The Synthesis of Polyfunctionalized, Cyclohexene-based Chirons from Tartaric Acid†

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10 † Dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday and in
recognition of his sustained and outstanding contributions to chemical synthesis

Abstract: Compound *ent*-**1** as well as certain related homochiral and polyfunctionalized
cyclohexenes have been prepared from the 1,2-diacetal **4** that is itself readily derived from *L*-tartaric
acid (**3**). Grignard addition and ring-closing metathesis processes constitute the key steps associated
15 with the reaction sequences involved. This work provides a method for obtaining a range of
potentially useful cyclohexenone-containing chirons that are enantiomerically related to those that
have been prepared from the homochiral *cis*-1,2-dihydrocatechol **2**, the product of the microbial
biotransformation of bromobenzene.

20 Introduction

In connection with a study focused on acetylcholine esterase (AChE) inhibitors, we prepared,
over five steps, the polyfunctionalized and homochiral α -bromocyclohexenone **1** from the
enantiomerically pure *cis*-1,2-dihydrocatechol **2**.¹ Compound **2** is the product of the microbial
dihydroxylation of bromobenzene, a transformation that can be achieved particularly effectively
25 with a genetically-engineered strain of *E. coli* that over-expresses the enzyme toluene dioxygenase
(TDO).² In order to fully explore the biological profiles of the AChE inhibitors in question, we
required the enantiomer of compound **1**, namely *ent*-**1**. While a logical precursor to this

Results and Discussion

The reaction sequence that allowed for the preparation of a series of poly-oxygenated and homochiral cyclohexenes from *L*-tartaric acid (**3**) is shown in Scheme 1 and started with the formation, under standard and operationally simple conditions, of diacetal diester **4** (72%). While commercially available, compound **4** is easily prepared in multi-gram scale quantities from the cheap and readily available *L*-tartaric acid. Reduction of the former compound to the corresponding dialdehyde was achieved using di-*iso*-butylaluminium hydride (DIBAL-H) in toluene at $-78\text{ }^{\circ}\text{C}$ and this was immediately reacted with vinylmagnesium bromide⁵ to give the bis-olefin **5** as an inseparable mixture of diastereoisomers in 88% combined yield. This mixture was treated with the Grubbs'-II catalyst in dichloromethane and so effecting a RCM reaction and thus forming a *ca.* 10:6:3 mixture of the three possible stereoisomeric forms of the anticipated cyclohexene **6** in 99% combined yield.

Scheme 1

This mixture of cyclohexenes, which was characterized as such, was subjected to a two-fold oxidation with the Dess-Martin periodinane (DMP) and so affording the corresponding enedione **7**

in 88% yield.

While enedione **7** was prone to two-fold enolization and concomitant formation of the isomeric hydroquinone,⁹ this C₂-symmetric compound could be stereoselectively reduced to the γ -hydroxyenone **8** (94%) under Luche-type conditions. Confirmation of the stereochemical outcome associated with this conversion, which involves axial delivery of hydride,¹⁰ was achieved through the single-crystal X-ray analysis of a halogenated derivative. Specifically, successive treatment of compound **8** with molecular bromine then triethylamine at 0 °C¹¹ afforded the crystalline α -bromoenone **9** (79% yield) that was subjected to such an analysis. The derived ORTEP is shown in Figure 1 while other results of this analysis are provided in the Experimental Section.

Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **9** (CCDC No. 1491822). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

The completion of the synthesis of the target synthon *ent*-**1** followed the pathway shown in Scheme 2 and involved the conversion of the γ -hydroxyenone **9** into the corresponding acetate, **10** (97%), under standard conditions. Luche reduction of compound **10** afforded a diastereoisomeric and chromatographically separable mixture of compounds **11** (7%) and **12** (79%). Subjection of the latter product to a Mitsunobu reaction, using *p*-methoxybenzoic acid as nucleophile and the

N,N,N,N'-tetramethylazodicarboxamide(TMAD)/tri-*n*-butylphosphine reagent combination,¹² then afforded ester **13** (79%). Finally, cleavage of this ester using potassium hydroxide in methanol gave the target *ent*-**1** in 96% yield.

