A NEW AND SHORT SYNTHESIS OF 7 *H*-BENZO[*a*]CYCLOHEPTEN-7-ONE AND SOME DERIVATIVES: OXIDATION OF 7-BROMO-5*H*-BENZO[*a*]CYCLOHEPTENE

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A NEW AND SHORT SYNTHESIS OF 7*H*-BENZO[*a*]CYCLOHEPTEN-7-ONE AND SOME DERIVATIVES: OXIDATION OF 7-BROMO-5*H*-BENZO[*a*]CYCLOHEPTENE

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ABSTRACT

Oxidation of 7-bromo-5*H*-benzo[*a*]cycloheptene with some oxidation reagents has been studied. Several 2,3- and 4,5-benzotropone derivatives has been obtained. The structures of the products were determined by ^{1}H-, ^{13}C NMR data and chemical transformation.

Tropone (**1**) and α-tropolone (**2**) have fascinated organic chemists for well over 50 years.[1] Early theoretical work suggested that carbocycles **1** and **2** may represent a new type of aromatic system which would possess resonance stabilisation due to contributions from

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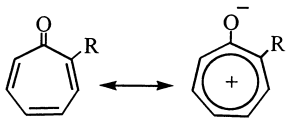
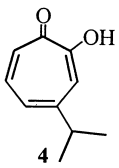
the tropylium oxide form **3**, for which a Hückel sextet of electrons can be drawn.



1 R =H
2 R = OH

3



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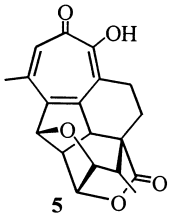

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Another significant reason for the interest in ring systems **1** and **2** is that they represent the key structural element in a wide range of natural products, many of which display interesting biological activity. According to a recent count, about more than 90 naturally occurring troponoids have been reported in the literature.[1] Such compounds range from the structurally simple, e.g. the monoterpene β-*thujaplicin* (**4**)[2] (a potent anti fungal and antibiotic agent isolated from the heartwood and essential oils of trees of the *cupressaceae* family) to the structurally complex, e.g. *harringtonolide* (**5**),[3] a compound which display plant growth inhibitory properties and virucidal activity). The final and perhaps most contemporary interest in troponoids stems from the recognition that such compounds can function as useful building blocks in the synthesis of complex natural products.[1]

Despite the considerable theoretical, biological and synthetic interest in troponoids, the development of general and flexible synthetic routes to these compounds remains a challenging problem. Several procedures for the synthesis 7*H*-benzo[*a*]cyclohepten-7-one (**8**) have been reported (Scheme 1). These methodologies for the preparation of benzotropone are of rather limited use because they have multisteps or low yield. The original procedure of Thiele, Schneider and Weitz[4] involves condensation of *o*-pthaldialdehyde (**6**) with diethyl acetonedicarboxylate and subsequent hydrolysis and decarboxylation. Similar variations of this synthesis were achieved by Cook[5] and Föhlisch et al.[6] For large scale synthesis, however, the cost of **6** becomes prohibitive and the requirements of an autoclave and 200°C in the final stage is an unattractive feature. Srivastava and Dev[7] have examined selenium dioxide oxidation of 5*H*-benzo[*a*]cycloheptene (**9**) and they obtained compound **8** in 27% yield. Battiste and co-workers[8] discovered a multistep route from the benzyne-furan adduct **11** to **8**. Ewing and Paquette[9] have synthesised **8** starting from *o*-xylylene dibromide **13** in several steps. Pomerantz and Swei[10] have reported a high-yield preparation of **8**

