Two-directional synthesis and stereochemical assignment toward a C_2 symmetric oxasqualenoid (+)-intricatetraol†

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The asymmetric synthesis of tetraol (+)-3, a degradation product derived from a C_2 symmetric oxasqualenoid intricatetraol 1, has been achieved through the two-directional synthesis starting from diol 7, realizing the further additional assignment of the incomplete stereostructure of 1, the stereochemistry of which is difficult to determine otherwise.

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.[1] Among them was intricatetraol **1** isolated from the red alga *Laurencia intricata* by Suzuki *et al.* in 1993, and a crude fraction including intricatetraol **1** as the major component exhibited cytotoxic activity against P388 with an IC_{50} of 12.5 μg mL^{-1}.[2] The structural analysis was mainly carried out by NMR 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 (Fig. 1). There have also been many other types of oxasqualenoids; 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 such as C6–C7 (C18–C19) and C10–C11 (C14–C15) in **1**. These contexts have prompted synthetic organic chemists to determine the stereostructures of oxasqualenoids by chemical synthesis.[3] Suzuki *et al.* have suggested a stereostructure **2** except for the C3 (C22) position as the possible one based on the hypothetical biogenesis.[2] In this paper, we report that the possible stereostructure **2** proposed for intricatetraol **1** is correct through the two-directional synthesis of the degradation product (+)-**3** derived from the natural product **1**.

The retrosynthetic analysis of the possible stereostructure **2** for (+)-intricatetraol is depicted in Scheme 1. It was envisioned that a two-directional synthetic strategy[4] could be efficient to synthesize the C_2 symmetric molecule **2**. The vicinal bromochloro functionality might be introduced by manipulation of the alkene in **3**, where the THF ring would be constructed in a two-directional manner through a Shi asymmetric epoxidation[5] of bishomoallylic alcohol **4** followed by the 5-*exo*-tet epoxide-opening reaction.[6] The

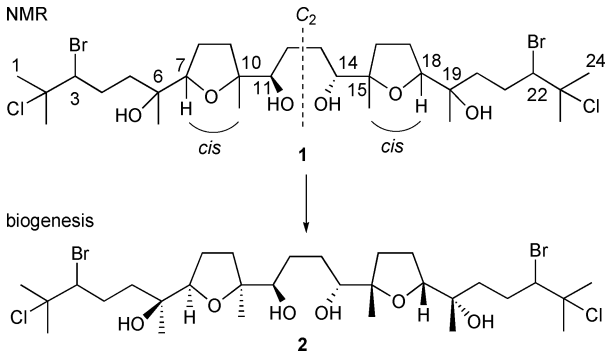
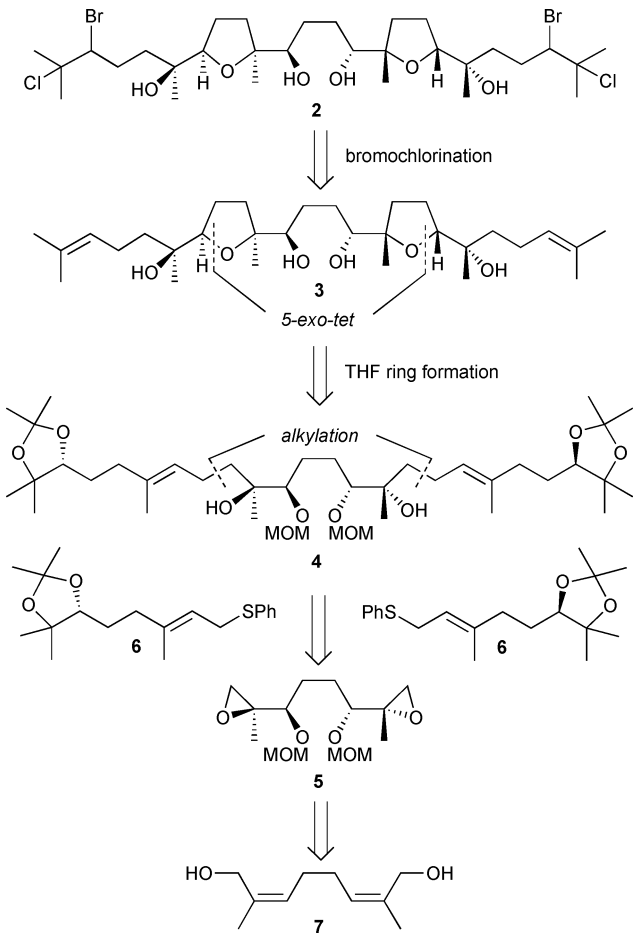


Fig. 1 Stereostructures **1** and **2** of intricatetraol based on NMR data and biogenesis.



Scheme 1 Retrosynthetic analysis of possible stereostructure **2**.

