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TOTAL SYNTHESIS OF THIENAMYCIN: A NEW APPROACH FROM ASPARTIC ACID

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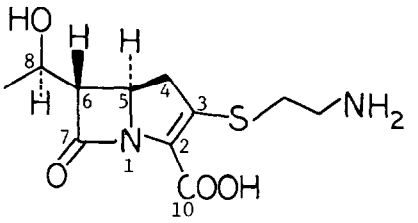
Summary: *A practical stereospecific synthesis of thienamycin 1 has been achieved. Key steps include a lead tetraacetate oxidative decarboxylation and subsequent insertion of a four carbon diazo containing unit into a 4-acetoxy-2-azetidinone.*

Recently, Salzmann *et al.*[1] have reported a synthesis of thienamycin (1) in which the chirality at C_5 was derived from L-aspartic acid (2).



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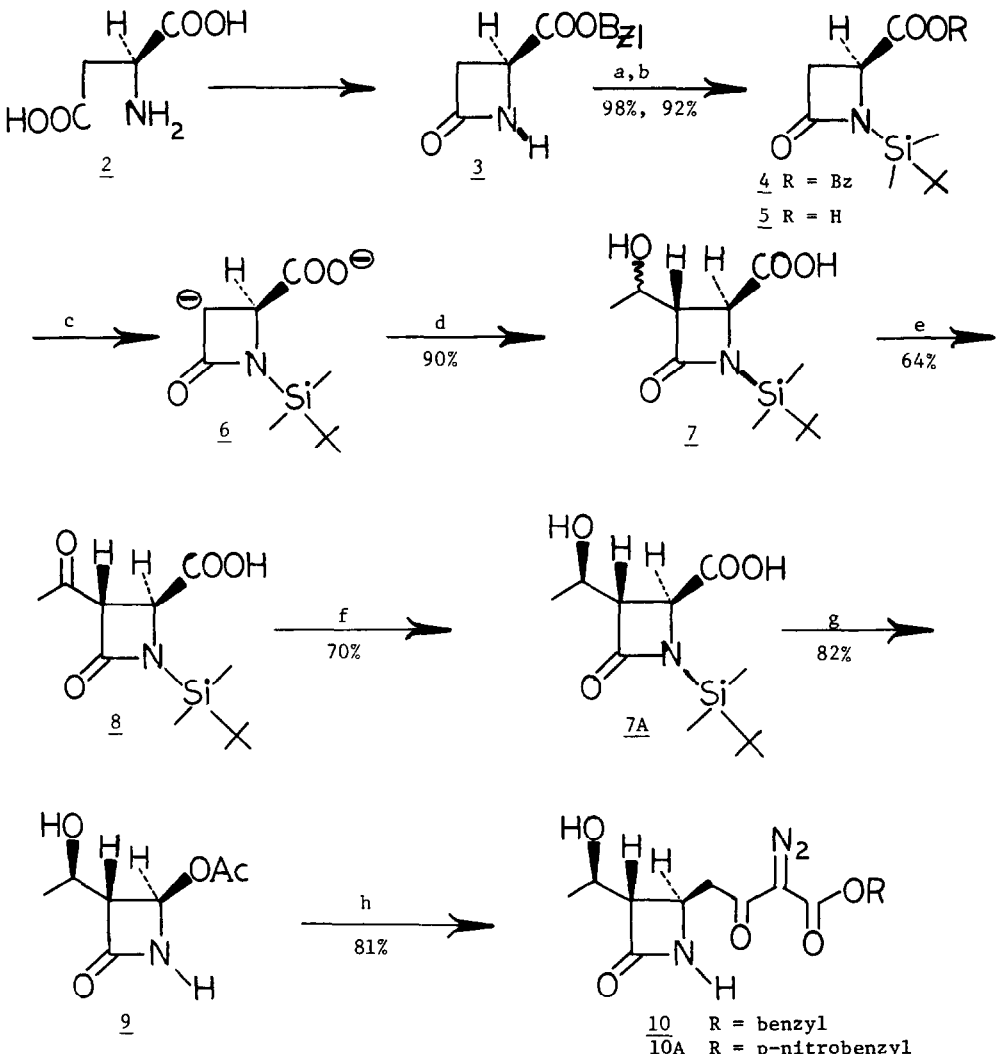
Their route entailed the formation of a chiral azetidinone benzyl ester (3) which was further elaborated to give the diazoester 10A.

In order to avoid breaking any bonds to C_5 and to maintain the original chiral center, it was necessary to introduce C_3 and then C_2-C_{10} (see structure 1) via an elaborate and somewhat lengthy series of reactions. We wish to report a simple, more direct synthesis starting from the same azetidinone 3.

Our approach (see Scheme I) involves the elaboration of the hydroxyethyl side chain[2] on the dianion 6 followed by conversion of the carboxyl group into a useable leaving group (acetoxy) by oxidative decarboxylation with lead tetraacetate[3]. The introduction at C_5 (carbapenem numbering) of a four carbon[4,5,6] diazo-containing unit in a trans-fashion leads to the properly functionalized azetidinone (10) ready for cyclization[7] and conversion to thienamycin (1)[1,8]. Thus, the original chiral center from aspartic acid is used in the dianion 6 to control the new chirality at the adjacent carbon (C_6) by subsequent formation of the thermodynamically favored trans-keto-acid (8). The stereospecific reduction[5] of the ketone yields the desired 5S,6S,8R-hydroxy acid (7A). The bond to C_5 can now be broken with a new bond forming in a trans-fashion to reestablish the necessary stereochemistry.

