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Chromatographic Separation and Absolute Configuration of Chiral Methyl 2-Oxobicyclo[3.2.1]octane-6-carboxylate

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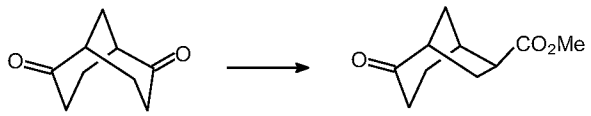
Enantiomer separation of methyl *exo*-2-oxobicyclo[3.2.1]octane-6-carboxylate **2** has been achieved by liquid chromatography on swollen microcrystalline triacetylcellulose and the absolute configuration of (−)-**2** and (+)-**2** assigned using circular dichroism spectra.

In recent years optically active compounds have been available thanks to the development of chromatographic methods for resolution of enantiomers.[1] We have reported on the resolution of bicyclo[3.3.1]nonane derivatives by liquid chromatography on swollen microcrystalline triacetylcellulose (TAC).[2] In the present work the synthesis and the enantiomer separation and absolute configuration of substituted bicyclo[3.2.1]octane is described. Interest in this bridged ring system arises from its chirality when substituents are attached at any of the C-2, C-3, C-6 or C-8 positions and from the fact that this framework is present as a structural element in a number of naturally occurring or biologically active compounds.[3]

The synthesis of 2,6-substituted bicyclo[3.2.1]octane was accomplished by oxidative rearrangement of bicyclo[3.3.1]-nonane-2,6-dione **1**.† The reaction of **1** with $Tl(NO_3)_3$ in acetic acid gave a mixture of stereoisomers and the yield was very moderate. Monoselective transformation of one carbonyl group was achieved with equimolar amounts of **1** and thallium(III) nitrate in methanol solution. The reaction gave one product with high yield. The *exo*-configuration of the ester group at C-6 was verified by the analogy of the reaction course of bicyclo[3.2.1]octan-2-one rearrangement into *exo*-bicyclo[2.2.1]heptane carboxylic acid reported in the literature,[4] and by a study using NMR spectroscopy with $Eu(fod)_3$ of the reaction product of the model reaction of bicyclo[3.3.1]nonane-2-one with $Tl(NO_3)_3$.[5]



1 **2**

Chromatography of the ketoester **2** on a TAC column with 95% aqueous ethanol as the mobile phase lead to separation of enantiomers. Although baseline separation was not achieved in the first run the fractions taken in the first and the last parts of the eluate gave enantiomerically enriched (−)- and (+)-ketoesters **2**. The first eluted enantiomer showed a negative rotation. The efficiency of enantiomer resolution is expressed by selectivity factor α. The capacity factors for the first and second eluted enantiomer k'_1 and k'_2 were 2.44 and 2.88, respectively and the selectivity factor α 1.18. Owing to low efficiency and relatively small selectivity factors a recycling technique[7] was used in the preparative enantiomer separation. Pure enantiomers of **2** were obtained by recycling the early and late fractions four times while discarding the intermediate fractions and complete separation of enantiomers was achieved after the fourth chromatographic cycle.

The circular dichroism (CD) spectrum of the (+)-enantiomer was recorded after chromatographic resolution. The CD curve observed for the (+)-ketoester **2** in ethanol solution exhibited an intense positive Cotton effect at *ca.* 290 nm and a less intense positive band around 210 nm (Fig. 1). The first band is ascribed to an $n \rightarrow \pi^*$ transition. The absolute configuration of the (+)-ketoester **2** was established using the octant rule.[8] The cyclohexanone ring in the

† *Experimental.* The CD spectra were recorded with a Jasco Model J-500 A spectropolarimeter and the UV spectra were recorded on a Cary 2290 spectrophotometer using spectral grade ethanol. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on a Varian XL 300 spectrometer and reported in ppm downfield from tetramethylsilane. The chromatographic equipment for enantiomeric separation was that described in ref. 11. Molecular mechanics calculations were performed with an MM2 force field.[10,12] Input structure was constructed by the molecular modelling program system MacMIMIC[13] and carried out on a Macintosh IIci computer.

Bicyclo[3.3.1]nonane-2,6-dione **1** was prepared according to the reported procedure cited in ref. 2.

exo-Methyl 2-oxobicyclo[3.2.1]octane-6-carboxylate **2**. To a rapidly stirred solution of 1.26 g (8.3 mmol) of dione **1** in 160 ml of dry methanol was added slowly and dropwise a solution of 3.25g (8.3 mmol) thallium(III) nitrate in 20 ml of dry methanol over 1.5 h. The mixture was stirred at room temperature for 10 h, the methanol evaporated, and the resulting suspension was dissolved in 50 ml of water acidified with 2 ml of conc. hydrochloric acid. The solution was extracted three times with 50 ml portions of chloroform. The organic extracts were combined, washed with water, dried over sodium sulfate, filtered, concentrated and evaporatively distilled to give 0.92 g (62%) of **2** as an oil, b.p. 120–123 °C/4 Torr, n_D^{20} 1.4915. IR (neat) 1700, 1715, λ_{max} (log ε): 283 (1.94), 197 (2.82). ^{1}H NMR 2.86 (m, 1H, H–C–COOMe), 2.74 (m, 1H, H at C-2), 2.65 (m, 1H, H at C-5), 2.4–1.75 (m, 11 H, methylene envelope and CH_3). ^{13}C NMR: 209.61, 173.22, 49.01, 48.26, 42.71, 36.04, 33.66, 31.53, 29.12, 28.20. Found: C, 66.08; H, 7.89%. Calc. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74%. (+)-**2** $[\alpha]_{365}^{20}$ +4.8 (0.026, EtOH), CD λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 210 (+8.0), 292 (12.5) at 20 °C.

