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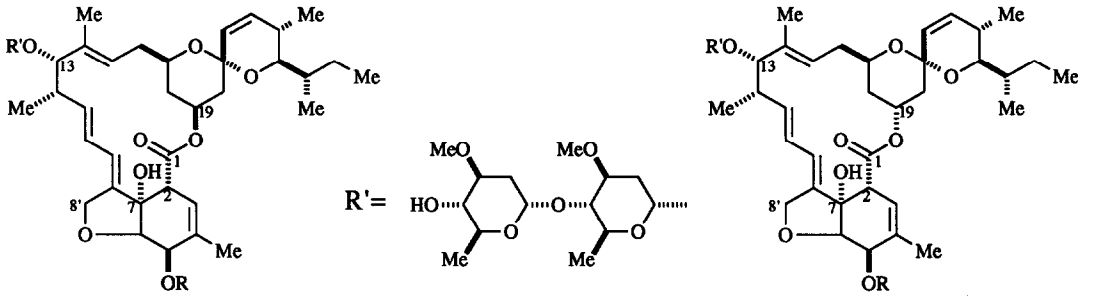
SYNTHESIS OF 19-EPI-AVERMECTIN A_{1a} FROM AVERMECTIN B_{1a}

Stephen Hanessian and Philippe Chemla
Department of Chemistry, Université de Montréal
C.P. 6128, Succ. A, Montréal, QC, CANADA, H3C 3J7

Abstract: The conversion of avermectin B_{1a} into 19-epi-avermectin A_{1a} was accomplished by an intramolecular Mitsunobu reaction of a Δ^2-conjugated seco acid with inversion of configuration, followed by a stereocontrolled deconjugation.

Since their discovery, the avermectin family of 16-membered macrolides have been the subject of intense research activity on several fronts.[1] Their biological profile encompasses among others, anthelmintic, miticidal and insecticidal activities utilizing unique modes of action at the molecular level.[2] Ivermectin,[3] a semi-synthetic 22,23-dihydro derivative of avermectin B_{1a} **1** (Figure 1), is a widely-used antiparasitic agent in veterinary practice.

