216. Bicyclo[2.2.2]octanes

Syntheses and Hydrolyses of 6-*exo*-substituted 2-*exo*- and 2-*endo*-Bicyclo[2.2.2]octyl *p*-Toluenesulfonates

Part 9

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Summary

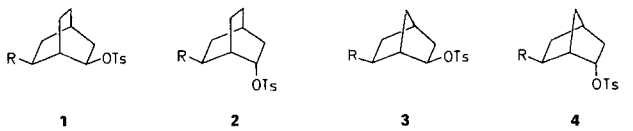
The synthesis of the title compounds and their hydrolysis products in 70% dioxane are described.

As described in [1], 6-substituted 2-*exo*- and 2-*endo*-bicyclo[2.2.2]octyl (BO) *p*-toluenesulfonates (BO tosylates) **1** and **2**, respectively, are suitable models for studies concerned with the transmission of inductive effects in the solvolysis of bicyclic compounds. In fact, the investigation of the rates and products of the series **1** and **2** complements our previous studies of inductivity in the solvolysis of 6-substituted 2-*exo*- and 2-*endo*-norbornyl tosylates **3** and **4**, respectively [2][1]). In this report, we describe the syntheses of the hitherto unknown 6-*exo*-substituted 2-*exo*- and 2-*endo*-bicyclo[2.2.2]octanols **5** and **6** (**b–j**), respectively, as well as the hydrolysis products of the corresponding tosylates **1** and **2**. The results are discussed in [1].

The *exo*- and *endo*-hydroxy-BO carboxylic acids **5c** and **6c**, respectively, or their methyl ester **5h** and **6h**, respectively, are obvious starting materials for the preparation of the other members of these series. While the former acid was unknown, the latter had been described without experimental details by *Liotta et al.* [4]. These acids have now become readily available by the following routes.

Cyclohexa-1,3-diene was allowed to react with ethyl acrylate, as described in [5], to yield a 18:82 mixture of the unsaturated *exo*- and *endo*-esters **7a** and **8a**, respectively. Saponification with NaOH, followed by addition of I_2, converted the *endo*-acid **8a** to the known iodolactone **9** [6], which was separated from the unsaturated *exo*-acid **7b**. Treatment of the iodolactone **9** with methanolic Et_3N led to the hydroxy ester **10a**, which was directly converted into the 2-tetrahydropyranyl (THP) ether **10b** and hydrogenated over Pd to yield the *endo*-ether **11**. When heated with MeOK and crown ether in benzene, the latter was converted to a 4:1 mixture of the stereoisomeric esters **12a** and **11**. After saponification and subsequent hydrolysis with aqueous HCl, the *endo*-

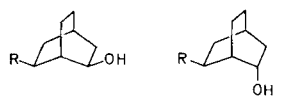
[1]) For reviews, see [3].



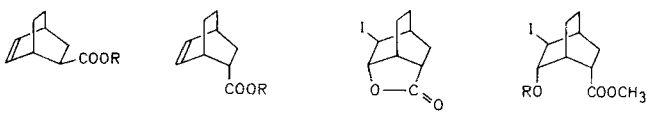
1 **2** **3** **4**

R =

a H **f** CH_2OAc
b CH_3 **g** CH_2OTs
c COOH **h** $COOCH_3$
d CH_2OCH_3 **i** CN
e CH_2OH **j** $CONH_2$

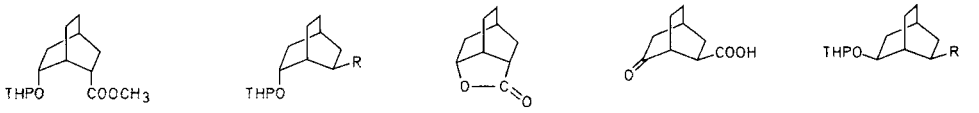


5 **6**

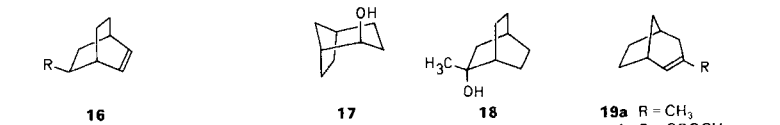


7 **8** **9** **10a** R = H **b** R = THP

a $R = C_2H_5$
b R = H



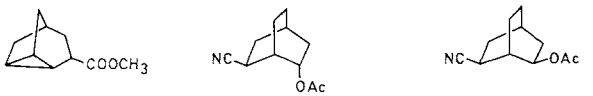
11 **12a** $R = COOCH_3$ **b** $R = CH_2OH$ **c** $R = CH_2OTs$ **d** $R = CH_2OCH_3$ **13** **14** **15a** $R = COOCH_3$ **b** $R = CH_2OH$ **c** $R = CH_2OTs$



16 **17** **18** **19a** $R = CH_3$ **b** $R = COOCH_3$

R =

a CH_2OH **e** CN
b CH_2OTs **f** CH_2OAc
c CH_3 **g** CH_2OCH_3
d $CONH_2$

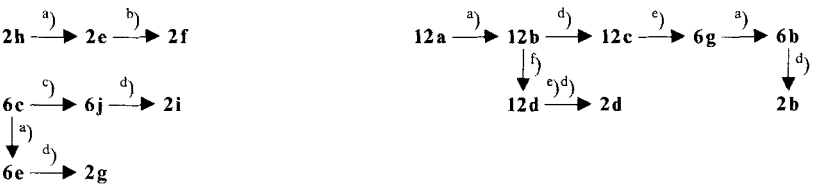


20 **21** **22**

endo-hydroxy acid liberated from **11** lactonized to **13** and was, hence, easily separated from the *endo-exo*-hydroxy acid **6c**. The latter was obtained in an overall yield of 38% and converted to the *exo-exo*-hydroxy acid **5c** by the following steps.

