DOI: 10.1002/cjoc.201400862

Synthesis of (*R*)-(–)-Muscone from (*R*)-5-Bromo-4-methylpentanoate: A Chiron Approach

Junwei Shen, Yong Shi,* and Weisheng Tian*

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, *Shanghai Institute of Organic Chemistry*, *Chinese Academy of Sciences*, *Shanghai 200032*, *China*

A synthesis of (*R*)-muscone (**1**), a valuable musk odorant, is presented. The stereogenic center of muscone was introduced from methyl (*R*)-5-bromo-4-methylpentanoate (**5**), a chiral pool molecule developed in our group, and the macrocyclic ring was prepared by ring-closing metathesis (RCM) reaction.

Keywords muscone, fragrances, macrocycles, chiral pool, (*R*)-5-bromo-4-methylpentanoate

Introduction

Musks are the most versatile odorants used in perfumery and indispensable to impart sensuality to a perfume, hence being considered the king of fragrances. Numerous odorants share common musk character, but, in general, three main structural classes of musk odorants are known: nitro musks (such as musk ketone **3**), polycyclic musks (PCMs, such as galaxolide **4**), and macrocyclic musks (MCMs, such as muscone **1** and exaltolide **2**) (Figure 1).[1] Today, nitro musks and PCMs are discussed controversially, because massive production volumes and nonbiodegradability have led to bioaccumulation. In contrast, the MCMs, which have superior odor characteristics than nitro musks and PCMs, are biodegradable, therefore, attractive molecular targets.

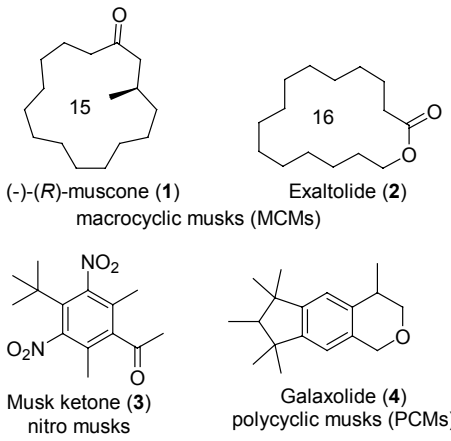


Figure 1 Structurally different musk odorant ingredients.

(*R*)-Muscone (**1**), the pheromone of the male musk deer *Moschus moschiferus*[2] and the natural lead of MCMs, is considered by perfumers to be one of the best musk odorants. Because natural sources of muscone are obsolete on both ethical and economical grounds, more than twenty approaches have been made towards the synthesis of muscone.

The key synthetic challenges of (*R*)-muscone are the construction of the macrocyclic ring and the establishment of the chiral methyl group. In racemic form muscone has been synthesized by many routes, which mainly dealt with the construction of the 15-membered ring, involving a variety of strategies such as ring expansion methods, acyloin condensation and fragmentation reactions.[3] Recent syntheses of (*R*)-muscone (**1**) not only put forward new methods for macrocycle closure, such as free radical macrocyclization, ring-closing metathesis (RCM), and macrocyclization of an ω-alkynal, but also developed many interesting ways to introduce the chiral methyl group.[4]

Two most adopted methods for establishing the chiral methyl group are asymmetrical conjugate addition of Me or hydrogenation of H on macrocyclic enones and chiral pool strategy. Inheriting the chirality from the starting material, the latter is naturally superior to the former in the term of stability of the product quality, but inferior in cost control, especially when the chiral citronellal and Roche ester are used as starting materials. Therefore, synthesis of this highly valuable target from less expensive chiral starting material is still welcomed. Herein, we report the synthesis of **1** from methyl (*R*)-5-bromo-4-methylpentanoate (**5**), a new chiral pool molecule we developed.

