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A NOVEL SYNTHETIC ROUTE TO THE HEXAHYDROBENZOFURAN SUBUNIT OF THE AVERMECTINS AND MILBEMYCINS

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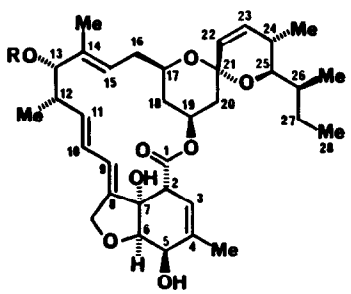
Summary - Radical-induced intramolecular Michael cyclization of a bromovinyl-type appendage onto a functionalized cyclohexene carboxylic acid derivative produces the corresponding oxahydrindanes which can be transformed into oxahydrindenes (hexahydrobenzofurans) related to the title compounds. (-)-Quinic acid is a useful optically active precursor.

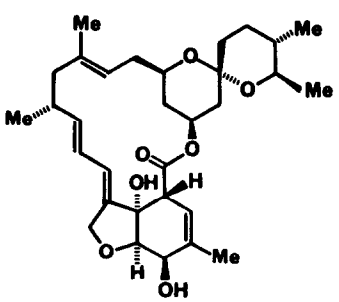
The recent discovery of the potent classes of anthelmintic agents such as the avermectins[1] and the milbemycins[2] have fostered a great deal of research activities on several fronts. Already a number of total syntheses in the milbemycin area have been reported,[3] and a synthesis of avermectin B_{1a} was recently reported from our laboratory.[4] These "megastructures" present a number of synthetic challenges, notably with regard to the hexahydrobenzofuran (oxahydrindene) subunit. The response from the community of synthetic organic chemists has been impressive, with the announcement of no less than four different approaches.[5-8] Three of the four routes[6-8] have actually produced derivatives of the intended bicyclic subunit in which the ester is reduced to an alcohol. This is understandable because of the possibility of β-elimination and subsequent aromatization when working with the acid or ester form (Scheme 1).

Scheme I

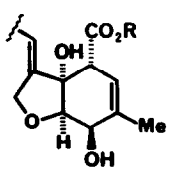


AVERMECTIN B1a

R = disaccharide

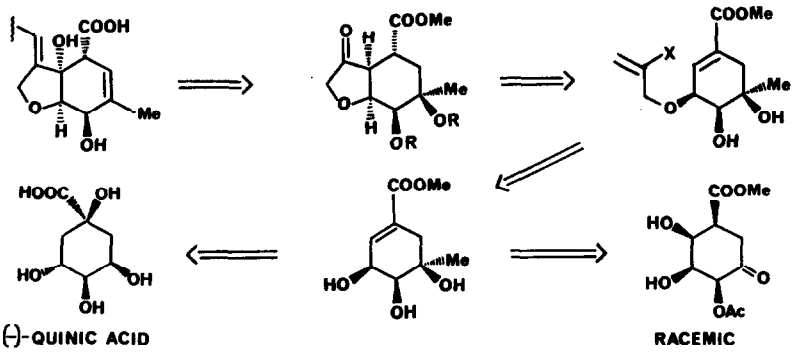


Milbemycin A_1



We describe herein a strategically novel and operationally different approach to the synthesis of the hexahydrobenzofuran subunit of avermectin B_{1a} and some of the milbemycins, based on the retrosynthetic analysis illustrated in Scheme II. Two of the critical bond-forming steps involved a free-radical mediated intramolecular ring closure, and an oxidative acetoxylation at a ring juncture.