Scheme 2

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The minor product, **11**, derived from the reduction of α -bromoenone **10** was readily and nearly quantitatively converted into compound *ent*-**1** through treatment (Scheme 3) with potassium carbonate in methanol. All the spectral data acquired on compound *ent*-**1** were consistent with the assigned structure and matched those recorded¹ on its enantiomer (*viz.* **1**) save for the specific rotation that was of similar magnitude but opposite in sign {*viz.* -76.5° (c 1.0 in CHCl_3) for *ent*-**1** vs

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+72.6 ° ($c = 1.1$ in CHCl_3) for **1**}. Given this relationship and that the structure of compound **1** has been established through the single-crystal X-ray analysis of a derivative,¹ the illustrated stereochemical array within compound *ent*-**1** is secure.

Scheme 3

Conclusion

Considering the ready availability of both *D*- and *L*-tartaric acid and the demonstrated utility of polyoxygenated and halogenated cyclohexenes in the synthesis,² the simple protocols defined above should provide a useful new means for the assembly of biologically active systems. Work directed towards such ends is now underway in our laboratories. Results will be reported in due course.

Experimental

General Experimental Procedures

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered CDCl_3 on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^1H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^1H NMR data are recorded as follows: chemical shift (δ [multiplicity, coupling constant(sJ (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual CHCl_3 appearing at δ_{H} 7.26 and the central resonance of the CDCl_3 “triplet” appearing at δ_{C} 77.1(6) were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer UTAR Two FTIR Spectrometer. Samples were analyzed as either thin films or finely divided solids. Low-resolution ESI mass spectra were

125 recorded on a Micromass LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while high-resolution measurements were conducted on an LCT Premier time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on an Autospec Premier Micromass magnetic-sector machine. Optical rotations were recorded in CHCl₃ at 20 °C on a Perkin Elmer Model 343 Polarimeter. Melting points were measured on an Optimelt automated melting point
130 system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F₂₅₄ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide
135 aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*¹³ with silica gel 60 (40–63 µm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were
140 purchased from the AJAX, BDH or Unilab Chemical Companies. Diethyl ether, *N,N*-dimethylformamide (DMF), dichloromethane and ethyl acetate were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*¹⁴ Where necessary, reactions were performed under an inert atmosphere.

Specific Experimental Procedures and Product Characterization

145 **Compound 4**

Using a modification of a procedure reported¹⁵ by Maycock and co-workers, a magnetically stirred solution of *L*-tartaric acid (11.87 g, 79.09 mmol), 2,3-butanedione (7.25 mL, 80 mmol) and trimethyl orthoformate (50 mL, 466 mmol) in dry methanol (100 mL) was treated with *p*-toluenesulfonic acid monohydrate (710 mg, 5 mol %). The resulting solution was heated under
150 reflux for 24 h and the resulting deep-red mixture then cooled to room temperature and neutralised

with NaHCO₃ (4.00 g). Stirring was continued for 0.5 h then the reaction mixture was concentrated under reduced pressure. The residue thus obtained was diluted with ethyl acetate (100 mL) then NaHCO₃ (30 mL of a saturated aqueous solution) and the separated organic phase washed with NaHCO₃ (1 × 30 mL of a saturated aqueous solution) then water (1 × 30 mL). The combined aqueous layers were extracted with ethyl acetate (3 × 30 mL) and the combined organic phases then washed with brine (2 × 20 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure. The yellow solid thus obtained was recrystallised (hexane/ethyl acetate) and the resulting solid collected and washed successively with ice-cold hexane and ice-cold ethyl acetate to give bis-ester **4**^{15,16} (16.73 g, 72%) as an off-white, crystalline solid, m.p. = 107–108 °C (lit.¹⁶ m.p. = 106–108 °C), [α]_D = –135.7 ° (c = 1.1, CHCl₃) {lit.¹⁶ [α]_D = –139.6 ° (c = 1.0, CHCl₃)} [Found: (M + K)⁺, 331.0777. C₁₂H₂₀KO₈ requires (M + K)⁺, 331.0795]. ¹H NMR (CDCl₃, 400 MHz) δ_H 4.54 (s, 2H), 3.77 (s, 6H), 3.32 (s, 6H), 1.36 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ_C 168.6, 99.4, 68.9, 52.7, 48.6, 17.5; IR (solid) ν_{max} 2992, 1736, 1443, 1377, 1282, 1202, 1139, 1110, 1026, 898, 886, 810, 744 cm^{–1}; MS (ESI, +ve) m/z 315 [(M + Na)⁺, 100%].

