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Stereocontrolled Synthesis of Enantiopure Substituted 4-Aminopyrrolidin-2-ones

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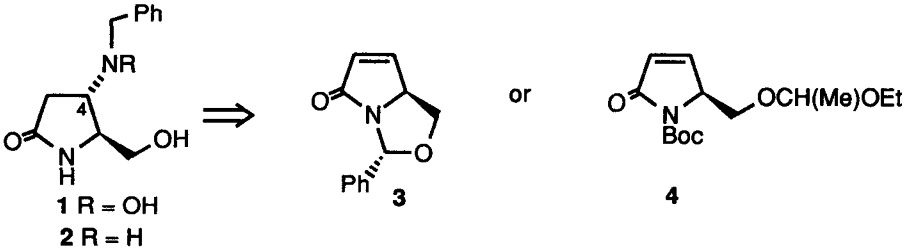
Abstract : The highly diastereoselective conjugate addition of *N*-benzylhydroxylamine and benzylamine to α,β–unsaturated lactam 3 provided an efficient entry to enantiopure (4*S*,5*S*)-4-amino-5-hydroxymethylpyrrolidin-2-ones. © 1997 Elsevier Science Ltd.

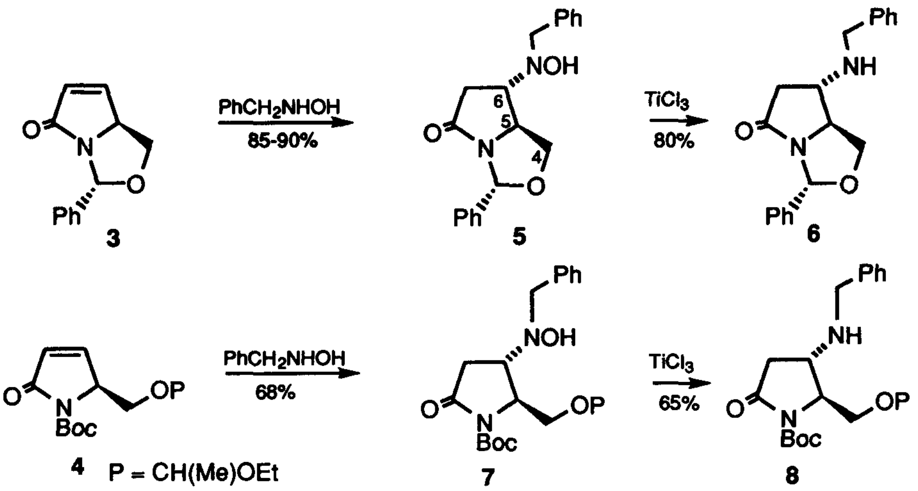
Enantiomerically pure 4-aminopyrrolidin-2-ones are useful precursors of interesting bioactive products such as γ-lactam bridged dipeptides.[1] Furthermore, the related 3-aminopyrrolidines, readily obtained by carbonyl reduction, are constituents of several medicinal compounds,[2] particularly of antibacterial quinolones.[3]



Scheme 1

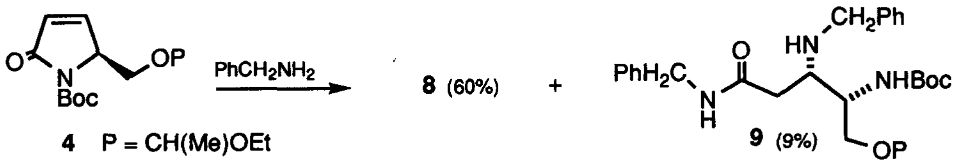
To synthesize the amino γ-lactams **1** and **2**, we anticipated efficient conjugate addition of primary amines to unsaturated derivatives of (*S*)-pyroglutaminol **3** and **4**,[4] although *N*-nucleophiles have received little attention in Michael addition to α,β-ethylenic lactams.[5-7] Indeed, easy diastereoselective 1,4-addition of *N*-alkyl hydroxylamines to **3** and **4** was already observed during previous studies as side-reaction,[4] and as an extension of this work, we report here the addition of *N*-benzylhydroxylamine and *N*-benzylamine following two types of experimental conditions.

