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A New Synthesis of Bromobenzotropones: Oxidation of 8-Bromo-5H-Benzo[a]cycloheptene

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The oxidation of 8-bromo-5H-benzo[a]cycloheptene with some oxidation reagents was studied. 2,3- and 4,5-benzotropone derivatives were obtained. The structures of the bromobenzotropones were determined by ^{1}H- and ^{13}C-NMR data.

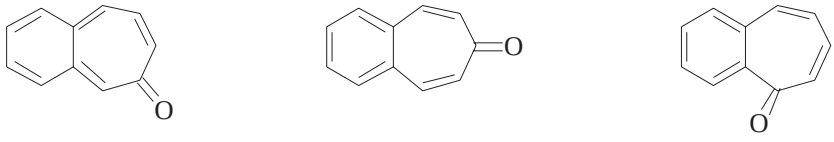
Key Words: Tropone, benzotropone, bromobenzotropone, selenium dioxide and chromium trioxide oxidation.

Introduction

Tropone and its derivatives have fascinated organic chemists for well over 50 years[1]. Early theoretical work suggested that tropone may represent a new type of aromatic system, which would possess resonance stabilization due to fact that it has Huckel's sextet electron system.

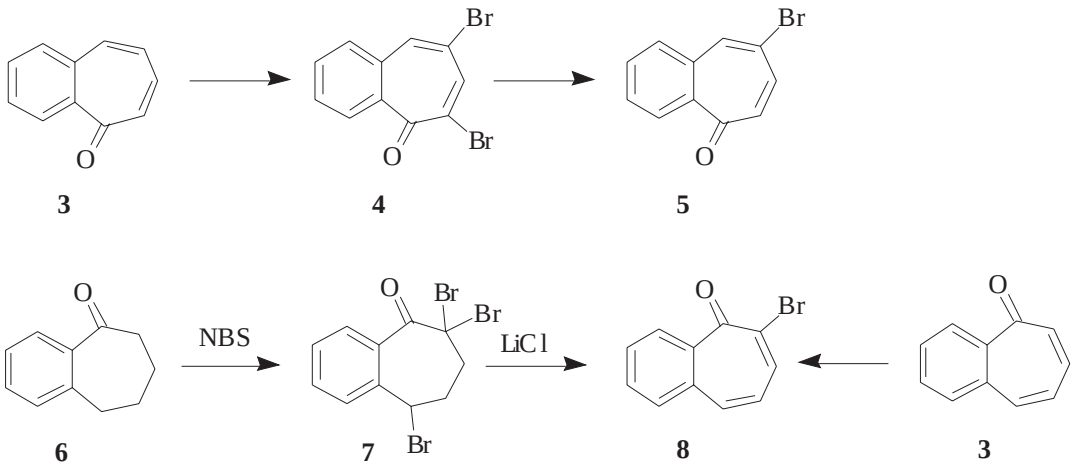
Another significant reason for the interest in the ring systems of tropones is that they represent the key structural element in a wide range of natural products, many of which display interesting biological activity. According to a very recent count, more than about 90 naturally occurring troponoids have been reported in the literature[1]. 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]. In particular, the rich variety of pericyclic reactions that tropones and tropolones can engage in has provided the synthetic chemist with a number of effective strategies for the preparation of natural products and related molecules. 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.

In the case of benzotropone systems, three isomers are possible: 3,4-benzotropone (**1**) 4,5-benzotropone (**2**) and 2,3-benzotropone (**3**).



1 **2** **3**

Inspection of these structures reveals that **1** may be regarded as a derivative of dimethylenecyclohexadiene and it is an unstable compound at room temperature. Despite extensive studies on troponoid compounds, information on 3,4-benzotropone (**1**) is surprisingly scarce. This molecule has recently been prepared and characterized as its dimer by Tsuji et al.[2] However, there are various methods[3] known for the preparation of 4,5– (**2**), and 2,3-benzotropone (**3**). Several procedures for the synthesis of halo-benzotropones have also been reported. These methodologies for the preparation of bromo-benzotropone are of rather limited use because of the multi steps and low yields. Ebine et al.[4] have developed a multi-step route for the synthesis of **5** starting from 2,3-benzotropone (**3**), and Collington and Jones[5] have synthesized **8** starting from benzosuberon (**6**) (Scheme 1).

