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ACID CATALYZED REARRANGEMENTS IN BICYCLO[3.3.1]NONANES

2-SUBSTITUTED-6-(1,3-DIOXOLAN-2-YL)-CYCLOOCTANONES FROM 1-SUBSTITUTED-2-HYDROXY-9,9-(ETHYLENEDIOXY)-BICYCLO[3.3.1]-NONANES

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Abstract—Treatment of *endo*-2 or *exo*-2-hydroxy-1-substituted ketals **1a–d** with *p*-toluenesulfonic acid in dry benzene results in a reversible C_9 bridge cleavage and affords equilibrium mixtures where 2-substituted-6-(1,3-dioxolan-2-yl)-cyclooctanones **6a–d** are present as main products. Yields in **6a–d** increase as the steric hindrance of the substituents at C_1 in the substrate increases as well. Deuterium exchange experiments are in favour of an intramolecular 1,3-hydride shift from C_2 to C_9.

Reactions affording cyclooctane derivatives are interesting because 8-membered rings are present in some classes of naturally occurring compounds.[1] Direct cyclization of linear precursors results in poor yields because of unfavorable entropic and, mainly, enthalpic factors.[2] Better results are obtained by one- or two-carbon ring expansions[3] as well as by fragmentation reactions of bicyclic precursors,[4] i.e. bicyclo[3.3.1]nonane derivatives.[5,6]

As far as bicyclononane fragmentations are concerned, one of us previously reported that the hydroxy ketal *endo*-**1a** affords the cyclooctanone **6a** (Scheme 1) in high yield when treated with *p*-toluenesulfonic acid (TsOH).[6] Since compound **6a** and/or related products are suitable for further synthetically useful modifications, and in view of the quite easy preparation of bicyclo[3.3.1]nonane derivatives,[7] we decided to study systematically the aforementioned reaction.

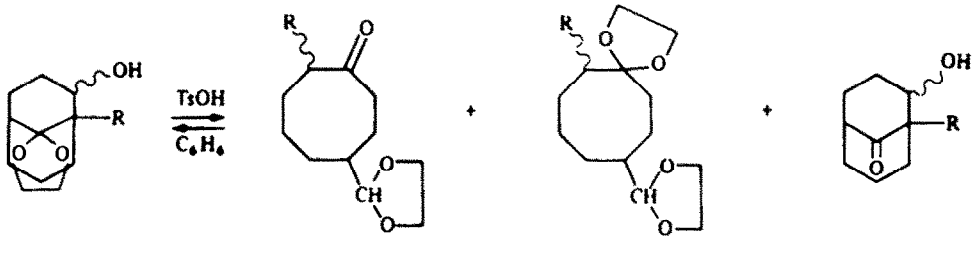
Thus, in order to investigate whether this rearrangement depends on (a) the nature of the substituent at C_1 and/or (b) the configuration at C_2 in the substrate, *exo*-2 and *endo*-2 epimers of compounds **1a–d** were prepared and treated with TsOH.

RESULTS AND DISCUSSION

Hydroxy-ketal *endo*-**1a** was prepared according to the literature,[6] while the epimer *exo*-**1a** was obtained, as expected,[8] from the alkene **3a**[5b] after epoxydation to **4a** followed by $LiAlH_4$ cleavage of the oxyrane ring. Lithium aluminium hydride converted the monoketals **2b** and **2c**, prepared from known substrates,[9,10] to the hydroxy-ketals **1b** and **1c** as mixtures of *endo*-2 and *exo*-2 epimers. Dioxolanation of 1-carbethoxy-bicyclo[3.3.1]non-2-en-9-one[11] gave the ketal **3d**, which was epoxidized to **4d**. Boron trifluoride catalyzed rearrangement of the latter compound gave, as expected,[12] a mixture of the *exo*-hydroxy alkenes **5**, which were hydrogenated to the hydroxyketal *exo*-**1d**. Subsequent equilibration over Raney nickel gave the epimer *endo*-**1d**.

Configurations of all *exo*-**1** epimers followed from the presence of a sharp signal in their IR spectra corresponding to a single intramolecular H-bond. On the contrary, only intermolecular H-bonds were detected in the IR spectra of all *endo*-**1** epimers.

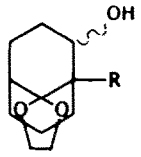
All reactions were performed in dry benzene with TsOH as a catalyst in 0.16 molar ratio with respect to



1 **6** **7** **8**

a R = Ph **b** R = CH_3 **c** R = H **d** R = CO_2Et

Scheme 1.



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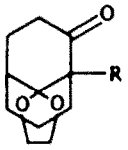

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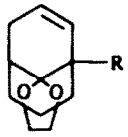

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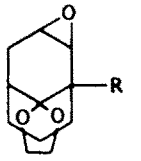

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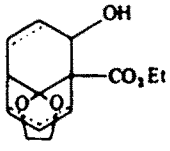

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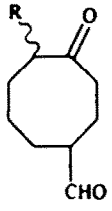

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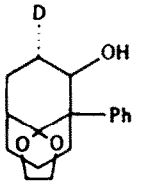

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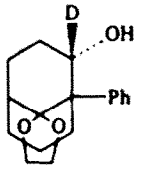

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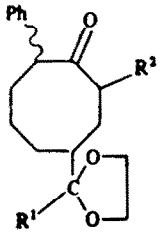


12

a R = Ph. **b** R = CH_3. **c** R = H. **d** R = CO_2Et. **e** R^1 = D, R^2 = H. **f** R^1 = H, R^2 = D

the substrates. The structures of the various reaction products are shown in Scheme 1, while the GC composition of the reaction mixtures obtained both under reflux and at room temperature is reported in Table 1 (runs 1–18).

