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A WITTIG APPROACH TO NOVEL C24 AND C25-SUBSTITUTED AVERMECTINS.

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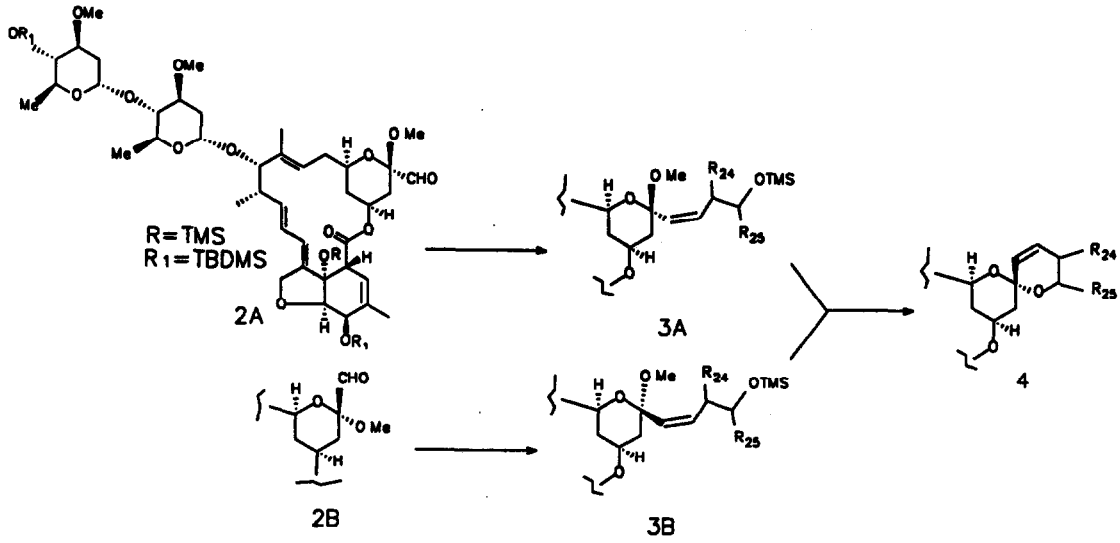
Abstract: The Wittig condensation of aldehydes **2A** and **2B** with the appropriate phosphonium ylids under Bestmann's "salt-free" conditions[3] gave the Z-olefin precursors **3A** and **3B** respectively. Treatment of **3A** and **3B** with methanolic pyridinium tosylate effected desilylation and intramolecular spiroketalization to generate synthetic avermectins (**4**) having the thermodynamic dioxaspirane configuration found in natural avermectins.

The avermectins and milbemycins have the distinction of being the most potent anthelminthic and acaricidal agents known. Their important biological activity and interesting complex structures have led to a considerable effort in both their total synthesis and synthetic modifications of the natural products[1]. We have recently reported the selective cleavage[2] of the 22-23 bond of avermectin B2a to arrive at the versatile precursor aldehydes **2A, 2B** and (2R,3R,4S)-2,4-dimethyl-3-hydroxyhexanoic acid. We now report their use in reassembling the complete spiroketal structure containing novel C24 and C25 substituents.

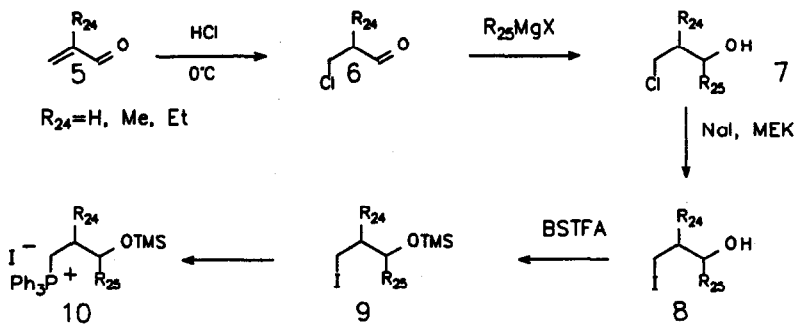
Our approach was to form a cis olefin (**3**) at the C22-23 juncture through a Wittig condensation[3] (**Scheme 1**). This allowed us to effect the well precedented acid catalysed intramolecular spiroketalization that sets the required C21 stereochemistry under thermodynamically equilibrating conditions[4]. The phosphonium salts are either commercially available or prepared[5] from acrolein or 2-substituted acroleins (**5**), hydrogen chloride, and Grignard reagents (**Scheme 2**). The intermediate 3-iodo-1-propanols (**8**) were silylated with bis(trimethylsilyl)trifluoroacetamide (BSTFA) in DMF (90% yield) prior to reaction with triphenylphosphine (100°C, 20 h, 70% yield) in toluene. Alternatively, the free hydroxyl groups of the phosphonium salts obtained commercially or from **8** and triphenylphosphine were silylated at room temperature with BSTFA/DMF (20 h, 80% yield) and recrystallized before use.

