

Synthesis of a Renewable Macrocyclic Musk: Evaluation of Batch, Microwave and Continuous Flow Strategies

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SUPPORTING INFORMATION

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GENERAL

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.¹ All chemical products were obtained from Millipore Sigma, Alfa Aesar or Oakwood Chemicals and were reagent quality. The ruthenium catalysts were obtained from Materia Inc. Technical solvents were obtained from Thermo Fisher Scientific or ACP Chemicals. Anhydrous solvents (CH₂Cl₂, toluene) were dried and deoxygenated using a GlassContour system (Irvine, CA). 2,6-Dimethylnonadeca-2,18-dien-8-ol was prepared by an established procedure.² Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still³ and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F₂₅₄). Visualization of TLC plate was performed by KMnO₄ stain. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. NMR spectra were taken in deuterated CDCl₃ using Bruker AV-400 and AV-500 instruments unless otherwise noted. Signals due to the solvent served as reference (CHCl₃: δ 7.27 for ¹H, δ 77.0 for ¹³C). The ¹H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. The ¹H NMR assignments were made based on chemical shift and multiplicity and were confirmed. The ¹³C NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using APPI mode of ionization unless otherwise noted.

¹ Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

² Narula, A. P. S.; Arruda, E. M.; Amorelli, B.; Schiet, F. T. 3-Methyl-6-cyclohexadecen-1-one and its use in perfume compositions, 2013. US 8450265.

³ Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923.

EXPERIMENTAL PROCEDURES

2,6-Dimethylnonadeca-2,18-dien-8-one (2): To a stirring solution of oxalyl chloride (1.25 mL, 14.6 mmol, 1.2 equiv.) in CH₂Cl₂ (60 mL) maintained at -78 °C, was slowly added a solution of dimethyl sulfoxide (2.10 mL, 29.2 mmol, 2.4 equiv.) in CH₂Cl₂ (60 mL) using an addition funnel. The reaction mixture was stirred for an additional 20 min before adding dropwise a solution of 2,6-dimethylnonadeca-2,18-dien-8-ol (**S1**) (3.75 g, 12.2 mmol, 1 equiv.) in CH₂Cl₂ (120 mL) using an addition funnel. The reaction mixture was stirred for an additional 20 min before adding triethylamine (8.50 mL, 60.8 mmol, 5 equiv.). The solution was warmed to room temperature and stirred an hour before quenching the reaction with water. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (1% Et₂O in hexanes) gave the desired product as a colorless oil (3.56 g, 96%). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.81 (ddt, *J* = 16.8, 10.4, 6.8 Hz, 1H), 5.11-5.07 (m, 1H), 4.99 (d, *J* = 17.2 Hz, 1H), 4.93 (d, *J* = 10.4 Hz, 1H), 2.41-2.35 (m, 2H), 2.23-2.17 (m, 1H), 2.07-1.92 (m, 5H), 1.68 (s, 3H), 1.60 (s, 3H), 1.57-1.54 (m, 2H), 1.39-1.14 (m, 15H), 0.89 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 211.4, 139.2, 131.4, 124.3, 114.1, 50.2, 43.4, 37.0, 33.8, 29.4 (3C), 29.2, 29.1, 28.9, 28.9, 25.7, 25.4, 23.8, 19.8, 17.6; HRMS (APPI) *m/z* calculated for C₂₁H₃₈O [M+H]⁺, 307.2995; found: 307.2998.

