Pergamon

Tetrahedron, Vol. 53, No. 14, pp. 5339-5348, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00196-8

Stereochemical Studies of Bicyclo[5.3.1]undecane-8,11-dione. Conformational Analysis, Enantiomer Separation, CD-Spectroscopy and Enolization

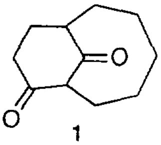
Ulf Berg[a],* Eugenius Butkus[b] Torbjörn Frejd[a] and Sara Bromander[a]

[a] Organic Chemistry 1, Department of Chemistry, P.O.Box 124, University of Lund, S-22100 Lund, Sweden, and,

[b] Department of Organic Chemistry, Vilnius University, 2734 Vilnius, Lithuania.

Abstract: The stereochemical properties of the title compound have been examined by various methods. Dynamic NMR spectroscopy shows the existance of two conformers or sets of conformational families separated by a barrier of 8.2±0.4 kcal/mol. At low temperatures only one conformer was appreciably populated. Chromatographic enantiomer enrichment was performed on a microcrystalline triacetylcellulose column and the circular dichroism (CD) spectrum was recorded. The conformational space was explored by MM3 calculations giving six conformers within 2 kcal/mol. The high energy barrier observed by DNMR was assigned a chair-boat inversion of the eight-membered ring. The CD spectrum of the conformational mixture given by the MM-computations was calculated by the method developed by Schellman, giving information about the absolute configuration of the first eluted enantiomer, and about the conformational mixture in solution. Formation of enol esters under equilibrium conditions gave 83% of the bridgehead enol ester. © 1997 Elsevier Science Ltd.

There has been considerable interest in recent years in the chemistry of bicyclic compounds. Carbonyl derivatives of bicyclic compounds were used in the study of transannular interactions,[1] stereochemical studies,[2] and as synthetic intermediates in organic chemistry.[3] Bicyclic systems appear in many natural products,[4] and the bicyclo[5.3.1]undecane skeleton is present as a subunit in taxanes (the A-B ring system), and its derivatives have been recognized as a potential building block of the taxane skeleton.[5] Bicyclo[5.3.1]undecane-8,11-dione **1** and other bicyclo[5.3.1]undecane derivatives were early recognized as potential anti-Bret's-rule candidates.[6] It is therefore of considerable interest to study the behaviour of such basic components. This report deals with a stereochemical analysis of **1** including conformational analysis, enantiomer separation and CD-spectroscopy. The absolute configuration is deduced from the calculated CD-spectrum. We also report on the preferential formation of the bridgehead enol ester.



1

Results and Discussion

Dynamic NMR spectroscopy. The ^{1}H- and ^{13}C-NMR-spectra of **1** was investigated down to – 120 °C in [$^2H_6$]-dimethyl ether. The ^{1}H-NMR spectrum underwent decoalescence below –50 °C and the signals resharpened at –110 °C. The spectrum was difficult to interpret due to overlapping signals, but appeared to originate from only one species. The {^{1}H}^{13}C-NMR spectrum was clearer and gave the expected 11 signals at room temperature, underwent the equivalent decoalescence phenomenon, resharpened at low temperature to give, again, 11 signals (Fig 1.). We interpret the observations as being due to the existence of two conformers or sets of conformers separated by a barrier of ca 8.2±0.4 kcal/mol (minor—>major conformer). At temperatures above ca –90 °C the minor conformer is still appreciably populated giving rise to normal decoalescence phenomenon, but at lower temperature the minor form comprises less than ca 3%. The important spectral changes at medium temperatures indicate a significant change in the population of the minor conformer and thus considerable difference in entropy between the two conformers.

