Enantiospecific Synthesis of the C-17—C-20 and C-21—C-27 Synthons of the Antineoplastic Macrolide Bryostatins†

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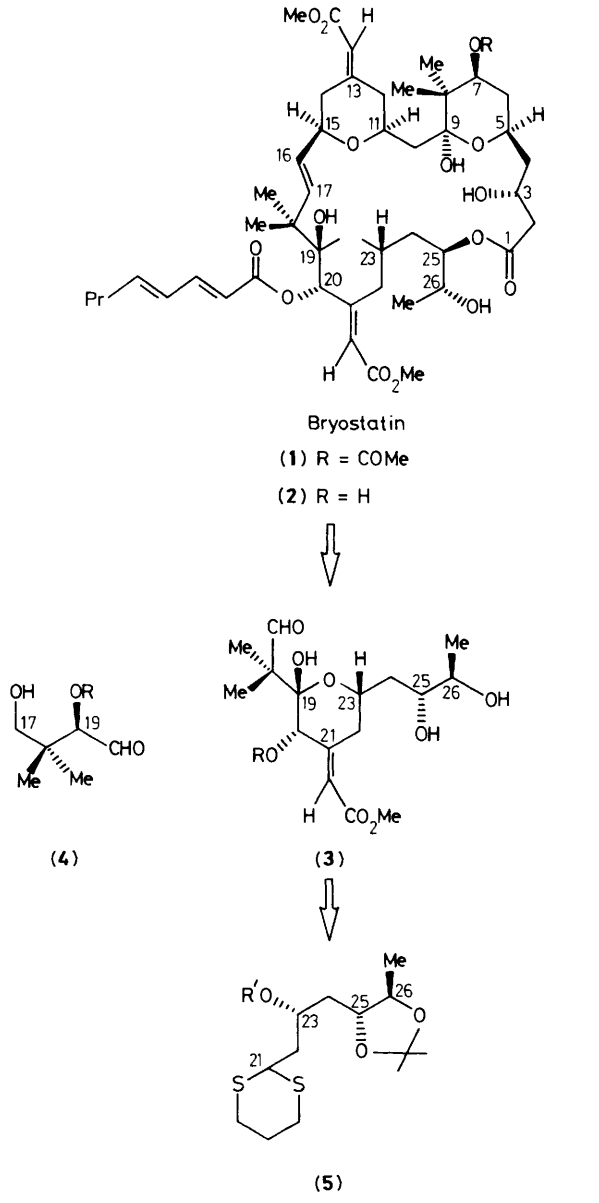
Synthons corresponding to the C-17—C-20 and C-21—C-27 fragments of the antineoplastic macrolide bryostatins have been synthesized starting from the readily available (*R*)-pantolactone and D-galactono-1,4-lactone respectively.

Bryostatins are a family of some 17 related macrocyclic lactones (Scheme 1) possessing an unprecedented bryopyran skeleton.[1] This unique family of compounds has been isolated from the marine Bryozoan *Bugula neritina* (Linnaeus). They constitute sedentary colonial filter-feeding organisms (moss animals) that attach to and grow on ship hulls.[2] Recently, bryostatins have attracted considerable interest due to their exceptionally high levels of antineoplastic activity against the murine P388 and L1210 lymphocytic leukaemia.[1] They have now reached Phase 2 of clinical trials. Their mode of action has been shown to depend upon their capacity to bind to the phorbol ester receptor protein kinase and, as a consequence, stimulate protein phosphorylation.[3] Structure activity relationships within this family of compounds have demonstrated that the C-20 (*E*,*E*)-octa-2,4-dienoate substituent was not an absolute prerequisite for their antineoplastic activity. However, it was postulated that the C-7 and C-20 ester substituents could influence the degree of cytotoxicity.[1]

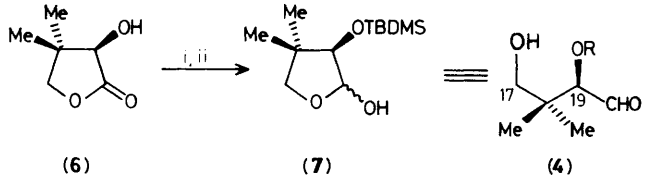
By virtue of their 14 stereogenic centres, these 20-membered ring lactones embedding masked 1,3-polyol units represent a formidable synthetic challenge. With the exception of Masamune's synthesis which is near completion,[4] efforts to synthesize bryostatins are still sparse and at an early stage.[5] Relative to other important macrolides which may be isolated in appreciable quantities from fermentation broths, bryostatins are obtained by a lengthy isolation procedure and in very low yields (10^{-5}%).[1] This aspect, coupled with their promising medicinal properties, justifies synthetic approaches. Our contribution toward this goal is depicted here and illustrates the usefulness of the chiron methodology[6] in elaborating the C-17—C-20 and C-21—C-27 synthons of bryostatins.

