An approach to the C(10)–C(16) fragment of the bryostatins: stereoselective exocyclic double-bond formation by vinyl radical cyclization

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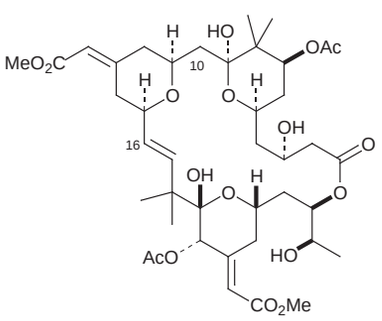
On treatment with tributyltin hydride, the vinyl bromide 11 and the vinyl iodide 26 cyclize to give mixtures of the (*E*)- and (*Z*)-4-(alkoxycarbonylmethylene)tetrahydropyrans 12/13 and 27/28 in which the (*E*)-isomers 12 and 27 are the major components accounting for 80% of the products. Addition of triphenyltin hydride to the alkyne 34 similarly initiates cyclization giving a mixture of products 35–37, the composition of the mixture depending upon the concentration of the tin hydride. These results are consistent with faster cyclization of the (*Z*)-vinyl radical with kinetic formation of five-membered ring containing products which are either trapped by hydrogen transfer from the tin hydride or which rearrange to form a 4-methylenetetrahydropyran. This chemistry was applied to prepare the *cis*-2,6-disubstituted 4-(methoxycarbonylmethylene)tetrahydropyran 50 which may be useful for the introduction of the C(10)–C(16) fragment into the bryostatins. Cyclization of the *p*-methoxybenzyl protected vinyl iodide 58 is less stereoselective, perhaps because of intramolecular hydrogen transfer from the *p*-methoxybenzyl group.

The bryostatins, *e.g.* bryostatin 7 **1**, comprise an important group of macrolides which are isolated from invertebrate filter feeders including *Bugula neritina* and which display potent antitumour activity.[1] The total synthesis of the bryostatins is of considerable interest at present because of the potential of these compounds as chemotherapeutic reagents with a need for a better understanding of their structure–activity relationships. To date one total synthesis of a bryostatin has been described[2] together with several reports of approaches to the synthesis of various fragments.[3–5]



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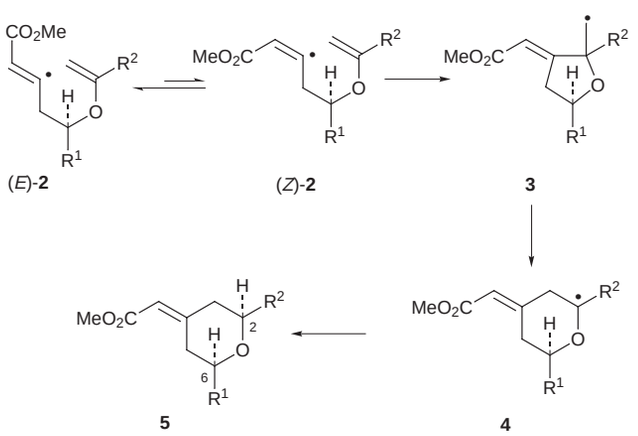
The C(10)–C(16) fragment of the bryostatins corresponds to a *cis*-2,6-disubstituted 4-(methoxycarbonylmethylene)tetrahydropyran. Any synthesis of this part of a bryostatin must address the question of control of the geometry of the exocyclic double-bond and the stereoselective introduction of the 2- and 6-substituents.† Several approaches for the control of the geometry of the exocyclic double-bonds in bryostatins have been reported including the use of a tethered, intramolecular Wadsworth–Emmons–Horner reaction and the use of an intermolecular Wadsworth–Emmons–Horner reaction on a sterically biased substrate.[4] We now report full details of our early study which used the stereoselective cyclization of a vinyl radical to control both the geometry of the exocyclic double-bond and the *cis*-configuration of the 2- and 6-substituents.[6]

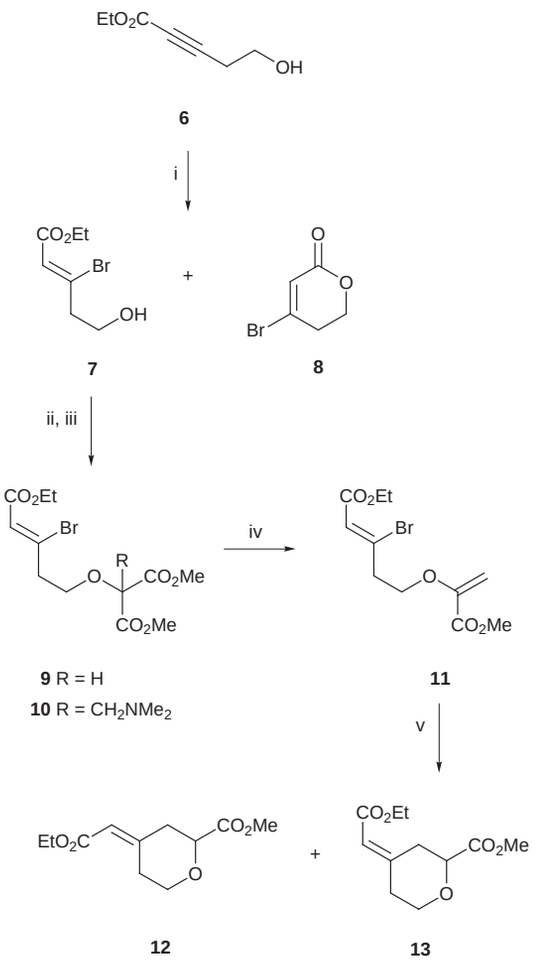
The idea behind this approach was that cyclization of the (*Z*)-component of a rapidly equilibrating mixture of the (*E*)- and (*Z*)-vinylic radicals **2** would be faster than cyclization of the (*E*)-isomer because of steric hindrance and would control the geometry of the exocyclic double-bond.[7,8] Moreover, although it was expected that five-membered ring formation would be kinetically preferred because of stereoelectronic control, it was thought that rearrangement of the initially formed primary radical **3** could lead to the formation of products containing the required tetrahydropyran ring system.[9] The relative configuration of the stereogenic centres at C(2) and C(6) would then depend upon the stereoselectivity of hydrogen transfer to the radical **4** which it was thought would be from the axial direction leading to products with the 2- and 6-substituents *cis*-disposed, *i.e.* both in equatorial positions with respect to the six-membered ring.



Results and discussion

Addition of gaseous hydrogen bromide to ethyl 5-hydroxypent-2-ynoate **6**[10] gave a mixture of the (*Z*)-vinylic bromide **7** (45%) and the bromolactone **8** (12%) (Scheme 1). Following the procedures developed by Ganem *et al.*,[11] the alcohol **7** was converted into the 2-alkoxymalonate **9** on treatment with dimethyl diazomalonate[12] in the presence of a catalytic amount of rhodium(II) acetate, and alkylation using triethylamine and Eschenmoser's salt[13] gave the 2-(dimethylaminomethyl)-malonate **10**. Quaternization and iodide induced decarboxyl-

† Tetrahydropyran numbering.

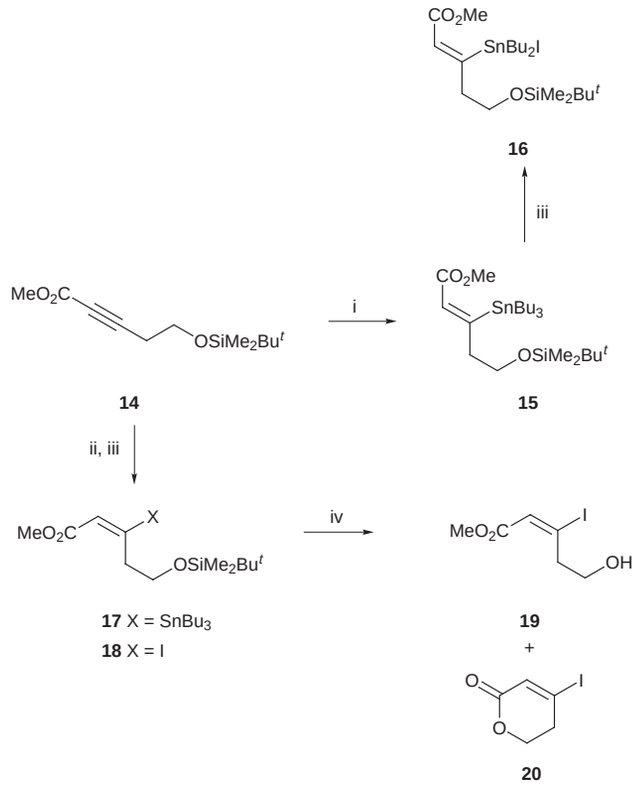


Scheme 1 *Reagents and conditions*: i, HBr (gaseous), ether, 0 °C (**7**, 45%; **8**, 12%); ii, $(MeO_2C)CN_2$, benzene, $Rh_2(OAc)_4$ (cat.), heat under reflux (65%); iii, Et_3N, $Me_2N^+{=}CH_2\ I^-$, CH_2Cl_2 (93%); iv, MeI, MeCN, heat under reflux, 48 h (79%); v, Bu_3SnH, AIBN (**12**, 32%; **13**, 8%)

ative elimination was then achieved by heating a solution of the amine **10** with an excess of methyl iodide in acetonitrile under reflux and gave the enol pyruvate **11** in a yield of 48% based on the alcohol **7**. Cyclization of the vinylic bromide **11** was carried out by treatment with tributyltin hydride and a trace of azoisobutyronitrile in benzene–acetonitrile heated under reflux and gave the (*E*)- and (*Z*)-diesters **12** and **13**, ratio **12**:**13** = 80:20, combined yield 40%.

The structures of the esters **12** and **13** were confirmed by comparison of their spectroscopic data with those of the analogous dimethyl esters, *vide infra*. However, although useful stereoselectivity had been obtained in the cyclization, the yields of the cyclized products **12** and **13** were rather modest and significant amounts of relatively non-polar, tin-containing, side-products were obtained. It was therefore decided to investigate the cyclization of analogous vinylic iodides to see whether better yields of the desired products could be isolated. The (*Z*)-vinyl iodide analogous to bromide **11** and its (*E*)-isomer were identified for initial studies.

Following conditions developed by Piers and co-workers,[14] methyl 5-*tert*-butyldimethylsilyloxypent-2-ynoate **14**[15] was treated with lithium (phenylthio)(tributylstannyl)cuprate to give either the (*Z*)-vinylstannane **15** (82%) or, in the presence of methanol, its (*E*)-isomer **17** (92%) (see Scheme 2). The (*E*)-vinyl stannane **17** was cleanly converted into the corresponding vinyl iodide **18** on treatment with iodine in diethyl ether, but its (*Z*)-isomer suffered cleavage of one of the butyl substituents from the tin to give the tin iodide **16**. Coordination of the *cis*-disposed vicinal methoxycarbonyl substituent to the tin in the transition structure for electrophilic substitution has been pro-

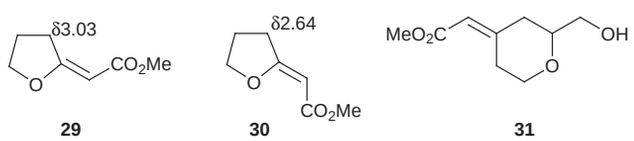


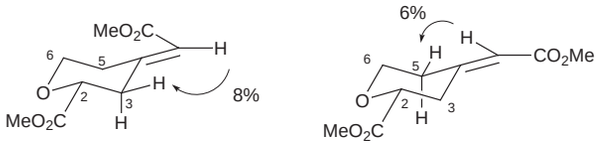
Scheme 2 *Reagents and conditions*: i, $Bu_3Sn{\cdot}PhSCuLi$, −78 °C (82%); ii, $Bu_3Sn{\cdot}PhSCuLi$, MeOH, THF, −10 to −78 °C (92%); iii, I_2, ether, rt (**16**, 93%; **18**, 99%); iv, HOAc, H_2O, THF, 20 °C, 48 h (**19**, 49%; **20**, 34%)

posed to explain similar behaviour.[16] Desilylation of the (*E*)-5-*tert*-butyldimethylsilyl ether **18** under acidic conditions was accompanied by lactonisation and gave a mixture of the required hydroxyester **19** (49%) and the corresponding lactone **20** (34%). The hydroxyester **19** was taken through to the enol pyruvate **26** by treatment with dimethyl diazomalonate, alkylation using Eschenmoser's salt, and decarboxylative elimination (46% overall), but in view of the difficulties associated with preparing the alcohol **19** an alternative synthesis involving introduction of the pyruvate earlier in the synthesis was investigated.

