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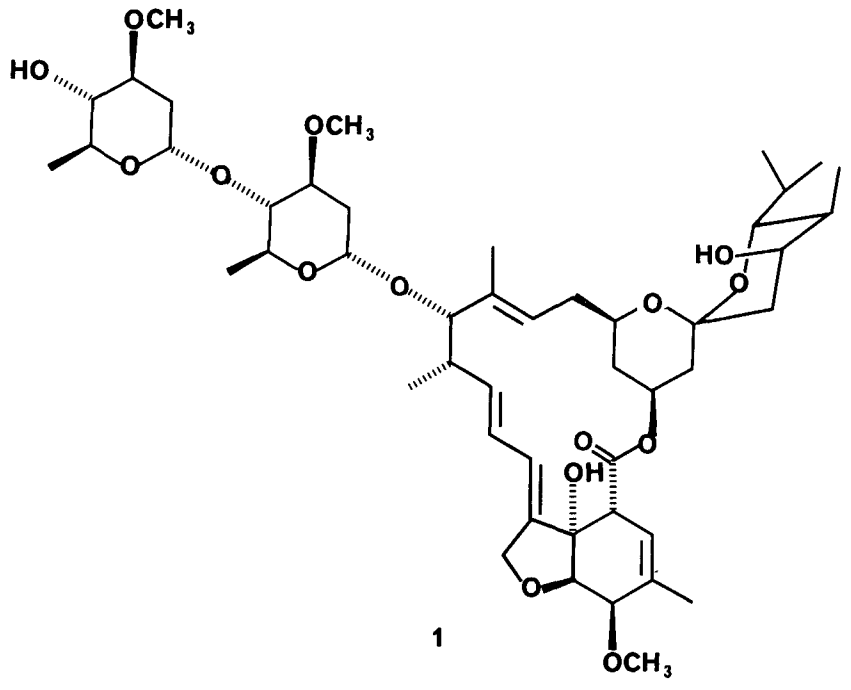
SYNTHETIC APPROACHES TO THE AVERMECTINS: STUDIES ON THE HEXAHYDROBENZOFURAN UNIT

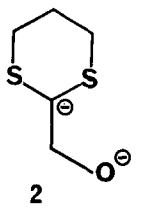
Anthony G.M. Barrett* and Nigel K. Capps
Department of Chemistry, Northwestern University, Evanston, Illinois 60201

SUMMARY: The condensation reaction of 2-lithio-2-lithio-oxymethyl-1,3-dithiane with an epoxy-ketone is used as the key step in a novel approach to the avermectin southern hexahydrobenzofuran unit.

The avermectins[1] and milbemycins[2] are potent parasiticidal and anthelmintic agents respectively produced by Streptomyces avermitilis and S. hygroscopicus subsp. aureolacrimosus Structurally these natural products are illustrated by one example avermectin A_{2b}(**1**). On account of their highly significant biological activities and unique structural features, the avermectins and milbemycins are attractive synthetic targets. Five total syntheses of the least complex natural product milbemycin β_3 have been developed.[3] Recently the first synthesis of avermectin B_{1a} using both synthetic and natural subunits has been communicated.[4] A considerable number of papers describing novel syntheses of spiro-ketals[5] and approaches to the total synthesis of more complex milbemycins and avermectins[6] have been published. In addition several approaches to molecules containing the avermectin southern hexahydrobenzofuran entity have been reported.[7]

