Synthesis of the Precursor of (+)-Thienamycin utilizing D-Glucosamine

Masaaki Miyashita, Noritaka Chida, and Akira Yoshikohsi*

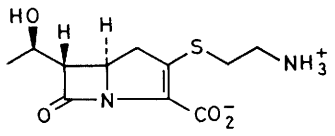
Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan

D-Glucosamine was transformed into the known synthetic intermediate (**18**) of (+)-thienamycin (**1**).

The rapidly expanding family of carbapenem antibiotics has attracted much attention owing to the wide spectrum of their antibacterial usage, and this has consequently stimulated synthetic efforts. Thienamycin (**1**), a representative of this family, has been synthesised in the racemic form,[1] and as its natural enantiomer from L-aspartic acid,[2] 6-aminopenicillanic acid,[3] D-allo-,[4] and L-threonine.[4]

We describe herein the chiral synthesis of (+)-(**1**) starting with commercially available D-glucosamine.

Methyl 2-deoxy-2-methoxycarbonylamino-α-D-glucopyr-

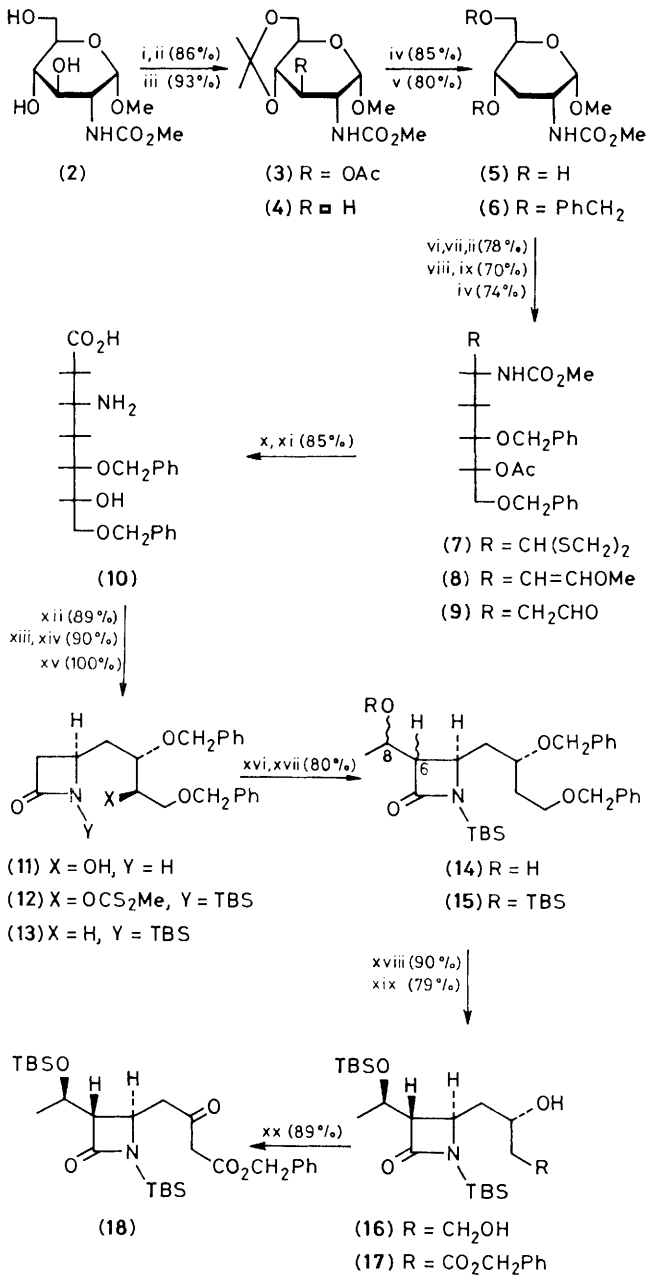


(1)

