Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3881–3888

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of β-amino acids. Part 9: Preparation of enantiopure α,α-disubstituted β-amino acids from 1-benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one[1,2]

Eusebio Juaristi,* Margarita Balderas and Yara Ramírez-Quirós

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 Mexico, D.F., Mexico

Received 10 September 1998; accepted 14 September 1998

Abstract

Double alkylation of enantiopure *N,N*-acetal pyrimidinone (*S*)-**1**, a masked chiral derivative of β-alanine prepared from (*S*)-asparagine, proceeds with high stereoselectivity to give C(5) disubstituted adducts (2*S*,5*R*)-**6**, (2*S*,5*S*)-**6**, (2*S*,5*R*)-**7**, and (2*S*,5*S*)-**7**. Acid hydrolysis of these derivatives affords enantiopure α,α-dialkylated β-amino acids (*R*)-**8**, (*S*)-**8**, (*R*)-**9**, and (*S*)-**9** in very good yields.

1. Introduction

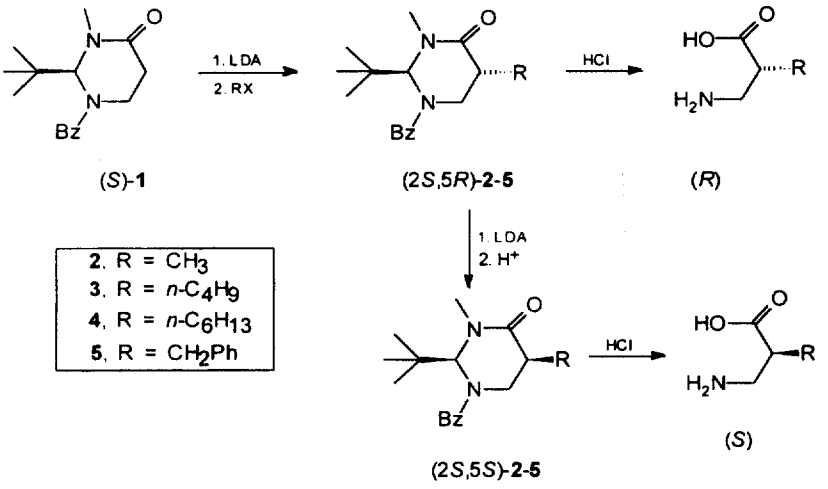
α,α-Dialkylated derivatives of proteinogenic amino acids are efficient inhibitors of those enzymes that metabolize the natural substrates.[3] Furthermore, synthetic peptides incorporating α,α-dialkylated α-amino acids adopt modified backbone conformations,[4] exhibiting increased lipophilicity,[5] and increased resistance to both enzymatic and chemical hydrolysis.[6] As a result of these features, the preparation of enantiopure α,α-dialkylated α-amino acids has recently attracted considerable attention.[7]

In contrast, oligomers of certain β-amino acids (so-called 'β-peptides') form unusually stable secondary structures such as β-sheet-like arrangements or helical conformations.[8] It may be anticipated that incorporation of α,α-disubstituted β-amino acids into unnatural peptides will confer peculiar conformational and chemical properties. Not surprisingly, reports describing the enantioselective synthesis of α,α-dialkylated β-amino acids have recently appeared.[9]

In this context, enantiopure pyrimidinone (*S*)-**1**, prepared from readily accessible (*S*)-asparagine,[10] has proved valuable for the preparation of either (*R*)- or (*S*)-α-alkylated β-amino acids in the enantiomerically pure state[11] (Scheme 1).

* Corresponding author. E-mail: ejuarist@mail.cinvestav.mx

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00392-9



Scheme 1.

The epimerization of (2*S*,5*R*)-**2**–**5** to (2*S*,5*S*)-**2**–**5** depicted in Scheme 1 is clear evidence that protonation (aqueous NH_4Cl) of enolates generated from the trans adducts takes place on the face opposite to the *tert*-butyl group. This finding was exploited in the present work, where (2*S*,5*R*)-**2**, -**3**, and -**5** were alkylated via their corresponding enolates to provide suitable precursors of enantiopure α,α-dialkylated β-amino acids.

