Pergamon

Tetrahedron Letters, Vol. 35, No. 30, pp. 5343-5346, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01056-0

Synthesis of Spiroketal-Modified Avermectin Analogs: 23-Nor-23-Oxa- and 23-Nor-23-Thia-Avermectins

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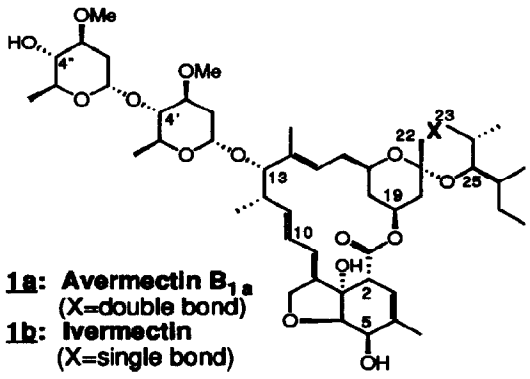
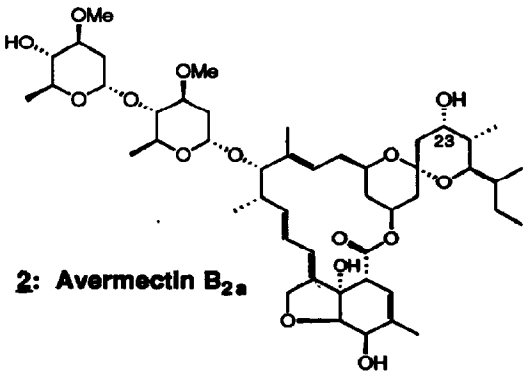
Abstract: *The concise synthesis of avermectin analogs wherein the C23 carbon has been excised and replaced with an oxygen or sulfur atom is described. The new, heteroatom-substituted avermectins represent isosteres of 22,23-dihydro-avermectin B_{1a} and, in the case of the sulfoxides and sulfones, are isosteric to avermectin B_{2a}. These new avermectins bear diverse functionality at C24 and C25.*

The discovery in 1979 of avermectins, a novel class of macrolides with unprecedented efficacy against endo- and ectoparasites,[2] initiated a new era in the treatment of animal disease. Although avermectin (**1a**, AVM) and its 22,23-dihydro analog, ivermectin (**1b**, IVM), are primarily employed as veterinary chemotherapy agents, IVM additionally has important human clinical uses, specifically for the treatment of individuals afflicted with onchocerciasis[3] (river blindness). The pronounced anthelmintic activity exhibited by these macrocycles stimulated significant efforts to identify new, structurally modified AVM analogs possessing enhanced and/or shifted biological properties.[4] It is recognized that modification of the spiroketal portion of the avermectin nucleus represents a rich area for the introduction of structural alterations while retaining the potent biological profile characteristic of this class of macrolides. For instance, the preparation of spiroketal-modified avermectins which possess 6,6-spiroketals bearing diverse substituents at C24 and C25 by both synthetic[5] and fermentation[6] pathways has been reported recently. Additionally, the synthesis of AVM derivatives wherein the C25 carbon has been completely excised, resulting in the preparation of ring-contracted, 6,5-spiroketal modified AVM derivatives, also has been reported.[7]



1a: Avermectin B_{1a} (X=double bond)
1b: Ivermectin (X=single bond)



2: Avermectin B_{2a}

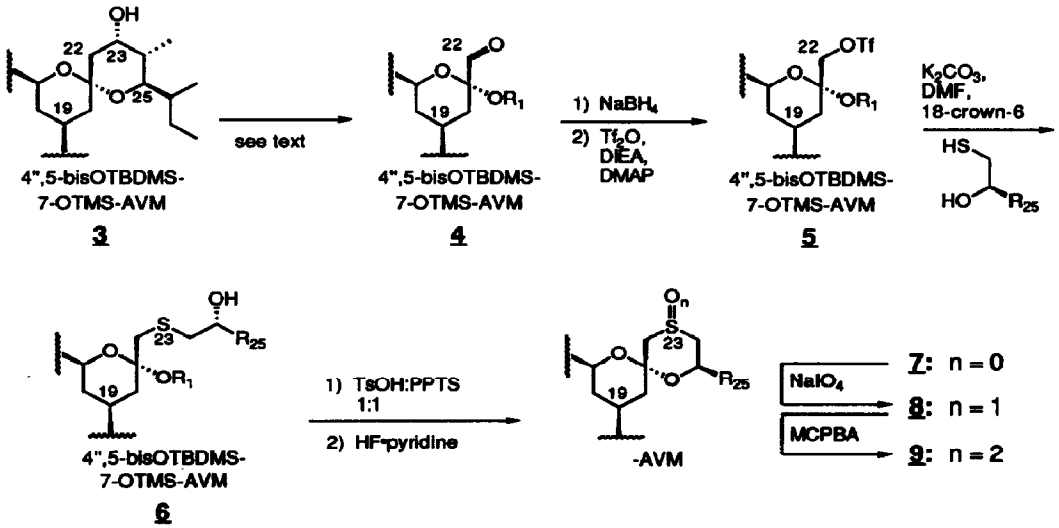
Our interest in this class of molecules has led to the preparation of a series of 6,6-spiroketal modified AVM analogs wherein C23 has been excised and replaced with an oxygen or sulfur atom, the design and

