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A simplified synthesis of (*R*)-(−)-muscone using a ring-opening reaction of (*R*)-(+)-β-methyl-β-propiolactone

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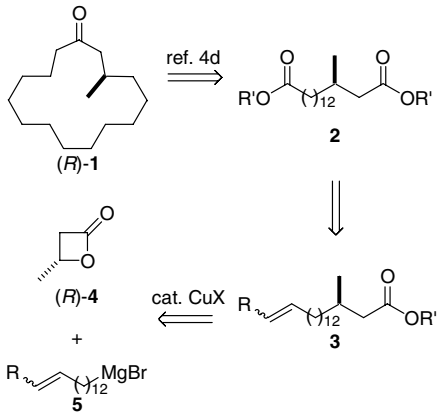
Abstract—A chiral macrocyclic precursor can be constructed via a ring-opening reaction of (*R*)-(+)-β-methyl-β-propiolactone with a functionalized organocuprate with no loss of enantiomeric excess. The carboxylic acid precursor was used as a chiral building block for the synthesis of chiral muscone and musky macrolactones.

1. Introduction

Musk is a fatty excretion produced by the male musk deer during the mating season to attract females. Dried musk glands have been sold at high prices for thousands of years. (*R*)-(−)-3-Methylcyclopentadecanone [(*R*)-muscone] (*R*)-**1** is the most important classical source of musk odors for perfumes and colognes. (*R*)-Muscone has a very nice musky, rich powerful fragrance, its odor threshold being 61 ppb. On the other hand, (*S*)-muscone is less fragrant, with its odor threshold only being 223 ppb. Due to overhunting, the musk deer is now a protected species, therefore a conventional chemical synthesis of homochiral (*R*)-**1** is needed. There are four main types of synthetic approaches to (*R*)-**1**; asymmetric Michael reaction,[1] asymmetric hydrogenation,[2] ring expansion,[3] and macrocyclization.[4,5] Dieckmann condensation of diester **2** is a promising macrocyclization.[4d,5b] However, diester **2** was previously prepared from ethyl cyanoacetate in 15 steps including a resolution using (+)-α-methylbenzylamine.[4d] A shortened synthesis of diester **2** might be the key to providing a practical and cheaper synthetic muscone (*R*)-**1**. In the early 1980s, Fujisawa et al. reported a regiospecific and stereoselective ring-opening reaction of β-methyl-β-propiolactone **4** with various organocuprates to give β-methylpropionic acid derivatives in high yields with high enantiomeric excesses, and synthesized optically active compounds such as (*R*)-(+)-citronellol, (*R*)-(+)-pulegone, (*S*)-(+)-ar-turmerone, and (*R*,*R*)-phytol.[6]

The key intermediate diester **2** can be prepared from β-methylcarboxylic acid derivative **3**, which was obtained by Fujisawa's ring-opening reaction of (*R*)-**4** with Grignard reagent **5** (Scheme 1). Herein, we report a greatly simplified asymmetric synthesis of chiral muscone (*R*)-**1** using Fujiwasa's ring-opening reaction as the key step.



Scheme 1. Retrosynthesis of (*R*)-(−)-muscone.

2. Results and discussions

The functionalized Grignard reagent **9** was prepared in three steps from readily available erucic acid [(*Z*)-13-docosenoic acid] **6**, which is a fatty acid found in rapeseed, wallflower seed, and mustard seed. Reduction of

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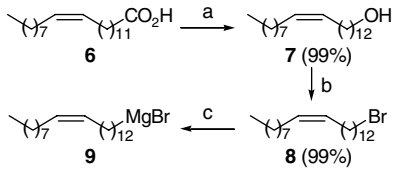
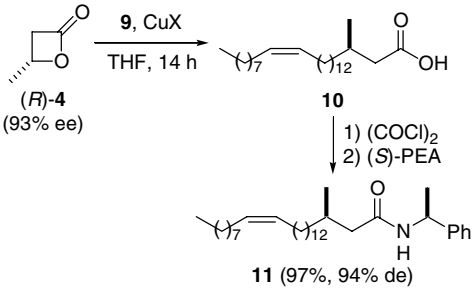
6 with lithium aluminum hydride (LAH) gave (*Z*)-13-docosen-1-ol **7** in 99% yield. Alcohol **7** was subsequently brominated with PPh_3–CBr_4 in 99% yield, and then Grignard reagent **9** was prepared in an approximately 0.5 M solution of THF (Scheme 2).



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 3 h; (b) PPh_3, CBr_4, CH_2Cl_2, rt, 3 h; (c) Mg, I_2, THF, reflux, 1 h.

