Stability of Norcaradienes. A Delicate Control by C-7 Substituents

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Recently, we reported the isolation of stable γ-lactone ring-fused norcaradienes, the first entry into a stable tricyclo[5.3.0.0^{1,6}]deca-2,4-diene skeleton.[1] The stability of this type of norcaradienes is due to the nature of the substituents at the C-7 position. Since the related system with methoxycarbonyl groups at the C-7 substituent did not afford the corresponding norcaradiene,[2] the dimethylvinyl group at C-7 might play an important role for the stability of this ring system. Also important is the γ-lactone linkage, an electron-withdrawing group, which is considered to stabilize a norcaradiene structure.[3] In order to elucidate the role of the γ-lactone moiety, reduction of norcaradiene **1** was performed, which revealed a very delicate stereochemical control by the C-7 substituents on the stability of the norcaradiene ring.

Lithium aluminum hydride reduction of **1** gave cycloheptatriene **2** (70%) and norcaradiene triol **3** (29%). Reduction of **1** with a large excess of lithium aluminum hydride resulted in almost quantitative formation of **3**. The former product corresponded to the partial reduction of the lactone moiety, which would initially result in the formation of alcohol **4**. The subsequent relactonization would afford the norcaradiene **5** in which the γ-lactone ring was spirally substituted at the C-7 position. Due to the severe steric repulsion between the isopropylidene group and cyclohexadiene ring in the norcaradiene form, the molecule exists almost completely as the cycloheptatriene structure **2**. The ^{13}C NMR chemical shifts of C-1 and C-6 of **2** are characteristic to those of cycloheptatriene and are quite distinct from the shifts of norcaradiene **1** (Table I). The C–H long-range relations in COLOC spectra of **2** attested to its structure and eliminated the possibility of the two other cycloheptatriene structures **7** and **8** which could be derived from initial reduction of benzyl ester moiety. It is quite remarkable to note that further reduction of the γ-lactone moiety of **2** completely altered its molecular framework from a cycloheptatriene to a norcaradiene skeleton **3**. Its structure has been confirmed by single-crystal X-ray analysis.[4] The hydroxyl groups

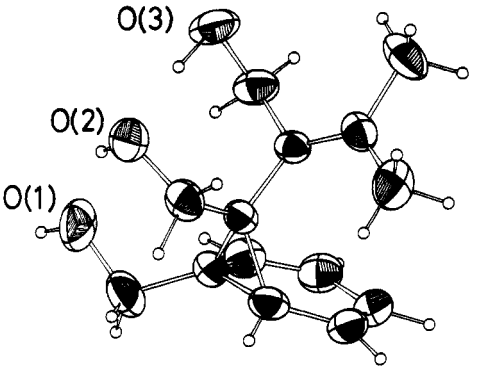

Figure 1. ORTEP view of **3**. Distance between two oxygen atoms: O(1)–O(2), 2.759 Å; O(2)–O(3), 2.755 Å.

Table I. Cyclopropane Ring Proton and Carbon Chemical Shifts (δ) of Norcaradienes and Cycloheptatrienes[a]

	H-6	C-1	C-6	C-7
1	2.72	21.77	39.80	41.53
2	5.54	143.82	132.88	49.23
3	2.21	29.71	38.75	40.84
10	2.25	24.52	37.77	40.60
11	2.90	23.10	47.80	52.31
13	3.55	86.43	79.57	34.78
14	3.24	71.75	70.68	27.59

[a] Measured at ambient temperature (25 ± 2 °C) except for **10** at 109.9 °C.

are strongly linked by intramolecular hydrogen bonding. Intermolecular hydrogen bonding exists between the neighboring conglomerate layers and also within a layer.

