Application of Ring Closing Metathesis to the First Total Synthesis of (*R*)-(+)-Muscopyridine: Determination of Absolute Stereochemistry

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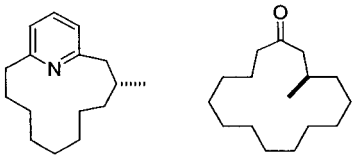
Musks are very precious and exotic natural perfumery ingredients isolated mainly from the musk gland of male musk deers *Moschus moschiferus* which are found in Tibet or Himalayas. Because of its noble flavor, musks have been highly appreciated as perfumery ingredients of the highest demand over 900 years.[1] The major constituent of musks, muscone **2**, was first isolated by Walbaum[2] in 1906, and the structure was solved by Ruzicka[3] in 1926 as the first macrocyclic compound. On the other hand, the structure of the basic minor constituent, muscopyridine **1**, had long been unknown until its empirical formula was determined by Ruzicka and Prelog[4] in 1946. Total synthesis by Büchi et al.[5] in 1957 proved the structure to be the macrocyclic compound involving a pyridine nucleus. Although they obtained the natural enantiomer by optical resolution, its absolute stereochemistry has not yet been established.



1 **2**

Since that time, only a few racemic syntheses appeared in the literature[6] due to a shortage of efficient methods to make the macrocyclic carbon framework and the difficulty of introducing the asymmetric center at C-3.

The recent development of stable metal alkylidene complexes changed the olefin metathesis reaction into a practical carbon−carbon bond forming reaction.[7] Especially worthy of note is that a wide variety of functional groups can be tolerated under the reaction condition since the catalysts are reactive only to olefins. Another characteristic feature is the ability of the catalysts to make especially large carbocyclic rings, now called ring closing olefin metathesis (RCM). Thus many cyclic natural and unnatural product syntheses[8] have employed the RCM strategy as a powerful tool.

Continuing our synthetic efforts in this area,[9] we delineate herein for the first time the asymmetric synthesis of muscopyridine **1** starting from (*R*)-(+)-citronellal **8**, utilizing the RCM strategy and determining its absolute stereochemistry.

In principle, the pyridine nucleus of muscopyridine **1** could be introduced by means of the 1,5-diketone **4** which in turn could be obtained by RCM protocol from the 1,16-diolefinic compound **5** (Scheme 1). The RCM substrate **5** with its asymmetric secondary methyl group would be synthesized from optically active citronellal **8** as a chiral source. Since RCM substrates are sensitive to steric hindrance close to the double bond to be metathesized, we chose to synthesize the terminal dimethylenic substrate **5** having 1,5-dicarbonyl moiety.

Citronellol was obtained by sodium borohydride reduction of citronellal **8** in 91% yield. To induce RCM reaction, the isopropylidene group existing in citronellol **8** was replaced by a terminal olefinic moiety. Ozonolysis followed by Wittig methylenation[10] provided in 70% yield olefinic alcohol **9** which was oxidized with sulfur trioxide pyridine and DMSO to give volatile olefinic aldehyde **10** (Scheme 2). In ozonolysis, gradual warming to room temperature was the key to success after addition of dimethyl sulfide. Alternative cleavage by osmium tetraoxide[11] was capricious in our hands. Subsequent addition of vinylmagnesium bromide to the aldehyde **10** afforded in 70% yield a diastereomeric mixture of allylic alcohol **11**. This was subjected to oxidation with a catalytic amount of tetrapropylammonium perruthenate (TPAP) to provide in 70% yield vinyl ketone **6**, the left moiety of RCM substrate **5**. β-Keto-ester **7** corresponding to the right moiety of **5** was prepared in 60% yield through alkylation of dianion of methyl acetoacetate **12**[12] with 4-butenyl bromide. Coupling of both moieties was achieved by Michael addition of the β-keto-ester **7** to the vinyl ketone **6** under phase transfer reaction conditions to afford β-keto-ester **13** in 93% yield (Scheme 3). Attempts employing trimethylsilylenol ether of 7-octen-2-one to the vinyl ketone **6** by Lewis acid promoted 1,4-conjugate addition leading directly to dimethylenic 1,5-dicarbonyl compound **5** have all failed. Decarboxylation of the β-keto-ester **13** was carried out without using

