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SYNTHESIS OF MILBEMYCINS FROM AVERMECTINS

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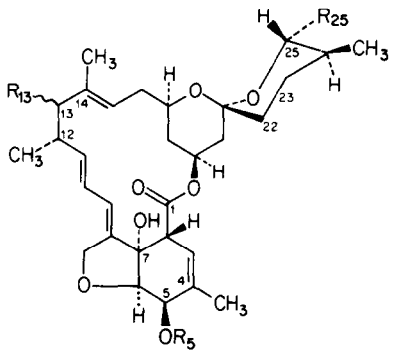
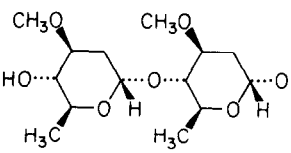
The structures of the avermectins and the milbemycins were interrelated by the conversion of 22,23-dihydroavermectin B_{1a} and B_{1b} aglycones (**4**) into 13-deoxy-22,23-dihydroavermectin B_{1a} aglycone (**9**) and 13-deoxy-22,23-dihydroavermectin B_{1b} aglycone (**11**) corresponding to 26-ethyl milbemycin-α_3 and milbemycin B-41D respectively via reduction of the protected 13-chloroaglycone derivatives.

The avermectins are a group of pentacyclic sixteen-membered lactones produced by the soil organism Streptomyces avermitilis.[1,2] They are of interest due to their outstandingly potent broad spectrum antiparasitic activities especially against helminths[3] and arthropods.[4] Their action on GABAergic nerve transmission has been the subject of several recent studies.[5] The semisynthetic 22,23-dihydroavermectin B_1 (ivermectin) **I**[6] was recently introduced as a broad spectrum antiparasitic agent for veterinary uses.





1 R_5=H, $R_{13\alpha}$= HO···, ···O···, ···O, R_{25} = $CH(CH_3)C_2H_5$ 85%, $CH(CH_3)_2$ 15 %

2 R_5=H, R_{13} = H, R_{25} = CH_3

3 R_5=H, R_{13} = H, R_{25} = C_2H_5

4 R_5=H, $R_{13\alpha}$ = OH, R_{25}= $CH(CH_3)C_2H_5$ 85%, $CH(CH_3)_2$ 15%

5 R_5 = $Si(CH_3)_2C(CH_3)_3$, $R_{13\alpha}$ = OH, R_{25} = $CH(CH_3)C_2H_5$

6 R_5 = $Si(CH_3)_2C(CH_3)_3$, $R_{13\alpha}$=OH, R_{25} = $CH(CH_3)_2$

7 R_5 = $Si(CH_3)_2C(CH_3)_3$, $R_{13\beta}$ =Cl, R_{25} = $CH(CH_3)C_2H_5$

8 R_5 = $Si(CH_3)_2C(CH_3)_3$, R_{13} = H, R_{25} = $CH(CH_3)C_2H_5$

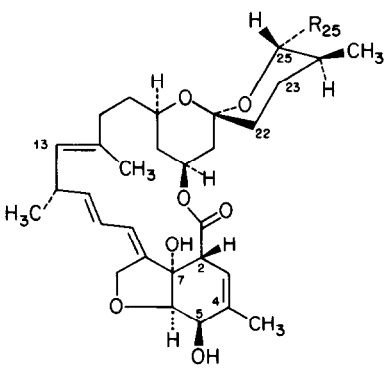
9 R_5 = H, R_{13} = H, R_{25} = $CH(CH_3)C_2H_5$

11 R_5 = H, R_{13} = H, R_{25} = $CH(CH_3)_2$

The milbemycins[7] are a group of fermentation products structurally closely related to the avermectin aglycones.[8] Milbemycins α_1 and α_3 (**2** and **3**) can be regarded as lower homologs of 13-deoxy-22,23-dihydroavermectin B_1 aglycone (**4**)[6] where C-25 is substituted by a methyl or ethyl group instead of the sec-butyl or isopropyl group of **4**. Deoxygenation of the 13-hydroxy group of **4** represents a synthesis of the milbemycins from the avermectins.[9]

