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STEREOREGULATED SYNTHESIS OF β-LACTAMS FROM SCHIFF BASES DERIVED FROM THREONINE ESTERS[1]

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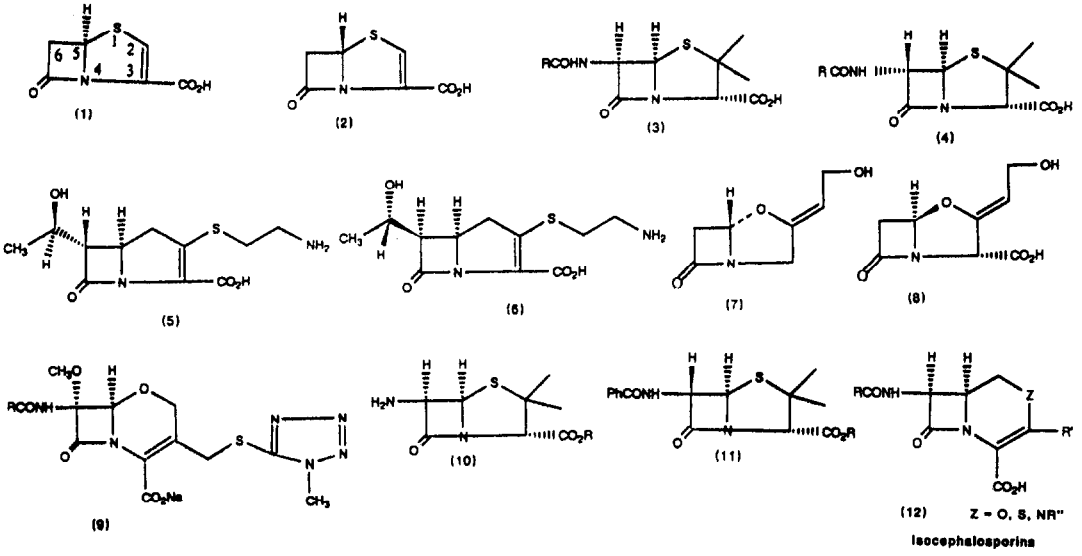
Abstract: *A variety of optically active 3-substituted-2-azetidinones has been prepared by the annelation of Schiff bases derived from cinnamaldehyde and D-threonine esters and their absolute configuration determined. When the β-hydroxyl group of threonine is unprotected, both enantiomeric forms of N-unsubstituted 3,4-disubstituted-2-azetidinones can be prepared from a single β-lactam-forming reaction. On the other hand, by converting the hydroxyl group of D-threonine to a bulky group (e.g., triphenylsilyl ether), very high diastereoselectivity can be induced. The multiple functional groups on these β-lactams can be easily modified to generate useful synthons for optically active sugars, alkaloids, and monocyclic and bicyclic β-lactam antibiotics.*

The antibiotic activity of β-lactams depends on the relative configuration of the substituents as well as the absolute configuration of certain chiral centers. Woodward et al.[2] showed that the 5R-enantiomer of the penem (1) is active while the 5S-enantiomer (2) is totally inactive. In the case of penicillins (3), the 6R-absolute configuration is essential for antibacterial activity of (3); 6-epi-penicillin (4) is devoid of activity.[3] On the other hand, both 6R- and 6S- configurations are associated with antibacterial activity in thienamycin (5) and epi-thienamycin (6)[4].



This paper is dedicated to Professor Gabor Fodor on the occasion of his 75th birthday

+Deceased

Wanning et al.[5] have determined the structure and absolute configuration of an antibiotic (7) of the clavulanic acid (8) type which is produced by a strain of *Streptomyces*. While (8) and the other known antibiotics of this family have the 5R-configuration, (7) has the 5S-configuration.

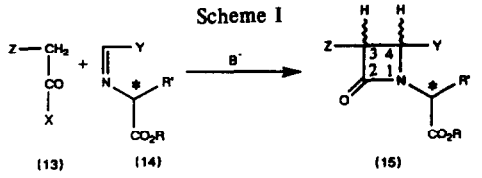
In the face of such disparate absolute configuration requirements for antibiotic activity, it becomes necessary to test both enantiomeric forms of any new β-lactam antibiotic obtained by synthesis. In the case of β-lactams produced by a series of stereospecific reactions, it may even be necessary to start with the wrong enantiomer at a critical center to accommodate an inversion step in the synthetic sequence. For example, during the elaboration of moxalactam (9) from 6-aminopenicillanic acid (10), Shionogi chemists[6] prepared a 6-epi-penam intermediate (11) so that the correct 5R-configuration could be achieved in the course of constructing the six-membered heterocyclic ring; later the inversion of C-6 was conducted to obtain the desired configuration at C-6 of the final product.

As part of a long term study aimed at devising novel β-lactam antibiotics - in particular, isocephalosporins,[7] e.g., (12) - we were interested in obtaining both enantiomers from the same synthetic sequence without resorting to optical resolution. In order to prepare β-lactams with useful substituents, annelation (Scheme 1) of Schiff bases (14) derived from α-amino acids appeared to be an attractive approach. We report here additional details of our earlier studies[8] and some new findings that permit the desired type of enantioselectivity at the β-lactam carbons (C-3 and C-4) in compounds of type (15).

