Tetrahedron Letters, Vol. 33, No. 13, pp. 1709-1712, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

AN UNUSUAL TWIST IN THE SYNTHESIS AND HYDROLYSIS OF THE 23,24-EPOXIDE OF 22,23-DIHYDROAVERMECTIN B_{1a}

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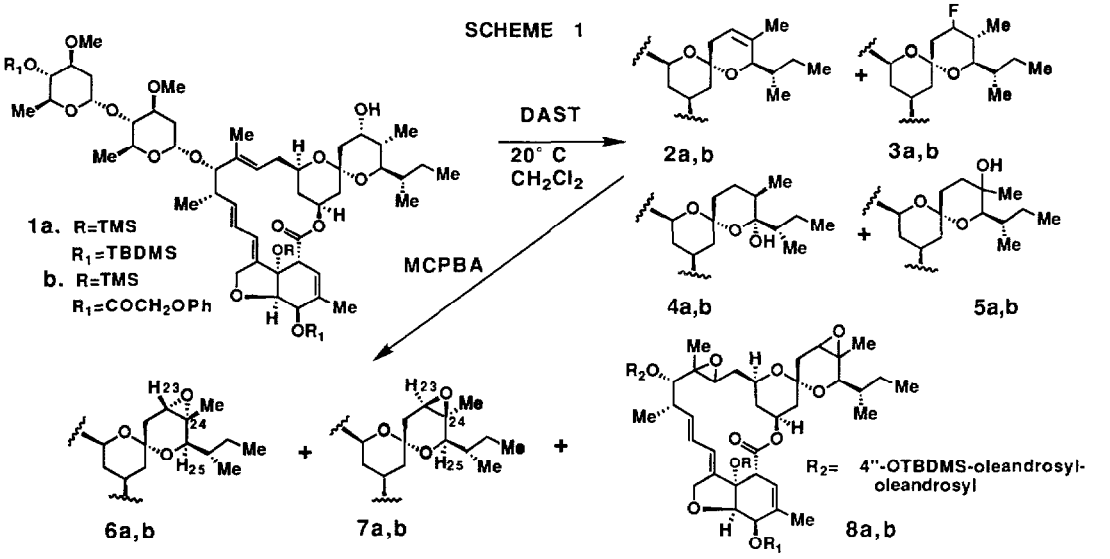
Abstract: Treatment of 4",5-di-O-tert-butyldimethylsilyl(or phenoxyacetyl)-7-O-trimethylsilyl-avermectin B_{2a} (**1a,b**) with diethylaminosulfur trifluoride (DAST) at 20ÁC in dichloromethane resulted in net elimination of water to yield 65% of the 23,24-olefin (**2a,b**), 5-10% 23-fluoroavermectin derivative (**3a,b**), and 20-25% of two rearranged products (**4a,b**:**5a,b** in a 2:1 ratio). The trisubstituted 23,24-olefin (**2a,b**) was selectively epoxidized with m-chloroperbenzoic acid to give a mixture of alpha (**6a,b** major) and beta (**7a,b** minor) 23,24-epoxides in 64% yield. The acid catalyzed hydrolysis of epoxide **6a,b** unexpectedly afforded hemiketal **9a,b** as the major product (60%) and the usual 23,24-diol **10a,b** as the minor product (6%). Subsequent Ley perruthenate oxidation of **9b** produced lactone **13b** in 15% yield. Lead tetracetate oxidation of **10a** produced the desired cleavage product **14a** in 40-50% yield.