165 **Compound 5**

A magnetically stirred solution of bis-ester **4** (3.10 g, 10.63 mmol) in dry toluene (30 mL) was cooled to –78 °C then DIBAL-H (22.3 mL of a 1 M solution in toluene, 22.3 mmol) added, *via* syringe-pump, over 0.75 h. The ensuing mixture was stirred at –78 °C for 2 h then vinyl magnesium bromide (74.4 mL of a 1 M solution in THF, 74.4 mL) was added dropwise over 0.5 h. The solution thus formed was stirred at –78 °C for 0.5 h then allowed to warm to room temperature. After 16 h the reaction mixture was cooled to 0 °C, quenched with Rochelle salt (100 mL of a saturated solution: CAUTION slow addition required) then re-warmed to room temperature and stirring continued for 3 h. The resulting biphasic mixture was transferred to a separatory funnel and the organic layer separated then washed with water (100 mL). The combined aqueous layers were extracted with ethyl acetate (3 × 30 mL) and the combined organic phases then washed with brine (3 × 30 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure. The

ensuing thick, orange oil was subjected to flash column chromatography (silica, hexane $\rightarrow$ 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions ($R_f = 0.5$ in 1:1 v/v ethyl acetate/hexane) afforded bis-allylic alcohol **5** (2.69 g, 88%) as a clear, colourless oil and a mixture of diastereoisomers [Found: $(M + Na)^+$, 311.1465. $C_{14}H_{24}NaO_6$ requires $(M + Na)^+$, 311.1471]. ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 138.1, 138.0, 136.7(2), 136.6(8), 117.2, 116.8, 116.1, 115.8, 99.0, 98.9, 98.8(1), 98.7(9), 72.6, 72.3, 72.1, 71.6, 71.3, 70.5, 48.1(0), 48.0(6), 17.6(1), 17.5(9), 17.5; IR (film) ν_{max} 3407, 2991, 2949, 2833, 1375, 1121, 1036, 997, 921, 852 cm^{-1} ; MS (ESI, +ve) m/z 311 [$(M + Na)^+$, 100%].

Compound 6

A solution of the bis-allylic alcohol **5** (2.67 g, 9.25 mmol) in dichloromethane (200 mL) was sonicated under an atmosphere of nitrogen for 0.5 h then Grubbs 2nd generation catalyst (157 mg, 2 mol %) was added in one portion. The ensuing mixture was heated under reflux for 1.5 hours then cooled to room temperature and the solvent removed under reduced pressure. The ensuing brown solid was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/hexane $\rightarrow$ ethyl acetate, gradient elution) and concentration of appropriate fractions ($R_f = 0.3$ in 2:1 v/v ethyl acetate/hexane) afforded cyclohexene **6** (2.39 g, 99%) as a white, amorphous solid and a mixture of diastereoisomers [Found: $(M + Na)^+$, 283.1165. $C_{12}H_{20}NaO_6$ requires $(M + Na)^+$, 283.1158]. ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 132.9, 130.0, 129.3, 126.6, 100.0, 99.8, 99.3, 99.1, 72.5, 70.6, 70.3, 69.7, 67.9, 65.9, 65.5, 65.3, 48.3, 48.2, 48.1(3), 48.0(7), 17.9(4), 17.9(0), 17.8(2), 17.8(0); IR (solid) ν_{max} 3313, 2948, 1465, 1373, 1204, 1117, 1030, 971, 915, 886, 847 cm^{-1} ; MS (ESI, +ve) m/z 283 [$(M + Na)^+$, 100%].

Compound 7

Dess-Martin periodane (23.80 g, 53.31 mmol) was added, in portions, to a magnetically stirred solution of compound **6** (4.63 g, 17.78 mmol) in dichloromethane (25 mL) maintained at 0 °C. After addition was complete (0.25 h) the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h before being concentrated under reduced pressure at 20 °C. The residue thus obtained was subjected to rapid flash chromatography (silica, 2:8 v/v pentane/diethyl

