cis-Dihydrocatechols as Precursors to Highly Oxygenated Troponoids: A Fully Regiocontrolled Synthesis of 3,4-Dimethoxy-α-tropolone

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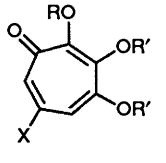
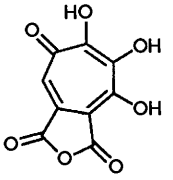
The highly oxygenated α-tropolone antibiotic 3,4-dimethoxy-α-tropolone **3** has been synthesized in a fully regiocontrolled manner from commercially available *cis*-1,2-dihydrocatechol **5**. Demethylation of 3,4-dimethoxy-α-tropolone **3** produced the potent antitumour agent 3,4-dihydroxy-α-tropolone **4**.

Compounds **1–4** constitute key members of the small group of troponoid natural products which contain four contiguously oxygenated ring-carbons. Puberulic acid **1** and puberulonic acid **2** were first isolated[1] in 1932 from cultures of various moulds and were subsequently shown to display useful activity against Gram-positive bacteria.[2] Puberulonic acid **2** is also active against HeLa human carcinoma cell culture.[3] In 1978 3,4-dimethoxy-α-tropolone **3** was isolated[4] from *Streptoverticillium hadanonense* fermentation broths and found to be active against both Gram-positive and Gram-negative bacteria. More recently,[5] the 'parent' system **4** (designated BMY-28438) has been obtained from cultured broths of *Streptomyces tropolofaciens* (No. K611-97) and shown to possess strong and specific cytotoxicity against B16 melanoma cells.[5] Therefore, the life span of mice bearing B16 melanoma was significantly increased by the intraperitoneal administration of compound **4**.[5] Compound **4** also displayed significant antifungal activity but proved to be ineffective as an antibacterial agent.

The biological activities associated with compounds **1–4** have prompted some synthetic studies but analysis of the reported routes to puberulic acid **1**,[6] puberulonic acid **2**[7] and BMY-28438 **4**[5] suggests that it is particularly difficult to establish the required oxygenation pattern with full regiochemical control. For example, compound **4** has been prepared[5] by persulfate oxidation of α-tropolone but it is necessary to separate the desired product from co-produced 5-hydroxy-, 7-hydroxy- and 4,7-dihydroxy-tropolone by using counter-current distribution methods. An additional and equally demanding feature associated with any projected synthesis of compound **3** (which has not been prepared previously) is the need for site-specific introduction of the two methyl groups on adjacent oxygens.



1 R = R' = H, X = CO_2H
3 R = X = H, R' = Me
4 R = R' = X = H



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We now describe a fully regiocontrolled synthesis of the title compound **3** involving a strategy which should be quite generalisable. A key feature of this work is the use of the commercially available *cis*-1,2-dihydrocatechol **5** as starting material. Compound **5** and its derivatives, which are obtained by microbial oxidation of arenes,[8] have been attracting increasing attention recently as useful chemical building blocks.[9] The present work provides the first example of their application to the synthesis of seven-membered-ring carbocyclic natural products. In addition, we have definitively established the structural relationship between natural products **3** and **4** as a result of demethylation of the former compound and thereby producing the latter.

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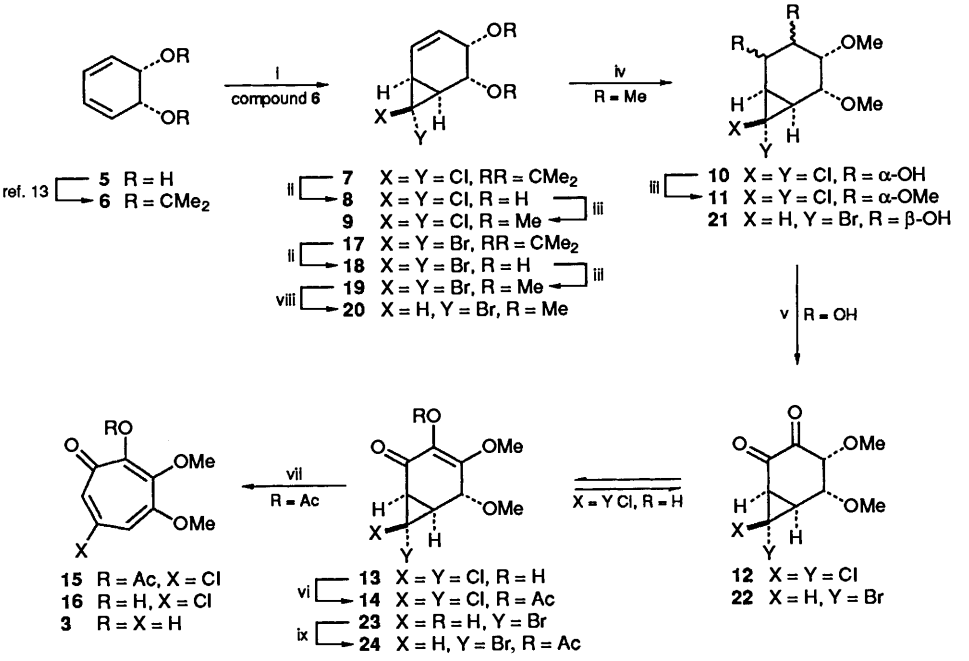
Results and Discussion