Annelation of Schiff Bases

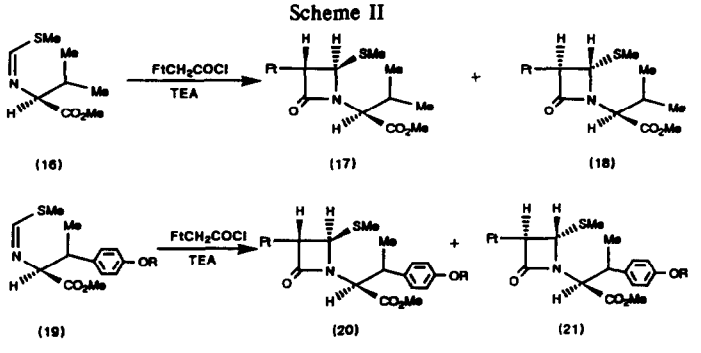
During monocyclic β-lactam formation from a Schiff base by reaction with a prochiral acid chloride (or equivalent) and a base (Scheme I), two cis and two trans β-lactams are possible since two new centers of asymmetry are generated. Thus, Bachi et al.[9] have observed the formation of two optically active trans β-lactams (17) and (18) when an acid chloride was allowed to react with the Schiff base (16) derived from L-valine. Kamiya[10] also made a similar observation when he obtained a diastereomeric mixture of trans β-lactams (20) and (21) by the reaction of phthalimidoacetyl chloride with the thioimidate (19) and triethylamine (Scheme II).

Scheme I



(13) (14) (15)

Scheme II



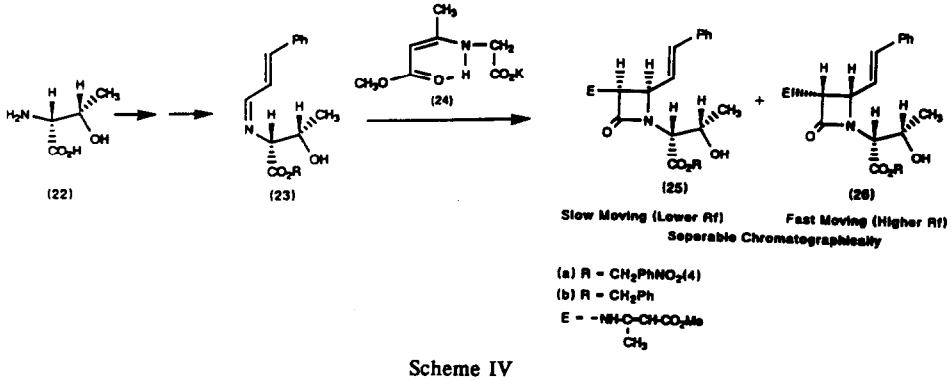
(16) (17) (18)

(19) (20) (21)

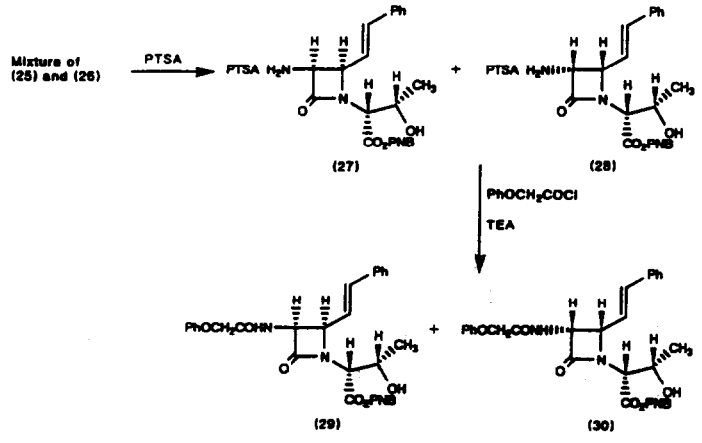
We selected threonine (22) as the starting point of our synthesis of monocyclic and bicyclic β-lactams for several reasons: (a) known methods can be used for providing selective protection for the three functional groups in this amino acid, (b) this amino acid has two chiral centers which can be manipulated independently of each other, (c) this amino acid is commercially available in either enantiomeric form at about the same cost.

Following the method of McLaren[11] D-threonine (22) was converted to a "Dane salt" by reaction with methyl acetoacetate and then transformed to a benzyl or p-nitrobenzyl ester. The correspondng free amino compounds could be converted to Schiff bases (23) in good yield. In earlier publications from our laboratory, we[12] have described a convenient and non-hazardous, synthesis of α-amino-β-lactams on a large scale using a Dane salt from glycine (24) for reaction with Schiff bases. By utilizing this methodology two diasteromeric β-lactams (25) and (26) were obtained in about 50:50 proportion from (23) and (24) (scheme III). On a small scale these two compounds could be separated by thin layer chromatography (TLC). Working on a larger scale, it was more convenient to treat the mixture of (25) and (26) with p-toluenesulfonic acid to remove the amino protective group and obtain a mixture of two α-amino-β-lactam tosylates (27) and (28). Reaction with phenoxyacetyl chloride in presence of an excess of triethylamine led to a mixture of two α-amido-β-lactams (29) and (30) which could be separated easily by columm chromatography (Scheme IV).

Scheme III



Scheme IV



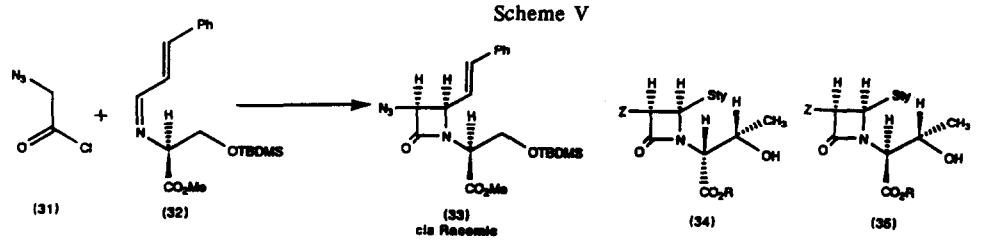
While our work was in progress Just and Liak[13a] reported the formation of a single racemic α-azido-β-lactam (33). They started with L-serine methyl ester hydrochloride , protected the primary hydroxyl group by forming the t-butyldimethylsilyl ether and prepared the Schiff base (32) which was allowed to react with azidoacetyl chloride (31) and triethylamine to generate (33) (Scheme V).

