Supplementary Material

Stereoselective synthesis of megastigmatrien-3-one using catalytic

olefin isomerization as key step

Demin Liang,^a Wei Zhang,^a Shengchao Wu,^a Chen Luo,^a Yunfei Sha,^a Jie Shen,^b Yao Xiao,^b Da Wu,^{*a} and Jian Li^{*b}

 ^a Technical Center of Shanghai Tobacco Group Co. Ltd., 3733 Xiupu Road, Shanghai 200082, P. R. China
^b Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, P. R. China Email: wud@sh.tobacco.com.cn; lijian@shu.edu.cn

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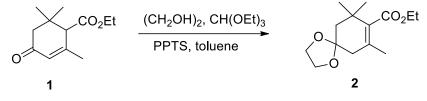
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1 General Information

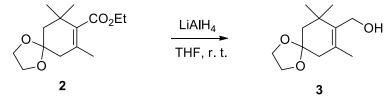
The NMR spectra were recorded on Bruker AC-500 spectrometer (500 MHz for ¹H NMR and 125 MHz for ¹³C NMR) with CDCl₃ as the solvent and TMS as internal reference. ¹H NMR spectral data were reported as follows: chemical shift (δ , ppm), multiplicity, integration, and coupling constant (Hz). ¹³C NMR spectral 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 detected 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.

2 General Procedure

a) General Procedure for the synthesis of compound 2

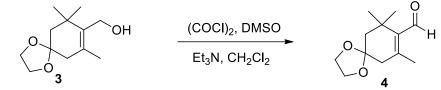


A round bottom flask was charged with 3,5,5-trimethoxy-2-cyclohexen-1-one-4-carboxylic acid ethyl ester **1** (1.05 g, 5 mmol), Ethylene glycol (40 mmol, 3.09 mL), triethyl orthoformate (20 mmol, 3.32 mL), 4-methylbenzenesulfonic acid pyridine (0.5 mmol, 120.6 mg) in toluene (60 mL), and the reaction vessel placed in an oil bath at 120 °C for 15 h. After the reaction was completed, it was cooled to room temperature and monitored by TLC. The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford product **2**. b) **General Procedure for the synthesis of compound 3**



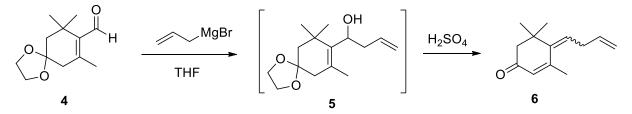
A round bottom flask was charged with lithium aluminum hydride (7.5 mmol, 0.285 g) and 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylic acid ethyl ester **2** (4 mmol, 1.27 g) in dry THF (20 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with 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 Na₂SO₄. 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 **3**.

c) General Procedure for the synthesis of compound 4



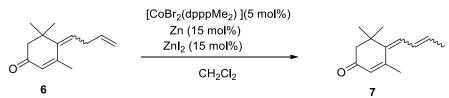
To a solution of oxalyl chloride (0.51 mL, 6 mmol) in 30 mL of CH_2Cl_2 at -78 °C was added DMSO (0.85 mL, 12 mmol) dropwise. After 5 min, a solution of **3a** (4 mmol, 0.848 g) in 10 mL of CH_2Cl_2 was added, and stirring was continued at -78 °C for 15 min. Et₃N (37 mL, 264 mmol, 5 eq.) was then added, 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 **4**.

d) General Procedure for the synthesis of compound 6



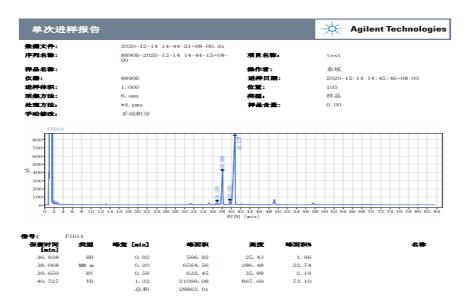
In a Schlenk flask filled nitrogen the compound **4** (2 mmol, 0.42 g) in dry THF (10 mL) was carefully added Allyl magnesium bromide (4 mmol, 8 mL, 0.5 M in THF). The reaction mixture was stirring at 0 °C for 3 h. Then the residue was quenched with saturated NH₄Cl solution, extracted with ethyl acetate and dried on MgSO₄. 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 MgSO₄. After removal of the solvent under reduced pressure, the crude product was quenched with Saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate and dried on MgSO₄. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (eluent: PE:EA = 10: 1) to give **6**.

