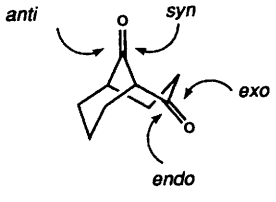
Stereochemistry of the Reduction of Bicyclo[3.3.1]nonane-2,9-dione by Complex Hydrides

Ulf Berg,*[a] Eugenius Butkus*[b] and Arvydas Stoncius[b]
[a] *Organic Chemistry 1, Chemical Center, PO Box 124, University of Lund, S-22100 Lund, Sweden*
[b] *Department of Organic Chemistry, Vilnius University, 2734 Vilnius, Lithuania*

Bicyclo[3.3.1]nonane-2,9-dione (**1**) has been reduced by sodium borohydride, lithium aluminium hydride and sodium cyanoborohydride. The regio- and diastereo-selectivity, as well as the product distribution of the four possible diastereoisomeric diols and four possible hydroxy ketones has been determined by a combination of GC and NMR spectroscopy. The first reduction step showed low regioselectivity between the two carbonyl groups but essentially total diastereoselectivity at reduction of either the 2- or the 9-carbonyl group. The 9-(catechol)acetal, which is regioselectively formed, gives an entry to the only diol which is not obtained in direct reduction of **1**. Benzoate or *p*-bromobenzoate esters were subjected to chiral chromatographic resolution on triacetylcellulose and CD spectroscopy gave information on the diastereochemistry as well as on the absolute configuration. Conformational preferences were established by molecular mechanics computations. The chair–chair conformation was calculated to be the most stable form of all the studied compounds except **1**, for which a chair–boat conformation is preferred. Transition structures for all possible lithium hydride additions to **1** were analysed by MNDO and *ab initio* methods.

Among the interesting aspects of the reduction of ketones, the stereoselectivity is a cornerstone. Exploration of the stereoselectivity of reductions has been performed with representative alkylcyclohexanones[1] and bicyclic and polycyclic compounds, *e.g.* adamantanones[2] and bicyclo[4.3.1]decanones.[3] The stereoselectivity of the reduction has been interpreted in terms of thermodynamic control,[4] torsional strain and steric approach control,[5] orbital symmetry control,[6] stereoelectronic effects[7–9] or electrostatic effects.[10] An attempt to predict the stereoselectivity in the reductions by a simple computational procedure has been reported.[11] Although *ab initio* molecular orbital calculations were used in support of different models to explain the experimental results, no one model and theory has been overwhelmingly satisfactory.[12]

The ketones possessing a bicyclo[3.3.1]nonane skeleton seem to be suitable models to understand the stereochemical control of reduction. Published data for hydride reduction of bicyclo[3.3.1]nonanones are available mainly for 2- and 9-monosubstituted ketones[13–15] and a few examples of symmetrically substituted bicyclononanediones are known.[16,17] We decided to undertake a study on the stereoselectivity of the reduction of bicyclo[3.3.1]nonane-2,9-dione (**1**) with some complex hydrides. This structure is of particular interest since the cyclohexanedione ring is calculated to exist preferentially in a boat conformation.[18] The conformation of the cyclohexanone ring was shown to affect the stereochemical course of hydride reduction of 9-substituted bicyclo[3.3.1]nonan-2-ones.[13] The complexity of the problem is obvious as four diastereoisomeric hydroxy ketones and four possible diastereoisomeric diols may be envisaged as reduction products of dione **1**. The possible sides of hydride attack are defined as *endo vs. exo* at position 2 and *syn vs. anti* at position 9 giving rise to *exo,anti*-, *exo,syn*-, *endo,anti*- and *endo,syn*-diols, respectively. The total product spectrum is shown in Scheme 1.

