Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2223–2227

A preliminary evaluation of a metathesis approach to bryostatins

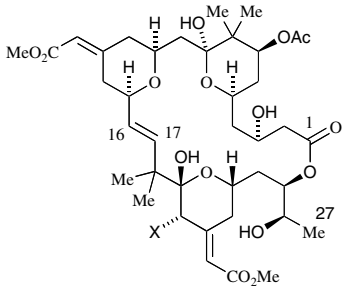
Matthew Ball, Benjamin J. Bradshaw, Raphaël Dumeunier, Thomas J. Gregson, Somhairle MacCormick, Hiroki Omori and Eric J. Thomas*

The School of Chemistry, The University of Manchester, Manchester M13 9PL, UK

Received 22 December 2005; accepted 18 January 2006
Available online 10 February 2006

Abstract—Preliminary investigations into the synthesis of bryostatins using ring-closing metathesis to form the C(16)–C(17) double bond led to a synthesis of the bryostatin analogue **51**; precursors **26** and **52**, which possess the geminal dimethyl group at C-18, did not undergo the required ring-closing metathesis.

The bryostatins are marine macrolides with potent antineoplastic activity. They act by modulation of the activity of protein kinase Cs and, in conjunction with other chemotherapies, are in clinical trials for the treatment of cancer.[1] Three total syntheses of bryostatins have been reported to date,[2] a novel series of advanced acetal-containing analogues has been prepared,[3] and aquaculture techniques are able to provide 100 g quantities of bryostatin 1 (**1**) per annum for clinical trials. Nevertheless, there remains a need for better access to bryostatins and analogues for further biological investigations.



1 X = ^{n}PrCH=CH-CH=CH-CO$_2$
2 X = H

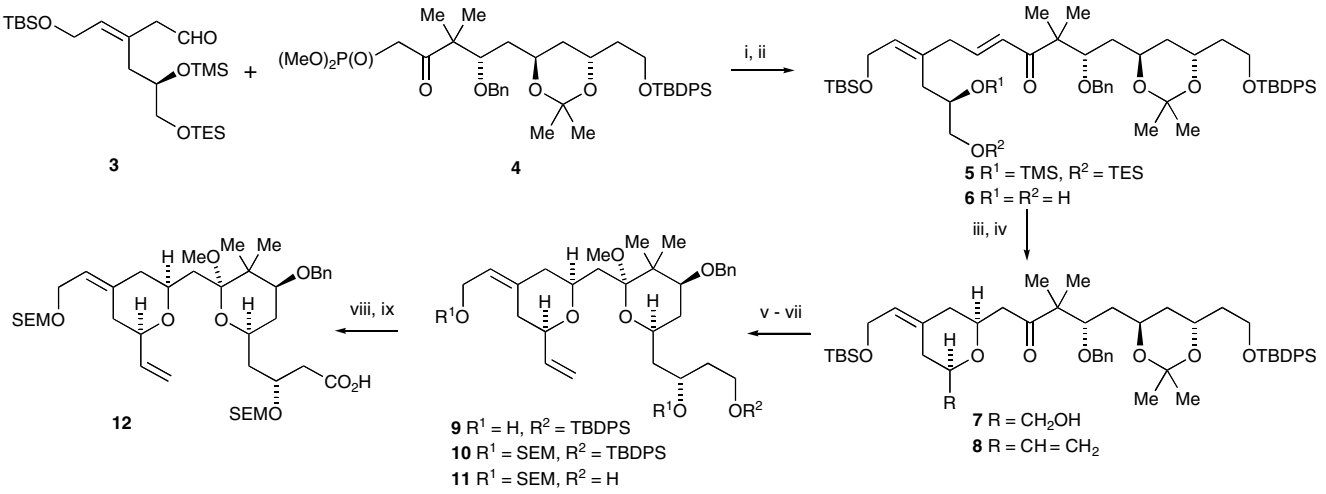
In the three bryostatin syntheses completed to date, the macrolide was assembled using a Julia reaction to form the C(16)–C(17) double bond followed by further elaboration and macrolactonisation.[2] However, the efficiency of this Julia reaction, which involves deprotonation α to a quaternary centre, is very substrate dependent,[1] and can result in low yields or in syntheses which lack convergency. It is therefore of interest to develop alternative strategies for assembly of the bryostatin nucleus.

