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

Maja Majerić-Elenkov, a Dinko Žiher, b Aleksandar Višnjevac, a Zdenko Hameršak, a Biserka Kajić-Prodić, a and Vitomir Šunjć a,**

a Ruder Bošković Institute, P.O. Box 180, Bijenička 54, 10002 Zagreb, Croatia

b PLIVA d.d., Research and Development, Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia

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-1H-1,4-benzodiazepin-2-one (2/3), syn/anti-7-bromo-3-(1'-hydroxy-1'-phenylethyl)-1-methyl-5-(2'-pyridyl)-2,3-dihydro-1H-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-1H-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 1H 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 (3R) absolute configuration was determined for (+)-enantiomers, and (3S) configuration for (−)-enantiomers. Consequently, (3R,1'S) configuration is assigned to syn-(+)-enantiomers and (3R,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.
** Author to whom correspondence should be addressed. (E-mail: sunjic@rudjer.irb.hr)
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 formulæ 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

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 \textit{in situ} prepared lithium-diisopropylamide (LDA) at $-78 \, ^\circ\text{C}$. 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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{Scheme 1.}
\end{figure}

\begin{table}
\centering
\caption{Aldol reaction of 5-pyrido-1,4-benzodiazepin-2-one 1}
\begin{tabular}{lcccc}
\hline
Products & RR1CO & HPLC & Yield \\
& & ratio\textsuperscript{a} & \% \\
\hline
2/3 & Ph & H & 80 : 20 & 68 \\
4/5 & Ph & CH\textsubscript{3} & 80 : 20 & 44 \\
6/7 & i-Pr & H & 7 : 93 & 50 \\
\hline
\end{tabular}
\textsuperscript{a} First eluted \textit{syn}-isomer, second eluted \textit{anti}-isomer.
\end{table}
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\textsuperscript{11} for 5-phenyl congeners (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.\textsuperscript{9a} Fast formation of disubstituted 3,3-dihydroxymethyl derivative of 1 was observed,\textsuperscript{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.\textsuperscript{13}

Two diastereomeric racemates, (±)-2 and (±)-3, were obtained 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,\textsuperscript{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.\textsuperscript{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\textsuperscript{5} 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 mechanisms also preferentially lead to the syn product.\textsuperscript{13} Cyclic anti TS\textsuperscript{5} 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,\textsuperscript{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).
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: (3R,12S) and (3S,12R) were encountered in 4, whereas (3S,12S) and (3S,12R) enantiomers were found in 7. However, 4 crystallizes in the triclinic noncentrosymmetric space group
Figure 1. ORTEP\textsuperscript{29} of 4 (A and B) with the atom numbering. Intramolecular hydrogen bond is shown. Thermal ellipsoids are scaled at the 20\% level.

Figure 2. ORTEP view of 7 with the atom numbering. Intramolecular hydrogen bond is shown. Thermal ellipsoids are scaled at the 30\% level.
with two crystallographically 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 (3R,12S and its enantiomeric pair) is syn [O13–C12–C3–N4, $-66.3(7)^\circ$ for A, and $64.6(7)^\circ$ for B]. In compound 7, C3–C12 bond connects two stereogenic centers of the same absolute configuration (3R,12R and its enantiomeric pair) and the relative configuration is anti [O13–C12–C3–N4, $176.8(6)^\circ$]. Never-
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 (symmetry code II; 0.5–x, y–0.5, 1–z), 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, nine have been selected for screening: Pseudomonas cepacia, Pseudomonas species, Pseudomonas fluorescens, Candida cylindracea, Lipozym IM, Novozym 435, Aspergillus niger, Penicillium camemberti, 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, and moderately enantioselective acetylation of Ic and Id, by Mucor miehei lipase (Lipozyme IM), and Candida antarctica (Novozym 435) lipase, respectively.