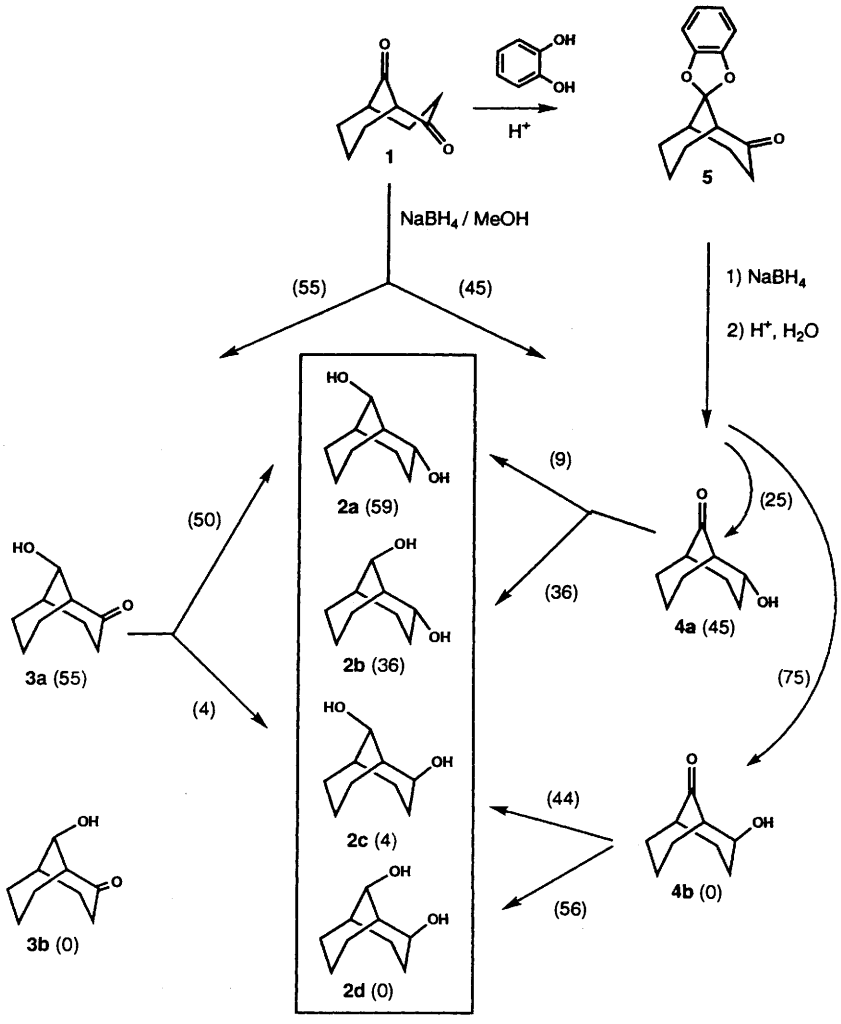


1

We report on the regio- and diastereo-selectivity of the reduction of **1** with sodium borohydride or sodium cyanoborohydride in methanol or water and with lithium aluminium hydride in tetrahydrofuran. The reaction course was followed by capillary GC and product ratios and identities were determined by GC and ^{1}H NMR spectroscopy. The dibenzoate or di-*p*-bromobenzoate esters have been subjected to chromatographic enantiomer separation on triacetylcellulose columns and the absolute configurations of the separated enantiomers have been determined. The conformational preferences of diols and esters were calculated by molecular mechanics[19] and transition structures for the first reduction step of **1** were localized by semiempirical and *ab initio* methods.

Results and Discussion

Reduction with Sodium Borohydride, Sodium Cyanoborohydride and Lithium Aluminium Hydride.—The regio- and diastereo-selectivity in hydride reduction of the 2- and 9-carbonyl groups of the dione **1** was examined by reaction with sodium borohydride in methanol at room temperature. The reaction was not regioselective but was totally diastereoselective for reaction at both 2- and 9-carbonyl groups. Thus the ratio of the 9-*anti*-hydroxybicyclo[3.3.1]nonan-2-one (**3a**) and 2-*endo*-hydroxybicyclo[3.3.1]nonan-9-one (**4a**) produced in reaction with 1 equiv. of hydride was found to be nearly constant during the reduction course and it was unexpectedly approximately 55:45 at room temperature. This ratio changed to 45:55 at lower temperature (−5 to 0 °C). No other hydroxyketone was formed. The amount of remaining unreduced dione was *ca.* 50% and of diols *ca.* 20%. The structures of the hydroxyketones **3a** and **4a** were defined by a combination of the NMR and GC data and by comparison with the NMR shifts reported in the literature.[15,20] Hydroxyketone **4** was, however, obtained as a mixture of *exo*/*endo* diastereoisomers, **4a** and **b** (ratio 1:3)



Scheme 1

Table 1 Product distribution of the diols **2** (%) for the reduction of **1** with various hydrides at 20 °C

Reaction conditions	2a	2b	2c	2d
$NaBH_3CN$–methanol	62	38	—	—
$NaBH_4$–methanol	59	36	4	—
$LiAlH_4$–THF	58	32	8	—

upon reduction of the C-9 carbonyl protected acetal **5** after hydrolytic deprotection. Essentially the same pattern was observed in reaction with lithium aluminium hydride in THF.