In the course of investigating the possibility of fluorine substitution[1] via the C23 hydroxy function in the avermectin B_{2a} structure (**1a** or **b**), we discovered that its reaction with DAST[2] gave mainly elimination exclusively to the 23,24-olefin (**Scheme 1**) in 65% yield. This regioselection was in marked contrast to that observed for the elimination of the C23-thionophenylcarbonate[3] which produced the 22,23-isomer avermectin B_{1a} via a syn-elimination mechanism. The mechanism by which the DAST reaction proceeded can best be explained by an E1 type transition state. Examination of the corresponding Dreiding model of avermectin B_{2a} provided a rationale for the observed result. The C24-hydrogen bond adjacent to the incipient developing carbocation is antiperiplanar to the breaking C23-OSF_2 bond and its participation in the transition state (highly E1-like) would be more favorable than the participation of the C22-hydrogen bond (which electronically is polarized towards the spiroketal carbon). In addition to the 23-fluoroavermectin **3**, a substantial amount (ca. 25% yield) of more polar byproducts was obtained. These polar materials were desilylated and purified to two homogeneous products[4] (**4,5** in a 2:1 ratio respectively). Their structures are consistent with products arising from the hydration of carbocations formed from rearrangement of a C23 carbocation intermediate.

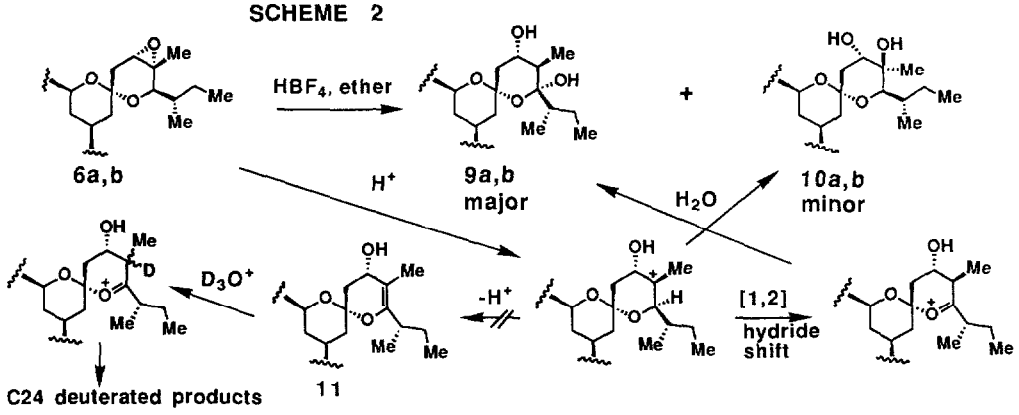
At the time of this study we were interested in modifications to the spiroketal region of the avermectin structure. The fact that we obtained a new olefinic function in this part of the molecule provided the opportunity to test the feasibility of selective epoxidation[5] of this double bond. Treatment of **2a** with 1.8 equiv of m-

chloroperoxybenzoic acid (MCPBA) in dichloromethane (20°C, 20 min) afforded a 76:6:18 ratio of alpha-epoxide(**6**):beta-epoxide(**7**):bis-epoxide(**8**). The yield of combined 23,24-monoepoxides[6] was 64% and the 14,15,23,24-bis-epoxide was obtained in 14% yield along with 16% recovered **2a**. *This result represents an unprecedented epoxidation of this region of the avermectin structure.*



