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Stereoselective Total Synthesis of Attenols A and B

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A highly stereoselective total synthesis of attenols A and B is described. The salient features of this synthesis are the utilization of a reductive radical cyclization strategy for methyl center creation, a Prins cyclization/reductive opening cascade for *anti*-1,3-diol motif generation, and a double alkylation tosylmethyl isocyanide (TosMIC) strategy to construct the spiro acetal segment.

Introduction

Attenols A and B figure among a novel class of spiroacetal[1] ether compounds isolated from the Chinese bivalve *Pinna attenuata* (Figure 1).[2] These natural products have attracted the attention of several synthetic organic chemists, not only for their structural complexity but also because of their biological significance.[3] Attenols A and B exhibit cytotoxicity against P388 cells, with IC_{50} values of 24 and 12 μg/mL, respectively. The availability of these compounds is scarce from natural sources, which limits their use for further biological screening. Attenols A and B contain a spiroacetal moiety with contiguous stereocenters, together with a *cis* double bond and a terminal olefin. In particular, the construction of the [5,4]- or [3,2,1]-spiroacetal core is a challenging task for synthetic chemists.[1]

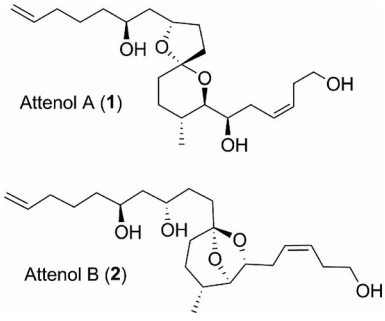

Figure 1. Structures of attenol A (**1**) and B (**2**).

As a part of our ongoing research program aimed at the total synthesis of naturally occurring polyketides,[4b,4c] we herein report a stereoselective approach to the total synthesis of attenols A and B. The strategy in the total synthesis of these compounds involves mainly the construction of the spiroacetal core from tosylmethyl isocyanide (TosMIC).[4] The diastereoselective creation of the methyl center was achieved by reductive cyclization and a consecutive Prins cyclization followed by a reductive opening cascade for *anti*-1,3-diol motifs.[6] The above strategies were thoroughly explored by our group.[4–6]

Results and Discussion

The retrosynthetic analysis of attenols A and B is depicted in Scheme 1. We envisioned that coupling of the "left" fragment **3** and "right" fragment **4** with TosMIC, followed by hydrolysis would deliver the required spiroacetal core. Iodo component **3** could easily be obtained from *anti*-1,3-diol motif **5**, which, in turn, could be prepared from **6**, which can be obtained through a highly stereoselective Prins cyclization between known (*S*)-homoallylic alcohol **7** and aldehyde **8**, followed by a reductive cleavage sequence.[7]

Another iodo component, **4**, was expected to be prepared from compound **9**, which, in turn, could easily be synthesized from epoxide **10** (Scheme 1). Compound **10** could be prepared from **11** through a sequence of reactions as depicted in Scheme 2.[8]

Accordingly, the synthesis of segment **4** of attenols commenced from known allylic alcohol **11** as depicted in Scheme 2. Compound **11** was treated with *N*-bromosuccinimide (NBS) and ethyl vinyl ether in the presence of $NaHCO_3$ to afford bromo acetal derivative **12** in 83% yield. Bromo acetal **12** was reduced by using tri-*n*-butyltin chloride and $NaBH_3CN$ in *tert*-butyl alcohol heated to reflux in the presence of a catalytic amount of azoisobutyronitrile (AIBN) to give monocyclic acetal **13** in 85% yield.[5] In this reductive radical cyclization, the methyl group was formed with *trans* orientation to the allyl group in **12**, due to a chair-like transition state of the radical intermediate formed

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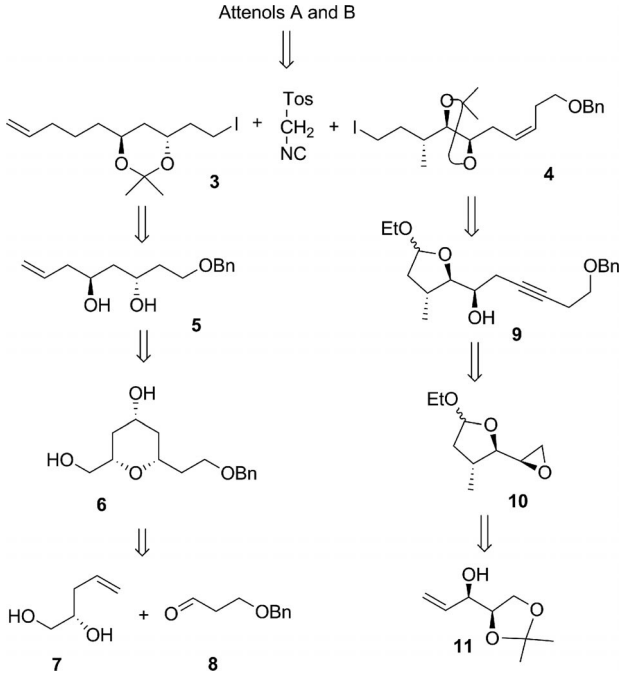
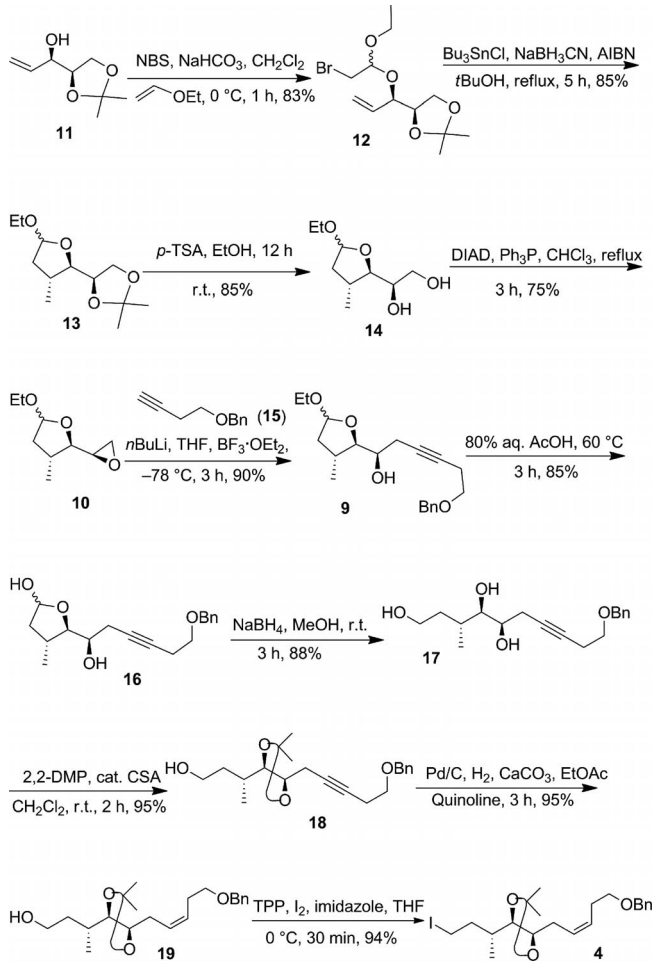


Scheme 1. Retrosythetic analysis of attenols A and B.

