

β -Lactam Templated Macrocyclization: Synthesis of 12-Membered Macrolide

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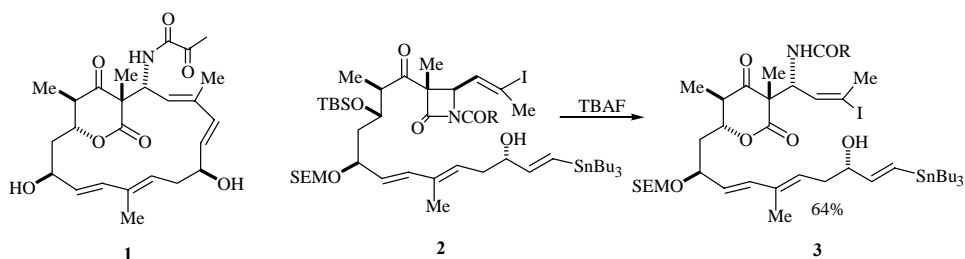
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Abstract: A novel macrolactonization method was developed using a chiral β -lactam as the template. This novel method features that the macrocyclization is simultaneously achieved while a TBS protected hydroxy group is deprotected.

Keywords: β -Lactam, macrolactonization, macrolide, templated cyclization.

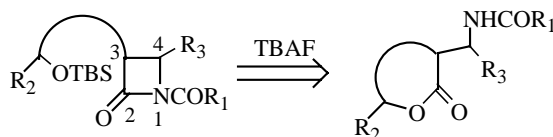
β -Lactam is the pharmacophore of the most important class of antibiotics used to combat bacteria infections. In recent years, β -lactams, especially those with stereogenic centers, have also been used successfully as chiral building blocks in various areas of organic synthesis¹. In our recent efforts^{2,3} towards the synthesis of macrocyclic antibiotic agent lankacidin C **1**, it was observed that a key intermediate **2** containing a N-acylated trisubstituted β -lactam moiety and a TBS protected hydroxy group at 3' position underwent rearrangement to form the β -keto- δ -valerolactone when the TBS protection was removed using TBAF (**Scheme 1**). This interesting transformation can be reasoned as the alkoxide, which was generated during the deprotection, intramolecularly attacking the lactam carbonyl that is sterically strained. Similar rearrangements have been observed under acidic conditions⁴⁻⁶.

Scheme 1

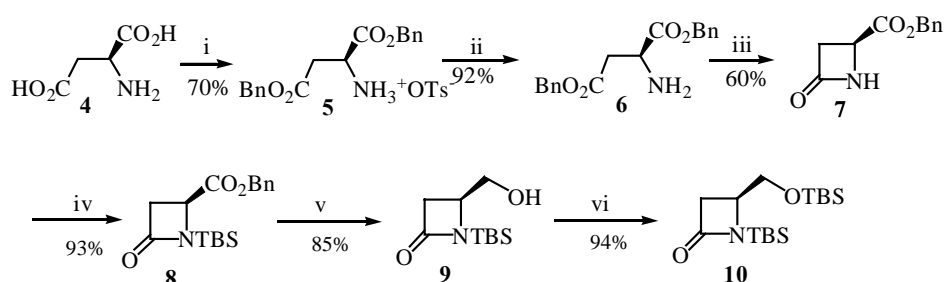


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Scheme 2



Scheme 3



i, BnOH, TsOH; ii, K_2CO_3 , H_2O , iii, Et_3N , TMSCl then $tBuMgCl$; iv, TBSCl, Et_3N ; v, $NaBH_4$, LiBr; vi, TBSCl, imidazole

From this observation it was envisaged that a β -lactam with suitable length of substituents locating at C3 or C4 could undergo similar reaction to form macrolactones (Scheme 2), which are important structure units in many biologically active natural products. In this letter we would like to report our preliminary finding of the synthesis of a 12 membered lactone employing this strategy.

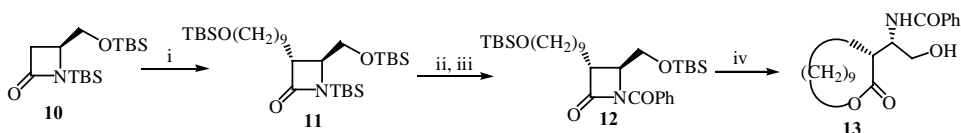
β -Lactam **10**, which was prepared by the known route⁵ from L-aspartic acid with modifications, was chosen as the template.

