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Registry No. **1a**, 24406-03-9; **1b**, 87302-52-1; **2**, 68926-81-8; **3**, 87249-20-5; **4**, 87249-21-6; **5**, 87249-22-7; **6**, 87304-45-8; **7**, 87249-23-8; **8**, 87249-24-9; **9**, 87249-25-0; **10**, 87304-46-9; **11**, 87226-67-3; $Cr(CO)_6$, 13007-92-6; methyl 4-(*p*-methoxyphenyl)-5-methylhexanoate, 87226-68-4; *trans*-7-methoxycalamenene, 87226-69-5; *cis*-7-methoxycalamenene, 87226-70-8; β-4-isopropyl-β-1-methyl-6-formyl-7-methoxy-1-tetralol, 87226-71-9; *cis*-7-methoxycalamenal, 87226-72-0.

Efficient Synthesis of Barbaralane

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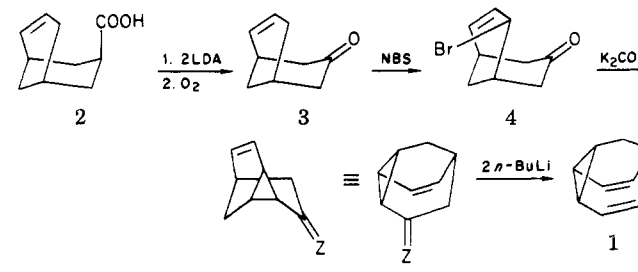
The properties of the barbaralane (tricyclo[3.3.1.$0^{2,8}$]-nona-3,6-diene) system (**1**) and its derivatives have been

1

of substantial interest since the ring system was first reported in 1963.[1] This system is one of several with fluxional character,[2,3] in which a degenerate Cope rearrangement occurs at ambient temperatures. Recently there has been renewed interest in the chemistry of these systems, particularly **1**, in which derivatives of the parent molecule have been used as substrates for spectroscopic[4–6] and mechanistic[7] investigations. Several groups have investigated the electronic states of derivatives of **1**, in light of the prediction[8,9] that with suitable substituents the system may exhibit homoaromatic character. While attempts to synthesize such a system are ongoing,[10,11] a derivative of **1** that shows this property has not yet been observed.

The two most widely recognized syntheses of **1** have not been especially convenient.[12,13] In both syntheses cyclopropanation is accomplished by carbene insertion into a preformed double bond. These approaches are characterized by one or more low-yield intermediate steps and the necessity of one or more complex separation steps. Other recent entries into the barbaralane system include the rearrangement of bicyclo[3.3.2] iron tricarbonyl cations[14] and the rearrangement of norbornadiene–carbene adducts,[15] but these routes do not proceed to the parent compound **1**.

Scheme I



5a, Z = O
b, Z = NNHTs

We now report a more generally useful synthesis of **1** and its derivatives under very mild conditions, one which does not depend on a carbenoid intermediate (Scheme I). The cyclopropane ring system is formed by way of a transannular ring closure before the diene system is in place. Thus treatment of 2-adamantanone (Aldrich) with sodium azide in methanesulfonic acid produced carboxylic acid **2** by the method of Sasaki, Eguchi, and Toru[16] in 80% yield. Using a variation of the method of Krishnamurthy and Fort,[17] oxidative decarboxylation of **2** was accomplished in 70% yield by treatment with 2.5 equiv of LDA at 0 °C followed by oxygenation of the resulting dianion at −78 °C. The intermediate α-hydroperoxy carboxylate was not isolated. Acid workup[16] afforded bicyclic ketone **3**. The remaining 30% of the product was unchanged **2**, which was recycled.

Allylic bromination of **3** with *N*-bromosuccinimide gave bromo ketone **4** as the only product in nearly quantitative yield. Successful bromination required the use of properly purified NBS. The use of recrystallized NBS that had been allowed to air-dry for at least 3 days afforded essentially only **4**. However, if either unpurified reagent or rigorously purified reagent was used, quantities of product resulted (20–30% of the product mixture) in which bromination occurred at the ketone α-positions. Such a mixture could not be purified by simple recrystallization but had to be subjected to a chromatographic separation. The stereochemical assignment of the bromine as exo was made on the basis of previous reports,[11] which have shown that allylic bromination in related systems proceeds by exclusive exo attack, and on the basis of NMR evidence, i.e., no evidence of epimers in the ^{13}C NMR spectrum.

