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A NOVEL, DOUBLE-ASYMMETRIC ALDOL APPROACH TO THE SYNTHESIS OF A 1β-METHYL CARBAPENEM ANTIBIOTIC PRECURSOR

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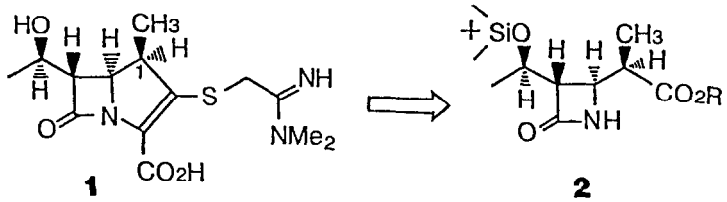
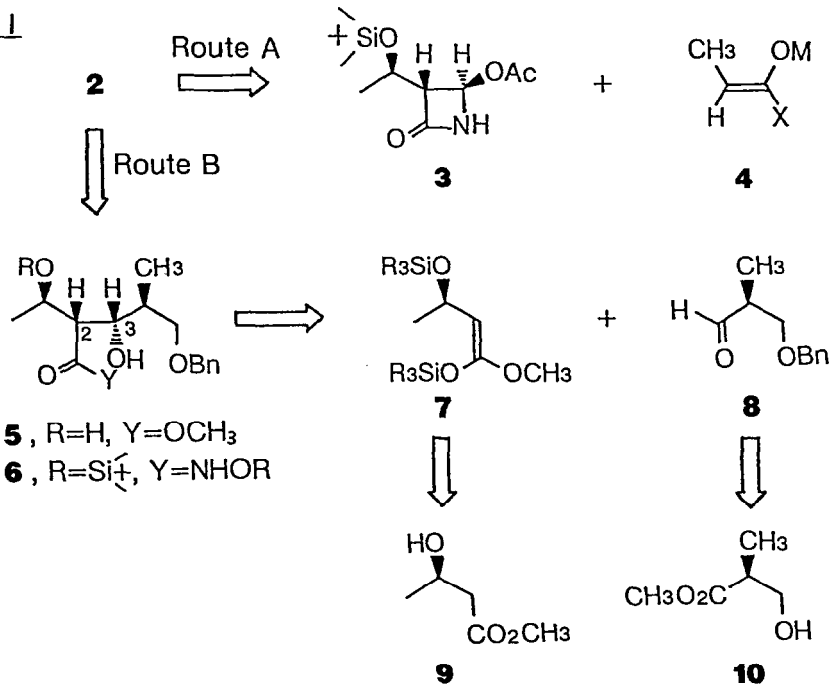
SUMMARY: A novel synthetic approach to the 1β-methyl carbapenem key precursor is described which involves the chelation-controlled double-asymmetric aldol reaction as the key step.

Since the discovery of the enhanced chemical and metabolic stability of 1β-methyl carbapenem antibiotics such as **1**,[2] considerable effort has been devoted to the stereocontrolled synthesis of the optically active key precursor **2**.[3] The most popular and successful entries to **2** have so far relied on the aldol-type reaction of the (+)-acetoxy azetidinone **3**[4] with properly designed chiral[3b,c] or achiral[3d-f] metal enolates **4** (Route A in Scheme I). Retrosynthetic analysis suggested an entirely different approach (Route B) which



