Tetrahedron Vol. 48, No. 46, pp. 10127-10132, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Synthesis of Enantiomerically Pure (2R, 5R) Disubstituted Pyrrolidines from D-Mannitol

M. Marzi*[a], P. Minetti [a], D. Misiti [b]

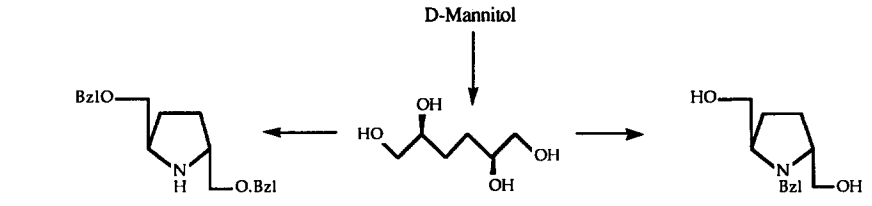
a. Sigma Tau SpA, Via Pontina km 30.400 , 00040 Pomezia (Italy)
b. Dip. Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, P.zza A.Moro 5, 00185 Rome (Italy)

(*Received in UK* 23 *July* 1992)

Abstract: Pyrrolidines 1 and 2 are obtained from D-Mannitol, giving good total yields and in an enantiomerically pure form. Some comments and studies regarding pyrrolidine ring closure (key step) are also reported.

Over the last few years, interest in pyrrolidine-type derivatives has grown considerably, from both a synthetic and pharmacological [1] point of view. Quite recently several syntheses of such compounds, destined for use as chiral auxiliaries, have been described [2]. However, only a few examples of asymmetric synthesis of trans-2, 5-disubstituted pyrrolidines have been reported [3]. We have therefore developed a process for the simple, concise asymmetric synthesis of trans-(2R, 5R)-bis(benzyloxymethyl)-N-benzyl-pyrrolidine **1** [4a] and trans-(2R, 5R)-bis (hydroxymethyl)-N-benzyl-pyrrolidine **2**, from the tetrahydroxy intermediate **3** in good yields, starting from the easily available D-mannitol [4a,b] (scheme I).

SCHEME I



Bzl = Benzyl

1 **3** **2**

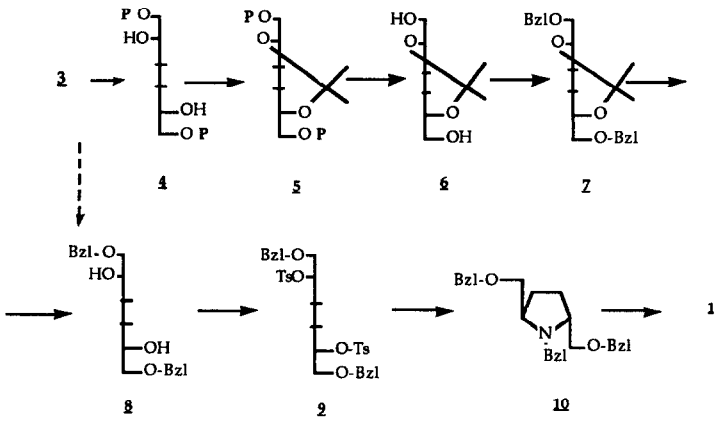
Our approach (see scheme II) foresees first of all the selective protection of the C-1 and C-6 hydroxy groups as t-butyl-diphenylsilyl derivatives, by reacting the above mentioned intermediate **3** with t-butyl-diphenylsilyl chloride and imidazole in N,N dimethylformamide [5] to give compound **4** in good yield. Compound **4** was successively converted to acetonide **5** [6] then to C-1, C-6 deprotected compound **6** [5] and finally into the dibenzyl derivative **7** [7].

The key intermediate **8** [4] , obtained by removal of the acetonide group [8] from **7**, was tosylated [9] and then cyclized to the tribenzyl pyrrolidine **10**, by heating compound **9** directly in benzylamine [4] (80% yield). The ring closure proceeded with complete inversion at C-2 and C-5 of **9**, giving enantiomerically pure pyrrolidine **10**. Optical purity was confirmed by NMR tests, using chiral shift reagents and, additionally, by chiral HPLC.

