Natural Products Synthesis

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Total Synthesis and Determination of the Absolute Configuration of (+)-Intricatetraol**

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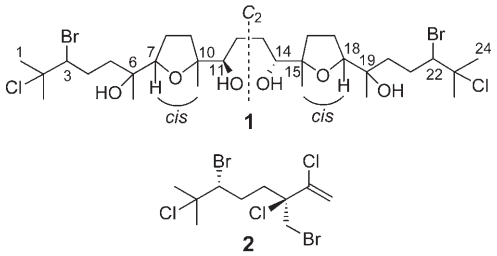
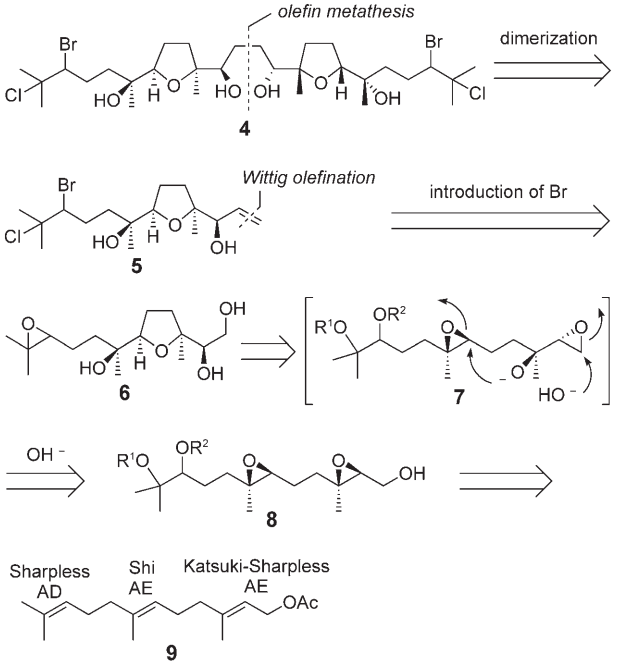
Intricatetraol (**1**), a member of a family of squalene-derived triterpene polyethers named oxasqualenoids,[1] was isolated



from the red alga *Laurencia intricata* by Suzuki et al. in 1993. A crude fraction containing intricatetraol (**1**) as the major component exhibited cytotoxic activity against P388 "leukemia cells" with an IC_{50} value of 12.5 $\mu g\,mL^{-1}$.[2] The structural analysis was mainly carried out by NMR spectroscopic methods. Although it was found that the molecule has C_2 symmetry, the *cis* configuration within the tetrahydrofuran ring, the *R* configuration at C11 (C14), the relative configurations at C6 and C7 (C18 and C19), C10 and C11 (C14 and C15), and at bromine-bonded C3 (C22) remained to be determined.

There are many other types of oxasqualenoids; however, it is often difficult to determine their configurations even by highly advanced spectroscopic methods, especially for the acyclic portions that include stereogenic quaternary carbon centers, such as C6–C7 (C18–C19) and C10–C11 (C14–C15) in **1**. These difficulties have prompted attempts to determine the configurations of oxasqualenoids by chemical synthesis.[3] Furthermore, the presence of the vicinal bromochloro functionality in **1** makes the problem of stereochemical assignment even more inaccessible. An enantioselective method for the synthesis of the vicinal bromochloro functionality,[4] which also occurs in the marine polyhalogenated monoterpene halomon (**2**), a promising anticancer agent,[5] has never been developed. Herein we report the total assignment of the configuration of (+)-intricatetraol (**1**) as **3** through the first asymmetric total synthesis of this natural product. The synthesis features the enantioselective construction of the vicinal bromochloro functionality through a pathway in which the configuration is secured.

Suzuki et al. suggested structure **4**, which disregards the configuration at C3 (C22), as a possibility on the basis of the hypothetical biogenesis,[2] and recently we[6] and Ujihara[7] independently confirmed this assignment. Our retrosynthetic analysis of the target compound **4** is depicted in Scheme 1. We envisaged that it would be efficient to dimerize by olefin metathesis the functionalized fragment **5**, 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 **5** could be introduced through epoxide chemistry. The desired trihydroxytetrahydrofuran **6** might be constructed by the stereospecific and stereoselective oxacyc-



Scheme 1. Retrosynthetic analysis of the target compound **4**. AD = asymmetric dihydroxylation, AE = asymmetric epoxidation.