synthesis of which are the subject of the present communication. It was envisaged that the synthesis of avermectin analogs bearing a sulfur or oxygen atom in lieu of a carbon would result in analogs which are isosteric with the parent IVM. Additionally, it was anticipated that corresponding sulfoxide and sulfone analogs would provide derivatives which are isosteric with avermectin B_{2a} (2), which bears an axial hydroxyl at C23. The introduction of a heteroatom for C23 was not thought to dramatically alter the spatial positioning of substituents at C24 or C25. Indeed, preliminary molecular modeling experiments indicate that the replacement of C23 by a heteroatom confers virtually no change in the orientation of functionality at C24 or C25.

Two distinct synthetic strategies were necessary to introduce sulfur and oxygen into the avermectin nucleus prior to reconstruction of the spiroketal moiety. However, in each instance, aldehyde **4** served as the common intermediate for heteroatom introduction. Aldehyde **4**, where R_1=Me[5a] or CH(sBu)CH(Me)CO_2Me,[7] was readily available from tris-silylated avermectin B_{2a} (3) via formation of the C23 ketone with subsequent Rubottom oxidation to generate the α-hydroxy ketone followed by lead tetraacetate-mediated oxidative cleavage.

Scheme I illustrates the route employed for the synthesis of the 23-nor-23-thia-AVM derivatives **7-9**. Reduction the C22 carbonyl of **4** with $NaBH_4$ followed by sulfonylation with $(CF_3SO_2)_2O$ produced triflate **5** in 83% yield for the two steps. The triflate preparation was readily amenable to gram scale synthesis since **5**, though labile to moisture, was stable at -16 °C for >6 months after lyophilization with negligible decomposition detected. Displacement of the sulfonate with thiols proceeded readily (DMF, K_2CO_3, 18-crown-6, RT, 60-90%) using chiral, vicinal thioalcohols derived from amino acids. Alternatively, the displacement could be run under identical conditions using α-mercaptoketones followed by chiral[8] (0.1 eq R-oxazaborolidine•BH_3 complex, 1 eq BH_3•SMe_2, PhMe, -10 °C, 6-12 hrs, yielding diastereomeric ratios of 95:5) or achiral ($NaBH_4$, MeOH, 0 °C) reduction. Cyclization of the resultant sulfide **6** proved problematic initially, as conditions satisfactory for the preparation of 6,6- or 6,5-spiroketals[5,7] yielded virtually no product and eventually led to significant decomposition of **6**. Ultimately, it was determined that cyclization proceeded satisfactorily (50-80%)

Scheme I



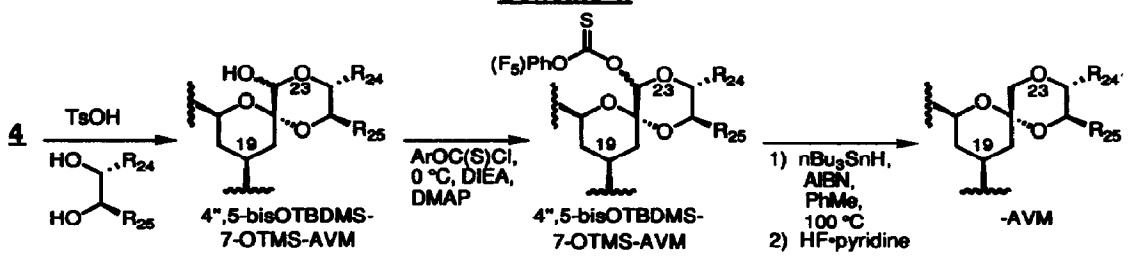
using 1:1 TsOH:PPTS in CH_2Cl_2 at RT, generating the cyclic sulfide **7** after HF•pyridine-mediated[9] desilylation. Subsequent oxidation to prepare sulfoxide **8** as an inseparable, ~1:1 mixture of sulfoxide diastereomers (1.1 eq $NaIO_4$, 1:1 MeOH:H_2O, RT) or sulfone **9** (1.1 eq MCPBA, CH_2Cl_2, 0 °C to 25 °C) proceeded uneventfully. Representative examples of these new avermectins are shown in **Table I**.