2. Results and discussion

2.1. Stereoselective alkylation of (2S,5R)-2, -3, and -5

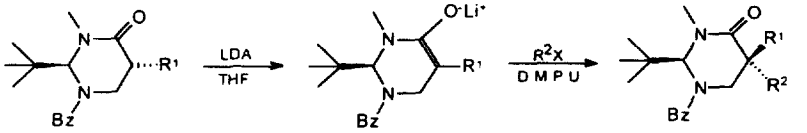
Enolates (2*S*)-**2**-Li, (2*S*)-**3**-Li, and (2*S*)-**5**-Li were generated upon treatment of the appropriate heterocycle with lithium diisopropylamide (LDA), in THF solvent and under nitrogen atmosphere. The electrophile (methyl iodide, *n*-butyl bromide, or benzyl bromide) in solvent *N*,*N*′-dimethylpropyleneurea (DMPU) was then added at −78°C to afford the dialkylated products in high diastereoselectivity (no NMR spectroscopic evidence for minor diastereoisomeric product was recorded[12]) and excellent yields (Table 1). The use of DMPU as cosolvent was necessary to achieve the dialkylation in high yield.[13] That addition of the electrophile takes place from the face opposite to the *tert*-butyl group was confirmed by determination of the X-ray crystallographic structures of (2*S*,5*R*)-**6** and (2*S*,5*R*)-**7** (Figs. 1 and 2), and by chemical correlation of (2*S*,5*S*)-**6** and (2*S*,5*S*)-**7** (see later section).

The high selectivity encountered in the addition of (2*S*)-**2**-Li, (2*S*)-**3**-Li, and (2*S*)-**5**-Li to electrophiles is explained in terms of a reactive enolate conformation with an axial *tert*-butyl group,[15–17] which sterically hinders the *syn*-enolate face for reaction with electrophiles. The α,α-dialkylated products, (2*S*,5*R*)-**6**, (2*S*,5*S*)-**6**, (2*S*,5*R*)-**7**, and (2*S*,5*S*)-**7** are all solids; analytically pure materials were readily obtained by recrystallization.

2.2. Hydrolysis of the C(5) dialkylated pyrimidinone derivatives 6 and 7 to give enantiopure α,α-dialkylated β-amino acids

Both Schoellkopf[18] and Seebach[19] have pointed out that hydrolysis of geminal disubstituted imidazolidinones necessitates drastic conditions. This also seems to be the case with α,α-disubstituted pyrimi-

Table 1
Diastereoselectivity of enolate (2*S*)-**2**-Li, (2*S*)-**3**-Li, and (2*S*)-**5**-Li alkylations



Product	R^1	R^2	ds (%)	mp	$[\alpha]_D^{29°C}$	yield (%)
(2*S*,5*R*)-**6**	CH_3	*n*-C_4H_9	> 95	184-5	+30.3	80.6
(2*S*,5*S*)-**6**	*n*-C_4H_9	CH_3	> 95	147-8	+12.6	87.9
(2*S*,5*R*)-**7**	CH_3	CH_2Ph	> 95	209-10	-48.8	96.0
(2*S*,5*S*)-**7**	CH_2Ph	CH_3	> 95	129-30	-38.7	92.0

