Synthesis and Chiroptical Properties of Methanocycloocta[*b*]indoles

Eugenius Butkus,*,† Ulf Berg,*,‡ Julė Malinauskienė,† and Jan Sandström‡

Department of Organic Chemistry, Vilnius University, 2734 Vilnius, Lithuania, and Organic Chemistry 1, Department of Chemistry, Lund University, P.O. Box 124, S-22100 Lund, Sweden

Received September 1, 1999

The synthesis of chiral methanocyclocta[*b*]indoles, the fused structures obtained from enantiomeric bicyclo[3.3.1]nonanones via Fisher indolization reaction, is reported. The starting optically active bicyclo[3.3.1]nonane-2,6-dione (**1**) was obtained by a chiral HPLC enantiomer separation on a swollen microcrystalline triacetylcellulose column and by the enzymatic resolution of the racemic dione. The circular dichroism (CD) spectra of the chiral structures **4**, **5**, and **7** were recorded, and the absolute configuration for the indole compounds was assigned. The theoretical calculations of the CD spectrum of diindole **4** reproduce the ^1B_b couplet at 229 nm but predict wrong signs for the ^1L_a and ^1L_b bands using standard polarization directions. The CD spectrum of indole ketone **5** is reproduced correctly.

Introduction

The indole ring system is a constituent of many naturally occurring molecules including the amino acid tryptophan. Since the latter is an essential amino acid, indoles are present in many peptides and other natural and synthetic biologically active systems.[1−4] Recent theoretical and spectroscopic studies of the indole chromophore are due to the fact that tryptophan is the most important emissive source in protein class B.[5] Therefore, this and related structures were used as useful probes in studies of local environments and dynamics in proteins.[6]

The indole ring is a strong planar chromophore, which in a chiral molecular structure is of considerable interest for circular dichroism (CD) spectroscopic studies of various natural and synthetic chiral molecules.[7,8] The chirality of molecules containing the indole ring has been the result of substitution with groups having stereogenic centers,[9] or incorporation of the indole in a polycyclic ring system.[10] The absolute configuration of a number of chiral indoles has been studied by CD spectroscopy though the absolute configuration could not be established using any reliable rule for correlation of the sign and magnitudes of the observed absorption with the absolute configuration. Thus, the interest in chiral indole compounds arises in view of the chiroptical properties of such structures.

We have prepared chiral indole derivatives, exhibiting a single spatial orientation of the chromophores, and examined their chiroptical properties by CD spectroscopy and computational methods.

Results and Discussion

Synthesis of Enantiomeric Methanocycloocta[*b*]-indoles from Optically Active Bicyclo[3.3.1]nonanones by the Indolization Reaction. The search for chiral molecules with the indole ring in a well-defined spatial orientation leads to the structure of an indole ring fused with an alicyclic framework. The construction of racemic compounds containing indole rings fused with bicyclo[3.3.1]nonanes has been accomplished earlier through the reaction of the corresponding 2,6-dione **1** with phenylhydrazine under the Fisher cyclization reaction conditions.[11] Therefore, the synthesis and the study of the enantiomeric molecules in which both structural fragments are available became a challenge.

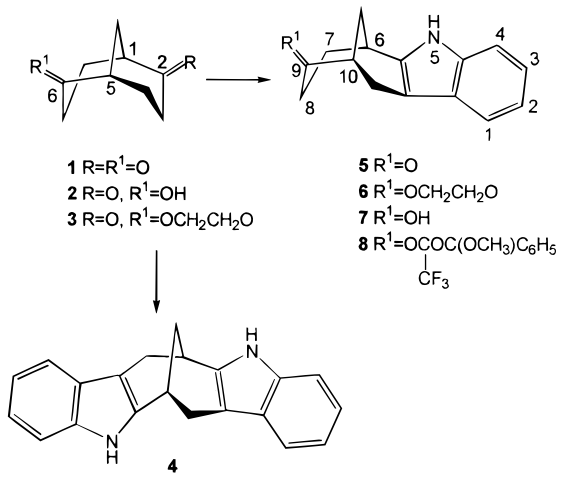
The synthesis of chiral compounds with this fused ring system requires the enantiomerically enriched carbonyl derivatives of bicyclo[3.3.1]nonane **1**. The enantiomers of the bicyclic 2,6-dione **1** could be obtained by a chromatographic resolution of the racemate on a swollen triacetylcellulose column on a semipreparative scale in quantities of 10−20 mg after a repeated process.[12] The absolute configuration of (−)-**1** and (+)-**1** was established using CD spectra.[12] To prepare the enantiomers of dione **1** on a larger scale, we used the enzymatic resolution of the racemic mixture. One of us has previously reported

* To whom correspondence should be addressed. E-mail: eugenijus.butkus@chf.vu.lt. Fax: 370-2-330987.
† Vilnius University.
‡ Lund University.

