Total Syntheses of (±)-(*Z*)- and (±)-(*E*)-9-(Bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one and (±)-Majusculone

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Abstract: A new total synthesis of the chamigrene sesquiterpenoids (*Z*)-9-(bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-diene-3-one and its 15-*E*-epimer has been accomplished in 13 steps. In our sequence, a Diels–Alder reaction and subsequent reductive alkylation of the resulting adduct was utilized as the key strategy to create the A-ring and the quaternary spirocenter with the suitable functionalities for accessing the B-ring. Additionally, from the advanced intermediate, a total synthesis of (±)-majusculone, a nor-chamigrene natural product, was also readily achieved in two steps.

Key words: chamigrenes, sesquiterpenes, majusculone, total syntheses, Diels–Alder reaction

In the past years, over one hundred members of chamigrene-type sesquiterpenoids have been isolated from natural sources.[1] Structurally, these natural products are characterized by a spiro[5.5]undecane skeleton with two vicinal quaternary carbon centers at C-5 and C-6 positions (Figure 1). Many chamigrenes, especially those being halogenated by bromine and/or chlorine atom(s), have been shown to possess a wide variety of interesting biological activities[1a] such as antibacterial[2b] and antifungal[2c] properties, and the cytotoxicity against a range of cancer cell lines.[1b,f,g,j,2a] Besides, this class of natural products has also attracted considerable interest from synthetic community, as reflected by a number of documented examples on their total syntheses.[3]

Belonging to the chamigrene family, (*Z*)-9-(bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-diene-3-one (**1**) and its 15-*E*-epimer **2** (Figure 1) were both isolated from the red algae *Laurencia majuscula* Harvey.[4,5] Their spirobicyclic framework is composed by an A-ring carrying a C1–C3 enone moiety and a B-ring containing a C7–C8 double bond conjugated with an *exo*-bromomethylene functionality. Like many other chamigrenes, the intriguing structural features make **1** and **2** attractive targets for total synthesis. In 1983, Iwata and co-workers reported the first total synthesis of **1** and **2** by using a copper-catalyzed cyclization of a phenolic α-diazo ketone to create the core structure (Scheme 1).[6] Following this, Niwa's group[7] described the second total synthesis by employing an acid-promoted spiroannulation of an enone aldehyde derived from anisole to construct the spirocyclic skeleton. In these synthetic routes, however, the key spirocyclic intermediates were produced either in a relatively low yield (22%)[6] or as an inseparable mixture with a tricyclic regioisomer.[7]

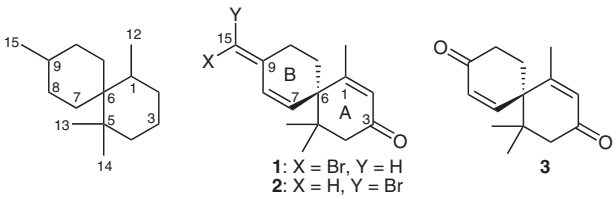
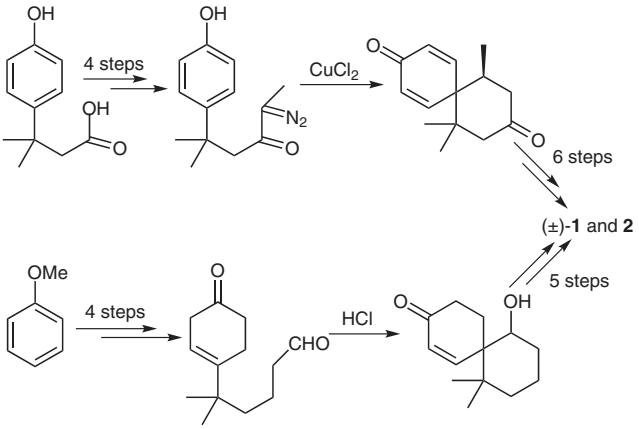


Figure 1 Skeleton of chamigrene and structures of **1**, **2**, and **3**



Scheme 1 Iwata's and Niwa's synthetic approaches to **1** and **2**

We herein wish to report the third total synthesis of (±)-**1** and (±)-**2** based on an approach to highly substituted cyclohexene system as recently developed by Liu's and our laboratories.[8] In our synthetic sequence, a Diels–Alder reaction of an α-cyano α,β-unsaturated ester and a lithium naphthalenide (LN)-induced reductive alkylation of the resulting adduct were employed as the key operations to create the A-ring and the quaternary spirocenter of **1** and **2**. In addition, a total synthesis of (±)-majusculone (**3**, Figure 1), a naturally occurring 9-norchamigrene-type metabolite first isolated with **2**,[1h,5] was also achieved from an advanced intermediate leading to **1** and **2** through simple operations.

As outlined in our initial retrosynthetic analysis (Scheme 2), we envisioned that the Diels–Alder reaction

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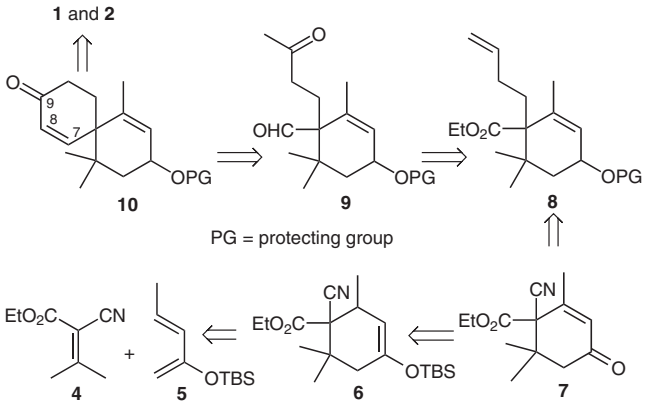
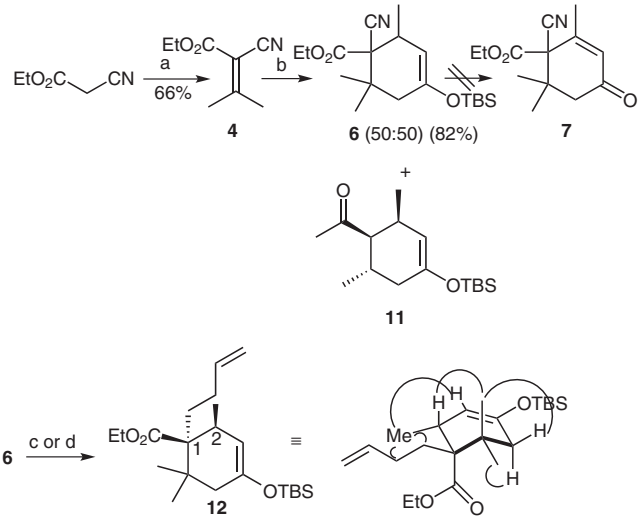
between 2-cyano-3-methylbut-2-enoic acid ethyl ester (**4**) and the Danishefsky-type diene **5** could be used to create the A-ring of **1** and **2** in a single step with the concomitant introduction of the C-5 quaternary center and the C-1 methyl group. In addition, the silyl enol ether moiety of the resulting adduct **6** would be easily converted into the requisite enone functionality to afford the intermediate **7**. After protecting the carbonyl group of **7**, the cyano group would be elaborated into a but-3-enyl appendage through a reductive alkylation operation to give the intermediate **8**. Then, the terminal vinyl moiety of **8** has to be changed into a keto functionality while the ester moiety has to be converted into a formyl group to afford the keto aldehyde **9**. Subsequent intramolecular aldol condensation of **9** would allow the establishment of the spirocyclic core, by giving rise to intermediate **10**. Finally, Wittig reaction of **10** with trimethylphosphonium bromomethylide (Ph_3P=CHBr) followed by the respective deprotection of the resulting *E*- and *Z*-isomers would complete the total synthesis of **1** and **2**.