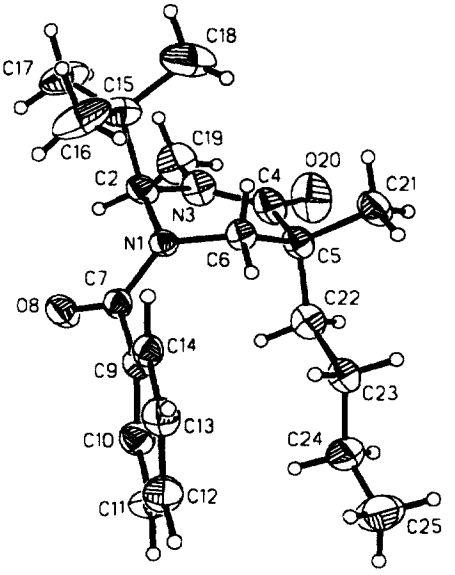


Figure 1. Structure and solid-state conformation of (2*S*,5*R*)-**6**[14]

dinones, since the hydrolysis of (2*S*,5*R*)-**6**, (2*S*,5*S*)-**6**, (2*S*,5*R*)-**7**, and (2*S*,5*S*)-**7**, required heating with 8 N HCl in a sealed tube at 100–140°C. While these drastic conditions may not be tolerated by sensitive amino acids,[20] they proved harmless to the α,α-disubstituted β-amino acids **8** and **9**. Nevertheless, milder conditions could be employed when *p*-dioxane was used as co-solvent, since improved solubility of the substrate in the aqueous medium resulted in much faster hydrolysis.[21] Enantiopure (*R*)-**8**, (*S*)-**8**, (*R*)-**9**, and (*S*)-**9** were purified by chromatography on an ion-exchange column or by treatment with propylene oxide.[22] (Table 2 and experimental section).

In summary, double alkylation of chiral β-alanine derivative (*S*)-**1** proceeds with very high stereoselectivity. Acid hydrolysis of the dialkylated adducts ($R^1 \neq R^2$) affords enantiopure α,α-dialkylated β-amino acids in good yields.

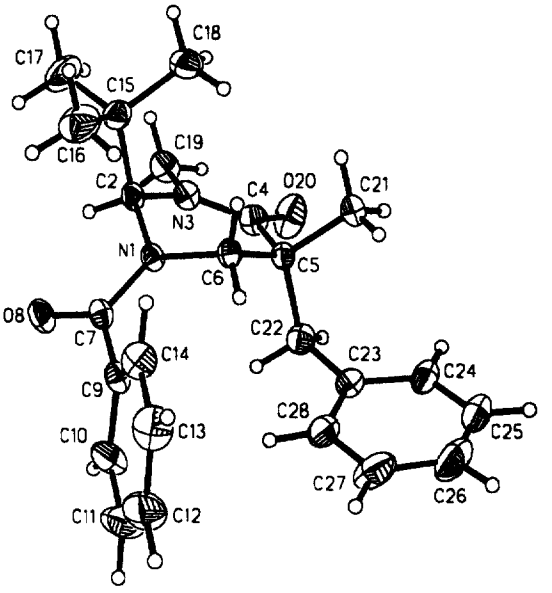
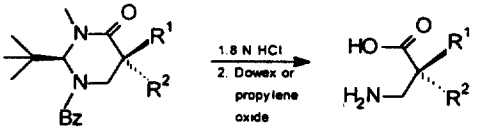


Figure 2. Structure and solid-state conformation of (2*S*,5*R*)-**7**[14]

Table 2
Hydrolysis of C(5) dialkylated products **6** and **7**



(2*S*,5*R*)-**6** or -**7** or (2*S*,5*R*)-**6** or -**7** → (*R*)-**8** or -**9** or (*S*)-**8** or -**9**

Product	R^1	R^2	isolated yield (%)	mp (°C)	$[\alpha]_D^{29°C}$
(*R*)-**8**	CH_3	n-C_4H_9	81.1	187-8	-6.8
(*S*)-**8**	n-C_4H_9	CH_3	75.9	187-8	+7.0
(*R*)-**9**	CH_3	CH_2Ph	87.3	205-6	-17.2
(*S*)-**9**	CH_2Ph	CH_3	85.9	205-6	+17.8

3. Experimental section

3.1. General

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120°C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[23] The n-butyl lithium employed was titrated according to the method of Juaristi et al.[24]

