On the Diastereoselectivity of the Aqueous-Acid-Catalyzed Intramolecular Aldol Condensation of 3-Oxocyclohexaneacetaldehydes[1])

by **Barbara De Santis**, **Anna Laura Iamiceli**, **Rinaldo Marini Bettolo***, **Luisa Maria Migneco**, and **Rita Scarpelli**

Dipartimento di Chimica and Centro di Studio del CNR per la Chimica delle Sostanze Organiche Naturali, Università degli Studi di Roma, 'La Sapienza', p.le Aldo Moro 5, I-00185 Roma

and **Giorgio Cerichelli**

Dipartimento di Chimica, Ingegneria Chimica e dei Materiali, Università de L'Aquila, Coppito Due, I-67010 L'Aquila

and **Giancarlo Fabrizi**

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi di Roma La Sapienza, p.le Aldo Moro 5, I-00185 Roma

and **Doriano Lamba***

International Centre for Genetic Engineering and Biotechnology, Area Science Park, Padriciano 99, I-34012 Trieste

Dedicated to the memory of Prof. *Giacomino Randazzo*

The factors responsible for the diastereoselective formation of the 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one by acid-catalyzed intramolecular aldol reaction of 3-oxocyclohexaneacetaldehydes have been investigated. This study, carried out on (1*SR*,4*RS*,6*RS*)-6-hydroxybicyclo[2.2.2]octan-2-one **1a**, (1*SR*,4*RS*,6*SR*)-6-hydroxybicyclo[2.2.2]octan-2-one **1b**, and 3,3-(ethylenedioxy)cyclohexaneacetaldehyde **2a**, allowed to demonstrate the absence of intramolecular H-bonding in **1a** as a stabilizing factor, and to ascertain the presence of unfavorable steric interactions in **1b**.

1. Introduction. – Although the intramolecular aldol reaction of 3-oxocyclohexane acetaldehydes leading to 6-hydroxybicyclo[2.2.2]octan-2-ones has been often exploited in the synthesis of some classes of natural products [1], to our knowledge, the diastereoselectivity of this reaction has not been yet examined.

This cyclization, which, in principle, might lead to two epimeric hydroxy ketones[2]), has been carried out – the experimental conditions are not always detailed – initially only in an aqueous mineral acid (HCl, H_2SO_4, H_3PO_4) and later in an aqueous mineral acid/polar co-solvent (THF, acetone) mixture; reaction temperatures and times varied

---

[1]) Preliminary reports of this work were presented at 'XXIV Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana', Salerno, Sept. 21st–25th 1997, Atti P28, and at the '12th International Conference on Organic Synthesis (ICOS-12)', Venezia, June 28th–July 2nd 1998, Book of Abstracts P B39, p. 350.

[2]) The formation, under milder conditions, of an unsaturated hemiacetal, resulting from the addition of the enolized formyl group to the ketone C=O group has also been recorded by us in the course of unpublished work, preliminary to that described in [1k], and by other authors [1l].

from one case to the other. Aqueous acidic conditions were necessary since 3-oxocyclohexaneacetaldehydes are obtained *in situ* from precursors in which the aldehyde (or ketone) C=O group is protected as an acetal.

In some cases, the epimeric product mixture was not separated nor analyzed, since this step was unimportant for the sake of the studies in which the hydroxy-ketone preparation had been carried out; in some cases the formation of only the *endo*-epimer was reported; finally, in other cases, implying equilibration of the formed epimers at reflux in a THF/aqueous HCl mixture, the *endo*-epimer was found to be the major product. On these grounds *Wiesner* and coworkers pointed out that the *endo*-epimer appears to be the product of thermodynamic control [1g].

When separately submitted to acid-catalyzed equilibration, both the *endo*- and *exo*-epimers led to mixtures in which the former predominated [1k] [2a].

As a part of our investigation on the synthesis of natural products *via* 6-*endo*-hydroxybicyclo[2.2.2]octan-2-ones and with respect to the general interest in this class of compounds [1][2], we decided to search for the factors which make the *endo*-epimer the thermodynamically controlled product of the title reaction.

(1*SR*,4*RS*,6*RS*)- and (1*SR*,4*RS*,6*SR*)-6-hydroxybicyclo[2.2.2]octan-2-ones (**1a** and **1b**, resp.) were selected as tools for our study. The preparation of **1a** and **1b** had been described for the first time by *Mori* and coworkers, who obtained **1a** and **1b** by intramolecular aldol condensation of 3-oxocyclohexaneacetaldehyde **2b**[3]) (*Scheme*), and **1b** from **1a**, by *Jones* oxidation of the latter, followed by *Birch* reduction of the resulting bicyclo[2.2.2]octane-2,6-dione [1f]. A diastereoisomeric mixture of **1a** and **1b** was obtained also by $NaBH_4$ reduction of bicyclo[2.2.2]octane-2,6-dione [2b]. Compound (−)-**1a** was obtained by enzymatic reduction of bicyclo[2.2.2]octane-2,6-dione [1o][2b], while (+)-**1a** was prepared from (−)-**1a** [2d].

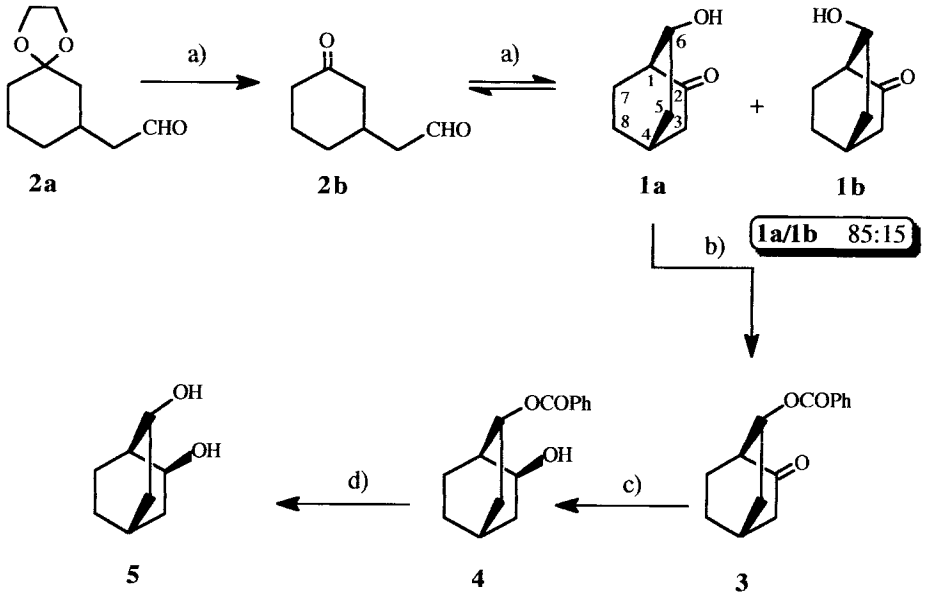
Structure determination of **1a**, and thus of **1b**, has not been 'rigorously proved' [1f] though ^{1}H-NMR spectroscopic evidences on a derivative of (−)-**1a** [1o] and experiments carried out for the preparation of (+)-**1a** from (−)-**1a** [2d] support its structure.