Ring-opening reactions of (*R*)-(+)-β-methyl-β-propiolactone (*R*)-**4** with organocuprates were examined (Table 1). In the presence of copper(I) chloride (0.02 equiv), carboxylic acid **10** was obtained in moderate yield at room temperature, while lowering temperature improved the chemical yield up to 94% yield (entries 1 and 2). When the catalyst loading was decreased to 0.01 equiv, the yield after 14 h was 92% (entry 3). Copper(I) iodide was also an efficient catalyst, and gave the desired product **10** in 98% yield (entry 4). No loss of enantiomeric excess was observed after the transformation of carboxylic acid **10** with (*S*)-1-phenylethylamine (PEA) to give amide **11** in 97% yield with 94% de. Carboxylic acid **10** had an (*R*)-configuration, which was determined by transformation of **10** to muscone **1** (vide infra), thereby, this ring-opening reaction proceeded in S_N2 mechanism.[6d]

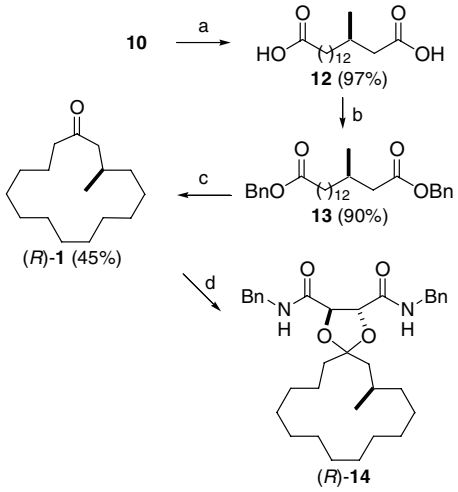
Table 1. Ring-opening reactions of (*R*)-(+)-β-methyl-β-propiolactone (*R*)-**4** with organocuprate[a]



Entry	CuX (equiv)	Temperature (°C)	Yield (%)
1	CuCl (0.02)	rt	59
2	CuCl (0.02)	0	94
3	CuCl (0.01)	0	92
4	CuI (0.02)	0	98

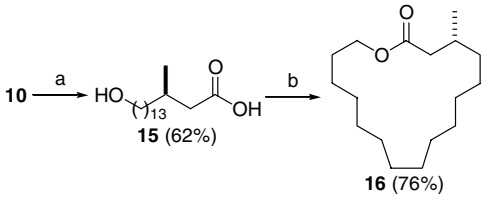
[a] Reactions were carried out using 2 equiv of Grignard reagent **9**.

The synthesis of chiral (*R*)-(−)-muscone (*R*)-**1** was carried out as shown in Scheme 3. Oxidation of olefin **10** to carboxylic acid **12**, following esterification gave dibenzylester **13** in high yield. This key intermediate diester **13** was prepared from (*R*)-**4** (93% ee) in overall 86% yield in three steps. Dieckmann cyclization followed by decarboxylation of diester **13** according to Nohira's procedure[4d] afforded (*R*)-**1** in 45% yield.[7] The spectral data and the sign of rotation of (*R*)-**1** were in agreement with reported values.[4d] The enantiomeric excess was determined by HPLC analysis of acetal **14**, which was prepared by the acetalization of **1** with *N*,*N*′-dibenzyl-L-tartaramide. Previously, the enantiomers of muscone **1** have been extremely difficult to separate by chiral chromatographic technique due to the lack of steric and electronic differences between (*S*)- and (*R*)-isomers; however, recently we have found that a diastereomeric mixture of acetal **14** can be separated by chiral HPLC.[8] Furthermore, simple recrystallization of acetal **14** gave chiral acetal (*R*)-**14**. The acetalization of (*R*)-**1** afforded the corresponding acetal **14** with almost no loss of enantiomeric purity (91% de).



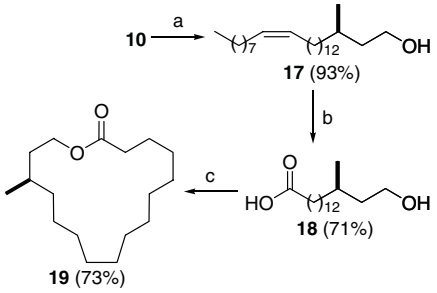
Scheme 3. Reagents and conditions: (a) $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O/acetone, rt, 3 days; (b) BnOH, *p*-TsOH·H_2O, reflux, 6 h; (c) $(Me_3Si)_2NLi$, THF, rt, 14 h, then decarboxylation; see Ref. 4d; (d) see Ref. 8.

Encouraged by these results, we next investigated the synthesis of chiral macrolactones from carboxylic acid **10**. One-pot ozone-oxidation following the reduction gave ω-hydroxycarboxylic acid **15** in 62% yield. Macrolactonization of **15** was initially performed by using 2,2′-dipyridyl disulfide and triphenylphosphine,[9] in which many spots were observed by TLC analysis. We found that 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(dimethylamino)pyridine (DMAP) reagents reported by Shiina et al.[10] gave the powdery and musky macrolactone **16**[11] in 76% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) O_3, $CHCl_3$, −20 °C, $NaBH_4$; (b) MNBA, DMAP, CH_2Cl_2, rt, 24 h.