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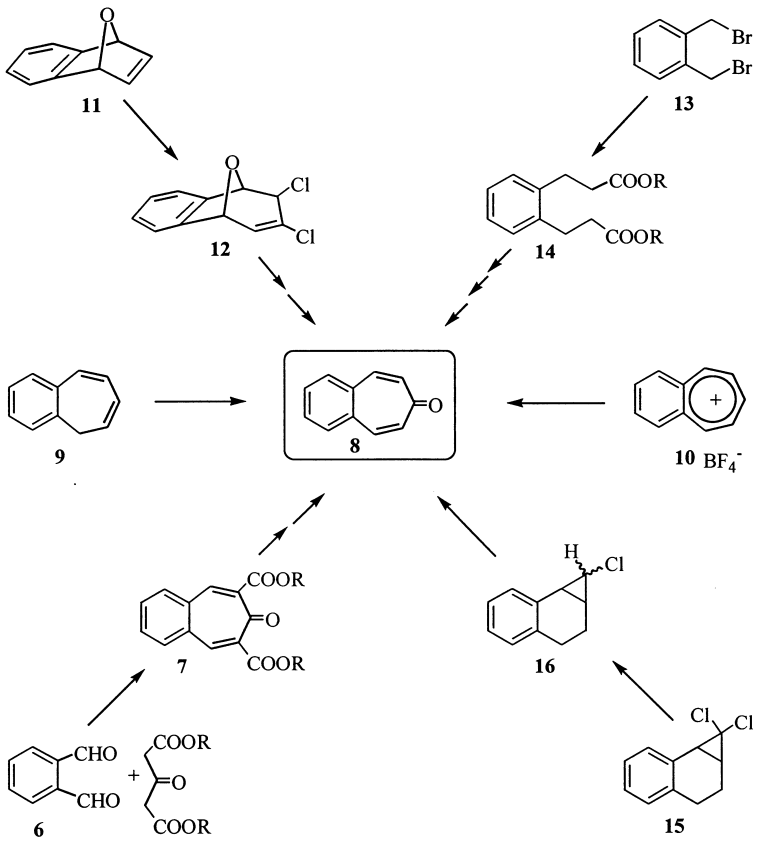

Scheme 1.

which consists of the oxidation of benzotropylium cation **10**. Moreover, tropylium cation **10** is not readily available. Lastly, Müller[11] and co-workers have reported an alternative synthesis for **8** from the carbene adduct **15** in two steps. In this paper, we report a new and short synthesis of 7*H*-benzo[*a*]cyclohepten-7-one (**8**) and some of its derivatives.

RESULTS AND DISCUSSION

The starting material **19**[12] was prepared by the addition of the dibromocarbene to 1,4-dihydronaphthalene (**17**) under phase-transfer conditions and subsequent reaction of dibromide **18**[13] with quinoline (Scheme 2).

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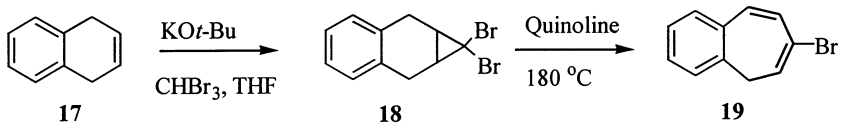
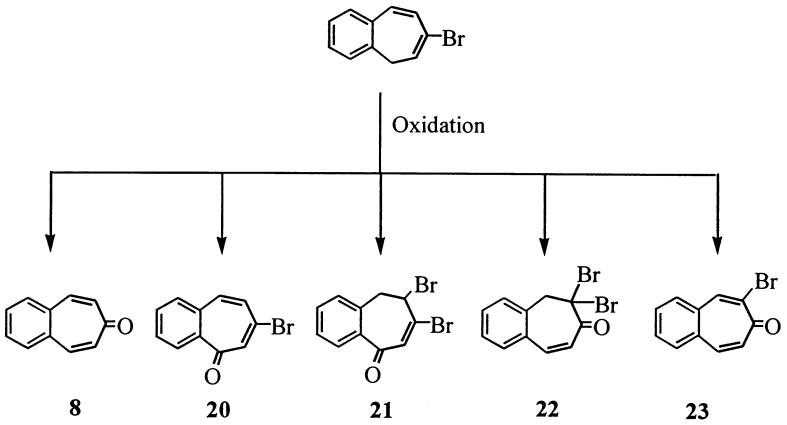
The oxidation of 7-bromo-5*H*-benzo[*a*]cycloheptene (**19**) in aqueous acetic acid using chromium trioxide gave 7*H*-benzo[*a*]cyclohepten-7-one (**8**) in 29% yield and 7,8-dibromo-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-one (**21**) in 13.4% yield (Scheme 3). From the oxidation of **19** with chromium trioxide in methylene chloride and pyridine, we obtained, a new benzotropone derivatives 7-bromo-5*H*-benzo[*a*]cyclohepten-5-one (**20**) in 48% yield and 7*H*-benzo[*a*]cyclohepten-7-one (**8**) in 14.2% yield. On the other hand, the oxidation of **19** with selenium dioxide in aqueous dioxane gives four products: 7*H*-benzo[*a*]cyclohepten-7-one (**8**) in 34% yield, 6-bromo-7*H*-benzo[*a*]cyclohepten-7-one (**23**)[14] in 9.2% yield,



