COMMUNICATION

2-Picolyl thioesters; a useful synthon for the preparation of 1-β-alkyl carbapenem intermediates[1]

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In this study, a highly stereoselective preparation of (3*S*,4*S*)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(1*R*)-1-carboxyethyl]-azetidin-2-one (**2**) is reported. It involves a Lewis acid mediated condensation of (3*S*,4*R*)-4-acetoxy-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one (**3**) with simple *O*-silylenol ethers of thiopropionates. From all the examples reported in this paper the 2-picolyl thiopropionate or similar arrangements were found to be essential for this stereoselection. Finally, a mechanism involving chelation control seems to be operative.

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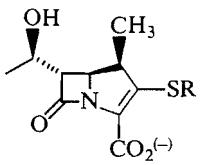
Dans ce travail, on rapporte une préparation hautement stéréosélective de la (3*S*,4*S*)-[(1*R*)-*tert*-butyldiméthylsilyloxy-1 éthyl]-3 [(1*R*)-carboxy-1 éthyl]-4 azétidinone-2 (**2**). Cette synthèse implique une condensation, sous l'influence d'un acide de Lewis, de la (3*S*,4*R*)-acétoxy-4 [(1*R*)-*tert*-butyldiméthylsilyloxy-1 éthyl]-3 azétidinone-2 (**3**) avec des éthers énoliques *O*-silylés simples de l'acide thiopropionique. En se basant sur tous les exemples rapportés dans cette publication, on a trouvé que le thiopropionate de picolyle-2 ou des composés semblables sont essentiels pour obtenir cette stéréosélectivité. Enfin, il semble que le mécanisme implique un contrôle par une chélation.

[Traduit par la revue]

The recent report, by Shih *et al.* (1), that a 1-β-methyl group imparts enzymatic as well as chemical stability to the carbapenem nucleus **1** has stimulated a rapid development of synthetic methods (2) directed towards the preparation of the key intermediate **2**. Although highly diastereoselective preparations of **2** have been recently published (2*i*,*j*,*k*), there remains a need for more efficient methods. Therefore an investigation of the C-4 alkylation of 4-acetoxyazetidinone **3** with simple *O*-enolsilyl ethers of thiopropionates **4** (Scheme 1) was initiated. Even though similar couplings have been reported (2*c*), poor or no β-diastereoselection was achieved. In this paper we would like to report a highly diastereoselective preparation of derivative **2** via a Lewis acid mediated condensation of 4-acetoxyazetidinone with simple *O*-silylenol ethers of thiopropionates.[3]



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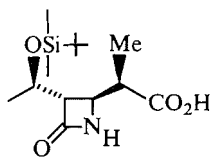

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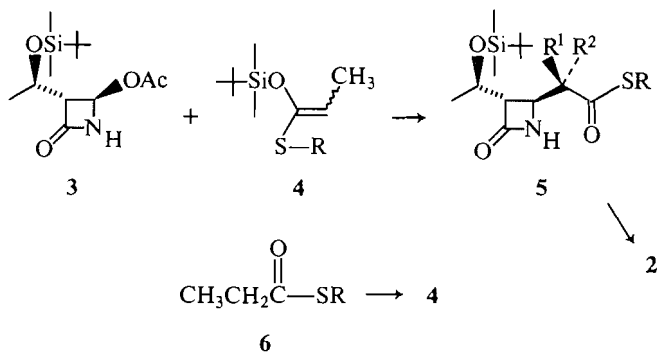
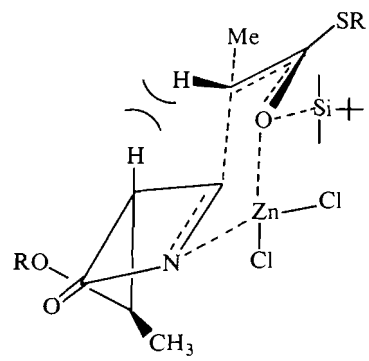


SCHEME 1

Preparation (see Experimental) of enol ethers **4**, generally obtained as mixtures of *E*/*Z* isomers, occurred upon trapping the enolates of thiopropionates **6** with *tert*-butyldimethylsilyl triflate (3). Reaction of these enol ethers **4** with the 4-acetoxyazetidinone **3** in the presence of $ZnCl_2$ afforded derivatives **5** with various α/β ratios, which are listed in Table 1.

