cis-Dihydrocatechols as Precursors to Highly Oxygenated Troponoids. Part 2.[1] Regiocontrolled Syntheses of Stipitatic and Puberulic Acids

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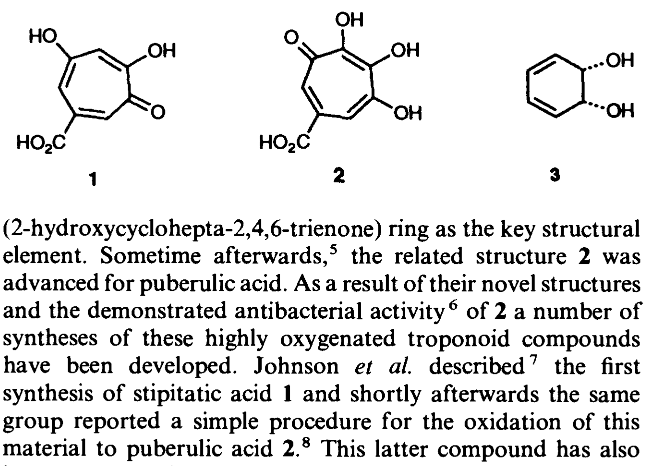
Stipitatic and puberulic acids, **1** and **2** respectively, have both been prepared in a fully regiocontrolled manner using commercially available *cis*-1,2-dihydrocatechol **3** as the common starting material. In the case of the former acid, compound **3** was converted over six simple steps into the ester **12**. Oxidation of this latter compound produced the σ-homo-*o*-benzoquinone **13** which acted as a Michael acceptor when treated with methoxide ion and the resulting conjugate could be trapped with acetic anhydride to give the acetoxy enone **14**. Base-promoted ring-expansion of **14** then afforded the troponoid **15**, the acquisition of which constitutes a formal total synthesis of stipitatic acid. Attempts to develop an analogous synthesis of puberulic acid failed. However, a successful synthesis of this natural product was achieved by elaborating the tetra-oxygenated compound **25**, which is readily prepared from the diol **3**, to the bromotropolone **28**. Palladium-catalysed methoxycarbonylation of this latter compound, followed by hydrolysis of the intermediate ester afforded the acid **29**, the structure of which was established by X-ray methods. Two-fold demethylation of compound **29** then delivered puberulic acid **2**.

The mould metabolites stipitatic acid **1**[2]† and puberulic acid **2**[3]† were first isolated in 1942 and 1932 respectively but it was not until 1945 that Dewar made the then dramatic proposal[4] that the former compound contained the 'aromatic' α-tropolone



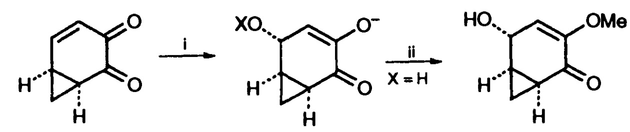
1 2 3

(2-hydroxycyclohepta-2,4,6-trienone) ring as the key structural element. Sometime afterwards,[5] the related structure **2** was advanced for puberulic acid. As a result of their novel structures and the demonstrated antibacterial activity[6] of **2** a number of syntheses of these highly oxygenated troponoid compounds have been developed. Johnson *et al.* described[7] the first synthesis of stipitatic acid **1** and shortly afterwards the same group reported a simple procedure for the oxidation of this material to puberulic acid **2**.[8] This latter compound has also been prepared by degrading the related but slightly more complex natural product puberulonic acid.[7] While no additional approaches to **2** have been reported to date, two further syntheses[9,10] of stipitatic acid **1** have appeared together with a description of one unsuccessful effort.[11]

Analysis of all these approaches to compounds **1** and **2** suggests that it is especially difficult to establish the correct substitution pattern on the troponoid ring with full regiochemical control. Indeed, Keith's synthesis[10] of stipitatic acid represents the only case in which this level of control has been achieved. Our recent development of fully regiocontrolled total syntheses of two related tetra-oxygenated troponoid natural products,[1] which exploited commercially available *cis*-1,2-dihydrocatechol **3** as starting material,[12] prompted us to examine whether similar strategies could be employed in the preparation of the title acids. The successful implementation of this approach is reported here. Noteworthy features of the work described include the exploitation of a new facet of the chemistry of σ-homo-*o*-benzoquinones[13] and the first example of the palladium-catalysed alkoxycarbonylation of a halogenated troponoid.

Results and Discussion

Formal Total Synthesis of Stipitatic Acid **1**.—In the course of investigating[13] the chemistry of σ-homo-*o*-benzoquinone **4**, which is easily prepared from compound **3**, we observed that the former compound readily dissolved in aqueous base but could be recovered quantitatively upon acidification. A ^1H NMR experiment, in which the product mixture from reaction of compound **4** with NaOD/D_2O was analysed, quite clearly suggested that Michael addition of DO^- to the substrate occurs leading to formation of the diosphenol anion **5** (Scheme 1).



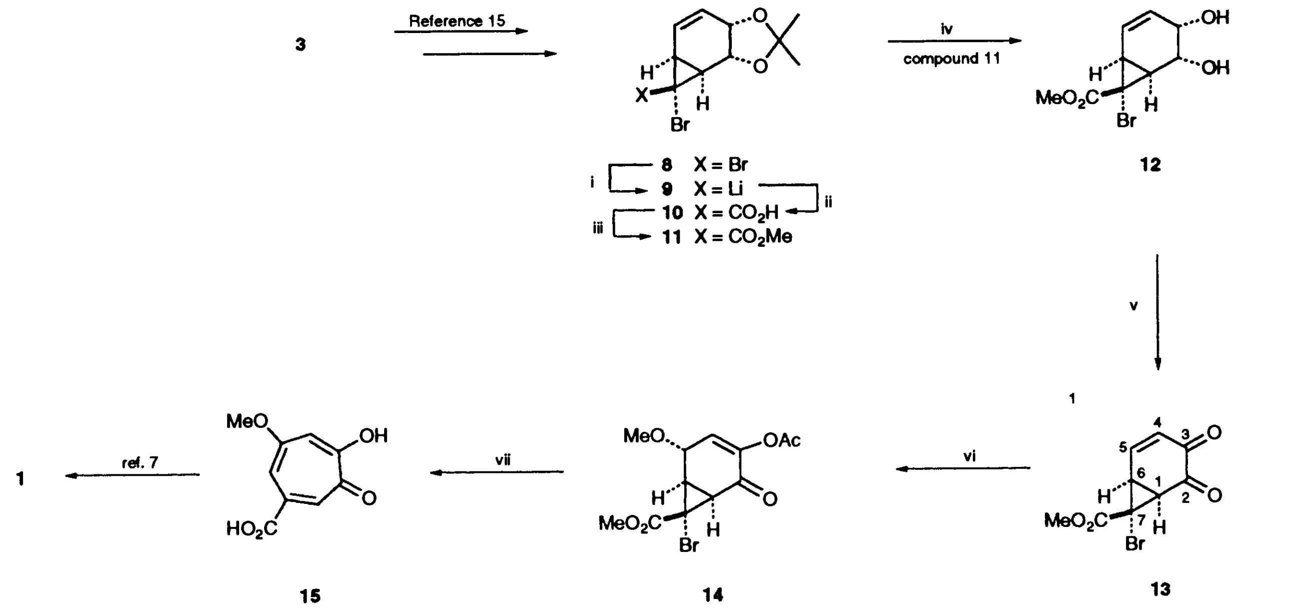
4 5 X=D 6 X=H 7

Scheme 1 *Reagents and conditions:* i, NaOD in D_2O, 18 °C or 2 mol dm^{-3} NaOH, 18 °C, 10 min; ii, $(MeO)_2SO_2$, triethylbenzylammonium chloride, 18 °C, 2.45 h

Furthermore, the non-deuteriated analogue of **5**, the anion **6**, which is derived by addition of HO^- to compound **4**, can be intercepted by dimethyl sulfate to give the adduct **7** as a single diastereoisomer in 52% yield. The illustrated α-stereochemistry for the 5-hydroxy group in compound **7** has been advanced on the basis that hydroxide ion would add to the less-hindered α-face of the σ-homo-*o*-benzoquinone.

A reaction sequence which capitalises on the observations described above and allows for a regiocontrolled synthesis of stipitatic acid **1** is shown in Scheme 2. Thus, reaction of the *gem*-dibromocyclopropane **8** (which is obtained from *cis*-1,2-dihydrocatechol **3** in two steps[14]) with butyllithium (BuLi) at −100 °C and quenching of the resulting lithium

† The illustrated structures for acids **1** and **2** are simply used in this paper to emphasise the relationship between these compounds and their synthetic precursors and are not meant to imply any particular tautomeric preference within these troponoid systems.



