Preparation of Bicyclic Lactones: Precursors for the Synthesis of Paniculides B and C

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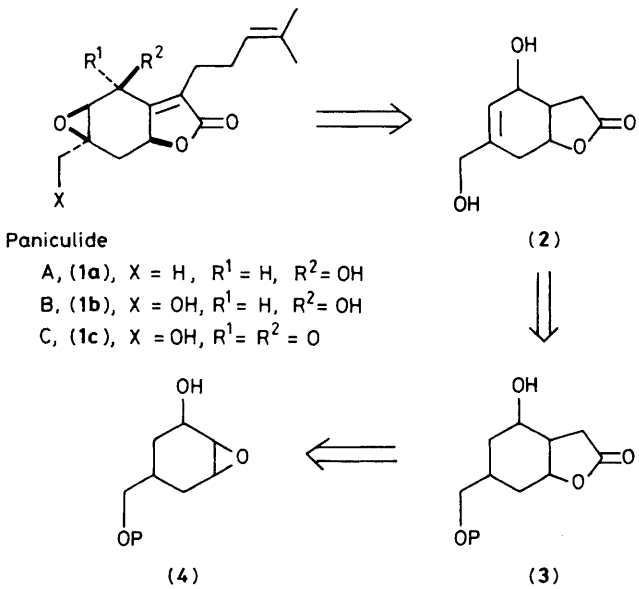
A stereoselective approach to the paniculide skeleton is reported utilising an approach based on the dilithioacetate opening of an epoxide and demonstrating the high degree of regio- and stereo-control possible in this reaction, epoxidation, reduction, and phenylselenation reactions.

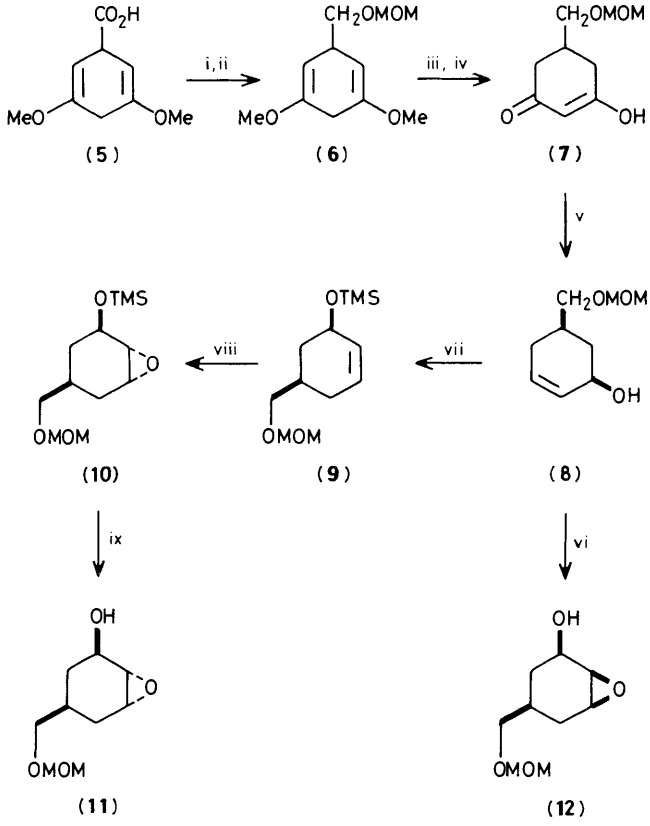
Three highly oxygenated lactones, paniculides A (**1a**), B (**1b**), and C (**1c**) were isolated in 1968 by Overton *et al.* from callus cultures derived from hypocotyl and stem tissues of *Andrographis paniculata* Nees (Acanthaceae).[1,2] The absolute configuration of paniculide B (**1b**) has been determined by *X*-ray crystal determination of the bis-*p*-bromobenzoate.[3] Recently two different approaches to the paniculides have been reported[4,5] and we now report our own studies in this field based on the retrosynthetic analysis described (Scheme 1). We envisaged that regiospecific opening of the epoxide (**4**) with dilithioacetate and subsequent cyclisation would yield the hydroxylactone (**3**). Regiospecific introduction of the unsaturation [(**2**)] would then be followed by a stereoselective epoxidation. We have now demonstrated that these transformations can be achieved with a high degree of regio- and stereo-control.

The starting point for our synthesis was 3,4,5-trimethoxybenzoic acid which underwent Birch reduction to yield 3,5-dimethoxy-1,4-dihydrobenzoic acid (**5**), m.p. 105—107 °C (diethyl ether–hexane) in 97% yield[6] (Scheme 2). Reduction of the carboxylic acid group and protection of the resulting hydroxy group as the methoxymethyl (MOM) ether (**6**) proceeded in excellent yield (92%). Treatment with toluene-*p*-sulphonic acid (*p*-TsOH) in ethanol yielded the

