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Stereocontrolled Synthesis of 3,5-Dialkyl-4-Amino Pyrrolidin-2-ones From β–Lactams as Chiral Templates.

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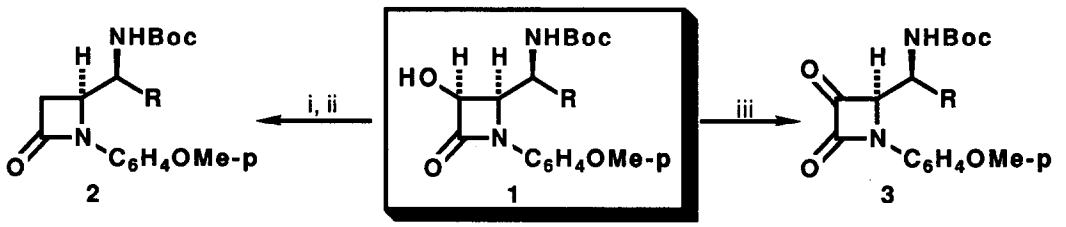
Abstract: A new approach to 3,5-dialkyl pyrrolidin-2-ones by intramolecular rearrangement of both *cis* and *trans* 3-alkyl-4-(1-aminoalkyl) β-lactams is described.

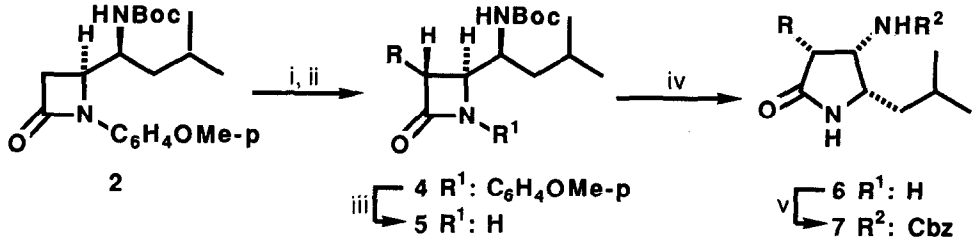
Although pyrrolidin-2-ones are important both as components of many medicinal compounds[1] and as intermediates in the synthesis of substituted pyrrolidines[2], there is still no general procedure for the stereocontrolled synthesis of 3,5-disubstituted pyrrolidin-2-ones. The most expedient synthesis of these compounds involves alkylation of the lithium enolate of either glutamic acid or pyroglutamic acid derivatives[3]. Nonetheless, this approach suffers from the lack of both reactivity and stereoselectivity. Although some solutions to these problems have recently been reported[4], their successfull implementation is based on the availability of glutamic and pyroglutamic acid as natural chiral pool materials. Recently we have described the asymmetric synthesis of homochiral β-lactams derived from N-Boc L-serinal acetonide derived imines via the Staudinger reaction[5]. As an extension of this work and in conjuction with our interest in β-lactam derived natural products we reasoned that β-lactams of type **1** would be useful starting materials for the stereocontrolled synthesis of 3,5-dialkyl-4-aminopyrrolidinones if effective formation of both *trans* and *cis*-3-alkyl β-lactams could be achieved from **1**.The following reasons led us to explore this proposal. First, the recent publications of Rae *et al.*[6] on 4-aminopyrrolidin-2-ones as γ-lactam bridged dipeptides. Second, the potential utility of a pyrrolidinone framework for the construction of γ-lactam analogues of β-lactam antibiotics[7]. Third, the possibility to transform the amino group into other functionalities in a stereocontrolled fashion. Finally, reduction of the carbonyl group would generate differentially substituted pyrrolidines.



Scheme 1. Reagents and Conditions: i, NaH, CS_2, THF then MeI. ii, n-Bu_3SnH, AIBN, toluene, 70°C. iii, CrO_3-pyridine, CH_2Cl_2, r.t., 15min.

In this paper we present our preliminary results on the stereocontrolled synthesis of 3,5-dialkyl pyrrolidinones epimeric at the C_3 position employing the α-hydroxy β-lactam **1** as a chiral template. The approach to these compounds having all the substituents in a *cis* relationship arises from the highly stereoselective α-alkylation of the lithium enolates of 3-unsubstituted β-lactams[8], which in our case would be

