The Total Synthesis of (+)-Milbemycin β_3

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We report the total synthesis of (+)-milbemycin β_3 from the optically pure precursors spiroacetal (**3**) and vinyl iodide (**2**), and the aromatic aldehyde (**4**).

The milbemycins comprise a group of natural products isolated from cultures of *Streptomyces* B-41-146, of which milbemycin β_3 (**1**) is the simplest.[1] Interest in these compounds has increased since the isolation and identification of a structurally related series of macrolides, the avermectins.[2] The avermectins are effective against helminths and arthropods at very low concentrations, giving these compounds enormous potential as broad spectrum anti-parasitic agents. To date, two total syntheses of milbemycin β_3 have been reported.[3,4] Our retrosynthetic analysis divided milbemycin β_3 (**1**) into the spiroacetal alcohol unit (**3**), the vinyl iodide bearing the remote chiral centre at C-12 (**2**), and the aromatic aldehyde (**4**). A feature common to the avermectins and milbemycins is the spiroacetal moiety, three carbon atoms of

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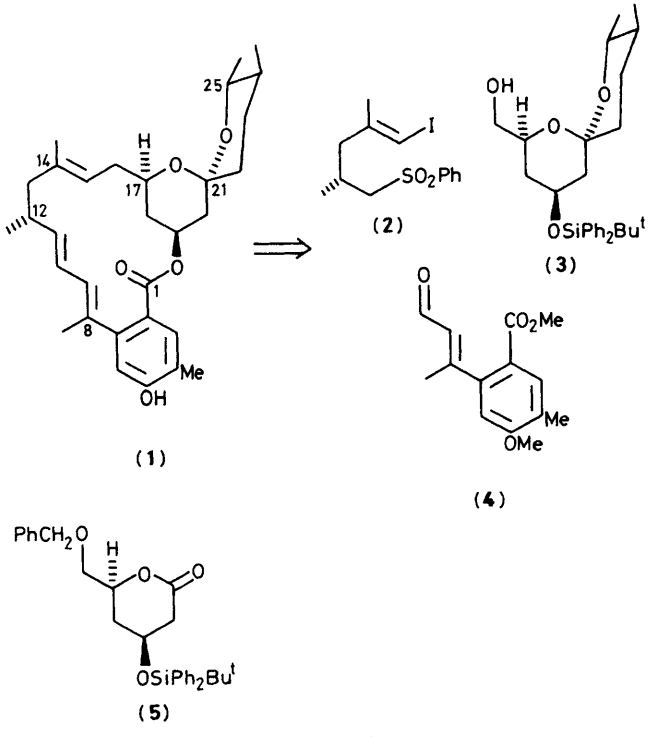
which form part of the sixteen-membered macrolide ring. We have previously reported the synthesis of the spiroacetal unit of milbemycins β_1 and β_3,[5] *via* the lactone (**5**), which was prepared from laevoglucosan. This lactone (**5**) has also been used in the synthesis of the spiroacetal fragments of avermectins B_{1b} and B_{2b}.[6] We now report the incorporation of the spiroacetal (**3**) into a total synthesis of milbemycin β_3.