(1) Gribble, G. W. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer: Wien, New York, 1996; Vol. 68, pp 119−122 and 141−165 and references therein.
(2) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, pp 290−307.
(3) (a) Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R., Sr.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. *J. Org. Chem.* **1997**, *62*, 9192−9202. (b) Joshi, K. C. *Pharmazie* **1982**, *37*, 1−12.
(4) Alvarez, M.; Salas, M. *Heterocycles* **1991**, *32*, 1391−1429.
(5) Serrano-Andres, L.; Roos, B. O. *J. Am. Chem. Soc.* **1996**, *118*, 185−195.
(6) Creed, D. *Photochem. Photobiol.* **1984**, *39*, 537−562.
(7) Sandström, J. Conformational Analysis of Planar Chromophores With an Attached Chiral Rotor by CD Spectroscopy. In *Circular Dichroism, Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: New York, Weinheim, 1994; pp 443−472.
(8) Sandström, J. *Chirality* **1995**, *7*, 181−192.
(9) Nilsson, I.; Berg, U.; Sandström, J. *Acta Chem. Scand.* **1987**, *B41*, 261−266.
(10) Hallberg, A.; Isaksson, R.; Martin, A. R.; Sandström, J. *J. Am. Chem. Soc.* **1989**, *111*, 4387−4392.
(11) Kadziauskas, P.; Butkus, E.; Vasiulyte, J.; Averina, N. V.; Zefirov, N. S. *Khim. Geterotsikl. Soed.* **1979**, 315−318.
(12) Berg, U.; Butkus, E. *J. Chem. Res. (S)* **1993**, 116−117.

10.1021/jo991385a CCC: $19.00
Published on Web 02/16/2000

Scheme 1



the enantiomer separation of dione **1** by using horse liver alcohol dehydrogenase (HLADH), a NADH-dependent alcohol dehydrogenase that catalyzes enantioselective carbonyl reductions.[13] Since the results were published in a less accessible journal, we briefly repeat the experimental conditions here. The racemic dione **1** was subjected to HLADH-catalyzed reduction on a ca. 1 g scale using sodium dithionite or ethanol as a coupled substrate for recycling a catalytic amount of the nicotinamide coenzyme employed. The dione **1** was converted to optically active *endo*-(−)-hydroxyketone **2**, and some amount of diol was formed in the reduction. The HLADH-catalyzed reduction proceeded until 50% of the racemic dione **1** had been consumed. In accordance with normal practice for racemic substrates, the reaction was terminated at the 50% stage, the point at which enantiomerically specific enzyme-mediated resolutions could stop automatically.[14] The progress of reduction was monitored by thin layer chromatography. The reaction products were isolated by chloroform extraction and separated by column chromatography on aluminum oxide, yielding (−)-(1*R*,5*R*)-dione **1** with ee 75%. The subsequent elution gave hydroxyketone **2**, which was the major product of the enzymatic reduction. The oxidation of the latter afforded the (+)-(1*S*,5*S*)-enantiomer of **1**, ee > 50%.

The synthesis of methanocycloocta[*b*]indoles has been reported to be realized through the reaction of a (±)-dione **1** with phenylhydrazine via intermediate hydrazone formation.[11] In this work the synthesis of the corresponding chiral structures was accomplished by an application of this methodology using enantiomerically enriched starting dione **1** (Scheme 1). The reaction of (−)-(1*R*,5*R*)-dione **1** with phenylhydrazine in the presence of hydrochloric acid gave bishydrazone at room temperature. Refluxing the mixture in an ethanol solution for 20 min effected the cyclization. The structure and the configuration of the obtained (+)-diindole **4**[15] was assigned on the basis of spectroscopic data. The ^{1}H signals for the 1,2-substituted benzene ring and for NH of the indole ring in the NMR spectrum and the disappearance of C=O absorption in the IR spectrum were diagnostic. The configuration of the stereocenters in this structure did not change and depends on the configuration in the starting molecule since the indolization reaction proceeds without participation of the bridged atoms in the reaction. However, the priority in the sequence of the substituents changes in the diindole structure **4**; therefore, we define the configuration of (+)-diindole as (*S*,*S*)-**4**. The diindole of the opposite configuration, i.e., (−)-(*R*,*R*)-**4**, was synthesized from the starting (+)-(1*S*,5*S*)-dione **1**.

