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Synthesis and Absolute Configurations of Six Natural Phenylpropanoids

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In an effort to find answers to the tantalizing questions about the absolute configurations of a group of long-known natural phenylpropanoids with very similar structures but different signs for the optical rotations, the compounds in question were synthesized in enantiomerically pure form using Evans asymmetric alkylation to generate the stereogenic centres with predefined absolute configurations. The ^{1}H and ^{13}C NMR spectra of the synthetic products were very consistent with those reported for their natural counterparts. In most cases, the optical rotations were also consistent with the corresponding data for the natural samples. The new findings not only allowed unequivocal assignments of the absolute configurations for the natural products, but also revealed that the configurations of closely related compounds from the same plant may be different.

Introduction

Natural phenylpropanoids **1**–**6** (Figure 1) were obtained from the plants *Aralia bipinnata* (**1**–**3**[1]), *Xanthoxylum nitidum* (**4**[2]), *Flindersia australis* (**5**[1b]), and *Fagara zanthoxyloides* (**5** and **6**[3]), respectively. Although their molecular architectures are by no means complex, for unspecified reasons their absolute configurations were not determined in the original studies, creating tantalizing questions for those who wish to gain complete structural information about these compounds. And judging by the time already elapsed since the isolation of these compounds (10–20 years), it seems that the situation will remain unchanged unless a synthetic study is carried out. Therefore, we synthesized compounds **1**–**6** in enantiopure form(s), which allowed unambiguous assignments of the absolute configurations of their natural counterparts. In this paper, we describe the details of this endeavour.

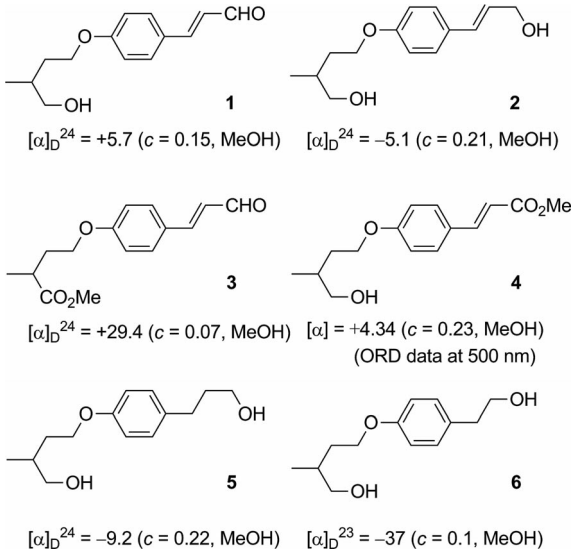

Figure 1. The planar structures for **1**–**6** provided in the literature along with corresponding literature optical rotation measurements for the natural samples.

Results and Discussion

Our synthesis began with the alkylation of *p*-hydroxybenzaldehyde (**7**) with ethyl 4-bromobutanoate in the presence of K_2CO_3 to give the intermediate ester (Scheme 1), which was directly hydrolysed with NaOH to give acid **8**[4] in 99% overall yield. Chiral oxazolidinone auxiliary **9**[5] was then introduced with the aid of EDCI. The unprotected aldehyde group survived all these steps without causing any adverse effects.

The chain extension from the aldehyde group in **10** was achieved using a Wittig reaction with either $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCO_2Me$. The (*E*)/(*Z*) ratio was ca. 94:6, and the (*E*) and (*Z*) isomers were separable from each other on silica gel in each case. The key enantioselective alkylation was then performed on the isolated pure (*E*) isomers under the widely used conditions introduced by Evans[6] et al. in the early 1980s. Thus, using NaN(SiMe$_3$)$_2$ (NaHMDS) as the base, deprotonation of **11a** or **11b** in THF at –78 °C followed by treatment with MeI pro-

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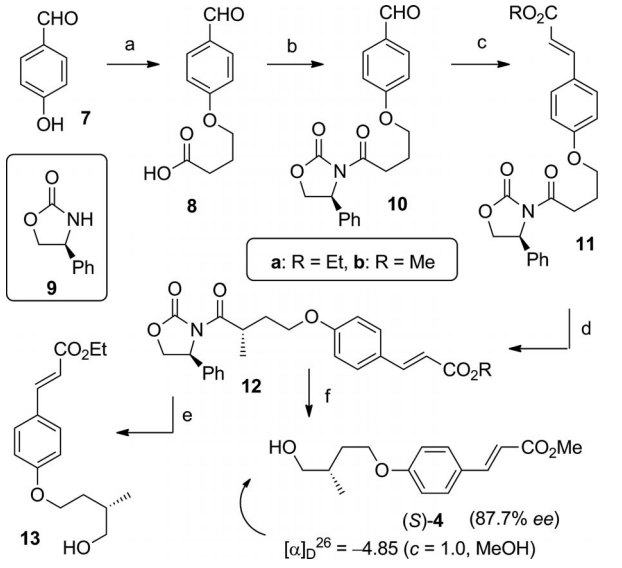
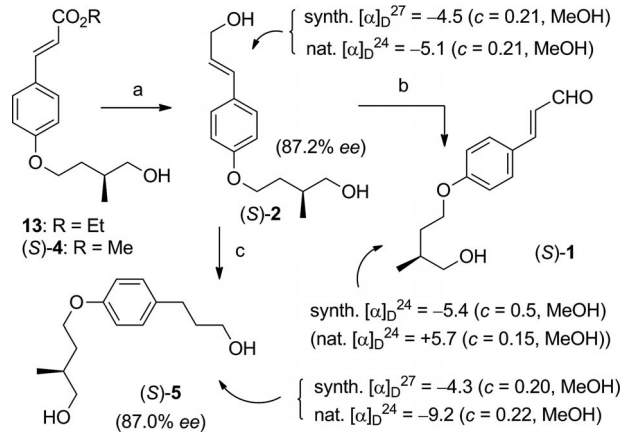


Scheme 1. Reagents and conditions: a) (i) $Br(CH_2)_3CO_2Et$, K_2CO_3, DMF, room temp., 12 h; (ii) NaOH, H_2O, 99%; b) **9**, EDCI, CH_2Cl_2, DMAP, room temp., 14 h, 78%; c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, room temp., 23 h, 82% for **11a** [(*E*)/(*Z*) = 94:6], or $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, room temp., 20 h, 79% for **11b** [(*E*)/(*Z*) = 96:4]; d) $NaN(SiMe_3)_2$, THF, MeI, –78 °C to room temp. 56% for **12a**, 46% for **12b**; e) $NaBH_4$, THF/H_2O, room temp., 12 h, 87% **13**; f) $NaBH_4$, THF/H_2O, room temp., 18 h, 90% for (*S*)-**4**; EDCI = *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.



Scheme 2. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, then to room temp. 5 h, 83% from **13** or 98% from (*S*)-**4**; b) MnO_2, CH_2Cl_2, room temp., 20 h, 80%; c) H_2 (1 atm), Pd-C, EtOH, room temp., 12 h, 96%; DIBAL-H = diisobutylaluminum hydride.

vided the desired product (i.e., **12a** or **12b**) in 56 or 46% yield, respectively, as an inseparable mixture of diastereomers [presumably with *de* = 87.7%, as deduced later from the *ee* value of (*S*)-**4**]. It is interesting to note that the ester and the conjugate alkene functionalities did not cause any serious problems in this carbanion-mediated alkylation.

Compounds **12a** and **12b** were next separately treated with $NaBH_4$ in THF/H_2O[7] to remove the chiral auxiliary, which gave **13** and (*S*)-**4** (87.7% *ee* by chiral HPLC) in 87 and 90% yields, respectively. Because the optical rotation of (*S*)-**4** is opposite to that of natural **4**, the configuration of the latter is expected to be (*R*) (vide infra).

Reduction (Scheme 2) of the ester group in **13** or (*S*)-**4** with DIBAL-H led to (*S*)-**2** (87.2% *ee* by chiral HPLC), whose ^1H and ^{13}C NMR spectra and optical rotation were consistent with those reported for natural **2**. The absolute configuration of natural **2** thus can be reliably assigned as (*S*).

