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Synthesis of a Bistetrahydrofuran C17–C32 Fragment of the Polyether Antibiotic Ionomycin

James A. Marshall* and Ann M. Mikowski

Department of Chemistry, University of Virginia, , P.O. Box 400319, Charlottesville, Virginia 22904

jam5x@virginia.edu

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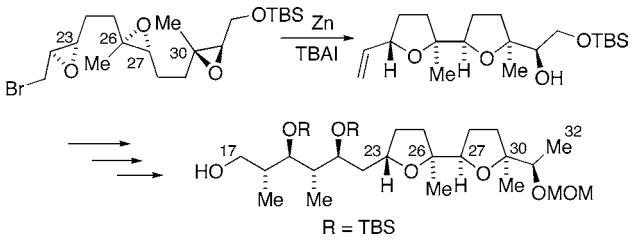
ABSTRACT



A Zn-initiated triepoxide cascade cyclization reaction was employed for the synthesis of the bistetrahydrofuran core segment of the polyether ionophore antibiotic ionomycin.

We recently described a novel variant of an epoxy−alcohol cyclization route to tetrahydrofurans wherein a terminal epoxy iodide, when treated with powdered zinc in ethanol, generates a transient allylic alkoxy zinc species which rapidly effects cyclization by a Lewis acid-initiated attack on an internal epoxide (Figure 1). In our initial report of this sequence, we showed that all four of the diastereomeric tetrahydrofurans represented by structure **A** could be prepared from the appropriate epoxide precursors in ca. 90% yield with excellent diastereoselectivity.[1] The objective of the present study was to explore the possibility of extending this epoxide cascade cyclization to certain bistetrahydrofuran segments of polyether natural products.[2] As a possible target to test the feasibility of the approach, we selected the tetrahydrofuran core unit of the ionophoric antibiotic ionomycin (Figure 2).[3]

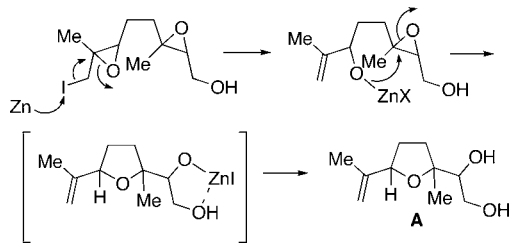


Figure 1. Proposed pathway for a zinc-initiated epoxide cascade cyclization.

Previous routes to ionomycin employed a stepwise construction of the two joined tetrahydrofuran rings. Evans and co-workers introduced the C27−C30 tetrahydrofuran segment through epoxidation of a C27 bis-homoallylic alcohol precursor with MCPBA resulting in a 1:1 mixture of diastereomeric tetrahydrofuran products (Figure 3).[4] Contemporaneously, Hanessian,[5] and later Lautens,[6] employed

* Address correspondence to this author.

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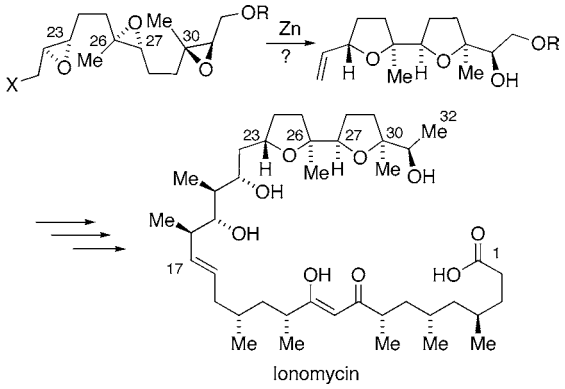


Figure 2. Proposed application of an epoxide cascade sequence to ionomycin.

a C30 hydroxy-directed vanadyl acac epoxidation to produce the C27−C30 tetrahydrofuran with 9:1 and 7.7:1 diastereoselectivity, respectively. Both Evans and Hanessian elaborated the attached C23−C26 tetrahydrofuran ring by intramolecular oxymercuration of a C26 bis-homoallylic alcohol whereas Lautens employed an intramolecular C23 tosylate displacement by a C26 alkoxide to fashion this ring. Our approach differs from those preceding it by directly forming both rings of the bistetrahydrofuran system from an acyclic precursor. In addition, the concomitant generation of a vinylic side chain in our cyclization sequence provides an appropriate functional appendage for further elaboration of the polyketide side chain.

