Pergamon

Tetrahedron 57 (2001) 2419–2425

TETRAHEDRON

Formation and cleavage of bisnoradamantane derivatives through SmI_2 reductions

Pelayo Camps,* Andrés E. Lukach and Santiago Vázquez

Laboratori de Química Farmacèutica, Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal 643, E-08028 Barcelona, Spain

Received 17 October 2000; revised 20 December 2000; accepted 11 January 2001

Abstract—The strain of the bisnoradamantane skeleton is shown by: (i) the easy homoketonization of tricyclo[3.3.0.0^{3,7}]octane-1,5-diol, **2a**, to *exo*-7-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one, **3a**, under silica gel column chromatography, and (ii) the cleavage of the C3–C7 bond of 1,5-dimethyl-3,7-dipivaloyltricyclo[3.3.0.0^{3,7}]octane, **9**, to give bicyclo[3.3.0]octane diketones, under attempted SmI_2-intramolecular pinacolization. In contrast, **2a** was obtained by SmI_2-pinacolization of cis-bicyclo[3.3.0]octane-3,7-dione, **1a**.

We have been much interested in the synthesis and reactivity of bisnoradamantane derivatives for the last 20 years.[1–8] Some time ago, Hoffmann et al. published the use of SmI_2 for intramolecular pinacolizations leading from diketone **1b** to diol **2b**,[9] and from different 1,4-diketones to cyclobutane-1,2-diols.[10] We published the synthesis of several 3,7-dialkyltricyclo[3.3.0.0^{3,7}]octane-1,5-diols,[4] by pinacolization of different 1,5-dialkyl-*cis*-bicyclo[3.3.0]octane-3,7-diones, using low-valent titanium species as the reducing agent. However, we failed to obtain the parent diol **2a**, by this procedure. To the best of our knowledge, compound **2a** has not been described yet. In this paper, we describe: (i) the preparation of compound **2a** by SmI_2-intramolecular pinacolization of dione **1a**, and its easy silica gel-promoted homoketonization to keto alcohol **3a**, and (ii) the cleavage of the C3–C7 bond of the tricyclic diketone **9**, to give bicyclo[3.3.0]octane diketones, under attempted SmI_2-intramolecular pinacolization.

1. Results and discussion

1.1. SmI_2 intramolecular pinacolization of *cis*-bicyclo[3.3.0]-octane-3,7-dione, 1a, and homoketonization of tricyclo-[3.3.0.0^{3,7}]octane-1,5-diol, 2a

Reduction of diketone **1a** with SmI_2 following a modification of the procedure described by Hoffmann et al.[9–11] gave pinacol **2a** in 30% isolated yield. Pinacol **2a** was fully converted into the *exo*-keto alcohol **3a**, on standing overnight in a silica gel column.

To establish the configuration of compound **3a**, its *endo*-stereoisomer **4** was prepared by reduction of diketone **1a** with a limited amount of $NaBH_4$. In this reduction, the main products were the *endo*-keto alcohol **4** and the *endo*,*endo*-diol **5**. Minor amounts of the *exo*-keto alcohol **3** were detected (GC/MS) while the minor *exo*,*exo*-diol **6** could be isolated and fully characterized. The configuration of keto alcohols **3a** and **4** was fully established by NOESY experiments. In the NOESY spectrum of the *exo*-keto alcohol **3a**, a cross-peak (nOe) was clearly observed for the pairs of protons 7-H/6(8)-Hβ, in accord with the *endo*-arrangament of 7-H. On the contrary, in the NOESY spectrum of the *endo*-keto alcohol **4**, a cross-peak (nOe) was observed for the pairs of protons 7-H/6(8)-Hα, in accord with expectations. The only literature reference for keto alcohols **3a** and **4** corresponds to a patent,[12] while *endo*,*endo*-diol **5** has been partially described from a mixture with other stereoisomers.[13,14]

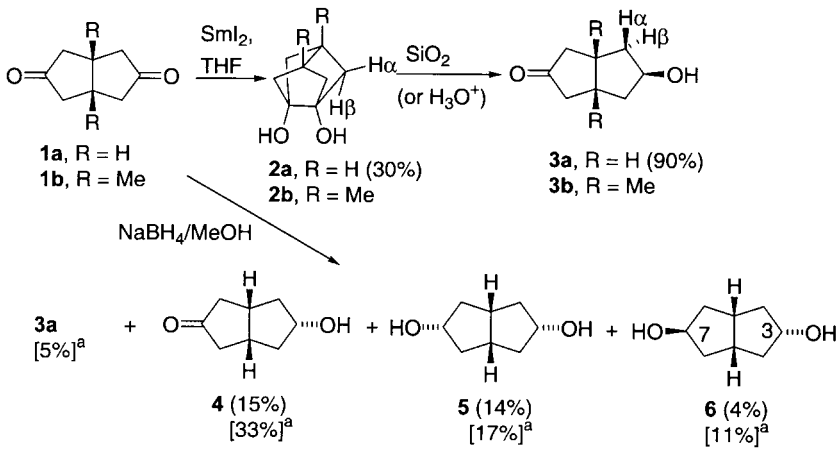
Conversion of pinacol **2a** into keto alcohol **3a** is an example of a homoketonization reaction. Several examples of homoketonization of non-cyclopropane strained alcohols are known.[15–19]

The stereochemistry of the base-catalyzed homoketonization of strained polycyclic alcohols was studied by Borden et al.,[16,20] using deuterium-labelling techniques. One of the cases studied was a compound closely related to **2a**, 3,7-dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol.[16] In the studied cases, the reaction took place with retention of configuration, i.e. the new C–H bond was formed from the same side of the broken C–C bond, which was explained through the intervention of an S_E2 mechanism.[21] In this mechanism, a transition state with a two electron-three center bond involving the two carbon atoms of the bond to be broken and a proton from the solvent was proposed

Keywords: cleavage reactions; coupling reactions; samarium diiodide; polycyclic aliphatic compounds.

