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THE SYNTHESIS OF POLYFUNCTIONALIZED, CYCLOHEXENE-BASED CHIRONS FROM TARTARIC ACID†

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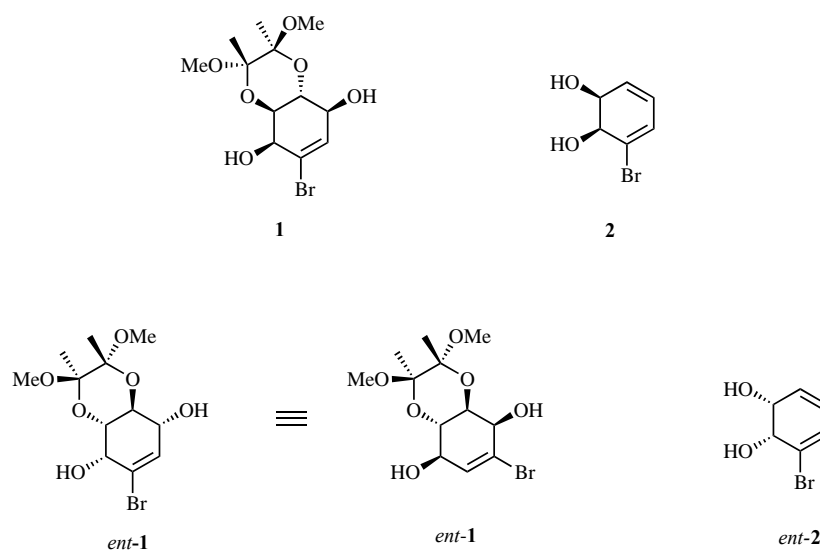
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† Dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday and in recognition of his sustained and outstanding contributions to chemical synthesis

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 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.

INTRODUCTION

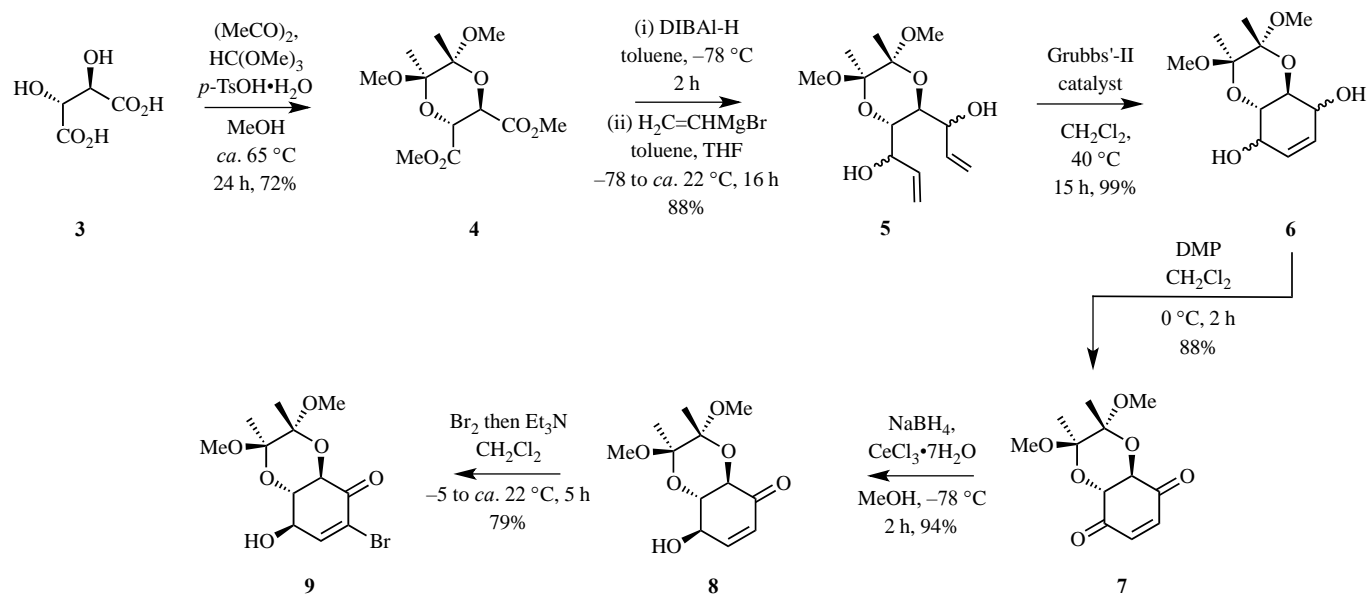
In connection with a study focused on acetylcholine esterase (AChE) inhibitors, we prepared, over five steps, the polyfunctionalized and homochiral α -bromocyclohexenone **1** from the enantiomerically pure *cis*-1,2-dihydrocatechol **2**.¹ Compound **2** is the product of the microbial dihydroxylation of bromobenzene, a transformation that can be achieved particularly effectively 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 brominated cyclohexene is the *cis*-1,2-dihydrocatechol *ent*-**2**, the latter is not as readily accessible, especially in homochiral form, as congener **2**.³ Accordingly, we sought another means for obtaining chiron *ent*-**1** as well as related systems that could serve as valuable building blocks for the synthesis of various polyoxygenated cyclohexenes and their saturated counterparts.