during the course of the reaction, which leads to monocyclic acetal **13**, which is explained in detail in our earlier report.[5,4b]

The formation of cyclic compound **13**, with a methyl group, was confirmed by the appearance of a doublet signal at δ = 1.08 ppm with an integral corresponding to three protons. Cyclic acetal **13** was then treated with a catalytic amount of *p*TsOH in ethanol to obtain 1,2-diol **14** in 85% yield.[9] In the next step, 1,2-diol **14** was converted into its corresponding oxirane **10** in 75% yield by using Ph_3P and diisopropyl azodicarboxylate (DIAD) in $CHCl_3$.[10] Regioselective opening of epoxide **10** with [(but-3-ynyloxy)-methyl]benzene (**15**) in the presence of *n*BuLi and $BF_3{\cdot}Et_2O$ in tetrahydrofuran (THF) at –78 °C afforded alkynol **9** in 90% yield.[11] After establishing the structure, compound **9** was treated with 80% aq. AcOH[12] and $NaBH_4$ in methanol sequentially to give triol **17** in 75% yield over two steps, with all the desired stereocenters. Triol compound **17** was protected as its acetonide by using 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of 10-camphorsulfonic acid (CSA) to obtain primary alcohol **18** in 95% yield.[13] Partial reduction of the alkyne functionality of **18** was performed by using Lindlar's catalyst in the presence of quinoline under hydrogen to afford (*Z*)-alkene **19** in 95% yield. This (*Z*)-alkene **19** was treated with I_2 in the presence of imidazole and Ph_3P to furnish fragment **4** in 94% yield, which was used immediately for the next reaction.

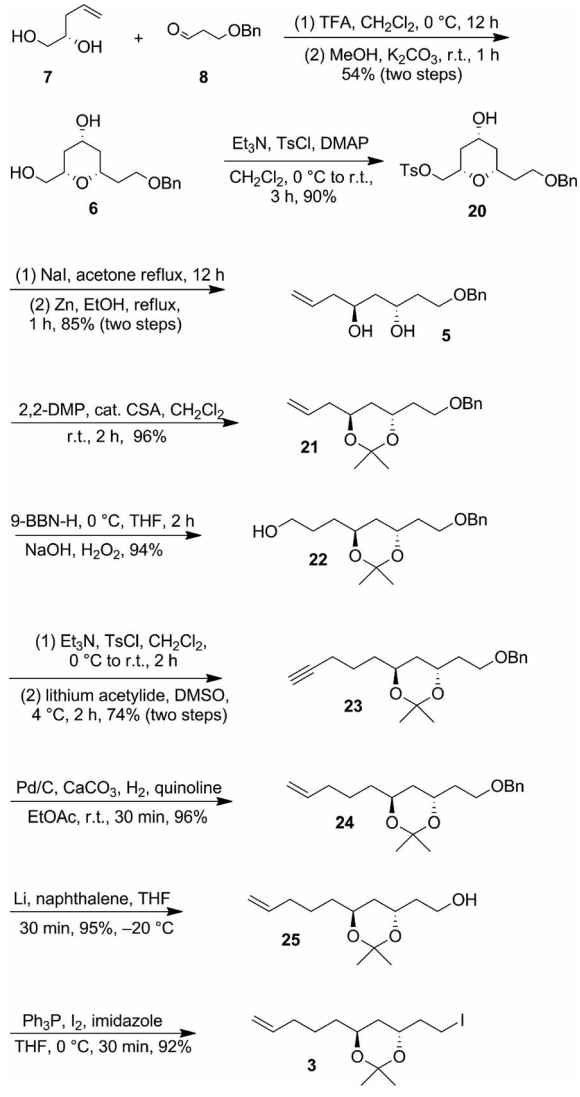
With fragment **4** in hand, we turned our attention towards the synthesis of segment **3** (Scheme 3). Accordingly, the synthesis of **3** began from known (*S*)-homoallylic alcohol **7**,[8] which was subjected to Prins cyclization with 3-(benzyloxy)propanal (**8**) in the presence of trifluoroacetic



Scheme 2. Synthesis of fragment **4**.

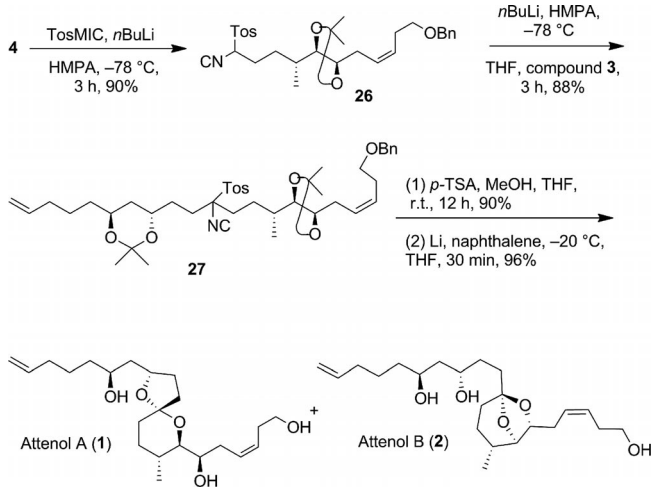
acid (TFA) in CH_2Cl_2 followed by hydrolysis of the resulting acetate with K_2CO_3 in methanol to afford trisubstituted tetrahydropyrandiol **6** in 53% yield over two steps. Diastereoselective formation of trisubstituted tetrahydropyran **6** was consistent with an earlier report.[6] Compound **6** was then subjected to chemoselective tosylation by using *p*-toluenesulfonyl chloride to obtain the corresponding tosylate **20**. Monotosylate **20** was converted into the corresponding iodo derivative by using NaI in acetone heated to reflux, which was immediately treated with zinc in ethanol at reflux to furnish *anti*-1,3-diol **5** in 76% yield over three steps.[14] The *anti*-1,3-diol **5** was protected as its acetonide **21** by using 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of CSA (96%). The appearance of a peak at δ = 100.2 ppm in the ^{13}C NMR spectrum of **21** confirmed both the acetonide protection and the *anti* configuration of the two hydroxy groups in **5**. To obtain the appropriate side chain for fragment **3**, a two-carbon homologation was performed on **21**. Accordingly, acetonide **21** was exposed to 9-borabicyclo[3.3.1]nonane (9-BBN-H) followed by oxidation of the intermediate organoborane to give the corresponding alcohol **22** as a single regioisomer in 94% yield. The latter primary alcohol **22** was converted into its tosyl derivative followed by treatment with lithium

acetylide to furnish the corresponding alkyne **23** (74% over two steps).[15] Formed alkyne **23** was converted into the corresponding alkene **24** by partial hydrogenation with Lindlar's catalyst under hydrogen in the presence of quinoline (95%). The olefinic compound **24** was then treated with Li/naphthalene[16] to induce debenzylation to obtain primary alcohol **25**, which was further treated with I_2 in the presence of imidazole and Ph_3P to furnish the left-hand fragment **3** of attenols (90% over two steps), which was immediately used for the next step.



Scheme 3. Synthesis of fragment **3**.

