

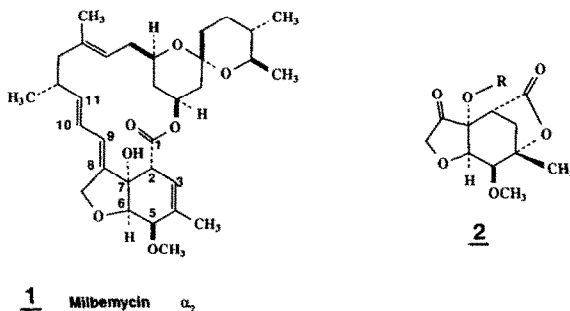
Synthesis of the Optically Active Hexahydrobenzofuran Nucleus of the Avermectins

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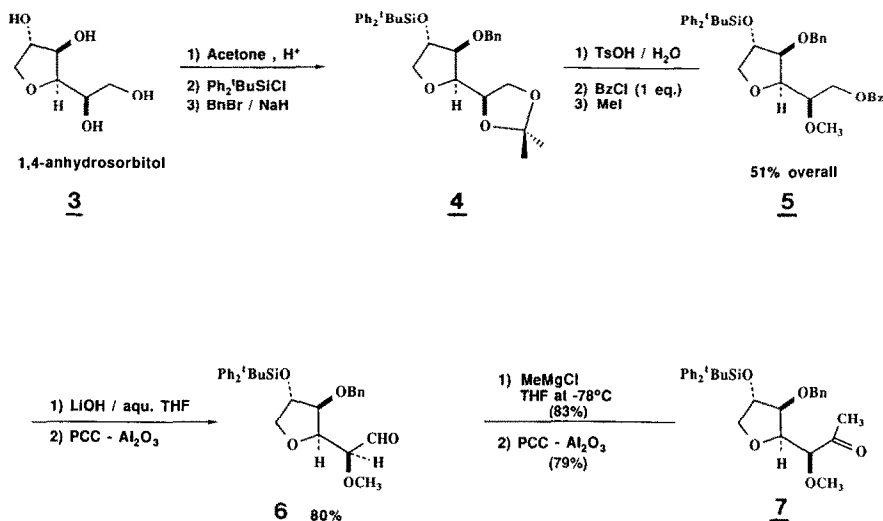
Summary: A preparation of an optically pure hexahydrobenzofuranone subunit common to the milbemycin-avermectin macrocycles is reported from 1,4-anhydrosorbitol.

The high potency and broad spectrum of insecticidal and antihelmintic properties of the milbemycin-avermectin macrolides has stimulated intense interest in the chemistry of these substances.¹ Very recently the highly functionalized C₁→C₁₀ hexahydrobenzofuran subunit, which is common to numerous examples of both the avermectin series as well as the milbemycin family, has been the subject of several communications.² In addition, a total synthesis of avermectin A_{1a} has been achieved by Danishefsky and coworkers.³ A recent report by Hirma and coworkers⁴ has prompted this communication of our studies leading to preparation of an optically pure hexahydrobenzofuran subunit **2** as a useful precursor toward total synthesis of milbemycin α_2 (**1**).