The isomeric macrolactone **19** was prepared from carboxylic acid **10** in a similar way to the above method. Reduction of carboxylic acid **10** to alcohol **17**, subsequent oxidation of the olefin to the carboxylic acid furnished ω-hydroxycarboxylic acid **18** in 66% yield in two steps. Macrolactonization afforded macrolactone **19**, which has a somewhat weak musky fragrance (Scheme 5).



Scheme 5. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 7 h; (b) (i) O_3, CH_2Cl_2–MeOH, −70 °C; (ii) H_2O_2, HCO_2H, reflux, 2 h; (iii) NaOH, MeOH, rt, 4 h; (c) MNBA, DMAP, CH_2Cl_2, rt, 20 h.

3. Conclusions

In conclusion, we have demonstrated that chiral macrocyclic precursor **10** can be constructed via a ring-opening reaction of (*R*)-(+)-β-methyl-β-propiolactone (*R*)-**4** employing functionalized organocuprate **9** with no loss of enantiomeric purity. Carboxylic acid **10** was used as a chiral building block for the synthesis of chiral muscone (*R*)-**1** and macrolactones **16** and **19**. This facile synthesis provides a practical route to synthetic muscone (*R*)-**1**.

4. Experimental

4.1. General

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash column chromatography was performed using silica gel 60N (particle size 63–210 μm). Melting points were measured on a Yanaco micromelting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-AL. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in hertz. The spectra were recorded in $CDCl_3$ as solvent at rt, TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. Infrared spectra were recorded on a SHIMADZU FTIR-8200A spectrometer. Mass spectra were recorded on a SHIMADZU GCMS-QP5050 spectrometer. HPLC was carried out using a SHIMADZU LC-10AD intelligent pump, SPD-10A UV detector, and C-R8A integrator. Microanalyses were performed with a Thermo Finnigan FlashEA 1112.

4.2. (*Z*)-13-Docosen-1-ol 7

To a suspension of $LiAlH_4$ (1.55 g, 40.9 mmol) in THF (40 mL) was slowly added a solution of erucic acid **6** (9.24 g, 27.3 mmol) dropwise in THF (45 mL) over 15 min at 0 °C. The reaction mixture was refluxed for 3.5 h. After complete consumption of **6**, the reaction mixture was cooled to 0 °C and quenched with ether (70 mL) and water (3 mL). 15% NaOH aq (3 mL) and H_2O (10 mL) were added to the reaction mixture. After filtration of the insoluble solid, the aqueous phase was extracted with ether (5 × 3 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude alcohol, which was purified by column chromatography (silica gel, hexane/EtOAc = 90/10) to give alcohol **7** (8.86 g, quant.) as a colorless liquid: registry number 629-98-1; $R_f = 0.22$ (hexane/EtOAc = 90/10); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.79$ (t, $J = 7.4$ Hz, 3H, –C*H*$_3$), 1.00–1.69 (m, 32H, 16 × –C*H*$_2$–), 1.90–2.10 (m, 4H, –C*H*$_2$–C=C–C*H*$_2$–), 3.63 (t, $J = 6.6$ Hz, 2H, –C*H*$_2$O–), 5.35 (t, $J = 5.0$ Hz, 2H, –C*H*=C*H*–).

4.3. (*Z*)-22-Bromo-9-docosene 8

To a solution of alcohol **7** (12.0 g, 36.9 mmol) in CH_2Cl_2 (30 mL) was slowly added dropwise a solution of CBr_4 (13.8 g, 44.3 mmol) in CH_2Cl_2 (15 mL), and then a solution of PPh_3 (10.7 g, 40.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at rt for 3.5 h. After complete consumption of **7**, O_2 gas was passed through the solution until an excess of PPh_3 was oxidized to Ph_3PO. The solvent was removed under reduced pressure. The residue was filtered and washed with ether/hexane (1/5, 90 mL). The filtrate was evaporated to give the crude product, which was purified by column chromatography (silica gel, hexane/EtOAc = 90/10) to give bromide **8** (14.1 g, 99%) as a colorless liquid: registry number 111924-39-1; $R_f = 0.73$ (hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, $J = 6.6$ Hz, 3H, –C*H*$_3$), 1.05–1.54 (m, 32H, 16 × –C*H*$_2$–), 1.90–2.10 (m, 4H, –C*H*$_2$–C=C–C*H*$_2$–), 3.40 (t, $J = 6.9$ Hz, 2H, –C*H*$_2$Br), 5.38 (t, $J = 3.6$ Hz, 2H, –C*H*=C*H*–).

4.4. (*Z*)-13-Docosenylmagnesium bromide 9

Grignard reagent stock solution (approximately 0.5 M solution in THF) was prepared as follows. Magnesium powder (1.21 g, 49.8 mmol) was finely divided by vigorous mechanical stirring for 1 day under an argon atmosphere. A slurry of this activated magnesium powder (1.21 g, 49.8 mmol) in THF (0.5 mL) was stirred with a small amount of bromide **8** and a trace quantity of iodine until the solution became colorless. After the exothermic reaction had started, a solution of bromide **8** (10.8 g, 27.8 mmol) in THF (29 mL) was added

dropwise over 1 h. After the addition of the solution, the reaction mixture was additionally refluxed for 1 h.

