Total Synthesis of Highly Symmetric Squalene-Derived Cytotoxic Polyethers
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Abstract: In this review article, we report our recent contributions to the total synthesis of the highly symmetric squalene-derived cytotoxic triterpene polyethers, teurilene (3), (+)-14-deacetyl eurylene (1), (+)-eurylene (4), (-)-glabrescol (5), and (-)-longilene peroxide (2), based on the concept of two-directional synthesis utilizing their intrinsic molecular symmetry as the fundamental strategy. In the course of these synthetic studies, syn oxidative cyclizations of bishomoallylic tertiary alcohols promoted by rhenium(VII) oxide have been accomplished with excellent diastereoselectivities. The critical trans or cis selectivity between the 2- and 5-positions of the tetrahydrofuran (THF) ring in the products has been observed, depending on the substrates employed. In addition, the meso structure 6 originally proposed by Jacobs et al. has been revised to the optically pure C2 symmetric structure 5 through its enantioselective total synthesis. Furthermore, the unknown absolute configuration of longilene peroxide has been determined by this synthesis as shown in the structural formula 2.

1. Introduction

Recently, biologically active and structurally unique triterpene polyethers with some THF rings, which are thought to be biogenetically squalene-derived natural products (oxasqualenoids), have been isolated from both marine and terrestrial plants. Among them, cytotoxic and highly symmetric molecules which have attracted our synthetic interest are shown in Fig. 1. Since teurilene (3), the first member of this family, was isolated from the red alga Laurencia obtusa by Kurosawa et al. in 1985,1 14-deacetyl eurylene (1), longilene peroxide (2), eurylene (4), and also teurilene (3) have been isolated from the wood of Eurycoma longifolia by Itokawa et al.2 In addition, pentaTHF polyether glabrescol was extracted from the branches and wood of Spathelia glabrescens (Rutaceae) by Jacobs et al., and the structure was originally proposed as C5 symmetric meso compound 6 by spectroscopic methods.3 The stereostructures and conformations of these polyethers have been elucidated by X-ray crystallographic analysis and spectroscopic methods. At that time, Itokawa et al. also proposed a very interesting relationship between the conformations and cytotoxicities of these polyethers 1-4: Compounds 1-3, which adopt the folded conformation, exhibit prominent cytotoxic activities on KB cells, whereas 4, possessing an extended conformation, does not (Table 1).2c Although there is no report on the biological activities of

<table>
<thead>
<tr>
<th>compound</th>
<th>IC50 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.52</td>
</tr>
<tr>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5</td>
<td>?</td>
</tr>
</tbody>
</table>

Table 1. Cytotoxic activities of 1-5 on KB cells

Figure 1. Conformation-cytotoxicity relationships of polyethers reported by Itokawa et al. and our hypothetical mechanism of action for their cytotoxicities.
glabrescol, this polyether containing five THF rings may be expected to exhibit cytotoxicity due to its folded conformation.

On the other hand, there are a variety of Annonaceous acetogenins structurally related to these polyethers, which possess a broad spectrum of important and potent biological activities. It has been suggested that the biological activities of neutral acetogenins involving oligoTHF rings might be attributed to their binding abilities with physiologically important divalent metal cations such as Ca$^{2+}$ and Mg$^{2+}$. Recent active research studies have reported such remarkable interactions (membrane transport and ion channel) of neutral oligotetrahydrofuranyl derivatives with metal cations in artificial systems as well as natural products. Similarly considering the natural polyethers 1–3 and 5 as conformationally pre-organized podand ionophores capable of complexing with physiologically important metal cations in biological systems, it has been hypothesized that such ionophoric interaction may be responsible for the occurrence of their cytotoxic activities (Fig. 1). The mechanism of action for the cytotoxic activities of these natural polyethers, however, remains to be clarified, because these molecules are available only in restricted amounts from natural sources. Therefore, the development of an efficient synthesis was desired for these polyethers. Thus, the structurally symmetric arrays and the biogenetically unique features coupled with their biological activities and ionophoric functions have promoted significant synthetic efforts for these polyethers. In this review, we report our recent contributions to the total synthesis of the highly symmetric squalene-derived cytotoxic triterpene polyethers, teurilene (3), 14-deacetyl eurylene (1), (+)-eurylene (4), (-)-glabrescol (5), and (-)-longilene peroxide (2), based on the concept of two-directional synthesis utilizing their intrinsic molecular symmetry as the fundamental strategy.

