A Synthesis of (+)-Milbemycin β_3. The 3,4-Dihydro-2*H*-pyran Approach

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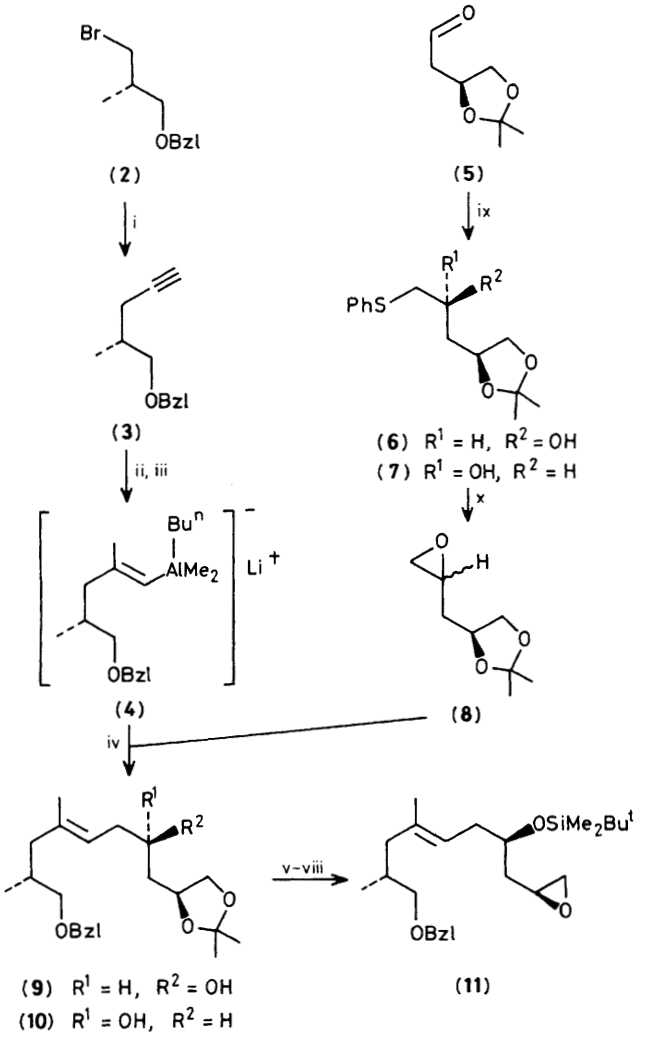
Nucleophilic scission of oxirane (**8**) by vinyl alanate (**4**) and oxirane (**11**) by metallated 3,4-dihydro-2*H*-pyran (**15**) were key steps in the synthesis of (+)-milbemycin β_3 (**1**).

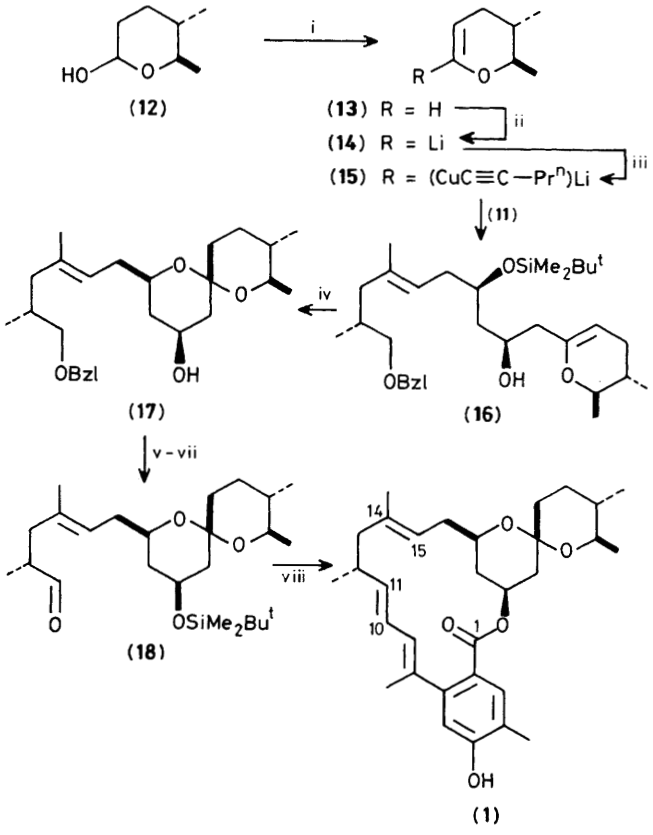
In the previous communication[1] we described a synthesis of (+)-milbemycin β_3 (**1**) in which the 1,7-dioxaspiro-[5.5]undecane moiety was constructed by a novel intramolecular directed aldol reaction and the C(14)–C(15) double bond was prepared by an Fe^{I}-catalysed coupling of a Grignard reagent and a vinyl sulphone. We report herein a more practical alternative synthesis of (**1**) which, like its predecessor, was accomplished in three phases, is highly convergent, and uses cheap chiral precursors. Once again stereoselective synthesis of the spiroacetal moiety and the C(14)–C(15) trisubstituted double bond were premier considerations.

