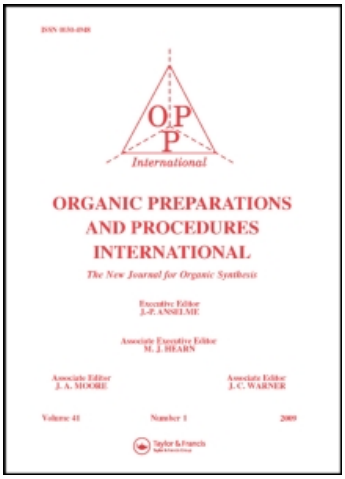

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AN EFFICIENT SYNTHESIS OF 5-BROMO-2-HYDROXYCYCLOHEPTA-2, 4, 6-TRIEN-1-ONE AND ITS METHYL ETHER

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AN EFFICIENT SYNTHESIS OF 5-BROMO-2-HYDROXYCYCLO-HEPTA-2,4,6-TRIEN-1-ONE AND ITS METHYL ETHER

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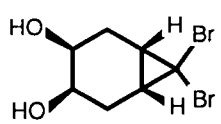
During studies on the transition-metal mediated coupling reactions of halogenocyclohepta-2,4,6-trien-1-ones, multigram quantities of the title compounds (2) were required. We have previously prepared 2a by subjecting the bicyclic diol 1 to modified Swern-oxidation conditions.[1] While this conversion proceeds in good yield (76%) and thus provides the first efficient route to this synthetically useful tropolone, trace



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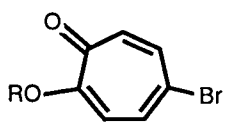
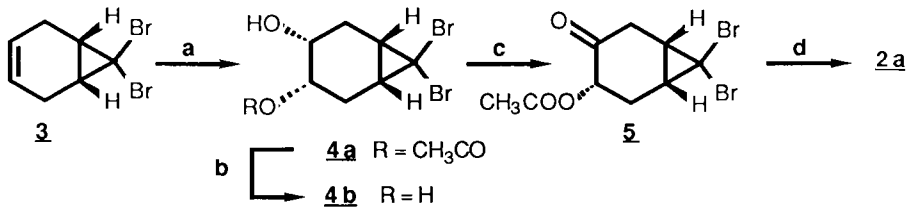


2a R=H **2b** R=CH_3

amounts of dimethyl sulfide (a by-product from the oxidation reaction) contaminate the product and seem to interfere with the desired coupling reactions. Although the contaminant could be removed by repeated recrystallisation of 2a, the resulting loss of material was significant prompting us to develop an alternative route to this compound. We now report an efficient new synthesis of 2a which involves, as the key step, a novel ring-expansion reaction of a bicyclo[4.1.0]heptan-3-one.

The successful three-step synthesis of tropolone 2a from the readily available[2] bicyclo[4.1.0]hept-3-ene 3 is outlined in Scheme 1. Reaction of alkene 3 with iodine and silver acetate in wet acetic acid[3] gave the



(a) I_2, $AgOCOCH_3$, CH_2CO_2H, H_2O (b) NaOH, CH_3OH

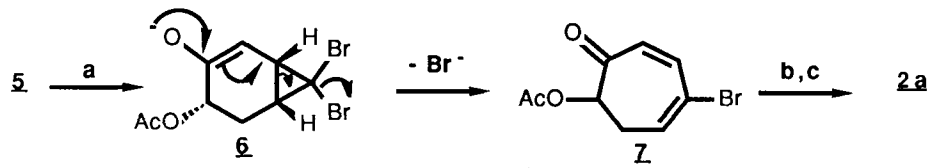
(c) PCC (d) K_2CO_3, CH_3OH, H_2O

Scheme 1

hydroxyacetate 4a as a white crystalline solid in 85% yield. On the basis of the generally accepted mechanism for the Woodward hydroxylation reaction,[3] it is assumed that the stereochemical outcome in this conversion involves overall syn-addition to the alkene from the more hindered side. Indirect evidence for this stereochemistry derives from the observation that hydrolysis of 4a gives a C_{2v} symmetric diol (4b) which is different from diol 1 (the compound obtained by reaction of alkene 3 with OsO_4).[1] Oxidation of alcohol 4a with pyridinium chlorochromate (PCC)[4] proceeded smoothly to give the crystalline α-acetoxyketone 5 in 96% yield. Finally, treatment of 5 with potassium carbonate in aqueous methanol gave, following acidic work-up, the target compound 2a in 96% yield after a single recrystallisation. This material was sufficiently pure for use in the coupling reactions mentioned earlier. Of the various procedures available for the methylation of tropolones,[5] we find that reaction of 2a with diazomethane[6] provides the most simple and efficient (97% yield) means of obtaining ether 2b.[7]

There are several noteworthy features associated with the present method for preparing tropolone 2a. Firstly, each step of the synthetic sequence proceeds in high yield. Furthermore, each of the intermediates, as well the final product, can be obtained in pure form by direct recrystallisation of the worked-up reaction mixture. Tedious chromatographic procedures are thus avoided.