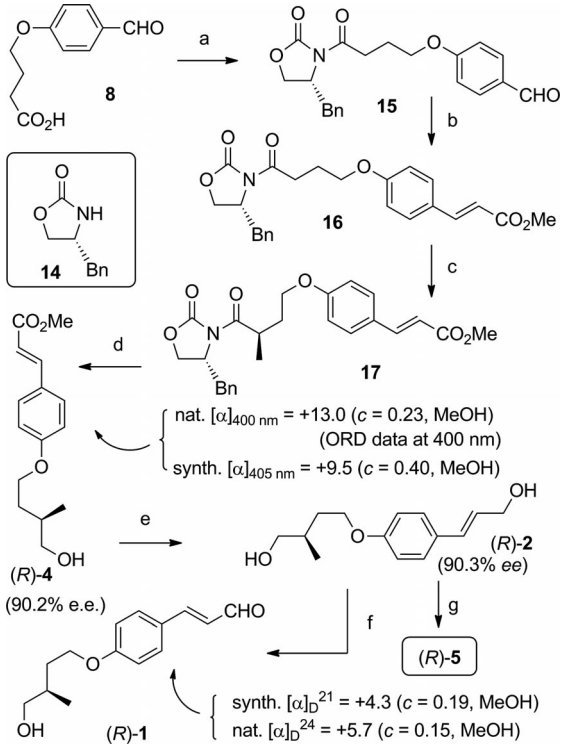
Selective oxidation of the allylic alcohol in (*S*)-**2** with MnO_2[8] gave the corresponding aldehyde [i.e., (*S*)-**1**]. Because natural **1** and **2** were isolated from the same plant at the same time, one would well expect that these two compounds had the same absolute configuration. However, very interestingly, this aldehyde turned out to be the antipode of natural **1**, as shown by the opposite sign of its optical rotation. Thus, the opposite signs of the optical rotations of natural **1** and **2** are not a result of the electron-withdrawing nature of the aldehyde group (in **1**) compared with the related alcohol (in **2**).

Hydrogenation of (*S*)-**2** over Pd-C (10%) delivered (*S*)-**5**, whose ^1H and ^{13}C NMR spectra were identical with those reported for natural **5**. The optical rotation was also consistent with that of the natural product, confirming the absolute configuration of natural **5** as (*S*).

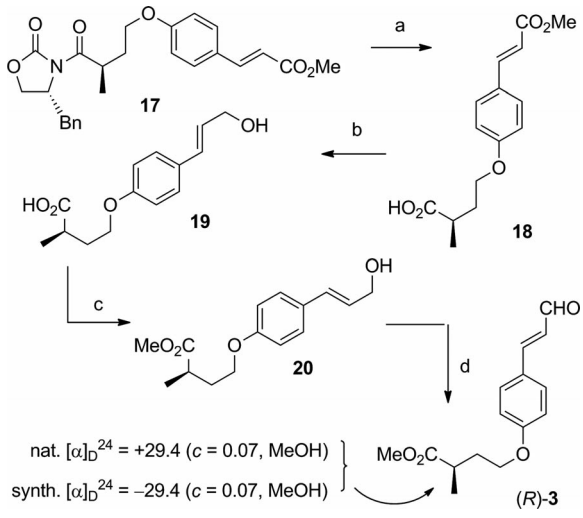
To access (*R*)-**1**, the natural enantiomer, we next carried out the synthesis shown in Scheme 3. Using EDCI[9] as the condensing agent, acid **8** was connected to chiral auxiliary **14**[5] to give **15**. Asymmetric alkylation was then performed similarly to the alkylation of **11** to give **12**, as mentioned above. This gave **17** in 84% yield [as an inseparable mixture of diastereomers, presumably with *de* = 90.2%, as deduced from the *ee* value of (*R*)-**4**]. Reductive removal of the chiral auxiliary with $NaBH_4$/THF/H_2O gave (*R*)-**4**, whose ^1H and ^{13}C NMR spectra and optical rotation sign were consistent with those reported for natural **4**. This confirmed the (*R*) configuration of natural **4**. Upon further reduction of (*R*)-**4** with DIBAL-H, (*R*)-**1** was obtained, whose ^1H and ^{13}C NMR spectra and optical rotation were consistent with those reported for natural **1**. This proved that the absolute configuration of natural **1** is (*R*).

(*R*)-**3** was synthesized as shown in Scheme 4. Instead of reduction with $NaBH_4$, as in the synthesis of **1**, **4**, and **5** shown above, the chiral auxiliary was removed from the substrate by perhydrolysis under the H_2O_2/LiOH[10] conditions introduced by Evans. The resulting acid (i.e., **18**) was then treated with DIBAL-H to selectively reduce the ester group to an alcohol. The carboxylic group was readily converted into its methyl ester by exposure to Me_3SiCHN_2.[11] The final transformation of allylic acohol **20** into end product (*R*)-**3** was achieved by oxidation with MnO_2. Unfortunately, this time we obtained the antipode of the natural product, as the sign of the optical rotation clearly showed.

Using the same sequence but with **12b** instead of **17** as the starting material, as shown in Scheme 5, natural enantiomer (*S*)-**3** was obtained, which confirmed that natural **3** does indeed have an (*S*) configuration.

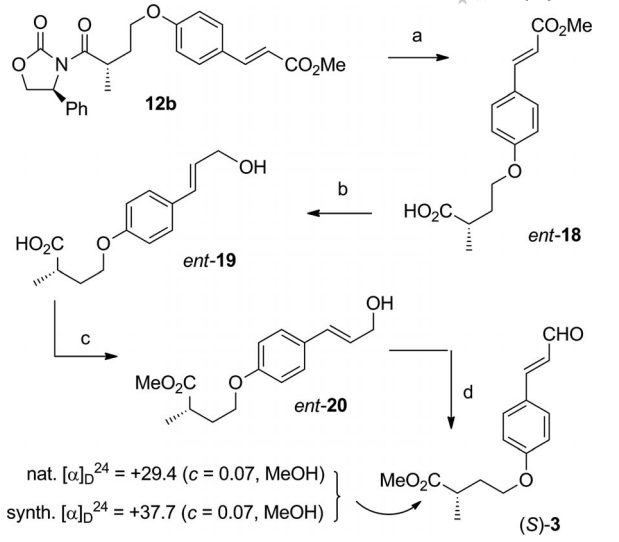


Scheme 3. Reagents and conditions: a) **14**, EDCI, CH_2Cl_2, DMAP, room temp., 13 h, 90%; b) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, room temp., 14 h, 82% (*E*)/(*Z*) = 96:4; c) $NaN(SiMe_3)_2$, THF, MeI, –78 °C to room temp. 84% for **17**; d) $NaBH_4$, THF/H_2O, room temp., 13 h, 96%; e) DIBAL-H, CH_2Cl_2, –78 °C, 3 h, then r.t. 4 h, 73% [along with 24% of recovered (*R*)-**4**]; f) MnO_2, CH_2Cl_2, room temp., 20 h, 84%; g) H_2 (1 atm), Pd-C, EtOH, room temp., 3 h, 100%; DIBAL-H = diisobutylaluminum hydride.

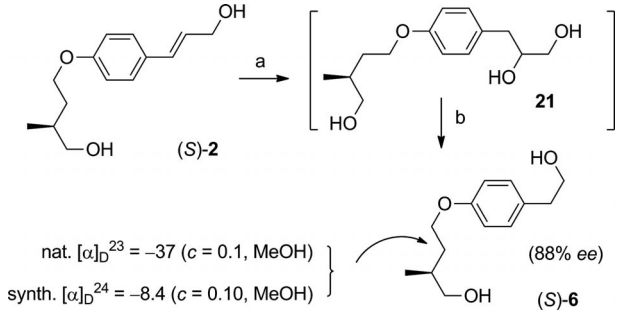


Scheme 4. Reagents and conditions: a) LiOH, H_2O_2, THF/H_2O, room temp., 1.5 h, 96%; b) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, then r.t. 12 h, 48% (along with 47% recovered **18**); c) Me_3SiCHN_2, Et_2O/MeOH, 0 °C, 20 min, 96%; d) MnO_2, CH_2Cl_2, room temp., 40 h, 74%.

To gain access to diol **6**, the (*S*)-**2** synthesized in Scheme 6 was treated with BH_3, followed by oxidation with H_2O_2 in the presence of NaOH. The reaction gave the desired triol (i.e., **21**) in 23% yield, along with an unidentified compound as the major product. The newly formed vicinal diol functionality was then oxidatively cleaved with $NaIO_4$. The intermediate aldehyde was reduced immediately with $NaBH_4$ to give the end product, diol **6**. As the ^1H and ^{13}C NMR spectra of this compound were fully consistent with those reported for natural **6**, and the signs for the optical rotations were negative in both cases, natural **6** must have an (*S*) configuration.



Scheme 5. Reagents and conditions: a) LiOH, H_2O_2, THF/H_2O, room temp., 3 h, 89% b) DIBAL-H, CH_2Cl_2, –78 °C, 3.5 h, then r.t. 12 h, 83%; c) Me_3SiCHN_2, Et_2O/MeOH, 0 °C, 5 min, 92%; d) MnO_2, CH_2Cl_2, room temp., 40 h, 86%.



Scheme 6. Reagents and conditions: a) (i) $BH_3{\cdot}Me_2S$, THF, room temp., 9 h; (ii) H_2O_2, NaOH, 23% from (*S*)-**2**; b) (i) $NaIO_4$, EtOH/H_2O, room temp., 20 min; (ii) $NaBH_4$, EtOH/H_2O, room temp., 10 min, 57% from **21**.

