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Total Synthesis of (-)-(7S,10R)-Calamenene and (-)-(7S,10R)-2-Hydroxycalamenene by Use of a Ring-Closing Metathesis Reaction. A Comparison of the *cis*- and *trans*-Isomers

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Abstract: The title compounds have been synthesized starting from *l*-menthone by application of a ring-closing metathesis reaction to confirm their reported absolute and relative stereochemistry. Comparisons of the NMR spectra and specific rotations are also discussed.

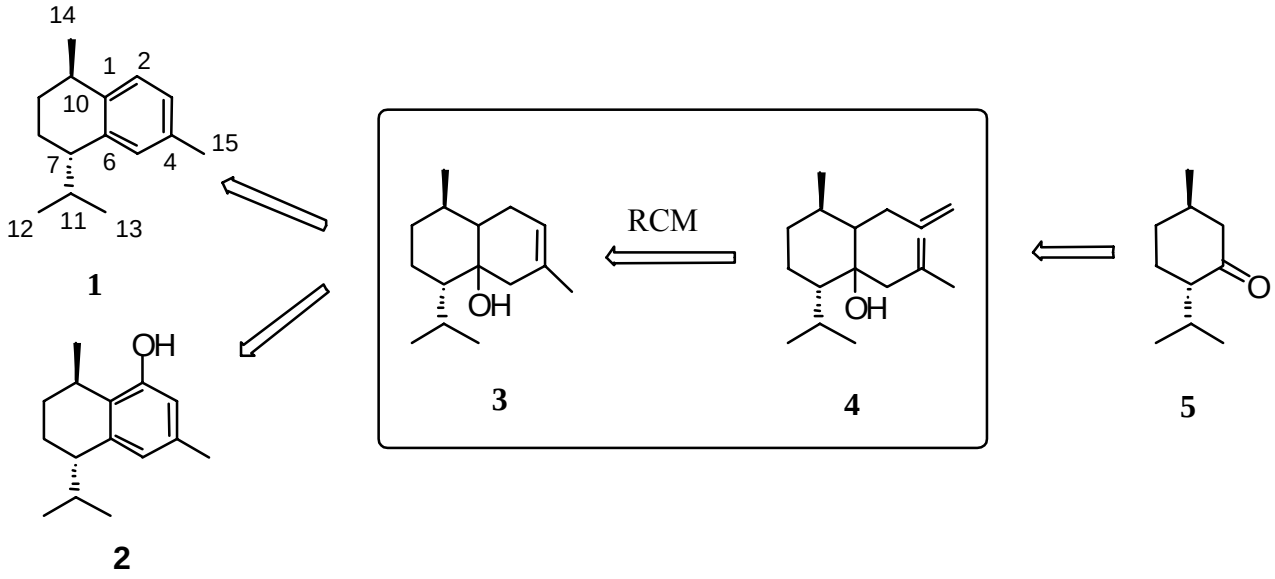
Keywords: Calamenene, hydroxycalamenene, ring closing metathesis, absolute configuration, sesquiterpene.

Introduction

The absolute configurations of both (7S,10R)-calamenene (**1**), isolated from *Chamaecyparis nootkatensis* by Andersen et al. [1] and (+)-2-hydroxycalamenene (**2**) [2], isolated from *Dysoxylum acutangulum* by Nishizawa et al. [3] were determined using CD spectra or X-ray analysis and chemical transformations. The stereochemistry of **1** was later revised after X-ray analysis [4]. We have been working on natural products found in the liverwort [5, 6] and have reported the isolation of several calamenenes [7, 8], including 5-hydroxycalamenene, whose structure was determined by X-ray analysis [8]. Up to now, total syntheses of these chiral substances have never been clearly reported because the final products were always a mixture of *cis*- and *trans*-isomers [9]. We are currently working on the

ring-closing metathesis reaction (RCM) [10, 11] and planned to synthesize these natural products possessing trisubstituted double bonds, in optically active forms, by application of RCM. As shown in Scheme 1, our synthetic plan is to construct the trisubstituted double bond by RCM [12-14] starting from *l*-menthone (**5**).

Scheme 1



Results and Discussion

l-Menthone (**5**) was first allylated with LDA and then a Grignard reaction of this ketone with methallylmagnesium chloride afforded alcohol **4**. No attempt was made to determine the stereochemistry because the newly created chiral center of compound **4** will be lost at a later stage. Now, the diene alcohol **4** was treated with Grubbs' catalyst (5 mol%) in CH_2Cl_2 (10 mM) at r.t. overnight to produce alkene **3** in 96% yield. The stereochemistry of alkene **3** was analyzed by NOESY, however, due to the overlapping of the protons the *cis*/*trans* stereochemistry at the ring junction was not known. Dehydration of alcohol **3** with $POCl_3$ afforded calamenene (**1**) and a small amount of diene **6**. The diene **6** was oxidized by DDQ to afford only cadalene (**7**) and no calamenene (**1**) was obtained. The alcohol **3** was also transformed into enone **8** by allylic oxidation and then dehydration of **8** produced phenol **2**, although the yield was low (Scheme 2).

