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Total synthesis and determination of the absolute configuration of (−)-longilene peroxide

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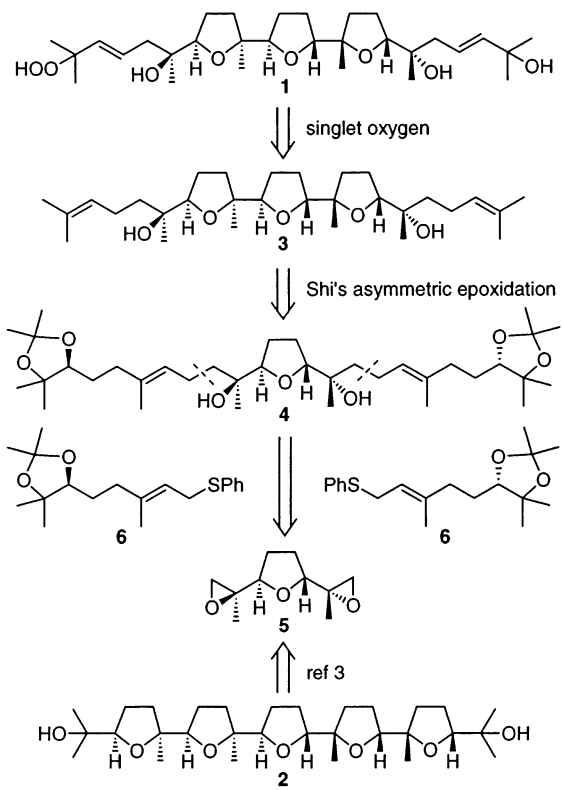
Abstract—The first asymmetric total synthesis of (−)-longilene peroxide (**1**) has been achieved starting from the optically active C_2-symmetric diepoxide **5** through the concept of two-directional synthesis utilizing its intrinsic molecular symmetry. Thus, the unknown absolute configuration of longilene peroxide has been determined by this synthesis as shown in the structural formula **1**.

Recently, biologically active and structurally unique triterpene polyethers, which are thought to be biogenetically squalene-derived natural products, have been isolated from both marine and terrestrial plants.[1] Among them is cytotoxic ($IC_{50}=5.3$ μg/mL against KB cells) longilene peroxide (**1**), isolated from the wood of *Eurycoma longifolia* by Itokawa et al.[2] (Scheme 1). Although the relative stereostructure and conformation of **1** have been elucidated by X-ray crystallographic analysis and spectroscopic methods, the absolute configuration had not hitherto been determined in spite of the biogenetic interest in the compound as well as the relevant polyethers.[3] In the context of extensive work for the total syntheses of the aforementioned polyethers, we have achieved the total syntheses of teurilene,[4] (−)-glabrescol (**2**),[3,5] (+)-eurylene, and (+)-14-deacetyl eurylene[6] through the concept of two-directional synthesis[7] utilizing their molecular symmetry as a fundamental strategy; however, the total synthesis of longilene peroxide (**1**) was not accomplished. In this paper, we report the first enantioselective total synthesis of (−)-longilene peroxide (**1**) along this line and the determination of its absolute configuration.

Our retrosynthetic analysis of **1** is depicted in Scheme 1. The structure of **1** may be characterized by eight asymmetric centers, three tetrahydrofuran (THF) rings, and a hydroperoxy functionality. It was envisaged that the hydroperoxy group can be introduced by oxidizing the terminal double bonds in the C_2-symmetric triTHF ether **3** with singlet oxygen.[8] The two 2,2,5-trisubsti-



Scheme 1. Retrosynthetic analysis of (−)-longilene peroxide (**1**).

Keywords: configuration; oxygen, singlet; peroxides; polyethers; terpenes and terpenoids.