The apparatus used was as follows: TLC: Merck-DC-F_{254} plates: detection by UV light. Flash column chromatography:[25] Merck silica gel (0.040–0.063 nm). Melting points: Mel-Temp apparatus:

not corrected. IR spectra: Nicolet MX-1 FT spectrometer. ^{1}H NMR spectra: Jeol Eclipse-400 (400 MHz) and Jeol GSX-270 (270 MHz) spectrometers. ^{13}C NMR spectra: Jeol Eclipse-400 (100 MHz) and Jeol GSX-270 (67.8 MHz). Chemical shifts (δ) in ppm downfield from internal TMS reference; the coupling constants (J) are given in hertz. Elemental analyses were obtained at Galbraith Laboratories, Inc., TN.

3.2. *General procedure for the alkylation of perhydropyrimidinones*

In a dry two-necked round-bottom flask, equipped with an addition funnel, rubber septa and thermometer, was placed, under nitrogen, diisopropylamine (1.1 mmol) in 15 ml of THF. This was then cooled to −20°C before the slow addition of 1.1 mmol of *n*-BuLi (ca. 2.3 M in *n*-hexane). The resulting solution was stirred at −20°C for 30 min before the dropwise addition of 1.0 mmol of monoalkylated heterocycle in 10 ml of THF. Stirring was continued for 1 h at −20°C in order to secure the complete formation of the enolate, before the reaction temperature was lowered to −78°C. The alkylating agent (1.2 mmol, 20% excess) and DMPU (1.1 mmol) was then added dropwise via syringe, and the reaction mixture was stirred at −78°C until no further changes were detected by TLC. At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, allowed to warm to ambient temperature, and extracted with two portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in a rotary evaporator.

3.3. (2S,5R)-*1-Benzoyl-2-*tert*-butyl-3,5-dimethyl-5-*n*-butylperhydropyrimidin-4-one (2S,5R)-**6**

The general procedure was followed for the alkylation of 180 mg (0.62 mmol) of (2*S*,5*R*)-**2** with 101 mg (0.74 mmol) of *n*-butyl bromide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate, 9:1) afforded 172 mg (80.6% yield) of (2*S*,5*R*)-**6**, mp 184.5–185.5°C. $[\alpha]_D^{29}$=+30.25 (c=0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ main *N*-Bz rotamer:[12] δ 0.37 (m, 1H), 0.69 (t, J=7.2 Hz, 3H), 0.98 (s, 3H), 1.0–1.5 (m, 5H), 1.15 (s, 9H), 3.07 (s, 3H), 3.44 (d, J=14.3 Hz, 1H), 3.73 (d, J=14.4 Hz, 1H), 5.91 (s, 1H), 7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ main *N*-Bz rotamer:[12] δ 13.9, 20.9, 22.9, 25.5, 28.6, 37.8, 38.2, 38.8, 41.7, 50.6, 73.7, 127.2, 128.6, 130.1, 134.9, 170.3, 174.5; MS, *m/z* 343 (M^+−1), 301, 105. Anal. calcd for $C_{21}H_{32}N_2O_2$: C, 73.26; H, 9.30. Found: C, 73.65; H, 9.50.

3.4. (2S,5S)-*1-Benzoyl-2-*tert*-butyl-3,5-dimethyl-5-*n*-butylperhydropyrimidin-4-one (2S,5S)-**6**