The route used in the preparation of compound **3**, which is based on our earlier work associated with the preparation of troponoids,[10] is shown in Scheme 1. Initial efforts to implement this sequence employed the dichlorocarbene adduct **7**[11,12] of the readily available acetonide derivative **6**[13] of **5**. Compound **7** was hydrolysed to diol **8**[12] which was in turn bis-*O*-methylated with methyl iodide in the presence of sodium hydride to give the dimethoxy compound **9** (97%). Attempts to develop a more direct route to compound **9** by bis-*O*-methylation of *cis*-1,2-dihydrocatechol **5** failed to provide the required product for subsequent dichlorocarbene addition. After extensive experimentation we established that the procedure described by Sharpless and co-workers[14] for osmium tetraoxide-mediated *cis*-dihydroxylation of alkenes allowed the smooth conversion of the cyclohexene **9** into the cyclohexane **10** (68%). The stereochemical outcome of this reaction was determined by effecting bis-*O*-methylation of diol **10**, using the conditions described previously, and thereby obtaining the C_2-symmetric tetramethoxy product **11** which showed only six signals in the 100 MHz $\{^1H\}^{13}C$ NMR spectrum. Trifluoroacetic anhydride (TFAA)-activated dimethyl sulfoxide (DMSO) oxidation[15] of diol **10** afforded a *ca.* 1:3 mixture of diketone **12** and the tautomeric α-hydroxy enone **13** (82% combined yield). Treatment of this mixture with acetyl chloride in the presence of potassium hydride then provided the α-acetoxy enone **14** (62%) which, upon reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene, underwent smooth ring-expansion to give the α-tropolone acetate **15** (100%). The structure of product **15** has been confirmed by single-crystal X-ray diffraction methods (Fig. 1).[16] DBU-promoted ring-expansion of compound **14**, followed by an alkaline work-up (to effect hydrolysis of the intermediate tropolone acetate **15**), provided the free tropolone **16** directly in 90% yield. However, all attempts to reductively dechlorinate compound **16** and thereby produce the natural product 3,4-dimethoxytropolone **3** failed. Either no reaction occurred or, under more forcing conditions, complete decomposition of the starting material was observed.



Scheme 1 *Reagents and conditions:* i, $CHCl_3$ or $CHBr_3$, benzene, 50% aq. NaOH, $PhCH_2NEt_3^+ Cl^-$, 18 °C, 24 h; ii, aq. HCl, THF, 18 °C, 48 h; iii, NaH, MeI, THF, 0–25 °C, 17 h; iv, OsO_4 (0.1 mol equiv.), Bu'OOH (3 mol equiv.), NaOAc (0.25 mol equiv.), $Et_3NH^+ Cl^- \cdot H_2O$ (0.125 mol equiv.), 40 °C, 5 h; v, DMSO (3.2 mol equiv.), TFAA (2.9 mol equiv.), −60 °C, 2 h; then Et_3N (6.7 mol equiv.), −60 °C, 1.5 h; then warm to 0 °C (1 h) [for **22**, allowed to warm to 20 °C (0.5 h) then stirred for 2 h]; vi, KH (3 mol equiv.), AcCl (2 mol equiv.), 0 °C, 0.5 h; vii, DBU (3 mol equiv.), benzene, 25 °C, 12 h (4 h at 50 °C for **24**); then (for isolation of **3** or **16**) aq. NaOH work-up; viii, BuLi (1.1 mol equiv.), THF, −100 °C, 5 h; then MeOH (1.1 mol equiv.); ix, Ac_2O (3 mol equiv.), pyridine, CH_2Cl_2, 25 °C, 15 h.

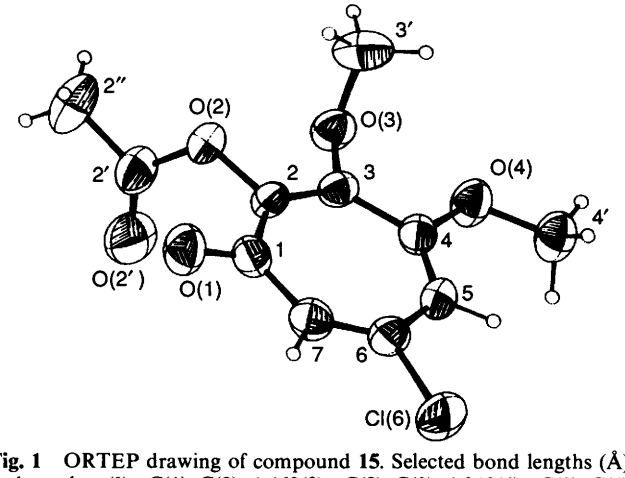


Fig. 1 ORTEP drawing of compound **15**. Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.469(3), C(2)–C(3) 1.348(4), C(3)–C(4) 1.455(3), C(4)–C(5) 1.353(3), C(5)–C(6) 1.425(4), C(6)–C(7) 1.338(1), C(7)–C(1) 1.442(3); C(2)–C(1)–C(7) 121.6(2), C(1)–C(2)–C(3) 132.5(2), C(2)–C(3)–C(4) 128.2(2), C(3)–C(4)–C(5) 127.8(2), C(4)–C(5)–C(6) 127.6(2), C(5)–C(6)–C(7) 131.5(2), C(6)–C(7)–C(1) 130.6(2).

In order to circumvent the problems of removal of halogen described above, the following reaction sequence was employed. The previously reported[15] dibromocarbene adduct of compound **6**, compound **17**, was readily hydrolysed to the corresponding diol **18** (92%) which was, in turn, converted into the bis-*O*-methyl ether **19** (80%) using conditions described earlier. Compound **19** was treated with butyllithium at −100 °C and the ensuing lithium halogenocarbenoid[17] was quenched with methanol to give the reductively mono-debrominated product **20** (*ca.* 70%). Mechanistic considerations[17] taken in conjunction with the observation of a doublet of doublets with vicinal coupling constants of 2.9 ($J_{7,1}$) and 3.9 ($J_{7,6}$) Hz[18] for 7-H established the *endo*-disposition of the newly introduced cyclopropyl hydrogen in compound **20**. *cis*-Dihydroxylation of compound **20** under the conditions used earlier provided two diastereoisomeric products (54%) in a 1:2.4 ratio. Bis-*O*-methylation of the major product provided an unsymmetrical tetramethoxy product as evidenced by the presence of eleven distinct signals in the 100 MHz $\{^1H\}^{13}C$ NMR spectrum. On this basis the predominant product from the dihydroxylation of compound **20** must be diol **21**. Oxidation of diol **21** under modified Swern conditions[15] then afforded the α-hydroxy enone **23** (57%). The tautomeric diketone **22** is presumably the primary product of reaction but was not detected. Treatment of compound **23** with acetic anhydride and pyridine afforded the α-acetoxy enone **24** (87%), which upon sequential treatment with DBU and then aq. sodium hydroxide afforded the 3,4-dimethoxytropolone **3** (95%), the IR and UV spectra of which were superimposable upon those reported[4] for the natural product. Further confirmation of the assigned structure stems from the observation that demethylation of compound **3**, using hydrogen bromide in aq. acetic acid, afforded compound **4** in 71% yield. Once again, the physical and spectroscopic data obtained on our sample of compound **4** were in good agreement with the corresponding data reported in the literature.[5]

Experimental

300 MHz ^1H NMR spectra and 75 MHz ^{13}C NMR spectra were obtained on a Varian UNITY 300 NMR spectrometer. *J*-Values are given in Hz. General experimental procedures have been reported elsewhere.[19] Light petroleum refers to the fraction boiling in the range 40–60 °C.

