}NaO_4Si$ [M + Na^+] 431.2588; found 431.2591.

{(2*R*,3*R*)-3-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-6-(4-methoxy-benzyloxy)hexyl]oxiran-2-yl}methanol (16): To a stirred solution of allyl alcohol **15** (5.9 g, 14.46 mmol) and $NaHCO_3$ (3.64 g, 43.38 mmol) in CH_2Cl_2 (50 mL) was added a solution of *m*CPBA (77% in water, 6.47 g, 28.92 mmol) in CH_2Cl_2 (50 mL) by using a dropping funnel at 0 °C over 1 h. The reaction mixture was stirred at the same temperature for another 3 h, then diluted with water (20 mL) and aqueous sodium thiosulfate (20 mL). After 1 h, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 30 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated to give *anti*- and *syn*-epoxides as a mixture (20:1 ratio). The crude residue was purified by silica gel chromatography (EtOAc/hexane, 30%) to give pure *anti*-epoxy alcohol **16** (5.1 g, 83%) as a clear oil. $[\alpha]_D^{20}$ = +19.7 (*c* = 0.81, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3440, 2937, 2858, 1514, 1463, 1248, 1096, 831, 774 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 4.42 (s, 2 H), 3.94–3.83 (m, 2 H), 3.80 (s, 3 H), 3.65–3.55 (m, 1 H), 3.44 (t, *J* = 6.0 Hz, 2 H), 3.10–3.04 (m, 1 H), 2.94–2.88 (m, 1 H), 1.96–1.87 (m, 1 H), 1.80–1.28 (m, 8 H), 0.89 (s, 9 H), 0.07 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 130.5, 129.2, 113.6, 72.4, 69.8, 61.6, 58.9, 55.2, 53.4, 39.1, 37.5, 29.7, 25.8, 21.6, 18.0, –4.4, –4.7 ppm. HRMS

(ESI): calcd. for $C_{23}H_{40}NaO_5Si$ [M + Na^+] 447.2536; found 447.2531.

(3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-non-1-yn-3-ol (17): To a solution of *anti*-epoxy alcohol **16** (5 g, 11.79 mmol) in anhydrous CH_2Cl_2 (50 mL) was added triphenylphosphane (3.7 g, 14.15 mmol) and propylene oxide (1.1 mL, 17.68 mmol) at 0 °C. *N*-Chlorosuccinimide (1.89 g, 14.15 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture dropwise at 0 °C, and the reaction mixture was stirred for an additional 2 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was subjected to silica gel column chromatography (hexane) to give the epoxy chloride, which was used directly in the next step. To a solution of the epoxy chloride (prepared above) in THF (30 mL) was added freshly prepared LDA (generated in situ from 35.5 mL of *n*BuLi and 9.5 mL of DIPA at 0 °C) dropwise at –40 °C over 10 min, and the mixture was stirred at the same temperature for 1 h. After complete consumption of the starting material, the reaction was quenched by the addition of saturated aq. NH_4Cl and the mixture diluted with EtOAc (50 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2× 50 mL). The combined organic extracts were dried with Na_2SO_4, filtered, concentrated, and the crude residue was purified by flash chromatography on silica gel (EtOAc/hexane, 5%) to give propargylic alcohol **17** (4.16 g, 87%) as a colorless oil. $[\alpha]_D^{20}$ = +24.01 (*c* = 0.81, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3418, 3297, 2939, 2865, 1514, 1462, 1249, 1090, 830, 775, 661 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.18 (d, *J* = 9.0 Hz, 2 H), 6.80 (d, *J* = 8.3 Hz, 2 H), 4.57–4.49 (m, 1 H), 4.35 (s, 2 H), 4.05–3.95 (m, 1 H), 3.72 (s, 3 H), 3.41–3.32 (m, 3 H), 2.37 (d, *J* = 2.2 Hz, 1 H), 1.88–1.73 (m, 2 H), 1.58–1.41 (m, 4 H), 1.35–1.23 (m, 2 H), 0.81 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 130.5, 129.2, 113.7, 84.9, 72.5, 72.4, 70.4, 69.7, 59.7, 55.2, 42.1, 36.5, 29.7, 25.8, 21.7, 17.9, –4.3, –4.7 ppm. HRMS (ESI): calcd. for $C_{23}H_{38}NaO_4Si$ [M + Na^+] 429.2432; found 429.2430.

