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THE ELECTRON IMPACT INDUCED FRAGMENTATIONS OF SOME 7-ALKYL-3-OXABICYCLO[3.3.1]NONANES

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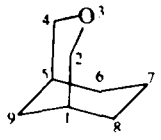
Abstract—The mass spectra of a series of 7-alkyl substituted 3-oxabicyclo[3.3.1]nonanes are recorded. The fragmentation has been studied by the use of the metastable DADI and defocussing techniques. The character of the alkyl group is found to influence the fragmentation pattern. Stereoselective fragmentations for the 7-t-butyl derivatives are observed. In the *endo*-isomer, in contrast to the *exo*-isomer, a transannular hydrogen transfer plays a role.

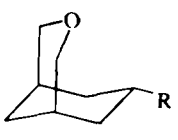
INTRODUCTION

In a previous paper it was shown that for t-butylcyclohexanecarboxylic acids the electron impact induced fragmentation is dependent on the ability of the carboxyl and the t-butyl group to interact.[1] In *cis*-2-, *trans*-2-, *cis*-3- and *cis*-4-t-butylcyclohexanecarboxylic acid a transannular hydrogen transfer is observed, resulting in loss of C_4H_8 and C_4H_7. Other examples of stereoselective fragmentations in cyclohexane derivatives have been given.[2]

With the aid of other instrumental techniques we have studied the configuration and conformation of some bicyclo[3.3.1]nonane derivatives.[3] These systems have a unique structure allowing interesting transannular interactions. Therefore in the mass spectrometry of these compounds stereoselective fragmentations, which might be helpful in configurational assignments, may be operative. Until now only a few studies on the mass



1



2

3

a: R = Me
b: R = i-Pr
c: R = t-Bu

spectral fragmentation of bicyclo[3.3.1]nonanes, most of them dealing with 2-substituted derivatives, have been published.[4]

In this paper the mass spectral fragmentations of 3-oxabicyclo[3.3.1]nonane (**1**), its 7-*exo*- (**2a–c**) and its 7-*endo*-alkyl (**3a–c**) derivatives are reported. The mass spectral fragmentation pattern of these compounds was elucidated using the defocussing technique as well as direct analysis of daughter ions (DADI method).

Synthesis of the 3-oxabicyclo[3.3.1]nonanes

The 7-*exo*-alkyl-3-oxabicyclo[3.3.1]nonanes (**2**) were synthesized following the procedure of Haggis and Owen.[5] 5-Alkylcyclohexane-*cis*-1,3-dicarboxylic acids (**4**) were converted to the methanol derivatives (**5**). Reaction with methanesulfonyl chloride afforded the mesylates (**6**), which gave the desired 7-*exo*-alkyl-3-oxabicyclo[3.3.1]nonanes (**2**) upon reaction with aqueous KOH (Scheme 1). Application of this route to the synthesis of the 7-*endo*-alkyl compounds (**3**) afforded complex mixtures, due to epimerizations during the reaction with KOH. Only the 7-*endo*-t-butyl derivative (**3c**) could be isolated from such a reaction mixture.

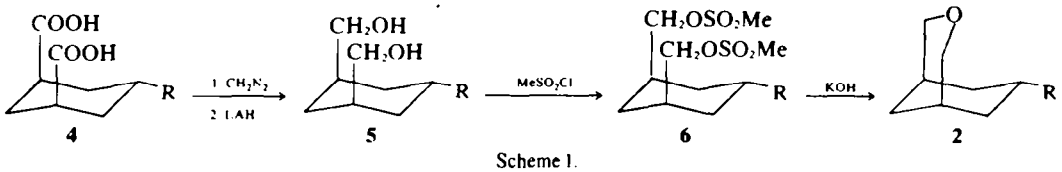
The 7-*endo*-methyl- and 7-*endo*-isopropyl-3-oxabicyclo[3.3.1]nonanes (**3a,b**) were synthesized starting from 4-oxacyclohexanone (**7**). α,α'-Annelation of the pyrrolidine enamine **8** with methyl β,β'-dibromoisobutyrate[7] afforded methyl 3-oxa-9-oxobicyclo[3.3.1]nonane-7-*endo*-carboxylate (**9**). After protection of the 9-oxo-function as the dimethyl acetal reduction with LAH and acid hydrolysis gave the 7-*endo*-methanol compound (**11**). The 9-oxo-function was removed by a Huang-Minlon reduction. Tosylation of the resulting methanol compound (**12**) and subsequent reduction with LAH gave 7-*endo*-methyl-3-oxabicyclo[3.3.1]nonane (**3a**). Reaction of **10** with MeMgBr resulted in the corresponding dimethylcarbinol (**13**). Treatment with 4 N H_2SO_4–dioxane (1:1) caused hydrolysis of the acetal and dehydration to yield 7-isopropyl-9-oxo-3-oxabicyclo[3.3.1]non-6-ene (**14**). Due to its special geometry this compound could be hydrogenated selectively to 9-hydroxy-7-*endo*-isopropyl-3-oxabicyclo[3.3.1]nonane (**15**). After oxidation of the 9-hydroxy-function, a Huang-Minlon reduction afforded the desired 7-*endo*-isopropyl-3-oxa-bicyclo[3.3.1]nonane (**3b**) (Scheme 2).

