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Synthesis of a Lactone Diastereomer of the Cembranolide Uprolide D

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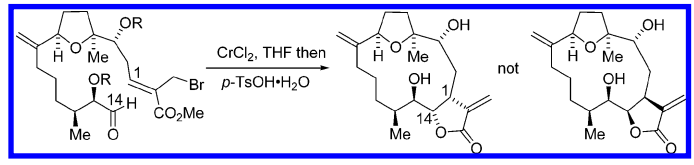
ABSTRACT



A convergent stereoselective synthesis of a C1/C14 bis-epimer of uprolide D is described in which an intramolecular Barbier-type reaction was employed for macrocyclization with concomitant introduction of the C1 and C14 stereocenters of a fused α-methylene lactone ring through an anti-Felkin−Anh transition state. Unlike previous examples of allyl chromium additions, none of the Felkin−Anh derived adduct could be detected.

Since the isolation of eupalmerin acetate from *Eunicea succinea* in 1972, soft corals of the genus *Eunicea* have proven to be a rich source of cembranolide natural products. In their ongoing investigations of Caribbean soft coral related to *Eunicea mammosa* indigenous to the waters of Puerto Rico, Rodríguez and co-workers isolated a number of structurally novel cytotoxic cembranolides, the uprolides, possessing an embedded tetrahydrofuran ring at C4/C7.[1] Biogenetically, the uprolides are thought to arise from epimeric epoxide derivatives of eupalmerin acetate (Figure 1). Intrigued by the structure and possible biological activity of these unusual cembranolides, we formulated plans for a synthesis of uprolide D that revolved around two metal-initiated cyclization reactions. The first of these involved a vinyl tetrahydrofuran cascade sequence (**B** → **C**),[2] and the second employed a type of Barbier macrocyclization (**D** → **E**), analogous to that reported by Semmelhack[3] and Chan[4] for fused-ring α-methylene lactones (Scheme 1).

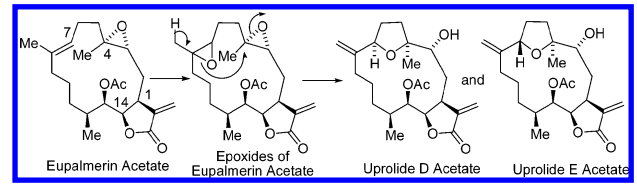


Figure 1. Proposed biosynthesis of uprolide D and E acetates.

The requisite precursor **A** for this approach was prepared by a convergent sequence in which two main segments, **2** and **4** (Scheme 2), were combined by a Wittig condensation (Scheme 3).

The aforementioned condensation of phosphonium ylide **2** and aldehyde **4** afforded the (*E*) conjugated ester **5** as the sole detectable isomer (Scheme 3). The first of the two epoxides required for precursor **B** of the tetrahydrofuran

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(1) Rodríguez, A. D.; Soto, J. J.; Pina, I. C. *J. Nat. Prod.* **1995**, *58*, 1209.
(2) Marshall, J. A.; Chobanian, H. R. *Org. Lett.* **2003**, *5*, 1931.
(3) (a) Semmelhack, M. F.; Wu, E. S. C. *J. Am. Chem. Soc.* **1976**, *98*, 3384. (b) Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, *43*, 1259.
(4) Bryan, V. J.; Chan, T. H. *Tetrahedron Lett.* **1996**, *37*, 5341.