e) General Procedure for the synthesis of compound 7

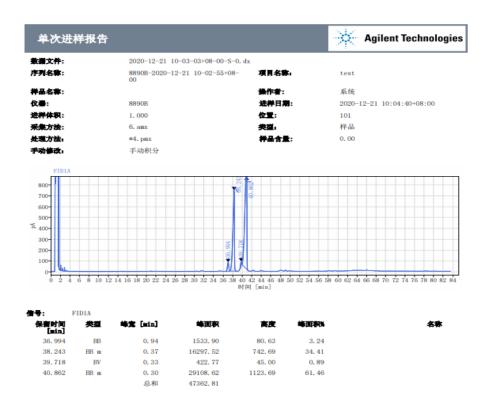


The cobalt catalyst (5 mol %), zinc powder (15 mol %) and zinc iodide (15 mol %) were combined under an atmosphere of nitrogen and suspended in CH_2Cl_2 . Then compound **6** (0.95 g, 5 mmol) was added and the reaction mixture was stirred at room temperature until complete conversion of the starting material was observed. The reaction was quenched with saturated 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 Na₂SO₄. 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 **7**.

Ratio of four isomers under r.t.



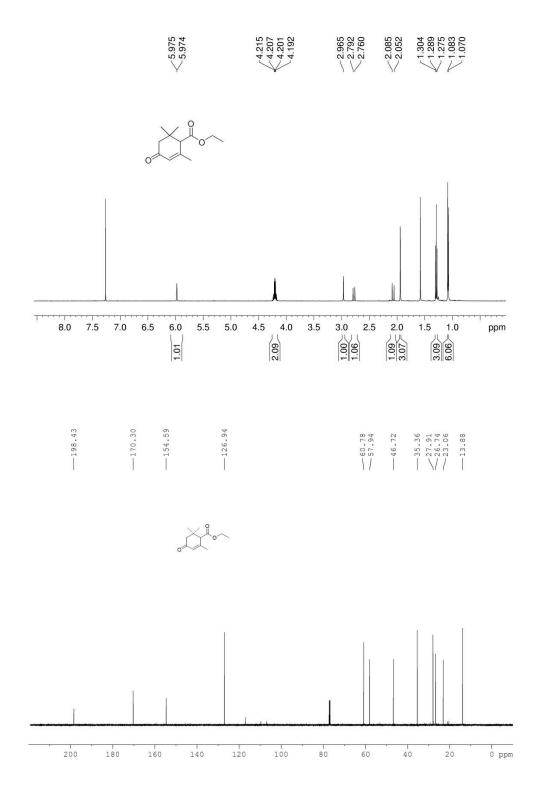
Ratio of four isomers under 40 °C.