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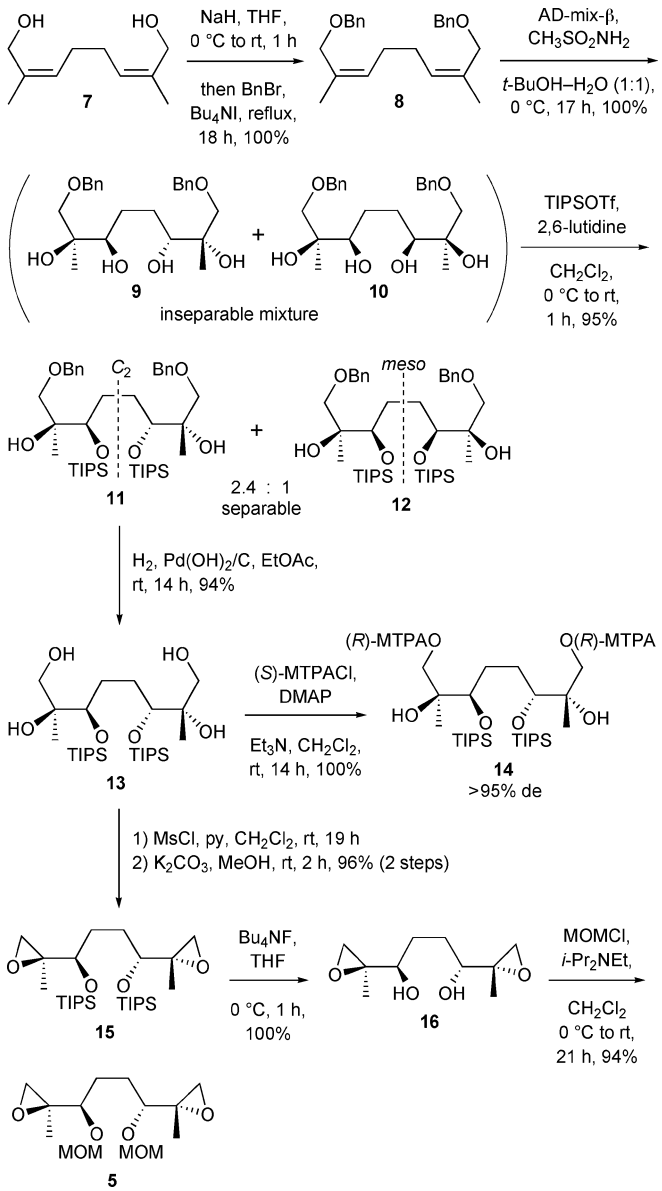
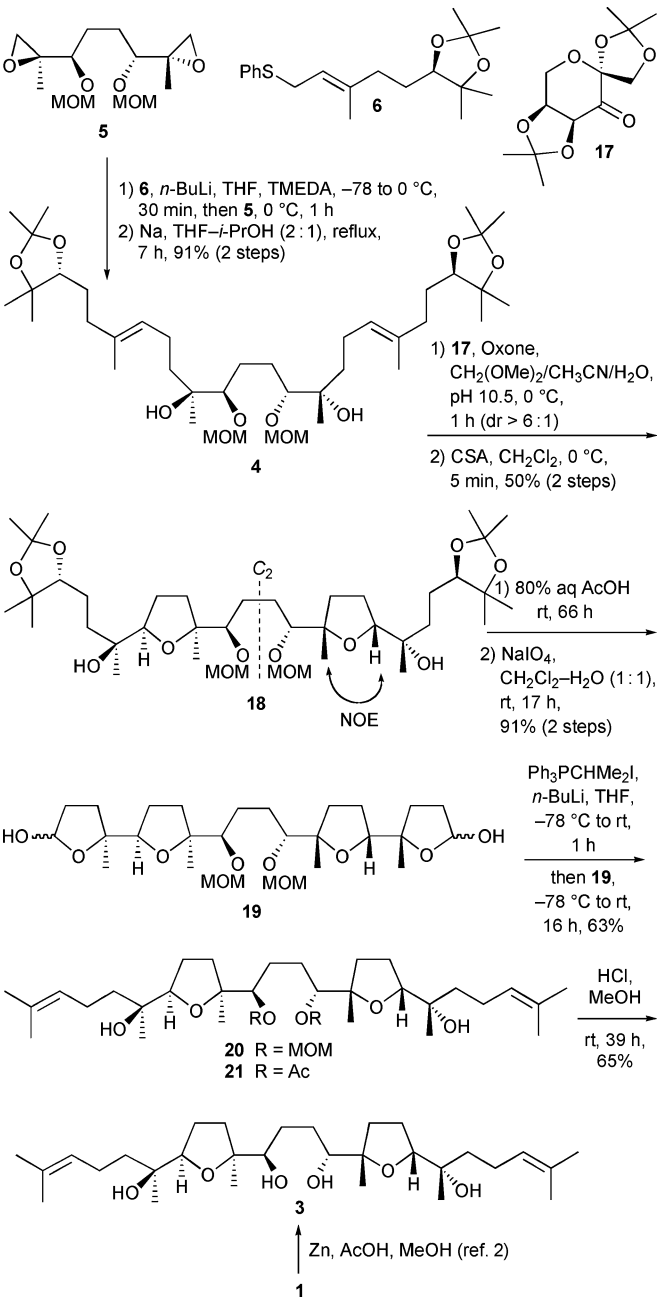
diol **4** would, in turn, be derived from diepoxide **5** by extending both side chains with the C_{10} unit **6**, still in the two-directional mode. Thus, we planned to prepare the C_2 symmetric chiral diepoxide **5** from the readily available diol **7** *via* the established Sharpless asymmetric dihydroxylation.[7]

