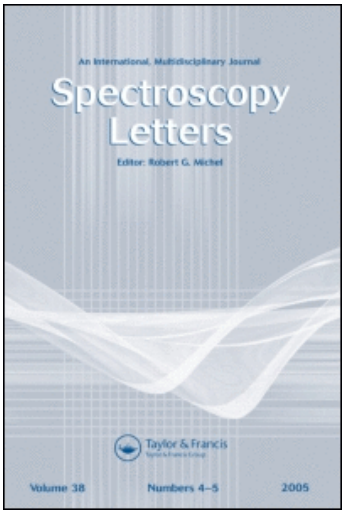


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

CD SPECTRA OF DIASTEREOMERIC α-ARYLETHYLAMIDES OF (-)-CAMPHANIC ACID

Zdenko Hameršak[a]; Marin Roje[a]; Miklòs Hollòsi[b]; Zsuza Majer[b]; Vitomir Šunjic[a]
[a] "Ruder Boškovic" Institute, Zagreb, Croatia [b] Department of Organic Chemistry, Eötvös University Budapest, Budapest, Hungary

Online publication date: 26 June 2002

To cite this Article Hameršak, Zdenko , Roje, Marin , Hollòsi, Miklòs , Majer, Zsuza and Šunjic, Vitomir(2002) 'CD SPECTRA OF DIASTEREOMERIC α-ARYLETHYLAMIDES OF (-)-CAMPHANIC ACID', Spectroscopy Letters, 35: 1, 73 — 82
To link to this Article: DOI: 10.1081/SL-120013134
URL: http://dx.doi.org/10.1081/SL-120013134

SPECTROSCOPY LETTERS, 35(1), 73–82 (2002)

CD SPECTRA OF DIASTEREOMERIC α-ARYLETHYLAMIDES OF (−)-CAMPHANIC ACID

Zdenko Hameršak,[1] Marin Roje,[1] Miklòs Hollòsi,[2] Zsuzsa Majer,[2] and Vitomir Šunjic[1,*]

[1]"Ruder Boškovic" Institute, P.O.B. 1016, HR-10000 Zagreb, Croatia
[2]Eötvös University Budapest, Department of Organic Chemistry, P.O.B. 32, H-1518 Budapest, Hungary

ABSTRACT

CD spectra of diastereomeric α-arylethylamides **2**,**3**, **4**,**5** and **6**,**7** exhibit nearly enantiomorphic CD curves. Interchromophoric charge-transfer interaction between the aromatic and the amide chromophore is observed only in the amide nπ* band region. MM2 calculations suggest that in the lowest-energy conformer of all diastereomeric pairs the aromatic rings as the major chromophores have mirror image positions relative to the plane defined by the amide-lactone chromophoric system.

Key Words: CD spectra; Interchromophoric interaction

*Corresponding author.

INTRODUCTION

Continuing our studies of the conformational and spectroscopic properties[1,2], and use of (−)-camphanic acid derivatives as chiral synthetic auxiliaries[3–5], we entered the study of the chiroptical properties of α-arylethylamides of (−)-camphanic acid (**1**–**7**) and of some model compounds. It is expected that analysis of their CD data will contribute to our understanding of their conformational properties and improve the design of chiral nitrogen ligands based on α-arylethylamines[6,7].

RESULTS AND DISCUSSION

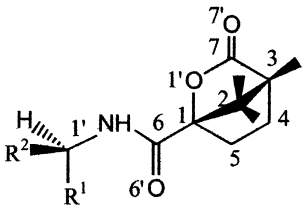
The CD data of the compounds **1**–**7** are summarized in the Tables 1–3. CD parameters of (*R*)-PEA$^+$ ClO_4^- (**8**), (*R*)-NEA$^+$ ClO_4^- (**9**)[11], and of the models **10**–**15** containing either the aromatic or lactone chromophore of **1**–**7** are listed in Table 2.