N-debenzylation of **10** was selectively accomplished by hydrogenation with palladium hydroxide as the catalyst [10]. Under such mild conditions, **10** was completely converted to **1** [4] in high yield; no O-debenzylated product was found in the hydrogenated mixture.

In order to simplify our synthetic route to pyrrolidine **1**, we looked at the possibility of obtaining the key intermediate directly from **3** by selective benzylation at the C-1 and C-6 hydroxy groups. After many attempts, success was finally obtained by preparing the organo-tin derivatives of **3** [4] ,with dibutyltin oxide and then by transforming the derivative obtained in this way into **8** in high yield (80%), with benzyl bromide and tetrabutyl ammonium bromide [11,12] (scheme II).

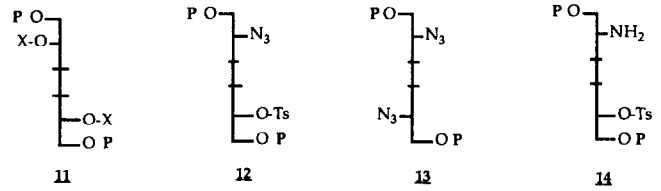
SCHEME II



P = t-butyl-diphenylsilyl

We noted that ring closure by nucleophilic attack at C-2 and C-5 to form a pyrrolidine derivative failed in presence of protecting groups such as the t-butyl-diphenylsilyl in the C-1 and C-6 positions. We therefore concluded that the steric hindrance of bulky groups at C-1 and C-6 affects ring closure and/or the nucleophilic substitution, more than, the nature of the leaving group at C-2 and C-5 or the nucleophilic characteristics of the amine.

In fact, the compounds **11**, which are easily obtained from **4** by introducing good leaving groups such as tosyl in **11a** [14] mesyl in **11b** [13] and triflyl in **11c** [15], failed to react even when using different amines such as benzylamine and its lithium salts, hydrazine, hydroxylamine and O-benzyl-hydroxylamine.



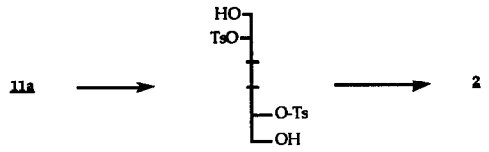
11a X = Tosyl, 11b X = Mesyl, 11c X = Triflyl

Moreover, even when ring closure was attempted by intramolecular attack, the result was unsuccessful. In effect, compound **11a** was transformed by reaction with the azide ion[16] to a mixture of the monoazide **12** and the diazide **13**: the azide group of **12** was then reduced to an amino group to give **14**, which revealed no evidence of cyclic products during the attempt at intramolecular substitution.

Further evidence of the above mentioned conclusions can be taken from the ring closure of C-1, C-6 unprotected compounds, to give pyrrolidine bearing free hydroxymethyl functions at the C-2 and C-5 positions of the ring.

In this case compound **11a** was easily converted, by acid removal of bulky protecting groups, into diol **15** which was then cyclized to pyrrolidine **2** under the same conditions used previously for pyrrolidine **1**. Trans (2R, 5R)-bis(hydroxymethyl)-N-benzyl-pyrrolidine **2** was obtained in moderate overall yield but without racemization (scheme III). Finally, pyrrolidine **2** was converted into above tribenzyl-derivative **10** with NaH and benzyl bromide.

SCHEME III



15

The results reported above can easily be generalized and represent a simple, practical way to obtain optically pure 2,5-disubstituted pyrrolidines and other useful related chirons.

