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Enantioselective synthesis of tarchonanthuslactone using proline-catalyzed asymmetric α-aminooxylation

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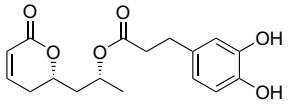
Abstract—A practical enantioselective synthesis of tarchonanthuslactone **1**, an important natural product with a polyol unit, is described. The sequence of synthetic reactions involves proline-catalyzed α-aminooxylation and iodine-induced electrophilic cyclization as the chiral inducing steps.

1. Introduction

Several natural products with 1,3-polyol/5,6-dihydro-2*H*-pyran-2-one structural units have been found to exhibit a wide range of biological activities. For instance, they act as plant growth inhibition as well as antifeedant, antifungal, antibacterial and antitumour agents.[1] Tarchonanthuslactone **1**, one of the members of this group, was isolated[2] from the leaves of *Tarchonanthus tribolus* in 1979 and its absolute configuration was established by synthesis.[4a] Subsequently, Hsu et al. found that **1** lowers the blood plasma level in diabetic rats as an important biological activity.[3] This important structural feature as well as the biological activity of **1** made it an ideal target to develop new asymmetric synthetic methodology for its construction.[4] Most of the methods reported[4] for the asymmetric synthesis of **1** involve the use of stoichiometric or exotic reagents, including toxic metal catalysts or the inherent loss of 50% yield of chiral materials in the case of hydrolytic kinetic resolution strategies. As part of our research efforts aimed at developing the stereocontrolled synthesis of bioactive molecules,[5] we herein report a highly efficient synthesis of tarchonanthuslactone **1**, using proline-catalyzed α-aminooxylation of *n*-butyraldehyde, as well as iodine-induced electrophilic cyclization as the chiral inducing steps (Scheme 2).



Tarchonanthuslactone **1**

2. Results and discussion

Asymmetric organocatalysis in organic chemistry has provided several new methods for obtaining chiral compounds in an environmentally friendly manner.[6] In connection with this, proline, an abundant, inexpensive aminoacid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[7] Proline is equally efficient for α-functionalization[8] of aldehydes and ketones. To demonstrate the synthetic utility of proline-catalyzed α-aminooxylation for the synthesis of natural products, we undertook the synthesis of tarchonanthuslactone **1**. We describe the successful application of α-functionalization of aldehydes using proline followed by diastereoselective iodine-induced electrophilic cyclization.

The retrosynthetic analysis of **1** is outlined in Scheme 1. Evidently, alcohol **2**, the key intermediate, can be obtained from *cis*-olefinic ester **3**. Iodocarbonate **4** is visualized to be prepared from olefin **5** via diastereoselective iodolactonization. The key chiral inducing step in the synthesis involves the proline-catalyzed α-aminooxylation of readily available *n*-butyraldehyde **6**.

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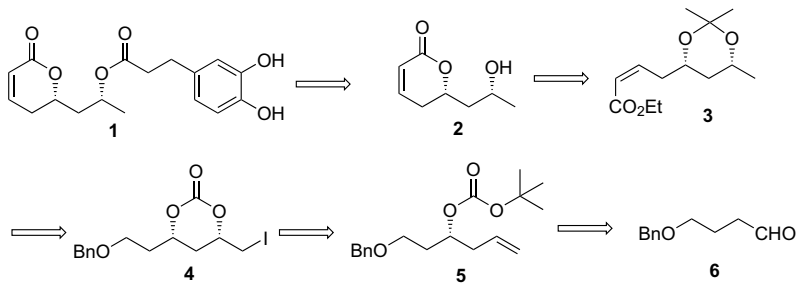
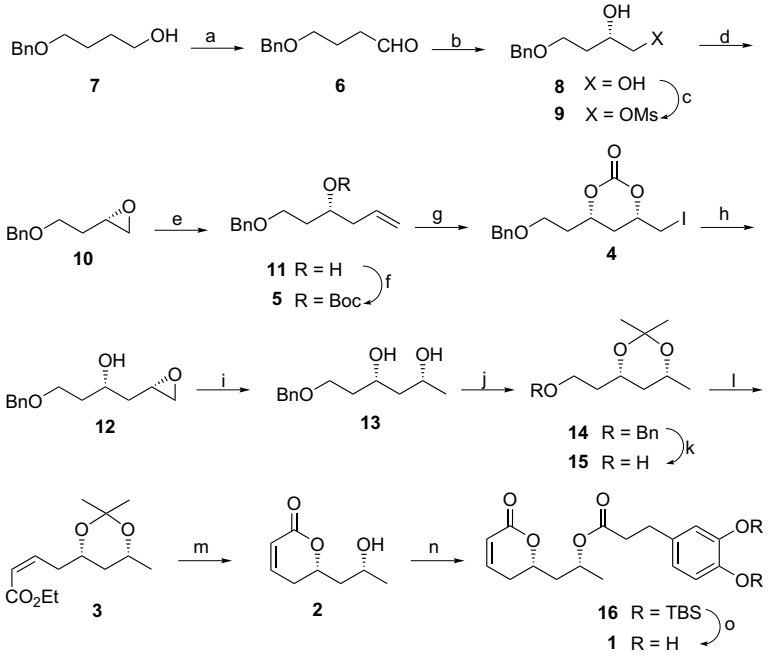


