A Total Synthesis of the Cyclic Carbonate-containing Natural Product Aspergillusol B from *D*-(–)-Tartaric Acid

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A total synthesis of compound **3** from *D*-(–)-tartaric acid is reported and thereby establishing that the structure, including relative stereochemistry, originally assigned to the cyclic carbonate-containing natural product aspergillusol B is correct.

INTRODUCTION

In 2014 Rukachaisirikul and co-workers reported[1] on the isolation and structural elucidation of a series of metabolites from the culture broth of the fungus *Aspergillus* sp. PSU-RSPG185 found in soil samples collected from Surat Thani Province in Thailand. Among these were (+)-asperpentyn (**1**)[2] and two novel cyclic carbonate-containing compounds, named aspergillusols A and B, and to which structures **2** and **3**, respectively, were assigned (Figure 1).[3]

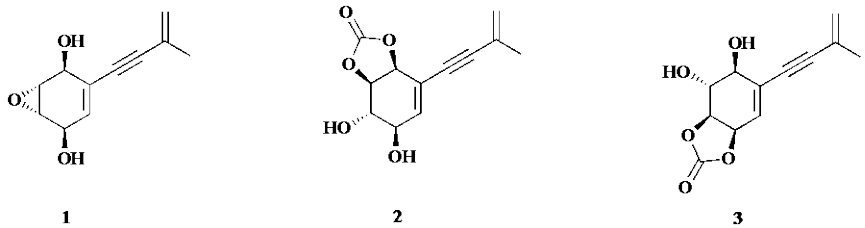
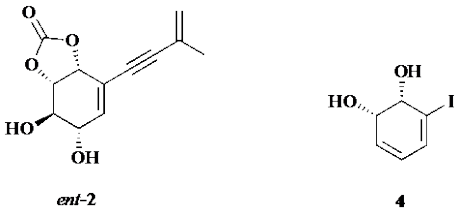


Figure 1: The Structures **1-3** Assigned to the Fungal Metabolites (+)-Asperpentyn, Aspergillusol A and Aspergillusol B, respectively.

The following year we detailed[4] syntheses of compound **1** and the enantiomer, *ent*-**2**, of the structure assigned to the first of these cyclic carbonates. The enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol **4**[5] was used as the starting material in this work and by such means we were able to confirm the structures of (+)-asperpentyn (**1**) and aspergillusol A save for the absolute stereochemistry of the latter. This ambiguity arose because of the significant difference in the specific rotation recorded for the synthetically-derived compound *ent*-**2** {$[\alpha]_D$ = +192.5 (*c* 0.2, methanol} and that reported for the natural product {$[\alpha]_D$ = –4.6 (*c* 0.49, methanol}.



ent-2 **4**

Figure 2: The Synthetically derived Compound *ent*-**2** and its Homochiral Precursor **4**

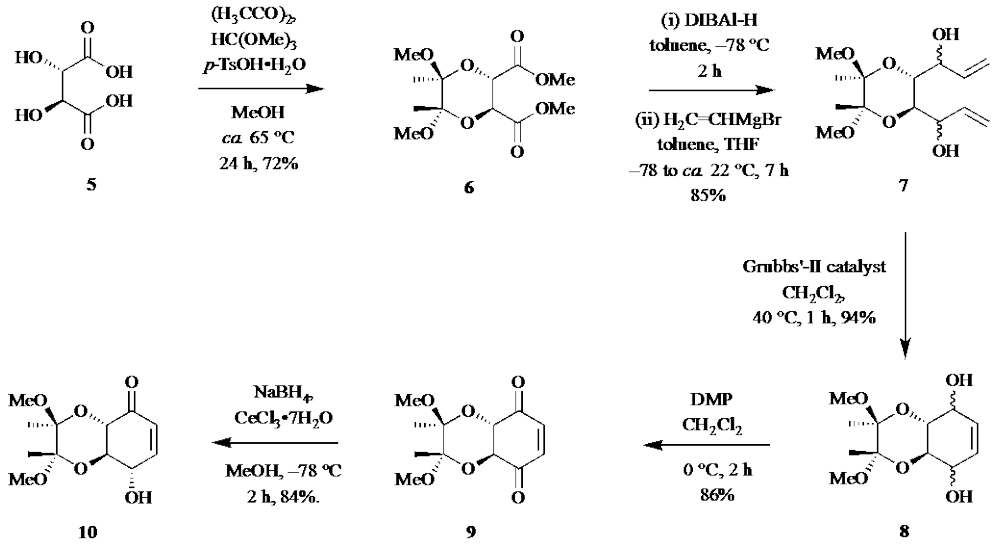
Recently, we reported[6] procedures that allow for the conversion of *L*-(+)-tartaric acid into a range of cyclohexene-based chirons that are likely to have broad applications in chemical synthesis. Of course, the enantiomeric forms of these chirons will be available by using *D*-(–)-tartaric acid and in order to showcase the utility of our protocols we now reported on the use of them to prepare, for the first time, compound **3** in enantiomerically pure form from this abundant and enantiomerically pure starting material.

