Synthesis of the Putative Biosynthetic Triene Precursor of Monensin A

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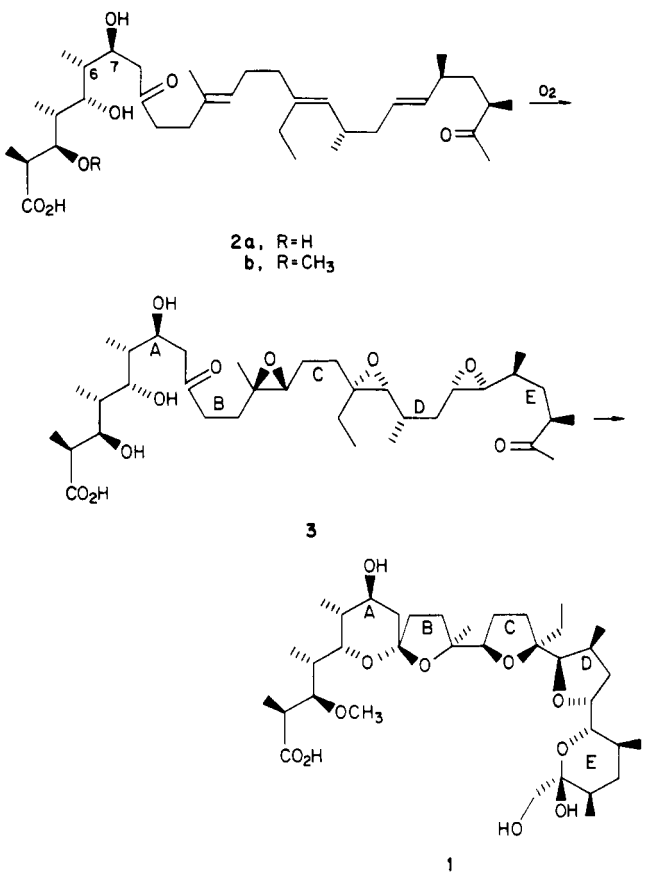
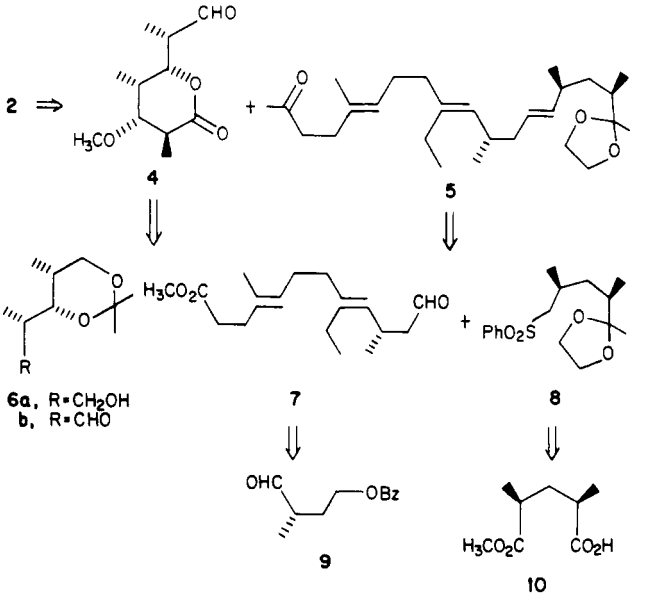
Monensin A (**1**), a pentacyclic polyether ionophore, is produced by *Streptomyces cinnamonensis*.[1] Its polyoxygenated branched carbon skeleton, derived from the building units acetate, propionate, and butyrate, possesses stereochemical features in common with many polyethers of its class.[2] One of the most intriguing yet still unresolved questions about Monensin A biosynthesis is the mechanism of formation of its five cyclic ethers. On the basis of the early suggestions of Westley,[3] and the elegant demonstration that molecular oxygen is incorporated into the ethereal oxygens of the C, D, and E rings of **1**, Cane and his co-workers[4] proposed the final biosynthetic steps as outlined in Scheme I. Implicit in this scheme is the enzymatic incorporation of molecular O_2 via epoxidation of the (*all-E*)-triene **2a**; the resulting triepoxide **3** then undergoes a cascade of ring closures to generate the final pentacycle **1**. If the biosynthesis of Monensin A indeed proceeds via such a cyclization process, the stereochemical complexity of