The mode of formation of tropolone 2a from ketone 5 is unclear at the present time. However, an interesting feature of this conversion is that a formal oxidation step must be involved, since concomitant ring--expansion and dehydrobromination of 5 will only produce a dihydrotropolone derivative. One possible sequence of events (Scheme 2) involves fragmentation of the base-generated enolate 6 to give dihydrotropolone acetate 7. Subsequent air oxidation of compound 7 would



(a) K_2CO_3 (b) air oxidation (c) K_2CO_3, then aqueous acid work-up

Scheme 2

give the corresponding tropolone acetate which on hydrolysis affords the observed product 2a. A similar process has recently been proposed[8] to account for the formation of 4,5,6-trichloro-2-hydroxycyclohepta-2,4,6-trien-1-one from 1,6,7,7-tetrachloro-4-hydroxybicyclo[4.1.0]heptan-3-one.

Applications of this new and potentially significant ring-expansion reaction are currently under investigation in our laboratory.

EXPERIMENTAL SECTION

Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Noice decoupled and single frequency off-resonance decoupled (SFORD) ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer. SFORD multiplicities for each carbon resonance observed in the noise decoupled

spectra are given in brackets (s = singlet, d = doublet, t = triplet, q = quartet). Other general experimental procedures have been reported elsewhere.[1]

(1α,3β,4β,6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-ol (4a).

Finely ground iodine (9.3 g, 36.6 mmol) was added in small portions over 0.5 h to a magnetically stirred mixture of (1α,6α)-7,7-dibromobicyclo-[4.1.0]hept-3-ene (3) (8.42 g, 33.4 mmol) and silver acetate (11.16 g, 66.9 mmol) in CH_3CO_2H (146 mL). Water (622 uL, 34.6 mmol) was then added in one portion and the resulting mixture was stirred at ambient temperatures in the dark for a further 48 h. The reaction mixture was then filtered (celite) to remove the precipitated silver iodide and the filtrate diluted with CH_2Cl_2 (300 mL). The organic phase was washed with water (2 x 200 mL) then sodium bicarbonate (saturated aqueous solution) until the washings remained alkaline to litmus, then with sodium meta-bisulphite (1 x 200 mL of a 20% aqueous solution) and water (1 x 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale yellow solid. Recrystallisation ($CHCl_3$/hexane) gave the title compound (9.31 g, 85%) as white needles: mp. 82-83°; ^1H NMR: δ 4.80 (m, 1H), 3.78 (m, 1H), 2.60-1.55 (complex m, 7H), 2.11 (s, 3H); ^{13}C NMR: δ 170.7 (s), 69.5 (d), 65.6 (d), 38.3 (s), 27.3 (d), 26.5 (two signals superimposed, d, t) 24.1 (t), 21.2 (q); IR (KBr) 3375, 1725, 1697, 1423, 1392, 1373, 1280, 1261, 1246, 1229, 1102, 1076, 1034, 729 cm^{-1}; MS, m/e 326 (< 1), 328 (< 1), 330 (< 1) [[M]·$^+$], 266 (2), 268 (4), 270 (2) [[M-CH_3CO_2H]·$^+$], 43 (100) [[CH_3CO]$^+$].

Anal. Calcd. for $C_9H_{12}Br_2O_3$: C, 32.96; H, 3.69; Br, 48.72.
Found: C, 33.21; H, 3.76; Br, 48.16.

(1α,3β,4β,6α)-7,7-Dibromobicyclo[4.1.0]heptane-3,4-diol (4b).- A solution of acetate 4a (200 mg, 0.6 mmol) in methanol (4.2 mL) maintained at room temperature was treated with sodium hydroxide pellets (50 mg, 1.3 mmol). After stirring for 6 h the reaction mixture was diluted with

hydrochloric acid (10 mL of a 2M aqueous solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid. Recrystallisation ($CHCl_3$/hexane) gave the diol 4b (171 mg, 98%) as fine white needles: mp 103-103.5°; ^1H NMR: δ 3.70 (m, 2H), 2.75-2.10 (complex m, 4H), 2.10-1.40 (complex m, 4H); ^{13}C NMR: δ 66.7 (d), 39.8 (s), 27.3 (d), 26.7 (t); IR (KBr): 3511, 3296, 2942, 2914, 2872, 1415, 1367, 1069, 1056, 1042, 948, 939 cm^{-1}; MS, m/e: 266 (3), 268 (4), 270 (3), [[M-H_2O]$\cdot^+$], 187 (35), 189 (37), [[M-H_2O-Br$\cdot$]$^+$], 79 (100).