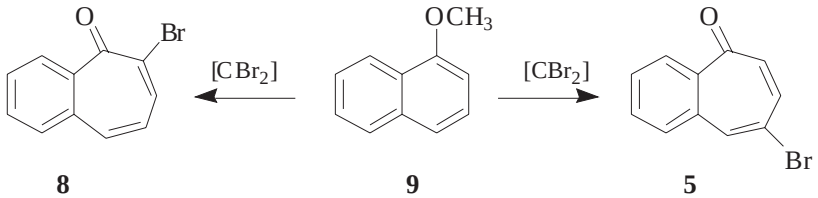


3 **4** **5**

6 **7** **8** **3**

Scheme 1

Parham[6], Saraf[7] and Saxena[8], independently, reported one-step preparation of **8** (and/or choloro derivative) starting from 1-methoxynaphthalene **(9)** by using different dibromocarbene reagents. However, Moncur and Grutzner[9] observed that the reaction of dibromocarbene with 1-methoxynaphthalene **(9)** yielded **5** rather than **8** (Scheme 2).

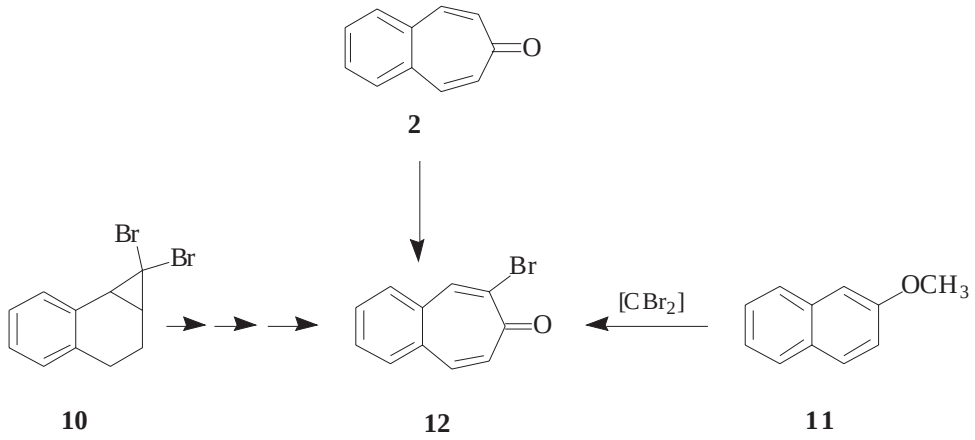


8 **9** **5**

Scheme 2

Similarly, the same researchers[6–8] have also examined the addition of dibromocarbene to 2-methoxynaphthalene (**11**) and obtained **12** in an average yield. Suzuki[10] achieved the synthesis of **12** starting from 2,3-

benzotropone (**2**). Lastly, we have reported an alternative synthesis for **12** from the carbene adduct **10** in three steps[11](Scheme 3).

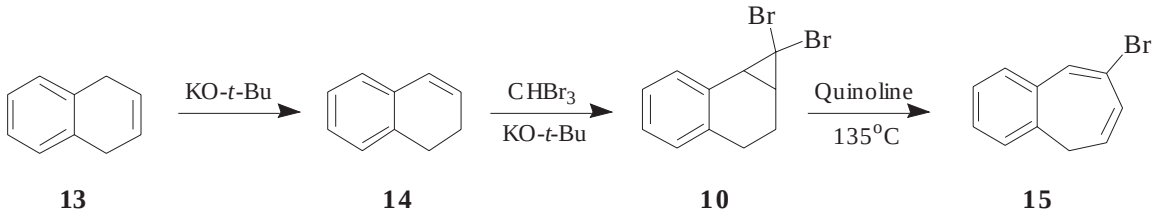


Scheme 3

In this paper we describe an alternative route leading to the synthesis of various bromobenzotropone derivatives, involving oxidation of 8-bromo-5*H*-benzo[*a*]cycloheptene (**15**).