Structures **6b–d** and **7b** and **c** were assigned by spectroscopic analogy with **6a**,† while the epimeric ketols **8b** were recognized by IR and ^{1}H-NMR comparison with the known stereoisomeric ketols **8c**.[13] Attempts to resolve the epimers **8d** were unsuccessful as well as their preparation through separate acid hydrolysis of the ethylenedioxy group in *exo*- and *endo*-**1d**. Therefore, *exo*- and *endo*-**8d** were recognized as acetates by GC comparison with samples obtained by separate acetylation of *exo*- and *endo*-**1d** followed by ketal hydrolysis under mild conditions.

Formation of cyclooctanones **6** proved to be reversible both under dry (runs 19–22 in Table 1) and under aqueous acidic conditions. Under the latter conditions, cyclooctanones **6b** and **c** behaved as previously reported for **6a**[6] to give epimeric mixtures of ketols **8b** and **c**, likely through spontaneous cyclization of the intermediate formylcyclooctanones **9b** and **c**. The same treatment of **6d** gave a complex mixture not further investigated.

Results of runs 1–18 in Table 1 show that the acid catalyzed rearrangement of bicyclononane derivatives **1** is a general way to obtain functionalized cyclooctanones **6**. Equilibria are shifted towards cyclooctanones at reflux temperature, but the yields are affected, in some instances, by competitive substituent-regulated (*vide infra*) transketalization processes. These latter progressively (compare runs 5 and 9) consume the cyclooctanones **6** to give diacetals **7** together with the unstable formylcyclooctanones **9**, which cyclize to ketols **8**. However, complex mixtures and low yields can be suppressed by carrying out the reactions in the presence of ethylene glycol, as shown in run 10 where diacetal **7c** is produced quantitatively.

The nature of the substituent at C_1 in the substrate plays a small effect on the bridge cleavage process. In fact, when the transketalizations are suppressed by carrying out the rearrangements at room temperature for a short time (runs 11–18 in Table 1), no significant differences in the amounts of the various cyclooctanones **6** are observed. On the contrary, the

† The proton carried by the 1,3-dioxolan-2-yl group appears as a pseudo-triplet in the ^{1}H-NMR spectra of **6a–d** and **7b** and **c**. This unexpected multiplicity is likely related to the carbonyl group (or dioxolan group) at C_1 because the proton in question appears as a doublet after Wolff–Kishner reduction of **6a**.[6]

Table 1. Action of TsOH (0.16 mol) on **1a–d** and **6a–d** in dry benzene

Run[a]	Substrate	Time (hr)	Reaction mixture composition (GC%)[b]				
			endo-**1**	*exo*-**1**	**6**	**7**	**8** (*endo* + *exo*)
1	*endo*-**1a**	3	2.1	tracc	93.6		-
2	*exo*-**1a**	3	1.8	trace	94.2	–	
3	*endo*-**1b**	3	8.7	10.3	66.7	4.5	4.0[c]
4	*exo*-**1b**	3	9.0	7.3	68.4	4.3	3.7[c]
5	*endo*-**1c**	3	2.9	9.8	38.9	22.0	18[d]
6	*exo*-**1c**	3	2.8	10.4	37.0	24.0	16[d]
7	*endo*-**1d**	3	3.2	4.1	58.0	-	10.6[c]
8	*exo*-**1d**	3	2.9	4.0	60.1	—	9.4[c]
9	*endo*-**1c**	6	0.9	4.5	19.3	32.7	28[d]
10	**1c** (*endo* + *exo*)[e]	3	trace	trace	—	97.4	
11	*endo*-**1a**	2	84.5	trace	13.5	—	
12	*exo*-**1a**	2	5.3	78.4	11.3	—	
13	*endo*-**1b**	2	81.5	10.7	5.4	-	—
14	*exo*-**1b**	2	6.7	85.8	3.8	-	—
15	*endo*-**1c**	2	83.0	10.6	2.7		–
16	*exo*-**1c**	2	4.5	90.5	1.8		—
17	*endo*-**1d**	2	95.5	1.0	1.0	–	
18	*exo*-**1d**	2	1.5	95.4	trace		
19	**6a**	18	4.5	trace	91.2		-
20	**6b**	18	8.6	10.3	75.3	-	–
21	**6c**	18	2.2	6.4	67.1	11.3	9[d]
22	**6d**	18	2.4	7.3	46.1	—	30.1[c]

[a] Runs 1–10 were carried out under reflux, while runs 11–22 were carried out at room temperature.

[b] All GC percentages are given with reference to n-eicosane as an internal standard, excluding runs 7, 8, 17, 18 and 22 where n-tetracosane was used.

[c] Value in defect as partial decomposition occurs under GC conditions.

