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Synthesis of a 4β-Carboxyethyl Derivative of Thienamycin

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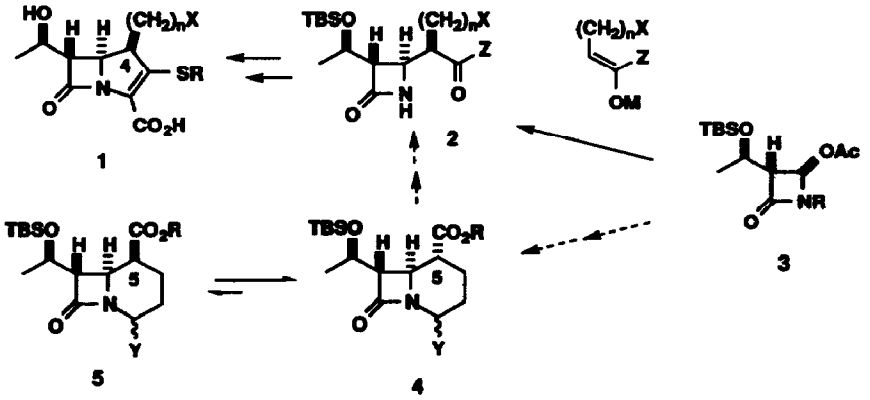
Summary: A stereoselective synthesis of the 4β-carboxyethyl derivative of thienamycin (**1**) is described. The stereochemistry of the substituent at C-4 of the carbapenem was obtained by equilibration of the ester group in the 1-azabicyclo[4.2.0]octane intermediates, **8** and **9**, with base. This favored the 5α-ester (**8**) which was then transformed into the imide (**14**). Regioselective opening of the imide with lithium allyloxide gave the azetidinone (**15**) which was converted into the title compound.

We examined a novel stereoselective route to substituted 4β-alkyl carbapenems while studying these compounds as antibacterial agents.[2] It utilizes the functionality that is present in a carbapenem precursor to obtain the desired stereochemistry at C-4. We have described the preparation of a 4-β hydroxymethyl carbapenem[3] by this approach and here we report the synthesis of a 4β-carboxyethyl derivative of thienamycin (**1**, n=2, X=CO_2H, R=$CH_2CH_2NH_2$).

Scheme I

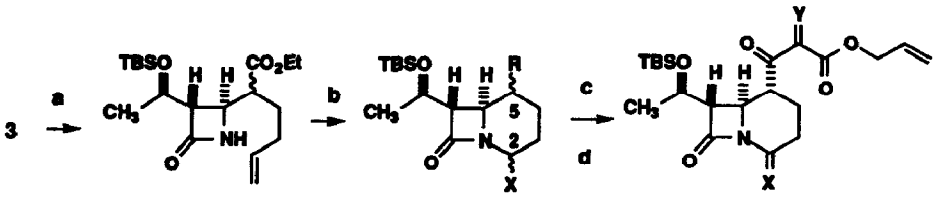


The azetidinone (**2**) is a key intermediate in the synthesis of 4β-substituted carbapenems[4] (Scheme I) and is generally available from the stereoselective reaction of the acetoxyazetidinone (**3**) with an enolate bearing a special auxiliary.[5] Our approach to the synthesis of **2** centers on the base-catalyzed equilibation of the ester function in the 1-azabicyclo[4.2.0]octanes, **4** or **5**. This should favor

the 5α-isomer (4) where this group is in the more stable pseudoequatorial configuration. Hydrolysis of the amidal function in 4 would then give the desired carbapenem precursor (2).

The preparation of the 1-azabicyclo[4.2.0]octane (4 or 5) intermediate is outlined in Scheme II. The acetoxyazetidinone (3, R=TMS) was treated with the trimethylsilyl derivative of the enolate of ethyl hex-5-enoate and a catalytic amount of trimethylsilyl trifluoromethanesulfonate[6] to give the ester (6) as a 1:1 mixture of epimers. Ozonolysis of 6 afforded the hemiamidals (7) which were treated with thiophenol in the presence of magnesium bromide[7] to give the thioamidals (8 and 9). Base-cat-