The spectral data of **1** were identical in all aspects to those reported in the literature [1], including the specific rotation. The spectral data of compound **2** were also identical to those found in the literature [3], however, the sign of the rotation was opposite to that reported. Thus, we conclude that the synthetic compound was the enantiomer of the natural product found by Nishizawa et al. [3] and the assigned absolute configuration was correct.

Scheme 2

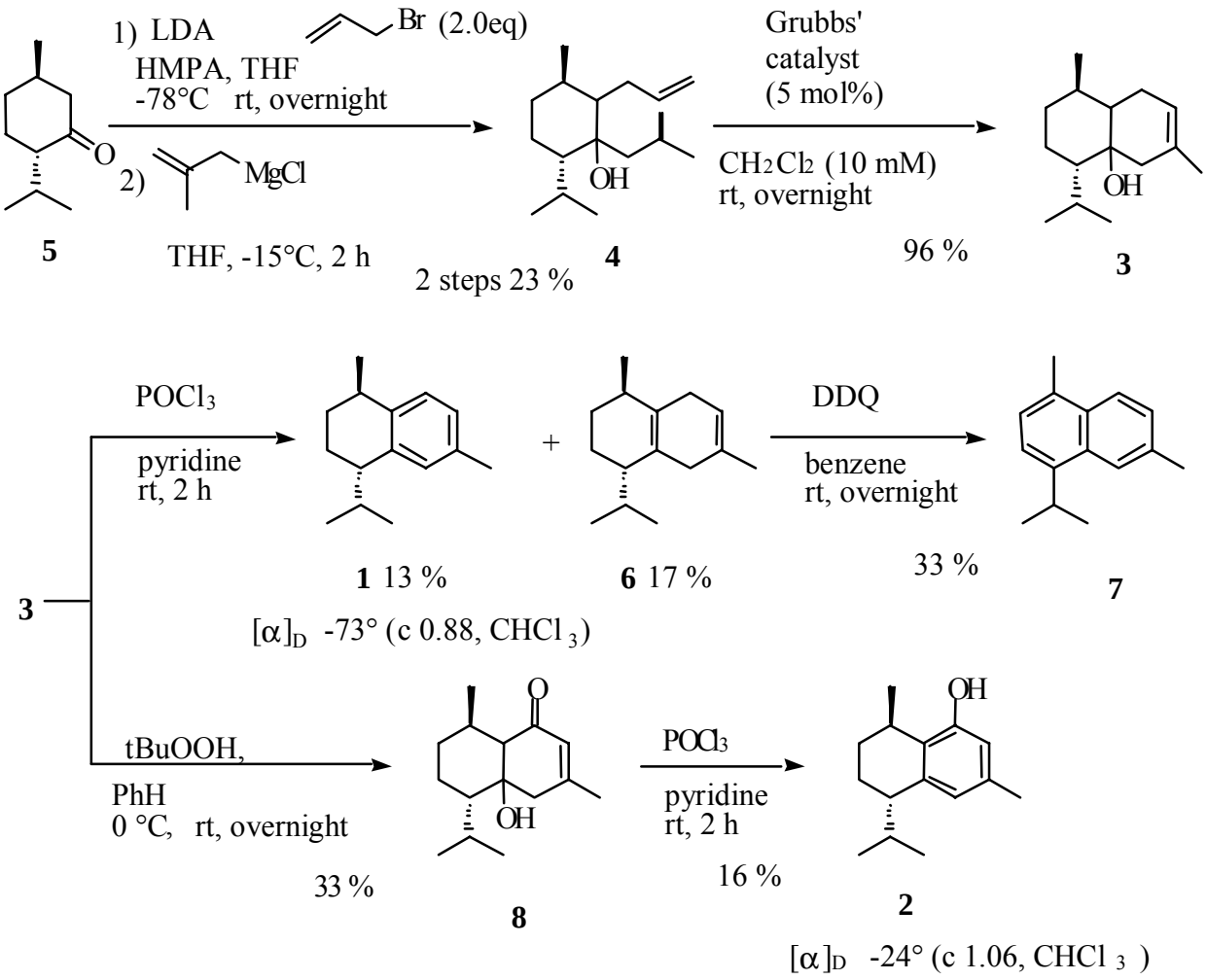


Figure 1. ^{1}H-NMR spectra of compound **1** (trans)