In examples 1, 2, 3, 4, 6, 7, and 9 the α-methyl isomer **5** (R^2 = Me) was obtained as the major product. Formation of the α-methyl isomer **5** can be rationalized as occurring (4) via a 6-membered transition state as depicted in **7**. Here the steric



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interaction between the methyl group of the incoming nucleophile and H-3 of azetidinone **4** is minimized when the methyl group takes the pseudo equatorial position, thus leading to the α-methyl isomer **5**.

In examples 10, 11, 12, and 14 the β-methyl isomer **5** (R^1 =

[1]Work presented at the 70th Annual CIC Conference held in Quebec City, June 7–11, 1987.

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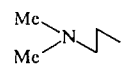
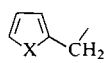
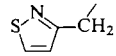
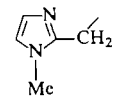
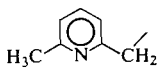
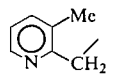
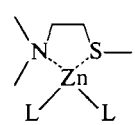
[3]This work is part of a Bristol–Myers U.S. Patent Application submitted on February 1985.

TABLE 1.

	R group in **4**, **5**, **6**		α:β in **5**	Yield of **5**
1.	*tert*-Butyl		92:8	74
2.	Phenyl		90:10	91
3.	CH_3SCH_2-		98:—	76
4.	MEM-		86:14	67
5.			1:1	49
6.		X = O	85:15	100
7.		X = S	81:19	84
8.		4-yl	60:40	58
9.		3-yl	92:8	37
10.		2-yl	13:87	80
11.			25:75	65
12.			1:9	85
13.			6:4	66
14.			—:>98	85–90

Me) was formed either as the major isomer or almost in a stereospecific manner (example 14). It is suggested that the ability of Zn(II) to form a chelate (see structure **8**) with the sulfur and nitrogen[4] atoms of the thioester is essential for high β-methyl stereoselection. Factors interfering with this chelation bring about a reduction in selectivity. For example, changing the N-heteroatom for O or S resulted in complete loss of β-methyl selectivity (examples 10, 12 vs. examples 6 and 7). Disruption of the chelate (steric factors) was apparent in example 5 and more strikingly in example 13 where the 6′-methyl group could interfere with the ligand around Zn. In this latter case the α/β ratio was 6:4 (see structure **9**). Alternatively, introduction of a 3′-methyl group (see structure 10) appears to favor the formation of the chelate **8** (example 14), and therefore a greater proportion of β-methyl isomer **5** was obtained relative to that for the parent compound (example 10).



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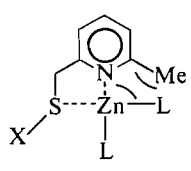

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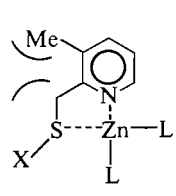

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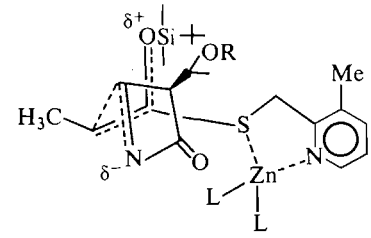
[4]There are ample literature precedents for chelates of type **8** (see ref. 5).

The effect of enol geometry on the stereochemical outcome of the reaction was examined in one case (example 14). The two geometric isomers of **4**-14 were separated (column chromatography) and reacted individually with azetidinone **3**. A high β-methyl stereoselectivity (>98%) was observed with the *Z*(O)-enol (isomer B, **4**-14) (assignment tentative) and an 84:16 ratio of β/α isomers was found with the *E*(O)-enol (isomer A, **4**-14) (6). This excellent β-methyl stereoselectivity was tentatively rationalized as resulting from the reaction occurring via a linear transition state such as **11** in which the Lewis acid is not intimately involved with the silyloxy group (2*d*, 7).

In summary, a highly stereoselective preparation of the β-methyl carbapenem precursor **2** has been developed. A mechanism involving chelation control seems to be operative. The 2-picolyl thiopropionates or similar structural arrangements were found to be essential for this stereoselection.



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Experimental

Base treatment (TEA) of thiopropionates **6** in CH_2Cl_2 and subsequent quenching with TBDMS–OTf gave enol **4** in generally good yields (60–95%). In the case of the 3-methyl-2-picolyl thiopropionate, formation of the enolate required a stronger base (LiHMDS, THF, −78°C). Coupling of **4** (2 equiv.) with the azetidinone **3** was started at 0°C (ice bath) under N_2 using $ZnCl_2$ (2 equiv.) as the Lewis acid. The mixture was allowed to stir at ca. 20°C for 18 h and then worked up (see Table 1). Generation of acid **2** occurred upon treatment of **5** in THF with aqueous NaOH in the presence of H_2O_2.