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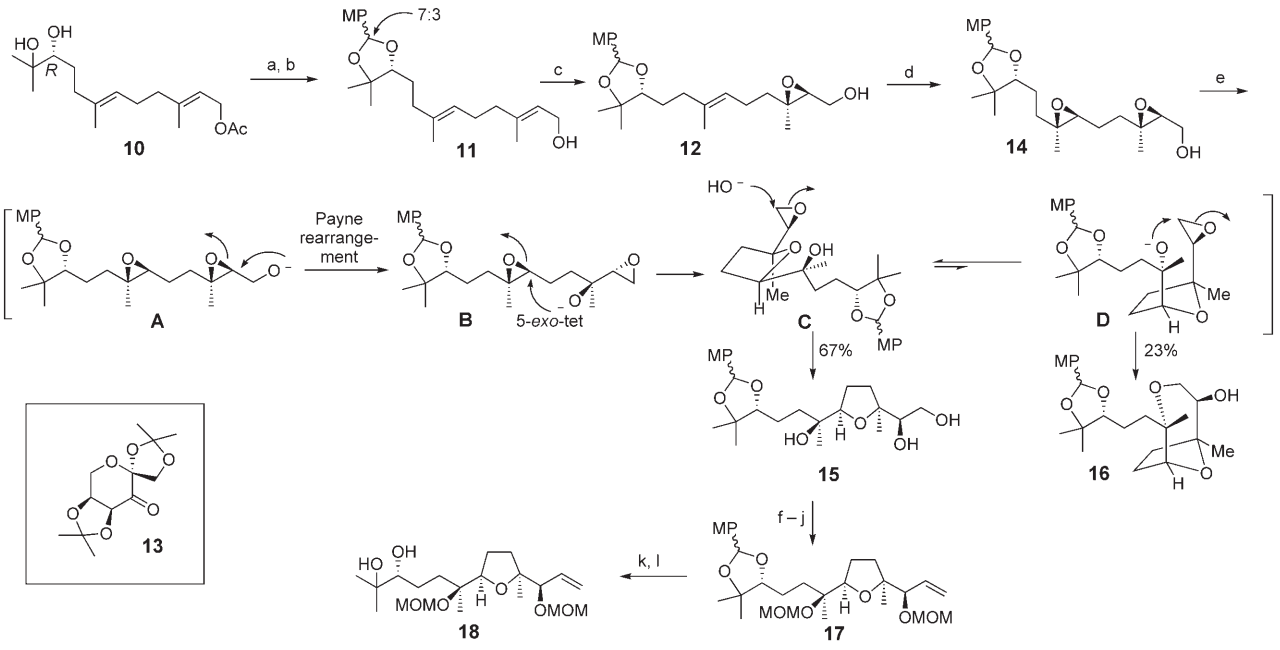
lization of the diepoxyalcohol **8** under alkaline conditions.[8] The required stereocenters in **8** would be introduced into commercially available *trans,trans*-farnesyl acetate (**9**) by established methods of asymmetric oxidation.