The complete reduction of dione **1** was achieved using excess of complex metal hydrides. The results are shown in Table 1. Two major diastereoisomeric diols were obtained. The ratio of the two diols varied between 57 and 62% of the major isomer and 38 and 33% of the second one, depending upon the hydride used. A minor isomer amounting to *ca.* 5% was also observed. Very similar hydroxyketone and diol ratios were found when only 1 equivalent of hydride was used and aliquots were analysed at various stages of reaction. Reduction with lithium aluminium hydride gave a similar ratio of the three diastereoisomers with a slight increase to 7–8% of the minor diol. The latter was, however, not formed in reduction with sodium cyanoborohydride. The major isomer was obtained in pure form after repeated crystallization from ethyl acetate.

Configurational Assignment.—The configuration of bicyclononane-2,9-diols could be determined by a combination of ^1H NMR and CD spectroscopy. The half width ($w_{\frac{1}{2}}$) and chemical shift of the signal from the proton adjacent to the hydroxy groups are illuminating.[20,21] The synthesis of the diols **2a** and **c** has been published, but no spectral data were reported.[13,22] Moreover, the same melting points were reported for **2a** and **c** by different authors.[13,20] In the case of the major diastereoisomeric diol obtained from dione **1**, 2-H gives a broad signal at δ 3.86 and 9-H gives a sharper signal at δ 3.55. The half width, $w_{\frac{1}{2}}$, of 2-H varies between 12 and 20 Hz in different solvents ([$^2H_6$]acetone, [$^2H_4$]methanol, D_2O). 2-*exo*-Protons are characteristically broad due to *trans* coupling to the axial 3-H. Independent evidence for the identity of **2a** is the selective NOE enhancement between 2- and 9-H obtained in a 2D ROESY experiment. Chemical shifts are given in Table 2.

Chromatographic Resolution and CD Spectroscopy.—Configurational assignment of the diols **2a–d** could be further confirmed by circular dichroism (CD) spectroscopy of the chiral dibenzoates [or bis(*p*-bromobenzoates) (**6a–d**)] of the diols employing the exiton chirality method.[23,24] According to molecular mechanics computations (*vide infra*), the dihedral angle between hydroxy or benzoyloxy groups is close to 0° in **2a** and **d** and should give no CD spectrum, whereas for **2b** and **c** the angles are approximately 120°.

Benzoylation or *p*-bromobenzoylation of the mixture of diols was accomplished by standard methods.[25] Flash chromato-

Table 2 ^{1}H NMR chemical shifts for compounds **2–6**

Compound	Solvent	a	b	c	d
2 H-2	CD_3OD	3.86(br)[a]	4.25(br)	4.32	4.14
H-9		3.55	4.00	4.04	3.91
3 H-9	$CDCl_3$	4.08	(4.07)[b]	—	—
4 H-2	$CDCl_3$	4.06(br)	4.36	—	—
6 H-2	$CDCl_3$	5.34(br)	5.60(br)	5.75	—
H-9		5.05	5.26	5.04	—

[a] b = broad signal ($w_{\frac{1}{2}} \geq 12$ Hz). [b] From ref. 15.

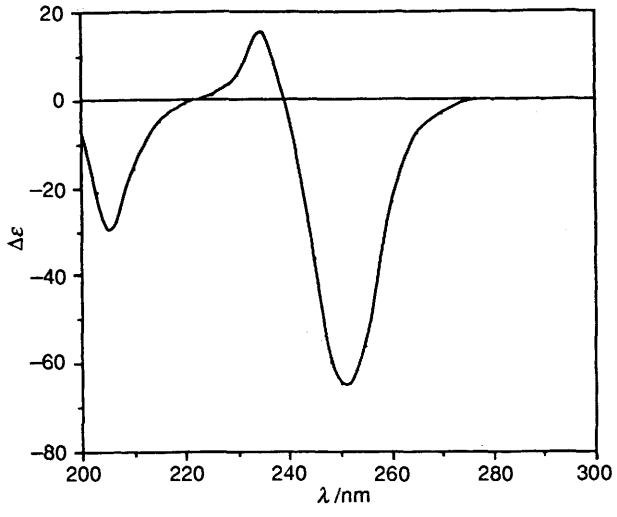


Fig. 1 CD-spectrum of the first eluted enantiomer of the bis-(*p*-bromobenzoate) of **2b** in ethanol