An assignment of the bands is given in the Table 3. Clearly, the CD spectra of **2**–**7** are dominated by the contribution of the aromatic chromophores. In spite of the diastereomeric conformations of camphanic acid derivatives **2**/**3**, **4**/**5**, and **6**/**7**, the CD spectra show an approximate mirror image relationship (Table 1, and Fig. 1).

In the CD spectra of α-phenylethylamino (PEA) derivatives **2** and **3** the nπ* band of the lactone chromophore turns up at 216 nm well separated from the ^1L_a band of phenyl chromophore. This assignment is based on the CD spectra (Table 2) of camphanic acid derivatives **10**, **11** and **15** which show a band at ~216 nm with definite vibrational fine structure. The nπ* band of amide is covered by that of the chirally stronger perturbed carbonyl nπ* transition within conformationally rigid lactone group. The increased ^1L_a band intensity in the spectra of **2**, **3** and **12**, relative to that of (*R*)-PEA $^+ClO_4^-$ and **1** (Tables 1 and 2), can also be explained by more limited rotational freedom of the acylated amine as compared to the protonated species. The appearance of the shoulder or weak band at ~230 nm in the spectra of **1**–**3** and the band at 223 nm (−1.30) in the CD spectrum of **1** is puzzling. Note, that in spite of the presence of an ester, hydrazide or amide chromophore the CD spectra of **10**, **11** and **15** show no further bands in this region.

In the CD spectra of α-naphthylethylamino (NEA) derivatives **4**, **5** and **13** the lactone and amide nπ* bands are overlapped by the much more intensive ^1B_b band of the naphthyl chromophore right above 220 nm. The lack of mirror image relationship in this region (Table 1) may be a sign of interchromophoric interaction which is different in the case of the (*R*) and (*S*)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

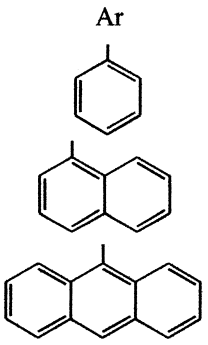


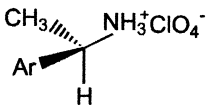
	R^1	R^2
1	Ar	H
2, 4, 6	Ar	CH_3
3, 5, 7	CH_3	Ar

1, 2, 3

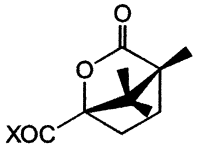
4,5

6,7

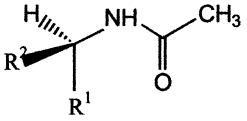


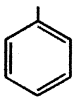
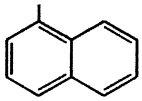
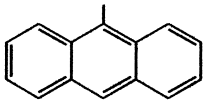


	Ar
8	Ph
9	α-Nphth



	X
10	OCH_3
11	$NHNH_2$
15	$NHCH_3$



	R^1	R^2
(*R*)-**12**		CH_3
(*R*)-**13**		CH_3
(*S*)-**14**	CH_3	

stereoisomers. The most complex spectra were measured for the α-anthracenylethylamino (AEA) derivatives **6**/**7** and **14**. The CD spectra are dominated by a band at 243 nm. The high intensity of this band can be explained by charge transfer interaction between the anthracene and amide chromophore. For the assignment of the bands see Table 3.

Conformational analysis of the compound **3** using MM2 calculations gave three energy minima (**A** through **C**, Fig. 2) revealing three stable conformers. Total energy and the dihedral angle φ O(6′)-C(6)-C(1)-O(1′) for each conformer are calculated; conformer **A** has the lowest energy (E_{tot}

Table 1. UV and CD Data in Methanol for Compounds **1**–**7**[a]