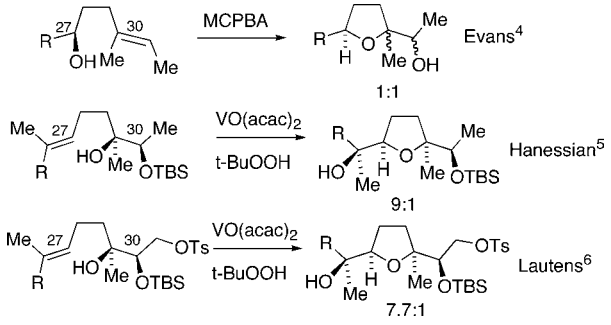
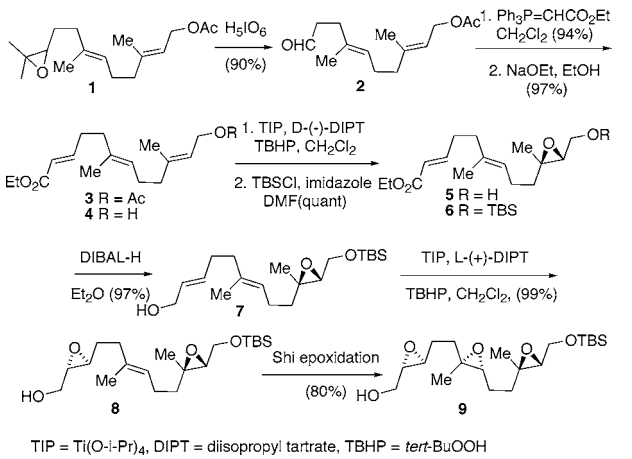


Figure 3. Previous routes to the C27−C30 tetrahydrofuran segment of ionomycin.

Our synthesis commenced with epoxide **1**, prepared in two steps (85% yield) from farnesyl acetate via the bromohydrin, as reported by van Tamelen et al.[7] Malaprade oxidation[8] with H_5IO_6 afforded the aldehyde **2**, which underwent Wittig homologation to afford the conjugated ester **3** as a separable 9:1 mixture of (*E*) and (*Z*) isomers (Scheme 1). Cleavage of

Scheme 1

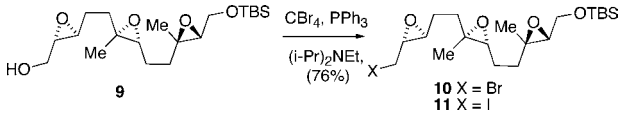


TIP = $Ti(O\text{-}i\text{-}Pr)_4$, DIPT = diisopropyl tartrate, TBHP = *tert*-BuOOH

the acetate followed by Sharpless asymmetric epoxidation[9] led to the epoxy alcohol **5** of ca. 90% enantiomeric purity, based on Mosher ester analysis.[10] Following alcohol protection and reduction of the conjugated ester with DIBAL-H, the Sharpless epoxidation was repeated on allylic alcohol **7** with the enantiomeric tartrate reagent to yield the epoxy alcohol **8** of ca. 90% isomeric purity. The central epoxide was introduced by means of the Shi asymmetric epoxidation protocol employing oxone and the catalyst prepared from D-fructose.[11]

We explored a number of alternative methods for the conversion of alcohol **9** to the iodide **11** (Scheme 2). Direct

Scheme 2



treatment with I_2 and imidazole-Ph_3P proceeded in low yield.[12] A two-step process involving displacement of the mesylate with NaI in acetone caused decomposition, but the use of tetrabutylammonium iodide produced the iodo product in 67% yield. Alternatively, the bromide **10** could be prepared directly from alcohol **9** in 76% yield with CBr_4, Ph_3P, and Hunig's base in CH_2Cl_2.[13] In the interest of synthetic

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(9) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

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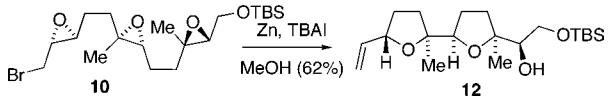
(13) Gareeg, P. J.; Samuelson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

efficiency, we decided to explore the epoxide cascade cyclization with bromide **10** rather than the less accessible and marginally less stable iodide **11**.

