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A Novel Asymmetric Synthesis of 2,5 -Dialkylpyrrolidines

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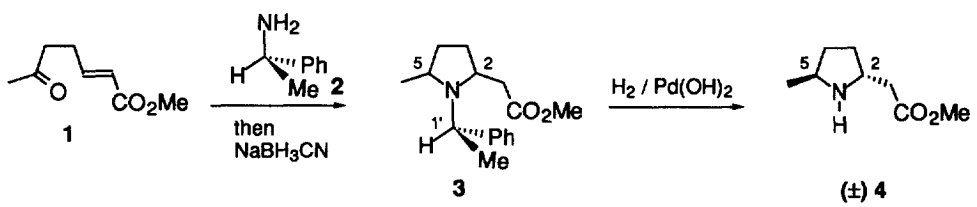
Abstract : $ZnCl_2$-promoted cyclization of enamino ester **8** furnished a 1.5:1 mixture of pyrrolidines **9** and **10**. $NaBH_4$-reduction of this mixture gave *cis* and *trans*-2,5-dialkylpyrrolidines **12** and **13** in the ratio 2:1. The latter derivative was obtained in its 2*S*, 5*S* enantiomerically pure form.

During the course of systematic studies devoted to the asymmetric Michael-type annulation, we discovered that condensation of keto enoate **1** with (*R*)-1-phenylethylamine **2** furnished, after NaBH3CN reduction of the crude, 2,5-dialkylpyrrolidine **3**.[1] This *N*-heterocyclization apparently involved the conjugate addition to the enoate of a transient carbinolamine primarily formed by addition of amine **2** to the keto group of **1**. Assignment of configuration at the two newly created stereogenic centers in **3** was made after reductive cleavage of the chiral *N*-appendage [**3** → **4**]. A rather good stereocontrol between the two side chains in **4** was observed (*trans*/*cis* ratio 6:1); this pyrrolidine however was obtained in its *racemic* form, thereby reflecting a complete lack of asymmetric induction in this ring closure.



In the light of these results, we assumed that the introduction of an ester function at the β-position of the keto group in starting material **1** might stabilize the open-chain amino intermediates, hence possibly restoring the π-facial discrimination at the subsequent annulation step.

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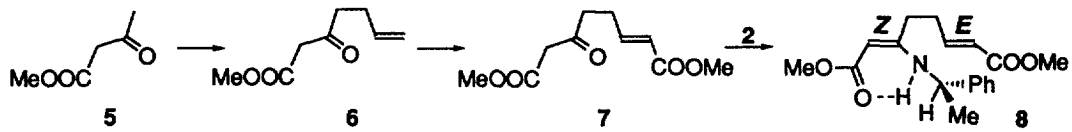
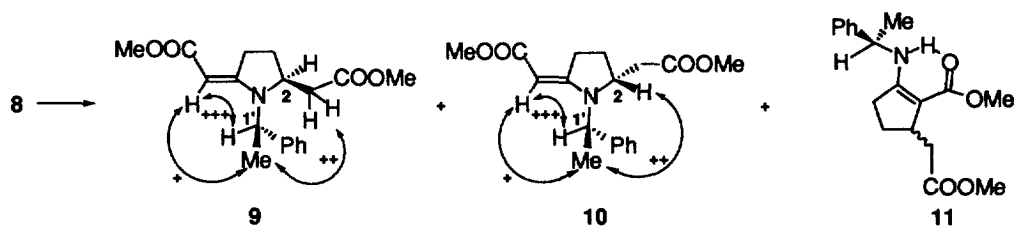
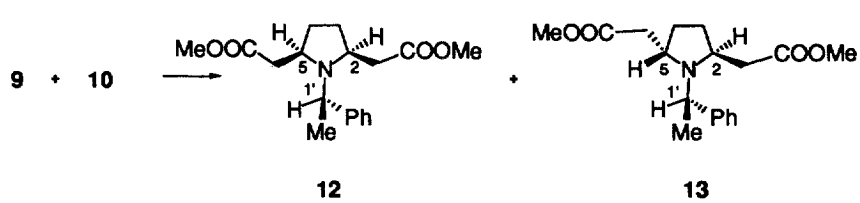
Requisite keto enoate **7** was prepared through allylation of methyl acetoacetate **5** (*i*: NaH, THF, 0 °C; *ii*: *n*-BuLi, 0 °C; *iii*: allyl bromide, 10 min at 20 °C, 79 % yield), followed by conversion of the resulting allylic derivative **6** into *E*-**7** (*i*: O_3, -78 °C; *ii*: Me_2S; *iii*: Ph_3P=CH-COOMe, 36 h at 20 °C; 42 % yield). Condensation of **7** with (*R*)-**2** (20 h in refluxing benzene) then afforded with a 84 % yield fully characterized enamino ester (*R*, *Z*, *E*)-**8**,[2] stabilized by intramolecular hydrogen bonding.



