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TOTAL SYNTHESIS OF IONOPHORES
THE MONENSIN BC-RINGS VIA PERMANGANATE PROMOTED STEREOSPECIFIC OXIDATIVE CYCLIZATION

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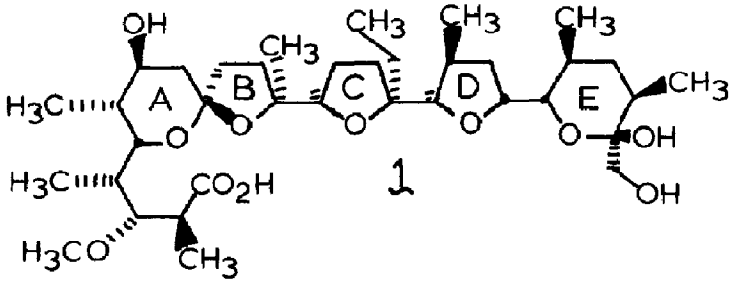
Summary: Complex tetrahydrofuran 8, containing the elements of the BC-rings of monensin with four chiral centers, and functionalized for further elaboration, is synthesized via permanganate promoted stereospecific oxidative cyclization of an acyclic, achiral 1,5-diene precursor.

Monensin (1)[1] belongs to the rapidly expanding class of natural products known as monocarboxylic acid ionophores. The intriguing structural characteristics, renowned biological activity and considerable commercial importance of this class of natural products have been reviewed.[2,3] Recent efforts in several laboratories have resulted in the first total syntheses of naturally occurring monocarboxylic acid ionophores,[4] including monensin.[5] However, a need for more efficient methods for construction of the structural units found in the ionophores is clearly extant.

In our approach to the total synthesis of racemic monensin, we propose to construct the natural product in a highly convergent manner by diastereoselective attachment of E-ring and A-ring side chain fragments to an appropriately functionalized BC-fragment of type 2.



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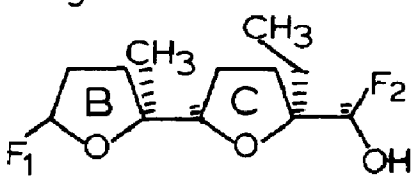

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A priori, efficient stereocontrolled preparation of large quantities of 2 represents one of the most challenging aspects of the total synthesis. We report here our successful synthesis of compounds of type 2 by a general method affording great flexibility with regard to alkylation pattern along the backbone and presence of peripheral functionality.

The key to construction of tetrahydrofurans (THFs) 2 is the novel oxidative cyclization of 1,5-dienes promoted by permanganate. We recently communicated results on the oxidation of the three isomeric 2,6-octadienes[6] showing that the cyclization of 1,5-diene affords a cis-tetrahydrofurandimethanol derivative with >97% syn-addition to both double bonds. Our synthesis of the monensin BC-rings thus simplifies to preparation of an appropriately functionalized (Z,Z)-1,5-diene, followed by oxidative cyclization.

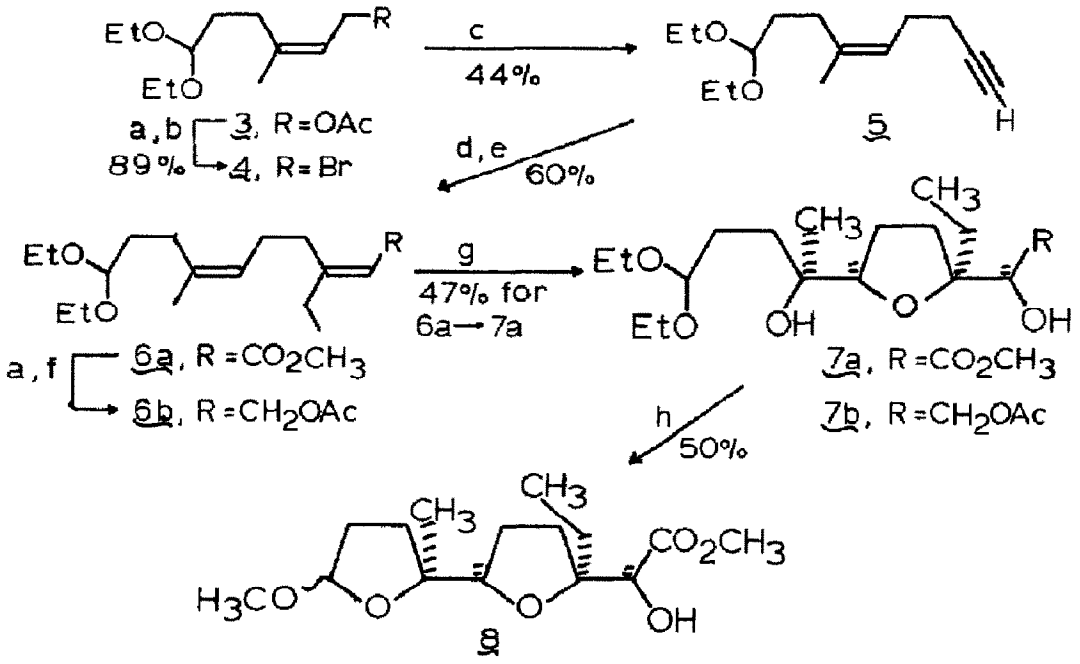
The successful execution of this plan is outlined in scheme 1. The initial goal of the synthesis, preparation of (Z,Z)-dienes 6, was achieved by modification of literature procedures. Thus, acetal acetate 3[7] was readily prepared in 25 gm. quantities from neryl acetate by selective double bond cleavage using modifications of the procedures of Casida,[8] and McCormick[9], followed by acetal formation (triethylorthoformate, benzene, p-toluenesulfonic acid). Removal of the acetate blocking group and treatment with phosphorous tribromide under carefully controlled conditions gave the labile bromide 4.[7] Bromide 4 seems particularly prone to decomposition via cationic intermediates, probably due to anchimeric assistance by the acetal moiety.[10] However, coupling with Corey's trimethylsilyl propargyllithium, followed by removal of the trimethylsilyl group,[11] produced acetylene 5[7] in fair yield. Methoxycarbonylation followed by addition of lithium diethylcuprate[12] stereoselectively affords the desired (Z,Z)-1,5-diene 6a[7] in 16% overall yield from neryl acetate.