The configuration of compounds **1–3** was proved by NMR spectroscopy with the use of lanthanide shift reagents.

Mass spectra

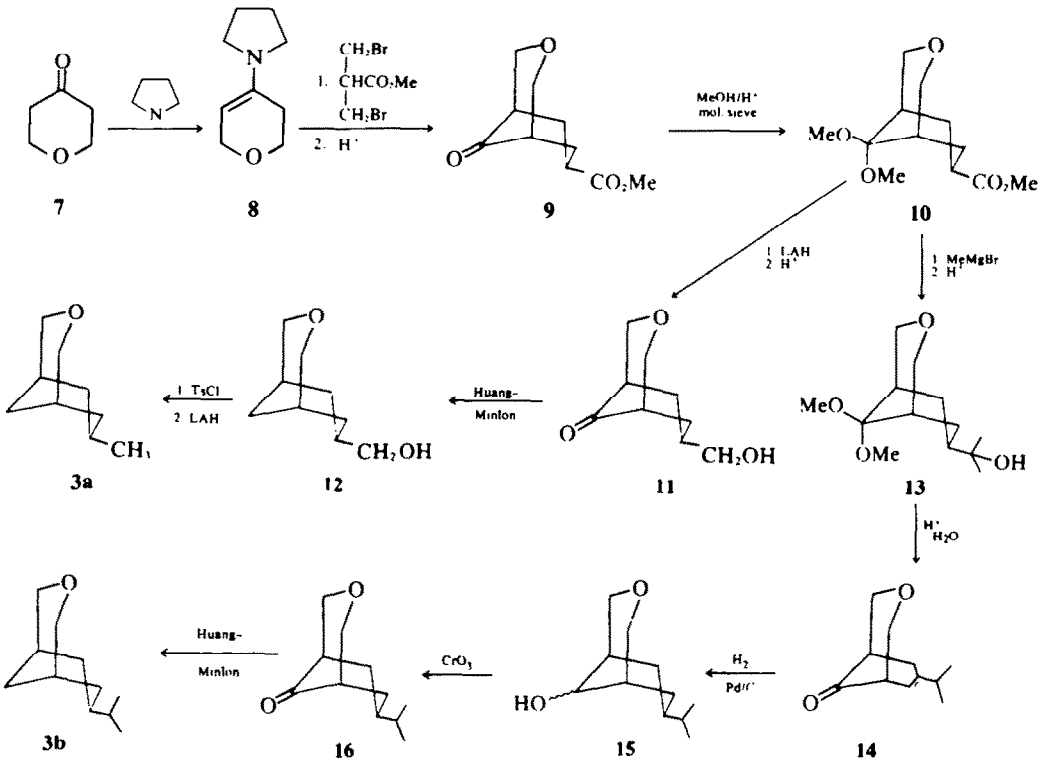
The mass spectra of the oxabicyclo[3.3.1] nonanes (Figs. 1–5)† show that in unsubstituted 3-

†Large-sized copies of the fragmentation maps are available from the authors.



4 5 6 2

Scheme 1.



Scheme 2.