graphy of the mixture of bis(*p*-bromobenzoates) gave diastereochemically pure compounds of the two major components. A rather striking observation was that attempted chromatographic separation on swollen microcrystalline triacetylcellulose (TAC)[26] gave good separation ($\alpha = 1.4$) for the minor component but failed for the major component both as benzoate and *p*-bromobenzoate. The CD spectrum of the first eluted enantiomer of the resolved (−)-bis-(*p*-bromobenzoate) showed intense split Cotton effects of the exiton coupling type, *i.e.* negative first Cotton effect at 251 nm ($\Delta\varepsilon$ −65.2) and positive second Cotton effect at 233 ($\Delta\varepsilon$ 17.1). The comparatively weak intensity of the second band is due to the interference with the strong low wavelength band at 207 nm ($\Delta\varepsilon$ −48.0; Fig. 1). Combination of NMR and CD results proves the 2-*endo*-9-*syn*-configuration, **2b**, of this isomer and the (1*R*,2*R*,5*S*,9*R*)-configuration of the first eluted enantiomer. Enantiomerically enriched dibenzoate of the major isomer, **2a**, was obtained by the following sequence: repeated separation of **1** on a TAC column,[18] reduction with $NaBH_4$, recrystallizations from ethyl acetate and benzoylation gave enriched dibenzoate ($[\alpha] = 81°$). It gave *no* CD activity above 200 nm, as expected for a compound with parallel transitions, as in the case of the 2-*endo*-9-*anti*-configuration of **2a**.

The 2-*exo*-9-*anti*-configuration of the third diastereoisomeric diol (**2c**) from the reduction of **1** follows from the ^{1}H NMR spectrum [δ 4.32 (2-H) and 4.04 (9-H)] and GC analysis. This diastereoisomer was formed in 44% yield from reduction of a mixture of 2-*endo*- and 2-*exo*-hydroxy-9-ones, **4a** and **b** (ratio 1:3), obtained from reduction of the 9-protected acetal **5** and subsequent hydrolysis. However, the diol **2c** was not isolated from the redution mixture.

Table 3 Relative energies of the three most stable conformations of compounds **1–5** calculated by the MM2(91) force field. The absolute steric energies for the most stable conformers are given in parentheses

	Relative energy/kJ mol^{-1}		
Compound	Chair–chair	Chair–boat[a]	Boat–chair[a]
1	1.8	0 (96.90)	9.7
2a	0 (89.26)	17.9	16.2
2b	0 (87.49)	26.6	15.6
2c	0 (87.87)	9.9	19.2
2d	0 (79.44)	20.9	10.0
3a	0 (90.37)	1.0	16.9
3b	0 (86.03)	21.3	14.3
4a	0 (101.69)	10.7	4.3
4b	0 (95.36)	11.0	3.8
5	0 (119.04)	1.8	16.6

[a] Nomenclature according to Scheme 2.

In Scheme 1 the values in parenthesis after the compound number gives the product distribution and the number on the arrow gives the product distribution of that step.

Molecular Mechanics Computations of the Conformational Stabilities.—The low energy conformations of all the discussed compounds were calculated by the MM2(91) force field.[19] The results are given in Table 3, in which chair–boat and boat–chair are defined as in Scheme 2. With one exception the chair–chair

Scheme 2

conformations were preferred throughout the series. Compound **1**, however, was calculated to be 1.88 kJ mol^{-1} more stable in the chair–boat conformation in the gas phase corresponding to *ca.* 70% chair–boat and 30% chair–chair at room temperature. The energy difference decreased in a medium of higher permittivity ($\Delta E = 0.92$ kJ mol^{-1} for $\varepsilon = 25$). Kinetically significant amounts of the chair–boat conformations are also predicted for **3a**, **b** and **5**.

Interpretation of the Selectivities.—The most striking feature in the reduction of **1** is the low regioselectivity as contrasted with the very high diastereoselectivity upon reduction of each of the carbonyl groups. In other reactions, such as the acetalization with catechol giving exclusively **5**, the 9-carbonyl is more reactive. The acetal formation is carried out under thermodynamic control and could be explained by release of strain in the dione and higher stability of this acetal. The 2-catechol acetal is calculated to be of 12.1 kJ mol^{-1} higher energy. The reduction reactions proceed, however, under kinetic control and the transition states have to be considered. A higher intrinsic reactivity at C-9 was also expected because of the difference in bond angle around the carbonyl carbon atoms; the C–C(=O)–C bond angle is 111° at C-9 and 116°/119° (chair–boat/chair–chair conformation) at C-2. The temperature effect on the regioselectivity, however, indicates that enthalpy slightly favours C-2 reduction. The fact that essentially the same product distribution was obtained for reduction by $NaBH_4$–methanol and $LiAlH_4$–THF seems to preclude any important difference in solvent effect as well as demonstrating the dominant role of cation co-ordination to the oxygen atom in determining the selectivity.

