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SELENIUM INITIATED CYCLIZATION-2,3 SIGMATROPIC REARRANGEMENT: SYNTHESIS OF THE C1 TO C10 FRAGMENT OF THE MILBEMYCINS AND THE AVERMECTINS

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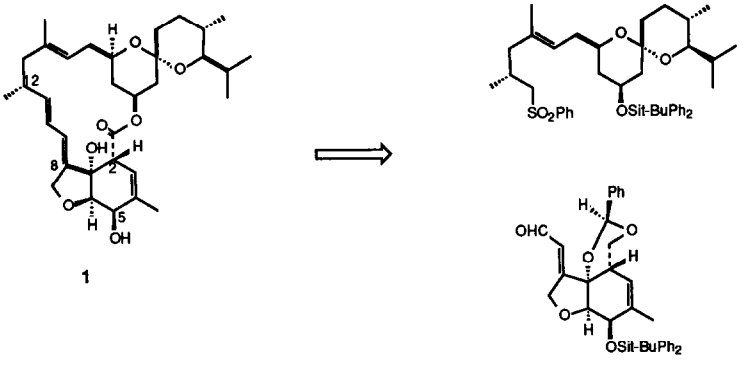
Summary: An efficient route to the C1 to C10 fragment of the milbemycins and the avermectins has been accomplished utilizing a selenium initiated electrophilic cyclization in conjunction with a [2,3] sigmatropic selenoxide rearrangement in the key transformation.

The structurally related avermectins[2] and milbemycins[3] have been shown to possess significant antiparasitic activity[4] and have recently been the targets of synthetic studies by a number of groups.[5-9] In the accompanying communication we describe our own studies which have culminated in the synthesis of the C11 to C31 fragment of milbemycin D (**1**), the primary target of our efforts. While numerous approaches to the dioxaspiroundecane portion of these important molecules have been reported,[5,6] considerably less success has been recorded with regard to the hexahydrobenzofuran subunit.[7,8] No previous totally synthetic preparation of the intact C1 to C10 fragment of the milbemycins and the avermectins has appeared. We report here a rapid, efficient entry into the C1 to C10 fragment **2** of the milbemycins and avermectins appropriately functionalized for connection to the spiroketal fragment and further elaboration.

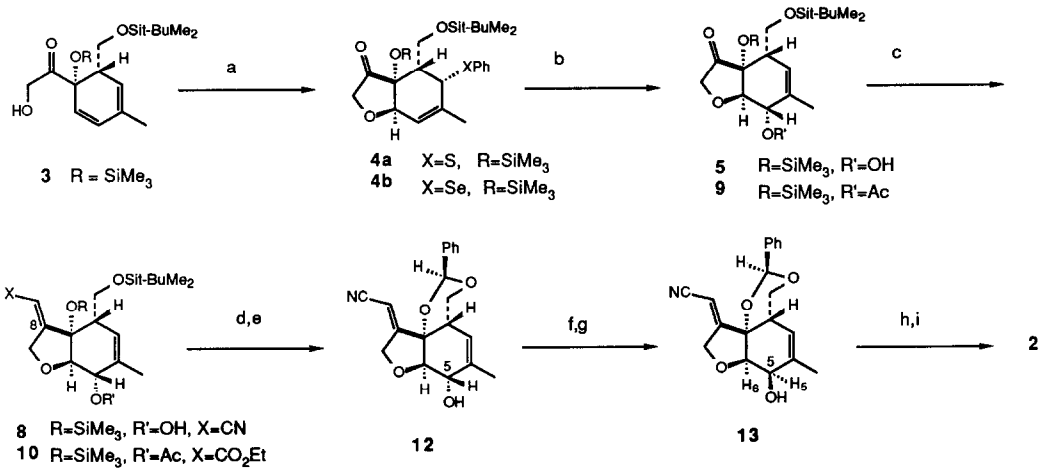


1 **2**

Our initial studies were centered around the preparation of α-hydroxy ketone **3**[7b] with the intent of executing an intramolecular electrophilic cyclization to close the five membered ring and introduce functionality at C5 in the cyclohexene ring. While we had previously utilized an NBS mediated cyclization of **3** to gain entry into the desired systems, this sequence proved lengthy and inefficient and we therefore sought an alternative method for the electrophilic cyclization. Exposure of α-hydroxy ketone **3** to phenylsulfenyl chloride in dichloromethane

