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A FACILE TRANSFORMATION OF BICYCLIC KETO ESTERS TO BISPROTECTED (±)-8-EPITHIENAMYCIN *VIA* ENOL ACTIVATION

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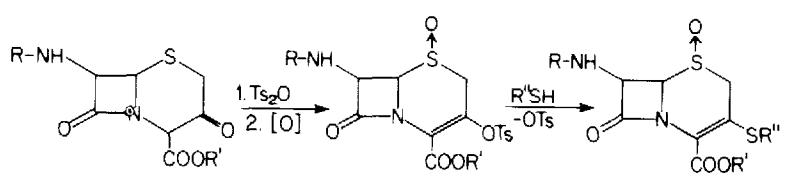
Summary : A facile "one-pot" transformation of bicyclic keto ester (**2**) to bisprotected (±)-8-epithienamycin *via* enol phosphate activation followed by the addition-elimination reaction of *N*-protected cysteamine derivatives is described.

Recently, an efficient and operationally simple synthesis of (±)-thienamycin (**1**) from diethyl 1,3-acetonedicarboxylate which is adaptable to large scale manipulation was achieved[1]. An interesting, stereocontrolled synthesis of (+)-thienamycin starting from *L*-aspartic acid has also recently been accomplished[2]. Both approaches rely upon the same intermediate namely, (5*R*,6*S*,8*R*) *p*-nitrobenzyl 6-(1-hydroxyethyl)-1-azabicyclo(3,2,0)heptan-3,7-dione-2-carboxylate which is derived from the efficient carbenoid cyclization reaction of the corresponding diazo ester[1]. This paper describes the methodology for a convenient transformation of racemic (5*R*,6*S*, 8*S*) bicyclic keto ester (**2**) to bisprotected (±)-8-epithienamycin (**5**).

The transformation of a bicyclic keto ester to a vinyl sulfide *via* an addition-elimination reaction using the vinyl tosylate as an activated intermediate was initially applied to the cephalosporin derivative by Scartazzini and co-workers[3] as shown in Scheme I. This approach was

Scheme I

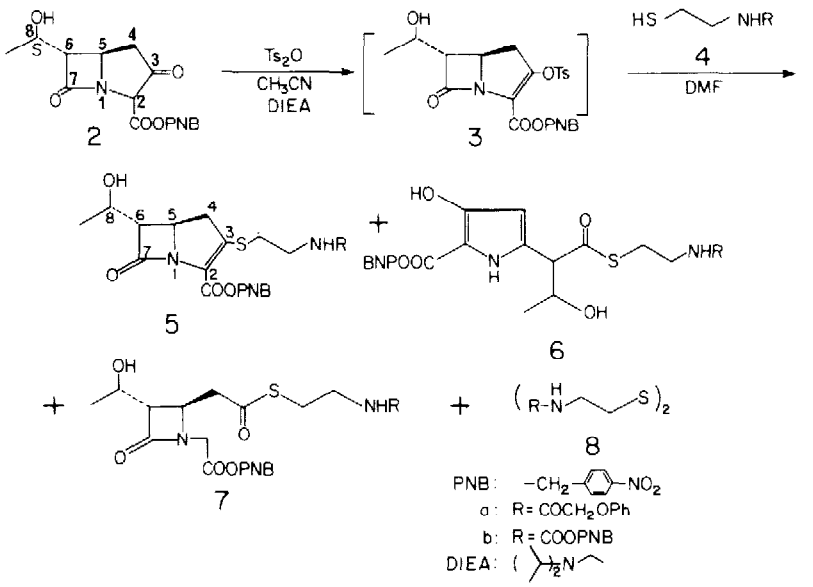


used in the total syntheses of northienamycin[4],homothienamycin[5] and deshydroxyethylthienamycin[6] derivatives. This addition-elimination reaction was investigated in depth using the model system (±)-(5*R*,6*S*,8*S*) bicyclic keto ester (**2**) which is a precursor of (±)-8-epithienamycin.

Based on the synthesis of deshydroxyethylthienamycin[6], we anticipated the chemistry developed for **2** should, in principle, be transferable to the keto ester which has the required (5*R*,6*S*,8*R*) thienamycin stereochemistry and in fact this has recently been accomplished[1,2]. The reaction of **2** with *p*-toluenesulfonic anhydride occured smoothly in acetonitrile in the presence of diisopropylethylamine to form enol tosylate (**3**). Without isolation of **3** , the solvent was displaced with *N*,*N*-dimethylformamide (DMF)[7], and futher reaction with *N*-phenoxyacetyl cysteamine (**4a**)[8] gave the desired bisprotected 8-epithienamycin, (**5a**) mp 135-138 °C (dec.) in 67 %

yield. The cysteamine derivative (**4b**) behaved similarly to form **5b**, mp 184-187 °C (dec.) in 85 % yield. In addition, small amounts of by-products such as the pyrrole derivative (**6a**)[9], monocyclic β-lactam (**7a**) and disulfide (**8a**) were isolated and characterized by ^{1}H and ^{13}C NMR[10].