Camph-CO-NH-Q Q	UV (λ, nm; $\varepsilon \times 10^4$)	CD (λ $\Delta\varepsilon$) Q
Bzl, **1**	< 195 (> 4.0) ~204sh (~ 1.30) 258 (0.03)[b] ~210sh (~ 1.00)	197 (1.50) 211 (−1.00) 223 (−1.30)[c] ~230 sh
R-PEA **2**	< 200 (> 1.5) ~230sh 257 (0.015)[c]	196 (28.4) 212.5 (10.6) 231.5 (−0.76) 260.5 (−0.28) [d]
S-PEA **3**	< 200 (> 2.0) ~217sh (~ 0.15) 257 (0.017)[d]	196 (−26.7) 212 (−13.7)230s 260.5 (+0.21)[d] 215.5 (−13.3)
R-NEA **4**	~208sh (~ 2.7) ~219sh (~ 5.5) 281 (0.67)[d] 223.5 (6.30)	< 190 (> +20.0) ~208sh 225.5 (−19.1) 281 (+1.90)[d] ~217 sh(~ −11.0)
S-NEA **5**	~208sh (~ 3.5) ~218sh (~ 7.1) 280.5 (0.94)[d] 223 (8.32)	< 195 (> −20.0) ~208sh 224 (+27.1) 280.5 (−1.90)[d] ~218 sh (~ +11.5)
R-AEA **6**	< 195 (> 3.0) 217 (1.54) ~247sh (~ 4.8) 365 (0.65)[d] 255 (8.36)	~195 (−12.6) 213.5 (−7.30) 243 (11.1) 283[e] ~225sh 264 (−1.52) 384 (0.14)[f]
S-AEA **7**	< 195 (> 3.0) 216 (1.65) ~249sh (~ 5.1) 365 (0.49)[d] 255 (6.89)	195 (12.9) 214 (3.83) 243 (−11.7)[g] 386 (−0.97)[f] ~225sh 263 (1.71)

[a]For the CD of compounds **6** and **7** see also Fig 1.
[b]The strongest central band of a triplet.
[c]Three or four very weak bands between 250–270 nm.
[d]The strongest band (second from the long-wavelength side) of a quadruplet.
[e]Weak band with two shoulders.
[f]The strongest long-wavelength band of a quadruplet between 345–400 nm.
[g]Three or four weak positive bands between 290–330 nm.

20.8 kcalmol^{-1} for φ 163°) which is considered as a global minimum. Conformers **B** (E_{tot} 25.2 kcalmol^{-1} for φ − 56°) and **C** (E_{tot} 25.4 kcalmol^{-1} for φ 60°) have somewhat higher energy contents comparing to conformer **A**. Stabilisation of **A** over **B** and **C** amounts 4.4 kcalmol^{-1} and 4.6 kcalmol^{-1}, respectively, and it is mainly due to the formation of a hydrogen bond between the amide hydrogen and lactone oxygen in the conformer **A**. The unusually high vCO frequency of the lactone carbonyl of the camphanic acid N-methylamide **15** in CCl_4 and CH_3CN supports the possible formation of H-bonding. In addition, in conformer **A** there is no electrostatic

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 2. CD Data for Compounds **8**–**13**

Compound		λ max (Δε)	
8 (*R*)-PEA $^{+}ClO_4$[a] MeCN		212 (0.93)	261 (−0.10)[b]
12 (*R*)-PEA-$COCH_3$ MeOH	195 (40.95)	212 (13.0) 215sh (+12.1)	260.5 (−0.13)[b]
9 (*R*)-NEA $^{+ClO_4-}$ MeCN		222 (−20.4)	282 (0.70)[b]
13 (*R*)-NEA-$COCH_3$ MeOH	∼203 sh(2.45)	∼217sh (−) 224(−15.5)	280.5 (1.90)[b]
14 (*S*)-AEA-$COCH_3$ MeOH	195 (19.75)	∼218sh (−), 242 (12.0)[c], 263.5 (−2.10), 387 (0.13)[d]	
10 Camph-$COOCH_3$ MeOH	< 200 (+)	215.5 (−1.02)	
11 Camph-$CONHNH_2$ MeOH	< 200 (+)	216.5 (−1.54)	
15 Camph-$CONHCH_3$ MeOH	< 200 (+)	215.5 (−2.70)	

