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STEREOSELECTIVE SYNTHESIS OF 1-β-METHYLCARBAPENEM

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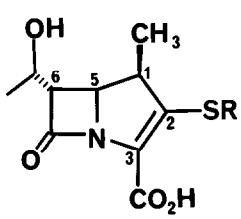
Summary: Stereoselective syntheses of the 1-β-methylcarbapenem intermediates 9B (R=SPh or OCH_3) have been accomplished by an aldol-type stereocontrolled reaction and stereoselective catalytic hydrogenation of an olefinic ester.

The discovery of the potent broad spectrum antibiotic thienamycin and its relatives has stimulated considerable interest in the synthesis of carbapenem analogs.[1] Recently, the Merck group has reported a total synthesis of 1-β-methylcarbapenem 1, a member of a new class of carbapenem antibiotics which possess remarkable dehydropeptidase-I stability and much improved chemical stability.[3] Recently highly stereoselective syntheses of 1-β-methylcarbapenem have been achieved by several groups.[2]

In this paper, we describe stereoselective synthesis of 1-β-methylcarbapenem intermediates based on either aldol-type stereocontrolled condensation or stereoselective catalytic hydrogenation of an olefinic ester. The starting material chosen for the synthesis of 1 was the acetoxyazetidinone 2, which is readily available by several routes.[4] Our synthetic plan was initially designed to form the C_1-C_5 carbon bond by direct coupling of enolsilane 3[5] with 2 under Lewis acid catalysis to generate 4. The intermediate 4 was converted to 1 via the bicyclic ketone 5 by using the efficient chemistry developed at Merck.[3] Thus, treatment of 2 with 3 (1 equivalent each) in CH_2Cl_2 in the presence of 5% trimethylsilyl trifluoromethanesulfonate as catalyst[6] (0°,2h) gave a 67:33 mixture of 4A and 4B in 85% yield. To confirm the stereochemical assignment, each isomer was separated (HPLC) and converted into the bicyclic ketone 5. The 1-β isomer 5B showed a significant Nuclear Overhauser Effect (NOE) between the C_1 and C_5 protons, whereas the 1-α isomer 5A showed no NOE for the C_1 and C_5 protons[7]. Reaction temperature, catalysts ($ZnCl_2$, ZnI_2, $TiCl_4$, etc.) and solvent changes had little effect on the stereochemical outcome (i.e., ratio of 4A/4B) and appear only to effect the chemical yield.

In order to achieve better selectivity in the introduction of the 1-β-methyl group, we turned our attention to the condensation of 2 with enolates derived from esters 6 and 7. As shown in the Table, treatment of 2 with the enolsilane of 6 gave approximately a 1:1 mixture of 1-α and 1-β methyl isomers. On the other hand, the enolsilane of 7A[9a] produced the 1-α-methyl isomer predominantly in high yield. It is not readily apparent why the 1-α-methyl selectivity is so high in this case. However, it is striking from the Table that there is a preponderance of the

1-β-methyl isomer when the zirconium enolates[8] (entries 4 and 5) were used. The geometry of those enolates 8 are assumed to be of the E (or Z(O)) configuration as described in the analogous work of Masamune[9] and others. The 1-β-methyl isomer (the erythro product) from this reaction may be reasonably rationalized by assuming a chair transition state (e.g. 10) which possesses the minimum number of non-bonding interactions (Zimmerman Model).[10] The acid 9B (R=OH), obtained by saponification of the thioester 9B (R=SPh) was converted into the diazoketo intermediate 4 by the procedure described by Merck.[3]



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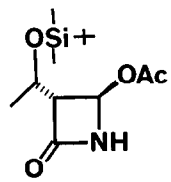

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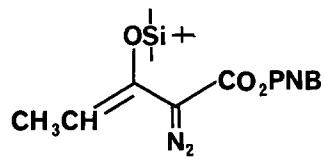