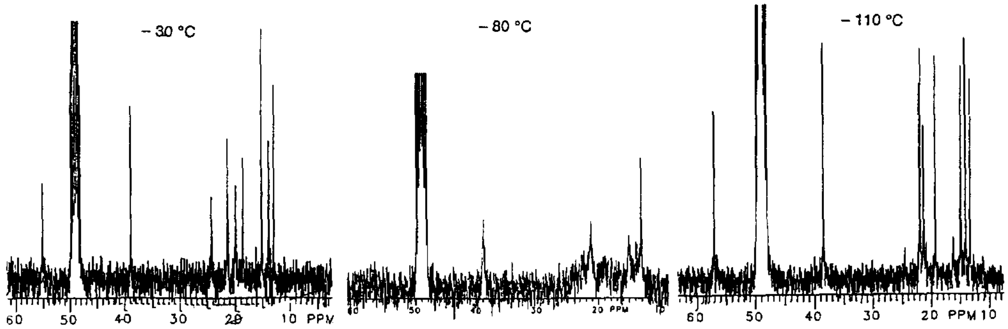
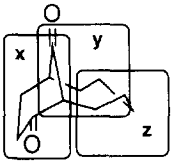


Figure 1 . The ^{13}C NMR spectrum of **1** in [$^2H_6$]-dimethyl ether at various temperatures. The carbonyl carbon signals are not shown. The truncated septet at δ49 originates from the solvent.

Molecular mechanics (MM) analysis of the conformations of **1** was performed using the MM3(92) force field[7] implemented in the MacMimic program package.[8] The stocastic search routine was adopted starting from various input geometries and the block-diagonal and full matrix method was used. The push length was maximized at 2 Å and 100 pushes were made for each entry. The conformations of **1** are characterized by using a three letter symbol as shown below for the *c,bc* conformation (c = chair, b = boat, and t = twist-boat):



x,yz

Twenty-four stationary points with energies not more than 10 kcal/mol above the global minimum could be localized. Five were pure transition states, but one of these was considered less interesting, since it was very close to a minimum in both structure and energy. Six conformations were identified within 2 kcal/mol above the global minimum, divided into three classes with respect to the conformation of the y-system in the formula above. Another nine conformations were found within 4 kcal/mol. The seven low-energy conformations are shown in the Table and in Fig. 2. The global minimum is the *c,bc*, the two *tt,t* conformers (*twist-1* and *twist-2*) come next.[9] Notably the *c,cc* conformer is calculated 3.60 kcal/mol above *c,bc*. A low barrier, of ca 3 kcal/mol, separates the two *twist* conformers, and the transition state is *b,bb*. Another transition state separating *chair* and *boat* conformers of the cyclohexadione ring at 7.71 kcal/mol was also found. The starting and final conformers around the transition states were verified by stocastic searches starting from the transition state with small push widths, typically 0.1 Å. However, the transition state corresponding to the high barrier for the inversion of the y-ring was not obtained in the search. In summary, a rather complicated picture emerges from this conformational analysis and a rather flexible molecule with three conformational families can be envisaged.

Chromatographic enantiomer resolution of dione 1 on a swollen microcrystalline triacetylcellulose column was performed using an equipment described earlier.[10] Fractions taken in the first and last parts of the eluate gave enantiomerically enriched (+)- and (-)-diones **1** [ee 25 %, capacity factors, k(+)1.40; k(-) 2.28; selectivity factor, α1.62]. The first eluted enantiomer showed a positive rotation at 365 nm. The chromatogram showed separated peaks only in the polarimeter trace but the weak UV trace was not resolved.

