Tetrahedron Letters, Vol. 34, No. 9, pp. 1407-1410, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

BIS-HOMO AVERMECTIN B_{1a} – A SEMI-SYNTHETIC ANALOG WITH A TRIENIC 18-MEMBERED MACROCYCLIC RING

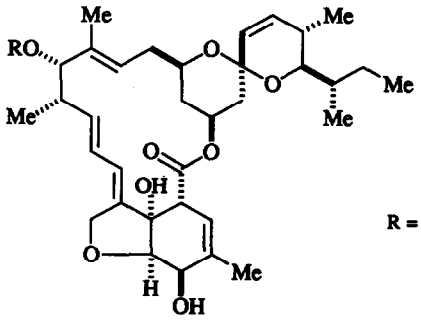
Stephen Hanessian*, Philippe Chemla and Yongxue Tu
Department of Chemistry, Université de Montréal
P.O. Box 6128, Station A, Montréal, P.Q., CANADA

Abstract: The title compound was synthesized from semi-synthetic subunits obtained from avermectin B_{1a} after homologation, coupling, lactonization and deconjugation.

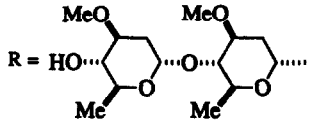
The avermectin family of anthelmintic 16-membered macrolides[1,2] continues to be the subject of much research activity in view of their enormous market potential. Numerous efforts to improve or modify the structure-activity profile of the avermectins, as exemplified by avermectin B_{1a}, **1** (Figure 1) have been reported in the literature, largely from the Merck Laboratories[3] as well as other groups.[4]

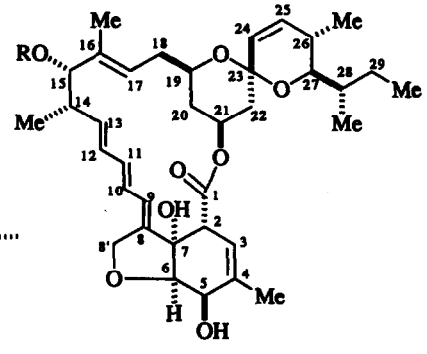
Inspection of the structure and topology of avermectin B_{1a} from ^1H NMR and X-ray crystal data[5] reveal two interesting features: a. the macrocyclic ring is in fact quite tightly packed with hardly any conformational flexibility; b. the concave hexahydrobenzofuran portion of the molecule adopts a conformation in which the carbonyl group of the lactone is pseudoequatorial and pointing away from the macrocycle.

