

An Optically Active Synthone for the Ubiquitous Hemiacetal Moiety of Polyene Macrolides

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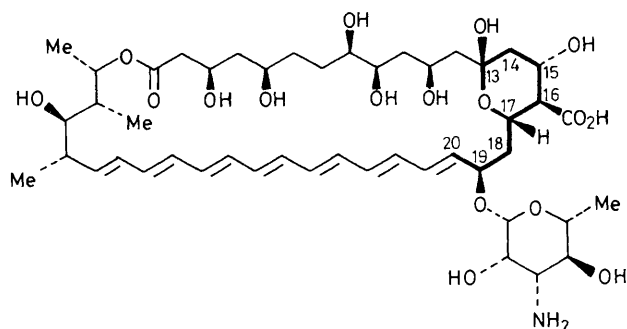
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A stereocontrolled synthesis of (2), a synthon for the hemiacetal moiety of amphotericin B (and, presumably, many other polyene macrolides) has been carried out in 16 steps (20% overall yield) from 'diacetone glucose'.

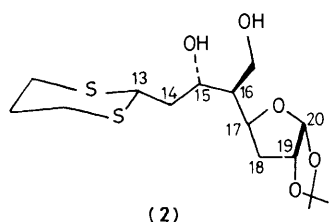
In the preceding communication we described certain requirements for achieving stereocontrol at 'off-template' sites in 1,2-*O*-isopropylidene glucofuranoses.¹ In this communication we describe the application of this strategy to the preparation of a key intermediate for the synthesis of polyene macrolides.² Although approximately 100 members of this group of

substances are known, and several have been widely used against fungal infections for over 20 years,³ the complete structure has been determined for only one member, amphotericin B, (1).⁴ For the others their amorphous condition and/or instability has frustrated attempts at characterization. Co-occurrence of several members in the same medium

suggests a common biosynthetic evolution and presumably a common stereochemical infrastructure. If so, the ubiquitous hemiacetal moiety would have the same stereochemistry, relative and absolute, as the segment highlighted in (1). Compound (2) has the salient features of this complex entity, and a ready procedure for its synthesis would therefore be advantageous.⁵



Amphotericin B (1)



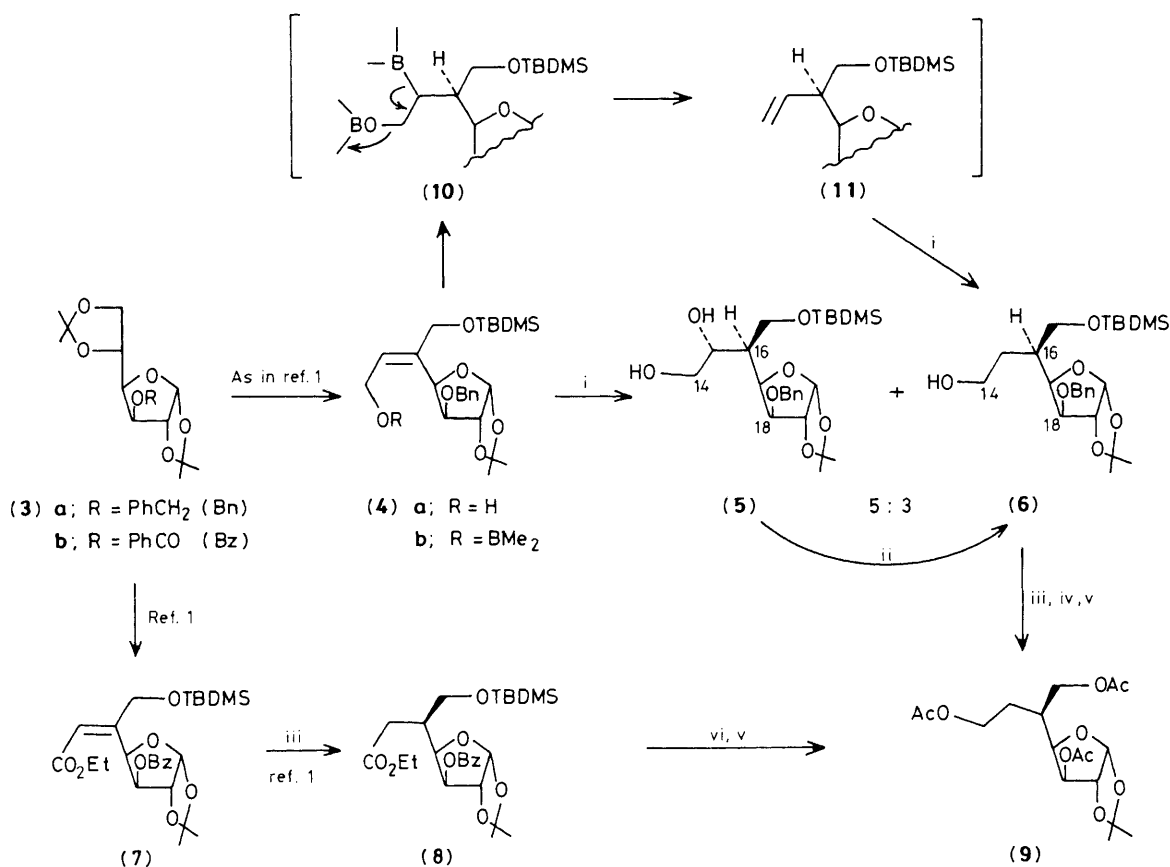
(2)

In our initial approach, the *O*-benzyl ether (3a)⁶ was transformed by standard steps into the allylic alcohol (4a) which was then treated with diborane. The product obtained in 50% yield, was a 5 : 3 mixture of (5) and the dihydro product (6), their relationship being clarified by means of a Barton thioncarbonate deoxygenation,⁷ whereby (5) was converted into (6) (Scheme 1). The (*S*) configuration at C(16) was established through triacetate (9) obtained from (6) as well as from the diesters (7) and (8).

