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Synthesis and Structural Revision of (±)-Laurentristich-4-ol

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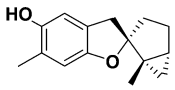
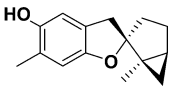


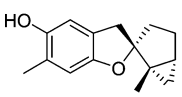
Proposed structure



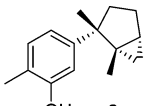
Revised structure

The structure of tetracyclic natural sesquiterpene laurentristich-4-ol was revised based on its synthetic studies. The proposed and the revised structures of laurentristich-4-ol were both synthesized with SmI_2-mediated ketyl radical cyclization as the key step to construct the spirocyclic ether skeleton.

Laurentristich-4-ol was one of the 14 sesquiterpenes isolated from the red alga *Laurencia tristicha* in the South Sea of China.[1] It possesses an unusual novel carbon skeleton not satisfying the isoprene rule. The proposed structure is shown as compound **1**, which has a novel tetracyclic skeleton with a spirocyclic ether structure. It was proposed that **1** might be biogenetically synthesized from the possible precursor cyclolauren-2-ol (**2**), which was another sesquiterpene also isolated from *Laurencia tristicha*, by an oxidative rearrangement procedure. Laurentristich-4-ol was tested against a few human cancer cell lines and no cytotoxicity was found.[1] Other biological activities of laurentristich-4-ol remain unknown.



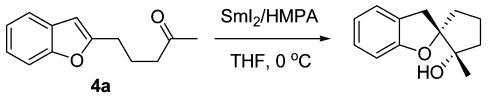
1



2

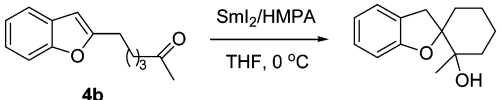
3

The unique structure of laurentristich-4-ol prompted us to study its total synthesis. The stereoselective generation of the 1-oxaspiro[4.4]nonane skeleton (**3**) was obviously the key to the synthesis of **1**. Surprisingly, few methods are available in the literature for its formation. These included the carbocation-based reaction of diols with acids,[2] the acid-catalyzed addition of phenols to C=C bonds,[3] the based-catalyzed intramolecular Diels−Alder reaction of furfuryl propargyl ethers,[4] the rhodium-catalyzed intramolecular C−H insertion of aryldiazoacetates,[5] and the intramolecular addition of a vinyl radical to benzofuran in a low efficiency.[6] Driven by our interest in carbon-centered radical cyclization reactions,[7] we envisioned that the SmI_2-mediated ketyl radical cyclization[8] onto benzofuran might be an efficient and convenient way for the construction of the spirocyclic ether. Thus, we prepared the model substrate **4a** to explore this possibility (vide infra). Treatment of ketone **4a** with SmI_2/HMPA in THF at rt for 16 h led to the clean formation of 5-*exo* cyclization product **5a** in 66% isolated yield with excellent regioselectivity and stereoselectivity, whose configuration was established by its NOESY experiments (eq 1). No other stereoisomers could be detected.

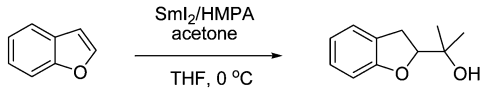


4a **5a** (66%) (1)

We then extended this methodology to the cyclization in a 6-*exo* mode with ketone **4b** as the substrate. The reaction of **4b** with SmI_2 under the above conditions also showed high regioselectivity and the expected 6-*exo* cyclization product **5b** was achieved in 72% yield as the mixture of two stereoisomers in a 2:1 ratio (eq 2). As a comparison, the intermolecular ketyl radical addition to benzofuran **6** gave the desired product **7**[9] in a low yield (eq 3). This observation should be attributed to the rich electron density of the C=C double bond in benzofuran while ketyl radicals are nucleophilic.[10]



4b **5b** (72%) (2)



6 **7** (20%) (3)

On the basis of the above results, the synthesis of **1** was then carried out as illustrated in Scheme 1. 2-Iodo-5-methylbenzene-1,4-diol (**8**) was used as the starting material, which was readily