The large discrepancy between the absolute values of the optical rotations for natural and synthetic **6** may deserve a few more words here. To exclude potential errors due to low sample concentrations, which have been observed[12] with some other diols, we took advantage of the quantities ample (compared with the natural products) of the synthetic samples, and measured the optical rotations at a range of concentrations (see Supporting Information). In the case of (*S*)-**6**, the data measured at concentrations ranging from *c* = 0.10 to 0.60 all fell into the –6.6 to –8.4 region, which by no means could come close to –37. These self-consistent

data, along with the enantiopurity of the synthetic sample (88% *ee*), argue convincingly for their reliability. Indeed, judging from the close structural relationship between **6** and **5**, there is no reason to expect that the optical rotation of **6** should be very different from that of **5**.

Conclusions

Using Evans asymmetric alkylation to create the stereogenic centres in the substrates, phenylpropanoids **1**–**6** were synthesized in enantiopure form(s). The chiral-auxiliary-induced asymmetric alkylation was examined for the first time in the presence of potentially interfering functionalities (to the best of our knowledge). The synthetic samples with reliable absolute configurations and known optical purities helped us to assign the absolute configurations of their natural counterparts on an unequivocal basis. Thus, the tantalizing questions about the absolute configurations of these natural products raised by the incomplete structural assignments in the literature years ago are solved (at least for **1**–**3**, **5**, and **6**). This set of compounds is the first with this particular type of stereogenic centres with known configurations and optical rotations, and thus these compounds may potentially serve as references (not available to date) for other related compounds. It is also interesting to note that, for instance, natural **1** and **2** have opposite configurations, despite their common biological origin. Such unexpected structural knowledge might be explained by the study of e.g., biosynthetic pathways and related enzymology.

Experimental Section

General Methods: NMR spectra were recorded with a Bruker Avance NMR spectrometer operating at 400 MHz for ^{1}H, unless otherwise stated. IR spectra were measured with a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired with a Shimadzu LCMS-2010EV mass spectrometer. ESI-HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FTMS spectrometer. EI-MS spectra were recorded with an Agilent Technologies 5973N spectrometer. EI-HRMS data were acquired with a Waters Micromass GCT Premier instrument. Optical rotations were measured with a Jasco P-1030 polarimeter [except for those values for (*R*)-**4** measured at the less common wavelengths, which were measured with a Rudolph Autopol VI polarimeter]. Melting points were measured with a hot-stage melting point apparatus equipped with a microscope. Dry THF was distilled from Na/Ph_2CO under argon before use. Dry toluene and CH_2Cl_2 were dried with activated 4 Å MS (molecular sieves). All reagents were reagent grade, and were used as supplied. Column chromatography was performed on silica gel (300–400 mesh) under a slightly positive pressure. PE (chromatography solvent) stands for petroleum ether (b.p. 60–90 °C).

Condensation of 8 with 9 To Give 10: A mixture of acid **8** (500 mg, 2.40 mmol), chiral auxiliary **9** (430 mg, 2.64 mmol), EDCI (690 mg, 3.60 mmol), and DMAP (59 mg, 0.48 mmol) in dry CH_2Cl_2 (10 mL) was stirred at ambient temperature for 14 h. When TLC showed that the reaction was complete, the mixture was concentrated on a rotary evaporator. EtOAc was added to the residue, the mixture was washed with water and brine, and the organic phase was dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave **10** (664 mg, 1.88 mmol, 78% from **8**) as a colourless oil. Data for **10**: M.p. 70–72 °C. $[\alpha]_D^{26}$ = +44.0 (*c* = 1.00, $CHCl_3$); $[\alpha]_D^{27}$ = +44.5 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 1 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 7.40–7.33 (m, 3 H), 7.32–7.28 (m, 2 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 5.44 (dd, *J* = 8.9, 3.7 Hz, 1 H), 4.70 (t, *J* = 8.9 Hz, 1 H), 4.30 (dd, *J* = 9.0, 3.7 Hz, 1 H), 4.06 (t, *J* = 6.0 Hz, 2 H), 3.20 (dt, *J* = 18.1, 7.2 Hz, 1 H), 3.14 (dt, *J* = 18.1, 7.0 Hz, 1 H), 2.14 (quint, *J* = 6.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 171.9, 163.8, 153.7, 138.9, 131.9, 129.9, 129.2, 128.7, 125.8, 114.7, 70.0, 66.9, 57.5, 31.9, 23.4 ppm. FTIR (film of a conc. solution in CH_2Cl_2): $\tilde{\nu}$ = 2924, 2854, 2739, 1779, 1688, 1599, 1577, 1509, 1470, 1456, 1384, 1314, 1257, 1212, 1159, 1112, 1080, 1042, 833, 701 cm^{-1}. ESI-MS: *m*/*z* = 354.4 [M + H]$^+$. ESI-HRMS: calcd. for $C_{20}H_{19}NO_5Na$ [M + Na]$^+$ 376.1155; found 376.1168.

Wittig Reaction of 10 To Give 11a: A mixture of **10** (152 mg, 0.43 mmol) and $Ph_3P{=}CHCO_2Et$ (150 mg, 0.43 mmol) in dry CH_2Cl_2 (10 mL) was stirred at ambient temperature for 14 h. Another portion of $Ph_3P{=}CHCO_2Et$ (75 mg, 0.22 mmol) was added. The mixture was stirred at the same temperature for another 9 h, after which TLC showed completion of the reaction. The mixture was purified by chromatography (PE/EtOAc, 3:1) on silica gel to give **11a** (149 mg, 0.35 mmol, 82% from **10**) as a white powder. Data for **11a**: M.p. 92–93 °C. $[\alpha]_D^{24}$ = +31.3 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 16.0 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.31–7.19 (m, 5 H), 6.76 (d, *J* = 8.7 Hz, 2 H), 6.22 (d, *J* = 16.2 Hz, 1 H), 5.35 (dd, *J* = 8.7, 3.7 Hz, 1 H), 4.61 (t, *J* = 8.8 Hz, 1 H), 4.23–4.14 (m, 3 H), 3.92 (t, *J* = 6.0 Hz, 2 H), 3.11 (dt, *J* = 17.9, 7.1 Hz, 1 H), 3.05 (dt, *J* = 18.0, 6.9 Hz, 1 H), 2.03 (quint, *J* = 6.6 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 167.3, 160.5, 153.7, 144.2, 139.0, 129.6, 129.2, 128.7, 127.2, 125.9, 115.7, 114.8, 70.0, 66.6, 60.3, 57.6, 32.0, 23.6, 14.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 3066, 3027, 2981, 2933, 2882, 1794, 1765, 1702, 1633, 1604, 1573, 1359, 1334, 1311, 1250, 1170, 828 cm^{-1}. ESI-MS: *m*/*z* = 446.6 [M + Na]$^+$. ESI-HRMS: calcd. for $C_{24}H_{25}NO_6Na$ [M + Na]$^+$ 446.1574; found 446.1590.

Wittig Reaction of 10 To Give 11b: Following the procedure used for the conversion of **10** into **11a**, but with $Ph_3P{=}CHCO_2Me$ instead of $Ph_3P{=}CHCO_2Et$, purification by chromatography (PE/EtOAc, 3:1) gave **11b** (201 mg, 0.491 mmol, 79% from **10**) as a white powder. Data for **11b**: M.p. 120–123 °C. $[\alpha]_D^{26}$ = +26.7 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 15.8 Hz, 1 H), 7.44 (d, *J* = 8.9 Hz, 2 H), 7.38–7.27 (m, 5 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 6.30 (d, *J* = 15.9 Hz, 1 H), 5.42 (dd, *J* = 8.6, 3.7 Hz, 1 H), 4.69 (dt, *J* = 1.1, 8.8 Hz, 1 H), 4.32–4.25 (m, 1 H), 3.99 (t, *J* = 6.3 Hz, 2 H), 3.79 (s, 3 H), 3.19 (dt, *J* = 17.9, 7.0 Hz, 1 H), 3.12 (dt, *J* = 17.9, 7.0 Hz, 1 H), 2.11 (quint, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 167.8, 160.6, 153.7, 144.5, 139.0, 129.7, 129.2, 128.8, 127.1, 125.9, 115.2, 114.8, 70.0, 66.6, 57.6, 51.5, 32.0, 23.6 ppm. FTIR (KBr): $\tilde{\nu}$ = 3025, 2994, 2949, 2923, 2871, 1775, 1700, 1635, 1603, 1573, 1511, 1472, 1434, 1378, 1291, 1147, 829 cm^{-1}. ESI-MS: *m*/*z* = 432.3 [M + Na]$^+$. ESI-HRMS: calcd. for $C_{23}H_{23}NO_6Na$ [M + Na]$^+$ 432.1418; found 432.1409.