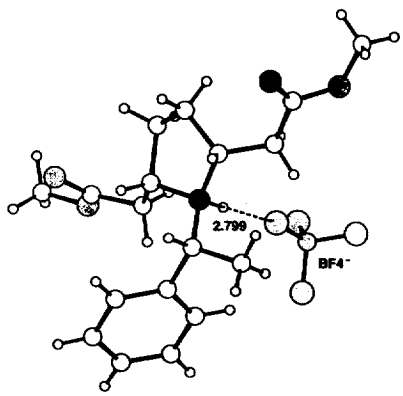
When **8** was treated with 0.3 eq. of $ZnCl_2$ (24 h in refluxing THF) pyrrolidines (1' *R*, 2 *S*, *E*)-**9** and (1' *R*, 2 *R*, *E*)-**10**,[3] products of *N*-heterocyclization were obtained, along with a small amount of cyclopentene **11**, product of carbocyclization, with a combined yield of 77 % (**9**/**10** ratio 1.5:1; **9** + **10**/**11** ratio 6:1). Flash chromatography over silica gel of this mixture then allowed an efficient separation of **11**, but not of pyrrolidines **9** and **10**. Stereochemical relationships in **9** and **10** were established by NMR spectroscopy, employing NOESY correlations (roughly quantified by crosses in corresponding formulas). Incidentally, this experiment also revealed that in both isomers **9** and **10** the chiral moiety at the nitrogen center exists largely in its energetically preferred conformation minimizing the $A^{(1,3)}$-type strain, namely the H group more or less eclipsing the vinylic hydrogen atom.



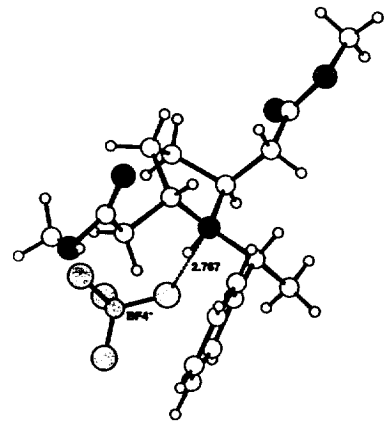
Reduction of mixture **9** + **10** into 2,5-dialkylpyrrolidines [4] was then examined using different reducing agents and conditions. The catalytic reduction employing PtO_2 as a catalyst (1 bar of H_2, in MeOH-AcOH at 20 °C) furnished with a 84 % yield a mixture of pyrrolidines (1' *R*, 2,5-*cis*)-**12**[5] and (1' *R*, 2 *S*, 5 *S*)-**13** [6] in the ratio 9:1. Ratio of *trans* isomer **13** was substantially increased (**13**/**12** ratio 1:2) by using $NaBH_4$ in AcOH (4 h at 0 °C, 74 % yield). At this stage, pure pyrrolidines **12** and **13** were isolated by simple chromatographic separation of the reaction mixture over silica gel (eluent: AcOEt/hexane 1:10).



Tentative configurational assignments for (*cis*)- and (*trans*)-2,5-dialkylpyrrolidines **12** and **13** were supported by ^{1}H and ^{13}C NMR data, on the basis of the effect of symmetry properties of the two isomers. However, since determination of configuration based on this methodology cannot be considered completely reliable, correctness of structures **12** and **13**, including the 2*S*, 5*S* absolute configuration of *trans* isomer **13**, was verified by X-ray diffraction analyses of the corresponding tetrafluoroborate salts **14** [7]and **15**.[8]



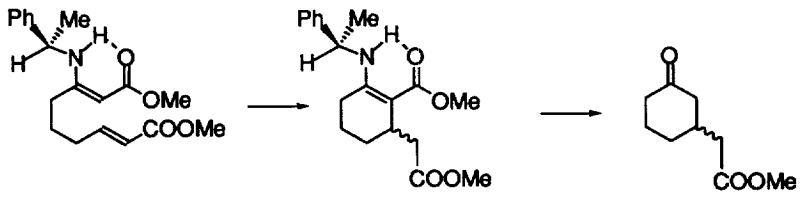
X-ray crystal structure of **14**, tetrafluoroborate salt of **12**



