The role of chemical synthesis in structure elucidation of oxasqualenoids

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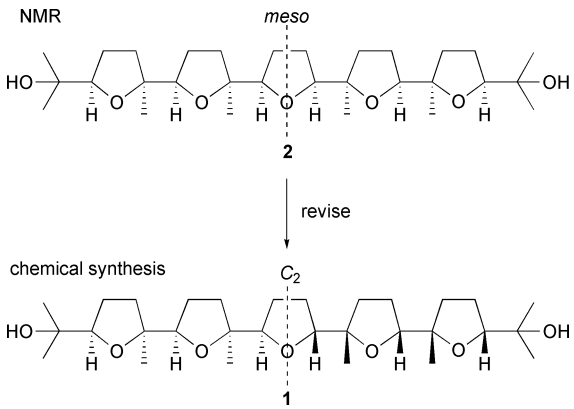
Recently, highly oxidized and structurally diverse triterpene polyethers, which are thought to be biogenetically squalene-derived natural products (oxasqualenoids), have been isolated from both marine and terrestrial organisms. However, it is often difficult to determine their stereostructures even by the current, highly advanced spectroscopic methods, especially in acyclic systems including stereogenic quaternary carbon centers. In such cases, it is effective to predict and synthesize the possible stereostructures. Herein, we report total assignments of the previously incomplete stereostructures of an epoxy tri-THF diol, intricatetraol and enshuol, members of the oxasqualenoids, through the first asymmetric total syntheses of the natural products, the configurations of which are difficult to determine by other means. Since this article is basically written as a communication without detailed experimental procedures and spectroscopic data, original papers with full data should follow.

Introduction

Glabrescol **1**, a member of a family of squalene-derived triterpene polyethers named oxasqualenoids,[1] was isolated from the branches and wood of *Spathelia glabrescens* (Rutaceae) by Jacobs *et al.* in 1995.[2] Although the structure of glabrescol was primarily proposed as a *meso* compound **2** by spectroscopic methods, the chemical synthesis of **2** and **1** by our[3] and Corey's[4] groups revealed that the *meso* structure **2** originally proposed for glabrescol must be revised to the optically pure C_2 symmetric structure **1** (Scheme 1).

Nowadays NMR methods are indispensable for structure elucidation of complex and diverse natural products. NMR technologies are advancing day by day, and recently it has been possible to even determine stereochemistries. The example shown in Scheme 1, however, exposes the technical limitations of the current highly advanced NMR spectroscopic methods used for the structural elucidation of complex and diverse natural products.[5] Although many other types of oxasqualenoids have been isolated,[1] it is often difficult to determine their stereostructures even by modern highly advanced spectroscopic methods, especially in the case of acyclic systems that include stereogenic quaternary carbon centers. Such difficulties coupled with the unique structures, biogenetic interests and biological activities of oxasqualenoids have prompted synthetic organic chemists to determine the



Scheme 1 Proposed structure **2** and revised structure **1** of glabrescol.

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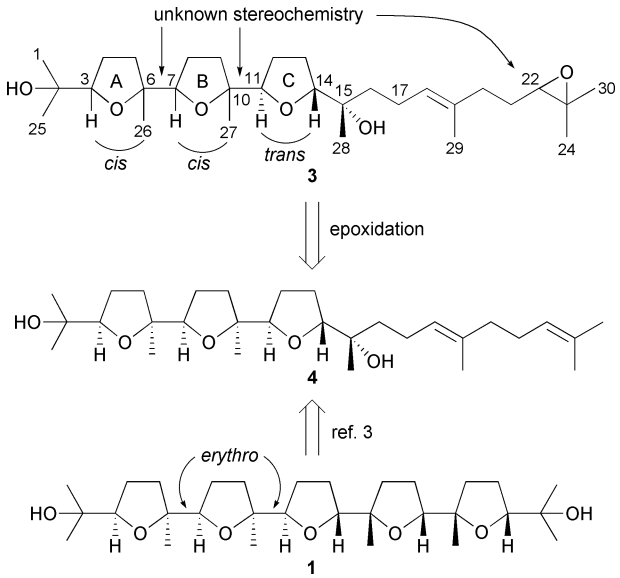
stereostructures of these natural products by chemical synthesis,[3,4,6] because it is difficult to determine their stereostructures by other means. In this article, we report the recent contribution to structure elucidation of oxasqualenoids by chemical synthesis from our laboratory.

Complete assignment of the stereostructure of a new squalene-derived epoxy tri-THF diol from *Spathelia glabrescens* by chemical synthesis

An epoxy tri-tetrahydrofuran (THF) diol **3** was isolated from the endemic Jamaican plant *Spathelia glabrescens* (Rutaceae) by Jacobs *et al.* (Scheme 2).[7] Although there is no report on the biological activity, the polyether containing three THF rings may be expected to exhibit ionophoric functions[8] as well as cytotoxicities,[9] because of the recent active research studies on remarkable interactions (membrane transport and ion channel) of neutral oligotetrahydrofuranyl derivatives with metal cations in natural products[10] and artificial systems.[11] The plane structure and partial relative configuration of **3**, as shown in the structure of **3**, were elucidated by NMR methods; however, determination of the entire stereochemistry of compound **3** has not been reached.

There are four possible *cis*,*cis*,*trans* stereoisomers of the C1–C15 fragment and the attached methyl groups with the relative stereochemistry as shown at C11, C14 and C15, and eight for the entire molecule **3**. We have previously accomplished the total synthesis of (−)-glabrescol **1** by way of the tri-THF intermediate



Scheme 2 Possible stereostructure for epoxy tri-THF diol **3**.

4.[3] Considering the relative stereochemistry between each A, B and C THF ring in **3**, it is likely that **3** also possesses the same *erythro* configuration of **1** on biogenetic grounds, because both **1** and **3** were isolated from *Spathelia glabrescens*. In practice, chemical shifts observed for C1–C17 and C25–C28 in the ^{13}C NMR spectrum of **3** are almost identical to those of **4** (Table 1),