RESULTS AND DISCUSSION

The synthetic route shown in Scheme 1 was used to convert *D*-(–)-tartaric acid (**5**) into a series of chiral cyclohexenes and this parallels, exactly, the one employed to make the enantiomeric systems. Thus, compound **5** was treated with a mixture of diacetyl, trimethyl orthoformate and catalytic amounts of *p*-toluenesulfonic acid monohydrate in hot methanol to give the Ley acetal **6** in 72% yield. Treatment of a toluene solution of the latter compound with two molar equivalents of di-*iso*-butylaluminium hydride (DIBAl-

H) at –78 °C and then with seven molar equivalents of vinylmagnesium bromide afforded, after allowing the reaction mixture to warm to ambient temperatures, a diastereoisomeric mixture of the anticipated *bis*-allylic alcohols in 85% yield. This mixture was subjected to ring-closing metathesis using Grubbs'-II catalyst in dichloromethane at *ca*. 40 °C and by such means the analogous mixture of cyclohexene diols **8** was obtained in 94% combined yield. Two-fold oxidation of this mixture using the Dess-Martin periodinane (DMP) in dichloromethane at 0 °C afforded the corresponding enedione **9** (86% yield). Unsurprisingly, and in keeping with earlier observations, compound **9** was rather prone to aromatization to the isomeric hydroquinone through a two-fold enolization process. Accordingly, this centrosymmetric species was immediately reduced with just over one molar equivalents of the Luche reagent in methanol at –78 °C and thereby delivering the γ-hydroxycyclohexenone **10** completely stereoselectively and in 84% yield. All the of IR, NMR and mass spectral data acquired on this last compound matched those reported for its enantiomer derived from *L*-(+)-tartaric acid. Furthermore, the specific rotation of compound **10** was of equal magnitude but opposite sign to that recorded[6] for its enantiomer (*viz*. *ent*-**10**).

Scheme 1: The Elaboration of *D*-(–)-tartaric acid (**5**) to Homochiral Cyclohexenone Derivatives

