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Synthesis-guided structure revision of the monoterpene alcohol isolated from *Mentha haplocalyx*

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ABSTRACT

The monoterpene isolated from *Mentha haplocalyx*, 3,3,5-trimethyl-2-oxabicyclo[2.2.2]oct-5-en-4-ol, was synthesized according to its proposed structure. However, the NMR data of the synthetic sample were not in agreement with those reported for the natural product. After considerable efforts, the genuine structure was confirmed as (1*R**,2*R**)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol.

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In 2010, Liu et al. reported the isolation of a novel monoterpene alcohol from the Chinese herb *Mentha haplocalyx* [1]. On the basis of NMR and mass spectral analyses, the structure of the natural product was proposed to be 3,3,5-trimethyl-2-oxabicyclo[2.2.2]oct-5-en-4-ol (**1**) (Figure 1). Inspired by the unique structure of **1**, we initiated studies toward its synthesis as a continuation of our synthetic studies on biologically active and/or structurally unique terpenoids [2,3]. Herein, we report the following step-by-step: 1) synthetic disproof of the proposed structure **1**; 2) reconsideration of the genuine structure based on NMR spectroscopy; 3) synthesis of the candidate structures (**2, 3**, *cis*- and *trans*-**4**); and 4) structural confirmation of the naturally occurring monoterpene isolated from *Mentha haplocalyx*.

Results and discussion

Our synthetic route to **1** is shown in Scheme 1. A commercially available ketoester **5** was converted into the corresponding enol phosphonate **6** (70%). After the conversion of **6** into **7** by treatment with Gilman reagent, **7** was exposed to MeLi to afford **8** (57% in 2 steps). Oxidation of **8** with singlet oxygen in the presence of methylene blue produced the peroxide **9** (61%), which was then reduced with zinc powder [4] in AcOH to furnish **10**. Finally, intramolecular etherification in S_N2 manner was successfully mediated by TsCl/DMAP in pyridine to afford the initial target compound **1** (71% in 2 steps).

As shown in Table 1, there are discrepancies between the ^{13}C and ^{1}H NMR spectral data obtained for the synthetic compound **1** and those for the natural product, which suggest that the assignation of **1** as the structure of the natural product is incorrect. We therefore decided to clarify the genuine structure of the monoterpene isolated from *Mentha haplocalyx* through the careful examination of the NMR data reported for the natural product and those of various candidate compounds with structural similarlities. Unexpectedly, we found that the reported ^{13}C and ^{1}H NMR data (in CD_3OD) were in good agreement with those reported for three other natural compounds, i.e., asiasarinol (**2**) [5], comosoxide B (**3**) [6,7], and (1*R**,2*S**)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol (*cis*-**4**) [8]. The close similarities among them strongly suggest that these isolated natural products [1,5,6,8] would have identical structure. This prompted us to undertake the synthesis of **2, 3**, and *cis*-**4**, which had not previously been synthesized.

Asianarinol (**2**) was isolated from the traditional medicine *Asiasarum sieboldii* in 1999, and its structure was proposed as **2** [5]. As depicted in Figure 1, compound **2** consists of a 7-oxabicyclo[2.2.1]hept-2-ene framework. As a starting point for the synthesis of **2** (Scheme 2), we performed the Diels–Alder reaction [9,10] between compound **11** [11] and 2-methylfuran, which was followed by hydrogenation to afford bromoester **13** (43% in 2 steps). The reductive removal of bromine from **13** was performed with zinc powder to give α,β-unsaturated ester **14** in 79% yield. Finally, 1,2-addition of MeMgCl in the presence of $CeCl_3$ furnished the target compound **2** in excellent yield. It is worth noting that only the 1,4-addition product was obtained in the absence of $CeCl_3$ [12].

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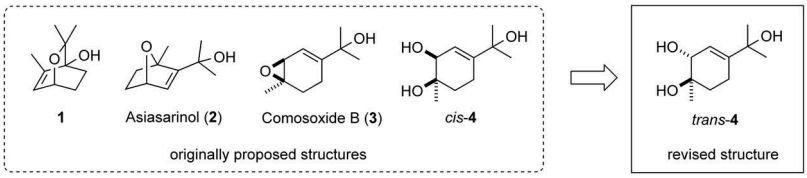
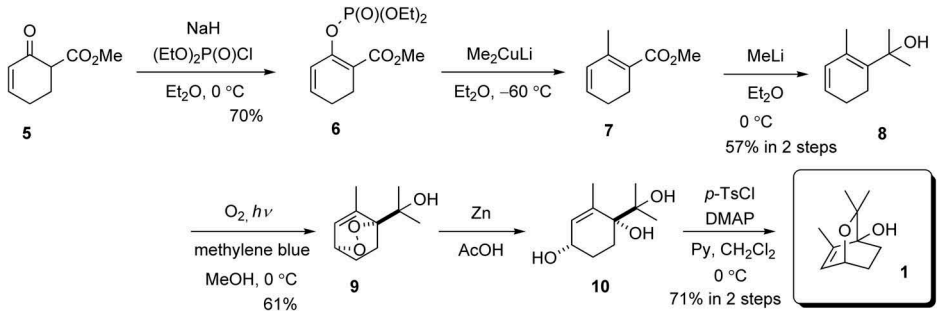


Figure 1. Structures of **1** and the related monoterpenes.