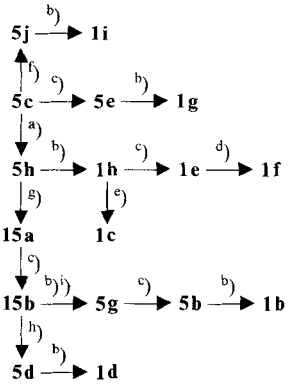
Oxidation of **6c** with *Jones'* reagent [7] afforded the keto acid **14**, which was reduced with $NaBH_4$ to give a 1:1 mixture of the 6-*exo*- and 6-*endo*-hydroxy acids **5c** and **6c**, respectively. Their methyl esters **5h** and **6h** were separated by chromatography on silica gel to yield 35% of the *exo-exo*-hydroxy acid **5c** after saponification. In contrast to the hydroxy acids **5c** and **6c**, their methyl esters **5h** and **6h** were readily converted to the corresponding tosylates **1h** and **2h** by reaction with TsCl and pyridine at 20° for 1 to 2 days. Mild saponification led to the tosylates **1c** and **2c**.

Scheme 1 (Series **2**)



[a]) $LiAlH_4$. [b]) Ac_2O. [c]) Isobutyl chloroformate/Et_3N, NH_3. [d]) TsCl/pyridine. [e]) CH_3OH/H^+. [f]) NaH, CH_3I.

Scheme 2 (Series **1**)



[a]) CH_2N_2.
[b]) TsCl/pyridine.
[c]) $LiAlH_4$.
[d]) Ac_2O/pyridine.
[e]) NaOH, HCl.
[f]) Isobutyl chloroformate/Et_3N, NH_3.
[g]) Dihydropyran/H^+.
[h]) NaH, CH_3I.
[i]) CH_3OH/H^+.

The carboxyl and ester groups in the above compounds are readily converted into the substituents R in the series **1** and **2** (**b**–**i**) by the procedures developed previously in the norbornane series **3** and **4** [8]. They are summarized in *Scheme 1* and *2* (letters in brackets refer to the footnotes) and are described in detail in the *Exper. Part.*

The hydrolyses of the tosylates **1** and **2**[2]) were carried out in 70% (v/v) dioxane in the presence of 1.1 equiv. of Et_3N[3]), for 10 half lives, except in the case of the dito-

Table. *Yields of Products in %*[a]*) from the Reactions of 6-*exo-*Substituted 2-*exo- (**1**) *and (in brackets) 2-*endo-*Bicyclo[2.2.2]octyl Tosylates* (**2**) *in 70%* (v/v) *Dioxane*

	R	5	6	16	17	18	19	20	13
a	H[b])	61			39				
b	CH_3	48(10)	20(50)	5(2.5)		20(3.5)	3(30)		
d	CH_2OCH_3	35(13)	45(55)	12(5)					
f	CH_2OAc	14(9)	55(65)	21(17)					
g	CH_2OTs	6(9)	55(62)	38(25)					
h	$COOCH_3$	2(5)	65(66)	22(13)			1(3)	6(7)	4(6)
i	CN	–(11)	55(41)	39(42)					

[a]) Beside unidentified rearrangement products.
[b]) See [1].

[2]) The products from the tosylates **1** and **2**, with R=COOH, CH_2OH and $CONH_2$ were not determined.
[3]) The procedure was the same as that described for the norbornane series **3** and **4** [9].

sylates **1g** and **2g**. In this case, the reaction was interrupted after 3½ half lives to avoid the slower hydrolysis of the primary TsO group. Products were separated by GC and identified by comparison with authentic samples. When this was not possible, as in the case of some products of **1h** and **2h**, they were isolated by preparative GC and investigated by spectrometric methods. The yields of products derived from the *exo-exo*-series **1** and (in brackets) from the *exo-endo*-series **2** are listed in the *Table*. Their modes of formation are discussed in [1].

The *Table* shows that the products are largely unrearranged alcohols **5** and **6** and unrearranged olefins **16**. In the cases of **1b** and **2b**, **1h** and **2h**, small amounts of rearranged alcohols and olefins were also obtained and, from **1h** and **2h**, even some methyl tricyclo[3.2.1.$0^{2,7}$]octane-3-carboxylate **20** and some lactone of 6-*endo*-hydroxybicyclo[2.2.2]-2-*endo*-carboxylic acid **13**. The preparation of the alcohols **5** and **6** (**f** and **i**) and the olfins **16** is summarized in *Scheme 3* and *4*. Compounds **18**, **19** (**a** and **b**) and **20** were isolated by preparative GC (see *Exper. Part*).

