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Enantioselective Synthesis of 1,2-Acetonide of (2*S*,3*R*)-3-*N*-Boc-3-Amino-4-Phenyl-1,2-Butanediol

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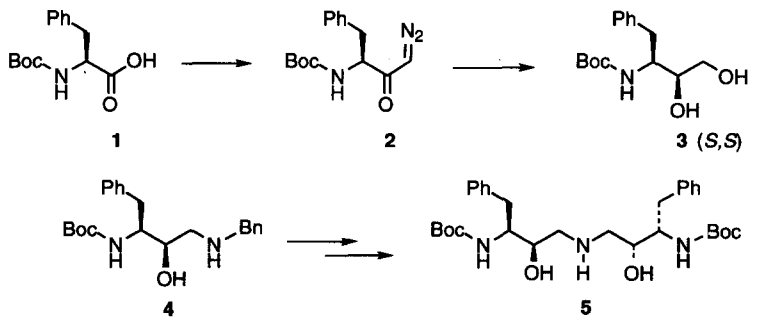
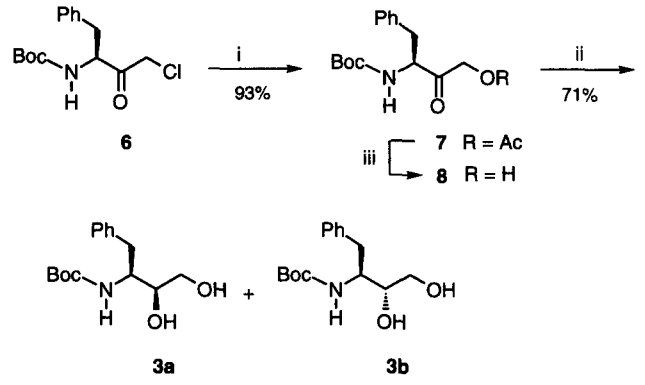
Abstract: An efficient and stereocontrolled preparation of the (2*S*,3*R*)-1,2-acetonide **15**, from hydrazone **10**, leading to a (D)-phenylalaninol derivative, potentially useful for the design of HIV protease inhibitors, is described. Copyright © 1996 Elsevier Science Ltd

In a search for new HIV-1 protease inhibitors,[1] BMS scientists have discovered that **5**,[2] is a powerful agent of this class. Compound **5** was synthesized from **3**, obtained from *N*-protected natural (*S*)-phenylalanine derivative **1** *via* the diazo derivative **2**. In order to prepare (*R,S*) and/ or (*R,R*) diol-analogues of **3**, avoiding hazardous reagents such as diazomethane, used to prepare intermediate **2**, we searched for an alternative pathway.



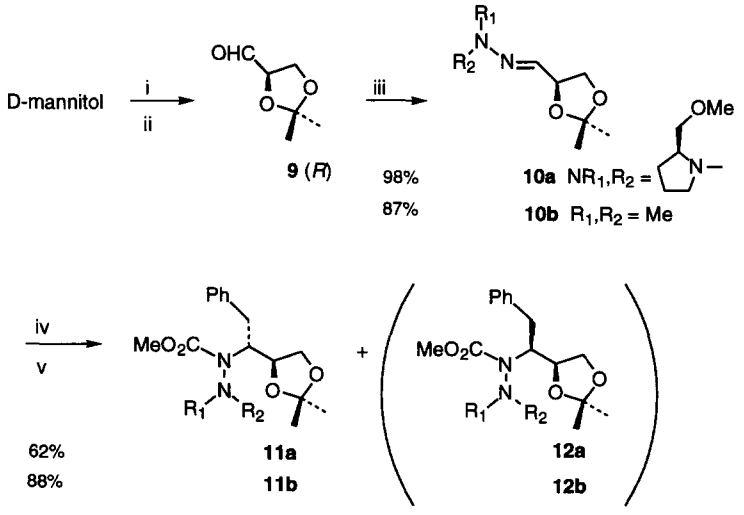
Scheme 1

As a model, we first tried to synthesize **3** through the chloromethylketone **6**[3] (Scheme 2). Substitution of **6** by an acetoxy group gave derivative **7**. Hydrolysis of **7** afforded the corresponding 1-hydroxymethylketone **8** in good yield. However, reduction of this ketone with $NaBH_4$ was not diastereoselective (**3a/3b**: 54/46). The same reduction in presence of $CeCl_3$[4] was not shown to increase significantly the diastereoselectivity (**3a/3b:** 70/30). Indeed, we discovered that partial racemization took place at C-3 during acetoxy substitution of the halogen atom of **6**.[5]



