ENANTIOCONTROLLED SYNTHESIS OF THE C_{9-27} SEGMENT OF MILBEMYCIN K FROM (*R*)- AND (*S*)-EPICHLOROHYDRINS

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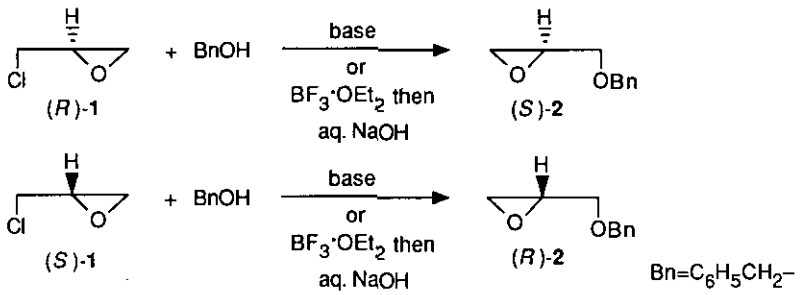
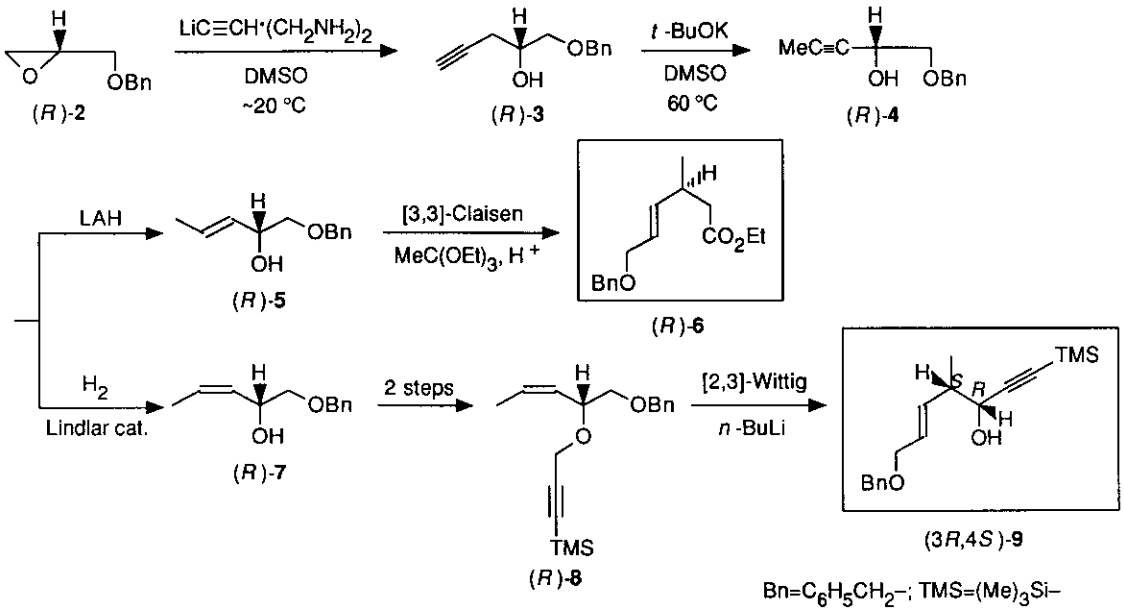
Abstract —— The C_{9-27} segment (**11**) of milbemycin K (**10**) has been synthesized using two molar equivalents of (*R*)-epichlorohydrin [(*R*)-**1**] and one molar equivalent of (*S*)-epichlorohydrin [(*S*)-**1**] as chiral building blocks.