[d] Isolated in mixture by PLC.

[e] Reaction carried out in the presence of excess ethylene glycol.

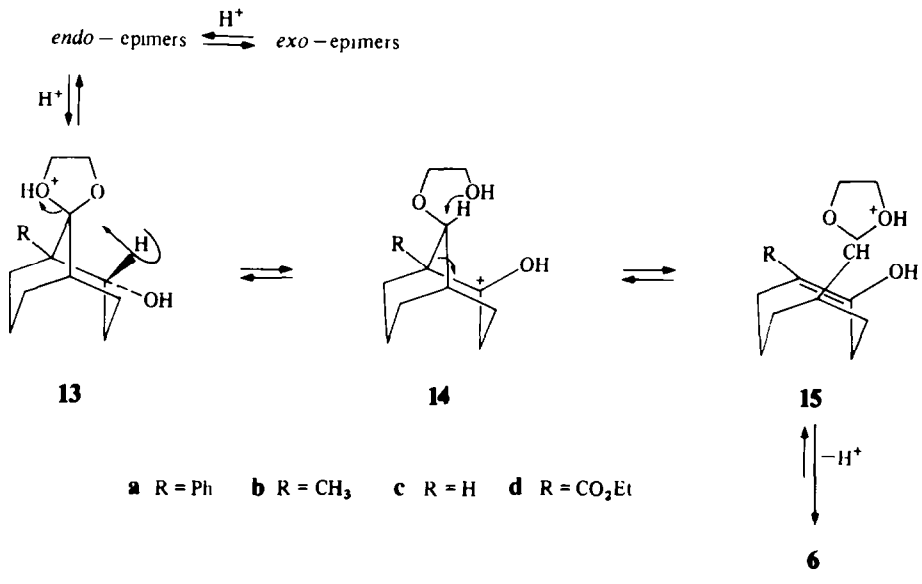
role of the substituent is important in determining the extent of the transketalization processes, which increase as the steric hindrance of the substituent at C_2 in **6** decreases. This is in agreement with the well-known order of dioxolanation of 2-substituted ketones.[14] The absence of diacetal **7d** in the reaction mixture of **1d** is likely due both to steric factors and to the high amount of enolic form in **6d**, while the presence of ketols **8d** can be a consequence of hydrolysis of the acid sensitive **1d** and **6d** during the workup.

The similar composition of the reaction mixtures obtained from pure *endo*- or *exo*-epimers **1** (runs 1–8) suggests that epimerization of the substrates and bridge cleavage compete at comparable rates. Accordingly, at room temperature (runs 11–18) the amounts of epimerized substrates are always comparable or higher than the rearranged ones. Therefore, no direct evidence can be drawn about stereochemical requirements in the bridge cleavage, but mechanistic considerations (*vide infra*) are in favour of the *endo* configuration as the reactive one.

Since previous experiments and considerations on the orbital symmetry conservation were in favour of a stepwise mechanism involving hydride shift from C_2 to C_9,[6] evidence for it to be intramolecular was obtained as follows. A 1:1 mixture of the deuterium labelled hydroxy ketals **10** and **11** was reacted to give a mixture of the labelled cyclooctanones **12e** and **12f** in high yield. ^{1}H-NMR data of the latter mixture accounted for all starting deuterium and allowed to assign the C_8 carbon and the 1,3-dioxolan-2-yl carbon as final incorporation sites. Mass spectrum of the starting mixture **10–11** in comparison with that of the **12e–f** mixture showed that neither dideuterated nor undeuterated materials were present in the latter mixture, so indicating the absence of any intermolecular hydride transfer. Consequently, only intramolecular shifts take place and the *endo*-**1** epimers should be the reactive species.

The mechanistic pathway which better accommodates, in our opinion, the experimental results can be described as depicted in Scheme 2. Protonated *endo* epimers **13**, coming from the starting material or after epimerization of the *exo* epimers, undergo intramolecular 1,3-hydride shift giving rise to the oxygen-stabilized ions **14**. Cleavage of C_1–C_9 bond follows and affords the enols **15**, the overall process being reversible. The formation of cyclooctane derivatives through C_1–C_9 bond cleavage of bicyclo[3.3.1]nonane derivatives has been already observed,[5] but these processes are base-promoted and require an *endo* leaving group at C_2. On the contrary, some acid catalyzed cyclizations of oxygenated cyclooctenes to bicyclo[3.3.1]nonanes have been reported,[15] these processes being related to our reversed reaction.

The behaviour of **1a–d** is at variance with that usually observed in reactions of 9-hydroxy and 9-tosyloxy-bicyclo[3.3.1]nonanes where C_9 carbonium ions are involved.[16] In these cases, hexahydroindenes are always produced through the shift to C_9 of the bridgehead bonds, the migration being strongly driven by the electron releasing abilities of the substituents at C_1. In our case, the protonated ketal group induces only a small amount of positive charge at C_9 and, as a consequence, the role of the substituent is reduced, the rearrangement being driven by the formation of the oxygen-stabilized ions **14**.



Scheme 2.