(1α,4α,5α,6α)-7,7-*Dichloro*-4,5-*dimethoxybicyclo*[4.1.0]*hept*-2-*ene* **9**.—A solution of diol **8**[12] (195 mg, 1.00 mmol) in tetrahydrofuran (THF) (4 cm^3) was added dropwise to a magnetically stirred suspension of sodium hydride (96 mg, 4.00 mmol) in THF (6 cm^3) maintained at ~0 °C (ice–water) under nitrogen. The chilled mixture was allowed to warm to ambient temperature and was stirred for 0.5 h before being re-chilled (ice–water) to ~0 °C. The re-chilled mixture was then treated

dropwise with methyl iodide (0.62 cm^3, 10.0 mmol). Upon completion of the addition the reaction mixture was once again allowed to warm to ambient temperatures and was stirred for a further 17 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographically filtered through a pad (5 cm deep) of TLC-grade silica gel (CH_2Cl_2 elution; 300 cm^3). The filtrate was concentrated under reduced pressure and the residue was distilled (80 °C/0.1 mmHg) to yield the *title compound* **9** (216 mg, 97%) as an oil (Found: M^+, 222.0214. $C_9H_{12}{}^{35}Cl_2O_2$ requires *M*, 222.0214); ν_{max}(NaCl)/cm^{-1} 2930, 2893, 2820, 1383, 1189, 1141, 1096, 1073, 1001 and 841; δ_H(400 MHz) 6.16 (1 H, ddd, $J_{3,2}$ 9.5, $J_{3,4}$ 5.9, $J_{3,1}$ 1.5, 3-H), 5.97 (1 H, ddd, $J_{2,3}$ 9.5, $J_{2,1}$ 2.9, $J_{2,6}$ 0.7, 2-H), 3.82 (1 H, dd, $J_{4,3}$ 5.9, $J_{4,5}$ 3.2, 4-H), 3.47 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.38 (1 H, dd, $J_{5,6}$ 4.9, $J_{5,4}$ 3.2, 5-H), 2.32 (1 H, ddd, $J_{1,6}$ 10.5, $J_{1,2}$ 2.9, $J_{1,3}$ 1.5, 1-H) and 2.02 (1 H, ddd, $J_{6,1}$ 10.5, $J_{6,5}$ 4.9, $J_{6,2}$ 0.5, 6-H); δ_C(100 MHz) 132.0, 126.8, 76.6, 71.2, 66.3, 56.9, 56.7, 31.0 and 29.5; *m/z* (15 eV) 222 (0.2%, M^+) and 189 (12) and 187 (37) [both $(M - Cl)^+$] and 75 (100).

(1α,2α,3α,4α,5α,6α)-7,7-*Dichloro*-4,5-*dimethoxybicyclo*[4.1.0]-*heptane*-2,3-*diol* **10**.—Tetraethylammonium chloride hydrate (103 mg, 0.56 mmol, 0.125 mol equiv.) and sodium acetate (92 mg, 1.12 mmol, 0.25 mol equiv.) were stirred in acetone (20 cm^3) for 1 h. This mixture was then treated with alkene derivative **9** (1.00 g, 4.48 mmol), *tert*-butyl hydroperoxide (70%; 6 cm^3, 3 mol equiv.) and osmium tetraoxide (4.5 cm^3 of a 2.5 wt % solution in *tert*-butyl alcohol). The resulting mixture was heated at reflux for 5 h. TLC analysis (CH_2Cl_2) of the reaction mixture at this stage showed no remaining substrate **9**. The mixture was cooled, and concentrated under reduced pressure to yield a pale green oil, which was partitioned between saturated aq. NaCl (50 cm^3) and diethyl ether (20 cm^3). The aqueous phase was separated and extracted with diethyl ether (3 × 40 cm^3). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a pale green oil. Chromatographic filtration of this material through a 5 cm pad of TLC-grade silica gel (CH_2Cl_2 elution; 500 cm^3) removed the more mobile impurities. The pad was then washed with diethyl ether (300 cm^3) and the ethereal filtrate was concentrated under reduced pressure to give *diol* **10** (789 mg, 68%) as an oil (Found: M^+, 256.0269. $C_9H_{14}Cl_2O_4$ requires *M*, 256.0269); ν_{max}(NaCl)/cm^{-1} 3429, 1103 and 1077; δ_H(400 MHz; $CDCl_3$ with a drop D_2O) 3.93 (1 H, d, *J* 4.4), 3.65 (1 H, br t, *J* 2.2), 3.53 (3 H, s, OMe), 3.46 (3 H, s, OMe), 3.40 (2 H, dd, *J* 4.9, 1.7), 3.39 (1 H, t, *J* 2.7), 2.23 (1 H, dd, *J* 11.2, 1.0) and 1.87 (1 H, dd, *J* 11.2, 2.7); δ_C(100 MHz) 81.1, 77.8, 68.1, 66.2, 61.1, 60.5, 57.4, 34.9 and 30.0; *m/z* (15 eV) 256 (0.4%, M^+) and 101 (100).