SCHEME I[10,11]



a) t-butyldimethylsilyl chloride, Et_3N;
b) Pd/C, H_2;
c) lithium diisopropylamide, 0°C;
d) CH_3CHO, 0°C, then citric acid;
e) $Na_2Cr_2O_7$, H_2SO_4, H_2O
f) diisopropylamine·borane, magnesium trifluoroacetate;
g) $Pb(OAc)_4$, DMF-HOAc;
h) $H_2C = C(OSiMe_3)-C(N_2)-CO_2-CH_2Ph$, ZnI_2.

Thus, the chiral benzyl ester[1] (3) was first protected as its N-t-butyldimethylsilyl derivative (4) and then debenzylated under catalytic conditions to yield the crystalline carboxylic acid 5 ($[\alpha]_D$ = -74°, c = 1, $CHCl_3$). Treatment of acid 5 with two equivalents of lithium diisopropylamide at 0°C gave the dianion 6 which was readily alkylated with acetaldehyde. An acidic work-up provided an epimeric mixture of hydroxy acids (7). Oxidation of these epimeric alcohols (7) gave the keto-acid 8 as the sole product. Subsequent stereospecific reduction using the method of Karady[5] (diisopropylamine-borane, magnesium trifluoroacetate) gave the crystalline 5S,6S,8R-hydroxy acid 7A ($[\alpha]_D$ = -53°, c = 1, $CHCl_3$).

The oxidative decarboxylation of the free hydroxy acid (7A) proceeded smoothly to introduce the acetoxy leaving group at C_5 exclusively from the side opposite the hydroxyethyl group at C_6. By running this reaction at 70°C the silyl protecting group was also removed to give the enantiomerically pure 5R,6R,8R-hydroxy acetate (9).

The Lewis acid (ZnI_2) mediated reaction[6] of acetate 9 with the silyl enolether of benzyl diazoacetoacetate[9] resulted in replacement of the C_5 acetoxy group to give specifically the 5R,6S,8R-diazohydroxyketoester 10 which has been cyclized with rhodium (II) acetate and converted to thienamycin (1)[5].

This approach significantly shortens the "up-to-now" best published chiral synthesis.

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References and Notes:

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8. Melillo, D.G., Shinkai, I., Liu, T., Ryan, K., Sletzinger, M., Tetrahedron Lett. 1980, 21, 2783.
9. This synthon was prepared from benzyl diazoacetoacetate as described in reference 5.
10. a) The hydroxyethyl stereochemistry was assigned by 60 MHz ^{1}H NMR (cf. ref. 2) specifically the CH_3-C(OH)H- doublet. The 8R-diastereomer, in all cases, appeared upfield of the 8S-diastereomer in d_6 acetone.
    b) The cis/trans relationship of substituents on the β-lactam (C_{5-6}) was determined by J_{5-6} in d_6 acetone as in reference 2. The trans substituted systems show J_{5-6} in a range of 1.5-2.9 Hz while the cis substituted systems show J_{5-6} in a range of 5-6 Hz.
11. Selected data:
    4: 60 MHz ^{1}H NMR ($CDCl_3$) δ 0.1, 3H (S); 0.25, 3H (S); 0.95, 9H (S); 3.2, 2H (M, ABX); 4.05, 1H (M, ABX); 5.2, 2H (S); 7.35, 5H (S).
    5: 60 MHz ^{1}H NMR ($CDCl_3$) δ 0.2, 3H (S); 0.3, 3H (S); 0.95, 9H (S); 3.3, 2H (M, ABX); 4.1, 1H (M, ABX).
    7: 200 MHz ^{1}H NMR (acetone d_6); 8R diastereomer (7A) δ 0.14, 3H (S); 0.28, 3H (S); 0.97, 9H (S); 1.27, 3H (d, J=6.4 Hz); 3.24, 1H (d of d, J=4.5, 2.8 Hz); 4.14, 1H (q of d, J=6.4, 4.5 Hz); 4.19, 1H (d, J=2.8 Hz).
    8S diastereomer δ 0.14, 3H (S); 0.28, 3H (S); 0.97, 9H (S); 1.33, 3H (d, J=6.4 Hz); 3.32, 1H (d of d, J=3.9, 2.9 Hz); 4.14, 1H (q of d, J=6.4, 3.9 Hz); 4.10, 1H (d, J=2.9 Hz).
    8: 60 MHz ^{1}H NMR ($CDCl_3$) δ 0.33, 6H (S); 0.95, 9H (S); 2.33, 3H (S); 4.37, 1H (d, J=2.5 Hz); 4.50, 1H (d, J=2.5 Hz); 6.83, 1H (broad).
    9: 60 MHz ^{1}H NMR ($CDCl_3$) δ 1.35, 3H (d, J=6 Hz); 2.1, 3H (S); 3.2, 1H (broad d, J=6 Hz); 3.4, 1H (broad S-OH); 4.2, 1H (quintet, J=6 Hz); 5.85, 1H (broad S); 7.0, 1H (broad S-NH).

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