In solution as well as in the crystalline state, **3** exists almost completely as a norcaradiene, even though it undergoes some conformational equilibration. This may due to the conformational changes of two seven-membered hydrogen-bonded rings. ^{1}H and ^{13}C NMR spectra of **3** show broad signals, but their H-6, C-1, and C-6 chemical shifts are characteristic of norcaradienes (shifts corresponded to sp^2 values).[5] We initially considered that intramolecular hydrogen bonding might be the factor responsible for stabilization of the norcaradiene structure. However, the triacetate **10** also exists exclusively as the norcaradiene. Its ^{1}H and ^{13}C NMR spectra at ambient temperature showed very broad signals thereby prohibiting an unequivocal structure assignment. Gradual sharpening of the signals was observed by elevating the measurement temperature (up to 109.9 °C in a sealed tube; solvent, $CDCl_3$), which allowed us to assign the structure of **10** as the norcaradiene at high temperature. Its three cyclopropane ring carbons showed characteristic ^{13}C NMR chemical shifts of a norcaradienoic form at 109.9 °C. Low-temperature ^{13}C NMR of **10** at −30.4 °C showed very complex spectra. The appearance of four sets of signals for C-6 (δ 38.45, 37.08, 34.46, and 32.01), and C-7 (δ 39.95, 35.44, 27.00, and 26.70) indicated the presence of four norcaradienoic conformers at this temperature. Severe steric repulsion in **9** and also in the corresponding triacetate might force conversion from cycloheptatriene to the

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(1) Kohmoto, S.; Kawatsuji, T.; Ogata, K.; Yamamoto, M.; Yamada, K. *J. Am. Chem. Soc.* **1991**, *113*, 5476–5478.

(2) Ledon, H.; Cannic, G.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1970**, 3971–3974. Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron* **1973**, *29*, 3609–3617.

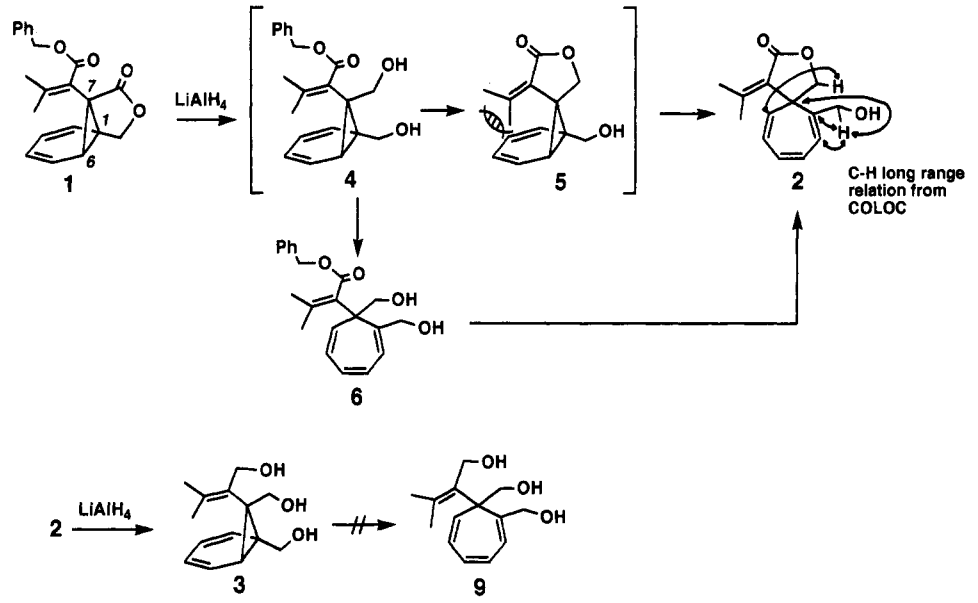
(3) Reviews see: Maier, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 402–413. Vogel, E. *Pure Appl. Chem.* **1969**, *20*, 237–262. Toda, T. *J. Synth. Org. Chem. Jpn.* **1972**, *30*, 412–423. Takeuchi, K. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 40–54.

(4) Colorless crystals of **3** are monoclinic, the space group is *Pbca* with a = 11.647(1) Å, b = 12.346(1) Å, c = 17.742(3) Å, V = 2550.5 Å^3, Z = 8, and d_{calcd} = 1.28 g/cm^3. The final residuals were R = 0.049 for 1781 data with $F_o > 3\sigma F_o$.