* Corresponding author. Tel.: +34-93402-4536; fax: +34-93403-59-41; e-mail: camps@farmacia.far.ub.es

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00096-5



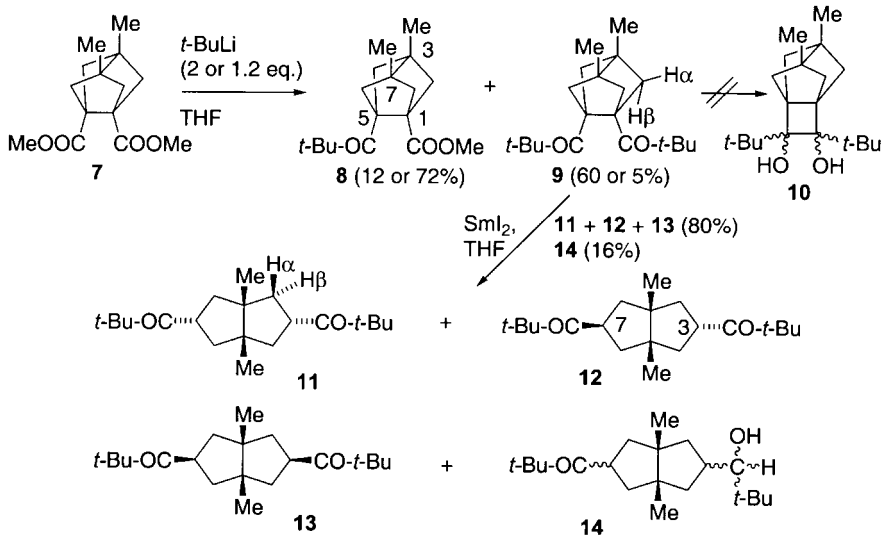
Scheme 1. Synthesis of tricyclo[3.3.0.0^{3,7}]octane-1,5-diol, **2a**, by SmI_2 reduction of *cis*-bicyclo[3.3.0]octane-3,7-dione, **1a**, and its homoketonization to 7-*exo*-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one, **3a**. [a]Yields in square brackets were obtained by GC analysis of the different column chromatographic fractions. Diketone **1a** (17%) was also recovered.

to explain the observed retention of configuration.[22,23] A similar mechanism may account for the observed stereochemistry in the acid-catalyzed homoketonization of pinacol **2a** to keto alcohol **3a**. When SmI_2-pinacolization of diketone **1a** was carried out under the conditions described by Hoffmann et al. for diketone **1b**,[9] (i.e. addition of 1 mmol of water per mmol of SmI_2, after heating the mixture of the diketone and SmI_2 under reflux for 1 h and then, continuing the reflux for a further 72 h), the yield of the isolated **2a** was only 13%. This result might be explained by homoketonization of **2a** under the acid reaction conditions, although no keto alcohol **3a** was isolated from this reaction. Probably, for the same reason, we were unable to obtain pinacol **2a** by low-valent titanium pinacolization of diketone **1a**.[4] However, by using the last procedure we could obtain several 3,7-dialkyltricyclo[3.3.0.0^{3,7}]octane-1,5-diols, stable easily crystallizable solids.

Table 1. Molecular mechanics (MM2 and MM3) and semiempirical (AM1) data [enthalpy of formation (ΔH_f, kcal mol^{-1}), strain energy (SE, kcal mol^{-1}), bond lengths (d, Å), dihedral angles (ϑ, degrees), reaction enthalpy and reaction enthalpy differences] calculated for compounds **2a**, **2b**, **3a** and **3b**.

2a	MM2	MM3	AM1
ΔH_f	−71.0	−54.7	−51.0
SE	44.65	55.8	–
d_{C1-C5}	1.542	1.599	1.632
d_{C3-C7}	1.582	1.635	1.611
$\vartheta_{H-C3-C7-H}$	−0.2	0.5	0.0
2b			
ΔH_f	−89.2	−71.0	−60.6
SE	43.2	56.7	–
d_{C1-C5}	1.541	1.597	1.637
d_{C3-C7}	1.587	1.634	1.624
$\vartheta_{Me-C3-C7-Me}$	0.1	−0.1	0.05
3a			
ΔH_f	−88.2	−88.6	−108.0
SE	15.7	11.9	–
d_{C1-C5}	1.550	1.570	1.550
$\vartheta_{Me-C1-C5-Me}$	3.9	3.7	0.8
3b			
ΔH_f	−103.2	−103.3	−111.6
SE	17.5	12.7	–
d_{C1-C5}	1.563	1.585	1.562
$\vartheta_{Me-C1-C5-Me}$	4.3	4.8	1.0
$\Delta H_{2a\rightarrow 3a}$	−17.2	−33.9	−57.0
$\Delta H_{2b\rightarrow 3b}$	−14.0	−32.3	−51.0
$\Delta H_{2a\rightarrow 3a} - \Delta H_{2b\rightarrow 3b}$	−3.2	−1.6	−6.0

The easy homoketonization of **2a** must be clearly associated with the strain of its bisnoradamantane skeleton that is liberated on conversion to **3a**. The question is why its 3,7-dimethyl-analog **2b** and other 3,7-dialkyl-derivatives are more stable than the parent diol **2a**. To understand this fact, we carried out calculations on pinacols **2a** and **2b** and keto alcohols **3a** and **3b**, using molecular mechanics (MM2[24] and MM3[25]) and semiempirical (AM1[26]) methods. Table 1 collects the calculated enthalpy of formation (ΔH_f), strain energy (SE), significant bond lenghts and dihedral angles for compounds **2a**, **2b**, **3a** and **3b** together with reaction enthalpies (**2a→3a** and **2b→3b**) and reaction enthalpy differences. Although the results from the different methods are quite different, from the data obtained with a particular method, the following observations can be made: (i) the C1–C5 bond length differences of **2a** and **2b** are very low to account for the observed greater relative instability of **2a**, (ii) the C3–C7 bond in **2b** and the C1–C5 bond in **3b** are usually somewhat larger than those of **2a** and **3a**, respectively, a fact that may be associated to a decrease of the steric interactions among the methyl substituents, (iii) the enthalpy difference for the conversion of **2a** to **3a** is higher than the corresponding difference for the conversion of **2b** to **3b**. The greater enthalpy for the conversion of **2a** to **3a** than for the conversion of **2b** to **3b** may be reflected in a lower energy product-like transition-state for the slow-step of this S_E2 reaction, i.e. the breaking of the C1–C5 bond in the protonated intermediate, thus explaining the greater instability of **2a** as compared with **2b**. A similar situation had been previously observed in a related case. 4,5,10,11-Tetramethylheptacyclo[8.2.1.1^{2,5}.1^{4,7}.1^{8,11}.0^{1,8}.0^{2,7}]hexadecane, the cyclobutane dimer derived from 3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1(5)-ene, showed to be more stable, towards its [2+2] retrocycloaddition to an isomeric diene, than its demethylated analog.[7]



Scheme 2. Synthesis of 3,7-dimethyl-1,5-dipivaloyltricyclo[3.3.0.0^{3,7}]octane, **9**, and its reduction with SmI_2.

