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SYNTHESIS OF THE SPIROKETAL FRAGMENT OF AVERMECTIN B_{1b}

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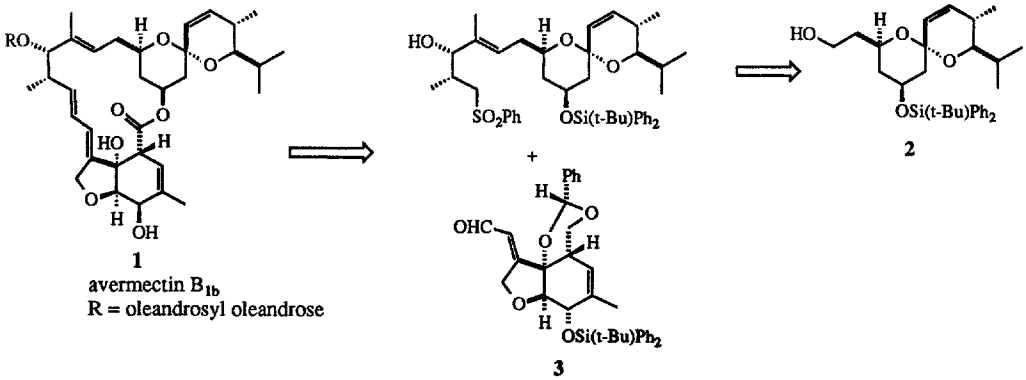
Summary: A new synthesis of the spiroketal fragment of the potent antiparasitic agent, avermectin B_{1b}, utilizing an improved procedure for the preparation of unsaturated spiroketals from lactones is described.

The remarkable potential of the avermectins and milbemycins as medicinal, veterinarial and agricultural products has been widely recognized and exploited.[2] These related compounds have been the subject of intense activity directed toward their total synthesis[3] since their discovery and characterization,[4] culminating in the recent total synthesis of avermectin A_{1a} by Danishefsky.[5] We report here a stereocontrolled synthesis of the spiroketal fragment **2** of avermectin B_{1b} **1** which is suitably functionalized for connection to an appropriate hexahydrobenzofuran subunit **3**.[6]



1
avermectin B_{1b}
R = oleandrosyl oleandrose

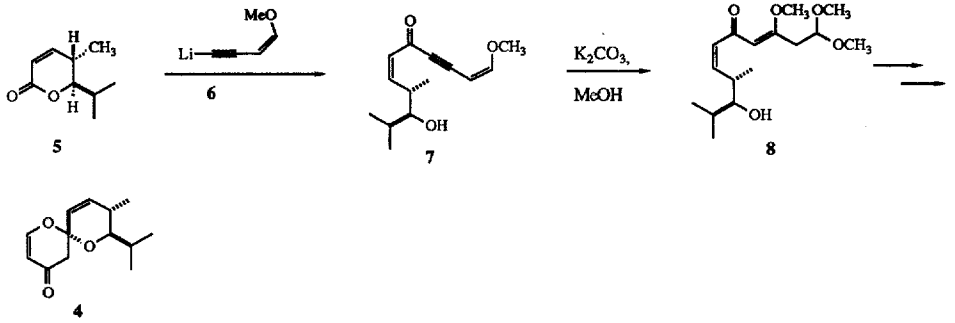
2

3

The original plan for the construction of the avermectin B_{1b} spiroketal was to utilize our previously successful methodology[7] for the preparation of unsaturated spiroketals from lactones on unsaturated lactone **5** to prepare the spirocyclic system **4** as a precursor to **2**. However, the addition of the lithium acetylide of 4-methoxy-3-buten-1-yne **6** proceeded poorly and the addition product **7** could not be transformed into the acetal **8** required for the spiroketalization. As an alternative, the phenylthiolactone **9** was prepared from diol **10**[8] by first selective tosylation of the primary alcohol followed by acylation of the secondary hydroxyl and conversion of the tosylate to the iodide. This iodoester was then treated with two equivalents of LDA at -78°C to provide the phenylthiolactone **9** in good yield.[9] Unfortunately, addition of **6** was accompanied by significant amounts of deprotonation of the lactone and yields for the addition were consistently low due to

