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A STEREOSELECTIVE SYNTHESIS OF THE TETRAHYDROFURAN UNIT IN IONOMYCIN

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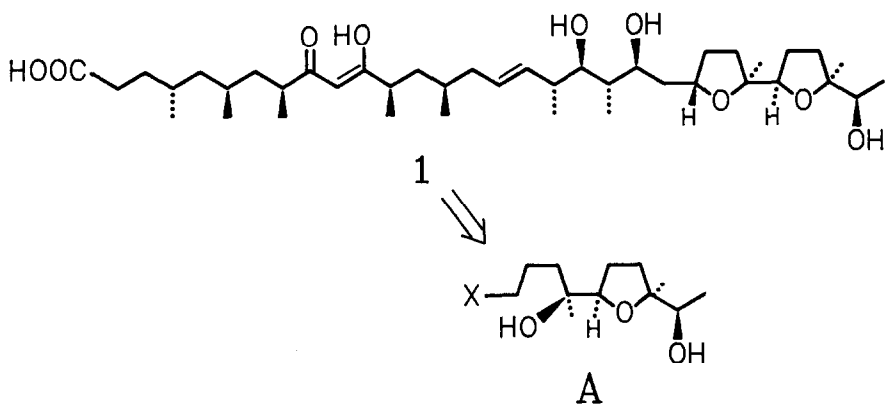
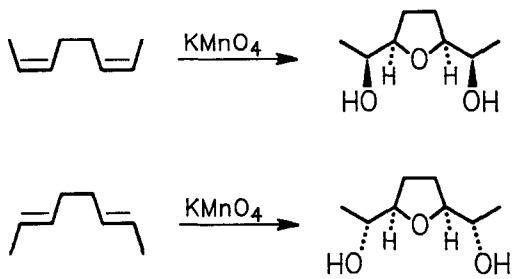
Abstract: The tetrahydrofuran unit corresponding to carbons 23 to 32 of the calcium ionophore, ionomycin, was prepared by a stereoselective permanganate cyclization of the (Z,Z)-diene **5**.

A potential synthetic route to the calcium selective ionophore antibiotic, ionomycin (1)[1] involves the synthesis of the tetrahydrofuran **A**. This fragment has been synthesized by Wuts et al. by a cyclization of a hydroxy epoxide.[2] This synthesis made elegant use of the Sharpless asymmetric epoxidation[3] to generate a 4,5-epoxy alcohol. In addition, Shih



has synthesized this unit by an epoxidation-cyclization of a bishomoallylic alcohol.[4] Unfortunately the stereoselectivity in the epoxidation step was low (1:1). We would like to report a synthesis of this unit via an oxidative cyclization of a 1,5-diene. In 1965, Klein and Rojahn reported that geranyl acetate and neryl acetate underwent a stereospecific cyclization with potassium permanganate to give a cis-tetrahydrofuran instead of the expected tetrol.[5] In a subsequent study, Walba et al. studied the $KMnO_4$ cyclization of the three stereoisomers of 2,6-octadiene and showed that these cyclizations

proceeded with high stereoselectivity (>97% one isomer) and that the stereochemistry of the four asymmetric centres in the resulting tetrahydrofuran depended on the geometry of the starting diene (eq 1).[6a] Walba and Edwards then applied this cyclization to a synthesis of a bis-tetrahydrofuran unit of monensin.[6b] These results indicated that the stereochemistry of the cyclization is indeed predictable and is controlled by the geometry of the double bonds.

