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On the use of the modified Julia olefination for bryostatin synthesis

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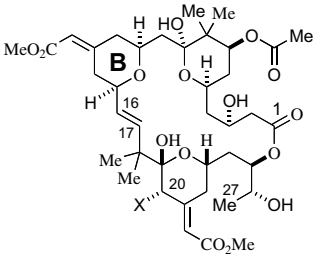
ABSTRACT

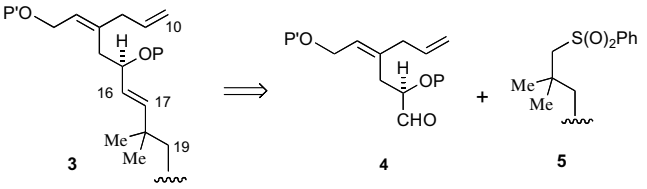
Modified Julia olefination reactions using aldehyde **27** and the benzothiazol-2-yl sulfones **13** and **39** provide efficient syntheses of alkenes **28** and **42,** which are advanced intermediates for syntheses of bryostatins.

The bryostatins, for example, bryostatin 1 (**1**), are important marine macrolides with the potential for development as anti-cancer chemotherapeutic agents.[1] Three total syntheses[2] of bryostatins and one formal total synthesis[3] have been reported to date, and many other synthetic approaches have been described.[1] In addition, interesting, biologically active analogues with a cyclic acetal in place of the B-ring have been synthesized,[4] and other macrocyclic analogues have been prepared using ring-closing metathesis.[5,6] Nevertheless, there remains a need for improved synthetic access to bryostatins for further studies of structure–activity relationships. We here report studies on the use of the modified Julia olefination for the assembly of advanced intermediates to be used in the synthesis of bryostatin 11 (**2**), a bryostatin which lacks the acyloxy substituent at C(20).

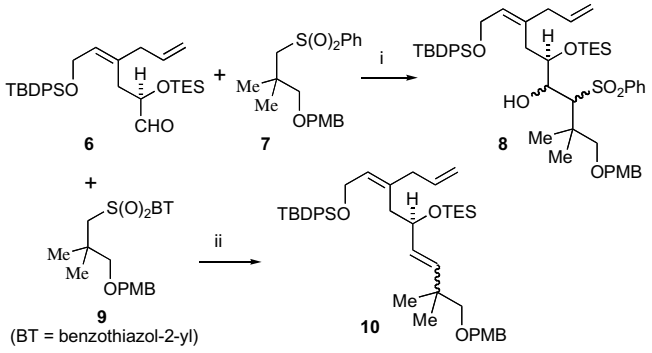


1 X = *n*-PrCH=CH-CH=CH-CO_2
2 X = H

In each of the three total syntheses of bryostatins reported to date,[2] the key assembly step involved formation of the 16,17-double-bond by classical Julia olefination, although only moderate yields were obtained in some cases. Thus, when planning the synthesis of bryostatin 11 (**2**), the use of Julia olefinations was considered for the synthesis of intermediates possessing the 16,17-double-bond. Since the B-ring can be formed by conjugate addition of a hydroxyl group at C(15) to an αβ-unsaturated ketone,[7] Julia reactions, for example, between aldehydes **4** and sulfone **5**, were investigated first for the synthesis of the open-chain C(10)–C(19) fragment **3**.



In the event, preliminary studies of the Julia olefination involving aldehyde **6**[8] and the phenyl sulfone **7**[9] were unsuccessful. The addition step gave a mixture of diastereoisomeric adducts **8**, see Scheme 1, but these could not be activated towards elimination by acylation and reductive elimination using samarium di-iodide gave complex mixtures of products. However, the one-pot, modified, Julia olefination[10] using the benzothiazol-2-yl sulfone **9**[11] was more successful and gave the alkene **10** in a 60% yield, albeit as 75:25 mixture of (*E*)- and (*Z*)-isomers.



Scheme 1. Reagents and conditions: (i) **7**, *n*-BuLi, THF, 10 min, −78 °C; add **6**, −78 °C (ca. 60%); (ii) **9**, LiHMDS, THF, 20 min, −78 °C, add **6**, −78 °C to rt (60%; *E*:*Z* = 75:25).

