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# Synthesis of the C(17)–C(27) fragment of the 20-deoxybryostatins

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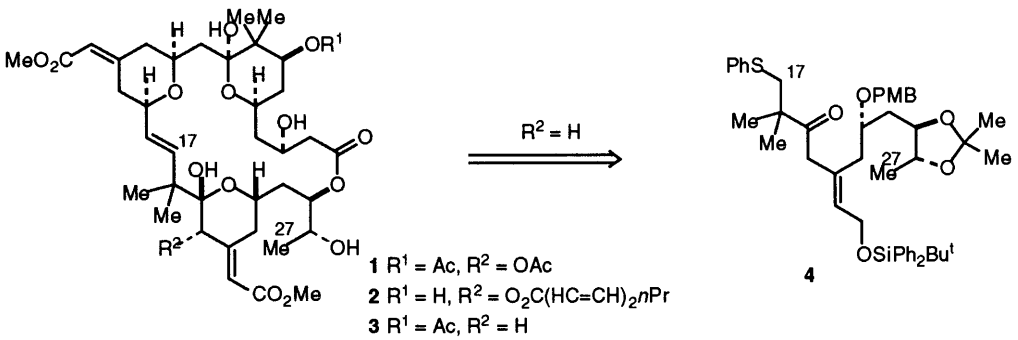
**Abstract**

A synthesis of the C(17)–C(27) fragment of the 20-deoxybryostatins is described in which the key step is a palladium(0) catalysed coupling of a tributyltin enolate with a vinylic bromide. 

The bryostatins are a group of complex marine macrolides isolated from *Bugula neritina* (Linaeus) which exhibit anti-tumour activity against the murine P388 lymphocytic leukemia and which are presently undergoing both phase I and phase II clinical trials.[1] The synthesis of the bryostatins is of considerable interest at present because of their biological activities and limited availability from natural sources. As well as many partial syntheses,[2] total syntheses of bryostatin 7 and 2, **1** and **2**, were first described by Masamune[3] and Evans[4] and biologically active macrocyclic analogues have been prepared by Wender.[5] No total synthesis of a 20-deoxybryostatin, e.g. bryostatin 11 **3**, has been published to date although two approaches to the C(17)–C(27) fragment of bryostatin 11 have been reported.[6]

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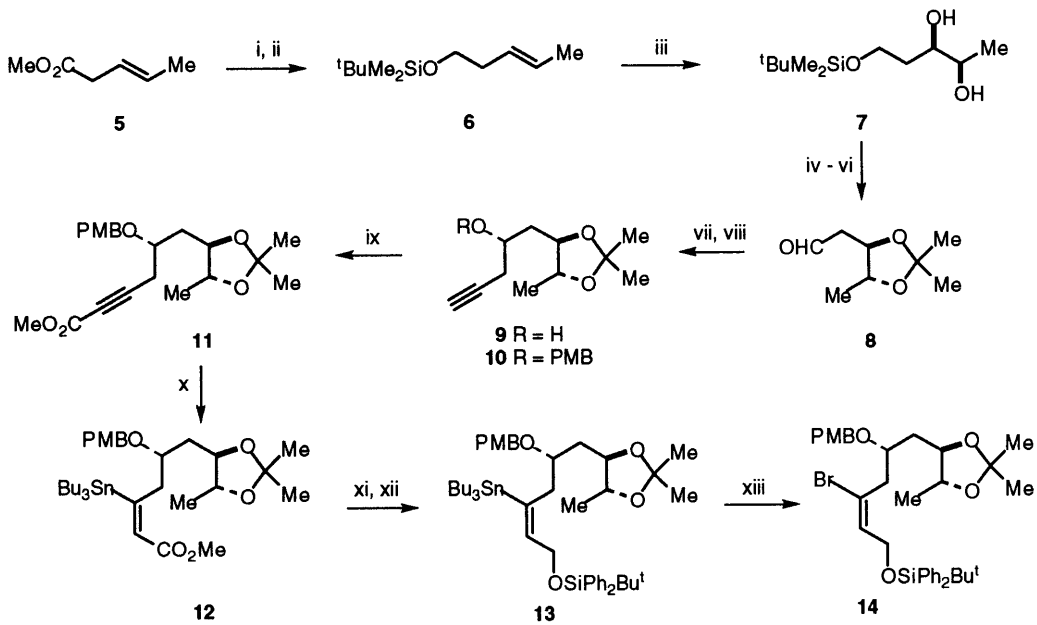
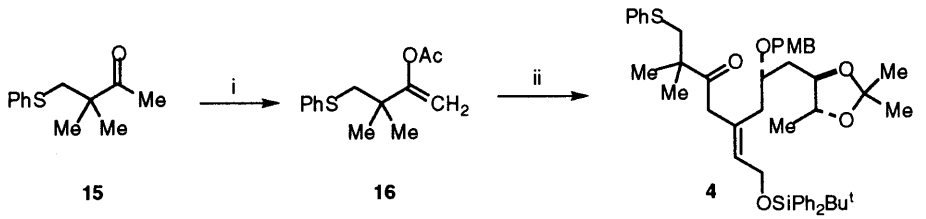
We here describe a stereoselective synthesis of the protected hydroxyketone **4** which is synthetically equivalent to the C(17)–C(27) fragment of bryostatin 11.[7] Our synthesis is based on the stereospecific palladium(0) catalysed coupling of a tributyltin enolate with the vinylic bromide **14**, a reaction first reported by Migita and coworkers.[8,9]

