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STEREO-CONTROLLED SYNTHESIS OF INTERMEDIATES OF (±)-THIENAMYCIN

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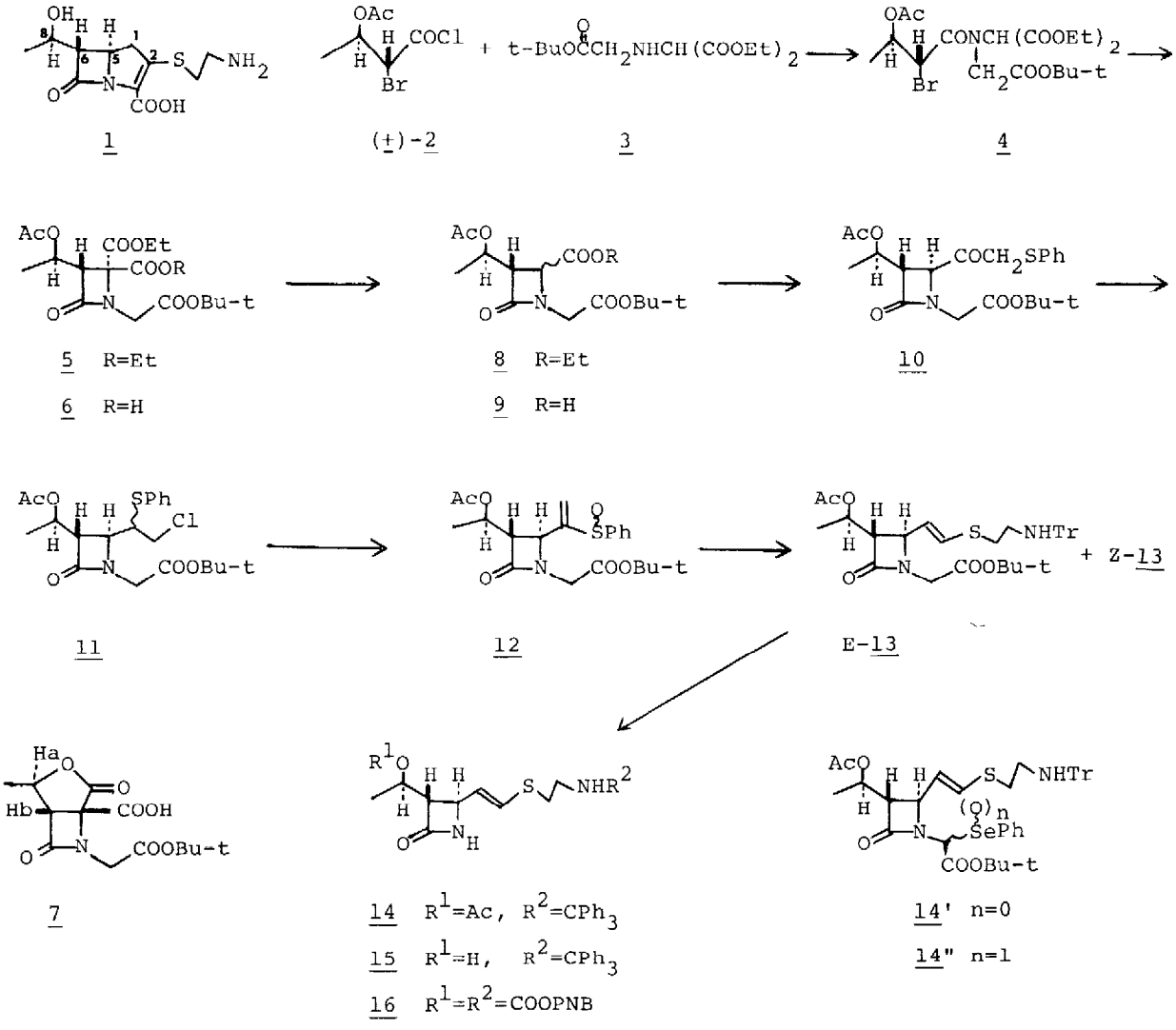
Summary: Stereo-controlled synthesis of (±)-thienamycin intermediates which have the correct relative configurations at three chiral centers is reported.

Thienamycin (1)[1] is a novel β-lactam antibiotic isolated from Streptomyces cattleya and exhibits broad antibiotic activity. The total synthesis of (±)-thienamycin has been reported.[2] We here wish to report a stereo-controlled establishments of three chiral centers in succession leading to the synthesis of (±)-thienamycin intermediates.

