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RAPID AND EFFICIENT SYNTHESIS OF A FULLY FUNCTIONALIZED SYNTHON FOR THE BOTTOM HALF OF THE ANTIPARASITIC AGENT, IVERMECTIN

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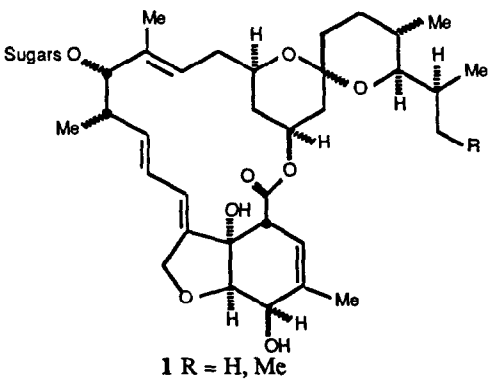
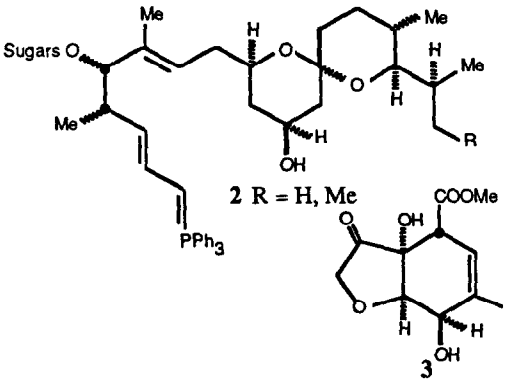
Abstract: The preparation of the bottom half of ivermectin **3** in 10 steps and 9% overall yield is reported.

The remarkable antiparasitic activity of the avermectins and milbemycins,[2] especially the commercial anthelmintic agent ivermectin **1**, has stimulated an enormous effort directed at the total synthesis of these compounds.[3,4] Nearly all groups have split the molecule retrosynthetically into top and bottom halves **2** and **3** ("northern" and "southern" "segments" or "hemispheres") with an eventual Wittig reaction and esterification planned to convert the pieces into **1**. At present, despite this intense synthetic effort, no total synthesis of a top or bottom half of ivermectin (or its derivatives) with all the numerous functionalities in their correct oxidation states has been reported.[5] We now report the first total synthesis of such a fully functionalized synthon for the bottom half of ivermectin which possesses all the required functionality in its correct stereochemistry and oxidation state, namely compound **3**.



1 R = H, Me



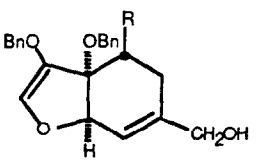
2 R = H, Me

3

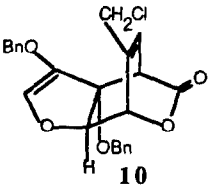
Our synthetic approach to **3** (Scheme 1) involves as the key constructive step the mild thermally induced cycloaddition of two aromatic compounds, 3,4-bis(benzyloxy)furan **4**[7] and 2-(trimethylsilyl)ethyl coumalate **5**[8] (MeOH/Δ/3h) to afford an 88% yield of the chromatographically separable endo and exo adducts **6n** and **6x** (mps 127-8°C and 120-2°C, respectively) in a ratio of 53:47.[4b,9] Although both adducts are potentially useful intermediates for the synthesis of **3**, the possible difficulties associated with isomerization at C-2[4a] led us to initially examine only the conversion of the endo adduct **6n** to **3**. It should be pointed out that this readily available compound **6n** possesses the entire molecular skeleton of the desired target **3** with functionality at all the necessary positions but with two major problems, namely an ester at C-4 instead of a methyl group and the incorrect stereochemistry at C-5.

