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Stereoselective synthesis of megastigmatrien-3-one using catalytic olefin isomerization as key step

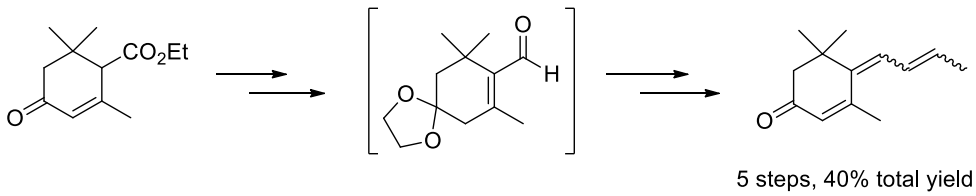
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Abstract

An unprecedented and efficient synthesis of megastigmatrien-3-one from readily available starting materials is reported. The transformation includes carbonyl group protection, reduction, oxidation, addition, elimination, and isomerization processes, which allows for the formation of resultant megastigmatrien-3-one with good purity and high stereoselectivity. This method features mild conditions and operational simplicity.

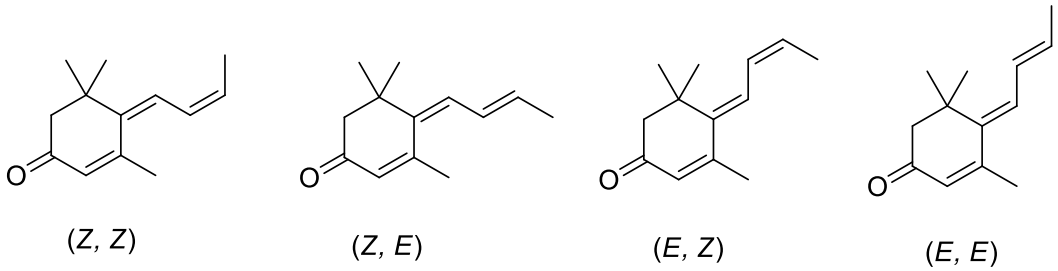


Keywords: Stereoselectivity, megastigmatrien-3-one, olefin isomerization, carbonyl group protection

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Introduction

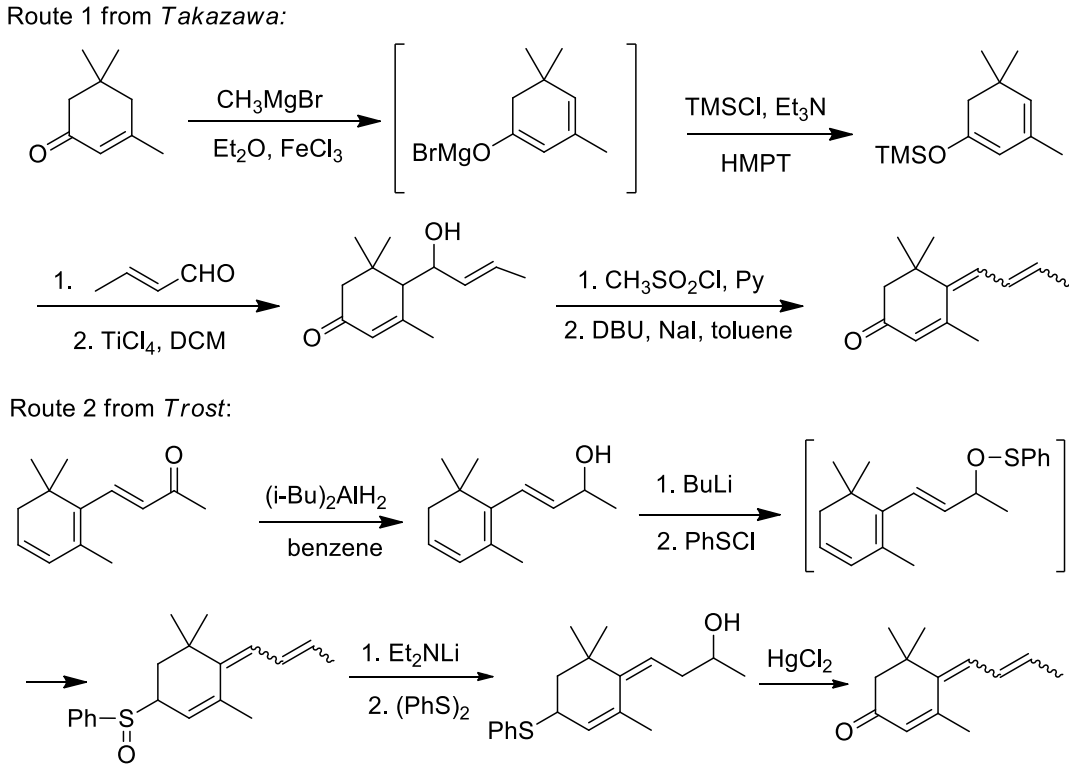
The isomers of megastigmatrien-3-one, also known as 3,5,5-trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one, are considered to be the most important aroma constituents of Burley and Virginia tobacco.[1-2] 3,5,5-Ttrimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one, occurs in nature, and can also be found in Greek and Turkish tobaccos.[3-5] It has been reported that tobacco condensate contains as much as 10% of megastigmatrien-3-one and also occurs in Kudzu oil (*Pueravia lobata* Ohwi).[6] 3,5,5-Trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one and its analogs can serve as synthetic intermediates towards carotenoids such as zeaxanthin. Megastigmatrien-3-one is composed of four isomers (Scheme 1) and their significance in the flavor industry has resulted in the focus on their synthesis.