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(1) Williams, A. S. *Synthesis* **1999**, 1707.
(2) Walbaum, H. *J. Prakt. Chem.* **1906**, *73*, 488.
(3) Ruzicka, L. *Helv. Chim. Acta* **1926**, *9*, 715, 1008.
(4) Schinz, H.; Ruzicka, L.; Geyer, U.; Prelog, V. *Helv. Chim. Acta* **1946**, *29*, 1524.
(5) Biemann, K.; Büchi, G.; Walker, B. H. *J. Am. Chem. Soc.* **1957**, *79*, 5558.
(6) (a) Tamao, K.; Kodama, S.; Nakatsuka, S.; Kiso, Y.; Kumada, M. *J. Am. Chem. Soc.* **1975**, *97*, 4405. (b) Hiyama, T.; Shinoda, M.; Saimoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2747. (c) Sakane, S.; Matsumura, Y.; Yamamura, Y.; Ishida, Y.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 674.
(7) (a) Grubbs, R. H.; Miller, J. S.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Furstner, A. *Top. Catal.* **1997**, *4*, 285. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875.
(8) Furstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, and references therein.
(9) Kamat, V. P.; Hagiwara, H.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2253.; Kamat, V. P.; Hagiwara, H.; Katsumi, T.; Suzuki, T.; Ando, M. *Tetrahedron* **2000**, 4397.
(10) The same procedure was reported during the course of our investigation. Boger, D. L.; Keim, H.; Oberhauser, H.; Schreiner, E. P.; Foster, C. A., *J. Am. Chem. Soc.* **1999**, *121*, 6197.
(11) Shing, T. K. M.; Yang, J. *J. Org. Chem.* **1995**, *60*, 5785.
(12) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

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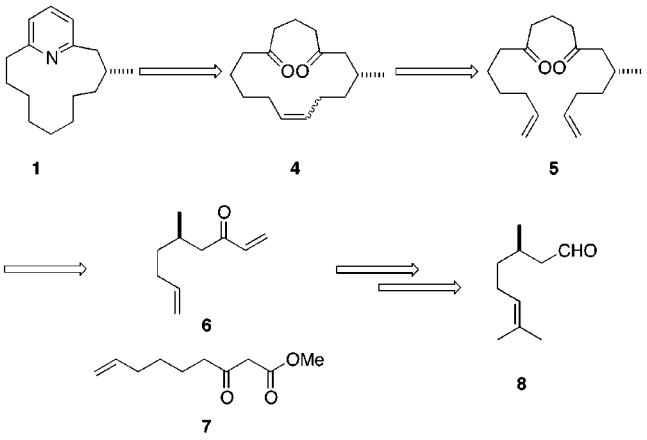
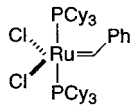
Scheme 1



aqueous alkaline reaction conditions to avoid intramolecular aldol condensation of the resulting 1,5-dicarbonyl product **5**. After several variations in reaction conditions were tried, treatment with lithium chloride at 120 °C in dimethylpropyleneurea (DMPU) gave keto-diene **5** in 72% yield. Other salts in highly polar aprotic solvents such as HMPA or DMSO gave unsatisfactory yields. With the requisite acyclic keto-diene **5** in hand, the key RCM macrocyclization of the keto-diene **5** in dichloromethane (3.4×10^{-3} M) was accomplished at 40 °C in the presence of 0.07 equiv of bis(tricyclohexylphosphine)benzylideneruthenium dichloride catalyst **3** to afford a 3:1 mixture



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of separable geometric isomers of the 15-membered carbocyclic olefins **4** in 90% combined yield. Geometry of the double bond of the major isomer was *E* as deduced from the narrow signals of the olefinic protons at δ 5.33−5.36.[13] Alternatively, the β-keto-ester **13** also underwent RCM macrocyclization to yield macrocyclic compound **15** in 61% yield. The carbocyclic olefin **4** was subjected to catalytic hydrogenation to give known diketone **14**[6b] in 98% yield. Finally introduction of the pyridine nucleus was accomplished with hydroxylamine hydrochloride in a sealed tube[6b] to furnish muscopyridine **1** in 61% yield. All spectral data and the agreement of the melting point of picrolonic acid salt indicated completion of muscopyridine synthesis. Finally, the X-ray crystallographic analysis of the picrolonate salt established the structure of synthetic muscopyridine **1** as shown in Supporting Information.

