Amino Acids, XII[1]:

(±)Pipecolic Acid Derivatives - Part 2: An Expedient Synthetic Entry to Substituted Pipecolic Acids[+)]

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The *Diels-Alder* product **1** is transformed by *Noyori* reaction and catalytic hydrogenation to **4**. Hydrolysis with concomitant decarboxylation of **4** furnishes the *trans* configuration amino acid **5**. Functional group transformation (reduction, lactonization) of **5** provides **7**, ring opening affords the pipecolic acid derivative **9**. On the other hand **1** is hydrolyzed to **10** and 4-oxo-pipecolic acid **11**. Reduction of **10** and subsequent hydrolysis with decarboxylation of **12** affords the amino acid **13a/13b** in a *cis/trans* ratio of 1:1. Contrary to this result, reduction of **11** provides **13a/13b** in a ratio of ≥ 95/5

Aminosäuren, 12 Mitt.[1]: (±)Pipecolinsäure-Derivate, Teil 2 – Eine ergiebige Synthese substituierter Pipecolinsäuren

Das *Diels-Alder* Produkt **1** reagiert nach *Noyori* zu **2**. Abspaltung von Methanol und katalytische Hydrierung liefert **4**. Durch Hydrolyse und Decarboxylierung erhält man *trans*-konfiguriertes **5**, das durch Reduktion und Lactonisierung zu **7** umgesetzt wird. Ringöffnung führt zur Aminosäure **9**. Andererseits liefert die Hydrolyse von **1** das Keton **10** bzw. 4-Oxo-pipecolinsäure **11**. Reduktion von **10** zu **12** und anschließende Hydrolyse und Decarboxylierung liefert *cis* und *trans* 4-Hydroxy-pipecolinsäure **13a/13b** im Verhältnis 1:1. Im Gegensatz dazu führt die Reduktion von **11** zu **13a/13b** im Verhältnis ≥ 95/5.

In the foregoing report[1] we described the [4+2] cycloaddition of electrophilic *N*-acyl-imines and *N*-sulfonyl-imines, resp., with various 1,3-dienes to 4-oxo-piperidine-2,2-dicarboxylates. In this publication we present an expeditious method for the synthesis of *cis* 4-hydroxy-pipecolic acid (**13a**) and its *trans* 5-benzyl derivative **9**. These reaction sequences will be useful in the synthesis of glycosidase inhibitors and especially modified aza sugars[2].

The stable *t*-Butyldimethylsilyl enol ether **1**, easily accessible by *Diels-Alder* reaction[1], was reacted with an excess of triethylammonium fluoride[3] in tetrahydrofuran to give **10**. These neutral reaction conditions were chosen, because with tetrabutylammonium fluoride in THF rearrangement of one of the methoxycarbonyl groups from position 2 to 5 occurred. The same held true when **10** was treated with strong bases (LDA, $NaOCH_3$)[4]. Furthermore, cleavage of the silyl enol ether **1** in basic medium gave major amounts of the 5,6-didehydro derivative of **10**. Hydrolysis and concomitant decarboxylation of **10** with HBr furnished 4-oxo-pipecolic acid hydrobromide **11**[5]. Reduction of **10** with $NaBH_4$ provided **12**, which on hydrolysis gave a diastereomeric mixture of *cis* and *trans* 4-hydroxy-pipecolic acid in the expected ratio of 1:1 (Scheme 1).

We reasoned first that reduction of **11** with $NaBH_4$ *via* formation of **11c** should provide the *trans* product **13b** with high diastereoselectivity[6] but this was not the case (Scheme 2).

^{1}H-NMR spectroscopy of **11** in DMSO-d_6 showed that the carboxyl group is in equatorial position, indicated by the H_a-2/H_a-3 coupling constant of 11.7 Hz, characteristic for a diaxial position of the two hydrogens. In methanol-d_4 the hemiketal **11a/11b** in a 1:1 mixture of diastereomers is the only detectable species as the ^{13}C-NMR spectrum clearly shows (scheme 3).

Treatment of **11** with $NaBH_4$ in Na_2CO_3-solution furnished **13** in a *cis/trans* ratio of ≥ 95/5. This can be rationalized by hydride attack of the 4-position from the less hindered side of **11**.

Chemical proof for the *cis* configuration of **13a** was given by the transformation of the tosyl-derivative **14a** to **15a**. This lactonization is not unreasonable for hydroxyl and carboxyl groups in 1,3 position[7]. On the other hand, *Mitsunobu* reaction[8] of **14b** provided also **15a** with inversion of the configuration. The highly strained lactone **15** reacted in THF with $LiBH_4$ to **16** instantaneously (Scheme 1).

To get more lipophilic derivatives of **13** we started with the silyl enol ether **1**. A representative example with the 5-benzyl derivative is given here. *Noyori* reaction[9] of **1** with benzaldehyde dimethyl acetal furnished **2**, elimination of methanol gave the *E*-configurated benzylidene derivative **3**, which was hydrogenated to **4** over Pd/C. Hydrolysis and decarboxylation of **4** gave only one diastereomer with *trans* configuration of the carboxyl and benzyl group, both in equatorial position. The axial position of the hydrogen on C-2 is characterized by the large coupling constant of $J_{2a,3a}$ = 13.0 Hz and $J_{2a,\ 3e}$ = 4.3 Hz, respectively. The more favorable equatorial position of the benzyl group is a result of the facile epimerization on C-5 by keto-enol tautomerization during acidic hydrolysis. Reduction of **5** with $NaBH_4$ furnished 5-benzyl-4-hydroxy-piperidine-2-carboxylic acid with all-equatorial positions of the substituents. Equatorial positions of the hydroxy group can easily be understood by arguments analogous to those of the reduction of **11** to **13a/13b**. Introduction of the Cbz-group into 5-benzyl-4-hydroxy-piperidine-2-carboxylic acid furnished lactone **7** after acidic work-up. This facile lactonization indicated *cis* configuration of the hydroxyl and the carboxyl group.

