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Synthesis of the 3-Hydroxy Oxiracetam Enantiomers, Potential Nootropic Drugs

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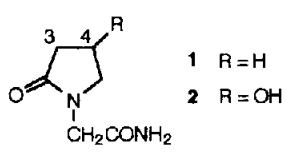
Abstract: The enantioselective synthesis of the potentially nootropic compounds **3-6** is reported. Derivative **3** was obtained from the readily available L-tartaric acid, by reduction of the imide **8** prepared with methyl glycinate. The other derivatives **4-6** were obtained from the dihydroxylactam **11**. Protection of one of the hydroxyl groups and a Mitsunobu reaction or triflate displacement of the other group produces the remaining stereoisomers. Aminoderivatives **25** and **27** were obtained by displacement with sodium azide and reduction.

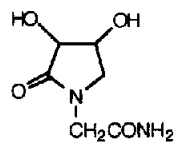
Introduction

Nootropics are drugs used in the therapy of primary dementia; they improve learning and memory,[1,2] although the precise mechanism of action is not known.[3] No definitive drug has yet been discovered and the known nootropics have lower activity in human beings than in the tested animals.[4]

Piracetam, **1**, a lactam derivative from γ-aminobutyric acid (GABA), is a prototype of nootropics, most of which are related to it. The most frequent structural changes correspond to the modification of the nitrogen substituent (etiracetam, pramiracetam, rolziracetam, dupracetam, aniracetam, etc.). However, the introduction of a hydroxyl group at C-4, as in oxiracetam, **2**,[5] improves the activity at lower doses as compared with piracetam.[6]



1 R = H
2 R = OH



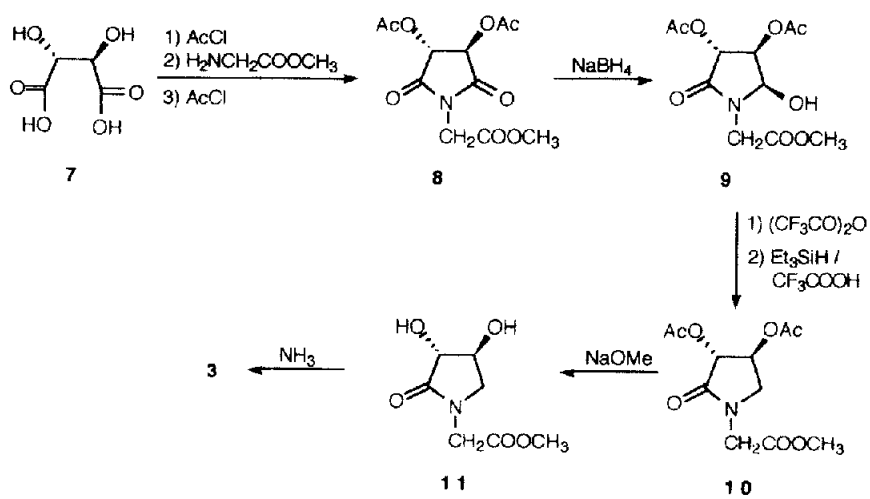
	C_3	C_4
3	····OH	— OH
4	— OH	— OH
5	····OH	····OH
6	— OH	····OH

Oxiracetam has been synthesized by three different methodologies: cyclization of ß-hydroxy-γ-aminobutyric acid (GABOB),[8] reduction of one carbonyl group in a pyrrolidine precursor,[9] and cyclization from suitably substituted primary amines.[10] In our previous paper we described a new method for the asymmetric synthesis of both enantiomers of oxiracetam from L- and D-malic acids.[11] We have now achieved the stereospecific synthesis of the four 3-hydroxyderivatives **3-6** starting from L-tartaric acid **7**. Our methodology has proved to be very convenient for the synthesis of polyhydroxy(amino)substituted cyclic compounds.

Results and Discussion

The chiral precursor, **7** was treated sequentially with acetyl chloride, methyl glycinate and then acetyl chloride again to give the C_2 symmetric succinimide **8** in 81 % overall yield. The methyl ester group of this compound is sensitive to sodium borohydride reduction, so very mild conditions (-40°C, 1mol) were required to produce the hydroxylactam **9**, which was obtained in 80 % yield after chromatography. The H-5 signal of the NMR spectrum of **9** appears as a doublet (J= 5.2 Hz), in agreement with the *cis* relationship between the acetate and the hydroxyl groups.[12] The 4,5-*cis*-lactam **9** was the only isolated isomer, although the *trans* carbinol could also be produced as a minor product. Compound **9** was first esterified with trifluoroacetic anhydride (TFAA) and then reduced with the hydrogenating pair triethylsilane/trifluoracetic acid to the pyrrolidone **10**, in 79 % yield. Deacylation of acetates with sodium methoxide led to the intermediate **11** (97 % yield), which was subjected to ammonolysis to yield the desired dihydroxy derivative **3**.

Scheme I



Compound **11** is a suitable intermediate for the synthesis of the remaining isomers **4-6**. Due to their relative position respect to the carbonyl group, the two hydroxyl groups have different reactivity, which allows selective protection and epimerization reactions for the synthesis of the desired derivatives.

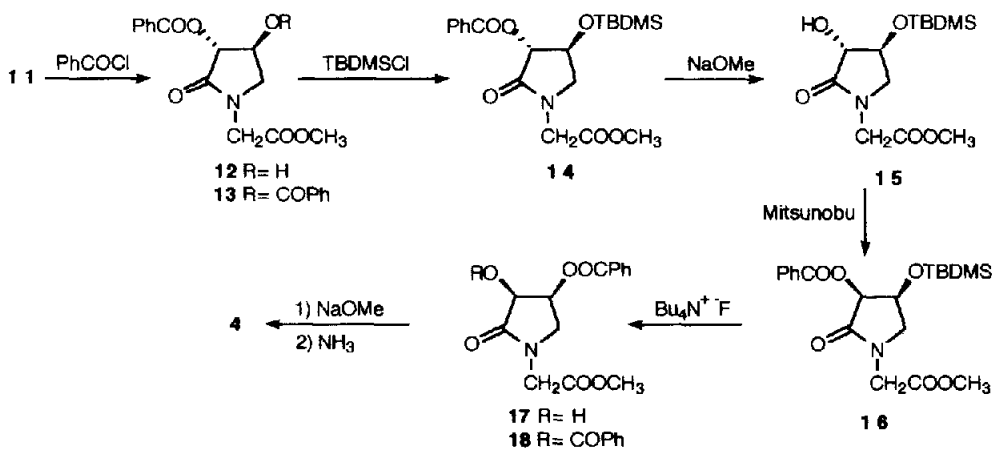
The synthesis of **4** from **11** requires a selective epimerization of the C-3 hydroxyl group. This is not an easy task, as has been shown in the work of Fleet's group[13] with similar hydroxy-δ-lactones. Triflate was

required to achieve S_N2 displacement at C-3 because other leaving groups failed in this transformation. The C-3 epimerization could also be done by the Mitsunobu[14] reaction.