Scheme 1. Four isomers of megastigmatrien-3-one.

The synthetic history of megastigmatrien-3-one can be dated to 1965 when Rowland reported the first synthesis from dehydroionone.[7-8] Takazawa and co-workers developed a synthetic route towards megastigmatrien-3-one with the four isomers in the ratio 3:10:1:6, from isophorone (Scheme 2, route 1). The key steps involved an aldol-type reaction of dienoxysilanes and subsequent Lewis acid-catalyzed reaction with aldehyde.[6] Demole and co-workers in Firmenich devised a synthesis from 2,6,6-trimethyl-4,4-ethylenedioxy-cyclohex-2-en-one. 1,2-Addition with but-3-yn-2-ol of the resultant unsaturated ketoacetal then gave an acetylenic diol. Reduction and hydrolysis gave megastigmatrien-3-ones in 27% yield in the ratio 1:7:1.5:10.[9-10] Trost and co-workers utilised dehydroionone as the starting material in a synthesis that included reduction, sulfenylation, and hydrolysis to give product in <25% yield (Scheme 2, route 2).[11] The key step involved a [2,7]-sigmatropic rearrangement of 3,4-dehydro-β-ionol, readily available from 3,4-dehydro-β-ionone. Although much has been achieved, the reported methods all resulted in low yields and involved harsh reaction conditions, difficulties with purification and suffered from low stereroselectivity. The four stereoisomers differ in odor. The isomer (*E*, *E*)-megastigmatrien-3-one is considered to be most typical of tobacco, while the (*E*, *Z*) and (*Z*, *Z*) isomers contribute little to the odor. As a consequence, the stereoselective synthesis of the isomers of megastigmatrien-3-one remains an important and challenging problem.

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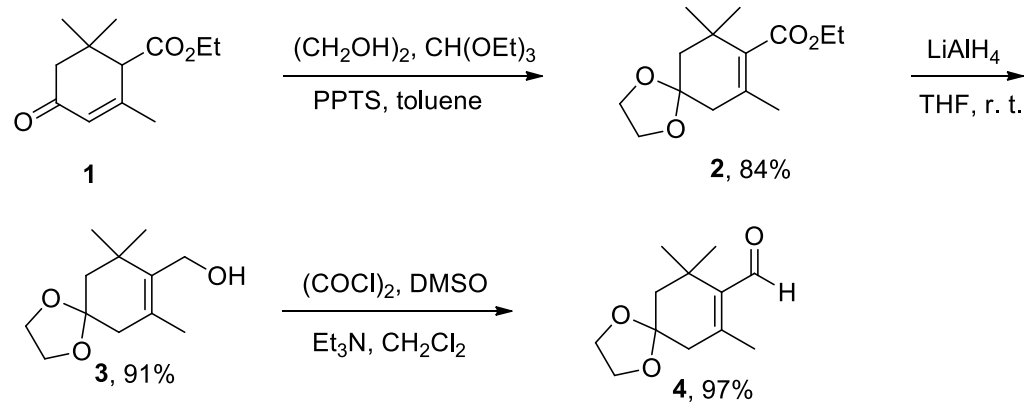
Scheme 2. Representative examples of the synthesis of megastigmatrien-3-one.