1.2. Cleavage of the C3–C7 bond of 1,5-dimethyl-3,7-dipivaloyltricyclo[3.3.0.0^{3,7}]octane, 9, on attempted SmI_2-intramolecular pinacolization

Diketone **9** was obtained in 60% yield together with minor amounts of keto ester **8** (12% yield) by reaction of diester **7** with 2 equiv. of *tert*-BuLi in anhydrous THF. Keto ester **8** was the main product (72% yield) when the amount of *tert*-BuLi was limited to 1.2 equiv. Compound **9** is a 1,4-diketone and we tried its SmI_2 intramolecular pinacolization to a cyclobutane-1,2-diol under the conditions described by Hoffmann for the pinacolization of other 1,4-diketones.[10,11] However, from the reaction of diketone **9** with SmI_2 (4 mmol per mmol diketone), no pinacol **10** was isolated.

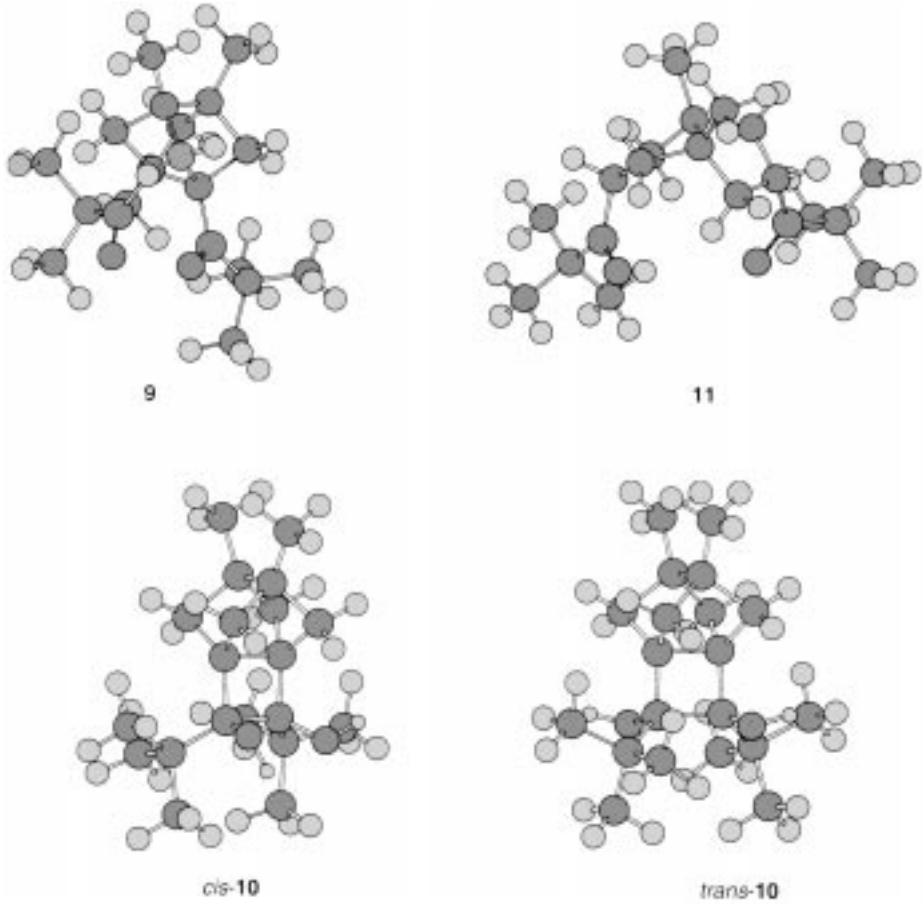


Figure 1. Preferred conformations obtained for diketones **9** and **11** and pinacols *cis*- and *trans*-**10** by molecular mechanics calculations (MM2).

The main product of this reaction was a mixture of the stereoisomeric bicyclic diketones **11**, **12** and **13** (80% yield) from which the main component, *endo*,*endo*-diketone **11**, could be isolated and fully characterized, compounds **12** and **13** being characterized as a mixture. From this reaction, a mixture of stereoisomeric keto alcohols **14** (16% yield) derived from the further reduction of diketones **11**–**13** was also obtained. As expected, the formation of keto alcohols **14** was reduced when a lower excess of SmI_2 was used.

A similar situation has been previously observed in the attempted pinacolization of several 2,3-diacetylbicyclo-[2.2.1]heptane derivatives[27] and aromatic 1,4-diketones[28] to the corresponding cyclobutane-1,2-diols. The cleavage of a C–C bond in other SmI_2-reductions has been usually observed in cyclopropanic systems[29–32] and sometimes in less strained compounds.[33–35] The cleavage of the C3–C7 bond in **9** instead of the cyclobutane-1,2-diol formation might be explained taking into account the enormous increase in strain energy associated with the intramolecular pinacolization as compared with the strain release derived from the cleavage of the bisnoradamantane skeleton. The initially formed diketyl radical, instead of coupling, undergoes homolysis of the C–C bond to produce a relatively less strained system.

Molecular mechanics calculations (MM2) carried out on diketones **9**, **11** and the possible diols *cis*- and *trans*-**10** gave the following formation enthalpies and strain energies (ΔH_f and SE, kcal/mol) for their minimum energy conformations (Fig. 1): **9** (ΔH_f=−113.0 kcal mol^{-1}, SE=53.25 kcal mol^{-1}), **11** (ΔH_f=−149.3 kcal mol^{-1}, SE=23.7 kcal mol^{-1}), *cis*-**10** (ΔH_f=−88.0 kcal mol^{-1}, SE=109.2 kcal mol^{-1}), and *trans*-**10** (ΔH_f=−96.9 kcal mol^{-1}, SE=100.3 kcal mol^{-1}). Similar results were obtained by using the MM3 program. These values show the enormous strain energy increase associated with the conversion of diketone **9** to the corresponding pinacols *cis*- or *trans*-**10**, and the high strain energy release for its conversion to the bicyclo[3.3.0]octane derivative **11**. Thus, it seems reasonable that the transition-state for the conversion of the intermediate diketyl radical derived from **9** to the bis-enolate derived from diketone **11** be of much lower energy than the corresponding transition-state for its conversion to the diolate derived whether from *cis*- or *trans*-**10**. Consequently, conversion of diketone **9** to **11**, via its diketyl radical, must be much faster than its conversion to *cis*- or *trans*-**10**, thus explaining the experimental result.

