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Catalytic Enantioselective Synthesis of (*S*)-8-Hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one, (*S*)-3-Hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one, and Their Epimers

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The total synthesis of (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one, (*S*)-3-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one, and their epimers has been successfully achieved. The key reactions include a catalytic enantioselective asymmetric epoxidation to introduce the chirality, and an Alder–Rickert reaction for the construction of the substituted phenyl ring.

Introduction

In 2010, Isaka and co-workers reported the isolation of the cyclodepsipeptide cordycommunin together with two unnamed dihydroisocoumarin natural products (**1a** and **1b**) from the extracts of fungus *Ophiocordyceps communis* BCC16475.[1] Later, the structures assigned to these anonymous dihydroisocoumarins were found to be already known in the literature .[2] The total synthesis of one of these dihydroisocoumarins, i.e., 7-demethoxyfusarentin **1a** and its methyl ether **1b** was reported by Reddy et al.[3]

Recently, Jennings et al. not only achieved the total synthesis of dihydroisocoumarin **1a**, but also named compound **1a** as 7-deoxy-6-*O*-methylfusarentin and **1b** as 7-deoxy-6,8-*O*-dimethylfusarentin, in analogy with the fusarentin parent skeleton[4] (Figure 1). The family of fusarentin molecules comprises a 4-oxy-isochroman-1-one motif connected to a pendant stereogenic hydroxy alkyl group or a substituted pyrone ring. Owing to the biological properties of these natural molecules,[5] several strategies have appeared for the synthesis of this class of compounds.[2–4,6] Most of these approaches use chiral synthons for the introduction of chirality. Published routes to (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one and (*S*)-3-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one lack flexibility for stereochemical modification (Figure 1). As a result of our continued interest in the development of catalytic enantioselective strategies for the synthesis of biologically active molecules,[7] we proposed a diastereodivergent route to (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one **1a** and its stereoisomers.

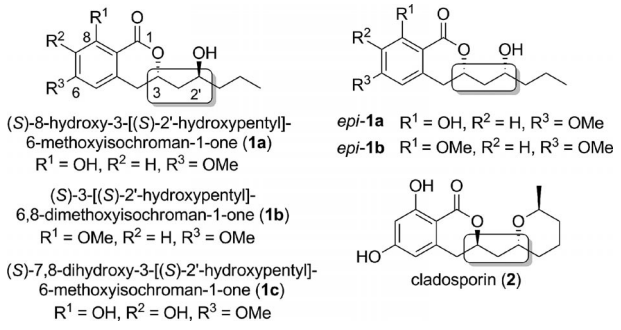

Figure 1. Dihydroisocoumarin natural products.

Results and Discussion

Recently, we reported a highly diastereoselective route to 1,3,5-skipped polyols based on an iterative catalytic enantioselective asymmetric epoxidation.[8] We intended to use this method to install the requisite 1,3-diol stereogenic centres, either *syn* or *anti*, as required for the fusarentin family, and in particular for (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one and (*S*)-3-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-8-dimethoxyisochroman-1-one. A retrosynthetic plan is shown in Scheme 1. Similarly to the previous synthesis of **1a**, we planned to construct the highly substituted phenyl ring by using an Alder–Rickert reaction between alkyne ester **3** and 1,5-dimethoxycyclohexa-1,4-diene (**4**). Key intermediate **3** can be accessed by ring-opening of a terminal epoxide **5** with an

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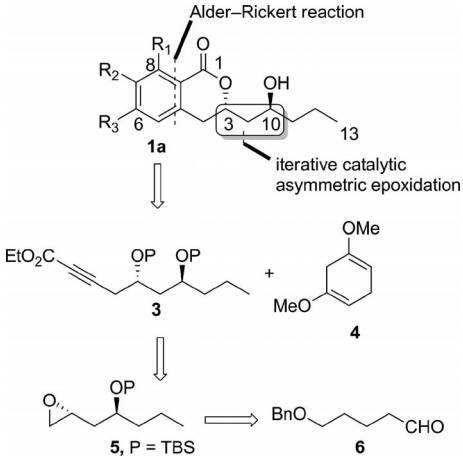
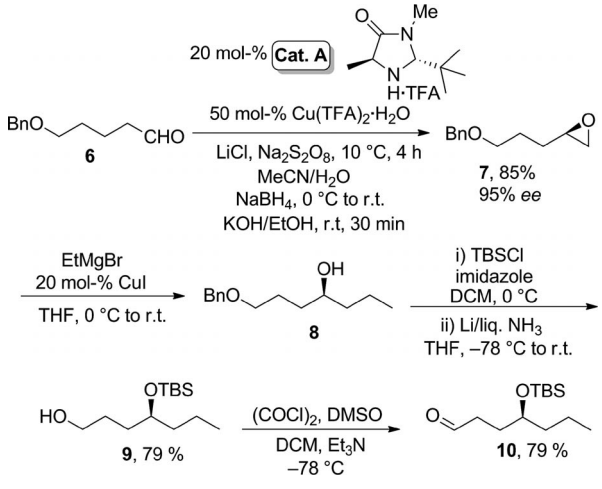
appropriately functionalized lithium acetylide. In turn, hydroxy-protected terminal epoxide **5** could be synthesized by an organocatalytic Macmillan epoxidation[9] starting from achiral aldehyde **6** (Scheme 1).