Ethyl 2,6,6-trimethyl-4-oxocyclohex-2-enecarboxylate as a readily available material has not been utilized to synthesize megastigmatrien-3-ones.[12] In addition, metal-catalyzed alkene isomerization has emerged as a powerful chemical transformation for [1,3]-hydrogen shifts[13-16] including Pd, Ru, Ir catalysts,[17-20] however their price and limited availability has prompted the use of biorelevant catalysts such as iron, cobalt, and nickel.[21-25] As a continuation of our previous research on the synthesis of carbocycles and heterocycles,[26-29] we envisioned the use of ethyl 2,6,6-trimethyl-4-oxocyclohex-2-enecarboxylate and metal-catalyzed alkene isomerization for the stereoselective synthesis of megastigmatrien-3-ones.

Results and Discussion

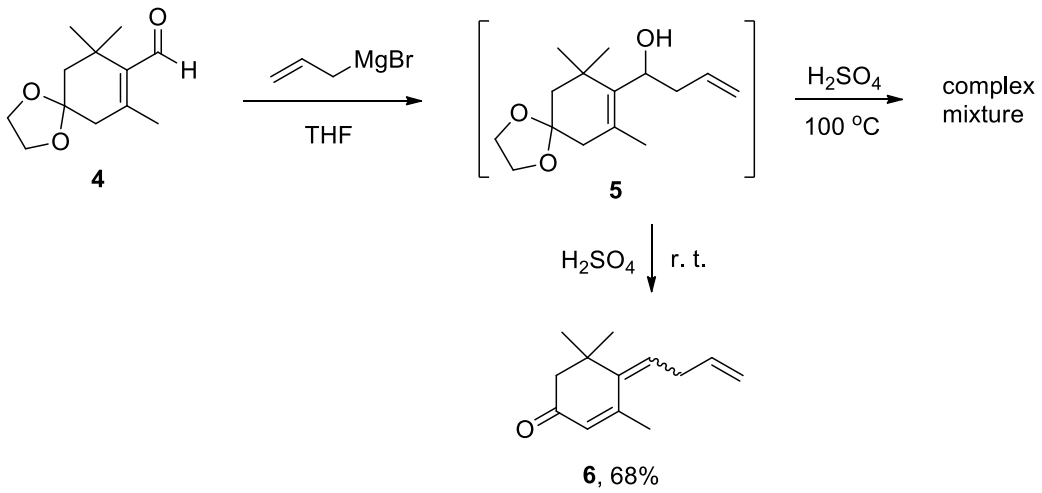
To verify the possibility of our hypothesis, reaction ethyl 2,6,6-trimethyl-4-oxocyclohex-2-enecarboxylate with ethylene glycol in the presence of PPTS in toluene led to an 84% yield of the ketal **2**, thus furnishing carbonyl protection (Scheme 3). Reduction of ketal **2** gave compound **3** in good yields. Alcohol **3** was oxidized to **4** in excellent yield under Swern oxidation conditions. Manganese dioxide in methylene chloride could also be used, however, the reaction time was long (2 days) and the yield lower (< 70%).

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Scheme 3. Initial protection, reduction, and oxidation processes.

Reaction of aldehyde **4** with allylmagnesium bromide gave diallyl alcohol intermediate **5**, which underwent hydrolysis to triene **6**. The two processes could be achieved without isolation of the intermediate **5**, thus, the triene **6** was readily obtained. A complex mixture was obtained when the second dehydration step was conducted at higher temperature (Scheme 4).