2. Results and Discussion. – 2.1. *Synthesis, and Chemical and Spectroscopical Characterization of* **1a** *and* **1b**. For the preparation of **1a** and **1b** (*Scheme*), we adopted the experimental protocol that previously allowed us and others to obtain, on related compounds, the *endo*-epimer as the major product: thus, the known 3,3-(ethylenedioxy)cyclohexaneacetaldehyde (**2a**) [1f], dissolved in THF/2N HCl 2:1, was refluxed for 24 h to give, *via* the 3-oxocyclohexaneacetaldehyde (**2b**), a 85:15 epimeric mixture of 6-hydroxybicyclo[2.2.2]octan-2-ones, which was separated by careful silica-gel column chromatography. A large difference between the melting points of **1a** (major product) and **1b** (minor product) recorded by us and those reported in the literature [1f], and the lack of an exhaustive spectroscopic analysis prompted us to characterize chemically and spectroscopically the two epimers.

Thus, **1a** was treated with PhCOCl in pyridine to give quantitatively **3**, which, dissolved in $MeOH/Et_2O$, was reduced at 0° with $NaBH_4$ to **4**. The formation of the hydroxy derivative **4** as the only product detectable on TLC, even by elution with various solvent systems, shows that one side of the C=O group is hindered. Hydrolysis of **4** by 1% KOH in MeOH, under N_2 at reflux, gave the *meso*-diol **5**; the ^{13}C-NMR spectrum of **5**

[3]) Compound **2b** has been also obtained in both optically active forms [3].

Scheme



a) THF/2N HCl 2:1, reflux. *b*) PhCOCl, py, r.t. *c*) $NaBH_4$, MeOH/Et_2O 1:1. *d*) 1% KOH in MeOH.

displays only six peaks, thus confirming the assignments made above. It follows that the OH groups in **1a** and **1b** are *endo*- and *exo*-configurated, respectively.

DEPT, HETCOR (*Figs. 1* and *3*), and 2D-COSY-45 (*Figs. 2* and *4*) experiments allowed us to assign most all the ^1H and ^{13}C resonances of **1a** and **1b** (*Tables 1* and *2*), and to confirm the information obtained by chemical means.

1D- and 2D-NMR experiments were carried out at 30° in C_6D_6, since, in this solvent, the ^1H-NMR signals showed larger chemical-shift differences than in $CDCl_3$ or in CD_3OD.

The ^1H-NMR (C_6D_6) of **1a** (*Table 1*) shows a *multiplet* at 3.88 ppm (1 H), a *singlet* at 3.20 ppm (1 H), a *multiplet* at 2.40 ppm (1 H), an *AB*-system *A* part at 2.20 ppm (1 H) and an *AB*-system *B* part at 1.90 ppm (1 H); both *A* and *B* parts, particularly the latter, show further couplings. The spectrum shows also *multiplets* between 1.80–1.58 (2 H), 1.55–1.40 (1 H), 1.40–1.28 (1 H), 1.25–1.08 (1 H), and 1.08–0.90 ppm (2 H). On the basis of their chemical shifts, those at 3.88 and 2.40 ppm were attributed to the H–C(6) and to the H–C(1), respectively.

The ^{13}C-NMR (C_6D_6) (*Table 1*) of **1a** shows eight peaks at 214.6, 69.0, 50.8, 44.5, 36.1, 27.9, 23.7, and 19.9 ppm. On the basis of their chemical shifts and on the basis of the DEPT spectrum (*Table 1*), the signals at 214.6, 69.0, 50.8, 44.5, 36.1, and 27.9 ppm were attributed at the C(2), C(6), C(1), C(3), C(5), and C(4) respectively.

The HETCOR and 2D-COSY-45 experiments (*Figs. 1* and *2*, resp.) led to a nearly complete assignment of ^1H and ^{13}C chemical shifts for **1a**. The HETCOR spectrum (*Fig. 1*) revealed that: *a*) the signals at 2.20 (1 H) and 1.90 ppm (1 H) correlate with the signal of the C(3) at 44.5 ppm, and were assigned to $CH_2(3)$; *b*) the *multiplet* at 1.80–1.58 ppm (2 H) correlates with the ^{13}C resonances at 36.1 and 27.9 ppm, and was assigned to H–C(4) and to one of the H–C(5); *c*) the *multiplet* at 1.55–1.40 ppm (1 H) correlates with the signal of the C(5) at 36.1 ppm and was assigned to the other H–C(5). The signal at 3.20 ppm, which does not correlate to any C-atom, was attributed to HO–C(6).

The assignment of the $CH_2(7)$ and $CH_2(8)$ signals was established by 2D-COSY-45 experiment, which shows (*Fig. 2*), among the others, a connectivity between the H–C(1) signal at 2.40 ppm (1 H) and the *multiplets* at 1.40–1.28 (1 H) and 1.25–1.08 ppm (1 H). These *multiplets* were, therefore, attributed to $CH_2(7)$ and the 19.9-ppm signal in the ^{13}C-NMR spectrum to C(7). As a consequence, the *multiplet* at 1.08–0.90 ppm (2 H) was assigned to $CH_2(8)$, and the signal at 23.7 ppm in the ^{13}C-NMR spectrum was attributed to C(8).

Table 1. *^{1}H-and ^{13}C-NMR Chemical Shifts and Assignments* (C_6D_6, 30°) *for* **1a**

C-Atom	^{13}C [ppm]	DEPT	^{1}H [ppm]	H-Atom
C(1)	50.8	CH	2.40 (*m*, 1 H)	H–C(1)
C(2)	214.6	C	–	–
C(3)	44.5	CH_2	2.20 (*A* of *AB*, J_{AB} = 18.7, 1 H) 1.90 (*B* of *AB*, J_{AB} = 18.7)	$H_{(pro\text{-}S)}$–C(3) $H_{(pro\text{-}R)}$–C(3)
C(4)	27.9	CH	1.80–1.58 (*m*, 1 H)	H–C(4)
C(5)	36.1	CH_2	1.80–1.58 (*m*, 1 H) 1.55–1.40 (*m*, 1 H)	H_{exo}–C(5) H_{endo}–C(5)
C(6)	69.0	CH	3.88 (*m*, 1 H)	H–C(6)
C(7)	19.9	CH_2	1.25–1.08 (*m*, 1 H) 1.40–1.28 (*m*, 1 H)	CH_2(7)
C(8)	23.7	CH_2	1.08–0.90 (*m*, 2 H)	CH_2(8)
–	–	–	3.20 (*s*, 1 H)	OH

Furthermore, *a*) the *AB*-system *A* part at 2.20 ppm, which correlates with the *multiplet* at 1.08–0.90 ppm, was assigned to $H_{(pro\text{-}S)}$–C(3), since it shows a coupling (*W*) with one of the CH_2(8); *b*) the *AB*-system *B* part at 1.90 ppm must, therefore, be attributed to the $H_{(pro\text{-}R)}$–C(3); since the signal of $H_{(pro\text{-}R)}$–C(3) correlates with the H–C(5) signal between 1.80–1.58 ppm, the latter signal was attributed to H_{exo}–C(5), and, as a consequence, the signal at 1.55–1.40 ppm was attributed to H_{endo}–C(5). The large deshielding effect experimented by $H_{(pro\text{-}S)}$–C(3), as compared to the $H_{(pro\text{-}R)}$–C(3) epimer, was attributed to the *endo*-configurated HO–C(6) field effect [1o][4]. The assignments for **1a** are summarized in *Table 1*.