Scheme 2 Retrosynthetic analysis of **1** and **2**

In a modified procedure, our synthetic effort began with the condensation of ethyl cyanoacetate with acetone to provide the known compound **4**[9] in 66% yield (Scheme 3). After this, the Diels–Alder reaction of **4** with diene **5**[10] was carried out. It was observed that with the assistance of zinc chloride, **4** could readily undergo the cycloaddition with **5** (5 equiv) in toluene at 80 °C, to afford the desired adduct **6** as a diastereomeric mixture (*ortho*-like, 50:50) in good yield (82%), together with the by-product **11** resulting from the self-addition of **5** (0.6 out of 5 equiv) as a single diastereomer.[11] As we designed, compound **6** should be directly transformed into enone **7**, and for this purpose, two commonly employed reagent systems for converting silyl enol ether into enone, including 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)/benzene[12a] and $Pd(OAc)_2$/Na_2CO_3/MeCN,[12b] were respectively attempted on **6** at different temperatures (r.t. to reflux). However, these reactions only led to recovered starting material or complex mixtures.

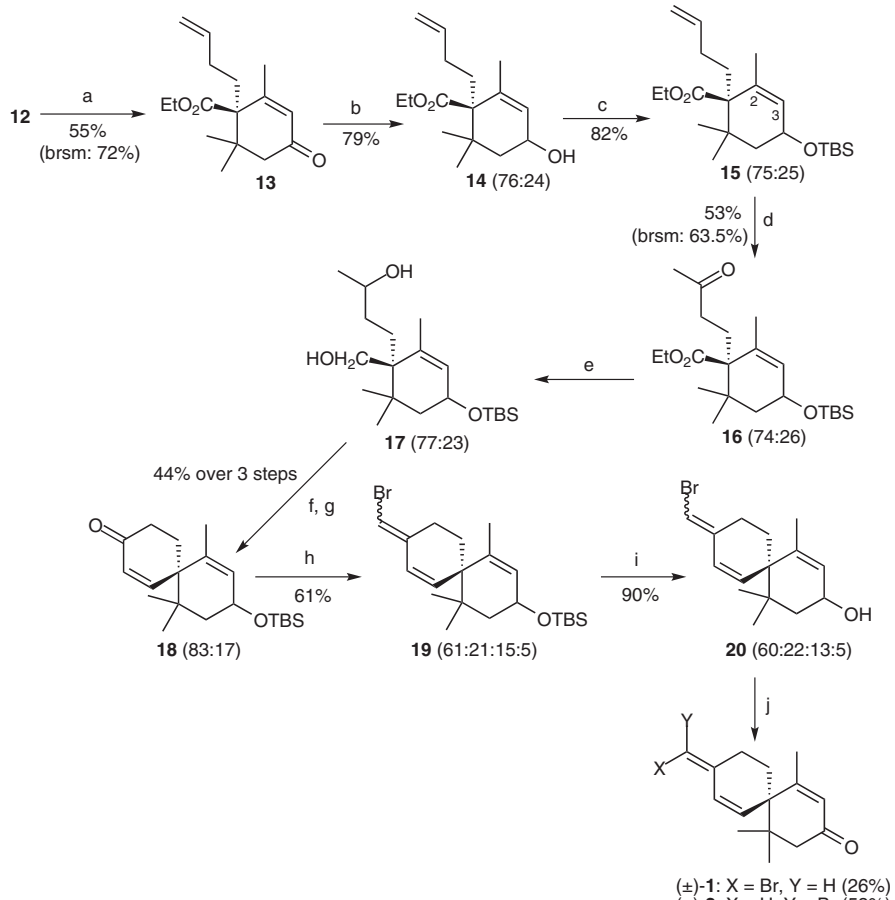
We envisaged that the failure met with the transformation of **6** into **7** through the DDQ oxidation might be attributed



Scheme 3 Reagents and conditions: (a) LiBr (5.0 equiv), MS 3Å, acetone, reflux, 18 h; (b) **5** (5.0 equiv), $ZnCl_2$ (1.0 equiv), toluene, 80 °C, 20 h; (c) LN (3.5 equiv), THF, –45 °C, 30 min, then H_2C=$CHCH_2CH_2Br$ (4 equiv), r.t., 24 h, 57% of **12**; (d) LN (3.5 equiv), THF, –45 °C, 30 min, then H_2C=$CHCH_2CH_2Br$ (4 equiv), HMPA (4 equiv), r.t., 12 h, 70% of **12**.

to the unfavorable electronic effect of the cyano group to the cation intermediate. In this regard, it was decided to reroute our original scheme by conducting the reductive alkylation of **6** first, to replace its cyano group with a but-3-enyl appendage. Following the previously established reaction conditions,[8] the reductive alkylation reaction was initially performed by treating **6** with LN (3.5 equiv)[13] in THF at –45 °C for 30 minutes, followed by trapping the resulting enolate from the reductive decyanation with 4-bromobut-1-ene (4 equiv), affording the alkylated product **12** in 57% yield as a single diastereomer. The *trans* steric relationship between C-1 butenyl and C-2 methyl groups was verified by 2D NOESY correlations as illustrated in Scheme 3. It was further discovered that a much better yield of **12** (70%) could be obtained by the use of hexamethylphosphoramide (HMPA) (4 equiv) as an activating reagent.

