

## A Synthesis of (+)-Milbemycin $\beta_3$ . The Directed Aldol Approach

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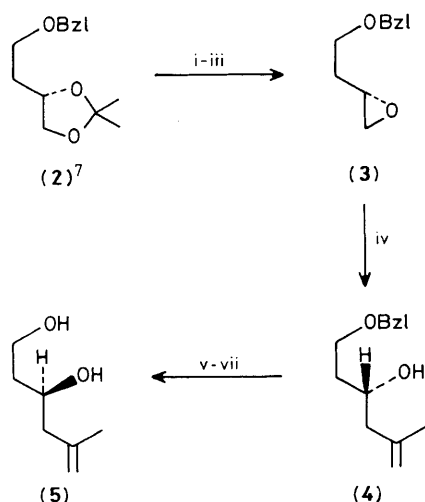
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A synthesis of (+)-milbemycin  $\beta_3$ , is reported in which key steps are the construction of the 1,7-dioxaspiro[5.5]undecane (**15**) by a Lewis acid-catalysed intramolecular directed aldol reaction and the use of sulphone-based olefination reactions for the construction of the double bonds at C(10)–C(11) and C(14)–C(15).

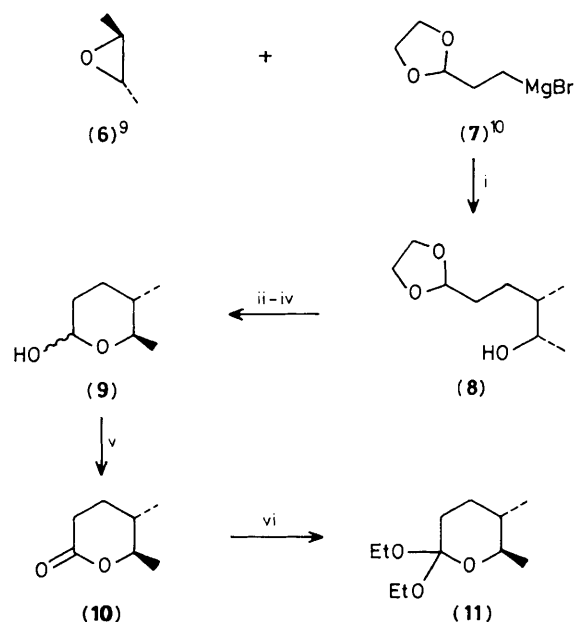
(+)-Milbemycin  $\beta_3$  (**1**) is the simplest member of a family of antiparasitic macrocyclic lactone spiroacetals.<sup>1,2</sup> We now report a highly convergent synthesis of (**1**)<sup>3–5</sup> in which all six of the chiral centres are derived from cheap, commercially available carboxylic acid derivatives: (*S*)-(–)-malic acid, (2*R*,3*R*)-(+)-tartaric acid, and (*R*)-(–)-methyl 3-hydroxy-2-methylpropionate. Noteworthy are the use of an intramolecular directed aldol reaction by which spirocyclic ortholactone (**14**) is converted into spiroacetal (**15**) and the Fe(acac)<sub>3</sub>-catalysed coupling of Grignard reagent (**19**) and vinyl sulphone (**18**) used to construct the trisubstituted double bond with high stereoselectivity (Hacac = pentane-1,4-dione).

Construction of the 1,7-dioxaspiro[5.5]undecane (**15**) (Scheme 3) was the first phase of the synthesis for which

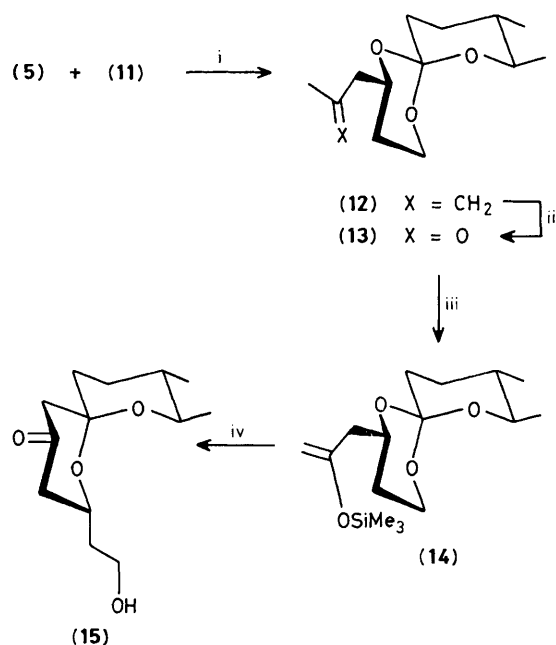
intermediates (**5**) and (**11**) were prepared by routine transformations as shown in Schemes 1 and 2 respectively. Diol (**5**) and ortholactone (**11**) condensed in the presence of acid to give a single spirocyclic ortholactone (**12**) in 75% yield, which was converted in two steps (Scheme 3) into the enol silane (**14**). A novel intramolecular directed aldol reaction<sup>6</sup> was used to convert (**14**) into spiroacetal (**15**) ( $[\alpha]_D^{22} + 49.8^\circ$ , *c* 1.2 in CHCl<sub>3</sub>) in 36% overall yield from ketone (**13**). Although the yield was modest in the key cyclisation, the reaction was clean in that only the most stable diastereoisomer (**15**) was formed<sup>11</sup> and the remainder of the mass was polymeric and easily separated by column chromatography on silica gel.