2. Highly Diastereoselective Cyclizations of Bishomoallylic Tertiary Alcohols Promoted by Rhenium(VII) Oxide

The first targets we chose out of the molecules shown in Fig. 1 are teurilene (3) and the structure 6 originally proposed for glabrescol. These unique polyethers 3 and 6 are achiral meso molecules due to $C_5$ symmetry despite possessing eight and ten asymmetric centers, respectively. In considering efficient synthesis of these polyethers, the stereoselective construction of the THF rings, especially of the 2,2,5-trisubstituted ones containing quaternary carbon centers, is the most important key event. Hydroxy-directed oxidative cyclizations of acyclic bishomoallylic alcohols promoted by a metal oxo species are a most efficient synthetic method of producing such THF skeletons (Scheme 1). It has been found that the vanadium(V)-catalyzed anti oxidative cyclizations of bishomoallylic tertiary alcohols such as the type 7 predominantly give cis-anti THF ring 10 via the alkoxyvanadium intermediate 8 and the epoxy alcohol 9. On the other hand, Kennedy and McDonald have pioneered diastereoselective methods for construction of these THF skeletons by means of syn oxidative cyclizations of bishomoallylic alcohols by rhenium(VII) oxide. The origin of high trans-syn diastereoselectivity in the reaction has been explained by steric (nonbonding) interaction in the alkoxyrhenium intermediate.

Our retrosynthetic analysis of both meso polyethers 3 and 6 takes their symmetry into consideration (Scheme 2). Except for the central cis 2,5-disubstituted THF ring common to these polyethers, the relative stereochemistry of both side THF rings, including the neighboring stereogenic centers, is trans-syn in the case of teurilene (3) and cis-anti in the proposed structure 6 of glabrescol. Therefore, if the Re(VII)-induced oxidative cyclizations of meso bishomoallylic diol 14 proceed in a two-directional manner, teurilene (3) will be produced in the trans-syn diastereoselectivity. Moreover, if the V(V)-catalyzed oxidative cyclizations of meso bishomoallylic diol 15 proceed in a two-directional and sequential mode, the proposed structure 6 of glabrescol will be produced in a single step with the cis-anti diastereoselectivity. The meso bishomoallylic diols 14 and 15 will be, in turn, constructed from the known meso tetraol 16 by extending both side chains with double neryl and geranyl units, respectively, still in the two-directional mode.

First, we attempted to find the reaction conditions compatible with tertiary alcohols using (CF$_3$CO$_2$)ReO$_3$ as rhenium(VII) oxide in the presence or absence of some additives in CH$_2$Cl$_2$ at various temperatures (Table 2), because the...
applicable substrates in the oxidative cyclizations by Re(VII) were limited to primary and secondary alcohols.\textsuperscript{17,18,19} Although treatment of 17 with an excess of Re(VII) oxide in the presence of 2,6-lutidine (2,6-Lu), reported as a standard additive,\textsuperscript{17c} at room temperature or 0°C afforded syn oxidative cyclization product 18, albeit in very low yields, the major product was dehydration compound 19 in contrast to primary and secondary alcohols (entries 1 and 2). The reaction did not proceed at 78°C (entry 3), and although the dehydration was inhibited at −45°C, most of the starting material 17 was recovered (entry 4). Because we thought 2,6-Lu as a base might be implicated in the dehydration of 17, in the absence of 2,6-Lu, the reaction was performed to give the desired 18 in reasonable yield (entry 5). Furthermore, it has also been found that trifluoroacetic anhydride (TFAA)\textsuperscript{17,19} accelerates the oxidative cyclization approximately five times that in the absence of TFAA (entry 6). An excess of the rhenium reagent was, however, essential to completely consume the starting material at a practical reaction rate (entry 7).

Since the optimal reaction conditions applicable to tertiary alcohols have been developed, various substrates such as 20 and 21 (R = Me, Et, i-Pr)\textsuperscript{15} were subjected to the syn oxidative cyclization promoted by Re(VII) oxide (Table 3). The reaction of geometric isomers 20 and 21 (R = Me)\textsuperscript{17c} stereospecifically proceeded to provide syn oxidative cyclization products 22 and 24 (R = Me), respectively, in good yields (entries 1 and 2). To evaluate the diastereoselectivity between 2- and 5-positions in the THF ring, substrates 20 and 21 (R = Me) were examined next. When R = Et, trans isomers 22 and 24 were obtained as a major product with modest diastereoselectivity of trans:cis = 4:1 (entries 3 and 4). When R = i-Pr, complete trans selectivity (trans:cis = >99:1) was observed (entries 5 and 6).