After several attempts to obtain monoindole **5** by use of an equimolar ratio of the (−)-dione **1** and phenylhydrazine had failed, the synthesis was accomplished through the monoacetal **3**. The latter was obtained from dione **1** by a standard procedure.[16] Subsequent addition of $PhNHNH_2$ to a solution of monoacetal **3** in an ethanol and acetic acid mixture gave monoindole **6** (Scheme 1). Hydrolysis of the protective group with 2 N sulfuric acid at room temperature gave the (+)-indole ketone **5**. Reduction of the latter with sodium borohydride led to diastereomeric indole alcohols **7** with a new stereogenic center at C-9. The *endo*-configuration of the hydroxyl group was assigned by the shape of the axial H-9 signal at δ 3.21 and is in accord with the stereochemistry of reductions of bicyclononanones.[17] A frequently used chiral reagent for the determination of the enantiomeric purity and configuration of chiral alcohols is α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), Mosher's reagent.[18] Reaction of (+)-(*S*)-MTPA chloride with hydroxyindole **7** in anhydrous pyridine at room temperature gave the (−)-indole ester **8**. The absolute configuration at C-9 was established from the ^{1}H NMR spectrum using the shift reagent $Eu(fod)_3$. The induced chemical shifts (LIS) of the methyl group in the NMR spectrum are related to the configuration of the secondary hydroxyl group. Addition of $Eu(fod)_3$ to the solution of (−)-indole **8** resulted in splitting of the OCH_3 group signal. The largest difference of LIS of diastereotopic methyl group signals was observed at a molar ratio of $Eu(fod)_3$ to (−)-**8** of 1:2, i.e., δ_H 7.06 and 5.52 ppm. The enantiomeric purity of the major diastereomer was obtained from the signal intensities of the methyl group and was found to be 92.5%. The absolute configuration of the C-9 followed from the observation that the larger induced shift corresponds to the (*R*)-configuration at the chiral center.[19,20] Therefore, the configuration of the major diastereomer (−)-**8** was defined as (*S*), and the same configuration was attributed to (−)-indole alcohol **7** obtained by hydrolysis of the (−)-indole ester **8** with sodium hydroxide.

CD Spectroscopic Studies and the Absolute Configuration of Methanocycloocta[*b*]indoles. Methods used to determine the absolute configuration of enantiomers include chemical correlation, X-ray anomalous scattering, and various spectroscopic methods.[21] The chiroptical methods and, in particular, CD have proved

(13) Malinauskiene, J.; Kadziauskas, P.; Malinauskas, A.; Kulys, J. *Liet. TSR Mokslu Akad. Darb., Ser. B* **1981**, 27−31; *Chem. Abstr.* **1981**, *95*, 203399.

(14) Haslegrave, J. A.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4666−4671.

(15) The IUPAC name for structure **4** is 3,14-diazahexacyclo-[10.10.1.0^{2,10}.0^{4,9}.0^{13,21}.0^{15,20}]tricosa-2(10),4(9),5,7,13(21),15(20),16,18-octaene, and that for structure **5** is 3-azatetracyclo[10.3.1.02,10.04,9]-hexadeca-2(10),4(9),5,7-tetraen-13-one.

(16) Klusacek, H.; Musso, H. *Chem. Ber.* **1970**, *103*, 3066−3075.

(17) (a) Berg, U.; Butkus, E.; Stoncius, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 97−102. (b) Butkus, E.; Malinauskiene, J.; Kadziauskas, P. *Z. Chem.* **1980**, *20*, 103.

(18) Dale, J. A.; Dull, D. L.; Mosher, S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(19) (a) Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* **1977**, 89−92. (b) Kalyanam, N.; Lightner, D. A. *Tetrahedron Lett.* **1979**, 415−418.

(20) Butkus, E.; Kadziauskas, P.; Malinauskiene, J. *Khim. Geterotsikl. Soed.* **1995**, 72−75.

to be indispensable tools for studying the absolute configurations of organic compounds.[22] The enormous number of applications of CD measurements led to the formulation of semiempirical rules for the correlation of the sign and magnitudes of observed Cotton effects (CE) with the absolute configurations of chiral structures. Among the best known are the octant rule, the dibenzoate chirality rule, and the benzene sector rule.[23] However, the use of the rules in the determination of the absolute configuration of molecules has a number of limitations; for example, some of the rules appear to have a weak theoretical basis, and for some chromophores, including the indole chromophore, no general rule of analysis of their CEs exists. It is possible for a given molecular geometry to calculate CD data employing two different groups of methods: the independent system approach[24] and the molecular orbital approach.[24,25] Thus, the application of CD spectroscopy in conjunction with calculations is one of the most reliable methods to prove the absolute configuration. Herein, the experimental CD spectra of indole compounds **4**, **5**, and **7** were studied, and theoretical CD spectra were calculated.

The absolute configuration for the compounds studied in this work was predetermined by the established configuration of the starting dione **1**. Further evidence for the absolute configuration of the indole compounds was obtained from CD spectroscopic studies and the theoretical calculations of the CD spectra. The indole ring is a planar chromophore attached to a chiral methanocyclooctane framework.

The CD spectrum of the diindole (*S*,*S*)-**4** (Figure 1) should mainly have its origin in interactions between the $\pi \rightarrow \pi^*$ transitions in the two indole rings. The transitions to be considered are summarized in Table 1. In a reasonable interpretation of the CD spectrum of (*S*,*S*)-**4**, the positive shoulder at 297 nm is due to the ^1L_b transitions, the positive peak at 288 nm to the ^1L_a transitions, the strong negative couplet centered at 229 nm to the ^1B_b transitions, and the positive band starting at 210 nm to the ^1B_a transitions.[26] In agreement with this, the UV spectrum of **4**, very similar in ethanol and acetonitrile, shows bands at 290 (ϵ = 15 000), 283 (ϵ = 17 000), 230 (ϵ = 69 000), and 196 nm (ϵ = 48 000).