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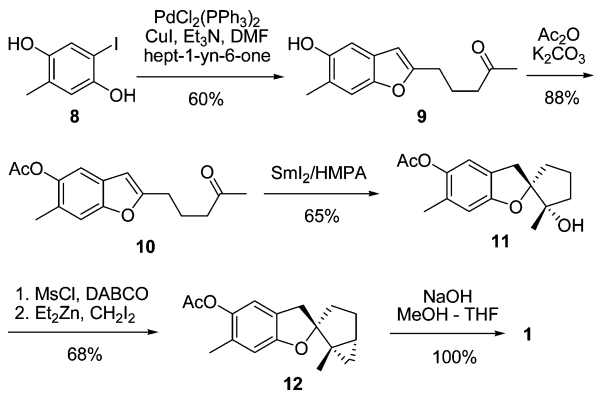
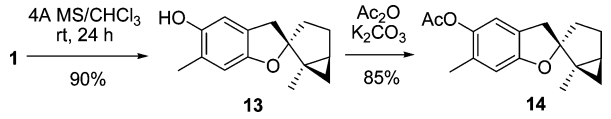
SCHEME 1. Synthesis of the Proposed Structure of (±)-Laurentristich-4-ol



prepared from the commercially available methylhydroquinone in three steps (methylation with dimethyl sulfate[11] followed by iodination with I_2[12] and subsequent demethylation with BBr_3)[13] according to the literature procedures.[11−13] The palladium-catalyzed coupling[14] of **8** with hept-1-yn-6-one led to the formation of benzofuran **9** in 60% isolated yield. The hydroxyl in **9** was then acylated by reaction with acetic anhydride and potassium carbonate. The treatment of the acylated compound **10** with SmI_2/HMPA in THF at 0 °C furnished the ketyl radical cyclization product **11** as a single stereoisomer in 65% yield. The dehydration of **11** with methanesulfonyl chloride and DABCO gave the olefin intermediate that underwent partial decomposition during its purification by flash chromatography on silica gel. Therefore, the crude dehydration intermediate was directly subjected to the treatment with diethylzinc[15] and diiodomethane in CH_2Cl_2 at room temperature. The expected cyclopropanation product **12** was thus obtained in the above two-stage, one-pot procedure in an overall 68% yield as the only stereoisomer whose structure was unambiguously established by its X-ray crystal analysis (see the Supporting Information). The stereoselective cyclopropanation could be attributed to the presence of the benzofuranyl oxygen, which might coordinate to diethylznic and thus direct the cyclopropanation at the same side. Finally, the deacylation of **12** with NaOH furnished the target molecule **1** in a quantitative yield.

Surprisingly, the ^{1}H NMR spectrum of **1** was dramatically different from that of laurentristich-4-ol reported in the literature, indicating that the structure of laurentristich-4-ol cannot be **1**. Fortunately and to our delight, the $CDCl_3$ solution of **1** in an NMR tube underwent slow isomerization and after 1 month, compound **1** was all isomerized and the resulting NMR spectrum was essentially identical with that of laurentristich-4-ol (see the Supporting Information for details). Our efforts showed that this process could be accelerated by the presence of molecular sieves (4 Å). To characterize the rearrangement product **13**, it was acylated with acetic anhydride to give compound **14** (Scheme 2), whose structure was then unambiguously established by its X-ray diffraction experiments (see the Supporting Information).

SCHEME 2. Structural Revision of (±)-Laurentristich-4-ol



It was clear that the methylene group of the cyclopropane in **1** flipped over to furnish **13**. Thus, the correct structure of (±)-laurentristich-4-ol should be **13** rather than **1**.

The stereochemical assignment of laurentristich-4-ol in the literature[1] was based on the strong NOE between one of the benzylic protons and the methyl protons attached to the cyclopropane ring. However, this was not conclusive as the two types of protons are at the 1,4-position. In fact, the NOE signal was strong both in **1** and in **13**. The crystal structures of **12** and **14** also revealed that these protons are very close in space in both cases. Our theoretical calculations at the HF/6-31G* level indicated that compound **13** is about 2.7 kcal/mol lower in energy than its stereoisomer **1** (see the Supporting Information). It can also be seen from the computed structures that the distance between the abovementioned two types of protons is shorter than 3 Å in both molecules (2.162 Å in **1** and 2.473 Å in **13**).