With the cyano group having been replaced by the alkyl group, treatment of **12** with DDQ (5 equiv) in benzene at 80 °C for 24 hours could indeed affect the formation of the enone moiety as evidenced by the low yield (~10%) of **13** obtained. To improve the yield of **13**, we continued to examine several reaction conditions by combining DDQ respectively with several bases, including K_2CO_3, 2,4,6-collidine,[14] and 2,6-lutidine, in benzene. Among the bases tested, the best result was obtained from the reaction of DDQ (4.8 equiv) in 2,6-lutidine (5.1 equiv) affording **13** in 55% yield (brsm: 72%), plus 30% of recovered **12** (Scheme 4). Regarding the inherent instability of the enone, we thought that the carbonyl group of **13** should be protected before creating the B-ring. To this end, **13** was first reduced under the Luche's conditions to give the allylic alcohol **14** in 79% yield as a diastereomeric mixture (76:24). The formation of two isomers in this case should



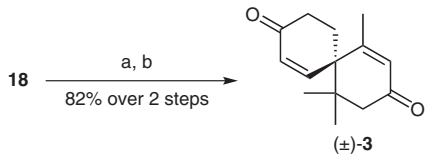
Scheme 4 *Reagents and conditions*: (a) DDQ (4.8 equiv), 2,6-lutidine (5.1 equiv), benzene, r.t., 24 h, 30% of **12** was recovered; (b) $CeCl_3 \cdot 7H_2O$ (1.5 equiv), $NaBH_4$ (1.8 equiv), MeOH–CH_2Cl_2 (1:1), 0 °C, 1 h; (c) TBDMSCl (1.5 equiv), imidazole (2.5 equiv), DMF, r.t., 12 h; (d) $PdCl_2$ (0.25 equiv), CuCl (1.4 equiv), O_2, DMF–THF–H_2O, r.t., 20 h, 20% of **15** was recovered; (e) $LiAlH_4$ (6 equiv), THF, 0 °C to r.t., 5 h; (f) PDC (3 equiv), CH_2Cl_2, r.t., 12 h; (g) KOH (1.6 equiv, 1.0 M in MeOH), THF, r.t., 3 h; (h) piperidine (2.94 equiv), *n*-BuLi (2.98 equiv), $BrCH_2(Ph)_3P^+Br^-$ (3.02 equiv), THF, 0 °C, 80 min; (i) TBAF (2.0 equiv), THF, r.t., 2 h; (j) PDC (2.0 equiv), CH_2Cl_2, r.t., 1 h.

be inconsequential to the final targets since the newly created stereogenic center would be eventually eliminated. Compound **14** was then subjected to the protection with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole to provide the silyl ether **15** (75:25) in 82% yield.

In an effort to access the spirocyclic core, the Wacker oxidation of **15** was first conducted under the standard reaction conditions,[15] to afford the keto ester **16** in 53% yield (74:26) (brsm: 63.5%), along with 20% of recovered starting material. Exposure of **16** to lithium aluminum hydride ($LiAlH_4$) in THF resulted in the formation of diol **17** with only two isomers (77:23) as detected by the ^1H NMR spectrum of the crude **17**. Without purification, the crude **17** was immediately subjected to oxidation with pyridinium dichromate (PDC), and the resulting keto aldehyde intermediate, still as a crude mixture, underwent the aldol condensation smoothly on treatment with KOH in a THF–MeOH solution,[16] to yield the key spiro intermediate **18** in 44% yield over three steps.

With **18** in place, the remainder of the synthesis then proceeded smoothly. As we expected, Wittig reaction of **18** with trimethylphosphonium bromomethylide generated from (bromomethyl)triphenylphosphonium bromide and lithium piperidide[17] proceeded smoothly to afford the bromomethylene derivative **19** as an isomeric mixture (*E*-major/*Z*-major/*E*-minor/*Z*-minor = 61:21:13:5) in 61% yield. Without separation, **19** was subsequently subjected to the deprotection with tetra-*n*-butylammonium fluoride (TBAF) in THF to afford the alcohol **20** (60:22:13:5) in an almost quantitative yield (90%). At the end, oxidation of **20** with PDC furnished the final targets (±)-**1** and its 15-*E*-epimer (±)-**2** in 26% and 53% yield, respectively. The spectral data (^1H and ^{13}C NMR) of both products were found to agree well with those reported in the literature.[5,7]

In addition to **1** and **2**, the total synthesis of (±)-majusculone (**3**), a 9-nor-chamigrene natural product, was also readily achieved from the advanced intermediate **18** in two steps. As shown in Scheme 5, deprotection of **18** with TBAF followed by treatment of the resulting crude alcohol with PDC completed the synthesis of **3** in 82% yield over two steps, the spectroscopic data of which were found to be identical to both natural[5] and synthetic products.[18]



Scheme 5 Reagents and conditions: (a) TBAF (5.0 equiv), THF, r.t., 3 h; (b) PDC (2.0 equiv, based on **24**), CH_2Cl_2, r.t., 2 h.

In summary, we have accomplished the total synthesis of **1** and **2** in 13 steps through a novel synthetic approach. Although the ultimate synthesis did not strictly follow the initially designed scheme, our original goals of using the Diels–Alder reaction to construct the A-ring and the reductive alkylation of the Diels–Alder adduct to create the spiro quaternary center with the suitable functionalities for accessing the B-ring have been well realized. In the synthetic sequence, some intermediates were produced as the isomeric mixtures, but the separations of them were shown to be unnecessary since all of the isomers could be eventually converted into either of the targets. In comparison with the previously reported syntheses (overall yields: 0.31%[6] and 4.51%[7] for **1**, 2.12%[6] and 0.45%[7] for **2**, respectively), the current study did not result in a significant improvement on the overall yields of **1** (0.85%) and **2** (1.74%), but the synthetic route developed by us appears to be more general and the generality has been demonstrated by the ready achievement of (±)-majusculone (**3**) from the intermediate leading to **1** and **2**. The application of the same strategy for the syntheses of other members of chamigrene family is the focus of our ongoing studies.

Unless otherwise noted, all starting materials and reagents were purchased from commercial suppliers and used without further purification. THF was distilled from sodium-benzophenone; toluene, benzene, CH_2Cl_2, and DMF were distilled from CaH_2 before use. TLC analysis and preparative TLC were performed on Macherey-Nagel DC-Fertigplatten. Durasil-25 UV_{254} glass-backed plates, and visualized by UV, or $KMnO_4$ or I_2 treatment. All of the products were purified by flash chromatography on Merck Kieselgel 60 (Art. 9385) (230–400 mesh) or neutral aluminum oxide. IR spectra were recorded on a Jasco FT/IR 410 spectrometer. NMR spectra (^1H, ^{13}C, DEPT, NOESY) were recorded on a Bruker Avance DPE-400 or a Bruker Avance DPE-600 spectrometer using $CDCl_3$ or C_6D_6 as solvent. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on a Finnigan/Thermo Quest MAT 95XL spectrometer in a fast atom bombardment (FAB) model.