2. Conclusions

Compounds containing the bisnoradamantane skeleton, such as **2a** and **9**, are highly strained and readily undergo fragmentation reactions to bicyclo[3.3.0]octane derivatives. Compound **2a**, formed by SmI_2-intramolecular pinacolization, easily experiences at room temperature silica gel catalyzed homoketonization by an S_E2 mechanism to give keto alcohol **3a**, while diketone **9** on attempted SmI_2-intramolecular pinacolization gives mainly a stereoisomeric mixture of bicyclic diketones **11**–**13** (Schemes 1 and 2).

3. Experimental

3.1. General

Melting points were determined with a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^{1}H NMR spectra were performed on a Varian VXR 500 spectrometer, 300 MHz ^{1}H and 75.4 MHz ^{13}C NMR spectra on a Varian Gemini 300, and 50.3 MHz ^{13}C NMR spectra on a Varian Gemini 200. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane (TMS). Assignments given for the ^{1}H and ^{13}C NMR spectra of the new compounds are based on DEPT, COSY ^{1}H/^{1}H, COSY ^{1}H/^{13}C (HMQC sequence) and NOESY experiments. IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model 1600. Routine MS spectra were taken on a Hewlett–Packard 5988A spectrometer, the sample was introduced directly or through a gas chromatograph, Hewlett Packard model 5890 Series II, equipped with a 30-meter HP-5 (5% diphenyl-95% dimethyl-polysiloxane) column [conditions: 10 psi, initial temperature: 100°C (2 min), then heating at a rate of 10°C/min till 250°C, then isothermic] and the electron impact technique (70 eV). Only significant ions are given: those with higher relative abundance, except for the ions with higher *m*/*z* values. High-resolution mass spectra were recorded on an Autospec-Q mass spectrometer from Micromass using the electron impact technique (70 eV) and direct sample introduction. Silica gel SDS 60 (70–200 μm) or (35–70 μm) was utilized for the standard and flash column chromatography, respectively. NMR and routine MS spectra were performed at the *Serveis Científico-Tècnics* of the University of Barcelona, while elemental analyses and high resolution mass spectra were carried out, respectively, at the Microanalysis Service and the Mass Spectrometry Laboratory of the *Centro de Investigación y Desarrollo* (C.I.D.), C.S.I.C., Barcelona, Spain.

3.1.1. Tricyclo[3.3.0.0^{3,7}]octane-1,5-diol (2a). *Procedure 1*. A solution of SmI_2 (0.1 M in anhydrous THF, 40 mL) was prepared under an Ar atmosphere, according to Molander's procedure.[36] The solution was diluted with anhydrous THF (60 mL) and a solution of diketone **1a** (138 mg, 1.0 mmol) in anhydrous THF (5 mL) was dropwise added at room temperature and then, the mixture was heated under reflux for 72 h. Most of the THF was distilled (95 mL), diethyl ether (30 mL) was added and the mixture was treated with 0.1N HCl (40 mL) until a yellow precipitate was dissolved. The organic phase was separated and the aqueous one was extracted with diethyl ether (6×30 mL). The combined organic phase and extracts were washed with aqueous 10% solution of $Na_2S_2O_3$ (2×25 mL) and brine (2×25 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a red residue (90 mg) which was submitted to column chromatography [aluminum oxide (5 g), ethyl acetate/methanol mixtures]. On elution with ethyl acetate/methanol in the ratio of 90:10, the *title compound* **2a** (40 mg, 30% yield) was eluted. The analytical sample was obtained by sublimation as a white solid, mp 165–166°C (sublimed at 50°C/1 Torr); [Found: C, 68.6; H, 8.8. $C_8H_{12}O_2$ requires C, 68.54; H, 8.63%]; ν_{max} (KBr) 3292 (OH st) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.47 [2H, s, 1(5)-OH], 2.21–2.16 [2H, m, 3(7)-H], 2.00–1.90 [4H, m, 2(4,6,8)-Hα], 1.51 [4H, broad d, J=6.5 Hz, 2(4,6,8)-Hβ]; δ_C (50.3 MHz,

$CDCl_3$) 79.3 [C, C1(5)], 50.3 [CH_2, C2(4,6,8)], 31.7 [CH, C3(7)]; *m/z* (EI) 138 [7 $(M-2H)^{\cdot+}$], 107 (13), 98 [70 $(M-C_3H_4)^{\cdot+}$], 95 [100 $(M-C_2H_5O)^+$], 82 [51 $(C_5H_6O)^{\cdot+}$], 80 [52 $(C_5H_4O)^{\cdot+}$], 79 (43).

Procedure 2. The procedure 1 was followed, except for the addition of a small amount of water (4 mmol) after refluxing the mixture of diketone **1a** and SmI_2 for 1 h.[9] After an identical work-up, the title compound **2a** was isolated in only 13% yield.

3.1.2. 7-*exo*-Hydroxy-*cis*-bicyclo[3.3.0]octan-3-one (3a). Pinacol **2a** (100 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (15 mL), silica gel (220 mg) was added and the solvent was evaporated at 40°C under reduced pressure. The residue was introduced in a chromatography column (1.5 cm internal diameter) containing silica gel (6 g). After standing for 24 h, the product was eluted with mixtures of hexane/ethyl acetate. On elution with a mixture of hexane/ethyl acetate in the ratio 65:35, the title compound **3a** (90 mg, 90% yield) was obtained. The analytical sample of **3a**, was obtained by distillation in a rotary microdistillation equipment as a viscous oil, bp 60°C/0.5 Torr; [Found: C, 65.2; H, 9.1. $C_8H_{12}O_2$ 0.4 H_2O requires C, 65.19; H, 8.75%]; ν_{max} (KBr) 3406 (OH st), 1734 (C=O st) cm^{-1}; δ_H (500 MHz, CD_3OD) 4.86 (s, OH), 4.37 [1H, tt, *J*=5.0, 2.5 Hz, 7-H], 2.98–2.89 [2H, m, 1(5)-H], 2.56–2.48 [2H, m, 2(4)-Hα], 2.03–1.95 [4H, m, 2(4)-Hβ and 6(8)-Hα], 1.65–1.59 [2H, m, 6(8)-Hβ]; δ_C (50.3 MHz, $CDCl_3$) 220.6 (C, C3), 74.1 (CH, C7), 44.5 [CH_2, C2(4)], 43.0 [CH_2, C6(8)], 37.5 [CH, C1(5)]; *m/z* (EI) 140 (60 $M^{\cdot+}$), 122 [6 $(M-H_2O)^{\cdot+}$], 97 [43 $(M-C_2H_3O)^+$], 95 [33 $(M-C_2H_5O)^+$], 81 [47 $(C_5H_5O)^+$], 80 [100 $(C_5H_4O)^{\cdot+}$], 79 (60), 71 (76), 70 (87).

