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On the Way to α-Methyl-α-amino Acids; Unusual Elimination-addition in 3,3-Disubstituted 1,4-Benzodiazepin-2-ones and Inversion of Enantioselectivity in the Lipase Catalyzed Acetylation

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(–)-3-Methanesulfoxymethyl-3-acetoxoymethyl-7-chloro-5-phenyl-1,4-benzodiazepin-2-one, (–)-**2**, reacts with ethanethiol in the presence of a strong base affording racemic elimination-addition product 3-ethylthiomethyl-7-chloro-5-phenyl-1,4-benzodiazepin-2-one (**4**). Intermediary 3-methylene-7-chloro-5-phenyl-1,4-benzodiazepin-2-one (**3**) is formed by pericyclic C–C bond breaking during elimination of both acyloxy groups. The second approach to α-methyl-α-amino acids comprises kinetic resolution of racemic 3-hydroxymethyl-3-benzyl-7-chloro-5-phenyl-1,4-benzodiazepin-2-one (**7**) *via* acetylation by Novozym 435 lipase; enantiomeric excess (e.e.) for alcohol (3*S*)-(+)-**7** 33.2%; e.e. for acetate (3*R*)-(–)-**8** 30.2%. Opposite direction of enantioselectivity during acetylation of **7** and the recently studied **9** (Ref. 3) was established by determination of absolute conformation and relative configuration at C(3) (pseudoaxial/pseudoequatorial) by combining CD and ^{1}H NMR spectroscopy.

Key words: 1,4-Benzodiazepin-2-ones, kinetic resolution, absolute configuration.

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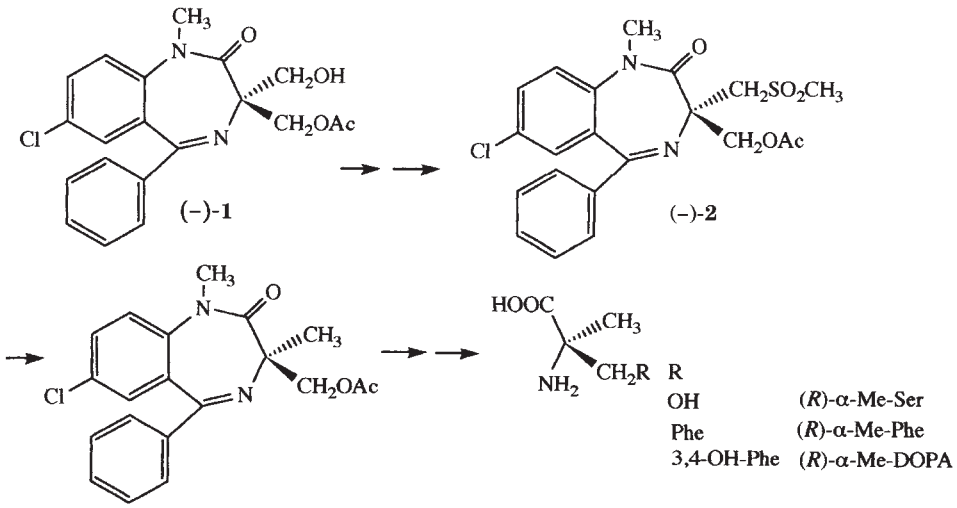
INTRODUCTION

Continuing our project on the preparation, determination of chiroptical properties, and application of 3-substituted 1,4-benzodiazepin-2-ones in chemoenzymatic syntheses of enantiomerically pure compounds (EPC),[1–3] we started investigation of 3,3-disubstituted 1,4-benzodiazepin-2-ones as chiral templates. In order to obtain α-methyl serine and α-methyl phenylalanine and its congeners in optically pure form, some template 1,4-benzodiazepines should be enzymatically transformed into chiral, enantiomerically enriched, 3,3-disubstituted derivatives, and by chemical specific chemical steps transformed into α-methyl-α-amino acids and their congeners.

