A Ring Expansion Route to Benzo Substituted Medium- and Large-Ring Systems. Synthesis of *trans*-7,8-Benzocyclododeca-5,7-dien-1-one

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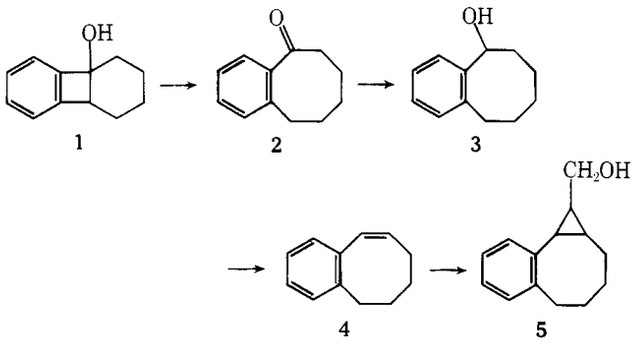
trans-7,8-Benzocyclododeca-5,7-dien-1-one (**9**) has been prepared in 11 steps from cyclohexanone using benzyne to generate 2,3-benzocyclooct-2-en-1-one which is converted to a cyclopropylcarbinyl alcohol. Acid-catalyzed rearrangement effects two-carbon ring expansion which leads to the precursor for the final siloxy-Cope two-carbon ring expansion.

The title compound has been prepared as part of an exploration of possible methods to prepare certain hormone model systems by ring expansion methods. The compound lacks some of the functionality which is ultimately desired; however, its synthesis demonstrates the feasibility of the general approach and the success of the two key ring expansions.

Results and Discussion

2,3-Benzocyclooct-2-en-1-one (**2**) was prepared via the cyclobutanol **1** by a modification of the reaction discovered by Caubere's group[1] in which the enolate of cyclohexanone is reacted with benzyne to give **1**. In our hands, the Girards reagent separation of 2-phenylcyclohexanone from **1** only gave good results if the extraction stage was done quickly under cold, neutral conditions. Otherwise the Girards adduct seemed to revert back to ketone which contaminated **1**. The rearrangement of **1** to **2** was carried out with potassium hydride in THF rather than the originally described sodium amide and HMPA which are more expensive and treacherous to work with. The overall yield is comparable to that reported.[1]

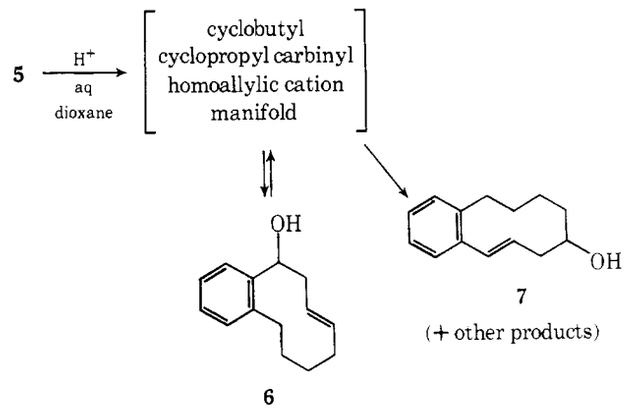
Sodium borohydride reduction smoothly gave 2,3-benzocyclooct-2-en-1-ol (**3**) which was converted to cycloalkene **4**



1 2 3 4 5

with polyphosphoric acid. This method gave the purest product of several methods tried, although some improvement may be possible since the vacuum transfer left behind a dimeric ether by-product. The addition of ethyl diazoacetate followed by lithium aluminum hydride reduction proceeded to **5** (>85% anti) in a straightforward manner as described earlier for the nonbenzo analog.[2] The structure of *anti*-**5** was ascertained mainly by NMR analysis including decoupling experiments that showed that the benzylic cyclopropyl proton has both cis and trans coupling constants (J = 8 and 5 Hz).

The acid-catalyzed rearrangement of bicyclo[6.1.0]nonane-9-methanol was shown earlier[2] to undergo an unprecedented rearrangement to cyclodec-3-en-1-ol. When **5** is treated under similar conditions, the rearrangement proceeds predominantly to **6**, which unfortunately is the wrong cyclodecenol for the next stage. Continued heating with increased acid concentration gives the less reactive alcohol **7** as the dominant product, but other products are also formed. Definite structure proofs were not possible on the minor components but some cyclobutanol product is clearly formed (1780-cm^{-1} band for the corresponding ketone) as well as an isomer having a cis double bond next to the benzene ring (J = 10 Hz). Most of the minor products were readily removed by dry column chromatography except for the cyclobutanol which had a similar R_f value. The structures of **6** and **7** follow readily from the spectra (see Experimental Section).