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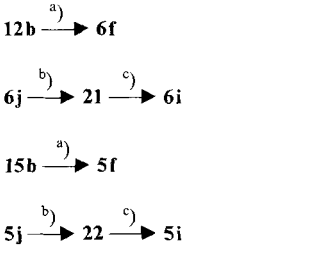
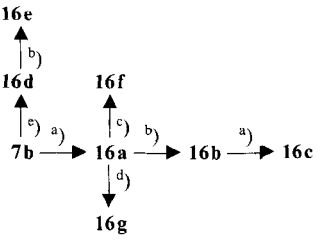
Scheme 3



a) Ac_2O/pyridine, CH_3OH/H^+.
b) Ac_2O.
c) NaOH.

Scheme 4 (Series **16**)



a) $LiAlH_4$. b) TsCl/pyridine.
c) Ac_2O. d) NaH, CH_3I.
e) Isobutyl chloroformate/Et_3N, NH_3.

Experimental Part

General. See [10]. Unless otherwise stated, the IR and ^{1}H-NMR spectra were in agreement with the structures of the pure compounds. Worked up as usual means extracting 3× with Et_2O, washing with H_2O and drying the combined extracts over anh. Na_2SO_4, followed by evaporation to dryness on a rotatory evaporator. Melting points (m.p.) were determined on a *Kofler* block and are corrected to ±2°. Boiling points (b.p.) are not corrected. Combustion analyses were carried out by Mr. *E. Thommen*.

Syntheses. – *5-exo-Iodobicyclo[2.2.2]octane-2,6-carbolactone* (**9**) *and Bicyclo[2.2.2]oct-5-ene-2-exo-carboxylic Acid* (**7b**). A 18:82 mixture of ethyl bicyclo[2.2.2]oct-5-ene-2-*exo*- and 2-*endo*-carboxylate **7a** and **8a** (370 g, 2.05 mol) [5] were saponified with 160 g NaOH in 1200 ml H_2O and 800 ml MeOH at 60° for 4 h. The solution was concentrated to *ca.* 1000 ml at 60°/150 Torr. After cooling to 10°, 485 ml of 4N HCl were added with vigorous stirring, followed by 20 g of KI and 2000 ml of CH_2Cl_2 and then by 427 g (1.68 mol) of I_2 in 50 g portions. Excess of I_2 was then reduced with aq. $Na_2S_2O_3$. The layers were separated and the aq. layer was extracted 5× with 500 ml CH_2Cl_2. The combined CH_2Cl_2-extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from AcOEt/petroleum ether to yield 450 g **9** (96% based on **8a**), m.p. 80–81° ([6]: 80–81°). Anal. calc. for $C_9H_{11}IO_2$ (278.09): C 38.86, H 3.99; found: C 38.79, H 4.06.

The above aq. layer was acidified and extracted 3× with 500 ml CH_2Cl_2. The extracts were washed with H_2O, combined, dried (Na_2SO_4), and evaporated to dryness. The residue was distilled at 100°/0.05 Torr to yield 47 g **7b** (84% based on **7a**), m.p. 46–48° ([11]: 46–48°). Anal. calc. for $C_9H_{12}O_2$ (152.20): C 71.03, H 7.95; found: C 71.07, H 7.89.

*Methyl-6-*endo-*(2H-Tetrahydropyran-2-yloxy)bicyclo[2.2.2]octane-2-*endo-*carboxylate* (**11**). A solution of 278 g (1.0 mol) of iodolactone **9** and 70 ml Et_3N in 1500 ml MeOH were kept in the dark for 12 h. Evaporation to dryness *in vacuo* yielded 312 g of crude hydroxy ester **10a**, which were dissolved in 1000 ml of dry CH_2Cl_2 and 274 ml (3 mol) of freshly distilled 2,3-dihydropyrane. After *ca.* 600 mg of TsOH had been added in 50–100 mg portions, the temp. rose temporarily to 44°. After standing at 20° for 14 h, the solution was diluted with 500 ml Et_2O and washed 3× with half-sat. aq. NaCl. After removal of the solvents *in vacuo* the crude ether **10b** was dissolved in 250 ml of MeOH, containing 140 ml (1.0 mol) of Et_3N, and hydrogenated over 25 g of 10% Pd/C. When H_2-uptake had ceased, the solution was filtered and evaporated to dryness *in vacuo*. The residue was taken up in Et_2O and extracted with aq. NaCl to remove $Et_3N \cdot HI$. The Et_2O-layer was dried and evaporated to dryness to yield 246 g of crude **11**. After distillation, 208 g (78%) of **11**, b.p. 105–110°/0.01 Torr, were obtained. To avoid some decomposition during distillation the crude product should be used for the next step. Anal. calc. for $C_{15}H_{24}O_4$ (268.36): C 67.13, H 9.02; found: C 67.22, H 9.25.

*6-*endo-*Hydroxybicyclo[2.2.2]octane-2-*exo-*carboxylic Acid* (**6c**). A solution of 263.3 g (1.0 mol) **11**, 7 g MeOK and 500 mg of 18-Crown-6 in 3.5 l benzene and 50 ml of MeOH was refluxed for 45 min. The benzene was removed *in vacuo* and the residue stirred with 1 l 2N NaOH and 500 ml acetone for 12 h. Then 500 ml 5N HCl and another 500 ml of acetone were added and stirring was continued for 2 h. After removal of the acetone *in vacuo* and addition of 750 ml of cold 2N NaOH, the mixture was extracted 3× with 250 ml of Et_2O to remove the lactone **13**. After recrystallization from pentane **13** had m.p. 204–205° ([6]: 205–206°). The alkaline solution was acidified and extracted 5× with 300 ml Et_2O. The extracts were dried and evaporated to yield 88 g (52%) of **6c**, m.p. 134.5–135.5° ([4]: 136.5–138°). Anal. calc. for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29; found: C 63.35, H 8.39.