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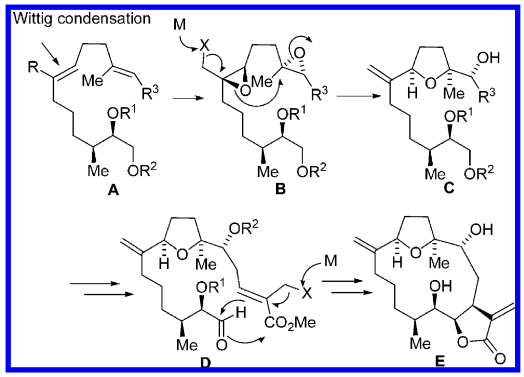
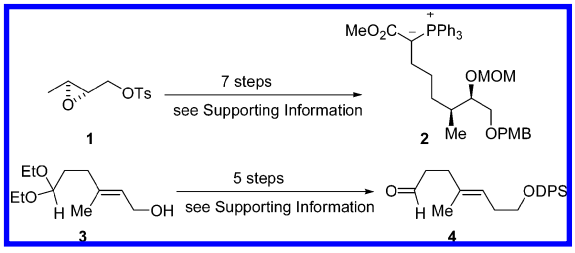
Scheme 1. Synthetic Plan for Uprolide D

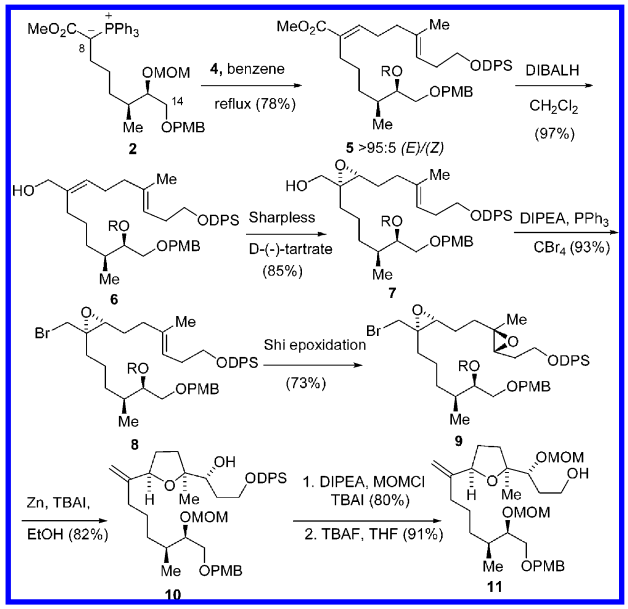


Scheme 2. Syntheses of Intermediates **2** and **4**



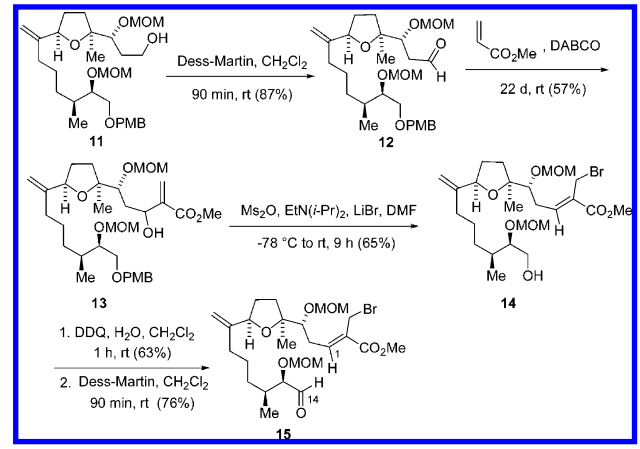
intermediate **C** was introduced with excellent enantiomeric purity by Sharpless epoxidation of the allylic alcohol **6**, obtained through reduction of ester **5** with DIBALH. The remaining double bond was epoxidized by Shi's methodology[5] after conversion of the epoxy alcohol **7** to the bromide **8**. Treatment of the resulting bromo epoxide intermediate **9** with Zn and TBAI in refluxing ethanol afforded the tetrahydrofuran **10** as a 4:1 mixture of diastereomers in 82% yield. Our previous studies have shown that the foregoing Zn cascade route to 2-vinyltetrahydrofurans is highly stereoselective.[2] Hence, we surmise that the mixture of tetrahydrofuran diastereomers must result from the Shi epoxidation. For further elaboration of the side chain segment, alcohol **10** was transformed to alcohol **11** after alcohol protection and selective DPS ether cleavage.