We then turned to the analysis of the ^{1}H-NMR spectrum of **1b** (*Table 2*) which reveals a *multiplet* at 3.84 (1 H), a *quartet* at 2.33 (1 H), a *multiplet* at 2.22–2.09 (1 H), a *doublet* at 2.00 (1 H), *multiplets* between 1.90–

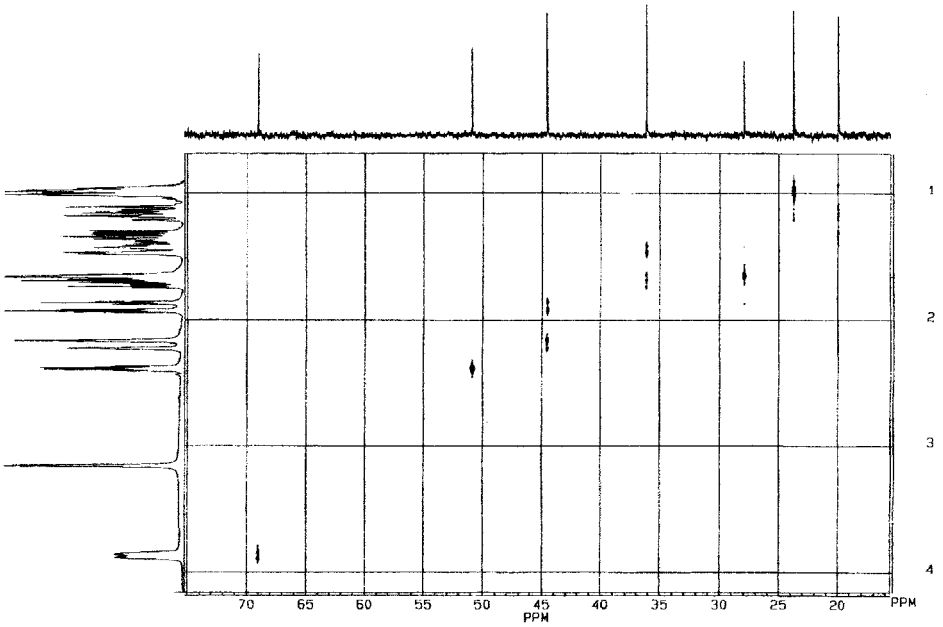


Fig. 1. *HETCOR Spectrum* (C_6D_6, 30°) *of* **1a**

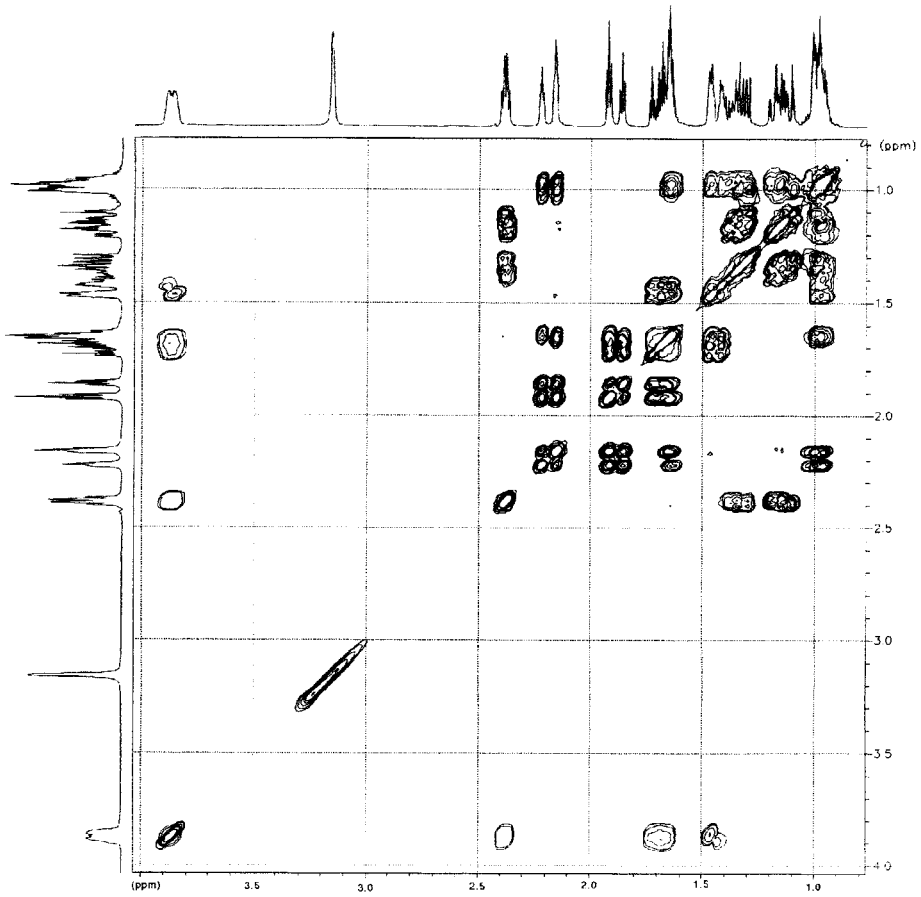


Fig. 2. *2D-COSY-45* (C_6D_6, 30°) *of* **1a**

Table 2. *^{1}H-and ^{13}C-NMR Chemical Shifts and Assignments* (C_6D_6, 30°) *for* **1b**

C-Atom	^{13}C [ppm]	DEPT	^{1}H [ppm]	H-Atom
C(1)	51.6	CH	2.33 (q, J = 3.1, 1 H)	H–C(1)
C(2)	214.3	C	–	–
C(3)	43.4	CH_2	1.98–1.68 (m, 2 H)	CH_2(3)
C(4)	27.9	CH	1.72–1.60 (m, 1 H)	H–C(4)
C(5)	36.4	CH_2	1.72–1.60 (m, 1 H) 1.35–1.22 (m, 1 H)	H_{endo}–C(5) H_{exo}–C(5)
C(6)	65.4	CH	3.84 (m, 1 H)	H–C(6)
C(7)	15.9	CH_2	2.22–2.09 (m, 1 H) 1.35–1.22 (m, 1 H)	H_{exo}–C(7) H_{endo}–C(7)
C(8)	24.6	CH_2	1.55–1.40 (m, 1 H) 1.18–1.06 (m, 1 H)	H_{exo}–C(8) H_{endo}–C(8)
–	–	–	2.00 (m, J = 3, 1 H)	OH

1.68 (2 H), 1.72–1.60 (2 H), 1.55–1.40 (1 H), 1.35–1.22 (2 H), and 1.18–1.06 ppm (1 H). On the basis of chemical shifts, the signals at 3.84 and 2.33 ppm were attributed to H–C(6) and H–C(1), respectively.

The ^{13}C-NMR spectrum of **1b** (*Table 2*) shows eight peaks at 214.3, 65.4, 51.6, 43.4, 36.4, 27.9, 24.6, and 15.9 ppm. By analogy with the ^{13}C-NMR spectrum of **1a** and on the basis of the DEPT spectrum (*Table 2*), these signals were attributed to the C(2), C(6), C(1), C(3), C(5), C(4), C(8), and C(7), respectively.