With the two terminal halogenated stereo intermediates **3** and **4** in hand, the spiroacetalization towards attenols A and B was achieved by the application of TosMIC tethering technology, which is a key step developed in our group for spiroacetalizations (Scheme 4). Initially, iodo fragment **4** was coupled with TosMIC in the presence of *n*BuLi to obtain the monoalkylated tosylmethyl isocyanide (TosMIC) **26** (90%). By iterating the same reaction conditions on monoalkylated TosMIC **26** with the other iodo fragment **3**, the advanced dialkylated TosMIC intermediate **27** was afforded in 88% yield.[4b] After establishing the structure of the dialkylated TosMIC compound **27**, treatment of the latter with *p*TsOH in MeOH/THF afforded attenols A and B as their benzyl ether derivatives (90%) as an inseparable mixture. In the TosMIC spiroacetalization approach, the tosyl and isocyanide functionalities in compound **27** were removed to furnish an oxo group, which, in turn, participates in a spiroacetalization step with the hydroxy groups formed by deprotection of the acetonides in a one-pot operation.



Scheme 4. Completion of the synthesis of attenols A (**1**) and B (**2**).

In contrast to dithiane-mediated spiroacetalization, TosMIC-derived spiroacetalization is a very simple and effective approach because of its easy removal followed by spiroacetalization in a single-step operation. Finally, the obtained benzyl ether derivatives were treated with Li/naphthalene to furnish the target molecules attenol A (70%) and B (15%), as a separable mixture, over two steps; the spectroscopic data of the synthesized attenols A (**1**) and B (**2**) were in good agreement with the data reported in the literature.[3]

Conclusions

We have developed a highly convergent route to synthesize attenols A and B in a highly stereoselective manner, involving the methodologies developed in our group, such as spiroacetal formation from tosylmethyl isocyanide, *anti*-1,3-diols from the Prins cyclization, and installation of the methyl center through radical cyclization. The total synthesis proceeded in 15 steps with 15.4% overall yield.

Experimental Section

General: All reactions were carried out in flame-dried glass apparatus under nitrogen. THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. DMF was distilled from CaH_2 at 15 Torr. CH_2Cl_2 was freshly distilled from CaH_2, and toluene and benzene were distilled from molten sodium metal. Anhydrous methanol was obtained by distillation from magnesium alkoxide and stored under nitrogen over activated 4 Å molecular

sieves. All the reactions were monitored by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized by using a UV lamp, phosphomolybdic acid, anisaldehyde, or β-naphthol solution or alkaline $KMnO_4$ solution. All commercially available reagents were typically used as supplied. Optical rotations were measured at ambient temperature (25 °C) on $CHCl_3$ solutions with a polarimeter by using 1 mL capacity cells with 100 mm path length. IR spectra were recorded by using a thin film supported by NaCl plates or as a solid embedded in a KBr disc. ^1H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified with a 300, 400 or 500 MHz spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes. Chemical shifts are quoted in ppm relative to the residual signals of chloroform (^1H: δ = 7.25 ppm; ^{13}C: δ = 77.0 ppm). Multiplicities in the ^1H NMR spectra are described as: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br.), quintet (quint); coupling constants are reported in Hz. Mass spectrometric data were obtained with MS (EI) ESI, HRMS mass spectrometers. High-resolution mass spectra (HRMS) (ESI+) were obtained with either a TOF or a double-focusing spectrometer.

(*R*)-4-[(*R*)-1-(2-Bromo-1-ethoxyethoxy)allyl]-2,2-dimethyl-1,3-dioxolane (12): Freshly recrystalized NBS (1.150 g, 6.46 mmol) was added to a stirred solution of allylic alcohol **11** (0.851 g, 5.38 mmol) and $NaHCO_3$ (500 mg, 2.69 mmol) at 0 °C in anhydrous CH_2Cl_2 (20 mL), followed by dropwise addition of ethyl vinyl ether (1.55 mL, 16.14 mmol) at 0 °C over a period of 10 min. The reaction mixture was stirred at the same temperature for an additional 1 h. After completion of the reaction (confirmed by TLC analysis), water (10 mL) was added at 0 °C, and the reaction mixture was extracted with CH_2Cl_2 (2× 15 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by neutral alumina flash column chromatography (ethyl acetate/hexane, 1:9) to afford bromo acetal **12** (1.37 g, 83%) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 2981, 2933, 1379, 1371, 1258, 1211, 1126, 1044, 938 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.62 (m, 1 H), 5.43–5.22 (m, 1 H),5.27 (d, J = 9.8 Hz, 1 H), 4.82–4.75 (m, 1 H), 4.71 (t, J = 5.5 Hz, 1 H), 4.16–4.02 (m, 2 H), 3.83–3.56 (m, 3 H), 3.41–3.27 (m, 2 H), 1.39 (t, J = 3.2 Hz, 3 H), 1.33 (t, J = 3.7 Hz, 3 H), 1.26–1.15 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.3, 133.5, 120.7, 119.2, 109.8, 109.7, 101.5, 98.8, 79.8, 79.0, 77.4, 65.63, 65.6, 62.6, 60.7, 32.3, 31.7, 26.5, 26.4, 25.2, 15.1, 14.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{21}BrO_4Na$ $[M + Na]^+$ 331.0515; found 331.0518.

(*R*)-4-[(2*R*,3*R*)-5-Ethoxy-tetrahydro-3-methylfuran-2-yl]-2,2-dimethyl-1,3-dioxolane (13): To a stirred solution of bromo acetal **12** (1.33 g, 4.32 mmol) in *tert*-butyl alcohol (25 mL) were added tri-*n*-butyltin chloride (0.24 mL, 0.86 mmol), a catalytic amount of AIBN, and $NaBH_3CN$ (535 mg, 8.63 mmol) slowly at room temperature. The reaction mixture was heated to reflux for 5 h and, when completion of the reaction was confirmed by TLC analysis, the reaction mixture was cooled to 0 °C and quenched by the addition of water (15 mL) followed by extraction with ethyl acetate (2× 15 mL). The combined organic layers were washed with water, brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9) to afford pure lactol ether **13** (844 mg, 85%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 2932, 1454, 1347, 1213, 1157 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.17–5.02 (m, 1 H), 4.20–4.07 (m, 1 H), 4.06–3.96 (m, 1 H), 3.83–3.71 (m, 2 H), 3.69–3.60 (m, 1 H), 3.48–3.37 (m, 1 H), 2.32–2.21 (m, 1 H), 2.14–2.00 (m, 1 H), 1.67–1.58 (m, 1 H), 1.54 (s, 3 H), 1.37 (s, 3 H), 1.18 (t, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 1 H), 1.08 (d, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.3, 109.2, 104.0, 103.4, 86.5, 84.4, 78.6, 65.8, 65.5, 62.9, 62.3, 42.0, 40.9, 34.0, 33.1, 26.4, 26.3, 25.4, 25.3, 18.9, 17.9, 15.2, 15.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{22}O_4Na$ $[M + Na]^+$ 253.1410; found 253.1404.