[a]Ref. 8.
[b]Strongest band of a multiplet.
[c]With two shoulders.
[d]Strongest band of a multiplet between 340–390 nm.

repulsion between the amide and lactone oxygen atoms. For **B** and **C** the angle φ is −56° and 60°, respectively, and considering the *trans* conformation of the amide bond, formation of intramolecular H-bonding is prevented in these conformers. Thus, stabilisation by H-bonding and the lack of

Table 3. Band Assignments for the Chromophores in Compounds **2**–**7**

Compounds	Nm, Klevens-Platt					
PEA derivates **2, 3**	195–200	^1B_b,	210–215	^1L_a,	∼260	^1L_b
NEA derivates **4, 5**	220–225	^1B_b,	= 280	^1L_a, ^1L_b		
AEA derivates **6, 7**	∼240	^1B_b,	340–390	^1L_a, ^1L_b		
Lacton chromophore	195	ππ*		216	nπ*	
Amide chromophore	215–225	nπ*				
	∼230	Amide charge transfer band				

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

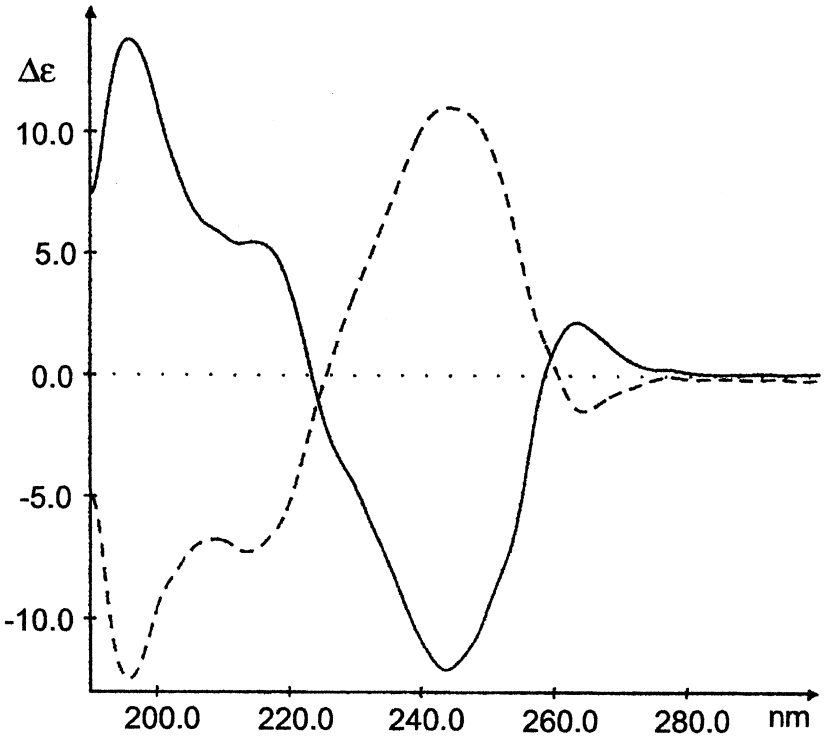


Figure 1. CD spectra of *R*-**6** (- - -) and *S*-**7** (—) 9′-anthracenylethylamides of (−)-camphanic acid in MeOH. For the long wavelength region of the spectra see Table 1.

electrostatic repulsion determines *s-trans* conformation of the two functionalities[11], and gives to the α-arylethylamine unit in **2**–**7** a property of chiral rotor attached to the planar chromophore[2,10]. Due to the same local chirality of the (−)-camphanic acid ring, conformer **A** is the major conformer in both the (1′*R*) and (1′*S*) series. The nearly mirror image CD curves are a consequence of nearly the same amount of the enantiomeric conformers due to rotation around the C(1′)-N bond.