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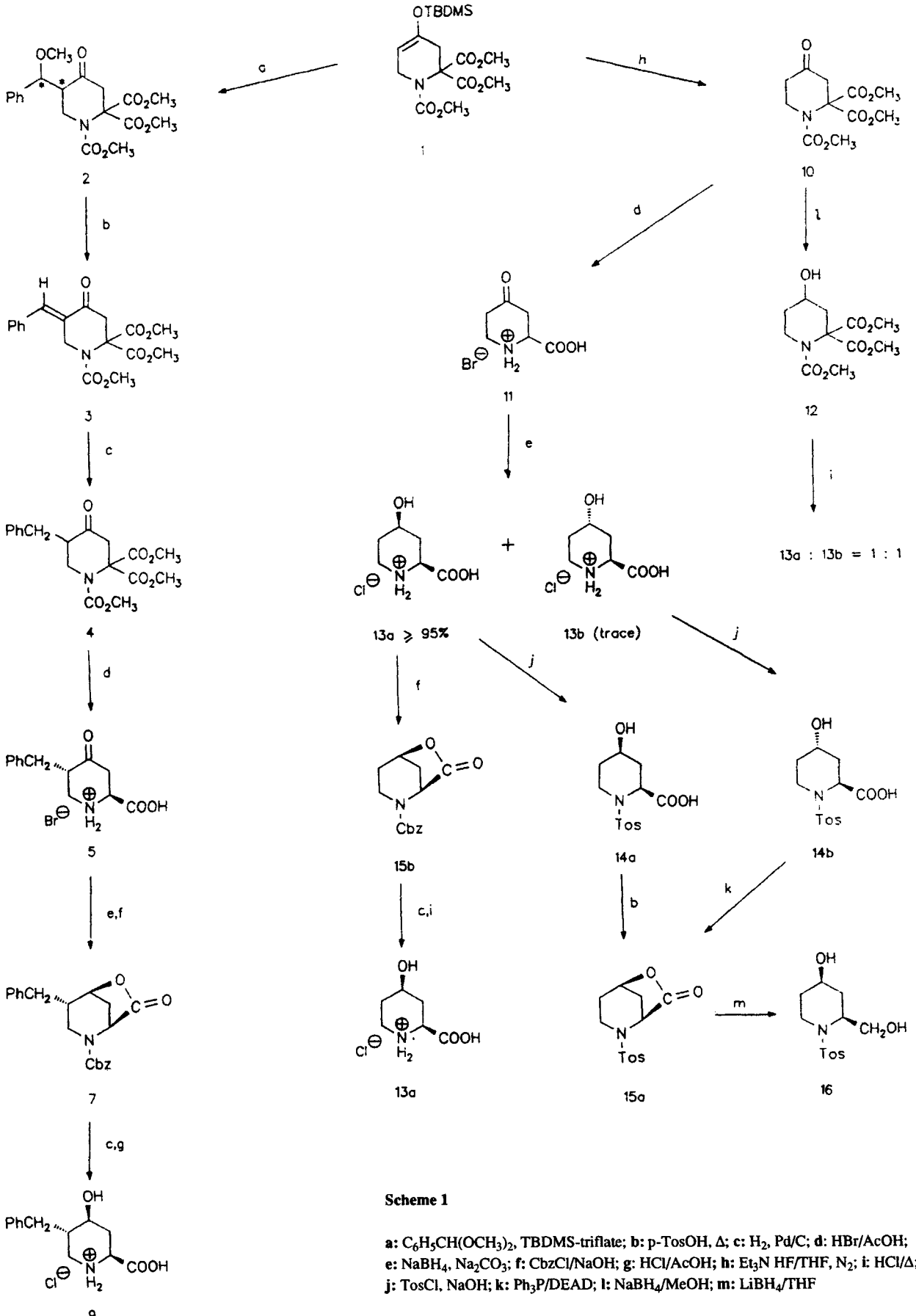
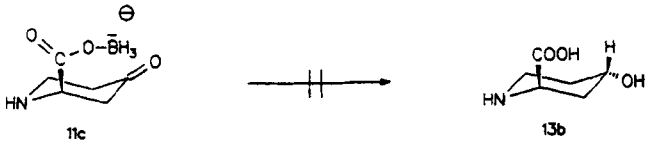


Scheme 1

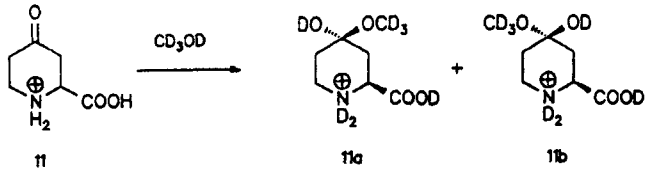
a: $C_6H_5CH(OCH_3)_2$, TBDMS-triflate; **b:** p-TosOH, Δ; **c:** H_2, Pd/C; **d:** HBr/AcOH; **e:** $NaBH_4$, Na_2CO_3; **f:** CbzCl/NaOH; **g:** HCl/AcOH; **h:** Et_3N HF/THF, N_2; **i:** HCl/Δ; **j:** TosCl, NaOH; **k:** Ph_3P/DEAD; **l:** $NaBH_4$/MeOH; **m:** $LiBH_4$/THF

* The compounds described are racemic, only one optical antipode is shown.



11c 13b

Scheme 2



11 11a 11b

Scheme 3

Experimental Part

General methods

Ether and tetrahydrofurane were distilled from sodium wire immediately before use.- Melting points are uncorrected.- IR spectra: Perkin-elmer Model 48.- ^{1}H- and ^{13}C-NMR-spectra: WP 200 Bruker.- Thin layer chromatography: Merck silicagel 60 F_{254} TLC plates, 0.25 mm; compound visualization: I_2-vapor.- Elemental analyses: Microanalytical Laboratory at the Chemistry Department of the University of Würzburg and from I. Beetz Laboratory, Kronach.