X-ray crystal structure of **15**, tetrafluoroborate salt of **13**

Stereochemical outcomes for the reduction of enamino ester mixture **9** + **10** can be interpreted as follows. As (*trans*)-2,5-dialkylpyrrolidine **13** was obtained in its 2 *S*, 5 *S* *single* form, it clearly resulted from the reduction of *the sole* component (2 *S*)-**9**. This remarkable stereodifferentiation in the reduction process parallels the observations made by Nikiforov[9] and Lhommet[10] in this field. Indeed, in the reduction of closely related pyrrolidine enamino esters, these authors established that a *S* 1-phenylethyl moiety at the nitrogen center "induced" predominantly a *R* configuration at the newly created stereogenic center on the pyrrolidine ring. The present obtention of (*trans*) (1' *R*, 2 *S*, 5 *S*)-**13** is consistent with these observations. However, since the highest ratio **13/9**, obtained by using $NaBH_4$ as reducting agent, did not exceed 1:1.8, substantial amounts of *cis* isomer **12** were necessarily formed in the reduction of enamino ester **9**, concurrently with **13**. This low stereoselectivity can be tentatively rationalized, invoking the "mismatched" relationship of the substituents at C-2 and at the nitrogen center in **9**: Approach of a reducing agent minimizing the steric interaction with the chiral *N*-appendage (*syn* to the Me group, leading to *trans* isomer **13**) is sterically hindered by the overhanging acetate side chain at C-2. In contrast, reduction of component (2 *R*)-**10** into (*cis*)-2,5-dialkylpyrrolidine **12** proved to be completely stereoselective. In that case **12** resulted from a "matched" approach of the reducing agent to **10**, *syn* to the Me group of the chiral fragment and *anti* to the acetate substituent at C-2.

Cyclization of enamino ester **16**, prepared in an analogous manner that **8**, was examined next. This reaction, also promoted by $ZnCl_2$ (0.2 eq. of $ZnCl_2$, 7 h in refluxing THF), furnished with a 75 % yield cyclohexene **17**, product of carbocyclization. This ring closure however proceeded with a disappointing π-facial selectivity, since keto ester **18**[11] derived from **17** (*i*: 10 % AcOH, 4 days at 40 °C; *ii*: NaCl, DMSO-H_2O, 7 h at 140 °C; 75 % overall yield) showed a very low ee (*ca.* 10 %).



16 17 18

To conclude, only a slight increase in the π-facial discrimination was observed in the (*R*)-1-phenylethylamine-promoted *N*-heterocyclization of keto enoate **7**, compared with **1**. However, as the $NaBH_4$ reduction of the resulting mixture of enamino esters **9** + **10** furnished with a satisfactory yield (*trans*)-2,5-dialkylpyrrolidine **13** in its 2 *S*, 5 *S* enantiomerically pure form, this method constitutes a simple and general access to these important chiral synthons, including auxiliaries and ligands of C_2-symmetry.

References and Notes

1- Dumas, F., d'Angelo, J. *Tetrahedron Lett.* **1992**, *33*, 2005-2008.

2- **8**: oil; $[\alpha]_D^{20}$ = - 259 (MeOH, c = 4.5); IR (neat, cm^{-1}) 3390, 1722, 1657, 1614; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.5 (d, J = 7 Hz, 3H), 2.2-2.4 (m, 4H), 3.6 (s, 3H), 3.65 (s, 3H), 4.45 (s, 1H), 4.55 (q, J = 7 Hz, 1H), 5.7 (d, J = 8 Hz, 1H), 6.8 (dt, J = 8, 7 Hz, 1H), 7.1-7.3 (m, 5H), 9.0 (d, J = 8 Hz, exch D_2O, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.8 (CH_3), 30.0 (CH_2), 30.2 (CH_2), 49.8 (CH_3), 51.1 (CH_3), 52.3 (CH), 82.1 (CH), 121.5 (CH), 125.1 (2 CH), 127.0 (CH), 128.6 (2 CH), 144.6 (C), 146.5 (CH), 163.2 (C), 166.3 (C), 170.8 (C).

3- Mixture **9** + **10**; ^1H NMR (400 MHz, $CDCl_3$, only the more significant signals are reported) **9** (*major isomer*) δ: 1.60 (d, J = 7.4 Hz, 3H), 3.57 (s, 3H), 3.59 (s, 3H), 3.78 (m, 1H), 4.58 (s, 1H), 4.80 (q, J = 7.4 Hz, 1H); **10** (*minor isomer*) δ: 1.62 (d, J = 7.4 Hz, 3H), 3.55 (s, 3H), 3.57 (s, 3H), 4.18 (m, 1H), 4.64 (s, 1H), 4.86 (q, J = 7.4 Hz, 1H).

4- For a recent asymmetric synthesis of 2,5-disubstituted pyrrolidines, see: Katritzky, A.R.; Cui, X.-L.; Yang, B.; Steel, P. J. *Tetrahedron Lett.* **1998**, *39*, 1697-1700.