Experimental

(*R*)-5-Bromo-4-methylpentan-1-ol (7)

To a suspension of $LiAlH_4$ (3.13 g, 82 mmol) in an-

* E-mail: shiong81@sioc.ac.cn; wstian@sioc.ac.cn
Received December 16, 2014; accepted January 6, 2015; published online March 9, 2015.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201400862 or from the author.

hydrous ether (200 mL) was added a solution of bromoester **5** (12.1 g, 58 mmol) in ether (40 mL) at −10 ℃. The mixture was stirred for 3 h at 0 ℃, cooled to −10 ℃ and quenched carefully with saturated aqueous sodium potassium tartrate (150 mL), and the mixture was stirred rapidly at room temperature for 30 min. The mixture was then separated and the aqueous layer was extracted with ether for three times. The combined organic layers were dried over Na_2SO_4 and purified by flash column chromatography on silica gel to provide **7** (10.2 g, 97%) as a colorless liquid. When the reaction was carried out at higher temperature, debromination also occurred to generate 4-methylpentan-1-ol at 33% yield (**7** in 45% yield). $[\alpha]_D^{25}$ +4.1 (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.67 (t, *J*=6.3 Hz, 2H), 3.34−3.42 (m, 2H), 1.75−1.87 (m, 1H), 1.52−1.68 (m, 3H), 1.24−1.38 (m, 1H), 1.04 (d, *J*=6.9 Hz, 3H); IR (KBr) *v*: 3320, 2956, 1459, 1380, 1232 cm^{-1}; EIMS (70 eV) *m/z* (%): 181 (M^+, 100). Anal. calcd for $C_6H_{13}BrO$: C 39.80, H 7.24; found C 39.66, H 7.09. For 4-methylpentan-1-ol: ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.64 (t, *J*=6.6 Hz, 2H), 1.62−1.52 (m, 3H), 1.27−1.19 (m, 2H), 0.90 (d, *J*=6.6 Hz, 6H).

(*R*)-6-Bromo-5-methylhex-1-ene (8)

To a solution of oxalyl chloride (3.9 mL, 45 mmol) in CH_2Cl_2 (120 mL) cooled at −78 ℃ was added dropwise a solution of dimethylsulfoxide (DMSO 6.4 mL, 90 mmol) in CH_2Cl_2 (30 mL). After 60 min, a solution of **7** (5.5 g, 30 mmol) in CH_2Cl_2 (30 mL) was added. The reaction mixture was then stirred for 2 h at −78 ℃ and triethylamine (27 mL) was added in one portion. After 15 min at −78 ℃, the mixture was allowed to warm to room temperature over 3 h, and quenched with water. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel gave aldehyde (5.0 g, 93%) as a colorless liquid, which was used directly after purification. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 9.78 (s, 1H), 3.34−3.41 (m, 2H), 2.48 (t, *J*=7.5 Hz, 2H), 1.81−1.88 (m, 2H), 1.57−1.65 (m, 1H), 1.04 (d, *J*=4.8 Hz, 3H).

To a suspension of methyltriphenylphosponium iodide (2.95 g, 7.3 mmol) in dry THF (40 mL) at ambient temperature under argon was added *n*-BuLi (3.4 mL of 2.0 mol/L solution in hexanes, 6.8 mmol). The mixture was stirred for 1 h, cooled to −78 ℃, and a solution of the aldehyde (1.0 g, 5.6 mmol) in THF (10 mL) was added. The mixture was allowed to warm to room temperature over 3 h and quenched with a saturated aqueous solution of NH_4Cl. The phases were separated, and the aqueous phase extracted with EtOAc for three times. The combined organic layers were washed with sturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Distillation under reduced pressure (45 ℃/10 mmHg) provides alkene **8** (624 mg, 63%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 5.78−5.83 (m, 1H), 4.96−5.04 (m, 2H), 3.34−3.39 (m, 2H), 2.05−2.12 (m, 2H), 1.80−1.85 (m, 1H), 1.55−1.58 (m, 1H), 1.51−1.53 (m, 1H), 1.04 (d, *J*=6.6 Hz, 3H); EIMS (70 eV) *m/z* (%): 176 (M^+, 100). Anal. calcd for $C_7H_{13}Br$: C 47.48, H 7.40; found C 47.35, H 7.39.