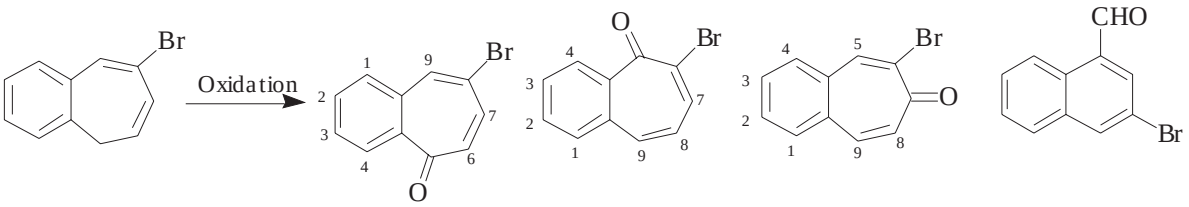
Results and Discussion

The starting material **15**[12] was prepared by the addition of dibromocarbene to 1,2-dihydronaphthalane (**14**), which was obtained by base-catalyzed isomerization of **13**. Phase-transfer catalyzed dibromocarbene addition to **14**, followed by thermal ring-opening reaction in the presence of quinoline, provided monobromide **15** in high yield (Scheme 4).



Scheme 4

The oxidation of 8-bromo-5*H*-benzo[*a*]cycloheptene (**15**) in aqueous acetic acid using chromium trioxide gave three products: 8-bromo-5*H*-benzo[*a*]cyclohepten-5-one (**5**) (21%), 6-bromo-5*H*-benzo[*a*]cyclohepten-5-one (**8**) (6.1%) and 6-bromo-7*H*-benzo[*a*]cyclo-hepten-7-one (**12**) (5.3%). From the oxidation of **15** with chromium trioxide in methylene chloride and pyridine, we obtained **5** (51%), **8** (16.1%) and **12** in 8% yield. However, the oxidation of **15** with selenium dioxide in aqueous dioxane resulted in the formation of four products: **5** (13.5%) **8** (8.3%), **12** (6.1%) and a ring-contracted product, 3-bromo-1-naphthaldehyde (**16**) in 9.5% yield (Scheme 5). The products were separated by column chromatography.



15 **5** **8** **12** **16**

Oxidation reagent				
a) CrO_3 / AcOH	21%	6.1%	5.3%	--
b) CrO_3 / Pyridine	51%	16.1%	8%	--
c) SeO_2 / H_2O	13.5%	8.3%	6.1%	9.5%