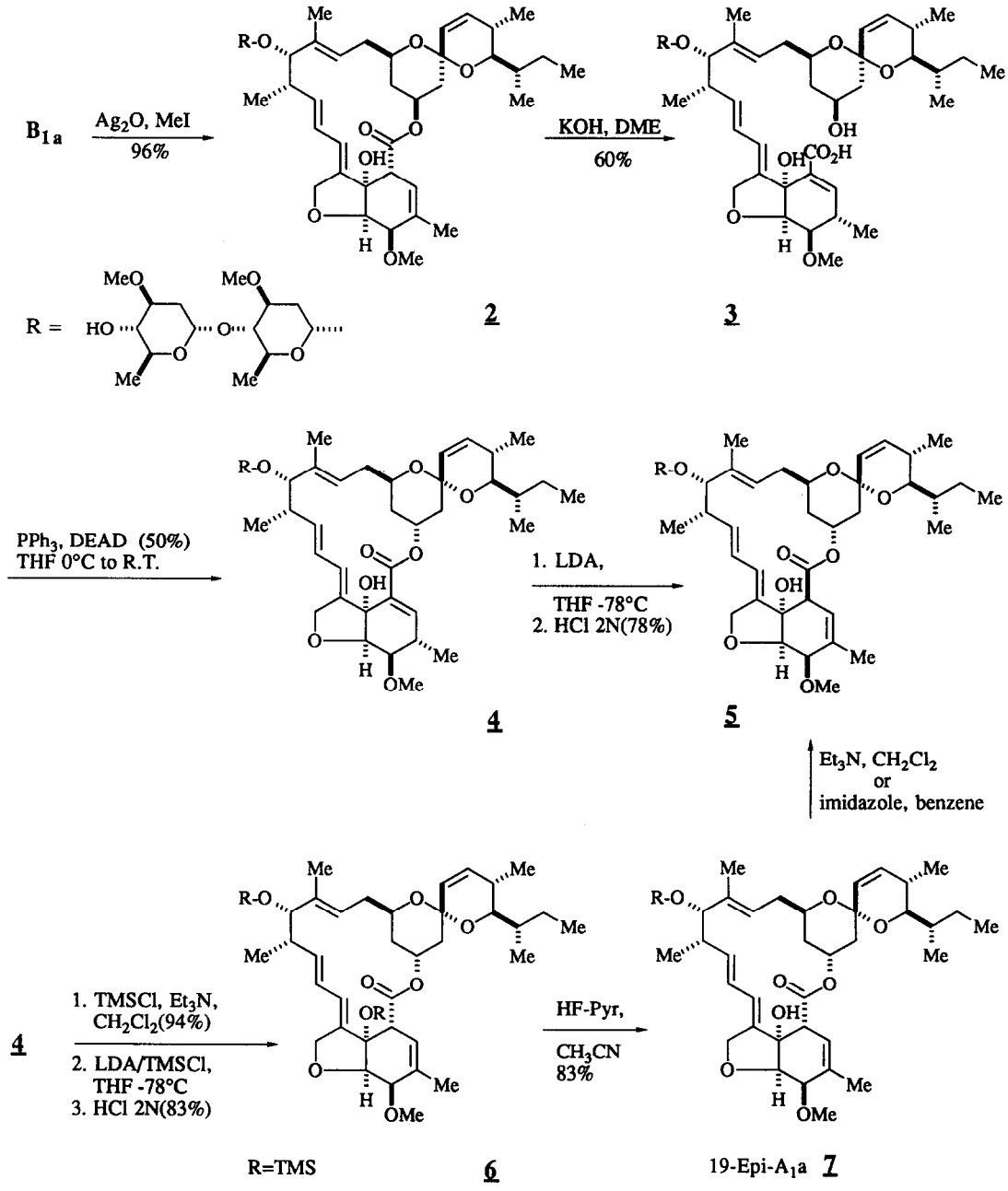
Figure 1



In an effort to improve or alter the spectrum of biological activity, researchers principally at the Merck laboratories have done extensive work on the chemical modification and derivatization of the avermectins. The large proportion of these studies have focussed on peripheral changes such as the selective functionalization of double bonds,[4-6] alterations at C-13,[7] and the disaccharide portion[8,9] to mention a few. These and related elegant studies have led to a better understanding of structure-activity relationships in these fascinating series of derivatives. For example, even seemingly small modifications such as the epimerization at C-2 in **1**, or moving the C-3/C-4 double bond in conjugation with the lactone carbonyl group results in a dramatic loss of biological activity.[1,2]

As part of a program concerned with the chemistry of the avermectins,[10,11] we embarked on a project aimed at transforming avermectin A_{1a} **2** into its 19-epi analog.[12] Our interest in this compound was stimulated by an appreciation of the unique geometry of the lactone ring in avermectin B_{1a}, as evidence by the elegant single crystal

Scheme 1


B1a
Ag2O, MeI
96%
KOH, DME
60%
R =
2
3
PPh3, DEAD (50%)
THF 0°C to R.T.
1. LDA,
THF -78°C
2. HCl 2N(78%)
4
5
Et3N, CH2Cl2
or
imidazole, benzene
4
1. TMSCl, Et3N,
CH2Cl2(94%)
2. LDA/TMSCl,
THF -78°C
3. HCl 2N(83%)
HF-Pyr,
CH3CN
83%
R=TMS
6
19-Epi-A1a 7

X-ray structure.[13] Furthermore, examination of a CPK model of this isomer reveals the extremely restricted free space within the macrocycle.[10a] We were therefore interested in the synthesis of the 19-epi-isomer, in which the lactone would involve an axially orientated oxygen atom. This in turn might lead to an altered conformation and possibly a different profile in biological activity compared to the natural isomer.

Treatment of **1** with methyl iodide and silver oxide resulted in a highly selective O-methylation at C-5 (92%) to give avermectin A_{1a}, **2**[1,14] which was easily separated from the 4"-O-methyl derivative (3.5%) by column chromatography (Scheme 1). The desired inversion reaction at C-19 was envisaged to occur during an intramolecular Mitsunobu reaction,[15] of the Δ-2 seco acid **3**, which was expected to be less susceptible to aromatization.[10a] Barrett and coworkers[16] have successfully applied a Mitsunobu inversion reaction in their total synthesis of milbemycin β_3, where an aromatic acid and an axial hydroxyl group were involved. Treatment of **2** with aqueous KOH in 1,2-dimethoxyethane led to the corresponding conjugated acid **3** after acidification. The Mitsunobu reaction performed under the usual conditions gave the desired macrocyclic lactone **4**, $[\alpha]_D^{25}$ +54.7° (c 1.47, $CHCl_3$), in 50% yield. This product was notably different from Δ-2 avermectin A_{1a} (t.l.c., ^1H NMR, ^{13}C NMR). As in our total synthesis of avermectin B_{1a}, our strategy called for a deconjugation step leading directly to be the desired 19-epi analog **7**, or initially to the 2,19-bis-epi-analog **5**, which would have to be epimerized at C-2 in order to attain the "natural" configuration at that center. Treatment of **4** with LDA in THF at -78° followed by an acidic workup led to the 2,19-bis-epi derivative **5** in 78% yield, $[\alpha]_D^{25}$ (c 0.57, $CHCl_3$). On the other hand, prior silylation of **5** to the corresponding 7-O-TMSi ether, $[\alpha]_D^{25}$ 91° (c 0.85, $CHCl_3$), followed by treatment with LDA and TMSiCl in THF at -78°, according to our previous protocol,[10a] and subsequent workup with dilute acid led to 7-O-trimethylsilyl 19-epi-avermectin A_{1a} **6** in excellent overall yield, $[\alpha]_D^{25}$ - 34° (c 0.72, $CHCl_3$). Finally, desilylation of **6** with HF-pyridine[17] led to the desired 19-epi-avermectin A_{1a} **7** in 85% yield, $[\alpha]_D^{25}$ -104° (c 1.09, $CHCl_3$). Compounds **5**, **6** and **7** showed distinct chemical shift differences in their ^1H NMR spectra, and they also differed significantly from the corresponding 19-"natural" isomers respectively.[18]

