Total Synthesis of (+)-Validoxylamine G

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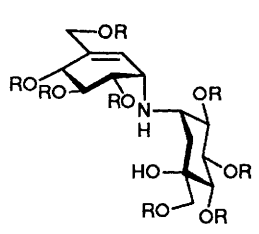
The first total synthesis of the antibiotic validoxylamine G as its octa-acetate is reported.

Validoxylamine G,[1] a new component of the antibiotic validamycin complex,[2] was isolated together with validamycin G[1] from a fermentation broth of *Streptomyces hygroscopicus* var. *limoneus* by Kameda and co-workers in 1986. Validoxylamine A consists of valienamine and validamine linked *via* an imino bond, whereas validoxylamine G is composed of valiolamine instead of validamine. We now describe the first total synthesis[3] of (+)-validoxylamine G.

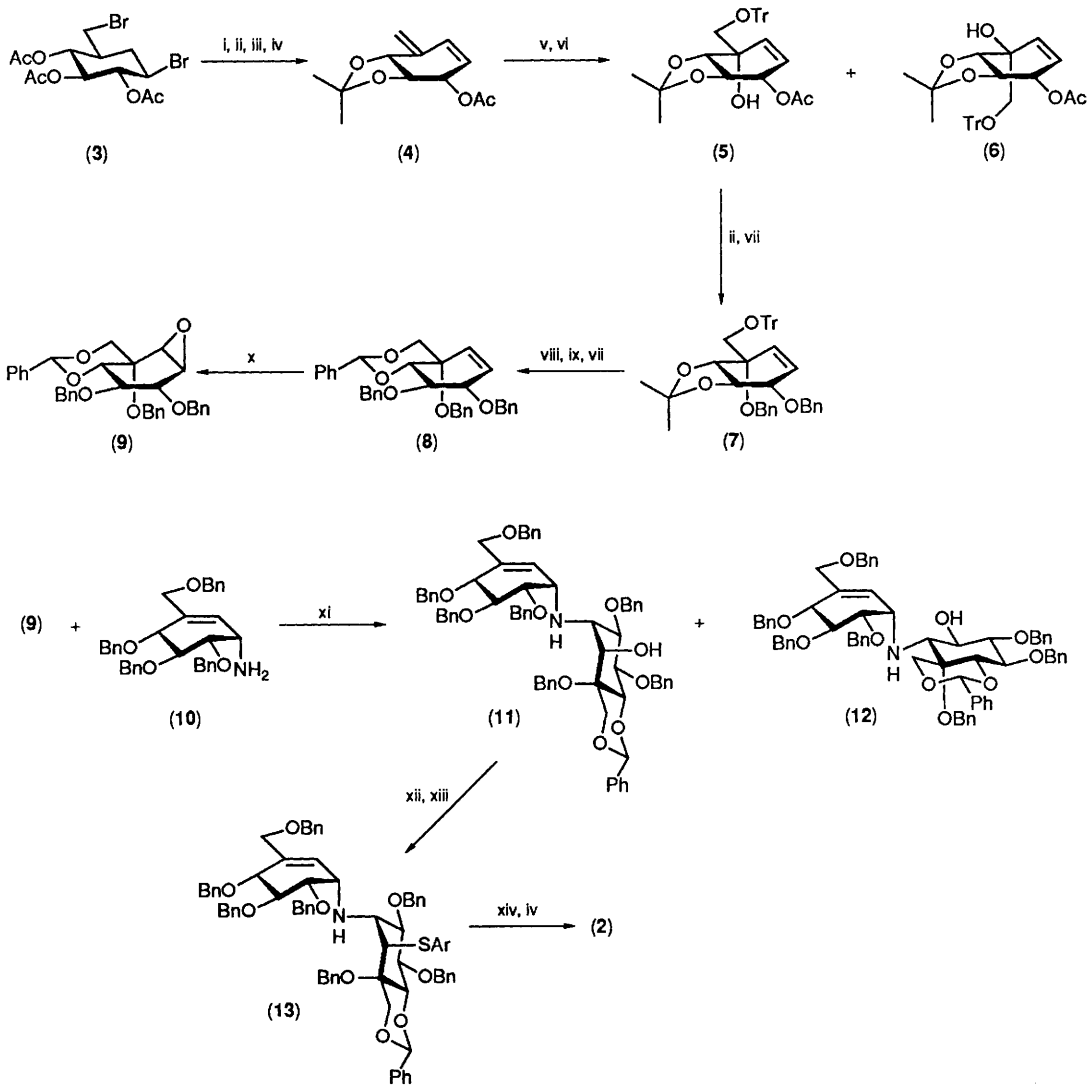
The dibromide (**3**), derived in four steps from an optically resolved Diels–Alder *endo* adduct[4] of furan and acrylic acid, was used as the starting compound. Compound (**3**) was converted into the protected diene (**4**), $[\alpha]_D^{26}$ −38° (*c* 1.5, $CHCl_3$), in four steps in 59% overall yield (Scheme 1), during which transformation isopropylidenation of the triol afforded only the desired isomer. Osmium oxidation† and tritylation of compound (**4**) gave the trityl ether (**5**) {11%, $[\alpha]_D^{28}$ +56° (*c* 1.0, $CHCl_3$)} and (**6**) {31%, $[\alpha]_D^{28}$ +7.4° (*c* 2.1, $CHCl_3$)}. *O*-Deacetylation of (**5**) with methanolic sodium methoxide (1 M), followed by treatment with sodium hydride (NaH) and benzyl bromide, afforded the dibenzyl ether (**7**), $[\alpha]_D^{26}$ −27° (*c* 1.1, $CHCl_3$), in 90% yield. The tertiary hydroxy group was protected in order to avoid formation of the spirobenzylidene derivative. Removal of the trityl and isopropylidene groups of compound (**7**) was effected by treatment with toluene-*p*-sulphonic acid, and successive benzylidenation and benzylation gave 54% of the alkene (**8**), $[\alpha]_D^{25}$ −20° (*c* 1.8, $CHCl_3$). Epoxidation of (**8**) with *m*-chloroperbenzoic acid (mCPBA) preferentially gave the β-epoxide (**9**), $[\alpha]_D^{25}$ −28° (*c* 1.6, $CHCl_3$), in 60% yield based on (**8**) consumed.

