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THE SYNTHESIS OF 3-(1'-HYDROXYETHYL)-2-AZETIDINONE-4-YL ACETIC ACID VIA DIANION CHEMISTRY - AN IMPORTANT INTERMEDIATE IN THIENAMYCIN TOTAL SYNTHESIS

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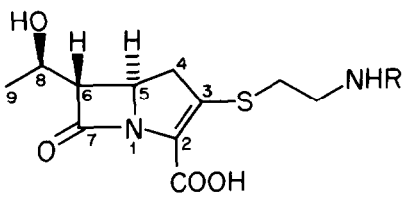
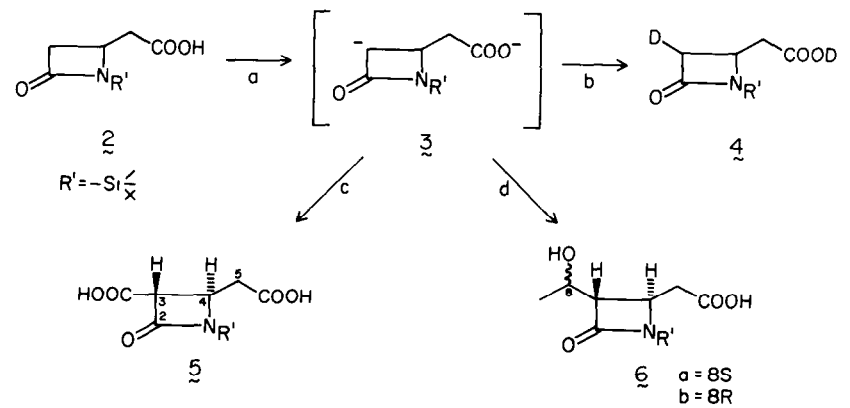
Summary A convenient synthesis of 3-(1'-hydroxyethyl)-2-azetidinone-4-yl acetic acid, one of the key intermediates in the thienamycin total synthesis, based on the chemistry of the dianion derived from readily available 2-azetidinone-4-yl acetic acid is described

Recently, a practical synthesis of (±)-thienamycin (1) starting from diethyl 1,3-acetonedicarboxylate was reported[1] This synthesis involves R,S,R²-3-(1'-hydroxyethyl)-2-azetidinone-4-yl acetic acid (6b) as a key intermediate[3] In this report, we wish to describe a convenient synthesis of 3-(1'-hydroxyethyl)-2-azetidinone-4-yl acetic acid (6) from the dianion derived from 2-azetidinone-4-yl acetic acid[4] (2)



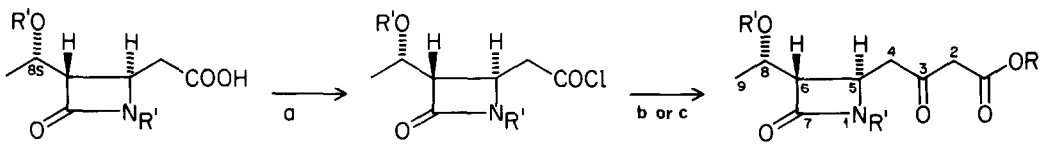
1

Stereocontrolled introduction of the hydroxyethyl group into the 3-position of 2-azetidinones via enolate anion has recently become an important reaction in thienamycin chemistry[5] The transmetallation of benzyl 2-azetidinone-4-yl acetate (LDA/THF/-60°C), followed by the addition of acetaldehyde, gave no desired aldol condensation but produced instead only β-lactam ring destruction[6] On the other hand, the formation of the dianion (3), by treatment of the free acid (2) with two equivalents of LDA in THF at -30°C, followed by the addition of D_2O afforded 4 with very little β-lactam ring opening (recovery yield of 4 was 91%) This result clearly demonstrated the formation of the desired dianion 3[7] Similarly, the



treatment of 3 with carbon dioxide gave 3-carboxy-2-azetidinone-4-yl acetic acid (5) in 35% yield with 32% recovery of 2. The trans configuration of H_3 and H_4 was supported by its spin-spin coupling constant ($J_{3,4}$=1.6 Hz)[8]. Furthermore, the reaction of 3 with acetaldehyde gave the desired hydroxyethyl derivative (6) in 70% yield as a mixture of 6a (8S) and 6b (8R)[9]. The R,S,R-intermediate (6b) was converted to 1 via the previously reported method[1]. Attempted oxidation of the hydroxyethyl group (DMSO-trifluoroacetic anhydride/triethylamine)[10] gave instead the methylthiomethyl ester[11] (12) via Pummerer type rearrangement in good yield.

