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A stereoselective synthesis of the C(1)–C(16) fragment of the bryostatins

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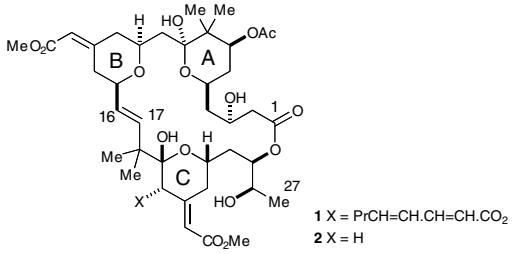
Abstract—A synthesis of the C(1)–C(16) fragment of the brysostatins has been developed. Key steps are the stereoselective copper(I) catalysed addition of allylmagnesium bromide to an alkynyl ester, a condensation of a βγ-unsaturated aldehyde with a ketophosphonate, and the formation of the B-ring under mild conditions by stereoselective intramolecular conjugate addition.

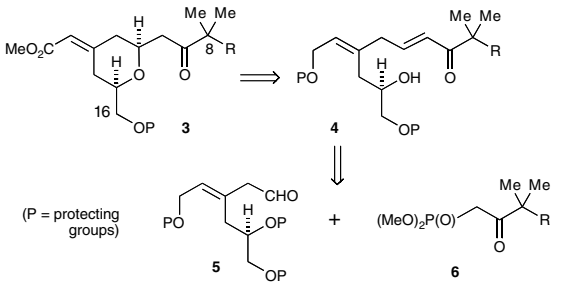
The bryostatins are an important group of complex macrocyclic natural products isolated from the marine filter feeder *Bugula neritina.* They have potent antineoplastic activity and are candidates for the treatment of cancer in conjunction with other chemotherapies.[1] This biological activity is based on their ability to modulate various protein kinase C's and has led to substantial interest into bryostatin synthesis with three total syntheses reported to date.[2–4] Recent developments in aquaculture techniques are able to provide 100 g quantities of bryostatin 1 (**1**) per annum for clinical trials, and several complex acetal-containing analogues have been prepared and their biological activities investigated.[5] However, there remains a need for better synthetic access to the bryostatins to provide additional analogues for biological evaluation. We identified the 20-deoxybryostatins, for example, bryostatin 11 (**2**), as our initial targets as they have not yet succumbed to total synthesis.[6]



1 X = PrCH=CH.CH=CH.CO$_2$
2 X = H

In the three total syntheses of bryostatins reported to date, the macrolide was assembled by using a Julia reaction to prepare the 16,17-double-bond followed by macrolactonisation. Other strategies, for example, formation of the macrolide by metathesis, have yet to be evaluated. We now report a scalable synthesis of the C(1)–C(16) fragment, which should allow fuller evaluation of assembly strategies.

Conjugate addition reactions have been used to assemble ring B of the bryostatins with the exocyclic, trisubstituted, double-bond introduced after the cyclisation step, but with only modest stereoselectivity.[7,8] An alternative approach would be to introduce this double-bond before ring B formation, hopefully with better stereochemical control. Our initial target was therefore identified as an enone **4**, which would provide the C(8)–C(16) fragment **3** after cyclisation and oxidation–esterification. Aldehydes **5** and ketophosphonates **6** were identified as precursors of enones **4**.



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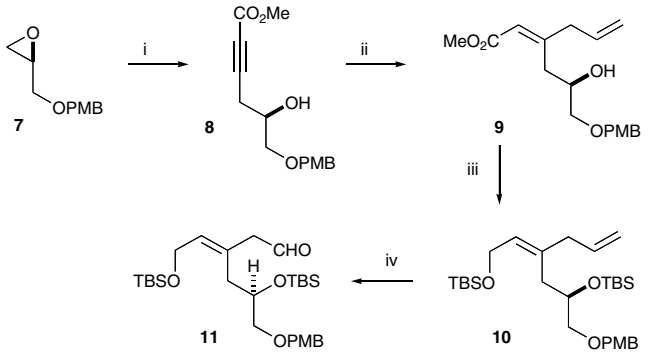
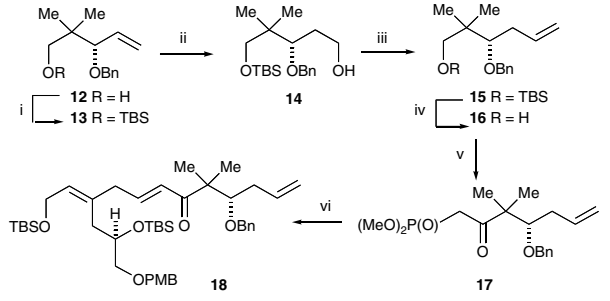


