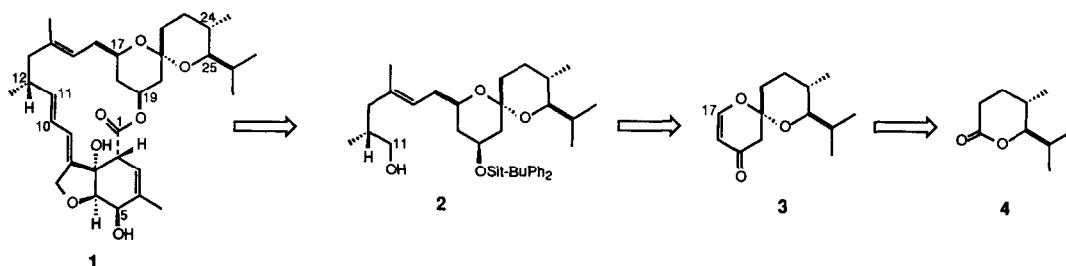# STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF THE MILBEMYCINS: SYNTHESIS OF THE C11 TO C31 FRAGMENT OF MILBEMYCIN D

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Summary: A highly stereocontrolled synthesis of the C11 to C31 fragment of the potent antimicrobial agent milbemycin D has been completed. This approach utilizes a unique hydrolysis-cyclization to construct the spiroketal portion of the molecule.

The milbemycins [2] and the avermectins[3] are two structurally related classes of macrocyclic lactones with remarkable biological activity.[4] These compounds show potent, broad spectrum anthelmintic, insecticidal, and acaracidal activity. Ivermectin, a semisynthetic derivative, is currently being employed as a veterinary medicine[5] and is being used to treat onchocerciasis ("river blindness") in humans on an experimental basis.[6]


Considerable effort has recently been directed toward the total synthesis of these important compounds. Several syntheses of milbemycin β_3, the simplest member of this class which lacks the complex hexahydrobenzofuran subunit, have been reported.[7] In addition, a number of approaches to the spiroketal fragment[8] and the hexahydrobenzofuran fragment[9] have appeared.[10] We report here a stereocontrolled preparation of the C11 to C31 fragment of milbemycin D (1). The basic synthetic plan was to construct a C1 to C10 fragment [9b] and a C11 to C31 fragment 2 leaving their connection for the final stages of the synthesis. Our strategy for the construction of the C11 to C31 portion centered around the preparation of the spirocyclic dihydropyranone 3 which would serve as a template to control the stereochemistry at C17 and C19 of the spiroketal. Spiroketal 3 was to be derived from lactone 4 by way of our previously reported method for spiroketalization.[11]

The preparation of spiroketal 3 (Scheme I) began with construction of lactone 4. Sharpless asymmetric epoxidation[12] of 4-methyl-2-penten-1-ol followed by regioselective opening of the epoxide with lithium dimethylcopper produced 90% yield of a 6:1 mixture of diol 5[13] and the corresponding 1,2-diol. The minor isomer could be readily removed by treating the mixture of diols with $NaIO_4$. Selective acetylation of the primary hydroxyl (CH_3COCl, Et_2O, pyr.) followed by formation of the secondary THP ether (dihydropyran, PPTS,

CH_2Cl_2) and subsequent removal of the primary acetate (K_2CO_3, MeOH) produced the alcohol **6** in high yield. Oxidation of the alcohol and condensation of the aldehyde **7**[14] with carboethoxymethylenetriphenylphosphorane gave an 89% yield of ester **8**. Removal of the THP ether followed by hydrogenation of the α,β-unsaturated ester and lactonization provided lactone **4** in 65% overall yield. Addition of the lithium acetylide of 1-methoxy-1-buten-3-yne to lactone **4** in THF at -78°C produced hydroxyketone **9** which was immediately treated with K_2CO_3 in methanol to give ketone **10** in 88% yield.[11] Exposure of **10** to 30% $HClO_4$ in dichloromethane in an ultrasonic cleaner produced a 63% yield of a 4:1 mixture of spiroketal **3** and the corresponding methanol adduct **11**. Use of ultrasonic waves is essential for the efficient execution of this hydrolysis-cyclization. Methyl ether **11** could be chromatographically separated and converted to **3** (moist amberlyst, CH_2Cl_2, 40°C, 75%).