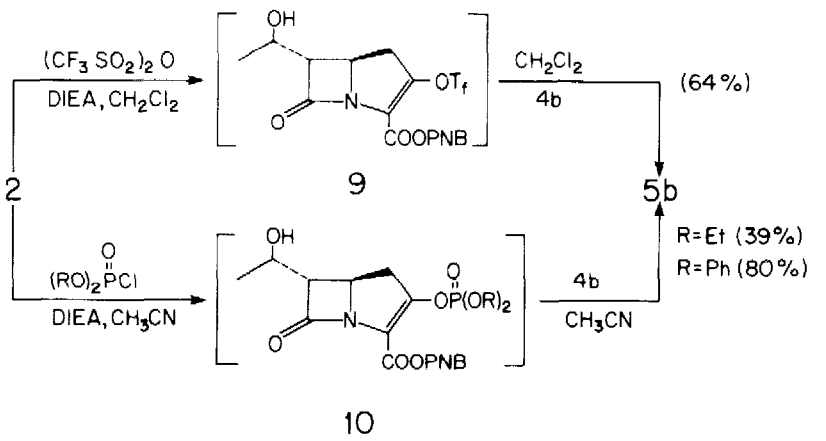
Scheme II



Since the above two step sequence required two different solvents, it was difficult to handle on large scale. A single solvent system for the transformation of **2** to **5** which would not entail the isolation of the reactive intermediate **3** was therefore desireable. The addition-elimination mechanism led us to consider the possibility of utilizing the enol triflate[11] and enol phosphate[12] which have good anionic leaving groups. We felt that one or both of these groups would offer advantages over the enol tosylate derivative.

The reaction of the bicyclic keto ester(**2**)with trifluoromethanesulfonic anhydride in dichloromethane at 0 °C yielded the enol triflate (**9**). An attempted isolation of **9** failed due to its instability. However, it was possible to react **9** with **4b** in the same solvent without isolation to yield **5b** in a 64 % yield. Unfortunately, because of instability of trifluoromethanesulfonic anhydride, we found that this reaction was very difficult to control. On the other hand, the enol phosphate derivative **10** satisfied all the requirements. This was easily made in acetonitrile from either dialkyl- or diarylchlorophosphate[13] using diisopropylethylamine as a base[14]. Thus treatment of **10** (R=Ph and Et) with **4b** gave **5b** (80 % and 39 %, respectively). The desired **5b** crystallized from the reaction mixture as analytically pure material. This new methodology is amenable to large scale manipulation.

Scheme III



Acknowledgements : We thank Dr. R. W. Ratcliffe for stimulating discussions and Drs. A.W. Douglas and B. H. Arison for the ^{1}H NMR assistance.

References and Notes

1. D. G. Melillo, I. Shinkai, T. Liu, K. M. Ryan and M. Sletzinger, accepted for publication in Tetrahedron Lett..
2. T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard and B. G. Christensen " Penicillin--50 Year After Fleming ", London, England, May, 1979. T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard and B. G. Christensen, accepted for publication in J. Am. Chem. Soc..
3. R. Scartazzini, P. Schneider and H. Bickel, Helv. Chim. Acta, 58, 2437 (1975). R. Scartazzini and H. Bickel, Heterocycles, 7, 1165 (1977).
4. D. G. Melillo and K. M. Ryan, European Patent Application Publication Number 0010312 ; publication date, April 30, 1980. In this case, the addition-elimination reaction does not involve a fused β-lactam keto ester system.
5. T. N. Salzmann, R. W. Ratcliffe and B. G. Christensen, Tetrahedron Lett., 21, 1193 (1980).
6. R. W. Ratcliffe, T. N. Salzmann and B. G. Christensen, Tetrahedron Lett., 21, 31 (1980).
7. This procedure required displacement of the solvent from acetonitrile to DMF. We found the activation step could not be carried out in DMF and addition-elimination step did not proceed well in acetonitrile.
8. Preparation of N-protected 2-aminoethanethiol, see: M. Sletzinger, T. Liu, R. A. Reamer and I. Shinkai, submitted for publication in Syntheses.
9. The formation of the pyrrole **6a** might be envisaged as a nucleophilic attack of the thiol

group on the β-lactam carbonyl group and subsequent β-lactam ring opening.