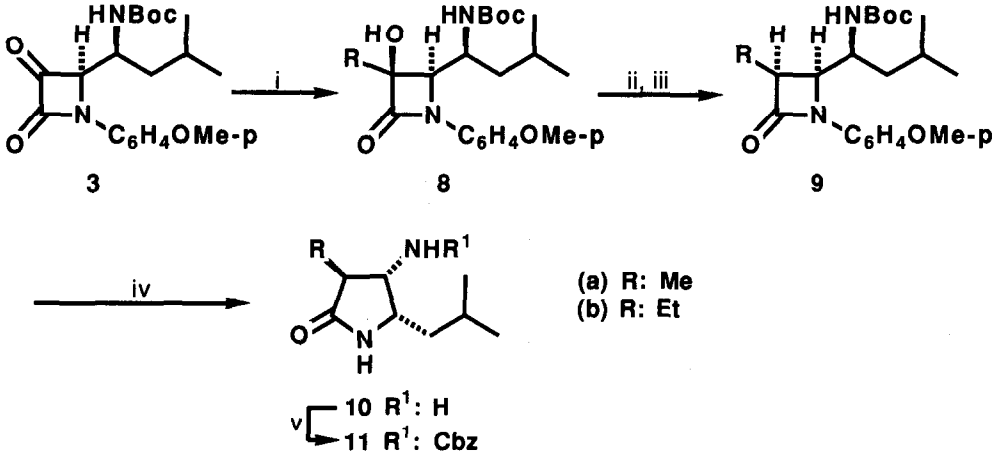
stereospecific due to the bulky substituent attached at the C_4 position of the β-lactam ring. For the same reason we expected that, deoxygenation of a 3-alkyl-3-hydroxy β-lactam, easily prepared from the α-keto β-lactam **3**, would generate the corresponding *cis*-isomers in a highly stereocontrolled fashion[9].



(a) R: Me, (b) R: Et, (c) R: $CH_2CH{=}CH_2$

Scheme 2. Reagents and Conditions: i, LDA (2.5equiv.), -78°C, THF, 30min. ii, R-X, -78°C→r.t. iii, $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, 0-5°C. iv, $ClSiMe_3$, MeOH, reflux, 1.5h. v, Cbz-Cl, NEt_3, CH_2Cl_2, r.t.

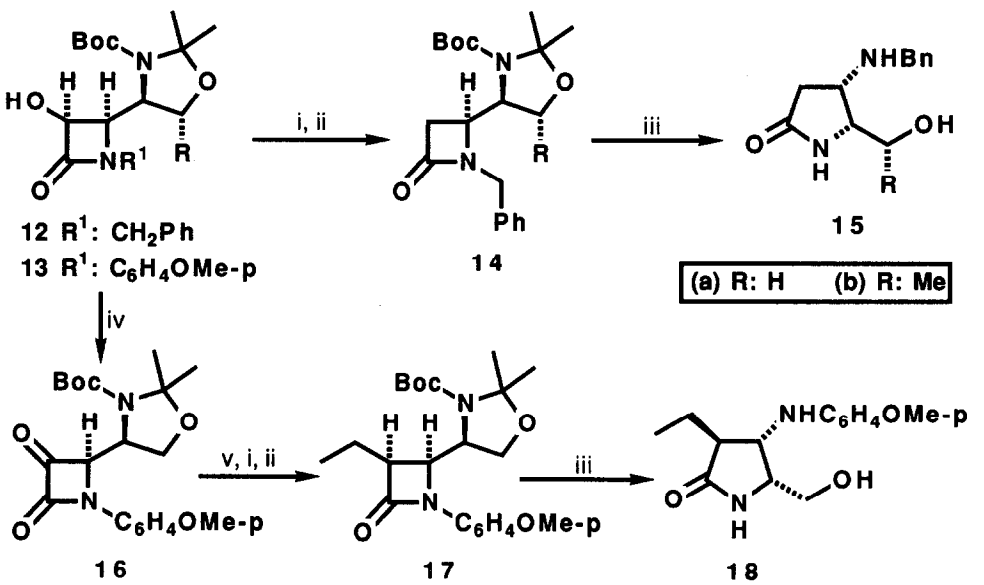
The 3-unsubstituted β-lactam **2** [m.p. 229-230°C (Et_2O/hexane); $[\alpha]^{25}_D$ = - 142.9 (c = 0.34, CH_2Cl_2)] was easily obtained in 75% overall yield following our recently reported procedure[10]. Compound **2** was then treated with LDA (2.5 equiv.) under the usual conditions and the resulting solution quenched with a fourfold excess of an electrophile to furnish the corresponding 3-alkyl β-lactams **4** soley as the *trans* isomers. N-dearylation[11] of **4** and further cyclization of the resulting N-unsubstituted β-lactams **5** under acidic conditions [12], led to the formation of the expected pyrrolidinones **6**. The crude compounds were then transformed into their Cbz derivatives **7** and isolated by column chromatography in good overall yields[13].



Scheme 3. Reagents and Conditions: i, RMgX 2.5equiv., THF, -70°C, 15min. ii, NaH, CS_2, THF then MeI. iii, n-Bu_3SnH, AIBN, toluene, 70°C. iv, $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, 0-5°C then $ClSiMe_3$, MeOH, reflux. v, Cbz-Cl, NEt_3, CH_2Cl_2, r.t.