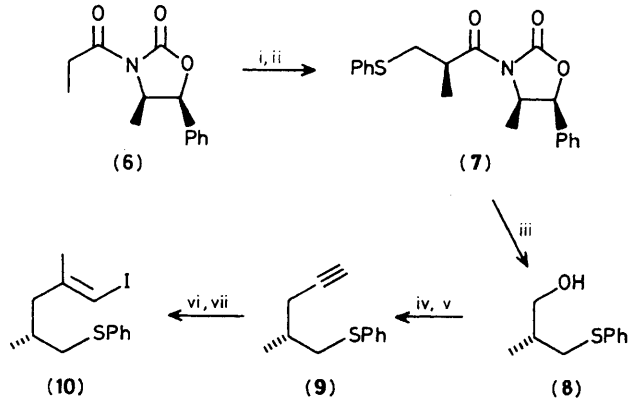
The alkyl chain portion of the macrocyclic ring, including the remote chiral centre at C-12 was generated *via* an enantiospecific alkylation of the oxazolidone (**6**)[7] to yield the sulphide (**7**). Reduction proceeded smoothly to furnish the alcohol (**8**) which was brominated (NBS–Ph_3P) in 75% yield; subsequent treatment with lithium acetylide gave the acetylene (**9**), $[\alpha]_D$ +33.6°, b.p. 67 °C at 0.3 mmHg; ^{1}H n.m.r. (60 MHz) δ 1.1 (3H, d, *J* 6 Hz, Me), 1.8—2.2 (1H, m, C*H*Me), 2.0 (1H, d, *J* 2 Hz, C≡CH), 2.3 (2H, m, CH_2C≡CH), 3.0 (2H, m, CH_2SPh), and 7.1—7.6 (5H, m, PhS) (80%). Carboalumination, followed by treatment of the alane with iodine,[8] yielded the vinyl iodide (**10**), $[\alpha]_D$ +10.8°, b.p. 82 °C at 0.33 mmHg; ^{1}H n.m.r. ($CDCl_3$) (60 MHz) δ 1.0 (3H, d, *J* 6 Hz, MeCH), 1.75 (3H, s, MeC=C), 2.15 (2H, m, CH_2C=C), 2.75 (2H, m, CH_2S), 5.9 (1H, br.s, =CHI), and 7.0—7.4 (5H, m, PhS), in a yield of 85%.

The required aromatic moiety could be efficiently prepared from 4-methoxy-3-methylbenzoic acid (**11**), itself readily available from *o*-cresol acetate, *via* Fries rearrangement, methylation (Me_2SO_4), and hypochlorite oxidation. Preparation of the oxazoline (**12**) (90%), followed by acylation in 90% yield, gave the ketone (**13**).[3] Treatment with allylmagnesium chloride and subsequent acid hydrolysis yielded the lactone (**14**) (70%). Ozonolysis, elimination (DBU), and methylation yielded the required aldehyde (**4**), $\nu_{max.}$ 1710 (CO_2Me) and 1690 cm^{-1} (CHO); ^{1}H n.m.r. ($CDCl_3$) (60 MHz) δ 2.2 (3H, br.s, Me), 2.45 (3H, br.s, Me), 3.80 (3H, s, OMe), 3.85 (3H, s, OMe), 5.9 (1H, d, *J* 9 Hz, =CH), 6.55 (1H, s, ArH), 7.8 (1H, s, ArH), and 10.2 (1H, d, *J* 9 Hz, HC=O), as a 3 : 1 mixture of *Z*- and *E*-isomers, easily separated by flash chromatography. The undesired *Z*-isomer could be isomerised to a 2 : 1 mixture of *Z*- and *E*-isomers by treatment with DBU in refluxing benzene (5 h) with 80% recovery of material.

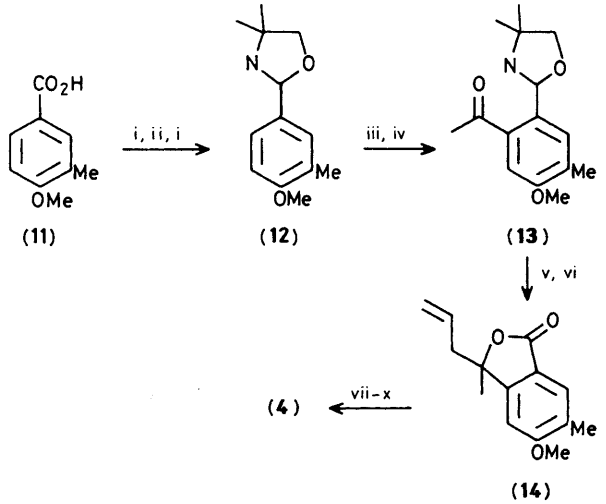
With the required fragments in hand, we turned our attention to the construction of the macrocyclic ring. Initial attempts at vinyl cuprate displacements of the tosylate or iodide derived from spiroacetal (**3**) proved disappointing but considerable efforts were expended in overcoming this problem. Coupling of a simple vinyl cuprate with either the tosylate (**15a**) or iodide (**15b**) was achieved in 70 and 30% yields respectively. Whilst the displacement of the tosylate (**16**) with alkyl cuprate was achieved in 80% yield, the corresponding reaction with the vinyl cuprate proceeded in 12% yield. Further studies indicated that heteroatom substitution in the vinyl moiety reduced the yield to unacceptable levels. Despite considerable effort and the use of a variety of ligands, solvents, and temperatures it proved impossible to improve the yield of this coupling. Coupling of fragments (**10**) and (**17**) was achieved by generation of the vinyl-lithium derivative from (**10**) (Bu^tLi, −80 °C), followed by reaction with the aldehyde (**17**) obtained by Swern oxidation of (**3**), yielding the allylic alcohol (**18**). Reaction of the alkoxide with carbon disulphide and methyl iodide yielded the dithiocarbonate