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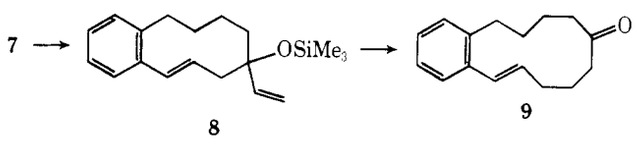
The conversion of **7** to the siloxy-Cope precursor followed the standard steps used previously[3] and the spectra confirm the expected structures. The thermolyses of **8** were similar to earlier studies although the yields were not quite as high.[4,5] Only two-carbon ring expansion was observed which is reasonable[6] since ring contraction would lead to a more strained system and the [3,3] shift product would be higher in energy than **9**. The structure of **9** was assigned from the spectra and from decoupling experiments on the Eu(fod)$_3$ shifted NMR spectrum which demonstrated that there are three methylene groups between the carbonyl and the double bond.



8 9

A complete kinetic study was not carried out but two- and three-point rate measurements at 243.7 °C ($10^5 k = 6 \pm 1$ s^{-1}) and at 274.1 °C ($10^4 k = 4 \pm 2$ s^{-1}) give activation parameter estimates (E_a = 42 kcal/mol, log A = 13) which are similar to those for the nonbenzo analogue.[5]

Experimental Section

General. Spectral measurements utilized Beckman IR8, Perkin-Elmer 727B, Varian Associates HA100, and CEC 110B instruments.[7] Analytical gas–liquid chromatography (GLC) used a Varian Aerograph Model 1200 instrument with capillary or high efficiency[8] 0.125 in. columns listed: (A) 0.01 in. × 100 ft DEGS, (B) 0.125 in. × 10 ft 10% DEGS on Chromosorb W, (C) 0.125 in. × 4 ft 3% AN 600 on Chromosorb G, (D) 0.125 in. × 4 ft 7% DEGS on Chromosorb W, (E) 0.125 in. × 2.75 ft 9% OV101 on Chromosorb W.

Preparative GLC used a Varian Aerograph A90 with the columns listed: (F) 0.25 in. × 9.5 ft 3% AN 600 on Chromosorb G.

7,8-Benzobicyclo[4.2.0]oct-7-en-1-ol (1). Alcohol **1** was prepared by the method outlined by Caubere.[1] Sodium amide was prepared from 58 g (2.5 mol) of sodium.[9] The ammonia was allowed to evaporate under nitrogen and 800 ml of dry THF was added. A solution of 100 ml (1.0 mol) of cyclohexanone in 200 ml of THF was dripped in with stirring so as to maintain a temperature of 30–35 °C (about 45 min). The reaction mixture was warmed to 40 °C for 2 h and then cooled to −5 °C at which time 56 g (0.35 mol) of bromobenzene was added. The −5 °C temperature was maintained for 14.5 h (no bromobenzene left in the GLC, column A) at which time 100 ml of water was added dropwise at 0 °C. The reaction mixture was poured into 300 ml of HCl and ice and 500 ml of ether was added. The organic layer was washed with water, 5% HCl, 10% sodium bicarbonate, and saturated sodium chloride. Drying ($MgSO_4$) and solvent removal gave 124 g of crude product. A second 500-ml ether extraction of the aqueous layer gave an additional 3.7 g which was 82% cyclohexanone. GLC analysis of the 124-g portion indicated 45% cyclohexanone, 25% 2-phenylcyclohexanone, and 30% of alcohol **1**. Most of the cyclohexanone was removed by Kugelrohr distillation and then the product was transferred in the same way (100 °C air bath, 0.1 mm) which gave 36.2 g of solid (59% of **1** by GLC). The ketones were removed by heating the mixture at 80 °C for 45 min with 22g of Girard Reagent T in 350 ml of ethanol and 39 ml of acetic acid. Two-thirds of the ethanol was removed and the mixture was poured into a large beaker containing 1 l. of ether, 120 g of sodium bicarbonate, and 1 l. of ice–water. The organic layer was quickly separated in a separatory funnel and washed with bicarbonate and sodium chloride solutions. If the separation was not done quickly, near 0 °C, near neutral pH, the ketones were less completely removed. The separation gave 17 g of **1** (97% pure by GLC). Recrystallization from hexane gave pure **1**, mp 108.5–109.5 °C (lit.[1] 108–109 °C).

2,3-Benzocyclooct-2-en-1-one (2).[10] A suspension of 5.3 g of potassium hydride (Ventron) in 100 ml of hexane and 100 ml of dry THF was stirred and 5.08 g of **1** dissolved in 100 ml of dry THF was added dropwise over 45 min. The reaction mixture was stirred for an additional 1 h at room temperature and was quenched with 30 ml of water. The THF was removed and the aqueous layer was extracted with three 50-ml portions of ether which were washed with water and dried ($MgSO_4$). The 4.8 g of product was transferred by Kugelrohr (73% of **2** by GLC, column C) and then purified on a 30 by 2 in. silica dry column ($CHCl_3$) which gave 3.3 g of **2** (60% yield, one peak on GLC) which could be crystallized from petroleum ether, mp 54–55 °C (lit.[1] 56–60 °C).