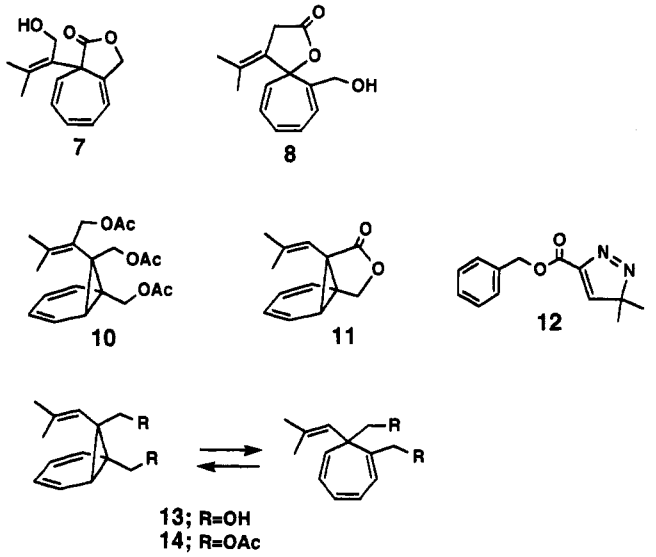
(5) Typical proton and carbon chemical shifts of norcaradienes, see: Hall, G. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 2203–2207. Takeuchi, K.; Kitagawa, T.; Toyama, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* **1982**, 313–314. Takeuchi, K.; Senzaki, Y.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* **1984**, 111–112. Daub, J.; Ludemann, H.-D.; Michna, M.; Strobl, R. M. *Chem. Ber.* **1985**, *118*, 620–633.

0022-3263/93/1958-4764$04.00/0

Scheme I



Scheme II



norcaradienoic form.[6] Since **3** is a stable norcaradiene, it is difficult to account for the formation of **2** via cycloheptatriene **6** in the reduction of **1**.

In a manner similar to that for the preparation of **1**,[1] we synthesized norcaradiene **11** by the photolysis of 3*H*-pyrazole **12** which was prepared by 1,3-dipolar cycloaddition of 2-diazopropane to the corresponding alkyne,[7] followed by the thermolysis of the initially formed cyclopropene.[8] Compound **11** is a fairly stable norcaradiene as judged by its ^{13}C NMR chemical shifts of the C-1 and C-6 carbons. In order to evaluate the steric effect of the hydroxymethyl and acetoxymethyl groups substituted at the 7-vinyl groups, diol **13** was prepared by lithium aluminum hydride reduction of **11**. Unlike triol **3**, the C-1 and C-6 carbon chemical shifts of **13** were intermediate between sp^3 and sp^2 values. Diacetate **14** showed C-1 and C-6 carbon chemical shifts similar to those of **13**. These results indicated that a severe steric hindrance was created by the hydroxymethyl substituent at the 7-position in **2** and **3** and that this steric interaction can delicately control the cycloheptatriene–norcaradiene valence isomerization.

It is quite interesting to note that the reduction of **1** converts its molecular framework from a norcaradiene to a cycloheptatriene and then back again to a norcaradiene.

Experimental Section

General Procedure. Reaction solutions were concentrated on a rotary evaporator at 15–20 mmHg. Chromatographic separations were accomplished by flash column chromatography on silica gel (Fuji gel BW 200). Further purification of products was carried out by a preparative HPLC run; column Merk LiChrosorb Si60 (7 μm, 10 × 250 mm), *n*-hexane/ethyl acetate as eluent.

Reduction of norcaradienes was carried out in THF (for **1**) or ether (for **11**) with 1.3 or 3.0 equiv of $LiAlH_4$, respectively. Norcaradienes were acetylated with 10 equiv of acetyl chloride in benzene in the presence of triethylamine at 0 °C.

6-(Hydroxymethyl)-4-isopropylidene-2-oxaspiro[4.6]undeca-6,8,10-trien-4-one (2): pale yellow oil; 41 mg (70%) from 90 mg of **1**; IR (NaCl) 3440, 1745, 1650, 1270, 1195 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.44–6.40 (m, 3 H), 6.22–6.18 (m, 1 H), 5.54 (d, J = 10.7 Hz, 1 H), 4.18 (d, J = 9.0 Hz, 1 H), 4.06 (s, 2 H), 3.37 (d, J = 9.0 Hz, 1 H), 2.37 (s, 3 H), 2.17 (br s, 1 H, exchanged with D_2O), 2.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.42 (s), 153.18 (s), 143.82 (s), 132.88 (d), 129.48 (d), 129.27 (d), 126.11 (d), 125.09 (s), 123.58 (d), 77.00 (t), 66.55 (t), 49.23 (s) 25.41 (q), 21.16 (q); HRMS (FAB) calcd for $C_{14}H_{17}O$ (MH^+) 233.1178, found 233.1178.