Dimethyl N-Methoxycarbonyl-5-(methoxyphenylmethyl)-4-oxo-piperidine-2,2-dicarboxylate (2) *(mixture of diastereomeres)*

To a solution of freshly recrystallized **1** (1.30 g, 3.35 mmol) in 30 ml CH_2Cl_2 benzaldehyde dimethyl acetal (0.536 g, 3.52 mmol) was added under N_2. The solution was cooled to -78°C and treated with tert-butyldimethyl silyl triflate (0.044 g, 0.17 mmol) in CH_2Cl_2 (1 ml). After 7 h (-78°C) the reaction was quenched with H_2O (30 ml) and $NaHCO_3$ solution (5 ml). Extraction with CH_2Cl_2 (3 x) drying (Na_2SO_4) and evaporation of the combined org. phases provided a colorless oil which was chromatographed on silica gel with petrol ether/H_3C-COOEt (Etac) (2+1). Fraction with R_F = 0.16 gave colorless crystals after trituration with diisopropyl ether and n-hexane.- Yield 1.04 g (79%).- (m.d. 5.3 : 1.0 / *syn* : *anti*).- $C_{19}H_{23}NO_8$ (393.4) Calcd. C 58.0 H 5.89 N 3.6 Found C 57.90 H 6.17 N 3.7.- IR (KBr): 3100-2840; 1760-1700 (C=O ester, ketone, urethane); 1450; 1380; 1255; 1210; 1180; 1115; 1070; 1035 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): *syn* δ (ppm) = 2.70 (1H, ddd, $J_{5a,6a}$ = 11.6 Hz, $J_{5a,6e}$ = 6.1 Hz, $J_{5a,PhCH}$ = 3.2 Hz, H_a-5), 2.91-3.23 (2H, m, H-3), 3.18 (3H, s, OCH_3 ether), 3.61 (3H, s, OCH_3 urethane), 3.74 (3H, s, OCH_3 ester), 3.84 (3H, s, OCH_3 ester), 3.55-4.15 (2H, m, H-6), 4.85 (1H, d, J = 3.2 Hz, PhC<u>H</u>).- ^{13}C-NMR ($CDCl_3$): *syn* δ (ppm) = 39.82 (C-6), 45.64 (C-3), 53.34 (OCH_3 2 x ester + urethane), 54.50 (C-5), 57.72 (OCH_3 ether), 67.47 (C-2), 81.51 (Ph-<u>C</u>H), 126.14, 127.91, 128.69, 138.04 (C arom.), 155.68 (<u>C</u>O_2CH_3 urethane), 168.09, 168.58 (<u>C</u>O_2CH_3 2 x ester), 204.00 (C-4).- *anti* δ (ppm) = 42.18 (C-6), 45.06 (C-3), 53.34 (OCH_3 2 x ester + urethane), 54.50 (C-5), 57.04 (OCH_3 ether), 67.47 (C-2), 80.79 (Ph-<u>C</u>H), 127.18, 128.24, 128.49, 137.35 (C arom.), 155.68 (<u>C</u>O_2CH_3 urethane), 168.09, 168.58 (<u>C</u>O_2CH_3 2 x ester), 203.59 (C-4).

Dimethyl (E)-5-Benzylidene-N-methoxycarbonyl-4-oxo-piperidine-2,2-dicarboxylate (3)

The solution of **2** (0.940 g, 2.39 mmol) and *p*-toluenesulfonic acid (0.180 g, 0.95 mmol) in absol. toluene (30 ml) was refluxed for 1.5 h. The volatiles were evaporated and the residue was chromatographed on silica gel with $CHCl_3$/Etac 9+1 (R_F = 0.31). Recrystallization from n-pentane/diisopropylether/Etac (3+2+1) gave colorless crystals.- m.p. 112°C.- Yield 0.702 g (81%).- $C_{18}H_{19}NO_7$ (361.3) Calcd. C 59.8 H 5.30 N 3.9 Found C 60.2 H 5.27 N 3.9.- IR (KBr): 3080-2850; 1755; 1740 (C=O ester), 1705; 1695 (C=O urethane, ketone); 1625 (C=C), 1575; 1465; 1440; 1395; 1290; 1240 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.19 (2H, s, H-3), 3.71 (3H, s, OCH_3 urethane), 3.81 (6H, s, 2 x OCH_3 ester), 4.84 (2H, bs, H-6), 7.35-7.50 (5H, m, H arom.), 7.68 (1H, t, J = 1.4 Hz, PhC<u>H</u>=).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 42.69 (C-6), 44.97 (C-3), 53.45 (OCH_3 2 x ester + urethane), 67.09 (C-2), 129.90 (C-5), 128.82, 129.82, 130.27, 133.67 (arom.), 137.19 (Ph-<u>C</u>H=), 155.60 (<u>C</u>O_2CH_3 urethane), 168.16 (<u>C</u>O_2CH_3 2 x ester), 192.79 (C-4).- MS: m/z = 361 (M^+, 28%), 329 (6), 302 (31), 254 (27), 175 (54), 142 (33), 115 (100).