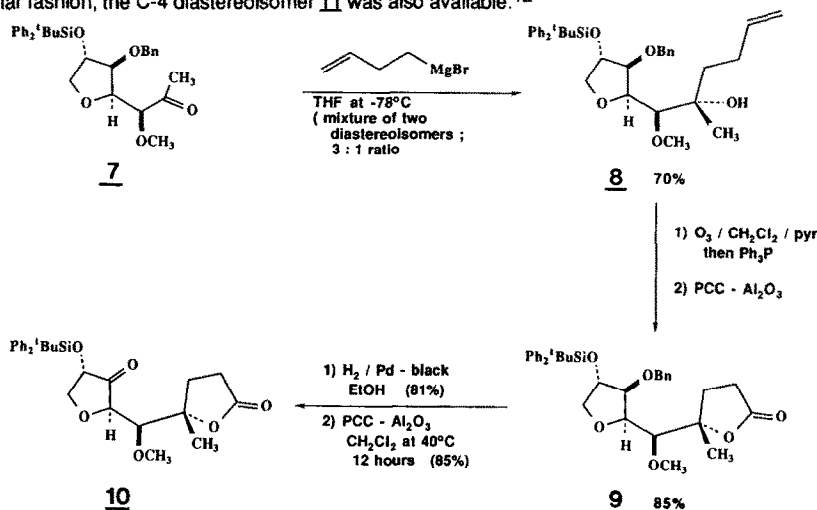


Several studies have now documented the problems of epimerization at C-2 of these natural metabolites, as well as subsequent isomerization of the C₃-C₄ carbon double bond to afford α,β -unsaturated conjugation.⁵ In view of the success of transesterification as a means of macrocyclic lactonization in the synthesis of milbemycin β_3 ,⁶ coupled with reports of eliminations of C-4 tertiary alcohols to afford the desired C₃-C₄ double bond,⁷ the bicyclic lactone **2** offered promising opportunities as a target for our synthetic endeavors. Results are illustrated in Scheme 1,⁸ beginning with 1,4-anhydrosorbitol (**3**), which is readily available in large quantities.⁹ Our first task was to distinguish each of the four hydroxyl groups. This was accomplished in high overall conversion on a preparative scale via formation of the monoacetonide of **3**, protection with one equivalent of *tert*-butyldiphenyl silyl chloride (CH₂Cl₂, Et₃N, DMAP, -10°→22°C), and benzylation of the remaining more hindered secondary alcohol (BnBr, THF, NaH, 0°→22°C), yielding **4**. Hydrolysis of the five-membered acetonide (cat. TsOH, MeOH, 22°C, 14h) gave the expected diol (mp. 56°C). Selective conversion to the primary benzoate (BzCl, 1 eq., CH₂Cl₂, Et₃N, DMAP, -78°→40°C) gave a crystalline solid (mp 65°C; [α]_D^{23.4} -43.3° (c 0.72, CHCl₃)), and methylation (CH₃, dry DMF, NaH, 0°C) provided **5** in 51% overall yield for the six step sequence. Saponification and Swern oxidation of the resulting primary alcohol at -60°C gave nearly quantitative yields of **6** without evidence of epimerization of the α -methoxy substituent. However, on larger scale (>50g) this oxidation was carried out using PCC on neutral alumina, allowing for a more convenient method for product isolation, albeit in slightly lower yields (80%). Transformation to the corresponding methyl ketone **7** ([α]_D^{24.4} -15.4° (c 0.95, CHCl₃)) was accomplished by a Grignard addition and subsequent oxidation.