RESULTS AND DISCUSSION

In the first approach, we took advantage of highly enantioselective enzymatic desymmetrization of prochiral 3,3-dihydroxymethyl-1,4-benzodiazepin-2-one,[2] and envisaged chemoenzymatic route from this diol *via* monoacetate (–)-**1** to the title compounds, as outlined in Scheme 1.

Transformation of (–)-2 into 3-acethoxymethyl-3-methyl derivative by substitution of mesyl group by ethylthiolate group, subsequent reduction, and final hydrolysis under conditions already explored in preparation of op-

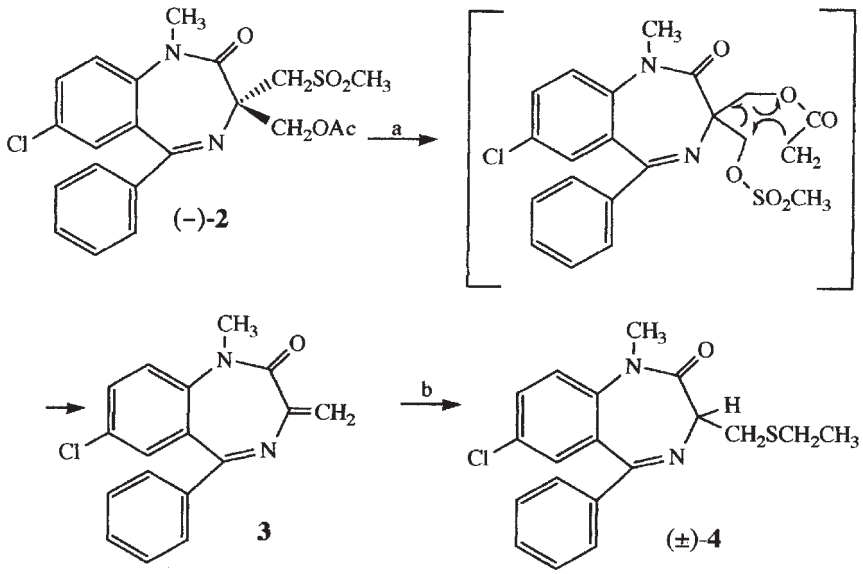


Scheme 1.

tically pure L-Cbo-serine,[1] should afford α-methyl-amino acids, and in particular open a novel approach to α-methyl-DOPA.[4–6] Optically active mesylate (–)-**2** was prepared and submitted to reductive elimination of mesyl group *via* ethylthiomethyl intermediate.[7] However, substitution of the mesyl group in (–)-**2** by ethylthiolate unexpectedly afforded *rac* **4**. The structure of **4** was deduced from ^{1}H NMR spectra, where characteristic AX_2 pattern appeared at 3.28–3.40 and 3.70 ppm, and confirmed by elemental analysis. Formation of **4** can be explained by the mechanism outlined in Scheme 2.

Ethylthiolate anion, obtained in the presence of NaH, reacts with (–)-**2** at reflux of THF to afford **4** in 66% yield. In order to ascertain intermediary formation of **3**, compound (–)-**2** was treated with an equimolar quantity of NaH in the absence of ethylthiolate anion, and **3** was isolated in 67% yield. Characteristic signals of $C{=}CH_2$ protons were found at 4.95 and 5.20 ppm, and for the carbons at 106.53, and 158.51 ppm.

In the first step, deprotonation of the most acidic methyl group in **2** takes place, forming carbanion that enters intramolecular nucleophilic displacement of mesyl group. This step presumably comprises a high level of