Scheme 3. Synthesis of **11**



Aldehyde **12**, obtained from alcohol **11** by Dess−Martin oxidation, afforded the acrylic ester **13** as a 1:1 mixture of diastereoisomers upon Baylis−Hillman condensation with methyl acrylate (Scheme 4).[6] Treatment of this alcohol

Scheme 4. Synthesis of Aldehyde **15**



mixture with methanesulfonic anhydride and lithium bromide led to the (*Z*)-α-bromomethyl acrylate **14** as the sole stereoisomeric product. We assume that this conversion proceeds by way of an intermediate mesylate, which undergoes in situ displacement with bromide to form the thermodynamically preferred (*Z*) isomer. Methanesulfonic anhydride rather than the chloride was selected for this conversion to avoid a possible competing reaction leading to the chloromethyl analogue of **14**. Aldehyde **15** was obtained by selective cleavage of the PMB ether **14** and Dess−Martin oxidation.

With the bromo aldehyde **15** in hand, we had arrived at a critical step in our planned synthesis, the intramolecular Barbier reaction. In a previously reported study of such reactions,[3,4] zinc or indium was used to prepare fused-ring α-methylene γ-butyrolactones from ω-formyl allylic bromides. The use of $CrCl_2$ for intramolecular additions of allylic bromides was reported as early as 1983 by Still and Mobilio[7] in their synthesis of the cembrane asperdiol and later by Paquette and co-workers[8] for the pseudopterolide, gorgi-

(5) (a) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1. (b) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9.

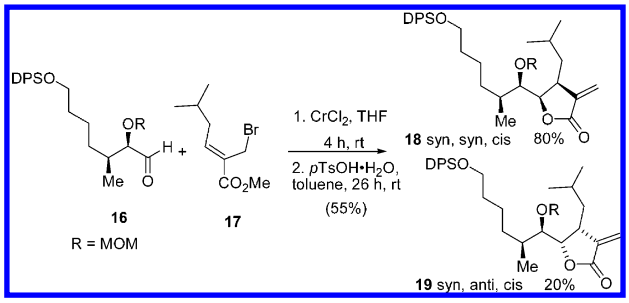
(6) (a) Drewes, S. E.; Hoole, R. F. A. *Synth. Commun.* **1985**, *15*, 1067. (b) Hoffmann, H. R. M.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849.

(7) Still, C. W.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785.

(8) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.

acerone. However, neither of these applications involved α-halomethyl acrylates or aldehydes with α stereocenters. For the present application, the proposed intramolecular Barbier reaction raises two stereochemical issues. The first of these, the relative stereochemistry of the lactone ring, can be predicted from the well-precedented cyclic transition state for additions of Lewis acidic allylmetal reagents to aldehydes in which the (*E*)/(*Z*) stereochemistry of the double bond correlates to the *anti*/*syn* stereochemistry of the adduct.[9] The second issue concerns the diastereoselectivity of additions to α-chiral aldehydes, usually referred to as Felkin−Anh control. With α-oxygenated aldehydes, Cram-chelate control is also possible. As only a few studies of additions to aldehydes such as **15** could be found,[9] we decided to conduct a model study utilizing the aldehyde **16** and the bromomethyl ester **17**, obtained by Baylis−Hillman homologation of isovaleraldehyde by a sequence analogous to that described in Scheme 4 (see Supporting Information).

