CROATICA CHEMICA ACTA CCACAA **74** (3) 707–724 (2001)

ISSN-0011-1643
CCA-2760 *Original Scientific Paper*

Diastereoselective Aldol Reaction of 7-Bromo-5-pyrido-1,4-benzodiazepin-2-one; Relative and Absolute Configuration of All Stereoisomers*

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Received April 10, 2001; revised June 7, 2001; accepted June 8, 2001

Aldol reaction of C(3) carbanion of 7-bromo-5-pyrido-1,4-benzodiazepin-2-one (**1**) with representative aliphatic and aromatic aldehydes and ketones afforded racemic mixtures *syn*/*anti*-7-bromo-3-(1′-hydroxy-1′-phenylmethyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (**2**/**3**), *syn*/*anti*-7-bromo-3-(1′-hydroxy-1′-phenylethyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (**4**/**5**) and *syn*/*anti*-7-bromo-3-(1′-hydroxy-2′-methylpropyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (**6**/**7**) with 60–85% diastereoselectivity. For prevailing diastereomeric racemates (±)-**2** and (±)-**4**, *syn* relative configuration is deduced, whereas the prevailing diastereomer (±)-**7** has *anti* configuration. Configurational assignment is based on ^{1}H NMR data and X-ray structure analysis, and the origin of inversion of diastereoselectivity is discussed. Racemic mixtures were separated on chiral HPLC column, and on the basis of the CD spectra (3*R*) absolute configuration was determined for (+)-enantiomers, and (3*S*) configuration for (–)-enantiomers. Consequently, (3*R*,1′*S*) configuration is assigned to *syn*-(+)-enantiomers and (3*R*,1′*R*)-configuration to *anti*-(+)-enantiomers. In an attempt to use enantiomerically pure com-

* Dedicated to Professor Smiljko Ašperger on the occasion of his 80th birthday.

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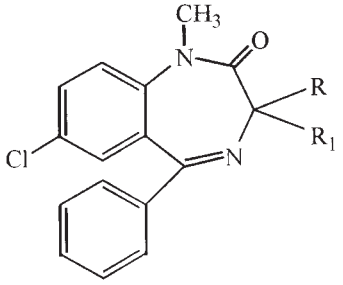
pounds **2**–**7** as catalysts in asymmetric alkylation of benzaldehyde by diethylzinc, these ligands proved chemically and configurationally unstable.

Key words: 1,4-benzodiazepines, enantioseparation, HPLC chiral chromatography, relative and absolute configuration.

INTRODUCTION

Rational design and synthesis of novel chiral molecules directed towards asymmetric synthesis or asymmetric molecular recognition is one of the most important goals in modern organic chemistry. In this context, a great number of enantiomerically pure compounds (EPC), or homochiral molecules, containing heteroatoms such as nitrogen, oxygen, sulphur or phosphorus as electron-pair donors, have been developed as asymmetric controllers.[1–3] These molecules are particularly effective in enantioselective (asymmetric) syntheses when applied as chiral ligands in catalytic organometallic complexes.[4–6] Such complexes catalyze a wide variety of reactions, though formation of a C–C bond in enantioselective fashion still represents one of the principal targets in this field.[7,8]

We have recently reported successful lipase catalyzed kinetic resolution of racemic 3-substituted-5-phenyl-1,4-benzodiazepines of the general formulae **Ib**–**d**,[9,10] and we have also completed a study of diastereoselective aldol reaction of the carbanion of the parent unsubstituted compound **Ia**.[11]



	R	R_1
Ia	H	H
Ib	H	CH_2OH
Ic	CH_3	CH_2OH
Id	$PhCH_2$	CH_2OH
Ie	H	CH(OH)Ph (*syn*)
If	H	CH(OH)Ph (*anti*)

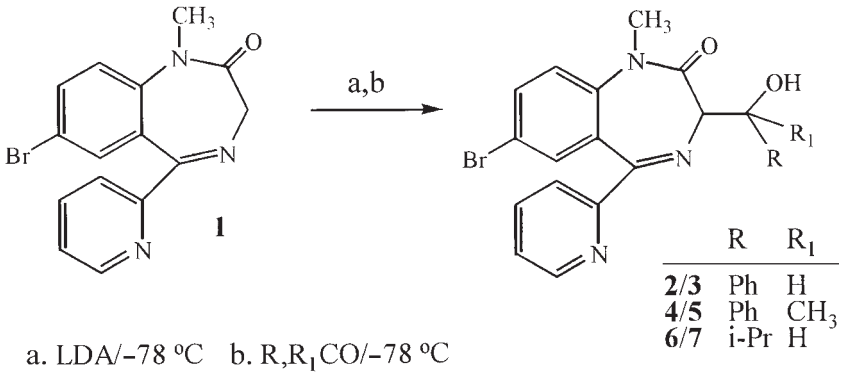
Prompted by these results, we have undertaken a study of the aldol reaction of 7-bromo-5-pyrido-1,4-benzodiazepin-2-one (**1**) in order to achieve diastereoselectivity in this reaction, separate *syn*/*anti* diastereomeric racemates, and subsequently resolve, by the lipase catalyzed kinetic resolution,[9,10] single enantiomers of each racemic mixture. Enantiomerically pure target compounds are envisaged as tridentate (N,N,O) ligands in catalytic organometallic complexes, as potentially biologically active compounds or their intermediates.

Herein we report the results of this synthetic study, as well as the determination of relative and absolute configuration of single enantiomers, as well as the first attempt to use some of these homochiral molecules as catalytic tridentate ligands in asymmetric alkylation of benzaldehyde by diethylzinc.

RESULTS AND DISCUSSION

Synthesis and Diastereoselectivity

Carbanion was generated by addition of compound **1** onto the *in situ* prepared lithium-diisopropylamide (LDA) at –78 °C. Its formation, and consumption on addition of carbonyl compound can be easily monitored by the appearance and disappearance of deep-red color in solution. Benzaldehyde, acetophenone or isobutyraldehyde were used as the carbonyl counterpart in aldol reaction, Scheme 1; preparative results are given in Table I.



Scheme 1.