1,7-Bis(hydroxymethyl)-7-[1-(hydroxymethyl)-2-methyl-1-propenyl]bicyclo[4.1.0]hepta-2,4-diene (3): mp 115–116 °C; 18 mg (29%) from 90 mg of **1**; IR ($CHCl_3$) 3290, 2920, 1450, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.14 (br d, J = 9.1 Hz), 5.95–5.80 (m, 3 H), 4.31 (br d, J = 11.0 Hz, 1 H), 4.12 (br d, J = 11.6 Hz, 1 H), 3.89 (br d, J = 12.1 Hz, 1 H), 3.80 (br d, J = 11.0 Hz, 1 H), 3.52 (br d, J = 11.6 Hz, 1 H), 3.37 (br d, J = 11.6 Hz, 1 H), 2.21 (br d, J = 3.8 Hz, 1 H), 1.66 (s, 6 H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) all peaks appeared as a broad signal (24 °C), 139.33 (s), 127.93 (s), 127.03 (d), 122.50 (d), 122.37 (d), 121.31 (d), 69.69 (t), 68.23 (t), 62.08 (t), 40.84 (s), 38.75 (d), 29.71 (s), 22.25 (q), 20.31 (q); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+) 237.1491, found 237.1496.

(6) Stabilization of norcaradiene structure by steric repulsion with C-7 substituents: Prinzbach, H.; Fischer, U.; Cruse, R. *Angew. Chem.* **1966**, *78*, 268–269. Prinzbach, H.; Fischer, U. *Helv. Chim. Acta* **1967**, *50*, 1692–1722.

(7) Padwa, A.; Wannamaker, M. W. *Tetrahedron* **1991**, *47*, 6139–6156 and references cited therein.

(8) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137–209.

1,7-Bis(acetoxymethyl)-7-[1-(acetoxymethyl)-2-methyl-1-propenyl]bicyclo[4.1.0]hepta-2,4-diene (10): 54 mg (70%) from 51 mg of **3**; colorless oil; IR ($CHCl_3$) 2950, 1740, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) at 109.9 °C in a sealed tube δ 6.10–5.80 (m, 4 H), 4.61 (d, J = 12.3 Hz, 1 H), 4.46 (d, J = 12.3 Hz, 1 H), 4.22 (d, J = 12.3 Hz, 1 H), 4.03 (s 2 H), 3.91 (d, J = 12.3 Hz, 1 H), 2.25 (d, J = 4.0 Hz, 1 H), 1.92 (s, 3 H), 1.91 (s, 3 H), 1.88 (s, 3 H), 1.73 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) at 109.9 °C in a sealed tube δ 170.23 (s), 170.15 (s), 169.97 (s), 141.80 (s), 124.83 (d), 124.02 (s), 123.87 (d), 123.16 (d), 123.01 (d), 68.23 (t), 65.51 (t), 65.07 (t), 40.60 (s), 37.77 (d), 24.52 (s), 22.22 (q), 20.73 (q), 20.40 (q), 20.31 (q), 20.25 (q); HRMS (FAB) calcd for $C_{20}H_{26}O_6Na$ (MNa^+) 385.1627, found 385.1629.

7-(2-Methyl-1-propenyl)-9-oxatricyclo[5.3.0.0^{1,6}]deca-2,4-dien-8-one (11). A benzene solution (4 mL) of **12** (60 mg, 0.26 mmol) in a Pyrex test tube was irradiated for 40 min at 0 °C with a 100-W USHIO high-pressure mercury lamp. The color of the solution changed to yellow due to the formation of the corresponding diazo compound and then faded. After addition of benzene (2 mL), the test tube was sealed and heated at 110 °C for 16 h. After evaporation of solvent, the residue was flash chromatographed on silica gel (*n*-hexane/ethyl acetate = 4:1) to give 20 mg of **11** in 38% yield: mp 84–85.5 °C; IR ($CHCl_3$) 3020, 2970, 2930, 1760, 1370, 1210, 1160, 1140, 1105, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.26 (dd, J = 8.9, 7.0 Hz, 1 H), 6.17 (ddd, J = 8.9, 6.9, 0.8 Hz, 1 H), 6.07 (ddd, J = 9.3, 5.4, 0.7 Hz, 1 H), 5.95 (d, J = 9.3 Hz, 1 H), 4.55 (d, J = 10.0 Hz, 1 H), 4.43 (qq, J = 1.5, 1.2 Hz, 1 H), 4.32 (d, J = 10.0 Hz, 1 H), 2.90 (d, J = 5.4 Hz, 1 H), 1.65 (d, J = 1.5 Hz, 3 H), 1.55 (d, J = 1.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 178.37 (s), 142.99 (s), 126.51 (d), 124.82 (d), 122.70 (d), 120.60 (d), 112.89 (d), 70.69 (t), 52.31 (s), 47.80 (d), 25.13 (q), 23.10 (s), 18.78 (q); HRMS calcd for $C_{13}H_{14}O_2$ 202.0992, found 202.0992. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.21; H, 6.97.