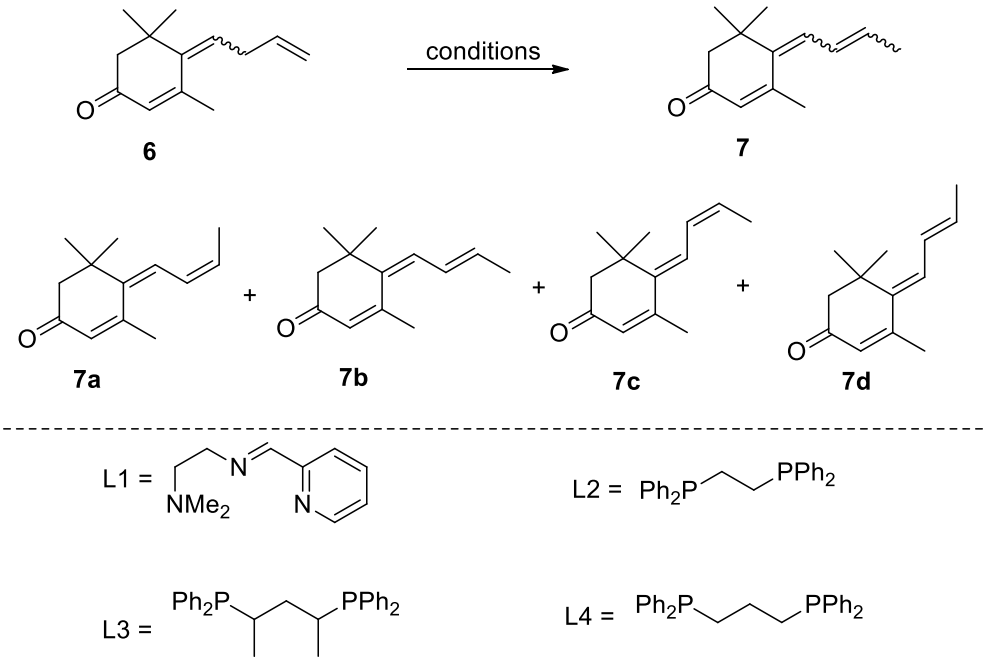


Scheme 4. Addition and hydrolysis towards key triene intermediate.

With the desired triene mixture **6** in hand, we then turned our attention to the desired olefin isomerization. As shown in Table 1, several common Mukaiyama conditions[30] with iron and cobalt catalysts and varying solvents were screened. Little reaction occurred with several iron catalysts (Table 1, entries 1-3). The employment of cobalt catalyst system resulted in some improvement (Table 1, entries 4-5). Cobalt catalytic system Co(II) with different ligands L1-L4 and additives increased the yield of megastigmatrien-3-one (Table 1, entries 6-9). A catalytic amount addition of $CoBr_2$(L3) significantly increased the yield of **7** to 79% (Table 1, entry 8) and the resultant megastigmatrien-3-ones isomers **7a**:**7b**:**7c**:**7d** were in the ratio = 2:23:2:73.[31-32]

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Table 1. Optimization of the alkene isomerization[a]