The groups of Madsen,⁴ Sulikowski⁵ and Yan⁶ have each demonstrated that the acetonide derived from *D*- or *L*-tartaric acid can be elaborated, *via* manipulation of the derived ester residues using reduction, vinyl Grignard addition and then ring-closing metathesis (RCM) steps, into various conduritols or amino pseudosugars. Prasad has described⁷ closely related chemistries. The RCM products so formed incorporate rather unstable acetonide-protected cyclohex-4-ene-*trans*-1,2-diol moieties. On the other hand, and during the course of establishing a total synthesis the macrolide antascomycin B (a potential immunosuppressive agent), Ley⁸ and co-workers used a butanediactal-protected dimethyl tartrate to construct, *via* a late-stage RCM, a complex cyclohexene annulated to a 1,4-dioxane and that embodies a stable masked *trans*-1,2-diol moiety. Herein we report on the exploitation of these types of protocols in the synthesis of the target chiron *ent-1* as well as a range of analogues that are likely to be of value in the synthesis of a variety of biologically active systems.

RESULTS AND DISCUSSION

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%). Reduction of the latter compound to the corresponding dialdehyde was achieved using di-*iso*-butylaluminium hydride (DIBAL-H) in toluene at -78 °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 C_2 -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

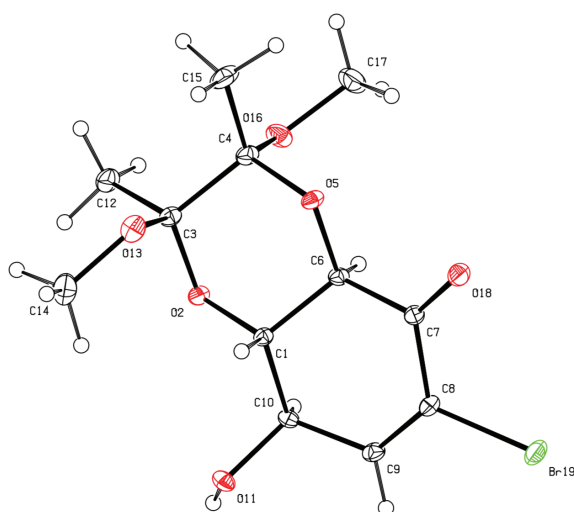
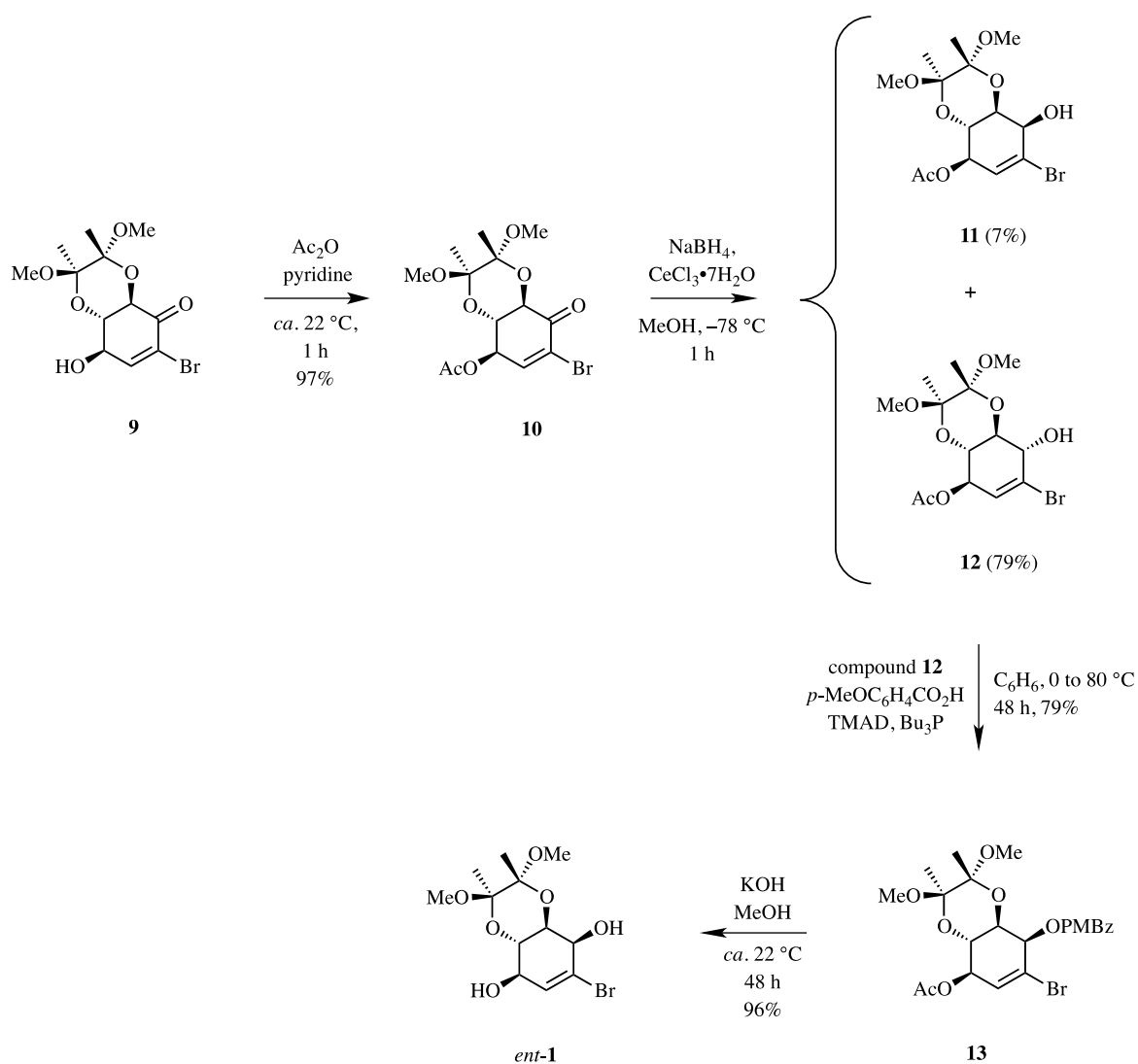


Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **9** (CCDC No. 1491822). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