We have developed synthetic approaches to the C(1)–C(16) and the C(17)–C(27) fragments of the 20-deoxybryostatin, bryostatin 11 (**2**).[4,5] We now report preliminary studies into the assembly of the bryostatin nucleus using ring-closing metathesis to form the C(16)–C(17) double bond.[6]

For a preliminary evaluation of the metathesis strategy for the preparation of bryostatin 11 (**2**), the C(1)–C(16) fragment **12** was prepared via a modification of our earlier route[4] as shown in Scheme 1. Condensation of the aldehyde **3** and phosphonate **4** using barium hydroxide as base gave the α,β-unsaturated ketone **5**, which was treated with the pyridine–hydrogen fluoride complex to give the diol **6**. This cyclised regio- and stereoselectively when reacted with a catalytic amount of potassium *tert*-butoxide in tetrahydrofuran to give the 4-methylenetetrahydropyran **7** as a single diastereoisomer. A Dess–Martin oxidation followed by a Wittig condensation then furnished the alkene **8**. This, on treatment, with trimethyl orthoformate in methanol containing a catalytic amount of pyridinium toluene *p*-sulfonate, gave the acetal **9**, in which the exo-cyclic allylic alcohol had also been deprotected. Protection of both the primary and secondary alcohols as trimethylsilylethoxymethyl

* Corresponding author. Tel.: +44 161 275 4614; fax: +44 161 275 4939; e-mail: e.j.thomas@manchester.ac.uk

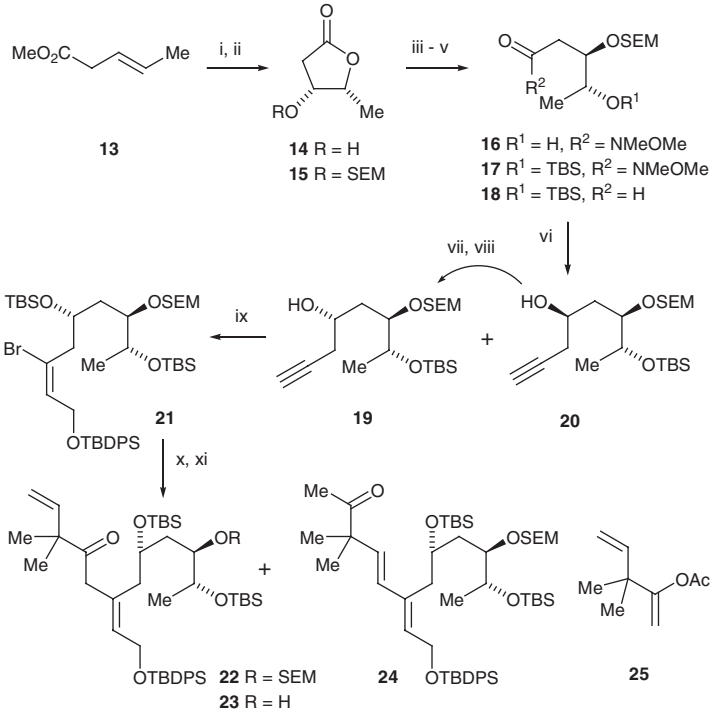
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.097



Scheme 1. Reagents and conditions: (i) $Ba(OH)_2$, THF, H_2O, rt; (ii), HF·py., rt, 12 min; (iii), ^{t}BuOK, THF, rt, 15 min (**7**, 48% from **4**); (iv) (a) Dess–Martin periodinane; (b) $Ph_3P^+MeBr^-$, ^{t}BuLi (60% from **7**); (v) $HC(OMe)_3$, MeOH, PPTS (58%); (vi) SEMCl, $^i Pr_2NEt$, CH_2Cl_2, rt (79%); (vii) $^n Bu_4NF$, THF, rt (85%); (viii) Dess–Martin periodinane; (ix) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, ^{t}BuOH.

(SEM) ethers followed by selective cleavage of the *tert*-butyldiphenylsilyl ether gave the alcohol **11**, which was oxidised to the acid **12** in two steps. This acid corresponds to the required C(1)–C(16)-fragment of the bryostatins **1** and **2**.