*Methyl 6-*endo-*hydroxybicyclo[2.2.2]octane-2-*exo-*carboxylate* (**6h**) was prepared from the acid **6c** with CH_2N_2 in Et_2O. Yield of an oil: 93%, b.p. 144–147°/12 Torr. Anal. calc. for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75; found: C 65.07, H 8.68.

*6-Oxobicyclo[2.2.2]octane-2-*exo-*carboxylic Acid* (**14**). To a solution of 34 g (0.2 mol) of **6c** in 250 ml acetone were added 50 ml of *Jones'* reagent [7] with ice-cooling. After stirring for 2.5 h at 0°, 10 ml i-PrOH were added and the solution was evaporated *in vacuo*. H_2O was added and the mixture extracted with Et_2O. The dried extracts were evaporated and the residue recrystallized from Et_2O petroleum ether. Yield 30 g (89%), m.p. 94–96°. Anal. calc. for $C_9H_{12}O_3$ (168.20): C 64.27, H 7.19; found: C 64.09, H 7.41.

*Methyl 6-*exo-*Hydroxybicyclo[2.2.2]octane-2-*exo-*carboxylate* (**5h**). Reduction of 67.28 g (0.4 mol) keto acid **14** in 1N NaOH with an excess of $NaBH_4$ for 4 h at 0–10° and subsequent acidification with 4N HCl and extraction with Et_2O yielded 63.3 g (93%) of a 1:1 mixture of the 2-*exo*- and 2-*endo*-hydroxy acids **5c** and **6c**, respectively. These acids were converted into the corresponding methyl esters **5h** and **6h** with CH_2N_2 in Et_2O in practically quantitative yield. The latter were separated by repeated chromatography on silica gel *(Merck 9385)* [12] with Et_2O/petroleum ether 7:3 (v/v) to yield 26.7 g (39%) of pure **5h** as an oil. Anal. calc. for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75; found: C 65.16, H 8.67. The fractions containing mixtures of **5h** and **6h** were reoxidized to the keto acid **14**.

*6-*exo-*Hydroxybicyclo[2.2.2]octane-2-*exo-*carboxylic Acid* (**5c**). The ester **5h** (34.04 g, 0.2 mol) were saponified with 100 ml of 3N NaOH for 12 h at 50°. After acidification with 6N HCl, extraction with AcOEt, drying and evaporation, the crude acid **5c** was recrystallized from AcOEt/hexane, m.p. 168–169.5°, yield 95%. Anal. calc. for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29; found C 63.37, H 8.51.

*Methyl 6-*endo-*(p-Toluenesulfonyloxy)bicyclo[2.2.2]octane-2-*exo-*carboxylate* (**2h**). The hydroxy ester **6h** was allowed to react with TsCl in pyridine following the procedure described in [8]. After recrystallization from hexane **2h** was obtained in 94% yield, m.p. 74–76°. Anal. calc. for $C_{17}H_{22}O_5S$ (338.43): C 60.34, H 6.55; found: C 60.20, H 6.76.

*6-*exo-*Hydroxymethylbicyclo[2.2.2]oct-2-*endo-*yl* p-*Toluenesulfonate* (**2e**). A solution of 6.77 g (20 mmol) **2h** in 50 ml dry Et_2O was slowly added to a stirred suspension of 500 mg (13.2 mmol) $LiAlH_4$ in 50 ml Et_2O. After further 15 min at 20° and cooling to 0°, sat. aq. NH_4Cl was added dropwise until the precipitation of the inorg. material was complete. This was filtered off and washed with Et_2O. The combined Et_2O-extracts were worked up as usual. The crude **2e** was chromatographed with benzene/Et_2O 1:1 on silica gel *(Merck 9385)* to yield 5.1 g (82%) of **2e** as an unstable oil. IR (film): 3550, 3400 (OH); 1599 (arom.) ^{1}H-NMR ($CDCl_3$): *0.8–2.4*

(*m*, 10H); 2.07 (*s*, 1H, OH, removed by D_2O); 2.43 (*s*, 3H, $ArCH_3$); 3.48 (*d*, $J = 7$, 2H, CH_2OH); 4.5–4.89 (*m*, 1H, H–C(6)); 7.28 and 7.72 (4H, *p*-subst. C_6H_4).

6-exo-*Acetoxymethylbicyclo[2.2.2]oct-2*-endo-*yl* p-*Toluenesulfonate* (**2f**). Treatment of **2e** with Ac_2O and usual workup yielded 80% of the oily acetate **2f** after chromatography on silica gel with Et_2O/petroleum ether. Anal. calc. for $C_{18}H_{24}O_5S$ (352.45): C 61.34, H 6.86; found: C 61.24, H 7.07.

6-endo-*(*p-*Toluenesulfonyloxy)bicyclo[2.2.2]octane-2*-exo-*carboxylic Acid* (**2c**) was obtained by mild saponification of **2h** according to [8] in 62% yield. From AcOEt/petroleum ether, m.p. 137–139°. Anal. calc. for $C_{16}H_{20}O_5S$ (324.40): C 59.25, H 6.22; found: C 59.06, H 6.33.