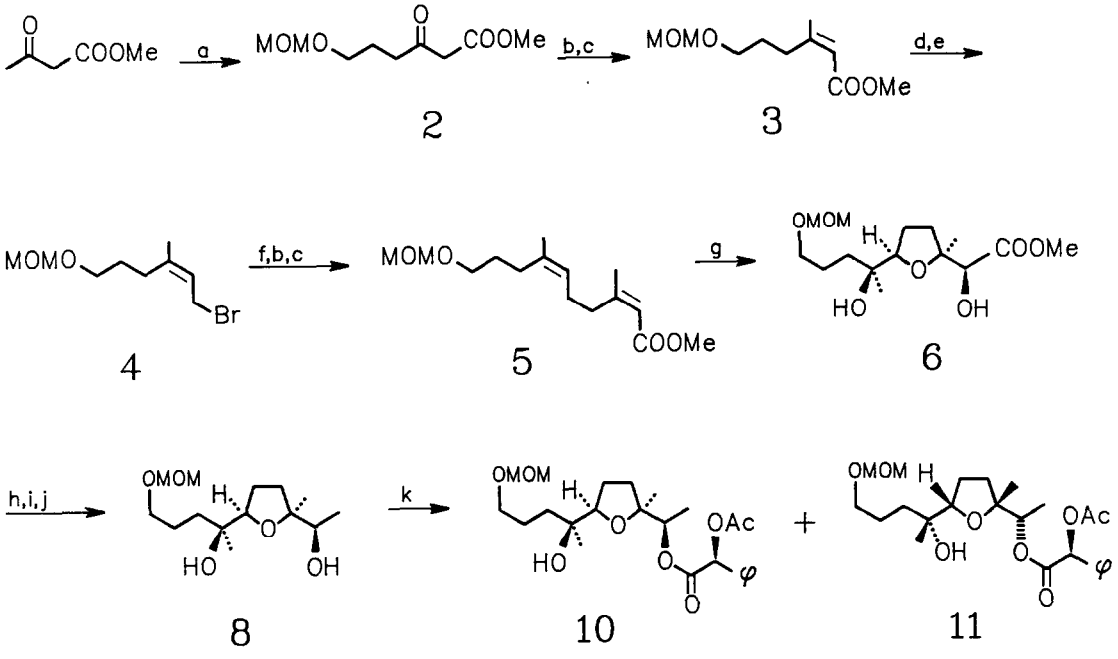


(1)[6]

We thought that the **A** fragment of ionomycin might be conveniently synthesized using the above $KMnO_4$ cyclization on the appropriate 1,5-diene. It was anticipated that the required 1,5-diene might be readily available using a stereospecific alkene synthesis that we developed recently.[7] Towards this end, the dianion of methyl acetoacetate[8] was alkylated with the methoxymethyl (MOM) protected derivative of 2-bromoethanol to give **2** in 80% yield. The E-enolate of **2** was selectively generated (triethyl amine, 4-dimethylaminopyridine, HMPA)[7b] and trapped with diethylchlorophosphate to give the E-enol phosphate. This enol phosphate was treated with the higher order magnesium cuprate[7b] to give the Z-alkene **3** in 65% yield from **2**. The Z-alkene **3** contained a small amount of the E-alkene (Z:E = 24:1).

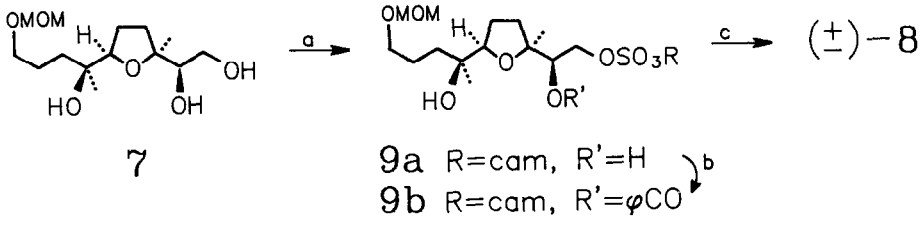
The α,β-unsaturated ester was converted into the alcohol (diisobutyl aluminum hydride) and subsequently to the bromide **4** in 80-85% yield for the two steps. A second methyl acetoacetate dianion alkylation and repeat of the enol phosphate-cuprate coupling gave the 1,5-diene **5** in 50% yield for these last three steps. Capillary gc revealed *ca*. 8-10% total of the other three isomeric dienes. No attempts were made to separate them at this stage. The oxidative ring formation was carried out as described by Walba *et al*.[6] to give the tetrahydrofuran **6** in 53% yield after chromatography. Capillary gc indicated that the cyclization product was >95% one isomer. The stereochemistry is assumed to be that shown, following the results of Walba *et al*. on similar 1,5-dienes. Additional evidence for the cis relationship between the methine and angular methyl groups on the tetrahydrofuran ring was obtained from a difference nuclear Overhauser experiment.