EXPERIMENTAL

M.ps are uncorrected. All distillations were carried out using a short path column. ^{1}H-NMR spectra were recorded on a Varian EM-360 instrument using TMS as internal standard. IR spectra were obtained on a Perkin–Elmer 257 instrument, while Mass spectra were recorded on an AEI-MS 12 spectrometer. The term column chromatography refers, unless otherwise stated, to the use of a Waters Prep LC-500 instrument with standard silica gel columns.

GC analyses were carried out on a HP-5880A instrument (FID) by using either a 2 m-long column (2% Carbowax 20M on Chromosorb G, 80–100 mesh) or a 0.6 m-long column (2% OV-101 on Chromosorb W, 100–120 mesh).

exo - 2,3 - *Epoxy* - 9,9 - (*ethylenedioxy*) - 1 - *phenylbicyclo*[3.3.1] - *nonane* (**4a**)

Alkene **3a** (3.0 g), prepared as described,[5b] was dissolved in dry $CHCl_3$ (100 ml) and treated with *m*-chloroperbenzoic acid (2.3 g) at room temp overnight. The usual workup left **4a** (3.1 g); m.p. 145–146° (from hexane); IR ν_{max} (CCl_4): 3100, 2940, 1180, 1145, 1000 cm^{-1}; ^{1}H-NMR δ (CCl_4): 7.70–6.80 (5H, m, Ph), 3.60–1.20 (15H, m); Mass spectrum *m/z* (%): 272 (M^+, 12), 184 (60), 157 (19), 155 (29), 113 (42), 99 (base peak).

exo - 2 - *Hydroxy* - 9,9 - (*ethylenedioxy*) - 1 - *phenylbicyclo* - [3.3.1]*nonane* (exo-**1a**)

Compound **4a** (3.0 g) in dry THF (100 ml) was added to a suspension of $LiAlH_4$ (0.5 g) in THF (300 ml) and the mixture was refluxed for 6 hr under N_2 stream. Excess hydride was destroyed with NH_4Cl and the organic layer was separated. Solvent removal gave *exo*-**1a** (2.5 g); m.p. 133–134° (from hexane); IR ν_{max} (CCl_4): 3520 (unaffected by dilution), 3060, 2920, 1175, 1115, 1025 cm^{-1}; ^{1}H-NMR δ (CCl_4): 7.80–6.85 (5H, m, Ph), 4.33 (1H, br s, OH), 4.18 (1H, br s, C_2—H), 4.10–3.65 (4H, m, O—CH_2—CH_2—O), 2.40–1.30 (11H, m); Mass spectrum *m/z* (%): 274 (M^+, 22), 256 (43), 212 (18), 184 (36), 170 (35), 115 (40), 113 (46), 103 (49), 99 (base peak). Found: C, 74.39; H, 8.00. Calc for $C_{17}H_{22}O_3$: C, 74.45; H, 8.03.

9,9 - (*Ethylenedioxy*) - 1 - *methylbicyclo*[3.3.1]*nonan* - 2 - *one* (**2b**)

1-Methylbicyclo[3.3.1]nonan-2,9-dione[8] (16.4 g), ethylene glycol (6.5 g) and TsOH (0.1 g) were refluxed in benzene (450 ml) for 24 hr by removing the formed water. Washing with N HCO_3 (sat soln), solvent removal and column chromatography (hexane–EtOAc 9:1 as eluent) gave starting material (4.5 g) and **2b** (15.5 g); b.p. 92°/0.5 mm; IR ν_{max} (CCl_4): 2940, 1715, 1130, 1120, 1060 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.93 (4H, s, O—CH_2—CH_2—O), 2.70–1.30 (11H, m), 0.93 (3H, s, C_1—CH_3); Mass spectrum *m/z* (%): 210 (M^+, base peak), 182 (71), 167 (24), 166 (23).

endo - 2 *and* exo - 2 - *Hydroxy* - 9,9 - (*ethylenedioxy*) - 1 - *methylbicyclo*[3.3.1]*nonane* (endo-**1b** *and* exo-**1b**)

Ketal **2b** (10.0 g) in 350 ml of dry Et_2O was reduced with 1 equivalent of lithium aluminium hydride at room temp. The usual workup followed by column chromatography (light petroleum–EtOAc 95:5 as eluent) gave *exo*-**1b** (2.3 g) in the first fractions; b.p. 118°/1 mm; IR ν_{max} (CCl_4): 3520 (unaffected by dilution), 2880, 1120, 1060, 1040 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.95 (4H, m, O—CH_2—CH_2—O), 3.77 (1H, br s, C_2—H), 2.30–1.20 (12H, m), 0.98 (3H, s, C_1—CH_3); Mass spectrum *m/z* (%): 212 (M^+, 90), 194 (30), 113 (86), 99 (base peak). Found: C, 67.15; H, 9.40. Calc for $C_{12}H_{20}O_3$: C, 67.29; H, 9.43. Later fractions contained *endo*-**1b** (7.2 g); m.p. 106–107° (from hexane–ethyl acetate); IR ν_{max} (CCl_4): 3560, 2980, 1120, 1060 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.92 (4H, s, O—CH_2—CH_2—O), 3.85 (1H, t, J = 5 Hz, C_2—H), 2.30–1.20 (12H, m), 0.93 (3H, s, C_1—CH_3); Mass spectrum *m/z* (%): 212 (M^+, 66), 113 (72), 108 (base peak). Found: C, 67.23; H, 9.45. Calc for $C_{12}H_{20}O_3$: C, 67.29; H, 9.43.