Dimethyl 5-Benzyl-N-methoxycarboxyl-4-oxo-piperidine-2,2-dicarboxylate (4)

3 (0.400 g, 1.11 mmol) was hydrogenated in MeOH/Etac (1:1) (20 ml) over 10% Pd/C (0.040 g) for 2 h at RT (5 bar). Filtration, evaporation of the solvent and "filtration" over silica gel with $CHCl_3$/Etac 9+1 furnished a colorless oil. Trituration with ether gave crystals. Recrystallization from diisopropyl ether/n-hexane/Etac (5+3+1) furnished colorless crystalls.- m.p. 87°C.- Yield 0.324 g (81%).- $C_{18}H_{21}NO_7$ (363.4) Calcd. C 59.5 H 5.83 N 3.8 Found C 59.7 H 5.99 N 3.8.- IR (KBr): 3060-2850; 1755 (C=O ester); 1735 (C=O ketone); 1710 (C=O urethane); 1600; 1500; 1445; 1360; 1295; 1255; 1205; 1070 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.60-2.82 (2H, m, PhC<u>H</u>$_2$), 2.94-3.20 (3H, m, H-3, H-5), 3.42 (1H, m, H-6), 3.71 (3H, s, OCH_3 urethane), 3.80+3.81 (6H, s + s, OCH_3 2 x ester), 3.99 (1H, m, H-6).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 33.51 (Ph-<u>C</u>H$_2$), 44.10 (C-6), 44.80 (C-3), 49.41 (C-5), 53.08 (OCH_3 urethane), 53.20 (OCH_3 2 x ester), 67.80 (C-2), 126.40, 128.38, 128.75, 137.79 (C arom.), 155.69 (<u>C</u>O_2CH_3 urethane), 167.82, 168.15 (<u>C</u>O_2CH_3 2 x ester), 204.91 (C-4).

(trans)-5-Benzyl-4-oxo-piperidine-2-carboxylic acid hydrobromide (5)

4 (0.258 g, 0.71 mmol) was refluxed for 5 h in Hbr/AcOH 33% (3 ml) and H_2O (0.3 g). After evaporation of the volatiles Etac was added and the org. material was brought to crystallization and isolated by suction. The mother liquor gave another crop of **5**.- m.p. 203-206°C.- Yield 0.172 g (77%).- $C_{13}H_{16}BrNO_3$ (314.2) Calcd. C 49.7 H 5.13 N 4.5 Found C 49.5 H 5.38 N 4.4.- IR (KBr): 3200-3080 (OH); 3030-2860; 2800-2600 (NH_2^+); 1745 (C=O acid); 1715 (C=O ketone); 1545; 1500; 1460; 1415; 1240; 1175; 700 cm^{-1}.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.43 (1H, m, Ph-HC<u>H</u>), 2.71 (1H, dd, $J_{3a,3e}$ = 15.0 Hz, $J_{2a,3e}$ = 4.3 Hz, H_e-3), 2.94 (1H, dd, $J_{3a,3e}$ = 15.0 Hz, $J_{2a,3a}$ = 13.0 Hz, H_a-3), 3.18-3.28 (4H, m, Ph-<u>H</u>CH; H_a-5; 2 x H-6), 4.55 (1H, dd, $J_{2a,3a}$ = 13.0 Hz, $J_{2a,3e}$ = 4.3 Hz, H_a-2), 7.19-7.36 (5H, m, H arom.), ≈ 9.6 (1H, bs, CO_2H).- ^{13}C-NMR (DMSO-d_6): 31.31 (Ph-<u>C</u>H$_2$), 39.92 (C-3), 45.14 (C-6), 46.20 (C-5), 55.39 (C-2), 126.34, 128.46, 128.76, 138.28 (C arom.), 168.70 (CO_2H), 201.72 (C-4).- ^{13}C-NMR (D_2O/acetone): 31.59 + 32.53 (Ph-<u>C</u>H$_2$), 39.80 + 40.80 (C-3), 45.15 + 45.58 (C-6), 46.78 + 47.48 (C-5), 56.23 + 57.27 (C-2), 92.44 (C-4 hydrate), 127.09 + 127.34, 129.41, 129.83, 138.89 + 140.06 (C arom.), 169.32 + 170.57 (CO_2H), 202.79 (C-4 ketone).- ketone in addition to hydrate.- MS: m/z = 233 (M^+, 4%), 215 (3), 188 (23), 142 (16), 131 (3), 117 (6), 91 (11), 82 (97), 81 (36), 80 (100), 79 (37), 56 (67), 44 (64).

Benzyl 4-syn-4-Benzyl-7-oxo-6-oxa-2-azabicyclo[3.2.1]octane-2-carboxylate (7)*)

To a solution of **5** (0.200 g, 0.64 mmol) and Na_2CO_3 (0.270 g, 2.55 mmol) in H_2O (5 ml) was added $NaBH_4$ (0.050 g, 1.32 mmol) at 0°C. Stirring was continued for 1 h. Acidification with dil. HCl and evaporation provided a crystalline mixture of **9** and NaCl. ^{1}H-NMR and ^{13}C-NMR spectra showed signals for only one diastereomer.

*) Carbon atoms are numbered in analogy to pipecolic acid derivatives.

To a solution of this mixture in H_2O (5 ml) and 2N-NaOH (pH 10) was added dropwise CbzCl (0.164 g, 0.96 mmol) and 2N-NaOH in such a way that the pH of the solution was between 8 and 10. After addition of another 0.030 g CbzCl stirring was continued for 1 h at ambient temp. Extraction with diethyl ether (3 x) furnished **7** as an oil which was chromatographed on silica gel (R_F = 0.51, $CHCl_3$/Etac 9+1).- Yield 0.146 g (65%).- $C_{21}H_{21}NO_4$ (351.4).- IR (neat): 3100-2880; 1790 (C=O lactone); 1705 (C=O urethane); 1605; 1590; 1495; 1450; 1415; 1355; 1290; 1255; 1220; 740; 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.15 (1H, bd, $J_{3a,3e}$ = 12.4 Hz, H_a-3), 2.31 (1H, bd, $J_{3a,3e}$ = 12.4 Hz, H_e-3), 2.40 (1H, bm, H_e-5), 2.65 (2H, bm, PhC$\underline{H}_2$-), 3.33 (1H, bd, $J_{6a,6e}$ = 14.3 Hz, H_a-6), 3.91 (1H, dd, $J_{6a,6e}$ = 14.3 Hz, $J_{5e,6e}$ ≈ 1 Hz, H_e-6), 4.70-4.90 (2H, bm, H_e-2, H_e-4), 5.10-5.30 (2H, bm, PhC$\underline{H}_2$O), 7.00-7.40 (10 H, m, H arom.).- rotameres.- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 31.59 (Ph$\underline{C}H_2$), 36.19 (C-3), 39.29 (C-5), 42.49 (C-6), 53.74 (C-2), 67.96 (Ph$\underline{C}H_2$O), 79.93 (C-4), 126.80, 128.12, 128.30, 128.57, 128.77, 135.95, 137.93 (C arom.), 154.77 (PhCH$_2$O$\underline{C}$O-), 172.64 (-$\underline{C}O_2$- lactone).