Scheme 1. Retrosynthetic analysis.

The complete synthetic sequences for tarchonanthuslactone **1**, commencing from the monoprotected 1,4-butane diol **7**, is shown in Scheme 2. The primary alcohol function in **7** was oxidized under IBX in DMSO to provide the corresponding precursor aldehyde **6**. The proline-catalyzed α-asymmetric aminooxylation of aldehyde **6** involves a two-step reaction sequence: (i) reaction of aldehyde **6** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at −20 °C[8a] followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol in situ and (ii) subsequent reduction of the crude aminoxy product with 30 mol % $CuSO_4$[9] yielded chiral diol **8** in 86% yield and >95% ee (as determined by ^1H NMR analysis of the corresponding Mosher's ester **17**, see experimental section); $[\alpha]_D^{25} = +5.0$ (*c* 1, $CHCl_3$). Selective mesylation[10] of the primary alcohol in **8** was achieved to afford mesylate **9**, which on treatment with K_2CO_3 in MeOH[10] yielded the terminal epoxide **10**; $[\alpha]_D^{25} = -16.2$ (*c* 3, $CHCl_3$) {lit.[11] $[\alpha]_D^{25} = +16.9$ (*c* 2.51, $CHCl_3$) for its antipode}.

Our next task was to construct the *syn*-1,3-diol moiety from epoxide **10**. In order to achieve this transformation with high diastereoselectivity, the iodine-induced carbonate cyclization methodology, originally published by Bartlett[12a] and later improved upon by Smith,[12b] was undertaken. Thus, epoxide **10** was first treated with vinylmagnesium bromide in the presence of CuI[13] in THF at −40 °C to give homoallylic alcohol **11**. The homoallylic *tert*-butyl carbonate **5**, prepared in high yields from the corresponding alcohol **11** on treatment with di-*tert*-butyldicarbonate in the presence of DMAP[13] in CH_3CN, was subjected to the diastereoselective iodolactonization using *N*-iodosuccinimide[14] in CH_3CN at low temperature (−40 to 0 °C) to furnish the cyclic carbonate derivative **4** in 85% yield as a single diastereomer (as determined by ^1H NMR analysis). Iodocarbonate **4**, upon exposure to basic methanolic solution,[14] gave the desired *syn*-epoxy alcohol **12** in 90% yield. Regioselective reduction of epoxy alcohol **12** using $LiAlH_4$[10] in THF furnished *syn*-1,3-diol **13** in 90% yield,



Scheme 2. Reagents and conditions: (a) IBX, DMSO, rt, 2 h, 95%; (b) (i) PhNO, D-proline (25 mol %), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$; (ii) $CuSO_4$ (30 mol %), MeOH, 0 °C, 10 h, 87% (over two steps); (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 92%; (d) K_2CO_3, MeOH, rt, 1 h, 95%; (e) vinylmagnesium bromide, THF, CuI, −40 °C, 1 h, 92%; (f) $(Boc)_2O$, DMAP, CH_3CN, rt, 5 h, 95%; (g) NIS, CH_3CN, −40 to 0 °C, 12 h, 85%; (h) K_2CO_3, MeOH, 0 °C to rt, 4 h, 90%; (i) $LiAlH_4$, THF, 50 °C, 6 h, 90%; (j) 2,2-dimethoxypropane, camphorsulfonic acid, rt, 4 h, 95%; (k) 10% Pd/C, H_2 (1 atm), MeOH, 12 h, 91%; (l) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (ii) ethyl (di-*o*-tolylphosphono) acetate, NaH, THF, −78 to 0 °C, 1.5 h, 80% (over two steps); (m) pyridinium-*p*-toluene sulfonate, ethanol, 55 °C, 12 h, 75%; (n) TBS-protected dihydrocaffeic acid, DCC, DMAP, CH_2Cl_2, 5 h, 81%; (o) TBAF, $PhCO_2H$, THF, rt, 88%.

which was then protected as its acetonide **14** on treatment with 2,2-dimethoxypropane in the presence of catalytic amounts of camphorsulfonic acid.[15] Deprotection of the benzyl group in **14** under catalytic hydrogenolysis conditions[16] [Pd/C, H_2 (1 atm), MeOH] provided primary alcohol **15** in 91% yield.