The HETCOR spectrum of **1b** revealed that (*Fig. 3*): *a*) the signal at 2.22–2.09 ppm (1 H) correlates with the signal at 15.9 ppm and was assigned to one of the CH_2(7) protons; *b*) the *multiplet* between 1.90–1.68 ppm (2 H), being connected with the signal at 43.4 ppm, was assigned to CH_2(3); *c*) the overlapping *multiplets* between 1.72–1.60 ppm (2 H) correlate with the signals at 36.4 and 27.9 ppm, and were, therefore, attributed to 1 H–C(5) and to H–C(4); *d*) the *multiplet* between 1.55–1.40 ppm (1 H) correlates with a signal at 24.6 ppm and was attributed to 1 H–C(8); *e*) the overlapping *multiplet* at 1.35–1.22 ppm (2 H), showing a connectivity with the signals at 36.4 (C(5)) and 15.9 (C(7)) ppm, was assigned to 1 H–C(5) and to 1 H–C(7); in view of the deshielding effect of HO–C(6) (see above), the signal at 2.22–2.09 (1 H) was attributed to H_{exo}–C(7); *f*) the *multiplets* between 1.18–1.06 (1 H) and 1.55–1.40 (1 H) ppm correlate with the peak at 24.6 ppm and were attributed to CH_2(8).

The 2D-COSY-45 spectrum (*Fig. 4*) of **1b** showed that the *multiplet* between 1.18–1.06 ppm (1 H) does not correlate with CH_2(3); it should be, therefore, attributed to the H_{endo}–C(8). Thus, it follows that the signal at 1.55–1.40 ppm is due to the H_{exo}–C(8). Owing to the deshielding effect of the HO–C(6) [1o][4], the signal of this proton occurs at lower field.

The absence of a cross-peak, between the H–C(6) at 3.84 and the H–C(7) at 2.22–2.09 ppm, confirmed the attribution of this signal to the H_{exo}–C(7). Finally, the *doublet* at 2.00 ppm (1 H), which does not correlate to any C-atom, and which displayed a small coupling with the H–C(6), was attributed to the HO–C(6). The assignments for **1b** are summarized in *Table 2*.

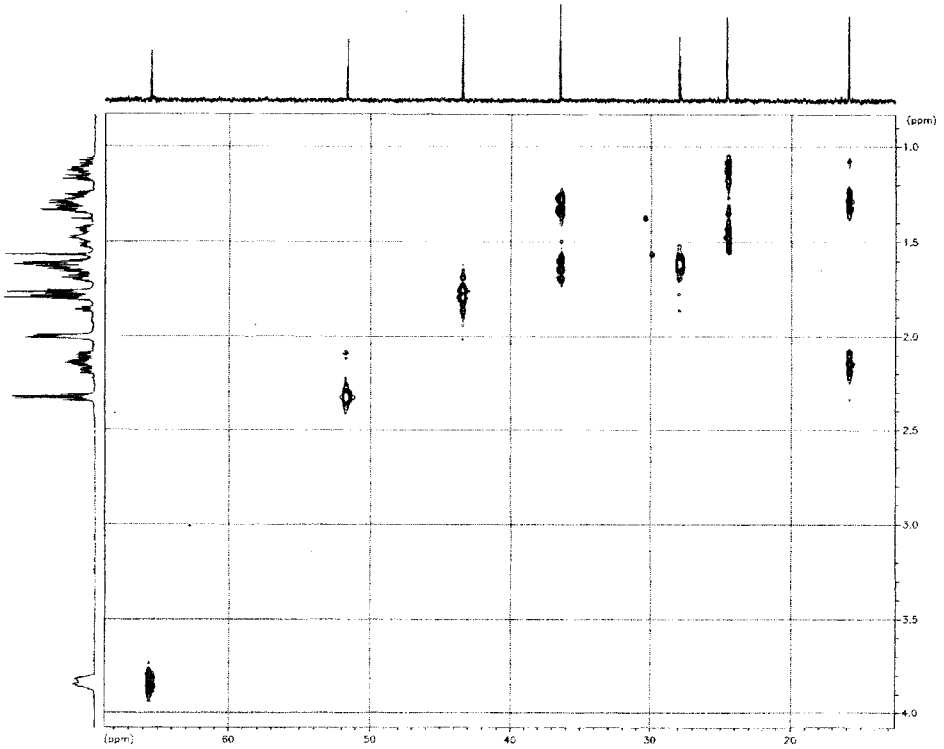


Fig. 3. *HETCOR Spectrum* (C_6D_6, 30°) *of* **1b**

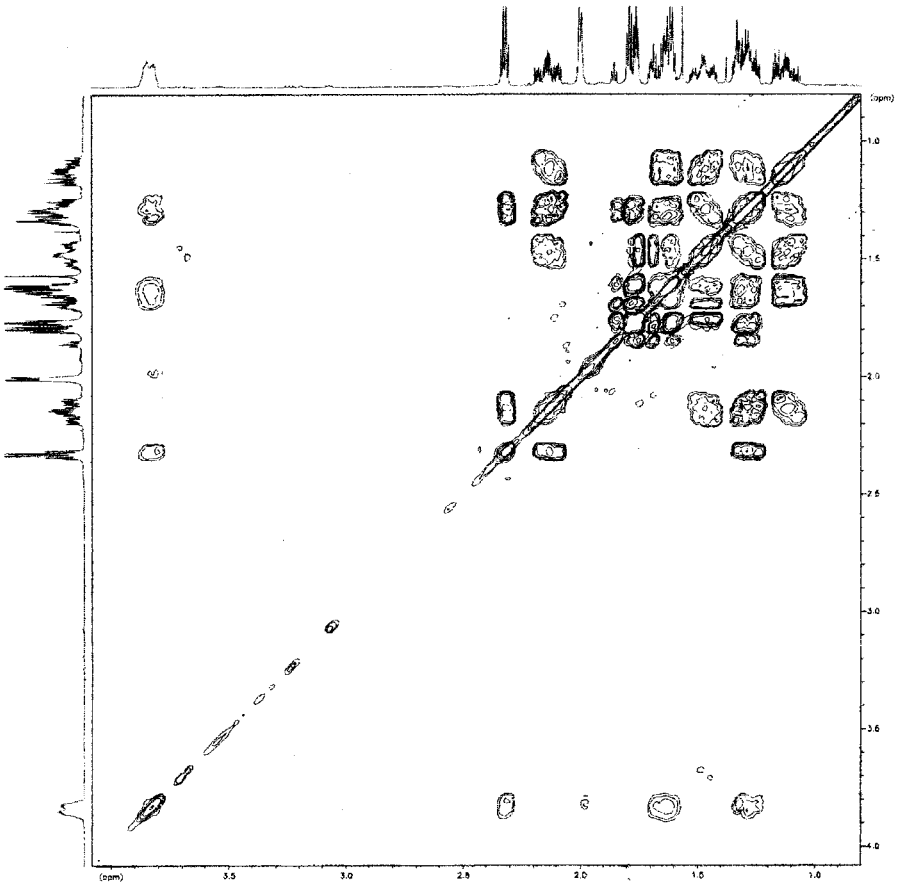


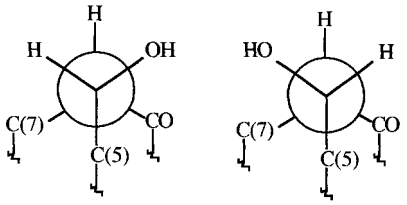
Fig. 4. *2D-COSY-45* (C_6D_6, 30°) *of* **1b**

Noticeable in the ^{13}C-NMR spectra of **1a** and **1b** are the C(6) and C(7) signals, which occur, in contrast to the signal of C(8), at higher field in **1b** than in **1a**[4]). This trend is a feature common to this class of compounds [1p][1r] and might turn out useful from a diagnostic point of view.