Table 2. Exploration of the reaction conditions compatible with tertiary alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Re(VII) (equiv)</th>
<th>additive</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>product (% yield)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2,6-Lu</td>
<td>78</td>
<td>1</td>
<td>18 (85.2) + 19 (18)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2,6-Lu</td>
<td>78</td>
<td>1</td>
<td>18 (85.5) + 19 (18)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2,6-Lu</td>
<td>78</td>
<td>1</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2,6-Lu</td>
<td>45</td>
<td>10</td>
<td>18 (71) + 17 (75)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2,6-Lu</td>
<td>45</td>
<td>8</td>
<td>18 (76)</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>TFAA</td>
<td>45</td>
<td>1.5</td>
<td>18 (66)</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>TFAA</td>
<td>45</td>
<td>8</td>
<td>18 (66) + 17 (40)</td>
</tr>
</tbody>
</table>

The critical results might be rationalized as follows. The formation of trans THFs from rhenium(VII)-promoted oxidative cyclizations in Table 3 is consistent with a chair-like conformation of the allyloxyrhenium intermediate 32 in which the alkene and sterically large group RL are pseudoequatorially positioned (Fig. 2). In the transition states 31 and 33 leading to cis THF rings, stereically encumbered A-1'3-strain and 1,3-diaxial-like interaction, respectively, occur due to the bulky Rz and RL. Therefore, the transition state 32 without such a repulsive interaction becomes relatively more stable than 31 and 33. As exemplified by the A-values (kcal/mol).
substrates 22-25 were treated with (CF₃CO₂)ReO₃.2CH₃CN (4 equiv) and TFAA (4 equiv) in CH₂Cl₂ in the presence of activated MS 4A (300 wt %) at -45°C for 4-8 h under N₂ atmosphere. Isolated yield. trans Isomer could not be detected by ¹H NMR except for entry 6. d As a mixture of 4:1. e As a mixture of 2:1.

of the substituents RL (Me = 1.70 < Et = 1.75 << i-Pr = 2.15), the lower trans selectivity in RL = Et than in RL = i-Pr may be attributed to deficiency in the steric bulkiness of RL in the conformer 33 required for the excellent diastereoselectivity.

On the other hand, a reversal of the diastereoselectivity (i.e., cis selectivity) in the second Re(VII)-promoted oxidative cyclizations must be apparently relevant to the THF ring neighboring the hydroxy group in the substrates, irrespective of the vicinal relative configuration (threo or erythro) (Table 4). The intramolecular coordination of the THF ring to rhenium could form alkoxyrhenium intermediates 34 and 35 from 22, 23 and 24, 25, respectively (Fig. 3). Considering the [3 + 2] mechanism in that chelation model, the least strained approach of the alkene toward the Re oxo moiety appears to be similar to that shown in Fig. 3 (i.e., methyl and the olefinic hydrogen are cis). Because trans selectivity is observed in erythro secondary alcohols even if the substrates have the neighboring THF ring, a tertiary property in the alcoholic substrates might play an important role in forming the rigid cyclic coordinative intermediates such as 34 and 35 (cf., geminal dialkyl effect). Although the reason for the lowered cis selectivity in entry 6 of Table 4 is not clear at present, 24 (R = i-Pr) appears to have difficulty in forming such a rigid chelation structure.

In summary, we have achieved steric (nonbonding) interaction-controlled trans and chelation-controlled cis highly diastereoselective cyclizations of bishomoallylic tertiary alcohols promoted by rhenium(VII) oxide (Scheme 3).

Table 4. cis Selective cyclizations of tertiary alcohols 22-25 by Re(VII) oxide and TFAA

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product (% yield)</th>
<th>ratio (cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22 (R = Me)</td>
<td>26 (71)</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>24 (R = Me)</td>
<td>28 (88)</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>22 (R = Et) + 23d</td>
<td>26 + 27 (79)d</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>24 (R = Et) + 25d</td>
<td>28 + 29 (71)d</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>22 (R = i-Pr)</td>
<td>28 (71)</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>24 (R = i-Pr)</td>
<td>28 + 30 (70)d</td>
<td>2:1</td>
</tr>
</tbody>
</table>

The total synthesis of meso Polyether Teurilene (3) is as follows.