(1α,2α,3α,4α,5α,6α)-7,7-*Dichloro*-2,3,4,5-*tetramethoxybicyclo*-[4.1.0]*heptane* **11**.—Bis-*O*-methylation of diol **10** (81 mg, 0.32 mmol) was carried out under the same conditions as employed for the conversion of diol **8** into bis-ether **9**. The crude reaction product was subjected to flash chromatography (Et_2O) to yield, after concentration of the appropriate fractions (R_f 0.8), the *title compound* **11** (20 mg, 22%) as a clear oil (Found: M^+, 284.0582. $C_{11}H_{18}Cl_2O_4$ requires *M*, 284.0582); ν_{max}(NaCl)/cm^{-1} 3007, 2931, 2827, 1215, 1097, 1066, 1014, 812, 756 and 667; δ_H(400 MHz) 3.51 (6 H, s, 2 × OMe), 3.49 (6 H, s, 2 × OMe), 3.46 (2 H, br d, *J* 4.0), 3.37 (2 H, br d, *J* 4.0) and 2.07–2.06 (2 H, m, 1- and 6-H); δ_C(100 MHz) 78.3, 75.5, 61.7, 59.0, 58.2 and 31.4; *m/z* (15 eV) 288 (0.6%), 286 (3) and 284 (4) (each M^+), 114 (100) and 101 (94).

(1α,4α,5α,6α)-7,7-*Dichloro*-4,5-*dimethoxybicyclo*[4.1.0]*hep-tane*-2,3-*dione* **12** *and* (1α,5α,6α)-7,7-*Dichloro*-3-*hydroxy*-4,5-*dimethoxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **13**.—A magnetically stirred solution of DMSO (0.6 cm^3, 8.45 mmol) in CH_2Cl_2 (30 cm^3) maintained under nitrogen at −60 °C was treated dropwise with TFAA (0.98 cm^3, 6.9 mmol). The resulting solution was stirred at −60 °C for 10 min and then a solution of diol **11** (684 mg, 2.66 mmol) in CH_2Cl_2 (6 cm^3) was added dropwise. The solution thus obtained was stirred at −60 °C for 1.5 h and was then treated dropwise with triethylamine (2.46 cm^3, 17.6 mmol). The resulting golden coloured solution was stirred for a further 2 h at −60 °C and was then allowed to warm slowly (1 h) to 0 °C. The reaction mixture was then poured into 2 mol dm^{-3} HCl (100 cm^3), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic phases were then washed with water (1 × 100 cm^3), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a golden coloured oil. This material was subjected to preparative TLC [(PLC) (9:1) CH_2Cl_2–Et_2O] and the resulting chromophoric band (R_f 0.6–0.7) was extracted to yield a *ca.* 1:3 mixture of the *title tautomeric compounds* **12** and **13** (550 mg, 82%) as a yellow oil (Found: M^+, 251.9956. $C_9H_{10}Cl_2O_4$ requires *M*, 251.9956); ν_{max}(NaCl)/cm^{-1} 3381, 1663, 1626, 1410, 1329, 1239 and 1063; δ_H(400 MHz) **13**: 5.95 (1 H, br s, OH), 4.53 (1 H, d, $J_{5,6}$ 2.0, 5-H), 4.07 (3 H, s, OMe), 3.47 (3 H, s, OMe), 2.83 (1 H, dd, $J_{6,1}$ 10.3, $J_{6,5}$ 2.0, 6-H) and 2.44 (1 H, d, $J_{1,6}$ 10.3, 1-H); δ_C(100 MHz) **12**: 190.7, 189.1, 84.8, 76.3, 58.6, 58.0, 39.4 and 35.0 (signal due to C-7 not observed); **13**: 183.9, 147.0, 134.6, 70.8, 59.1, 58.9, 55.6, 35.1 and 32.7; *m/z* (17 eV) 256 (1%), 254 (4) and 252 (6) (each M^+), 224 (1), 222 (2) and 220 (2) [each $(M - CO)^+$] and 88 [100, $(MeOCH{=}CHOMe)^+$].

(1α,5α,6α)-3-*Acetoxy*-7,7-*dichloro*-4,5-*dimethoxybicyclo*-[4.1.0]*hept*-3-*en*-2-*one* **14**.—A solution of the 1:3 mixture of compounds **12** and **13** (345 mg, 1.36 mmol) in THF (2 cm^3) was added dropwise to a stirred, chilled (ice–water) mixture of potassium hydride (60 mg, 1.5 mmol) in THF (9 cm^3) maintained under nitrogen. After evolution of hydrogen had ceased the solution was stirred for a further 5 min and then acetyl chloride (194 mm^3, 2.73 mmol) was added. The resulting mixture was allowed to warm to ambient temperature after 0.5 h and was then treated with chloroform (30 cm^3) and saturated aq. sodium hydrogen carbonate (40 cm^3). The phases were separated and the aqueous phase was washed with chloroform (2 × 20 cm^3). The combined organic phases were washed with saturated aq. sodium hydrogen carbonate (30 cm^3), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield an orange oil. Subjection of this oil to PLC [(9:1) CH_2Cl_2–Et_2O] afforded a single major and chromophoric band (R_f 0.7), which upon extraction yielded a pale yellow solid. Recrystallisation of the solid yielded the *title compound* **14** (248 mg, 62%) as needles, m.p. 99–100 °C (from Et_2O–light petroleum) (Found: C, 45.0; H, 4.1; Cl, 24.3%; M^+, 294.0062. $C_{11}H_{12}Cl_2O_5$ requires C, 44.8; H, 4.1; Cl, 24.0%; *M*, 294.0062); ν_{max}(KBr)/cm^{-1} 2361, 1765, 1664, 1629, 1371, 1253, 1201, 1148, 1114 and 1074; δ_H(400 MHz) 4.79 (1 H, br s, 5-H), 4.00 (3 H, s, OMe), 3.45 (3 H, s, OMe), 2.84 (1 H, dd, $J_{6,1}$ 9.5, $J_{6,5}$ 1.7, 6-H), 2.45 (1 H, dd, $J_{1,6}$ 9.5; $J_{1,5}$ 1.0, 1-H) and 2.25 (3 H, s, COMe); δ_C(100 MHz) 180.8, 167.8, 157.7, 131.0, 69.1, 58.1, 57.9, 54.2, 36.8, 32.4 and 20.3; *m/z* (70 eV) 296 (2.3%) and 294 (4) (both M^+), 256 (3), 254 (17) and 252 (27) [each $(M - CH_2CO)^+$] and 43 (100, $MeCO^+$).