Although the mechanism of the rearrangement of **1** remains unclear, it might be possible that the oxidation of the phenoxyl group to phenoxy radical initiates the cleavage of the spiro-C−O bond to give the 1,4-benzoquinone intermediate and the reverse of this process leads to the formation of the more stable isomer **13**. This was evidenced by the fact that both phenols **1** and **13** were very unstable in air and underwent partial decomposition during their purification by column chromatography on silica gel while the *O*-acylated compounds **12** and **14** were remarkably stable. The role of molecular sieves in accelerating the isomerization of **1** might be attributed to the introduction of a catalytic amount of air absorbed in the molecular sieves into the reaction mixture.

In summary, the proposed structure of tetracyclic natural sesquiterpene laurentristich-4-ol was synthesized in six steps from compound **8** in an overall 23% yield. The structure of laurentristich-4-ol was then revised to be **13**, which was synthesized for the first time in seven steps from **8** in an overall 21% yield. Moreover, the SmI_2-mediated ketyl radical cyclization in the construction of sterically congested spirocyclic ether skeletons described above should find further application in natural product synthesis.

Experimental Section

5-Hydroxy-6-mentyl-2-(4-oxopentanyl)benzofuran (9). Hept-1-yn-6-one (340 mg, 3.1 mmol) was added to the mixture of 2-iodo-5-methylbenzene-1,4-diol (**8**) (308 mg, 1.23 mmol), $PdCl_2(Ph_3P)_2$ (64 mg, 0.06 mmol), CuI (30 mg, 0.16 mmol), and triethylamine (1 mL) in DMF (3 mL) at rt under N_2 atmosphere. The mixture was stirred at rt for 1 h and then at 80 °C for another 16 h. The resulting mixture was then cooled to rt and poured into water (50 mL). The two layers were separated and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic phase was washed with aqueous NaOH solution (10 mL) and water (20 mL) and then dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with petroleum−ethyl acetate (4:1, v:v) as the eluent to give compound **9** as a white solid. Yield: 170 mg (60%). Mp 144−146 °C. IR (KBr): ν (cm^{-1}) 3380, 2947, 2889, 1703, 1424, 1381, 1182, 953, 854. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95−2.05 (m, 2H), 2.13 (s, 3 H), 2.32 (s, 3 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.71 (t, J = 7.2 Hz, 2 H), 4.52 (br, 1 H), 6.25

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(s, 1 H), 6.85 (s, 1 H), 7.15 (s, 1 H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 16.8, 22.6, 28.2, 42.7, 102.7, 105.2, 105.4, 112.5, 121.8, 128.1, 150.1, 152.1, 159.2, 207.7. EIMS: *m*/*z* (rel intensity) 232 (M^+, 14), 174 (100), 173 (20), 161 (22), 105 (8), 77 (7), 43 (21). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.29; H, 6.96.

5-Acetoxy-6-methyl-2-(4-oxopentanyl)benzofuran (10). Potassium carbonate (380 mg, 2.75 mmol) was added into the CH_2Cl_2 (20 mL) solution of 5-hydroxy-6-mentyl-2-(4-pentanon-1-yl)benzofuran (**9**) (318 mg, 1.37 mmol) at rt. Acetic anhydride (5.2 mmol, 0.30 mL) was then added and the mixture was stirred at rt overnight. The resulting mixture was concentrated under reduced pressure and the residue was poured into water (20 mL). The aqueous mixture was then extracted with ether (3 × 20 mL). The combined extracts were washed with 1 N hydrochloric acid solution and then dried over anhydrous $MgSO_4$. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with petroleum−ethyl acetate (5:1, v:v) as the eluent to give 5-acetoxy-6-methyl-2-(4-pentanon-1-yl)-benzofuran (**10**) as a white solid. Yield: 329 mg (88%). Mp 67−68 °C. IR (KBr): ν (cm^{-1}) 3111, 2935, 1759, 1717, 1602, 1472, 1368, 1157, 913, 873. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97−2.03 (m, 2 H), 2.13 (s, 3 H), 2.25 (s, 3 H), 2.33 (s, 3 H), 2.47 (t, J = 7.2 Hz, 2 H), 2.74 (t, J = 7.2 Hz, 3 H), 6.32 (s, 1 H), 6.09 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 20.8, 21.6, 27.5, 29.9, 42.4, 102.5, 112.3, 112.7, 125.6, 127.4, 145.1, 152.7, 159.0, 169.8, 208.2. EIMS: *m*/*z* (rel intensity) 274 (M^+, 13), 232 (8), 216 (8), 174 (100), 175 (12), 161 (11), 115 (3), 77 (2), 43 (6). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.89; H, 6.63.