produced a single regio and stereoisomer **4a**. Oxidation of the sulfide to the sulfoxide with m-CPBA at -78°C proceeded cleanly, however, attempts to effect rearrangement of the sulfoxide[11] under a variety of conditions failed to produce any of the desired allyl alcohol **5**. Alternatively, treatment of **3** with phenylselenenyl chloride (CH_2Cl_2, $NaHCO_3$) followed directly by oxidation (H_2O_2, pyr., CH_2Cl_2) provided alcohol **5**[10] (via selenide **4b**) in a single operation in 70% yield.[12,13] When diol **6** (Scheme II) was exposed to similar conditions (PhSeCl, hexane, -78°C) diol **7** was produced in 45% yield. The lower yield of this reaction and our inability to easily differentiate the two allylic alcohols prompted further investigation of modifications on alcohol **5** {$[\alpha]^{D}_{20}$ = +29.6°, $CHCl_3$, c = 0.0115 g/mL}.

Scheme I



(a) PhSeCl, $NaHCO_3$, CH_2Cl_2, 0°C, 15 min. (b) H_2O_2, CH_2Cl_2, pyr. (1.5 equiv), 0°C, 15 min, 70% 2 steps. (c) Ph_3P=CHCN, $CH_3C_6H_5$, 110°C, 12h, 85%.. (d) 1% HF, CH_3CN, 30 min. (e) $PhCH(OCH_3)_2$, CH_2Cl_2, p-TsOH, 76% 2 steps . (f) Jones reagent, acetone, 0°C, 5 min. (g) $NaBH_4$, MeOH, 10 min, 79% 2 steps. (h) t-$BuPh_2SiCl$, DMF, imidazole, DMAP, 48h, 95%. (i) Dibal-H, toluene, -78°C, 3h, 50%.

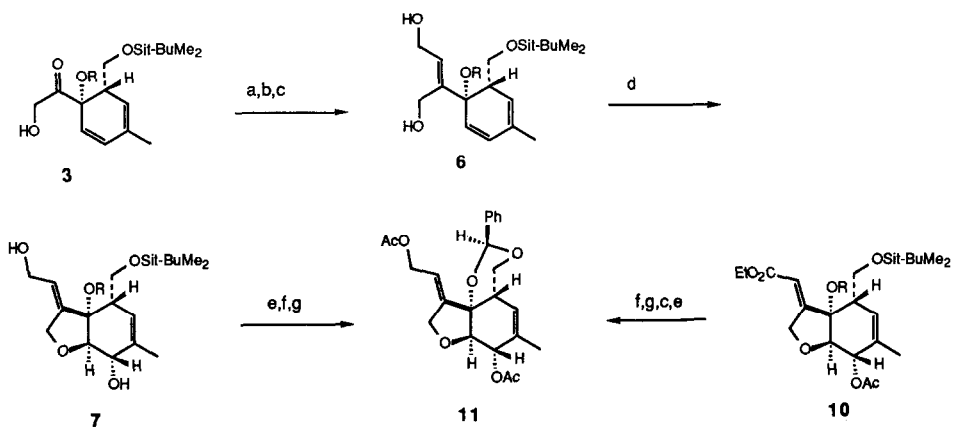
Completion of the C1 to C10 from **5** fragment required inversion of the C5 hydroxyl and connection of two carbons at C8. Exposure of ketone **5** to cyanomethylenetriphenylphosphorane (Ph_3P=CHCN) in toluene at reflux resulted in clean olefination at the C8 ketone to give **8** (E:Z >15:1, 85% yield). Alternatively, condensation of ketoacetate **9** with carboethoxymethylene triphenylphosphorane ($PhCH_3$, 110°C, 48h) produced the unsaturated ester **10** in 70% yield (E:Z >15:1). Successful execution of a Wittig olefination at the C8 ketone is highly significant, since the viability of this approach had previously been questioned.[14] Cleavage of the trimethylsilyl and t-butyldimethylsilyl ethers (1% HF, CH_3CN) and protection of the resultant diol as its benzylidene [$PhCH(OCH_3)_2$, CH_2Cl_2, p-TsOH, 76% from **8**] gave **12** which was primarily (5:1) the β benzylidene. Conversion to the benzylidene allowed confirmation of the relative stereochemistry at C2 by examining ^1H NMR coupling constants.[7] It is important to note that if **5** is converted to the benzylidene (as above) prior to the Wittig olefination the α benzylidene predominates (15:1). The C8,9 olefin geometry was

