

Total Synthesis of (+)-Validoxylamine G

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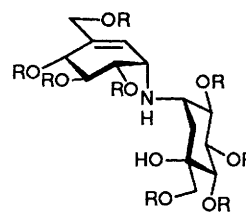
The first total synthesis of the antibiotic validoxylamine G as its octa-acetate is reported.

Validoxylamine G,¹ a new component of the antibiotic validamycin complex,² was isolated together with validamycin G¹ 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 valiolineamine instead of validamine. We now describe the first total synthesis³ of (+)-validoxylamine G.

The dibromide (3), derived in four steps from an optically resolved Diels–Alder *endo* adduct⁴ of furan and acrylic acid, was used as the starting compound. Compound (3) was converted into the protected diene (4), [α]_D²⁶ -38° (*c* 1.5, CHCl₃), 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%, [α]_D²⁸ $+56^\circ$ (*c* 1.0, CHCl₃)} and (6) {31%, [α]_D²⁸ $+7.4^\circ$ (*c* 2.1, CHCl₃)}. *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), [α]_D²⁶ -27° (*c* 1.1, CHCl₃), 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

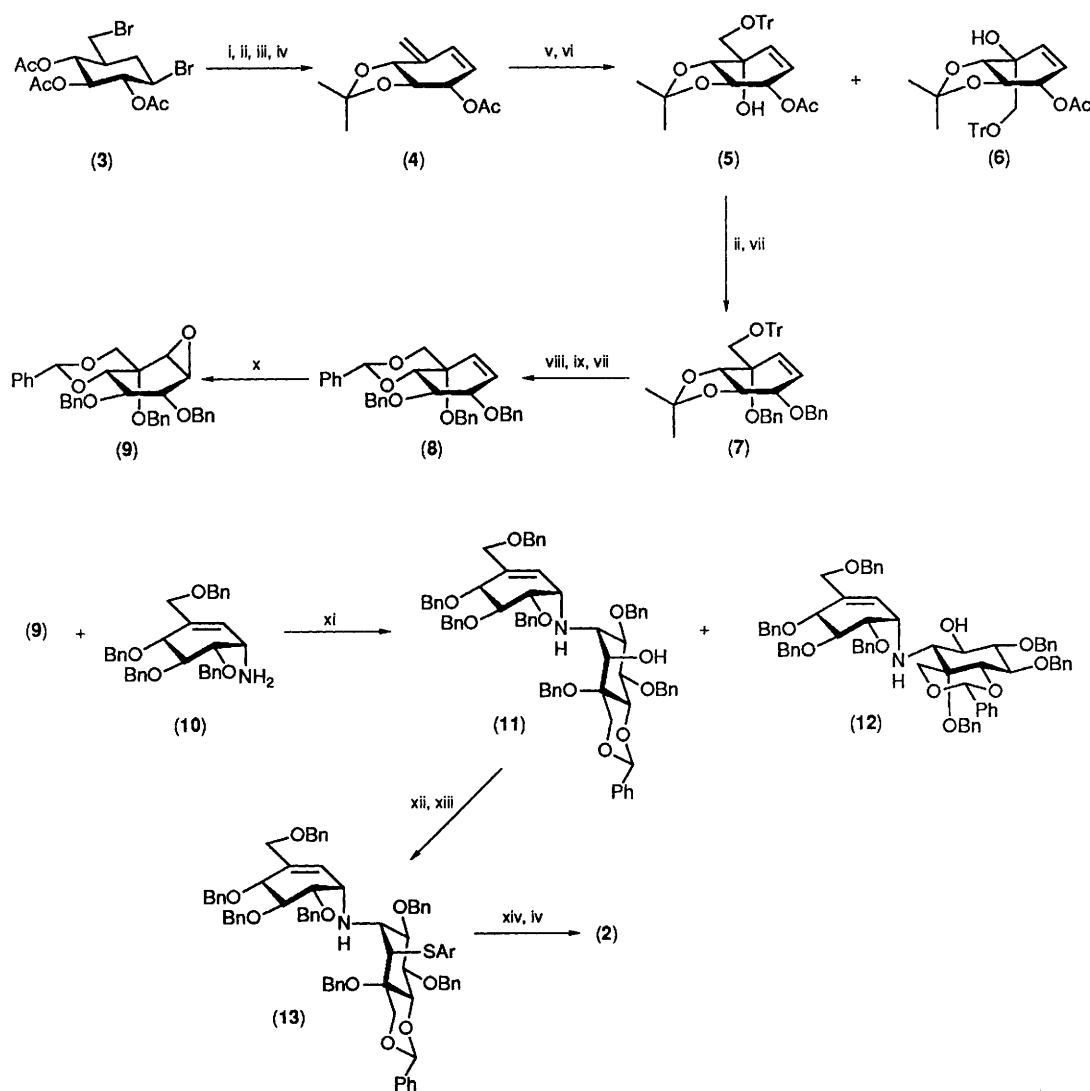
compound (7) was effected by treatment with toluene-*p*-sulphonic acid, and successive benzyldienation and benzylation gave 54% of the alkene (8), [α]_D²⁵ -20° (*c* 1.8, CHCl₃). Epoxidation of (8) with *m*-chloroperbenzoic acid (mCPBA) preferentially gave the β -epoxide (9), [α]_D²⁵ -28° (*c* 1.6, CHCl₃), in 60% yield based on (8) consumed.

Coupling of (9) with tetra-*O*-benzylvalienamine⁵ (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%, [α]_D²⁵ $+7.5^\circ$ (*c* 1.3, CHCl₃)}, together with the diaxial opening compound (11) {18%, [α]_D²⁵ $+2.1^\circ$ (*c* 0.7, CHCl₃)} as a side product. On treatment with NaH and sulphuryldiimidazole (Imd₂SO₂), 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).



Scheme 1. Reagents: i, 1,8-Diazabicyclo[5.4.0]undec-7-ene/toluene; ii, MeONa/MeOH; iii, Me₂C(OMe)₂, *p*-TsOH/*N,N*-dimethylformamide (DMF) (Ts = MeC₆H₄SO₂); iv, Ac₂O/pyridine; v, OsO₄, 4-methylmorpholine *N*-oxide/acetone-H₂O; vi, TrCl/pyridine; vii, NaH, BnBr/DMF; viii, *p*-TsOH/MeOH; ix, PhCH(OMe)₂, *p*-TsOH/DMF; x, mCPBA, phosphate buffer/CH₂ClCH₂Cl; xi, in propa-2-nol in a sealed tube; xii, NaH, Imd₂SO₂/DMF; xiii, toluene-*p*-thiol/propan-2-ol; xiv, Na/liq. NH₃.

alcohol (11) was transformed into the sulphide (13) {38% in two steps, $[\alpha]_D^{25} \sim 0^\circ$ (*c* 2.0, CHCl₃)} 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%, $[\alpha]_D^{18} +74^\circ$ (*c* 0.68, CHCl₃)}, identified by comparison with a known sample on the basis of the 400 MHz ¹H NMR spectral data.¹

Received, 6th February 1990; Com. 0/00543F

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