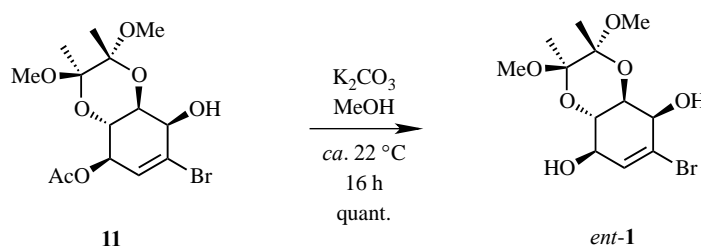
bromine then triethylamine at 0 °C¹¹ afforded the crystalline α -bromo enone **9** (79% yield) that was subjected to such an analysis. The derived ORTEP is shown in Figure 1 while other results of this analysis are provided in the Experimental Section.

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 -hydroxy enone **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

The minor product, **11**, derived from the reduction of α -bromo enone **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 $+72.6$ (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

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, especially various conduritols and related compounds.¹⁵ 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 presented as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (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 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 CHCl_3 at 20 °C on a Perkin Elmer Model 343 Polarimeter. Melting points were measured on an Optimelt™ automated melting point 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 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 purchased from the AJAX, BDH or Unilab Chemical Companies. Diethyl ether, *N,N*-dimethylformamide (DMF), CH_2Cl_2 and EtOAc 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

Dimethyl (2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate (4)

Using a modification of a procedure reported¹⁶ 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 MeOH (100 mL) was treated with *p*-toluenesulfonic acid monohydrate (710 mg, 5 mol%). The resulting solution was heated under reflux for 24 h and the ensuing deep-red mixture then cooled to room temperature and neutralized with NaHCO_3 (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 EtOAc (100 mL) then NaHCO_3 (30 mL of a saturated aqueous solution) added and the separated organic phase washed with NaHCO_3 (1 \times 30 mL of a saturated aqueous solution) then water (1 \times 30 mL). The combined aqueous layers were extracted with EtOAc (3 \times 30 mL) and the combined organic phases then washed with brine (2 \times 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow solid thus obtained was recrystallized (hexane/EtOAc) and the resulting solid collected and washed successively with ice-cold hexane and ice-cold EtOAc to give bis-ester **4**^{16,17} (16.73 g, 72%) as an off-white, crystalline solid, mp 107–108 °C (lit.¹⁷ mp 106–108 °C), $[\alpha]_{\text{D}} -135.7$ (*c* 1.1, CHCl_3) {lit.¹⁷ $[\alpha]_{\text{D}} -139.6$ (*c* 1.0, CHCl_3)} [Found: (M + K)⁺, 331.0777. $\text{C}_{12}\text{H}_{20}\text{KO}_8$ requires (M + K)⁺, 331.0795]. ¹H NMR (CDCl_3 , 400 MHz) δ_{H} 4.54 (s, 2H), 3.77 (s, 6H), 3.32

(s, 6H), 1.36 (s, 6H); ^{13}C NMR (CDCl_3 , 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 $[(\text{M} + \text{Na})^+]$, 100%].

1,1'-((2S,3S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(prop-2-en-1-ol) (5)