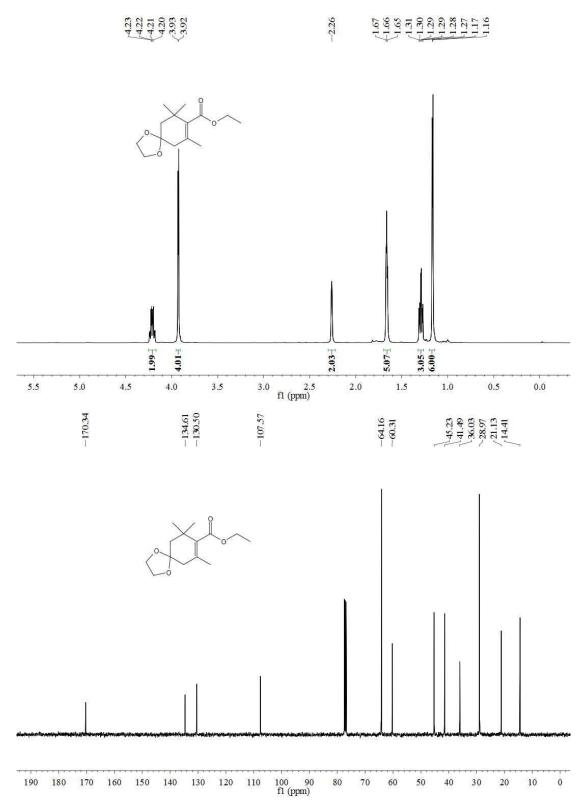


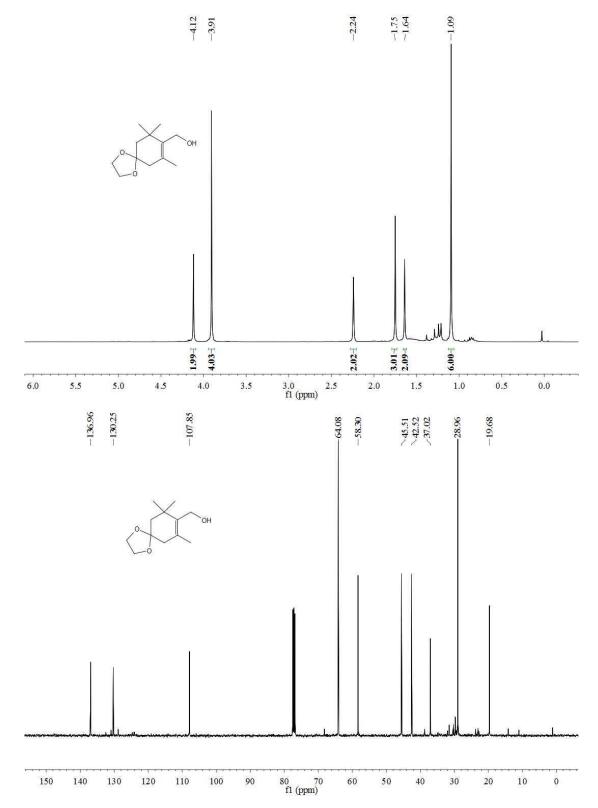
f) General Procedure for the synthesis of compound 8

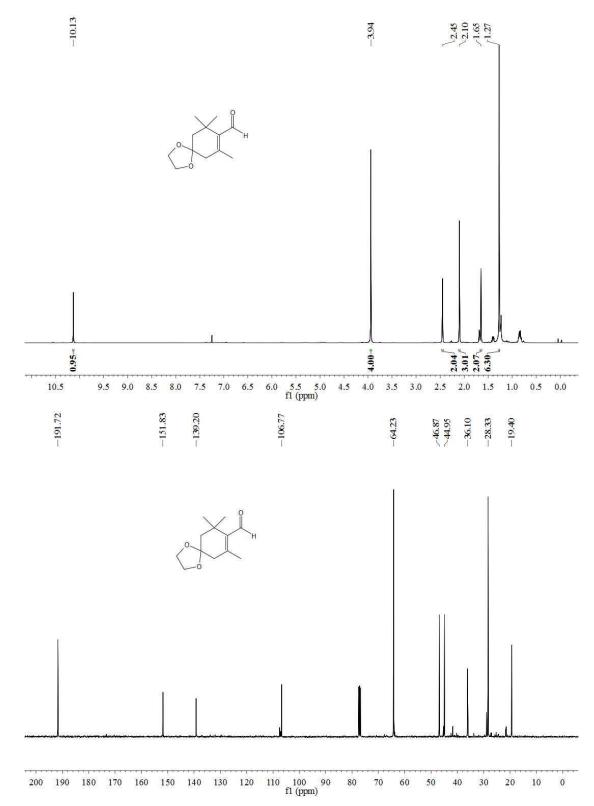
To a cold solution (0 °C) of **7** (187.5 mg, 1 mmol) in dry dichloromethane (5 mL) was added *m*-chilrlperbenzoic acid (215.8 mg, 1.25 mmol) and the mixture was stirred at 0 °C for 2 h. The mixture was washed with a 1 % solution of NaOH and brine, dried over MgSO₄, and concentrated. The resdue was added 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 precipitata was filtered off and washed with ether (10 mL). The filtrate was washed with a saturated solution of NaHCO₃ and brine, dried over MgSO₄, and then concentrated. Purification by silica-gel column chromatography (hexane-ether) afford **8** (65%).