Retrosynthetic analysis readily suggested disconnection at the lactone linkage and at the C-16—C-17 *trans* double bond to afford the key intermediate (**3**) (Scheme 1). A further disconnection revealed fragments (**4**) and (**5**) having four and seven carbon frameworks respectively. These fragments were transposed to naturally occurring chiral building blocks. Thus, synthon (**4**) was derived by standard procedures from (*R*)-(−)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone [D-pantolactone, (**6**)] as outlined in Scheme 2 (78% overall). Although not obvious because of the ketonic nature of C-19 in bryostatins, the judicious choice of this chiral template was based on the realization that it already possessed the gem-dimethyl functionality at C-18 and also because the

† A preliminary account of this work has been presented at the 3rd Chemical Congress of North America (joint A.C.S.-C.I.C.) in Toronto, Ontario, Canada, June 5—10, 1988.



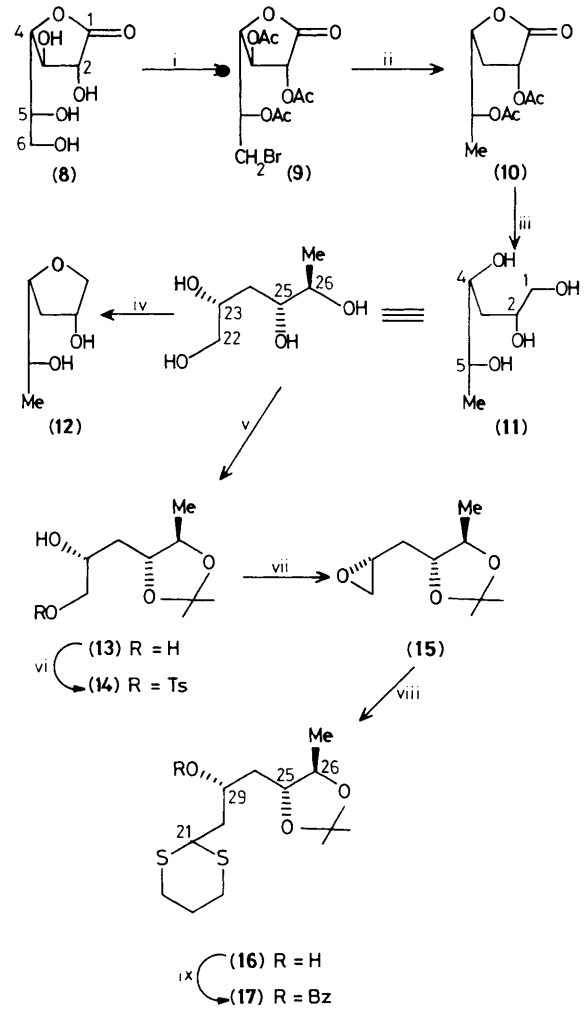
Scheme 1



Scheme 2. *Reagents and conditions*: i, Bu^tMe_2SiCl(TBDMSCl), 4-*N*,*N*-dimethylaminopyridine (DMAP), Et_3N, CH_2Cl_2, 95%; ii, di-isobutylaluminiumhydride (DIBAL), THF, −78 °C, 87%.

chirality at C-19 could be temporarily used for 1,2-asymmetric induction. Indeed, it is expected that this stereocentre would allow high diastereofacial selectivity in the addition of the dithianyl fragment (**5**).[7] It is noteworthy that this useful fragment (**4**) [in its lactol form, (**7**)] is an integral constituent of the C-6—C-9 segment of the bryostatins.[8]

D-Galactono-1,4-lactone (**8**) was selected as a template for the synthesis of fragment (**5**) when it became apparent that



