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Metal-oxo induced *syn*-oxidative polycyclizations of hydroxypolyenes: Biomimetic synthesis of polycyclic ether natural products

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Abstract: The development and application of *syn*-oxidative cyclization methodologies for the stereoselective synthesis of polyether structures corresponding to polyketide and acetogenin natural products will be described. This synthesis strategy mimics a novel but unproven proposal for the biosynthesis of these polyether natural products. Our results with nonbiological reagents indicate that the *syn*-oxidative cyclization biosynthesis hypothesis is mechanistically and stereochemically viable for the chemical synthesis of polycyclic ether natural products such as monensin and goniocin.

Polycyclic ether structures are found in many biologically active natural products. For instance, monensin 1 is a valuable anticoccidiostatic agent which is also a highly selective ionophore for sodium ion transport (Fig. 1)(ref. 1). The acetogenin natural products exemplified by goniocin 2 exhibit potent antitumor activities *in vitro*, and may also exert their biological effects by ion complexation and ion transport across biomembranes (ref. 2). Goniocin 2 is a novel tristetrahydrofuran acetogenin natural product, but like the majority of mono- and bicyclic acetogenin natural products, each ether ring is a *trans*-substituted tetrahydrofuran (ref. 3).

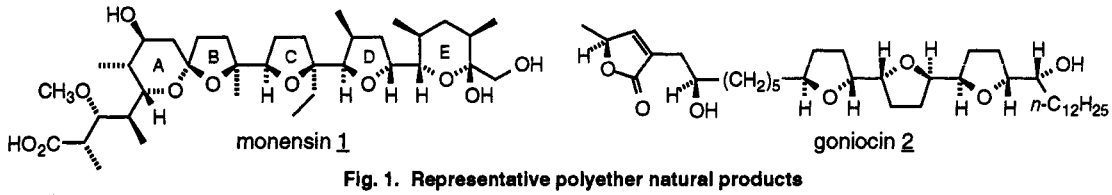

Fig. 1. Representative polyether natural products

The biosynthesis of these polyether natural products probably occurs by a cascade of oxygenation/cyclization reactions from a hypothetical polyalkene precursor. In the specific case of monensin, Cane has established that the oxygen atoms of rings C, D, and E arise from incorporation of molecular oxygen rather than from polyketide precursors (ref. 4). This finding supports the notion of late-stage oxygenation onto a complete carbon chain polyalkene, and a general hypothesis for polyether biosynthesis featuring polyepoxidation of a polyalkene and subsequent tandem *anti*-cyclization of a hydroxypolyepoxide has been proposed for many classes of polycyclic ether natural products, including 1 and 2 (ref. 5). However, the mechanistic alternative of polyether biosynthesis via tandem, hydroxyl-directed *syn*-oxidative polycyclization of a hydroxypolyene is also possible, as first proposed by Townsend (ref. 6). A general mechanism for *syn*-oxidative cyclization of hydroxyalkenes is shown in Fig. 2.

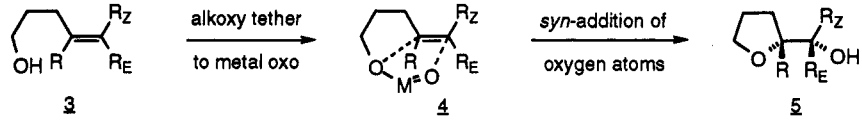

Fig. 2. Hydroxyl-directed *syn*-oxidative cyclization

The relative novelty of the Townsend biosynthesis hypothesis encouraged our efforts in the development and application of *syn*-oxidative polycyclization strategies for the chemical synthesis of polyether natural products including monensin 1 and goniocin 2. In the course of this work we realized that stereoinduction parameters for hydroxyl-directed epoxidations of acyclic hydroxypolyene precursors for compounds 1 - 2 were inconsistent with the stereochemistry of the cyclic ether rings of both of these natural products (ref. 7). This lecture describes our progress in the development of methodologies for *syn*-oxidative cyclization, and applications to stereoselective syntheses of polyether networks corresponding to the natural products 1 - 2.