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



Scheme 1

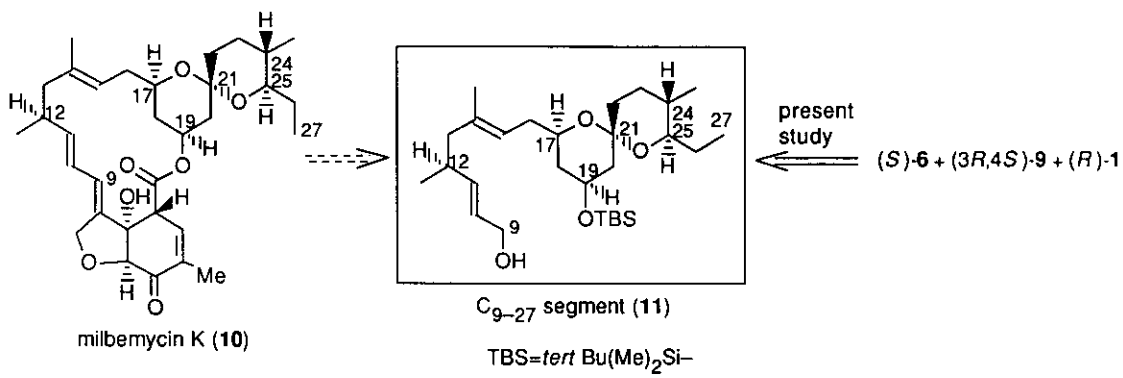
synthesis of potentially useful two chiral synthons (**6**) and (**9**) having secondary methyl group employing a [3,3]-Claisen rearrangement and a [2,3]-Wittig rearrange-



Scheme 2

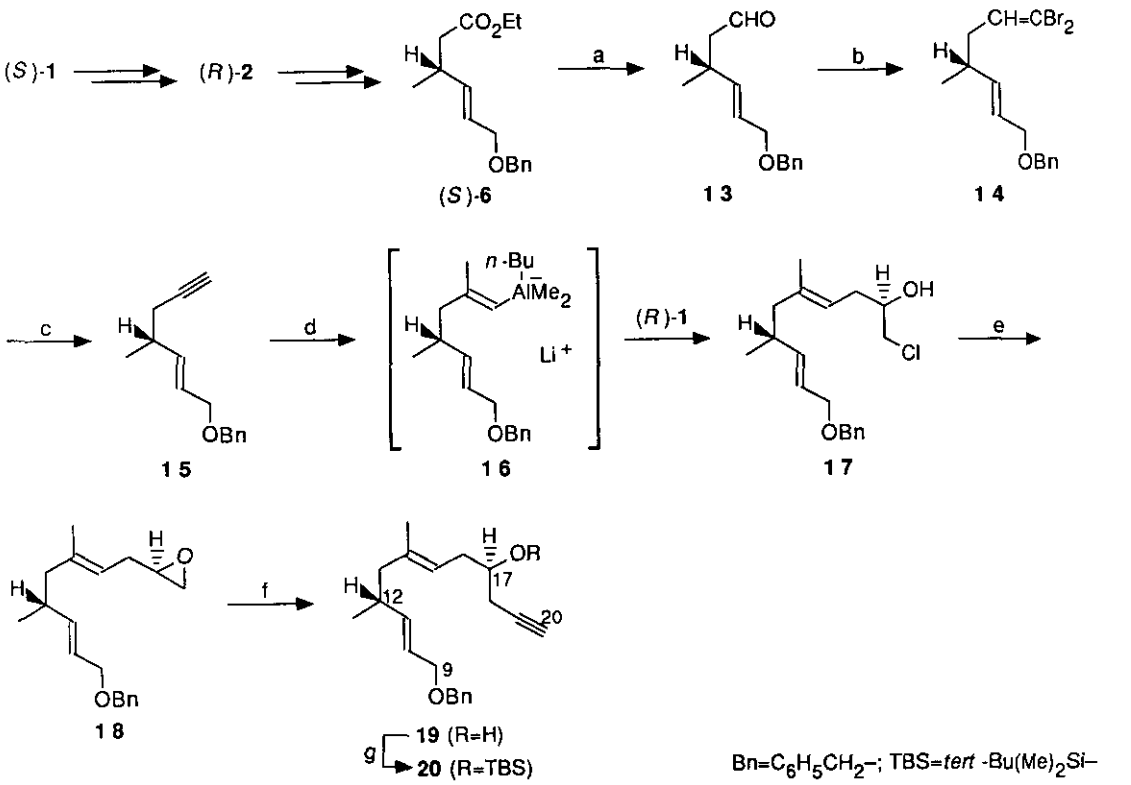
ment *via* the common acetylene intermediates[2] (**4**) (**Scheme 2**). We report herewith an utilization of these two chiral synthons for the construction of the $C_{9\text{-}27}$ segment (the northern hemisphere) (**11**) of an antiparasitic milbemycin K[3~5] (**10**) by combination with an additional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

