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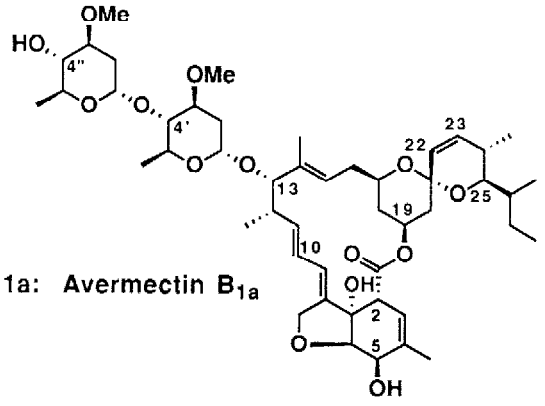
SYNTHESIS OF RING-CONTRACTED, 25-NOR-6,5-SPIROKETAL-MODIFIED AVERMECTIN DERIVATIVES

Peter T. Meinke,* Stephen P. O'Connor, Helmut Mrozik and Michael H. Fisher

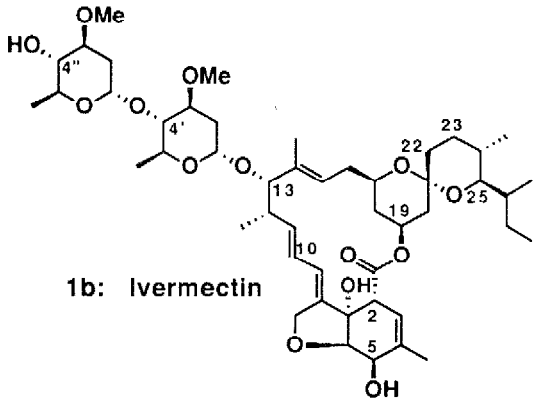
Department of Basic Medicinal Chemistry
Merck Sharp and Dohme Research Laboratories
Rahway, NJ 07065-0900

Abstract: A versatile, high yielding strategy for the synthesis of ring-contracted, 25-nor-6,5-spiroketal-modified avermectin analogs (7A - 7N) bearing diverse substituents at C24 is described. In addition, an efficient $Pb(OAc)_4$-mediated oxidative cleavage to produce the key intermediate, aldehyde 3, is presented.

Avermectin B_{1a} (**1a**, AVM), the primary fermentation product of *Streptomyces avermitilis*, and its derivatives are structurally complex and useful natural products with pronounced biological activities. The 22,23-dihydro derivative, ivermectin (**1b**), for instance, has found widespread use as a potent, broad spectrum anthelmintic agent.[1] The novel molecular architecture and impressive biological activities of these macrolides has prompted efforts towards AVM synthesis and the preparation of structurally modified analogs with enhanced biological activity profiles.[2] Modifications of the C25 substituent in the 6,6-spiroketal ring system of natural avermectins by synthetic[3,4] or microbial[5] pathways have been reported recently. We report herein the synthesis of C24-substituted AVM derivatives (**7A - 7N**) bearing the new ring-contracted, 25-nor-6,5-spiroketal system. These analogs retained or surpassed the potent biological activities of the parent natural product.



