

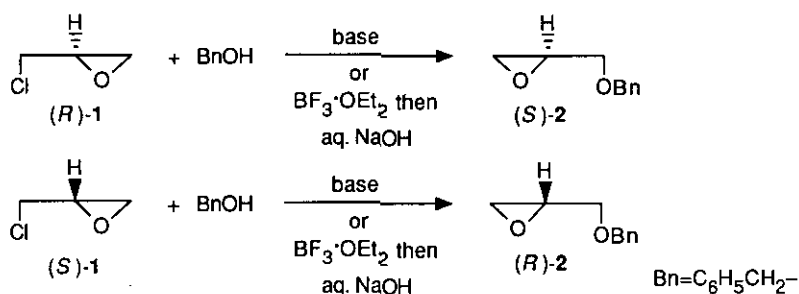
ENANTIOCONTROLLED SYNTHESIS OF THE C₉₋₂₇ SEGMENT OF MILBEMYCIN K FROM (*R*)- AND (*S*)-EPICHLOROHYDRINS

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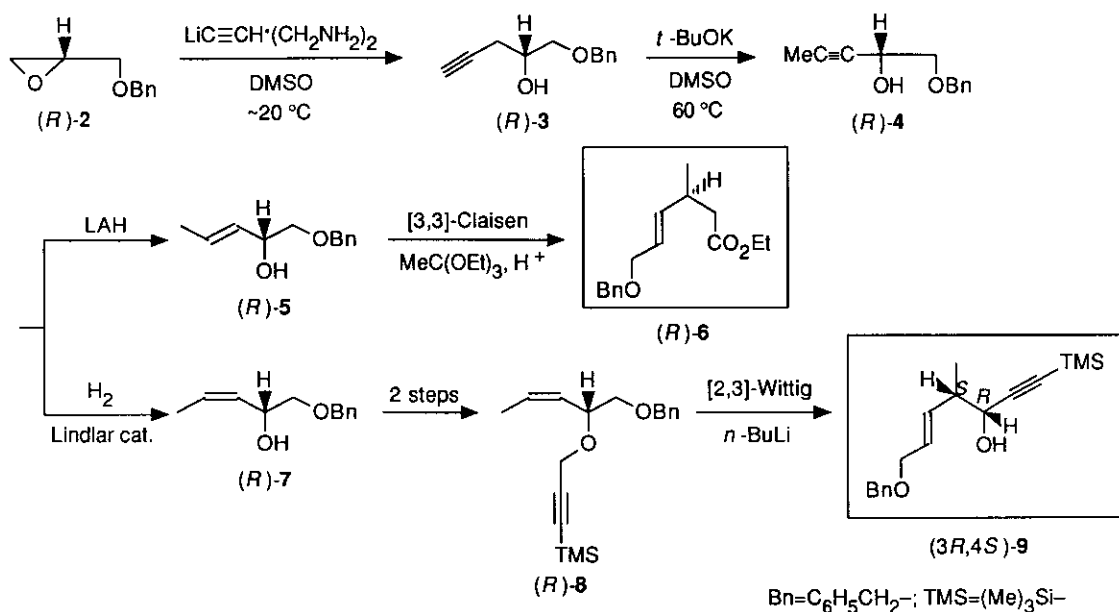
Abstract — The C₉₋₂₇ segment (**11**) of milbemycin K (**10**) has been synthesized using two molar equivalents of (*R*)-epichlorohydrin [(*R*)-**1**] and one molar equivalent of (*S*)-epichlorohydrin [(*S*)-**1**] as chiral building blocks.

Starting with optically active epichlorohydrin (**1**) we have recently developed an efficient synthesis of optically active *O*-benzylglycidol¹ (**2**) (Scheme 1). Utilizing optically active *O*-benzylglycidol (**2**) we also have achieved a highly diastereospecific