Methyl 5-hydroxypent-2-ynoate **21**[17] was converted into the enol pyruvate **24** following the usual three-step procedure (54% overall)[11] (Scheme 3), and conjugate addition of a tributyltin cuprate[14] gave the (*E*)-vinyl stannane **25**. Treatment of this stannane with iodine at room temperature in diethyl ether gave the vinyl iodide **26** which was cyclized using tributyltin hydride in the presence of azoisobutyronitrile in solution in benzene heated under reflux to give a mixture of the (*E*)- and (*Z*)-diesters **27** and **28**, ratio, **27**:**28** = 80:20, combined yield 87%.

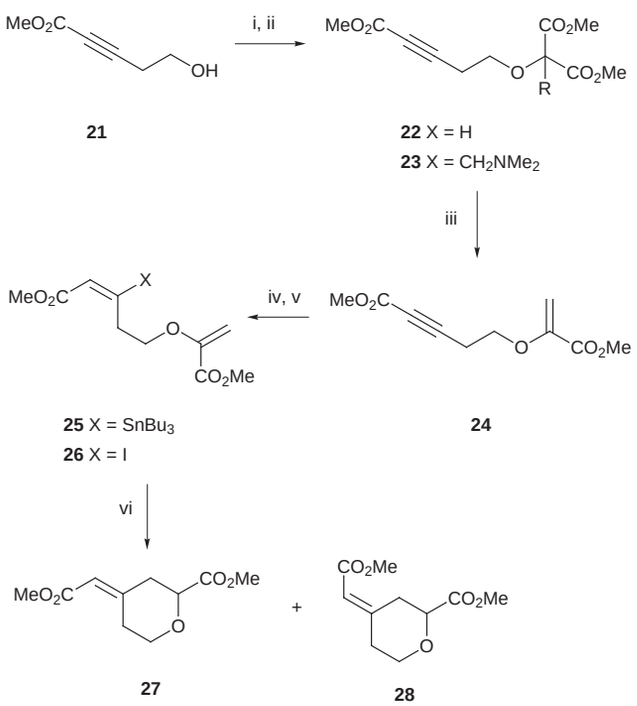
Structures were assigned to the tetrahydropyrans **27** and **28** on the basis of spectroscopic data with assignments of protons in their ^1H NMR spectra being made on the basis of spin decoupling experiments. The geometries of the exocyclic double-bonds then followed from chemical shifts (Fig. 1), since methoxycarbonyl substituents on exocyclic double-bonds are known to deshield *cis*-disposed protons, *cf*. the chemical shifts of 3-H_2 reported for the (*E*)- and (*Z*)-2-(methoxycarbonylmethylene)tetrahydrofurans **29** and **30**.[18] NOE enhancements observed on irradiation of the vinylic protons confirmed these assignments.





27	δ	**28**	δ
5-H_{eq}	3.45	5-H_{eq}	1.49
3-H_{eq}	2.14	3-H_{eq}	3.95

Fig. 1



Scheme 3 *Reagents and conditions*: i, $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$, benzene, heat under reflux (78%); ii, $Me_2N^+{=}CH_2\ I^-$, Et_3N, CH_2Cl_2 (94%); iii, MeI, MeCN, heat under reflux, 48 h (74%); iv, $Bu_3SnLi{\cdot}CuBr{\cdot}Me_2S$, −48 to −78 °C, MeOH (69%); v, I_2, ether, 20 °C (95%); vi, Bu_3SnH, A*I*BN, benzene, heat under reflux, 1 h (**27**, 70%; **28**, 17%)

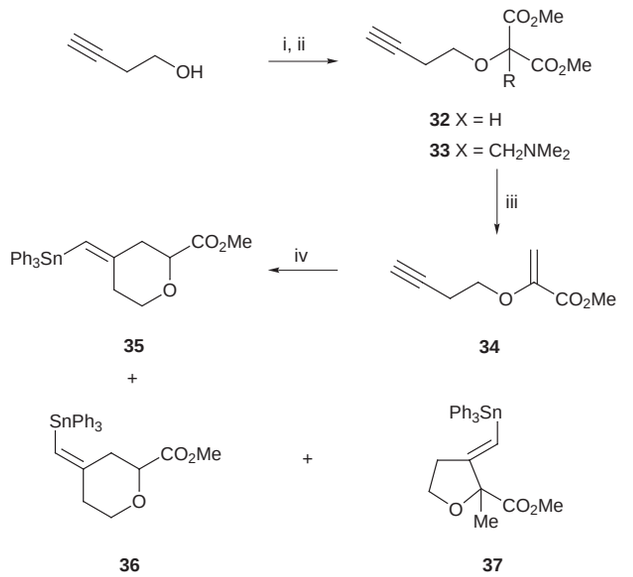
It would appear that the (*Z*)-vinyl bromide **11** and the (*E*)-vinyl iodide **26** both cyclise to give mixtures of 4-(alkoxycarbonylmethylene)tetrahydropyrans, in which the (*E*)-isomer predominates, with better yields being obtained using the vinyl iodide **26**. The two methoxycarbonyl groups in the diester **27** could be modified separately; for example, regioselective reduction using sodium borohydride in tetrahydrofuran–methanol heated under reflux[19] gave the hydroxyester **31** (72%).

As an alternative approach to substituted 4-methylenetetrahydropyrans based on free-radical cyclization, but-3-ynol was converted into the enol pyruvate **34** (Scheme 4). Cyclization was carried out by the addition of triphenyltin hydride under free-radical conditions[20] and gave a mixture of three products which were identified as the two methylenetetrahydropyrans **35** and **36** together with the 3-methylenetetrahydrofuran **37**.

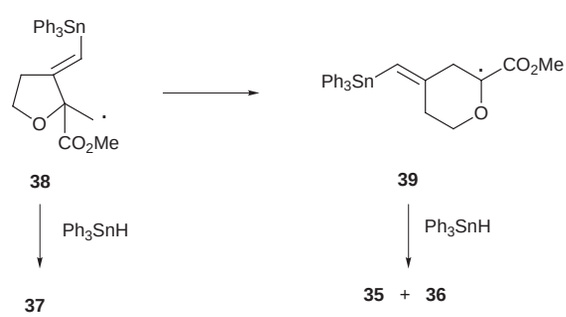
The structures of these products were assigned on the basis of spectroscopic data. Interestingly the relative amounts of the products was found to depend upon the concentration of the starting material and tin hydride at the beginning of the reaction (Table 1) with the formation of the five-membered ring product **37** becoming more significant at higher initial concentrations. This result is consistent with the initial cyclization of the vinyl radical giving the tetrahydrofuranylmethyl radical **38** which is trapped by tin hydride to give **37** or which can rearrange to the more stable tetrahydropyranyl radical **39** and so give rise to **35** and **36**.[9,21] Similar processes may well be

Table 1 Dependence of the yields of cyclized products **35**, **36** and **37** on concentration

	Isolated yields (%)		
[34]/M	**35**	**36**	**37**
0.005	61	12	15
0.01	46	9	23
0.02	30	6	28



Scheme 4 *Reagents and conditions*: i, $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$, benzene, heat under reflux (62%); ii, Et_3N, $Me_2N^+{=}CH_2\ I^-$, (87%); iii, MeI, MeCN, heat under reflux, 48 h (79%); iv, Ph_3SnH, benzene, heat, 1.5 h (for yields see Table 1)

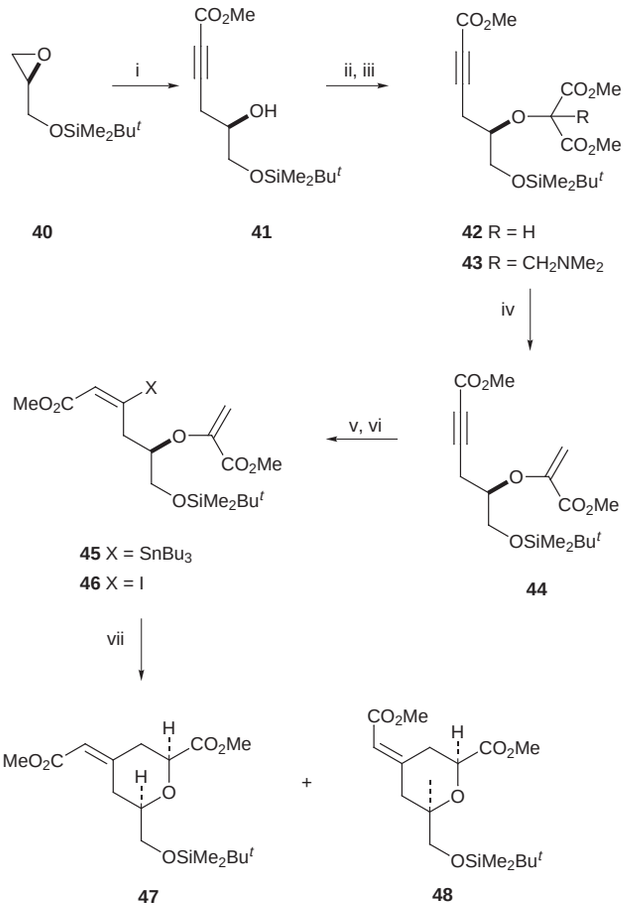


involved in the cyclizations of the vinylic radicals derived from the vinyl bromide **11** and iodide **26** although in these cases the tetrahydrofuranyl products were not detected.

Having shown that 4-methylenetetrahydropyrans are available with reasonable levels of control of the geometry of the exocyclic double-bond by free-radical cyclization, it remained to establish the stereoselectivity of formation 2,6-disubstituted 4-(methoxycarbonylmethylene)tetrahydropyrans using this approach.

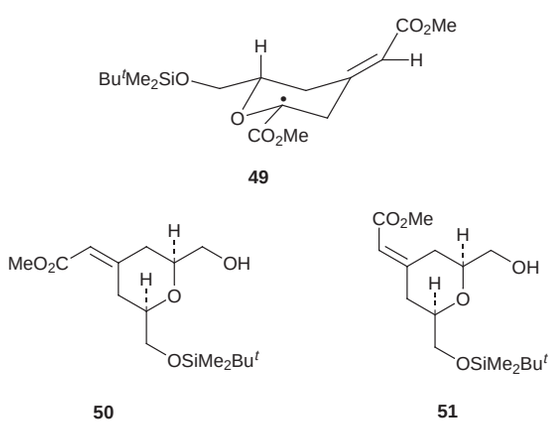
Treatment of the *tert*-butyldimethylsilyl ether of (*R*)-glycidol **40** with lithiated methyl propiolate–boron trifluoride–diethyl etherate gave the hexynoate **41** (65%) which was converted into the enol pyruvate **44** (50% overall) (Scheme 5). Conjugate addition followed by tin–halogen exchange then gave the (*E*)-vinyl iodide **46** which was cyclized by treatment with tributyltin hydride–azoisobutyronitrile in benzene heated under reflux to give a mixture of the 2,6-*cis*-disubstituted (*E*)- and (*Z*)-diesters **47** and **48**, combined yield 85%, ratio **47**:**48** = 80:20.

Structures were assigned to the cyclized products **47** and **48** on the basis of spectroscopic data. In particular, NOE enhancements of H(2) were observed on irradiation of H(6) (4.1% for **47**; 6.3% for **48**) and from coupling constants H(2) and

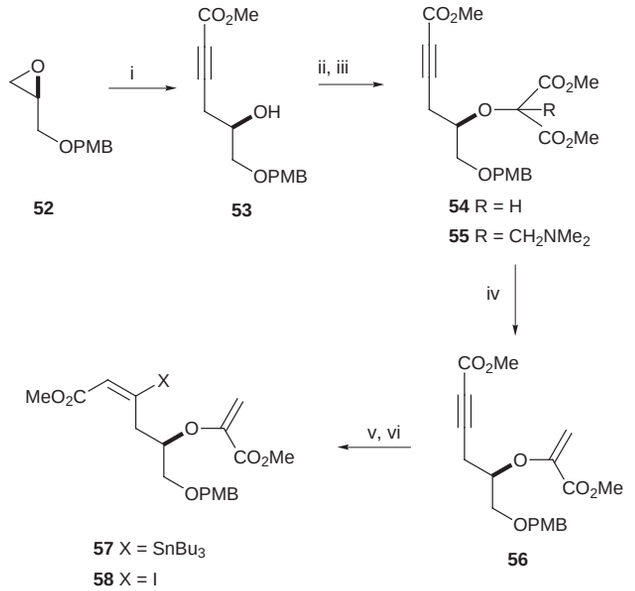


Scheme 5 *Reagents and conditions*: i, LiC≡CCO$_2$Me, BF$_3$·Et$_2$O, THF, −78 °C (65%); ii, (MeO$_2$C)$_2$CN$_2$, Rh$_2$(OAc)$_4$ (cat.), benzene, heat under reflux, 25 h (78%); iii, Et$_3$N, Me$_2$N$^+$=CH$_2$ I$^-$ (95%); iv, MeI, MeCN, reflux, 72 h (70%); v, Bu$_3$SnLi·CuBr·Me$_2$S, MeOH, −78 °C, 3 h (82%); vi, I$_2$, ether, 20 °C, 2 h (94%); vii, Bu$_3$SnH, AIBN (85%; **47**:**48** = 80:20)

H(6) were axial in both products, so establishing the *cis*-2,6-configuration. It would appear that transfer of a hydrogen atom from tributyltin hydride to the tetrahydropyranyl radical **49** takes place preferentially from the axial direction leading to the *cis*-2,6-configuration. Selective reduction of a mixture of the diesters **47** and **48** gave the 2-hydroxymethyltetrahydropyrans **50** and **51** which were characterized separately.