1a: Avermectin B_{1a}

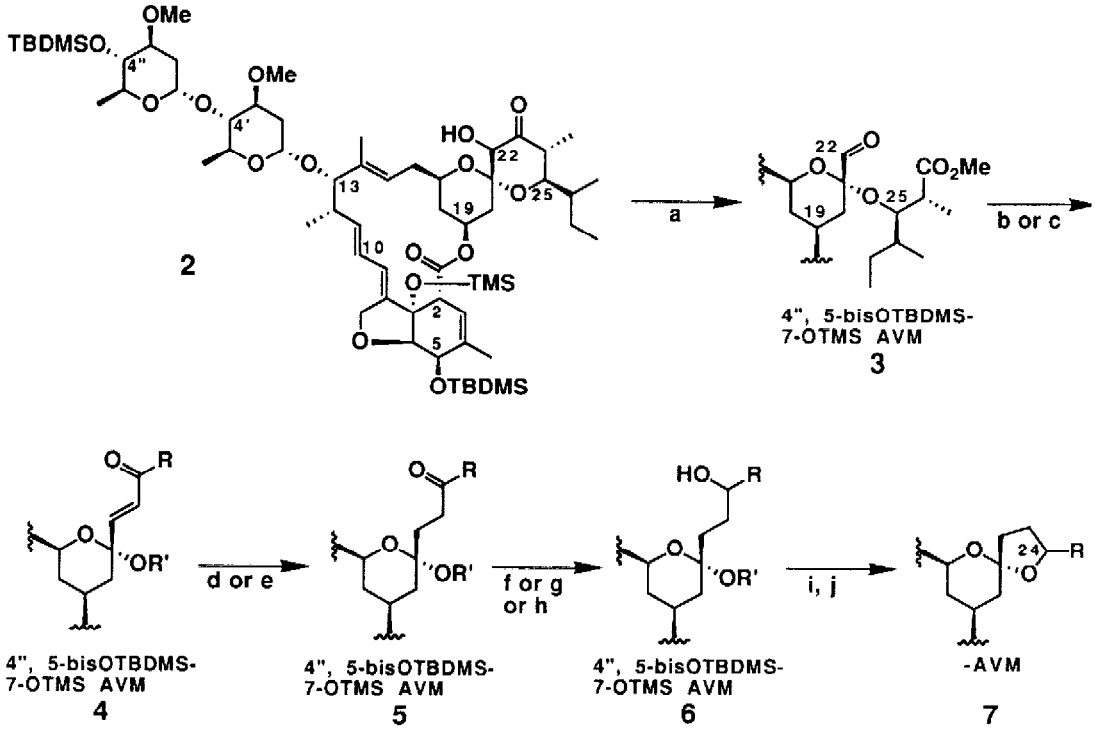


1b: Ivermectin

It was envisaged that Horner-Emmons olefination of aldehyde **3** would represent an efficient method for the introduction of carbons 23 and 24 (**Scheme I**). Conjugate reduction of enone **4** prior to reduction of ketone **5** and acid-catalyzed cyclization of the resultant alcohol **6** under thermodynamic control would culminate in the formation of the desired ring-contracted, spiroketal-modified avermectin analogs **7A - 7N**.

Aldehyde **3** was produced in excellent yield (95% on 35 g scale) via $Pb(OAc)_4$-mediated oxidative

SCHEME I



a) $Pb(OAc)_4$, MeOH, pyr; **b)** $(MeO)_2P(O)CH_2C(O)R$, LiCl, DIEA; **c)** $Ph_3PCHC(O)R$;
d) 9 eq $Na_2S_2O_4$, 18 eq $NaHCO_3$; 1:1 $PhH:H_2O$, reflux; **e)** $Pd(PPh_3)_4$, nBu_3SnH;
f) $NaBH_4$; **g)** RMgBr; **h)** $BH_3.SMe_2$, oxazaborolidine, 0° C; **i)** 4:1 PPTS:TsOH; **j)** HF.pyr

TABLE I: 25-NOR-24-SUBSTITUTED AVERMECTIN ANALOGS[15]

Entry	R	Yield (%, 3 → 7)	Entry	R	Yield (%, 3 → 7)
A)	H[a]	62	H)	CH_2OMe[a]	57
B)	Me[a,b]	42	I)	CH_2OPh[a]	43
C)	*i*-Pr[a,c]	68	J)	Ph[a,b,c]	38
D)	*t*-Bu[a]	76	K)	(*p*-F)Ph[a]	30
E)	*n*-C_8H_{17}[c]	41	L)	(*p*-MeO)Ph[a]	42
F)	*c*-C_6H_{11}[a]	59	M)	2-Furyl[a]	25
G)	CH_2OH[a]	48	N)	OMe[d]	56

(a) Method **A**: $(MeO)_2P(O)CH_2C(O)R$.
(b) Method **B**: $Ph_3PCHC(O)R$.
(c) Method **C**: Grignard addition to **5A**.
(d) Method **D**: $BF_3.OMe_2$-mediated cyclization of **5A** where R' = OMe.

cleavage[6] of hydroxy-ketone **2**[7] by the simple expedient of performing the reaction in methanol with one weight equivalent of pyridine.[8] Treatment of **3** with the appropriate β-ketophosphonate[9] under Masamune conditions[10] (1 eq **3**, 1.5 eq $(MeO)_2P(O)CH_2C(O)R$, 3 eq LiCl, 6 eq DIEA, MeCN, RT) resulted in the generation of **4** (79 - 96%). Enone **4** was readily reduced using either dithionite[11] (9 eq $Na_2S_2O_3$, 18 eq $NaHCO_3$, 1:1 benzene:water, reflux, 5 - 10 min) or palladium-catalyzed tin hydride conjugate addition[12] (0.1 eq $Pd(PPh_3)_4$, 4 Å molecular sieves, 1.1 eq nBu_3SnH, THF, RT, 10 min). Both methods produced the desired saturated ketones (**5**) in high yields (58 - 96%).

Stabilized Wittig reagents[9] also were reacted with aldehyde **3** although extended reaction times or higher temperatures occasionally were required. When $Ph_3PCHCHO$ was employed as the chain homologating agent, addition of Grignard reagents (pursuant to conjugate reduction) provided rapid access to diverse substituents at C24 from **5A**, a common intermediate. In addition, treatment of **5A** (after transketalization using PPTS in methanol) with $BF_3{\cdot}OMe_2$ (CH_2Cl_2, -78°C, 3 min) formed **7N** directly as a 1:1 diastereomeric mixture at C24.[13]

The C24 carbonyl of **5** was reduced with sodium borohydride in methanol at RT producing alcohol **6** in quantitative yield in a 1:1 ratio of alcohol diastereomers. Alternatively, reduction of **5** to yield optically pure **6** (either antipode) was possible following the Corey protocol[14] (0.1 eq chiral oxazaborolidine·BH_3 complex, 1 eq $BH_3{\cdot}SMe_2$, toluene, 0°C, 4-8 hrs) yielding diastereomeric ratios of 95:5.