Scheme I
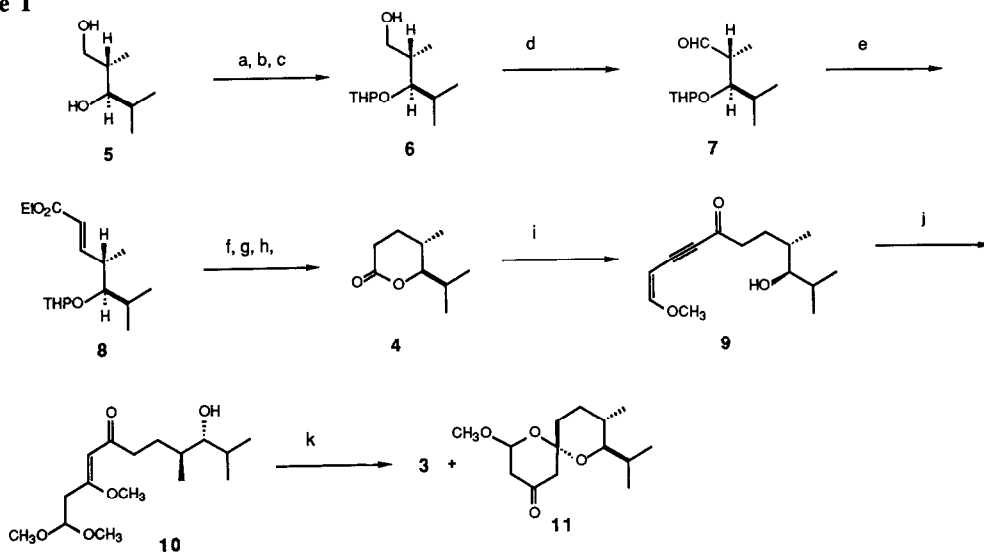
(a) CH_3COCl, Et_2O, pyridine, 0°C, 1h. (b) Dihydropyran, PPTS, CH_2Cl_2, 3h. (c) K_2CO_3, MeOH, 25°C, 2h. (d) $(COCl)_2$, Me_2SO, CH_2Cl_2, Et_3N. (e) Ph_3P=$CHCO_2Et$, C_6H_6, 80°C, 24h. (f) MeOH, PPTS, 5h. (g) H_2, Pd/C, EtOH. (h) CH_2Cl_2, PPTS, 40°C, 45 min. (i) CH_3OCH=$CHCCLi$, THF, -78°C, 1h. (j) MeOH, K_2CO_3, 18h. (k) 30% $HClO_4$, CH_2Cl_2, ultrasound, 20 min.

Copper catalyzed conjugate addition of vinylmagnesium bromide to enone **3** provided a >25:1 preference for equatorial addition to give 78% of ketone **12** (Scheme II). The remarkable diastereoselectivity observed in this reaction is most likely attributable to the C25 isopropyl group which serves to block axial approach. In contrast to the high diastereoselectivity obtained in the cuprate addition, reduction ($NaBH_4$, MeOH, 98%) of the C19 ketone produced a meager 2:1 preference for the equatorial alcohol **13a**. Fortunately, the undesired axial alcohol **13b** could be readily recycled in high yield (Jones, acetone, 80%; $NaBH_4$, MeOH).