Table 4 Transition-state properties for the reduction of **1** calculated by the MNDO method. Energies in kJ mol^{-1} and distances in Å. The *endo*, *exo*, *syn* and *anti* notions signify the orientation of hydroxy group in the product

Property	**4a** c,b-*endo*	**4b** c,b-*exo*	**3a** c,b-*anti*	**3b** c,b-*syn*	**4a** c,c-*endo*	**4b** c,c-*exo*	**3a** c,c-*anti*	**3b** c,c-*syn*
E^a	−255.7	−248.2	*b*	*c*	−262.9	−257.4	−253.1	−251.5
d_{C-O}	1.269	1.270			1.268	1.269	1.265	1.266
d_{C-H}	1.888	1.896			1.912	1.906	1.914	1.923
d_{H-Li}	1.507	1.509			1.507	1.505	1.508	1.503
d_{O-Li}	2.031	2.016			2.036	2.023	2.026	2.023

[a] Heat of formation of the transition state. [b] Minimizes to c,c-*anti*. [c] Minimizes to c,c-*syn*.

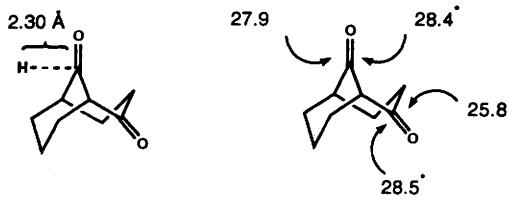


Fig. 2 Transition-state model (left) and calculated 'transition state energies' (kcal mol^{-1}) for the various hydride attacks as calculated by MM2(1991). The values marked with an asterisk represent attack on chair–chair conformation which in those cases had the lowest energy.

The first hydride attack occurs from *exo*-2-(C=O) or *syn*-9-(C=O) sites. We tested the steric requirement of a hydride in a simple transition-state model with the hydride placed 2.30 Å from the carbonyl carbon atom and perpendicular to the carbonyl plane and calculated the steric energies with the MM2 (91) force field. The calculated steric energies for the various transition states are shown in Fig. 2. The experimentally observed diastereoselectivity is sterically supported at C-2 but not at C-9.

We also performed calculations of the two kinetically significantly populated conformations of **1** using both semiempirical (AM1 and MNDO) and *ab initio* methods (STO 3G and 3-21G levels) in the Spartan program package.[27] The chair–boat conformation is calculated to be more stable by 0.4–2.5 kJ mol^{-1} in agreement with the MM2 results. A dominating electrostatic effect should show up in the electron density surface, which, however, turned out to be difficult to interpret. A much better picture is accomplished when the LUMO orbital coefficients were superimposed on the electron density surface. 9-*Syn* and 2-*exo* attack are favoured by large overlapping LUMO regions. Substantial transannular orbital interactions between the carbonyl groups in **1** are indicated by the ^{13}C NMR chemical shifts and in the CD-spectrum.[28] Thus, co-operative orbital and electrostatic control of the diastereoselectivity at both C-2 and -9 is nicely visualized by this approach.

Transition structures were localized using the MNDO Hamiltonian for all possible approaches of lithium hydride to **1**. The results are given in Table 4. The MNDO transition states are earlier than the 3-21G transition states, calculated by Wu *et al.*,[3] with respect to lithium transfer to oxygen but later with respect to hydride transfer. Pyramidalization of the carbonyl carbon is very weak in both methods. The chair–chair conformation was favoured in all transition states. Single point calculations at the 3-21G level gave the same stability order of the transition structures as MNDO. These results agree with the observed diastereoselectivity for the first hydride attack at both C-2 and -9. The calculations strongly favour C-2 over -9 regioselectivity. The experimental results show low selectivity, but the temperature effect indicates that attack on C-2 has a lower activation enthalpy.

In the second reduction step the structure of the substrate is less obvious. The alkoxyborohydride adduct first formed may undergo direct reduction in a second step, but another possibility is that, in methanol and water solutions, reaction with solvent to give free hydroxy ketones **3a** and **4a** takes place prior to hydride attack, or alternatively, the hydroxy ketones are formed directly in the reaction *via* solvent participation.[29] This step is thus less accessible to interpretations by transition-structure calculations.

In summary, the diastereoselectivity at C-2 can be understood in terms of steric, stereoelectronic or electrostatic effects, whereas the diastereoselectivity at C-9 seems to have a stereoelectronic and electrostatic origin. The low regioselectivity seems to stem from opposed enthalpy and entropy contributions, which makes it more complicated to interpret. The MNDO localized transition-state energies reproduce diastereoselectivities at both C-2 and -9, and suggest a regioselectivity, which is in agreement with the apparent activation enthalpy differences.