Permanganate oxidation of ester 6a, and the derived acetate 6b, proved difficult, as for other systems we have studied.[6] In initial experiments, treatment of 6a or 6b with potassium permanganate in 10% aqueous acetone at -30°C with CO_2 ebbulition followed by filtration of the brown manganese dioxide precipitate, and multiple chromatographies on silica gel gave THFs 7a and 7b, respectively, though in only 20% isolated yield. Though a priori assignment of relative stereochemistry in THFs 7 is not possible from the ^1H or ^{13}C NMR spectra, only a single diastereomeric THF could be isolated from the reactions, as indicated by ^{13}C NMR spectra. Assignment of stereochemistry follows from our previous work.[6] As expected, oxidation of a mixture containing ester 6a and its E-enoic ester counterpart, gave an inseparable mixture of THF diastereomers readily distinguishable by both ^1H and ^{13}C NMR spectra of the mixture.

Considerable effort was expended to optimize conditions for oxidation of ester 6a. It appears the oxidation itself proceeds in fair yield, but losses are experienced in the workup and purification processes. We have settled upon a workup procedure involving reduction of manganese dioxide with a large excess of aqueous sodium bisulfite. Use of this procedure after oxidation of ester 6a as described above, followed by extraction of the resulting colorless, homogeneous aqueous acetone phase with ethyl acetate, and flash chromatography[13] of the crude product, gives THF 7a in 45-47% yield. The modified workup

avoids tedious filtration and washing of the manganese dioxide precipitate, and affords a much cleaner crude product, greatly facilitating purification of the desired material. Apparently, several carbonyl containing by-products remain in the aqueous phase during the modified workup, presumably as their bisulfite adducts.

Scheme 1: Synthesis of THF of type 2[a]



[a] a) LAH; b) PBr_3, pentane, K_2CO_3; c) 1. $^{\ominus}CH_2C{\equiv}CTMS$, 2. $AgNO_3$, $^{\ominus}CN$; d) nBuLi, $ClCO_2Me$; e) Et_2CuLi; f) Ac_2O/pyr; g) $KMnO_4$, 10% aqu. acetone, -30°C, CO_2 ebbulition, 4 hrs.; h) $HC(OMe)_3$, C_6H_6, TsOH.

Treatment of 7a with trimethylorthoformate in benzene in the presence of toluenesulfonic acid yields the bicyclic THF 8[7] as a mixture of acetal epimers. The cyclization reaction appears quantitative by TLC. Instability of the product during chromatographic purification accounts for the low isolated yield in this step.

Thus, we have developed an efficient, stereocontrolled synthesis of an appropriately functionalized monensin BC-ring fragment of type 2, easily adaptable to large scale preparation. Studies directed towards the total synthesis of monensin, and other ionophores, based upon this methodology are in process.

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7) Compounds 3, 5, and 6a were shown to be homogeneous by TLC, had spectral properties (^{1}H, ^{13}C NMR, IR, MS) consistent with the assigned structures, and gave satisfactory combustion analyses. Compounds 4, 7a, and 8 were characterized as above, but proved too labile for combustion analysis.

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