(3*R*,5*S*)-9-(4-Methoxybenzyloxy)non-1-yne-3,5-diol (18): To a solution of **17** (3.7 g, 9.11 mmol) in THF (20 mL) was added TBAF (1 M in THF, 13.67 mL, 13.67 mmol) dropwise, and the resulting brown solution was stirred for 2 h. The reaction was quenched by the addition of aqueous NH_4Cl (30 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (3× 30 mL), and the combined organic extracts were washed successively with brine, water, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (EtOAc/hexane, 30%) to afford 1,3-*anti*-diol **18** (2.58 g, 97%) as a clear oil. $[\alpha]_D^{20}$ = +8.86 (*c* = 0.39, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3560, 3285, 2934, 1513, 1247, 1087, 1035, 824, 667 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 4.67–4.60 (m, 1 H), 4.43 (s, 2 H), 4.18–4.06 (m, 1 H), 3.80 (s, 3 H), 3.45 (t, *J* = 6.0 Hz, 2 H), 2.48 (d, *J* = 2.2 Hz, 1 H), 1.85–1.76 (m, 2 H), 1.69–1.56 (m, 2 H), 1.55–1.38 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 130.4, 129.3, 113.7, 84.5, 73.1, 72.6, 69.8, 69.4, 60.8, 55.2, 42.2, 37.2, 29.3, 22.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{24}NaO_4$ [M + Na^+] 315.1568; found 315.1566.

(4*R*,6*S*)-4-Ethynyl-6-[4-(4-methoxybenzyloxy)butyl]-2,2-dimethyl-1,3-dioxane (5): A solution of 1,3-*anti*-diol **18** (2.3 g, 7.87 mmol) in CH_2Cl_2 (20 mL) was treated with 2,2-DMP (2.89 mL, 23.63 mmol) and CSA (18 mg, 0.08 mmol) at 0 °C and stirred until the starting material was consumed (ca. 30 min). The reaction was quenched by the addition of Et_3N (1 mL) and the mixture diluted with water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography (EtOAc/hexane, 5%) to give alkyne **5** (2.53 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ = +0.4 (*c* = 1.23, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3288, 2930, 1699, 1514, 1458, 1246, 1100, 1036, 825, 665 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.75–4.68 (m, 1 H), 4.43 (s, 2 H), 4.09–3.99 (m, 1 H), 3.80 (s, 3 H), 3.45 (t, *J* = 6.4 Hz, 2 H), 2.49 (d, *J* = 2.4 Hz, 1 H), 1.85–1.77 (m, 2 H), 1.69–1.40 (m, 9 H), 1.36 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 130.6, 129.1, 113.7, 100.3, 84.3, 73.6, 72.4, 69.8, 65.5, 59.2, 55.2, 36.9, 35.5, 28.5, 28.4, 23.5, 21.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}NaO_4$ [M + Na^+] 355.1879; found 355.1872.