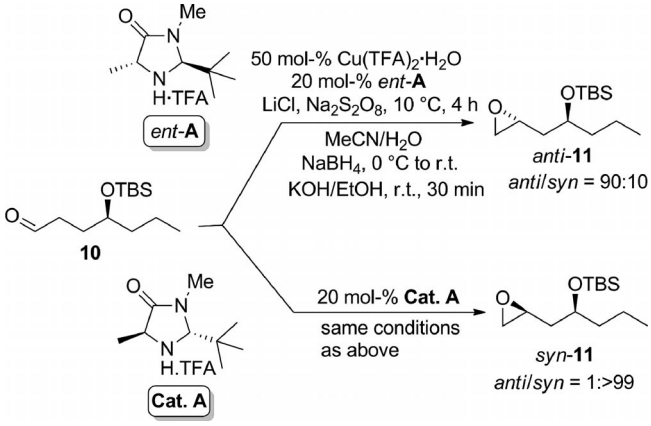
Scheme 1. Retrosynthesis of (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one and (*S*)-3-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one.

Accordingly, enantioenriched terminal epoxide **7** with 95% *ee* was prepared from benzyloxy pentanal **6** by a catalytic asymmetric epoxidation. The *ee* of **7** was determined by comparison of its optical rotation value, and its absolute configuration was assigned based on the sign of the specific rotation reported in the literature.[9] Cu^{I}-catalysed regioselective ring opening[10] of (*R*)-oxirane **7** with ethylmagnesium bromide gave secondary alcohol **8**. The secondary alcohol was protected as its TBS (*tert*-butyldimethylsilyl) ether, and subsequent debenzylation with Li in liquid NH_3 gave compound **9** in 79% yield. Subsequent oxidation of alcohol **9** gave aldehyde **10**, which was used in the next catalytic asymmetric epoxidation (Scheme 2).



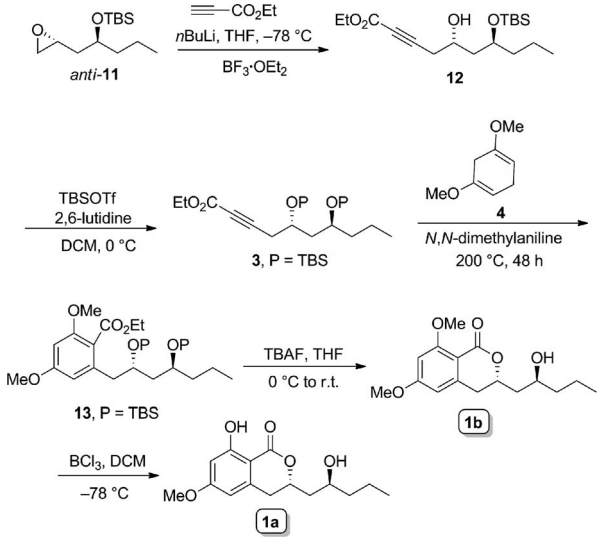
Scheme 2. Synthesis of enantioenriched TBS-protected aldehyde; TFA = trifluoroacetate.

Having established a route to aldehyde **10**, we planned to evaluate the catalyst-directed iterative MacMillan asymmetric epoxidation and the diastereoselectivity of this reaction. When aldehyde **10** was subjected to the catalytic epoxidation using *ent*-**A**, terminal epoxide *anti*-**11** was formed in 90% yield with a 90:10 diastereomeric ratio, as estimated by ^{13}C NMR spectroscopy. Similarly, when catalyst **A** (20 mol-%) was used under otherwise identical conditions, terminal epoxide *syn*-**11** was formed with a >99:1 diastereomeric ratio. This indicates that the catalyst directs the stereochemical outcome of the reaction, inducing a high diastereoselectivity, consistant with our previous observations (Scheme 3).[8]



Scheme 3. Diastereodivergent synthesis of terminal epoxides.

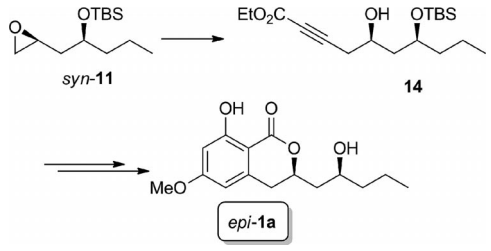
Subsequent addition of lithium ethyl propiolate to terminal epoxide *anti*-**11** led to acetylene alcohol **12**,[11] and subsequent protection of the secondary alcohol with TBSOTf under basic conditions gave silyl ether **3** in 97% yield. Next, we carried out a typical Alder–Rickert cycloaddition reaction[12] to construct the substituted aromatic moiety. The reaction of **3** with diene **4** was heated in a sealed tube under neat conditions at 200 °C with a catalytic amount of *N*,*N*-dimethylaniline to produce the desired aromatic ester (i.e., **13**) in 60% yield (Scheme 4).



