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A PRACTICAL SYNTHESIS OF (±)-THIENAMYCIN

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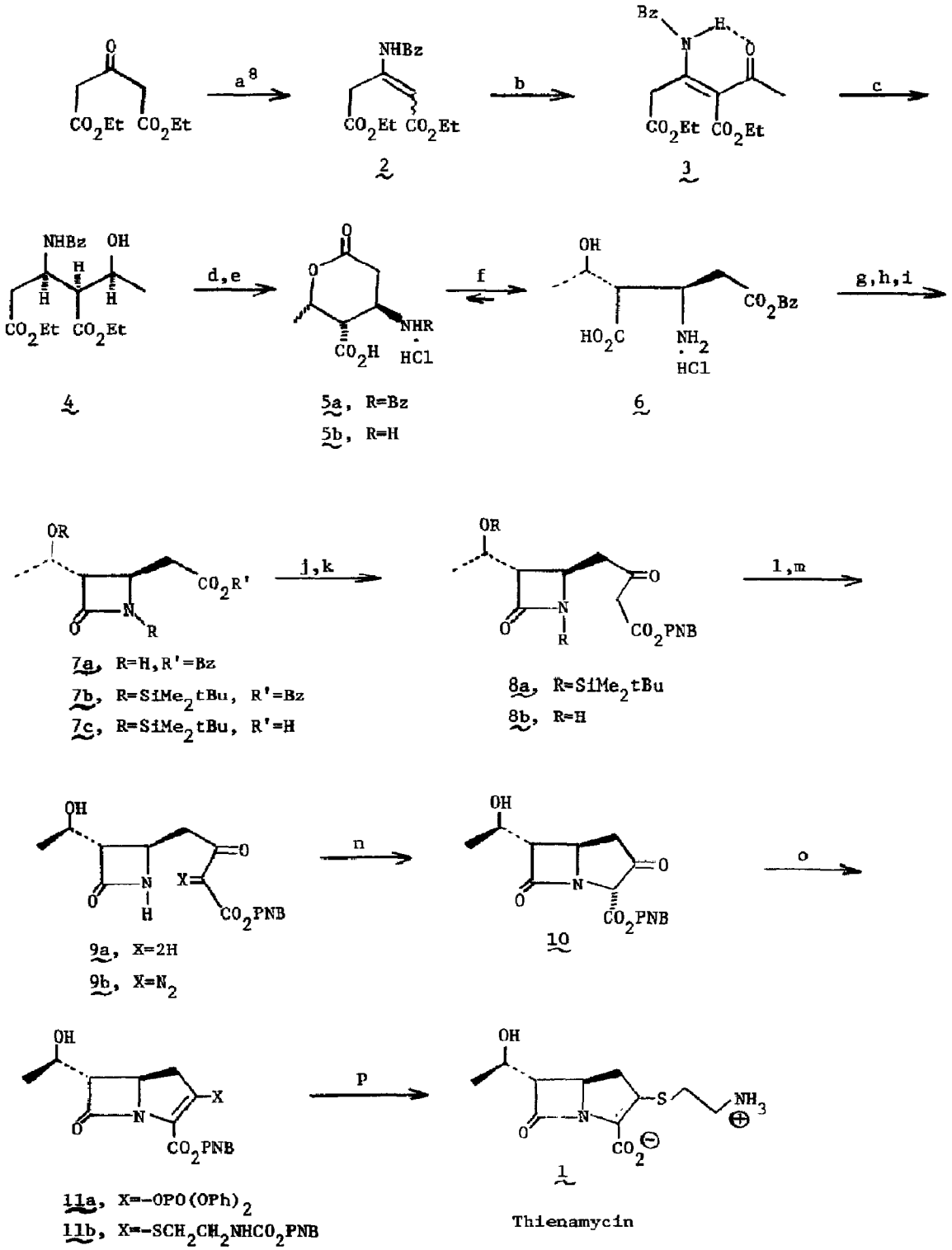
Summary: An efficient and operationally simple synthesis of (±)-thienamycin is described.

Thienamycin (1), the uniquely structured and highly potent β-lactam antibiotic[1], has attracted a great deal of synthetic activity[2] most of which is conceptually interesting. We wish to report an operationally simple and high-yielding total synthesis of (±)-thienamycin which is adaptable to large scale operation. It is characterized by: 1) the formation of a highly-functionalized, triply-asymmetric acyclic derivative 4 via a stereoselective reduction, 2) the very efficient formation of a monocyclic β-lactam using classical carbodiimide chemistry 6 → 7a, 3) the equally efficient carbenoid insertion reaction[3] to form the bicyclic system 9b → 10, and 4) an inversion reaction to adjust relative stereochemistry 8b → 9a.