(*S*)-4-Benzyl-3-[(*R*)-5-(*tert*-butyldimethylsilyloxy)-2-methylpentanoyl]oxazolidin-2-one (19): To a stirred solution of amide **9** (9.2 g, 33.69 mmol) in THF (30 mL) at 0 °C was added dropwise a solution of 9-BBN (9.04 g, 37.06 mmol) in THF (50 mL). After 1 h, the reaction was quenched by the addition of aqueous pH 7 buffer (30 mL) and H_2O_2 (30 mL, 30% aqueous) at 0 °C. After 3 h, the reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (4× 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under vacuum to give the crude alcohol, which was used for the next step immediately. A solution of the alcohol in CH_2Cl_2 (40 mL) was treated with imidazole (4.58 g, 67.38 mmol) at 0 °C. TBSCl (5.56 g, 37.06 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of aqueous NH_4Cl and the mixture diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2× 25 mL), and the combined organic phases were dried and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 25%) to give TBS ether **19** (9.82 g, 72% for two steps) as a viscous liquid. $[\alpha]_D^{20}$ = +21.20 (*c* = 1.58, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2931, 2858, 1783, 1699, 1386, 1249, 1212, 1100, 836, 774, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.42–7.21 (m, 5 H), 4.79–4.65 (m, 1 H), 4.27–4.15 (m, 2 H), 3.88–3.74 (m, 1 H), 3.73–3.61 (m, 2 H), 3.39–3.30 (dd, *J* = 3.0, 13.2 Hz, 1 H), 2.80–2.68 (dd, *J* = 9.8, 13.2 Hz, 1 H), 1.91–1.75 (m, 1 H), 1.74–1.51 (m, 3 H), 1.22 (d, *J* = 6.7 Hz, 3 H), 0.93 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.1, 153.0, 135.3, 129.3, 128.9, 127.2, 65.9, 62.9, 55.3, 38.0, 37.2, 30.2, 30.0, 25.9, 18.3, 16.8, –5.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{35}NaO_4Si$ [M + Na^+] 428.2228; found 428.2215.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-methylpentan-1-ol (20): To a solution of **19** (9.8 g, 24.19 mmol) in anhydrous THF (100 mL) at 0 °C was added ethanol (5.6 mL, 96.76 mmol) and, portionwise, $LiBH_4$ (632 mg, 29.03 mmol). After 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. The reaction was then quenched by the addition of saturated aq. NH_4Cl and the mixture concentrated under reduced pressure. The aqueous layer was extracted with EtOAc (3× 50 mL), the combined organic extracts were dried with Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel (EtOAc/hexane, 10%) to give pure alcohol **20** (4.49 g, 80%) as a viscous liquid. $[\alpha]_D^{20}$ = +8.8 (*c* = 0.17, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3390, 2932, 2858, 1251, 1219, 1097, 835, 772 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.61 (t, *J* = 6.2 Hz, 2 H), 3.55–3.38 (m, 2 H), 1.69–1.36 (m, 4 H), 1.23–1.10 (m, 1 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s. 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 68.2, 63.4, 35.5, 30.0, 29.2, 25.9, 16.6, –5.2 ppm. HRMS (ESI): calcd. for $C_{12}H_{28}NaO_2Si$ [M + Na^+] 255.1451; found 255.1442.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-methylpentan-1-ol (21): Dess–Martin periodinane (9.43 g, 22.24 mmol) was added at 0 °C under nitrogen to a solution of alcohol **20** (4.3 g, 18.53 mmol) in CH_2Cl_2 (60 mL). The resultant mixture was warmed to room temperature. After 30 min, the reaction was quenched by the addition of aqueous $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ (1:1, 60 mL). The mixture was stirred vigorously until a clear solution resulted. The organic portion was collected, and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic portions were dried with Na_2SO_4, filtered, and concentrated in vacuo to give crude aldehyde **21** (4.1 g, 96% yield). The aldehyde was immediately used in the next step.

(*R*,*E*)-2,2,9,14,14,15,15-Heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-7-ene (23): KHMDS (0.7 M in toluene, 56.2 mL, 39.20 mmol) was added dropwise to a solution of sulfone **22** (21.12 g, 44.55 mmol) in anhydrous THF (100 mL) at –78 °C, and the mixture was stirred at the same temperature for 1 h to obtain a clean ylide. Subsequently, a solution of aldehyde **21** in THF (20 mL) was added dropwise to the ylide at –78 °C, and the mixture was stirred for 1 h, then quenched by the addition of saturated aq. NH_4Cl. The separated aqueous layer was extracted with EtOAc (2× 20 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5%) to give (*E*)-olefin **23** (7.09 g, 78%) as a single isomer. $[\alpha]_D^{20}$ = +1.7 (*c* = 0.86, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3072, 2932, 2859, 1469, 1428, 1376, 1253, 1105, 1089, 834, 779, 703, 613, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.68 (d, *J* = 7.5 Hz, 4 H), 7.46–7.33 (m, 6 H), 5.42–5.27 (m, 2 H), 3.67 (t, *J* = 6.7 Hz, 2 H), 3.57 (t, *J* = 6.0 Hz, 2 H), 2.32–2.20 (m, 2 H), 2.11–1.98 (m, 1 H), 1.59–1.40 (m, 2 H), 1.35–1.22 (m, 2 H), 1.05 (s, 9 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 135.5, 134.0, 129.4, 127.5, 124.8, 64.0, 63.4, 36.5, 36.0, 33.1, 30.6, 26.8, 25.9, 20.7, 19.2, 18.3, –5.2 ppm. HRMS (ESI): calcd. for $C_{31}H_{54}NO_2Si_2$ [M + NH_4^+] 528.3688; found 528.3719.