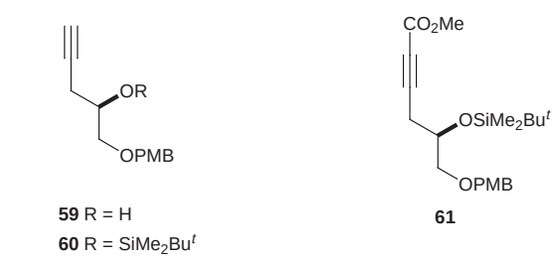


The major *cis*-2,6-disubstituted 4-(methoxycarbonylmethylene)tetrahydropyran **50** has functionality and stereochemistry corresponding to the C(10)–C(16) fragment of the bryostatins and may be useful for bryostatin synthesis. However, the stereoselectivity of the vinyl radical cyclization was found to depend on the protecting groups used in the synthesis. The *p*-methoxybenzyl ether **53** was prepared by treatment of the epoxide **52**



Scheme 6 *Reagents and conditions*: i, LiC≡CCO$_2$Me, BF$_3$·Et$_2$O, THF, −78 °C (72%); ii, (MeO$_2$C)$_2$CN$_2$, Rh$_2$(OAc)$_4$ (cat.), benzene, heat under reflux, 5 h (74%); iii, Et$_3$N, Me$_2$N$^+$=CH$_2$ I$^-$ (92%); iv, MeI, MeCN, reflux, 72 h (70%); v, Bu$_3$SnLi·CuBr·Me$_2$S, MeOH, −78 °C, 3 h (76%); vi, I$_2$, ether, 20 °C, 2 h (65%)

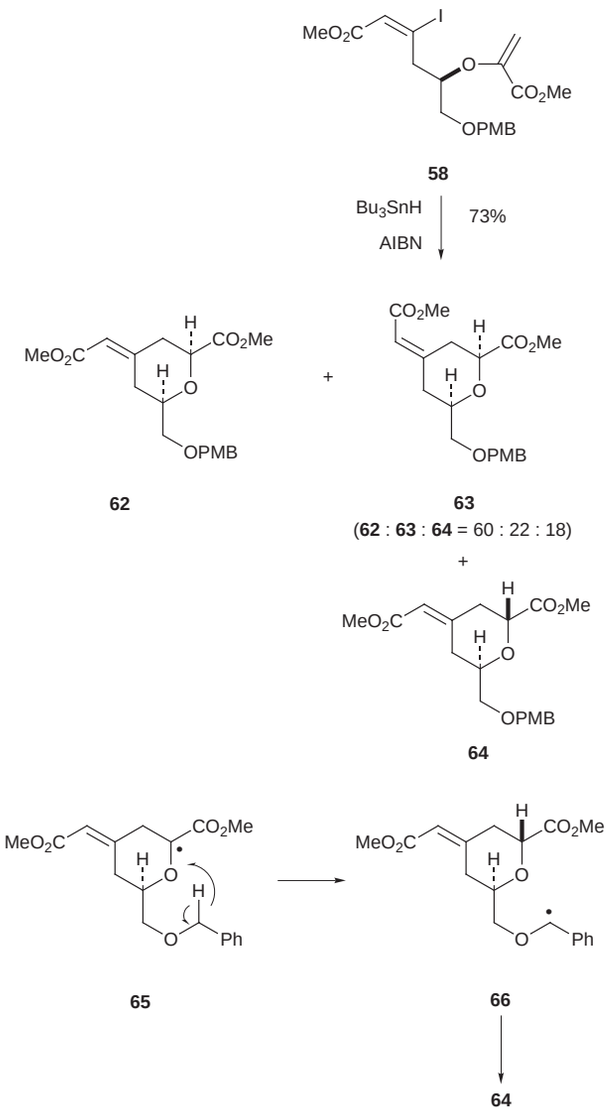
with lithiated methyl propiolate and taken through to the enol pyruvate **58** (Scheme 6). Alternatively, for larger scale work, the epoxide **52** was ring-opened using lithium acetylide to give the alkynol **59** which was converted into the hex-2-ynoate **53** by



the three-step sequence; *O*-silylation, *C*-acylation and *O*-desilylation. When the *p*-methoxybenzyl ether **58** was subjected to the cyclization conditions, a mixture of three products was obtained. These were separated by chromatography and identified as the (*E*)- and (*Z*)-2,6-*cis*-isomers **62** and **63** and the (*E*)-2,6-*trans*-isomer **64** on the basis of spectroscopic data, ratio **62**:**63**:**64** = 60:22:18, respectively. The formation of the 2,6-*trans*-isomer **64** was attributed to intramolecular transfer of a hydrogen atom from the CH$_2$ of the *p*-methoxybenzyl group to C(2) in the tetrahydropyranyl radical **65**. However, notwithstanding this loss of stereoselectivity in the cyclization of **58**, the stereoselective formation of the (*E*)-2,6-*cis*-disubstituted ester **47** on cyclization of the vinyl iodide **46** may be useful for the synthesis of the tetrahydropyranyl fragment of the bryostatins.

Experimental

All non-aqueous reactions were performed under an atmosphere of argon or nitrogen. Proton nuclear magnetic resonance spectra were recorded on Varian Unity 500 (500 MHz), Varian XL 300 (300 MHz), Bruker AC 300 (300 MHz) and Varian Gemini 200 (200 MHz) spectrometers in [^{2}H]chloroform. Chemical shifts are given in ppm; *J* values in Hz. Infrared spectra were recorded on Perkin-Elmer 297 or 1710 FT spectrometers as evaporated films unless otherwise stated. Mass spectra were recorded on a VG Micromass 16F, 3F or ZAB-1F spectrometer using electron impact (EI), chemical ionisation



(CI) or field ionisation (FI) modes with peaks corresponding to ^{120}Sn being quoted.

Chromatography refers to flash column chromatography and was carried out using Merck silica gel 60H (40–63 μ, 230–300 mesh) or May and Baker Sorbsil C60 silica gel (40–60 μ) as the stationary phase. Light petroleum refers to the fraction which distils between 40 and 60 °C, ether refers to diethyl ether, and THF to tetrahydrofuran. All solvents were dried and distilled before use.

Methyl 5-*tert*-butyldimethylsiloxypent-2-ynoate **14**[15] (9.5 g, 72%); ν_{max}/cm^{-1} 2248, 1720, 1253, 1112, 1078 and 839; δ_H 0.08 [6 H, s, Si(CH$_3$)$_2$], 0.92 [9 H, s, SiC(CH$_3$)$_3$], 2.56 (2 H, t, *J* 6.5, 4-H$_2$), 3.78 (3 H, s, OCH$_3$) and 3.81 (2 H, t, *J* 6.5, 5-H$_2$) was prepared from 4-*tert*-butyldimethylsiloxybutyne[22] (10.0 g, 54.3 mmol) by treatment with ethylmagnesium bromide (40 cm^3, 1.8 M in ether) and methyl chloroformate (6.7 cm^3, 86.7 mmol). Methyl 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-ynoate (18.8 g, 68%); ν_{max}/cm^{-1} 2240, 1716, 1255, 1080 and 1034; δ_H 1.50–1.87 (6 H, m), 2.65 (2 H, t, *J* 6, 4-H$_2$), 3.53 (2 H, m, OCH$_2$), 3.77 (3 H, s, OCH$_3$), 3.87 (2 H, m, 5-H$_2$) and 4.67 (1 H, br s, OCHO); was prepared from 4-(tetrahydro-2*H*-pyran-2-yloxy)butyne (20.0 g, 0.130 mol), ethylmagnesium bromide (90 cm^3, 1.90 M in ether) and methyl chloroformate (13.5 cm^3, 0.175 mol). Solvolysis of methyl 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-ynoate (10.0 g, 47 mmol) in methanol (200 cm^3) containing toluene-*p*-sulfonic acid (0.89 g, 4.7 mmol) gave methyl 5-hydroxypent-2-ynoate **21**[17] (5.49 g, 91%); ν_{max}/cm^{-1} 3410, 2242, 1714, 1437, 1262, 1079, 1056 and 754; δ_H 2.23 (1 H, br s, OH), 2.62 (2 H, t, *J* 6, 4-H$_2$), 3.77 (3 H, s, OCH$_3$) and 3.83 (2 H, t, *J* 6, 5-H$_2$); *m*/*z* (CI) 146 (M$^+$ + 18, 100%). Products were obtained as colourless oils unless otherwise stated.

Ethyl (*Z*)-3-bromo-5-hydroxypent-2-enoate 7 and 3-bromopent-2-en-5-olide 8

A solution of ethyl 5-hydroxypent-2-ynoate **6**[10] (2.01 g, 14 mmol) in ether (120 cm^3) was cooled to 0 °C and hydrogen bromide gas bubbled through the solution for 20 min. The reaction mixture was concentrated under reduced pressure, the residue taken up in ether (100 cm^3), washed with water (3 × 50 cm^3), dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (1 : 1) gave 3-bromopent-2-en-5-olide **8** (0.30 g, 12%), δ_H 2.89 (2 H, dt, *J* 1, 7, 4-H$_2$), 4.44 (2 H, t, *J* 7, 5-H$_2$) and 6.43 (1 H, t, *J* 1, 2-H), and the *title compound* **7** (1.42 g, 45%) (Found: M$^+$, 221.9892. C$_7$H$_{11}$BrO$_3$ requires *M*, 221.9892); ν_{max}/cm^{-1} 3415, 1712, 1636, 1305, 1178 and 1047; δ_H 1.28 (3 H, t, *J* 7, CO$_2$CH$_2$C*H*$_2$), 2.20 (1 H, br s, OH) 2.82 (2 H, t, *J* 6, 4-H$_2$), 3.88 (2 H, t, *J* 6, 5-H$_2$), 4.19 (2 H, q, *J* 7, CO$_2$C*H*$_2$CH$_3$) and 6.40 (1 H, s, 2-H); *m*/*z* (CI) 242, 240 (M$^+$ + 18, 45%) and 225, 223 (20).

Ethyl (*Z*)-5-[bis(methoxycarbonyl)methoxy]-3-bromopent-2-enoate 9

Dimethyl diazomalonate[12] (2.55 g, 16 mmol) in benzene (10 cm^3) was added dropwise, over 15 min, to a solution of rhodium acetate (trace) and alcohol **7** (3.0 g, 13 mmol) in benzene (15 cm^3) heated under reflux. The mixture was heated under reflux for 40 min before being cooled and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ethyl acetate (7 : 3) gave the *title compound* **9** (3.09 g, 65%); ν_{max}/cm^{-1} 1728, 1637, 1436, 1261, 1177, 1024 and 806; δ_H 1.30 (3 H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$), 2.94 (2 H, t, *J* 6, 4-H$_2$), 3.83 (6 H, s, 2 × OCH$_3$), 3.87 (2 H, t, *J* 6, 5-H$_2$), 4.21 (2 H, q, *J* 7, CO$_2$C*H*$_2$CH$_3$), 4.55 (1 H, s, 1′-H) and 6.45 (1 H, s, 2-H); *m*/*z* (CI) 372, 370 (M$^+$ + 18, 80%), 292, 290 (100) and 275, 273 (90).

