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BICYCLO[3.3.1]NONANES AS SYNTHETIC INTERMEDIATES XIII.[1] NOVEL TRANSANNULAR HYDRIDE SHIFTS ENFORCED BY RELIEF OF THE STERIC CONSTRAINT IN THE BICYCLO[3.3.1]NONANE SYSTEM BEARING ENDO-SUBSTITUENTS AT POSITION 7

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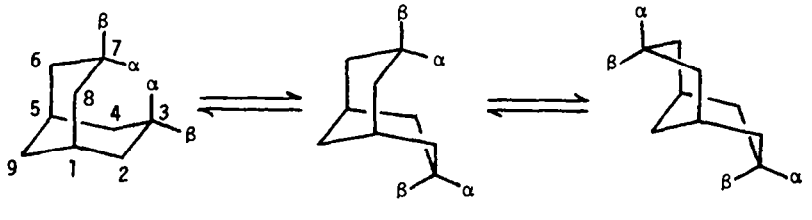
Abstract -- The Huang-Minlon reduction of 7α-hydroxymethylbicyclo[3.3.1]-nonan-3-one (**1**) gave 7β-methylbicyclo[3.3.1]nonan-3β-ol (**2**), a product formed as a result of the transannular 1,6-hydride shift enforced by relief of the steric constraint in the system. Another example of the intramolecular hydride transfer on the same basis was observed in the deketalization of 9,9-disubstituted 7,7-ethylenedioxybicyclo[3.3.1]-nonan-3β-ol (**13** and **18**) resulting in the formation of 7β-(2-hydroxy-ethoxy)bicyclo[3.3.1]nonan-3-one (**15** and **20**).

Compounds of the bicyclo[3.3.1]nonane skeleton have been the subject of numerous conformational and spectrometric studies.[2] Much interest in these compounds arises from their twin cyclohexane structure giving rise to 'chair-boat' interchanges, and three groups of conformations can be envisaged in this system: 'chair-chair' (**cc**), 'chair-boat' (**cb** or **bc**) and 'boat-boat' (**bb**).[2a] For bicyclo-[3.3.1]nonane itself, the most stable form is of 'chair-chair', with the 'boat-chair' and 'boat-boat' conformation being higher in energy by 2.3 kcal/mol and 5.0 kcal/mol, respectively.[2b] When substituents are introduced at the endo 3- and/or 7-positions,[2c,2d] the conformer distribution varies, large substituents forcing the rings that bear them into the boat conformation.



cc **cb or bc** **bb**

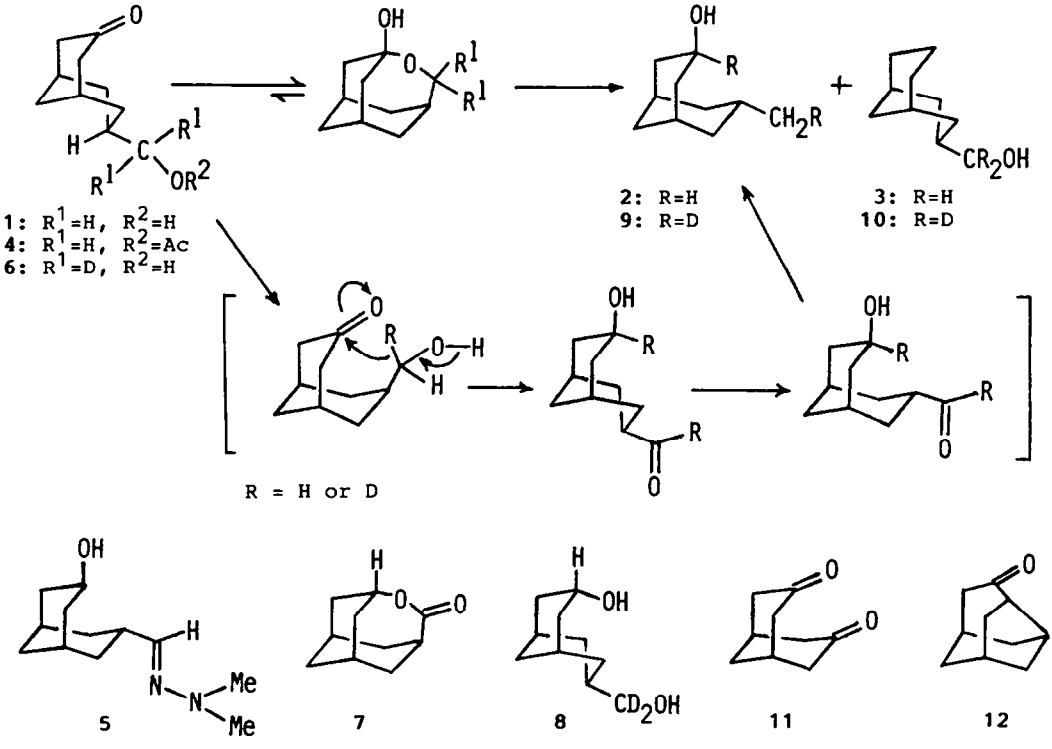
In the course of our exploratory study on the reactivity of the bicyclo-[3.3.1]nonane system, we have observed two characteristic intramolecular hydride shifts, both of which were triggered by relief of the steric constraint evoked by introduction of the endo-substituent at position 7.

1,6-Hydride Transfer in 7α-Hydroxymethylbicyclo[3.3.1]nonan-3-one (1)

The Huang-Minlon reduction of 7α-hydroxymethylbicyclo[3.3.1]nonan-3-one (**1**)[3] gave an unexpected exo-alcohol, 7β-methylbicyclo[3.3.1]nonan-3β-ol (**2**),[4] as a main product (in 42% isolated yield) accompanied by a small amount (in 7% isolated yield) of a normally reduced primary alcohol, 3α-hydroxymethylbicyclo[3.3.1]nonane (**3**).[2a] The reduction of the corresponding acetate (**4**) under the same condition also gave the same result. The physical and spectroscopic properties of the products (**2**, **3**) were in good accordance with those reported.[2a,4] As the treatment of **1** with N,N-dimethylhydrazine resulted in the formation of an aldo hydrazone (**5**), a path via a base-catalyzed intramolecular 1,6-hydride shift followed by inversion of the configuration[5] of the substituent as was shown in Scheme 1 was postulated for the formation of **2**.