(7*R*,8*R*,9*R*)-2,2,9,14,14,15,15-Heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadecane-7,8-diol (24): To a stirred solution of (*E*)-olefin **23** (6 g, 11.76 mmol) in *t*BuOH/H_2O (1:1, 100 mL) was added methanesulfonamide (1.67 g, 17.64 mmol) at 0 °C. Subsequently, AD-mix-β (16.46 g, 1.4 g for 1 mmol of starting material) was added, and the resulting pale-yellow solution was stirred at 0 °C for 24 h. The reaction was quenched by the addition of sodium sulfite (16 g) and the mixture vigorously stirred for 30 min. *t*BuOH was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3× 40 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (EtOAc/hexane, 30%) to give diol **24** (5.69 g, 89%) as a pale-yellow oil. $[\alpha]_D^{20}$ = +2.69 (*c* = 0.92, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3429, 3072, 2931, 2858, 1469, 1428, 1254, 1105, 835, 774, 703, 613, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.68 (d, *J* = 7.5 Hz, 4 H), 7.46–7.36 (m, 6 H), 4.04–3.95 (m, 1 H), 3.89 (t, *J* = 5.3 Hz, 2 H), 3.61 (t, *J* = 6.0 Hz, 2 H), 3.32 (d, *J* = 2.2 Hz, 1 H), 3.20–3.11 (m, 1 H), 2.55–2.47 (m, 1 H), 2.00–1.85 (m, 1 H), 1.77–1.57 (m, 4 H), 1.56–1.39 (m, 1 H), 1.29–1.14 (m, 1 H), 1.06 (s, 9 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 135.5, 132.8, 132.7, 129.8, 127.8, 78.3, 70.8, 63.6, 62.9, 35.9, 35.4, 30.2, 28.0, 26.7, 25.9, 19.0, 18.3, 16.2, –5.2 ppm. HRMS (ESI): calcd. for $C_{31}H_{53}O_4Si_2$ [M + H^+] 545.3477; found 545.3478.

***tert*-Butyl(2-{(4*R*,5*R*)-5-[(*R*)-5-(*tert*-butyldimethylsilyloxy)pentan-2-yl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethoxy)diphenylsilane (25):** Diol **24** (4.9 g, 9.0 mmol) was dissolved in CH_2Cl_2 (20 mL), and 2,2-DMP (3.3 mL, 27.02 mmol) and CSA (20 mg, 0.09 mmol) were added while stirring. The resulting bright-yellow solution was stirred for 30 min and the reaction quenched by the addition of Et_3N (2 mL). The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel (EtOAc/hexane, 10%) to give 1,2-acetonide **25** (5.04 g, 96%) as a clear oil. $[\alpha]_D^{20}$ = +19.9 (*c* = 1.63, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2933, 2859, 1467, 1428, 1377, 1244, 1110, 1081, 878, 738, 703, 613, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.72–7.65 (m, 4 H), 7.44–7.34 (m, 6 H), 4.06–3.97 (m, 1 H), 3.88–3.80 (m, 2 H), 3.65–3.57 (m, 2 H), 3.55–3.48 (m, 1 H), 1.95–1.43 (m, 6 H), 1.36 (s, 3 H), 1.64 (s, 3 H), 1.24–1.10 (m, 1 H), 1.06 (s, 9 H), 0.95–0.87 (m, 12 H), 0.06 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 135.57, 135.5, 133.9, 133.8, 129.5, 127.5, 107.7, 85.0, 75.5, 63.4, 61.0, 37.7, 35.9, 30.4, 28.9, 27.3, 27.2, 26.8, 25.9, 19.1, 18.3, 15.6, –5.2 ppm. HRMS (ESI): calcd. for $C_{34}H_{57}O_4Si_2$ [M + H^+] 585.379; found 585.3798.

(*R*)-4-{(4*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}pentan-1-ol (26): Pyridinium *p*-toluenesulfonate (PPTS; 210 mg, 0.83 mmol) was added to a solution of compound **25** (4.9 g, 8.39 mmol) in ethanol (20 mL), and the resulting solution was stirred at room temperature for 12 h. Et_3N (2 mL) was added to quench the reaction, and the mixture was concentrated in vacuo. The obtained residue was subjected to column chromatography on silica gel (EtOAc/hexane, 20%) to give primary alcohol **26** (3.55 g, 90%) as a colorless oil. $[\alpha]_D^{20}$ = 24.34 (*c* = 0.76, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3399, 2933, 2859, 1377, 1244, 1110, 1081, 738, 703, 613, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.71–7.63 (m, 4 H), 7.47–7.33 (m, 6 H), 4.06–3.96 (m, 1 H), 3.87–3.80 (dd, *J* = 5.0, 7.3 Hz, 2 H), 3.68–3.59 (m, 2 H), 3.50 (t, *J* = 6.9 Hz, 1 H), 1.94–1.80 (m, 1 H), 1.79–1.42 (m, 6 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.05 (s, 9 H), 0.92 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 135.5, 133.9, 133.8, 129.5, 127.5, 107.8, 85.0, 75.7, 63.1, 61.0, 37.7, 36.1, 30.1, 29.0, 27.3, 27.1, 26.8, 19.1, 15.7 ppm. HRMS (ESI): calcd. for $C_{28}H_{43}O_4Si$ [M + H^+] 471.2925; found 471.2958.