Experimental

Melting points (m.p.) were taken using Buchi 535 melting point apparatus and have not been corrected. Optical rotation was measured on a Polartronic I (Schmidt Maensch) polarimeter. Elemental analyses (C, H, N, S) were carried out with a Carlo Erba EA 1108 instrument and the found values are in accordance with the calculated values. Infrared spectra (I.R.) were recorded using a Perkin Elmer 781 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on: Varian EM-360 (60 MHz), Varian XL200 (200 MHz) or Varian VXR 300 (300 MHx) spectrometers.
If not otherwise stated, 60 MHz with $CDCl_3$ as the solvent were used.NMR data are reported as follows: chemical shifts (δ) in parts per million (p.p.m.) down field from tetramethyl silane (TMS). Thin Layer Chromatography (TLC) was performed on precoated 0.25 mm silica gel 60 F 254 plates (Merck). The Rf values are reported. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck), and flash chromatography carried out using silica gel 60 (40-63 mesh, Merck). Commercial reagents were purchased from Fluka or Aldrich. Organic solutions, taken from extraction of the aqueous phase, were dried over anhydrous $MgSO_4$ or Na_2SO_4 and evaporated under reduced pressure by water pump.

1,6-di-O-(t-butyl-diphenyl)-silyl-3,4-dideoxy-D-threo-hexitol 4.
Compound **3** [4] (1.32 g, 8.8 mmol) was dissolved in DMF (16 ml, redist.) and then imidazole (1.31 g, 19 mmol) was added. This solution was cooled at 0° C and then t-butyl-diphenyl silyl chloride (4.86 ml, 19 mmol) added dropwise, the solution was stirred at 0° C for 1h and then at RT overnight. DMF was removed by distillation under vacuum and the resulting syrup diluted with EtOAc, washed with H_2O and then concentrated. The oily residue was purified using chromatography (ether/hexane 3:7) to give pure **4** (4.4 g, 80%): $C_{38}H_{50}O_4Si_2$; m.p. = 56 - 60°C from hexane; $[\alpha]_D^{25}$= - 3.21° (c =1, $CHCl_3$) ; TLC (ether/hexane 1:1) = 0.3; ^{1}H-NMR: 7.8-7.1 (m, 20 H, arom.), 3.8-3.5 (m, 2H, CH-O), 3.5-3.3 (m, 4H, CH_2-O), 3.0-2.5 (br, 2H, OH), 1.7-1.6 (m, 4H, CH_2), 1.1 (s, 18H, $C(CH_3)_3$)

1,6-di-O(t-butyl-diphenyl)-silyl-2,5-di-O-isopropylidene-3,4-dideoxy-D-threo-hexitol 5.
To a cooled solution of **4** (3.9 g, 6.22 mmol) and p-TsOH (0.1 g, 0.5 mmol) in anh. THF (35 ml), a solution of isopropenyl methyl ether (2 ml, 21.3 mmol) in THF (10 ml) was added dropwise at 0°C. The reaction was quenched with solid $NaHCO_3$, when the compound **4** disappeared from the thin layer chromatogram. After 2h (pH = 7), the solution was filtered and concentrated to give **5** in a quantitative yield (4.11 g, oil): $C_{41}H_{54}O_4Si_2$; $[\alpha]_D^{25}$= -31.3° (c =1, CH_2Cl_2); TLC (hexane/ether 95:5) = 0.67; ^{1}H-NMR: 7.8-7.2 (m, 20 H, arom.), 4.1-3.7 (m, 2H, CH-O), 3.7-3.3 (m, 4H, CH_2-O), 1.8-1.4 (m, 4H, CH_2), 1.3 (s, 6H, $C(CH_3)_2$), 1.1 (s, 18H, $C(CH_3)_3$)

1,6-di-hydroxy-2,5-di-O-isopropylidene-3,4-dideoxy-D-threo-hexitol 6.
A solution of **5** (1.1 g, 1.65 mmol) and tetrabutyl ammonium fluoride (1.12 g, 3.5 mmol) in anh. THF (10 ml) was stirred at RT for 2h, the solvent was then evaporated and the residue oil was purified by column chromatography (ether/MeOH 9:1) to give pure **6** (0.313 g, white solid, quantitative yield): $C_9H_{18}O_4$;

$[\alpha]_D^{25}$ = -22.87° (c=1, MeOH); TLC (ether/MeOH 8:2) = 0.5; ^{1}H-NMR (DMSO-D6): 3.6-3.3 (m, 4H, CH-O, OH) 3.2-3.0 (m, 4H, CH-O), 1.7-1.3 (m, 4H, CH_2), 1.2 (d, 6H, $C(CH_3)_2$).