Scheme 5

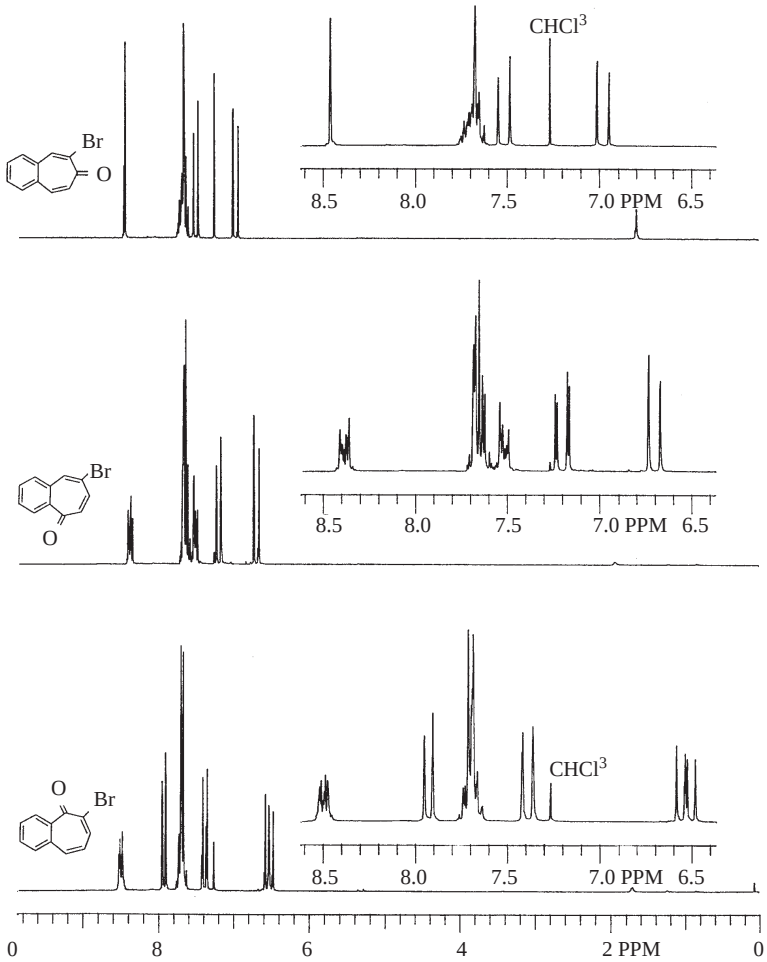
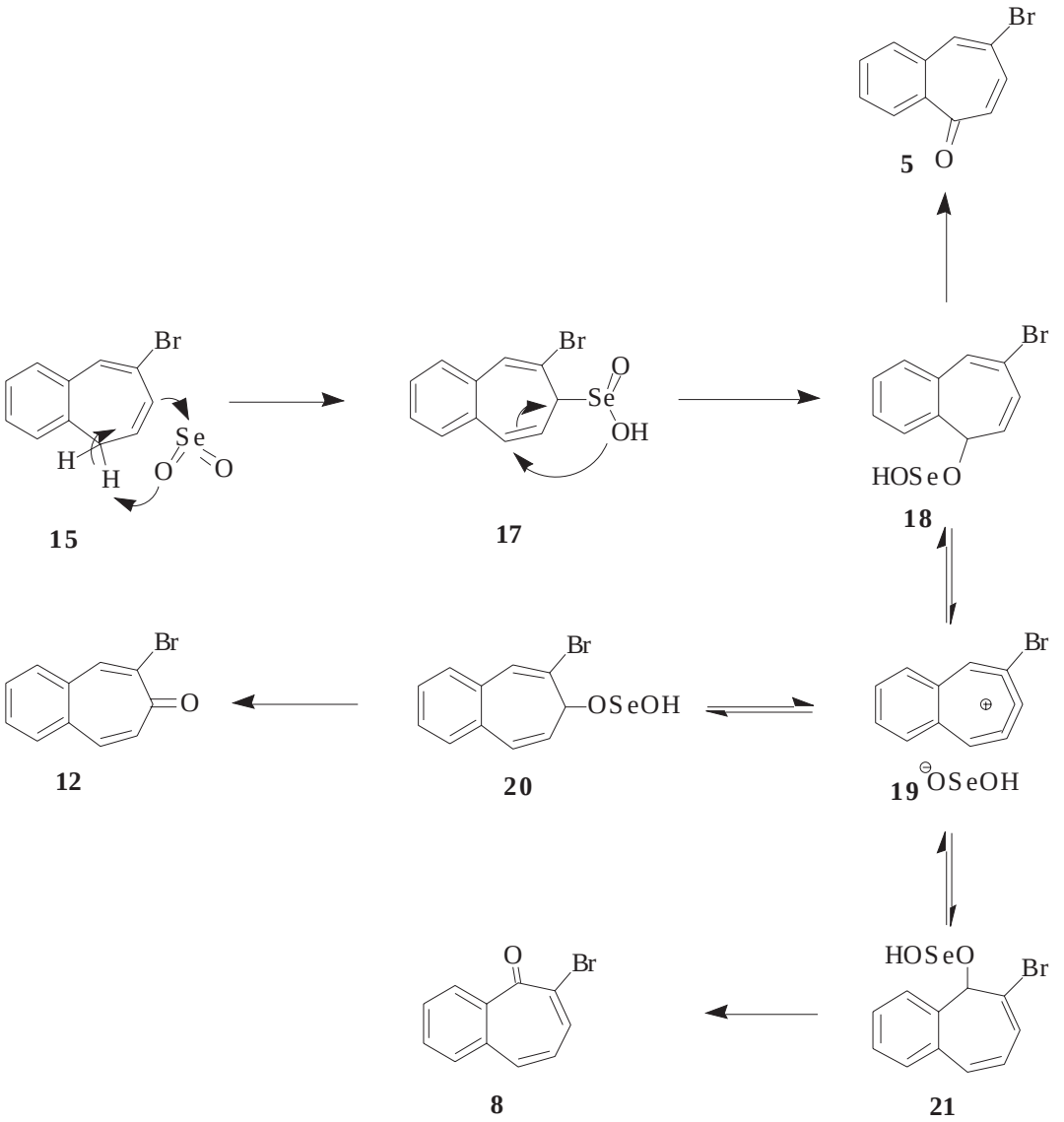