Table 1 ^{13}C NMR data for compounds **3–6**

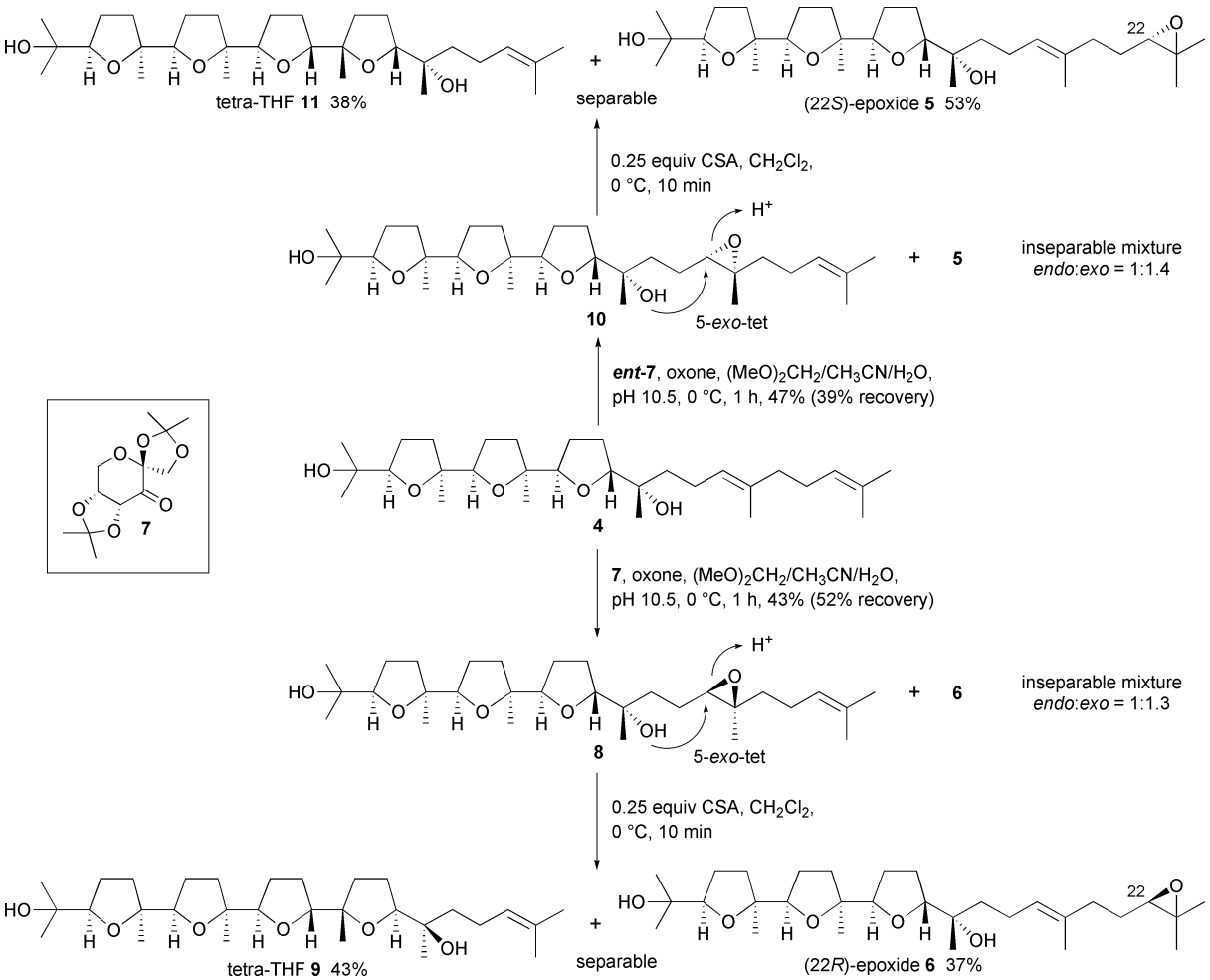
Position	**3**[a]	**4**[a]	**3** (2.6 mM)[b]	**5** (16 mM)[b]	**6** (8.7 mM)[b]	$\Delta\delta = \delta_5 - \delta_3$	$\Delta\delta = \delta_6 - \delta_3$
1	25.2	25.2	25.392	25.370	25.386	−0.022	−0.006
2	72.3	72.3	72.462	72.458	72.446	−0.004	−0.016
3	85.9	85.9	86.012	85.993	86.004	−0.019	−0.008
4	26.0	26.1	26.199	26.188	26.192	−0.011	−0.007
5	29.8	30.0	30.072	30.052	30.060	−0.020	−0.012
6	86.1	86.1	86.169	86.162	86.166	−0.007	−0.003
7	82.7	82.9	82.828	82.836	82.819	+0.008	−0.009
8	28.9	28.9	28.773	28.787	28.768	−0.014	−0.005
9	30.8	31.0	30.706	30.732	30.706	+0.026	0.000
10	85.9	85.9	85.866	85.880	85.862	+0.014	−0.004
11	84.2	84.3	84.303	84.301	84.297	−0.002	−0.006
12	29.5	29.5	29.648	29.642	29.641	−0.006	−0.007
13	26.4	26.5	26.657	26.636	26.648	−0.021	−0.009
14	85.8	85.8	85.977	85.993	85.979	+0.016	+0.002
15	72.9	73.0	73.076	73.058	73.077	−0.018	+0.001
16	36.6	36.8	36.957	36.954	36.915	−0.003	**−0.042**
17	22.1	22.1	22.375	22.354	22.354	−0.021	−0.021
18	125.3	124.7	125.678	125.650	125.711	−0.028	**+0.033**
19	133.9	134.9	134.020	134.010	133.981	−0.010	**−0.039**
20	36.2	39.7	36.512	36.489	36.531	−0.023	+0.019
21	27.3	26.7	27.645	27.621	27.598	−0.024	**−0.047**
22	64.1	124.3	64.039	64.056	64.056	+0.017	+0.017
23	58.4	131.3	58.022	58.051	58.041	+0.029	+0.019
24	18.7	17.6	18.775	18.766	18.773	−0.009	−0.002
25	27.8	27.8	28.003	27.981	27.990	−0.022	−0.013
26	25.2	25.2	25.203	25.197	25.198	−0.006	−0.005
27	23.4	23.3	23.304	23.314	23.302	+0.010	−0.002
28	24.0	24.1	24.272	24.252	24.229	−0.020	**−0.043**
29	15.9	16.0	16.025	16.018	15.980	−0.007	**−0.045**
30	24.8	25.7	24.888	24.882	24.890	−0.006	+0.002

[a] The data for **3** and **4** were cited from refs. 7 and 3*a*, respectively. [b] The spectra were recorded at 300 K and the indicated concentrations in 60% $CDCl_3$–40% C_6D_6 on a Bruker AVANCE 600 (150 MHz) spectrometer. Chemical shifts are in ppm downfield from the peak of TMS as an internal standard.

strongly suggesting that the relative configurations of **3** and **4** are the same. Therefore, we decided to synthesize the two remaining possible stereoisomers **5** and **6** by epoxidation of our synthetic intermediate **4** to compare their spectroscopic data with those of the natural product **3**.

We adopted Shi asymmetric epoxidation as a reliable method for predicting the stereochemical outcome of the reaction,[12] because many examples for trisubstituted alkene substrates similar to **4** have been reported without exception.[4,6b,13] Reagent-controlled epoxidation of the optically active diene **4**, $[\alpha]_D^{24}$ −12.5 (*c* 1.32, $CHCl_3$),[3a] with Shi's chiral dioxirane generated *in situ* from ketone **7**[12a] afforded monoepoxides *endo*-**8** and *exo*-**6** as an inseparable 1 : 1.3 mixture, respectively, in 43% yield along with 52% recovery of the starting material **4** (Scheme 3). For the purpose of separating the two products, the mixture was treated with (±)-10-camphorsulfonic acid (CSA) to give the diastereomerically homogeneous (22*R*)-epoxide **6**, $[\alpha]_D^{22}$ −13.1 (*c* 0.14, $CHCl_3$), and tetra-THF **9** in 37% and 43% isolated yields, respectively, after column chromatography on silica gel. On the other hand, the same procedure for the diene **4** using ketone *ent*-**7**,[12b] enantiomeric to **7**, furnished monoepoxides *endo*-**10** and *exo*-**5** as a mixture (**10** : **5** = 1 : 1.4 in 47% yield and recovered **4** in 39% yield), acid treatment of which provided (22*S*)-epoxide **5**, $[\alpha]_D^{22}$ −12.3 (*c* 0.235, $CHCl_3$), in 53% yield and tetra-THF **11** (38%).

