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AVERMECTIN-MILBEMYCIN SYNTHETIC STUDIES. 6. STEREOSELECTIVE ELABORATION OF THE "SOUTHERN HEMISPHERE" OXAHYDRINDENE

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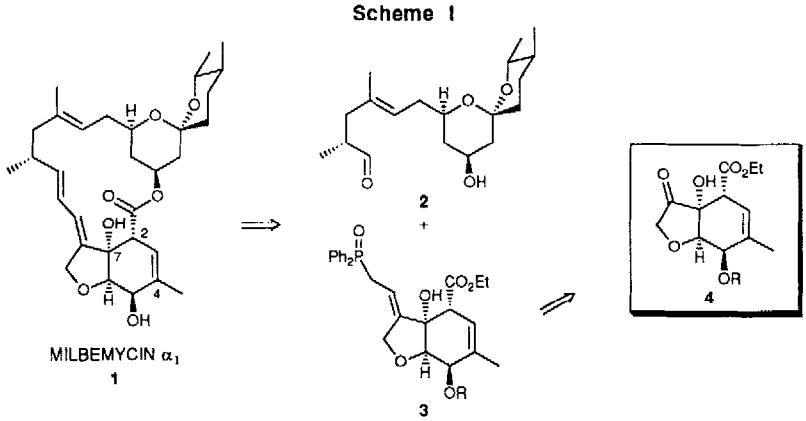
Summary: An economic, stereoselective synthesis of the highly oxygenated oxahydrindene nucleus of the avermectin-milbemycin family of anthelmintics has been achieved, exploiting a facile intramolecular S_N2' cyclization as the key step.

The avermectin and milbemycin macrolides, isolated from *Streptomyces Avermitilis*,[1] and *S. hygroscopicus*,[2] exhibit potent broad-spectrum endo- and ectoantiparasitic activity in both humans and animals.[3] Ivermectin, a semi-synthetic derivative marketed by Merck & Co., may soon eradicate the scourge of river blindness from the Third World.[3] Not surprisingly, these architecturally challenging natural products have attracted considerable attention in the synthetic community during the past decade.[4] In the early 1980's, we reported the first total synthesis of a member of this family (i.e., milbemycin β_3).[5] In that venture we: (a) developed a viable, stereocontrolled route to the "northern hemisphere" spiroketal (**2**); (b) effected Horner-Emmons union with a suitably functionalized β_3 aromatic unit; and (c) completed the synthesis via a remarkably simple and efficient macrolactonization tactic. The more complex, biologically active members of this class, including the avermectins and α milbemycins, embody highly oxygenated oxahydrindene subunits (Scheme I). Coupling of our northern hemisphere (**2**) with an appropriate southern fragment (e.g., **3**) followed by macrolactonization would extend our strategy to the more important members of this family. Central to the latter scenario was the development of an end-game protocol that would avoid the well known,[4c,m,n] problematic isomerization of a C(2,3) olefin to the C(3,4) position with concomitant epimerization at C(2). To this end, we describe here an effective, stereoselective synthesis of (±)-**4**, the key building block for the "southern hemisphere" (**3**) of the avermectins and milbemycins.

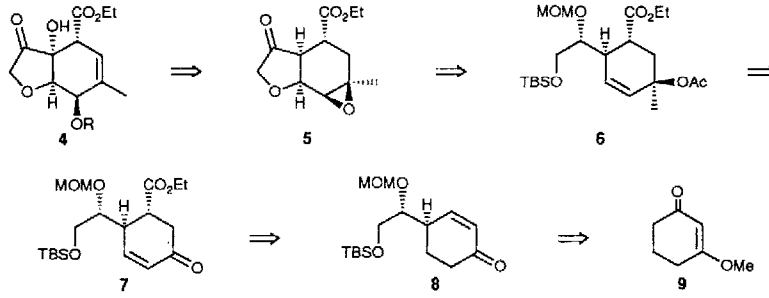
Scheme I



From the retrosynthetic perspective, we envisioned the intermediacy of oxahydrindane **5**, wherein the epoxide would serve as progenitor of the allylic alcohol moiety (Scheme II). Hydroxylation at C(7) and regioselective epoxide ring opening would then complete functionalization of **4**. The oxahydrindane nucleus of **5** in turn would derive from an intramolecular S_N2' cyclization of **6**. En route to the latter, conjugate addition of an α-ethoxy vinyl unit to enone **8**,