9,9 - (*Ethylenedioxy*) - *bicyclo*[3.3.1]*nonan* - 2 - *one* (**2c**)

9,9-(Ethylenedioxy)bicyclo[3.3.1]non-3 - en - 2 - one (5.0 g), prepared as described,[10] was hydrogenated over 10% Pd/C in ethyl acetate at room temp. The usual workup gave **2c** (5.04 g); b.p. 115°/1 mm; IR ν_{max} (CCl_4): 2940, 1715, 1120 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.83 (4H, s, O—CH_2—CH_2—O), 2.50–1.00 (12H, m); Mass spectrum *m/z* (%): 196 (M^+, 56), 168 (39), 152 (33), 140 (29), 125 (54), 112 (base peak).

endo - 2 *and* exo - 2 - *Hydroxy* - 9,9 - (*ethylenedioxy*) - *bicyclo*[3.3.1]*nonane* (endo-**1c** *and* exo-**1c**)

Ketone **2c** (5.0 g) was added dropwise to a suspension of $LiAlH_4$ (0.25 g) in diethyl ether. After 0.5 hr stirring, the usual workup gave a crude mixture which was separated by column chromatography (light petroleum–diethyl ether 3:2 as eluent). First fractions contained *exo*-**1c** (2.5 g); b.p. 123°/1 mm; IR ν_{max} (CCl_4): 3520 (unaffected by dilution), 2980, 1120, 1085, 1040 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.95 (4H, m, O—CH_2—CH_2—O), 3.75 (1H, br s, C_2—H), 3.54 (br s, OH),

2.30–0.80 (12H, m); Mass spectrum *m/z* (%): 198 (M^+, base peak), 180 (18), 141 (38), 128 (24). Found: C, 66.60; H, 9.07. Calc for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Subsequent fractions gave *endo*-**1c** (2.5 g); m.p. 101–102° (from hexane–Et_2O); IR ν_{max} (CCl_4): 3610, 2980, 1120, 1050 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.08 (1H, br s, C_2—H), 3.87 (4H, s, O—CH_2—CH_2—O), 3.35 (1H, br s, OH), 2.20–0.80 (12H, m); Mass spectrum *m/z* (%): 198 (M^+, base peak), 180 (13), 141 (30), 128 (20), 127 (30). Found: C, 66.63; H, 9.10. Calc for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09.

9,9 - (*Ethylenedioxy*) - 1 - *carbethoxybicyclo*[3.3.1]*non* - 2 - *ene* (**3d**)

1 - Carbethoxybicyclo[3.3.1]non - 2 - en - 9 - one (4.2 g), prepared as described,[11] was ketalized with ethylene glycol as usual, and afforded **3d** (5 g); b.p. 125°/0.6 mm; IR ν_{max} (CCl_4): 2980, 1730, 1240, 1125, 1060 cm^{-1}; ^{1}H-NMR δ (CCl_4): 5.80 (1H, tt, J = 9.0, 3.0 Hz, C_3—H), 5.52 (1H, tt, J = 9.0, 1.5 Hz, C_2—H), 4.07 (2H, q, J = 7.0 Hz), 3.85 (4H, br s, O—CH_2—CH_2—O), 2.20–1.20 (9H, m), 1.20 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 252 (M^+, 36), 179 (base peak), 99 (80).

exo - 2,3 - *Epoxy* - 9,9 - (*ethylenedioxy*) - 1 - *carbethoxybicyclo* - [3.3.1]*nonane* (**4d**)

Alkane **3d** (4.7 g), *m*-chloroperbenzoic acid (3.5 g) and dry $NaHCO_3$ (1.7 g) were refluxed under stirring in dry $CHCl_3$ (120 ml) for 2 hr. After the usual workup, solvent removal gave **4d** (5.0 g); b.p. 76°/0.05 mm; IR ν_{max} (CCl_4): 2990, 2940, 1735, 1250, 1155, 1110, 1080 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.14 (2H, q, J = 7.0 Hz), 3.85 (4H, m, O—CH_2—CH_2—O), 3.08 (2H, m, C_2—H and C_3—H), 2.50–1.00 (9H, m), 1.30 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 268 (M^+, 25), 222 (29), 113 (21), 99 (base peak).

exo - 2 - *Hydroxy* - 9,9 - (*ethylenedioxy*) - 1 - *carbethoxybicyclo* - [3.3.1]*nonane* (exo-**1d**)

