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ENANTIOSPECIFIC SYNTHESIS OF β-LACTAMS VIA CYCLOADDITION[1]

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Summary: Enantiospecific synthesis of variously substituted cis-β-lactams can be achieved by the annelation of Schiff bases from optically active ketal aldehydes derived from D-threonine. Similar annelation of Schiff bases from the triphenylsilyl ether of D-threonine ester and cinnamaldehyde leads to cis-β-lactams with high diastereofacial selectivity.

Synthesis of optically pure compounds without a wasteful resolution step at the end of a preparative sequence is a desirable goal for many chemists[2]. We report here the synthesis of optically active β-lactams (3) via the reaction of an activated carboxylic acid (1) and an imino compound (2) in presence of a base[3] (Scheme I). Two approaches using a chiral Schiff base were investigated - one involved an optically active amino component and the other, an optically active aldehyde.

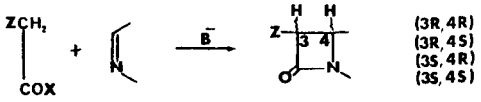
Since two new centers of asymmetry, C-3 and C-4, are created during β-lactam formation, four diastereomers could possibly be formed. It is known that antibacterial activity is shown by one enantiomer only of β-lactam antibiotics. The aim, therefore, is to discover conditions leading selectively to a desired optically pure isomer.

A. Amino component as chiral starting material

Our previous studies[3] have shown that the Schiff base (4) from cinnamaldehyde and an ester of D-threonine produce two optically active cis-β-lactams, but no trans-β-lactams (Scheme II). The two isomers (e.g., 5 and 6) formed in this reaction are nearly equal in amount. The use of D-threonine with two centers of asymmetry constitutes an advantage: the α-carbon in (4), being next to an ester group and an imino function, could perhaps undergo inversion[4] but the chirality of the β-carbon would remain unchanged. The various reactions used for β-lactam synthesis do not alter the S-configuration of the β-carbon of D-threonine.

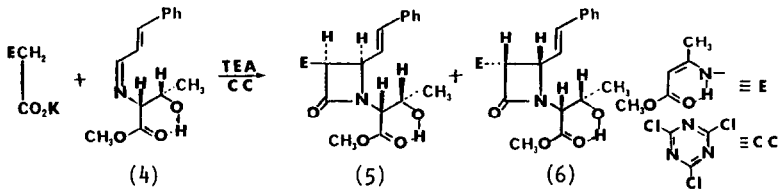
The nearly complete lack of diastereofacial selectivity during the annelation of (4) could be ascribed to an almost planar structure for the Schiff base caused by strong hydrogen bonding between the β-hydroxyl and the α-ester carbonyl groups. This planar structure would permit nearly equal ease of approach by a reactant from either the si or the re face of (4). When we used phenylserine in place of threonine, the two faces were no longer equally accessible because of the bulk of the phenyl group and therefore stereoselective annelation was observed: two diastereomeric cis-β-lactams were formed in 80:20 proportion.

Scheme I



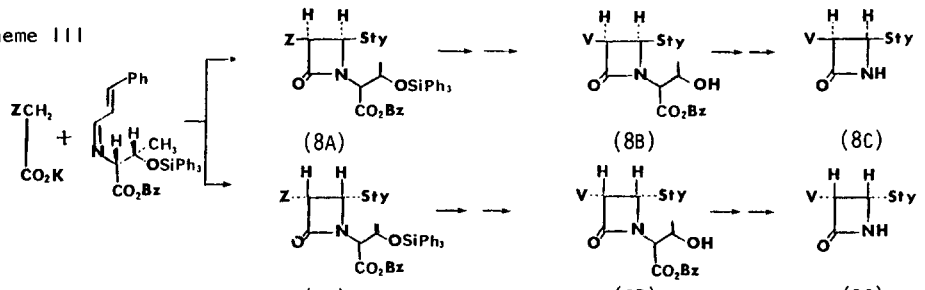
(1) (2) (3)

Scheme II



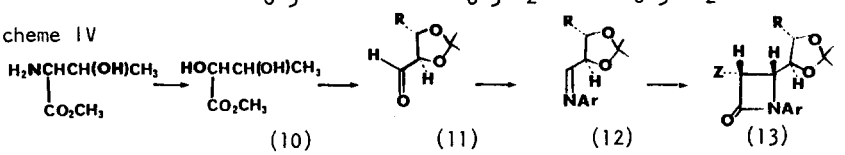
(4) (5) (6)

Scheme III



Sty = $C_6H_5CH{=}CH-$, Bz = $C_6H_5CH_2-$, V = $C_6H_5OCH_2CONH-$, Z = E, N_3

Scheme IV



(a) R = CH_3; (b) R = H

Ar = $C_6H_4OCH_3$(p), Z = N_3, PhO, CH_3O

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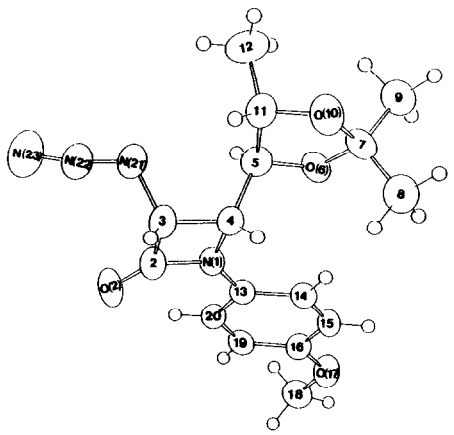
Fig 1



