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Avermectin-Milbemycin Studies. 2. An Efficient Chemical Degradation of Avermectin B_{1a}

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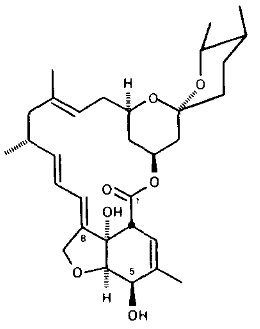
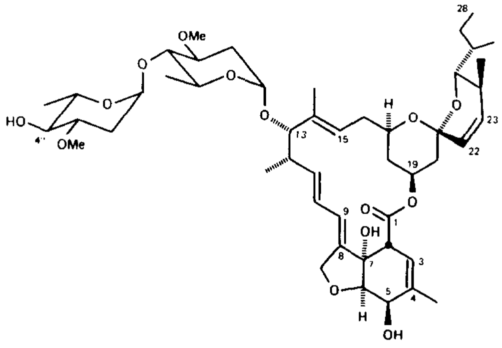
Summary: An efficient chemical degradation of avermectin B_{1a} affording intact northern and southern hemispheres has been achieved.

During the past several years considerable effort in our and other laboratories[2] has been directed at the synthesis of members of the avermectin-milbemycin class of potent anthelmintic-insecticidal agents.[3] This effort culminated in 1982 at Penn[2a] and at Indiana[2b] with the first total syntheses of milbemycin β_3, the simplest member of the avermectin-milbemycin class. Our recent attention has been focused on the total synthesis of the more complex members of the milbemycin α series. Noting the many structural similarities between avermectin B_{1a} and milbemycin α_1, in particular the C_1-C_8 segment, we initiated a parallel program designed to degrade avermectin B_{1a}.[4a] At the outset, we identified three principle objectives for this venture. First, we hoped to obtain intact both the northern [C(9-28)] and southern segments [C(1-8)] in order to confirm the structure of intermediates derived from our synthetic program. Second, we anticipated that the availability of quantities of these advanced intermediates would permit us to probe their chemical reactivity and thereby test key synthetic operations prior to their availability *via* total synthesis. Third, samples obtained by degradation would be submitted for biological testing.[4b] In this way, the structural feature(s) of the avermectin-milbemycin skeleton responsible for the biological activity might be targeted. In this and the accompanying Letter we disclose the results of this study.[11]



Milbemycin α_1



Avermectin B_{1a}

From the extensive work carried out by the Merck group,[5] we recognized that conventional approaches (i.e., ozonolysis, macrolide hydrolysis) to this problem would not be suitable. For example, saponification of the macrolide would be met with epimerization at C(2) and eventually to aromatization of the cyclohexene ring, while ozonolysis would result in oxidation of the C(3,4)-olefin, thereby disrupting the hexahydrobenzofuran ring. A simple, mild method for the chemoselective functionalization of the C(8,9)-olefin became apparent when it was seen as part of an allylic alcohol system (Scheme I). Toward this end, protection of the more reactive C(5)-hydroxyl (also an allylic alcohol) as a tert-butyldiphenylsilyl ether and the C(4")-disaccharide hydroxyl as a tert-butyldimethylsilyl ether afforded 3.[7a,b] This operation, carried out in a single-flask [(a) TBDPSCl (1.25 eq), imidazole (2.5 eq), DMAP, DMF, 48 h; (b) TBDMSCl (1.25 eq); imidazole (2.5 eq), DMF, 24 h; 90% overall yield], enabled us to epoxidize selectively the C(8,9)-olefin via the Sharpless hydroxyl directed protocol [tBuOOH (2.0 eq), $VO(acac)_2$ (0.2 eq), benzene, rt, 4 h; 78%].[6] After some experimentation (*vide infra*), we concluded that the C(7)-hydroxyl would also require protection in order to effect selective cleavage of the C(8,9)-epoxide unit. Thus, treatment of 4[7a,b] with excess diazomethane in ether cleanly afforded methoxy ether 5[7a,b] in 85-90%. The epoxide was then opened employing aqueous fluoboric acid [25% - ether (two phase system), rt, 1 h] to give diol 6a.[7a,b] Reductive-cleavage of the ester functionality with $LiAlH_4$ (10 eq, ether, 0^{o}, 1 h) and treatment of the resultant tetraol with $Pb(OAc)_4$ (1.5 eq, CH_2Cl_2, 0.°C, 2 h) afforded the intact northern and southern segments, 7a[7a,b] and 8a,[7a] respectively in 61% and 40% overall yield for the two steps.