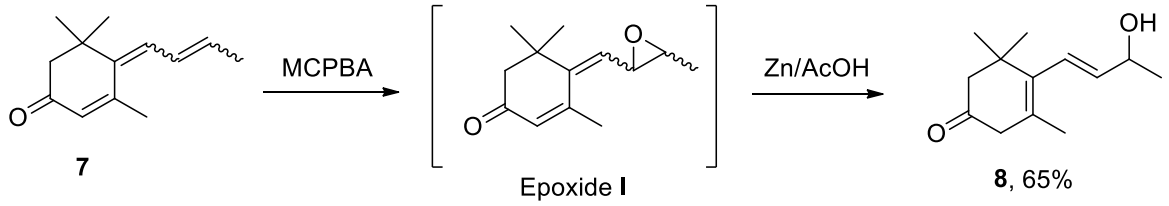


Entry	Catalyst	Yield (%)[b]
1	50 mol% $Fe(acac)_3$, 10 mol% $PhSiH_3$, benzene, r. t.	0
2	50 mol% $Fe(acac)_3$, 10 mol% $PhSiH_3$, EtOH, 50 °C	trace
3	5 mol% $Fe(CO)_5$, NaOH, diglyme, 80 °C	0
4	5 mol% $Co(acac)_3$, $PhSiH_3$, benzene, r. t.	trace
5	5 mol% $Co(acac)_3$, $PhSiH_3$, benzene, 50 °C	<10
6	5 mol% $CoBr_2$(L1), 15 mol% Zn/ZnI_2, CH_2Cl_2, r. t.	0
7	5 mol% $CoBr_2$(L2), 15 mol% Zn/ZnI_2, CH_2Cl_2, r. t.	<10
8	5 mol% $CoBr_2$(L3), 15 mol% Zn/ZnI_2, CH_2Cl_2, r. t.	79
9	5 mol% $CoBr_2$(L4), 15 mol% Zn/ZnI_2, CH_2Cl_2, r. t.	26
10	5 mol% $CoBr_2$(L3), 15 mol% Zn/ZnI_2, CH_2Cl_2, 40 °C	70
11	5 mol% $CoBr_2$(L3), 15 mol% Zn/ZnI_2, CH_2Cl_2, 80 °C	trace

[a] Unless otherwise noted, all reactions were carried out with 0.5 mmol intermediate **6**, catalyst, solvent (3 mL), 3 hours. [b] Yields after silica gel chromatography.

The transformation was sensitive to temperature, such that lower yields and stereoselectivity **7a**:**7b**:**7c**:**7d** = 3:34:1:62 were obtained when the reaction was conducted at 40 °C, whereas only a trace amount of **7** was obtained at 80 °C (Table 1, entries 10-11).

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Scheme 5. Further application of megastigmatrien-3-one.

To further explore the application of the present conversion, the resultant megastigmatrien-3-one isomers were subjected to oxidation with MCPBA to give epoxide intermediates I (Scheme 5). Selective reduction of **I** gave 7-hydroxy-3,5-dienone **8** (3-oxo-β-ionol), which is a key intermediate towards important spices.

Conclusions

In conclusion, we have described an unprecedented synthesis of megastigmatrien-3-one from readily available starting material ethyl 2,6,6-trimethyl-4-oxocyclohex-2-enecarboxylate. This strategy features high stereoselectivity (with *E*, *E* isomer > 70%) over traditional methods with total yield of about 40%. The whole transformation sequence includes functional group protection, reduction, oxidation, and nucleophilic addition followed by hydrolysis. In the last step, the cheap and readily available metal catalyst delivers the desired product with low cost. Considering the excellent stereoselectivity and simple operation, the present method has potential to be further applied in organic synthesis and flavor industry.

Experimental Section

General. The NMR spectra were recorded on Bruker AC-500 spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) with $CDCl_3$ as the solvent and TMS as internal reference. ^{1}H NMR spectral data were reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constant (Hz). ^{13}C NMR spectral data were reported in terms of the chemical shift. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Low-resolution mass spectra were obtained on a Shimadzu LCMS-2010EV spectrometer in ESI mode and reported as *m/z*. High-resolution mass spectra (HRMS) were recorded on a Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS instrument. GC analysis was caarriedout on an Agilent 8890B instrument. Melting points were obtained on a X-4 digital melting point apparatus without correction. Purification of products was accomplished by column chromatography packed with silica gel. Unless otherwise stated, all reagents were commercially purchased and used without further purification.

