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Stereoselective Synthesis of (2*S*,3*S*)-3-*N*-Benzylaminoprolinol and (7*S*,8*R*)-7-*N*-Benzylaminopyrrolizidin-3-one

Nicole Langlois* and Marie-Odile Radom

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France#

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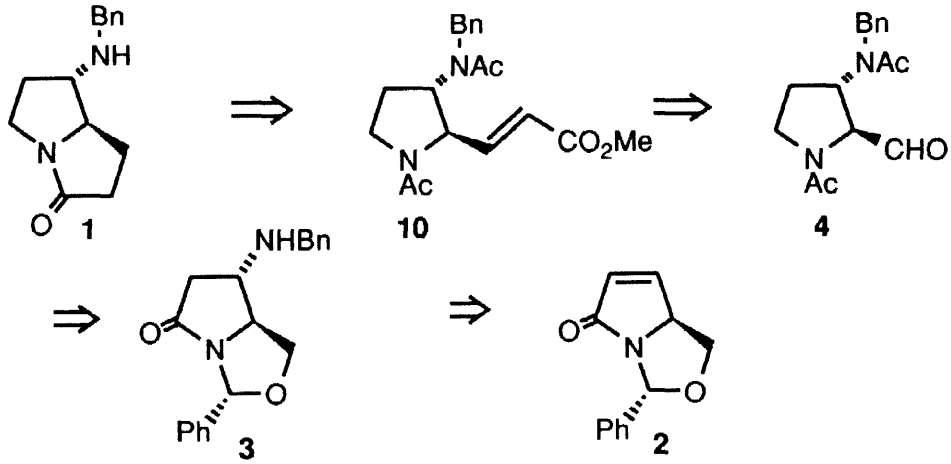
Abstract : The highly stereoselective synthesis of of (2*S*,3*S*)-3-*N*-benzylaminoprolinol and derivatives involved the conjugate addition of *N*-benzylamine to α,β–unsaturated lactam **2**. Wittig-Horner reactions with 1-acetyl-3-*N*-acetyl-*N*-benzylaminoprolinal provided a simple access to (7*S*,8*R*)-7-*N*-benzylaminopyrrolizidin-3-one.

Substituted pyrrolizidines have attracted much synthetic interest due to their therapeutic potential.[1,2] Thus, several polyhydroxylated pyrrolizidines are glycosidase inhibitors and exhibit antiviral activities and their syntheses have been recently reviewed.[3] Aminopyrrolizidines are less developed although this ring system constitutes a common subunit of interesting natural,[4-6] or synthetic[7,8] compounds such as Linaceae alkaloids [6] and $5HT_3$ receptor antagonists.[7]

Only few enantioselective syntheses of the amino-azabicyclo[3.3.0]octane skeleton have been reported,[9,10] and there is still a need for straightforward stereoselective access to these compounds. The synthesis of the direct precursor **1**, derived from (*S*)-pyroglutaminol, is described here, as an application of the conjugate addition of *N*-benzylamine to α,β-unsaturated lactam **2** developed in our laboratory.[11,12] Indeed, we have shown that this 1,4-addition gives **3** with high yield and high diastereoselectivity.[12,13] Furthermore, two carbon elongation of the side chain of the prolinal derivative **4** by Wittig-Horner reaction is an efficient procedure which allows further substitution of the newly introduced double bond.[14-18] In this way, the versatile synthetic route depicted in scheme 1 should be extended to higher substituted pyrrolizidines.



Scheme 1

Fax : 01-69 07 72 47. E-mail : Nicole.Langlois@icsn.cnrs-gif.fr

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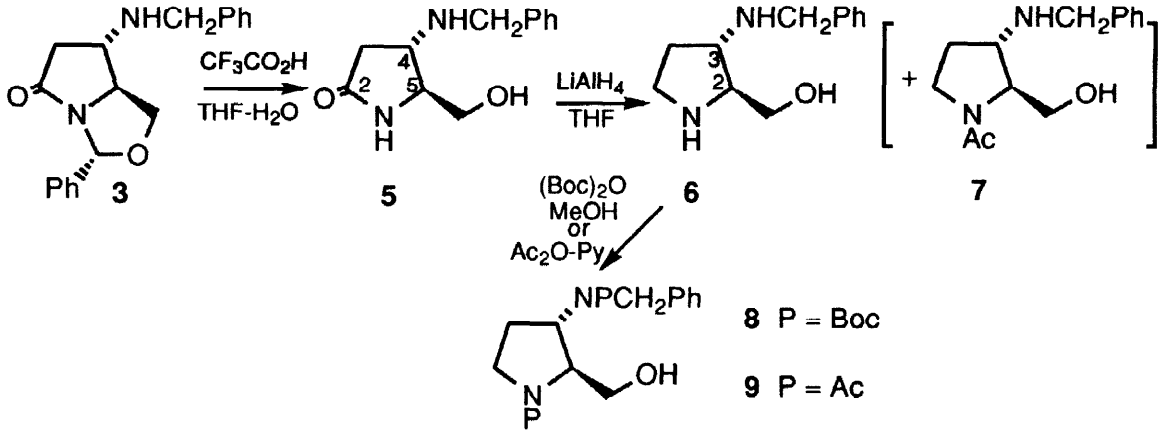
(4*S*,5*S*)-4-*N*-Benzylamino-5-hydroxymethylpyrrolidin-2-one **5**, quantitatively obtained from **3** by acidic deprotection,[12] was reduced with $LiAlH_4$ in excess to 3-*N*-benzylaminoprolinol **6** (Scheme 2). However, the monoacetylated derivative **7** was also formed when the excess of reagent was destroyed by addition of ethyl acetate. This unexpected reaction could be easily avoided by using saturated sodium sulfate solution to hydrolyze the reaction mixture, and, following this procedure, the diaminoalcohol **6** was isolated in 85% yield.[19]

