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A NEW APPROACH TO THE DIASTEREOSELECTIVE SYNTHESIS OF ALDOLS: INTRODUCTION OF THE 6α-(1*R*-HYDROXYETHYL) SIDE CHAIN OF THE CARBAPENEM AND PENEM ANTIBIOTICS

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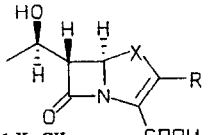
Summary: The 6α-(1*R*-hydroxyethyl) side chain has been introduced via a stereocontrolled aldol reaction with a silyl ketone as a hindered acetaldehyde equivalent. The derived *trans-S* silyl carbinol undergoes a completely stereospecific rearrangement to the desired *trans-R* O-silyl ether. The two-step sequence may be done in one-pot in overall yields of 70-90%.

Thienamycin[1] (1, R=$SCH_2CH_2NH_2$) was the first fully-characterized member of a new class of β-lactam antibiotics known as the carbapenems. Closely related to the carbapenems are the penems (2) which are not found in nature. Both the carbapenems and the penems require a 6α-(1*R*-hydroxyethyl) side chain for maximum potency and breadth of spectrum. Despite intensive effort in recent years



1 X=CH_2
2 X=S

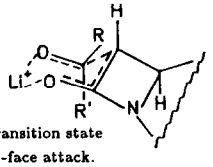


Figure: Aldol transition state for preferred α-face attack.

toward the development of efficient total syntheses of the carbapenems and the penems, the incorporation of the hydroxyethyl side chain in a straightforward and stereocontrolled manner has remained a challenge. Typically, it is incorporated early in a synthetic scheme in order to minimize manipulation of subsequent more sensitive bicyclic intermediates.[2]

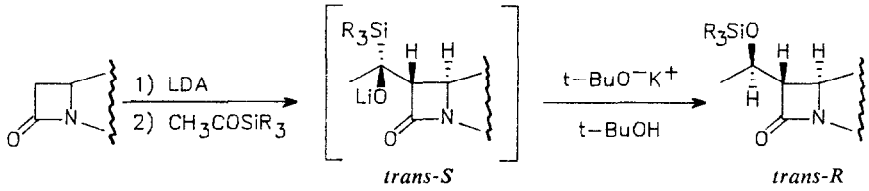
Direct introduction of the hydroxyethyl side chain onto a C-3 unsubstituted azetidin-2-one *via* an aldol reaction in which a lithium enolate is condensed with acetaldehyde produces a mixture of at least three of the four possible diastereomers.[3] Depending on the substituents on nitrogen and at C-4, 80-90% of the aldol mixture consists of the two *trans* diastereomers in approximately equal amounts while the remaining 10-20% consists primarily of the *cis-R* diastereomer with only trace amounts of the *cis-S* diastereomer being formed. As expected, the preferred direction of attack is from the face of the enolate opposite to the substituent at C-4. However, there is little selection for methyl *vs.* hydrogen in the presumed six-membered, chair-like transition state (Figure: R,R'=H,CH_3). Derivatization and tedious chromatography are necessary in order to isolate the desired *trans-R* diastereomer in chemical yields of only about 40%. Recently, an aldol mixture consisting of 87% of the *trans-R* isomer has been

produced *via* a zirconium enolate.[4] The zirconium enolate was formed *via* a lithium enolate and hexamethylphosphoramide was necessary to obtain the high stereoselectivity.

The hydroxyethyl side chain has been introduced stereoselectively *via* two different two-step sequences. Acetylation of an azetidinone enolate produces exclusively the thermodynamically favored *trans* β-keto lactam which can be stereoselectively reduced to provide the desired (*R*)-carbinol in good overall yield.[5] Alternatively, the two-carbon side chain has been introduced in one-carbon fragments *via* a formylation-methylation sequence with equally good stereoselectivity.[6] Neither of these processes have, however, proven useful for the large scale preparation of hydroxyethylated intermediates.