a) NaH/THF, r.t., b) CH_3CH_2SH/THF, Δ

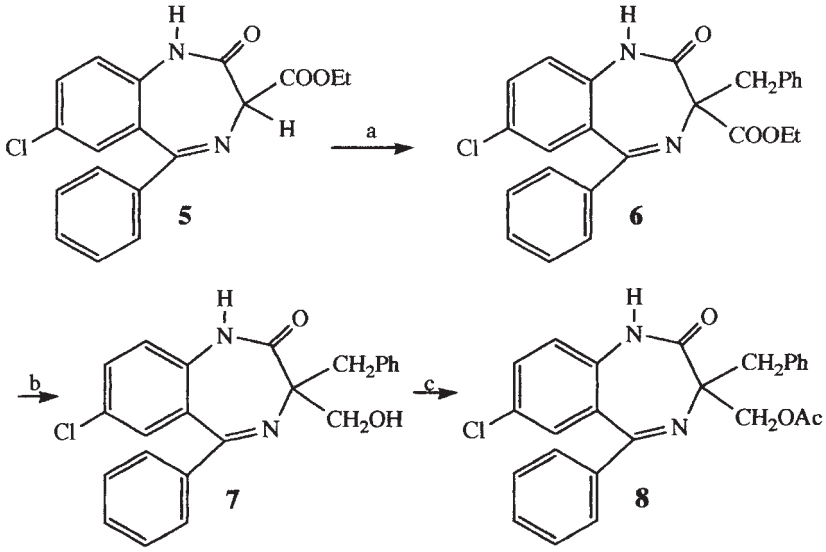
Scheme 2.

concertedness, proceeding *via* cyclic transition state to **3**. Peculiarity of the overall process resides in the C–C bond breaking, an energetically demanding step.[8] Driving force of the elimination-addition process seems to involve ring-strain release on sp^3---sp^2 rehybridization of C(3), and in the extended conjugation of the azomethine (C=N) bond to the exocyclic C=C bond in the product.

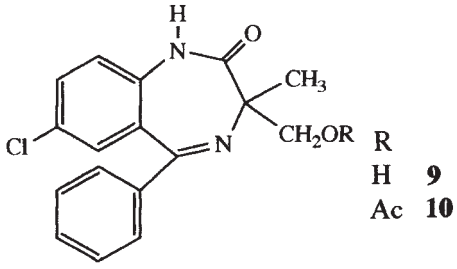
Undesired formation of *rac* **4** prompted another approach to optically active 3,3-disubstituted 1,4-benzodiazepines. To this aim, *rac* **7** was prepared, from **5**, Scheme 3, and kinetic resolution was completed by the immobilized lipase Novozym 435, as already reported for its C(3)-methyl congener **9**. The e.e.% of alcohol (–)-**9** and acetate (+)-1**0** were notably lower than for C(3)H,CH_2OH congeners.[3] Obviously, additional methyl group at C(3) in **9** diminishes the difference in steric requirements for two enantiomers. We therefore expected that the larger benzyl group at C(3) in **7** would enhance steric differentiation of the enantiomers and consequently the enantioselectivity of enzymatic acetylation.

Enzyme catalyzed acetylation of *rac* **7** afforded products with enantiomorphic properties to those obtained from **9**. Acetate (–)-8 was obtained from *rac* **7** with 30.2% e.e., whereas from *rac* **9** acetate (+)-**10** was obtained with 24.5% e.e, Table I; all e.e. were determined by HPLC using chiral columns. Acetates, (–)-**8** and (+)-1**0** exhibited opposite $[\alpha]_D$ values and nearly enantiomorphic CD curves, Figure 1; for comparison CD of alkohol (+)-**7** is included. Reversal of enantioselection with the change of methyl to benzyl group on C(3) is not unexpected, however. This effect was observed in kinetic resolution catalyzed by lipases even for structurally similar racemates that differ in some groups distant from the chiral center.[9–11] In our case, there are two possible explanations; either both acetates have the same absolute configuration, *i.e*. no inversion of enantioselection in kinetic resolution has taken place but opposite conformers of acetates **8** and **10** prevail in the solution, or inversion of stereoselection has taken place and enantiomorphic conformations belong to the enantiomers with opposite configuration at C(3). The opposite configuration is entirely supported by the CD spectra in Figure 1. Positive Cotton effect (CE), or positive couplet, is present at *ca.* 260 nm in the CD spectra of (+)-**7** and (+)-**10**, and negative CE in the CD of (–)-**8**. They unequivocally reveal the presence of *M*-conformer in solution for (+)-**10**, and *P*-conformer of (–)-**8**.[2,3]