verified as illustrated in Scheme II. Conversion of **10** to the β benzylidene (1% HF, CH_3CN; then $PhCH(OCH_3)_2$, p-TsOH) followed by reduction of the ester ($LiAlH_4$) and formation of the diacetate gave **11**. This was identical to material independently prepared from diol **7**.

With the C8,9 double bond in place, inversion of the C5 hydroxyl to the β stereochemistry was the only transformation remaining. Careful oxidation with Jones reagent (acetone, 0°C, 5 min) followed immediately by reduction with sodium borohydride in methanol produced exclusively the β alcohol **13** in 79% yield (Scheme I). The stereochemistry at C 5 was evident from the coupling constant of H_5 with H_6 (5.5 Hz) in contrast to that in the alcohol **12** (2 Hz). These are nearly identical to those of natural milbemycin D and its C5 epimer respectively.[2] Protection of the secondary hydroxyl as its t-butyldiphenylsilyl ether was readily accomplished (DMF, imidazole, DMAP, Ph_2t-BuSiCl) in 95% yield. The nitrile was then reduced with diisobutylaluminum hydride in toluene at -78°C to provide the desired aldehyde **2**.

Thus, the utilization of a selenium initiated electrophilic cyclization in conjunction with a [2,3] sigmatropic selenoxide rearrangement provides an efficient, rapid entry into the C1 to C10 fragment of the milbemycins and the avermectins and should provide ready access to structural analogs. Additionally, the demonstration that intermediates which incorporate a carbonyl at C8 are viable synthetic intermediates for preparation of the hexahydrobenzofuran subunit of the milbemycins and avermectins is of major significance. Experiments regarding the connection of this C1 to C10 fragment to the spiroketal subunit are in progress and will be reported in due course.

Scheme II



(a) $(EtO)_2POCH_2CO_2H$, DCC, CH_2Cl_2, 30 min., 95%. (b) K_2CO_3, DME, t-BuOH, 80°C, 3h, 88%. (c) $LiAlH_4$, Et_2O, 2h, 70%. (d) PhSeCl, hexane, -78°C; then H_2O_2, pyr., 0°C, 30 min, 45%. (e) CH_3COCl, CH_2Cl_2, pyr, 1h, 90%. (f) 1% HF, CH_3CN, 30 min, 90%. (g) $PhCH(OCH_3)_2$, p-TsOH, CH_2Cl_2, 2h, 80%.

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References

1. a) Fellow of the Alfred P. Sloan Foundation, 1986-88. b) National Science Foundation Predoctoral Fellow.

2. Avermectins: a) Albers-Schonberg, G. *et.al. J. Am. Chem. Soc.* **1981**, *103*, 4216. b) Springer, J.P.; Arison, B.H.; Hirschfield, J.M.; Hoogsteen, K. *Ibid* 4221.

3. Milbemycins: a) Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito, A. *Tetrahedron Lett.* **1975**, 711. b) Mishima, H.; Junya, I.; Muramatsu, S.; Ono, M. *J. Antibiotics* **1983**, *36*, 980. c) Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *J. Antibiotics* **1983**, *36*, 991.