(2,4-cis/2,5-trans)-5-Benzyl-4-hydroxy-piperidine-2-carboxylic acid hydrochloride (**9**)

To a solution of **7** (0.100 g, 0.28 mmol) in absol. MeOH (5 ml) was added 10% Pd/C (0.010 g). The mixture was hydrogenated for 1 h at 5 bar. After filtration and evaporation the residue was refluxed in AcOH/2N-HCl (1+1) (1 ml) for 3 h. Evaporation of the volatiles and trituration with Etac gave crystalline **9**, m.p. 228-230°C.- Yield 0.065 g (84%).- $C_{13}H_{18}ClNO_3$ (271.7) Calcd. C 57.5 H 6.68 N 5.1 Found C 57.2 H 6.38 N 5.1.- IR (KBr): 3300 (OH); 3080-2900; 2450 (NH_2^+); 1745 (C=O acid); 1615; 1495; 1450; 1405; 1240; 1195; 1035; 695 cm^{-1}.- ^{1}H-NMR (MeOH-d_4): δ (ppm) = 1.71 (1H, dt, J3a,3e = 13.3 Hz ≈ $J_{2a,3a}$ = 13.2 Hz, $J_{3a,4a}$ = 10.9 Hz, H_a-3), 1.93 (1H, m, H_a-5), 2.40 (1H, dd, $J_{6a,6e}$ = 13.8 Hz, $J_{5a,6a}$ = 10.1 Hz, H_a-6), 2.57 (1H, ddd, $J_{3a,3e}$ = 13.3 Hz, $J_{3e,4a}$ = 4.4 Hz ≈ $J_{2a,3e}$ = 3.2 Hz, H_e-3), 2.79 (1H, dd, J_{gem} = 12.9 Hz ≈ $J_{5a,PhHCH}$ = 12.3 Hz, PhH$\underline{C}$H), 3.11 (1H, dd, J_{gem} = 12.9 Hz, $J_{5a,PhCH}$ = 4.2 Hz, PhH$\underline{C}$H), 3.36 (1H, dd, $J_{6a,6e}$ = 13.8 Hz, $J_{5a,6e}$ = 3.4 Hz, H_e-6), 3.62 (1H, dt, $J_{3a,4a}$ = 10.9 Hz ≈ $J_{4a,5a}$ = 10.6 Hz, $J_{3e,4a}$ = 4.4 Hz, H_a-4), 4.03 (1H, dd, $J_{2a,3a}$ = 13.2 Hz, $J_{2a,3e}$ = 3.2 Hz, H_a-2), 7.18-7.36 (5H, m, H arom.).- ^{13}C-NMR (MeOH-d_4): δ (ppm) = 35.87, 36.08 (Ph-$\underline{C}H_2$-, C-3), 43.81 (C-5), 46.71 (C-6), 57.27 (C-2), 69.89 (C-4), 127.65, 129.72, 130.18, 139.57 (C arom.), 170.56 (-COOH).- MS: m/z = 236 (M^+, 0.6%), 217 (0.8), 204 (8), 190 (100), 172 (11), 117 (13), 91 (26), 56 (91).

Dimethyl N-Methoxycarbonyl-4-oxo-piperidine-2,2-dicarboxylate (**10**)

1 (1.00 g, 2.58 mmol) in THF (20 ml) was reacted with triethylammonium fluoride (0.78 g, 6.45 mmol) under N_2 at RT for 2 h. The mixture was evaporated to remove volatile compounds and chromatographed on silica-gel with $CHCl_3$/Etac 9+1.- Yield 0.55 g (78%) colorless crystals (n-hexane/Etac 4+1).- m.p. 86°C. For another method of preparation, for spectroscopic data and elemental analyses see ref.[1] (compound **3a**).

4-Oxo-piperidine-2-carboxylic acid hydrobromide (**11**)

