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FURTHER STUDIES ON THE ACETONEDICARBOXYLATE ROUTE TO THIENAMYCIN----STEREOCHEMICAL INVERSION AT THE LACTONE STAGE.

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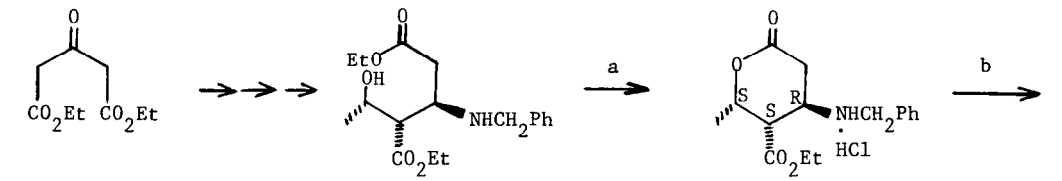
Summary: Stereochemical inversion of an easily prepared δ-lactone has culiminated in the preparation of a key intermediate for the synthesis of thienamycin.

We have recently described[1] a practical synthesis of (±)-thienamycin[2] from diethyl 1,3-acetonedicarboxylate. The synthesis involved the production of an S,S,R-intermediate 2[3], the stereochemistry of which was preserved until a very late stage of the synthesis (the hydroxy epimer of 8) at which point the relative stereochemistry was adjusted to the required R,S,R-configuration via an intermolecular S_N2 reaction. In this report we wish to describe our results on an early stereochemical adjustment involving an intramolecular inversion and the subsequent conversion to the β-keto ester 8 which has been shown to be an efficient precursor of thienamycin[1,4].

The lactone 3[5,6] was prepared as previously described[1] for the analogous lactone acid except that the lactonization was performed under milder, anhydrous conditions in order to preserve the ester function. This crystalline S,S,R-lactone was solvolyzed in water to afford the acyclic hydroxy acid 4. Our intention at this point was to relactonize using reverse activation; that is, instead of the normal lactonization procedures involving the activation of the acid function followed by attack by the hydroxy group, we planned to activate the hydroxy group and attack with the carboxy group. Only this latter situation would be capable of giving the required inversion of stereochemistry. In fact, Seuring and Seebach have reported[7] accomplishing a manipulation of this type on diolides and a large-ring lactone using Mitsunobu's reaction[8]. Hence, the alcohol 4 was reacted with Ph_3P and diethyl azodicarboxylate (DEAD). A new lactone 5a was isolated, initially by column chromatography, which possessed the desired R,S,R-stereochemistry. The column isolation procedure, being far from convenient or effective, was subsequently avoided by acid hydrolysis of the entire inversion product. Crystallization from acetone afforded the hydrochloride of the acid lactone 5b in 53% overall yield from S,S,R-lactone 3[9].

Before proceeding, it is worthy of note that this inversion has been accomplished in similar yield with two other reagent combinations, Ph_3P/diethyl ketomalonate[10] and $Ph_3PO/(CF_3SO_2)_2O$[11]. Undoubtedly, each of these combinations forms an active species capable of transforming the target hydroxy group into an S_N2-prone alkoxyphosphonium intermediate 9[12].

Scheme I[a]



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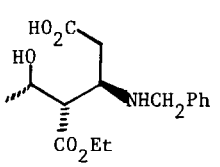
3



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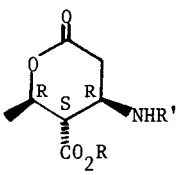
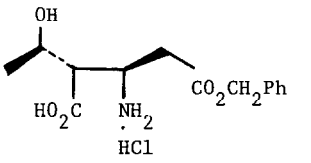