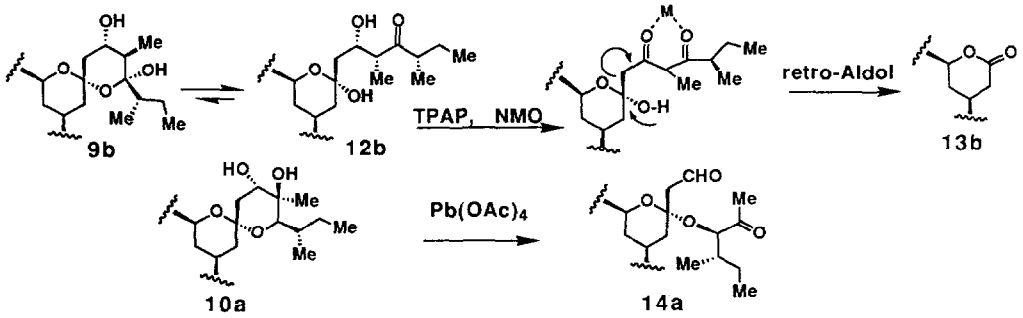
Subsequent investigation of the reactivity of epoxides **6** and **7** revealed an unexpected rearrangement during the acid catalyzed hydrolysis of epoxide **6a** or **b** (**Scheme 2**). Treatment of 9 g of **6a** or **b** in 100 mL of ether with 8 mL of 40% HBF_4 for 1 minute followed by neutralization with aqueous sodium bicarbonate afforded a 10:1 mixture of isomeric diols, **9a,b** (60% yield)[7] and **10a,b** (6% yield)[8] respectively. Diol **10** was the expected epoxide hydration product whereas **9** was formed as the result of a facile, fast, and perhaps concerted hydride migration from C25 to C24 followed by hydration of the oxonium-ion[9] intermediate. Another path was considered where instead of a hydride migration, the carbocation could eliminate a proton to give an intermediate dihydropyran **11** which was then hydrated via the oxonium ion to the product. However, several other observations do not support this alternate mechanism. We repeated the acidic hydrolysis in deuterated acid and found no deuterium incorporation in the products. In addition the observed reaction product **9** was exclusively one isomer[9] at C24 whereas if the dihydropyran was the intermediate we would expect a mixture at C24. Interestingly, epoxide **7**, when subjected to identical reaction conditions (ether, HBF_4, 20°C, 1 min), reacted very slowly (ca. 90% recovered **7**) to yield mainly the expected 23,24-diol[4] (10%). *Evidently the ease of hydride migration from C25 to C24 was dependent on the syn-stereochemistry of the adjacent hydride bond to the developing carbocation center.* In retrospect, the 2:1 ratio of products **4** to **5** obtained in the related DAST-induced rearrangement may reflect that the rate of the second hydide shift is exceedingly fast compared to the rate of hydration of the C24 carbocation.

SCHEME 2



We next focused our efforts to exploring the reactivities of our diol intermediates. The NMR of **9b** indicated that in chloroform the favored form is the keto-hemiketal **12b** (**Scheme 3**). Oxidation utilizing tetrapropylammonium perruthenate[10], N-methylmorpholine-N-oxide, and 4A sieves in dichloromethane gave a single mobile product on TLC. Isolation of this product in 10-15% yield and analysis by NMR indicates the molecule has undergone a fragmentation to yield lactone **13b**. This could be rationalized by a retro-aldol cleavage of the intermediate beta-diketone-metal complex. We then turned our attention to diol **10a** which was readily cleaved by lead tetraacetate (1.5 equiv., benzene, 20°C, 3h) to aldehyde[4] **14a** in 40-50% yield. Efforts toward the reconstruction of avermectin B_{2a}-type derivatives from **14a** are underway.

SCHEME 3



In conclusion, the regiospecific functionalization of the spiroketal portion of the avermectin structure to yield the C23,24 double bond and its corresponding epoxides has been realized. The acid catalyzed hydrolysis of epoxy-tetrahydropyrans of the sort represented by the upper right portion of structure **6** may give rise to rearranged products in addition to the normal 1,2-diols.

REFERENCES AND NOTES

1. Fluorine has been used extensively to replace hydrogen or hydroxy groups in a wide range of biologically active molecules. For leading references see: J. T. Welch, Tetrahedron, *43*, 3123-3197, **1987**. The avermectins are a class of potent antiparasitic compounds. For leading references and reviews see: T. Blizzard, M.H. Fisher, H. Mrozik, and T.L. Shih, In Recent Progress in the Chemical Synthesis of Antibiotics; Lukacs, G. and Ohno, M.,Eds.; Springer-Verlag: New York, 1990; Chapter 3, p 65-102.

2. W.J. Middleton, J. Org. Chem., *40*, 574-578, **1975**.

3. H. Mrozik, P. Eskola, and M.H. Fisher, Tetrahedron Lett. *23*, 2377-2378, **1982**.We also utilized the Mitsunobu dehydration (see T.L. Shih, M.J. Wyvratt, and H. Mrozik, J. Org. Chem. *52*, 2029-2033, **1987** and T. Iimori, Y. Ohtsuka, and T. Oishi, Tetrahedron Lett. *32*, 1209-1212, **1991**.) and obtained mainly the 22,23-olefin (silylated avermectin B_{1a}) in 80% yield from **1a**.