We first examined the construction of the $C_{9\text{-}20}$ 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**), $[\alpha]_D^{26}$ –20.43° (*c* 1.00, $CHCl_3$), in 88% yield. Upon treatment with carbon tetrabromide and triphenylphosphine,[6] **13** afforded the dibromoolefin (**14**), $[\alpha]_D^{26}$ –6.67° (*c* 1.05, $CHCl_3$) (88%), which was exposed to *n*-butyllithium[6] to give the terminal acetylene (**15**), $[\alpha]_D^{24}$ –6.40° (*c* 1.00, $CHCl_3$), in 82% yield. Treatment of the acetylene (**15**) with trimethylaluminum in the presence of zirconocene dichloride[7,8] followed by *n*-butyl-



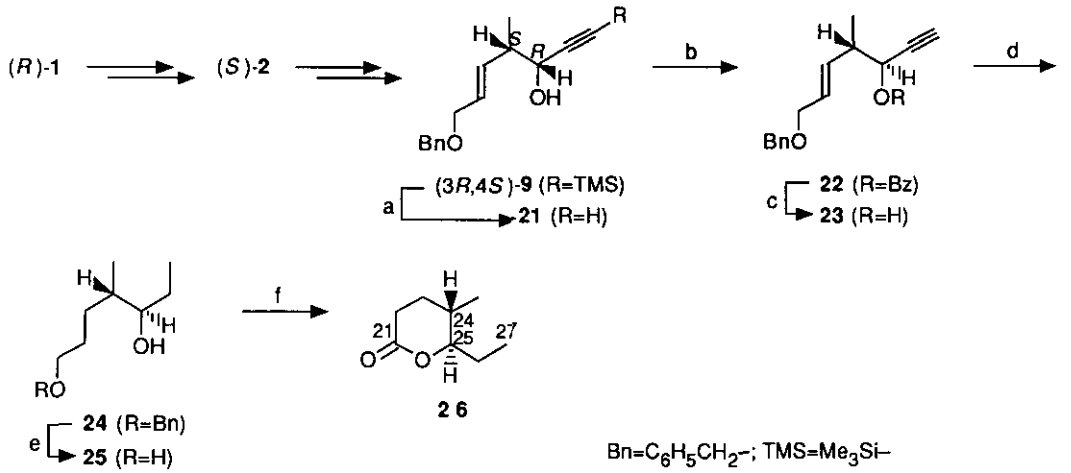
Scheme 4

Reagents and conditions: a, $(^iBu)_2AlH$, toluene, –90 °C, acid work up; b, CBr_4, PPh_3, CH_2Cl_2, 0 °C; c, *n*-BuLi, THF, –78 °C; d, (i) zirconocene dichloride, Me_3Al, CH_2Cl_2, 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**), $[\alpha]_D^{24}$ +9.80° (*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**), $[\alpha]_D^{24}$ –3.35° (*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 $C_{9\text{-}20}$ acetylenic alcohol (**19**), $[\alpha]_D^{25}$ +7.35° (*c* 1.03, $CHCl_3$) (80%), which was transformed into the *tert*-butyldimethylsilyl (TBS) ether (**20**), $[\alpha]_D^{26}$ +3.96° (*c* 1.01, $CHCl_3$), quantitatively (**Scheme 4**).