At this stage, we turned our attention to the construction of the pyranone functionality of tarchonanthuslactone **1**. To achieve this, we converted alcohol **15** into the corresponding *cis*-enoate **3** as follows: alcohol **15** on Swern oxidation gave the aldehyde in situ which was then subjected to Horner–Wittig–Emmons olefination with ethyl (di-*o*-tolylphosphono) acetate[17] and NaH in THF in order to obtain the *Z*-unsaturated ester **3** (confirmed by ^{1}H NMR analysis) in 80% yield over the two steps. The deprotection of acetonide unit in **3** followed by its cyclization was achieved by treating **3** with pyridinium-*p*-toluene sulfonate (PPTS) in ethanol at 55 °C to give pyranone **2** in 75% yield. Esterification of **15** with TBS-protected dihydrocaffeic acid[4d] provided ester **16** in 85% yield. Finally, desilylation of **16** with tetrabutyl ammonium fluoride (TBAF) and benzoic acid[4d] in THF furnished tarchonanthuslactone **1** in 90% yield. The spectral data of **1** are in complete agreement with the reported values.[4d]

3. Conclusion

An efficient and straightforward enantioselective synthesis of the polyketide natural product tarchonanthuslactone **1** has been described. The initial D-proline-catalyzed α-aminooxylation of aldehydes for the introduction of chirality and the subsequent diastereoselective iodine-induced electrophilic cyclization constitute as key reactions for constructing *syn*-1,3-diol moiety. The synthetic strategy described here has significant potential for the synthesis of a variety of other biologically important substituted 1,3-polyol/5,6-dihydropyran-2-one containing natural products.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV-200, AV-400 and BRX-500 NMR spectrometers, respectively. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer.

4.1.1. 4-(Benzyloxy)butan-1-ol 7. To a solution of 1,4-butane diol (3.6 g, 40 mmol) in anhydrous DMF was slowly added 60% NaH in oil suspension (1.42 g, 44 mmol) followed by the addition of benzyl bromide (5.25 mL, 44 mmol). The reaction mixture was stirred at 25 °C for 4 h, quenched with cold water, extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude material which was then purified by column chromatography on silica gel using petroleum ether/EtOAc (7:3) to give **7** (6.8 g, 95%) as a colourless oil. IR ($CHCl_3$) ν_{max} 3624, 3413, 3017, 2941, 2867, 2401, 1952, 1702, 1496, 1455, 1363, 1216, 1099, 957, 932, 850, 771 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62–1.73 (m, 4H), 2.41 (br s, 1H), 3.50 (t, $J = 5.61$ Hz, 2H), 3.61 (t, $J = 5.73$ Hz, 2H), 4.50 (s, 2H), 7.27–7.33 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.04, 29.28, 61.71, 69.91, 72.54, 127.25, 127.33, 128.02, 137.9. Elemental analysis: $C_{11}H_{16}O_2$ required C, 73.30, H, 8.95. Found: C, 73.01, H, 9.26.

4.1.2. 4-(Benzyloxy)butanal 6. To a solution of alcohol **7** (6.48 g, 36 mmol) in DMSO (100 mL) was slowly added IBX (11.09 g, 39.6 mmol). The reaction mixture was stirred for 2 h at 25 °C followed by quenching with cold water. The reaction mixture was filtered and the filtrate was then extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehyde which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give **6** (6.1 g, 95.3%) as a colourless oil. IR ($CHCl_3$) ν_{max} 3032, 2933, 2864, 1706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (m, 2H), 2.49 (t, $J = 7.08$ Hz, 2H), 3.45 (t, $J = 6.01$ Hz, 2H), 4.43 (s, 2H), 7.26 (m, 5H), 9.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.57, 40.95, 69.13, 72.95, 127.58, 128.36, 128.39, 138.28, 202.17. Elemental analysis: $C_{11}H_{14}O_2$ required C, 74.13, H, 7.92. Found: C, 74.40, H, 7.61.

