Stereocontrolled Synthesis of 1,3,5 . . . (2*n* + 1) Polyols†

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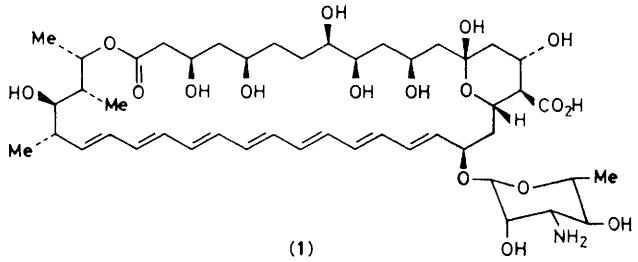
A method for the stereoselective synthesis of 1,3,5 . . . (2*n* + 1) polyols based on the Sharpless asymmetric epoxidation and regioselective epoxide opening by di-isobutylaluminium hydride is reported.

In connection with a programme directed towards the total synthesis of amphotericin B (**1**)[1] we were in need of stereochemically defined 1,3-diol segments. Inspection of this molecular target reveals several such units, which, furthermore, upon retrosynthetic analysis translate into higher members of the polyol series 1,3,5 . . . (2*n* + 1). In this communication, we report a highly efficient and stereocontrolled synthesis of 1,3-diols which is extendable to higher homologues of this series by repetition.[2]

Our approach utilizes the allylic alcohol functionality and relies on (a) the recently discovered Sharpless epoxidation[3] reaction and (b) the formation and regioselective reduction of γ,δ-epoxy-α,β-unsaturated esters by di-isobutylaluminium hydride (DIBAL) to afford allylic-homoallylic alcohols. The sequence is given in Scheme 1. Thus, Sharpless asymmetric epoxidation of allylic alcohol (**2**) resulted in (**3**)§ (80% yield, 99:1 stereoselectivity) which upon Swern oxidation (80% yield) followed by Wittig extension gave the γ,δ-epoxy-α,β-unsaturated ester (**4**) (84% yield, *E*:*Z* 84:16, chromatographically separated). The crucial regioselective epoxide opening (attack at α-carbon), necessary for the success of this method, was cleanly (92% yield) effected with DIBAL leading to the monoprotected intermediate (**5**), *via* temporary protection of the primary OH as a pivaloate ester, silylation of the secondary OH, and finally deprotection of the primary OH (77% overall yield). Compound (**5**) when subjected to the slightly modified sequence a, b, and d led to the higher homologue intermediate (**7**) *via* (**6**) (stereoselectivity of epoxidation *ca.* 91:9) in similar yields. The 1,3-diol derivative (**7**) was similarly extended by the sequence of a, b, and e to the 1,3,5-triol system (**8**) (stereoselectivity of epoxidation *ca.*



(1)

† This work was first reported at the 65th Canadian Chemical Conference, Toronto, Canada, May—June, 1982.

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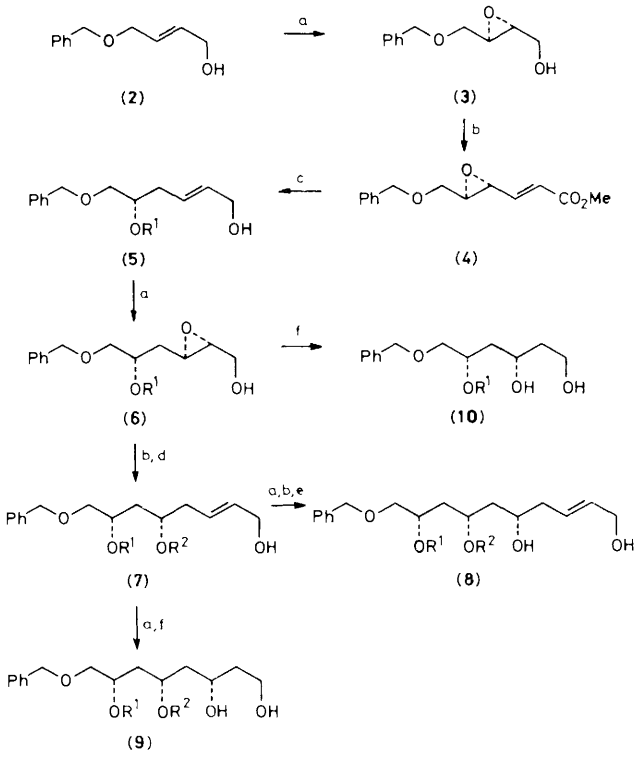
§ Satisfactory spectroscopic (i.r., ^{1}H n.m.r., and mass) and optical rotation data and exact mass data were obtained for all new compounds.



Scheme 1. R^1 = $SiBu^tPh_2$, R^2 = $SiBu^tMe_2$. *Reagents:* a, 1.1 equiv. Bu^tOOH, 2.2 equiv. $Ti(OPr^i)_4$, 1.1 equiv. (−)-diethyl-tartrate, CH_2Cl_2, −23 °C; b, 1.5 equiv. $(COCl)_2$, 2.0 equiv. dimethyl sulphoxide, 5.0 equiv. Et_3N, CH_2Cl_2, −78 to 25 °C; 1.1 equiv. $Ph_3P{=}CHCO_2Me$, PhH, 25 °C; c, 6.0 equiv. DIBAL, CH_2Cl_2, −78 °C; 1.1 equiv. Bu^tCOCl, 4.0 equiv. pyridine, CH_2Cl_2, 25 °C; 1.2 equiv. Bu^tPh_2SiCl, 4.0 equiv. imidazole, 25 °C; 2.5 equiv. DIBAL, CH_2Cl_2, −78 °C; d, as for c except Bu^tPh_2SiCl replaced by Bu^tMe_2SiCl; e, as for c but first part of sequence only; f, 1.1 equiv. REDAL, tetrahydrofuran, 0—25 °C.

95:5) which in principle could be homologated to higher members of the series 1,3,5 . . . $(2n + 1)$ polyols. On the other hand, the sequence can be terminated at the hydroxyepoxide stage by regioselective REDAL [$NaAlH_2(OCH_2CH_2OMe)_2$] reduction[2a,2b,4] giving rise to the polyols (**10**) [90% yield from (**6**)] and (**9**) [65% overall from (**7**)]. Furthermore, since the Sharpless asymmetric epoxidation could, in principle, provide either enantiomeric epoxide, the flexibility of the above sequence in producing any desired stereochemical combination is considerably enhanced.

The present technology and the polyhydroxy-intermediates reported here with conveniently differentiated hydroxy-groups set the stage for the total synthesis of complex and highly oxygenated natural products including amphotericin B (**1**).

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