Several comments concerning the above transformations are in order. First, use of the silyl protecting groups is not essential.[8] An identical reaction sequence wherein the C(5) and C(4")-hydroxyl groups were protected as their acetates [Ac_2O, Et_3N, DMAP, CH_2Cl_2, 18h; 95%] afforded the corresponding northern and southern hemispheres (7b and 8b, respectively 16% and 11% for the six step sequence). We prefer the silyl ether route however in that the hydroxyl groups in 8a are differentiated. Second, protection of the C(7)-hydroxyl group is critical for successful isolation of the southern hemisphere. When the C(7)-hydroxyl was not protected,[9] we were unable to isolate any products derived from the southern hemisphere upon $Pb(OAc)_4$ treatment. In this case presumably the C(7,8)-bond is first cleaved with $Pb(OAc)_4$, followed by cleavage of the C(8,9)-bond to give aldehyde 7a. Support for this assumption derives from the observation that no aldehyde (i.e., 7a) is produced upon treatment of the C(7,8,9)-triol derived from 6b with 1.0 equivalent of $Pb(OAc)_4$; however, when a second equivalent of $Pb(OAc)_4$ is added aldehyde 7a is formed in 83%.

In summation, we have developed a short, highly efficient degradative sequence for avermectin B_{1a} which leads to intact northern and southern hemisphere units. The sequence proceeds in six steps in good overall yield, and for the most part can be carried out on large scale (*ca.*, 10 g).[10] Further chemical transformations of these intermediates are reported in the accompanying Letter.[11]

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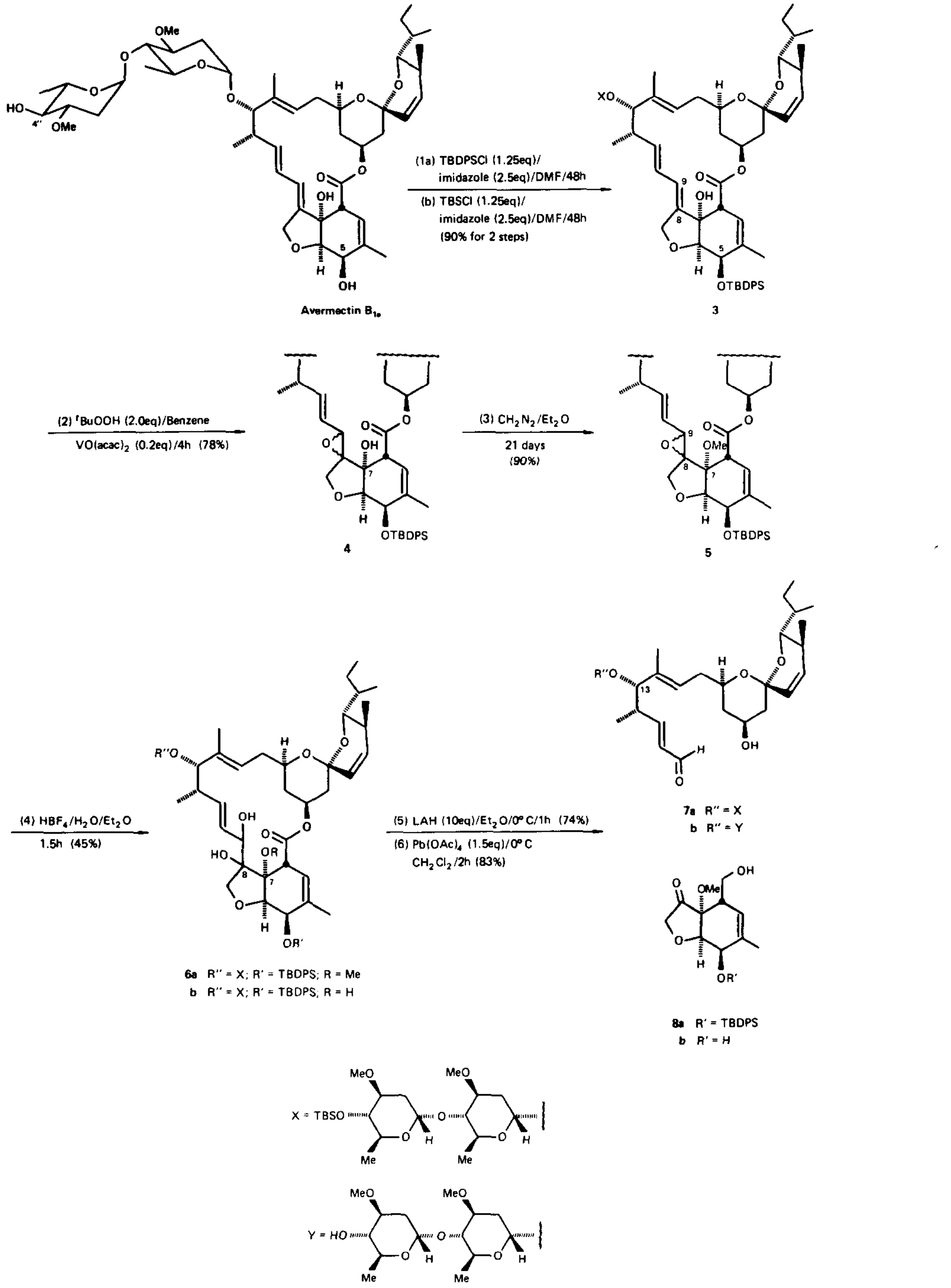
Scheme 1


