Tetrahedron Letters, Vol. 34, No. 21, pp. 3491-3492, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

The Total Synthesis of Ritipenems. Construction of Penem Thiazoline Ring by Incorporation of Two 2C Units of Glycolic Acid.

Walter Cabri,* Franco Zarini, Matteo D'Anello, Marcello Marchi, Angelo Bedeschi* and Giovanni Franceschi

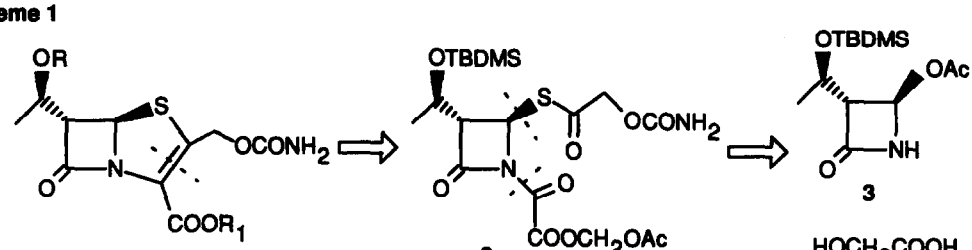
Farmitalia Carlo Erba, R&D, Process Research, Via Giovanni XXIII,23 20014-Nerviano (MI), Italy.

Abstract: Short syntheses of Ritipenem Acoxyl **1a** and Ritipenem **1b** are reported. The syntheses start from (R)-4-acetoxy-(S)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]azetidin-2-one **3** and are based on the incorporation of two 2C units obtained by manipulation of glicolyc acid **4**.

The discovery of the penem antibiotics[1] fostered a great deal of research world-wide directed to the development of their synthesis.[2] The commercial availability (R)-4-acetoxy-(S)-3-[(R)-1-(t-butyldimethylsilyl-oxy)ethyl]azetidin-2-one **3**[3] prompted several research groups to define total syntheses of these non classical β-lactams.[4]

Herein, we report our studies on the synthesis of the Farmitalia's Ritipenem Acoxyl (FCE 22891) **1a** and Ritipenem (FCE 22101) **1**.[5] The main goal of this work was the development of a practical synthetic approach that minimised the use of protective groups.