Ethyl (*Z*)-3-bromo-5-[1-(methoxycarbonyl)ethenyloxy]pent-2-enoate 11

Triethylamine (0.95 cm^3, 6.82 mmol) was added to a suspension of the 2-alkoxymalonate **9** (1.5 g, 4.25 mmol) and Eschenmoser's salt[13] (1.15 g, 6.21 mmol) in dichloromethane (90 cm^3) at 20 °C. The mixture became homogeneous over 10 min and was stirred at 20 °C for 18 h before being concentrated under reduced pressure. The residue was dissolved in chloroform (60 cm^3) and the solution washed with saturated aqueous sodium hydrogen carbonate (2 × 25 cm^3). The combined aqueous washes were backwashed with chloroform (2 × 25 cm^3) and the organic solvent extracts combined, dried (MgSO$_4$) and concentrated under reduced pressure to give the tertiary amine **10** which was used without further purification. For characterization purposes, flash chromatography, eluting with light petroleum–ethyl acetate (3 : 2), gave the amine **10** (1.62 g, 93%); δ_H 1.30 (3 H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$), 2.28 (6 H, s, 2 × NCH$_3$), 2.92 (2 H, t, *J* 6, 4-H$_2$), 2.93 (2 H, s, CH$_2$N), 3.82 (6 H, s, 2 × OCH$_3$), 3.87 (2 H, t, *J* 6, 5-H$_2$), 4.22 (2 H, q, *J* 7, CO$_2$C*H*$_2$CH$_3$) and 6.43 (1 H, s, 2-H); *m*/*z* (CI) 412, 410 (M$^+$ + 1, 40%).

A solution of the amine **10** (0.76 g, 1.85 mmol) and iodomethane (1.15 cm^3, 18.5 mmol) in acetonitrile (8 cm^3) was heated under reflux for 48 h. The mixture was then cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 cm^3) and washed with water (2 × 5 cm^3). The combined aqueous washes were backwashed with dichloromethane (2 × 5 cm^3) and the organic extracts combined, dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (4 : 1) gave the *title compound* **11** (0.45 g, 79%); ν_{max}/cm^{-1} 1726, 1622, 1324 and 1171; δ_H 1.30 (3 H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$), 3.03 (2 H, t, *J* 6, 4-H$_2$), 3.80 (3 H, s, CO$_2$CH$_3$), 4.00 (2 H, t, *J* 6, 5-H$_2$), 4.21 (2 H, q, *J* 7, CO$_2$C*H*$_2$CH$_3$), 4.68 and 5.39 (each 1 H, d, *J* 3,

2′-H), and 6.43 (1 H, s, 2-H); *m/z* (CI) 325, 323 (M^+ + 17, 100%), 308, 306 (M^+, 70) and 279, 277 (50).

(*E*)- and (*Z*)-4-(ethoxycarbonylmethylene)-2-methoxycarbonyltetrahydro-2*H*-pyran 12 and 13

A solution of vinyl bromide **11** (200 mg, 0.65 mmol) in benzene (31 cm^3) containing a catalytic amount of azoisobutyronitrile and tributyltin hydride (0.193 cm^3, 0.72 mmol) was degassed with argon and heated under reflux for 1 h. The reaction was cooled and concentrated under reduced pressure and the residue stirred rapidly for 1 h with ether (5 cm^3) and saturated aqueous potassium fluoride (5 cm^3). The mixture was filtered, extracted with ether (3 × 5 cm^3) and the ether extracts dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (3:1) gave the (*E*)-isomer of the *title compound* **12** (48 mg, 32%) (Found: M^+, 228.0994. $C_{11}H_{16}O_5$ requires *M*, 228.0998); ν_{max}/cm^{-1} 1738, 1710, 1654, 1437, 1383, 1245, 1200, 1184, 1148, 1042 and 869; δ_H 1.30 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 2.37–2.63 (3 H, overlapping m, 3-H_2 and 5-H_{ax}), 3.53 (1 H, dt, *J* 3, 11, 6-H_{ax}), 3.63 (1 H, br d, *J* 14, 5-H_{eq}), 3.80 (3 H, s, CO_2CH_3), 4.10 (1 H, dd, *J* 4, 10, 2-H), 4.17 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 4.22 (1 H, ddd, *J* 4, 5, 11, 6-H_{eq}) and 5.77 (1 H, s, 4-CH); *m/z* (CI) 246 (M^+ + 18, 40%), 229 (M^+ + 1, 41) and 183 (100); and the (*Z*)-isomer of the *title compound* **13** (13 mg, 8%) (Found: M^+, 228.0996; $C_{11}H_{16}O_5$ requires *M*, 228.0998); ν_{max}/cm^{-1} 1756, 1709, 1652, 1437, 1378, 1243, 1207, 1174, 1154, 1106, 1042 and 870; δ_H 1.32 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 2.22 (1 H, br d, *J* 14, 5-H_{eq}), 2.37–2.58 (2 H, m, 3-H_{ax} and 5-H_{ax}), 3.58 (1 H, dt, *J* 3, 11, 6-H_{ax}), 3.80 (3 H, s, CO_2CH_3), 4.03 (1 H, br d, *J* 14, 3-H_{eq}), 4.05 (1 H, dd, *J* 4, 10, 2-H), 4.18 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 4.25 (1 H, ddd, *J* 4, 5, 11, 6-H_{eq}) and 5.78 (1 H, s, 4-CH); *m/z* (CI) 246 (M^+ + 18, 5%), 229 (M^+ + 1, 100), 183 (80) and 169 (82).

Methyl (*Z*)-5-*tert*-butyldimethylsilyloxy-3-(tributylstannyl)pent-2-enoate 15

Tetrahydrofuran (20 cm^3) and diisopropylamine (1.84 cm^3, 13.1 mmol) were stirred at 0 °C while butyllithium (1.61 M in hexane; 7.0 cm^3, 11.3 mmol) was added dropwise. After stirring at 0 °C for 5 min, tributyltin hydride (3.0 cm^3, 11.3 mmol) was added. After 15 min the solution was cooled to −20 °C and solid yellow phenylthiocopper (2.34 g, 13.6 mmol) added portionwise. After stirring at −20 °C for 10 min the reaction was cooled to −78 °C and a solution of the alkyne **14**[15] (2.27 g, 9.4 mmol) in tetrahydrofuran (10 cm^3) was added dropwise. The mixture was stirred at −78 °C for 15 min before warming to −50 °C and was subsequently allowed to warm to 0 °C over 1 h. After being cooled to −50 °C for 30 min, methanol (5 cm^3) was added at −50 °C and the mixture warmed to 20 °C. The mixture was diluted with ether (100 cm^3) and filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum gave the *title compound* **15** (4.1 g, 82%) (Found: M^+ + H, 533.2622. $C_{24}H_{51}O_3Si^{118}Sn$ requires *M*, 533.2625); ν_{max}/cm^{-1} 1710, 1598, 1331, 1183, 1092, 837 and 776; δ_H 0.07 [6 H, s, $Si(CH_3)_2$], 0.87–1.53 [36 H, m, $SiC(CH_3)_3$ and $Sn(C_4H_9)_3$], 2.64 (2 H, t, *J* 7, 4-H_2), 3.65 (2 H, t, *J* 7, 5-H_2), 3.73 (3 H, s, OCH_3) and 6.3 (1 H, s, 2-H); *m/z* (CI) 533 (M^+ + 1, 4%), 477 (56), 475 (41) and 473 (22).

Methyl (*E*)-5-*tert*-butyldimethylsilyloxy-3-(tributylstannyl)pent-2-enoate 17

Tetrahydrofuran (40 cm^3) and diisopropylamine (4.0 cm^3, 28.5 mmol) were stirred at 0 °C while butyllithium (1.50 M in hexane; 16.5 cm^3, 24.8 mmol) was added dropwise. After stirring at 0 °C for 5 min, tributyltin hydride (6.7 cm^3, 24.8 mmol) was added. After 15 min the solution was cooled to −20 °C and solid yellow phenylthiocopper (4.27 g, 24.8 mmol) added portionwise. After stirring at −20 °C for 20 min the reaction was cooled to −100 °C and the alkyne **14** (3.0 g, 12.4 mmol) in tetrahydrofuran (20 cm^3) containing methanol (0.85 cm^3, 21.0 mmol) was added dropwise over 10 min. The mixture was stirred at −100 °C for 15 min and then at −78 °C for 3 h. Methanol (3 cm^3) was added at −78 °C and the mixture warmed to 20 °C. The mixture was added to an equal volume of water and filtered through Celite. The filtrate was extracted with ether (3 × 50 cm^3) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (49:1) gave the *title compound* **17** (6.1 g, 92%) (Found: M^+ + H, 533.2598. $C_{24}H_{51}O_3Si^{118}Sn$ requires *M*, 533.2625: M^+ + H, 535.2605. $C_{24}H_{51}O_3Si^{120}Sn$ requires *M*, 535.2628); ν_{max}/cm^{-1} 1721, 1594, 1255, 1169, 1090, 836 and 778; δ_H 0.08 [6 H, s, $Si(CH_3)_2$], 0.88–1.63 [36 H, m, $SiC(CH_3)_3$ and $Sn(C_4H_9)_3$], 3.05 (2 H, t, *J* 7, 4-H_2), 3.68 (2 H, t, *J* 7, 5-H_2), 3.71 (3 H, s, CO_2CH_3) and 6.02 (1 H, s, 2-H); *m/z* (CI) 535, 533 (M^+ + 1, 100%).

Methyl (*Z*)-5-*tert*-butyldimethylsilyloxy-3-(dibutyliodostannyl)-pent-2-enoate 16

Iodine (0.48 g, 1.89 mmol) was added portionwise to a stirred solution of vinylstannane **15** (1.0 g, 1.87 mmol) in ether (30 cm^3). The solution was stirred at 20 °C for 2 h then washed with saturated aqueous sodium thiosulfate (1 × 15 cm^3). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (49:1) gave the *title compound* **16** (1.05 g, 93%); ν_{max}/cm^{-1} 1718, 1659, 1341, 1252, 1092 and 838; δ_H 0.07 [6 H, s, $Si(CH_3)_2$], 0.87–1.70 [27 H, m, $SiC(CH_3)_3$ and $Sn(C_4H_9)_2$], 2.95 (2 H, t, *J* 7, 4-H_2), 3.78 (2 H, t, *J* 7, 5-H_2), 3.88 (3 H, s, OCH_3) and 6.65 (1 H, s, 2-H); *m/z* (CI) 547 (M^+ − 57, 14%), 545 (8), 477 (100), 475 (79) and 473 (45).

Methyl (*E*)-5-*tert*-butyldimethylsilyloxy-3-iodopent-2-enoate 18

Iodine (4.5 g, 17.7 mmol) was added portionwise to a stirred solution of vinylstannane **17** (8.7 g, 16.3 mmol) in ether (300 cm^3). The solution was stirred at 20 °C for 2 h then washed with saturated aqueous sodium thiosulfate (1 × 100 cm^3). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (49:1) gave the *title compound* **18** (6.0 g, 99%) (Found: M^+ + H, 371.0530. $C_{12}H_{24}O_3SiI$ requires *M*, 371.0541); ν_{max}/cm^{-1} 1724, 1612, 1256, 1173, 1105 and 837; δ_H 0.08 [6 H, s, $Si(CH_3)_2$], 0.89 [9 H, s, $SiC(CH_3)_3$], 3.37 (2 H, t, *J* 6, 4-H_2), 3.71 (3 H, s, OCH_3), 3.82 (2 H, t, *J* 6, 5-H_2) and 6.73 (1 H, s, 2-H); *m/z* (CI) 371 (M^+ + 1, 88%) and 313 (19).

Methyl (*E*)-5-hydroxy-3-iodopent-2-enoate 19 and 3-iodopent-2-en-5-olide 20

A solution of acetic acid, water, and tetrahydrofuran (1:1:3, 20 cm^3) was added to a solution of the silyl ether **18** (1.65 g, 4.46 mmol) in tetrahydrofuran (20 cm^3) and the mixture stirred at 20 °C for 48 h. Water (20 cm^3) was added and the mixture extracted with ether (3 × 30 cm^3). The ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ethyl acetate (7:3) gave the *title compound* **20** (0.34 g, 34%) (Found: M^+, 223.9336. $C_5H_5O_2I$ requires *M*, 223.9336); ν_{max}/cm^{-1} 1712, 1602, 1395, 1283, 1214, 1074, 1048 and 863; δ_H 2.93 (2 H, dt, *J* 1.5, 6, 4-H_2), 4.38 (2 H, t, *J* 6, 5-H_2) and 6.77 (1 H, t, *J* 1.5, 2-H); *m/z* (CI) 242 (M^+ + 18, 75%) and 225 (M^+ + 1, 54); and the *title compound* **19** (0.56 g, 49%); ν_{max}/cm^{-1} 3432, 1719, 1617, 1348, 1279, 1217, 1176, 1081, 1054 and 870; δ_H 2.24 (1 H, br s, OH), 3.38 (2 H, t, *J* 6, 4-H_2), 3.73 (3 H, s, OCH_3), 3.86 (2 H, t, *J* 6, 5-H_2) and 6.80 (1 H, s, 2-H).