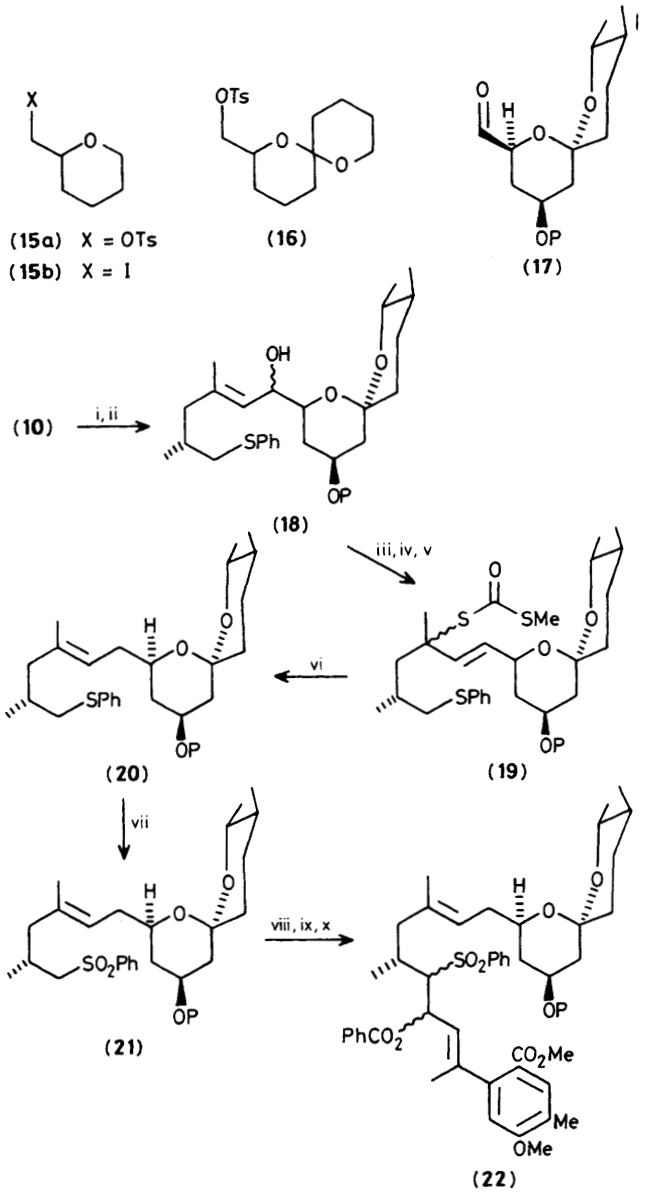
Scheme 1



Scheme 2. *Reagents:* i, LDA; ii, $PhSCH_2I$, −20 °C, THF, 5 days; iii, $LiAlH_4$, Et_2O; iv, NBS, Ph_3P, CH_2Cl_2; v, LiC≡CH, NH_3, overnight; vi, $Me_3Al/ZrCp_2Cl_2$, CH_2ClCH_2Cl, 12 h; vii, I_2,THF, −10 °C.
LDA = lithium di-isopropylamide; THF = tetrahydrofuran; NBS = *N*-bromosuccinimide; Cp = cyclopentadienyl.