Since the optimal reaction conditions applicable to tertiary alcohols have been developed, we embarked on the total synthesis of teurilene (3) according to the synthetic strategy in Scheme 2. The meso tetraol 16 required for the two-directional substrate was conveniently prepared by subjecting bisglysidic alcohol (-)-36, which was produced from commercially available methyl tiglate in four steps by Franck’s method, to Hoye’s procedure (Scheme 4). The mesylation of both primary hydroxy groups in the tetraol 16 and subsequent basic treatment of the dimesylate afforded the desired meso diepoxide 37 in 86% yield in two steps. The lithiation of neryl sulfide 38, prepared from commercially available neryl in 97% yield (Ph₂S₂, n-Bu₃P, THF, rt, 2 h), and alklylation of the lithio derivative with the diepoxide 37 were carried out in situ at -78°C in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) to yield the bisulfide 39 having the total carbon framework as a mixture of diastereomeric sulfides. The bisulfide 39 was desulfurized under Bouvaunt-Blanc conditions to provide the expected diol 14 in 75% isolated yield. With the requisite two-directional diol 14 in hand, we examined the crucial rhenium(VII)-promoted oxidative cyclization. The addition of TFAA was essential to induce any of the cyclization. Application of our standard reaction conditions (Table 4) using 8 equiv of Re(VII) oxide (i.e., 4 equiv of Re(VII) oxide for each bishomoallylic hydroxy group) to the diol 14 only provided the dicyclized product teurilene (3) in very low yield. After many experiments, optimal reaction conditions involved treating diol 14 with 12 equiv of (CF₃CO₂)ReO₃.2CH₃CN and 15 equiv of TFAA in a mixed solvent system (CH₂Cl₂/CH₃CN = 50:1) at -45°C for 8 h to diastereoselectively give teurilene (3) under steric conditions.
control (Scheme 3) in 29% yield, along with the monocy- 
clized alcohol 40 as a byproduct (Scheme 4). The material 
balances other than 3 and 40 were the recovered starting diol 
14 (3.8%) and a large amount of unidentifiable complex mix-

It is worthwhile noting that only the trans-syn diastereoselec-
ty (stERIC control) has been obtained in the Re(VII)-
induced oxidative cyclization of the two-directional substrate 
14, because we have previously observed that the Re(VII)-
promoted cyclizations of bishomoallylic tertiary alcohols 
22-25 possessing a neighboring THF ring give rise to the 
cis-syn diastereoselectivity (chelation control), due to the 
intramolecular coordination of the THF ring to rhenium 
(Fig. 3). However, this result might be rationalized as follows 
by considering the characteristics in the two-directional sub-
strate 14 (i.e., the neighboring THF ring is a cis 2,5-disubsti-
tuted one for both hydroxy groups). Because an excess of 
rhenium reagent was used, a bisalkoxyrhenium like 41 or 42 
could be generated as a reaction intermediate (Fig. 4). At 
that time, chelation control model 42, wherein the coordina-
tion of the THF ring to one rhenium encounters a significant 
steric repulsion with the second alkoxyrhenium moiety, 
appears to be more disfavored than steric control model 41 
without such steric hindrance. These results are also consis-
tent with the rule reported by Sinha et al.24 that if the vicinal 
oxygen functions formed in the first cyclization have an ery-
 thro relationship, the next cyclization produces a trans THF 
ring.

In summary, we have accomplished the efficient total syn-
thesis of meso polyether teurilene (3) in only 10 steps by 
effectively combining the concept of two-directional syn-
thesis with the rhenium(VII) chemistry.10,11 This synthesis pro-
cceeded in 6.1% overall yield in 10 steps from commercially 
available methyl tiglate and was significantly more efficient 
than the previous one (0.67% overall yield in 25 steps).10

4. Total Synthesis of (+)-14-Deacetyl Eurylene (1) and 
(+)-Eurylene (4)12

Our retrosynthetic analysis of 1 and 4 is depicted in Scheme 
5. The key events for the total synthesis are the stereo-
selective construction of the trans and cis THF rings and the 
differentiation of the 14-hydroxy group. To solve both problems 
at the same time, we devised a concurrent two-directional 
and stereodivergent synthesis toward 1, based on the rule for 
hydroxy-directed syn oxidative cyclizations of acyclic 
bishomoallylic alcohols promoted by rhenium(VII) oxide. 
This approach is in contrast to the two-directional and stere-
convergent one in the teurilene (3) synthesis (Scheme 2). 
Thus, the trans THF A-ring will be constructed under steric 
control at the bishomoallylic monool moiety by applying our 
Re(VII) protocol to triol 43 because of the negligible coordi-
nation ability of the neighboring 11-acetoxy group, while the 
cis THF B-ring may be constructed under chelation control 
at the bishomoallylic vicinal diol due to a coordination of 
the 14-hydroxy group to rhenium. The nearly meso triol 43 will, 
in turn, be derived from the appropriately protected diepox-
ide 44 by extending the side chains with two neryl units in a 
bidirectional manner. It was envisaged that the diepoxide 44
can be prepared by Sharpless asymmetric epoxidation of the readily available diol 45 and subsequent regioselective ring-opening reactions.