10 (0.800 g, 2.93 mmol) was refluxed in HBr/AcOH 33% (5 ml) and H_2O (0.5 ml) for 3 h. After evaporation of the volatiles the residue was treated with acetone (1 ml), cooled and isolated by suction.- Yield 0.481 g (73%) colorless powder.- m.p. 205-210°C (Lit. 134-135°C (HCl); ref.[5]).- $C_6H_{10}BrNO_3$ (224.1) Calcd. C 32.2 H 4.50 N 6.2 Found C 31.9 H 4.29 N 6.1.- IR (KBr): 3500-3400; 3100-2900; 2430 (NH_2^+); 1755; 1740 (C=O acid, ketone); 1550; 1465; 1410; 1395; 1340; 1245; 1200 cm^{-1}.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.40-2.88 (4H, m#, $J_{3a,3e}$ = 16.0 Hz, H-5, H-3), 3.35 (1H, dt, $J_{6a,6e}$ = 12.1 Hz ≈ $J_{5a,6a}$ = 12 Hz, $J_{5e,6a}$ = 4.4 Hz, H_a-6), 3.56 (1H, ddd, $J_{6a,6e}$ = 12.1 Hz, $J_{5a,6e}$ = 6.7 Hz, $J_{5e,6e}$ = 2.6 Hz, H_e-6), 4.54 (1H, dd, $J_{2a,3a}$ = 11.7 Hz, $J_{2a,3e}$ = 5.3 Hz, H_a-2). # (overlapping with the DMSO-signal).- ^{1}H-NMR (D_2O): **11**-hydrate: δ (ppm) = 1.86-2.14 (3H, m, H_a-3, H_a-5, H_e-5), 2.41 (1H, ddd, $J_{3a,3e}$ = 14.3 Hz, $J_{2a,3e}$ = 4.0 Hz, $J_{3e,5e}$ = 2.2 Hz, H_e-3), 3.23 (1H, ddd, $J_{6a,6e}$ = 13.0 Hz, $J_{5a,6a}$ = 11.3 Hz, $J_{5e,6a}$ = 4.3 Hz, H_a-6), 3.51 (1H, td, $J_{6a,6e}$ = 13.0 Hz, $J_{5e,6e}$ = 4.3 Hz, H_e-6), 4.16 (1H, dd, $J_{2a,3a}$ = 11.5 Hz, $J_{2a,3e}$ = 4.0 Hz, H_a-2).- ^{13}C-NMR (DMSO-d_6): δ (ppm) = 35.46 (C-5), 30.09 (C-3), 40.94 (C-6), 54.66 (C-2), 168.97 (CO_2H), 201.15 (C-4).- ^{13}C-NMR (D_2O): **11**-hydrate: δ (ppm) = 34.62 (C-5), 38.21 (C-3), 41.93 (C-6), 55.91 (C-2), 91.58 (C-4), 171.61 (CO_2H).- ^{13}C-NMR (MeOH-d_4): **11a/11b** (hemiketal): δ (ppm) = 32.17 + 33.05 (C-5), 36.66 + 36.84 (C-3), 42.24 + 42.39 (C-6), 56.03 + 56.25 (C-2), 94.25 + 94.59 (C-4), 170.79 (COOD).- MS: m/z = 98 (10%), 82 (71), 81 (28), 80 (73), 79 (30), 56 (17), 44 (100).

Dimethyl 4-Hydroxy-N-methoxycarbonyl-piperidine-2,2-dicarboxylate (**12**)

10 (0.400 g, 1.46 mmol) was dissolved in MeOH (10 ml) and Etac (6 ml). $NaBH_4$ (0.080 g, 2.11 mmol) was added and ambient temp. and the mixture was stirred for 40 min. Addition of buffer solution (pH 7), extraction with CH_2Cl_2 (5 x), drying of the combined org. phases and evaporation furnished a viscous oil. Trituration with diisopropyl ether at -30°C provided a colorless powder. Crystals from n-hexane/Etac 1+1.- m.p. 104.5°C.- Yield 0.285 g (71%).- $C_{11}H_{17}NO_7$ (275.3) Calcd. C 48.0 H 6.23 N 5.1 Found C 48.2 H 6.43 N 5.1.- IR (KBr): 3555; 3450 (OH); 3010-2860; 1740 (C=O ester); 1690 (C=O urethane); 1455; 1450; 1370; 1260; 1230; 1225; 1205; 1110; 1070 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): 1.60-1.77 (2H, m, H_a-5, OH), 1.84-1.96 (1H, m, H_e-5), 2.33 (1H, dd, $J_{3a,3e}$ = 13.4 Hz, $J_{3a,4a}$ = 7.4 Hz, H_a-3), 2.48 (1H, dd, $J_{3a,3e}$ = 13.4 Hz, $J_{3e,4a}$ = 2.3 Hz, H_e-3), 3.36 (1H, ddd, $J_{6a,6e}$ = 13.3 Hz, $J_{5a,6a}$ = 7.9 Hz, $J_{5e,6a}$ = 4.4 Hz, H_a-6), 3.66-3.92 (2H, m, H_e-6, H_a-4), 3.74 (3H, s, OCH_3 urethane), 3.81 (6H, s, OCH_3 2 x ester).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 31.30 (C-5), 39.25 (C-3), 39.59 (C-6), 52.80, 52.87, 52.91 (OCH_3 urethane + 2 x ester), 63.38 (C-4), 67.66 (C-2), 157.40 ($\underline{C}O_2CH_3$ urethane), 168.75 ($\underline{C}O_2CH_3$ 2 x ester).- MS: m/z = 175 (M^+, 2%), 257 (0.3), 243 (0.6), 216 (100), 199 (5), 184 (37), 172 (18), 160 (44), 156 (13), 128 (44), 100 (12), 59 (17).

(cis)-4-Hydroxy-piperidine-2-carboxylic acid hydrochloride (**13a**)

To a solution of **15b** (0.095 g, 0.36 mmol) in absol. MeOH (5 ml) was added 10% Pd/C (0.010 g). The mixture was hydrogenated for 1 h at 5 bar pressure. After filtration and evaporation the residue was heated in 4N-HCl (1 ml) at 80°C for 3 h. Evaporation of the volatiles and trituration with acetone gave **13a** as colorless crystals. m.p. 203°C (decomp.).- Yield 0.057 g (86%).- $C_6H_{12}ClNO_3$ (181.6) Calcd. C 39.7 H 6.66 N 7.7 Found C 39.5 H 6.88 N 7.7.- IR (KBr): 3420; 3220 (OH); 3030-2800; 2500 (NH_2^+); 1745 (C=O acid); 1585; 1450; 1425; 1395; 1265; 1205; 1080; 1070 cm^{-1}.- ^{1}H-NMR (MeOH-d_4): δ (ppm) = 1.60-1.78 (2H, m, H_a-5, H_a-3), 2.10 (1H, m, $J_{5a,5e}$ = 13.9 Hz, H_e-5), 2.38 (1H, m, $J_{3a,3e}$ = 13.5 Hz, H_e-3), 3.08 (1H, dt, $J_{5a,6a}$ ≈ $J_{6a,6e}$ = 12.9 Hz, $J_{5e,6a}$ = 3.2 Hz, H_a-6), 3.49 (1H, td, $J_{6a,6e}$ = 12.9 Hz, $J_{5a,6e}$ ≈ $J_{5e,6e}$ ≈ 3.9 Hz, H_e-6), 3.92 (1H, m, H_a-4), 4.06 (1H, dd, $J_{2a,3a}$ = 12.0 Hz, $J_{2a,3e}$ = 3.5 Hz, H_a-2).- ^{13}C-NMR (MeOH-d_4): δ (ppm) = 31.66 (C-5), 35.54 (C-3), 42.58 (C-6), 56.55 (C-2), 65.83 (C-4), 170.77 (COOH).