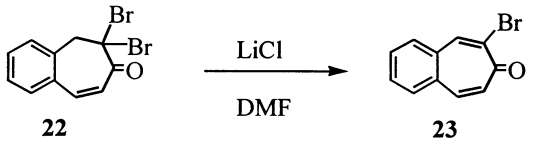
Scheme 2.



a) CrO_3 AcOH	29%	—	13.4%	—	—
b) CrO_3 Pyridine	14.2%	48%	—	—	—
c) SeO_2 H_2O	34%	—	2.1%	3.0%	9.2%

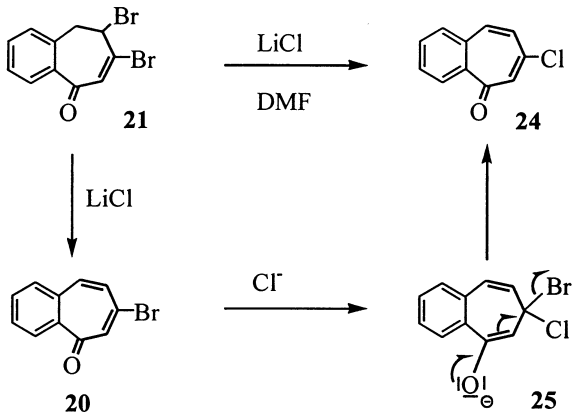
Scheme 3.

6,6-dibromo-5,6-dihydro-7*H*-benzo[*a*]cyclohepten-7-one (**22**) in 3% yield and 7,8-dibromo-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-one (**21**) in 2.1% yield. The structures of products were determined on the basis of spectral data and chemical transformations. We assume that the dibromides **21** and **22** were formed by oxidation, followed by addition of HBr, which is formed under the reaction conditions. The structures of dibromides **21** and **22** were also supported by chemical transformation. When pure **22** was subjected to dehydrobromination by lithium chloride in DMF, **23** was obtained in high yield as the sole product. However, the reaction of dibromide **21** with lithium chloride gave 7-chloro-5*H*-benzo[*a*]cyclohepten-5-one (**24**) in 90% yield. For this conversion we propose the



22 **23**

following reaction mechanism (Scheme 4). Firstly, bromo-tropone **20** is formed. Then the chloride ion attacks the β-position of the carbonyl group forming the intermediate **25**, from which bromide is eliminated as the better leaving group. In order to test this proposed mechanism, we reacted pure **20** with LiCl under the same reaction conditions and obtained **24** as the sole product.



21 **24** **20** **25**

Scheme 4.

In summary, we have found a simple and inexpensive synthetic method for the preparation of 7*H*-benzo[*a*]cyclohepten-7-one (**8**). Furthermore, two new benzotropon derivatives **20** and **24** were obtained.

