Asymmetric Synthesis of the (2*S*,4*S*,6*S*)-2,4,6-Trimethylnonyl Subunit of Siphonarienes

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Abstract: The paper describes an asymmetric approach to the synthesis of the (2*S*,4*S*,6*S*)-2,4,6-trimethylnonyl segment of siphonarienes. The key step used is a newly developed methodology to obtain *sec*-dialkyl acetylenes based on the intramolecular hydride transfer from a secondary γ-benzyloxy group with well-defined absolute stereochemistry, ensured by a Sharpless asymmetric epoxidation reaction, to a cation generated by Lewis acid treatment of a tertiary $Co_2(CO)_6$-complexed propargylic alcohol.

1. INTRODUCTION

Polypropionates have been reported from a number of marine pulmonate mollusks belonging to the genera *Siphonaria*,[1] *Tridachia*,[2] and *Onchidium*.[3] The siphonarienes (**1**) are fully reduced polypropionates produced by *Siphonaria* characterized by possessing a (2*S*,4*S*,6*S*)-2,4,6-trimethylnonyl fragment connected through an olefinic linker to a more polar, oxygen-containing group.[4] These animals are air-breathing gastropod mollusks found in the high intertidal region, which may represent an evolutionary link between marine and terrestrial gastropods.[5] The secondary metabolites produced are believed to be employed in chemical defense against predators, and most are active against gram-positive bacteria, yeast, and several human cancer cell lines.[4b,d] Selected examples of these types of metabolites are given in Fig. 1.

In the course of our studies on the synthesis of marine natural products,[6] we addressed our attention to the siphonarienes. Two main approaches have been developed for the construction of such polypropionates; by iterative alkylations of chiral nucleophiles[7] and by deoxygenation of polypropionates obtained by asymmetric aldol condensations.[4c,8]

We speculated that an alternative methodology to gain access to this kind of molecule could make use of an alkyne such as **2** in which the three stereocenters of the alkynyl moiety are defined (Fig. 2).

Recently, we reported on a very efficient protocol to obtain *sec*-dialkyl acetylenes with absolute stereochemical control in which the key step is the intramolecular hydride transfer from a secondary γ-benzyloxy group with defined absolute stereochemistry to a cation generated by Lewis acid treatment of a tertiary $Co_2(CO)_6$-complexed propargylic alcohol (Fig. 3).[9] We report herein on our efforts to achieve the asymmetric total synthesis of **2**, taking advantage of this new stereoselective reduction.

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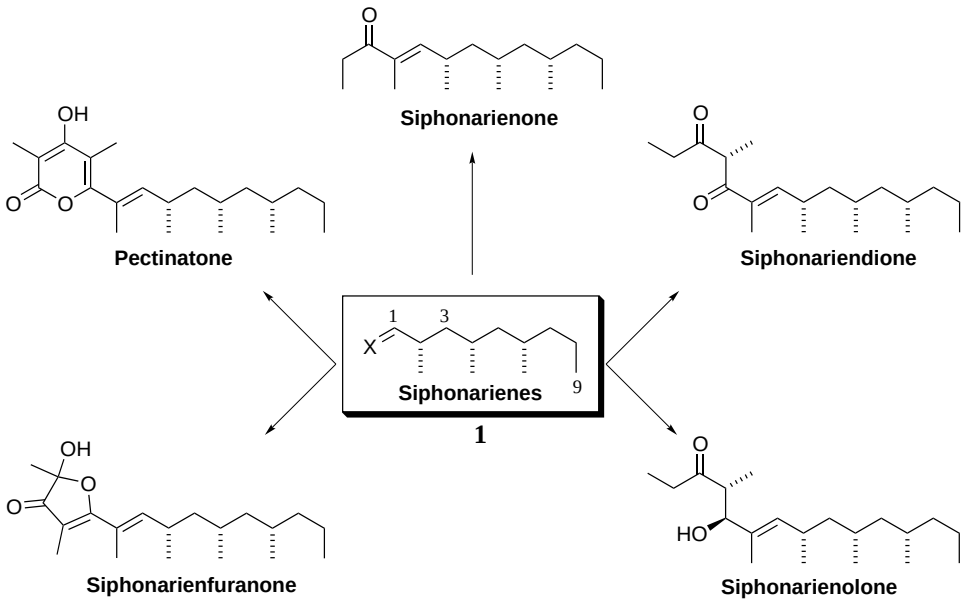


Fig. 1. Representative metabolites isolated from *Siphonaria grisea*.