Figure 1



Avermectin B_{1a}, **1**

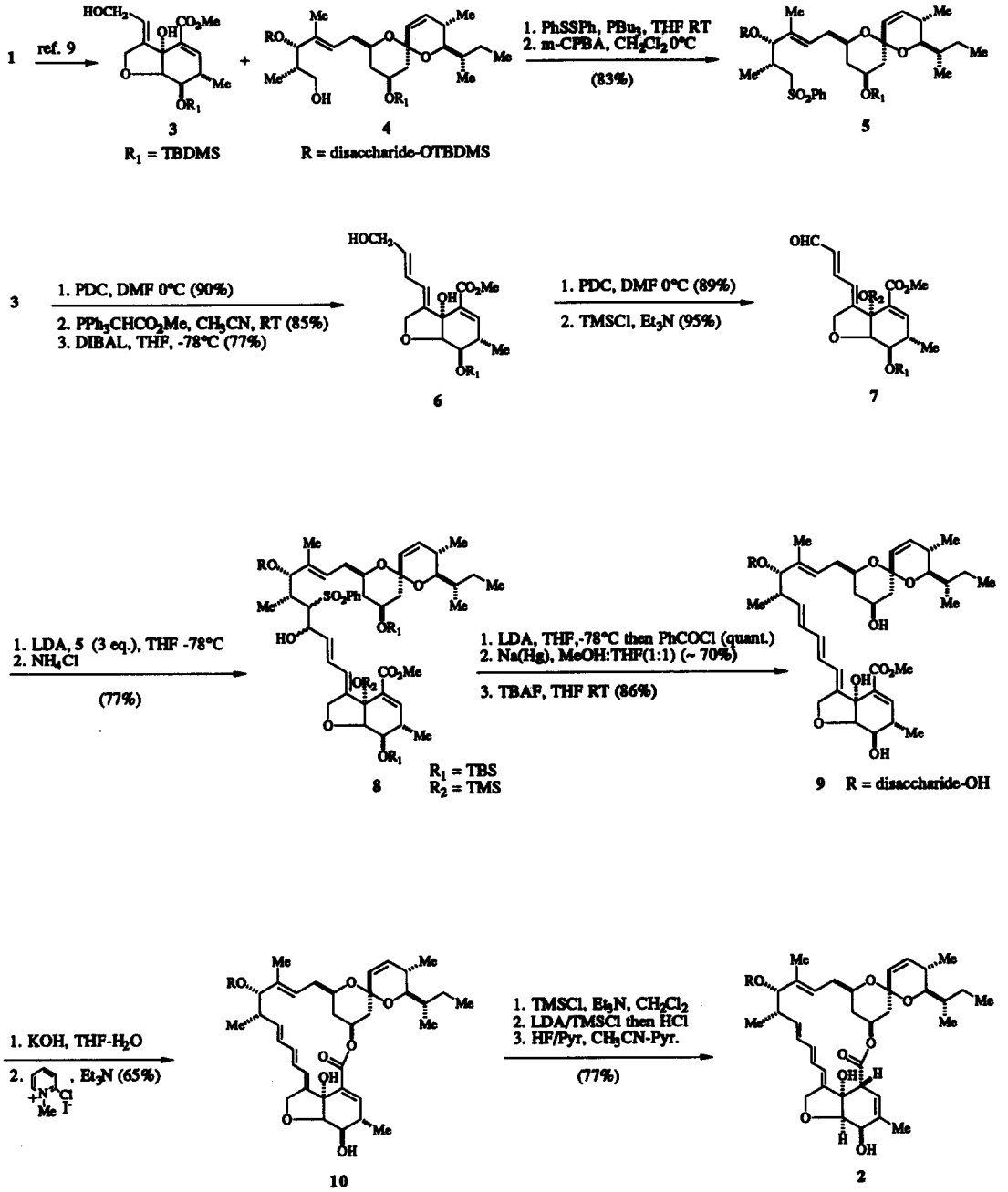




Triene analog, **2**

Previous results from our laboratory and from the Merck group, have shown that even minor alterations in the basic structure involving configurational inversions at C-2,[6] or at C-19,[7,8] for example result in drastic erosion of anthelmintic activity. Intrigued by this unforgiving nature of the natural product vis-a-vis subtle structural and

Scheme 1


1
ref. 9
3
4
R1 = TBDMS
R = disaccharide-OTBDMS
1. PhSSPh, PBu3, THF RT
2. m-CPBA, CH2Cl2 0°C
(83%)
5
3
1. PDC, DMF 0°C (90%)
2. PPh3CHCO2Me, CH3CN, RT (85%)
3. DIBAL, THF, -78°C (77%)
6
1. PDC, DMF 0°C (89%)
2. TMSCl, Et3N (95%)
7
1. LDA, 5 (3 eq.), THF -78°C
2. NH4Cl
(77%)
8
R1 = TBS
R2 = TMS
1. LDA, THF,-78°C then PhCOCl (quant.)
2. Na(Hg), MeOH:THF(1:1) (~ 70%)
3. TBAF, THF RT (86%)
9 R = disaccharide-OH
1. KOH, THF-H2O
2. , Et3N (65%)
10
1. TMSCl, Et3N, CH2Cl2
2. LDA/TMSCl then HCl
3. HF/Pyr, CH3CN-Pyr.
(77%)
2

stereochemical modifications, we envisaged the synthesis of a *bis*-homo triene analog of avermectin B_{1a} in which the macrocycle was enlarged to an 18-membered lactone as shown in structure **2** (Figure 1). Inspection of molecular models indicated that such a structure would exhibit a greater degree of conformational freedom. Of prime interest was to probe the effect of macrocyclic lactone ring enlargement on the biological activity and profile of the natural 16-membered lactone.