(*R*)-4-{(4*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}pentanal (6): To a solution of oxalyl chloride (1.91 mL, 22.32 mmol) in anhydrous CH_2Cl_2 (20 mL) at –78 °C was added a solution of DMSO (3.17 mL, 44.64 mmol) in CH_2Cl_2 (10 mL) dropwise (***Caution:*** Huge effervescence occurs during the reaction). The resulting mixture was stirred for 15 min before a solution of alcohol **26** (3.5 g, 7.44 mmol) in CH_2Cl_2 (20 mL) was added. The resulting mixture was stirred for another 2 h before Et_3N (9.34 mL, 66.96 mmol) was added. The resulting mixture was stirred for 30 min before warming to room temperature and stirring for a further 30 min. The reaction mixture was diluted with water (100 mL) and CH_2Cl_2 (50 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give a light-yellow oil. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 20%) to afford aldehyde **6** (2.92 g, 84%) as a colorless oil. $[\alpha]_D^{20}$ = +19.58 (*c* = 4.3, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3071, 2933, 2859, 1727, 1378, 1110, 1085, 739, 704, 613, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.66 (s, 1 H), 7.64–7.55 (m, 4 H), 7.37–7.23 (m, 6 H), 3.98–3.89 (m, 1 H), 3.79–3.71 (m, 2 H), 3.39 (t, *J* = 7.5 Hz, 1 H), 2.59–2.30 (m, 2 H), 1.92–1.37 (m, 5 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 0.97 (s, 9 H), 0.82 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 202.3, 135.5, 135.4, 133.7, 133.6, 129.5, 127.5, 107.9, 84.7, 75.9, 60.8, 41.4, 37.5, 36.0, 27.2, 27.1, 26.7, 25.4,

19.1, 15.7 ppm. HRMS (ESI): calcd. for $C_{28}H_{41}O_4Si$ [M + H^+] 469.2769; found 469.2758.

(*R*)-6-{(4*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-1-{(4*R*,6*S*)-6-[4-(4-methoxybenzyloxy)butyl]-2,2-dimethyl-1,3-dioxan-4-yl}hept-1-yn-3-one (4): *n*BuLi (1.6 M in hexane, 1.7 mL, 2.71 mmol) was added dropwise to a solution of alkyne **5** (0.9 g, 2.71 mmol) in anhydrous THF (15 mL) at –78 °C under nitrogen. After 1 h, a solution of aldehyde **6** (1.52 g, 3.25 mmol) in THF (10 mL) was added dropwise over 10 min, and the resulting solution was stirred at –78 °C for an additional 3 h before the reaction was quenched by the addition of saturated aq. NH_4Cl and the mixture diluted with ethyl acetate (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography by using silica gel (EtOAc/hexane, 30%) gave the diastereomeric alcohol (1.78 g, 82%), which was immediately used for next step without further characterization. A suspension of the above alcohol (1.78 g, 2.22 mmol) and activated MnO_2 (1.93 g, 22.25 mmol) in CH_2Cl_2 (40 mL) was vigorously stirred at room temperature for 12 h. After completion of the reaction, the solution was filtered through a pad of Celite and the residue washed with CH_2Cl_2 (30 mL). The filtrate was concentrated in vacuo to yield alkynone **4** (1.63, 92%) as a clear oil. $[\alpha]_D^{20}$ = +10.43 (*c* = 0.57, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2933, 2859, 1678, 1513, 1375, 1247, 1109, 822, 704, 613 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.70–7.64 (m, 4 H), 7.45–7.33 (m, 6 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.87 (t, *J* = 4.9 Hz, 1 H), 4.43 (s, 2 H), 4.06–3.94 (m, 2 H), 3.87–3.77 (m, 5 H), 3.49–3.40 (m, 3 H), 2.75–2.55 (m, 2 H), 2.05–1.39 (m, 16 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.05 (s, 9 H), 0.92 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 187.2, 157.3, 135.5, 133.7, 133.6, 129.5, 129.2, 127.5, 113.7, 108.0, 100.3, 91.4, 84.8, 84.4, 76.0, 72.5, 69.8, 65.6, 60.9, 59.4, 55.2, 43.0, 37.6, 35.9, 35.8, 35.6, 29.5, 28.7, 27.2, 27.1, 26.8, 23.2, 21.6, 19.1, 15.7 ppm. HRMS (ESI): calcd. for $C_{48}H_{70}NO_8Si$ [M + NH_4^+] 816.4865; found 816.4877.