First we obtained the monoprotected hydroxypyrrolidone **12** by selective monobenzoylation of **11**. *Tert*-butyldimethylsilylation (TBDMS) of the C-4 hydroxyl group produced **14**, and debenzoylation gave **15**, (52 % overall yield) (Scheme II).

The epimerized benzoate **16** was prepared in 46 % yield by treating a mixture of alcohol **15** and benzoic acid with diethyl azodicarboxylate (DEAD) and triphenylphosphine (TTP). As removal of the silylether in **16** does not take place under acidic conditions (AcOH/H_2O/THF 3:1:1), fluoride ion[15] had to be used. While handling, deprotection took place with partial intramolecular transesterification of the benzoyl group from the C-3 to the C-4 hydroxyl group.[16] This transformation was completed during chromatographic purification to give product **17** (56 % yield). Such transesterification also confirms the *cis*-relationship of both hydroxyl groups. Finally, deprotection with sodium methoxide followed by ammonolysis gave **4** in 58 % yield.

Scheme II



Conversion of **12** into **5** requires C-4 epimerization, which takes place spontaneously in the benzyloxytriflate **19**. Treatment of monobenzoate **12** with triflic anhydride in pyridine[17] gave the triflate **19**. This compound undergoes an internal S_N2 displacement of the benzoyl group through the benzoxonium ion **20**, which on hydrolysis[18] afforded the monobenzoate **21** in 98 % yield. The spectroscopic properties of compound **21** were identical to those of compound **17** and its specific rotation had similar absolute values but opposite sign. Treatment of **21** with NaOMe, followed by NH_3 gave compound **5** in 58 % yield.

The last isomer **6** was obtained from **21** by Mitsunobu's epimerization at C-3 to give **23** (53 % yield), which on hydrolysis and ammonolysis gave **6** (58 % yield) (Scheme III). This isomer was also obtained by the same procedure described for compound **3**, but starting from D-tartaric acid.

In order to corroborate the assigned configurations to the four stereoisomers the CD curves of the respective dibenzoate derivatives were recorded. According to the CD Exciton Chirality Method applied to α–glycol dibenzoates,[19] a first Cotton effect appears at λ= 237 nm and a second Cotton effect, of opposite sign[20]

appears at λ= 222 nm with nearly half the intensity. The data from CD curves shown in table I are in agreement with the assigned configurations.

To check the posibilities of our strategy for the preparation of amino analogs and derivatives of oxiracetam, we have accomplished the synthesis of compounds **25-27** (Scheme IV). Between the reactions described to

Scheme III

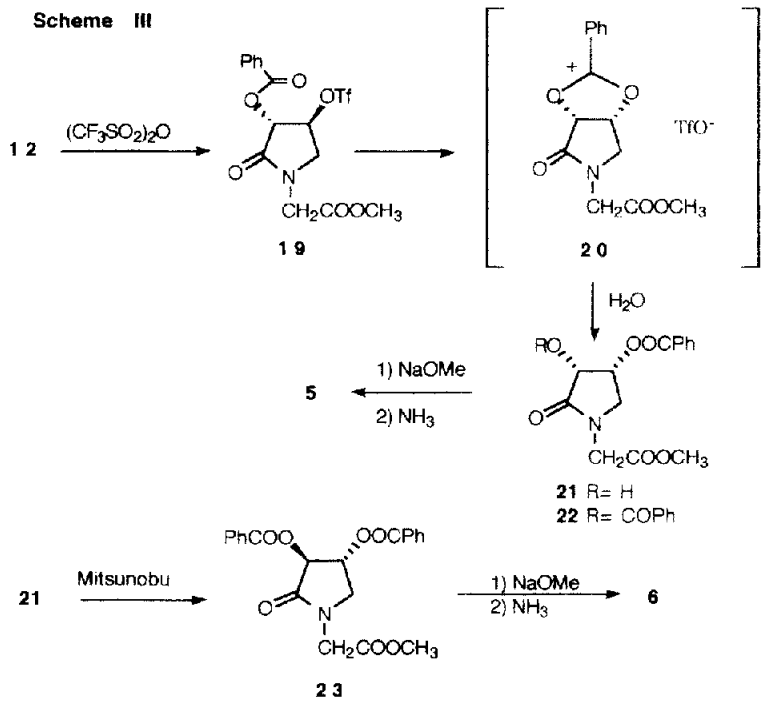


Table I. Chiroptical properties of 1,2-dibenzoates: **13**, **18**, **22** and **23**.

ISOMER	C[a]	$\Delta\varepsilon_1$	$\Delta\varepsilon_1/\Delta\varepsilon_2$	θ[b]
3R,4S **13**	+	+28.7	-	+87
3S,4R **23**	-	-27.2	-	-87
3R,4R **22**	-	-15.3	2.2	-41
3S,4S **18**	+	+16.7	1.9	+41

[a]Chirality

[b]Dihedral angles estimated from minimized molecular models

replace a hydroxyl group by an amino group,[21] we chose the displacement of a triflate group by sodium azide[14] which gave better yields and made the workup easier. Thus, azide **24** was obtained from alcohol **15** in 87 % yield, and azide **26** was obtained from alcohol **20** in 94 % yield. The reduction of both azides was achieved by catalytic hydrogenation,[22] so the amine **25** was obtained in 52 % yield from **24** and the amine **27** in 60 % yield from **26**. Amine **27** readily eliminates the benzoyl group to give **28**.