Ethyl 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate (2). A round bottom flask was charged with 3,5,5-trimethoxy-2-cyclohexen-1-one-4-carboxylic acid ethyl ester **1** (1.05 g, 5 mmol), ethylene glycol (40 mmol, 3.09 mL), triethyl orthoformate (20 mmol, 3.32 mL), 4-methylbenzenesulfonic acid pyridine (0.5 mmol, 120.6 mg) in toluene (60 mL), and the reaction vessel placed in an oil bath at 120 °C for 15 h and monitored by TLC. The mixture was cooled to room temperature, the solvent removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: PE:EA = 50:1) to afford ethyl 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate (**2**). 1.06 g, 84% yield, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) =

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4.21 (qd, *J 7.1*, 3.1 Hz, 2H), 3.93 (d, *J* 3.2 Hz, 4H), 2.26 (s, 2H), 1.66 (t, *J* 3.4 Hz, 5H), 1.29 (td, *J 7.1*, 3.0 Hz, 3H), 1.16 (d, *J* 3.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.3, 134.6, 130.5, 107.6, 64.2, 60.3, 45.2, 41.5, 36.0, 28.9, 21.1, 14.4. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{22}NaO_4$ 277.1416; Found 277.1410.

(7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-en-8-yl)methanol (3). A round bottom flask was charged with lithium aluminum hydride (7.5 mmol, 0.285 g) and 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylic acid ethyl ester **2** (4 mmol, 1.27 g) in dry THF (20 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with two additional portions of ethyl acetate. The combined organics were washed with brine before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was purified by column chromatography on silica gel (eluent: PE:EA = 5:1) to afford (7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-en-8-yl)methanol (**3**). 0.77 g, 91% yield, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.13 (s, 2H), 3.92 (s, 4H), 2.25 (s, 2H), 1.76 (s, 3H), 1.65 (s, 2H), 1.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 136.9, 130.3, 107.9, 64.1, 58.3, 45.5, 42.5, 37.0, 28.9, 19.7. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{20}NaO_3$ 235.1310; Found 235.1305.

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carbaldehyde (4). To a solution of oxalyl chloride (0.51 mL, 6 mmol) in 30 mL of CH_2Cl_2 at –78 °C was added DMSO (0.85 mL, 12 mmol) dropwise. After 5 min, a solution of **3** (4 mmol, 0.848 g) in 10 mL of CH_2Cl_2 was added, and stirring was continued at –78 °C for 15 min. Et_3N (37 mL, 264 mmol, 5 eq.) was then added, the cooling bath was removed, and stirring was continued. After 1 h, TLC analysis indicated complete consumption of the starting material and formation of the product. The reaction was quenched with saturated sodium bicarbonate and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with two additional portions of CH_2Cl_2. The combined organics were washed with brine before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was purified by column chromatography on silica gel (eluent: PE:EA = 10: 1) to afford 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carbaldehyde (**4**). 0.814 g, 97% yield, clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.13 (s, 1H), 3.94 (s, 4H), 2.45 (s, 2H), 2.10 (s, 3H), 1.65 (s, 2H), 1.28 (d, *J* 5.4 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 191.7, 151.8, 139.2, 106.8, 64.2, 46.9, 44.9, 36.1, 28.3, 19.4. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{18}NaO_3$ 233.1154; Found 233.1148.

4-(But-3-en-1-ylidene)-3,5,5-trimethylcyclohex-2-enone (6). In a Schlenk flask filled nitrogen the compound **4** (2 mmol, 0.42 g) in dry THF (10 mL) was carefully added allylmagnesium bromide (4 mmol, 8 mL, 0.5 M in THF). The reaction mixture was stirring at 0 °C for 3 h. Then the residue was quenched with saturated NH4Cl solution, extracted with ethyl acetate and dried on $MgSO_4$. After removal of the solvent under reduced pressure, the crude product put into a solution in 10 mL of THF followed by the addition of 36% sulfuric acid aqueous solution (4 mL) dropwise. The reaction mixture was stirring at at room temperature for 4 h. Then the residue was quenched with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate and dried on $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (eluent: PE:EA = 10: 1) to give 4-(but-3-en-1-ylidene)-3,5,5-trimethylcyclohex-2-enone (**6**). 0.342 g, 68% yield, clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.93 (dd, *J* 18.4, 10.6 Hz, 3H), 5.07 (s, 2H), 3.18 (t, *J* 6.9 Hz, 2H), 2.33 (s, 2H), 2.05 (s, 3H), 1.29 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 199.4, 155.3, 142.6, 136.3, 132.6, 125.8, 116.2, 54.0, 38.4, 34.1, 29.1, 22.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{19}O$ 191.1436; Found 191.1425.