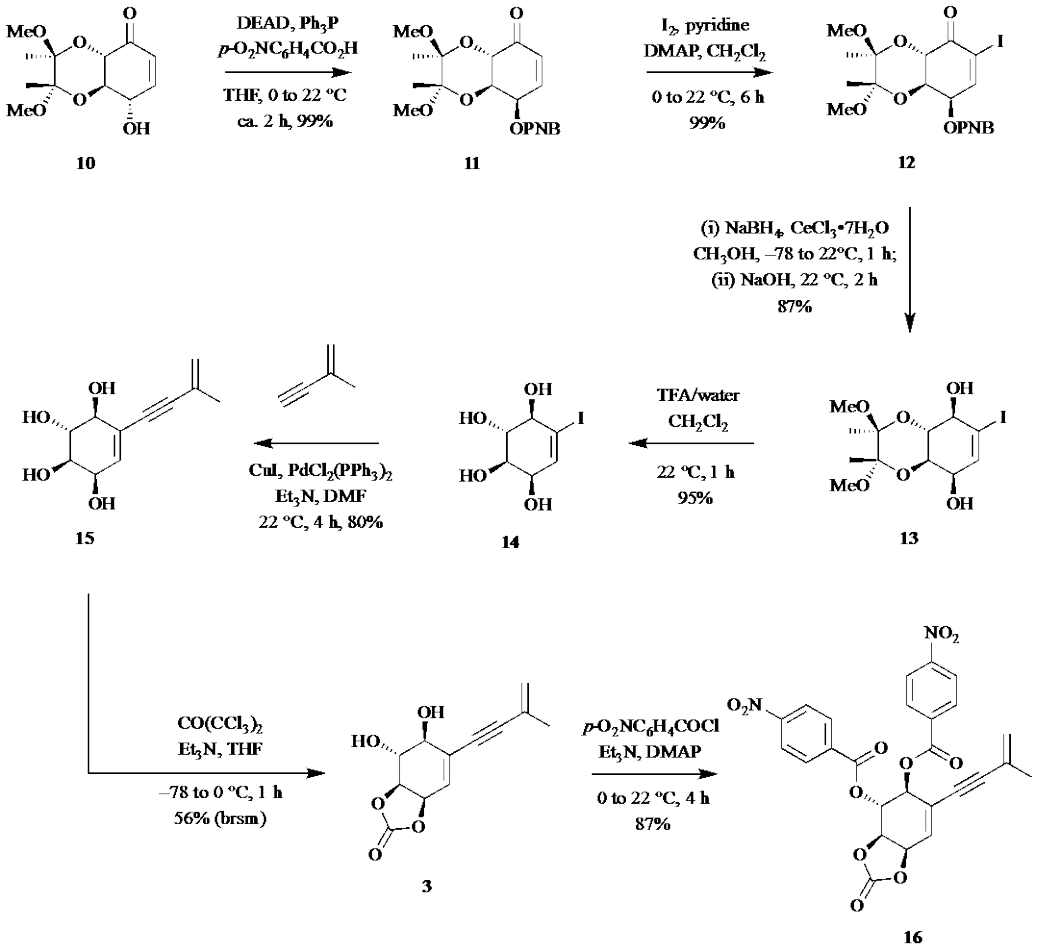


The conversion the γ-hydroxycyclohexenone **10** into the target cyclic carbonate **3** followed the reaction pathway shown in Scheme 2. Thus, the former compound was engaged in a Mitsunobu reaction using *p*-nitrobenzoic acid as nucleophile and the enone-ester **11** (99%) so-formed subjected to a Johnson α-iodination reaction using molecular iodine and pyridine in dichloromethane in the presence of a catalytic amound of DMAP. By such means compound **12** (99%) was obtained. Luche reduction of enone **12** in methanol at –78 °C proceeded stereoselectively and after the intermediate diol mono-ester was saponified, using aqueous sodium hydroxide, diol **13** was obtained in 87% yield. Cleavage of the Ley acetal unit within the last compound was achieved using a mixture of trifluoroacetic acid (TFA) and water in dichloromethane at 22 °C and by such means the iodocondurtitol **14** (95%) was obtained. Tetra-ol **14** is a known compound but because the reported[7] spectral data did not match those we acquired on this material, a single-crystal X-ray analysis was carried out (Figure 3)[8] and this served to confirm the illustrated structure (including absolute stereochemistry) for the compound obtained by the present pathway. Following protocols established in our earlier studies,[4,9] iodide **14** was engaged in a Sonogashira cross-coupling reaction with commercially available 2-methylbut-1-en-3-yne using copper(I) iodide, $PdCl_2(PPh_3)_2$ and triethylamine in DMF. In this way the rather insoluble dienyne **15** (80%) was obtained. In the final step of the reaction sequence, compound **15** was treated with bis(trichloromethyl)carbonate (triphosgene) in the presence of triethylamine and using THF as solvent. Compound **3** was thereby obtained as a white powder in 26% yield (56% brsm). All the spectral data acquired on this cyclic carbonate were in complete accord with the assigned structure. Diol **3** was converted, under standard conditions, into the crystalline *bis p*-nitrobenzoate **16** (87%). While the spectral data acquired on this derivative were also in complete accord with the illustrated structure, all efforts to secure a single-crystal X-ray analysis of this crystalline material were unsuccessful.

A comparison of the spectral data derived from compound **3** with the equivalent data reported[1] for aspergillusol B by Rukachaisirikul and co-workers revealed a very good match (see Table 1). Unfortunately, this group did not report a specific rotation for the naturally derived material. Accordingly, while the absolute stereochemistry of the

synthetic material is as illustrated, the corresponding configuration of the natural product cannot be defined at the present time.

Scheme 2: The Conversion of Compound **10** into Cyclic Carbonate **3**.