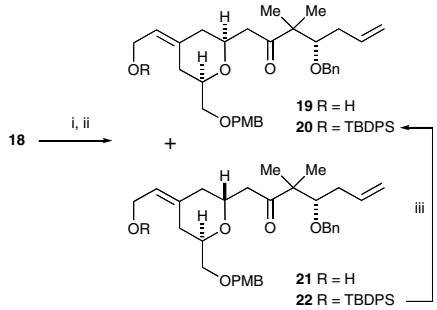
Scheme 1. Reagents and conditions: (i) methyl propiolate, *n*-BuLi, BF_3·THF (94%); (ii) CuI, LiCl, 2 mol equiv allylmagnesium bromide, −78 °C; (iii) (a) DIBAL-H, THF, (b) TBSOTf, 2,6-lutidine (85% from **8**); (iv) (a) ADmix β, *n*-BuOH, H_2O, 5 mol% OsO_4 (70%), (b) $NaIO_4$, MeOH (ca. 100%).

The aldehyde **11** was prepared as outlined in Scheme 1. Reaction of the protected hydroxyepoxide **7** with lithiated methyl propiolate is known to give the hydroxy ester **8**.[9] Copper(I) catalysed conjugate addition of allylmagnesium bromide to this ester gave the (*Z*)-αβ-unsaturated ester **9** with excellent stereoselectivity, and reduction followed by protection gave the bis-*tert*-butyldimethylsilyl ether **10** in an excellent, 85%, overall yield. Regioselective oxidation of the terminal double-bond to give the aldehyde **11** was best achieved by hydroxylation using ADmix β followed by cleavage of the intermediate vicinal diol using sodium periodate in methanol.

The ketophosphonate **17** was prepared as outlined in Scheme 2. Alcohol **12** is available in three steps (ca. 60% overall yield) from (*R*)-pantolactone[7] and was protected as its *tert*-butyldimethylsilyl ether **13**. Hydroboration–oxidation gave the primary alcohol **14**, which was converted into the alkene **15** by oxidation to the corresponding aldehyde followed by a Wittig condensation. Removal of the *tert*-butyldimethylsilyl group gave the alcohol **16**, which was taken through to the ketophosphonate **17** by oxidation, addition of lithiated dimethyl methylphosphonate and further oxidation.



Scheme 2. Reagents and conditions: (i) TBSCl, imid., DMAP (91%); (ii) BH_3·THF, 3 h, then NaOH, aq H_2O_2 (72%); (iii) (a) $(COCl)_2$, DMSO, then Et_3N, (b) Ph_3PMeBr, *t*-BuOK (58% from **14**); (iv) TBAF (ca. 100%); (v) (a) $(COCl)_2$, DMSO, then Et_3N, (b) $(MeO)_2P(O)Me$, *n*-BuLi, (c) Dess–Martin periodinane (83% from **16**); (vi) LiCl, **11**, MeCN then *i*-Pr_2NEt (73%).



Scheme 3. Reagents and conditions: (i) 5% v/v concd aq HCl in MeOH, 40 °C, 15 min; (ii) TBDPSCl, imid. (**20**, 63%; mixed 19%); (iii) KO*t*-Bu, THF, 10 min (**20**, a further 12%, 75% combined yield of **20** based on **18**).

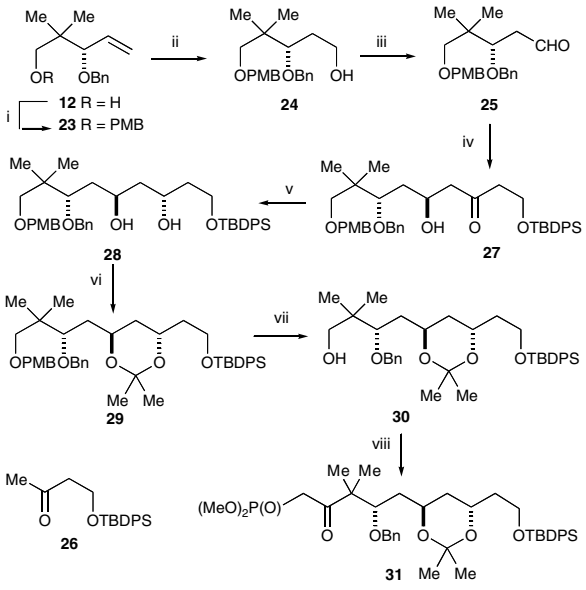
Condensation of the phosphonate **17** with the aldehyde **11** using lithium chloride in acetonitrile then gave the required enone **18** in a 73% yield.