Ethyl 2-Cyano-3-methylbut-2-enoate (4)

This known compound was prepared by a modified procedure as follows. LiBr (7.82 g, 0.09 mol) and molecular sieves 3Å (300 mg) were added to a mixture of ethyl cyanoacetate (2.0 g, 0.018 mol) and acetone (60 mL). The suspension was refluxed for 18 h, cooled to r.t., filtered, and concentrated in vacuo. The residue was diluted with EtOAc (300 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), and concentrated. The crude mixture was subjected to chromatographic purification on silica gel (hexane–EtOAc, 20:1) to yield **4** (1.82 g, 66%).

4-(*tert*-Butyldimethylsilyloxy)-1-cyano-2,6,6-trimethylcyclohex-3-enecarboxylic Acid Ethyl Ester (6) and 1-[(1*R,2*S**,6*S**)-4-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylcyclohex-3-enyl]ethanone (11)**

To a flame-dried 100 mL round-bottom flask were added anhyd $ZnCl_2$ (804 mg, 5.9 mmol) and anhyd toluene (20 mL). The resulting suspension was stirred under a N_2 atmosphere for 20 min before treating with a solution of **4** (904 mg, 5.9 mmol) in anhyd toluene (4 mL). After stirring for an additional 30 min, a solution of diene **5**[10] (5.85 g, 29.5 mmol) in anhyd toluene (8 mL) was added to the mixture. The mixture was then stirred at 80 °C for 20 h, cooled to r.t., and diluted with EtOAc (120 mL). The solution was successively washed with H_2O (2 × 30 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Chromatographic purification of the crude residue on silica gel (hexane–EtOAc, 100:1, 60:1, and 40:1) afforded **11**[11] (500 mg, generated from 0.6 out of 5 equiv of **5**) as a colorless sticky oil, followed by **6** (1.7 g, 82%) as a mixture of two isomers (50:50).

6

IR (neat): 2960, 2931, 2857, 2242, 1739, 1671, 1463, 1363, 1259, 1207, 838, 781 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (isomer 1) = 4.57 (br s, 1 H), 4.35–4.16 (m, 2 H), 3.04–2.95 (m, 1 H), 2.42 (br d, *J* = 17.5 Hz, 1 H), 1.76 (d, *J* = 17.5 Hz, 1 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 1.18–1.05 (m, 9 H), 0.90 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H); δ (isomer 2) = 4.51 (br s, 1 H), 4.35–4.16 (m, 2 H), 2.90–2.82 (m, 1 H), 2.41 (d, *J* = 17.3 Hz, 1 H), 1.74 (d, *J* = 17.3 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.24 (s, 3 H), 1.16–1.05 (m, 6 H), 0.90 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (isomer 1) = 167.7, 148.7, 117.6, 105.6, 62.4, 58.9, 43.0, 37.6, 33.4, 27.1, 25.6, 22.0, 18.2, 17.9, 14.2, –4.3, –4.6; δ (isomer 2) = 165.9, 149.3, 119.8, 103.7, 61.9, 57.2, 40.5, 37.0, 35.9, 26.8, 26.0, 25.6, 17.9, 17.3, 14.2, –4.3, –4.5.

HRMS-FAB: *m*/*z* calcd for $C_{19}H_{34}NO_3Si$ $[M + H]^+$: 352.2308; found: 352.2298.

11[11]

IR (neat): 2958, 2929, 1712, 1673, 1253, 1195, 1180, 838, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.87 (dd, *J* = 5.2, 1.8 Hz, 1 H), 2.63 (dd, *J* = 12.3, 6.5 Hz, 1 H), 2.51 (dd, *J* = 10.9, 5.3 Hz, 1 H), 2.19–2.10 (m, 1 H), 2.14 (s, 3 H), 2.07 (dd, *J* = 17.0, 5.9 Hz, 1 H), 1.75–1.68 (m, 1 H), 0.92 (d, *J* = 4.7 Hz, 3 H), 0.91 (s, 9 H), 0.80 (d, *J* = 7.0 Hz, 3 H), 0.13 (s, 3 H), 0.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 149.2, 109.1, 57.4, 37.9, 30.7, 30.6, 25.6, 24.8, 19.8, 18.0, 17.9, –4.3, –4.4.

HRMS-FAB: *m*/*z* calcd for $C_{16}H_{31}O_2Si$ $[M + H]^+$: 283.2093; found: 283.2098.

(1*S,2*S**)-1-But-3-enyl-4-(*tert*-butyldimethylsilyloxy)-2,6,6-trimethylcyclohex-3-enecarboxylic Acid Ethyl Ester (12)**

To a solution of **6** (548 mg, 1.56 mmol) in anhyd THF (10 mL) precooled at –45 °C was added a THF solution of lithium naphthalenide (0.34 M, 16.1 mL, 5.46 mmol)[13] via syringe under the protection of a N_2 atmosphere. The resulting dark green solution was stirred at –45 °C for 30 min and successively treated with 4-bromobut-1-ene (0.63 mL, 6.24 mmol) and HMPA (1.09 mL, 6.24 mmol). The reaction mixture was stirred at r.t. for 12 h, then poured into sat. aq NH_4Cl (10 mL), and extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL), and concentrated. Chromatographic purification of the crude mixture on silica gel (hexane–EtOAc, 100:1) afforded **12** as a colorless oil (416 mg, 70%).

IR (neat): 2958, 2929, 2902, 2857, 1735, 1673, 1641, 1149, 1130, 989, 939 cm^{-1}.

^{1}H NMR [600 MHz, $CDCl_3$ + C_6D_6 (1:1)]: δ = 5.86–5.77 (ddt, *J* = 17.3, 10.2, 6.6 Hz, 1 H), 5.05 (dm, *J* = 17.3 Hz, 1 H), 4.96 (dm, *J* = 10.2 Hz, 1 H), 4.60 (br s, 1 H), 4.10–3.97 (m, 2 H), 2.47 (d, *J* = 17.0 Hz, 1 H), 2.36–2.30 (m, 1 H), 2.29–2.19 (m, 2 H), 1.92–1.85 (m, 1 H), 1.70–1.64 (m, 1 H), 1.60 (d, *J* = 17.0 Hz, 1 H), 1.12 (t, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.03 (s, 3 H), 0.97 (br s, 12 H), 0.18 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 148.0, 139.8, 114.1, 108.6, 59.6, 53.9, 44.6, 37.5, 35.9, 33.9, 31.8, 26.9, 25.8, 25.7, 18.8, 18.0, 14.4, –4.2, –4.4.

HRMS-FAB: *m*/*z* calcd for $C_{22}H_{41}O_3Si$ [M + H]$^+$: 381.2825; found: 381.2815.