M-Conformation found for alcohol (+)-**7** reveals that the more reactive enantiomer, alcohol (3*R*)-(–)-**7**, should possess *P*-conformation in solution; the acetylated product (3*R*)-(–)-**8** retains the same conformation. Thus, enzymatic acetylation proceeds without change of conformation in the product. For the more reactive (3*R*)-**7** acetylation presumably proceeds by pathway



a) n-BuLi/n-hexane; $(i\text{-}Pr)_2NH$,-50°; $PhCH_2Cl$,0°, b) $[(Et)_2AlH_2]Na$/THF,0°, c) AcCl/py, r.t.



Scheme 3.

TABLE I

Enantioselectivity of acylation of 3-alkyl-3-hydroxymethyl-1,4-benzodiazepines **7** and **9**

Compd.	Conv. / %	alcohol e.e. / % (config.)	acetate e.e. / % (config.)	Note
7	54.3	33.2 (3*S*)	30.2 (3*R*)	This work
9	54.7	33.8 (3*R*)	24.5 (3*S*)	Ref. 3

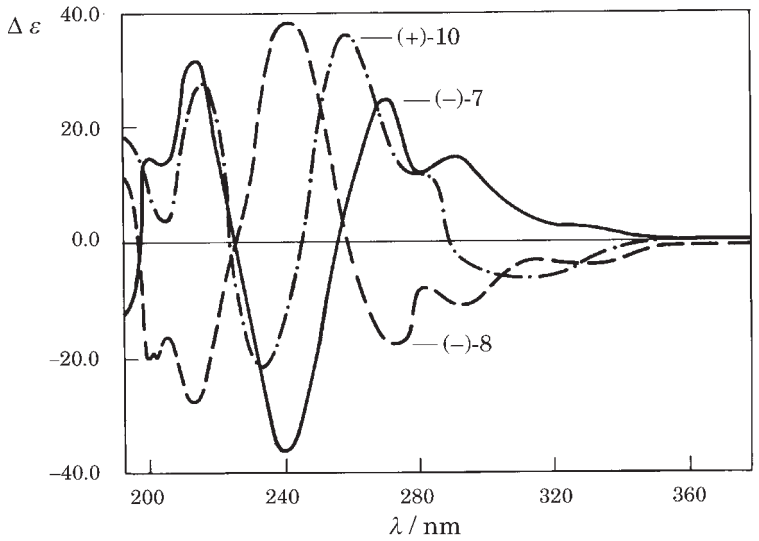
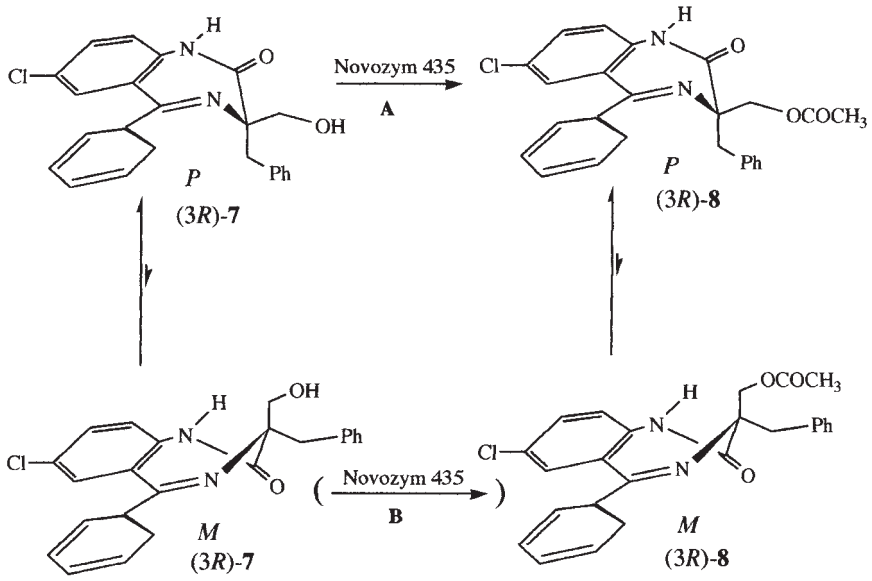