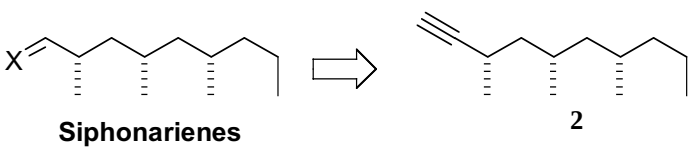


Fig. 2. Plausible general strategy to obtain the (2*S*,4*S*,6*S*)-2,4,6-trimethylnonyl segment of siphonarienes.

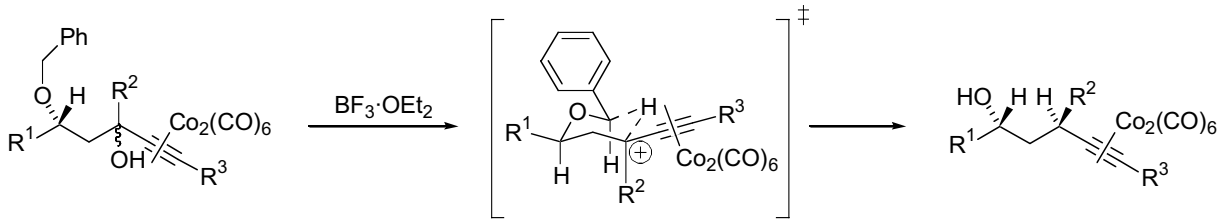


Fig. 3. Stereoselective hydride transfer to $Co_2(CO)_6$-propargylic cations.

2. RESULTS AND DISCUSSION

Iterative application in both directions of the above-described procedure, taking a central benzyloxy group as the stereochemical director, could allow the enantiomeric synthesis of reduced polypropionates such as **2**. In this sense, the stereocontrolled synthesis of **2** could be envisioned from a secondary alcohol such as **3**, available by application of our methodology to a $Co_2(CO)_6$-complexed tertiary carbinol such as **4** (Fig. 4). The synthesis of an additional tertiary alcohol forces us to perform the first reductive process over a substrate with an additional protected hydroxyl group **6**, this molecule being easily available from the corresponding (4*S*)-4,6-bis(phenylmethoxy)hexan-2-one **7** synthesized previously by our group,[10] where the stereocenter configuration is ensured by a Katsuki–Sharpless asymmetric epoxidation reaction (>95% ee).[11]

In order to perform the above-mentioned intramolecular reduction, the necessary $Co_2(CO)_6$-diastereomeric mixture of tertiary propargylic alcohols **8** (ca. 1.5:1) was obtained by addition of lithium trimethylsilyl acetylide to the ketone **7** and further complexation with $Co_2(CO)_8$. The key reduction was performed by Lewis acid treatment, affording **9** as the only detected isomer