2,3-Benzocyclooct-2-en-1-ol (3). Sodium borohydride reduction carried out in the same way as described for related compounds[11] gave **3** in 95% yield: IR (CCl_4) 3620, 2950, 1430, 1020, 1070, 750, 690 cm^{-1}; NMR (CCl_4) δ 1.2–2.2 (m, 9 H), 2.7 (m, 2 H), 5.1 (m, 1 H), 7.0–7.6 (m, 4 H); high-resolution mass spectrum, 176.121 (calcd for $C_{12}H_{16}O$ (M^+), 176.120).

1,2-Benzocycloocta-1,3-diene (4). A mixture of 39 g of phosphorus pentoxide and 98 ml of 85% orthophosphoric acid was warmed to 95 °C for 15 min at which time 6.8 g (0.039 mol) of **3** was added. The reaction mixture was kept at 95 °C for 35 min and then poured over ice and extracted into ether. The organic layer was washed with bicarbonate and brine and dried ($MgSO_4$). Concentration and Kugelrohr distillation give 3.73 g (61% yield) of **4** (95% pure by GLC): IR (CCl_4) 3027, 2930, 2860, 1480, 1445, 1075, 1050, 970, 770, 750, 720, 695 cm^{-1}; NMR (CCl_4) δ 2.1–2.3 (m, 2 H), 1.5–1.8 (m, 4 H), 2.8 (m, 2 H), 5.8 (d of t, J = 12 and 6 Hz, 1 H), 6.4 (d, J = 12 Hz, 1 H), and 7.1 (s, 4 H); high-resolution mass spectrum, 158.109 (calcd for $C_{12}H_{14}$ (M^+), 158.110).

2,3-Benzobicyclo[6.1.0]non-2-ene-9-methanol (5). A mixture of 75 mg of anhydrous cupric sulfate and 3.7 g (0.023 mol) of **4** was stirred under nitrogen at 70 °C as 13 ml of ethereal ethyl diazoacetate[2] (ca. 0.1 mol) was dripped in over 2 h. After 2.5 h at 75 °C the dark brown solution was filtered, concentrated, and purified by alumina chromatography to give 3.6 g of the ester: IR (CCl_4) 3200, 2970, 2400, 1700, 1430, 1360, 1300, 1150, 1175, and 1050 cm^{-1}; NMR (CCl_4) δ 0.4–0.7 (m, 1 H), 1.22 (t, J = 7 Hz, 3 H), 1.1–2.3 (m, 7 H), 2.5–3.1 (m, 3 H), 4.2 (q, J = 7 Hz, 2 H), 7.0 (s, 4 H).

A solution of 2.74 g (0.011 mol) of ester in 10 ml of ether was dripped into 2 g (0.05 mol) of $LiAlH_4$ in 40 ml of ether and stirring was continued for 16 h. The reaction mixture was quenched with 20% Rochell's salt, filtered, and dried ($MgSO_4$). Removal of solvent gave 1.92 g of **5** (54% yield from **4**, >85% anti): IR (CCl_4) 3315, 3050, 2910, 2850, 1470, 1430, and 1250 cm^{-1}; NMR (CCl_4) δ 0.7–2.2 (m, 10 H), 2.5–3.4 (m, 2 H), 3.4–3.7 (m, 2 H), 6.9 (s, 4 H); high-resolution mass spectrum, 202.135 (calcd for $C_{14}H_{18}O$ (M^+), 202.136).

Acid-Catalyzed Rearrangement of 5. A solution of 183 mg of **5**, 5 ml of *p*-dioxane, 1.2 ml of water, and 0.25 ml of 2.3 M perchloric acid was heated at 85–90 °C for 10 h, at which point 95% of **5** was gone (GLC analysis on column D, 180 °C). The reaction mixture was extracted into ether, washed with saturated $NaHCO_3$, and dried ($MgSO_4$). This gave five major components with retention times and percentages shown: 4.8 (14%), 6 (9%), 8.5 (5%), 11.2 (53%), and 13.6 (17%). The later two products were shown to be **6** and **7** (see below). When the acid concentration was doubled and heating continued for 26 h, the ratio of **6** and **7** changed from 3:1 to 1:10 [internal GLC standard experiments gave a 52% yield of **7** which was purified by dry column chromatography ($CHCl_3$ eluent) or GLC (column F, 200 °C)]. Pure **6** was shown to give mainly **7** under the same conditions.