EXPERIMENTAL

General: Melting points are uncorrected. Infrared spectra were obtained from KBr pellets on a regular instrument. The ^{1}H- and ^{13}C-NMR spectra were recorded on 200- and 60-MHz spectrometers. Apparent splitting are given in all cases. Mass spectra (electron impact) were recorded at 70 eV as *m*/*z*. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminum plates.

The CrO_3 oxidation of 7-bromo-5*H*-benzo[*a*]cycloheptene (19) in aqueous acetic acid: To a magnetically stirred solution of monobromide **19** (1.0 g, 4.52 mmol) in 10 mL acetic acid cooled to 10°C was added dropwise a solution of CrO_3 (1.36 g, 13.6 mmol) and H_2O (1.2 mL) in 7 mL acetic acid during 30 min. This solution was stirred for 3 h at 10°C and for an additional 19 h at RT. The mixture was extracted with ether (3 × 80 mL). The extract was washed with saturated $NaHCO_3$ solution, water and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed over silica gel (90 g), with hexane/ethyl acetate (97:3) as the eluent. The first fraction identified as **7,8-dibromo-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-one (21):** (193 mg, 13.4%), mp 102–103°C, colourless crystals from methylene chloride/hexane (2:1). **^{1}H-NMR (200 MHz, $CDCl_3$):** 7.79–7.20 (m, 4H, aryl), 6.87 (d, $J_{68} = 0.8$ Hz, 1H, H_6), 5.13 (ddd, $J_{89} = 5.9$, $J_{89'} = 2.2$, $J_{68} = 0.8$ Hz, 1H, H_8), 3.87 (dd, A-part of AB-system, $J_{99'} = 15.2$, $J_{89'} = 2.2$ Hz, 1H, H_9), 3.18 (dd, B-part of AB-system, $J_{99'} = 15.2$, $J_{89} = 5.9$ Hz, 1H, $H_{9'}$). ^{13}C-NMR (50 MHz, $CDCl_3$): 189.29, 143.71, 138.59, 137.37, 134.69, 133.27, 131.74, 130.54, 128.65, 53.11, 42.28. Ms (70 eV) *m*/*z*: 318/316 (M^+, 12), 235/237 (M^+-HBr, 33), 156/157 (M^+-HBr-Br, 42), 128 (M^+-HBr-Br-CO, naphthalene, 100). Anal. Calcd. for $C_{11}H_8Br_2O$: C, 41.81; H, 2.55. Found: C, 41.14, H, 2.46. IR (KBr, cm^{-1}): 3043, 3027, 2960, 2880, 1625, 1602, 1590, 1446, 1428, 1298, 1285, 1262, 1152, 1035.

Then the column was eluted with hexane/ethyl acetate (90:10). The second fraction identified as **7*H*-benzo[*a*]cyclohepten-7-one (8):** (205 mg, 29%), mp 67–68°C, colorless crystals from methylene chloride/hexane (2:1) Lit. mp: 66–67,[4] 69,[8] 68–69°C.[9] ^{1}H-NMR (200 MHz, $CDCl_3$): 7.63–7.49 (AA′BB′ system, 4H, aryl), 7.38 (d, A-part of AB-system, $J_{56} = J_{89} = 13.4$, 2H, H_5, H_9), 6.74 (d, B-part of AB-system, $J_{56} = J_{89} = 13.4$, 2H,

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H_6, H_8). ^{13}C-NMR (50 MHz, $CDCl_3$): 188.75, 141.93, 136.37, 135.31, 134.47, 130.98. IR (KBr, cm^{-1}): 3030, 2920, 1640.