Scheme 1

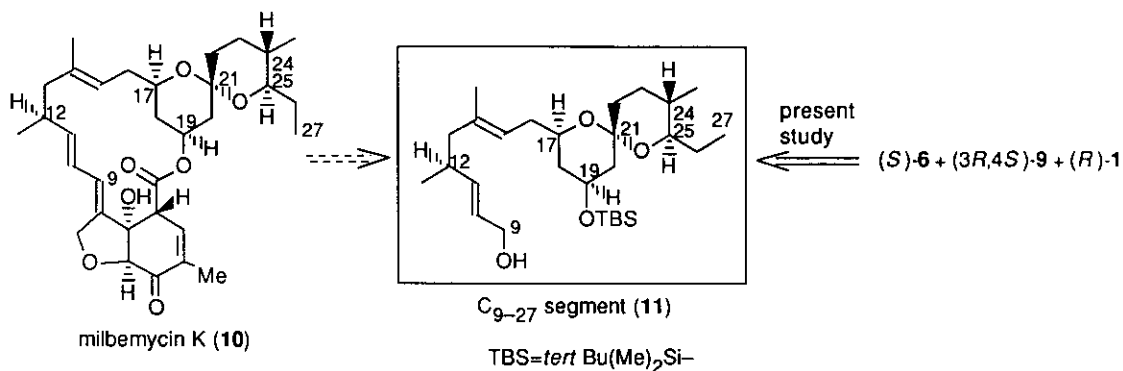
synthesis of potentially useful two chiral synthons (**6**) and (**9**) having secondary methyl group employing a [3,3]-Claisen rearrangement and a [2,3]-Wittig rearrange-



Scheme 2

ment *via* the common acetylene intermediates² (4) (Scheme 2). We report herewith an utilization of these two chiral synthons for the construction of the C_{9-27} segment (the northern hemisphere) (11) of an antiparasitic milbemycin K^{3-5} (10) by combination with an additional one molar equivalent of optically active epichlorohydrin molecule (Scheme 3).

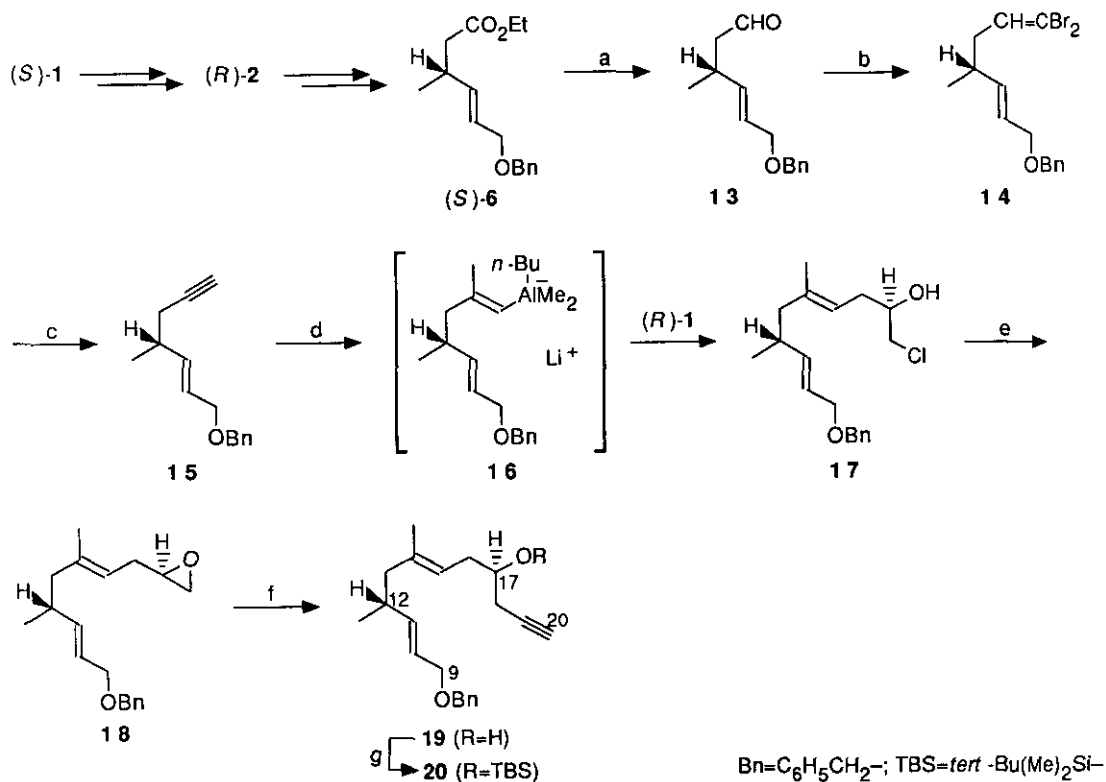
We first examined the construction of the C_{9-20} segment (20) starting with (*S*)-ester



Scheme 3

[(*S*)-6]² originated from (*S*)-epichlorohydrin [(*S*)-1] via (*R*)-*O*-benzylglycidol [(*R*)-2].