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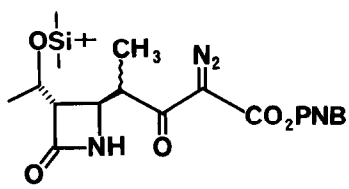
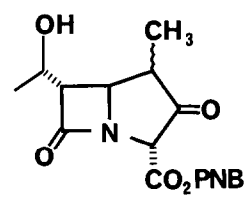
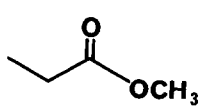


4 A = 1-α-Me
B = 1-β-Me



5 A = 1-α-Me
B = 1-β-Me



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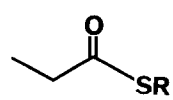
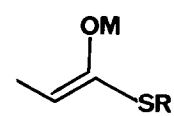


7 A, R = Ph
B, R = CH2- 



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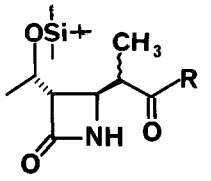

9 A = 1-α-Me
B = 1-β-Me

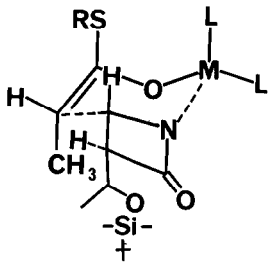

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Table. Enol Condensations with 2[a]

Entry	Esters	Enolate[b]	Product 9	9A:9B	Yield(%)[d]
1	6	LDA	---	---	0
2	6	LDA-Me_3SiCl	R=OCH_3	52:48	75
3	7A	LDA-Me_3SiCl	R=SPh	95:5	87
4	7A	LDA-$Zr(Cp)_2Cl_2$[c]	R=SPh	3:97	52
5	7B	LDA-$Zr(Cp)_2Cl_2$	R=SCH_2- 	15:87	47

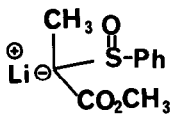
a. All reactions were carried out in the presence of $(Me)_3SiOSO_2CF_3$ catalyst.

b. All enolates were generated in THF at -70°.

c. Cp = cyclopentadienyl

d. The isolated yield.

Another approach to the 1-β-methylcarbapenem intermediate 9B involved the stereoselective hydrogenation of the olefinic ester 13. Condensation of 2 with the sulfoxide anion 11 gave the trans product 12, which upon heating (toluene, reflux) produced 13 in 70% overall yield. Catalytic hydrogenation (10% Pd/C, 20 psi H_2, CH_2Cl_2) of 13 gave a 65:35 mixture of 9A (R=OCH_3) and 9B (R=OCH_3). However, when 13 was silylated (TMSCl-TEA) prior to hydrogenation, a 25:75 mixture of 9A (R=OCH_3) and 9B (R=OCH_3) was obtained. Thus significant reversal of stereochemistry was achieved by simply protecting the N-H of 13. Although the origin of selectivity for the 1-β-methyl isomer is not apparent in this case, the intramolecular hydrogen bonding in the azetidinone 13 appears to play an important role in determining the stereochemical outcome of the hydrogenation.



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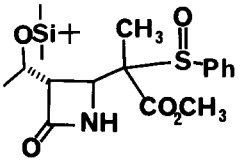

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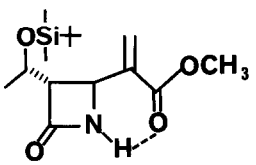

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References and Notes

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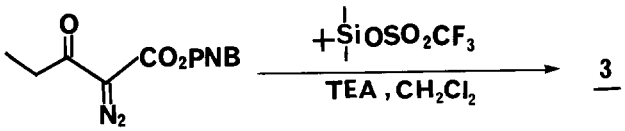
5. The enol silane 3 was prepared as shown below, and the olefin was obtained as a 9:1 mixture of stereoisomers.



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For a similar coupling reaction, see Reider, P. J.; Rayford, R.; Grabowski, E. J. J. Tetrahedron Lett. 1982, **23**, 379.

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