Amphoteronolide B Methyl Ester. Novel Oxidative Deglycosidation of Amphotericin B

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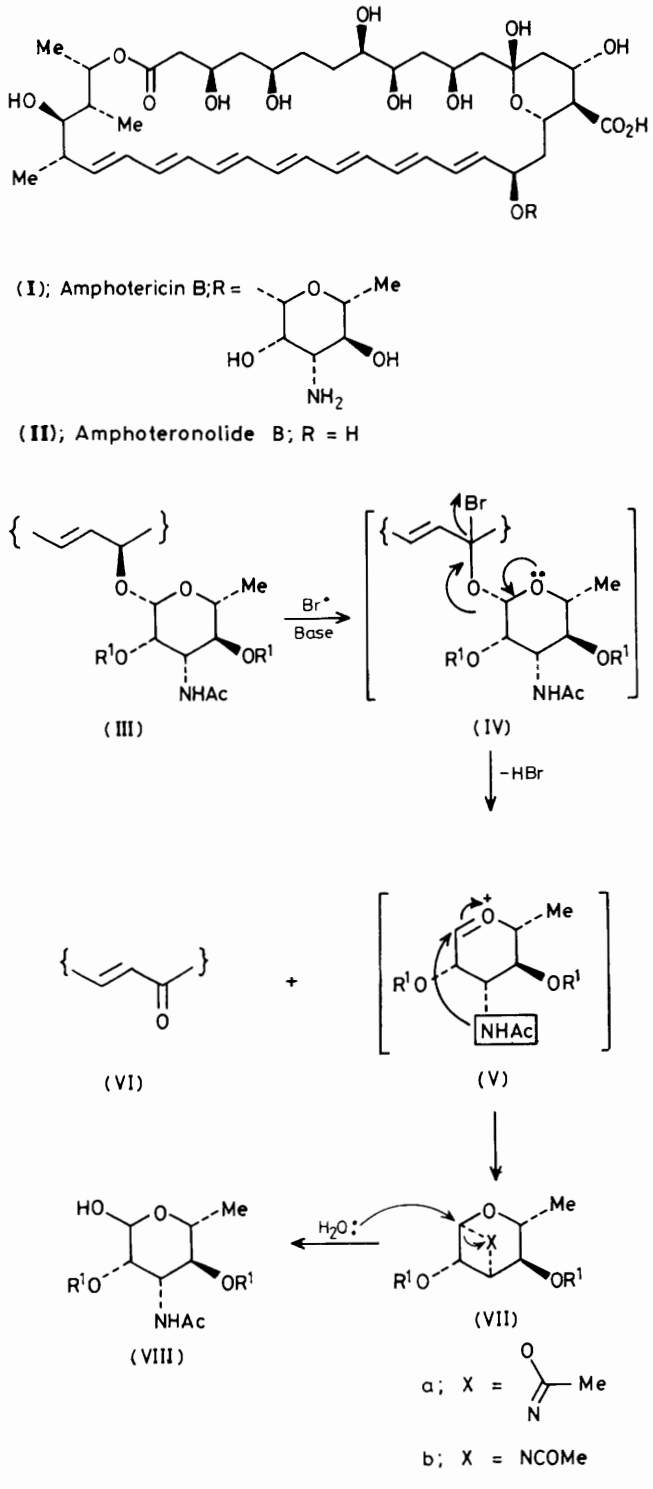
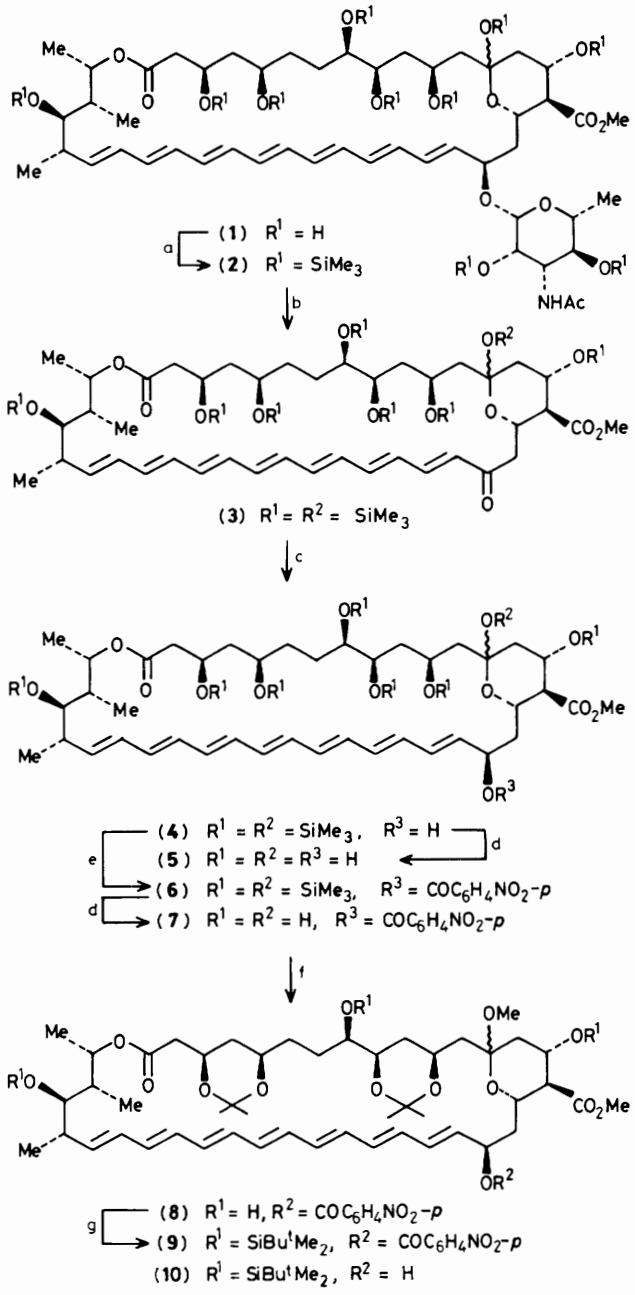
Amphoteronolide B methyl ester (**5**) was prepared for the first time from amphotericin B by a sequence involving a novel oxidative deglycosidation reaction, and a number of other amphotericin B aglycone derivatives have also been prepared by this method.