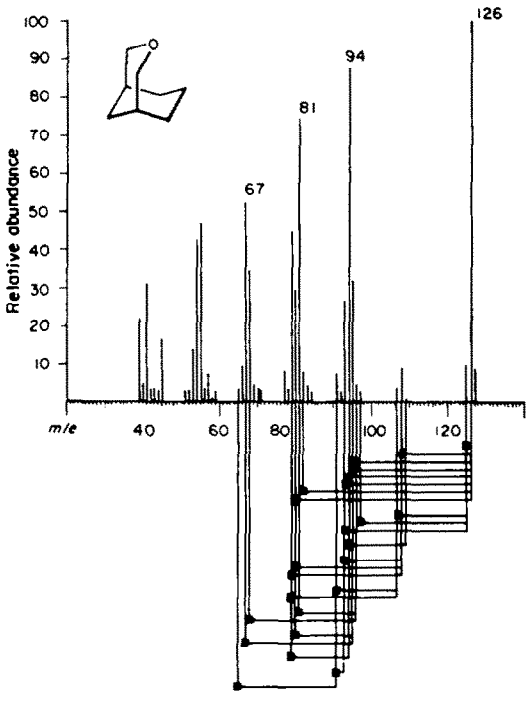


Fig. 1. Fragmentation map of 3-oxabicyclo[3.3.1]nonane.

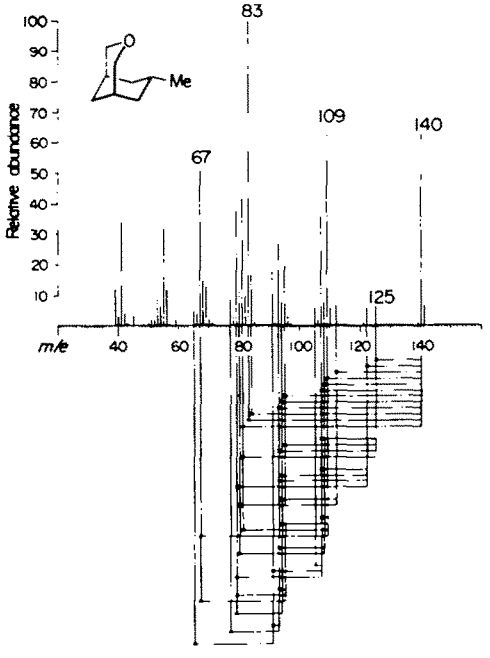


Fig. 2. Fragmentation map of 7-*exo*-methyl-3-oxabicyclo-[3.3.1]nonane.

oxabicyclo[3.3.1]nonane (**1**) the fragmentation is invoked with the expulsion of an oxygen-containing fragment (H_2O, CH_2O, $CH_3O\cdot$, CH_3OH and CH_3OCH_3), whereas in the 7-isopropyl (**2b**, **3b**) and 7-t-butyl (**2c**, **3c**) derivatives loss of the alkyl group dominates the fragmentation. The 7-methyl derivatives (**2a**, **3a**) show both types of fragmentations.

The most important difference in mass spectral behaviour occurs between 7-*exo*-t-butyl-3-oxabicyclo-[3.3.1]nonane (**2c**) and the corresponding 7-*endo*-derivative (**3c**). In **2c** the t-Bu group is eliminated as $C_4H_9\cdot$ to yield the ion at *m/e* 125. In the spectrum of **3c**, in addition to the peak at *m/e* 125, relative intensive peaks are found at *m/e* 126 and 127 (loss of C_4H_8 and $C_4H_7\cdot$ respectively). In this compound the t-Bu group is able to

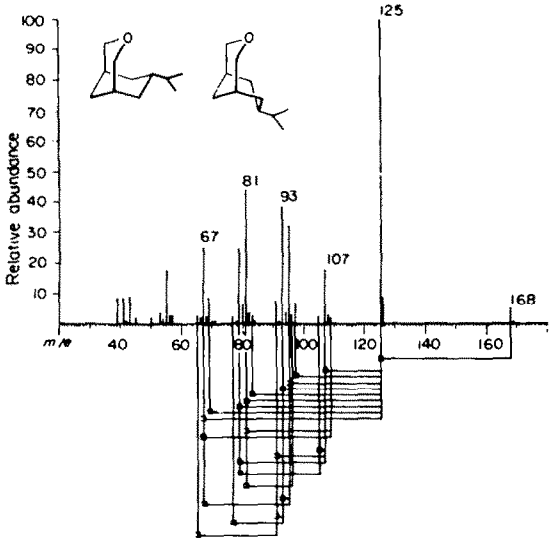


Fig. 3. Fragmentation map of 7-*exo*- and 7-*endo*-isopropyl-3-oxabicyclo[3.3.1]nonane.

