Tetrahedron Vol. 48, No. 43, pp. 9461-9472, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

A Synthesis of the Hexahydrobenzofuran Portion of the Avermectins I. Model Studies

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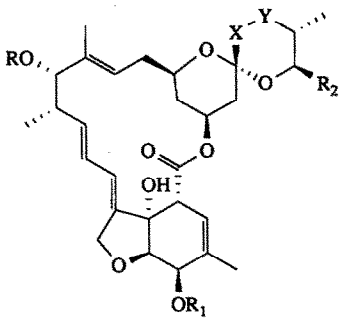
(*Received in UK* 17 *August* 1992)

Abstract: A tandem radical cyclisation has been used to construct a model for the synthesis of the hexahydrobenzofuran moiety present in the avermectins.

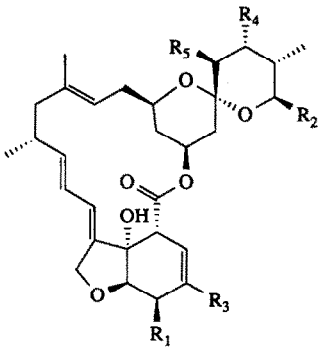
INTRODUCTION

Parasitic diseases in animals and man constitute serious problems worldwide. Hitherto most treatments have proved unsatisfactory[1] and an important breakthrough in this area came with the discovery of the avermectins (I)[2] and milbemycins of general structure (II)[3] (three examples cited here).



I

Avermectins	R= - L - Oleandrosyl - L - Oleandrosyl		
	R_1	R_2	X-Y
Avermectin A1a	Me	Bu^s	CH=CH
Avermectin A1b	Me	Pr^i	CH=CH
Avermectin A2a	Me	Bu^s	CH_2-CH(OH)
Avermectin A2b	Me	Pr^i	CH_2-CH(OH)
Avermectin B1a	H	Bu^s	CH=CH
Avermectin B1b	H	Pr^i	CH=CH
Avermectin B2a	H	Bu^s	CH_2-CH(OH)
Avermectin B2b	H	Pr^i	CH_2-CH(OH)



II

Milbemycins

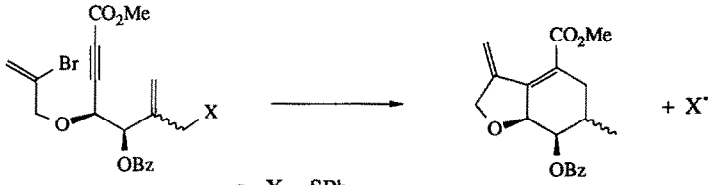
	R_1	R_2	R_3	R_4	R_5
Milbemycin α_1	OH	Me	Me	H	H
Milbemycin α_2	OMe	Me	Me	H	H
Milbemycin α_3	OH	Et	Me	H	H

The avermectins were isolated in 1979[2] during an intensive programme of screening actinomycetes isolated from Japanese soil. These natural products were shown to possess exceedingly potent antiparasitic activity coupled with a highly desirable low toxicity. Intense synthetic interest followed[4,5] and has culminated in the total syntheses of avermectin by Danishefsky[6], Ley[7], White[8], Hanessian[9], and their co-workers.

Existing routes to the hexahydrobenzofuran unit of avermectins are rather long, however, and we initiated model studies in this area[10] in order to develop a relatively short approach to this unit. In this paper we present the results of our model studies together with the assignment of relative stereochemistry as determined by nOe studies.

THE TANDEM RADICAL CYCLISATION APPROACH

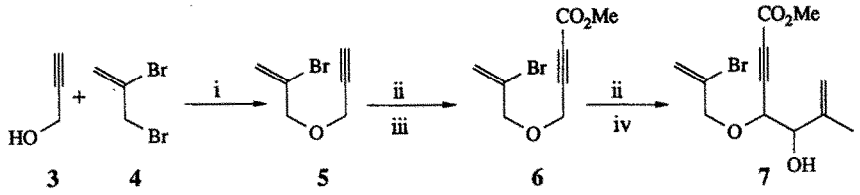
Through choice of an appropriate leaving group (*e.g.* X=SPh) a tandem radical cyclisation/elimination reaction of ester (1) should give the desired hexahydrobenzofuran. This paper will detail our initial model studies on the tandem cyclisation of ester 1b (X=H).



1 a X = SPh, b X = H; Bz= $PhCH_2$ **2**

Scheme 1

We thought that we could assemble the ester 1b rapidly by following the route set out in Scheme 2.



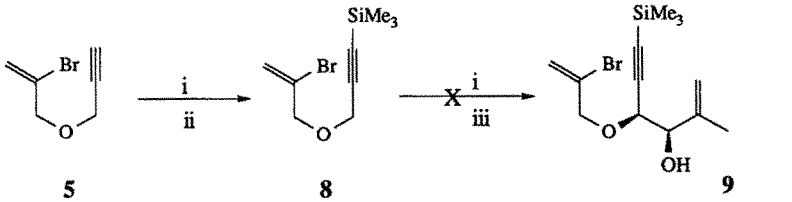
3 4 5 6 7

Reagents (i) 50% NaOH (aq)/CH_2Cl_2/CETAB (ii) n-BuLi

(iii) MeOCOCl (iv) methacrolein

Scheme 2

Phase transfer mediated[11] etherification of propargyl alcohol (3) with 2,3-dibromo-1-propene (4) gave the ether (5) in 60% isolated yield. When the ether (5) was treated with n-BuLi (1.1 mol. eq.) followed by inverse addition of the resulting anion to methyl chloroformate, the ester (6) was isolated in 78% yield. Attempted conversion of (6) into the alcohol (7) failed, always resulting in the decomposition of ether (6). It was decided to make the silane (8) since the propargylic anion derived from (8) should be harder and hence react more readily with methacrolein. (Scheme 3)