Freshly distilled BF_3 etherate (12.0 ml) was added dropwise to a stirred, ice cooled soln of **4d** (4.9 g) in dry ether (200 ml), and the mixture was left at room temp overnight. After washing with $NaHCO_3$ and brine, the organic layer was evaporated to give the *exo*-**5** (4.6 g) in mixture (three peaks in 2 : 1 : 1 GC ratio) not further purified; IR ν_{max} (CCl_4): 3520 cm^{-1} (unaffected by dilution); ^{1}H-NMR δ (CCl_4): 5.80–5.30 (2H, m, vinylic protons), 4.50–3.30 (7H, m), 2.70–1.00 (8H, m), 1.25 (3H, t, J = 7.0 Hz); Mass spectrum: M^+ at 268 *m/z*. The mixture **5** (4.4 g) was hydrogenated in EtOH over 10% Pd/C at room temp and gave *exo*-**1d** (4.0 g); b.p. 92°/0.05 mm; IR ν_{max} (CCl_4): 3520 (unaffected by dilution), 2980, 2940, 1740, 1260, 1230, 1200, 1160, 1120, 1060 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.23 (1H, br d, J = 4.5 Hz, C_2—H), 4.05 (2H, q, J = 7.0 Hz), 3.92 (4H, m, O—CH_2—CH_2—O), 3.88 (1H, br s, OH), 2.30–1.00 (11H, m), 1.20 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 270 (M^+, 59), 252 (19), 224 (57), 179 (58), 99 (base peak). Found: C, 62.20; H, 8.10. Calc for $C_{14}H_{22}O_5$: C, 62.22; H, 8.15.

endo - 2 - *Hydroxy* - 9,9 - (*ethylenedioxy*) - 1 - *carbethoxybicyclo* - [3.3.1]*nonane* (endo-**1d**)

Raney Ni (15 g) and *exo*-**1d** (0.5 g) in dry isopropanol (20 ml) were warmed at 110° in a rocking steel bomb for two days. Filtration, solvent removal and column chromatography (light petroleum–EtOAc 9 : 1 as eluent) afforded starting material (0.11 g) and *endo*-**1d** (0.37 g); b.p. 94°/0.05 mm; m.p. 44–46°; IR ν_{max} (CCl_4): 3600, 3520, 2980, 2940, 1730, 1260, 1205, 1120, 1070 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.55 (1H, dd, J = 10.0, 2.0 Hz, C_2—H), 4.05 (2H, q, J = 7.0 Hz), 3.75 (4H, br s, O—CH_2—CH_2—O), 2.67 (1H, br s, OH), 2.50–1.00 (11H, m), 1.25 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 270 (M^+, base peak), 252 (10), 224 (27), 197 (30), 179 (26), 99 (69). Found: C, 62.24; H, 8.12. Calc for $C_{14}H_{22}O_5$: C, 62.22; H, 8.15.

Action of TsOH *on* endo- *and* exo-**1** *under reflux*

All reactions were carried out by refluxing for 3 hr 0.07 M dry benzenic solns of the appropriate substrate and TsOH monohydrate in 1 : 0.16 molar ratio. The mixtures were washed with $NaHCO_3$ (sat soln) and dried over anhyd Na_2SO_4, and the solvent was removed under reduced pressure. Separation of the mixtures was performed by column chromatography using light petroleum–EtOAc (9 : 1) as eluent. Products obtained from each substrate are reported below in elution order and their properties are listed at the end of the various paragraphs.

(a) *Products from* exo-**1a**. Chromatography of the mixture from *exo*-**1a** (1.0 g) gave **6a** (0.88 g) and *endo*-**1a** (0.05 g) both identical to authentic samples.[6]

(b) *Products from* endo- *and* exo-**1b**. Compound *endo*-**1b** (4.0 g) gave 1,1 - (*ethylenedioxy*) - 6 - (1,3 - *dioxolan* - 2 - *yl*) - 2 - *methylcyclooctane* (**7b**, 0.19 g, 4%), 6-(1,3-*dioxolan*-2-*yl*)-2-*methylcyclooctanone* (**6b**, 2.6 g, 65%), *exo*-**1b** (0.45 g), *endo*-**1b** (0.35 g), endo - 2 - *hydroxy* - 1 - *methylbicyclo*[3.3.1]*nonan* - 9 - *one* (*endo*-**8b**, 0.09 g, 2.8%) and its *exo*-2 epimer (*exo*-**8b**, 0.03 g, 0.9%). The two latter compounds were obtained in mixture from the chromatography and were separated by repeated PLC. In the same way, epimer *exo*-**1b** (1.0 g) afforded **7b** (0.04 g), **6b** (0.68 g), *exo*-**1b** (0.06 g), *endo*-**1b** (0.08 g) and epimers **8b** in mixture (0.03 g).

Compound **6b**: b.p. 106°/2 mm; IR ν_{max} (CCl_4): 2940, 2860, 1710, 1150, 1130 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.82 (1H, pseudo t, O—CH—O), 4.05–3.75 (4H, m, O—CH_2—CH_2—O), 2.55–0.80 (12H, m), 1.02 (3H, d, J = 7.0 Hz, C_1—CH_3); Mass spectrum *m/z* (%): 212 (M^+, 8), 113 (5), 99 (13), 73 (base peak). Found: C, 67.30; H, 9.40. Calc for $C_{12}H_{20}O_3$: C, 67.29; H, 9.43.

Compound **7b**: b.p. 125°/2 mm; IR ν_{max} (CCl_4): 2940, 2860, 1150, 1130 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.80 (1H, pseudo t, O—CH—O), 4.10–3.80 (8H, m, 2 O—CH_2—CH_2—O), 2.50–0.90 (12H, m), 0.95 (3H, d, J = 7.0 Hz, C_1—CH_3); Mass spectrum *m/z* (%): 256 (M^+, 3), 156 (21), 127 (5), 113 (base peak). Found: C, 65.60; H, 9.35. Calc for $C_{14}H_{24}O_4$: C, 65.63; H, 9.38.