6-*Chloro*-3,4-*dimethoxy*-α-*tropolone Acetate* **15**.—DBU (92 mm^3, 0.62 mmol) was added dropwise to a chilled (ice–water) solution of enol acetate **14** (183 mg, 0.62 mmol) in dry benzene (5 cm^3) maintained under nitrogen. The reaction mixture immediately turned yellow and a white precipitate formed rapidly. After being stirred for 20 h at ambient temperature the reaction mixture was concentrated under reduced pressure and

the residue was subjected to PLC [(9:1) CH_2Cl_2–Et_2O]. Extraction of the major chromophoric band (R_f 0.6) afforded a solid which was recrystallised to give the tropolone acetate **15** (160 mg, 100%) as pale orange plates, m.p. 114.5–118 °C (from EtOH–light petroleum) (Found: C, 51.1; H, 4.4; Cl, 13.7%; M^+, 258.0295. $C_{11}H_{11}ClO_5$ requires C, 51.1; H, 4.3; Cl, 13.7%; *M*, 258.0295); λ_{max}(EtOH)/nm 328, 251 and 237 (log ε/dm^3 mol^{-1} cm^{-1} 3.9, 4.5 and 4.4); ν_{max}(KBr)/cm^{-1} 1761, 1612, 1584, 1518, 1252, 1218, 1203, 1191, 1161, 1138 and 1050; δ_H(400 MHz) 7.12 (1 H, d, $J_{7,5}$ 2.0, 7-H), 6.54 (1 H, br d, $J_{5,7}$ 2.0, 5-H), 3.91 (3 H, d, *J* 0.5, OMe), 3.83 (3 H, s, OMe) and 2.37 (3 H, s, OAc); δ_C(100 MHz) 167.9, 161.1, 157.8, 153.3, 142.6, 130.8, 121.8, 112.5, 61.4, 57.0 and 20.6; *m/z* (70 eV) 260 (5%) and 258 (13) (both M^+) and 218 (46) and 216 (100) [both $(M - CH_2CO)^+$].

6-*Chloro*-3,4-*dimethoxy*-α-*tropolone* **16**.—Treatment of enol acetate **14** with DBU under the same conditions as used above afforded a reaction mixture which was stirred for 20 h at ambient temperatures. After this time the reaction mixture was concentrated under reduced pressure and the residue was partitioned between diethyl ether (25 cm^3) and 1 mol dm^{-3} NaOH (50 cm^3). The phases were separated and the organic layer was extracted with 1 mol dm^{-3} NaOH (2 × 25 cm^3). The combined aqueous phases were washed with diethyl ether (2 × 25 cm^3), acidified with 2 mol dm^{-3} HCl, and was then extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a brown solid. Sublimation of this solid (120 °C/30 mmHg) yielded the *title tropolone* **16** (121 mg, 90%) as pale cream needles, m.p. 128–132 °C (Found: 50.0; H, 4.1; Cl, 16.6%; M^+, 216.0189. $C_9H_9ClO_4$ requires C, 49.9; H, 4.2; Cl, 16.4%; *M*, 216.0189); λ_{max}(EtOH)/nm 392, 367 and 345 (log ε/dm^3 mol^{-1} cm^{-1} 2.5, 2.9 and 2.9); ν_{max}(KBr)/cm^{-1} 1600, 1488, 1438, 1396, 1341, 1269, 1235, 1205, 1040 and 859; δ_H(400 MHz) 7.26 (1 H, d, $J_{7,5}$ 1.5, 7-H), 6.69 (1 H, d, $J_{5,7}$ 1.5, 5-H), 3.98 (3 H, s, OMe) and 3.92 (3 H, s, OMe) (OH not observed); δ_C(100 MHz) 170.9, 161.2, 160.9, 145.2, 144.5, 121.7, 109.7, 60.5 and 57.0; *m/z* (70 eV) 218 (33%) and 216 (100) (both M^+) and 203 (15) and 201 (44) [both $(M - CH_3)^+$].

(1α,4α,5α,6α)-7,7-*Dibromo*-4,5-*dimethoxybicyclo*[4.1.0]*hept*-2-*ene* **19**.—Bis-*O*-methylation of diol **18**[15] using the same conditions as employed for the conversion of compound **8** into **9** afforded a yellow oil on work-up, which was subjected to Kugelrohr distillation (120 °C/0.01 mmHg) and gave the *title compound* **19** (80%) as an unstable yellow oil. A spectroscopically pure sample was obtained by PLC (CH_2Cl_2, R_f 0.7) {Found: [$(M - MeO)^+$], 278.9020. $C_8H_9{}^{79}Br_2O$ requires $(M - MeO)$, 278.9020}; ν_{max}(NaCl)/cm^{-1} 2927, 2891, 2820, 1380, 1188, 1141, 1097, 1068, 758 and 736; δ_H(400 MHz) 6.18 (1 H, ddd, $J_{3,2}$ 9.5, $J_{3,4}$ 6.1, $J_{3,1}$ 1.7, 3-H), 5.94 (1 H, ddd, $J_{2,3}$ 9.5, $J_{2,1}$ 2.9, $J_{2,6}$ 0.7, 2-H), 3.82 (1 H, dd, $J_{4,3}$ 6.1, $J_{4,5}$ 3.2, 4-H), 3.49 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.27 (1 H, dd, $J_{5,6}$ 4.9, $J_{5,4}$ 3.2, 5-H), 2.40 (1 H, ddd, $J_{1,6}$ 10.5, $J_{1,2}$ 2.9, $J_{1,3}$ 1.7, 1-H) and 2.05 (1 H, ddd, $J_{6,1}$ 10.5, $J_{6,5}$ 4.9, $J_{6,2}$ 0.7, 6-H); δ_C(100 MHz) 132.0, 128.8, 79.0, 71.4, 56.9, 56.7, 38.0, 31.8 and 30.3; *m/z* (20 eV) 283 (2%), 281 (4.4) and 279 (2) [each $(M - MeO)^+$], 233 (25) and 231 (27) [both $(M - Br)^+$] and 75 (100).