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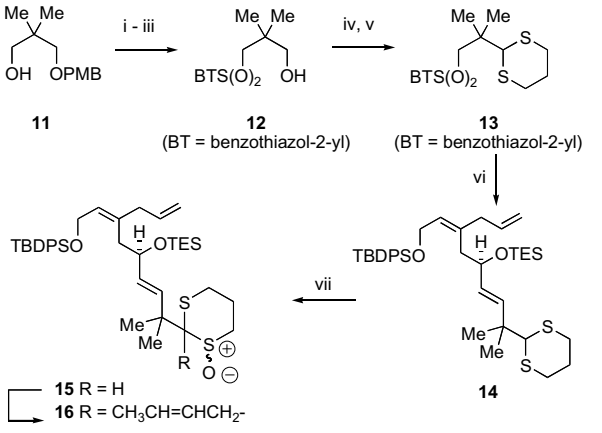
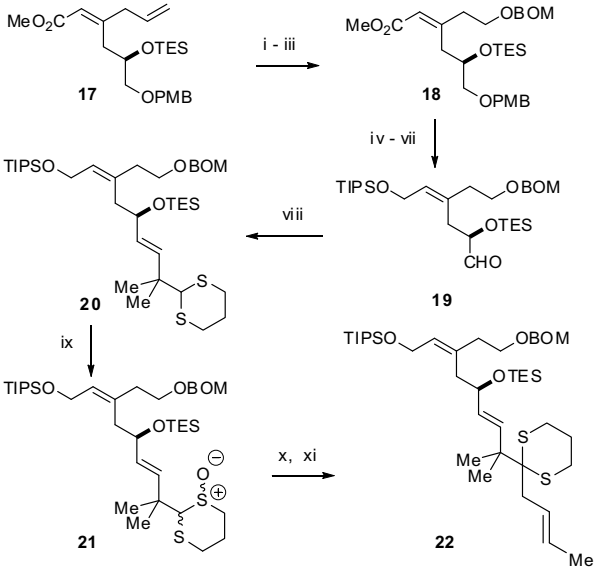
With a view to incorporating the C(20)–C(27) fragment using an acyl carbanion equivalent at C(19),[12] the dithianylalkyl benzothiazol-2-yl sulfone **13** was prepared from the monoprotected diol **11**,[13] see Scheme 2. Conversion into the hydroxyalkyl sulfone **12** was achieved using a Mitsunobu reaction, sulfide oxidation[14] and oxidative removal of the *p*-methoxybenzyl group. Following oxidation to the corresponding aldehyde, treatment with propane-1,3-dithiol[15] gave the dithianylalkyl sulfone **13**. Deprotonation of this sulfone using lithium hexamethyldisilazide and reaction with aldehyde **6** gave alkene **14** with excellent stereoselectivity in favour of the (*E*)-isomer. However, the strongly basic conditions required to deprotonate dithiane **14** led to the formation of complex mixtures of products. To enhance the acidity of the dithiane moiety, dithiane **14** was oxidized to the monosulfoxide **15**[16] which was isolated as a mixture of diastereoisomers. Deprotonation could now be achieved using LDA, and the lithiated species was alkylated using (*E*)-crotyl bromide to give the 2,2-dialkyldithiane monoxides **16** in a reasonable yield. However, attempts to reduce these dialkylated dithiane monoxides **16** back to the corresponding dithiane using P_2I_4[17] in the presence of triethylamine were unsuccessful, and complex mixtures of products were obtained.