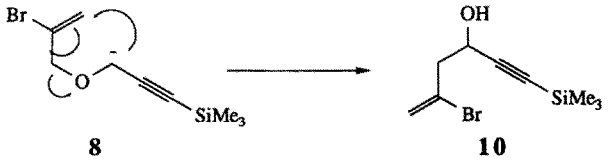


5 8 9

Reagents: (i) n-BuLi (ii) Me_3SiCl (iii) methacrolein

Scheme 3

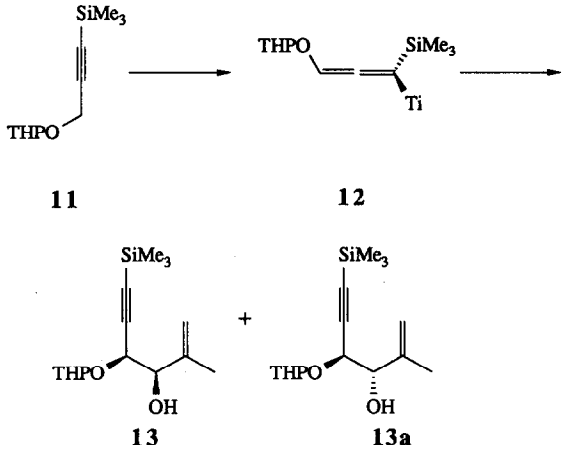
The ether (5) was smoothly converted into the silane (8) by sequential treatment of (5) with n-BuLi and then chlorotrimethylsilane. Attempted metallation of (8) with n-BuLi at -78°C followed by addition of methacrolein resulted in the clean formation of the homoallylic alcohol (10); none of the desired allylic alcohol (9) was formed due to a facile 2,3-sigmatropic rearrangement occurring in preference to alkylation[12] (Scheme 4).



8 10

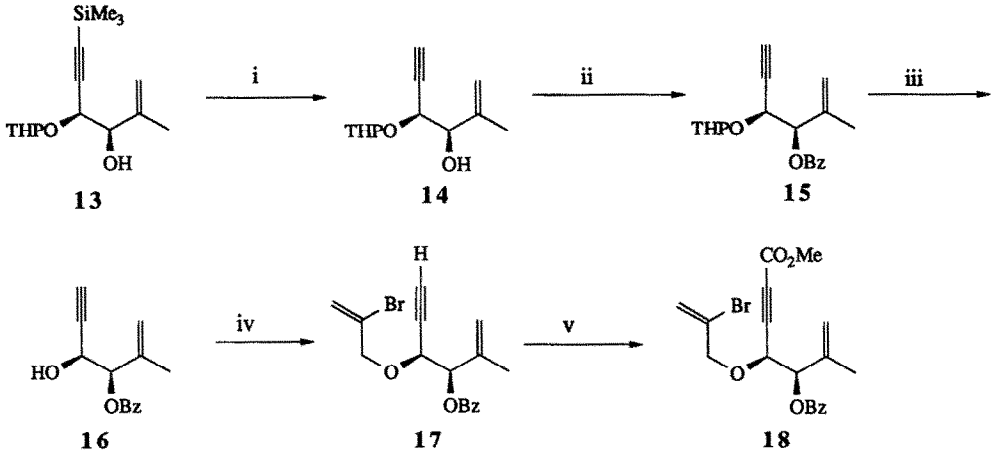
Scheme 4

In the light of our observations we were forced to redesign our route to the allylic alcohol (7). Yamamoto[13] has reported the regio and stereo controlled addition of the allenic titanium reagent (12) to aldehydes resulting in a greater than 7:1 ratio of isomeric alcohols in favour of the erythro isomer. Deprotonation of the silane (11)[13] with t-BuLi followed by the addition of freshly distilled titanium (IV) isopropoxide gave the allenyl titanium species (12) which was quenched with methacrolein. In our hands a 10:1 ratio of alcohols was obtained in 86% yield in favour of the desired erythro isomer. (Scheme 5).



Scheme 5

Treatment of the silane (13) with NaOH/MeOH gave the alcohol (14) (98%) which was converted into the benzyl ether (15). Removal of theTHP protecting group in (15) was achieved with methanolic HCl (90% yield). The resulting alcohol (16) was converted into the ether (17) under phase transfer conditions. Conversion of (17) into the key ester (18) (n-BuLi and then methyl chloroformate) proved to be capricious until we discovered that inverse addition of the acetylenic anion to methyl chloroformate gave a reproducible yield of 67% of the desired ester (18) (Scheme 6).

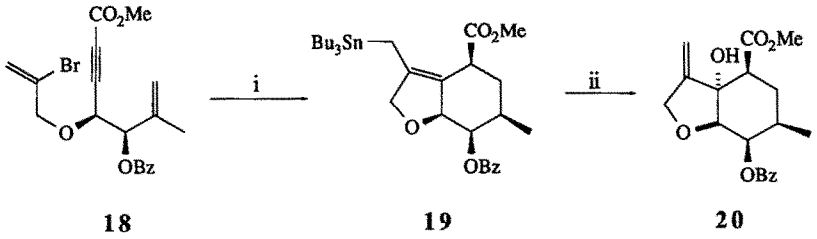


Reagents: (i) NaOH/MeOH , (ii) NaH/BzBr/DME , (iii) HCl/MeOH ,
(iv)  /CH_2Cl_2/50% NaOH/CETAB, (v) n-BuLi, then MeOCOCl

Scheme 6

With the ester (18) in hand we were able to test the linear tandem radical cyclisation. Using one equivalent of Bu_3SnH in benzene we found that none of the desired bicyclic ester (2) was formed; instead, the more desirable allyl stannane (19) was isolated in 15% yield.

When this reaction was repeated using two equivalents of Bu_3SnH at a concentration of 15 mmol, the stannane (19) was isolated in 43% yield.

