Synthesis and Absolute Configuration of an Optically Active Bisnoradamantane Derivative, (−)-6-Oxotricyclo-[3.3.0.0^{3,7}]octane-2-carboxylic Acid

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(Received November 12, 1985)

Synopsis. 6-Isopropylidenetricyclo[3.3.0.0^{3,7}]octane-2-carboxylic acid (**11**) was prepared from the dimethylfulvene–ethyl acrylate adduct **5**. Optical resolution of **11** was carried out via the (+)-1-(2-naphthyl)ethylamine salt, and (−)-**11** was transformed into (−)-6-oxotricyclo[3.3.0.0^{3,7}]octane-2-carboxylic acid (**14**) whose absolute configuration and absolute rotation were established.

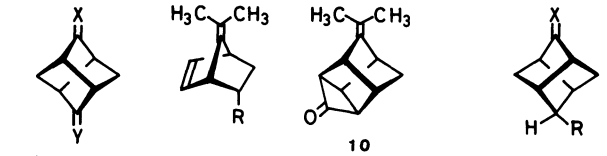
The smallest rings in the tricyclo[3.3.0.0^{3,7}]octane (bisnoradamantane)[1] ring system are all five membered. Because of the highly symmetrical arrangement of the fused cyclopentane rings within this system, the hydrocarbon **1** is achiral ($3C_2$, $2\sigma_v$; D_{2d} symmetry) and four CH_2 groups in **1** are a pair of enantiotopic molecular subunits. Conversion of two of these CH_2 groups oriented coaxially along one of C_2 axes into π-systems desymmetrizes the D_{2d} symmetry inherent to **1**, leading to formation of chiral molecules, e.g. **2**, **3**, and **4**. Among these molecules, 6-methylenebisnoradamantan-2-one (**2**) (C_2 symmetry) and bisnoradamantane-2,6-dione (**3**) (D_2 symmetry) were prepared in racemic forms in our laboratory.[2] Gleiter and Kissler[3] reported the synthesis of (±)-2,6-dimethylenebisnoradamantane (**4**) (D_2 symmetry) and mentioned that this molecule is an interesting model for studying the intramolecular interaction of two π-fragments via a six membered ring. Our continuing interests in high-symmetry chiral cage-shaped molecules prompted us to prepare the bisnoradamantane derivative having two coaxially oriented unsaturated centers in an optically active modification.

In the preceding paper,[2] we reported that the eleven-step conversion of the maleic anhydride–cyclopentadiene adduct to 6-methylenebisnoradamantane-2-carboxylic acid (**17**) proceeded in 3% overall yield. The carboxylic acid **17** was the key intermediate for the preparation of **2**, **3**, and **4**.[2,3] We now chose 5-*endo*-ethoxycarbonyl-7-isopropylidenebicyclo[2.2.1]hept-2-ene (**5**) as the starting material for the preparation of bisnoradamantane derivative possessing two substituents. The Diels–Alder reaction of dimethylfulvene with ethyl acrylate yielded a 28% yield of **5**, which was transformed into **11** in 6% overall yield in seven steps.

The adduct **5**, without removing its *exo*-isomer, was reduced with $LiAlH_4$ to give **6** which was converted into **7** by tosylation followed by treatment with sodium cyanide. Alkaline hydrolysis of **7** yielded **8** in 42% overall yield from **5**. By use of Sauers' procedure,[4] **8** was converted into **10** via **9** in 27% overall yield. The cleavage reaction of **10** was accomplished with potassium *t*-butoxide and water. Contrary to our expectation that the ring opening of the cyclobutanone moiety in **10** should yield a mixture of two isomeric carboxylic acids depending upon the direction of bond cleavage, 6-isopropylidenebisnoradamantane-2-carboxylic acid (**11**) was the sole product isolated from the reaction mixture. Confirmation of structure **11** was obtained by its conversion into methyl 6-oxobisnoradamantane-2-carboxylate (**13**) which has been prepared in a racemic form.[2] Optical resolution of **11** was accomplished using (+)-1-(2-naphthyl)-ethylamine as the resolving agent. The resolved carboxylic acids, (−)-**11** ($[\alpha]_D$ −74.1°) and (+)-**11** ($[\alpha]_D$ +67.7°) were obtained respectively from the sparingly soluble and the soluble salts. Esterification of (+)-**11**, $[\alpha]_D$ +67.7°, with CH_2N_2 gave (+)-**12**, $[\alpha]_D$ +72.5°, which exhibited a singlet signal at δ 3.53 ppm due to CO_2CH_3 protons in its ^1H NMR spectrum. Addition of Eu(tfc)$_3$ [(+)-**12**/shift reagent=1.0/0.45 molar ratio] split the signal into two singlets at δ 5.90 and 5.98 ppm, and their integrated intensities indicated an enantiomer ratio of 90.5:9.5 corresponding to 81% optical purity.