Scheme 1. Synthesis of **1.**

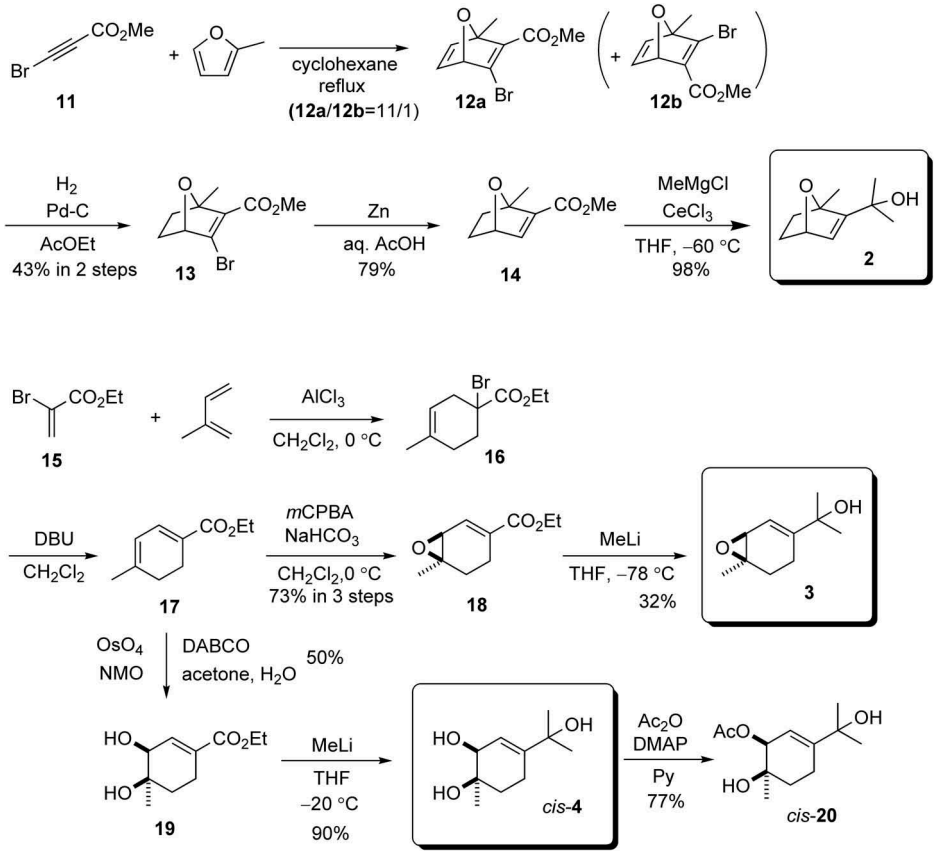
Table 1. ^{13}C and ^{1}H NMR data (in CD_3OD) of the natural product, synthetic **1**, and those of the related compounds.

Natural [1]		Synthetic **1**		**2** [5]		**3** [6]		*cis*-**4** [8]	
δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
21.8	1.15 (Me)	16.6	0.92 (Me)	21.9	1.15	21.9	1.15	21.9	1.14
24.1	1.29 (2xMe)	23.8	1.24 (Me)	24.2	1.29	24.2	1.29	24.3	1.27
29.0 (x2)		25.5	1.85 (Me)	29.0		29.0		29.1	
	1.60–1.70 (2H)	26.3	1.32 (1H)	29.1	1.62	29.1	1.64	29.2	1.60–1.70
34.7		28.1	1.44 (1H)	34.7	1.69	34.7	1.69	34.8	
72.5	2.12 (1H)	68.6		72.5	2.10	72.5	2.11	72.7	
	2.22 (1H)		1.90–2.00 (2H)						2.10–2.20
72.9		76.3		72.9	2.24	72.8	2.24	73.1	
74.7	3.92 (1H)	77.8	4.76 (1H)	74.7	3.92	74.7	3.92	74.9	3.90
122.3	5.59 (1H)	123.6	5.94 (1H)	122.2	5.59	122.3	5.60	122.4	5.58
147.0		148.3		146.9		147.1		147.2	

Meanwhile, comosoxide B (**3**) was isolated from the Thai herbal medicine *Curcuma comosa* in 2008, and the structure **3** depicted in Figure 1, which exhibits a popular *p*-menthane framework with an epoxy ring, was proposed [6]. As shown in Scheme 2, our synthesis of **3** commenced with the Diels–Alder reaction between dienophile **15** [13] and isoprene in the presence of $AlCl_3$. Then, following the reported procedure [14], dehydrobromination with DBU was conducted to afford diene **17**. Regioselective epoxidation of **17** with *m*CPBA produced **18** (73% in 3 steps), which was then treated with MeLi to furnish the desired epoxide **3** (32%). This epoxyalcohol **3** was found to be highly unstable in protic solvents and on silica gel; this prevented us from obtaining ^{13}C NMR data of sufficient quality in CD_3OD.