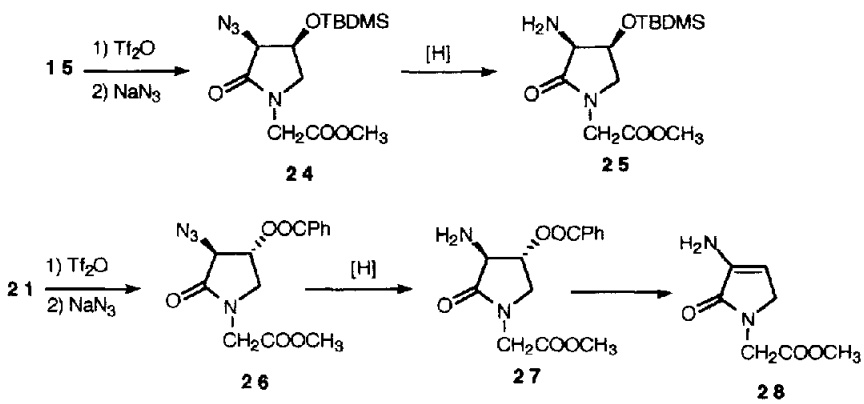
The 3,4-*cis* or *trans* configuration for these aminoderivatives **25** and **27** could not be inferred from the coupling constant $J_{3,4}$ because in both cases this constant displays similar values (J= 5 and 7 Hz respectively). Nevertheless, the ^{1}H-NMR coupling constants of the C-5 methylene hydrogens are suitable for this purpose.

According to the reported NMR data for 3,4-dibenzoyloxytetrahydrofuran-2-ones[23] and those for the preceding oxiracetam derivatives, the 3,4-*cis* isomers show a smaller coupling constant $J_{4,5a}$ than the *trans* isomers (*cis* = 0-2 Hz ; *trans* = ≥ 5 Hz).[24]

Thus, the observed coupling constants for the amino oxiracetam derivatives suggest 3,4-*cis* configuration for **25** and 3,4-*trans* for **27**, which agrees with an inversion of the C-3 configuration in the azide displacement of the triflate leaving group.

In conclusion, we have achieved the stereospecific synthesis of the four 3-hydroxy oxiracetam stereoisomers. In addition, we have opened a stereocontrolled route to different derivatives, such as 3-aminooxiracetam analogs, as well as to other polyhydroxy and polyamino lactones and pyrrolidones.

Scheme IV



EXPERIMENTAL.

General --Melting points are uncorrected. IR were measured in a Bomem MB-100 FT instrument. ^{1}H-NMR spectra were recorded on a Bruker WP 200 SY at 200 MHz. CD curves were recorded in a Jobin-Yvon MarkIII Dichrograph in ethanol. Optical rotations were measured with a 1-dm cell. Column chromatography separations were carried out on SiO_2 (silicagel 60, 0.063-0.200 mm, Merck) or on florisil (florisil 60-100, 0.150-0.250 mm, Merck) when specified. All organic extracts prior to concentration under reduced pressure, were dried over anhydrous Na_2SO_4 .

(3*R*,4*R*) 3,4-diacetoxy-*N*-methoxycarbonylmethyl-2,5-pyrrolidinedione (8). To a freshly prepared solution of glycine methyl ester[25] (2.6g, 29 mmol) in Et_2O at 5 °C (30 mL) a solution of (2*R*,3*R*) 2,3-diacetoxy tartaric anhydride (6.3 g, 29 mmol), from **7** and acetyl chloride, in CH_2Cl_2 (90 mL) was added dropwise. After evaporation of the solvent, acetyl chloride (20 mL, 22 g, 280 mmol) was added. This suspension was heated under reflux for 20 hours. Excess of solvent was removed in vacuo, $CHCl_3$ (70 mL)

was added, and the solution was washed once with water and twice with saturated $NaHCO_3$. Evaporation of the dried organic layer gave 3.6 g (81 %) of **8** as a syrup. A sample was purified by column chromatography (1:1 hexane-EtOAc as eluent): IR (neat): 1755, 1724 cm^{-1}; NMR ($CDCl_3$) δ : 5.63 (s, 2H, CHOAc) , 4.31 (s, 2H, NCH_2) , 3.75 (s, 3H, OCH_3) , 2.17 (s, 3H, $COCH_3$). Anal. Calcd for $C_{11}H_{13}NO_8$: C, 46.00; H, 4.56; N, 4.88. Found: C, 45.61; H, 4.77; N, 4.57.

(3*R*,4*R*,5*R*) 3,4-diacetoxy-5-hydroxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (9). To a solution of succinimide **8** (3.5 g, 12 mmol) in THF (40 mL) and water (2 mL) at -40 °C, powdered $NaBH_4$ (460 mg, 12 mmol) was added in portions for one minute. The suspension was stirred for 3 hours, and then was allowed to slowly warm to 0 °C. After quenching the excess of $NaBH_4$ with 2N ClH, the solvent was vacuum evaporated and the residue was taken with $CHCl_3$ (50 mL). The dried solvent was evaporated and the syrup was purified by florisil column chromatography with 2:1 hexane-EtOAc as eluent to afford 2.8 g (80 %) of carbinol lactam **9** as a white solid: mp 68-72 °C (Hexane/AcOEt); $[\alpha]_D^{20}$ +11.2 (c 1%, MeOH); IR (Neat): 3269, 1763, 1738, 1724, 1697 cm^{-1}; NMR ($CDCl_3$) δ: 5.26 (d, J= 5.2 Hz, 1H, CHOH), 5.15 (m, 2H, CHOAc), 4.29 (d, J= 17.7 Hz, 1H, NCH_A), 4.01 (d, J= 17.7 Hz, 1H, NCH_B), 3.73 (s, 3H, OCH_3), 2.14 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$).Anal. Calcd for $C_{11}H_{15}NO_8$: C, 45.68; H, 5.23; N, 4.84. Found: C, 45.53; H, 5.34; N, 4.77.