***N*-Methoxy-*N*-methylundec-10-enamide (9)**

A mixture of undec-10-enoic acid (20 g, 109 mmo) and thionyl chloride (15 mL) in dry CH_2Cl_2 (60 mL) was reflux for 4 h, then concentrated *in vacuo* to remove the volatile solvent. Harvested by distillation under reduced pressure (70 ℃/1 mmHg) as a colorless liquid, the acid chloride (18.5 g, 92 mmol, 84% from acid) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (9.4 g, 96 mmol) and *i*-Pr_2NEt (32 mL, 193 mmol) in dry CH_2Cl_2 (200 mL) at 0 ℃ under argon. The reaction mixture was stirred at ambient temperature for 6 h, quenched with water, extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (100 ℃/15 Pa) to yield Weinreb amide **9** (19 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 5.78−5.82 (m, 1H), 4.92−4.97 (m, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.38−2.43 (m, 2H), 2.02−2.07 (m, 2H), 1.60−1.65 (m, 2H), 1.30 (br, 10H).

(*R*)-1-Bromo-5-(methoxymethoxy)-2-methylpentane (12)

To a solution of bromo alcohol **7** (5.8 g, 32 mmol) and *i*-Pr_2NEt (8.0 mL, 48 mmol) in dry CH_2Cl_2 (30 mL) was added MOMCl (3.9 mL, 50 mmol) at ambient temperature under argon. The reaction mixture was stirred for 5 h, diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography on silica gel afforded **12** (6.7 g, 93%) as a colorless liquid. $[\alpha]_D^{25}$ +1.9 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 4.61 (s, 2H), 3.50 (t, *J*=6.3 Hz, 2H), 3.30−3.41 (m, 5H), 1.78−1.86 (m, 1H), 1.50−1.65 (m, 3H), 1.30−1.37 (m, 1H), 1.04 (d, *J*=6.9 Hz, 3H); IR (KBr) *v*: 2934, 2883, 1459, 1380, 1232, 1112, 1046, 919 cm^{-1}; EIMS (70 eV) *m/z* (%): 226 (M^+, 100). Anal. calcd for $C_8H_{17}BrO_2$: C 42.68, H 7.61, Br 35.49; found C 42.66, H 7.58, Br 35.31.

(*R*)-1-(Methoxymethoxy)-4-methylhexadec-15-en-6-one (13)

To a suspension of Li (94 mg, 0.5 wt% Na, 13.4 mmol) and a catalytic amount of 1,2-dibromoethane in dry ether (7 mL) was added a solution of bromide **12** (1.0 g, 4.5 mmol) in ether (10 mL) slowly at −10 ℃ under argon. The reaction was stirred for 2 h, cooled to −78 ℃ and added a solution of Weinreb amide **9** (0.51 g, 2.2 mmol) in dry ether, then warmed to ambient temperature over 3 h. The mixture was diluted with EtOAc (100 mL), washed with a saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on silica gel af-

CHINESE JOURNAL OF CHEMISTRY

forded ketone **13** (0.53 g, 76%) as a colorless oil. $[\alpha]_D^{25}$ +2.9 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.75−5.86 (m, 1H), 4.90−5.03 (m, 2H), 4.61 (s, 2H), 3.50 (t, *J*=6.6 Hz, 2H), 3.36 (s, 3H), 2.33−2.42 (m, 3H), 2.18−2.25 (m, 1H), 1.98−2.06 (m, 3H), 1.50−1.64 (m, 4H), 1.27−1.35 (m, 12H), 0.88 (d, *J*=6.9 Hz, 3H); IR (KBr) *v*: 2929, 2856, 1714, 1112, 1047 cm^{-1}; EIMS (70 eV) *m/z* (%): 281 (M^+−31, 100). Anal. calcd for $C_{19}H_{36}O_3$: C 73.03, H 11.61; found C 73.04, H 11.23.