4. All structures were assigned based on NMR and mass spectral data.

5. Epoxidation of avermectin B_1a utilizing MCPBA or the vanadium(acac)$_2$-TBHP Sharpless-Michaelson procedure usually provides the 8,9-epoxide (H. Mrozik, **1985**, U.S. Pat. 4,530,921) or 3,4-epoxide (T. Blizzard et al, Tetrahedron Lett. *31*, 4965-4968, **1990**). Utilization of m-chloroperbenzoic acid results in epoxidation at the 14,15-double bond of milbemycin D (B. Frei, P. Huxley, P. Maienfisch, H.B. Mereyala, G. Rist, and A.C. O'Sullivan, Helv. Chim. Acta, *73*, 1905-1917, **1990**).

6. All compounds were fully characterized by 400 MHz NMR and mass spectra. The stereochemistry of **6b** and **7b** was determined by NOE difference spectroscopy. Irradiation of the C24-methyl signal (at 1.30 ppm) in **7b** resulted in about equal enhancement of H23 (at 2.89 ppm) and H25 (at 3.69 ppm) whereas irradiation of the same methyl protons in **6b** (at 1.595 ppm) resulted in a strong enhancement of H23 (3.01 ppm) but a weak enhancement of H25 (3.81 ppm).

7. NMR (400 MHz, TMS, $CDCl_3$) of **9a**: 0.09(d), 0.12(s), 0.84(m), 0.88(t), 0.89(s), 0.93(s), 1.05(d), 1.14(d), 1.18(d), 1.21(d), 1.26(d), 1.30-1.48(m), 1.50(s), 1.52-1.70(m), 1.78(s), 1.88(m), 2.24(q), 2.32(m), 2.44(dd), 2.56(m), 2.62(m), 3.14(t), 3.22(t), 3.25((dd), 3.33(s), 3.34(m), 3.44(s), 3.64(m), 3.69(dd), 3.74(t), 3.82(d), 3.85(m), 3.97(br s), 4.09(dt), 4.40(m), 4.58(dt), 4.65(m), 4.79(d), 4.95(m), 5.20(br d), 5.25(d), 5.31(d), 5.48(q), 5.56(dd), 5.68(dt), 5.76(dd).

8. NMR (400 MHz, TMS, $CDCl_3$) of **10a**: 0.07(d), 0.12(s), 0.87(m,s), 0.91(s), 0.94(t), 1.06(d), 1.17(d), 1.19(d), 1.20(s), 1.24(d), 1.26-1.48(m), 1.50(s), 1.57(m), 1.76(s), 1.77(m), 2.06(dd), 2.18-2.34(m), 2.38(dd), 2.56(m), 3.12(t), 3.22(t), 3.25(dd), 3.31(s), 3.32(m), 3.40(s), 3.42(m), 3.57-3.75(m), 3.76(sh d), 3.80(d), 3.97(br s), 4.38(br s), 4.60(dq), 4.77(d), 4.84(m), 5.09(m), 5.28(d), 5.29(m), 4.45(d), 5.59(dd), 5.65(dt), 5.75(dd).

9. The stereochemistry at C24 has not been rigorously established although the homogeneity of the sample has been determined by 400 MHz NMR, mass spectral data, and reverse phase HPLC. The drawn structural assignment assumes a suprafacial migration of the hydride.

10. The oxidation was run following the conditions outlined by W. P. Griffith, S. V. Ley, G. P. Whitcombe, and A. D. White, J. Chem. Soc., Chem. Commun. 1625 (**1987**) with the modification of by-passing the aqueous sodium sulfite workup and directly filtering the reaction mixture through a short column of silica gel with ethyl acetate.

(Received in USA 6 November 1991)