The stereoselective preparation of the diepoxide 44 began with monoprotection of the known diol 45 as a tert-butyldimethylsilyl (TBS) ether (Scheme 6). Sharpless asymmetric epoxidation of the allylic alcohol 46 using D(-)-DET afforded the epoxy alcohol 47 in high optical purity. The pivalate group was introduced regioselectively into 47 by a titanium-assisted epoxide-opening reaction to yield 1,2-diol 48 as a single diastereomer; subsequent acetonide protection and desilylation furnished the allylic alcohol 50 in good overall yield. The asymmetric epoxidation of 50 using L(+)-DET provided the epoxy alcohol 51, which was subjected to a Ti(OMPM)4-mediated epoxide-opening reaction with p-anise alcohol (MPMOH) to produce the desired 1,2-diol 52 and a 1,3-diol derivative in a ratio of approximately 3:1. Deprotection of the acetonide in 1,2-diol 52, mesylation of both primary hydroxy groups in the resultant tetraol, and subsequent basic treatment of the dimesylate finally gave the requisite diepoxide 44 in 41% yield (based on four steps from 51).

The bidirectional chain extension proceeded smoothly by alkylation of a large excess of 53, the lithio derivative of neryl phenyl sulfide (38), with the diepoxide 44 in the presence of TEMDA followed by desulfurization to provide the triol 54, and selective acetylation of the sec-alkol afforded the triol acetate 55 in good overall yield (Scheme 7). The MPM protecting group in 55 was converted into the 4-methoxybenzylidene acetal through interaction of the neighboring hydroxy groups with DDQ. Subsequent acidic hydrolysis furnished the key substrate 43 required for the oxidative cyclizations. The optimal conditions were determined, and the treatment of triol 43 with 8 equiv of (CF3CO2)ReO3.2CH3CN and 10 equiv of TFAA in a mixed solvent system (CH2Cl2/CH3CN = 9/1) at -40°C for 1.5 h diastereoselectively gave the trans THF product 56 in 84% yield; the right-hand part of the molecule was intact. Although the two-directional and stereodivergent approach was investigated for 14-MPM, MOM, and Bn ethers as well as the 14-hydroxy substrate 43 itself, the cis THF B-ring could not be formed under a variety of reaction conditions examined.

To overcome this problem, we decided to use oxochromium(VI) reagents, stronger oxidants than oxorhenium(VII) ones. When 56 was treated with 1 equiv of pyridinium chlorochromate (PCC) in CH2Cl2 at rt for 30 min, thebishomoallylic vicinal diol moiety was oxidatively cyclized, probably via a chelated dialkoxychromium intermediate with complete cis diastereoselectivity to produce (+)-14-deacetyl eurylene (1). It is postulated that, in this case, the formation of the chelated dialkoxychromium intermediate 57 is favored over that of the monoalkoxychromium counterpart of the left-hand moiety due to use of 1 equiv of PCC. The material balances other than 1 in this reaction were the oxidatively cleaved products of the vicinal diol moiety, the corresponding aldehyde (33%) and nerylacetone (40%). The spectral characteristics of synthetic 1 were identical to those reported for the natural product. Finally, selective acetylation of the 14-hydroxy group in 1 afforded another objective, (+)-eurylene (4), whose spectral data were also consistent with the 1H NMR spectrum of an authentic sample and with the data reported for the natural product. In conclusion, we have accomplished the first total synthesis of (+)-14-deacetyl eurylene (1), featuring chemoselective THF ring formations stereocontrolled by syn oxidative cyclizations of thebishomoallylic monol and diol induced by oxorhenium(VII) and chromium(VI) species, respectively. The challenging concurrent formation of A and B rings, based on the more efficient two-directional and stereodivergent strategy using Re(VII) chemistry, is under investigation in our laboratory.

Scheme 6

Scheme 7

Reaction conditions: a) Compound 53, TEMDA, THF, -78°C, 30 min, then 0°C, 2 h; b) Na, THF/PrOH (2/1), reflux, 15 h, 86% (2 steps); c) Ac2O, Py, rt, 12 h, 91%; d) DDQ, MS 4A, CH2Cl2, 0°C, 2 h, 68%; e) AcOH/H2O (4/1), rt, 16 h, 59%; f) (CF3CO2)ReO3-2CH3CN, TFAA, CH2Cl2/CH3CN (9/1), -40°C, 1.5 h, 84%; g) PCC, CH2Cl2, rt, 30 min, 47%; h) Ac2O, Py, rt, 40 h, 80%.