It appears that the synthetic compounds **5** and **6** and the natural product **3** are indistinguishable from one another by their 600 MHz ^{1}H NMR spectra, even in a $CDCl_3$–C_6D_6 mixed solvent system with comparatively good proton resolution. Therefore, the stereostructure of **3** must be either **5** or **6**; however, it seems difficult to distinguish **5** from **6**. Thus, we focused on the critical stereochemical discussions utilizing carbon chemical shift differences ($\Delta\delta$) below the 0.1 ppm level reported by Kishi *et al*.[14] 150 MHz ^{13}C NMR data of **3**, **5** and **6** measured by the same spectrometer are summarized in Table 1. Comparing the chemical shifts, $|\Delta\delta = \delta_5 - \delta_3|$ of all the carbons in **5** is less than 0.03 ppm, while there are six carbons (C16, C18, C19, C21, C28 and C29) of $|\Delta\delta = \delta_6 - \delta_3| > 0.03$ ppm in the region linking the C15 and C22 chiral carbons of **6**. An optical rotation of the authentic sample **3**, $[\alpha]_D^{25}$ −11.5 (*c* 0.03, $CHCl_3$),[7] remeasured by us is also nearer to that of (22*S*)-**5** than that of (22*R*)-**6**. Furthermore, to rule out the possibility that the chemical shift differences $|\Delta\delta = \delta_6 - \delta_3| > 0.03$ ppm are an experimental error and unambiguously differentiate the synthetic **6** from the natural **3**, 150 MHz ^{13}C NMR spectrum of a 1.3 : 1 mixture of **6** and **3**, respectively, was



Scheme 3 Synthesis of the two possible stereoisomers **5** and **6**.

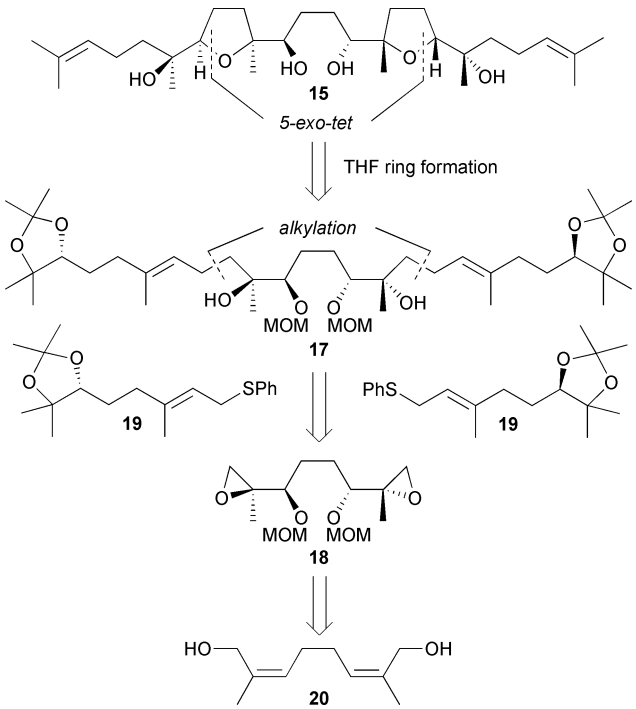
measured at 300 K and 6.1 mM in 60% $CDCl_3$–40% C_6D_6. Seven distinguishable peaks, with $\Delta\delta = \delta_6 - \delta_3$ indicated in parentheses, were observed for the carbons C16 (−0.025), C18 (+0.052), C19 (−0.029), C20 (+0.037), C21 (−0.030), C28 (−0.027) and C29 (−0.042), still in the region linking the C15 and C22 chiral carbons and with the same signs as those of $\Delta\delta$ independently measured (Table 1). On the other hand, a mixture of **3** and **5** completely overlapped in the ^{13}C NMR spectrum. From these facts, we judged that the spectral characteristics including the optical rotation of the synthetic (22*S*)-**5** are identical to those of the natural product **3**. Thus, it has been found that the hitherto unknown relative and absolute configuration of the epoxy tri-THF diol **3** is as indicated in the structural formula **5**, which possesses the same absolute stereochemistry as glabrescol **1**.[6d]

Total synthesis and determination of the absolute configuration of (+)-intricatetraol

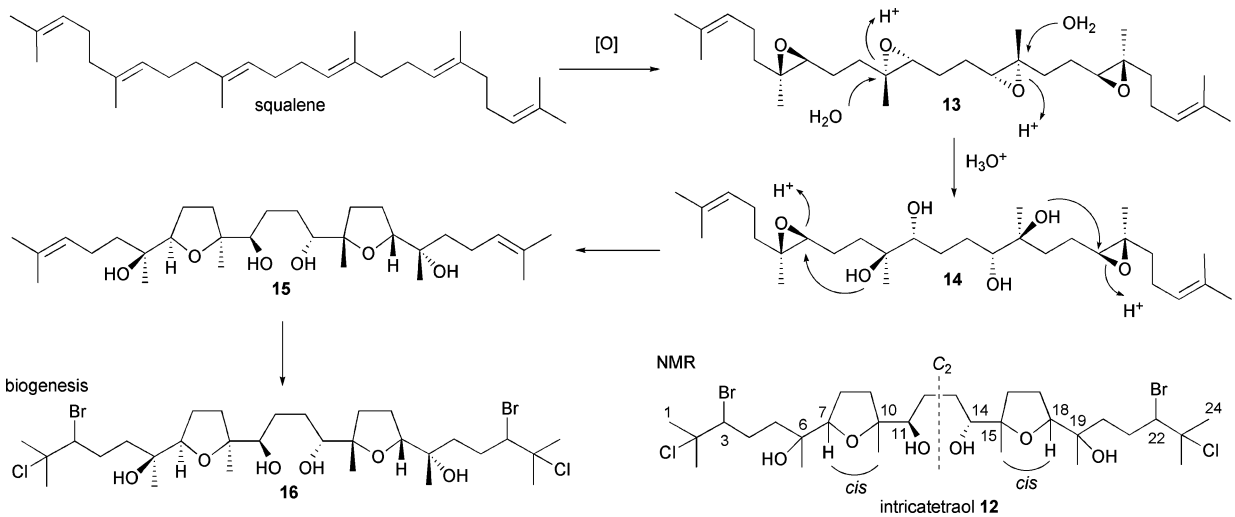
Intricatetraol **12** was isolated from the red alga *Laurencia intricata* by Suzuki *et al.* in 1993, and a crude fraction including intricatetraol **12** as the major component exhibited cytotoxic activity against P388 "leukemia cells" with an IC_{50} value of 12.5 μg mL^{-1}.[15] The structural analysis was mainly carried out by NMR spectroscopic methods. Although it has been found that the molecule has C_2 symmetry, *cis* configuration within the THF ring and *R* configuration at the C11 (C14) position, the stereochemistries between C6 and C7 (C18 and C19) and C10 and C11 (C14 and C15) and at the bromine-attached C3 (C22) position remain to be determined (Scheme 4). In particular, the presence of the vicinal bromochloro functionality in **12** makes the problem of stereochemical assignment even more inaccessible. Suzuki *et al.*[15] have suggested a stereostructure **16** except for the C3 (C22) position as the possible one based on the hypothetical biogenesis. Too many stereostructures were possible for **12** if NMR spectroscopic data alone was considered; therefore, we decided to synthesize the stereostructure **16** on the basis of the hypothetical biogenetic pathway.

Two-directional synthesis approach

The retrosynthetic analysis of the possible stereostructure **16** for (+)-intricatetraol is depicted in Scheme 5. It was envisioned that a two-directional synthetic strategy[16] could be efficient to synthesize the C_2 symmetric molecule **16**. The vicinal bromochloro functionality might be introduced by manipulation of the alkene in **15**, where the THF ring would be constructed in a two-directional manner through a Shi asymmetric epoxidation[12] of bishomoallylic alcohol **17** followed by a 5-*exo*-tet epoxide-opening reaction.[17] The diol **17** would, in turn, be derived from diepoxide **18** by extending both side chains with the C_{10} unit **19**, still in the two-directional mode. Thus, we planned to prepare the C_2 symmetric chiral



Scheme 5 Retrosynthetic analysis of possible stereostructure **16**.