The conformation of muscone and its related compounds are very flexible with an estimated 40−190 conformers within 1 kcal/mol.[14] The X-ray data revealed a folded conformation of muscopyridine 1 for the first time. Since the sign and degree of optical rotation of synthetic muscopyridine 1 were identical with those reported,[4] the absolute stereochemistry at C-3 of muscopyridine 1 was determined to be *R* as shown in structure 1.

(13) Paquette, L. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301.

(14) Private communication from Prof. H. Goto, Toyohashi University of Technology.

Thus, convergent total synthesis of one of constituents of musks, muscopyridine **1**, has been achieved in its enantiomerically natural form by RCM strategy, enabling the determination of absolute stereochemistry after more than 50 years.

Experimental Section

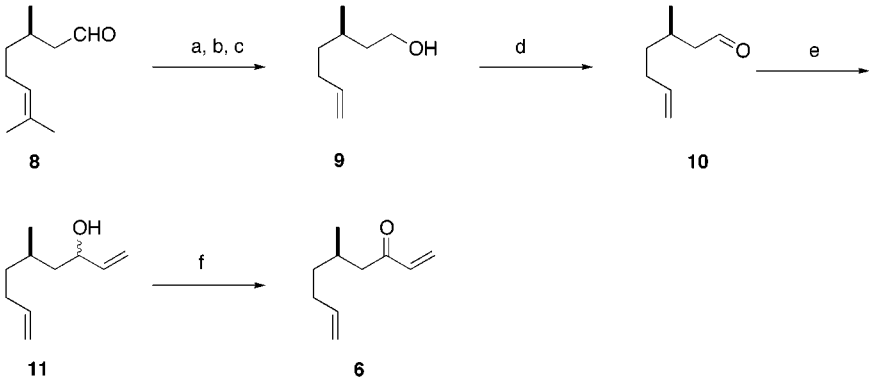
Melting points were determined with a Yanaco MP hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were obtained for solutions in deuteriochloroform on a Varian Gemini 200H with tetramethylsilane as internal standard. ^{1}H NMR (500 MHz) were run on a Varian Unity 500 plus instrument. An X-ray crystallographic analysis was carried out on a Rigaku AFC7S diffractometer. Specific rotations were determined on a Horiba SEPA-200 polarimeter. Medium-pressure liquid chromatographies (MPLC) were carried out on a JASCO PRC-50 instrument with a prepacked silica gel column. Microanalyses were carried out in the microanalytical laboratory of the Instrumental Analysis Center for Chemistry, Tohoku University. (*R*)-(+)-Citronellal **8** used in this work was procured from Tokyo Kasei Kogyo Co, Ltd (optical purity 95%).

