

Assignment of the Absolute Configuration of the Marine Pentacyclic Polyether (+)-Enshuol by Total Synthesis**

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Enshuol (**1**), a member of a family of squalene-derived triterpene polyethers named oxasqualenoids,^[1] was isolated from the red alga *Laurencia omaezakiana* Masuda sp. by Suzuki and co-workers in 1995.^[2] Although the planar structure and partial configuration of **1** were elucidated by spectroscopic and chemical analysis, until now the entire configuration had not been determined. Many other types of oxasqualenoids have been isolated;^[1] however, 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 as C10–C11, C14–C15, and C18–C19 in **1**. Such systems expose the technical limitations of the current highly advanced NMR spectroscopic methods used for the structural elucidation of diverse and complex natural products.^[3] Such difficulties coupled with the unique structures of the oxasqualenoids have prompted synthetic organic chemists to determine the stereostructures of these natural products by chemical synthesis.^[4] Herein, we report the total assignment of the previously incomplete stereostructure of (+)-enshuol (see structure **22**) through the first asymmetric total synthesis of (+)-enshuol, the configuration of which is difficult to determine by other means.

Recently, we reported the assignment of the absolute configuration of (+)-intricatetraol (**6**) by chemical synthesis.^[4h,5] Biogenetic considerations led Suzuki et al. to suggest structure **5** for (+)-intricatetraol (Scheme 1).^[6] Therefore, in this case, on the basis of the proposed biogenesis of **1**, we chose compound **9** as the synthetic target. Too many stereostructures were possible for **1** if NMR spectroscopic data alone was considered. Suzuki and co-workers also suggested structure **9** to be the correct stereostructure of (+)-enshuol, again on the basis of the hypothetical biogenetic pathway.

Our retrosynthetic analysis of the target molecule **9** is shown in Scheme 2. We planned to construct the A ring by 7-*endo*-trig bromoetherification of the corresponding precursor **10**. The B, D, and E rings would be formed by 6-*endo*-tet or 5-*exo*-tet epoxide opening of the corresponding bishomoepoxy alcohols.^[7] The required carbon framework (see **11**) could be assembled in a convergent manner from suitable building blocks.

We began our synthesis with the chain extension of the known chiral epoxide **14**^[4g] by using a lithio derivative of the chiral allylic sulfide **12**.^[4d] The acetone **15**^[8] was obtained after desulfurization of the resulting sulfide (Scheme 3). Deprotection of the acetone in **15** and epoxide formation from the vicinal diol^[9] to give **17**, followed by Shi asymmetric epoxidation^[10] of the alkene, furnished the diepoxy alcohol **19**. The treatment of **19** with ($\pm$)-10-camphorsulfonic acid (CSA) in dichloromethane led to a regioselective 5-*exo*-tet tandem oxacyclization^[7] to afford the tricyclic system of adjacent tetrahydrofuran rings **20**, which was deprotected to give the triol **21**.

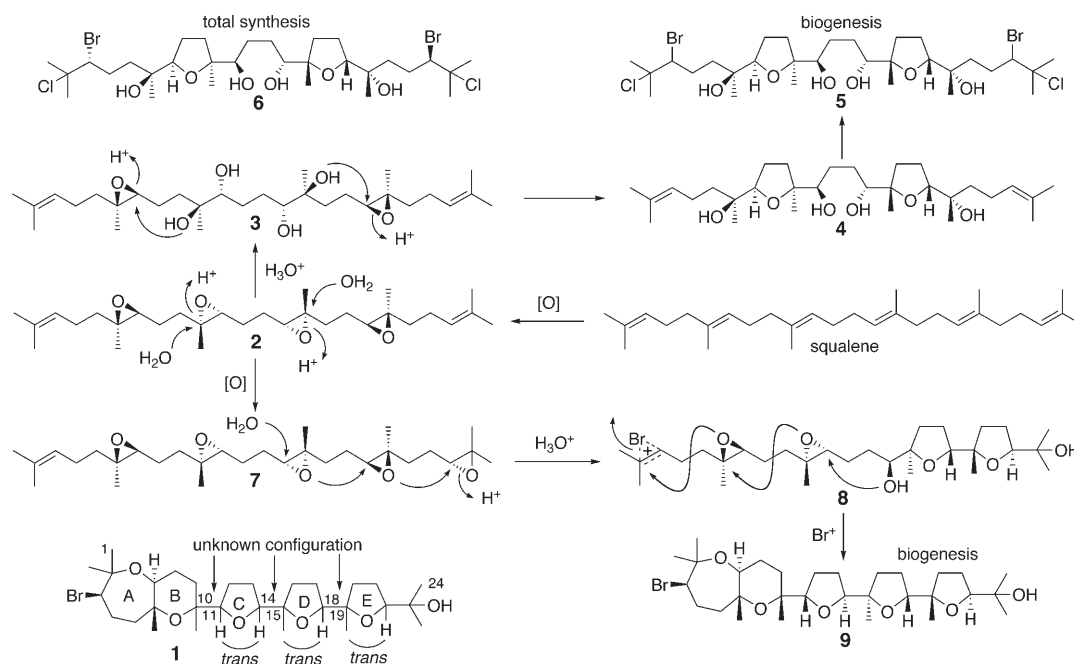
At this stage, the NMR spectroscopic data obtained (in CDCl₃) for the synthetic C,D,E ring system **21** were compared with those of natural enshuol (Scheme 4).^[2] The $\Delta\delta$ values denote differences in the chemical shifts observed for the synthetic and natural compounds. The chemical shifts for the synthetic material are given in red 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,^[4,5] that the *trans,trans,trans* configuration proposed in **9** for the three contiguous tetrahydrofuran rings of enshuol might be incorrect. We have previously completed total syntheses of glabrescol^[4b] and aurilol,^[4g] 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 C₂-symmetric glabrescol and the left-hand side of aurilol (see structures in Scheme 4) are almost coincident with those for the right and left halves of natural enshuol, respectively, as shown by the presence of a single red $|\Delta\delta|$ value for each substructure and spectrum. Thus, a hybrid stereostructure **22** of glabrescol and aurilol became our next target.

