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Systematic Strategy for the Synthesis of Cyanobacterin and Its Stereoisomers. 2. Asymmetric Total Synthesis of the 2- and 3-Epimers of Dechloro-cyanobacterin

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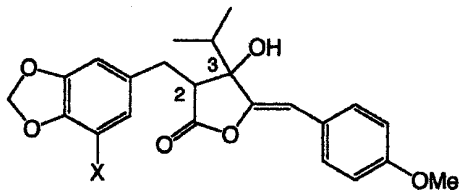
Stereocontrolled total syntheses of the (2*S*,3*R*)- and (2*R*,3*S*)-isomers of the non-chlorinated analog of cyanobacterin, a potent photosynthesis inhibitor, were achieved. Since both the (2*R*,3*R*)- and (2*S*,3*S*)-isomers of this compound had been previously synthesized from the same starting material, a systematic strategy for the synthesis of all stereoisomers could be established.

Key words: cyanobacterin; natural photosynthesis inhibitor; synthesis of stereoisomers; Evans and non-Evans aldol condensation; diastereoselective alkynylation

Cyanobacterin (**1** in Fig. 1) has been isolated from the cyanobacterium, *Scytonema hofmanni*, as a potent photosynthesis inhibitor.[1] Its effect against both algae and angiosperms is known to act by inhibiting photosynthetic electron transport in the oxygen-evolving system of photosynthesis (photosystem Ⅱ).[2,3] Racemic **1** synthesized by Jong *et al.*[4] and some less-active analogs have been assayed.[5,6] However, the investigation has not given satisfactory knowledge to explain the structure-activity relationship, especially concerning the stereochemistry at both asymmetric carbons. These features of this compound prompted us to develop a new and efficient synthetic route to **1** and its all stereoisomers.

In the previous paper,[7] we have described the stereoselective total synthesis of dechloro derivative **2** as a model compound of **1** and its enantiomer **3**. Both compounds were prepared from the same starting material **7** by using an asymmetric aldol reaction in the presence or absence of $TiCl_4$, respectively producing non-Evans-type and Evans-type products as the key step. We thought that the synthetic procedure utilized would be suitable for preparing the two diastereomers of **2**, enabling all four stereoisomers to be able obtained and examined for their biological activity.

The most important aspect of our study is the development of a systematic strategy for the synthesis of **1** and all its stereoisomers. Therefore, the starting material and basic plan for the synthesis of **4** and **5** were required to be similar to those in the previous report.[7] The retrosynthetic analysis of **4** is shown in Scheme 1. The stereochemistry at the C-3 position of **4** was achieved by chelation-controlled diastereoselective alkynylation of β-hydroxy ketone **6** before exposing to Ag^+-catalyzed *exo*-cyclization. Intermediate **6** was obtained stereoselectively by the Evans aldol reaction between **7** and **8**. 3-Epimer **5** could be synthesized by applying the non-Evans aldol reaction instead of the Evans type.



1 X=Cl, (2*R*, 3*R*) Cyanobacterin
2 X=H, (2*R*, 3*R*) Dechloro-cyanobacterin
3 X=H, (2*S*, 3*S*) Enantiomer of **2**
4 X=H, (2*S*, 3*R*) 2-Epimer of **2**
5 X=H, (2*R*, 3*S*) 3-Epimer of **2**

Fig. 1. Structures of Cyanobacterin **1** and Its Dechlorinated Analogs (**2–5**).

Results and Discussion

Acylated oxazolidinone **7** was subjected to the Evans aldol reaction[8,9] with commercially available isobutyraldehyde **8** to provide a single isomer of Evans *syn* aldol adduct **9** in an 81.4% yield (Scheme 2). On the other hand, in the presence of $TiCl_4$ (Ⅳ),[10] condensation between **7** and **8** gave a mixture of the two non-Evans aldol adducts, *anti*-(**10-a**) and *syn*-(**10-b**), in an 88.2% yield. The reaction was diastereoselective, and **10-a** was predominantly produced (80.2:19.8), contrary to the *syn* selective reaction of **7** with 4-methoxyphenylpropynal described in the previous paper.[7] Although Walker and Heathcock[9] have discussed the selectivity from the

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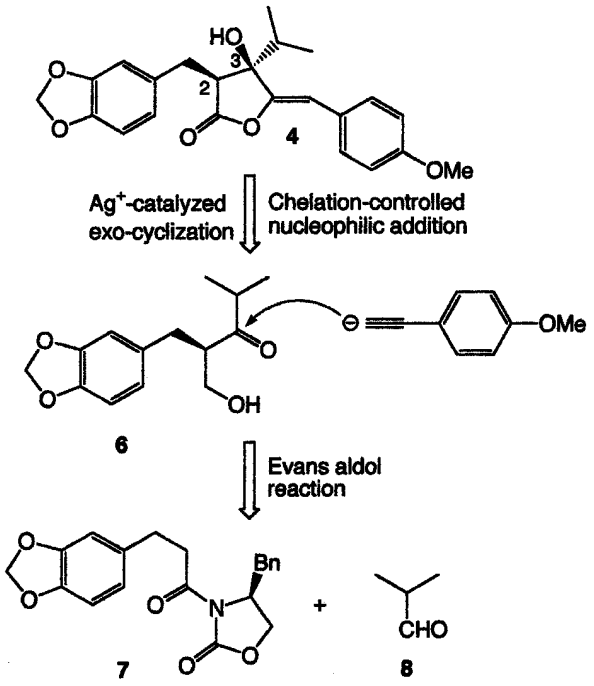
viewpoint of steric bulk and the addition rate of Lewis acid, the stereochemistry at the C-3 position of **10** was not significant in this step of our strategy.

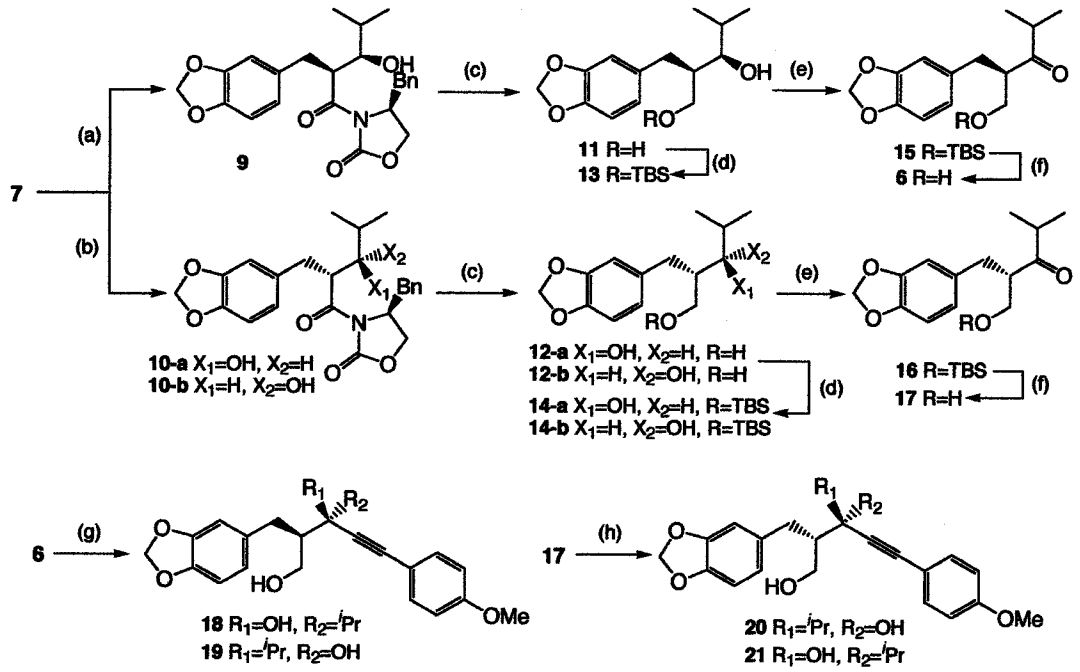
Resulting **9** and **10**, which had an inverse configuration at the C-2 position, were readily reduced with lithium tetrahydroborate in aqueous Et_2O.



Scheme 1. Retrosynthetic Analysis of **4**.