The formation of racemic (33) served to indicate racemization of the schiff base (32) during or before β-lactam formation[13b]. Similar epimerization of the asymmetric carbon next to the imino and ester groups in (23) would lead to a diasterecomeric mixture rather than the racemate of (23) since the second chiral center would be expected to be unchanged during or before β-lactam formation. The possibility remained, however, that the diastereomeric cis β-lactams differed only at the chiral center adjacent to the ester group [for example, (34) and (35)].

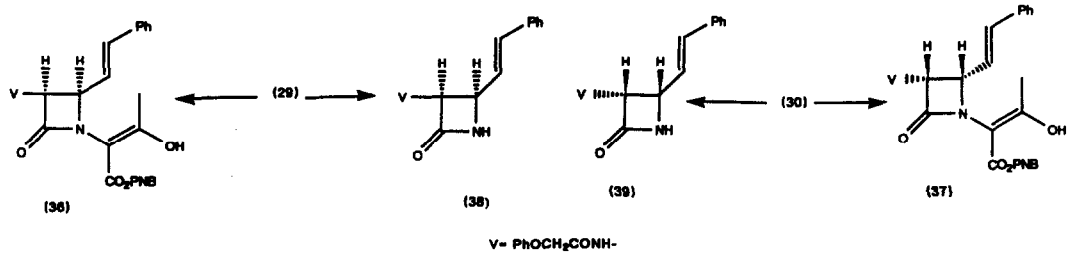
In light of the earlier work by Bachi[9] and by Kamiya et al.[10] it seemed more likely that (25) and (26) differed in the absolute configuration at C-3 and C-4. To obtain information on these points, the following study was undertaken.

At first we attempted to remove the asymmetry of the N-substituent by oxidation of the secondary hydroxyl group in (29) and (30). Oxidation with Jones reagent under carefully monitored conditions led to a keto compound which seemed to exist essentially in the enolic form (Scheme VI). The two compounds (36) and (37) obtained in this way had opposite signs of optical rotation as is to be expected if the stereochemistry

Scheme V



Scheme VI

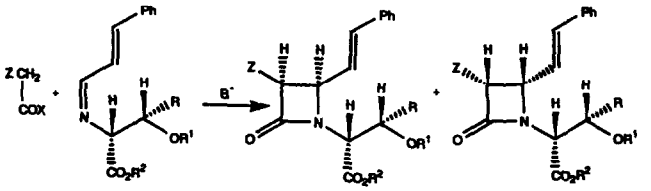


postulated in Scheme IV is correct. The specific rotations were opposite in sign but not equal to each other, perhaps because of the effect of keto-enol tautomerism.

In a previous publication[8] we have reported that N-unsubstituted β-lactams can be prepared easily from β-lactams of general type (30) by oxidation with an excess of Jones reagent. When we applied this reaction to (29) and (30), the corresponding β-lactams (38) and (39) were obtained. These compounds had identical melting point, infrared and ^{1}H-NMR spectra. Their circular dichroism spectra were essentially equal and opposite. These observations are in agreement with the steric course of the reaction proposed in Scheme VI.

In the Schiff bases (40a-d, R^1 = H) with a free β-hydroxyl group, there exists strong hydrogen bonding between the ester carbonyl group and the β-hydroxyl group thereby giving the Schiff base an almost planar structure. Nearly equal ease of access from either face would then lead to annelation without strong diastereselectivity during the creation of new chiral centers at C-3 and C-4 of the β-lactams formed. In case of phenylserine the two faces of the Schiff base (40d) are not equally accessible because of the phenyl ring; in consequence, substantial diastereroselectivity (80:20) is observed during annelation. (See Table 1).

Table 1



Entry	z	R	R^1	R^2	Ratio* (41:42)
a[8]	N_3	H	H	PNB	50:50
b[8]	N_3	Me	H	PNB	50:50
c	N_3	Me	H	Bzl	50:50
d[8]	N_3	Ph	H	PNB	80:20
e[14]	N_3	Me	TBDMS	Bzl	90:10
f[16]	N_3	Me	TPS	Bzl	95:5
g	N_3	Me	TPS	PNB	95:5
h	N_3	Me	TPS	Et	93:7
i	N_3	Me	TPS	Me	90:10
j[16]	E	Me	TPS	Bzl	95:5

Bzl = benzyl, TPS = triphenylsilyl

PNB = p-nitro-benzyl, TBDMS = t-butyldimethylsilyl

E = -NHC(Me) = $CHCO_2Me$

*All β-lactam forming reactions were carried out at -20°C except for (f) which was conducted at -40°C.

Tenneson and Belleau[14] have reported that the reaction of the O-silylated Schiff base (40e) with azidoacetyl chloride produced two cis-β-lactams (41e and 42e) in the proportion of 90:10 (Table 1).

The high diastereoselectivity shown during annelation of the t-butyldimethylsilyl ethers of the Schiff base (43) must mean that in the absence of the hydrogen bonding, one face of these Schiff bases is no longer as accessible as the other face. When we used the very bulky triphenylsilyl group for the protection of the β-hydroxyl group, the diastereoselectivity was very high 95:5 - especially at low reaction temperatures (Table 1).

In Table 1 are listed the observations from our more extended studies on the annelation of the Schiff bases (40) from trans-cinnamaldehyde and β-hydroxy-α-aminoesters with or without silylation of the β-

hydroxyl group. When a Dane salt of glycine[8] is used in place of the far less bulkier azidoacetic acid, the diastereoselectivity in β-lactam formation follows the same trend. It is the bulk on the β-carbon of the threonine ester that appears to be the most relevant factor in determining the steric course of this β-lactam-forming reaction.

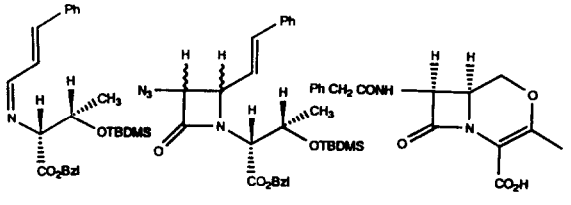
Determination of Absolute Configuration.