Scheme 1 shows the route followed to the intended target. Thus, the readily available degradation product **3**, obtained via ozonolysis and reduction of **1**,[9] was homologated in three efficient steps to produce the *bis*-allylic alcohol **6**, $[\alpha]_D$ 182° (c 0.97, $CHCl_3$). Oxidation to the aldehyde and protection of the tertiary alcohol group as the TMS ether gave **7**, which was ready for condensation with a nucleophilic "upper" segment en route to the triene system.

The dioxaspiroacetal subunit with the appended disaccharide was also obtained from the ozonolysis of **1**.[9] Selective phenylthioetherification[10] of the primary alcohol group proceeded uneventfully to give the phenylthioether, $[\alpha]_D$ -52° (c 1.01, $CHCl_3$), which was subsequently oxidized to the sulfone **5**, $[\alpha]_D$ -37°, $CHCl_3$). Formation of the anion with LDA followed by treatment with the aldehyde **7** led to the β-hydroxysulfone **8** as a mixture of diastereomers. Introduction of the double bond took place smoothly via the well known sequence involving benzoylation and reductive elimination with sodium amalgan.[11] Finally, desilylation gave the *seco* ester derivative **9**, $[\alpha]_D$ +40° (c 1.19, $CHCl_3$) in excellent yield. There now remained to form the macrolactone ring and to deconjugate[15] en route to the target molecule.

Basic hydrolysis, acidification and treatment with the Mukaiyama reagent[12] led to the conjugated macrolactone **10**. We had previously developed a protocol for the deconjugation and partial equilibration of 2-epi avermectin B_{1a}, a sequence that has been successfully utilized by other groups[3,4] in the final stages of their elegant syntheses of avermectin A_{1a}[13] and B_{1a}[14] respectively, and their immediate derivatives. We had also used the same reactions in the synthesis of 19-epi avermectin A_{1a} from avermectin B_{1a},[7] where deconjugation of an O-silyl protected derivative led directly to the desired configuration at C-2.

When **10** was O-silylated then treated with LDA (THF, -78°C) followed by an acidic workup, there was obtained a product to which we assign structure **2**, $[\alpha]_D$ -40.53° (c 0.15, MeOH) based on extensive NMR studies at 500 MHz (1D, 2D NMR, 2D COSY, ROESY with complete JJ and nOe connectivities). A nOe enhancement can be seen between H-2 and H-8' but not between H-2 and H-5 or H-6 in the 2D ROESY spectrum. Treatment of **10** without protection of the hydroxy groups with LDA under the same conditions as above did not result in any change. It is of interest that deconjugation of the avermectin B_{1a} derivative corresponding to **10** led to the C-2 *epi* product almost exclusively. In this case, equilibration to the natural product could be achieved by refluxing in benzene in the presence of imidazole.[6,15] However, treatment of **2** under the same conditions led to conjugation, and the formation of **10** as the major product.

Compound **2** was completely devoid of biological activity when evaluated in *C.elegans* motility (IC_{50} >10000ng/1mL) and in brine shrimp (*A.salina*) immobilization assays (IC_{50} >55500 ng/mL) compared to avermectin B_1 (15 ng/1mL and 430 ng/mL respectively).[16]

In spite of the lack of activity, the synthesis of the ring-enlarged *bis*-homotrienic analog of avermectin B_{1a} provides insight into the intriguing structure-activity requirements for this fascinating group of macrocyclic lactones.[17]

Acknowledgements. We thank NSERCC, Merck-Frosst and Merck for generous financial assistance. We also are grateful to Dr. Schaeffer, Merck, Rahway for the biological testing.

References and Notes.