TABLE I

Aldol reaction of 5-pyrido-1,4-benzodiazepin-2-one **1**

Products	R,R_1CO		HPLC ratio[a]	Yield
	R	R_1		%
2/3	Ph	H	80 : 20	68
4/5	Ph	CH_3	80 : 20	44
6/7	i-Pr	H	7 : 93	50

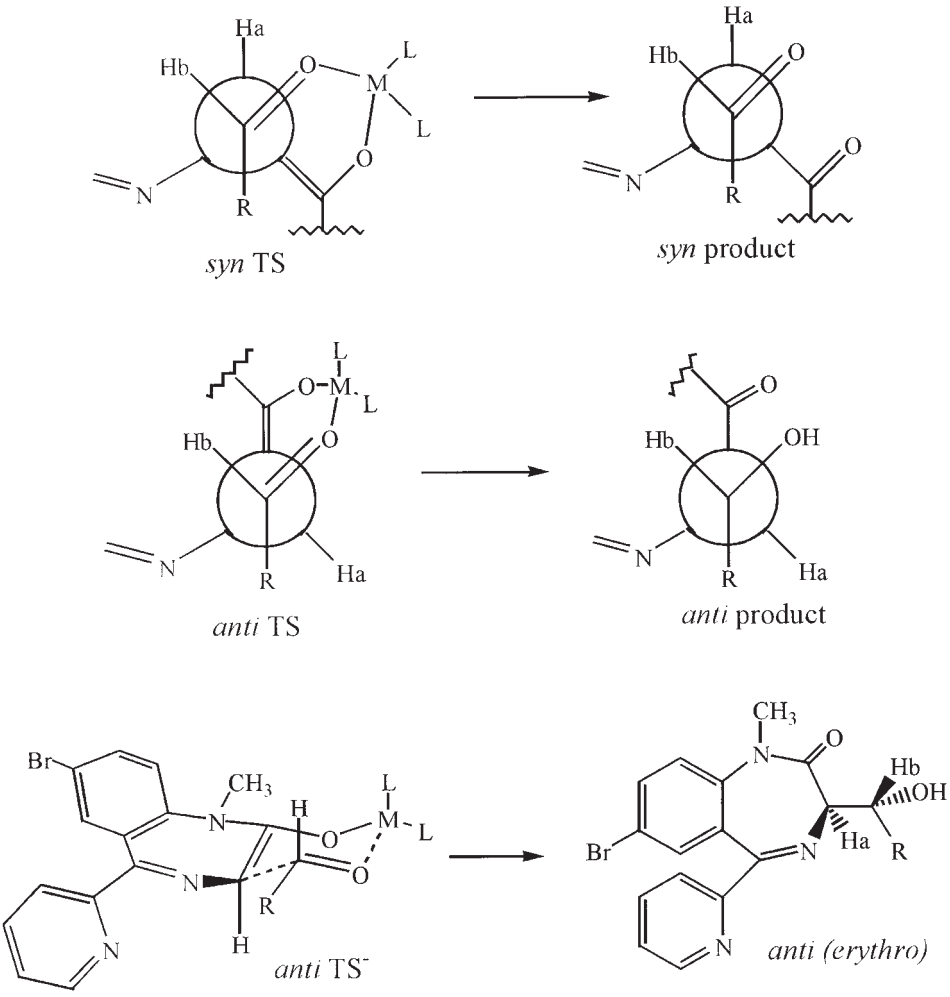
[a] First eluated *syn*-isomer, second eluated *anti*-isomer.

Diastereoselectivity of the aldol reaction of **1** with a representative aromatic aldehyde and ketone was nearly the same, and notably lower than with aliphatic aldehyde. Interestingly, the direction of diastereoselectivity for **2**/**3** and **4**/**5** is opposite to that for **6**/**7**, and to that observed[11] for 5-phenyl congener (**Ia**) in reactions with a series of aromatic and aliphatic aldehydes. This indicates that enolate derived from **1** is more reactive than that derived from **Ia**, and it follows from the observation that compound **1** is more reactive than **Ia** in the aldol reaction with formaldehyde, the least crowded aldehyde.[9a] Fast formation of disubstituted 3,3-dihydroxymethyl derivative of **1** was observed,[12] which either reflects higher reactivity of its enolate as compared to **Ia**, or the reversibility of aldol reaction, which is common for stabilized enolates.[13]

Two diastereomeric racemates, (±)-**2** and (±)-**3**, were obainted by chromatographic separation on silica gel column, whereas for the other two pairs, **4**/**5** and **6**/**7**, only the prevailing diastereomers (±)-**4** and (±)-**7** were isolated for further studies. According to the Karplus equation,[14a,b] *syn* configuration can be assigned to compound **2** $J_{a,b}$ = 4.5 Hz, and Ha–C–C–Hb dihedral angle of *ca.* 40°, whereas compound **3** exhibits twice as large $J_{a,b}$ constant (9.0 Hz), and possesses *anti* configuration with a *ca.* 160° Ha–C–C–Hb dihedral angle. Analogous *syn*/*anti* assignment for diastereomeric racemates **Ie** and **If** was confirmed in a straightforward way by X-ray structure analysis.[11] Correlation of relative NMR data for (±)-**2** and (±)-**3** with those of **If** and **Ie**, for which relative configurations are determined by X-ray structure analysis, strongly supports the assignment of their respective *syn* and *anti* configurations.

The results with 5-pyrido-1,4-benzodiazepine **1** points to the conclusion that the prevailing *syn* diastereomers (±)-**2**, (±)-**4** and *anti* diastereomer (±)-**7** are products of the kinetic control, Scheme 2. Cyclic *syn* TS‡ is characterized by the π-systems overlap when R = Ph, and more crowding if R = i-Bu than Ph, but if there is Me in place of Hb (acetophenone), there is no more crowding, though open-chain mechanims also preferentally lead to the *syn* product.[13] Cyclic *anti* TS‡ is characterised by the absence of π-overlap when R = Ph, and less crowding if there is i-Bu than Ph, but if there is Me in place of Hb, there is more crowding. Assuming the kinetic control of *syn*/*anti* diastereomeric ratio **4**/**5**, and higher steric congestion of the phenyl over methyl group, as recently confirmed also by CD spectroscopy,[21] *syn* configuration can be deduced for the prevailing diastereomer (±)-**4**, and *anti* for minor diastereomer (±)-**5**.

