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# Synthesis of the C(1)–C(16) fragment of bryostatins

Matthew O'Brien, Nicholas H. Taylor and Eric J. Thomas*

*The Department of Chemistry, The University of Manchester, Manchester M13 9PL, UK*

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**Abstract**—A synthesis of the C(1)–C(16) fragment **43** of the bryostatins is reported which features a stereoselective equivalent of an 'ene' reaction between the allylsilane **35** and the alkynone **33** and the stereoselective conjugate addition–cyclisation of the dienyl ketone **36** to give the acetal **39** after acetalisation. 

The bryostatins are a group of complex natural products first isolated from the marine filter feeding bryozoan *Bugula neritina* and shown to have potent antineoplastic activity against a number of cell lines.[1] Presently the bryostatins are involved in over 40 phase I and phase II clinical trials either alone or in combination with other drugs. Many studies have been published concerned with approaches to the synthesis of bryostatins and several total syntheses have been completed.[2–4] Nevertheless, the scarcity of natural material and the promising biological activity of analogues ensures that synthetic studies in this area are still of importance.

A well established strategy for the assembly of bryostatins involves a Julia reaction between a C(1)–C(16) aldehyde and a C(17)–C(27) sulphone followed by functional group modification and macrolactonisation as indicated for bryostatin 11 **1**, a 20-deoxybryostatin which has not been synthesised to date. We here report the evolution of a synthesis of the bicyclic acetal **43** which corresponds to the C(1)–C(16) fragment of the bryostatins. In our approach the 4-methylenetetrahydropyran unit **3** is assembled by a stereoselective conjugate addition–cyclisation of a hydroxyenone **2**, followed by development of the exocyclic methoxycarbonylmethylene group later in the synthesis.[5]

Preliminary studies to evaluate the proposed cyclisation are outlined in Scheme 1. Copper-catalysed reactions of the Grignard reagent derived from the allylsilane **5**,[6] which had been prepared from the dibromide **4**, with the racemic protected epoxyalcohols **6** and **7**, gave the alcohols **8** and **9** in good yield. It was intended to examine conjugate addition reactions of the *tert*-butyldimethylsilyl ethers **10** and **11**, prepared from these alcohols, with propargylic ketones as a route to 5-methylenealk-2-enones ready for cyclisation. However, in the presence of zinc iodide, the allylsilanes **10** and **11** were found to react with *tert*-butyl ethynyl ketone to give the 5-[(*Z*)-trimethylsilylmethylene]-alk-2-enones **12** and **13** with excellent stereocontrol of both double-bonds.[7] Although these reactions are formally equivalent to 'ene reactions, it is likely that two step processes are involved.[8,9]

Cyclisations of the dienes **12** and **13** were examined under acidic conditions. Thus, treatment with aqueous hydrogen fluoride in acetonitrile at room temperature removed the protecting and trimethylsilyl groups and induced cyclisation, to give mixtures of the corresponding 2,6-*cis*- and -*trans*-disubstituted-4-methylenetetrahydropyrans **14** and **16**, which were characterised and separated as their acetates **15** and **17**.[10] When the

* Corresponding author.

