A Synthesis of (+)-Milbemycin β_3. The Directed Aldol Approach

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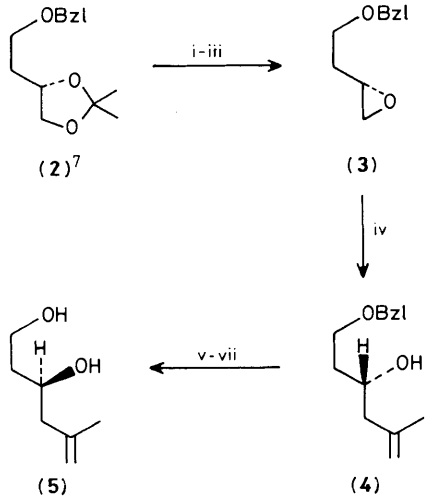
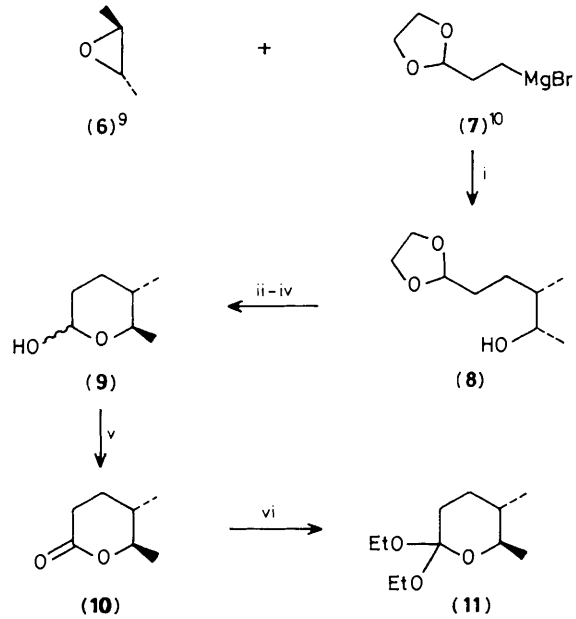
A synthesis of (+)-milbemycin β_3, is reported in which key steps are the construction of the 1,7-dioxaspiro[5.5]undecane (**15**) by a Lewis acid-catalysed intramolecular directed aldol reaction and the use of sulphone-based olefination reactions for the construction of the double bonds at C(10)–C(11) and C(14)–C(15).

(+)-Milbemycin β_3 (**1**) is the simplest member of a family of antiparasitic macrocyclic lactone spiroacetals.[1,2] We now report a highly convergent synthesis of (**1**)[3—5] 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 $Fe(acac)_3$-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).

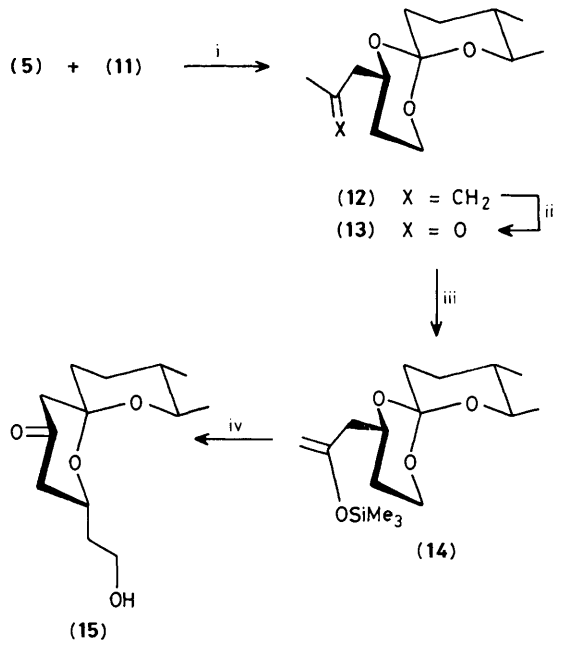
Construction of the 1,7-dioxaspiro[5.5]undecane (**15**) (Scheme 3) was the first phase of the synthesis for which intermediates (**5**) and (**11**) were prepared by routine transformations as shown in Schemes 1 and 2 respectively. Diol (**5**) and ortholactone (**11**) condensed in the presence of 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[6] was used to convert (**14**) into spiroacetal (**15**) ($[\alpha]_D^{22}$ + 49.8°, *c* 1.2 in $CHCl_3$) 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[11] and the remainder of the mass was polymeric and easily separated by column chromatography on silica gel.



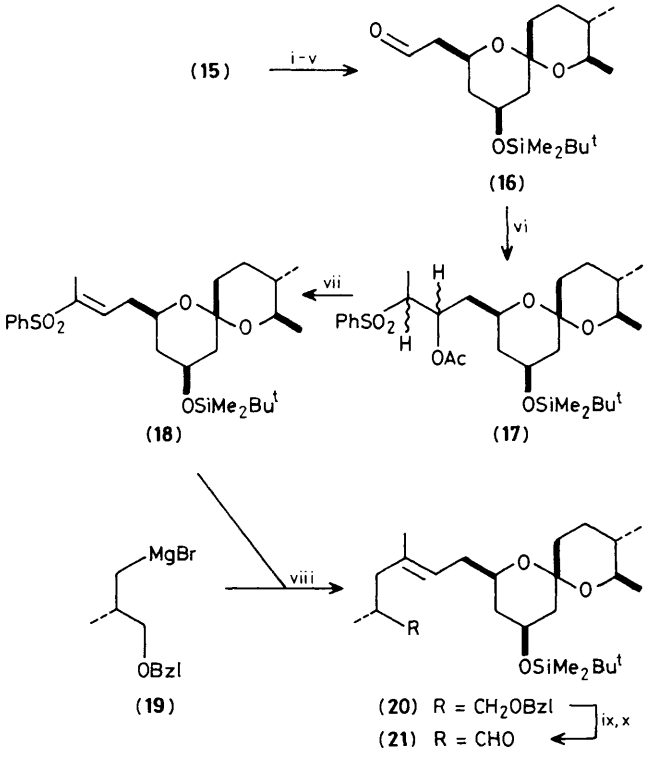
Scheme 1. *Reagents:* i, H_3O^+/tetrahydrofuran (THF), (100%); ii, *p*-$MeC_6H_4SO_2Cl$/pyridine, (90%); iii, K_2CO_3/MeOH, (75%); iv, isopropenylmagnesium bromide, 10 mol % CuI/THF, (94%); v, $Na/NH_3(l)$, (75%); vi,[8] *p*-$NO_2C_6H_4CO_2H$, $Et_2OC{-}N{=}N{-}CO_2Et$, Ph_3P, (80%); vii, NaOMe/MeOH, (80%).