(1*R**,2*S**)-4-(1′-Hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol (*cis*-**4**) was isolated from *Riella helicophylla* in 1999 [15], from *Protium heptaphyllum* in 2002 [8], and also from *Asarum sieboldii* in 2012 [16]. According to the former two studies, the *cis*-relative configuration was determined based on NOE experiments. It should be noted that only reference [8] reported the NMR data measured in CD_3OD. For the synthesis of *cis*-**4**, we started from intermediate **17**. Through treatment with OsO_4, NMO, and DABCO, **17** was dihydroxylated to give *cis*-diol **19** (50%), which was converted into the target *cis*-**4** by treating with MeLi in 90% yield.

Table 2 summarizes the ^{13}C and ^{1}H NMR data of the synthetic compounds **2, 3**, and *cis*-**4**, where obvious discrepancies with those of the natural product can be observed. After a careful examination of all the spectral data, it seemed reasonable to assign *trans*-**4** as the genuine structure of the monoterpene isolated from *Mentha haplocalyx*, on the basis of the considerable degree of similarity between the spectral data of the natural product and those of the synthetic *cis*-**4**. Notably, to the best of our knowledge, no report has described the synthesis or isolation of *trans*-**4**.



Scheme 2. Synthesis of **2, 3** and *cis*-**4.**

Table 2. ^{13}C and ^{1}H NMR data (in CD_3OD) of the synthetic **2, 3**, and *cis*-**4.**

Natural [6][a]		Synthetic **2**		Synthetic **3**	Synthetic *cis*-**4**	
δ_C	δ_H	δ_C	δ_H	δ_H	δ_C	δ_H
21.9	1.15	20.0	1.35	1.25	23.6	1.17
24.2	1.29	28.9	1.37	1.26	25.3	1.28
29.0		29.5	1.72	1.39	28.9	1.29
29.1	1.64	29.6	1.28–1.50	1.55–1.65	29.0	1.54
34.7	1.69	32.6			32.6	1.82
72.5	2.11	70.6		2.00–2.17	70.7	2.05
72.8	2.24	78.5	1.94		72.6	2.28
74.7	3.92	88.5	4.17	3.13	73.0	3.78
122.3	5.60	129.5	6.02	5.92	121.3	5.65
147.1		148.3			148.0	

[a] NMR data reported in ref [6]. were shown as the representative.

It should be mentioned that the NMR data of the synthetic *cis*-**4** recorded in "$CDCl_3$" were in good agreement with those of the monoterpene isolated from *Riella helicophylla* reported in ref [15]. It means that the monoterpene isolated from *R. helicophylla* possesses the structure *cis*-**4**, unlike that from *Protium heptaphyllum* [8]. We also converted *cis*-**4** into *cis*-**20**, the NMR data of which were identical to those of the naturally occurring *cis*-**20** isolated from Asiasari Radix [17].

We also tackled the synthesis of *trans*-**4**, which was achieved through inversion of the secondary hydroxy group in *cis*-**4** as follows (Scheme 3). After oxidation of *cis*-**4** to the corresponding ketone **21** [18], reduction of **21** under Luche conditions produced the desired *trans*-**4** in 72% yield with a small amount of *cis*-**4** (18%). The NMR data (in CD_3OD) of the synthetic *trans*-**4** were almost identical to those reported for the natural products [1,5,6,8].

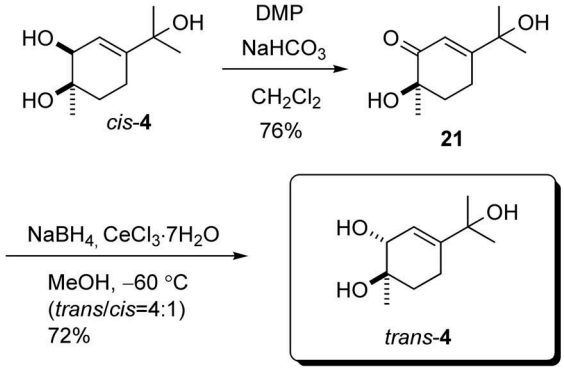
Conclusion

The first racemic synthesis of the incorrectly proposed structure for the monoterpene isolated from *Mentha haplocalyx* (**1**) was achieved. We also found that the reported NMR data of four independently isolated and characterized natural compounds, i.e., **1**, asiasarinol (**2**), comosoxide B (**3**), and *cis*-**4**, were almost identical. By synthesizing these compounds, we proved that all the proposed structures were incorrect. Finally, the genuine structure of not only the monoterpene isolated from *Mentha haplocalyx* but also those of asiasarinol, comosoxide B and the monoterpene isolated from *Protium heptaphyllum* was confirmed to be *trans*-**4**. Studies toward the asymmetric synthesis of *trans*-**4** are currently in progress and will be reported in due course.

Experimental

General procedures

All air- and/or water-sensitive reactions were carried out under Ar atmosphere in dry solvents. Solvents



Scheme 3. Synthesis of *trans*-**4.**

were dried as follows; THF and ether over sodium-benzophenone, dichloromethane over P_2O_5. All melting points (mps) were uncorrected. Melting points were recorded on a Yanaco Melting Point Apparatus. IR spectra were measured with a Jasco FT/IR-230 spectrophotometer. ^{1}H NMR (300, 400 and 500 MHz) and ^{13}C NMR (75, 100 or 125 MHz) data were recorded by JEOL JNM AL300, JEOL ECS400 or JEOL JNM LA500, respectively. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: δ_H = 7.26, δ_C = 77.0; C_6D_6: δ_H = 7.15, δ_C = 128.4; CD_3OD: δ_H = 3.30, δ_C = 49.0). Mass spectra were recorded on JEOL JMS SX102 or JEOL JMS-T100GCV. Column chromatography was performed on Merck silica gel 60 (0.060–0.200 mm), TLC was carried out on Merck glass plates pre-coated with silica gel 60 F_{254} (0.25 mm) and preparative TLC was carried out on Merck glass plates pre-coated with silica gel 60 F_{254} (0.5 mm).