The addition of a geranyl side chain to the epoxide **14** and subsequent Shi asymmetric epoxidation of the resulting diene **23** catalyzed by *ent*-**18**, the enantiomer of **18**, provided the diepoxy alcohol **24** (Scheme 5). The tandem oxacyclization of **24** with CSA gave the desired tricyclic ring system **25**. Cleavage of the SEM ether in **25**, conversion of the resulting vicinal diol into an epoxide, and the introduction of the diene

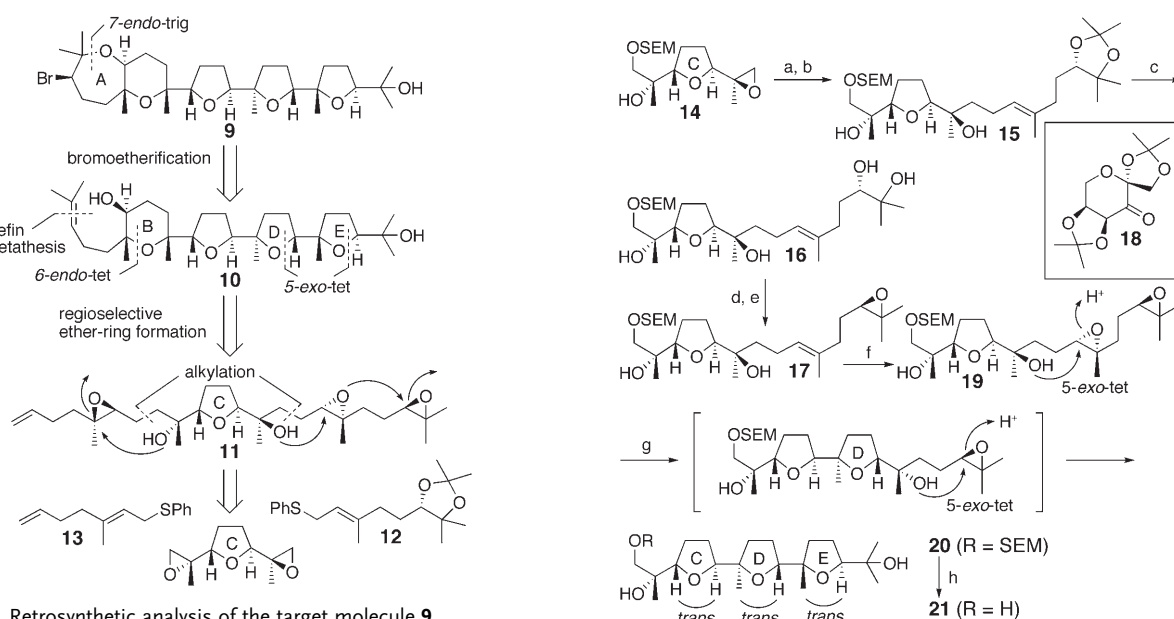
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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 1. Possible biogenesis proposed by Suzuki and co-workers for intricatetraol (5) and enshuol (9).