(*R*)-4-Methyl-6-oxohexadec-15-enal (14)

A solution of ketone **13** (3.2 g, 12.1 mmol) in MeOH was added concentrated HCl (0.50 mL) and heated to reflux for 6 h. The solvent was removed and the residue was dissolved in EtOAc (200 mL), washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on silica gel afforded alcohol (2.7 g, 98%) as a colorless oil, which was directly used in the next step. $[\alpha]_D^{25}$ +3.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.77−5.86 (m, 1H), 4.90−5.03 (m, 2H), 3.64 (br s, 2H), 2.34−2.44 (m, 3H), 2.20−2.27 (m, 1H), 1.98−2.06 (m, 3H), 1.50−1.58 (m, 4H), 1.23−1.38 (m, 12H), 0.89 (d, *J*=6.6 Hz, 3H); IR (KBr) *v*: 3407, 2929, 2856, 1712 cm^{-1}; ESIMS (*m/z*): 269 ($[M+H]^+$). Anal. calcd for $C_{17}H_{32}O_2$: C 75.54, H 11.89; found C 75.55, H 12.06.

To a solution of oxalyl chloride (0.24 mL, 2.7 mmol) in CH_2Cl_2 (10 mL) cooled at −78 ℃ was added dropwise a solution of dimethylsulfoxide (DMSO 0.4 mL, 5.6 mmol) in CH_2Cl_2 (5 mL). After 1 h, a solution of alcohol (0.5 g, 1.9 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was then stirred for 1 h at −78 ℃ and triethylamine (2 mL) was added in one portion. After 15 min at −78 ℃, the mixture was allowed to warm to room temperature over 3 h, and quenched with water. The mixture was diluted with CH_2Cl_2, washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel gave aldehyde **14** (0.46 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$ +4.6 (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.79−5.89 (m, 1H), 4.95−5.02 (m, 2H), 2.22−2.50 (m, 6H), 1.98−2.04 (m, 3H), 1.27−1.57 (m, 14H), 0.89 (d, *J*=6.9 Hz, 3H); IR (KBr) *v*: 2929, 2856, 1713, 1460, 1412 cm^{-1}; ESIMS (*m/z*): 267 ($[M+H]^+$). Anal. calcd for $C_{17}H_{30}O_2$: C 76.64, H 11.35; found C 76.20, H 11.12.

(*R*)-5-Methylheptadeca-1,16-dien-7-one (10)

To a suspension of methyltriphenylphosponium iodide (2.0 g, 5.0 mmol) in dry THF (20 mL) at ambient temperature under argon was added *n*-BuLi (2.4 mL of 2.0 mol/L solution in hexanes, 4.8 mmol). The mixture was stirred for 1 h, cooled to −78 ℃, and a solution of the aldehyde **14** (1.2 g, 4.5 mmol) in THF (10 mL) was added. The mixture was allowed to warm to room temperature for 24 h and quenched with a saturated aqueous solution of NH_4Cl. The phases were separated, and the aqueous phase extracted with EtOAc for three times. The combined organic layers were washed with sturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Distillation under reduced pressure (45 ℃/10 mmHg) provided alkene **10** (880 mg, 73%) as a colorless liquid. $[\alpha]_D^{25}$ +3.19 (*c* 0.94, MeOH, lit. +2.94, *c* 0.9, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.77−5.87 (m, 2H), 4.93−5.04 (m, 4H), 2.30−2.36 (m, 3H), 2.18−2.24 (m, 1H), 1.97−2.05 (m, 4H), 1.54−1.62 (m, 3H), 1.24−1.37 (m, 12H), 0.88 (d, *J*=6.3 Hz, 3H); IR (KBr) *v*: 3076, 2926, 2854, 1713, 909 cm^{-1}; EIMS (70 eV) *m/z* (%): 264 (M^+, 100).