Figure. 200 MHz ^{1}H-NMR spectra of bromobenzotropones **5, 8** and **12** (in $CDCl_3$)

The structures of the products were determined on the basis of spectral data. The ^{1}H-NMR spectrum of **12** shows a sharp singlet for proton H_5 at 8.46 ppm. The other olefinic protons (H_8 and H_9) gave rise

to an AB system ($J_{8,9}$=12.8 Hz) which is peculiar to typical α,β-unsaturated ketones. The other spectral data were also in accord with the formulation. The structures of **5** and **8** were distinguished easily. The vicinal olefinic protons of **5** appear as an AB system centred at 6.70 ppm (H_6, $J_{6,7}$=12.8 Hz) 7.20 ppm (H_7, $J_{6,7}$=12.8 and $J_{7,9}$=2.2 Hz). Proton H_9 resonates at 7.67 ppm as a doublet ($J_{7,9}$=2.2 Hz). The low-field resonance (8.4 ppm) of one of the aromatic protons is an indication that the carbonyl group is located at the α–position to the benzene ring. 6-Bromo-5*H*-benzo[*a*]cyclohepten-5-one (**8**) shows an entirely different NMR spectrum. The high field resonance (6.53 ppm) of the olefinic protons shows a splitting of a doublet of doublets. The analysis of these systems reveals two different coupling constants ($J_{8,9}$=11.5 and $J_{7,8}$=9.1 Hz), which are in agreement only with the vicinal location of the three olefinic protons. The fact that one of the aromatic protons appears at very low field (8.4 ppm) is in agreement only with structure **8**.

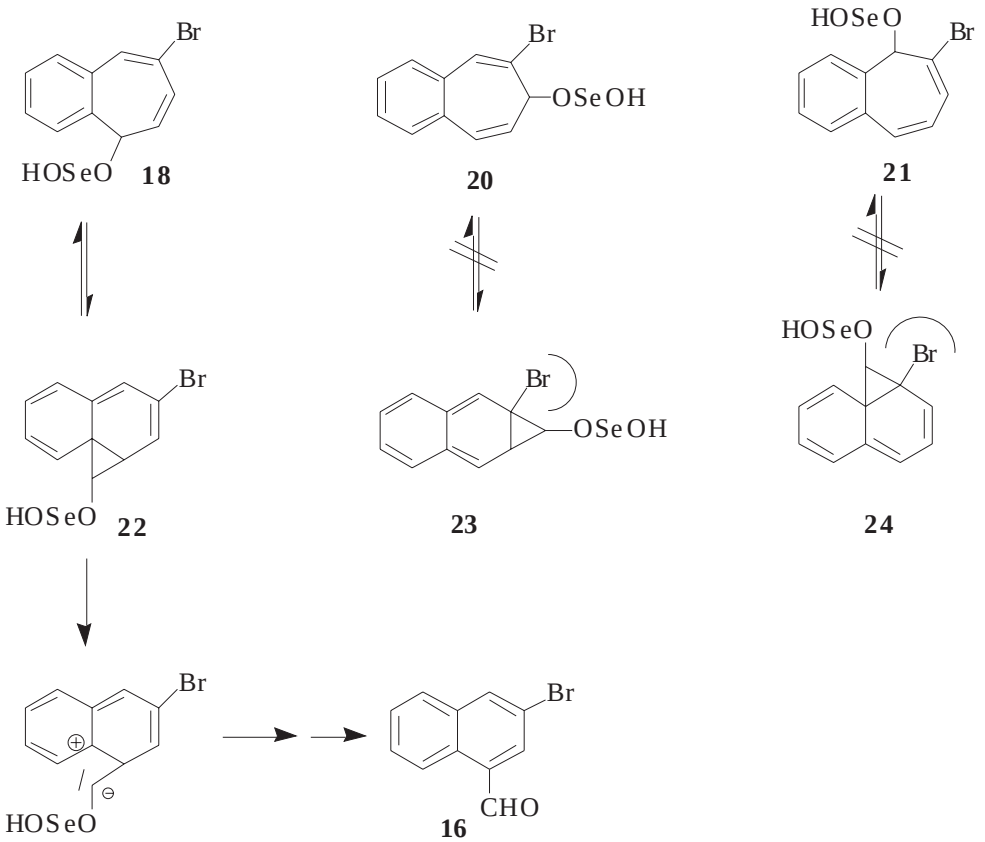


Scheme 6

The structure of aldehyde **16**, which is observed only in the SeO_2 oxidation of **15**, was also determined by NMR data. It is noteworthy that proton H_8 resonates at low field (9.12 ppm) because of the α-position