METHODOLOGY DEVELOPMENT

When we began our studies in 1993, chromium and rhenium oxo-induced *syn*-oxidative cyclizations of hydroxyalkene substrates had been reported (ref. 8, 9). However, a *syn*-oxidative polycyclization reaction analogous to the Townsend biosynthesis hypothesis had not been reported. We discovered that commercially available pyridinium chlorochromate would induce highly stereospecific *syn*-oxidative cyclizations of hydroxydienes such as the nerol-derived substrate 6 to afford the bicyclic products 7 and 8 (Fig. 3) (ref. 10). The second tetrahydrofuran ring of product 7 was formed with high *trans*-stereoinduction, but the generality of this method was hampered by oxidative cleavage pathways in the formation of lactone 8 as well as the limitation to tertiary alcohol substrates.

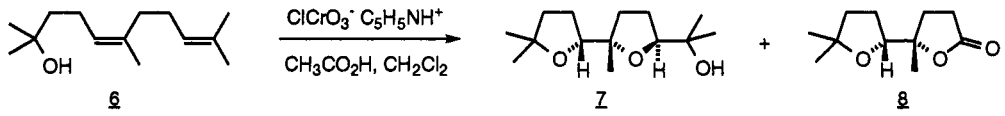

Fig. 3. Chromium-induced *syn*-oxidative polycyclization

Although literature precedents suggested that the rhenium (VII) methodologies developed by Kennedy (ref. 9) would be more promising for tandem polycyclization, we initially found that this reaction was unsatisfactory with several hydroxydiene substrates including 9 which afforded predominantly non-stereoselective acid-catalyzed cyclohydration products 11 and 12 (Fig. 4), even in the presence of the base 2,6-lutidine. We reasoned that the highly acidic perrhenic acid (O_3ReOH, pK_a = -1.25), formed as a byproduct from formation of the perrhenate ester intermediate (13, Fig. 5) might be replaced by a less acidic leaving group such as a carboxylic acid. Several acylperrhenate reagents 15 (Fig. 6) (ref. 11) were evaluated for *syn*-oxidative cyclization of hydroxydiene substrates.

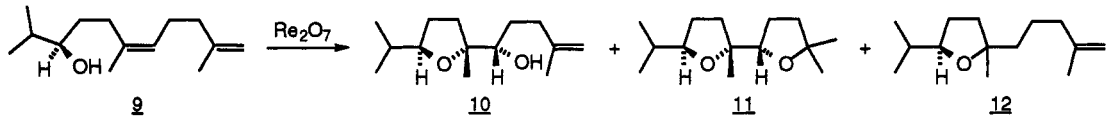

Fig. 4. Problems with Re_2O_7-induced cyclizations

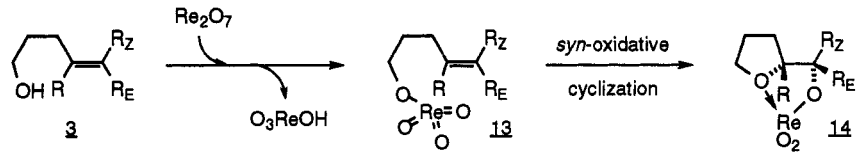

Fig. 5. Generation of perrhenic acid ($HOReO_3$) in the formation of perrhenate ester 13

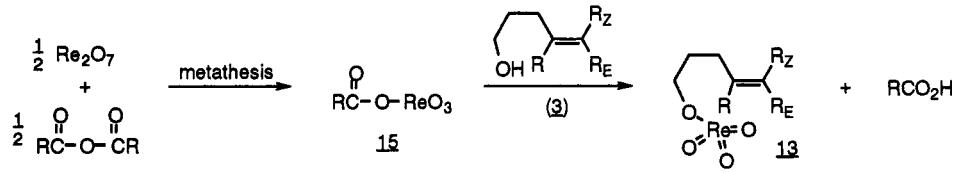

Fig. 6. Preparation of acylperrhenates 15

The optimal acylperrhenate reagent was eventually determined by correlating the yields of bistetrahydrofuran alcohol products with carboxylic acid pK_a. In general the stereoselective *syn*-oxidative monocyclization of acid-sensitive hydroxydienes such as 16 can be accomplished in excellent yields with trifluoroacetyl-perrhenate in the presence of an equivalent of pyridine or lutidine. The base serves to inhibit further cyclization of the hydroxyalkene product 17, presumably by stabilizing coordination of the tetrahydrofuran ring oxygen with the Lewis acidic rhenium center (i.e. 14). In the absence of base, the desired bistetrahydrofuranyl alcohol products are observed; for acid-sensitive substrate 17 the best reagent for producing 18 is dichloroacetylperrhenate in the presence of dichloroacetic anhydride (Fig. 7), which serves as an acid trap in the event that any perrhenic acid is produced (ref. 12).