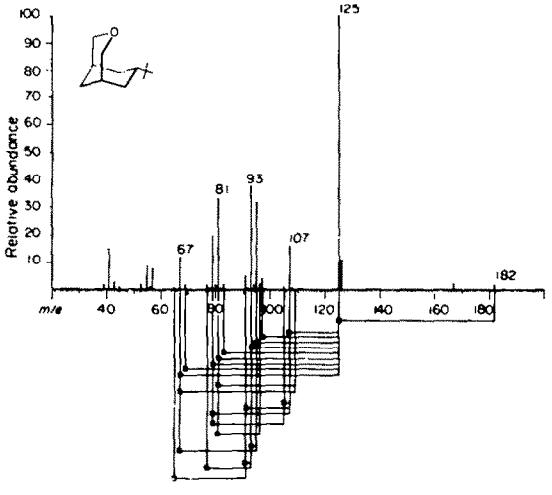


Fig. 4. Fragmentation map of 7-*exo*-t-butyl-3-oxabicyclo-[3.3.1]nonane.

approach the O atom by the conversion of the boat ring into a (flattened) chair, allowing a transannular hydrogen transfer (Scheme 3). Then elimination of C_4H_8 by a simple cleavage reaction affords the ion at *m/e* 126. Here as well

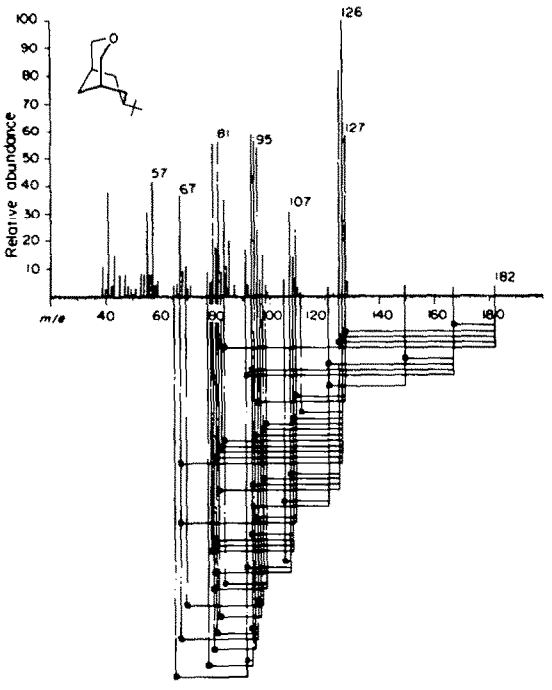
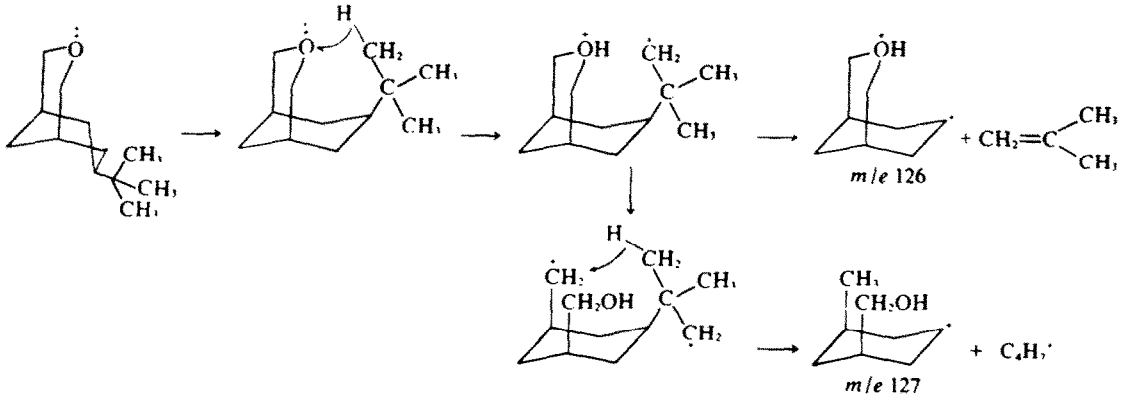