Scheme 2, *Reagents and conditions*: i, NaI, AcOK, DMF, rt, 18h; ii, K_2CO_3, MeOH/H_2O, 3h, rt; iii, $NaBH_4$, THF/MeOH: 50/50, 0 °C, 1h, quant.

We therefore envisaged the preparation of a diol analogue of **3** *via* addition of a nucleophile to a hydrazone of type **10**. It has been reported that cyclohexylmethyllithium when reacted with hydrazone **10b**, afforded a mixture (3:1) of *anti* and *syn* isomers.[6] Other authors stated that when **10b** was reacted with MeLi at low temperature, the same kind of diastereoselectivity (3:1, *anti/syn*) was obtained, whereas in the presence of 0.1 equivalent of CuI, in the same conditions, a reverse ratio of 3:1 in favor of the *syn* adduct was encountered.[7]

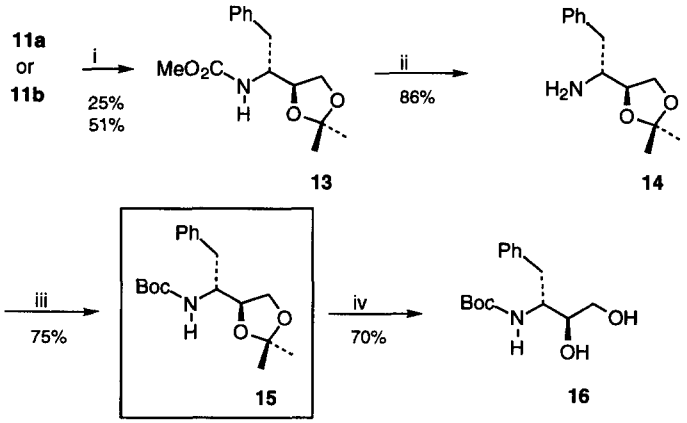


Scheme 3, *Reagents and conditions*: i, ii, see ref. 9; iii, *N,N*-dimethylhydrazine or SAMP, $MgSO_4$, Et_2O, 0°C then rt; iv, $PhCH_2Li$ 1.5 eq., Et_2O, -75 °C then rt, 3h; v, $ClCO_2Me$, 4 eq., - 10°C.

Compounds **10a** and **10b** were obtained from the 1,2-acetonide of (*R*)-glyceraldehyde **9**,[8] the latter synthesized from (D)-mannitol according to known methods,[9] in the presence of $MgSO_4$ in 87% and 98% yield

respectively. Nucleophilic addition of benzyllithium, prepared from phenyllithium and triphenylbenzyltin,[6] to these hydrazones, followed by quenching with an excess of methyl chloroformate, gave exclusively, in the crude reaction mixture, the *anti* carbazates **11a** or **11b** in good yield (Scheme 3). Attempts to obtain *syn* carbazates **12b**, or a mixture of **11b** and **12b**, in the same conditions, by addition of a 10% catalytic amount of CuI resulted only in loss of yield, while with addition of an equimolar quantity of CuI, $ZnCl_2$ or $Ti(OiPr)_4$ to the reaction, no benzylation was observed. It is noteworthy that no real difference was seen for the benzyllithium addition between SAMP-hydrazone **10a** and *N,N*-dimethylhydrazone **10b**. As a matter of fact, the SAMP hydrazone route did not show any advantage when compared to the *N,N*-dimethyl hydrazone pathway. Thus, by virtue of a single stereogenic center on the acetonide group, with hydrazone **10b**, an excellent *anti* diastereoselectivity was encountered towards the approach of benzyllithium.

Finally, cleavage of the hydrazine moiety of **11a** or **11b** was performed with Li in liquid ammonia[10] to give the methyl carbamate **13** in 25% and 51% yield respectively (Scheme 4).



