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A New Synthetic Route to the Key Precursor of 1β-Methylcarbapenem Antibiotics from (S)-Methyl 3-Hydroxy-2-methylpropanoate

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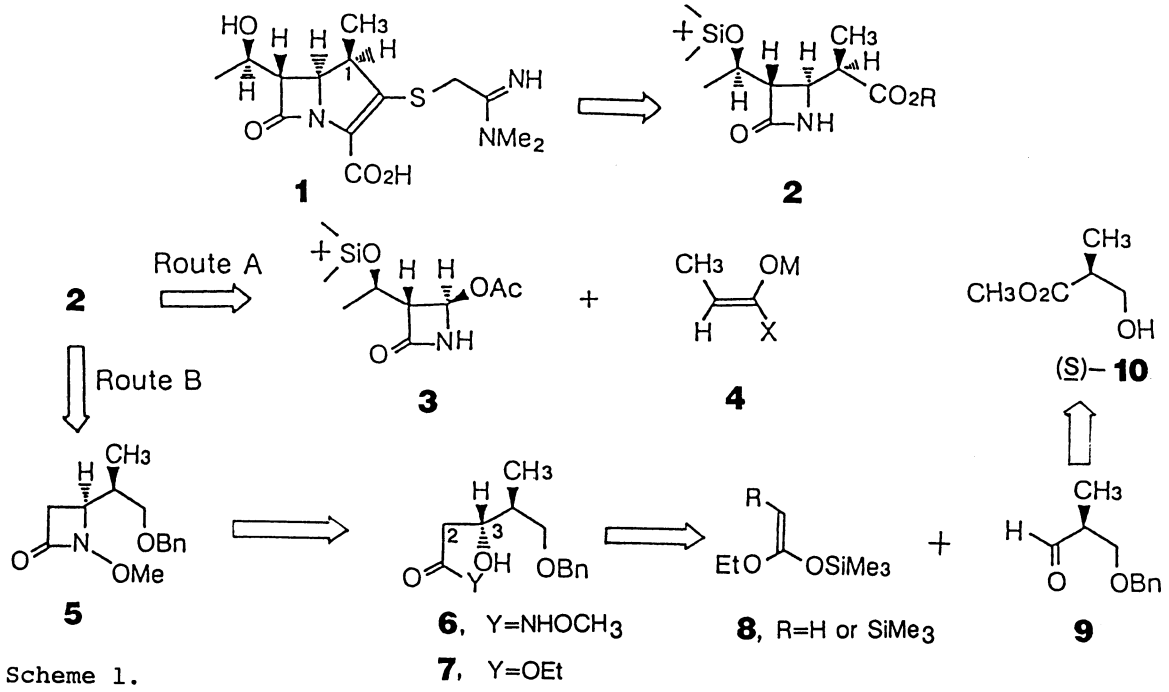
A new synthetic route to the 1β-methylcarbapenem precursor from (S)-methyl 3-hydroxy-2-methylpropanoate has been developed which involves as a key step the chelation-controlled aldol reaction of (S)-3-benzyloxy-2-methylpropanal with ketene trimethylsilyl acetal of ethyl (trimethylsilyl)acetate.

Since the Merck group reported the favorable chemical and metabolic stability of 1β-methylcarbapenem antibiotics such as **1**,[1] the development of synthetic routes to the key precursor **2** has been the subject of considerable synthetic activities.[2] However, most of the routes reported so far are based on the aldol-type reaction of the 4-acetoxy azetidinone **3** with the properly-designed metal enolates **4** (Route A in Scheme 1). Herein we wish to report a conceptionally new approach to **2** from commercially available (S)- or (R)-methyl 3-hydroxy-2-methylpropanoate **10** (Route B in Scheme 1).[3]



Scheme 1.

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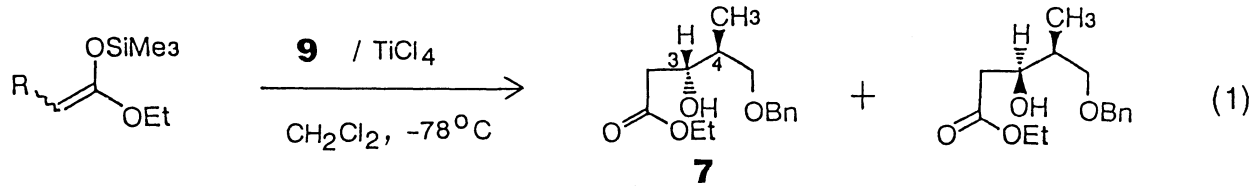
Our basic strategy relies on the aldol reaction using the (S)-β-benzyloxy aldehyde **9** easily obtained from (S)- or (R)-**10**[4] followed by the well-established "N-C_4 cyclization"[5] of the hydroxamate **6**. Thus, major stereochemical problems in this strategy are associated with the aldol process and the introduction of the 1-silyloxyethyl side chain into the β-lactam **5**.

