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Highly Stereocontrolled Synthesis of a Novel Tribactam by Reaction of an Ester Enolate with a *N*-Trimethylsilylimine.

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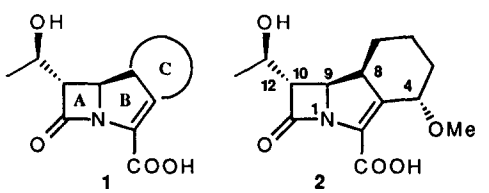
Abstract: The azetidinone **14**, a key intermediate in the synthesis of novel tribactam antibiotics (*e.g.* **2**) was obtained *via* condensation of an ester enolate with a *N*-trimethylsilylimine. Copyright © 1996 Published by Elsevier Science Ltd

Since the discovery of the highly active carbapenems and 1β-methyl carbapenems, a variety of stereoselective syntheses of these compounds and their analogues have been published.[1] Amongst the routes reported, the most popular have relied on aldol-type reactions of (+)-4-acetoxyazetidin-2-one with properly designed metal enolates.[2] An important alternative is the ester enolate-imine condensation which has become highly used not least because its simplicity and versatility for the preparation of different 3,4 substituted azetidinones.[3] The possibility of using *N*-trimethylsilyl imines, readily obtainable from the corresponding aldehydes, has increased the importance of this methodology since *N*-unsubstituted β–lactam are easily obtained at the end of the cyclization process.

Fig. 1



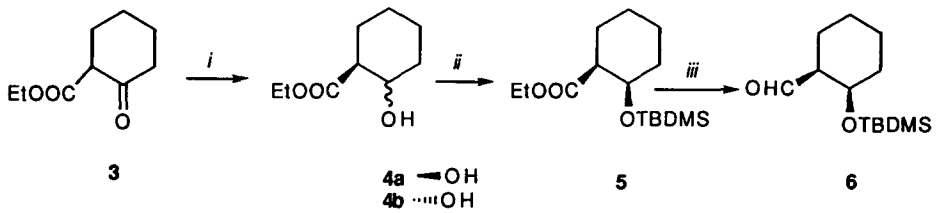
Recently a new family of totally synthetic β-lactam antibiotics, the tribactams **1** (Fig. 1), has been discovered by Glaxo S.p.A.[4] and prepared *via* a route involving(+)-4-acetoxy azetidin-2-one.[5] It is noteworthy

that the tricyclic β-lactam **2** has been the subject of considerable study due to its bacterial activity, resistance to β-lactamases and stability to renal dehydropeptidase.[6]

In the course of our earlier studies, [7] we demonstrated that α- or β-silyloxy *N*- trimethylsilylimines may be utilised as chiral substrates to induce the appropriate stereochemistry in target molecules. In this paper we report the stereocontrolled synthesis of acetonide **14**, a key intermediate for the preparation of tribactams through the *N*-trimethylsilylimine approach.

Reduction of commercially available 2-ethoxycarbonyl-cyclohexanone **3** by means of H_2/PtO_2 afforded the corresponding hydroxy derivatives **4a** and **4b** (98% yield) in the ratio 75/25 respectively.[8] After separation by distillation the cis isomer **4a** was protected using*tert*-butyldimethylsilyl chloride (TBDMSCl/Imidazole/DMF r.t. 8 hr 90%) to give the corresponding silyloxy derivative **5**. Finally reduction of the ester moiety using diisobutylaluminium hydride (DIBAH/ Ether/ -78°C/ 45 min) afforded the desired aldehyde **6** in 76% yield.(Scheme 1)

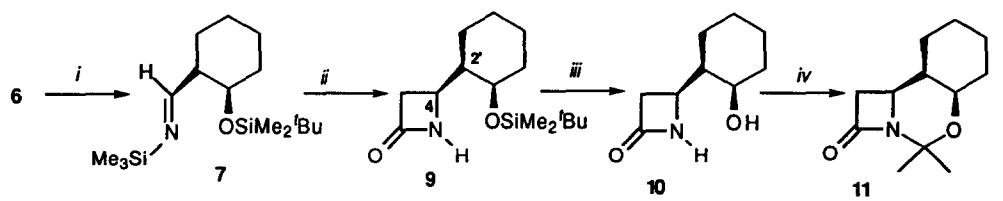
Scheme 1



i: H_2/PtO/EtOH, 98%, **4a/4b** 75/25; *ii:* TBDMSCl/Imidazole/DMF, r.t. 8hr, 90%; *iii*: DIBAH/ Et_2O/-78°C, 76%.

This aldehyde represents the key compound in our strategic plan. Conversion of the aldehyde **6** to the azetidinone **9** was carried out in one pot, in 55% yield, through the formation of the cyclohexyl-2-*tert*-butyldimethylsilyloxy-1-methan-(*N*-trimethylsilyl) imine **7** (LiHMDSA/THF/-78/30min) and subsequent treatment of the latter compound with the lithium enolate of *t*-butyl acetate **8**, obtained, in turn, from *tert*-butyl acetate and LiHMDSA.[9] The azetidinone[10] **9** has the correct stereochemistry at the C-4 and C-2' stereocenters as determined by careful analysis of the ^1H and ^{13}C NMR of both this compound and the corresponding acetonide derivative **11** (*vide infra*).