The structure of **6** was shown to be *trans*-2,3-benzocyclodeca-2,8-dien-1-ol [IR (CCl_4) 3400, 2930, 2850, 2470, 2430, 2020, 970, 710 cm^{-1}; NMR δ 1.2–2.3 (m, 6 H), 2.4–2.8 (m, 5 H), 4.7–5.3 (m, 3 H), 6.97 (m, 3 H), 7.40 (m, 1 H)] from its spectra and those of the corresponding ketone: IR (CCl_4) 3000, 2920, 2850, 1680, 1430, 1240, 1010, 960, 720 cm^{-1}; NMR (CCl_4) δ 0.6–2.2 (m, 6 H), 2.3–2.6 (m, 2 H), 3.15 (d, J = 7 Hz, 2 H), 5.15 (d of t, J = 16, 7 Hz, 1 H), 5.33 (d of t, J = 16, 7 Hz, 1 H), 6.9–7.3 (m, 4); high-resolution mass spectrum, 200.119 (calcd for $C_{14}H_{16}O$ (M^+), 200.120).

The structure of **7** was shown to be *trans*-5,6-benzocyclodeca-3,5-dien-1-ol [IR (CCl_4) 3400, 3000, 2920, 2850, 1470, 2430, 1020, 970, 710 cm^{-1}; NMR (CCl_4) δ 1.2–2.5 (m, 7 H), 2.5–2.9 (m, 4 H), 3.77 (m, 1 H), 5.64 (m, 1 H), 6.92 (d, J = 16 Hz, 1 H), 7.32 (s, 4 H)] from its spectra and that of the corresponding ketone: IR (CCl_4) 3000, 2920, 2850, 1702, 1445, 1200, 1106, 980, 750 cm^{-1}; NMR (CCl_4) δ 1.3–2.4 (m, 4 H), 2.4–2.7 (m, 4 H), 3.15 (d, J = 8 Hz, 2 H), 5.42 (d of t, J = 16, 8 Hz, 1 H), 6.86 (d, J = 16 Hz, 1 H), 7.0–7.2 (m, 4 H); high-resolution mass spectrum, 200.119 calcd for $C_{14}H_{16}O$ (M^+), 200.120).

1-Trimethylsiloxy-1-vinyl-5,6-benzocyclodeca-3,5-diene (8). Jones oxidation[12] (54% yield) followed by reactions with vinylmagnesium bromide and Tri-Sil (70% yield) as described previously[3] gave **8**: IR (CCl_4) 3050, 3005, 2940, 2850, 1455, 1410, 1250, 1110, 1080, 1050, 980, 920, 880, 840 cm^{-1}; NMR (CCl_4) δ 0.03 (s, 9 H), 0.8–2.1 (m, 6 H), 2.37 (d, J = 7 Hz, 2 H), 2.3–2.8 (m, 2 H), 5.13 (d, J = 10 Hz, 1 H), 5.31 (d, J = 16 Hz, 1 H), 5.63 (d of t, J = 16, 7 Hz, 1 H), 6.05 (d of d, J = 10, 16 Hz, 1 H), 6.70 (d, J = 16 Hz, 1 H), 7.05 (s, 4 H); high-resolution mass spectrum, 300.194 (calcd for $C_{19}H_{28}OSi$ (M^+), 300.191).

Thermolyses of 8 were carried out at 243–293 °C in the gas phase in evacuated Pyrex ampules as described previously.[3] The product mixture was hydrolyzed[3] and analyzed by GLC (column F, 165 °C). This gave smooth conversion (52% yield by internal GLC standard) to *trans*-7,8-benzocyclododeca-5,7-dien-1-one (**9**): IR (neat) 3050, 3000, 2910, 2845, 1705, 1440, 1120, 970, 750 cm^{-1}; NMR δ 1.3–1.7 (m, 4 H), 1.7–2.1 (m, 2 H), 2.2–2.7 (m, 8 H), 5.55 (d of t, J = 16, 7 Hz, 1 H), 6.55 (d, J = 16 Hz, 1 H), 7.00 (s, 4 H); high-resolution mass spectrum, 228.153 (calcd for $C_{16}H_{20}O$ (M^+), 228.151).

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Registry No.—**2**, 829-14-1; **3**, 35448-00-1; **4**, 60676-30-4; **5**, 60676-31-5; **6**, 60676-32-6; **6** ketone, 60676-33-7; **7**, 60676-34-8; **7** ketone, 60676-35-9; **8**, 60676-36-0; **9**, 60676-37-1; ethyl 2,3-benzobicyclo[6.1.0]non-2-ene-9-carboxylate, 60676-38-2.

References and Notes

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(6) Only 10% of the [3,3] shift product is formed with the nonbenzo analogue. Since GLC separation is more difficult with these less volatile compounds, small amounts of [3,3] shift product or cis isomer of **9** could be missed if they were too small to see in the NMR spectrum.
(7) We thank the University of Oregon for the use of their instrument and Richard Weilesec for technical assistance.
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