Fig. 5. Fragmentation map of 7-*endo*-t-butyl-3-oxabicyclo-[3.3.1]nonane.

as in the t-butylcyclohexanecarboxylic acids,[1] the elimination of C_4H_8 is accompanied by the loss of C_4H_7·. Most probably the latter fragmentation also starts with a transannular hydrogen transfer. This might be followed by heterolytic cleavage and one or more hydride shift(s) with elimination of C_4H_7· (Scheme 3).

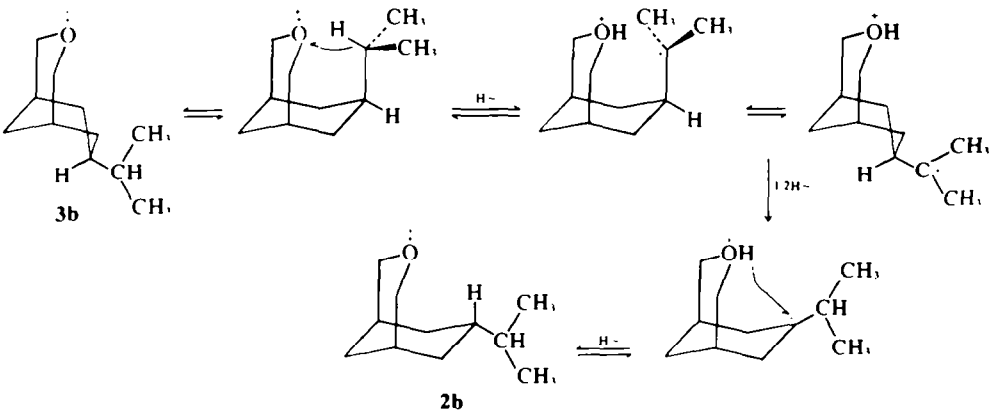
It may be noted that, in contrast to the spectra of **2c** and **3c**, the spectra of *endo* and *exo*-7-isopropyl-3-oxabicyclo[3.3.1]nonane (**2b, 3b**) are almost identical. The fragmentations producing the ions at *m/e* 126 and 127 were not observed to any extent. This similarity in mass spectral behaviour prompted us to investigate the mass spectra of *cis*- and *trans*-4-isopropylcyclohexanecarboxylic acid. Here indeed, in contrast to the corresponding t-Bu derivatives, the same similarity was observed. This does not imply that in the *endo*-compound **3b** (or *cis*-4-isopropylcyclohexanecarboxylic acid) a transannular hydrogen transfer is absent. It is well established that transfer of a tertiary hydrogen is preferred over a primary one;[9,10] both transfers would be allowed by the geometry. The first hydrogen transfer rationalizes the absence of loss of



Scheme 3.

C_3H_6 and $C_3H_5^+$. Subsequent hydrogen transfers could result in epimerization of the *endo*-compound (**3b**) to the *exo*-compound (**2b**) (or *cis* to *trans*-4-isopropylcyclohexanecarboxylic acid). If this isomerization is relatively fast (with respect to fragmentation) the similarity of mass spectra can be explained. A possible mechanism for **3b** is outlined in Scheme 4.

From this investigation and that of the 4-alkylcyclohexanecarboxylic acids[1] it may be concluded that for t-alkyl substituted compounds, differences in mass spectral behaviour, due to presence or absence of interaction between the alkyl group and the cation radical site, may be quite helpful in configurational assignments.



Scheme 4.

EXPERIMENTAL

Mass spectra were recorded on a Varian-MAT 311A mass spectrometer, operating at 70 eV and 3 mA emission current. Samples were introduced via a heated reservoir inlet system. The metastable DADI experiments were carried out by a scan of the electrostatic analyzer voltage from 500 to 50 V. The metastable defocussing experiments were carried out by a scan of the accelerating voltage from 1–3 kV. The metastable analyses were carried out for the ions between *m/e* 65 and the parent ion.