(1*R)-1-But-3-enyl-2,6,6-trimethyl-4-oxocyclohex-2-enecarboxylic Acid Ethyl Ester (13)**

To a solution of DDQ (721 mg, 3.18 mmol) in anhyd benzene (7 mL) was added dropwise 2,6-lutidine (0.39 mL, 3.37 mmol) under a N_2 atmosphere. The resulting dark mixture was stirred for 20 min before adding a solution of **12** (252 mg, 0.66mmol) in anhyd benzene (2 mL). The reaction mixture was stirred at r.t. for 24 h, then filtered through a Celite pad, washed with EtOAc (20 mL), and concentrated. The crude residue was subjected to chromatographic purification on silica gel (hexane–EtOAc, 40:1, 5:1) to provide 30% of recovered **12** (76 mg), followed by 55% (brsm: 72%) of **13** (96 mg) as a yellowish oil.

IR (neat): 2969, 2917, 1724, 1671, 1641, 1220, 1205, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 1 H), 5.81–5.71 (dm, *J* = 17.1 Hz, 1 H), 5.03 (br d, *J* = 17.1 Hz, 1 H), 4.97 (br d, *J* = 10.3 Hz, 1 H), 4.30–4.14 (m, 2 H), 2.54 (d, *J* = 17.2 Hz, 1 H), 2.17 (d, *J* = 17.2 Hz, 1 H), 2.17–2.00 (m, 3 H), 2.01 (s, 3 H), 1.96–1.91 (m, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.12 (s, 3 H), 1.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.0, 171.8, 160.7, 137.9, 128.5, 115.2, 60.9, 59.1, 49.7, 39.4, 33.4, 30.7, 27.1, 25.5, 24.0, 14.2.

HRMS-FAB: *m*/*z* calcd for $C_{16}H_{25}O_3$ [M + H]$^+$: 265.1804; found: 265.1805.

(1*R)-1-But-3-enyl-4-hydroxy-2,6,6-trimethylcyclohex-2-enecarboxylic Acid Ethyl Ester (14)**

To a solution of **13** (219 mg, 0.83 mmol) in MeOH–CH_2Cl_2 (1:1, 16 mL) at 0 °C was added $CeCl_3{\cdot}7H_2O$ (463 mg, 1.24 mmol) and $NaBH_4$ (56 mg, 1.49 mmol). The reaction mixture was stirred at the same temperature for 1 h, then diluted with EtOAc (80 mL), and washed with H_2O (2 × 15 mL) and brine (10 mL). After concentration, the crude mixture was purified by flash chromatography on silica gel (hexane–EtOAc, 5:1) to furnish **14** (174 mg, 79%) as an isomeric mixture (76:24).

IR (neat): 3450, 2960, 2931, 1731, 1673, 1149, 1033, 838, 779 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) = 5.85–5.70 (m, 1 H), 5.68 (br s, 1 H), 5.02 (dm, *J* = 17.0 Hz, 1 H), 4.93 (dm, *J* = 10.2 Hz, 1 H), 4.30–4.21 (tm, *J* = 9.0 Hz, 1 H), 4.24–4.04 (m, 2 H), 2.19–1.75 (m, 5 H), 1.73 (t, *J* = 1.5 Hz, 3 H), 1.64–1.57 (m, 1 H), 1.54 (d, *J* = 10.3 Hz, 1 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 1.10 (s, 3 H), 0.88 (s, 3 H); δ (minor) = 5.85–5.70 (m, 1 H), 5.69 (br s, 1 H), 5.02 (dm, *J* = 17.0 Hz, 1 H), 4.93 (dm, *J* = 10.2 Hz, 1 H), 4.30–4.21 (tm, *J* = 9.0 Hz, 1 H), 4.24–4.04 (m, 2 H), 2.19–1.75 (m, 5 H), 1.70 (t, *J* = 1.5 Hz, 3 H), 1.64–1.57 (m, 1 H), 1.51 (d, *J* = 10.0 Hz, 1 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ (major) = 173.2, 138.9, 134.8, 130.4, 114.4, 64.9, 59.8, 57.2, 44.6, 36.6, 33.1, 31.4, 26.9, 26.2, 21.6, 13.9; δ (minor) = 173.5, 139.3, 135.7, 129.3, 114.2, 64.5, 60.0, 57.2, 44.0, 36.3, 32.2, 31.4, 28.0, 25.6, 22.0, 13.9.

HRMS-FAB: *m*/*z* calcd for $C_{16}H_{27}O_3$ [M + H]$^+$: 267.1960; found: 267.1967.

(1*R)-1-But-3-enyl-4-(*tert*-butyldimethylsilyloxy)-2,6,6-trimethylcyclohex-2-enecarboxylic Acid Ethyl Ester (15)**

tert-Butyldimethylsilyl chloride (143 mg, 0.95 mmol) and imidazole (108 mg, 1.58 mmol) were successively added to a solution of **14** (168 mg, 0.63 mmol) in anhyd DMF (13 mL) under a N_2 atmosphere. The mixture was stirred for 12 h, then quenched with H_2O (13 mL), and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), and concentrated. Flash chromatography of the crude residue on silica gel (hexane–EtOAc, 100:1, 50:1, and 20:1) afforded **15** (197 mg, 82%) as a mixture of two isomers (75:25).

IR (neat): 2958, 2929, 1724, 1675, 1251, 1213, 1174, 1070, 836, 777 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ (major) = 5.77 (br s, 1 H), 5.67 (dm, *J* = 16.8 Hz, 1 H), 4.94 (dm, *J* = 16.8 Hz, 1 H), 4.89 (dm, *J* = 10.2 Hz, 1 H), 4.42–4.34 (tm, *J* = 9.0 Hz, 1 H), 4.00–3.81 (m, 2 H), 2.20–1.80 (m, 5 H), 1.77 (t, *J* = 1.4 Hz, 3 H), 1.59 (ddd, *J* = 12.5, 6.5, 1.0 Hz, 1 H), 1.11 (s, 3 H), 0.99 (s, 12 H), 0.92 (t, *J* = 7.1 Hz, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H); δ (minor) = 5.79 (dm, *J* = 17.1 Hz, 1 H), 5.76 (br s, 1 H), 5.06 (dm, *J* = 17.1 Hz, 1 H), 4.99–4.94 (m, 1 H), 4.22–4.16 (m, 1 H), 4.00–3.81 (m, 2 H), 2.20–1.80 (m, 5 H), 1.72 (t, *J* = 1.4 Hz, 3 H), 1.68 (dd, *J* = 13.5, 5.9 Hz, 1 H), 1.15 (s, 3 H), 0.99 (s, 12 H), 0.91 (t, *J* = 7.1 Hz, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ (major) = 173.2, 138.9, 134.6, 130.7, 114.3, 66.3, 59.8, 57.2, 45.1, 36.8, 33.2, 31.3, 27.1, 26.3, 25.9, 21.7, 18.2, 13.9, –4.5, –4.6; δ (minor) = 173.4, 139.3, 135.3, 129.0, 114.2, 65.4, 59.9, 57.2, 44.2, 36.1, 32.6, 31.4, 30.0, 28.2, 25.9, 22.1, 18.1, 13.9, –4.4, –4.6.