(1α,4α,5α,6α)-exo-7-*Bromo*-4,5-*dimethoxybicyclo*[4.1.0]*hept*-2-*ene* **20**.*—A stirred solution of dibromide **19** (1.0 g, 3.2 mmol) in THF (25 cm^3) maintained at −100 ± 5 °C under nitrogen was treated dropwise with BuLi (2.2 cm^3 of a 1.6 mol dm^{-3} solution in hexane, 3.5 mmol) during 0.5 h. The red reaction mixture was stirred for a further 3.5 h at −100 ± 5 °C before a 3:1 mixture of THF and methanol (1.0 cm^3) was added dropwise. The solution immediately became yellow and was stirred for a further 2.5 h at −100 ± 5 °C before being allowed to slowly warm to ambient temperature. The mixture was then transferred to a separating funnel containing water (50 cm^3) and diethyl ether (30 cm^3). The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a yellow oil. Kugelrohr distillation (110 °C/1 mmHg) of this material yielded a ~12:1 mixture (as determined by ^{13}C NMR analysis) of *title alkene* derivative **20** and its *C*-7 *epimer* (557 mg, 75%) as an oil [Found: $(M - Br)^+$, 153.0915. $C_9H_{13}O_2$ requires *m/z*, 153.0915]; ν_{max}(NaCl)/cm^{-1} 2979, 2929, 2821, 1398, 1202, 1118, 1062, 995, 796, 742; δ_H(400 MHz) **20**: 6.13 (1 H, ddd, $J_{3,2}$ 10.0, $J_{3,4}$ 4.2, $J_{3,1}$ 1.7, 3-H), 5.58 (1 H, ddd, $J_{2,3}$ 10.0, $J_{2,1}$ 2.4, $J_{2,6}$ 1.0, 2-H), 3.91 (1 H, t, $J_{4,3}$ 3.4, $J_{4,5}$ 3.4, 4-H), 3.53 (1 H, m, 5-H), 3.50 (3 H, s, OMe), 3.41 (3 H, s, OMe), 2.67 (1 H, dd, $J_{7,6}$ 3.9, $J_{7,1}$ 2.9, 7-H), 1.98 (1 H, m) and 1.88 (1 H, m); δ_C(100 MHz) (major isomer) 127.3, 126.1, 74.1, 71.5, 57.6, 56.9, 25.0, 24.5 and 21.7; δ_C(100 MHz) (minor isomer) 130.8, 129.1, 71.9, 65.7, 56.5, 33.5, 17.9, 16.7 and 15.1; *m/z* (70 eV) 153 [33%, $(M - Br)^+$] and 75 (100).

(1α,2β,3β,4α,5α,6α)-exo-7-*Bromo*-4,5-*dimethoxybicyclo*-[4.1.0]*heptane*-2,3-*diol* **21** *and* (1α,2α,3α,4α,5α,6α)-exo-7-*Bromo*-4,5-*dimethoxybicyclo*[4.1.0]*heptane*-2,3-*diol*.—*cis*-Dihydroxylation of the *ca.* 12:1 mixture of alkene derivative **20** and its C-7 epimer was carried out using the same conditions as employed for the conversion of the chloro analogue **9** into compound **10** with the exception that the reaction was run at ambient temperature for 24 h (rather than for 5 h at reflux). The oil obtained on work-up was subjected to PLC (Et_2O). Extraction (Et_2O) of the band R_f 0.1–0.5 yielded a *ca.* 24:1 mixture of diastereoisomeric diols (54% combined yield) which was then subjected to flash chromatography (Et_2O).

Concentration of the fractions containing the more mobile component (R_f 0.4) gave a solid, which upon recrystallisation afforded *diol* **21** as needles, m.p. 119–119.5 °C (from CH_2Cl_2–light petroleum) [Found: C, 40.8; H, 5.6; Br, 29.6%; $(M - H_2O - Br)^+$ 169.0865. $C_9H_{15}BrO_4$ requires C, 40.5; H, 5.7; Br, 29.9%; $C_9H_{13}O_3$ requires *m/z*, 169.0865]; ν_{max}(KBr)/cm^{-1} 3505, 3464, 1194, 1116, 1098, 1056, 1023, 973 and 943; δ_H(400 MHz) 4.51–4.43 (1 H, m), 4.10 (1 H, m), 3.81 (1 H, dd, *J* 10.0, 4.9), 3.51 (3 H, s, OMe), 3.42 (3 H, s, OMe), 3.10 (1 H, t, $J_{7,1}$ 3.9, $J_{7,6}$ 3.9, 7-H), 3.00 (1 H, dd, *J* 10.0, 3.2), 2.82 (1 H, d, *J* 1.2), 2.78 (1 H, s, OH), 1.88–1.85 (2 H, m, 1- and 6-H); δ_C(100 MHz) 76.3, 73.1, 67.2, 64.1, 58.2, 57.4, 27.4, 25.8 and 17.6; *m/z* (15 eV) 250 (0.2%) and 248 (0.2) [both $(M - H_2O)^+$], 169 [16, $(M - H_2O - Br)^+$] and 113 (100).

Concentration of the fractions containing the less mobile component (R_f 0.3) gave (1α,2α,3α,4α,5α,6α)-exo-7-*bromo*-4,5-*dimethoxybicyclo*[4.1.0]*heptane*-2,3-*diol* as an oil [Found: $(M - H_2O - Br)^+$, 169.0865. $C_9H_{13}O_3$ requires *m/z*, 169.0865]; ν_{max}(KBr)/cm^{-1} 3441, 2929, 2831, 1453, 1392, 1190, 1161, 1078 and 995; δ_C(100 MHz) 80.1, 78.5, 67.8, 67.5, 60.2, 58.1, 29.2, 25.4 and 19.6; *m/z* (15 eV) 169 [3%, $(M - H_2O - Br)^+$], 113 (73) and 111 (100).