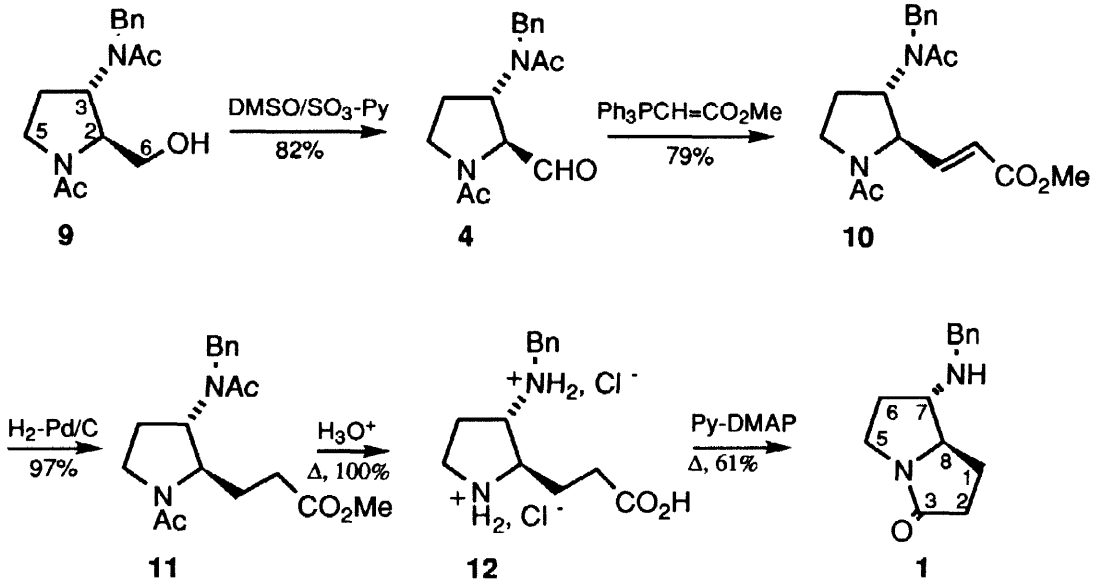


Scheme 2

Both nitrogens of **6** were protected either by *tert*-butoxycarbonyl or acetyl groups to give rise respectively to **8** and **9**.[20] Acetylation under Schotten-Baumann conditions led to a mixture of **7** and diacetate **9** and the best way to prepare **9** (86%) needed *N,N,O*-triacetylation followed by treatment with NaOH-MeOH at room temperature. The enantiopurity of **9** was controlled by esterification with MTPA chlorides.[21]

Some difficulties appeared to oxidize the primary alcohols **8** and **9** into aldehydes. These primary alcohols were found to be unreactive towards DMSO-$(CF_3CO)_2O$, a very efficient oxidizing system with a sterically hindered *cis* 2,3-disubstituted pyrrolidine derivative,[22] and classical Swern oxidation (DMSO-oxalyl chloride) of **9** provided only traces of aldehyde. Other reagents (PDC, CrO_3-Py) were tested without success[23-25] and the best results were obtained with DMSO-SO_3-pyridine complex.[26] The oxidation of **9** proceeded cleanly at room temperature to give 82% of the crude aldehyde **4** (Scheme 3) and it is worthy to note that the *N*-benzyl group was unaffected in this reaction. The diamidoaldehyde **4** is rather unstable although it could be reduced ($NaBH_4$-MeOH) into the initial alcohol **9** in 90% yield.

The crude aldehyde **4** was submitted directly to Horner-Wadsworth-Emmons or Wittig reactions to avoid epimerization at C-2 during a purification step. No stereoselectivity was observed in the condensation of **4** with the lithium salt of methyl diethylphosphonoacetate in THF, which led, in 65% yield, to a mixture of *Z* and *E* enoates . The use of methyl triphenyl phosphoranylidene acetate in the same solvent[17] produced only the *E* configured methyl ester **10** (79%, Scheme 3) and this high stereoselectivity could be interesting in further syntheses of polysubstituted aminopyrrolizidines with defined relative configurations.