Bromo ketone **4** is ideally set up for base-catalyzed ring closure to tricyclic ketone **5a**, which is a direct precursor to **1**. Indeed, treatment of **4** with any of several bases, including NaOMe or K_2CO_3, produced **5a** in >95% isolated yield. Conversion of **5a** to **1** in 59% purified yield was then easily accomplished by using *n*-BuLi in THF by way of a Bamford–Stevens type elimination[18] of the corresponding

(1) Lambert, J. B. *Tetrahedron Lett.* **1963**, 1901.
(2) Schroder, G.; Oth, J. F. M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 414 and references cited therein.
(3) Cheng, A. K.; Anet, F. A. L.; Mioduski, J.; Meinwald, J. *J. Am. Chem. Soc.* **1974**, *96*, 2887.
(4) Greifenstein, L. G.; Lambert, J. B.; Broadhurst, M. J.; Paquette, L. A. *J. Org. Chem.* **1973**, *38*, 1210.
(5) Engdahl, C.; Jonsall, G.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* **1979**, 626.
(6) Engdahl, C.; Ahlberg, P. *J. Am. Chem. Soc.* **1979**, *101*, 3940.
(7) Kumagai, T.; Ohba, Y.; Mukai, T. *Tetrahedron Lett.* **1982**, *23*, 439.
(8) Hoffmann, R.; Stohrer, W.-D. *J. Am. Chem. Soc.* **1971**, *93*, 6941.
(9) Dewar, M. J. S.; Nahlovska, Z.; Nahlovsky, B. D. *J. Chem. Soc. D* **1971**, 1377.
(10) Quast, H.; Gorlach, Y.; Stawitz, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 93.
(11) Quast, H.; Christ, J.; Gorlach, Y.; von der Saal, W. *Tetrahedron Lett.* **1982**, *23*, 3653.
(12) Doering, W. v. E.; Ferrier, B. M.; Fossel, E. T.; Hartenstein, J. H.; Jones, M., Jr.; Klumpp, G.; Rubin, R. M.; Saunders, M. *Tetrahedron* **1967**, *23*, 3943.
(13) Biethan, U.; Klusacek, H.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 176.
(14) Abramson, S.; Eisenstadt, A. *Tetrahedron* **1980**, *36*, 105.
(15) Jefford, C. W.; Rossier, J.-C.; Zuber, J. A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 549.
(16) Sasaki, T.; Eguchi, S.; Toru, T. *J. Org. Chem.* **1970**, *35*, 4109.
(17) Krishnamurthy, V. V.; Fort, R. C., Jr. *J. Org. Chem.* **1981**, *46*, 1388.

0022-3263/83/1948-3858$01.50/0

tosylhydrazone **5b**. Other base/solvent combinations (e.g., MeLi in THF, MeLi in ether, or *n*-BuLi in ether) afforded substantially lower product yields and more difficulty in workup.

The product yield of **1** in the final step has not been optimized. It is our belief that this low yield is due in part to product volatility, and with more rigorous efforts to isolate and contain **1**, it is likely that the yield could be improved further. Nevertheless, the overall isolated yield of **1** was 42% from 2-adamantanone when the quantity of recovered **2** is considered (30% without recovery). Considering the ease and mildness of conditions with which the synthesis is carried out as well as the absence of complex product mixtures, we propose this method as the one of choice for the synthesis of **1**. Moreover, ketone **5a** may represent a useful intermediate for the production of general substitution at the 3-position of **1**, as well as for elaboration of other polycyclic ring systems. Further studies of the nature of such systems are currently underway.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from calcium hydride. Hexamethylphosphoramide (HMPA) was distilled from barium oxide. NBS was recrystallized from water and air-dried for at least 3 days prior to use. ^{1}H NMR spectra were recorded on a Perkin-Elmer R24B instrument operating at 60 MHz. ^{13}C NMR spectra were recorded on a Bruker WM500 spectrometer, and IR spectra were recorded on a Beckman 620MX spectrometer. Assignment of ^{13}C NMR resonances was accomplished by using gated decoupling techniques. Elemental analyses were performed by Baron Consulting, Orange, CT.

Bicyclo[3.3.1]non-6-ene-*endo*-3-carboxylic acid (2) was synthesized in 80% yield starting from 2-adamantanone (Aldrich) by a modification of the method of Sasaki, Eguchi, and Toru.[16] Spectra were identical with published values.[16]

Bicyclo[3.3.1]non-6-en-3-one (3). To a solution of 10.0 g (0.06 mol) of **2** in 100 mL of THF at 0 °C under argon was added a solution of lithium diisopropylamide, prepared by mixing 75 mL of THF, 0.151 mol of diisopropylamine, and 0.151 mol of *n*-butyllithium, at 0 °C. The dianion complex occasionally tended to precipitate from solution. When this occurred, addition of up to 50 vol % of HMPA effected solution. The solution was stirred for 3 h, the temperature was reduced to −78 °C, and dry oxygen was bubbled through the reaction mixture for 1 h. Water (6 mL) was added and the temperature of the solution was gradually increased to 25 °C. The mixture was then stirred for 8 h, poured into cold 10% HCl, and then extracted with several portions of ether. The ether extracts were washed with 10% Na_2CO_3, dried over $MgSO_4$, and concentrated to yield 5.73 g (70%) of a pale yellow semisolid, which was sublimed at 100 °C (5 mm) to give **3** as a white solid: mp 99–101 °C; IR (Nujol) 3020 and 1719 cm^{-1}; NMR ($CDCl_3$) δ 1.6–2.9 (m, 8 H, ring Hs), 5.6 (br s, 2 H, HC=CH); mass spectrum, M$^+$ found *m/e* 136.0887 (calcd for $C_9H_{12}O$, *m/e* 136.0888).