Scheme I

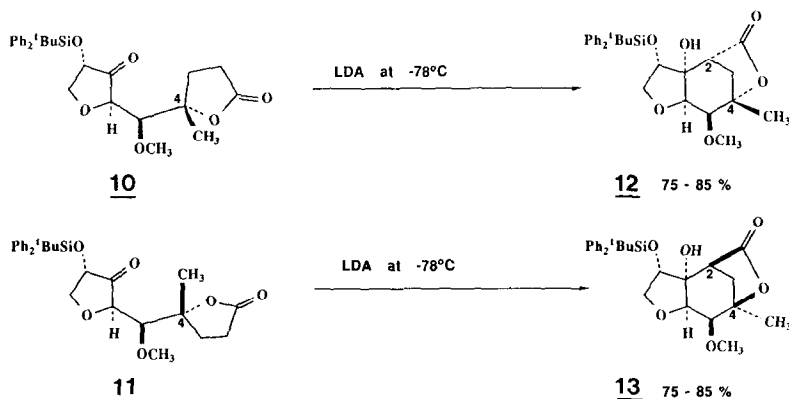


Addition of 3-butenylmagnesium bromide resulted in a separable mixture of diastereoisomers in approximately 3:1 ratio with subsequent assignment of the major tertiary alcohol as **8** (mp $45^\circ C$; $[\alpha]_D^{26} -24.9^\circ$ (c 2.0, $CHCl_3$)). On the other hand, the corresponding diastereomer (**8a**) was produced as the major component (85:15 ratio) by exchanging the sequential steps of the Grignard additions cited above.¹⁰ Conversion to the optically pure butyrolactone **9** ($[\alpha]_D^{23.4} -24.0^\circ$ (c 0.84, $CHCl_3$)) was readily completed via ozonolysis of the terminal alkene¹¹ and subsequent oxidation of the intermediate lactol with PCC on neutral alumina. Hydrogenolysis and oxidation afforded the critical intermediate ketoester **10**, and in similar fashion, the C-4 diastereoisomer **11** was also available.¹²

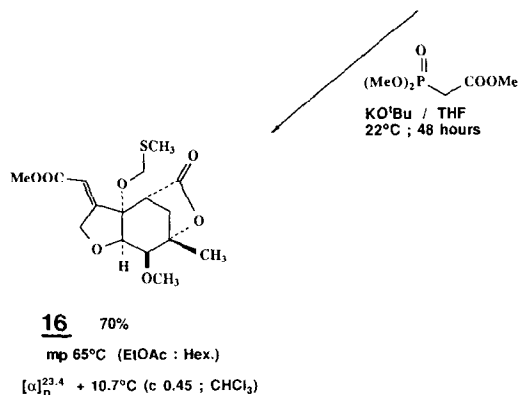
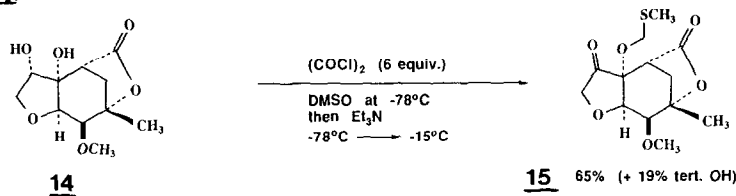


Intramolecular Claisen condensations, constructing the central cyclohexane ring as illustrated in **2**, proceeded by inverse addition of a solution of lithium diisopropylamide (THF at $0^\circ C$) to a solution of keto-ester in anhydrous tetrahydrofuran at $-78^\circ C$. In each case, we observed regioselective deprotonations and stereocontrolled formation of a

single *cis*-fused oxahydrindane, **12** and **13**, respectively, in isolated yields ranging from 75-85%.¹³ Interestingly, our molecular models suggest considerable rigidity for these transition states, featuring an appropriate alignment for enolate condensation, with a chair-like conformation of the new cyclohexane leading to **13**, whereas boat-like characteristics are present in the developing ring leading to **12**. These condensations apparently occur without competing deprotonations adjacent to the ketone function as we find no evidence of α -epimerization or β -alkoxy eliminations. Our stereochemical assignments were unambiguously confirmed by X-ray diffraction studies of the highly crystalline C-8 monobenzoate of **13** obtained following fluoride-induced deprotection ($n\text{-Bu}_4\text{N}^+\text{F}^-$, THF, -30°C) and benzylation of the resulting *cis*-diol from **13**.¹⁴



Swern oxidation of the diol **14** (mp $151\text{-}155^\circ\text{C}$, $[\alpha]_{\text{D}}^{26} +50.0^\circ$ (c 0.53, CH_3OH)) using excess oxalyl chloride (6 equiv.) and dimethylsulfoxide (12 equiv.) in methylene chloride (at -78°C with warming to -50°C over 10 minutes, Et_3N (15 equiv) at -78°C) led to formation of the C-8 ketone and protection of the adjacent tertiary alcohol as its methylthiomethyl ether **15** (65% yield). An additional amount (19%) of the corresponding unprotected alcohol was also isolated. Furthermore, we have demonstrated that ketone **15** may be a potentially useful precursor for construction of the $\text{C}_3\text{-C}_{11}$ diene of the natural products since phosphonate anion condensation allowed for selective formation of the desired *E*- α,β -unsaturated ester **16**.¹⁵