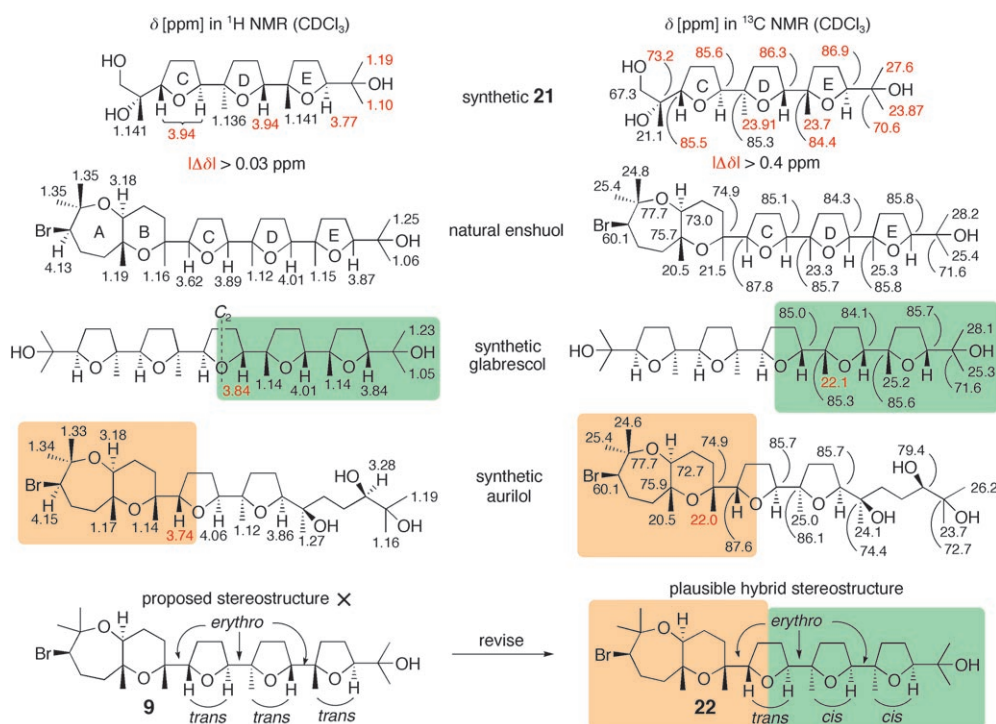
Scheme 2. Retrosynthetic analysis of the target molecule 9.

side chain with the sulfide **13**^[4g] yielded the bishomoallylic alcohol **27**. Shi asymmetric epoxidation of the diene **27** proceeded in a regioselective manner to provide the mono-epoxide **28** with the terminal alkene intact. A 6-*endo*-tet cyclization to form the B ring occurred regioselectively upon treatment of the bishomoepoxy alcohol **28** with triisopropylsilyl triflate (TIPSOTf) and 2,6-lutidine in nitromethane at 0°C for 15 min^[7a] to afford the mono- and bis(triisopropylsilyl ether)s **29** and **30**, respectively, in a total yield of 71%.

After the removal of the silyl ethers in **29** and **30**, cross-metathesis of the olefin **31** with 2-methyl-2-butene in the presence of the Grubbs second-generation catalyst **32** pro-

Scheme 3. Reagents and conditions: a) **12**, BuLi, TMEDA, THF, −78°C, 1 h; b) Na, *i*PrOH, THF, reflux, 14 h, 73% (2 steps); c) aq AcOH (80%), RT, 16 h, 100%; d) MsCl, pyridine, CH₂Cl₂, 0°C→RT, 2 h; e) K₂CO₃, MeOH, RT, 40 min, 67% (2 steps); f) **18**, oxone, Bu₄NHSO₄, CH₂(OMe)₂/CH₃CN/H₂O, pH 10.5, 0°C, 2.5 h, 97% (d.r. > 6:1); g) CSA, CH₂Cl₂, RT, 1 h, 53%; h) Bu₄NF, THF, reflux, 18 h, 88%. Ms = methanesulfonyl, SEM = 2-(trimethylsilyl)ethoxymethyl, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

vided the trisubstituted alkene **33** in 97% yield.^[11] Fortunately, the ¹H and ¹³C NMR spectral characteristics of the synthetic compound **33** with the *cis,cis* configuration within the D,E tetrahydrofuran rings were consistent with those reported for the compound derived from natural ensuol by