The C_3 endo-hydrogen in **2** was proved to be a hydrogen, by origin, of the endo-methanol moiety at C_7 in **1** by subjecting the corresponding bideuteriated alcohol (**6**) to the same reduction. Thus, the bideuteriated methanol (**6**) was synthesized by the lithium aluminum deuteride ($LiAlD_4$) reduction of 4-oxahomoadamantan-5-one (**7**)[6] and subsequent $CAN/NaBrO_3$ oxidation[3b,7] of the resulting bideuteriated glycol, 7α-hydroxymethylbicyclo[3.3.1]nonan-3α-ol-d_2 (**8**). The Huang-Minlon reduction of **6** gave the corresponding β-alcohol (**9**) in 45 % yield. The migration of the deuterium to the endo-3 position was evidenced for the reduction product (**9**) by the complete disappearance of a characteristic multiplet of seven lines centered at δ 4.34 corresponding to the 3α-hydrogen in **2** in the ^{1}H-NMR spectrum.

The course of the reaction can be rationalized in terms of the relief of the steric constraint which was evoked by introduction of the endo-substituent at C_7 in the molecule.



Scheme 1

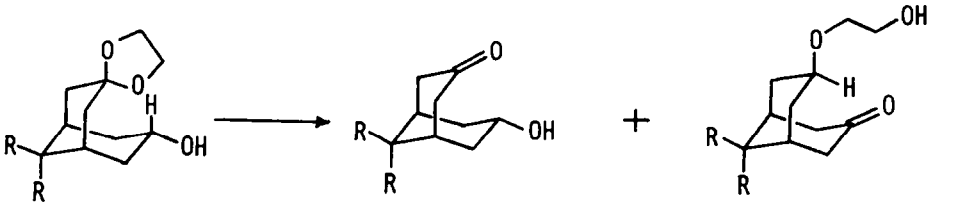
The unusual behavior of **1** toward the PDC oxidation leading to bicyclo[3.3.1]-nonane-3,7-dione (**11**)[3a] or the characteristic ring closure of **1** into 4-proto-adamantanone (**12**)[3b] has been reported. The present result is another specificity encountered in this system, and is a rare example[8] of the hydride shift which occurs across the 1 and 6 positions. For the intramolecular hydride shift,[9] the most common types are of orders 1,2; 1,3; and 1,5.

1,5-Hydride Transfer in 9,9-Disubstituted Bicyclo[3.3.1]nonane-3,7-dione 7-Ethylene Ketal (**13**, **18**)

Although introduction of an endo C_3-substituent on the bicyclo[3.3.1]nonane system forces that ring into the boat conformation, the boat form is no longer stable when a gem-dimethyl group is present at position 9, and the chair-chair conformation is again the most probable form.[10] Since the presence of an endo-substituent at position 3 or 7 itself provides the system with the severe steric hindrance, a 'boat cyclohexane' ring possessing an axial methyl at C_9 suffers from unbearable steric constraint.

In the studies on the properties of a series of 9,9-dimethylbicyclo[3.3.1]-nonane compounds possessing various substituents at position 3 and/or 7, Fetizon and co-workers[10] tried deketalization of 9,9-dimethyl-7,7-ethylenedioxybicyclo-[3.3.1]nonan-3β-ol (**13**) to give a normally deketalized ketol, 9,9-dimethyl-7β-hydroxybicyclo[3.3.1]nonan-3-one (**14**), as the sole product in 89% yield. Under more mild reaction conditions, we found an alternative reaction to take place which gave 9,9-dimethyl-7β-(2-hydroxyethoxy)bicyclo[3.3.1]nonan-3-one (**15**) as a main product.

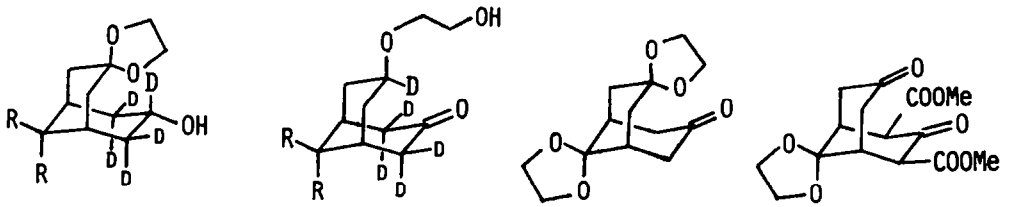
The treatment of **13** with para-toluenesulfonic acid (TsOH) in acetone at room temperature gave a 1 : 4 mixture of **14** and **15**. The structural assignment for **15** was accomplished on the basis of its IR, ^{1}H- and ^{13}C-NMR spectra. The IR spectrum indicated the presence of the hydroxyl (a band at 3419 cm^{-1}) and ketone (a band at 1696 cm^{-1}) functionalities. The assignment of exo stereochemistry rests on the ^{1}H-NMR spectrum (the CHOR signal appears as a triplet of triplets centered at δ 3.44, partially obscured by the signal for the 2-hydroxyethoxyl protons). The apparent magnitudes of the couplings are consistent with the CHOR signal being the X portion of an A_2B_2X system with J_{AX} ca. 11 and J_{BX} ca. 6 Hz, and these values, in turn, are consistent with the proton being axially oriented in a 'chair' cyclohexane.[11]



13: R=Me
18: R_2=

14: R=Me
19: R_2=

15: R=Me
20: R_2=



16: R=Me
21: R_2=

17: R=Me

22

23

Table 1

reactant	ketol		keto-ether
13	1	:	4.0
16	1	:	1.5
18	2.0	:	1
21	6.7	:	1

The product ratio was consistent among several experiments repeated, and the treatment of **15** with TsOH in acetone resulted in recovery of the starting material unchanged.