Compound endo-**8b**: b.p. 59°/0.07 mm; IR ν_{max} (CCl_4): 3620, 2960, 2850, 1710, 1090 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.55 (1H, t, J = 9.0 Hz, C_2—H), 2.72 (1H, br s, OH), 2.50–1.00 (11H, m), 0.98 (3H, s, C_1—CH_3); Mass spectrum *m/z* (%): 168 (M^+, 22), 124 (base peak), 111 (56), 109 (22). Found: C, 71.45; H, 9.50. Calc for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52.

Compound exo-**8b**: b.p. 64°/0.07 mm; IR ν_{max} (CCl_4): 3630, 2995, 2860, 1720, 1090 cm^{-1}; ^{1}H-NMR δ (CCl_4): 3.90 (1H, br s, C_2—H), 2.75 (1H, br s, OH), 2.50–1.00 (11H, m), 0.98 (3H, s, C_1—CH_3); Mass spectrum *m/z* (%): 168 (M^+, 24), 124 (base peak), 112 (17), 111 (46), 109 (17). Found: C, 71.44; H, 9.52. Calc for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52.

(c) *Products from* endo- *and* exo-**1c**. Compound *endo*-**1c** (2.50 g) gave 1,1 - (*ethylenedioxy*) - 4 - (1,3 - *dioxolan* - 2 - *yl*) - *cyclooctane* (**7c**, 0.64 g, 21%), 4-(1,3-*dioxolan*-2-*yl*)-*cyclooctanone* (**6c**, 0.87 g, 35%), *exo*-**1c** (0.21 g), *endo*-**1c** (0.06 g), *endo*-2-*hydroxy*-*bicyclo*[3.3.1]*nonan*-9-*one* (*endo*-**8c**, 0.18 g, 9%), and its *exo*-2 epimer (*exo*-**8c**, 0.22 g, 11%). The two latter compounds showed to be unstable under GC conditions and their properties (m.p., IR and ^{1}H-NMR spectra) were identical to those described.[13] In the same way epimer *exo*-**1c** (1.00 g) gave **7c** (0.27 g), **6c** (0.38 g), *exo*-**1c** (0.09 g), *endo*-**1c** (0.03 g) and epimers **8c** in mixture (0.12 g).

Compound **6c**: b.p. 126°/3 mm; IR ν_{max} (CCl_4): 2920, 2850, 1710, 1140, 1130, 1040 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.72 (1H, pseudo t, O—CH—O), 3.78 (4H, m, O—CH_2—CH_2—O), 2.40–1.00 (13H, m); Mass spectrum *m/z* (%): 198 (M^+, 8), 136 (9), 99 (14), 73 (base peak). Found: C, 66.70; H, 9.03. Calc for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09.

Compound **7c**: b.p. 135°/3 mm; IR ν_{max} (CCl_4): 2940, 2865, 1145, 1130 cm^{-1}; ^{1}H-NMR δ (CCl_4): 4.72 (1H, pseudo t, O—CH—O), 3.95–3.68 (8H, m, 2 O—CH_2—CH_2—O), 2.10–0.90 (13H, m); Mass spectrum *m/z* (%): 242 (M^+, 4), 142 (12), 113 (20), 99 (base peak). Found: C, 64.44; H, 9.07. Calc for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09.

(d) *Products from* endo- *and* exo-**1d**. Since trial experiments showed that the usual chromatographic separation resulted in product decomposition, the tarry reaction mixture obtained from *exo*-**1d** (2.0 g) was adsorbed on 260 g of prewashed SiO_2

(stirred with 1 N HCl overnight, washed with hot water until negative test for chloride ion and activated at 110° overnight). Elution with the usual solvent gave 6-(1,3-*dioxolan*-2-*yl*)-2-*carbethoxycyclooctanone* (**6d**, 0.74 g, 37%), *endo*-**1d** (0.2 g), *exo*-**1d** (0.05 g) and an unseparable thermally unstable mixture of endo-2 and exo-2-*hydroxy*-1-*carbethoxybicyclo*[3.3.1]*nonan*-9-*one* (*endo*- and *exo*-**8d**, 0.22 g, 13%). In the same way epimer *endo*-**1d** (0.2 g) afforded **6d** (0.06 g) and the epimeric mixture **8d** (0.02 g) together with traces of *exo*- and *endo*-**1d**.

Compound **6d**: b.p. 90°/0.05 mm; IR ν_{max} (CCl_4): 2980, 2940, 1740, 1715, 1650, 1610, 1225, 1040 cm^{-1}; ^{1}H-NMR δ (CCl_4): 12.08 (0.5H, s, enolic OH), 4.67 (1H, pseudo t, O—CH—O), 4.08 (2H, q, J = 7.0 Hz), 3.75 (4H, m, O—CH_2—CH_2—O), 2.70–1.10 (11.5H, m), 1.26 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 270 (M^+, 59), 224 (14), 208 (22), 170 (17), 99 (29), 73 (base peak). Found: C, 62.18; H, 8.10. Calc for $C_{14}H_{22}O_5$: C, 62.22; H, 8.15.