In view of these results the next logical aspect we examined was the preparation of the corresponding epimeric compounds at the C_3 position. The selected strategy, depicted in scheme 3, was guided by our previous observation that tributyltin hydride desulphuration of a 3-alkyl-3-arylthio β-lactam gave manly *cis*-3-

alkyl β-lactams and by the fact that the *cis*-isomer ratio was increased when bulkier groups at the C_4 position of the β-lactam ring were involved[9]. First, compound **3** was prepared in 65% yield by oxidation of **1** with CrO_3-pyridine complex[14] and its optical purity was established by NMR spectroscopy, HPLC analysis and borohydride reduction to the starting hydroxy derivative **1**. Particularly noteworthy is that this reduction proceeded with complete stereoselectivity. Subsequent Grignard addition[15] to the carbonyl group in **3** afforded the carbinol **8a** in 60% isolated yield. Similarly, addition of EtMgBr to **3** led to **8b** as single isomer[16]. Although the absolute stereochemistry of compounds **8a** and **8b** was not determined the NMR spectra showed that only a single diastereomer was formed. Nonetheless, since borohydride reduction was stereospecific it is assumed that the stereochemistry of the adduct is as depicted. Both stereoselectivities could be explained by the attack of the nucleophile from the less hindered side of the carbonyl group[17]. Next compound **8a** was subjected to Barton-McCombie deoxygenation to give **9a** as single diastereomer. Finally, the pyrrolidinone **10a** was obtained in 60% yield by N-dearylation of **9a** followed by treatment of the resulting N-unsubstituted β-lactam with $ClSiMe_3$ in methanol at reflux and isolated as the Cbz derivative **11a**. Following the same sequence of reactions as above, the pyrrolidinone **11b** was obtained in 40% overall yield from **8b** [m.p. 95-96°C (hexane/CH_2Cl_2); $[\alpha]^{25}_D$ = - 69.5 (c = 0.78, CH_2Cl_2)].



Scheme 4. Reagents and Conditions: i, NaH, CS_2, THF then MeI. ii, n-Bu_3SnH, AIBN, toluene, reflux. iii, 6N or 12N HCl, EtOH, reflux, 48h. iv, CrO_3-pyridine, CH_2Cl_2, r.t., 15min. v, EtMgBr, -78°C, THF.

The potential scope of the above methodology is further exemplified in scheme 4. The β-lactam **14a** [m.p. 135-137 °C (hexane); $[\alpha]^{25}_D$ = -14.0° (c = 1, CH_2Cl_2)] prepared by deoxygenation of its corresponding α-hydroxy derivative **12a**, when treated with 6N HCl in ethanol at reflux for 48h smoothly produced the pyrrolidinone **15a** in 82% yield. Similarly, **14b** [m.p. 122-123°C (hexane); $[\alpha]^{25}_D$ = -14.7° (c = 1, CH_2Cl_2)] produced **15b** in 80% yield. On the other hand, compound **13a**[5] when oxidized to **16**, *vide supra*, followed by Grignard addition and subsequent deoxygenation of the resulting carbinol gave **17** soley as the *cis*-isomer. Treatment of **17** with 12N HCl in ethanol at reflux furnished the pyrrolidinone **18** in 90% yield[18].

From the results reported here it is clear that these methodologies allow construction of the fully substituted pyrrolidinone framework in a completely stereocontrolled manner which could be extended to other β-lactams derived from N-Boc α-aminoimines via the Staudinger reaction. Further applications of this chemistry to the synthesis of natural products are underway in our laboratory.

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13.-Representative data: **4a**, 93% yield, m.p. 139-140°C (Hexane/Et_2O), $[\alpha]^{25}_D$ = - 23.1 (c = 0.7, CH_2Cl_2); **4b**, 89% yield, m.p. 110-111°C (Hexane/Et_2O), $[\alpha]^{25}_D$ = - 29.7 (c = 0.66, CH_2Cl_2); **4c**, 78% yield, m.p. 140-141°C (Hexane/CH_2Cl_2), $[\alpha]^{25}_D$ = - 40.9 (c = 0.9, CH_2Cl_2). **7b**, 55% yield, m.p. 133-134.5°C (Hexane/CH_2Cl_2); **7c**, 48% yield, m.p. 114-116°C (Hexane/CH_2Cl_2), $[\alpha]^{25}_D$ = - 49.6 (c = 0.8, CH_2Cl_2). The optical purity of such compounds was established by deprotection of the Cbz group and further acylation of the free amino group using (+)-MTPA acid chloride and triethylamine. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

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16.-Grignard addition of EtMgBr to compound **3** in THF either at room temperature or at -70°C caused formation of **8b** together with the reduced product **1** in a 85/15 ratio respectively.

17.-By presaturation of the methyl group of the β-lactam **8a**, a 23% NOE was observed in the signal corresponding to the C_4-H proton, whereas in the case of *cis*-β-lactams very small or undetectable enhancements were detected. These observations are indicative of the proposed stereochemistry for the Grignard adducts.

18.-For an analogous rearrangement on 4-(1-hydroxyalkyl) β-lactams to form γ-lactones, see: Wagle, D.R.; Garai, Ch.; Chiang, J.; Monteleone, M.G.; Kurys, B.E.; Strohmeyer, T.W.; Hegde, V.R.; Manhas, M.S.; Bose, A.K. *J. Org. Chem.* **1988**, *53*, 4227.

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