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Tandem Electrophilic and Nucleophilic Additions to Bicyclic *tert*-Butyldimethylsilyloxypyrrole derived from (*S*)-Pyroglutaminol

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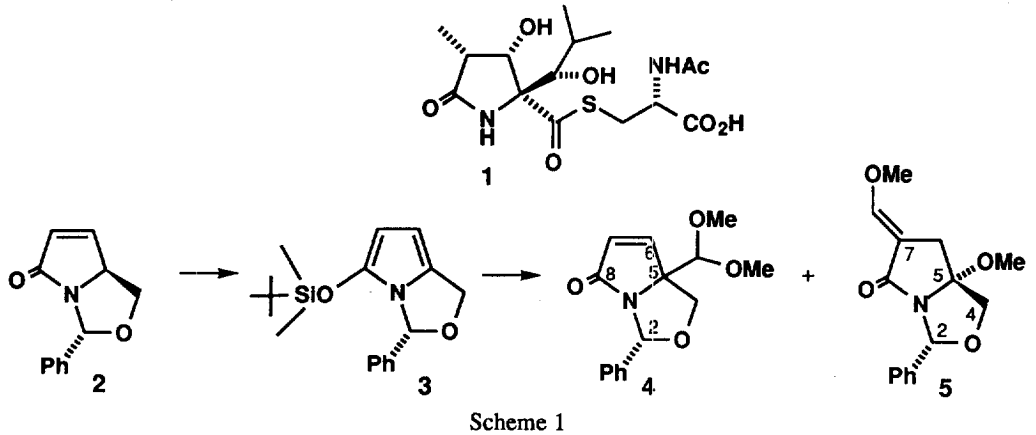
Abstract : The silyloxypyrrole derivative **3**, treated with $SnCl_4$ and aqueous $NaHCO_3$, afforded the 5-hydroxylated pyrrolidinone **7**. This compound was shown to be a key intermediate for the diastereoselective introduction of other hetero- and C-nucleophiles at the same position.

The development of diastereoselective and enantioselective synthetic routes to highly substituted pyrrolidin-2-ones has attracted considerable attention, principally because of the wide-ranging biological activities of these compounds. In particular, 5,5-disubstituted pyrrolidin-2-ones are encountered in several interesting natural products such as epolactaene,[1] PI-091,[2] and the first non-protein neurotrophic factor lactacystin **1**.[3] Mukaiyama-type aldol reaction[4,5] of 2-silyloxypyrroles, assisted by Lewis acids, is a well documented method to introduce functionalities at the γ-position in the synthesis of 5-substituted or 5,5-disubstituted pyrrolidinones.[6-14] This method was recently extended to the addition to imines in vinylogous Mannich reactions.[15] The addition to isobutyraldehyde allowed to introduce the α-hydroxyisobutyl chain of lactacystin **1**, starting from a suitable bicylic unsaturated lactam related to **2**.[10] We illustrate here the possibility of nucleophilic addition at C-5 to the bicyclic silyloxypyrrole **3** derived, through **2**, from (*S*)-pyroglutaminol.