The origin of the hydrogen at endo-7 position of **15** was proved to be from the endo-hydrogen at C_3 of the starting material (**13**) by subjecting the corresponding pentadeuteriated analog (**16**) to the same procedure. The aforementioned multiplet at δ 3.44 for **15** disappeared completely in the ^{1}H-NMR spectrum of the product (**17**).

A typical deuterium isotope effect was encountered in the reaction as evidenced by relative reduction of the migration product (**17**). As the strain energy of **13** was calculated to be as much as 45.77 kcal/mol,[10] relief of the strain would be the main driving force in the process of the reaction.

When an analogous hydroxy ketal, 7,7,9,9-bisethylenedioxybicyclo[3.3.1]nonan-3β-ol (**18**) was treated under the same condition, the reaction proceeded in a similar manner to give a mixture of the same type of compounds, 9,9-ethylenedioxy-7β-hydroxybicyclo[3.3.1]nonan-3-one (**19**) and 7β-(2-hydroxyethoxy)bicyclo[3.3.1]-nonan-3-one (**20**), but in a ratio of 2 : 1. Table I shows the product ratios in a series of the deketalization.

The hydroxy ketal (**18**) was obtained in a highly stereospecific manner by the radical reduction of 7,7,9,9-bisethylenedioxybicyclo[3.3.1]nonan-3-one (**22**), which was obtained by ketalization of dimethyl 9,9-ethylenedioxy-3,7-dioxobicyclo-[3.3.1]nonane-2,4-dicarboxylate (**23**)[12] followed by decarboxylation under a neutral condition.

Although a variety of interaction between 3 and 7 positions such as intra-molecular hydride shift[13] has been reported, this is of interest as an example which represents the characteristic stereochemical feature of a highly strained bicyclo[3.3.1]nonane system.

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Experimental Melting points and boiling points are uncorrected. IR spectra were taken with a Hitachi 260-30 or a Shimadzu IR-435 grating spectrometer. ^{1}H-(199.5 MHz) and ^{13}C- (50.1 MHz) NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer with TMS as an internal standard. Coupling constants (J) are given in Hz, and following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad peak). Mass spectra (MS) were taken at 70 or 20 eV on a Hitachi M-70 mass spectrometer. High-resolution MS (HRMS) were taken with a JEOL JMS-D 300 or a JEOL JMS-HX 100 mass spectrometer. All the column chromatography were performed using LiChroprep® Si 60 (Merck Art. 9319, particle size 0.005-0.020 mm) with a pump (FMI Model RP). All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

The Huang-Minlon Reduction of 7α-Hydroxymethylbicyclo[3.3.1]nonan-3-one (1)
A mixture of **1** (2.00 g, 11.9 mmol), 90% hydrazine hydrate (12 ml, 222 mmol), potassium hydroxide (1.6 g, 29 mmol) and diethylene glycol (50 ml) was stirred at 110° for 3 h, and then at 200° for 5 h. During the heating at 200°, gradual sublimation of the products onto the condenser was observed. The cooled mixture was poured into brine (60 ml) and was extracted with ether (40 ml x 5). The extract

was combined with the ether washings of the sublimate, and washed with brine (30 ml x 1). Removal of the solvent left 1.30 g of a colorless oil, which on column chromatography (eluent; methylene chloride) gave 770 mg (42 %) of 7β-methylbicyclo[3.3.1]nonan-3β-ol (**2**) as a colorless solid, and 130 mg (7 %) of bicyclo[3.3.1]nonane-3α-methanol (**3**) as a colorless oil. The physical and spectroscopic properties of **2** and **3** were in good accordance with those reported.[2a,4]

2: mp. 68-71°(needles from n-hexane), lit.[4] mp. 72-75°.

3: bp. 105-110°/1 mmHg, lit.[2a] bp. 88-90°/0.2 mmHg.

7α-(Acetoxymethyl)bicyclo[3.3.1]nonan-3-one (**4**)

A solution of **1** (2.80 g, 16.7 mmol) in acetic anhydride (30 ml) was heated under reflux for 8 h. The cooled solution was poured into brine (10 ml), and the resulting mixture was extracted with chloroform (40 ml x 3). The extract was washed with a satd. sodium bicarbonate soln., and evaporated to give 3.72 g of a pale yellow oil, which on distillation gave 2.6 g (74%) of **4** as a colorless oil, bp. 160-164°/2 mmHg. IR (neat) cm^{-1}; 2910, 1740, 1710, 1462, 1442, 1426, 1363, 1245, 1032. ^{1}H-NMR ($CDCl_3$) δ; 0.93 (2H, ddd, J=14.0, 10.0, 2.5), 1.63 (1H, dt, J=13.0, 2.0), 1.82-2.18 (4H, m), 2.01 (3H, s), 2.30 (2H, d, J=14.5), 2.44 (2H, dd, J=14.5, 5.0), 2.54 (2H, m), 3.81 (2H, d, J=6.8). ^{13}C-NMR ($CDCl_3$) δ; 20.8 (q), 28.1 (d), 28.4 (t), 28.7 (d), 30.8 (t), 50.3 (t), 68.8 (t), 170.9 (s), 212.0 (s). MS m/z (%): 210 (M^+, 0.4), 192 (52), 150 (100), 108 (29), 107 (25), 95 (91), 93 (55), 92 (71), 67 (33). HRMS m/z; 210.1260 ($C_{12}H_{18}O_3$ requires 210.1256).