4.5. (*R*)-3-Methylpentacos-16-enoic acid 10

To a suspension of CuI (17 mg, 0.1 mmol) in THF was slowly added a solution of Grignard reagent **9** (26 mL, 11.2 mmol) in THF at 0 °C under an argon atmosphere. To this solution, (*R*)-(+)-β-methyl-β-propiolactone **4** (570 mg, 6.62 mmol) in THF (8 mL) was added dropwise. The mixture was stirred for 14 h at 0 °C. After complete consumption of **4**, the reaction mixture was quenched with 3M HCl aq (4 mL). The aqueous phase was extracted with ether (5 × 3 mL), the combined organic extracts washed with water (5 mL), brine (5 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude carboxylic acid, which was purified by column chromatography (silica gel, hexane/EtOAc = 85/15) to give carboxylic acid **10** (2.55 g, 98%) as a colorless liquid: $R_f = 0.46$ (hexane/EtOAc = 70/30); $[\alpha]_D^{25} = +3.2$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.91$ (d, $J = 6.0$ Hz, 3H, –CH_3), 0.58–1.06 (m, 3H, –CH_3), 1.06–1.60 (m, 34H, 17 × –CH_2–), 1.80–2.45 (m, 7H, –CH–, –CH_2–C=C–CH_2–, –CH_2–CO–) 5.35 (t, J = 4.8 Hz, 2H, –CH=CH–); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 179.9$ (–C=O), 130.4, 130.0 (C=C), 41.6, 36.7, 32.7, 32.0, 30.2, 29.81, 29.76, 29.71, 29.70, 29.60, 29.56, 29.4, 29.2, 27.2, 27.0, 22.7 (–CH_2–), 19.7, 14.1 (–CH_3); IR (neat) 3265–2759 (m/br), 3004, 2852 (s), 1708 (s), 1465 (m), 1296 (m), 721 (m) cm^{-1}; MS (EI) *m*/*e* 395 (M^++1, 0.2), 376 (5), 334 (5), 83 (34), 69 (50), 55 (100); HRMS (FAB) Calcd for $C_{26}H_{51}O_2$ (MH^+): 395.3889, found: 395.3873.

4.6. (*R*)-*N*-(1-Phenylethyl)-3-methylpentacos-16-enamide 11

A solution of carboxylic acid **10** (145 mg, 0.5 mmol) in oxalyl chloride (0.1 mL, 1.2 mmol) was refluxed for 3 h. Excess oxalyl chloride was removed under reduced pressure. The crude carbonylchloride was dissolved in ether (5 mL) and cooled to 0 °C. To this solution a solution of (*S*)-1-phenylethylamine in ether (4.7 mL, 0.4 M) was added at 0 °C, then warmed to rt and stirred for 15 h. After complete consumption of carboxylic acid **10**, the reaction mixture was quenched with 1 M HCl aq (3 mL). The aqueous phase was extracted with ether (5 × 3 mL), the combined organic extracts washed with satd $NaHCO_3$ aq (5 mL), water (5 mL), brine (5 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude amide, which was purified by column chromatography (silica gel, hexane/EtOAc = 90/10) to give amide **11** (197 mg, 98%) as a colorless solid: $R_f = 0.29$ (hexane/EtOAc = 80/20); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H, –$CH_2C H_3$), 0.92 (d, $J = 6.3$ Hz, 3H, –CH(CH_3)–), 1.15–1.40 (m, 34H, 17 × –CH_2–), 1.49 (d, $J = 6.9$ Hz, 3H, –NH-CH(CH_3)Ph), 1.85–2.25 (m, 7H, –CH_2CH=CHCH_2, –CH–, –CH(CH_3)CH_2CONH–), 5.16 (qd, $J = 7.5$, 7.2 Hz, 1H, NHCH(CH_3)Ph), 5.35 (t, $J = 4.8$ Hz, 2H, –CH=CH–), 5.61 (br d, $J = 7.5$ Hz, 1H, –NH-CH(CH_3)Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.6 (–C=O), 143.2, 129.9, 128.6, 127.3, 126.2 (C=C, –Ph), 29.8, 29.7, 29.5, 27.2 (–CH_2–), 19.6, 14.1 (–CH_3); IR (KBr) 3300 (m), 2918, 2851 (s), 1636 (s), 1547 (m), 1468 (m), 721 (w), 696 (m) cm^{-1}; MS (EI) *m*/*e* 497 (M^+, 16), 190 (16), 163 (46), 120 (39), 105 (100), 69 (27), 55 (48). Anal. Calcd for $C_{34}H_{59}NO$: C, 82.03; H, 11.95; N, 2.81. Found: C, 82.03; H, 12.22; N, 2.76.