Avermectin B1a
(1a) TBDPSCl (1.25eq)/ imidazole (2.5eq)/DMF/48h
(b) TBSCl (1.25eq)/ imidazole (2.5eq)/DMF/48h (90% for 2 steps)
3
(2) tBuOOH (2.0eq)/Benzene VO(acac)2 (0.2eq)/4h (78%)
4
(3) CH2N2/Et2O 21 days (90%)
5
(4) HBF4/H2O/Et2O 1.5h (45%)
6a R'' = X; R' = TBDPS; R = Me
b R'' = X; R' = TBDPS; R = H
(5) LAH (10eq)/Et2O/0°C/1h (74%)
(6) Pb(OAc)4 (1.5eq)/0°C CH2Cl2/2h (83%)
7a R'' = X
b R'' = Y
8a R' = TBDPS
b R' = H
X = TBSO
Y = HO
OTBDPS
OMe
MeO
Me
OR'
OR
XO
R''O
HO
OH
4''
5
7
8
9
13

References and Footnotes

1. Camille and Henry Dreyfus Teacher-Scholar, 1978-1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980-1985.

2. (a) Milbemycin Synthesis: Smith, A. B.,III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. J. Am. Chem. Soc. 1982, 104, 4015. (b) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. Ibid. 1982, 104, 4708. (c) Avermectin approaches: Wuts, P..G. M.; Bigelow, S. S. J. Org. Chem. 1983, 48, 3489. Hanessian, S.; Ugolini, A.; Therein, M. Ibid. 4427. Nicolaou, K. C.; Dolle, R. E.; Paphatjis, D. P.; Randall, J. L. J. Am. Chem. Soc. 1984, 106, 4189. Jung, M. E.; Street, L. J. Ibid. 8327. Prashad, M.; Fraser-Reid, B. J. Org. Chem. 1985, 50, 1566.

3. For leading references on isolation, see: (a) Milbemycin series: : Mishima, H.; Kurabayashi, M.; Tamura, C. Tetrahedron Lett. 1975, 711. Also see: Takiguchi,; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. J. Antibiotics 1980, 33, 1120 (b) Avermectin series: : Albers-Schonberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. J. Am. Chem. Soc. 1981, 103, 42116. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. Ibid. 4221.

4. (a) A generous sample of avermectin B_{1a} was provided by Merck Sharp & Dohme Research Laboratories. The sample contained approximately 10-15% of avermectin β_{1b}, which incorporates an isopropyl group at C-25. Avermectin B_{1a} was separated from B_{1b} after silylation of the secondary hydroxyl groups at C-4" and C-5. (b) All new compounds generated from this study were tested for anthelmintic activity at Merck Sharp & Dohme Research Laboratories.