The Huang-Minlon Reduction of **4**

A mixture of **4** (250 mg, 1.19 mmol), 90 % hydrazine hydrate (1.2 ml), potassium hydroxide (260 mg) and diethylene glycol (15 ml) was heated at 110° for 3h and then at 200° for 5h. Work-up in a manner similar to that for the reduction of **1** gave 120 mg of a waxy solid, which on column chromatography (eluent; methylene chloride) gave 92 mg of **2** and 12 mg of **3**. The physical and spectroscopic properties of the products were completely in accordance with those of the specimens obtained by the Huang-Minlon reduction of **1**.

Treatment of **1** with N,N-Dimethylhydrazine: the N,N-Dimethylhydrazone (**5**)

A mixture of **1** (100 mg, 0.60 mmol), dimethylhydrazine (1 ml, 13 mmol), potassium hydroxide (100 mg, 1.79 mmol) and diethylene glycol (5 ml) was heated at 80° for 2 h. The cooled solution was poured into brine (20 ml), and the mixture was extracted with ether. The extract was washed with brine, and evaporated to give 103 mg (82 %) of **5** as pale yellow needles (from n-hexane), mp. 59-60°. IR (KBr) cm^{-1}; 3360, 3255, 2905, 2880, 2840, 2780, 1462, 1440, 1153, 1093, 1075, 1040, 1002, 972, 808. ^{1}H-NMR ($CDCl_3$) δ; 1.36-1.62 (6H, m), 1.64-1.84 (2H, m), 1.98-2.18 (4H, m), 2.38-2.64 (2H, m), 2.68 (6H, s), 4.40 (1H, septet, J=12.0, 6.0), 6.34 (1H, d, J=6.0). ^{13}C-NMR ($CDCl_3$) δ; 29.4 (d), 34.1 (t), 35.8 (t), 37.8 (d), 41.2 (t), 43.3 (q), 66.5 (d), 144.8 (s). MS m/z (%); 210 (M^+, 100), 138 (55), 95 (70), 73 (85), 59 (88). HRMS m/z; 210.1713 ($C_{12}H_{22}N_2O$ requires 210.1734).

Lithium Aluminum Deuteride ($LiAlD_4$) Reduction of 5-Oxahomoadamantan-4-one (**7**)

To a suspension of $LiAlD_4$ (2.0 g, 47.6 mmol) in dry ether (50 ml) was added dropwise a solution of **7** (7.9 g, 47.6 mmol) in dry ether (100 ml) under ice-cooling, and the resulting mixture was heated under reflux for 12 h. To the cooled mixture were added successively wet ether (50 ml), water (2 ml) and 15% sodium hydroxide soln. (4 ml). The resulting gel was collected by filtration with suction, and was washed with hot THF (50 ml x 7). The filtrate and the washings were combined, and removal of the solvent gave 7.4 g (90 %) of 7α-hydroxybicyclo[3.3.1]nonane-3α-methanol-α,α-d_2 (**8**) as colorless plates (from chloroform), mp. 170-171°. IR (KBr) cm^{-1}; 3280, 2900, 2170, 2070, 1445, 1330, 1305, 1265, 1240, 1140, 1120, 1100, 1085, 1040, 1010, 970, 945, 888, 782. ^{1}H-NMR (MeOH-d_4) δ; 1.19 (1H, dt, J=14.0, 2.0), 1.54-2.18 (12H, m), 4.08 (1H, tt, J=4.5, 2.5). ^{13}C-NMR (MeOH-d_4) δ; 25.6 (d), 29.2 (t), 31.2 (t), 33.9 (d), 40.9 (t), 68.2 (d), 69.0 (CD_2). MS m/z (%); 172 (M^+, 0.1), 154 (18), 136 (38), 122 (36), 121 (76), 95 (64), 94 (52), 93 (68), 81 (44), 80 (84), 79 (100), 67 (32). HRMS m/z; 172.1418 ($C_{10}H_{16}D_2O_2$ requires 172.1430).

Ceric Ammonium Nitrate (CAN) Oxidation of **8**

To a stirred suspension of **8** (186 mg, 1.08 mmol) in acetonitrile-water (25 ml, 4 : 1) were added sodium bromate (163 mg, 1.08 mmol) and CAN (59 mg, 0.108 mmol). After being stirred for 35 min at room temperature, the mixture was poured into a satd. sodium bicarbonate soln. (100 ml), and was extracted with methylene chloride (15 ml x 4). The extract was washed with a satd. sodium bicarbonate soln. and then with brine. Removal of the solvent gave 174 mg (95%) of 7-oxobicyclo[3.3.1]nonane-3α-methanol-α,α-d_2 (**6**) as colorless needles (from ether), mp. 130-134°. IR (KBr) cm^{-1}; 3300, 2900, 2830, 2190, 2135, 2095, 1440, 1430, 1358, 1320, 1302, 1252, 1195, 1150, 1127, 1100, 1048, 968, 930, 905, 842, 796, 730. ^{1}H-NMR ($CDCl_3$) δ; 1.0 (m), 1.46-2.20 (m), 2.20-2.60 (m), 2.97 (br s). ^{13}C-NMR ($CDCl_3$) δ; 26.8(d), 28.3 (d), 29.1 (t), 30.9 (t), 31.7 (d), 33.4 (d), 34.8 (t), 36.1 (t), 44.0 (t), 50.0 (t), 70.4 (CD_2), 100.0 (s), 212.7 (s). MS m/z (%); 170 (M^+, 10), 152 (17), 138 (13), 110 (15), 109 (19), 95 (38), 94 (100), 80 (19), 79 (18). HRMS m/z; 170.1307 ($C_{10}H_{14}D_2O_2$ requires 170.1277).