Treatment of bromide **10** with zinc dust in ethanol afforded mainly unreacted starting material. However, when tetrabutylammonium iodide was added to generate the iodide **11** in situ, the reaction proceeded as planned (Scheme 3). Of

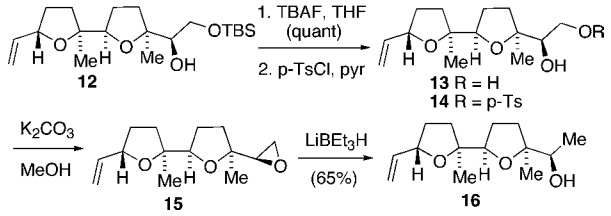
Scheme 3



the alcohol solvents examined, methanol was found to be superior to ethanol or isopropyl alcohol. With methanol as solvent the bistetrahydrofuran **12** was obtained in 62% yield (compared to 45% in ethanol) as a 10:1 mixture of inseparable diastereomers. The use of aprotic solvents THF, DME, DMF, DMSO, CH_3CN, or Et_2O for this reaction led to decomposition or recovered starting material.

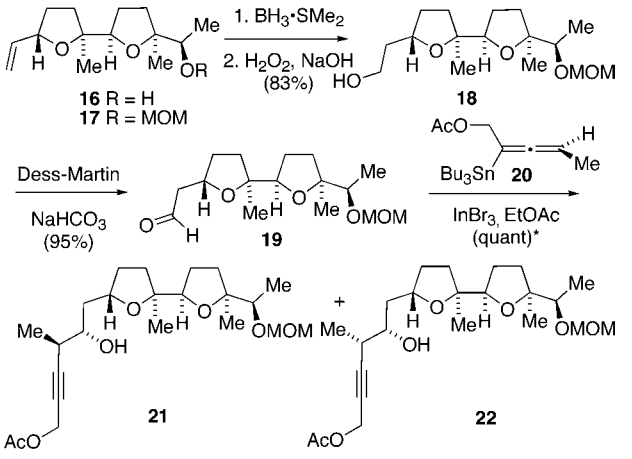
For completion of the C21−C32 segment of ionomycin it was necessary to effect hydrogenolysis of the C32 OH group. Lautens achieved this transformation by treatment of a C32 tosylate with NaI followed by hydrogenolysis of the iodide with Bu_3SnH.[6] We elected to convert the diol **13** to the epoxide **15** via the hydroxyl tosylate **14** (Scheme 4). Reduction with $LiBEt_3H$ completed the sequence to alcohol **16**.

Scheme 4



The next phase of our studies entailed elaboration of the polyketide segment onto the bistetrahydrofuran core. To that end, alcohol **16** was converted to the MOM ether **17** and the aldehyde **19** was prepared by sequential hydroboration−oxidation of the terminal alkene of **17** and Dess−Martin periodinane oxidation of the primary alcohol **18** (Scheme 5).[14] Addition of allenylstannane **20** and equimolar $InBr_3$ to aldehyde **19** in EtOAc effected quantitative conversion to a 2:1 mixture of isomeric homopropargylic alcohol adducts.[15] We initially surmised that this mixture was comprised of two anti adducts, **21** and the C20, C21 enantiomer of **21**, the latter arising from partial racemization of the transient allenylindium reagent. However, we were forced to recon-

Scheme 5



20 + $InBr_3$ premix time	21:22
none	2:1
15 min	3:1
30 min	7:1
45 min	>20:1

sider this conclusion when mandelic ester analysis of the two adducts revealed that the alcohol stereocenters of both possessed the (*S*)-configuration.[10b] Accordingly, these adducts differ only in their configuration at C20 and must therefore be the anti and syn isomers **21** and **22**. The formation of a significant amount of a syn diastereomer from an allenylindium/aldehyde addition is unprecedented in our experience. We therefore postulated that the syn adduct **22** must arise from an $InBr_3$-promoted addition of the allenylstannane **20** to aldehyde **19** by way of an acyclic transition state (Figure 4). Such additions strongly favor syn products.[16] This