1,6-di-O-benzyl-2,5-di-O-isopropylidene-3,4-dideoxy-D-threo-hexitol 7.

Small amounts of NaH (0.64 g, 80% oil dispersion, 21.3 mmol) were added to a solution of **6** (2.044 g, 11 mmol) in anh. THF (4 ml) at 0°C and the mixture was then stirred for 30 mins. Benzyl bromide (2.68 ml, 22.6 mmol) was added dropwise to this solution at 0°C. The reaction, carried out at RT, was monitored by TLC and finally quenched with water and AcOEt. The organic layer was separated and concentrated to give an oily residue that was purified on preparative TLC (hexane/ether 80:20). **7** (2.78 g, yellow oil, 70%): $C_{23}H_{30}O_4$; $[\alpha]_D^{25}$ = -22.55° (c=1, MeOH); TLC (hexane/ether 80:20) = 0.22; ^{1}H-NMR: 7.3 (s, 10 H, arom.), 4.5 (s, 4H, O-$\underline{CH_2}$-Ph), 4.2-3.7 (m, 2H, CH-O), 3.4-3.2 (m, 4H, CH_2-O), 1.6-1.3 (m, 4H, CH_2), 1.3 (s, 6H, CH_3)

1,6-di-O-benzyl-3,4-dideoxy-D-threo-hexitol 8.

a. Procedure from **3**: a mixture of **3** (1.5 g, 10 mmol) and Bu_2SnO (5 g, 20 mmol) in anh. toluene (40 ml) was refluxed in an N_2 atmosphere for 4h, in a Dean-Stark apparatus, permitting water to be removed. When the mixture became a clear solution at 100-150°C, $(Bu)_4NBr$ (3.22 g, 10mmol) and benzyl bromide (5 ml, 42.2 mmol) were added and the solution refluxed for a further 24 h. The reaction mixture was concentrated and the residue purified by column chromatography (acetone/hexane 3:7) to give pure **8** (1.73, yellow oil, 80%): $C_{20}H_{26}O_4$; $[\alpha]_D^{25}$ -5.9° (c=1, MeOH); TLC (CH_2Cl_2/MeOH 95:5) = 0.3; ^{1}H-NMR: 7.2 (s, 10 H, arom.), 4.3 (s, 4H, O-$\underline{CH_2}$-Ph), 3.9-3.3 (m, 4H, CH-O, OH), 3.1 (d, 4H, CH_2-O), 1.5-1.2 (m,4H, CH_2).

b. Procedure from **7**: **7** (1.2 g, 3.25 mmol) was dissolved in THF (30 ml) containing 1N HCl (30 ml) and the resulting solution was stirred for 30 mins. at RT. The compound obtained after evaporation of the solvent (0.96 g, yellow oil, 97%) was compared with the compound obtained by procedure **a**: the two compounds exhibit the same physico-chemical properties and are identical.

1,6-di-O-benzyl-2,5-di-0-tosyl-3,4-dideoxy-D-threo hexitol 9.

Small amounts of tosyl chloride (1.3 g, 6.82 mmol) were added at 0°C to a solution of **8** (0.6 g, 1.8 mmol) in freshly distilled pyridine (10 ml). After one night AcOEt (100 ml) was added to the reaction mixture and the organic layer washed with 1N HCl and then with H_2O. The residue obtained by removal of the solvent was chromatographed on a silica gel column (ether/hexane 7:3) and successively triturated with ethanol giving **9** as a white solid (0.9 g, 70%); $C_{32}H_{34}O_8S_2$; m.p.= 66-68°C from ethanol; $[\alpha]_D^{25}$ = 3.25° (c=0.5,CH_2Cl_2): TLC (ether/hexane 7:3) = 0.6; ^{1}H-NMR: 7.7-7.4 and 7.2-6.8 (m, 8H arom, p-tolyl), 7.1 (s, 1O H, C_6H_5), 4.7-4.5 (m, 2H, CH-O), 4.2 (s, 4H, O-$\underline{CH_2}$-Ph), 3.4 (d, 4H, CH_2-O), 2.4 (s, 6H, CH_3), 1.7-1.5 (m, 4H, CH_2).