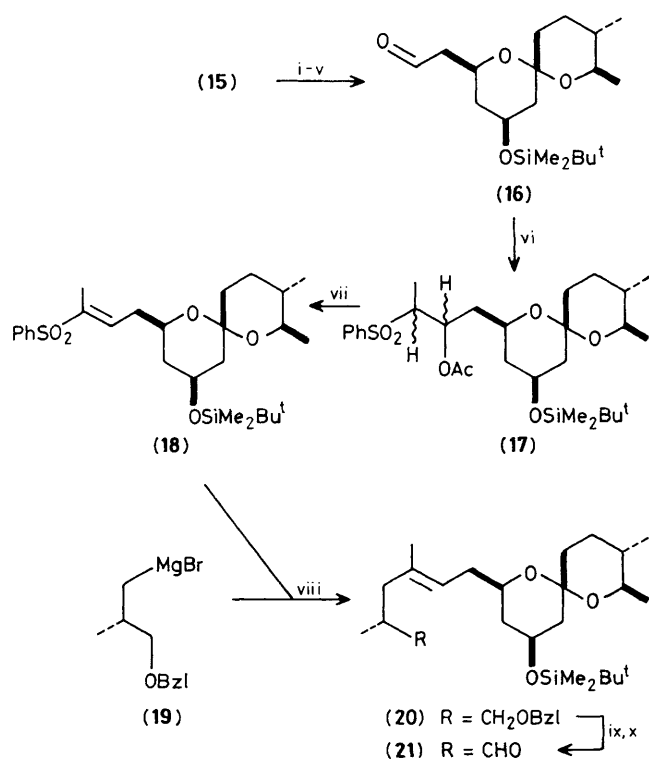
**Scheme 1.** Reagents: i, H<sub>3</sub>O<sup>+</sup>/tetrahydrofuran (THF), (100%); ii, *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl/pyridine, (90%); iii, K<sub>2</sub>CO<sub>3</sub>/MeOH, (75%); iv, isopropenylmagnesium bromide, 10 mol % CuI/THF, (94%); v, Na/NH<sub>3</sub>(l), (75%); vi, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, Et<sub>2</sub>OC–N=N–CO<sub>2</sub>Et, Ph<sub>3</sub>P, (80%); vii, NaOMe/MeOH, (80%).



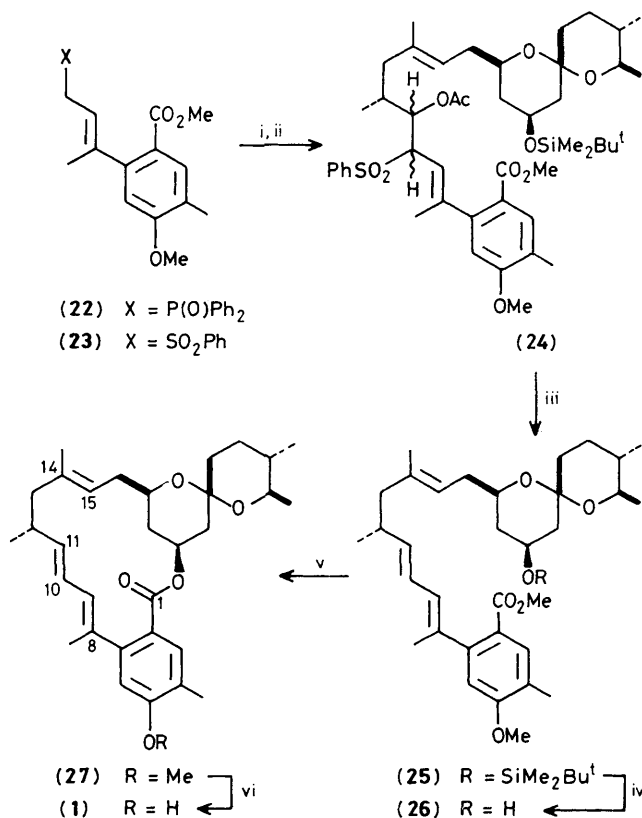
**Scheme 2.** Reagents: i, 10 mol % CuI/THF, (82%); ii, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, EtO<sub>2</sub>C–N=N–CO<sub>2</sub>Et, PPh<sub>3</sub>, (71%); iii, KOH/MeOH, (88%); iv, H<sub>3</sub>O<sup>+</sup>/THF, (90%); v, Br<sub>2</sub>, NaOAc/H<sub>2</sub>O–HOAc, (72%); vi, Et<sub>3</sub>OBF<sub>4</sub>/CH<sub>2</sub>Cl<sub>2</sub>, followed by NaOEt/EtOH, (72%).