Definite proof of relative *syn* configuration for the prevailing diastereomeric racemate (±)-**4** and *anti* configuration for (±)-**7** came from their X-ray structure analysis (described below).



Scheme 2.

Description of the Molecular and Crystal Structures of ***4*** *and* ***7***

The structures of **4** and **7** with the atom numbering and intramolecular hydrogen bonds are shown in Figures 1 and 2. Hydrogen bonds are listed in Table II. Hydrogen bond pattern in the crystal packing of **7** is shown in Figure 3.

Both crystal structures are racemic mixtures: (3*R*,12*S*) and (3*S*,12*R*) were encountered in **4**, whereas (3*R*,12*R*) and (3*S*,12*S*) enantiomers were found in **7**. However, **4** crystallizes in the triclinic noncentrosymmetric space group

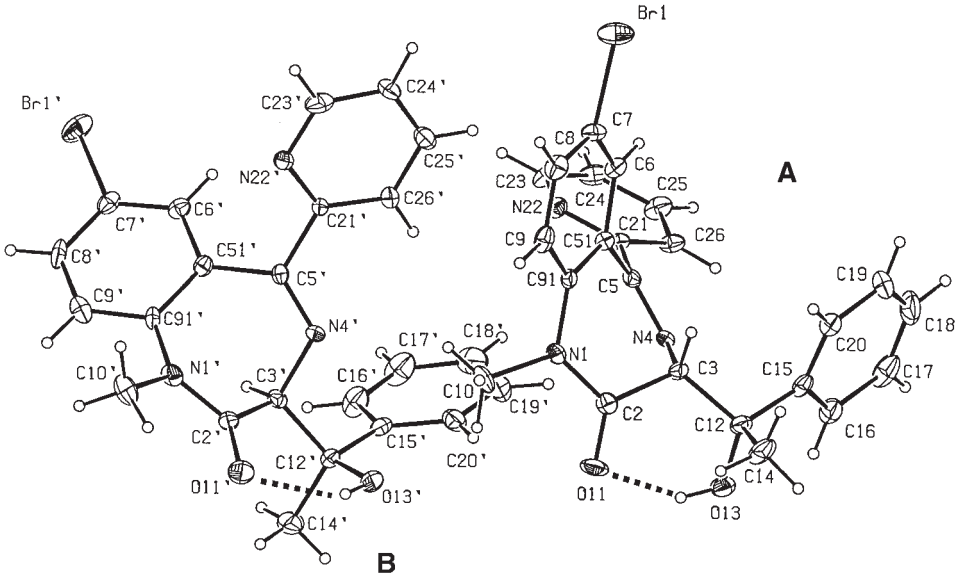


Figure 1. ORTEP[29] of **4** (**A** and **B**) with the atom numbering. Intramolecular hydrogen bond is shown. Thermal ellipsoides are scaled at the 20% level.

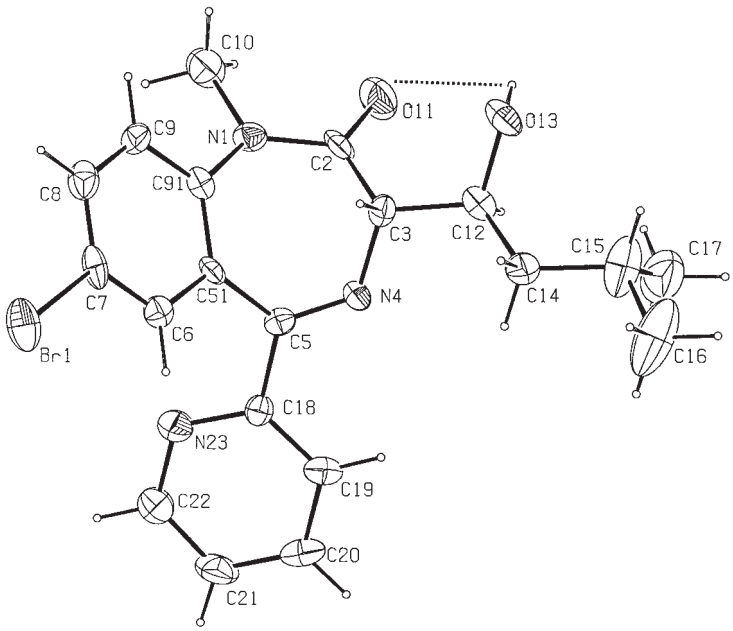


Figure 2. ORTEP view of **7** with the atom numbering. Intramolecular hydrogen bond is shown. Thermal ellipsoides are scaled at the 30% level.

TABLE II

Hydrogen bonds in the crystals of **4** and **7**[a,b]

	D···A / Å	D–H / Å	H···A / Å	D–H···A / °	Symmetry oper. on A
4					
O13–H13 ··· O11	2.742(9)	0.820	2.064	139.85	–
O13′–H13′ ··· O11′	2.718(9)	0.820	2.062	136.72	–
7					
O13–H13–O11	2.888(8)	0.820	2.537	107.21	–
O13–H13–O11[i]	2.814(8)	0.820	2.082	148.40	*–x*, 1–*y*, *–z*

[a] D, donor; A, acceptor.
[b] Estimated standard deviations given in parentheses.

TABLE III

Selected torsional angles / ° in **4**[a,b]

	A	**B**
C14–C12–C15–C20	–61.6(10)	–123.1(8)
C14–C12–C15–C16	119.7(8)	58.9(10)
O13–C12–C15–C20	179.0(8)	–3.8(9)
C3–C12–C15–C16	–118.9(8)	–62.2(10)
O13–C12–C15–C16	0.3(10)	178.2(7)
C3–C12–C15–C20	59.8(10)	115.8(8)

[a] **A**, **B**; crystallographically independent molecules.
[b] Estimated standard deviations given in parentheses.

with two crystalographically independent molecules **A** and **B**. In the crystal, these two molecules reveal slightly different conformations, Table III. 1,4-Benzodiazepin-2-one rings reveal a *boat* conformation with an approximate C_s symmetry.