10. All new compounds have been fully characterized and their spectral data, elemental composition and mass spectra are in accord with their assigned structures. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian SC-300 (300 MHz) and Varian XL-100 (100 MHz) spectrometers and ^{13}C spectra were recorded on a Varian CFT-20 NMR spectrometer. All chemical shifts are reported with respect to internal Me_4Si (δ=0). Selected data. **2**, ^{1}H NMR (100 MHz), δ ($CDCl_3$) 1.43 (d,3,J=6.4,CH_3), centered at 2.72 (ABX,2,J=6.8,7.7 and 18.9, H_4 and H_4'), 3.31 (dd,1,J=2.0 and 5.3,H6), 4.13 (ABX,1,J=2.0,6.8 and 7.7,H_5), 7.42 (d,2,J=8.7,Ar) and 8.25 (d,2,J=8.7,Ar). **2**, ^{13}C NMR δ(DMSO-d_6) 21.1 (CH_3), 40.3 (C_4), 51.2 (C_5), 63.2,63.8 and 66.7 (C_2,C_6 and C_8), 65.4 (OCH_2), 123.5, 128.3, 143.2 and 147.1 (Ar), 165.4 ($COOCH_2$), 173.5 (C_7) and 208.6 (C_3). **5a** ^{1}H NMR (100 MHz), δ($CDCl_3$) 1.41 (d,3,J=6.8,CH_3), centered at 3.00 (m,5,H_4,H_4',SCH_2 and H_6), 3.52 (m,2,NCH_2), 4.20 (m,2,H_5 and H_8), 4.50 (s,2,CH_2OPh), 5.40 (AB,2,J=14.0,$COOCH_2Ar$),7.0 (m,4,NH and Ar), 7.32 (m,2,Ar), 7.69 (d,2,J=9.0,Ar) and 8.26 (d,2,J=9.0,Ar). **5b**,^{1}H NMR (300 MHz), δ(Acetone-d_6) 1.31 (d,3,J=6.0,CH_3), 3.08 (m,2, CH_2S), centered at 3.41 (ABX, 2,J=8.5,10.0 and 18.5,H_4 and H_4'), 3.47 (dd,1,J=3.0 and 6.5, H_6), 3.42 (q,2,J=6.5,CH_2N), 4.2 (dq,1,J=6.0 and 6.2,H_8), 4.27 (ABX,J=3.0 and 8.0,H_5), 5.26 (s,2,$NHCOOCH_2Ar$), 5.30 and 5.57 (AB,2,J=14.0,$COOCH_2Ar$), 6.92 (m,1,NH), 7.67 (d,2,J=8.5,Ar), 7.83 (d,2,J=8.5,Ar) and 8.27 (d,4,J=8.5,Ar). **5b**,^{13}C NMR, δ(DMSO-d_6) 21.3 (CH_3), 31.5 (SCH_2), 51.7 (C_5), 63.6 (CH-OH), 65.8 (C_6), 122.3 (C_2), 150.4 (C_3), 155.9 (NHCOO), 160.5 ($COOCH_2Ar$), 177.6 (C_7) besides aromatic carbon signals. **6a**,^{1}H NMR (100 MHz), δ(Acetone-d_6) 1.08 (d,3,J=6.0,CH_3), 3.07 (t,2,J=7.0,SCH_2), 3.50 (q,2,J=6.0,NCH_2), 3.87 (d,1,J=8.0,CHCOS), 4.25 (b,1,CH-OH), 4.40 (m,1,$CHCH_3$),4.47 (s,2,$COCH_2OPh$), 5.48 (s,2,$COOCH_2$), 5.80 (d,1,J=2.0, Hβ in pyrrole), 7.0 (m,3,Ar), 7.32 (m,2,Ar), 7.76 (d,2,J=8.4,Ar), 7.80(m,2,OH in pyrrole ring and NHCO), 8.30 (d,2,J=8.4,Ar) and 10.3 (broad s,1,NH). **7a**,^{1}H NMR (100 MHz), δ($CDCl_3$) 1.31 (d,3,J=6.5,CH_3), centered at 3.0 (m,5,SCH_2,H_3 and CH_2COS),3.5 (q,2,J=6.0,NCH_2), 4.1 (AB,2,J=18.2,NCH_2COOAr), 4.1 (m,2,H_4 and CH-OH), 4.52 (s,2,$COCH_2OPh$), 5.27 (s,2,$COOCH_2Ar$), 7.2(m,6,NH and Ar), 7.56 (d,2,J=9.0,Ar) and 8.26 (d,2,J=9.0,Ar). **7a**,^{13}C NMR, δ($CDCl_3$) 21.0 (CH_3), 28.8 (SCH_2), 38.5 (NCH_2), 42.4 (CH_2COS), 47.1 (NCH_2COOAr), 51.8 (C_4), 65.5 (CH-OH), 67.2 (C_3), 168.0 (C_2) and 197.0 (CH_2COS) besides other carbon signals.

11. P. J. Stang and T. E. Dueber, Org.Synth., 54, 79 (1974).

12. W. Perkow, Chem.Ber., 87, 755 (1954).I. J. Borowitz, S. Firstenberg, E.W.R. Casper and R. K. Crouch, J. Org. Chem., 36, 3282 (1971).

13. The formation of enol phosphate using diphenylchlorophosphate was first achieved in the case of deshydroxyethyl bicyclic keto ester by Dr. R. W. Ratcliffe and results will be published.

14. The intermediacy of **10** was proven by ^{13}C NMR, δ(CD_3CN) 21.6 (CH_3),37.1 (C_4), 51.7 (C_5), 64.8 (CH-OH), 65.9 ($COOCH_2Ar$), 67.7 (C_6), 119.4 (C_2,$^{3}J_{CP}$=11.0), 153.9 (C_3,$^{2}J_{CP}$=7.2), 160.0 ($COOCH_2Ar$) and 179.8 (C_7) besides aromatic carbon signals.

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