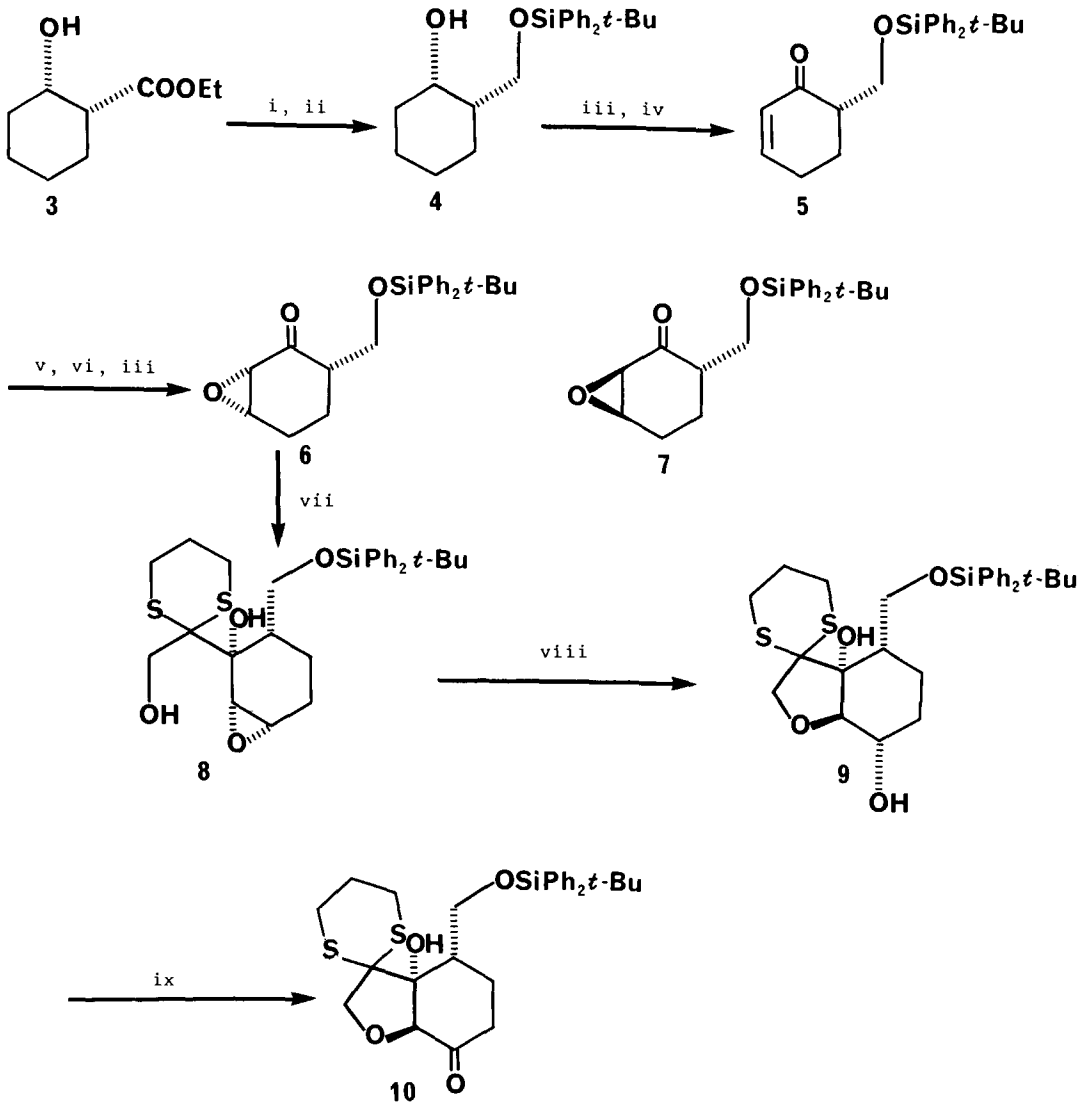


1



2

Scheme



REAGENTS: (i) $LiAlH_4$, Et_2O, 0 °C; (ii) $Ph_2{}^tBuSiCl$, imidazole, DMF, 0 °C; (iii) PDC, DMF; (iv) $LiN^{iso}Pr_2$, THF, -78° C; PhSeCl; H_2O_2; (v) $NaBH_4$, $CeCl_3$, MeOH, 0 °C; (vi) $3\text{-}ClC_6H_4\text{-}CO_3H$, CH_2Cl_2, 0 °C; (vii) 2, THF, -78 °C; HOAc; (viii) $TsOH\cdot H_2O$, CH_2Cl_2, 25 °C; (ix) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C; Et_3N, -78° to 25 °C.

In this communication we report studies on a novel synthetically concise approach to the southern hexahydrobenzofuran moiety of avermectin A_{2b} (**1**). The key step in our methodology is the condensation reaction of the dithiane dianion **2** with the ketone **6** (Scheme). The yeast mediated reduction of commercial ethyl 2-oxocyclohexanecarboxylate according to the method of Ridley[8] and Fráter[9] gave the diastereoisomerically pure β-hydroxy-ester **3** (75%) ($[\alpha]_D$ = + 24.5° (c 1.00, $CHCl_3$) lit.[9] + 24.25°) with an enantioselectivity of 13:1.[9] Lithium aluminum hydride reduction of ester **3** and selective primary t-butyldiphenylsilylation[10] gave the silyl ether **4** (89%).[11] This material was converted into the enone **5** via sequential pyridinium dichromate (PDC) oxidation[12] and phenylselenylation with a hydrogen peroxide work-up. The direct epoxidation of enone **5** using alkaline hydrogen peroxide gave both **6** and **7** (89%) with the undesired isomer **7** as the predominant species (1:6).[13] Alternatively, reduction of **5** using sodium borohydride and cerium (III) chloride[14] gave the corresponding allylic alcohols as a 5:2 mixture of diastereoisomers. Without separation this mixture was epoxidized using 3-chloroperoxybenzoic acid and the resultant crude epoxy-alcohol mixture oxidized using PDC to produce **6** and **7**. Epoxidation of enone **5** by this three step redox protocol gave **6** (55%) and **7** (25%). This ratio of easily separated isomers reflected the diastereoselectivity of reduction of the enone **5**. Following the elegant Paulsen precedent[15] 2-hydroxymethyl-1,3-dithiane was converted into the dianion **2** using n-butyllithium in THF at -78°C. Addition of the epoxy-ketone **6** smoothly provided the epoxy-alcohol **8** (83%) and this was readily cyclized under acidic conditions to produce the octahydrobenzofuran derivative **9** (54%). Finally, Swern oxidation[16,17] of the alcohol **9** gave the corresponding ketone **10** (65%). Clearly, the condensation reaction of dianion **2** with the epoxy ketone **6** provides a convenient entry to the bicyclic southern unit of the avermectin skeleton. Further studies on the functionalization of ketone **10** will be reported in due course.

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