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SYNTHESIS OF AN AVERMECTIN-NEMADECTIN HYBRID.

Thomas L. Shih*, Mark A Holmes, Helmut Mrozik, Michael H. Fisher.

Merck Sharp & Dohme Research Laboratories, Rahway NJ 07065

Abstract: The Wittig condensation of (2R,3R,4E)-2,6-dimethyl-3-trimethylsilyloxy- 4-heptenyltriphenylphosphorylidene with aldehyde **1** produced the desired cis olefin **11** in 45% yield. Treatment of this intermediate with pyridinium tosylate in methanol effected spiroketalization and desilylation with hydrogen fluoride-pyridine in THF afforded the avermectin-nemadectin hybrid **2**.

Avermectin B_1 (abamectin) and its semisynthetic 22,23-dihydro analog (ivermectin) have been in use as potent antiparasitic and insecticidal agents for over a decade.[1a] Numerous studies[1b] reflect an intense interest in the total synthetic approaches and structural modifications to the avermectins and structurally related milbemycins. Additional natural milbemycin-like macrolides[2] were discovered more recently. These structures are unique in having additional unsaturation in the side-chain attached to the spiroketal portion of the molecule. Nemadectin (anthelmintic LL-F28249α[3] or antibiotic S 541[4]) as one example contains a new trisubstituted olefin side chain at C25, and chemical modifications of this compound[4] and their effect on biological activities[5] have been described. To further explore the structure-activity relationship and compare the effects of introducing the same substituent in the analogous positions of the avermectin-milbemycin structure we were intrigued by the prospect of synthesizing an avermectin analog having the B_1 configuration with this new side-chain. We have recently demonstrated an effective means to vary the substituents at the spiroketal part of the structure[6] starting with aldehyde **1**. Thus, we projected that the synthesis of avermectins having unsaturated C25 side-chains is viable once the requisite Wittig ylid is available. Therefore, we set out to prepare the required chiral phosphorus ylid according to **Scheme 1**. Commercially available (S)-(+)-methyl 3-hydroxy-2-methylpropionate was protected with benzyloxymethylchloride (1.25 eq. BOM-Cl, excess i-Pr_2EtN, 2h 0°C 80% yield), reduced with lithium aluminum hydride (0.67 eq $LiAlH_4$, ether, 1h 0°C, 83%), and oxidized (Swern, 70%) to afford the chiral aldehyde **3b** ($[\alpha]_D$=+19.3°C , c=1.05, dichloromethane).

The source of the trisubstituted olefinic fragment was commercially available 4-methyl-2-pentyne. Initially we tried to utilize the vinylborane chemistry reported by Brown[7] and hydroborated the pentyne with 9-BBN. However, upon refluxing a THF solution of the vinylborane and aldehyde **3b** we noticed that the predominant mode of reaction was reduction of the aldehyde back to **3a**. Therefore we chose to explore the alternative method of Still's chelation-controlled addition[8] of an organometallic fragment derived from the vinyl iodide **4**. Hydroalumination of 4-methyl-2-pentyne with diisobutylaluminum hydride (1.1 eq., 50°C 4h) followed by iodination (0°C, 1.2 eq. I_2, 30 min, 58%) gave a 70:30 mixture[9] of vinyl iodides (**4,5**). Transmetalation with tert-butyllithium at -78°C gave the corresponding vinyl lithium reagents which reacted with aldehyde **3b** to afford a 1:1 mixture of threo and erythro adducts (**6a,b**). Attempts to improve the 1,2 stereoselection through the use of copper ($CuBr{\bullet}SMe_2$) and BF_3-etherate are summarized by **Table 1**. Those results are comparable to the degree of modest diastereoselection observed by Still and Schneider[8a] for sp^2 organic anions. The mixture of **6a** and **6b** was readily separable by column chromatography and their structures were confirmed upon removal of the BOM group (sodium, liquid ammonia, 95%) and comparing the coupling constants of the relevant protons of their acetonides (**7a,b**).[10]

