Total Synthesis of (+)-Milbemycin β_3

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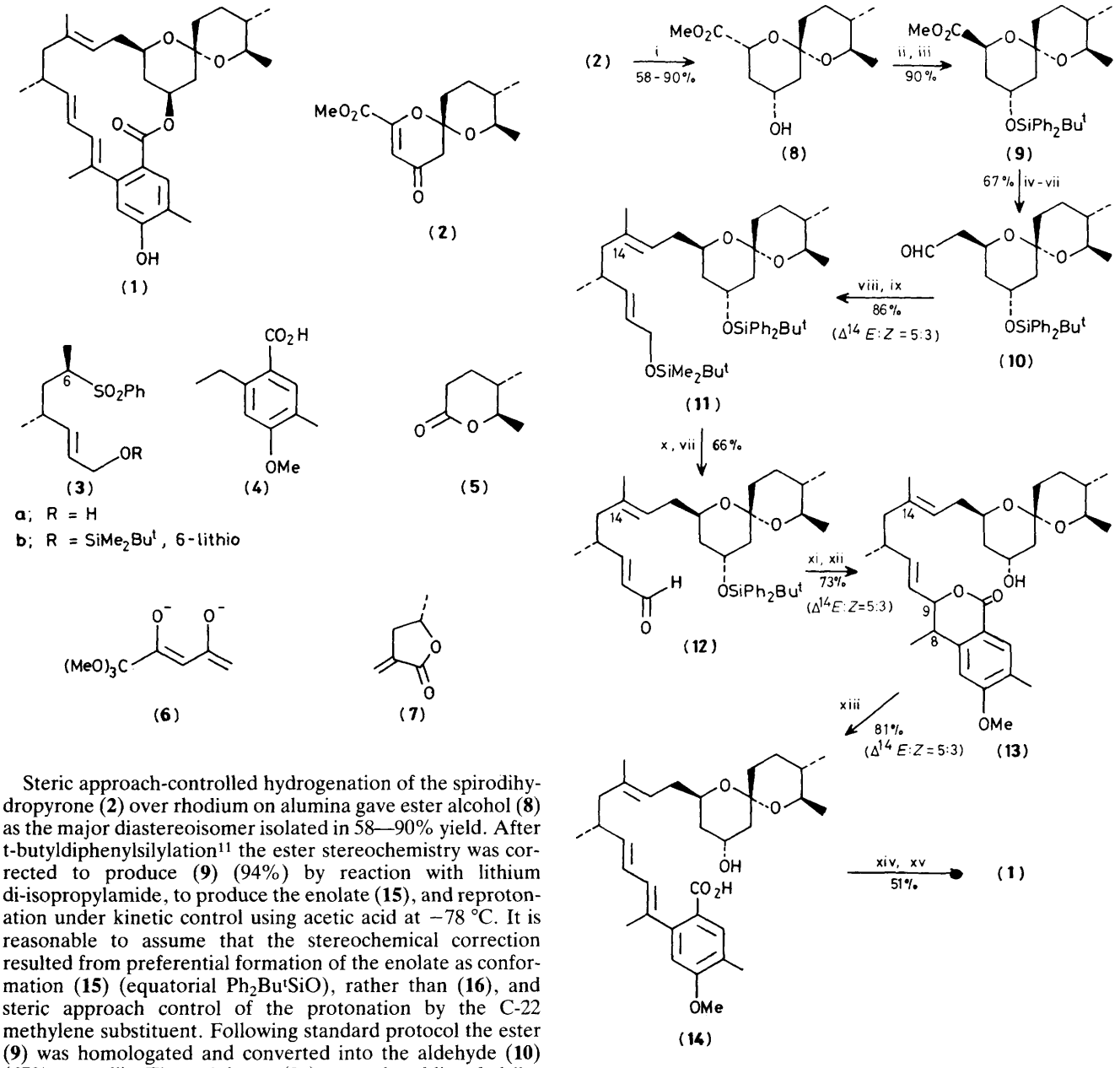
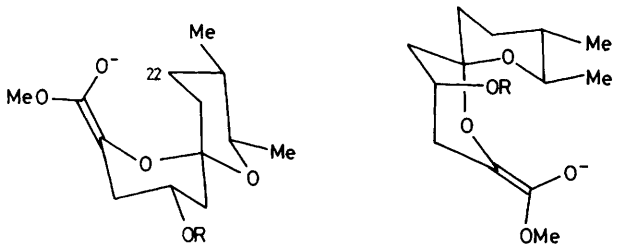
(+)-Milbemycin β_3 (**1**) was prepared by total synthesis from (6*S*,8*R*,9*S*)-methyl 8,9-dimethyl-4-oxo-1,7-dioxaspiro[5.5]undec-2-ene-2-carboxylate (**2**), (4*R*,6*R*)-4-methyl-6-phenylsulphonyl-(*E*)-hept-2-en-1-ol (**3a**), and 2-ethyl-4-methoxy-5-methylbenzoic acid (**4**) using Julia–Lythgoe and benzylic anion chemistry to establish the carbon framework and a Mitsunobu reaction to close the lactone ring.