In compound **4**, the relative configuration about the bond C3–C12 connecting two stereogenic centers of different absolute configurations (3*R*,12*S* and its enantiomeric pair) is *syn* [O13–C12–C3–N4, –66.3(7)° for **A**, and 64.6(7) for **B**]. In compound **7**, C3–C12 bond connects two stereogenic centers of the same absolute configuration (3*R*,12*R* and its enantiomeric pair) and the relative configuration is *anti* [O13–C12–C3–N4, 176.8(6)°]. Never-

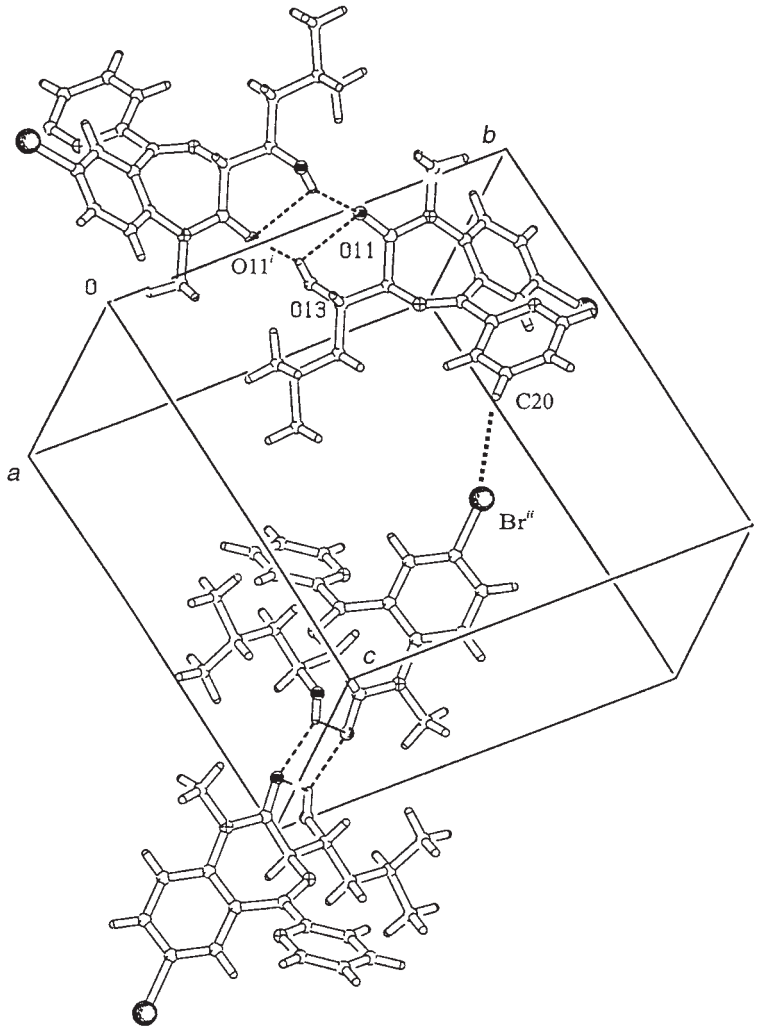


Figure 3. Crystal packing of **7**. Dimers related by an inversion symmetry through O···H···O hydrogen bonds are connected into an infinite chain through a weak C–H···Br interaction (symmetry code II; 0.5–*x*, *y*–0.5, 1–*z*).

theless, the proton donor groups (hydroxyl O13–H) in both compounds are oriented towards carbonyl O11, and the intramolecular hydrogen bond is formed. In addition, hydroxyl O13–H in **7** acts also as a donor in an intermolecular hydrogen bond to a carbonyl oxygen in the neighboring molecule, thus forming a centrosymmetric dimer through bifurcated hydrogen bonding arrangement. These dimers are connected into an infinite chain through a weak C–H··Br interaction (Br··H20 3.219 Å), Figure 3.

Resolution and Absolute Configuration of the Enantiomers

All attempts at lipase catalyzed kinetic resolution of the chromatographically separated racemic mixtures **2**–**4** and **7** have failed. Out of *ca.* 30 microbial and fungal lipases previously tested in enantioselective acetylation of rac 5-phenyl-3-hydroxymethyl-1,4-benzodiazepines,[9,10] nine have been selected for screening; *Pseudomonas cepacia, Pseudomonas species, Pseudomonas fluorescens, Candida cylindracea*, Lipozym IM, Novozym 435, *Aspergillus niger, Penicillium cammemberti*, and pig pancreas lipase. No lipase proved active in acetylation of **2**–**4** and **7**. Large steric crowd in these secondary and tertiary alcohols seems to be the origin of the failed acceptance by lipases, since highly effective resolution was achieved by acetylation of **Ib**,[9] and moderately enantioselective acetylation of **Ic** and **Id**,[10] by *Mucor mieihei* lipase (Lipozyme IM),[9] and *Candida antarctica* (Novozym 435) lipase,[10b] respectively.

Enantioseparation was then attempted by screening some commercial and in-house prepared chiral HPLC columns,[16a,b,17] and Chiralpak AS column was selected as the most effective. This column separated all racemates to the base line and proved useful for preparative separation of enantiomers on the milligram scale, see Experimental. It is interesting to note that (–)-enantiomers of *syn* diastereomers **2** and **4** were slower running on this chiral column, whereas (+)-enantiomer of *anti* diastereomer **7** was slower running. This is not surprising in view of the structure of the chiral stationary phase in Chiralpak AS column; it comprises amylose carbamate of (+)-phenylethylisocyanate, which provides a number of carbamate groups with phenyl ring on the stereogenic center, contributing to chiral recognition.[17] In **2** and **4**, the aromatic systems are *syn* and shield one π-face of each other, and therefore they offer less π-interaction space for the phenyl rings of phenylcarbamate moiety than **7**, where all π-faces are exposed to the chiral phase in the column.

Slower running enantiomers were taken for chiroptical studies, and the faster running ones were used as ligands in the catalytic experiments. In order to determine the absolute configuration of all stereoisomers, CD spectra of the slower running enantiomers of **2**–**4** and **7** were determined, Figure 4.