Methyl 2-diethoxyphosphoryloxycyclohexa-1,3-diene-1-carboxylate (6)

To a suspension of NaH (60% oil dispersion; 288 mg, 7.20 mmol) in ether (10 mL) was added a solution of **5** (904 mg, 5.86 mmol) in ether (3 mL) under Ar at 0 °C. After stirring for 3 h at the same temperature, diethyl chlorophosphate (1.04 mL, 7.23 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was poured into sat. aq. NH_4Cl and extracted with ether. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. EtOAc/EtOAc (1/1) gave **6** (1.18 g, 4.07 mmol, 70%) as a colorless oil. IR (film) ν_{max} 2987, 2952, 2838, 1717, 1646, 1299, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 1.36 (3H, t, *J* = 7.2 Hz), 2.21–2.29 (2H, m), 2.53–2.61 (2H, m), 3.75 (3H, s), 4.22 (2H, q, *J* = 7.2 Hz), 4.24 (2H, q, *J* = 7.2 Hz), 6.17 (1H, d, *J* = 9.9 Hz), 6.26 (1H, dt, *J* = 9.9, 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.99, 16.08, 22.47, 22.92, 51.43, 64.58, 64.66, 110.70, 123.51, 123.54, 136.41, 149.98; HR-FIMS *m/z* calcd for $C_{12}H_{19}O_6P$ $[M]^+$ 290.0919, found 290.0935.

Methyl 2-methylcyclohexa-1,3-diene-1-carboxylate (7)

To a suspension of CuI (1.16 g, 6.09 mmol) in ether (25 mL) was added MeLi (1.07 M in ether; 11.4 mL, 12.2 mmol) under Ar at 0 °C. After stirring for 5 min, a solution of **6** (1.18 g, 4.07 mmol) in ether (10 mL) was added to the reaction mixture at −78 °C. After stirring for 10 h at −60 °C, the reaction mixture was poured into sat. aq. NH_4Cl and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude **7** (0.66 g), which was used in the next step without further purification. An analytical sample of **7** was obtained by column chromatography on silica gel (hexane-EtOAc, 50/1) as a colorless oil. IR (film) ν_{max} 3037, 2949, 2881, 2832, 1708, 1575, 1434, 1268, 1218, 1076 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, s), 2.10–2.20 (2H, m), 2.41 (2H, dd, *J* = 9.0, 9.6 Hz), 3.73 (3H, s), 5.90 (1H, d, *J* = 9.3 Hz), 6.09 (1H, dt, *J* = 9.3, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.43, 22.92, 23.12, 51.09, 121.16, 130.90, 132.33, 142.93, 168.88; HR-FIMS *m/z* calcd for $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0851.

2-(2′-Methylcyclohexa-1′,3′-dien-1′-yl)propan-2-ol (8)

To a solution of crude **7** (0.63 g) in ether (15 mL) was added MeLi (1.07 M in ether, 11.2 mL, 12.0 mmol) under Ar at 0 °C. After stirring for 30 min, the reaction mixture was poured into sat. aq. NH_4Cl solution and extracted three times with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. EtOAc/EtOAc (10/1) gave **8** (338 mg, 2.22 mmol, 57% in 2 steps) as a yellow oil. IR (film) ν_{max} 3419,

3033, 2976, 2930, 2871, 2823, 1728, 1667, 1437, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (6H, s), 1.99 (3H, s), 2.00–2.15 (4H, m), 5.74 (2H, br s); HR-FIMS *m/z* calcd for $C_{10}H_{16}O$ $[M]^+$ 152.1201, found 152.1184. The ^{13}C NMR data of **8** were not of sufficient quality due to its instability in $CDCl_3$.

2-(6′-Methyl-2′,3′-dioxabicyclo[2.2.2]oct-5′-en-1′-yl)propan-2-ol (9)

A solution of **8** (456 mg, 3.00 mmol) and methylene blue (46 mg) in methanol (120 mL) was irradiated with visible light for 40 min under O_2 atmosphere at 0 °C. After removal of MeOH *in vacuo*, the residue was filtered through silica gel, and the filtrate was concentrated *in vacuo*. A solution of the residue in CH_2Cl_2 (10 mL) was treated with *p*-TsOH·H_2O (10 mg) at room temperature for 1 h. The resulting mixture was chromatographed over silica gel. Elution with pentane/ether (2/1) gave **9** (338 mg, 1.83 mmol, 61%) as a yellow oil. This peroxide **9** was used for the next step immediately. IR (film) ν_{max} 3489, 2981, 2947, 1638, 1454, 1376, 1180, 933, 867, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.40 (3H, s), 1.46–1.51 (2H, m), 2.17 (3H, s), 2.22–2.28 (2H, m), 4.57 (1H, m), 6.32 (1H, dd, *J* = 0.9, 3.9 Hz).