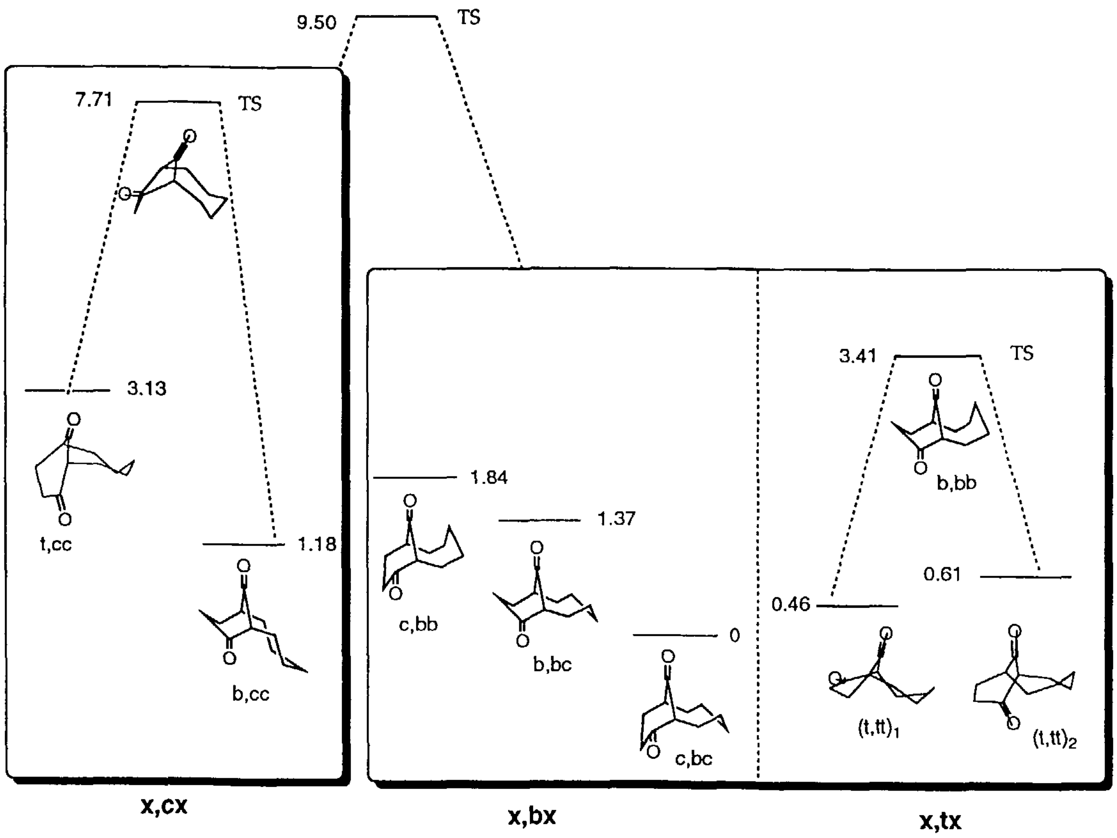


Figure 2. Conformations and there energies of the seven most stable conformations of (1S,7R)-**1** calculated by MM3.

Table Steric energies (kcal/mol) calculated by the MM3(92) force field and population from a Boltzmann distribution at 20 °C for the seven most populated conformers. The four most populated conformers were included in the calculation of the CD-spectrum.

	$\varepsilon = 1.5$			$\varepsilon = 24$		
Conformer	Steric energy	ΔE	%	Steric energy	ΔE	%
c,bc	29.92	0	48	27.89	0	59
twist-1	30.38	0.46	21	28.44	0.55	23
twist-2	30.53	0.61	17	29.09	1.20	7
b,cc	31.11	1.19	6	29.43	1.53	4
b,bc	31.29	1.37	4	29.77	1.87	2
c,bb	31.74	1.82	2	29.62	1.73	3
t,cc	32.11	2.19	1	30.10	2.20	1

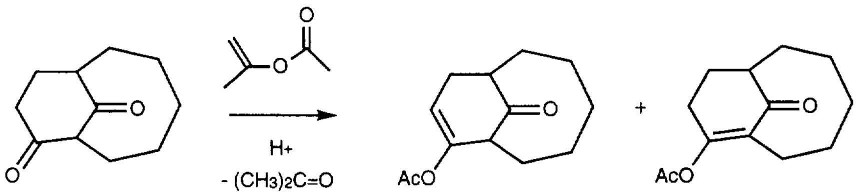
The circular dichroism (CD) spectra of both enantiomers were recorded, and the first eluted (+)-enantiomer gave the spectrum shown in Fig 3a. The (-)-enantiomer gave the expected inverted CD spectrum. (+)-**1** showed a CD band at 300 nm with a positive sign ascribed to the n—>π* transition and a negative band at 212 nm for the π—>π* transition.