The Huang-Minlon Reduction of **6**

A mixture of **6** (200 mg, 1.18 mmol), 90 % hydrazine hydrate (1.1 ml, 21 mmol) and potassium hydroxide (330 mg) in diethylene glycol (15 ml) was heated at 110° for 3 h, and then at 200° for 7 h. Work-up in a manner similar to that for the reduction of **1** gave 101 mg of a colorless oil, which on column chromatography (eluent; methylene chloride : n-pentane = 2 : 1) gave 83 mg (45 %) of 7β-(mono-

deuteriomethyl)-3α-deuteriobicyclo[3.3.1]nonan-3β-ol (**9**) and 7 mg (4%) of bicyclo-[3.3.1]nonane-3α-methanol-α,α-d_2 (**10**).

9: mp. 73-74°. IR (KBr) cm^{-1}; 3434, 3210, 2908, 2167, 1460, 1443, 1360, 1297, 1089, 1067, 955, 917. ^{1}H-NMR ($CDCl_3$) δ; 0.82 (2H, m), 1.16 (2H, m), 1.28-1.56 (4H, m), 1.56-1.78 (4H, m), 1.94-2.10 (4H, m). ^{13}C-NMR ($CDCl_3$) δ; 23.9 (CD), 28.6 (d), 30.1 (d), 34.6 (t), 40.2 (t), 41.5 (t), 66.7 (CD). MS m/z (%); 156 (M^+, 1), 138 (70), 137 (21), 122 (56), 96 (100), 95 (62), 94 (30), 82 (27), 81 (29), 68 (19). HRMS m/z; 156.1467 ($C_{10}H_{16}D_2O$ requires 156.1482).

10: bp. 70-73°/2 mmHg. IR ($CHCl_3$) cm^{-1}; 3601, 3426, 2906, 2850, 2185, 2082, 1461, 1448, 1280, 1142, 1115, 1102, 1080, 1036, 1007, 957, 889. ^{1}H-NMR ($CDCl_3$) δ; 0.89 (2H, m), 1.10 (1H, m), 1.20-1.45 (5H, m), 1.50 (1H, br s, OH), 1.60-1.80 (3H, m), 1.80-2.12 (4H, m). ^{13}C-NMR ($CDCl_3$) δ; 15.9 (t), 25.1 (d), 29.4 (t), 32.5 (d), 33.5 (t), 68.5 (CD_2). MS m/z (%); 156 (m^+, 0.2), 138 (87), 123 (87), 122 (31), 96 (43), 95 (56), 94 (25), 81 (100), 80 (26), 67 (34). HRMS m/z; 156.1453 ($C_{10}H_{16}D_2O$ requires 156.1479).

Dimethyl 7,7,9,9-Bisethylenedioxy-3-oxobicyclo[3.3.1]nonane-2,4-dicarboxylate (**24**)

A mixture of dimethyl 9,9-ethylenedioxy-3,7-dioxobicyclo[3.3.1]nonane-2,4-dicarboxylate (**23**)[12] (1.0 g, 3.1 mmol), ethylene glycol (0.7 ml, 12.5 mmol) and para-toluenesulfonic acid (TsOH, 15 mg) in benzene (30 ml) was heated under reflux with a Dean-Stark apparatus until formation of water ceased. Work-up in a usual manner gave 1.0 g (88 %) of colorless cubics (from ethyl acetate), mp. 132-133°. IR (KBr) cm^{-1}; 2941, 1724, 1653, 1618, 1444, 1383, 1357, 1282, 1251, 1217, 1198, 1157, 1126, 1046, 1015, 1001, 984, 950, 831, 816. ^{1}H-NMR ($CDCl_3$) δ; 1.70-1.88 (2H, m), 2.18 (1H, dd, J=14.0, 4.0), 2.24 (1H, dd, J=14.0, 6.0), 2.70 (1H, m), 2.78 (1H, m), 3.32 (1H, s), 3.73 (3H, s), 3.76 (3H, s), 3.78-4.10 (8H, m), 12.40 (1H, s). ^{13}C-NMR ($CDCl_3$) δ; 36.6 (d), 36.7 (t), 38.6(t), 39.4 (d), 51.4 (d), 51.6 (q), 52.6 (q), 63.1 (t), 64,8 (t), 101.1 (s), 106.9 (s), 107.5 (s), 167.8 (s), 171.8 (s). MS m/z (FAB); 371 (M^++1).

7,7,9,9-Bisethylenedioxybicyclo[3.3.1]nonan-3-one (**22**)

A mixture of **24** (500 mg, 1.35 mmol), dimethyl sulfoxide (10 ml) and water (0.4 ml) was heated at 100-110° for 1 h. Sodium chloride (1.15 g) was added and the mixture was heated under reflux for 2 h. The solvent was removed under reduced pressure and the residue was washed with hot ethyl acetate. The washings were combined and evaporated to give 315 mg (92 %) of colorless needles (from cyclohexane), mp. 88-89°. IR (KBr) cm^{-1}; 2958, 2896, 1700, 1428, 1410, 1385, 1298, 1288, 1226, 1194, 1143, 1110, 1076, 1026, 976, 946, 924, 898, 731, 666. ^{1}H-NMR ($CDCl_3$) δ; 1.72 (2H, d, J=12.0), 2.20 (2H, m), 2.22 (2H, dd, J=12.0, 4.0), 2.42 (2H, d, J=19.0), 2.70 (2H, dd, J=19.0, 7.0), 3.76-4.00 (4H, m), 4.01 (4H, s). ^{13}C-NMR ($CDCl_3$) δ; 36.4 (d), 37.8 (t), 43.8 (t), 63.5 (t), 64.3 (t), 64.6 (t), 64.8 (t), 106.9 (s), 108.6 (s), 207.7 (s). MS m/z (%); 254 (M^+, 91), 179 (4), 169 (4), 154 (8), 140 (10), 126 (6), 113 (95), 112 (15), 100 (17), 99 (100), 86 (38), 55 (19). HRMS m/z; 254.1128 ($C_{13}H_{18}O_5$ requires 254.1154).