(1R*,4S*)-1-(1′-Hydroxy-1′-methylethyl)-2-methylcyclohex-2-ene-1,4-diol (10)

To a solution of **9** (27.6 mg, 0.150 mmol) in acetic acid (0.5 mL) was added zinc powder (49 mg, 0.75 mmol) at room temperature. After stirring for 3 h, the reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to give **10** (37 mg), which was used in the next step without further purification. An analytical sample of **10** was obtained by column chromatography on silica gel (EtOAc) as a colorless oil. IR (film) ν_{max} 3384, 2977, 2870, 1715, 1660, 1446, 1381 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.10 (3H, s), 1.18 (3H, s), 1.35–1.50 (2H, m), 1.60–2.00 (2H, m), 1.86 (3H, s), 3.95 (1H, br s), 5.55 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ 21.85, 24.76, 25.87, 29.94, 32.38, 68.27, 76.08, 76.46, 134.45, 139.05; HR-ESIMS *m/z* calcd for $C_{10}H_{18}NaO_3$ $[M+ Na]^+$ 209.1154, found 209.1156.

3,3,5-Trimethyl-2-oxabicyclo[2.2.2]oct-5-en-4-ol (1)

To a solution of **10** (37 mg) in pyridine (0.5 mL) and CH_2Cl_2 (1 mL) were added DMAP (55 mg, 0.45 mmol) and *p*-TsCl (34 mg, 0.18 mmol) at 0 °C. After stirring for 1 day, the reaction mixture was concentrated *in vacuo* and chromatographed over silica gel. EtOAc/EtOAc (5/1) gave **1** (17.8 mg, 0.106 mmol, 71% in 2 steps) as colorless needles. mp 92–96 °C; IR (film) ν_{max} 3373, 3038, 2968, 2939, 2872, 1650, 1440, 1126, 980 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.93 (3H, s), 1.24 (3H, s), 1.32 (1H, dd, *J* = 4.2, 10.8 Hz), 1.44 (1H, dt, *J* = 12.0, 1.8 Hz), 1.85 (3H, d, *J* = 1.8 Hz), 1.90–2.00 (2H, m), 4.17 (1H, m), 5.94 (1H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 16.64, 23.78, 25.53, 26.34, 28.14, 68.56, 76.29, 77.80, 123.57, 148.35; HR-ESIMS *m/z* calcd for $C_{10}H_{16}NaO_2$ $[M+ Na]^+$ 191.1043, found 191.1037.

Methyl 3-bromo-1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (12a)

A solution of 2-methylfuran (15.7mL, 174 mmol) and methyl 3-bromopropiolate **11** (7.10 g, 43.6 mmol) in cyclohexane (100 mL) was refluxed for 1 d. After removal of the solvent, the resulting mixture of **12a** and **12b** was used in the next step without purification.

12a: ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (3H, s), 3.79 (3H, s), 5.21 (1H, d, *J* = 1.8 Hz), 6.99 (1H, d, *J* = 5.1 Hz), 7.14 (1H, dd, *J* = 1.8, 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.43, 51.65, 87.98, 91.49, 142.12, 146.96, 149.94, 153.89, 163.49.

The ratio of **12a:12b** was determined to be 11:1 based on ^1H NMR analysis. The signal due to 1-*Me* of **12b** was observed at δ = 1.74.

Methyl 3-bromo-1-methyl-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (13)

To a solution of a mixture of **12a** and **12b** in EtOAc (100 mL) was added Pd/C (5%; 400 mg). The mixture was stirred under H_2 (0.1 MPa) at room temperature. After stirring for 15 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and chromatographed over silica gel. EtOAc/EtOAc (20/1) gave **13** (4.62 g, 18.7 mmol, 43% in 2 steps) as a yellow oil. IR (film) ν_{max} 2982, 2951, 2871, 1715, 1602, 1435, 1327, 1267, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (1H, m), 1.58 (2H, m), 1.76 (3H, s), 2.03 (1H, ddd, *J* = 5.1, 7.2, 16.5 Hz), 3.79 (3H, s), 4.83 (1H, d, *J* = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.12, 27.29, 31.56, 51.58, 83.83, 89.17, 135.79, 138.39, 163.14; HR-FIMS *m/z* calcd for $C_9H_{11}BrO_3$ $[M]^+$ 245.9892, found 245.9907.

Methyl 1-methyl-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (14)

To a suspension of **13** (4.13 g, 16.7 mmol), zinc powder (3.28 g, 50.2 mmol) in water (70 mL) was added AcOH (10.0 g, 167 mmol) dropwise at room temperature. After stirring for 1 h, the reaction mixture was neutralized with $NaHCO_3$ and filtered through Celite. The filtrate was extracted with ether. The organic layer was dried over

$MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with pentane/ether (8/1) gave **14** (2.22 g, 13.2 mmol, 79%) as a yellow oil. IR (film) ν_{max} 2980, 2951, 2872, 1719, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27–1.42 (2H, m), 1.55 (1H, m), 1.76 (3H, s), 2.04 (1H, m), 3.72 (3H, s), 4.93 (1H, ddd, *J* = 0.9, 1.8, 5.1 Hz), 7.00 (1H, d, *J* = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.67, 27.10, 30.01, 51.36, 77.45, 86.07, 141.53, 145.56, 164.03; HR-FIMS *m*/*z* calcd for $C_9H_{12}O_3$ $[M]^+$ 168.0786, found 168.0788.

