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Improvement of the Synthesis of Chiral Non-Racemic Bicyclic Lactams in the Piperidin-2-ones Series

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IMPROVEMENT OF THE SYNTHESIS OF CHIRAL NON-RACEMIC BICYCLIC LACTAMS IN THE PIPERIDIN-2-ONES SERIES.

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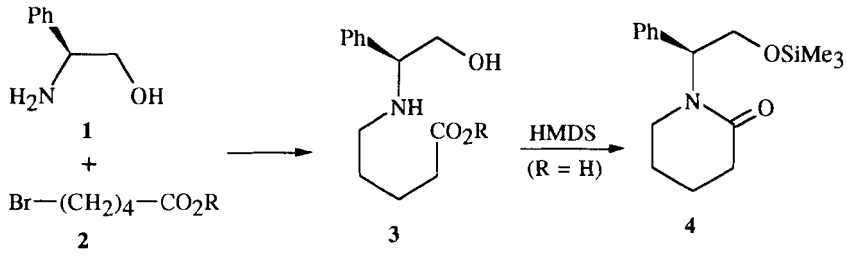
Abstract : Bicyclic lactams **8** have been prepared in enantiomerically pure form from the corresponding amino esters **5** and glutaric anhydride. The key step is the reduction of imides **7** in methanol. Selective reduction of **8** furnished N-substituted lactams **9**.

In continuation of our work on diastereoselective substitution of the piperidine ring[1], the large-scale preparation of **9** was required. Though several methods for preparing these compounds are known[2,3], none of them allowed their synthesis in satisfactory yields. In the classical condensation of (*S*)-(+)-phenylglycinol **1** with δ-bromo carboxylic acid derivatives **2**, we were faced with the problem of cyclisation of aminoester **3** to the lactam system **4**. The latter could

be obtained as a TMS derivative from the acid (R = H) using HMDS but only in poor yield (20-30 %) (Figure 1).

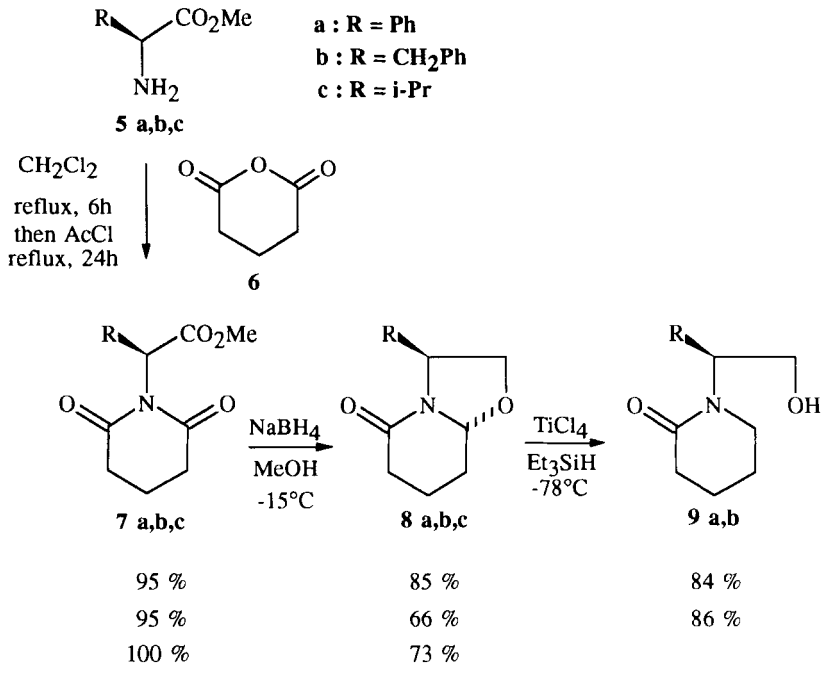
FIG. 1



Selective reduction of chiral non-racemic bicyclic lactam **8** with Et_3SiH[4] appeared a convenient way to prepare synthon **9**. Meyers[4] has developed a method for the synthesis of **8** based on the reduction of imides according to Speckamp's procedure.[5,6] Unfortunately condensation of β-aminoalcohols with glutaric anhydride gives the imide in low yield. In contrast, we have recently shown that an imide can be obtained in high yield when using an aminoester instead of an aminoalcohol.[3] Our previous attempts to reduce both the ester and the imide function in a one-pot procedure led to the expected bicyclic lactam **8** in moderate yield.[3] Indeed when ethanol and hydrochloric acid are used according to the classical procedure[6], side reactions are unavoidable. Thus the search for a better reduction system became the focal point in our efforts to prepare **9**.

The conditions of Chamberlin[7] using methanol as solvent without acid, below 0°C, efficiently reduced **7** to a single diastereomer of **8**. In these conditions only the kinetic product was isolated. It is interesting to note that for the preparation of **8c**, the only previously described compound, the overall yield from glutaric anhydride was 16 %, compared with 73 % by our procedure (Figure 2).