N-Benzyl-trans-(2R,5R)-bis(benzyloxymethyl)-pyrrolidine 10.

A solution of **9** (0.48 g, 7.5 mmol) in benzylamine (2 ml) was stirred for 30 mins. at 120°C. The benzylamine was then distilled under reduced pressure and the resulting syrup was treated with ether allowing precipitation of the benzylamine salts. The ethereal solution was filtered, evaporated and the oily residue was purified by flash-chromatography (ether/hexane 2:8). **10**: (0.272 g, oil, 90%): $C_{27}H_{31}NO_2$; $[\alpha]_D^{25}$= 68.3° (c=1, CH_2Cl_2); TLC (ether/hexane 4:6) = 0.6; ^{1}H-NMR (200 MHz): 7.2 (s, 15H, arom.), 4.5 (s, 4H, O-$\underline{CH_2}$-Ph), 4.15-3.8 (dd, 2H, CH_2N), 3.4-3.34 (dd, 4H, CH_2-O), 3.3-2.8 (q, 2H, CH-O) 2.1-1.9 (m, 2H, CH cis of the ring), 1.8-1.6 (m, 2H, CH trans of the ring).

NMR: Eu(fod), Pr(fod) and Eu(dcm) were used as chiral shift reagents for the determination of enantiomeric excess. The experiments were carried out with NMR 300 MHz in $CDCl_3$ using three different concentrations for each chiral shift reagent. No evidence of the other enantiomer was proved.

Chiral HPLC: compound **10** resulted enantiomerically pure by chromatography on a chiral column DACH-DNB [17] in a different normal phase condition.

Trans-(2R,5R)-bis(benzyloxymethyl)-pyrrolidine 1.

A solution of compound **10** (0.401 g, 1 mmol) in abs. ethanol (4 ml) was hydrogenated under H_2 pressure (60 psi) for 20h at RT in the presence of Pd $(OH)_2$/C at 10% (0.14 g). Pure **1** was isolated after filtration and evaporation of the solvent as an oil (0.28 g, 90%): $C_{20}H_{25}NO_2$; $[\alpha]_D^{25}$= -3.27° (c=1, MeOH); TLC (CH_2Cl_2/MeOH 9:1) = 0.5; ^{1}H-NMR (300 MHz); 7.2 (s, 10 H, arom.), 4.45 (s, 4H, O-$\underline{CH_2}$-Ph), 3.5-3.2 (m,

6H, CH_2-O, CH), 3.2-3.0 (br, 1H, NH), 1.9-1.68 (m, 2H CH cis of the ring), 1.5-1.3 (m, 2H, CH trans of the ring);

HPLC: Compound **1** was derivatized with S (+) MPTACl (Mosher's acid chloride) or alternatively with (+)camphor-10-sulphonyl chloride. The resulting amides were analyzed in the reverse phase (Techpack C-18 and μ-Bondapack C-18), using different mixtures of CH_3CN and buffer (KH_2PO_4 0.05 M) as the mobile phase. The resulting chromatograms showed only one peak for the enantiomerically pure compound **1**.

1,6-di-O-(t-butyl-diphenyl)-silyl-2,5-di-O-tosyl-3,4-dideoxy-D-threo-hexitol 11a.