As repeatedly shown by us,[18a,b] and others,[19,20] the absolute configuration at the stereogenic center (C3) can be deduced for 3-substituted 1,4-benzodiazepines from their CD spectra. For (–)-**2**, a strong positive Cotton effect (bisignate curve or couplet), with negative and positive extrema at 260 nm and 234 nm, is observed. Since the large (C3)–CH(OH)Ph group is placed in pseudoeqautorial position, and coupled chromophores possess *M*-absolute

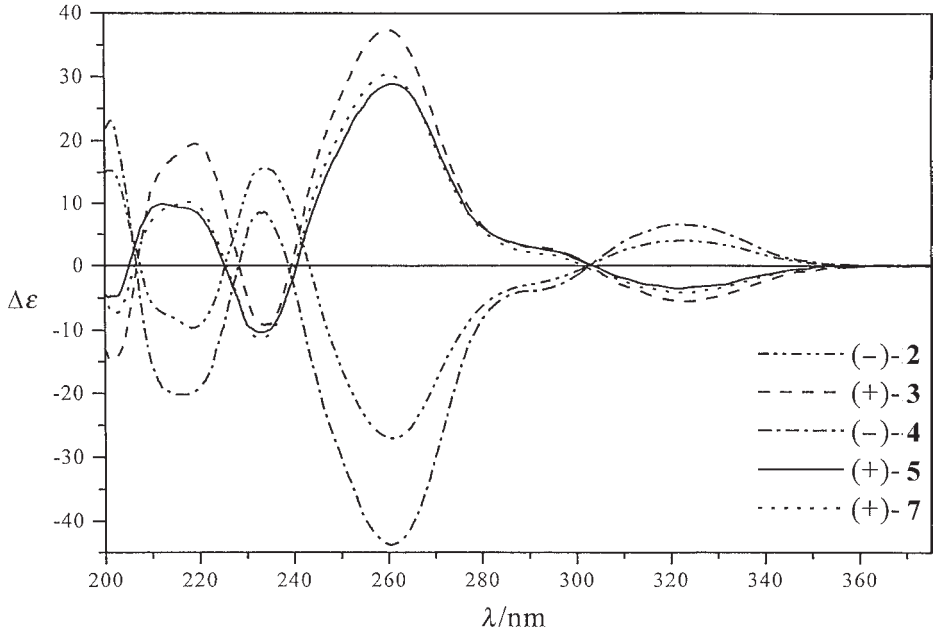


Figure 4. CD spectra of (–)-**2**, (+)-**3**, (–)-**4**, (+)-**5** and (+)-**7**, in MeCN.

conformation, (3*R*) absolute configuration can be deduced with complete confidence by observing the stereoformula or Dreiding model.*

In the same way, the absolute configuration at (C3) for (+)-**3** and (+)-**7** is assigned as (3*S*), for (–)-**4** as (3*R*). Since for (–)-**2** and (+)-**3** relative configuration is already determined as *anti* and *syn*, respectively, assignment of the absolute configuration at (C3) reveals absolute configuration at the second stereogenic center; it is (C12*S*) for (–)-**2** and also (C12*S*) for (+)-**3**. Following the same argumentation, absolute configuration of (–)-**4** is assigned as (C3*R*,C12*R*), of (+)-**5** as (C3*S*,C12*S*), and of (+)-**7** as (C3*S*,C12*S*).

It is interesting, however, that CD couplets of (–)-**2** and (+)-**3**, which have opposite configurations at (C3) and the same at (C12), exhibit amplitudes, *i.e.* *A*-values ($A = \Delta\varepsilon_{1max} - \Delta\varepsilon_{2max}$),[21] that differ in intensity by *ca.* 10%; *A* for (–)-**2** and (+)-**3** amounting is –42.3 and +46.6, respectively. Since in the *syn* diastereomer, rotation around (C3)–(C12) bond is more restricted

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* Note. In this paper we now use, contrary to the common practice in our previous papers,[18a–c] and those of other authors,[19a–d] atoms N(1)–C(2)–C(3)–N(4) instead of C(2)–C(3)–N(4)–C(5) to define the torsional angle Φ, Figure 5. According to the present selection, which is in accord with the CIP priority rules, stable absolute conformation of (3*R*) enantiomers with the larger substituent in psudoequatorial position is *M*, while according to the other selection, introduced by the late Prof. G. Snatzke and used by all previous authors, it was assigned as *P*.[20]

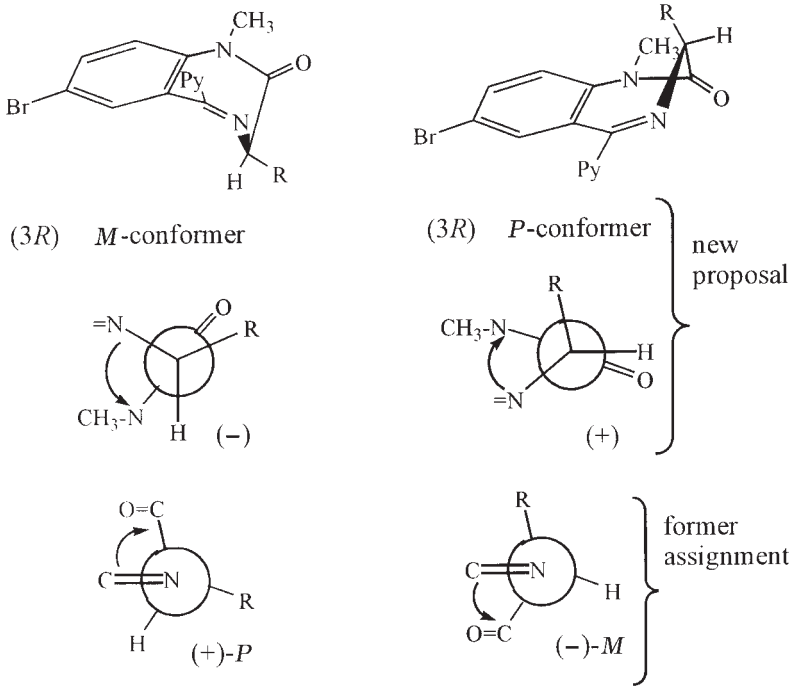
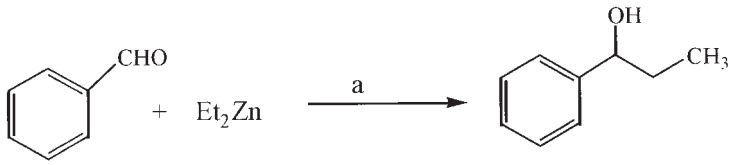


Figure 5. Assignment of *M*/*P* configuration of 1,4-benzodiazepines according to the CIP priority rules.

by stronger intramolecular hydrogen bonding (C12)–OH ··· O=C, it presumably allows another exciton interaction between phenyl groups on (C12) and (C5) atoms. Observation of dreiding models reveals the positive sign of this interaction, which offers a tentative explanation for compensation of the negative CE in the CD of (–)-2.