2-(1′-Methyl-7′-oxabicyclo[2.2.1]hept-2′-en-2′-yl)-propan-2-ol (2)

To a solution of $CeCl_3$ (4.33 g, 17.6 mmol) in THF (30 mL) was added a solution of **14** (492 mg, 2.93 mmol) in THF (20 mL) at room temperature under Ar. After stirring for 30 min, MeMgCl (3.0 M in THF; 3.90 mL, 11.7 mmol) was added to the mixture at −60 °C. After stirring for 40 min at the same temperature, the reaction mixture was poured into sat. aq. NH_4Cl and extracted with ether. The organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/EtOAc (2/1) gave **2** (483 mg, 2.87 mmol, 98%) as a colorless oil. IR (film) ν_{max} 3418, 2978, 2944, 2871, 1650, 1461, 1384 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.35 (3H, s), 1.36 (3H, s), 1.40–1.53 (3H, m), 1.71 (3H, s), 1.94 (1H, dddd, *J* = 4.0, 4.5, 9.0, 11.0 Hz), 4.76 (1H, dd, *J* = 2.0, 4.5 Hz), 6.02 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 19.96, 28.91, 29.50, 29.60, 32.60, 70.59, 78.49, 88.50, 129.52, 156.90; HR-FIMS *m*/*z* calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1161.

Ethyl 4-methyl-3,4-epoxycyclohex-1-ene-1-carboxylate (18)

According to the reported procedure [13,14], the known ester **17** was prepared from **15** in 2 steps, which was used for this step without purification. To a suspension of **17** (1.47 g, 7.48 mmol) and $NaHCO_3$ (0.75 g, 8.9 mmol) in CH_2Cl_2 (22 mL) was added *m*CPBA (65%; 2.34 g, 8.81 mmol) portionwise under Ar at 0 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was filtered through a silica gel pad, and the filtrate was washed with sat. aq. $Na_2S_2O_3$, sat. aq. Na_2CO_3 and brine successively, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/EtOAc (15/1) gave **18** (1.03 g, 5.47 mmol, 73% in 3 steps) as a yellow oil. IR (film) ν_{max} 2981, 2930, 1714, 1643, 1263, 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 6.9 Hz), 1.46 (3H, s), 1.64 (1H, m), 2.04–2.18 (2H, m), 2.53 (1H, dd, *J* = 6.0, 15.6 Hz), 3.16 (1H, d, *J* = 4.2 Hz), 4.17 (2H, q, *J* = 6.9 Hz), 7.05 (1H, dd, *J* = 3.0, 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 20.63, 21.45, 26.50, 53.63, 60.67, 61.93, 133.77, 134.18, 166.15; HR-FIMS *m*/*z* calcd for $C_{10}H_{14}O_3$ $[M]^+$ 182.0943, found 182.0943.

2-(4′-Methyl-3′,4′-epoxycyclohex-1′-en-1′-yl)-propan-2-ol (3)

To a solution of MeLi (1.14 M in ether; 526 μL, 0.600 mmol) in THF (1 mL) was added a solution of **18** (36.4 mg, 0.200 mmol) in THF (0.8 mL) under Ar at −78 °C. After stirring for 1 h at the same temperature, the reaction mixture was poured into sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/EtOAc (2/1) gave **3** (10.9 mg, 0.0648 mmol, 32%) as a colorless oil. IR (film) ν_{max} 3424, 2975, 2927, 2871, 1726, 1650, 1376, 1253 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.25 (3H, s), 1.26 (3H, s), 1.39 (3H, s), 1.55–1.65 (2H, m), 2.00–2.11 (2H, m), 3.13 (1H, d, *J* = 4.5 Hz), 5.92 (1H, dd, *J* = 2.7, 4.5 Hz); ^1H NMR (300 MHz, C_6D_6) δ 1.06 (3H, s), 1.08 (3H, s), 1.20 (3H, s), 1.20 (1H, m), 1.76–1.86 (2H, m), 2.07 (1H, m), 2.85 (1H, d, *J* = 4.2 Hz), 5.78 (1H, dd, *J* = 3.0, 4.2 Hz);^{13}C NMR (75 MHz, C_6D_6) δ 21.39, 21.67, 27.57, 28.05, 28.20, 54.29, 59.23, 71.69, 107.70, 114.82; HR-FIMS *m*/*z* calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1146.

Compound **3** was highly unstable against protic solvents and decomposed in CD_3OD or D_2O within 0.5 h at room temperature.