Scheme 1

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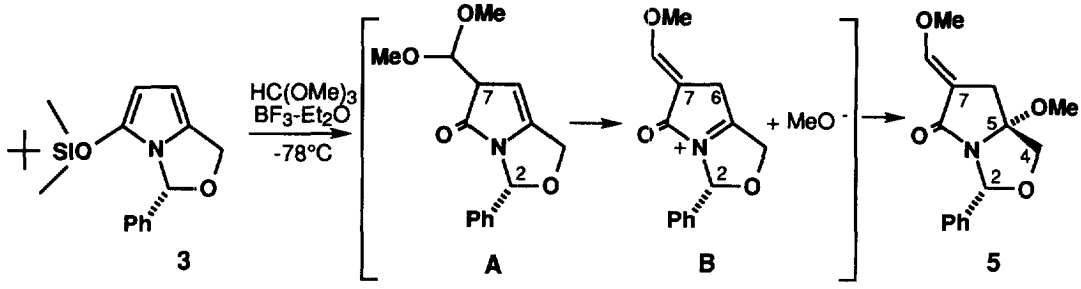
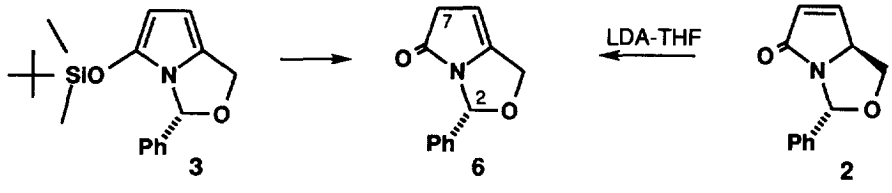
The silyloxypyrrole **3** was prepared in 91% yield from the α,β-unsaturated lactam **2**[16] with TBSOTf and 2,6-lutidine, following the procedure reported for *N-tert*-butoxycarbonyl-2-*tert*-butyldimethylsilyloxypyrrole.[7] With the aim of introducing a formyl equivalent at the γ-position, **3** was treated with trimethylorthoformate in the presence of BF_3-Et_2O, in dichloromethane at -78 °C.[13] This experiment led to a mixture from which the expected 5-dimethoxymethyl derivative **4** was obtained in poor yield (12%), together with another dimethoxylated compound **5** (23%), as the only isolable products (Scheme 1). In the ^1H NMR spectrum of **5**, the pure AB system related to the protons at C-4 indicated the tetrasubstitution of C-5, this quaternary aminoacetal carbon giving rise to a signal at 96.9 ppm. Another methylene, C-6, gave two doublets of doublets with small couplings with the ethylenic proton at 7.15 ppm. The chemical shifts of the corresponding tertiary and quaternary ethylenic carbons, respectively at 153.6 and 108.9 ppm, agree with the presence of an enol ether in the molecule which was suggested to have the structure **5**, the double bond geometry being assigned on the basis of steric factors. This deduction was supported by the signal of one of the two methoxyl groups (^1H, δ : 3.86 ppm; ^{13}C : 61.8 ppm). The structure **5** was confirmed by X-ray crystal analysis which precised the configuration at C-5.[17] The formation of **5** could be explained by the addition of the formyl cation equivalent at C-7, followed by the protonation at C-6 of the resulting enamide **A** leading to the electrophilic *N*-acyliminium ion **B** (Scheme 2). The regioselectivity of this electrophilic addition of trimethylorthoformate to the silyloxypyrrole **3** at C-7, in a "non-vinylogous" manner, is unusual.



Scheme 2

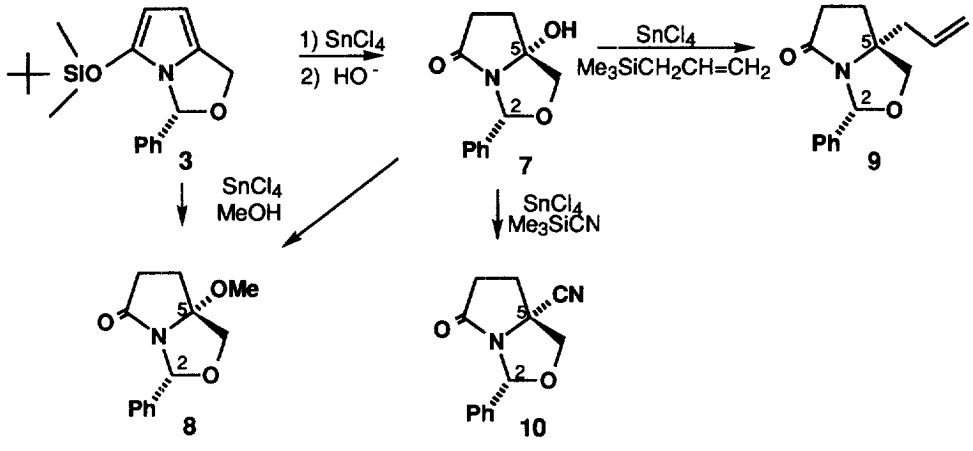
A selective protonation at C-7 was also observed during slow partial degradation of the starting silyloxy pyrrole **3**, due to its moisture sensitivity, giving rise to the deconjugated β,γ-unsaturated pyrrolidinone **6**. Compound **6** could also be obtained, albeit in low yield (15%), from the starting lactam **2**, in a deprotonation-protonation sequence, although the reaction gave rise both to **2** and probably dimeric by-products. Furthermore, the enamide **6** was rather unstable and difficult to purify.