In a typical Wittig reaction: To a mixture of 151 mg (0.275 mmol) of [3-t-butyldimethylsilyloxypropyl]triphenylphosphonium bromide in 1 mL of freshly distilled toluene under argon was added 0.44 mL (0.22 mmol) of a 0.5 M toluene solution of potassium bis(trimethylsilyl)amide. The orange mixture was stirred at 20°C for 30 min before cooling to -78°C. A solution of 202 mg (0.185 mmol) of aldehyde **2A** in 0.5 mL of toluene was added dropwise and the mixture was then allowed to warm to 20°C. After 1 h the reaction mixture was quenched with 10 mL of sodium bicarbonate solution and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered and concentrated to afford 329 mg of solid.

Scheme 1



Scheme 2



Purification by flash column chromatography with 10% ethyl acetate-hexane yielded 173 mg of cis-olefin adduct[6] **3A**. For the spiroketalization: to a solution of 6.3 mg of pyridinium p-toluenesulfonate (PPTS) in 1.2 mL of sieve-dried methanol was added 18 mg of adduct **3A** or **3B**. After 2 days[7] at 20°C, the methanol was removed in vacuo and the residue was taken up in dichloromethane and separated by preparative silica gel layer chromatography (PLC) to afford the identical product mixture from the two epimeric structures **3A**, **3B**; 10 mg of 4",5-di-O-t-butyldimethylsilyl-7-O-trimethylsilyl-24-demethyl-25-de(2-butyl)-avermectin B1a and 5 mg of

4",5-di-O-t-butyldimethylsilyl-24-demethyl-25-de(2-butyl)-avermectin B1a. For the desilylation: to a polypropylene vial containing 129 mg of a purified mixture of 4",5-di-O-t-butyldimethylsilyl-7-O-trimethylsilyl-24-demethyl-25-de(2-butyl)-avermectin B1a and 4",5-di-O-t-butyldimethylsilyl-24-demethyl-25-de(2-butyl)-avermectin B1a was added 10 mL of hydrogen fluoride-pyridine in tetrahydrofuran (1:3:6 volume dilution of commercially available HF-pyridine complex: freshly distilled pyridine: THF). The anhydrous solution was stirred at 20°C for 2 days before dilution with ether and removal of the HF with an aqueous sodium bicarbonate wash. The ethereal extracts were combined and dried over $MgSO_4$. After filtration and removal of the solvent, the 24-demethyl-25-de(2-butyl)-avermectin B1a was purified by flash chromatography on silica gel (56 mg)[8].

In order to reconstitute avermectin B1a from **2B**, (2R,3R,4S)-2,4-dimethyl-3-hydroxyhexanoic acid[2] was converted to phosphonium iodide **10** (R_{24}=Me, R_{25}=2-butyl) by esterification with diazomethane (90%, $[\alpha]_D$ =-9.5°, c=8.9g/dL CH_2Cl_2), reduction with lithium aluminum hydride (diol, 95%, $[\alpha]_D$=+24.5°, c=13.1 g/dL CH_2Cl_2), monotosylation (77%), sodium iodide displacement of primary tosylate (98%, $[\alpha]_D$=-12.6°, c=12.3 g/dL CH_2Cl_2), silylation (80%, trimethylsilyltriflate), triphenylphosphine (100°C, toluene, 80%). The Wittig condensation gave a 55% yield of olefinic product and subsequent cyclization and desilylation in HF-pyridine-THF afforded an 80% yield of avermectin B1a identical by NMR (^1H, ^{13}C), mass spectrum, and UV to the natural product. The other cases are tabulated in Table 1[9].

TABLE 1

Entry	Ylid	Product(4)	Yield(2 to 4)
A	$Ph_3P{=}CHCH_2CH_2OSi(Me_2)(t\text{-}Bu)$	R_{24}=H, R_{25}=H	44%
B	(R or S)-$Ph_3P{=}CHCH(Me)CH_2OSiMe_3$	R_{24}=Me, R_{25}=H	40%
C	(S)-$Ph_3P{=}CHCH_2CHPh(OSiMe_3)$	R_{24}=H, R_{25}=Ph	41%
D	(R,S)-$Ph_3P{=}CHCH_2CH(OSiMe_3)C_6H_{11}$	R_{24}=H, R_{25}=cyclohexyl	39%
E	(R,S)-$Ph_3P{=}CHCH_2CH(OSiMe_3)C_5H_9$	R_{24}=H, R_{25}=cyclopentyl	40%
F	(R or S)-$Ph_3P{=}CHCH_2CH(OSiMe_3)Me$[10]	R_{24}=H, R_{25}=Me	45%
G	$Ph_3P{=}CHCH(Et)CH(OSiMe_3)(sec\text{-}Bu)$[11]	R_{24}=Et, R_{25}=sec-Bu	33%
H	$Ph_3P{=}CHCH(Me)CH(OSiMe_3)(sec\text{-}Bu)$[12]	R_{24}=Me, R_{25}=sec-Bu	49%