HRMS-FAB: *m*/*z* calcd for $C_{22}H_{41}O_3Si$ [M + H]$^+$: 381.2825; found: 381.2837.

(1*R)-4-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethyl-1-(3-oxobutyl)cyclohex-2-enecarboxylic Acid Ethyl Ester (16)**

To a solution of **15** (179 mg, 0.47 mmol) in DMF–THF–H_2O (4:1:1, 6 mL) were successively added CuCl (65 mg, 0.66 mmol) and $PdCl_2$ (21 mg, 0.12 mmol). O_2 gas was bubbled through the mixture for 15 min and the mixture was stirred under an atmosphere of O_2 for 18 h. The mixture was then diluted with sat. aq NH_4Cl (6 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (15 mL). After concentration, the crude mixture was subjected to flash chromatography on silica gel (hexane–EtOAc, 20:1, 10:1) to afford **16** as a pale yellow oil (99 mg, 53%, 74:26) (brsm: 64%), along with 20% of recovered **15** (36 mg).

IR (neat): 2954, 2930, 2857, 1720, 1658, 1234, 1172, 1072, 836, 775 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ (major) = 5.74 (br s, 1 H), 4.42–4.31 (tm, *J* = 8.3 Hz, 1 H), 4.00–3.80 (m, 2 H), 2.45–2.05 (m, 4 H), 1.75 (br s, 3 H), 1.73–1.55 (m, 2 H), 1.55 (s, 3 H), 1.08 (s, 3 H), 0.98 (s, 9 H), 0.97 (s, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 0.09 (s, 6 H); δ (minor) = 5.66 (br s, 1 H), 4.25–4.18 (m, 1 H), 4.00–3.80 (m, 2 H), 2.45–2.05 (m, 3 H), 1.91 (dd, *J* = 13.3, 6.3 Hz, 1 H), 1.71–1.57 (m, 2 H), 1.68 (s, 3 H), 1.64 (s, 3 H), 1.09 (s, 3 H), 0.99 (s, 9 H), 0.91 (s, 3 H), 0.90 (t, *J* = 7.1 Hz, 3 H), 0.12 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ (major) = 205.3, 173.0, 134.5, 130.8, 66.2, 59.9, 56.7, 45.0, 40.5, 36.7, 29.2, 27.1, 26.8, 26.4, 25.9, 21.5, 18.2, 13.9, –4.5, –4.6; δ (minor) = 205.5, 173.3, 134.9, 129.7, 65.5, 60.1, 56.7, 44.2, 41.0, 36.5, 29.3, 28.0, 26.2, 25.9, 25.5, 22.0, 18.1, 13.9, –4.4, –4.5.

LRMS-FAB: *m*/*z* calcd for $C_{21}H_{37}O_4Si$ [M – CH_3]$^+$: 381; found: 381.

(6*R)-9-(*tert*-Butyldimethylsilyloxy)-7,11,11-trimethylspiro[5.5]undeca-1,7-dien-3-one (18)**

A solution of **16** (137 mg, 0.35 mmol) in anhyd THF (3 mL) was added to a stirred suspension of $LiAlH_4$ (79 mg, 2.07 mmol) in anhyd THF (7 mL) under N_2. The mixture was stirred at the same temperature for 5 h and slowly diluted with EtOAc (80 mL), and washed with aq 5% NaOH (15 mL), H_2O (2 × 15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated to afford 139 mg of the crude diol **17** (77:23).

17

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) = 5.53 (br s, 1 H), 4.24–4.16 (m, 1 H), 3.77–3.59 (m, 3 H), 1.73 (br s, 3 H), 1.67–1.38 (m, 8 H), 1.20 (d, *J* = 6.2 Hz, 3 H), 1.12–0.94 (m, 6 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); δ (minor) = 5.64 (br s, 1 H), 4.24–4.16 (m, 1 H), 3.77–3.59 (m, 3 H), 1.75 (br s, 3 H), 1.67–1.38 (m, 8 H), 1.19 (d, *J* = 5.6 Hz, 3 H), 1.12–0.94 (m, 6 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H).

The crude **17** was dissolved in anhyd CH_2Cl_2 (10 mL) and treated with pyridinium dichromate (395 mg, 1.05 mmol). The reaction mixture was stirred under N_2 for 12 h at r.t., then filtered through a Celite pad, washed with CH_2Cl_2 (2 × 5 mL), and concentrated. Without further purification, the crude keto aldehyde intermediate was immediately dissolved in THF (4 mL) and added to methanolic KOH solution (1.0 M, 0.56 mL, 0.56 mmol). The reaction mixture was stirred at r.t. for 3 h, then diluted with EtOAc (60 mL), washed with H_2O (2 × 10 mL) and brine (10 mL), and concentrated. The crude residue was purified by flash chromatography on silica gel (hexane–EtOAc, 8:1) to provide **18** (83:17) as a pale yellow oil (51 mg, 44% from **12**).

IR (neat): 2958, 2927, 1718, 1685, 1612, 1540, 1259, 1070, 1016, 833, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) = 6.62 (dd, *J* = 10.6, 0.9 Hz, 1 H), 6.17 (d, *J* = 10.6 Hz, 1 H), 5.48 (br s, 1 H), 4.32–4.21 (m, 1 H), 2.67–2.40 (m, 2 H), 2.27–2.00 (m, 2 H), 1.66 (br s, 3 H), 1.99–1.55 (m, 2 H), 1.03 (s, 3 H), 0.98 (s, 3 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); δ (minor) = 6.74 (dd, *J* = 10.4, 1.0 Hz, 1 H), 6.09 (d, *J* = 10.4 Hz, 1 H), 5.40 (br s, 1 H), 4.45–4.35 (m, 1 H), 2.67–2.40 (m, 2 H), 2.17–1.80 (m, 2 H), 1.74 (br s, 3 H), 1.80–1.43 (m, 2 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ (major) = 196.4, 151.5, 138.3, 131.0, 128.7, 66.2, 45.5, 42.7, 38.8, 35.6, 27.8, 26.7, 25.9, 24.2, 20.9, 18.1, –4.6; δ (minor) = 196.2, 151.6, 137.4, 129.8, 126.4, 65.8, 44.9, 42.5, 37.7, 35.6, 25.9, 23.8, 22.0, 21.4, 21.1, 18.0, –4.6, –4.8.

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{34}O_2Si$ [M + H]$^+$: 335.2406; found: 335.2395.