5-Methyloctadeca-1,17-dien-7-one (2a): To a solution of diene **2** (100 mg, 0.326 mmol, 1 equiv.) in dry toluene (65 mL, 5 mM) was bubbled ethylene. Stewart-Grubbs catalyst **SG** (18.6 mg, 0.033 mmol, 10 mol%) was then added. The mixture was stirred at room temperature under an atmosphere of ethylene for 24 h. The catalyst was quenched by adding ethyl vinyl ether (2mL) to the solution before concentration in vacuo. Purification by silica gel chromatography (100% hexanes to 1% MeOt-Bu in hexanes) afforded a mixture of the desired product and the starting material (**2**). Analysis by ¹H NMR using 10 mol % of 1,4-dimethoxybenzene as internal standard estimates a 56% yield of **2a** and 34% residual starting material. Further purification, or resubmitting the mixture to the ethenolysis can improve conversion. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.86-5.76 (m, 2H), 5.03-4.97 (m, 2H), 4.96-4.92 (m, 2H), 2.39-2.35 (m, 2H), 2.24-2.19 (m, 1H), 2.14-1.93 (m, 5H), 1.57-1.54 (m, 2H), 1.43-1.14 (m, 15H), 0.90 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 211.2, 139.2, 138.7, 114.4, 114.1, 50.1, 43.4, 36.1, 33.8, 31.2, 29.4 (3C), 29.2, 29.1, 28.9, 28.7, 23.8, 19.7; HRMS (ESI) *m/z* calculated for C₁₉H₃₄O [M+H]⁺, 279.2682; found: 279.2679.

3,7-Dimethyloct-6-en-1-yl dec-9-enoate (S2) : To a solution of citronellol (1.15 mL, 6.4 mmol, 1 equiv.) and 9-decenoic acid (1.80 mL, 9.6 mmol, 1.5 equiv.) in CH₂Cl₂ (32 mL, 0.2 M) were added *N,N'*-dicyclohexylcarbodiimide (1.98 g, 9.6 mmol, 1.5 equiv.) and 4-(dimethylamino)pyridine (782 mg, 6.4 mmol, 1 equiv.). The mixture was stirred at room temperature for 22 h. The precipitated urea was removed by filtration. The filtrate was purified by silica gel chromatography (0.5% → 2% EtOAc in hexanes) to afford the desired product as a colorless oil (1.71 g, 88%). NMR data was in accordance with what was previously reported.⁴

(4) Nakazawa, Y.; Aoki, T.; Toyabe, T. 13-methyl-9-cyclopentadecen-15-olide, 2014. EP 2781515.

2-(2,6-Dimethylhept-5-en-1-yl)-2-(undec-10-en-1-yl)-1,3-dioxolane (S3): To a solution of diene **2** (500 mg, 1.63 mmol, 1 equiv.) and p-toluenesulfonic acid (31.0 mg, 0.163 mmol, 10 mol%) in dry toluene (3.3 mL, 0.5 M) were added ethylene glycol (0.27 mL, 4.89 mmol, 3 equiv.) and trimethylorthoformate (0.54 mL, 4.89 mmol, 3 equiv.). The reaction was stirred at room temperature for 24 h. The mixture was then diluted with an aqueous solution of NaHCO₃ (satd) mixed with 10% MeOH. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine. The organic layer was dried with Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (0.25% Et₂O in hexanes) gave the desired product as a colorless oil (550 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.82 (ddt, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.13-5.09 (m, 1H), 5.03-4.97 (m, 1H), 4.95-4.92 (m, 1H), 3.94-3.89 (m, 4H), 2.07-2.02 (m, 2H), 1.99-1.93 (m, 2H), 1.69 (s, 3H), 1.66-1.58 (m, 7H), 1.45-1.28 (m, 16H), 1.22-1.13 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 139.2, 131.1, 124.9, 114.1, 112.2, 64.6, 64.5, 43.4, 38.2, 37.4, 33.8, 29.9, 29.6, 29.5, 29.5, 29.1, 28.9, 28.4, 25.7, 25.5, 23.8, 20.9, 17.6; HRMS (APPI) *m/z* calculated for C₂₃H₄₂O₂ [M+H]⁺, 351.3258; found: 351.3253.