Cyclization of **6** to form **7** proceeded smoothly in methylene chloride using 4:1 PPTS:TsOH at RT and was typically complete within 5 - 15 minutes. Use of protic solvents during this cyclization resulted in extended reaction times, partial desilylation and deglycosidation. The cyclized products subsequently were deprotected (69 - 95%) with 1 mL HF.pyridine solution[3] (25 g HF·pyridine, 10 mL pyridine, 25 mL THF) over 48 hours. At this juncture, the C24 isomers, if present, could be resolved readily by reversed phase HPLC. Representative ring-contracted avermectin derivatives synthesized by this route are shown in **Table I**.

In summary, a synthetic route involving the oxidative cleavage of **2** and rapid reassembly of the ring-contracted 25-nor-6,5-spiroketal modified avermectin analogs is presented. The conditions employed for this six step reaction sequence are exceedingly mild. Mild conditions are critical due to the well-documented lability of these macrocycles to both acid and base.[1] The chemical yield of each individual step is very high and most reactions are complete in 5 - 15 minutes. The versatility of this strategy is evidenced by the observation that diverse substituents at the C24 position may be incorporated readily from Horner-Emmons reagents, stabilized Wittig reagents or by Grignard addition to the chain-homologated aldehyde **5A**. In addition, the C24-hydroxymethyl group of **7G** provides a convenient functional handle for further synthetic manipulations.

ACKNOWLEDGEMENTS: We thank Drs. P. Eskola and D. Ok for the preparation of large quantities of hydroxy-ketone **2**.

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Abbreviations: AVM, avermectin B_{1a}; DIEA, diisopropylethylamine; PPTS, pyridinium *p*-toluenesulfonate; TsOH, *p*-toluenesulfonic acid.

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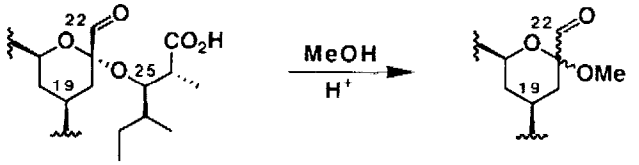
8) Originally,[7] the oxidative cleavage was run in benzene to give aldehyde-acid **8** (not aldehyde-ester **3**) in 60-80% yield. This material required transketalization in MeOH using PPTS (70 - 90%) to form methoxy-aldehyde **9** as a 1:1 mixture of anomers prior to reconstruction of the 6,6-spiroketal ring system.



4", 5-bisOTBDMS-7-OTMS AVM
8

4", 5-bisOTBDMS-7-OTMS AVM
9

9) For leading references describing the preparation and use of β-ketophosphonates and stabilized Wittig reagents see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*(4), 863-927; (b) Bhattacharya, A. K.; Thyagarajan, G. *Chem Rev.* **1981**, *81*(4), 415-430.

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15) All compounds gave satisfactory ^1H, ^{13}C NMR and mass spectra. Representative data is provided below for compound **7D** (24-S isomer). **HPLC**: 8:2 (v:v) MeOH:H_2O, 2 mL/min, retention time = 10.1 min. **TLC**: 3:1 EtOAc:hexanes, rf = 0.30. Partial data: **^1H NMR** (300 MHz, $CDCl_3$, δ): 5.62 - 5.83 (m, 3H, C9,C10,C11), 5.41 (s, 1H, C3), 5.37 (d, J = 3 Hz, 1H, C1"), 5.36 (m, 1H, C19), 5.01 (br d, 1H, C15), 4.78 (d, J = 3.2 Hz, 1H, C1'), 4.66 (s, 2H, C8a), 4.27 (br t, 1H, C5), 4.07 (s, 1H, 7-OH), 3.94 (d, J = 6.4 Hz, 1H, C6), 3.92 (s, 1H, C13), 3.42 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.27 (br s, 1H, C2), 3.21 (t, J = 9.0 Hz, 1H, C4"), 3.14 (t, J = 9.4 Hz, 1H, C4'), 2.57 (br s, 1H), 2.38 (d, J = 8.3 Hz, 1H), 1.85 (s, 3H, C4a), 1.47 (s, 3H, C14a), 1.28 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$, δ): 173.91, 139.62, 138.04, 137.93, 134.74, 124.72, 120.33, 118.35, 117.98, 106.39, 98.51, 94.61, 86.35, 81.38, 80.43, 80.26, 79.37, 79.06, 78.19, 76.07, 69.12, 68.47, 68.08, 67.97, 7.72, 67.18, 56.65, 56.41, 45.67, 39.75, 39.11, 38.00, 36.85, 34.63, 34.36, 34.17, 33.57, 25.53, 24.44, 20.32, 19.96, 18.44, 17.71, 15.17. **MS**: calc for $C_{46}H_{70}O_{14}$ + Li: 853.4924. Found (M + Li): 853.4925

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