Experimental

Analytical GC was performed on a Varian Model 3400 F/I instrument on a 30 m × 0.25 mm diameter DB-Wax column. Column flash chromatography was carried out on TLC-Kieselgel 60H, mean particle size 15 μm (Merck, Germany). NMR spectra were recorded on a Varian XL 300 spectrometer and are reported in ppm downfield from tetramethylsilane. UV spectra were recorded with a Varian Cary 2290 spectrometer and IR spectra on a Perkin-Elmer 296 instrument. Chromatographic enantiomer resolution was performed on microcrystalline triacetylcellulose columns using a procedure already described.[30] The CD spectra were recorded with a Jasco Model J-500 A spectrometer. Optical rotations at the sodium D line were measured in a 0.5 cm microcell on a Perkin-Elmer 141 polarimeter. M.p.s were determined in a Kofler apparatus and are uncorrected.

Molecular mechanics calculations were performed with the MM2(1991) force field.[19,31] Input structures were constructed by the molecular modelling program system MacMIMIC[32] and carried out on a Macintosh IIci computer. The SPARTAN computations were performed on a Silicon Graphics Iris Indigo work station.

Reduction with Sodium Borohydride (and Sodium Cyanoborohydride).—To a stirred solution of dione **1** (0.022 g, 0.14 mmol) in methanol (5 cm^3) (or water) was added sodium borohydride (0.014 g, 0.37 mmol). The mixture was stirred at room temperature for 4 h and hydrochloric acid (1 mol dm^{-3}; 1 cm^3) was added. The solution was evaporated to dryness under reduced pressure and the solid residue was continuously extracted with diethyl ether in a Soxhlet apparatus. The ether was evaporated, giving 0.21 g (97%) of a diastereoisomeric mixture. Bicyclo[3.3.1]nonane-2-*endo*-9-*anti*-diol (**2a**) (0.06 g, 28%) was obtained after repeated crystallizations from ethyl

acetate, m.p. 233 °C; $\delta_H(CD_3OD)$ 1.36–2.14 (m, 14 H), 3.55 (t, 1 H) and 3.86 (m, 1 H).

The reduction was also followed using various amounts of sodium borohydride (0.5–1 equiv.). Aliquots were quenched, extracted and analysed by GC. Reduction with sodium cyanoborohydride was conducted as above. After 24 h, 80% of a mixture of the two diols **2a** and **b** were obtained.

Reduction with Lithium Aluminium Hydride.—To a suspension of $LiAlH_4$ (0.02 g, 0.5 mmol) in dry tetrahydrofuran (THF) (10 cm^3) was added dropwise a solution of dione **1** (0.025 g, 0.16 mmol) in THF (10 cm^3). The mixture was heated under reflux for 4 h. After cooling hydrochloric acid (1 mol dm^{-3}) was added to give an acidic solution and the mixture was stirred at room temperature for 1 h. The inorganic solid was filtered off and the solution was evaporated. The residue was continuously extracted with diethyl ether using a Soxhlet apparatus; yield 78%.

Spiro[benzo-1,3-dioxole-2,9'-bicyclo[3.3.1]nonan]-2'-one **5**. —Phosphorous pentoxide (1.4 g, 0.01 mol) was added to a solution of **1** (0.76 g, 5 mmol) and benzene-1,2-diol (0.83 g, 7.5 mmol) in toluene (7 cm^3). The mixture was heated under reflux until the dione **1** had reacted (*ca.* 1 h, monitored by TLC, CCl_4–EtOAc 4:1). The cooled reaction mixture was concentrated and water was added to destroy the excess of P_2O_5. The organic layer was separated and the water layer was extracted three times with benzene. Combined extracts were dried ($MgSO_4$), the solvent evaporated and the residue purified by flash chromatography (toluene–EtOAc 5:1). Yield 0.46 g (39%), m.p. 101–103 °C (recrystallized from light petroleum); ν(KBr)/cm^{-1} 1700, 1240 and 1080; λ(EtOH)/nm (log ε) 228 (3.52) and 283 (3.7); $\delta_H(CDCl_3)$ 1.21–2.56 (m, 10 H), 2.61–2.74 (m, 1 H), 2.84–2.93 (m, 1 H) and 6.71–6.82 (m, 4 H); $\delta_C(CDCl_3)$ 18.29, 22.87, 27.25, 29.99 (alicyclic C), 35.24 (CH–CO), 37.62 (CH), 54.33 (CH–CO), 108.93 (O–C–O), 118.37, 118.64, 121.36, 121.43, 121.46, 146.64 (aromatic) and 212.01 (C=O).