Scheme 4, *Reagents and conditions*: i, Li, NH_3, THF, -33 °C; ii, 2N NaOH/ EtOH, reflux, 18 h; iii, Boc_2O, DIPEA, MeOH, rt, 18h; iv, PTSA, MeOH, rt, 3h.

Compound **13** was hydrolyzed in the presence of sodium hydroxide to furnish **14** in 86% yield. Protection of **14** with a Boc group afforded **15** in 75% yield. To check the enantiomeric purity of **15**, we prepared **16** which enantiomer was known in the literature.[11] The acetonide protecting group was cleaved with one equivalent of *p*-toluenesulfonic acid in MeOH to give **16** in 70% yield. Compound **16** was found to display a similar absolute optical rotation than that of its enantiomer.[12]

Recently other authors[13] reported that noncoded (D)-aminoacids derivatives might be incorporated into efficient HIV-protease inhibitors. Therefore, preparation of pure **15**, a (D)-phenylalaninol derivative could lead to powerful inhibitors of this type.

In conclusion, the methodology described in this paper offered an efficient and enantiospecific route to unnatural (D)-phenylalaninol derivatives as **14** and **15**, potentially useful for HIV-1 protease inhibitors synthesis, starting from the cheap material (D)-mannitol.

EXPERIMENTAL

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Melting points were taken in a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis were performed by the Bristol-Myers Squibb Analytical Department. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Bruker ARX 500 spectrometer at 500 Mhz. The ^1H chemical shifts are reported in ppm from H_2O as external signal. Infra-red spectra were recorded on a Nicolet FT-IR SXC spectrophotometer. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer model 241 polarimeter. Concentrations were given in g/mL. Positive electrospray ionisation, electron impact and chemical ionization mass spectra were obtained using a Fisons VG-Quattro, with an analyzer of quadripolar type. Merck silica gel 60 was used in the chromatographic purification of all specified products.

Chloromethylketone pathway:

1-Acetoxy-3-[[(1,1-dimethylethoxy)carbonyl]amino]-4-phenyl-2-Butanone 7

To a solution of 4 g (13.4 mmoles) of chloromethylketone **6**[3a,3b] in 20 mL of dry DMF, under nitrogen, was added 2.01 g (13.4 mmoles) of NaI, and 2.63 g (26.8 mmoles) of AcOK. The reaction mixture was stirred at room temperature for 18 hrs, and poured into 40 mL of an aqueous sat. NH_4Cl. The resulting precipitate was filtered, washed 4 times with 10 mL of H_2O to give 4.02 g of **7**. Yield 97%; m.p. 98°C. Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.53%; H, 7.21%; N, 4.36%. Found: C, 63.32%; H, 6.99.%; N, 4.55%. IR (KBr) ν 3348, 2985, 1756, 1692, 1518, 1226, 1168 cm^{-1}. ^1H NMR (dmso-d_6): δ 1.36 (s, 9H, $CO_2C(\mathbf{CH_3})_3$); 2.13 (s, 3H, $CH_2OCO\mathbf{CH_3}$); 2.78 (dd, $^2J_{HH}$ = 14 Hz, $^3J_{HH}$ = 10.5 Hz, 1H, Ph-$\mathbf{CH_2}$-CH); 3.07 (dd, $^2J_{HH}$ = 14 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, Ph-$\mathbf{CH_2}$-CH); 4.32 (m, 1H, Ph-CH_2-**CH**); 4.87 (d, $^2J_{HH}$ = 17 Hz, 1H, CO$\mathbf{CH_2}$-OAc); 4.93 (d, $^2J_{HH}$ = 17 Hz, 1H, CO$\mathbf{CH_2}$-OAc); 7.30 (m, 5H, $\mathbf{C_6H_5}$).