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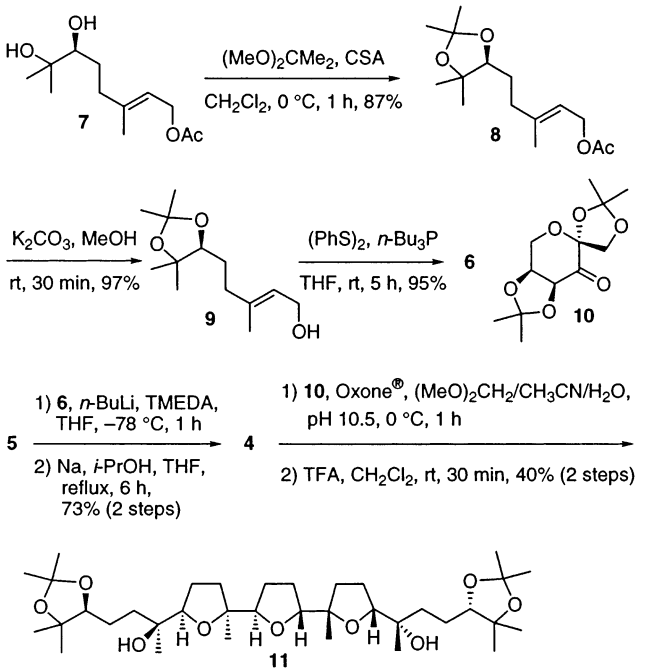
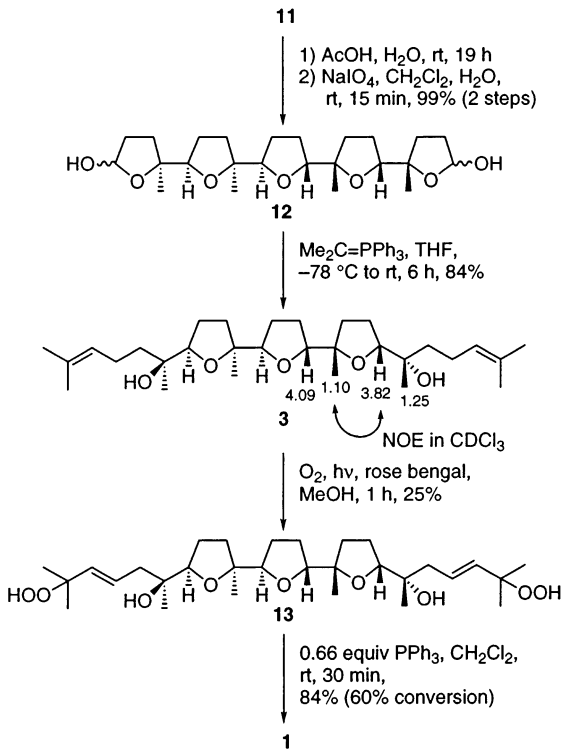
tuted THF rings in **3** will be constructed in a two-directional manner through Shi's asymmetric epoxidation[9] of bishomoallylic alcohol **4** followed by epoxide-opening reactions.[10] The monoTHF ether **4** will be, in turn, derived from the diepoxide **5** by extending both side chains with the C_{10} unit **6**, still in the two-directional mode. We have previously accomplished the total synthesis of (−)-glabrescol (**2**) using the optically active C_2-symmetric diepoxide **5**, $[\alpha]_D^{25}$ +9.75 (*c* 0.843, $CHCl_3$),[3] and revised the proposed *meso* structure[11] to the C_2-symmetric **2**. Therefore, we decided to employ the chiral diepoxide **5** with the same absolute configuration for the asymmetric synthesis of **1** in view of the biogenetic relationship between **1** and **2**.[3]

The preparation of the C_{10} unit **6**, required for the two-directional chain extension of **5**, began with acetonide protection of the readily available chiral diol **7**, $[\alpha]_D^{27}$ −24.9 (*c* 0.78, $CHCl_3$) [lit.[12] $[\alpha]_D^{20}$ −22.9 (*c* 1.1, $CHCl_3$)], as shown in Scheme 2. Deacetylation of the acetonide **8**‡ afforded the allylic alcohol **9**, whose treatment with diphenyl disulfide and tributylphosphine[13] provided the allylic sulfide **6** in good overall yield. The lithiation of **6** and alkylation of the lithio derivative with the diepoxide **5** were carried out in situ at −78°C in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and the resulting bissulfide as a mixture of diastereomeric sulfides was desulfurized under Bouvault–Blanc conditions[4,5a] to yield the expected diol **4**, contaminated with minor products including the *endo*-migrated (disubstituted) double bond. Reagent-controlled epoxidation of **4** using Shi's chiral dioxirane from ketone **10**[9] followed by treating the diepoxide with trifluoroacetic acid (TFA) gave the diastereomerically homogeneous triTHF ether **11** as a major product in 40% yield over two steps, together with 15% of the other minor triTHF diastereomers.



Scheme 2. Synthesis of C_2-symmetric triTHF ether **11**.

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 **11** and subsequent cleavage of the resultant 1,2-diol with sodium metaperiodate afforded pentaTHF ether **12**, which is found to be present mostly as a hemiacetal in the ^1H NMR spectrum, in quantitative yield over two steps (Scheme 3). The Wittig reaction of the hemiacetal **12** with an excess of isopropylidene triphenylphosphorane, prepared in situ by treating commercially available isopropyltriphenylphosphonium iodide with *n*-butyllithium, provided the desired triTHF ether **3**§ in 84% yield. The



Scheme 3. Total synthesis of (−)-longilene peroxide (**1**).

‡ All new compounds in this paper were satisfactorily characterized by ^1H and ^{13}C NMR, IR, MS, and HRMS spectra.

§ Compound **3**: mp 87.0–87.5°C; $[\alpha]_D^{32}$ +9.93 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.14–5.05 (2H, m), 4.37 (2H, br s), 4.09 (2H, dd, J=10.1, 5.5 Hz), 3.82 (2H, dd, J=7.6, 5.6 Hz), 2.15–1.94 (10H, m), 1.91–1.80 (2H, m), 1.67 (6H, s), 1.61 (6H, s), 1.58–1.39 (6H, m), 1.32–1.20 (2H, m), 1.25 (6H, s), 1.10 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 125.0, 85.3, 85.1, 84.3, 73.0, 38.6, 30.6, 29.4, 25.7, 25.3, 24.3, 23.4, 22.3, 17.6; IR (KBr) 3422, 3350, 2968, 2928, 2876, 2856, 1452, 1375, 1196, 1173, 1142, 1097, 1076, 1059, 1038, 1011, 961, 949 cm^{-1}; EI-MS m/z (relative intensity) 492 (M^+, 2.4), 459 (6.0), 405 (7.0), 347 (11), 305 (7.0), 279 (46), 211 (100), 193 (58), 135 (52), 69 (50); EI-HRMS calcd for $C_{30}H_{52}O_5$ (M^+) 492.3814, found 492.3835.