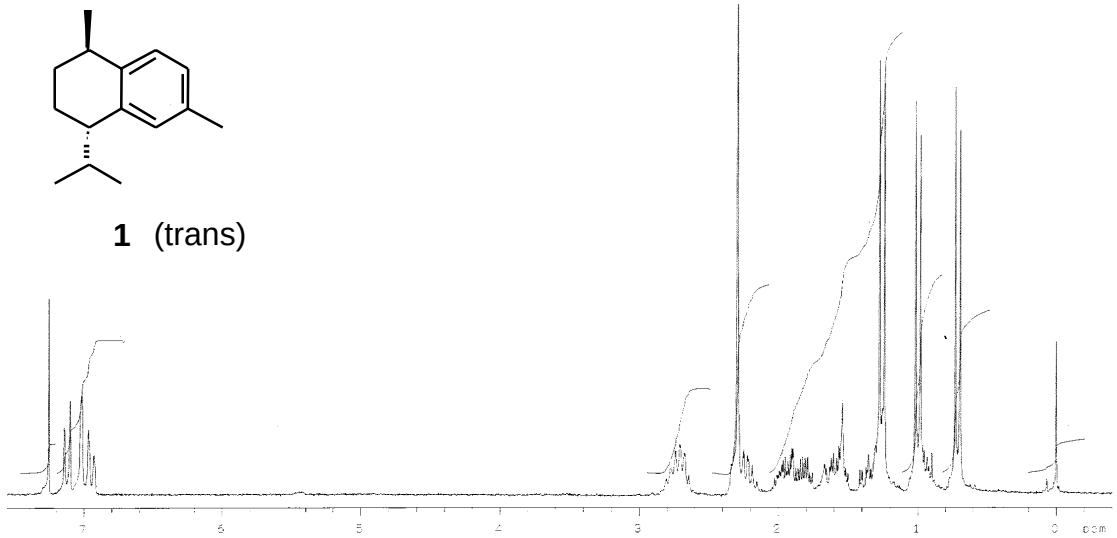


Figure 1 (cont). [1]H-NMR spectra of compound **20** (cis)

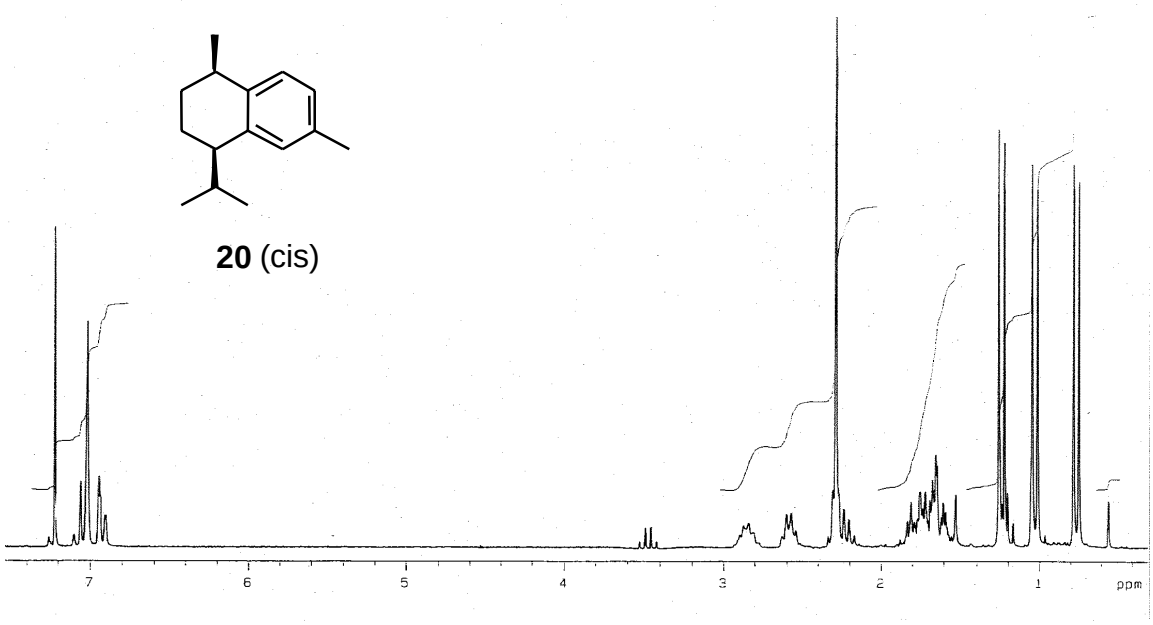


Figure 2. [1]H-NMR spectra of compound **2** (trans)