6-endo-*Hydroxybicyclo[2.2.2]octane-2*-exo-*carboxamide* (**6j**). To a stirred solution of 1.70 g (10 mmol) of **6c** and 1.54 ml (11 mmol) of Et_3N in 35 ml THF were added dropwise 2 ml (25 mmol) isobutyl chloroformate *(Fluka)* with cooling to −15°. After further stirring for 1 min, the solution was saturated with gaseous NH_3 and left to warm to 20° for 1 h. The white precipitate was filtered off and washed with THF. The filtrates were evaporated *in vacuo* and the residue was recrystallized from AcOEt/petroleum ether to yield 1.430 g (85%) of **6j**, m.p. 154.5–156°. Anal. calc. for $C_9H_{15}NO_2$ (169.23): C 63.88, H 8.94, N 8.28; found: C 63.90, H 9.09, N 8.16.

6-exo-*Cyanobicyclo[2.2.2]oct-2*-endo-*yl* p-*Toluenesulfonate* (**2i**) was obtained from **6j** by treatment with 2.5 equiv. of TsCl and pyridine according to [8] in 89% yield, m.p. 64.5–67°, after recrystallization from hexane. Anal. calc. for $C_{16}H_{19}NO_3S$ (305.40): C 62.94, H 6.27, N 4.59; found: C 62.78, H 6.49, N 4.66.

6-exo-*Hydroxymethylbicyclo[2.2.2]octan-2*-endo-*ol* (**6e**). Following the procedure described in [13], 3.4 g (20 mmol) of **6c** were reduced with excess $LiAlH_4$ in Et_2O. Yield 2.2 g (70%) after recrystallization, from acetone/benzene, m.p. 92.5–95°. Anal. calc. for $C_9H_{16}O_2$ (156.23): C 69.19, H 10.32; found: C 68.99, H 10.52.

[6-endo-*(*p-*Toluenesulfonyloxy)bicyclo[2.2.2]oct-2*-exo-*yl]methyl* p-*Toluenesulfonate* (**2g**) was obtained from **6e** with TsCl and pyridine in the usual way. Yield 5.2 g (92%) after recrystallization, from Et_2O, m.p. 98.5–101.5°. Anal. calc. for $C_{23}H_{28}O_6S_2$ (464.61): C 59.47, H 6.08; found: C 59.24, H 6.31.

[6-endo-*(2*H-*Tetrahydropyran-2-yloxy)bicyclo[2.2.2]oct-2*-exo-*yl]methanol* (**12b**). The hydroxy ester **6h** (12.85 g, 70 mmol) was converted to the THP-ether **12a** following the procedure of *Miyashita et al.* [14] to yield 17.7 g (95%). The crude product was reduced with 2.66 g (70 mmol) $LiAlH_4$ in Et_2O according to [8]. Chromatography of the crude product on silica gel *(Merck 7734)* with Et_2O/petroleum ether yielded 15.5 g (93%) **12b** as a viscous liquid. Anal. calc. for $C_{14}H_{24}O_3$ (240.35): C 69.96, H 10.07; found: C 69.94, H 10.22.

(6-endo-*Hydroxybicyclo[2.2.2]oct-2*-exo-*yl)methyl* p-*Toluenesulfonate* (**6g**). The alcohol **12b** (10 g, 41.6 mmol) was converted to the tosylate **12c** in the usual way. The crude tosylate was treated with 60 ml MeOH and 1 g (4 mmol) of pyridinium *p*-toluenesulfonate according to [14] to yield 11.8 g (91%) of the alcohol **6g**, m.p. 73–74.5°. Anal. calc. for $C_{16}H_{22}O_4S$ (310.42): C 61.95, H 7.14; found: C 62.02, H 7.36.

6-exo-*Methylbicyclo[2.2.2]octan-2*-endo-*ol* (**6b**). A solution of 1.55 g (5 mmol) **6g** in 10 ml THF was added dropwise to 2.3 g $LiAlH_4$ in 20 ml THF with stirring. After refluxing for 30 h, the mixture was cooled to 0° and then treated with 2N H_2SO_4. After removing most of the THF *in vacuo* the mixture was extracted with CH_2Cl_2. The dried extracts were evaporated *in vacuo* and the residue was chromatographed on silica gel with Et_2O/petroleum ether 2:3 to yield 610 mg (87%) of **6b**; after sublimation at 60°/0.5 Torr, m.p. 93–94°. **6b** was converted directly to *6*-exo-*methylbicyclo[2.2.2]oct-2*-endo-*yl* p-*toluenesulfonate* (**2b**) in 93% yield after recrystallization from pentane, m.p. 47–48°. Anal. calc. for $C_{16}H_{22}O_3S$ (294.42): C 65.27, H 7.53; found: C 65.23, H 7.60.

6-exo-*(Methoxymethyl)bicyclo[2.2.2]octan-2*-endo-*ol (***6d**). The alcohol **12b** (962 mg, 4 mmol) and 192 mg (8 mmol) of NaH *(Fluka)* were heated under reflux in 20 ml THF for 2 h. Then 1 ml (16 mmol) of MeI was added and heating continued for 4 h. Et_2O (20 ml) and H_2O (4 ml) were added to the cooled mixture with vigorous stirring. The Et_2O-layer containing **12d** was separated and evaporated to dryness. MeOH (5 ml) and pyridinium *p*-toluenesulfonate (100 mg) were then added and the solution was heated for 4 h at 40° to cleave the THP-ether. After evaporation *in vacuo* the residue was chromatographed on silica gel *(Merck 9385)* with Et_2O/petroleum ether 7:3. The fraction containing **6d** was distilled in a bulb-tube at 130°/0.1 Torr to give 600 mg (88%) of pure **6d** as a hygroscopic oil. The derived *6*-exo-*methoxymethylbicyclo[2.2.2]oct-2*-endo-*yl* p-*toluenesulfonate* (**2d**) was an oil. Anal. calc. for $C_{17}H_{24}O_4S$ (324.44): C 62.95, H 7.46; found: C 62.75, H 7.46.

