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Synthesis of (S,S)-3-Prolylazetidin-2-one: A Key Component in the Synthesis of an HIV gp120 Constrained Immunogen

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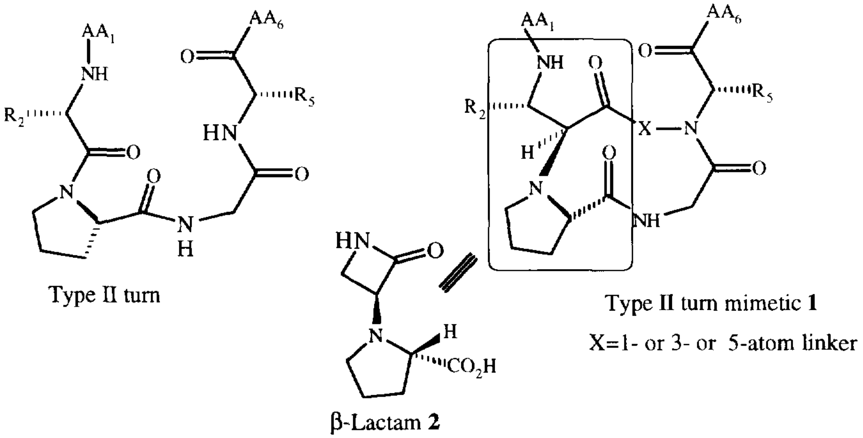
Abstract: The title compound (**2**) was synthesized in 5 steps from D-serine. In the absence of protection of the carboxyl group, the β-lactam nucleus underwent a facile rearrangement to provide the undesired diazabicyclo[4.3.0] nonane compound, under acidic or basic conditions.

The β-lactam nucleus continues to be an important moiety for its antibiotic activities, as well as for its role as a synthetic intermediate for the construction of complex, highly functionalized natural and unnatural products.[1, 2, 3]

HIV gp120 is the envelope glycoprotein that binds to the T-cell surface receptor CD4. The binding and the subsequent cleavage of gp120 are apparently prerequisites for infectivity of lymphocytes[4] and as such represent a critical step in HIV infection. As part of a program to synthesize and evaluate constrained gp120 V3 loop immunogens[5], we wished to prepare a family of β-turn mimetics of general structure **1** (Scheme 1).[6] A key component in the synthesis is the azetidinone **2**. Although there is extensive literature dealing with the synthesis

Scheme 1



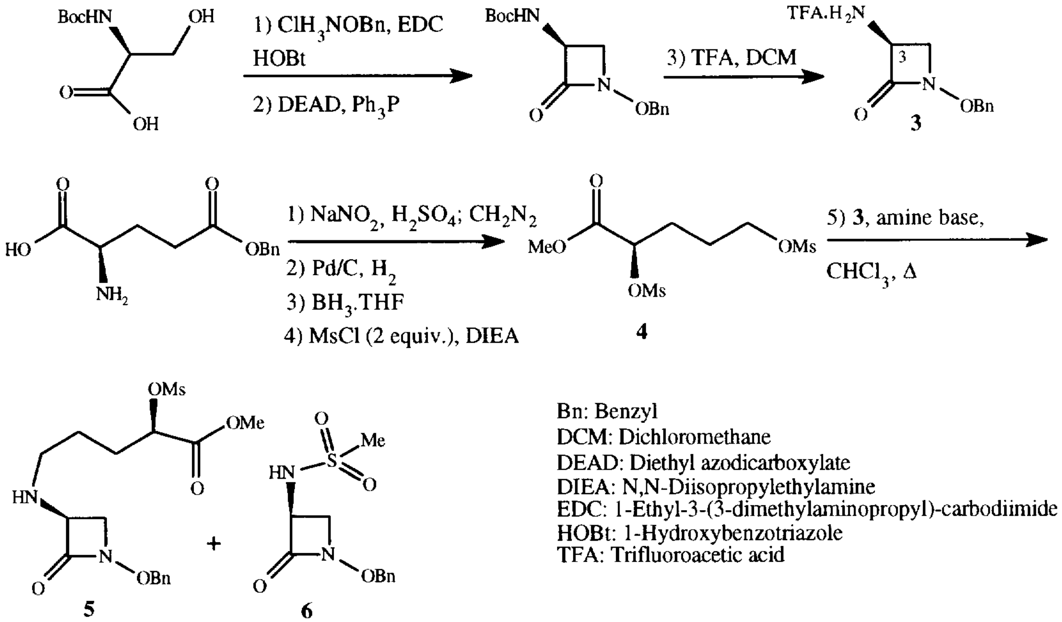
β-Lactam **2**

of substituted β-lactams, relatively few deal with the introduction of functionalized nitrogen-heterocycle at the 3-position.[7]