Scheme 2

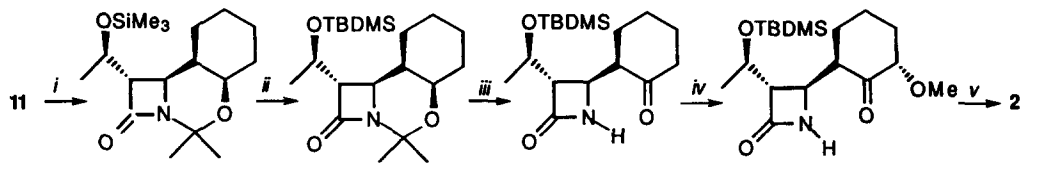


i: LiHMDSA/-78°C/THF/30 min; *ii:* $LiCH_2COO^tBu$ (**8**); *iii*: LiHMDSA/TBAF/THF/8hrs;*iv* : DMP/BF_3/CH_2Cl_2/r.t.

The intermediate **9** was converted into the requisite target compound by a sequential treatment with LiHMDSA and TBAF (-78°C, then r.t. 12hrs, 77%) (in order to remove the *O*-protecting group), formation of

the acetonide **11** by means of dimethoxy propane (DMP) in the presence of BF_3 etherate (CH_2Cl_2, r.t., 0.5 hr, 84%) and introduction of the C-3 ring appendage by the Merck procedure[11] (LDA, acetyl trimethylsilane, potassium *t*-buthoxide, 95% yield, 95% d.e.). Once again it was gratifying to observe the formation of a almost single isomer with the correct stereochemistry. TMS-Protection of the hydroxy ethyl side chain was removed and substituted by the more stable TBDMS group using 4-*tert*-butyldimethylsiloxy-3-penten-2-one (DMF, PTSA, r.t. 98%)[12]. Finally the acetonide **14** was converted to azetidinone **15** (74%) by means of pyridine chlorochromate (PCC) oxidation in the presence of catalytic amount of Jones reagent[13]. This compound has been already elaborated to produce the desired tribactam.[14]

Scheme 3



i: LDA/$CH_3COSiMe_3$/^{t}ButOK; *ii*  DMF/PTSA/r.t.; *iii*: PCC/Jones (5%); *iv* Ref. 14 *v* Ref. 4

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It should be stressed out that our synthesis allows the introduction of five (four of which are contiguous, chiral centres with high diastereoselectivity using the stereogenic centres present in the starting aldehyde as the initial control elements.

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References and Notes.

1 (a) Kametani, T. *Heterocycles*, **1982**, *17*, 463. (b) Shih, H.D.; Baker, F.; Cama, L.; Christensen, G.B., *Heterocycles*, **1984**, *21*, 29; (c) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, H.K., *Angew. Chem., Int. Ed.* , **1985**, *24*, 180. (d) Nagahara, T.; Kametani, T. **1987**,*25*, 729. (e) Georg, G.I. in "*Studies in Natural Product Chemistry* " Rahman, A-ur, Ed., Elsevier Science: Amsterdam, Vol. 4, 1991. (e) For a three component approach to chiral 1β-methyl carbapenem see: (a) Tsukada, N.; Shimada, T.; Gyoung, Y.S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143. (b) Datta, A.; Georg, G.I. *ChemTracts*, **1995**, *7*, 306 and references therein cited.

2 (a) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.*, **1981**, *29*, 2899. (b) Martel, A.; Daris, P.J., USP, 1986, 4 596 677. (c) Endo, M., *Synth. Commun.* **1987**, *17*, 1029. (d) Shirai, F.; Nakai, T. *J. Org. Chem.* , **1987**, *52*, 5491. (e) Shibata, T.; Sugimura, Y. *J. Antibiot.*, **1989**, *42*, 374. (f) Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron*, **1991**, *47*, 2801. The 4-acetoxyazetidin-2-one is available from Kanegafuchi Chemical Industry Co. Ltd, Osaka, Japan.

3 (a) Hart, D.J.; Ha D-Chan, *Chem. Rev.* **1989**, *89*, 1447. (b) Brown, M.J. *Heterocycles*, **1989**, *29*, 2225. (c) van der Steen, F.H.; van Koten, G. *Tetrahedron*, **1991**, *47*, 7503.

4 (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Andreotti, D.; Gaviraghi, G.; Carlesso, R.; Bismara, C. (Glaxo S.p.A.), Eur. Pat. App. O 416 953 A2, 1991; (b) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Gaviraghi, G.; Tarzia, G., *Recent Advances in the Chemistry of Anti-Infective Agents*, ed. Bentley, P.H. and Ponsford, R., RSC, Cambridge, 1992, pp 21-35. (c) Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thoma, R.T. *Tetrahedron Lett.* **1995**, *36*, 4283.