CONCLUSION

In the case of α-arylethylamide derivatives of camphanic acid the CD spectra are dominated by the contribution of the aromatic chromophore, and are close to mirror image relationship. This reveals the presence of most

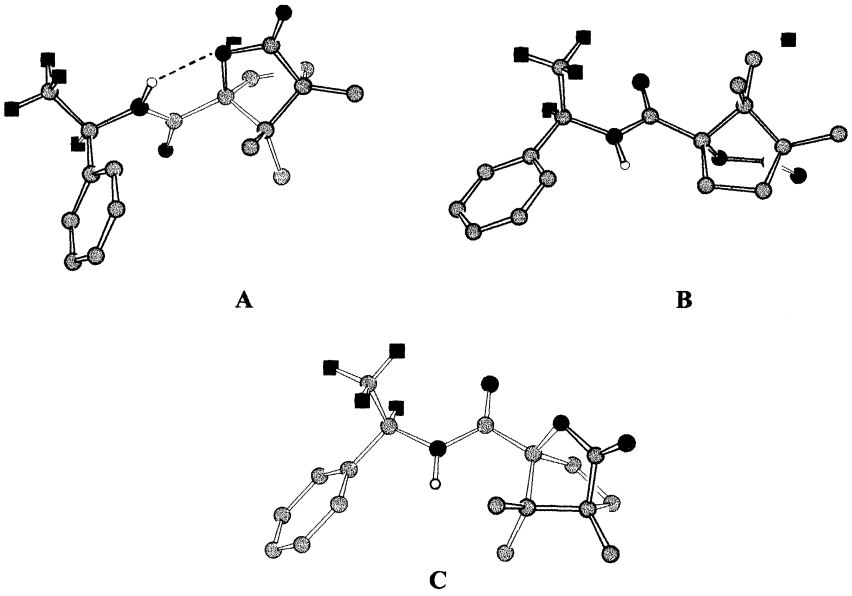


Figure 2. MM2 calculated conformers of **3**.

stable conformers, which for all diastereomeric pairs (**2**,**3**; **4**,**5**; **6**,**7**) characterized by mirror-related relation of the aromatic rings according to the plane defined by the amide-lactone chromophoric system, and others that do not contribute to the CD spectrum.

EXPERIMENTAL

IR: *Perkin Elmer 297* spectrometer for KBr pellets. ^{1}H- and ^{13}C-NMR: *Varian Gemini XL 300* spectrometer for $CDCl_3$ solutions, δ in ppm relative to TMS as internal reference, and *J* in Hz. GC: GC purities were determined on HP 5890 chromatograph with 20 m HP‡ 1 column. MS: High resolution MS spectra were obtained on Extrel FTMS 2001 DD Instrument. M. p.: *Electrothermal Apparatus*, not corrected. Optical rotations: *Optical Activity AA-10* Automatic Polarimeter in a 1 dm cell; c in g/100 mL. CD spectra were recorded on a Jobin-Yvon Mark VI dichrograph (calibrated with epiandrosterone) using a 0.02 cm cell for measurement between 195 and 240 nm and 0.1, 1.0 cm cells between 240–400 nm. Methanol (MeOH) was used as the solvent and the concentrations were 1–5 mmole dm^{-3}.

Elemental analyses were performed in the Microanalytical laboratory of "Ruder Boškovic" Institute.

Preparation of compounds **1**–**7** has been recently reported[2], preparations of the compounds **8** and **9**[11] and **10** and **11**[12] have also been published previously.

(*R*)-N-Acetyl-1-phenylethylamine (12)

Solution of 86 mg (0.7 mmol) of (*R*)-(+)-1-phenylethylamine in acetic anhydride (2.0 mL) was stirred at room temperature for 2 hours. The reaction mixture was poured on water, pH adjusted to neutral with solid sodium carbonate, and the product was extracted with dichloromethane. Upon drying and evaporation, 115 mg (99%) of (*R*)-N-acetyl-1-phenylethylamine were obtained, 97% pure by GC M.p. 101–102°C (lit m.p. 101–102°C)[13]. ^{13}C NMR ($CDCl_3$): 21.4, 22.9, 48,5, 126.1, 127.1, 128.5, 143.2, 169.3. ^{1}H NMR ($CDCl_3$): 1.43 (d, $J = 7$ Hz, 3H), 1.92(s, 3H), 5.07 (m, 1H), 6.33 (brs, 1H), 7.20–7.33 (m, 5H). IR (KBr): 3270, 3090, 1645, 1550, 1360, 1060, 760, 700. $[\alpha]_D = +140$ ($CHCl_3$, c = 1, 30°C).