Methylation of 11a To Give 12a: NaHMDS (1.0 M solution in THF; 3.35 mL, 3.35 mmol) was added dropwise to a stirred solution of **11a** (1.290 g, 3.05 mmol) in dry THF (20 mL) at –78 °C (EtOH/dry ice bath) under argon (balloon). The mixture was stirred at the

same temperature for 2.5 h, then MeI (0.39 mL, 7.62 mmol) was added. The mixture was stirred for 11.5 h, during which time the bath was allowed to warm up from –78 °C to –5 °C. Saturated aqueous NH_4Cl (2 mL) was then added. The mixture was concentrated on a rotary evaporator. The residue was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave **12a** (745 mg, 1.70 mmol, 56% from **11a**) as a white powder. Data for **12a**: M.p. 74–74 °C. $[\alpha]_D^{26}$ = +115.5 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 15.9 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.41–7.30 (m, 3 H), 7.27 (dd, *J* = 8.3, 1.6 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.30 (d, *J* = 16.3 Hz, 1 H), 5.41 (dd, *J* = 8.8, 3.9 Hz, 1 H), 4.58 (t, *J* = 8.7 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 4.21 (dd, *J* = 9.5, 3.6 Hz, 1 H), 4.10–3.95 (m, 3 H), 2.22 (ddt, *J* = 14.4, 8.3, 6.2 Hz, 1 H), 1.88 (dq, *J* = 14.0, 5.6 Hz, 1 H), 1.33 (t, *J* = 7.3 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 167.3, 160.5, 153.3, 144.1, 139.1, 129.7, 129.2, 128.7, 127.2, 125.6, 115.8, 114.8, 69.7, 65.8, 60.3, 57.7, 34.8, 32.3, 17.8, 14.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 3063, 3030, 2978, 2938, 2881, 1782, 1708, 1633, 1602, 1513, 1386, 1242, 1159, 826 cm^{-1}. ESI-MS: *m*/*z* = 460.4 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{25}H_{27}NO_6Na$ $[M + Na]^+$ 460.1731; found 460.1737.

Methylation of 11b To Give 12b: The procedure described above for the conversion of **11a** into **12a** was used, but with **11b** instead of **11a**. This gave **12b** (1.014 g, 2.396 mmol, 46% from **11b**) as a white powder. Data for **12b**: M.p. 107–111 °C. $[\alpha]_D^{27}$ = +123.1 (*c* = 0.50, $CHCl_3$), $[\alpha]_D^{27}$ = +121.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.8 Hz, 1 H), 7.46 (d, *J* = 8.6 Hz, 2 H), 7.42–7.26 (m, 5 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.31 (d, *J* = 15.8 Hz, 1 H), 5.41 (dd, *J* = 8.8, 4.0 Hz, 1 H), 4.59 (t, *J* = 9.0 Hz, 1 H), 4.22 (dd, *J* = 8.9, 3.9 Hz, 1 H), 4.09–3.95 (m, 3 H), 3.79 (s, 3 H), 2.22 (ddt, *J* = 14.2, 8.2, 6.0 Hz, 1 H), 1.88 (dq, *J* = 13.3, 6.5 Hz, 1 H), 1.21 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 167.7, 160.6, 153.3, 144.5, 139.1, 129.7, 129.2, 128.7, 127.2, 125.7, 115.3, 114.8, 69.8, 65.8, 57.7, 51.6, 34.8, 32.3, 17.8 ppm. FTIR (KBr): $\tilde{\nu}$ = 3066, 2982, 2948, 1778, 1699, 1633, 1603, 1513, 1454, 1390, 1250, 1204, 1167, 1037, 834, 747 cm^{-1}. ESI-MS: *m*/*z* = 446.3 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{24}H_{25}NO_6Na$ $[M + Na]^+$ 446.1574; found 446.1562.

Reductive Cleavage of the Chiral Auxiliary in 12b To Give (*S*)-4: $NaBH_4$ (196 mg, 5.182 mmol) was added to a stirred solution of **12b** (731 mg, 1.727 mmol) in THF (8 mL) and H_2O (1 mL) at ambient temperature. After 18 h, TLC showed that the reaction was complete. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 5:2) on silica gel gave (*S*)-**4** (411 mg, 1.556 mmol, 90% from **12b**) as a white powder. Data for (*S*)-**4**: M.p. 57–58 °C. $[\alpha]_D^{26}$ = –4.85 (*c* = 1.00, MeOH); $[\alpha]_D^{27}$ = –5.75 (*c* = 0.50, MeOH); $[\alpha]_D^{27}$ = –7.06 (*c* = 0.25, MeOH); $[\alpha]_D^{27}$ = –10.9 (*c* = 0.20, MeOH) [ref.[2] data for natural **4**: $[\alpha]_{500}$ = +4.34 (*c* = 0.23, MeOH); cf. also the data at different wavelengths for (*R*)-**4** below]. *ee* = 87.7% [t_R for (*S*)-**4** = 16.577 min, t_R for (*R*)-**4** = 15.627 min], as measured by HPLC with a Phenomenex Lux 5 µm Cellulose-3 column (25 × 0.46 cm), eluting with *n*-hexane/*i*PrOH, 8:2, at a flow rate of 0.7 mL/min, with the detector set to 214 nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 16.2 Hz, 1 H), 7.46 (d, *J* = 8.9 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 4.12–4.01 (m, 2 H), 3.79 (s, 3 H), 3.55 (d, *J* = 5.9 Hz, 2 H), 2.00–1.87 (m, 2 H), 1.79 (br. s, 1 H), 1.72–1.64 (m, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 160.7, 144.5, 129.7, 127.1, 115.2, 114.8, 67.9, 66.3, 51.5, 33.1, 32.6, 16.7 ppm. FTIR (KBr): $\tilde{\nu}$ = 3521, 2975, 2955, 2932, 2875, 1698, 1633, 1604, 1511, 1473, 1448, 1423, 1332, 1306, 1288, 1257, 1206, 1175, 1051, 1010, 984, 828 cm^{-1}. ESI-MS: *m*/*z* = 265.2 $[M + H]^+$. ESI-HRMS: calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1254; found 287.1253.

Reductive Cleavage of the Chiral Auxiliary in 12a To Give 13: The procedure described above for the conversion of **12b** into (*S*)-**4** was used, but with **12a** instead of **12b**. After purification by chromatography (PE/EtOAc, 3:1), this gave **13** (115 mg, 0.413 mmol, 87% from **12a**) as a white powder. Data for **13**: M.p. 75–78 °C. $[\alpha]_D^{24}$ = –5.1 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 16.5 Hz, 1 H), 7.46 (d, *J* = 8.3 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.30 (d, *J* = 15.7 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.11–4.02 (m, 2 H), 3.55 (d, *J* = 6.1 Hz, 2 H), 1.98–1.88 (m, 2 H), 1.85 (br. s, 1 H), 1.72–1.64 (m, 1 H), 1.33 (t, *J* = 7.4 Hz, 3 H), 1.00 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 160.6, 144.2, 129.7, 127.2, 115.7, 114.8, 67.9, 66.3, 60.3, 33.1, 32.6, 16.7, 14.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 3364, 2972, 2949, 2932, 2913, 2872, 1704, 1633, 1604, 1513, 1424, 1313, 1256, 1178, 1045, 985, 831 cm^{-1}. ESI-MS: *m*/*z* = 279.2 $[M + H]^+$. ESI-HRMS: calcd. for $C_{16}H_{22}O_4Na$ $[M + Na]^+$ 301.1410; found 301.1420.

DIBAL-H Reduction of (*S*)-4 To Give (*S*)-2: DIBAL-H (1.0 M solution in cyclohexane; 4.2 mL, 4.2 mmol) was added to a stirred solution of (*S*)-**4** (371 mg, 1.405 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C (EtOH/dry ice bath) under argon (balloon). The mixture was stirred at the same temperature for 2 h, then satd. aq. sodium potassium tartrate (2 mL) was added carefully, followed by CH_2Cl_2 (4 mL). Stirring was continued at ambient temperature for 5.5 h, after which time the system had become a two-phase clear mixture. The phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed in turn with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:1) on silica gel gave (*S*)-**2** [327 mg, 1.373 mmol, 98% from (*S*)-**4**] as a white powder. Data for (*S*)-**2**: M.p. 70–71 °C. $[\alpha]_D^{27}$ = –6.9 (*c* = 1.00, $CHCl_3$); $[\alpha]_D^{27}$ = –4.5 (*c* = 0.21, MeOH) [ref.[1a] data for natural **2**: $[\alpha]_D^{24}$ = –5.1 (*c* = 0.21, MeOH)]. *ee* = 87.2% [t_R for (*S*)-**2** = 59.927 min, t_R for (*R*)-**2** = 64.427 min], as measured by HPLC with a Phenomenex Lux 5 µm Amylose-2 column (25 × 0.46 cm), eluting with *n*-hexane/*i*PrOH, 9:1, at a flow rate of 0.7 mL/min, with the UV detector set to 214 nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 6.55 (d, *J* = 16.0 Hz, 1 H), 6.23 (dt, *J* = 15.8, 6.0 Hz, 1 H), 4.29 (dd, *J* = 5.9, 1.2 Hz, 2 H), 4.07 (dt, *J* = 9.6, 5.8 Hz, 1 H), 4.02 (ddd, *J* = 9.5, 7.2, 6.0 Hz, 1 H), 3.55 (d, *J* = 5.6 Hz, 2 H), 1.97–1.86 (m, 2 H), 1.72–1.63 (m, 3 H, including 2 OH), 1.00 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 130.9, 129.5, 127.7, 126.3, 114.6, 67.9, 66.2, 63.9, 33.2, 32.8, 16.8 ppm. FTIR (KBr): $\tilde{\nu}$ = 3306, 2933, 2874, 1604, 1511, 1244, 1174, 1059, 970, 833 cm^{-1}. ESI-MS: *m*/*z* = 259.2 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ 259.1305; found 259.1306.