Scheme 3

Nevertheless, the possibility to convert *in situ* the silyloxypyrrole **3** into an acyliminium ion precursor, such as **A** (Scheme 2) was encouraging in our prospect to functionalize the C-5 position. In this way, the previous results were extended to the introduction of various hetero- and C-nucleophiles at C-5.

Thus, the silyloxypyrrole **3** was successively treated at -78 °C in dichloromethane with $SnCl_4$ (1.5 equiv.) and saturated aqueous $NaHCO_3$ solution to afford mainly the hydroxy-pyrrolidinone **7** (74% yield),[18] together with a small amount of the enamide **6** (c.a. 5%) whereas the α,β-unsaturated lactam **2** was not found. Only one diastereoisomer of the hydroxylated derivative **7** was isolated, but a NOESY experiment was not conclusive to establish the configuration of the newly created quaternary center C-5. The NMR spectrum showed a singlet at 6.18 ppm related to the proton at the aminoacetal center C-2, a chemical shift supporting a *cis* relationship between the phenyl group at this position and the substituent at C-5 (Scheme 4).[19] However, the stereoselectivity of the complexation of **3** could depend on the Lewis acid used[11, 14] and, for this reason, the structure determination of **7** was confirmed by X-ray crystal analysis.[17] In similar conditions, **3** gave rise in the presence of methanol, to the methoxylated derivative **8** (35 % yield), together with **6** (10%) and **7** (21%). This result led us to consider the hydroxylated derivative **7** as a key intermediate for the substitution with other nucleophiles at the same position. Thus, the compound **7** was treated at -35°C with methanol and $SnCl_4$ to produce **8** quantitatively. This alternative protocol, more efficient than the direct reaction of **3**, was applied to introduce other nucleophiles. C-Nucleophiles such as allyl and cyano groups were added at the same temperature by means of allyltrimethylsilane and trimethylsilylcyanide, respectively (Scheme 4). The clean reactions afforded the derivatives **9** (50%) and **10** (56%) and recovered starting material **7**. The relative configurations of **8-10** were assigned on the basis of similitudes of their ^1H NMR data with those of **7**.



Scheme 4

In conclusion, it was shown that sequential protonation of *tert*-butyldimethylsilyloxypyrrole **3** at C-7 and C-6 allowed a highly stereoselective nucleophilic addition of a hydroxyl group at C-5. The hydroxylated derivative obtained by this way was used to introduce other nucleophiles at C-5 with moderate to excellent yield and high diastereoselectivity. Particularly, the addition of C-nucleophiles could be useful in the synthesis of more complex 5,5-disubstituted pyrrolidinones related to lactacystin **1**.

Acknowledgements

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18. Data of **7** : mp : 119-121 °C (Et_2O). $[\alpha]_D^{26}$ = +183 (c = 2.41, $CHCl_3$). IR ($CHCl_3$, ν cm^{-1}) : 3580, 3394, 3025, 2850, 1709, 1339. MS (CI, isobutane) : 220 [$(M + H)^+$, 100%], 202, 107. ^1H NMR [300 MHz, $CDCl_3$, δ = 0 : TMS, J (Hz)] : 7.52 (2H, H-Ar), 7.34 (m, 3H, H-Ar), 6.18 (s, 1H, H-2), 4.14 (d, 1H, J_{AB} = 9.1, Ha-4), 3.74 (d, 1H, J_{AB} = 9.1, Hb-4), 3.30 (s, 1H, exch., OH), 3.00 (m, 1H), 2.44 (m, 1H), 2.28 (m, 2H) : H_2-7 and H_2-6. ^{13}C NMR (75.0 MHz) : 176.83 (CO), 138.33 (qC, Ar), 128.93 (CH, Ar), 128.63 (CH, Ar), 126.41 (CH, Ar), 95.71 (C-5), 88.10 (C-2), 77.35 (C-4), 33.41, 31.43 (C-7, C-6). Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found : C, 65.57; H, 6.18; N, 6.29.
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