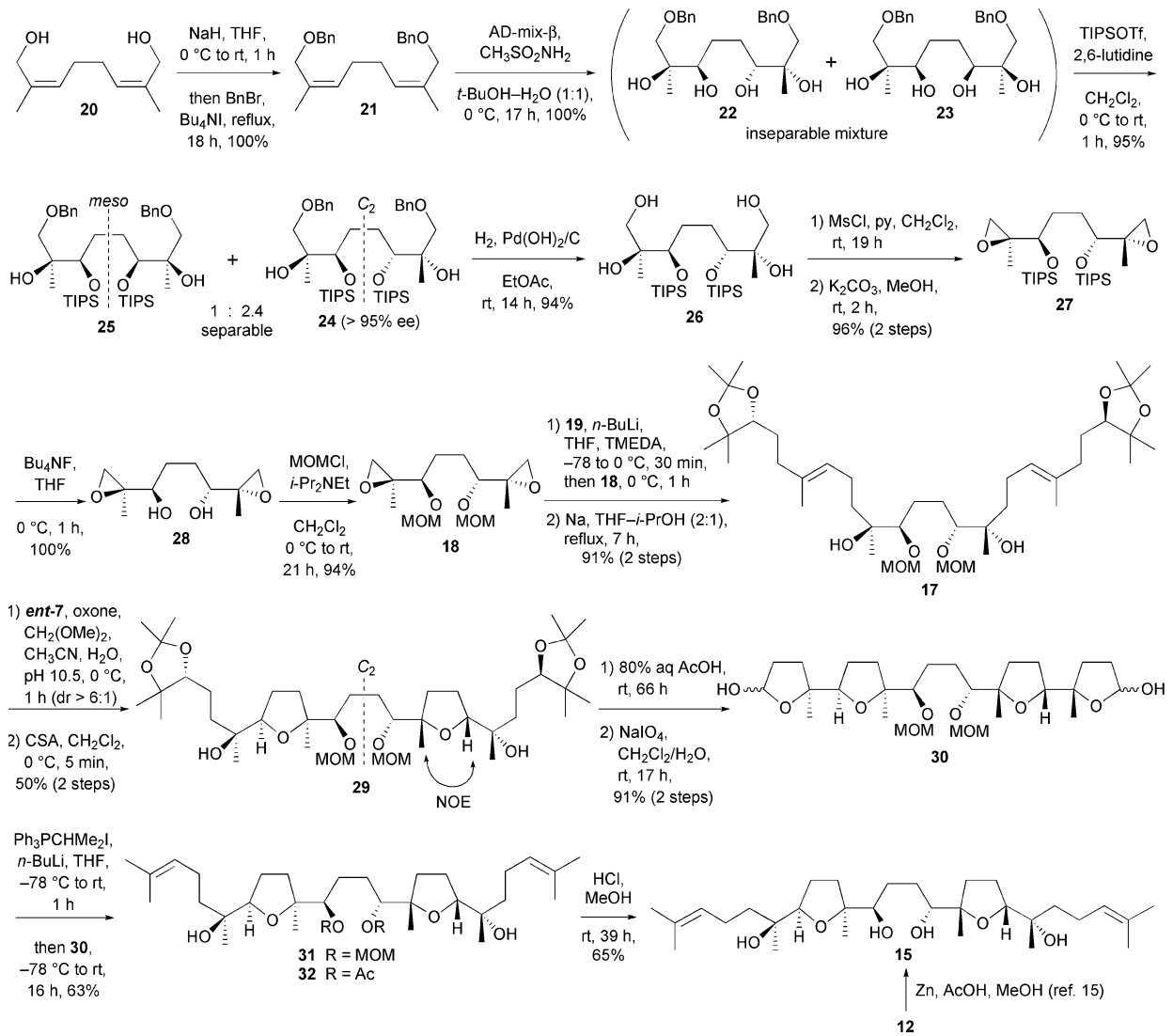
Scheme 4 Stereostructures **12** and **16** of intricatetraol based on the NMR data and the hypothetical biogenesis, respectively.

diepoxide **18** from the readily available diol **20** *via* the established Sharpless asymmetric dihydroxylation.[18]

Preparation of the diepoxide **18** began with protection of the known diol **20**[3a] as a benzyl ether (Scheme 6). Sharpless asymmetric dihydroxylation of the diene **21** using AD-mix-β[18] afforded an inseparable mixture of diastereomeric tetraols in quantitative yield. Subsequent selective TIPS protection of the secondary hydroxy groups in the mixture resulted in separation of the diastereomers to provide diols **24** (>95% ee) and **25** in 67 and 28% yields, respectively, after column chromatography on silica gel. Both symmetric diols **24** and **25** were assigned to C_2 and *meso* isomers, respectively, by their optical rotations, **24**: $[\alpha]_D^{26}$ +4.8 (*c* 1.03, $CHCl_3$); **25**: $[\alpha]_D^{22}$ 0 (*c* 0.95, $CHCl_3$). Deprotection of the benzyl ether in the desirable major diol **24**, mesylation of both primary hydroxy groups in the resulting tetraol **26** and subsequent basic treatment of the dimesylate gave diepoxide **27** in good overall yield. Replacement of the bulky TIPS ether in **27** with a relatively small MOM ether yielded the requisite diepoxide **18**.

The lithiation of the known allylic sulfide **19**[6e] and alkylation of the lithio derivative with the diepoxide **18** were carried out in the presence of TMEDA, and the resulting disulfide, as a mixture of diastereomeric sulfides, was desulfurized under Bouveault–Blanc conditions[19] to yield the expected diol **17**. Shi asymmetric epoxidation of the bishomoallylic alcohol **17** catalyzed by chiral ketone *ent*-**7** followed by treating of the resulting labile bishomoepoxy alcohol with CSA in dichloromethane brought about a regioselective 5-*exo*-tet oxacyclization[17b] to produce diol **29** in 50% yield over two steps. The C_2 symmetric structure and the *cis* stereochemistry of the THF ring in **29** ($C_{40}H_{74}O_{12}$) could be confirmed by the observation of only 20 signals in the ^{13}C NMR spectrum and NOE, shown in the structure of **29**, respectively.

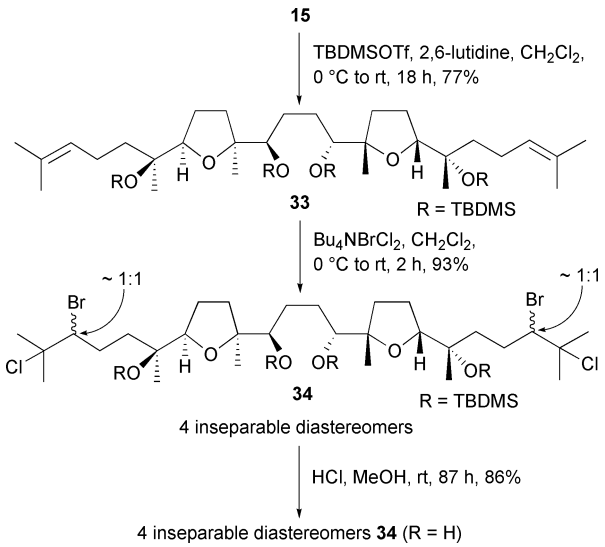
The remaining task was the generation of trisubstituted double bonds. Selective deprotection of the acetonide group in diol **29** and subsequent cleavage of the resultant vicinal diol with sodium metaperiodate afforded tetra-THF ether **30**, which was found to be present mostly as a hemiacetal in the ^1H NMR spectrum, in 91% yield over two steps. The Wittig olefination of the hemiacetal **30** with an excess of isopropylidene triphenylphosphorane provided the desired diene **31** in 63% yield. Removal of the MOM protective group in the diene **31** furnished tetraol **15**. The spectral



