STEREOSPECIFIC SYNTHESIS OF RACEMIC INTERMEDIATES OF THE PENEMS AND THE CARBAPENEMS FROM TRANS-CROTONIC ACID

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Abstract--- Stereocontrolled syntheses of two (±)-3-(1-t-butyldimethylsilyloxyethyl)-4-acetoxy-2-azetidinones (cis-10 and trans-10), which are key intermediates for the penems and the carbapenems, from trans-crotonic acid are reported.

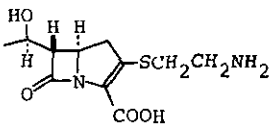
Since the discovery of thienamycin, various analogues of 1-carbapenem antibiotics have been found,[1] and fascinated many organic chemists to synthesize these compounds. Recently, it has become recognized that [3R-[3α(R*),4β]]-3-(1-hydroxyethyl)-4-acetoxy-2-azetidinone is a key intermediate for the synthesis of the novel carbapenem nucleus.[2] In our previous paper,[3] we described the stereoselective synthesis of chiral cis-acetylazetidinone (cis-10) via the bicyclic lactone (7), and also the synthesis of trans-10 via the hydroxyazetidinone-4-carboxylic acid (15) as a minor by-product from D-allo-threonine. This synthetic route could not avoid passing through the step of decarboxylation resulting in the loss of stereospecificity. In this paper, we wish to report both stereospecific synthesis of racemic cis-10 via 7 and stereoselective synthesis of trans-10 through the same intermediate (hydroxydicarboxylic acid, 2) obtained from trans-crotonic acid.

The racemic compound (1) obtained in several steps[4] via (±)-erythro-2-bromo-3-acetoxybutyryl chloride from crotonic acid was saponified with 3 equiv of 1N NaOH in pyridine to give a hydroxydicarboxylic acid (2) as a crystalline solid[5] in 61% yield. Lactonization of 2 with conc HCl in THF gave a bicyclic lactone-carboxylic acid (3), mp 162-165°C, quantitatively, which was converted to the corresponding methyl ester (4) with diazomethane. Treatment of 4 with $NaBH_4$ in MeOH at -50°C for 2 hr gave a 1:3 mixture of diastereomeric hemiacetals (5, mp 113-117°C) as a crystalline mixture (accompanied by 11.4% recovery of 4) in 59% yield, which was further treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF-H_2O (4:1) at reflux temperature for 2 hr to give a decarbomethoxylated

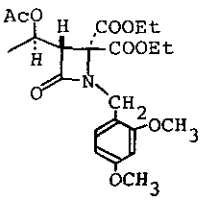
hemiacetal (6) as a single isomer in 96% yield. The relative configuration of 6 was determined as being depicted in the scheme by the data of ^{1}H NMR of 6.[6] There are no couplings either between the C-1 bridge head proton (Ha) and the C-2 hemiacetal constructing proton (Hb) or between that of the C-5 bridge head (Hd) and the C-4 proton (Hc). This fact reveals that each of the dihedral angles of the two pairs is near 90°, and the relative configuration depicted in the scheme is correct. Treatment of 6 with Jones reagent in acetone gave a lactone (7) in 62% yield.

On the other hand, the base-catalized decarboxylation of 3 to 7 was disappointing, and another stereospecific method was attempted. Treatment of 3 with oxalyl chloride in THF at reflux temperature gave a corresponding acid chloride (8), quantitatively. Treatment of 8 with t-butyl hydroperoxide and pyridine in CH_2Cl_2 at 0°C gave a peroxycarboxylate,[7] and then without purification a solution of 9 in ethyl phenylacetate was heated at 140°C for 10 min under nitrogen to give lactone 7 (31% yield from 3). The obtained 7 through the two different routes was the same in all respects, and converted to cis-10 according to the previous reported method.[3] Thus cis-10 was obtained stereospecifically from trans-crotonic acid. After trimethylsilylation of cis-10, the reaction with trimethylsilyl enol ether of benzyl acetate according to Barrett's method[2a] gave a trans-benzyl ester (11)[3] in 58% yield, which was also an intermediate to thienamycin. Therefore, this fact reveals that cis-10 is also a key intermediate for the synthesis of the carbapenems.