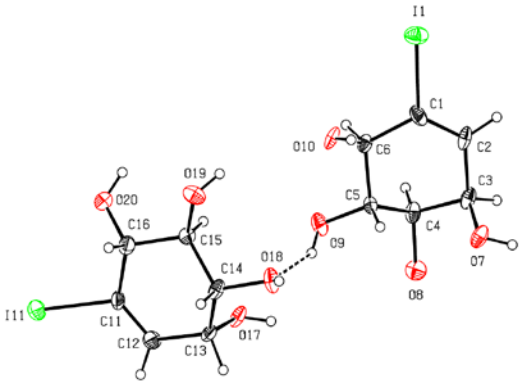


Figure 3. ORTEP derived from the single-crystal X-ray analysis of compound **14** (CCDC 1533559) with labeling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii and the hydrogen-bonding linking the two molecules in the unit cell is shown by a dotted line.

TABLE 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 3 with Those Reported[1] for Aspergillusol B

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
Aspergillusol B[a]	Compound **3**[b]	Aspergillusol B[c]	Compound **3**[d]
153.4	153.6	6.06, dd, *J* = 3.9 and 2.1 Hz, 1H	6.13, broad s, 1H
130.2	130.3	5.36, quintet, *J* = 3.9, and 1.8 Hz, 1H	5.44, broad s, 1H
125.7	125.7	5.34, quintet, *J* = 1.8 Hz, 1H	5.38, broad s, 1H
124.5	124.5	5.15, ddd, *J* = 7.8, 3.9 and 2.1 Hz, 1H	5.21, dd, *J* = 7.5 and 3.4 Hz, 1H
124.3	124.3	4.64, dd, *J* = 8.7 and 7.8 Hz, 1H	4.71, apt. t, *J* = 8.5 Hz, 1H
96.7	96.6	4.03, dt, *J* = 8.7 and 1.8 Hz, 1H	4.09, d, *J* = 8.4 Hz, 1H
82.5	82.6	4.19, m, 1H	–
77.3	77.4	3.76, t, *J* = 8.7 Hz, 1H	3.83, broad t, *J* = 8.7 Hz, 1H
73.0	72.9[e]	1.88, t, *J* = 1.2 Hz, 3H	1.95, s, 3H[f]
72.8	72.9[e]	–	–
69.0	69.0	–	–
23.0	23.1	–	–

[a]Data obtained from reference 1 – recorded in $CDCl_3$ at 125 MHz. [b]Data recorded in $CDCl_3$ containing 1% $(H_3C)_4Si$ at 100 MHz. [c]Data obtained from reference 1 – recorded in $CDCl_3$ at 500 MHz. [d]Data recorded in $CDCl_3$ containing 1% $(H_3C)_4Si$ at 400 MHz. [e]When the ^{13}C NMR spectrum of compound **3** was recorded in slightly acidic $CDCl_3$ these signals appeared as distinct resonances at δ_C 73.2 and 73.0 ppm. [f]Signals due to hydroxyl group protons not observed.

CONCLUSIONS

The studies reported herein not only serve to confirm the structure assigned to aspergillusol B but also highlight the capacities of our recently reported protocols[6] to

deliver a range of synthetically useful, homochiral polyoxygenated cyclohexenes in either enantiomeric form from *D*- or *L*-tartaric acid, each of which is an abundant material. Efforts to further demonstrate the utility of such chirons are currently underway in our laboratories and results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. 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 ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded 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. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as either thin films or finely divided solids. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} 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.[10] 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. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[11] Where necessary, reactions were performed under an nitrogen atmosphere.

Synthesis of 1,1'-((2*R*,3*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)-bis(prop-2-en-1-ol) (7). The previously reported[12] diester **6** (3.41 g, 11.7 mmol), which is readily derived from *D*-tartaric acid (**5**), was treated, successively, with di-*iso*-butylaluminium hydride in toluene and then with vinyl magnesium bromide as described[6] for the reaction of compound *ent*-**6**. By such means compound **7** (2.87 g, 85%) was obtained as a mixture of three diastereoisomers.

*Compound **7**:* clear, colorless oil; The ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[6] for the corresponding mixture of enantiomers.

Synthesis of (2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydro-benzo[*b*][1,4]dioxine-5,8-diol (8). Compound **7** (5.50 g, 19.1 mmol) was subjected to ring-closing metathesis using the Grubbs'-II catalyst (in dichloromethane at 40 °C) in the same manner as applied to its enantiomer (*ent*-**7**) and thereby affording cyclohexene **8** (4.68 g, 94%) as a mixture of three diastereoisomers.

*Compound **8**:* white, amorphous solid; The ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[6] for the corresponding mixture of enantiomers.