To check whether the difficulties in manipulating the dithiane **14** and the derived monosulfoxides were due to the skipped diene, the sequence of a modified Julia reaction using the sulfonyl-dithiane **13** and subsequent alkylation was repeated using the aldehyde **19**, see Scheme 3. This aldehyde was prepared from the dienyl ester **17**[8] by regioselective hydroxylation using osmium tetroxide, followed by cleavage using sodium periodate with reduction of the aldehyde so obtained using sodium borohydride. Protection gave the benzyloxymethyl (BOM) ether **18**, and reduction of the ester with protection of the primary alcohol as its tri-isopropylsilyl ether followed by oxidative removal of the *p*-methoxybenzyl ether gave aldehyde **19** after a Dess–Martin oxidation. Reaction of this aldehyde with the lithiated dithiane **13** was very efficient, and gave the (*E*)-alkene **20** in excellent yield (95% from **19**) with only the (*E*)-isomer of the alkene being isolated. Unlike dithiane **14**, dithiane **20** could be deprotonated directly and was alkylated using (*E*)-crotyl bromide to give the 2,2-dialkyldithiane **22**, albeit only in a modest 35% yield. Alternatively, oxidation of dithiane **20** using *m*-chloroperoxybenzoic acid to the dithiane monoxides **21** followed by alkylation using (*E*)-crotyl bromide and reduction using P_2I_4 gave the 2,2-dialkyldithiane **22** in a slightly better overall yield. Dithiane



Scheme 2. Reagents and conditions: (i) 2-mercaptobenzothiazole, Ph_3P, DIAD, THF, rt; (ii) $Mo_7O_{24}(NH_4)_8{\cdot}4H_2O$, H_2O_2, EtOH, H_2O (80% from **11**); (iii) DDQ, pH 7, phosphate buffer, CH_2Cl_2, rt, 45 min (ca. 100%); (iv) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N (94%); (v) propane-1,3-dithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt (79%); (vi) LiHMDS, THF, −78 °C, 30 min, add **6**, −78 °C to rt, 1.5 h (60%); (vii) MCPBA, CH_2Cl_2, 0 °C, 5 min (78%); (viii) LDA, HMPA, THF, −78 °C to −60 °C, 30 min, (*E*)-crotyl bromide, −78 °C to rt, 40 min (67%).

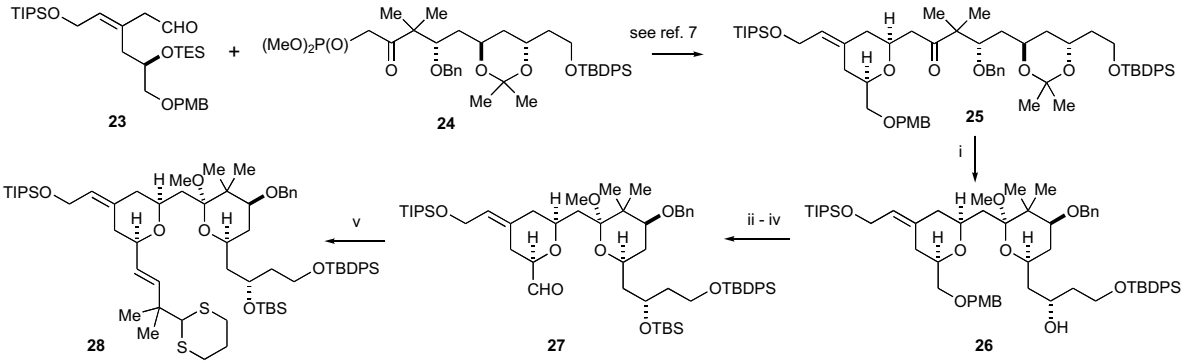


Scheme 3. Reagents and conditions; (i) OsO_4 (8 mol %, NMO, acetone, H_2O, *t*-BuOH, rt, 4 h (76%); (ii) $NaIO_4$, MeOH, THF, H_2O, 0 °C, 1 h, then $NaBH_4$, 0 °C, 1 h (76%); (iii) BOMCl, TBAI, *i*-Pr_2NEt, THF, 0 °C, 16 h (93%); (iv) DIBAL-H, tol., −78 °C, 45 min (88%); (v) TIPSCl, imid., CH_2Cl_2, rt, 16 h (98%); (vi) DDQ, pH 7, phosphate buffer, CH_2Cl_2, 0 °C, 1 h then rt 2 h (71%); (vii) Dess–Martin periodinane, py., CH_2Cl_2, rt, 45 min; (viii) **13**-Li, THF, −78 °C to rt, 1 h (95%, two steps); (ix) MCPBA, CH_2Cl_2, 0 °C, 5 min (95%); (x) LDA, THF, −78 °C to −60 °C, 30 min then (*E*)-crotyl bromide, −78 °C to rt, 40 min (87%); (xi) P_2I_4 (0.55 mol equiv), Et_3N, CH_2Cl_2, 0 °C, 40 min in the dark (70%).