Reduction of Ketoacetal **5**.—To a solution of **5** (0.49 g, 2 mmol) in a minimum volume of ethanol–water (3:1) was added an excess of sodium borohydride. The reaction mixture was stirred until **5** had been consumed (monitored by TLC, EtOAc–toluene 1:2), neutralized with HCl (1 mol dm^{-3}) and the solvents evaporated. The solid residue was continuously extracted in a Soxhlet apparatus with diethyl ether: evaporation gave 0.42 g (85%), m.p. 105–106 °C (from light petroleum–diethyl ether); ν(KBr)/cm^{-1} 3425–3200br, 1235, 1090 and 1080; λ(EtOH)/nm (log ε) 199 (4.66), 233 (3.51) and 285 (3.67); $\delta_H(CDCl_3)$ 1.20–2.40 (m, 13 H), 4.04 (m, 0.2 H, H-2'-*endo*), 4.33 (m, 0.8 H, H-2'-*exo*) and 6.70–6.85 (m, 4 H); $\delta_C(CDCl_3)$ 18.62, 19.89, 21.74, 25.59, 26.12, 28.87, 29.89, 30.17, 35.45, 35.91, 43.37 (alicyclic C), 70.16, 74.06 (C–OH), 108.48, 108.84 (O–C–O), 120.69, 120.94, 120.98, 121.13, 121.16, 121.64, 147.05 and 147.18 (aromatic).

2-endo- *and* 2-exo-*Hydroxybicyclo[3.3.1]nonan-9-one* **4a** *and* **b**.—The monoacetal **5** (0.1 g, 0.4 mmol) was dissolved in 10 cm^3 of methanol–water (7:3) and an excess of sodium borohydride (0.02 g, 0.5 mmol) was added. The reaction mixture was stirred for 3 h, then acidified with aq. HCl (1 mol dm^{-3}) solution and heated for 2 h. The solution was neutralized with $NaHCO_3$ solution, concentrated and extracted with chloroform. Evaporation yielded 0.4 g (71%). The product was a 1:3 mixture of *endo*/*exo* isomers, **4a** and **b**, as determined by NMR spectroscopy: $\delta_H(CDCl_3)$ 1.40–2.48 (m, 13 H), 4.06 (br m, 0.25 H, 2-H, **4a**) and 4.36 (m, 0.75 H, 2-H, **4b**).

General Procedure for the Benzoylation of Diols.—The mixture of diols (0.03 g, 0.2 mmol) and an excess of redistilled benzoyl or *p*-bromobenzoyl chloride (0.6 mmol) in pyridine (0.5 cm^3) was heated for 1 h and $NaHCO_3$ solution (1 cm^3; 5%) was added to the cold reaction mixture. It solidified on cooling giving an oily mass which was decanted and washed through a layer of silica gel. Flash chromatography afforded the diastereoisomers: bicyclo[3.3.1]nonane-2-*endo*-9-*anti*-diyl bis(*p*-bromobenzoate) (**6a**), m.p. 150–152 °C; $\delta_H(CDCl_3)$ 1.40–2.22 (m, 11 H), 2.48 (t, 1 H), 5.05 (t, 1 H), 5.34 (m, 1 H), 7.58 (dd, 4 H) and 7.92 (dd, 4 H); bicyclo[3.3.1]nonane-2-*endo*-9-*syn*-diyl bis(*p*-bromobenzoate) (**6b**), m.p. 175–177 °C; $\delta_H(CDCl_3)$ 1.42–2.58 (m, 11 H), 2.50 (t, 1 H), 5.26 (t, 1 H), 5.60 (m, 1 H), 7.58–7.61 (dd, 4 H) and 7.90–7.94 (dd, 4 H) (Calc. for $C_{17}H_{22}Br_2O_4$: C, 52.90; H, 4.25; Br, 30.60. Found: C, 53.5; H, 4.5; Br, 30.3); bicyclo[3.3.1]nonane-2-*exo*-9-*anti*-diyl bis(*p*-bromobenzoate) (**6c**), was not isolated; $\delta_H(CDCl_3)$ 5.02 (t, 1 H) and 5.75 (br m, 1 H).

Acknowledgements

We thank the Swedish Institute for a scholarship to E. B., the University of Lund for a grant to A. S. and the Fund available for the co-operation between Lund and Vilnius Universities for financial support. This work was supported by the Swedish Natural Science Research Council.