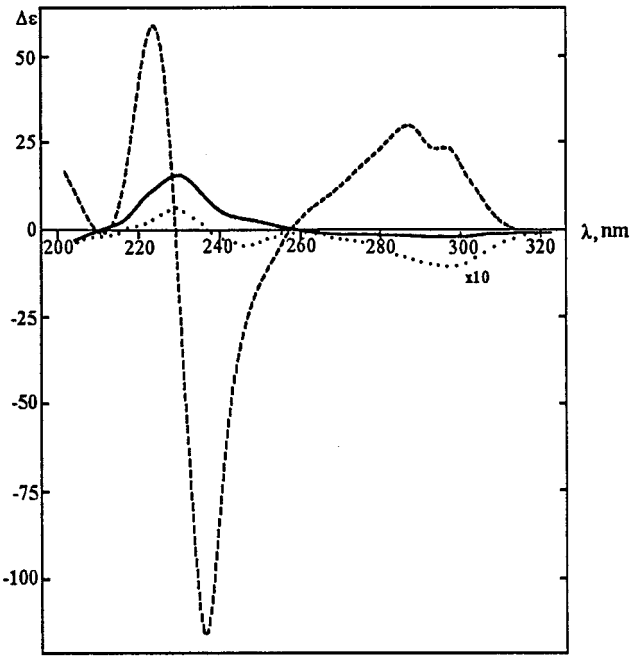


Figure 1. CD spectra of (+)-diindole **4** (- - -), (+)-indole ketone **5** (—), and (−)-indole alcohol **7** (···, intensity enhanced by 10).

The CD spectrum of indole ketone **5** exhibits a negative band at 300 nm typical for the indole ^1L_b transition. At shorter wavelength there is a negative couplet with the bands at 241 and around 234 nm (Figure 1).

The weak negative bands around 270 and 300 nm for indole alcohol **7** were assigned to the indole ^1L_a and ^1L_b transitions. The CD curve between 200 and 230 nm is composed of a stronger positive indole ^1B_b band at 230 nm and a negative minimum below 200 nm assigned to the indole ^1B_a band.

The compounds of reverse configuration gave the inverse CD spectra.

The polarization directions obtained by different methods and summarized in Table 1 agree to within ±10 or better, and in principle it should be possible to use these directions and the corresponding transition charge distributions to reproduce the CD spectrum at least semiquantitatively with the aid of the matrix method of Schellman and co-workers.[27] The diindole **4**, a rigid molecule with two chirally disposed chromophores, should be a suitable model for testing the correctness of the polarization directions. Only the coupled oscillator mechanism[28,29] needs to be considered, and the required input is the geometry of the molecule, the transition energies, the strengths and directions of the transition moments, and the transition charges. The structure of the diindole **4** was minimized by MM2(91) and PM3 computations, and a view of a superposition is presented in Figure 2.[30] A single conformation of the molecule was obtained by either method. The MM2 geometry was chosen for the

(21) For a recent discussion of the applicability and restriction of various methods with extensive references see: (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, Chichester, 1994. (b) *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, R. W., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Workbench ed. E21, Vol. 1.

(22) Gawronski, J. Determination of Absolute and Relative Configuration by Chiroptical Methods. In *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, R. W., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Workbench ed. E21, Vol. 1, pp 499−533 and references therein.

(23) For corresponding references see the respective chapters in *Circular Dichroism, Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: New York, Weinheim, 1994: (a) Lightner, D. A. The Octant Rule. pp 259−299. (b) Nakanishi, K.; Berova, N. The Exciton Chirality Method. pp 361−398. (c) Smith, H. E. Circular Dichroism of the Benzene Chromophore. pp 413−442.

(24) (a) Charney, E. The *Molecular Basis of Optical Activity-Optical Rotatory Dispersion and Circular Dichroism*; John Wiley & Sons: New York, 1979. (b) Mason, S. F. *Molecular Optical Activity and Chiral Discrimination*; Cambridge University Press: Cambridge, U.K., 1982.

(25) Hansen, A. E.; Bouman, T. D. *Adv. Chem. Phys.* **1980**, *44*, 545−644.

(26) (a) Strickland, E. H.; Horwitz, J.; Billups, C. *Biochemistry* **1969**, *8*, 3205−3213. (b) Strickland, E. H.; Horwitz, J.; Billups, C. *Biochemistry* **1970**, *9*, 4914−4921. (c) Strickland, E. H.; Billups, C.; Kay, E. *Biochemistry* **1972**, *19*, 3657−3662.