Scheme II

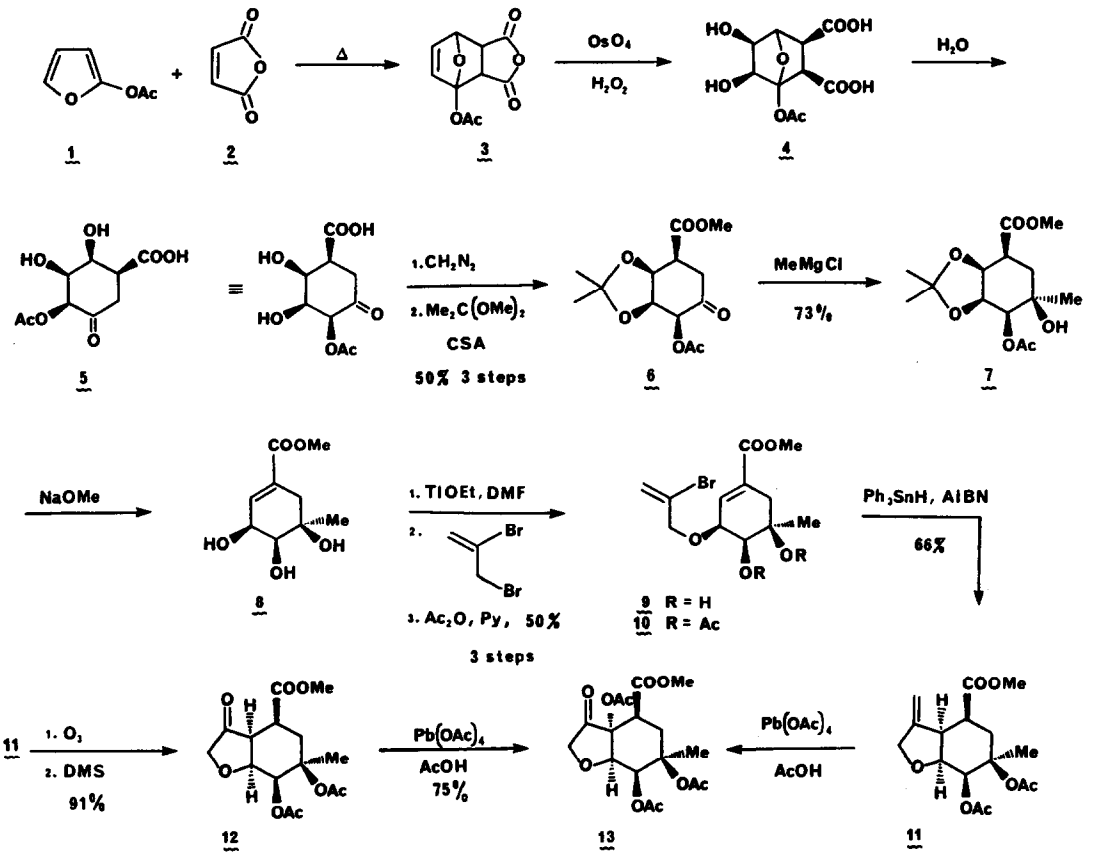


A Diels-Alder reaction between 2-acetoxyfuran and maleic anhydride[9] led to the adduct 3, which was hydroxylated to the known diacid 4[10] in excellent overall yield. Upon stirring the diacid 4 in water, a remarkable transformation took place wherein the keto acid 5 was now formed[11]. Esterification gave the corresponding methyl ester, mp 154-155° (63%) which in turn was converted into the acetonide derivative 6, mp 149-150° (93%).[12] Treatment with methylmagnesium bromide in THF (5 min at 0°, total contact time) gave the adduct 7, mp 188-190° (72% based on recovered starting material).[13] Concomitant de-O-acetylation and β-elimination of the acetonide group upon treatment with sodium methoxide led to the triol 8, mp 200-203°, which was purified as its diacetate, mp 128-129.5° (50% overall from 7). At this juncture we explored a number of alkylation procedures with 2,3-dibromo-1-propene[14] (NaH, KH, Ag_2O, etc) which were problematic. Successful alkylation took place when freshly prepared thallium ethoxide[15] in DMF was used, to give the desired ether 9 as an oil in 69% yield (Scheme III).

The free-radical[16] mediated intramolecular Michael cyclization, was successfully accomplished using triphenyltin hydride and AIBN. The structure of the product 11, mp 159-161°, (66%) was fully substantiated by 400 MHz ^{1}H n.m.r. spectroscopy and by decoupling experiments. We next had to address the all-important oxidative insertion of hydroxyl or its equivalent at the ring juncture.[17] Thus, ozonolysis of 11 led to the corresponding ketone 12 which upon treatment with lead tetraacetate in glacial acetic acid[18] at 75°C gave the desired α-acetoxy oxahydrindane derivative 13 in 75% yield.

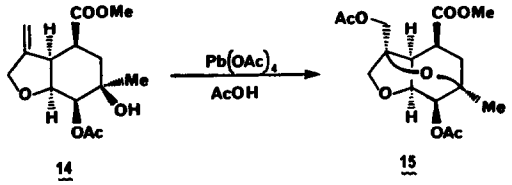
Surprisingly, treatment of 11 under the same conditions also led to the desired 13 in 30% yield, presumably via cleavage of a transient diol, followed by α-acetoxylation of the resulting ketone. When the corresponding monoacetate 14 was subjected to the same reaction, the cyclic ether 15 was the major product. Inspection of molecular models reveal the proximity of the tertiary hydroxyl group to the activated exocyclic olefin in this cup-shape molecule (Scheme IV).

Scheme III

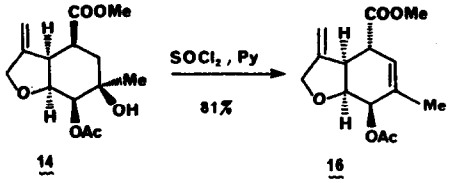


Unlike the published syntheses, the novel route described herein for the construction of functionalized oxahydrindanes leads to the 1-carbomethoxy derivatives which have their full complement of the required pattern of substitution in the intended subtarget. The tertiary hydroxyl group at C-4 (avermectin numbering) is a useful handle for the introduction of the endocyclic C-3/C-4 double bond at the opportune moment. We were successful in demonstrating the feasibility of such a regiospecific elimination by treatment of 11 with thionyl chloride in pyridine to give the oxahydrindene derivative 16 in 81% yield with concomitant epimerization at C-2 (Scheme V)[19].

Scheme IV

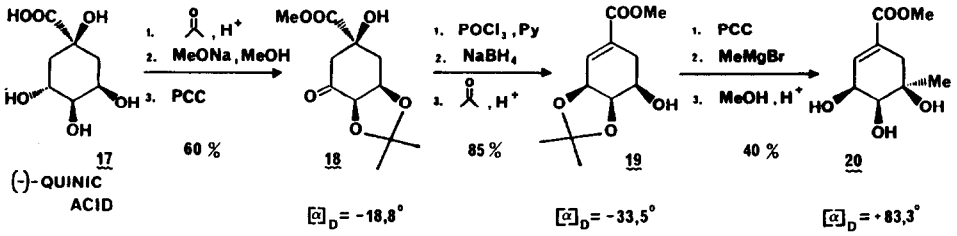


Scheme V



Having worked out a viable synthetic route to racemic 13, we next developed a synthesis of an enantiomerically pure advanced precursor from the readily available(-)-quinic acid 17 (Scheme VI). Thus, adapting the methodology already developed[20] to our needs, we were able to perform the transformations shown in Scheme VI, and to obtain the optically active triol 20. The synthesis of the bicyclic ketone 13 in optically pure form should therefore be feasible according to the sequence developed in Scheme III.

Scheme VI



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