Methyl 5-[bis(methoxycarbonyl)methoxy]pent-2-ynoate 22

Dimethyl diazomalonate (9.5 g, 60.0 mmol) in benzene (50 cm^3) was added dropwise to rhodium acetate (trace) and methyl 5-hydroxypent-2-ynoate **21** (7.0 g, 54.7 mmol) in benzene (100

cm^3) heated under reflux, over 20 min. The mixture was kept at reflux for 90 min before being cooled and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ethyl acetate (7:3) gave the *title compound* **22** (11.0 g, 78%); ν_{max}/cm^{-1} 2242, 1747, 1715, 1437, 1261, 1136 and 1081; δ_H 2.74 (2 H, t, *J* 7, 4-H$_2$), 3.77 (3 H, s, OCH$_3$), 3.80 (2 H, t, *J* 7, 5-H$_2$), 3.83 (6 H, s, 2 × OCH$_3$) and 4.59 (1 H, s, CH); *m*/*z* (CI) 376 (M$^+$ + 18, 100%) and 259 (M$^+$ + 1, 9).

Methyl 5-[2-dimethylamino-1,1-bis(methoxycarbonyl)ethoxy]-pent-2-ynoate 23

Triethylamine (4.36 cm^3, 31.3 mmol) was added at 20 °C to a mixture of alkoxymalonate **22** (5.0 g, 19.4 mmol) and Eschenmoser's salt (5.24 g, 28.3 mmol) suspended in dichloromethane (200 cm^3). The mixture became homogeneous over 10 min and was stirred at 20 °C for 18 h before being concentrated at reduced pressure. The residue was dissolved in chloroform (100 cm^3) and washed with saturated, aqueous sodium hydrogen carbonate (2 × 35 cm^3). The combined aqueous washes were washed with chloroform (2 × 35 cm^3) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure to give the amine **23** which could be used without further purification. Flash chromatography, eluting with light petroleum–ethyl acetate (3:2) gave the *title compound* **23** (5.7 g, 94%) (Found: M$^+$ + H, 316.1386. $C_{14}H_{22}O_7N$ requires *M*, 316.1396); ν_{max}/cm^{-1} 2242, 1742, 1717, 1436, 1259, 1199, 1148, 1105, 1079 and 1043; δ_H 2.30 [6 H, s, N(CH$_3$)$_2$], 2.71 (2 H, t, *J* 7.5, 4-H$_2$), 2.92 (2 H, s, CH$_2$N), 3.76 (3 H, s, OCH$_3$), 3.80 (6 H, s, 2 × OCH$_3$) and 3.81 (2 H, t, *J* 7.5, 5-H$_2$); *m*/*z* (CI) 316 (M$^+$ + 1, 100%) and 302 (6).

Methyl 5-[1-(methoxycarbonyl)ethenyloxy]pent-2-ynoate 24

A solution of the amine **23** (3.0 g, 9.52 mmol) and iodomethane (5.92 cm^3, 95.2 mmol) in acetonitrile (70 cm^3) was heated under reflux for 48 h then cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 cm^3) and washed with water (2 × 20 cm^3). The aqueous washings were backwashed with dichloromethane (2 × 20 cm^3) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (4:1) gave the *title compound* **24** (1.49 g, 74%) (Found: M$^+$ + H, 213.0764. $C_{10}H_{13}O_5$ requires *M*, 213.0763); ν_{max}/cm^{-1} 2242, 1715, 1624, 1438, 1327, 1259, 1202, 1171, 1080, 972, 860, 795 and 753; δ_H 2.85 (2 H, t, *J* 7, 4-H$_2$), 3.78 and 3.81 (each 3 H, s, OCH$_3$), 3.95 (2 H, t, *J* 7, 5-H$_2$) and 4.65 and 5.43 (each 1 H, d, *J* 3, 2′-H); *m*/*z* (CI) 230 (M$^+$ + 18, 100%), 213 (M$^+$ + 1, 40) and 183 (42).

Methyl (*E*)-5-[1-(methoxycarbonyl)ethenyloxy]-3-(tributylstannyl)pent-2-enoate 25

Tetrahydrofuran (45 cm^3) and diisopropylamine (3.96 cm^3, 28.2 mmol) were stirred at 0 °C while butyllithium (1.38 M in hexane; 17.30 cm^3, 23.0 mmol) was added dropwise. After stirring at 0 °C for 5 min, tributyltin hydride (6.47 cm^3, 24.0 mmol) was added. After 15 min the solution was cooled −48 °C and solid white copper(I) bromide–dimethyl sulfide complex (4.95 g, 24.0 mmol) was added portionwise. After stirring at −48 °C for 20 min, the reaction was cooled to −78 °C and the alkyne **24** (1.70 g, 8.0 mmol) in tetrahydrofuran (15 cm^3) was added dropwise. After stirring at −78 °C for 3 h, methanol (3 cm^3) was added and the reaction warmed to 20 °C over 30 min. The mixture was added to an equal volume of water and filtered through Celite. The filtrate was extracted with ether (3 × 30 cm^3) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (9:1) gave the *title compound* **25** (2.78 g, 69%); ν_{max}/cm^{-1} 1739, 1717, 1621, 1438, 1375, 1324, 1195, 1167 and 1045; δ_H 0.86–1.54 [27 H, m, Sn(C$_4$H$_9$)$_3$], 3.33 (2 H, t, *J* 7, 4-H$_2$), 3.73 and 3.80 (each 3 H, s, OCH$_3$), 3.85 (2 H, t, *J* 7, 5-H$_2$), 4.68 and 5.36 (each 1 H, d, *J* 3, 2′-H) and 6.08 (1 H, s, 2-H); *m*/*z* (EI) 445 (M$^+$ − 57, 15%).

Methyl (*E*)-3-iodo-5-[1-(methoxycarbonyl)ethenyloxy]pent-2-enoate 26

Iodine (1.47 g, 5.73 mmol) was added portionwise to a stirred solution of vinylstannane **25** (2.62 g, 5.21 mmol) in ether (100 cm^3). The solution was stirred at 20 °C for 2 h then decolourised by washing with saturated aqueous sodium thiosulfate (1 × 25 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (4:1) gave the *title compound* **26** (1.68 g, 95%) (Found: M$^+$ + H, 340.9868. $C_{10}H_{14}O_5I$ requires *M*, 340.9888); ν_{max}/cm^{-1} 1721, 1620, 1437, 1326, 1199, 1171 and 1088; δ_H 3.63 (2 H, t, *J* 7, 4-H$_2$), 3.73 and 3.82 (each 3 H, s, OCH$_3$), 3.99 (2 H, t, *J* 7, 5-H$_2$), 4.74 and 5.42 (each 1 H, d, *J* 3, 2′-H) and 6.78 (1 H, s, 2-H); *m*/*z* (CI) 358 (M$^+$ + 18, 34%) and 341 (M$^+$ + 1, 10).

(*E*)- and (*Z*)-2-methoxycarbonyl-4-(methoxycarbonylmethylene)tetrahydro-2*H*-pyran 27 and 28

A solution of the vinyl iodide **26** (200 mg, 0.59 mmol) in benzene (28 cm^3) containing azoisobutyronitrile (trace) and tributyltin hydride (0.175 cm^3, 0.65 mmol) was degassed with argon and heated under reflux for 1 h then cooled and concentrated under reduced pressure. The residue was stirred rapidly with ether (5 cm^3) and saturated aqueous potassium fluoride (5 cm^3) for 1 h. The mixture was filtered and extracted with ether (3 × 5 cm^3) and the ethereal extracts dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (3:2), gave the (*E*)-isomer of the *title compound* **27** (87 mg, 70%) as a white solid, mp 109–110 °C (Found: C, 56.2; H, 6.7. $C_{10}H_{14}O_5$ requires C, 56.05; H, 6.6%); ν_{max}(KBr disc)/cm^{-1} 1749, 1716, 1647, 1435, 1380, 1276, 1253, 1221, 1209, 1181, 1153, 1115, 1056, 864 and 624; δ_H(C_6D_6) 2.14 (1 H, dd, J_{2a3e} 3.5, J_{3a3e} 13.5, 3-H$_{eq}$), 2.27 (1 H, ddd, $J_{3a,4\text{-}CH}$ 1.5, J_{2a3a} 9.5, J_{3a3e} 13.5, 3-H$_{ax}$), 2.35 (1 H, dddd, $J_{5a,4\text{-}CH}$ 1.5, J_{5a6e} 5.5, J_{5a6a} 10, J_{5a5e} 14.3, 5-H$_{ax}$), 3.16 (1 H, ddd, J_{5e6a} 3.5, J_{5a6a} 10, J_{6a6e} 11.5, 6-H$_{ax}$), 3.29 and 3.38 (each 3 H, s, OCH$_3$), 3.45 (2 H, br ddd, J_{5e6a} 3.5, H_{5e6e} 4, J_{5a5e} 14.5, 5-H$_{eq}$), 3.78 (1 H, dd, J_{2a3e} 3.5, J_{2a3a} 9.5, 2-H), 3.84 (1 H, ddd, J_{5e6e} 4, J_{5a6e} 5.5, J_{6a6e} 11.5, 6-H$_{eq}$) and 5.59 (1 H, br s, 4-CH); *m*/*z* (CI) 232 (M$^+$ + 18, 100%), 215 (M$^+$ + 1, 30) and 183 (60); together with the (*Z*)-isomer of the *title compound* **28** (22 mg, 17%) as a white solid, mp 73–75 °C (Found: C, 56.2; H, 6.6. $C_{10}H_{14}O_5$ requires C, 56.05; H, 6.6%); ν_{max}(KBr disc)/cm^{-1} 1753, 1714, 1652, 1436, 1361, 1267, 1245, 1224, 1206, 1174, 1157, 1110, 1055, 872 and 614; δ_H(C_6D_6) 1.49 (1 H, br ddd, J_{5e6a} 3.5, J_{5e6e} 4, J_{5a5e} 13.5, 5-H$_{eq}$), 1.85 (1 H, dddd, $J_{5a,4\text{-}CH}$ 1.5, J_{5a6e} 5.5, J_{5a6a} 10.5, J_{5a5e} 13.5, 5-H$_{ax}$), 2.69 (1 H, ddd, $J_{3a,4\text{-}CH}$ 1.5, J_{2a3a} 9.5, J_{3a3e} 14, 3-H$_{ax}$), 3.07 (1 H, ddd, J_{5e6a} 3.5, J_{5a6a} 10.5, J_{6a6e} 10.5, 6-H$_{ax}$), 3.26 and 3.37 (each 3 H, s, OCH$_3$), 3.79 (1 H, ddd, J_{5a6e} 4, J_{5a6e} 5.5, J_{6a6e} 10.5, 6-H$_{eq}$), 3.87 (1 H, dd, J_{2a3e} 3.5, J_{2a3a} 9.5, 2-H), 3.95 (1 H, br dd, J_{2a3e} 3.5, J_{3a3e} 3.5, J_{3a3e} 14, 3-H$_{eq}$) and 5.56 (1 H, br s, 4-CH); *m*/*z* (CI) 232 (M$^+$ + 18, 25%), 215 (M$^+$ + 100) and 200 (20).

(*E*)-2-(Hydroxymethyl)-4-(methoxycarbonylmethylene)-tetrahydro-2*H*-pyran 31

Sodium borohydride (71 mg, 1.88 mmol) was added to a solution of diester **27** (200 mg, 0.935 mmol) in tetrahydrofuran (15 cm^3) in one portion at 20 °C. The reaction was then immediately heated under reflux and methanol (3 cm^3) added over 1 h by syringe pump. The heat was removed, water (2 cm^3) was added, and, after concentration under reduced pressure, the residue was extracted with dichloromethane (3 × 5 cm^3). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (7:3), gave the *title compound* **31** (130 mg, 75%), mp 47–49 °C (Found: M$^+$ + NH$_4$, 204.1228. $C_9H_{18}NO_4$ requires *M*, 204.1236); ν_{max}(KBr disc)/cm^{-1} 3459, 1720, 1655, 1438, 1244, 1204, 1179, 1151, 1098 and 1059; δ_H 2.08–2.37 (4 H, br m, 3-H$_2$, 5-H$_{ax}$ and OH), 3.43–3.73 (4 H, m, 2-H, 6-H$_{ax}$ and 2-CH$_2$), 3.70

(3 H, s, OCH_3), 3.78 (1 H, br d, *J* 14.5, 5-H_{eq}), 4.17 (1 H, ddd, *J* 1.5, 6, 11, 6-H_{eq}) and 5.72 (1 H, s, 4-CH); *m/z* (CI) 204 ($M^+ + 18$, 100%) and 187 ($M^+ + 1$, 31).