4.1.3. (+)-(*S*)-4-(Benzyloxy)butane-1,2-diol 8. To a pre-cooled (−20 °C) acetonitrile (50 mL) solution of aldehyde **6** (6.05 g, 34 mmol) and nitrosobenzene (1.82 g, 17 mmol) was added D-proline (0.49 g, 25 mol %). The reaction mixture was allowed to stir at the same temperature for 24 h, followed by the addition of MeOH (20 mL) and $NaBH_4$ (1.94 g, 51 mmol) to the reaction mixture, which was stirred for 10 min. After the addition of the phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly used for the next step without purification.

To a MeOH (50 mL) solution of the crude aminooxyalcohol was added $CuSO_4{\cdot}5H_2O$ (1.28 g, 5.1 mmol) at 0 °C. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 60 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude diol, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give **8** (2.9 g, 87%) as a colourless oil. $[\alpha]_D^{25} = +5.0$ (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3684, 3618, 3470, 3020, 2927, 2400, 2252, 1602, 1521, 1455, 1424, 1216, 1094, 1051, 929, 850, 771, 669 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–1.94 (m, 2H), 2.50 (br s, 2H), 3.45–3.72 (m, 4H), 3.87–3.98 (m, 1H), 4.53 (s, 2H), 7.29–7.37 (m, 5H). ^{13}C NMR

(50 MHz, $CDCl_3$) δ 32.71, 66.14, 67.13, 69.78, 72.74, 127.44, 127.49, 128.17, 137.84. Elemental analysis: $C_{11}H_{16}O_3$ required C, 67.32, H, 8.22. Found: C, 67.64, H, 7.95.

4.1.4. (+)-(*S*)-4-(Benzyloxy)-2-hydroxybutyl methanesulfonate 9. A solution of diol **8** (2.94 g, 15 mmol) in CH_2Cl_2 (50 mL) was treated with methane sulfonyl chloride (1.75 mL, 22.5 mmol) and Et_3N (4.21 mL, 30 mmol) at 0 °C. After being stirred for 15 min, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude mesylate, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give mesylate **9** (3.78 g, 92%) as a colourless oil. $[\alpha]_D^{25} = +0.4$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3407, 3019, 2927, 2400, 1719, 1518, 1454, 1364, 1215, 1176, 1047, 928, 756, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.71–1.75 (m, 2H), 2.94 (s, 3H), 3.16 (br s, 1H), 3.52–3.65 (m, 2H), 3.98–4.07 (m, 2H), 4.11–4.15 (m, 1H), 4.43 (s, 2H), 7.19–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.43, 37.36, 67.59, 68.61, 73.27, 127.68, 127.84, 128.47, 137.64. Elemental analysis: $C_{12}H_{18}O_5S$ required C, 52.54, H, 6.61, S, 11.69. Found: C, 52.25, H, 6.99, S, 11.77.

4.1.5. (−)-(*S*)-4-(Benzyloxy)-1,2-epoxybutane 10. To a solution of mesylate **9** (3.56 g, 13 mmol) in MeOH (50 mL) was added K_2CO_3 (1.79 g, 13 mmol) and the mixture was stirred at 25 °C for 1 h. After the reaction was completed (monitored by TLC), the mixture was evaporated and the residue extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give epoxide **10** (2.2 g, 95%) as a colourless oil. $[\alpha]_D^{25} = -16.2$ (*c* 3, $CHCl_3$) {lit.[11] $[\alpha]_D^{25} = +16.9$ (*c* 2.51, $CHCl_3$) for its antipode}. IR ($CHCl_3$) ν_{max} 3477, 3015, 2925, 2864, 2402, 1725, 1496, 1455, 1362, 1217, 1102, 1028, 910, 831, 766 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.62–1.97 (m, 2H), 2.50 (dd, $J = 2.7$, 5.06 Hz, 1H), 2.76 (dd, $J = 4.06$, 4.94 Hz, 1H), 3.01–3.10 (m, 1H), 3.58–3.64 (m, 2H), 4.52 (s, 2H), 7.29–7.35 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.76, 46.68, 49.68, 66.76, 72.79, 127.32, 128.13, 128.80, 138.11. Elemental analysis: $C_{11}H_{14}O_2$ required C, 74.13, H, 7.92. Found: C, 74.46, H, 7.69.