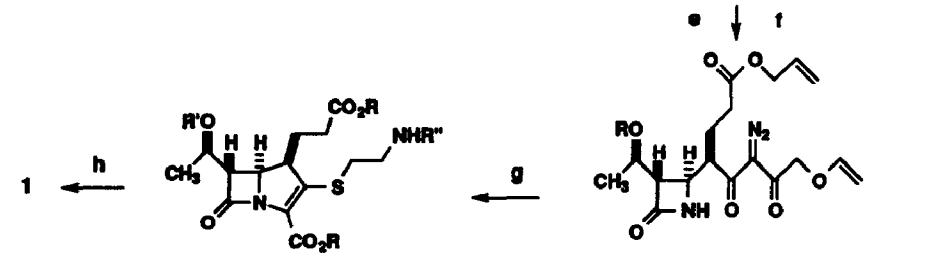
Scheme II



6

7 R=CO_2Et, X=OH
8 R=α-CO2Et, X=SPh
9 R=β-CO2Et, X=SPh
10 R=α-CO_2H, X=SPh

11 X=H, SPh; Y=H_2
12 X=H, SPh; Y=N_2
13 X=H, OH; Y=N_2
14 X=O, Y=N_2



18 R=CH_2CHCH_2,R'=TMS, R"=$CO_2CH_2CHCH_2$

15 R=TBS
16 R=H
17 R=TMS

a) 1-Ethoxy-1-trimethylsilyloxy-hexa-1,5-diene (1.5 equiv), TMSOTf (0.3 equiv), CH_2Cl_2, R.T., 17 h (95%) *b)* O_3, MeOH, -78°C then Me_2S, R.T., 19 h; then thiophenol (1.2 equiv), $MgBr_2$ (1.3 equiv), Et_2O, R.T., 20 h; then DBU (1.5 equiv), toluene, reflux, 38 h; 2.5 M aq. NaOH (3 equiv), MeOH, 4°C, 2 h, then R.T. 1h, then aqueous HCl (78%) *c)* carbonyldiimidazole (1.1 equiv), CH_3CN, R.T.; then magnesium allyl malonate (1.5 equiv), benzene, reflux, 0.5 h; then p-toluenesulfonyl azide (1.1 equiv), TEA (1.05 equiv) CH_3CN, 0°C to R.T.; then NBS (1.0 equiv), aqueous acetone, 4°C, 5 min (86%) *d)* PCC (2.7 equiv), 3 A° sieves, CH_2Cl_2 (86%). *e)* Lithium allyloxide (0.5 M in THF, 1 equiv), THF, -78°C, 0.5 h; then 5% aq. HCl, MeOH, R.T., 3 h (71%) *f)* trimethylsilylimidazole (1.3 equiv), THF, R.T., 15 min (89%) *g)* Rhodium (II) octanoate (cat.), EtOAc-hexane, reflux, 0.5 h; then diphenyl chlorophosphate (1.05 equiv), Hünig's base (1.07 equiv), DMAP (cat), CH_3CN, 4°C, 1 h; then N-allyloxycarbonylcysteamine (1.9 equiv), Hünig's base (1.1 equiv), 4°C, 20 h *h)* acetic acid (4 equiv), aq. THF, 0°C to R.T., 3 h; then N-methylaniline (5 equiv), bis(dibenzylideneacetone)-palladium (0) (0.1 equiv), triphenylphosphine (0.4 equiv), THF, 1.25 h, then aq. $NaHCO_3$ to pH 7.0 (46%).

alyzed equilibration of **8** and **9** was then examined. They were found to be converted from a 1:1 to a 9:1 mixture of epimers on treatment with DBU in refluxing toluene. The epimers could be separated by chromatography and the coupling data from their respective ^{1}H NMR spectra[8,9] indicated that the major epimer (**8**) had the desired configuration at C-5.

The 5α-acid (**10**) could be obtained free of its 5β–isomer[10] by base-catalyzed hydrolysis of the equilibrated mixture of ester epimers. The carboxyl group in **10** was then transformed (**10** to **11** to **12**) into the α-diazo-β-ketoester side chain that is used in the Merck carbapenem synthesis.[4] Hydrolysis of the thioamidal function in **12** gave the hemiamidal (**13**). The next step of the carbapenem synthesis, rhodium-catalyzed cyclization, was not examined since the ^{1}H NMR spectrum of **13** indicated that it was not in equilibrium with the aldehyde form of the molecule. Instead, the hemiamidal (**13**) was oxidized with pyridinium chlorochromate to give the imide (**14**) and this was regioselectively[11] opened with lithium allyloxide in THF to give the azetidinone (**15**). The t-butyldimethyl silyl protecting group was replaced with the more labile trimethylsilyl group (**15** to **16** to **17**) and then **17** was converted to the protected carbapenem (**18**). Removal of the silyl protecting group and the three allyl groups afforded the 4β-carboxyethyl analog of thienamycin (**1**, n=2, X=CO_2H, R=$CH_2CH_2NH_2$).

In summary, the synthesis of a 4β-carboxyethyl carbapenem was achieved by making use of functionality in the molecule to obtain the desired sterochemistry at C-4. Analogs of **1** can readily be generated from the imide (**14**) by the regioselective reaction of **14** with other nucleophiles. These results and the biological activity of the compounds that were obtained will be reported.