anoside[5] (**2**), readily accessible from D-glucosamine, was converted into an acetonide, and then acetylated to give (**3**), whose acetoxy-group was then removed photochemically[6] (Scheme 1). Selective acid hydrolysis of the resulting 3-deoxy-derivative (**4**) gave the known compound (**5**),[7] m.p. 163.5—164 °C, $[\alpha]_D^{23}$ +126° (MeOH), which was benzylated to give (**6**), m.p. 100—103 °C, $[\alpha]_D^{23}$ +84.1° ($CHCl_3$). After acid hydrolysis, (**6**) was converted into (**7**) by thio-acetalisation and acetylation. For one-carbon homologation, (**7**) was hydrolysed to an unstable aldehyde, which, without purification was submitted to the Wittig reaction with methoxymethylenetriphenylphosphorane. The resulting vinyl ether (**8**) was hydrolysed by acid to the homoaldehyde (**9**), $[\alpha]_D^{21}$ −9.8° ($CHCl_3$), under mild conditions in order to suppress the eliminative deamination of the product. Upon oxidation followed by alkaline hydrolysis, (**9**) provided the β-amino acid (**10**), m.p. 167—169 °C, $[\alpha]_D^{23}$ −45.6° (MeOH), after chromatographic purification on Dowex 50W (H^+ form). The key β-lactam (**11**), $[\alpha]_D^{25}$ +2.9° ($CHCl_3$), was obtained in high yield by treatment of (**10**) with 2,2′-dipyridyl disulphide–Ph_3P.[8] After the NH group in (**11**) had been protected by silylation, the product was converted into the xanthate (**12**), $[\alpha]_D^{24}$ −53.1° ($CHCl_3$), and then submitted to trialkylstannane reduction yielding the deoxy compound (**13**), $[\alpha]_D^{23}$ −41.9° ($CHCl_3$), quantitatively. Trapping of the lithium enolate of (**13**) with acetaldehyde gave an inseparable mixture of the diastereoisomers of (**14**), which by silylation and the subsequent chromatographic separation, furnished the pure desired diastereoisomer (6*S*, 8*R*)-(**15**),† $[\alpha]_D^{25}$ −42.9° ($CHCl_3$), in 39% yield from (**13**). The undesired diastereoisomers, (6*S*, 8*S*)-, (6*R*, 8*R*)-, and (6*R*, 8*S*)-(**15**), were efficiently recycled to (6*S*, 8*R*)-(**14**) as follows: a mixture of these undesired isomers was hydrolysed with acid (HCl, aqueous MeOH) and the product was selectively *N*-silylated [Bu^tMe_2SiCl, Et_3N, dimethylformamide (DMF)]. The single ketone, obtained from the *N*-silylated product by Swern oxidation [$(CF_3CO)_2O$, Me_2SO, Et_3N, CH_2Cl_2], provided a mixture of (6*S*, 8*R*)- and (6*S*, 8*S*)-(**14**) in the ratio *ca.* 10:1 on reduction with K-Selectride[2,9] (63% combined overall yield).

The diastereoisomer (6*S*, 8*R*)-(**15**) was debenzylated by Hanessian's procedure[10] to give the diol (**16**), m.p. 139—141 °C, $[\alpha]_D^{21}$ −70.1° ($CHCl_3$). The selective oxidation of the primary hydroxyl group of (**16**) was achieved by Pt-catalysed autoxidation yielding a hydroxy acid, which was then esterified to give (**17**), m.p. 131—132 °C, $[\alpha]_D^{25}$ −41.7° ($CHCl_3$). Collins oxidation of (**17**) provided the reported synthetic intermediate[3] (**18**), m.p. 77.5—79 °C, $[\alpha]_D^{20}$ −48.4° ($CHCl_3$), of (+)-thienamycin (**1**), which was identified by spectral comparison.

The optical purity of (**18**) was checked by the transformation of the key intermediate (**13**) into (**19**) as follows: (**13**) was debenzylated (H_2, Pd–C) and then oxidised (O_2, Pt). The hydroxy acid obtained was esterified [$PhCH_2Br$, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)], oxidised (Collins reagent), and finally desilylated (HCl, aqueous MeOH) to give the known (+)-enantiomer of (**19**),[11,12] $[\alpha]_D^{21}$ +49.2° (PhH),‡ in