Earlier studies on the formation of ring B by conjugate addition had indicated that useful stereoselectivity required thermodynamic control.[7] Fairly vigorous and prolonged reaction conditions, incompatible with many protecting groups, were therefore used to effect simultaneous 15-hydroxyl deprotection[†] and conjugate addition.[7] In the present work, milder reaction conditions were investigated for these transformations.

Removal of the *tert*-butyldimethylsilyl groups from enone **18** using hydrochloric acid in methanol, 15 min, rt, was accompanied by cyclisation to give a 72% yield of a mixture of the 2,6-*cis*- and 2,6-*trans*-tetrahydropyrans **19** and **21**, ratio 80:20 in favour of the required *cis*-isomer **19** (Scheme 3). Following silylation of this mixture,[10] the silyl ethers **20** and **22** were separated by flash column chromatography and fractions enriched in the minor 2,6-*trans*-isomer **22** were treated with potassium *tert*-butoxide[11] in THF, 10 min, rt to effect *cis*:*trans* equilibration giving more of the required *cis*-isomer **20**. Overall, the required 2,6-*cis*-isomer **20** was isolated in yields of 75% based on the enone **18**.

Having achieved the formation of ring B by conjugate addition under mild conditions, it was necessary[12] to synthesise an enone with the C(1)–C(9) fragment present before attempting to synthesise the intact C(1)–C(16) fragment of the bryostatins. The ketophosphonate **31** was therefore prepared as outlined in Scheme 4. Protection of the alcohol **12** as its *p*-methoxybenzyl ether **23** and hydroboration–oxidation gave the alcohol **24**, which was oxidised to the aldehyde **25**. The aldol condensation of this aldehyde with the lithium enolate of the methyl ketone **26** was subject to chelation control[13] and gave the 1,3-*anti*-adduct **27**. Reduction to the *anti*-diol **28** was achieved using lithium tris-*tert*-butoxyaluminium hydride and the diol was protected as its acetonide **29**. Oxidative removal of the *p*-methoxybenzyl ether then gave the primary alcohol **30**, which was taken through to the ketophosphonate **31** by oxidation to the

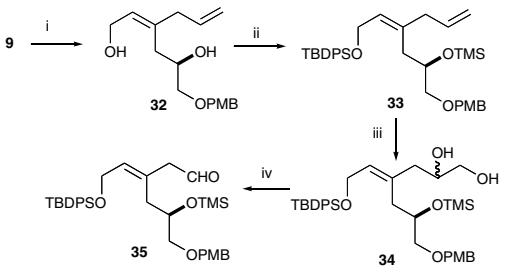
[†] Bryostatin numbering.



Scheme 4. Reagents and conditions: (i) NaH, PMBCl, DMF, TBAI (88%); (ii) BH_3·THF, then NaOH, H_2O_2 (72%); (iii) $(COCl)_2$, DMSO, then Et_3N (92%); (iv) **26**·LDA, THF, −78 °C (76%); (v) Li(*t*-BuO)$_3$AlH, LiI; (vi) 2,2-dimethoxypropane, TsOH·H_2O (91% from **27**); (vii) DDQ, pH7 buffer (63%); (viii) (a) $(COCl)_2$, DMSO, then Et_3N, (b) $(MeO)_2P(O)Me$, *n*BuLi, (c) Dess–Martin periodinane (80% from **30**).

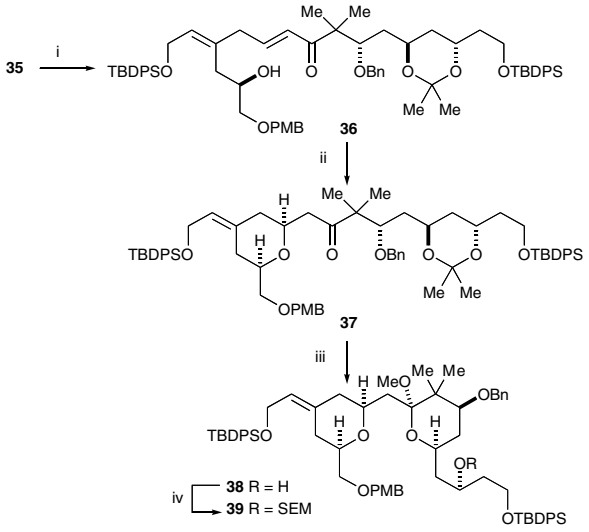
aldehyde, addition of lithiated dimethyl methylphosphonate, and further oxidation.