(*R*)-N-Acetyl-1-(1′)-naphthylethylamine (13)

This compound was prepared in the same manner as described for **12**; 98% yield, 96% GC purity. M.p. 158–160°C. ^{13}C NMR ($CDCl_3$): 20.4, 22.9, 44.3, 122.4, 123.3, 125.1, 125.7, 126.4, 128.1, 128.6, 130.9, 133.8, 138.3, 169.0. ^{1}H NMR ($CDCl_3$): 1.60 (d, $J = 7$ Hz, 3H), 1.88 (s, 3H), 5.85 (M, 1H), 6.15 (brs, 1H), 7.39–7.54 (m, 4H), 7.75–7.86 (m, 2H), 8.05–8.07 (m, 1H) ppm. IR (KBr): 3300, 2980, 1635, 1540, 1370, 1125, 965, 780. $\alpha_D = +126$ ($CHCl_3$, c = 1, 30°C). Anal. calcd for $C_{14}H_{17}NO$ (213.28): C 78.84, H 7.09, N 6.57%. Found: C 79.06, H 7.09, N 6.64%.

(*S*)-N-Acetyl-1-(9′)-anthracenylethylamine (14)

To the solution of 400 mg (1.8 mmol) of *rac*-9-anthracenylethylamine[14] in 200 mL of *n*-hexane and 100 mL of *iso*-propylacetate, 2.2 g of lipase from *Candida antarctica* (Altus Co.) were added at 30°C. After 74 hours, the reaction mixture was filtered and evaporated. The oily residue was purified on a silicagel column using dichloromethanemethanol (9:1) as eluens. (*S*)-(−)-N-Acetyl-anthracenylethylamine was obtained in 40% yield (157 mg) and > 96% optical purity. Optical purity was determined on a Chiralcel OD-R

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

column, using 90% methanol, detection at 254 nm. $[\alpha]_D = -91$ ($CHCl_3$, c = 1, 30°C). To confirm absolute configuration remaining, optically enriched (+)-amine was converted to its camphanyl derivatives; its spectral properties were compared with literature data and revealed formation of **6** with (1′*R*)-configuration[2,15]. M.p. 235–237°C. ^{13}C NMR ($CDCl_3$): 21.4, 23.1, 44.8, 123.9, 124.8, 126.1, 128.0, 128.8, 129.7, 131.7, 133.8, 169.8. ^{1}H NMR ($CDCl_3$): 1.91 (d, J = 8Hz, 3H), 1.92 (s, 3H), 6.56–6.61 (m, 2H), 7.42–7.54 (m, 4H), 7.99–8.02 (m, 2H), 8.41–8.44 (m, 3H). IR (KBr): 3260, 3060, 1630, 1550, 1450, 1380, 890, 730. Anal. calcd for $C_{18}H_{21}NO$ (263.33): C 82.10, H 6.51, N 5.32%. Found: C 82.05, H 6.39, N 5.31%.

Camphanic Acid Methylamide (15)