A magnetically stirred solution of bis-ester **4** (3.10 g, 10.63 mmol) in dry toluene (30 mL) was cooled to $-78\text{ }^\circ\text{C}$ 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 $-78\text{ }^\circ\text{C}$ for 2 h then vinylmagnesium bromide (74.4 mL of a 1 M solution in THF, 74.4 mmol) was added dropwise over 0.5 h. The solution thus formed was stirred at $-78\text{ }^\circ\text{C}$ for 0.5 h then allowed to warm to room temperature. After 16 h the reaction mixture was cooled to $0\text{ }^\circ\text{C}$, 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 separating funnel and the organic layer separated then washed with water ($1 \times 100\text{ mL}$). The combined aqueous layers were extracted with EtOAc ($3 \times 30\text{ mL}$) and the combined organic phases then washed with brine ($3 \times 30\text{ mL}$) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing thick, orange oil was subjected to flash column chromatography (silica, hexane \rightarrow 1:1 v/v EtOAc/hexane gradient elution) and concentration of appropriate fractions ($R_{\text{f}} = 0.5$ in 1:1 v/v EtOAc/hexane) afforded bis-allylic alcohol **5** (2.69 g, 88%) as a clear, colorless oil and a mixture of diastereoisomers [Found: $(\text{M} + \text{Na})^+$, 311.1465. $\text{C}_{14}\text{H}_{24}\text{NaO}_6$ requires $(\text{M} + \text{Na})^+$, 311.1471]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} (mixture of three diastereoisomers) 6.12–5.94 (complex m, 2H), 5.40–5.15 (series of m, 4H), 4.31–4.17 (complex m, 2H), 4.03–3.65 (series of m, 2H), 3.24–3.19 ($4 \times$ s, 6H), 2.70–2.30 (series of m, 2H), 1.28–1.27 ($3 \times$ s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ_{C} (mixture of three diastereoisomers) 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 $[(\text{M} + \text{Na})^+]$, 100%].

(2R,3R,4aS,8aS)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[b][1,4]dioxine-5,8-diol (6)

A solution of the bis-allylic alcohol **5** (2.67 g, 9.25 mmol) in CH_2Cl_2 (200 mL) was sonicated under an atmosphere of nitrogen for 0.5 h then Grubbs'-II catalyst (157 mg, 2 mol%) was added in one portion. The ensuing mixture was heated under reflux for 1.5 h then cooled to room temperature and the solvent removed under reduced pressure. The resulting brown solid was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/hexane \rightarrow EtOAc gradient elution) and concentration of appropriate fractions ($R_{\text{f}} = 0.3$ in 2:1 v/v EtOAc/hexane) afforded cyclohexene **6** (2.39 g, 99%) as a white, amorphous solid and a mixture of diastereoisomers [Found: $(\text{M} + \text{Na})^+$, 283.1165. $\text{C}_{12}\text{H}_{20}\text{NaO}_6$ requires $(\text{M} + \text{Na})^+$, 283.1158]. ^1H NMR (CDCl_3 , 400 MHz) δ_{H} (mixture of three diastereoisomers) 6.07–5.62

(series of m, 2H), 4.51–4.20 (complex m, 2H), 4.10–3.57 (series of m, 2H), 3.49 (broad m, 1H), 3.36–3.24 (4 × s, 6H), 2.64–2.09 (series of broad m, 1H), 1.39–1.28 (4 × s, 6H). ^{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%].

(2R,3R,4aR,8aR)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydrobenzo[*b*][1,4]dioxine-5,8-dione (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 CH_2Cl_2 (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/ Et_2O elution) and concentration of the relevant fractions ($R_f = 0.7$ in 1:2 v/v $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$) at 20 °C afforded enedione **7** (4.01 g, 88%) as a bright yellow, crystalline solid, mp 115–117 °C (dec.), $[\alpha]_{\text{D}} -121.0$ (c 0.9 in CHCl_3) [Found: (M + Na) $^+$, 279.0850. $\text{C}_{12}\text{H}_{16}\text{NaO}_6$ requires (M + 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) m/z 343 [(M + 2 × CH_3OH + Na) $^+$, 100%], 311 [(M + CH_3OH + Na) $^+$, 50], 279 [(M + Na) $^+$, 10].