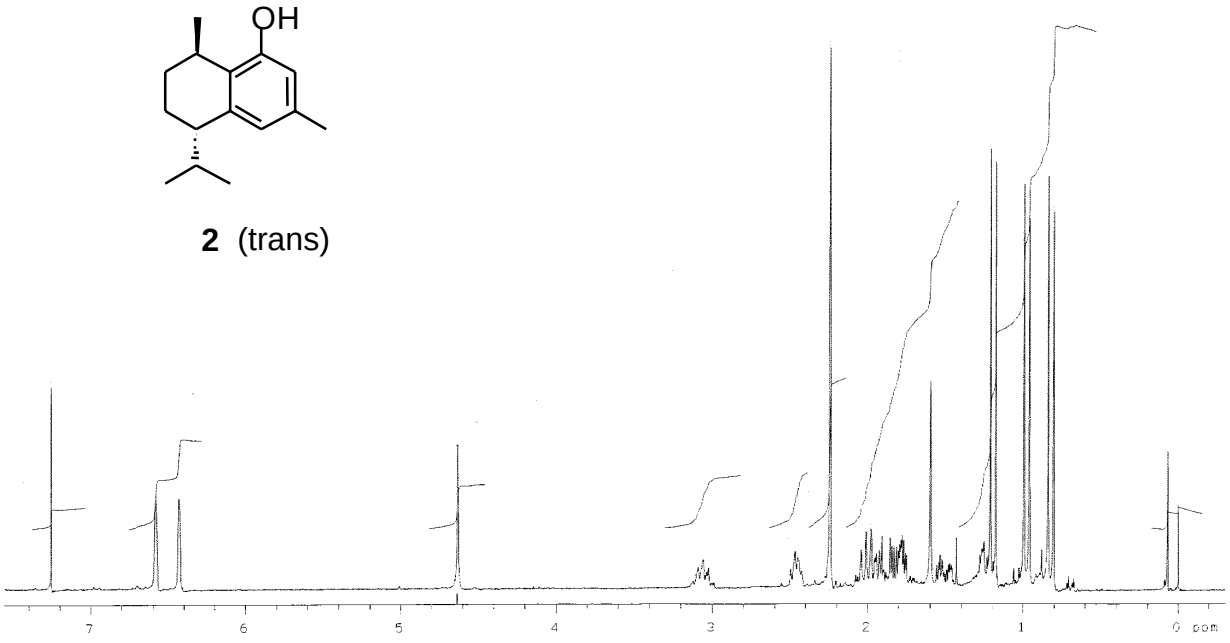
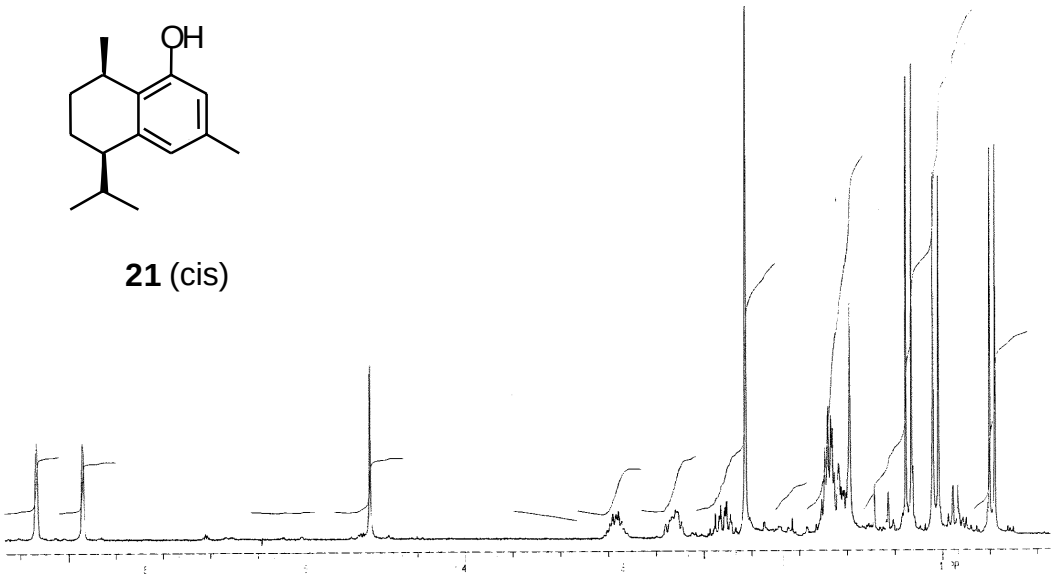
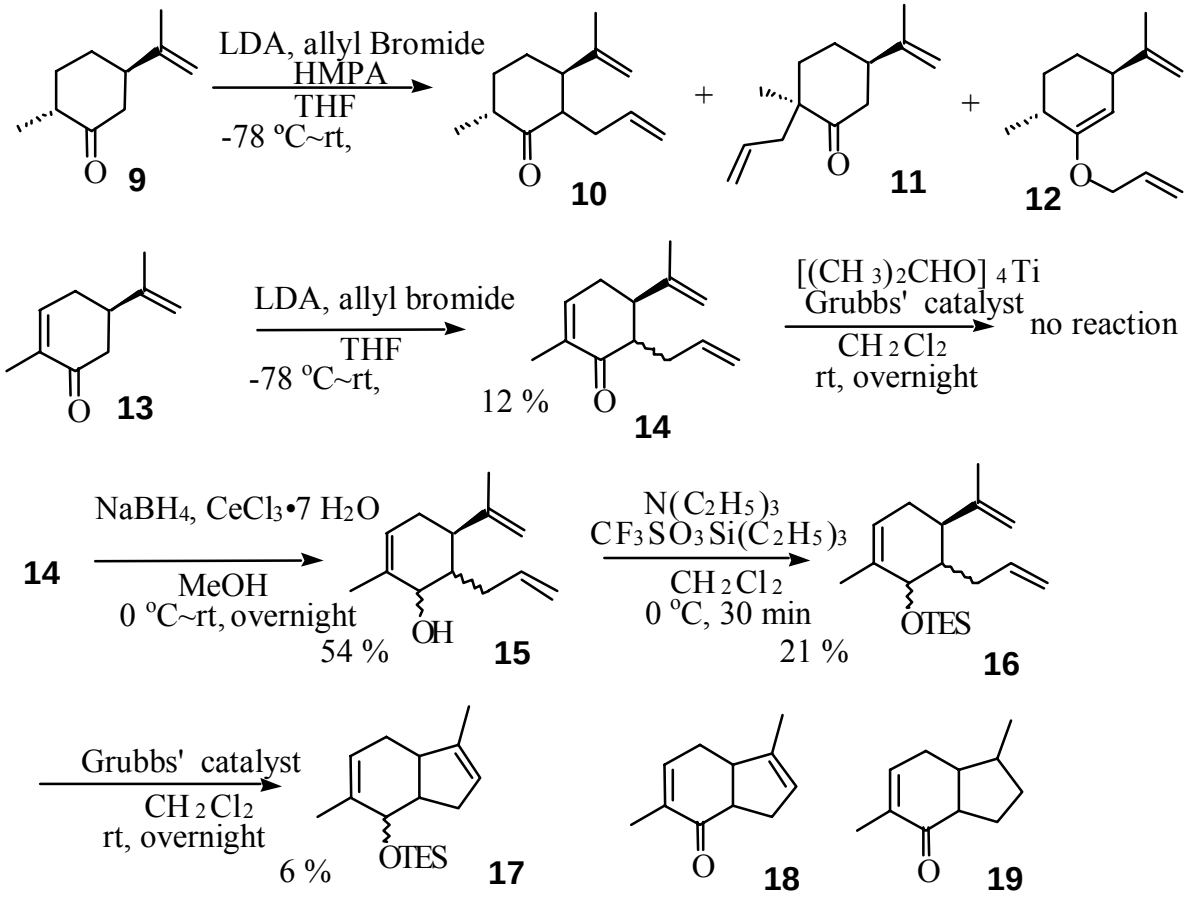