Regioselective protection of the primary hydroxyl groups in **11** and **12** as the *tert*-butyldimethylsilyl (TBS) ether and subsequent Swern oxidation of the secondary hydroxyl groups of resulting **13** and **14** almost exclusively provided **15** and **16**. The TBS protecting groups in these compounds were removed in an acidic medium to afford **6** and **17** in 64.9% and 68.1% yields, respectively, in 4 steps.

In the next diastereoselective alkynylation step, the stereochemistry at the C-3 position of 1,3-diol **18** was constructed. The chelation-controlled neucleophilic attack of metal acetylide to **6** led to **18** and its isomer **19**. The former had the desired configuration and the latter was thought to have been produced by application of the Felkin-Anh model.[11] These two reactions were probably competitive and would favorably act depending on the reagent and condition used. Indeed, as shown in Table 1, when lithium was used as a counter cation, the latter reaction predominantly proceeded and selectively provided **19**. As a second trial, the use of cuprate instead of the lithium cation resulted in an improved *ratio* of objective **18**. Furthermore, the addition of Lewis acid under this condition led to a reverse in the selectivity. The addition of $TiCl_4$ (Ⅳ) gave the desired compound in a 68.0% yield with moderate selectivity (81.7:18.3, determined by ^{1}H-NMR). Similarly, (2*S*)-isomer **17** afforded **20** along with its isomer **21** in a yield of 58.5% with similar selectivity (78.9:21.1). According to the HPLC analysis performed with a Chiralcel OF



Scheme 2. Synthesis of 1,3-Diols **18** and **20**.

Reagents and conditions: (a) isobutyraldehyde (**8**), ^{n}Bu$_2$BOTf, ^{i}Pr$_2$NEt, CH_2Cl_2, −78°C—−15°C, 81.4%; (b) **8**, ^{n}Bu$_2$BOTf, ^{i}Pr$_2$NEt, $TiCl_4$, CH_2Cl_2, −78°C—0°C, 88.2% (**10-a**:**10-b** = 80.2:19.8); (c) $LiBH_4$, Et_2O, 91.2% (**11**), 90.8% (**12-a**), 89.0% (**12-b**); (d) TBS-Cl, Et_3N, DMAP, DMF, 98.3% (**13**), 99.7% (**14-a**), 98.2% (**14-b**); (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C, 90.8% (**15**), 90.9 % (**16**); (f) AcOH/THF/H_2O (2:1:1), 79.7% (**6**), 82.8% (**17**); (g) see Table 1; (h) 4-methoxyphenylacetylene, ^{n}BuLi, CuI, $TiCl_4$, Et_2O, −78°C—r.t., 58.5% (**20**:**21** = 78.9:21.1).

column (4.6×250 mm, Daicel Chemical Industries), it was found that the enantiomeric excess values for **18** and **20** were 98.1% and 99.1%, respectively. Each major product in this reaction (**18** and **20**) was identical with the minor isomer described in our previous report.[7] Similarly, each minor product, (**19** and **21**), corresponded to the objective compound in the previous paper. The IR, ^{1}H- and ^{13}C-NMR spectral date and specific rotation of the corresponding compounds were identical with each other. Accordingly, it was confirmed that our synthetic strategy enabled the preparation of all four stereoisomers of the 1,3-diol (**18**–**21**) which were the important intermediates of the desired product.

The next step was the oxidation of each primary hydroxyl group in **18** and **20** to carboxylic acid and *exo*-cyclization to construct a γ-ylidene-γ-butyrolactone framework. As shown in Scheme 3, their oxidation could be achieved with two kinds of oxidant. The combination of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine-*N*-oxide (NMO) followed by sodium chlorite in the presence of 2-methyl-2-butene gave desired carboxylic acids **22** and **23** in 68.4% and 67.6% yields, respectively. Finally, Ag^+-catalyzed annulation[12] of **22** and **23** furnished exo-cyclic products **4** and **5** in 43.8% and 40.3% yields, respectively. The specific rotation of both these compounds was almost the same value with the opposite sign (+46.1 and −46.7, respectively), and their melting point (mp), and IR, ^{1}H- and ^{13}C-NMR spectral data were identical. Although further efforts to improve the yield in last step and the diastereoselectivity in the alkynylation reaction would be necessary for this synthetic procedure, both **4** and **5** were obtained with high optical purity.

Table 1. Diastereoselective Alkynylation of **6**

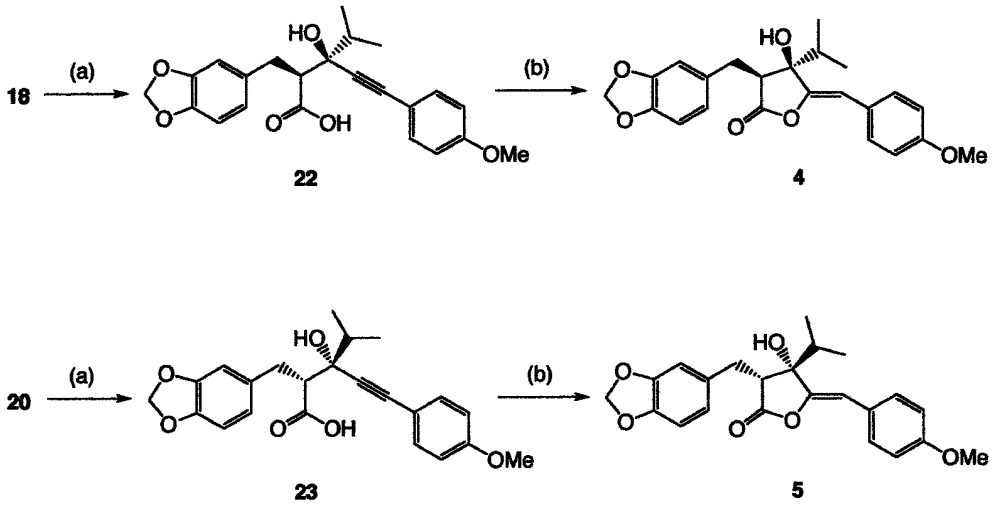
Reagents and conditions[a]	Yield (%)	Ratio (**18**:**20**)[b]
Ar—≡—Li, THF, −78°C	65.4	29.8:70.2
(Ar—≡—)$_2$CuLi, Et_2O, −78°C	39.5	46.1:54.9
(Ar—≡—)$_2$CuLi, $TiCl_4$, Et_2O, −78°C–r.t.	68.0	81.7:18.3

[a] Ar = 4-methoxyphenyl, [b] Determined by ^{1}H-NMR.

In conclusion, we accomplished the stereoselective total synthesis of the 2- and 3-epimers (**4** and **5**) of dechloro-cyanobacterin **2** in 12 steps with overall yields of 7.9% and 7.0%, respectively. Since we have previously reported the synthesis of **2** and **3**, we could establish a systematic strategy for the synthesis of all four stereoisomers of this model compound from the same starting material. This strategy will enable us to synthesize natural occurring product **1** and all its stereoisomers.

Experimental

All melting point (mp) data are uncorrected. IR spectra were recorded by a Shimadzu FTIR-8100 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL JNM-EX400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported relative to internal tetramethylsilane (TMS, 0.00 ppm) or chloroform-*d* ($CDCl_3$, 7.26 ppm) for ^{1}H and relative to $CDCl_3$ (77.00 ppm) or acetone-d_6 (30.30 ppm) for ^{13}C. Optical rotation values were determined with a Horiba SEPA-200 polarimeter. Silica gel 60 (100–210 μm) was obtained from Kanto Chemical Co. TLC and preparative TLC were respectively carried out by using Merck silica gel 60 F_{254} precoated plastic plates of 0.2 mm in thickness and Merck silica gel 60 F_{254} precoated glass plates of 0.5 mm in thickness.



Scheme 3. Synthesis of the 2-Epimer (**4**) and 3-Epimer (**5**).
Reagents and conditions: (a) (1) TPAP, NMO, MS-4A, CH_2Cl_2; (2) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{t}BuOH/H_2O (4:1), 0°C, 68.4% (**22**), 67.6% (**23**); (b) $AgNO_3$, MeOH, 43.8% (**4**), 40.3% (**5**).