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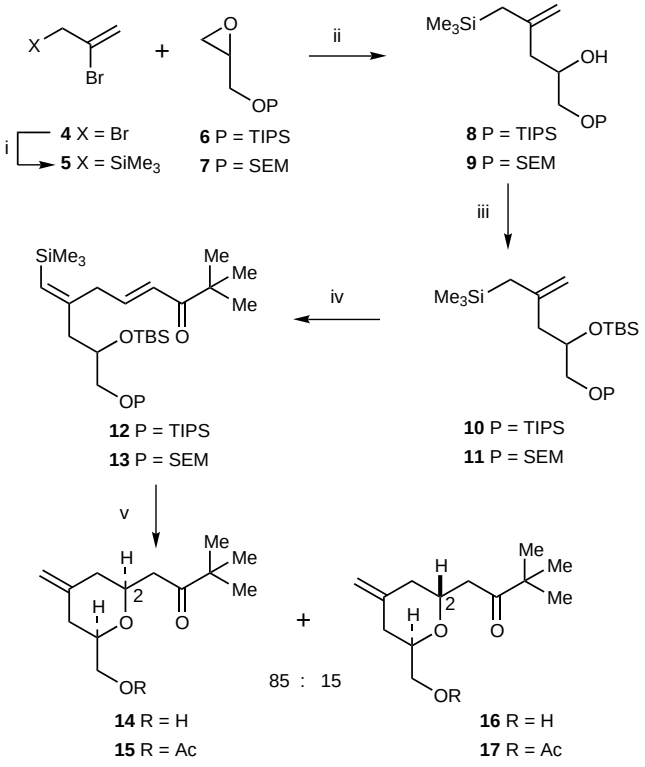
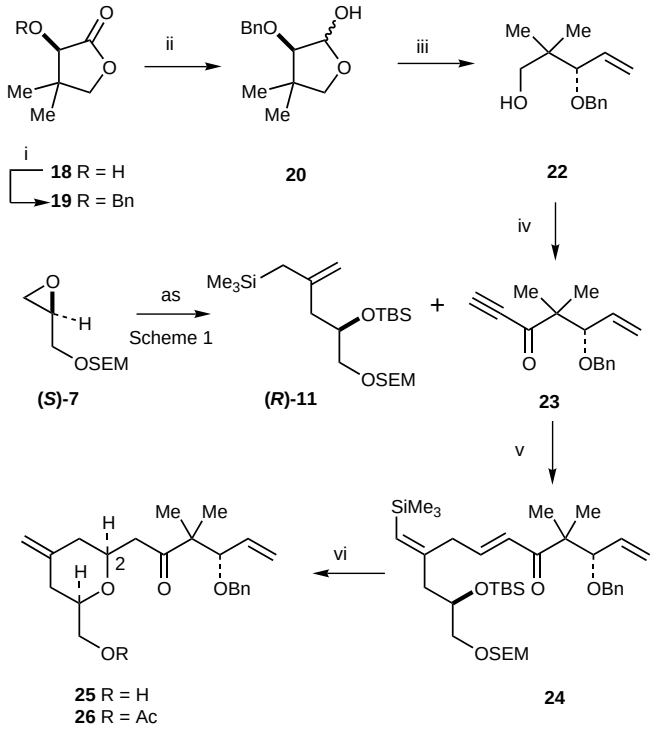
deprotection and cyclisation reactions were carried out at room temperature overnight, the cyclisations were reasonably stereoselective and gave the 2,6-*cis*- and -*trans*-isomers in ratios of ca. 85:15 in favour of the *cis*-isomer **14**. However, when milder conditions were used, e.g. to remove the *tert*-butyldimethylsilyl group selectively from the SEM-ether **13**, the stereoselectivity of cyclisation dropped suggesting that the 85:15 mixtures were the result of thermodynamic control.

These studies indicated that the combination of the 'ene' reactions between the allylsilanes and the propargylic ketones followed by conjugate addition–cyclisation provides a short and convergent entry to the C(9)–C(15) component of the bryostatins. The use of this approach to prepare an intermediate for a bryostatin synthesis is outlined in Scheme 2.

(*R*)-Pantolactone **18** was protected as its benzyl ether **19** which was reduced to the lactol **20**.[11] A Wittig reaction using phosphonium salt **21** then gave the alkenol **22** which was converted into the alkynone **23** by oxidation to the corresponding aldehyde, addition of ethynylmagnesium bromide and further oxidation using Dess–Martin periodinane. (*S*)-Glycidol was protected (2 mol equiv. $^{i}Pr_2NEt$, SEMCl, dichloromethane, 20°C, 16 h) as its trimethylsilylethoxymethyl (SEM) ether (*S*)-**7** which was taken through to the allylsilane (*R*)-**11**. This allylsilane and the alkynone **23** were then coupled using zinc(II) iodide to give the trienylketone **24** with excellent stereoselectivity at the di- and trisubstituted double-bonds. Deprotection–cyclisation was again accomplished using aqueous HF in acetonitrile to give the 2,6-*cis*-substituted tetrahydropyran **25** together with 15% of its epimer at C(2) which were conveniently separated as their acetates.




**Scheme 1.** *Reagents and conditions*: (i) $Cl_3SiH$, $Et_3N$, cat. CuCl, $Et_2O$, 0°C to rt, 15 h, then 3 M MeMgBr in $Et_2O$, 0°C, 15 h (70%); (ii) Mg, THF, reflux, 0.5 h then add to CuI and **6** or **7** in THF, −10°C to rt, 1 h (**8**, 95%; **9**, 88%); (iii) TBSOTf, 2,6-lutidine, dichloromethane (DCM), rt, 18 h (77–90%); (iv) HCC·CO·$CMe_3$, $ZnI_2$, DCM, protected from light, rt, 24 h (**12**, 52%; **13**, 62%); (v) a. 60% aq. HF, MeCN, 18 h, rt; b. $Ac_2O$, py, DCM (72% from **12**/**13**).




