Pergamon

Tetrahedron Letters, Vol. 35, No. 15, pp. 2275-2278, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0307-J

A Stereoselective Synthesis of A Key 1β-Methylcarbapenem Intermediate Via a Diastereoselective Decarboxylation

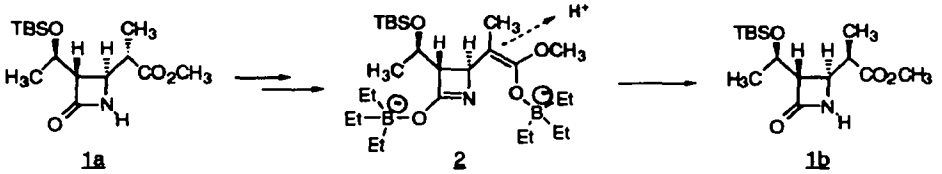
Woo-Baeg Choi*, Hywyn R.O. Churchill, Joseph E. Lynch, Andrew S. Thompson, Guy R. Humphrey, R. P. Volante, Paul J. Reider, Ichiro Shinkai

Department of Process Research, Merck Research Laboratories, Division of Merck & Co., Inc., P. O. Box 2000, Rahway, New Jersey 07065

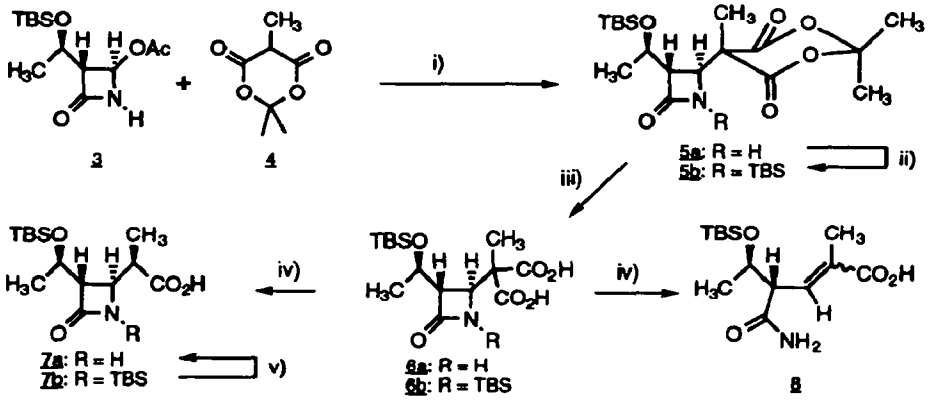
Abstract: (3S,4S)-3-[(R)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone 7a was prepared from (3R,4R)-4-acetoxy-3-[(R)-1-*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone 3 via a sequence involving coupling with 2,2,5-trimethyl-1,3-dioxan-4,6-dione 4, *N*-silylation, solvolysis of the methylmeldrum's acid moiety and a stereoselective acid catalyzed decarboxylation.

Since the presence of a 1β-methyl substituent has been found to enhance the chemical and metabolic stability of synthetic carbapenem antibiotics[1], a number of stereoselective syntheses of the key 1β-methyl intermediate 7a have been reported.[2-10] Many of these methods involve the use of reagents that are either expensive or difficult to handle on a large scale. Herein, we would like to report a simple, scalable and highly diastereoselective synthesis of 7a via a novel decarboxylation of diacid 6.

Recently, Bender et. al. reported[11] a highly diastereoselective method for epimerization of the 1α-methylester 1a to the 1β-methyl isomer 1b, via enolborate formation and subsequent kinetic protonation from the less hindered α-face of the enolate 2 (Scheme I). We envisioned that a similar transformation might also be possible by decarboxylation of a diacid 6 and stereoselective protonation of the resultant enol 9.



Scheme I.



Scheme II.

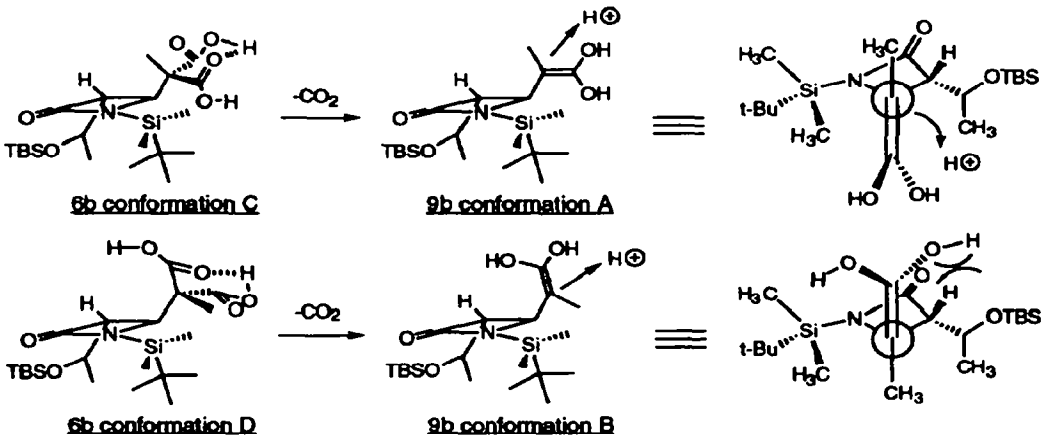
i) Et_3N,EtOAc, 65°C, 4h; ii) TBSCl, NaI, Et_3N, DMF, 60°C, 3h; iii) 2N aq. NaOH, THF, 0-2°C, 1h, then 2N aq. HCl; iv) HCO_2H, EtOAc, 80°C, 4h; v) 2N aq. NaOH, THF, 20°C, 2h, then 2N aq. HCl.