Thus, *N*-benzylhydroxylamine was added to **3** either in refluxing toluene by method a (amine 1.2 equiv., 4 h) or by using a mixture of amine (1.8 equiv.) and H_2O (5 equiv.) at room temperature (method b). The method a led to the adduct **5** in 85% yield (Scheme 2) as a single diastereomer along with 10% unreacted **3**. According to previous observations,[8] the reaction proceeded faster in the presence of water (method b) ; it went to completion in less than 2 h and gave slightly improved yield (90%). The same method was applied to *N*-benzylamine addition to **3** giving rise to **6** in 88% yield.[9]



Scheme 2

Starting from the *N*-Boc derivative **4** and *N*-benzylhydroxylamine, the aminolactam **7** was isolated in 68% yield by method a.[10] This lower yield could be explained by the presence of a carbamate as nitrogen protective group. This electron withdrawing group makes the lactam carbonyl more sensitive to nucleophilic 1,2-addition with ring opening. Thus, treatment of **4** with *N*-benzylamine following method b led to the kinetically favoured 1,4-adduct **8** (60%), together with a small amount of the acyclic *N*-benzyl-3-benzylamino-4-(*tert*-butoxycarbonyl)aminopentanamide derivative **9** (9%, Scheme 3).

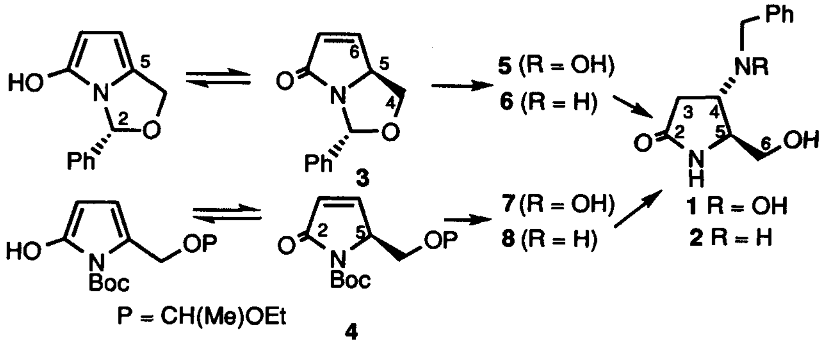


Scheme 3

In each case, the nucleophilic attack occurred with high facial selectivity since only one 1,4-adduct could be detected. These results can be compared with high stereoselectivity of phenylthioacetate and malonate[11,12] or ethyl thioglycolate[13] Michael addition to α,β-unsaturated lactams derived from (*S*)-pyroglutaminol.

The predictable 1,2 asymmetric induction led to assign a *trans* relationship between the two substituents of the lactam ring and consequently the *S* configuration at the newly created asymmetric center. This assignment was confirmed in **5**, since a strong nOe was observed between the proton C-6-H and one of the protons at C-4. Furthermore, we established chemical correlations between *N*-benzylhydroxylamine and benzylamine adducts to prove their identical configuration at these asymmetric centers. The reductive cleavage of the N-O bond of **5** and **7** was accomplished by treatment with $TiCl_3$ at room temperature,[14] which furnished **6** (80%) and **8** (65%, Scheme 2), respectively.

An enolization of the starting α,β-unsaturated pyrrolidinones **3** and **4** cannot be excluded although the compound **3** recovered after addition reaction was optically pure. In the case of rigid bicyclic **3**, a diastereospecific reprotonation at C-5 could be anticipated. Such a stereospecificity induced by the C-2 asymmetric center, should lead to retention of the 5*S* configuration according to previous results related to the concept of "self-reproduction of chirality" by Seebach (Scheme 4).[15-17]



Scheme 4

However, an enolization of **4** before the conjugate addition could be responsible for the epimerization at C-5. The optical rotations of the common deprotected products (4*S*,5*S*)-4-(*N*-benzyl-*N*-hydroxy)amino-5-hydroxymethylpyrrolidin-2-one **1** and 4-(*N*-benzyl)amino-5-hydroxymethylpyrrolidin-2-one **2** (prepared from **3** and **4** by acid hydrolysis of **5**-**8** with trifluoroacetic acid, 100%, Scheme 4) were compared to clarify this point. A partial racemization was observed for the compound **2** synthesized from **4**, following method b.[18,19]

Therefore, these results prove the greater potential of bicyclic α,β-unsaturated γ-lactam **3** for asymmetric syntheses of 3-aminopyrrolidine containing compounds.

The application of this work to the preparation of interesting bioactive examples is under investigation.