1-Hydroxy-3-[[(1,1-dimethylethoxy)carbonyl]amino]-4-phenyl-2-Butanone 8

To a solution of 4.03 g (12.54 mmoles) of **7** in 100 mL of a mixture of MeOH/H_2O 4:1 was added 0.4 g (32.6 mmoles) of solid K_2CO_3. After 30 mn an additional 40 mg (3.26 mmoles) of K_2CO_3 was added. After 3 hours and five other additions of K_2CO_3, the reaction mixture was concentrated under reduced pressure and taken up with 20 mL of EtOAc. The organic layer was washed three times with H_2O, dried ($MgSO_4$) and chromatographed over silica gel (heptane/EtOAc:70/30) to provide 2.52 g of **8** in 72% yield. M.p. 81-82 °C; Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50%; H, 5.01%; N, 7.58%. Found: C, 64.41%; H, 4.75%; N, 7.60%. IR (KBr) ν 3448, 3363, 2982, 2931, 1730, 1686, 1515, 1171 cm^{-1}; MH^+ (ESP): 280. ^1H NMR (dmso-d_6): δ 1.36 (s, 9H, $CO_2C(\mathbf{CH_3})_3$); 2.72 (dd, $^2J_{HH}$ = 14 Hz, $^3J_{HH}$ = 10 Hz, 1H, Ph-$\mathbf{CH_2}$-CH); 3.05 (dd, $^2J_{HH}$ = 14 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, Ph-$\mathbf{CH_2}$-CH); 4.16 (dd, $^2J_{HH}$ = 18.7 Hz, $^3J_{HH}$ = 15.9 Hz , 1H, CO$\mathbf{CH_2}$-OH); 4.31 (dd, $^2J_{HH}$ = 18.7 Hz, $^3J_{HH}$ = 5.9Hz , 1H, CO$\mathbf{CH_2}$-OH); 4.36 (m, 1H, Ph-CH_2-**CH**); 5.14 (m, 1H, **NH**-CO); 7.27 (m, 5H, $\mathbf{C_6H_5}$).

[2,3-Dihydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester 3a + 3b

To a solution of 2.4 g (8.6 mmoles) of **8** in 80 ml of a mixture of THF/MeOH: 50/50 cooled to -10°C was added 0.325 g (8.6 mmoles) of $NaBH_4$ while maintaining the temperature below 0°C. The solution was stirred for 1 hr at 0°C. The solution was then poured into 100 ml of EtOAc, which was washed successively

with 80 ml of an aqueous solution of 2N $KHSO_4$, 80 ml of 10 % $NaHCO_3$, and finally 80 ml of brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to leave 2.39 g of **3a + 3b** (54/46 mixture of dias). Yield 99%. ^1H NMR (mixture of dias in dmso-d_6): δ 1.31and 1.36 (2s, 18H, $CO_2C(\mathbf{CH_3})_3$); 2.60 (dd, $^2J_{HH}$ = 14 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, Ph-$\mathbf{CH_2}$-CH, cis isomer); 2.71 and 2.82 (dd, $^2J_{HH}$ = 8.5Hz, $^3J_{HH}$ = 7 Hz, 1H, Ph-$\mathbf{CH_2}$-CH, trans isomer); 2.99 (dd, $^2J_{HH}$ = 14 Hz, $^3J_{HH}$ = 10 Hz, 1H, Ph-$\mathbf{CH_2}$-CH, cis isomer); 3.35 and 3.45 (2m, 6H, 2 $\mathbf{CH_2}$-OH, 2 **CH**-NH); 3.63 and 3.76 (2m, 2H, 2 **CH**-OH); 4.40 and 4.45 (2m, 2H, CH_2-**OH**); 4.70 and 4.75 (2m, 2H, CH-**OH**); 6.29 and 6.56 (2m, 2H, **NH**-CO); 7.24 (m, 10H, $\mathbf{C_6H_5}$).

Acetonide pathway:

_N_-[[[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-methylidene]amino]-_N_-methyl]Methylamine 10b

