

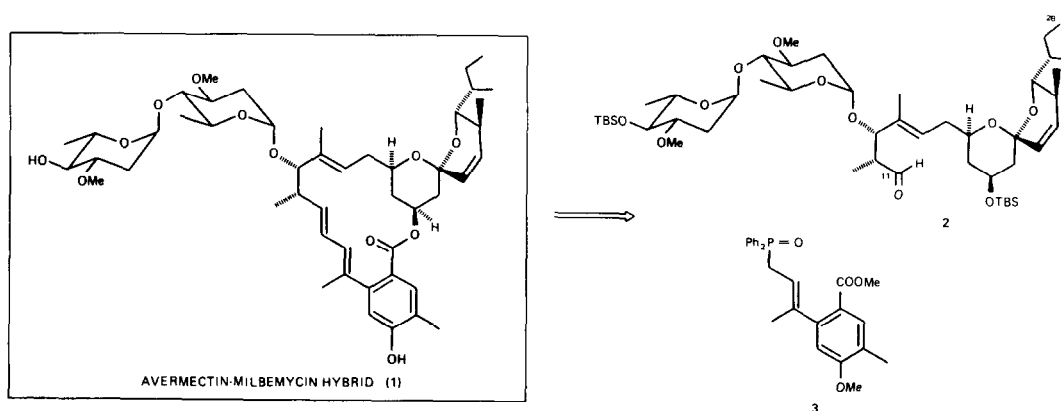
Avermectin-Milbemycin Studies. 3. Synthesis of a
Milbemycin-Avermectin Hybrid

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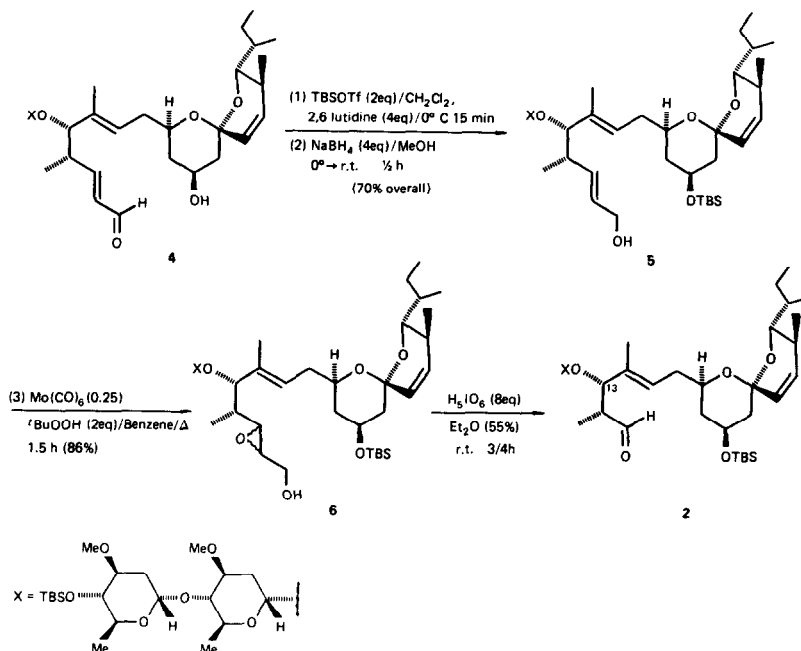
Summary: An efficient synthesis of a milbemycin-avermectin hybrid (i.e. 1) has been achieved.

In the preceding Letter,² we described our program to develop an effective chemical degradation of avermectin B_{1a}. A major objective of this venture was to obtain advanced synthetic intermediates in order to probe their chemical reactivity prior to their availability via total synthesis. In this regard, we envisioned construction of a milbemycin-avermectin hybrid (e.g., 1), which would comprise an avermectin B_{1a} northern hemisphere and a milbemycin β₃ southern hemisphere. While the immediate goal of this project would be to exploit the chemistry developed during our β₃ synthesis³ on a more highly functionalized system, success with this venture would be essential for a synthetic strategy which called for the union of an intact northern segment [C(11-28) including the disaccharide] with an appropriately designed southern segment [C(1-8)] employing a Horner-Emmons coupling. Given the structural similarity between the proposed hybrid and the avermectins, biological screening might also provide information vis a vis the avermectin-milbemycin pharmacophore.