The CD spectrum of **1** was calculated using a program developed by Schellman and coworkers.[11] The theoretical calculations of CD spectra in our studies are based on a formalism, which was originally developed by Tinoco.[12] The treatment comprises both electrically and magnetically allowed transitions and it makes use of the three mechanisms: the one-electron,[13] the coupled oscillator,[14,15] and the magnetic-electric coupling.[11,16] The π—>π* transition is placed at 185 nm[17] and the n—>π* transition at 302 nm based upon the experimental spectra. Magnetic moments and quadrupole charges of the n—>π* transition were obtained from a CNDO/S calculation of acetone (50 CI). The π—>π* transition was given a transition moment of 1.89 D, and the monopoles of the electronic transition charge density are placed in the centra of the atoms. The static charges are obtained from AM1 calculations using geometries optimized by MM3 calculations. Rotational strengths were calculated using the same geometries.

According to MM3 calculations, **1** exists as a mixture of several conformations as shown in Fig. 2 and the Table. The CD spectra have been calculated for the four low-energy conformations of (1S,7R)-**1** based upon the MM geometries and are shown in Figure 3b. Like the experimental spectra, the calculated spectra display two bands in the wavelength range $\lambda > 200$ nm, an $n \rightarrow \pi^*$ band at 306 nm and a $\pi \rightarrow \pi^*$ at ca 212 nm. The two bands are calculated to have opposite signs for the *c,bc* and *b,cc* conformations with the $n \rightarrow \pi^*$ band positive, but for *twist-1* and *twist-2* both bands are negative, the one for *twist-2* of high intensity. Using the Boltzmann distribution at 20 °C the weighted sum of the spectra has been calculated (Figure 3c). This calculated spectrum does not reproduce the change in sign of the two bands, although the $n \rightarrow \pi^*$ band is of very low intensity. The contribution of the negative Cotton effects of the two *twist* conformers leads to slightly negative $n \rightarrow \pi^*$ band. However, the MM calculations were performed with default dielectric constant, $\varepsilon = 1.5$, whereas the experimental CD-spectra were recorded in ethanol ($\varepsilon = 24$). Thus, the conformational distribution was recalculated at $\varepsilon = 24$, using the default bond dipole-dipole interaction to account for the electrostatic interactions. The results are shown in the Table. This leads to correct sign reversal of the CD-bands, but the intensity of the $n \rightarrow \pi^*$ band is too small. The most reasonable interpretation is that the relative energies from the MM calculationes do not reproduce the free energy differences, a discrepancy that may be explained by solvation and other effects that could change both relative enthalpy and entropy of the conformers, as well as by deficiencies in the force field. Actually, the experimental CD-spectrum is quite satisfactorily reproduced by the calculated spectrum of the *c,bc* conformer alone. Furthermore, we have observed earlier that the relative intensities of the CD-bands in diones are not perfectly reproduced by the rotational strength calculations.[2c]

Considering especially the $\pi \rightarrow \pi^*$ band, the absolute configuration of the (+)-enantiomer can safely be assigned (1S,7R)-bicyclo[5.3.1]undecane-8,11-dione. This assignment was also obtained using the octant rule, which usually but not always, gives correct result.[2c]

Bridgehead olefin formation. Although no traces of the enols of **1** could be observed by NMR spectroscopy in any of the solvents $[^2H]$-chloroform, $[^2H_6]$-dimethyl ether or $[^2H_8]$-toluene, it was of interest to determine which of the four possible enols could actually be trapped as enol acetates. This information may become useful for subsequent synthesis of taxanes. Swindell *et al.* demonstrated by MM2 calculations that the bridgehead olefin position did not impose severe strain in bicyclo[5.3.1]undecene systems in comparison with the corresponding saturated compound.[6e]



1 **2a** **2b**

Other examples of bridgehead bicyclo[5.3.1]undecenone systems were earlier investigated by House *et al.*[6b] and Marshall *et al.*[18] In general it seems that the double bond at the bridgehead position in these structures is not particularly strained. One would therefore expect that the bridgehead conjugated enone **2b** would be the major component. This turned out to be true. When **1** was heated in isopropenyl acetate with catalytic amounts of p-toluenesulfonic acid for 2 h, and after quenching workup conditions, a mixture of **2a** and **2b** in the ratio 17:83 was obtained.