(6*R)-(9-Bromomethylene-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-yloxy)-*tert*-butyldimethylsilane (19)**

To a stirred solution of piperidine (0.067 mL, 0.68 mmol) in anhyd THF (2 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M in hexane, 0.43 mL, 0.685 mmol) under a N_2 atmosphere. The mixture was stirred at 0 °C for 20 min and was dropwise added to a stirred suspension of (bromomethyl)triphenylphosphonium bromide (303 mg, 0.69 mmol) in anhyd THF (2 mL) via a syringe. The resulting orange solution was stirred for 20 min at 0 °C and a THF (1.5 mL) solution of **18** (76 mg, 0.23 mmol) was added in one portion. After stirring at 0 °C for 3 h, the mixture was diluted with EtOAc (70 mL) and washed with H_2O (2 × 10 mL) and brine (10 mL), and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (hexane, hexane–EtOAc, 100:1) to give **19** (57 mg, 61%) as a mixture of four isomers (61:21:15:5).

IR (neat): 3066, 3027, 2956, 2856, 1735, 1654, 1577, 1257, 1068, 833, 777 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer, major) = 6.27 (d, *J* = 10.4 Hz, 1 H), 6.13 (br s, 1 H), 5.53 (d, *J* = 10.4 Hz, 1 H), 5.40 (br s, 1 H), 4.27–4.19 (m, 1 H), 2.66–2.28 (m, 2 H), 2.06–1.90 (m, 2 H), 1.76–1.51 (m, 2 H), 1.58 (br s, 3 H), 0.96–0.85 (m, 15 H), 0.09 (s, 3 H), 0.08 (s, 3 H); δ (*Z*-isomer, major) = 6.69 (d, *J* = 10.5 Hz, 1 H), 5.88 (br s, 1 H), 5.75 (d, *J* = 10.5 Hz, 1 H), 5.36 (br s, 1 H), 4.27–4.19 (m, 1 H), 2.66–2.28 (m, 2 H), 2.06–1.90 (m, 2 H), 1.76–1.51 (m, 5 H), 0.96–0.85 (m, 15 H), 0.07 (s, 3 H), 0.06 (s, 3 H); δ (*E*-isomer, minor) = 6.19 (d, *J* = 10.3 Hz, 1 H), 6.11 (br s, 1 H), 5.64 (d, *J* = 10.3 Hz, 1 H), 5.34–5.33 (m, 1 H), 4.27–4.19 (m, 1 H), 2.66–2.28 (m, 2 H), 2.06–1.90 (m, 2 H), 1.76–1.51 (m, 5 H), 0.96–0.85 (m, 15 H), 0.10–0.06 (m, 6 H); δ (*Z*-isomer, minor) = 6.60 (d, *J* = 10.4 Hz, 1 H), 6.33 (d, *J* = 10.4 Hz, 1 H), 5.83 (br s, 1 H), 5.34 (m, 1 H), 4.27–4.19 (m, 1 H), 2.66–2.28 (m, 2 H), 2.06–1.90 (m, 2 H), 1.76–1.51 (m, 5 H), 0.96–0.85 (m, 15 H), 0.10–0.06 (m, 3 H), 0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*E*-isomer, major) = 140.2, 138.9, 133.2, 128.6, 126.6, 105.2, 66.7, 45.6, 42.8, 38.8, 29.7, 27.4, 26.3, 26.0, 24.7, 21.1, 18.3, –4.4, –4.5; δ (*Z*-isomer, major) = 140.2, 136.8, 134.1, 126.8, 126.5, 101.2, 66.6, 46.0, 42.9, 38.8, 29.6, 29.3, 29.1, 27.7, 26.0, 21.3, 14.1, –4.5; δ (part of the signals of other two isomers) = 139.3, 138.7, 137.8, 136.7, 133.0, 129.6, 128.4, 127.3, 127.2, 126.2, 110.9, 104.9, 66.1, 45.0, 43.3, 37.7, 31.9, 29.5, 25.4, 24.2, 22.7, 22.0, 18.3.

LRMS-FAB: *m*/*z* calcd for $C_{21}H_{36}{}^{79}BrOSi$ [M + H]$^+$: 411; found: 411.

(6*R)-9-Bromomethylene-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-ol (20)**

To a solution of **19** (63 mg, 0.15 mmol) in THF (1.5 mL) was added Bu_4NF (75 wt% in H_2O, 0.082 mL, 0.30 mmol) The mixture was stirred at r.t. for 1 h, then diluted with EtOAc (20 mL), and washed with H_2O (2 × 5 mL) and brine (5 mL). After concentration, the crude mixture was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1) to afford **20** as a colorless oil (41 mg, 90%, 60:22:13:5).

IR (neat): 3345, 2952, 2923, 1733, 1716, 1654, 1558, 1243, 1025, 786, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer, major) = 6.28 (d, *J* = 10.4 Hz, 1 H), 6.14 (br s, 1 H), 5.53 (d, *J* = 10.4 Hz, 1 H), 5.50 (t, *J* = 1.1 Hz, 1 H), 4.26–4.18 (m, 1 H), 2.63–2.54 (dm, *J* = 17.0 Hz, 1 H), 2.52–2.34 (m, 1 H), 2.01–1.90 (m, 1 H), 1.72–1.62 (m, 5 H), 1.61 (br s, 3 H), 0.95 (s, 1 H), 0.94 (s, 1 H); δ (*Z*-isomer, major) = 6.70 (d, *J* = 10.5 Hz, 1 H), 5.90 (br s, 1 H), 5.53 (d, *J* = 10.5 Hz, 1 H), 5.51–5.54 (m, 1 H), 4.32–4.18 (m, 1 H), 2.63–2.34 (m, 2 H), 2.01–1.83 (m, 1 H), 1.80–1.59 (m, 8 H), 0.97 (s, 3 H), 0.95 (s, 3 H); δ (*E*-isomer, minor) = 6.23 (d, *J* = 10.3 Hz, 1 H), 6.07 (br s, 1 H), 5.60 (d, *J* = 10.3 Hz, 1 H), 4.32–4.18 (m, 1 H), 263–2.34 (m, 2 H), 2.01–1.83 (m, 1 H), 1.80–1.59 (m, 8 H), 0.93 (s, 3 H), 0.92 (s, 3 H); δ (*Z*-isomer, minor) = 6.63 (d, *J* = 10.5 Hz, 1 H), 5.81 (br s, 1 H), 5.68 (d, *J* = 10.7 Hz, 1 H), 4.32–4.26 (m, 1 H), 2.63–2.34 (m, 2 H), 2.01–1.83 (m, 1 H), 1.80–1.59 (m, 8 H), 0.90 (s, 3 H), 0.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*E*-isomer, major) = 141.8, 138.7, 132.8, 128.8, 125.6, 105.5, 66.0, 45.8, 42.6, 38.8, 29.7, 27.3, 26.3, 24.5, 21.2; δ (*Z*-isomer, major) = 136.4, 133.5, 127.8, 126.9, 126.2, 101.5, 65.9, 43.1, 38.8, 31.9, 29.3, 29.2, 27.9, 22.7, 14.1; δ (part of the signals of other two isomers) = 136.7, 136.5, 125.5, 65.5, 29.6, 29.5, 21.3, 14.0.