To a solution of 0.581 g (4.5 mmoles) of isopropylidene-D-glyceraldehyde **9**,[9] in 8 ml Et_2O cooled to 0°C was added 1.37 mL (18 mmoles) of *N,N*-dimethylhydrazine and 1.08 g (9 mmoles) of $MgSO_4$. After 1 hr at room temperature; the suspension was filtered and the filtrate concentrated under reduced pressure to furnish 0.7 g of **10b** as a colorless oil. Yield 87 %. $[\alpha]_D^{20}$ -84 (c 1.7, $CHCl_3$); ^1H NMR (dmso-d_6): δ 1.35 and1.4 (2s, 6H, $(\mathbf{CH_3})_2C$); 2.8 (s, 6H, $N(\mathbf{CH_3})_2$); 3.75 (t, 1H, $^3J_{HH}$ = 8 Hz, O-$\mathbf{CH_2}$-CH); 4.1 (dd, 1H, $^2J_{HH}$ = 8 Hz, $^3J_{HH}$ = 6.45 Hz, O-$\mathbf{CH_2}$-CH); 4.55 (dd, 1H, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 6.5 Hz, -CH_2-**CH**-C=N); 6.45 (d, 1H, $^3J_{HH}$ = 6.5 Hz, 1H, -**CH**=N-).

[1-[[[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-methylidene]amino]-2-(2*S*)-methoxymethyl]Pyrrolidine 10a

The synthesis of **10a** was performed according to the same procedure described for **10b**. Yield 98 %. ^1H NMR (dmso-d_6): δ 1.81 and 1.82 (2s, 6H, $(\mathbf{CH_3})_2C$); 2.05 (m, 1H, $\mathbf{CH_2}$-CH-N); 2.15 (m, 3H, $\mathbf{CH_2}$-CH-N and $\mathbf{CH_2}$-CH_2N); 2.72 (m, 1H, $\mathbf{CH_2}$-N); 2.99-3.02 (m, 2H, $\mathbf{CH_2}$-N and $\mathbf{CH_2}$-OCH_3); 3.00 (s, 3H, $CH_2O\mathbf{CH_3}$); 3.12 (m, 3H, $\mathbf{CH_2}$-OCH_3 and CH_3OCH_2-**CH**); 3.25 and 3.50 (2dd, $^2J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz, 2H, O$\mathbf{CH_2}$-CH-O); 3.76 (m, 1H, OCH_2-**CH**-O); 4.89 (d, $^3J_{HH}$ = 4 Hz, 1H, N=**CH**-CH).

[[[(1*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl]ethyl]-*N*-[*N,N*-dimethylamino]]carbamic Acid, Methyl Ester 11b

To a solution of 0.7 g (4.07 mmoles) of **10b** in 10 ml of Et_2O cooled to -75°C was added 102 ml (733 mmoles) of a 0.072 M solution of benzyllithium[6] in Et_2O, the temperature being kept below -60°C. The solution was allowed to reach room temperature for 3 hrs. The solution was cooled to -10°C and quenched with 1.26 ml (16.3 mmoles) of $ClCO_2CH_3$ in 5 ml of Et_2O. After stirring at room temperature for 17 hrs, brine was poured to the reaction mixture. The organic layer was decanted and washed with saturated $NaHCO_3$, then brine, dried ($MgSO_4$). After evaporation under reduced pressure, a crude oil was obtained which was chromatographed (heptane/EtOAc) to furnish 1.31 g of **11b** in 87.6 % yield. $[\alpha]_D^{20}$ +12.6 (c 2, $CHCl_3$); IR (KBr) ν 3062, 3028, 2986, 2947, 1704, 1439, 1374, 1326, 1219, 1068, 859 cm^{-1}; Anal. Calcd. for $C_{17}H_{26}N_2O_4$: C, 63.33%; H, 8.13%; N, 8.69%. Found: C, 63.06%; H, 8.04%; N, 8.64%; MH^+ (ESP): 323; ^1H NMR (mixture of conformers in $CDCl_3$): δ 1.35 and 1.38 (2s, 6H, $C(\mathbf{CH_3})_2$); 2.52 and 2.66 (2s, 6H, $N(\mathbf{CH_3})_2$); 2.71 (m, 1H, Ph-$\mathbf{CH_2}$-CH); 3.01 (m, 1H, Ph-$\mathbf{CH_2}$-CH); 3.60 (s, 3H, $CO_2\mathbf{CH_3}$); 3.76 (m, 1H, Ph-CH_2-**CH**); 3.93 (m, 1H, O-$\mathbf{CH_2}$-CH-O); 4.28 (m, 1H, O-$\mathbf{CH_2}$-CH-O); 4.40 (m, 1H, OCH_2-**CH**-O); 7.2-7.28 (m, 5H, $\mathbf{C_6H_5}$).