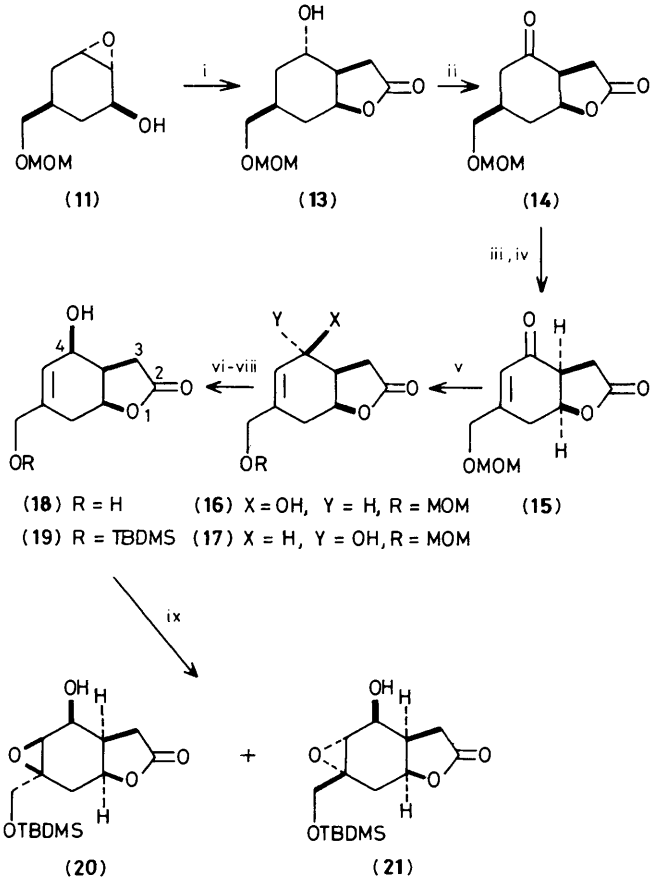


Paniculide
A, (1a), X = H, R^1 = H, R^2 = OH
B, (1b), X = OH, R^1 = H, R^2 = OH
C, (1c), X = OH, R^1 = R^2 = O

Scheme 1



Scheme 2. i, $LiAlH_4$; ii, MOMCl, Pr^i_2NEt; iii, *p*-TsOH, EtOH; iv, KOH, H_2O; v, $LiAlH_4$; vi, MCPBA, $CHCl_3$; vii, Me_3SiCl, Et_3N; viii, MCPBA, CH_2Cl_2, 0 °C; ix, NH_4Cl.



Scheme 3. i, $LiCH_2CO_2Li$, dimethoxyethane (DME), hexamethylphosphoramide, 50 °C; ii, PCC on alumina; iii, PhSeCl, EtOAc; iv, H_2O_2; v, $LiEt_3BH$; vi, HBr, DME; vii, $NaBH_4$; viii, Bu^tMe_2SiCl, Et_3N; ix, MCPBA, CH_2Cl_2, 0 °C.

vinylogous ester and subsequent hydrolysis with aqueous potassium hydroxide yielded the dione (**7**), m.p. 68—70 °C. Lithium aluminium hydride reduction proceeded smoothly to furnish the corresponding allylic alcohol (**8**) in an overall yield of 60% from (**6**). Protection of the alcohol as the trimethylsilyl (TMS) ether (**9**) followed by epoxidation (**10**) with *m*-chloroperbenzoic acid (MCPBA) at 0 °C and subsequent hydrolysis yielded a mixture of *trans*- and *cis*-α-hydroxy epoxides (**11**) and (**12**) in a ratio of 99 : 1 and an overall yield of 90%. In contrast, directed epoxidation of the allylic alcohol (**8**) gave a 12 : 1 mixture of the *cis*- and *trans*-epoxides (**12**) and (**11**) in 70% yield; these two epoxides were easily separated by flash chromatography.

The next stage in our synthesis utilised the directing effect of an α-hydroxy group in the dilithioacetate opening of an epoxide.[7] Thus treatment of epoxide (**11**) with 5 equiv. of dilithioacetate followed by cyclisation afforded the more stable *cis*-lactone (**13**) in 93% yield (based on recovered starting material) (Scheme 3). The *cis*-ring junction ensured that the concave nature of the molecule should provide a high degree of stereocontrol in subsequent steps. Oxidation with pyridinium chlorochromate (PCC) on alumina proceeded in 81% yield to give the ketone (**14**). The required α,β-unsaturation was then introduced *via* regiospecific phenylselenation from the least hindered α-face followed by oxidative *syn*-elimination to yield the required enone (**15**) in 85% yield. A small amount (<10%) of the undesired regioisomer was also isolated.

Stereoselective reduction of the enone from the least hindered α-face using triethyl lithium borohydride gave a 92% yield of two epimeric alcohols (**16**), a white crystalline solid, m.p. 64—65 °C (ethyl acetate–pentane) and (**17**) in a ratio of 98 : 2. Deprotection of the major desired[8] epimer (**16**) gave the unstable diol (**18**) in 72% yield. Reprotection of the primary alcohol with t-butyldimethylsilyl (TBDMS) chloride proceeded to (**19**) in 70% yield. The change in protecting group was felt necessary because of the anticipated difficulties in removal of the MOM protecting group at a later stage. Epoxidation using MCPBA then proceeded in 81% yield in a highly stereoselective manner to yield a mixture of two epoxylactones (**20**) and (**21**) (95 : 5). As anticipated, the major isomer (**20**), m.p. 82—84 °C, was that derived *via* C(4)-hydroxy directed epoxidation. The epoxide (**20**) has been demonstrated to be readily converted into paniculides B and C.[4]

In an analogous series of reactions the lactone (**22**) available from the acid catalysed transesterification of (**13**) was converted into the epoxide (**23**); epoxidation in this case took place in a 100% stereoselective manner.

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