We have developed a novel method for the stereoselective introduction of the hydroxyethyl side chain as outlined in the Scheme. Stereocontrol of the aldol condensation is achieved by use of a silyl ketone as a hindered acetaldehyde equivalent[7] to give a product mixture containing 85-100% of the

Scheme



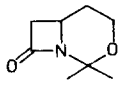
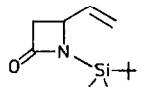
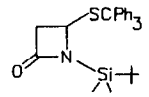
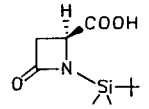
trans-S *trans-R*

trans-S silyl carbinol. The silyl carbinol undergoes a completely stereospecific rearrangement to the desired *trans-R* O-silyl ether upon treatment with potassium *t*-butoxide/*t*-butanol. The two-step sequence can be done in one pot in overall yields of 70-90%. This procedure directly provides hydroxyethylated intermediates protected as *t*-butyldimethylsilyl ethers, a form of protection commonly used in carbapenem and penem work. The results obtained on a variety of azetidinone intermediates are summarized in the Table. The process is compatible with N-*t*-butyldimethylsilyl protected azetidinones (entries 2-4) and no problems were encountered with the dianion chemistry developed for the C-3 substitution of an azetidinone carboxylic acid[8] (entry 4). The highest degree of stereoselectivity was obtained with the penem intermediate (entry 3) bearing a bulky tritylthio group at C-4, giving exclusively the *trans-R* O-silyl ether.[9]

Although silyl ketones are considered to be rather unreactive carbonyl compounds as a result of both steric hindrance and electronic deactivation of the carbonyl group, no change in the aldol conditions relative to those for acetaldehyde[3a] was necessary. The assignment of *trans-S* to the preferred aldol product based on mechanistic considerations (Figure 1: R=SiR_3,R'=CH_3) was confirmed by x-ray crystallographic analysis[10] of the silyl carbinol **3** derived from **4**[3a] and methyl trimethylsilyl ketone.[11a,b] Rearrangement of **3** gave O-silyl ether **5** accompanied by free carbinol **6**.[3a,12] None of the oppositely configured O-silyl ether or carbinol was observed. Thus, the rearrangement is completely stereospecific with retention of configuration[13] within the limits of NMR detection.

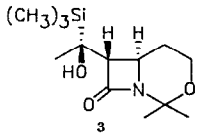
The conditions used by Wilson[7] to effect the α-hydroxy silane rearrangement (KH/HMPA with no mention of a proton source) resulted in the destruction of our subtrate (**3**). As the formation of a potassium salt is apparently essential for a rapid rearrangement of α-silyl carbinols lacking adjacent anion stabilizing substituents, we were led to try the *t*BuO^-K^+/*t*BuOH system. An experiment in which a lithium alkoxide was given an opportunity to rearrange under otherwise identical conditions (repeat of

Table: Stereoselective Silyloxyethylation of Representative Carbapenem and Penem Intermediates

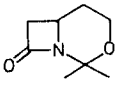
Entry	Substrate[a]	Reaction Conditions[b-e]	Product Mixture[f]	Isolated Yield(%)[g]
1		A	95:4:1 *trans-R/cis-R/trans-S*	72% *trans-R*
2		A	85:8:7 *trans-R/cis-R/trans-S*	75% mixture
3		A	*trans-R*	79%, 11%[h] *trans-R*
4		B	87:13 *trans-R/trans-S*	77% *trans-R*

[a]All substrates are racemic except entry 4. [b]All reactions were run in THF at an initial substrate concentration of 0.1-0.25M. [c]A 1) 1.1 eq LDA, -78°C, 5 min 2) 1.1 eq $CH_3COSitBu(CH_3)_2$[11c], 10 min 3) 1.1 eq $tBuO^-K^+$/tBuOH[d], -78 to 0°C, 10 min 4) sat'd aqueous NH_4Cl; B 1) 2 eq LDA, 0°C, 5-10 min 2) and 3) as above at 0°C 4) 1:1 citric acid H_2O/H_2O. [d]1M $tBuO^-K^+$ in tBuOH. [e]Workup involved extraction into Et_2O, washing with H_2O(2X) and drying with $MgSO_4$. [f]Ratio determined by 200MHz ^{1}H-NMR. Assignment of side chain configuration of cis diastereomer based on mechanistic considerations. [g]After fractional crystallization and/or chromatography. [h]Based on 85% conversion. Minor product N-desilylated.

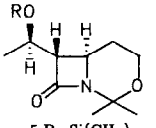
entry 1 omitting the tBuO$^-$K$^+$) gave only 9% of the alkoxysilane. While the rearrangement is, in principle, catalytic with respect to the tBuO$^-$K$^+$, an experiment using only 0.1 equivalent of the base gave only 9% of rearranged product. An attempt to further streamline the process by using potassium hexamethyldisilazide instead of LDA to, after the aldol condensation, directly provide the potassium alkoxide was unsuccessful.