22,23-Dihydroavermectin B_1 aglycone (**4**) was readily available as a mixture containing approximately 85% of the 25-sec-butyl homolog "a" and 15% of the isopropyl homolog "b"[6] which was used without further separation as starting material. First, the reactive 5-hydroxy group of **4** was selectively protected as a 5-O-tert-butyldimethylsilyl derivative[10] [$ClSi(CH_3)_2C(CH_3)_3$, 3 eq., imidazole, 6 eq., DMF, 45 min, 18°C] obtained as a mixture of **5** and **6** [75%, UV λ_{max} (MeOH) 243 nm (ε 30000), TLC (SiO_2, CH_2Cl_2-EtOAc-95:5) two spots with R_f 0.56 (**5**) and 0.44 (**6**), HPLC (Waters C_{18} μBondapak reverse phase column, MeOH-H_2O-9:1) retention time 8.8 (**5**) and 8.0 (**6**) min., MS: M^+ 700 (**5**) and 686 (**6**)]. At this stage, the surprisingly large separation of the homologous mixture on thin layer silica gel plates suggested a good possibility for separation of **5** and **6**. Repeated column chromatography gave the homologs **5**[11] and **6**[11] in better than 97% purity.

Preliminary experiments using methanesulfonyl or p-toluenesulfonyl derivatives of the allylic 13-hydroxy group as intermediates for the preparation of a halogen derivative suitable for reduction were not encouraging. However, we found that reaction of **5** with 2-nitrobenzenesulfonyl chloride (5 eq., 4-dimethylaminopyridine 6 eq., diisopropylethylamine 6 eq., CH_2Cl_2, 2 hrs, 18°C)[12] gave the 13-deoxy-13-β-chloroaglycone **7**[11] directly in 55% yield. This compound presumably formed *via* the 13-α-(2-nitrobenzenesulfonate) ester, which reacted under the experimental conditions with the available chloride ions. Reduction of **7** with tri-n-butyltin hydride [10 eq., 2,2'-azobis(2-methylpropionitrile) catalytic amount, toluene, 2 hrs, 85°C] gave the desired 13-deoxy aglycone **8**[11] (80%) containing as a by-product a 13,14-double bond isomer (not isolated, see below), obtained in the reduction of the allylic radical.[13] Removal of the tert-butyldimethylsilyl protecting group with p-toluenesulfonic acid monohydrate (1% in



10 $R_{25} = CH(CH_3)C_2H_5$
12 $R_{25} = CH(CH_3)_2$

MeOH, 30 min, 18°C) from **8** gave after preliminary purification on a silica gel column a 9:1 mixture of **9** and **10** (77%). Pure **9**[11] and **10**[11] were obtained by separation *via* reverse phase chromatography in batches of 50 to 500 mg on a Whatman Partisil 10/50 ODS-3 M20 column with MeOH-H_2O-85:15 as mobile

phase. The protected 25-isopropyl aglycone derivative **6** gave in an identical series of reactions 13-deoxy-22,23-dihydroavermectin B_{1b} aglycone (**11**)[11] together with the isomeric **12**.[11] A compound with structure **11** was recently isolated from a milbemycin-producing organism and named milbemycin B-41D,[14] thus completing our conversion of an avermectin into a naturally-occurring milbemycin.

