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A Biosynthetically-Inspired Synthesis of the Tetrahydrofuran Core of Obtusallenes II and IV

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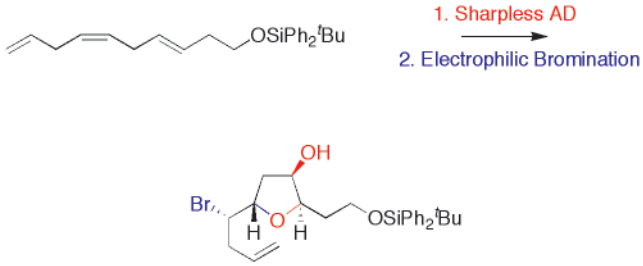
ABSTRACT



Sharpless asymmetric dihydroxylation was regioselective for the *trans* olefin in an *E* vs *Z* vs terminal triene substrate. To test a biosynthetic hypothesis, the resulting diol underwent diastereoselective bromoetherification to provide the *des*-chloro core of marine natural products obtusallenes II and IV. Alternatively, anionic chloride ring-opening of a *Z*-*β*,*γ*-unsaturated epoxide gave separable regioisomeric halohydrins. Bromoetherification gave the fully elaborated core of obtusallenes II and IV with all of the relative stereochemistry correctly set.

Recently, we presented a biosynthetic hypothesis for the obtusallene family of marine natural products from *Laurencia* species.[1] Accordingly, we are now pursuing biosynthetically inspired chemical synthetic routes to the obtusallenes. The hypothesis predicts that obtusallenes II (**1**)[2] and IV (**2**)[3,4] are the first members of the family to be encountered on the biosynthetic pathway (Figure 1). Obtusallenes II and IV have identical tetrahydrofuran cores and differ only by being epimeric at C_4 and having the oppositely configured chiral bromoallene unit. The tetrahydrofuran core of obtusallenes II and IV is proposed to arise via bromoetherification of an acyclic precursor. Previous work by Murai[5] has identified laurediol **3** as a biosynthetic precursor to the wider family of metabolites isolated from red algae of the genus *Laurencia*. Laurediol itself has been suggested to ultimately arise from (*Z*,*Z*,*Z*)-hexadeca-4,7,10-trienoic acid via epoxide **4**.[5] In this paper, we report on an asymmetric synthesis of laurediol "surrogate" (*R*,*R*)-**5**. Subsequent biosynthetically inspired bromoetherification proceeds in a highly diastereoselective fashion to give the *des*-chlorotetrahydrofuran core of obtusallenes **1** and **2**. Moreover, we also report on a

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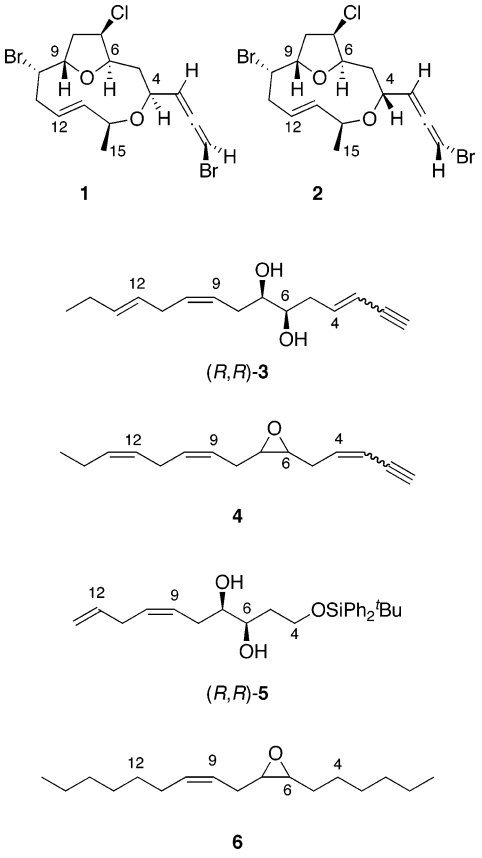


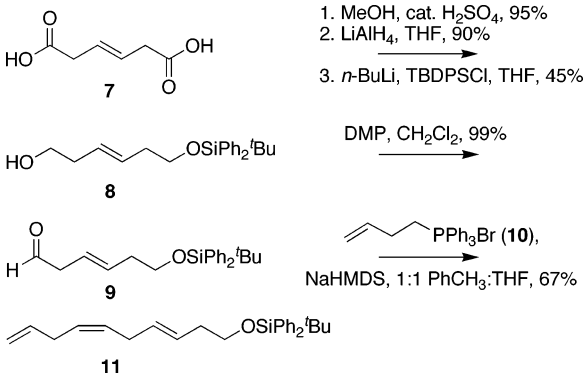
Figure 1. Structures **1**−**6**. The numbering on the structures relates to the relative positions in the obtusallenes **1** and **2**.

racemic model epoxide system **6**, which allows early chloride incorporation followed by bromoetherification to give the fully elaborated tetrahydrofuran cores for obtusallenes II and IV with all of the relative stereochemistry correctly set. The results of these studies are consistent with the early steps of the biosynthetic hypothesis for the obtusallene family.