FIG. 2



Transformation of **8a** and **8b** to the lactams **9a** and **9b** respectively was accomplished by reduction with Et_3SiH in the presence of $TiCl_4$ as described by Meyers [4].

In conclusion, we have developed an efficient method for the preparation of chiral oxazolopiperidones **8** and lactams **9** which allows the preparation of these compounds on a multigram scale (5-10 g). Compounds of type **9** are of particular interest for the asymmetric synthesis of polysubstituted piperidines.[1]

Experimental.

NMR spectra were recorded on a Bruker AC-300 spectrometer ; chemical shift values are given in ppm (δ), tetramethylsilane being used as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 infrared spectrometer.

Preparation of imide (**7a**) ; typical procedure : To a solution of (*S*)-methyl phenylglycinate (10 g, 6.06 10^{-2} mol) in CH_2Cl_2 (15 mL) at 0°C was added portionwise glutaric anhydride (7.2 g, 6.31 10^{-2} mol). The solution was then refluxed for 6 h. Acetyl chloride (100 ml) was then added and the reflux was maintained for 24 h. After distillation of the solvent and acetyl chloride, water (50 ml) and CH_2Cl_2 (50 ml) were added to the crude material. K_2CO_3 was added until neutralisation. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). After removal of the drying agent, the solvent was evaporated furnishing **7a** (15.0 g, 95 %). Similarly, compounds **7b** and **c** were synthesized in 95% and 100% yield respectively.

7a : oil, $[\alpha]^{20}_D$: - 56 (c = 0.9 ; $CHCl_3$), IR ($CHCl_3$) : ν = 1730 and 1675 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ : 1.92 (m, 2H-4), 2.65 (t, J=8.7 Hz, 4H, H3 and H-5), 3.71 (s, OMe), 6.35 (s, H-7), 7.3-7.45 (5H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 16.9 (C-4), 18.8 and 21.8 (Me-10 and Me-11), 27.2 (C-9), 32.5 (C-3 and C-5), 52.0 (OMe), 57.9 (C-7), 170.1 ($\underline{C}O_2Me$), 172.2 (C-2 and C-6).

7b : mp = 101°C (AcOEt), $[\alpha]^{20}_D$: - 119 (c = 1.7 ; $CHCl_3$), IR ($CHCl_3$) : ν = 1730 and 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ : 1.65 (m, 2 H-4), 2.50 (m, 2 H-3 and 2 H-5), 3.32 (dd, J=10.7, 13.9 Hz, H-8), 3.45 (s, OMe), 3.48 (dd, J=13.9, 5.9Hz, H-8), 5.62 (dd, J=10.7, 5.9Hz, H-7), 7.12-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ : 16.3 (C-4), 32.0 (C-3 and C-5), 34.0 (C-8), 52.0 (C-7), 52.4 (C-10), 126.3, 127.9, 128.9 and 136.7 (C ar.), 169.6 ($\underline{C}O_2Me$), 171.5 (C-2 and C-6). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09; Found : C, 65.11; H, 6.32; N, 5.07.

7c : oil, $[\alpha]^{20}_D$: - 64 (c = 0.7 ; $CHCl_3$), IR ($CHCl_3$) : ν = 1730 and 1675 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ : 0.72 (d, J=6.3 Hz, Me), 1.20 (d, J=6.3 Hz, Me), 2.00 (m, 2 H-4), 2.57 (m, H-8), 2.71 (t, J=6.2 Hz, 2 H-3 and 2 H-5), 3.65 (s, OMe), 4.90 (d, J=9.4 Hz, H-7). ^{13}C NMR (75 MHz, $CDCl_3$) : δ : 16.9 (C-4),

18.8 and 21.8 (2 Me), 27.2 (C-8), 32.5 (C-3 and C-5), 52.0 (OMe), 57.9 (C-7), 170.1 (C-11), 172.2 (C-2 and C-6).

Oxazolopiperidone **8a** ; typical procedure : To a solution of imide **7a** (3g, 1.15 10^{-2} mol) in methanol (30 ml) was added sodium borohydride (3g, 8.82 10^{-2} mol) portionwise at -15° in such a way that temperature was maintained between -20° and -10°C. A solution of HCl in methanol was then added until pH = 1, then the reaction mixture was stirred for 3 hours at room temperature. Water (20 mL) was then added and the solution was carefully neutralized with K_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). Combined organic layers were dried ($MgSO_4$) then evaporated. The residue was purified by column chromatography (CH_2Cl_2/MeOH : 97/3) furnishing **8a** as a colorless oil (2.1 g, 85 %). The same procedure was applied for the synthesis of **8b** (Y=66%) and **8c** (Y=73%).