Ethyl (3S*,4R*)-3,4-dihydroxy-4-methylcyclohex-1-ene-1-carboxylate (19)

To a solution of **17** (166 mg, 1.00 mmol) in acetone (5 mL) and water (5 mL) were added DABCO (6.7 mg, 0.060 mmol), OsO_4 (1% solution in *t*-BuOH; 0.76 mL, 0.030 mmol) and NMO (50% aq. solution; 234 mg, 1.00 mmol) successively at 0 °C. After stirring for 15 h at room temperature, the reaction mixture was poured into sat. aq. $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/EtOAc (1/1) gave **19** (101 mg, 0.502 mmol, 50%) as colorless crystals. mp 76 °C; IR (film) ν_{max} 3404, 2975, 2938, 1696, 1651, 1445, 1375, 1256, 1137, 1037 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.23 (3H, s), 1.27 (3H, t, *J* = 7.2 Hz), 1.60 (1H, ddd, *J* = 6.0, 9.0, 14.1 Hz), 1.85 (1H, ddd, *J* = 4.2,

6.0, 14.1 Hz), 2.22 (1H, dddt, *J* = 4.2, 6.0, 18.3, 2.1 Hz), 2.45 (1H, dddd, *J* = 2.7, 6.0, 9.0, 18.3 Hz), 3.95 (1H, dt, *J* = 4.2, 2.7 Hz), 4.18 (2H, q, *J* = 7.2 Hz), 6.70 (1H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 14.52, 23.01, 25.92, 33.78, 61.70, 70.24, 72.50, 132.61, 140.44, 168.50; HR-FIMS *m/z* calcd for $C_{10}H_{16}O_4$ $[M]^+$ 200.1049, found 200.1047.

(1R*,2S*)-4-(1'-Hydroxy-1'-methylethyl)-1-methylcyclohex-3-ene-1,2-diol (cis-4)

To a solution of MeLi (1.14 M in ether; 2.6 mL, 3.0 mmol) in THF (3 mL) was added a solution of **19** (98.9 mg, 0.494 mmol) in THF (1 mL) under Ar at −20 °C. After stirring for 20 min at the same temperature, the reaction mixture was poured into sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with CH_2Cl_2/MeOH (10/1) gave *cis*-**4** (83.0 mg, 0.446 mmol, 90%) as a white solid. mp 120 °C; IR (film) ν_{max} 3387, 2974, 2933, 2902, 1662, 1378, 1131 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.34 (6H, s), 1.61 (1H, m), 1.85 (1H, dt, *J* = 13.5, 6.0 Hz), 2.07 (1H, dt, *J* = 18.0, 6.0 Hz), 2.31 (1H, m), 3.88 (1H, br s), 5.73 (1H, m); ^{1}H NMR (300 MHz, CD_3OD) δ 1.17 (3H, s), 1.28 (3H, s), 1.29 (3H, s), 1.54 (1H, dt, *J* = 13.2, 6.3 Hz), 1.82 (1H, ddd, *J* = 5.7, 6.6, 13.2 Hz), 2.05 (1H, dddt, *J* = 5.7, 6.6, 18.0, 1.5 Hz), 2.28 (1H, dddt, *J* = 6.0, 7.2, 18.0, 1.8 Hz), 3.78 (1H, m), 5.65 (1H, dt, *J* = 3.6, 1.8 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 23.64, 25.25, 28.91, 29.03, 33.59, 70.68, 72.63, 72.98, 121.26, 147.95; HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1255.

(1R*,2S*)-1-Hydroxy-4-(1'-hydroxy-1'-methylethyl)-1-methylcyclohex-3-en-2-yl acetate (cis-20)

To a solution of *cis*-**4** (16.0 mg, 0.0859 mmol) and DMAP (11.5 mg, 0.0941 mmol) in pyridine (1 mL) was added Ac_2O (16.3 μL, 0.172 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was poured into dil. HCl and extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with dichloromethane/methanol (20/1) gave *cis*-**20** (16.2 mg, 0.0664 mmol, 77%) as a white solid. mp 89–90 °C; IR (film) ν_{max} 3419, 2976, 2933, 2851, 1716, 1372, 1254 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.33 (6H, s), 1.65 (1H, ddd, *J* = 6.0, 7.5, 13.5 Hz), 1.89 (1H, dt, *J* = 13.5, 6.0 Hz), 2.09 (1H, m), 2.12 (3H, s), 2.37 (1H, dddt, *J* = 6.0, 7.5, 17.5, 2.0 Hz), 5.15 (1H, m), 5.61 (1H, dt, *J* = 3.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.22, 22.32, 25.40, 28.76, 28.97, 33.07, 68.90, 72.52, 74.57, 116.35, 149.25, 170.80; HR-FIMS *m/z* calcd for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1356.

The NMR data described above were almost identical with those reported in ref [16]. Therefore, the structure of the monoterpene isolated from *Riella helicophylla* was proven to be *cis*-**4**.