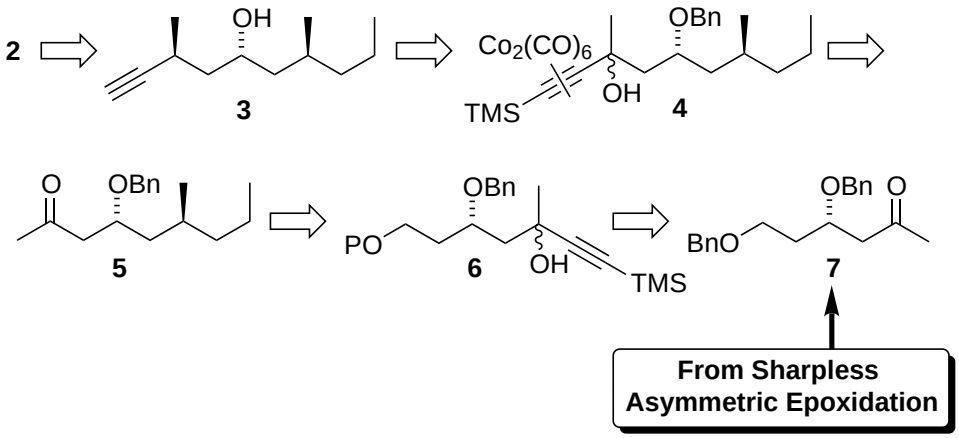
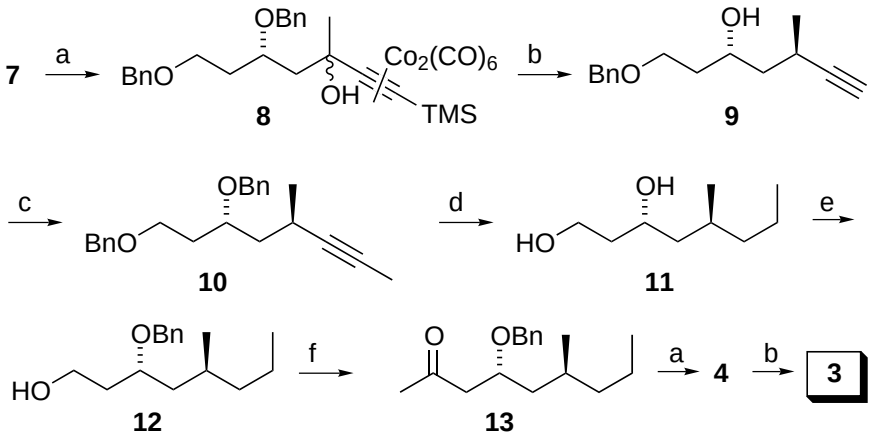
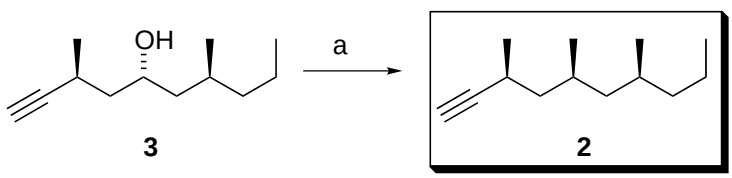


Fig. 4. Suggested protocol for the synthesis of (3*S*,5*S*,7*S*)-3,5,7-trimethyl-1-decyne (**2**).



Scheme 1. (a) (i) LiC≡CTMS, THF, –78 °C; (ii) $Co_2(CO)_8$, CH_2Cl_2, rt; (b) (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C, (ii) CAN, acetone, 0 °C, (iii) *n*-Bu_4NF, THF, rt, 62% overall from **7**; (c) (i) $PhCH_2Br$, NaH, *n*-Bu_4NI (cat), THF, rt, 94%, (ii) MeI, *n*-BuLi, THF, 0 °C, 98%; (d) H_2, Pd/C, MeOH, 99%; (e) (i) $PhCH(OMe)_2$, CSA (cat), CH_2Cl_2, (ii) DIBAL-H, CH_2Cl_2, 0 °C, 82% overall; (f) (i) Oxalyl chloride, DMSO, Et_3N, –78 °C, (ii) MeMgCl, THF, –78 °C, (iii) Oxalyl chloride, DMSO, Et_3N, –78 ºC, 73% overall.



Scheme 2. **(**a) (i) TsCl, Py, 45 °C, (ii) $(CH_3)_2CuLi$, THF, 50 °C, 63% overall.

after CAN and fluoride treatments.[12] Reprotection of the secondary alcohol and homologation of one carbon provided the correct terminal carbon framework. Catalytic hydrogenation produced simultaneous reduction of the triple bond and deprotection of the two benzyl ethers, affording the saturated diol **11**. At this point in the synthesis and considering the necessity to apply a new intramolecular reduction, we obtained the secondary benzyloxy ether **12** by reduction of the suitable benzylidene obtained from **11**. The primary alcohol was oxidized to the corresponding aldehyde, which, after Grignard addition and further oxidation, provided the methyl ketone **13.** An iterative process similar to that applied to **7** yielded the free alcohol **3** (63% overall yield) with the stereochemically well-defined methyl groups located at the α-position relative to the triple bond (Scheme 1).

In order to introduce the additional methyl group of

the alkyl chain of **2**, we took advantage of the existence of the secondary alcohol with the opposed stereochemistry in the carbinolic carbon carrying out a nucleophilic displacement with inversion of the configuration of this stereocenter. Thus, the alcohol **3** was tosylated and treated with the suitable dimethylcuprate,[13] affording **2** as the sole detected stereoisomer by ^{1}H and ^{13}C NMR analysis (Scheme 2).