4.7. (*R*)-3-Methylhexadecanedioic acid 12

To a solution of carboxylic acid **10** (251 mg, 0.64 mmol) and K_2CO_3 (263 mg, 1.91 mmol) in acetone/H_2O (1/1, 10 mL) was added a solution of $KMnO_4$ (13 mg, 0.08 mmol) and $NaIO_4$ (1.09 g, 5.08 mmol) in H_2O (10 mL) at room temperature. The mixture was stirred at room temperature for 3 days. After complete consumption of carboxylic acid **10**, the reaction mixture was filtered. The filtrate was acidified with 10% H_2SO_4 aq (5 mL), extracted with ether (5 × 3 mL), the organic extracts washed with water (5 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude acid, which was purified by column chromatography (silica gel, hexane/EtOAc = 85/15) to give acid **12** (185 mg, 97%) as a colorless powder: registry number 101592-14-7; $R_f = 0.42$ (hexane/EtOAc = 40/60); $[\alpha]_D^{26} = +1.5$ (*c* 1.0, $CHCl_3$) {lit.[4d] $[\alpha]_D = +3.5$ (*c* 5, $CHCl_3$)}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H, –CH_3), 1.1–1.4 (m, 20H, 10 × –CH_2–), 1.52–1.70 (m, 2H, $HO_2CCH_2CH_2$–), 1.80–2.03 (m, 1H, –CH–), 2.15 (dd, $J = 14.7$, 7.8 Hz, 1H, –CH(CH_3)CH$H$$CO_2$H), 2.23–2.50 (m, 3H, –CH(CH_3)C$H$$HCO_2$H, –C$H_2CHHCO_2$H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 180.4$, 178.0 (–C=O), 130.3, 129.9 (C=C), 41.7, 36.5, 34.1, 30.2, 29.6, 29.56, 29.50, 29.4, 29.3, 29.1, 29.01, 29.0, 26.8, 24.7 (–CH_2–), 19.7 (–CH_3); IR (KBr) 3323–3000 (m/br), 2918, 2851 (s), 1706 (s), 1470 (w), 1200 (w) cm^{-1}.

4.8. (*R*)-Dibenzyl 3-methylhexadecanedioate 13

Dicarboxylic acid **12** (246 mg, 0.82 mmol) and benzylalcohol (353 mg, 3.26 mmol) in toluene (10 mL) were refluxed for 6 h in the presence of *p*-TsOH·H_2O (46 mg, 0.24 mmol) using a Dean–Stark trap. After complete consumption of dicarboxylic acid **12**, the reaction mixture was cooled to room temperature and washed with satd $NaHCO_3$ aq (4 mL), H_2O (4 mL) and brine (4 mL). The organic solution was dried over anhydride Na_2SO_4, and concentrated to give the crude diester, which was purified by column chromatography (silica gel, hexane/EtOAc = 95/5) to give diester **13** (353 mg, 90%) as a colorless liquid: $R_f = 0.42$ (hexane/EtOAc = 90/10); $[\alpha]_D^{21} = +1.1$ (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.92$ (d, $J = 6.6$ Hz, 3H, –CH_3), 1.05–1.40 (m, 20H, 10 × –CH_2–), 1.55–1.70 (m, 2H, –C$H_2$$CH_2$CO), 1.85–2.05 (m, 1H, –CH–), 2.15 (dd, $J = 8.0$, 14.7 Hz, 1H, –CHCHHCO), 2.30–2.39 (m, 3H, CHCHHCO, –CH_2CO), 5.11 (s, 4H, 2 × CH_2Ar), 7.27–7.40 (m, 10H, 2 × *Ar*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 173.7$, 173.2 (C=O), 136.1, 128.5, 128.2, 128.1 (Ar), 65.9, 65.9 (2 × PhCH_2–), 41.7 (CH), 36.5, 34.2, 30.2, 29.6, 29.4, 29.3, 29.1, 28.9, 26.7, 24.8 (CH_2), 19.6 (CH_3); IR (neat), 2927, 2853 (s), 1736 (s), 1456 (m), 1163 (s) 696 (s) cm^{-1}; MS (EI) *m*/*e* 481 (M^+, 0.3),

283 (100), 91 (95), 69 (22), 55 (33). Anal. Calcd for $C_{31}H_{44}O_4$: C, 77.46; H, 9.23. Found: C, 77.18; H, 9.53.