8a : oil, $[\alpha]^{20}_D$: + 111 (c = 1.2, EOH), IR (film) : ν = 1654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ = 1.50 (m, H-5), 1.75 (m, H-4), 1.95 (m, H-4), 2.40 (m, H-5, H-3), 2,50 (dd, J = 6.1 and 18,2 Hz, H-3), 3.70 (t, J = 8.4 Hz, H-8), 4.50 (dd, J = 8.1 and 8.8 Hz, H-8), 5.00 (dd, J = 4.5 and 8.8 Hz, H-6), 5,25 (t, J = 7.8 Hz, H-7), 7.30 (m, 5H, Ar.). ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 17.1, 28.4, 31.9 (C-3, C-4, C-5), 58.1 (C-8), 72.4 (C-7), 88.6 (C-6), 126.0, 127.6, 139.4 (C, Ar.), 168.8 (C-2).

8b : oil, $[\alpha]^{20}_D$: + 17 (c = 1.13, EtOH), IR (film) : ν = 1655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ : 1,37-2,45 (m, 2xH-3, 2xH-4 and 2xH-5), 2.92 (dd, J = 6.1 and 9.0 Hz, H-9), 3.25 (dd, J = 2.4 and 9.0 Hz, H-9), 3.48 (dd, J = 5.1 and 6.0 Hz, H-8), 3.73 (dd, J = 5.1 and 6.0 Hz, H-8), 4.08 (m, H-6 and H-7), 7.1-7.3 (m, 5H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 17.2, 28.3, 31.4, 37.8 (C-3,

C-4, C-5, C-9), 55.1 (C-7), 69.4 (C-8), 87.4 (C-6), 126.8, 128.7, 129.6, 136.9 (C, Ar), 168.7 (C-2).

8c : oil, $[\alpha]^{20}_D$: + 13 (c = 1.1, EtOH), IR (film) : ν = 1655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ : 0.91 and 0.92 (2d, J = 6.6 Hz, 2 x Me), 1.43-2.49 (m, 2 x H-3, 2 x H-4, 2 x H-5, H-9), 3.63 (dd, J = 7.0 and 8.4 Hz, H-8), 4.03 (dd, J = 7.9 and 8.4 Hz, H-8), 4.20 (m, H-7), 4.72 (dd, J = 4.7 and 8.7, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 17.1 (2xMe), 19.1, 28.5, 31.7 (C-3, C-4, C-5), 30.1 (C-9), 59.2 (C-7), 66.6 (C-8), 87.7 (C-6), 169.2 (C-2).

Lactams **9** : typical procedure : To a solution of oxazolopiperidone **8a** (2.0 g, 9.2 10^{-3} mol) in CH_2Cl_2 (70 mL) at -78°C, was added Et_3SiH (2.78 mL, 17.5 10^{-3} mol). A solution of $TiCl_4$ (1M in CH_2Cl_2) (20 mL, 20 10^{-3} mol) was then added slowly. The resulting mixture was stirred at room temperature for 16h, then water (20 mL) was added. The organic layer was washed, dried over Na_2SO_4 and evaporated to dryness. Crude material was purified by flash-chromatography (2 elutions : AcOEt then CH_2Cl_2/MeOH : 95/5) furnishing lactam **9a** (1.7g, 84%) as a white powder which crystallized from AcOEt/cyclohexane (90/10). The same procedure was used for the preparation of compound **9b** (Y=86%).

9a : $[\alpha]^{20}_D$: + 82 (c = 1.0, $CHCl_3$), mp : 95°C (AcOEt/cyclohexane : 90/10). ^1H NMR (300 MHz, $CDCl_3$) : δ : 1.60-1.80 (m, 4H, 2 H-4 and 2 H-5), 2.45 (m, 2 H-3), 2.90 (m, H-6), 3.20 (m, H-6), 3.35 (m, OH), 4.10 (m, 2 H-8), 5.85 (dd, J = 7.3, 5.5 Hz, H-7), 7.2-7.4 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ : 22.9, 23.2 (C-4, C-5), 32.7 (C-3), 43.8 (C-6), 58.9 (C-7), 61.8 (C-8), 127.9, 128.7, 137.0 (C ar), 171.8 (C-2). MS IE : 219, 217, 202, 201, 188, 172, 160, 104, 91. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; Found : C, 71.34; H, 7.67; N, 6.43.

9b : oil, $[\alpha]^{20}_D$: -27 (c = 0.8, EtOH). ^1H NMR (300 MHz, $CDCl_3$) : δ : 1.52-1.63 (m, 2H-4, 2H-5), 2.30- 2.39 (m, 2H-3), 2.75- 2.85 (m, H-6), 2.91 (dd, J = 6.1and 13.9 Hz, H-9), 3.07- 3.17 (m, H-9, H-6), 3.73- 3.86 (m, 2H-8), 3.92-4.03 (m, H-7), 7.21- 7.38 (m, 5H, Ar.). ^{13}C NMR (75 MHz, $CDCl_3$) : δ : 20.4, 23.0 (C-4, C-5), 32.6 (C-9), 33.9 (C-3), 46.9 (C-6), 61.7 (C-7), 63.2 (C-8), 126.4, 128.4, 129.0 , and 138.4 (C ar.), 171.7 (C-2). MS IE : 233, 202, 142, 100, 91, 84.

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