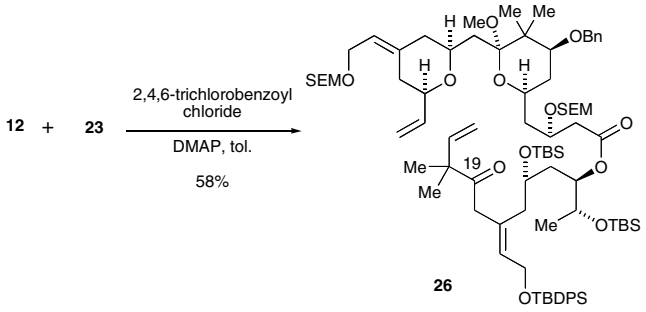
A preparation of the C(17)–C(27) fragment **23** based on our earlier work,[5] is outlined in Scheme 2. Asymmetric dihydroxylation of methyl (3*E*)-pent-3-enoate **13** using AD-mix-β gave the lactone **14**.[7] Following hydroxyl protection giving the SEM-ether **15**, ring opening of the lactone gave the Weinreb amide **16** which was protected as its *tert*-butyldimethylsilyl ether **17** and reduced to the aldehyde **18**. Addition of allenylzinc bromide to **18** was expected[5] to proceed with chelation control but a mixture of epimers **19** and **20** was obtained. However, these could be separated and, following inversion of the unwanted epimer **20** via a Mitsunobu reaction and saponification, the required alcohol **19** was obtained in an overall yield of 70%.[8]



Scheme 2. Reagents and conditions: (i) AD-mix-β, ^{t}BuOH, H_2O (59%); (ii) SEMCl, $^i Pr_2NEt$, DMAP, 3 days (95%); (iii) MeNHOMe, HCl, $AlMe_3$; (iv) TBSCl, imid. (66% from **15**); (v) DIBAL-H, THF, −78 °C (87%); (vi) propargyl bromide, Zn powder, −15 to −78 °C (78%; **19**:**20** = 50:50); (vii) Cl_2CHCO_2H, PPh_3, DIAD, THF; (viii) NaOH, MeOH (70% of **19** based on **18**); (ix) (a) TBSOTf, 2,6-lutidine (94%); (b) ^{n}BuLi, MeOCOCl, −78 °C (92%); (c) $(Bu_3Sn)_2$, ^{n}BuLi, CuBr·DMS, THF, −50 °C (88%); (d) DIBAL-H, DCM, −78 °C (83%); (e) TBDPSCl, imid. DCM (100%); (f) NBS, DCM, rt (97%); (x) $PdCl_2$·dppe, Bu_3SnOMe, tol., **25**, 120 °C (**22**, 43%; **24**, 38%); (xi) $MgBr_2$, ^{n}BuSH, K_2CO_3 (64%).

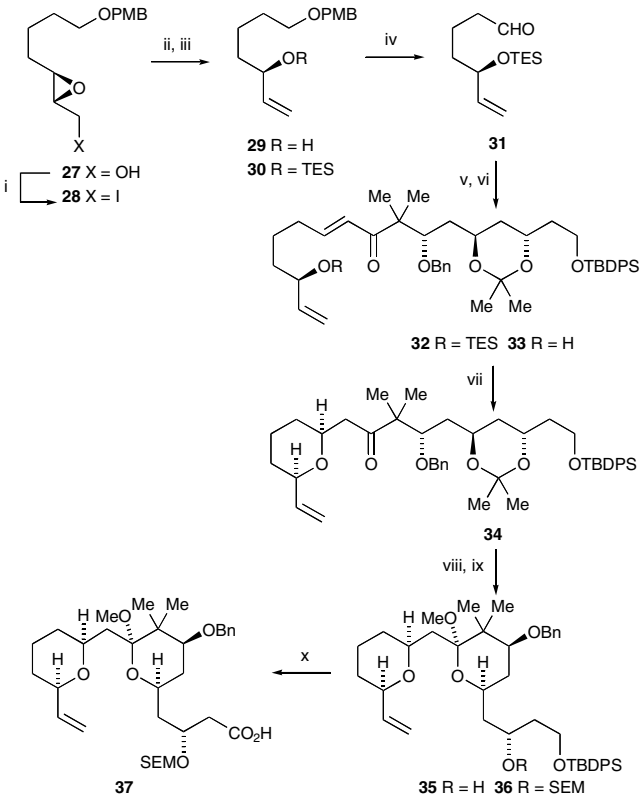
The alcohol **19** was taken through to the vinyl bromide **21** via protection, methoxycarbonylation, stereoselective addition of a tin cuprate, reduction of the ester, further protection and substitution of the vinyl stannane using *N*-bromosuccinimide. Palladium(0) catalysed coupling of the vinylic bromide **21** with the enol acetate **25** then gave a mixture of the required non-conjugated ketone **22** and the Heck product **24**,[9] but the ketone **22** could be isolated in a yield of 43% which was sufficient to enable the metathesis to be evaluated. Selective removal of the SEM group gave the alcohol **23**, which corresponds to the C(17)–C(27) fragment of bryostatin 11 (**2**).