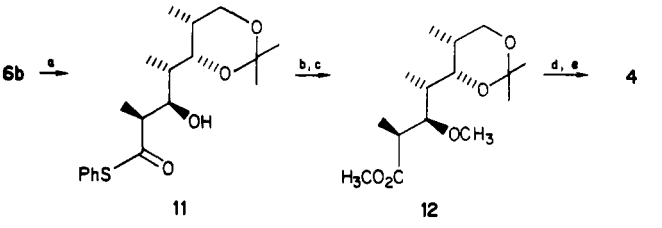
Scheme I

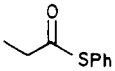


Scheme II

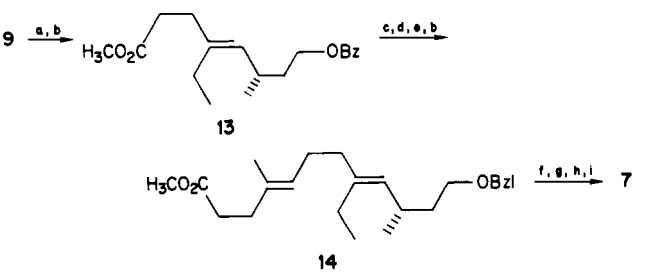


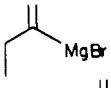
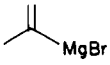
Scheme III[a]



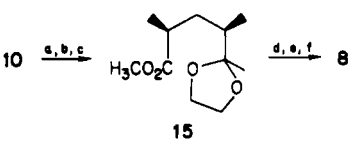
[a] Reagents: (a)  , 9-BBN-OTf; (b) $HgCl_2$, $CdCO_3$, MeOH, CH_3CN; (c) CH_3I, Ag_2O; (d) TsOH; (e) $(COCl)_2$, Me_2SO.

Scheme IV[a]



[a] Reagents: (a)  ; (b) $CH_3C(OCH_3)_3$, H^+, toluene 110 °C; (c) $LiAlH_4$; (d) PCC; (e)  ; (f) LiOH; (g) Na/NH_3; (h) CH_2N_2; (i) $(COCl)_2$, Me_2SO.

Scheme V[a]



[a] Reagents: (a) $(COCl)_2$; (b) $(CH_3)_2CuLi$; (c)  , PPTS; (d) $LiAlH_4$; (e) PhSSPh, *n*-Bu_3P, Pyr; (f) *m*-CPBA, $NaHCO_3$.

polyene to polyether transformation would rival the squalene to sterol cyclization.[5] To investigate these final stages of Monensin A biosynthesis, we have now completed a convergent chiral syn-

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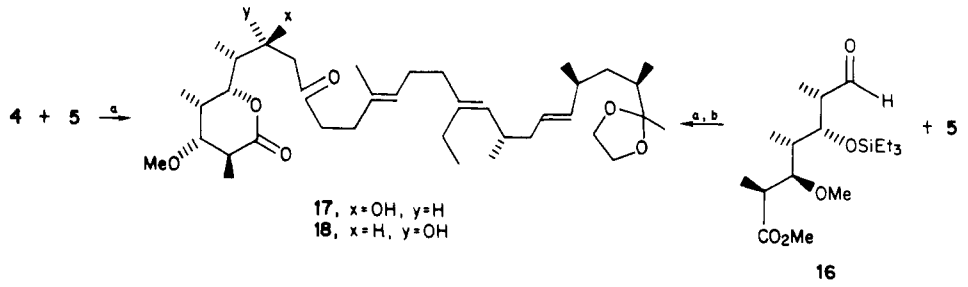
Scheme VI[a]



[a] Reagents: (a) LDA, THF, -78 °C; (b) n-$Bu_4N^+F^-$, THF.

thesis of **2b** which takes advantage of the biochemical methodology developed in these labs for the preparation of the key chiral intermediates.