(4S)-4-Benzyl-[(2S,3R)-3-hydroxy-4-methyl-2-(3,4-methylenedioxybenzyl)valeryl]-2-oxazolidinone (9). To a stirred solution of **7** (2.08 g, 5.89 mmol) in CH_2Cl_2 (30 ml) was added dibutylboron triflate (5.7 ml of a 1.0 M solution in CH_2Cl_2, 5.7 mmol) and *N*,*N*-diisopropylethylamine (1.28 ml, 7.35 mmol) at −20°C under an N_2 atmosphere. The reaction mixture was allowed to warm to 0°C and stirred for 2 h, before cooling to −78°C. A solution of **8** (0.58 ml, 6.39 mmol) in CH_2Cl_2 (1 ml) was added to this mixture, and the resulting solution was stirred for 1 h at the same temperature before being allowed to warm to −15°C. After stirring for 3 h, the reaction mixture was quenched by adding the mixed solvent of a phosphate buffer solution (pH 6.86, 25 ml) and CH_3OH (25 ml) and then 30% H_2O_2 (25 ml) and CH_3OH (25 ml). After stirring vigorously for 1 h at 0°C, the organic layer was separated, and the aqueous phase was extracted with Et_2O (2×20 ml). The combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying (Na_2SO_4) and concentration, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 3:1 to 3:2). After removing the solvent *in vacuo*, the resulting residue was recrystallized from hexane-2-propanol (2:1) to give **9** as white crystals. The mother liquor was evaporated, and the residue was purified by column chromatography on silica gel (hexane-EtOAc, 2:1) to provide **9** as a second crop (total 2.04 g, 81.4%), R_f 0.31 (hexane-EtOAc, 3:2), mp 64–65°C, $[\alpha]_D^{25}$ +3.4° (*c* 3.87, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, *J*=6.8 Hz, C*H*$_3$), 1.05 (3H, d, *J*=6.8 Hz, C*H*$_3$), 1.78–1.86 {1H, m, $(CH_3)_2CH$}, 2.32 (1H, dd, *J*=9.3, 13.7Hz, Ph–C*H*$_2$), 2.54 (1H, br, –O*H*), 2.93 (1H, dd, *J*=2.9, 13.3 Hz, Ar$_1$–C*H*$_2$CHC=O), 2.96 (1H, dd, *J*=4.9, 13.3Hz, Ar$_1$–C*H*$_2$CHC=O), 3.09 (1H, dd, *J*=11.2, 13.7 Hz, Ph–C*H*$_2$), 3.53 {1H, dd, *J*=3.4, 7.8 Hz, C*H*(OH)}, 4.02 (1H, dd, *J*=2.7, 9.0 Hz, NCHC*H*$_2$O), 4.10 (1H, dd, *J*=8.3, 9.0 Hz, NCHC*H*$_2$O), 4.59–4.66 (2H, m, C*H*C=O, and NC*H*CH$_2$O), 5.84 (1H, d, *J*=1.5 Hz, O–C*H*$_2$–O), 5.90 (1H, d, *J*=1.5 Hz, O–C*H*$_2$–O), 6.70–6.78 (3H, m, Ar$_1$–*H*), 6.98 (2H, d, *J*=7.8 Hz, Ph–*H*), 7.16–7.29 (3H, m, Ph–*H*); ^{13}C-NMR ($CDCl_3$) δ: 19.71, 19.75, 32.02, 32.46, 38.05, 47.45, 55.69, 66.32, 77.83, 101.52, 108.85, 110.68, 123.10, 128.01, 129.61, 129.98, 132.23, 135.77, 146.81, 148.26, 153.52, 176.64; IR ν_{max} ($CHCl_3$) cm^{-1}: 1786, 1683, 1508, 1491, 1457, 1393, 1358, 1247, 1217, 1196, 1115, 1046, 940, 816, 777, 760, 739, 709. *Anal.* Found: C, 67.58; H, 6.40; N, 3.12%. Calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29%.

(4S)-4-Benzyl-[(2R,3R/S)-3-hydroxy-4-methyl-2-(3,4-methylenedioxybenzyl)valeryl]-2-oxazolidinone (10-a) and (10-b). To a stirred solution of **7** (3.88 g, 11.0 mmol) in CH_2Cl_2 (40 ml) was added dibutylboron triflate (11.5 ml of a 1.0 M solution in CH_2Cl_2, 11.5 mmol) and then *N*,*N*-diisopropylethylamine (2.39 ml, 13.7 mmol) at −20°C under an N_2 atmosphere. The reaction mixture was allowed to warm to 0°C and stirred for 2 h, before cooling to −78°C. In another flask, to a solution of $TiCl_4$ (IV) (2.65 ml, 24.2 mmol) in CH_2Cl_2 (50 ml) was added dropwise a solution of **8** (1.10 ml, 12.1 mmol) in CH_2Cl_2 (2 ml) at −78°C under an N_2 atmosphere, and the mixture stirred for 15 min. To the reaction mixture was added the above-mentioned solution of the boron enolate *via* a cannula under N_2 pressure. The resulting solution was stirred for 1 h at the same temperature, before being allowed to warm to 0°C and stirred for another 4 h. The mixture was quenched by adding of a mixed solvent of a phosphate buffer solution (pH 6.86, 30 ml) and CH_3OH (30 ml), and then 30% H_2O_2 (30 ml) and CH_3OH (30 ml). After stirring vigorously for 1 h at 0°C, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2×20 ml). The combined organic phase was successively washed with sat. $NaHCO_3$ and brine. After drying (Na_2SO_4) and concentrating, the residue was purified by column chromatography on silica gel (toluene-EtOAc, 15:1) to provide an *anti*-adduct (**10-a**) and *syn*-adduct (**10-b**) separately. After removing the solvent, **10-a** was recrystallized from $^iPr_2O$. After concentrating the mother liquor, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 3:2) to provide a second crop of **10-a** (total yield 4.12 g, 88.2%).

10-a: R_f 0.37 (toluene-EtOAc, 12:1), mp 85–86°C, $[\alpha]_D^{25}$ +108° (*c* 2.40, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, *J*=6.8 Hz, C*H*$_3$), 1.02 (3H, d, *J*=6.8 Hz, C*H*$_3$), 1.73–2.02 {1H, m, $(CH_3)_2CH$}, 2.72 (1H, dd, *J*=9.8, 13.2 Hz, Ph–C*H*$_2$), 2.92 (1H, dd, *J*=7.3, 13.2 Hz, Ar$_1$–C*H*$_2$CHC=O), 2.97 (1H, dd, *J*=8.3, 13.2 Hz, Ar$_1$–C*H*$_2$CHC=O), 3.09 (1H, d, *J*=10.3 Hz, –O*H*), 3.27 (1H, dd, *J*=3.4, 13.2 Hz, Ph–C*H*$_2$), 3.38 {1H, ddd, *J*=4.4, 6.3, 10.3 Hz, C*H*(OH)}, 3.89 (1H, dd, *J*=8.3, 9.0 Hz, NCHC*H*$_2$O), 4.08 (1H, dd, *J*=2.2, 9.0 Hz, NCHC*H*$_2$O), 4.39 (1H, ddd, *J*=4.4, 7.3, 8.3 Hz, C*H*C=O), 4.49–4.52 (1H, m, NC*H*CH$_2$O), 5.90 (2H, s, O–C*H*$_2$–O), 6.70–6.75 (3H, m, Ar$_1$–*H*), 7.21 (2H, d, *J*=6.8 Hz, Ph–*H*), 7.27–7.34 (3H, m, Ph–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.87, 19.53, 32.44, 36.26, 37.95, 46.70, 55.47, 66.01, 77.74, 100.89, 108.15, 109.60, 122.19, 127.42, 128.99, 129.45, 131.94, 135.15, 146.20, 147.57, 153.12, 176.65; IR ν_{max} ($CHCl_3$) cm^{-1}: 1790, 1679, 1611, 1512, 1495, 1452, 1388, 1358, 1256, 1217, 1200, 1115, 1051, 940, 816, 777, 764, 739, 709. *Anal.* Found: C, 67.68; H, 6.77; N, 3.08%. Calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29%.