5a, R=Et, R'=CH_2Ph
b, R=H , R'=CH_2Ph
c, R=R'=H



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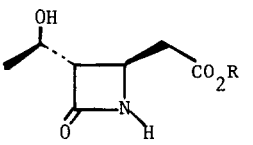
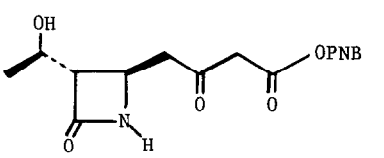
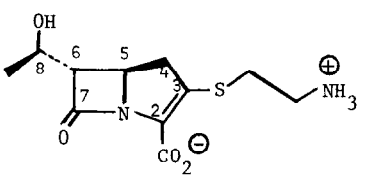


7a, R=CH_2Ph
b, R=H



8

PNB= $-CH_2C_6H_4NO_2(p)$

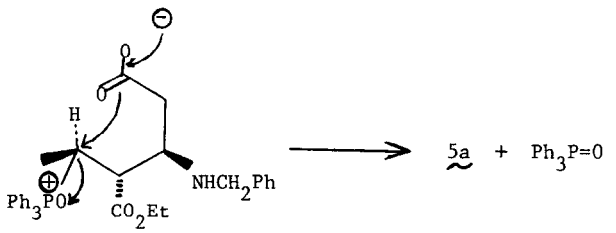


1

Thienamycin

8R, 6S, 5R ≡ R,S,R

[a](a) HCl,CH_2Cl_2, room temp.; (b) 1 eq. $NaHCO_3$, H_2O; (c) 1.3 eq. Ph_3P, 1.3 eq. DEAD, THF; (d) conc. aq. HCl, reflux 3 hrs; (e) 20% $Pd(OH)_2/C$, 40 psi H_2, HOAc; (f) $PhCH_2OH$ (7 ml/g 5c), 70°, 4.5 hrs.; (g) 1.0 eq. NEt_3, 1.0 eq. DCC, $PhCH_2OH$, 55°, 4.5 hrs; (h) 40 psi H_2, Pd/C, MeOH; (i) (1) 1.0 eq. CDI, MeCN/DMF; (2) 1.2 eq. $Mg(O_2CCH_2CO_2PNB)_2$, room temp. 16 hrs.



9

The R,S,R-lactone thus obtained was processed in a manner similar to the S,S,R-series although several operational changes have been made and silyl protection during the chain-elongation reaction has been avoided. After catalytic removal of the N-benzyl group, the crystalline lactone 5c was heated in benzyl alcohol to establish an equilibrium between the opened ester 6 and lactone 5c (approximately 2/1 respectively by NMR). These reaction partners were separated simply by cooling the reaction solution to room temperature. The unreacted lactone precipitates and is collected by filtration (37% recovered). The filtrate containing pure acyclic ester 6 could be used directly in the subsequent carbodiimide reaction or it could be diluted with MeCN to give the crystalline amino acid 6 in 86% yield based on recovered lactone. A solution of this amino acid in benzyl alcohol was cleanly dehydrated with N,N'-dicyclohexylcarbodiimide (DCC) to give the crystalline β-lactam 7a in 88% yield. After catalytic removal of the benzyl ester, the resulting acid 7b in a mixture of MeCN and DMF was treated with N,N'-carbonyldiimidazole (CDI) followed by a slight excess (both carboxylates are used) of the magnesium salt of p-nitrobenzyl hydrogen malonate[13]. The R,S,R- β-keto ester 8 (80% pure by HPLC assay[14] 82% weight yield from 7a) is more than pure enough for the subsequent reactions[1] leading to (±)-thienamycin. Alternatively, the crude material can be recrystallized to afford pure 8 identical in every respect to the previously reported sample.

Acknowledgement: We would like to thank Dr. A. W. Douglas and Mr. R. A. Reamer for their expertise in the determination and interpretation of NMR spectra that guided this work from the beginning.

Notes & References

1) D. G. Melillo, I. Shinkai, T. Liu, K. Ryan and M. Sletzinger, Tetrahedron Lett., 21, 2783 (1980).

2) For a discussion of the exceptional potency of this uniquely structured antibiotic see J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff and J. Birnbaum. J. Antibiot., 32, 1(1978) and references therein.