(*R*)-1-[(2*R*,3*R*)-5-Ethoxy-tetrahydro-3-methylfuran-2-yl]ethane-1,2-diol (14): A catalytic amount of *p*-TsOH was added to a stirred solution of **13** (800 mg, 3.48) in ethanol (15 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h until completion of the reaction was confirmed by TLC analysis. The reaction was quenched by addition of solid $NaHCO_3$ (500 mg), then the solvent was removed under reduced pressure and the crude product was diluted with water and extracted with ethyl acetate (3× 15 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, then the solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 4:6) to afford diol **14** (562 mg, 85%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 3394, 2971, 2958, 1374, 1114, 1060 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.18–5.11 (m, 1 H), 4.92 (d, J = 3.2 Hz, OH), 3.96–3.78 (m, 2 H), 3.78–3.59 (m, 3 H), 3.52–3.39 (m, 1 H), 2.53–2.37 (m, 1 H), 2.36–2.20 (m, 1 H), 1.58–1.46 (m, 1 H), 1.28–1.16 (m, 3 H), 1.12–0.95 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.1, 104.0, 87.3, 84.9, 70.5, 70.1, 65.3, 65.1, 63.9, 62.5, 41.2, 40.7, 31.6, 29.2, 17.3, 17.2, 15.2, 15.0 ppm. HRMS (ESI): calcd. for $C_9H_{18}O_4Na$ $[M + Na]^+$ 213.1102; found 213.1090.

(2*R*,3*R*)-5-Ethoxy-tetrahydro-3-methyl-2-[(*R*)-oxiran-2-yl]furan (10): To a stirred solution of diol **14** (510 mg, 2.68 mmol) in $CHCl_3$ (20 mL) were added triphenylphosphane (1.05 g, 4.03 mmol) and diisopropyl azodicarboxylate (0.81 mL, 4.12 mmol) sequentially at room temperature. The reaction mixture was heated to reflux overnight. Upon completion of the reaction (determined by TLC analysis), the mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9) to furnish epoxide **10** (346 mg, 75%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 2974, 2932, 1444, 1372, 1248, 1258, 1108, 1081 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.57–5.11 (m, 1 H), 3.84–3.72 (m, 1 H), 3.50–3.40 (m, 2 H), 3.04–2.97 (m, 1 H), 2.84–2.78 (m, 1 H), 2.77–2.72 (m, 1 H), 2.44–2.32 (m, 1 H), 2.20–2.06 (m, 1 H), 1.56–1.48 (m, 1 H), 1.22–1.15 (m, 3 H), 1.13 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 103.9, 103.5, 87.7, 83.8, 63.2, 62.3, 54.1, 52.5, 43.8, 43.7, 41.5, 40.9, 35.5, 34.0, 17.3, 15.2, 15.1 ppm. HRMS (ESI): calcd. for $C_9H_{16}O_3Na$ $[M + Na]^+$ 195.0997; found 195.0997.

(*R*)-6-(Benzyloxy)-1-[(2*R*,3*R*)-5-ethoxy-tetrahydro-3-methylfuran-2-yl]hex-3-yn-1-ol (9): To a stirred solution of alkyne **15** (558 mg, 3.49 mmol) in anhydrous THF (8 mL) at –78 °C was added *n*-butyllithium (1.6 M in hexane, 2.18 mL, 3.49 mmol) under nitrogen. The reaction mixture was stirred for 15 min, then $BF_3{\cdot}OEt_2$ (0.22 mL, 1.74 mmol) was added, and stirring was continued at the same temperature for an additional 15 min. A solution of epoxide **10** (300 mg, 1.74 mmol) in anhydrous THF (2 mL) was added to the reaction mixture dropwise, and stirring was continued at the same temperature for 3 h. When the reaction was complete (determined by TLC analysis), the reaction was quenched by the addition of saturated NH_4Cl (5 mL), the crude product was extracted with ethyl acetate (3× 15 mL) and dried with anhydrous Na_2SO_4. Solvent was removed under reduced pressure to the afford the crude alcohol, which was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to afford alkyne **9** (520 mg, 90%) as a colorless viscous liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 3980, 2910, 1410, 1220,

1050 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 5.15–5.11 (m, 1 H), 4.55 (s, 2 H), 3.88–3.62 (m, 3 H), 3.56 (t, J = 6.6 Hz, 2 H), 3.51–3.41 (m, 1 H), 2.53–2.38 (m, 4 H), 2.35–2.27 (m, 1 H), 2.20–2.07 (m, 1 H), 1.67–1.59 (m, 1 H), 1.20 (t, J = 6.6 Hz, 3 H), 1.09 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.1, 138.07, 128.3, 127.6, 126.9, 103.88, 103.86, 87.9, 85.0, 78.9, 78.5, 77.7, 77.5, 72.9, 72.8, 70.2, 70.0, 68.7, 68.67, 63.4, 63.1, 41.6, 41.1, 33.6, 32.2, 25.2, 20.1, 18.0, 17.5, 15.3, 15.1 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}O_4Na$ $[M + Na]^+$ 355.1885; found 355.1870.

(4*R*,5*R*)-5-[(*R*)-6-(Benzyloxy)-1-hydroxyhex-3-ynyl]-tetrahydro-4-methylfuran-2-ol (16): The ethyl acetal containing alkyne **9** (420 mg, 1.27 mmol) was taken up in 80% aq. AcOH (12 mL) solution, and the reaction mixture was heated to reflux for 4 h. The mixture was cooled to 0 °C, neutralized with saturated $NaHCO_3$, and extracted with ethyl acetate (2× 15 mL). The combined organic extracts were washed with water (2× 15 mL) followed by brine and dried with anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 3:7) to afford lactol **16** (327 mg, 85%) as a colorless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3421, 2921, 1370, 1353, 1198, 732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 5.48–5.42 (m, 1 H), 4.55 (s, 2 H), 3.80–3.74 (m, 1 H), 3.68–3.61 (m, 1 H), 3.57 (t, J = 6.6 Hz, 2 H), 2.59–2.33 (m, 5 H), 2.12–2.05 (m, 1 H), 1.70–1.50 (m, 1 H), 1.08 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.4, 127.7, 98.0, 96.1, 87.8, 85.6, 79.0, 77.6, 72.9, 70.1, 69.6, 69.1, 68.6, 68.0, 42.7, 42.1, 31.9, 31.5, 25.3, 25.2, 20.1, 17.8, 17.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}O_4Na$ $[M + Na]^+$ 327.1566; found 327.1575.

(3*R*,4*R*,5*R*)-10-(Benzyloxy)-3-methyldec-7-yne-1,4,5-triol (17): To a stirred solution of lactol **16** (310 mg, 1.02 mmol) in MeOH (10 mL) was added $NaBH_4$ (309 mg, 8.15 mmol) over a period of 10 min. After the addition, stirring was continued at room temperature for 1.5 h, then the reaction was quenched by addition of water (0.2 mL) at 0 °C. The reaction mixture was separated from its undissolved solids by filtration through a plug of Na_2SO_4, and the solvent was removed from the crude product under reduced pressure followed by purification by flash column chromatography (ethyl acetate/hexane, 7:3) to afford triol **17** (252 mg, 88%) as a colorless liquid. $[\alpha]_D^{25}$ = +4.2 (c = 0.31, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3402, 2923, 2869, 1453, 1093, 739, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H), 4.55 (s, 2 H), 3.84–3.72 (m, 2 H), 3.70–3.62 (m, 1 H), 3.57 (t, J = 6.6 Hz, 2 H), 3.36 (dt, J = 2.6, 7.0 Hz,1 H), 2.55–2.38 (m, 4 H), 1.96–1.83 (m, 1 H), 1.79–1.69 (m, 1 H), 1.68–1.59 (m, 1 H), 0.99 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 128.4, 127.7, 79.5, 77.7, 76.7, 72.9, 70.0, 68.6, 60.3, 35.5, 33.5, 24.9, 20.1, 17.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}O_4Na$ $[M + Na]^+$ 329.1728; found 329.1718.