1. For leading references, see Ivermectin and Abamectin, Campbell, W.C., Ed., Springer-Verlag, New York, 1989.
2. For recent reviews of synthetic approaches, see Davis, H.G.; Green, R.H. Nat. Prod. Rep. *Chem. Soc. Rev.*, **1991**, *211*, 271; Vaillancourt, V.; Pratt, N.E.; Perron, F.; Albizati, K.F. in The Total Synthesis of Natural Products, ApSimon, J., Ed. Wiley-Interscience, New York, **1992**, vol. 8, p. 353.
3. Blizzard, T.; Fisher, M.H.; Mrozik, H.; Shih, T.L. in Recent Progress in the Chemical Synthesis of Antibiotics, Lukacs, G.; Ohno, M. Eds. Springer-Verlag, New York, Chapter 3, p. 65, 1990; Fisher, M.H.; Mrozik, H. in Marcolide Antibiotics, Omura, S., Ed., Academic Press, Orlando, 1985, p. 553; Fisher, M.H. in Recent Advances in the Chemistry of Insect Control; Janes, N.F. Ed.; Royal Society of Chemistry; London, 1985, p. 53.
4. Albers-Schönberg, G.; Arison, B.H.; Chabala, J.C.; Douglas, A.W., Eskola, P.; Fisher, M.H.; Lusi, A.; Mrozik, H.; Smith, J.L.; Tolman, R.L. *J. Am. Chem. Soc.*, **1981**, *103*, 4216; Mrozik, H.; Eskola, P.; Arison, B.H.; Albers-Schönberg, G.; Fisher, M.H. *J. Org. Chem.*, **1982**, *47*, 489.
5. For selected recent references, see Meinke, P.T.; O'Connor, S.P.; Mrozik, H.; Fisher, M.H. *Tetrahedron Lett.*, **1992**, *33*, 1203; Shih, T.L.; Holmes, M.A.; Mrozik, H.; Fisher, M.H. *Tetrahedron Lett.*, **1991**, *32*, 3363; Banks, B.J.; Fenner, B.R.; Voss, V.F.; Witty, M.J. *Synlett*, **1991**, 873, 875
6. Hanessian, S.; Dubé, D.; Hodges, P.J. *J. Am. Chem. Soc.*, **1987**, *109*, 7063; See also ref. 3.
7. Hanessian, S.; Chemla, P. *Tetrahedron Lett.*, **1991**, *32*, 2719.
8. Blizzard, T.; Bosttrom, L.; Margiatto, G.; Mrozik, H.; Fisher, M.H., *Tetrahedron Lett.*, **1991**, *32*, 2723.
9. Hanessian, S.; Ugolini, A.; Hodges, P.J.; Dubé, D. *Tetrahedron Lett.*, **1986**, *27*, 2699.
10. Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc.*, Perkin I, **1983**, 1315.
11. Julia, M.; Paris, J.-M. *Tetrahedron Lett.*, **1973**, 4833; Morzycki, J.; Schnoes, H.K.; Deluca, H.F. *J. Org. Chem.*, **1984**, *49*, 2148.
12. Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.*, **1986**, 49.
13. Danishefsky, S.; Armistead, D.M.; Wincott, F.E.; Selnick, H.G.; Hungate R. *J. Am. Chem. Soc.*, **1989**, *111*, 2967 and previous papers.
14. White, J.D.; Bolton, G.L. *J. Am. Chem. Soc.*, **1990**, *112*, 1626.
15. For other observations concerning conjugation and deconjugation in the avermectin series, see ref. 3; see also Pivnichny, J.V.; Shim, J.-S.K.; Simmerman, L.A. *J. Pharm. Sci.*, **1983**, *72*, 1447; Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.*, **1987**, *109*, 933.
16. Blizzard, T.A.; Ruby, C.L.; Mrozik, H.; Preiser, F.A.; Fisher, M.A. *J. Antibiot.*, **1989**, *42*, 1304.
17. New compounds were characterized and analyzed by a combination of spectroscopic and analytical techniques. (^{1}H, ^{13}C NMR, 2D NMR, HRMS, elemental analyses, etc.). Optical rotations were measured at 25°C.

(Received in USA 5 November 1992; accepted 4 December 1992)