(18) Shapiro, R. H. *Org. React.* (*N.Y.*) **1976**, *23*, 405.

***exo*-8-Bromobicyclo[3.3.1]non-6-en-3-one (4).** A suspension of 2.5 g (0.018 mol) of **3**, 3.27 g (0.018 mol) of NBS, and 10 mg of benzoyl peroxide in 25 mL of CCl_4 was heated to reflux for 10 min. The mixture was cooled to 5 °C for 2 h and filtered. Concentration of the filtrate afforded 3.9 g (99%) of **4** as a white solid. Recrystallization from ether–pentane gave pure **4** as colorless plates: mp 80–82 °C; IR (Nujol) 3040 and 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.7–3.1 (m, 8 H, ring CHs), 4.48 (m, 1 H, C=CCH), 5.73 (br s, 2 H, HC=CH); ^{13}C NMR ($CDCl_3$) δ 25.3 (C-9), 30.4 (C-1), 38.9 (C-5), 45.6 and 46.8 (C-2 + C-4), 50.6 (C-8), 127.3 (C-6), 133.2 (C-7), 208.6 (C-3); mass spectrum, M$^+$ found *m/e* 213.9983 (calcd for $C_9H_{11}OBr$, *m/e* 213.9993).

Tricyclo[3.3.1.0^{2,8}]non-6-en-3-one (5a). A reaction vessel was charged with 400 mg (2.9 mmol) of anhydrous potassium carbonate, 10 mL of MeOH, and 200 mg (0.93 mmol) of **4** and was heated to reflux for 12 h. The solvent was removed under reduced pressure, and the residue was taken up in ether and then washed with water. The aqueous phase was extracted once with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated to afford a colorless oil, which was subjected to distillation in vacuo to give 127 mg (95%) of **5a** as a low-melting solid: bp 105–110 °C (2 mm); mp 36–39 °C; IR ($CHCl_3$) 3042, 2937, 1678, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15–2.28 (m, 8 H, ring Hs), 5.65–6.15 (m, 2 H, HC=CH); ^{13}C NMR ($CDCl_3$) δ 205.76, 130.04, 124.85, 46.18, 33.42, 27.42, 22.56, 22.11, 18.99; mass spectrum, M$^+$ found *m/e* 134.0717 (calcd for $C_9H_{10}O$, *m/e* 134.0732). Anal. Calcd for $C_9H_{10}O$: C, 80.12; H, 7.31. Found: C, 80.56; H, 7.51.

Tricyclo[3.3.1.0^{2,8}]non-6-en-3-yl Toluenesulfonylhydrazone (5b). An 845-mg portion (4.45 mmol) of toluenesulfonohydrazide was dissolved in 3 mL of 60% aqueous MeOH and then added to a solution of 597 mg (4.45 mmol) of **5a** in 9 mL of 60% aqueous MeOH. The solution was heated to 60 °C in a warm water bath and then allowed to stand at 5 °C for 15 h. Colorless crystalline **5b** was obtained upon filtration (1275 mg, 95%): mp 187.5–189 °C dec; IR (Nujol) 3221 and 3039 cm^{-1}; NMR (Me_2SO-d_6) δ 1.10–2.25 (m, 7 H, ring Hs), 2.35 (s, 3 H, Ar CH_3), 5.55–5.98 (m, 2 H, HC=CH), 7.28 (d, 2 H, Ar H), 7.63 (d, 2 H, Ar H). Anal. Calcd for $C_{16}H_{18}O_2N_2S$: C, 63.57; H, 6.00; N, 9.26. Found: C, 63.29; H, 6.24; N, 9.51.

Tricyclo[3.3.1.0^{2,8}]nona-2,6-diene (Barbaralane, 1). To a suspension of 334 mg (1.11 mmol) of **5b** in 10 mL of THF at −78 °C was added 1.52 mL of 1.6 M *n*-butyllithium (2.43 mmol). The temperature was allowed to increase to 25 °C, after which stirring was continued for 5 h. A 1-mL portion of water was added to destroy any excess *n*-butyllithium. The residue was taken up in water and extracted with pentane. The aqueous layer was washed three times with pentane, and the combined organic phases were dried over Na_2SO_4, concentrated, and fractionally distilled to produce 77 mg (59%) of **1** as a colorless low-melting solid: mp 39–40 °C (lit.[12] mp 30–31 °C); ^{1}H NMR spectrum was identical with published values;[12] ^{13}C NMR ($CDCl_3$) δ 17.8 (C-9), 24.3 (C-1 + C-5), 74.0 (C-2, C-4, C-6, C-8), 121.4 (C-3, C-7).

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Registry No. **1**, 14693-11-9; **2**, 21932-98-9; **3**, 87012-22-4; **4**, 87012-23-5; **5a**, 87012-24-6; **5b**, 87012-25-7; bicyclo[3.3.1]non-6-en-3-ol, 25048-65-1.