(*R*)-3-Methylcyclopentadec-6-en-1-one (16)

To a solution of diene **10** (60 mg, 0.23 mmol) in dry benzene (60 mL) at ambient temperature under argon was added bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (**15**, 19 mg, 0.02 mmol) in benzene (10 mL). The mixture was heated to reflux for 36 h before filtered through a pad of Florisil/silica. The pad was washed with CH_2Cl_2, and the solvent was removed by evaporation. The residue was purified by flash column chromatography on silica gel to yield **16** (40 mg, 74%) as a colorless oil, along with a dimer (10 mg, 19%). ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.32−5.40 (m, 2H), 2.34−2.45 (m, 3H), 2.02−2.20 (m, 6H), 1.54−1.63 (m, 1H), 1.25−1.38 (m, 13H), 0.91 (d, *J*=6.6 Hz, 3H); IR (KBr) *v*: 2928, 2855, 1710, 1459, 971 cm^{-1}; EIMS *m/z* (%): 237 (M^++1, 100). For dimer: ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.37−2.43 (m, 4H), 2.36−2.43 (m, 6H), 1.96−2.23 (m, 12H), 1.54−1.62 (m, 2H), 1.20−1.38 (m, 26H), 0.86−0.94 (m, 6H); IR (KBr) *v*: 2926, 2852, 1706, 1467, 1407, 1375, 973 cm^{-1}; ESIMS (*m/z*): 495($[M+H]^+$).

(*R*)-3-Methylcyclopentadecan-1-one (1, muscone)

A reaction flask containing alkene **16** (30 mg, 0.13 mmol), Pd/C (10%, 5 mg), and MeOH (10 mL) was evacuated and back-filled with hydrogen (1 atm). The reaction mixture was stirred at 40 ℃ under hydrogen for 5 h and then filtered over a plug of silica gel topped with Celite (MeOH eluent). The filtrate was concentrated and purified by flash column chromatography on silica gel to give muscone (**1**, 28 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ −12.4 (*c* 0.92, MeOH, lit. −12.7, *c* 0.9, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.38−2.46 (m, 3H), 2.18 (dd, *J*=5.1, 15.0 Hz, 1H), 1.97−2.11 (m, 1H), 1.57−1.68 (m, 2H), 1.15−1.40 (br, 20H), 0.92 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.0, 23.0, 25.0, 26.1, 26.2, 26.52, 26.57, 26.6, 26.7, 27.1, 27.5, 29.0, 35.5, 42.0, 50.4, 212.0; IR (KBr) *v*: 2962, 2929, 2858, 1714, 1461, 1261, 1093, 1021 cm^{-1}; EIMS *m/z* (%): 238 (M^+, 100); HRMS-EI M^+ calcd for $C_{16}H_{30}O$: 238.2297, found 238.2308.

Results and Discussion

Our group's efforts in developing new degradation methods of steroidal sapogenins allowed us to collect

(*R*)-4-methyl-*δ*-valerolactone, as a byproduct, in a kilogram scale. Bromoester **5** was therefore prepared and used as a chiral pool molecule in the syntheses of several natural products including the synthesis of muscone presented herein.[5]

Our retrosynthetic analysis of muscone (**1**) is outlined in Figure 2. Macrocycle of muscone was to be closed by the RCM reaction at C(6)—C(7) position, and its precursor by a nucleophilic addition of organometallic reagent derived from **5** to undec-10-enoic acid **6**, which is very cheap and available in large quantity.