4.1.6. (+)-(*R*)-6-(Benzyloxy)-1-hexen-4-ol 11. Vinyl bromide (6.44 M in THF, 7.76 mL, 50 mmol) was added slowly to Mg (0.61 g, 25 mmol) in THF (25 mL) at 0 °C and the mixture was stirred for 10 min; then cooled to −40 °C and CuI (0.34 g, 15 mol %) was added. The resulting reaction mixture was stirred for 30 min at −40 °C and a solution of epoxide **10** (2.14 g, 12 mmol) in THF (30 mL) was added. After being stirred for 1 h, the mixture was quenched with saturated NH_4Cl solution, extracted with diethyl ether (3 × 100 mL), washed with brine and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give **11** (2.27 g, 92%) as a colourless oil. $[\alpha]_D^{25} = +1.55$ (*c* 1.1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3469, 3067, 3016, 2918, 2866, 2401, 1952, 1811, 1640, 1496, 1455, 1424, 1363, 1216, 1095, 1027, 921, 769 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.71–1.80 (m, 1H), 1.86–1.94 (m, 1H), 2.16–2.28 (m, 1H), 3.26 (dd, $J = 3.45$, 5.05 Hz, 1H), 3.42 (dd, $J = 2.65$, 5.05 Hz, 1H), 3.57–4.04 (m, 3H), 4.52 (s, 2H), 5.05–5.14 (m, 1H), 5.72–5.93 (m, 1H), 7.27–7.35 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.70, 41.72, 68.38, 69.74, 72.97, 117.28, 127.42, 127.54, 128.22, 134.65, 137.76. Elemental analysis: $C_{13}H_{18}O_2$ required C, 75.69, H, 8.80. Found: C, 75.33, H, 9.01.

4.1.7. *tert*-Butyl (*R*)-1-(benzyloxy)hex-5-en-3-yl carbonate 5. To a solution of alcohol **11** (2.06 g, 15 mmol) in acetonitrile (40 mL) were added $(Boc)_2O$ (3.27 g, 15 mmol) and DMAP (0.48 g, 4 mmol). After stirring for 5 h, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (30 mL) and imidazole (3.34 g, 49 mmol) was added. The resulting mixture was stirred at 25 °C for 15 min and then CH_2Cl_2 was added. The organic phase was washed with 5% HCl solution (3 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **5** (2.75 g, 95%) as a colourless oil. $[\alpha]_D^{25} = +33.3$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3686, 3625, 3019, 2983, 2870, 2401, 1737, 1644, 1455, 1395, 1370, 1280, 1216, 1160, 1093, 926, 770 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.90 (dd, $J = 6.5$, 12.89 Hz, 2H), 2.34–2.41 (m, 2H), 3.53 (t, $J = 6.41$ Hz, 2H), 4.49 (s, 2H), 4.83–4.96 (m, 1H), 5.04–5.15 (m, 2H), 5.69–5.86 (m, 1H), 7.28–7.35 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.60, 33.70, 38.77, 66.30, 72.89, 73.66, 81.43, 117.78, 127.35, 127.45, 128.16, 133.20, 138.20, 153.05. Elemental analysis: $C_{18}H_{26}O_4$ required C, 70.56, H, 8.55. Found: C, 70.89, H, 8.29.

4.1.8. (−)-(4*S*,6*S*)-4-[2-(Benzyloxy)ethyl]-6-(iodomethyl)-1,3-dioxan-2-one 4. To a stirred solution of **5** (2.76 g, 9 mmol) in acetonitrile (60 mL) was added *N*-iodosuccinimide (4.05 g, 18 mmol) at −40 °C. The mixture was then warmed up and stirred at 0 °C for 12 h. After the reaction was completed (monitored by TLC), 50 mL aqueous sodium thiosulfate solution was added, followed by 50 mL of aq $NaHCO_3$. The reaction mixture was then extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (7:3) to give **4** (2.87 g, 85%) as a colourless oil. $[\alpha]_D^{25} = -3.1$ (*c* 1.3, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3019, 2400, 1751, 1523, 1399, 1216, 1104, 988, 770, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.65–1.76 (m, 1H), 1.92–2.04 (m, 2H), 2.40 (dt, $J = 3.03$, 14.36 Hz, 1H), 3.25 (dd, $J = 7.37$, 10.53 Hz, 1H), 3.38 (dd, $J = 4.42$, 10.52 Hz, 1H), 3.59–3.64 (m, 1H), 3.67–3.73 (m, 1H), 4.39–4.45 (m, 1H), 4.47–4.55 (m, 2H), 4.64–4.71 (m, 1H), 7.28–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.95, 32.96, 34.87, 64.71, 72.79, 75.48, 76.68, 127.40, 127.44, 128.13, 137.67, 148.09. Elemental analysis: $C_{14}H_{17}IO_4$ required C, 44.70, H, 4.55, I, 33.73. Found: C, 44.45, H, 4.77, I, 33.65.