The 300 MHz H-NMR and mass spectra of milbemycin α_3 (**3**)[14] and its avermectin-derived homologs **9** and **11** are in full agreement with their structural assignments. The 13-C NMR spectra of aglycone **4** and deoxyaglycone **9** are identical with the exception of the expected upfield shift of C-13 (-29.2 ppm) and minor shifts for the adjacent carbons (C-11, 12, 12a, 14, 14a and 15 by 5.7, -3.5, 3.1, -1.8, 1.0 and 3.6 ppm respectively). The identity of the 13-C-NMR spectra of the homologous pair **9** and **11** was complete except for carbon 25 and the attached sec. butyl side chain of **9** (C-25, 26, 26a, 27 and 28: 77.2, 35.6, 12.6, 27.4 and 11.9 ppm respectively) and C-25 and the attached isopropyl chain of **11** (C-25, 26, 26a, 27: 78.5, 28.4, 14.2 and 21 respectively). The identical absolute stereochemistry for the avermectins and milbemcyins was previously deduced[2a] and is further confirmed by the optical rotations of **3**[7] and **9** (+106° and +100° respectively). The 13,14-position was assigned to the double bond of isomer **10** based on the observation of a new doublet at 5.07 ppm in the H-NMR spectrum, which collapsed to a singlet upon irradiation of the C_{12}-proton. The E-configuration is favored as it resembles closest the conformation of the avermectin aglycones,[2b] but this has not been proven.