3. CONCLUSION

In summary, a new asymmetric synthesis of the (2*S*,4*S*,6*S*)-2,4,6-trimethylnonyl segment of siphonarienes has been achieved, starting from readily available (4*S*)-4,6-bis(phenylmethoxy)hexan-2-one **7** and using alkyne–cobalt complexes chemistry. The method is very efficient for the stereocontrolled synthesis of highly-branched alkyl chains, and considering that the source of chirality is the Katsuki–Sharpless asymmetric epoxidation, the alternative choice of the tartrate auxiliary easily permits control of the absolute configuration in the final product.

4. EXPERIMENTAL

4.1. General Methods and Materials

^{1}H and ^{13}C NMR spectra were recorded at 400 and 75 MHz, respectively, and chemical shifts were reported relative to internal Me_4Si. Optical rotations were determined for solutions in chloroform. Column chromatography was performed on Merck silica gel, 60 Å and 230–400 mesh. Compounds were visualized by use of UV light and/or 2.5% phosphomolybdic acid in ethanol with heating. All solvents were purified by standard techniques.[14] Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

*4.2. Preparation of (3R,5R)-1-(benzyloxy)-5-methyl-6-heptyn-3-ol (**9**)*

n-BuLi (1.01 mL, 1.9 M in hexanes, 1.92 mmol) was added to a solution of trimethylsilylacetylene (0.24 mL, 2.07 mmol) in dry THF (7 mL) at –78 °C. After the addition, the mixture was warmed to 0 °C for 0.5 h. Then, this mixture was cooled to –78 °C and a solution of **7** (500 mg, 1.60 mmol) in dry THF (12 mL) was added dropwise. The mixture was stirred at –78 °C for 1 h, whereupon it was quenched with saturated NH_4Cl solution and Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a mixture of alcohols in which one diastereoisomer slightly predominated (ca. 1.5:1).

To a solution of the above-obtained mixture in dry CH_2Cl_2 (16 mL), $Co_2(CO)_8$ (715 mg, 2.08 mmol) was added at room temperature. The reaction mixture was stirred at room temperature until TLC showed complete conversion to the hexacarbonyldicobalt complex (ca. 1 h). The mixture was filtered through a pad of silica gel and concentrated to yield **8** as a brown solid that was used without any purification.

To a stirred solution of the crude $Co_2(CO)_6$ complex in dry CH_2Cl_2 (16 mL), $BF_3{\cdot}OEt_2$ (0.13 mL, 1.65 mmol) was slowly added at –20 °C. The reaction mixture was stirred for 5 min and poured into saturated aqueous $NaHCO_3$ at 0 °C. The resulting mixture was vigorously stirred for 15 min and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a complexed acetylene that was employed in the next step without further purification.

To a stirred solution of the complexed acetylene in dry acetone (4 mL), CAN (10 g, 3.29 mmol) was added in one portion at 0 °C. The reaction mixture was stirred at 0 °C until TLC showed completion of the reaction (ca. 5 min). The mixture was evaporated and the residue diluted with water and extracted with Et_2O. The combined organic solutions were dried ($MgSO_4$), filtered, and concentrated. To a solution of the crude obtained in dry THF (30 mL), *n*-Bu_4NF (1 M in THF, 1.5 mL, 1.5 mmol) was slowly added at 0 °C. After this addition, the mixture was allowed to warm to rt for 1 h with stirring, diluted with Et_2O, and H_2O was added. The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried, filtered, concentrated and purified by column chromatography to afford **9** (230 mg, 62% overall yield) as a colorless oil: $[\alpha]^{25}_D$ = –5.8 (*c* 4.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.20 (d, *J* = 7.7 Hz, 3H), 1.22–1.56 (m, 1H), 1.70–1.80 (m, 3H), 2.07 (br s, 1H), 2.59–2.63 (m, 1H), 3.04 (br s, 1H), 3.64–3.74 (m, 2H), 3.98 (m, 1H), 4.52 (br s, 2H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7 (q), 22.4 (d), 36.4 (t), 43.9 (t), 68.6 (d), 68.8 (t), 69.2 (d), 73.2 (t), 89.1 (s), 127.7 (d), 128.4 (d), 137.9 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3440, 3298, 2970, 1454, 1096; MS *m*/*z* (relative intensity) 233 $(M + 1)^+$ (0.5), 232 $(M)^+$ (2.4), 155 $(M - C_6H_5)^+$ (0.5), 141 $(M - C_7H_7O)^+$ (1.5), 120 (6.0), 107 (22.0), 91 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.29; H, 8.84.