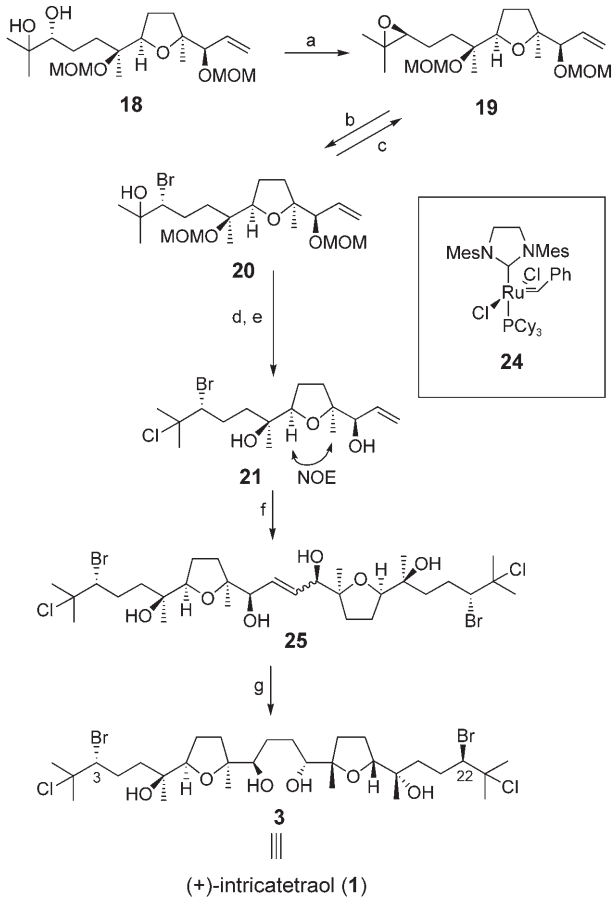
The protection of the chiral diol **10** (>95% *ee*)[9] as a *p*-methoxybenzylidene acetal (7:3 mixture) and subsequent deacetylation afforded the allylic alcohol **11**[10] (Scheme 2). Katsuki–Sharpless asymmetric epoxidation of **11** in the presence of (+)-diethyl L-tartrate (L-(+)-DET) provided the epoxyalcohol **12**. Asymmetric epoxidation of the alkene **12** by the method of Shi and co-workers[11] with ketone **13** as the chiral catalyst then gave the diepoxyalcohol **14**. Treatment of the diepoxyalcohol **14** with 1M aqueous solution of lithium hydroxide and 1,4-dioxane (1:1) under reflux furnished the desired trihydroxytetrahydrofuran product **15** with high stereospecificity. It was thought from our previous studies[3g,8] 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 in the more stable conformer **C**. In this reaction, the bicyclic ether **16** was also formed as a by-product. Compound **16** could be generated from the less stable conformer **D** by an intramolecular attack of the tertiary alkoxide on the epoxide ring. Selective *tert*-butyldimethylsilyl (TBDMS) protection of the primary hydroxy group in the triol **15**, methoxymethyl (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 **17** in good overall yield. Oxidation of the *p*-methoxybenzylidene acetal **17** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [12] provided a 3:7 mixture of regioisomeric benzoate esters, which upon reduction with lithium aluminum hydride gave the deprotected diol **18**.

Selective mesylation of the secondary hydroxy group in the diol **18** followed by treatment of the mesylate with potassium carbonate yielded the epoxide **19** (Scheme 3).[13] The epoxide-opening reaction of **19** with dilithium tetrabromonickelate in THF proceeded regioselectively to produce the secondary bromide **20** with inversion of configuration at the less hindered carbon atom.[14] It has been reported that dilithium tetrabromonickelate reacts with epoxides through an S_N2 mechanism. We confirmed that the bromohydrin **20** is reconverted into the starting epoxide **19** upon treatment with a base. Chlorination[15] of the bromohydrin **20** and subsequent deprotection of the alcohols protected as MOM ethers afforded the fully functionalized half fragment **21** with a *cis* tetrahydrofuran ring, as confirmed by the observation of an NOE between the hydrogen atoms indicated in structure **21**.

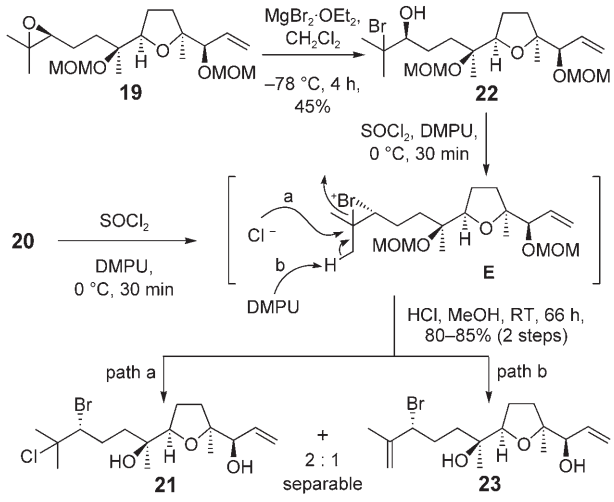
In the chlorination of bromohydrin **20** with thionyl chloride in DMPU, the major (chlorination) and minor (dehydration) products **21** and **23** were formed in a 2:1 ratio (Scheme 4). We also prepared the regioisomeric bromohydrin **22** by treating the epoxide **19** with magnesium bromide etherate.[16] When the bromohydrin **22** was subjected to the same chlorination conditions, products **21** and **23** were formed in almost the same ratio as in the reaction of **20**. Therefore, it seems that the chlorination proceeds via a common bromonium-ion intermediate **E**, as described previously for a similar chlorination by Mioskowski and co-workers.[4a]