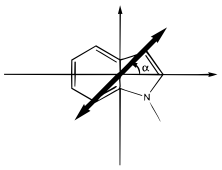
(27) (a) Bayley, P. M.; Nielsen, E. B.; Schellman, J. A. *J. Phys. Chem.* **1969**, *8*, 228−243. (b) Nielsen, E. B.; Schellman, J. A. *Biopolymers* **1971**, *10*, 1559−1581. (c) Madison, V.; Schellman, J. A. *Biopolymers* **1972**, *11*, 1041−1076.

(28) Kirkwood, J. G. *J. Chem. Phys.* **1937**, *5*, 479−491.

(29) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; Oxford University Press: Oxford, 1983.

(30) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

Table 1. Transition Directions (α) and Oscillator Strengths (*f*) for Indole



	transition					
	^1L_b	^1L_a	^1B_b	^1L_a	method	ref
α (*f*)	+49 (0.010)	−42 (0.112)			crystal spectra	32
	+54 (0.028)	−41 (0.125)	+18 (0.417)	−61 (0.730)	PPP	32
	+59 (0.01)	−50 (0.077)			INDO/S-SDCI	34
	+45	−45			vacuum UV	35
	+45	−54			stretched film	36
	+42	−46	+7		stretched film	37
	+44 (0.0035)	−42 (0.0174)	+6 (0.180)	−39 (0.099)	CNDO/S-CI	31
	+37 (0.050)	−36 (0.081)	+16 (0.458)	−55 (0.257)	ab initio CAS	5

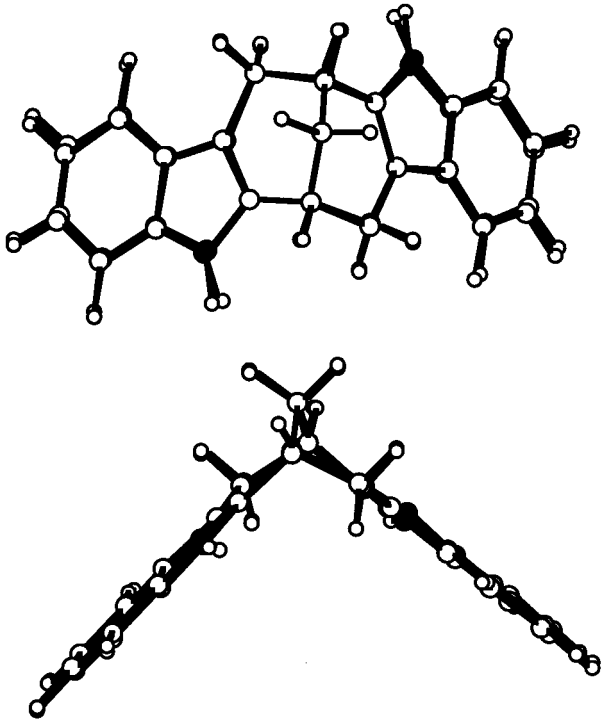


Figure 2. Superposition of MM2 and PM3 geometries of diindole **4** in two orthogonal projections.

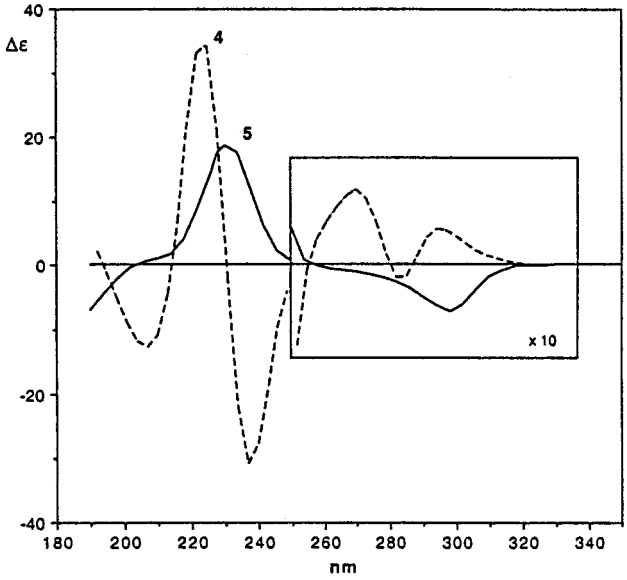


Figure 3. Calculated CD spectra of (+)-(*S*,*S*)-diindole **4** and (+)-(6*R*,10*S*)-indole ketone **5** using a dielectric constant of 2.

CD calculations. The calculations were based on the geometry of the (*S*,*S*)-**4** enantiomer, and the transition moments and transition charges were taken from a study of the CD spectra of 1- and 3-(1-phenylethyl)indoles.[31] The theoretical spectrum (Figure 3) reproduces the ^1B_b couplet at 229 nm satisfactorily and gives the correct sign to the ^1B_a band, but it deviates from the experimental spectrum by predicting negative ^1L_a and ^1L_b bands. This discrepancy could be due to the use of incorrect polarization directions (Table 1), and considering the strengths of the respective transitions, the directions of the ^1B_b and ^1L_a transitions should be expected to play a dominant role.