*4.3. Preparation of [(3R,5R)-3-(benzyloxy)-5-methyl-6-heptynyl]oxy(methyl)benzene (**10**)*

To a stirred suspension of NaH (60% in mineral oil, 52 mg, 1.29 mmol) in dry THF (10 mL), at 0 ºC, a solution of **9** (230 mg, 0.99 mmol) in THF (5 mL), a catalytic amount of *n*-Bu_4NI, and benzyl bromide (0.18 mL, 1.5 mmol) were sequentially and slowly added. The reaction mixture was stirred at room temperature for 24 h. Then, the mixture was diluted with Et_2O, washed with brine, dried, concentrated, and purified by column chromatography yielding the corresponding dibenzyl ether (300 mg, 94%) as a colorless oil: $[\alpha]^{25}_D$= –14.3 (*c* 5.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.16 (d, *J* = 6.9 Hz, 3H), 1.52–1.60 (m, 1H), 1.85–1.94 (m, 3H), 2.04 (br s, 1H), 2.54–2.62 (m, 1H), 3.6 (t, *J* = 6.1 Hz, 2H), 3.72–3.80 (m, 1H), 4.48 (br s, 2H), 4.50 (br s, 2H), 7.20–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.0 (q), 22.2 (d), 34.1 (t), 41.2 (t), 66.8 (d), 68.4 (d), 71.0 (t), 73.0 (t), 74.3 (d), 88.9 (s), 127.0 (d), 127.5 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.3 (d), 129.0 (d), 129.7 (d), 138.5 (s), 138.7 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3294, 2968, 1745, 1454, 1097; MS *m* / *z* (relative intensity) 322 $(M)^+$ (0.2), 321 $(M - 1)^+$ (0.5), 231 (3.0), 230 $(M - C_6H_5 - CH_3)$ + (1.0), 169 (2.0), 91 (100). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.92; H, 8.31.

To a solution of the above dibenzyl ether (300 mg,

0.93 mmol) in THF (10 mL) under nitrogen, *n*-BuLi (1.9 M in hexanes, 0.54 mL, 1.03 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 15 min and then CH_3I (0.09 mL, 1.40 mmol) was added. The reaction was allowed to warm to rt and stirred for 1 h, after which the reaction mixture was added to a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography yielding **10** (287 mg, 98%) as a colorless oil: $[\alpha]^{25}_D$= –8.5 (*c* 1.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, *J* = 7.3 Hz, 3H), 1.45–1.55 (m, 1H), 1.75 (br s, 3H), 1.79–1.97 (m, 3H), 2.50 (m, 1H), 3.59 (t, *J* = 6.5 Hz, 3H, 2H), 3.75 (m, 1H), 4.43–4.55 (m, 4H), 7.28–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) 3.4 (q), 21.5 (q), 22.5 (d), 34.1 (t), 41.7 (t), 66.9 (t), 70.8 (s), 72.9 (t), 74.5 (t), 75.8 (d), 83.5 (s), 127.5 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.9 (d), 129.0 (d), 138.5 (s), 138.8 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2931, 1716, 1453, 1276, 1097; MS *m/z* (relative intensity) 336 $(M)^+$ (0.1), 335 $(M - 1)^+$ (0.2), 259 $(M - C_6H_5)^+$ (0.5), 245 $(M - C_7H_7O)^+$ (2.3), 243 (1.5), 139.7 (7.0), 91 (100). Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.18; H, 8.60.

*4.4. Preparation of (3*R, *5*S*)-5-methyl-1,3-octanediol (**11**)*

To a solution of **10** (250 mg, 0.75 mmol) in MeOH (8 mL), 10% Pd/C (22 mg) was added at room temperature. The resulting suspension was vigorously stirred under an atmosphere of H_2 (1 atmosphere) for 2 h at room temperature. After removal of the catalyst by filtration through a small pad of Celite, the filtrate was concentrated and purified by column chromatography, yielding **11** (136 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$= +10.0 (c 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.89 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 1.13–1.35 (m, 5H), 1.55–1.71 (m, 4H), 2.52 (br s, 2H), 3.81–3.98 (m, 3H); ^{13}C NMR ($CDCl_3$) 14.3 (q), 19.2 (q), 20.0 (t), 28.7 (d), 39.1 (t), 40.0 (t), 45.3 (t), 61.8 (t), 69.9 (d); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3347, 2956, 1457, 1054; MS *m/z* (relative intensity) 161 $(M + 1)^+$ (0.1), 160 $(M)^+$ (0.1), 159 $(M - 1)^+$ (0.3), 143 $(M - OH)^+$ (1.6), 124 $(M - 2\ H_2O)^+$ (1.6), 113 (16.0), 75 (100). Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.63; H, 12.60.