Scheme 2 *Reagents and conditions:* i, BuLi, THF, −100 °C, 5 h; ii, CO_2 (g), THF, −100 °C, 0.5 h then HCl; iii, CH_2N_2, Et_2O, 18 °C; iv, 2 mol dm^{-3} aq. HCl, THF, 18 °C; v, TFAA, DMSO, CH_2Cl_2, −60 °C, 1.5 h, then Et_3N, −60 °C, 10 min; vi, MeONa, MeOH, 18 °C, 10 min then Ac_2O, 18 °C, 45 min; vii, DBU, THF, −40 °C, 1.5 h, 18 °C for 1 h, 2 mol dm^{-3} aq. KOH for 1.0 h then 2 mol dm^{-3} aq. HCl

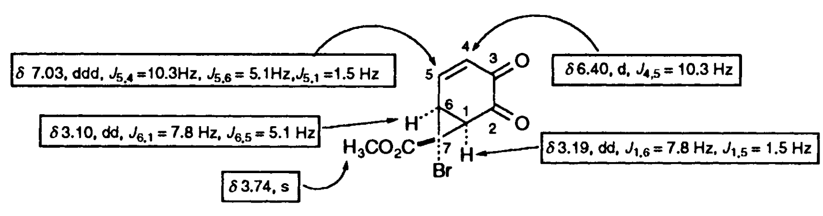


Fig. 1 Assignment of 400 MHz ^{1}H NMR spectral data for compound **13** (spectrum obtained at 18 °C in $CDCl_3$)

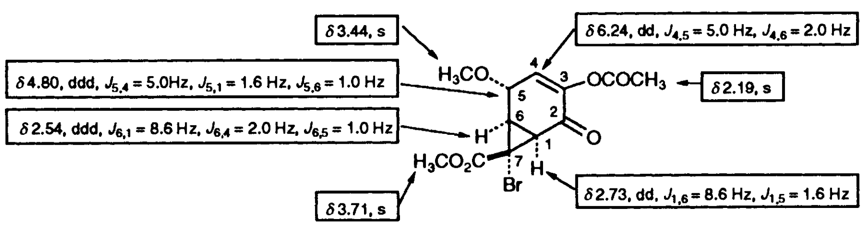


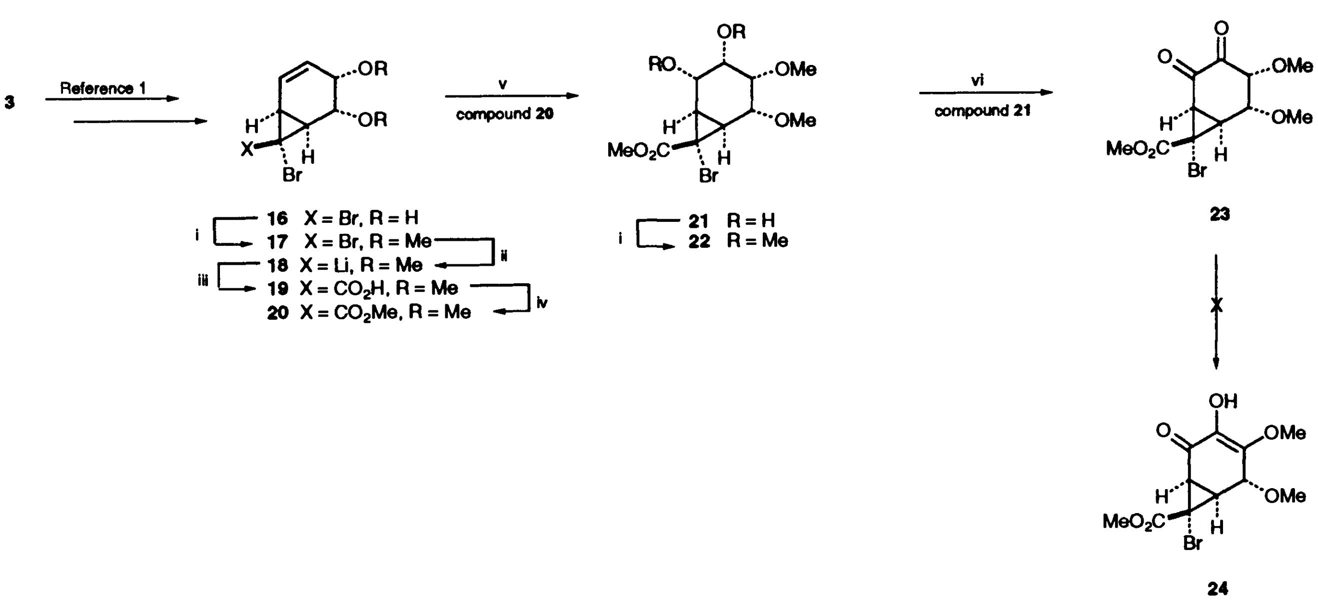
Fig. 2 Assignment of 400 MHz ^{1}H NMR spectral data for compound **14** (spectrum obtained at 18 °C in $CDCl_3$)

halogenocarbenoid **9** with gaseous carbon dioxide afforded, after acidification, the crystalline carboxylic acid **10** in near quantitative yield. The illustrated *endo*-stereochemistry for the newly introduced hydroxycarbonyl group in **10** follows from mechanistic considerations and there is ample precedent for this outcome.[15] Removal of the acetonide group in compound **10** was carried out under standard conditions but the resulting dihydroxy carboxylic acid proved very difficult to handle because of its extremely high polarity. Consequently, the acid **10** was methylated using diazomethane and the resulting ester acetonide **11** then subjected to acid-catalysed hydrolysis to give the more easily handled ester diol **12**. Oxidation of this last compound under modified-Swern conditions[14] then afforded the key σ-homo-*o*-benzoquinone **13** (75%) as a yellow crystalline solid.

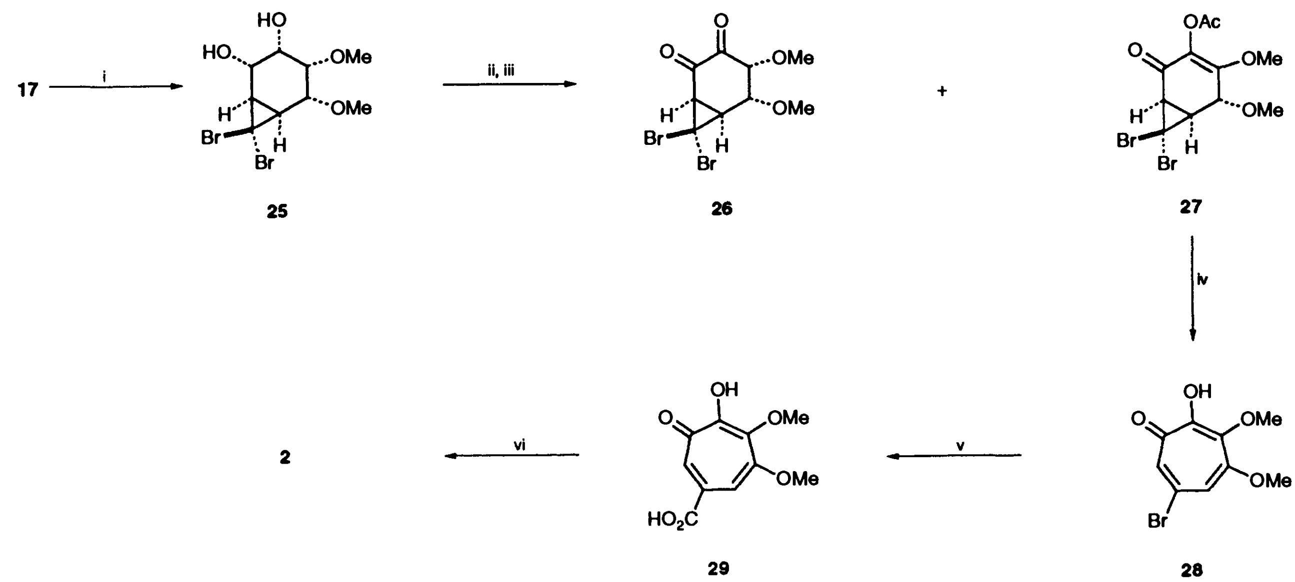
The spectral and microanalytical data obtained on compound **13** supported the assigned structure. For example, the $\{^1H\}^{13}C$ NMR spectrum displayed the expected nine resonances including two low-intensity signals at δ 183.0 and 176.9 which are assigned to C-2 and C-3 and another low intensity signal at δ 164.9 which is assigned to the ester carbonyl carbon. In the IR spectrum diagnostic carbonyl stretching bands were observed at 1721, 1709 and 1680 cm^{-1}. The 400 MHz ^{1}H NMR spectrum of compound **13** was completely first-order and could be fully assigned (Fig. 1).