The 7-*exo*-alkyl-3-oxabicyclo[3.3.1]nonanes (**1**, **2**) and 7-*endo*-t-butyl-3-oxabicyclo[3.3.1]nonane (**3c**) were synthesized following the procedure of Haggis and Owen,[5] starting from the corresponding 5-alkylcyclohexane-*cis*-1,3-dicarboxylic acids.[6]

3-Oxabicyclo[3.3.1]*nonane* (**1**). Purification was achieved via the thiourea inclusion compound, followed by sublimation; m.p. 111–113°. ^{1}H NMR (CCl_4, 100 MHz); δ 3.86 (2H, broad d), 3.65 (2H, broad d), 1.4–2.8 (10H).

7-Exo-*methyl-3-oxabicyclo*[3.3.1]*nonane* (**2a**). Purification was achieved via the thiourea inclusion compound and distillation; b.p. 170°/760 mm. ^{1}H NMR (CCl_4, 100 MHz); δ 3.76 (2H, broad d), 3.57 (2H, broad d), 2.55 (1H, broad septet), 0.83 (3H d), 0.8–2.1 (8H).

7-Exo-*isopropyl-3-oxabicyclo*[3.3.1]*nonane* (**2b**). Purification was achieved via the thiourea inclusion compound followed by distillation; b.p. 103°/26 mm. ^{1}H NMR ($CDCl_3$, 100 MHz); δ 3.84 (2H, broad d), 3.66 (2H broad d), 2.20 (1H), 0.88 (6H), 1.0–2.1 (9H).

7-Exo-t-*butyl-3-oxabicyclo*[3.3.1]*nonane* (**2c**). Purification was achieved via the thiourea inclusion compound, followed by distillation; b.p. 104°/18 mm; ^{1}H NMR ($CDCl_3$, 100 MHz): δ 3.86 (2H, broad d), 3.70 (2H, broad d), 0.87 (9H, s), 1.1–2.0 (9H).

Pyrrolidine enamine of 4-oxacyclohexanone (**8**). In a nitrogen atmosphere, a mixture of 73.4 g 4-oxacyclohexanone[8] (0.73 mole), 165 ml pyrrolidine and 2 g *p*-TsCl was boiled in 750 ml benzene. Water was separated by means of a Dean–Stark trap. After 3 hr no more water was formed. The benzene was evaporated off under vacuo and the residue was used in the next reaction step without further purification.

Methyl 3-oxa-9-oxobicyclo[3.3.1]*nonane-7-endo-carboxylate* (**9**). In a nitrogen atmosphere to a stirred boiling soln of the crude product of the preceding step and 70.7 g Et_3N in 530 ml MeCN was added dropwise in 1 hr a soln of 131.6 g methyl β,β'-dibromoisobutyrate (0.51 mole) in 400 ml MeCN. Then the soln was boiled under reflux for 1 hr. After addition of 50 ml 5% HOAc the mixture was boiled for another hr. From the resulting soln the greater part of the solvents were evaporated under vacuum. The residue was diluted with sat NaCl aq (1 l) and extracted with EtOAc (6 × 150 ml). The EtOAc layers were washed with sat NaCl aq (2 × 150 ml), and dried over $MgSO_4$. Evaporation of the solvents yielded 52.6 g crude **9**. After distillation 31.4 g pure **9** (0.16 mole, 31%) was obtained; b.p. 112°/0.8 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3.66 (3H, s), 1.8–4.4 (11H), mass spectrum (70 eV): important peaks at *m/e* 198, 170, 169, 168, 167, 166, 165, 152, 139.