1 **2**

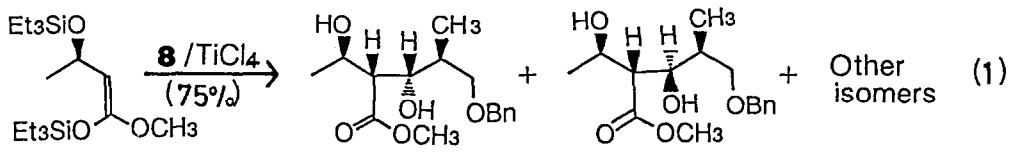
Scheme I

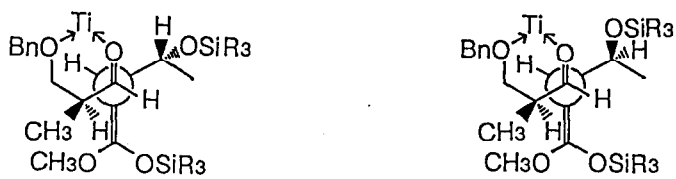


would incorporate the connection of the chiral "left-half" **7** with the chiral "right-half" **8** via an aldol reaction followed by the well-established $\underline{N}$-C_4 cyclization of hydroxamate **6**.[5] We now report the successful realization of this novel approach starting with the two optically active β-hydroxy esters **9** and **10**, both commercially available in quantity. The key feature is the remarkable high efficiency of consonant double stereodifferentiation in the double-asymmetric aldol process.[6]

Stereochemical analysis of the asymmetric aldol process led us to employ chelation-controlled conditions.[7,8] Thus, we carried out reactions of the silyl ketene acetal **7** (R=Me or Et)[9] with the β-benzyloxy aldehyde **8** derived from **10**[10] in dichloromethane at -70∼-40 °C under Lewis acid conditions [$TiCl_4$, ($\underline{i}$-PrO)$TiCl_3$, or $SnCl_4$]. We found that the aldol reaction was best achieved by the specific combination of **7** (R=Et) with $TiCl_4$ to afford 75% yield[11] of the desired aldol **5** in a remarkably high diastereomeric purity (≥97%) as shown by eq 1.[12,13] The relative stereochemistry of **5**, while eventually confirmed by its conversion to **2**, could be deduced from 500 MHz ^1H NMR comparision of its acetonide with other diastereomeric acetonides separately prepared.[8,14] Thus the crucial aldol reaction established the four contiguous chiral centers required.

As expected, a similar reaction of the antipode of **7** with **8** resulted in a dramatic decrease in diastereofacial selectivity (eq 2).[15] Thus, the chelation-controlled aldol reaction of the **7**($\underline{R}$)/**8**($\underline{S}$) pair is clearly demonstrated to show the favorable double stereo-differentiation in which the inherent diastereoface preference of the two reactants may reinforce one another, as visualized the transition state **A**, compared with **B** for the **7**($\underline{S}$)/**8**($\underline{S}$) pair.

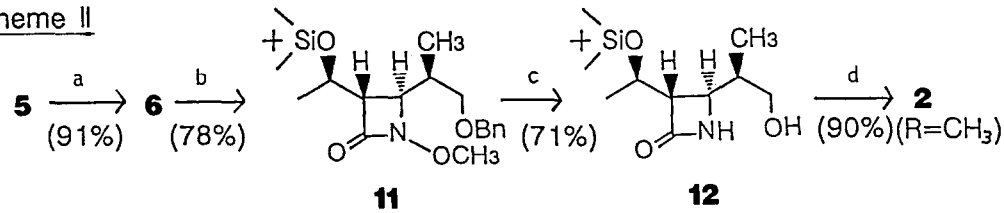




The transformation of the aldol **5** to the key precursor **2** is straightforward (Scheme II). Thus, aldol **5** was converted, after selective silylation, to hydroxamate **6** by the modification

of Weinreb's method.[16,17] Cyclization of **6** was best achieved by the mesylation/hydroxaminolysis sequence[5] to give the β-lactam **11** with >95% diastereomeric purity (HPLC).[18] The β-lactam **11** was then subjected to the Birch reduction to give the azetidinone **12**.[19] Finally, oxidation of **12** followed by treatment with diazomethane furnished the desired key precursor **2** (R=CH_3) in essentially 100% ee. Its physical and spectral data were identical with those reported [mp 119-120 °, $[\alpha]_D^{25°}$-21.1° (c 0.60, CH_2Cl_2); lit.[2] mp 120-121 °C, $[\alpha]_D^{22°}$-21.0° (c 2.09, CH_2Cl_2)].