A solution of tosyl chloride (1.25 g, 6.55 mmol) in anh. CH_2Cl_2 (5 ml) was added dropwise at 0°C to a solution of **4** (1.25 g, 2 mmol) and freshly distilled TEA (1 ml, 7.2 mmol) in anh. CH_2Cl_2(5 ml). After 18h at 5°C the solution was washed with 2N NaOH, 2N HCl and finally dried on Na_2SO_4. The solvent was then removed and the residue recrystallized from ether. **11a** (1.7 g, 89.7%): $C_{52}H_{62}O_8S_2Si_2$; m.p.= 111-113°C; $[\alpha]_D^{25}$ = -8.96° (c=1, CH_2Cl_2); TLC (ether/hexane 4:6) = 0.6; ^{1}H-NMR: 7.8-7.0 (m, 28 H, arom.), 4.6-4.2 (m, 2H CH-O), 3.6-3.3 (d, 4H, CH_2-O), 2.3 (s, 6H, C_6H_4-p$\underline{CH}_3$), 1.8-1.5 (m, 4H, CH_2), 1.1-0.9 (s, 18H, $C(CH_3)_3$)

2,5-di-O-mesyl derivative 11b.

A solution of mesyl chloride (0.36 ml, 4.6 mmol) in anh. CH_2Cl_2 (5 ml) was added at 0°C to a solution of **4** (1.25 g, 2 mmol) and redist. TEA (1 ml, 7.2 mmol) in anh. CH_2Cl_2 (5 ml). After standing overnight the reaction mixture was worked up as described for **11a**. Crude **11b** was purified by chromatography (hexane/ether 7:3). **11a** (oil, 68%): $C_{40}H_{54}O_8S_2Si_2$; $[\alpha]_D^{25}$= -7.4° (c=1, CH_2Cl_2); TLC (ether/hexane 1:1) = 0.4; ^{1}H-NMR 7.7-7.2 (m, 20 H, arom.), 4.8-4.5 (m, 2H, CH-O), 3.8-3.6 (m, 4H, CH_2-O), 2.8 (s, 6H, CH_3SO_2), 1.8-1.6 (m, 4H, CH_2), 1.1-1.0 (s, 18 H, $C(CH_3)_3$).

2,5-di-O-triflyl derivative 11c.

To a solution of **4** (0.624 g, 1 mmol) and TEA (0.5 ml, 3.6 mmol) in anh. CH_2Cl_2 (2.5 ml) was added $(CF_3SO_2)_2O$ (0.46 ml, 2.8 mmol) at 0°C. After 1h the reaction mixture was worked up as described above. **11c** (oil, 37%): $C_{40}H_{48}F_6O_8S_2Si_2$; TLC (hexane/ether 3:7)= 0.9; ^{1}H-NMR: 7.8-7.2 (m, 20 H, arom.), 4.2-3.9 (m, 2H, CH-O), 3.8-3.6 (m, 4H, CH_2-O), 1.9-1.7 (m, 4H, CH_2), 1.0 (s, 18H, $C(CH_3)_3$)

Tentative ring closure from compounds 11a or 11b or 11c:

a. compound **11a** or **b** or **c**, dissolved in benzylamine, was kept at room temperature or heated at 80°C and 120°C. The corresponding reactions were monitored by TLC for 4 days: the starting material remained unreacted and no ring closure was observed.

b. solutions of compounds **11a** or **b** or **c**, in anh. O-benzyl-hydroxylamine were kept at RT or heated at 120°C: the corresponding reactions were monitored for 14h by TLC. No ring closure was observed.

c. compound **11a** or **b** or **c** together with several amines (benzylamine, hydroxylamine, hydrazine, benzylamine lithium salts, respectively) was dissolved in freshly distilled DMF or DMSO. The different solutions were kept at RT or heated at 120°C for 16h and checked by TLC. No ring closure was observed.

Preparation of the azido derivatives 12 and 13.