Scheme 4. Synthesis of **1a** and **1b**. TBAF = tetrabutylammonium fluoride.

Finally, fluoride-induced deprotection of the silyl groups and concomitant lactonization gave (*S*)-3-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one **1b** in 90% yield. Selective demethylation[13] of the 8-methoxy group in **1b** using boron trichloride in dichloromethane at –78 °C gave target molecule **1a** in 80% yield. The analytical data (^{1}H and ^{13}C NMR spectroscopic data) and specific rotation {$[\alpha]_D^{32}$ = –15.7 (*c* = 0.5, $CHCl_3$); ref.[1] $[\alpha]_D^{26}$ = –14.0 (*c* = 0.13, $CHCl_3$)} of **1a** were in good agreement with the reported values (Scheme 4).

We went on to carry out the stereoselective synthesis of *syn* variants *epi*-**1b** and *epi*-**1a**. Thus, exposure of *syn*-**11** to conditions similar to those described above for the conversion of *anti*-**11** into **1b** and **1a** led to the expected *epi*-**1b** and *epi*-**1a** in 73 and 68% yields, respectively (Scheme 5).



Scheme 5. Synthesis of the 2′-epimer of (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one **1a**.

Conclusions

In conclusion, a diastereodivergent total synthesis of (*S*)-8-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one (**1a**) and (*S*)-3-hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one (**1b**) and their unnatural diastereomers has been accomplished. Compound **1a** was synthesised in 10 steps and 20% overall yield. This strategy facilitates the synthesis of diastereomeric analogues by using a complementary chiral catalyst. Further work involving the application of this strategy for the synthesis of related biologically active natural products is in progress.

Experimental Section

General Information: Reactions were carried out under an inert argon atmosphere where specified. The apparatus used for reactions was completely dried in an oven. CH_3CN was distilled from CaH_2. Diethyl ether was distilled from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 300 MHz (Avance) and Varian Unity 500 MHz (Innova) spectrometers in $CDCl_3$. *J* values are given in Hertz, and chemical shifts (δ) are reported relative to tetramethylsilane (δ = 0.0 ppm), which was used as an internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. IR data were measured using an FTIR spectrometer using KBr pellets or as films. Mass spectral (MS and HRMS) data were recorded using the electrospray ionization (ESI) method. Optical rotations were recorded with a digital polarimeter at 589 nm (sodium ^{d}-line).

(*R*)-2-[3-(Benzyloxy)propyl]oxirane (7): Aldehyde **6** (5.418 g, 28.2 mmol) was added to a stirred solution of catalyst **A** (1.60 g, 5.63 mmol), lithium chloride (1.73 g, 42.25 mmol), copper trifluoroacetate hydrate (4.17 g, 14.08 mmol), and sodium persulfate (6.706 g, 28.2 mmol) in acetonitrile (200 mL) and water (1.12 mL) at 10 °C, and the resulting mixture was stirred vigorously for 2 h. The reaction mixture was cooled to 0 °C, and then $NaBH_4$ (2.68 g, 70.42 mmol) was added. After 10 min, the mixture was warmed to room temperature. A freshly prepared ethanolic aqueous solution of KOH [KOH (20 g) dissolved in EtOH (20 mL) and distilled H_2O (40 mL)] was added, and the resulting mixture was stirred vigorously for 30 min. Distilled water (200 mL) was then added, and the mixture was extracted with pentane (3× 150 mL). The combined organic extracts were washed with brine (1× 50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated, with the bath temperature kept at 30 °C. The resulting residue was purified by column chromatography on silica gel (pentane/ether) to give epoxide **7** (4.58 g, 85%) as a colourless oil. $[\alpha]_D^{31}$ = +10.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.33–7.26 (m, 5 H), 4.51 (s, 2 H), 3.57–3.48 (m, 2 H), 2.96–2.92 (m, 1 H), 2.74 (t, *J* = 4.88 Hz, 1 H), 2.47 (dd, *J* = 2.75, 5.03 Hz, 1 H), 1.83–1.56 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 128.2, 127.4, 72.7, 69.6, 51.9, 46.9, 29.1, 26.0 ppm. MS (ESI): *m*/*z* = 193 $[M + H]^+$, 215 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{12}H_{17}O_2$ 193.1223; found 193.1217.