7,7,9,9-Bisethylenedioxybicyclo[3.3.1]nonan-3β-ol (**18**)

To a refluxing suspension of sodium (1.0 g, 43.5 mmol) in dry benzene (20 ml) was added dropwise a solution of **22** (500 mg, 1.97 mmol) in absolute ethanol (10 ml) with vigorous stirring. After 30 min, another 1.0 g of sodium was added, and the heating was continued until the foaming ceased (4 h). Water (10 ml) was added, and the resulting mixture was extracted with benzene. The extract was washed with brine, and evaporated to give 474 mg (94 %) of pale yellow needles (from n-hexane-benzene), mp. 85-86°. IR (KBr) cm^{-1}; 3428, 2919, 1437, 1419, 1390, 1360, 1338, 1304, 1267, 1250, 1213, 1136, 1112, 1089, 1055, 1040, 1030, 1013, 977, 946, 935, 902. ^{1}H-NMR ($CDCl_3$) δ; 1.70-2.04 (9H, m), 2.32 (2H, dd, J=15.0, 6.0). 3.76-4.04 (4H, m), 3.94 (4H, s), 4.94 (1H, m). ^{13}C-NMR ($CDCl_3$) δ; 36.4 (d), 38.3 (t), 39.5 (t), 62.3 (d), 63.2 (t), 64.3 (t), 107.0 (s), 109.3 (s). MS m/z (%); 256 (M^+, 17), 156 (26), 152 (34), 143 (77), 139 (30), 113 (73), 100 (36), 99 (100), 86 (28), 55 (23). HRMS m/z; 256.1292 ($C_{13}H_{20}O_5$ requires 256.1311).

7,7-Ethylenedioxy-9,9-dimethylbicyclo[3.3.1]nonan-3β-ol-2,2,3,4,4-d_5 (**16**)

Two hundred mg (0.79 mmol) of 7,7-ethylenedioxy-9,9-dimethylbicyclo[3.3.1]-nonan-3-one[10] was treated with sodium (1.00 g, 43.4 mmol) and ethanol-d_1 (3 ml) in the same manner as that for the preparation of **18** to give 185 mg (92 %) of colorless needles (from n-hexane), mp. 61-62°. IR (KBr) cm^{-1}; 3422, 2920, 2868, 2188, 2100, 1448, 1425, 1368, 1306, 1220, 1168, 1103, 1066, 1040, 1012, 969, 946, 926, 830. ^{1}H-NMR ($CDCl_3$) δ; 1.06, (3H, s), 1.12 (3H, s), 1.61 (2H, d, J=6.0), 1.72 (1H, s, OH), 1.78 (2H, d, J=16.0), 2.25 (2H, dd, J=16.0, 6.0), 3.76-4.02 (4H, m). ^{13}C-NMR ($CDCl_3$) δ; 26.8 (q), 26.9 (q), 32.0 (s), 36.7 (CD_2), 38.4 (d), 39.2 (t), 62.3 (CD), 63.1 (t), 64.0 (t), 107.3 (s). MS m/z (%); 231 (M^+, 36), 230 (17), 161 (13), 144 (11), 143 (100), 142 (30), 125 (19), 124 (14), 123 (14), 115 (23), 114 (21), 100 (11), 99 (42), 87 (16), 86 (74). HRMS m/z; 231.1853 ($C_{13}H_{17}D_5O_3$ requires 231.1883).

7,7,9,9-Bisethylenedioxybicyclo[3.3.1]nonan-3β-ol-2,2,3,4,4-d_5 (**21**)

Two hundred mg (0.79 mmol) of **22** was treated with sodium (800 mg, 34.8 mmol) and ethanol-d_1 (2 ml) in the same manner as that for the preparation of **18** to give 190 mg (93 %) of colorless needles (from n-hexane-benzene), mp. 81-82°. IR (KBr) cm^{-1}; 3425, 2925, 2900, 2200, 2180, 1420, 1389, 1215, 1136, 1112, 1087, 1072, 1055, 1033, 1007, 985, 971, 945. ^{1}H-NMR ($CDCl_3$) δ; 1.52 (1H, br s, OH), 1.88 (2H, d, J=15.0), 1.92 (2H, d, J=6.0), 2.32 (2H, dd, J=15.0, 6.0), 3.76-4.06 (4H, m), 3.96 (4H, s). ^{13}C-NMR ($CDCl_3$) δ; 36.2 (d), 37.8 (CD_2), 39.5 (t), 61.8 (CD),

63.2 (t), 64.2 (t), 64.4 (t), 107.0 (s), 109.3 (s). MS m/z (%); 261 (M^+, 21), 256 (25), 160 (21), 155 (24), 146 (78), 145 (53), 143 (25), 142 (23), 115 (81), 114 (90), 113 (30), 101 (61), 100 (100), 99 (92), 86 (43), 55 (29). HRMS m/z; 261.1616 ($C_{10}H_{15}D_5O_5$ requires 261.1625).

Ketal Exchange of 7,7-Ethylenedioxy-9,9-dimethylbicyclo[3.3.1]nonan-3β-ol (13) with Acetone

A solution of **13**[10] (175 mg, 0.774 mmol) and TsOH (30 mg) in acetone (25 ml) was stirred at room temperature for 2 h. A satd. sodium bicarbonate soln. was added to the solution, and the resulting mixture was concentrated under reduced pressure. The residue was extracted with chloroform. The extract was washed with brine, and evaporated to give 167 mg of a pale yellow oil, 110 mg of which was subjected to column chromatography (eluent; benzene : acetone = 30 : 1) to give 20 mg of 7β-hydroxy-9,9-dimethylbicyclo[3.3.1]nonan-3-one (**14**) and 79 mg of 7β-(2-hydroxyethoxy)-9,9-dimethylbicyclo[3.3.1]nonan-3-one (**15**) as colorless solids.