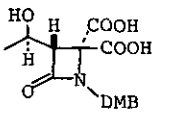
Instead of cis-10, we devised a stereoselective method to obtain trans isomer from the common intermediate 2. Treatment of hydroxydicarboxylic acid (2) with 2 equiv of oxalyl chloride in THF, and successive treatment of acid chloride with excess t-butanol and pyridine in THF at reflux temperature gave a mixture of trans-12, cis-12 (mp 125-127°C), and 13 in 40, 5, and 3% yields, respectively. Saponification of trans-12 in THF-H_2O (2:1) by use of DBU as a base gave 14 in 94% yield. Treatment of 14 with CF_3COOH in CH_2Cl_2 at room temperature gave a corresponding carboxylic acid (15, 77% yield) characterized as its methyl ester, and 15 had already been converted to trans-10.[3] Thus trans-10, which had been a minor product in the previous report,[3] was obtained stereoselectively from trans-crotonic acid, and it had already been correlated to thienamycin.[2c] These compounds (cis-10 and trans-10) are key intermediates for the syntheses of the penems[8] and the carbapenems.[1,2] As a chiral starting material, the use of



thienamycin



1



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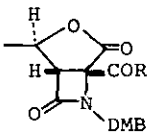


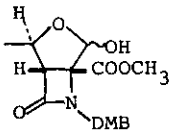
3. R=OH

4. R=OCH_3

8. R=Cl

9. R=$OOBu^t$

13. R=OBu^t



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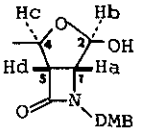

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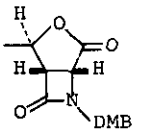

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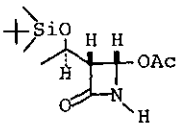
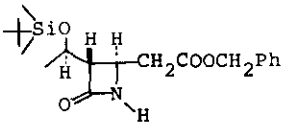


cis-10



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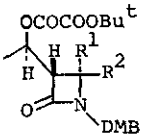
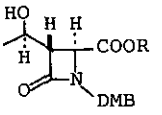


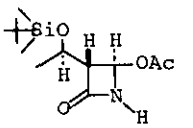
trans-12. R^1=H, R^2=$COOBu^t$

cis-12. R^1=$COOBu^t$, R^2=H



14. R=Bu^t

15. R=H



trans-10

(2R,3R)-2-bromo-3-acetoxybutyryl chloride obtained from D-allo-threonine instead of (±)-erythro-2-bromo-3-acetoxybutyryl chloride obtained from trans-crotonic acid gives stereo-specifically or -selectively chiral intermediates (cis-10 or trans-10), and consequently D-allo-threonine is a useful synthetic source for the chiral thienamycin skeleton.

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3. M. Shiozaki, N. Ishida, T. Hiraoka, and H. Yanagisawa, Tetrahedron Letters, 1981, 22, 5205.
4. M. Shiozaki and T. Hiraoka, Ibid., 1980, 21, 4473.
5. During the measurement of the melting point of 2, lactonization occurred at 124-125°C, and then melting at 157-166°C.
6. 60 MHz ^{1}H NMR of 6, ($CDCl_3$) δ 1.27 (3H, d, J=6.5 Hz), 3.47 (1H, d, J=4 Hz, Hd), 3.76 (3H, s), 3.78 (3H, s), 3.98 (1H, d, J=4 Hz, Ha), 4.08, 4.38 (2H, AB-q, J=14.5 Hz, NCH_2), 4.49 (1H, q, J=6.5 Hz, Hc), 4.69 (1H, d, J=3 Hz, OH, this proton peak disappeared on addition of D_2O, and coupled with Hb), 5.21 (1H, d, J=3 Hz, this proton peak changed to a singlet on addition of D_2O, Hb), 6.33 (1H, dd, J=2, 9 Hz), 6.38 (1H, J=2 Hz), 7.03 (1H, d, J=9 Hz). There is no coupling either between Ha and Hb, or between Hc and Hd.
7. H. Langhals and C. Ruchardt, Chem. Ber., 1975, 108, 2156.
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