Synthesis of (2*S*,3*S*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydroben-zo[*b*][1,4]dioxine-5,8-dione (9). Compound **8** (1.26 g, 4.85 mmol) was subjected to two-fold oxidation using three molar equivalents of the Dess-Martin periodinane in the same manner as employed for its enantiomer (*ent*-**8**) and so affording enedione **9** (1.07 g, 86%).

*Compound **9**:* bright-yellow, crystalline solid {mp = 162–165 °C), lit.[6] mp (for enantiomer) = 115–117 °C (dec.); $[\alpha]_D$ = +115.0 (*c* 1.1 in $CHCl_3$), lit.[6] $[\alpha]_D$ (for enantiomer) = –121.0 (*c* 0.9 in $CHCl_3$)}; The ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[6] for its enantiomer.

Synthesis of (2*S*,3*S*,4a*S*,8*S*,8a*R*)-8-hydroxy-2,3-Dimethoxy-2,3-dimethyl-2,3,8,8a-tetrahydrobenzo[*b*][1,4]dioxin-5(4a*H*)-one (10). Compound **9** (1.74 g, 6.77 mmol) was subjected to reduction under the same conditions as used for its enantiomer (*ent*-**9**), *viz*. using a slight excess of the Luche reagent, and so producing γ-hydroxyenone **10** (1.47 g, 84%).

*Compound **10**:* white, crystaline solid (mp = 171–172 °C); {$[\alpha]_D$ = +225.5 (*c* 1.0 in $CHCl_3$), lit.[6] $[\alpha]_D$ (for enantiomer) = –215.0 (*c* 0.5 in $CHCl_3$)}; The ^1H and ^{13}C NMR spectral data obtained on this material were identical with those reported[6] for its enantiomer.

Synthesis of (2*S*,3*S*,4a*R*,5*R*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl 4-nitrobenzoate (11). A magnetically stirred solution of compound **10** (480 mg, 1.86 mmol), triphenylphosphine (585 mg, 2.23 mmol) and *p*-nitrobenzoic acid (373 mg, 2.23 mmol) in dry THF (40 mL) was cooled to 0 ºC and diethyl azodicarboxylate (360 μL, 2.23 mmol) was added over 0.25 h. The resulting solution was stirred at 0 °C for 0.5 h before being allowed to warm to 22 ºC then stirred at this temperature for another 1.5 h. The solution thus obtained was concentrated under reduced pressure and the light-yellow solid thus obtained was subjected to flash chromatography (silica, dichloromethane → 1:19 v/v diethyl ether/dichloromethane gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:19 v/v diethyl ether/dichloromethane) afforded *p*-nitrobenzoate **11** (750 mg, 99%).

*Compound **11**:* white, crystalline solid, mp = 183–185 ºC; $[\alpha]_D^{20}$ +156 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.24 (m, 2H), 7.03 (dd, *J* = 10.1 and 5.8 Hz, 1H), 6.26 (d, *J* = 10.1 Hz, 1H), 5.83 (dd, *J* = 5.8 and 3.8 Hz, 1H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.24 (dd, *J* = 11.0 and 3.8 Hz, 1H), 3.37 (s, 3H), 3.27 (s, 3H), 1.43 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 164.4, 150.9, 139.4, 135.5, 133.0, 131.1, 123.8, 100.5, 100.0, 70.3, 67.9, 67.3, 48.8, 48.4, 17.7, 17.6; IR ν_{max} 2980, 1721, 1710, 1610, 1528, 1344, 1278, 1111, 1091, 1027, 721 cm^{-1}; MS (ESI, +ve) *m/z* 431 and 430 [$(M + Na)^+$, 20 and 100%]; HRMS calcd for $C_{19}H_{21}NNaO_9$ 430.1114, found 430.1118

Synthesis of (2*S*,3*S*,4a*R*,5*R*,8a*S*)-7-Iodo-2,3-dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl 4-nitrobenzoate (12). A solution of molecular iodine (415 mg, 1.64 mmol) in dichloromethane/pyridine (4 mL of a 1:1 v/v

mixture) was added over 0.25 h to a magnetically stirred solution of compound **11** (268 mg, 0.66 mmol) and DMAP (4 mg, 0.03 mmol) in dichloromethane/pyridine (10 mL of 7:3 v/v mixture) maintained at 0 ºC. The ensuing mixture was stirred for 16 h at 0 °C after which time it was allowed to warm to 22 ºC. The resulting solution was diluted with ethyl acetate (40 mL) and washed successively with HCl (2 × 10 mL of a 1 M aqueous solution), water (1 × 10 mL) and Na_2SO_3 (2 × 10 mL of a saturated aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 10 mL) and combined organic phases washed with brine (3 x 10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Heptane (20 mL) was added to the ensuing residue and the mixture thus obtained concentrated under reduced pressure (so as to remove any remaining traces of pyridine) to give compound **12** (351 mg, 99%).