**Scheme 3.** Reagents: i, H<sup>+</sup>/CH<sub>2</sub>Cl<sub>2</sub>, (75%); ii, O<sub>3</sub>/MeOH, -78 °C followed by excess of Me<sub>2</sub>S, (75%); iii, Pr<sub>2</sub>NLi/THF, -78 °C followed by excess of Me<sub>3</sub>SiCl, (ca. 100%); iv, BF<sub>3</sub>·Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, (36%).



**Scheme 4.** Reagents: i, AcCl/pyridine, (94%); ii, NaBH<sub>4</sub>/MeOCH<sub>2</sub>CH<sub>2</sub>OMe, 0 °C, (55%); iii, Bu<sup>n</sup>Me<sub>2</sub>SiCl/dimethylformamide (DMF)-NEt<sub>3</sub>, (90%); iv, LiAlH<sub>4</sub>/Et<sub>2</sub>O, (98%); v, pyridinium chlorochromate/CH<sub>2</sub>Cl<sub>2</sub>, (89%); vi, PhSO<sub>2</sub>CH(Li)Me/THF, -78 °C followed by Ac<sub>2</sub>O, (90%); vii, NaOH/dioxane, (80%); viii, Fe(acac)<sub>3</sub>, (30%); ix, Na/NH<sub>3</sub>(l), (95%); x, CrO<sub>3</sub>·2 pyridine/CH<sub>2</sub>Cl<sub>2</sub>, (94%).



**Scheme 5.** Reagents: i, Pr<sub>2</sub>NLi/THF, -78 °C followed by (21); ii, Ac<sub>2</sub>O, (94%); iii, Na(Hg)/THF-MeOH, -20 °C, (55%); iv, Bu<sup>n</sup><sub>4</sub>NF/THF, (90%); v, (Me<sub>3</sub>Si)<sub>2</sub>NK/THF, 20 °C, (55%); vi, EtSn/DMF, (85%).

The second phase of the synthesis involved simultaneous construction of the trisubstituted C(14)–C(15) double bond and introduction of the remote chiral centre at C(12). A highly stereoselective 4-step procedure of Julia and co-workers<sup>12</sup> was the cornerstone of the sequence used to convert aldehyde (16), obtained from (15) by trivial functional group manipulation (Scheme 4), to aldehyde (21). Thus, the lithio derivative of phenyl ethyl sulphone gave an adduct with aldehyde (16) which was acetylated to give a mixture of four diastereoisomeric β-acetoxysulphones (17) which without separation underwent smooth β-elimination on treatment with powdered NaOH in dioxane. The resultant vinyl sulphone (18) was formed as a single (*E*)-isomer within the limits of <sup>1</sup>H n.m.r. analysis. Coupling of the vinyl sulphone (18) and Grignard reagent (19)<sup>13</sup> in the presence of Fe(acac)<sub>3</sub> proceeded with retention of stereochemistry at the double bond to give (20) as a single isomer. Routine transformations were then used to transform (20) to the aldehyde (21) previously prepared in racemic form by Smith and co-workers.<sup>3</sup>

The third and final phase of the synthesis involved construction of the C(10)–C(11) double bond and macrolactonisation (Scheme 5). This had previously<sup>3</sup> been achieved from racemic aldehyde (21) and the phosphine oxide (22). However, we chose to exploit the well established<sup>14</sup> *trans*-selectivity of the Julia olefination<sup>15</sup> for the construction of the C(10)–C(11) double bond. Unfortunately, union of the lithio derivative of sulphone (23) and aldehyde (21) followed by acetylation proceeded smoothly but subsequent reductive elimination of the mixture of diastereoisomeric β-acetoxysulphones (24) was capricious and the stereochemistry of the

C(10)–C(11) double bond in diene (**24**) varied from (*E*):(*Z*) = 2:1 at worst to 4:1 at best. We have not yet been able to suppress the base-catalysed side reactions responsible for this erratic behaviour.

Chromatographic separation of the mixture of isomeric dienes (**25**) was not possible; however, macrolactonisation of the (*E*)-hydroxy ester (**26**) proceeded rapidly and efficiently to give (**27**), whereas the corresponding (*Z*)-isomer remained unchanged and was easily separated from (**27**). Finally demethylation of (**27**) afforded (+)-milbemycin  $\beta_3$  ( $[\alpha]_{\text{D}}^{20} + 32.8^\circ$ ,  $c$  0.3 in MeOH) which gave high field  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra which were identical with spectra of the authentic compound.

Although the closing stages of this synthesis of (+)-milbemycin  $\beta_3$  were sullied by variable stereoselectivity in the reductive elimination step (**24**)  $\rightarrow$  (**25**), a novel approach to the construction of the spiroacetal moiety and the tri-substituted double bond was achieved. An alternative synthesis is reported in the following communication.<sup>16</sup>

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