**Scheme 2.** *Reagents and conditions*: (i) $BnOC(NH)CCl_3$, DCM, TFA, rt, 15 h (98%); (ii) DIBAL-H, THF, −35°C, 5 h, MeOH quench at −78°C (88%); (iii) $Ph_3PMeBr$ **21**, *n*-BuLi, THF, from −78°C to rt, 18 h (82%); (iv) a. $(COCl)_2$, DMSO, DCM, 1 h −78°C then $Et_3N$ with warming to rt; b. HCCMgBr, THF, −78°C to rt, 18 h; c. Dess–Martin periodinane, DCM, 0°C to rt, 3 h (87% from **22**); (v) $ZnI_2$, 4 Å MS, DCM, rt, 24 h (75%); (vi) a. 60% aq. HF, aq. MeCN, rt, 18 h; b. $Ac_2O$, py, rt, 18 h [64% from **24**; 85:15 mixture of epimers at C(2)].

To complete a synthesis of the C(1)–C(16) fragment of a bryostatin from acetate **26** it remained to introduce the C(1)–C(5) fragment and the exocyclic methoxycarbonyl–methylene group, stereoselectively. However, preliminary investigations indicated that epoxidation, hydroboration and hydroxylation of the acetate **26** all took place regioselectively on the exocyclic methylene group. Moreover, the ketone carbonyl group complicated hydroboration of the terminal double-bond.[12] For these reasons it was decided to assemble the C(1)–C(9) fragment before the 'ene' and cyclisation reactions.

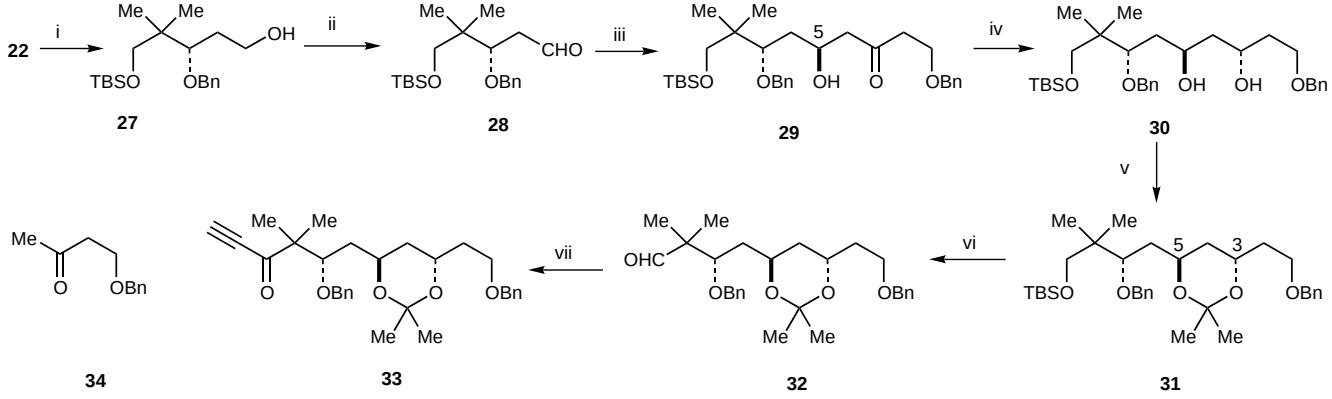
To this end, the alcohol **22** was protected as its *tert*-butyldimethylsilyl ether which was hydroborated to

give the alcohol **27**, see Scheme 3. Oxidation gave the aldehyde **28** which, following a literature precedent,[13] was subjected to an aldol condensation with the lithium enolate of 4-benzyloxybutan-2-one **34** to give the *anti*-adduct **29**,[14] the product of chelation control, with excellent stereoselectivity. The configuration of adduct **29** at C(5) was assigned by analogy with the literature[13] and was confirmed by comparison of the $^1$H NMR spectra of its (*R*)- and (*S*)-acetylmandelates. Reduction of hydroxyketone **29** with tetramethylammonium triacetoxyborohydride gave a good yield of the *anti*-diol **30** which was protected as its acetonide **31**, the relative chemical shifts of the acetonide methyl groups confirming the assigned 3,5-*anti*-stereochemistry. Selective deprotection followed by oxidation then gave the aldehyde **32** which, by addition of ethynylmagnesium bromide and oxidation, gave the alkynone **33**.