The avermectins are a group of *Streptomyces avermitilis* metabolites noted for their most potent activity against two major classes of parasites: the nematodes and arthropods.[1] Since the corresponding mammalian toxicity is very low, the avermectins have emerged as important anthelmintic and ectoparasiticidal agents. The milbemycins are a group of structurally related natural products which exhibit a comparable spectrum of activity.[2] The structurally least complex molecule in the series is milbemycin β_3 (**1**). Smith,[3] Williams,[4] and recently Baker[5] and Kocienski[6] have published total syntheses of (**1**). In addition a considerable number of papers describing novel syntheses of spiro-acetals[7] and approaches to total synthesis of more complex milbemycins or avermectins[8] have been published. Recently we have reported the preparation of three intermediates (**2**), (**3a**), and (**4**) for milbemycin β_3 (**1**) synthesis.[9] The spirodihydropyrone (**2**) was prepared stereospecifically and in one step from the condensation of optically pure lactone (**5**) with dianion (**6**). (+)-Sulphone (**3a**) was prepared from (*S*)-propylene oxide *via* lactone (**7**) and the benzoic acid derivative (**4**) was prepared from ethyl pent-2-ynoate using Danishefsky Diels–Alder chemistry.[10] Herein we report the completion of a concise total synthesis of milbemycin β_3 (**1**) (Scheme 1) that unequivocally establishes spirodihydropyrones as versatile intermediates.

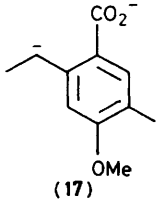


Scheme 1. *Reagents:* i, H_2, $Rh–Al_2O_3$, EtOH; ii, Bu^tPh_2SiCl, dimethylformamide (DMF), imidazole; iii, $LiNPr^i_2$, THF, −78 °C; HOAc; iv, Bu^i_2AlH, PhMe, −78 °C; v, $Ph_3P{=}CH_2$, THF, 0 °C; vi, B_2H_6, Et_2O; NaOH, H_2O_2; vii, $pyH^+CrO_3Cl^-$ (py = pyridine), CH_2Cl_2; viii, (**3b**), Et_2O, 0 °C; Ac_2O; ix, Na–Hg, THF, MeOH, −20 °C; x, HOAc, H_2O, THF; xi, (**17**), THF, −50 °C; CF_3CO_2H; xii, Bu_4NF, THF, 45 °C; xiii, KH, 18-crown-6, Et_2O, −5 °C; xiv, Ph_3P, $EtO_2C\tilde{N}{=}NCO_2Et$, THF, xv, EtSNa, DMF, heat.

Steric approach-controlled hydrogenation of the spirodihydropyrone (**2**) over rhodium on alumina gave ester alcohol (**8**) as the major diastereoisomer isolated in 58—90% yield. After t-butyldiphenylsilylation[11] the ester stereochemistry was corrected to produce (**9**) (94%) by reaction with lithium di-isopropylamide, to produce the enolate (**15**), and reprotonation under kinetic control using acetic acid at −78 °C. It is reasonable to assume that the stereochemical correction resulted from preferential formation of the enolate as conformation (**15**) (equatorial Ph_2Bu^tSiO), rather than (**16**), and steric approach control of the protonation by the C-22 methylene substituent. Following standard protocol the ester (**9**) was homologated and converted into the aldehyde (**10**) (67% overall). The sulphone (**3a**) was t-butyldimethylsilylated[12] (95%) and subsequently α-metallated using n-butyllithium in tetrahydrofuran (THF) at 0 °C to generate the anion (**3b**). This was condensed with aldehyde (**10**) to produce alkene (**11**) (74%) on work up by acetylation and subsequent reductive elimination of the intermediate β-acetoxy-sulphone mediated by sodium amalgam. Geometric control in the production of the trisubstituted alkene (**11**) by the Julia–Lythgoe procedure[13] was low ($E:Z$ = 5:3). However, separation of the mixture of geometric isomers was conveniently carried out at stage (**14**) (*vide infra*). Selective de-t-butyldimethylsilylation of alkene (**11**) using aqueous acetic acid[12] and subsequent pyridinium chlorochromate oxidation[14] gave aldehyde (**12**) (70%). Following the very elegant Williams precedent[4] the benzoic acid derivative (**4**) was doubly deprotonated using sodium hydride followed by t-butyl-lithium and the resultant dianion (**17**) condensed with aldehyde (**12**) to give lactone (**13**) (73%) on acidification and subsequent desilylation. Although the lactone (**13**) was obtained as a mixture of diastereoisomers (at C-8 and C-9), base mediated elimination for stereospecific introduction of the Δ^8 double bond simplified the mixture. Thus, using a variation of Williams chemistry, lactone (**13**) was treated with potassium hydride and 18-crown-6[15] in diethyl ether at −5 °C to produce rapidly the diene carboxylic acid (**14**) (81%). Chromatographic separation of the Δ^{14} geometric isomers was most conveniently carried out at this point. The *E*-isomer (**14**) was smoothly cyclised under Mitsunobu conditions[16] to produce, after Smith[3] phenol de-*O*-methylation, milbemycin β_3 (**1**) (51%). The sample {$[\alpha]_D^{22}$ + 102°(*c* 0.17, MeOH)} was



(15) R = Bu^tPh_2Si (16)



(17)

authenticated by complete correlation of physical properties and spectroscopic data [m.p., and ^1H n.m.r. (400 MHz), ^{13}C n.m.r., i.r., u.v., and high resolution mass spectra] with both the Smith and the Williams synthetic materials.

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