The upfield shift of C(7) in **1a** and **1b** was attributed to the well-known γ shielding effect. This effect is more pronounced in the *exo*-epimer, in which the C(7) is configurated *gauche* to the heteroatom, than in the *endo*-epimer in which the same C-atom is configurated *anti* [5] (*Fig. 5*).

2.2. *Product Distribution under Thermodynamic and Kinetic Control*. The product distribution for the reaction **2a** → **2b** ⇌ **1a** + **1b** (see *Sect. 2.1*) was the same after 24 and 48 h of reaction. We have also submitted epimers **1a** and **1b** separately to the same equilibrium conditions: starting from **1a**, we recorded a 85 : 15 *endo*/*exo* ratio both after 24 and 48 h. Starting from **1b**, we recorded 74 : 26 after 24 h and 85 : 15 (after 48 h)

4) Similar results were obtained carrying out the ^{1}H- and ^{13}C-NMR measurements in $CDCl_3$.



1a **1b**

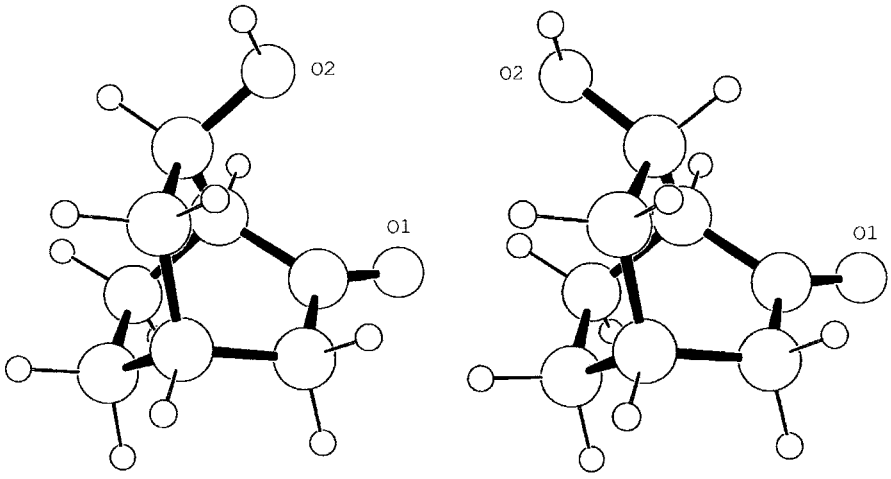
Fig. 5. Newman *projections of* **1a** *and* **1b** *along the C(6)–C(1) bond*

endo/*exo*-ratios. Furthermore, interrupting the reaction after 1 h reflux, we could record a 93 : 7 *endo*/*exo* ratio. When we submitted separately for 1 h **1a** to the same equilibrium conditions, **1b** was not detectable in the reaction mixture. On the contrary, starting from **1b**, after 1 h, a 10 : 90 *endo*/*exo* ratio had been established.

Under these experimental conditions, the *endo*-epimer represents, therefore, the product of thermodynamic as well as kinetic control of this aldol reaction, which appears to proceed through a synclinal transition state [6].

2.3. *Absence of Intramolecular H-Bonding in* **1a**. According to the inspection of *Dreiding* models, a stabilization of **1a**, due to intramolecular H-bonding between the C(2)=O and HO–C(6), does not appear very likely. Nevertheless, to confirm this assumption, we carried out molecular mechanics (MM) calculations and NMR and X-ray experiments.

An O(1)···O(2) distance of 3.44 Å was obtained for **1a** by MM calculations [7], indicating the lack of the necessary spatial requirements for intramolecular H-bonding [8] (*Fig. 6*).



1a **1b**

Fig. 6. *Optimized structures of* **1a** *and* ***1b***

The effect of a temperature variation on the HO–C(6) chemical shift in the ^{1}H-NMR spectra of **1a** and **1b** (*Fig. 7*), in agreement with precedents in the literature [9], supported the MM-calculation results: in fact, when the temperature is increased the signals of the HO–C(6) in both **1a** and **1b** approach a similar chemical-shift value.

In the meantime, because of the impossibility of an X-ray structure analysis of **1a** (see *Exper. Part*), we submitted methyl 13-*endo*-hydroxy-16-oxo-17-noratisan-18-oate (**6**; preparation described in [1r]) to X-ray analysis. The results obtained (*Fig. 8*) confirmed the absence of an intramolecular H-bonding, the O(3)···O(4) distance being 3.454(3) Å; they allowed us also to establish that O(3) and O(4) are involved in an intermolecular H-bonding, the O(3)···O(4) $(-x-1/2,\ -y+2,\ z+1/2)$ distance being 2.798(4) Å.

2.4. *NOE Experiments and Geometric Analysis.* As it can be inferred from molecular models, the C(1)–C(6)–C(5)–C(4)–C(8)–C(7) six-membered ring in **1a** and **1b** is fixed in a boat conformation (*Fig. 8*).

In analogy to the results of *Ouellette* and *Booth*, who compared the interaction between an *exo*-configurated substituent at C(6) in bicyclo[2.2.2]oct-2-ene and the H_{exo}–C(7) to the 1,3 boat-axial interaction in cyclohexane [10], an interaction between the *pseudo*-axially oriented HO–C(6) and the H_{exo}–C(7) should be present in **1b**. For this reason, we performed on **1b** NOE difference experiments which allowed us to obtain some interatomic H-distances.

The agreement between NOE difference experiments and MM calculations carried out on **1b** (*Table 3*) supports the value of the latter results leading, for **1a** and **1b**, to a H–C(6)···H_{exo}–C(7) and HO–C(6)···H_{exo}–C(7) distance of 2.59 Å and 2.61 Å, respectively.

Considering the *van der Waals* radii values of H and O [11], the hypothesis of a repulsive interaction in **1b**, between the *pseudo*-axially oriented HO–C(6) and the

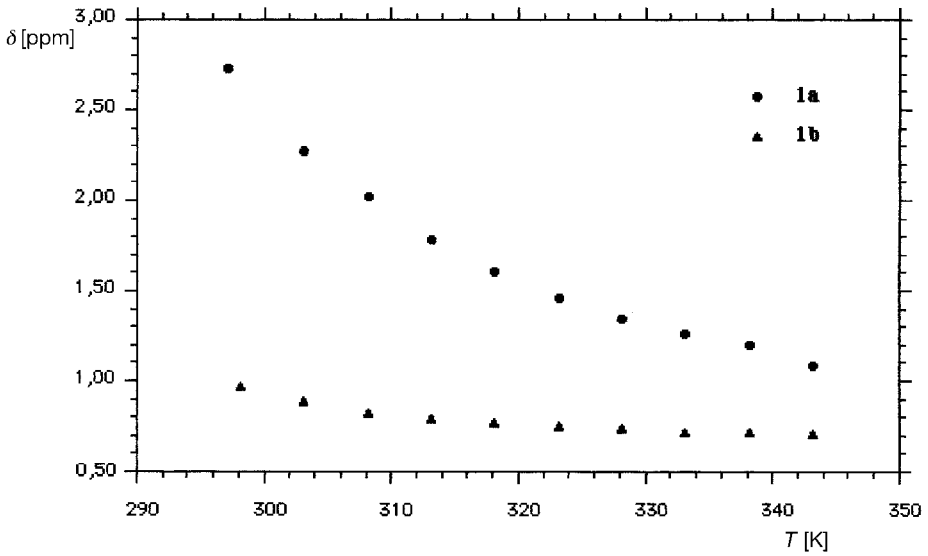
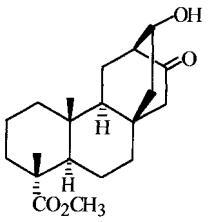


