Tetrahedron Letters,Vol.27,No.40,pp 4857-4860,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

HIGHLY CHEMOSELECTIVE AND STEREOCONTROLLED ACCESS TO 6-ALPHA-ALLYL PENICILLANATES

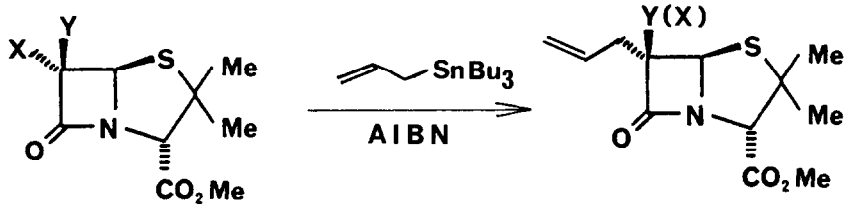
Stephen Hanessian* and Marco Alpegiani
Department of Chemistry, Université de Montréal
Montréal, Québec, Canada H3C 3J7

Summary - Treatment of 6-bromo penicillanates with allyltributyltin under free-radical conditions results in the formation of 6-alpha allyl derivatives.

The discovery of the remarkably potent β-lactam antibiotic thienamycin[1] has fostered intensely pursued research activities in a host of laboratories worldwide. One of the unique features that was unveiled by Nature in this class of carbapenem antibiotics was the presence of an α-orientated hydroxyethyl side-chain at C-6. In fact, the introduction of this side-chain in the penem series[2] such as in penem FCE 22101,[3] results in markedly enhanced antibacterial activity.[4] The introduction of functionality other than amino at the 6-position of the penam nucleus has also been shown to generate inhibitors to β-lactamase enzymes.[5] In all instances, the alpha or beta orientation of side-chains seem to be primordial for eliciting the desired biological response.

To the best of our knowledge, there exist two general methods for the preparation of 6-mono-alkyl penams. One relies on the hydrogenation of an alkylidene derivative,[6] and the other on a radical induced substitution of a preexisting 6,6-disubstituted derivative by hydrogen.[7,8] In both instances, the corresponding 6-β-alkyl penicillinate was the predominant product.

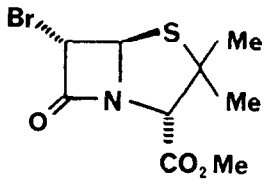
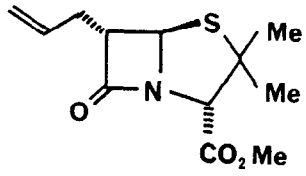
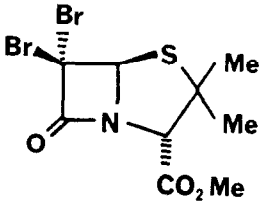
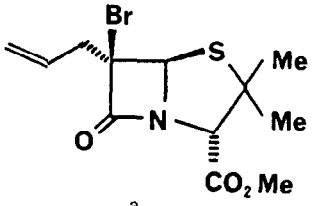
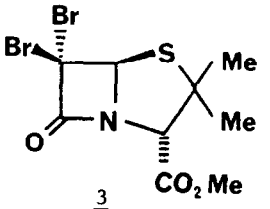
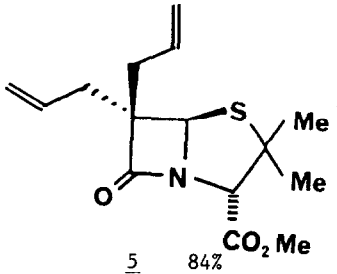
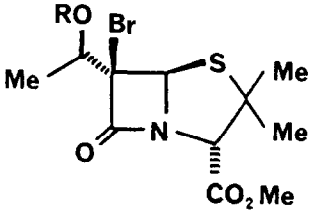
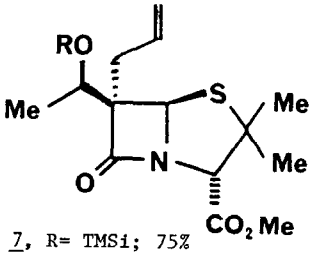
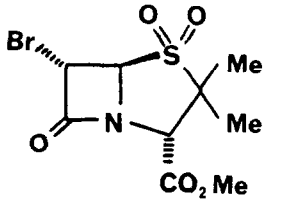
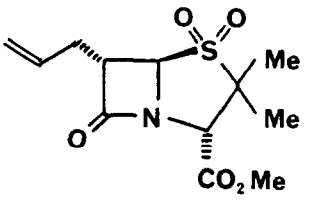
We report on a novel method for the introduction of the functionally versatile allyl group at C-6 in the penam nucleus, and on the synthesis of several 6-alpha substituted derivatives as well as 6,6-disubstituted derivatives. To this end, we have exploited the direct free-radical allylation[9] of 6-bromopenicillanates with allyltributyltin in the presence of a catalytic amount of AIBN. The reactions proceed efficiently under mild conditions, and with a remarkable degree of stereocontrol as shown in Table 1.