Treatment of (*S*)-6 with one equivalent of diisobutylaluminum hydride at low temperature allowed partial reduction to give the aldehyde (**13**), [α]_D²⁶ -20.43° (*c* 1.00, CHCl₃), in 88% yield. Upon treatment with carbon tetrabromide and triphenylphosphine,⁶ **13** afforded the dibromoolefin (**14**), [α]_D²⁶ -6.67° (*c* 1.05, CHCl₃) (88%), which was exposed to *n*-butyllithium⁶ to give the terminal acetylene (**15**), [α]_D²⁴ -6.40° (*c* 1.00, CHCl₃), in 82% yield. Treatment of the acetylene (**15**) with trimethylaluminum in the presence of zirconocene dichloride^{7,8} followed by *n*-butyl-



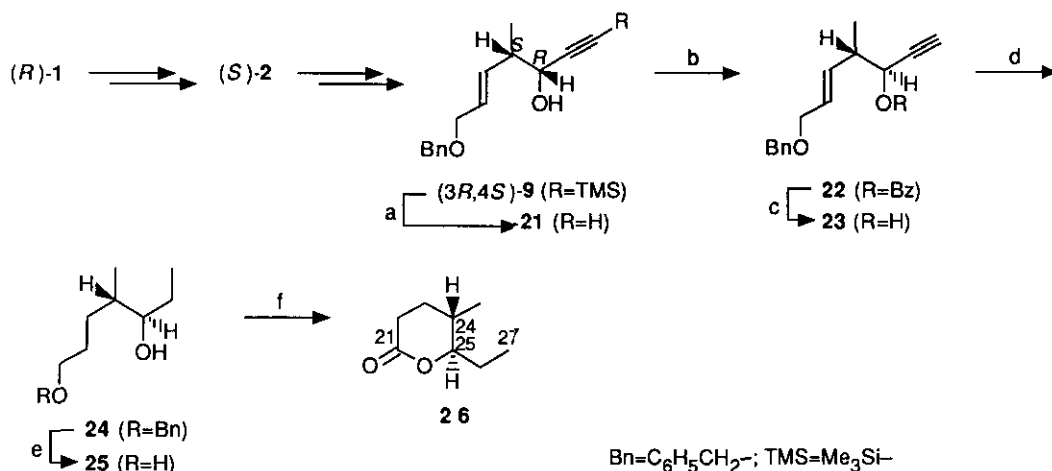
Scheme 4

Reagents and conditions: a, (iBu)₂AlH, toluene, -90 °C, acid work up; b, CBr₄, PPh₃, CH₂Cl₂, 0 °C; c, *n*-BuLi, THF, -78 °C; d, (i) zirconocene dichloride, Me₃Al, CH₂Cl₂, room temperature, (ii) evaporation, (iii) *n*-BuLi, hexane, -78 - -30 °C, then (*R*)-1, -20 °C; e, powdered NaOH, THF, room temperature; f, NaH, acetylene, DMSO, room temperature, then **18** in DMSO, room temperature; g, *tert*-Bu(Me)₂SiCl, imidazole, DMF, room temperature.

lithium formed the complex (16) which on reaction with (*R*)-epichlorohydrin [(*R*)-1] in the same flask furnished the chlorohydrin (17), $[\alpha]_{\text{D}}^{24} +9.80^\circ$ (*c* 1.02, CHCl_3), in 68% yield. The chlorohydrin (17) was then treated with powdered sodium hydroxide in THF to give the epoxide (18), $[\alpha]_{\text{D}}^{24} -3.35^\circ$ (*c* 1.01, CHCl_3), in 93% yield. Reaction of the epoxide (18) with sodium acetylide prepared in situ in the same DMSO solution afforded the C_{9-20} acetylenic alcohol (19), $[\alpha]_{\text{D}}^{25} +7.35^\circ$ (*c* 1.03, CHCl_3) (80%), which was transformed into the *tert*-butyldimethylsilyl (TBS) ether (20), $[\alpha]_{\text{D}}^{26} +3.96^\circ$ (*c* 1.01, CHCl_3), quantitatively (Scheme 4).