Table I: 23-Nor-23-Thia-Avermectin Derivatives[11]

Entry	R_{25}	n =	Entry	R_{25}	n =
7a	H	0	**8a**	H	1
7b	Me	0	**8c**	*i*-Pr	1
7c	*i*-Pr	0	**8d**	*c*-C_6H_{11}	1
7d	*t*-Bu	0	**8f**	Ph	1
7e	*c*-C_6H_{11}	0	**9a**	H	2
7f	Ph	0	**9d**	*c*-C_6H_{11}	2
			9f	Ph	2

The avermectin analogs bearing the 23-oxa function also were prepared via aldehyde **4**, although a conceptually distinct synthetic strategy was adopted; this route is shown in **Scheme II**. While introduction of the oxygen at the 23-position via nucleophilic displacement of triflate **5** was not viable, transketalization of **4** with vicinal diols (1 eq TsOH, 2-10 eq diol, CH_2Cl_2, RT, 5-15 min, 80-95%) generated the desired spiroketal **10** bearing an anomeric hydroxyl at C22 as a 1:1 mixture of C22 epimers. This reaction proceeded rapidly whether a mono- or 1,2-disubstituted vicinal diol was used. With monosubstituted-1,2-diols a ~1:1 mixture of regioisomers was formed, leading to adducts wherein the newly introduced R group may be at either position 24 or 25 (**12b-k**). Use of appropriate chiral diols permitted retention of the natural AVM stereochemistry at these sites. In the case of 1,2-disubstituted-1,2-diols, selecting diols possessing a trans relationship between R_{24} and R_{25} permitted control of the relative stereochemistry at these two positions. Examples include transketalization with R,S-2,3-butanediol or *trans*-1,2-cyclohexanediol leading to **12l** and **12m**, respectively.

Scheme II



The newly formed anomeric hydroxyl at C22 was reductively removed via the Barton protocol (nBu_3SnH, AIBN, PhMe, 100 °C, 15 min)[10] after preparing the corresponding pentafluorophenylthionocarbonate. Other reducible functionality probed included Cl, Br, SPh or SePh. However, these reactions were

plagued by either poor yields in halide/pseudohalide incorporation and/or reduction. Deprotection of the three silyl groups with HF•pyridine[9] proceeded smoothly to form the new 23-nor-23-oxa-AVM derivatives **12a-m** shown in **Table II**. It was at this juncture that the C24 and C25 monosubstituted regioisomeric pairs **12b-k** were most readily separable by reversed-phase HPLC.

Table II: 23-Nor-23-Oxa-Avermectin Analogs[11]

Entry	R_{24}	R_{25}	Entry	R_{24}	R_{25}
12a	H	H	**12h**	H	*c*-C_6H_{11}
12b	H	Me	**12i**	*c*-C_6H_{11}	H
12c	Me	H	**12j**	H	Ph
12d	H	*i*-Pr	**12k**	Ph	H
12e	*i*-Pr	H			
12f	H	*t*-Bu	**12l**	Me	Me
12g	*t*-Bu	H	**12m**	-$CH_2CH_2CH_2CH_2$-	

In summary, the synthetic protocols disclosed in this communication represent facile methods for the introduction of an oxygen or sulfur atom in lieu of C23 in the avermectin structure. These new oxa- and thia-avermectin derivatives represent isosteres of the parent AVM. Additionally, the sulfoxy and sulfonyl derivatives are designed to be isosteric with AVM B_{2a}. The biological efficacies of these new, heteroatom-substituted AVM analogs will be reported elsewhere.

Acknowledgements: We gratefully thank Dr. Christopher Culberson for molecular modeling support.

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(*Received in USA* 7 *April* 1994; *revised* 27 *May* 1994; *accepted* 31 *May* 1994)