The polyene macrolide class of antibiotics[1] is one of the most challenging areas of natural products chemistry and, from the synthetic point of view, one of the few structural types remaining unconquered. Challenging difficulties in this area include lack of crystallinity and solubility in common organic solvents and high chemical sensitivity. Amphotericin B (I), a widely used antifungal agent, is the only member of this family of compounds whose structure has been fully established by *X*-ray crystallographic analysis.[2] Amphoteronolide B (II), the aglycone of amphotericin B, and its derivatives are important chemical entities from a number of perspectives including (a) possible biological activitiy and natural occurrence, (b) potential starting points for enzymatic and chemical production of amphotericin B analogues, and (c) advanced intermediates and comparison/relay stages for an eventual total synthesis of amphotericin B itself.

In this communication we report a novel oxidative deglycosidation procedure for polyene macrolide antibiotics and the



Scheme 1. Proposed mechanism for the oxidative deglycosidation of amphotericin B.



Scheme 2. *Reagents and conditions:* a, excess Me_3SiOTf (Tf = CF_3SO_2), 2,6-lutidine, 0 °C, 15 min, 90%; b, NBS (0.95 equiv.), $CaCO_3$ (10 equiv.), CCl_4, 25 °C, 5—8 h, 20—25%; c, $NaBH_4$ (10 equiv.), MeOH, 0 °C, 95—98%; d, excess HF–pyridine, THF, O—25 °C, 15 min, 80—85%; e, *p*-$NO_2C_6H_4COCl$ (1.5 equiv.), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2 equiv.), CH_2Cl_2, 0—25 °C, 2 h, 85—90%; f, MeOH–$Me_2C(OMe)_2$ (3 : 1), camphorsulphonic acid (CSA) (cat.), 25 °C, 1 h, 68%; g, excess Bu^tMe_2SiOTf, 2,6-lutidine, CH_2Cl_2, 0—25 °C, 30 min, 85—90%.

first synthesis of amphoteronolide B methyl ester (**5**) and a number of its derivatives from amphotericin B. The problems associated with the removal of the mycosamine unit from amphotericin B while leaving the aglycone intact have long been recognized. They may be attributed to the combination of resistance of the nitrogen-containing sugar to depart under mild conditions and the lability of the aglycone to strong acid conditions. To circumvent these problems, a new method for deglycosidation involving oxidative removal of the carbohydrate unit under mild conditions was devised. Scheme 1

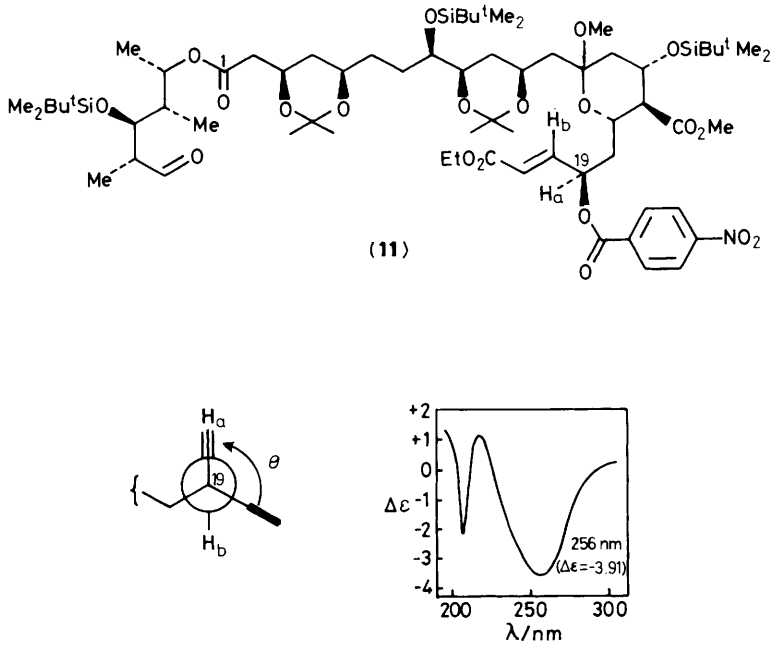


Figure 1. C.d. spectrum of 19(*R*)-nitrobenzoate (**11**) in hexane. Newman projection shows the preferred conformation ($J_{a,b}$ 6.0 Hz); ■ = *O*-*p*-nitrobenzoate; absolute configuration (*R*).

presents the mechanistic rationale† on which this new reaction was based. According to this scheme, free radical substitution at the indicated allylic position of intermediate (III) was expected to lead to the labile intermediate (IV) and thus trigger the desired cleavage, with anticipated assistance from the ring oxygen and/or the amide group. In practice, this scenario proved to be viable: *N*-bromosuccinimide (NBS) in carbon tetrachloride was found to be an effective cleaving agent, producing enone (VI) and bicyclic system (VII a or b) from precursor (III) (Scheme 1). The novel heterocycle (VII a or b), being rather easily hydrolysed to the monocyclic mycosamine derivative (VIII) was isolated by careful chromatographic procedures.‡