The synthesis of the vinylic bromide **14** is outlined in Scheme 1. The *tert*-butyldimethylsilyl ether **6** of (*E*)-pent-3-enol was prepared from the methyl ester **4** by reduction and protection. Asymmetric hydroxylation using ADmix-β gave the vicinal diol **7**,[10] estimated to have an ee of 85 (±5)%,[11] which was protected as its acetonide, desilylated and oxidized to give the aldehyde **8**. Chelation controlled addition of allenylzinc bromide gave the (4*S*)-alcohol **9** together with its 4-epimer, ratio 80:20. The configuration assigned to the alcohol **9** is consistent with literature examples[3] and was confirmed by comparison of the $^1$H NMR spectra of its acetyl mandelates.[12] After chromatographic separation, the alcohol **9** was protected as its *p*-methoxybenzyl ether **10** which was taken through to the methyl ester **11** by alkyne deprotonation and acylation using methyl chloroformate. Stereoselective conjugate addition of a tri-*n*-butyltin cuprate[13] gave the (*E*)-αβ-unsaturated ester **12**, which was reduced and protected to give the *tert*-butyldiphenylsilyl ether **13**. Treatment with freshly recrystallized *N*-bromosuccinimide gave the vinylic bromide **14**.




Scheme 1. Reagents and conditions: (i) DIBAL-H, −78–20°C (80%); (ii) *t*-BuMe$_2$SiCl, imid. (90%); (iii) ADmix-β, 0°C (81%; 85% ee); (iv) 2,2-dimethoxypropane, PPTS (97%); (v) TBAF (80%); (vi) DMSO, (COCl)$_2$, then 4 equiv. Et$_3$N, −78°C (95%); (vii) HCCCH$_2$Br, zinc (50%); (viii) NaH, PMBCl; (ix) *n*-BuLi, MeO$_2$CCl (61% from **9**); (x) (Bu$_3$Sn)$_2$, *n*-BuLi, CuBr·DMS (68%); (xi) DIBAL-H, −78–20°C; (xii) *t*-BuPh$_2$SiCl, imid. (77% from **12**); (xiii) NBS (93%)

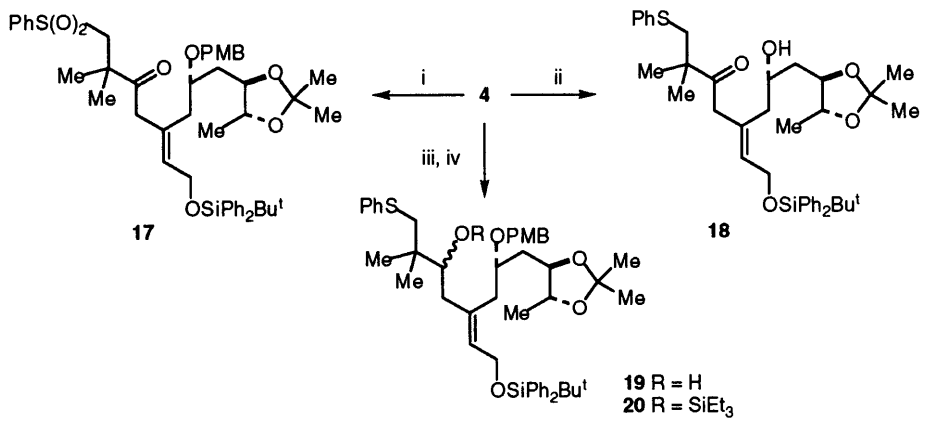
The enol acetate **16** was prepared from the ketone **15**[9] by treatment with lithium hexamethyldisilazide and acetic anhydride. Coupling the vinylic bromide **14** with the enol acetate was accomplished by heating in a degassed solution in toluene in the presence of tributyltin methoxide and freshly prepared PdCl$_2$(*o*-tolyl$_3$P)$_2$ at 100°C for 1 h to give the βγ-unsaturated ketone **4** in 73% yield free from any of its geometrical isomer ($^1$H NMR[14]). The structure of the product **4** was assigned on the basis of spectroscopic data and by analogy with previous work.