4.1.9. (+)-(2*S*,4*S*)-6-(Benzyloxy)-1,2-epoxyhexan-4-ol 12. To a stirred solution of **4** (2.6 g, 7 mmol) in MeOH (50 mL) was added K_2CO_3 (4.83 g, 35 mmol) at 0 °C. The mixture was then warmed up and stirred at 25 °C. After the reaction was completed (monitored by TLC), 50 mL aq $NaHCO_3$ was added and the reaction mixture was then extracted with EtOAc (3 × 60 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (6:4) to give **12** (1.39 g, 89.7%) as a colourless oil. $[\alpha]_D^{25} = +8.0$ (*c* 1.25, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3682, 3491, 3019, 2922, 2400, 2258, 1733, 1479, 1455, 1424, 1362, 1216, 1093, 927, 770, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.59–1.88 (m, 4H), 2.48 (dd, $J = 2.64$, 5.06 Hz, 1H), 2.75 (dd, $J = 4.22$, 4.96 Hz, 1H), 3.04–3.15 (m, 2H), 3.59–3.78 (m, 2H), 3.99–4.11 (m, 1H), 4.52 (m, 2H), 7.26–7.35 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.34, 39.70, 46.31, 49.70, 68.41, 68.82, 73.11, 127.49, 127.58, 128.28, 137.78. Elemental analysis: $C_{13}H_{18}O_3$ required C, 70.24, H, 8.16. Found: C, 70.59, H, 7.89.

4.1.10. (+)-(2*R*,4*S*)-6-(Benzyloxy)hexane-2,4-diol 13. A solution of epoxy alcohol **12** (1.33 g, 6 mmol) in THF (30 mL) was added to a stirred slurry of $LiAlH_4$ (0.47 g, 12 mmol). After being stirred for 6 h at 50 °C, the reaction was carefully quenched with water. The reaction mixture was then extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (5:5) to give diol **13** (1.2 g, 89.6%) as a colourless oil. $[\alpha]_D^{25} = +3.0$ (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3616, 3461, 3019, 2934, 2400, 1519, 1454, 1378, 1215, 1095, 930, 758, 668 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (d, $J = 6.53$ Hz, 3H), 1.54 (t, $J = 3.62$ Hz, 2H), 1.71–1.88 (m, 2H), 2.99 (br s, 2H), 3.62–3.78 (m, 2H), 4.01–4.15 (m, 2H), 4.52 (s, 2H), 7.29–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.66, 36.94, 44.58, 68.31, 71.71, 73.13, 127.57, 127.64, 128.33, 137.72. Elemental analysis: $C_{13}H_{20}O_3$ required C, 69.61, H, 8.99. Found: C, 69.99, H, 7.54.

4.1.11. (+)-(4*S*,6*R*)-4-[2-(Benzyloxy)ethyl]-2,2,6-trimethyl-1,3-dioxane 14. To a solution of diol **13** (0.68 g, 3 mmol) in 2,2-dimethoxypropane (6 mL) was added camphorsulfonic acid (69 mg, 0.3 mmol) and the reaction mixture was stirred at 25 °C for 4 h. The organic layer was concentrated under reduced pressure to afford the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **14** (0.75 g, 94.9%) as a colourless oil. $[\alpha]_D^{25} = +4.0$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3610, 3019, 2400, 1716, 1646, 1523, 1456, 1381, 1215, 1097, 929, 758, 669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, $J = 5.89$ Hz, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 1.53–1.64 (m, 1H), 1.69–1.77 (m, 3H), 3.50–3.60 (m, 2H), 3.92–4.01 (m, 2H), 4.48 (s, 2H), 7.25–7.34 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.92, 22.30, 30.34, 36.61, 38.89, 65.11, 65.95, 66.18, 73.00, 98.41, 127.54, 127.63, 128.35, 138.56. Elemental analysis: $C_{16}H_{24}O_3$ required C, 72.69, H, 9.15. Found: C, 73.01, H, 7.21.