X-ray Diffraction Studies

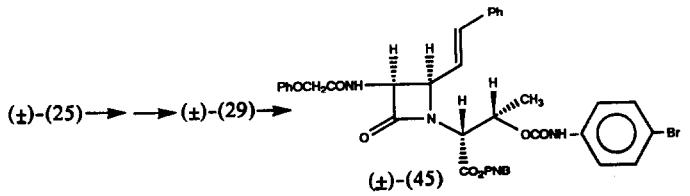
Since the two cis-β-lactams (**38**) and (**39**) are enantiomers, it becomes necessaby to ascertain the absolute configuration of either (**29**) or (**30**) for fully delineating the steric course of β-lactam formation. Our preferred method for this purpose was single crystal X-ray diffraction of a suitable optically active β-lactam. However, one of the promising candidates gave crystals which proved unsuitable for X-ray diffraction studies.

As an alternative approach, DL-threonine was used as the starting material for our synthesis and (±)-(**25**), the slower moving (lower R_f on a silica gel TLC plate) isomer, was isolated. Conversion to (±)-(**29**) followed by, reaction with p-bromophenylisocyanate produced (±)-(**45**) in crystalline form that proved to be suitable for X-ray diffraction studies (Scheme VII). The crystal structure was solved by standard methods but the refinement was not complete. However, unequivocal determination of the relative configuration at the various centers of the racemic compound could be made.

The absolute configuration of (**25**) obtained from D-threonine could now be deduced from this relative configuration in racemic (**45**) because the S-configuration of the methyl carbinol group in D-threonine is carried unchanged into (**25**) and (**45**). An ORTEP drawing for (**45**) was produced which corresponded to the S-configuration at the methyl carbinol group. The configuration at the β-lactam carbons (Scheme VI) from this drawing corresponded to the stereo structures (**29**) and (**38**) not (**30**) and (**39**). Thus, although the β-lactam synthesis was conducted with racemates and X-ray diffraction studies were made on a racemic product, it was possible to establish the details of asymmetric induction during β-lactam formation.



Scheme VII



PNB = p-nitrobenzyl

Chemical Correlation Studies

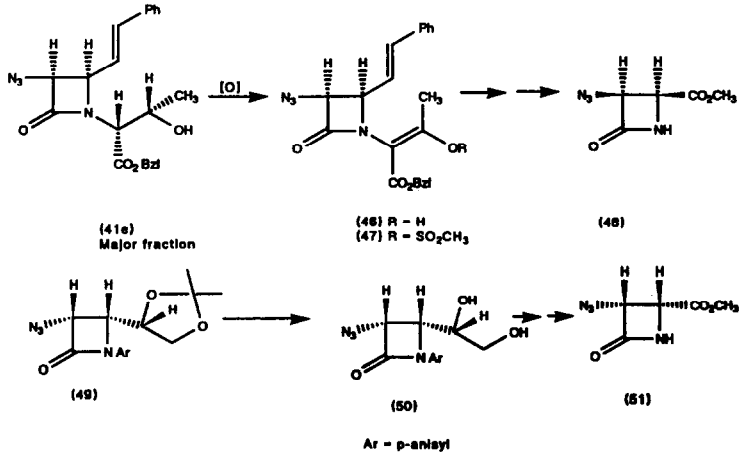
Independent work in two laboratories [16,17] has led to an enantiospecific synthesis of α-amino-β-lactams using a Schiff base derived from an optically active aldehyde and an achiral amine. Recently, we have prepared (49) of known absolute configuration based on this synthetic approach. Through a series of chemical steps (Scheme VIII) not involving the β-lactam carbons, (49) was converted into optically pure (+)-cis-(3R,4R)-3-azido-4-methoxycarbonyl-2-azetidinone of stereostructure (51). Comparison was made of the optical rotation of this compound with the compounds prepared by other synthetic approaches for purposes of chemical correlation.

The reaction of azidoacetyl chloride with the Schiff base, (43) from the t-butyldimethylsilyl ester of the benzyl ester of D-threonine gave the diastereomeric mixture of cis β-lactams (44) in the proportion of 90:10. After deprotection of the t-butyldimethylsilyl group with trifluoroacetic acid the β-lactams (41e) and (42e) were separated by silica gel chromatography (See Scheme VIII). The major product (lower R_f value) (41e) was carefully oxidized with Jones reagent to the enol (46) which was converted to the enol mesylate (47) and then oxidized (RuO_4) and esterified to optically active (-)-cis-3-azido-4-methoxycarbonyl-2-azetidinone (48)[15b].

The optical rotation of (48) was found to be equal and opposite of (51)[15b]. Thus, the absolute configuration of this α-azido-β-lactam was established as (3S, 4S). This finding validates the conclusions drawn based on the earlier X-ray diffraction studies on racemic (45).

Scheme X shows the chemical correlation involving the major product from α-azido-β-lactam synthesis when the triphenylsilyl group was used for protecting the hydroxyl group of D-threonine. The diastereoisomeric mixture of the cis β-lactams (41g) and (42g) after deprotection of the triphenylsilyl ether group was separated by column chromatography. The azido group in the major isomer (41g) was reduced with hydrogen sulfide/triethylamine to the amino functionality. Acylation with phenoxyacetyl chloride followed oy oxidative cleavage of the nitrogen substituent gave (38) which was identical in all respects to the product obtained from (41c) as described in Scheme IX. Similarly, (38) could also be obtained from a mixture of (41g) and (42g) by first reducing the azido group to (57).