Scheme 3

Catalytic hydrogenation of the enoate **10** (Pd/C 10%) was chemoselective and afforded, in 97% yield, the dihydro derivative **11**, in which the *N*-benzyl group was retained. It was fully hydrolyzed by heating with 6N HCl into the crude diaminoacid hydrochloride **12** which was directly cyclized in the conditions described for the synthesis of (-)-isoretronecanol (Py-DMAP, reflux).[17] Only one cyclization product was isolated (61% for two steps) and its structure aminopyrrolizidine **1** was deduced from spectral data.[27] Therefore, this favoured cyclisation process constitutes a simple access to the aminopyrrolizidine framework. The conversion of **1** into Mosher's amides with (+) and (-)-MTPA chlorides indicated an ee > 95%.[28]

Thus, we have shown that *N*-benzylamino-γ-lactam **3**, easily prepared from (*S*)-pyroglutamic acid,[29] is a good precursor of optically pure (3*S*)-3-aminoprolinol as well as (7*S*,8*R*)-7-aminopyrrolizidin-3-one derivatives and further applications are currently under investigation in our laboratory.

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References and Notes

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13. We isolated the pure diastereomer **3** in 88% yield.[12] This result differs from the recent finding of another group : Chan, P.W.H.; Cottrell, I.F.; Moloney, M.G. *Tetrahedron Lett.* **1997**, *38*, 5891-5894. In the latter work, the same unsaturated γ-lactam **2** was found to be unreactive towards *N*-benzyl amine.
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19. The new compounds gave satisfactory spectral data.
20. **9** : $[\alpha]_D^{28}$ = -47 (c = 1.50, $CHCl_3$). IR ($CHCl_3$, ν cm-1) : 3402, 3000, 1626, 1446, 1421. MS : 290 ($M^{+\cdot}$), 272, 259, 217, 111, 99, 91 (100%), 69, 68. HRMS (CI) : calcd for $C_{16}H_{23}N_2O_3$ $(M+H)^+$: 291.1711, Found : 291.1711. ^1H NMR [300 MHz, $CDCl_3$, δ = 0 ppm : TMS, J (Hz)] : 7.38 (dd, 2H, H-Ar), 7.32 (dd, H-Ar), 7.18 (d, 2H, H-Ar), 4.99 (m, 1H, H-3), 4.65, 4.47 (2d, 2H, J = 17, $C\underline{H}_2Ph$), 3.99 (m, 1H, H-2), 3.80 (dd, 1H, J = 12, J' = 2, Ha-6), 3.67 (dd, 1H, J = 12, J' = 6.5, Hb-6), 3.54 (m, 1H, Ha-5), 3.41 (m, 1H, Hb-5), 2.09 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.9 (m, 2H, H_2-4). ^{13}C NMR (75.0 MHz) : 172.66 (CO), 171.20 (CO), 137.20 (qC, Ar), 129.20 (CH, Ar), 127.71 (CH, Ar), 125.51 (CH, Ar), 64.50 (C-6), 62.97 (NCH), 55.51 (NCH), 48.71 ($N\underline{C}H_2Ph$), 46.95 (NCH_2), 28.04 (C-4), 22.53 ($CO\underline{C}H_3$), 22.48 ($CO\underline{C}H_3$).
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27. **1**: mp : 85-7°C. $[\alpha]_D^{29}$ = +44 (c = 1.61, $CHCl_3$). IR ($CHCl_3$, ν cm-1) : 2917, 1676, 1476, 1450, 1420. MS (CI, isobutane) : 231 [$(M+H)^+$, 100%]. HRMS (CI) : calcd for $C_{14}H_{19}N_2O$ $(M+H)^+$: 231.1497, Found : 231.1493. ^1H NMR (300 MHz) : 7.33 (m, 5H, H-Ar), 3.83, 3.81 (2d, 2H, J_{AB} = 13, $C\underline{H}_2Ph$), 3.69 (m, 1H, H-8), 3.58, (m, 1H, Ha-5), 3.21 (ddd, 1H, Hb-5), 2.88 (m, 1H, H-7), 2.69 (m, 1H, Ha-2), 2.40 (m, 2H, Hb-2, Ha-6), 2.31 (m, 1H, Ha-1), 1.9 (m, 1H, Hb-6), 1.82 (m, 1H, Hb-1). ^{13}C NMR (75.0 MHz) : 174.58 (CO), 139.71 (qC, Ar), 128.57 (CH, Ar), 128.00 (CH, Ar), 127.31 (CH, Ar), 67.34 (C-8), 63.48 (C-7), 52,76 ($N\underline{C}H_2Ph$), 40.00 (C-5), 34.67 (C-2), 34.10 (C-6), 26.28 (C-1).
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