DIBAL-H Reduction 13 To Give (*S*)-2: DIBAL-H (1.0 M solution in cyclohexane; 1.3 mL, 1.3 mmol) was added to a stirred solution of **13** (121 mg, 0.435 mmol) in dry CH_2Cl_2 (4 mL) at –72 °C (EtOH/dry ice bath) under argon (balloon). The mixture was stirred at the same temperature for 1.5 h, and then satd. aq. sodium potassium tartrate (2 mL) was added carefully, followed by CH_2Cl_2 (4 mL). Stirring was continued at ambient temperature for 5 h, after which time the system had become a two-phase clear mixture. The phases were separated. The aqueous layer was extracted with

CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed in turn with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:1) on silica gel gave (*S*)-**2** (85 mg, 0.36 mmol, 83% from **13**) as a white powder, along with recovered **13** (20 mg, 0.072 mmol, 17%). For data for (*S*)-**2**, see above.

MnO_2 Oxidation of (*S*)-2 To Give (*S*)-1: A mixture of activated MnO_2 (88%, 66 mg, 0.64 mmol) and (*S*)-**2** (20 mg, 0.0847 mmol) in dry CH_2Cl_2 (0.5 mL) was stirred at ambient temperature for 20 h, after which time TLC showed that the reaction was complete. The solids were removed by filtration [washing with CH_2Cl_2 (40 mL)]. The combined filtrate and washings were concentrated on a rotary evaporator to dryness to give rather pure (*S*)-**1** [16 mg, 0.0683 mmol, 80% from (*S*)-**2**] as a white powder. Data for (*S*)-**1**: M.p. <26 °C. $[\alpha]_D^{27}$ = –5.50 (*c* = 1.00, $CHCl_3$); $[\alpha]_D^{24}$ = –5.42 (*c* = 0.50, MeOH); $[\alpha]_D^{24}$ = –6.95 (*c* = 0.20, MeOH); $[\alpha]_D^{25}$ = –6.70 (*c* = 0.14, MeOH); $[\alpha]_D^{25}$ = –7.58 (*c* = 0.10, MeOH); $[\alpha]_D^{25}$ = –10.03 (*c* = 0.08, MeOH); $[\alpha]_D^{25}$ = –10.85 (*c* = 0.07, MeOH); $[\alpha]_D^{25}$ = –13.12 (*c* = 0.05, MeOH); $[\alpha]_D^{25}$ = –22.72 (*c* = 0.025, MeOH) [ref.[1a] data for natural **1**: $[\alpha]_D^{27}$ = +5.7 (*c* = 0.15, MeOH)]. ^1H and ^{13}C NMR, FTIR, and ESI-MS spectroscopic data were the same as those for (*R*)-**1** (the natural isomer) given below. ESI-HRMS: calcd. for $C_{14}H_{18}O_3Na$ $[M + Na]^+$ 257.1148; found 257.1143.

Hydrogenation of (*S*)-2 To Give (*S*)-5: A mixture of (*S*)-**2** (50 mg, 0.21 mmol) and Pd/C (10%; 5 mg) in commercially sourced anhydrous EtOH (2 mL) was stirred at ambient temperature under H_2 (atmospheric pressure) for 12 h, after which time TLC showed that the reaction was complete. The solids were removed by filtration [washing with EtOH (50 mL)]. The combined filtrate and washings were concentrated on a rotary evaporator. The residue was purified by chromatography (PE/EtOAc, 1:1) on silica gel to give (*S*)-**5** (48 mg, 0.20 mmol, 96%) as a white powder. Data for (*S*)-**5**: M.p. 56–57 °C. $[\alpha]_D^{27}$ = –4.10 (*c* = 0.50, MeOH); $[\alpha]_D^{27}$ = –4.34 (*c* = 0.20, MeOH); $[\alpha]_D^{27}$ = –3.6 (*c* = 0.40, MeOH); $[\alpha]_D^{27}$ = –6.97 (*c* = 1.00, $CHCl_3$) [ref.[3] data for natural **5**: $[\alpha]_D^{23}$ = –9.2 (*c* = 0.22, MeOH)]. *ee* = 87.0% [t_R for (*S*)-**5** = 7.363 min, t_R for (*R*)-**5** = 6.460 min], as measured by HPLC with a Phenomenex Lux 5 μm Cellulose-4 column (25 × 0.46 cm), eluting with MeCN/H_2O, 9:1, at a flow rate of 0.7 mL/min, with the UV detector set to 254 nm. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.05 (dt, *J* = 9.5, 5.8 Hz, 1 H), 4.00 (ddd, *J* = 8.6, 7.1, 5.5 Hz, 1 H), 3.67 (t, *J* = 6.5 Hz, 2 H), 3.55 (d, *J* = 5.4 Hz, 2 H), 2.65 (t, *J* = 7.8 Hz, 2 H), 1.95–1.82 (m, 4 H), 1.73–1.63 (m, 1 H), 1.65–1.57 (br. s, 2 H, 2 OH), 1.00 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 134.0, 129.3, 114.4, 68.0, 66.2, 62.3, 34.4, 33.4, 32.9, 31.1, 16.8 ppm. FTIR (film of a conc. solution in CH_2Cl_2): $\tilde{\nu}$ = 3348, 2927, 2873, 1611, 1582, 1512, 1472, 1455, 1388, 1301, 1243, 1176, 1111, 1041, 983, 911, 832 cm^{-1}. ESI-MS: *m*/*z* = 239.2 $[M + H]^+$. ESI-HRMS: calcd. for $C_{14}H_{22}O_3Na$ $[M + Na]^+$ 261.1461; found 261.1469.

Conversion of (*S*)-2 into (*S*)-6: $BH_3{\cdot}Me_2S$ (2 M solution in THF; 1.05 mL, 2.1 mmol) was added to a stirred solution of (*S*)-**2** (100 mg, 0.42 mmol) in dry THF (2 mL) in an ice–water bath under argon (balloon). After the addition was complete, the mixture was stirred at ambient temperature for 9 h, after which time TLC showed that the reaction was complete. The flask was opened and cooled in an ice–water bath, and NaOH (6 N aq.; 0.5 mL) was added slowly, followed by H_2O_2 (30%; 1 mL). The mixture was stirred at ambient temperature for 5 h, then it was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed in turn with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:2) on silica gel gave intermediate **21** [24 mg, 23% from (*S*)-**2**] as a colourless oil.

This material was directly dissolved in EtOH (1 mL), and a solution of $NaIO_4$ (30 mg, 0.142 mmol) in H_2O (0.2 mL) was added. The milky mixture was stirred at ambient temperature for 20 min, after which time TLC showed that the reaction was complete. $NaBH_4$ (5 mg, 0.132 mmol) was then added to the mixture. Stirring was continued at the same temperature for another 10 min, and then satd. aq. NH_4Cl (1 mL) was added. The mixture was extracted with EtOAc (2 × 35 mL). The combined organic layers were washed in turn with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:1) on silica gel gave (*S*)-**6** (12 mg, 0.0535 mmol, 57% from **21**) as a white powder. Data for (*S*)-**6**: M.p. 68–70 °C. $[\alpha]_D^{25}$ = –7.1 (*c* = 0.60, MeOH); $[\alpha]_D^{26}$ = –6.6 (*c* = 0.30, MeOH); $[\alpha]_D^{26}$ = –7.6 (*c* = 0.20, MeOH); $[\alpha]_D^{24}$ = –8.0 (*c* = 0.12, MeOH); $[\alpha]_D^{24}$ = –8.4 (*c* = 0.10, MeOH) [ref.[3] data for natural **6**: $[\alpha]_D^{23}$ = –37 (*c* = 0.1, MeOH)]. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 4.05 (dt, *J* = 9.1, 6.0 Hz, 1 H), 4.00 (ddd, *J* = 8.9, 6.9, 6.1 Hz, 1 H), 3.81 (t, *J* = 6.3 Hz, 2 H), 3.54 (d, *J* = 5.9 Hz, 2 H), 2.80 (t, *J* = 6.7 Hz, 2 H), 1.94–1.86 (m, 2 H), 1.81–1.73 (br., 2 H, 2 OH), 1.71–1.63 (m, 1 H), 0.99 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 130.5, 130.0, 114.6, 67.9, 66.2, 63.8, 38.2, 33.3, 32.8, 16.8 ppm. FTIR (film of a conc. solution in CH_2Cl_2): $\tilde{\nu}$ = 3285, 2922, 2870, 1608, 1581, 1512, 1455, 1372, 1298, 1248, 1209, 1179, 1115, 1051, 1033, 968, 919, 828 cm^{-1}. ESI-MS: *m*/*z* = 225.1 $[M + H]^+$. ESI-HRMS: calcd. for $C_{13}H_{20}O_3Na$ $[M + Na]^+$ 247.1305; found 247.1312.