We have calculated CD spectra for (*S*,*S*)-**4** for a selection of combinations of α values (Table 1) for the ^1B_b and ^1L_a transitions while keeping the values for the ^1B_a and ^1L_b transitions unchanged. We have used the transition charges from ref 32 as starting values, and for each new value we have used the Lagrangian multiplier technique suggested by Rizzo and Schellman[33−37] to obtain the new set of transition charges, which with minimal change from the original one reproduces the new transition moment.

In a first approach we calculated the sign and strength of the ^1B_b couplet as a function of α in the range +90° to −90° in steps of 10°, leaving out the other transitions. The result was that the couplet is positive except for the ranges −90° < α < −75° and +55° < α < +90°. The strongest interaction, corresponding to $\Delta\epsilon = \pm 650$, was found at α = −30°.

In the next step, rotational strengths for all four kinds of transitions were calculated for a grid of α(^1L_a) in the range −85° to +85° and α(^1B_b) in the range +50° to −70°,

(31) Nilsson, I.; Berg, U.; Sandström, J. *Acta Chem. Scand.* **1986**, *B40*, 625−651.
(32) Yamamoto, Y.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1362−1366.
(33) Rizzo, V.; Schellman, J. A. *Biopolymers* **1984**, *23*, 435−470.
(34) Callis, P. R. *J. Chem. Phys.* **1991**, *95*, 4230−4240.
(35) Philips, L. A.; Levy, D. H. *J. Chem. Phys.* **1986**, *85*, 1327−1332.
(36) Albinsson, B.; Kubista, M.; Nordén, B.; Thulstrup, E. *J. Phys. Chem.* **1989**, *93*, 6646−6654.
(37) Albinsson, B.; Nordén, B. *J. Phys. Chem.* **1992**, *96*, 6204−6212.

both in steps of 10°. Inspection of the results reveals that the $^1L_a-^1B_b$ interactions in some regions are much more important than the $^1L_a-^1L_a$ and $^1B_b-^1B_b$ interactions. Thus, the ^1B_b couplet is practically eliminated for $\alpha(^1B_b) = 0°$ in the entire $\alpha(^1L_a)$ range, although a calculation with only ^1B_b transitions and $\alpha(^1B_b) = 0$ predicts a positive couplet with $\Delta\epsilon = \pm 270$.

Only in the range $+15° < \alpha(^1L_a) < +25°$ and $+10° < \alpha(^1B_b) < +20°$ does the calculated spectrum show acceptable similarity with the experimental one (Figure 3). This requires that the ^1B_b couplet has the right sign and approximately correct intensity, that the positive and negative ^1L_a components are so close that they only give rise to one band, and that the positive ^1L_a component has the highest intensity. These conditions are fulfilled in the α area given above, and besides, the ^1L_b components give only one band.

A similar variation of the direction of the ^1B_a transition while keeping the directions of the other transitions as in ref 31 produced only moderate intensity changes and no changes of sign in the other transitions.

However, although we have no good explanation for the failure of the calculation with standard polarization directions, we do not want to imply that the results presented here shall be seen as a proof for a positive α value for the ^1L_a transition. As an argument for the opposite, analysis of CD spectra of 1- and 3-(1-phenylethyl)indoles[31] clearly show that the polarizations of the ^1L_a and ^1L_b transitions show approximate mirror symmetry with respect to the *x* axis (Table 1) with $\alpha(^1L_b)$ positive and $\alpha(^1L_a)$ negative. Furthermore, the transition moment directions from ref 31 correctly reproduce the CD spectrum of the indole ketone **5** (Figure 3).

The high intensity of bands in the CD spectrum of diindole (+)-**4** compared to those for **5** and **7** could be explained by a through space interaction of the transitions in the indole chromophores.

In conclusion, the synthesis of chiral methanocycloocta-[*b*]indoles was accomplished using the enantiomers of bicyclo[3.3.1]nonanones, and the absolute configuration of the fused structures containing several chiral centers was proved by the CD spectra. The theoretical calculations of the CD spectrum of diindole **4** reproduce the ^1B_b couplet at 229 nm but predict the wrong sign for the ^1L_a and ^1L_b bands using standard polarization directions. The CD spectrum of indole ketone **5** is reproduced correctly.

Experimental Section

For general experimental and instrumentation details, see ref 17a. ^{1}H NMR spectra are reported in δ (ppm) downfield from internal reference TMS. Mass spectra were recorded in a direct inlet mode (EI, 70 eV). The CD spectra were recorded using 95% aqueous ethanol, and UV spectra were recorded using spectral grade ethanol. Optical rotations at the sodium D line were measured in a 0.5 cm microcell. Enantiomer separation of the dione **1** on a swollen microcrystalline triacetylcellulose (TAC) column was performed using the equipment described earlier[38] with 95% aqueous ethanol as the mobile phase. Thin layer chromatography was performed by using Silufol aluminum sheets precoated with aluminum oxide. Column chromatography was carried out by using aluminum oxide L40/250 (Czech Republic). Melting points are uncorrected.