Figure 1. CD spectra of the compounds (–)-**7** (—), (–)-**8** (– –), (+)-**10** (– · –), in MeCN.

A, Scheme 4, although *P*---*M* inversion of conformation at the enzyme active site, and acetylation of the less stable *M*-conformer (pathway **B**) cannot be entirely excluded.

It is interesting to note that ^{1}H NMR signals for CH_2Ph protons in *rac* alcohol **7** and acetate **8** are very close, at 2.90 and 2.96 ppm, confirming the same relative configuration in both compounds. Larger benzylic group is situated in pseudoaxial (φa) position on both compounds, since hydroxymethyl group in the starting alcohols **7** and **9** is in psuedoequatorial (φe) position, for reasons discussed previously.[2,3] Strong shielding of CH_2OH methylene protons in **7**, found at 4.05, as compared to those in **9**, found at 4.6 ppm, is effected by the aromatic ring of the benzylic group.

In conclusion, we have reported a parallel study of two approaches to α-methyl-α-alkyl amino acids. The first resulted in a peculiar elimination-addition process, and its mechanistic explanation is offered. The second comprised enantioselective acetylation of **7** by commercial lipase. By combining CD and NMR data, it was established that **7** and **9** are present in the same relative conformations in solution, and opposite enantioselection in acetylation of **7** as compared to **9** takes place with Novozym 435. The search for a more selective microbial lipase, and exploration of a novel addition-elimination reaction, varying the structure of the starting 3,3-disubstituted 1,4-benzodiazepin-2-one and nucleophile, is envisaged.



Scheme 4.

EXPERIMENTAL

General Information

IR spectra were run on Perkin Elmer 297 spectrometer for KBr pallets. ^1H and ^{13}C NMR spectra were obtained with Varian Gemini XL 300 spectrometer in $CDCl_3$ solutions, δ in ppm is relative to TMS as internal reference, and J in Hz. HPLC: HPLC chromatography was performed on HP 1050 chromatograph with C_{18} RP (Supelco, 250 × 4.6 mm) reverse phase column; separation was monitored by HP 1050 UV detector set up at 254 nm and connected to HP 3396A integrator. Enatiomeric excess (e.e.) was determined for **3**, **4**, **5**, and **6** on 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 in g/100 ml. CD-spectra were run on Jobin-Yvon; λ_{max} ($\Delta\varepsilon$) in nm.

All commercial reagents were used as received.

During usual workup, all organic extracts were dried over Na_2SO_4 or $MgSO_4$ and evaporated *in vacuo* on a Büchi rotary evaporator.

*(–)-3-Acethoxymethyl-5-phenyl-7-chloro-3-methanesulfonylmethyl-1-methyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (**2**)*

To the solution of compound (–)-**1** (0.20 g, 0.252 mmol), prepared as in Ref. 3 in dichloromethane (5.0 ml), triethylamine (145 μl, 1.0 mmol) was added at 3 °C, then

after 15 min stirring methansulfonyl chloride (80 ml, 1.0 mmol) was added dropwise. After additional stirring for 3 h, 0.1% HCl(aq) (5.0 ml) was added, and reaction mixture was extracted with dichloromethane (3 × 10 ml), washed with $NaHCO_3$ (3 × 10 ml) and water (3 × 10 ml). Organic extract was worked up, and crude product was purified on silica gel column with dichloromethane–acetone (9.5 : 0.5) as eluant. 210 mg (87.2%) of crystalline (–)-**2**, was obtained m.p. 74–77 °C, $[\alpha]_D$ = –107.0° (c = 1.7, in THF). CD (MeCN) λ_{max} / nm ($\Delta\varepsilon$): 212 (+9.14), 238, (+10.80), 266 (–21.78), 291 (–7.52), 326 (+1.71).