4-Hydroxy-piperidine-2-carboxylic acid hydrochloride (**13a/13b**) *(mixture of diastereomeres 1+1)*

12 (0.200 g, 0.73 mmol) was refluxed in 4N-HCl (3 ml) for 8 h. Evaporation of the volatiles and trituration with acetone gave **13a** + **13b** as a colorless, hygroscopic powder. The ^{13}C-NMR-spectrum shows signals for *cis*- and *trans*-isomer in a ratio about 1:1.- Yield 0.103 g (78%).- $C_6H_{12}ClNO_3$ (181.6).- ^{13}C-NMR (MeOH-d_4): *cis* δ (ppm) = = 31.63 (C-5), 35.48 (C-3), 42.57 (C-6), 56.49 (C-2), 65.80 (C-4), 170.71 (COOH).- *trans* δ (ppm) = = 29.53 (C-5), 33.94 (C-3), 40.01 (C-6), 53.12 (C-2), 62.10 (C-4), 171.62 (COOH).

Benzyl 7-Oxo-6-oxa-2-azabicyclo[3.2.1]octane-1-carboxylate (**15b**)

To a solution of **11** (0.130 g, 0.58 mmol) and Na_2CO_3 (0.030 g, 0.28 mmol) in H_2O (5 ml) was added at ambient temp. $NaBH_4$ (0.033 g, 0.87 mmol). Stirring was continued for 1 h. Acidification with dil. HCl and evaporation provided a crystalline mixture. ^{1}H-NMR- and ^{13}C-NMR-spectra showed quantitative reduction of **11** to mainly **13a** (≥ 95%) and only traces of **13b**. Then the mixture was treated with CbzCl (0.150 g, 0.88 mmol) and 2N-NaOH and worked up as described for **7**. The fraction with R_F = 0.35 ($CHCl_3$/Etac 9+1) gave **15b** as colorless oil.- Yield 0.095 g (63% from **11**).- $C_{14}H_{15}NO_4$ (261.3°.- IR (neat): 3080-2870; 1785 (C=O lactone); 1700 (C=O urethane); 1585; 1495; 1410; 1335; 1290; 1255; 1215; 1155; 1115; 1055; 950 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.80-2.10 (3H, m, H_a-5, H_a-3), 2.30 (1H, m, $J_{3a,3e}$ = 12.2 Hz, H_e-3), 3.25 (1H, bm, H_a-6), 4.11 (1H, bm, H_e-6), 4.75-5.00 (2H, bm, H_e-2, H_e-4), 5.15 (2H, s, OCH_2Ph), 7.30-7.37 (5H, m, H arom.).- rotameres.- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.61 (C-5), 36.61 (C-3), 38.74 (C-6), 53.70 (C-2), 67.94 (OCH_2Ph), 77.89 (C-4), 128.15, 128.37, 128.67, 136.09 (C arom.), 154.50 (CO_2CH_2Ph), 173.03 (-CO_2-lactone).

cis-4-Hydroxy-N-tosyl-piperidine-2-carboxylic acid (**14a**)

13a (0.050 g, 0.28 mmol) was dissolved in H_2O (3 ml) and treated with 2N-NaOH (0.5 ml, 1.0 mmol) and TosCl (0.080 g, 0.42 mmol) in ether (3 ml). After stirring at ambient temp. for 15 h, the mixture was alkalized, extracted with ether (2 x), the aqueous phase acidified and extracted with CH_2Cl_2 (6 x). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated to furnish **14a**.- Yield 0.051 g (62%) colorless crystals.- m.p. 165°C.- $C_{13}H_{17}NO_5S$ (299.3) Calcd. C 52.2 H 5.72 N 4.7 Found C 52.0 H 5.78 N 4.7.- IR (KBr): 3530; 3420 (OH); 3000-2860; 1715 (C=O acid); 1595; 1495; 1445; 1425; 1340; 1325; 1225; 1155; 1095; 940; 900; 820; 725; 655 cm^{-1}.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.29 (1H, m, H-5), 1.47 (1H, m, $J_{5a,5e}$ = 13.1 Hz, H-5), 1.63 (1H, ddd, $J_{3a,3e}$ = 13.9 Hz, $J_{2,3a}$ = 6.9 Hz, $J_{3a,4}$ = 2.3 Hz, H_a-3), 2.14 (1H, m, $J_{3a,3e}$ = 13.9 Hz, H_e-3), 2.38 (3H, s, CH_3), 3.39 (1H, m, H_e-6), 3.58 (1H, ddd, $J_{6a,6e}$ = 12.9 Hz, $J_{5a,6a}$ = 9.8 Hz, $J_{5e,6a}$ = 3.1 Hz, H_a-6), 3.81 (1H, m, H-4), 4.37 (1H, dd, $J_{2,3a}$ = 6.9 Hz, $J_{2,3e}$ = 2.3 Hz, H-2), 4.65 (1H, bs, OH), 7.37 (2H, d, J = 8.3 Hz, H arom.), 7.69 (2H, d, J = 8.3 Hz, H arom.), 12.41 (1H, bs, COOH).- ^{13}C-NMR (DMSO-d_6): δ (ppm) = 20.95 (CH_3), 30.74 (C-5), 33.62 (C-3), 36.99 (C-6), 51.75 (C-2), 61.03 (C-4), 126.71, 129.57, 137.91, 142.69 (C arom.), 172.08 (COOH).