On the other hand, the construction of the C_{21-27} segment⁹ (26) was started with (3*R*,4*S*)-eneynol² (9) prepared from (*R*)-epichlorohydrin [(*R*)-1] via (*S*)-*O*-benzylglycidol [(*S*)-2]. Treatment of the terminal acetylene (21), $[\alpha]_{\text{D}}^{26} +18.15^\circ$ (*c* 1.15, CHCl_3), obtained in 96% yield from (3*R*,4*S*)-9 with tetra-*n*-butylammonium fluoride, with benzoic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate¹⁰ afforded the benzoate 22, $[\alpha]_{\text{D}}^{25} -31.74^\circ$ (*c* 1.01, CHCl_3) (75%) with inversion of 3*R*-center, which on methanolysis gave the (3*S*,4*S*)-eneynol (23), $[\alpha]_{\text{D}}^{25} -15.38^\circ$ (*c* 1.01, CHCl_3), in 97% yield. This compound was hydrogenated in the presence of platinum oxide to give the saturated benzyl ether (24), $[\alpha]_{\text{D}}^{22} -7.72^\circ$ (*c* 1.01, CHCl_3), which then was hydrogenolyzed on palladium hydroxide to give the diol (25), $[\alpha]_{\text{D}}^{24} -7.39^\circ$ (*c* 1.01, CHCl_3), in 98% overall yield. Oxygenation of the diol (25) on platinum black¹¹ proceeded regioselectively at the primary hydroxy group to furnish the desired C_{21-27} δ -lactone (26), $[\alpha]_{\text{D}}^{26} +49.32^\circ$ (*c* 1.03, CHCl_3), in 78% yield, after azeotropic reflux in benzene (Scheme 5).

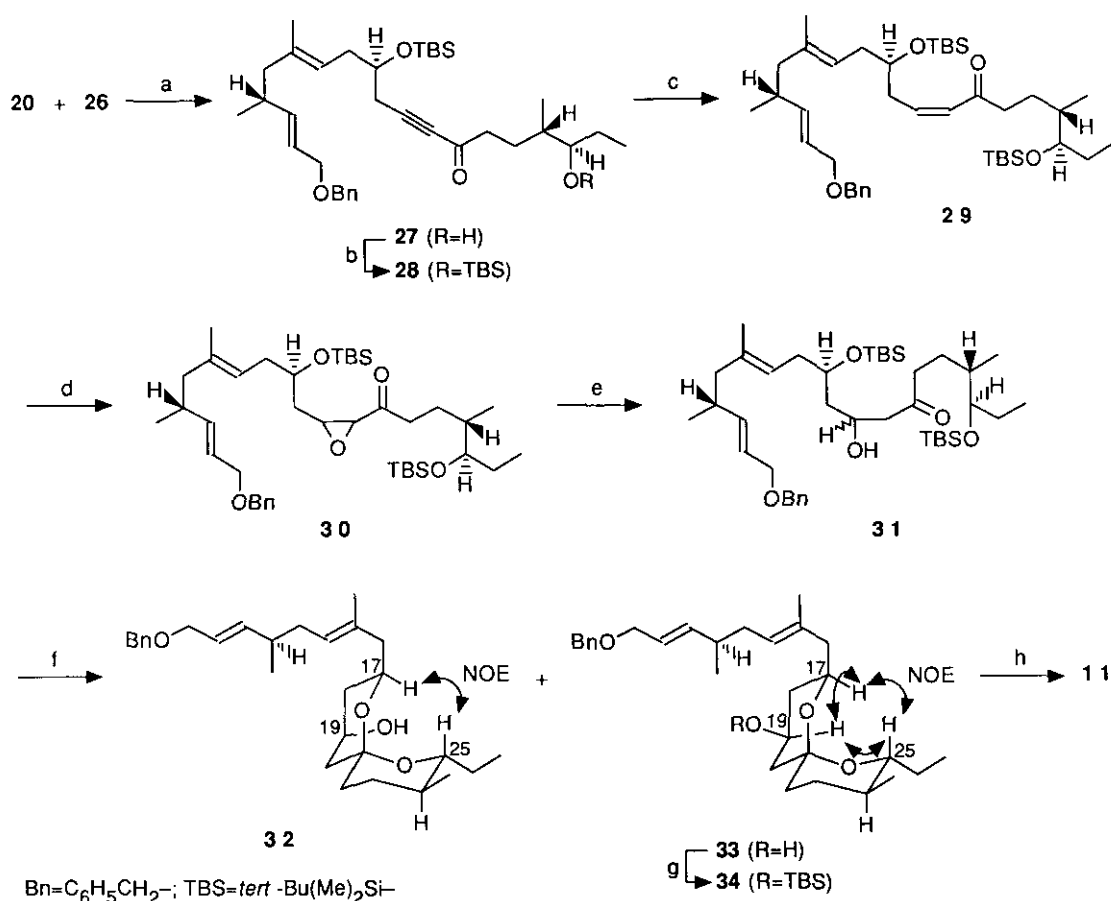
Having obtained the requisite C_{9-20} (20) and C_{21-27} (26) segments, we next examined the synthesis of the C_{9-27} segment (11) by coupling each other. Treatment of the alkyne (20) with *n*-butyllithium followed by the lactone (26) yielded the unstable ketol (27) which was immediately transformed into the TBS ether (28), $[\alpha]_{\text{D}}^{28} -6.20^\circ$ (*c* 1.03, CHCl_3), in 66% overall yield (83% overall based on consumed 20). Partial hydrogenation of the acetylene (28) in the presence of Lindlar catalyst gave the *Z*-olefin (29), $[\alpha]_{\text{D}}^{25} -6.31^\circ$ (*c* 1.01, MeOH), in 91% yield. Upon oxidation with aqueous