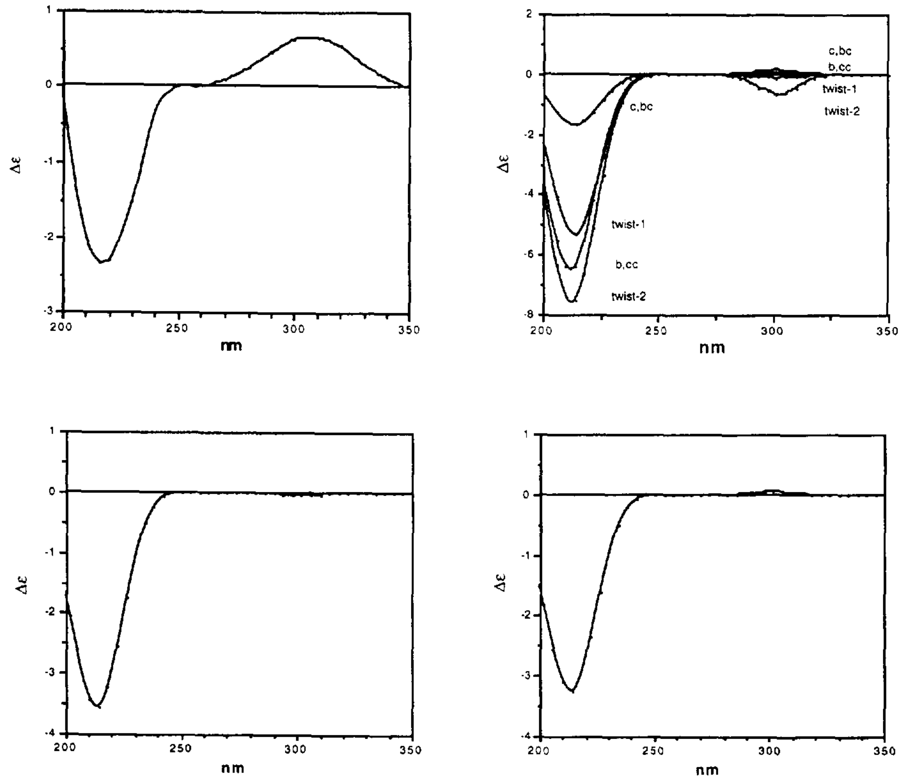


Figure 3. a) Experimental CD spectrum of (+)-**1** in ethanol. b) Calculated CD spectra of the four low-energy conformers of **1**. The n->π^* band of the *b,cc* conformer is weakly positive and nearly hidden in the base line. c) Boltzmann weighted spectrum of the spectra in (b) at $\varepsilon = 1.5$. d) Boltzmann weighted spectrum of the spectra in (b) at $\varepsilon = 24$.

Conclusion

Bicyclo[5.3.1]undecane-8,11-dione is a stereochemically versatile molecule, which exists as a mixture of several conformers. According to MM calculations the *c,bc* and two *twist* type conformations dominate. Low temperature NMR spectroscopy reveals a dynamic process with a barrier of ca 8.2 kcal/mol, separating two conformational sets of which one is strongly dominating below – 100 °C (> 97%). The exchange process represents an inversion of the eight-membered ring. In addition there are several processes with lower barriers. Partial optical resolution was accomplished by chromatography on swollen microcrystalline triacetylcellulose, the first eluted enantiomer being (+)-**1**. The CD spectrum of (+)-**1** showed a negative $\pi \longrightarrow \pi^*$ band at 212 nm and a positive $n \longrightarrow \pi^*$ band 300 nm. Rotational strength calculations of the four low-energy conformations from MM computations give varying sign of the $n \longrightarrow \pi^*$ band, which can be used to discriminate among the conformers. A comparison of the various data indicates that the *c,bc* conformer is probably more dominating than suggested by the MM computations, at the expense of the *twist* conformers. The conjugated, anti-Bret enol acetate was predominantly formed under equilibrium conditions, indicating that suitably functionalized derivatives of **1** may be used as starting material in taxane synthesis.