(*R*)-3-Methyl-6-heptenal (10). (*R*)-(+)-Citronellal **8** was reduced with sodium borohydride in methanol in 91% yield to give (*R*)-(+)-3,7-dimethyloct-6-en-1-ol (citronellol). Citronellol (3.13 g, 20 mmol) in dichloromethane (60 mL) was treated with a stream of O_3/O_2 at −78 °C until a blue color appeared. The mixture was flushed with N_2, and dimethyl sulfide (3 mL) was added. The flask was allowed to warm to room temperature gradually, and stirring was continued for 12 h. The mixture was washed with H_2O and sat. aqueous sodium chloride. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (*R*)-6-hydroxy-4-methylhexanal as a colorless oil. To a stirred suspension of methyltriphenylphosphonium bromide (13.10 g, 36.7 mmol) in THF (110 mL) under nitrogen atmosphere was added *n*-BuLi (1.50 M solution in hexane, 24.0 mL, 36 mmol) at 0 °C. The mixture was stirred for 1 h and cooled to −78 °C. A solution of crude (*R*)-6-hydroxy-4-methylhexanal in THF (10 mL) was slowly added by cannula. The mixture was stirred at −78 °C and allowed to warm to 25 °C. After being stirred for 13 h, the reaction was quenched by aq ammonium chloride and the product was extracted with ethyl acetate (× 2). Combined organic layer was washed with sat. sodium chloride (× 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and subsequent purification of the residue by silica gel column chromatography (EtOAc/hexane 1:25 to 1:10) provided (*R*)-3-methyl-6-heptenol **9** as a colorless oil (1.79 g, 70%): $R_f = 0.50$ (EtOAc/hexane 1:5); $[\alpha]^{22}_D$ +2.8 (*c* 1.4, $CHCl_3$); IR (CCl_4) 3638, 3088, 2961, 1641, 1240, 914 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.5 Hz), 1.41 (m, 5H), 1.91 (brs, 1H), 2.08 (m, 2H), 3.69 (m, 2H), 4.96 (m, 2H), 5.81 (ddt, 1H, J = 17.1, 10.2, 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.4 (q), 28.9 (d), 31.2 (t), 36.2 (t), 39.7 (t), 60.9 (t), 114.2 (t), 139.0 (d).

To a stirred solution of (*R*)-3-methyl-6-heptenol **9** (1.30 g, 10.0 mmol) in dichloromethane (40 mL) under nitrogen atmosphere were added dimethyl sulfoxide (14.0 mL, 197 mmol), triethylamine (4.2 mL, 30.1 mmol), and sulfur trioxide−pyridine complex (2.40 g, 15.1 mmol) successively at 0 °C. The resulting solution was stirred for 1.5 h by gradual warming to 25 °C and then diluted with pentane. The organic layer was successively washed with water, 1 N hydrochloric acid, aq sodium hydrogen carbonate, and sat. sodium chloride and dried over anhydrous Na_2SO_4. Careful evaporation of the solvent followed by purification of the residue by passing through a short silica gel column afforded the aldehyde **10** (1.47 g) which was used immediately for the next reaction; $R_f = 0.63$ (EtOAc/hexane 1:5); IR (CCl_4) 2959, 2928, 2856, 2736, 1730, 1644, 1462, 1379, 1263, 909 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, J = 6.6 Hz), 1.32 (m, 3H), 2.1 (m, 2H), 2.38 (m, 2H), 5.00 (m, 2H), 5.80 (ddt, 1H, J = 17.0, 10.2, 6.7 Hz), 9.75 (t, 1H, J = 2.3 Hz).

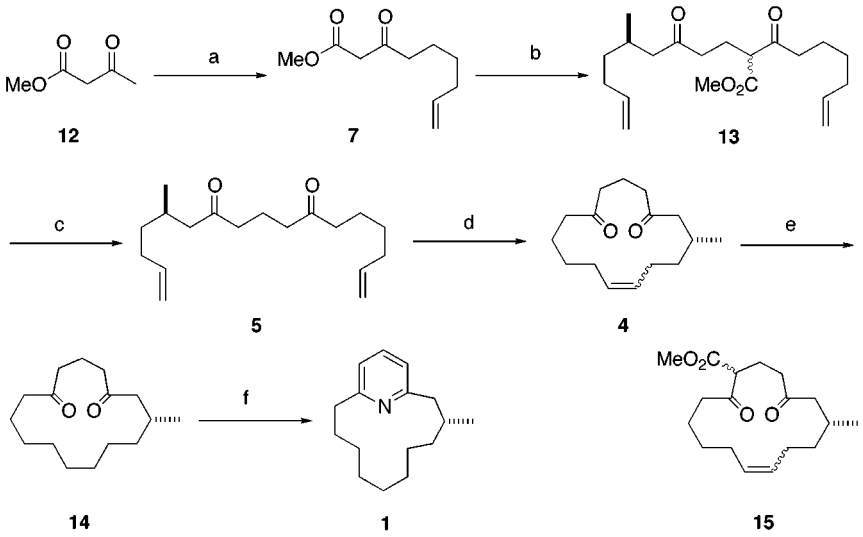
(3*RS*,5*R*)-3-Hydroxy-5-methylnona-1,8-diene (11). To a stirred solution of vinylmagnesium bromide (0.98 M solution in THF, 30.0 mL, 30.6 mmol) in THF (30 mL) under nitrogen atmosphere was added a solution of crude aldehyde **10** (1.47 g,