Batch Procedure for Macrocyclization Using Slow Addition (A): Diene **2** (100 mg, 0.326 mmol, 1 equiv.) and ruthenium catalyst (0.010 mmol, 3 mol%) were each separately dissolved in dry CH₂Cl₂ (2 x 22 mL) and placed in two different syringes (24 mL). Both solutions were added slowly and simultaneously over 17 h (0.0216 mL/min) with a syringe pump to a 250 mL round bottom flask containing 22 mL of anhydrous CH₂Cl₂ stirred at room temperature. The catalyst was quenched by adding a 2 mL of ethyl vinyl ether to the solution before concentration in vacuo. Purification by silica gel chromatography (1% Et₂O in hexanes) allowed to remove the catalyst and side-products. Recovered starting material and desired product were collected as a mixed fraction and the yield was determined by NMR using 10 mol % of 1,4-dimethoxybenzene as internal standard.

Batch Procedure for Macrocyclization (B): Diene (1 equiv.) and Stewart-Grubbs catalyst **SG** (10 mol %) were stirred in dry toluene (5, 10 or 20 mM) at room temperature for 5 days. The catalyst was quenched by adding ethyl vinyl ether (2mL/100 mg of starting material) to the solution before concentration in vacuo. Purification by silica gel chromatography (0.25% Et₂O in hexanes) afforded the desired product.

Microwave Procedure for Macrocyclization(C): In a microwave vial (size 10-20 mL) equipped with a stirring bar, diene (1 equiv.) and Stewart-Grubbs catalyst **SG** (10 mol %) were dissolved in dry toluene (10 or 20 mM), and the mixture was stirred at room temperature until homogeneity. The vial was then sealed with a microwave cap. The reaction was heated at 70 °C for 1 h with a Biotage Initiator I-60 microwave apparatus. The catalyst was quenched by adding 2 mL of ethyl vinyl ether to the solution before concentration in vacuo. Purification by silica gel chromatography (1% Et₂O in hexanes) allowed to remove the catalyst and side-products. Recovered starting material and desired product were collected as a mixed fraction and the yield was determined by NMR using 10 mol % of 1,4-dimethoxybenzene as internal standard.

Continuous Flow Procedure for Macrocyclization (D): The reaction was performed in continuous flow using a Vapourtec R4 reactor and a R2+ pumping module. Diene (1 equiv.) and catalyst **SG** (10 mol%) were separately placed in two pear-shape flasks and dissolved in equal amounts of dry toluene (5, 10 or 20 mM in total). Each solution was pumped at a rate of 1,00 mL/min (5 min of residence time) and mixed through a T-mixer.

The reaction mixture passed through a stainless-steel coil reactor (10 mL) heated at 150 °C and a cooling loop (1 m). A quenching column (Omnifit, 15 mm diameter) containing a mix of ≈ 2 g of silica and ≈ 2 g of charcoal corresponding to a reactor of 8 mL was then placed before a back pressure regulator (IDEX 250 psi). The reaction mixture was finally collected in an empty round-bottom flask and concentrated in vacuo. In general, purification by silica gel chromatography (0.25% Et₂O in hexanes) afforded the desired product. For entries at 5 and 20 mM in Figure 5: Purification by silica gel chromatography (1% Et₂O in hexanes) allowed to remove the catalyst and side-products. Recovered starting material and desired product were collected as a mixed fraction and the yield was determined by NMR using 10 mol % of 1,4-dimethoxybenzene as internal standard.