3.2. Reduction of diketone 1a with $NaBH_4$: obtention of 7-*endo*-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one (4), *cis*-bicyclo[3.3.0]octane-3-*endo*,7-*endo*-diol (5), and *cis*-bicyclo[3.3.0]octane-3-*endo*,7-*exo*-diol (6)

A solution of diketone **1a** (1.00 g, 7.2 mmol) in methanol (12 mL) was treated at room temperature under stirring with $NaBH_4$ (62 mg, 1.63 mmol). After a 10 min period, more $NaBH_4$ (62 mg, 1.63 mmol) was added, and stirring was continued for 10 min more. Then, aqueous 2N HCl (2 mL) and aqueous 2N NaOH (25 mL) were added and the mixture was extracted with diethyl ether (4×50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue (850 mg) was submitted to column chromatography [aluminum oxide (35 g), hexane/ethyl acetate mixtures]. On elution with hexane/ethyl acetate in the ratio of 80:20, starting diketone **1a** (170 mg) was obtained. Further elution with hexane/ethyl acetate in the ratio of 70:30, gave a mixture of ketoalcohols **3a** and **4**, in the approximate ratio of 15:85 (350 mg) which was recrystallized from hexane (2 mL) to give pure ketoalcohol **4** (150 mg, 15% yield). On elution with hexane/ethyl acetate in the ratio of 60:40, a mixture of ketoalcohols **4** and diol **6** (80 mg) in the approximate ratio of 50:50 and a mixture of diols **5** and **6** (60 mg) in the approximate ratio of 20:80 were succesively eluted. Recrystallization of the last mixture of diols from ethyl acetate (2 mL) gave pure diol **6** (40 mg, 4% yield). On elution with hexane/ethyl acetate in the ratio of 40:60, a mixture of diols **5** and **6** (50 mg) in a ratio of about 50:50 and pure diol **5** (140 mg, 14% yield) were successively eluted. Sublimation of the last eluted fraction gave the analytical sample of **5**.

3.2.1. Analytical and spectroscopic data of 4. White solid, mp 46.3–47.3°C (AcOEt/hexane); [Found: C, 68.6; H, 8.7. $C_8H_{12}O_2$ requires C, 68.54; H, 8.63%]; ν_{max} (KBr) 3417 (OH st), 1732 (C=O st) cm^{-1}; δ_H (500 MHz, CD_3OD) 4.86 (s, OH), 4.29 (1H, quint, *J*=5.0 Hz, 7-H), 2.85–2.76 [2H, m, 1(5)-H], 2.58–2.50 [2H, m, 2(4)-Hα], 2.20 [2H, dd, *J*=19.5, 4.0 Hz, 2(4)-Hβ], 2.14 [2H, ddd, *J*=14.0, 8.5, 5.0 Hz, 6(8)-Hα], 1.52 [2H, dt, *J*=14.0, 5.0 Hz, 6(8)-Hβ]; δ_C (50.3 MHz, $CDCl_3$) 221.1 (C, C3), 74.7 (CH, C7), 45.6 [CH_2, C2(4)], 42.9 [CH_2, C6(8)], 37.7 [CH, C1(5)]; *m/z* (EI) 140 (37 $M^{\cdot+}$), 122 [41 $(M-H_2O)^{\cdot+}$], 95 [29 $(C_6H_7O)^+$], 94 (25), 81 [37 $(C_5H_5O)^+$], 80 [100 $(C_5H_4O)^{\cdot+}$], 79 (59).

3.2.2. Analytical and spectroscopic data of 5. White solid, mp 80.5–81.5°C (sublimed at 90°C/1 Torr); [Found: C, 67.5; H, 9.9. $C_8H_{14}O_2$ requires C, 67.57; H, 9.93%]; ν_{max} (KBr) 3320 (OH st) cm^{-1}; δ_H (500 MHz, CD_3OD) 4.86 (s, OH), 4.12 [2H, tt, *J*=7.5, 6.0 Hz, 3(7)-H], 2.43–2.33 [2H, m, 1(5)-H], 2.10–2.03 [4H, m, 2(4,6,8)-Hα], 1.52 [2H, dt, *J*=13.0, 7.0 Hz, 2(4,6,8)-Hβ]; δ_C (75.4 MHz, CD_3OD) 76.3 [CH, C3(7)], 43.4 [CH_2, C2(4,6,8)], 40.2 [CH, C1(5)]. *m/z* (EI)143 [0.4 $(M+H)^+$], 142 (0.4 $M^{\cdot+}$), 124 [19 $(M-H_2O)^{\cdot+}$], 106 [35 $(M-2H_2O)^+$], 95 [100 $(C_6H_7O)^+$], 91 (30), 82 (39), 81 [52 $(C_5H_5O)^+$], 80 [70 $(C_5H_4O)^{\cdot+}$], 79 (38).

3.2.3. Analytical and spectroscopic data of 6. White solid, mp 75–76°C (AcOEt); [Found: C, 67.4; H, 9.8. $C_8H_{14}O_2$ requires C, 67.57; H, 9.93%]; ν_{max} (KBr) 3302 (OH st) cm^{-1}; δ_H (500 MHz, CD_3OD) 4.84 (s, OH), 4.35 (1H, quint, *J*=5.0 Hz, 7-H), 4.07 (1H, tt, *J*=8.0, 6.0 Hz, 3-H), 2.59–2.50 [2H, m, 1(5)-H], 2.10–2.04 [2H, m, 2(4)-Hα], 1.80–1.73 [2H, m, 6(8)-Hα], 1.65 [2H, dt, *J*=12.5, 5.0 Hz, 6(8)-Hβ], 1.24 [2H, dt, *J*=12.5, 7.5 Hz, 2(4)-Hβ]; δ_C (50.3 MHz, $CDCl_3$) 75.4 (C) and 75.0 (C) (C3 and C7), 42.7 (CH_2) and 42.4 (CH_2) [C2(4) and C6(8)], 38.9 [CH, C1(5)]; *m/z* (EI) 124 [20, $(M-H_2O)^{\cdot+}$], 106 [14 $(M-2H_2O)^{\cdot+}$], 95 [100 $(C_6H_7O)^+$], 91 (30), 82 (35), 81 [39 $(C_5H_5O)^+$], 80 [33 $(C_5H_4O)^{\cdot+}$], 79 (38).