Fig. 7. *HO–C(6) Chemical shifts* (0.1M in C_6D_6) *for* **1a** *and* **1b** *at different temperatures*



6

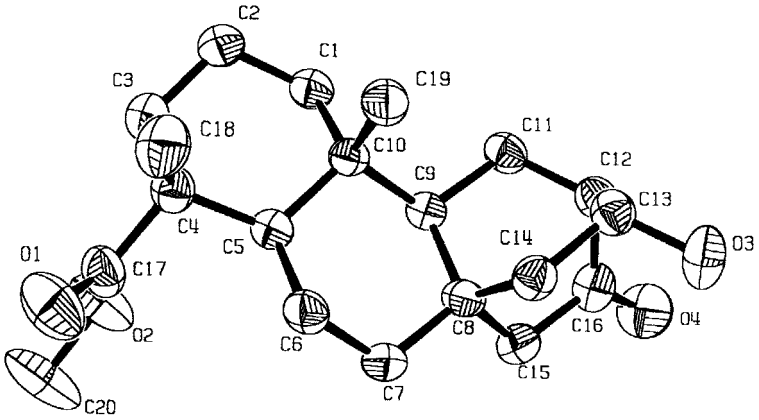


Fig. 8. *ORTEP-3 Drawing and atom numbering of* **6**

Table 3. *Some* $H_{irr}O-C(6)\cdots H_{obs}$ *Interproton Distances Obtained by NOE Difference Experiments and MM Calculations on* **1b**

H_{obs}	% Enhancement[a]) (d [Å])	% Enhancement[b]) (d [Å])	d [Å] MM
H–C(6)	6.5(2.70)	4.7(2.70)	2.70
H–C(1)	2.8(3.11)	1.9(3.14)	3.10
H_{exo}–C(7)	1.4(3.49)	1.0(3.49)	3.46

[a]) 15-s Irradiation time. [b]) 5-s Irradiation time.

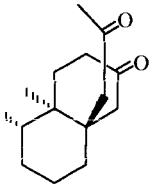
H_{exo}–C(7), seems, therefore, confirmed; in accord, MM calculations showed that the *endo*-epimer **1a** has a strain energy by 0.6 kcal/mol lower than the *exo*-epimer **1b**.

According to *Ermer* and *Dunitz* [12], the molecular-geometry parameter $\langle \Phi^2 \rangle^{1/2}$ for the 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one moiety in the crystal structure of **6** is 2.0°, showing no significant deviation from the D_{3h} symmetry. Analogously, the values and symmetry for the MM models of **1a** (0.5, D_{3h}) and **1b** (6.9, D_3) do not indicate relevant distortion owing to the presence of the C(2)=O and HO–C(6), and, thus, support a 1,3 boat-axial interaction in **1b**.

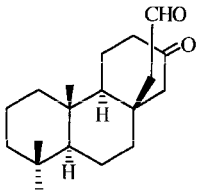
3. Conclusions. – The experiments and calculations described above seem, therefore, to suggest that the *endo*/*exo*-equilibrium distribution of **1a** and **1b** is due to the 1,3 boat-axial interaction present in the *exo*-epimer between the *pseudo*-axially

oriented HO–C(6) and the H_{exo}–C(7). The same interaction seems also responsible for the kinetic distribution.

The results described above solve also, in our opinion, the '*contrast*' found by *Kelly* and coworkers [1h] in obtaining a 1:1 epimeric mixture and '*apparently only a single epimer*' from the intramolecular aldol condensation of dione **7** [13] and of the ketoaldehyde **8**, respectively [1h].



7



8

Financial support by *Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST)* is finally gratefully acknowledged.

Experimental Part

General. All solns. were evaporated to dryness under vacuum. All solvents were of anal. grade. TLC: *Merck* silica gel *60* F_{254}. CC: silica gel *60*, 70–230 mesh ASTM. M.p.: *Mettler-FP-61* apparatus (uncorrected). IR Spectra: *Perkin-Elmer-298* and *Shimadzu-470* scanning IR spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker AC 300 P* at 300.13 and 75 MHz, resp.; *Varian-Gemini-200* at 200 and 50 MHz resp.; δ in ppm rel. to internal Me_4Si (= 0 ppm), J in Hz. DEPT, HETCOR, and 2D-COSY-45, and NOE difference experiments were the standard sequences from the *Bruker* Library. DEPT, HETCOR, and 2D-COSY-45 samples were prepared by dissolving separately **1a** and **1b** (20 mg, 0.14 mmol) in C_6D_6 (0.6 ml). All spectra were recorded at 30°; 30° pulses have been used for both ^1H and ^{13}C acquisitions. ^1H: $SW = 3000$ Hz, $TD = 16$ K; zero filling to 64 K, prior of transformation. ^{13}C: $SW = 18000$ Hz, $TD = 32$ K; zero filling to 128 K, 1 Hz of line broadening for the exponential multiplication, prior of transformation. NOE Difference experiment on **1b**: *Bruker AM 200*. NOE-Difference-experiment samples were prepared by dissolving **1b** (15 mg, 0.11 mmol) in C_6D_6 (0.5 ml) + (D_6)DMSO (0.02 ml) and were recorded at 298 K: $SI = 16$ K, $SW = 1602$ Hz, $D_1 = 10$ s, $D_2 = 15$ or 5 s (dp = 40 L), 8 scans every exper. for 50 exper. $AQ = 5$ s.

EI-MS and microanalyses were performed by the *Servizio di Spettrometria di Massa* and by the *Laboratorio di Microanalisi at the Area della Ricerca di Roma del Consiglio Nazionale delle Ricerche* (CNR).

X-Ray Crystal-Structure Analysis of **1a**. Colorless prismatic crystals of **1a** were obtained by slow concentration from a benzene/hexane soln. The crystals were unstable under the X-ray beam, even if sealed in a capillary. This prevented a full data set to be collected and a structure analysis to be performed. Unit cell parameters and space group have been determined on a *Siemens R3m/V* diffractometer (graphite-monochromated CuK_α radiation): $a = 6.544(4)$ Å, $b = 8.109(4)$ Å, $c = 10.141(5)$ Å, $\alpha = 104.75(4)°$, $\beta = 103.70(4)°$, $\gamma = 96.04(4)°$, $V = 502.8(5)$ Å^3, $D_x = 1.085$ g cm^{-3}, $Z = 2$, space group $P1$.