*4.5. Preparation of (3*R, *5*S*)-3-(benzyloxy)-5-methyl-1-octanol (**12**)*

To a solution of the diol **11** (125 mg, 0.78 mmol) in dry CH_2Cl_2 (8 mL), a catalytic amount of CSA (19 mg, 0.08 mmol) and benzaldehyde dimethylacetal (0.10 mL, 0.94 mmol) were sequentially added at room temperature. The reaction mixture was stirred for 1 h, after which TLC showed complete reaction. Then, Et_3N was added until pH = 7, stirred for 5 min, and evaporated under reduced pressure. The residue was used without further purification.

To a solution of the crude benzylidene derivative obtained in dry CH_2Cl_2 (5 mL), DIBAL-H (7.5 mL, 1 M solution in cyclohexane, 7.5 mmol) was slowly added at 0 ºC. The reaction mixture was allowed to warm to rt over a period of 15 min. The mixture was diluted with CH_2Cl_2 and aqueous HCl (5%) was added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography to yield **12** (320 mg, 82% overall yield) as a colorless oil: $[\alpha]^{25}_D$= –14.1 (*c* 1.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (br s, 3H), 0.89 (br s, 3H), 0.90–1.58 (m, 1H), 1.2–1.35 (m, 5H), 1.58–1.63 (m, 1H), 1.67–1.78 (m, 2H), 1.82–1.92 (m, 1H), 3.69–3.74 (m, 2H), 3.76–3.82 (m, 1H), 4.54 (m, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3 (q), 19.9 (q), 20.0 (t), 29.1 (d), 36.3 (t), 39.5 (t), 41.6 (t), 60.5 (t), 70.9 (t), 76.6 (d), 127.7 (d), 127.9 (d), 128.4 (d), 138.4 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3368, 2928, 1717, 1455, 1067; MS *m/z* (relative intensity) 250 $(M)^+$ (0.3), 249 $(M - 1)^+$ (0.2), 232 $(M - H_2O)^+$ (2.7), 205 (0.6), 147 (7.0), 91 (100). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.77; H, 10.51.

*4.6. Preparation of (4*R,*6*S*)-4-(benzyloxy)-6-methyl-2-nonanone (**13**)*

To a solution of oxalyl chloride (0.11 mL, 1.2 mmol) in dry CH_2Cl_2 (2 mL) at –78 °C, DMSO (0.11 mL, 1.5 mmol) was added. The mixture was stirred for 15 min, and then product **12** (150 mg, 0.60 mmol) was added. The reaction mixture was stirred for 1 h at –78 °C. After this time, Et_3N (0.42 mL, 3 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 10 min, it was diluted with Et_2O and a saturated aqueous NH_4Cl solution was added. The mixture was extracted with Et_2O and washed with brine. The combined organic extracts were dried, filtered, and concentrated, providing an aldehyde that was suitable for use without further purification.

To a solution of the crude aldehyde in THF (5 mL), MeMgCl (0.30 mL, 3 M in THF, 0.90 mmol) was added dropwise at –78 °C. After the mixture was stirred for 0.5 h, saturated NH_4Cl solution was added, and the resulting slurry extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. The residual oil was used without further purification.