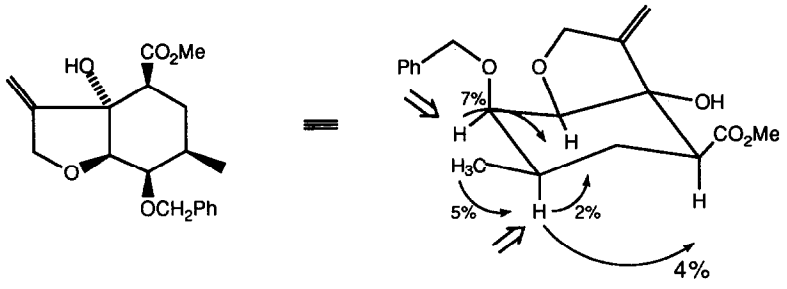


Reagents: (i) Bu_3SnH (2 equiv), AIBN, C_6H_6, (ii) m-Nitroperoxybenzoic acid, Et_2O, -78°C ⟶ rt.

Scheme 7

Isolation of the allylic stannane was indeed an added bonus because we felt that by analogy with allyl silane chemistry [14], the allyl stannane (19) could perhaps be converted into the desired tertiary alcohol (20). This would complete our initial model studies in this area. Conversion of (19) into (20) proved to be fraught with difficulties; the usual epoxidising agents (peracetic acid, m-chloroperoxybenzoic acid) failed to give the tertiary alcohol (20). Eventually we found that m-nitroperoxybenzoic acid clearly converted the allylstannane (19) into the alcohol (20) (Scheme 7).

At this point in time we were still unsure about the stereochemistry of alcohol (20). Detailed nOe studies revealed that the one diastereomer formed in this reaction had the correct relative stereochemistry at three centres, but was epimeric at the carbonyl centre (Figure 1, Table 1). The key nOe experiments are shown in Figure 1. The strong nOe observed between the hydrogens at C-5 and C-6 proves them to be *cis* and hence confirms the erythro selectivity of the titanium mediated coupling reaction used to form alcohol (13).



20 **20**

Figure 1.

EXPERIMENTAL

Where appropriate, reactions were conducted under an atmosphere of nitrogen in dry glassware. Ethers were distilled from sodium benzophenone ketyl, benzene and dichloromethane from CaH_2. For the radical cyclisation reactions, the benzene was degassed with argon.

Thin layer chromatography (tlc) was carried out using Merck Kieselgel 60H silica plates (25 mm thickness) and visualized by U.V., ceric sulphate, vanilin or potassium permanganate. Two methods of quantitative chromatographic separations were used: (a) suction flash chromatography using Merck Kieselgel 60H (art 7736) and (b) flash column chromatography on Silica Gel 60 (230-400 mesh)[15]. The melting points (m.p.) were recorded on an Electrothermal apparatus and are not corrected. The solvent in parenthesis refers to the solvent used for recrystallisation. Infrared (i.r.) spectra were taken on a Perkin-Elmer 298 spectrometer. Their spectra were standardised using a polystyrene film.

The proton nuclear magnetic spectra were recorded at either 60 MHz on a Perkin-Elmer R24B spectrometer, or at 270 MHz on a Jeol JMM GX270, or at 360 MHz on the Bruker AM360. All proton spectra were recorded using either tetramethylsilane (δ = O) or residual chloroform (δ = 7.27) as standard. The carbon-13 n.m.r. spectra were recorded at 90.56 MHz on a Bruker AM360, or at 63.9 MHz on a Jeol JMM GX270. Dept 135 and Dept 90 pulse sequences were used to aid spectral identification. Mass spectra were taken on a Kratos MS30 spectrometer using a DS55S data system or on a V.G. 70-250-S.E. double focussing mass spectrometer.

1-[2-Bromo-2-propen-1-yloxy]-prop-2-yne (5). Propargyl alcohol (7.0 cm^3, 120 mmol) was added to a vigorously stirred solution of dichloromethane (120 cm^3) and 50% aqueous sodium hydroxide solution (120 cm^3), containing cetyltrimethylammonium bromide (6.50 g, 0.15 mol. eq.). After 10 minutes, 2,3-dibromo-1-propene (12.5 cm^3, 1 mol. eq.) was added and stirring continued for a further 60 minutes. The

organic layer was then separated and the aqueous layer extracted with dichloromethane (2 x 30 cm^3). The combined organic extracts were dried over magnesium sulphate, and the solvent removed by distillation, at atmospheric pressure. Purification by suction flash chromatography (40:1 petrol/ether eluant) gave *1-[2-bromo-2-propen-1-yloxy]-prop-2-yne* (5) as a colourless oil (13.20 g, 63%). (The product was prone to decomposition on distillation). b.p. 115-120°C at 760 mm Hg. IR (film) 3300s, 2130s, 1625m, 1450m, 1100br s, 900s cm^{-1}. δ_H (100 MHz, $CDCl_3$) 6.10 (1H, m, $CBr=CH_2$), 5.7 (1H, d, J 2Hz, $CBr=CH_2$), 4.3 (4H, br d, OCH_2), 2.5 (1H, t, $J_{1,3}$ 3Hz, C-1). m/z (E.I.) 176 (3.5%, $[M(^{81}Br)]^+$), 174 (3%, $[M(^{79}Br)]^+$), 95 (7.9%, $[M-Br]^+$). HRMS found 173.9679; C_6H_7BrO requires 173.9681.