4.9. (*R*)-(−)-Muscone (*R*)-1

To a solution of HMDS (2.23 mL, 5.10 mmol) in dry THF (1 mL) was added 1.5 M *n*-BuLi in a hexane solution (3.4 mL, 5.10 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min and then diluted with THF (75 mL). A solution of diester **13** (296 mg, 0.62 mmol) in THF (120 mL) was added to a solution of prepared [$(Me_3Si)_2NLi$] over a period of 14 h with a dropping funnel. After the addition was completed, the mixture was stirred for an additional hour. The reaction mixture was quenched with H_2O (5 mL), and the aqueous phase extracted with ether (4 × 4 mL). The combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried over anhydride Na_2SO_4 and concentrated. To the crude was added 10% NaOH aq (4 mL) and MeOH (1 mL), and the reaction mixture was refluxed for 3 h. After cooling down, the mixture was acidified with 10% H_2SO_4 aq (5 mL) and refluxed for 2 h. The mixture was evaporated under reduced pressure and the residue was extracted with ether (4 × 4 mL). The organic extracts were washed with water (4 mL) and brine (4 mL), dried over anhydride Na_2SO_4 and concentrated to give the crude muscone, which was purified by column chromatography (silica gel, hexane/EtOAc = 98/2) to give muscone **1** (65 mg, 45%) as a colorless liquid: registry number 10403-00-6; $R_f = 0.53$ (hexane/EtOAc = 90/10); $[\alpha]_D^{20} = -11.0$ (*c* 1.0, MeOH) {lit.[4g] $[\alpha]_D = -12.6$ (*c* 1.0, MeOH)}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.87$ (d, $J = 8.7$ Hz, 3H, –C(C*H*$_3$)H–), 1.10–1.50 (m, 20H, 10 × –C*H*$_2$–), 1.50–1.80 (m, 2H, –COCH$_2$C*H*$_2$–), 1.94–2.10 (m, 1H, –C*H*(CH$_3$)–), 2.18 (dd, $J = 5.3$, 14.7 Hz, 1H, –COCH-*H*C(CH$_3$)H–), 2.30–2.51 (m, 3H, –COC*H*HC(CH$_3$)H–, –COC*H*$_2$–).

4.10. (2*R*,3*R*,7*R*)-*N*,*N*′-Dibenzyl-7-methyl-1,4-dioxaspiro[4.14]nonadecane-2,3-dicarboxamide 14[8]

To a solution of muscone **1** (47.7 mg, 0.2 mmol) and *N*,*N*′-dibenzyl-L-tartaramide (131 mg, 0.4 mmol) in MeCN (1.0 mL) were added trimethyl orthoformate (43.8 μL, 0.4 mmol) and $Sc(OTf)_3$ (9.8 mg, 0.02 mmol) at reflux. The reaction mixture was stirred for 5 h and then cooled to room temperature. After evaporation of MeCN, the solid was filtered and washed with ether (5 mL). The filtrate was concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane/ethyl acetate as an eluent) to give acetal **14** in excellent yield. $R_f = 0.37$ (hexane/EtOAc = 70/30); HPLC (Daicel CHIRALPAK AD, hexane/EtOH = 90/10, flow rate 0.5 mL/min, $\lambda = 254$ nm); $t_R = 29.52$ [(*R*)-isomer], 70.10 [(*S*)-isomer] min; $[\alpha]_D^{18} = -9.7$ (*c* 0.780, $CHCl_3$); mp 136–137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (d, $J = 6.5$ Hz, 3H, –CH$_3$), 0.97–1.47 (m, 23H), 1.47–1.90 (m, 4H), 4.37–4.59 (m, 4H, 2 × –CH$_2$Ph), 4.60 (d, $J = 6.9$ Hz, 1H, –CHOC–), 4.67 (d, $J = 6.9$ Hz, 1H, –CHOC–), 7.10–7.44 (m, 12H, 2 × –Ph, –NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.7, 169.7, 137.7, 137.7, 128.8, 127.8, 127.7, 116.9, 77.6, 77.1, 43.7, 43.3, 43.2, 35.9, 35.7, 27.6, 27.0, 26.9, 26.5, 26.5, 26.4, 26.2, 26.0, 25.9, 24.7, 22.2, 20.6; IR (KBr) 3364, 2928, 2856, 1686, 1672, 1649, 1526, 1456, 1109, 698 cm^{-1}; MS (EI) *m*/*e* 548 (M^+, 0.4), 379 (2), 310 (6), 176 (36), 106 (33), 91 (100); HRMS (FAB) Calcd for $C_{34}H_{49}N_2O_4$ (MH^+): 549.3699, found: 549.3689. Anal. Calcd for $C_{34}H_{48}N_2O_4$: C, 74.42; H, 8.82; N, 5.10. Found, C, 74.36; H, 9.13; N, 4.91.