of the aldehyde group. In addition the coupling constant (J=2.1 Hz) extracted from the resonance signal of the proton H_2 confirms the *meta* position of the bromine atom.

The metal-mediated oxidation of organic compounds has been studied extensively[14]. The oxidation with chromic oxide involves hydroxylation of methylene and methine groups, conversion of methylene groups into carbonyls, oxidation of aromatic compounds and phenols to quinones and oxidation of alkenes to ketones[14]. However, the most important applications of selenium dioxide oxidation are conversions of alkenes into allylic alcohols, which can be further oxidized to the corresponding ketones by forming stable conjugated systems.[15] The mechanism of selenium dioxide-mediated allylic oxidation has been thoroughly studied[16]. It is thought that this reaction occurs by an initial ene reaction of SeO_2 with the alkene to form selenic acid **17**. This intermediate then undergoes a [2,3]sigmatropic shift to form selenate **18**, which is readily cleaved to form the corresponding allylic alcohol. In the oxidaton reaction of **15** with either CrO_3 or SeO_2, we assume that the initially formed selenate **17** or the corresponding chromate derivative undergoes rearrangement to form the stable tropylium cation **19**, which allows the distribution of selenate intermediates. Such equilibriums during the selenate and chromate oxidations are responsible for the formation of substituted bromo-benzotropone derivatives **5**, **8** and **12**.



Scheme 7

For the formation of the naphthalene derivative **16** we propose the following mechanism (Scheme 7). The formed selenates are part of a cycloheptatriene system. It is well established that the cycloheptatriene unit is in equilibrium with its valance isomer norcaradiene[17]. All three intermediates **18**, **20**, and **21** could be in equilibrium with their valance isomers norcaradienes **22, 23** and **24**, respectively. Inspection of the

formed norcaradiene structures reveals that the formation of norcaradienes **23** and **24** is prevented by steric interactions between the bulky bromine atom and the other group since the is bromine directly attached to the cyclopropane ring. However, norcaradiene **22,** free of any steric repulsion, can easily rearrange to the corresponding naphthalene derivative **16**, where the *meta* configuration is determined by the configuration of the starting material.

In summary, we developed a simple and inexpensive synthetic method for the preparation of some bromo benzotropone derivatives. Isomer **5** can in particular be synthesized in high yield. Further transformations (substitution of bromine) open up an entry to the synthesis of the substituted benzotropone derivatives.

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 (50)- and 60-MHz spectrometers. Apparent splittings are given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminium plates.

The CrO_3 oxidation of 8-bromo-5*H*-benzo[*a*]cycloheptene (15) in aqueous acetic acid: To a magnetically stirred solution of monobromide **15**[12] (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 over 30 min. The solution was stirred for 3 h at 10°C and for an additional 19 h at RT. The mixture was extracted with ether (3X80 mL). The extract was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed over silica gel (90 g), with hexane/ethyl acetate (90:10) as the eluent.

First fraction, **8-bromo-5*H*-benzo[*a*]cyclohepten-5-one (5):** (223 mg, 21%), mp 106°C, pale yellow crystals from methylene chloride/hexane (1:1). Lit[4]. mp: 102-103.5°C, ^{1}H-NMR (200 MHz, $CDCl_3$): 8.39 (m, 1H, H_4,), 7.67 (d, $J_{7,9}$=2.2 Hz, 1H, H_9) 7.66-7.49 (m, 3H, H_{aryl}), 7.20 (dd, A part of AB system, $J_{6,7}$=12.8, $J_{7,9}$=2.2, 1H, H_7), 6.70 (d, B part of AB system, $J_{6,7}$=12.8, 1H, H_6). ^{13}C-NMR (50 MHz, $CDCl_3$): 187.7, 141.1, 139.5, 138.57, 135.4 135.2, 133.9, 133.3, 131.3 (2C), 121.9. IR (KBr, cm^{-1}): 3055, 1620, 760.