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- For examples, see: Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 5071, and reference 2(a).
- All compounds were fully characterized by proton magnetic resonance (300 MHz), infrared, and high resolution mass spectrometry.
- For preparation of 1,4-anhydrosorbitol from D-glucitol (\$12.75/kg) see: Bock, K.; Pederson, C.; Thøgersen, H. *Acta Chem. Scand.* **1981**, *B35*, 441. Each of the reactions leading to the primary alcohol of **5** has been conducted on a 55 to 75 gram scale.
- Partial characterizations of the tertiary alcohol **8**: $^1\text{H-NMR}$ (360 MHz, CDCl_3/TMS) δ 1.08 (s, 9H), 1.23 (s, 3H), 1.72 (m, 2H, methylene C-4), 2.23 (m, 2H, allylic C-3), 3.33 (s, 3H, OCH_3), 3.42 (d, 1H, $J = 9.6$ Hz, benzylic), 3.62 (s, 1H, OH), 3.80 (d, 1H, $J = 10$ Hz, methylene C-10), 3.82 (obsured, 1H, methine C-6), 3.95 (d, 1H, $J = 9.6$ Hz, benzylic), 4.00 (dd, 1H, $J = 3.8$, $J = 9.2$ Hz, methine C-8), 4.02 (d, 1H, $J = 10$ Hz, methylene C-10), 4.20 (dd, 1H, $J = 3.6$, $J = 9.8$ Hz, methine C-7), 4.30 (d, 1H, $J = 3.6$ Hz, methine C-9), 4.96 (m, 1H, vinyl), 5.06 (m, 1H, vinyl), 5.93 (dddd, 1H, $J = 6.0$, $J = 6.1$, $J = 10.0$, $J = 16.4$ Hz, vinyl), 7.1 - 7.7 (m, 15H); Diastereomeric alcohol, **8a**: $^1\text{H NMR}$ (360 MHz, CDCl_3/TMS) δ 1.12 (s, 9H), 1.30 (s, 3H), 1.68 (m, 2H, methylene C-4), 2.26 (m, 2H, allylic C-3), 3.34 (s, 3H, OCH_3), 3.48 (d, 1H, $J = 9.4$ Hz, methylene C-10), 3.82 (d, 1H, $J = 2.9$ Hz, methine C-6), 3.84 (d, 1H, $J = 9.6$ Hz, methine C-8), 3.93 (s, 1H, OH), 3.95 (d, 1H, $J = 12.6$ Hz, benzylic), 4.00 (d, 1H, $J = 12.6$ Hz, benzylic), 4.03 (dd, 1H, $J = 3.9$, $J = 9.6$ Hz, methylene C-10), 4.23 (dd, 1H, $J = 2.9$, $J = 9.4$ Hz, methine C-7), 4.34 (d, 1H, $J = 3.5$ Hz, methine C-9), 4.95 (dm, $J = 9.9$ Hz, vinyl), 5.06 (dm, 1H, $J = 16.8$ Hz, vinyl), 5.90 (dddd, 1H, $J = 6.5$, $J = 6.5$, $J = 9.9$, $J = 16.8$ Hz, vinyl), 7.1 - 7.8 (m, 15H).
- The intermediate ozonide is particularly stable, and is only very slowly reduced by dimethylsulfide.