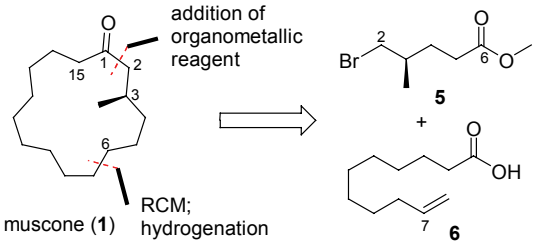
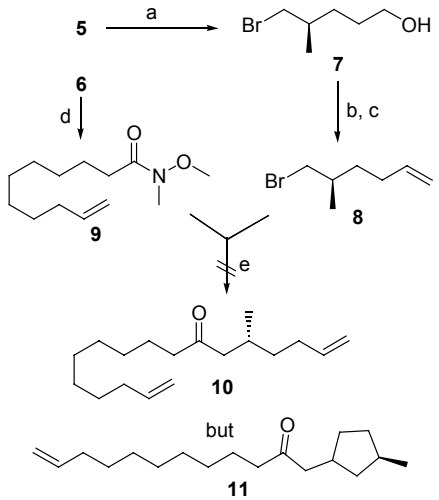


Figure 2 Retrosynthetic analysis of muscone (**1**).

We first transformed bromoester **5** into alkene **8** to minimize employing protecting groups, as shown in Scheme 1. Reduction with $LiAlH_4$ at 0 ℃ provided alcohol **7** chemoselectively in high yield, whereas at higher temperature it also removed the bromine atom reductively to give 4-methylpentan-1-ol. Thus maintaining the reaction temperature below 0 ℃ is important. Swern oxidation of **7** followed by Wittig olefination provided the desired **8** in good yield. Acid **6** was converted into acid chloride which was immediately treated with *N*,*O*-dimethylhydroxylamine to give the corresponding Weinreb amide **9** effectively.

Scheme 1 Failed attempt

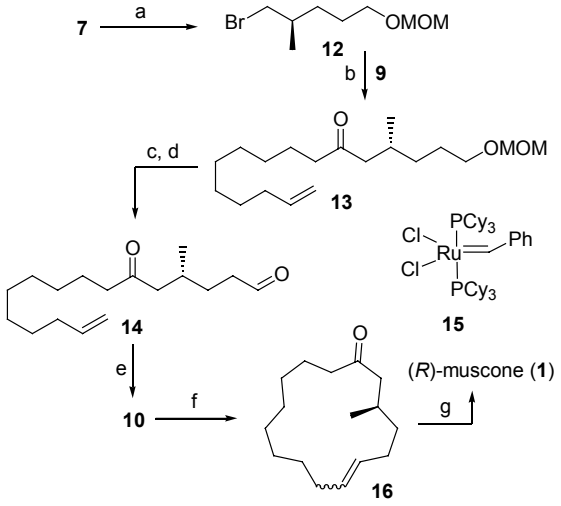


Conditions and reagents: (a) $LiAlH_4$, ether, 0 ℃, 3 h, 97%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 ℃, 1 h, **7**, 2 h, Et_3N, warm to r.t., 3 h, 93%; (c) Ph_3PMeI, *n*-BuLi, THF, r.t., 1 h, aldehyde, −78 ℃ to r.t., 3 h, 63%; (d) $SOCl_2$, CH_2Cl_2, reflux, 4 h; MeONHMe•HCl, *i*-Pr_2NEt, CH_2Cl_2, 0 ℃ to r.t., 6 h, 91%; (e) failed conditions: Mg/Et_2O; *t*-BuLi/Et_2O; Li/Na (0.5%), Et_2O, *etc*.

We then tried to perform a Weinreb ketone synthesis and found that it is difficult to prepare organometallic reagents from bromide **8**. Being treated with magnesium in ether, **8** underwent Wurtz-type only completely, providing no ketone **10** after amide **9** was added. Lithium-halogen exchange between bromide **8** or its iodo analogue and *t*-BuLi or Li/Na delivered no **10** but a small amount of **11**, which was raised from, we supposed, a 5-exo-trig cyclization of the organolithium[6] followed by a nucleophilic addition of the newly generated organolithium reagent to amide **9**.