Methyl-4-[2-bromo-2-propen-1-yloxy]-2-butynoate (6). n-BuLi (1.55 M, 14.2 cm^3, 1.1 mol. eq.) was added dropwise to a solution of the acetylene (5)[6] (3.50 g, 20 mmol) in ether (25 cm^3) at -78°C. The temperature was allowed to warm to -20°C, then cooled back to -78°C and the contents of the flask transferred via double ended needles to a solution of methyl chloroformate (3.1 cm^3, 2 mol. eq.) in ether (5 cm^3) at -78°C. The flask was allowed to warm to room temperature over 2 hours and its contents poured into water (5 cm^3). The organic phase was separated and the aqueous phase extracted with ether (3 x 20 cm^3). The combined organic extracts were dried over magnesium sulphate and the solvent removed *in vacuo*. Purification by flash column chromatography (6:1 petrol/ether eluant) gave *methyl-4-[2-bromo-2-propen-1-yloxy]-2-butynoate* (6) as a colourless oil (2.10 g, 45%). IR (CH_2Cl_2) 2960m, 2150m, 1720s, 1440br m, 1300br s, 1100s, 1070s cm^{-1}. U.V. (hexane) 198nm (ε 1430 $dm^3mol^{-1}cm^{-1}$). δ_H (360 MHz, $CDCl_3$) 5.96 (1H, t, J 1.6Hz, $CBr=CH_2$), 5.68 (1H, t, J 1.4Hz, $CBr=CH_2$), 4.34 (2H, br s, $C(Br)-CH_2O$), 4.22 (2H, br s, $OCH_2-C\equiv C$), 3.8 (3H, s, OCH_3). HRMS found 231.9731; $C_8H_9BrO_3$ requires 231.9735.

1-[2-Bromo-2-propen-1-yloxy]-3-trimethylsilyl-prop-2-yne (8). n-BuLi (1.55 M, 14.2 cm^3, 1.1 mol. eq.) was added dropwise to a solution of the acetylene (5) (3.50 g, 20 mmol) in ether (25 cm^3) at -70°C. After stirring for 30 minutes, chlorotrimethylsilane (2.8 cm^3, 1.1 mol. eq.) was added to the resulting yellow solution. The flask was allowed to warm to room temperature and its contents poured into water (50 cm^3), with the organic layer being separated. Extraction of the aqueous phase with ether (3 x 10 cm^3), followed by drying of the combined organic phases over magnesium sulphate, and removal of the solvent *in vacuo* gave the crude product. Purification by suction flash column chromatography (50:1 petrol/ether eluant) gave *1-[2-bromo-2-propen-1-yloxy]-3-trimethylsilyl prop-2-yne* (8) as a colourless oil (3.90 g, 80%). IR (film) 2980s, 2190m, 1640w, 1350m, 1255s, 1100s, 1000br m, 900 br s cm^{-1}. δ_H (60 MHz, $CDCl_3$) 5.95 (1H, m, $CBr=CH_2$), 5.60 (1H, d, J 2Hz, $CBr=CH_2$), 4.20 (4H, br s, OCH_2), 0.2 (9H, s, $Si(CH_3)_3$). HRMS found 246.0072, $C_9H_{15}BrOSi$ requires 246.0075.

5-Bromo-1-trimethylsilyl-5-hexen-1-yn-3-ol (10). n-BuLi (1.55 M, 0.57 cm^3, 1.1 mol. eq.) was added dropwise to a solution of the silylated acetylene (8) (0.20 g, 0.8 mmol) in ether (20 cm^3) at -60°C. The solution was stirred at this temperature for 90 minutes before adding sat. ammonium chloride solution (5 cm^3). After warming to room temperature the aqueous phase was extracted with ether (3 x 10cm^3) and the combined ethereal extracts dried over magnesium sulphate. Removal of the solvent *in vacuo*, followed by purification by flash column chromatography (5:1 petrol/ether eluant) gave *5-bromo-1-trimethylsilyl-5-hexen-1-yn-3-ol* (10) as a

colourless oil (0.13 g, 65%). IR (CH_2Cl_2) 3600 br s, 2990s, 2190m, 1640s, 1390br m, 1250m, 1205m, 1100br s, 850br s cm^{-1}. δ_H (100 MHz, $CDCl_3$) 5.65 (1H, d, J 2Hz, $=CH_2$), 5.5 (1H, d, J 2Hz, $=CH_2$), 4.6 (1H, m, D_2O shake gave t, $J_{3,4}$ 6Hz, C-3), 2.75 (2H, d, $J_{3,4}$ 6Hz, C-4), 2.05 (1H, d, $J_{4,OH}$ 6Hz, collapse on D_2O shake, OH), 0.2 (9H, s, $Si(CH_3)_3$). HRMS found 246.0079, C9H15BrOSi requires 246.0076.