Experimental

Bicyclo[5.3.1]undecane-8,11-dione, 1, has been described earlier.[6a] The sample used was 99% pure according to GC. $\delta_H((CD_3)_2O)$ 1.5-1.9 (m, 7H), 1.9-2.2 (m, 4H), 2.3-2.6 (2m, 2H), 2.65-2.80 (m, 0.5H), 2.92 (p, 1H), 3.12 (t, 0.5H). $\delta_C((CD_3)_2O$ at 59.40) 23.41, 24.36, 25.60, 28.98, 30.34, 31.80, 34.70, 49.37, 65.50, 208.85, 215.04. $[\alpha]_D^{20} = +0.4$ (0.03), $CHCl_3$).

Enol acetate formation. Dione **1** (100 mg) was heated at reflux with *p*-toluenesulfonic acid (5 mg) in 8 ml isopropenyl acetate for 2 h. After cooling to room temperature the solution was poured into a mixture of ice and saturated sodium bicarbonate solution and extracted with ether. After drying over magnesium sulfate and evaporation the residue was analysed. The two isomeric enol esters could not be separated, but were unequivocally identified by GC chromatography, NMR and MS spectroscopy. The crucial information for diagnostic purpose was the vinylic proton in **2a** at δ5.51. Once **2a** was identified GC gave the exact ratio and combination of ^1H, ^{13}C NMR and MS the identities: MS: $C_{13}H_{18}O_3$ **2a**: 222 (31, M^+), 180 (60), 162 (32), 152 (29), 134 (66), 125 (43), 112 (100), 95 (28). **2b**: 222 (28, M^+), 180 (100), 162 (28), 152 (42), 126 (26).

The circular dichroism spectra (CD) were recorded with a Jasco Model J-500 A spectropolarimeter and the ultraviolet spectra (UV) were recorded on a Cary 2290 spectrophotometer using spectral grade ethanol. Optical rotations at the sodium D line were measured in a 0.5 cm microcell on a Perkin-Elmer polarimeter 141. Nuclear magnetic resonance spectra were recorded on Varian XL 300 or Brucker DRX 400 spectrometers and are reported in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Jeol JMS-SX 102 spectrometer. The chromatographic equipment for enantiomeric separation was described by Isaksson and Roschester.[10]

Analytical gas chromatography (GC) was performed on a Varian Model 3400 F/I instrument on a DB-Wax 30 m x 0.25 mm-diameter column and chiral phase GC on a BETA-DEX 120 column (Supelco).

Acknowledgment: We thank Professor Jan Sandström for advice concerning the use of the Schellman program, the faculty of mathematics and natural sciences at the Lund University for a grant, and the Fund available for the cooperation between Lund and Vilnius Universities for financial support. This work was supported by the Swedish Natural Science Research Council.

References

1. a) Doerner, T., Gleiter, R., Robbins, T. A., Chayangkoon, P. and Lightner, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 3235-3241; b) Pérard-Viret, J. and Rassat, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1-4.
2. a) Zefirov, N. S. and Palyulin, V. A. In *Topics in Stereochemistry*, Eliel, E. L. and Whilen, S. H. Eds.; John Wiley, 1991; vol. *20*, pp.171-230; b) Berg, U. and Butkus, E. *J. Chem. Res. (S)* **1993**, 116-117; c) Berg, U. and Butkus, E. *J. Chem. Res. (S)* **1994**, 356-357; d) Butkus, E., Martins, J. and Berg, U. *J. Incl. Phenom.*, in press.
3. a) Momose, T., Muraoka, O., Shimada, N., Tsujimoto, C. and Minematsu, T. *Chem. Pharm. Bull.* **1989**, *37*, 1909-1912; b) Krow, G. R. *Tetrahedron* **1987**, *43*, 3-38; c) Quast, H., Witzel, M., Peters, E.-M., Peters, K. and von Schnering, H. G. *Liebig Ann.* **1995**, 725-738; *ibid.* **1995**, 1159-68; d) Quast, H. *Janssen Chim. Acta* **1986**, 24-6 ; e) Butkus, E., Berg, U., Stoncius, A. and Zilinskas, A. *Mendeleev Commun.* **1995**, 96-97; f) Berg, U., Butkus, E. and Stoncius, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 97-102; g) Almquist, F., Eklund, L. and Frejd, T. *Synth. Commun.* **1993**, *23*, 1499-1505; h) Almquist, F. and Frejd, T. *Tetrahedron: Asymmetry* **1995**, *6*, 957-960; i) Almquist, F., Ekman, N. and Frejd, T. *J. Org. Chem.* **1996**, *61*, 3794-3798; k) Mori, K. and Nagano, E. *Biocatalysis* **1990**, *3*, 25-36; l) Watanabe, H. and Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2919-2934; m) Mori, K. and Matsushima, Y. *Synthesis* **1993**, 406-410; n) Mori, K. and Matsushima,Y. *Synthesis* **1994**, 417-421; o) Paquette, L. A. and Tsui, H.-C. *J. Org. Chem.* **1996**, *61*, 142-145.
4. see e.g. Nakanishi, K., Goto, T., Itô, S., Natori, S. and Nozoe, S. Eds., *Natural*