To a solution of compound **11a** (1.3 g, 1.4 mmol) in freshly distilled DMF (3 ml), NaN_3 (0.091 g, 1.4 mmol) was added at 40°C. After 4 days the solvent was removed under reduced pressure and the oily residue was purified by flash chromatography on silica gel (ether/hexane 1:9). Compound **13** was first eluted and isolated as white crystals (33%): $C_{38}H_{48}N_6O_2Si_2$; m.p. = 81-82°C from ethanol; $[\alpha]_D^{25}$ = 25° (c=1, CH_2Cl_2); TLC (ether/hexane 3:7) = 0.9; ^{1}H-NMR: 7.6-7.1 (m, 20 H, arom.), 3.7-3.5 (d, 4H, CH_2-O), 3.2-3.0 (m, 2H, CH-N_3), 1.6-1.4 (m, 4H, CH_2), 1.0 (s, 18H, $C(CH_3)_3$).

Compound **12** was then eluted and isolated as oil (0.46 g. 40%): $C_{44}H_{53}N_3O_5SSi_2$; $[\alpha]_D^{25}$= 1.17° (c=10, CH_2Cl_2); TLC (ether/hexane 3:7) = 0.68; IR (KBr) 2100 cm^{-1} (N_3); ^{1}H-NMR: 7.8-7.0 (m, 24 H, arom.), 4.6-4.2 (m, 1H, CH-O), 3.7-3.4 (d, 4H, CH_2-O), 3.2-3.0 (m, 1H, CH-N_3), 2.2 (s, 3H, C_6H_4-p-$\underline{CH}_3$), 1.8-1.1 (m, 4H, CH_2), 1.1 (s, 18H, $C(CH_3)_3$).

Preparation of the amino derivative 14.

The mono azido derivative **12** (0.8 g, 1 mmol) was dissolved in abs.ethanol (16 ml) and 10% Pd/$BaSO_4$ (0.09 g) was added. After 24h under H_2 pressure (65 psi) at RT, the hydrogenated mixture was concentrated. The oily residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 95:5). **14** (0.6 g, oil, 78%);

$[\alpha]_D^{25}$= 4.52° (c=1, CH_2Cl_2); TLC (CH_2Cl_2/MeOH 95:5) = 0.5; ^{1}H-NMR: 7.8-7.0 (m, 24 H, arom.), 3.6-3.2 (m, 9H, CH-O, CH-N, C_6H_4-p-$\underline{CH_3}$, CH_2-O), 2.5 (d, 2H, NH_2), 1.5-1.2 (m, 4H, CH_2), 1.0 (s, 18H, $C(CH_3)_3$).

Attempt at ring closure from 14.

Solutions of the amino derivative **14**, in different solvents (DMF or THF) and in the presence of different bases (NaH, LiH, BuLi) were kept at 80°C for 3 days and monitored by TLC. The starting material remained unreacted and no ring closure was observed.

N-benzyl-trans-(2R,5R)-bis(hydroxymethyl)-pyrrolidine 2.

Compound **11a** was dissolved in 3% HCl methanolic solution (4 ml) and the resulting solution was then stirred for 16h following the formation of the reaction product **15** by TLC (AcOEt, Rf = 0.67). The solvent was evaporated and the residue syrup on treatment with ether gave crude **15** in the form of a white solid. ^{1}H-NMR: 7.5 (q, 8H, arom.), 4.6 (m, 2H, CH-O), 3.7 (m, 4H, CH_2-O), 2.5 (s, 6H, C_6H_4-p-$\underline{CH_3}$), 2.2-1-1 (br, 2H, OH), 1.6 (m, 4H, CH_2).

The crude **15**, above obtained, was then reacted with benzylamine at 80°C (2 ml) and after 30 mins. the solvent was distilled under reduced pressure. Crude compound **2** was purified by chromatography. **2** (0.095 g, oil, 40%): $C_{13}H_{19}NO_2$; TLC (AcOEt/MeOH/NH_4OH 95:5:0.1) = 0.83; $[\alpha]_D^{25}$ = 49.2° (c=0.5 MeOH); ^{1}H-NMR (300 MHz): 7.15 (m, 5H, arom.), 3.95 (dd, 2H, Ph-$\underline{CH_2}$-N), 3.7-3.5 (m, 4H, CH_2-O), 3.22 (m, 2H, CH), 2.5 (br., 2H, OH), 2.1-1.9 (m, 2H, CH cis of the ring), 1.9-1.78 (m, 2H, CH trans of the ring).