10-b: R_f 0.29 (toluene-EtOAc, 12:1), colorless oil, $[\alpha]_D^{25}$ +113° (*c* 0.87, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, *J*=6.8 Hz, C*H*$_3$), 1.07 (3H, d, *J*=6.8

Hz, CH_3), 1.76–1.86 {1H, m, $(CH_3)_2CH$}, 2.53 (1H, d, J=4.1 Hz, –OH), 2.70 (1H, dd, J=9.3, 12.7 Hz, Ph–CH_2), 2.97 (2H, d, J=7.9 Hz, Ar_1–CH_2CHC=O), 3.20 (1H, dd, J=3.4, 12.7 Hz, Ph–CH_2), 3.65 {1H, ddd, J=3.9, 4.1, 7.3 Hz, CH(OH)}, 3.77 (1H, dd, J=8.2, 9.0 Hz, NCHCH_2O), 4.01 (1H, dd, J=2.4, 9.0 Hz, NCHCH_2O), 4.38–4.44 (1H, m, NCHCH$_2$O), 4.50 (1H, ddd, J=3.9, 7.8, 8.1 Hz, CHC=O), 5.88 (2H, s, O–CH_2–O), 6.62–6.70 (3H, m, Ar_1–H), 7.18 (2H, d, J=6.8 Hz, Ph–H), 7.26–7.34 (3H, m, Ph–H); ^{13}C-NMR ($CDCl_3$) δ: 18.58, 19.14, 31.36, 32.54, 38.06, 46.87, 55.30, 66.00, 76.67, 100.83, 108.09, 109.56, 121.93, 127.37, 128.92, 129.38, 132.55, 135.13, 146.21, 147.55, 153.07, 175.88; IR ν_{max} ($CHCl_3$) cm^{-1}: 1790, 1679, 1512, 1495, 1452, 1393, 1358, 1252, 1217, 1200, 1115, 1046, 940, 816, 781, 764, 743, 709. *Anal.* Found: C, 67.48; H, 6.56; N, 3.18%. Calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29%.

Procedure for reductive cleavage of the chiral auxiliary. Lithium tetrahydroborate (1.5 eq) was added to the solution of **9** (7.90 mmol) or **10** (7.17 mmol) in Et_2O (7 ml/mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 6 h, before slowly adding 2 M-HCl at 0°C. After decomposing the excess reducing agent, the ethereal layer was separated. The aqueous phase was extracted with EtOAc (2×10 ml), and the combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying (Na_2SO_4) and concentrating, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 2:1) to provide the products.

*(2R,3R)-4-Methyl-2-(3,4-methylenedioxyphenyl)-methyl-1,3-pentanediol (**11**)*: 91.2% yield, mp 113°C, $[\alpha]_D^{25}$ −31.0° (*c* 1.42, $CHCl_3$); ^{1}H-NMR (acetone-d_6) δ: 0.91 (3H, d, J=6.8 Hz, CH_3), 0.99 (3H, d, J=6.4 Hz, CH_3), 1.79–1.89 {2H, m, $(CH_3)_2CH$ and Ar–CH_2CH}, 2.59 (1H, dd, J=10.5, 13.9 Hz, Ar_1–CH_2), 2.78 (1H, dd, J=3.7, 13.9 Hz, Ar_1–CH_2), 2.79 (1H, br, –OH), 3.46–3.51 {(2H, m, CH_2OH and CHOH), D_2O exchange; 3.50 (1H, dd, J=3.9, 7.9 Hz, CHOD), 3.51 (1H, dd, J=3.9, 10.7 Hz, CH_2OD)}, 3.52–3.59 {(1H, m, CH_2OH), D_2O exchange; 3.56 (1H, dd, J=5.9, 10.7 Hz, CH_2OD)}, 3.70 (1H, ddd, J=4.4, 8.5, 9.3 Hz, –OH), 5.93 (2H, s, O–CH_2–O), 6.69–6.76 (3H, m, Ar_1–H); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=6.3 Hz, CH_3), 1.05 (3H, d, J=6.3 Hz, CH_3), 1.82–1.90 {2H, m, $(CH_3)_2CH$ and Ar–CH_2CH}, 2.14 (1H, br, –OH), 2.52 (1H, br, –OH), 2.72 (1H, d, J=7.8 Hz, Ar_1–CH_2), 3.55 (1H, dd, J=2.7, 8.8 Hz, CH_2OH), 3.65 (2H, m, CH_2OH and CHOH), 5.92 (2H, s, O–CH_2–O), 6.67–6.74 (3H, m, Ar_1–H); ^{13}C-NMR (acetone-d_6) δ: 19.57, 20.44, 31.69, 31.99, 46.12, 63.58, 79.17, 102.10, 109.14, 110.81, 123.32, 136.96, 146.95, 148.93; ^{13}C-NMR ($CDCl_3$) δ: 19.17, 19.23, 29.67, 31.08, 43.47, 64.58, 80.95, 100.78, 108.19, 109.48, 121.91, 134.55, 145.92, 147.74; IR ν_{max} ($CHCl_3$) cm^{-1}: 1722, 1658, 1564, 1546, 1512, 1495, 1448, 1252, 1222, 1196, 1046, 940, 820, 781, 764, 756, 743. *Anal.* Found: C, 66.37; H, 8.04%. Calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99%.

*(2S,3R)-4-Methyl-2-(3,4-methylenedioxyphenyl)methyl-1,3-pentanediol (**12-a**)*: 90.8% yield from **10-a**, colorless oil, $[\alpha]_D^{25}$ +13.7° (*c* 2.49, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=6.8 Hz, CH_3), 1.00 (3H, d, J=6.8 Hz, CH_3), 1.84–1.95 {2H, m, Ar_1–CH_2CH and $(CH_3)_2CH$}, 2.37 (1H, dd, J=9.5, 13.9 Hz, Ar_1–CH_2), 2.69–2.73 {(2H, m, Ar_1–CH_2 and OH), D_2O exchange; 2.73 (1H, dd, J=5.6, 13.9 Hz, Ar_1–CH_2)}, 3.28–3.36 {(1H, m, CHOH), D_2O exchange; 3.32 (1H, dd, J=5.4, 7.1 Hz, CHOD}, 3.67 (1H, dd, J=6.8, 10.8 Hz, CH_2OH), 3.87–3.92 {2H, m, CH_2OH and OH, D_2O exchange; 3.89 (1H, dd, J=4.4, 10.8 Hz, CH_2OD)}, 5.93 (2H, s, O–CH_2–O), 6.63–6.74 (3H, m, Ar_1–H); ^{13}C-NMR ($CDCl_3$) δ: 16.11, 19.46, 30.54, 34.85, 43.27, 64.63, 80.35, 100.93, 108.27, 109.12, 121.80, 132.50, 146.13, 147.87; IR ν_{max} ($CHCl_3$) cm^{-1}: 1722, 1658, 1564, 1516, 1495, 1448, 1252, 1222, 1192, 1042, 944, 820, 777, 764, 756, 743. *Anal.* Found: C, 66.46; H, 7.98%. Calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99%.

*(2S,3S)-4-Methyl-2-(3,4-methylenedioxyphenyl)-methyl-1,3-pentanediol (**12-b**)*: 89.0% yield from **10-b**, mp 108–110°C, $[\alpha]_D^{25}$ −34.8° (*c* 2.01, $CHCl_3$); ^{1}H-NMR (acetone-d_6) δ: 0.91 (3H, d, J=6.8 Hz, CH_3), 0.98 (3H, d, J=6.3 Hz, CH_3), 1.78–1.88 {2H, m, $(CH_3)_2CH$ and Ar_1–CH_2CH}, 2.58 (1H, dd, J=10.8, 13.7 Hz, Ar_1–CH_2), 2.76 (1H, dd, J=3.9, 13.7 Hz, Ar_1–CH_2), 2.78 (1H, s, –OH), 3.45–3.50 {(2H, m, CH_2OH and CHOH), D_2O exchange; 3.49 (1H, dd, J=3.9, 7.3 Hz, CHOD), 3.50 (1H, dd, J=3.9, 10.5 Hz, CH_2OD)}, 3.51–3.58 {(1H, m, CH_2OH), D_2O exchange; 3.53 (1H, dd, J=5.9, 10.5 Hz, CHOD)}, 3.70 (1H, ddd, J=4.9, 9.0, 9.5 Hz, –OH), 5.92 (2H, s, O–CH_2–O), 6.68–6.75 (3H, m, Ar_1–H); ^{13}C-NMR ($CDCl_3$) δ:19.17, 19.25, 29.27, 31.07, 43.46, 64.56, 80.93, 100.78, 108.19, 109.48, 121.98, 134.55, 145.72, 147.63; IR ν_{max} ($CHCl_3$) cm^{-1}: 1722, 1658, 1564, 1512, 1495, 1448, 1256, 1222, 1196, 1046, 940, 820, 781, 764, 756, 743. *Anal.* Found: C, 66.23; H, 8.13%. Calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99%.