Scheme 2. Reagents and conditions: (i) $LiN(SiMe_3)_2$, LiCl, $Ac_2O$, −78°C (65%); (ii) **14**, $Pd(o\text{-tolyl}_3P)_2Cl_2$, $Bu_3SnOMe$, $PhCH_3$, 100°C (73%)

In particular, the trisubstituted double-bond was shown to have retained its geometry and not to have migrated into conjugation with the ketone (Scheme 2).[9,14]

Ketone **4** corresponds to the C(17)–C(27) fragment of a 20-deoxybryostatin, e.g. **3**. Further elaboration for incorporation into a synthesis of a bryostatin would include protection of the ketone, perhaps as a cyclic acetal, and oxidation of the sulfide to a sulfone for coupling with a C(16)-aldehyde, e.g. via a Julia coupling. As preliminary studies for this work, the sulfide **4** was oxidized to the sulfone **17**, deprotected to give the alcohol **18** and reduced to the epimeric mixture of alcohols **19** which were protected as their triethylsilyl ethers **20**. Present work is concerned with the conversion of these intermediates into a cyclic acetal and incorporation into a synthesis of a bryostatin (Scheme 3).




Scheme 3. Reagents and conditions: (i) MCPBA (74%); (ii) DDQ (54%); (iii) lithium triethylborohydride (50:50; 75%); (iv) $Et_3SiOTf$, $Et_3N$ (75%)

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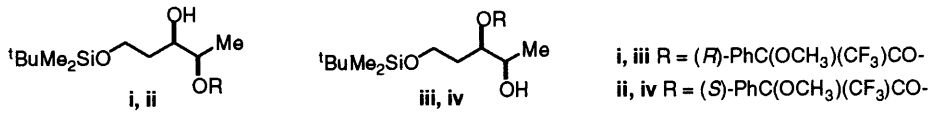
11. Esterification of the diol **7** using (*R*)-α-methoxy-α-trifluoromethyl(phenyl)acetic (Mosher's) acid and dicyclohexylcarbodiimide in the presence of DMAP gave a mixture of the 2- and 3-esters **i** and **iii** which were separated, isolated yields 66 and 8%, respectively. Reaction with the (*S*)-enantiomer of Mosher's acid similarly gave the esters **ii** (68%) and **iv** (8%). The enantiomeric excess of the diol **7** was estimated by comparison of the $^1$H NMR spectra of the corresponding (*R*)- and (*S*)-esters, i.e. **i** with **ii** and **iii** with **iv**.

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14. **4**: $\delta_H$ ($CDCl_3$) 1.08 [9H, s, $SiC(CH_3)_3$], 1.2 (3H, d, *J* 6 Hz, 11-$H_3$), 1.28 (6H, s, 2×$CH_3$), 1.36 (6H, s, 2×$CH_3$), 1.35–1.58 (2H, m, 8-$H_2$), 2.24 and 2.34 (each 1H, dd, *J* 14, 6.5, 6-H), 3.19 (2H, s, 1-$H_2$), 3.30 and 3.34 (each 1H, d, *J* 17, 4-H), 3.45–3.67 (3H, m, 7-H, 9-H and 10-H), 3.82 (3H, s, $OCH_3$), 4.3 (2H, m, 2′-$H_2$), 4.41 and 4.47 (each 1H, d, *J* 11, OHC*H*Ar), 5.55 (1H, t, *J* 6, 1′-H), 6.85 (2H, d, *J* 8, ArH), 7.15–7.5 (13H, m, ArH) and 7.71 (4H, m, ArH).