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5. Revised Structure of Squalene-Derived PentaTHF Polyether, Glabrescol, through Its Enantioselective Total Synthesis

Our synthetic strategy for the proposed structure 6 of glabrescol is based on taking its intrinsic symmetry into consideration, and on the sequential hydroxy-directed anti oxidative cyclizations of acyclic bishomoallylic alcohols with vanadium catalyst and teri-buty1 hydroperoxide (TBHP) to stereoselectively construct such THF rings via epoxides (Scheme 2). In practice, our synthesis began with the same C₅ symmetric meso diepoxide 37 as used in the synthesis of teurilene (3) (Scheme 8). Attachment of geranyl side chains to 37 was carried out in 64% yield over two steps to afford tetraenediol 15. Monoacetylation of the diol 15 produced substrate 58, and set the stage for the key sequential V-catalyzed anti oxidative cyclizations. The previous reaction conditions for the double cyclizations reported by Shirahama and McDonald required AcOH in the reaction media to promote the in situ ring-opening of the epoxide intermediates into THF rings. Although it was envisaged that the desirable pentaTHF 6 could straightforwardly be synthesized from the diol 15 in a single step by the two-directional and sequential oxidative cyclizations, as shown in Scheme 2, direct oxidative cyclizations of the diol 15 using AcOH unfortunately resulted in complex mixtures. Application of similar reaction conditions using AcOH to 58 for 4-5 h resulted in incomplete termination at the epoxide and monocyclized intermediates along with a small amount of dicyclized products. However, use of TFA instead of AcOH dramatically improved the results. Optimized conditions for the double cyclization of 58 (0.02 equiv VO(acac)₂, 2.5 equiv TBHP, 2 equiv TFA, CH₂Cl₂, rt, 30 min) provided the desired triTHF ether 59 as a major product in 28% yield over two steps, together with 23% of other minor diastereomers. The treatment of 59 under similar conditions gave the original meso structure 6 as the predominant product in 30% yield. Unfortunately, the ¹H and ¹³C NMR spectra of our synthetic 6 were not identical with those of the natural glabrescol kindly provided by Jacobs.

The relative stereochemistry between the 2- and 5-positions within each THF ring, except for the central THF ring, in the pentaTHF ether 6 and natural glabrescol generously supplied by Jacobs was determined by the presence of NOEs observed between the oxymethine proton and the methyl group in a relationship cis to that proton in their NOE spectra, as shown in Scheme 8. Reviewing in detail the original elucidation of the stereostructure of glabrescol by Jacobs et al., it appeared to us that the assignments of the relative stereocenters (threo or erythro) between each THF ring revealed an ambiguity. Therefore, we decided to synthesize the three remaining possible meso structures 60-62 by utilizing the same synthetic strategy as that of 6. Polyether 60 was prepared from the diol 14 by the same sequence of reactions as shown in Scheme 8. On the other hand, 61 and 62 were derived from the known diol 63 via another meso diepoxide 64, diastereomeric to 37, by attaching the geranyl and neryl side chains, respectively. Disappointingly, the ¹H and ¹³C NMR spectra of our synthetic 60-62 were again inconsistent with those of the natural product.

Although Jacobs et al. proposed a meso structure for glabrescol based on the optical inactivity [lit. [α]D 0.0 (c 0.4, CHCl₃)] and the presence of 15 signals in the ¹³C NMR spec-
trum, the above results cannot support any meso structure for glabrescol. The other possibilities fulfilling the criteria are that glabrescol is $C_2$ symmetric and racemic or that glabrescol is $C_2$ symmetric and the value of the optical rotation is near zero. Thus, we embarked on the enantioselective total synthesis of the $C_2$ symmetric structure 5 possessing the same relative stereochemistry as that of longilene peroxide (2) in view of the biogenetic relationship between 2 and 5 (Scheme 9).

Scheme 9. Enantioselective total synthesis of $C_2$ symmetric (-)-5

\[
\begin{align*}
46 & \xrightarrow{\text{a}} \quad \begin{array}{c}
\text{OH} \\
\text{TBSO}
\end{array} \\
& \xrightarrow{\text{b-d}} \quad \begin{array}{c}
\text{OMOM} \\
\text{HO}
\end{array} \\
& \xrightarrow{\text{e, f}} \quad \begin{array}{c}
\text{R} \\
\text{O} \\
\text{H}
\end{array} \\
& \xrightarrow{\text{g}} \quad \begin{array}{c}
\text{R} \\
\text{O} \\
\text{H}
\end{array} \\
& \xrightarrow{\text{h}} \quad \begin{array}{c}
\text{R} \\
\text{Ac}
\end{array} \\
5 & \text{(revised)}
\end{align*}
\]