3.3. Methyl 3,7-dimethyl-5-pivaloyltricyclo[3.3.0.0^{3,7}] octane-1-carboxylate (8) and 1,5-dimethyl-3,7-dipivaloyltricyclo[3.3.0.0^{3,7}]octane (9)

Procedure 1. To a cold (−78°C) magnetically stirred solution of tricylic diester **7** (1.52 g, 6.03 mmol) in anhydrous THF (60 mL), a solution of *tert*-BuLi in pentane (1.7 M, 7.2 mL, 12.2 mmol) was added dropwise, keeping the reaction mixture in an Ar atmosphere. When the addition was completed, the reaction mixture was stirred at −78°C for 15 min and allowed to warm to room temperature for 18 h. The mixture was acidified with 1N HCl (30 mL) and extracted with ethyl acetate (3×60 mL). The combined organic extracts were washed with brine (2×60 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue (1.7 g) was submitted to column chromatography [silica gel (68 g) hexane/ethyl acetate mixtures]. On elution with a mixture of hexane/ethyl acetate in the ratio of 98:2,

diketone **9** (1.1 g, 60% yield), was obtained. On elution with a mixture of hexane/ethyl acetate in the ratio of 90:10, keto ester **8** (200 mg, 12% yield) was isolated.

Procedure 2. When the above reaction was carried out by using 1.2 mol *tert*-BuLi per mol starting diester, diketone **9** (5% yield) and keto ester **8** (72% yield) were obtained.

3.3.1. Analytical and spectroscopic data of 8. Viscous oil, bp 60°C/1 Torr); [Found: C, 73.2; H, 9.4. $C_{17}H_{26}O_3$ requires C, 73.34; H, 9.42%]; ν_{max} (KBr) 1738 (ester C=O st), 1680 (ketone C=O st) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.61 (3H, s, O*Me*), 2.03 [2H, d, *J*=8.2 Hz, 4(6)-Hβ], 1.91 [2H, d, *J*=8.4 Hz, 2(8)-Hβ], 1.82 [2H, dd, *J*=8.2, 3.8 Hz, 4(6)-Hα], 1.67 [2H, dd, *J*=8.4, 3.8 Hz, 2(8)-Hα], 1.16 [6H, s, 3(7)-*Me*], 1.15 [9H, s, C*Me*$_3$]; δ_C (75.4 MHz, $CDCl_3$) 214.4 (C, *C*OCMe$_3$), 173.7 (C, *C*OOMe), 65.5 (C, C5), 59.8 (C, C1), 58.5 [CH_2, C4(6)], 56.1 [CH_2, C2(8)], 51.3 (CH_3, O*Me*), 47.6 [C, C3(7)], 44.9 [C, *C*Me$_3$], 26.5 [CH_3, C*Me*$_3$], 16.2 [CH_3, 3(7)-*Me*]; *m/z* (EI) 247 [3 $(M-MeO)^+$], 221 [51 $(M-C_4H_9)^+$], 189 [18 $(M-C_4H_9$-MeOH$)^+$], 161 [30 $(M-C_5H_9O$-MeOH$)^+$], 133 [49 $(C_{10}H_{13})^+$], 91 (29), 77 (22), 57 (100 $C_4H_9^+$).

3.3.2. Analytical and spectroscopic data of 9. White crystals, mp 65.5–66.5°C (pentane); [Found: C, 78.8; H, 10.5. $C_{20}H_{32}O_2$ requires C, 78.89; H, 10.60%]; ν_{max} (KBr) 1677 (C=O st) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.02 [4H, d, *J*=7.0 Hz, 2(4,6,8)-Hβ], 1.82 [4H, d, *J*=7.0 Hz, 2(4,6,8)-Hα], 1.17 [18H, s, 1(5)-COC*Me*$_3$], 1.15 [6H, s, 3(7)-*Me*]; δ_C (75.4 MHz, $CDCl_3$) 215.1 [C, 1(5)-*C*OCMe$_3$], 68.0 [C, C1(5)], 59.0 [CH_2, C2(4,6,8)], 47.8 [C, C3(7)], 45.1 [C, 1(5)-CO*C*Me$_3$], 26.8 [CH_3, 1(5)-COC*Me*$_3$], 16.4 [CH_3, 3(7)-*Me*]; *m/z* (EI) 305 [4 $(M+H)^+$], 247 [28 $(M-C_4H_9)^+$], 219 [10 $(M-C_5H_9O)^+$], 133 [14 $(C_{10}H_{13})^+$], 57 (100 $C_4H_9^+$). HRMS (EI): M^+, found 304.2404. $C_{20}H_{32}O_2$ requires 304.2402.

3.4. Reaction of diketone 9 with SmI_2: obtention of 1,5-dimethyl-3*endo*,7*endo*-dipivaloyl-*cis*-bicyclo[3.3.0] octane (10), mixture of 1,5-dimethyl-3*endo*,7*exo*-dipivaloyl-*cis*-bicyclo[3.3.0]octane (11) and 1,5-dimethyl-3*exo*,7*exo*-dipivaloyl-*cis*-bicyclo[3.3.0]octane (12), and mixture of stereoisomers of 3-[(1-hydroxy-2,2-dimethyl)propyl]-1,5-dimethyl-7-pivaloyl-*cis*-bicyclo[3.3.0]octane (13).

Procedure 1. A 0.1 M solution of SmI_2 in anhydrous THF (40 mL) was prepared under an Ar atmosphere, according to Molander's procedure.[36] The solution was diluted with anhydrous THF (60 mL), a solution of diketone **9** (304 mg, 1.0 mmol) in anhydrous THF (5 mL) was added dropwise at room temperature and then, the mixture was stirred for 2 h. The reaction mixture was treated with 1N HCl (10 mL) until the yellow precipitate formed was dissolved. The mixture was extracted with ethyl acetate (3×60 mL) and the combined organic extracts were washed with aqueous 10% solution of $Na_2S_2O_3$ (2×50 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The yellow residue obtained (350 mg) was submitted to flash column chromatography [silica gel (35 g), hexane/ethyl acetate mixtures]. On elution with a mixture of hexane/ethyl acetate in the ratio of 97:3, a stereoisomeric mixture of diketones **11**, **12** and **13** (245 mg, 80% yield) was obtained. On elution with a mixture of hexane/ethyl acetate in the ratio of 70:30, a stereoisomeric mixture of keto alcohols **14** (50 mg, 16% yield) was obtained.