References

1 J. R. Boone and E. C. Ashby, *Top. Stereochem.*, 1979, **11**, 53.
2 C. K. Cheung, L. T. Tseng, M.-H. Lin, S. Srivastava and W. J. le Noble, *J. Am. Chem. Soc.*, 1989, **111**, 8447.
3 Y.-D. Wu, J. A. Tucker and K. N. Houk, *J. Am. Chem. Soc.*, 1991, **113**, 5018.
4 W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Am. Chem. Soc.*, 1956, **76**, 2579.
5 M. Cherest and H. Felkin, *Tetrahedron Lett.*, 1971, 383.
6 (*a*) N. T. Anh, O. Eisenstein, J. M. Lefour and M. R. Tran Huu Dau, *J. Am. Chem. Soc.*, 1973, **95**, 6146; (*b*) N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61.
7 A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540.
8 (*a*) A. S. Cieplak, L. T. Tait and C. R. Johnson, *J. Am. Chem. Soc.*, 1989, **111**, 8447; (*b*) C. R. Johnson, L. T. Tait and A. S. Cieplak, *J. Am. Chem. Soc.*, 1987, **109**, 5975.
9 For a recent example, see Y. Senda, S. Nakano, H. Kunii and H. Itoh, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1009.
10 M. N. Paddon-Row, Y.-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, 1992, **114**, 10638.
11 B. Ganguly, J. Chandrasekhar, F. A. Khan and G. Mehta, *J. Org. Chem.*, 1993, **58**, 1734.
12 H. Li and W. J. le Noble, *Recl. Trav. Chim. Pays-Bas*, 1992, **111**, 199.
13 A. Gambacorta, A. R. Dello Jacono, M. Bota and A. Tati, *Gazz. Chim. Ital.*, 1992, **122**, 355.
14 S. H. Graham, H. A. James and T. Suavansri, *J. Chem. Res.*, 1980, (*S*) 292, (*M*) 3670.
15 O. R. Duthaler and C. Ganter, *Helv. Chim. Acta*, 1975, **58**, 1366.
16 E. Butkus, J. Malinauskiene and P. Kadziauskas, *Z. Chem.*, 1980, **20**, 103 and refs. 3–7 cited therein.
17 J. Cable and J. K. Macleod, *Austr. J. Chem.*, 1973, **26**, 2147.
18 U. Berg and E. Butkus, *J. Chem. Res.* (*S*), 1993, 116.
19 U. Burkert and N. L. Allinger, *Molecular Mechanics*, Am. Chem. Soc., Washington, DC, 1982.
20 W. Kraus, W. Rothenwöhrer and R. Chassin, *Tetrahedron Lett.*, 1969, 4581.
21 A. Kasal, *Collect. Czech. Chem. Commun.*, 1978, **43**, 498.
22 R. A. Appleton, J. R. Dixon, J. M. Evans and S. H. Graham, *Tetrahedron*, 1967, 805.
23 N. Harada and K. Nakanishi, in *Circular Dichroic Spectroscopy. Exiton Coupling in Organic Chemistry*, University Science Books, Mill Valley, CA, 1983.
24 N. Harada and K. Nakanishi, *Acc. Chem. Res.*, 1972, **5**, 257.
25 A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longman, 5th edn., 1989, 646.
26 A. Mannschreck, H. Koller, R. Wernicke, *Kontakte* (*Darmstadt*), 1985, **1**, 40.

27 SPARTAN, version 3.0, W. J. Hehre, L. D. Burke, A. J. Shusterman and W. J. Pietro, Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA, 92715.
28 U. Berg and E. Butkus, *J. Chem. Res.* (*S*), 1994, 356.
29 H. O. House, *Modern Synthetic Organic Reactions*, Benjamin, New York, 1972, 45ff.
30 R. Isaksson and J. Roschester, *J. Org. Chem.*, 1985, **50**, 2519.
31 T. Liljefors, J. Tai, S. Li and N. L. Allinger, *J. Comput. Chem.*, 1987, **8**, 1051; the MM2 program is available from the Quantum Chemistry Program Exchange (University of Indiana, Bloomington, IN 47405).
32 (*a*) T. Liljefors, *J. Mol. Graphics*, 1983, **1**, 111; (*b*) C. W. Von der Lieth, R. E. Carter, D. P. Dolata and T. Liljefors, *J. Mol. Graphics*, 1984, **2**, 117; the Macintosh version of MIMIC is available from InStar Software AB, Ideon Research Park, S-223 70 Lund, Sweden.

Paper 4/04215H
Received 11*th July* 1994
Accepted 8*th September* 1994