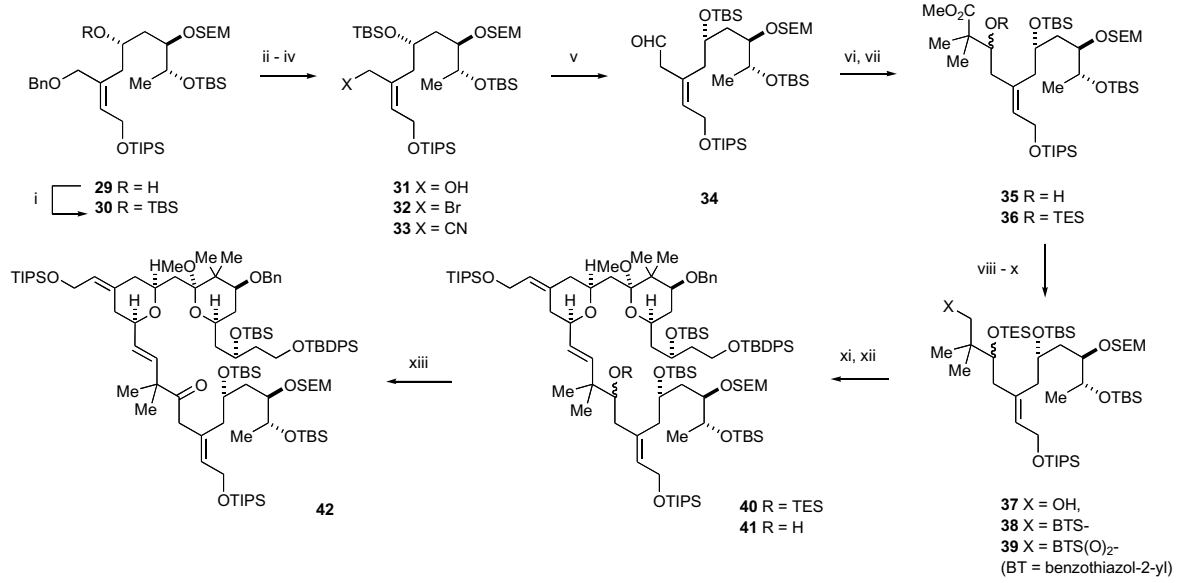
22 corresponds to the C(10)–C(21) fragment of a 20-deoxybryostatin.

As the modified Julia olefination between sulfone **13** and the aldehyde **19** was very efficient, it was decided to see whether an aldehyde attached to the fully developed C(1)–C(15) fragment would also react usefully with this sulfone. The 4-(tri-isopropylsilyloxyethylidene)tetrahydropyran **25** was prepared from aldehyde **23** and ketophosphonate **24** using chemistry reported earlier,[3,7] see Scheme 4, and an excellent yield obtained for the conversion of the ketone **25** into the cyclic acetal **26** using PPTS as catalyst. The free hydroxyl group was then protected as its *tert*-butyldimethylsilyl ether and the *p*-methoxybenzyl group removed using DDQ under buffered conditions although some reacetalization was necessary before oxidation to the aldehyde **27**. However, the stereoselectivity of the Julia reaction of this aldehyde with the dithianylalkyl sulfone **13** varied with the reaction conditions. Better yields, up to 78%, were obtained if the reaction mixture was allowed to warm from −78 °C to room temperature immediately after addition of the aldehyde to the lithiated sulfone, but the stereoselectivity was only 2:1 in favour of the (*E*)-isomer. In contrast, the (*E*)-alkene **28** was the only product obtained if the reaction mixture was stirred for 20 min after the addition of the aldehyde at −78 °C before being allowed to warm up, but the isolated yield was only ca. 50% (Scheme 4).