We have tested optically pure compounds as chiral 1,4-N,O-ligands in enantioselective alkylation of benzaldehyde by Et_2Zn, Scheme 3.



a. chiral ligand, toluene / 0 °C

Scheme 3.

First, we repeated the protocol with (1*R*,2*S*)-*N*-methyl ephedrine as bidentate ligand; 68% e.e. of 1-phenylpropanol at 90% conversion was obtained, as compared to the published data: 64% e.e. at 66% conversion.[22] The results with new ligands were quite disappointing, however; alkylation was slow, 20–40% of benzylalcohol was formed as a side-product; enantioselectivity was 20% with (–)-**2**, 14% with (+)-**3**, and negligible with (–)-**4** and (+)-**7**. The origin of the poor catalytic activity of these ligands was traced when stability of the selected ligand (–)-**2** was tested in the presence of Et_2Zn in toluene; enantiomeric purity diminished to 90% after 2 h stirring at 0 °C, and dropped down to 56% after 70 h, accompanied by intensive chemical decomposition. Presumably, Et_2Zn acts as a strong base, causing a retro-aldol reaction and racemization *via* enolization. In this context it is worth noticing that the only bidentate ligand with an amide group as yet used in alkylation by Et_2Zn comprises the neopentyl unit $(CH_3)_3C–CONR_2$, *i.e.* no C–H acidic proton is present on the α-carbon of the amide carbonyl group.[23]

Since optically pure enantiomers of **2** and **3** can be hydrolyzed without loss of optical purity, as we have recently reported on similar racemic substrates,[11] the results reported here offer a new approach to all four enantiomers of phenylserine, α-amino-β-hydroxy acid that plays an essential role as a chiral synthetic building block.[24]

In conclusion, a number of enantiomerically pure derivatives of 3-substituted 5-pyrido-1,4-benzodiazepin-2-one were prepared on the milligram scale, thermodynamic control of diastereoselectivity was established, and absolute configuration of all enantiomers separated using chiral HPLC was determined. If non-chromatographic resolution could be completed, these compounds would be useful intermediates in preparation of α-amino β-hydroxy acids. They proved unstable in the presence of the strong base Et_2Zn when enantioselective alkylation of benzaldehyde was attempted. Preparation of their 2-deoxy congeners avoiding the lactame carbonyl group is envisaged, expecting their high configurational stability eliminating enolization, and better enantioselectivity in asymmetric alkylation.

EXPERIMENTAL

General

IR spectra were run on a Perkin Elmer 297 spectrometer for KBr pallets. ^1H and ^{13}C NMR spectra were obtained with a Varian Gemini XL 300 spectrometer in $CDCl_3$ solutions, δ is given in ppm relative to TMS as internal reference, and J in Hz. HPLC chromatography was performed on a HP 1050 chromatograph with NucleosilC_{18} *RP* (Supelco, 250 × 4.6 mm) reverse phase column, separation was monitored by a HP 1050 UV detector set at 254 nm and connected to a HP 3396A integrator. Enatiomeric

excess (e.e.) was determined for **3**, **4**, **5**, and **7** on a chiral OD-R column (Diacel Co.), using various ratios of 0.5 M $NaClO_4/HClO_4$ (pH = 2) : MeOH. M.p.s were determined on Electrothermal Apparatus, and are not corrected. Optical rotations were obtained with Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell; *c* given in g/100 ml. CD-Spectra were run on a Jasco J-810 spectropolarimeter.

Elemental analyses were performed either by HR/MS, on an Extrel-FTMS 2001DD instrument, or by the combustion method; in both cases HPLC purity of analytical samples was ≥ 99.5%.

All commercial reagents were used as received.

*Aldol Reaction of **1**. General Procedure*

To the solution of $(i\text{-}Pr)_2NH$ (1.65 ml, 12 mmol) in dry THF (20.0 ml), 2.5 M solution of n-BuLi in n-hexane (4.7 ml, 12 mmol) was added under argon at 0 °C. After 15 min stirring at –78 °C, the solution of **1** (3.0 g, 9.1 mmol) in THF (20.0 ml) was added, and after 30 min of stirring, benzaldehyde (2.5 g, 22.0 mmol) was added. After 1 h of stirring, reaction was quenched by addition of 5% aq. hydrochloric acid, adjusting pH to 5–6. Then, the reaction mixture was extracted with CH_2Cl_2 (3 × 50 ml), organic extracts were dried over Na_2SO_4 and evaporated in vacuo on a Büchi rotary evaporator. Diastereomeric ratio **2/3** (80 : 20, at 96% conversion) was determined using the mobile phase $MeOH/H_2O$ (1:1), at a flow rate of 0.8 ml/min. Crude product was crystallized from $CH_2Cl_2/(i\text{-}PrO)_2O$ affording 2.6 g (53%) of pure diastereomer **2**. Mother liquors were evaporated and *anti* isomer was isolated by column chromatography on silicagel (100 g) with $CH_2Cl_2/(i\text{-}PrO)_2O/MeOH/Et_3N$ (50 : 50 : 5.0 : 0.5) as eluent; 0.57 g (15%) of pure isomer **3** was obtained.

syn-*7-Bromo-3-(1′-hydroxy-1′-phenylmethyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**2**)*

M.p. 213–214 °C (decc.). IR ν_{max}/cm^{-1}: 3400, 1670, 1400, 110, 830, 700. ^1H NMR δ/ppm: 3.36 (3H, s), 3.79 (1H, d, J = 4.6 Hz), 4.53 (1H, bs), 5.50 (1H, d, J = 4.4 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.24–7.38 (4H, m), 7.44 (1H, d, J = 2.2 Hz), 7.53 (2H, d, J = 7.2 Hz), 7.62 (1H, dd, $J1$ = 8.7 Hz, $J2$ = 2.3 Hz), 7.82 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.8 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.58 (1H, dd, J_1 = 4.1 Hz, J_2 = 0.8 Hz). ^{13}C NMR δ/ppm: 35.0, 68.1, 72.3, 117.0, 123.2, 123.9, 124.9, 127.3, 127.5, 128.0, 129.4, 133.4, 134.4, 136.9, 140.8, 142.1, 148.6, 155.2, 167.2, 169.5. HR/MS m/z calcd. for $C_{22}H_{18}N_3O_2Br^+H^+$ ($M\text{-}H^+$): 436.0655; found: 436.0592.