The anti configuration required for the aldol **7** led us to employ chelation-controlled conditions for the aldol reaction concerned.[6,7] Thus, we first carried out the reaction of the ketene silyl acetal **8** (R=H) with the (S)-aldehyde **9** derived from (S)-**10**[4] in dichloromethane at -70 °C in the presence of titanium(IV) chloride. Unfortunately, however, the anti/syn ratio for **7** thus obtained was found to be quite low[8] (Eq. 1). This low diastereoselectivity was rather surprising in view of 97% anti-selectivity reported for a similar reaction of **9** with a ketene silyl acetal of methyl 2-methylpropanoate.[6] After many attempts, we found that the use of **8** (R=$SiMe_3$) derived from commercially available ethyl (trimethylsilyl)acetate provided, after desilylation (KF, aq.MeOH), the desired anti-aldol **7** in an extremely high diastereomeric purity (Eq. 1).[8] The anti configuration of **7** was assigned on the basis of ^{1}H NMR comparison of its acetonide with the syn counterpart.[9]

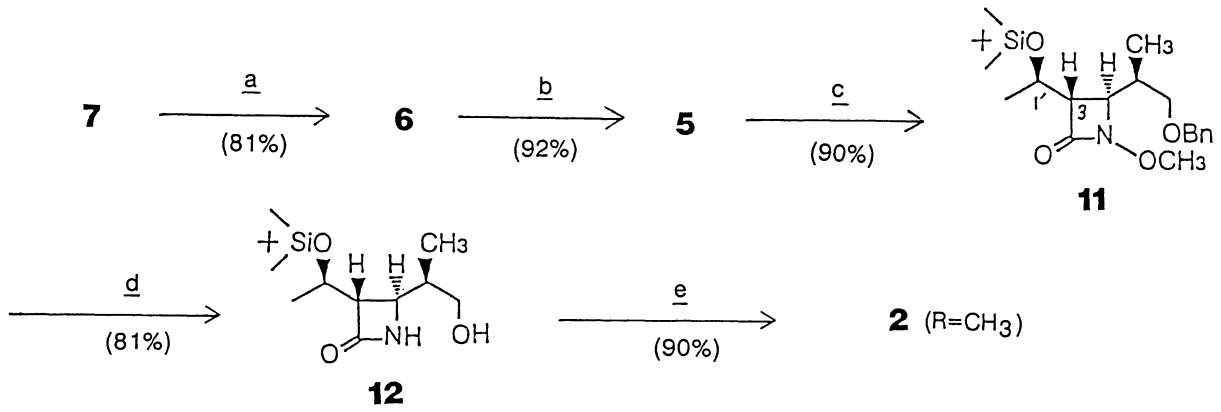


8, R=H or $SiMe_3$

7

R= H	66	:	34	(96%)
R= $SiMe_3$	99	:	1	(95%)

With the aldol **7** of high diastereomeric purity in hand, we next carried out the stereocontrolled transformation of **7** (92% ee)[10] to the key precursor **2** (Scheme 2). Thus, **7** was converted, by the Weinreb procedure,[11] to the hydroxamate **6** which was then subjected to the N-C_4 cyclization under the Mitsunobu condition[5,12] to afford the β-lactam **5** with complete inversion of configuration. The next task is the stereoselective introduction of the 1-siloxyethyl side chain into **5**, which is one of the most serious problems frequently encountered in carbapenem synthesis. After unsuccessful attempts,[13] we found that this problem was successfully (but not completely) solved by applying the procedure of Bouffard and Salzmann.[14] Thus, a lithium enolate generated from **5** was reacted with t-butyldimethylsilyl methyl ketone[15] followed by the Brook rearrangement to afford the desired 1',3-syn isomer (**11**) as a single diastereomer in 57% yield (90% based on reacted **5**), along with 37% recovery of **5**. The ^{1}H NMR spectrum of **11** thus obtained was in accord with that of an authentic sample independently prepared in our laboratory.[3b] The three-step conversion of **11** to **2** was carried out in the



(a) $AlMe_3/MeONH_2HCl$, toluene, 25 °C; (b) $MeOCON{=}NCO_2Me$(DMAD)/PPh_3, THF, 25 °C (c) i) $LiN(i\text{-}Pr)_2$, THF, -78 °C; ii) t-$BuMe_2SiCOCH_3$, -78 °C; iii) t-BuOK, t-BuOH, -78°C; (d) Li, $EtNH_2$-t-BuOH-THF (3:1:1), -40 °C; (e) i) CrO_3, pyridine, 25 °C; ii) CH_2N_2, Et_2O, 25 °C.