We designed the convergent synthetic approach shown in Scheme 2. We envisioned the pyrrolidine ring could be assembled by a double displacement reaction of the dimesylate **4** by β-lactam **3**. The advantage of this approach is the ease with which the requisite components **3** and **4** are prepared.

The 3-amino -β -lactam (**3**, as its TFA salt) was synthesized in 3 steps from Boc-L-Serine (in 80% overall yield) following the procedure of Miller (Scheme 2).[8] Commercially available D-Glu-γ-OBn ester was transformed in four steps into the dimesylate **4** (Scheme 3). Diazotization and esterification afforded the hydroxy diester. Debenzylation, reduction with diborane and dimesylation afforded **4**. β-Lactam **3** and **4** were refluxed in chloroform in the presence of DIEA, providing **5** and **6** as the major products. Attempts to reduce the amount of **6** formed or to effect cyclization of **5** were unsuccessful.

Scheme 2

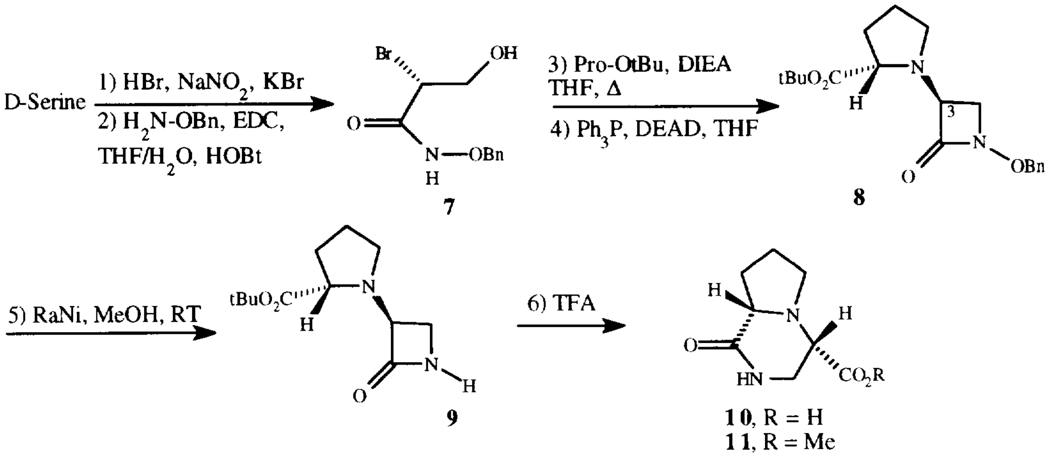


Bn: Benzyl
DCM: Dichloromethane
DEAD: Diethyl azodicarboxylate
DIEA: N,N-Diisopropylethylamine
EDC: 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide
HOBt: 1-Hydroxybenzotriazole
TFA: Trifluoroacetic acid

We turned our attention to an alternative dissection in which the pyrrolidine ring is derived from the amino acid proline. The critical step is the introduction of the proline at the incipient 3-position of the β-lactam (Scheme 3).