On the other hand, the construction of the $C_{21\text{-}27}$ segment[9] (**26**) was started with (3*R*,4*S*)-eneynol[2] (**9**) prepared from (*R*)-epichlorohydrin [(*R*)-**1**] *via* (*S*)-*O*-benzylglycidol [(*S*)-**2**]. Treatment of the terminal acetylene (**21**), $[\alpha]_D^{26}$ +18.15° (*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 azodicarboxylate[10] afforded the benzoate **22**, $[\alpha]_D^{25}$ –31.74° (*c* 1.01, $CHCl_3$) (75%) with inversion of 3*R*-center, which on methanolysis gave the (3*S*,4*S*)-eneynol (**23**), $[\alpha]_D^{25}$ –15.38° (*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**), $[\alpha]_D^{22}$ –7.72° (*c* 1.01, $CHCl_3$), which then was hydrogenolyzed on palladium hydroxide to give the diol (**25**), $[\alpha]_D^{24}$ –7.39° (*c* 1.01, $CHCl_3$), in 98% overall yield. Oxygenation of the diol (**25**) on platinum black[11] proceeded regioselectively at the primary hydroxy group to furnish the desired $C_{21\text{-}27}$ δ-lactone (**26**), $[\alpha]_D^{26}$ +49.32° (*c* 1.03, $CHCl_3$), in 78% yield, after azeotropic reflux in benzene (**Scheme 5**).

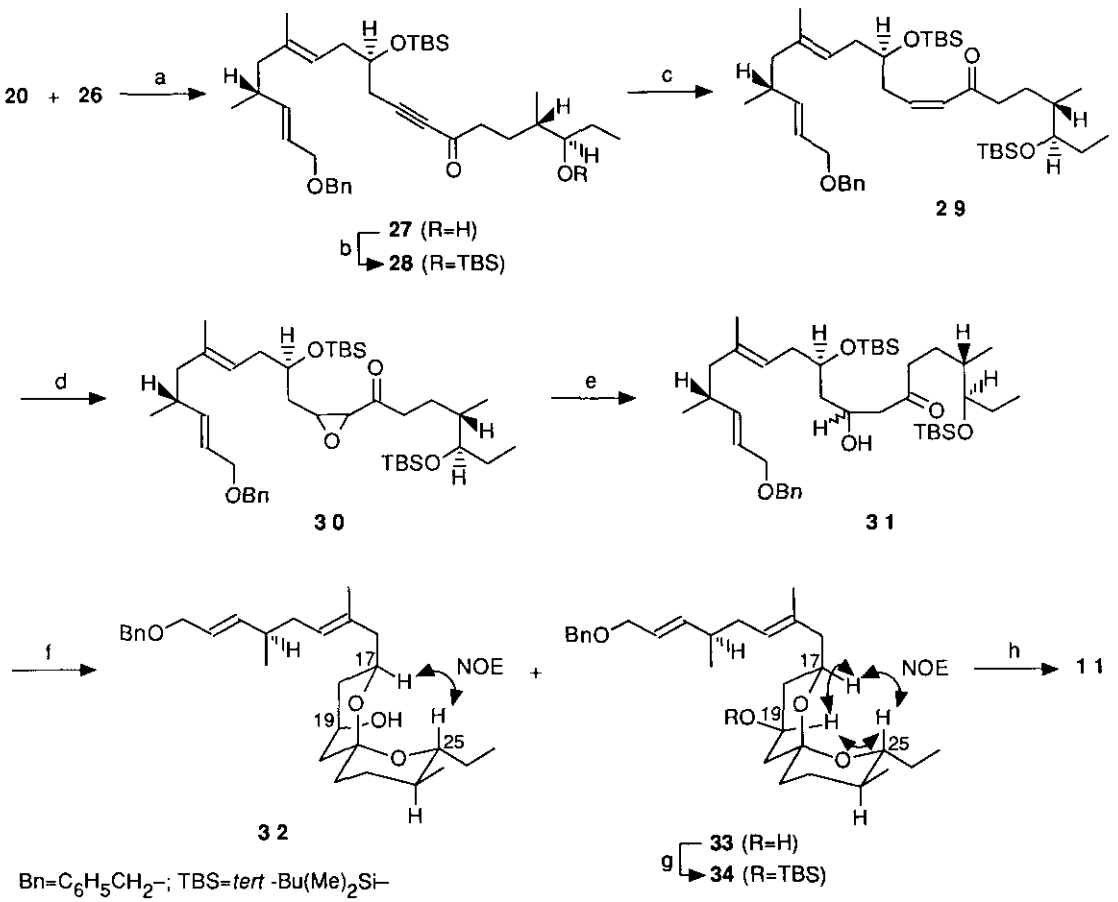
Having obtained the requisite $C_{9\text{-}20}$ (**20**) and $C_{21\text{-}27}$ (**26**) segments, we next examined the synthesis of the $C_{9\text{-}27}$ segment (**11**) by coupling each other. Treatment of the alkyne (**20**) with *n*-butyllithium followed by the lactone (**26**) yielded the unstable ketol (**27**) which was immediately transformed into the TBS ether (**28**), $[\alpha]_D^{28}$ –6.20° (*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**), $[\alpha]_D^{25}$ –6.31° (*c* 1.01, MeOH), in 91% yield. Upon oxidation with aqueous