We adopted the method reported by Sheehan et al[3] for the formation of a β-lactam ring as a key step. The acid chloride (2) obtained from the corresponding (+)-erythro carboxylic acid[4] was treated with the lithium salt of amine (3) in THF at -78° for 1h and at 20° for 20h to give 4. The amide (4) cyclized to the β-lactam compound (5) on treatment with DBN in benzene at 80° for 1h. This cyclization proceeded via a complete S_N2 mechanism. The relative configuration of 5 was confirmed as the desired 6SR, 8RS[5] from ^1H NMR spectroscopic data of the lactone (7), mp. 152.5-154.5°C, which was converted from 5 on successive treatment with 3 eq of 1N-aq NaOH-pyridine (2:1) at 20° and conc HCl. The dihedral angle between Ha on the lactone ring and bridge head Hb is approximately 100°, and that between the methyl group on the lactone ring and Hb is nearly 10° when measured by using a Dreiding molecular model for the lactone 7 with desired stereochemistry. The observed coupling constant (J_{HaHb}=1.5 Hz) supports the relative configuration of 7 as being correct. The hydrolysis of 5 with 1 eq of 1N-aq NaOH-pyridine (2:1) at 0° gave the monoacid (6, mp 121-123°, 50.5% yield from 3). Since the saponification would occur at the less hindered side, the C-4 carboxy group of 6 should be trans to the C-3 α-acetoxyethyl group. This was confirmed from another experiment.[6] Decarboxylation of 6 with 1 eq of pyridine at 140-150° for 1h gave a mixture of cis and trans isomers (1:1) in 71% yield. Saponification of the mixture of cis-8 and trans-8 (1:1) with 1 eq of 1N-aq NaOH-pyridine (2:1) at 0° for 18h and then 20° for 6h gave a mixture of carboxylic acids (9, cis:trans=3:4) in 77% yield, and recovered cis-8, mp 79-81°, in 12% yield. The mixture of cis-9 and trans-9 (3:4) was treated with oxalyl chloride in THF at 60° for 1h to give a mixture of acid chlorides which was converted to the corresponding diazoketones with excess diazomethane and these



diazoketones were further transformed to chloromethyl ketones with HCl in THF at 0° for 5 min, which gave a mixture of C-4 phenylthiomethyl ketones (cis:trans= 3:4)[7] on treatment with thiophenol and Et_3N at 20° in THF for 15h. Equilibration of the cis and trans mixture of phenylthiomethyl ketones with 1.1 eq of DBU in DMF at 25° for 1h[8] formed trans isomer (10),[9] mp 91.5-92.5°, (54.4% yield from 9). This compound (10) has the same relative configurations at three chiral centers of thienamycin (1).

Reduction of the ketone (10) with $NaBH_4$ in EtOH at 0° for 20 min and chlorination of the epimeric mixture of the resulting alcohols with $SOCl_2$ in THF at 20° for 10h yielded a mixture of diastereomeric sulfides (11, 1:2) which was

obtained from the double migration of a chlorine atom and phenylthio group via the intermediate of episulfonium chloride.[10] Oxidation of the sulfide (11) with m-chloroperbenzoic acid in $CHCl_3$ at 0° for 30 min and elimination of hydrogen chloride with DBU at 20° for 1h afforded a mixture of diastereomeric vinyl sulfoxides (12). Treatment of 12 with N-trityl cysteamine and DBU in benzene at 0° for 5 min and quick column chromatography on silica gel gave four racemic mixtures which were refluxed in toluene in the presence of Na_2CO_3 for 1h to give a mixture of vinyl thioether (13, E:Z=2:1). 13 was separated by silica gel chromatography to give E-13[11] (30% yield from 10) as a foam, and Z-13 (15% from 10) as a foam. Treatment of E-13 with 2.3 eq of $LiN(SiMe_3)_2$ in THF at -78° and successive addition of 2.8 eq of benzeneseleneninyl chloride[12], and quenching with acetic acid and water gave the starting E-13 (12.5% recovery), 14[13] (33% yield), and 14' (11% yield), which was separable on a preparative silica gel plate. The desired 14" was not formed. A potentially useful thienamycin intermediate 14 was further converted into 16 as follows. Deacetylation of 14 with 0.1N-aq NaOH-pyridine (1:1) at 20° for 15h gave the alcohol (15)[14], and detritylation of 15 with CF_3COOH in CH_2Cl_2 at 0° for 10 min and further protection of the resulting aminoalcohol with p-nitrobenzyloxycarbonyl chloride and dimethylaminopyridine in CH_2Cl_2 for 2h gave 16[15] which had already been correlated with (±)-thienamycin.[2]