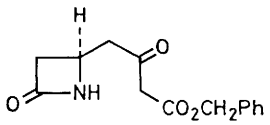
Scheme 1. TBS = Bu^tMe_2Si *Reagents:* i, $Me_2C(OMe)_2$, *p*-$MeC_6H_4SO_3H$, DMF; ii, Ac_2O, pyridine; iii, *hν*, aqueous hexamethylphosphoric triamide; iv, aqueous HOAc; v, $PhCH_2Br$, NaH, dimethoxyethane; vi, HCl, aqueous HOAc; vii, $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$; viii, MeI, aqueous MeCN; ix, Ph_3PCH_2OMeCl, $EtMe_2CONa$, PhH; x, Jones reagent; xi, aqueous $Ba(OH)_2$; xii, $(C_5H_4NS)_2$, Ph_3P, MeCN; xiii, Bu^tMe_2SiCl, Et_3N, DMF; xiv, CS_2, NaH, tetrahydrofuran (THF) then MeI; xv, Bu_3SnH, azoisobutyronitrile, PhMe; xvi, lithium di-isopropylamide, MeCHO, THF; xvii, Bu^tMe_2SiCl, imidazole, DMF; xviii, cyclohexene, $Pd(OH)_2$, EtOH; xix, O_2, Pt, aqueous dioxan, then $PhCH_2Br$, DBU, MeCN; xx, CrO_3–pyridine.

† This diastereoisomer was the major product and its ratio to the other isomers (6*S*, 8*S*), (6*R*, 8*R*), and (6*R*, 8*S*) was 49:29:13:9 (or 49:29:9:13) respectively, as revealed by h.p.l.c. analysis.

‡ Lit.[11] $[\alpha]_D^{20}$ +43.2° (PhH).

34% overall yield. Although the optical rotation of (**18**) has not been reported, the observed optical rotational value of (**19**) demonstrates that our synthesis, in which all the carbon atoms of D-glucosamine were included in the target molecule, was probably performed throughout without loss of optical purity.

The authors thank Professor S. Takano (Pharmaceutical School, this University) and Dr. S. Karady (Merck Sharp &



(19)

Dohme) for providing us with the spectra of (**19**) and (**18**), respectively.

Received, 24th August 1982; Com. 1031

References

1 D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 313; S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1142; T. Kametani, S.-P. Huang, T. Nagahara, S. Yokohama, and M. Ihara, *J. Chem. Soc., Perkin Trans.* 1, 1981, 964 and references therein; M. Shibasaki, A. Nishida, and S. Ikegami, *Tetrahedron Lett.*, 1982, **23**, 2875; D. G. Mellilo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, *ibid.*, 1980, 2783; *ibid.*, 1981, **22**, 913.

2 T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6163; P. J. Reider and E. J. J. Gravowski, *Tetrahedron Lett.*, 1982, **23**, 2293.

3 S. Karady, J. S. Amato, R. A. Reaman, and L. M. Weinstock, *J. Am. Chem. Soc.*, 1981, **103**, 6765.

4 M. Shiozaki, N. Ishida, T. Hiraoka, and H. Yanagisawa, *Tetrahedron Lett.*, 1981, **22**, 5205.

5 D. Ikeda, T. Tsuchiya, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2529.

6 H. Deshayes, J.-P. Pete, C. Portella, and D. Scholler, *J. Chem. Soc., Chem. Commun.*, 1975, 439; J.-P. Pete, C. Portella, C. Monneret, J.-C. Florent, and Q. Khuong-Huu, *Synthesis*, 1977, 774; T. Kishi, T. Tsuchiya, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3015.

7 T. Tsuchiya, I. Watanabe, M. Yoshida, F. Nakamura, T. Usui, M. Kitamura, and S. Umezawa, *Tetrahedron Lett.*, 1978, 3365.

8 M. Ohno, S. Kobayashi, T. Ishimori, Y.-F. Wang, and T. Izawa, *J. Am. Chem. Soc.*, 1981, **103**, 2405; S. Kobayashi. T. Iimori, T. Izawa, and M. Ohno, *ibid.*, 1981, **103**, 2406.

9 F. Pecquet and J. d'Angelo, *Tetrahedron Lett.*, 1982, **23**, 2777.

10 S. Hanessian, T. J. Liak, and B. Vanasse, *Synthesis*, 1981, 396.

11 N. Ikota, H. Shibata, and K. Koga, *Heterocycles*, 1980, **14**, 1077.

12 S. Takano, C. Kasahara, and K. Ogasawara, *Chem. Lett.*, 1982, 631.