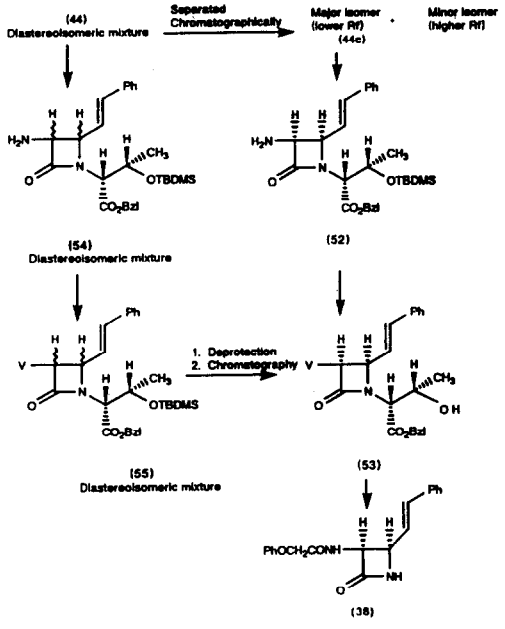
Scheme VIII



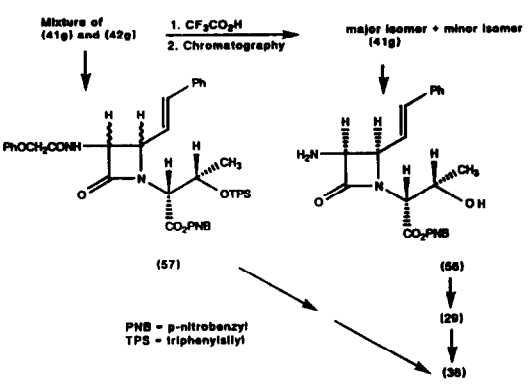
We have repeated the work of Tenneson and Belleau using azidoacetyl chloride and the Schiff base (**40**, R^1 = Me, R = TBDMS, R^2 = Bzl) derived from D-threonine. The major product (**41e**) was reduced with hydrogen sulfide to (**52**) and acylated to the amido-β-lactam (**53**). The β-lactam (**53**) was then converted to (**38**) as described in Scheme IX. An alternate route to (**38**) involved leaving the TBDMS protective group in place until after reduction of the azido group to give (**54**) and N-acylation of (**54**) to afford (**55**). The protective TBDMS group was then removed from (**55**) and the product -the major component after silica gel chromatography - gave (**38**).

Tenneson and Belleau[14] had converted their major β-lactam isomer from (**43**) to the isocephalosporin (**58**) which was found to have twice the antibiotic activity of a racemic version prepared earlier. On the basis of this biological activity Tenneson and Belleau had assumed that the absolute configuration of the β-lactam hydrogens of the major isomer isolated from (**44**) matched that of penicillin G. The correlation described here proves the correctness of this assumption.

Scheme IX



Scheme X



Conclusion

Our studies indicate that for preparing a single enantiomer of an α-amido-β-lactam, the method of choice is to use the triphenylsilyl ether of a D-or L-threonine ester for forming the Schiff base. Thus, **41g** and **42g** were obtained in about 60% yield from **40g**; these two diastereomers were formed in the ratio of 95:5. After a) desilylation of this mixture, b) removal of the N-protective group, and c) N-acylation of the α-amino-β-lactams, a mixture of α-amido-β-lactams was obtained. The trace amount of the minor isomer (**30**) in this mixture could be easily removed by silica gel chromatography and the major isomer (**29**) obtained optically pure and in high yield.

For preparing both enantiomers of β-lactams of the type 41b,c or 42b,c the method of choice is to use Schiff bases from an ester of threonine with the hydroxy group unprotected.

Several methods are known now for preparing optically active α-amino-β-hydroxy compounds including homologs of threonine. Our studies show that one enantiomer of these compounds would be enough for preparing both antipodal forms of substituted β-lactams.

If, however, the aim of a study is to establish the correlation between the absolute configuration of the starting α-amino-β-hydroxy compound and the resulting β-lactam, the racemic form of the aminoalcohol with two or more chiral centers would be adequate as the starting material. The racemic β-lactam from the reaction conducted with all racemic reagents and a racemic starting material should be converted to a crystalline derivative and submitted to single crystal X-ray diffraction studies.

EXPERIMENTAL SECTION

MATERIALS. All the chemicals used were reagent grade. The methylene chloride was distilled in the presence of phosphorous pentoxide and kept over molecular sieves. Flash chromatographic solvents were undistilled and reagent grade. Spectroscopic data were obtained using a Bruker WP/200 FT-NMR, Perkin-Elmer 1310 Infrared Spectrometer, Perkin-Elmer 1760 Fourier Transform Infrared Spectrometer, and a Biospect. mass spectrometer. Single crystal X-ray studies were performed using an Enraf-Nonius CAD 4 diffractometer. Thin layer chromatography was performed with Whatmann plates, and the spot were detected in a UV viewing chamber. Microanalyses were performed by Schwarzkop Microanalytical Laboratory, Woodside, New York.

p-Nitrobenzyl D-threonine p-toluenesulfonate. It was prepared from D-threonine (22) according to the method of Bose et al.[8]

Benzyl D-threonine p-toluenesulfonate. Benzyl D-threonine p-toluenesulfonate was synthesized from D-threonine and benzyl bromide by the method of Bose et al.[8]