(1α,2α,3α,4β,5β,6α)-7-exo-*Bromo*-2,3,4,5-*tetramethoxybicyclo*-[4.1.0]*heptane*.—Bis-*O*-methylation of diol **21** (102 mg, 0.38 mmol) using the same conditions as employed for the conversion of diol **8** into bis-ether **9** afforded an oil on work-up. This material was subjected to flash chromatography (Et_2O) and concentration of the appropriate fractions (R_f 0.7) gave the *title compound* (70 mg, 62%) as an oil [Found: $(M - MeO)^+$,

* In this paper, the stereochemical designator *exo* relates the stereochemistry of the C-7 substituent to that of the bridgehead hydrogens such that they both point to the same face (α or β) of the molecule.

263.0283. $C_{10}H_{16}BrO_3$ requires *m/z*, 263.0283]; ν_{max}(NaCl)/cm^{-1} 2977, 2926, 2823, 1462, 1377, 1190, 1149, 1100, 1050 and 1016; δ_H(400 MHz) 3.97 (1 H, dd, *J* 6.8, 4.6), 3.75 (1 H, dd, *J* 3.2, 2.0), 3.62 (1 H, dd, *J* 7.3, 4.6), 3.50 (3 H, s, OMe), 3.47 (3 H, s, OMe), 3.45 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.39 (1 H, dd, *J* 7.3, 3.2), 3.06 (1 H, t, $J_{7,1}$ 3.9, $J_{7,6}$ 3.9, 7-H), 1.79 (1 H, ddd, *J* 10.0, 6.8, 3.9) and 1.71 (1 H, ddd, *J* 10.0, 3.9, 2.0); δ_C(100 MHz) 76.9, 76.8, 75.6, 72.6, 59.2, 58.9, 58.0, 56.7, 26.9, 24.5 and 19.6; *m/z* (15 eV) 265 (0.2%) and 263 (0.3) [both (M − MeO)$^+$], 215 [1.2, (M − Br)$^+$], 183 [45, (M − MeOH − Br)$^+$] and 75 (100).

(1α,5α,6α)-exo-7-*Bromo*-3-*hydroxy*-4,5-*dimethoxybicyclo*-[4.1.0]*hept*-3-*en*-2-*one* **23**.—A magnetically stirred solution of DMSO (161 mm^3, 2.27 mmol) in CH_2Cl_2 (10 cm^3) maintained under nitrogen at −60 °C was treated dropwise with TFAA (291 mm^3, 2.06 mmol). The resulting solution was stirred at −60 °C for 10 min and then a solution of diol **21** (190 mg, 0.71 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise. The solution thus obtained was stirred at −60 °C for 2 h and was then treated dropwise with triethylamine (0.66 cm^3, 4.77 mmol). The resulting golden coloured solution was stirred for a further 1.5 h at −60 °C, then was allowed to warm slowly (0.5 h) to 20 °C and was then stirred for a further 2 h. The reaction mixture was then poured into 2 mol dm^{-3} HCl (20 cm^3), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 cm^3). The combined organic phases were then washed with water (1 × 50 cm^3), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a golden coloured oil containing crystals. This material was recrystallised to yield the *title compound* **23** (106 mg, 57%) as light-yellow cubes, m.p. 139.5–141.5 °C (from CH_2Cl_2–light petroleum) (Found: M$^+$, 261.9841. $C_9H_{11}{}^{79}BrO_4$ requires *M*, 261.9841); ν_{max}(KBr)/cm^{-1} 3266, 1665, 1649, 1643, 1632, 1336, 1309, 1242, 1189 and 1062; δ_H(400 MHz) 5.91 (1 H, br s, OH), 4.62 (1 H, t, *J* 1.5, 5-H), 4.01 (3 H, s, OMe), 3.42 (3 H, s, OMe), 2.82 (1 H, dd, *J* 4.4, 2.8, 7-H), 2.49 (1 H, ddd, *J* 8.1, 2.8, 1.5) and 2.26 (1 H, ddd, *J* 8.1, 4.4, 1.5); δ_C(100 MHz) 187.9, 144.6, 132.5, 71.7, 58.5, 55.0, 30.7, 26.5 and 20.8; *m/z* (70 eV) 264 (8%, M$^+$) 262 (8, M$^+$), 233 (2) and 231 (2) [both (M − MeO)$^+$] and 183 [100, (M − Br)$^+$].

(1α,5α,6α)-3-*Acetoxy*-exo-7-*Bromo*-4,5-*dimethoxybicyclo*-[4.1.0]*hept*-3-*en*-2-*one* **24**.—To a stirred, chilled (ice–water) solution of α-hydroxy enone **23** (84 mg, 0.32 mmol) in CH_2Cl_2 (2 cm^3) was added acetic anhydride (91 mm^3, 0.96 mmol) followed by pyridine (52 mm^3, 0.63 mmol). The mixture was allowed to warm to ambient temperature and was stirred for 15 h, and then concentrated under reduced pressure. The residue was subjected to PLC [(1:9) Et_2O–CH_2Cl_2]. Extraction (Et_2O) of the only major and chromophoric band (R_f 0.7) afforded a solid, which upon recrystallisation gave the *title compound* **24** (75 mg, 87%) as cubic crystals, m.p. 124.5–125.0 °C (from CH_2Cl_2–light petroleum) (Found: C, 43.5; H, 4.6; Br, 26.1%; M$^+$, 303.9946. $C_{11}H_{13}BrO_5$ requires C, 43.3; H, 4.3; Br, 26.2%; *M*, 303.9946); ν_{max}(KBr)/cm^{-1} 1747, 1664, 1636, 1360, 1254, 1213, 1147, 1107, 1083 and 1064; δ_H(400 MHz) 4.81 (1 H, br s, 5-H), 3.93 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.06 (1 H, t, ill defined coupling, 7-H), 2.49 (1 H, ddd, *J* 8.5, 2.9, 1.5), 2.25 (1 H, ddd, *J* 8.5, 4.4, 1.2) and 2.23 (3 H, s, Me); δ_C(100 MHz) 185.2, 168.2, 154.9, 128.8, 70.3, 57.6, 54.0, 32.7, 26.4, 20.3 and 19.8; *m/z* (70 eV) 306 (0.7%) and 304 (0.7) (both M$^+$) and 183 [100, (M − HBr − MeCO)$^+$].