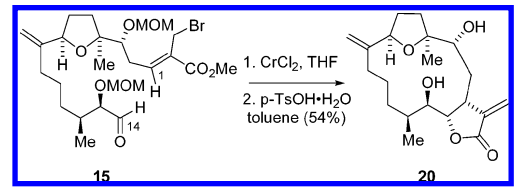
Scheme 5. Intermolecular Barbier Reaction



The model Barbier addition (Scheme 5) was first examined with excess indium in refluxing THF, which afforded a complex mixture of at least three isomeric lactones in 40% yield. With zinc as the initiating metal most of the aldehyde was recovered along with decomposition byproducts. The use of $CrCl_2$ in THF proved the most promising, resulting in a 4:1 mixture of lactones **18** and **19** in 55% yield after treatment of the reaction mixture with *p*-TsOH to lactonize the initially formed hydroxy ester intermediates.[10]

In accord with the results of these model studies we elected to employ $CrCl_2$ in THF for the cyclization of bromo aldehyde **15**, whereupon a mixture of hydroxy esters, separable into two major fractions by flash chromatography, was obtained (Scheme 6). Treatment of the major fraction with *p*-toluenesulfonic acid effected both lactonization and cleavage of the MOM ethers affording the lactone **20** as the only identifiable product in 54% yield based on the bromo aldehyde. The proton and carbon spectra of this lactone closely resembled the published spectral data for uprolide D, but the optical rotation of our synthetic material, $[\alpha]_D$ =

Scheme 6. Intramolecular Barbier Reaction



+76.0, differed in both magnitude and sign from that reported for the natural product ($[\alpha]_D$ = −19.9). As NOE data supported a *cis* fused lactone ring, we surmise that the synthetic product must have the *syn*, *anti*, *cis* arrangement, epimeric with uprolide D at C1 and C14 and corresponding to the minor product (**19**) of our model studies.[11] Treatment of the minor fraction of the foregoing mixture with *p*-toluenesulfonic acid afforded a complex mixture of lactone and other products. The proton NMR spectrum of this mixture lacked several of the signals reported for uprolide D. Thus while the outcomes of the intermolecular and intramolecular Barbier reactions are comparable, insofar as both afford *cis* lactones, they differ considerably in the degree of Felkin−Anh selectivity.

A possible explanation for this discrepancy can be constructed from an examination of Newman formulas representing possible transition states for the additions. Previous studies of Felkin−Anh versus chelation control, unlike the present examples, employed (*E*) allylmetal reagents (Figure 2).[9,12] In these reactions the chelating ability

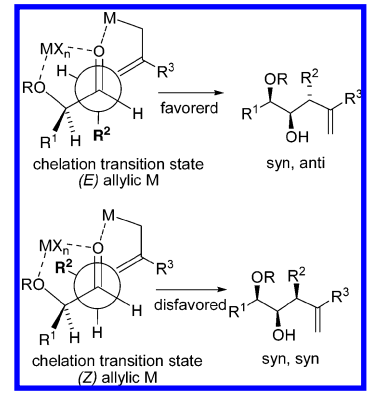


Figure 2. Chelation transition states for allylmetal additions.

of MX_n would play a major role in the diastereoselectivity of the addition. However, with (*Z*) allylmetal reagents, chelation control suffers from the necessity of the R^2

(9) Review: Denmark, S. E., Almstead, N. G. Allylation of Carbonyls: Methodology and Stereochemistry. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 369−370, 376, 386−388.

(10) For the structure determination of these lactones, see Supporting Information.

(11) Lactone **20** was submitted to NCI for biological evaluation, but after preliminary screening, it was not selected for futher testing.

(12) Paquette and co-workers have studied indium-initiated Barbier reactions of methyl (*Z*)-2-bromomethylpropenoate to various α-silyloxy and benzyloxy aldehydes in aqueous media. These additions also proceed by anti-Felkin−Anh transition states. Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333.

substituent to occupy a position directly over the chelate ring. Therefore chelation control is deemed extremely unlikely for additions involving (*Z*) allylmetal reagents in reactions proceeding through cyclic transition states.