Nevertheless, these successful alkene syntheses suggested that the modified Julia olefination might be applicable to a convergent bryostatin assembly involving aldehyde **27** and an intact C(17)–C(27) benzothiazol-2-yl sulfone containing fragment. To investigate this possibility, alcohol **29**[12] was converted into the aldehyde **34** by protection, selective removal of the *O*-benzyl group, substitution of the primary alcohol via bromide **32** to give nitrile **33** and reduction to the aldehyde **34**. Aldol addition of lithiated methyl 2-methylpropanoate to this aldehyde gave a 1:1 mixture of epimers **35**, which were protected as their triethylsilyl ethers **36**. Reduction of the methoxycarbonyl group then gave alcohol



Scheme 4. Reagents and conditions: (i) PPTS, $HC(OMe)_3$, MeOH, CH_2Cl_2, THF (88%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h (86%); (iii) DDQ, pH 7, phosphate buffer, rt, 1 h, then PPTS, $HC(OMe)_3$, MeOH, CH_2Cl_2 (60%); (iv) TPAP, NMO, 4 Å sieves, CH_2Cl_2, rt, 1 h (60%); (v) **13**-Li, THF, −78 °C, 20 min, to rt, 2 h [51%: (*E*)-only] or −78 °C to rt, 16 h [78%; (*E*):(*Z*) = 2:1].



Scheme 5. Reagents and conditions: (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt (89%); (ii) Li, naphthalene, THF, −20 °C (88%); (iii), CBr_4, Ph_3P, CH_2Cl_2, 0 °C (94%); (iv) NaCN, DMF, 0 °C, 2.5 h (75%); (v) DIBAL-H, CH_2Cl_2, −78 °C, 45 min then satd aq NH4Cl, −78 °C to rt, 30 min; (vi) methyl 2-methylpropanoate, LDA, THF, −78 °C, 70 min, add **34**, THF, −78 °C, 30 min, rt 30 min (50% from **33**); (vii) TESCl, imid., DMF, 0 °C to rt, 16 h (79%); (viii) DIBAL-H, tol., −78 °C, 1 h (82%); (ix) 2-mercaptobenzothiazole, Ph_3P, DIAD, THF, rt, 24 h (95%); (x) $Mo_7O_{24}(NH_4)_8{\cdot}4H_2O$, H_2O_2, H_2O, EtOH, *i*-PrOH (**39**, 41%; sulfoxides, 50%); (xi) **39**, LiHMDS, THF, −78 °C to −60 °C, 30 min, add **27**, THF, −78 °C, 20 min, rt, 30 min (70%); (xii) PPTS, $HC(OMe)_3$, MeOH, rt, 3 d (64%); (xiii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 30 min (85%).

37, which was converted into the benzothiazol-2-yl sulfone **39** via a Mitsunobu reaction using 2-mercaptobenzothiazole followed by oxidation (Scheme 5).

Deprotonation of the sulfone **39** was achieved using lithium hexamethyldisilazide and addition of the aldehyde **27** at −78 °C with warming to room temperature after 20 min gave the (*E*)-alkene **40**, with excellent stereoselectivity, no (*Z*)-isomer being isolated, in a reasonable yield (71% from aldehyde **27**). Alkene **40** was isolated as a mixture of epimers at C(19) (bryostatin numbering), these being derived from the mixture of epimers at the corresponding carbon in sulfone **39**. However, the 1:1 mixture of epimers in the sulfone was replaced by an apparent 2:1 mixture in alkene **40** suggesting a small degree of kinetic resolution in the Julia reaction. That the two products were the two C(19) epimers was established by selective removal of the triethylsilyl group using PPTS and oxidation of the epimeric mixture of alcohols **41** using the Dess–Martin periodinane to give the corresponding ketone **42** which was characterized as a single compound.

This work has explored the application of the modified, one-pot, Julia olefination using benzothiazol-2-yl sulfones for the stereoselective assembly of the C(16)–C(17) double-bond in advanced intermediates for incorporation into syntheses of bryostatins. Both the dithiane **28**, which corresponds to the C(1)–C(19) component of bryostatins, and ketone **42**, which has the intact bryostatin skeleton, may be useful for the syntheses of bryostatins and their analogues. Of general interest is the use of the benzothiazol-2-yl dithianylalkyl sulfone **13** which may have a wider application in synthesis. The present work is concerned with applying this chemistry to complete total syntheses of naturally occurring bryostatins and their analogues.

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