X=Br; Y=H
X,Y=Br
X=Br; Y= Me OH
X= ; Y=Br

Y=H
Y=Br
Y=Me OH
X=

Table 1

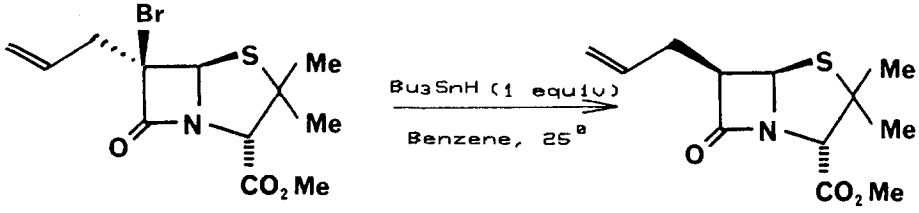
Bromo Penam	Equiv.  reflux, h.	Product; yield	Physical Data
	1.5 5 h		$[\alpha]_D$+237° (c 4.1 $CHCl_3$); ν_{max} (film) 1775,1750 cm^{-1} MS, 256 (M+1); H-5, 5.06 ppm, d, J= 1.6 Hz, ($CDCl_3$)
1 (ref. 12)		2 90%	
	1.7 3 h		$[\alpha]_D$+211° (c 1.1, $CHCl_3$); ν_{max} (film) 1790, 1750 cm^{-1}; MS 335, 333 (M+1); H-5, 5.33 p.p.m., s; ($CDCl_3$)
3 (Ref. 12, 14)		4[a] 54%	
	3 6 h		$[\alpha]_D$+256° (c 0.47, $CHCl_3$) ν_{max} (film) 1770, 1750 cm^{-1}; MS, 296 (M+1); H-5, 5.15 p.p.m; s, ($CDCl_3$)
3		5 84%	
	1.5 4 h		R=TMSi; $[\alpha]_D$+195° (c 0.45, $CHCl_3$); ν_{max} (film) 1770, 1750 cm^{-1}; MS, 372 (M+1); H-5, 5.08 p.p.m., s, ($CDCl_3$) R=H;
6, R= TMSi (ref. 13) 8, R= H (ref. 14)		7, R= TMSi; 75% 9, R= H; 81%	R=H; $[\alpha]_D$+202° (C 0.98, $CHCl_3$); ν_{max} (film) 1755 cm^{-1}; MS, 300 (M+1); H-5, 5.19 p.p.m., s; ($CDCl_3$)
	1.2 5 h		mp 93-95°; $[\alpha]_D$+169° (c 1.5, $CHCl_3$); ν_{max} (KBr) 1795, 1750 cm^{-1}; MS 288 (M+1) H-5, 4.36 p.p.m., d, J= 1.8 Hz., ($CDCl_3$)
10 (ref. 15)		11 93%	

a. The remainder consisted of a 1:1 mixture of starting material and diallyl derivative

A typical experimental procedure is as follows: A solution of the methyl 6-bromopenicillanate derivative (1 mmole), allytributyltin (1.5-3 mmole) and a catalytic amount of azobisisobutyronitrile (AIBN) in benzene (15 ml) was refluxed under argon (2-6h, Table 1). The allylated products were obtained as colorless syrups by flash chromatography (n-hexane/ethyl-acetate), followed by partitioning between acetonitrile and n-hexane.

In all cases studied, the allyl group was introduced from the α-face as confirmed by detailed ^{1}H n.m.r. analysis at 400 MHz, and NOE experiments. For example, irradiation of H-5 in 7 caused a 4.6% NOE enhancement of only one of the allyl methylene hydrogen atoms. The stereochemistry of compounds 4 and 9 was assigned by analogy.

Access to the 6-beta series was easily accomplished by reduction of the corresponding 6-beta-bromo-6-alpha-allyl derivative 4, which gave 12 in 87% yield; $[\alpha]_D$+304° (c2.6, $CHCl_3$); ν_{max} (film) 1780, 1755 cm^{-1}; MS, 256 (M+1); H-5, 5.44 p.p.m, J= 4.5 Hz; H-6, 3.7 p.p.m, m ($CDCl_3$). It should be noted that hydroxyethyl group in the olivanic acid[10] group of carbapenem antibiotics has a β-orientation.



4 12

The bromopenicillins reported in this work are amenable to routine handling and chromatography. It is somewhat surprising that the trichloroethyl ester corresponding to 4, and obtained from the treatment of trichloroethyl 6-diazopenicillanate with neat allyl bromide in the presence of $Cu(acac)_2$ has been reported as being rather unstable.[11] Reduction of this "unstable" bromide has been reported to give the 6-beta-allyl derivative (no details or physical constants[11]).

The presently reported methodology provides a direct access to 6-alpha penam derivatives which are configurationally related to the thienamycins and certain penems. The same methodology can also lead to the novel 6,6-di-alkyl penams. It is clear that the allyl group in such derivatives can be further manipulated chemically, to produce versatile, functionally useful compounds.