Cinnamylidene N-(1-p-nitrobenzyloxycarbonyl-2-hydroxypropyl) amine 23a. p-Nitrobenzyl D-threonine p-toluenesulfonate (6.67g., 15.6 mmol) and potassium carbonate (3.25g, 23.5 mmol) were suspended in dichloromethane (100 mL) layered with water (50 mL). The mixture was shaken vigorously for 10 min and the organic layer was separated. The aqueous layer was extracted with additional dichloromethane (50 mL), the organic extracts were combined, dried (K_2CO_3), filtered and the filtrate was evaporated at room temperature under reduced pressure to yield the amino ester (3.68g, 94%) which was dissolved in anhydrous dichloromethane (30 mL). To this solution was added *trans*-cinnamaldehyde (2g, 15.1 mmol), the reaction mixture was then refluxed for 3 min and stirred at room temperature for 1h in the presence of molecular sieves. The cloudy solution thus obtained was dried (K_2CO_3), filtercd and the filtrate evaporated to give a yellow oil which was triturated with petroleum ether to obtain crude **23a**. It was crystallized from ethyl acetate/petroleum ether to yield the pure **23a** (5.5g), m.p. 98-99°C; IR($CHCl_3$) : 3100, 1750, 1625 cm^{-1}; ^{1}H-NMR($CDCl_3$)δ : 1.2 (d,J=7Hz, 3H), 2.80 (s,br, 1H), 3.85 (d,J=7Hz, 1H), 4.35 (m, 1H), 5.25 (s, 2H), 7.00 (d, 2H), 7.2-7.6 (m, 7H), 8.20 (d,J=8Hz, 3H) ; CIMS (CH_4 reagent gas) : m/z 369 $(M+1)^+$.

Cis-1-(1 -p-Nitrobenzyloxycarbonyl-2 -hydroxypropyl)-3-(N-α -methyl-β -carbomethoxyvinyl)-4-styryl-azetidin-2-one. 25a and 26a. The potassium salt of N-(α -methyl-b-carbomethoxyvinyl) glycine **24**[12] (3.16g, 15 mmol) and triethylamine (2.75 mL, 20 mmol) were suspended in dry tetrahydrofuran (200 mL) and stirred at room temperarture for 30 min under nitrogen atmosphere. The contents were cooled to -20°C and ethyl chloroformate (1.42 mL, 15 mmol) was added dropwise and stirring continued for 45 min. A solution of imine **23a** (3.68g, 10 mmol) in tetrahydrofuran (60 mL) was then added dropwise and stirring continued for additional 2h at -20°C and allowed to come to room temperature overnight. The solvent was evaporated and the residue was redissolved in dichloromethane (100 mL), washed with water and brine, dried (Na_2S0_4), filtered and the filtrate evaporated to afford 4.12g of diastereomeric mixture of β -lactams **25a** and **26a** as a fluffy solid. The column chromatography on silica gel using chloroform-ethyl acetate (10:1) as eluent yielded a mixture (1:1) of pure diastereomeric β -lactams **25a** and **26a** (3.19g, 61%), m.p. 148-150°C; IR (Nujol): 3350, 1744, 1720, 1640, 1610 cm^{-1}; ^{1}H-NMR($CDCl_3$)δ: 1.28 (d,J=6.5Hz, 3H), 1.90 (s, 3H), 3.6 (s, 3H), 3.9 (m, 1H), 4.5 (m, 2H), 4.8 (s, 1H), 5.0 (m, 1H), 5.22 (m, 2H), 6.15 (m, 1H), 6.5 (d,J=15Hz, 1H), 7.2-7.5 (m, 7H), 8.1 (m, 1H), 9.1 (m, 1H); CIMS (CH_4 reagent gas): m/e 524 $(M+1)^+$.

The β -lactams reported in Table I were prepared by this method.

Benzyl D-threonine triphenylsilyl ether. To the benzyl D-threonine p-toluenesulfonate (5.75g, 15.13 mmol) in dry dimethylformamide (90 mL) was added imidazole (4.11g, 60.5 mmol) and triphenylsilyl chloride (4.46g, 15.11 mmol). The solution was stirred at room temperature overnight and then partitioned between ether (250 mL) and water (200 mL). The ether extract was successively washed with water (4 x 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and the filtrate evaporated. The crude silyl ether when filtered through Florisil using ethyl acetate-hexanes (1:4) as eluent, afforded a nearly quantitative yield of benzyl D-threonine triphenylsilyl ether as an oil (6.6g, 97.05%), IR(neat): 3340, 3100, 1725, 1680, 1620, 1110, 735, 705, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ: 1.22 (d,J=6Hz, 3H), 2.21 (bs, 2H), 3.4 (bd,J=3Hz), 4.55 (dd,J=6Hz and 3Hz, 1H), 4.9 (dd,J=13.5Hz, 2H), 7.15-8.2 (m, 20H).

Cinnamylidene N-(1′-benzyloxycarbonyl-2′-triphenylsilyloxypropyl) amine 40f. To a solution of benzyl D-threonine triphenylsilyl ether (4.67g, 10 mmol) in dry dichloromethane (70 mL) was added cinnamaldehyde (1.32g, 10 mmol). The solution was warmed to 40°C for 5 min and then molecular sieves were added and reactant stirred for 10h at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was filtered and the filtrate evaporated to give the Schiff base **40f** as an oil which was used as such without purification. (5.32g, 91%), IR (neat): 1725, 1670, 1625, 1580, 1420, 1110, 735, 705, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ: 1.21 (d,J=6.2Hz, 3H), 3.95 (d,J=6.5Hz, 1H), 5.45 (m, 1H), 6.15 (dd,J=13.5Hz, 2H), 6.89 (m, 2H), 7.26-8.15 (m, 26H).

Cis-1-(1′-Benzyloxycarbonyl-2′-triphenylsilyloxypropyl)-3-azido-4-styrylazetidin-2-one 41f and 42f. To a suspension of Schiff base **40f** (3.5g, 6.02 mmol), triethylamine (2.5 mL, 18 mmol) and potassium azido acetate (1.82g, 12.05 mmol) in dry dichloromethane (180 mL) at -20°C under nitrogen atmosphere, was added dropwise ethyl chloroformate (0.95g, 9.0 mmol) in dichloromethane (20 mL) over a period of 1h. The contents were stirred at this temperature for 4h and left overnight at room temperature. The reaction mixture was

washed with water (3x50 mL), brine and dried (Na_2SO_4). Evaporation of the solvent afforded an oil which was chromatographed over silica gel using ethyl acetate-hexanes (1:4) as eluent to give a diastereomeric mixture of pure β-lactams **41f** and **42f** (2.5g, 64%). These diastereomers appeared as one single spot on TLC. IR(neat): 2045, 1760, 1730, 1110, 730, 705, 690 cm^{-1}; ^{1}H-NMR($CDCl_3$)δ: 1.21 (d,J=6.2Hz, 3H), 4.42 (d,J=3.5Hz, 1H), 4.5 (d,J=4.5Hz, 1H), 4.65 (m, 1H), 4.91 (d,J=5.5Hz, 1H), 5.11 (d,J=13.5Hz, 1H), 5.15 (bs, 1H), 6.35 (m, 2H), 7.4-7.65 (m, 25H).