X-Ray Crystal-Structure Analysis of **6**. Colorless prismatic crystals of **6** were grown from MeOH at 277 K. Crystal data: $C_{20}H_{30}O_4$; $M_r = 334.44$; space group orthorhombic $P2_12_12_1$; $a = 8.9395(6)$ Å, $b = 31.378(8)$ Å, $c = 6.3644(16)$ Å; $V = 1785.3(7)$ Å^3; $Z = 4$; $F(000) = 728$; $D_x = 1.244$ g cm^{-3}; Cu$K_\alpha = 1.54184$ Å, $\mu = 0.680$ mm^{-1}. X-Ray data were collected with a *Rigaku AFR5C* automated diffractometer (graphite-monochromated CuK_α radiation). Intensity data were collected, the experimental conditions being $(\sin\theta/\lambda)_{max} = 0.57$ Å^{-1}; $2\theta-\omega$ scan mode; scan range 1.0°, scan rate 1.0–16.0° min^{-1} (depending on reflection intensity), background count time a quarter of the scan time. There was no significant intensity variation for 3 standard reflections measured every 150 (1.04%). *Lorentz*, polarization, absorption (minimum and maximum transmission factors 0.92 and 1.00), but no extinction corrections were applied. Of the 1744 reflections measured, 1702 were unique and 1676 with $I > 2.0\sigma(I)$ were considered as observed. The structure was solved by direct methods and refined based on F^2, using the SHELXL-97 package [14]. Difference-*Fourier* syntheses, using only data with $\sin\theta/\lambda = 0.50$ Å^{-1}, computed at the end of the anisotropic least-squares refinement, showed all H-atoms in configurationally

feasible positions. The final refinements were carried out by full-matrix with the H-atoms allowed to ride on the corresponding C- and O-atoms (221 parameters). The final R values are 0.0433 for 1292 $F_o > 4\sigma(F_o)$ and 0.0779 for all 1676 data. The wR value is 0.1105 and the goodness of fit S is 1.063 for all 1676 data, based on F^2. Heights in final difference-*Fourier* map $\rho_{max} = 0.15$ $\rho_{min} = -0.20$ eÅ^{-3}. A perspective view of the molecular structure of **6** was prepared using ORTEP-3 [7b].

Crystallographic data (excluding structure factors) for the structure of compound **6** reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-102186. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

*(1*SR,*4*RS,*6*RS*)- and (1*SR,*4*SR,*6*SR*)-6-Hydroxybicyclo[2.2.2]octan-2-one* (**1a** and **1b**, resp.). *3,3-(Ethylenedioxy)cyclohexaneacetaldehyde* (**2a**; 100 mg, 0.54 mmol) dissolved in THF/2N HCl 2:1 (30 ml) was refluxed under Ar for 24 h. After neutralization with 1N NaOH and evaporation of the org. solvent, the residue was taken up with H_2O and thoroughly extracted with CH_2Cl_2. The combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; petroleum ether (40–70°)/Et_2O 4:6): **1a** and **1b** in 61 and 11% yield, resp. TLC (petroleum ether (40–70°)/Et_2O 3:7): R_f(**1a**) < R_f(**1b**) (at least 2 developments). *Data of* **1a**: M.p. (benzene/hexane) 165.3–167.2° ([1f]: 201°). IR ($CHCl_3$): 3410, 1720, 1090. ^{1}H- and ^{13}C-NMR (C_6D_6): see *Table 1*. EI-MS: 140 (5, M^+). Anal. calc. for $C_8H_{12}O_2$ (140.18): C 68.55, H 8.63; found: C 68.70, H 8.72. *Data of* **1b**: M.p. (benzene/hexane) 146.0–149.0° ([1f]: 225°). IR ($CHCl_3$): 3415, 1720, 1110. ^{1}H- and ^{13}C-NMR (C_6D_6): see *Table 2*. EI-MS: 140 (35, M^+). Anal. calc. for $C_8H_{12}O_2$ (140.18): C 68.55, H 8.63; found: C 68.75, H 8.74.

*(1*SR,*2*RS,*4*RS*)-6-Oxobicyclo[2.2.2]octan-2-yl Benzoate* **3**. To a soln. of **1a** (80 mg, 0.57 mmol) in pyridine (1 ml), PhCOCl (0.5 ml, 4.3 mmol) was added and the reaction mixture stirred at r.t. overnight. H_2O (0.3 ml) was then added, followed, after stirring for an additional h, by the addition of Et_2O (30 ml). The org. layer was separated. The aq. layer was then thoroughly extracted with additional Et_2O. The combined org. extracts were washed with 2N HCl and H_2O, till neutral, brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; petroleum ether (40–70°)/Et_2O 4:6): **3** in 75% yield. TLC (petroleum ether (40–70°)/Et_2O 2:8): R_f(**3**) > R_f(**1a**). M.p. (Et_2O/hexane) 98.9–99.6°. IR ($CHCl_3$): 1720, 1270, 1110. ^{1}H-NMR ($CDCl_3$): 8.00–7.90 (*m*, 2 arom. H_o); 7.60–7.30 (*m*, 2 arom. H_m, 1 arom. H_p); 5.50–5.30 (*m*, H–C(2)); 2.70–2.60 (*m*, H–C(1)). ^{13}C-NMR ($CDCl_3$): 213.5 (C(6)); 165.8 (C=O); 133.3 (C_p); 130.1 (C_{ipso}); 129.8 (C_o); 128.5 (C_m); 71.6 (C(2)); 46.9, 44.4 (C(1), C(5)); 34.2, 27.5, 23.5, 19.9 (C(3), C(4), C(7), C(8)). EI-MS: 244 (2, M^+). Anal. calc. for $C_{15}H_{16}O_3$ (244.29): C 73.74, H 6.61; found: C 73.57, H 6.51.

*(1*SR,*2*RS,*4*RS,*6*SR*)-6-Hydroxybicyclo[2.2.2]octan-2-yl Benzoate* **4**. To a stirred soln. of **3** (25 mg, 0.10 mmol) in MeOH/Et_2O 1:1 (3 ml), $NaBH_4$, in excess, was added portionwise. When TLC (petroleum ether (40–70°)/Et_2O 6:4, R_f(**4**) < R_f(**3**)) indicated the complete disappearance of **3**, the mixture was neutralized with 2N HCl. The org. solvents were then evaporated and the residue was thoroughly extracted with $CHCl_3$. Combined org. extracts were then washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; petroleum ether (40–70°)/Et_2O 8:2): **4** in 87% yield. M.p. (Et_2O/hexane) 75.6–76.6°. IR ($CHCl_3$): 3590, 1718, 1712, 1270, 1110. ^{1}H-NMR ($CDCl_3$): 8.05–7.90 (*m*, 2 arom. H_o); 7.60–7.38 (*m*, 2 arom. H_m, 1 arom. H_p); 5.36–5.23 (*m*, H–C(2)); 3.95 (br. *s*, H–C(6)). ^{13}C-NMR ($CDCl_3$): 166.1 (C=O); 133.2 (C_p); 130.5 (C_{ipso}); 129.6 (C_o); 128.7 (C_m); 73.7 (C(6)); 69.4 (C(2)); 38.4, 35.1, 29.6, 24.6, 22.5, 21.5 (C(1), C(3), C(4), C(5), C(7), C(8)). EI-MS: 124 (13, [M – $PhCO_2H$]$^+$). Anal. calc. for $C_{15}H_{18}O_3$ (246.31): C 73.13, H 7.37; found: C 72.90, H 7.27.

*(2*SR,*6*RS*)-Bicyclo[2.2.2]octane-2,6-diol* **5**. A 1% KOH (MeOH) soln. (2 ml) of **4** (20 mg, 0.08 mmol) was refluxed under Ar, until TLC (petroleum ether (40–70°)/Et_2O 4:6; R_f(**5**) < R_f(**4**)) indicated that the conversion of **4** into **5** was completed. The mixture was then neutralized with 2N HCl and the org. solvent evaporated. The residue was taken up in $CHCl_3$ and the org. layer washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was then purified by CC (SiO_2; petroleum ether (40–70°)/Et_2O 6:4; R_f(**5**) < R_f(**4**)): **5** in 72% yield. M.p. 144–146° (Et_2O/hexane). IR ($CHCl_3$): 3510, 1085. ^{1}H-NMR ($CDCl_3$): 4.10–3.90 (*m*, H–C(2), H–C(6)); 3.00 (br. *s*, OH). ^{13}C-NMR ($CDCl_3$): 70.4 (C(2), C(6)); 38.2 (C(3), C(5)); 36.5 (C(1)); 24.6, 22.6, 21.0 (C(4), C(7), C(8)). EI-MS: 124 (9, [M – H_2O]$^+$). Anal. calc. for $C_8H_{14}O_2$ (142.20): C 67.56, H 9.93; found: C 67.85, H 9.98.