(*R*)-6-{(4*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-1-[(4*S*,6*S*)-6-(4-hydroxybutyl)-2,2-dimethyl-1,3-dioxan-4-yl]heptan-3-one (27): To a solution of alkynone **4** (1.6 g, 2.00 mmol) in ethyl acetate (20 mL) was added 10% Pd/C (300 mg) at room temperature. The mixture was purged with nitrogen three times and then connected to a balloon filled with hydrogen. After stirring at room temperature for 16 h, the Pd/C was removed by filtration, and the filtrate was then concentrated under reduced pressure to give saturated alcohol **27** (1.25 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ = +30.64 (*c* = 0.31, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3460, 2933, 2859, 1714, 1378, 1222, 1110, 1083, 772, 704, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.72–7.62 (m, 4 H), 7.45–7.32 (m, 6 H), 4.05–3.95 (m, 1 H), 3.87–3.70 (m, 4 H), 3.65 (t, *J* = 6.0 Hz, 2 H), 3.46 (t, *J* = 7.5 Hz, 1 H), 2.63–2.34 (m, 4 H), 2.09–1.38 (m, 13 H), 1.37–1.27 (m, 14 H), 1.04 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 210.5, 135.5, 134.0, 133.8, 129.5, 127.5, 106.8, 100.2, 84.9, 76.0, 66.6, 66.0, 62.8, 60.9, 40.4, 38.7, 38.6, 37.7, 36.0, 35.5, 32.5, 29.7, 27.3, 27.2, 26.8, 24.7, 21.7, 19.1, 15.7 ppm. HRMS (ESI): calcd. for $C_{40}H_{66}NO_7Si$ [M + NH_4^+] 700.4603; found 700.4625.

(*R*)-6-{(4*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-1-[(4*S*,6*S*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl]heptan-3-one (28): Dess–Martin periodinane (752 mg, 1.77 mmol) was added at 0 °C under nitrogen to a solution of alcohol **27** (1.1 g, 1.61 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred for 10 min and then warmed to room temperature. After 45 min, the reaction was quenched by the addition of aqueous $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ (1:1, 20 mL). The mixture was stirred vigorously until a clear solution resulted. The organic portion was collected, and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic portions were dried with Na_2SO_4, filtered, and concentrated in vacuo to give the crude aldehyde, which was used for next step without further purification or characterization. *n*BuLi (1.6 M in THF, 2.22 mL, 3.54 mmol) was added to a solution of methyltriphenylphosphonium bromide (1.44 g, 4.03 mmol) in anhydrous THF (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min to generate a dark-yellow solution of ylide before cooling to –78 °C. A solution of aldehyde (prepared above) in anhydrous THF (10 mL) was added and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated aq. NH_4Cl and the mixture diluted with EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (2× 10 mL). The combined organic extracts were dried and concentrated in vacuo. The crude residue was purified by flash chromatography (EtOAc/hexane, 15%) to yield **28** (809 mg, 74%) as a viscous liquid. $[\alpha]_D^{20}$ = +21.15 (*c* = 0.26, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2933, 2859, 1715, 1376, 1223, 1110, 1084, 704, 613, 505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.71–7.62 (m, 4 H), 7.46–7.32 (m, 6 H), 5.87–5.72 (m, 1 H), 5.05–4.90 (m, 2 H), 4.05–3.95 (m, 1 H), 3.87–3.68 (m, 4 H), 3.46 (t, *J* = 6.8 Hz, 1 H), 2.64–2.33 (m, 4 H), 2.11–1.98 (m, 2 H), 1.95–1.37 (m, 13 H), 1.37–1.27 (m, 12 H), 1.04 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 210.5, 138.7, 135.5, 133.8, 129.5, 127.6, 114.5, 100.7, 84.8, 79.9, 66.5, 65.9, 60.9, 40.4, 38.7, 38.6, 37.6, 36.0, 35.7, 35.3, 33.6, 29.6, 27.3, 27.1, 26.8, 24.7, 19.1, 15.7 ppm. HRMS (ESI): calcd. for $C_{41}H_{66}NO_6Si$ [M + NH_4^+] 696.4654; found 696.4653.