Cis-1-(1′-Benzyloxycarbonyl-2′-hydroxypropyl)-3-azido-4-styryl-azetidin-2-one 41c, 42c. Trifluoro acetic acid (6 mL) was added to a stirred and cooled (0°C) solution of a mixture of β-lactams **41f** and **42f** (1.63g) in tetrahydrofuran (3 mL) and water (3 mL). The reaction mixture was stirred at 0°C for 1h and diluted with ethyl acetate (20 mL) The organic phase was washed with 5% sodium bicarbonate solution (2x30 mL), brine (50 mL) and dried (Na_2SO_4). The evaporation of the solvent resulted in a crude diastereomeric mixture of β-lactams **41f** and **42f** in the ratio 95:5 as inferred from ^{1}H-NMR spectrum of the crude sample. The crude mixture was passed through a silica gel column and eluted with ethyl acetate- hexanes mixture (1:2) and both β-lactams **41f** and **42f** were separated in pure form (total yield 0.81g, 86%).

The faster moving minor isomer **42c** was obtained as oil, R_f 0.25, IR(neat): 3345, 2100, 1740, 1720, 1640, 740, 690 cm; ^{1}H-NMR ($CDCl_3$)δ: 1.31 (d,J=6.29Hz, 3H), 3.83(s, 1H), 4.47(m, 3H), 4.98(d,J=4.9Hz, 1H), 5.24(s, 2H), 6.09(dd,J=5.9Hz and 9.5Hz, 1H), 6.7(d,J=15.92 Hz, 1H), 7.37(m, 10H); ^{13}C-NMR ($CDCl_3$)δ: 20.40, 60.63, 64.00, 66.75, 66.77, 120.88, 126.88, 128.21, 128.60, 128.70, 128.81, 128.92, 135.05, 135.33, 138.62, 135.46, 167.96; CIMS (CH_4 reagent gas): m/z 407 $(M+1)^+$.

The slower moving major isomer **41c** was crystallized from ether/hexane, m.p. 82-84°C, R_f 0.15, rot. $[\alpha]_D^{26}$ -85.5° (MeOH); IR (KBr): 3340, 2100, 1740, 1720, 1640, 745, 685 cm^{-1}; ^{1}H-NMR($CDCl_3$)δ: 1.25 (d,J=6.47Hz, 3H), 3.53(d,J=9.45Hz, exchangable with D_2O, 1H), 3.97(d,J=4.3Hz, 1H), 4.41(bm, 1H), 4.55 (dd,J=4.9Hz and 9.45Hz, 1H), 4.9(d,J=4.92Hz, 1H), 5.15(s, 2H), 6.25(dd,J=15.91Hz and 9.52Hz, 1H), 6.67 (d,J=15.96Hz, 1H), 7.3(m, 10H); ^{13}C-NMR($CDCl_3$)δ: 20.39, 62.11, 63.45, 67.20, 67.69, 122.51, 126.97, 128.38, 128.62, 128.70, 128.81, 135.05, 135.50, 138.01, 165.51, 168.15: CIMS (CH_4 reagent gas): m/z 407 $(M+1)^+$. Anal. Calc. for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.45; N, 13.78. Found : C, 65.37; H, 5.21; N, 13.94.

Cis-1-(1′-p-Nitrobenzyloxycarbonyl-2′-hydroxypropyl)-3-phenoxyacetamido-4-styryl-azetidin-2-one 29 and 30. These were prepared by the method described earlier[8].

Cis-3-Phenoxyacetamido-4-styryl-azetidin-2-one. 38 and 39. To a solution of the slow moving β-lactam **29** (1g, 1.9 mmol) in dry acetone (10 mL) was added dropwise Jones reagent (3.9 mL, 3.6 equivalents of CrO_3). After stirring the reaction contents for 3h at room temperature, acetone was removed under reduced pressure and the residue was taken in ethyl acetate. The organic layer was washed with 5% sodium bicarbonate solution, brine and dried (Na_2SO_4). It was filtered and concentrated to give an oil which upon chromatographic purification [silica gel, chloroform-ethyl acetate (10:3)] yielded N-unsubstituted β-lactam **38** as a white solid (190 mg, 29%), m.p. 183-185°C (CH_2Cl_2-pet.ether), IR (KBr): 3250, 3200, 1770, 1715, 1665 cm^{-1}; ^{1}H-NMR($CDCl_3$-DMSO-d_6)δ: 4.52(s,1H, dd hidden, 1H), 5.3(d,J=6Hz, 1H), 6.2(dd,J=7Hz and 16Hz, 1H), 6.7(d,J=16Hz, 1H), 6.7-7.4 (m, 10H), 8.47(s, 1H), 8.85(d,J=9Hz, 1H); FAB-HRMS m/z 322.1324 (M^+); rot: $[\alpha]_D^{21}$ + 122.5° (c=3.2x10^{-5}, trifluoroethanol); circular dichroism: $[\theta]_{255}$ =+3.7x10^3, $[\theta]_{217}$ =-4.5x10^3.