5. We wish to thank Drs. M. Fisher and H. Mrozik (Merck Sharp & Dohme Research Laboratories) for helpful discussions during the course of this investigation.

6. Sharpless, K. B.; Michaelson, R. C. J. Am. Chem. Soc. 1973, 95, 6136.

7. (a) All new compounds gave 250 MHz ^1H NMR, IR, and high resolution mass spectra in accord with the structures given. (b) This compound also gave satisfactory C,H combustion analysis. All yields recorded here are based upon isolated material which was >97% pure. The rotation, ^1H NMR and IR data of representative intermediates are given below. 5: $[\alpha]_D^{20}$ + 42.13 (c = 2.53 $CHCl_3$); IR ($CHCl_3$) 2935 (br. s), 1740 (m), 1115 (s), 985 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.75-2.00 (m, 27H), 0.94 (s, 9H), 1.14 (s, 9H), 1.56 (s, 3H), 1.82 (s, 3H), 2.12-2.45 (m, 5H), 2.64 (m, 1H), 2.94 (s, 3H), 3.05-4.00 (m, 11H), 3.36 (s, 3H), 3.42 (s, 3H) 4.03 (d, J = 4.3 Hz, 1H), 4.32 (br. s, 1H), 4.38-4.43 (d, J = 11.0 Hz, 1H), 4.77 (s, 1H), 4.90-5.18 (m, 4H), 5.25-5.40 (m, 2H), 5.47-5.53 (dd, J = 9.8, 2.4 Hz, 1H), 5.69-5.74 (d, J = 9.8 Hz, 1H), 6.15-6.25 (dd, J = 15.6, 8.3 Hz, 1H), 7.30-7.50 (m, 6H), 7.65-7.90 (m, 4H); 7a: $[\alpha]_D^{20}$ - 59.69 (c = 0.784 $CHCl_3$); IR ($CHCl_3$) 3610 (w), 3480 (br), 2950 (br. s), 1695 (s), 1120 (br. s), 995 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.75-1.75 (m, 21 H), 0.90 (s, 9H), 1.20 (app t, J = 6Hz, 6H), 1.54 (s, 3H), 1.82-2.45 (m, 6H), 2.66 (m, 1H), 3.00-3.86 (m, 9H), 3.67 (s, 3H), 3.71 (s, 3H), 4.10 (m, 1H), 4.72 (br. s, 1H), 5.25 (br. s, 1H), 5.44 (br. t, J = 7Hz, 1H), 5.52 (dd, J = 9.9, 2.4 Hz, 1H) 5.69 (d, J = 9.9 Hz, 1H), 6.08-6.18 (dd, J = 15.6, 7.9 Hz, 1H), 6.80-6.90 (dd, J = 15.6, 7.9 Hz, 1H), 9.53 (d, J = 7.9 Hz, 1H). 8a: $[\alpha]_D^{20}$ + 2.48 (c = 2.62 $CHCl_3$); IR ($CHCl_3$) 3560 (br), 2935 (br. s), 1770 (s), 1110 (br. s), 910 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.77 (s, 3H), 2.26 (m, 1H), 2.62 (m, 1H), 2.92 (s, 3H), 3.69 (m, 2H), 3.73 (d, J = 17Hz, 1H), 3.90 (d, J = 4.2 Hz, 1H), 4.33 (d, J = 17Hz, 1H), 4.40 (s, 1H), 5.35 (s, 1H), 7.34-7.50 (m, 6H), 7.68-7.88 (m, 4H).

8. The decision to use a tert-butyldiphenylsilyl ether at C-5 was made in order to deliver a "southern hemisphere" with a reasonably stable protecting group.

9. The yield of epoxide opening was much higher (80-85%), when the C-7 hydroxyl was not protected.

10. Protection of the C(7)-hydroxy group (e.g., excess diazomethane) is not recommended on a scale larger than 500 mg. The other reactions in this sequence were performed on scales as large as 10 g.

11. The following Letter in this issue of Tetrahedron Letters.

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