As an alternative to our previously published procedure[1,3] the β-keto ester[12] intermediate (9) which was shown to be an excellent precursor to thienamycin was made by the following procedure. Treatment of 7a with oxalyl chloride (catalytic amount of DMF) at 0°C gave the relatively stable acid chloride (8) in quantitative yield. Subsequent reaction of 8 with the magnesium enolates formed via reaction of t-butylmagnesium chloride with hydrogen malonates in THF gave excellent yields of the desired β-keto esters 9a (82%) and 9b (98%)[13]. Furthermore, the treatment of 8 with Meldrum's acid[14] in the presence of 4-dimethylaminopyridine (DMAP) gave acylated Meldrum's acid which was reacted further with p-nitro benzyl alcohol to give the desired β-keto ester (9c) in 62% overall yield[15]. Catalytic debenzylation of 9b (Pd/H_2/MeOH) gave an unstable β-keto acid[16] which was immediately reacted with dicyclohexylcarbodiimide and p-nitrobenzyl alcohol in the presence of DMAP[17] to give 9c in 71% overall yield. The S,S,R-intermediate (9c) was converted to (±)-8-epithienamycin[1,18] as reported. The configuration at C_8 (8S) in 10 was inverted to 8R by the reported method[19] using diethyl azodicarboxylate-triphenylphosphine complex[20] to give 11 which is a key intermediate in the thienamycin synthesis[21].

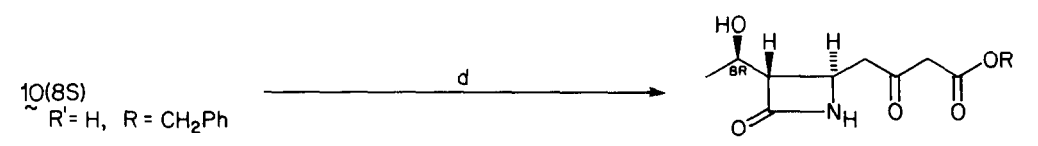


7 a = 8S
b = 8R

8 (8S)

9 (8S)
a R = t-C_4H_9
b R = CH_2Ph
c R = PNB

R' = —Si(CH$_3$)$_2$X, PNB = p-Nitrobenzyl-



11 (8R)

a $(COCl)_2$/DMF/CH_2Cl_2
b Mg^{++} $^-CH(COO^-)COOR$/THF
c Meldrum's acid / 4-Dimethylaminopyridine and then PNB–OH
d Ph_3P/EtOOCN=NCOOEt/HCOOH and then H_3O^+

References and Notes

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2 The stereochemical descriptors refer to the atoms that are to become 8,6 and 5 of thienamycin respectively Since all intermediates are racemic, this nomenclature is meant to denote relative stereochemistry, not absolute For the sake of readability, the descriptors for one antipode are omitted

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9 The ratio of 6a (8S) to 6b (8R) is not clear After the t-butyldimethylsilyl protection of the hydroxyl group, the carboxylic acid was converted to benzylester and then this diastereomeric mixture was separated by prep tlc (SiO_2), hexanes/ethyl acetate = 3/2) Catalytic debenzylation (10%-Pd/C/MeOH) provided 7a (8S) and 7b (8R) 7a mp 90-91°C, ^{1}H NMR δ($CDCl_3$), 0 06 (s,6,$SiMe_2$), 0 19 (s,3,SiMe), 0.26 (s,3,SiMe), 0 92 (s,9,t-butyl-Si), 0 98 (s,9,t-butyl-Si), 1 35 (d,3,J=6 0,Me), centered at 2.76 (ABX,2,J=4 0,10 0 and 16 0,CH_2), 3.00 (dd,1,J=3 0, 6 2,H_3), 3 83 (ABX,1,H_4), 4 18 (dq,1,J=6.0 and 6 2,CH-OSi) and 10 2 (b,1,COOH), ν($CHCl_3$), 1735 and 1720 cm^{-1} 7b mp 168-169°C, ^{1}H NMR δ($CDCl_3$), 0 06 (s,6,$SiMe_2$), 0 08 (s,6,$SiMe_2$), 0 88 (s,9,t-butyl-Si), 0 96 (s,9,tbutyl-Si), 1 18 (d,3,J=6 2,CH_3), centered at 2 72 (ABX,2, J=4 5,8 5 and 14.9,CH_2), 3 02(dd,1,J=2 6 and 4 4,H_3), 4 0(ABX,1,H_4), 4 18 (dq,1,J=4 3 and 6 2,CH-OSi) and 10 6(b,1,COOH)