SCHEME 1

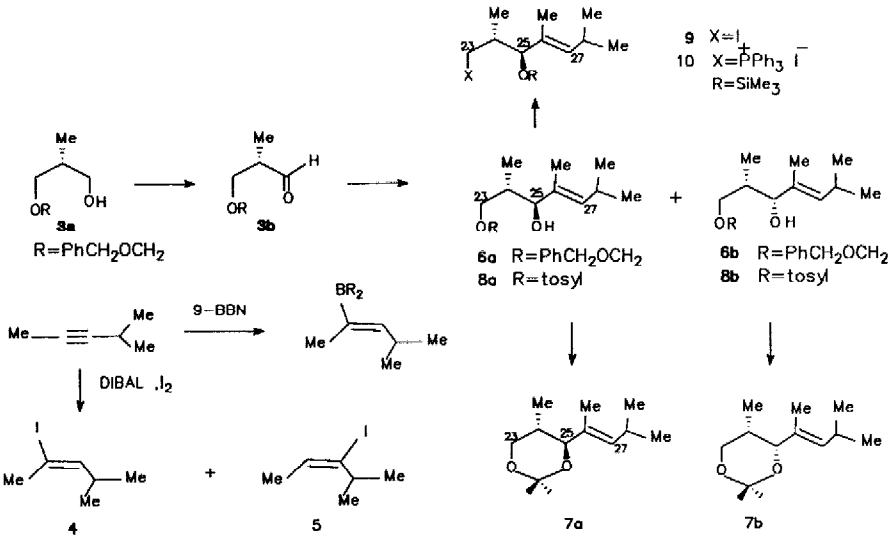


Table 1 (Ratio's determined by capillary column GC)*

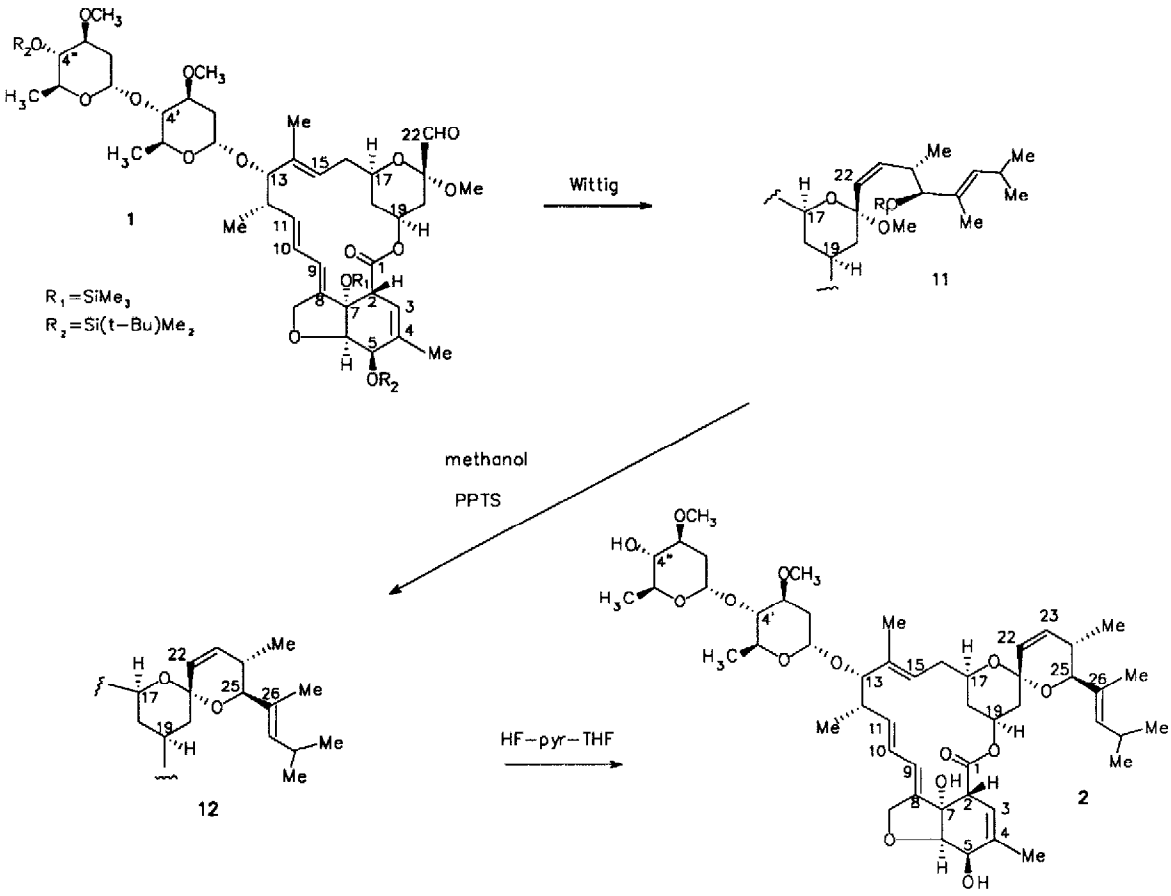
Metal	BF_3 etherate	6a:6b
Li	0 equiv.	61:39
Li	1 equiv.	52:48
LiCu	0 equiv.	66:34
LiCu	1 equiv.	74:26