Since the acidic conditions used for the removal of the *tert*-butyldimethylsilyl groups from the cyclisation precursor **18**, see Scheme 3, would be incompatible with the acetonide protecting group derived from the phosphonate **31**, it was necessary to protect the 15-hydroxyl group using a more labile protecting group. Therefore, after protection of the primary hydroxyl group of diol **32**, obtained by reduction of the ester **9**, as its *tert*-butyldiphenylsilyl ether, the secondary hydroxyl was converted into its trimethylsilyl derivative to give intermediate **33** (Scheme 5). This was hydroxylated using ADmix β to give diol **34** and the vicinal diol oxidatively cleaved to the aldehyde **35** using lead(IV) acetate, as the trimethylsilyl group was hydrolysed by aqueous sodium periodate.

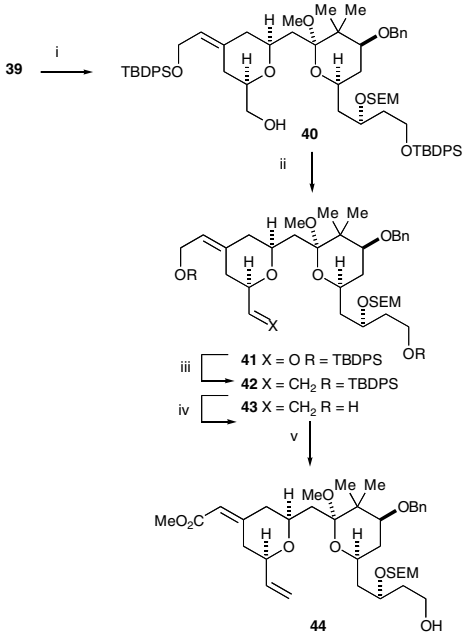


Scheme 5. Reagents and conditions: (i) DIBAL-H, THF; (ii) (a) TBDPSCl, imid. (93% from **9**), (b) TMSCl, Et_3N (91%); (iii) ADmix β, 5% OsO_4, *n*-BuOH (70%); (iv) $Pb(OAc)_4$, py (ca. 100%).

Condensation of aldehyde **35** with the phosphonate **31** was carried out using barium hydroxide as the base and the crude product was immediately treated with HF·pyridine complex, 30 s, 0 °C, to effect removal of the trimethylsilyl group. This gave the hydroxyenone **36**, which was isolated, after flash column chromatography, in a 65% yield based on the phosphonate **31**, see Scheme 6. Stereoselective cyclisation of the free alcohol was accomplished using potassium *tert*-butoxide, 5 min,



Scheme 6. Reagents and conditions: (i) (a) **31**, $Ba(OH)_2$, THF, 18 h, (b) HF·py, 30 s (65% from **31**); (ii) KO*t*-Bu, THF, 5 min; (iii) $(MeO)_3CH$, MeOH, PPTS (cat.), MeOH, 19 h, rt (60% from **36**); (iv) SEMCl, *i*-Pr_2NEt, DCM (85%).



Scheme 7. Reagents and conditions: (i) DDQ, DCM then $(MeO)_3CH$, MeOH, PPTS (71%); (ii) Dess–Martin periodinane; (iii) Ph_3PMeBr, KO*t*-Bu (71% from **40**); (iv) TBAF (76%); (v) MnO_2, then add KCN, MeOH, AcOH (40%).

rt, and gave the tetrahydropyran **37** essentially as a single diastereoisomer, equilibration occurring under the basic reaction conditions. Without purification, this intermediate was treated with trimethyl orthoformate in methanol under acidic conditions, which removed the acetonide group and induced cyclisation to give the acetal **38**. Finally, the 3-hydroxyl group was protected as its trimethylsilylethoxymethyl (SEM) ether to give the fully protected C(1)–C(16) fragment **39**.

This synthesis of the acetal **39** can provide multigramme quantities for investigation of different assembly strategies. For example, the advanced metathesis precursor **44** was prepared as outlined in Scheme 7.

Selective removal of the *p*-methoxybenzyl ether to give the alcohol **40** was effected using DDQ. In this reaction, although buffered conditions were used, partial acetal hydrolysis was observed and so the crude product had to be resubjected to the acetal forming conditions to give the required alcohol **40** in 71% overall yield. Oxidation then gave aldehyde **41**, which was condensed with methylenetriphenylphosphorane to give the alkene **42**. Selective removal of the two *tert*-butyldiphenylsilyl groups using TBAF gave the diol **43** and preliminary studies indicated the viability of selective oxidation of the exocyclic allylic primary hydroxyl group through to the methyl ester **44** via the corresponding aldehyde in a one-pot process.[14] The aldehyde **41** may also be incorporated into a Julia assembly of the bryostatins.

This work has developed a scalable procedure for the synthesis of the C(1)–C(16) fragment of bryostatins. Key steps are the stereoselective conjugate addition of allylmagnesium bromide to an alkynyl ester and the formation of ring B by an intramolecular conjugate addition under mild conditions. Present work is concerned with evaluating different procedures for assembly of the macrocycle.

Acknowledgements

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