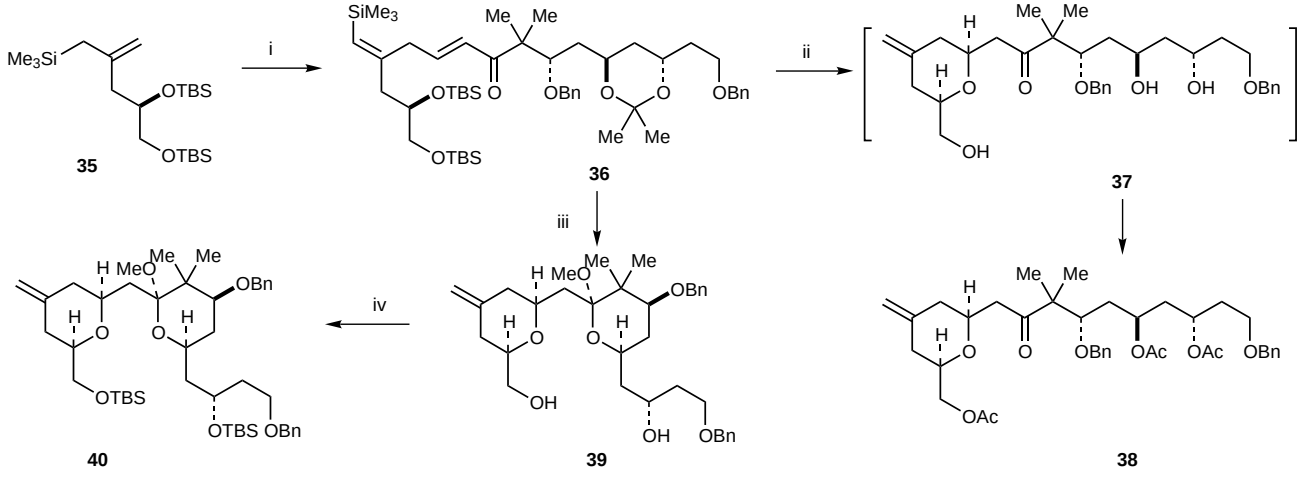
The zinc iodide-promoted reaction of the alkynone **33** with the (*R*)-allyl silane **35** prepared from (*S*)-glycidol gave the dienylketone **36** with excellent stereocontrol, see Scheme 4. This was deprotected and cyclised using aqueous HF in acetonitrile at room temperature to give the triacetate **38**, after treatment with an excess of acetic anhydride, so confirming participation of the intermediate triol **37**.

Attempts were now made to trap the initially formed trihydroxyketone **37** as an acetal. Indeed treatment of the crude product from the cyclisation–deprotection with trimethyl orthoformate in the presence of an acid gave the acetal **39**. This was further protected as its bis-silyl ether **40**.

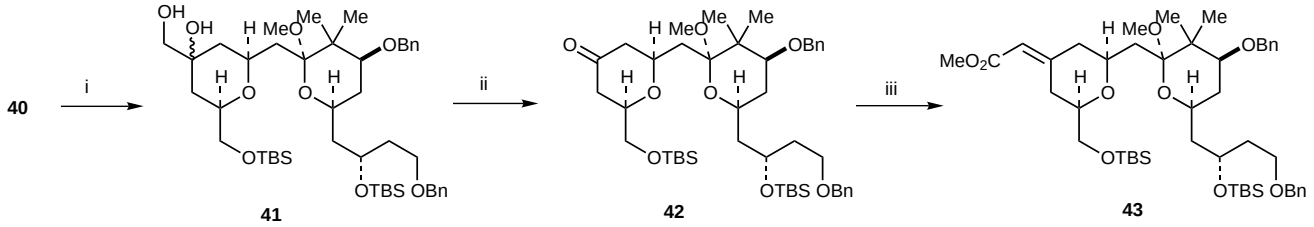
It now remained to introduce the exocyclic methoxycarbonylmethylene group and this was achieved as outlined in Scheme 5. Hydroxylation of **40** and cleavage of the diol **41** using sodium periodate gave the ketone **42**. This was condensed with the chiral phosphine oxide **44**, a reagent used previously in bryostatin synthesis,[3] to give the required αβ-unsaturated ester **43** together with its geometrical isomer, ratio 72:28, in favour of **43**.