Compounds endo- and exo-**8d** (in mixture): IR ν_{max} (CCl_4): 3440, 1740, 1710 cm^{-1}; Mass spectrum: M^+ at 226 *m/z*. Ketols *endo*- and *exo*-**8d** were recognized after acetylation of the mixture in the usual way and GC comparison with samples obtained as follows. Alcohol *endo*-**1d** (0.1 g) was acetylated at room temp to give quantitatively the *endo*-2-acethoxy derivative (b.p. 98°/0.05 mm; IR ν_{max} (CCl_4): 1745, 1730 cm^{-1}) which was suspended in aqueous tartaric acid (sat soln) and stirred overnight at room temp. Extraction with Et_2O, washing with $NaHCO_3$ and PLC (hexane–EtOAc 8:2) afforded the endo-2-*acethoxy*-1-*carbethoxybicyclo*[3.3.1]-*nonan*-9-*one*; b.p. 95°/0.05 mm; IR ν_{max} (CCl_4): 1745, 1730, 1720 cm^{-1}; ^{1}H-NMR δ (CCl_4): 5.14 (1H, m, C_2—H), 4.15 (2H, q, J = 7.0 Hz), 2.60–2.10 (11H, m), 1.90 (3H, s, OC—CH_3), 1.25 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 268 (M^+, 16), 226 (22), 208 (43), 180 (base peak). In a similar way alcohol *exo*-**1d** (0.1 g) was acetylated under reflux for 1 hr and deketalized to give the exo-2-*acethoxy*-1-*carbethoxybicyclo*[3.3.1]*nonan*-9-*one*; b.p. 89°/0.05 mm; IR ν_{max} (CCl_4): 1745, 1730, 1715 cm^{-1}; ^{1}H-NMR δ (CCl_4): 5.44 (1H, br s, C_2—H), 4.13 (2H, q, J = 7.0 Hz), 2.60–1.00 (11H, m), 1.90 (3H, s, OC—CH_3), 1.27 (3H, t, J = 7.0 Hz); Mass spectrum *m/z* (%): 268 (M^+, 16), 226 (25), 208 (32), 180 (base peak).

Quantitative GC analyses. All rearrangements were repeated both under reflux and at room temp by using 50 mg of each substrate and 0.2 mol of the appropriate GC standard. Standards, reaction conditions and product yields are reported in Table 1 (runs 1–18). In run 5, after 3 hr reflux the mixture was halved. A portion was analyzed to give results reported as run 5, and the residual portion was refluxed for additional 3 hr to give results reported as run 9. In run 10, excess ethyleneglycol was added to an equimolar mixture of *endo*- and *exo*-**1c** (50 mg) and a trap was used to remove the produced water.

Action of acids on **6b–d** *at room temperature*

(a) *Under dry conditions.* The usual amount of TsOH was added to benzenic solutions of **6b–d** containing the appropriate GC standard, and the mixtures were stirred at room temp for 18 hr. After the usual workup, GC analyses gave the results reported in Table 1 (runs 19–22).

(b) *Under aqueous conditions.* Pure samples of **6b–d** (50 mg) were suspended in 2 N HCl (1 ml) and stirred at room temp for 1 hr. The resulting mixtures were extracted with Et_2O, washed with $NaHCO_3$ and purified by PLC. Compound **6b** gave *endo*-**8b** (26 mg) and *exo*-**8b** (10 mg), compound **6c** afforded *endo*-**8c** (22 mg) and *exo*-**8c** (12 mg), while **6d** gave a complex mixture not further investigated.

exo - 2 - *Hydroxy* - 9,9 - (*ethylenedioxy*) - 1 - *phenylbicyclo* - [3.3.1]*nonane* - 3 - d_1 (**10**)

The epoxy derivative **4a** (0.15 g) and excess $LiAlD_4$ were refluxed in dry dimethoxyethane (25 ml) for 8 hr. The usual workup, followed by PLC allowed to isolate **10** (0.12 g); ^{1}H-NMR ($CDCl_3$): identical to that of *exo*-**1a**, but the integration in the range 2.40–1.30 δ accounts for 10H. Mass spectrum *m/z* (%): 275 (M^+, 34), 257 (57), 213 (21), 185 (32), 171 (23), 99 (base peak).

Deuterium exchange experiment. Compound **11** (50 mg), prepared as described,[6] and **10** (50 mg) were dissolved in dry benzene and treated with the usual amount of TsOH at room temp overnight. The usual workup followed by PLC gave **12e** and **12f** (80 mg) as a mixture identical (TLC, GC, IR) to **6a**; ^{1}H-NMR δ (CCl_4) showed **12e** and **12f** in 1:1 ratio: 7.40–7.10 (5H, m, Ph), 4.82 (0.5H, pseudo t, O—CH—O), 3.83 (4H, m, O—CH_2—CH_2—O), 3.56 (1H, m, C_2—H), 2.60–2.20 (1.5H, m, C_6=H_2), 2.20–1.10 (9H, m); Mass spectrum: $M_r/M+1$ = 5.1, $M_r/M-1$ = 58.6. The $M_r/M+1$ and $M_r/M-1$ values recorded for the starting mixture of **10** and **11** are 5.2 and 58.8, respectively.

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