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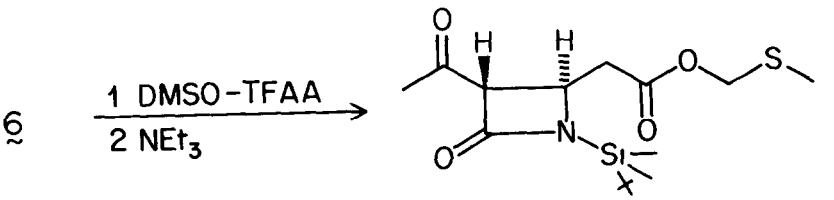
11 12 ^{1}H NMR, δ($CDCl_3$), 0 22 (s,3,SiMe), 0 28 (s,3,SiMe), 0 96 (s,9,t-butyl-Si), 2 23 (s,3, $COCH_3$), 2 31 (s,3,SCH_3), centered at 2 75 (ABX,2,J=4.0,9 3 and 16 3, $CH_2COOCH_2SCH_3$), 4 22 (d,1,J=1.5,H_3), 4 30 (ABX,1,H_4) and 4 15 (s,2,$CH_2COOCH_2SCH_3$) ^{13}C NMR, δ($CDCl_3$), -5.6 and -5 7 ($SiMe_2$), 15 6 (SCH_3), 18 43 (Si-CMe_3), 26 1 (Si-CMe_3), 30 0 ($COCH_3$), 39 3 (CH_2COOCH_2 SCH_3), 47 3 (C_4), 69 0 ($CH_2COOCH_2SCH_3$), 70 0 (C_3), 167 4 ($CH_2COOCH_2SCH_3$), 169.4 (C_2) and 199 32 ($COCH_3$) The synthetic use of methylthiomethyl esters for the protection of carboxylic acids has been discussed in a recent review, see Haslam, E , Tetrahedron, 1980, 36, 2409, Ho, T -L , Wong, C. M , J Chem Soc , Chem , Commun , 1973, 224, idem , Synth Commun , 1973, 3, 145, Gerdes, J M , Wade, L G , Jr , Tetrahedron Lett , 1979, 689, Wade, L G , Jr , Gerdes, J M , Wirth, R P , ibid , 1978, 731



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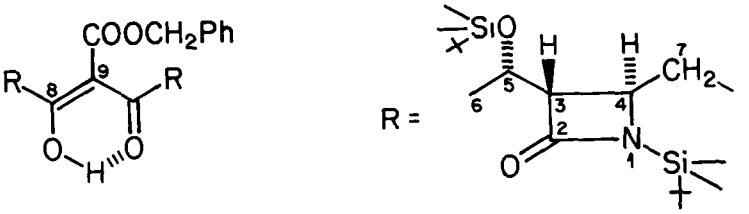
13 In a large scale run, 1 2 adduct 13 was isolated as a by-product Selected data· 13 ^{13}C NMR δ(CDCl3), -6 0,-5 4,-4 7 and -4.5 (two Si-Me_2), 18 07 (Si-CMe_3), 21 2 (CH_3), 25 9 and 26.2 (Si-CMe_3), 43 8 (C_7), 48 5 (C_4), 64 6 (C_3), 65 7 (C_5), 67.2 (COOCH_2Ph), 108 9 (C_9), 165.0 (COO-CH_2Ph), 172 6 (C_2) and 195 5 (C_8)



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22 All new compounds have been fully characterized and their spectral data are in accord with their assigned structures Melting points were obtained on a Thomas-Hoover melting points apparatus and are uncorrected ^1H NMR spectra were recorded on a Varian SC-300 (300 MHz) and a Varian XL-100 (100 MHz) spectrometers and ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer All chemical shifts are reported with respect to internal Me_4Si (δ=0) Selected data 2 ν($CHCl_3$) 1750 and 1700 cm^{-1}, ^1H NMR δ($CDCl_3$), 0 23 (s,3,SiMe), 0 26 (s,3, SiMe), 0 97 (s,9,t-butyl-Si), centered at 2 76 (ABX,2,J=4 0,10 2 and 16 0, CH_2COOH), 2 97 (ABX, 2,J=2 4,5 2 and 16 0,H_3 and H_3') and 3 90 (ABX,1,H_4), 6 ^{13}C NMR, δ(acetone-d_6), -6 2 ($SiMe_2$), 18 4 (siCMe_3), 25.8 (SiCMe_3), 38 5 (C_5), 49 4 (C_4) and 62 1 (C_3) 9a ^{13}C NMR δ($CDCl_3$), -4 4, -5 4 and -5 0 ($SiMe_2$), 18 1 (SiCMe_2), 21 4 (C_9), 25 9 and 26 2 (SiCMe_3), 28 0 (COOCMe_3), 47 6 (C_4), 48 6 (C_5), 50 9 (C_2), 65 1 (C_6), 65 9 (C_8), 82 3 (COOCMe_3), 166.0 (COOCMe$_3$), 172 8 (C_7) and 200 6 (C_3); 10 ^1H NMR, δ($CDCl_3$), 1 2 (d,3,J=6 0,CH_3), 2 61 (m,1,H_6), centered at 2 75 (ABX,2,H_4), 3 34 (s,2,H_2), 3 80 (m,1,H_5), 4 15 (m,1,H_8), 5.10 (s,2,COOCH_2Ph) and 7.8 (s,5,Ph)

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