Scheme 2. Reagents and conditions: a) *p*-$MeOC_6H_4CH(OMe)_2$, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 0°C→RT, 16 h; b) K_2CO_3, MeOH, RT, 7 h, 99% (2 steps); c) *t*BuOOH, $Ti(OiPr)_4$, L-(+)-DET, M.S. (4 Å), CH_2Cl_2, −20°C, 21 h, 95% (d.r. > 20:1); d) **13**, oxone, Bu_4NHSO_4, $CH_2(OMe)_2$/CH_3CN/H_2O, pH 10.5, 0°C, 2.5 h, 87% (d.r. > 6:1); e) aq. LiOH (1M), 1,4-dioxane, 100°C, 7 h; f) TBDMSCl, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, RT, 26 h, 96%; g) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 0°C→RT, 36 h, 96%; h) Bu_4NF, THF, 0°C→RT, 15 h, 100%; i) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0°C, 30 min, 100%; j) $Ph_3P{=}CH_2$, THF, 0°C, 1 h, 90%; k) DDQ, H_2O, CH_2Cl_2, RT, 2 h; l) $LiAlH_4$, THF, 0°C, 1.5 h, 96% (2 steps). DMSO = dimethyl sulfoxide, MP = *p*-methoxyphenyl.



Scheme 3. Reagents and conditions: a) methanesulfonyl chloride, pyridine, CH_2Cl_2, 0 °C→RT, 14 h; then K_2CO_3, MeOH, RT, 3 h, 90%; b) $Li_2[NiBr_4]$, THF, RT, 56 h, 76%; c) K_2CO_3, MeOH, RT, 1 h, 92%; d) $SOCl_2$, DMPU, 0 °C, 30 min; e) HCl, MeOH, RT, 66 h, 55% (2 steps); f) **24**, CH_2Cl_2, 40 °C, 7 h, 86%; g) $(KOCON)_2$, AcOH, MeOH, RT, 70 h, 56%. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone.



Scheme 4. Possible mechanism for the chlorination of bromohydrins **20** and **22**.

The dimerization of fragment **21** was carried out in 86% yield by olefin metathesis with the Grubbs second-generation catalyst **24** (Scheme 3; Cy = cyclohexyl).[17] Although catalytic hydrogenation of the alkene **25** under standard conditions afforded the dehalogenated product by overreduction, diimide reduction[18] provided the target compound **3** without dehalogenation. The respective spectra of the synthetic compound **3** ($[\alpha]_D^{23} = +51.3$ ($c = 0.41$, $CHCl_3$)), prepared from the *R* alcohol **10**, were identical to those of the natural product ($[\alpha]_D^{20} = +53.0$ ($c = 0.625$, $CHCl_3$)).[2,6,7] Thus, it was found that the hitherto unknown absolute configuration of (+)-intricatetraol (**1**) is shown by the structural formula **3**.[19]

In conclusion, we have completed the first asymmetric total synthesis of the marine bromochloro-functionalized triterpene polyether (+)-intricatetraol (**1**). Our synthesis features the enantioselective construction of the unique vicinal bromochloro functionality in an approach that may be applied to the synthesis of other bromochloro compounds, such as halomon (**2**), and an efficient olefin-metathesis strategy that takes the intrinsic molecular symmetry of the natural product into consideration. The total synthesis resulted in the assignment of the absolute configuration of intricatetraol (**1**), which is difficult to determine by other means. Further contributions to structure elucidation by organic synthesis are in progress.

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