14: needles (from ether), mp. 192-194°(in a sealed tube), lit.[10] mp. 195-197°. IR (KBr) cm^{-1}; 3256, 2930, 2885, 1691, 1458, 1443, 1410, 1381, 1375, 1351, 1340, 1327, 1200, 1169, 1108, 1094, 1070, 1055, 1046, 927. ^{1}H-NMR ($CDCl_3$) δ; 1.18 (3H, s), 1.22 (3H, s), 1.66-2.04 (7H, m), 2.31 (2H, d, J=18.0), 2.73 (2H, dd, J=18.0, 7.0), 3.80 (1H, septet, J=11.0, 5.5). ^{13}C-NMR ($CDCl_3$) δ; 26.6(q), 32.3 (s), 37.6 (t), 39.7 (d), 44.7 (t), 63.4 (d), 212.2 (s). MS m/z (%); 182 (M^+, 100), 124 (20), 123 (33), 109 (21), 107 (21), 95 (28), 70 (43), 69 (36), 55 (24). HRMS m/z; 182.1326 ($C_{11}H_{18}O_2$ requires 182.1307).

15: mp. 121-122°. IR (KBr) cm^{-1}; 3419, 2931, 2900, 1696, 1464, 1439, 1410, 1370, 1359, 1222, 1201, 1173, 1104, 1079, 1037, 964, 931, 889. ^{1}H-NMR ($CDCl_3$) δ; 1.19 (3H, s), 1.22 (3H, s), 1.80-2.00 (6H, m), 2.13 (1H, br s, OH), 2.31 (2H, d, J=18.0), 2.72 (2H, dd, J=18.0, 6.0), 3.44 (1H, tt, J=10.7, 6.3), 3.49 (2H, t, J=5.0), 3.67 (2H, m). ^{13}C-NMR ($CDCl_3$) δ; 26.6 (q), 32.5 (s), 34.7 (t), 39.6 (d), 44.7 (t), 62.1 (t), 69.4 (t), 71.1 (d), 211.1 (s). MS m/z (%); 226 (M^+, 100), 181 (55), 166 (24), 165 (42), 147 (22), 123 (75), 114 (29), 107 (67), 95 (33), 81 (34), 70 (21), 69 (29), 67 (26), 55 (20). HRMS m/z; 226.1562 ($C_{13}H_{22}O_3$ requires 226.1569).

Ketal Exchange of **18** with Acetone

A solution of **18** (189 mg, 0.74 mmol) and TsOH (30 mg) in acetone (25 ml) was stirred at room temperature for 2 h. Work-up in a manner similar to that for the reaction of **13** gave 147 mg of a pale yellow oil, which on column chromatography (eluent; benzene : acetone = 30 : 1) gave 75 mg of 9,9-ethylenedioxy-7β-hydroxybicyclo[3.3.1]nonan-3-one (**19**) and 38 mg of 9,9-ethylenedioxy-7β-(2-hydroxyethoxy)bicyclo[3.3.1]nonan-3-one (**20**) as colorless solids.

19: mp. 73-75° (in a sealed tube). IR (KBr) cm^{-1}; 3446, 3237, 2930, 1688, 1441, 1414, 1402, 1396, 1354, 1276, 1250, 1212, 1123, 1104, 1091, 1061, 1033, 1010, 947, 938. ^{1}H-NMR ($CDCl_3$) δ; 1.84-1.98 (4H, m), 2.18 (3H, br s), 2.38 (2H, d, J=18.0), 2.85 (2H, dd, J=18.0, 6.0), 3.86 (1H, tt, J=10.0, 7.0), 4.02 (4H, s). ^{13}C-NMR ($CDCl_3$) δ; 37.7 (d), 38.7 (t), 44.8 (t), 62.7 (d), 64.6 (t), 64.8 (t), 108.2 (s), 210.5 (s). MS m/z (%); 212 (M^+, 24), 184 (17), 167 (7), 141 (8), 139 (7), 125 (6), 113 (100), 99 (48), 96 (12), 89 (20), 81 (6), 69 (9), 55 (20). HRMS m/z; 212.1048 ($C_{11}H_{16}O_4$ requires 212.1049).

20: mp. 87-88°. IR (KBr) cm^{-1}; 3400, 2930, 1702, 1482, 1459, 1440, 1405, 1390, 1344, 1324, 1254, 1223, 1208, 1120, 1090, 1056, 1038, 1019, 950, 927, 915, 897. ^{1}H-NMR ($CDCl_3$) ; 1.86-2.02 (4H, m), 2.20 (3H, br s), 2.36 (2H, d, J=18.0), 2.86 (2H, dd, J=18.0, 6.0), 3.48 (2H, t, J= 5.0), 3.42-3.62 (1H, m), 3.64 (2H, m), 4.02 (4H, s). ^{13}C-NMR ($CDCl_3$) δ; 35.6 (t), 37.6 (d), 44.9 (t), 62.0 (t), 64.7 (t), 64.8 (t), 69.5 (t), 70.3 (d), 108.2 (s), 210.4 (s). MS m/z (%); 256 (M^+, 39), 228 (13), 211 (12), 195 (16), 183 (16), 167 (15), 151 (8), 139 (10), 133 (13), 113 (100), 100 (14), 99 (52), 89 (12), 55 (20). HRMS m/z; 256.1300 ($C_{13}H_{20}O_5$ requires 256.1310).