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4. We intend to show that the present system indeed conforms to stereoelectronic control in the cyclization step by reconstituting avermectin B1a from the chiral phosphonium ylid and aldehyde **2B** and that both adducts **3A** and **3B** gave the same cyclized product **4** in case A (**table 1**). In addition when we attempted to combine the desilylation and cyclization process in one step with HF-pyridine in THF, we were able to isolate the kinetic cyclization product having the epimeric C21 stereochemistry. This isomer when subjected to PPTS in methanol gradually reverted to the thermodynamic C21 stereomer.

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6. NMR δ 0.06(s), 0.09(d,J=6Hz), 0.13 (s), 0.14(s), 0.89 (s), 0.94(s), 1.18(d,J=7Hz), 1.22(d,J=6Hz), 1.26(d,J=6Hz), 1.40(t,J=12Hz),1.52(s), 1.78(s), 2.24-2.6(m), 3.13 (t,J=9Hz), 3.22(t,J=9Hz), 3.30(s), 3.33(s), 3.43(s), 3.6(m), 3.68 (t,J=7Hz), 3.82 (d,J=6Hz), 3.98(s), 4.38(d,J=3Hz), 4.6(m), 4.6(dq,J=2,15Hz), 4.80(d,J=3Hz), 5.13(t,J=7Hz), 5.30(d,J=3Hz), 5.4(d,J=12Hz), 5.5 (s), 5.5-5.9(m); C13 NMR (olefinic) 118, 120.3, 120.6, 125.1, 127.5, 134.57, 134.66, 135.4, 136.5, 140.5;mass spectra FAB 1255 (M+Li).. The analogous reaction was run with aldehyde **2B** to afford a similar yield of adduct **3B**: NMR δ 0.04 (s), 0.08(d,J=6Hz), 0.14(s), 0.87(s), 0.89(s), 0.94(s), 1.18(d,J=7Hz), 1.21(d,J=6Hz), 1.26(d,J=6Hz), 1.52(s), 1.6(m), 1.78(s), 2.2-2.6(m), 3.13(t,J=9Hz), 3.14(s), 3.23(t,J=9Hz), 3.26(s), 3.32(s), 3.33(m), 3.45(s), 3.63(t,J=6Hz), 3.7(m), 3.82(d,J=6Hz), 3.98 (s), 4.38(d,J=6Hz), 4.6(dq,J=2,15Hz), 4.82(d,J=3Hz), 4.93(m,J=5Hz), 5.15(dd,J=3,9Hz), 5.29(d,J=12Hz), 5.30(d,J=3Hz), 5.48-5.80(m); C13 NMR (olefinic) 118.4, 120.56, 120.67, 125.05, 131.00, 131.2, 134.36, 135.07, 136.56, 140.51.

7. In the other cases where the trimethylsilyl group is used to block the C25 hydroxyl function, reaction was over in less than 2 h. When there is substitution at C25, the use of the TBDMS protecting group led to complex mixtures since the methoxy ketal undergoes hydrolysis and fragmentation before the C25 hydroxyl is freed to cyclize and stabilize the incipient carbocation intermediate.

8. NMR (C13) 15.09, 17.66, 18.38, 19.90, 20.29, 24.41, 34.13, 34.22, 34.58, 36.49, 39.69, 40.16, 45.62, 56.36, 56.61, 57.78, 67.16, 67.66, 68.04, 68.17, 68.39, 76.01, 78.14, 79.04, 79.33, 80.22, 80.36, 81.33, 94.59, 94.99, 98.46, 117.95, 118.12, 120.21, 124.72, 128.76, 129.03, 134.99, 137.88, 139.64, 173.59; mass spectra FAB 809 (M+Li).

9. All compounds are fully characterized by their NMR and mass spectra.

10. From (R) or (S)-1,3-butanediol by selective tosylation of the primary hydroxyl and conversion to the iodide as in case H.

11. Ylid is obtained from the diastereomeric mixture of phosphonium salts and three major isomeric products were obtained after cyclization. The stereochemistry at C24 and C25 were not assigned.

12. Prepared from (2R, 3R, 4S)-2,4-dimethyl-3-hydroxyhexanoic acid (Ref. 2).

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