Scheme 3. *Reagents:* i, $SOCl_2$, Et_2O; ii, $H_2NCMe_2CH_2OH$; iii, Bu^sLi, Et_2O, 0 °C; iv, Ac_2O, Et_2O; v, allyl MgCl, THF; vi, H_3O^+; vii, O_3, CH_2Cl_2; viii, NEt_3; ix, DBU, C_6H_6, 10 min; x, MeI, 5 min.
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

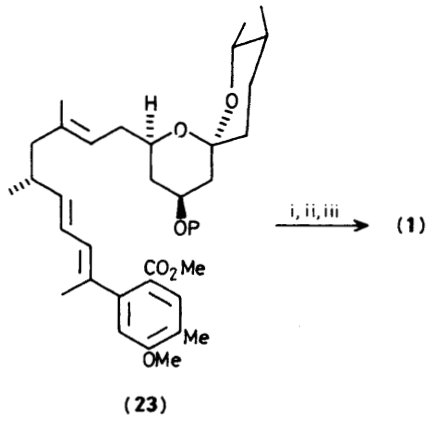


Scheme 4. *Reagents:* i, Bu^tLi, Et_2O, 1 h; ii, (**17**), Et_2O, −120 °C, 1 h; iii, NaH, THF; iv, CS_2, THF, reflux; v, MeI; vi, Bu_3SnH, AIBN, MePh; vii, $KHSO_5$, EtOH, 0 °C, h; viii, Bu^nLi, THF, −80 °C; ix, (**4**), THF, −80 °C, 1 h; x, PhCOCl, room temp., 2 h.

AIBN = azoisobutyronitrile.

(**19**); reduction (Bu_3SnH) yielded the required alkene (**20**) as the major product in addition to the regioisomeric alkene.[4] Oxidation of the sulphide (**20**) yielded the sulphone (**21**), ^1H n.m.r. (360 MHz) δ 0.76 (d, *J* 7 Hz, 3H, 3-Me), 0.96 (d, *J* 7 Hz, 3H, 2-Me), 1.05 (br.s, 12H, Bu^t and 15-Me), 1.1—1.7 (m, 9H), 1.5 (s, 3H, 13-Me), 1.8—2.2 (m, 5H), 2.8—3.2 (m, 4H, $-CH_2S-$ and 2 × >CHO–), 4.1—4.3 (m, 1H, –CHOSi–), 5.1 (t, *J* 7 Hz, 1H, vinylic), and 7.3—8.0 (m, 15H, ArH), in 80% yield.

Incorporation of the aromatic portion was achieved by the Lythgoe–Kocienski modification of the Julia reaction.[9] Treatment with Bu^tLi generated the corresponding anion which was treated with the aldehyde (**4**) and the reaction quenched by



Scheme 5. *Reagents:* i, Bu_4NF, THF; ii, KH, THF; iii, EtSNa, DMF. DMF = dimethylformamide.

the addition of benzoyl chloride to yield the benzoates (**22**). Reductive elimination with sodium amalgam generated the *trans*-butadienyl system (**23**),[3] ^1H n.m.r. (360 MHz) δ 0.78 (3H, d, *J* 7 Hz, 25-Me), 0.98 (3H, d, *J* 7 Hz, 24-Me), 1.0—1.1 (12H, br.s, Bu^t and 12-Me), 1.6 (3H, s, =CMe), 1.1—2.4 (14H, m), 2.1 (3H, s, diene-Me), 2.23 (3H, s, ArMe), 3.15 (1H, m, >CHO–), 3.3 (1H, m, >CHO–), 3.85 (3H, s, ArOMe), 3.9 (3H, s, CO_2Me), 4.2 (1H, m, >CHOSi), 4.75 (1H, m, 15-H), 5.15 (1H, m, 11-H), 5.9 (1H, d, *J* 11 Hz, 9-H), 6.35 (1H, m, 10-H), 6.65 (1H, s, 6-H), 7.3 (1H, s, 3-H), and 7.3—7.8 (10H, m, Ar), in good overall yield (70—80%). The synthesis was completed using a small modification of the protocol developed by Smith *et al.*[3] In our hands desilylation was best achieved with Bu^n_4NF in refluxing THF for 10 min. Cyclisation (KH, THF) was conducted at 25 °C for 16 h and deprotection (NaSEt, DMF) yielded milbemycin β_3 (**1**), m.p. 185—87 °C, $[\alpha]_D$ + 26.1°, with an n.m.r. spectrum identical to that supplied by Professor Smith and in agreement with that previously reported.[10]

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