(3*R*,4*R*) 3,4-diacetoxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (10). To a solution of carbinol lactam **9** (7.2 g, 25 mmol) in $CHCl_3$ (60 mL) at r.t., TFAA (6.3 g, 30 mmol) was added. After 30 min. the solvent was evaporated. The remaining oil was dissolved in TFA (10 mL), and triethylsilane (3.4 g, 29 mmol) was added. The solution was stirred for one hour at r.t., then concentrated under vacuum until a viscous oil was obtained. This oil was dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$, dried, and the solvent was evaporated to give 5.4 g (79 %) of lactam **10** as an oil. A sample was purified by column chromatography with EtOAc: $[\alpha]_D^{20}$ +78.6 (c 1%, MeOH); IR (neat): 3339, 2957, 1746, 1659 cm^{-1}; NMR ($CDCl_3$) δ 5.44 (d, 1H, J= 6.2 Hz, COCHOAc), 5.28 (ddd, J= 6.2, 8 and 6 Hz, 1H, $CH_2\underline{C}HOAc$), 4.18 (d, J= 17.6 Hz, 1H, CH_2COO), 3.88 (d, J=17.6 Hz, 1H, CH_2COO), 3.80 (dd, J= 8 and 10 Hz, 1H, $C\underline{H}_ACHOAc$), 3.68 (s, 3H, OCH_3), 3.36 (dd, J= 6 and 10 Hz, 1H, $C\underline{H}_BCHOAc$), 2.08 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$). Anal. Calcd for $C_{11}H_{15}NO_7$: C, 48.35; H, 5.53; N, 5.12. Found: C, 48.60; H, 5.39; N, 4.84.

(3*R*,4*S*) 3,4-dihydroxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (11). The crude lactam **8** (5.4 g, 20 mmol) was dissolved in MeOH (50 mL) and a few drops of sodium methoxide in MeOH was added. After five min. glacial acetic acid was dropped to quench the solution and the solvent was evaporated. The crude product was crystallized in MeOH to afford 3.6 g of alcohol **11** as colorless crystals: mp 139-142 °C (MeOH); $[\alpha]_D^{20}$ +57.9 (c 1%, MeOH); IR (Nujol): 3318, 3173, 1749, 1734, 1680 cm^{-1}; NMR (DMSO d_6) δ 5.71 (d, J= 5.7 Hz, 1H, OH), 5.51 (d, J= 4.5 Hz, 1H, OH), 4.08 (d, J= 17.5 Hz, 1H, CH_ACOO), 3.97 (m, 1H, $CH_2C\underline{H}OH$), 3.93 (d, J= 17.5 Hz, 1H, CH_BCOO), 3.84 (m, 1H, $COC\underline{H}OH$), 3.64 (s, 3H, OCH_3), 3.44 (dd, J= 9.2 and 7.3 Hz, 1H, $C\underline{H}_ACHOH$), 3.04 (dd, J= 9.2 and 6.9 Hz, 1H, $C\underline{H}_BCHOH$). Anal. Calcd for $C_7H_{11}NO_5$: C, 44.45; H, 5.86; N, 7.40. Found: C, 44.59; H, 5.98; N, 7.24.

(3*R*,4*S*) 3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (3). Alcohol **11** (3.7 g, 20 mmol) was dissolved in dry MeOH and the solution saturated with ammonia gas. After one hour the solvent was evaporated and the residue crystallized in MeOH to give 2.08 g (60 %) of **3** as colorless crystals: mp 145-146 °C (MeOH); $[\alpha]_D^{20}$ +67.1 (c 1%, MeOH); IR (Nujol): 3374, 3318, 3208, 1690, 1657 cm^{-1}; NMR (DMSO d_6) δ 7.35 (s, 1H, NH), 7.07 (s, 1H, NH), 5.61 (d, J= 5.7 Hz, 1H, OH), 5.46 (d, J= 5 Hz, 1H, OH), 3.98 (m, 1H, $CH_2C\underline{H}OH$), 3.93 (m, 1H, $COC\underline{H}OH$), 3.85 (d, J= 17 Hz, 1H, CH_ACONH_2), 3.63 (d, J= 17 Hz, 1H, CH_BCONH_2), 3.39 (dd, J= 7 and 9.1 Hz, 1H, $C\underline{H}_ACHOH$), 3.05 (dd, J= 6.7 and 9.1 Hz, 1H, $C\underline{H}_BCHOH$). Anal. Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.08. Found: C, 41.31; H, 5.77; N, 16.09.

(3*R*,4*S*) 3-benzoyloxy-4-hydroxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (12). Benzoyl chloride (3.06 g, 22 mmol) was added to a solution of **11** (3.82 g, 20 mmol) in pyridine (75 mL) at -30 °C. After one hour the solution was allowed to slowly warm to 0 °C (3 hours). Then the solution was poured into EtOAc (100 mL) and washed with 2N HCl. Evaporation of the dried organic layer gave an oil that was purified on column chromatography with 1:1 hexane-EtOAc as eluent to afford 4.2 g (71%) of **12** as a white solid: mp 98-100 °C (hexane/EtOAc); $[\alpha]_D^{20}$ +79.1 (c 1%, MeOH); IR (nujol) 3265, 3173, 2926, 1751, 1723 cm^{-1}; NMR ($CDCl_3$) δ 8.09 (m, 2H, PhH), 7.57 (m, 1H, PhH), 7.43 (m, 2H, PhH), 5.34 (d, J= 6 Hz, 1H, CHOOCPh), 4.56 (dt, J= 6 and 8 Hz, $C\underline{H}OH$), 4.20 (d, J= 18 Hz, 1H, CH_ACOO), 4.05 (d, J= 18 Hz, 1H, CH_BCOO), 3.75 (s, 3H, OCH_3), 3.74 (m, 1H, $C\underline{H}_ACHOH$), 3.47 (dd, J= 6 and 10 Hz, 1H, $C\underline{H}_BCHOH$). Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.59; H, 5.08; N, 4.53.

(3*R*,4*S*) 3,4-dibenzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (13): mp 96-98 °C (hexane/EtOAc); $[\alpha]_D^{20}$ +134.6 (c 1%, MeOH); $\Delta\varepsilon_{237}$ (6.5 10^{-4}M, EtOH)= +28.7; IR (nujol): 1746, 1723, 1713, 1601, 1582 cm^{-1}; NMR ($CDCl_3$) δ 8.06 (m, 4H, PhH), 7.56 (m, 2H, PhH), 7.44 (m, 4H, PhH), 5.95 (d, J= 6 Hz, 1H, COCH), 5.70 (dt, J= 6 and 8 Hz, $CH_2C\underline{H}$), 4.36 (d, J=18 Hz, 1H, CH_ACOO), 4.10 (dd, J= 8 and 10 Hz, 1H, $C\underline{H}_ACH$), 3.98 (d, J= 18 Hz, 1H, $C\underline{H}_BCOO$), 3.76 (s, 3H, OCH_3), 3.62 (dd, J= 6 and 10 Hz, $C\underline{H}_BCH$) Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.63; H, 4.95; N, 3.70.