Diethyl 1,3-acetonedicarboxylate was converted to the keto enamine 3[4,5] as shown in the Scheme. The most noteworthy features are the rather clean mono-C-acetylation of the enamine 2 and the high degree of rigidity displayed by 3 due to a very strong hydrogen-bond. This latter feature generated the hope for the stereoselective reduction that follows. Reduction of the crude keto enamine 3 (ca. 90% pure by NMR) with $NaCNBH_3$ resulted in the reduction of both the double bond and the ketone moieties. A single isomer 4 could be isolated in 61% overall yield from the starting ketone by column chromatography on silica gel. This isomer, out of the four that are possible, was the predicted product resulting from an all-cis-reduction of the keto enamine[6]. Instead of purifying 4 we found it much more expeditious to lactonize and hydrolyze the crude reduction product. Upon cooling the reaction mixture, the isomerically pure lactone 5a[7] crystallized as a hydrate in 40% overall yield from the acetonedicarboxylate. The lactionization step not only constitutes a simple purification-isolation procedure but, as will be seen, it introduces a needed bias between the two carboxyl groups.

After catalytic debenzylation of 5a, the lactone 5b was solvolyzed in benzyl alcohol to give an equilibrium mixture of the acyclic ester 6 and starting lactone 5b (3/1 respectively) in essentially quantitative yield. This mixture could be used directly in the next reaction or preferably the solid mixture was washed with isopropanol leaving pure 6. The material in the

Scheme[8]



filtrate can be recycled. The pure amino acid 6 was dehydrated with N,N'-dicyclohexylcarbodiimide (DCC) to give a 92% yield of crystalline β-lactam 7a. The β-lactam, without purification, was silylated, hydrogenolyzed, and chain-elongated using a modification of the published procedure[9] to give the β-keto ester 8a, which was crystallized from isopropanol in 60-72% overall yield from 7a. After desilylation, the stereochemistry of the hydroxyethyl group was cleanly inverted using a variant of the Mitsunobu procedure[10]. The resulting inverted formate ester was readily hydrolyzed with dilute acid to give alcohol 9a possessing the required relative stereochemistry. A solution of this crude product, which contained impurities accumulated since the purification of 8a, was subjected to standard diazo transfer conditions. Within minutes, pure diazo keto ester 9b crystallized from the reaction mixture in 65% yield from 8a. Decomposition of 9b with a catalytic amount of rhodium diacetate resulted in selective N-H insertion of the carbenoid intermediate[3]. Without purification, the bicyclic ketone 10 in MeCN was converted to the enol phosphate 11a to which was added the N-protected cysteamine derivative. The pure, bis-protected thienamycin 11b precipitated directly from the reaction mixture in 76% yield from 9b. Finally, catalytic deprotection was accomplished in 90% yield affording racemic thienamycin which was identical in every expected aspect to a natural sample.

By virtue of the simplicity and overall yield (>10%) we feel that this series of transformations forms the basis for a practical synthesis of thienamycin. Additional process improvements including a resolution will be the subject of future communications.

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Notes & References

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3) This reaction was pioneered on the model carbapen-2-em ring system by another Merck group, see R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, Tetrahedron Lett., 31(1980). These workers have also prepared chiral 9b in a stereocontrolled fashion starting from L-aspartic acid and converted it to thienamycin using methodology common to both routes (Reported at: "Penicillin--50 Years After Fleming", London, England, May 2, 1979.)

T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard, B. G. Christensen, Proc. Royal Soc. (London), in press.

4) Satisfactory infrared, mass, and NMR spectral data was obtained on each isolated synthetic intermediate.