3



4



5 R=Si(CH$_3$)$_3$
6 R=H

In conclusion, we believe this one-pot silyloxyethylation process represents an improvement over currently available methodology for the stereoselective hydroxyethylation of C-3 unsubstituted azetidinones while, more generally, extending the utility of the aldol condensation with regard to the *threo*-selective generation of β-hydroxy carbonyl compounds.[14]

References and Notes

1) G. Albers-Schonberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkle, R.B. Morin and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).

2) For reviews, see: (a) T. Kametani, K. Fukumoto and M. Ihara, *Heterocycles*, 17, 463 (1982); (b) R.W. Ratcliffe and G. Albers-Schonberg, *Chemistry and Biology of β-Lactam Antibiotics*, Chapter 4, Ed. by R.B. Morin and M. Gorman, Academic Press, New York (1982); (c) I. Ernest, *ibid.*, Chapter 5.

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4) J. d'Angelo and F. Pecquet-Dumas, Tetrahedron Letters, 1403 (1983).

5) (a) F.A. Bouffard and B.G. Christensen, *J. Org. Chem.*, **46**, 2208 (1981); (b) F. Pecquet and J. d'Angelo, *Tetrahedron Letters*, 2777 (1982).

6) U.K. Patent Application 2,042,514, Bristol-Myers Co.

7) S.R. Wilson, M.S. Hague and R.N. Misra, *J. Org. Chem.*, **47**, 747 (1982).

8) (a) I. Shinkai, T. Liu, R.A. Reamer and M. Sletzinger, *Tetrahedron Letters*, 23, 4899 (1982); (b) P.J. Reider and E. J. Grabowski, *ibid.*, 23, 2293 (1982).

9) Structural assignments for the *trans-R O-tert*-butyldimethylsilyl ethers obtained in entries 2-4 were confirmed *via* correlation with related intermediates of known stereochemistry as follows: entries 2 and 3 - silylation (*t*BuMe$_2$SiCl, ImH, DMF) of carbinol precursors;[5a,3f] entry 4 - selective O-desilylation (CH_2Cl_2, CF_3COOH, H_2O). We thank Dr. F. DiNinno and Mr. K. Wildonger of these laboratories for providing NMR spectra of the correlation compounds for entries 2 and 3, respectively, for comparison.

10) We thank Dr. James Springer of these laboratories for this analysis. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

11) (a) A. G. Brook, J. M. Duff, P. F. Jones and N. R. Davis, *J. Am. Chem. Soc.*, **89**, 431 (1967); (b) E. J. Corey, D. Seebach and R. Freedman, *ibid.*, 434 (1967); (c) Methyl *tert*-butyldimethylsilyl ketone was prepared analogously to the trimethylsilyl ketone: dithiane precursor $C_{11}H_{24}SiS_2$; 87%; b.p. 115-117°(1mm); $\delta_H(CDCl_3)$ 0.20 (s, 6H), 1.04 (s, 9H), 1.81 (s, 3H), 2.02 (m, 2H), 2.44 (ddd, J=3.1, 4.8 and 14.2 Hz, 2H), 3.17 (ddd, J=3.0, 12.3 and 14.2 Hz, 2H); EI-MS *(m/e)* 248(M+), 233, 191, 133. Silyl ketone $C_8H_{18}SiO$: 48%; b.p. 144°; $\nu(CH_2Cl_2)cm^{-1}$ 1642; $\delta(CDCl_3)$ 0.20 (s, 6H), 0.94 (s, 9H), 2.26 (s, 3H); EI-MS *(m/e)* 115.

12) Partial desilylation observed here, either by the *t*BuO$^-$K$^+$ or upon aqueous workup, did not occur with the less labile *t*-butyldimethylsilyl group. The sole isolable product after PLC of the 5/6 product mixture on silica gel was the carbinol.

13) A. G. Brook, *Accounts Chem. Res.*, 7, 77 (1974): The sense of stereospecificity in our and Wilson's work[7] is opposite to that observed by Brook suggesting that a different mechanism is involved in the rearrangement of silyl carbinols lacking adjacent anion stabilizing substituents.