Dimethyl 2-(but-3-ynyloxy)malonate 32

Dimethyl diazomalonate (8.4 g, 53 mmol) in benzene (40 cm^3) was added dropwise to rhodium acetate (trace) and but-3-ynol (3.5 g, 50 mmol) in benzene (80 cm^3) heated under reflux, over 15 min. The mixture was kept at reflux for 90 min before being cooled and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (2:1) gave the *title compound* **32** (6.2 g, 62%) (Found: $M^+ + NH_4$, 218.1024. $C_9H_{16}O_5N$ requires *M*, 218.1028); ν_{max}/cm^{-1} 3286, 2121 and 1748; δ_H 1.98 (1 H, t, *J* 2, 4′-H), 2.56 (2 H, dt, *J* 2, 7, 2′-H_2), 3.75 (2 H, t, *J* 7, 1′-H_2), 3.81 (6 H, s, 2 × OCH_3) and 4.60 (1 H, s, 2 H); *m/z* (CI) 218 ($M^+ + 18$, 100%) and 201 ($M^+ + 1$, 30).

Dimethyl 2-(but-3-ynyloxy)-2-(dimethylamino)malonate 33

Triethylamine (6.96 cm^3, 50 mmol) was added to a mixture of the 2-alkoxymalonate **32** (6.2 g, 31 m mol) and Eschenmoser's salt (8.35 g, 45 mmol) in dichloromethane (250 cm^3) at 20 °C. The mixture became homogeneous over 10 min and was stirred at 20 °C for 18 h before being concentrated at reduced pressure, dissolved in chloroform (150 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3). The aqueous washes were backwashed with dichloromethane (2 × 50 cm^3) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure to give the dimethylamine **33** which could be used without further purification. Flash chromatography, eluting with light petroleum–ether 3:2) gave the *title compound* **33** (7.0 g, 87%) (Found: $M^+ + H$, 258.1340. $C_{12}H_{20}O_5N$ requires *M*, 258.1341); ν_{max}/cm^{-1} 3289, 2122, 1743 and 1436; δ_H 1.95 (1 H, t, *J* 2, 4′-H), 2.33 (6 H, s, 2 × NCH_3), 2.56 (2 H, dt, *J* 2, 7, 2′-H_2), 2.94 (2 H, s, NCH_2), 3.74 (2 H, t, *J* 7, 1′-H_2) and 3.80 (6 H, s, 2 × OCH_3); *m/z* (CI) 258 ($M^+ + 1$, 100%) and 218 (5).

Methyl 2-(but-3-ynyloxy)prop-2-enoate 34

A solution of the dimethylamine **33** (7.0 g, 27 mmol) and iodomethane (16.8 cm^3, 0.27 mol) in acetonitrile (300 cm^3) was heated under reflux for 48 h then the mixture was cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane (150 cm^3) and washed with water (2 × 50 cm^3). The aqueous washes were backwashed with dichloromethane (2 × 50 cm^3) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (9:1) gave the *title compound* **34** (3.3 g, 79%) (Found: $M^+ + NH_4$, 172.0961. $C_8H_{14}O_3N$ requires *M*, 172.0970; ν_{max}/cm^{-1} 3290, 2123, 1738, 1625, 1328, 1204 and 1173; δ_H 2.04 (1 H, t, *J* 2.5, 4′-H), 2.69 (2 H, dt, *J* 2.5, 7.5, 2′-H_2), 3.82 (3 H, s, OCH_2), 3.90 (2 H, t, *J* 7.5, 1′-H_2) and 4.66 and 5.40 (each 1 H, d, *J* 3, 3-H); *m/z* (CI) 172 ($M^+ + 18$, 100%), 155 ($M^+ + 1$, 80) and 125 (80).

(*E*)- and (*Z*)-2-methoxycarbonyl-4-(triphenylstannylmethylene)-tetrahydro-2*H*-pyran 35 and 36 and (*E*)-2-methoxycarbonyl-2-methyl-2-(triphenylstannylmethylene)tetrahydrofuran 37

A solution of alkyne **34** (100 mg, 0.65 mmol) in benzene containing azoisobutyronitrile (trace) and triphenyltin hydride (250 mg, 0.712 mmol) was degassed with argon and subsequently heated under reflux for 1.5 h. The reaction mixture was then cooled and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (3:1) gave the cyclised products **35–37**, for yields see Table 1. The (*E*)-isomer of the *title compound* **35** had the following data: ν_{max}/cm^{-1} 1758, 1617, 1481, 1429, 1258, 1175, 1126, 1075, 730 and 700; δ_H 2.23 (1 H, m, 5-H_{eq}), 2.41 (1 H, br dt, *J* 5, 13, 5-H_{ax}), 2.63 (1 H, dd, *J* 10, 14, 3-H_{ax}), 2.83 (1 H, br dd, *J* 4, 14, 3-H_{eq}), 3.38 (1 H, dt, *J* 3, 11, 6-H_{ax}), 3.82 (3 H, s, OCH_3), 4.06 (1 H, ddd, *J* 4, 5, 11, 6-H_{eq}), 4.12 (1 H, dd, *J* 4, 10, 2-H), 5.98 (1 H, s, 4-CH) and 7.36–7.69 (15 H, m, ArH); *m/z* (CI) 507 ($M^+ + 1$, 10%) and 429 (100). The (*Z*)-isomer of the *title compound* **36** had the following data: ν_{max}/cm^{-1} 1759, 1714, 1617, 1481, 1430, 1369, 1260, 1205, 1177, 1134, 1075, 730 and 700; δ_H 2.39 (2 H, br m, 5-H_2), 2.67 (2 H, br m, 3-H_2), 3.55 (1 H, dt, *J* 3, 11, 6-H_{ax}), 3.58 (1 H, s, OCH_3), 3.82 (1 H, dd, *J* 4, 10, 2-H), 4.26 (1 H, ddd, *J* 4, 5, 11, 6-H_{eq}), 5.98 (1 H, s, 4-CH) and 7.37–7.70 (15 H, m, ArH); *m/z* (CI) 507 ($M^+ + 1$, 6%) and 429 (100). The (*E*)-isomer of the *title compound* **37** was a white solid, mp 77–78 °C (Found: M^+, 506.0898. $C_{26}H_{26}O_3S$ requires *M*, 506.0903); ν_{max}(KBR disc)/cm^{-1} 1735, 1621, 1481, 1429, 1253, 1122, 1075, 1060, 1044, 1022, 730 and 700; δ_H 1.68 (3 H, s, 2-CH_3), 2.57 (2 H, m, 4-H_2), 3.82 (3 H, s, OCH_3), 4.06 (2 H, m, 5-H_2), 6.40 (1 H, m, 3-CH) and 7.38–7.68 (15 H, m, ArH); *m/z* (CI) 507 ($M^+ + 1$, 8%) and 446 (16).

Methyl 6-*tert*-butyldimethylsilyloxy-5-hydroxyhex-2-ynoate 41

A solution of butyllithium (1.55 M in hexane; 2.58 cm^3, 4.0 mmol) was added dropwise to a solution of methyl propiolate (340 mg, 4.0 mmol) in tetrahydrofuran (5 cm^3) at −78 °C. After stirring at −78 °C for 30 min, boron trifluoride diethyl etherate (0.49 cm^3, 4.0 mmol) was added dropwise and the mixture stirred at −78 °C for 20 min. A solution of the epoxide **40** (0.5 g, 2.66 mmol) in tetrahydrofuran (5 cm^3) was added dropwise and the mixture stirred at −78 °C for 2 h. Saturated aqueous ammonium chloride (4 cm^3) was added and the mixture allowed to warm to 20 °C. The mixture was extracted into ether (3 × 10 cm^3), washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (7:3) gave the *title compound* **41** (470 mg, 65%) (Found: $M^+ + NH_4$, 290.1786. $C_{13}H_{28}O_4NSi$ requires *M*, 290.1787); ν_{max}/cm^{-1} 3416, 2240, 1719, 1436, 1258, 1121 and 1077; δ_H 0.10 [6 H, s, $Si(CH_3)_2$], 0.92 [9 H, s, $SiC(CH_3)_3$], 2.52 (1 H, d, *J* 6, OH), 2.58 (2 H, d, *J* 6.5, 4-H_2), 3.63 (1 H, dd, *J* 5.5, 10, 6-H), 3.72 (1 H, dd, *J* 4, 10, 6-H′), 3.77 (3 H, s, OCH_3) and 3.89 (1 H, m, 5-H); *m/z* (CI) 290 ($M^+ + 18$, 100) and 273 ($M^+ + 1$, 80).

Methyl 5-[bis(methoxycarbonyl)methoxy]-6-*tert*-butyldimethylsilyloxyhex-2-ynoate 42

Dimethyl diazomalonate (3.5 g, 22.2 mmol) in benzene (30 cm^3) was added dropwise to rhodium acetate (trace) and hydroxyester **41** (1.7 g, 6.25 mmol) dissolved in benzene (25 cm^3) heated under reflux over 20 min. The mixture was kept under reflux for 5 h before being cooled and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (7:3) gave the *title compound* **42** (1.98 g, 78%) (Found: $M + NH_4^+$, 420.2073. $C_{18}H_{34}O_8NSi$ requires *M*, 420.2054); ν_{max}/cm^{-1} 2241, 1750, 1717, 1437, 1259, 1126, 1077 and 839; δ_H 0.06 and 0.07 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 2.70 (2 H, m, 4-H_2), 3.77 (3 H, s, OCH_3), 3.78–3.82 (3 H, m, 6-H_2 and 5-H), 3.80 and 3.82 (each 3 H, s, 2 × OCH_3) and 4.94 (1 H, s, 1′-H); *m/z* (CI) 420 ($M^+ + 18$, 90%) and 403 ($M^+ + 1$, 100).

Methyl 6-*tert*-butyldimethylsilyloxy-5-[2-(dimethylamino)-1,1-bis(methoxycarbonyl)ethoxy]hex-2-ynoate 43

Triethylamine (0.56 cm^3, 4.00 mmol) was added to a mixture of the 2-alkoxymalonate **42** (1.0 g, 2.49 mmol) and Eschenmoser's salt (672 mg, 3.63 mmol) suspended in dichloromethane (40 cm^3) at 20 °C. The mixture became homogeneous over 10 min and was stirred at 20 °C for 18 h then concentrated under reduced pressure. The residue was dissolved in chloroform (40 cm^3) and the solution washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3). The aqueous washes were backwashed with chloroform (2 × 20 cm^3) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure to give the dimethylamine **43** which was used without

further purification. For characterisation, flash chromatography, eluting with light petroleum–ether (2:1) gave the *title compound* **43** (1.08 g, 95%); ν_{max}/cm^{-1} 2240, 1766, 1745, 1719, 1436, 1258, 1102, 838 and 730; δ_H 0.05 [6 H, s, Si(CH$_3$)$_2$], 0.88 [9 H, s, SiC(CH$_3$)$_3$], 2.30 (6 H, s, 2 × NCH$_3$), 2.73–3.00 (4 H, m, CH$_2$N and 4-H$_2$), 3.73 (2 H, m, 6-H$_2$), 3.75 (3 H, s, OCH$_3$), 3.78 and 3.80 (each 3 H, s, 2 × OCH$_3$) and 4.13 (1 H, m, 5-H); *m*/*z* (CI) 460 (M$^+$ + 1, 80%).

Methyl 6-*tert*-butyldimethylsilyloxy-5-[1-(methxoycarbonyl)-ethenyloxy]hex-2-ynoate 44

A solution of the dimethylamine **43** (1.34 g, 2.92 mmol) and iodomethane (1.82 cm^3, 29.2 mmol) in acetonitrile (70 cm^3) was heated under reflux for 72 h. The mixture was then cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 cm^3) and washed with water (2 × 25 cm^3). The aqueous washes were backwashed with dichloromethane (2 × 25 cm^3) and the organic extracts combined, dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (4:1) gave the *title compound* **44** (0.61 g, 79%) (Found: M$^+$ + H, 357.1732. C$_{17}$H$_{29}$O$_6$Si requires *M*, 357.1733); ν_{max}/cm^{-1} 2242, 1740, 1719, 1624, 1437, 1323, 1258, 1201, 1170, 1078 and 838; δ_H 0.08 and 0.09 (each 3 H, s, SiCH$_3$), 0.90 [9 H, s, SiC(CH$_3$)$_3$], 2.71 (1 H, dd, *J* 5.5, 17.5, 4-H), 2.83 (1 H, dd, *J* 6.5, 17.4, 4-H′), 3.77 (3 H, s, OCH$_3$), 3.80 (3 H, s, OCH$_3$), 3.82 (2 H, m, 6-H$_2$), 4.23 (1 H, m, 5-H) and 4.80 and 5.52 (each 1 H, d, *J* 3, 2′-H); *m*/*z* (CI) 374 (M$^+$ + 18, 41%) and 357 (M$^+$ + 1, 40).

