SYNTHESIS OF THE HEXAHYDROBENZOFURAN SUBUNIT OF THE MILBEMYCINS AND THE AVERMECTINS

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Summary: A synthesis of the hexahydrobenzofuran subunit of milbemycins J and K has been accomplished in 17 steps from 4-methyl-1,4-pentadienol.

The milbemycins are a class of insecticidal antimicrobial agents which are structurally related to the potent anthelmintic avermectins. The potential practical applications of these compounds due to their impressive antiparasitic properties, in addition to their complex structures, make them attractive targets for the synthetic chemist. Smith and Williams have reported successful approaches to the synthesis of milbemycin θ, which lacks the complex hexahydrobenzofuran subunit while Hanessian and Baker have described approaches to the spiroketal fragment of the avermectins. Fraser-Reid has recorded the only successful attack on the hexahydrobenzofuran (southern) subunit to date. This report describes the preparation of the southern subunit of milbemycins J and K, 2,3. This fragment can easily be utilized in the synthesis of the other members of the milbemycin-avermectin series as well.

It is known from studies on the naturally occurring milbemycins that if a ketone is present at C-5 instead of the secondary hydroxyl which is present in most milbemycins, reduction of the C-5 ketone with sodium borohydride results in regeneration of the naturally occurring material (correct configuration at C-5). Additionally, the C-2 carbomethoxyl is prone to epimerization if the ester is not part of the macrocycle. Thus we chose to prepare a suitable substitute for subunit 4 which took the form of 1 with a reduced C-2 carbomethoxyl and an oxidized C-5.

Oxahydrindene 1 can be readily constructed from diene 5 through a Diels-Alder strategy. Diene 5 can be prepared from methacrolein in three steps (1. Ph$_3$P=CHCO$_2$Et, CH$_2$Cl$_2$; 2. LiAlH$_4$, 291
Scheme I

**Et₂O, -20 °C; 3. t-BuMe₂SiCl, CH₂Cl₂, DMAP, imidazole, 75% overall.** Diels-Alder reaction of propiolaldehyde 12 with diene 5 at 120 °C in benzene produced 98% of aldehyde 6 (Scheme I). Addition of methylmagnesium iodide to aldehyde 6 gave 83% yield of a mixture of diastereomers 7a:7b in a ratio of 1.5:1. The ratio of these two isomers could be influenced somewhat by changing solvent and organometallic reagent (see Table).

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Directed epoxidation [VO(acac)₂, t-BuOOH, CH₂Cl₂]₁³ of 7a gave exclusively 8a while 7b was converted into only 8b, both in 98% yield. Although this sequence generates racemic material, optically pure material can be obtained by the route outlined in Scheme II. Reduction of aldehyde 6 to the allylic alcohol followed by asymmetric epoxidation [t-BuOOH, Ti(O i-pr)₄, (+)-diethyl tartrate, CH₂Cl₂] produced epoxyalcohols 10.₁⁴ Oxidation of 10a,b to the aldehydes, addition of methyllithium and oxidation to the ketone provides ketone 9 in high (95% ee) optical purity after chromatographic separation from its diastereomer.
Treatment of ketone 9 with LDA followed by tert-butyldimethylsilyl chloride gave enol ether 11. Rearrangement of the epoxide by the action of lithium diethylamide in ether occurred with partial transfer of the silyl group to the tertiary hydroxyl to yield 55% of diene 12 and 30% of enol ether 13. Hydroxylation of ketone 12 via m-CPBA oxidation of its silyl enol ether generated alpha-hydroxy ketone 14 in 75% yield. Subsequent experiments have illustrated that epoxy ketone 9 can be directly converted to enol ether 15 with excess LDA (4 equiv) and excess trimethylsilyl chloride (−78 °C to 25 °C) in quantitative yield. This enol ether can be oxidized to hydroxy ketone 16 in 60% overall yield from 9.

Several methods were examined for the electrophilic ring closure of diene 14 to 17, but N-bromosuccinimide was the only reagent which was found to effect high yields of the desired transformation. This particular reaction resulted in isolation of the 1,4 adduct 17. The relative stereochemistry of 17 was determined by converting 17 to the corresponding benzylidene 18. If the relative stereochemistry were as shown in 18a (trans fused 6,6), a large vicinal coupling constant for $H_a$ and $H_c$ (ca. 8 to 12 Hz) would necessarily be expected due to their trans diaxial disposition. However, if the stereochemistry is as shown in 18b (cis fused 6,6), $H_a$ and $H_b$ (equatorial-equatorial) as well as $H_a$ and $H_c$ (equatorial-axial) would be expected to have relatively small (0 to 3 Hz) coupling. The observed coupling for this system is $J_{a,b} = 2$ Hz and $J_{a,c} = 2$ Hz confirming the structure as 18b. Additionally, $J_{a,d} = 9$ Hz indicating a trans diaxial relationship between $H_a$ and $H_d$ and establishing the equatorial disposition of the bromine substituent. Thus, a syn 1,4 addition to the diene is observed.

Thus it remained only to effect the net S$_N$2' displacement of bromide to incorporate oxygen at C-5. This bromide was found to be remarkably inert to a wide variety of strong nucleophiles, but treatment of 17 with silver acetate in methanol or acetic acid did result in intramolecular displacement of halogen to produce tricyclic ether 19. If silyl ether 17 was selectively deprotected (5% HF, CH$_3$CN) followed by oxidation with PCC to aldehyde 20 (85% yield), the silver acetate induced cyclization (Scheme III) resulted in isolation of acetals 21.
(21a in methanol, 21b in acetic acid) in 70% yield. Lithium aluminum hydride reduction of 21b results in the formation of 22 which can be converted to 1 by selective protection of the primary hydroxyl and subsequent oxidation with Jones reagent in 54% overall yield.\(^\text{17}\)

Scheme III

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\begin{align*}
\text{Scheme III} & \\
\begin{array}{c}
\text{20} \xrightarrow{\text{AgOAc, R'OH}} \text{21a} \\
\text{21a} & \xrightarrow{\text{LiAlH}_4} \text{22} \\
\text{22} & \xrightarrow{1, BuMe_2SO} 1
\end{array}
\end{align*}
\]

References

10. Smith, A. B., private communication.
11. All new compounds gave satisfactory combustion analyses and consistent 250 MHz \(^1\)H NMR and infrared spectra.
17. We thank the National Institutes of Health (AI-19544) for financial support.

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