Esterification of the acid **12** using the alcohol **23** gave the ester **26**, but attempts to form the bryostatin macrocycle using ring-closing metathesis using the Grubbs 2 catalyst[6] were unsuccessful with a complex mixture of products being obtained.



During these attempted metatheses, the double bond attached to the C(1)–C(16) fragment was lost, but the more hindered double bond attached to the (C17)–C(27) fragment remained unchanged. These problems in accessing a bryostatin directly by ring-closing metathesis of the alkene **26** were disappointing but were not totally unexpected. Ring-closing metatheses of terminal alkenes with geminal allylic methyl groups are known but would appear to be very sensitive to minor structural modifications.[10] In the case of the metathesis precursor **26**, it was not clear whether the geminal dimethyl group at C(18), the presence of a ketone at C(19), the presence of chelating groups in the vicinity of the alkenes involved in the metathesis, for example, the SEM group, or the flexible open-chain structure of the C(17)–C(23) fragment, was the major factor responsible for the difficulties in the ring-closing metathesis. It was therefore decided to study the ring-closing metathesis using simpler systems to attempt to establish the major factors which might be involved.

The C(1)–C(16) fragment **37** lacking the exocyclic alkoxymethylene group was prepared as outlined in Scheme 3. The hydroxy-epoxide **27** prepared by Sharpless epoxidation of the corresponding (*E*)-alkene[7] was converted into iodide **28**, which gave allylic alcohol **29** on treatment with *tert*-butyllithium. Following protection of the secondary alcohol as its triethylsilyl (TES) derivative **30**, selective removal of the *p*-methoxybenzyl ether and oxidation gave aldehyde **31**. This was condensed with keto-phosphonate **4** to give enone **32**. After selective

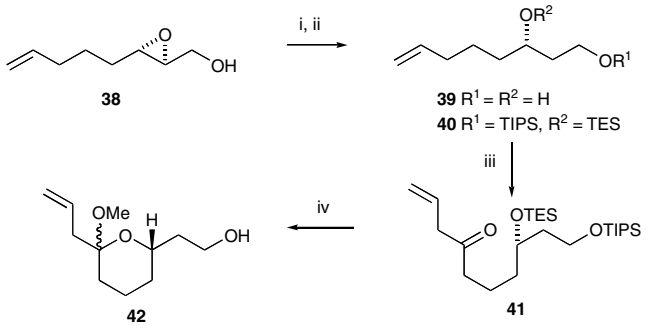


Scheme 3. Reagents and conditions: (i) I_2, PPh_3, imid. (89%); (ii) ^{t}BuLi, THF, −78 °C, 15 min; (iii) TESCl, imid., rt, 2 h (99% from **28**); (iv) (a) DDQ, DCM, pH 7 buffer (70%); (b) Dess–Martin periodinane; (v) $Ba(OH)_2$, THF, rt, 18 h (86% over two steps); (vi) HF·py, THF, rt, 15 min (100%); (vii) ^{t}BuOK, THF, rt (90%); (viii) $HC(OMe)_3$, PPTS, MeOH, rt (86%); (ix) SEMCl, ^{i}Pr$_2$NEt, DMAP (80%); (x) (a) TBAF·THF; (b) Dess–Martin periodinane; (c) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, ^{t}BuOH (94%).