Anal. Cald. for $C_7H_{10}Br_2O_2$: C, 29.40; H, 3.52; Br, 55.89.
Found: C, 29.61; H, 3.70, Br, 55.58.

(1α,4β,6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-one (5).- Pyridinium chlorochromate (10.3 g, 47.8 mmol) was added in one portion to a solution of hydroxyacetate 4a (6.28 g, 19.2 mmol) in CH_2Cl_2 (250 mL). The resulting mixture was stirred magnetically at ambient temperatures for 24 h before being concentrated to one-fifth of the original volume then diluted with Et_2O (250 mL) and filtered through a 6 cm deep bed of TLC grade silica gel. The solids thus retained were washed with additional CH_2Cl_2/Et_2O (1:1) and the combined filtrates then concentrated under reduced pressure to give a light yellow solid. Recrystallisation ($CHCl_3$/hexane) afforded the ketone 5 (6.00 g, 96%) as white needles: mp. 118-120°; ^1H NMR: δ 5.15 (m, 1H), 3.15-1.80 (complex m, 6H), 2.15 (s, 3H); ^{13}C NMR: δ 202.0 (s), 169.8 (s), 72.3 (d), 38.1 (t), 37.2 (s), 29.1 (t), 29.0 (d), 26.0 (d), 20.6 (q); IR (KBr) 1745, 1721, 1384, 1253, 1078, 1028, 733 cm^{-1}; MS, m/e: 324 (< 1), 326 (< 1), 328 (< 1) [[M]$\cdot^+$], 264 (2), 266 (5), 268 (2), [[M-CH_3CO_2]$\cdot^+$], 43 (100) [[CH_3CO]$^+$].

Anal. Cald. for $C_9H_{10}Br_2O_3$: C, 33.16; H, 3.09; Br, 49.02.
Found: C, 33.07; H, 3.08; Br, 49.17.

5-Bromo-2-hydroxycyclohepta-2,4,6-trien-1-one (2a).- Potassium carbonate (5.08 g, 36.8 mmol) was added in one portion to a solution of ketone 5

(4.00 g, 12.3 mmol) in aqueous methanol (800 mL of a 5:95 water/methanol mixture) contained in a flask open to the atmosphere. The resulting yellow reaction mixture was stirred at ambient temperatures for 12 h then diluted with HCl (800 mL of a 2M aqueous solution) and extracted with CH_2Cl_2 (5 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow solid. Recrystallisation ($CHCl_3$/hexane) afforded the tropolone 2a (2.33 g, 95%) as pale yellow needles: mp. 192-193° (sealed tube) (lit.[1] mp. 192-193°). This material was identical by ^1H NMR ^{13}C NMR and IR with an authentic sample of 2a.

5-Bromo-2-methoxycyclohepta-2,4,6-trien-1-one (2b).- A magnetically stirred suspension of tropolone 2a (1.20 g, 6.0 mmol) in tetrahydrofuran (20 mL) was cooled on an ice-water bath and treated, in portions, with ethereal diazomethane (60 mL of a ca. 0.6 M solution, ca. 36 mmol). The reaction mixture was allowed to warm to room temperature and after 1.5 h excess diazomethane was destroyed by the dropwise addition of glacial acetic acid. The resulting solution was concentrated under reduced pressure to give a light yellow solid. Recrystallisation ($CHCl_3$/hexane) afforded 2b (1.25 g, 97%) as pale yellow needles: mp. 135-137° (lit.[7] mp. 135-137°); ^1H NMR: δ 7.45 (m, 2H), 7.0 (d, J = 14.5 Hz, 1H), 6.48 (d, J = 11 Hz, 1H), 3.94 (s, 3H); ^{13}C: NMR δ 179.4 (s), 164.8 (s), 140.0 (d), 136.1 (d), 134.3 (d), 122.5 (s), 111.5 (d), 56.5 (q); IR (KBr): 1608, 1592, 1567, 1496, 1440, 1351, 1277, 1253, 1116, 840, 834 cm^{-1}; MS, m/e: 214 (51), 216 (51) [[M]$\cdot^+$]], 183 (63) [[M-$CH_3O\cdot$]$^+$] 185 (100) [[M-$CH_3O\cdot$]$^+$ and [M-CO-H$\cdot$]$^+$] 187 (43) [[M-CO-H$\cdot$]$^+$]; HRMS calcd for [M$\cdot^+$] 213.9630 obsd 213.9632; UV ($CHCl_3$): 246 (log ϵ = 4.0), 328 (3.8) 356 (infl.) 378 (infl.) nm.

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