5-Methyl-3-(tetrahydro-2-pyranyloxy)-1-trimethylsilyl-5-hexen-1-yn-4-ol (13) t-BuLi (1.4 M, 19.2 cm^3, 1.2 mol. eq.) was added dropwise to a solution of the acetylene (11) (4.77 g, 22.5 mmol) in THF (120 cm^3) at -78°C. The resulting red solution was stirred at this temperature for 10 minutes then cooled to - 85°C, before adding titanium (IV) isopropoxide (6.7 cm^3, 1 mol. eq.) dropwise. After stirring at -80°C for 10 minutes, methacrolein (1.9 cm^3, 1 mol. eq.) was added dropwise and the solution allowed to warm to room temperature over one hour. The solution was diluted with ether (100 cm^3), then dilute hydrochloric acid added dropwise until precipitation of titanium salts stopped. These salts then were removed by filtration through celite. The ethereal solution was dried over sodium sulphate, and the solvent removed *in vacuo*. Purification by flash column chromatography (8:1 petrol/ether eluant) gave *threo-5-methyl-3-(tetrahydro-2-pyranyloxy)-trimethylsilyl-5-hexen-1-yn-4-ol* (13a) as a colourless oil (0.49 g, 8%). IR (film) 3450br m, 2960s, 2080w, 1650w, 1400s, 1230m, 1200s, 1120s, 1060br s, 850br s cm^{-1}. δ_H (360 MHz, $CDCl_3$) 4.93 (1H, br s, C-6), 4.80 (1H, br s, C-6), 4.71 (1H, t, J 3.0Hz, OCHO), 4.30 (1H, d, $J_{3,4}$ 4.4Hz, C-3), 4.05 (1H, d, $J_{4,3}$ 4.4Hz, C-4), 3.85 (1H, m, OCH_2), 3.39 (1H, m, OCH_2), 3.02 (1H, br s, OH), 1.6 (3H, s, CH_3-5), 1.5-1.3 (6H, m, CH_2), 0.1(9H, s, $Si(CH_3)_3$). Further elution of the column gave *erythro-5-methyl-3-(tetrahydro-2-pyranyloxy)-1-trimethylsilyl-5-hexen-1-yn-4-ol)* (13) as a colourless solid (4.96 g, 78%) (erythro:threo 10:1). Erythro-isomer m.p. 58-59°C (n-hexane); IR (CH_2Cl_2) 3460br m, 2960s, 2090w, 1650w, 1400s, 1250s, 1200s, 1120s, 1050br s, 850br s cm^{-1}. δ_H (360 MHz, $CDCl_3$) 5.11 (1H, br s, C-6), 4.98 (1H, br s, C-6), 4.89 (1H, t, J 3.3Hz, OCHO), 4.46 (1H, d, $J_{3,4}$ 4.3Hz, C-3), 4.20 (1H, t, J 3.7Hz, C-4), 4.02 (1H, dt. J 2.9Hz, J 9.5Hz, OCH_2), 3.57 (1H, m, OCH_2), 3.17 (1H, d, $J_{4,OH}$ 3.6Hz, OH), 1.79 (3H, s, CH_3-5), 1.6-1.4 (6H, m, CH_2), 0.1 (9H, s, $Si(CH_3)_3$). δ_C (90.1 MHz, $CDCl_3$) 143.2 (s, C-5), 113.7 (t, C-6), 98.2 (d, OCHO), 76.7 (d, C-3), 72.4 (d, C-4), 63.1 (t, OCH_2), 30.8 (t), 25.8 (t), 19.7 (q, CH_3-5), 19.3 (t), 0.26 (q, $Si(CH_3)_3$) quaternary acetylene peaks not seen even on increasing T_1. m/z (E.I.) 181 (3%, $[M\text{-}THP\text{-}OH]^+$), 85 (100%, $[DHP]^+$). Found: C, 63.8%; H, 9.3%. $C_{15}H_{26}O_3Si$ requires C, 63.8%; H, 9.0%.

Erythro-5-methyl-3-(tetrahydro-2-pyranyloxy)-5-hexen-1-yn-4-ol (14) Aqueous sodium hydroxide (1M, 40 cm^3, 1.4 mol. eq.) was added, with stirring to a solution of the acetylene (13) (8.06 g, 28 mmol) in methanol (150 cm^3) at room temperature. After stirring for 60 minutes, dilute hydrochloric acid was added to pH7. The reaction mixture was diluted with water (100 cm^3), then extracted with dichloromethane (5 x 50 cm^3). The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Purification by flash column chromatography (3:1 petrol/ether eluant) gave *erythro-5-methyl-3-(tetrahydro-2-pyranyloxy)-5-hexen-1-yn-4-ol* (14) as a colourless oil (5.80 g, 98%). IR (CH_2Cl_2) 3600m, 3450br s, 3310m, 2980s, 1970m, 1650m, 1450s, 1360s, 1130s, 1080s, 1050br s, 910s cm^{-1}. δ_H (360 MHz, $CDCl_3$) 5.17 (1H, br s, C-6), 5.01 (1H, br s, C-6), 4.92 (1H, t, J 3.4Hz, OCHO), 4.54 (1H, dd, $J_{3,4}$ 3.9Hz, $J_{3,1}$ 2.2Hz, C-3), 4.24 (1H, br s, OH), 4.02 (1H, m, OCH_2), 3.59 (1H, m, OCH_2), 3.31 (1H, d, $J_{4,3}$ 3.3Hz, C-4), 2.54 (1H, d, $J_{1,3}$ 2.1Hz, C-1), 1.64 (3H, s, CH_3-5), 1.55-1.45 (6H, m, CH_2). δ_C (90.1 MHz, $CDCl_3$) 142.4 (s, C-5), 113.4 (t, C-6),

97.7 (d, OCHO), 79.6 (s, C-2), 76.3 (d, C-3), 76.0 (d, C-1), 71.2 (d, C-4), 62.9 (t, OCH_2), 30.5 (t), 25.3 (t), 19.3 (t), 19.1 (q, CH_3-5). m/z (FAB) 233 (2.4%, $[M+Na]^+$), 211 (3.9%, $[M+H]^+$), 107 (8.8%, [M-THP-OH]$^+$), 85 (100%, $[DHP]^+$). HRMS found 210.1258, $C_{12}H_{18}O_3$ requires 210.1256.