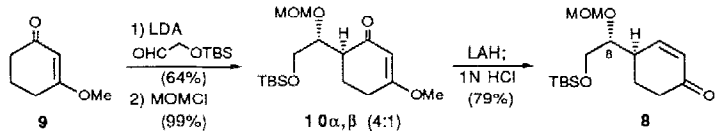
selective α' deprotonation, and selenylation would set the stage for an oxidation leading to cleavage of the enol ether and elimination of the selenide. 1,2-Addition of methyl lithium to enone **7** and acetylation would then complete construction of **6**. Finally, **8** was envisioned to arise via an aldol condensation of **9** with the *tert*-butyldimethylsilyl ether of glycolaldehyde, followed by hydroxyl protection and 1,3-carbonyl transposition.

Scheme II



With this scenario in mind, aldol reaction of **9** (Scheme III) with the TBS ether of glycolaldehyde[6] [THF, LDA, -78 °C] and protection of the resultant secondary alcohol with MOMCl [CH_2Cl_2, $(i\text{-Pr})_2NEt$, 0 °C][7] furnished a 4:1 mixture of enones **10α**[8] and **10β**[8] in 64% yield for the two steps. After separation by flash chromatography, reduction of **10α** with $LiAlH_4$ and treatment with 1N HCl afforded enone **8**[8] in 79% yield, without epimerization at C(8) (avermectin-milbemycin numbering).

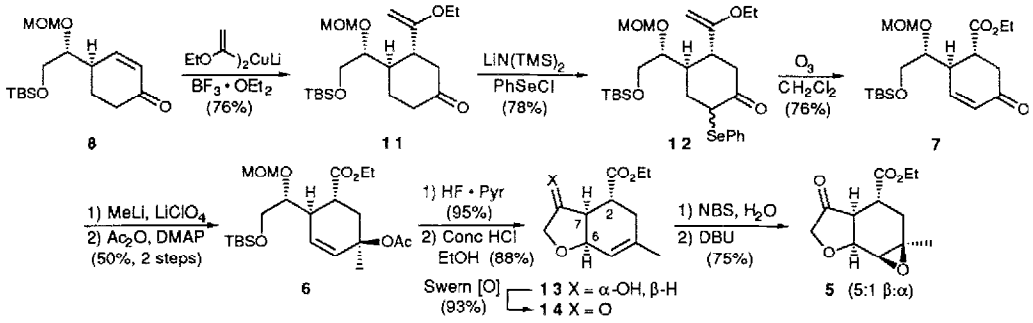
Scheme III



Initial attempts to execute conjugate addition of lithium di(α-ethoxyvinyl)cuprate[9] to enone **8** led to a 1:1 mixture of 1,2- and 1,4-adducts in modest yield. In an effort to improve both the regioselectively and efficiency of this reaction, we employed $BF_3{\cdot}Et_2O$ to activate the carbonyl group.[10] The cuprate was prepared via metalation of ethyl vinyl ether with *t*-BuLi at -78 °C, followed by warming to 0 °C and addition of the pale yellow solution to a suspension of Cu(I)I in THF at -78 °C; the resultant mixture was then warmed to -40 °C and stirred for 1h.[9] Addition of the cuprate to a solution of enone **8** and $BF_3{\cdot}Et_2O$ (4 equiv) in THF at -78 °C furnished 1,4-adduct **11**[8] in 76% yield (Scheme IV). Regioselective enolate formation [THF, $LiN(TMS)_2$, -78 °C][11] followed by trapping with PhSeCl produced selenide **12**[8] in 78% yield, whereupon ozonolysis cleaved the vinyl group and effected a selenoxide elimination; the yield of enone **7**[8] was 76%.