Reaction conditions: a) TBHP, Ti(OrPr)$_3$, L-(+)-DET, MS 4A, CH$_2$Cl$_2$, -20°C, 4 h, 88% (98% ee); b) MOMCl, i-Pr$_2$NEt, CH$_2$Cl$_2$, 0°C to rt, 17 h, 96%; c) TBAF, THF, 0°C, 1 h, 98%; d) TBHP, Ti(OrPr)$_3$, D-(--)-DET; MS 4A, CH$_2$Cl$_2$, -25°C, 4 h, then citric acid, n-Bu$_3$P, 85%; e) 1 M aq NaOH, 1,4-dioxane, reflux, 1 h, then acetylated with HCl (pH 2), reflux, 10 min, 88%; f) h, i in Scheme 8, 75% (2 steps); g) a, b in Scheme 8, 65% (2 steps); h) e in Scheme 8, 50%; j, d, e in Scheme 8, 26% (2 steps); j, d in Scheme 8, 40%; k) 0.05 equiv VO(acac)$_2$, 5 equiv TBHP, 2 equiv TFA, CH$_2$Cl$_2$, rt, 30 min, 18%.

The allylic alcohol 46 was subjected to Sharpless asymmetric epoxidation$^{27}$ using L-(-)-DET to furnish the epoxy alcohol 65 in high optical purity. MOM protection, desilylation, and the second epoxidation using D-(--)-DET; MS 4A, CH$_2$Cl$_2$, -25°C, 4 h, then citric acid, n-Bu$_3$P, 85% was followed by diepoxidation to provide the $C_2$ symmetric diepoxide 66. The THF ring formation according to Hoye's procedure$^{106}$ was followed by diepoxidation to provide the $C_2$ symmetric diepoxide 67 in high overall yield. Introduction of the geranyl side chains and monoacetylation yielded an alcohol 69, whose double cyclizations under the optimized conditions gave triTHF 70 as a major product after deacetylation. Repeating the double cyclization on 70 produced predominantly the desired $C_2$ symmetric pentaTHF structure 5 in 40% yield. Fortunately, the spectral characteristics ($^1$H and $^{13}$C NMR, IR, MS, and HRMS) including the CD spectrum ($\Delta\varepsilon(\alpha) = +3.45$ in CH$_2$CN) of the synthetic 5, [$$\alpha$$]$_D$$^{25}$ -22.4 (c 1.27, CHCl$_3$), were identical to those of the natural glabrescol ($\Delta\varepsilon(\alpha) = +3.03$ in CH$_3$CN). Thus, the correct stereostructure of glabrescol must be revised from the Cs symmetric 6 to the $C_2$ symmetric 5 with the indicated absolute configuration.

Since an authentic sample generously supplied by Jacobs was too small to obtain a constant [$$\alpha$$]$_D$ value, we employed the CD spectrum to determine the absolute configuration of glabrescol. After our structural revision of glabrescol, Corey and Xiong have also achieved the enantioselective total synthesis of (-)-5, [$$\alpha$$]$_D$$^{23}$ -25.2 (c 0.3, CHCl$_3$), and independently arrived at the same $C_2$ symmetric stereostructure 5 as ours.$^{36}$ In that article, it was reported that an optical rotation of a recently determined sample of natural glabrescol was measured by Jacobs and the sample indicated [$$\alpha$$]$_D$ about -28.

Can glabrescol (5) be constructed in a single step from tetraenediol 68 by a two-directional double cyclization, as shown in Scheme 2? Such a cyclization would produce four THF rings and six stereogenic centers. It has, indeed, been found that the double cyclizations of 68 by our protocol in the presence of TFA can proceed in a two-directional manner to provide 5 as a major diastereomer in 18% yield along with 15 other minor diastereomers in 61% combined yield based on the HPLC analysis (Scheme 9).

In conclusion, we have accomplished the total synthesis of the four possible meso structures 6 and 60-62 and one optically active $C_2$ symmetric 5 of glabrescol through the key one- and two-directional double cyclizations utilizing VO(acac)$_2$, TBHP, and TFA, and revised the structural formula 6 proposed by Jacobs et al. to 5.$^{36}$ These results may imply that the $C_2$ symmetric glabrescol (5) is biogenetically related to the nearly $C_2$ symmetric longilene peroxide (2); therefore, it would be interesting to determine the unknown absolute configuration of 2, which possesses the same relative stereochemistry. Application of this synthetic strategy to 2 is the subject of the next chapter.