The CrO_3 oxidation of 7-bromo-5*H*-benzo[*a*]cycloheptene (19) in pyridine/methylene chloride: To a magnetically stirred solution of CrO_3 (2.94 g, 29.41 mmol) in 30 mL pyridine and 20 mL methylene chloride cooled to $0 \pm 5^{\circ}C$ was added dropwise a solution of monobromide **19** (1.0 g, 4.52 mmol) in 10 mL methylene chloride during 15 min. This solution was stirred for 2 h at $0 \pm 5^{\circ}C$ and for an additional 46 h at RT. The solvent (pyridine and methylene chloride) was removed by rotaevaporation. To the residue, 100 mL methylene chloride was added and filtered to remove precipitated material. The extract was washed with 1 M (20 mL) HCl solution, water and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed over silica gel (90 g), with hexane/ethyl acetate (97:3) as the eluent. The first fraction identified as **7-Bromo-5*H*-benzo[*a*]cyclohepten-5-one (20):** (510 mg, 48%), mp 81–82°C, a pale yellow crystals from methylene chloride/ether (1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.42 (m, 1H-aryl), 7.75–7.59 (m, 3H, aryl), 7.41 (d, $J_{68} = 2.2$, 1H, H_6), 7.07 (d, A-part of AB-system, $J_{89} = 12.1$, 1H, H_9), 6.90 (dd, B-part of AB-system, $J_{89} = 12.1$, $J_{68} = 2.2$ Hz, 1H, H_8). ^{13}C-NMR (50 MHz, $CDCl_3$): 185.41, 139.01, 138.81, 138.30, 136.04, 134.91, 134.71, 133.29, 132.00, 131.91, 131.44. Ms (70 eV) *m*/*z*: 234/235 (M^+, 15), 208/207 (M^+-CO, 58), 128/127 (M^+-CO-Br, naphthalene, 100). Anal. Calcd. for $C_{11}H_7BrO$: C, 56.20; H, 3.00. Found: C, 55.90, H, 2.98. IR (KBr, cm^{-1}): 3072, 3045, 3038, 1602, 1580, 1446, 1330, 1299, 1126, 889.

Then the column was eluted with hexane/ethyl acetate (90:10). The second fraction identified as **7*H*-benzo[*a*]cyclohepten-7-one (8)** (100 mg, 14%).

The SeO_2 oxidation of 7-bromo-5*H*-benzo[*a*]cycloheptene (19) in dioxane: A mixture of monobromide **19** (1.0 g, 4.52 mmol), SeO_2 (1.51 g, 13.60 mmol), KH_2PO_4 (0.2 g, 1.47 mmol), dioxane (20 mL) and H_2O (1.35 g) were gently refluxed for 60 h. After the removed dioxane relatively in reduced pressure, to the residue, 100 mL chloroform was added. The solution was filtered to remove precipitated Se. The extract was washed with water, brine and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed over silica gel (90 g), with hexane/ethyl acetate (97:3) as the eluent. The first fraction identified as **6,6-dibromo-5,6-dihydro-7*H*-benzo[*a*]cyclohepten-7-one (22):** (43 mg, 3%), mp 141°C, colourless crystals from methylene chloride/hexane (1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.47–7.27 (m, 4H, aryl), 7.17 (d, A-part of AB-system, $J_{89} = 12.8$ Hz, 1H, H_9), 6.31 (d, B-part of AB-system, $J_{89} = 12.8$ Hz, 1H, H_8), 4.05 (s, 2H, H_5). ^{13}C-NMR (50 MHz, $CDCl_3$): 187.84, 142.89, 137.68, 134.64, 132.70, 131.76, 131.35, 129.09, 123.72, 69.73, 52.05. Ms (70 eV) *m*/*z*: 316

(M^+, 1), 236 (M^+-HBr, 3), 209 (M^+-HBr-CO, 20), 156/157 (M^+-HBr-Br, 9), 128/127 (M^+-HBr-Br-CO, naphthalene, 100). Anal. Calcd. for $C_{11}H_8Br_2O$: C, 41.81; H, 2.55. Found: C, 41.58, H, 2.57. IR (KBr, cm^{-1}): 3051, 3036, 3019, 1639, 1606, 1318, 1276, 1206, 1098, 964.