(4*S*)-(1-Benzyloxy-4-hydroxy)heptane (8): Magnesium (2.5 equiv., 0.63 g, 26 mmol) was put into a flame-dried two-necked round-bottomed flask capped with septa and with an argon balloon, and the magnesium was activated by heating the flask to 80 °C for 20 min. The flask was cooled to room temp., then THF (15 mL) and a few iodine crystals were added. Bromoethane (2.5 equiv., 1.94 mL, 26 mmol) was dissolved in THF (30 mL), and a small portion of this solution was added to the flask containing the magnesium while stirring gently until the brown iodine colour disappeared. Subsequently, the remaining bromoethane/THF solution was added dropwise to the reaction mixture over a period of 10 min. After the addition was complete, the reaction mixture was stirred for a further 20 min, then it was cooled to 0 °C. Copper iodide (0.07 equiv., 0.98 g, 1.04 mmol) was added, and the resulting mixture was stirred for 20 min. A solution of oxirane (*S*)-**7** (2.0 g, 10.4 mmol) in THF (30 mL) was added dropwise over a period of 10 min to the resulting purple-black suspension. The reaction mixture was gradually allowed to warm to r.t. and stirred for 30 min. Subsequently, the reaction mixture was cooled to 0 °C, and pre-cooled (0 °C) saturated aqueous NH_4Cl solution (30 mL) was added for quenching. The aqueous layer was extracted with Et_2O (3× 20 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:9) to give **8** (1.76 g, 76%) as a colourless oil. $[\alpha]_D^{35}$ = 0.61 (*c* = 1.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.33–7.26 (m, 5 H), 4.52 (s, 2 H), 3.65–3.58 (m, 1 H), 3.51 (t, *J* = 6.10 Hz, 2 H), 2.24 (br. s, 1 H), 1.79–1.67 (m, 3 H), 1.66–1.59 (m, 1 H), 1.49–1.31 (m, 4 H), 0.92 (t, *J* = 7.17 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.0, 128.2, 127.5, 72.8, 71.0, 70.4, 39.5, 34.4, 26.0, 18.8, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3364, 2929, 1452, 1097, 772, 697 cm^{-1}. MS (ESI): *m*/*z* = 223 $[M + H]^+$, 245 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{23}O_2$ 223.1692; found 223.1685.

(4*S*)-[1-Benzyloxy-4-*tert*-butyldimethylsilyloxy]heptane (8a): *t*BuMe$_2$SiCl (1.3 equiv., 0.99 g, 6.6 mmol) was added portionwise to a stirred solution of **8** (1.0 equiv., 1.13 g, 5 mmol) and 1*H*-imidazole (2.0 equiv., 0.69 g, 10.2 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with

CH_2Cl_2 (2× 15 mL). The combined organic extracts were washed with H_2O and brine (10 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by column chromatography (EtOAc/hexanes, 1:9) to give (*S*)-**8a** (1.52 g, 89.4%) as a colourless oil. $[a]_D^{35}$ = –4.2 (*c* = 2.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.34–7.33 (m, 3 H), 7.30–7.26 (m, 2 H), 4.50 (s, 2 H), 3.69–3.64 (m, 1 H), 3.46 (t, *J* = 6.56 Hz, 2 H), 1.74–1.59 (m, 2 H), 1.59–1.53 (m, 2 H), 1.43–1.24 (m, 4 H), 0.90–0.87 (m, 15 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.6, 128.3, 127.5, 127.4, 72.7, 71.8, 70.6, 39.4, 33.5, 25.9, 18.5, 18.1, 14.3, –4.4 ppm. IR (KBr): $\tilde{\nu}$ = 2954, 2929, 2855, 1457, 1035, 833, 773 cm^{-1}. MS (ESI): *m*/*z* = 337 $[M + H]^+$, 359 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{20}H_{37}O_2Si$ 337.2557; found 337.2549.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-heptanol (9): Lithium metal (0.325 g, 46.5 mmol) was added to freshly condensed liquid NH_3 (50 mL) at –78 °C. Then, a solution of **8a** (5.21 g, 15.5 mmol) in THF (50 mL) was added at –78 °C. The resulting mixture was stirred for 10 min at –78 °C, and then it was quenched by the addition of solid NH_4Cl. The NH_3 was then allowed to evaporate. The residue was partitioned between H_2O (50 mL) and Et_2O (50 mL), and the aqueous phase was extracted with Et_2O (2× 50 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (hexane/EtOAc, 7:3) to give **9** (3.47 g, 91%) as a clear colourless liquid. $[a]_D^{35}$ = –18 (*c* = 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77–3.70 (m, 1 H), 3.69–3.55 (m, 1 H), 2.19 (br. s, 1 H), 1.65–1.51 (m, 4 H), 1.50–1.39 (m, 2 H), 1.39–1.23 (m, 2 H), 0.92–0.90 (m, 12 H), 0.06 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 71.8, 63.2, 38.7, 33.3, 28.0, 25.8, 18.7, 18.0, 14.2, –4.5 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2925, 2856, 1219, 1039, 772 cm^{-1}. MS (ESI): *m*/*z* = 247 $[M + H]^+$, 269 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{13}H_{31}O_2Si$ 247.2087; found 247.2080.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)heptanal (10): A solution of oxalyl chloride (0.66 mL) in CH_2Cl_2 (8.0 mL) was cooled to –78 °C, and dry DMSO (1.12 mL) was added. The mixture was stirred for 15 min, then a solution of alcohol **9** (8.0 mL) in CH_2Cl_2 (7.0 mL) was added, and the resulting solution was stirred at same temperature for 45 min. Then, Et_3N (3.6 mL) was added, and the mixture was stirred for 15 min at –78 °C. Thereafter, the reaction mixture was removed from the cooling bath and allowed to stir at room temperature for 1 h. Finally, the reaction was quenched with water. The mixture was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (2× 50 mL). The combined organic extracts were dried, and the solvents were evaporated. The residue was purified by silica gel column chromatography (acetone/hexanes, 4:96) to give (*S*)-**10** (0.61 g, 89.4%) as a yellow oil. $[a]_D^{39}$ = +7.0 (*c* = 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.78 (s, 1 H), 3.76–3.68 (m, 1 H), 2.51–2.44 (m, 2 H), 1.89–1.78 (m, 1 H), 1.75–1.64 (m, 1 H), 1.51–1.25 (m, 4 H), 0.92–0.88 (m, 12 H), 0.04–0.03 (d, *J* = 2.08 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$,75 MHz): δ = 202.7, 70.8, 39.6, 39.2, 28.8, 25.8, 18.4, 18.0, 14.2, –4.5 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2928, 2856, 2712, 1728, 1253, 1070, 835, 774 cm^{-1}. MS (ESI): *m*/*z* = 245 $[M + H]^+$. HRMS (ESI): calcd. for $C_{13}H_{29}O_2Si$ 245.1933; found 245.1931.