Using similar reaction conditions the faster moving β-lactam **30** was oxidized to the N-unsubstituted β-lactam **39** in 25% yield, m.p.183-184°C; IR(KBr): 3260, 3200, 1770, 1720, 1670 cm^{-1} ; ^{1}H-NMR ($CDCl_3$-DMSO-d_6)δ: 4.5(s, 2H, dd hidden, 1H), 5.28(d,J=6Hz, 1H), 6.2(dd,J=7Hz and 16Hz, 1H), 6.68(d,J=16Hz, 1H), 6.7-7.4(m, 10H), 8.46(s, 1H), 8.83(d, J=9Hz, 1H); FAB-HRMS: m/z 322.1324(M^+); Calc.for $C_{19}H_{18}N_2O_3$ m/z 322.1317; rot: $[\alpha]_D^{21}$ -119.4°(C=3.2x10^{-5}, trifluoroethenol); circular dichromism: $[\theta]_{255}$ =-4.5x10^3, $[\theta]_{218}$ =+4.8x10^3.

Cis-1-(1′-Benzyloxycarbonyl-2′-hydroxypropyl)-3-phenoxyacetamido-4-styryl-azetidin-2-one (53). Hydrogen sulfide gas was bubbled through a stirred solution of β-lactam **41e** (2.03g, 5 mmol) in anhydrous dichloromethane (50 mL) containing triethylamine (1.5g, 15 mmol) at 0°C for 30 min. After completion of the reaction (TLC) the solvent was evaporated and the residue dissolved in dry benzene and filtered. The filtrate was evaporated and the crude 3-amino-β-lactam **52** so obtained was acylated with phenoxyacetyl chloride (0.95g, 5.5 mmol) in dry methylene chloride using triethylamine as base at 0°C. The reaction mixture was stirred at room temperature for 3h and thereafter washed with 5% aqueous sodium bicarbonate solution (2x20 mL), brine (25 mL) and dried. Evaporation of the solvent under vacuum yielded the crude product (2.8g) which on chromatographic purification using silica gel and eluting with ethyl acetate-pet. ether (1:1) yielded pure **53** (1.74, 68%), m.p. 131-132°C; IR(neat): 3250-3150, 1750, 1740, 1655, 1520, 1355, 1115, 730 and 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ: 1.41(d, J=6.2Hz, 3H), 3.92(d, J=3.0Hz, 1H), 4.45(s, 2H), 4.55(m, 2H), 5.19 (s, 2H) 5.30(m, 1H) 6.1(dd, J=9.4 and 16.0Hz, 1H), 6.6-7.35(m, 15H), 7.55(d, J=9.4Hz, 1H), 8.22(d, J=9.0Hz, 1H).

Cis-1-(1′-p-Nitrobenzyloxycarbonyl-2′-triphenylsilyloxypropyl)-3-phenoxyacetamido-4-styryl-azetidin-2-one 57. To a stirred solution of mixture of β-lactams **41g** and **42g** (3.5 g, 5 mmol) in dry dichloromethane (50 mL) containing triethylamine (1.5 g, 15 mmol) was bubbled hydrogen sulfide gas at 0°C for 30 min. The progress of the reaction was checked by TLC and worked up as reported for **53**. The crude 3-amino-β-lactam was further acylated using phenoxyacetyl chloride (0.95 g, 5.5 mmol) in dry dichloromethane using triethylamine as the base to yield crude acylated β-lactam which on passing through silica gel column gave a diastereomeric mixture of β-lactam **57** (3.1 g, 74 %) as a thick oil. The two diastereomeric compounds appeared as very closely spaced spots on TLC, IR(neat): 3350-3190, 2950,2040, 1755, 1738, 1640, 1620, 1110, 730, 705, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ: 1.24(d, J=6.0Hz, 3H), 4.36(s, 2H), 4.45(d, J=13.7Hz, 1H), 4.55(dd, J=5.3Hz and 9Hz, 1H), 4.65(m, 1H), 4.91(dd, J=5.4Hz and 9.0Hz, 1H), 5.11(d, J=13.7Hz, 1H), 5.17(bs, 1H), 6.42(m, 2H), 6.75-8.15(m, 31H).

The solution of this mixture of diastereomers (1.7g, 2 mmol) in tetrahydrofuran (3 mL) and water (3 mL) at 0°C was treated with trifluoroacetic acid (9 mL,) and stirred for 1h. After usual work up the two diamsteromeric 3-amido-β-lactams **41g**(R^1=H) and **42g**(R^1=H) were obtained (major: slow moving and minor: fast moving) as an oil in 95:5 ratio as derived from ^{1}H-NMR spectrum of the crude sample. The two diastereomers were separated by column chromatography using silica gel as the adsorbant and chloroform-ethyl acetate (1:1) mixture as the eluent. Both the major and the minor 3-amido-β-lactams gave spectral data comparable to β-lactams **29** and **30** respectively as reported earlier. The major amido β-lactam was oxidised by Jones reagent to the corresponding N-unsubstituted β-lactam **38**.

Cis-1-(1′-Benzyloxycarbonyl-2′-tert.butyldimethylsilyloxypropyl)-3-phenoxyacetamido-4-styryl-azetidin-2-one 55. Hydrogen sulfide gas was bubbled for 30 min through a solution of the mixture of β-lactams **44** (2.6g, 5.5 mmol) in dry methylene chloride (50 ml) containing triethylamine (2 mL, 15 mmol at 0°C. After the reaction was complete (TLC), it was worked up as reported for **52**. The crude 3-amino-β-lactam mixture **54** was further acylated using phenoxyacetyl chloride (0.95g 5.5 mmol) in dry dichloromethane using triethylamine as base at 0°C to yield the diastereomeric mixture **55** as a thick oil (2.2 g, 72 %) which was used as such for the next reaction.

(3S,4S)-(-)-Cis-3-Azido-4-carbomethoxy-azetidin-2-one 48. This was prepared from **41e** as described by Bose et al.[15b]

(3R,4R)-(+)-Cis-3-Azido-4-carbomethoxy-azetidin-2-one 51. This was obtained from **49** as described by Bose et al.[15b]

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