(6-endo-*Hydroxybicyclo[2.2.2]oct-2*-exo-*yl)methyl Acetate* (**6f**) was obtained from **12b** with Ac_2O in pyridine. The crude acetate **12e** was heated as usual with MeOH and pyridinium tosylate to cleave the THP-ether. Chromatography on silica gel *(Merck 7734)* with petroleum ether 7:3 yielded 97% of a viscous oil. It was characterized as the *3,5-dinitrobenzoate*, which was recrystallized from EtOH/H_2O, m.p. 124.5–125.5°. Anal. calc. for $C_{18}H_{20}N_2O_8$ (392.37): C 55.10, H 5.14, N 7.14; found: C 55.15, H 5.36, N 7.13.

6-exo-*Cyanobicyclo[2.2.2]oct-2*-endo-*yl Acetate* (**21**) was obtained from **6i** by refluxing with Ac_2O for 12 h. The usual workup and bulb-tube distillation at 110°/0.05 Torr yielded 95% of pure **21**. Anal. calc. for $C_{11}H_{15}NO_2$ (193.25): C 68.37, H 7.82, N 7.25; found: C 68.13, H 8.05, N 7.29.

6-endo-*Hydroxybicyclo[2.2.2]octane-2*-exo-*carbonitrile* (**6i**) was obtained from **21** by mild saponification as described for **5c**. After sublimation at 140°/0.05 Torr, **6i** was obtained in 96% yield, m.p. 147–150°. Anal. calc. for $C_9H_{13}NO$ (151.21): C 71.49, H 8.67, N 9.26; found: C 71.40, H 8.77, N 9.16.

Methyl 6-exo(p-*toluenesulfonyloxy)bicyclo[2.2.2]octane-2*-exo-*carboxylate* (**1h**) was obtained from **5h** with TsCl in pyridine. Chromatography on silica gel *(Merck 9385)* with AcOEt/cyclohexane gave **1h** in 98% yield after recrystallization from hexane, m.p. 61.5–62.5°. Anal. calc. for $C_{17}H_{22}O_5S$ (338.43): C 60.34, H 6.55; found: C 60.08, H 6.58.

6-exo-*Hydroxymethylbicyclo[2.2.2]oct-2*-exo-*yl* p-*Toluenesulfonate* (**1e**) was prepared from **1h** by reduction with $LiAlH_4$ as described for **2e**. Chromatography on silica gel *(Merck 9385)* with Et_2O/benzene 7:3 yielded **1e** in 88% yield after recrystallization from Et_2O/pentane, m.p. 67–69°. Anal. calc. for $C_{16}H_{22}O_4S$ (310.42): C 61.92, H 7.15; found: C 62.05, H 7.37.

[6-exo(p-*Toluenesulfonyloxy)bicyclo[2.2.2]oct-2*-exo-*yl]methyl Acetate* (**1f**) was obtained from **1e** with Ac_2O and pyridine. Chromatography of the crude product on silica gel with Et_2O/petroleum ether 7:3 yielded **1f** (85%) as an oil. Anal. calc. for $C_{18}H_{24}O_5S$ (352.45): C 61.35, H 6.86; found: C 61.11, H 7.10.

6-exo(p-*Toluenesulfonyloxy)bicyclo[2.2.2]octane-2*-exo-*carboxylic Acid* (**1c**) was obtained by mild saponification of **1h** as described [8]. After recrystallization from AcOEt/petroleum ether, m.p. 148–150°, yield 53%. Anal. calc. for $C_{16}H_{20}O_5S$ (324.40): C 59.25, H 6.22; found: C 59.10, H 6.38.

6-exo-*Hydroxybicyclo[2.2.2]octane-2*-exo-*carboxamide* (**5j**) was prepared from **5c** by the same procedure as **6j**. After recrystallization from AcOEt/petroleum ether, m.p. 143–144°, yield 93%. Anal. calc. for $C_9H_{15}NO_2$ (169.23): C 63.88, H 8.94, N 8.28; found: C 63.80, H 9.12, N 8.13.

6-exo-*Cyanobicyclo[2.2.2]oct-2*-exo-*yl* p-*Toluenesulfonate* (**1i**) was prepared from **5j** as described for **2i**. After recrystallization from hexane, m.p. 99–101°. Anal. calc. for $C_{16}H_{19}NO_3S$ (305.4): C 62.94, H 6.27, N 4.59; found: C 62.78, H 6.27, N 4.60.

6-exo-*(Methoxymethyl)bicyclo[2.2.2]octan-2*-exo-*ol* (**5e**) was prepared by reduction of **5c** with $LiAlH_4$ as described for **6e**. After recrystallization from CH_2Cl_2/petroleum ether, m.p. 115–116°, yield 93%. Anal. calc. for $C_9H_{16}O_2$ (156.23): C 69.19, H 10.32; found: C 69.16, H 10.59.