Scheme 6 Two-directional synthesis of tetraol **15**.

characteristics (^{1}H and ^{13}C NMR) of the synthetic **15**, $[\alpha]_D^{29}$ +11.5 (*c* 0.175, $CHCl_3$), were identical to those reported for the dehalogenated product **15**, $[\alpha]_D^{20}$ +13.6 (*c* 0.77, $CHCl_3$), derived from the natural intricatetraol **12** by Suzuki *et al.*[15] Thus, it has been found that the possible stereostructure **16** proposed for (+)-intricatetraol based on the hypothetical biogenesis is correct.[6f] Independently from us, Ujihara has also reported the same partial stereochemistry of (+)-intricatetraol as ours through the synthesis of diacetate **32** derived from the natural product.[20]

We have achieved the synthesis of tetraol **15**, a degradation product of natural (+)-intricatetraol **12**. For the total synthesis of (+)-intricatetraol **12**, we have nonstereoselectively synthesized four diastereomers from the tetraol **15** as shown in Scheme 7. Unfortunately, the four diastereomers **34** (R = H) were obtained as an inseparable mixture. Therefore, we embarked on another olefin metathesis synthesis approach featuring the enantioselective construction of the vicinal bromochloro functionality through a pathway in which the configuration was secured, because an enantioselective method for the synthesis of the vicinal bromochloro functionality has never been developed.

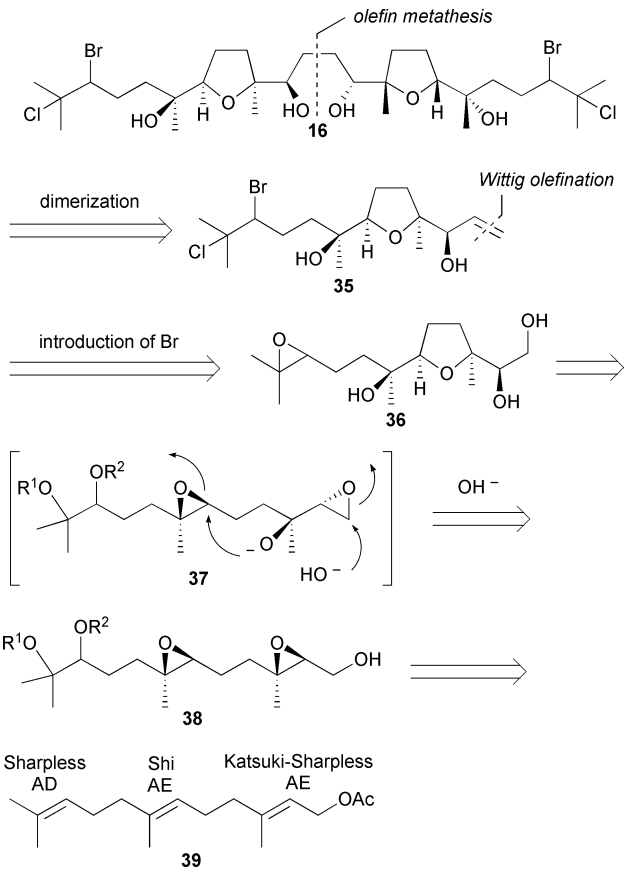


Scheme 7 Nonstereoselective syntheses of four possible diastereomers **34** (R = H) for (+)-intricatetraol.

Olefin metathesis synthesis approach

The retrosynthetic analysis of the target compound **16** is depicted in Scheme 8. We envisaged that it would be efficient to dimerize by olefin metathesis the functionalized fragment **35**, which represents half of the molecule, because of the C_2 symmetry of the natural product. The *R* or *S* configuration at the carbon atom attached to bromine in **35** could be introduced through epoxide chemistry. The desired trihydroxyTHF **36** might be constructed by the stereospecific and stereoselective oxacyclization of the diepoxyalcohol **38** under alkaline conditions.[21] The required stereocenters in **38** would be introduced into commercially available *trans*,*trans*-farnesyl acetate **39** by established methods of asymmetric oxidation.

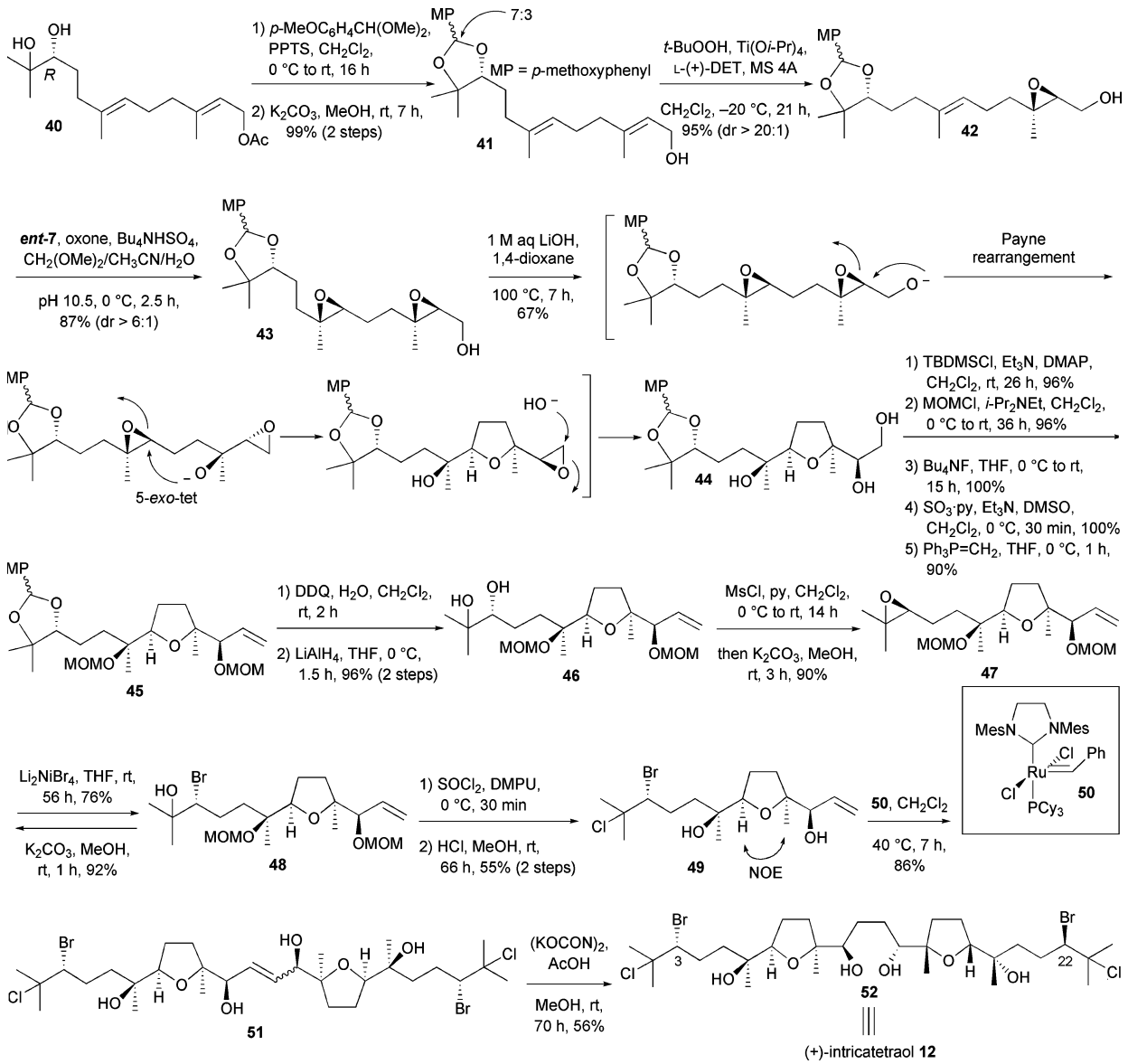
The protection of the chiral diol **40** (>95% ee)[22] as a *p*-methoxybenzylidene acetal (7 : 3 mixture) and subsequent