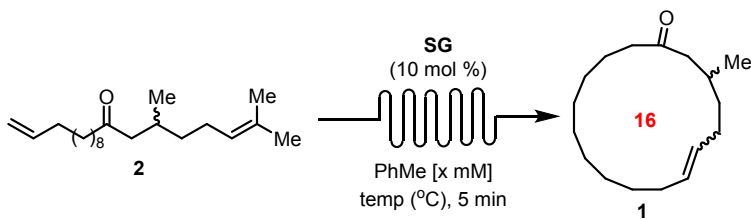
3-Methylcyclohexadec-6-en-1-one (1): Following procedure D, diene **2** (1.00 g, 3.26 mmol, 1 equiv.) and catalyst **SG** (186 mg, 0.326 mmol, 10 mol%) were both dissolved in 163 mL of dry toluene in separate pear-shape flasks. The continuous flow set-up was the same as described in procedure D except for the quenching: the reaction mixture went through the back pressure regulator (IDEX 250 psi) before being quenched by passing in an iLOK cartridge (70 mL) containing a mix of silica/charcoal (≈ 4 g of silica at each end of the column + ≈ 22 g of silica mixed with ≈ 3.8 g of charcoal in the middle). Purification by silica gel chromatography (0.25% Et₂O in hexanes) was performed to afford the desired product as a yellow oil (261 mg, 32%) ¹H NMR (400 MHz, CDCl₃) δ ppm 5.39-5.29 (m, 2H), 2.52-2.29 (m, 3H), 2.14-1.95 (m, 6H), 1.72-1.67 (m, 1H), 1.58-1.51 (m, 1H), 1.40-1.18 (m, 14H), 0.95 (d, $J = 6.8$ Hz, 13% of 3H), 0.90 (d, $J = 6.8$ Hz, 87% of 3H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 211.9, 131.3, 130.3, 51.0, 41.0, 36.4, 31.9, 29.6, 28.8, 28.1, 27.5, 27.4, 27.1, 26.8, 26.2, 22.1, 19.2 (note that the product was obtained as a mixture of diastereoisomers, only the major peaks are reported to simplify the data); HRMS (APPI) m/z calculated for C₁₇H₃₀O [M+H]⁺, 251.2369; found: 251.2363.

13-Methyl-9-cyclopentadecen-15-olide (3): Following procedure B, diene **S2** (200 mg, 0.648 mmol, 1 equiv.) and catalyst **SG** (37.0 mg, 0.065 mmol, 10 mol%) were dissolved in dry toluene (130 mL, 5 mM). Purification by silica gel chromatography (0.25% Et₂O in hexanes) was performed to afford the desired product as a yellow oil (134 mg, 82%). NMR data was in accordance with what was previously reported.²⁷

7-Methyl-1,4-dioxaspiro[4.15]icos-10-ene (4): Following procedure B, diene **S3** (200 mg, 0.570 mmol, 1 equiv.) and catalyst **SG** (32.5 mg, 0.057 mmol, 10 mol%) were dissolved in dry toluene (114 mL, 5 mM). Purification by silica gel chromatography (0.25% Et₂O in hexanes) was performed to afford the desired product as a yellow oil (101 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.42-5.29 (m, 2H), 3.93-3.87 (m, 4H), 2.14-2.02 (m, 3H), 1.74-1.55 (m, 5H), 1.47-1.17 (m, 17H), 1.00 (d, $J = 6.4$ Hz, 19% of 3H), 0.93 (d, $J = 6.4$ Hz, 81% of 3H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 130.6, 130.5, 112.3, 64.3, 64.1, 42.6, 36.9, 35.3, 31.1, 29.3, 27.6, 27.1, 26.9, 26.8, 26.5, 26.2, 26.2, 22.0, 19.5 (note that the product was obtained as a mixture of diastereoisomers, only the major peaks are reported to simplify the data); HRMS (APPI) m/z calculated for C₁₉H₃₄O₂ [M+H]⁺, 295.2632; found: 295.2633.

MACROCYCLIZATION IN FLOW

Table S1: Flow Experiments to Form Macrocycle 1 from Diene 2.



	[mM]	Temp (°C)	Unreacted 2 (%) ^a	Yield 1 (%) ^a
1	20	150	16	15
2	10	150	30	(32)
3	5	150	24	26
4	10	130	20	30
5	10	110	12	20
6	10	90	13	14
7	10	70	25	2

^a Estimated yields by ¹H NMR with 1,4-dimethoxybenzene as internal standard. Isolated yields are shown in brackets.

NMR DATA FOR ALL NEW COMPOUNDS