2-Tosyl-6-oxa-2-azabicyclo[3.2.1]octane-7-one (**15a**)*)

14a (0.035 g, 0.12 mmol) and *p*-toluenesulfonic acid (0.020 g, 0.12 mmol) were refluxed in toluene for 2 h. After evaporation of the solvent the residue was chromatographed on a short column of silica gel with $CHCl_3$/Etac 9+1.- Yield 0.019 g (58%) colorless crystals (Etac/n-hexane 1+3).- m.p. 145°C.- $C_{13}H_{15}NO_4S$ (281.3) Calcd. C 55.5 H 5.37 N 5.0 Found C 55.8 H 5.51 N 4.9.- IR (KBr): 3020-2860; 1790 (C=O lactone); 1595; 1450; 1350; 1335; 1160; 145; 965; 945 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.05 (2H, m, H-5), 2.13 (1H, dd, $J_{3a,3e}$ = 14.1 Hz, $J_{3a,4e}$ = 2.1 Hz, H_a-3), 2.34 (1H, m, H_e-3), 2.43 (3H, s, CH_3), 2.80 (1H, ddd, $J_{6a,6e}$ = 12.2 Hz, $J_{5a,6a}$ = 10.3 Hz, $J_{5e,6a}$ = 6.1 Hz, H_a-6), 3.87 (1H, m, H_e-6), 4.60 (1H, d, $J_{2e,3e}$ = 4.3 Hz, H_e-2), 4.90 (1H, m, H_e-4), 7.33 (2H, d, J = 8.2 Hz, H arom.), 7.74 (2H, d, J = 8.2 Hz, H arom.).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.57 (CH_3), 28.49 (C-5), 37.40 (C-3), 40.32 (C-6), 55.26 (C-2), 76.21 (C-4), 128.07, 129.62, 133.91, 144.22 (C arom.), 170.97 (-CO_2- lactone).- MS: m/z = 281 ($M^{+\cdot}$, 8.5%), 237 (76), 155 (35), 106 (10), 91 (97), 82 (100).

cis-2-Hydroxymethyl-N-tosyl-piperidine-4-ol (**16**)

15a (0.040 g, 0.14 mmol) in absol. THF (5 ml) was treated with $LiBH_4$ (0.010 g, 0.46 mmol). After 1 h N-HCl was added and THF was evaporated. Extraction with CH_2Cl_2 (3 x), drying (Na_2SO_4) of the combined org. phases and evaporation furnished a colorless powder. Recrystallization from Etac/n-hexane 1+1 gave colorless crystals.- Yield 0.037 g (91%).- m.p. 110°C.- $C_{13}H_{19}NO_4S$ (285.4) Calcd. C 54.7 H 6.71 N 4.9 Found C 55.1 H 6.62 N 4.7.- IR (KBr): 3170 (OH); 3020-2840; 1595; 1490; 1460; 1335; 1315; 1150; 1110; 945; 835; 810; 685 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.54 (2H, m, H-5), 1.77 (2H, m, H-3), 2.43 (3H, s, CH_3), 2.83 (2H, bs, 2 x OH), 3.50-4.10 (6H, 3 x m, H-6, CH_2O, H-2, H-4), 7.30 (2H, d, J = 8.1 Hz, H arom.), 7.74 (2H, d, J = 8.1 Hz, H arom.).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.51 (CH_3), 31.41 (C-5), 32.92 (C-3), 37.37 (C-6), 52.90 (C-2), 62.88 (C-4), 64.97 (CH_2OH), 126.96, 129.80, 138.01, 143.32 (C arom.).

References

1 Part XI: C. Herdeis and W. Engel, Arch. Pharm. *325*, 411 (1992).

2 M.K. Tong, E.M. Blumenthal, and B. Ganem, Tetrahedron Lett. *31*, 1683 (1990); B.L.J. Liotta, R.C. Bernotas, D.B. Wilson, and B. Ganem, J. Am. Chem. Soc. *111*, 783 (1989).

3 S. Hünig and G. Wehner, Synthesis *1975*, 180; H.U. Reissig and E. Hirsch, Angew. Chem. Int. Ed. *19*, 813 (1980).

4 W. Engel, lecture at the meeting of the German Pharmaceutical Society (DPhG) at Berlin, Sept. 1990; Arch. Pharm. (Weinheim) *323*, 632 (1990).

5 For other methods see: P. Hartmann and J.-P. Obrecht, Synth. Commun. *18*, 553 (1988); from (*S*)-*cis*-4-hydroxypipecolic acid: G. Jollès, G. Piget, J. Robert, B. Terlain, and J.-P. Thomas, Bull. Soc. Chim. France *1965*, 2252; M.Y. Essawi and P.S. Portoghese, J. Heterocycl. Chem. *20*, 477 (1983). Leading references for the synthesis of substituted pipecolic acid derivatives: S.R. Angle and D.O. Arnaiz, Tetrahedron Lett. *30*, 515 (1989); see reference 3 and 4.

6 P.J. Harrison showed that in a similar case the diastereoselectivity of the reduction is pH-dependent. In alkaline medium the *cis* diastereomer is the only product: J.P. Harrison, Tetrahedron Lett. *30*, 7125 (1989).

7 See *e.g.*: B.J. Arnold, S.M. Mellows, P.G. Sammes, and T.W. Wallace, J. Chem. Soc. Perkin Trans. I, *1974*, 401; J.L. Charlton and K. Koh, Synlett *6*, 333 (1990).

8 O. Mitsunobu, Synthesis *1981*, 1.

9 S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc. *102*, 3248 (1980). [Ph945]

*) Carbon atoms are numbered in analogy to pipecolic acid derivatives.