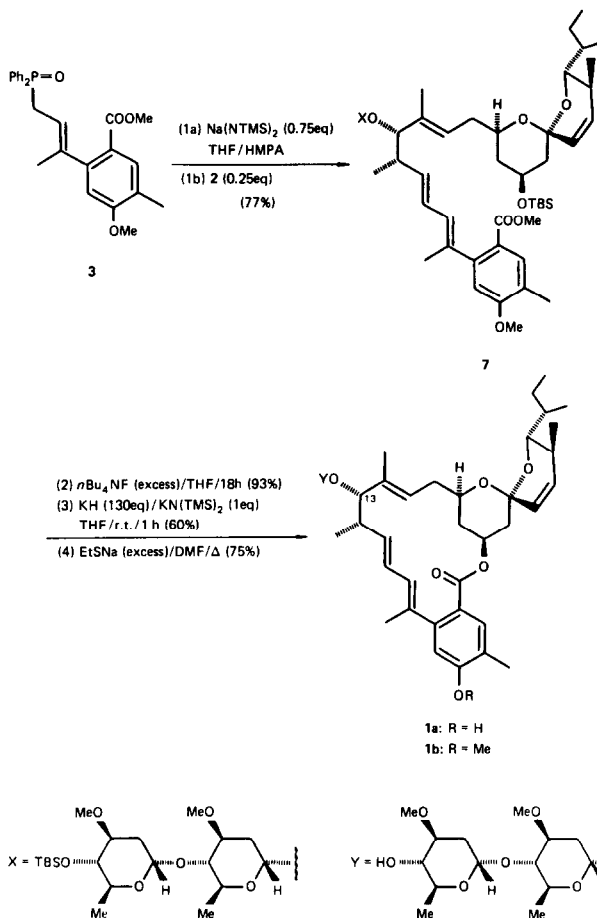
To initiate the synthesis, we required a ready source of aldehyde 2. Toward this end, protection of enal 4 [available in five steps (36% yield) from avermectin B_{1a}]⁴ as the tert-butyldimethylsilyl ether [TBSOTf (2 eq), 2,6-lutidine⁵ (4 eq), CH₂Cl₂, rt, 0.25 h] afforded the disilyl

derivative, 6, which in turn was reduced (NaBH_4 , MeOH) to give allylic alcohol 5, in 70% yield for the 2 steps. Epoxidation employing the Sharpless molybdenum hexacarbonyl/tert-butylhydrogen peroxide protocol⁷ then afforded a diastereomeric mixture of epoxides (6) in 86%. Final oxidative-cleavage [H_5IO_6 (8 eq), ether, rt, 40 min] gave the desired aldehyde 2⁸; the overall yield for this four step sequence was 33%.



Aldehyde 2, while analogous to our β_3 northern aldehyde,³ possesses the additional feature of an α -L-oleandrosyl- α -L-oleandrosyloxy disaccharide unit at C(13) which is β to the aldehyde carbonyl. This functional group arrangement represented a potentially serious problem vis a vis our planned Horner-Wittig strategy for the union of the north and south segments; in particular, a facile β -elimination may prove competitive with olefination. Indeed, initial attempts at coupling the northern and southern segments employing 2 eq of $\text{Na}(\text{TMS})_2$ to generate the anion of phosphine oxide 3 [THF, HMPA (15eq), -78°] led only to β -elimination. Fortunately, this problem could be circumvented by employing an excess of phosphine oxide 3 (ca. 4 eq) with only 3 eq of $\text{Na}(\text{TMS})_2$. Under these conditions the desired trans olefin 7⁸ was obtained in 77% yield as the sole product.