Our next task is the determination of absolute configuration of these new compounds. Ozonization of (−)-**12**, $[\alpha]_D$ −77.5° (86.6% e.e.), followed by reductive work-up provided **13**. Its ^1H NMR spectrum and GLC behavior were identical with those of (±)-**13**.[2] Alkaline hydrolysis of **13** yielded (−)-**14**, $[\alpha]_D$ −60.8°. Calculation based on the optical purity of (−)-**12** assigns absolute rotation $[\alpha]_D$ −7.2° to (−)-**14**. The Wolff-Kishner reduction of (−)-**14** followed by esterification with CH_2N_2 furnished methyl (−)-(1*R*,3*R*,5*R*,7*R*)-bisnoradamantane-2-carboxylate (**16**) whose absolute configuration has been reported in our preceding paper.[5] The result eventually assigns the (1*R*,3*R*,5*R*,7*R*) configuration to (−)-**14**.

The optically active compounds **11** and **14** may serve as precursors for preparing bisnoradamantane derivatives having two coaxially oriented π-systems in an optically active form.



1 X= Y= H_2
2 X= O Y= CH_2
3 X= Y= O
4 X= Y= CH_2

5 R= $CO_2C_2H_5$
6 R= CH_2OH
7 R= CH_2CN
8 R= CH_2CO_2H
9 R= CH_2COCl

10

(−)-11 X= $C(CH_3)_2$ R= CO_2H
(−)-12 X= $C(CH_3)_2$ R= CO_2CH_3
13 X= O R= CO_2CH_3
(−)-14 X= O R= CO_2H
15 X= H_2 R= CO_2H
(−)-16 X= H_2 R= CO_2CH_3
17 X= CH_2 R= CO_2H

Experimental

Preparative GLC were done on a JGC-20K equipped with a TCD and using a 2 m×3 mm column of 10% PEG 20 M on

Chromosorb W.

5-Ethoxycarbonyl-7-isopropylidenebicyclo[2.2.1]hept-2-ene (5). A mixture of dimethylfulvene[6] (142 g, 1.34 mol) and ethyl acrylate (134 g, 1.34 mol) was heated at 100 °C for 44 h. Distillation of the product provided 78.5 g of **5** (28% yield); bp 78—82 °C (4 mmHg**). IR (neat film) 3060, 1735, 1180, 730 cm^{-1}.

Found: C, 75.72; H, 8.81%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

5-Hydroxymethyl-7-isopropylidenebicyclo[2.2.1]hept-2-ene (6). A solution of **5** (15.8 g, 0.0814 mol) in dry ether (200 mL) was added to a suspension of $LiAlH_4$ (2.50 g, 0.0658 mol) in dry ether (200 mL) and then the mixture was refluxed for 4.5 h. After a usual workup, the product was distilled to give 9.20 g of **6** (74% yield); bp 98—100 °C (4 mmHg). IR (neat film) 3450, 3060, 1030, 730, 710, 700 cm^{-1}.

Found: C, 80.31; H, 9.79%. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83%.

5-Cyanomethyl-7-isopropylidenebicyclo[2.2.1]hept-2-ene (7). Tosylation of **6** (9.20 g, 0.0605 mol) with tosyl chloride (13.9 g, 0.0728 mol) in pyridine (55 mL) gave 16.7 g of the tosylate as a viscous oil, which was mixed with NaCN (45.0 g, 0.918 mol) and *N,N*-dimethylformamide (520 mL). The mixture was heated at 110 °C for 20 h and a workup followed by distillation provided 7.22 g of **7** (80% yield); bp 114—118 °C (4 mmHg). IR (neat film) 3060, 2240, 730, 710, 700 cm^{-1}.

Found: C, 83.01; H, 8.70; N, 8.05%. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09%.

5-Carboxymethyl-7-isopropylidenebicyclo[2.2.1]hept-2-ene (8). A mixture of **7** (36.7 g, 0.212 mol), KOH (35.7 g, 0.635 mol), and ethylene glycol (420 mL) was stirred at 140—150 °C for 8 h. A usual workup followed by distillation gave 31.2 g of **8** (77% yield); bp 142—146 °C (1 mmHg). IR (neat film) 1710, 720, 710 cm^{-1}.

Found: C, 74.88; H, 8.22%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

3-Isopropylidenetetracyclo[5.1.1.0^{2,6}.0^{4,8}]nonan-9-one (10). By use of a procedure similar to that reported by Sauers,[4] **8** (27.8 g, 0.145 mol) was converted into 6.80 g of **10** (32% yield) after alumina chromatography (pentane eluent) as a colorless oil; ^1H NMR (CCl_4) δ=1.60 (s, 3H), 1.63 (s, 3H), 1.4—1.6 (m, 2H), 2.2—3.0 (m, 6H). IR (neat film) 1780 cm^{-1}. The oily material was without further purification used in the next reaction.