[6-exo-(p-*Toluenesulfonyloxy)bicyclo[2.2.2]oct-2*-exo-*yl]methyl* p-*Toluenesulfonate* (**1q**) was prepared from **1e** with TsCl and pyridine in the usual way. Chromatography on silica gel with Et_2O/petroleum ether yielded **1g** in 97% yield. After recrystallization from hexane, m.p. 74.5–76°. Anal. calc. for $C_{23}H_{28}O_6S_2$ (464.61): C 59.47, H 6.08; found: C 59.27, H 6.35.

(6-exo-*Hydroxybicyclo[2.2.2]oct-2*-exo-*yl)methyl* p-*Toluenesulfonate* (**5g**) was prepared from **5h** in 3 steps without purification of intermediates. **5h** was converted to the THP-ether **15a** by the general method of *Miyashita et al.* [14] and reduced to **15b** with $LiAlH_4$ [8]. After tosylation to **15c**, the THP-ether was cleaved with MeOH and pyridinium tosylate to give **5g** in 89% overall yield. After recrystallization from Et_2O/petroleum ether, m.p. 94.5–96°. Anal. calc. for $C_{16}H_{22}O_4S$ (310.42): C 61.92, H 7.15; found: C 61.84, H 7.34.

6-exo-*Methylbicyclo[2.2.2]octan-2*-exo-*ol* (**5b**) was obtained by reduction of **5g** with $LiAlH_4$, as described for **6b**. After chromatography on silica gel with Et_2O/petroleum ether 2:3 and sublimation at 55°/1 Torr, m.p. 49–50°, yield 75%. **5b** was converted directly to *6*-exo-*methylbicyclo[2.2.2]oct-2*-exo-*yl* p-*toluenesulfonate* (**1b**) in 93% yield, which was recrystallized from pentane, m.p. 27–29°. Anal. calc. for $C_{16}H_{22}O_3S$ (294.42): C 65.27, H 7.53; found: C 65.29, H 7.71.

6-exo-*(Methoxymethyl)bicyclo[2.2.2]octan-2*-exo-*ol* (**5d**) was prepared from **15b** as described for **6d**. After chromatography on silica gel *(Merck 9385)* with Et_2O/petroleum ether 7:3, the crude alcohol **5d** was distilled in a bulb-tube at 130°/0.1 Torr to yield 94% of a hygroscopic oil. IR (film): 3490 (OH). ^{1}H-NMR ($CDCl_3$): 0.67–2.3 (*m*, 11H); 2.6 (*s*, 1H, OH, removed by D_2O); 3.33 (*s*, 3H, CH_3O); 3.3 (*d*, J = 7, 2H, CH_2O); 3.7–4.1 (*m*, 1H. H–C(2)).

6-exo-*(Methoxymethyl)bicyclo[2.2.2]oct-2*-exo-*yl* p-*Toluenesulfonate* (**1d**). After recrystallization from hexane, m.p. 35–37°. Anal. calc. for $C_{17}H_{24}O_4S$ (324.44): C 62.95, H 7.46; found: C 62.86, H 7.66.

(6-exo-*Hydroxybicyclo[2.2.2]oct-2*-exo-*yl)methyl Acetate* (**5f**) was prepared by acetylation of crude **15b** (see under **5g**) and subsequent removal of the THP group with MeOH and pyridinium tosylate. After chromatography on silica gel with Et_2O/petroleum ether 7:3, **5f** was obtained as an oil in 88% yield. IR (film): 3420 (OH); 1738 (C=O). ^{1}H-NMR ($CDCl_3$): 0.8–2.5 (*m*, 11H); 2.05 (*s*, 3H, CH_3C=O); 2.28 (*s*, 1H. OH, removed by D_2O); 3.77–4.22 (*m*, 1H, H–C(2)); 4.06 (*d*, J = 7, 2H, CH_2OAc). *3,5-Dinitrobenzoate of* **5f**. After recrystallization from EtOH/Et_2O, m.p. 94–95°. Anal. calc. for $C_{18}H_{20}N_2O_8$ (392.37): C 55.10, H 5.14, N 7.14; found: C 55.09, H 5.17, N 7.14.

6-exo-Cyanobicyclo[2.2.2]oct-2-exo-yl Acetate (**22**) was prepared by heating **5j** with Ac_2O under reflux for 6 h. Bulb-tube distillation yielded **22** in 79% yield as an oil. Anal. calc. for $C_{11}H_{15}NO_2$ (193.25): C 68.37, H 7.82, N 7.25; found: C 68.12, H 8.04, N 7.38.

6-exo-Hydroxybicyclo[2.2.2]octane-2-exo-carbonitrile (**5i**) was prepared by mild saponification of the acetate **22**. After sublimation at 140°/0.05 Torr, **5i** was obtained in 94% yield, m.p. 140–142°. Anal. calc. for $C_9H_{13}NO$ (151.21): C 71.49, H 8.67, N 9.26; found: C 71.32, H 8.86, N 9.16.

(Bicyclo[2.2.2]oct-5-en-2-exo-yl)methanol (**16a**) was prepared from **7b** by reduction with $LiAlH_4$ in boiling Et_2O for 24 h. Distillation at 80°/0.1 Torr yielded **16a** in 83% yield as an oil, which was converted into *bicyclo[2.2.2]oct-5-en-2-exo-yl p-toluenesulfonate* (**16b**); the latter was recrystallized from hexane, m.p. 40–41°. Anal. calc. for $C_{16}H_{20}O_3S$ (292.40): C 65.74, H 6.90; found: C 65.64, H 7.04.