Methyl 9,9-dimethoxy-3-oxabicyclo[3.3.1]*nonane-7-endo-carboxylate* (**10**). Compound **9** (31.0 g, 0.16 mole) was stirred with 105 ml MeOH and 10 g *p*-TsOH in 500 ml dry hexane. The stirrer was stopped and 90 g molecular sieve KA was added. After 1 min the stirrer was started again. After 20 min 10 g *p*-TsOH and 30 g KA powder were added. After another 10 min the mixture was filtered and the sieve was washed with dry ether. The filtrate was washed with sat $NaHCO_3$ aq (2 × 100 ml). The washings were extracted with ether (2 × 100 ml). The combined organic layers were dried over $MgSO_4$–K_2CO_3. After evaporation 29.2 g **10** (0.12 mole, 76%) was obtained; ^{1}H NMR (60 MHz, CCl_4); δ 3.5–3.8 (4H), 3.55 (3H, s), 3.10 (6H, s), 0.9–2.7 (7H).

3-Oxa-9-oxobicyclo[3.3.1]*nonane-7-endo-methanol* (**11**). To a stirred suspension of 8.6 g LAH (0.23 mole) in 260 ml dry ether was added dropwise a soln of 15.1 g **10** (0.062 mole) in 90 ml dry ether. Then the mixture was boiled for 3 hr. After cooling 50 ml H_2O and 200 ml 4 N H_2SO_4 were added dropwise subsequently. The aqueous layer was extracted with EtOAc (5 × 100 ml). The combined organic layers were washed with sat NaCl aq (2 × 100 ml) and dried over $MgSO_4$. After evaporation of the solvents 6.7 g **11** (0.039 mole, 64%) was obtained. This compound was used in the next step without further purification.

3-Oxabicyclo[3.3.1]*nonane-7-endo-methanol* (**12**). Compound **11** (6.7 g) was boiled with 6.3 ml 100% hydrazine and 7.90 g KOH in 55 ml triethylene glycol for 1.5 hr. Then the mixture was distilled until a bottom temp of 200° was reached. The residue was boiled under reflux for another 5 hr. The residue and the destillate were combined and diluted with 150 ml sat NaCl aq. After filtration, the suspension was extracted with ether (5 × 50 ml). The ether extract was washed with sat NaCl aq and dried over $MgSO_4$. After evaporation of the solvents 3.67 g **12** (0.024 mole, 62%) was obtained, which was used in the next step without purification.

Tosylate of compound **12**. Crude **12** (3.60 g, 0.023 mole) was dissolved in 40 ml pyridine. After adding 7.0 g TsCl (0.037 mole)

the mixture was stored at 0° for 12 hr. Then the mixture was poured onto 250 ml 1 N HCl (0°). The dispersion obtained was extracted with EtOAc (6 × 50 ml). The EtOAc layers were washed with 2 N HCl (2 × 50 ml) and sat NaCl aq (2 × 50 ml) and dried over $MgSO_4$. After evaporation of the solvents 3.57 g of a tosylate mixture was obtained.

7 - Endo - *methyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**3a**). To a suspension of 2.0 g LAH (0.053 mole) in 60 ml ether, a soln of the crude product of the preceding step in 30 ml ether was added dropwise. The mixture was boiled under reflux for 4 hr. After cooling 10 ml H_2O and 90 ml 4 N H_2SO_4 were added dropwise subsequently. The aqueous layer was extracted with ether (4 × 30 ml). The combined organic layers were washed with H_2O (2 × 30 ml) and dried over $MgSO_4$. After filtration the ether was distilled off. The residue, which consisted of **3a** and small amounts of **2a**, **12** and some unidentified products, was further purified by means of preparative GLC (6 m OV-17, 115°). After that **3a** was still contaminated with a small amount of **2a**. GC–MS analysis showed no essential differences between the mass spectra of **3a** and **2a**; ^{1}H NMR (60 MHz, CCl_4): δ 3.46 (4H, AA'BB'-system), 0.88 (3H, d: J = 6 Hz), 0.8–2.1 (9H).