ether elution) and concentration of the relevant fractions ($R_f = 0.7$ in 1:2 v/v
205 dichloromethane/diethyl ether) at 20 °C afforded enedione **7** (4.01 g, 88%) as a bright yellow,
crystalline solid, m.p. = 115–117 °C (dec.), $[\alpha]_D = -121.0^\circ$ ($c = 0.9$ in CHCl_3) [Found: $(\text{M} + \text{Na})^+$,
279.0850. $\text{C}_{12}\text{H}_{16}\text{NaO}_6$ requires $(\text{M} + \text{Na})^+$, 279.0845]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 6.84 (s, 2H),
4.73 (s, 2H), 3.26 (s, 6H), 1.41 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} 192.1, 140.1, 100.6, 73.9,
48.7, 17.6; IR (solid) ν_{max} 2954, 2849, 1699, 1380, 1133, 1113, 1027, 823, 543 cm^{-1} ; MS (ESI, +ve)
210 m/z 343 $[(\text{M} + 2 \times \text{CH}_3\text{OH} + \text{Na})^+, 100\%]$, 311 $[(\text{M} + \text{CH}_3\text{OH} + \text{Na})^+, 50]$, 279 $[(\text{M} + \text{Na})^+, 10]$.

Compound 8

Sodium borohydride (770 mg, 20.35 mmol) was added, in portions over 0.08 h, to a magnetically
stirred solution of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (7.60 g, 20.40 mmol) in methanol (50 mL) maintained at 0 °C. The
ensuing mixture was stirred at this temperature for 0.25 h then transferred to a pressure-equalised
215 dropping funnel and added dropwise to a magnetically solution of endione **7** (4.01 g, 15.67 mmol)
in methanol (150 mL) that had been cooled to -78°C . After 1.5 h further portions of NaBH_4 (5×10
mg, 1.32 mmol) were slowly added until the yellow reaction mixture became colourless and at
which point it was quenched with acetone (20 mL). At this point NH_4Cl (100 mL of a saturated
aqueous solution) was then added to the reaction mixture so-formed and allowed to warm to room
220 temperature. The ensuing mixture was concentrated under reduced pressure and the residue thus
obtained diluted with ethyl acetate (100 mL) and water (50 mL). The separated aqueous layer was
extracted with ethyl acetate (3×50 mL) and the combined organic phases then washed with brine
(2×50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The
residue thus generated was subjected to flash column chromatography (silica, dichloromethane $\rightarrow$
225 1:2 v/v diethyl ether/ dichloromethane gradient elution) and concentration of appropriate fractions
($R_f = 0.2$ 1:1 v/v ethyl acetate/hexane) afforded enone **8** (3.79 g, 94%) as a clear, colourless oil, $[\alpha]_D$
 $= -215.0^\circ$ ($c = 0.5$, CHCl_3) [Found: $(\text{M} + \text{Na})^+$, 281.1006. $\text{C}_{12}\text{H}_{18}\text{NaO}_6$ requires $(\text{M} + \text{Na})^+$,
281.1001]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 6.85 (dd, $J = 10.5$ and 2.0 Hz, 1H), 6.07 (dd, $J = 10.5$
and 2.6 Hz, 1H), 4.67 (m, 1H), 4.25 (d, $J = 11.4$ Hz, 1H), 3.96 (dd, $J = 11.4$ and 8.7 Hz, 1H), 3.31

230 (s, 3H), 3.28 (s, 3H), 2.55 (d, $J = 3.9$ Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} 193.5, 148.6, 128.4, 100.3, 99.4, 74.3, 72.3, 70.1, 48.7, 48.2, 17.7(3), 17.6(6); IR (film) ν_{max} 3452, 2958, 1683, 1379, 1118, 1028, 967, 947, 881, 806, 634, 585, 540 cm^{-1} ; MS (ESI, +ve) m/z 281 $[(\text{M} + \text{Na})^+, 100\%]$.