The ester group in **6** was reduced to give the alcohol **7** which was selectively tosylated at the primary alcohol and reduced to give **8** in excellent yield. Presumably this reaction involves formation of the intermediate epoxide. At this stage we decided to resolve the compound and, at the same time, separate it from any diastereomers which might have been carried from the cyclization step. Attempts to resolve earlier intermediates were not



a) NaH, n-BuLi, THF, 0° → rt then MOMO-CH_2CH_2-Br; b) TEA, DMAP, HMPA, $ClPO(OEt)_2$, -20° → rt; c) MeMgCl, MeLi, CuI, THF, -45°; d) DIBAL, 0°; e) $P\phi_3$, CBr_4, CH_2Cl_2, -78° → rt; f) $^-CH_2COCH^-COOMe$, THF, 0° → rt; g) $KMnO_4$, acetone - H_2O, CO_2, -25°; h) LAH, THF, 0°; i) TsCl, py, 0°; j) LAH, THF, Δ; k) (S)-(+)-O-acetyl mandelic acid, DCC, DMAP, CH_2Cl_2, 0° then chromatographic separation.

successful. For example, the camphorsulphonates **9a** and **9b** prepared from **7** were readily reduced to racemic **8**. But we were totally unable to separate the diastereomers of **9a** or **9b**.

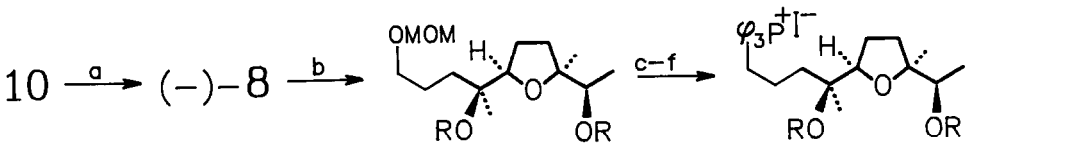


a) Cam-SO_2Cl, py, 0°; b) $\phi COCl$, py, 0°; c) LAH, THF, Δ.

The diol **8** was selectively condensed at the secondary alcohol with (S)-(+)-O-acetyl mandelic acid in excellent yield and the resulting diastereomers were separated by silica

gel chromatography (hexane - acetone = 6:1). The diastereomer eluting first ($[\alpha]_D$ = +29.4°, c = 0.83 acetone) was obtained in greater than 99% purity (capillary gc) and was assigned the absolute stereochemistry shown in **10** on the basis of the ^1H nmr spectrum.[9] The compound eluting second ($[\alpha]_D$ = +58.3°, c = 1.2 acetone) was assigned structure **11**.

The resolving agent was hydrolyzed in **10** to give the optically active diol **8** ($[\alpha]_D$ = -9.8°, c = 0.46 acetone) which was protected as its bis-t-butyldimethylsilyl ether **12** in 80% yield from **10**. The MOM protecting group in **12** was hydrolyzed with dimethylboron bromide[10] to yield the primary alcohol. This alcohol was then converted into the phosphonium salt **13** by standard methods. The phosphonium salt **13** was prepared by Evans and Shih using a totally different route.[4] The spectral data and physical properties of the compounds from the two routes were identical. This confirmed the absolute stereochemistry of our product, and reassured us that the Walba cyclization did occur with the stereochemistry anticipated and that the Mosher method of assigning the absolute stereochemistry of **10** held. This completed the synthesis of fragment **A** of ionomycin.[11]



12 R=TBDMS **13** R=TBDMS

a) NaOH, H_2O; b) TBDMS-OTf, TEA, CH_2Cl_2; c) Me_2BBr, CH_2Cl_2, -78°; d) MsCl, TEA, CH_2Cl_2, 0°; e) NaI, TEA, $NaHCO_3$, acetone; f) $P\phi_3$, i-Pr_2NEt, ϕMe -MeCN.

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