3) The stereochemical descriptors refer to the atoms that are to become carbons 8, 6 and 5 of thienamycin respectively. Since all the 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.

4) T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard, and B. G. Christensen, Phil. Trans. R. Soc. Lon. B. 289, 191(1980); J. Am. Chem. Soc., 102, 6161(1980).

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

6) Selected data. 3: mp 185-7° (dec); free base, δ($CDCl_3$),1.21(t,3,J=7.1,CH_2Me), 1.31(d,3,J=5.6, Me), 1.44(bs,1,NH), centered 2.69(ABX,2,J=6.4,6.6 and 16.8,H_3 and H_3'), 2.76(dd,1,J=3.7 and 3.9,H_5), 3.5(ABX,1,J=3.9,6.4 and 6.6,H_4), 3.79(s,2,CH_2N), 4.19(q,2,J=7.1,CH_2Me), 4.87(dq, 1,J=3.7 and 5.6,H_6) and 7.2(s,5,Ph). 5a: δ($CDCl_3$), 1.28(t,3,J=7.2,CH_2Me), 1.40(d,3,J=6.2, Me), 1.66(bs,1,NH), 2.55(dd,1,J=7.5 and 10.4,H_5), centered 2.73(ABX,2,J=5.9,6.6 and 16.7,H_3 and H_3'), 3.45(ABX,1,J=7.5,5.9 and 6.6,H_4), 3.76 and 3.93(AB,2,J=12,NCH_2), 4.22(q,2,J=7.2, CH_2Me), 4.50(dq,1,J=6.2 and 10.4,H_6), and 7.31(s,5,Ph). 5c: mp 184-6° (dec). 6: mp 160-3° (dec). 7a: mp 99-101.5°; ν($CHCl_3$), 3700-3150, 1763, and 1735 cm^{-1}; δ($CDCl_3$), 1.34(d,3,J=6.3, Me), 2.17(b,1,OH), 2.79(d,2,J=6.9,CH_2COOR), 2.93(dd,1,J=2.0 and 6.8,H_3), 3.98(dt,1,J=2.0 and 6.8,H_4), 4.20(dq,1,J=6.3 and 6.7,CH-OH), 5.19(s,2,COOCH_2Ph), 6.05(b,1,NH) and 7.43(s,5,Ph).

7) B. Seuring and D. Seebach, Liebigs Ann. Chem., 2044(1978).

8) T. Kurihara, Y. Nakajima, and O. Mitsunobu, Tetrahedron Lett.,2455(1976).

9) Care must be exercised during this sequence of steps to avoid a number of competing side-reactions which include lactonization without inversion (4 to 3) both before and after the Ph_3P/DEAD reaction and also partial oxidation of the N-benzyl group to the Schiff base during the inversion reaction. This latter reaction was discovered by Dr. G. Gal and Mr. R. Purick of these labs.

10) O. Achmatowicz and G. Grynkiewicz, Tetrahedron Lett., 3179(1977).

11) The triphenylphosphine ditriflate that is formed is a known reagent, see J. B. Hendrickson and S. M. Schwartzman, Tetrahedron Lett., 277(1975). However, this is a novel application.

12) An attempt has been made to explain the selectivity of phosphonium transfer reagents of this type towards hydroxy activation relative to carboxy activation in the case of β-hydroxy acids; see: J. Mulzer, G. Brüntrup, and A. Chucholowski, Ang. Chem. Int. Ed. Engl., 18, 622 (1979). Whether these arguments, which are based on reasonance energy and steric hindrance, are directly applicable to δ-hydroxy acids is questionable.

13) This procedure, which is a modification of a published procedure [D. W. Brooks, L.D.-L. Lu, and S. Masamune, Ang. Chem. Int. Ed. Engl., 18, 72(1979)], was optimized for the S,S,R-counterpart of 7b, by Dr. R. Volante and Mr. H. Barkemeyer of these labs and directly applied to this series.

14) We thank Dr. W. B. Caldwell for this measurement.

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