Condensation of 8 with 14 To Give 15: The procedure described above for the conversion of **8** into **10** was used,but with **14** instead of **9**. Purification by chromatography (PE/EtOAc, 3:1) gave **15** (6.336 g, 17.26 mmol, 90% from **8**) as a white powder. Data for **15**: M.p. 84–85 °C. $[\alpha]_D^{20}$ = –51.8 (*c* = 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 7.84 (d, *J* = 8.5 Hz, 2 H), 7.36–7.27 (m, 3 H), 7.21 (d, *J* = 6.7 Hz, 2 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 4.69 (dq, *J* = 13.1, 3.5 Hz, 1 H), 4.21 (dt, *J* = 13.1, 8.0 Hz, 2 H), 4.12 (t, *J* = 6.1 Hz, 2 H), 3.31 (dd, *J* = 13.4, 3.5 Hz, 1 H), 3.20 (dt, *J* = 17.8, 7.2 Hz, 1 H), 3.15 (dt, *J* = 18.2, 7.0 Hz, 1 H), 2.78 (dd, *J* = 13.5, 9.7 Hz, 1 H), 2.24 (quint, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 172.3, 163.7, 153.4, 135.1, 131.9, 129.8, 129.3, 128.8, 127.3, 114.6, 66.9, 66.2, 55.0, 37.7, 31.9, 23.5 ppm. FTIR (film of a conc. solution in CH_2Cl_2): $\tilde{\nu}$ = 3070, 3030, 3009, 2967, 2942, 2878, 2848, 2757, 1784, 1704, 1683, 1601, 1577, 1386, 1355, 1247, 1205, 1159, 1045, 990, 933, 853, 820, 745, 701 cm^{-1}. ESI-MS: *m*/*z* = 390.3 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{21}H_{21}NO_5Na$ $[M + Na]^+$ 390.1312; found 390.1320.

Wittig Reaction of 15 with $Ph_3P{=}CHCO_2Me$ To Give 16: A mixture of **15** (4.000 g, 10.90 mmol) and $Ph_3P{=}CHCO_2Me$ (9.100 g, 27.24 mmol) in CH_2Cl_2 (20 mL) was stirred at ambient temperature for 14 h, after which time TLC showed that the reaction was complete. The mixture was concentrated by rotary evaporation. The residue was purified by chromatography (PE/EtOAc, 5:2) on silica gel to give **16** (3.757 g, 8.878 mmol, 82% from **15**) as a white powder. (*E*)/(*Z*) = 96:4, as seen by ^1H NMRspectroscopy; after recrystallization from EtOAc, (*E*)/(*Z*) = 98:2. Data for **16**: M.p. 124–126 °C. $[\alpha]_D^{26}$ = –42.2 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 15.9 Hz, 1 H), 7.47 (d, *J* = 8.7 Hz, 2 H), 7.36–7.27 (m, 3 H), 7.21 (d, *J* = 6.6 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.31 (d, *J* = 15.7 Hz, 1 H), 4.78 (dq, *J* = 13.2, 3.4 Hz, 1 H), 4.21 (t, *J* = 9.4 Hz, 1 H), 4.18 (dd, *J* = 9.0, 3.3 Hz, 1 H), 4.10 (t, *J* = 6.2 Hz, 2 H), 3.79 (s, 3 H), 3.31 (dd, *J* = 13.5, 3.4 Hz, 1 H), 3.19

(dt, J = 17.8, 7.2 Hz, 1 H), 3.13 (dt, J = 17.0, 7.2 Hz, 1 H), 2.88 (dd, J = 13.3, 9.6 Hz, 1 H), 2.21 (quint, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 167.7, 160.6, 153.4, 144.5, 135.2, 129.7, 129.4, 128.9, 127.4, 127.1, 115.2, 114.8, 66.7, 66.3, 55.1, 51.5, 37.9, 32.0, 23.7 ppm. FTIR (KBr): $\tilde{\nu}$ = 3067, 3029, 2949, 2918, 2882, 1782, 1704, 1633, 1603, 1434, 1388, 1352, 1289, 1252, 1209, 1170, 985, 830, 762, 703 cm^{-1}. ESI-MS: m/z = 446.4 [M + Na]$^+$. ESI-HRMS: calcd. for $C_{24}H_{25}NO_6Na$ [M + Na]$^+$ 446.1574; found 446.1586.

Methylation of 16 To Give 17: The procedure described above for the conversion of **11a** into **12a** was used, but with **16** instead of **11a**. Purification by chromatography (PE/EtOAc, 3:1) gave **17** (1.113 g, 2.546 mmol, 84% from **16**) as a white powder. Data for **17**: M.p. 100–101 °C. $[\alpha]_D^{24}$ = –72.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 15.9 Hz, 1 H), 7.45 (d, J = 8.9 Hz, 2 H), 7.36–7.27 (m, 3 H), 7.22–7.19 (m, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.30 (d, J = 15.8 Hz, 1 H), 4.65 (ddt, J = 9.3, 8.0, 3.2 Hz, 1 H), 4.16–4.12 (m, 1 H), 4.11–4.05 (m, 2 H), 4.04–3.96 (m, 2 H), 3.79 (s, 3 H), 3.25 (dd, J = 13.6, 3.2 Hz, 1 H), 2.78 (dd, J = 13.2, 9.6 Hz, 1 H), 2.29 (ddt, J = 14.0, 8.0, 6.0 Hz, 1 H), 1.95 (dq, J = 13.9, 6.0 Hz, 1 H), 1.32 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 167.7, 160.5, 153.0, 144.4, 135.2, 129.7, 129.4, 128.9, 127.4, 127.2, 115.3, 114.7, 66.0, 65.9, 55.3, 51.6, 37.9, 34.8, 32.7, 18.0 ppm. FTIR (KBr): $\tilde{\nu}$ = 3031, 2950, 2890, 1787, 1765, 1711, 1698, 1634, 1602, 1511, 1481, 1385, 1252, 1197, 1174, 1013, 985, 826, 762, 725, 698 cm^{-1}. ESI-MS: m/z = 460.3 [M + Na]$^+$. ESI-HRMS: calcd. for $C_{25}H_{27}NO_6Na$ [M + Na]$^+$ 460.1731; found 460.1738.

Reductive Cleavage of the Chiral Auxiliary in 17 To Give (*R*)-4: The procedure described above for the conversion of **12b** into (*S*)-**4** was used, but with **17** as starting material. This gave (*R*)-**4** (174 mg, 0.659 mmol, 96% from **17**) as a white powder. Data for (*R*)-**4**: M.p. 60–61 °C. $[\alpha]_D^{23}$ = +4.5 (c = 0.26, MeOH); $[\alpha]_D^{23}$ = +4.2 (c = 0.55, MeOH); the $[\alpha]^{20}$ (c = 0.40, MeOH) for (*R*)-**4** was also measured on another polarimeter (Rudolph Autopol VI, with changeable wavelength): +3.4 (633 nm), +4.6 (589 nm), +5.8 (546 nm), +8.7 (436 nm), +9.5 (405 nm); data were also measured at a lower concentration (c = 0.23, MeOH): +3.1 (633 nm), +5.3 (589 nm), +6.4 (546 nm), +9.6 (436 nm), +9.3 (405 nm); [ref.[2] data for natural **4**: $[\alpha]_{500}$ = +4.34 (c = 0.23, MeOH)]. *ee* = 90.2% [t_R for (*R*)-**4** = 15.417 min, t_R for (*S*)-**4** = 16.727 min], as measured by HPLC with a Phenomenex Lux 5 µm Cellulose-3 column (25 × 0.46 cm), eluting with *n*-hexane/*i*PrOH, 8:2, at a flow rate of 0.7 mL/min, with the UV detector set to 214 nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 15.9 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 6.31 (d, J = 16.0 Hz, 1 H), 4.06 (ddd, J = 12.5, 9.2, 7.3 Hz, 1 H), 4.09 (dt, J = 9.2, 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.55 (d, J = 5.6 Hz, 2 H), 1.99–1.87 (m, 2 H), 1.83 (br. s, 1 H), 1.72–1.62 (m, 1 H), 1.00 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 160.7, 144.5, 129.7, 127.1, 115.2, 114.8, 67.9, 66.2, 51.6, 33.1, 32.6, 16.7 ppm. FTIR (film): $\tilde{\nu}$ = 3322, 2927, 2873, 1714, 1636, 1604, 1574, 1513, 1456, 1434, 1288, 1259, 1171, 1111, 1014, 983, 831, 818 cm^{-1}. ESI-MS: m/z = 265.2 [M + H]$^+$. ESI-HRMS: calcd. for $C_{15}H_{20}O_4Na$ [M + Na]$^+$ 287.1254; found 287.1257.