Products Chemistry, Kodansha and Academic Press, **1974**, Vol. 1, and **1975**, Vol. 2.

5. a) Lythgoe, B. In *The Alkaloids* Manske, R.F. Ed., Academic Press, vol X pp. 1968, 597; b) Trost, B. M., and Fray, M. J. *Tetrahedron Lett.* **1984**, *25*, 4605-4608; c) Romero, M. A., Franco, R. P., Cruz-Almanza, R. and Padilla, F. *Tetrahedron Lett.* **1994**, *35*, 3255-3258.
6. a) Marshall, J. A. and Scanio, C. J. V. *J. Org. Chem.* **1965**, *30*, 3019-3023; b) House, H. O., Sieloff, R. F., Lee, T. V. and DeTar, M. B. *J. Org. Chem.* **1980**, *45*, 1800-1806; c) House, H. O., Sieloff, R. F. and VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 4639-4643; d) Shea, K. J. and Gilman, J. W. *Tetrahedron Lett.* **1984**, *25*, 2451-2454; e) Swindell, C. S., Isaacs, T. F. and Kanes, K. J. *Tetrahedron Lett.* **1985**, *26*, 289-292.
7. a) Burkert, U. and Allinger, N. L. *Molecular Mechanics;* American Chemical Society; Washington, DC 1982; b) Allinger, N. L., Yuh, Y. H. and Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551-8565; c) Lii, J. H. and Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566-8575; d) *ibid.* **1989**, *111*, 8576-8582.
8. a) Liljefors, T. *J. Mol. Graphics* **1983**, *1*, 111-117; b) Von der Lieth, C. W., Carter, R. E., Dolata, D. P. and Liljefors, T. *J. Mol. Graphics* **1984**, *2*, 117-123; the Macintosh version of MIMIC is available from InStar Software AB, Ideon Research Park, S-223 70 Lund, Sweden.
9. The *twist* conformers are two oppositely twisted *twist-boat, twist-boat* and *twist-boat* conformations.
10. Isaksson, R. and Roschester, J. *J. Org. Chem.* **1985**, *50*, 2519-2521.
11. a) Bayley, P. M., Nielsen, E. B. and Schellman, J. A. *J. Phys. Chem.* **1969**, *8*, 228-243; b) Nielsen, E. B. and Schellman, J. A. *Biopolymers* **1971**, *10*, 1559-1581; c) Madison, V. and Schellman, J. A. *Biopolymers* **1972**, *11*, 1041-1076.
12. Tinoco, Jr., I. *Adv. Chem. Phys.* **1962**, *4*, 113-160.
13. Condon, E. U., Altar, W. and Eyring, H. *J. Chem. Phys.* **1937**, *5*, 753-775.
14. Kirkwood, J. G. *J. Chem. Phys.* **1937**, *5*, 479-491.
15. Harada, N. and Nakanishi, K. *Circular Dichroism Spectroscopy - Exiton Coupling in Organic Stereochemistry*; Oxford University Press 1983.
16. Schellman, J. A. *Acc. Chem. Res.* **1968**, *1*, 144-151.
17. Jaffé, H. H. and Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy,* J. Wiley and Son, N.Y. 1962.
18. Marshall, J. A. and Flynn, K. E. *J. Am. Chem. Soc.* **1982**, *104*, 7430-7435.

(*Received in UK* 27 *January* 1997; *revised* 13 *February* 1997; *accepted* 20 *February* 1997)