2-exo-Methylbicyclo[2.2.2]oct-5-ene (**16c**) was prepared from **16b** by reduction with $LiAlH_4$ in boiling Et_2O for 24 h. Bulb-tube distillation at 105° yielded 93% of pure **16c** as shown by GLC. ^{1}H-NMR ($CDCl_3$): 0.7–2.65 (*m*, 12H); 1.02 (*d*, *J* = 7); 6.2 (*m*, 2H, HC=).

(Bicyclo[2.2.2]oct-5-en-2-exo-yl)methyl Acetate (**16f**) was prepared by acetylation of **16a**. After bulb-tube distillation at 125°/14 Torr, **16f** was obtained in 99% yield as an oil. Anal. calc. for $C_{11}H_{16}O_2$ (180.25): C 73.30, H 8.95; found: C 73.20, H 9.03.

2-exo-(Methoxymethyl)bicyclo[2.2.2]oct-5-ene (**16g**) was prepared from **16a** with NaH and MeI as described for **6d**. Bulb-tube distillation gave **16g** in 96% yield as an oil. Anal. calc. for $C_{10}H_{16}O$ (152.24): C 78.89, H 10.89; found: C 78.46, H 10.59.

Bicyclo[2.2.2]oct-5-ene-2-exo-carboxamide (**16d**) was prepared from **7b** by the procedure described for **6j**. After recrystallization from AcOEt/hexane, m.p. 154–155°, yield 93%. Anal. calc. for $C_9H_{13}NO$ (151.21): C 71.49, H 8.67, N 9.26; found: C 71.34, H 8.86, N 9.23.

Bicyclo[2.2.2]oct-5-ene-2-exo-carbonitrile (**16e**) was prepared from **16d** with TsCl and pyridine as described [8]. After bulb-tube distillation at 118°/13 Torr, **16e** was obtained in 83% yield, m.p. 55–56° ([15]: 52–53°). IR ($CDCl_3$): 2240 (CN). ^{1}H-NMR ($CDCl_3$): 1.1–3.1 (*m*, 9H); 6.22 (*m*, 2H, HC=).

2-Methylbicyclo[2.2.2]octan-2-ol (**18**) was prepared as described by *Kraus* [16], m.p. 122–123° ([16]: 121–122°). ^{1}H-NMR ($CDCl_3$): 1.15–2.2 (*m*, 12H); 1.3 (*s*, 3H, CH_3); 1.6 (*s*, 1H, OH (disappeares with D_2O)).

3-Methylbicyclo[3.2.1]oct-2-ene (**19a**) was prepared as described by *Kraus & Dewald* [17]. The ^{1}H-NMR spectrum was consistent with published data [18].

Methyl Bicyclo[3.2.1]oct-2-ene-3-carboxylate (**19b**) *and of Methyl Tricyclo[3.2.1.0^{2,7}]octane-3-carboxylate* (**20**). A 0.04M solution of **2h** in 70% (v/v) dioxane, containing 1.1 equiv. of Et_3N, was heated in a sealed ampoule for 150 min, at 100°. The cooled solution was diluted with the twice its volume of H_2O and extracted 5× with pentane. The extracts were washed with a small amount of H_2O, combined and dried (Na_2SO_4). The pentane solution was carefully concentrated over a *Vigreux* column and then separated by prep. GLC on 3% *Carbowax 20 M*.

19b. IR (film): 2950, 2865, 2840 (C–H); 1715 (conj. C=O); 1640 (conj. C=C); 750 (HC=C⟨). ^{1}H-NMR ($CDCl_3$): 1.37–2.05 (*m*, 6H, H–C(6), H–C(7), H–C(8)); 2.21–2.38 (*m*, 1H, H–C(5)); 2.46–2.64 (*m*, 3H, H–C(1), H–C(4)); 3.7 (*s*, 3H, $COOCH_3$); 7.14 (*d* with further coupling [19], *J* = 7, 1H, H–C(2)). MS: 166 (97, M^+), 151 (5), 138 (55), 137 (34), 135 (30), 134 (28), 124 (28), 107 (43), 106 (27), 105 (27), 100 (25), 93 (25), 91 (49), 80 (18), 79 (100), 78 (25), 77 (52), 67 (76), 66 (27), 65 (18), 59 (30), in agreement with the MS spectra of recently reported bicyclo [3.2.1]octanes [20].

20. IR (film): 3040 (cyclopropyl); 2940, 2970 (C–H); 1738 (ester C=O). ^{1}H-NMR ($CDCl_3$): 0.88–1.08 (*dt*, 1H, H–C(2), *J*(H–C(2), H–C(3)) = 3, decoupling reveals H–C(2) as a *t*, *J* = 8); 1.26–2.22 (*m*, 9H); 2.82–3.03 (*ddd*, 1H, H–C(3), *J*(H–C(3), H(*cis*)–C(4)) = 11, *J*(H–C(3), H(*trans*)–C(4)) = 6. For analogous spectra see [21]. MS: 166 (10, M^+), 135 (2.5), 134 (8), 107 (20), 106 (4), 105 (4), 91 (5), 90 (12.5), 88 (6), 87 (100), 80 (72), 79 (80).

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