14) This work was presented at the 18th Middle Atlantic Regional Meeting, American Chemical Society, May 21-23, 1984, Newark, N.J.

15) Physical data. **3**: m.p. 102°; $\nu(CH_2Cl_2)cm^{-1}$ 3571-3704 (br, w), 1742; $\delta_H(CDCl_3)$ 0.10 (s, 9H), 1.26 (s, 3H), 1.42 and 1.76 (s, each 3H), 1.86 (m, 2H), 3.04 (d, J=2 Hz, 1H), 3.46 (ddd, J=2, 5 and 10.5 Hz, 1H), 3.86 (m,2H); EI-MS *(m/e)* 256, 213, 198; Anal. C,H,N,Si.
5: $\delta_H(CDCl_3)$ 0.12 (s, 9H), 1.22 (d, J=6 Hz, 2H), 1.40 and 1.62 (s, each 3H), 1.84 (m, 2H), 2.78 (dd, J=1.5 and 6 Hz, 1H), 3.56 (ddd, J=1.5, 6 and 10.6 Hz, 1H), 3.90 (m, 2H), 4.14 (dq, J=6 and 6 Hz, 1H).
(6*RS*,7*SR*)-2,2-dimethyl-7-[(*RS*)-1-*tert*-butyldimethylsilyloxyethyl]-3-oxa-8-oxo-1-azabicyclo[4.2.0]-octane (entry 1): $\nu(CH_2Cl_2)cm^{-1}$ 1730; $\delta_H(CDCl_3)$ 0.06 (s, 6H), 0.86 (s, 9H), 1.18 (d, J=6.2 Hz, 3H), 1.39 and 1.73 (s, each 3H), 1.83 (m, 2H), 2.77 (dd, J=1.9 and 4.7 Hz, 1H), 3.63 (ddd, J = 1.9, 4.7 and 10.7 Hz, 1H), 3.86 (apparent dd, J=2.6 and 8.4 Hz, 2H), 4.18 (dq, J=4.7 and 6.2 Hz, 1H).
(3*SR*,4*RS*)-1-*tert*-butyldimethylsilyl-3-[(*RS*)-1-*tert*-butyldimethylsilyloxyethyl]-4-vinylazetidin-2-one (entry 2): $\delta_H(CDCl_3)$ 0.06, 0.08, 0.18 and 0.20 (s, each 3H), 0.88 and 0.94 (s, each 9H), 1.17 (d, J = 6 Hz, 3H), 2.90 (dd, J=2.5 and 4.5 Hz, 1H), 4.10 (dd, J=2.5 and 9, 1H), 4.21 (dq, J=4.5 and 6 Hz, 1H), 5.16 (dd, J=1 and 10 Hz, 1H), 5.30 (dd, J=1 and 17.5 Hz, 1H), 5.88 (ddd, J=9, 10 and 17.5 Hz, 1H).
(3*SR*,4*RS*)-1-*tert*-butyldimethylsilyl-3-[(*RS*)-1-*tert*-butyldimethylsilyloxyethyl]-4-tritylthio-azetidinone (entry 3): $\delta_H(CDCl_3)$ 0.06 and 0.14 (s, each 3H), 0.56 (d, J=6.5 Hz, 3H), 0.78 and 0.91 (s, each 9H), 3.44 (dd, J=2.5 and 2.5 Hz, 1H), 3.9 (m, 1H), 3.94 (dd, J=2.5 and 6.5 Hz, 1H), 4.18 (d, J=2.5 Hz, 1H), 7.36 (m, 15H).
(3*S*,4*S*)-1-*tert*-butyldimethylsilyl-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-azetidin-2-one-4-carboxylic acid (entry 4): m.p. 146-7°; $[\alpha]_D$ +49.1° (c 3.30, $CHCl_3$); ν (Nujol mull)cm^{-1} 1742, 1689; δ_H ($CDCl_3$) 0.08, 0.10, 0.19 and 0.27 (s, each 3H), 0.90 and 0.98 (s, each 9H), 1.24 (d, J = 6.2 Hz, 3H), 3.34 (dd, J=3.2 and 3.2 Hz, 1H), 4.21 (d, J=3.2 Hz, 1H), 4.27 (dq, J=3.2 and 6.2 Hz, 1H); EI-MS (*m/e*) 372, 330.

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