In the remaining critical functionalisation step of the reaction sequence (Scheme 2), compound **13** was treated with sodium methoxide and the conjugate addition product then trapped with acetic anhydride. In this way a 96% yield of the acetoxy enone **14** was realised. The spectral data obtained on this product clearly established that a single diastereoisomer had been formed. In the 400 MHz ^{1}H NMR spectrum of compound **14** (Fig. 2) the resonance due to 4-H appeared as a doublet of doublets at δ 6.24 with couplings of 5.0 and 2.0 Hz. The magnitude of the larger coupling, which is assigned to the spin-spin splitting between 4-H and 5-H, suggests a dihedral angle of *ca.* 60° between these protons and the α-configuration for the newly introduced methoxy group. This conclusion is based on the assumption (supported by molecular mechanics calculations) that the six-membered ring in compound **14** adopts a near planar conformation.

Following earlier work,[1,16] which had demonstrated that 7-halogenobicyclo[4.1.0]hept-3-en-2-ones undergo based promoted ring-expansion to give the corresponding troponoid, the enone **14** was treated sequentially with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (to effect ring-expansion) and then



Scheme 3 *Reagents and conditions:* i, NaH, MeI, THF, 18 °C, 17 h; ii, BuLi, THF, −100 °C, 4 h; iii, CO_2 (g), −100 °C, 0.5 h; iv, CH_2N_2, Et_2O, 18 °C; v, OsO_4, Bu^{t}OOH, Me_2CO, AcONa, Et_4NCl, 18 °C, 72 h; vi, TFAA, DMSO, −60 °C, 2 h then Et_3N, −60 °C, 1.5 h



Scheme 4 *Reagents and conditions:* i, OsO_4, Bu^{t}OOH, Me_2CO, AcONa, Et_4NCl, 18 °C, 72 h; ii, 4-AcNH-TEMPO, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2, 18 °C, 48 h; iii, Ac_2O, C_6H_5N, CH_2Cl_2, 18 °C, 16 h; iv, DBU, THF, 18 °C, 1 h then 5% aq. NaOH then 2 mol dm^{-3} aq. HCl; v, $Pd(OAc)_2$, 1,1′-bis(diphenylphosphino)ferrocene, DMF, Et_3N, MeOH, CO (g), 60 °C, 16 h then 5% aq. NaOH, 18 °C, 0.5 h then 2 mol dm^{-3} aq. HCl; vi, 48% HBr in AcOH, reflux, 1.5 h

aqueous KOH (to effect hydrolysis of the ester moieties within the initial ring-expansion product). As a result, the expected stiptitatic acid *O*-methyl ether **15** was formed but only in 10% yield. Various attempts to increase the yields in these last steps have proved fruitless. The physical and spectral data obtained for the known troponoid **15** matched those reported in the literature[7] and/or were consistent with the assigned structure. The acquisition of troponoid **15** constitutes a formal and fully regiocontrolled total synthesis of stipitatic acid **1** since the former compound has been efficiently converted into the latter by Johnson and co-workers.[7]

Total Synthesis of Puberulic Acid **2**.—Our first attempt (Scheme 3) to develop a fully regiocontrolled synthesis of puberulic acid **2** involved the application of lithium halogenocarbenoid chemistry to introduce the carboxylic acid moiety associated with the target molecule. Thus, the known[13] dibromocarbene adduct, **16**, of dihydrocatechol **3** was *O*-methylated to give the dimethoxy compound **17**.[1] Metallation (with BuLi) of compound **17** afforded the carbenoid **18** which was trapped with dry gaseous carbon dioxide at −100 °C to give, after acidic work-up, the carboxylic acid **19**. Esterification (with diazomethane) of the acid **19** was then effected to ensure that chromatographically mobile materials were obtained in subsequent steps of the synthesis. Subjection of the resulting ester **20** to *cis*-dihydroxylation with osmium tetroxide afforded modest (44%) yields of the diol **21**. The illustrated stereochemistries for the newly introduced hydroxy groups in substrate **21** were readily established by conversion of this compound into the tetramethoxy derivative **22**, the C_2-symmetry of which was evidenced by the appearance of only eight signals in the $\{^1H\}^{13}C$ NMR spectrum. Oxidation of the diol **21** under modified-Swern conditions[15] afforded the yellow crystalline diketone **23** in 56% yield. Unfortunately, all attempts

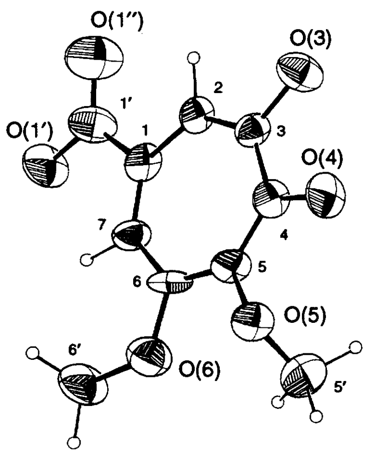


Fig. 3 ORTEP[23] Drawing of compound **29**. Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.39(1), C(2)–C(3), 1.37(2), C(3)–C(4) 1.46(1), C(4)–C(5) 1.43(1), C(5)–C(6) 1.42(2), C(6)–C(7) 1.37(2), C(7)–C(1) 1.36(1), C(3)–O(3) 1.35(1), C(4)–O(4) 1.24(1), O(1′)–C(1′) 1.31(1), O(1″)–C(1′) 1.22(1); C(2)–C(1)–C(7) 130.1(8), C(1)–C(2)–C(3) 129.1(8), C(2)–C(3)–C(4) 130.1(8), C(3)–C(4)–C(5) 123.7(8), C(4)–C(5)–C(6) 128.5(4), C(5)–C(6)–C(7) 130.5(8), C(1)–C(7)–C(6) 127.8(8)

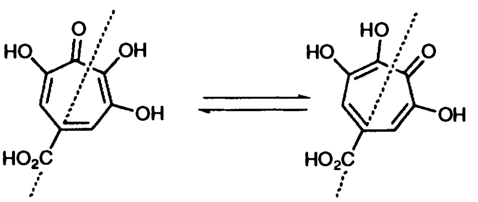


Fig. 4 Degenerate tautomerisation within puberulic acid **2** and the resulting pseudo-symmetry of the molecule (other tautometric forms are also possible but have not been included here so as to simplify presentation)

to induce enolisation of the C-3 carbonyl moiety and thereby form the hydroxy enone **24** (a necessary prelude to the key ring-expansion reaction) failed. The reasons for the reluctance of the dione **23** to undergo enolisation are unclear but may be a reflection of the low kinetic acidity of 4-H. Regardless of the correct explanation, the nett result of this impasse was the abandonment of the synthetic sequence shown in Scheme 3.

The ultimately successful route to puberulic acid **2**, which is shown in Scheme 4, involved initial *cis*-dihydroxylation of the alkene **17** to give the corresponding diol **25** (75%). The illustrated stereochemistry in compound **25** was established by its conversion (using NaH/methyl iodide) into the C_2-symmetric tetramethoxy derivative. While reaction of compound **25** under modified Swern conditions failed to provide either the corresponding α-diketone or the related mono-enolic tautomer, oxidation of the same substrate with the oxo-ammonium salt[17] derived from 4-acetamido-TEMPO and toluene-*p*-sulfonic acid (*p*-TsOH) afforded, after acetylation of the crude reaction mixture, a *ca.* 5:3 mixture of compounds **26** and **27** (85% combined yield). These reaction products could be separated chromatographically. Disappointingly, under no circumstances could satisfactory conversions of the former product into the latter be achieved. However, sequential treatment of the enone **27** with DBU then aqueous NaOH afforded, after acidic work-up, the crystalline α-tropolone **28** in 79% yield. Palladium-catalysed methoxycarbonylation[18] of compound **28** then gave the intermediate ester which was hydrolysed (using aqueous NaOH) to the corresponding acid **29** (71% overall yield). Compound **29** was isolated as a crystalline solid and its structure was established unequivocally by single crystal X-ray analysis (Fig. 3 and Table 1). Completion of the synthesis of compound **2** was effected by two-fold demethylation of the di-ether **29** using hydrobromic acid in acetic acid/water. In this way puberulic acid **2** was produced in 90% yield. The physical and spectroscopic data obtained on compound **2** were identical with those reported previously.[8] The $\{^1H\}^{13}C$ NMR spectrum of this eight-carbon compound contained only five resonances, due to the pseudo-symmetry within the molecule (Fig. 4). Furthermore, the 300 MHz ^1H NMR spectrum of the acid **2** was exceptionally simple showing only a singlet at δ 7.94 due to the two equivalent ring-protons and a broad four-proton singlet at δ 4.70 due to the OH protons.