Procedure for regioselective silylation. To a stirred solution of **11** (6.54 mmol) or **12** (6.35 mmol) in DMF (2 ml/mmol) was added imidazole (2.50 eq), a catalytic amount of DMAP, and TBS-Cl (1.05 eq) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h before quenching with sat. NH_4Cl (20 ml). After stirring for 5 min, the organic layer was separated, and the aqueous phase was extracted with Et_2O (2×5 ml). The combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying and concentrating, the residue was purified by column chro-

matography on silica gel (hexane-EtOAc, 9:1) to provide a silyloxy alcohol.

(2R,3R)-1-tert-Butyldimethylsilyloxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanol ***(13)***: 98.3% yield, colorless oil, $[\alpha]_D^{25}$ −21.5° (*c* 4.23, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.02 (3H, s, Si–CH_3), 0.04 (3H, s, Si–CH_3), 0.91 (3H, d, J=6.3 Hz, CH_3), 0.92 {9H, s, (CH_3)×3}, 1.06 (3H, d, J=6.8 Hz, CH_3), 1.79–1.90 {2H, m, $(CH_3)_2$CH and Ar_1–CH_2CH}, 2.72 (2H, d, J=7.8 Hz, Ar_1–CH_2), 3.50 (1H, s, OH), 3.52 {1H, d, J=8.8 Hz, CH(OH)}, 3.63 (2H, d, J=2.9 Hz, CH_2OSi), 5.92 (2H, s, O–CH_2–O), 6.61–6.73 (3H, m, Ar_1–H); ^{13}C-NMR ($CDCl_3$) δ: −5.75, −5.70, 18.05, 19.20, 19.45, 25.86, 29.18, 30.82, 43.26, 65.37, 81.20, 100.76, 108.04, 109.45, 122.00, 134.86, 145.62, 147.56; IR ν_{max} ($CHCl_3$) cm^{-1}: 3495, 2983, 2876, 1512, 1495, 1478, 1393, 1367, 1252, 1196, 1149, 1081, 1046, 995, 940, 841, 781, 769, 750, 739, 692. *Anal.* Found: C, 65.26; H, 9.53%. Calcd. for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35%.

(2S,3R)-1-tert-Butyldimethylsilyloxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanol ***(14-a)***: 99.7% yield from **12-a**; colorless oil, $[\alpha]_D^{25}$ +9.0° (*c* 3.65, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H, s, Si–CH_3), 0.05 (3H, s, Si–CH_3), 0.85 (3H, d, J=6.3 Hz, CH_3), 0.90 {9H, s, (CH_3)×3}, 1.02 (3H, d, J=6.8 Hz, CH_3), 1.75–1.85 {2H, m, $(CH_3)_2$CH and Ar_1CH_2CH}, 2.69 (1H, dd, J=8.8, 13.7 Hz, Ar–CH_2), 2.78 (1H, dd, J=6.8, 13.7 Hz, Ar_1–CH_2), 3.18 {1H, ddd, J=4.3, 7.3, 8.0 Hz, CH(OH)}, 3.29 (1H, d, J=7.3 Hz, –OH), 3.58 (1H, dd, J=3.7, 10.2 Hz, CH_2OSi), 3.87 (1H, dd, J=3.2, 10.0 Hz, CH_2OSi), 5.91 (2H, s, O–CH_2–O), 6.31–6.73 (3H, m, Ar_1–H); ^{13}C-NMR ($CDCl_3$) δ: −5.76, −5.69, 18.02, 18.59, 19.44, 25.79, 25.83, 32.00, 35.26, 42.96, 63.20, 79.56, 100.71, 108.01, 109.41, 121.99, 134.43, 145.65, 147.53; IR ν_{max} ($CHCl_3$) cm^{-1}: 2983, 2876, 1512, 1495, 1478, 1448, 1393, 1367, 1256, 1200, 1149, 1085, 1046, 999, 940, 841, 781, 773, 751, 739, 692. *Anal.* Found: C, 65.27; H, 9.36%. Calcd. for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35%.

(2S,3S)-1-tert-Butyldimethylsilyloxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanol ***(14-b)***: 98.2% yield from **12-b**, colorless oil, $[\alpha]_D^{25}$ +17.3° (*c* 1.91, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.02 (3H, s, Si–CH_3), 0.03 (3H, s, Si–CH_3), 0.91 (3H, d, J=6.3Hz, CH_3), 0.92 {9H, s, (CH_3)×3}, 1.06 (3H, d, J=6.3 Hz, CH_3), 1.79–1.90 {2H, m, $(CH_3)_2$CH and Ar_1–CH_2CH}, 2.72 (2H, d, J=7.3 Hz, Ar_1–CH_2), 3.48–3.53 (2H, m, CH(OH) and –OH), 3.63 (2H, d, J=3.4 Hz, CH_2OSi), 5.92 (2H, s, O–CH_2–O), 6.62–6.66 (2H, m, Ar_1–H), 6.72 (1H, d, J=7.8 Hz, Ar_1–H); ^{13}C-NMR ($CDCl_3$) δ: −5.75, −5.70, 18.05, 19.20, 19.46, 25.87, 29.16, 30.82, 43.24, 65.37, 81.22, 100.76, 108.05, 109.45, 122.01, 134.85, 145.62, 147.56; IR ν_{max} ($CHCl_3$) cm^{-1}: 3495, 2983, 2876, 1508, 1495, 1478, 1448, 1393, 1367, 1256, 1200, 1149, 1081, 1051, 995, 944, 845, 790, 777, 764, 739, 692. *Anal.* Found: C, 65.40; H, 9.42%. Calcd. for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35%.

Procedure for Swern oxidation. Four equivalents of dimethyl sulfoxide (DMSO) was added to a stirred solution of oxalyl chloride (2.0 eq) in CH_2Cl_2 (10 ml/mmol) at −78°C under an N_2 atmosphere. The resulting solution was stirred for 15 min before adding a solution of **13** (3.60 mmol) or **14** (3.49 mmol) in CH_2Cl_2 (10 ml). After stirring for 2 h, triethylamine (6.0 eq) was added to the solvent, and the resulting mixture was allowed to warm to 0°C over 30 min. To the mixture was then added sat. NH_4Cl (50 ml), and this was allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted with Et_2O (2×10 ml). The combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying and concentrating, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 7:1) to provide a silyloxy ketone.

(2R)-1-tert-Butyldimethylsilyloxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanone ***(15)***: 90.8% yield, colorless oil, $[\alpha]_D^{25}$ +11.2° (*c* 0.86, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.01 (3H, s, Si–CH_3), 0.02 (3H, s, Si–CH_3), 0.81 (3H, d, J=6.8 Hz, CH_3), 0.87 {9H, s, (CH_3)×3}, 0.99 (3H, d, J=6.8 Hz, CH_3), 2.37–2.48 {1H, m, $(CH_3)_2$CH}, 2.59 (1H, dd, J=6.4, 13.7 Hz, Ar–CH_2), 2.70 (1H, dd, J=8.8, 13.7 Hz, Ar_1–CH_2), 3.13–3.20 (1H, m, Ar_1–CH_2 CH}, 3.61 (1H, dd, J=5.0 , 9.5 Hz, CH_2OSi), 3.74 (1H, dd, J=8.3, 9.5 Hz, CH_2OSi), 5.92 (2H, s, O–CH_2–O), 6.55–6.70 (3H, m, Ar_1–H); ^{13}C-NMR ($CDCl_3$) δ: −5.64, −5.57, 17.12, 17.20, 18.18, 25.80, 34.71, 42.09, 55.01, 64.72, 100.79, 108.15, 109.32, 121.87, 133.25, 145.93, 147.56, 216.57; IR ν_{max} ($CHCl_3$) cm^{-1}: 2940, 2876, 1713, 1512, 1495, 1474, 1448, 1367, 1256, 1222, 1196, 1098, 1046, 1012, 944, 841, 820, 790, 756, 739. *Anal.* Found: C, 65.45; H, 9.15%. Calcd. for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85%.