(*R*)-3-{(4*R*,5*R*)-5-[5-(Benzyloxy)pent-2-ynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}butan-1-ol (18): To an ice-cooled, stirred solution of 1,4,5-triol **17** (235 mg, 0.77 mmol) in anhydrous CH_2Cl_2 (5 mL) were added a catalytic amount of CSA followed by dropwise addition of 2,2-dimethoxypropane (0.28 mL, 2.30 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 1 h. Upon complete consumption of the starting material (TLC analysis), the reaction was quenched by addition of solid $NaHCO_3$ (300 mg) at the same temperature and stirred for 30 min. The reaction mixture was poured into water (10 mL), extracted with CH_2Cl_2 (3× 10 mL), and the combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to furnish the crude product, which was purified by column chromatography (EtOAc/hexanes, 3:7) to give acetonide **18** (0.252 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +12.1 (c = 0.45, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3390, 2920, 2360, 1385, 1097, 741, 598 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 4.54 (s, 2 H), 3.95–3.86 (m, 1 H), 3.78–3.70 (m, 1 H), 3.57 (t, J = 7.0 Hz, 2 H), 3.49 (dt, J = 2.6, 7.9 Hz, 1 H), 3.40 (dd, J = 7.4, 9.3 Hz, 1 H), 2.55–2.44 (m, 4 H), 1.93–1.78 (m, 2 H), 1.67–1.57 (m, 1 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 0.98 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0, 128.3, 127.7, 127.6, 108.5, 84.4, 79.2, 77.3, 72.9, 68.6, 60.8, 36.3, 33.4, 27.3, 27.2, 24.2, 20.1, 16.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{30}O_4Na$ $[M + Na]^+$ 369.2036; found 369.2035.

(*R*)-3-{(4*R*,5*R*)-5-[(*Z*)-5-(Benzyloxy)pent-2-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}butan-1-ol (19): Lindlar's catalyst (Pd/$CaCO_3$, catalytic amount) was added to a stirred solution of alkyne **18** (0.211 g, 0.61 mmol) and quinoline (diluted in EtOAc, 0.1 mL) in EtOAc (10 mL) at room temperature. The mixture was stirred vigorously under hydrogen for 3 h. Upon completion of the reaction (TLC analysis), the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane, 3:7) to give *cis*-alkene **19** (199 mg, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +14.6 (c = 0.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3426, 3019, 2989, 1381, 1215, 1058, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 ppm, –7.27 (m, 5 H), 5.65–5.50 (m, 2 H), 4.51 (s, 2 H), 3.85 (dt, J = 4.1, 7.3 Hz, 1 H), 3.77–3.67 (m, 1 H), 3.66–3.57 (m, 1 H), 3.55–3.43 (m, 3 H), 2.52 (br. s, 1 H), 2.46–2.27 (m, 4 H), 1.84–1.65 (m, 2 H), 1.61–1.45 (m, 1 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 0.94 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 128.3, 128.1, 127.6, 127.5, 126.7, 108.1, 84.7, 79.2, 72.9, 69.7, 60.1, 36.9, 34.1, 32.0, 28.2, 27.3, 27.1, 16.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_4Na$ $[M + Na]^+$ 371.2198; found 371.2215.

(2*S*,4*R*,6*S*)-2-[2-(Benzyloxy)ethyl]tetrahydro-6-(hydroxymethyl)-2*H*-pyran-4-ol (6): Trifluoroacetic acid (10 mL) was added slowly to a stirred solution of homoallylic alcohol **7** (450 mg, 4.41 mmol) and 3-(benzyloxy)propanal **8** (1.085 g, 6.62 mmol) in CH_2Cl_2 (20 mL) at room temperature under nitrogen. The reaction mixture was stirred for 3 h, then saturated aq. $NaHCO_3$ (30 mL) was added after complete consumption of starting materials (TLC analysis), and the pH was adjusted to pH > 7 by addition of triethylamine. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL), the organic layers were combined, and the solvent was removed under reduced pressure. The crude residue was dissolved in ethanol (20 mL) and stirred with potassium carbonate (1.826 g, 13.23 mmol) for 1 h. Upon completion of the reaction (TLC), ethanol was removed under reduced pressure, and the mixture was washed with water and extracted with CH_2Cl_2 (3× 15 mL). The combined organic layers were washed with brine (15 mL) and dried with anhydrous Na_2SO_4, then the solvent was removed under reduced pressure. Purification by silica gel column chromatography (ethyl acetate/hexane, 6:4) gave tetrahydropyrandiol **6** (622 mg, 53%) as a colorless oil. $[\alpha]_D^{25}$ = –23.5 (c = 0.31, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 3019, 2953, 1413, 1215, 1084, 758, 700, 669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 4.50 (dd, J = 11.9, 18.9 Hz, 2 H), 3.87–3.81 (m, 1 H), 3.64–3.58 (m, 2 H), 3.58–3.51 (m, 3 H), 3.49–3.43 (m, 1 H), 1.99–1.94 (m, 1 H), 1.89–1.82 (m, 2 H), 1.81–1.75 (m, 1 H), 1.27–1.15 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.3, 127.6, 75.9, 72.9, 72.6, 67.6, 66.4, 65.7, 41.0, 36.63, 35.96 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}O_4Na$ $[M + Na]^+$ 289.1415; found 289.1427.

{(2*S*,4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-tetrahydro-4-hydroxy-2*H*-pyran-2-yl}methyl 4-Methylbenzenesulfonate (20): To a stirred solution of tetrahydropyrandiol **6** (595 mg, 2.24 mmol) in anhydrous CH_2Cl_2 (15 mL) were added Et_3N (0.47 mL, 3.35 mmol) and TsCl (514 mg,

2.68 mmol) at 0 °C. The reaction mixture was warmed to room temperature gradually and stirred for 3 h. The reaction mixture was then treated with aq. 1 M HCl (5 mL) and extracted with CH_2Cl_2 (3× 10 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (10 mL) followed by brine (10 mL) and dried with anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane, 4:6) to afford monotosylated compound **20** (845 mg, 90%) as a colorless liquid. $[\alpha]_D^{25} = -13.1$ (c = 0.71, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3452, 2921, 1630, 1357, 989, 661 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.0 Hz, 2 H), 7.36–7.28 (m, 7 H), 4.48 (dd, J = 10.9, 13.9 Hz, 2 H), 4.02 (dd, J = 6.0, 10.0 Hz, 1 H), 3.96 (dd, J = 4.0, 10.0 Hz, 1 H), 3.82–3.75 (m, 1 H), 3.58–3.44 (m, 4 H), 2.43 (s, 3 H), 1.95–1.87 (m, 2 H), 1.77–1.70 (m, 2 H), 1.17–1.09 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 138.4, 132.9, 129.7, 128.3, 127.9, 127.6, 127.5, 72.9, 72.72, 72.66, 71.9, 67.5, 66.3, 40.7, 36.8, 35.9, 21.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{28}O_6SNa$ $[M + Na]^+$ 443.1504; found 443.1504.