Ca. 30 mg of (±)-**2** was separated on Chiralpak AS column with n-hexane/i-propanol (25 : 75) as eluent. R_t for (+)-**2**: 21.7 min, R_t for (–)-**2**: 31.4 min, $[\alpha]_D = -81.8$ (c = 0.22 g/100 ml, $CHCl_3$).

anti-*7-Bromo-3-(1′-hydroxy-1′-phenylmethyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**3**)*

M.p. 111–113 °C. IR ν_{max}/cm^{-1}: 3450, 1670, 1400, 1330, 1110, 700. ^1H NMR δ/ppm: 3.43 (3H, s), 3.73 (1H, d, J = 9.0 Hz), 3.99 (1H, bs), 5.71 (1H, d, J = 9.0 Hz), 7.23 (1H, d, J = 9.0 Hz), 7.28–7.36 (5H, m), 7.50–7.53 (2H, m), 7.62 (1H, dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz), 7.75 (1H, dt, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.87 (1H, d, J = 7.7 Hz), 8.55 (1H, d, J = 4.3 Hz). ^{13}C NMR δ/ppm: 35.1, 69.2, 73.8, 117.0, 123.1, 123.8, 124.7, 127.3,

127.6, 128.0, 129.3, 133.4, 134.3, 136.8, 140.6, 142.1, 148.5, 155.3, 165.8, 170.4. HR/MS m/z calcd. for $C_{22}H_{18}N_3O_2Br^+H^+$ ($M\text{-}H^+$): 436.0655; found: 436.0654.

Ca. 30 mg of (±)-**3** was separated on Chiralpak AS column with n-hexane/i-propanol (25 : 75) as eluent. R_t for (–)-**3**: 12.2 min, R_t for (+)-**3**: 16.3 min, $[\alpha]_D$ = +161 (c = 0.14 g/100 ml $CHCl_3$).

syn-*7-Bromo-3-(1′-hydroxy-1′-phenylethyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**4**)*

Starting from **1** (1.0 g, 3.0 mmol) and acetophenone (0.36 g, 3.0 mmol), the reaction was performed as described above. At 60% conversion, the reaction was quenched and the crude product was purified using the same chromatographic conditions as described above. 405 mg of mixture **4**/**5** and 190 mg of pure **4** was obtained; yield 44%. M.p. 201–203 °C (decc). IR ν_{max}/cm^{-1}: 3460, 1660, 1330, 1110, 880, 700. ^{1}H NMR δ/ppm: 1.80 (s, 3H), 3.43 (3H, s), 3.79 (1H, s), 5.52 (1H, bs), 7.21–7.38 (7H, m), 7.49–7.57 (2H, m), 7.65–7.71 (2H, m), 8.52 (1H, dd, J_1 = 4.6 Hz, J_2 = 0.5 Hz). ^{13}C NMR δ/ppm: 27.6, 35.2, 69.6, 74.8, 117.4, 123.5, 124.3, 124.8, 125.7, 126.5, 127.9, 129.4, 133.4, 134.5, 137.0, 142.2, 145.6, 148.4, 155.5, 166.5, 170.0.

Anal. calcd. for $C_{23}H_{20}N_3O_2Br$ (M_r = 450.33): C 61.34, H 4.48, N 9.33%; found: C 61.82, H 4.88, N 9.36%.

Ca. 30 mg of (±)-**4** was separated on Chiralpak AS column with n-hexane/i-propanol (15 : 85) as eluent. R_t for (+)-**4**: 12.4 min, R_t for (–)-**4**: 19.7 min, $[\alpha]_D$ = –158 (c = 0.31 g/100 ml $CHCl_3$).

anti-*7-Bromo-3-(1′-hydroxy-2′-methylpropyl)-1-methyl-5-(2′-pyridyl)-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**7**)*

Starting from **1** (1.0 g, 3.0 mmol) and isobutyraldehyde (0.48 ml, 3.0 mmol), the reaction was completed in 30 min at –78 °C. Crude product was separated and purified using standard chromatographic conditions to give 230 mg mixture of **6**/**7** and 440 mg of pure **7**; yield 50%, m.p. 185–187 °C (decc). IR ν_{max}/cm^{-1}: 3450, 1670, 1330, 820, 700. ^{1}H NMR δ/ppm: 0.98 (d, 3H), J = 6.7 Hz), 1.04 (3H, d, J = 6.4 Hz), 1.34 (1H, m), 1.54 (1H, m), 2.01 (1H, m), 3.39 (3H, s), 3.41 (1H, d, J = 6.5 Hz), 4.66 (1H, m), 7.22 (1H, d, J = 9.0 Hz), 7.37 (1H, m), 7.53 (1H, s), 7.64 (1H, d, J = 8.7 Hz), 7.83 (1H, t, J = 7.7 Hz), 8.15 (1H, d, J = 7.9 Hz), 8.60 (1H, d, J = 4.3 Hz). ^{13}C NMR δ/ppm: 21.6, 23.9, 24.2, 34.9, 42.2, 68.6, 69.9, 117.0, 123.2, 123.7, 124.8, 129.7, 133.4, 134.4, 136.9, 142.3, 148.7, 155.3, 166.0, 170.7.

Anal. calcd. for $C_{20}H_{22}N_3O_2Br$ (M_r = 416.31): C 57.70, H 5.33, N 10.09; found: C 57.94, H 5.06, N 9.93%.

Ca. 20 mg of (±)-**7** was separated on Chiralpak AS column with n-hexane/i-propanol (30 : 70) as eluent. R_t for (–)-**7**: 7.5 min, R_t for (+)-**7**: 12.6 min, $[\alpha]_D$ = + 164 (c = 0.28 g/100 ml $CHCl_3$).