The structures of **5** and **6** were unambiguously established by detailed ^1H and ^{13}C NMR studies including extensive use of nOe enhancement measurements at C-2, C-6, and C-8'.[19] Unlike in 2-epi-avermectin B_{1a} and A_{1a} which were susceptible to partial epimerization to the natural product in the presence of imidazole in refluxing benzene,[10a,14] the analogous bis-epi derivative **5** remained unchanged under these conditions. In fact, treatment of **6** or **7** with Et_3N in dichloromethane or with imidazole in benzene at 50° resulted in an irreversible conversion to the 2-epi-analog **5**, and in high yield.[20]

The inversion of C-19 in avermectin A_{1a} from an equatorial to an axial configuration has a profound effect on the conformation of the enolate lactone and its subsequent protonation. Evidently when the C-7 hydroxyl group is free as in **4**, formation of the 2-epi derivative **5** is favored either by direct protonation of the enolate dianion from the convex (exo) face of the oxahydrindene ring system,[21] or by initial protonation of the C-7 alkoxide followed by internal proton transfer. When the 7-OH in **4** is substituted by a TMSi ether group, protonation of the enolate (or the ketene acetal) takes place from the concave (endo) face of the oxahydrindene subunit, a process which is not favored in the B_{1a} series.[10a,21,22] It is possible that the presence of the 7-OTMSi group directs the protonation from the normally unfavored face due to a subtle conformational change. Unfortunately compounds **4**, **5** and **7** showed no activity relative to avermectin B_{1a} (IC_{100}, 328 ng/mL) in the brine shrimp assay[23] (IC_{100}>50,000 ng/mL). Experimental details for the conversion **3**-**4** and **4**-**6**-**7** can be found in ref. 24.

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18. ^1H chemical shifts ($CDCl_3$, 300 MHz): δppm 6.15 (H-3 in Δ-2 avermectin A_{1a}); 6.78 (H-3 in 4); 5.39 (H-3 in 2); 6.14 (H-3 in 7); 4.94 (H-15, in Δ-2 avermectin A_{1a}); 5.20 (H-15 in 4); 4.98 (H-15 in 2); 5.50 (H-15 in 7); 5.38 (H-19 in Δ-2 avermectin A_{1a}); 5.33 (H-19 in 4); 5.39 (H-19 in 2); 5.30 (H-19 in 7).
19. n.O.e. enhancements were observed in compounds **6** (H-2 and Hβ-8'; H-6 and Hα8') and the 7-O-TMSi ether of **5** (H-6 and Hα-8').
20. Preliminary results show that the aglycone of structure **5** is more stable by at least 5Kcal/mol than the aglycone of **7**, using the conformational searching techniques of BAKMDL ver KS 2.96 in the MODEL (ver KS 2.96) set of programs. We thank Prof. K. Steliou of this department for this calculation.
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24. Experimental procedures: Mitsunobu Reaction **3**→**4**: To a solution of **3** (566 mg, 0.626 mmol), Ph_3P (494mg, 1.88 mmol) in THF (100 mL) was added over 1h 296 μL (1.88 mmol) of DEAD over 1h at 0°. After 3h at 0°, and 2h at r.t., the solution was evaporated and the residue chromatographed (40% EtOAc in hexanes to 10% MeOH in EtOAc) to give **4** (262 mg, 50%), ^1H NMR; ^{13}C NMR; FAB-MS. Deconjugation **4**→**6**: To a solution of LDA in THF (0.35 mmol) was added TMSiCl (1.4 mmol) at -78°, followed by a pre-cooled solution of 7-OTMS **4** (60 mg). After 2 min at -78°, the mixture was quenched with 1:1 THF-0.2 N HCl. Workup and flash chromatography (50% EtOAc in hexanes gave **6** (47 mg, 85%); ^1H NMR; ^{13}C NMR; FAB-MS. Treatment of **6** with HF-pyridine in acetonitrile gave **7**; ^1H NMR; ^{13}C NMR; FAB-MS.
All compounds gave satisfactory microanalytical results. Complete NMR spectroscopic data available.

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