4.11. (*R*)-16-Hydroxy-3-methylhexadecanoic acid 15

Ozone was passed through a stirred solution of carboxylic acid **10** (440 mg, 1.11 mmol) in $CHCl_3$ (10 mL) at −20 °C. After complete consumption of carboxylic acid **10**, the solution was purged with argon and added slowly a suspension of $NaBH_4$ (330 mg, 8.7 mmol) in cooled EtOH (5 mL). The reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was quenched with 10% H_2SO_4 aq (7 mL). After evaporation of the solvent, the residue was extracted with ether (4 × 4 mL), washed with water (4 mL) and brine (4 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude hydroxy acid, which was purified by column chromatography (silica gel, hexane/EtOAc = 60/40) to give ω-hydroxycarboxylic acid **15** (196 mg, 62%) as a colorless powder: $R_f = 0.30$ (hexane/EtOAc = 60/40); $[\alpha]_D^{26} = +3.8$ (*c* 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H, –C(C*H*$_3$)H–), 1.14–1.42 (m, 22H, 11 × –C*H*$_2$–), 1.50–1.65 (m, 2H, –C*H*$_2$CH$_2$OH), 1.85–2.05 (m, 1H, –C*H*(CH$_3$)–) 2.13 (dd, $J = 8.1$, 15.0 Hz, 1H, –CH(CH$_3$)C*H*HCO–), 2.34 (dd, $J = 6.0$, 15.0 Hz, 1H, –CH(CH$_3$)CH*H*CO–), 3.55 (t, $J = 6.6$ Hz, 2H, –C*H*$_2$OH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 178.8$ (–C=O), 63.0 (–*C*H$_2$OH), 41.5, 36.6, 32.7, 30.1, 29.6, 29.5, 29.4, 26.8, 25.7 (–CH$_2$–), 19.7 (–CH$_3$); IR (KBr) 3595–3113 (m/br), 2916, 2850 (s), 1687 (s), 1469 (m) cm^{-1}; MS (EI) *m*/*e* 286 (M^+, 0.1), 268 (0.8), 98 (36), 55 (100). Anal. Calcd for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found: C, 71.21; H, 12.18.

4.12. (*R*)-3-Methylhexadecanolide 16

To a solution of MNBA (119 mg, 0.35 mmol) and DMAP (83 mg, 0.68 mmol) in CH_2Cl_2 (45 mL) was added dropwise a solution of **15** (82 mg, 0.29 mmol) in CH_2Cl_2 (113 mL) with an addition funnel over 24 h at room temperature. After addition of the solution, the reaction mixture was stirred for an additional hour at room temperature. The reaction mixture was concentrated to ca. 20 mL by evaporation of the solvent under reduced pressure, and then satd $NaHCO_3$ aq (5 mL) was added at 0 °C. The mixture was extracted with CH_2Cl_2 (4 × 4 mL), and the organic extracts washed with water (3 mL) and brine (3 mL), dried over anhydride Na_2SO_4 and concentrated to give the crude lactone, which was purified by column chromatography (silica gel, hexane/EtOAc = 98/2) to give lactone **16** (58 mg, 76%) as a colorless liquid: registry number 258354-57-3; $R_f = 0.52$ (hexane/EtOAc = 90/10); $[\alpha]_D^{24} = +1.5$ (*c* 0.94, MeOH) {lit.[11] $[\alpha]_D^{24} = +1.7$ (*c* 1.0, MeOH)}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.89$ (d, $J = 6.7$ Hz, 3H, –C(C*H*$_3$)–), 1.00–1.40 (m, 22H, 11 × –C*H*$_2$–), 1.40–1.60 (m, 2H, –C*H*$_2$CH$_2$O–), 1.80–2.00 (m, 1H, –C*H*–), 2.14

(m, 2H, –CH_2CO–), 3.92–4.04 (m, 1H, –CHH–O–), 4.05–4.16 (m, 1H, –CHH–O–); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 173.1$ (C=O), 63.7 (C–O), 41.9, 35.0, 29.6, 28.1, 27.5, 27.0, 26.7, 26.5, 26.3, 26.2, 26.1, 25.2, 24.9 (–CH_2–) 19.8 (–CH_3); IR (neat) 2926, 2856 (s), 1735 (s) cm^{-1}.

4.13. (*R*)-3-Methylpentacos-16-en-1-ol 17

To a suspension of $LiAlH_4$ (75 mg, 1.98 mmol) in THF (1 mL) was added a solution of carboxylic acid **10** (441 mg, 1.12 mmol) dropwise in THF (4 mL) over 1 min. After the addition of the solution, the reaction mixture was refluxed for 7 h. After complete consumption of carboxylic acid **10**, the reaction mixture was cooled to 0 °C, and quenched with ether (3 mL) and H_2O (1 mL). 15% NaOH aq (1 mL) and H_2O (2 mL) were added to the reaction mixture. Following filtration of the solid, the aqueous phase was extracted with ether (5×3 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude hydroxy acid, which was purified by column chromatography (silica gel, hexane/EtOAc = 90/10) to give alcohol **17** (397 mg, 93%) as a colorless powder: $R_f = 0.50$ (hexane/EtOAc = 70/30); $[\alpha]_D^{27} = +1.8$ (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.82$–0.98 (m, 6H, –CH_3, –C(CH_3)–), 1.00–1.80 (m, 38H, $17 \times$–CH_2–, –CH–, –CH_2CH_2–, –OH), 1.90–2.10 (m, 4H, –CH_2–C=C–CH_2–), 3.68 (m, 2H, –CH_2–O–), 5.35 (t, $J = 4.7$ Hz, 2H, –CH=CH–); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 130.4$, 129.9 (C=C), 64.3 (C–O), 40.0, 37.2, 32.6, 32.0, 30.0, 29.8, 29.72, 29.69, 29.68, 29.58, 29.54, 29.51, 29.3, 29.2, 27.2, 27.0, 22.7 (–CH_2–) 19.7, 14.1 (–CH_3); IR (neat) 3300 (br/s), 2923, 2852 (s), 1466 (m) cm^{-1}; MS (EI) *m*/*e* 380 (M^+, 0.2), 362 (10), 347 (2), 334 (2), 81 (73), 55 (100); HRMS (FAB) Calcd for $C_{26}H_{53}O$ (MH^+): 381.4096, found: 381.4095.