Catalytic Addition of Zn(Et)$_2$ on Benzaldehyde. General Procedure

1,4-Benzodiazepine ligand (2.5 mmol) was dissolved in abs. dry toluene (0.5 ml) under argon, and 1 M solution of $Zn(Et)_2$ (1.0 ml, 1.0 mmol) was added. After 15 min

TABLE IV

Crystallographic data, structure solution and refinement of compounds **4** and **7**

	4	**7**
Molecular formula	$C_{23}H_{20}N_3O_2Br$	$C_{20}H_{22}N_3O_2Br$
M_r	450.32	416.31
Crystal system	triclinic	monoclinic
Space group	$P1$	$P2_1/a$
a / Å	8.372 (3)	9.560 (3)
b / Å	10.92 (2)	14.000(2)
c / Å	11.880 (10)	14.685(2)
α / °	74.40 (10)	90.00
β / °	84.39(5)	95.96(3)
γ / °	78.56(4)	90.00
V / Å^3	1024(2)	1954.2(9)
Z	2	4
F (000)	460	856
D_x / g cm^{-3}	1.461 (4)	1.415(2)
μ (Mo-Kα) / mm^{-1}	2.03	2.12
Absorption correction	Ψ-scan	no correction
Total data collected	4388	4315
Unique data	4388	3975
Observed data [criterion]	2250 [$I > 2\sigma(I)$]	1026 [$I > 2\sigma(I)$]
R_{int}	0.0775	0.0555
θ_{max} / °	26.29	26.38
R_1 [F_o>4$\sigma(F_o)$]	0.042	0.060
wR_2 (F^2), all data	0.1012	0.1473
Goodness of fit, S	0.958	0.863
Number of refined variables	530	240
$\Delta\rho_{max}$, $\Delta\rho_{min}$ / e Å^{-3}	0.38, –0.48	0.34, –0.58
Data reduction program	HELENA[24]	HELENA
Structure solution program	SIR97[25]	SIR97
Struct. refinement program	SHELXL97[26]	SHELXL97
Preparation of material for publication (program)	PLATON98[27]	PLATON98

stirring at 0 °C, solution of benzaldehyde (52 mg, 0.5 mmol) in abs. toluene (0.5 ml) was added. After 24 h stirring at ambient temperature, 5.0 ml of 1 M HCl (aq) was added, the reaction mixture was extracted with CH_2Cl_2, and the extract was dried overnight. After evaporation of the solvent, conversion was determined by GC analysis (HP-17 column, temperature gradient 70–150 °C, at 5 °C/min), and e.e. was determined by HPLC (Chirlacel OD-H column, n-hexane/i-PrOH (95 : 5) as mobile phase).

*X-ray Analysis of **4** and **7***

Compounds **4** and **7** were crystallized from a mixture of ethanol and dichloromethane (vol. ratio 1:1), with a few drops of THF, at 4 °C. Table IV summarizes the crystal data and experimental details of data collection, refinement and the software used. The data were corrected for Lorentz and polarization effects. The crystal structure determination of **4** revealed two molecules (**A** and **B**) in the asymmetric unit. The overall conformations of **A** and **B** are slightly different, with the opposite chirality at the stereogenic centers (*S*,*R* and *R*,*S*) forming a racemate in the triclinic noncentrosymmetric space group. All H-atoms were calculated on stereochemical grounds and subsequently refined using the SHELXL riding model. Atomic scattering factors and anomalous dispersion values for bromine were those included in SHELX97.

Supplementary materials. – Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre at deposition Nos. CCDC-159563 and CCDC-159564. 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).

Acknowledgements. – The authors thank Dr. D. Srzić and Mr. Z. Marinić, both of the Ruđer Bošković Institute, for providing HR/MS and NMR spectra, respectively. The authors from IRB acknowledge financial support by the Ministry of Science and Technology of the Republic Croatia (Grants Nos. 980701 and 980608).

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SAŽETAK

Dijastereoselektivna aldolska reakcija 7-brom-5-pirido-1,4-benzodiazepin-2-ona; relativne i apsolutne konfiguracije svih stereoizomera

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Aldolska reakcija C(3) karbaniona 7-brom-5-pirido-1,4-benzodiazepin-2-ona (**1**) s predstavnicima alifatskih i aromatskih aldehida i ketona dala je racemične smjese *syn*/*anti*-7-brom-3-(1′-hidroksi-1′-fenilmetil)-1-metil-5-(2′-piridil)-2,3-dihidro-1*H*-1,4-benzodiazepin-2-ona (**2**/**3**), *syn*/*anti*-7-brom-3-(1′-hidroksi-1′-feniletil)-1-metil-5-(2′-piridil)-2,3-dihidro-1*H*-1,4-benzodiazepin-2-ona (**4**/**5**) i *syn*/*anti*-7-brom-3-(1′-hidroksi-2′-metilpropil)-1-metil-5-(2′-piridil)-2,3-dihidro-1*H*-1,4-benzodiazepin-2-ona (**6**/**7**) s 60–85%-tnom dijastereoselektivnošću. Utvrđena je *syn* relativna konfiguracija za pretežno nastale dijastereomere racemata (±)-**2** i (±)-**4**, dok pretežni dijastereomer (±)-**7** posjeduje *anti*-konfiguraciju. Određivanje konfiguracije zasnovano je na podacima ^{1}H NMR i kristalografske strukturne analize, i razmatra se uzrok inverzije dijastereoselektivnosti. Enantiomeri su razdvojeni na kiralnim HPLC kolonama. Na temelju spektara CD određena je apsolutna konfiguracija (3*R*) za (+)-enantiomere, a konfiguracija (3*S*) za (–)-enantiomere. Prema tome, konfiguracija *anti*-(+)-enantiomera je (3*R*,1'*S*), a konfiguracija *syn*-(+)-enantiomera je (3*R*,1'*R*). Pri pokušaju primjene enantiomerno čistih spojeva **2**–**7** kao katalizatora za enantioselektivnu alkilaciju benzaldehida dietilcinkom, ti su se ligandi pokazali kemijski i konfiguracijski nestabilnima.