(3*R*,4*S*) 3-benzoyloxy-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (14). A mixture of **12** (3.9 g, 13 mmol), TBDMSCl (2.41 g, 16 mmol), DMAP (690 mg, 6 mmol) and TEA (1.39 g, 14 mmol) was stirred 5 hours at rt. Then EtOAc was added and the solution washed with 2N HCl and dried. The solvent was evaporated to give 5.16 g (95 %) of **14** as a solid: mp 84-86 °C (hexane/EtOAc); $[\alpha]_D^{20}$ +75.0 (c 1%, MeOH); IR (nujol) 1736, 1724, 1711, 1601, 1585 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (m, 2H, PhH), 7.54 (m, 1H, PhH), 7.43 (m, 2H, PhH), 5.62 (d, J= 7 Hz, 1H, CHOOCPh), 4.68 (c, J= 7 Hz, 1H, CHOSi), 4.17 (d, J= 18 Hz, 1H, CH_ACOO), 4.03 (d, J= 18 Hz, 1H, CH_BCOO), 3.74 (s, 3H, OCH_3), 3.61 (dd, J= 7 and 10 Hz, 1H, $C\underline{H}_ACHOSi$), 3.41 (dd, J= 7 and 10 Hz, 1H, $C\underline{H}_BCHO$), 0.84 (s, 9H, $C(CH_3)_3$), 0.036 (s, 3H, $SiCH_3$), 0.015 (s, 3H, $SiCH_3$). Anal. Calcd for $C_{20}H_{29}NO_6Si$: C, 58.94; H, 7.17; N, 3.43. Found: C, 59.23; H, 7.38; N, 3.22.

(3*R*,4*S*) 3-Hydroxy-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (15). Crude **14** (4.9 g, 12 mmol) was dissolved in a solution of sodium methoxyde in MeOH. After 3

hours, glacial acetic acid was dropped to quench the methoxyde. The solvent was vacuum evaporated and the oil purified on florisil column chromatography with EtOAc as eluent to afford 2.63 g (72 %) of alcohol **15** as an oil: $[\alpha]_D^{20}$ +40.0 (c 1%, MeOH); IR (neat): 3366 (broad), 2955, 2935, 1753, 1701 cm^{-1}; NMR ($CDCl_3$) δ 4.33 (c, J= 7 Hz, 1H, CHOSi), 4.21 (d, J= 7 Hz, 1H, C<u>H</u>OH), 4.15 (d, J= 18 Hz, 1H, CH_ACOO), 3.91 (d, J= 18 Hz, 1H, CH_BCOO), 3.71 (s, 3H, OCH_3), 3.44 (dd, J= 7 and 9 Hz, 1H, C<u>H</u>$_A$CHOSi), 3.26 (dd, J= 7 and 9 Hz, 1H, C<u>H</u>$_B$CHOSi), 0.87 (s, 9H, $C(CH_3)_3$), 0.11 (s, 3H, $SiCH_3$), 0.082 (s, 3H, $SiCH_3$). Anal. Calcd for $C_{13}H_{25}NO_5Si$: C, 51.45; H, 8.30; N, 4.62. Found: C, 51.63; H, 8.50; N, 4.48.

(3*S*,4*S*) 3-Benzoyloxy-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (16). A solution of TTP (1.7 g, 6.5 mmol) and DEAD (1.14 g, 6.5 mmol) in dry THF (20 ml) was added dropwise under nitrogen to a solution of alcohol **15** (1.5 g, 5 mmol) and benzoic acid (0.8 g, 6.5 mmol) in dry THF (40 ml) at 5 °C. After 16 hours at r.t. the solvent was evaporated and the residue purified on florisil column chromatography with EtOAc as eluent to give 925 mg (46 %) of **16** as an oil: $[\alpha]_D^{20}$ +30.4 (c 1%, MeOH); IR (neat) 2955, 2932, 2895, 2859, 1753, 1721, 1603, 1584 cm^{-1}; NMR ($CDCl_3$) δ 8.08 (m, 2H, PhH), 7.48 (m, 1H, PhH), 7.37 (m, 2H, PhH), 5.40 (d, J= 5 Hz, 1H, CHOOCPh), 4.68 (m, 1H, CHOSi), 4.37 (d, J= 18 Hz, 1H, CH_ACOO), 3.87 (d, J= 18 Hz, 1H, CH_BCOO), 3.68 (s, 3H, OCH_3), 3.79 (dd, J= 4 and 10 Hz, 1H, CH_ACHOSi), 3.28 (dd, J= 1 and 10 Hz, 1H, CH_BCHOSi), 0.72 (s, 9H, $C(CH_3)_3$), -0.027 (s, 3H, $SiCH_3$), -0.15 (s, 3H, $SiCH_3$). Anal. Calcd for $C_{20}H_{29}NO_6Si$: C, 58.94; H, 7.17; N, 3.44. Found: C, 59.18; H, 7.32; N, 3.29.

(3*S*,4*S*) 3-hydroxy-4-benzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (17). Tetrabutylammonium fluoride (510 mg, 1.6 mmol) was added to a solution of **16** (0.5 g, 1.2 mmol) and glacial acetic acid (98 mg, 1.6 mmol) in THF (20 mL). After 15 hours at r.t. the solvent was evaporated. The residue was taken up with EtOAc (30 mL) and washed with water. The solvent of the dried organic layer was evaporated to afford 400 mg of an oil that was purified on column chromatography with EtOAc as eluent to give 200 mg (56 %) of alcohol **17** as white crystals: mp 101-104 °C (hexane/EtOAc); $[\alpha]_D^{20}$ +9.1 (c 1%, MeOH); IR (nujol): 3339, 3265, 1736, 1722, 1711 cm^{-1}; NMR ($CDCl_3$) δ 8.04 (m, 2H, PhH), 7.53 (m, 1H, PhH), 7.40 (m, 2H, PhH), 5.72 (t, J= 5 Hz, 1H, CHOOCPh), 4.56 (t, J= 5 Hz, 1H, C<u>H</u>OH), 4.32 (d, J= 18 Hz, 1H, CH_ACOO), 3.92 (d, J= 18 Hz, 1H, CH_BCOO), 3.90 (dd, J= 4 and 11 Hz, 1H, C<u>H</u>$_A$CHOOCPh), 3.69 (s, 3H, OCH_3), 3.50 (d, J= 11 Hz, 1H, C<u>H</u>$_B$CHOOCPh), 3.46 (d, J=5 Hz, 1H, CHO<u>H</u>). Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.51; H, 5.36; N, 4.64.