Coupling of (**9**) with tetra-*O*-benzylvalienamine[5] (**10**) was conducted in propan-2-ol in a sealed tube at 120 °C. In this reaction, axial attack seems to be disadvantageous because of an interaction between the tertiary axial benzyloxy group and the attacking amine (**10**). The main product was the diequatorial opening compound (**12**) {64%, $[\alpha]_D^{25}$ +7.5° (*c* 1.3, $CHCl_3$)}, together with the diaxial opening compound (**11**) {18%, $[\alpha]_D^{25}$ +2.1° (*c* 0.7, $CHCl_3$)} as a side product. On treatment with NaH and sulphuryldiimidazole (Imd_2SO_2), the



(1) R = H (validoxylamine G)
(2) R = Ac

† Epoxidation of the diene, the protecting group of which was replaced with benzyl instead of the acetyl group, with mCPBA was later found to yield only the desired α-spiroepoxide, which was converted to (**7**) in four steps (overall yield 24% from the diene).



Tr = Ph_3C, Bn = $PhCH_2$, Ar = p-MeC_6H_4

Scheme 1. *Reagents*: i, 1,8-Diazabicyclo[5.4.0]undec-7-ene/toluene; ii, MeONa/MeOH; iii, $Me_2C(OMe)_2$, p-TsOH/*N*,*N*-dimethylformamide (DMF) (Ts = $MeC_6H_2SO_2$); iv, Ac_2O/pyridine; v, OsO_4, 4-methylmorpholine *N*-oxide/acetone–H_2O; vi, TrCl/pyridine; vii, NaH, BnBr/DMF; viii, p-TsOH/MeOH; ix, $PhCH(OMe)_2$, p-TsOH/DMF; x, mCPBA, phosphate buffer/CH_2ClCH_2Cl; xi, in propa-2-nol in a sealed tube; xii, NaH, Imd_2SO_2/DMF; xiii, toluene-p-thiol/propan-2-ol; xiv, Na/liq. NH_3.

alcohol (**11**) was transformed into the sulphide (**13**) {38% in two steps, $[\alpha]_D^{25}$ ~0° (*c* 2.0, $CHCl_3$)} *via* the intermediate aziridine. Axial attack of toluene-*p*-thiol at the aziridine was very slow owing to steric hindrance of the benzyl groups, giving a rather poor yield of (**13**). Reduction of the sulphide (**13**) with sodium in liquid ammonia at −78 °C, followed by conventional acetylation gave validoxylamine G octa-acetate (**2**) {39%, $[\alpha]_D^{18}$ +74° (*c* 0.68, $CHCl_3$)}, identified by comparison with a known sample on the basis of the 400 MHz ^{1}H NMR spectral data.[1]

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