Scheme 1

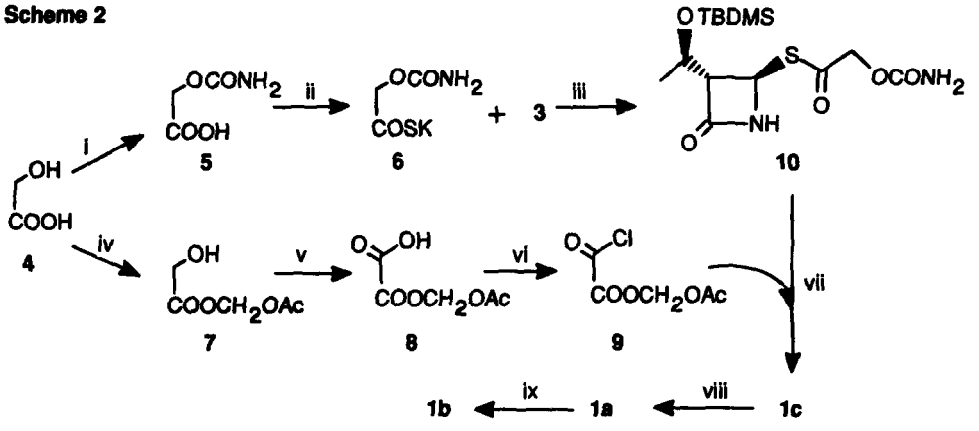


R = H R_1= CH_2OAc **1a**
R = H R_1= H **1b**
R = TBDMS R_1= CH_2OAc **1c**

We identified as possible starting materials, by disconnection of the C_2-C_3 of **1**, azetidinone **3** and glycolic acid **4** (Scheme 1). Starting from a single compound **4**, we planned the synthesis of the two highly functionalized 2C moieties that bear the sensitive acetoxymethyl and carbamoyl functions (Scheme 2). Glycolic acid **4** was reacted with chlorosulfonylisocyanate (CSI),[6] and then transformed into the corresponding thioacid K salt **6** in 66% overall yield. A five steps synthesis of **9** starting from oxalic acid has been reported,[7] however in contrast, esterification of **4** with bromomethylacetate, followed by Jones oxidation, and chlorination with oxalyl chloride gave **9** in three steps in 62% overall yield. The development of the straightforward approach to **1a** described in Scheme 2 was prevented by the use of standard conditions[8] (protic solvents in the presence

of a base) for the reaction between **3** and **6**. In fact, both **6** and **10** were found to be unstable under these conditions. In contrast, we found that the coupling, when carried out in dioxane, afforded **10** in 52% yield with an high diasteroselectivity (>97%). The reaction conversion was 65%, and 32% of **3** was recovered and recycled. One pot selective acylation of the azetidinone nitrogen of **10** and carbonyl-carbonyl coupling afforded **1c** in high yield. Deprotection of the TBDMS group gave Ritipenem Acoxyl **1a** in 28% overall yield from **3**. Subsequent enzymatic hydrolysis of the ester group of **1a** afforded Ritipenem **1b**.

Scheme 2



i: CSI, 85%; ii: ClCOOEt, CH_2Cl_2, H_2S then KOMe, 77%; iii: dioxane, 40°C, 50%; iv: CH_3COOCH_2Br, CH_3CN, 50°C, 85%; v: CrO_3/H_2SO_4, CH_3COCH_3, rt, 79%; vi: $(COCl)_2$, Et_2O, rt, 92%; vii: Et_3N, toluene, 0°C, then $P(OEt)_3$, reflux, 71%; viii: n-Bu_4NF, CH_3COOH, THF, rt, 76%; ix: PLE, phosphate buffer, pH 7, quantitative.

The mechanism of the critical step of this approach, the nucleophilic attack of **6** at C-4 of azetidinone **3**, is currently under investigation.

References and Notes

1. Woodward.R.B. *Recent Advances in the Chemistry of β-Lactam Antibiotics;* Elks,J., Ed.; Special Publication No. 28; The Royal Chemical Society: London,1977; p 167. Ernest,I.; Gosteli,J.; Greengrass, C.W.; Holick,W.; Jackman,D.E.; Pfaendler,H.R.; Woodward,R.B. *J.Am.Chem.Soc.* **1978**,*100*,8214.
2. Perrone,E.; Franceschi,G. *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukas,G. and Ohno,M., Eds.; Springer-Verlag: Berlin,1990; p 613.
3. See reference 2 and Murahashi,S.-I.; Naota,T.; Kuwabara,T.; Saito,T.; Kumobayashi,H.; Akugatawa,S. *J.Am.Chem. Soc.* **1990**,*112*,7820.
4. Volkmann,R.A.; Kelbaugh,P.R.; Nason,D.M.;Jasys,V.J. *J.Org.Chem.* **1992**,*57*,4352. Ishiguro,M.; Iwata,H.; Nakatsuka,T.; Tanaka,R.; Maeda,Y.; Nishihara,T.; Noguchi,T.; Nishino,T. *J.Antibiotics* **1988**,*41*,1685.
5. Franceschi,G.; Foglio,M.; Alpegiani,M.; Battistini,C.; Bedeschi,A.; Perrone,E.; Zarini,F.; Arcamone,C.: Della Bruna ,C.; Sanfilippo,A. *J.Antibiotics* **1983**,*36*,938.
6. Franceschi,G.; Alpegiani,M.; Battistini,C.; Bedeschi,A.; Perrone,E.; Zarini,F. *Pure & Appl.Chem.* **1987**,*59*,467.
7. Kaye,R.L.; Volkmann,R.A.; Lindner,D.L. EPA 223397 (1987).
8. Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**,*539*.

(Received in UK 26 March 1993)