(3*S*,4*S*) 3,4-dibenzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (18). A solution of **17** (128 mg, 0.44 mmol) and benzoyl chloride (90 mg, 0.65 mmol) in pyridine (2 mL) was kept at -5°C all over the night, then poured into EtOAc (25 mL) and washed with 2N HCl. Evaporation of dried organic layer gave an oil which was purified on column chromatography with hexane/EtOAc 8:2 and crystallized in EtOH to afford 180 mg (73%) of **18** as fine white needles: mp 99-100 °C (EtOH); $[\alpha]_D^{20}$ +40.2 (c 1%, MeOH); $\Delta\varepsilon_{237}$ ($6.5\ 10^{-4}$M, EtOH)= +16.7; IR (nujol) 1744, 1732, 1711, 1603, 1585 cm^{-1}; NMR ($CDCl_3$) δ 7.95 (m, 4H, Ph); 7.50 (m, 2H, Ph); 7.35 (m, 4H, Ph); 5.90 (m, 1H, CHOOCPh); 5.85 (d, 1H, J= 5.6 Hz, CHOOCPh); 4.38 (d, 1H, J= 18 Hz, CH_ACOO); 4.05 (dd, 1H, J= 11 and 6 Hz, C<u>H</u>$_A$CHOOCPh); 4.00 (d, 1H, J= 18 Hz, CH_BCOO); 3.74 (s, 3H, OCH_3); 3.64 (d, 1H, J= 11 Hz, C<u>H</u>$_B$CHOOCPh) Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.57; H, 4.86; N, 3.63.

(3*S*,4*S*) 3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (4). To a solution of alcohol **17** (200 mg, 1 mmol) in MeOH (10 mL), a few drops of a solution of sodium methoxide in MeOH were added. After 15 min. glacial acetic acid was dropped to quench the methoxide and the solution was saturated with ammonia gas. Evaporation of the solvent one hour later and purification of the syrup on column chromatography with 7:3 $CHCl_3$-MeOH as eluent gave 70 mg (59 %) of **4** as colorless crystals: mp 146-148 °C (MeOH); $[\alpha]_D^{20}$ -10.3 (c 1%, MeOH); IR (Nujol): 3466, 3391, 3318, 3214, 1688, 1668, 1624 cm^{-1}; NMR (DMSO d_6) δ 7.24 (s, 1H, NH), 7.16 (s, 1H, NH), 5.39 (d, J= 7 Hz, 1H, COCHOH), 4.98 (d, J= 4 Hz, 1H, CH_2CHOH), 4.13 (m, 1H, COCHOH), 4.11 (m, 1H, CH_2CHOH), 3.91 (d, J= 17 Hz, 1H, CH_ACOO), 3.56 (d, J= 17 Hz, 1H, CH_BCOO), 3.52 (dd, J= 4 and 11 Hz, 1H, CH_ACHOH), 3.06 (d, J= 11 Hz, 1H, CH_BCHOH). Anal. Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.08. Found: C, 41.12; H, 5.84; N, 15.88.

(3*R*,4*R*) 3-hydroxy-4-benzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (21). A solution of triflic anhydride (3.34 g, 12 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a well stirred solution of alcohol **12** (3.04 g, 10 mmol) and pyridine (860 mg, 11 mmol) in dry CH_2Cl_2 (30 mL) at 5 °C. After two hours the solution was washed twice with water and then once with saturated $NaHCO_3$. The solvent of dried organic layer was evaporated to give 3.0 g (98 %) of alcohol **21** as white crystals: mp 102-105 °C (hexane/EtOAc); $[\alpha]_D^{20}$ -9.7 (c 1%, MeOH). Spectroscopic data identical to those of **17**. Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.10; H, 5.07; N, 4.82.

(3*R*,4*R*) 3,4-dibenzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (22). Compound **21** was treated as described above to give dibenzoate **22** : mp 99-101 °C (EtOH); $[\alpha]_D^{20}$ -39.9 (c 1%, MeOH); $\Delta\varepsilon_{237}$ (6.5 10^{-4}M, EtOH)= -15.3. Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.62; H, 4.89; N, 3.71.

(3*R*,4*R*) 3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (5). Alcohol **21** (1g, 5 mmol) was treated as described above from **17** to **4** to afford 350 mg (59 %) of **5** as colorless crystals: mp 144-146 °C (MeOH); $[\alpha]_D^{20}$ +9.3 (c 1%, MeOH). The spectroscopic data were identical to those of **4**. Anal. Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.1. Found: C, 41.20; H, 5.82; N, 15.92. This substance was also obtained from D-tartaric acid according the procedure described for the synthesis of **3** (Scheme I).

(3*S*,4*R*) 3,4-dibenzoyloxy-*N*-methoxycarbonylmethyl-2-oxopyrrolidinone (23). A solution of TTP (600 mg, 2.3 mmol) and DEAD (400 mg, 2.3 mmol) in dry THF (4 mL) was dropped for 5 min, under nitrogen, on a solution of **21** (340 mg, 1.2 mmol) and benzoic acid (167 mg, 1.4 mmol) in dry THF at 5 °C. After 5 hours at r.t. the solvent was evaporated and the residue purified on column chromatography with 8:2 hexane-EtOAc as eluent to give 244 mg (53 %) of **23** as an oil: $[\alpha]_D^{20}$ -130.3 (c 1%, MeOH); $\Delta\varepsilon_{237}$ (5.3 10^{-4}M, EtOH)= -27.2.Spectroscopic data identical to those of **13**.Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.66; H, 4.92; N, 3.69.

(3*S*,4*R*) 3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (6). Compound **6** was prepared from **23** following the same procedure described wvobe for the synthesis of **4**. Thus, 244 mg (6 mmol) of **23** were

converted into 50 mg (48 %) of **6**. mp 148-149 °C (MeOH); $[\alpha]_D^{20}$ -70.1 (c 1%, MeOH). Spectroscopic data identical to those of **3**. Anal. Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.08. Found: C, 41.26; H, 5.76; N, 16.04.