5- **12**: oil; $[\alpha]_D^{20}$ = - 18.4 (CH_2Cl_2, c = 4.3); IR (neat, cm^{-1}) 1738; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.41 (d, J = 7 Hz, 3H), 1.45-1.6 (m, 2H), 1.7-1.9 (m, 2H), 2.1 (d, J = 7 Hz , 2H), 2.30 (dd, J = 8.5, 15 Hz , 1H), 2.50 (dd, J = 5, 15 Hz, 1H), 3.3-3.5 (m, 2H), 3.58 (s, 3H), 3.64 (s, 3H), 3.96 (q, J = 7 Hz, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.8 (CH_3), 30.2 (CH_2), 30.6 (CH_2), 41.9 (CH_2), 42.4 (CH_2), 51.2 (CH_3), 51.3 (CH_3), 56.5 (CH), 58.3 (CH), 58.5 (CH), 126.8 (CH), 127.8 (2 CH), 128.1 (2 CH), 143.5 (C), 172.7 (2 C); Anal. Calcd. for $C_{18}H_{25}NO_4$: C, 67.68; H, 7.88; N, 4.38. Found: C, 67.70; H, 7.83; N, 4.30.

6- **13**: oil;$[\alpha]_D^{20}$ = + 77 (CH_2Cl_2, c = 0.65); IR (neat, cm^{-1}) 1738; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.45 (d, J = 6.5 Hz, 3H), 1.45-1.6 (m, 2H), 1.95 (dd, J = 14.5, 10 Hz, 4H), 2.15 (dd, J = 3.5, 14.5 Hz, 2H), 3.4-3.55 (m, 2H), 3.6 (s, 6H), 3.7 (q, J = 6.5 Hz, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.0 (CH_3), 28.6 (2 CH_2), 37.1 (2 CH_2), 51.3 (2 CH_3), 57.4 (2 CH), 58.4 (CH), 127.3 (CH), 127.9 (2 CH), 128.3 (2 CH), 145.0 (C), 172.9 (2C); Anal. Calcd. for $C_{18}H_{25}NO_4$: C, 67.68; H, 7.88; N, 4.38. Found: C, 67.52; H, 7.94; N, 4.36.

7- **14**: solid; mp 139-141 °C (MeOH); Crystal data of **14**: $(C_{18}H_{26}NO_4)^+ (BF_4)^-$, M_W = 407.21 , colorless crystal of 0.3 x 0.30 x 0.40 mm, monoclinic P 2_1, Z = 4, a = 10.480 (2), b = 8.504 (2), c = 11.611 (3) Å, β = 97.95 (3)° V = 1024.8 $Å^3$, dcalc = 1.320 g cm^{-3}, F(000) = 428, λ (Cu Kα) = 1.5418 Å, μ = 0.987 mm^{-1}; Nonius CAD4 diffractometer, 1981 data measured up to θ = 68 °; 1882 unique (Rint = 0.060) of which 1341 considered as observed with I ≥ 2 σ(I)). The structure was solved using program SHELX86 and refined by full-matrix least-squares with SHELX93, R_1 (F) = 0.0938 for 1341 observed reflexions and wR_2 (F^2)= 0.2773 for all the 1882 data. Residual electron density between -0.35 and 0.41 e$Å^3$.

8- **15**: solid; mp 179-181 °C (MeOH); Crystal data of **15**: $(C_{18}H_{26}NO_4)^+ (BF_4)^-$, M_W = 407.21 , colorless crystal of 0.10 x 0.16 x 0.53 mm, orthorhombic P 2_1, 2_1, 2_1 Z = 4, a = 8.577 (2), b = 12.729 (6), c = 18.607 (4) Å, V = 2031.4 $Å^3$, dcalc = 1.331 g cm^{-3}, F(000) = 856, λ (Cu Kα) = 1.5418 Å, μ = 0.996 mm^{-1}; Nonius CAD4 diffractometer, 4775 data measured up to θ = 68 °; 2346 unique (Rint = 0.039) of which 1497 considered as observed with I ≥ 2 σ(I)). The structure was solved using program SHELX86 and refined by full-matrix least-squares with SHELX93, R = 0.0665 for 1497 observed reflexions and wR2 = 0.2171 for all the 2346 data. Residual electron density between -0.30 and 0.49 e$Å^3$.

9- Nikiforov, T., Stanchev, S., Milenkov, B., Dimitrov, V. *Heterocycles* **1986**, *24*, 1825-1829.

10- Blot, J.; Bardou, A. ; Bellec, C.; Fargeau-Bellassoued, M.-C.; Célérier, J.P.; Lhommet, G.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett.* **1997**, *38*, 8511-8514.

11- Dumas, F., d'Angelo, J. *Tetrahedron : Asymmetry* **1990**, *1*, 167-170.