Molecular mechanics (MM) analysis was performed using the MM2(91)[39] force field implemented in the MacMimic program package.[30,40] Quantum mechanical calculations were performed on a Silicon Graphics 02 workstation using the SPARTAN 5.0 program.[41]

Racemic bicyclo[3.3.1]nonane-2,6-dione (**1**) and 6,6-ethylenedioxybicyclo[3.3.1]nonan-2-one (**3**) were prepared according to the procedures reported in the literature,[16,42] respectively.

HLADH-Catalyzed Reduction of (±)-1. The dione **1** (1.5 g, 0.01 mol) was dissolved in 500 mL of 0.1 M potassium phosphate buffer (pH 7.5) at 30 °C. NAD^+ (0.23 g, 0.03 mol) and ethanol (24 mL) were then added. The reaction was initiated by the addition of HLADH (38 mg). The course of reaction was monitored by TLC. After 24 h 50% of the reduction had occurred, and the reaction mixture was evaporated to 50 mL and then continuously extracted with $CHCl_3$. The dried ($MgSO_4$) extract was evaporated in vacuo and the residue chromatographed on aluminum oxide. The unchanged dione (−)-**1** (R_f 0.69) and hydroxyketone **2** (R_f 0.19) were eluted by using dichloromethane to give (−)-dione **1** (0.53 g, 34%, 80% ee, $[\alpha]^{20}_D = -149°$ (*c* 0.3, dioxane)) and (−)-hydroxyketone **2** (0.37 g, 24%, $[\alpha]^{20}_D = -6°$ (*c* 0.26, dioxane)). The subsequent elution with chloroform−methanol (14:1) solvent system afforded the corresponding (−)-diol, a product of complete reduction of 1.

[*S*-(*S*,*S*)- and *R*-(*R*,*R*)]-5,6,7,12,13,14-Hexahydro-6,13-methanocycloocta[1,2-*b*:5,6-*b*′]diindoles 4. To a stirred and heated mixture of phenylhydrazine (0.12 g, 1.1 mmol) in an ethanol−water mixture (5 mL, 90%) acidified with 0.1 mL of hydrochloric acid was added (−)-(1*R*,5*R*)-dione **1** (0.084 g, 0.55 mmol, $[\alpha]^{20}_D = -149°$) or the corresponding (+)-(1*S*,5*S*)-dione **1**. The reaction mixture was refluxed for 20 min, cooled, and left to crystallize. The crystals were filtered and washed with water and ethanol. Recrystallization from acetone gave diindole **4** (0.13 g, 65% yield, mp > 300 °C): (+)-**4**, $[\alpha]^{20}_D = +84°$ (*c* 0.43, dioxane); (−)-**4**, $[\alpha]^{20}_D = -63°$ (*c* 0.38, dioxane); IR (KBr) 3380, 757 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.72−1.91 (m, 8H), 3.32 (s, 2H), 6.53−7.44 (m, 8H); UV (ethanol) λ_{max} (log ϵ) 232 (4.75), 285 (4.13); CD λ_{max} ($\Delta\epsilon$/mol^{-1} cm^{-1}) 224 (+58.5), 237 (−115.7), 288 (+30.0), 297 (+24.2); MS *m*/*z* (%) 298 (M^+, 100), 283 (30), 269 (12), 168 (17), 148 (26), 130 (19), 94 (5). Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.38. Found: C, 84.51; H, 6.10; N, 9.51.

[6*R*-(6α,10α)]-(9,9-Ethylenedioxy)-6,10-methano-1*H*-cyclooct[*b*]indole (6). To a solution of monoacetal **3** (0.19 g, 1.0 mmol) in ethanol (5 mL) were added phenylhydrazine (0.12 g, 1.1 mmol) and acetic acid (2 mL). The mixture was heated at 80 °C for 1 h and cooled to room temperature, and the resulting crystals were filtered and washed with water and ethanol to give **6** (0.14 g, 54% yield, mp 185−187 °C (from ethanol)): ^{1}H NMR ($(CF_3CO)_2O$) δ 1.38−3.52 (m, 10H), 4.01 (s, 4H), 6.72 (br s, 1H), 7.01−7.23 (m, 4H); IR (Nujol) 3410 cm^{-1}; UV λ_{max} (log ϵ) 229 (4.54), 283 (3.84). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.61; H, 6.98; N, 4.82.