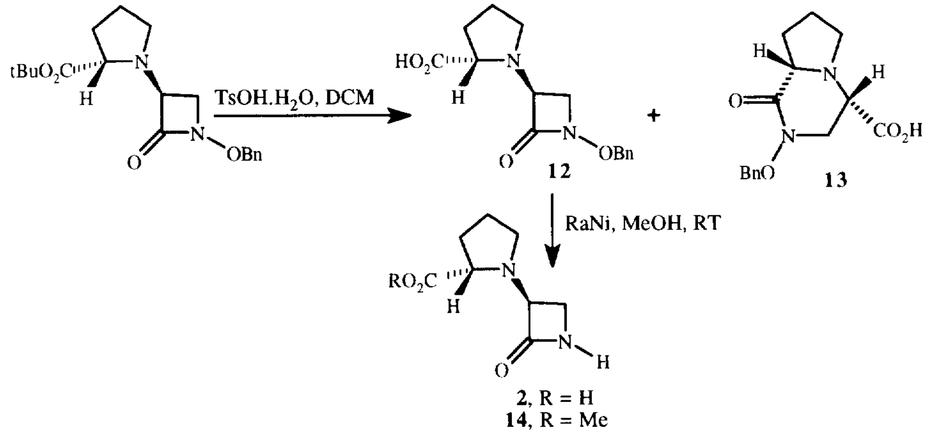
Starting with commercially available D-serine, bromination[9] and coupling to O-benzylhydroxylamine afforded bromohydroxamate **7** as a white solid (Scheme 3). Treatment of compound **7** with proline t-butyl ester in refluxing THF in the presence of DIEA led to the formation of the requisite product in 88% yield.[10] Mitsunobu cyclization afforded β-lactam **8** (80% yield) whose α-proton displayed characteristic β-lactam coupling constants of 5 and 2 Hz. The hydroxamate moiety was cleaved, without any incidents, with RaNi™[11] to provide β-lactam **9**.

Scheme 3



Unfortunately treatment of **9** with TFA/DCM in the presence of anisole led, to the formation of the bicyclic compound **10** (quantitative) and not to the requisite β-lactam. The structure of **10** was established through analysis of the spectral data of the methyl ester derivative **11**. The coupling constants of the α-proton were 10 and 5 Hz in the rearranged product versus 5 and 2 Hz in the β-lactam. In addition, the IR stretch at 1760 cm^{-1} corresponding to the β-lactam carbonyl disappeared and another peak corresponding to the lactam functionality appeared at 1670 cm^{-1}.

Scheme 4



This type of rearrangement has been reported by several groups.[12] To circumvent this problem, we modified the sequence of events by inverting the order of the deprotection steps and replacing TFA with the less acidic TsOH for the t-butyl ester cleavage step[13] (Scheme 4). Treatment of β-lactam **8** with TsOH acid in DCM afforded the β-lactam **12** in 40% isolated yield (70% based on recovered **8**) along with 15% of the rearranged material **13**. The pure lactam **12** was treated with prewashed RaNi™ in MeOH for 1-2 hrs[14] to afford the fully deprotected β-lactam **2**. To facilitate the characterization of the product, the β-lactam was converted to its methyl ester derivative (**14**) by treatment with diazomethane. β-Lactam **14**[15] displayed the characteristic coupling constants of 5 and 2 Hz. In addition, it displayed two intense stretches in the IR spectrum at 1756 and1738 cm^{-1} corresponding to the β-lactam and methyl ester carbonyls respectively.

In conclusion, the (S,S)-3-prolylazetidin-2-one, which is crucial for the construction of our mimetic of the conserved GPGR region in the HIV V3 loop, was synthesized in five steps from D-serine. A key step in the synthesis was the diastereospecific displacement of the bromide with proline t-butyl ester. An interesting rearrangement of the β-lactam structure, under both acidic and basic conditions, was observed. The resultant structure is also of interest as a similar diazabicyclo[4.3.0]nonane compounds has been used as a dipeptide mimic.[16] Future work in this area will be reported in due course.

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10. Flash chromatography afforded the (S,S) diastereomer (67%) in addition to an approximately 1:1 mixture of the (S,S) and (R,S) diastereomers (21%). The (R,S) diastereomer was obtained from the displacement of the (S)-bromohydroxamate (ent **7**), which was formed during the bromination step.
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14. Prewash of the RaNi™ and duration of the reaction are necessary to eliminate rearrangement.
15. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.94 (3H, m), 2.19 (1H, m), 2.80 (1H, dd, J = 17.0, 8.5 Hz), 3.20 (1H, m), 3.40 (1H, dd, J = 5.5, 2.5 Hz), 3.44 (1H, dd, J = 5.5, 5.5 Hz), 3.71 (3H, s), 3.81 (1H, dd, J = 8.5, 5.5 Hz), 4.45 (1H, ddd, J = 5.0, 2.5, 1.5 Hz), 5.68 (1H, br s).
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