**Scheme 3.** *Reagents and conditions*: (i) a. TBSCl, imid., DMAP (cat.), TBAI (cat.), rt, 30 min (97%), b. 1 M $BH_3$ in THF, −18°C to rt, 18 h, then NaOH, 30% aq. $H_2O_2$, 50°C, 3 h (67%); (ii) $(COCl)_2$, DMSO, DCM, −78°C, 20 min then $Et_3N$, −78°C to rt; (iii) **34**, LDA, −78°C, 30 min, then add **28**, −78°C, 2 min, MeOH quench (49%); (iv) $Me_4NBH(OAc)_3$, AcOH, MeCN (1:1), −20°C, 18 h (95%); (v) $Me_2C(OMe)_2$, PPTS (cat.), rt, 18 h (74%); (vi) a. TBAF, THF, rt, 18 h (95%), b. $(COCl)_2$, DMSO, −78°C, 20 min, then $Et_3N$, −78°C to rt (ca. 100%); (vii) a. HCCMgBr, THF, −78°C to rt (ca. 100%), b. Dess–Martin periodinane, DCM, rt 4 h (99%).

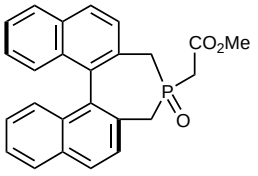


**Scheme 4.** *Reagents and conditions*: (i) **33**, DCM, $ZnI_2$, 4 Å MS, protect from light, rt, 18 h (55%); (ii) a. 56% aq. HF, MeCN, rt, 18 h, b. $Ac_2O$, py, DMAP (cat.), rt, 18 h (65% from **36**); (iii) a. 56% aq. HF, MeCN, rt 24 h, b. $HC(OMe)_3$, MeOH, PPTS (cat.), rt, 3 h (34% from **36**); (iv) TBSCl, imid., TBAI, DMAP, DCM, rt (ca. 100%).




**Scheme 5.** *Reagents and conditions*: (i) $Na_2CO_3$, $OsO_4$ (cat.), NMO, acetone–$^t$BuOH–$H_2O$, rt, 18 h (55%); (ii) $NaIO_4$, $Na_2CO_3$, MeOH–THF–$H_2O$, rt 30 min (69%); (iii) **44**, NaHMDS, −78°C, 30 min, then add **42**, −50°C, 18 h, then −15°C, 18 h (49%; **43** plus geometrical isomer 72:28).

This synthesis of the ester **43** completes a synthesis of the C(1)–C(16) fragment of the bryostatins and features the formal 'ene' reaction between the allylsilane **35** and the alkynone **33** together with the stereoselective conjugate addition–cyclisation of **36**. Further work is in progress to incorporate the exocyclic trisubstituted double-bond earlier in the synthesis, to replace the benzyl with more labile protecting groups, and to attempt to complete a synthesis of a natural bryostatin.




**44**

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5. A related conjugate addition has recently been used in a related approach to this fragment of bryostatins: Yadav, J. S.; Bandyopadhyay, A.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4907–4911.
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7. The geometries of all the allylsilanes were confirmed by NOE studies.
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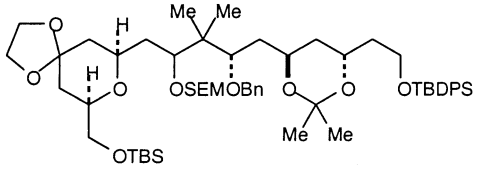
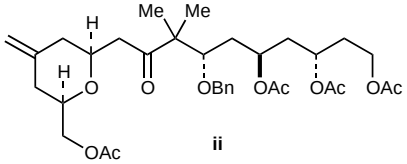
10. The *cis*- and *trans*-configurations of **15** and **17** were established by NOE studies.
11. The benzyl ether was chosen because of its stability to the acidic conditions used in the thermodynamic cyclisation reactions. Partial deprotection was observed during the cyclisation if, for example, *p*-methoxybenzyl protection was used.
12. The acetate **26** has been converted into the fully protected polyol **i** which also corresponds to the C(1)–C(17) fragment of a bryostatin, albeit lacking the exocyclic methoxycarbonylmethylene group, by cleavage of the exocyclic methylene group, protection of the ketone so formed and reduction/protection of the 2′-ketone, followed by addition of the C(1)–C(4) fragment via a hydroboration/oxidation, aldol condensation, reduction and acetalisation sequence.




**i**

13. De Brabander, J.; Vanderwalle, M. *Synthesis* **1994**, 855–865.
14. This aldol reaction of ketone **34** was complicated by competing deprotonation of the ketone at the α-methylene group leading to the formation of regioisomers as minor products (ca. 20%). This could be avoided by using the analogous 4-*tert*-butyldiphenylsilyloxybutan-2-one which gave a better, 76%, yield of aldol product, but this led to the formation of the tetra-acetate **ii** on cyclisation followed by acetylation since the *tert*-butyldiphenylsilyloxy group was not stable under the acidic cyclisation conditions. The chemistry of **ii** has not been studied further at present.




**ii**