The general procedure was followed for the alkylation of 246 mg (0.75 mmol) of (2*S*,5*R*)-**3** with 142 mg (0.9 mmol) of methyl iodide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate, 95:5) afforded 229 mg (87.9% yield) of (2*S*,5*S*)-**6**, mp 147–148°C. $[\alpha]_D^{29}$=+12.6 (c=0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ main *N*-Bz rotamer:[12] 0.81 (t, J=7.4 Hz, 3H), 0.97 (s, 3H), 1.01–1.40 (m, 5H), 1.16 (s, 9H), 1.62 (m, 1H), 3.08 (s, 3H), 3.41 (dd, J^1=13.9 Hz, J^2=1.1 Hz, 1H), 3.68 (d, J=13.9 Hz, 1H), 5.90 (d, J=1.1 Hz, 1H), 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ main *N*-Bz rotamer:[12] 13.9, 23.3, 25.5, 26.3, 28.8, 36.5, 37.7, 38.5, 42.3, 51.4, 73.8, 127.1, 128.7, 130.0, 135.1, 170.8, 173.9; MS, *m/z* 329 (M^+−15), 287, 105. Anal. calcd for $C_{21}H_{32}N_2O_2$: C, 73.26; H, 9.30. Found: C, 73.07; H, 9.25.

3.5. (2S,5R)-1-Benzoyl-2-tert-butyl-3,5-dimethyl-5-benzylperhydropyrimidin-4-one (2S,5R)-7

The general procedure was followed for the alkylation of 522 mg (1.81 mmol) of (2*S*,5*R*)-**2** with 371 mg (0.26 ml, 2.17 mmol) of benzyl bromide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate, 80:20) afforded 657 mg (96.0% yield) of (2*S*,5*R*)-**7**, mp 209.5–210.5°C. $[\alpha]_D^{29}=-48.8$ (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ main *N*-Bz rotamer:[12] 1.18 (s, 9H), 1.28 (s, 3H), 2.55 (d, J=13.4 Hz, 1H), 2.80 (d, J=13.4 Hz, 1H), 3.16 (s, 3H), 3.46 (d, J=14.3 Hz, 1H), 4.01 (d, J=14.3 Hz, 1H), 6.00 (s, 1H), 6.39–7.58 (m, 10H); ^{13}C NMR ($CDCl_3$, 10 MHz) δ Main *N*-Bz rotamer:[12] 23.9, 28.6, 38.2, 39.2, 42.5, 43.3, 50.6, 74.0, 126.5, 127.8, 128.3, 128.5, 128.8, 130.3, 134.5, 136.9, 169.8, 174.2; MS, *m/z* 377 (M^+-1), 287, 210, 196, 91. Anal. calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99. Found: C, 76.23; H, 8.02.

3.6. (2S,5S)-1-Benzoyl-2-tert-butyl-3,5-dimethyl-5-benzylperhydropyrimidin-4-one (2S,5S)-7

The general procedure was followed for the alkylation of 539 mg (1.48 mmol) of (2*S*,5*R*)-**5** with 0.11 ml (1.78 mmol) of methyl iodide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate, 80:20) afforded 541 mg (92.0% yield) of (2*S*,5*S*)-**7**, mp 129–130°C. $[\alpha]_D^{29}=-38.7$ (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ Main *N*-Bz rotamer:[12] 0.55 (s, 3H), 0.75 (s, 9H), 2.21 (d, J=13.6 Hz, 1H), 3.05 (s, 3H), 3.39 (d, J=14.1 Hz, 1H), 3.42 (d, J=13.6 Hz, 1H), 3.65 (d, J=14.1 Hz, 1H), 5.80 (s, 1H), 7.1–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ Main *N*-Bz rotamer:[12] 28.1, 28.3, 37.8, 38.0, 42.2, 44.2, 50.1, 73.8, 126.7, 127.1, 128.2, 128.6, 130.0, 130.8, 135.1, 137.0, 170.9, 172.6; MS, *m/z* 245, 105, 77. Anal. calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99. Found: C, 76.31; H, 8.01.