(*R*)-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)pentyl]oxirane (*anti*-11): Aldehyde **10** (6.89 g, 28.2 mmol) was added to a stirred solution of catalyst **A** (20 mol-%, 1.60 g, 5.63 mmol), lithium chloride (1.5 equiv., 1.73 g, 42.25 mmol), copper trifluoroacetate hydrate (50 mol-%, 4.17 g, 14.08 mmol), and sodium persulfate (1 equiv., 6.706 g, 28.2 mmol) in acetonitrile (200 mL) and water (2.2 equiv., 1.12 mL, 61.97 mmol) at 10 °C, and the mixture was stirred vigorously for 2 h at same temperature. The mixture was then cooled to 0 °C, and $NaBH_4$ (2.5 equiv., 2.68 g, 70.42 mmol) was added. After a further 10 min, the mixture was warmed to room temperature. A freshly prepared solution of KOH [KOH (20 g) dissolved in EtOH (20 mL) and distilled water (40 mL)] was added, and the resulting mixture was stirred vigorously for 30 min. Distilled water (200 mL) was added, and the mixture was extracted with pentane (3× 150 mL). The combined organic extracts were washed with brine (1× 50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated, with the bath temperature kept at 30 °C. The residue was purified by silica gel column chromatography (pentane/ether) to give epoxide *anti*-**11** (6.20 g, 90%) as a colourless oil. $[a]_D^{31}$ = +15.45 (*c* = 2.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.92–3.84 (m, 1 H), 3.04–2.98 (m, 1 H), 2.79 (t, *J* = 5.29 Hz, 1 H), 2.47 (q, *J* = 2.27 Hz, 1 H), 1.68–1.55 (m, 2 H), 1.54–1.43 (m, 2 H), 1.40–1.25 (m, 2 H), 0.92–0.87 (m, 12 H), 0.06 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 69.9, 49.9, 47.7, 40.2, 40.1, 25.8, 18.2, 18.0, 14.2, –4.4, –4.7 ppm. IR (KBr): $\tilde{\nu}$ = 2928, 2855, 1253, 1074, 834, 773 cm^{-1}. MS (ESI): *m*/*z* = 245 $[M + H]^+$, 267 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{13}H_{28}O_2NaSi$ 267.1750; found 267.1749.

Ethyl (5*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxydec-2-ynoate (12): A solution of *n*-butyllithium (1.6 M in toluene; 3.76 mL, 6.02 mmol) was added dropwise to a THF (6 mL) solution of ethyl propiolate (0.58 mL, 5.7 mmol) at –78 °C under an argon atmosphere. After 45 min, a THF (5 mL) solution of *anti*-**5** (0.35 g, 1.43 mmol) was added dropwise, followed by $BF_3{\cdot}OEt_2$ (0.23 mL, 1.86 mmol). The resulting solution was stirred at same temperature for 30 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with diethyl ether (3× 10 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 3:97) to give **12** (0.41 g, 85%) as a colourless dense liquid. $[a]_D^{31}$ = +10.2 (*c* = 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.21 (q, *J* = 7.17 Hz, 2 H), 4.05–4.01 (m, 1 H), 3.91 (d, *J* = 1.98 Hz, 1 H), 2.57–2.52 (dd, *J* = 5.65, 17.09 Hz, 1 H), 2.46 (dd, *J* = 6.56, 16.94 Hz, 1 H), 1.76–1.73 (m, 2 H), 1.64–1.51 (m, 2 H), 1.37–1.26 (m, 5 H), 0.92 (t, *J* = 7.32 Hz, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.5, 85.7, 74.7, 71.4, 66.5, 61.8, 40.1, 38.0, 27.6, 25.7, 18.9, 17.8, 14.1, 13.9, –4.6, –4.8 ppm. IR (KBr): $\tilde{\nu}$ = 3501, 2930, 2236, 1712, 1252, 1072, 773 cm^{-1}. MS (ESI): *m*/*z* = 343 $[M + H]^+$, 365 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{35}O_4$ 343.2299; found 343.2286.