[[[(1*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl]ethyl]-*N*-[(2*S*)-2-methoxymethylpyrrolidin-1-yl]]carbamic Acid, Methyl Ester 11a

Using the same methodology as for **11b**, and after silica gel chromatography (heptane/EtOAc: 90/10), derivative **11a** was obtained in 62 % yield. MH^+ (ESP): 393.5; ^1H NMR (dmso-d_6): δ 1.35 and 1.37 (2s, 6H, C(**CH_3**)$_2$); 1.58, 1.65, 1.76 and 2.0 (4m, 4H, CH-**CH_2**-**CH_2**-CH); 2.68 (dd, 1H, Ph-**CH_2**-CH); 2.98 (m, 1H, Ph-**CH_2**-CH); 3.12 (s, 3H, CH_2O**CH_3**); 3.32 (m, 1H, N-**CH_2** pyrrolidine); 3.25 (s, 3H, **CH_3**-OCO); 3.45 (m, 1H, N-**CH**-pyrrolidine); 3.58 (m, 3H, O-**CH_2**-CH-O + **CH_2**-OCH_3); 4.09 (m, 1H, O-**CH_2**-CH-O); 4.28 (m, 2H, OCH_2-**CH**-O + N-**CH**-CH_2Ph); 7.28 (m, 5H, **C_6H_5**).

[[(1*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl]ethyl]carbamic Acid, Methyl Ester 13

To a solution of 1.1 g (3.4 mmoles) of **11b** dissolved in 10 ml of THF and 50 ml of ammonia at - 78 °C was added 0.10 g (14.4 mmoles) of lithium. The resulting blue solution was stirred for 30 mn at - 70 °C , then 1h 30 mn at - 33°C. The reaction mixture was allowed to reach - 20°C and the reaction was quenched with 0.74 g (13.8 mmoles) of NH_4Cl. The solution was taken up in 15 ml of H_2O, and extracted four times with 15 ml of tert-butylmethylether. The organic layer was dried ($Na_2S_2O_4$) then filtered on a celite pad. Concentration of the organic layer under reduced pressure and chromatography of the residue on silica gel (heptane/EtOAc: 80/20) gave 0.49 g of **13** as an oil. Yield 51 %; $[\alpha]_D^{20}$ +26.8 (c 4, $CHCl_3$). Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50%; H, 5.01%; N, 7.58%. Found: C, 64.26%; H, 4.92%; N, 7.37%; MH^+ (ESP): 280; ^1H NMR ($CDCl_3$): δ 1.34 and 1.47 (2s, 6H, (**CH_3**)$_2$C); 2.86 (dd, 1H, Ph-**CH_2**-CH); 2.94 (dd, 1H, Ph-**CH_2**-CH); 3.66 (s, 3H, **CH_3**-OCO-); 3.92 (m, 2H, O-**CH_2**-CH-O); 4.11 (m, 1H, Ph-CH_2-**CH**); 4.96 (m, 1H, OCH_2-**CH**-O); 7.3 (m, 5H, **C_6H_5**).

Using the same procedure, the carbazate **11a** gave carbamate **13** in 25% chromatographed yield.

[[(1*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl]ethyl]Amine 14

To a solution of 0.140 g (0.5 mmole) of **13** in a mixture of 4 mL of H_2O/EtOH: 75/25 was added 2.5 ml (5 mmoles) of aqueous 2N NaOH and the reaction mixture was brought to reflux for 3 hrs. An additional 2.5 ml (5 mmoles) of 2N NaOH was added and the reflux was continued for 17 hrs. To complete the hydrolysis 1.25 ml (2.5 mmoles) of 2N NaOH and 5 hrs of reflux were necessary. Most of EtOH was evaporated under reduced pressure and the residue was extracted twice with EtOAc. The organic layer was dried ($MgSO_4$), evaporated to dryness to furnish 0.095 g of **14** as an oil which was used as it for the next step. Yield 86 %. ^1H NMR (dmso-d_6): δ 1.30 and 1.38 (2s, 6H, (**CH_3**)$_2$C); 2.60 (dd, 1H, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9 Hz, Ph-**CH_2**-CH); 2.69 (dd, 1H, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5 Hz, Ph-**CH_2**-CH); 2.90 (m, 1H, Ph-CH_2-**CH**-NH_2); 3.74 (m, 1H, O-**CH_2**-CH-O); 3.90 (m, 1H, O-**CH_2**-CH-O); 3.93 (m, 1H, O-CH_2-**CH**-O); 7.29 (m, 5H, **C_6H_5**).

