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# Stereoselective synthesis of *gem*-dimethyl-5,5-pyrrolidine-*trans*-lactam (5-oxo-hexahydropyrrolo[3,2-*b*]pyrrole)

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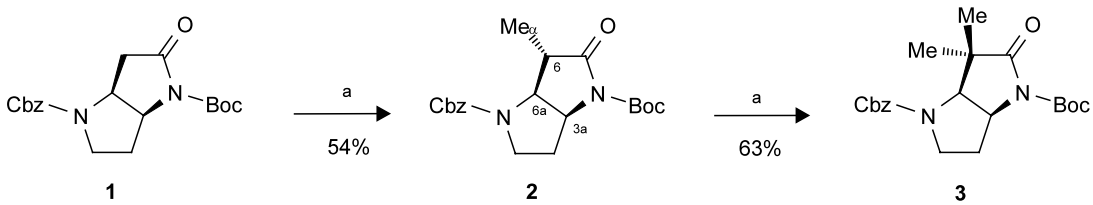
**Abstract**—The *gem*-dimethyl-*trans*-lactam **6** could be prepared by alkylation of the β-methyl isomer **7** but not by alkylation of the α-isomer **5**. 

Selectivity for particular serine proteases in the novel, strained, pyrrolidine-5,5-*trans*-lactam inhibitors is determined[1] by the substituent adjacent to the acylating centre of the *trans*-lactam carbonyl group. We have investigated[2] the alkylation of the pyrrolidine-5,5-*trans*-lactam and pyrrolidine-5,5-*cis*-lactam ring systems with the aim of introducing a range of substituents into this position.

We have shown[2] that methylation of the 5,5-*cis*-lactam ring **1** gave the corresponding α-methyl-5,5-*cis*-lactam **2** where the enolate was alkylated, from the less hindered convex side of the molecule, on the same face as the ring-junction protons. Further methylation of **2**, presumably from the less hindered convex side of the molecule, gave the dimethyl analogue **3** in 63% yield (Scheme 1).

We have also shown that a range of substituents can be introduced stereoselectively at the corresponding position in the novel, strained, unsubstituted 5,5-*trans*-lactam ring **4** by alkylation of the corresponding enolate[3] to give a series of α-alkyl-5,5-*trans*-lactams.[2] However, attempts to introduce a second methyl group into the α-methyl-5,5-*trans*-lactam **5** to give the *gem*-dimethyl-5,5-*trans*-lactam **6** failed (Scheme 2).

In the corresponding 3-methyl-5,6-*trans*-fused γ-lactam[5] and γ-lactone[4] systems epimerisation, with potassium *tert*-butoxide and stereoselective protonation of the lithium enolate respectively, gave the corresponding epimers. However, this does not happen with the more strained pyrrolidine-5,5-*trans*-lactam or cyclopentane-5,5-*trans*-lactone[6] series ring systems, and neither deuterium nor a methyl group could be incorporated into the β-face of the α-substituted ring **5**. As the α-methyl-5,5-*trans*-lactam **5** was prepared by alkylating the enolate of the unsubstituted ring **4** from the less hindered α-face it was reasoned that the *gem*-dimethyl-5,5-*trans*-lactam could be prepared by alkylating the