C_2-symmetric structure and the *cis* stereochemistry of the 2,2,5-trisubstituted THF rings newly formed in **3** could be confirmed by the presence of 15 signals in the ^{13}C NMR spectrum and NOE shown in **3**, respectively.

Under irradiation with visible light (589 nm, 240 W sodium lamp) in the presence of molecular oxygen and a minute amount of rose bengal as a sensitizer, the trisubstituted alkene **3** underwent an ene reaction with singlet oxygen to give the C_2-symmetric photooxygenation product **13** bearing only *trans* olefins ($J=15.9$ Hz between the olefinic protons). The regioselectivities in the photooxygenation of **3** (95% total yield; *tert*,*tert*-hydroperoxide **13**:*tert*,*sec*-hydroperoxide:*sec*,*sec*-hydroperoxide = ca 1:2:1) were, however, reflected only by those observed in the known singlet oxygen reactions.¶ Finally, monoreduction of the bishydroperoxide **13** to an alcohol was effected by 0.66 equiv. of triphenylphosphine to produce (−)-longilene peroxide (**1**),‖ mp 135.5–136.5°C (diisopropyl ether–hexane); $[\alpha]_D^{27}$ −44.8 (*c* 0.40, $CHCl_3$) [lit.[2] mp 142–143°C; $[\alpha]_D^{25}$ −23.0 (*c* 0.44, $CHCl_3$)], in 84% yield based on 40% recovery of the starting material **13**. The spectral characteristics (^1H and ^{13}C NMR, IR) of the synthetic **1** were identical to those reported for the natural product.[2] Thus, it has been found that the hitherto unknown absolute configuration of longilene peroxide is as indicated in the structural formula **1**, which possesses the same absolute stereochemistry as glabrescol (**2**).

In conclusion, we have accomplished the first asymmetric total synthesis of (−)-longilene peroxide (**1**) starting from the C_2-symmetric chiral diepoxide **5** through a two-directional strategy which takes its intrinsic symmetry into consideration, and determined the absolute configuration of **1**. The ionophoric activities anticipated from the polyether structure **1** are currently under investigation in our laboratory.[1]

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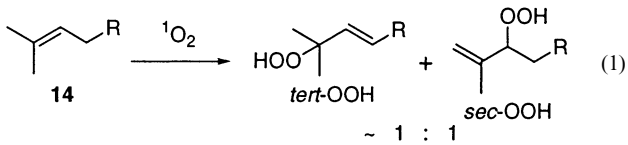
¶ It has been reported that trisubstituted alkenes such as **14** give a nearly 1:1 mixture of two allylic *tert*- and *sec*-hydroperoxide products as shown in Eq. (1) (Refs. 8 and 14).



(1)

‖ Compound **1**: ^1H NMR (400 MHz, $CDCl_3$) δ 10.67 (1H, s), 5.83 (1H, ddd, $J=15.4$, 8.5, 6.3 Hz), 5.78 (1H, dt, $J=15.2$, 7.6 Hz), 5.63 (1H, d, $J=15.6$ Hz), 5.45 (1H, d, $J=15.6$ Hz), 5.29 (1H, s), 5.07 (1H, d, $J=1.7$ Hz), 4.17–4.09 (2H, m), 3.73 (2H, t, $J=6.6$ Hz), 3.37 (1H, s), 2.20 (2H, dd, $J=13.5$, 7.4 Hz), 2.14–1.97 (6H, m), 1.93–1.83 (3H, m), 1.79 (1H, dd, $J=13.2$, 8.8 Hz), 1.56–1.41 (4H, m), 1.39 (3H, s), 1.34 (3H, s), 1.30 (6H, s), 1.22 (3H, s), 1.21 (3H, s), 1.11 (3H, s), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 137.0, 125.7, 122.2, 85.7, 85.5, 85.4, 85.10, 85.08, 84.1, 81.0, 73.9, 73.7, 70.5, 41.3, 40.7, 30.1, 29.9, 29.8, 29.7, 29.5, 29.3, 26.9, 25.7, 25.2, 24.3, 24.2, 24.1, 23.6; IR (KBr) 3323, 2970, 1456, 1371, 1086, 1074 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 541 [$(M+H)^+$, 6.0], 523 (6.0), 505 (7.0), 471 (8.0), 389 (24), 325 (53), 237 (41), 153 (39); FAB-HRMS calcd for $C_{30}H_{53}O_8$ [$(M+H)^+$] 541.3740, found 541.3734.