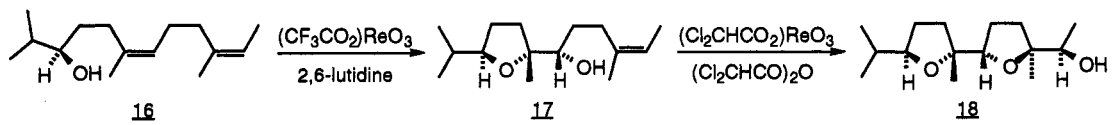

Fig. 7. Acylperrhenate-promoted *syn*-oxidative cyclizations of hydroxydienes

BIOMIMETIC MODEL SYSTEM FOR POLYKETIDE POLYETHER SYNTHESIS

Townsend and Basak suggested that polyether natural products such as monensin (1) might be biosynthesized by *syn*-oxidative polycyclization of a putative (*Z, Z, Z*)-"premonensin" triene (19). We felt that a series of *syn*-oxidations and *syn*-oxidative cyclizations might be effectively evaluated with the triene fragment 22 as a biomimetic synthesis study for the C and D rings. The central trisubstituted *Z*-alkene of compound 21 was prepared from three-component coupling featuring metallate rearrangement / alkylation (ref. 13) from 20, and standard alkene homologation provided the all-*Z*-triene 22 (Fig. 8).

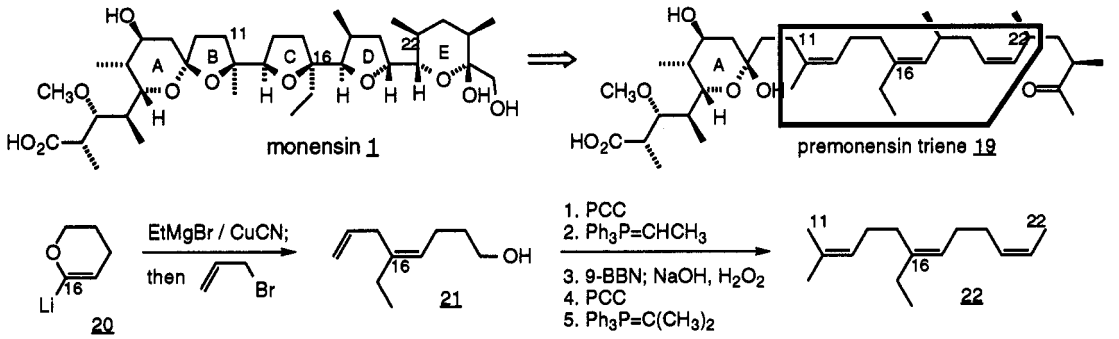

Fig. 8. Preparation of all-*Z*-triene model 22

With triene 23 in hand, we then applied the sequence of *syn*-dihydroxylation, *cis*-selective *syn*-oxidative cyclization of a diol-alkene substrate, and *trans*-selective *syn*-oxidative cyclization of a monohydroxyalkene (Fig. 9). Specifically, asymmetric *syn*-dihydroxylation of triene 22 with AD-mix β (ref. 14) gave the diol 23 as the only significant regioisomer. The relative inertness of the *cis*-disubstituted alkene of 22 is consistent with precedent (ref. 15); although the high regioselectivity for dihydroxylation of the terminal trisubstituted alkene was unexpected, we surmise that the C16-ethyl substituent of 22 provided significant additional steric hindrance to dihydroxylation of the internal alkene. *Syn*-oxidative cyclization of the diol-alkene 23 with Collins oxidant (ref. 16) was highly stereoselective and afforded a good yield of the C-ring tetrahydrofuranyl ketone 24. After protection of the tertiary alcohol of 24, sodium borohydride / cerium chloride reduction (ref. 17) of the ketone gave the secondary alcohol 25 with essentially complete diastereoselectivity consistent with the Felkin-Anh model. The D-ring was then formed by *syn*-oxidative cyclization of the hydroxyalkene 25 with dichloroacetylperrhenate, thus completing the stereoselective synthesis of a model system corresponding to the C and D rings of monensin (1) (ref. 18).

