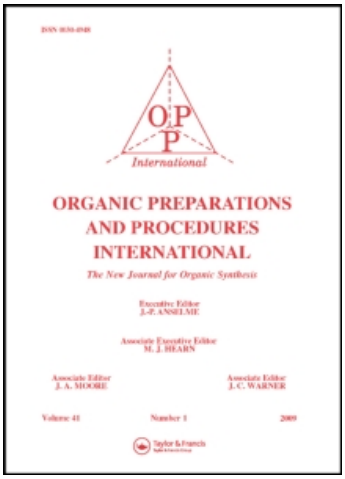

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STEREOSELECTIVE REDUCTION OF PIVALOYLOXYMETHYL (2S,5R,6S)-6-ACETYL-3,3-DIMETHYL-7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPTANE-2-CARBOXYLATE WITH SODIUM BOROHYDRIDE

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E.M. (m/e): 311 (M^+, 6.0); 190 (100.0); 177 (19.8); 122 (23.2).

Anal. Calcd for $C_{19}H_{21}O_3N$: C, 73.37; H, 6.81; N, 4.50. Found: C, 73.38; H, 6.80; N, 4.48

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REFERENCES

1. G. Seidl, R. Huisgen, and J. H. M. Hill, *Tetrahedron*, **20**, 633, (1964).

2. K. Brewster, R. A. Chittenden, R. M. Pinder and M. Skeeis, *J. Chem. Soc., Perkin I*, 941 (1972).

3. *Org. React., Coll. Vol. III*, John Wiley & Sons, Inc., London, 383 (**1954**).

4. O. H. Oldenzeil, D. van Leusen and A. M. van Leusen, *J. Org. Chem.*, **42**, 3114 (1977).

5. L. Crombie, M. J. Powel and P. Tuchinda, *Tetrahedron Lett.*, **21**, 3603 (1980).

6. R. F. Nystron and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738, (1948).

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STEREOSELECTIVE REDUCTION OF PIVALOYLOXYMETHYL (2S,5R,6S)-6-ACETYL-3,3-DIMETHYL-7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPTANE-2-CARBOXYLATE WITH SODIUM BOROHYDRIDE

Submitted by (07/08/91)

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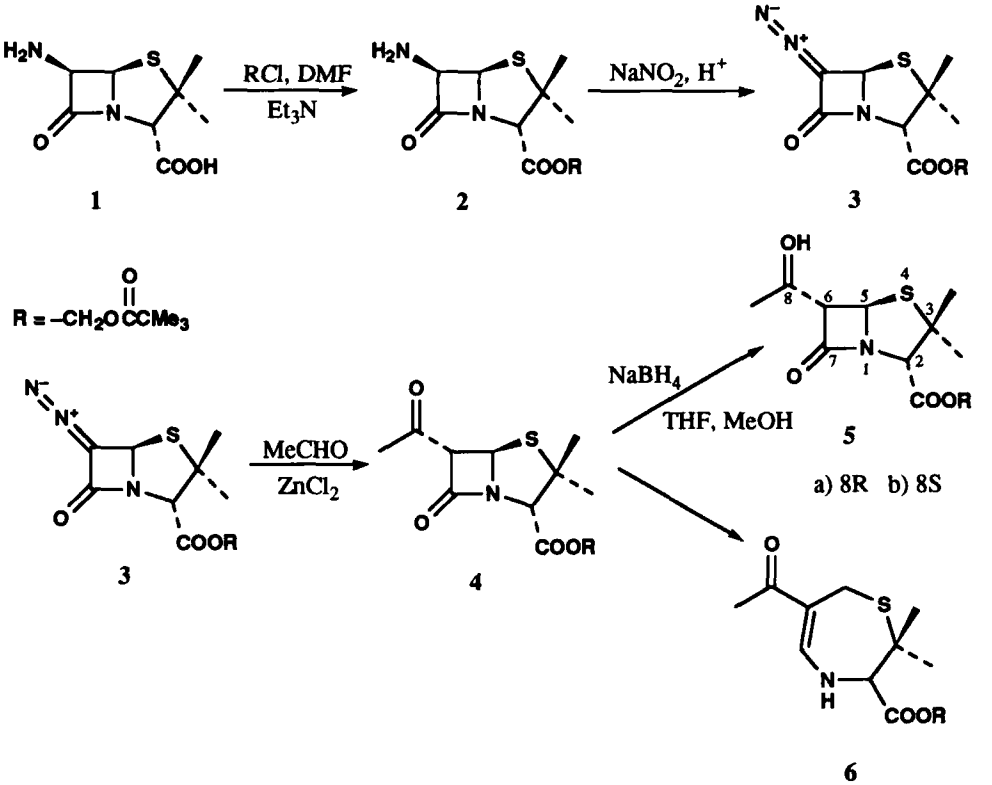
Since the discovery of thienamycin in 1976, several classes of active β-lactam antibiotics enhanced the importance of the hydroxyalkyl side chain[1] at the C-3 position of the β-lactam ring. In particular, the insertion of the α-oriented (1R)-hydroxyethyl chain at the C-6 has been found to be essential, both for antibacterial activity and resistance toward β-lactamases of the penem and carbapenem classes.[2] During our search for new β-lactam antibiotics, we identified pivaloyloxymethyl (S)-6-[(R)-1-hydroxyethyl]penicillanate as a key intermediate and set up a convenient method to prepare it on a laboratory scale. The introduction of the (1R)-hydroxyethyl chain on β-lactams has been widely described;[3] however, the direct introduction of the (1R)-hydroxyethyl chain at position 6 of the penicillanates has been described only in a few cases[3a,c,e,h] and in particular, it has been described only once for the pivaloyloxymethyl ester.[3h] Karaday *et al.*[3a] obtained excellent