To the solution of 216 mg (1.0 mmol) of (−)-camphanic acid chloride in 20 mL of dichloromethane 2 mL of 40% aq. methylamine were added. The reaction mixture was stirred at room temperature for two hours, layers were separated, organic layer was washed with 5% HCl, saturated bicarbonate solution, and water. Upon drying end evaporation of solvent 190 mg (90%) of camphanic acid methylamide were obtained; 99% pure by GC. M.p. 127–128°C. ^{13}C NMR ($CDCl_3$): 9.4, 16.2, 16.5, 25.5, 28.8, 30.0, 53.6, 55.0, 92.5, 167.6, 178.8. ^{1}H NMR ($CDCl_3$): 0.90 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.63–1.73 (m, 1H), 1.85–2.00 (m, 2H), 2.49–2.60 (m, 1H), 2.88 (d, J = 5 Hz, 3H), 6.62 (brs, 1H). IR; νCO (lactone) 1798 cm^{-1} in CCl_4, and 1788 cm^{-1} in MeCN, NH 3452 cm^{-1}, 3411 cm^{-1} (broad) in the same solvents; (KBr): 3400, 2960, 1780, 1675, 1535, 1270, 1160, 715. $[\alpha]_D = -44$ ($CHCl_3$, c = 1, 30°C). Mol mass calcd for $C_{11}H_{17}NO_3$ 211.12084. Found; 211.12025, corresp. to C 62.54, H B.11, N 6.63.

MM2 Calculations were performed using ChemOffice Ultra 4.5, *CambridgeSoft Corp*., Massachusetts (USA), Serial # 496311. The convergence criteria for the gradient of the potential energy surface (RMS gradient) was set to 0.1.

ACKNOWLEDGMENTS

The authors are indebted to Dr. A. Lesac for her help with MM2 calculations. M. Hollosi acknowledges the support of OTKA TO22913, and V. Šunjic the support of Ministry of Science of Republic of Croatia, Project 980701. This collaboration was also supported through the co-operation between the Eötvös University of Budapest and University of Zagreb.

REFERENCES

1. Klaic, B.; Raza, Z.; Marcec, R.; Vinkovic, V.; Šunjic, V. Spectrosc. Lett. **1995**, *28*, 683.
2. Hameršak, Z.; Selestrin, A.; Lesac, A.; Šunjic, V. Tetrahedron: Asymmetry **1998**, *9*, 1891.
3. Comisso, G.; Sega, A.; Lisini, A.; Šunjic, V. Croat. Chem. Acta **1981**, *54*, 375.
4. Rusman, S.; Kojic-Prodic, B.; Ružic-Toroš, Ž.; Šunjic, V.; Lenstra, A. H. T. Croat. Chem. Acta **1990**, *63*, 701.
5. Kojic-Prodic, B.; Marcec. R.; Nigovic, B.; Raza, Z.; Šunjic, V. Tetrahedron: Asymmetry **1992**, *3*, 1.
6. Kirin, I.S.; Vinkovic, V. Šunjic, V. Chirality **1995**, *7*, 115.
7. Majer, Zs.; Hollosi, M.; Kirin, I.S.; Šunjic, V. Chirality **1996**, *8*, 244.
8. Somogyi, L.; Huszthy, P.; Bradshaw, J.S.; Izatt, R.M.; Hollosi, M. Chirality **1997**, *9*, 945.
9. Smith, H.E. In *Circular Dichroism, Principles and Application* Nakanishi, K., Berova, N., Woody, R.W., Eds.; VCH Publishers Inc.: 1994; 413–442.
10. Sandstrom, J. *ibid.* pp. 443–472.
11. Eliel, E.L., Wilen, S.H. *Stereochemistry of Organic Compounds*, Wiley Intersc.: 1994; 615–629.
12. Šunjic, V.; Kajfež, F.; Oklobdžija M.; Štromar, M. Croat. Chem. Acta **1973**, *45*, 569.
13. Götze, J. Ber. Deutsch. Chem. Ges. **1938**, 2289.
14. Martynoff, M.; Chanvin, M.; Crumez. M.; Lefevre, N. Bull. Soc. Chim. Fr. **1958**, 164.
15. When this manuscript was completed, an independent assignment of (1′*R*)-configuration to (+)-1-(9′-anthracenyl)ethylamine was reported, Iuliano, A.; Voir, I.; Salvadori, P. J. Org. Chem. **1999**, *64*, 5754.

Received July 4, 2000
Accepted August 1, 2001

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Request Permission or Order Reprints Instantly!