*5-Phenyl-7-chloro-3-methylene-1-methyl-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**3**)*

When the reaction with (–)-**2** was performed as described for **4**, but using equimolar quantities of NaH, the crude product was isolated after usual work up. After chromatography on silica gel column with dichloromethane–acetone (9.5 : 0.5) as eluent, pure **3** was obtained in 67% yield; colourless crystalls, m.p. 138–141 °C. IR ν_{max} / cm^{-1}: 1710, 1670, 1440, 1030, 700. ^{1}H NMR δ/ppm: 3.40 (s, 3H), 4.95 (s, 1H), 5.20 (s, 1H), 7.24–7.73 (m, 8H). ^{13}C NMR δ/ppm: 35.06, 106.53, 122.59, 127.66, 128.41, 129.17, 129.69, 130.43, 131.17, 131.43, 137.27, 141.61, 148.51, 165.43, 170.37.

Anal. Calcd. for $C_{17}H_{13}N_2OCl$ (M_r = 296.74): C 68.81, H 9.42, N 9.44%; found: C 68.92, H 4.46, N 9.51%.

*3-Ethylthiomethyl-5-phenyl-7-chloro-1-methyl-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**4**)*

To the solution of ethanthiol (132 μl, 1.8 mmol) in dry THF (5.0 ml), 80% NaH (63 mg, 2.1 mmol) was added under stirring at ambient temperature. After 20 min, (–)-**2** (165 mg, 0.35 mmol) in THF (3.0 ml) was aded. Upon 2 hours heating under reflux, the reaction mixture was cooled to ambient temperature, water (10 ml) was added and the product was extracted with dichloromethane (3 × 10 ml). After usual work up and chromatography on silica gel column with dichloromethane–acetone (9 : 1) as eluent, pure *rac* **4** was obtained (100 mg, 66%); colorless crystals, m.p. 103–107 °C. IR ν_{max} / cm^{-1}: 1710, 1630, 1230, 1030, 700. ^{1}H NMR δ/ppm: 1.23 (t, J = 7.2 Hz, 3H), 2.59 (q, J = 7.3 Hz, 2H), 3.28–3.42 (m, 2H), 3.44 (s, 3H), 3.70 (t, J = 6.4 Hz, 1H), 7.16–7.57 (m, 8H). ^{13}C NMR δ/ppm: 14.74, 26.69, 33.38, 34.98, 64.70, 122.89, 128.35, 129.23, 129.55, 129.68, 130.18, 130.68, 131.60, 137.84, 142.02, 167.27, 169.52.

Anal. Calcd. for $C_{19}H_{19}N_2SOCl$ (M_r = 358.88): C 63.59, H 5.34, N 7.80%; found: C 63.74, H 5.51, N 7.69%.

*5-Phenyl-7-chloro-3-benzyl-3-ethoxycarbonyl-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**6**)*

Lithium diisopropylamide (LDA) was prepared from n-BuLi in cyclohexane (1.3 ml, 26.25 mmol, Aldrich) and diisopropylamine (3.75 ml, 26.3 mmol) in dry THF (10 ml). After 30 min stirring under argon atmosphere at ambient temperature, the solution was cooled to –50 °C (acetone–dry ice), and soln. of *rac* **5** (3.5 g, 10.2 mmol, CRC, Comp. Ric. Chim.) in THF (15 ml) was added with a syringe. After 20 min stir-