Experimental

Unless otherwise specified, ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform at 400 and 100 MHz, respectively. Positive-ion electron-impact mass spectra were recorded at 70 eV unless otherwise specified. Other general procedures have been reported elsewhere.[19]

(1α,5α,6α)-5-*Hydroxy*-3-*methoxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **7**.—A solution of the diketone **4**[13] (20 mg, 0.164 mmol) in aqueous NaOH (1 mol dm^{-3} solution; 2 cm^3) containing triethylbenzylammonium chloride (10 mg) was treated with dimethyl sulfate (230 mm^3*) and the resulting mixture stirred at ambient temperature for 0.75 h, after which time a further aliquot (2 cm^3) of aqueous NaOH was added. The reaction mixture was stirred for an additional 2 h after which water (10 cm^3) was added and the mixture extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$), filtered and then concentrated under reduced pressure to afford the *title compound* **7** (13 mg, 52%) as a clear yellow oil [Found: (M − H)$^+$, 153.0552. $C_8H_{10}O_3$ requires (*M* − H)$^+$, 153.0552]; ν_{max}(NaCl)/cm^{-1} 3583, 2926, 1680, 1626, 1453, 1210, 1175 and 1075; δ_H 5.35 (dd, *J* 6.0 and 1.8, 1 H, 4-H), 4.49 (dt, *J* 6.0 and 1.5, 1 H, 5-H), 3.37 (s, 3 H, OCH_3), 2.15 (m, 1 H, 1-H or 6-H), 2.00 (m, 1 H, 6-H or 1-H), 1.29 (m, 1 H, 7_{exo}-H) and 0.82 (m, 1 H, 7_{endo}-H); δ_C 191.9 (C-2), 151.2 (C-3), 105.2 (C-4), 55.0, 53.9 (OCH_3 and C-5), 25.3, 20.2 and 13.9; *m*/*z* (%) 153 (4) [(M − H)$^+$], 137 (55) [(M − OH)$^+$], 126 [100, (M − CO)$^+$] and 109 [90, (M − CO − OH)$^+$]; λ_{max}(ethanol)/nm 254 (log ε 3.52).

(3aα,5aβ,6β,6aβ,6bα)-6-*Bromo*-2,2-*dimethyl*-3a,6,6a,6b-*tetrahydro*-5aH-*cyclopropa*[e]-1,3-*benzodioxole*-6-*carboxylic Acid* **10**.—A solution of the acetonide **8**[14] (2.0 g, 6.17 mmol) in THF (50 cm^3) was cooled to −100 °C and then BuLi in hexane (1.4 mol dm^{-3} solution; 4.4 cm^3, 6.17 mmol) was added dropwise while the temperature of the reaction was maintained at −100 °C. The resulting mixture was stirred at −100 °C for 5 h after which time dry gaseous carbon dioxide was bubbled through the reaction mixture at a rapid rate for 10 min. A mixture of aqueous HCl (2 mol dm^{-3} solution; 2 cm^3) and THF (2 cm^3) was then added and the reaction mixture slowly allowed to warm to room temperature before being partitioned between water (30 cm^3) and diethyl ether (30 cm^3). The aqueous phase was extracted with further diethyl ether (2 × 30 cm^3) and the combined organic phases were then extracted into aqueous NaOH (1 mol dm^{-3} solution; 2 × 50 cm^3). The combined aqueous phases were washed with diethyl ether (1 × 50 cm^3) and then acidified and extracted with diethyl ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* **10** (1.72 g, 97%) as a pale yellow oil which crystallised with time. This material was suitable for use in the next reaction. Recrystallisation (twice from toluene) of a sample of this material afforded analytically pure compound **10** as

* 1 mm^3 = 1 μl.

colourless prisms, m.p. 114–115 °C (Found: C, 45.8; H, 4.4; Br, 27.8. $C_{11}H_{13}BrO_4$ requires C, 45.7; H, 4.5; Br, 27.6%); ν_{max}(KBr)/cm^{-1} 2988, 2935, 1732, 1700, 1427, 1384, 1374, 1311, 1287, 1266, 1202, 1163, 1044 and 1024; δ_H 9.50 (br s, 1 H, OH), 5.94 (dd, *J* 10.6 and 5.1, 1 H, 5-H), 5.77 (dd, *J* 10.6 and 3.2, 1 H, 4-H), 4.98 (dd, *J* 7.5 and 1.0, 1 H, 6b-H), 4.35 (ddd, *J* 7.5, 3.2 and 1.0, 1 H, 3a-H), 2.38 (dd, *J* 9.1 and 5.1, 1 H, 5a-H), 2.26 (d, *J* 9.1, 1 H, 6a-H), 1.42 (s, 3 H, CH_3) and 1.38 (s, 3 H, CH_3); δ_C 171.2 (C=O), 128.5, 120.5 (C-4 and C-5), 109.8 (C-2), 69.6, 68.0 (C-3a and C-6b), 31.4 (C-6), 28.4, 27.4 (C-5a and C-6a), 27.5 and 25.3 (2 × CH_3); *m/z* (15 eV) (%) 290 (0.3) 288 (0.3, M^+), 275 (9), 273 [9, $(M - CH_3)^+$], 232 (23) 230 {23, $[M - (CH_3)_2CO]^+$} and 151 {100, $[M - (CH_3)_2CO - Br]^+$}.

Methyl (3aα,5aβ,6β,6aβ,6bα)-6-*Bromo*-2,2-*dimethyl*-3a,6,6a,6b-*tetrahydro*-5aH-*cyclopropa*[e]-1,3-*benzodioxole*-6-*carboxylate* **11**.—A solution of the acid **10** (100 mg, 0.346 mmol) in diethyl ether (15 cm^3) was treated with a solution of diazomethane in diethyl ether until a light yellow colouration persisted in the reaction mixture and TLC analysis indicated the complete consumption of starting material. The reaction mixture was then concentrated under reduced pressure to afford the *title compound* **11** (110 mg, 100%) as a clear colourless solid which was sufficiently pure for use in the next step of the reaction sequence. Recrystallisation (hexane) of this material afforded an analytically pure sample of compound **11** as colourless prisms, m.p. 51–52 °C (Found: M^+, 302.0153; C, 47.8; H, 4.9; Br, 26.1. $C_{12}H_{15}{}^{79}BrO_4$ requires M^+, 302.0154; C, 47.5; H, 5.0; Br, 26.4%); ν_{max}(KBr)/cm^{-1} 2981, 1722, 1441, 1372, 1314, 1245, 1208, 1165 and 1048; δ_H 5.89 (dd with further splitting, *J* 10.3 and 4.9, 1 H, 5-H), 5.66 (dd, *J* 10.3 and 2.9, 1 H, 4-H), 4.99 (d with further splitting, *J* 7.1, 1 H, 6b-H), 4.29 (ddd, *J* 7.1, 2.9 and 1.0, 1 H, 3a-H), 3.68 (s, 3 H, OCH_3), 2.26 (dd, *J* 9.2 and 4.9, 1 H, 5a-H), 2.20 (d with further splitting, *J* 9.2, 1 H, 6a-H), 1.38 (s, 3 H, CH_3) and 1.36 (s, 3 H, CH_3); δ_C 167.0 (C=O), 127.9, 121.0 (C-4 and C-5), 109.5 (C-2), 69.6, 68.0 (C-3a and C-6b), 53.1 (CO_2CH_3), 32.0 (C-6), 27.6 (2 × CH_3), 26.2, 25.4 (C-5a and C-6a); *m/z* (%) 304 (1) 302 (1, M^+), 289 (3), 287 [3, $(M - CH_3)^+$], 246 (9), 244 {9, $[M - (CH_3)_2O]^+$} and 165 {100, $[M - (CH_3)_2CO - Br]^+$}.