**1** **2** **3**

**Scheme 1.** *Reagents and conditions*: (a) LHMDS (1.1 equiv.)/THF, −78°C, then MeI (2 equiv.).

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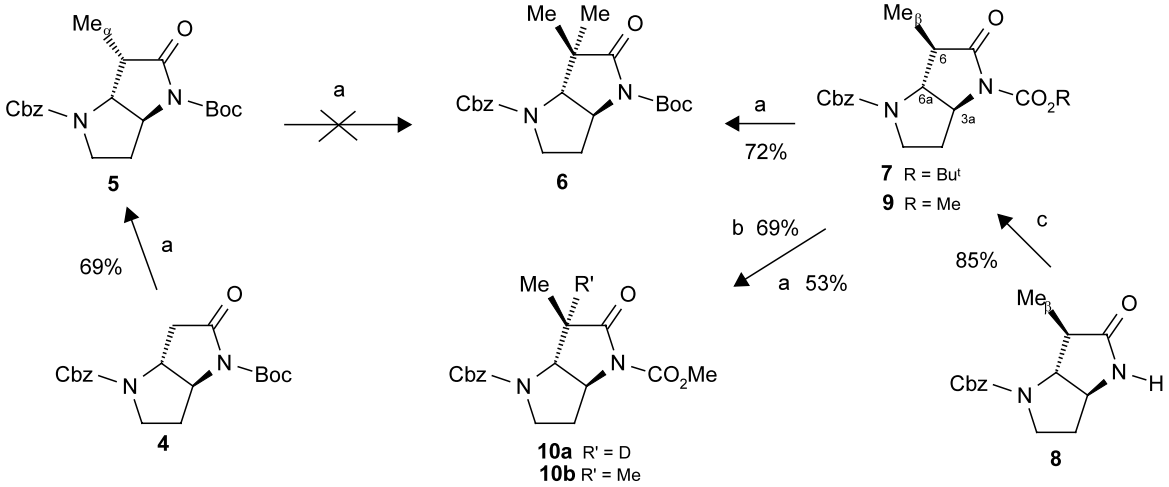


**Scheme 2.** *Reagents and conditions*: (a) LHMDS (1.3 equiv.), THF, −78°C, 30 min, then titration of excess MeI; (b) LHMDS (1.3 equiv.), THF, −78°C, 30 min, then excess $D_2O$ added; (c) LHMDS (1.2 equiv.)/THF, −78°C, 30 min, then $(Boc)_2O$ (2.8 equiv.)/THF or $(MeOCO)_2O$, −78°C.

β-methyl-5,5-*trans*-lactam ring **7** from the α-face (Scheme 2). Protection of **8**[1b] with di-*tert*-butyl or dimethyl pyrocarbonate gave the protected lactams **7**[7] and **9**. Preliminary experiments demonstrated that the *gem*-disubstituted analogues **10a** and **10b** could be prepared by incorporating electrophiles into the α-face of β-isomer **9**. Similarly the required *gem*-dimethyl analogue **6** was prepared in 72% yield by methylation of the β-methyl-*trans*-lactam **7** with methyl iodide.

Mechanistically, the observed stereoselectivity can be explained on the basis of the extreme rigidity of the 5,5-*trans*-lactam system and the consequent great difference in alignment of the α- and β-C–H bonds with the carbonyl π-system. Molecular modelling (Insight 2000) shows that, in the only energetically accessible conformation of the *trans*-lactam **4**, the C–H bond to the α-proton is almost parallel to the carbonyl π-system (dihedral angle 4.3°) whereas that to the β-proton has far less favourable overlap (dihedral angle 53.5°). Unlike the corresponding *cis*-lactam **1** the *trans*-lactam ring system **4** is too rigid to allow the flexion necessary to achieve good overlap between the β-C–H and the carbonyl π-system, so deprotonation and alkylation occur on the α-face. Likewise, the β-methyl-5,5-*trans*-lactam **2** shows excellent overlap of the carbonyl π-system with the α-C–H bond (dihedral angle 0.2°) while the corresponding overlap of the β-C–H bond in the analogous α-methyl compound **7** is relatively poor (dihedral angle 51.8°).

This stereoelectronic control should be enhanced by allylic strain effects, whereby an electrophile approaching the enolate from the β-face would experience severe proximal strain whilst the strain and steric hindrance for α-face attack would be significantly less.[8]

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7. Compound **7** [$J_{3a,6a}$ 11 Hz, $J_{6,6a}$ 11 Hz, NOE Me→H6 (6%), Me→H6a (5%)] and lactam **2** [$J_{3a,6a}$ 11 Hz, $J_{6,6a}$ 6.6 Hz, NOE Me→H6 (6%), Me→H3a (6%)].
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