Scheme 2 details some of the degradation chemistry made possible by this neutral and mild deglycosidation reaction and the synthesis of a number of amphotericin B aglycone derivatives including amphoteronolide B methyl ester (**5**). Thus, *N*-acetylamphotericin B methyl ester (**1**) was fully silylated to compound (**2**)§ by exposure to trimethylsilyl trifluoromethanesulphonate (90%) and exposed to NBS in CCl_4 to produce heptaenone (**3**) (20—25%). Despite the large-ring nature of heptaenone (**3**), molecular models pointed to a stereoselective reduction by peripheral attack at the carbonyl group, an expectation fully realized upon treatment with $NaBH_4$ resulting in (**4**) as a single stereoisomer (95%). Desilylation of compound (**4**) then furnished amphoteronolide B methyl ester (**5**)¶ (80%, single anomer). The issue of stereochemistry at C-19 of the aglycone and its derivatives was resolved by employing Nakanishi's circular dichroism (c.d.) method[3] on the *p*-nitrobenzoate derivative (**11**) (Figure 1) prepared from (**4**) by (i) *p*-nitrobenzoylation [(**4**) → (**6**), 85%], (ii) desilylation [(**6**) → (**7**), 85%], (iii) acetonization–methylglycosidation [(**7**) → (**8**), 68%], (iv) silylation [(**8**) → (**9**), 90%], and (v) O_3–PPh_3 followed by chemoselective condensation with $Ph_3P{=}CHCO_2Et$ [(**9**) → (**11**), 78% overall]. The c.d. spectrum of compound (**11**) exhibited a negative Cotton effect (Figure 1) indicating the (*R*) configuration, as desired, for amphoteronolide B (**5**) and its derivatives, including compound (**10**), a key intermediate in our total synthesis of amphoteronolide B (**5**)[4] and amphotericin B (**1**).[5]

The described chemistry establishes, for the first time, a novel and mild method for the oxidative deglycosidation of sensitive polyene macrolide antibiotics. This method allowed the preparation of a number of amphotericin B aglycone derivatives, including amphoteronolide B methyl ester for biological and chemical investigations.‖

† An alternative mechanism for this degradation involves the allylic radical corresponding to (IV) suffering a β-cleavage to the enone (VI) and a mycosaminyl radical which then undergoes electron transfer oxidation to the carbocation (V). A third plausible mechanism, suggested by a referee, involves H-atom abstraction at the anomeric site followed by β-cleavage giving a mycosaminyl radical; electron transfer oxidation then results in carbocation generation and trapping by the amido group.

‡ At present, distinction between the oxazine (VIIa) and azetidine (VIIb) structures is not clear. Further studies to establish firmly the structure of this intermediate are under way and will be reported in due course.

§ New compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogenous materials.

¶ *Spectroscopic data* for (**5**): ^{1}H n.m.r. [250 MHz, $(CD_3)_2SO$ δ 6.5—5.9 (m, 12H, olefinic), 5.8 (dd, $J_{20,21}$ 14.0, $J_{20,19}$ 8.0 Hz, 1H, H-20), 5.5 (dd, $J_{33,32}$ 13.6, $J_{33,34}$ 9.9 Hz, 1H, H-33), 5.05 (m, 1H, H-37), 4.57 (m, 1H, H-19), 4.5—3.0 (m, 8H, CH—O), 3.63 (s, 3H, CO_2Me), 2.4—0.7 [m, 19H, CH_2C(O), CHC(O), allylic, CH_2-, CH], 1.09 (d, *J* 6.2 Hz, 3H, Me-38), 1.01 (d, *J* 6.2 Hz, 3H, Me-40), 0.89 (d, *J* 6.9 Hz, 3H, Me-39). The O*H* protons appear in the range 5—3 (9H).

‖ The methoxy configuration of the reported intermediates was not assigned. In most instances both anomers were observed in varying ratios (t.l.c. and/or ^{1}H n.m.r., MeO signals). Single anomers were sometimes used, but anomerizations were frequently observed, particularly in acidic media. Amphoteronolide B methyl ester (**5**) appeared to be a single anomer presumed to be of the same stereochemistry (β) as amphotericin B *N*-iodoacetate.[2]

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