Methyl (1α,2α,3α,6α,7α)-7-*Bromo*-2,3-*dihydroxybicyclo*[4.1.0]*hept*-4-*ene*-7-*carboxylate* **12**.—A solution of the acetonide **11** (1.2 g, 3.96 mmol) in THF (60 cm^3) was treated with aqueous HCl (3 mol dm^{-3} solution; 24 cm^3) and the resulting mixture stored at room temperature until TLC analysis revealed that all the starting material had been consumed (5 days). The reaction mixture was then poured into water (60 cm^3) and extracted with diethyl ether (3 × 60 cm^3). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. This material was subjected to flash chromatography (diethyl ether elution) and the appropriate fractions (R_f 0.6) were combined and concentrated under reduced pressure to afford the *title compound* **12** (700 mg, 67%) as a clear, colourless oil (Found: M^+, 261.9840. $C_9H_{11}{}^{79}BrO_4$ requires M^+, 261.9841); ν_{max}(NaCl)/cm^{-1} 3373, 2950, 1729, 1437, 1310, 1202, 1169 and 1069; δ_H 6.08 (dddd, *J* 10.1, 4.5, 1.7 and 0.8, 1 H, 5-H), 5.73 (dd, *J* 10.1 and 3.4, 1 H, 4-H), 4.39 (br s, 1 H, 2-H), 3.92 (br s, 1 H, 3-H), 3.72 (s, 3 H, CH_3), 2.69 (br s, 1 H, 2-OH), 2.53 (br s, 1 H, 3-OH), 2.24 (dd, *J* 9.2 and 4.5, 1 H, 6-H) and 2.18 (ddd, *J* 9.2, 3.1 and 0.8, 1 H, 1-H); δ_C 167.0 (C=O), 129.7 (C-4), 125.0 (C-5), 63.9 (C-3), 62.9 (C-2), 53.3 (OCH_3), 33.6 (C-7), 31.4 (C-1) and 25.7 (C-6); *m/z* (%) 264 (0.3), 262 (0.3, M^+), 246 (3), 244 [3, $(M - H_2O)^+$], 165 [89, $(M - H_2O - Br)^+$] and 77 (100).

Methyl (1α,6α,7α)-7-*Bromo*-2,3-*dioxobicyclo*[4.1.0]*hept*-4-*ene*-7-*carboxylate* **13**.—A solution of dimethyl sulfoxide (DMSO) (590 mm^3, 7.62 mmol) in CH_2Cl_2 (36 cm^3) maintained at −60 °C under nitrogen was treated with trifluoroacetic anhydride (TFAA) (1.1 cm^3, 7.78 mmol) and then a solution of the diol **12** (680 mg, 2.59 mmol) dissolved in a minimum volume of CH_2Cl_2/DMSO. After 1.5 h triethylamine (2.5 cm^3, 17.44 mmol) was added and the resulting yellow solution allowed to warm slowly to −20 °C before being poured into aqueous HCl (3 mol dm^{-3} solution; 30 cm^3). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic phases were washed with water (1 × 70 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow solid which was recrystallised (ethyl acetate) to give the *title compound* **13** (500 mg, 75%) as yellow needles, m.p. 154–156 °C (Found: C, 41.7; H, 2.7; Br, 30.6. $C_9H_7BrO_4$ requires C, 41.7; H, 2.7; Br, 30.9%). ν_{max}(KBr)/cm^{-1} 3009, 1721, 1709, 1680, 1441, 1330, 1309, 1270 and 1203; δ_H see Fig. 1; δ_C 183.0 (C-2), 176.9 (C-3), 164.9 (CO_2CH_3), 140.1 (C-5), 132.4 (C-4), 54.6 (OCH_3), 41.7 (C-1), 39.6 (C-7) and 36.0 (C-6); *m/z* (18 eV, heated) (%) 179 [45, $(M - Br)^+$], 151 [100, $(M - Br - CO)^+$] and 121 (42); λ_{max}(ethanol)/nm 276 (log ε 2.63) and 2.43 (2.69).

Methyl (1α,5α,6α,7α)-3-*Acetoxy*-7-*bromo*-5-*methoxy*-2-*oxobicyclo*[4.1.0]*hept*-3-*ene*-7-*carboxylate* **14**.—A solution of the diketone **13** (150 mg, 0.58 mmol) in methanol (2 cm^3) was treated with methanolic sodium methoxide (1.45 mol dm^{-3} solution; 1 cm^3). After the addition of the methoxide solution a colour change from bright yellow to dark orange was observed. After 10 min acetic anhydride (0.3 cm^3, 2.94 mmol) was added and the mixture stirred at ambient temperature for 45 min. After dilution with water (10 cm^3) the mixture was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic phases were washed with aqueous sodium hydrogen carbonate (saturated solution; 2 × 20 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* **14** (186 mg, 96%) as a yellow oil. This material could be used in the next step of the reaction sequence without further purification. Subjection of a portion of this material to semi-preparative HPLC (μ-Porasil column, 1:9 ethyl acetate–hexane elution, flow rate 3 cm^3 min^{-1}) afforded an analytically pure sample of compound **14** (R_t 1200 s) (Found: M^+, 331.9895. $C_{12}H_{13}{}^{79}BrO_6$ requires M^+, 331.9895); ν_{max}(KBr)/cm^{-1} 3055, 2955, 2933, 1769, 1735, 1692, 1650, 1298, 1266, 1203, 1148, 1123 and 1083; δ_H see Fig. 2; δ_C 182.0 (C-2), 167.7 (O–C=O), 165.0 (O–C=O), 145.5 (C-3), 129.1 (C-4), 68.6 (C-5), 55.6 (OCH_3), 53.9 (OCH_3), 37.1 (C-1), 34.1 (C-6), 29.3 (C-7) and 20.5 ($COCH_3$); *m/z* (%) 334 (1), 332 (1, M^+), 292 (5), 290 [5, $M - CH_2CO)^+$], 260 (18), 258 [17, $(M - CH_2CO - CH_3OH)^+$], 211 [100, $(M - CH_2CO - Br)^+$] and 179 (52); λ_{max}(ethanol)/nm 242sh (log ε 3.86).

4-*Hydroxy*-6-*methoxy*-3-*oxocyclohepta*-1,4,6-*triene*-1-*carboxylic Acid* **15**.—A solution of the enone **14** (98 mg, 0.294 mmol) in THF (1 cm^3) was cooled to −40 °C and DBU (55 mm^3, 0.368 mmol) was added to it. The initially pale yellow solution rapidly darkened to brown. The reaction mixture was maintained at *ca.* −40 °C for 1.5 h and then an additional aliquot of DBU (50 mm^3) was added to it and the mixture allowed to slowly warm to room temperature. Stirring was then continued for a further 1 h before the addition of aqueous KOH (2 mol dm^{-3} solution; 1 cm^3). After 1 h the mixture was acidified (to pH 2) by the addition of aqueous HCl (2 mol dm^{-3} solution) and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic phases were extracted with aqueous NaOH (1 mol dm^{-3} solution; 3 × 15 cm^3). The combined aqueous phases were then re-acidified (to pH 2) with aqueous HCl (2 mol dm^{-3} solution) and extracted with CH_2Cl_2 (3 × 15 cm^3). The organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a cream coloured powder.

Recrystallisation (methanol) of this material afforded the title compound **15** (4 mg, 10%) as pale yellow needles, m.p. 256–258 °C [lit.,[7] m.p. 262–264 °C (decomp.)] (Found: M^+, 196.0372. $C_9H_8O_5$ requires M^+, 196.0372); ν_{max}(KBr)/cm^{-1} 3424, 3049, 1712, 1597, 1483, 1413, 1374, 1256, 1220 and 1179; $\delta_H(CD_3OD)$ 7.61 (m, 2 H), 6.95 (d, J 2.7, 1 H) and 3.89 (s, 3 H, OCH_3); $\delta_C(CD_3OD)$ 177.4, 168.7, 136.9, 125.0, 114.6, 113.6 and 56.8 (two carbon resonances not observed); m/z (%) 196 (81, M^+), 168 [41, $(M - CO)^+$] and 56 (100); λ_{max}(ethanol)/nm 359 (log ε 4.05), 316sh (3.99) and 258 (4.87).