(*R*)-1-[(4*S*,6*S*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl]-6-[(4*R*,5*R*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]heptan-3-one (29): TBAF (1 M in THF, 2.07 mL, 2.06 mmol) was added to a solution of compound **28** (700 mg, 1.03 mmol) in anhydrous THF (15 mL) at 0 °C. After 6 h, the reaction was quenched by the addition of saturated aq. NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2× 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc/hexane, 40%) to give primary alcohol **29** (431 mg, 95%) as a viscous liquid. $[\alpha]_D^{20}$ = +27.28 (*c* = 0.55, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3468, 2931, 2879, 1713, 1376, 1224, 1169, 1061, 909, 876 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ = 5.84–5.75 (m, 1 H), 5.00 (d, *J* = 16.9 Hz, 1 H), 4.94 (d, *J* = 10.1 Hz, 1 H), 4.53–4.50 (m, 1 H), 3.99–3.93 (m, 1 H), 3.85–3.70 (m, 4 H), 3.52 (t, *J* = 6.7 Hz, 1 H), 2.60–2.49 (m, 2 H), 2.48–2.39 (m, 2 H), 2.08–2.02 (m, 2 H), 1.91–1.82 (m, 2 H), 1.82–1.74 (m, 2 H), 1.71–1.60 (m, 2 H), 1.57 (t, *J* = 7.9 Hz, 1 H), 1.54–1.35 (m, 12 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 210.6, 138.6, 114.5, 108.3, 100.1, 85.1, 78.4, 66.5, 65.9, 61.0, 40.2, 38.8, 38.6, 36.4, 35.4, 35.2, 33.6, 29.6, 27.2, 27.1, 26.9, 24.7, 24.6, 15.8 ppm. HRMS (ESI): calcd. for $C_{25}H_{48}NO_6$ [M + NH_4^+] 458.3476; found 458.3477.

2-[(4*R*,5*R*)-5-{(*R*)-7-[(4*S*,6*S*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl]-5-oxoheptan-2-yl}-2,2-dimethyl-1,3-dioxolan-4-yl]-acetaldehyde (30): Dess–Martin periodinane (462 mg, 1.09 mmol) was added at 0 °C under nitrogen to a solution of alcohol **29** (400 mg, 0.91 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred for 10 min and then warmed to room temperature. After 1 h, the reaction was quenched by the addition of aqueous $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ (1:1, 20 mL). The mixture was stirred vigorously until a clear solution resulted. The organic portion was

collected, and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic portions were dried with Na_2SO_4, filtered, and concentrated in vacuo to give aldehyde **30** (382 mg, 96%), which was used for the next step without further purification and characterization.

(*R*)-6-{(4*R*,5*R*)-5-[(*Z*)-5-(*tert*-Butyldimethylsilyloxy)pent-2-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-1-[(4*S*,6*S*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl]heptan-3-one (3): To a solution of [3-(*tert*-butylsilyloxy)propyl]triphenylphosphonium bromide (**31**; 717 mg, 1.39 mmol) in anhydrous THF (15 mL), was added KHMDS (0.7 M in THF, 1.75 mL, 1.22 mmol) dropwise at –78 °C, and the mixture was stirred for 30 min to obtain a clean ylide. A solution of aldehyde **30** (382 mg, 0.872 mg) in anhydrous THF (10 mL) was added dropwise to the ylide at –78 °C, and the mixture was stirred for 20 min and slowly warmed to –30 °C in 30 min and stirred for a further 2 h. The reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) and the mixture diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2× 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give the crude residue. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 20%) to give pure olefinic compound **3** with (*Z*) stereochemistry (461 mg, 89%) as a colorless oil. $[\alpha]_D^{20}$ = +12.5 (*c* = 0.1, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2929, 2857, 1716, 1462, 1377, 1252, 1224, 1097, 837, 777 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.85–5.75 (m, 1 H), 5.61–5.49 (m, 2 H), 5.00 (br. d, *J* = 18.9 Hz, 1 H), 4.94 (br. d, *J* = 12.0 Hz, 1 H), 3.87–3.80 (m, 1 H), 3.81–3.69 (m, 2 H), 3.61 (t, *J* = 7.0 Hz, 2 H), 3.48 (t, *J* = 7.1 Hz, 1 H), 2.61–2.24 (m, 8 H), 2.10–2.01 (m, 2 H), 1.93–1.21 (m, 11 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 0.92–0.87 (m, 12 H), 0.05 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 210.4, 152.2, 138.7, 128.1, 126.6, 114.5, 108.7, 100.2, 84.6, 78.9, 77.2, 66.5, 66.0, 62.7, 40.3, 38.8, 38.6, 35.7, 35.3, 32.2, 31.3, 29.7, 27.3, 27.2, 26.9, 25.9, 24.7, 21.0, 16.0, 14.2, –5.2 ppm. HRMS: calcd. for $C_{34}H_{66}NO_6Si$ [M + NH_4^+] 612.4654; found 612.4652.