To a solution of oxalyl chloride in dry CH_2Cl_2 (2 mL) at –78 °C, DMSO (0.11 mL, 1.2 mmol) was added. The mixture was stirred for 15 min, and then the crude diastereomeric alcohols were added. The reaction mixture was stirred for 2 h at –78 °C. After this time, Et_3N (0.42 mL, 3 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 10 min it was diluted with Et_2O and a saturated aqueous NH_4Cl solution was added. The mixture was extracted with Et_2O and washed with brine. The combined organic extracts were dried, filtered, and concentrated. The resulting viscous oil was purified by flash column chromatography to yield **13** (115 mg, 73% overall yield) as a colorless oil: $[\alpha]^{25}_D$= +1.4 (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.86 (br s, 3H), 0.87 (br s, 3H), 0.93–1.63 (m, 7H), 2.16 (s, 3H), 2.50 (dd, *J* = 15.8, 5.3 Hz, 1H), 2.76 (dd, *J* = 15.8, 6.7 Hz, 1H), 4.00 (m, 1H), 4.51 (br s, 2H), 7.28–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 14.3 (q), 19.6 (q), 19.9 (t), 29.0 (d), 31.2 (q), 39.7 (t), 42.6 (t), 49.1 (t), 71.6 (t), 73.8 (d), 127.5 (d), 127.8 (d), 128.3 (d), 138.5 (s), 207.7 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2956, 1717, 1359, 1096; MS *m/z* (relative intensity) 262 $(M)^+$ (0.1), 219 $(M - C_2H_3O)^+$ (0.2), 204 $(M - C_2H_3O - CH_3)^+$ (2.4), 177 (0.3), 138 (15.5), 113 (8.0), 91 (100). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 78.10; H, 10.24.

*4.7. Preparation of (3S,5R,7S)-3,7-dimethyl-1-decyn-5-ol (**3**)*

The same procedure used above to obtain **9** from **7** was applied to **13** on a 100 mg (0.55 mmol) scale, yielding **3** (73 mg, 73% overall yield) as a colorless oil: $[\alpha]^{25}_{D}$= +18.0 (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.89 (br s, 3H), 0.91 (br s, 3H), 1.22 (d, *J* = 6.7 Hz m, 3H), 1.22–1.71 (m, 8H), 2.11 (br s, 1H), 2.59 (m, 1H), 3.88 (m, 1H); ^{13}C NMR ($CDCl_3$) 13.7 (q), 19.1 (q), 20.0 (t), 21.1 (q), 23.1 (d), 28.8 (d), 39.6 (t), 40.0 (t), 68.4 (d), 69.1 (d), 89.0 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2929, 2360, 2341, 1730; MS *m*/*z* (relative intensity) 183 $(M + 1)^+$ (8.0), 182 $(M)^+$ (1.7), 149 (100), 125 (6.7), 105 (13.9), 91 (52.0). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.32; H, 12.47.

*4.8. Preparation of (3S,5S,7S)-3,5,7-trimethyl-1-decyne (**2**)*

To a stirred solution of **3** (50 mg, 0.23 mmol) in dry pyridine (3 mL) was added TsCl (105 mg, 0.55 mmol) at 0 ºC. The reaction mixture was allowed to warm to 45 ºC and stirred for 6 h, after which TLC showed complete reaction. The mixture was then diluted with H_2O and the aqueous layer was extracted with Et_2O. The ethereal extracts were washed with H_2O, saturated $CuSO_4$ solution, and brine, dried, and concentrated. The tosylate was used without further purification.

To a stirred slurry of copper(I) iodide (262 mg, 1.38 mmol) in dry THF (3 mL) under nitrogen at –20 ºC, methyllithium (2.2 M in Et_2O, 1.3 mL, 1.3 mmol) was added. The solution became clear and was stirred for 0.5 h. A solution of the crude tosylate in dry THF was added dropwise, and the mixture stirred overnight with warming to 50 ºC. The reaction was quenched with ammonium hydroxide-saturated aqueous NH_4Cl solution. The solution was stirred until the copper salts were completely dissolved in the aqueous layer. The aqueous layer was extracted with ether, and the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to yield **2** (31 mg, 63% yield overall) as a colorless oil: $[\alpha]^{25}_{D}$= + 6.5 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.83–1.03 (m, 9H), 1.11–1.26 (m, 8H), 1.36 (br s, 3H), 1.65 (m, 2H), 1.78 (br s, 1H), 2.57 (m, 1H); ^{13}C NMR ($CDCl_3$) 14.3 (q), 17.4 (q), 19.1 (t), 19.8 (q), 20.4 (q), 20.6 (t), 23.1 (d), 28.8 (d), 29.2 (d), 39.7 (t), 45.0 (t), 43.5 (t), 66.0 (d), 68.6 (s), 89.1 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2360, 2341, 1730, 1096; MS *m*/*z* (relative intensity) 180 $(M)^+$ (10), 165 $(M - CH_3)^+$ (17), 152 (34), 136 (100). HMRS calcd for $C_{13}H_{24}$ $(M)^+$:180.1878. Found: 180.1883.

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