Scgene 2[a]



[a] Reagents and conditions: (1) $NaBH_4$, MeOH, 91%; (b) O_3, DMS, CH_2Cl_2; (c) THF, $Ph_3P{=}CH_2$, 70% (two steps); (d) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2; (e) $CH_2{=}CHMgBr$, THF, 68% (two steps); (f) TPAP, NMO, CH_2Cl_2, 70%.

Scheme 3[a]



[a] Reagents and conditions: (1) NaH, BuLi, 5-bromobutene, 60%; (b) K_2CO_3, $(n\text{-Bu})_4Nl$, **6**, 93%; (c) LiCl, DMPU, 120 °C, 72%; (d) Ru Catalyst, CH_2Cl_2, 40 °C, 90%; (e) Pd−C, H_2, EtOH, 98%; (f) NH_2OH·HCl, 61%.

11 mmol) in THF (3 mL) dropwise at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was quenched by the addition of aq. ammonium chloride and extracted with ethyl acetate (× 2). The combined organic layer was washed with sat. sodium chloride (× 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification of the residue by MPLC (EtOAc/hexane 1:5) gave the allylic alcohol **11a** (542 mg, 35% in two steps) and **11b** (501 mg, 33% in two steps). More polar diastereomer **11a** had $R_f = 0.37$ (EtOAc/hexane 1:5); $[\alpha]^{19}_D$ −1.94 (*c* 0.90, $CHCl_3$); IR (CCl_4) 3619, 3080, 2928, 2872, 1642, 1462, 1425, 1377, 1240, 1047 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, 3H, $J = 6.5$ Hz), 1.44 (m, 6H), 2.05 (m, 2H), 4.17 (m, 1H), 5.08 (m, 4H), 5.82 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8 (q), 28.9 (d), 31.1 (t), 36.10 (t), 44.3 (t), 71.6 (d), 114.2 (t), 114.8 (d), 139.0 (d), 141.4 (d). Less polar diastereomer **11b** had $R_f = 0.40$ (EtOAc/hexane 1:5); $[\alpha]^{19}_D$ −4.33 (*c* 0.85, $CHCl_3$); IR (CCl_4) 3632, 3088, 2963, 2930, 2872, 1641, 1462, 1373, 912 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 3H, $J = 6.6$ Hz), 1.45 (m, 6H), 2.07 (m, 2H), 4.20 (m, 1H), 5.08 (m, 4H), 5.81 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2 (q), 28.6 (d), 31.1 (t), 36.6 (t), 44.4 (t), 71.0 (d), 114. 1 (t), 114.2 (t), 139.1 (d), 141.8 (d).

(*R*)-5-Methyl-3-oxonona-1,8-diene (6). To a stirred suspension of a mixture of alcohol **11a** and **11b** (91 mg, 0.59 mmol) and 4 Å molecular sieves powder (82 mg) in dichloromethane (5 mL) under nitrogen atmosphere were added TPAP (27 mg, 0.076 mmol) and 4-methyl morpholine-*N*-oxide (234 mg, 2.0 mmol) in one lot at 0 °C. After being stirred at room temperature for 15 h, the reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite. Removal of the solvent followed by purification of the residue by MPLC (EtOAc−*n*-hexane 1:6) gave the ketone **6** as a colorless oil (63 mg, 70%); $R_f = 0.62$ (EtOAc/hexane 1:5); $[\alpha]^{22}_D$ +5.74 (*c* 1.0, $CHCl_3$); IR (CCl_4) 3080, 2959, 2928, 2874, 2851, 1703, 1687, 1641, 1541, 1460, 1365, 1294, 968 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, 3H, $J =$ 6.6 Hz), 1.19−1.57 (m, 2H), 1.98−2.17 (m, 3H), 2.39 (dd, 1H, J = 15.5, 7.9 Hz), 2.58 (dd, 1H, $J = 15.5$, 5.8 Hz), 4.90−5.18 (m, 2H), 5.70−5.91 (m, 2H), 6.20 (dd, 1H, $J = 17.6$, 1.8 Hz), 6.37 (dd, 1H, $J = 17.6$, 9.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7 (q), 29.0 (d), 31.2 (t), 36.1 (t), 114.4 (t), 128.0 (t), 136.8 (d), 138.6 (d), 200.7 (s).