Benzylation of pyrrolidine 2.

A solution of compound **2** (0.11 g, 0.5 mmol) was cooled at 0°C in anh. THF (1 ml) then NaH (80% oily dispersion, 0.35 g, 1.1 mmol) was added, followed after 30 mins. by benzyl bromide (0.172 g, 1.1 mmol). At the end of the reaction, the solvent was evaporated to give an oily residue which was purified by chromatography (ether/hexane 4:6). The dibenzyl derivative was isolated and was found to be identical to compound **10** isolated previously.

Acknowledgment: The Authors wish to thank Prof. C. Scolastico for helpful discussion and Dr F. Calorio for technical assistance

REFERENCES

1. Evans, S.V.; Fellows, L.E.; et al.. Phytochemistry **1985**, 24, 1953; Palamarczyz, G.; Mitchell, M.; et al.. Arch. Biochem. Biophys. **1985**, 35, 243.; Bushyal, G.W.J.; Fleet,G.W.J.; Cough,M.J.; Smith, P.W..Tetrahedron **1987**, 43, 3083.
2. Kawanami, Y.; Fujitu, I.; Taniguchi, Y.; et al.. Chem Lett **1987**, 2021 ; Kawanami,Y.; Ito, Y.; et al.. Tetrahedron Lett. **1984**, 25, 857; Kawanami,Y.; Katsuki,T.; Yamaguchi,M.; Bull. Chem. Soc. Japan **1987**, 60, 4190.
3. Shing, T.K.M.. J. Chem. Soc. Chem. Comm. **1987**, 262; Schlessinger, R.M.; Iwandwige, E.J.. Tetrahedron Lett. **1987**, 28, 2083; Takano, S.; Moriya, M. et al.. Tetrahedron Lett. **1989**, 30, 3805; Takano, S. et al.. J. Amer. Chem.Soc **1984**, 106, 4539
4. a) Marzi, M.; Misiti, D.. Tetrahedron Lett. **1989**, 30, 6075, b) Kuzman, J.;Sohar, P..Carbohydrate Res. **1980**, 83, 6372
5. Hanessian, S.; Lavallé, P.. Can. J. Chem. **1975**, 53, 2975 and **1977**, 55, 562.
6. Fanton, E.; Gelas, J., Horton, D.. J. Chem. Soc. Chem.Comm. **1980**, 21.
7. Just, G.; Potuin, P.J.. Can. J. Chem. **1980**, 58, 2173.
8. Corey, E.; Kim, S.; Yoo, S. et al.. J. Amer. Chem. Soc.**1978**, 100, 4620.
9. Golding, B.T. et al.. J. Chem. Soc. Chem.Comm. **1983**, 19, 1051.
10. Yoshida, K.; Nakajima, S.; Wakanatsy, T.; Ban, Y.. Heterocycles **1988**, 27, 1167; Zilcha, A.; Rachinan, E.S.; Rivlin, J; J. Org. Chem. **1961**, 26, 376.
11. David, S.; Hanessian, S.. Tetrahedron **1985**, 41, 463.
12. Dasgupta, F.; Garegg, P.J.. Synthesis **1988**, 8, 626; Garegg, P.J.; Lindberg, B.. Carbohydrate Res. **1988**, 173, 205.
13. Borcherding, P.R.; Schultz, J.A.; Bochardt, R.J.. J.Org. Chem. **1984**, 52, 5447.
14. Cohen, N.; Bauner, B.L.et al.. J. Amer. Chem. Soc. **1983**, 105, 3661.
15. Kemp, J.E. et al.. Tetrahedron Lett. **1980**, 21, 2991.
16. Ohra, H.; Kuzuhara, M.; Emoto, S.. Agr. Biol. Chem. **1971**, 35, 754.
17. Gasparrini, F.; La Torre, F.; Misiti, D.; Villani, C.. J. Chromatography **1991**, 539, 25.