Ethyl (5*S*,7*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)dec-2-ynoate (3): 2,6-Lutidine (0.2 mL, 1.75 mmol) and (*tert*-butyldimethylsilyl)trifluoromethanesulfonate (0.33 mL, 1.46 mmol) were added to a stirred solution of **11** (0.5 g, 1.46 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to stir for 15 min at 0 °C, and then it was quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/Hexane, 1:99) to give **3** (0.65 g, 97%) as a colourless oil. $[a]_D^{33}$ = +8.33 (*c* = 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.21 (q, *J* = 7.18 Hz, 2 H), 4.0–3.91 (m, 1 H), 3.8–3.72 (m, 1 H), 2.56–2.4 (m, 2 H), 1.74–1.67 (m, 2 H), 1.47–1.25 (m, 7 H), 0.88 (m, 21 H), 0.10–0.06 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.6, 86.4, 69.9, 68.4, 61.6, 45.3, 40.2, 28.4, 25.7, 25.9, 18.3, 17.9, 14.1, 14.0, –3.3, –4.1, –4.2, –4.4 ppm. IR (KBr): $\tilde{\nu}$ = 2924,

2237, 1715, 1465, 1250, 1072, 773 cm^{-1}. MS (ESI): *m*/*z* = 479 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{48}O_4NaSi_2$ 479.2983; found 479.2979.

Ethyl 2-[(2*S*,4*S*)-2,4-Bis(*tert*-butyldimethylsilyloxy)heptyl]-4,6-dimethoxybenzoate (13): A mixture of acetylenic ester **3** (0.20 g, 0.45 mmol), diene **4** (0.19 g, 1.36 mmol), and a catalytic amount of *N*,*N*-dimethylaniline (0.01 g, 0.09 mmol) was heated in a sealed tube at 200 °C for 48 h under an inert atmosphere. After TLC indicated that the reaction was complete, the residue was purified by column chromatography over silica gel (EtOAc/hexane, 1:9) to give compound **13** (0.15 g, 60%) as a colourless oil. $[\alpha]_D^{30}$ = –25.0 (*c* = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.38 (d, *J* = 2.14 Hz, 1 H), 6.32 (d, *J* = 2.14 Hz, 1 H), 4.34 (q, *J* = 7.17 Hz, 2 H), 3.98–3.92 (m, 1 H), 3.78 (d, *J* = 3.81 Hz, 6 H), 3.72–3.68 (m, 1 H), 2.79 (dd, *J* = 5.49, 13.58 Hz, 1 H), 2.63 (dd, *J* = 7.63, 13.58 Hz, 1 H), 1.59 (t, *J* = 6.26 Hz, 3 H), 1.49–1.23 (m, 6 H), 0.90 (t, *J* = 7.02 Hz, 3 H), 0.84 (s, 9 H), 0.82 (s, 9 H), 0.02 (s, 3 H), 0.003 (s, 3 H), –0.03 (s, 3 H), –0.18 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.2, 160.8, 158.0, 138.9, 117.3, 107.4, 96.9, 70.6, 69.8, 60.8, 55.9, 55.2, 46.0, 41.8, 39.8, 25.9, 18.4, 14.2, –4.2, –4.6 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2853, 1726, 1604, 1463, 1330, 1255, 1155, 1099, 834, 774 cm^{-1}. MS (ESI): *m*/*z* = 569 [M + H]$^+$, 591 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{30}H_{56}O_6NaSi_2$ 591.3507; found 591.3487.