Attenol A and B (1 and 2): To a solution of ketone **3** (300 mg, 0.51 mmol) in methanol (10 mL) was added *p*-toluenesulfonic acid (19 mg, 0.10 mmol), and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of pyridine (1 mL) and the mixture concentrated under vacuum. The crude product was subjected to silica gel column chromatography (acetone/benzene, 20%) to give attenol A (**1**; 100 mg, 52%) and B (**2**; 23 mg, 12%) as colorless oils.

Attenol A (1): $[\alpha]_D^{20}$ = –5.2 (*c* = 0.22, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3460, 2954, 2894, 2853, 1458, 1363, 1252, 1228, 1097, 854, 768 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.90–5.72 (m, 1 H), 5.72–5.60 (m, 1 H), 5.60–5.45 (m, 1 H), 5.08–4.91 (m, 2 H), 4.38–4.22 (m, 1 H), 3.89–3.75 (m, 1 H), 3.75–3.54 (m, 4 H), 3.30 (d, *J* = 10.5 Hz, 1 H), 2.58–2.34 (m, 2 H), 2.33–2.20 (m, 1 H), 2.20–1.92 (m, 6 H), 1.88–1.36 (m, 14 H), 0.87 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.6, 129.4, 127.9, 114.5, 106.2, 77.9, 70.0, 69.4, 61.8, 43.7, 38.4, 36.5, 33.8, 33.6, 32.8, 30.8, 30.3, 28.9, 24.9, 17.2 ppm. HRMS (ESI): calcd. for $C_{22}H_{38}O_5Na$ [M + Na^+] 405.2617; found 405.2628.

Attenol B (2): $[\alpha]_D^{20}$ = +25.9 (*c* = 0.09, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3460, 2954, 2894, 2853, 1458, 1363, 1252, 1228, 1097, 854, 768 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.86–5.75 (m, 1 H), 5.57–5.48 (m, 2 H), 5.03–4.97 (dd, *J* = 1.5, 17.0 Hz, 1 H), 4.94 (d, *J* = 10.1 Hz, 1 H), 4.08 (t, *J* = 6.2 Hz, 1 H), 3.98–3.90 (m, 4 H), 3.72 (s, 1 H), 3.69–3.57 (m, 2 H), 2.63 (m, 1 H), 2.42–2.34 (m, 2 H), 2.33–2.25 (m, 2 H), 2.11–1.98 (m, 3 H), 1.91–1.71 (m, 3 H), 1.70–1.48 (m, 8 H), 1.48–1.38 (m, 2 H), 1.36–1.30 (dd, *J* = 5.4, 13.2 Hz, 1 H), 1.11 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.8, 128.5, 127.7, 114.5, 109.6, 83.0, 80.0, 69.9, 69.0, 61.8, 42.5, 36.8, 34.3, 33.74, 33.7, 31.2, 31.1, 30.38, 30.3, 25.0, 23.0, 16.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{38}O_5Na$ [M + Na^+] 405.2617; found 405.2624.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data and ^1H and ^{13}C NMR spectroscopic data of all compounds.

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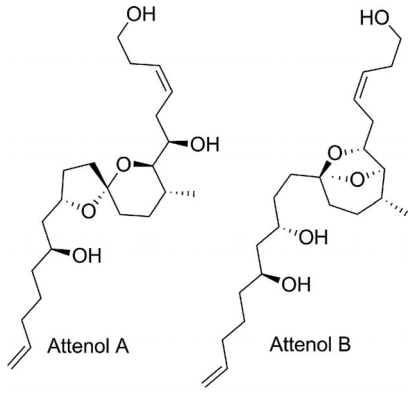
Total Synthesis

The convergent total synthesis of two novel ethereal compounds, attenols A and B is achieved with excellent stereocontrol. The synthetic route comprises Sharpless asymmetric dihydroxylation, palladium(0)-catalyzed asymmetric reduction, stereoselective *m*CPBA-mediated epoxidation and Julia–Kocienski olefination.



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