(1α,4α,5α,6α,7α)-7-*Bromo*-4,5-*dimethoxybicyclo*[4.1.0]*hept*-2-*ene*-7-*carboxylic Acid* **19**.—A stirred solution of compound **17**[1] (6.0 g, 19.2 mmol) in THF (150 cm^3) maintained at −100 °C under nitrogen was treated dropwise over 0.5 h with BuLi in hexane (1.6 mol dm^{-3} solution; 12 cm^3, 19.2 mmol). The resulting solution was stirred for a further 5 h at −100 °C before dry gaseous carbon dioxide was bubbled into the solution for 5 min whilst the internal temperature was kept at < −90 °C. The reaction mixture was stirred for a further 0.5 h at −100 °C before aqueous HCl (12 mol dm^{-3} solution; 1.5 cm^3) was added and the whole mixture then allowed to slowly warm to ambient temperature. The resulting solution was concentrated under reduced pressure and the residue partitioned between $CHCl_3$ (60 cm^3) and water (60 cm^3). The phases were separated and the aqueous phase extracted with $CHCl_3$ (3 × 30 cm^3). The combined organic phases were extracted with aqueous $NaHCO_3$ (saturated solution; 4 × 50 cm^3) and the combined basic extracts were acidified (to pH 2) with aqueous HCl (2 mol dm^{-3} solution) and extracted with diethyl ether (4 × 70 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a pale yellow solid. Recrystallisation (four times from toluene) of this material then yielded the *title compound* **19** (2.54 g, 48%) as colourless needles, m.p. 164–165 °C (partial sublimation at *ca.* 127 °C) (Found: M^+, 275.9997; C, 43.1; H, 4.6; Br, 28.8%. $C_{10}H_{13}{}^{79}BrO_4$ requires M^+, 275.9997; C, 43.3; H, 4.7; Br, 28.8%); ν_{max}(KBr)/cm^{-1} 2984, 2924, 1706, 1384, 1375, 1311, 1258, 1200, 1043 and 1029; δ_H 8.10–7.40 (br s, 1 H, CO_2H), 6.11–6.10 (m, 2 H, 2-H and 3-H), 3.81 (m, 1 H), 3.60 (dd, J 4.9 and 3.4, 1 H), 3.50 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 2.36 (dd, J 10.0 and 0.9, 1 H) and 2.13 (dd, J 10.0 and 4.9, 1 H); δ_C 170.5 (CO_2H), 130.8, 127.5 (C-2 and C-3), 75.2, 71.6 (C-4 and C-5), 57.0, 56.9 (2 × OCH_3), 34.2 (C-7), 31.4 and 28.2 (C-1 and C-6); m/z (%) 278 (0.4), 276 (0.5, M^+), 197 [8, $(M - Br)^+$] and 75 (100).

Methyl (1α,4α,5α,6α,7α)-7-*Bromo*-4,5-*dimethoxybicyclo*-[4.1.0]*hept*-2-*ene*-7-*carboxylate* **20**.—Methylation of the acid **19** (355 mg, 1.28 mmol) with diazomethane using the procedure of Lombardi[20] afforded, after standard work-up, the *title compound* **20** (352 mg, 94%) as a clear, colourless oil [Found: $(M - Br)^+$, 211.0970. $C_{12}H_{15}BrO_4$ requires $(M - Br)^+$, 211.0970]; ν_{max}(NaCl)/cm^{-1} 2928, 2895, 2820, 1733, 1435, 1303, 1199, 1167, 1141 and 1097; δ_H 6.09 (ddd, $J_{2,3}$ 9.5, $J_{2,1}$ 2.7 and $J_{2,6}$ 0.5, 1 H, 2-H), 6.03 (ddd, $J_{3,2}$ 9.5, $J_{3,4}$ 5.4 and $J_{3,1}$ 1.2, 1 H, 3-H), 3.73 (dd, $J_{4,3}$ 5.4 and $J_{4,5}$ 3.2, 1 H, 4-H), 3.72 (s, 3 H, OCH_3), 3.51–3.46 (complex m, 1 H, 5-H), 3.49 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 2.28 (ddd, $J_{1,6}$ 10.0, $J_{1,2}$ 2.7 and $J_{1,3}$ 1.2, 1 H, 1-H) and 2.06 (ddd, $J_{6,1}$ 10.0, $J_{6,5}$ 4.9 and $J_{6,2}$ 0.5, 1 H, 6-H); δ_C 166.6 (C=O), 130.5, 127.6 (C-2 and C-3), 75.2, 71.7 (C-4 and C-5), 56.9(7), 56.9(5), 52.9 (3 × OCH_3), 34.5 (C-7), 30.6 and 27.5 (C-1 and C-6); m/z (15 eV) (%) 228 (1), 226 [1, $(M - C_2H_6O_2)^+$], 211 [7, $(M - Br)^+$], 179 [20, $(M - C_2H_6O_2 - Br)^+$] and 75 (100).

Methyl (1α,2α,3α,4α,5α,6α,7α)-7-*Bromo*-2,3-*dihydroxy*-4,5-*dimethoxybicyclo*[4.1.0]*heptane*-7-*carboxylate* **21**.—Tetraethylammonium chloride monohydrate (21 mg, 0.12 mmol) and sodium acetate (19 mg, 0.23 mmol) were stirred in acetone (2.0 cm^3) for 1 h. This mixture was then treated with compound **20** (270 mg, 0.93 mmol), *tert*-butyl hydroperoxide (70% aqueous solution; 1.0 cm^3) and osmium tetroxide (2.5 wt% in *tert*-butyl alcohol; 1.2 cm^3). The resulting mixture was stirred at ambient temperature for 3 days at which stage analytical TLC (diethyl ether elution) showed no remaining alkene **20**. The mixture was concentrated under reduced pressure and the resulting yellow oil subjected to preparative TLC (diethyl ether elution). Extraction (diethyl ether) of the appropriate band (R_f 0.2–0.5) yielded the *title diol* **21** (133 mg, 44%) as a clear, colourless oil [Found: $(M - CH_3OH - H_2O)^+$, 273.9841. $C_{11}H_{17}{}^{79}BrO_6$ requires $(M - CH_3OH - H_2O)^+$, 273.9841]; ν_{max}(NaCl)/cm^{-1} 3466, 2934, 1729, 1437, 1396, 1312, 1203, 1111, 1078 and 978; δ_H 4.13 (dd, J 11.5 and 4.4, 1 H), 3.75 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 3.54 (m, 1 H), 3.46 (s, 3 H, OCH_3), 3.38 (t, J 2.9, 1 H), 3.30 (br s, 1 H, OH), 3.28 (br s, 1 H, OH), 3.24 (br m, 1 H), 2.20 (dd, J 11.0 and 1.0, 1 H, 1-H) and 1.88 (dd, J 11.0 and 3.2, 1 H); δ_C 167.0 (C=O), 81.4, 76.6, 68.1, 66.1, 61.1, 57.5, 53.3, 34.3, 30.2 and 28.4 (C-7); m/z (15 eV) (%) 276 (1), 274 [1, $(M - CH_3OH - H_2O)^+$], 195 [55, $(M - CH_3OH - H_2O - Br)^+$], 169 (73) and 101 (100).

Methyl(1α,2α,3α,4α,5α,6α,7α)-7-*Bromo*-2,3,4,5-*tetramethoxybicyclo*[4.1.0]*heptane*-7-*carboxylate* **22**.—A solution of the diol **21** (96 mg, 0.30 mmol) in THF (2 cm^3) was added dropwise to a magnetically stirred suspension of sodium hydride (21 mg, 0.89 mmol) in THF (3 cm^3) maintained at *ca.* 0 °C (ice–water bath), under nitrogen. The chilled mixture was allowed to warm to ambient temperature and then stirred for a further 1 h before being re-cooled to *ca.* 0 °C. The chilled mixture was then treated dropwise with methyl iodide (55 mm^3, 0.89 mmol) and then allowed to warm to ambient temperature. After being stirred for a further 17 h the reaction mixture was concentrated under reduced pressure and the residue then subjected to chromatographic filtration (1 cm deep pad of TLC grade silica, diethyl ether elution, 50 cm^3). The filtrate was concentrated under reduced pressure to yield a colourless solid which was recrystallised (diethyl ether–hexane) to give the *title compound* **22** (50 mg, 48%) as colourless prisms, m.p. 79.5–82 °C [Found: $(M - C_2H_6O_2)^+$, 290.0154; C, 44.2; H, 6.0%. $C_{13}H_{21}{}^{79}BrO_6$ requires $(M - C_2H_6O_2)^+$, 290.0154; C, 44.2; H, 6.0%]; ν_{max}(KBr)/cm^{-1} 2980, 2886, 1722, 1449, 1216, 1192, 1128, 1116, 1092 and 1071; δ_H 3.79 (s, 3 H, OCH_3), 3.53 (br dm, J 3.2, 2 H), 3.49 (s, 3 H, OCH_3), 3.47 (s, 6 H, 2 × OCH_3), 3.42 (dm, J 3.2, 2 H) and 2.11 (t, J 1.1, 2 H, 1-H and 6-H); δ_C 167.8 (C=O), 78.5, 74.8 (C-2–5), 59.0, 58.1, 53.3 (3 × OCH_3), 32.7 (C-1 and C-6) and 29.5 (C-7); m/z (15 eV) (%) 292 (2), 290 [2, $(M - C_2H_6O_2)^+$], 242 [12, $(M - Br - OCH_3)^+$], 114 (100) and 75 (97).