5-(Benzyloxycarbonyl)-3,3-dimethyl-3*H*-pyrazole (12). To an etheral solution (60 mL) of acetylenecarboxylic acid benzyl ester (474 mg, 2.96 mmol) was added a THF solution of dimethyldiazomethane at 0 °C. The progress of the reaction was monitored to avoid the second addition of dimethyl diazomethane. After evaporation of solvent, the residue was flash chromatographed (*n*-hexane/ethyl acetate = 1:1) to give 474 mg of **12** in 70% yield: mp 85–86.7 °C (hexane–ethyl acetate); IR ($CHCl_3$) 3010, 1730, 1618, 1455, 1265, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.65 (s, 1 H), 7.50–7.20 (m, 5 H), 5.38 (s, 2 H), 1.43 (s, 6 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 160.61 (s), 154.16 (d), 146.60 (s), 135.08 (s), 128.47 (d), 128.45 (d), 128.39 (d), 94.96 (s), 67.01 (t), 19.58 (q); MS (relative intensity) 230 (M^+, 1.4), 172 (5), 157 (4), 143 (5), 129 (6), 91 (100), 83 (29). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.00, H, 6.05; N, 12.36.

1,7-Bis(hydroxymethyl)-7-(2-methyl-1-propenyl)-bicyclo[4.1.0]hepta-2,4-diene (13): 316 mg (79%) from 390 mg of **11**; colorless oil; IR (NaCl) 3388, 2960, 2920, 1448, 1378, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.25–6.11 (m, 3 H), 6.05–5.97 (m, 1 H), 4.92 (br s, 1 H), 4.04 (d, J = 12.3 Hz, 1 H), 3.93 (d, J = 11.2 Hz, 1 H), 3.76 (d, J = 12.3 Hz, 1 H), 3.62 (d, J = 11.2 Hz, 1 H), 3.55 (d, J = 7.7 Hz, 1 H), 3.02 (br s, 2 H, exchanged with D_2O), 1.63 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 136.91 (s), 126.05 (d), 125.81 (d), 125.51 (d), 123.60 (d), 123.51 (d), 86.43 (s), 79.57 (d), 67.30 (t), 66.17 (t) 34.78 (s), 25.74 (q), 19.36 (q); HRMS (FAB) calcd for $C_{13}H_{17}O$ ($MH^+ - H_2O$) 189.1280, found 189.1290.

1,7-Bis(acetoxymethyl)-7-(2-methyl-1-propenyl)-bicyclo[4.1.0]hepta-2,4-diene (14): 34 mg (78%) from 31 mg of **13**; colorless oil; IR (neat) 2930, 1745, 1460, 1385, 1245, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.25–5.90 (m, 4 H), 4.98 (qq, J = 1.4, 1.2 Hz, 1 H), 4.33 (d, J = 13.1 Hz, 1 H), 4.15 (d, J = 13.1 Hz, 1 H), 3.95 (s, 2 H), 3.24 (dd, J = 5.1, 1.8 Hz, 1 H), 1.98 (s, 3 H), 1.95 (s, 3 H), 1.61 (d, J = 1.2, 3 H), 1.58 (d, J = 1.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 170.98 (s), 170.65 (s), 137.74 (s), 125.48 (d), 125.36 (d), 124.92 (d), 123.60 (d), 122.68 (d), 71.75 (s), 70.68 (d), 68.17 (t), 65.19 (t), 27.59 (s), 25.68 (q), 20.82 (q), 19.27 (q); HRMS (FAB) calcd for $C_{17}H_{23}O_4$ (MH^+) 291.1596, found 291.1593.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of **2**, **3**, **10**, **13**, and **14** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.