Scheme II



(a) (i) t-$BuMe_2SiCl$, imidazole, DMF, 25°C;(ii) $AlMe_3$/$MeONH_2HCl$, toluene, 25°C. (b) (i) $MeSO_2Cl$, pyridine, 25°C;(ii) K_2CO_3, MeOH, 25°C. (c) Li, $EtNH_2$-t-BuOH-THF (3:1:1), -40°C. (d) (i) CrO_3, pyridine, 25°C;(ii) CH_2N_2, Et_2O, 25°C

In summary, we have developed a novel, efficient approach to the 1β-methyl carbapenem precursor employing the chelation-controlled double-asymmetric aldol reaction as the key step. The easy availability of the optically active starting materials, coupled with the high efficacy of stereocontrol, places the present approach in a unique position for the practical synthesis of 1β-methyl carbapenem antibiotics. Further improvement of this approach as well as mechanistic studies on this interesting aldol process are under way.

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(8) We found that the non-chelation-controlled reaction of the dilithium enolate of **9** with **8** provided a 1:1:2:6 mixture of the aldol diastereomers(63% yield). The major diastereomer was not **5** but the 2-epimer of **5** based on the HPLC and NMR of its acetonide (cf. ref 14).

(9) The silyl ketene acetals **7** (R=Me and Et) were prepared by silylation of the dilithium (Z)-enolate generated from **9** (LDA, THF) with Me_3SiCl and Et_3SiCl, respectively, in ca. 75% distilled yields. A similar silylation with t-$BuMe_2SiCl$ was unsuccessful.

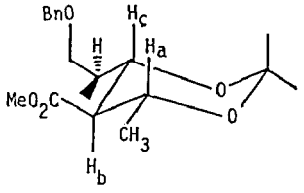
(10) The procedure of A. I. Meyers, et al. [J. Am. Chem.Soc. **1983**, 105, 5015] was adopted.

(11) The aldol yields varied critically in the range of 55-75% with slight changes in timing and rate of addition of **7** to a mixture of **8** and $TiCl_4$. A major byproduct was methyl crotonate, an elimination product of **7**, and unreacted aldehyde was recovered unchanged.

(12) The stereopurity was determined by HPLC [Zorbax SIL, hexane/AcoEt (4:1)] of the product mixture and confirmed by capillary GLC (Ulbon HR-20M, 50 m) of its acetonide.

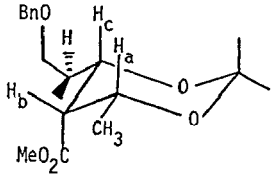
(13) Other combinations such as **7**(R=Me)/$TiCl_4$, **7**(R=Me)/(i-PrO)$TiCl_3$, and **7**(R=Et)/(i-PrO)$TiCl_3$ provided much lower yields (15%, 32%, and 10%, respectively), although the stereopurities of the aldol were comparably high (≥95%). The combination of **7**(R=Et)/$SnCl_4$ afforded 30% yield of **5** in only 79% diastereomeric purity.

(14) The most informative are the coupling constants for the diastereomeric acetonides as exemplified below. For similar stereochemical assignments of structurally related



(acetonide of **5**)

J_{ab}=10.5 Hz, J_{bc}=10.5 Hz



(acetonide of the 2-epimer of **5**)

J_{ab}=3.0 Hz, J_{bc}=2.7 Hz

acetonides, see: Thaisrivongs, S.; Seebach, D. J. Am. Chem. Soc. **1983**, 105, 7407. The stereiochemical assignment of each diastereomer will be fully discussed in a full paper.

(15) The stereoisomeric ratio and the relative stereochemistry were determined in the same ways as described above.

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(17) The conventional hydrolysis/hydroxaminolysis sequence[5] provided only 50% yield of **6**.

(18) Direct cyclization via the Mitsunobu reaction (dimethyl azodicarboxylate/Ph_3P) afforded only 38% yield of **11**.

(19) Under the conditions described in Scheme II, 29% of **11** was recovered. Particularly noteworthy is that the presence of t-BuOH is essential for deprotecting both the N-methoxy and benzyl groups, otherwise only the N-demethoxylation product was obtained quantitatively.

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