(1′*S,2′*S**)-5-Acetoxy-1′-hydroxy-1′,6-dimethyl-3*H*-spiro[benzofuran-2,2′-cyclopentane] (11).** A solution of **10** (158 mg, 0.58 mmol) and ^{t}BuOH (87 μL, 1.15 mmol) in THF (20 mL) was added to the mixture of SmI_2 (0.1 M, 28.8 mL, 2.88 mmol) and HMPA (2 mL, 11.5 mmol) in THF (5 mL) at 0 °C. The solution was stirred at 0 °C for 16 h and then quenched with saturated aqueous $NaHCO_3$ (30 mL). The two layers were separated and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic phase was washed with brine and then dried over anhydrous $MgSO_4$. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with petroleum−ethyl acetate (3:1, v:v) as the eluent to give **11** as a colorless liquid. Yield: 103 mg (65%). IR (neat): ν (cm^{-1}) 3054, 2961, 2933, 1758, 1493, 1370, 1213, 1159, 917. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 3 H), 1.76−1.86 (m, 3 H), 1.99−2.11 (m, 6 H), 2.28 (s, 3 H), 2.95 (d, J = 16.2 Hz, 1 H), 3.35 (d, J = 16.2 Hz, 1 H), 6.55 (s, 1 H), 6.79 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 19.0, 20.8, 20.9, 33.4, 37.3, 38.5, 81.5, 98.9, 110.7, 118.1, 125.6, 129.2, 142.5, 156.8, 169.9. EIMS: *m*/*z* (rel intensity) 276 (M^+, 7), 234 (24), 216 (10), 201 (9), 161 (8), 137 (36), 97 (20), 55 (19), 43 (100). HRMS calcd for $C_{16}H_{20}O_4$ 276.1362, found 276.1357.

(1′*S,2′*S**)-5-Acetoxy-1′,6-dimethyl-3*H*-spiro[benzofuran-2,2′-bicyclo[3.1.0]hexane] (12).** A solution of **11** (25 mg, 0.09 mmol) in dry dichloromethane (5 mL) was allowed to cool to 0 °C. DABCO (103 mg, 0.9 mmol) and methanesulfonyl chloride (69 μL, 0.9 mmol) were added successively. The mixture was stirred at 0 °C for 4 h and then at rt overnight. The resulting mixture was diluted with ether (10 mL), washed successively with water, saturated aqueous NH_4Cl, and 10% aqueous Na_2CO_3, and then dried over anhydrous $MgSO_4$. After the removal of the solvent under reduced pressure, the crude product was dissolved in dichloromethane (2 mL) under N_2 atmosphere and the solution was cooled down to −23 °C. Diethyl zinc (0.5 mL, 0.5 mmol, 1.0 M solution in hexane) and diiodomethane (80.5 μL, 1 mmol) were added. The reaction mixture was stirred vigorously at −23 to 0 °C for 10 h. The resulting mixture was then treated with aqueous NH_4Cl (10 mL) and extracted with ether (3 × 20 mL). The combined ether solution was washed with saturated $NaHCO_3$ and then dried over Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with petroleum−ethyl acetate (20:1, v:v) as the eluent to give **12** as a white solid. Yield: 17.2 mg (68%). Mp 80−82 °C. IR (KBr): ν (cm^{-1}) 3015, 2956, 2928, 2876, 1756, 1492, 1368, 1203, 1177, 1159, 1010, 911. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.39 (dd, J = 7.8, 5.1 Hz, 1 H), 1.00 (dd, J = 5.1, 3.9 Hz, 1 H), 1.14 (s, 3 H), 1.16−1.21 (m, 1 H), 1.65−1.80 (m, 4 H), 2.09 (s, 3 H), 2.29 (s, 3 H), 2.74 (d, J = 15.6 Hz, 1 H), 3.45 (d, J = 15.6 Hz, 1 H), 6.61 (s, 1 H), 6.79 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 16.3, 16.4, 20.8, 23.4, 24.2, 27.9, 34.2, 38.6, 98.4, 110.7, 118.3, 125.4, 129.1, 142.3, 157.6, 169.9. EIMS: *m*/*z* (rel intensity) 272 (M^+, 35), 258 (13), 230 (100), 215 (49), 201 (19), 161 (10), 137 (92), 93 (20), 77 (12). HRMS calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1410. The structure was further confirmed by its X-ray diffractional analysis.