Figure 2 (cont). ^{1}H-NMR spectra of compound **21** (cis)



We next attempted the synthesis of compounds **18** or **19**, which are potential intermediates for the synthesis of tamariscol [15, 16] and other terpenoids.

Scheme 3

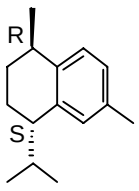
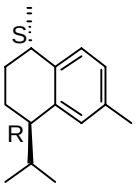
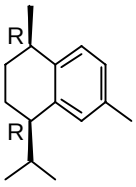
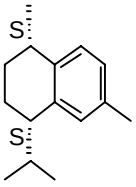
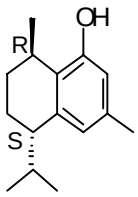
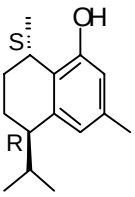
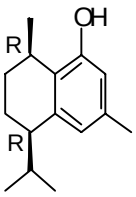
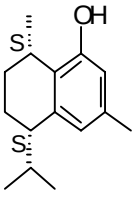


Thus, dihydrocarvone (**9**) was allylated with LDA and allyl bromide, however, the desired product **10** was only formed in minute amounts. Instead, compounds **11** and **12** were produced in larger quantities. Therefore, allylation of carvone (**13**) itself was tried. Again the yield was low, however, the RCM was attempted with Grubbs' catalyst. No reaction occurred in the case of compound **14**. In an alternate approach, the carbonyl group in **14** was reduced and protected with a TES group to afford **16**. Then, compound **16** was treated with Grubbs' catalyst, but the cyclized product **17** was produced only in 6% yield (Scheme 3).

Conclusions

We have applied the RCM reaction to the construction of a trisubstituted alkene and thus synthesized two calamenene-type natural products, **1** and **2**. The ^{1}H-NMR spectra of **1** and **2** were compared with those of the *cis*-isomers (Figures 1 and 2) [8]. Confusion about the stereochemistry (Table 1) as well as the different numbering systems and names used for these compounds [2], made it very difficult to identify each compound unambiguously.