6-Isopropylidenetricyclo[3.3.0.0^{3,7}]octane-2-carboxylic Acid (11). By use of a procedure similar to that reported by Sauers,[4] **10** (11.2 g, 0.0644 mol) was converted into **11** (3.84 g, 31% yield) after crystallization from pentane; mp 98—101 °C (in a sealed tube). IR (KBr) 1700 cm^{-1}.

Found: C, 75.13; H, 8.48%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

Optical Resolution of 11. To a solution of **11** (7.00 g, 0.0364 mol) in ethanol (70 mL) was added (+)-1-(2-naphthyl)ethylamine (6.23 g, 0.0364 mol). The deposited salt (6.26 g), $[\alpha]_D^{30}$ −8.71° (*c* 0.875, $CHCl_3$), was freed from the mother liquor which was reserved for isolation of the enantiomer (+)-**11**. Several times recrystallization of the salt from ethanol gave 3.49 g of the salt, $[\alpha]_D^{28}$ −32.6° (*c* 0.730, $CHCl_3$), which was stirred for 6 h with 10% HCl at room temperature. A usual workup provided 1.40 g of (−)-**11**, $[\alpha]_D^{28}$ −74.1° (*c* 0.805, $CHCl_3$). The carboxylic acid (−)-**11** (200 mg, 1.04 mmol) was treated with excess of a solution of diazomethane in ether with ice-cooling. A usual workup followed by prep. GLC separation (at 160 °C) gave 140 mg of (−)-**12** (65% yield); $[\alpha]_D^{27}$ −79.4° (*c* 0.903, $CHCl_3$). ^1H NMR (CCl_4) δ=1.7—1.9 (m, 4H), 1.51 (s, 6H), 2.4—2.8 (m, 5H), 3.53 (s, 3H). IR (neat film) 1730 cm^{-1}.

Found: C, 75.52; H, 8.75%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

From the dextrorotatory salt (1.44 g), $[\alpha]_D^{28}$ +53.3° (*c* 0.110, $CHCl_3$), isolated from the mother liquor, 550 mg of (−)-**11**, $[\alpha]_D^{28}$ +67.7° (*c* 0.950, $CHCl_3$), was obtained. Esterification of (+)-**11** (530 mg) gave 395 mg of (+)-**12**, $[\alpha]_D^{27}$ +72.5° (*c* 0.890, $CHCl_3$), after prep. GLC separation.

6-Oxotricyclo[3.3.0.0^{3,7}]octane-2-carboxylic Acid (14). Ozonization of (−)-**12**, $[\alpha]_D^{27}$ −77.5°, (900 mg, 4.37 mmol) followed by treatment with zinc powder and acetic acid was carried out by the similar procedure reported in our preceding paper[2] to give 235 mg of **13** (30% yield) after alumina chromatography (pentane–ether 1:1) followed by sublimation (75 °C at 30 mmHg); mp 63—65 °C (in a sealed tube) (lit,[2] (±)-**13**; mp 64—64.5 °C).

Found °C, 66.62; H, 6.78%. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

The ester **13** (210 mg, 1.17 mmol) was stirred under reflux for 3 h in 4 mL of 50% aqueous methanol with KOH (205 mg) to give 158 mg of **14** (81% yield) after sublimation (110 °C at 10 mmHg); mp 120—121 °C (lit,[2] (±)-**14**; mp 125—126 °C). $[\alpha]_D^{25}$ −60.8° (*c* 0.875, MeOH). IR (KBr) 1760, 1710 cm^{-1}.

Found: C, 64.99; H, 6.09%. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%.

Methyl (−)-Tricyclo[3.3.0.0^{3,7}]octane-2-carboxylate (16). By use of a procedure similar to that reported in our preceding paper,[2] the Wolff-Kishner reduction of (−)-**14** (130 mg, 0.783 mmol), $[\alpha]_D^{25}$ −60.8°, was carried out with KOH (282 mg) and hydrazine hydrate (310 mg, 6.20 mmol) in triethylene glycol (3 mL) to give 105 mg of **15**. Esterification of **15** with diazomethane yielded (−)-**16** (80 mg, 62% overall yield) after alumina chromatography followed by prep. GLC (at 120 °C); $[\alpha]_D^{26}$ −13.1° (*c* 0.655, $CHCl_3$) [lit,[5] bp 83—84 °C at 4 mmHg; $[\alpha]_D^{17}$ +14.5° ($CHCl_3$)].

Found: C, 72.34; H, 8.62%. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%.

References

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**1 mmHg=133.322 Pa.