The Wittig olefination was then moved to later stage of the synthesis, and protecting groups were therefore required. As depicted in Scheme 2, alcohol **7** was protected as its methoxymethyl (MOM) ether **12**, the lithium anion derivative of which smoothly underwent Weinreb ketone synthesis to provide ketone **13** in 76% yield. MOM ether of **13** was removed upon refluxing in acidic MeOH solution, which was followed by a Swern oxidation and a Wittig olefination of the resulting aldehyde to provide diene **10** in good yield.

Scheme 2 Completion of the synthesis of muscone



Conditions and reagents: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, r.t., 5 h, 93%; (b) **12**, Li/Na (0.5%), Et_2O, 0 ℃, 2 h, then **9**, −78 ℃ to r.t., 3 h, 76%; (c) MeOH, HCl, refulx, 6 h, 98%; (d) DMSO, $(COCl)_2$, CH_2Cl_2, −78 ℃, 1 h, substrate, 1 h, Et_3N, warm to r.t., 3 h, 92%; (e) Ph_3PMeI, *n*-BuLi, THF, r.t., 1 h, aldehyde, −78 ℃ to r.t., 24 h, 73%; (f) Grubbs 1st generation catalyst **15** (10 mol%), benzene, reflux, 36 h, 74%, dimer, 19%; (g) 10% Pd/C, H_2, MeOH, 40 ℃, 5 h, 93%.

With **10** in hand, the subsequent RCM reaction was immediately practiced. Treatment of a 0.004 mol/L benzene solution of **10** under reflux with 9 mol% of Grubbs' first generation catalyst **15** provided cyclic ketone **16** as a mixture of *E*/*Z* macrocycles in an overall yield of 74%, along with a dimer in 19% yield. The double bond in **16** was saturated by catalytic hydrogenation to deliver muscone (**1**) in high yield. Synthetic (*R*)-muscone matched in all respects with physical and

spectroscopic data provided for the natural product.

Conclusions

We have accomplished the synthesis of (*R*)-muscone (**1**) from **5**, a new chiral pool molecule developed by our group, in eight steps with an overall yield of 32%. Key transformations are a Weinreb ketone synthesis and a RCM reaction. Efforts to synthesis of other related MCMs from **5** with a similar strategy are ongoing.

References

[1] *Perspectives in Flavor and Fragrance Research*, Eds: Kraft, P.; Swift, K. A. D., WILEY-VCH, Weinheim, **2005**.

[2] Ruzicka, L. *Helv. Chim. Acta* **1926**, *9*, 715.

[3] (a) Baker, R.; Blackett, B. N.; Cookson, R. C. *J. Chem. Soc.*, *Chem. Commun.* **1972**, 802; (b) Stork, G.; MacDonald, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 1264; (c) Korzeniowski, S. H.; Vanderbilt, D. P.; Hendry, L. B. *Org. Prep. Proced. Int.* **1976**, *8*, 81; (d) Ito, Y.; Saegusa, T. *J. Org. Chem.* **1977**, *42*, 2326; (e) Fliri, H.; Scholz, D.; Stütz, A. *Monatsh. Chem.* **1979**, *110*, 245; (f) Schulte-Elte, K. H.; Hauser, A.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 2673; (g) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680; (h) Tsuji, J.; Yamada, T.; Shimizu, I. *J. Org. Chem.* **1980**, *45*, 5209; (i) Takahashi, T.; Nagashima, T.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 1359; (j) Brunner, R. K.; Borschberg, H.-J. *Helv. Chim. Acta* **1983**, *66*, 2608; (k) Thies, R. W.; Daruwala, K. P. *J. Chem. Soc.*, *Chem. Commun.* **1985**, 1188; (l) Taechachoonhakit, S.; Ratananukul, P. *Chem. Lett.* **1986**, *15*, 911; (m) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963; (n) Thies, R. W.; Daruwala, K. P. *J. Org. Chem.***1987**, *52*, 3798; (o) Deprés, J.-P.; Navarro, B.; Greene, A. E. *Tetrahedron* **1989**, *45*, 2989; (p) Rautenstrauch, V.; Snowden, R. L.; Linder, S. M. *Helv. Chim. Acta* **1990**, *73*, 896; (q) Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132; (r) Erden, I.; Cao, W.; Price, M.; Colton, M. *Tetrahedron* **2008**, *64*, 5497.

