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

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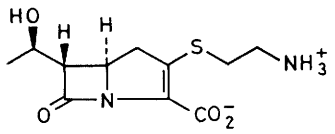
D-Glucosamine was transformed into the known synthetic intermediate (**18**) of (+)-thienamycin (**1**).

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-



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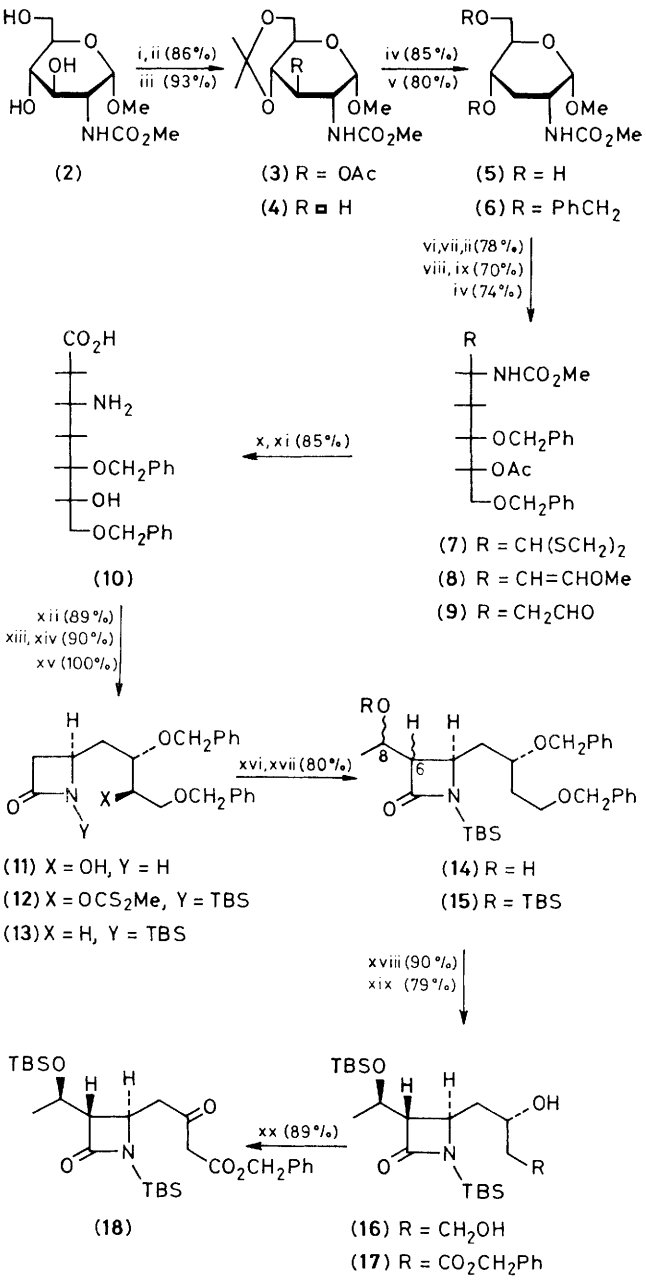
anoside[5] (**2**), readily accessible from D-glucosamine, was converted into an acetonide, and then acetylated to give (**3**), whose acetoxy-group was then removed photochemically[6] (Scheme 1). Selective acid hydrolysis of the resulting 3-deoxy-derivative (**4**) gave the known compound (**5**),[7] 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.

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.

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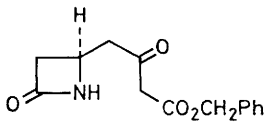
† This diastereoisomer was the major product and its ratio to the other isomers (6*S*, 8*S*), (6*R*, 8*R*), and (6*R*, 8*S*) was 49 : 29 : 13 : 9 (or 49 : 29 : 9 : 13) respectively, as revealed by h.p.l.c. analysis.

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



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

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