Second fraction, **6-bromo-5*H*-benzo[*a*]cyclohepten-5-one (8):** (65 mg, 6.1%), mp: 78-79°C. Lit.[5] mp: 79-81°C. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.49 (m, 1H, H_4), 7.91 (bd, A part of AX system, $J_{7,8}$=9.1, $J_{7,9}$¡1.0 Hz, 1H, H_7), 7.76-7.64 (m, 3H, H_{aryl}), 7.39 (bd, A part of AX system, $J_{8,9}$=11.5, $J_{7,9}$¡1.0 Hz, 1H, H_9), 6.53 (dd, X parts of AX systems, $J_{8,9}$=11.5, $J_{7,8}$=9.1 Hz, 1H, H_8), ^{13}C-NMR (50 MHz, $CDCl_3$): 182.8, 139.8, 138.8, 136.2, 135.5, 134.2, 133.9, 133.1, 132.4, 131.7, 124.8. IR (KBr, cm^{-1}): 3090, 3049, 3000, 1601, 1576, 1471, 1357, 1334, 1259, 1002.

Third fraction, **6-bromo-7*H*-benzo[*a*]cyclohepten-7-one (12):** (56 mg, 5.3%), mp 138°C, as pale yellow crystals from methylene chloride/hexane (2:1), Lit. mp: 134[10], 142-143[7], 135[8]°C. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.46 (s, 1H, H_5), 7.75-7.62 (m, 4H, aryl), 7.52 (d, A-part of AB-system, $J_{8,9}$=12.8 Hz, 1H, H_9), 6.98 (d, B-part of AB-system, $J_{8,9}$=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 CrO_3 oxidation of 8-bromo-5*H*-benzo[*a*]cycloheptene (15) 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±5°C was added dropwise a solution of the monobromide **15** (1.0 g, 4.52 mmol) in 10 mL methylene chloride over 15 min. This solution was stirred for 2 h at 0 ±5°C and for an additional 46 h at RT. The solvent (pyridine and methylene chloride) was removed under reduced pressure. 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 and water and dried over $MgSO_4$. After removal of the solvent, the residue was purified as described above and three compounds were isolated: **5** (542 mg, 51%), **8** (171 mg, 16.1%) and **12** (85 mg, 8%) in that order.

The SeO_2 oxidation of 8-bromo-5*H*-benzo[*a*]cycloheptene (15) in dioxane: A mixture of monobromide **15** (1.0 g, 4.52 mmol), SeO_2 (1.51g, 13.60 mmol), KH_2PO_4 (0.2 g,1.47 mmol), dioxane (20 mL) and H_2O (1.35 g) was gently refluxed for 60 h. After the removal of dioxane under reduced pressure, 100 mL chloroform was added to the residue. The solution was filtered to remove precipitated Se. The extract was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel (90 g), with hexane/ethyl acetate (90:10) as the eluent.

First fraction, **3-bromo-1-naphthaldehyde (16):** (101 mg, 9.5%), mp 58°C, colourless crystals from methylene chloride/hexane (1:3). ^{1}H-NMR (200 MHz, $CDCl_3$): 10.30 (s, 1H, aldehyde), 9.12 (m, 1H, H_8), 8.19 (bd, $J_{2,4}$=2.1, 1H, H_4), 7.99 (bd, $J_{2,4}$=2.1, 1H, H_2), 7.82-7.55 (m, 3H, H_5 , H_6, H_7), ^{13}C-NMR (50 MHz, $CDCl_3$) 192.4, 139.1, 137.7, 135.5, 133.2, 129.8, 129.5, 128.4, 128.1, 125.4, 119.0. Anal. Calcd. for $C_{11}H_7BrO$: C, 56.20; H, 3.00. Found: C, 56.37, H, 3.03. IR (KBr, cm^{-1}): 2855, 2844, 2800, 2738, 2707, 1685, 1567, 1500, 1363, 1212. Second, third and fourth fractions are: **5** (145 mg, 13.5%), **8** (88 mg, 8.3%) and **12** (65 mg, 6.1%) in that order.

Acknowledgements

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