We first corrected the functionality at C-4 as follows. Fluoride-promoted hydrolysis of the silylethyl ester of **6n** furnished the crystalline acid **7** (mp 170-1°C) in 86% yield. Many methods, e.g., borane, lithium (triethoxy)aluminumhydride, sodium borohydride on the mixed anhydride, were attempted to reduce this acid to produce the allylic

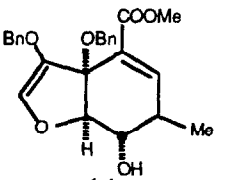
alcohol **8** but the yields were generally low (20-25%). In most cases, the preferred reaction pathway involved 1,4-reduction of the acrylate moiety with opening of the strained lactone to produce ring-opened allylic alcohols such as **9**, with either an acid or hydroxymethyl function at C-2. An attempt to apply the method of Luche[10] for 1,2-reduction of enones, namely $NaBH_4/CeCl_3$/MeOH, to the mixed anhydride formed from **7** failed due to methanolysis of the anhydride to give the methyl ester corresponding to **7**. Clearly it was necessary to find a trivalent lanthanide complex which was soluble in aprotic solvents. The best of the several tried was samarium iodide which is partially soluble in THF. Thus, conversion of the acid **7** into its mixed anhydride (Et_3N, ClCOOEt, THF, 0°C) which was then added to a suspension of samarium triiodide in THF at 0°C followed by slow addition of sodium borohydride at 5-15°C produced the desired allylic alcohol **8** (mp 131-2°C) in 71% yield. Conversion of the hydroxymethyl group to methyl was accomplished in a relatively straightforward manner. The chloride **10**, prepared in 98% yield from **8** by treatment with Ph_3P in CCl_4-THF, was reduced with sodium (trimethoxy)borohydride (HMPA, 70°C, 3h) to give an 82:18 mixture of the desired endocyclic olefin **11** and its exocyclic isomer **12** in 84% yield. We were unable initially to separate these isomers[12] and thus used the mixture in subsequent steps.