results in the stereoselective synthesis of benzyl (S)-6-[(R)-1-hydroxyethyl]penicillanate, starting from the corresponding 6-diazo derivative, which was reacted with acetaldehyde to yield the 6-acetyl ester. The latter was then stereoselectively reduced with diisopropylamine-borane in the presence of five-fold excess of anhydrous magnesium trifluoroacetate in ether. However, as the latter procedure did not appear to be practical to prepare large amounts of the desired product, particularly because of the nature and the amount of the required reagents, we decided to investigate the same reaction sequence with the aim of finding a simpler reducing method.

Thus pivaloyloxymethyl 6-hydroxyethyl penicillanate (**5**) was prepared starting from 6-aminopenicillanic acid (**1**) (6-APA), as outlined below. Pivaloyloxymethyl 6-diazopenicillanate (**3**) was prepared according to the reported method[4] and used without any purification. Initial attempts to introduce the acyl function under carbene generating conditions with rhodium acetate as a catalyst,[4] failed. Then, according to a published procedure,[3a] 6-diazopenicillanate (**3**) was treated with zinc chloride and acetaldehyde, to afford pivaloyloxymethyl (S)-6-acetylpenicillanate (**4**) in 70% yield;[5] however, it was completely converted into the thiazepinone (**6**) on the attempted purification by silica gel chromatography.[6] Thus, the crude derivative, which can be stored at -20° overnight without decomposition, was used in the next step. The reduction of the acetyl group can, in principle, be



performed according to several methods previously described either for 6-acetylpenicillanates and 3-acetylazetidinones.[7] However, we found that some of these methods, such as K-Selectride,[3d,7c]

failed on our bicyclic system, probably because of enhanced steric hindrance.[7e] Moreover, the use of a simple reducing agent such as sodium borohydride has been reported mainly for the reduction of azetidinone derivatives; Jephcote *et al.* reduced crude 2,2,2-trichloroethyl (R)-6-acetyl-6-methylpenicillanate (obtained from the corresponding 6-diazopenicillanate by reaction with acetone in the presence of BF_3-Et_2O) by using $NaBH_4$ in dioxane-phosphate buffer (pH 7) and obtained the desired 2,2,2-trichloroethyl (R)-6-(1'-hydroxyethyl)-6-methylpenicillanate in 60% yield as a 2.3:1 mixture of 1'-epimers,[7d] but our unstable substrate was not reduced under such conditions and complete decomposition occurred. Thus we were prompted to further investigate the use of $NaBH_4$ to determine the best conditions for its application in the stereoselective reduction of 6-acylpenicillanates. The best results were obtained by carrying out the reaction in tetrahydrofuran-methanol solution, as described below.

In conclusion, the method described simplifies the earlier procedures and makes it possible to obtain good stereoselectivity, carrying out the whole procedure in a few hours.

EXPERIMENTAL SECTION

The spectra were recorded at 300 MHz on a Varian VXR-5000 spectrometer in $CDCl_3$ at 20°, and the chemical shifts (δ) were measured relative to internal TMS. HPLC analysis of compounds **5a** and **5b** were carried out by using a 25 cm x 0.46 cm id Spherisorb S5W column and *n*-hexane-ethanol (95:5 v/v) as mobile phase (flow rate 1 mL/min); the retention time observed were typically 8.1 min for isomer **5b** and 9.1 min for isomer **5a**.