Erythro-4-benzyloxy-5-methyl-3-(tetrahydro-2-pyranyloxy)-5-hexen-1-yne (15). The alcohol (14) (5.67g, 27 mmol) in DME (10 cm^3) was added dropwise to an ice cooled suspension of sodium hydride (60% dispersion; 1.29 g, 1.2 mol. eq.) in DME (100 cm^3). After effervescence had ceased, stirring was continued for a further 10 minutes, before adding benzyl bromide (3.5 cm^3, 1.1 mol. eq.). The solution was stirred at room temperature for 1 hour. before adding water (20 cm^3) and extracting with ether (4 x 50 cm^3). The combined organics were washed with sat. sodium chloride solution (30 cm^3), dried over magnesium sulphate then concentrated *in vacuo*. Purification by flash column chromatography (8:1 petrol/ether eluant) gave *erythro-4-benzyloxy-5-methyl-3-(tetrahydro-2-pyranyloxy)-5-hexen-1-yne* (15) as a colourless oil (7.19 g, 89%). IR (CH_2Cl_2) 3320m, 3040m, 2960s, 2060w, 1680w, 1650w, 1600w, 1460s, 1210s, 1170br s, 1070 v br s, 1030s, 910s cm^{-1}. δ_H (360 MHz, $CDCl_3$), 7.32 (5H, m, ArH), 5.10 (1H, br s, C-6), 5.06 (1H, br s, C-6), 4.72 (1H, t, J 3.3Hz, OCHO), 4.61 (1H, d, J_{gem} 12.2Hz, $PhCH_2O$), 4.44 (1H, dd, $J_{3,4}$ 6.2Hz, $J_{3,1}$ 1.9Hz, C-3), 4.39 (1H, d, J_{gem} 12.2Hz, $PhCH_2O$), 4.00 (1H, m, OCH_2), 3.88 (1H, d, $J_{4,3}$ 6.1Hz, C-4), 3.52 (1H, m. OCH_2), 2.43 (1H, d, $J_{1,3}$ 1.9Hz, C-1), 1.77 (3H, s, CH_3-5), 1.6-1.4 (6H, m, CH_2). δ_C (90.1 MHz, $CDCl_3$) 142.4 (s, C-5), 113.4 (t, C-6), 97.7 (d, OCHO), 79.6 (s, C-2), 76.3 (d, C-3), 76.0 (d, C-1), 71.2 (d, C-4), 62.9 (t, OCH_2), 30.5 (t), 25.3 (t), 19.3 (t), 19.1 (q, CH_3-5). m/z (FAB) 301 (4.5%, $[M+H]^+$), 91 (76.5%, $[C_7H_7]^+$), 85 (100%, $[DHP]^+$). HRMS found 300.1725, $C_{19}H_{24}O_3$ requires 300.1725.

Erythro-4-benzyloxy-5-methyl-5-hexen-1-yn-3-ol (16). Dilute hydrochloric acid (2 M, 0.5 cm^3, 0.04 mol. eq.) was added to a stirred solution of the acetylene (15) (7.20 g, 24 mmol) in methanol (150 cm^3). After 15 minutes sodium hydroxide solution (2 M) was added to pH7. The reaction mixture was diluted with water (50 cm^3) and extracted with dichloromethane (3 x 50 cm^3). The combined extracts were washed with sat. sodium chloride solution (30 cm^3), then dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol/ether eluant) gave *erythro-4-benzyloxy-5-methyl-5-hexen-1-yn-3-ol* (16) as a colourless oil (4.64 g, 90%). IR (KBr disc) 3400br m, 3250s, 3050m, 2950m, 2125w, 1650w, 1500m, 1460s, 1380m, 1090br s, 910m, 640m, cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.25 (5H, m, ArH), 5.10 (1H, t, J 1.5Hz, C-6), 5.06 (1H, br s, C-6), 4.60 (1H, d, J_{gem} 11.9Hz, OCH_2Ph), 4.37 (1H, ddd, $J_{3,OH}$ 7.1Hz, $J_{3,4}$ 5.3Hz, $J_{3,1}$ 2.1Hz, C-3), 4.31 (1H, d, J_{gem} 11.8Hz, OCH_2Ph), 3.84 (1H, d, $J_{4,3}$ 5.4 Hz, C-4), 2.40 (1H, d, $J_{1,3}$ 2.2Hz, C-1), 2.31 (1H, d, $J_{OH,4}$ 7.3Hz, OH), 1.74 (3H, s, CH_3-5). δ_C (90.1 MHz, $CDCl_3$) 141.5 (s, C-5), 139.5 (s, Ar), 128.7 (d, Ar), 128.1 (d, Ar), 127.9 (d, Ar), 116.3 (t, C-6), 84.3 (t, OCH_2Ph), 82.7 (s, C-2), 73.4 (d, C-1), 71.5 (d, C-3), 67.4 (d, C-4), 19.1 (q, CH_3-5). m/z (E.I.) 216 (1.0%, $[M]^+$), 91 (100%, $[C_7H_7]^+$). HRMS found 216.1150, $C_{14}H_{16}O_2$ requires 216.1150.

Erythro-4-benzyloxy-3-(2-bromo-2-propen-1-yloxy)-5-methyl-5-hexen-1-yne (17) 2,3-Dibromo-1-propene (1.46 cm^3, 1 mol. eq.) was added to a solution of the acetylene (16) (3.02 g, 14 mmol) in dichloromethane (15 cm^3) and 50% aqueous sodium hydroxide solution (15 cm^3), containing cetyltrimethylammonium bromide (1.02 g, 0.2 mol. eq.). After stirring for 3 hours the organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 15 cm^3). The combined organic extracts were washed with sat. sodium chloride