(3*S*,5*S*)-1-(Benzyloxy)oct-7-ene-3,5-diol (5): To a solution of compound **20** (816 mg, 1.94 mmol) in acetone (20 mL) was added NaI (2.89 g, 19.4 mmol), and the reaction mixture was heated to reflux for 24 h. After completion of the reaction (TLC analysis), acetone was removed under reduced pressure. The residue was poured into water (10 mL), extracted with CH_2Cl_2 (2× 15 mL), and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane, 1:9) to furnish the corresponding iodo compound (694 mg, 95%) as a colorless liquid, which was immediately used for next reaction. To a solution of the iodide (694 mg, 1.85 mmol) in EtOH (15 mL) was added activated Zn dust (2.47 g, 3.69 mmol), and the resulting mixture was stirred and heated to reflux for 2 h and then cooled to room temperature. The reaction was quenched by addition of solid NH_4Cl and Et_2O (30 mL). The resulting mixture was stirred for 5 min to give a gray suspension, which was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification of the crude product by silica gel flash column chromatography (ethyl acetate/hexane, 1:9) afforded *anti*-1,3-diol **5** (413 mg, 90%) as a colorless liquid. $[\alpha]_D^{25} = +18.4$ (c = 0.66, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3417, 3079, 2919, 1424, 1364, 1089, 1074, 741, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 5.83 (ddt, J = 7.0, 10.0, 17.0 Hz, 1 H), 5.15–5.08 (m, 2 H), 4.53 (s, 2 H), 4.20–4.14 (m, 1 H), 4.03–3.96 (m, 1 H), 3.74 (quint, J = 5.0 Hz, 1 H), 3.68 (dt, J = 4.0, 9.0 Hz, 1 H), 2.27 (t, J = 7.0 Hz, 2 H), 1.95–1.86 (m, 1 H), 1.74–1.67 (m, 1 H), 1.66–1.61 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.7, 134.8, 128.4, 127.7, 127.6, 117.6, 73.3, 69.1, 68.9, 68.0, 42.1, 42.0, 36.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{23}O_3Na$ $[M + H]^+$ 251.1641; found 251.1648.

(4*S*,6*S*)-4-Allyl-6-[2-(benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxane (21): To an ice-cooled solution of *anti*-1,3-diol **5** (388 mg, 1.52 mmol) and a catalytic amount of CSA in anhydrous CH_2Cl_2 (7 mL) was added 2,2-dimethoxypropane (0.28 mL, 2.28 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. After complete consumption of the starting material, solid $NaHCO_3$ (300 mg) was added to quench the reaction, and the mixture was stirred further for a period of 30 min. The reaction mixture was poured into water (10 mL), extracted with CH_2Cl_2 (3× 10 mL), and the combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to furnish the crude product, which was purified by silica gel column chromatography (ethyl acetate/hexane, 1:20) to afford acetonide **21** (423 mg, 96%) as a colorless liquid. $[\alpha]_D^{25} = +14.7$ (c = 0.65, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2990, 2940, 1442, 1379, 1223, 1171, 1118, 1028, 998, 925, 758, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5 H), 5.79 (ddt, J = 7.0, 10.0, 17.0 Hz, 1 H), 5.12–5.02 (m, 2 H), 4.49 (dd, J = 11.9, 13.9 Hz, 2 H), 4.03–3.95 (m, 1 H), 3.90–3.82 (m, 1 H), 3.60–3.50 (m, 2 H), 2.34–2.26 (m, 1 H), 2.23–2.14 (m, 1 H), 1.81–1.73 (m, 2 H), 1.65–1.57 (m, 2 H), 1.33 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 134.4, 128.3, 127.6, 127.5, 116.7, 100.2, 73.1, 66.6, 66.2, 63.7, 40.1, 38.0, 36.0, 24.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 313.1779; found 313.1790.

3-{(4*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}-propan-1-ol (22): To a stirred solution of alkene **21** (400 mg, 1.38 mmol) in THF (15 mL) was added 9-BBN-H (0.5 M in THF, 5.51 mL, 2.76 mmol) at 0 °C under nitrogen, and the reaction mixture was stirred for 2 h. NaOH (1 M, 3.5 mL) followed by H_2O_2 (60% in H_2O, 1.4 mL) were then added to the reaction mixture, and stirring was continued for 1 h. The reaction mixture was diluted with Et_2O (50 mL) and quenched with saturated aq. $NaHCO_3$ (20 mL). The layers were separated, and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo to give the crude product, which was purified by silica gel flash column chromatography (ethyl acetate/hexane, 3:7) to afford alcohol **22** (399 mg, 94%) as a colorless liquid. $[\alpha]_D^{25} = +3.5$ (c = 0.58, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3425, 3032, 2940, 2984, 2862, 1493, 1379, 1274, 1223, 1173, 1103, 1072, 1057, 1028, 903, 737, 714, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 5 H), 4.46 (s, 2 H), 4.02–3.90 (m, 1 H), 3.84–3.70 (m, 1 H), 3.65–3.55 (m, 2 H), 3.54–3.44 (m, 2 H), 1.77–1.67 (m, 2 H), 1.66–1.46 (m, 6 H), 1.32 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 128.3, 127.6, 127.5, 100.4, 73.0, 66.8, 66.5, 63.7, 62.6, 38.5, 35.9, 32.5, 29.1, 24.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{28}O_4Na$ $[M + Na]^+$ 331.1879; found 331.1874.

(4*S*,6*S*)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-6-(pent-4-ynyl)-1,3-dioxane (23): To a stirred solution of alcohol **22** (325 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.22 mL, 1.58 mmol) followed by TsCl (242 mg, 1.27 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 15 min, and then DMAP (330 mg, 2.77 mmol) was added. The reaction mixture was warmed to room temperature and then stirred for 3 h. Upon completion of the reaction (TLC analysis), saturated aq. NH_4Cl was added, and the mixture was extracted with EtOAc (2× 10 mL). The combined organic layers were washed with water and brine and dried with anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the residue was purified by silica gel flash column chromatography (ethyl acetate/hexane, 1:9) to give the tosylated compound, which was immediately used for the next reaction. To the solution of the above tosylate in anhydrous DMSO (5 mL) was added lithium acetylide–ethylenediamine complex (485 mg, 5.27 mmol) slowly at room temperature, and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) and then extracted with diethyl ether (3× 15 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9) to afford alkyne **23** (246 mg, 74% over two steps) as a colorless oil. $[\alpha]_D^{25} = +9.3$ (c = 0.56, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3030, 2986, 2940, 2866, 2116, 1495, 1453, 1379, 1224, 1172, 1126, 1101, 1027, 738, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.49 (s, 2 H), 4.03–3.95 (m, 1 H), 3.82–3.75 (m, 1 H), 3.59–3.50 (m, 2 H), 2.23–2.16 (m, 2 H), 1.94 (t, J = 2.0 Hz, 1 H), 1.80–1.74 (m, 2 H), 1.70–1.63 (m, 1 H), 1.62–1.51 (m, 5 H), 1.32 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =

138.4, 128.3, 127.6, 127.5, 100.2, 84.3, 73.0, 68.4, 66.6, 66.2, 63.7, 38.6, 36.0, 34.8, 24.7, 24.68, 24.5, 18.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}O_3Na$ [M + Na]$^+$ 339.1936; found 339.1922.