(*S*)-3-Hydroxy-3-[(*S*)-2′-hydroxypentyl]-6,8-dimethoxyisochroman-1-one (1b): TBAF (1 M in THF; 1.12 mL, 1.12 mmol) was added to a stirred solution of **13** (0.16 g, 0.28 mmol) in anhydrous THF (10 mL) at 0 °C. The reaction mixture was warmed to room temperature, and stirring was continued for 6 h. After TLC indicated that the reaction was complete, it was quenched by the addition of H_2O (5 mL). The THF was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3× 10 mL). The combined organic layers were washed with brine (15 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica column chromatography (EtOAc/hexane, 80:20) to give lactone **1b** (0.05 g, 90%) as a colourless oil. $[\alpha]_D^{30}$ = –47.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone, 500 MHz): δ = 6.53 (d, *J* = 2.29 Hz, 1 H), 6.47 (d, *J* = 2.29 Hz, 1 H), 4.60–4.55 (m, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.74 (d, *J* = 5.65 Hz, 1 H), 2.92–2.80 (m, 2 H), 1.82 (dd, *J* = 2.29, 9.31 Hz, 1 H), 1.59 (dd, *J* = 3.20, 10.07 Hz, 1 H), 1.53–1.36 (m, 4 H), 0.93 (t, *J* = 7.02 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]acetone, 125 MHz): δ = 166.1, 164.8, 162.7, 146.2, 109.0, 105.9, 99.4, 75.9, 67.9, 57.1, 56.9, 44.6, 42.2, 37.0, 20.4, 15.4 ppm. IR (KBr): $\tilde{\nu}$ = 3423, 2922, 1701, 1603, 1462, 1245, 1161, 1086, 772 cm^{-1}. MS (ESI): *m*/*z* = 295 [M + H]$^+$, 317 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{23}O_5$ 295.1540; found 295.1532.

(*S*)-8-Hydroxy-3-[(*S*)-2′-hydroxypentyl]-6-methoxyisochroman-1-one (1a): A solution of BCl_3 in hexane (1.0 M; 1.36 mL, 1.36 mmol) was added dropwise to a stirred solution of **1b** (0.2 g, 0.68 mmol) in CH_2Cl_2 (80 mL) at –78 °C, and the mixture was stirred for 30 min at the same temperature. NaOH solution (5% aq.) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica column chromatography (EtOAc/hexane, 35:65) to give diol **1a** (0.15 g, 80%) as a colourless oil. $[\alpha]_D^{32}$ = –15.7 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.15 (s, 1 H), 6.33 (d, *J* = 2.0 Hz, 1 H), 6.22 (br. s, 1 H), 4.85–4.79 (m, 1 H), 4.06–4.02 (m, 1 H), 3.82 (s, 3 H), 2.93–2.82 (m, 2 H), 2.03–1.82 (m, 2 H), 1.70–1.65 (m, 1 H), 1.51–1.23 (m, 4 H), 0.95 (t, *J* = 7.01 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.7, 165.7, 164.4, 141.0, 106.1, 101.6, 99.4, 76.2, 66.9, 55.5, 42.2, 40.1, 33.7, 18.6, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3443, 1661, 1628, 1512, 1420, 1161, 672 cm^{-1}. MS (ESI): *m*/*z* = 281 [M + H]$^+$, 298 [M + NH_4]$^+$. HRMS (ESI): calcd. for $C_{15}H_{21}O_5$ 281.1367; found 281.1383.

(*S*)-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)pentyl]oxirane (*syn*-11): A similar procedure to that described for compound *anti*-**11** was followed, except instead of catalyst **A**, *ent*-**A** was used, yield 3.10 g, 90%. $[\alpha]_D^{33}$ = –15.3 (*c* = 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.89–3.82 (m, 1 H), 3.04 (t, *J* = 4.53 Hz, 1 H), 2.44 (dd, *J* = 2.64, 4.91 Hz, 1 H), 1.76–1.55 (m, 2 H), 1.50 (t, *J* = 6.80 Hz, 2 H), 1.44–1.25 (m, 2 H), 0.93–0.89 (m, 12 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 70.1, 49.4, 46.7, 40.1, 39.3, 25.7, 18.6, 14.1, –4.6 ppm. IR (KBr): $\tilde{\nu}$ = 2928, 2855, 1253, 1074, 834, 773 cm^{-1}. MS (ESI): *m*/*z* = 245 [M + H]$^+$, 267 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{28}O_2NaSi$ 267.1750; found 267.1749.

Ethyl (5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxydec-2-ynoate (14): An analogous procedure to that described above for compound **11** was followed, yield 0.20 g, 85%. $[\alpha]_D^{34}$ = +8.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.23 (q, *J* = 7.17 Hz, 2 H), 4.01–3.94 (m, 2 H), 3.6 (d, *J* = 1.83 Hz, 1 H), 2.56 (dd, *J* = 5.50, 17.09 Hz, 1 H), 2.49 (dd, *J* = 6.71, 16.94 Hz, 1 H), 1.83–1.79 (m, 1 H), 1.69–1.59 (m, 2 H), 1.52–1.48 (m, 2 H), 1.30 (t, *J* = 7.17 Hz, 3 H), 1.25 (s, 1 H), 0.93–0.90 (m, 12 H), 0.11 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.5, 85.7, 74.7, 72.8, 68.9, 61.8, 41.5, 40.0, 29.6, 27.4, 25.7, 17.8, 17.7, 14.1, 13.9, –4.7, –4.0 ppm. IR (KBr): $\tilde{\nu}$ = 3501, 2930, 2236, 1712, 1252, 1072, 773 cm^{-1}. MS (ESI): *m*/*z* = 343 [M + H]$^+$, 365 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{18}H_{35}O_4Si$ 343.2299; found 343.2286.