solution (30 cm^3), dried over magnesium sulphate then concentrated *in vacuo*. Purification by flash column chromatography (8:1 petrol/ether eluant) gave *erythro-4-benzyloxy-3-(2-bromo-2-propen-1-yloxy)-5-methyl-5-hexen-1-yne* (17) as a colourless oil (3.14 g, 67%). IR (CH_2Cl_2) 3320m, 3050w, 2940m, 2130w, 1640m, 1630m, 1490w, 1450m, 1100br s, 910s cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.32 (5H, m, ArH), 5.93 (1H, d, J 1.4Hz, C-3'), 5.60 (1H, br s, C-3'), 5.12 (1H, d, J 1.4Hz, C-6), 5.08 (1H, br s, C-6), 4.62 (1H, d, J_{gem} 12.1 Hz, OCH_2Ph), 4.42 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.32 (1H, d, J_{gem} 14.0Hz, C-1'), 4.24 (1H, dd, $J_{3,4}$ 6.7Hz, $J_{3,1}$ 1.9Hz, C-3), 4.19 (1H, d, J_{gem} 14.0Hz, C-1'), 3.95 (1H, d, $J_{4,3}$ 6.7Hz, C-4), 2.49 (1H, s, $J_{1,3}$ 1.6Hz, C-1), 1.78 (3H, s, CH_3-5). δ_C (90.1 MHz, $CDCl_3$) 141.2 (s, C-5), 138.6 (s, C-2'), 131.7 (s, Ar), 128.3 (d Ar), 127.9 (d, Ar), 127.7 (d, Ar), 118.5 (t, C-3'), 116.5 (t, C-6), 81.1 (d, C-3), 80.5 (t, OCH_2Ph), 74.9 (s, C-2), 73.2 (d, C-1), 71.4 (d, C-4), 71.0 (t, C-1'), 17.2 (q, CH_3-5). m/z (FAB) 337 (1%, $[M(^{81}Br)+H]^+$), 335 (1% $[M(^{79}Br)+H]^+$), 91 (100%, $[C_7H_7]^+$). HRMS found 334.0540, $C_{17}H_{19}BrO_2$ requires 334.0568.

Methyl-5-benzyloxy-4-(2-bromo-2-propen-1-yloxy)-6-methyl-6-hepten-2-ynoate (18). n-BuLi (1.5 M, 2.03 cm^3, 1.2 mol. eq.) was added dropwise to a solution of the acetylene (17) (0.85 g, 2.5 mmol) in ether (20 cm^3) at -78°C. The solution was allowed to warm to -20°C, then transferred via double ended needles to a solution of methyl chloroformate (0.4 cm^3, 2 mol. eq.) in ether (5 cm^3) at -10°C. The solution was stirred at 0°C for 1 hr, then at room temperature for 30 minutes. Water (20 cm^3) was added, the organic layer separated and the aqueous phase extracted with ether (2 x 10 cm^3). The combined organic extracts were washed with sat. sodium chloride solution (10 cm^3), dried over magnesium sulphate and the solvent removed *in vacuo*. Purification by flash column chromatography (10:1 petrol/ether eluant) yielded *methyl-5-benzyloxy-4-(2-bromo-2-propen-1-yloxy)-6-methyl-6-hepten-2-ynoate* (18) as a colourless oil (0.66 g, 67%). U.V. (n-hexane) 250.0nm (ε 250 dm^3 mol^{-1} cm^{-1}), 191 (20500). IR (CH_2Cl_2) 3020w, 2960br m, 2250-m, 1710s, 1640w, 1430m, 1240s, 1060br s cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.3-7.2 (5H, m. ArH), 5.87 (1H, dd, J_{gem} 1.5Hz, $J_{3',1'}$ 1.4Hz, C-3'), 5.56 (1H, t, J 0.9Hz, C-3'), 5.08 (1H, dd, J_{gem} 2.0Hz, $J_{7,6'}$ 1.4Hz, C-7), 5.02 (1H, br s, C-7), 4.55 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.37 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.24 (1H, d, J not measurable, C-1'), 4.23 (1H, d, $J_{4,5}$ 7.2Hz, C-4), 4.11 (1H, d, J_{gem} 13.8Hz, C-1'), 3.91 (1H, d, $J_{5,4}$ 7.2Hz, C-5), 3.74 (3H, s, OCH_3), 1.71 (3H, s, CH_3-6). δ_C (90.1 MHz, $CDCl_3$) 153.8 (s, C-1), 140.8 (s, C-6), 137.9 (s, C-2'), 131.4 (s, Ar), 128.4 (d, Ar), 127.9 (d, Ar), 127.7 (d, Ar), 118.9 (t, C-3'), 117.0 (t, C-7), 84.3 (s, C-2), 83.5 (d, C-4), 78.4 (s, C-3), 73.3 (t, OCH_2Ph), 70.9 (t, C-1'), 70.5 (d, C-5), 52.7 (q, OCH_3), 17.6 (q, CH_3-6). m/z (FAB) 395 (1%, $[M(^{81}Br)+H]^+$), 393 (1.3%, $[M(^{79}Br)+H]^+$), 91 (100%, $[C_7H_7]^+$). HRMS found 392.0624, $C_{19}H_{21}BrO_4$ requires 392.0624.

7-Benzyloxy-6-methyl-3-(1-tri-n-butylstannylmethyl)-2,4,5,6,7,7a-hexahydrobenzofuran-4-carboxylic acid, methyl ester (19). A thoroughly degassed solution of the acetylene (18) (0.115 g, 0.29 mmol) in benzene (31.5 cm^3, 20 mmol final concentration in Sn), containing AIBN (5mg, 0.1 mol. eq.) and maintained under an atmosphere of argon, was brought to reflux using a 150W desk lamp. Tri-n-butyltin hydride (0.17 cm^3, 2.2 mol. eq.) in benzene (0.5 cm^3) was added dropwise over 5 minutes and reflux maintained for a further 2 hours. The solvent was removed *in vacuo*, and the tin residues removed from the product by flash column chromatography (15:1 petrol/ether eluant). *7-Benzyloxy-6-methyl-3-(1-tri-n-butylstannylmethyl)-2,4,5,6,7,7a-hexahydrobenzofuran-4-carboxylic acid, methyl ester* (19) was isolated as a colourless oil (76 mg, 43%) (note