With the union secure, there remained only macrolactonization and removal of the protecting groups to complete a synthesis of the avermectin-milbemycin hybrid (1). Proceeding in exact analogy to our milbemycin β_3 synthesis, removal of the silyl groups [$(n\text{-Bu})_4\text{NF}$, THF, 25° , 4 h] and treatment of the resultant alcohol-ester with excess potassium hydride and 1 eq of $\text{KN}(\text{TMS})_2$ (THF, rt 1 h) afforded 1b⁸ in 56% yield (two steps). Demethylation was then effected with an excess of NaSEt (DMF at reflux, 1 h) to afford 1a⁸ in 75% yield. That indeed avermectin-milbemycin hybrid 1 was in hand derived from careful comparison of the high field NMR spectra with that derived from avermectin B_{1a} and milbemycin β_3 .



In summary, synthesis of milbemycin-avermectin hybrid **1** has been achieved. The synthetic route proved short (*i.e.*, 13 steps), moderately efficient (4% overall yield) and demonstrated for the first time the viability of a synthetic strategy based on a Horner-Emmons coupling of an intact avermectin B_{1a} northern hemisphere. Studies directed at the implementation of this strategy in the total synthesis of the more complex members of the avermectin-milbemycin class will be reported in due course.

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References and Footnotes

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2. Smith, A. B., III; Thompson, A. S. Tetrahedron Lett. 1985, preceding paper in this issue of Tetrahedron Letters.
3. Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. W. J. Am. Chem. Soc. 1982, 104, 4017.
4. This yield is obtained when omitting the protection of the C-7 hydroxyl during the degradation sequence; see preceding Letter.
5. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. Tetrahedron Lett. 1981, 3455.
6. This procedure can also be used to attach a tert-butyldimethylsilyl ether on the C-4" position when starting with an unprotected enal.
7. Sharpless, K. B.; Michaelson, R. C. J. Am. Chem. Soc. 1973, 95, 6136.
8. All new compounds gave 250-MHz ^1H NMR, IR, and high resolution mass spectra in accord with the structures given. All yields reported here are based upon isolated material which was $> 97\%$ pure. The NMR and IR spectra of representative intermediates are given below. 5: $[\alpha]_{\text{D}}^{20} - 35.62$ ($c = 1.21$ CHCl_3); IR (CHCl_3) 3490 (br. w), 2930 (br. s), 1100 (br s), 985 (s), 835 (s) cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.08 (s, 6H), 0.10 (s, 3H), 0.12 (s, 3H) 0.65-1.62 (m, 26H), 0.96 (s, 9H), 0.98 (s, 9H), 1.52 (s, 3H), 1.82 (m, 2H), 2.00-2.56 (m, 6H), 3.05-3.84 (m, 9H), 3.34 (s, 6H), 4.10 (m, 3H), 4.72 (br. s, 1H), 6.34-6.58 (m, 4H), 6.64-6.82 (m, 2H). 