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Total synthesis of a 20-deoxybryostatin†

Anthony P. Green, Alan T. L. Lee and Eric J. Thomas*

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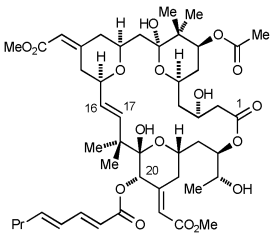
The 20-deoxybryostatin 40 has been prepared using a modified Julia olefination to form the 16,17-double-bond, followed by macrolactonisation, selective deprotection and oxidation. This is the first total synthesis of a 20-deoxybryostatin.

The bryostatins are macrocyclic natural products with potent anti-cancer activity due in part to protein kinase C inhibition.[1] They also show a range of other biological activities including cognition enhancement. Representative examples include the widely studied bryostatin 1 (**1**) and bryostatin 10 (**2**)[2] which lacks an oxygen function at C(20). Five total syntheses of bryostatins have been described to date,[3] together with a formal synthesis,[4] syntheses of close analogues[5–7] and many partial syntheses.[1a,8] Moreover, analogues with simplified C(1)–C(16) fragments have been prepared with improved biological activity.[9] However the isolation of bryostatins from natural sources is difficult and only limited quantities are available for SAR studies.[2b,10] For these reasons the synthesis of bryostatins and analogues is still of interest.[8]



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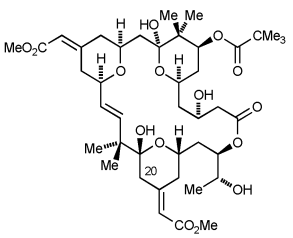

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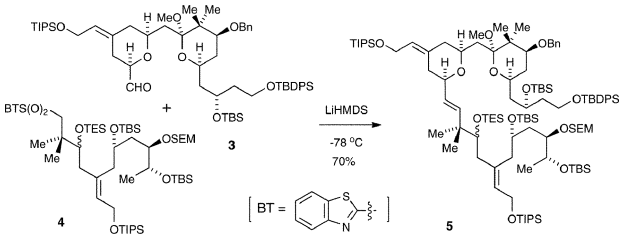
Convergent syntheses of bryostatins can be envisaged with assembly of the 16,17-double-bond as a key step. Indeed, the early total syntheses of bryostatins used classical Julia reactions to form this bond.[3] However, formation of the 16,17-double-bond using ring-closing metathesis was successful only for a ring-expanded derivative[6] and for analogues which lacked the geminal dimethyl groups at C(18).[7] The (*E*)-alkene **5** was recently prepared from the aldehyde **3** and sulfone **4** using a modified Julia olefination.[11,12] We now report the synthesis of a benzyl ether of a 20-deoxybryostatin, a biologically active sub-group of the bryostatins that has yet to succumb to total synthesis, using the modified Julia approach.

At this stage, it was necessary to modify the protecting group strategy and to develop an improved synthesis of sulfone **4**. Thus, the hydroxydecylphosphonate **8**, prepared by desilylation of silyl ether **7**,[12] was condensed with aldehyde **6** using barium hydroxide as the base to give the (*E*)-enone **9**, see Scheme 1. Selective removal of the triethylsilyl protecting group using the hydrogen fluoride-pyridine complex gave the secondary alcohol **10** that was cyclised immediately using potassium *tert*-butoxide in tetrahydrofuran to give the 2,5-*cis*-disubstituted tetrahydropyran **11** stereoselectively. Oxidation of the primary alcohol gave the corresponding acid and alkylation under basic conditions using prop-2-enyl bromide gave the allyl ester **12**. Treatment with pyridinium toluene *p*-sulfonate in methanol containing trimethyl orthoformate then initiated methanolysis of the acetonide with formation of the methoxy acetal **13** and silylation of the C(3)-alcohol gave the fully protected ester-acetal **14**. Finally, oxidative removal of the *p*-methoxybenzyl group delivered the alcohol **15** that corresponds to the C(1)–C(16) fragment of the bryostatins.