[4] (a) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721; (b) Terunuma, D.; Motegi, M.; Tsuda, M.; Sawada, T.; Nozawa, H.; Nohira, H. *J. Org. Chem.* **1987**, *52*, 1630; (c) Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc.*, *Chem. Commun.* **1990**, 795; (d) Xie, Z. F.; Sakai, K. *J. Org. Chem.* **1990**, *55*, 820; (e) Ogawa, T.; Fang, C. L.; Suemune, H.; Sakai, K. *J. Chem. Soc.*, *Chem. Commun.* **1991**, 1438; (f) Dowd, P.; Choi, S. C. *Tetrahedron* **1992**, *48*, 4773; (g) Wang, D.; Zhou, C.; Wang, D. *Chin. Chem. Lett.* **1992**, *3*, 235; (h) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593; (i) Wang, D.-S.; Wang, D.-Q.; Zhou, C.-H. *Acta Chim. Sinica* **1995**, *53*, 909; (j) Matsumura, Y.; Fukawa, H.; Terao, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1484; (k) Alexakis, A.; Benhaim, C.; Fournioux, X.; Van den Heuvel, A.; Leveque, J.-M.; March, S.; Rosset, S. *Synlett* **1999**, 1811; (l) Kamat, V. P.; Hagiwara, H.; Katsumi, T.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron* **2000**, *56*, 4397; (m) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312; (n) Fujimoto, S.; Yoshikawa, K.; Itoh, M.; Kitahara, T. *Biosci.*, *Biotechnol.*, *Biochem.* **2002**, *66*, 1389; (o) Yamamoto, T.; Ogura, M.; Kanisawa, T. *Tetrahedron* **2002**, *58*, 9209; (p) Fehr, C.; Galindo, J.; Etter, O. *Eur. J. Org. Chem.* **2004**, 1953; (q) Fehr, C.; Galindo, J.; Farris, I.; Cuenca, A. *Helv. Chim. Acta* **2004**, *87*, 1737; (r) Guo, Y.; Wu, X. L.; Li, J. L.; Xu, R. Q.; Shi, Z. *Synth. Commun.* **2005**, *35*, 2489; (s) Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172; (t) Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854; (u) Takabe, K.; Sugiura, M.; Asumi, Y.; Mase, N.; Yoda, H.; Shimizu, H. *Tetrahedron Lett.* **2005**, *46*, 3457; (v) Bulic, B.; Lucking, U.; Pfaltz, A. *Synlett* **2006**, 1031; (w) Knopff, O.; Kuhne, J.; Fehr, C. *Angew. Chem.*, *Int. Ed.* **2007**, *46*, 1307; (x) Rohanna, J. C.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 493; (y) Fehr, C.; Buzas, A. K.; Knopff, O.; de Saint Laumer, J.-Y. *Chem. Eur. J.* **2010**, *16*, 2487; (z) Chapuis, C.; Robvieux, F.; Cantatore, C.; Saint-Leger, C.; Maggi, L. *Helv. Chim. Acta* **2012**, *95*, 428; (aa) Hagiwara, H.; Adachi, T.; Doya, M.; Hoshi, T.; Suzuki, T. *Flavour Fragr. J.* **2012**, *27*, 54.

[5] (a) Wang, Z.; Tian, W.; Pan, X. *Acta Chim. Sinica* **2007**, *65*, 705; (b) Wang, Z.; Xu, Q.; Tian, W.; Pan, X. *Tetrahedron Lett.* **2007**, *48*, 7549; (c) Zhang, S.; Dong, H.; Gui, J.; Tian, W. *Tetrahedron Lett.* **2012**, *53*, 1882.

[6] (a) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742; (b) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720; (c) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787.

(Lu, Y.)

