Tetrahedron Letters, Vol.27, No.3, pp 291-294, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF THE HEXAHYDROBENZOFURAN SUBUNIT OF THE MILBEMYCINS AND THE AVERMECTINS

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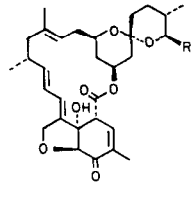
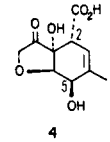
Summary: A synthesis of the hexahydrobenzofuran subunit of milbemycins J and K has been accomplished in 17 steps from 4-methyl-1,4-pentadienol.

The milbemycins are a class of insecticidal antimicrobial agents[1,2] which are structurally related to the potent anthelminthic avermectins.[3,4] 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[5] and Williams[6] have reported successful approaches to the synthesis of milbemycin β_3 which lacks the complex hexahydrobenzofuran subunit while Hanessian[7] and Baker[8] have described approaches to the spiroketal fragment of the avermectins. Fraser-Reid[9] has recorded the only successful attack on the hexahydrobenzofuran (southern) subunit to date. This report describes the preparation of the southern subunit 1 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.



2 R = CH_3
3 R = CH_2CH_3



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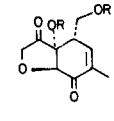
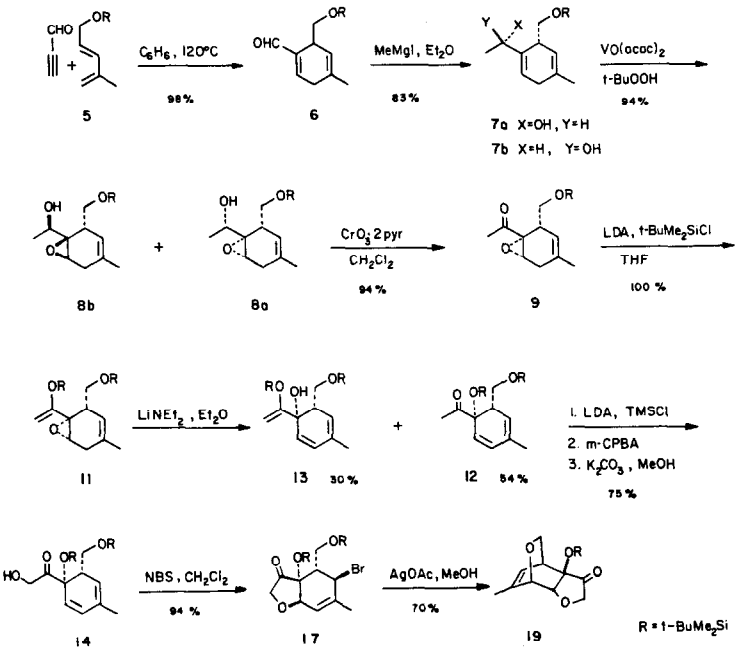


1 R = t-BuMe$_2$Si

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).[1] Additionally, the C-2 carbomethoxyl is prone to epimerization if the ester is not part of the macrocycle.[10] 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.

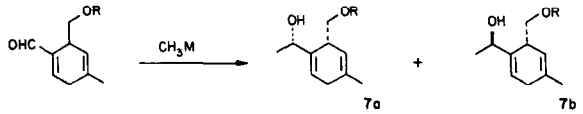
Oxahydrindene 1 can be readily constructed from diene **5** through a Diels-Alder strategy. Diene **5**[11] can be prepared from methacrolein in three steps (1. $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; 2. $LiAlH_4$,

Scheme I



Et_2O, -20 °C; 3. t-$BuMe_2SiCl$, CH_2Cl_2, 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).

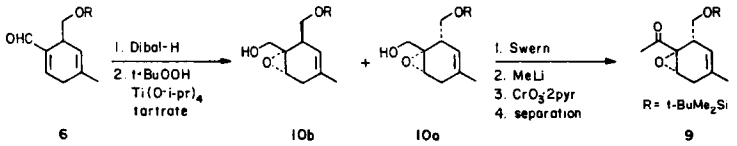
Table



R = H	CH_3MgI, Et_2O, 25°	1	1
	THF, TMEDA, -78°	4	1
	CH_2Cl_2, 25°	1	1.2
R = Si-t-$BuMe_2$	CH_3Li, Et_2O, -78°	1	6.2
	THF, -78°	1	1.9
	THF, TMEDA, -78°	1	1.7
	CH_3MgI, Et_2O, -78°	1.1	1
	THF, -78°	1	1.4
	THF, TMEDA, -78°	1.1	1
	Et_2O, 25°	1.47	1

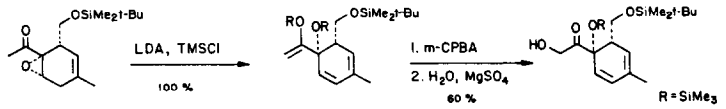
Directed epoxidation [$VO(acac)_2$, t-BuOOH, CH_2Cl_2][13] of **7a** gave exclusively **8a** while **7b** was converted into only **8b**, both in 98% yield. Although this sequence generates racemic material, optically pure material can be obtained by the route outlined in Scheme II. Reduction of aldehyde **6** to the allylic alcohol followed by asymmetric epoxidation [t-BuOOH, Ti(O i-pr)$_4$, (+)-diethyl tartrate, CH_2Cl_2] 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.

Scheme II



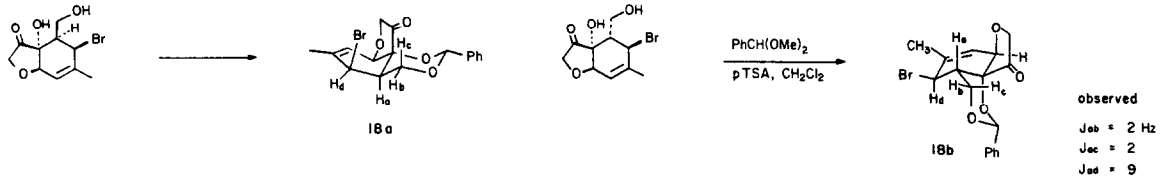
6 10b 10a 9

Treatment of ketone **9** with LDA followed by t-butyldimethylsilyl chloride gave enol ether **11**. Rearrangement of the epoxide by the action of lithium diethylamide[15] 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[16] 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**.



9 15 16

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 ot the 1,4 adduct **17**. The relative stereochemistry of **17** was determined by converting **17** to the corresponding benzylidene **18**.[9] 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.

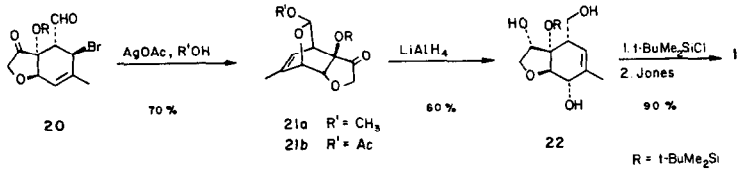


18a 18b

Thus it remained only to effect the net S_N2' 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_3CN) 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.[17]

Scheme III



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17. We thank the National Institutes of Health (AI-19544) for financial support.

(Received in USA 1 October 1985)