Methyl (1α,4α,5α,6α,7α)-7-*Bromo*-4,5-*dimethoxy*-2,3-*dioxobicyclo*[4.1.0]*heptane*-7-*carboxylate* **23**.—A magnetically stirred solution of DMSO (235 mm^3, 3.31 mmol) in CH_2Cl_2 (25 cm^3) maintained under nitrogen at −60 °C was treated in a dropwise fashion with TFAA (423 mm^3, 3.00 mmol). The resulting colourless solution was stirred at −60 °C for 10 min and then a solution of the diol **21** (336 mg, 1.03 mmol) in DMSO (3 cm^3) was added. The reaction mixture was stirred at −60 °C for 2 h and then treated dropwise with triethylamine (965 mm^3, 6.92 mmol). The resulting golden coloured solution was stirred for a further 1.5 h at −60 °C and then allowed to warm slowly (1.0 h) to 20 °C when it was poured into aqueous HCl (2 mol dm^{-3} solution; 20 cm^3). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 30 cm^3) and 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 yellow solid. Recrystallisation (CH_2Cl_2–hexane) of this material afforded the *title compound* **23** (186 mg, 56%) as bright yellow cubes, m.p. 129.5–132.0 °C (Found: M^+, 319.9895; C, 41.2; H, 4.3; Br, 24.9%. $C_{11}H_{13}{}^{79}BrO_6$ requires M^+, 319.9895; C, 41.1; H, 4.1; Br, 24.9%); ν_{max}(KBr)/cm^{-1} 1748, 1713, 1692, 1439, 1324, 1298, 1222, 1135, 1099 and 1079; δ_H 3.97 (dd, $J_{4,5}$ 2.8 and $J_{4,6}$ 1.0, 1 H, 4-H), 3.81 (s, 3 H, OCH_3), 3.74 (t, $J_{5,6}$ 2.8 and $J_{5,4}$ 2.8, 1 H, 5-H), 3.49 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 2.88 (d, $J_{1,6}$ 10.0, 1 H, 1-H) and 2.50 (ddd, $J_{6,1}$ 10.0, $J_{6,5}$ 2.8 and $J_{6,4}$ 1.0, 1 H, 6-H); δ_C 187.6, 185.3, 168.1, 83.6, 74.3 (C-4 and C-5), 58.6, 57.5, 55.0 (3 × OCH_3), 38.6, 37.1 (C-1 and C-6) and 33.7 (C-7); m/z (%) 322 (3), 320 (3, M^+), 241 [62, $(M-Br)^+$], 213 [92, $(M - Br - CO)^+$], 181 [100, $(M - Br - CO_2CH_3 - H)^+$], 153 (97) and 88 (95); λ_{max}(ethanol)/nm 293 (log ε 2.0), 250sh (1.8) and 215 (2.4).

(1α,2α,3α,4α,5α,6α)-7,7-*Dibromo*-4,5-*dimethoxybicyclo*-[4.1.0]*heptane*-2,3-*diol* **25**.—*cis*-Dihydroxylation of the alkene **17** (400 mg, 1.28 mmol), using the same conditions as employed in the conversion of compound **20** into compound **21**, afforded a pale yellow oil on work-up. Subjection of this material to preparative TLC (diethyl ether elution) followed by extraction (diethyl ether) of the appropriate band (R_f 0.1–0.5) yielded the *title compound* **25** (330 mg, 75%) as a colourless oil (Found: M^+, 343.9259. $C_9H_{14}{}^{79}BrO_4$ requires M^+, 343.9259); ν_{max}(NaCl)/cm^{-1} 3434, 2932, 1642, 1383, 1189, 1162, 1100, 1079, 710 and 676; δ_H($CDCl_3$ with one drop of D_2O) 3.89 (d, J 4.6, 1 H), 3.71 (t, J 2.4, 1 H), 3.58 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.44 (dd, J 4.6 and 1.3, 1 H), 3.27 (t, J 2.4, 1 H), 2.44 (dd, J 11.2 and 1.3, 1 H) and 1.99 (dd, J 11.2 and 2.4, 1 H) (OH resonances not observed); δ_C 81.5, 80.0, 68.4, 67.5, 61.3, 57.4, 36.4, 31.2 and 29.7.

Bis-*O*-methylation of the diol **25**, using the same conditions as employed for the conversion of compound **21** into compound **22**, afforded a solid on work-up. Recrystallisation (diethyl ether–hexane) of this material afforded (1α,2α,3α,4α,5α,6α)-7,7-*dibromo*-2,3,4,5-*tetramethoxybicyclo*[4.1.0]*heptane* (41%) as white crystalline mass, m.p. 81.5–83 °C (Found: C, 35.4; H, 4.8; Br, 42.7. $C_{11}H_{18}Br_2O_4$ requires C, 35.3; H, 4.9; Br, 42.7%); ν_{max}(KBr)/cm^{-1} 1467, 1444, 1372, 1208, 1191, 1091, 1068, 1010, 774 and 713; δ_H 3.53 (s, 6 H, 2 × OCH_3), 3.50 (s, 6 H, 2 × OCH_3), 3.41 (dm, J 5.0, 2 H), 3.38 (dm, J 5.0, 2 H) and 2.19 (t, J 1.5, 2 H, 1-H and 6-H); δ_C 78.5, 77.3, 59.0, 58.1, 32.6 and 32.2; m/z (15 eV) (%) 263 (0.5), 261 [0.5, $(M - Br - CH_3O - H)^+$] and 114 (100).

(1α,4α,5α,6α)-7,7-*Dibromo*-4,5-*dimethoxybicyclo*[4.1.0]-*heptane*-2,3-*dione* **26** *and* (1α,5α,6α)-3-*Acetoxy*-7,7-*dibromo*-4,5-*dimethoxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **27**.—A magnetically stirred mixture of the diol **25**[1] (100 mg, 0.29 mmol) and *p*-TsOH·H_2O (330 mg, 1.73 mmol) in CH_2Cl_2 (2 cm^3) maintained at *ca.* 0 °C (ice–water bath) was treated in a dropwise fashion with a solution of 4-acetamido-TEMPO (Aldrich) (370 mg, 1.73 mmol) in CH_2Cl_2 (5 cm^3). The resulting solution was stirred at 0 °C for a further 1 h before being warmed to room temperature and stirred for 2 days. Ethanol (0.5 cm^3) was added to the mixture which was then stirred for a further 30 min. Following the addition of water (50 cm^3) the separated aqueous phase was extracted with CH_2Cl_2 (3 × 5 cm^3). The combined organic phases were washed with brine (1 × 50 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to chromatographic filtration (1 cm deep pad of TLC grade silica, 1:9 diethyl ether–CH_2Cl_2 elution, 80 cm^3) and the combined filtrates were concentrated under reduced pressure. The concentrate was taken up in cold (*ca.* 0 °C) CH_2Cl_2 (10 cm^3) and acetic anhydride (82 mm^3, 0.58 mmol) and pyridine (47 mm^3, 0.58 mmol) were added to the solution. The resulting mixture was allowed to warm to ambient temperature and stirred for a further 16 h before being concentrated under reduced pressure. The residue was subjected to preparative TLC (1:9 diethyl ether–CH_2Cl_2 elution) and two chromophoric bands A and B (R_f 0.6 and 0.8 respectively) were thereby obtained.

Extraction (diethyl ether) of band A yielded the *α-diketone* **26** (53 mg, 54%) as a yellow oil (Found: M^+, 339.8942. $C_9H_{10}{}^{79}Br_2O_4$ requires M^+, 339.8946); ν_{max}(NaCl)/cm^{-1} 2934, 2832, 1744, 1718, 1453, 1324, 1189, 1126, 1096 and 975; δ_H(300 MHz) 4.03 (br d, $J_{4,5}$ 2.4, 1 H, 4-H), 3.98 (t, $J_{5,4}$ 2.4 and $J_{5,6}$ 2.4, 1 H, 5-H), 3.58 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 3.05 (d, $J_{1,6}$ 10.0, 1 H, 1-H) and 2.48 (dd, $J_{6,1}$ 10.0 and $J_{6,5}$ 2.4, 1 H, 6-H); δ_C(75 MHz) 190.2, 189.3 (C-2 and C-3), 84.6, 78.4 (C-4 and C-5), 58.6, 57.8 (OCH_3), 39.8, 35.3 (C-1 and C-6) and 25.7 (C-7); m/z (%) (20 eV, heated) 344 (1), 342 (4), 340 (1, M^+), 263 (96) and 261 [100, $(M - Br)^+$].