6-Hydroxy-3-(1'-Hydroxy-1'-methylethyl)-6-methylcyclohex-2-en-1-one (21)

To a solution of *cis*-**4** (83.0 mg, 0.446 mmol) in CH_2Cl_2 (8 mL) were added $NaHCO_3$ (75 mg, 0.89 mmol) and DMP (227 mg, 0.535 mmol) at 0 °C. After stirring for 20 h at room temperature, the reaction mixture was poured into sat. aq. $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with sat. aq. Na_2CO_3 and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/EtOAc (1/1.5) gave **21** (62.1 mg, 0.337 mmol, 76%) as a yellow viscous oil. IR (film) ν_{max} 3419, 2977, 2936, 2872, 1669, 1364, 1326, 1134 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, s), 1.39 (3H, s), 1.40 (3H, s), 1.98 (1H, ddd, *J* = 5.2, 11.6, 12.8 Hz), 2.13 (1H, ddd, *J* = 2.8, 4.8, 12.8 Hz), 2.33 (1H, br s), 2.43 (1H, dddd, *J* = 2.4, 4.8, 11.6, 19.2 Hz), 2.56 (1H, ddd, *J* = 2.8, 5.2, 19.2 Hz), 3.71 (1H, br s), 6.16 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.85, 24.73, 28.56, 28.70, 35.73, 72.60, 72.63, 119.31, 171.35, 203.10; ^{1}H NMR (500 MHz, CD_3OD) δ 1.28 (3H, s), 1.35 (3H, s), 1.37 (3H, s), 1.99–2.02 (2H, m), 2.47 (1H, dddd, *J* = 2.0, 5.5, 9.5, 19.0 Hz), 2.60 (1H, dt, *J* = 19.0, 4.0 Hz), 6.08 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 23.71, 25.57, 28.56, 28.71, 37.65, 73.12, 73.60, 120.90, 173.39, 204.04; HR-FIMS *m/z* calcd for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1103.

(1R*,2R*)-4-(1'-Hydroxy-1'-methylethyl)-1-methylcyclohex-3-ene-1,2-diol (trans-4)

To a solution of **21** (258 mg, 1.40 mmol) in MeOH (7 mL) was added a solution of $CeCl_3{\cdot}7H_2O$ (782 mg, 2.10 mmol) in MeOH (3.5 mL) under Ar at −60 °C. After stirring for 5 min, $NaBH_4$ (58.2 mg, 1.54 mmol) was added to the resulting mixture at the same temperature. After stirring for 15 min, water was added and methanol was removed under reduced pressure. The residual aqueous layer was saturated with NaCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The

residue was chromatographed over silica gel. Elution with CH_2Cl_2/MeOH (15/1 to 8/1) gave *cis*-**4** (46.2 mg, 0.248 mmol, 18%) and *trans*-**4** (187.4 mg, 1.01 mmol, 72%) as a white solid. mp 138 °C; IR (film) ν_{max} 3288, 3211, 2980, 2930, 2873, 1451, 1358, 1311 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (3H, s), 1.34 (3H, s), 1.35 (3H, s), 1.68–1.80 (2H, m), 2.16 (1H, dddt, *J* = 6.0, 9.0, 18.0, 2.0 Hz), 2.27 (1H, dddt, *J* = 6.0, 7.5, 18.0, 1.5 Hz), 4.09 (1H, q, *J* = 2.5 Hz), 5.68 (1H, ddd, *J* = 1.5, 2.0, 2.5 Hz); ^1H NMR (500 MHz, CD_3OD) δ 1.15 (3H, s), 1.29 (6H, s), 1.60–1.71 (2H, m), 2.11 (1H, dddt, *J* = 6.0, 8.0, 18.0, 2.0 Hz), 2.23 (1H, dtt, *J* = 18.0, 1.5, 6.0 Hz), 3.92 (1H, m), 5.59 (1H, dt, *J* = 3.0, 1.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 21.85, 24.13, 29.01, 29.06, 34.71, 72.50, 72.90, 74.78, 122.31, 147.05; HR-FIMS *m*/*z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1261.

(1R,2R*)-1-Hydroxy-4-(1'-hydroxy-1'-methylethyl)-1-methylcyclohex-3-en-2-yl acetate (trans-20)*

In the same manner as described before, *trans*-**4** (16.0 mg, 0.0859 mmol) was converted to *trans*-**20** (18.6 mg, 0.0762 mmol, 89%). mp 106–108 °C; IR (film) ν_{max} 3411, 2978, 2933, 2854, 1718, 1372, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.33 (6H, s), 1.77–1.80 (2H, m), 2.10 (3H, s), 2.16 (1H, ddt, *J* = 6.0, 8.5, 2.0 Hz), 2.26 (1H, dtt, *J* = 18.0, 1.3, 5.5 Hz), 5.20 (1H, dd, *J* = 2.5, 4.5 Hz), 5.57 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.23, 21.94, 22.95, 28.87, 34.13, 70.50, 72.43, 117.38, 148.24, 171.78; HR-FIMS *m*/*z* calcd for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1362.

NOE experiments on cis- and trans-4

Synthetic *cis*- and *trans*-**4** were subjected to NOE experiments. The NOE correlation between 1-Me and 2-H was observed in both isomers as shown below (Figure 2). This might be the reason for structural confusion between *cis*- and *trans*-**4**.

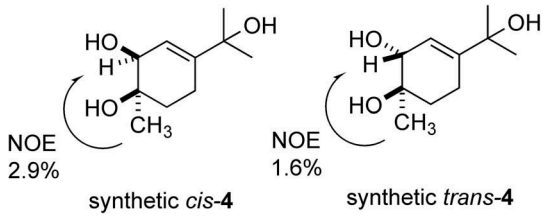


Figure 2.

Author Contribution

H.W. designed this study. S.K. carried out the experiments. N.M. contributed to analytical works. S.K. and H.T. wrote the manuscript with assistance from all authors.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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