that avermectin numbering has been used for the n.m.r. assignments).
IR (CH_2Cl_2) 2950s, 1745s, 1460m, 1200m, 1100m, 1060br s, 910m cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.4-7.2 (5H, m. ArH), 4.85 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.67 (1H, br s, C-6), 4.59 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.48 (2H, br d, J 3.4Hz, C-8'), 3.72 (3H, s, OCH_3), 3.57 (1H, t, J 1.7Hz, C-5), 3.08 (1H, br d, J 10Hz, C-2), 1.6-0.8 (3H, m. including δ 0.95, d, $J_{4,4'}$ 6.6Hz, CH_3-C4). δ_C (67.9Hz, C_6D_6) 174.0 (s, C-1), 139.8 (s, C-8), 130.7 (s, Ar), 118.8 (s, C-7), 92.2 (d, C-6), 80.6 (t, OCH_2Ph), 80.5 (t, C-8'), 75.1 (d, C-5), 51.0 (q, OCH_3), 43.2 (d, C-2), 33.6 (d, C-4), 32.4 (t), 30.2 (t), 29.5 (t, C-9), 27.8 (t), 18.2 (q, CH_3-4), 13.9 (q, $CH_3C_3H_6Sn$), 10.3 (t, $C_3H_7CH_2Sn$, $J_{Sn,C}$ 152Hz, $J_{Sn,C}$ 158Hz), (C_6D_6 used to prevent coincidents observed in $CDCl_3$ at δ 80.5. However $CDCl_3$ allowed the identification of the aromatic peaks). δ_C (67.9 MHz, $CDCl_3$) 172.4 (s, C-1), 139.8 (s, C-8), 130.8 (s, Ar), 128.2 (d, Ar), 128.1 (d, Ar), 128.0 (d, Ar), 118.0 (s, C-7), 91.9 (d, C-6), 80.5 (t, OCH_2Ph, C-8'), 74.8 (d, C-5), 51.6 (q, OCH_3), 43.0 (d, C-2), 33.5 (d, C-4), 31.9 (t), 29.8 (t), 29.1 (t), 27.5 (t), 18.1 (q, CH_3-4), 13.8 (q, $CH_3C_3H_6Sn$), 10.0 (t, C-9). m/z (C.I.) 607 (4.1%, $[M(^{120}Sn)+H]^+$), 605 (3.0%, $[M(^{118}Sn)+H]^+$), 603 (1%, $[M(^{116}Sn)+H]^+$), 549 (6.1%, $[M(^{120}Sn)-Bu]^+$), 547 (5.6%, $[M(^{118}Sn)-Bu]^+$), 545 (2.9%, $[M(^{116}Sn)-Bu]^+$), 291 (15.5%, $[Bu_3(^{120}Sn)+H]^+$), 289 (7%, $[Bu_3(^{118}Sn)+H]^+$), 287 (7%, $Bu_3(^{116}Sn)+H]^+$), 225 (17.5%, $[M-Bu_3Sn-C_7H_7+H]^+$).

7-Benzyloxy-3a-hydroxyl-6-methyl-3-methylene-2,3a,4,5,6,7,7a-heptahydrobenzofuran-4-carboxylic acid methyl ester (20). m-Nitroperoxybenzoic acid (20 mg, 1.2 mol. eq.) in ether (1 cm^3) was added dropwise to a solution of the allyl stannane (19) (54 mg, 0.13 mmol) in ether (5 cm^3) at -78°C. The solution was allowed to warm to room temperature over 2 hours then diluted with ether (20 cm^3). The ethereal solution was then washed with sat. sodium hydrogen carbonate solution (15 cm^3), dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash column chromatography (2:1 petrol/ethyl acetate eluant) gave *7- benzyloxy-3a-hydroxyl-6-methyl-3-methylene-2,3a,4,5,6,7,7a-heptahydrobenzofuran-4-carboxylic acid, methyl ester* (20) as a colourless oil (24mg, 81%) (note that avermectin numbering has been used for n.m.r. assignments). IR (CH_2Cl_2) 3560br m, 2975s, 2930s, 2880s, 1740s, 1710m, 1610w, 1500m, 1460m, 1220s, 1100m, 1080s, 910 cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.30 (5H, m. ArH, 4.91 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.80 (1H, br s, C-9), 4.75 (1H, m, C-9), 4.65 (1H, dt, J_{gem} 12.0Hz, $J_{8',9}$ 2.4Hz, C-8'), 4.51 (1H, d, J_{gem} 12.0Hz, OCH_2Ph), 4.42 (1H, dt, J_{gem} 12Hz, $J_{8',9}$ 1.9Hz, C-8'), 4.14 (1H, s, OH), 4.09 (1H, s, $J_{6,5}$ 4.4Hz, C-6), 3.81 (3H, s, OCH_3), 3.61 (1H, dd, $J_{5,4}$ 2.1Hz, $J_{5,6}$ 4.3Hz, C-5), 2.95 (1H, dd, ABX system, $J_{2,3\text{-ax}} + J_{2,3\text{-eq}}$ 16.8Hz, C-2), 1.8-1.5 (3H, m, C-3, C-4), 0.9 (3H, d , $J_{4,4'}$ 6.5Hz, CH_3-4). δ_C (90.1 MHz, $CDCl_3$) 174.3 (s, C-1), 139.5 (s, C-8), 129.1 (s, Ar), 128.2 (d, Ar), 127.1 (d, Ar), 126.8 (d, Ar), 102.9 (t, C-9), 87.9 (d, C-6), 80.6 (d, C-5), 74.9 (t, OCH_2Ph), 72.2 (t, C-8'), 68.3 (s, C-7), 52.1 (q, OCH_3), 47.8 (d, C-2), 34.0 (d, C-4), 27.1 (t, C-3), 17.6 (q, CH_3-4). m/z (C.I.) 333 (80%, $[M+H]^+$), 274 (17%, $[M-CO_2CH_3+H]^+$). HRMS found 332.1624, $C_{19}H_{24}O_5$ requires 332.1623.

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Acknowledgements

We would like to thank Fisons Pharmaceuticals and the SERC for a CASE award to PW and Mr. N.F.Badham for his careful proof-reading and helpful comments on this manuscript.