4-(but-2-en-1-ylidene)-3,5,5-trimethylcyclohex-2-enone (7). The cobalt catalyst (5 mol %), zinc powder (15 mol %) and zinc iodide (15 mol %) were combined under an atmosphere of nitrogen and suspended in CH_2Cl_2. Then compound **6** (95.1 mg，0.5 mmol) was added and the reaction mixture was stirred at room temperature until complete conversion of the starting material was observed. The reaction was quenched with saturated

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sodium bicarbonate and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with two additional portions of CH_2Cl_2. The combined organics were washed with brine before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was purified by column chromatography on silica gel (eluent: PE:EA = 10: 1) to afford megastigmatrien-3-one 4-(but-2-en-1-ylidene)-3,5,5-trimethylcyclohex-2-enone (**7**). 0.751 g, 79% yield, clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.75 (d, *J* 1.5 Hz, 1H), 6.46 (d, *J* 11.6 Hz, 1H), 5.99 - 5.90 (m, 1H), 5.89 (s, 1H), 2.35 (s, 2H), 2.07 (d, *J* 0.7 Hz, 3H), 1.87 (dd, *J* 6.9, 1.4 Hz, 3H), 1.33 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 199.4, 155.4, 139.9, 137.2, 132.8, 128.7, 125.9, 54.1, 38.5, 29.9, 22.4, 19.1. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{18}NaO$ 213.1255; Found 213.1250.

(*E*)-4-(3-Hydroxybut-1-en-1-yl)-3,5,5-trimethylcyclohex-3-enone (8). To a cold solution (0 °C) of **7** (187.5 mg, 1 mmol) in dry dichloromethane (5 mL) was added *m*-chloroperbenzoic acid (215.8 mg, 1.25 mmol) and the mixture was stirred at 0 °C for 2 h. The mixture was washed with a 1% solution of NaOH and brine, dried over MgSO4, and concentrated. The resdue was added to a mixture of zinc power (326.7 mg) and acetic acid (1.5 mL) at room temperature. After the mixture was stirred for 2 h at room temperature, the precipitate was filtered off and washed with ether (10 mL). The filtrate was washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and then concentrated. Purification by silica-gel column chromatography (hexane-ether) afford (*E*)-4-(3-hydroxybut-1-en-1-yl)-3,5,5-trimethylcyclohex-3-enone (**8**). 0.134 g, 65% yield, clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.04 (d, *J* 15.9 Hz, 1H), 5.55 (dd, *J* 15.9, 6.3 Hz, 1H), 4.40 (t, *J* 6.3 Hz, 1H), 2.83 (s, 2H), 2.34 (s, 2H), 1.70 (s, 3H), 1.32 (d, *J* 6.4 Hz, 3H), 1.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 204.3, 133.1, 132.0, 119.9, 119.7, 63.2, 48.8, 40.1, 33.3, 22.5, 17.8, 14.6.

1-(7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-en-8-yl)but-3-en-1-ol (5): 0.312 g, clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.86 (qd, *J* = 9.9, 7.2 Hz, 1H), 5.08 (t, *J* 13.8 Hz, 2H), 4.28 (dd, *J* 10.4, 2.6 Hz, 1H), 3.89 (s, 4H), 2.62 (dt, *J* 14.2, 9.2 Hz, 1H), 2.24 (dd, *J* 4.8, 3.1 Hz, 1H), 2.19 (d, *J* 7.4 Hz, 2H), 1.85 (s, 3H), 1.65-1.55 (m, 2H), 1.15 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 138.8, 136.3, 128.4, 107.71, 69.9, 64.1, 64.0, 45.8, 43.5, 41.4, 37.7, 29.2, 29.5, 21.1. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{24}NaO_3$ 275.1623; Found 275.1618.

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Supplementary Material

The experimental procedures and ^{1}H NMR and ^{13}C NMR spectra associated with this article are available as supplementary data.

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