*Compound **12**:* White foam; $[\alpha]_D^{20}$ –59.0 (*c* 0.9, $CHCl_3$); R_f 0.6 in 1:19 v/v diethyl ether/dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.23 (m, 2H), 7.81 (d, *J* = 6.2 Hz, 1H), 5.68 (dd, *J* = 6.2 and 3.9 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.24 (dd, *J* = 11.0 and 3.9 Hz, 1H), 3.37 (s, 3H), 3.26 (s, 3H), 1.42 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 164.2, 150.9, 147.3, 135.2, 131.2, 123.8, 110.3, 100.6, 99.9, 69.5, 69.1, 66.8, 48.9, 48.5, 17.6, 17.5; IR ν_{max} 2952, 1718, 1607, 1528, 1342, 1264, 1141, 1101, 1035, 719 cm^{-1}; MS (ESI, +ve) *m/z* 588 [(M + methanol + Na)$^+$, 70%], 557 and 556 [(M + Na)$^+$, 25 and 100], 430 (50); HRMS calcd for $C_{19}H_{20}INNaO_9$ 556.0080, found 556.0081

Synthesis of (2*S*,3*S*,4a*R*,5*R*,8*R*,8a*R*)-6-Iodo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxine-5,8-diol (13). Sodium borohydride (15 mg, 0.40 mmol) was added, in portions over 0.08 h, to a magnetically stirred solution of enone **12**, (100 mg, 0.19 mmol) and $CeCl_3$•$7H_2O$ (70 mg, 0.19 mmol) in methanol (5 mL) maintained at –78 ºC. After 0.5 h the reaction mixture was allowed to warm to 22 ºC and water (0.5 mL) then added dropwise. When evolution of hydrogen gas had subsided (*ca.* 0.25 h) NaOH (0.5 mL of a 1 M aqueous solution) was added to the reaction mixture and the resulting solution stirred for 2 h at 22 °C then diluted with ethyl acetate (20 mL) and washed with $NaHCO_3$ (2 × 5 mL of a saturated aqueous solution). The combined aqueous washings were extracted with ethyl acetate (3 × 5 mL) and combined organic layers then washed with brine (3 × 5 mL) before being dried (Na_2SO_4), filtered, and

concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, dichloromethane → 1:9 v/v methanol/dichloromethane gradient elution) and concentration of the relevant fractions (R_f = 0.2 in 1:19 v/v methanol/dichloromethane) afforded compound **13** (62 mg, 87%).

*Compound **13**:* white, amorphous solid; $[\alpha]_D^{20}$ +85.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 5.8 and 1.8 Hz, 1H), 4.17–4.04 (complex m, 3H), 3.68 (dd, *J* = 10.8 and 4.1 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 2.57 (broad d, *J* = 1.7 Hz, 1H), 2.47 (d, *J* = 4.5 Hz, 1H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 109.5, 99.8, 99.4, 74.5, 68.2, 67.5(1), 67.4(9), 48.3, 48.2, 17.9, 17.7; IR ν_{max} 3429, 2949, 1376, 1115, 1028, 919, 849, 815, 656 cm^{-1}; MS (ESI, +ve) *m/z* 409 [(M + Na)$^+$, 100%]; HRMS calcd for $C_{12}H_{19}INaO_6$ 409.0124, found 409.0123.

Synthesis of (1*R*,2*R*,3*S*,4*R*)-5-Iodocyclohex-5-ene-1,2,3,4-tetraol (14). Water (200 μL) then trifluoroacetic acid (200 μL) were added successively to a magnetically stirred solution of compound **13** (66 mg, 0.17 mmol) in dichloromethane (3 mL) maintained under a stream of nitrogen at 22 ºC. The solution thus obtained was allowed to evaporate to dryness (ca. 0.25 h), the ensuing residue diluted with dichloromethane (3 mL) and the resulting solution again treated with water (200 μL) then trifluoroacetic acid (200 μL L). After evaporation to dryness (*ca.* 0.25 h) the residue was subjected to flash chromatography (silica, 10:9:1 v/v hexane/ethyl acetate/methanol → 1:8:1 v/v hexane/ethyl acetate/methanol gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:8:1 v/v hexane/ethyl acetate/methanol) afforded compound **14** (44 mg, 95%).