The above procedure was repeated, and the stereoisomeric mixture of diketones **11**, **12** and **13** from both operations (450 mg) was resubmitted to flash column chromatography [silica gel (55 g), hexane/ethyl acetate mixtures], the fractions being analyzed by GC. In order of elution it was obtained: (i) a colorless oil (120 mg), mixture of diketones **12** and **13** in a ratio of about 1:1, (ii) a white solid (100 mg) consisting mainly of diketone **11**. The rest of the product (220 mg) consisted on mixtures of the different stereoisomers.

3.4.1. Analytical and spectroscopic data of 11. White crystals, mp 126–127°C (hexane, 60 mL/g); [Found: C, 78.4; H, 11.3. $C_{20}H_{34}O_2$ requires C, 78.37; H, 11.19%]; ν_{max} (KBr) 1693 (C=O st) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.49 [2H, quint, *J*=8.8 Hz, 3(7)-H], 2.04 [4H, dd, *J*=13.3, 8.8 Hz, 2(4,6,8)-Hβ], 1.58 [4H, d, *J*=13.3, 8.8 Hz, 2(4,6,8)-Hα], 1.10 [18H, s, C*Me*$_3$], 0.95 [6H, s, 3(7)-*Me*]; δ_C (75.4 MHz, $CDCl_3$) 218.6 (C, *C*OCMe$_3$), 54.0 [C, C1(5)], 44.2 [C, *C*Me$_3$], 43.7 [CH_2, C2(4,6,8)], 43.4 [CH, C3(7)], 26.2 [CH_3, C*Me*$_3$], 22.0 [CH_3, 1(5)-*Me*]; *m/z* (EI) 307 [1 $(M+H)^+$], 249 [33 $(M-C_4H_9)^+$], 221 [45 $(M-C_5H_9O)^+$], 135 [18 $(C_{10}H_{15})^+$], 85 (19), 57 (100 $C_4H_9^+$).

3.4.2. Analytical and spectroscopic data of the mixture of 12 and 13. Colorless oil, bp 70°C/0.5 Torr; ν_{max} (KBr) 1701 (C=O st) cm^{-1}; [Found: C, 78.6; H, 11.3. $C_{20}H_{34}O_2$ requires C, 78.37; H, 11.19%]; **12**: δ_H (500 MHz, $CDCl_3$) 3.47 (1H, tt, *J*=11.0, 6.5 Hz, 7-H), 3.28 (1H, tt, *J*=11.0, 7.0 Hz, 3-H), 1.82–1.76 [4H, m, 2(4)-Hβ and 6(8)-Hβ], 1.65–1.61 [2H, m, 2(4)-Hα], 1.58–1.53 [2H, m, 6(8)-Hα], 1.131 (9H, s) and 1.128 (9H, s) (3-COC*Me*$_3$ and 7-COC*Me*$_3$], 1.00 [6H, s, 1(5)-*Me*]; δ_C (75.4 MHz, $CDCl_3$) 218.48 (C) and 218.46 (C) (3-*C*OCMe$_3$ and 7-*C*OCMe$_3$], 51.2 [C, C1(5)], 47.8 [CH_2, C2(4)], 46.4 [CH_2, C6(8)], 44.6 (C) and 44.5 (C) (3-CO*C*Me$_3$ and 7-CO*C*Me$_3$), 42.9 (CH, C3), 41.3 (CH, C7), 26.12 (C) and 26.08 (C) (3-COC*Me*$_3$ and 7-COC*Me*$_3$), 24.3 [CH_3, 1(5)-*Me*]; *m/z* (GC/MS, r_t 14.07 min, 49% relative area, EI) 307 [2 $(M+H)^+$], 306 (6 $M^{\cdot+}$), 249 [14 $(M-C_4H_9)^+$], 221 [46 $(M-C_5H_9O)^+$], 135 [16 $(C_{10}H_{15})^+$], 85 (19), 57 (100 $C_4H_9^+$).

13: δ_H (500 MHz, $CDCl_3$) 3.36 [2H, quint, *J*=9.0 Hz, 2(4,6,8)-Hβ], 1.74–1.72[8H, m, 2(4,6,8)-Hα and 2(4,6,8)-Hβ], 1.14 [18H, s, 3(7)-COC*Me*$_3$], 1.03 [6H, s, 1(5)-*Me*]; δ_C (75.4 MHz, $CDCl_3$) 218.2 [C, 3(7)-*C*OCMe$_3$], 51.8 [C, C1(5)], 47.0 [CH_2, C2(4,6,8)], 44.4 [C, 3(7)-CO*C*Me$_3$], 43.7 [CH, C3(7)], 26.2 [CH_3, 3(7)-COC*Me*$_3$], 24.3 [CH_3, 1(5)-*Me*]; *m/z* (GC/MS, r_t 13.90 min, 44% relative area, EI) 307 [0.3 $(M+H)^+$], 306 (0.3 $M^{\cdot+}$), 249 [19 $(M-C_4H_9)^+$], 221 [27 $(M-C_5H_9O)^+$], 135 [9 $(C_{10}H_{15})^+$], 85 (22), 57 (100 $C_4H_9^+$).

3.4.3. Analytical and spectroscopic data of the stereoisomeric mixture 14. Colorless oil, bp 80°C/0.5 Torr; [Found: C, 77.9; H, 11.7. $C_{20}H_{36}O_2$ requires C, 77.86; H, 11.77%]; ν_{max} (KBr) 3518 (OH st), 1698 (C=O st) cm^{-1};

Significant δ_C (75.4 MHz, $CDCl_3$) 81.9 (CH), 81.6 (CH), 81.5 (CH), 81.3 (CH). *m/z* (GC/MS, stereoisomer of r_t 14.62 min, 35% relative area, EI) 309 [0.4 $(M+H)^+$], 291 (1), 290 [1 $(M-H_2O)^{\cdot+}$], 251 [41 $(M-C_4H_9)^+$], 233 [11 $(M-C_4H_9\text{-}H_2O)^+$], 205 [33 $(M-C_5H_9O\text{-}H_2O)^+$], 149 [23 $(M-C_5H_9O\text{-}H_2O\text{-}C_4H_8)^+$], 135 [64 $(C_{10}H_{15})^+$], 107 (22), 95 (28), 57 (100 $C_4H_9^+$). *m/z* (GC/MS, stereoisomer of r_t 14.93 min, 55% relative area, EI) 309 [0.05 $(M+H)^+$], 308 (0.05 $M^{\cdot+}$), 291 (1), 290 [3 $(M-H_2O)^{\cdot+}$], 251 [20 $(M-C_4H_9)^+$], 233 [54 $(M-C_4H_9\text{-}H_2O)^+$], 205 [20 $(M-C_5H_9O\text{-}H_2O)^+$], 135 [27 $(C_{10}H_{15})^+$], 107 (25), 57 (100 $C_4H_9^+$).