3.7. General procedure for the hydrolysis of the dialkylated pyrimidinones 6 and 7

A suspension of 1.0 mmol of adduct in 15 ml of 8 N HCl was heated in a sealed ampule to 100–140°C until complete reaction (see later section). The solution was then allowed to cool to ambient temperature and the precipitate of benzoic acid was removed by filtration. The filtrate was extracted with three 20 ml portions of EtOAc and the aqueous phase was concentrated at reduced pressure to afford a 1:1 mixture of the amino acid hydrochloride and methylammonium chloride, which was adsorbed onto acidic ion-exchange resin Dowex 50WX8. The resin was washed with distilled water until the washings emerged neutral, and then the free amino acid was recovered with 1 N ammonium hydroxide. Evaporation afforded the free amino acid, which was dried under high vacuum at 40°C.

3.8. (R)-(−)-α-Methyl-α-n-butyl-β-aminopropionic acid (R)-8

Derivative (2*S*,5*R*)-**6** (172 mg, 0.5 mmol) was hydrolyzed according to the general procedure (100°C, 48 h) to afford 64.5 mg (81.1% yield) of pure, free amino acid (*R*)-8, mp 187–188°C. $[\alpha]_D^{29}=-6.8$ (c=1, H_2O); ^1H NMR (D_2O, 270 MHz) δ 0.82 (t, J=7.1 Hz, 3H), 1.11 (s, 3H), 1.20 (m, 4H), 1.50 (m, 2H), 2.82 (d, J=12.9 Hz, 1H), 3.10 (d, J=12.9 Hz, 1H); ^{13}C NMR (D_2O, 67.8 MHz) δ 13.4, 21.2, 22.8, 26.3, 37.2, 45.1, 46.4, 183.4.

3.9. (S)-(+)-α-Methyl-α-n-butyl-β-aminopropionic acid (S)-8

The derivative (2*S*,5*S*)-**6** (180 mg, 0.52 mmol) was hydrolyzed according to the general procedure (100°C, 12 h) to afford 63.2 mg (75.9% yield) of pure, free amino acid (*S*)-**8**, mp 187–188°C. $[\alpha]_D^{29}=+7.0$

(c=1, H_2O); ^1H NMR (D_2O, 400 MHz) δ 0.81 (t, J=7.1 Hz, 3H), 1.10 (s, 3H), 1.15 (m, 2H), 1.23 (m, 2H), 1.46 (m, 2H), 2.82 (d, J=12.8 Hz, 1H), 3.10 (d, J=12.8 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 13.3, 21.0, 22.6, 26.2, 37.1, 45.0, 46.2, 183.2.

3.10. (R)-(−)-α-Methyl-α-benzyl-β-aminopropionic acid (R)-9

The derivative (2*S*,5*R*)-**7** (505 mg, 1.33 mmol) was hydrolyzed according to the general procedure (135°C, 72 h)[26] to afford 224 mg (87.3% yield) of pure, free amino acid (*R*)-**9**, mp 205–206°C. $[\alpha]_D^{29}=-17.2$ (c=1, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.15 (s, 3H), 2.75 (d, J=13.4 Hz, 1H), 2.82 (d, J=12.8 Hz, 1H), 2.91 (d, J=13.4 Hz, 1H), 3.01 (d, J=12.8 Hz, 1H), 7.1–7.35 (m, 5H); ^{13}C NMR (D_2O, 100 MHz) δ 22.2, 44.7, 47.4, 47.6, 128.1 129.7, 131.2, 138.4, 183.1

3.11. (S)-(+)-α-Methyl-α-benzyl-β-aminopropionic acid (S)-9

The derivative (2*S*,5*S*)-**7** (368 mg, 0.97 mmol) was hydrolyzed according to the general procedure (140°C, 45 min) to afford 161 mg (85.9% yield) of pure, free amino acid (*S*)-**9**, mp 205–206°C. $[\alpha]_D^{29}=+17.8$ (c=1, H_2O); ^1H NMR (D_2O, 270 MHz) δ 1.18 (s, 3H), 2.75 (d, J=13.5 Hz, 1H), 2.84 (d, J=12.9 Hz, 1H), 2.94 (d, J=13.5 Hz, 1H), 3.05 (d, J=12.9 Hz, 1H), 7.15–7.40 (m, 5H); ^{13}C NMR (D_2O, 67.8 MHz) δ 21.8, 44.3, 47.1, 47.2, 128.2, 129.8, 131.4, 138.6, 183.5.