(2S)-1-tert-Butyldimethylsilyloxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanone ***(16)***: 90.9% yiel,; colorless oil, $[\alpha]_D^{25}$ −16.6° (*c* 1.67, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.00 (3H, s, Si–CH_3), 0.01 (3H, s, Si–CH_3), 079 3H, d, J=6.8 Hz, CH_3), 0.86 {9H, s, (CH_3)×3}, 0.98 (3H, d, J=6.8 Hz, CH_3), 2.36–2.47 {1H, m, $(CH_3)_2$CH}, 2.58 (1H, dd, J=5.9, 13.4 Hz, Ar_1–CH_2), 2.69 (1H, dd, J=8.8, 13.4 Hz, Ar_1–CH_2), 3.12–3.19 (1H, m, Ar–CH_2 CH}, 3.60 (1H, dd, J=5.1, 9.5 Hz, CH_2OSi), 3.74 (1H, dd, J=8.3, 9.5 Hz, CH_2OSi), 5.90 (2H, s, O–CH_2–O), 6.56 (1H, d, J=7.8 Hz, Ar–H), 6.61 (1H, s, Ar_1–H), 6.68 (1H, d, J=7.8 Hz, Ar–H); ^{13}C-NMR ($CDCl_3$) δ: −5.64, −5.58, 17.12, 17.18, 18.17, 25.80, 34.70, 42.07, 55.00, 64.71, 100.78, 108.16, 109.31, 121.86, 133.24, 145.92, 147.56, 216.54; IR

ν_{max} ($CHCl_3$) cm^{-1}: 2940, 2876, 1713, 1512, 1495, 1478, 1452, 1367, 1256, 1217, 1196, 1098, 1046, 1012, 948, 841, 820, 786, 751, 739. *Anal.* Found: C, 65.82; H, 9.06%. Calcd. for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85%.

Procedure for cleavage of the silyl ether. Acetic acid (12 ml) was added to a solution of **15** (3.54 mmol) or **16** (3.12 mmol) in THF (6 ml) and H_2O (6 ml) at room temperature. The reaction mixture was stirred for 16 h and diluted with EtOAc (10 ml) and H_2O (10 ml). The organic layer was separated, and the aqueous phase was extracted with EtOAc (5 ml). The combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying and concentrating, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 2:1) to provide a hydroxy ketone.

(2R)-1-Hydroxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanone (6): 79.7% yield, yellow oil, $[\alpha]_D^{25}$ +72.3° (*c* 3.63, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6.8 Hz, CH_3), 1.05 (3H, d, J=6.8 Hz, C*H*$_3$), 2.21 (1H, br, O*H*), 2.47–2.57 {1H, m, $(CH_3)_2$C*H*}, 2.69 (1H, dd, J=7.5, 13.6 Hz, Ar_1–C*H*$_2$), 2.81 (1H, dd, J=7.8, 13.6 Hz, Ar_1–C*H*$_2$), 3.09 (1H, ddd, J=4.1, 7.8, 13.9 Hz, Ar–CH_2C*H*}, 3.67 (1H, dd, J=4.1, 11.1 Hz, C*H*$_2$OH), 3.74 (1H, dd, J=6.4, 11.1 Hz, C*H*$_2$OH), 5.92 (2H, s, O–C*H*$_2$–O), 6.59–6.73 (3H, m, Ar_1–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.13, 17.89, 34.51, 41.37, 53.77, 62.81, 100.87, 108.26, 109.22, 121.86, 132.57, 146.12, 147.69, 218.10; IR ν_{max} ($CHCl_3$) cm^{-1}: 3474, 2983, 2897, 1709, 1512, 1495, 1470, 1452, 1393, 1367, 1252, 1217, 1196, 1157, 1119, 1085, 1046, 940, 867, 820, 781, 756, 743, 696. *Anal.* Found: C, 67.04; H, 7.23%. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

(2S)-1-Hydroxy-4-methyl-2-(3,4-methylenedioxyphenyl)methyl-3-pentanone (17): 82.8% yield, yellow oil, $[\alpha]_D^{25}$ −77.3° (*c* 4.09, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=6.8 Hz, C*H*$_3$), 1.06 (3H, d, J=6.8 Hz, C*H*$_3$), 2.10 (1H, br, –O*H*), 2.47–2.57 {1H, m, $(CH_3)_2$C*H*}, 2.69 (1H, dd, J=7.3, 13.7 Hz, Ar_1–C*H*$_2$), 2.81 (1H, dd, J=7.6, 13.7 Hz, Ar_1–C*H*$_2$), 3.10 (1H, ddd, J=4.1, 7.6, 14.2 Hz, Ar–CH_2C*H*}, 3.68 (1H, dd, J=4.1, 10.9 Hz, C*H*$_2$OH), 3.74 (1H, dd, J=6.8, 10.9 Hz, C*H*$_2$OH), 5.92 (2H, s, O–C*H*$_2$–O), 6.56 (1H, d, J=7.8 Hz, Ar_1–*H*), 6.61 (1H, s, Ar_1–*H*), 6.68 (1H, d, J=7.8 Hz, Ar_1–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.15, 17.96, 34.53, 41.36, 53.73, 62.81, 100.90, 108.30, 109.25, 121.90, 132.57, 146.16, 147.73, 218.14; IR ν_{max} ($CHCl_3$) cm^{-1}: 3474, 2983, 2897, 1705, 1508, 1491, 1470, 1448, 1388, 1367, 1252, 1217, 1199, 1157, 1115, 1085, 1042, 935, 867, 816, 781, 756, 743, 696. *Anal.* Found: C, 66.86; H, 7.40%. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

Procedure for diastereoselective alkynylation. To a stirred solution of 4-methoxyphenylacetylene (4.75 eq) in Et_2O (20 ml) was added dropwise *n*-BuLi (a 1.58 M solution in hexane, 5.00 eq) at −78°C under an N_2 atmosphere. After stirring for 30 min, the resulting solution was added to a suspension of CuI (95% purity, 2.30 eq) in Et_2O (30 ml) at the same temperature, and the reaction mixture was stirred for 30 min. In another flask, to a stirred Et_2O solution (40 ml) was added $TiCl_4$ (IV) (2.20 eq) followed by a solution of **6** (3.05 mmol) or **17** (3.20 mmol) in Et_2O (10 ml) at −78°C under an N_2 atmosphere. The mixture was aged for 15 min before adding of the above-mentioned cuprate solution *via* a cannula under N_2 pressure. The resulting solution was allowed to warm to room temperature and stirred for 12 h before quenching with sat. NH_4Cl (100 ml). After removing the resulting precipitate by suction filtration, the filtrate was extracted with Et_2O (2× 15ml). The combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying and concentrating the residue was purified by column chromatography on silica gel (toluene-EtOAc, 7:1) to provide crude **18** or **20**, together with minor isomer **19** or **21**, respectively. The resulting crystals of **18** or **20** were recrystallized from hexane-EtOAc (5:1) to give white crystals. The mother liquor was evaporated, and the residue was purified by column chromatography on silica gel (hexane-EtOAc, 3:1) to provide a second crop of crystals.