Preparation of the diepoxide **5** began with protection of the known diol **7** [3b] as a benzyl ether (Scheme 2). Sharpless asymmetric dihydroxylation of the diene **8** using AD-mix-β[7] 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 **11** and **12** in 67 and 28% yields, respectively, after column chromatography on silica gel. Both symmetric diols **11** ‡ and **12** were assigned to C_2 and *meso* isomers, respectively, by their optical rotations, **11**: $[\alpha]_D^{26}$ +4.8 (*c* 1.03, $CHCl_3$); **12**: $[\alpha]_D^{22}$ 0 (*c* 0.95, $CHCl_3$). Deprotection of the benzyl ether in the desirable major diol **11**, mesylation of both primary hydroxy groups in the resulting tetraol **13**, and subsequent basic treatment of the dimesylate gave diepoxide **15** in good overall yield. Replacement of the bulky TIPS ether in **15** with a relatively small MOM ether yielded the requisite diepoxide **5**.§

The lithiation of the known allylic sulfide **6** [3f] and alkylation of the lithio derivative with the diepoxide **5** were carried out in the presence of TMEDA, and the resulting disulfide as a mixture of diastereomeric sulfides was desulfurized under Bouvault–Blanc conditions[8] to yield the expected diol **4** (Scheme 3). Shi asymmetric epoxidation of the bishomoallylic alcohol **4** catalyzed by chiral ketone **17** [5] followed by treating the resulting labile bishomoepoxy alcohol with (±)-10-camphorsulfonic acid (CSA)



Scheme 2 Two-directional synthesis of diepoxide **5**.



Scheme 3 Two-directional synthesis of tetraol **3**.

in dichloromethane brought about a regioselective 5-*exo*-tet oxacyclization[6b] to produce diol **18** in 50% yield over two steps. The C_2 symmetric structure and the *cis* stereochemistry of the THF ring in **18** ($C_{40}H_{74}O_{12}$) could be confirmed by the observation of only 20 signals in the ^{13}C NMR spectrum and NOE shown in **18**, respectively.

The remaining task is the generation of trisubstituted double bonds. Selective deprotection of the acetonide group in diol **18** and subsequent cleavage of the resultant vicinal diol with sodium metaperiodate afforded tetraTHF ether **19**, 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 **19** with an excess of isopropylidene triphenylphosphorane provided the desired diene **20** in 63% yield. Removal of the MOM protective group in the diene **20** furnished tetraol **3**. The spectral characteristics (^1H and ^{13}C NMR) of the synthetic **3**, $[\alpha]_D^{29}$ +11.5 (*c* 0.175, $CHCl_3$), were identical to those reported for the dehalogenated product **3**, $[\alpha]_D^{20}$ +13.6 (*c* 0.77, $CHCl_3$), derived from the natural intricatetraol **1** by Suzuki *et al*.[2] Thus, it has been found that the possible stereostructure **2** proposed for (+)-intricatetraol based on the hypothetical biogenesis is correct.¶

In conclusion, we have accomplished the asymmetric synthesis of tetraol (+)-**3**, a degradation product derived from the natural product, through a two-directional strategy that takes its intrinsic molecular symmetry into consideration. The synthesis has realized the further additional assignment of the incomplete stereostructure of intricatetraol **1**, the stereochemistry of which is difficult to determine otherwise. The total synthesis and complete assignment of the stereostructure of (+)-intricatetraol **2** are currently under investigation in our laboratory.

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Notes and references

‡ The optical purity of **11** was determined to be >95% ee by derivatization of debenzylated tetraol **13** to diMTPA ester **14** [MTPA = α-methoxy-α(trifluoromethyl)phenylacetyl] and integration of the signals in the ^1H NMR spectrum (J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543–2549).

§ The replacement of the protective group of the C11 and C14 hydroxy groups was necessary to bring about Shi epoxidation which is sensitive to steric factors in **4** – Shi epoxidation of **4** where it is protected by a bulky TIPS group instead of the MOM group resulted in no reaction. At the stage of tetraols after the Sharpless asymmetric dihydroxylation, we could not selectively protect the secondary hydroxy groups as MOM ethers.

¶ Independently of us, Dr K. Ujihara, Sumitomo Chemical, has also reported the same partial stereochemistry of (+)-intricatetraol as ours through the synthesis of diacetate **21** derived from the natural product (K. Ujihara, Ph.D. Thesis, The University of Tokyo, Tokyo, Japan, 2004).

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