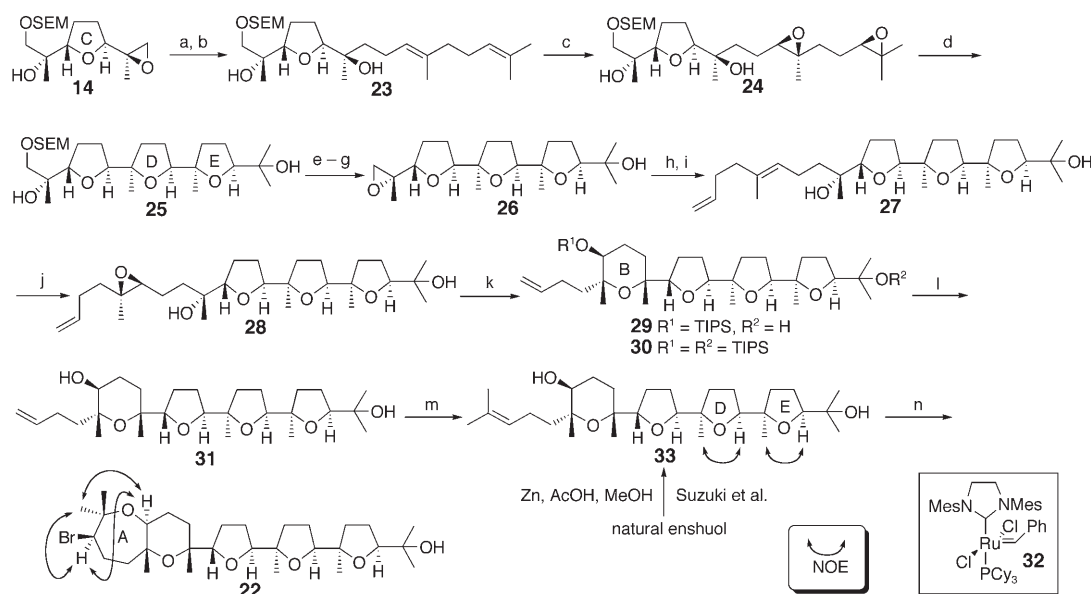
Scheme 4. Comparison of the NMR spectroscopic data of our synthetic compounds with those of natural enshuol.

opening of the A ring.^[2] Finally, 7-*endo*-trig bromoetherification of the trishomoallylic alcohol **33** with *N*-bromosuccinimide (NBS) in 1,1,1,3,3,3-hexafluoro-2-propanol^[12] gave the target molecule **22**.^[13] The ^1H and ^{13}C NMR spectra of the

enshuol occurs via a common tetraepoxide intermediate **2** did not. This example illustrates the important role of chemical synthesis in combination with spectroscopic methods and biogenetic considerations in the structure elucidation of

synthetic compound **22** ($[\alpha]_{\text{D}}^{28} = +21.2$ ($c = 0.04$, CHCl_3)) were identical to those of the natural product ($[\alpha]_{\text{D}}^{22} = +22.7$ ($c = 1.00$, CHCl_3)).^[2] Thus, the entire configuration of (+)-enshuol is shown by the structural formula **22**, as predicted from our NMR spectroscopic data.

In conclusion, the absolute configuration of (+)-enshuol was predicted from NMR spectroscopic data of previously synthesized natural products and confirmed to be that depicted by structure **22** through the first asymmetric total synthesis of the pentacyclic polyether. In the case of intricatetraol (**5**), biogenetic considerations led to the prediction of the correct stereostructure; however, the postulate that the biogenesis of



Scheme 5. Reagents and conditions: a) geranyl phenyl sulfide, BuLi, TMEDA, THF, -78°C , 1.5 h; b) Na, *i*PrOH, THF, reflux, 16 h, 90% (2 steps); c) *ent*-**18**, oxone, Bu_4NHSO_4 , $\text{CH}_2(\text{OMe})_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 10.5, 0°C , 2 h, 74% (d.r. > 6:1); d) CSA, CH_2Cl_2 , RT, 1 h, 66%; e) Bu_4NF , THF, reflux, 22 h, 100%; f) MsCl, pyridine, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, 1 h; g) K_2CO_3 , MeOH, RT, 1 h, 93% (2 steps); h) **13**, BuLi, TMEDA, THF, -78°C , 1 h; i) Na, *i*PrOH, THF, reflux, 18 h, 92% (2 steps); j) **18**, oxone, Bu_4NHSO_4 , $\text{CH}_2(\text{OMe})_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 10.5, 0°C , 1 h, 77% (d.r. > 8:1); k) TIPSOTf, 2,6-lutidine, CH_3NO_2 , 0°C , 15 min, **29**: 22%, **30**: 49%; l) Bu_4NF , THF, reflux, 16 h, 92%; m) **32**, 2-methyl-2-butene, reflux, 19 h, 97%; n) NBS, $(\text{CF}_3)_2\text{CHOH}$, 4-Å molecular sieves, 0°C , 10 min, 20%. Cy = cyclohexyl, Mes = mesityl.

diverse and complex natural products.^[3] Further structural elucidation by chemical synthesis is in progress.

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