Scheme 8 Retrosynthetic analysis of the target compound **16**. AD = asymmetric dihydroxylation, AE = asymmetric epoxidation.

deacetylation afforded the allylic alcohol **41** (Scheme 9). Katsuki–Sharpless asymmetric epoxidation of **41** in the presence of L-(+)-DET provided the epoxyalcohol **42**. Asymmetric epoxidation of the alkene **42** by the method of Shi and co-workers[12] with ketone *ent*-**7** as the chiral catalyst then gave the diepoxyalcohol **43**. Treatment of the diepoxyalcohol **43** with 1 M aqueous solution of lithium hydroxide and 1,4-dioxane (1 : 1) under reflux furnished the desired trihydroxyTHF product **44** with high stereospecificity. It was thought from our previous studies[6e,21b] that the reaction proceeds through a Payne rearrangement, 5-*exo*-tet formation of the ether ring and an intermolecular attack of hydroxide ion on the epoxide. Selective TBDMS protection of the primary hydroxy group in the triol **44**, MOM protection of the remaining hydroxy groups, deprotection of the silyl ether, Parikh–Doering oxidation of the alcohol and Wittig methylenation of the resulting aldehyde afforded the terminal alkene **45** in good overall yield. Oxidation of the *p*-methoxybenzylidene acetal **45** with DDQ[23] provided a 3 : 7 mixture of regioisomeric benzoate esters, which upon reduction with lithium aluminum hydride gave the deprotected diol **46**.

Selective mesylation of the secondary hydroxy group in the diol **46** followed by treatment of the mesylate with potassium carbonate yielded the epoxide **47**.[24] The epoxide-opening reaction of **47** with dilithium tetrabromonickelate in THF proceeded regioselectively to produce the secondary bromide **48** with inversion of configuration at the less hindered carbon atom.[25] It has been reported that dilithium tetrabromonickelate reacts with epoxides



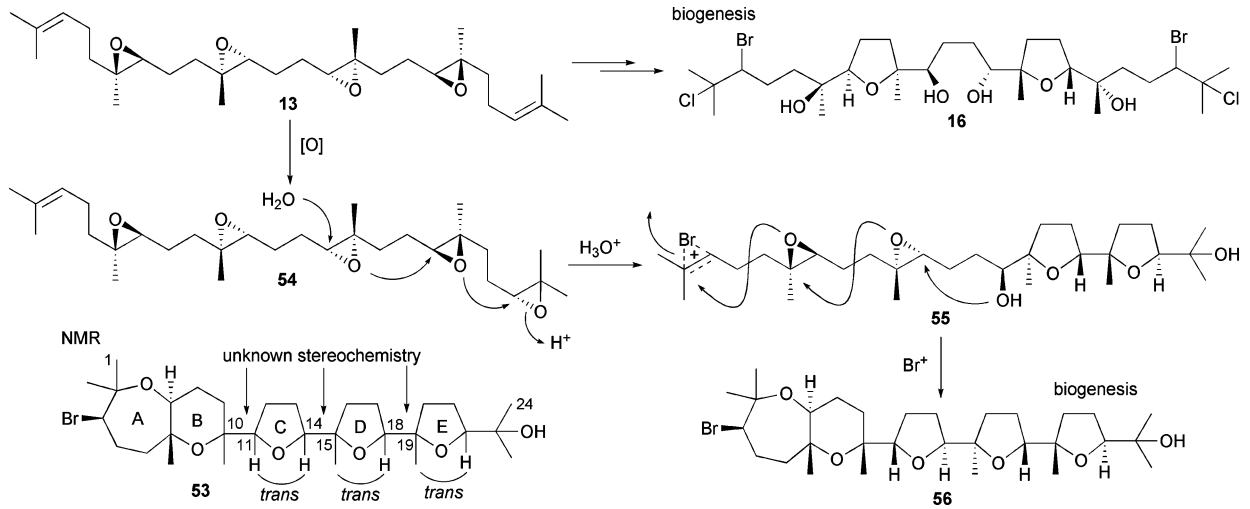
Scheme 9 Total synthesis of (+)-intricatetraol **52**.

through an S_N2 mechanism. We confirmed that the bromohydrin **48** is reconverted into the starting epoxide **47** upon treatment with a base. Chlorination[26] of the bromohydrin **48** and subsequent deprotection of the alcohols protected as MOM ethers afforded the fully functionalized half fragment **49** with a *cis* THF ring, as confirmed by the observation of an NOE between the hydrogen atoms, indicated in the structure of **49**.

The dimerization of fragment **49** was carried out in 86% yield by olefin metathesis with the Grubbs second-generation catalyst **50**.[27] Although catalytic hydrogenation of the alkene **51** under standard conditions afforded the dehalogenated product by overreduction, diimide reduction provided the target compound **52** without dehalogenation. The respective spectra of the synthetic compound **52**, $[a]_D^{23}$ +51.3 (*c* 0.41, $CHCl_3$), prepared from the *R* alcohol **40**, were identical to those of the natural product, $[a]_D^{20}$ +53.0 (*c* 0.625, $CHCl_3$).[15] Thus, it was found that the hitherto unknown absolute configuration of (+)-intricatetraol **12** is shown by the structural formula **52**.[6g]

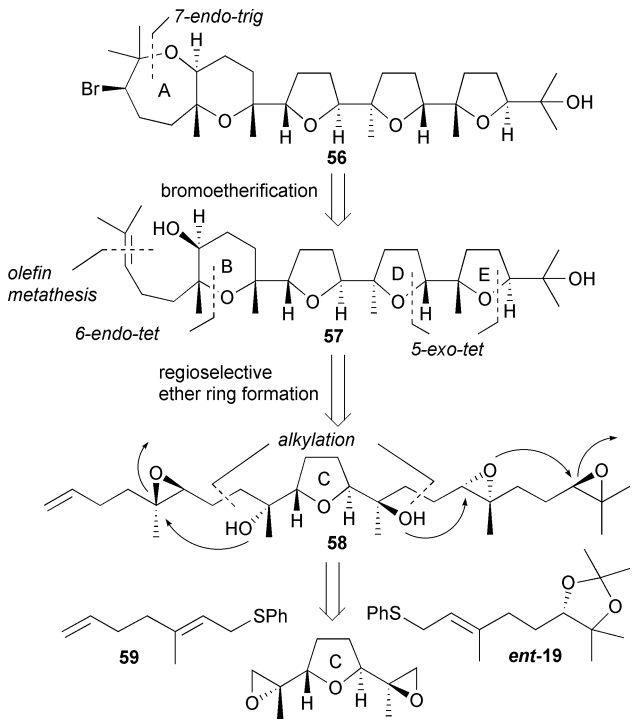
Assignment of the absolute configuration of the marine pentacyclic polyether (+)-enshuol by total synthesis

Enshuol **53**, a member of the oxasqualenoids, was isolated from the red alga *Laurencia omaezakiana* Masuda by Suzuki and co-workers in 1995.[28] Although the planar structure and partial configuration of **53** were elucidated by spectroscopic and chemical analysis, until now the entire configuration had not been determined. In the preceding section, we described the assignment of the absolute configuration of (+)-intricatetraol **12** by chemical synthesis. In that case, the biogenetic consideration by Suzuki *et al.* played an important role in deciding the synthetic target **16** (Scheme 4). In the case of (+)-enshuol, Suzuki and co-workers also suggested structure **56** to be the possible stereostructure of (+)-enshuol, again on the basis of the hypothetical biogenetic pathway *via* the same tetraepoxide intermediate **13** as that of (+)-intricateraol (Scheme 10). Therefore, we chose compound **56** as the synthetic target.