ring, the reaction solution was warmed up to –20 °C, and benzylchloride (3.50 ml, 30.0 mmol) was added in 45 min with a syringe. Reaction solution was slowly warmed up to 0 °C, and then stirred for 2 h. Then water (30 ml) was added, and after usual work up, the crude product was purified by column chromatography with dichloromethane–acetone (8.0 : 2.0) as eluent to afford **6** (2.22 g, 50.3%), colorless crystals; m.p. 179–182 °C IR ν_{max} / cm^{-1}: 1720, 1680, 1490, 1320, 700. ^{1}H NMR δ/ppm: 0.66 (t, J = 7.2 Hz, 3H*), 3.*45 (q, J = 7.3 Hz, 2H), 3.74 (d, J = 13. Hz, 1H), 3.86 (d, J = 13.6 Hz, 1H), 7.06–7.60 (m, 13H), 9.01 (s, 1H). ^{13}C NMR δ/ppm: 13.20, 43.68, 61.06, 74.55, 122.74, 126.85, 127.69, 128.32, 128.95, 130.01, 130.18, 130.32, 130.86, 130.94, 131.83, 135.44, 136.06, 139.16, 167.77, 169.43, 170.09.

Anal. Calcd. for $C_{25}H_{21}N_2O_3Cl$ (M_r = 432.89): C 69.36, H 4.89, N 6.47%; found: C 69.45, H 4.81, N 6.45%.

*5-Phenyl-7-chloro-3-benzyl-3-hydroxymethyl-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**7**)*

To the solution of *rac* **6** (0.50 g, 1.15 mmol) in dry THF (10.0 ml), [$(Et)_2AlH_2$]Na (3.0 ml, 6.0 mmol, Aldrich) was added at 0 °C. After 3 h, 15% NaOH (3.0 ml) was added keeping the temperature below 3 °C. Thereafter, pH was adjusted to 5.0 by HCl(aq) (1:1), and stirring was continued for 1 h at 3–5 °C. Reaction mixture was extracted with ethylacetate (3 × 20 ml), and organic phase was evaporated after drying over Na_2SO_4. Product **7** was isolated after chromatography on silica gel using dichloromethane–ethylacetate (8 : 2) as eluent; yield 0.33 g (73.4%), m.p. 100–103 °C. IR ν_{max} / cm^{-1}: 3480, 2910, 1720, 1490, 700. ^{1}H NMR δ/ppm: 2.85 (d, J = 13.6 Hz, 1H), 2.95 (d, J = 13.6 Hz, 1H), 3.99 (d, J = 11.5 Hz, 1H), 4.09 (d, J = 11.6 Hz, 1H), 4.21 (t, J = 7.3 Hz, 1H), 7.00–7.72 (m, 13H), 9.65 (s, 1H). ^{13}C NMR δ/ppm: 29.49, 31.49, 65.29, 121.83, 126.91, 128.20, 128.35, 128.75, 129.08, 129.65, 130.17, 130.55, 130.83, 132.40, 135.07, 136.43, 140.12, 167.41, 174.35.

Anal. Calcd. for $C_{23}H_{19}N_2O_2Cl$ (M_r = 390.85): C 70.68, H 4.90, N 7.16%; found: C 70.77, H 4.96, N 7.22%.

*5-Phenyl-7-chloro-3-benzyl-3-acetoxymethyl-2,3-dihydro-1*H-*1,4-benzodiazepin-2-one (**8**)*

To the solution of **7** (200 mg, 0.50 mmol) in DMF (5.0 ml), at ambient temperature, pyridine (0.2 ml) was added first, then acetyl chloride (50 μl, 0.68 mmol) over a 10 min period. The solvent was evaporated to dryness after 1 h stirring, the oily residue was dissolved in ethylacetate (10 ml), washed with 10% HCl(aq) (3 x 5 ml), then with satd. aq. bicarbonate (3 × 5 ml), and water. After usual work up and chromatography on silica gel with dichloromethane–ethylacetate (8.0 : 2.0), 184 mg (83.6%) of **4** was obtained; colorless crystals, m.p. 97–100 °C. IR ν_{max} / cm^{-1}: 1700, 1670, 1480, 1230, 700. ^{1}H NMR δ/ppm: 2.21 (s, 3H), 2.93 (d, J = 11.06 Hz, 1H), 2.99 (d, J = 11.1 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 11.3 Hz, 1H), 7.01–7.50 (m, 13H), 10.12 (s, 1H). ^{13}C NMR δ/ppm: 21.03, 33.26, 65.55, 68.90, 121.89, 127.03, 128.29, 128.35, 128.49, 128.92, 129.77, 130.01, 130.49, 131.12, 132.27, 135.29, 136.52, 140.09, 166.81, 170.84, 172.36.