(2R,3R,4aR,8R,8aS)-8-Hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,8,8a-tetrahydrobenzo[*b*][1,4]dioxin-5(4a*H*)-one (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 MeOH (50 mL) maintained at 0 °C. The ensuing mixture was stirred at this temperature for 0.25 h then transferred to a pressure-equalized dropping funnel and added dropwise to a magnetically solution of endione **7** (4.01 g, 15.67 mmol) in MeOH (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 colorless and at which point it was quenched with acetone (20 mL). NH_4Cl (100 mL of a saturated aqueous solution) was added to the reaction mixture so-formed that was then allowed to warm to room temperature. The ensuing mixture was concentrated under reduced pressure and the residue thus obtained diluted with EtOAc (100 mL) and water (50 mL). The separated aqueous layer was extracted with EtOAc (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, $\text{CH}_2\text{Cl}_2 \rightarrow$ 1:2 v/v $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ gradient elution) and concentration of appropriate fractions ($R_f = 0.2$ in 1:1 v/v EtOAc/hexane) afforded enone **8** (3.79 g, 94%) as a clear, colorless oil, $[\alpha]_{\text{D}} -215.0$ (c 0.5, CHCl_3)

[Found: (M + Na)⁺, 281.1006. C₁₂H₁₈NaO₆ requires (M + Na)⁺, 281.1001]. ¹H NMR (CDCl₃, 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 (s, 3H), 3.28 (s, 3H), 2.55 (d, *J* = 3.9 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ¹³C NMR (CDCl₃, 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 [(M + Na)⁺, 100%].

(2*R*,3*R*,4*aR*,8*R*,8*aS*)-6-Bromo-8-hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,8,8*a*-tetrahydrobenzo[*b*][1,4]dioxin-5(4*aH*)-one (9)

Molecular bromine (400 μL of a 10% v/v solution in CH₂Cl₂, 0.79 mmol) was added, dropwise, to a magnetically stirred solution of enone **8** (185 mg, 0.72 mmol) in CH₂Cl₂ 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 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 NH₄Cl (3 × 5 mL of an aqueous solution) then the combined aqueous washings were extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (2 × 10 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, CH₂Cl₂ → 1:9 v/v Et₂O/CH₂Cl₂ gradient elution) and concentration of appropriate fractions (*R_f* = 0.2 in 1:9 v/v Et₂O/CH₂Cl₂) afforded bromoenone **9** (190 mg, 79 %) as a white, crystalline solid, mp 178–181 °C, [α]_D -146.6 (*c* 0.5, CHCl₃) [Found: (M + Na)⁺, 359.0100. C₁₂H₁₇⁷⁹BrNaO₆ requires (M + Na)⁺, 359.0106]. ¹H NMR (CDCl₃, 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 (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); ¹³C NMR (CDCl₃, 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 [(M + Na)⁺, 98 and 100%, respectively].

(2*R*,3*R*,4*aS*,5*R*,8*aR*)-7-Bromo-2,3-dimethoxy-2,3-dimethyl-8-oxo-2,3,4*a*,5,8,8*a*-hexahydrobenzo[*b*][1,4]dioxin-5-yl acetate (10)

Acetic anhydride (120 μL, 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, [α]_D -366.5 (*c* 0.6, CHCl₃) [Found: (M + Na)⁺, 401.0217. C₁₄H₁₉⁷⁹BrNaO₇ requires (M + Na)⁺, 401.0212]. ¹H NMR (CDCl₃, 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 [(M + 2 \times CH_3OH + Na), 98 and 100%, respectively], 403 and 401 [(M + Na) $^+$, 30 and 29, respectively].