Compound 9

235 Molecular bromine (400 μL of a 10% v/v solution in dichloromethane, 0.79 mmol) was added, dropwise, to a magnetically stirred solution of enone **8** (185 mg, 0.72 mmol) in dichloromethane maintained at -5°C . The resulting solution was stirred at this temperature for 1 h then triethylamine (300 μL , 2.15 mmol) added dropwise. The cooling bath was then removed and the reaction mixture stirred at room temperature for 16 h before being quenched with sodium sulfite (2
240 mL of a saturated aqueous solution). The separated organic layer was washed successively with sodium sulfite (3×5 mL of a saturated aqueous solution) and NH_4Cl (3×5 mL of an aqueous solution) then the combined aqueous washings were extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with brine (2×10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash column
245 chromatography (silica, dichloromethane $\rightarrow$ 1:9 v/v diethyl ether/dichloromethane gradient elution) and concentration of appropriate fractions ($R_{\text{f}} = 0.1$: 9 v/v diethyl ether/ dichloromethane) afforded bromoenone **9** (190 mg, 79 %) as a white, crystalline solid, m.p. = $178\text{--}181^\circ\text{C}$, $[\alpha]_{\text{D}} = -146.6^\circ$ ($c = 0.5$, CHCl_3) [Found: $(\text{M} + \text{Na})^+$, 359.0100. $\text{C}_{12}\text{H}_{17}^{79}\text{BrNaO}_6$ requires $(\text{M} + \text{Na})^+$, 359.0106]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 7.29 (d, $J = 2.3$ Hz, 1H), 4.63 (ddd, $J = 8.6$, 4.1 and 2.3 Hz, 1H), 4.28
250 (d, $J = 11.4$ Hz, 1H), 3.98 (dd, $J = 11.4$ and 8.6 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.57 (d, $J = 4.1$ Hz, 1H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} 186.3, 148.6, 123.2, 100.5, 99.3, 73.6, 71.6, 70.5, 48.8, 48.3, 17.6(3), 17.5(9); IR (solid) ν_{max} 3480, 2945, 1712, 1601, 1450, 1373, 1334, 1279, 1205, 1141, 1110, 1023, 907, 888, 870, 858, 606, 782, 663, 606, 517, 440 cm^{-1} ; MS (ESI, +ve) m/z 361 and 359 $[(\text{M} + \text{Na})^+, 98$ and 100%, respectively].

255 Compound 10

Acetic anhydride (120 μ L, 1.25 mmol) was added to a magnetically stirred solution of bromoenone **9** (140 mg, 0.416 mmol) in pyridine (5 mL). Stirring was continued at room temperature for 1 h then the reaction mixture was concentrated under reduced pressure to afford acetate **10** (153 mg, 97%) as a white foam, $[\alpha]_D = -366.5^\circ$ ($c = 0.6$, CHCl_3) [Found: $(\text{M} + \text{Na})^+$, 401.0217. $\text{C}_{14}\text{H}_{19}^{79}\text{BrNaO}_7$ requires $(\text{M} + \text{Na})^+$, 401.0212]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 7.13 (d, $J = 2.4$ Hz, 1H), 5.67 (dd, $J = 8.9$ and 2.4 Hz, 1H), 4.39 (d, $J = 11.2$ Hz, 1H), 4.18 (dd, $J = 11.2$ and 8.9 Hz, 1H), 3.29 (s, 3H), 3.25 (s, 3H), 2.16 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} 185.9, 170.1, 144.8, 124.3, 100.5, 99.3, 71.7, 71.0, 70.6, 48.7, 48.1, 20.9, 17.6, 17.5. IR (solid) ν_{max} 2952, 1751, 1720, 1377, 1220, 1135, 1113, 1028, 979, 918, 886, 853, 786, 662 cm^{-1} ; MS (ESI, +ve) m/z 467 and 465 $[(\text{M} + 2 \times \text{CH}_3\text{OH} + \text{Na})$, 98 and 100%, respectively], 403 and 401 $[(\text{M} + \text{Na})^+$, 30 and 29, respectively].

Compounds 11 and 12

Sodium borohydride (211 mg, 5.59 mmol) was added, in portions over 0.08 h, to a magnetically stirred solution of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.09 g, 2.93 mmol) in methanol (20 mL) maintained at 0°C . The ensuing mixture was stirred at this temperature for 0.25 h then transferred to a pressure-equalised dropping funnel and added dropwise to a magnetically solution of acetate **10** (1.06 g, 2.79 mmol) in methanol (100 mL) maintained at -78°C . After 1 h the reaction mixture was allowed to warm to room temperature, quenched with water (5 mL) and concentrated under reduced pressure. The residue thus obtained was diluted with ethyl acetate (100 mL) and NH_4Cl (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic phases then washed with brine (2×50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v diethyl ether/dichloromethane) to afford two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$ in 1:19 v/v diethyl ether/dichloromethane) afforded compound **11** (76 mg, 7%) as a clear, colourless oil, $[\alpha]_D = -160.0^\circ$ ($c = 0.9$, CHCl_3) [Found: $(\text{M} +$