Ethyl (5*R*,7*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)dec-2-ynoate (*epi*-3): A similar procedure to that described above for TBS protection was followed, yield 0.32 g, 97%. $[\alpha]_D^{36}$ = –8.0 (*c* = 1.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.20 (q, *J* = 7.18 Hz, 2 H), 4.0–3.92 (m, 1 H), 3.80–3.72 (m, 1 H), 2.57–2.40 (m, 2 H), 1.72 (t, *J* = 6.23 Hz, 2 H), 1.47–1.25 (m, 4 H), 0.92–0.88 (m, 21 H), 0.09–0.04 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 153.6, 86.5, 74.7, 69.1, 67.6, 61.6, 44.5, 39.3, 27.8, 25.8, 18.3, 17.9, 14.3, 14.0, –4.6 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2237, 1715, 1465, 1250, 1072, 773 cm^{-1}. MS (ESI): *m*/*z* = 479 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{48}O_4NaSi_2$ 479.2983; found 479.2979.

Ethyl 2-[(2*R*,4*S*)-2,4-Bis(*tert*-butyldimethylsilyloxy)heptyl]-4,6-dimethoxybenzoate (*epi*-13): A similar procedure to that described for compound **12** was followed, yield 0.30 g, 60%. $[\alpha]_D^{35}$ = –10.6 (*c* = 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.38 (d, *J* = 2.27 Hz, 1 H), 6.32 (d, *J* = 2.27 Hz, 1 H), 4.34 (q, *J* = 6.80 Hz, 2 H), 4.01–4.92 (m, 1 H), 3.78 (d, *J* = 3.02 Hz, 7 H), 2.81–2.68 (m, 2 H), 1.74–1.41 (m, 2 H), 1.34 (t, *J* = 7.55 Hz, 3 H), 1.29–1.21 (m, 2 H), 0.86 (d, *J* = 6.04 Hz, 21 H), 0.04–0.02 (m, 9 H), –0.15 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.2, 160.7, 157.9, 138.8, 117.5, 107.1, 96.7, 70.1, 69.2, 64.2, 60.9, 55.8, 55.2, 44.8, 42.1, 38.9, 25.8, 25.2, 18.3, 18.0, 17.8, 14.2, –4.3, –4.5, –4.7, –4.8 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2853, 1726, 1604, 1463, 1330, 1255, 1155, 1099, 834, 774 cm^{-1}. MS (ESI): *m*/*z* = 569 [M + H]$^+$, 591 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{30}H_{56}O_6NaSi_2$ 591.3507; found 591.3487.

(*R*)-3,4-Dihydro-3-[(*S*)-2-hydroxypentyl]-6,8-dimethoxyisocoumarin (*epi*-1b): The lactonization procedure described above was followed, yield 0.10 g, 90%. $[\alpha]_D^{33}$ = +48.6 (*c* = 0.35, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 6.54 (d, *J* = 2.08 Hz, 1 H), 6.48 (s, 1 H), 4.60–4.51 (m, 1 H), 3.86 (d, *J* = 8.69 Hz, 6 H), 3.62 (d, 1 H), 3.04–2.82 (m, 2 H), 1.95–1.86 (m, 1 H), 1.82–1.74 (m, 1 H), 1.52–

1.29 (m, 4 H), 0.91 (t, J = 7.18 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]-acetone, 125 MHz): δ = 166.1, 164.9, 162.5, 146.0, 106.0, 99.5, 76.8, 68.9, 57.1, 56.9, 44.0, 41.7, 36.2, 20.4, 15.3 ppm. IR (KBr): $\tilde{\nu}$ = 3423, 2922, 1701, 1603, 1462, 1245, 1161, 1086, 772 cm^{-1}. MS (ESI): m/z = 295 [M + H]$^+$, 317 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{23}O_5$ 295.1540; found 295.1532.

(*R*)-3,4-Dihydro-8-hydroxy-3-[(*S*)-2-hydroxypentyl]-6-methoxyisocoumarin (*epi*-1a): A similar procedure to that described for compound **1a** was followed, yield 0.07 g, 80%. $[\alpha]_D^{32}$ = –15.0 (c = 0.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.17 (s, 1 H), 6.37 (d, J = 2.0 Hz, 1 H), 6.26 (br. s, 1 H), 4.81–4.72 (m, 1 H), 3.96–3.89 (m, 1 H), 3.83 (s, 3 H), 2.96–2.93 (m, 2 H), 2.09–1.99 (m, 2 H), 1.90–1.82 (m, 2 H), 1.58–1.40 (m, 4 H), 0.95 (t, J = 6.99 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.4, 165.8, 164.6, 140.8, 106.3, 101.6, 99.4, 77.8, 68.7, 55.5, 41.9, 39.8, 33.2, 18.6, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3443, 1661, 1628, 1512, 1420, 1161, 672 cm^{-1}. MS (ESI): m/z = 281 [M + H]$^+$, 294 [M + NH_4]$^+$. HRMS (ESI): calcd. for $C_{15}H_{21}O_5$ 281.1367; found 281.1383.

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

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