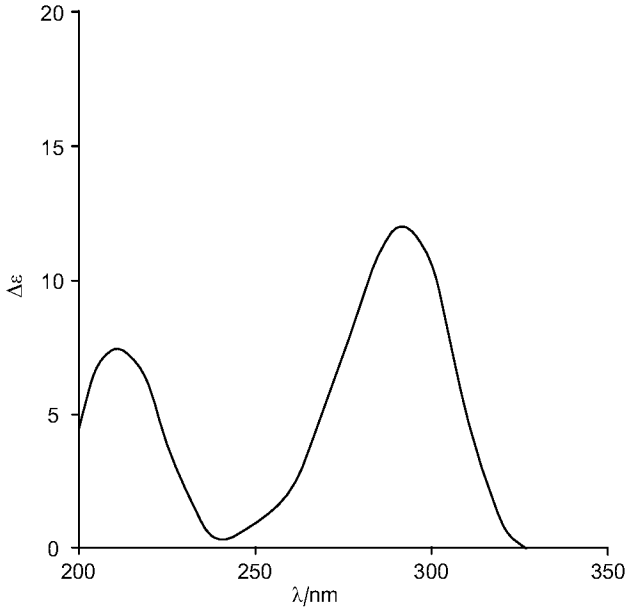


Fig. 1 Circular dichroism spectra of (+)-(1*R*, 5*S*, 6*S*)-methyl 2-oxobicyclo[3.2.1]octane-6-carboxylate.

bicyclo[3.2.1]octane framework was shown to exist predominantly in the chair conformation.[9] Molecular mechanics calculations performed in this work[10] of the two conformations of the structure **2** also reveal that the chair cyclohexanone conformer of bicyclooctane **2** has 2.2 kcal mol^{-1} lower energy than the boat. According to the octant rule the absolute configuration of (+)-ketoester **2** is assigned as (1*R*,5*S*,6*S*). The projection of the location of the bicyclic structure in the octants and the molecular structure of conformer with the lowest energy are shown in Fig. 2.

The CD spectrum of (−)-ketoester **2** is a mirror image of (+)-**2** with the same Δε values but opposite in sign and we therefore consider the fractions to be enantiomerically pure. Thus the configuration of (−)-ketoester **2** is assigned as (1*S*, 5*R*, 6*R*).

References

1 S. Allenmark, *Chromatographic Enantioseparations: Methods and Applications*, 2nd edn., Ellis Horwood, Chichester, 1991.
2 U. Berg and E. Butkus, *J. Chem. Res. (S)*, 1993, 116.

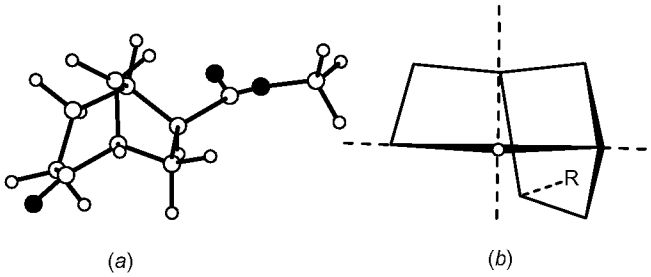


Fig. 2 (*a*) MM2 minimized structure of (+)-(1*R*, 5*S*, 6*S*) ketoester **2**; (*b*) octant diagram for chair cyclohexanone conformer of (+)-(1*R*, 5*S*, 6*S*)-**2** (R = CO_2Me).

3 (*a*) T.-L. Ho, *Carbocyclic Construction in Terpene Synthesis*, VCH Publishers, 1988; (*b*) in *Natural Products as Medicinal Agents*, eds. J. L. Beal and E. Reinhard, Hypokrates Verlag, Stuttgart, 1981, p. 151.
4 A. J. Irwin and J. B. Jones, *J. Org. Chem.*, 1977, **42**, 2176.
5 E. Butkus, A. Zilinskas, P. Kadziauskas and N. S. Zefirov, *Zh. Org. Khim.*, 1986, **22**, 871 [*J. Org. Chem. USSR (Engl. Transl.)*, 1986, **22**, 778].
6 Ref. 1, sec. 4.1
7 R. Isaksson, M. Oki, J. Sandstrom, M. R. Suissa and S. Toyota, *Acta Chem. Scand.*, 1993, **47**, 570.
8 (*a*) W. Klyne and D. N. Kirk, in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*, eds. F. Ciasdelli and P. Salvadori, Heyden & Son Ltd., 1973, pp. 89–108; (*b*) *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, ed. G. Snatzke, Heyden & Son, London, 1967, sec. 9.2.
9 B. V. Crist, S. L. Rodgers and D. A. Lightner, *J. Am. Chem. Soc.*, 1982, **104**, 6040.
10 U. Burkert and N. Allinger, *Molecular Mechanics*, American Chemical Society, Washington, DC, 1982.
11 R. Isaksson and J. Rochester, *J. Org. Chem.*, 1985, **50**, 2519.
12 T. Liljefors, J. Tai, S. Li and N. L. Allinger, *J. Comput. Chem.*, 1987, **8**, 1051; the MM2 program is available from Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405.
13 T. Liljefors, *J. Mol. Graphics*, 1983, **1**, 111; 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.

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