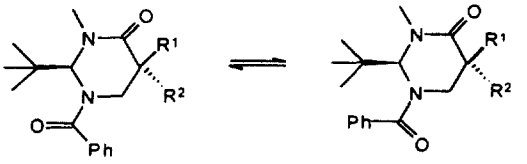
Acknowledgements

We are indebted to E. García-Pérez for carrying out preliminary experiments. We are also grateful to V. González-Díaz, G. Uribe, and H. López-Ruiz for recording the NMR spectra, and to CONACYT for financial support (Grant No. L0006-E9607).

References

1. For part 8, see: Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706.
2. Presented in part during the Fifth Chemical Congress of North America, Cancún, México, November 13, 1997. *Book of Abstracts*, Paper No. 1476 ('Special Topics in Organic Chemistry').
3. See, for example: Jung, M. J. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p. 227.
4. Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363.
5. See, for example: Christensen, H. N.; Handlogten, M. E.; Vadgama, J. V.; de la Cuesta, E.; Ballesteros, P.; Trigo, G. C.; Avendaño, C. *J. Med. Chem.* **1983**, *26*, 1374.
6. See, for example: Turk, J.; Panse, G. T.; Marshall, G. R. *J. Org. Chem.* **1975**, *40*, 953.
7. See, for example: (a) Schoellkopf, U.; Hartwig, W.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 212. (b) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p. 55. (c) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194. (d) Coppola, G. M.; Shuster, H. F. *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987; pp. 20, 78, 267. (e) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: London, 1989; pp. 1, 34, 62, 87, 208. (f) Ohfune, Y.; Moon, S. H.; Horikawa, M. *Pure and Appl. Chem.* **1996**, *68*, 645. (g) Obrecht, D.; Abrecht, C.; Altorfer, M.; Bohdal, U.; Grieder, A.; Kleber, M.; Pfyffer, P.; Müller, K. *Helv. Chim. Acta* **1996**, *79*, 1315. (h) Matsushita, M.; Maeda, H.; Kodama, M. *Tetrahedron Lett.* **1998**, *39*, 3749. (i) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225.
8. (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015, and references cited therein. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173, and references cited therein.

9. (a) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695. (b) Gaucher, A.; Bintein, F.; Wakselman, M.; Mazaleyrat, J. P. *Tetrahedron Lett.* **1998**, *39*, 575. (c) Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1409.
10. Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723.
11. Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233.
12. Slow rotation around the *N*-benzoyl group in the disubstituted heterocyclic products gives rise to two sets of signals for the corresponding isomers. A single set of signal is observed at T=145°C (DMSO-d_6).



13. DMPU has been recommended as solvent in various alkylation reactions. See Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243, and references cited therein.
14. Full details will be published elsewhere.
15. Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553.
16. The axial orientation of the *tert*-butyl group in **1** is due to $A^{1,3}$ strain: Seebach, D.: Lamatsch, B.: Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913.
17. See, also: Juaristi, E.; Seebach, D. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; Chapter 13, pp. 261–277.
18. Schoellkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 117.
19. Seebach, D.; Gees, T.; Schuler, F. *Liebigs Ann. Chem.* **1993**, 785.
20. Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237.
21. By contrast, no significant Lewis-acid assistance was observed upon addition of boron trifluoride etherate (0.3 equiv.) to the reaction medium.
22. Chambers, J. R.; Isbell, A. F. *J. Org. Chem.* **1964**, *29*, 832.
23. Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p. 256.
24. Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603.
25. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
26. When the heterocycle (100 mg) was dissolved in *p*-dioxane (3.0 ml), the hydrolysis reaction proceeded efficiently at 100°C, and was complete after 16 hours.