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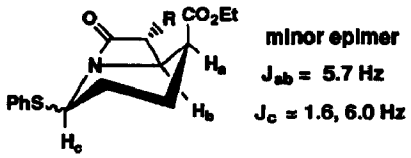
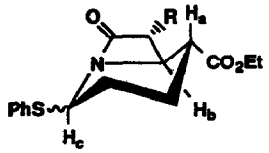
(7) Park, J.H.; Sunggak, K; *Chem Lett.* **1989**, 629. We found that thioaminal formation proceeds more readily if the magnesium bromide is generated *in situ* from 1,2-dibromoethane and magnesium turnings.

(8) The major epimer (**8**): Rf 0.16 (silica gel tlc, EtOAc:hexane = 1:4); $[a]^{23}_{D}$ -103°(c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) -0.03 (s, 3H), 0.02 (s, 3H), 0.80 (s, 9H), 1.09 (d, 3H, J=6.2 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.76-2.22 (m, 4H), 2.33 (ddd, 1H, J=3.7, 10.2, 11.6 Hz), 2.96 (dd, 1H, J=4.4, 1.8 Hz), 3.77 (dd, 1H, J=10.2, 1.8 Hz), 4.01 (dq, 1H, J=6.2, 4.4 Hz), 5.48 (m, 2H), 5.49 (dd, 1H, J=0.5, 4.9 Hz), 7.19-7.46 (m, 5H). The minor epimer (**9**): Rf 0.28 (silica gel tlc, EtOAc:hexane = 1:4); $[a]^{23}_{D}$ -69°(c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) 0.02 (s, 6H), 0.82 (s, 9H). 1.11 (d, 3H, J=6.2 Hz), 1.25 (t, 3H, J=7.1 Hz), 1.57-1.73 (m, 1H), 1.89-2.45 (m, 3H), 2.84 (m, 1H), 3.04 (dd, 1H, J=6.7, 1.9 Hz), 3.68 (dd, 1H, J=5.7, 1.9 Hz), 3.73 (dq, 1H, J=6.2, 6.7 Hz), 4.15 (q, 2H, J=7.1 Hz) 5.51 (dd, 1H, J=1.6, 6.0 Hz), 7.20-7.46 (m, 5H). 4β-carboxyethyl thienamycin (**1**) : IR (KBr) 3420, 1750, 1580 (br) cm^{-1}; UV (phosphate buffer, pH 7.4, 0.07 M) 304 nm (ε 6500); ^1H NMR (D_2O) 1.37(d, 3H, 6.4 Hz), 1.66-1.74 (m, 1H), 2.14-2.48 (m, 3H), 2.91-3.42 (m, 5H), 3.51 (dd, 1H, J=2.7, 6.0Hz), 4.28 (dd, 1H, J=2.7, 8.3 Hz), 4.31 (dq, 1H, J=6.0, 6.4 Hz); half life of 86 h (phosphate buffer, pH 7.4, 0.07 M, 37.5°C).

(9) The vicinal coupling constants between methine hydrogen atoms H_a and H_b in the ^1H NMR spectra of the major (**8**) and minor (**9**) epimers are consistent with the ester group being in pseudoequatorial and pseudoaxial positions respectively. For the 5α– and 5β-methyl isomers of 5-methyl 3-oxa-1-azabicyclo-[4.2.0]octanes, the corresponding coupling constants were 10.0 and 5.0 Hz respectively, see: Shih, D.H.; Fayter, J.A.; Cama, L.D.; Christensen, B.G.; Hirshfield, J. *Tetrahedron Lett.* **1985**, *26*, 583. The configuration of C-2 is the same in both isomers since they can be interconverted under conditions where the thioamidal function remains intact. However, we could not make an assignment based on the NMR coupling data.



minor epimer
J_{ab} = 5.7 Hz
J_c = 1.6, 6.0 Hz



major epimer
J_{ab} = 10.2 Hz
J_c = 0.5, 4.9 Hz

(10) The quasiaxial ester group in the minor epimer most likely undergoes saponification at a much slower rate than that of its isomer, see Eliel, E.L.; Hanbenstock, H.; Acharya, R.V.; *J. Amer. Chem. Soc.*, **1961**, *83*, 2351. Unsaponified ester was removed by extraction into an organic solvent but was not characterized.

(11) The regioselectivity is most likely steric in origin. For a related reaction, see: Evans, D.A.; Ennis, M.D.; Mathre, D.J.; *J. Amer. Chem. Soc.*, **1982**, *104*, 1737.

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