DIDBAL-H Reduction of (*R*)-4 To Give (*R*)-2: DIBAL-H (1.0 M solution in cyclohexane; 0.48 mL, 0.48 mmol) was added to a stirred solution of (*R*)-**4** (63 mg, 0.242 mmol) in dry CH_2Cl_2 (3 mL) at –78 °C (EtOH/dry ice bath) under argon (balloon). The mixture was stirred at the same temperature for 1 h, then satd. aq. NH_4Cl (2 mL) was added carefully, followed by CH_2Cl_2 (4 mL). Stirring was continued at ambient temperature for 4 h, after which time the system had become a two-phase clear mixture. The phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed in turn with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:1) on silica gel gave (*R*)-**2** [41 mg, 0.174 mmol, 73% from (*R*)-**4**] as a white powder. Data for (*R*)-**2**: M.p. 64–68 °C. $[\alpha]_D^{23}$ = +3.47 (c = 0.4, MeOH); $[\alpha]_D^{23}$ = +4.14 (c = 0.21, MeOH) [ref.[1a] data for natural **2**: $[\alpha]_D^{24}$ = –5.1 (c = 0.21, MeOH)]. *ee* = 90.3% [t_R for (*R*)-**2** = 63.777 min, t_R for (*S*)-**2** = 60.477 min], as measured by HPLC with a Phenomenex Lux 5 µm Amylose-2 column (25 × 0.46 cm), eluting with *n*-hexane/*i*PrOH, 9:1, at a flow rate of 0.7 mL/min, with the UV detector set to 214 nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.9 Hz, 2 H), 6.55 (d, J = 15.7 Hz, 1 H), 6.24 (dt, J = 15.9, 5.9 Hz, 1 H), 4.30 (dd, J = 6.1, 1.6 Hz, 2 H), 4.08 (dt, J = 9.7, 5.8 Hz, 1 H), 4.02 (ddd, J = 9.3, 6.9, 5.6 Hz, 1 H), 3.56 (d, J = 5.7 Hz, 2 H), 1.97–1.87 (m, 2 H), 1.74–1.63 (m, 1 H), 1.00 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 130.8, 129.5, 127.6, 126.3, 114.6, 67.9, 66.1, 63.8, 33.2, 32.7, 16.8 ppm. FTIR (film of a conc. solution in CH_2Cl_2): $\tilde{\nu}$ = 3383, 3030, 2925, 2876, 1714, 1699, 1633, 1605, 1574, 1512, 1506, 1471, 1452, 1433, 1393, 1303, 1248, 1173, 1113, 1087, 1017, 969, 933, 837, 798 cm^{-1}. ESI-MS: m/z = 259.2 [M + Na]$^+$. ESI-HRMS: calcd. for $C_{14}H_{20}O_3Na$ [M + Na]$^+$ 259.1305; found 259.1306.

MnO_2 Oxidation of (*R*)-2 To Give (*R*)-1: A mixture of (*R*)-**2** (25 mg, 0.1059 mmol) and activated MnO_2 (88%, 78 mg, 0.794 mmol) in dry CH_2Cl_2 (1 mL) was stirred at ambient temperature for 20 h, after which time TLC showed that the reaction was complete. The solids were removed by filtration [washing with CH_2Cl_2 (70 mL)]. The combined filtrate and washings were washed with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave rather pure (*R*)-**1** [21 mg, 0.0897 mmol, 84% from (*R*)-**2**] as a white powder. Data for (*R*)-**1**: M.p. <26 °C. $[\alpha]_D^{21}$ = +4.3 (c = 0.19, MeOH) [ref.[1a] data for natural **1**: $[\alpha]_D^{24}$ = +5.7 (c = 0.15, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, J = 7.8 Hz, 1 H), 7.44 (d, J = 8.9 Hz, 2 H), 7.35 (d, J = 15.7 Hz, 1 H), 6.86 (d, J = 8.9 Hz, 2 H), 6.53 (dd, J = 15.9, 7.8 Hz, 1 H), 4.00 (dt, J = 9.6, 6.5 Hz, 1 H), 4.05 (dt, J = 9.4, 6.1 Hz, 1 H), 3.49 (d, J = 5.6 Hz, 2 H), 1.90 (dt, J = 12.6, 6.1 Hz, 1 H), 1.84 (dt, J = 12.3, 6.1 Hz, 1 H), 1.84–1.74 (br. s, 1 H), 1.61 (dq, J = 13.1, 6.5 Hz, 1 H), 0.94 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 161.5, 152.8, 130.4, 126.7, 126.4, 115.0, 67.8, 66.4, 33.0, 32.6, 16.7 ppm. FTIR (film): $\tilde{\nu}$ = 3439, 3037, 2957, 2926, 2874, 1673, 1621, 1600, 1570, 1511, 1473, 1426, 1392, 1308, 1259, 1175, 1129, 1014, 973, 819 cm^{-1}. ESI-MS: m/z = 235.1 [M + H]$^+$. ESI-HRMS: calcd. for $C_{14}H_{19}O_3$ [M + H]$^+$ 235.13287; found 235.1331.

Hydrogenation of (*R*)-2 To Give (*R*)-5: The procedure described above for the conversion of (*S*)-**2** into (*S*)-**5** was used [with (*R*)-**2** instead of (*S*)-**2** as the starting material]. This gave (*R*)-**5** (6 mg, 0.025 mmol, 100%) as a white solid. Data for (*R*)-**5**: M.p. 56–57 °C. $[\alpha]_D^{24}$ = +5.7 (c = 0.25, MeOH). *ee* = 88.0% [t_R for (*R*)-**5** = 6.451 min, t_R for (*S*)-**5** = 7.379 min], as measured by HPLC with a Phenomenex Lux 5 µm Cellulose-4 column (25 × 0.46 cm), eluting with MeCN/H_2O, 9:1, at a flow rate of 0.7 mL/min, with the UV detector set to 254 nm. Other data were the same as those reported for (*S*)-**5**. ESI-HRMS: calcd. for $C_{14}H_{22}O_3Na$ [M + Na]$^+$ 261.14612; found 261.1467.

Conversion of 17 into 18: H_2O_2 (30%; 0.18 mL) was added to a stirred solution of **17** (400 mg, 0.915 mmol) and LiOH (monohydrate; 46 mg, 1.098 mmol) in THF (5 mL) and H_2O (0.5 mL) in an

ice–water bath. Stirring was continued at the same temperature for 1.5 h, after which time TLC showed that the reaction was complete. Saturated aqueous Na_2SO_3 (2 mL) was added (to decompose the peroxide). HCl (1 N aq.; 4 drops from a pipette) was then added, to acidify the mixture to ca. pH 2. The mixture was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed in turn with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and chromatography (PE/EtOAc, 3:2) gave pure **18** (244 mg, 0.877 mmol, 96% from **17**) as a white powder. Data for **18**: M.p. 50–52 °C. $[\alpha]_D^{25}$ = –36.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 16.2 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 6.30 (d, *J* = 15.8 Hz, 1 H), 4.06 (t, *J* = 6.1 Hz, 2 H), 3.79 (s, 3 H), 2.79 (br. sext, *J* = 7.0 Hz, 1 H), 2.28–2.18 (m, 1 H), 1.97–1.87 (m, 1 H), 1.29 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.3, 167.9, 160.5, 144.6, 129.7, 127.1, 115.1, 114.7, 65.5, 51.6, 36.2, 32.5, 17.0 ppm. FTIR (film of a conc. solution in CH_2Cl_2): $\tilde{\nu}$ = 3201 (br), 3075, 3037, 2952, 2878, 1714 (br), 1633, 1604, 1574, 1512, 1464, 1435, 1304, 1289, 1254, 1202, 1172, 1041, 983, 937, 829 cm^{-1}. ESI-MS: *m*/*z* = 279.2 $[M + H]^+$. ESI-HRMS: calcd. for $C_{15}H_{18}O_5Na$ $[M + Na]^+$ 301.1046; found 301.1045.