Formation of an ether from the β-hydroxyl group eliminates hydrogen bonding and makes the two faces of the Schiff base unequal. Therefore, a reaction with (7) should show marked diastereofacial selectivity[5]. We have tested the efficacy of the very bulky triphenylsilyl ether derivative, (7), for preparing optically active β-lactams. Indeed, annelation at -20° with a Dane salt from glycine, triethylamine and ethyl chloroformate[3b] led in 50-60% yield to an optically active cis-β-lactam (8A) with only a trace amount (5%) of another cis β-lactam (9A). After chemical manipulation α-amido-β-lactams (8B, 9B) were obtained which could be easily separated by chromatography over a silica gel column (Scheme III). Oxidative degradation[6] of (8B) and (9B) led to (8C) and (9C) which were found to be mirror images of each other based on their circular dichroism spectra. Stereostructures (8C) and (9C) indicating absolute configuration have been deduced on the basis of x-ray crystallographic studies[7].

B. Aldehyde as chiral starting material

We have studied the enantiofacial selectivity achieved by using a bulky, chiral aldehyde to make the two faces of a Schiff base, such as (13a), unequal to approach by reagent molecules. D-threonine was diazotized[8] to 2,3-dihydroxybutyric acid (10) which was converted to the ketal aldehyde (11a) and the Schiff base (12a). Cycloaddition was successful with several activated acids. In each case, a single optically active, cis β-lactam (13) was obtained in 50-60% yield. In other words, this annelation reaction is entirely stereospecific (Scheme IV).

Single crystal x-ray diffraction study was the method of choice for determining the absolute configuration of the optically active β-lactams prepared during this investigation. However, suitable crystals were obtained from only (±)-13a [$Z=N_3$] prepared by starting with DL-threonine. The x-ray derived structures from such crystals contain both enantiomeric forms. An ORTEP drawing (Fig. 1) was made of that enantiomer of the β-lactam that had the S-configuration of the methyl carbinol group (corresponding to the unaltered β-carbon of D-threonine). It could be deduced from this ORTEP drawing for (13a) that i) the absolute configuration of the α-carbon of D-threonine had not changed during diazotization and subsequent reactions; and ii) the absolute configuration at C-3 of (13a) was R when $Z= N_3$.

We have observed that glyceraldehyde acetal (11b) derived from L-serine[8] can be used in place of (11a) for enantiospecific synthesis of β-lactams[9]. Our findings will be reported in another communication.

Conclusions

Enantiospecific synthesis of β-lactams from ketal aldehyde and near enantiospecific synthesis from the triphenylsilyl ether of threonine can lead to optically pure cis β-lactams[10] with a variety of functional groups which serve as chiral synthons for other heterocycles[11]. The N-(p-methoxyphenyl) group can be removed by cerium (IV) ammonium nitrate oxidation[12] to produce N-unsubstituted β-lactams which are suitable for the preparation of a variety of bicyclic β-lactam antibiotics. It is interesting to note that by starting with the same D-threonine, one can generate either enantiomeric form of monocyclic β-lactams depending on whether a chiral aldehyde or a chiral amine derived from D-threonine is used for preparing the Schiff base.

Acknowledgment

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10. New compounds were characterized by I.R. and N.M.R. spectra and elemental analyses and/or mass spectra; for example, the major product from the condensation of (7) with azidoacetyl chloride and triethylamine followed by the removal of the silyl protective group led to 8A (Z=N_3): cis 1-(1 -carbobenzyloxy-2 -triphenylsilyloxy propyl)-3-azido-4-styryl--2-azetidinone (8A,Z=N_3): oily liquid, i.r. (neat): 2045, 1760, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : 1.21 (3H, d, J=6.2 Hz), 4.42 (1H, d, J=13.5 Hz), 4.5 (1H, d, J=4.5 Hz), 4.65 (1H, m), 4.97 (1H, d, J=5.5 Hz), 5.11 (1H, d, J=13.5 Hz), 5.15 (1H, bs), 6.35 (2H, m), 7.0 - 7.65 (25 H, m); (b) the only β-lactam from the condensation of azidoacetic acid, triethylamine, cyanuryl chloride, and (12a) was cis 1-(p-anisyl)-3-azido-4-(2 ,2 ,5 -trimethyl-1,3 -dioxalan-4 -yl)--2-azetidinone (13a): 59% yield; m.p. 97-98°; i.r. (KBr): 2090, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : 1.33(3H, s), 1.38 (3H, d, J=6 Hz), 1.43 (3H, s), 3.8 (3H,3s), 4.17-3.9 (2H,m), 4.33 (1H, t, Hz), 4.77 (1H, d, J=6 Hz), 7.5-6.7 (4H, dd, AB pattern); ^{13}C-NMR ($CDCl_3$) : 161.57, 157.18, 130.43, 120.60, 114.32, 109.78, 81.27, 74.82, 64.66, 58.33, 55.53, 27.65, 27.28, 18.63; CIMS (NH_3 carrier gas) m/e : 350 $(M+18)^+$; Anal. Calcd, for $C_{16}H_{20}N_4O_4$:C,57.82, H,6.07, N,16.86 Found: C,57.78, H,5.86, N,16.71.
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13. 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, U. K. Any request should be accompanied by the full literature citation for this communication.

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