Methyl 3-Oxonona-8-enoate (7). Sodium hydride (82 mg, 60% dispersion in mineral oil, 2.05 mmol) was washed with *n*-hexane twice under nitrogen atmosphere. To the suspension of sodium hydride in THF (2 mL) was added methyl acetoacetate **12** (215 μL, 2.0 mmol) dropwise at 0 °C, and stirring was continued for 15 min. *n*-BuLi (1.54 M solution in hexane, 1.2 mL, 1.8 mmol) was then added dropwise over a period of 5 min to give a yellow solution. After being stirred for 30 min, 5-bromo-1-pentene (230 μL, 1.94 mmol) was added, and the solution was allowed to warm gradually to room temperature and stirring was continued for an additional 2.5 h. The reaction was quenched with aq. ammonium chloride, and product was extracted with ethyl acetate (× 2). Combined organic layer was washed with sat. sodium chloride (× 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification of the product by silica gel column chromatography (EtOAc/hexane 1:7) provided keto-ester **7** as a pale yellow oil (216 mg, 60%); R_f = 0.70 (EtOAc/hexane 1:5); IR (CCl_4) 3088, 2980, 2860, 1747,

1722, 1641, 1548, 1437, 1236, 914 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.61 (m, 2H), 2.05 (m, 2H), 2.55 (t, 2H, J = 7.2 Hz), 3.45 (s, 2H), 3.74 (s, 3H), 4.98 (m, 2H), 5.79 (ddt, 1H, J = 17.1, 10.2, 6.7 Hz). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.37; H, 8.88.

(*R*)-5-Methyl-7,11-dioxo-10-methoxycarbonylheptadeca-1,16-diene (13). To a stirred suspension of the keto-ester **7** (121 mg, 0.66 mmol), potassium carbonate (95 mg, 0.69 mmol), and tetra-*n*-butylammonium iodide (13 mg, 0.048 mmol) in DME (0.40 mL) was added a solution of vinyl ketone **6** (58 mg, 0.38 mmol) in DME (0.70 mL). After being stirred for 1 h, the reaction mixture was quenched with aq. 1 N hydrochloric acid and extracted with ethyl acetate (× 2). Combined organic layer was washed with water and brine and evaporated to dryness. Purification of the residue by MPLC (EtOAc/hexane 1:5) provided keto-ester **13** (119 mg, 93%) as a colorless oil along with recovered **7** (40 mg 0.22 mmol); R_f = 0.37 (EtOAc/hexane 1:5); $[\alpha]^{19}_D$ −1.58 (*c* 0.57, $CHCl_3$); IR (CCl_4) 3088, 2978, 2953, 2932, 2743, 1720, 1641, 1437, 1373, 1165, 1047, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 6.6 Hz), 1.43 (m, 4H), 2.26 (m, 15H), 3.55 (t, 1H, J = 7.1 Hz), 3.73 (s, 3H), 5.01 (m, 4H), 5.79 (ddt, 2H, J = 17.1, 10.1, 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6 (q), 21.7 (t), 22.8 (t), 28.1 (t), 28.7 (t), 31.1 (t), 33.4 (t), 35.9 (t), 40.0 (t), 41.8 (t), 50.1 (t), 52.3 (q), 57.2 (d), 114.5 (t), 114.6 (t), 138.3 (d), 138.5 (d), 167.0 (s), 204.9 (s), 209.5 (s). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found C, 71.28; H, 9.61.