*Compound **14**:* white, crystalline solid, mp = 139–141 ºC (from ethyl acetate–hexane), lit. mp[7] = 145–149 (from acetone/methanol); $[\alpha]_D^{20}$ –39.5 (*c* 0.6, methanol), lit.[7] $[\alpha]_D^{20}$ –45 (*c* 0.5, methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 6.54 (dd, *J* = 5.3 and 1.2 Hz, 1H), 4.05 (dd, *J* = 5.4 and 4.1 Hz, 1H), 3.82-3.77 (complex m, 2H), 3.55 (m, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 139.5, 109.8, 78.5, 73.4, 72.1, 69.7; IR ν_{max} 3279, 2907, 1618, 1264, 1089, 1066, 1046, 1019, 821 cm^{-1}; MS (ESI, +ve) *m/z* 295 [(M + Na)$^+$, 100%]; HRMS calcd for $C_6H_9INaO_4$ 294.9443, found 294.9443

Synthesis of (1*R*,2*R*,3*R*,4*S*)-5-(3-Methylbut-3-en-1-yn-1-yl)cyclohex-5-ene-1,2,3,4-tetraol (15). A magnetically stirred mixture of iodide **14** (34 mg, 0.125 mmol) and triethylamine (2 mL) in DMF (1 mL) maintained at 22 °C was degassed by sonication under an atmosphere of nitrogen for 0.5 h then treated with CuI (5 mg, 0.046 mmol), $PdCl_2(Ph_3P)_2$ (21 mg, 0.030 mmol) and 2-methyl-1-buten-3-yne (150 μL, 1.58 mmol). The resulting solution was stirred at 22 °C for 4 h and then the volatiles were removed under reduced pressure. The residue thus obtained was dissolved in THF (1 mL) and subjected to flash column chromatography (silica, 45:50:5 v/v hexane/ethyl acetate/methanol → 23:70:7 v/v hexane/ethyl acetate/methanol gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:8:1 v/v hexane/ethyl acetate/methanol) afforded compound **15** (50 mg, 80%).

*Compound **15**:* white, amorphous solid; $[\alpha]_D^{20}$ –57.1 (*c* 0.6, methanol) ^{1}H NMR (400 MHz, CD_3OD) δ 6.06 (dd, *J* = 5.2 and 1.8 Hz, 1H), 5.30 (m, 1H), 5.27 (m, 1H), 4.23 (app t, *J* = 4.4 Hz, 1H), 3.85 (dd, *J* = 7.2 and 1.8 Hz, 1H), 3.71 (dd, *J* = 9.8 and 7.2 Hz, 1H), 3.49 (dd, *J* = 9.8 and 4.4 Hz, 1H), 1.91 (app. t, *J* = 1.3 Hz, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 134.1, 128.3(), 128.3(1), 122.5, 92.5, 87.5, 74.4, 73.4, 72.1, 67.6, 23.5; IR ν_{max} 3249, 2883, 1664, 1630, 1608, 1429, 1258, 1092, 1051, 898, 633 cm^{-1}; MS (ESI, +ve) *m/z* 443 [$(2M + Na)^+$, 50%], 233 [$(M + Na)^+$, 100]; HRMS calcd for $C_{11}H_{14}NaO_4$ 233.0790, found 233.0790.

Synthesis of (3a*S*,4*R*,5*S*,7a*R*)-4,5-Dihydroxy-6-(3-methylbut-3-en-1-yn-1-yl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-2-one (3). A magnetically stirred soltuion of tetraol **15** (37 mg, 0.18 mmol) in THF (2 mL) maintained at −78 °C was treated with triethylamine (90 μL, 0.65 mmol) and then with a solution of triphosgene (27 mg 0.09 mmol) in THF (1 mL). The resulting mixture was stirred at −78 °C for 0.5 h then allowed to warm to 0 ºC and stirred at this temperature for another 0.5 h. The suspension thus obtained was poured into ice-cold NH_4Cl (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, hexane → 65:35 v/v hexane/ethyl acetate gradient elution) to afford two fractions, A and B

Concentration of fraction A (R_f = 0.3 in 10:9:1 v/v hexane/ethyl acetate/methanol) afforded compound **3** (11 mg, 26% or 58% brsm).