(1′*S,2′*S**)-5-Hydroxy-1′,6-dimethyl-3*H*-spiro[benzofuran-2,2′-bicyclo[3.1.0]hexane] (1).** NaOH (20 mg, 0.5 mmol) was added into the solution of compound **12** (13.0 mg, 0.048 mmol) in MeOH (0.5 mL) and THF (1.5 mL) at rt. After the mixture was stirred for 30 min, 2 N aqueous HCl was added until the pH was close to 7. The resulting aqueous solution was extracted with ether (3 × 20 mL). The combined organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with petroleum−ethyl acetate (10:1, v:v) as the eluent to give the pure **1** as a colorless liquid. Yield: 11.5 mg (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.39 (dd, J = 7.8, 5.1 Hz, 1 H), 1.00 (dd, J = 5.1, 3.9 Hz, 1 H), 1.11 (s, 3 H), 1.15−1.20 (m, 1 H), 1.60−1.77 (m, 4 H), 2.19 (s, 3 H), 2.73 (d, J = 15.6 Hz, 1 H), 3.43 (d, J = 15.6 Hz, 1 H), 6.55 (s, 1 H), 6.63 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 16.1, 16.3, 24.2, 26.9, 27.9, 34.1, 38.5, 97.6, 110.6, 112.0, 122.7, 125.2, 147.2, 153.9. EIMS: *m*/*z* (rel intensity) 230 (M^+, 35), 216 (30), 201 (34), 188 (13), 161 (8), 137 (100), 93 (25), 84 (49). HRMS calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1315.

(1′*S,2′*R**)-5-Hydroxy-1′,6-dimethyl-3*H*-spiro[benzofuran-2,2′-bicyclo[3.1.0]hexane] (13).** Molecular sieves (4 Å, 0.5 g) was added into the solution of **1** (20 mg, 0.087 mmol) in $CHCl_3$ (2 mL) at rt and the mixture was stirred for 24 h. The resulting mixture was filtered and the filtrate was concentrated in vacuo to give **13** as a colorless liquid. Yield: 18 mg (90%). The ^{1}H and ^{13}C NMR spectra were identical with those reported in the literature.[1]

(1′*S,2′*R**)-5-Acetoxy-1′,6-dimethyl-3*H*-spiro[benzofuran-2,2′-bicyclo[3.1.0]hexane] (14).** Compound **14** was prepared by the acylation of **13** in 85% yield according to the procedure outlined for the synthesis of **10**. White solid. Mp 86−88 °C. IR (KBr): ν (cm^{-1}) 3025, 2930, 2867, 1759, 1628, 1492, 1369, 1204, 1157, 1007, 914. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.31−0.35 (m, 1 H), 0.40−0.43 (m, 1 H), 1.11 (s, 3 H), 1.33−1.36 (m, 1 H), 1.59−1.73 (m, 2 H), 1.94−2.06 (m, 2 H), 2.09 (s, 3 H), 2.29 (s, 3 H), 2.91 (d, J = 15.9 Hz, 1 H), 3.34 (d, J = 15.9 Hz, 1 H), 6.58 (s, 1 H), 6.77 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.9, 16.5, 20.8, 24.9, 25.6, 30.9, 35.8, 36.2, 99.3, 110.7, 117.9, 125.6, 129.2, 142.2, 157.0, 170.0. EIMS: *m*/*e* (rel intensity) 272 (M^+, 34), 258 (2), 230 (100), 215 (48), 201 (12), 161 (10), 137 (66), 93 (21), 77 (12). HRMS calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1407. The structure was further confirmed by its X-ray diffractional analysis.

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Supporting Information Available: Characterizations of compounds **4**−**8**, ^{1}H and/or ^{13}C NMR spectra of **9**−**14**, and theoretical calculations on **1** and **13**, as well as crystal structures of **12** and **14** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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