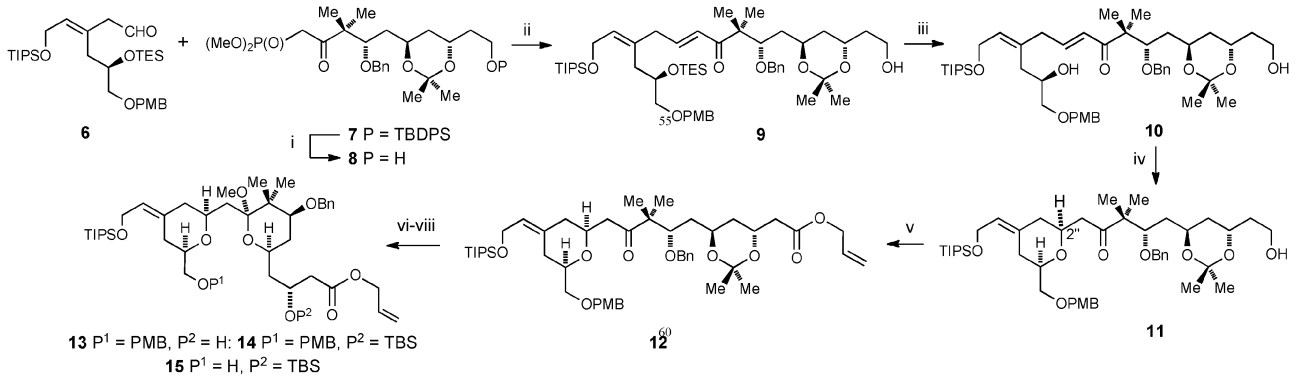
In the original synthesis of sulfone **4** the final step involved oxidation of the corresponding sulfide and was complicated by competing oxidation of the alkene.[12] A more efficient synthesis of sulfone **4** was required.

The alcohol **16**[13] was converted to the bromide **19** by protection of the secondary alcohol as its triethylsilyl (TES) ether **17**, debenzylation and conversion of the allylic alcohol **18** into the bromide **19**, see Scheme 2. Selective removal of the TES ether and acylation of the resulting alcohol **20** using acryloyl chloride then gave the bromoalkenyl acrylate **21**.

If an organometallic reagent derived from bromide **21** could be reacted with aldehyde **22**,[13] ring-closing metathesis, reduction and protection would give the required sulfone directly. However, such organometallic reagents were expected to be unstable due to the possibility of competing intramolecular reactions with the

School of Chemistry, University of Manchester, Manchester, M13 9PL, UK. E-mail: e.j.thomas@manchester.ac.uk; Fax: 00 44 (0)161 275 4939; Tel: 00 44 (0)161 275 4614

† Electronic supplementary information (ESI) available: full experimental details and spectra of key compounds. See DOI: 10.1039/c1cc12332g



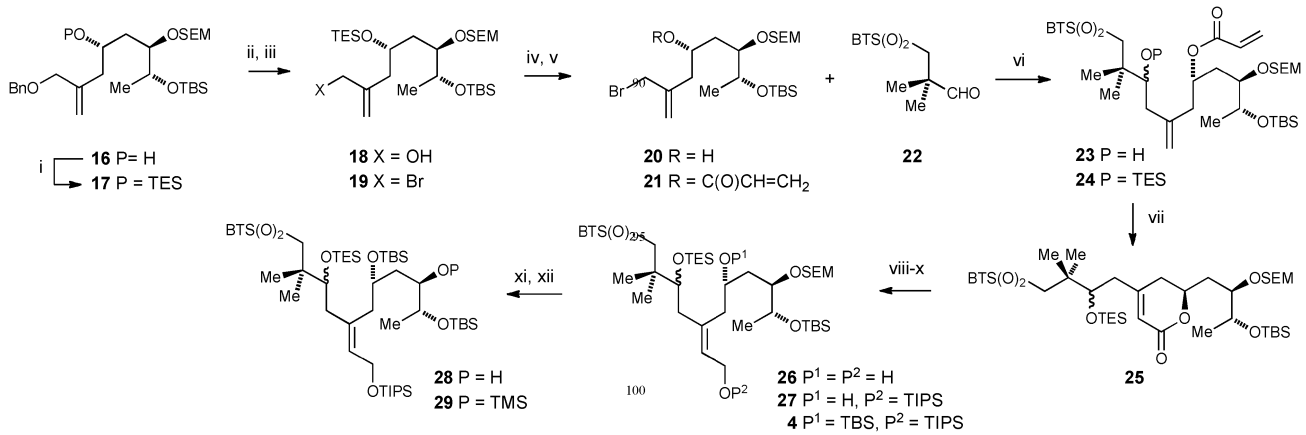
Scheme 1 **Synthesis of the C(1)-C(16) fragment 15:** ***Reagents and conditions***: (i) TBAF, THF, r.t., 16 h (*ca.* 100%); (ii) $Ba(OH)_2$, THF, H_2O, 0 °C - r.t., 16 h; (iii) HF.py, THF, 0 °C, 25 min; (iv) ^{t}BuOK, THF, r.t., 5 min (49% of **11** based on **8**); (v) (a) DMP, py, DCM, r.t., 1 h; (b) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, THF, ^{t}BuOH, H_2O, r.t., 1 h; (c) allyl bromide, $NaHCO_3$, DMF, 70 °C, 16 h (70% of **12** based on **11**); is (vi) PPTS, MeOH, $HC(OMe)_3$, DCM, r.t., 1 h (66%); (vii) TBSOTf, 2,6-lut., DCM, −78 °C, 1 h (84%); (viii) DDQ, MeOH, DCM, r.t. 2 h (72%).