Esterification of L-aspartic acid with benzyl alcohol and *p*-toluenesulphonic acid gave its dibenzoate tosylate salt **5**, which was further treated with saturated potassium carbonate aqueous solution to give the free amine **6**. Treatment of **6** with trimethylsilyl chloride followed by *tert*-butyl magnesium chloride gave β -lactam **7**. Since an enolate would have to be formed at C3, the ester group in **7** was reduced to avoid possible racemisation at C4 chiral center. Thus the lactam amide nitrogen in **7** was TBS protected. Lithium bromide mediated sodium borohydride reduction of the benzyl ester in **8** followed by further TBS protection of the resulting hydroxy group afforded the required β -lactam **10**.

With the β -lactam template **10** in hand, the attachment of a side chain at C3 and the crucial rearrangement reaction were investigated. Alkylation at C3 *via* the enolate using TBS protected 1-iodononan-1-ol afforded a pair of diastereomeric isomers in *ca.* 1:3 mixture in favor of the *trans* isomer **11**. The two isomers were separated by silica gel column chromatography. The stereochemistry of the substituent at C3 relating to C4 was revealed by the coupling constants of H-3 and H-4 in the 1H NMR spectra in which the *trans* isomer display a coupling constant of 7.5 Hz, larger than its *cis* counterpart (~5.0 Hz).

Before the macrolactonization was attempted it was necessary to exchange the TBS

Scheme 3



i, LDA, -78°C then $\text{TBSO}(\text{CH}_2)_9\text{I}$, separation; ii, KF, MeOH; iii, PhCOCl , Et_3N ; iv, TBAF

protecting group on the β -lactam nitrogen in **11** into an acyl group so that the lactam carbonyl was activated for the rearrangement. The selective deprotection of N-TBS in **11** was achieved by treatment with potassium fluoride in methanol. Acylation of the resulting amide with benzoyl chloride in the presence of triethylamine gave the acylated lactam **12** in 91% yield. Finally treatment of **12** in THF (0.15 mol/L) with TBAF removed the two TBS groups on oxygen and concomitantly opened the lactam ring to give the 12 membered macrolide **13** in 64% yield.

In conclusion we have developed a novel macrolactonization strategy using β -lactam as a template. This method features that the macrocyclization is achieved while an TBS protection of a hydroxy group is removed. This strategy coupling with the structural diversity of β -lactams could provide a valuable method for the synthesis of biologically active macrolides with various ring sizes and functional groups. Further investigation on the application of this macrocyclization strategy is underway.

Acknowledgments

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References and Notes

1. I. Ojima, *Acc. Chem. Res.*, **1995**, *28*, 383.
2. C. T. Brain, A. Chen, A. Nelson, N. Tanikkul *et al.*, *Tetrahedron Lett.*, **2001**, *42*, 1247.
3. A. Chen, A. Nelson, N. Tanikkul, E. J. Thomas, *Tetrahedron Lett.*, **2001**, *42*, 1251.
4. E. J. Thomas, A. C. Williams, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 351.
5. J. M. Roe, E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 359.
6. A. S. Kendy, K. Liu, I. Kaldor, G. Dorey, K. Koch, *J. Am. Chem. Soc.*, **1995**, *117*, 8258.
7. To a solution of **12** (36 mg, 0.062 mmol) in THF (0.4 mL) was added TBAF (1.0 mol/L in THF, 0.19 mL, 0.19 mmol, 3eq) under nitrogen at 0°C . The pale yellow solution was stirred at room temperature for 6 h. Saturated aqueous NH_4Cl solution (2 mL) was added followed by EtOAc (6 mL). The organic phase was separated and washed with brine and dried. Evaporation of the solvent followed by purification by column chromatography on silica gel afforded the macrolide **13** (14 mg, 64%) as a white solid. Selected data for **13**: $[\alpha]_D^{20}$ -83.5 (c 0.4, CH_2Cl_2); MS (m/z) Found: (M+1) 348.2171, calcd. for $\text{C}_{20}\text{H}_{30}\text{NO}_4$: 348.2174; IR (EF) ν (cm^{-1}): 3330, 3010, 1735, 1028, 710; $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm): 1.3-1.60 [m, 14H, $-(\text{CH}_2)_7$], 1.78 (m, 1H, H-3), 2.68 (m, 2H, OCH_2CH_2-), 3.65 (t, 2H, $J=6.5\text{Hz}$, OCH_2CH_2-), 4.19 (dd, 1H, $J=9.5, 4.8\text{Hz}$, H-2'), 4.70 (dd, 1H, $J=9.5, 6.7\text{Hz}$, H-2'), 4.72 (m, 1H, H-1'), 7.00 (d, 1H, $J=6.7\text{Hz}$, NH), 7.45-7.84 (m, 5H, Ph-); $^{13}\text{C-NMR}$ (75MHz, CDCl_3 , δ ppm): 25.6, 26.7, 29.1, 29.2, 29.3, 32.6, 45.8, 51.9, 63.0, 71.7, 77.2, 127.1, 128.7, 132.1, 133.3, 167.6, 177.8.

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