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9. **6** : $[\alpha]_D^{29}$ = +146 (c = 2.25, $CHCl_3$). SM : 308 ($M^{+\cdot}$), 202, 134, 133,132 (100%), 118, 104, 91, 77. IR ($CHCl_3$, ν cm-1) : 3309, 3083, 3030, 2925, 1702, 1497, 1457, 1350. ^1H NMR [300 MHz, $CDCl_3$, δ = 0 ppm : TMS, J (Hz))] : 7.34 (m, 10H, H-Ar), 6.32 (s, 1H, H-2), 4.14 (dd, 1H, J = 9, J' = 8, Ha-4), 3.92 (m, 1H, H-5), 3.77 (2d, 2H, $C\underline{H}_2Ph$), 3.61 (dd, 1H, J = 9, J' = 8, Hb-4), 3.44 (m, 1H, H-6), 2.82 and 2.70 (2m, 2H, H_2-7). ^{13}C NMR (62.5 MHz) : 175.5 (CO), 139.1 (qC, Ar), 138.3 (qC, Ar), 128.7, 128.5, 128.1, 127.6, 126.0 (CH, Ar), 86.95 (C-2), 70.6 (C-4), 66.0 (CHN), 59.0 (CHN), 52.4 (NCH_2), 42.0 (C-7). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09; Found : C, 73.69; H, 6.72; N, 9.11.
10. **7** : MS(CI, isobutane) (m/z) : 409 $(M + H)^+$ 391, 309, 264, 184, 158, 140, 124, 73. IR : 3570, 2960, 1782, 1743, 1709, 1370, 1313. ^1H NMR(300 MHz) : 7.29 (m, 5H, H-Ar), 4.84 (m, 1H, NH), 4.67, 4.62 (2m, 1H, OCHO), 4.46 (m, 1H, H-5), 3.89, 3.74 and 3.55 (OCH_2), 3.86 and 3.78 (2d, J ~ 13.5, $C\underline{H}_2Ph$), 3.55, 3.38 (OCH_2), 3.41 (m, H-4), 2.83 (broad dd, 1H, $J_{3a,3b}$ = 17.5, $J_{3a,4}$ ~ 6.5, Ha-3), 2.66 (broad d, $J_{3a,3b}$ = 17.5, Hb-3), 1.53 (s, 9H, *t*-Bu), 1.26 (2d, 3H, $CHC\underline{H}_3$), 1.16 (2t, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75.0 MHz) : 173.71-173.56 (C-2), 149.90 (NCO_2), 136.88 (qC, Ar), 129.50, 128.54, 127.69 (CH, Ar), 99.84-99.45 (OCHO), 83.01 (qC, *t*-Bu), 64.58-64.28 and 61.47- 61.25 (2 x OCH_2 et $N\underline{C}H_2Ph$), 60.90 and 60.84 (C-4, C-5), 35.80 (C-3), 28.13 (CH_3, *t*-Bu), 19.69-19.51 ($CH\underline{C}H_3$), 15.31 $CH_2\underline{C}H_3$). Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.74; H, 7.90; N, 6.86; Found : C, 61.45; H, 7.67; N, 6.81.
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18. In the case of **2**, as trifluoroacetate prepared from **4** through the method <u>b</u>, 50% e.e. was observed by comparison with the $[\alpha]_D^{28}$ value of the same product obtained from **6** : mp (dec.) : 184-6°C. $[\alpha]_D^{28}$ = +13 (c =1.13, MeOH). ^1H NMR (300 MHz, D_2O, HOD : 4.80 ppm) : 7.52 (broad s, 5H, H-Ar), 4.33 (2H, $C\underline{H}_2Ph$), 4.05 (m, 2H, H-4, H-5), 3.71 (2H, H_2-6), 3.07 (dd, 1H, J = 18, J' = 8.5, Ha-3), 2.65 (dd, 1H, J = 18, J' = 2, Hb-3). ^{13}C NMR (75.0 MHz, D_2O, dioxane δ = 67.34 ppm) : 177.18 (CO), 130.86, 130.56, 130.16 (CH, Ar), 62.76 (CH_2), 59.72 (NCH), 55.57 (NCH), 50.15 (CH_2), 34.54 (C-3). Anal. Calcd for $C_{14}H_{17}F_3N_2O_4$: C, 50.20; H, 5.13; N, 8.38; Found : C, 49.98; H, 5.08; N, 8.16.
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