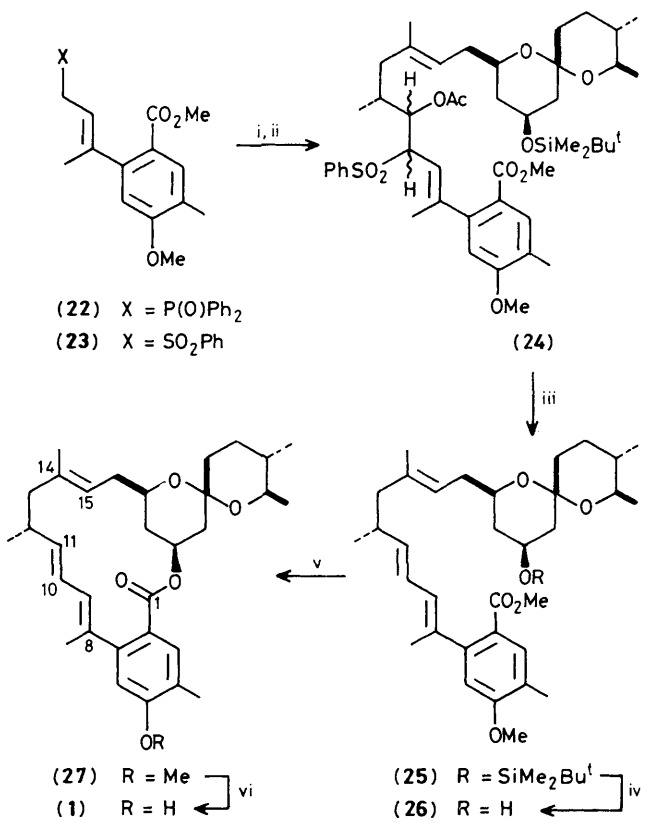
Scheme 2. *Reagents:* i, 10 mol % CuI/THF, (82%); ii,[8] *p*-$NO_2C_6H_4$-CO_2H, $EtO_2C{-}N{=}N{-}CO_2Et$, PPh_3, (71%); iii, KOH/MeOH, (88%); iv, H_3O^+/THF, (90%); v, Br_2, NaOAc/H_2O–HOAc, (72%); vi, Et_3OBF_4/CH_2Cl_2, followed by NaOEt/EtOH, (72%).



Scheme 3. *Reagents:* i, H^+/CH_2Cl_2, (75%); ii, O_3/MeOH, −78 °C followed by excess of Me_2S, (75%); iii, Pr^i_2NLi/THF, −78 °C followed by excess of Me_3SiCl, (*ca.* 100%); iv, $BF_3 \cdot Et_2O/CH_2Cl_2$, −78 °C, (36%).



Scheme 4. *Reagents:* i, AcCl/pyridine, (94%); ii, $NaBH_4$/$MeOCH_2CH_2OMe$, 0 °C, (55%); iii, Bu^tMe_2SiCl/dimethylformamide (DMF)–NEt_3, (90%); iv, $LiAlH_4/Et_2O$, (98%); v, pyridinium chlorochromate/CH_2Cl_2, (89%); vi, $PhSO_2CH(Li)Me$/THF, −78 °C followed by Ac_2O, (90%); vii, NaOH/dioxane, (80%); viii, $Fe(acac)_3$, (30%); ix, $Na/NH_3(l)$, (95%); x, $CrO_3 \cdot 2$ pyridine/CH_2Cl_2, (94%).



Scheme 5. *Reagents:* i, Pr^i_2NLi/THF, −78 °C followed by (**21**); ii, Ac_2O, (94%); iii, Na(Hg)/THF–MeOH, −20 °C, (55%); iv, Bu^n_4NF/THF, (90%); v, $(Me_3Si)_2NK$/THF, 20 °C, (55%); vi, EtSNa/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[12] 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 ^1H n.m.r. analysis. Coupling of the vinyl sulphone (**18**) and Grignard reagent (**19**)[13] in the presence of $Fe(acac)_3$ 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.[3]

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[3] been achieved from racemic aldehyde (**21**) and the phosphine oxide (**22**). However, we chose to exploit the well established[14] *trans*-selectivity of the Julia olefination[15] 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 β_3 ($[\alpha]_D^{20}$ + 32.8°, *c* 0.3 in MeOH) which gave high field ^1H and ^{13}C n.m.r. spectra which were identical with spectra of the authentic compound.

Although the closing stages of this synthesis of (+)-milbemycin β_3 were sullied by variable stereoselectivity in the reductive elimination step (**24**) → (**25**), a novel approach to the construction of the spiroacetal moiety and the trisubstituted double bond was achieved. An alternative synthesis is reported in the following communication.[16]

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