(3*S*,4*S*) 3-Azido-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (24). Alcohol **14** (0.5 g, 1.7 mmol) and dry pyridine (160 mg, 2 mmol) was dissolved in dry $CHCl_3$ (10 mL) and cooled to 5 °C. Then a solution of triflic anhydride (5.5 g, 2 mmol) in dry $CHCl_3$ (8 mL) was dropped. One hour later more $CHCl_3$ (20 mL) was added and the solution washed with water. The organic layer was dried and the solvent evaporated. The oil was dissolved in dry DMF (2 mL) and sodium azide (0.5 g, 8 mmol) was added. The suspension was stirred for 3 hours at r.t. Then EtOAc (40 mL) was added and the solution washed with water. The solvent of the dried organic layer was evaporated and the residue was purified on column chromatography with 8:2 hexane-EtOAc as eluent to afford 485 mg (87 %) of azide **24** as an oil: $[\alpha]_D^{20}$: + 32.1 (c 1%, MeOH); IR (neat) 2114, 1751, 1709 cm^{-1}; NMR ($CDCl_3$) δ 4.51 (dt, J= 2 and 5 Hz, 1H, CHOSi), 4.46 (d, J= 18 Hz, 1H, CH_ACOO), 3.82 (d, J= 18 Hz, 1H, CH_BCOO), 3.79 (d, J= 5 Hz, 1H, CHN_3), 3.75 (dd, J= 10 and 5 Hz, 1H, $C\underline{H}_ACHOSi$), 3.74 (s, 3H, OCH_3), 3.26 (dd, J= 10 and 2 Hz, 1H, $C\underline{H}_BCHOSi$), 0.92 (s, 9H, $C(CH_3)_3$), 0.17 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$). Anal. Calcd for $C_{13}H_{24}N_4O_4Si$: C, 47.54; H, 7.37; N, 17.06. Found: C, 47.29; H, 7.57; N, 16.99.

(3*S*,4*S*) 3-Amino-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (25). A stirred suspension of palladium over charcoal at 5 % (270 mg) in EtOAc (10 mL) was kept one hour in H_2 at r.t.Then azide **24** (369 mg, 2.2 mmol) was added and hydrogenation went on for 4 more hours. The charcoal was filtered off and washed thoroughly with EtOAc. The solvent was evaporated and the oil purified on florisil column chromatography with EtOAc as eluent to afford 175 mg (52 %) of amine **25** as an oil: $[\alpha]_D^{20}$ +16.8 (c 1%, MeOH); IR (neat) 3385, 3325, 2930, 1751, 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.43 (t, J=5 Hz, 1H, CHOSi), 4.39 (d, J= 18 Hz, 1H, CH_ACOO), 3.78 (d, J= 18 Hz, 1H, $C\underline{H}_BCOO$), 3.73 (m, 1H, $C\underline{H}_ACHOSi$), 3.72 (s, 3H, OCH_3), 3.40 (d, J= 5 Hz, 1H, $C\underline{H}NH_2$), 3.16 (d, J= 10 Hz, 1H, $C\underline{H}_BCHOSi$), 1.69 (bs, 2H, NH_2), 0.88 (s, 9H, $C(CH_3)_3$), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$). Anal. Calcd for $C_{13}H_{26}N_2O_4Si$: C, 51.63; H, 8.67; N, 9.26. Found: C, 51.82; H, 9.11; N,8.51.

(3*S*,4*R*) 3-Azido-4-benzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (26). Alcohol **21** (0.5 g, 1.7 mmol) was treated as described above for **14**, to afford 0.5 g (94 %) of azide **26** as an oil: $[\alpha]_D^{20}$ -154.0 (c 1, MeOH); IR (neat) 2112, 1747, 1724, 1604, 1581 cm^{-1}; NMR ($CDCl_3$) δ 8.03 (m, 2H, PhH), 7.57 (m, 1H, PhH), 7.46 (m, 2H, PhH), 5.30 (dt, J= 6 and 7 Hz, 1H, CHOOCPh), 4.46 (d, J= 6 Hz, 1H, CHN_3), 4.27 (d, J= 18 Hz, 1H, CH_ACOO), 3.99 (dd, J= 7 and 10 Hz, 1H, $C\underline{H}_ACHOOCPh$), 3.90 (d, J= 18 Hz, 1H, CH_BCOO), 3.76 (s, 3H, OCH_3), 3.53 (dd, J= 6 and 10 Hz, $C\underline{H}_BCHOOCPh$) Anal. Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.6. Found: C, 52.68; H, 4.54; N, 17.55.

(3*S*,4*R*) 3-Amino-4-benzoyloxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (27). Azide **26** (460 mg, 1.5 mmol) was hydrogenated, as azide **24** , with Pd/C 5 % (190 mg) in EtOAc (10 mL) for 2 hours to give amine **27** (260 mg, 60 %) as an oil:.IR (film): 3774, 3324, 1748, 1713, 1660, 1603, 1582 cm^{-1}; NMR ($CDCl_3$) δ 8.03 (m, 2H, PhH), 7.57 (m, 1H, PhH), 7.44 (m, 2H, PhH), 5.25 (c, J= 7 Hz, 1H, CHOOCPh), 4.26 (d, J= 18 Hz, 1H, CH_ACOO), 3.95 (d, J= 18 Hz, 1H, CH_BCOO), 3.92 (dd, J= 7 and 10 Hz, $C\underline{H}_ACH$),

3.88 (d,J= 7 Hz, 1H, C<u>H</u>NH$_2$), 3.74 (s, 3H, OCH$_3$), 3.51 (dd, J= 7 and 10 Hz, 1H, C<u>H$_B$</u>CH), 1.88 (bs, 2H, NH$_2$). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.80; H, 5.73; N, 9.37.

2,5-Dihydro-4-amino-2-oxo-*N*-methoxycarbonylmethylpyrrole (28). The amine **27** on standing for one night at r.t. gave rise to a solid that was purified by column chromatography with EtOAc as eluent to afford benzoic acid and **28** as colorless crystals: mp 162-165°C (Hexane/EtOAc); IR(nujol):3383, 3144, 1732, 1693, 1663, 1651 cm^{-1}; NMR ($CDCl_3$) δ 5.85 (t, J=2.3 Hz, 1H, CH$_2$C<u>H</u>), 4.26 (s, 2H, CH$_2$COO), 4.05 (d, J= 2.3 Hz, 2H, C<u>H$_2$</u>CH), 3.72 (s, 3H, OCH$_3$). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.30; H, 5.88; N, 16.28.