Concentration of fraction B (R_f = 0.1 in 10:9:1 v/v hexane/ethyl acetate/methanol) afforded the starting material **15** (20 mg, 54% recovery). The ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with derived from an authentic sample.

*Compound **3**:* white powder mp = 115-117 ºC (dec.). $[\alpha]_D^{20}$ –12 (*c* 0.5, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) s ^{13}C NMR (100 MHz; $CDCl_3$) s ν_{max} 3412, 2957, 2922, 2189, 1791, 1628, 1357, 1169, 1046, 889, 772, 727 cm^{-1}; MS (ESI, +ve) *m/z* 495 [(2M + Na)$^+$, 70%], 259 [(M + Na)$^+$, 100], 102 (75); HRMS calcd for $C_{12}H_{12}NaO_5$ 259.0582, found 259.0583.

Synthesis of (3a*R*,4*R*,5*S*,7a*R*)-6-(3-Methylbut-3-en-1-yn-1-yl)-2-oxo-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl bis(4-nitrobenzoate) (16). A magnetically stirred solution of compound **3** (5.1 mg, 0.022 mmol), triethylamine (100 μL, 0.72 mmol) in dry dichloromethane (2 mL) maintained at 0 °C was treated sequentially with *p*-nitrobenzoyl chloride (16 mg, 0.086 mmol) and DMAP (one crystal, *ca* 0.1 mg). The ensuing mixture was allowed to warm to 22 °C, stirred at this temperature for 4 h then diluted with diethyl ether (5 mL) and quenched with phosphate buffer (5 mL of a 1 M, pH 7 aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 × 1 mL) and the combined organic phases then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-yellow residue thus obtained was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.6) gave compound **16** (10 mg, 87%).

*Compound **16**:* white amorphous solid; $[\alpha]_D^{20}$ +77.7 (*c* 0.5, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30-8.25 (complex m, 4H), 8.21-8.17 (complex m, 2H), 8.17-8.13 (complex m, 2H), 6.39 (dd, *J* = 4.1 and 1.8 Hz, 1H), 5.99 (ddd, *J* = 8.0, 1.8 and 1.3 Hz, 1H), 5.83 (dd, *J* = 8.1 and 8.0 Hz, 1H), 5.43 (ddd, *J* = 7.9, 4.1 and 1.3 Hz, 1H), 5.22 (app p, *J* = 1.3 Hz, 1H), 5.12 (broad t, *J* = 1.3 Hz, 1H), 5.09 (dd, *J* = 8.1 and 7.9 Hz, 1H), 1.67 (app t, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 163.4, 152.5, 151.2, 133.9, 133.8, 131.2(4), 131.1(9), 126.9, 126.2, 125.4, 125.1, 123.9(4), 123.9(2), 97.2, 82.4, 74.2, 72.3, 71.0, 68.9, 22.7 (one signal obscured or overlapping); IR ν_{max} 3932, 2852, 1809,

1732, 1607, 1524, 1347, 1259, 1095, 1051, 907, 716 cm^{-1}; MS (ESI, +ve) *m/z* 557 [$(M + Na)^+$, 100], 337(70); HRMS calcd for $C_{26}H_{18}N_2NaO_{11}$ 557.0803, found 557.0808

Crystallographic Studies. *Crystallographic Data.*

Compound **14**. $C_6H_9IO_4$, M = 272.03, T = 150 K, monoclinic, space group $P2_1$, Z = 4, a = 9.4654(3) Å, b = 7.09196(19) Å, c = 13.2976(5) Å; V = 835.51(5) $Å^3$, D_x = 2.163 g cm^{-3}, 3355 unique data ($2\theta_{max}$ = 147.8°), R = 0.081 [for 3304 reflections with $I > 2.0\sigma(I)$]; Rw = 0.225 (all data), S = 1.05.

Structure Determination. Diffraction images for compound **14** were measured on a diffractometer (Mo Kα, mirror monochromator, λ = 0.71073 Å) fitted with an area detector and the data extracted using the DENZO/Scalepack package.[13] The structure solutions for all four compounds were solved by direct methods (SIR92)[14] then refined using the CRYSTALS program package.[15] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1533559). 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.

ASSOCIATED CONTENT

Supporting Information

Data derived from the single-crystal X-ray analyses of compound **14**; ^1H and ^{13}C NMR spectra of compounds **3** and **11**-**16**. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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