6: $[\alpha]_{\text{D}}^{20} - 42.39$ ($c = 3.59$ CHCl_3); IR (CHCl_3) 3480 (br. w), 2940 (br. s), 1105 (br. s), 985 (s), 835 (s) cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.04 (s, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.58-1.64 (m, 29H), 0.86 (s, 18H), 1.80 (m, 2H), 1.98-2.50 (m, 6H), 2.76-3.45 (m, 6H), 3.28 (s, 3H), 3.32 (s, 3H), 3.50-3.95 (m, 7H), 4.08 (m, 1H), 4.76 (br. s, 1H), 5.32 (br. s, 1H), 5.42 (m, 1H), 5.50 (dd, $J = 10.0, 2.4$ Hz, 1H), 5.66 (d, $J = 10\text{Hz}$, 1H). 2: $[\alpha]_{\text{D}}^{20} - 41.48$ ($c = 1.08$ CHCl_3); IR (CHCl_3) 2935 (br. s), 1725 (s), 1110 (br. s), 985 (s) cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.08 (s, 6H), 0.10 (s, 3H), 0.12 (s, 3H), 0.75-1.64 (m, 20H), 0.85 (s, 9H), 0.87 (s, 9H) 1.19 (d, $J = 9\text{Hz}$, 3H), 1.21 (d, $J = 9\text{Hz}$, 3H), 1.51 (s, 3H), 1.72-1.92 (m, 2H), 2.02-2.40 (m, 4H), 2.60 (m, 1H), 3.04-3.84 (m, 8H), 3.31 (s, 3H), 3.33 (s, 3H), 4.10 (m, 2H), 4.76 (br. s, 1H), 5.25 (br. s, 1H), 5.52 (m, 1H), 5.52 (dd, $J = 10.0, 2.4$ Hz, 1H), 5.68 (d, $J = 10.0$ Hz, 1H), 9.71 (d, $J = 3.4$ Hz, 1H). 7: $[\alpha]_{\text{D}}^{20} - 22.93$ ($c = 2.9$ CHCl_3); IR (CHCl_3) 2940 (br. s), 1715 (m), 1260 (s), 1150 (m), 1100 (s), 985 (s), 835 (s) cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.10 (s, 6H) 0.65-1.64 (m, 21H), 0.84 (s, 9H), 0.86 (s, 9H), 1.16 (d, $J = 7\text{Hz}$, 3H), 1.22 (d, $J = 7\text{Hz}$, 3H), 1.52 (s, 3H), 1.82 (m, 2H), 2.00-2.56 (m, 4H), 2.06 (s, 3H), 2.17 (s, 3H), 2.96-3.88 (m, 9H), 2.98 (s, 3H), 3.32 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.08 (m, 1H), 4.72 (br. s, 1H), 5.34 (br. s, 1H), 5.38 (m, 1H), 5.51 (d, $J = 9.9$ Hz, 1H), 5.68 (d, $J = 9.9$ Hz, 1H), 5.72 (m, 1H), 5.96 (d, $J = 10.7$ Hz, 1H), 6.40 (dd, $J = 14.7, 10.7$ Hz, 1H) 6.60 (s, 1H), 7.62 (s, 1H). 1b: $[\alpha]_{\text{D}}^{20} + 66.4$ ($c = 0.5$ CHCl_3); IR (CHCl_3) 3580 (w), 2950 (br. s), 1700 (m), 1270 (s), 1160 (s), 1110 (s), 1050 (s), 990 (br. s) cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.68-0.96 (m, 11H), 1.10-1.66 (m, 7H), 1.18 (d, $J = 7\text{Hz}$, 3H), 1.28 (app. t, $J = 6\text{Hz}$, 6H), 1.55 (s, 3H), 1.88-2.62 (m, 8H), 2.11 (s, 3H), 2.18 (s, 3H), 3.08-4.04 (m, 8H), 3.39 (s, 3H), 3.47 (s, 3H), 3.81 (s, 3H), 4.76 (br. s, 1H), 4.92 (br. d, $J = 9.8$ Hz, 1H), 5.40 (br. s, 1H), 5.38-5.60 (m, 3H), 5.68-5.82 (m, 2H), 6.10 (dd, $J = 15.0, 10.9$ Hz, 1H), 6.61 (s, 1H), 7.37 (s, 1H). 1a: $[\alpha]_{\text{D}}^{20} + 68.13$ ($c = 0.48$ CHCl_3); IR (CHCl_3) 3590 (w), 3340 (br), 2940 (br. s), 1700 (m), 1285 (s), 1160 (s), 1110 (s), 1050 (s), 990 (br. s) cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.68-0.98 (m, 11H), 1.05-1.34 (m, 1H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.28 (app. t, $J = 6$ Hz, 6H), 1.36-1.68 (m, 6H), 1.56 (s, 3H), 1.84-2.60 (m, 8H), 2.06 (s, 3H), 2.22 (s, 3H), 3.08-4.02 (m, 8H), 3.39 (s, 3H), 3.47 (s, 3H), 4.77 (br. s, 1H), 4.92 (br. d, $J = 9.8$ Hz, 1H), 5.02 (s, 1H), 5.38-5.60 (m, 3H), 5.40 (br. s, 1H), 5.68-5.82 (m, 2H), 6.08 (dd, $J = 14.8, 10.8$ Hz, 1H), 6.62 (s, 1H), 7.38 (s, 1H).

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