(*R*)-5-Methyl-7,11-dioxoheptadeca-1,16-diene (5). Lithium chloride (1.14 g, 26.9 mmol) was added to a solution of the keto-ester **13** (679 mg, 2.0 mmol) in DMPU (3 mL), and the reaction mixture was heated at 120 °C for 7 h. The reaction was quenched by addition of water. The organic layer was extracted with ethyl acetate (× 2) and washed with water and brine. Evaporation of the solvent in vacuo followed by purification of the residue by MPLC (EtOAc/hexane 1:5) gave dimethylene **5** (404 mg, 72%) as a colorless oil; R_f = 0.40 (EtOAc/hexane 1:5); $[\alpha]^{22}_D$ +3.18 (*c* 0.64, $CHCl_3$); IR (CCl_4) 3088, 2953, 1716, 1641, 1410, 1371, 998 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 6.6 Hz), 1.56 (m, 9H), 2.12 (m, 4H), 2.40 (m, 8H), 4.99 (m, 4H), 5.78 (ddt, 2H, J = 17.1, 10.1, 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7 (t), 19.6 (q), 23.2 (t), 28.4 (t), 28.7 (d), 31.2 (t), 33.5 (t), 36.0 (t), 41.5 (t), 42.1 (t), 42.6 (t), 50.1 (t), 114.5 (t), 114.6 (t), 138.4 (d), 138.6 (d), 210.4 (s), 210.6 (s). Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.64; H, 10.86. Found: C, 77.65; H, 10.74.

(*R*)-3-Methyl-1,12-dioxocyclopentadeca-6-ene (4). To a solution of bis(tricyclohexylphosphine)benzylideneruthenium dichloride **3** (25 mg, 0.030 mmol) in dry degassed dichloromethane (100 mL) was added a solution of dimethylene **5** (171 mg, 0.616 mmol) in dichloromethane (80 mL) via a dropping funnel over a period of 2 h. The resulting purple solution was stirred for 16.5 h at 40 °C and then concentrated under reduced pressure to afford an oily brown residue. Purification of the residue by silica gel column (EtOAc/hexane 1:5) gave cyclic olefins **4a** (104 mg, 67%) and **4b** (35 mg, 23%) as a colorless oil. Major cyclic olefin **4a** had R_f = 0.33 (EtOAc/hexane 1:5); $[\alpha]^{22}_D$ +13.5 (*c* 0.71, $CHCl_3$); IR (CCl_4) 2932, 2862, 1712, 1462, 1404, 1371 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.5 Hz), 1.26−1.56 (m, 6H), 1.85−1.93 (m, 3H), 2.00−2.15 (m, 6H), 2.30−2.43 (m, 7H), 5.31−5.33 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.1 (t), 19.7 (q), 23.9 (t), 27.9 (t), 28.3 (t), 29.7 (t), 31.9 (d), 35.9 (t), 40.9 (2C, t), 42.8 (t), 51.0 (t), 130.8 (d), 131.2 (d), 210.8 (s), 211.9 (s). Minor cyclic olefin **4b** had R_f = 0.36 (EtOAc/hexane 1:5); $[\alpha]^{20}_D$ −8.8 (*c* 0.27, $CHCl_3$); IR (CCl_4) 3007, 2934, 2862, 1712, 1462, 1435, 1371 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, 3H, J = 7.0 Hz), 1.13 (m, 1H), 1.23−1.33 (m, 3H), 1.52−1.57 (m, 2H), 1.86−2.03 (m, 7H), 2.16 (dd, 1H, J = 15.3, 5.3 Hz), 2.25−2.50 (m, 6H), 2.68 (m, 1H), 5.33−5.37 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.9 (t), 20.8 (q), 24.5 (t), 24.8 (t), 26.6 (t), 28.8 (t), 29.3 (d), 36.4 (t), 40.0 (t), 40.7 (t), 42.9 (t), 50.3 (t), 129.3 (d), 130.1 (d), 211.1 (s), 212.1 (s). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.65; H, 10.64.