References and Notes

1. a) Nicholson, C. D.; *Psychopharmacol.* **1990**, *101*, 147; b) Moos, W. H.; Davis, R. E.; Schwarz, R.D.; Gamzu, E.R.; *Medicinal Research Reviews*, **1988**, *8(3)*, 353.
2. a) Ponzio, F.; Pozzi, D.; Banfi, S.; Dorigotti, L.; *Pharmacopsych.* **1989**, *22 (Supl.)*, 111; b) Pepeu, G.; Spignoli, G.; *Ibid.*, **1989**, *13 (Supl. 3)* , 577; c) Marchi, M.; Besana, E.; Raiteri, M.; *Eur. J . Pharmacol.*, **1990**, *185*, 247; d) Mondadori, C.; Petschke, F.; Hausler, A.; *Pharmacopsych.*, **1989**, *22 (Supl. 2)*, 106; e) Mondadori, C.; Bhatnagar, A.; Borkowski, J.; Hausler, A.; *Brain Research*, **1990**, *506 (1)*, 101.
3. Cooper, J.K.; *Arch.-Intern. Med.*, **1991**, *151(2)*, 254
4. Gottfries, C.G.; *Pharmacopsych.* **1989**, *22 (Supl. 2)*, 129.
5. Nicolaus, B.; *Drug Development Research*, **1982**, *2*, 463.
6. Krylova, I.; Antonova, L.V.; Kamenskii, A.A.; Yasnetsov, V.V.; *Farmakov. Toksikol. (Moscow)*, **1991**, *54(1)*, 14.
7. Aschwanden, W.; Kyburz, E.; *Ger. Offen. DE 3 227 649*, **1983**. *C.A.*, **1983**, *98*, 160582.
8. a) Miyamoto, S.; Mori, A.; *Neurosciences*, **1985**, 11, 1; b) Monguzzi, R.; Pifferi, G.; *Ger. Offen. DE 2 759 033*, **1978**. *C.A.*, **1979**, *90*, 22797; c) Banfi, S.; Pellegata, R.; Pifferi, G.; Pinza, M.; *Ger. Offen. DE 2 758 937*, **1978**. *C.A.*, **1978**, *89*, 197330.
9. a) Pifferi, G.; Pinza, M.; *Ger. Offen. DT 2 635 853*, **1977**. *C.A.*, **1977**, *86*, 171253; b) Meul, T.; McGarrity, J.; *Eur. Pat. Appl. EP 249 018*, **1987**. *C.A.* **1988**, *108*, 167293; c) Meul, T.; *Eur. Pat. Appl. EP 252 353*, **1986**. *C.A.*, **1988**, *108*, 167294; d) Meul, T.; McGarrity J.; *Eur. Pat. Appl. EP 216 325*, **1987**. *C.A.*, **1987**, *107*, 115483.
10. a) Pinza, M.; Pfeiffer, U.; *Eur. Pat. Appl. EP 154 490*, **1985**. *C.A.*, **1986**, *104*, 68751; b) Pinza, M.; Pfeiffer, U.; *Eur. Pat. Appl. 156 655*, **1985**. *C.A.*, **1986**, *104*, 129789; c) Iriuchijima, Sh.; Kobayashi, H.; Aoki, K.; Oda, T.; Shinoyama, M.; Nosaka, Y.; *Eur. Pat. Appl. EP 223 328*, **1987**. *C.A.*, **1987**, *107*, 154235; d) Linan, I.; Oliver, M.; *Span ES 537 842*, **1985**. *C.A.*, **1986**, *105*, 190922; e) Hirano, H.; Kaneko, H.;Shimizui, T.; Aoki, K.; Uchida, T.; *Jpn Kokai Tokkyo Koho JP 62 286 964*, **1987**. *C.A.*, **1988**, *109*, 92772; f) Iruchijima, Sh.; Masuda, T.; *Jpn. Kokai Tokkyo Koho JP 63 132 872*, **1988**. *C.A.*, **1988**, *109*, 128824; g) Orena, M.; Porzi, G.; Sanchi, S.; *J. Chem. Res. Synop.*, **1990**, *11*, 376.
11. Almeida, J.F.; Anaya, J.; Martín, N.; Grande, M.; Morán, J.R.; Caballero, M.C.; *Tetrahedron: Asym.*, **1992**, *3* , 1431.

12. McAlees, A.J.; McCrindle, R.; *J. Chem. Soc. (C)*, **1969**, 2425.
13. Austin, G.N.; Fleet, G.W.J.; Peach, J.M.; Proust, K.; Jong C. S.; *Tetrahedron Lett.*, **1987**, *28*, 4741.
14. Mitsunobu, O.; Yamada, M.; *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 2380.
15. Acetic acid (1.1 eq.) was added to avoid by-products from alcoholate intermediate.
16. This compound is more stable than its C-3 analog due to the intramolecular hydrogen bond with the carbonyl group in lactam ring.
17. Su, T.M.; Sliwinski, W.F.; Schleyer, P.V.R.; *J. Am. Chem. Soc.*, **1969**, *91*, 5386.
18. a) Binkley, R.W.; Sivik, M.R.; *J. Org. Chem.*, **1986**, *51*, 2619; b) Binkley, R.W.; *Ibid.*, **1991**, *56*, 3892.
19. Harada N.; Nakanishi K.; "*Circular Dichroic Spectroscopy. Exciton Coupling in Organic Chemistry*", University Science Books, Oxford University Press, Oxford **1983**.
20. In *trans* isomers the 2nd Cotton effect is not clear. For more information see Harada N.; Nakanishi, K.; *J. Am. Chem. Soc.*, **1969**, *91*, 3989.
21. a) Csuk, R.; Hönig, J.; Nimpf, H.; Weidmann, H.; *Tetrahedron Lett.*, **1980**, *21*, 2135; b) Mitsunobu, O.; Wada, M.; Sano, T.; *J. Am. Chem. Soc.*, **1972**, *94*, 679.
22. Bashyal, B.P.; Chow, H.-F.; Fleet, G.W.J.; *Tetrahedron*, **1987**, *43*, 423.
23. Harmatha, J.; Budesinsky, M.; Trka, A.; *Collect. Czech. Chem. Comm.*, **1982**, *47*, 644.
24. H-5a designs the proton of the methylene group giving the higher-field signal in NMR.
25. Frankel, M.; Katchaski, E.; *J. Am. Chem. Soc.*, **1942**, *64*, 2264