- For identification of our keto-esters: **10**: $^1\text{H NMR}$ (360 MHz, CDCl_3/TMS) δ 1.10 (s, 9H), 1.41 (s, 3H), 1.78 (m, 1H, H at C-3), 2.50 (m, 3H, methylene C-2 and H at C-3), 3.41 (s, 3H), 3.51 (d, 1H, $J = 1.3$ Hz, methine C-5), 3.57 (dd, 1H, $J = 9.4$, $J = 9.4$ Hz, H at C-9), 3.99 (dd, 1H, $J = 8.8$, $J = 9.4$ Hz, H at C-9), 4.02 (d, 1H, $J = 1.3$ Hz, methine C-6), 4.52 (dd, 1H, $J = 8.8$, $J = 9.4$ Hz, methine C-8), 7.4 - 7.75 (m, 10H); **11**: $^1\text{H NMR}$ (360 MHz, CDCl_3/TMS) δ 1.10 (s, 9H), 1.36 (s, 3H), 1.80 (m, 1H, H at C-3), 2.5 (m, 3H, methylene C-2 and H at C-3), 3.36 (s, 3H), 3.47 (d, 1H, $J = 2$ Hz, methine C-5), 3.65 (dd, 1H, $J = 9$ Hz, H at C-9), 4.02 (d, 1H, $J = 2$ Hz, methine C-6), 4.10 (dd, 1H, $J = 9$ Hz, methine C-8), 4.36 (dd, 1H, $J = 8.8$, $J = 9.4$ Hz, H at C-9), 7.4 - 7.8 (m, 10H).
- For partial characterizations of our *cis*-fused oxahydrindanes: **12**: $^1\text{H NMR}$ (300 MHz; CDCl_3/TMS) δ 1.10 (s, 9H), 1.29 (ddd, 1H, $J = 1.0$, $J = 5.5$, $J = 14.3$ Hz), 1.32 (s, 3H), 1.68 (d, 1H, $J = 14.3$ Hz), 2.23 (d, 1H, $J = 5.5$ Hz), 3.27 (dd, 1H, $J = 1.0$, $J = 6.0$ Hz), 3.39 (s, 3H), 3.88 (dd, 1H, $J = 8.2$, $J = 8.8$ Hz), 3.98 (dd, 1H, $J = 8.2$, $J = 8.8$ Hz), 4.14 (d, 1H, $J = 6.0$ Hz), 4.51 (dd, 1H, $J = 8.2$, $J = 8.8$ Hz), 7.4 - 7.7 (m, 10H), and **13**: $^1\text{H NMR}$ (300 MHz, CDCl_3/TMS) δ 1.08 (s, 9H), 1.50 (s, 3H), 2.10 (dd, 1H, $J = 5.5$, $J = 12.5$ Hz), 2.33 (dd, 1H, $J = 1.2$, $J = 5.5$ Hz), 2.44 (d, 1H, $J = 12.5$ Hz), 3.38 (dd, 1H, $J = 4.5$, $J = 10.5$ Hz), 3.43 (d, 1H, $J = 4.7$ Hz), 3.48 (s, 3H), 3.89 (dd, 1H, $J = 6.2$, $J = 10.5$ Hz), 4.02 (dd, 1H, $J = 1.5$, $J = 4.8$ Hz), 4.43 (dd, 1H, $J = 4.5$, $J = 6.2$ Hz), 7.4 - 7.7 (m, 10H).
- The X-ray diffraction study was undertaken using a rhombic crystal of the C_8 monobenzoate of **13** at -155°C . All atoms were located and refined by full-matrix least-squares to final residuals of $R(F) = 0.045$ and $R_w(F) = 0.044$. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 87066.
- Partial characterization of methyl ester **16**: $^1\text{H NMR}$ (360 MHz, CDCl_3/TMS) δ 1.46 (s, 3H), 1.88 (ddd, 1H, $J = 1.2$, $J = 5.6$, $J = 13.5$ Hz), 2.22 (s, 3H), 2.27 (d, 1H, $J = 13.5$ Hz), 3.31 (d, 1H, $J = 5.6$ Hz), 3.54 (s, 3H), 3.53 (obsured, 1H), 3.78 (s, 3H), 4.44 (d, 1H, $J = 5.9$ Hz), 4.50 (d, 1H, $J = 10.4$ Hz), 4.63 (d, 1H, $J = 10.4$ Hz), 4.98 (dd, 1H, $J = 2.0$, $J = 17.5$ Hz), 5.16 (dd, 1H, $J = 2.0$, $J = 17.5$ Hz), 5.82 (dd, 1H, $J = 2.0$ Hz).

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