Scheme 2.

same manners as previously reported.[3b] Thus, simultaneous deprotection of the benzyl and N-methoxy groups via the Birch reduction followed by oxidation and methylation furnished the key precursor **2** (R=CH_3) in 91% ee: mp 110-112 °C, $[\alpha]_D^{19}$ -19.2° (c 0.48, CH_2Cl_2); lit.[1] mp 120-121 °C, $[\alpha]_D^{22}$ -21.0° (c 2.09, CH_2Cl_2). Its spectral data were identical with those of an authentic sample (100% ee).

In summary, we have developed a novel synthetic route to the 1β-methylcarbapenem key precursor (**2**) from (S)- or (R)-**10**, both commercially available in quantity. Thus, the easy availability of the starting chiral material, coupled with the efficient stereocontrol in the two aldol processes involved, places the present approach in an unique position for 1β-methylcarbapenem synthesis. Further improvements of this approach are in progress.

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References

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2) Review: Y. Nagao, Kagaku, 42, 190 (1986). For a reference list of synthesis of **2**: F. Shirai and T. Nakai, J. Org. Chem., 52, 5491 (1987).
3) Recently Terashima and co-workers have reported a synthetic route to **2** from (S)-**10** based on an entirely different strategy: a) T. Kawabata, Y. Kimura, Y. Ito, and S. Terashima, Tetrahedron Lett., 27, 6241 (1986). We have also reported a different approach to **2** employing (S)- **10** as one of the

two chiral starting materials: b) F. Shirai and T. Nakai, Tetrahedron Lett., in press.

4) For the preparation of **9** from (S)-**10**: H. Nagaoka and Y. Kishi, Tetrahedron, 37, 3873 (1981). The (S)-aldehyde **9** is also obtainable from (R)-**10** using the Meyers procedure [A. I. Meyers, et al., J. Am. Chem. Soc., 105, 5015 (1983)].

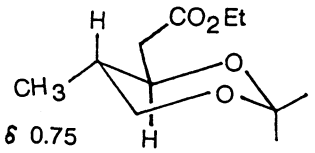
5) M. J. Miller, Acc. Chem. Res., 19, 49 (1986), and references cited herein.

6) For review on chelation vs. non-chelation in aldol-type reactions: M. T. Reetz, Angew. Chem., Int. Ed. Engl., 24, 1 (1984).

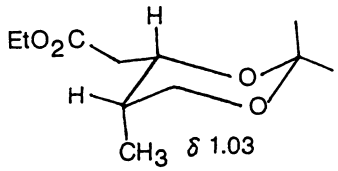
7) We found that the non-chelation-controlled reaction of a lithium enolate of ethyl acetate with **9** afforded 42:58 mixture of the aldol diastereomers.

8) The isomeric ratio was determined by capillary GLC (Ulbon HR-20M, 50 m, 120 °C) of the acetonides derived from **7** (H_2/Pd-C, $(CH_3)_2C(OCH_3)_2$, p-TsOH); cf. Ref. 9.

9) The most informative are the chemical shifts of the 4-methyl group as shown below. For similar stereochemical assignments of structually related acetonides: S. Thaisrivongs and D. Seebach, J. Am. Chem. Soc., 105, 7407 (1983).



(acetonide of **7**)
Rf(GLC)=5.28 min



(acetonide of the 3-epimer of **7**)
Rf(GLC)=4.28 min

10) Determined by HPLC analysis [Zorbax SIL, hexane/AcOEt (8:1)] of the (-)-MTPA-ester of **7**. The relatively low optical purity is due to the partial racemization during the preparation of **9** and/or during the aldol reaction. We are now investigating this point.

11) J. I. Levin, E. Turos, and S. M. Weinreb, Synth. Commun., 12, 989 (1982).

12) Particularly notable here is that the use of diethyl azodicarboxylate (DEAD) instead of the dimethyl derivative (DMAD) provided only 46% yield of **5**.

13) We found that the aldol reaction of acetaldehyde with a Li- and Zr-enolate generated from **5** followed by silylation with t-$BuMe_2SiCl$ provided a mixture of **11** and its 1'-epimer in a ratio of 17 : 83 (37% yield) and 56 : 44 (49% yield), respectively.

14) F. A. Bouffard and T. N. Salzmann, Tetrahedron Lett., 26, 6285 (1985).

15) Prepared according to the procedure reported: A. G. Brook, J. M. Duff, and P. F. Jones, J. Am. Chem. Soc., 89, 431 (1967).

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