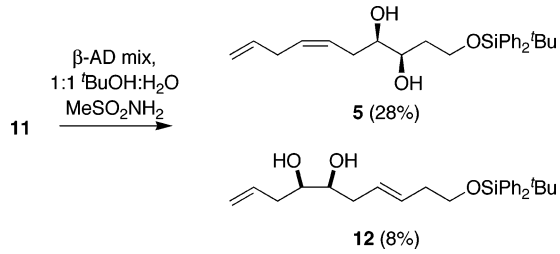
Synthesis of laurediol "surrogate" **5** commenced with commercially available *trans*-β-hydromuconic acid (**7**) (Scheme 1). Double esterification and double reduction,[6] followed by monoprotection,[7] gave protected alcohol **8**.[8] Dess−Martin periodinane oxidation[9] gave aldehyde **9**, which underwent *Z*-selective Wittig olefination[10] with the ylide generated from phosphonium salt **10**[11] to generate triene **11**.

Triene **11** has three different types of olefin: *E*, *Z*, and terminal. Sharpless asymmetric dihydroxylation of triene **11** under "standard conditions" using β-AD-mix with methanesulfonamide as an additive[12,13] proved to be regioselective for the *E* olefin giving the desired diol (*R*,*R*)-**5** in 28% isolated yield after chromatography (Scheme 2) and in a 93% ee by di-Mosher ester formation[14] (see the Supporting Information). The *R*,*R* configuration was assigned on the basis of the Sharpless mnemonic[13] and subsequently confirmed by X-ray crystallography of a derivative (vide infra). Diol **12** resulting from dihydroxylation of the *cis* olefin in triene **11** was also isolated in 8% yield (absolute stereochemistry unassigned). Unreacted triene **11** (20%) was also recovered, but the major components (40%) were tetrols and hexols from multiple dihydroxylations. On the basis of the previously measured relative rates for various alkene substitution patterns,[15] we had predicted that the *E* olefin would be preferentially dihydroxylated. However, to the best of our knowledge, this is the first example of a regioselective dihydroxylation of an *E* vs *Z* vs terminal olefin in the same substrate. Further attempted optimization of this reaction—either by changing the alcohol protecting group and/or changing the conditions—did not improve the isolated yield of desired diol **5**.

Scheme 1. Preparation of Triene **11**



Scheme 2. Sharpless AD of Triene **11**



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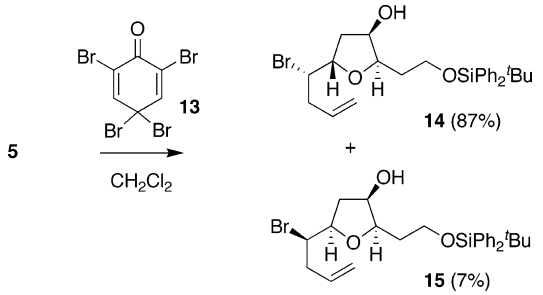
(*R*,*R*)-Diol **5** was designed as a lauredio "surrogate" to test the proposed biomimetic bromination. Since diol **5** has two hydroxyl groups and two olefins, and bromonium ion formation can occur on either face of each double bond, there are *16* possible bromoether products. However, on the basis of Baldwin's rules,[16] and if our biosynthetic hypothesis is valid,[1] the desired 5-*exo* cyclization mode should dominate. Much to our delight, we found that treating diol **5** with 1.8 equiv of tetrabromocyclohexadienone (TBCO)[17] (**13**) gave the desired *anti*-tetrahydrofuran **14** in 87% isolated yield along with the minor *syn*-diastereoisomer **15** in 7% yield, i.e., a 12:1 diastereomeric ratio (Scheme 3). Transition state

Scheme 3. Bromoetherification of Diol **5**



16 (Figure 2) is proposed to be responsible for the high level of diastereoselectivity, where both the $C_{10}-C_{13}$ chain and C_4-C_5 chain occupy pseudo-equatorial positions and the unprotected alcohol at C_7 adopts a pseudoaxial position. The minor diastereoisomer would arise from TS **17** where the $C_{10}-C_{13}$ chain is pseudoaxial.

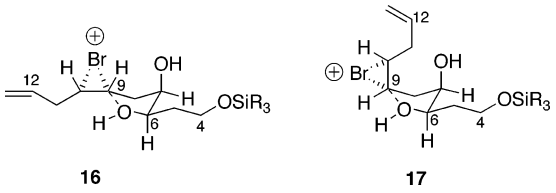
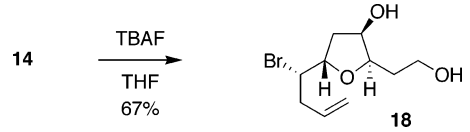


Figure 2. Proposed transition states for bromoetherification.