All new compounds gave ir, ^{1}Hmr, and combustion analyses consistent with their assigned structures.

Physical data of selected derivatives

4-*10*: Mixture of 2 isomers (45:55); ir (CH_2Cl_2) ν_{max}: 1635 (double bond) and 1595 (ar) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 8.55–6.95 (4H, m, ar), 4.98 (1H, 5 lines, isomeric H-vinyl), 4.04 and 3.97 (2H, 2s, isomeric -CH_2-), 1.54 and 1.55 (3H, 2d, J = 6.9 Hz, J = 6.7 Hz, isomeric -CH_3), 0.99 and 0.95 (9H, 2s, *tert*-butyl), 0.19 and 0.23 (6H, 2s, dimethyl) ppm.

4-*14*: A 2:8 mixture of 2 isomers; *isomer A* (R_f 0.75, 25% ether – petroleum ether): ir (CH_2Cl_2) ν_{max}: 1635 (olefin) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 8.40–8.34 (1H, m, H-aromatic), 7.37–7.06 (2H, m, H-aromatic), 5.03 (1H, d, J = 6.8 Hz, olefinic-H), 4.10 (2H, s, CH_2), 2.38 (3H, s, CH_3), 1.56 (3H, d, J = 6.8 Hz, CH_3), 0.96 (9H, s, *tert*-butyl-Si), 0.20 (6H, s, $(CH_3)_2$-Si) ppm; *isomer B* (R_f 0.68, 25% ether – petroleum ether): ir (CH_2Cl_2) ν_{max}: 1635 (olefin) cm^{-1}; ^{1}Hmr (80 MHz, $CDCl_3$) δ: 8.39, 8.34 (1H, m, H-aromatic), 7.37–6.95 (2H, m, H-aromatic), 5.00 (1H, q, J = 6.8 Hz, olefinic-H), 4.04 (2H, s, CH_2), 2.35 (3H, s, CH_3), 1.34 (3H, d, J = 6.8 Hz, CH_3), 0.97 (9H, s, *tert*-butyl-Si), 0.21 (6H, s, $(CH_3)_2$-Si) ppm.

5-*10*: (88.7% oil, 80% crystalline, heptane) mp 55–58°C; an 87:13 mixture of β- and α-methyl isomers. *β-methyl*: ir (CH_2Cl_2) ν_{max}: 3410 (N-H), 1765 (β-lactam), 1682 (thioester), and 1594 (ar) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 5.82 (1H, s, N-H), 4.30 (2H, s, -CH_2), 4.30–4.00 (1H, m, H-1′), 3.88 (1H, dd, J = 2.2 Hz, J = 6.4 Hz, H-4), 3.15–2.7 (2H, m, H-3, -CH—C—S-), 1.25 (3H, d, 6.9 Hz, CH_3-2′), 1.07 (3H, d, J = 6.3 Hz, -CH_3), 0.86 (9H, s, *tert*-butyl), 0.05 (6H, dimethyl-Si-) ppm. *α-methyl*: ir (CH_2Cl_2) ν_{max}: 3410 (N-H), 1765 (β-lactam C=O) and

1680 (thioester) cm^{-1}; ^{1}Hmr (80 MHz, $CDCl_3$) δ: 8.55, 8.54, 8.50, 8.49 (1H, m, H-arom), 7.75, 7.72, 7.65, 7.62, 7.55, 7.53 (1H, m, H-arom), 7.22–7.00 (2H, m, H-arom), 6.21 (1H, 6s, N-H), 4.42, 4.29, 4.25 (2H, part of ABq, J = 14 Hz, CH_2-S), 4.17, 4.09, 4.08 (1H, m, part of H-1), 3.78, 3.75, 3.66, 3.63 (1H, dd, J = 2.0 Hz, J = 9.6 Hz, H-4), 2.95–2.55 (2H, m, H-3, H-1″), 1.31, 1.22 (3H, d, J = 7.0 Hz, CH_3), 1.26, 1.18 (3H, d, J = 6.2 Hz, CH_3), 0.87 (9H, s, *tert*-butyl-Si), 0.07 (6H, $(CH_3)_2$-Si) ppm.

Acknowledgments

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