Independent Equilibration of Compounds **1**. To a 10-ml round-bottom flask, equipped with a reflux condenser, Ar inlet, and magnetic stirring bar, containing compound **1** (10 mg, 0.7 mmol), THF/2N HCl 2:1 (3 ml) was added. After the addition, the flask was dipped into a pre-heated oil bath (80°) and refluxed for the required time. The flask was then removed from the oil bath and immediately cooled by means of an ice bath. The mixture was then neutralized with 1N NaOH and the org. solvent evaporated; the residue was taken up with

H_2O and thoroughly extracted with CH_2Cl_2. The combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Each equilibration was performed at least three times. **1a**/**1b** Ratios were determined with a *HP 5890* gas chromatograph equipped with a variable-temp. program, a flame ionization detector, and a *Chromopack* 30-m *CP SIL8CB* capillary column (carrier gas H_2, flow rate 30 ml/min; T_{det} 250°; T_{inj} 200°). Each equilibrium mixture was run at least three times to determine the reproducibility of the analysis.

REFERENCES

[1] a) R. A. Bell, R. E. Ireland, *Tetrahedron Lett*. **1963**, 269; b) Z. Valenta, K. Wiesner, C. M. Wong, *ibid*. **1964**, 2437; c) R. W. Guthrie, A. Philipp, Z. Valenta, K. Wiesner, *ibid*. **1965**, 2945; d) R. W. Guthrie, Z. Valenta, K. Wiesner, *ibid*. **1966**, 4645; e) R. A. Bell, R. E. Ireland, R. A. Partyka, *J. Am. Chem. Soc*. **1966**, *31*, 2530; f) K. Mori, Y. Nakahara, M. Matsui, *Tetrahedron* **1972**, *28*, 3217; g) K. Wiesner, T. Y. R. Tsai, K. Huber, S. Bolton, *Tetrahedron Lett*. **1973**, 1233; h) R. B. Kelly, J. Eber, H. K. Hung, *Can. J. Chem*. **1973**, *51*, 2534; i) K. Wiesner, *Pure Appl. Chem.* **1975**, *41*, 93; j) R. B. Kelly, M. L. Harley, S. J. Alward, *Can. J. Chem.* **1980**, *58*, 755; k) D. Bravetti, R. Marini Bettolo, A. Lupi, *Helv. Chim. Acta* **1982**, *65*, 371; l) R. B. Kelly, M. L. Harley, S. J. Alward, R. N. Rej, G. Gowda, A. Mukhopadhyay, P. S. Manchand, *Can. J. Chem.* **1983**, *61*, 269; m) R. Marini Bettolo, P. Tagliatesta, A. Lupi, D. Bravetti, *Helv. Chim. Acta* **1983**, *66*, 760; n) R. Marini Bettolo, P. Tagliatesta, A. Lupi, D. Bravetti, *ibid*. **1983**, *66*, 1922; o) K. Mori, E. Nagano, *Biocatalysis* **1990**, *3*, 25; p) M. Berettoni, R. Marini Bettolo, V. Montanari, T. Prencipe, S. Romeo, *Helv. Chim. Acta* **1991**, *74*, 1671; q) A. Bartoletti, M. Berettoni, F. Catteruccia, G. De Chiara, R. Marini Bettolo, C. Mastrangeli, R. Scarpelli, C. Tozzi, D. Lamba, *Gazz. Chim. Ital*. **1996**, *126*, 223; r) M. Berettoni, G. De Chiara, T. Iacoangeli, P. Lo Surdo, R. Marini Bettolo, L. Montagnini di Mirabello, L. Nicolini, R. Scarpelli, *Helv. Chim. Acta* **1996**, *79*, 2035.

[2] a) K. Mori, Y. Matsushima, *Synthesis* **1993**, 406; b) F. Almqvist, L. Eklund, T. Frejd, *Synth. Commun.* **1993**, *23*, 1499; c) K. Mori, Y. Matsushima, *Synthesis* **1995**, 845; d) F. Almqvist, T. Frejd, *Tetrahedron: Asymmetry* **1995**, *6*, 957; e) F. Almqvist, N. Ekman, T. Frejd, *J. Org. Chem.* **1996**, *61*, 3794.

[3] D. H. Hua, R. Chan-Yu-King, J. A. McKie, L. Myer, *J. Am. Chem. Soc.* **1987**, *109*, 5026.

[4] M. J. Fernández, R. Huertas, M. S. Toledano, E. Gálvez, J. Server, M. Martínez-Ripoll, *Magn. Reson. Chem.* **1997**, *35*, 821.

[5] a) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, D. W. Cochran, *J. Am. Chem. Soc*. **1975**, *97*, 322; b) J. B. Stothers, C. T. Tan, K. C. Teo, *J. Magn. Reson.* **1975**, *20*, 570; c) J. B. Stothers, C. T. Tan, *Can. J. Chem.* **1976**, *54*, 917; d) H. Beierbeck, J. K. Saunders, *ibid*. **1976**, *54*, 2985; e) P. J. Garratt, R. Riguera, *J. Org. Chem.* **1976**, *41*, 465; f) S. Berger, *ibid*. **1978**, *43*, 209; g) A. Heumann, H. Kolshorn, *ibid*. **1979**, *44*, 1575.

[6] a) D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413; b) S. E. Denmark, W. Lee, *Tetrahedron Lett*. **1992**, 7729.

[7] a) HYPERCHEM Release 3 for Windows – Molecular modelling System (1993) Hypercube, Inc. and Autodesk Inc., developed by Hypercube Inc; b) ORTEP-3, Version 1.0.2, C. K. Johnson and M. N. Burnett Windows version 1.01b (April 1997), Dept. of Chemistry, University of Glasgow, UK.

[8] G. A. Jeffrey, W. Saenger, 'Hydrogen Bonding in Biological Structures', Springer-Verlag, Berlin, 1991.

[9] I. Torrini, G. Pagani Zecchini, M. Paglialunga Paradisi, G. Lucente, E. Gavuzzo, F. Mazza, G. Pochetti, S. Traniello, S. Spisani, G. Cerichelli, *Biopolymers* **1994**, *34*, 1291.

[10] R. J. Ouellette, G. E. Booth, *J. Am. Chem. Soc*. **1965**, *30*, 423.

[11] a) L. Pauling, 'The Nature of the Chemical Bond', 2nd edn., Cornell University Press, Ithaca, N.Y., 1948, pp. 187–193; b) A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441; c) R. S. Rowland, R. Taylor, *ibid*. **1996**, *100*, 7384.

[12] O. Ermer, J. D. Dunitz, *Helv. Chim. Acta* **1969**, *52*, 1861.

[13] R. B. Kelly, J. Zamecnik, B. A. Beckett, *Can. J. Chem.* **1972**, *50*, 3455.

[14] G. M. Sheldrick, SHELXL-97, Universität, Göttingen, 1997.

Received September 3, 1998