Table 1. Comparison of specific rotations

Compound	 **1**	 *ent*-**1**	 **20**	 *ent*-**20**
Synthetic product (this work)	-73			
Reported data	-96 [1] -77 [18]	+31 [7]	-22 [1, wrong] +43 [4] +33.4 [8]	-31 [17]
Compound	 **2**	 *ent*-**2**	 **21**	 *ent*-**21**
Synthetic product (this work)	-24	-	-	-
Reported data	-	+38 [3]	+40[20]	-

The original assignment by Andersen et al. [1] was later revised by Croft et al. [4] and other syntheses have always afforded mixtures of *cis* and *trans* products. We now offer reliable data for the *trans* derivatives and also give NMR data for comparison with those of *cis*-isomers [7, 8, 18, 19]. The ^{13}C-NMR spectrum for compound **20** in ref. [18] was measured with an 80 MHz machine, while our spectrum was taken with a 400 MHz spectrometer (Table 2). Because some peaks are congested in a narrow region, some problems could have resulted with the assignments and our data have not yet been fully assigned [20]. It is noteworthy that a condensed cyclopentene ring was not easy to construct by the RCM reaction, presumably due to the fact that stereochemistry was not correct for cyclization.

Table 2. ^{13}C-NMR data for the calamenes

No.	**1** this work*	**1** [18]	**20** [20]*	**20** [18]	**2** this work*	ent-**2** [3]	**21** [20]*
1	140.1	140.3	139.7	140.0	126.1	126.5	126.7
2	126.8	127.0	128.5	128.5	153.2	153.2	153.0
3	126.2	126.4	126.3	126.5	113.4	113.8	112.8
4	134.5	134.6	134.5	134.6	135.1	135.1	135.7
5	128.8	129.0	128.7	128.9	123.0	123.1	120.8
6	140.0	140.3	139.9	140.2	141.3	141.3	141.3
7	43.8	44.1	43.6	43.8	43.0	43.2	43.3
8	21.1	21.3	23.3	23.3	19.1	19.2	16.4
9	30.8	31.0	28.7	28.9	27.1	27.2	28.8
10	32.5	32.6	31.1	31.2	26.5	26.7	26.5
11	31.9	32.1	32.5	32.7	33.1	33.2	30.9
12	17.3	17.5	17.6	17.8	19.6	19.7	17.3
13	21.5	21.6	21.4	21.5	21.0	21.1	20.5
14	22.3	22.3	19.7	22.5	22.1	22.2	21.2
15	21.3	21.3	21.2	21.2	21.1	21.3	21.1

*assignment is tentative.

Acknowledgements

We thank Dr. Masami Tanaka and Ms. Yasuko Okamoto (our university) for measurement of the NMR and MS spectra, respectively.

Experimental

General

The IR spectra were measured with a JASCO FT/IR-500 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL ECP-400, a Varian Unity 200, or a Varian Gemini 200 spectrometer. Deuteriochloroform was used for NMR and chemical shifts were expressed in ppm and the coupling constant in Hz. The mass spectra, including high-resolution mass spectra, were taken with a JEOL AX-500 spectrometer. The specific rotation was measured with a JASCO DIP-100 polarimeter. Silica gel BW-300 (200-400 mesh, Fuji silycia) was used for column chromatography, and silica gel $60F_{254}$ plate (0.25 mm, Merck) were used for TLC. All reactions were carried out under an argon atmosphere. THF was distilled from $LiAlH_4$ and then from Na-benzophenone prior to use. RCM reagent was weighed in a dry box and was used without purification. Anhydrous dichloromethane and benzene used for the reactions were purchased from Kanto Chemical, Japan and were used without further purification.

*Preparation of [1ξ,2ξ,3R,6S]-2-allyl-6-isopropyl-3-methyl-1-(2-methylpropyl)cyclohexan-1-ol (**4**).*

l-Menthone (300 mg, 1.95 mmol) was treated with LDA (*n*-BuLi, 1.5 eq.; *i*Pr_2NH, 1.5 eq.) in THF at -78˚C for 1 h, then, allyl bromide (0.39 mL, 2.0 eq.) was added. The temperature was gradually raised to r.t. overnight. Water was added and the solvent was removed. The mixture was extracted with ether and the organic layer was washed with 1M HCl and brine, dried ($MgSO_4$), and evaporated to afford a residue which was purified by silica gel column chromatography (hexane-EtOAc, 0-25%) to give 2-allylmenthone (65.3g, 17%); FTIR: 1720 cm^{-1}; ^{1}H-NMR (200 MHz) δ 0.84 (3H, d, J = 6.4 Hz), 0.89 (3H, d, J = 6.4 Hz), 1.04 (3H, d, J = 6.4 Hz), 1.47 (3H, m), 1.87 (1H, m), 2.06 (4H, m), 2.34 (2H, m), 4.94 (1H, br d, J = 10.4 Hz), 5.00 (1H, br d, 16.8 Hz), 5.84 (1H, ddt, J = 16.8, 10.4, 5.6 Hz); ^{13}C-NMR (50 MHz) δ 18.8 (CH_3), 20.5 (CH_3), 21.4 (CH_3), 26.1 (CH), 29.1 (CH_2), 30.4 (CH_2), 34.7 (CH_2), 39.9 (CH), 56.9 (CH), 57.5 (CH), 115.5 (CH_2), 137.3 (CH), 212.0 (C); MS (EI) *m/z* 194 $[M]^+$ 194 (base), 179, 151, 138, 123, 109, 95, 81, 69, 55; HRMS (EI) Found *m/z* 194.1664 $[M]^+$. $C_{13}H_{22}O$ requires 194.1670.