acrylate. Indeed, preliminary studies of indium mediated addition of bromide **21** to the aldehyde **22** gave complex mixtures of products. However, it was thought that for an organobismuth species generated from the bromoalkenyl acrylate **21** and bismuth(0) *in situ*,[14,15] an *inter*molecular reaction with an aldehyde might be able to compete with any *intra*molecular reaction with the acrylate. Indeed, the bismuth(0) mediated reaction of bromide **21** with aldehyde **22** followed by silylation of the resulting alcohols **23** gave a 60% yield of the silyl ethers **24**. Ring-closing metathesis[13] then gave the lactone **25** which was reduced to the diol **26** using Luche's conditions. Protection of the primary and secondary alcohols gave the sulfone **4** which was converted into the trimethylsilyl ether **29**.

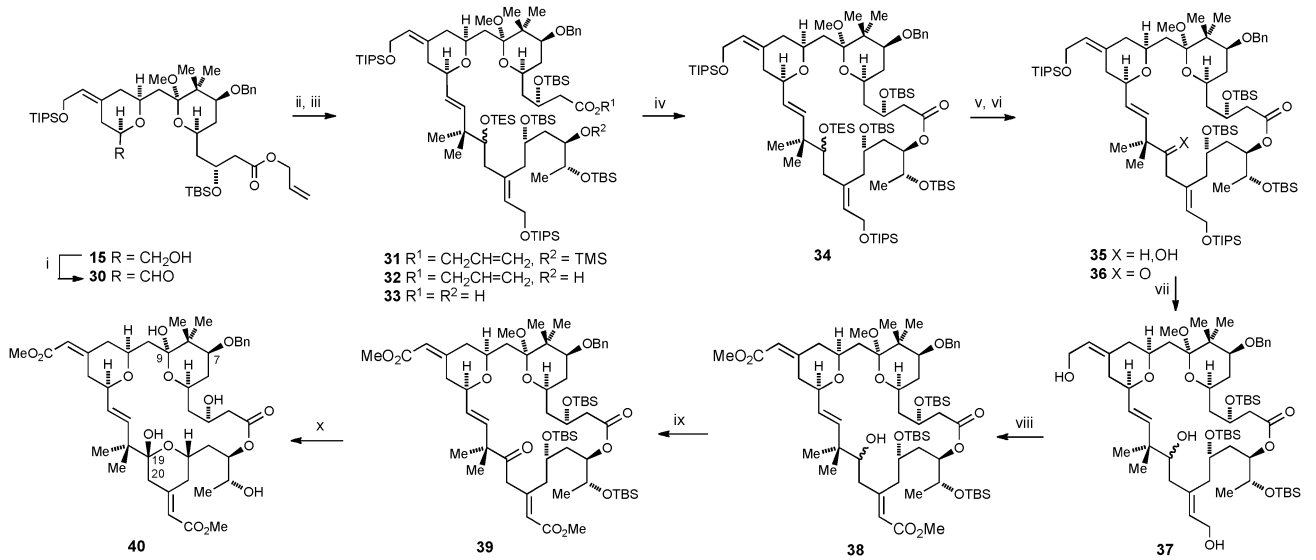
The modified Julia reaction of the aldehyde **30**, prepared by oxidation of the alcohol **15**, and the sulfone **29** gave the (*E*)-alkene **31**, see Scheme 3. Methanolysis of the trimethylsilyl ether gave the alcohol **32** and cleavage of the allyl ester provided the *seco*-acid **33** that was cyclised under Yamaguchi conditions to the macrolide **34**.

Conversion of the macrolide **34** into 7-des-*O*-pivolyl-7-*O*-benzylbryostatin 10 **40** is outlined in Scheme 3. Pyridinium toluene *p*-sulfonate in methanol containing trimethyl *ortho*-formate selectively removed the triethylsilyl group to give the 19-alcohol **35** which was characterised as the ketone **36**. Removal of the tri*iso*propylsilyl groups from alcohol **35** using tetrabutylammonium fluoride in acetic acid then gave the triol **37**. Stepwise oxidation of the exocyclic allylic hydroxyl groups using manganese dioxide and a Pinnick oxidation followed by esterification using trimethylsilyl diazomethane gave the bis-methyl ester **38** which on oxidation using the Dess–Martin periodinane was converted into the sensitive ketone **39**. Finally, desilylation using hydrogen fluoride in pyridine—tetrahydrofuran gave the 20-deoxybryostatin **40** which corresponds to bryostatin 10 **2** except for the presence of the benzyloxy group at C(7).