4.1.12. (−)-(4*S*,6*R*)-2-(2,2,6-Trimethyl-1,3-dioxan-4-yl)ethanol 15. To a solution of **14** (0.53 g, 2 mmol) in MeOH (20 mL) was added a catalytic amount of 10% Pd/C and the resulting heterogeneous mixture was stirred for 12 h at 25 °C. The reaction mixture was then filtered through a pad of Celite and the solvent removed under reduced pressure to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (5:5) to give **15** (0.32 g, 91%) as a colourless oil. $[\alpha]_D^{25} = -15$ (*c* 0.4, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3502, 3054, 2930, 2103, 1734, 1541, 1427, 1382, 1265, 1201, 1111, 1051, 951, 866, 739 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.13–1.23 (m, 4H), 1.37 (s, 3H), 1.44 (s, 3H), 1.53–1.74 (m, 3H), 3.05 (br s, 1H), 3.71–3.81 (m, 2H), 3.96–4.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.81, 22.08, 30.87, 38.38, 44.66, 60.76, 65.03, 69.21, 98.56. Elemental analysis: $C_9H_{18}O_3$ required C, 62.04, H, 10.41. Found: C, 62.36, H, 10.12.

4.1.13. (−)-(5*S*,7*R*,2*Z*)-Ethyl-5,7-(isopropylidenedioxy)octenoate 3. To a precooled (−78 °C) solution of $(COCl)_2$ (0.11 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.17 mL, 2.4 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at −78 °C for 15 min, then alcohol **15** (0.1 g, 0.6 mmol) was added. The reaction mixture was stirred for 40 min at −78 °C followed by the addition of Et_3N (0.5 mL, 3.6 mmol). The mixture was allowed to warm to 0 °C. After 30 min, the reaction was diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehydes, which were immediately used in the next step.

A solution of ethyl (di-*o*-tolylphosphono)acetate (0.23 g, 0.66 mmol) in THF (5 mL) was treated with NaH (17 mg, 0.72 mmol) at −78 °C for 15 min. To the above mixture was added a freshly prepared aldehyde in THF (3 mL) and the resulting mixture was stirred at −78 °C. After TLC showed completion of the starting material, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 20 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **3** (0.12 g, 80%) as a colourless oil. $[\alpha]_D^{25} = -23.5$ (*c* 0.17, $CHCl_3$). IR ($CHCl_3$) ν_{max} 2995, 2940, 2401, 1713, 1645, 1417, 1381, 1216, 1185, 1035, 995, 826, 755, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, $J = 6.09$ Hz, 3H), 1.29 (t, $J = 7.31$ Hz, 3H), 1.36 (d, $J = 1.49$ Hz, 1H), 1.40 (s, 3H), 1.44 (s, 3H), 1.50 (dt, $J = 2.49$, 13.05 Hz, 1H), 2.69–2.77 (m, 1H), 2.88–2.96 (m, 1H), 3.92–4.02 (m, 2H), 4.17 (q, $J = 7.29$ Hz, 2H), 5.85 (dt, $J = 1.54$, 11.49 Hz, 1H), 6.35 (dt, $J = 7.25$, 11.46 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.26, 19.83, 22.16, 30.23, 35.50, 38.27, 59.86, 65.05, 68.41, 98.56, 121.06, 145.82, 166.37. Elemental analysis: $C_{13}H_{22}O_4$ required C, 64.44, H, 9.15. Found: C, 64.11, H, 9.39.

4.1.14. (−)-(5*S*,7*R*)-7-Hydroxy-5-(oct-2-enolide) 2. To a solution of **3** (0.11 g, 0.45 mmol) in EtOH (5 mL) was added pyridinium-*p*-toluene sulfonate (10 mg, 10 mol %) and stirred for 12 h at 55 °C. The solvent was then evapo-

rated and the residue extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (5:5) to give **2** (49 mg, 75%) as a colourless oil. $[\alpha]_D^{25} = -108$ (*c* 0.13, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3550, 2958, 1718, 1472, 1380, 1255, 1216 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, $J = 6.28$ Hz, 3H), 1.71 (br s, 1H), 1.74–1.79 (m, 1H), 2.01 (dt, $J = 8.07$, 14.4 Hz, 1H), 2.38–2.41 (m, 2H), 4.06–4.12 (m, 1H), 4.60–4.67 (m, 1H), 6.02 (dt, $J = 1.73$, 9.81 Hz, 1H), 6.88 (dt, $J = 4.3$, 8.52 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.76, 29.53, 43.58, 65.36, 76.85, 121.30, 145.12, 163.91. Elemental analysis: $C_8H_{12}O_3$ required C, 61.52, H, 7.74. Found: C, 61.85, H, 7.43.