4.14. (*R*)-16-Hydroxy-14-methylhexadecanoic acid 18

Ozone was passed through a stirred solution of alcohol **17** (181 mg, 0.48 mmol) in MeOH (1.8 mL) and CH_2Cl_2 (8 mL) at −70 °C. After complete consumption of alcohol **17**, the solution was evaporated under reduced pressure at −30 °C. To the crude product, formic acid (0.4 mL) and 31% H_2O_2 aq (0.51 mL) were added and the mixture refluxed for 2 h. The mixture was extracted with ether (4×3 mL), washed with water (3 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude carboxylic acid **18** and the ester, which was formed by intermolecular esterification. To a solution of the crude product in MeOH (3 mL) was added 10% NaOH aq (3 mL), and stirred for 4 h at room temperature. The reaction mixture was acidified with 10% H_2SO_4 aq (5 mL), concentrated, and extracted with ether (5×3 mL) and EtOAc (5×3 mL). The organic extracts were washed with water (3 mL) and brine (3 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude carboxylic acid **18**, which was purified by column chromatography (silica gel, hexane/EtOAc = 60/40) to give the ω-hydroxycarboxylic acid **18** (97 mg, 71%) as a colorless powder: $R_f = 0.29$ (hexane/EtOAc = 50/50); $[\alpha]_D^{27} = +1.5$ (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.89$ (d, $J = 6.5$ Hz, 3H, –C(CH_3)–), 1.00–1.80 (m, 26H, $11 \times$–CH_2–, –CH–, –CH_2CH_2O–, –OH), 2.34 (t, $J = 7.5$ Hz, 2H, –CH_2CO–), 3.60–3.78 (m, 2H, –CH_2–O–); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 179.6$ (C=O), 61.2 (C–O), 29.37 (–CH–), 39.8, 37.0, 33.9, 29.8, 29.52, 29.47, 29.41, 29.3, 29.1, 28.9, 26.8, 24.6 (–CH_2–), 19.5 (–CH_3); IR (KBr) 3272 (br/w), 2918, 2851 (s), 1684 (m), 1471 (m) cm^{-1}; MS (EI) *m*/*e* 286 (M^+, 0.1), 268 (0.9), 256 (2), 222 (2), 213 (2), 55 (100). Anal. Calcd for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found: C, 71.32; H, 12.12.

4.15. (*S*)-14-Methylhexadecanolide 19

To a solution of MNBA (120 mg, 0.34 mmol) and DMAP (91 mg, 0.74 mmol) in CH_2Cl_2 (45 mL) was added a solution of the ω-hydroxycarboxylic acid **18** (83 mg, 0.29 mmol) dropwise in CH_2Cl_2 (113 mL) with an addition funnel over 20 h at room temperature. After addition of the solution, the reaction mixture was stirred for another hour at room temperature. The reaction mixture was concentrated to ca. 20 mL by evaporation of the solvent under reduced pressure, and then satd $NaHCO_3$ aq (5 mL) was added at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (4×5 mL), and the organic extracts were washed with water (3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude lactone, which was purified by column chromatography (silica gel, hexane/EtOAc = 95/5) to give lactone **19** (57 mg, 73%) as a colorless liquid: registry number 207552-35-0 (racemate); $R_f = 0.35$ (hexane/EtOAc = 95/5); $[\alpha]_D^{27} = -7.3$ (*c* 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.83$ (d, $J = 6.5$ Hz, 3H, –C(CH_3)–), 1.00–1.80 (m, 25H, $11 \times$–CH_2–, –CH–, –CH_2CH_2O–), 2.34 (t, $J = 7.5$ Hz, 2H, –CH_2CO–), 4.01 (ddd, $J = 4.1$, 8.2, 11.0 Hz, 1H, –CHH–O–), 4.15 (ddd, $J = 4.3$, 6.2, 11.0 Hz, 1H, –CHH–O–); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 173.3$ (C=O), 61.4 (C–O), 34.8, 34.7, 33.6, 27.8, 27.1, 26.6, 26.5, 26.2, 26.1, 26.0, 25.9, 24.8, 23.8 (–CH_2–) 18.8 (–CH_3); IR (neat) 2926, 2856 (s), 1736 (s), 1460 (m), 1259 (m) cm^{-1}.

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