Extraction (diethyl ether) of band B yielded a solid which upon recrystallisation ($CHCl_3$–hexane) afforded the *enone* **27** (35 mg, 30%) as colourless plates, m.p. 120–122 °C (Found: C, 34.6; H, 3.3; Br, 41.8. $C_{11}H_{12}Br_2O_5$ requires C, 34.4; H, 3.2; Br, 41.6%); ν_{max}(KBr)/cm^{-1} 1766, 1648, 1619, 1342, 1251, 1200, 1175, 1149, 1106 and 1071; δ_H(300 MHz) 4.73 (br s, 1 H, 5-H), 4.00 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 2.91 (dd, $J_{6,1}$ 9.3 and $J_{6,5}$ 1.5, 1 H, 6-H), 2.51 (d, $J_{1,6}$ 9.3, 1 H, 1-H) and 2.25 (s, 3 H, $COCH_3$); δ_C(75 MHz) 181.6 (C-2), 167.7 (C=O), 157.7 (C-4), 131.0 (C-3), 70.0 (C-5), 57.9, 54.3, 37.5, 33.1, 23.0 and 20.2; m/z (%) 343 (8), 341 (16), 339 [7, $(M - COCH_3)^+$], 262 (24), 260 [24, $(M - COCH_3 - Br)^+$], 203 (11), 201 (12) and 43 (100).

6-*Bromo*-2-*hydroxy*-3,4-*dimethoxycyclohepta*-2,4,6-*trienone* **28**.—DBU (83 mm^3, 0.56 mmol) was added dropwise to a chilled (ice–water bath) solution of the α-acetoxy enone **27** (71 mg, 0.19 mmol) in THF (2 cm^3). The initially clear solution rapidly discoloured and a white precipitate formed. After the mixture had been stirred for 45 min, aqueous NaOH (5% solution; 2 cm^3) was added to it and stirring continued for a further 5 min. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between diethyl ether (25 cm^3) and aqueous NaOH (1 mol dm^{-3} solution; 50 cm^3). The layers were separated and the organic phase extracted with aqueous NaOH (1 mol dm^{-3} solution; 2 × 25 cm^3). The combined aqueous phases were washed with diethyl ether (2 × 25 cm^3) and then acidified to pH 2 (using 2 mol dm^{-3} aqueous HCl). The resulting mixture was extracted with $CHCl_3$ (3 × 50 cm^3) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield an off-white solid. Sublimation (100 °C/30 mmHg) of this material yielded the *title tropolone* **28** (38 mg, 79%) as pale cream needles, m.p. 109–112 °C (Found: M^+, 259.9685. $C_9H_9{}^{79}BrO_4$ requires M^+, 259.9684); ν_{max}(KBr)/cm^{-1} 3180, 1596, 1486, 1439, 1392, 1340, 1265, 1233, 1204 and 1039; δ_H(300 MHz) 9.50 (br s, 1 H, OH), 7.48 (d, J 1.6, 1 H), 6.87 (d, J 1.6, 1 H), 3.96 (s, 3 H, OCH_3) and 3.91 (s, 3 H, OCH_3); δ_C(75 MHz) 170.7, 161.2, 161.1, 145.5, 134.0, 125.0, 113.1, 60.5 and 57.1; m/z (%) 262 (96), 260 (100, M^+), 247 (41), 245 [42, $(M-CH_3)^+$], 163 (53) and 121 (79); λ_{max}(methanol)/nm (log ε) 380sh (2.47), 366 (2.62), 337 (2.66), 278sh (3.11) and 263 (3.41).

4-*Hydroxy*-5,6-*dimethoxy*-3-*oxocyclohepta*-1,4,6-*triene*-1-*carboxylic Acid* **29**.—DMF (1 cm^3) was added to palladium acetate (37 mg, 0.16 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (183 mg, 0.33 mmol). The resulting mixture was purged with carbon monoxide (**CAUTION-FUMEHOOD**) for 5 min after which triethylamine (92 mm^3, 0.66 mmol), methanol (270 mm^3, 6.6 mmol) and a solution of the tropolone **28** (86 mg, 0.33 mmol) in DMF (100 mm^3) were added to it. The reaction mixture was again purged with carbon monoxide (for 15 min) and then sealed under a balloon of carbon monoxide and heated at 60 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue treated with aqueous NaOH (5% solution; 5 cm^3) and stirred for 30 min at ambient temperatures. The mixture was then diluted with water (10 cm^3) and washed with diethyl ether (3 × 10 cm^3). The aqueous phase was then acidified (to pH 1) with aqueous HCl (2 mol dm^{-3} solution) and extracted with $CHCl_3$ (6 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow solid which was recrystallised (methanol) to give the *title compound* **29** (26 mg, 47%) as yellow needles, m.p. 204.5–205 °C (Found: M^+, 226.0479. $C_{10}H_{10}O_6$ requires M^+, 226.0478); ν_{max}(Nujol)/cm^{-1} 1700; δ_H(CD_3OD) (90 MHz) 7.80 (br s, 2 H), 4.10 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3) and 3.0 (br s, 1 H, OH) (one signal not observed); δ_C[$(CD_3)_2CO$] 169.4, 167.6, 166.9, 161.8, 152.4, 133.1, 116.3, 115.0, 60.2 and 57.9; *m/z* (%) 226 (100, M^+), 211 [57, $(M - CH_3)^+$], 198 [30, $(M - CO)^+$] and 197 [33, $(M - CO - H)^+$].

The mother liquors from the recrystallisation process were subjected to chromatography (Sephadex LH-20, methanol elution) which yielded further quantities of the title tropolone **29** (13 mg, 24%, 71% combined yield).

Puberulic Acid **2**.—Aqueous hydrobromic acid (48% aqueous solution; 1.5 cm^3) was added to a solution of the tropolone **29** (19 mg, 0.08 mmol) in acetic acid (1.5 cm^3) and the resulting mixture stirred at reflux for 1.5 h. The cooled reaction was concentrated under reduced pressure to give a solid which was subjected to column chromatography (Sephadex LH-20, methanol elution). The combined eluents were concentrated under reduced pressure to give a solid which was recrystallised (methanol) affording the *title compound* **2** (14 mg, 90%) as pale yellow needles, m.p. 312 °C (with decomp.) (lit.,[8] m.p. 317 °C) (Found: M^+, 198.0166. Calc. for $C_8H_6O_6$: M^+, 198.0164); ν_{max}(KBr)/cm^{-1} 3264, 1692, 1591, 1536, 1503, 1391 and 1207; δ_H(300 MHz) [$(CD_3)_2CO$] 7.94 (s, 2 H) and 4.70 (br s, 4 H + H_2O); δ_C[75 MHz; $(CD_3)_2CO$] 167.3, 159.4, 155.5, 128.5 and 119.4; *m/z* (%) 198 (100, M^+), 170 [62, $(M - CO)^+$] and 153 [85, $(M - CO_2H)^+$]; λ_{max}(water)/nm (log ε) 350 (2.56) and 267 (3.35).

Single-crystal X-Ray Diffraction Analysis of Compound **29**.—*Crystal data.** $C_{10}H_{10}O_6 \cdot CH_3OH$, $M = 258.2$, triclinic space group $P\bar{1}$, $a = 7.593(3)$, $b = 9.890(4)$, $c = 9.014(2)$ Å, $\alpha = 74.22(3)$, $\beta = 79.56(2)$, $\gamma = 71.13(2)°$, $V = 613.1(4)$ Å^3, $Z = 2$, $D_c = 1.399$ g cm^{-3}, μ(Cu-Kα) = 9.74 cm^{-1}. Since the crystals from methanol were unstable in air, and only a small amount of sample was available, a crystal fragment was cut under Nujol and sealed in a Lindeman-glass tube. Intensities were recorded on a Rigaku-AFC diffractometer (graphite monochromatised Cu-Kα radiation, $\lambda = 1.5418$ Å) at 291(1) K to $2\theta_{max} = 100°$. During data collection the intensities of three standard reflections decreased by 33%; the data were scaled accordingly. The structure was solved by direct methods (SHELXS86)[21] and full-matrix least squares refinement (SHELX-76)[22] converged at $R = 0.096$, $wR = 0.103$, for 771 data ($I \geq 3\sigma I$). The hydroxy and carboxy H atoms were not located, the remainder included at calculated positions. The solved structure is shown as an ORTEP[23] plot in Figure 3.

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

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