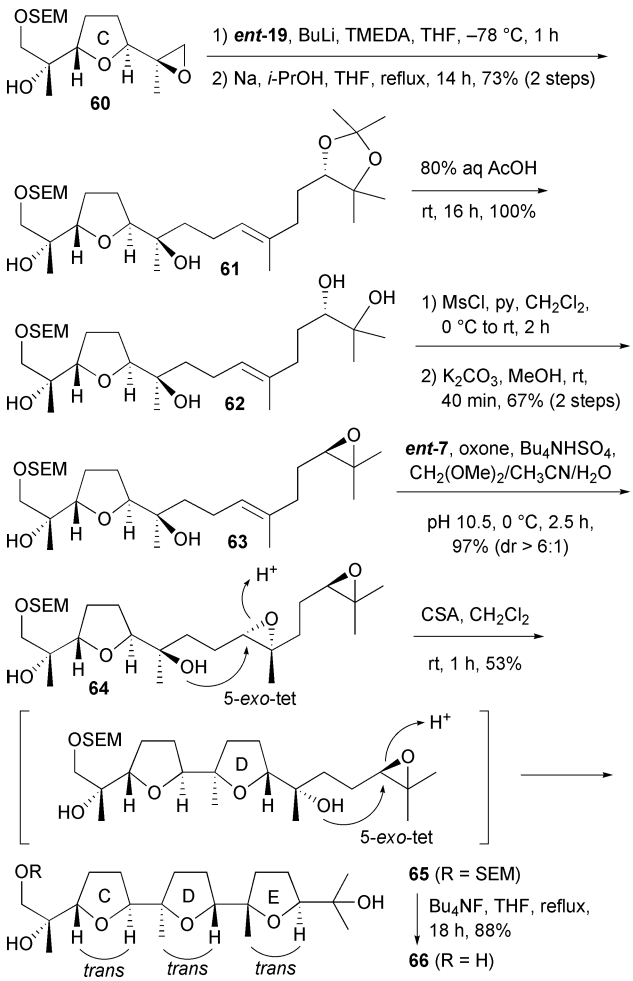
Scheme 10 Possible biogenesis proposed by Suzuki and co-workers for enshuol **56**.

Our retrosynthetic analysis of the target molecule **56** is shown in Scheme 11. We planned to construct the A ring by 7-*endo*-trig bromoetherification of the corresponding precursor **57**. The B, D and E rings would be formed by 6-*endo*-tet or 5-*exo*-tet epoxide-opening of the corresponding bishomoepoxy alcohols.[17b] The required carbon framework (see **58**) could be assembled in a convergent manner from suitable building blocks.



Scheme 11 Retrosynthetic analysis of the target molecule **56**.

We began our synthesis with the chain extension of the known chiral epoxide **60**[6e] using a lithio derivative of the chiral allylic sulfide *ent*-**19**,[6b] enantiomeric to **19** (Scheme 12). The acetonide **61** was obtained after desulfurization of the resulting sulfide. Deprotection of the acetonide in **61** and epoxide formation from the vicinal diol[24] to give **63**, followed by Shi asymmetric epoxidation[12] of the alkene, furnished the diepoxy alcohol **64**. The treatment of **64** with CSA in dichloromethane led to a regioselective 5-*exo*-tet tandem oxacyclization to afford the tricyclic system of adjacent THF rings **65**, which was deprotected to give the triol **66**.

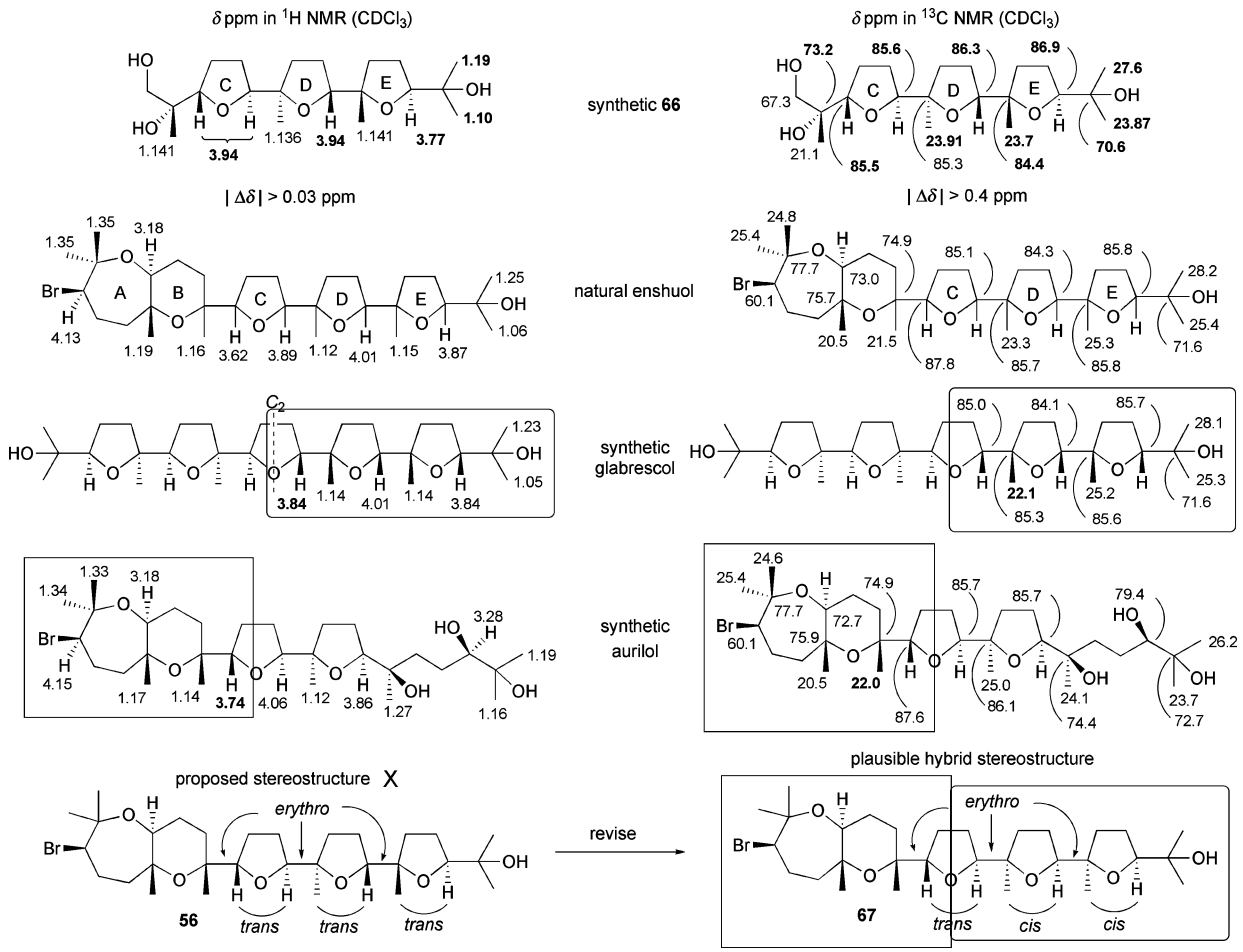


Scheme 12 Synthesis of tri-THF **66**.