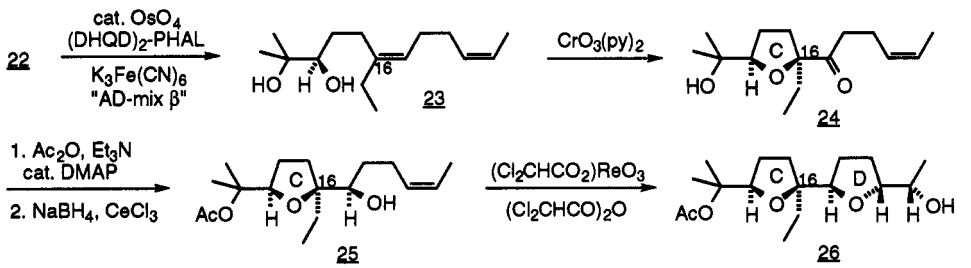

Fig. 9. Sequential *syn*-oxidations of triene 22 to bistetrahydrofuran 26

BIOMIMETIC MODEL SYSTEM FOR ACETOGENIN SYNTHESIS

We envisioned that a *syn*-oxidative polycyclization strategy might also be employed for the synthesis of acetogenin natural products. In the case of goniocin (2), the biomimetic synthesis precursor would be the (*E, E, E*)-"pregoniocin" triene 27 (Fig. 10), which might then undergo a tandem *syn*-oxidative polycyclization procedure to give the three *trans*-tetrahydrofuran rings of the target compound.

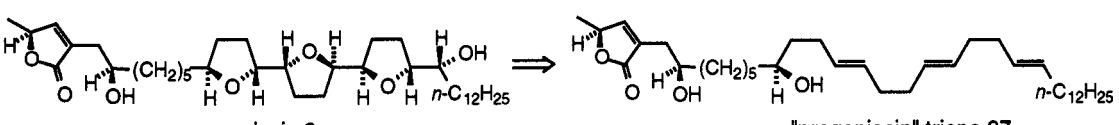

Fig. 10. "Pregoniocin" triene, a possible biosynthesis precursor for acetogenins

Reiterative application of orthoester-Claisen rearrangement methodology (ref. 19) afforded the triene aldehyde 28 with excellent *E*-selectivity (Fig. 11). Conversion to the chiral non-racemic secondary alcohol 29 was achieved by asymmetric addition of diethylzinc (ref. 20). We found that the optimal reagent for stereoselective *syn*-oxidative tricyclization of 29 was trifluoroacetylperrhenate, which afforded the all-*trans* tristetrahydrofuranyl alcohol product 30 as a single diastereomer (ref. 21). Note that the efficient generation of one stereocenter in hydroxytriene 29 was rewarded by the induction of six additional stereocenters in the single step production of tristetrahydrofuranyl alcohol 30.

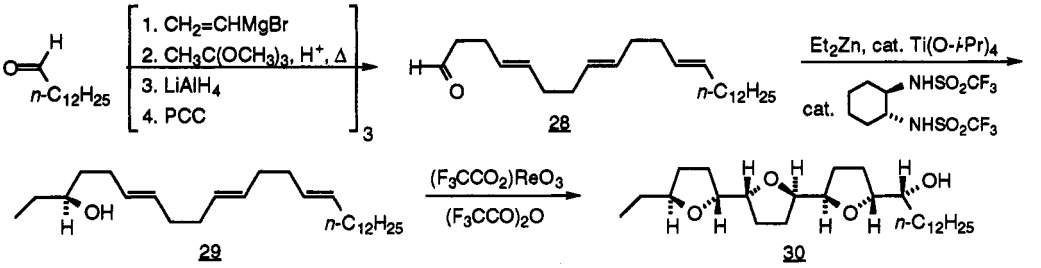

Fig. 11. Stereoselective *syn*-oxidative tricyclization

In summary we have developed effective reagents for achieving *syn*-oxidative cyclization in the laboratory, and have successfully applied this methodology to synthetic approaches to polyketide and acetogenin natural products. We are currently working on extending this methodology to larger ring sizes, and developing catalytic substoichiometric organometallic reagents for *syn*-oxidative cyclization. In addition the model studies presented herein represent the possibility of preparing the polyene compounds required for rigorously testing the Townsend (*syn*-oxidative cyclization) biosynthesis hypothesis.

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