The second fraction identified as dibromide **21** (30 mg, 2.1%). Then the column was eluted with hexane/ethyl acetate (95:5). The third fraction identified as **6-bromo-7*H*-benzo[*a*]cyclohepten-7-one (23):** (98 mg, 9.2%), mp 138°C, a pale yellow crystals from methylene chloride/hexane (2:1), Lit. mp: 134,[14a] 142–143,[14b] 135°C.[14c] ^{1}H-NMR (200 MHz, $CDCl_3$): 8.45 (s, 1H, H_5), 7.75–7.62 (m, 4H, aryl), 7.50 (d, A-part of AB-system, $J_{89} = 12.8$ Hz, 1H, H_9), 6.98 (d, B-part of AB-system, $J_{89} = 12.8$ Hz, 1H, H_8). ^{13}C-NMR (50 MHz, $CDCl_3$): 181.09, 144.56, 141.04, 135.31, 134.60, 134.29, 134.10, 134.06, 131.55 (3C), IR (KBr, cm^{-1}): 3030, 1620, 1600, 1540, 1340, 1285, 1190, 995.

The fourth fraction was identified as **7*H*-benzo[*a*]cyclohepten-7-one (8**) (243 mg, 34%).

Reaction of 7,8-dibromo-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-one 21 with LiCl: A mixture of the dibromoketone **21** (200 mg, 0.63 mmol), anhydrous lithium chloride (80 mg, 1.89 mmol), and dry dimethylformamide (15 mL) was boiled and stirred under nitrogen for 3 h. The mixture was cooled, and dimethylformamide was removed under reduced pressure. Water was added, and the mixture thoroughly extracted with ether (3×60 mL). The combined extracts were dried over $MgSO_4$. After the removal of solvent, the residue was chromatographed over silica gel (10 g) with hexane/ethylacetate (95 : 5) as the eluant, to give 108 mg (90%) **7-chloro-5*H*-benzo[*a*]cyclohepten-5-one (24):** Colourless crystals mp 65–66°C from methylene chloride/hexane (1/3). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.47 (m, 4H, aryl), 7.77–7.61 (m, 3H, aryl), 7.20 (d, 1H, $J_{89} = 12.1$ Hz, 1H, H_9), 7.19 (d, $J_{68} = 2.5$ Hz, 1H, H_6), 6.77 (dd, $J_{89} = 12.1$, $J_{68} = 2.5$ Hz, 1H, H_8). ^{13}C-NMR (50 MHz, $CDCl_3$): 185.27, 145.39, 139.05, 138.36, 135.28, 134.95, 134.77, 133.22, 131.91, 131.45, 129.63. Ms (70 eV) *m/z*: 190 (M^+, 28), 164/162 (M^+-CO, 100), 128/127 (M^+-CO-Cl naphthalene, 100). Anal. Calcd. for $C_{11}H_7ClO$: C, 69.31; H, 3.70, Found: C, 67.11, H, 3.60. IR (KBr, cm^{-1}): 3062, 3048, 1610, 1580, 1564, 1447, 1332, 1311, 1130, 1090.

Dehydrobromination of 6,6-dibromo-5,6-dihydro-7*H*-benzo[*a*]cyclohepten-7-one (22) with LiCl: The reaction was carried out as described above by using 200 mg (0.63 mmol) dibromoketone **22**, anhydrous lithium chloride (80 mg, 1.90 mmol), and dry dimethylformamide (15 mL). After work-up we isolated 138 mg (93%) of benzotropone **23**.

Reaction of 7-bromo-5*H*-benzo[*a*]cyclohepten-5-one (20) with LiCl: The reaction was carried out as described above by using 150 mg (0.64 mmol) benzotropone **20**, anhydrous lithium chloride (54 mg, 1.28 mmol), and dry

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dimethylformamide (15 mL) and we obtained 117 mg (96%) **7-chloro-5*H*-benzo[*a*]cyclohepten-5-one (24)**.

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