Enantioseparation was then attempted by screening some commercial and in-house prepared chiral HPLC columns, 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. 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, and others, 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 pseudoequatorial position, and coupled chromophores possess M-absolute
conformation, (3R) 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 (3S), for (-)-4 as (3R). 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 (C12S) for (-)-2 and also (C12S) for (+)-3. Following the same argumentation, absolute configuration of (+)-4 is assigned as (C3R,C12R), of (+)-5 as (C3S,C12S), and of (+)-7 as (C3S,C12S).

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 ($A = \Delta\varepsilon_{1\text{max}} - \Delta\varepsilon_{2\text{max}}$), 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

* 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 $\phi$, Figure 5. According to the present selection, which is in accord with the CIP priority rules, stable absolute conformation of (3R) enantiomers with the larger substituent in pseudoequatorial 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 $P$.$^{20}$
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 Et₂Zn, Scheme 3.

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

Scheme 3.

**a. chiral ligand, toluene / 0 °C**
First, we repeated the protocol with \((1R,2S)\)-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 \(\text{Et}_2\text{Zn}\) 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, \(\text{Et}_2\text{Zn}\) acts as a strong base, causing a retro-aldol reaction and racemization via enolization. In this context it is worth noting that the only bidentate ligand with an amide group as yet used in alkylation by \(\text{Et}_2\text{Zn}\) comprises the neopentyl unit \((\text{CH}_3)_3\text{C–CONR}_2\), i.e. no C–H acidic proton is present on the \(\alpha\)-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, \(\alpha\)-amino-\(\beta\)-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 \(\alpha\)-amino \(\beta\)-hydroxy acids. They proved unstable in the presence of the strong base \(\text{Et}_2\text{Zn}\) 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. \(^1\)H and \(^13\)C NMR spectra were obtained with a Varian Gemini XL 300 spectrometer in CDCl\(_3\) solutions, \(\delta\) is given in ppm relative to TMS as internal reference, and \(J\) in Hz. HPLC chromatography was performed on a HP 1050 chromatograph with Nucleosil\(C_{18}\) \(RP\) (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. Enantiomeric
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 NaClO₄/HClO₄ (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-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 CH₂Cl₂ (3 × 50 ml), organic extracts were dried over Na₂SO₄ 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/H₂O (1:1), at a flow rate of 0.8 ml/min. Crude product was crystallized from CH₂Cl₂/(i-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 CH₂Cl₂/(i-PrO)₂O/MeOH/Et₃N (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-1H-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, J₁ = 7.8 Hz, J₂ = 1.8 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.58 (1H, dd, J₁ = 4.1 Hz, J₂ = 0.8 Hz). ¹³C 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 C₂₂H₁₈N₃O₂Br⁺ (M⁺): 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. Rₗ for (+)-2: 21.7 min, Rₗ for (−)-2: 31.4 min, [α]₀ = −81.8 (c = 0.22 g/100 ml, CHCl₃).

**anti-7-Bromo-3-(1’-hydroxy-1’-phenylmethyl)-1-methyl-5-(2’-pyridyl)-2,3-dihydro-1H-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, J₁ = 9.0 Hz, J₂ = 2.3 Hz), 7.75 (1H, dt, J₁ = 7.7 Hz, J₂ = 1.3 Hz), 7.87 (1H, d, J = 7.7 Hz), 8.55 (1H, d, J = 4.3 Hz). ¹³C 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_{3}O_{2}Br^+ (M-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, [α]_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-1H-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 ν/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 ν/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_{3}O_{2}Br (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, [α]_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-1H-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 ν/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 ν/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_{26}H_{22}N_{3}O_{2}Br (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, [α]_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