Anal. Calcd. for $C_{25}H_{21}N_2O_3Cl$ (M_r = 432.89): 69.37, H 4.89, N 6.47%; found: C 69.35, H 4.97, N 6.51%.

Enzymatic Enantioselective Acetylation of **7**

Racemic **7** (1.1 mmol) and Novozym 435 (1.75 g) were slurried in dry ethylacetate (50 ml), thermostated at 10 °C in a double-wall glass reactor, and magnetically stirred. Reaction was started by addition of vinylacetate (5.0 ml, Aldrich). Samples (20 μl) were taken at regular intervals, filtered through teflon-filter and analyzed by HPLC on the riverse-phase column. Reaction was stopped at 52.3% conversion after 47 h. Immobilized enzyme was collected on filter, washed with ethylacetate and deposited for recycling. Filtrate was evaporated to dryness and the reaction mixture was purified on silica gel column with dichloromethane–ethylacetate (9.0 : 1.0) as eluent. 152 mg (36.1%) of alcohol (+)-**7** was obtained, e.e. 33.2%, $[\alpha]_D$ = +109.2° (c = 0.83 in THF). CD (CH_3CN) ν_{max} / cm^{-1} ($\Delta\varepsilon$): 225 (+31.04), 241 (–41.47), 270 (–25.20), 300 (+11.84).

Acetate (–)-**8** was obtained as colorless crystals, 210 mg (45.3%), e.e. 30.2%, mp. 98–101 °C, $[\alpha]_D$ = –97.2° (*c* = 1.00 in THF). CD (CH_3CN) λ_{max} / nm) ($\Delta\varepsilon$): 225 (–30.94), 242 (+43.67), 271 (–25.86), 300 (–12.17).

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SAŽETAK

Na putu prema α-metil-α-aminokiselinama; neuobičajena adicija-eliminacija u 3,3-disupstituiranom 1,4-benzodiazepin-2-onima i inverzija enantioselektivnosti u lipazom kataliziranoj acetilaciji

Amir Avdagić i Vitomir Šunjić

(–)-3-Metansulfoksimetil-3-acetoksimetil-7-kloro-5-fenil-1,4-benzodiazepin-2-on, (–)-**2**, reagira s etantiolom u prisutnosti jake baze, dajući racemični produkt eliminacije-adicije 3-etiltiometil-7-klor-5-fenil-1,4-benzodiazepin-2-on (**4**). Intermedijarni 3-metilen-7-klor-5-fenil-1,4-benzodiazepin-2-on (**3**) nastaje pericikličkim cijepanjem veze C–C u tijeku eliminacije obje aciloksi-skupine. Drugi pristup α-metil-α-amino-kiselinama sastoji se u kinetičkoj rezoluciji racemičnog 3-hidroksimetil-3-benzil-7-klor-5-fenil-1,4-benzodiazepin-2-ona (**7**) acetiliranjem lipazom Novozym 435; enantiomerni višak (e.v.) za alkohol (3*S*)-(+)-**7** iznosio je 33,2%, e.v. za acetat (3*R*)-(–)-**8** iznosio je 30,2%. Suprotni smjer enantioselektivnosti u acetilaciji **7** i nedavno proučavanog **9** (Ref. 2) utvrđen je određivanjem apsolutne konformacije i relativne konfiguracije na C(3) (pseudoaksijalna/pseudoekvatorijalna), kombinirajući podatke CD i NMR spektroskopije.