Retrosynthetic analysis of the triene **2b** is shown in Scheme II. Our strategy entails the successive assembly of the prefabricated chirons (**6b**, **9**, **10**) which contain the stereochemical and structural features of **2**. On the basis of the literature precedent,[6] we envisaged that the final aldol condensation of **4** and **5** should predominantly produce triene **2b** with the desired Cram stereochemistry at C-6 and C-7. The five contiguous chiral centers of the fragment **4** could be elaborated from the chiron **6b**, readily available via enzymatic enantioselective hydrolysis.[7] The (*all-E*)-triene **5** could be formed using sulfone methodology to combine components **7** and **8**, which, in turn, may be prepared from the biochemically derived chirons **9**[8] and **10**,[9] respectively.

Condensation[10] of the boron enolate of (*S*)-phenyl thiopropionate with **6b** gave **11** (65%) as the major product with the desired 2,3-syn and 3,4-anti configuration. Transesterification and methylation of **11** afforded **12**, which, upon acid-catalyzed deprotection, lactonized spontaneously. Swern oxidation produced the lactone–aldehyde **4**, whose stereochemical assignment was confirmed by comparison to a sample of **4** derived from degradation of Monensin A (Scheme III).[11]

Addition of 1-buten-2-ylmagnesium bromide to **9** afforded the allylic alcohol, which upon ortho-ester Claisen rearrangement[12] produced the ester **13** (83% from **9**). Repetition of this addition–rearrangement sequence with the aldehyde, derived from **13** and 1-propen-2-ylmagnesium bromide, gave **14** (55% from **13**). To avoid overreduction, the ester grouping **14** was cleaved prior to reductive debenzylation. Reesterification and oxidation yielded the desired aldehydic fragment **7** (68% from **14**, 75% conversion) (Scheme IV).

The chiral half-ester–acid **10** was transformed into **15** following standard methodology[13] using mild acid catalysis to avoid epimerization of the α-methyl ketone. Reduction of **15** was followed by a direct conversion[14] of the resulting alcohol to the phenyl sulfide whose oxidation to **8** (64% from **15**) required buffered conditions to retain the ketal (Scheme V). The union of **7** and **8** was accomplished by the Kocienski–Lythgo–Julia procedure.[15] Thus, the anion of **8** (n-BuLi, THF, −78 °C) underwent smooth addition to **7**, and the product was trapped with benzoyl chloride. The resulting sulfone benzoate intermediate upon reductive elimination [Na(Hg), CH_3OH, EtOAc] gave the *E* olefin (35%). The ester was in turn transformed to the methyl ketone **5** via cuprate addition to the derived acid chloride [(a) NaOH; (b) $(COCl)_2$; (c) $(CH_3)_2CuLi$; 85% overall].

Aldol condensation[16] (LDA, THF, −78 °C) of **4** and **5** afforded a 9:1 mixture of diastereomeric aldols (80%; 81% conversion). The major diastereomer was assigned **17** on the basis of structural correlation with the major diastereomer from the aldol condensation of **5** and **16**[11] under identical conditions (2.6:1; 88%; 76% conversion) (Scheme VI). This assignment is in accord with theoretical predictions and earlier observations.[6b] The ketal and lactone of **17** were cleaved [(a) PPTS, 5:1 acetone–H_2O; (b) 4:1 THF–0.05 N NaOH, 90%] to complete the synthesis of the putative precursor **2b**.[17]

This convergent synthesis not only provides access to **2b** but also vividly demonstrates the value of enzymatic methods in complex natural product synthesis. Incorporation experiments using isotopically labeled **2b** to verify the triene–triepoxide biosynthetic model of Monensin A are now in progress.

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(16) The lactone aldehyde **4** is extremely unstable and should be freshly prepared just prior to use.
(17) All compounds herein described gave satisfactory elemental or MS analyses and their NMR spectra were consistent with the assigned structures.

Enzymatic Synthesis of Unusual Sugars:[1] Galactose Oxidase Catalyzed Stereospecific Oxidation of Polyols

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Recently, there has been a large amount of interest in the synthesis of unnatural sugars.[2-4] Since the majority of natural sugars occur in only one enantiomeric form, unnatural sugars are

(1) Supported by the National Science Foundation Grant CHE-8318217 and the Robert A. Welch Foundation Grant A-1004.
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