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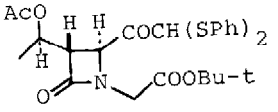
3. (a) J.C. Sheehan and A.K. Bose, J. Am. Chem. Soc., 72, 5158 (1950). (b) B.G. Chatterjee and D.P. Sahu, Tetrahedron Letters, 1129 (1977).
4. (±)-Erythro-2-bromo-3-acetoxybutyric acid was prepared from the reaction of trans crotonic acid with NBS in acetic acid at room temp for 7-14 days, or alternatively prepared from the acetylation of (±)-erythro-2-bromo-3-hydroxybutyric acid.[16]

5. Numbering corresponds to that of thienamycin.
6. The results will be published in detail elsewhere.
7. It is difficult to separate chromatographycally cis and trans isomers, however we can obtain the cis isomer, mp 102-103.5°, from cis-8. This cis isomer is also isomerized to trans isomer (10) in 83% yield.
8. The prolonged reaction time causes gradually increasing formation of a by-product (1).



(1)

9. ^{1}H NMR of 10, δ($CDCl_3$) 1.22 (3H, d, J=6 Hz), 1.30 (9H, s), 1.92 (3H, s), 3.10 (1H, dd, J= 2.5, 7 Hz), 3.45 (1H, d, J=18.5 Hz), 3.69 (2H, s), 4.17 (1H, d, J=18.5 Hz), 4.68 (1H, d, J=2.5 Hz), 5.20 (1H, qd, J=6, 7 Hz).
10. There is no detection of regio isomer of 11.
11. ^{1}H NMR of E-13, δ($CDCl_3$) 1.27 (3H, d, J=6.7 Hz), 1.40 (9H, s), 1.86 (1H, bs, NH), 1.95 (3H, s), 2.35 (2H, t, J=6 Hz), 2.78 (2H, t, J=6 Hz), 2.90 (1H, dd, J=2, 7.5 Hz), 3.29 (1H, d, J=18 Hz), 3.95 (1H, d, J=18 Hz), 4.13 (1H, dd, J= 2, 9 Hz, C_4-H), 5.24 (1H, qd, J=6.7, 7.5 Hz), 5.36 (1H, dd, J=9, 15 Hz), 6.23 (1H, d, J=15 Hz), 7.32 (15H, m).
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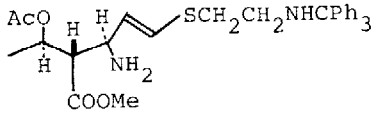
13. We cannot present the precise mechanisms for the formation of 14 and 14'. ^{1}H NMR of 14, δ($CDCl_3$) 1.28 (3H, d, J=6.5 Hz), 1.43 (1H, s, NHTr), 1.95 (3H, s), 2.2-2.5 (2H, m), 2.6-2.9 (2H, m), 2.89 (1H, dd, J=7.5, 2 Hz, C_3-H), 4.03 (1H, dd, J=2, 7 Hz, C_4-H), 5.24 (1H, m), 5.50 (1H, dd, J=7, 15 Hz), 6.21 (1H, d, J=15 Hz), 7.72 (15H, m).
14. Treatment of 14 with NaOMe in MeOH at 0° for 1h gave the β-lactam ring fission product (11) in good yield without deacetylation.



(11)

15. ^{1}H NMR of 16, δ($CDCl_3$) 1.44 (3H, d, J=6.5 Hz), 2.77-2.92 (2H, m), 3.10 (1H, dd, J=2, 7 Hz, C_3-H), 3.33-3.52 (2H, m), 4.20 (1H, dd, J=2, 8 Hz, C_4-H), 5.0-5.4 [6H; 5.22 (2H, s), 5.26 (2H, s), NH, C_1, -H], 5.66 (1H, dd, J=8, 15 Hz), 5.85 (1H, s, NH), 6.24 (1H, d, J=15 Hz), 7.48-7.60 (4H, m), 8.20-8.30 (4H, m).
16. C.A. 54, P 4394h. (Brit. 822,797, Oct. 28, 1959).

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