Protection of the hydroxyl as its t-butyldiphenylsilyl ether (DMAP, DMF, t-$BuPh_2SiCl$, imidazole, 48h) proceeded in quantitative yield. Hydroboration (9-BBN, THF, ultrasound; then H_2O_2)[15] of the vinyl substituent and subsequent Swern oxidation[16] provided 97% of aldehyde **14**. Exposure of aldehyde **14** to carboethoxyethylidenetriphenylphosphorane in benzene at reflux resulted in a single detectable olefin isomer **15** in

89% yield. Reduction of the ester with diisobutylaluminum hydride (3 equiv, -78°C, 91%)gave the allylic alcohol **16**. Treatment of **16** with carbon tetrabromide and triphenyl phosphine in acetonitrile generated the desired allylic bromide **17** in 93% yield. It is of interest to note that this same transformation failed when the C19 alcohol was protected as its t-butyldimethylsilyl ether. The conditions of the reaction resulted only in removal of the protecting group without bromination. With bromide **17** in hand it remained only to execute an Evans asymmetric alkylation[17] to introduce the C12 secondary methyl with the correct relative and absolute stereochemistry. Initial experiments with stoichiometric quantities of bromide **17** and the Evans lithium enolate derived from (L)-valinol proved disappointing, but when an excess (10 equiv) of the enolate was employed, good yields of the alkylated material were obtained. It proved most practical to carry out the alkylation and the subsequent reductive removal (LiAlH$_4$, Et$_2$O) of the chiral auxiliary without isolation of the intermediate oxazolidinone. In this manner yields of 60-70%[18] of alcohol **2** {>95% e.e.; $[\alpha]^D_{20}$=+ 51.6°,CHCl$_3$, c = 0.0185 g/mL} were obtained for the two steps (d.e. >95%). Thus the C11 to C31 fragment of milbemycin D has been prepared in 13 steps in approximately 15% overall yield from lactone **4**. Current efforts are directed toward the connection of the C1 to C10 and the C11 to C31 fragments to complete the synthesis of milbemycin D.

Scheme II[a]

12 13a R$_1$=OH, R$_2$=H 13b R$_1$=H, R$_2$=OH 14 15 16 17 2
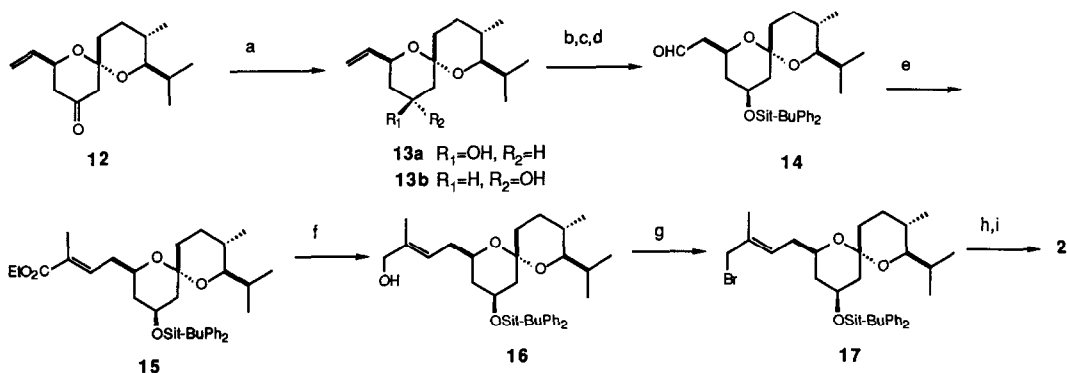
(a) NaBH$_4$, MeOH, 30 min. (b) t-BuPh$_2$SiCl, DMAP, DMF, imidazole, 48h. (c) 9-BBN, THF, ultrasound, 1h; then H$_2$O$_2$. (d) (COCl)$_2$, Me$_2$SO, CH$_2$Cl$_2$, Et$_3$N, -78°C. (e) Ph$_3$P=C(CH$_3$)CO$_2$Et, C$_6$H$_6$, 80°C, 1h. (f) Dibal-H, THF, -78°C, 3h. (g) CBr$_4$, Ph$_3$P, CH$_3$CN, 1h. (h) Evans alkylation. (i) LiAlH$_4$, Et$_2$O, 0°C, 1h.

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13.   All new compounds gave consistent NMR and IR data as well as satisfactory elemental analyses. All yields are for chromatographically pure material.

14.   This aldehyde has been previously prepared by Baker by a similar route (see ref. 8b).

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18.   These yields are based on the amount of allylic halide recovered by chromatography prior to the reduction