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<td>α / °</td>
<td>74.40 (10)</td>
<td>90.00</td>
</tr>
<tr>
<td>β / °</td>
<td>84.39 (5)</td>
<td>95.96 (3)</td>
</tr>
<tr>
<td>γ / °</td>
<td>78.56 (4)</td>
<td>90.00</td>
</tr>
<tr>
<td>V / Å³</td>
<td>1024 (2)</td>
<td>1954.2 (9)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>F (000)</td>
<td>460</td>
<td>856</td>
</tr>
<tr>
<td>D_x / g cm⁻³</td>
<td>1.461 (4)</td>
<td>1.415 (2)</td>
</tr>
<tr>
<td>μ (Mo-Kα) / mm⁻¹</td>
<td>2.03</td>
<td>2.12</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Ψ-scan</td>
<td>no correction</td>
</tr>
<tr>
<td>Total data collected</td>
<td>4388</td>
<td>4315</td>
</tr>
<tr>
<td>Unique data</td>
<td>4388</td>
<td>3975</td>
</tr>
<tr>
<td>Observed data [criterion]</td>
<td>2250 [I &gt; 2σ(I)]</td>
<td>1026 [I &gt; 2σ(I)]</td>
</tr>
<tr>
<td>R_{int}</td>
<td>0.0775</td>
<td>0.0555</td>
</tr>
<tr>
<td>θ_{max} / °</td>
<td>26.29</td>
<td>26.38</td>
</tr>
<tr>
<td>R_1 [F_o&gt;4σ(F_o)]</td>
<td>0.042</td>
<td>0.060</td>
</tr>
<tr>
<td>wR_2 (R^2), all data</td>
<td>0.1012</td>
<td>0.1473</td>
</tr>
<tr>
<td>Goodness of fit, S</td>
<td>0.958</td>
<td>0.863</td>
</tr>
<tr>
<td>Number of refined variables</td>
<td>530</td>
<td>240</td>
</tr>
<tr>
<td>Δρ_{max}, Δρ_{min} / e Å⁻³</td>
<td>0.38, –0.48</td>
<td>0.34, –0.58</td>
</tr>
<tr>
<td>Data reduction program</td>
<td>HELENA²⁴</td>
<td>HELENA</td>
</tr>
<tr>
<td>Structure solution program</td>
<td>SIR97²⁵</td>
<td>SIR97</td>
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<tr>
<td>Struct. refinement program</td>
<td>SHELXL97²⁶</td>
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<tr>
<td>Preparation of material for publication (program)</td>
<td>PLATON98²⁷</td>
<td>PLATON98</td>
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</table>
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$_2$Cl$_2$, 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 (Chiralcel 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 Ruder 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).

REFERENCES

13. The authors are indebted to the referee who has drawn our attention to this mechanistic possibility.
20. V. Š. is indebted to Prof. A. Antus, University of Debrecen, and to Prof. M. Simonyi, Institute of Chemistry, Hungarian Academy of Sciences, who have pointed to the ambiguity in the former nomenclature and suggested the modification presented here.

SAŽETAK

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

Maja Majerić-Elenkov, Dinko Žiher, Aleksandar Višnjevac, Zdenko Hameršak, Biserka Kojić-Prodić i Vitomir Šunjić

Aldolska reakcija C(3) karbaniona 7-brom-5-pirido-1,4-benzodiazipin-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-1H-1,4-benzodiazipin-2-ona (2/3), syn/anti-7-brom-3-(1’-hidroksi-1’-feniletil)-1-metil-5-(2’-piridil)-2,3-dihidro-1H-1,4-benzodiazipin-2-ona (4/5) i syn/anti-7-brom-3-(1’-hidroksi-2’-metilpropil)-1-metil-5-(2’-piridil)-2,3-dihidro-1H-1,4-benzodiazipin-2-ona (6/7) s 60–85%-tom 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 1H 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 (3R) za (+)-enantiomere, a konfiguracija (3S) za (–)-enantiomere. Prema tome, konfiguracija anti-(+)-enantiomera je (3R,1’S), a konfiguracija syn-(+)-enantiomera je (3R,1’R). Pri pokušaju primjene enantiomerno čistih spojeva 2–7 kao katalizatora za enantioselektivnu alkilaciju benzaldehida dietylcomicu, ti su se ligandi pokazali kemijski i konfiguracijski nestabilnima.