The Grignard reagent was prepared from methallyl chloride (1 mL, 10 mmol) and Mg (243 mg, 10 mmol) in THF (8 mL) with aid of dibromoethane (0.05 mL, 0.1 eq.) at -15˚C. One half of this Grignard reagent was introduced into a solution of 2-allylmenthone (100 mg, 0.52 mmol) in THF at -15˚C over 2 h. Saturated NH_4Cl solution and water were added and the mixture was extracted with ether. The organic layer was washed with sat. NH_4Cl soln. and brine, dried ($MgSO_4$), and was evaporated to afford a residue which was purified by silica gel column chromatography (hexane-EtOAc, 0-10%) to give **4** (122 mg. 95%). **4**; FTIR: 3600, 1640 cm^{-1}; ^{1}H-NMR (200 MHz) δ 0.92 (9H, m), 1.29 (2H, m), 1.41-1.58 (4H, m), 1.80 (1H, m), 1.83 (3H, m), 2.24 (1H, m), 2.36-2.72 (4H, m), 4.84 (1H, br s), 4.94 (1H, br s), 5.02 (1H, d, J = 9.6 Hz), 5.18 (1H, d, J = 17.4 Hz), 6.08 (1H, m); ^{13}C-NMR (50 MHz) δ 18.2 (CH_3), 20.4 (CH_3), 20.9 (CH_3), 23.2 (CH_3), 25.1 (CH_3), 26.6 (CH), 31.7 (CH), 32.4 (CH_2), 35.9 (CH_2), 44.3 (CH_2), 48.3 (CH), 49.8 (CH), 79.6 (C), 114.7 (CH_2), 116.1 (CH), 138.7 (CH), 141.9 (C); MS (EI) *m/z* 250 $[M]^+$ 250, 217,

195 (base), 177, 139, 121, 109, 97, 83, 69, 55; HRMS (CI) Found *m/z* 251.2373 $[M+ H]^+$. $C_{13}H_{22}O$ requires 251.2375.

*Preparation of [1ξ,6ξ,7R,10S]-10-isopropyl-3,7-dimethylbicyclo[4.4.0]dec-3-en-1-ol (**3**).*

To a stirred solution of **4** (350 mg, 1.4 mmol) in degassed CH_2Cl_2 (125 mL) was added a solution of Grubbs reagent (57.6 mg, 5 mol%) in CH_2Cl_2 (15 mL) under Ar at room temperature. The mixture was stirred overnight at r.t. The septum was removed and the mixture was stirred for further 30 min. and then the solvent was removed. The residue was directly purified by silica gel column chromatography (hexane-EtOAc, 0-20%) to afford **3** (298 mg, 96%): FTIR: 3450-3600 cm^{-1}; ^{1}H-NMR (600 MHz)δ 0.86 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.9 Hz), 0.94 (3H, d, J = 6.9 Hz), 1.02 (2H, m), 1.08 (1H, m), 1.38 (1H, m), 1.50 (2H, m), 1.67 (3H, s), 1.71 (1H, m), 1.73 (1H, m), 1.96 (1H, br d, J = 18 Hz), 2.21 (3H, m), 5.44 (1H, br s); ^{13}C-NMR (50 MHz) δ 18.2 (CH_3), 19.9 (CH_3), 20.3 (CH_2), 23.7 (CH_3), 23.7 (CH_3), 25.5 (CH), 26.9 (CH_2), 33.3 (CH), 35.5 (CH_2), 42.8 (CH_2), 46.8 (CH), 51.9 (CH), 72.5 (C), 120.2 (CH), 130.8 (CH); MS (EI) *m/z* 222 $[M]^+$ 204, 189, 179, 161 (base), 139, 119, 105, 93, 84, 69, 55; HRMS (EI) Found *m/z* 222.1991 $[M]^+$. $C_{15}H_{26}O$ requires 222.1983.