9 R = CH_2OH, COOH



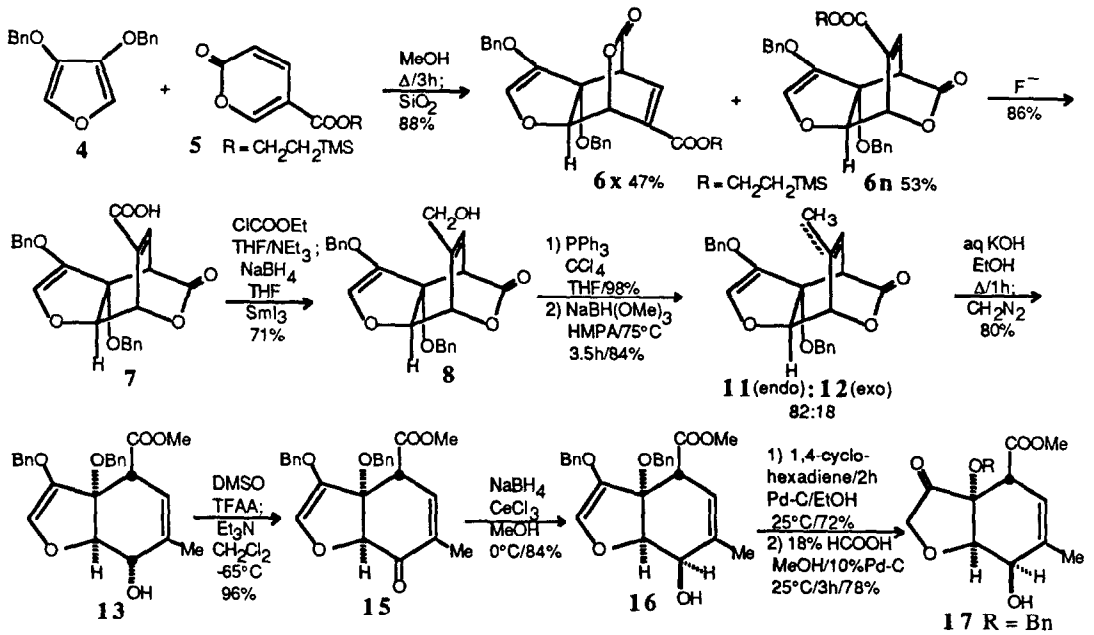
10



14

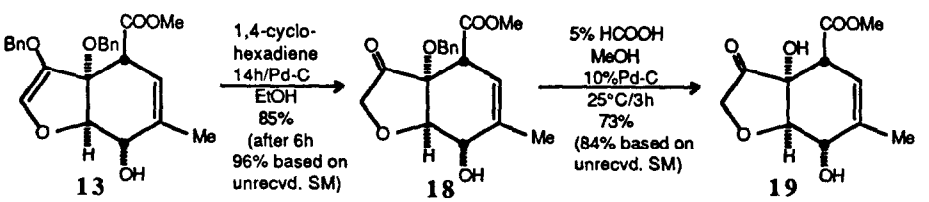
Having converted the ester to the desired methyl group at C-4, we next turned to the final synthetic challenge, namely the inversion of stereochemistry at C-5. Hydrolysis of the 82:18 mixture of lactones **11** and **12** (KOH, aq. EtOH, Δ, 1h) produced the hydroxy acid which was immediately esterified with diazomethane to give the hydroxy ester **13** in 80% overall yield.[13] We observe none of the α,ß-unsaturated ester **14** in this reaction. This ß,γ-unsaturated ester **13** is stable indefinitely at 25°C and can be purified by silica gel chromatography without conjugation to the α,ß-unsaturated isomer **14**.[14] Thus our system differs significantly from the structurally similar one of Fraser-Reid and the natural material.[4a] Oxidation of the allylic alcohol **13** (DMSO, TFAA, Et_3N, -78°C) afforded the enone **15** in 96% yield. Reduction of this enone **15** under conditions ($NaBH_4$, MeOH, 0°-25°C) reported[15] to convert 5-Oxomilbemycin D to Milbemycin D, namely the 5ß-hydroxyl, furnished only the starting alcohol **13**, namely the 5α-hydroxyl. Thus it appears that the free hydroxyl group at C-7 is required to direct this simple reduction from the α-face of the molecule. However, we were able to circumvent this problem by using $CeCl_3$ as an additive and carrying out the reduction at -78°C. Under these conditions, reduction of **15** furnished a 9:1 mixture of the desired 5ß-alcohol **16** and the 5α-alcohol **13** in 84% yield.[16] Presumably the cerium salts promote complexation of the 7-benzyl ether with the borohydride reagent to internally deliver hydrogen from the α-face. That the 5ß-alcohol **16** had indeed been formed was inferred from the 500 MHz ^1H NMR in which the coupling constant between the hydrogens at C-5 and C-6, $J_{5,6}$, was calculated to be 5.8 Hz; in the starting 5α-alcohol **13**, $J_{5,6}$ is 12 Hz.

The synthesis of **3** was completed in two steps of transfer hydrogenation. Reduction of the sterically more accessible benzyl enol ether of **16** with 1,4-cyclohexadiene and 10% Pd/C in EtOH at 25°C for 2h furnished the cyclopentanone **17** in 72% yield. Removal of the more hindered tertiary benzyl ether of **17** required a more reactive hydrogen source. Treatment of **17** with 18% HCO_2H in methanol and 10% Pd/C at 25°C for 3.5h afforded the desired target molecule **3** in 78% yield (based on unrecovered starting material).[17] The structure assignment of **3** is again based on spectroscopic data - IR, MS, and especially 500 MHz ^1H NMR, which indicates the $J_{5,6}$ is 5.6 Hz, a value that corresponds well with those of the natural product and its derivatives.[3,15] The 5α-epimer of **3**, compound **19**,



Scheme 1: Synthesis of the Ivermectin Synthon 3

could also be prepared by this sequence. Transfer hydrogenation of the 5α-alcohol **13** with 1,4-cyclohexadiene and 10% Pd/C produced the ketone **18** which on treatment with 5% HCO_2H and 10% Pd/C afforded the 5α-epimer **19**. The yield for these two steps, again based on unrecovered starting material, was 81%. The stereochemistry of the C-5 hydroxyl is again assigned by analysis of the 500 MHz ^1H NMR; $J_{5,6}$ for **19** is 1.75 Hz, which agrees well with similar 5α-derivatives in the literature.[15]



The synthesis of **3** requires only 10 steps and proceeds in an overall yield of approximately 9%. Likewise **19** is available in 8 steps and 17% overall yield. We are currently attempting to extend this first synthesis of a fully functionalized synthon for the bottom half of ivermectin to the preparation of other derivatives (e.g., the 4-acyloxymethyl compounds), the macrocyclic natural products themselves, and several analogues.[18]

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1. UCLA Gold Shield Faculty Awardee, 1986-88; Glenn T. Seaborg Awardee, 1987.