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11) All compounds have been characterized by 200 or 300 MHz H-NMR, mass and UV spectral data, and elemental analysis and/or high resolution mass spectra. Their purity was established by TLC (SiO_2, CH_2Cl_2-EtOAc or hexane-EtOAc) and/or reverse phase column chromatography (Whatman Partisil PXS 10/25 ODS-3, MeOH-H_2O 85:15 to 95:5). Significant spectral data are recorded below (UV in MeOH; NMR in $CDCl_3$; $[\alpha]_D$ in acetone): **5**: UV λ_{max} 244 nm (ε = 28750); H-NMR: δ 0.13 [s, $Si(CH_3)_2$], 0.80 (d, 6 Hz, $C_{24}CH_3$), 0.86 (d, 6 Hz, $C_{26}CH_3$), 0.92 [s, $SiC(CH_3)_3$], 0.97 (t, 6 Hz, $C_{27}CH_3$), 1.18 (d, 6 Hz, $C_{12}CH_3$), 1.78 (s, C_4CH_3), 3.20 (bd, 8 Hz, $C_{25}H$), 3.37 (q, 2.5 Hz, C_2H), 3.84 (d, 6 Hz, C_6H), 4.03 (bs, $C_{13}H$), 4.11 (s, C_7OH), 4.45 (bm, C_5H); MS: 700 (M^+), 682, 625, 458, 440, 375, 307. **6**: UV λ_{max} 244 nm (ε = 28100); H-NMR: δ 0.12 [s, $Si(CH_3)_2$], 0.80 (d, 6 Hz, $C_{24}CH_3$), 0.85 (d, 6 Hz, $C_{26}CH_3$), 0.92 [s, $SiC(CH_3)_3$], 1.04 (d, 6 Hz, $C_{26}CH_3$), 1.16 (d, 6 Hz, $C_{12}CH_3$),1.79 (bs, C_4CH_3), 3.08 (bd, 9 Hz, $C_{25}H$), 3.36 (q, 2.3 Hz, C_2H), 3.83 (d, 6 Hz, C_6H), 4.03 (bs, $C_{13}H$),4.07 (s, C_7OH), 4.46 (bm, C_5H). MS: 686 (M^+), 668, 611, 444, 426, 375, 293. **7**: UV λ_{max} 246 nm (ε = 30600); H-NMR: δ 0.13 [s, $Si(CH_3)_2$], 0.92 [s, $SiC(CH_3)_3$], 1.82 (s, C_4CH_3), 3.38 (q, 2.3 Hz, C_2H), 3.84 (d, 6 Hz, C_6H), 4.12 (d, 10 Hz, $C_{13}H$), 4.02 (s, C_7OH), 4.46 (bm, C_5H); MS: 718 (M^+), 661, 643, 625, 607, 476, 195, 151, 95. **8**: UV λ_{max} 244 nm (ε = 28400); H-NMR: δ 0.13 [s, $Si(CH_3)_2$], 0.93 [s, $SiC(CH_3)_3$], 1.81 (s, C_4CH_3), 3.37 (m, C_2H), 3.83 (d, 6 Hz, C_6H), 4.11 (s, C_7OH), 4.46 (bd, 6 Hz, C_5H), 4.95 (bt, 5.5 Hz, $C_{15}H$), $C_{13}H$ obscured in the aliphatic region. MS: 684 (M^+), 627, 609, 592, 442, 424, 415, 407, 356, 314, 292, 273, 248, 223, 195, 151. **9**: UV λ_{max} 244 nm (ε = 30100); H-NMR: δ 0.84 (d, 7.5 Hz, $C_{26}CH_3$), 0.95 (t, 7.5 Hz, $C_{27}CH_3$), 1.00 (d, 7.5 Hz, $C_{12}CH_3$), 1.87 (s, C_4CH_3), 2.33 (d, 8 Hz, C_5OH), 3.19 (bd, 8 Hz, $C_{25}H$), 3.27 (q, 2.5 Hz, C_2H), 3.97 (d, 6 Hz, C_6H), 4.07 (s, C_7OH), 4.30 (bt, 8 Hz, C_5H), 4.95 (t, 7.5 Hz, $C_{15}H$), $C_{13}H$ obscured in the aliphatic region; MS: 570 (M^+), 513, 442, 424, 407, 356, 344, 314, 273, 248, 223, 151 $[\alpha]_D$ = +100° (c = 0.745). **10**: UV λ_{max} 247 nm (ε = 28050); H-NMR; δ 1.91 (bs, C_4CH_3), 2.47 (d, 8 Hz, C_5OH), 3.10 (bd, 7.5 Hz, $C_{25}H$), 3.38 (q, 2 Hz, C_2H), 3.96 (s, C_7OH), 4.03 (d, 6.5 Hz, C_6H), 4.34 (bt, 7 Hz, C_5H), 5.07 (bd, 6 Hz, $C_{13}H$); MS: 570 (M^+), 513, 484, 442, 424, 407, 388, 356, 314, 277, 259, 248, 229, 195, 183, 167, 150. $[\alpha]_D$ = +29.6° (c = 0.250). **11**: UV λ_{max} 243 nm (ε = 30450); H-NMR: δ 0.87, 1.01 (two d, 7 Hz, two $C_{26}CH_3$), 1.06 (d, 7 Hz, $C_{12}CH_3$), 1.89 (bs, C_4CH_3), 2.35 (d, 8 Hz, C_5OH), 3.10 (dd, 9 and 2 Hz, $C_{25}H$), 3.29 (q, 2.3 Hz, C_2H), 3.99 (d, 6 Hz, C_6H), 4.11 (s, C_7OH), 4.33 (bt, 7.5 Hz, C_5H), 4.99 (bt, 8 Hz, $C_{15}H$), $C_{13}H$ obscured in the aliphatic region; MS: 556 (M^+), 513, 428, 410, 393, 356, 314, 278, 259, 248, 209, 181, 151. $[\alpha]_D$ = +102° (c = 0.265). **12**: UV λ_{max} 249 nm (ε = 32960); H-NMR: δ 0.79 (d, 7 Hz, $C_{24}CH_3$), 0.86 (d, 7 Hz, $C_{26}CH_3$), 0.95 (d, 7 Hz, $C_{26}CH_3$), 1.07 (d, 7 Hz, $C_{12}CH_3$), 1.89 (d, 7 Hz, C_4CH_3), 3.00 (bd, 9 Hz, $C_{25}H$), 3.36 (q, 2.3 Hz, C_2H), 3.88 (s, C_7OH), 4.02 (d, 6 Hz, C_6H), 4.33 (bt, 6 Hz, C_5H), 5.07 (bd, 7 Hz, $C_{13}H$); MS: 556 (M^+), 513, 484, 428, 410, 393, 356, 314, 248, 181.

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