9,9 - *Dimethoxy* - 7 - endo - [2 - (2 - *hydroxypropyl*)] - 3 - *oxabicyclo* [3.3.1] *nonane* (**13**). A MeMgBr soln was prepared from 7.45 g Mg (0.31 mole) in 50 ml THF and a 3.50 M soln of MeBr in THF (100 ml, 0.35 mole). This soln was cooled to 0°. Then a soln of **10** (14.0 g, 0.057 mole) in 50 ml THF was added dropwise in 30 min. After that the reaction mixture was boiled under reflux for 3 hr. After cooling to 0° sat $(NH_4)_2SO_4$ (500 ml) was added dropwise. The aqueous layer was extracted with EtOAc (5 × 80 ml). The combined organic layers were washed with sat NaCl aq (3 × 80 ml) and dried over $MgSO_4$–K_2CO_3. After evaporation of the solvents 13.8 g **13** (0.057 mole, 100%) was obtained; ^{1}H NMR (60 MHz, CCl_4): δ 3.3–3.8 (4H, AA'BB'), 3.12 (3H, s), 3.15 (3H, s), 1.10 (6H, s), 1.0–2.8 (8H).

7 - *Isopropyl* - 9 - *oxo* - 3 - *oxabicyclo*[3.3.1]*non* - 6 - *ene* (**14**). The product of the preceding reaction step was boiled with 50 ml H_2O, 50 ml dioxane and 50 ml 4 N H_2SO_4 for 2 hr. Then the reaction mixture was extracted with ether (3 × 50 ml) and EtOAc (2 × 50 ml). The combined organic layers were washed with sat NaCl aq (2 × 50 ml) and dried over $MgSO_4$. Evaporation of the solvents gave 13.9 g alkenes mainly **14**; b.p. 80–110°/0.10 mm; ^{1}H NMR (60 MHz, CCl_4): δ 5.42 (1H, broad d: J = 6 Hz), 1.08 (6H, d: J = 7 Hz), 1.5–4.2 δ (11H).

9 - *Hydroxy* - 7 - endo - *isopropyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**15**). Compound **14** (4.50 g, 0.025 mole) was hydrogenated in 50 ml EtOAc with 700 mg 10% Pd/C as catalyst at 60° and 1 atm H_2. When no more H_2 was taken up, the catalyst was filtered and from the filtrate the solvents were evaporated off to yield 4.32 g almost pure **15** (2 epimers) (0.024 mole, 96%).

7 - Endo - *isopropyl* - 9 - *oxo* - 3 - *oxabicyclo*[3.3.1]*nonane* (**16**). At 0°, to a soln of the crude product of the preceding step in 25 ml acetone 6 ml of Jones reagent (26.7 g CrO_3 in 23 ml 100% H_2SO_4, diluted with H_2O to 100 ml) was added dropwise. The mixture was stirred at room temp. for 1 hr. Then 15 ml MeOH was added. After another 30 min the mixture was diluted with H_2O (50 ml) and then extracted with $CHCl_3$ (5 × 15 ml). The $CHCl_3$-layers were washed with H_2O (3 × 15 ml) and dried over $MgSO_4$. The solvents were evaporated off and the residue (3.72 g) was purified via the thiourea inclusion compound to yield 0.72 g chromatographically pure **16**; mass spectrum (70 eV): important peaks at m/e 184, 182, 165, 149, 121, 119, 109, 107 and 105.

7 - Endo - *isopropyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**3b**). Compound **16** (720 mg) was boiled with 0.6 ml 100% hydrazine and 770 mg KOH in 10 ml triethylene glycol for 1.5 hr. Then the mixture was distilled. In 7 hr, the bottom temp. was slowly raised to 200°. The distillate and the residue were combined and then diluted with 15 ml H_2O. The mixture obtained was extracted with ether (6 × 15 ml). The ether layers were extracted with sat NaCl aq and dried over $MgSO_4$. After filtration 40 ml of ether was distilled off. The residue was purified via preparative GLC (6 m OV-17, 150°); ^{1}H NMR (60 MHz, CCl_4): δ 3.44 (4H, AA'BB'-system), 0.88 (6H, d: J = 5.5 Hz), 1.0–2.4 (10H).

7 - Endo - t - *butyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**3c**). According to Scheme 1 a mixture was obtained, containing **3c** as well as **2c**. Rough purification was achieved by distillation. The fraction, which boiled at 90–100°/5 mm was further purified by chromatography over alumina with $CHCl_3$ as eluent, followed by distillation; b.p. 110°/5 mm. ^{1}H NMR (CCl_4, 60 MHz): δ 3.40 (4H, AA'BB'-system), 0.90 (9H, s), 1.0–2.5 (9H).

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