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3. For an excellent review, see: Davies, H. G.; Green, R. H. *Natural Prod. Rep.* **1986**, *3*, 87.

4. For recent synthetic work, see: a) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933. b) Jung, M. E.; Street, L. J.; Usui, Y. *Ibid.* **1986**, *108*, 6810. c) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *Ibid.* **1986**, *108*, 2776. d) Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III *Ibid.* **1986**, *108*, 2662. e) Barrett, A. G. M.; Capps, N. K. *Tetrahedron Lett.* **1986**, *27*, 5571. f) Greck, C.; Grice, P.; Ley, S. V.; Wonnacott, A. *Ibid.* **1986**, *27*, 5277. g) Hanessian, S.; Beaulieu, P. ; Dubé, D. *Ibid.* **1986**, *27*, 5071. h) Hirama, M.; Nakamine, T.; Ito, S. *Ibid.* **1986**, *27*, 4281. i) Baker, R.; O'Mahony, M. J.; Swain, C. J. *Ibid.* **1986**, *27*, 3059. j) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Dubé, D. *Ibid.* **1986**, *27*, 2699. k) Crimmins, M. T.; Lever, T. G. *Ibid.* **1986**, *27*, 291. l) Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta* **1986**, *69*, 1273. m) Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc. Chem. Commun.* **1986**, 874. n) Attwood, S. V.; Barrett, A. G. M.; Carr, R. A. E.; Richardson, G. *Ibid.* **1986**, 479. o) Attwood, S. V.; Barrett, A. G. M.; Carr, R. A. E.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840. p) Mrozik, H.; Eskola, P.; Fisher, M. H. *Ibid.* **1986**, *51*, 3058. q) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dubé, D.; André, C. *Pure Appl. Chem.* **1987**, *59*, 299.

5. The closest analogues prepared thus far are those of Fraser-Reid,[4a,6] Hanessian,[4g] Crimmins,[4k] and Ireland.[4l]

6. Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1564.

7. Prepared in five steps and 20% overall yield from commercially available diglycolic acid by a modification of the route of Eugster. Iten, P. X.; Hofman, A. A.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 430.

8. Prepared from commercially available coumalic acid by conversion to the acid chloride (80%) and coupling with 2-(trimethylsilyl)ethanol (65%).

9. All new compounds exhibited spectral data (500 MHz ^{1}H NMR, IR, MS, and elemental analysis) in full accord with their assigned structures.

10. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. Gemal, A. L.; Luche, J.-L. *Ibid.* **1981**, *103*, 5454. Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc. Chem. Commun.* **1978**, 601.

11. The hydroxymethyl compound **8** should be an excellent precursor of the milbemycin derivatives having an acyloxymethyl group at C-4, namely milbemycin α_9, α_{10}, and F.[3]

12. We have now been able to crystallize **11** from the mixture and have obtained good analytical data on it.

13. We do not know if the undesired isomer **12** is converted into **13** or if the product is derived solely from **11**.

14. That the ester group at C-2 of **13** was still α and had not epimerized was shown by recyclization of the hydroxy ester **13** to the lactone **11** (during an attempted reduction of the benzyl groups by treatment with calcium in ammonia). Thus the hydroxyl and ester groups both still have the α-stereochemistry.

15. Mishima, H.; Ide, J.; Muramatsu, S.; Ono, M. *J. Antibiot.* **1983**, *36*, 980.

16. All the DMSO must be removed from **15** since its presence in the reduction step lowers the stereoselectivity.

17. Carrying out the reaction until all of the starting material has disappeared results in the formation of the overreduced product in which the 3,4-double bond has also been reduced.

18. Since the original submission of this manuscript, a total synthesis of a synthon for the ivermectin bottom half has appeared. Crimmins, M. T.; Hollis, W. G., Jr.; Lever, J. G. *Tetrahedron Letters* **1987**, *28*, 3647.

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