The goal of the first phase of the synthesis was the construction of the oxirane (**11**) from the known chiral precursors (**2**)[2] and (**5**)[3] (Scheme 1) which are derived from (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate and (*S*)-(−)-malic acid respectively. Reaction of phenylthiomethyl-lithium with aldehyde (**5**) gave a mixture of diastereoisomers (**6**) and (**7**) (1:2) which were difficult to separate chromatographically; therefore, the mixture was transformed to the diastereoisomeric oxiranes (**8**) which reacted cleanly and efficiently with the vinyl alanate (**4**) derived from carboalumination[4] of the acetylene (**3**). The mixture of diastereoisomers (**9**) and (**10**) (1:2 respectively) was easily separated by column chromatography on silica gel and the undesired major isomer (**10**) converted into the desired isomer (**9**) by a Mitsunobu inversion.[5] Routine functional group manipulations were then used to prepare the key oxirane (**11**) from (**9**).

The goal of the second phase was construction of the 4-hydroxy-1,7-dioxaspiro[5.5]undecane (**17**) using a strategy which had previously been employed in the synthesis of an olive-fly pheromone[6] and talaromycin B.[7] The cardinal step in this strategy was the nucleophilic scission of an oxirane by a metallated 3,4-dihydro-2*H*-pyran. Thus, lithiation[8] of (**13**) followed by reaction with n-pentynylcopper gave a yellow



Scheme 1. *Reagents:* i, $HC{\equiv}CLi/Me_2SO$, (55%); ii, Me_3Al–$(C_5H_5)_2ZrCl_2/ClCH_2CH_2Cl$, 20 °C; iii, Bu^nLi/hexane, −78 → −30 °C; iv, −30 → 0 °C over 40 min, (79%); v, H^+/MeOH, (78%); vi, *p*-$MeC_6H_2SO_2Cl$/pyridine (95%); vii, K_2CO_3/MeOH, (80%); viii, Bu^tMe_2SiCl/dimethylformamide (DMF)–NEt_3, (93%); ix, PhS-CH_2Li/tetrahydrofuran (THF), (68%); x, Me_3OBF_4/CH_2Cl_2 followed by aqueous NaOH, (80%).



Scheme 2. *Reagents:* i, $MeSO_2Cl/CH_2Cl_2$–NEt_3, 0 °C; then reflux 4 h, (80%); ii, Bu^tLi/THF, −70 → 0 °C; iii, $Pr^nC{\equiv}CCu$/THF, 0 → 20 °C; iv, camphorsulphonic acid/MeOH, 20 °C, [55% from (**11**)]; v, Bu^tMe_2SiCl/DMF–NEt_3, (98%); vi, Na/NH_3(l), (95%); vii, $CrO_3 \cdot 2$ pyridine/CH_2Cl_2, (94%); viii, ref. 1.

heterogeneous mixed organocuprate which reacted with oxirane (**11**) at 0 to 20 °C cleanly and efficiently. Without further purification the sensitive intermediate (**16**) was converted into spiroacetal (**17**) using camphorsulphonic acid in MeOH in 55% overall yield from (**11**).

Synthesis of the Smith aldehyde[9] (**18**) from (**17**) was easily accomplished (Scheme 2) and set the stage for the third and final phase of the synthesis: construction of the C(10)–C(11) double bond and macrolactonisation as reported in the previous communication.[1]

All of the reactions reported above could be performed on a substantial scale and gave products which were easily purified making the 3,4-dihydro-2*H*-pyran approach to (+)-milbemycin β_3 more practical than the directed aldol approach. The one blemish in the sequence, the poor stereoselectivity in the reaction of (**5**) with phenylthiomethyllithium, was ameliorated by the easy separation and interconversion of diastereoisomers (**9**) and (**10**) at a later stage.

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