Procedure 2. A similar procedure to that described before was used, except for the use of 2.4 mmol SmI_2 per mol of diketone **9**. From **9** (1 mmol), after the flash column chromatography, a mixture of bicyclic diketones **11**, **12**, and **13** (288 mg, 94% yield) was obtained. Only minor amounts of keto alcohols **14** were detected.

Acknowledgements

A fellowship from *Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)* (Argentina) to A. E. L. and financial support from Comissionat per a Universitats i Recerca of the Generalitat de Catalunya (project 1999-SGR-00080) are gratefully acknowledged. We also thank the *Serveis Científico-Tècnics* of the University of Barcelona and particularly Drs M. Feliz and A. Linares for recording the NMR spectra, and Ms P. Domènech from the *Centro de Investigación y Desarrollo* (C.I.D.) (Barcelona, Spain) for carrying out the elemental analyses.

References

1. Camps, P.; Figueredo, M. *Can. J. Chem.* **1984**, *62*, 1184–1193.
2. Camps, P.; Iglesias, C.; Lozano, R.; Miranda, M. A.; Rodríguez, M. J. *Tetrahedron Lett.* **1987**, *28*, 1831–1832.
3. Camps, P.; Iglesias, C.; Rodríguez, M. J.; Grancha, M. D.; Gregori, M. E.; Lozano, R.; Miranda, M. A.; Figueredo, M.; Linares, A. *Chem. Ber.* **1988**, *121*, 647–654.
4. Camps, P.; Estiarte, M. A.; Vázquez, S.; Pérez, F. *Synth. Commun.* **1995**, *25*, 1287–1293.
5. Camps, P.; Font-Bardia, M.; Pérez, F.; Solans, X.; Vázquez, S. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 912–914.
6. Camps, P.; Font-Bardia, M.; Pérez, F.; Solà, L.; Solans, X.; Vázquez, S. *Tetrahedron Lett.* **1996**, *37*, 8601–8604.
7. Camps, P.; Luque, F. J.; Orozco, M.; Pérez, F.; Vázquez, S. *Tetrahedron Lett.* **1996**, *37*, 8605–8608.
8. Camps, P.; Font-Bardia, M.; Méndez, N.; Pérez, F.; Pujol, X.; Solans, X.; Vázquez, S.; Vilalta, M. *Tetrahedron* **1998**, *54*, 4679–4696.
9. Hoffmann, H. M. R.; El-Khagawa, A. M.; Oehlerking, H.-H. *Chem. Ber.* **1991**, *124*, 2147–2147.
10. Hoffmann, H. M. R.; Münnich, I.; Nowitzki, O.; Stucke, H.; Williams, D. J. *Tetrahedron* **1996**, *52*, 11783–11798.
11. Nowitzki, O.; Münnich, I.; Nowitzki, O.; Stucke, H.; Hoffmann, H. M. R. *Tetrahedron* **1996**, *52*, 11799–11810.
12. Gandolfi, C.; Passarotti, C.; Fava, W.; Fumagalli, A.; Faustini, F.; Ceserani, R. Belg. 873.731 (1979); *Chem. Abstr.* **1980**, *92*, 6137w.
13. Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878–3882.
14. Stoss, P.; Erhardt, E. *Arch. Pharm.* **1987**, *320*, 621–624.
15. Howe, R.; Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 915–916.
16. Borden, W. T.; Varma, V.; Cabell, M.; Ravindranathan, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 3800–3801.
17. Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In *Rearrangements in Ground and Excited States*, de Mayo, P., Ed.; Academic: New York, 1980; pp 391.
18. Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205–268.
19. Klunder, A. J. H.; Zwanenburg, B. *Chem. Rev.* **1989**, *89*, 1035–1050.
20. Crow, A. B.; Borden, W. T. *Tetrahedron Lett.* **1976**, 1967–1970.
21. Cram, D. J. In *Fundamentals of Carbanion Chemistry*, Academic: New York, 1965; pp 137–158.
22. Crow, A. B.; Borden, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 6666–6670.
23. Borden, W. T. *Synlett* **1996**, 711–719.
24. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134 (MM2 (91) version was used: Molecular Design Ltd., 2132 Farallon Dr., San Leandro, CA 94577, US).
25. Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8565 (MM3 (92) Program, Technical Utilization Corporation, 235 Glen Village Court, Poweell, Ohio 43063, USA).
26. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909. Semiempirical calculations were performed with the MOPAC 6.0 program on a PC computer. Stewart, J. P. P. *QCPE*, **1990**, 455.
27. Haque, A.; Ghosh, S. *Chem. Commun.* **1997**, 2039–2040.
28. Williams, D. B. G.; Blann, K.; Holzapfel, C. W. *J. Org. Chem.* **2000**, *65*, 2834–2836.
29. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112–4120.
30. Batey, R. A.; Harlling, J. D.; Motherwell, W. B. *Tetrahedron* **1996**, *52*, 11421–11444.
31. Beerli, R.; Bruner, E. J.; Borschberg, H. J. *Tetrahedron Lett.* **1992**, *33*, 6449–6452.
32. Molander, G. A.; Alonso-Alija, C. *Tetrahedron* **1997**, *53*, 8067–8084.
33. Ananthanarayan, T. P.; Gallagher, T.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1982**, 709–710.
34. Honda, T.; Naito, K.; Yamane, S.; Suzuki, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 1218–1220.
35. Lange, G. L.; Furlan, L.; MacKinnon, M. C. *Tetrahedron Lett.* **1998**, *39*, 5489–5492.
36. Molander, G. A. Reductions with Samarium (II) Iodide. Paquette, L. A., Ed., *Org. React.* **1994**, *46*, 211–367.