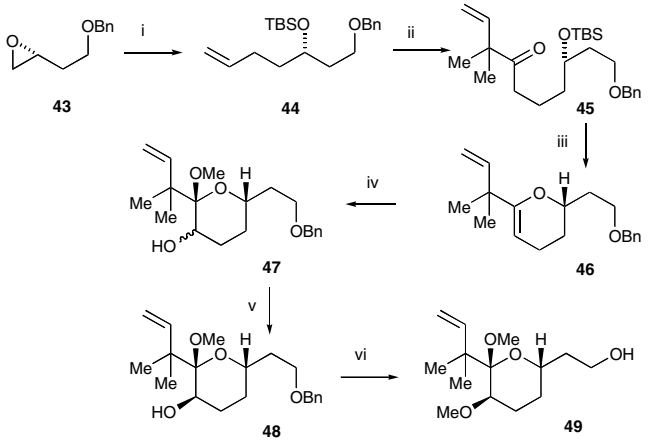
TES deprotection, base-induced cyclisation gave tetrahydropyran **34**, which was converted to acetal **35** by treatment with trimethyl orthoformate in acidic methanol. Following protection of the secondary alcohol as its SEM-ether **36**, desilylation and oxidation gave acid **37**.

Simpler C(17)–C(27)-fragments with and without the geminal dimethyl group at C(18) (bryostatin numbering) were prepared as outlined in Schemes 4 and 5. Thus, reduction of the epoxide **38**, prepared by Sharpless epoxidation of the corresponding (*E*)-alkene,[7] gave diol **39**, which was differentially protected to give the bis-silyl ether **40**. This was taken through to the βγ-unsaturated ketone **41** and acetalisation and desilylation gave a mixture of the inseparable epimeric acetals **42** (Scheme 4).

The second modified C(17)–C(27) fragment **49** was prepared by copper(I) catalysed reaction of epoxide **43**[11] with allylmagnesium bromide followed by protection to give the *tert*-butyldimethylsilyl ether **44** (Scheme 5). Hydroboration/oxidation followed by a Swern oxidation, a zinc-mediated reaction with 3,3-dimethylallyl bromide and further oxidation gave the ketone **45**. Desilylation and cyclisation then gave enol ether **46**,[12] which gave a mixture of the hydroxyacetals **47** on oxidation



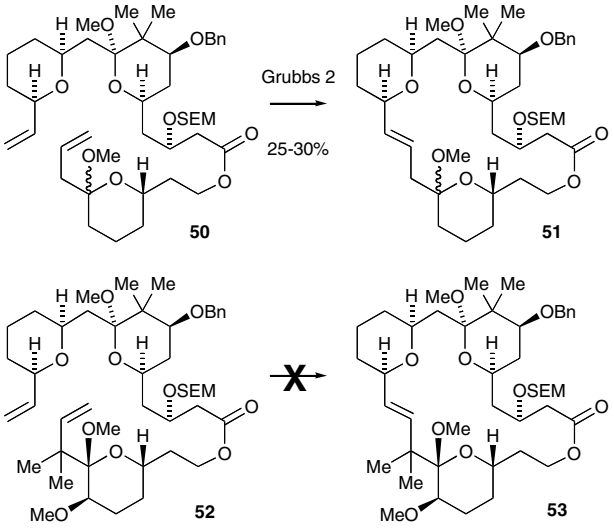
Scheme 4. Reagents and conditions: (i) Red-Al, THF, 0 °C (99%); (ii) (a) TIPSCl, imid., rt, 2 h (99%); (b) TESCl, imid., rt, 2 h (99%); (iii) (a) O_3, DCM, then PPh_3, −78 °C; (b) allylmagnesium bromide, THF (68% over two steps); (c) Dess–Martin periodinane (80%); (iv) (a) $HC(OMe)_3$, PPTS, MeOH, rt (68%); (b) TBAF, THF, rt (85%).



Scheme 5. Reagents and conditions: (i) (a) allylmagnesium bromide, CuI (83%); (b) TBSCl, imid. (93%); (ii) (a) BH_3·THF then H_2O_2/NaOH (86%); (b) $(COCl)_2$, DMSO, then Et_3N; (c) $Me_2C{=}CHCH_2Br$, Zn dust (67% over two steps); (d) $(COCl)_2$, DMSO, then Et_3N; (iii) (a) TBAF (85% over two steps); (b) camphor sulfonic acid, benzene, MS 4A (99%); (iv) *m*CPBA, MeOH; (v) (a) Dess–Martin periodinane (86% from **46**); (b) $LiBHEt_3$ (88%); (vi) (a) NaH, MeI, DMF (87%); (b) Na, liq. NH_3, THF (96%).

using *m*-chloroperoxybenzoic acid. Further oxidation gave the corresponding ketone, which was reduced stereoselectively using lithium triethylborohydride to give the alcohol **48**. O-Methylation and debenzylation then gave the primary alcohol **49**.