(2R,3R,4aS,5R,8aR)-7-Bromo-2,3-dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl acetate (11) and (2R,3R,4aS,5R,8S,8aS)-7-Bromo-8-hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl acetate (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 MeOH (20 mL) maintained at 0 °C. The ensuing mixture was stirred at this temperature for 0.25 h then transferred to a pressure-equalized dropping funnel and added dropwise to a magnetically solution of acetate **10** (1.06 g, 2.79 mmol) in MeOH (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 EtOAc (100 mL) and NH_4Cl (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with EtOAc (3 \times 50 mL) and the combined organic phases then washed with brine (2 \times 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 $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) to afford two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$ in 1:19 v/v $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) afforded compound **11** (76 mg, 7%) as a clear, colorless oil, $[\alpha]_{\text{D}} -160.0$ (c 0.9, CHCl_3) [Found: (M + Na) $^+$, 403.0373. $\text{C}_{14}\text{H}_{21}^{79}\text{BrNaO}_7$ requires (M + Na) $^+$, 403.0368]. ^1H NMR (CDCl_3 , 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); ^{13}C NMR (CDCl_3 , 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 $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) afforded compound **12** (840 mg, 79%) as a clear, colorless oil, $[\alpha]_{\text{D}} -204.7$ (c 0.9, CHCl_3) [Found: (M + Na) $^+$, 403.0367. $\text{C}_{14}\text{H}_{21}^{79}\text{BrNaO}_7$ requires (M + Na) $^+$, 403.0368]. ^1H NMR (CDCl_3 , 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); ^{13}C NMR (CDCl_3 , 100 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 (film) 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].

(2R,3R,4aR,5R,8R,8aS)-8-Acetoxy-6-bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl 4-methoxybenzoate (13)

Tri-*n*-butylphosphine (520 μ L, 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, CH₂Cl₂ \rightarrow 1:19 v/v Et₂O/CH₂Cl₂ gradient elution) and concentration of appropriate fractions ($R_f = 0.5$ in 1:9 v/v Et₂O/CH₂Cl₂) afforded ester **13** (422 mg, 79%) as a white, amorphous solid, $[\alpha]_D -28.3$ (*c* 1.1, CHCl₃) [Found: (M + Na)⁺, 537.0734. C₂₂H₂₇⁷⁹BrNaO₉ requires (M + Na)⁺, 537.0736]. ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 [(M + Na)⁺, 100 and 98%, respectively].

(2R,3R,4aS,5R,8R,8aS)-6-Bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]-dioxine-5,8-diol (*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 MeOH (10 mL) and the ensuing mixture stirred at room temperature for 48 h. The MeOH was then removed under reduced pressure and the residue thus obtained diluted with EtOAc (10 mL) and NH₄Cl (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with EtOAc (3 \times 5 mL) and the combined organic phases washed with brine (2 \times 5 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure. The resulting white solid was subjected to flash column chromatography (silica, \rightarrow 1:24 v/v Et₂O/CH₂Cl₂ gradient elution) and concentration of appropriate fractions ($R_f = 0.3$ in 1:19 v/v MeOH/CH₂Cl₂) afforded enediol *ent*-1 (65 mg, 96%) as a white foam, $[\alpha]_D -76.5$ (*c* 1.0, CHCl₃) [Found: (M + Na)⁺, 361.0260. C₁₂H₁₉⁷⁹BrNaO₆ requires (M + Na)⁺, 361.0263]. ¹H NMR (CD₃OD, 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); ¹³C NMR (CD₃OD, 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 (film) 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 [(M + Na)⁺, 98 and 100%, respectively].

Method ii (ex. Compound II): Potassium carbonate (50 mg, 0.36 mmol) was added to a magnetically stirred solution of ester **11** (76 mg, 0.20 mmol) in MeOH (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 EtOAc (10 mL) and water (10 mL) then the separated aqueous layer extracted with EtOAc (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 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 $P2_12_12_1$, $Z = 4$, $a = 6.8265(1)$, $b = 11.4217(1)$, $c = 17.8288(1)$ Å; $V = 1390.12(1)$ Å³; $D_x = 1.611$ g cm⁻³; 2750 unique data ($2\theta_{\max}$ 144.6°), $R = 0.021$ [for 2718 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.052$ (all data), $S = 1.03$.

Structure Determination

Images were measured on an Agilent SuperNova CCD diffractometer (CuK α , mirror monochromator, $\lambda = 1.54184$ Å) and data extracted using the CrysAlis package.¹⁸ Structure solution was by direct methods (SIR92).¹⁹ The structure of compound **9** was refined using the CRYSTALS program package.²⁰ 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 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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