4. a) Miller, T.W. *et.al. Antimicrob. Agents and Chemotherapy* **1979**, *15*, 368. b) Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiotics* **1980**, *33*, 1120. c) Chabala, J.C.; Mrozik, H.; Tolman, R.L.; Eskola, P.; Lusi, A.; Peterson, L.H.; Woods, M.F.; Fisher, M.H.; Campbell, W.C.; Egerton, J.R.; Ostlind, D.A. *J. Med. Chem.* **1980**, *23*, 1134. d) Cupp, E.M.; Bernardo, M.J..; Kiszewski, A.E.; Collins, R.C.; Taylor, H.R.; Aziz, M.A.; Greene, B.M. *Science*, **1986**, *231*, 740.

5. Milbemycin β3: a) Smith, A.B., III; Schow, S.R.; Bloom, J.D.; Thompson, A.S.; Winzenberg, K.N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Schow, S.R.; Bloom, J.D.; Thompson, A.S.; Winzenberg, K.N.; Smith, A.B., III *Ibid.* **1986**, *108*, 2662. b) Williams, D.R.; Barner, B.A.; Nishitani, K.: Phillips, J.G. *J. Am. Chem. Soc.* **1982**, *104*, 4708. c) Street, S.D.A.; Yeates, C.; Kocienski, P.; Campbell, S.F. *J. Chem. Soc. Chem. Comm.* **1985**, 1386. d) Yeates, C.; Street, S.D.A.; Kocienski, P.; Campbell, S.F. *Ibid.*, 1388. e) Baker, R.; O'Mahony, M.J.; Swain, C.J. *J. Chem. Soc. Chem. Comm.* **1985**, 1326. f) Barrett, A.G.M. ; Attwood, S.V.; Richardson, G.; Walshe, N.D.A.; *J. Org. Chem.* **1986**, *51*, 4840 g) Crimmins, M.T.; Bankaitis-Davis, D.M.; Hollis, W.G., Jr.; unpublished results.

6. Spiroketal studies: a) Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427. b)Baker, R.; Swain, C.J.; Head, J.C. *J. Chem. Soc. Chem. Comm.* **1985**, 309. c) Kocienski, P.; Street, S.D.A. *Ibid.* **1984**, 571. d) Godoy, J.; Ley, S.V.; Lygo, B. *Ibid.* **1984**, 1381. e) Culshaw, D.; Grice, P.; Ley, S.V.; Strange, G.A. *Tetrahedron Lett.* **1985**, *26*, 5837. f) Crimmins, M.T.; Hollis, W.G., Jr.; Bankaitis, D.M.accompanying communication.

7. a) Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1564. b) Crimmins, M.T.; Lever, J.G. *Tetrahedron Lett.* **1986**, *27*, 291.

8. a) Jung, M.E.; Street, L.J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. b) Kozikowski, A.P.; Maloney-Huss, K.E. *Tetrahedron Lett.* **1985**, *26*, 5759. c) Ireland, R.E.; Obrecht, D.M. *Helv. Chim. Acta* , **1986**, *69*, 1273. d) Hanessian, S.; Beaulieu, P.; Dube', D. *Tetrahedron Lett.* **1986**, *27*, 5071. e) Barrett, A.G.M.; Capps, N. *Tetrahedron Lett.* **1986**, *27*, 5571.

9. The first report of a synthetic preparation of an avermectin has appeared: Hanessian, S.; Ugolini, A.; Dube',D.; Hodges, P.J.; Andre', C. *J. Am. Chem. Soc.*; **1986**, *108*, 2776. See also a related study: Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.

10. All new compounds gave consistent NMR and IR data as well as satisfactory elemental analyses. All yields are for chromatographically pure material except where noted.

11. Evans, D.A.; Andrews, G.C. *Accts. Chem. Res.* **1974**, *7*, 147.

12. Sharpless, K.B.; Lauer, R.F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

13. A similar transformation has been reported utilizing a selenolactonization. Pearson, A.J.; Kole, S.L.; Ray, T. *J. Am. Chem. Soc.* **1984**, *106*, 6060.

14. Private communications.

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