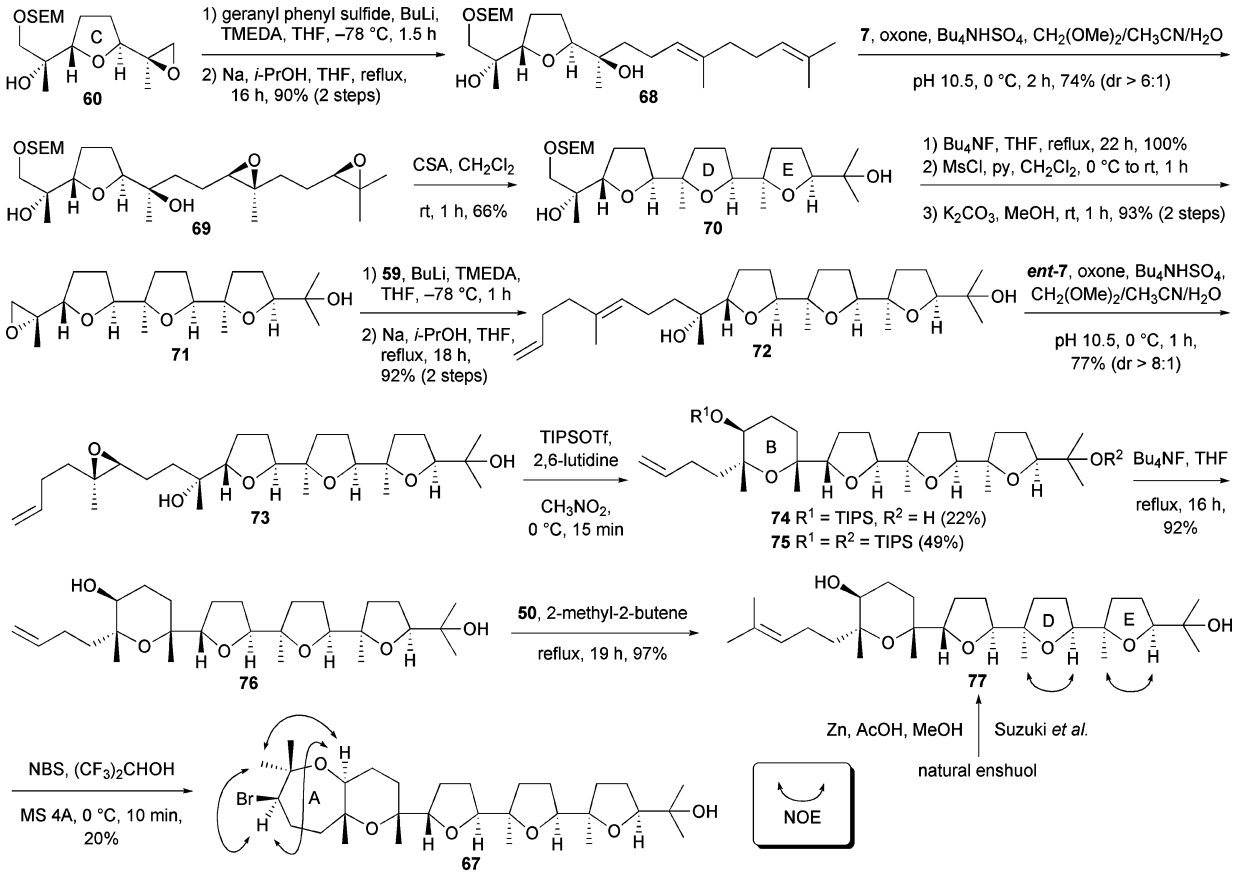
At this stage, the NMR spectroscopic data obtained (in $CDCl_3$) for the synthetic C,D,E ring system **66** were compared with those of natural enshuol (Scheme 13).[28] The $\Delta\delta$ values denote differences in the chemical shifts observed for the synthetic and natural compounds. The chemical shifts for the synthetic material are given in boldface for hydrogen atoms when $|\Delta\delta| > 0.03$ ppm and for carbon atoms when $|\Delta\delta| > 0.4$ ppm, except in the case of methylene carbon and hydrogen atoms. Upon comparison of the data, we felt, from experience in our laboratory,[3,6] that the *trans*,*trans*,*trans* configuration proposed in **56** for the three contiguous THF rings of enshuol might be incorrect. We have previously completed total syntheses of glabrescol[3] and aurilol,[6e] the structures of which are closely related to that of enshuol. When we compared the NMR spectroscopic data that we had obtained for glabrescol and aurilol with those of natural enshuol, we found that the data for half of C_2-symmetric glabrescol and the left-hand side of aurilol (see structures in Scheme 13) are almost coincident with those for the right and left halves of natural enshuol, respectively, as shown by the presence of a single bold $|\Delta\delta|$ value for each substructure and spectrum. Thus, a hybrid stereostructure **67** of glabrescol and aurilol became our next target.

The addition of a geranyl side chain to the epoxide **60** and subsequent Shi asymmetric epoxidation of the resulting diene **68** catalyzed by **7** provided the diepoxyalcohol **69** (Scheme 14). The tandem oxacyclization of **69** with CSA gave the desired tricyclic ring system **70**. Cleavage of the SEM ether in **70**, conversion of the resulting vicinal diol into an epoxide and the introduction of the diene side chain with the sulfide **59**[6e] yielded the bishomoallylic alcohol **72**. Shi asymmetric epoxidation of the diene **72** proceeded in a regioselective manner to provide the monoepoxide **73** with the terminal alkene intact. A 6-*endo*-tet cyclization to form the B ring occurred regioselectively upon treatment of the bishomoepoxy alcohol **73** with TIPSOTf and 2,6-lutidine in nitromethane at 0 °C for 15 min[17b] to afford the mono- and bis(TIPS ether)s **74** and **75**, respectively, in a total yield of 71%.

After the removal of the silyl ethers in **74** and **75**, cross metathesis of the olefin **76** with 2-methyl-2-butene in the presence of the Grubbs second-generation catalyst **50** provided the trisubstituted alkene **77** in 97% yield.[29] Fortunately, the ^1H and ^{13}C NMR spectral characteristics of the synthetic compound **77** with the *cis*,*cis* configuration within the D,E THF rings were consistent with those reported for the compound derived from natural enshuol by opening of the A ring.[28] Finally, 7-*endo*-trig bromoetherification of the trishomoallylic alcohol **77** with NBS in 1,1,1,3,3,3-hexafluoro-2-propanol[30] gave the target molecule **67**. The ^1H and ^{13}C NMR spectra of the synthetic compound **67**, $[a]_D^{28}$ +21.2 (*c* 0.04, $CHCl_3$), were identical to those of the natural product, $[a]_D^{22}$ +22.7 (*c* 1.00, $CHCl_3$).[28] Thus, the entire configuration of (+)-enshuol is shown by the structural formula **67**, as predicted from our NMR spectroscopic data.[6h]



Scheme 13 Comparison of the NMR spectroscopic data of our synthetic compounds with those of natural enshuol.



Scheme 14 Total synthesis of (+)-enshuol **67**.

Conclusions

The stereostructures of (−)-epoxy tri-THF diol and (+)-enshuol were predicted from NMR spectroscopic data of previously synthesized intermediate **4** and natural products glabrescol **1** and aurilol, and confirmed to be those depicted by structures **5** and **67**, respectively, through their first asymmetric total syntheses (Schemes 3 and 14). In the case of (+)-intricatetraol **16**, biogenetic considerations led to the prediction of the correct stereostructure; however, the postulate that the biogenesis of enshuol occurs *via* a common tetraepoxide intermediate **13** did not (Scheme 10). This example illustrates the important role of chemical synthesis in combination with spectroscopic methods and biogenetic considerations in the modern structure elucidation of complex and diverse natural products.

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