(4*S*,6*S*)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxane (24): Lindlar's catalyst (Pd/$CaCO_3$, catalytic amount) was added to a solution of alkyne **23** (0.220 g, 0.70 mmol) and quinoline (diluted in EtOAc, 0.1 mL) in EtOAc (10 mL) at room temperature under hydrogen; then the reaction mixture was vigorously stirred at room temperature for 0.5 h. Upon complete consumption of the starting material, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9) to give alkene **24** (212 mg, 92%) as a colorless liquid. $[\alpha]_D^{25}$ = +4.5 (*c* = 0.52, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2976, 2940, 2866, 1485, 1465, 1380, 1255, 1136, 1121, 1017, 734, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 5.80 (ddt, *J* = 6.2, 9.9, 17.7 Hz, 1 H), 5.00 (d, *J* = 15.5 Hz, 1 H), 4.94 (d, *J* = 9.9 Hz, 1 H), 4.49 (s, 2 H), 4.02–3.95 (m, 1 H), 3.81–3.72 (m, 1 H), 3.59–3.51 (m, 2 H), 2.06 (q, *J* = 6.6 Hz, 2 H), 1.81–1.73 (m, 2 H), 1.62–1.56 (m, 2 H), 1.54–1.47 (m, 2 H), 1.46–1.36 (m, 2 H), 1.33 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 138.4, 128.3, 127.6, 127.5, 114.5, 100.2, 73.1, 66.6, 66.5, 63.7, 38.7, 36.0, 35.3, 33.6, 24.7, 24.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{30}O_3Na$ [M + Na]$^+$ 341.2087; found 341.2098.

2-[(4*S*,6*S*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl]ethanol (25): To a stirred solution of naphthalene (283 mg, 2.21 mmol) in THF (3 mL) was added lithium (11.6 mg, 1.66 mmol) in small pieces. The reaction mixture was stirred at room temperature under argon until the lithium had completely dissolved (2 h). The resulting dark-green solution of lithium naphthalenide was cooled to –20 °C, and a solution of alkene **24** (0.176 g, 0.55 mmol) in THF (2 mL) was added dropwise over 2 min. The resulting mixture was stirred at the same temperature for 30 min. Upon completion of the reaction (TLC), NH_4Cl (3 mL) was added, the resulting solution was extracted with diethyl ether (3× 15 mL), and the combined extracts were washed with water and brine, dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford a crude product, which was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to afford alcohol **25** (120 mg, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +29.6 (*c* = 0.6, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3323, 3075, 2987, 2939, 1641, 1436, 1380, 1225, 1167, 1122, 1055, 1018, 909 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80 (ddt, *J* = 6.8, 10.5, 17.3 Hz, 1 H), 5.01 (dd, *J* = 1.5, 17.3 Hz, 1 H), 4.95 (dd, *J* = 2.3, 10.5 Hz, 1 H), 4.11–4.00 (m, 1 H), 3.85–3.71 (m, 3 H), 2.57 (br. s, 1 H), 2.06 (q, *J* = 6.8 Hz, 2 H), 1.79–1.71 (m, 2 H), 1.71–1.61 (m, 2 H), 1.60–1.54 (m, 1 H), 1.53–1.41 (m, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6, 114.5, 100.3, 67.0, 66.5, 61.2, 38.4, 37.6, 35.2, 33.6, 24.8, 24.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{24}O_3Na$ [M + Na]$^+$ 251.1623; found 251.1627.

(4*R*,5*R*)-4-[(*Z*)-5-(Benzyloxy)pent-2-enyl]-5-[(2*R*)-5-isocyano-5-tosylpentan-2-yl]-2,2-dimethyl-1,3-dioxolane (26): To a stirred solution of alcohol **19** (0.170 g, 0.49 mmol) in THF (5 mL) at 0 °C were added triphenylphosphane (0.154 g, 0.59 mmol), imidazole (83 mg, 1.21 mmol), and iodine (0.161 g, 1.32 mmol). The reaction mixture was stirred for 1 h, then diluted with diethyl ether (20 mL), then quenched by the addition of aqueous 10% $Na_2S_2O_3$. The two layers were separated, and the aqueous layer was extracted with EtOAc (2× 5 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification by passage through a short pad of silica gel afforded the iodo compound **4** (210 mg, 94%) as a yellow liquid, which was used for the next step without further purification. To a solution of TosMIC (0.179 g, 0.92 mmol) in THF (5 mL) at –78 °C was added *n*BuLi (1.6 M in hexane, 0.56 mL, 0.88 mmol), and the resulting mixture was stirred for 30 min. To the reaction mixture, HMPA (1 mL) was added, and stirring was continued for an additional 15 min, before a solution of iodo compound **4** (0.210 g, 0.46 mmol) in THF (2 mL) was added by using a cannula. The reaction mixture was warmed to room temperature over 1 h and then quenched by the addition of saturated aq. NH_4Cl (5 mL). Solvent was removed under reduced pressure, and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3× 15 mL), and the combined organic layers were washed with brine and dried with Na_2SO_4, and solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9) to give monoalkylated TosMIC compound **26** (217 mg, 90%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 2945, 1440, 1340, 1230, 1165, 1071, 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.3 Hz, 2 H), 7.43 (d, *J* = 8.3 Hz, 2 H), 7.36–7.27 (m, 5 H), 5.60–5.53 (m, 2 H), 4.51 (s, 2 H), 4.44 (dd, *J* = 3.4, 10.8 Hz, 1 H), 3.86–3.76 (m, 1 H), 3.54–3.41 (m, 3 H), 2.49 (s, 3 H), 2.45–2.29 (m, 4 H), 1.89–1.72 (m, 1 H), 1.52–1.19 (m, 4 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 164.9, 146.4, 146.3, 138.3, 131.1, 130.0, 129.9, 128.2, 128.1, 127.5, 127.4, 126.5, 108.1, 84.3, 84.1, 79.1, 79.0, 73.1,72.8, 69.5, 35.8, 35.7, 32.0 (2 C), 28.7, 28.2, 27.2, 27.1, 26.1, 26.0, 21.6, 16.2, 15.8 ppm. HRMS (ESI): calcd. $C_{30}H_{39}NO_5SNa$ [M + Na]$^+$ 548.2441; found 548.2434.