Scheme 5

Reagents and conditions: a, *n*-Bu_4NF, THF, room temperature; b, $PhCO_2H$, Ph_3P, $^iPrOCON{=}NCO_2{}^iPr$, THF, 0 °C; c, K_2CO_3, MeOH, room temperature; d, H_2, PtO_2, AcOEt, room temperature; e, H_2, $Pd(OH)_2$, MeOH, room temperature; f, (i) O_2, Pt black, H_2O, 55 °C, (ii) Dean-Stark apparatus, benzene, reflux.

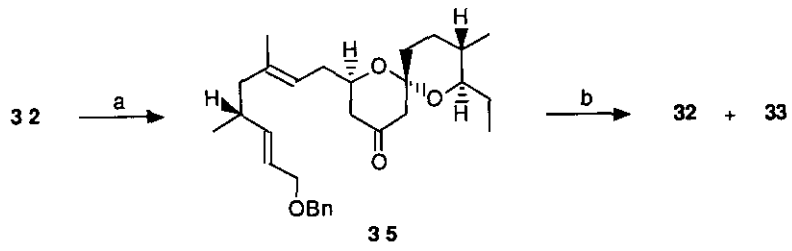
alkaline hydrogen hydroperoxide, **29** gave the epoxide (**30**) in 96% yield as an inseparable mixture. Reduction of this mixture (**30**) with the complex[12] generated from diphenyl diselenide and sodium borohydride proceeded in a regioselective way to give the β-ketol (**31**) in 97% yield as an inseparable mixture of epimers. Very fortunately, the mixture on exposure to hydrofluoric acid at –30 °C in aqueous acetonitrile underwent concurrent desilylation and cyclization to furnish two readily separable spiroacetals, the 'unnatural' α-alcohol (**32**), $[\alpha]_D^{26}$ +43.95° (*c* 0.93, $CHCl_3$), and the 'natural' β-alcohol (**33**), $[\alpha]_D^{26}$ +35.79° (*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 $C_{9\text{-}27}$ segment (**11**), $[\alpha]_D^{29}$ +44.9° (*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)$_2$SiCl, imidazole, DMF; c, H_2, Lindlar catalyst, benzene, room temperature; d, 30% H_2O_2, 0.5 N NaOH, aq. MeOH, room temperature; e, PhSeSePh, $NaBH_4$, AcOH (cat.), EtOH, room temperature; f, 4 N HF, aq. MeCN, –30 °C.

Birch reduction *via* the TBS ether (**34**), $[\alpha]_D^{26}$ +41.10° (*c* 0.80, $CHCl_3$) (**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**), $[\alpha]_D^{26}$ +39.36° (*c* 0.95, $CHCl_3$) (71%), by Swern oxidation,[13] which was then reduced with sodium borohydride in dimethoxyethane[14] 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, $NaBH_4$, dimethoxyethane, –20 °C

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