Addition of methyllithium (Et_2O, $LiClO_4$, -78 °C) to enone **7** proceeded stereoselectively (ca. 6:1), furnishing after acetylation (CH_2Cl_2, Ac_2O, DMAP, rt) allylic acetate **6**.[8] Desilylation with HF • pyridine (excess, CH_3CN, 0 °C) unmasked the primary alcohol, which in turn underwent a facile, intramolecular S_N2' cyclization to afford the oxahydrindene ring system in 95% yield.[12] Removal of the MOM protecting group (EtOH, concd HCl, at reflux)[7] gave alcohol **13**[8] in 88% yield; Swern oxidation (oxalyl chloride, DMSO, CH_2Cl_2, and then Et_3N, -20 °C)[13] then led to ketone **14**[8] (93%). High-field (250-MHz) ^1H NMR decoupling and NOE experiments[14] revealed a cis relationship for the C(6,7) vicinal hydrogens and a trans disposition of the C(2,7) hydrogens in **13**. Specifically, a 6.7% NOE was observed for the C(6,7) hydrogens.

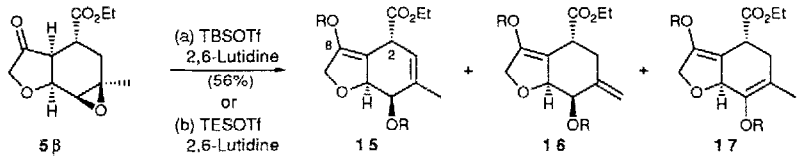
Scheme IV



The requisite epoxide moiety in **5** was next introduced via a two-step tactic.[15] Bromohydrin formation with NBS in aqueous DMSO at room temperature followed by treatment with DBU (1.2 equiv) in CH_2Cl_2 at 0 °C provided **5**[8] as a 5:1 mixture of diastereomers (β:α) in 75% yield. The initial stereochemical assignment based on literature precedent[15] was subsequently confirmed by conversion of **5**β to southern hemisphere **4**.

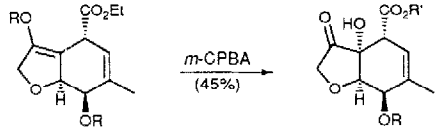
To this end, ring opening of the epoxide in **5**β (Scheme V) and silyl enol ether formation (CH_2Cl_2, TBSOTf, 2,6-lutidine, rt)[16] were effected in a single operation, affording a ternary mixture (ca. 2:1:1) of the desired allylic silyl ether **15a**,[8] and isomers **16a**[8] and **17a**.[8] A significant improvement in product distribution was achieved with the more reactive[16] triethylsilyl triflate (TESOTf, 2,6-lutidine, CH_2Cl_2, -30 °C → rt); this protocol furnished only **15b**[8] and **16b**[8] (4:1). The latter were easily separated by flash chromatography on silica. Products epimeric at C(2) or containing a C(8) silyl enol ether moiety were not obtained in either case.

Scheme V



Finally, chemoselective *m*-CPBA oxidations of both **15a** and **15b** a la White[4g] provided the target oxahydrindenes **4a**[8] and **4b**,[8] respectively (Scheme VI).[17] The structure and stereochemistry of **4a** and **4b** were assigned via detailed NMR analysis, including complete ^1H decoupling and NOE experiments and comparison with a closely related derivative (i.e., **18**) kindly provided by Professor Jung (UCLA).[18]

Scheme VI



In summary, an efficient, stereoselective construction of a "southern hemisphere" subunit for the avermectins and milbemycins has been achieved. Progress toward the total synthesis of milbemycin α_1 will be reported in due course.

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18. We thank Professor Jung (UCLA) for providing the NMR spectrum of **18**.

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