Scheme 5

Reagents and conditions: a, $n\text{-Bu}_4\text{NF}$, THF, room temperature; b, PhCO_2H , Ph_3P , $i\text{PrOCON}=\text{NCO}_2i\text{Pr}$, THF, 0°C ; c, K_2CO_3 , MeOH, room temperature; d, H_2 , PtO_2 , AcOEt, room temperature; e, H_2 , $\text{Pd}(\text{OH})_2$, MeOH, room temperature; f, (i) O_2 , Pt black, H_2O , 55°C , (ii) Dean-Stark apparatus, benzene, reflux.

alkaline hydrogen hydroperoxide, **29** gave the epoxide (**30**) in 96% yield as an inseparable mixture. Reduction of this mixture (**30**) with the complex¹² generated from diphenyl diselenide and sodium borohydride proceeded in a regioselective way to give the β -ketol (**31**) in 97% yield as an inseparable mixture of epimers. Very fortunately, the mixture on exposure to hydrofluoric acid at $-30\text{ }^{\circ}\text{C}$ in aqueous acetonitrile underwent concurrent desilylation and cyclization to furnish two readily separable spiroacetals, the 'unnatural' α -alcohol (**32**), $[\alpha]_{\text{D}}^{26} +43.95^{\circ}$ (*c* 0.93, CHCl_3), and the 'natural' β -alcohol (**33**), $[\alpha]_{\text{D}}^{26} +35.79^{\circ}$ (*c* 1.03, CHCl_3), in yields of 25 and 45%. Stereochemistry of both compounds could be deduced by NOE experiment in which the former showed significant NOE only between 17 and 25 hydrogens indicating the 19- α -hydroxy structure (**32**), while the latter showed apparent NOE between 17 and 19, 17 and 25, and 19 and 25 hydrogens, respectively, indicating the 19- β -hydroxy structure (**33**). The latter isomer (**32**) was readily transformed into the target C₉₋₂₇ segment (**11**), $[\alpha]_{\text{D}}^{29} +44.9^{\circ}$ (*c* 1.10, CHCl_3), in 61% overall yield, by sequential protection of the secondary hydroxy group and cleavage of the benzyl ether by a

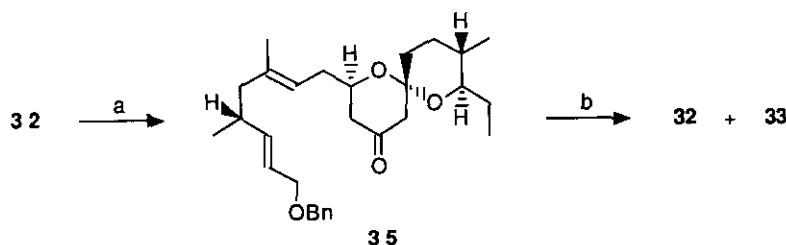


Scheme 6

Reagents and conditions: a, *n*-BuLi, THF, -78 - -5 °C; b, *tert*-Bu(Me)₂SiCl, imidazole, DMF; c, H₂, Lindlar catalyst, benzene, room temperature; d, 30% H₂O₂, 0.5 N NaOH, aq. MeOH, room temperature; e, PhSeSePh, NaBH₄, AcOH (cat.), EtOH, room temperature; f, 4 N HF, aq. MeCN, -30 °C.

Birch reduction *via* the TBS ether (34), [α]_D²⁶ +41.10° (*c* 0.80, CHCl₃) (Scheme 6).

Since direct inversion of the unnatural α -epimer (32) into the natural β -epimer (33) was failed, 32 was first transformed into the ketone (35), [α]_D²⁶ +39.36° (*c* 0.95, CHCl₃) (71%), by Swern oxidation,¹³ which was then reduced with sodium borohydride in dimethoxyethane¹⁴ to give a separable mixture of 32 and 33 in yields of 37 and 47%, the former of which may be recycled (Scheme 7).



Scheme 7

Reagents and conditions: a, Swern oxid.; b, NaBH₄, dimethoxyethane, -20 °C

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