Methyl (*E*)-6-*tert*-butyldimethylsilyloxy-5-[1-(methoxy-carbonyl)ethenyloxy]-3-(tributylstannyl)hex-2-enoate 45

Butyllithium (1.38 M in hexane; 2.32 cm^3, 3.20 mmol) was added dropwise to diisopropylamine (0.53 cm^3, 3.78 mmol) in tetrahydrofuran (10 cm^3) at 0 °C. After stirring at 0 °C for 5 min, tributyltin hydride (0.87 cm^3, 3.23 mmol) was added. After 15 min the solution was cooled to −48 °C and solid white copper(I) bromide–dimethyl sulfide complex (665 mg, 3.23 mmol) was added portionwise. After stirring at −48 °C for 20 min the reaction was cooled to −78 °C and the alkyne **44** (380 mg, 1.07 mmol) in tetrahydrofuran (5 cm^3) was added dropwise. After stirring at −78 °C for 3 h, methanol (3 cm^3) was added and the reaction warmed to 20 °C over 30 min. The mixture was added to an equal volume of water and filtered through Celite. The filtrate was extracted with ether (3 × 15 cm^3) and the organic extracts dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (1:19) gave the *title compound* **45** (566 mg, 82%); ν_{max}/cm^{-1} 1734, 1725, 1621, 1600, 1463, 1447, 1256, 1195, 1167, 1075, 838 and 778; δ_H 0.05 and 0.06 (each 3 H, s, SiCH$_3$), 0.86–1.52 [36 H, m, SiC(CH$_3$)$_3$ and Sn(C$_4$H$_9$)$_3$], 3.25 (2 H, m, 4-H$_2$), 3.71 (3 H, s, OCH$_3$), 3.72 (2 H, m, 6-H$_2$), 3.75 (3 H, s, OCH$_3$), 4.23 (1 H, m, 5-H), 4.75 and 5.41 (each 1 H, d, *J* 2.5, 2′-H) and 6.06 (1 H, s, 2-H).

Methyl (*E*)-6-*tert*-butyldimethylsilyloxy-3-iodo-5-[1-(methoxy-carbonyl)ethenyloxy]hex-2-enoate 46

Iodine (319 mg, 1.26 mmol) was added to a solution of the vinylstannane **45** (625 mg, 0.97 mmol) in ether (7 cm^3). The solution was stirred at 20 °C for 2 h then decolourised by washing with saturated aqueous sodium thiosulfate (1 × 3 cm^3). The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (9:1) gave the *title compound* **46** (439 mg, 94%); ν_{max}/cm^{-1} 1727, 1621, 1436, 1326, 1255, 1198, 1171, 838 and 779; δ_H 0.06 and 0.07 (each 3 H, s, SiCH$_3$), 0.89 [9 H, s, SiC(CH$_3$)$_3$], 3.45 (1 H, dd, *J* 5.5, 14.5, 4-H), 3.61 (1 H, dd, *J* 7, 14.5, 4-H′), 3.72 (3 H, s, OCH$_3$), 3.73 (1 H, dd, *J* 5, 11, 6-H), 3.77 (3 H, s, OCH$_3$), 3.85 (1 H, dd, *J* 5.5, 11, 6-H), 4.40 (1 H, m, 5-H), 4.91 and 5.46 (each 1 H, d, *J* 2.5, 2′-H) and 6.74 (1 H, s, 2-H).

(*E*)- and (*Z*)-6-*tert*-butyldimethylsilyloxymethyl-2-methoxy-carbonyl-4-(methoxycarbonylmethylene)tetrahydro-2*H*-pyran 47 and 48

A solution of the vinyl iodide **46** (200 mg, 0.41 mmol) in benzene (21 cm^3) containing azoisobutyronitrile (trace) and tributyltin hydride (0.122 cm^3, 0.46 mmol) was degassed with argon and subsequently heated under reflux for 45 min. The reaction was then cooled and concentrated under reduced pressure and the residue stirred rapidly with ether (5 cm^3) and saturated aqueous potassium fluoride (5 cm^3) for 1 h. The mixture was filtered, extracted with ether (3 × 5 cm^3), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (17:3) gave a mixture of (*E*)- and (*Z*)-4-(methoxycarbonylmethylene)tetrahydropyrans **47** and **48** (124 mg, 85%; **47**:**48** = 80:20). Samples of each isomer were obtained for characterisation. The (*E*)-isomer of the *title compound* **47** had the following data (Found: M$^+$ + H, 359.1890. C$_{17}$H$_{31}$Si$_6$ requires *M*, 359.1890): ν_{max}(CHCl$_3$)/cm^{-1} 1766, 1722, 1657, 1437, 1378, 1282, 1254, 1202, 1154, 1108, 1027, 837 and 780; δ_H(C$_6$D$_6$) 0.10 and 0.12 (each 3 H, s, SiCH$_3$), 0.99 [9 H, s, SiC(CH$_3$)$_3$], 1.91 (1 H, m, $J_{5a4\text{-}CH}$ 1.5, J_{3a5a} 1.5, J_{5a6a} 12, J_{5a5e} 13.5, 5-H$_{ax}$), 2.12 (1 H, m, $J_{3e4\text{-}CH}$ 1.5, J_{3e5e} 1.5, J_{2a3e} 2.5, J_{3a3e} 13.5, 3-H$_{eq}$), 2.21 (1 H, m, $J_{3a4\text{-}CH}$ 1.5, J_{3a5a} 1.5, J_{2a3a} 11.5, J_{3a3e} 13.5, 3-H$_{ax}$), 3.25 (1 H, m, 6-H$_{ax}$), 3.30 and 3.38 (each 3 H, s, OCH$_3$), 3.58 and 3.64 (each 1 H, dd, *J* 4.5, 11, 6-CH), 3.72 (1 H, dd, J_{2a3e} 2.5, J_{2a3a} 11.5, 2-H), 4.10 (1 H, m, $J_{5e4\text{-}CH}$ 1.5, J_{5e4a} 2, J_{5e5a} 13.5, 5-H$_{eq}$) and 5.60 (1 H, br s, 4-CH); *m*/*z* (CI) 376 (M$^+$ + 18, 34%) and 359 (M$^+$ + 1, 100). The (*Z*)-isomer **48** had the following data (Found: M$^+$ + H, 359.1893. C$_{17}$H$_{31}$SiO$_6$ requires *M*, 359.1890): ν_{max}(CHCl$_3$)/cm^{-1} 1764, 1722, 1657, 1438, 1361, 1253, 1206, 1173, 1154, 1107, 1021, 837 and 780; δ_H(C$_6$D$_6$) 0.09 and 0.11 (each 3 H, s, SiCH$_3$), 0.97 [9 H, s, SiC(CH$_3$)$_3$], 1.87 (1 H, m, $J_{5e,4\text{-}CH}$ 1.5, J_{3e5e} 1.5, J_{5e6a} 2, J_{5a5e} 13.5, 5-H$_{eq}$), 1.99 (1 H, m, $J_{5a,4\text{-}CH}$ 1.5, J_{5a6a} 12.5, J_{5a5e} 13.5, 5-H$_{ax}$), 2.22 (1 H, m, $J_{3a4\text{-}CH}$ 1.5, J_{3a5a} 1.5, J_{2a3a} 12, J_{3a3e} 14.5, 3-H$_{ax}$), 3.19 (1 H, m, 6-H$_{ax}$), 3.26 and 3.37 (each 3 H, s, OCH$_3$), 3.49 and 3.58 (each 1 H, dd, *J* 5, 11, 6-CH), 3.81 (1 H, dd, J_{2a3e} 2, J_{2a3a} 12, 2-H$_{ax}$), 4.47 (1 H, m, J_{3e2a} 1.5, J_{3e5e} 2, J_{3a3e} 14.5, 3-H$_{eq}$) and 5.65 (1 H, br s, 4-CH); *m*/*z* (CI) 376 (M$^+$ + 18, 42%) and 359 (M$^+$ + 1, 100).

(*E*)- and (*Z*)-6-*tert*-butyldimethylsilyloxymethyl-2-hydroxy-methyl-4-(methoxycarbonylmethylene)tetrahydro-2*H*-pyran 50 and 51

Sodium borohydride (13.7 mg, 0.36 mmol) was added in one portion to a solution of the diesters **47** and **48** (65 mg, 0.18 mmol) in tetrahydrofuran (4 cm^3) at 20 °C. The reaction was brought immediately to reflux and methanol (0.8 cm^3) was added over 1 h by syringe pump. The heat was then removed and water (2 cm^3) was added. After concentration under reduced pressure, the residue was extracted with dichloromethane (3 × 5 cm^3) and the extracts dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum–ether (11:9) gave a mixture of the alcohols **50** and **51** (39 mg, 65%; **50**:**51** = 80:20) which were separated for characterisation by HPLC. The (*E*)-isomer **50** had the following data (Found: M$^+$ + H, 331.1948. C$_{16}$H$_{31}$O$_5$Si requires *M*, 331.1941); ν_{max}(CHCl$_3$)/cm^{-1} 3396, 1721, 1652, 1436, 1362, 1255, 1154, 1106, 837 and 779; δ_H(C$_6$D$_6$) 0.14 [6 H, s, Si(CH$_3$)$_2$], 1.05 [9 H, s, SiC(CH$_3$)$_3$], 1.43 (1 H, br s, OH), 1.63 (1 H, m, 3-H$_{eq}$), 1.98 (2 H, m, 3-H$_{ax}$ and 5-H$_{ax}$), 3.23 (1 H, m, 6-H), 3.38 (3 H, m, 2-CH$_2$ and 2-H), 3.50 (3 H, s, OCH$_3$), 3.63 (2 H, m, 6-CH$_2$), 4.25 (1 H, m, 5-H$_{eq}$) and 5.73 (1 H, s, 4-CH); *m*/*z* (CI) 348 (M$^+$ + 18, 30%) and 331 (M$^+$ + 1, 100). The (*Z*)-isomer **51** had the following data (Found: M$^+$ + H, 331.1932. C$_{16}$H$_{31}$O$_5$Si requires *M*, 331.1941): ν_{max}(CHCl$_3$)/cm^{-1} 3469, 1721, 1652, 1437, 1362, 1253, 1205, 1176, 1153, 1104, 836 and 779; δ_H(C$_6$D$_6$) 0.13 [6 H, s, Si(CH$_3$)$_2$], 1.04 [9 H, s, SiC(CH$_3$)$_3$], 1.43 (1 H, br s, OH), 1.89–2.09 (3 H, m, 3-H$_{ax}$ and 5-H$_2$), 3.26–3.62 (6 H, m, 2-CH$_2$, 6-CH$_2$, 2-H and 6-H), 3.49 (3 H, s, OCH$_3$),

4.08 (1 H, m, 3-H_{eq}) and 5.80 (1 H, s, 4-CH); *m/z* (CI) 348 (M^+ + 18, 57%) and 331 (M^+ + 1, 100).

Methyl 5-hydroxy-6-(4-methoxybenzyloxy)hex-2-ynoate 53

Following the procedure outlined for the preparation of the 6-silyl analogue **41**, the *p*-methoxybenzyl ether of glycidol **52** (200 mg, 1 mmol) and methyl propiolate (131 mg, 1.6 mmol) gave the *title compound* **53** (200 mg, 72%) (Found: M^+, 278.1152. $C_{15}H_{18}O_5$ requires *M*, 278.1154); ν_{max}/cm^{-1} 3442, 2240, 1715, 1613, 1586, 1514, 1436, 1254, 1177, 1078, 822 and 753; δ_H 2.20 (1 H, br s, OH), 2.59 (2 H, *J* 6, 4-H_2), 3.48 (1 H, dd, *J* 9.5, 6, 6-H), 3.58 (1 H, dd, *J* 9.5, 4, 6-H′), 3.76 and 3.81 (each 3 H, s, OCH_3), 4.01 (1 H, m, 5-H), 4.49 (2 H, s, CH_2Ar) and 6.89 and 7.26 (each 2 H, d, *J* 8.5, ArH); *m/z* (EI) 278 (M^+, 8%).

Methyl 5-[bis(methoxycarbonyl)methoxy]-6-(4-methoxybenzyloxy)hex-2-ynoate 54

Following the procedure outlined for the preparation of the 2-alkoxymalonate **42**, the alcohol **53** (2.97 g, 11 mmol) was converted into the *title compound* **54** (3.14 g, 74%) (Found: $M^+ + NH_4$, 426.1752. $C_{20}H_{28}NO_9$ requires *M*, 426.1764); ν_{max}/cm^{-1} 2241, 1748, 1715, 1613, 1514, 1437, 1260, 1122, 1032 and 821; δ_H 2.71 (2 H, m, 4-H_2), 3.64 (2 H, m, 6-H_2), 3.75, 3.76, 3.79 and 3.81 (each 3 H, s, OCH_3), 3.93 (1 H, m, 5-H), 4.45 (2 H, s, CH_2Ar), 4.90 (1 H, s, 1′-H), and 6.89 and 7.21 (each 2 H, d, *J* 8.5, ArH); *m/z* (CI) 426 (M^+ + 18, 17%).