Using dicyclohexycarbodiimide (DCC), esterification of the acid **37** using the alcohol **42** gave the ester **50** (88%), as a mixture of diastereoisomers. This on treatment with the Grubbs 2 catalyst underwent stereoselective ring-closing metathesis to give the macrolide **51**, a macrocyclic analogue of the bryostatins, in which the C(16)–C(17) double bond had the (*E*)-configuration. In contrast, the ester **52** prepared from the acid **37** and the alcohol **49**, (DCC, 85%) did not undergo ring closing metathesis with the Grubbs 2, Hoveyda or Schrock catalysts under a variety of conditions.[13] As observed for the ester **26**, complex mixtures of products were obtained in which the less hindered terminal double bond attached to the tetrahydropyran seemed to have been destroyed whilst the more hindered terminal double bond with geminal allylic methyl groups was mainly unchanged. A small amount of a dimeric material was detected by MS.



These results indicate that the ring-closing metathesis can be carried out on systems which lack the geminal dimethyl groups at C(18), for example, the successful metathesis of **50**, although it would appear that ring-closing metatheses of substrates in which these methyl groups are present, for example, the dienes **26** and **52**, are more difficult to carry out. Diene **52** has the unnatural configuration at C(20), cf. bryostatin 1 (**1**), and the C(17)–C(27) fragment of intermediate **26** lacks the conformational constraint of the six-membered cyclic hemiacetal present in bryostatins. It may be that these factors are important in affecting the ring-closing metathesis and so clearly more work is required to delineate fully all the factors involved in this system. However, ring-closing metathesis does provide access to bryostatin analogues, which may well be biologically active, albeit lacking the geminal dimethyl groups at C(20). Finally, this work confirms that advanced intermediates for bryostatin synthesis are available using the chemistry described herein, so that different strategies for assembly of the bryostatin system can now be evaluated.

Acknowledgements

We thank the EPSRC for support (to B.B. and R.D.).

References and notes

1. Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841; Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigero, M. *Nat. Prod. Reports* **2002**, *19*, 413.
2. Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587; Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfrai, P.; Whitenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407; Evans, D. A.; Carter, P. H.;

Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2354; Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540; Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290.

3. Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534; Wender, P. A.; De Brabander, J.; Harran, P. G.; Hinkle, K. W.; Lippa, B.; Pettit, G. R. *Tetrahedron Lett.* **1998**, *39*, 8625; Wender, P. A.; Lippa, B. *Tetrahedron Lett.* **2000**, *41*, 1007.
4. Ball, M.; Baron, A.; Bradshaw, B.; Omori, H.; MacCormick, S.; Thomas, E. J. *Tetrahedron Lett.* **2004**, *45*, 8737.
5. Almendros, P.; Rae, A.; Thomas, E. J. *Tetrahedron Lett.* **2000**, *41*, 9565; Gracia, J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853.
6. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.
7. The ee's of the hydroxylactone **14** and the hydroxyepoxides **27** and **38** were shown to be $\geqslant 90\%$ and their absolute configurations as shown using the Mosher's method. Full details will be reported in a full paper.
8. Alternative procedures for the stereoselective conversion of aldehyde **18** into the alcohol **19** using enantiomerically enriched reagents were investigated. Full details will be reported in a full paper.
9. An alternative sequence for the synthesis of the ketone **23** based on the stereoselective addition of an allylic Grignard reagent to a conjugated acetylenic ketone has also been developed (cf. Ref. 4). Full details will be reported elsewhere.
10. Michalak, M.; Wicha, J. *Synlett* **2005**, 2277; Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4629.
11. Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, *7*, 621.
12. Attempts to convert the hydroxyketone formed on desilylation of ketone **45** into the corresponding methoxy acetal were unsuccessful; the enol ether **46** was the only product which could be isolated.
13. The linear ketone **34** was also desilylated, oxidised to the corresponding carboxylic acid, and esterified using the alcohols **42** and **49**. The ester of alcohol **42** lacking the geminal dimethyl groups at C(18) underwent ring-closing metathesis, whereas the ester derived from alcohol **49** did not. These results are consistent with those reported here and will be described elsewhere.