6. Total Synthesis and Determination of the Absolute Configuration of (-)-Longilene Peroxide (2)$^{13}$

Our retrosynthetic analysis of 2 is depicted in Scheme 10. The structure of 2 may be characterized by eight asymmetric centers, three THF rings, and a hydroperoxy functionality. It was envisaged that the labile hydroperoxy group can be introduced at the final stage of the synthesis by oxidizing the...
trisubstituted double bonds in the C$_2$ symmetric triTHF ether 71 with singlet oxygen.$^{34}$ The two 2,2,5-trisubstituted THF rings in 71 will be constructed in a two-directional manner through Shi’s asymmetric epoxidation$^{35}$ of bishomoallylic alcohol 72 followed by epoxide-opening reactions.$^{36}$ The monoTHF ether 72 will be, in turn, derived from the C$_2$ symmetric diepoxide 67, used for the total synthesis of (-)-glabrescol (5), by extending both side chains with the C$_{10}$ unit 73, still in the two-directional mode. In view of the biogenetic relationship between 2 and 5,$^{8b,e}$ we decided to employ the chiral diepoxide (+)-67 with the same absolute configuration for the asymmetric synthesis of 2.

The preparation of the C$_{10}$ unit 73, required for the two-directional chain extension of 67, began with acetonide protection of the readily available chiral diol (-)-74,$^{37}$ as shown in Scheme 11. Deacetylation of the acetonide 75 afforded the allylic alcohol 76, whose treatment with diphenyl disulfide and tributylphosphine$^{26}$ provided the allylic sulfide 73 in good overall yield. The lithiation of 73 and alkylation of the lithio derivative with the diepoxide 67 were carried out in situ at $-78^\circ$C in the presence of TMEDA, and the resulting bissulfide was desulfurized to yield the expected diol 72. Reagent-controlled epoxidation of 72 using Shi’s chiral dioxirane from ketone 77$^{35}$ followed by treating the diepoxide with TFA gave the diastereomerically homogeneous triTHF ether 78 as a major product in 40% yield over two steps, together with 15% of other minor triTHF diastereomers. The diastereoselectivities for the epoxidation of 72 (approximately 6:1 per one double bond on an average) were not so high as the selectivities reported by Shi et al.$^{35}$

The next stage was the generation of trisubstituted double bonds requisite for introduction of the tertiary hydroperoxy functional group. Deprotection of the acetonide in the triTHF ether 78 and subsequent cleavage of the resultant 1,2-diol with sodium metaperiodate afforded pentaTHF ether 79, which is found to be present mostly as a hemiacetal in the $^1$H NMR spectrum, in quantitative yield over two steps (Scheme 12). The Wittig reaction of the hemiacetal 79 with an excess of isopropylidene triphenylphosphorane provided the desired triTHF ether 71 in 84% yield. The C$_2$ symmetric structure and the cis stereochemistry of the 2,2,5-trisubstituted THF rings newly formed in 71 could be confirmed by the presence of 15 signals in the $^{13}$C NMR spectrum and NOE shown in 71, respectively.

Scheme 11. Synthesis of C$_2$ symmetric triTHF ether 78

Scheme 12. Total synthesis of (-)-longilene peroxide (2)
7. Conclusion

We have achieved total syntheses of the highly symmetric squalene-derived cytotoxic triterpene polyethers, teurilene (3), (+)-14-deacetyl eurylene (I), (+)-eurylene (4), (+)-glabrescol (5), and (+)-longilene peroxide (2), based on the concept of two-directional synthesis utilizing their intrinsic molecular symmetry as the fundamental strategy. In these target-oriented synthetic studies, we have accomplished steric interaction-controlled trans and chelation-controlled cis highly diastereoselective cyclizations of bishomoallylic tertiary alcohols promoted by rhenium(VII) oxide, and also one- and two-directional modes of prompt double THF ring formations with VO(acac)2, TBHP, and TFA. In the biological aspects of these polyethers, it has been found that their triTHF podand models exhibit selective cation transport abilities for physiologically important Na+ and K+, which might be related to our hypothesis on the mechanism of action for cytotoxicities of these polyethers (Fig. 1). Many types of oxasqualenoids have been isolated; however, it is often difficult to determine their stereostructures only by spectroscopic analysis, especially in systems including acyclic quaternary carbon centers. In such cases, it is effective to predict and synthesize the possible stereoisomers, as exemplified for 5 and 2 in this study, and more recently for a new squalene-derived epoxy triTHF diol. These will be useful to deduce the biogenetic relationships among the relevant oxasqualenoids.

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References

34) For a review, see Clennan, E. L. Tetrahedron 2000, 56, 9151.
36) Unfortunately, application of our protocol (VO(acac)2, TBHP, TFA) to bishomoallylic alcohols 68 and 72 did not give satisfactory results.

PROFILE

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