5) Selected data. 3: mp 87-8°C; ν($CHCl_3$) 1740, 1685, and 1600 cm^{-1}. 5a: mp 166-170° (dec.); ν(nujol) 1750 and 1724 cm^{-1}. 7a: mp 67.5-68.5°; ν($CHCl_3$) 3470, 1770, and 1730 cm^{-1}. 8b: mp 82-4°; ν($CHCl_3$) 1760 and 1725 cm^{-1}; δ($CDCl_3$) 1.33(d,3,J=6.3,Me), 1.90(b,1,OH), centere at 2.90(ABX,2,CH_2), 2.90(m,1,H_3), 3.58(s,2,$COCH_2CO_2$), 3.84(ABX,1,H_4), 4.15(dq,1,J=6.0 and 6.3, CHOH), 5.28(s,2,OCH_2), 6.10(b,1,NH), 7.53(d,2,J=8.7,Ar) and 8.25(d,2,J=8.7,Ar). 9a: mp 97-9°; ν($CHCl_3$) 1765 and 17.25 cm^{-1}; δ($CDCl_3$) 1.31(d,3,J=6.3,Me), 1.81(b,1,OH), 2.85(d J=2.2 and 7.0, H_3), centered at 2.98(ABX,2,J=5.5,7.5 and 18.4, CH-CH_2-CO), 3.59(s,2,$COCH_2$ 3.97(ABX,1,H_4), 4.17(dq,1,J=6.3 and 7.0,CH-CH_3), 5.28(s,2,CO_2CH_2), 6.08(b,1,NH), 7.53(d,2 Ar) and 8.25(d,2,Ar). 9b: mp 160.5-2° (dec.): ν(nujol) 3475, 3275, 2155, 1742, 1722 and cm^{-1}. 10: mp 112-4°; ν($CHCl_3$) 1760, 1735 and 1720 cm^{-1}. 11b: mp 183-5° (dec.); ν(KBr), 1690, 1660 cm^{-1}; δ(acetone-d_6, 300 MHz) 1.26(d,3,J=6.01,Me), 3.08(m,2,CH_2S), 3.32(dd,1,J= and 6.0,H_6), 3.44(dt,2,J-6.5,CH_2N), centered at 3.43(ABX,2,J=8.5,10 and 18.0, H_4 and H_4') 4.12(dq,1,J=6.0 and 6.2,H_8), 4.27(ABX,1,H_5), 5.25(s,2,$NHCO_2CH_2Ar$), 5.30 and 5.54(AB,2,J=1 CO_2CH_2Ar), 6.92(t,1,J=6.0,NH), 7.66(d,2,J=8.5,Ar), 7.83(d,2,J=8.5,Ar) and 8.27(d,2,J=8.5,

6) Undoubtedly during the course of the reduction the hydrogen of the hydrogen-bond is repla by boron to give an equally rigid system. In fact, a partially reduced boron chelate has been isolated by column chromatography when $NaBH_4$ was used as the reducing agent.

7) A similar lactonization using HCl under anhydrous conditions afforded the ester lactone. Inspection of the crude product by ^{13}C-NMR revealed the presence of a major lactone and t minor stereoisomers, each 12% of the major by peak-heights. The only isomer not seen is all-cis-substituted lactone.

8) Experimental conditions. (a) $BzNH_2$, toluene, molecular sieves; (b) ketene gas, toluene (filtrate from (a)); (c) $NaCNBH_3$, HOAc; (d) conc. aq. HCl, reflux: (e) $Pd(OH)_2/C$, 40 psi HOAc; (f) BzOH, HOAc (catalyst), 70°, 16 hrs; (g) NEt_3, DCC, MeCN, 60°, 4 hrs.; (h) $ClSiMe_2t$-Bu, NEt_3, DMF; (i) Pd/C, 40 psi H_2, MeOH; (j) 1) Carbonyldiimidazole, CH_2Cl_2; 2) Meldrum's acid, 4-dimethylaminopyridine; 3) p-nitrobenzyl alcohol (PNB-OH), MeCN, refl (k) HCl, aq. MeOH; (l) 1) 1.9 $Ø_3P$, 1.9 $(NCO_2i\text{-}Pr)_2$, $3HCO_2H$, THF, 25°, 1 hr.; 2) HCl, aq. MeOH, 25°, 1.5 hrs.; (m) TsN_3, NEt_3, EtOAc; (n) 1% $Rh_2(OAc)_4$, toluene, 80°, 1 hr.; (o) 1) 1.1 $(PhO)_2POCl$, 1.1 $i\text{-}Pr_2NEt$, CH_3CN, 0°, 10 min.; 2) 1.1 $HSCH_2CH_2NHCO_2PNB$, 1.1 $i\text{-}Pr_2NEt$, 0°, 1 hr.; (p) 40 psi H_2, PtO_2, THF, H_2O, buffered at pH 7.0 with morpholinopropane sulfonic acid.

9) Y. Oikawa, K. Sugano, O. Yonemitsu, J. Org. Chem., 43, 2087(1978).

10) O. Mitsunobu, J. Kimura, K. Iizumi, and N. Yanagida, Bull. Chem. Soc. Jap., 49, 510(1976 and references therein. Presumably this reaction proceeds via activation of the alcohol as an alkoxyphosphonium salt which is displaced by formic acid in an S_N2 fashion to give the inverted formate ester.

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