incomplete reaction. The corresponding benzyloxylactone **11**, which was prepared in a similar manner, gave excellent yields (>95%) of the addition product **12**. This crude material could be converted to the desired unsaturated spiroketal in 85% overall yield as follows:[10] treatment with K_2CO_3 in methanol produced the trimethoxy ketone **13** which was cyclized with p-TSA in 4:1 THF:H_2O at 65°C to give a 1:1 mixture of pyrone **14** and spiroketal **15.** This crude mixture was then taken up in benzene and treated with catalytic CF_3CO_2H to give a 2:1 mixture of the spiroketals **15a,b** in 82% overall yield after chromatography from the lactone **11.** That the major isomer was indeed the axial benzyloxy derivative was evident from the small (J = 3.0, 3.0 Hz) coupling constants for the proton α to the benzyloxy group in the major isomer.

Scheme 1



5 7 8

4

Completion of the spiroketal fragment required addition of a 2 carbon subunit at C17, reduction of the C19 carbonyl and elimination of the benzyloxy group to introduce the C22-23 double bond. Addition of vinyl magnesium bromide in the presence of $[CuI(PBu_3)]_4$ produced the vinyl spiroketals **16a,b** in 80% yield. The stereoselectivity for this addition is >97% since none of the minor isomer was detected by NMR. The axial and equatorial benzyloxy isomers were then separated by flash chromatography and carried on separately for ease of analysis. While reduction of the C19 carbonyl ($NaBH_4$, DME) gave only a 3.3:1 preference for the axial alcohol **17a**, the minor isomer could be easily recycled by an oxidation-reduction sequence. Protection of **17a** as its t-butyldimethylsilyl ether was accomplished by treatment with t-butyldimethylsilyl triflate in dichloromethane. The rate of hydroboration of the vinyl group with 9-BBN was dramatically increased by ultrasonic irradiation[11] to give the primary alcohol **18a** in 89% yield. Protection of the primary alcohol as its acetate and subsequent hydrogenolysis of the benzyl ether gave the secondary alcohol **19a** in 85% yield.

At this stage the only remaining operation was to dehydrate the axial hydroxyl to introduce the C22-23 double bond. While the axial alcohol would seemed properly oriented for a simple anti-elimination, this proved surprisingly difficult to execute. Treatment of the hydroxyl with either thionyl chloride or phosphorous oxychloride produced the corresponding inorganic ester rather than effecting elimination, even at temperatures >100°C. The mesylate **20** could be formed readily, but exposure to DBU in benzene at 80°C gave no elimination. When the mesylate was treated with DBU in DMF at reflux, trace amounts of the olefin could be detected. Finally, exposure of the mesylate to DBU in DMSO at 150°C in the presence of added LiCl effected clean elimination. If "dry" DMSO was utilized the primary acetate remained intact providing **21.** However, if no attempt was made to remove any water from the DMSO, the acetate was hydrolyzed to produce the primary alcohol **2** directly. We have, as yet, been unable to effect elimination of the equatorial alcohol, although efforts are continuing.

Thus, the spiroketal fragment **2** of avermectin B_{1b} has been prepared in 16 steps in good overall yield from the diol **10**. Efforts directed toward connecting the spiroketal and hexahydrobenzofuran fragments and completing a synthesis of avermectin B_{1b} are continuing and will be reported in due course.