Na)⁺, 403.0373. C₁₄H₂₁⁷⁹BrNaO₇ requires (M + Na)⁺, 403.0368]. ¹H NMR (CDCl₃, 400 MHz) δ_H 6.12 (d, *J* = 2.5 Hz, 1H), 5.30 (dd, *J* = 8.4 and 2.5 Hz, 1H), 4.35 (d, *J* = 4.0 Hz, 1H), 4.16 (dd, *J* = 11.0 and 8.4 Hz, 1H), 3.78 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.27 (s, 3H), 3.26 (s, 3H), 2.74 (broad s, 1H), 2.09 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ_C 170.5, 130.6, 123.8, 100.1, 99.3, 72.2, 72.1, 67.6, 65.1, 48.4, 48.0, 21.1, 17.8, 17.7; IR (film) ν_{max} 3475, 2950, 1750, 1733, 1371, 1230, 1135, 1116, 1033, 970, 933, 886, 851, 732 cm⁻¹; MS (ESI, +ve) *m/z* 405 and 403 [(M + Na)⁺, 100 and 98%, respectively].

Concentration of fraction B [*R*_f = 0.2 in 1:19 v/v diethyl ether/dichloromethane] afforded compound **12** (840 mg, 79%) as a clear, colourless oil, [α]_D = -204.7 ° (*c* = 0.9, CHCl₃) [Found: (M + Na)⁺, 403.0367. C₁₄H₂₁⁷⁹BrNaO₇ requires (M + Na)⁺, 403.0368]. ¹H NMR (CDCl₃, 400 MHz) δ_H 6.04 (app. t, *J* = 2.1 Hz, 1H), 5.38 (m, 1H), 4.35 (m, 1H), 3.90 (dd, *J* = 11.0 and 8.3 Hz, 1H), 3.81 (dd, *J* = 11.0 and 7.8 Hz, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 2.53 (s, 1H), 2.09 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ_C 170.3, 128.5, 127.1, 99.4, 99.2, 72.1, 71.8, 71.4, 68.6, 48.2, 48.0, 21.1, 17.7, 17.6; IR (KBr) ν_{max} 3474, 2919, 2850, 1737, 1369, 1229, 1118, 1020, 969, 914, 886, 852, 795, 736 cm⁻¹; MS (ESI, +ve) *m/z* 405 and 403 [(M + Na)⁺, 100 and 98%, respectively].

Compound 13

Tri-*n*-butylphosphine (520 μL, 2.08 mmol) was added to a magnetically stirred solution of allylic alcohol **12** (397 mg, 1.04 mmol) and *p*-methoxybenzoic acid (316 mg, 2.08 mmol) in benzene (7 mL). The solution thus obtained was cooled to 0 °C then *N,N,N',N'*-tetramethylazodicarboxamide (TMAD) (376 mg, 2.08 mmol) was added in one portion. The ensuing mixture was stirred at 0 °C for 0.25 h then heated under reflux for 48 h. The cooled solution was filtered through a short pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, dichloromethane → 1:19 v/v diethyl ether/dichloromethane gradient elution) and concentration of appropriate fractions (*R*_f = 0.5 in 1:9 v/v diethyl ether/dichloromethane) afforded ester **13** (422 mg, 79%) as a white, amorphous solid,

$[\alpha]_D = -28.3^\circ$ ($c = 1.1$, CHCl_3) [Found: $(\text{M} + \text{Na})^+$, 537.0734. $\text{C}_{22}\text{H}_{27}^{79}\text{BrNaO}_9$ requires $(\text{M} + \text{Na})^+$, 537.0736]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 8.05 (d, $J = 8.9$ Hz, 2H), 6.94 (d, $J = 8.9$ Hz, 2H), 6.24 (d, $J = 2.5$ Hz, 1H), 5.97 (d, $J = 4.2$ Hz, 1H), 5.37 (dd, $J = 8.5$ and 2.5 Hz, 1H), 4.28 (dd, $J = 11.1$ and 8.5 Hz, 1H), 3.95 (dd, $J = 11.1$ and 4.2 Hz, 1H), 3.88 (s, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 2.14 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} 170.4, 165.8, 163.6, 132.6, 132.3, 122.5, 121.0, 113.7, 99.6, 99.3, 72.2, 71.9, 66.7, 66.0, 55.6, 48.4, 47.9, 21.1, 17.7, 17.4; IR (film) ν_{max} 2980, 1724, 1605, 1511, 1372, 1254, 1226, 1166, 1117, 1083, 1051, 1028, 971, 933, 765, 699, 663, 611 cm^{-1} ; MS (ESI, +ve) m/z 539 and 537 [$(\text{M} + \text{Na})^+$, 100 and 98%, respectively].