Preparation of Compound 5.- A catalytic amount of zinc chloride (about 40 mg) was added to a solution of freshly distilled acetaldehyde (30 mL) in anhydrous methylene chloride (300 mL), after which pivaloyloxymethyl 6-diazopenicillanate (**3**, 9 g) was added to the suspension and the mixture was stirred at 10-15° during 30 minutes. It was then poured into a 5% phosphoric acid solution (30 mL). The organic layer was washed with brine and dried over magnesium sulfate and concentrated. The crude 6-acetyl derivative (**4**) was dissolved in a mixture of tetrahydrofuran (86 mL) and methanol (48 mL) and the solution was added, over a period of 10 minutes, to a cold solution of sodium borohydride (1.35 g) in methanol (30 mL) at -20°. After 20 minutes at the same temperature (at a lower temperature the reaction was very slow and at a higher temperature the stereoselectivity was lower), the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and the crude solid was purified by flash chromatography (Merck kieselgel 60, 230-400 mesh, cyclohexane-ethyl acetate 9/1) to afford **5** as a foam (2.7 g, 30% yield from 6-diazopenicillanate) as a 95:5 mixture (by ^1H NMR analysis) of 8R and 8S epimers. The epimers were separated by semi-preparative HPLC (the analytical conditions were scaled up by using a 25 cm x 2.54 cm id column) and then fully identified by NMR techniques. The configurations of **5a** (8R) and **5b** (8S) can be deduced from the ^1H NMR spectra, from a number of different NOE measurements (on H-8, H-5 and H-6), NOESY experiments and the coupling constant values.

^1H NMR of **5a** (8R): δ 5.85, 5.78 (2H, ABq, $-CO_2CH_2OCO-$), 5.22 (1H, d, J = 1.5 Hz, H5); 4.49 (1H,

s, H2); 4.21 (1H, m, H8); 3.38 (1H, dd, J = 6.3 Hz, 1.5 Hz, H6); 1.62 (3H, s, 2β-CH_3); 1.48 (3H, s, 2α-CH_3); 1.37 (3H, d, J = 6.3Hz, -CH-CH_3); 1.21 (9H, s, $SiCMe_3$).

^{1}H NMR spectra of **5b** (8S): δ 5.87, 5.78 (2H, ABq, -CO_2CH_2OCO-), 5.28 (1H, d, J = 1.5 Hz, H5); 4.48 (1H, s, H2); 4.26 (1H, m, H8); 3.31 (1H, dd, J = 6.3 Hz, 1.5 Hz, H6); 1.63 (3H, s, 2β-CH_3); 1.48 (3H, s, 2α-CH3); 1.34 (3H, d, J = 6.3 Hz, -CH-CH_3); 1.22 (9H, s, $SiCMe_3$).

The ^{1}H NMR spectra of **5a** (8R) and **5b** (8S) show small vicinal coupling constants, $J_{5,6} < 2$ Hz, for the two β-lactam hydrogens; on this basis, the *trans* β-lactam configuration was confirmed, i. e. the stereochemistry is R at C_5 and S at C_6. The absolute configuration at C_8 was also determined by different NOE effects between H_5 and 8-CH_3 in the two cases, by applying Mosher's[8] NMR configuration-correlation method on similar derivatives and from literature data.[9]

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REFERENCES

1. See for example: G. I. Gregory, "*Recent Advances in the Chemistry of β-Lactams*", The Royal Society of Chemistry, London, **1981**; A. G. Brown and S. M. Roberts, "*Recent Advances in the Chemistry of β-Lactams*", The Royal Society of Chemistry, London, **1985**

2. E. Perrone, Il Farmaco (Pavia), **43**, 1075 (1988) and references cited therein.

3. a) S. Karaday *et al.*, *J. Am. Chem. Soc.*, **103**, 6765 (1981); b) T. N. Salzmann *et al.*, *ibid.*, **102**, 6161 (1980); c) A. Yoshida *et al.*, *Chem. Pharm. Bull. Japan*, 29, 2899 (1981); d) H. Ona *et al.*, *ibid.*, **33**, 4382 (1985); e) F. Di Ninno *et al.*, *J. Org. Chem.*, **42**, 2960 (1977); f) F. A. Bouffard and T. N. Salzmann, *Tetrahedron Lett.*, **26**, 6285 (1985); g) Y. Ito *et al.*, *ibid.*, **27**, 5751(1986); h) R. L. Rosati *et al.*, *J. Med. Chem.*, **33**, 291 (1990).

4. S. A. Matlin, *J.Chem. Soc., Perkin Trans. I*, 89-96 (1990)

5. The stereochemistry at C_6 was confirmed by ^{1}H NMR, which showed small vicinal coupling constants, J = 1.7 Hz for the hydrogens H_5 and H_6, typical of a β-lactam trans configuration.

6. The structure was confirmed by comparing the spectral data with those reported for the corresponding 2,2,2-trichloroethylester [J. C. Sheehan *et al.*, *J. Org. Chem.*, **43**, 4856 (1978)].

7. See refs. 3a,d,g; a) J. H. Bateson *et al.*, *Chem. Comm.*, 1151 (**1986**); b) M. Sato *et al.*, *Tetrahedron Lett.*, **27**, 6091 (1986); c) F. Pecquet and J. d'Angelo, *ibid.*, **23**, 2777 (1982); d) V. J. Jephcote *et al.*, *ibid.*, **25**, 2919 (1984); e) F. A. Bouffard and B. G. Christensen, *J. Org. Chem.*, **46**, 2208 (1981);

8. A. J. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

9. H. R. Pfaendler *et al.*, *ibid.*, **102**, 2039 (1980).

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