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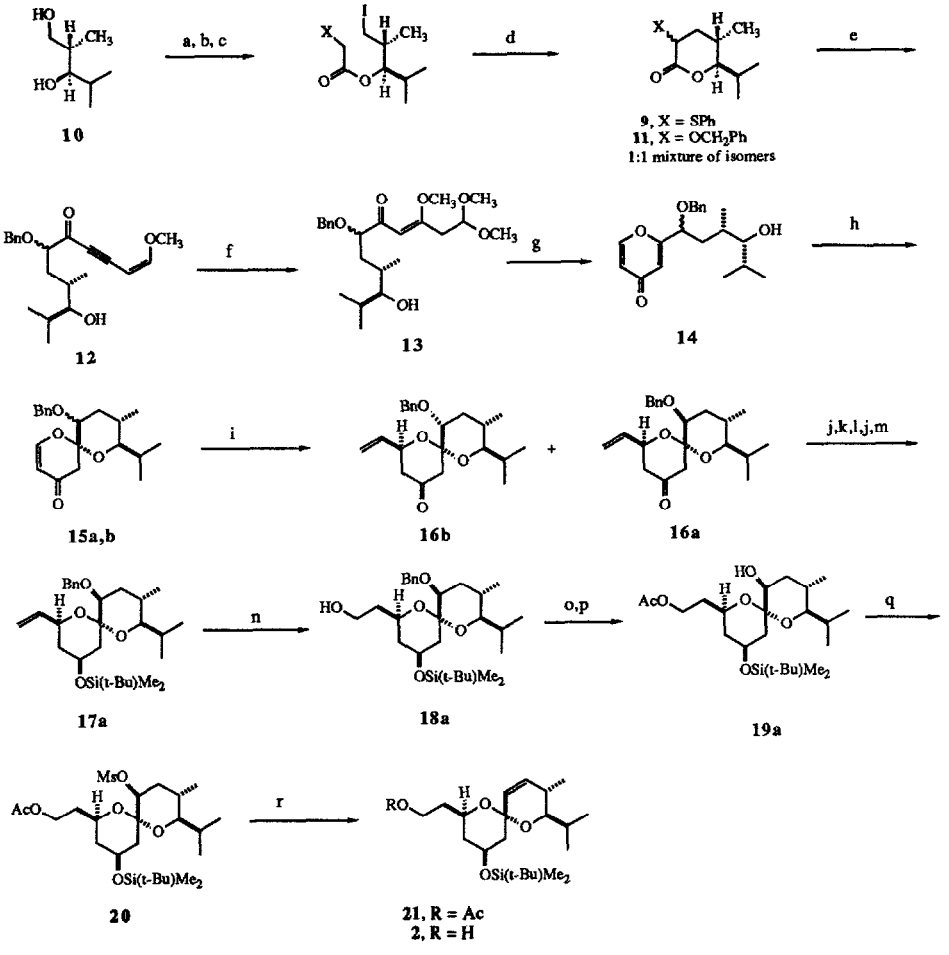
Scheme 2



a) TsCl, CH_2Cl_2, Et_3N, 82%. b) $PhCH_2OCH_2COCl$, Et_3N, CH_2Cl_2, 84%. c) NaI, $CH_3CH_2COCH_3$, 80°C, 96%. d) LDA (2.2 equiv.), THF, HMPA, -78°C, 76%. e) LiC≡CCH=CHOMe, THF, -78°C. f) K_2CO_3, CH_3OH. g) p-TSA, 4:1 THF:H_2O, 65°C, 12h. h) CF_3CO_2H, C_6H_6, 82% for 4 steps i) CH_2=$CHMgBr$, $[CuI(PBu_3)]_4$, THF, 80%. j) separate benzyloxy isomers, then $NaBH_4$, DME, 0°C, 89%. k) separate alcohol isomers. l) Jones, acetone, 99%. m) t-$BuMe_2SiOTf$, lutidine, CH_2Cl_2, 94%. n) 9-BBN, THF, ultrasound, then NaOH, H_2O_2, 89%. o) Ac_2O, pyridine, 93%. p) 10% Pd/C, H_2, EtOH, 87%. q) CH_3SO_2Cl, CH_2Cl_2, Et_3N, 95%. r) DBU, LiCl, moist DMSO, 150°C, 2h, 75%.

References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1986-90

2. Fisher, M.H. "The Avermectins" in "Recent Advances in Insect Control," Janes, N.F., Ed., The Royal Chemical Society Special Publication no.53., London, p. 53 (1985). See also reference 3.

3. For a review see Crimmins, M.T.; Hollis, W.G., Jr.; O'Mahony, R."Studies Directed Toward the Total Synthesis of the Milbemycins and Avermectins" in "Studies in Natural Products Chemistry" Vol 1, Part A, Atta-ur-Rahman, Ed., Elsevier, Amsterdam, p. 435, (1988). See also reference 5 and references cited therein.

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7. Crimmins, M.T.; Bankaitis, D.M. *Tetrahedron Lett.* **1983**, *24*, 4551.
8. Avaialable in two steps in 80% overall yield (1. t-BuOOH, Ti(i-PrO)$_4$, DET, CH_2Cl_2. 2. Me_2CuLi, Et_2O) from trans-4-methyl-2-penten-1-ol. Crimmins, M.T.; Hollis, W.G., Jr.; Bankaitis-Davis, D.M. *Tetrahedron Lett.* **1987**, *28*, 3651.

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

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