Conversion of 18 into 20 via 19: DIBAL-H (1.0 M solution in cyclohexane; 1.35 mL, 1.35 mmol) was added to a stirred solution of **18** (188 mg, 0.676 mmol) in dry CH_2Cl_2 (3.3 mL) at –78 °C (EtOH/dry ice bath) under argon (balloon). The mixture was stirred at the same temperature for 2 h, then satd. aq. sodium potassium tartrate (2 mL) was added slowly, followed by CH_2Cl_2 (4 mL). Stirring was continued at ambient temperature for 12 h, after which time the system had become a two-phase clear mixture. The phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed in turn with water and brine, and then dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:2) on silica gel gave **19** (79 mg, 0.316 mmol, 48% from **18**) as a white powder, along with recovered **18** (88 mg, 0.318 mmol, 47%). Some characteristic data for **19**: M.p. 88–90 °C. $[\alpha]_D^{26}$ = –35.9 (*c* = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.53 (d, *J* = 15.7 Hz, 1 H), 6.22 (dt, *J* = 15.8, 6.1 Hz, 1 H), 4.29 (dd, *J* = 5.7, 1.3 Hz, 2 H), 4.03 (t, *J* = 6.1 Hz, 2 H), 2.78 (br. sext, *J* = 7.1 Hz, 1 H), 2.21 (ddt, *J* = 13.8, 8.0, 6.1 Hz, 1 H), 1.92 (dq, *J* = 14.3, 6.0 Hz, 1 H), 1.28 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.5, 158.5, 131.0, 129.5, 127.7, 126.2, 114.6, 65.5, 63.9, 36.1, 32.7, 17.1 ppm. FTIR (film of a solution in CH_2Cl_2): $\tilde{\nu}$ = 3305 (br), 3075, 2954, 2924, 2853, 1729, 1684, 1605, 1512, 1458, 1269, 1247, 1218, 1174, 1083, 1056, 1004, 969, 834 cm^{-1}. EI-MS: *m*/*z* = 250 $[M]^+$.

The compound **19** (46 mg, 0.184 mmol) obtained as described above was dissolved in Et_2O (1 mL) and MeOH (1 mL). The solution was cooled in an ice–water bath, and Me_3SiCHN_2 (2 M solution in hexanes; 0.4 mL, 0.8 mmol) was added. The transparent yellowish solution was stirred at the same temperature for 20 min, after which time TLC showed that the reaction was complete. The solvents were removed on a rotary evaporator. The residue was purified by chromatography (PE/EtOAc, 2:1) on silica gel to give ester **20** (47 mg, 0.178 mmol, 96% from **19**) as a white crystalline solid. Data for **20**: M.p. 38–41 °C. $[\alpha]_D^{26}$ = –31.9 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.53 (d, *J* = 15.7 Hz, 1 H), 6.21 (dt, *J* = 15.8, 6.0 Hz, 1 H), 4.28 (dd, *J* = 6.0, 1.3 Hz, 2 H), 3.98 (dt, *J* = 1.8, 6.2 Hz, 2 H), 3.68 (s, 3 H), 2.74 (br. sext, *J* = 7.0 Hz, 1 H), 2.18 (ddt, *J* = 14.2, 8.0, 6.0 Hz, 1 H), 2.10–1.90 (br., 1 H, OH), 1.87 (dq, *J* = 13.8, 6.2 Hz, 1 H), 1.23 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 158.4, 130.7, 129.4, 127.6, 126.3, 114.5, 65.5, 63.7, 51.6, 36.2, 32.9, 17.1 ppm. FTIR (film): $\tilde{\nu}$ = 3446 (br), 3032, 2955, 2926, 2853, 1731, 1606, 1575, 1510, 1456, 1434, 1377, 1247, 1196, 1173, 1137, 1069, 1012, 967, 839, 800 cm^{-1}. ESI-MS: *m*/*z* = 287.2 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{15}H_{18}O_5Na$ $[M + Na]^+$ 287.1254; found 287.1253.

MnO_2 Oxidation of 20 To Give (*R*)-3: A mixture of **20** (44 mg, 0.1666 mmol) and activated MnO_2 (88%, 108 mg, 1.09 mmol) in dry CH_2Cl_2 (1 mL) was stirred at ambient temperature for 40 h, after which time TLC showed that the reaction was complete. The solids were removed by filtration. The filtrate was concentrated by rotary evaporation. The residue was purified by chromatography (PE/EtOAc, 3:1) on silica gel to give (*R*)-**3** (32 mg, 0.122 mmol, 74% from **20**) as a colourless oil. Data for (*R*)-**3**: $[\alpha]_D^{26}$ = –34.9 (*c* = 1.55, MeOH); $[\alpha]_D^{26}$ = –34.9 (*c* = 0.44, MeOH); $[\alpha]_D^{26}$ = –34.9 (*c* = 0.22, MeOH); $[\alpha]_D^{26}$ = –31.0 (*c* = 0.11, MeOH); $[\alpha]_D^{26}$ = –29.4 (*c* = 0.07, MeOH) [ref.[1a] data for natural **3**: $[\alpha]_D^{24}$ = +29.4 (*c* = 0.07, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, *J* = 7.9 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.42 (d, *J* = 15.8 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.61 (dd, *J* = 15.8, 7.8 Hz, 1 H), 4.07 (dt, *J* = 9.8, 6.0 Hz, 1 H), 4.04 (dt, *J* = 9.9, 6.1 Hz, 1 H), 3.69 (s, 3 H), 2.75 (br. sext, *J* = 7.0 Hz, 1 H), 2.21 (ddt, *J* = 14.3, 8.3, 6.1 Hz, 1 H), 1.91 (dq, *J* = 14, 6.1 Hz, 1 H), 1.25 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 176.5, 161.4, 152.7, 130.3, 126.8, 126.4, 115.0, 65.8, 51.7, 36.2, 32.7, 17.2 ppm. FTIR (film): $\tilde{\nu}$ = 2976, 2950, 2882, 2828, 1732, 1674, 1621, 1602, 1573, 1511, 1473, 1434, 1362, 1303, 1250, 1195, 1175, 1128, 1072, 1047, 1011, 971, 848, 818 cm^{-1}. ESI-MS: *m*/*z* = 263.2 $[M + H]^+$. ESI-HRMS: calcd. for $C_{15}H_{18}O_4Na$ $[M + Na]^+$ 285.1097; found 285.1096.

Conversion of 12b into *ent*-18: The procedure described above for the conversion of **17** into **18** was used (with **12b** as the substrate instead of **17**). Purification by chromatography (PE/EtOAc, 3:2) gave *ent*-**18** as a white powder (79 mg, 0.284 mmol, 89% from **12b**). Data for *ent*-**18**: M.p. 50–54 °C. $[\alpha]_D^{26}$ = +35.8 (*c* = 1.00, $CHCl_3$). ^{1}H and ^{13}C NMR, FTIR and ESI-MS spectroscopic data were the same as those for **18**. ESI-HRMS: calcd. for $C_{15}H_{18}O_5Na$ $[M + Na]^+$ 301.1046; found 301.1043.

Conversion of *ent*-18 into *ent*-20 via *ent*-19: The procedure described above for the conversion of **18** into **20** via **19** was used (with *ent*-**18** and *ent*-**19** instead of **18** and **19**, respectively). After chromatography (PE/EtOAc, 1:2), *ent*-**19** (39 mg, 0.156 mmol, 83% from *ent*-**18**) was obtained as a white powder. Data for *ent*-**19**: M.p. 87–88 °C. $[\alpha]_D^{26}$ = +31.4 (*c* = 1.00, $CHCl_3$). ^{1}H and ^{13}C NMR, FTIR, and ESI-MS spectroscopic data were the same as those for **19**.

After chromatography (PE/EtOAc, 2:1), *ent*-**20** (22 mg, 0.083 mmol, 92% from *ent*-**19**) was obtained as a white powder. Data for *ent*-**20**: M.p. 39–41 °C. $[\alpha]_D^{26}$ = +31.2 (*c* = 1.00, $CHCl_3$). ^{1}H and ^{13}C NMR, FTIR, and ESI-MS spectroscopic data were the same as those reported for **20**. ESI-HRMS: calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1254; found 287.1252.

MnO_2 Oxidation of *ent*-20 To Give (*S*)-3: The procedure described above for the MnO_2 oxidation of **20** to give (*R*)-**3** above was used. Purification by chromatography (PE/EtOAc, 3:1) gave (*S*)-**3** (18 mg, 0.069 mmol, 86% from *ent*-**20**) as a colourless oil. Data for (*S*)-**3**: $[\alpha]_D^{25}$ = +36.7 (*c* = 0.85, MeOH); $[\alpha]_D^{25}$ = +37.6 (*c* = 0.43, MeOH); $[\alpha]_D^{25}$ = +37.4 (*c* = 0.21, MeOH); $[\alpha]_D^{26}$ = +36.9 (*c* = 0.11, MeOH); $[\alpha]_D^{26}$ = +37.7 (*c* = 0.07, MeOH) [ref.[1a] data for natural **3**: $[\alpha]_D^{24}$ = +29.4 (*c* = 0.07, MeOH)]. ^{1}H and ^{13}C NMR, FTIR, and ESI-MS spectroscopic data were the same as those reported for (*R*)-**3**. ESI-HRMS: calcd. for $C_{15}H_{18}O_4Na$ $[M + Na]^+$ 285.1097; found 285.1101.

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

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