Diacid 6 was readily prepared from azetidinone 3 and 2,2,5-trimethyl-1,3-dioxan-4,6-dione 4 as illustrated in Scheme II. The coupling of 3 and 4 in the presence of triethylamine provided the adduct 5a in 95% yield. The diacid 6a was obtained from the ring opening of 5a in sodium hydroxide aqueous THF solution at 0°C followed by acidification of the dicarboxylate with 2 N aqueous hydrochloric acid. However, when the diacid 6a was subjected to the decarboxylation conditions[12] (refluxing in ethyl acetate with formic acid as catalyst), the major product was the ring opened amide 8. We envisioned that substitution of the lactam nitrogen with an electron-donating group might suppress the ring opening.[13] Thus, we prepared the *N*-silylated diacid 6b as follows. The lactam nitrogen of 5a was silylated with a mixture of TBSCl, NaI and triethylamine in DMF at 60°C in 95% yield. Base hydrolysis of 5b as described above followed by acidification gave the *N*-silylated diacid 6b. When diacid 6b was subjected to the above decarboxylation conditions, the reaction proceeded in a highly stereoselective manner providing the *N*-silylated acid in 94:6 ratio of β:α isomers. The silyl group on nitrogen was selectively removed by treatment with sodium hydroxide in aqueous THF at room temperature. Subsequent acidification followed by crystallization afforded the title compound 7a in 64% yield (from 5b to 7a), in >99% β-isomer.

The observed protonation selectivity can be rationalized as follows. Assuming that the enol 9b could be formed by decarboxylation of either carboxyl group of diacid 6b, the bulky *N*-silyl group of enol 9b forces the enol to orient in one of two conformations, A or B, in Scheme III. Conformation A

is expected to be preferred due to the unfavorable A-1,3 strain between the enol hydroxy group and the C_3 methine proton in conformation B. Protonation of A would be expected to occur from the least hindered α-face (the β-face is blocked by the bulky *N*-silyl group) resulting in the formation of the desired β-methyl acid 7b. In the absence of the large *N*-silyl group, it is assumed that the enol can more easily adopt a conformation in which the C_4-N bond in the lactam ring is orthogonal to the enol π bond resulting in elimination to give 8.

Addition of methoxide to the meldrum's acid adduct 5b followed by acidification gave a diastereomeric mixture of two methylester acids (5:1). Curiously only one of these diastereomers underwent decarboxylation to give the methylester of 7a (β:α = 94:6); the other diastereomer remained unchanged even after 3 days at 80°C. This suggests the possibility that the conformation of the enol 9b is the result of a diastereospecific decarboxylation of diacid 6b. The decarboxylation may be controlled by the conformation of the precursor diacid 6b and the law of microscopic reversibility, ie, just as protonation of 9b can only occur from the less hindered α-face, loss of CO_2 likewise can only occur from the same face, away from the *N*-silyl group. The diacid of conformation C undergoes a diastereospecific decarboxylation of the pro (S) carboxyl to give enol 9b in the preferred A conformation, which would then be protonated from the least hindered α-face to give the desired β-methyl acid 7b. Conversely, the diacid of conformation D would be expected to undergo diastereospecific decarboxylation of the pro (R) carboxyl to give the undesired α-methyl acid 7b via selective protonation of the less stable enol conformation B. More detailed mechanistic study results, including a C-13 labelling study of diacid 6b as well as molecular mechanics calculations, will be published shortly.



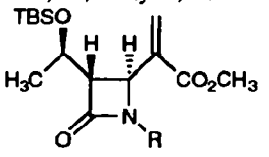
Scheme III.

Acknowledgment

Authors wish to thank R. Reamer for his NMR support.

References

1. Shih, D.H.; Baker, F.; Cama, L.; Christensen, B.G. *Heterocycles* **1984**, *21*, 29.
2. Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673.
3. Fuentes, L.M.; Shinkai, I.; Salzmann, T.N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.
4. Iimore, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2149.
5. Cama, L.; Christensen, B.G. *J. Org. Chem.* **1987**, *52*, 2563.
6. Ito, Y.; Terashima, S. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 606.
7. Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron* **1988**, *44*, 2149.
8. Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, 47, 2801.
9. Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143.
10. Prasad, J.S.; Liebeskind, L.S. *Tetrahedron Lett.* **1987**, *28*, 1857.
11. Bender, D.R.; DeMarco, A.M.; Melillo, D.G.; Riseman, S.M.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2411 and references therein.
12. For a review of the mechanism, see Richardson and O'Neal, in Bamford and Tipper, Comprehensive Chemical kinetics, **1972**, Vol. 5, pp. 447-482. For recent examples of selective decarboxylation, see Miyamoto, K.; Tsuchiya, S.; Ohta, H. *J. Fluorine Chem.* **1992**, *59*, 225.
13. Kim et. al. have also shown that the nature of the *N*-substituent can have a profound effect on the conformation and hence the selectivity of reactions involving 4-vinyl substituted β-lactams such as 10. See Kim, C.U.; Luh, B.; Partyka, R. *Tetrahedron Lett.* **1987**, *28*, 507.



10 R = H, TMS

(*Received in USA* 12 *November* 1993; *revised* 3 *January* 1994; *accepted* 3 *February* 1994)