* The reactions were carried out in 1:1 pentane-ether.

The threo isomer was converted to the primary tosylate **8a** (2 eq tosyl chloride, TEA, 20°C 2h, 72%) and then to the corresponding iodide **9** (NaI, acetone, 16h, 95%). Treatment of the iodide with triphenylphosphine (100°C, toluene, 16h, 85%) and then trimethylsilyldimethylamine (5 equiv. dichloromethane, 100%) gave the phosphonium salt **10**. Wittig condensation of aldehyde **1** (**Scheme 2**) with 1 equivalent of the ylid derived from **10** and potassium hexamethyldisilylamide in toluene (-78°C to 20°C) afforded a 45% yield of olefin **11**. Cyclization to the spiroketal proceeded in methanol-PPTS to yield 90% of **12**. Desilylation in HF-pyridine-THF afforded the desired product[11] **2** in 80% yield. A comparison of the bioactivity of **2** with avermectin B_1 and nemadectin showed the following IC_{100}(ng/mL) values in the A. Salina assay[12]: **2**(870), avermectin B_1(340), nemadectin(110).

In conclusion, the synthesis of an avermectin-nemadectin hybrid has been achieved with the new structural perturbation retaining good activity as an antiparasitic agent, although less potent than either parent.

SCHEME 2



References and Notes

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9. This mixture of vinyl iodides was used without further purification or separation. Correlation of the products from the addition to aldehyde **3b** and their stereo- and regiochemistry was achieved by analysis of the NMR and G.C. ratios of the separable adducts **6a,b**.

10. $J_{erythro}$=0 Hz, J_{threo}=10.5 Hz.

11. All compounds were characterized by their NMR and mass spectra. NMR of **2** (400 MHz, TMS, $CDCl_3$): d 0.83(d,J=7Hz, C24 methyl), 0.85(m), 0.9-1.0(m), 0.95(d,J=7Hz, C28 methyl), 1.01(d,J=7Hz, C28 methyl), 1.16(d,J=7Hz, C12 methyl), 1.25(d,J=6Hz, C5' or C5" methyl), 1.28(d,J=6Hz, C5' or C5" methyl), 1.49(s, C26 methyl), 1.5(m), 1.65(d,J=2Hz, C14 methyl), 1.78(m), 1.88(s, C4 methyl), 2.04(m), 2.22-2.40(m), 2.46(d,J=2Hz), 2.52(m, C12H), 2.58(m, C28H), 3.17(dt,J=2,10Hz, C4"H), 3.23(t,J=9Hz, C4'H), 3.29(q,J=2Hz, C2H), 3.419(s, C3' or C3" methoxy), 3.42(s, C3' or C3" methoxy), 3.47(m, C3"H), 3.59(m, C3'H), 3.73(d,J=10 Hz, C25H), 3.7-3.9(m), 3.94(br s), 3.96(d,J=6Hz, C6H), 4.06(s,C7OH), 4.29(br t,J=8Hz, C5H), 4.68(m, C8aH), 4.79(d,J=3Hz, C1'H), 5.01(d,J=10 Hz, C15H), 5.22(dd,J=2,9Hz, C27H), 5.39(d,J=3Hz, C1"H), 5.42(s, C3H), 5.47(m, C19H), 5.57(dd,J=2,10Hz, C22 or C23H), 5.7(m), 5.79(dd,J=2, 10 Hz, C22 or C23H), 5.83(m); mass spec calcd for $C_{50}H_{74}O_{14}$ 898.5076 found 898.5307.

12. For a more detailed description of this assay see: T. A. Blizzard, C.L. Ruby, H. Mrozik, F. A. Preiser, and M. H. Fisher, J. Antibiotics *42*, 1304, 1989.

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