(4*S*,6*S*)-4-[(6*R*)-6-{(4*R*,5*R*)-5-[(*Z*)-5-(Benzyloxy)pent-2-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-isocyano-3-tosylheptyl]-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxane (27): To a stirred solution of alcohol **25** (0.1 g, 0.44 mmol) in THF (4 mL) cooled to 0 °C were added triphenylphosphane (138 mg, 0.53 mmol), imidazole (0.075 g, 1.10 mmol), and iodine (0.145 g, 0.57 mmol). The reaction mixture was stirred for 1 h and then diluted with diethyl ether (15 mL) followed by the addition of aqueous 10% $Na_2S_2O_3$ solution. The mixture was extracted with ethyl acetate (2× 5 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Solvent was removed in vacuo, and the residue was passed through a short pad of silica gel (ethyl acetate/hexane, 1:9) to afford iodo compound **3** (136 mg, 92%) as a pale-yellow oil, which was used for the next step without further purification. To a stirred solution of monoalkylated TosMIC compound **26** (0.177 g, 0.34 mmol) in THF (5 mL) cooled to –78 °C was added *n*BuLi (1.6 M in hexane, 0.27 mL, 0.44 mmol), and the resulting reaction mixture was stirred for 30 min. HMPA (1 mL) was added to the reaction mixture, and stirring was continued for an additional 15 min before the solution of iodo **3** (0.135 g, 0.40 mmol) in THF (1 mL) was added by using a cannula. The reaction mixture was warmed to room temperature, stirred further for 1 h, and then quenched by the addition of saturated aq. NH_4Cl. Solvent was removed in vacuo, and water (5 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3× 15 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the crude product was purified through a short pad of silica gel (ethyl acetate/hexane, 1:9) to afford the dialkyl-tethered TosMIC compound **27** (218 mg, 88%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 2122, 1453, 1368, 1223, 1151, 1083, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.3 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.36–7.27 (m, 5 H), 5.80 (ddt, *J* = 6.8, 10.6, 17.4 Hz, 1 H), 5.62–5.51 (m, 2 H), 5.00 (dd, *J* = 1.5, 17.4 Hz, 1 H), 4.95 (br. d, *J* = 10.6 Hz, 1 H), 4.52 (s, 2 H), 3.85–3.62 (m, 3 H), 3.53–3.42 (m, 3 H), 2.48 (s, 3 H), 2.44–2.29 (m, 4

H), 2.14–1.92 (m, 4 H), 1.83–1.24 (m, 13 H), 1.36 (s, 3 H), 1.34 (s, 6 H), 1.29 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 146.1, 138.4, 131.0, 130.9, 129.8, 129.5, 128.1, 128.0, 127.4, 127.3, 127.3, 126.4, 114.4, 107.9, 100.0, 84.0, 83.8, 81.4, 79.0, 78.9, 72.6, 69.4, 66.1, 65.8, 38.3, 38.2, 36.1, 36.0, 35.0, 33.4, 31.9, 29.6, 29.5, 29.2, 28.9, 28.0, 27.1, 26.4, 26.3, 24.6, 24.5, 24.4 ppm. HRMS (ESI): calcd. $C_{43}H_{61}NO_7NaS$ $[M + Na]^+$ 758.4061; found 758.4047.

Attenol A (1) and B (2): To a solution of dialkyl-tethered TosMIC compound **27** (0.200 g, 0.27 mmol) in THF and MeOH (1:1, 10 mL) was added *p*TsOH (26 mg, 0.14 mmol). The resulting reaction mixture was stirred at room temperature for 24 h before being quenched by the addition of saturated aq. $NaHCO_3$. The clear layers were separated, and the aqueous layer was extracted with ethyl acetate (2× 10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (ethyl acetate/hexane, 3:7) to afford a mixture of compounds that were used in the next step. To a stirred solution of naphthalene (0.102 g, 0.80 mmol) in THF (2 mL) was added lithium (4.2 mg, 0.6 mmol). The reaction mixture was stirred at room temperature under argon until the lithium was completely dissolved (2 h). The resulting dark-green solution of lithium naphthalenide was cooled to –25 °C, and a solution of the mixture of spiro compounds obtained from compound **27** (0.095 g, 0.20 mmol) in THF (2 mL) was added dropwise over 2 min. The resulting mixture was stirred at the same temperature for 30 min. The reaction was quenched by addition of saturated aq. NH_4Cl (2 mL), and the resulting solution was extracted with diethyl ether (3× 10 mL). The combined extracts were washed with water, brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 7:3) to give attenol A (**1**; 74 mg, 70%) as a colorless liquid and attenol B (**2**; 16 mg, 15%) over two steps as a colorless liquid.

Attenol A (1): $[\alpha]_D^{30}$ = –7.1 (c = 0.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3321, 2930, 1437, 1186, 1043 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81 (ddt, J = 6.7, 10.2, 16.9 Hz, 1 H), 5.72–5.64 (m, 1 H), 5.62–5.50 (m, 1 H), 5.01 (dd, J = 1.8, 17.2 Hz, 1 H), 4.95 (d, J = 10.1 Hz, 1 H), 4.35–4.28 (m, 1 H), 3.87–3.79 (m, 1 H), 3.74–3.58 (m, 3 H), 3.32 (dd, J = 1.4, 10.1 Hz, 1 H), 2.56–2.48 (m, 1 H), 2.47–2.37 (m, 1 H), 2.34–2.23 (m, 1 H), 2.16–2.06 (m, 3 H), 2.05–1.97 (m, 2 H), 1.89–1.79 (m,1 H), 1.79–1.61 (m, 7 H), 1.58–1.40 (m 5 H), 0.88 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 129.4, 128.0, 114.5, 106.3, 77.9, 70.0, 69.5, 61.8, 43.7, 38.5, 36.6, 33.8, 33.6, 32.8, 30.8, 30.3, 29.0, 25.0, 17.2 ppm. HRMS (ESI): calcd. for $C_{22}H_{38}O_5Na$ $[M + Na]^+$ 405.2611; found 405.2601.

Attenol B (2): $[\alpha]_D^{30}$ = +28 (c = 0.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3322, 2931, 1437, 1044 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81 (ddt, J = 7.0, 10.1, 17.1 Hz, 1 H), 5.57–5.49 (m, 2 H), 5.01 (dd, J = 1.6, 17.1 Hz, 1 H), 4.95 (br. d, J = 10.1 Hz, 1 H), 4.08 (t, J = 7.0 Hz, 1 H), 4.00–3.89 (m, 2 H), 3.93 (br. s, OH), 3.73 (br. s, OH), 3.67–3.58 (m, 2 H), 2.63 (br. s, OH), 2.43–2.35 (m, 2 H), 2.34–2.25 (m, 2 H), 2.12–2.04 (m, 2 H), 2.04–1.98 (m, 1 H), 1.92–1.83 (m, 2 H), 1.82–1.74 (m, 1 H), 1.73–1.49 (m, 8 H), 1.48–1.38 (m, 2 H), 1.34 (dd, J = 5.4, 14.0 Hz, 1 H), 1.12 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 128.4, 127.7, 114.5, 109.6, 83.0, 80.0, 69.8, 68.9, 61.8, 42.5, 36.8, 34.2, 33.7, 33.6, 31.2, 31.1, 30.3, 30.2, 25.0, 23.0, 16.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{39}O_5$ $[M + H]^+$ 383.2792; found 383.2794.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all compounds.

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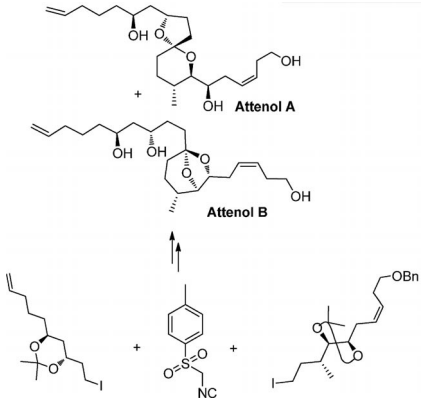
Total Synthesis

A highly convergent total synthesis of attenols A and B is described utilizing a double alkylation tosylmethyl isocyanide (TosMIC) strategy to construct the spiroketal segment.



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