Scheme 3. *Reagents and conditions*: i, HBr in HOAc then Ac_2O, 87%;[9] ii, H_2, 5% Pd/C, Et_3N, EtOAc, 82%; iii, $LiBH_4$, THF, 0—25 °C, 96%; iv, TsCl, pyridine, quant.; v, $Me_2C(OMe)_2$, TsOH, C_6H_6, 87%; MeOH, TsOH, 12 h, 25 °C or 1% I_2 in MeOH, 77%; vi, TsCl, pyridine, −10 to 25 °C, 84%; vii, K_2CO_3, MeOH, 83%; viii, dithiane, Bu^nLi, THF, −20 °C, 18 h, 47%; ix, BzCl (Bz = PhCO), pyridine, 74%.

direct transposition of the predisposed stereogenicities at C-2 (C-23), C-4 (C-25) and C-5 (C-26) would greatly simplify the synthetic task. Furthermore, the intrinsic 1,4-lactone functionality of (**8**) was known to undergo facile β-elimination at its C-3 (C-24) substituent.[9] Therefore, simultaneous deoxygenation at C-3 and C-6 (sugar numbering) was anticipated.

Hence, D-galactono-1,4-lactone (**8**) was transformed *via* a high-yielding sequence into the known[9] 2,5-di-*O*-acetyl-3,6-dideoxy-D-xylo-hexono-1,4-lactone [(**10**), m.p. 86—87 °C] (Scheme 3). The stereospecificity of the hydrogenolysis step (H_2, Pd/C, Et_3N), through the intermediacy of an enol acetate, was due to steric hindrance of the bottom face caused by the orientation of the C-4 side chain. Isolation of the tetrol (**11**) obtained by reduction of the acetoxy-lactone (**10**) proved troublesome with $LiAlH_4$,[9] presumably because of stable aluminate complex formation. However, reduction of (**10**) with $LiBH_4$ followed by cation exchange resin treatment afforded a high yield (96%) of the known[9,10] 3,6-dideoxy-D-xylo-hexitol [(**11**), m.p. 95—96 °C]. Attempts at obtaining the C-22—C-23 epoxide by direct tosylation followed by base treatment of the tetrol (**11**) failed due to inevitable formation

of the 1,4-anhydro diol (**12**) during the tosylation step. The problem was overcome by sequential bis-acetonation [$Me_2C(OMe)_2$, TsOH (Ts = $OSO_2C_6H_4Me$), 87%] and kinetic deacetonation (1% I_2; MeOH, 77%)[11] to give acetonide diol (**13**). Monotosylation of the primary hydroxy group followed by base treatment (K_2CO_3, MeOH) gave epoxide (**15**) which was contaminated with 6% epimeric C-23 epoxide originating from partial tosylation at the secondary hydroxy group. Complete regioselectivity in the sulphonation of the primary hydroxy group was achieved by the use of the bulkier 2,4,6-tri-isopropylbenzenesulphonyl chloride. However, since the overall yield was somewhat lower, the first approach was preferred and pure epoxide (**15**) was obtained after purification by silica gel chromatography (syrup, $[\alpha]_D$ +23°). Homologation of synthon (**15**) with 2-lithiodithiane [Bu^nLi, tetrahydrofuran (THF), −20 °C, 47%, not optimized] afforded the C-21—C-27 fragment of bryostatins. Benzoylation [BzCl (Bz = benzoyl), pyridine] of the resulting alcohol gave (**17**). As mentioned previously, model studies[7] indicated that fragments (**4**) and (**5**) should react with high diastereoselectivity.

These enantiospecific sequences leading to fragments (**4**) and (**5**) of bryostatins compare well to the synthesis of similar fragments described by Masamune.[4]‡ The judicious choice of the starting chiral templates allowed maximal overlap of stereogenicities while keeping group interconversion to a minimum.

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‡ All intermediates showed satisfactory spectral and/or analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

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7 Model reactions with (**7**) and 2-lithiodithiane exhibited high diastereoselectivity in favour of the anticipated *anti*-diol in accord with non-chelation addition (*anti*/*syn* = 96:4). The unprotected lactol provided the reversed *syn*-diol diastereoselectivity (*anti*/*syn* = 2:98) following chelation (*anti*-Cram) addition. R. Roy and A. W. Rey, unpublished results.

8 See P. Lavallée *et al.* in ref. 5; R. Roy and A. W. Rey, unpublished results.

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