3,4-*Dimethyl*-α-*tropolone* **3**.—DBU (110 mm^3, 0.74 mmol) was added dropwise to a chilled (0 °C) solution of compound **24** (75 mg, 0.25 mmol) in THF (6 mm^3). The reaction mixture was stirred at 50 °C for 3 h after which TLC analysis showed all the starting material had been consumed. 5% Aq. sodium hydroxide (3 cm^3) was added and the mixture was stirred for 0.5 h before being concentrated under reduced pressure and then partitioned between diethyl ether (25 cm^3) and 1 mol dm^{-3} NaOH (50 cm^3). The phases were separated and the aqueous layer was extracted with diethyl ether (2 × 25 cm^3). The aqueous phase was then acidified with 2 mol dm^{-3} HCl and then extracted with chloroform (3 × 50 cm^3). The combined chloroform extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a brown solid. Sublimation of this solid (120 °C/30 mmHg) yielded a light solid, which was recrystallised to give the title tropolone **3** (42 mg, 94%) as pale cream needles, m.p. 77.0–78.0 °C (toluene–light petroleum) (lit.,[4] 78.5–79.5 °C) (Found: C, 59.3; H, 5.6. Calc. for $C_9H_{10}O_4$: C, 59.3; H, 5.5%); λ_{max}(EtOH)/nm 360, 345 and 258 (log ε/dm^3 mol^{-1} cm^{-1} 2.80, 2.80 and 3.52); ν_{max}(KBr)/cm^{-1} 1579, 1527, 1498, 1447, 1429, 1393, 1300, 1249, 1142 and 1041; δ_H(400 MHz) 7.27 (1 H, t, *J* 11.0, 6-H), 7.12 (1 H, dd, $J_{5,6}$ 11.0, $J_{5,7}$ 0.7, 5-H*), 6.67 (1 H, br d, $J_{7,6}$ 11.0, 7-H*), 3.99 (3 H, s, OMe) and 3.95 (3 H, s, OMe); δ_C(100 MHz) 171.5, 163.5, 162.8, 147.1, 134.3, 119.4, 109.7, 60.3 and 56.9; *m/z* (70 eV) 182 (100%, M$^+$), 167 [87, (M − Me)$^+$], 136 (54), 122 (62) and 39 (70).

3,4-*Dihydroxy*-α-*tropolone* **4**.—48% Aq. HBr (2.5 cm^3) was added to a solution of the tropolone **3** (34 mg, 0.19 mmol) in acetic acid (5 cm^3). The reaction mixture was stirred at reflux for 2 h and then cooled, and concentrated under reduced pressure to give a solid. The solid was then subjected to chromatography (Sephadex LH-20; MeOH). The eluent was concentrated and the resulting solid was recrystallised to give the title compound **4** (20 mg, 71%) as pale yellow needles, m.p. 175–250 °C (decomp.) (from EtOH) (lit.,[5] >166 °C); λ_{max}(EtOH)/nm 366 and 274 (log ε/dm^3 mol^{-1} cm^{-1} 3.1 and 2.4); ν_{max}(KBr)/cm^{-1} 3493, 3151, 1592, 1518, 1416, 1347, 1223, 1183, 985 and 725; δ_H(300 MHz) 6.99 (3 H, m, 5-, 6-, 7-H) and 5.00 (3 H, br s, 3 × OH); δ_C(75.4 MHz) 156.8, 156.5, 127.2 and 117.6 (lit.,[5] 156.7, 156.5, 127.1 and 117.5); *m/z* (70 eV) 154 (100%, M$^+$), 126 [62, (M − CO)$^+$], 108 [23, (M − CO − H_2O)$^+$] and 80 (29).

Table 1 Final atomic co-ordinates (× 10^4) with esds in parentheses, for compound **15**

Atoms	*x*	*y*	*z*
C(1)	−986(3)	4655(3)	1654(3)
O(1)	−1609(3)	3980(2)	820(2)
C(2)	882(3)	3837(3)	1959(2)
O(2)	1708(2)	2391(2)	1183(2)
C(2′)	1456(4)	912(3)	1644(3)
O(2′)	663(3)	801(3)	2714(2)
C(2″)	2334(8)	−474(6)	644(6)
C(3)	1944(3)	4294(3)	2744(2)
O(3)	3655(2)	3195(2)	2804(2)
C(3′)	4734(4)	3626(5)	1727(4)
C(4)	1500(3)	5803(3)	3575(2)
O(4)	2951(2)	5812(2)	4175(2)
C(4′)	2826(4)	7223(4)	5010(3)
C(5)	−88(3)	7053(3)	3765(3)
C(6)	−1696(3)	7205(3)	3170(3)
Cl(6)	−3437(1)	9044(1)	3663(1)
C(7)	−2085(3)	6213(3)	2300(3)

Single-crystal X-Ray Diffraction Analysis of Compound **15**.—*Crystal data.* $C_{11}H_{11}ClO_5$, *M* = 258.7, triclinic, space group $P\bar{1}$, *a* = 8.294(1), *b* = 8.310(1), *c* = 9.389(1) Å, α = 84.97(1), β = 87.60(1), γ = 67.96(1)°, *V* = 597.5(2) Å^3, *F*(000) = 268, *Z* = 2, D_m = 1.44(1), D_c = 1.438 g cm^{-3}, μ = 29.54 cm^{-1}.

* These assignments may be interchanged.

Intensities were recorded on a Rigaku-AFC diffractometer (graphite-monochromatised Cu-Kα radiation, $\lambda = 1.5418$ Å), at 289(1) K to $2\theta_{max}$ 130°. The structure was solved by direct methods and full-matrix refinement (SHELX76)[20] converged at $R = 0.037$, $wR = 0.053$ for 1540 unique data ($I \geqslant 2\sigma I$). All hydrogen-atom sites were located and the H-atom parameters (x,y,z, U_{iso}) were refined. The solved structure is shown as an ORTEP plot in Fig. 1. Atomic co-ordinates are given in Table 1.*

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* *Supplementary data* (see section 5.6.3 of Instructions to Authors, in the January issue). Bond lengths and angles, H-atom co-ordinates, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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