[6*R*-(6α,10α)]-6,10-Methano-1*H*-cyclooct[*b*]indol-9-one (5). A mixture of indole **6** (0.08 g, 0.29 mmol) and sulfuric acid (1.6 mL, 2 N) was heated at 50−60 °C for 24 h, cooled, and filtered to give indole ketone **5** (0.06 g, yield 94%, mp 151−153 °C (from ethanol)): $[\alpha]^{20}_D = +14.50$ (*c* 0.2, $CHCl_3$); IR (Nujol) 3400, 1705 cm^{-1}; UV λ_{max} (log ϵ) 224 (4.66), 283 (4.03); CD λ_{max} ($\Delta\epsilon$/mol^{-1} cm^{-1}) 230 (+15.70), 300 (−1.60). Anal. Calcd

(38) Isaksson, R.; Rochester, J. *J. Org. Chem*. **1985**, *50*, 2519−2521.

(39) (a) Liljefors, T.; Allinger, N. L. *J. Comput. Chem*. **1985**, *6*, 478−480. (b) Liljefors, T.; Tai, J.; Li, S.; Allinger, N. L. *J. Comput. Chem*. **1987**, *8*, 1051−1056.

(40) (a) Liljefors, T. *J. Mol. Graphics* **1983**, *1*, 111−117. (b) Von der Lieth, C. W.; Carter, R. E.; Dolata, D. P.; Liljefors, T. *J. Mol. Graphics* **1984**, *2*, 117−123. The Macintosh35 version of MIMIC is available from InStar Software AB, Ideon Research Park, S-223 70 Lund, Sweden.

(41) SPARTAN, version 3.0: Hehre, W. J.; Burke, L. D.; Shusterman, A. J.; Pietro,W. J. Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

(42) (a) Meerwein, H.; Schurmann, W. *Liebigs Ann. Chem*. **1913**, *397*, 196−250. (b) Lightner, D. A.; Chang, T. C.; Hefelfinger, D. T.; Jackman, D. E.; Wijekoon, W. M. D.; Givens, J. W., III. *J. Am. Chem. Soc*. **1985**, *107*, 7499−7508. (c) Quast, H.; Witzel, M. *Liebigs Ann. Chem*. **1993**, 699−700.

for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.21. Found: C, 79.59; H, 6.70; N 6.01.

[6*R*-(6α,9α,10α)]-6,10-Methano-1*H*-cyclooct[*b*]indol-9-ol (7). To indole ketone **5** (0.057 g, 0.25 mmol) in methanol (5 mL) was added sodium borohydride (0.01 g, 0.26 mmol) in portions over a 1 h period. The mixture was stirred at room temperature for 8 h and neutralized with dilute hydrochloric acid, and the solvents were evaporated in vacuo. The residue was continuously extracted in a Soxhlet apparatus with benzene. The solvent was evaporated to give indole alcohol **7** (0.056 g, yield 95%, mp 219−220 °C (from benzene)): $[\alpha]^{20}_D$ = −16.0° (*c* 0.2, $CHCl_3$); ^{1}H NMR ($(CF_3CO)20$) δ 0.75−2.62 (m, 10H), 3.21 (m, 1H), 4.72 (br s, 1H), 6.51−7.22 (m, 4H), 7.43 (br s, 1H); IR (Nujol) 3300, 3580 cm^{-1}; CD λ_{max} ($\Delta\epsilon$/mol^{-1} cm^{-1}) 230 (+0.74), 245 (−0.70), 300 (−1.14); MS *m*/*z* (%) 227 (M^+, 94), 209 (35), 180 (20), 169 (17), 168 (100), 156 (12), 143 (21), 130 (18), 91 (5). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.15; H, 7.67; N 5.91.

[6*R*-(6,9,10)]-6,10-Methano-1*H*-cyclooct[*b*]indol-9-yl-α-methoxy-α-(trifluoromethylphenyl) ethanoate (8). To a solution of (+)-(*S*)-MTPA chloride (0.11 g, 0.43 mmol) in dry pyridine (4.0 mL) was added a solution of indole alcohol **7** (0.07 g, 0.32 mmol) in tetrachloromethane (10 mL). The mixture was kept at room temperature overnight, and then water was added to dissolve the precipitate. The solution was extracted with ether, and the extracts were combined, washed (dilute hydrochloric acid, brine, and cold Na_2CO_3 solution), dried over magnesium sulfate, filtered, and concentrated. Fractional crystallization from dry ether gave (−)-**8** (0.05 g, yield 20%, mp 167−169 °C): $[\alpha]^{20}_D$ = −51° (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75−2.75 (m, 10H), 3.60 (s, 3H), 5.25 (m, 1H), 7.01−7.70 (m, 11H). Anal. Calcd for $C_{25}H_{24}F_3NO_3$: C, 67.71; H, 5.45; N, 3.16. Found: C, 67.50; H, 5.37; N 3.31.

Acknowledgment. This research was partially supported by grants from the Lithuanian Science and Studies Foundation and the fund available for the cooperation between Lund and Vilnius Universities. We thank Dr. B. Bossenbroek, Chemical Abstract Service, for helping to correctly name and number methanocycloocta[*b*]indoles, and Mr. Rytis Kubilius for the mass spectra.

JO991385A