TBAF-mediated deprotection of the silyl group at C_4 in major diastereoisomer **14** gave diol **18** (Scheme 4), which proved to be crystalline. Single-crystal X-ray analysis (see the Supporting Information) confirmed the absolute and relative stereochemistry, thereby verifying the stereochemical course of both the Sharpless AD (vide supra) and the bromoetherification. Interestingly, the C_9-C_{10} bromoether proved to be in a gauche conformation ($Br-C_9-C_{10}-O$ torsion angle = 64°) with the hydrogen atoms on C_9 and C_{10} aligned *anti* to the electronegative atoms. This experimentally confirmed gauche conformation is expected to be

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 374−376.

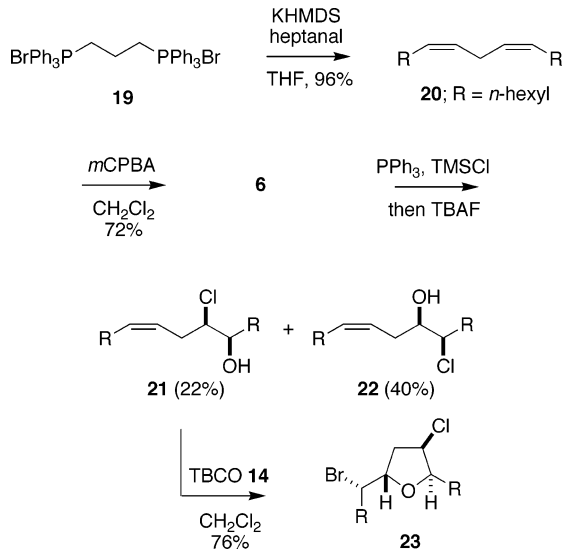
Scheme 4. Deprotection of Major Diastereoisomer **14**



a controlling element in the proposed macrobromoetherification to form obtusallenes II and IV.[1]

We have also investigated a second system in line with our biosynthetic hypothesis with early chloride incorporation. Thus, diene **20** was prepared by double *Z*-selective (>9:1 *Z*/*E*) Wittig olefination using bis-phosphonium salt **19**[18] and KHMDS with heptanal (Scheme 5). Monoepoxidation with

Scheme 5. Synthesis of Tetrahydrofuran **23**



m-CPBA gave epoxide **6**, which was subject to anionic chloride ring-opening with trimethylsilyl chloride and triphenylphosphine[19] and an in situ TBAF quench to give the two regioisomeric hydrohalins **21** and **22** in a 1.0:1.7 ratio as judged by ^{1}H NMR of the crude mixture (67%). The desired chlorohydrin **21** could be isolated by careful column chromatography (22%) and was treated with TBCO **13**. Smooth bromoetherification[20] occurred to give the desired bromochlorotetrahydrofuran **23** as a single diastereoisomer (76%), and the relative stereochemistry was assigned by analogy of the conversion of diol **5** into tetrahydrofuran **14**. Extensive NMR experiments (^{1}H, ^{13}C, COSY, HMQC) firmly established the connectivity as a 2,3,5-trisubstituted

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tetrahydrofuran. In particular a 8 ppb chlorine-induced isotopic shift of the carbon resonance at 62.9 ppm in the ^{13}C NMR spectrum identified this resonance as the carbon bearing the chlorine (Figure 3).[21] This currently under-used

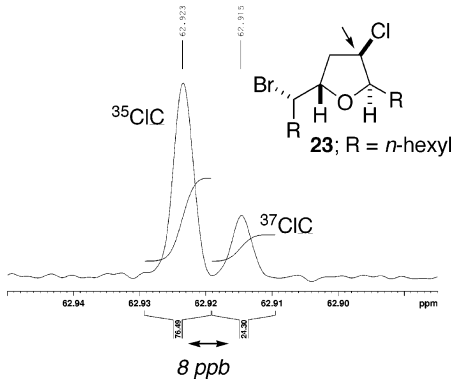

Figure 3. Isotope induced shift for the resonance arising from the chlorine-bearing carbon.

technique should find wide applicability in unambiguously identifying carbon-bearing chlorines in natural product systems.[22]

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In the above sequence of epoxidation, anionic chloride ring-opening, and bromoetherification, we noted that all of these reactions had been performed in dichloromethane solution. It was also noted that of the two halohydrins **21** and **22**, only **21** has a favorable ring-closing mode. Thus, the possibility of a one-pot synthesis of tetrahydrofuran **23** directly from diene **20** was explored. Accordingly, to a solution of *Z,Z*-skipped diene **20** in dichloromethane were added sequentially *m*-CPBA, TMSCl and PPh_3, TBAF, and then TBCO. Pleasingly, after workup and chromatography of the complex mixture, chlorobromotetrahydrofuran **23** was isolated in 18% yield and in >95% purity.

Further work is in progress toward the synthesis of the obtusallene family of natural products via electrophilic bromination and will be reported in due course.

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Supporting Information Available: Full experimental procedures and characterization data for compounds **5**, **6**, **8**−**12**, **14**, **15**, **18**, and **20**−**23**, determination of the ee for **5** via di-Mosher's ester formation, copies of ^{1}H and ^{13}C NMR spectra for compounds **5**, **6**, **11**−**12**, **14**, **15**, and **20**−**23**, and X-ray crystallographic data for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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