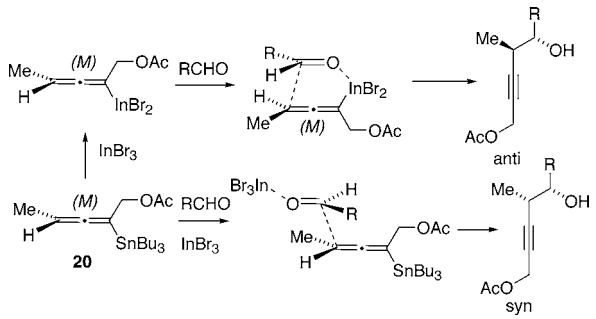


Figure 4. Alternative pathways for allenylstannane/$InBr_3$ additions

conclusion implies that the transmetalation of allenylstannane **20** with $InBr_3$ must be slow relative to the allenylmetal additions. To test this hypothesis, we studied the effect of premixing the allenylstannane **20** and $InBr_3$ for various time intervals before adding aldehyde **19**. As expected, the anti:syn ratios increased as a function of the premixing times

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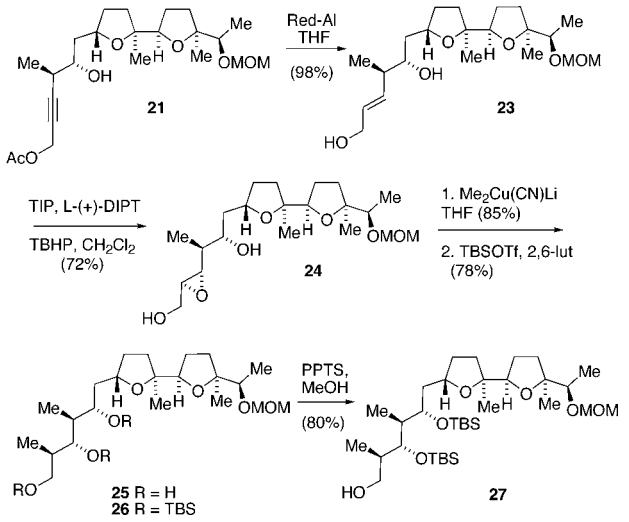
from 2:1 at $t = 0$ to 3:1 after 15 min, 7:1 after 30 min, and >20:1 after 45 min. In all cases, the yield of adducts was nearly quantitative.

Final elaboration of the C17−C21 stereotetrad side chain segment of ionomycin was effected by a precedented sequence of alkyne reduction, Sharpless asymmetric epoxidation, and ensuing epoxide cleavage with methyl cyanocuprate (Scheme 6).[17] The resulting triol **25** was converted

Scheme 6



to the tris-TBS ether **26**, which was selectively cleaved with PPTS in methanol to afford the alcohol **27**. A close analogue of this alcohol in which the two secondary alcohols of the stereotetrad are protected with a TIPS and benzoyl group instead of TBS was employed by Lautens and co-workers in their total synthesis of ionomycin.[6] Presumably an analogous sequence leading to ionomycin could be carried out on alcohol **27**, as well.

In conclusion, we have shown that a Zn-initiated epoxide cascade cyclization sequence can be employed for the construction of the bistetrahydrofuran segment of ionomycin. Other related structures should also be amenable to synthesis by this methodology.[2] The diastereoselectivity of the process is high and limited only by the efficiency of the several epoxidation steps leading to the acyclic precursors. In the process of side-chain elaboration en route to our targeted ionomycin intermediate, we encountered a previously unobserved competing reaction in which a chiral allenylindium regent, derived through in situ transmetalation of an allenylstannane with $InBr_3$, adds to an aldehyde to afford a mixture of anti and syn adducts. The formation of the syn adduct was shown to result from incomplete transmetalation of the allenylstannane precursor. By delaying the addition of the aldehyde substrate, thereby enabling complete transmetalation to take place, we obtained the anti adduct as the sole product of the reaction.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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