Compound *ent*-1

Method i (ex. Compound 13): Potassium hydroxide (60 mg, 1.07 mmol) was added to a magnetically stirred solution of compound **13** (103 mg, 0.20 mmol) in methanol (10 mL) and the ensuing mixture stirred at room temperature for 48 h. The methanol was then removed under reduced pressure and the residue so obtained diluted with ethyl acetate (10 mL) and NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3×5 mL) and the combined organic phases washed with brine (2×5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting white solid was subjected to flash column chromatography (silica, $\rightarrow$ 1:24 v/v diethyl ether/dichloromethane gradient elution) and concentration of appropriate fractions ($R_f = 0.3$ in 1:19 v/v methanol/dichloromethane) afforded diol *ent*-1 (65 mg, 96%) as a white foam, $[\alpha]_D = -76.5^\circ$ (c 1.0 in CHCl_3) [Found: $(\text{M} + \text{Na})^+$, 361.0260. $\text{C}_{12}\text{H}_{19}^{79}\text{BrNaO}_6$ requires $(\text{M} + \text{Na})^+$, 361.0263]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 6.05 (d, $J = 2.5$ Hz, 1H), 4.22 (d, $J = 4.1$ Hz, 1H), 4.06 (dd, $J = 7.9$ and 2.5 Hz, 1H), 3.87 (dd, $J = 11.1$ and 7.9 Hz, 1H), 3.63 (dd, $J = 11.1$ and 4.1 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} 135.3, 124.0, 100.8, 100.2, 73.1, 71.8, 69.9, 69.2, 48.3(1), 48.2(5), 18.1, 18.0; IR (KBr) ν_{max} 3236, 3007, 2954, 2905, 2834, 1114, 1074, 1054, 1030, 985, 912, 884, 852, 760, 665, 617, 599 cm^{-1} ; MS (ESI, +ve) m/z 363 and 361 [$(\text{M} + \text{Na})^+$, 98 and 100%, respectively].

Method ii (ex. Compound 11): Potassium carbonate (50 mg, 0.36 mmol) was added to a
335 magnetically stirred solution of ester **11** (76 mg, 0.20 mmol) in methanol (10 mL) and the resulting
mixture stirred at room temperature for 12 h then concentrated under reduced pressure. The residue
thus obtained was diluted with ethyl acetate (10 mL) and water (10 mL) then the separated aqueous
layer extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with
brine (2 × 5 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure to
340 give enediol *ent*-**1** (67 mg, 99%) as a white foam. This material was identical, in all respects, with
that obtained by Method i.

X-ray Crystallographic Study

Crystallographic Data

Compound 9: C₁₂H₁₇BrO₆, *M* 337.17, *T* 150 K, orthorhombic, space group *P*2₁2₁2₁, *Z* 4, *a*
345 6.8265(1), *b* 11.4217(1), *c* 17.8288(1) Å; *V* 1390.12(1) Å³; *D_x* 1.611 g cm⁻³; 2750 unique data
(2θ_{max} 144.6°), *R* 0.021 [for 2718 reflections with *I* > 2.0σ(*I*)]; *R_w* 0.052 (all data), *S* 1.03.

Structure Determination

Images were measured on an Agilent SuperNova CCD diffractometer (CuKα, mirror
monochromator, λ 1.54184 Å) and data extracted using the CrysAlis package.¹⁷ Structure solution
350 was by direct methods (SIR92).¹⁸ The structure of compound **9** was refined using the CRYSTALS
program package.¹⁹ Atomic coordinates, bond lengths and angles, and displacement parameters
have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1491822). These
data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing
data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12
355 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Supplementary Material

The ¹H and ¹³C NMR spectra of compounds **4–13** and *ent*-**1** are available on the Journal's website.

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