HRMS-FAB: *m*/*z* calcd for $C_{15}H_{20}{}^{79}BrO$ [M – H]$^+$: 295.0698; found: 295.0707.

(±)-(*Z*)-9-(Bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one [(±)-1] and (±)-(*E*)-9-(Bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one [(±)-2]

PDC (53 mg, 0.14 mmol) was added to a stirred solution of **20** (21 mg, 0.071 mmol) in anhyd CH_2Cl_2 (1 mL) under a N_2 atmosphere. The reaction mixture was stirred at r.t. for 1 h, then filtered through a Celite pad, washed with CH_2Cl_2 (5 mL), and concentrated. The crude mixture was purified by preparative TLC (hexane–EtOAc, 10:1) to afford (±)-**1** (5 mg, 26%) and (±)-**2** (11 mg, 53%) as colorless oils.

(±)-1

IR (neat): 3066, 2871, 2852, 1668, 1616, 831 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (dd, *J* = 10.6, 1.0 Hz, 1 H), 6.01 (br s, 1 H), 5.90 (br s, 1 H), 5.88 (br d, *J* = 10.6 Hz, 1 H), 2.57–2.40 (m, 3 H), 2.30–2.20 (dm, *J* = 16.8 Hz, 1 H), 2.15–2.04 (m, 1 H), 1.90 (d, *J* = 1.2 Hz, 3 H), 1.78–1.69 (m, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H).

^1H NMR (90 MHz, $CDCl_3$):[7] δ = 6.82 (dd, *J* = 10.8, 1.0 Hz, 1 H), 6.00 (br s, 1 H), 5.89 (br s, 1 H), 5.88 (br d, *J* = 10.8 Hz, 1 H), 2.6–1.0 (m, 6 H), 1.88 (d, *J* = 1.1 Hz, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.0, 166.2, 135.5, 133.8, 128.8, 126.8, 103.4, 49.2, 47.2, 40.8, 29.1, 28.6, 25.4, 24.7, 23.7.

^{13}C NMR (25 MHz, $CDCl_3$):[5] δ = 198.0, 165.9, 135.4, 133.4, 128.1, 126.2, 102.9, 48.7, 47.6, 40.3, 28.5, 28.5, 25.4, 24.8, 23.3.

LRMS-FAB: *m/z* calcd for $C_{15}H_{20}{}^{79}BrO$ [M + H]$^+$: 295 and $C_{15}H_{20}{}^{81}BrO$ [M + H]$^+$: 297; found: 297.

(±)-2

IR (neat): 3029, 2962, 2933, 1668, 1577, 794 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.39 (d, *J* = 10.3 Hz, 1 H), 6.25 (br s, 1 H), 5.90 (d, *J* = 1.0 Hz, 1 H), 5.68 (d, *J* = 10.3 Hz, 1 H), 2.70–2.58 (m, 1 H), 2.56–2.42 (m, 2 H), 2.32–2.18 (dm, *J* = 16.6 Hz, 1 H), 2.14–2.03 (m, 1 H), 1.88 (d, *J* = 1.0 Hz, 3 H), 1.82–1.72 (m, 1 H), 1.04 (s, 3 H), 1.02 (s, 3 H).

^1H NMR (90 MHz, $CDCl_3$):[7] δ = 6.38 (d, *J* = 10.6 Hz, 1 H), 6.23 (br s, 1 H), 5.88 (q, *J* = 1.0 Hz, 1 H), 5.66 (d, *J* = 10.6 Hz, 1 H), 1.0–2.7 (m, 6 H), 1.87 (d, *J* = 1.0 Hz, 3 H), 0.99 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 166.3, 137.9, 130.3, 129.9, 126.5, 107.1, 48.8, 47.5, 40.3, 27.5, 25.7, 25.6, 25.0, 23.4.

^{13}C NMR (25 MHz, $CDCl_3$):[5] δ = 198.1, 166.1, 137.7, 130.1, 129.7, 126.2, 107.0, 48.6, 47.3, 40.2, 27.3, 25.5, 25.4, 24.9, 23.3.

HRMS-FAB: *m/z* calcd for $C_{15}H_{20}{}^{79}BrO$ [M + H]$^+$: 295.0698; found: 295.0691.

(±)-Majusculone [(±)-3]

To a solution of **18** (54 mg, 0.16 mmol) in THF (2 mL) was added Bu_4NF (75 wt% in H_2O, 0.22 mL, 0.80 mmol). The mixture was stirred at r.t. for 3 h, then diluted with EtOAc (40 mL), and washed with H_2O (3 × 10 mL) and brine (10 mL). After concentration, the crude alcohol was dissolved in anhyd CH_2Cl_2 (2 mL) and treated with PDC (121 mg, 0.32 mmol). The mixture was stirred at r.t. for 2 h, then filtered through a Celite pad, washed with CH_2Cl_2 (10 mL), and concentrated. Chromatographic purification of the crude residue on silica gel (hexane, hexane–EtOAc, 2:1) afforded (±)-**3** as a waxy solid (29 mg, 82% over two steps).

IR (neat): 3032, 2965, 1666, 1614, 904, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 10.6 Hz, 1 H), 6.29 (d, *J* = 10.6 Hz, 1 H), 5.97 (br s, 1 H), 2.66–2.30 (m, 5 H), 2.11–2.05 (m, 1 H), 1.96 (br s, 3 H), 1.11 (s, 3 H), 1.10 (s, 3 H).

^1H NMR (400 MHz, $CDCl_3$):[18] δ = 6.77 (d, *J* = 10.8 Hz, 1 H), 6.29 (d, *J* = 10.8 Hz, 1 H), 5.98 (s, 1 H), 2.68–2.30 (m, 6 H), 2.14–2.06 (m, 1 H), 1.98 (s, 3 H), 1.11 (d, *J* = 4.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 197.4, 163.1, 149.8, 132.0, 127.4, 48.6, 47.4, 41.0, 35.1, 27.5, 25.6, 25.0, 23.1.

^{13}C NMR (25 MHz, $CDCl_3$):[5] δ = 197.5, 197.3, 163.0, 149.8, 131.9, 127.4, 48.6, 47.4, 41.0, 35.1, 27.5, 25.5, 25.0, 23.0.

HRMS-FAB: *m/z* calcd for $C_{14}H_{19}O_2$ [M + H]$^+$: 219.1385; found: 219.1387.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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