Ketal Exchange of **16** with Acetone

A solution of **16** (162 mg, 0.701 mmol) and TsOH (30 mg) in acetone (30 ml) was stirred at room temperature for 1.5 h. Work-up in a manner similar to that for the reaction of 13 gave 142 mg of a pale yellow oil, which on column chromatography (eluent; benzene : acetone = 30 : 1) gave 57 mg of 7β-(2-hydroxyethoxy)-9,9-dimethylbicyclo[3.3.1]nonan-3-one-2,2,4,4,7-d_5 (**17**) and 38 mg of 9,9-dimethyl-7β-hydroxybicyclo[3.3.1]nonan-3-one-6,6,7,8,8-d_5 (**25**) as colorless solids.

17: mp. 122-123° (in a sealed tube). IR (KBr) cm^{-1}; 3416, 2923, 2200, 2135, 1690, 1461, 1364, 1356, 1271, 1173, 1106, 1079, 1048, 988, 970, 886, 865. ^{1}H-NMR ($CDCl_3$) δ; 1.20 (3H, s), 1.22 (3H, s), 1.76-2.00 (6H, m), 2.40 (1H, br s, OH), 3.49 (2H, t, J=4.5), 3.67 (2H, t, J=4.5). ^{13}C-NMR ($CDCl_3$) δ; 26.5 (q), 32.4 (s), 34.5 (t), 39.4 (d), 44.4 (CD_2), 62.0 (t), 69.4 (t), 70.6 (CD), 212.0 (s). MS m/z (%); 231 (M^+, 100), 230 (72), 229 (39), 185 (43), 170 (58), 169 (45), 125 (49), 123 (54), 108 (99), 107 (40), 70 (41). HRMS m/z; 231.1888 ($C_{13}H_{17}D_5O_3$ requires 231.1883).

25: mp. 181-183°. IR (KBr) cm^{-1}; 3262, 2900, 2198, 2100, 1694, 1412, 1390, 1369, 1338, 1240, 1221, 1196, 1167, 1122, 1112, 1091, 1080, 1052, 1029, 995, 963, 918. ^{1}H-NMR ($CDCl_3$) δ; 1.20 (3H, s), 1.23 (3H, s), 1.91 (2H, d, J=6.0), 2.30 (2H, d, J=18.0), 2.50 (1H, s, OH), 2.72 (2H, dd, J=18.0, 6.0). ^{13}C-NMR ($CDCl_3$) δ; 26.5 (q), 32.2 (s), 37.0 (CD_2), 39.5 (d), 44.6 (t), 62.4 (CD), 212.3 (s). MS m/z (%); 187 (M^+, 100), 186 (45), 185 (27), 126 (25), 125 (37), 124 (28), 99 (26), 97 (27), 72 (28), 71 (34), 70 (50), 69 (32). HRMS m/z; 187.1621 ($C_{11}H_{13}D_5O_2$ requires 187.1620).

Ketal Exchange of 21 with Acetone

A solution of **21** (100 mg, 0.383 mmol) and TsOH (15 mg) in acetone (10 ml) was stirred at room temperature for 2 h. Work-up in a manner similar to that for the reaction of 13 gave 90 mg of a colorless oil, which on column chromatography (eluent; benzene : acetone = 30 : 1) gave 67 mg of 9,9-ethyledioxy-7β-hydroxybicyclo[3.3.1]nonan-3-one-6,6,7,8,8-d_5 (**26**) and 10 mg of 9,9-ethylenedioxy-7β-(2-hydroxyethoxy)bicyclo[3.3.1]nonan-3-one-2,2,4,4,7-d_5 (**27**) as colorless solids.

26: mp. 103-105° (in a sealed tube). IR (KBr) cm^{-1}; 3450, 2950, 2900, 2210, 2110, 1688, 1406, 1379, 1280, 1198, 1114, 1073, 1038, 1008, 982, 942, 920. ^{1}H-NMR ($CDCl_3$) δ; 1.79 (1H, br s, OH), 2.18 (2H, d, J=6.0), 2.37 (2H, d, J=18.0), 2.85 (2H, dd, J=18.0, 6.0), 4.02 (4H, s). ^{13}C-NMR ($CDCl_3$) δ; 37.5 (d), 38.2 (CD_2), 44.8 (t), 62.1 (CD), 64.6 (t), 64.8 (t), 108.2 (s), 210.5 (s). MS m/z (%); 217 (M^+, 58), 216 (35), 215 (22), 189 (20), 188 (12), 116 (22), 115 (100), 114 (58), 113 (11), 101 (11), 100 (16), 99 (40), 89 (41). HRMS m/z; 217.1339 ($C_{11}H_{11}D_5O_4$ requires 217.1363).

27: mp. 102-103°(needles from n-hexane). IR (KBr) cm^{-1}; 3406, 2932, 2120, 1702, 1382, 1278, 1253, 1119, 1042, 1008, 949. ^{1}H-NMR ($CDCl_3$) δ; 1.84-2.06 (5H, m), 2.21 (2H, br s), 3.48 (2H, t, J=5.0), 3.66 (2H, m), 4.02 (4H, s). ^{13}C-NMR ($CDCl_3$) δ; 35.4 (t), 37.5 (d), 44.6 (CD_2), 62.1 (t), 64.7 (t), 64.8 (t), 69.4 (t), 69.8 (CD), 108.2 (s), 210.6 (s). MS m/z (%); 261 (M^+, 68), 260 (64), 259 (43), 258 (19), 171 (14), 133 (14), 115 (100), 114 (71), 101 (28), 100 (28), 89 (19). HRMS m/z: 261.1606 ($C_{13}H_{15}D_5O_5$ requires 261.1624).

References and Notes

1. The previous paper entitled "Favorskii Reaction of 2-Bromobicyclo[3.3.1]nonan-3-one" [T. Itooka, K. Matoba, T. Yamazaki, O. Muraoka and T. Momose, Chem. Pharm. Bull., **34**, 2391 (1986)] constitutes Part XII of this series. Part XI: O. Muraoka, T. Minematsu, J. Tsuruzawa and T. Momose, Heterocycles, **23**, 853 (1985).
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