4.1.15. TBS-protected tarchonanthuslactone 16. To a solution of alcohol **2** (47 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added TBS-protected hydrocaffeic acid (0.14 g, 0.33 mmol), dicyclohexylcarbodiimide (77 mg, 0.33 mmol) and DMAP (16 mg, 0.13 mmol). The reaction mixture was stirred for 3 h. Ether was added to the solution, and the mixture filtered through a pad of Celite. Removal of solvent under reduced pressure provided the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give **16** (0.13 g, 81%) as a colourless oil. $[\alpha]_D^{25} = -44$ (*c* 1.2, $CHCl_3$). IR ($CHCl_3$) ν_{max} 1723, 1505, 1255, 900, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.19 (s, 6H), 0.98 (s, 9H), 0.99 (s, 9H), 1.26 (d, $J = 6.5$ Hz, 3H), 1.78–1.85 (m, 1H), 2.13–2.29 (m, 1H), 2.30–2.35 (m, 2H), 2.52–2.60 (m, 2H), 2.78–2.86 (m, 2H), 4.36–4.50 (m, 1H), 5.06–5.15 (m, 1H), 6.01 (d, $J = 9.5$ Hz, 1H), 6.61–6.85 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.23, 18.28, 20.14, 25.82, 28.98, 30.10, 36.09, 40.66, 67.00, 74.79, 120.77, 120.94, 121.02, 121.19, 133.31, 144.75, 145.07, 146.48, 163.88, 172.36. Elemental analysis: $C_{29}H_{48}O_6Si_2$ required C, 63.46, H, 8.81, Si, 10.23. Found: C, 63.74, H, 8.60, Si, 10.01.

4.1.16. Tarchonanthuslactone 1. Benzoic acid (40 mg, 0.33 mmol) was added to a solution of TBS-protected tarchonanthuslactone **16** (59 mg, 0.11 mmol) in THF (2 mL). A 1.0 M solution of TBAF in THF (0.25 mL) was added to the solution. The mixture was stirred at 25 °C for 2 h. The solvent was evaporated and the residue extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give **1** (30 mg, 88%) as a colourless oil. $[\alpha]_D^{25} = -76$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3412, 1720, 1600, 1520, 1445, 1380, 1260, 1010 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, $J = 5.78$ Hz, 3H), 1.70–1.75 (m, 1H), 2.0–2.10 (m, 1H), 2.15–2.30 (m, 2H) 2.58 (t, $J = 6.6$ Hz, 2H), 2.80 (t, $J = 6.61$ Hz, 2H), 4.13–4.18 (m, 1H), 5.04–5.12 (m, 1H), 5.98 (d, $J = 9.42$ Hz, 1H), 6.55 (d, $J = 7.17$ Hz, 1H), 6.67–6.83 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.36, 28.94, 30.14, 35.94, 40.78, 67.19, 75.24, 115.39, 120.26, 120.74, 132.60, 142.40, 143.97, 145.78, 165.28, 172.96. Elemental analysis: $C_{17}H_{20}O_6$ required C, 63.74, H, 6.29. Found: C, 63.41, H, 6.52.

4.1.17. Preparation of Mosher's ester of (+)-(*S*)-4-(benzyloxy)butane-1,2-diol 17. A two-neck 10 mL flask equipped with septum was charged with (49 mg, 0.24 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), a catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under an argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of diol **8** (40 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. This was allowed to stir for an additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (51 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for an additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give Mosher's ester **17** (47 mg, 75%) as a thick syrup. $[\alpha]_D^{25} = +36$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3484, 3019, 2856, 2401, 1749, 1496, 1453, 1363, 1266, 1216, 1171, 1106, 1021, 928, 759, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.80 (m, 2H), 2.88 (br s, 1H), 3.56 (s, 3H), 3.60–3.71 (m, 2H), 4.08–4.14 (m, 1H), 4.26–4.35 (m, 2H), 4.50 (s, 2H), 7.29–7.40 (m, 8H), 7.53–7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.76, 55.47, 67.87, 68.56, 69.50, 73.34, 84.58, 127.38, 127.69, 127.84, 128.43, 128.49, 129.66, 132.17, 137.72, 166.49. Elemental analysis: $C_{21}H_{23}F_3O_5$ required C, 61.16, H, 5.62, F, 13.82. Found: C, 61.49, H, 5.43, F, 13.60.

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