Finally, it is of interest to point out the chemoselective nature[9] of free-radical C-C bond forming reactions of the type reported herein, and the compatibility of delicately balanced penicillin-type functionality with the reaction conditions.[16]

Acknowledgments. We thank NSERCC and Farmitalia - Carlo Erba (Milan) for generous financial support and a sabbatical leave to Marco Alpegiani. We also thank Dr. Phan Viet Tan for assisting in ^{1}H n.m.r. NOE measurements, and Michael Evans for mass spectra.

References

1. For a review and pertinent references, see, R.W. Ratcliffe and G. Albers-Schönberg, in "Chemistry and Biology of β-lactam Antibiotics", R.B. Morin and M. Gorman, eds., Academic Press, New-York, N.Y. Vol. 2 (1982), p. 227;
2. For a review, see J. Ernest, in "Chemistry and Biology of β-lactam Antibiotics", R.B. Morin and M. Gorman, eds., Academic Press, New York, N.Y. Vol. 2 (1982), p. 315.
3. For a recent synthesis, see S. Hanessian, A. Bedeschi, C. Battistini and N. Mongelli, J. Am. Chem. Soc., 107, 1438 (1985); Lectures in Heterocyclic Chemistry p. 43 (1986), and references cited therein.
4. G. Franceschi, M. Foglio, M. Alpegiani, C. Battistini, A. Bedeschi, E. Perrone, F. Zarini and F. Arcamone, J. Antibiotics, 36, 938 (1983)
5. M.J. Loosemore and R.F. Pratt, J. Org. Chem., 43, 3611 (1978).
6. J.C. Sheehan, A. Buku, E. Chacko, T.J. Commons, Y.S. Lo, D.R. Ponzi and W.C. Schwarzel, J. Org. Chem., 42, 4045 (1977); F. DiNinno, J. Am. Chem. Soc., 100, 3251 (1978); S. Adam, W. Arnold and P. Schönholzer, Tetrahedron 39, 2485 (1983); S. Chandrasekaran, A.F. Kluge and J.A. Edwards, J. Org. Chem., 42, 3972 (1977); S.A. Matlin and L. Chan, J.C.S. Chem. Comm., 10 (1981).
7. P.J. Giddings, D.I. John and E.J. Thomas, Tetrahedron Lett., 21, 399 (1980); D.I. John, E.J. Thomas and N.D. Tyrrell, J.C.S. Chem. Comm., 345 (1979).
8. For some other modes of introduction of 6-alkyl chains in penams, see G.V. Kaiser, C.W. Ashbrook and J.E. Baldwin, J. Am. Chem. Soc., 93, 2342 (1971); M.M. Campbell, R.G. Harcus and S.J. Ray, Tetrahedron Lett., 1441 (1979); J.E. Arrowsmith, C.W. Greengrass and M.J. Newman, Tetrahedron, 39, 2469 (1983).
9. See for example, G.E. Keck and J.B. Yates, J. Am. Chem. Soc., 104, 5829 (1982); J. Grignon, C. Servens and M. Pereyre, J. Organometal. Chem., 96 225 (1975); See also T. Migita, K. Nagai and M. Kosugi, Bull. Chem. Soc. Japan, 56, 2480 (1983) and references cited therein.
10. D.F. Corbett, A.J. Eglington and T.T. Howarth, J.C.S. Chem. Comm. 953 (1977).
11. P.J. Giddings, D.I. John and E.J. Thomas, Tetrahedron Lett., 21, 395 (1980); D.I. John, N.D. Tyrrel and E.J. Thomas, Tetrahedron, 39, 2477 (1983).
12. J.P. Clayton, J. Chem. Soc., (C), 2123 (1969).
13. Prepared by silylation (trimethylsilyl chloride/imidazole, DMF, r.t., overnight, 95% yield) of the hydroxy derivative 8; mp. 64-65°; $[\alpha]_D$ + 192° (c0.8, $CHCl_3$); ν_{max} (film) 1785, 1745 cm^{-1}; H-5, 5.60 p.p.m., s ($CDCl_3$).
14. W.J. Leanza, F. DiNinno, D.A. Muthard, R.R. Wilkening, K.J. Wildonger, R.W. Ratcliffe and B.G. Christensen, Tetrahedron, 39, 2505 (1983); V.M. Girijavallaban, A.K. Ganguly, S.W. McCombie, P. Pinto and P. Rizvi, Tetrahedron Lett., 22, 3485 (1981).
15. Obtained by oxidation (MCPBA, $CHCl_3$, 0°→r.t., few hours, 82% yield) of the sulphide 1. mp 142-4°; $[\alpha]_D$ + 162° (c1.8, $CHCl_3$); ν_{max} (KBr) 1795, 1755 cm^{-1}; H-6 and H-5, 5.15 and 4.71 p.p.m., two d., J= 1.5 Hz ($CDCl_3$).
16. For some other free-radical reactions in this area, see M.D. Bachi and C. Hoornaert, Tetrahedron Lett., 2689 (1981); ibid. 2693 (1981); ibid. 2505 (1982); M.D. Bachi, F. Frolow and C. Hoornaert, J. Org. Chem. 48, 1841 (1983); H. Fliri and C.P. Mak, J. Org. Chem., 50, 3438 (1985).

(Received in USA 27 June 1986)