(2R,3R)-5-(4-Methoxyphenyl)-2-(3,4-methylenedioxybenzyl)-3-(1-methylethyl)-4-pentyne-1,3-diol (18): 68.0% yield, mp 103–104°C, R_f 0.50 (hexane-EtOAc, 3:2), $[\alpha]_D^{25}$ −8.7° (*c* 1.72, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.09 (1H, d, J=6.4 Hz, C*H*$_3$), 1.19 (1H, d, J=6.4 Hz, C*H*$_3$), 1.97–2.01 (1H, m, Ar–CH_2C*H*), 2.20–2.30 {1H, m, $(CH_3)_2$C*H*}, 2.19 (1H, br, –O*H*), 2.85–2.90 (2H, m, Ar–C*H*$_2$), 3.66 (1H, d, J=11.2 Hz, C*H*$_2$OH), 3.81 (4H, s, OC*H*$_3$ and –O*H*), 4.38 (1H, d, J=11.2 Hz, C*H*$_2$OH), 5.93 (2H, s, O–C*H*$_2$–O), 6.70–6.76 (3H, m, Ar_1–*H*), 6.83 (2H, d, J=8.8 Hz, Ar_2–*H*), 7.36 (2H, d, J=8.8 Hz, Ar_2–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.22, 18.00, 29.43, 34.53, 46.80, 55.29, 62.73, 79.08, 86.30, 88.51, 100.82, 108.25, 109.55, 113.91, 114.82, 122.02, 133.09, 134.19, 145.83, 147.66, 159.62; IR ν_{max} ($CHCl_3$) cm^{-1}: 3473, 2983, 1615, 1517, 1495, 1452, 1299, 1256, 1222, 1179, 1110, 1046, 940, 841, 794, 764, 739, 713. *Anal.* Found: C, 72.24; H, 6.99%. Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85%.

(2R,3S)-isomer 19: 15.2% yield, yellow oil, R_f 0.45 (hexane-EtOAc, 3:2); $[\alpha]_D^{25}$ +32.8° (*c* 0.37, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6.4 Hz, −C*H*$_3$), 1.16 (3H, d, J=6.8 Hz, −C*H*$_3$), 2.10–2.17 (1H, m, Ar_1CH_2C*H*), 2.18–2.24 {1H, m, $(CH_3)_2$ C*H*}, 2.65 (1H, dd, J=11.5, 13.9 Hz, Ar_1C*H*$_2$), 2.82 (1H, s, –O*H*), 3.05 (1H, dd, J=3.2, 13.9 Hz, Ar_1C*H*$_2$), 3.21 (1H, br, –O*H*), 3.82 (5H, br, –OC*H*$_3$ and C*H*$_2$OH), 5.92 (2H, s, O–C*H*$_2$–O), 6.68–6.75 (3H, m, Ar_1–*H*), 6.86 (2H, d, J=8.8 Hz, Ar_2–*H*),

7.40 (2H, d, $J=8.8$ Hz, Ar_2–*H*); ^{13}C-NMR ($CDCl_3$) δ: 16.42, 18.09, 33.16, 35.35, 47.53, 55.32, 62.00, 79.24, 86.35, 88.37, 100.83, 108.20, 109.46, 113.98, 114.73, 122.07, 133.19, 134.19, 145.86, 147.67, 159.74.

(2S,3S)-5-(4-Methoxyphenyl)-2-(3,4-methylenedioxybenzyl)-3-(1-methylethyl)-4-pentyne-1,3-diol (20): 58.5% yield, mp 103–104°C, R_f 0.50 (hexane-EtOAc, 3:2); $[\alpha]_D^{25}$ +12.9° (*c* 2.58, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, $J=6.4$ Hz, C*H*$_3$), 1.18 (3H, d, $J=6.4$ Hz, C*H*$_3$), 1.95–2.00 (1H, m, Ar_1CH_2CH), 2.19–2.29 {1H, m, $(CH_3)_2CH$}, 2.45 (1H, br, OH), 2.85 (2H, d, $J=13.6$ Hz, $ArCH_2$), 3.65 (1H, dd, $J=4.9$, 11.2 Hz, C*H*$_2$OH), 3.79 (3H, s, –OC*H*$_3$), 3.85 (1H, br, –O*H*), 4.38 (1H, dd, $J=3.6$, 11.2 Hz, C*H*$_2$OH), 5.92 (2H, s, O–C*H*$_2$–O), 6.69–6.75 (3H, m, Ar_1–*H*), 6.81 (2H, d, $J=9.3$ Hz, Ar_2–*H*), 7.36 (2H, d, $J=9.3$ Hz, Ar_2–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.22, 17.98, 29.41, 34.50, 46.76, 55.26, 62.64, 79.08, 86.25, 88.49, 100.77, 108.22, 109.54, 113.88, 114.84, 122.01, 133.07, 134.21, 145.77, 147.63, 159.57; IR ν_{max} ($CHCl_3$) cm^{-1}: 3474, 2983, 1615, 1517, 1495, 1448, 1299, 1256, 1226, 1179, 1106, 1046, 940, 841, 790, 767, 739, 713. *Anal.* Found: C, 72.37; H, 7.04%. Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85%.

(2S,3R)-isomer 21: 15.6% yield, yellow oil, R_f 0.44 (hexane-EtOAc, 3:2), $[\alpha]_D^{25}$ −36.8° (*c* 2.61, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, $J=6.4$ Hz, −C*H*$_3$), 1.15 (3H, d, $J=6.8$ Hz, −C*H*$_3$), 2.10–2.15 (1H, m, Ar_1–CH_2CH), 2.16–2.25 {1H, m, $(CH_3)_2CH$}, 2.65 (1H, dd, $J=11.7$, 13.7 Hz, Ar_1–C*H*$_2$), 2.82 (1H, s, –O*H*), 3.04 (1H, dd, $J=3.3$, 13.7 Hz, Ar_1–C*H*$_2$), 3.34 (1H, br, –O*H*), 3.80 (1H, dd, $J=8.3$, 10.3 Hz, C*H*$_2$OH), 3.81–3.85 (4H, m, –OC*H*$_3$ and C*H*$_2$OH), 5.91 (2H, s, O–C*H*$_2$–O), 6.68–6.74 (3H, m, Ar_1–*H*), 6.85 (2H, d, $J=8.8$ Hz, Ar_2–*H*), 7.40 (2H, d, $J=8.8$ Hz, Ar_2–*H*); ^{13}C-NMR ($CDCl_3$) δ: 16.41, 18.09, 33.15, 35.34, 47.47, 55.30, 61.96, 79.21, 86.30, 88.38, 100.80, 108.17, 109.45, 113.96, 114.73, 122.00, 133.17, 134.19, 145.84, 147.65, 159.71. *Anal.* Found: C, 71.90; H, 7.02%. Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85%.

Procedure for oxidation. To a stirred solution of **18** (0.95 mmol) or **20** (1.25 mmol) in CH_2Cl_2 (10 ml/mmol) were added NMO (1.5 eq) and crushed molecular sieves at room temperature under an N_2 atmosphere. The reaction mixture was stirred for 5 min before adding a catalytic amount of TPAP. After stirring for 12 h, H_2O (10 ml) was added to the mixture, and resulting biphasic solution was stirred for 5 min before passing through a Celite filter. The filtrate was extracted with Et_2O (2×10 ml), and the combined organic layer was successively washed with sat. $NaHCO_3$ and brine. After drying and concentrating, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 3:1) to provide an aldehyde which was used in next step without further purification.

To a stirred solution of this aldehyde in ^{t}BuOH and H_2O (4:1) were added NaH_2PO_4 (2.7 eq) and 2-methyl-2-butene (10 eq) at room temperature. The solution was aged for 10 min and cooled to 0°C, before treating with $NaClO_2$ (80% purity, 1.1 eq). The resulting mixture was stirred for 1.5 h at the same temperature, and then EtOAc (5 ml) and H_2O (5 ml) were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×5 ml). The combined organic layer was washed with brine. After drying and concentrating, the residue was purified by column chromatography on silica gel (hexane-EtOAc, 2:1 to 1:2) to provide the desired acid.

(2S,3R)-3-Hydroxy-5-(4-methoxyphenyl)-2-(3,4-methylenedioxybenzyl)-3-(1-methylethyl)-4-pentynoic acid (22): 68.4% yield, yellow oil, $[\alpha]_D^{25}$ −38.8° (*c* 0.98, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, $J=6.8$ Hz, C*H*$_3$), 1.20 (3H, d, $J=6.8$ Hz, C*H*$_3$), 1.26 (1H, s, O*H*), 2.09–2.19 {1H, m, $(CH_3)_2CH$}, 2.93–3.00 (2H, m, Ar_1CH_2CH and Ar_1CH_2CH), 3.13 (1H, dd, $J=4.9$, 10.3 Hz, Ar_1CH_2CH), 3.76 (3H, s, OC*H*$_3$), 5.91 (2H, s, O–C*H*$_2$–O), 6.62–6.70 (3H, m, Ar_1–*H*), 6.74 (2H, d, $J=8.8$ Hz, Ar_2–*H*), 7.26 (2H, d, $J=8.8$ Hz, Ar_2–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.45, 17.79, 32.02, 33.88, 54.88, 55.22, 74.92, 86.45, 86.78, 100.91, 108.36, 109.18, 113.84, 114.38, 121.81, 131.92, 133.20, 146.30, 147.73, 159.69, 179.99.