Methyl 6-(4-methoxybenzyloxy)-5-[1-(methoxycarbonyl)-ethenyloxy]hex-2-ynoate 56

Following the procedure outlined for the preparation of the dimethylamine **43**, the 2-alkoxymalonate **54** (123 mg, 0.3 mmol) gave the amine **55** (128 mg, 92%); ν_{max}/cm^{-1} 2240, 1744, 1716, 1613, 1514, 1436, 1259, 1101, 1036 and 821; δ_H 2.30 (6 H, s, 2 × NCH_3), 2.85–3.08 (4 H, m, NCH_2 and 4-H_2), 3.6 (2 H, m, 6-H_2), 3.66, 3.77, 3.81 and 3.84 (each 3 H, s, OCH_3), 4.30 (1 H, m, 5-H), 4.45 and 4.51 (each 1 H, d, *J* 9.5, HC*H*Ar), and 6.91 and 7.29 (2 H, d, *J* 8.5, ArH). This was converted into the *title compound* **56** (0.66 g, 70%) following the procedure outlined for the synthesis of the enol pyruvate **44** (Found: $M^+ + NH_4$, 380.1721. $C_{19}H_{26}NO_7$ requires *M*, 380.1709); ν_{max}/cm^{-1} 2241, 1716, 1624, 1587, 1514, 1438, 1254, 1202, 1171, 1079 and 821; δ_H 2.43 (1 H, dd, *J* 17, 5, 4-H), 2.55 (1 H, dd, *J* 17, 6.5, 4-H′), 3.31, 3.37 and 3.40 (each 3 H, s, OCH_3), 3.53 (2 H, d, *J* 5, 6-H_2), 4.10 (1 H, m, 5-H), 4.31 and 4.37 (each 1 H, d, *J* 12, HC*H*Ar), 4.46 and 5.53 (each 1 H, d, *J* 2.5, 2′-H), and 6.87 and 7.23 (each 2 H, d, *J* 8.5, ArH); *m/z* (CI) 380 (M^+ + 18, 23%).

Methyl (*E*)-6-(4-methoxybenzyloxy)5-[1-(methoxycarbonyl)-ethenyloxy]-3-tributylstannylhex-2-enoate 57

Following the procedure outlined for the synthesis of the vinyl stannane **45**, the alkyne **56** (1.35 g, 3.7 mmol) was converted into the *title compound* **57** (1.85 g, 76%) (Found: $M^+ - C_4H_9$, 597.1873. $C_{27}H_{41}O_7{}^{120}Sn$ requires *M*, 597.1874); ν_{max}/cm^{-1} 1716, 1620, 1589, 1514, 1463, 1438, 1249, 1196, 1169 and 823; $\delta_H(C_6D_6)$ 0.9–1.7 [27 H, m, $Sn(C_4H_9)_3$], 3.38, 3.45 and 3.48 (each 3 H, s, OCH_3), 3.56–3.84 (4 H, m, 4-H_2 and 6-H_2), 4.46 (2 H, s, CH_2Ar), 4.78 (1 H, m, 5-H), 4.89 and 5.62 (each 1 H, d, *J* 2, 2′-H), 6.46 (1 H, s, 2-H), and 6.87 and 7.31 (each 2 H, d, *J* 8.5, ArH); *m/z* (CI) 597 ($M^+ - 57$, 7%).

Methyl (*E*)-6-(4-methoxybenzyloxy)-3-iodo-5-[1-(methoxycarbonyl)ethenyloxy]hex-2-enoate 58

Following the procedure outlined for the synthesis of the vinyl iodide **46**, the vinyl stannane **57** (160 mg, 0.25 mmol) gave the *title compound* **58** (78 mg, 65%) (Found: $M^+ + NH_4$, 508.0829. $C_{19}H_{27}INO_7$ requires *M*, 508.0834); ν_{max}/cm^{-1} 1721, 1615, 1513, 1436, 1324, 1248, 1199, 1172 and 820; δ_H 3.49 (1 H, dd, *J* 14, 6, 4-H), 3.55–3.74 (3 H, m, 4-H′ and 6-H_2), 3.69, 3.78 and 3.81 (each 3 H, s, OCH_3), 4.51 (3 H, m, 5-H and CH_2Ar), 4.92 and 5.46 (each 1 H, d, *J* 2.5, 2′-H), 6.74 (1 H, s, 2-H), and 6.87 and 7.25 (each 2 H, d, *J* 8.5, ArH); *m/z* (CI) 508 (M^+ + 18, 55%).

1-(4-Methoxybenzyloxy)pent-4-yn-2-ol 59

Lithium acetylide–ethylene diamine complex (95%; 10.3 g, 106 mmol) was added to a solution of the epoxide **52** (10.19 g, 52 mmol) in tetrahydrofuran (24 cm^3) and dimethyl sulfoxide (33 cm^3) at 2 °C and the mixture was stirred at this temperature for 4 h. Brine was added and the mixture extracted with ether. The organic extracts were washed with aqueous hydrochloric acid (3 M) and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (3:1) gave the *title compound* **59** (10.86 g, 94%) (Found: M^+, 220.1104. $C_{13}H_{16}O_3$ requires *M*, 220.1099); ν_{max}/cm^{-1} 3438, 3291, 1613, 1587, 1514, 1303, 1249, 1176, 1105, 1035 and 820; δ_H 2.05 (1 H, t, *J* 3, 5-H), 2.3 (1 H, br s, OH), 2.45 (2 H, m, 3-H_2), 3.48 (1 H, dd, *J* 9.5, 7, 5-H), 3.59 (1 H, dd, *J* 9.5, 4, 5-H′), 3.81 (3 H, s, OCH_3), 3.98 (1 H, m, 2-H), 4.52 (2 H, s, CH_2Ar), 6.9 and 7.26 (each 2, d, *J* 8.5, ArH); *m/z* (CI) 238 (M^+ + 18, 17%) and 221 (M^+ + 1, 1).

4-*tert*-Butyldimethylsilyloxy-5-(4-methoxybenzyloxy)pentyne 60

The alcohol **59** (1.68 g, 7.6 mmol) in *N*,*N*-dimethylformamide (2 cm^3) was added to a solution of imidazole (0.79 g, 11.6 mmol) and *tert*-butyldimethylsilyl chloride (1.42 g, 9.4 mmol) in *N*,*N*-dimethylformamide (2 cm^3). The mixture was stirred for 18 h at room temperature, then saturated aqueous ammonium chloride was added under reduced pressure. Flash chromatography using light petroleum–ether (15:1) gave the *title compound* **60** (2.45 g, 96%) (Found: $M^+ + NH_4$, 352.2311. $C_{19}H_{34}NO_3Si$ requires *M*, 352.2308); ν_{max}/cm^{-1} 3311, 2122, 1614, 1587, 1514, 1465, 1363, 1302, 1250, 1174, 1124, 1038 and 838; δ_H 0.08 and 0.1 (each 3 H, s, $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.96 (1 H, t, *J* 2.5, 1-H), 2.35 and 2.48 (each 1 H, ddd, *J* 16.5, 6, 2.5, 3-H), 3.47 (2 H, m, 5-H_2), 3.81 (3 H, s, OCH_3), 3.96 (1 H, m, 4-H), 4.48 (2 H, s, CH_2Ar), and 6.88 and 7.27 (each 2 H, d, *J* 8.5, ArH); *m/z* (CI) 352 (M^+ + 18, 25%).

Methyl 5-*tert*-butyldimethylsilyloxy-6-(4-methoxybenzyloxy)-hex-2-ynoate 61

Butyllithium (1.6 M, 1.3 cm^3) in hexane was added to a solution of the alkyne **60** (0.63 g, 1.88 mmol) in tetrahydrofuran (1.1 cm^3) at −78 °C and the mixture stirred for 45 min. Methyl chloroformate (0.19 cm^3, 2.44 mmol) was added and the stirring continued for a further 20 min. The mixture was allowed to warm to room temperature and was stirred for 18 h. Saturated aqueous ammonium chloride was added and the mixture extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography using light petroleum–ether (10:1) gave the *title compound* **61** (0.625 g, 85%) (Found: $M^+ + NH_4$, 410.2356. $C_{21}H_{36}NO_5Si$ requires *M*, 410.2363); ν_{max}/cm^{-1} 2241, 1718, 1514, 1253 and 838; δ_H 0.08 and 0.11 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 2.49 (1 H, dd, *J* 17, 6, 4-H), 2.65 (1 H, dd, *J* 17, 5, 4-H′), 3.43 (2 H, m, 6-H_2), 3.76 and 3.81 (3 H, s, OCH_3), 4.01 (1 H, m, 5-H), 4.47 (2 H, s, CH_2Ar), and 6.87 and 7.25 (each 2 H, d, *J* 8.5, ArH); *m/z* (CI) 410 (M^+ + 18, 28%).

Concentrated hydrochloric acid (5 cm^3) was added to a solution of the silyl ether **61** (5.92 g, 15 mmol) in methanol (100 cm^3) at 0 °C and the mixture allowed to warm to room temperature and stirred for 2 h. Saturated aqueous sodium hydrogen carbonate was added and the mixture extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (1:3) gave the hydroxyester **53** (3.74 g, 89%).

Reductive cyclization of vinyl iodide 58

Following the procedure outlined for the cyclization of the vinyl iodide **46**, the vinyl iodide **58** (176 mg, 0.36 mmol) gave a mix-

ture of the tetrahydropyrans **62–64** (95 mg, 73%; **62:63:64** = 60:22:18) which were separated by HPLC for characterization. The 2,6-*cis*-(*E*)-isomer **62** had the following data: ν_{max}/cm^{-1} 1758, 1716, 1656, 1514, 1437, 1249, 1204, 1177, 1154, 1104, 1031 and 820; $\delta_H(C_6D_6)$ 2.05 (1 H, m, 5-H_{ax}), 2.19 (1 H, m, 3-H_{eq}), 2.31 (1 H, m, 3-H_{ax}), 3.37, 3.38 and 3.46 (each 3 H, s, OCH_3), 3.41–3.59 (3 H, m, 6-H and 6-CH_2), 3.82 (1 H, dd, *J* 11.5, 3, 2-H), 4.21 (1 H, d, *J* 14, 5-H_{eq}), 4.43 (2 H, s, CH_2Ar), 5.75 (1 H, s, 4-CH), and 6.86 and 7.29 (each 2 H, d, *J* 8.5, ArH). The 2,6-*cis*-(*Z*)-isomer **63** had the following data (Found: M^+, 364.1519. $C_{19}H_{24}O_7$ requires *M*, 364.1522); ν_{max}/cm^{-1} 1758, 1715, 1655, 1612, 1586, 1513, 1438, 1247, 1207, 1174, 1155, 1102, 1031 and 820; $\delta_H(C_6D_6)$ 1.95 (1 H, m, 5-H_{eq}), 2.07 (1 H, m, 5-H_{ax}), 2.3 (1 H, m, 3-H_{ax}), 3.34, 3.40 and 3.45 (each 3 H, s, OCH_3), 3.32–3.55 (3 H, m, 6-H and 6-CH_2), 3.92 (1 H, dd, *J* 11.5, 2.5, 2-H), 4.44 (2 H, s, CH_2Ar), 4.54 (1 H, m, 3-H_{eq}), 5.68 (1 H, s, 4-CH), and 6.88 and 7.29 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (CI) 382 (M^+ + 18, 51%). The 2,6-*trans*-(*E*)-isomer **64** had the following data: ν_{max}/cm^{-1} 1744, 1713, 1657, 1612, 1513, 1436, 1367, 1245, 1206, 1174, 1150, 1094, 1031 and 818; $\delta_H(C_6D_6)$ 2.24 (1 H, ddd, *J* 13, 6.5, 1, 3-H_{eq}), 2.36–2.52 (2 H, m, 3-H_{ax} and 5-H_{ax}), 3.29, 3.37 and 3.42 (each 3 H, s, OCH_3), 3.49 (1 H, m, 6-H), 3.56 (2 H, m, 6-CH_2), 4.07 (1 H, dd, *J*, 14, 2.5, 5-H_{eq}), 4.40 (1 H, m, 2-H), 4.42 (2 H, s, CH_2Ar), 5.84 (1 H, s, 4-CH), and 6.86 and 7.30 (each 2 H, d, *J* 8.5, ArH).

Acknowledgements

We thank the EPSRC and Glaxo-Wellcome for a CASE Award (to S. P. M.) and Rhône Poulenc Rorer for a studentship (to R. J. M.).

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Paper 8/03422B
Received 6*th May* 1998
Accepted 26*th June* 1998