3 ¹H NMR and ¹³C NMR Spectra of All Compounds

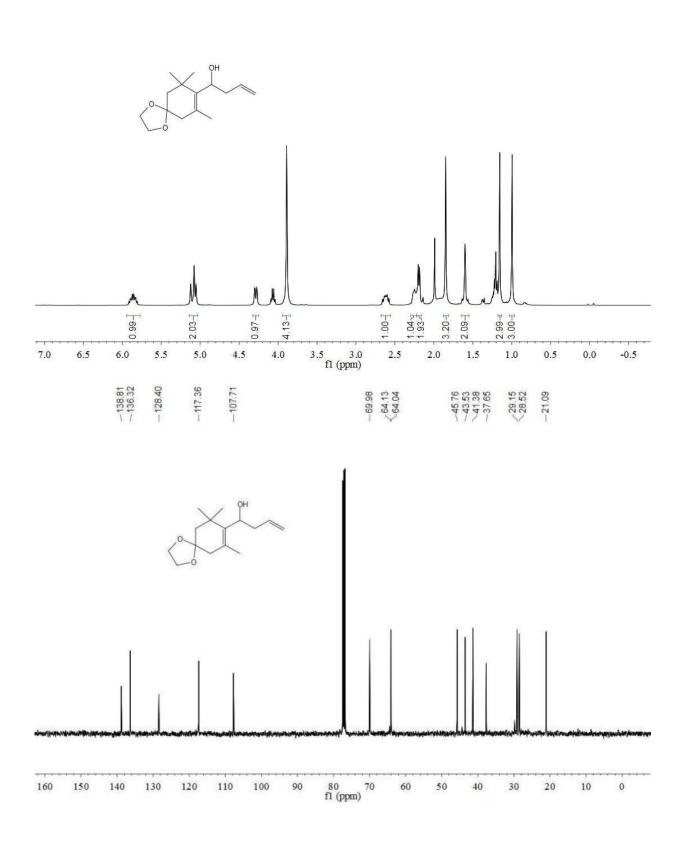


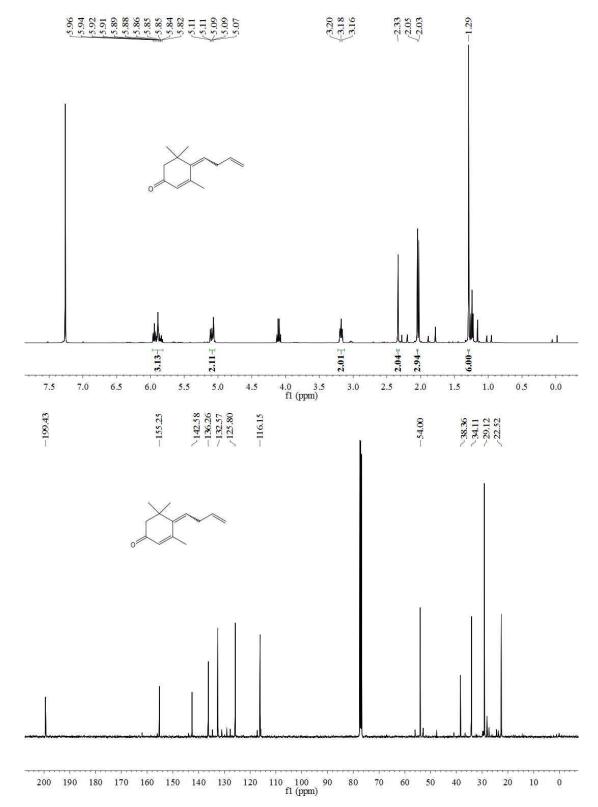


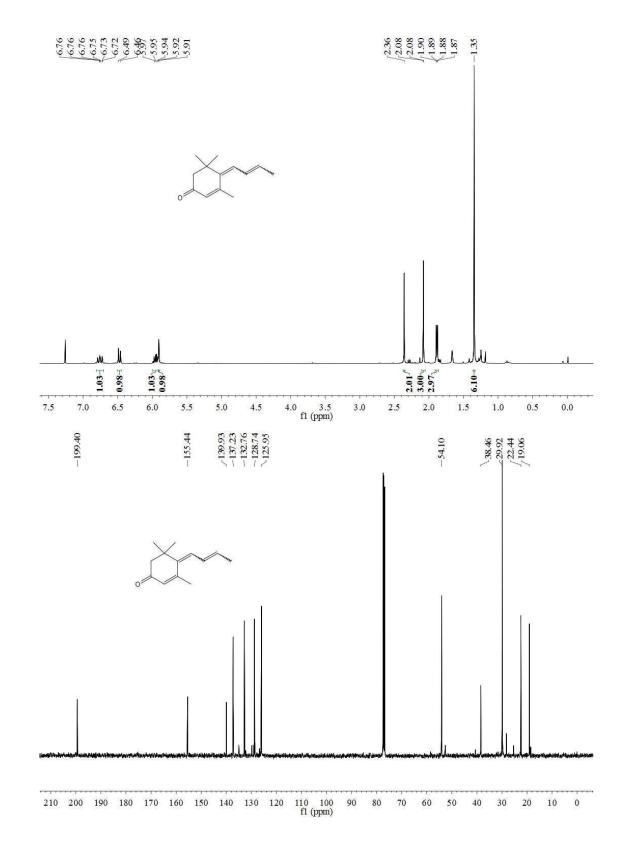


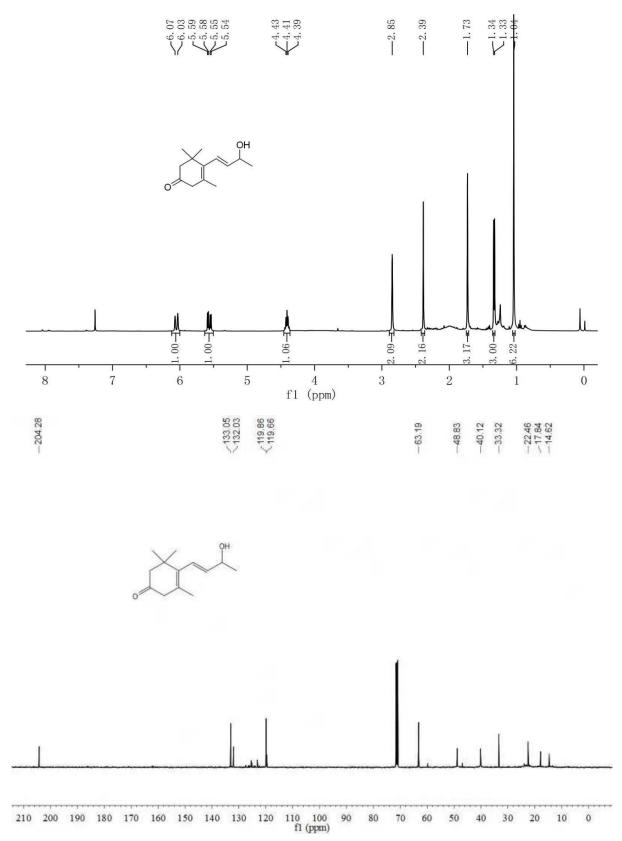


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4 HRMS of new compounds and significant compounds

HRMS of compound 1

Display Report Analysis Info Acquisition Date 8/28/2021 8:50:18 AM Analysis Name Method D:\Data\2021MS\LJ\0828\1_BD1_01_386.d tune_low_20-400_pos-3min.m Operator gftang Sample Name micrOTOF 10257 1 Instrument / Ser# Comment Acquisition Parameter Source Type Focus Scan Begin Scan End ESI Not active 22 m/z 400 m/z ion Polarity Positive Set Nebulizer Set Dry Heater Set Dry Gas 1.0 Bar 200 °C 4.0 Vmin 2500 V -500 V Set Capillary Set End Plate Offset Set Divert Valve Waste Intens +MS, 1.8min #105 x10⁴ 137.0967 1.25 1.00 109,1006 165.0916 121.1000 0.75 227.1262 149.0243 213.1639 0.50 247.1312 267.1565 289,1414 0.25 301.1420 0.00 260 300 m/z 120 220 240 290 100 140 160 190 200 Intens +MS, 1.8min #105 233.1149 1000 800 600 400 235,1129 200 234.1195 0 C12H18O3, M+nNa .233.12 233.1148 2000 1500 1000-500 234.1182 235.1215 0 232 233 234 235 236 237 238 m/z 231 printed: Bruker Compass DataAnalysis 4.0 8/28/2021 8:55:02 AM Page 1 of 1

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