(2R,3S)-3-Hydroxy-5-(4-methoxyphenyl)-2-(3,4-methylenedioxybenzyl)-3-(1-methylethyl)-4-pentynoic acid (23): 67.6% yield, yellow oil, $[\alpha]_D^{25}$ +35.5° (*c* 0.84, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, $J=6.4$ Hz, C*H*$_3$), 1.20 (3H, d, $J=6.4$ Hz, C*H*$_3$), 1.25 (1H, s, O*H*), 2.09–2.19 {1H, m, $(CH_3)_2CH$}, 2.93 (1H, dd, $J=10.5$, 15.3 Hz, Ar_1CH_2CH), 2.97 (1H, dd, $J=5.1$, 15.3 Hz, $ArCH_2CH$), 3.13 (1H, dd, $J=5.1$, 10.5 Hz, Ar_1CH_2CH), 3.76 (3H, s, –OC*H*$_3$), 5.92 (2H, s, O–C*H*$_2$–O), 6.62–6.70 (3H, m, Ar_1–*H*), 6.75 (2H, d, $J=8.8$ Hz, Ar_2–*H*), 7.26 (2H, d, $J=8.8$ Hz, Ar_2–*H*); ^{13}C-NMR ($CDCl_3$) δ: 17.45, 17.79, 32.04, 33.89, 54.77, 55.24, 74.93, 86.44, 86.79, 100.92, 108.36, 109.20, 113.86, 114.38, 121.82, 131.93, 133.21, 146.31, 147.74, 159.71, 179.99.

Procedure for lactonization. To a stirred solution of carboxylic acid **22** (0.51 mmol) or **23** (0.24 mmol) in CH_3OH (12 ml/mmol) was added 0.1 M-$AgNO_3$ (1.2 ml/mmol) at room temperature. The reaction mixture was stirred for 2 days in the dark. After concentrating the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (CCl_4-EtOAc, 12:1), and the resulting crystals were recrystallized from CH_2Cl_2-petroleum ether (1:2) to give **4** or **5**. The mother liquor was concentrated, and the residue was purified by column chromatography

on silica gel (CCl_4-EtOAc, 9:1) to provide a second crop of crystals.

(2S,3R,4Z)-3-Hydroxy-5-(4-methoxyphenyl)-(3,4-methylenedioxybenzyl)-3-(1-methylethyl)-4-penten-4-olide (4): 43.8% yield, mp 129–130°C, $[\alpha]_D^{25}$ +46.1° (*c* 0.98, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=2.9 Hz, CH_3), 0.96 (3H, d, J=2.9 Hz, CH_3), 1.88–2.02 {1H, m, (CH$_3$)CH}, 2.03 (1H, s, –OH), 2.86–2.92 (2H, m, Ar$_1$–CH_2CH and Ar$_1$–CH$_2$CH), 3.13 (1H, dd, J=8.3, 17.3 Hz, Ar$_1$–CH_2), 3.82 (3H, s, OCH_3), 5.68 (1H, s, Ar$_2$–CH), 5.86 (1H, s, O–CH_2–O), 5.90 (1H, s, O–CH_2–O), 6.72 (2H, s, Ar$_1$–H), 6.78 (1H, s, Ar$_1$–H), 6.87 (2H, d, J=8.8 Hz, Ar$_2$–H), 7.51 (2H, d, J=8.8 Hz, Ar$_2$–H); ^{1}H-NMR (acetone-d_6) δ: 0.85 (3H, d, J=4.4 Hz, CH_3), 0.86 (3H, d, J=4.4 Hz, CH_3), 1.92–2.01 {1H, m, (CH$_3$)CH}, 2.85 (1H, dd, J=8.3, 14.2 Hz, Ar$_1$–CH_2), 2.97 (1H, dd, J=5.4, 8.3 Hz, Ar$_1$–CH$_2$CH), 3.17 (1H, dd, J=5.4, 14.2 Hz, Ar$_1$–CH_2), 4.71 (1H, s, –OH), 5.81 (1H, s, Ar$_2$–CH), 5.92 (1H, s, O–CH_2–O), 5.93 (1H, s, O–CH_2–O), 6.72–6.80 (2H, m, Ar$_1$–H), 6.89–6.91 (1H, m, Ar$_1$–H), 6.92 (2H, d, J=8.8 Hz, Ar$_2$–H), 7.51 (2H, d, J=8.8 Hz, Ar$_2$–H); ^{13}C-NMR ($CDCl_3$) δ: 16.44, 16.86, 32.93, 38.19, 47.24, 55.29, 81.30, 100.99, 104.51, 108.36, 109.43, 113.91, 122.06, 125.94, 130.09, 131.49, 146.50, 147.89, 151.44, 158.79, 174.34; IR ν_{max} ($CHCl_3$) cm^{-1}: 3025, 1803, 1735, 1687, 1611, 1516, 1491, 1448, 1294, 1256, 1213, 1179, 1106, 1042, 995, 944, 863, 786, 769, 751, 739.

(2R,3S,4Z)-3-Hydroxy-5-(4-methoxyphenyl)-(3,4-methylenedioxybenzyl)-3-(1-methylethyl)-4-penten-4-olide (5): 40.3% yield, mp 130°C, $[\alpha]_D^{25}$ −46.7° (*c* 3.45, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=2.0 Hz, CH_3), 0.95 (3H, d, J=2.4 Hz, CH_3), 1.93–2.01 {1H, m, (CH$_3$)CH}, 2.13 (1H, s, –OH), 2.85–2.93 (2H, m, Ar$_1$–CH$_2$CH and Ar$_1$–CH_2CH), 3.12 (1H, dd, J=8.8, 16.9 Hz, Ar$_1$–CH_2), 3.81 (3H, s, OCH_3), 5.68 (1H, s, Ar$_2$–CH), 5.85 (1H, s, O–CH_2–O), 5.89 (1H, s, O–CH_2–O), 6.71 (2H, s, Ar$_1$–H), 6.78 (1H, s, Ar$_1$–H), 6.86 (2H, d, J=8.8 Hz, Ar$_2$–H), 7.50 (2H, d, J=8.8 Hz, Ar$_2$–H); ^{1}H-NMR (acetone-d_6) δ: 0.85 (3H, d, J=4.4 Hz, CH_3), 0.86 (3H, d, J=4.4 Hz, CH_3), 2.05–2.14 {1H, m, (CH$_3$)CH}, 2.85 (1H, dd, J=8.1, 14.2 Hz, Ar$_1$–CH_2), 2.97 (1H, dd, J=5.9, 8.1 Hz, Ar$_1$–CH$_2$CH), 3.17 (1H, dd, J=5.9, 14.2 Hz, Ar$_1$–CH_2), 4.71 (1H, s, –OH), 5.81 (1H, s, Ar$_2$–CH), 5.92 (1H, s, O–CH_2–O), 5.93 (1H, s, O–CH_2–O), 6.72–6.80 (2H, m, Ar$_1$–H), 6.89–6.91 (1H, m, Ar$_1$–H), 6.92 (2H, d, J=8.8 Hz, Ar$_2$–H), 7.51 (2H, d, J=8.8 Hz, Ar$_2$–H); ^{13}C-NMR ($CDCl_3$) δ: 16.41, 16.85, 32.85, 38.14, 47.22, 55.26, 81.23, 100.95, 104.47, 108.31, 109.43, 113.89, 122.04, 125.93, 130.06, 131.51, 146.44, 147.83, 151.43, 158.75, 174.37; IR ν_{max} ($CHCl_3$) cm^{-1}: 3025, 1803, 1735, 1687, 1611, 1512, 1491, 1448, 1294, 1252, 1213, 1179, 1102, 1042, 995, 940, 863, 786, 769, 751, 739. *Anal.* Found: C, 69.66; H, 6.10%. Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10%.

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