(*R*)-3-Methyl-1,12-dioxocyclopentadecane (14). A stirred suspension of a mixture of cyclic olefins **4a** and **4b** (109 mg, 0.43 mmol) and 5% palladium on charcoal (50 mg) in ethanol (12 mL) was stirred under hydrogen atmosphere at room temperature for 5 h. After filtration of the catalyst, the filtrate was concentrated in vacuo followed by purification of the residue by MPLC (EtOAc/hexane 1:5) to give carbocycle **14** (108 mg, 98%) as a white solid; mp 31.2−34.9 °C; R_f = 0.42 (EtOAc/hexane 1:5); $[\alpha]^{22}_D$ −7.2 (*c* 0.89, $CHCl_3$); IR (CCl_4) 2932, 2858, 1712, 1524 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 6.7 Hz), 1.22 (m, 11H), 1.68 (m, 6H), 2.34 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3 (t), 21.6 (q), 23.2 (t), 25.1 (t), 26.5 (t), 27.1 (t), 27.2 (t), 27.9 (t), 28.8 (d), 36.3 (t), 41.2 (2C, t), 41.5 (t), 50.0 (t), 211.1 (s), 211.9 (s). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.00; H, 11.50.

(3*R*)-Methyl-16-azabicyclo[10.3.1]hexadeca-1(16),12,14-triene or (*R*)-Muscopyridine (1). A solution of the carbocycle **14** (25 mg, 0.10 mmol) in ethanol (5 mL) and hydroxylamine hydrochloride (172 mg, 2.48 mmol) was heated at 150−160 °C in a sealed tube (capacity 30 mL) for 16 h. After being cooled to room temperature, the reaction mixture was diluted with ether, and trace sodium bicarbonate (powder) was added to the solution. The mixture was filtered by short silica gel column, and a white precipitate was removed. The filtrate was concentrated in vacuo and the residue was purified by MPLC (EtOAc/hexane 1:5) to give (+)-muscopyridine **1** (14 mg, 61%) as a colorless oil; R_f = 0.62 (EtOAc/hexane 1:5); $[\alpha]^{23}_D$ +12.5 (*c* 1.80, $CHCl_3$), lit.,[4] $[\alpha]^{23}_D$ +17.1 (*c* 1.92, $CHCl_3$), lit.,[5] $[\alpha]^{25}_D$ +13.3 (*c* 0.90, $CHCl_3$); IR (CCl_4) 2928, 2858, 1576, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, 3H, J = 6.8 Hz), 0.88−1.31 (m, 13H), 1.80 (m, 2H), 2.04 (m, 1H), 2.50 (dd, 1H, J = 13.1, 10.1 Hz), 2.85 (m, 2H), 6.94 (dd, 2H, J = 7.6, 2.1 Hz), 7.48 (t, 1H, J = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1 (q), 22.8 (t), 25.0 (t), 26.0 (t), 26.1 (t), 26.3 (t), 27.8 (t), 33.5 (d), 34.0 (t), 36.9 (t), 45.3 (t), 120.2 (d), 120.5 (d), 136.1 (d), 160.7 (s), 161.5 (s). Picrolonic acid salt of **1** was prepared according to the literature precedent[4] and had mp 161−163 °C (lit.,[4] 163−165 °C).

Crystallographic data of picrolonic acid salt of 1 (23 °C): yellow crystals (from *n*-hexane and 1,2-dichloroethane); formula $C_{26}H_{33}N_5O_5$, fw = 495.58; triclinic, space group $P\bar{1}$ (no. 2), a = 11.439(4) Å, b = 11.722(4) Å, c = 10.697(5) Å; α = 95.05(3) deg., β = 115.12(3) deg., γ = 88.53(3) deg.; V = 1293.5(9) $Å^3$, Z = 2, D_{calcd} = 1.272 g/cm^3, μ(Mo Kα) = 0.90 mm^{-1}. A total of reflection 5293, 1726 ($I > 3.00\sigma(I)$) were used in refinement: R = 0.091, R_w = 0.128. The reflection intensities were collected on a Rigaku AFC7S diffractometer with a rotating anode (50 kV, 30 mA) using graphite monochromated Mo Kα (λ = 0.7107 Å).

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Supporting Information Available: An ORTEP drawing of picrolonic acid salt of **1** and tables of X-ray crystallographic data and copies of ^1H and ^{13}C NMR spectra of all compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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