The differing outcomes of the inter- and intramolecular allylchromium additions relating to aldehydes **16** and **15** can thus be considered in the light of four possible nonchelating transition state arrangements. Two of these conform to Felkin−Anh (Figure 3, **FA 1** and **FA 2**), and two have the

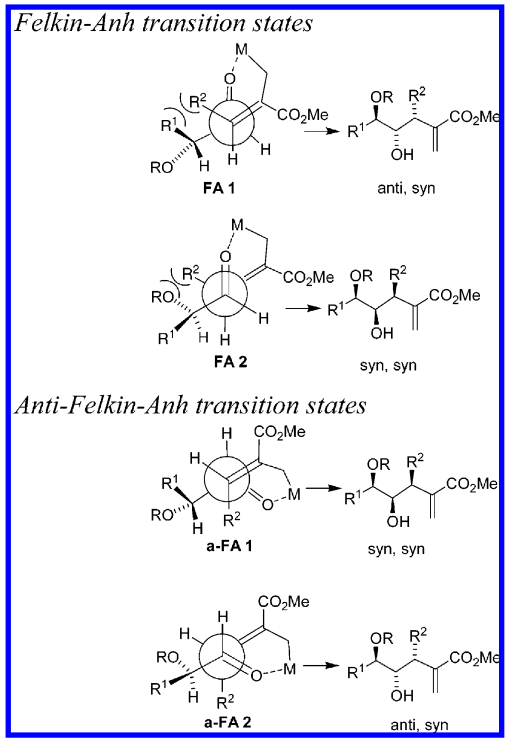


Figure 3. Non-chelation transition states for allylmetal additions.

so-called anti-Felkin−Anh arrangement (**a-FA 1** and **a-FA 2**). For the *intermolecular* addition the **FA 1** array would expectedly be highly disfavored by a *syn*-pentane interaction between R^1 and R^2.[13] The **FA 2** arrangement would likewise suffer from an interaction between the R^2 and OR substituents. Both of the anti-Felkin−Anh arrangements **a-FA 1** or **a-FA 2** are free of *syn*-pentane interactions and predominance of one or the other would depend on the stereoelectronic preference for an antiperiplanar OR or R^1 group and the relative magnitude of interactions between the attacking allylmetal nucleophile and R^1, in **a-FA 1** or the OR substituent in **a-FA 2**.

For the *intramolecular* addition leading from aldehyde **15** to the *syn*, *anti*, *cis* adduct **20**, the substituents represented by R^1 and R^2 in Figure 3 are connected by a tether of 10 atoms, including a tetrahydrofuran ring. We believe that the closer proximity of R^1 and R^2 in the Felkin−Anh orientation **FA 1** leading to the observed *anti*, *syn* adduct **20** permits greater flexibility of this connecting tether and thereby engenders fewer steric interactions than the corresponding Felkin−Anh **FA 2** or anti-Felkin−Anh alternatives. Thus while **FA 1** is disfavored for *intermolecular* additions, it is the preferred arrangement for *intramolecular* additions.

The present synthesis is noteworthy for the high degree of stereoselection of the key tetrahydrofuran cascade sequence and the Cr-initiate Barbier cyclization reaction. In fact, except for the Shi epoxidation, all stereochemically defining steps proceed with 90% or higher selectivity. Regrettably an unforeseen conformational control element in the allylchromium ring-forming reaction resulted in a C1/14 diastereoisomer of uprolide D as the only identifiable lactone product. Conceivably, the present approach would be well suited to cembranoid natural products with this *syn*, *anti*, *cis* array at C12/C13/C14/C1.[14] However, incorporation of the present allylmetal strategy in a future synthesis of the currently known uprolide natural products would best be confined to intermolecular applications.

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Supporting Information Available: Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. Review: Roush, W. R. Allylorganometallics. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1, pp 24−27.

(14) A likely precursor to an uprolide analogue of structure **20**, bis-12,13-*epi*-eupalmerin acetate, was isolated in 1993 by Rodríguez and Dhasmana: Rodríguez, A. D.; Dhasmana, H. *J. Nat. Prod.* **1993**, *56*, 564.