[[(1*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl]ethyl]carbamic Acid, 1,1-Dimethylethyl Ester 15

To a solution of 0.184 g (0.835 mmole) of **14** in 6 mL of MeOH was added 0.182 g (0.835 mmole) of di-*tert*-butyldicarbonate, followed by 0.29 mL (1.66 mmoles) of DIPEA. After 3 hrs an additional 0.0182 g (0.085 mmole) of di-*tert*-butyldicarbonate was added. After 2 hrs, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between *tert*-butylmethylether and 0.2N aqueous HCl . The organic

layer was washed with 15 ml of sat. $NaHCO_3$ and finally 15 ml of brine, dried ($MgSO_4$) and concentrated to obtain 0.294 g of crude material which was purified over silica gel (heptane/EtOAc: 80/20) to furnish 0.201 g of **15**. Yield 75 %. M.p. 89-90 °C; $[\alpha]_D^{20}$ +35.8 (c 1.5, $CHCl_3$). IR (KBr) ν 3401, 2982, 2929, 1695, 1517, 1250, 1175, 1058 cm^{-1}; Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.26%; H, 8.46%; N, 4.35%. Found: C, 66.79%; H, 8.30%; N, 4.02%; MH^+ (ESP): 322; ^1H NMR ($CDCl_3$): δ 1.13 (s, 3H, $(\mathbf{CH_3})_2$C); 1.16 (s, 9H, $(\mathbf{CH_3})_3$C-OCO); 1.27 (s, 3H, $(\mathbf{CH_3})_2$C); 2.68 (m, 2H, Ph-$\mathbf{CH_2}$-CH); 3.46 (m, 1H, O-$\mathbf{CH_2}$-CH-O); 3.70 (m, 3H, O-$\mathbf{CH_2}$-CH-O + **CH**-NH-Boc); 3.89 (m, 1H, O-CH_2-**CH**-O); 4.60 (m, 1H, **NH**-CO); 7.06 (m, 5H, $\mathbf{C_6H_5}$).

[(1*R*, 2*S*)-2,3-dihydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester 16

To a solution of 0.132 g (0.41 mmole) of **15** in 6 mL of MeOH was added 3 mL of a 0.068 M solution (0.204 mmole) of *p*-toluenesulfonic acid, hydrate in MeOH. The reaction mixture was stirred for 2 hrs at room temperature. To complete the reaction 3 mL (0.204 mmole) of an additional PTSA 0.068 M solution in MeOH was added and the reaction mixture stirred for one more hour. The reaction was quenched with 0.057 g (0.41 mmole) of solid K_2CO_3. The reaction mixture was diluted with 15 mL of EtOAc and washed three times with 15 mL of brine, dried ($MgSO_4$) to furnish after silica gel chromatography (EtOAc/heptane: 40/.60) 0.08 g of **16** in 70% yield. M.p. 90-91 °C; $[\alpha]_D^{20}$ +35.6 (c 3, $CHCl_3$) (Lit.[11] $[\alpha]_D^{20}$ +36.8 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.40 (s, 9H, $(\mathbf{CH_3})_3$C-OCO); 2.9 (d, 2H, J_{HH} = 7.5 H, Ph-$\mathbf{CH_2}$-CH); 3.33 (m, 1H, **CH**-NH-Boc); 3.50 (m, 1H, $\mathbf{CH_2}$-OH); 3.55 (m, 1H, $\mathbf{CH_2}$-OH); 3.67 (m, 1H, HO-**CH**-CH_2OH); 3.91 and 4.99 (2m, 2H, **OH**); 7.21-7.28 (m, 5H, $\mathbf{C_6H_5}$).

REFERENCES AND NOTES

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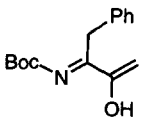

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