5 (a) Padova, A.; Roberts, M.S.; Donati, D.; Perboni, A.; Rossi, T. *J. Chem. Soc. , Chem. Commun.* **1994**, 441. (b) Padova, A.; Roberts, S.M.; Donati, D.; Marchioro, C.; Perboni, A. *J. Chem. Soc., Chem. Commun.* **1995**, 661. (c) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R.J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604.

6 Di Modugno, E.; Erbetti, I.; Ferrari, L.; Galassi, G.; Hammond, S.H.; Xerri, L. *Antimicrob. Agents Chemother.* **1994**, *38*, 2362.

7 (a) Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G.; Bandini, E: NATO-ASI *"Chemical synthesis: Gnosis and Prognosis"* 1995, in Press. (b) Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G.; Bandini, E: Da Col, M. *Tetrahedron*, **1996**, *52*, 000. (c) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1995**, *51*, 5067. (d Bongini, A.; Camerini, R.; Hoffman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045. (e Bandini, E.; Cainelli, G.; Giacomini, D.; Martelli, G.; Panunzio, M.; Spunta, G. *Biorganic and Medicinal Chem.* **1993**, *3*, 2347. (f) Bandini, E.; Cainelli, G.; Martelli, G.; Panunzio, M.; Spunta, G. *Gazz. Chim. It.* **1993**, *123*, 509. (g) Bandini, E.; Giacomini, D.; Panunzio M. in *"Seminars in Organic Synthesis"* Gasparrini, F. Eds.; S.C.I., 1993, pp. 47-69. and references cited therein.

8 Pascual, J.; Sistare, J.; Regas, A. *J. Chem. Soc.* **1949**, 1943. All compounds in this work have been prepared as racemic mixtures; for the sake of clarity only one enantiomer for each compound has been reported.

9 The synthesis of azetidin-2-one **9** was carried out in the following way.
To a stirred solution of aldehyde **6** (100mmol) in THF (300 ml) was added dropwise, at -78°C, a solution of LiHMDSA in THF (100 ml, 1 M solution, Aldrich). The solution was stirred for 1 hr at r.t., then a previous prepared solution of lithium *tert*-buthoxy acetate (400 mmoles), prepared at -78° C from LiHMDSA and *tert*-buthoxy acetate, was added. The mixture was stirred for 8 hr while the temperature reached spontaneously r.t. The reaction was quenched with saturated ammonium chloride solution. After usual work-up, the oily product was treated with ether to give pure crystalline **9** (55%).

10 All the product gave spectral data, as well as exact mass spectra, consistent with the assigned structure. Selected spectra as follows: Compound **9**: m.p.154 °C. I.r. (nujol) 3182, 1757, 1732 cm^{-1}. ^1H NMR ($CDCl_3$): 1.5-1.36 (m, 4H); 1.53 (m, 1H); 1.62 (m, 1H); 1.78 (m, 2H); 2.65 (ddd, 1H); 2.99 (ddd, 1H); 3.57 (m, 1H); 3.95 (m, 1H); 5.79 (s, 1H). ^{13}C NMR ($CDCl_3$): -5.10, -4.40, 17.21, 19.66, 22.69, 24.95, 25.71, 33.44, 41.82, 47.27, 50.31, 68.09, 168.47. M.S. 267. Compound **11**: m.p. 84°C. I.r. ^1H NMR ($CDCl_3$): 1.30 (m, 1H); 1.42 (s, 3H); 1.42-1.7 (m, 7H); 1.78 (s, 3H); 1.8-1.9 (m, 2H); 2.83 (dd, 1H); 2.88 (dd, 1H); 3.74 (m, 1H); 4.00 (m, 1H). ^{13}C NMR ($CDCl_3$): 18.98, 19.45, 22.88, 24.82, 26.37, 31.67, 35.74, 38.14, 47.41, 66.13, 82.63, 163.80. M.S. 209. Compound **14**: I.r. (nujol) 1750 cm^{-1}. ^1H NMR ($CDCl_3$): 0.09 (s, 6H); 0.90 (s, 9H); 1.18 (d, 3H); 1.2-1.7 (m, 6H); 1.76 (s, 3H); 1.86 (m, 2H); 3.05 (dd, 1H); 3.79 (dd, 1H); 4.00 (bs, 1H), 4.19 (m, 1H). ^{13}C NMR ($CDCl_3$): -4.38, -4.96, 17.89, 19.57, 22.72, 25.07, 26.59, 31.84, 35.91, 49.94, 58.88, 66.32, 82.56, 164.25. Exact mass: 368.261690 (Calc. 368.262098).

11 Bouffard, A.F.; Salzmann, N.T., *Tetrahedron Lett.* **1985**, *26*, 6285.

12 Veysoglu, T.; Mitscher, L.A. *Tetrahedron Lett.*, **1981**, *22*, 1299.

13 The correct amount of freshly prepared Jones reagent is crucial for the success of the reaction to avoid deprotection and oxidation of the C-3 side chain.

14 Perboni, A. (Glaxo S.p.A.), Eur. Pat. Appl. O 502 488 A2, 1992;

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