*Preparation of (-)-calamenene (**1**) and [7S,10R]-2,5-dihydrocalamenene (**6**).*

A solution of **3** (100 mg, 0.45 mmol) in pyridine (5 mL) was treated with $POCl_3$ (0.084 mL, 2.0 eq.) at r.t. overnight. Water was added and the mixture was extracted with ether. The organic layer was washed with 1M HCl and brine, dried ($MgSO_4$) and evaporated to afford a residue which was purified by silica gel column chromatography (hexane-EtOAc, 0-20%) to give (-)-calamenene (**1**) (12.0 mg, 13%) and **6** (15.4 mg, 17%). **1**: $[\alpha]_D$ -73 ° (c 0.88, $CHCl_3$); FTIR: 1510-1470 cm^{-1}; ^{1}H-NMR (200 MHz) δ 0.72 (3H, d, J = 7.2 Hz), 1.00 (3H, d, J = 7.2 Hz), 1.26 (3H, d, J = 7.2 Hz), 1.39 (1H, m), 1.60 (1H, m), 1.81 (1H, m), 1.95 (1H, m), 2.22 (1H, m), 2.30 (3H, s), 2.70 (2H, m), 6.94 (1H, br d, J = 8.0 Hz), 7.02 (1H, br s), 7.12 (1H, d, J = 8.0 Hz); ^{13}C-NMR (50 MHz) Table 1); MS (EI) *m/z* 202 $[M]^+$ 202, 159 (base), 144, 129, 115, 115, 105, 91; HRMS (EI) Found *m/z* 202.1696 $[M]^+$. $C_{15}H_S$ requires 202.1722. **6**; ^{1}H-NMR (200 MHz) δ 0.91(3H, d, J = 5.9 Hz), 0.93 (3H, d, J = 5.9 Hz), 0.98 (3H, d, J = 5.9 Hz), 1.68 (3H, br s), 5.42 (1H, m).

*Preparation of [1ξ,6ξ,7S,10R]-6-hydroxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-3-en-2-one (**8**).*

A solution of **3** (100 mg, 0.45 mmol) in benzene (10 mL) was treated with Celite (1.05 g), *t*BuOOH (0.31 mL), and PDC (1.2 g, 1.35 mmol) at 0˚C and the mixture was stirred overnight. The temperature was gradually raised to room temperature overnight. A solution of $Na_2S_2O_3$ was added and the mixture was filtered through Celite. The filtrate was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to afford a residue which was purified by silica gel column chromatography (hexane-EtOAc, 0-30%) to give **8** (35.4 mg, 33%); FTIR: 3400, 1660 cm^{-1}; ^{1}H-NMR (200 MHz) δ 0.90 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.6 Hz), 0.95 (1H, m), 1.08 (3H, d, J = 5.8 Hz),

1.30 (3H, m), 1.55 (1H, m), 1.85 (1H, m), 1.89 (3H, s), 2.10 (2H, m), 2.40 (1H, br d, J = 17.6 Hz), 2.65 (1H, d, J = 17.6 Hz), 5.79 (1H, s); ^{13}C-NMR (50 MHz) δ 18.1 (CH_3), 19.6 (CH_2), 22.1 (CH_3), 23.7 (CH_3X2), 25.5 (CH), 27.3 (CH), 34.9 (CH_2), 44.2 (CH_2), 52.0 (CH), 60.7 (CH), 77.1 (C), 126.4 (CH), 153.7 (C) 200.5 (C); MS (EI) *m/z* 236 $[M]^+$, 236, 221, 193, 175, 165, 151, 137 (base), 125, 111, 95, 83, 69, 55; HRMS (EI) Found *m/z* 236.1770 $[M]^+$. $C_{15}H_{24}O_2$ requires 236.1777.

*Preparation of (-)-[7S,10R]-2-hydroxycalamenene (**2**).*

A solution of **8** (63 mg, 0.27 mmol) in pyridine (2 mL) was treated with $POCl_3$ (0.13 mL, 5 eq.) at 0˚C. The mixture was stirred at r.t. overnight. Water was added and the mixture was extracted with ether. The organic layer was washed with 1M HCl, and brine, dried ($MgSO_4$) and evaporated to afford a residue which was purified by silica gel column chromatography (hexane-EtOAc, 0-50%) to give **2** (18.7 mg, 16%); $[\alpha]_D$ -24° (c 1.06, $CHCl_3$); FTIR: 3450, 1620, 1580 cm^{-1}; ^{1}H-NMR (200 MHz) δ 0.82 (3H, d, J = 7.2 Hz), 0.99 (3H, d, J = 7.2 Hz), 1.20 (3H, d, J = 7.2 Hz), 1.51 (1H, m), 1.81 (1H, m), 1.99 (2H, m), 2.24 (3H, s), 2.46 (1H, m), 3.05 (1H, s), 4.64 (1H, s), 6.43 (1H, s), 6.58 (1H, s); ^{13}C-NMR (50 MHz) (Table 1); MS (EI) *m/z* 218 $[M]^+$, 218, 175 (base), 160, 147, 121, 115, 105, 91; HRMS (EI) Found *m/z* 218.1691 $[M]^+$. $C_{15}H_{22}O$ requires 218.1671.

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Sample Availability: Samples are not available.

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