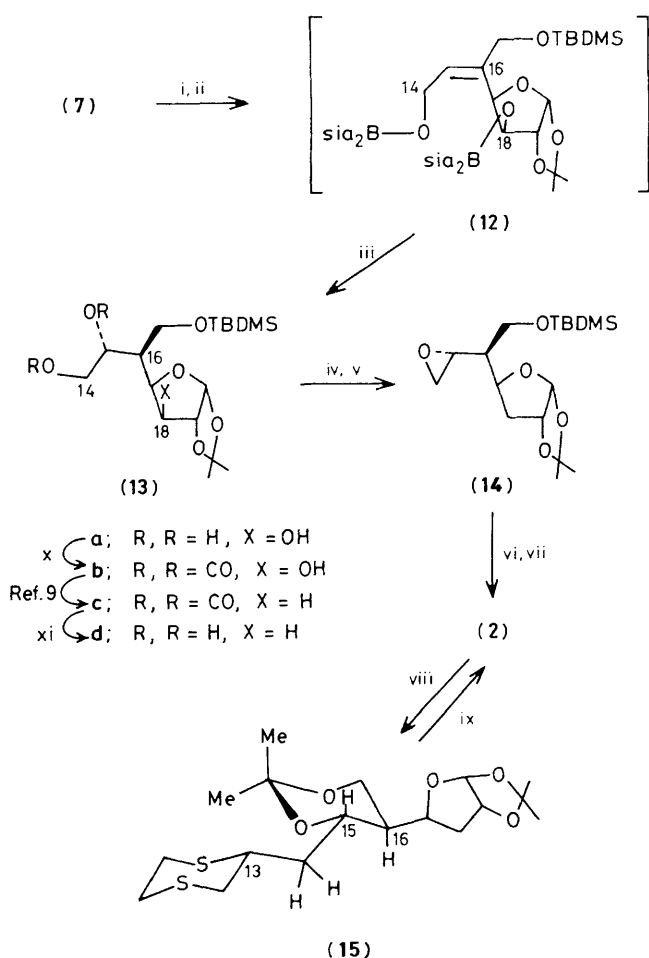
The C(16), and hence C(15), configurations of (5) were therefore as desired, but the large amount of by-product (6) was clearly unacceptable. The formation of (6) can be rationalized as proceeding through the borate ester (10) whose hydroboration product (11) undergoes reductive elimination to alkene (11).⁸ This turn of events could presumably be obviated by use of a hindered borane and hence the study summarized in Scheme 2 was evolved.

The diol obtained by reduction of the Wittig addition product (7) was first treated with an excess of disiamyl borane (*sia*₂BH) in the expectation of producing compound (12). This intermediate would then have the requisite bulky substitution at C(18) for controlling the stereochemical outcome at C(16) in the next step. With *sia*₂BH, the hydroboration was too slow; but when, after a two-hour period, an excess of diborane was added, hydroboration was complete in the following 12 h. The resulting triol (13a) was ready for conversion into carbonate (13b) and subsequently for deoxygenation⁹ to (13c).

Compound (13c) was then processed to give epoxide (14) which reacted with 2-lithiodithiane in hexamethylphosphoramide-tetrahydrofuran. Subsequent desilylation afforded (2) in 85% overall yield. Characterization was carried out on the crystalline diacetone (15) whose n.m.r. parameters verified



Scheme 1. i, B₂H₆; NaOH-H₂O₂; ii, di-imidazoletioncarbonate; Buⁿ₃SnH; iii, H₂; iv, Buⁿ₄NF; v, Ac₂O; vi, LiAlH₄.



Scheme 2. i, $(Bu^t)_2AlH$; ii, sia_2BH ; iii, B_2H_6 ; $NaOH-H_2O_2$; iv, $p-MeC_6H_4SO_2Cl$; v, $NaOMe$; vi, 2-lithiodithiane; vii, Bu^t_4NF ; viii, dimethoxypropane-pyridinium toluene-*p*-sulphonate; ix, 30% $HOAc$; x, $COCl_2$; xi, $Ba(OH)_2$.

the C(15)/C(16) relationship. Not surprisingly the 1,3-dioxane ring of (15) can be selectively hydrolysed without affecting the 1,3-dioxolane counterpart, to regenerate (2).

The preparation of compound (2) from diacetone glucose occurs in 20% overall yield, requiring sixteen steps. The route is completely stereoselective, so that separation of isomers, of any type, is never confronted.

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