20-Deoxybryostatins are known to dehydrate to give the 19,20-enol ethers[2] and analogous dehydrations had been observed during model studies. However, extensive NMR studies confirmed the desilylated product was the 20-deoxy-bryostatin **40** rather than the analogous enol ether **41**. In particular, no carbon was seen at *ca.* δ150 in its ^{13}C NMR spectrum, *cf.* C(19) of brysotatin 16 **42**.[16] Moreover neither of the two peaks at *ca.* δ102 in the ^{13}C NMR spectrum of the

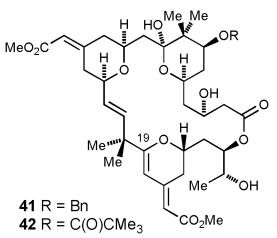


Scheme 2 **Synthesis of sulfone 29:** ***Reagents and conditions***: (i) TESCl, imid., DCM, r.t., 1 h (98%); (ii) Li, naph., THF, −25 °C (97%); (iii) CBr_4, Ph_3P, NEt_3, DCM, 0 °C, 20 min (95%); (iv) PPTS, MeOH, $CH(OMe)_3$, THF, r.t., 3 h (95%); (v) acryloyl chloride, ^{i}Pr$_2$NEt, DCM, 0 °C, 40 min (97%); (vi) (a) BiI_3, Zn, THF, then add **21** and **22**, THF, reflux, 4.5 h; (b) TESCl, imid., DCM, r.t., 90 min (61% of **24** from **21**); (vii) Grubbs' 2 cat., (5 mol%), syringe pump, 20 h, 1,2-DCE, reflux (90%); (viii) $NaBH_4$, $CeCl_3$, MeOH, THF, 0 °C to r.t., 7.5 h (75%); (ix) TIPSCl, imid., DCM, r.t., 12 h (86%); (x) TBSOTf, 2,6-lut., DCM, r.t., 2 h (93%); (xi) ^{n}BuSH, $MgBr_2{\cdot}Et_2O$, K_2CO_3, Et_2O, r.t., 1 h (96%); (xii) TMSCl, Et_3N, DCM, 0 °C to r.t., 3 h (100%).



Scheme 3 **Synthesis of a 20-deoxybryostatin:** ***Reagents and conditions*****:** (i) (a) SO_3.py, DMSO, $^iPr_2NEt$, DCM, r.t., 1 h; (ii) (a) **29**, LiHMDS, THF, −60 °C, 30 min then add **30**, −78 °C, 1 h to r.t., 20 min; (b) PPTS, MeOH, $CH(OMe)_3$, DCM. r.t., 1 h (60% of **32** from **30**); (iii) $Pd(Ph_3P)_4$, morpholine, THF, r.t., 16 h; (iv) 2,4,6 $Cl_3C_6H_2COCl$, Et_3N, THF, r.t., 16 h, toluene, DMAP, 40 °C, 14 h (85% of **34** from **32**); (v) PPTS, MeOH, $CH(OMe)_3$, DCM, r.t., 48 h (54%); (vi) TPAP, NMO, 4 Å sieves, DCM, r.t., 6 h (50%); (vii) TBAF, AcOH, r.t., 40 h (53%); (viii) (a) MnO_2, DCM, r.t., 1 h (b) $NaOCl_2$, 2-methylbut-2-ene, ^tBuOH, r.t., 1 h (c) $TMSCHN_2$, MeOH, tol., 0 °C, 1 h (40% of **38** from **37**); (ix) DMP, py., DCM, r.t., 2 h; (x) HF, py., THF, r.t., 24 h, py. and HF·H_2O, added, r.t. 24 h (50% of **40** from **38**).

product correlated with a hydrogen and so were assigned to the hemi-acetal carbons C(9) and C(19). In the ^1H NMR spectrum of the product **40**, the methylene protons at C(20) and the 19-hydroxyl group were observed at *ca.* δ2.1 and as a singlet at δ5.3, as would be expected.[2b]†



The synthesis of the bryostatin 10 analogue **40** amounts to the first total synthesis of a 20-deoxybryostatin. The reliability of the modified Julia reaction for the stereoselective assembly of the 16,17-(*E*)-double-bond and the use of organobismuth chemistry for assembly of the metathesis precursor **24** together with the selective late-stage desilylation reactions and isolation of the 20-hemiacetal **40** are of interest.

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