DOI: 10.1002/cjoc.201500334

Synthesis of Tribolure, the Common Aggregation Pheromone of Four *Tribolium* Flour Beetles

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Herein we report a synthesis of the natural tribolure, an aggregation pheromone which consists of (4*R*,8*S*)-, (4*R*,8*R*)-, (4*S*,8*S*)-, and (4*S*,8*R*)-4,8-dimethyldecanals in a ratio of 4/4/1/1, from (*R*)-4-methyl-*δ*-valerolactone, a by-product of the degradation of steroidal sapogenins. Merging the stereoisomers of the same ratios into one synthetic target and using the same chiron for the construction of the C4 stereocenters are notable features of this synthesis.

Keywords aggregation pheromone, tribolure, synthesis, *Tribolium* flour beetle, (*R*)-4-methyl-*δ*-valerolactone

Introduction

Aggregation pheromones attract both sexes within the same species to specific locations, thereby providing a powerful and environmentally friendly tool for pest control. The purposes of organic synthesis in pheromone science are twofold: establishing the structures and providing sufficient samples for biological studies and practical use.

The red flour beetle, *Tribolium castaneum*, and the confused flour beetle, *Tribolium confusum*, are worldwide pests that attack stored grains and foods in the pantry. Their aggregation pheromone has been identified as 4,8-dimethyldecanal (**1**), which was given the name "tribolure" later when it was found to be the aggregation pheromone of *Tribolium freeman* (Figure 1).[1] In 2002, it was detected also in *Tribolium madens*.[2] Since its first disclosure, the four possible stereoisomers have been synthesized many times by Mori and others, but none of them alone matched the bioactivity of the natural tribolure.[3] Recently Mori and co-workers found that the natural tribolure is a 4/4/1/1 mixture of (4*R*,8*S*)-**1**, (4*R*,8*R*)-**1**, (4*S*,8*S*)-**1**, and (4*S*,8*R*)-**1**,[4] suggesting that in the course of the biosynthesis of **1** configuration at C8 is not controlled and at C4 partially controlled.

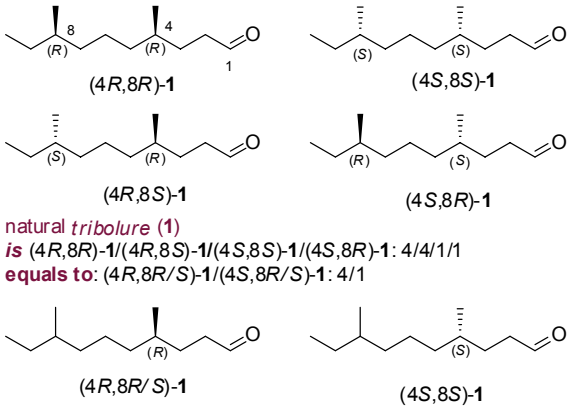

Figure 1 Chemical structures of natural tribolure.

Two reasons attracted us to pursue a synthesis of **1**. One is that we have developed several chiral methyl chirons from industrial waste and been interested in applying them in the syntheses of the chiral methyl-branched natural products.[5] Another is that all the previous syntheses of **1** aimed to create both stereocenters of a specific isomer but not to treat **1** as a whole. Herein, we report our synthesis of the natural tribolure.

Experimental

All reactions sensitive to air or moisture were performed in flame-dried round bottom flasks with rubber septum under a positive pressure of argon or nitrogen atmosphere, unless otherwise noted. Air and moisture-sensitive liquids and solutions were transferred via syringe and stainless steel cannula. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as visualizing agent and an ethanolic solution of phosphomolybic acid, and heat as developing agents. NMR spectra were recorded on Bruker DRX-400 instrument and calibrated using residual undeuterated solvent as an internal reference [^{1}H NMR: $CHCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.16)]. We

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Received April 28, 2015; accepted May 14, 2015; published online June 10, 2015.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500334 or from the author.

also reported the chemical shifts of the ^{13}C NMRs of the mixtures herein for further reference.

Methyl (*R*)-5-(methoxymethoxy)-4-methylpentanoate (5)

To a solution of **2** (5.00 g, 43.8 mmol) in MOMOM (dimethoxymethane, 200 mL) was added concentrated H_2SO_4 (3 mL). After being stirred at room temperature for 5 h, the solution was neutralized with the saturated solution of $NaHCO_3$ and filtered. The filtrate was evaporated under reduced pressure to remove most of the organic solvent and then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford crude **5** as colorless oil. b.p. 56 ℃/33 Pa; $[\alpha]_D^{24}$ +5.15 (*c* 1.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.58 (s, 2H), 3.64 (s, 3H), 3.37−3.34 (m, 2H), 3.33 (s, 3H), 2.41−2.25 (m, 2H), 1.82−1.67 (m, 2H), 1.52−1.43 (m, 1H), 0.92 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3 (C=O), 96.6 (CH_2), 72.7 (CH_2), 55.2 (CH_3), 51.6 (CH_3), 33.1 (CH), 31.8 (CH_2), 28.8 (CH_2), 16.8 (CH_3); IR (KBr) ν: 2953, 2883, 1740, 1438, 1256, 1174, 1152, 1109, 1047, 920 cm^{-1}; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_9H_{18}O_4$: 191.1278, found 191.1277. Anal. calcd for $C_9H_{18}O_4$: C 56.82, H 9.54; found C 56.77, H 9.37.

(*R*)-5-(Methoxymethoxy)-4-methylpentan-1-ol

To a suspension of $LiAlH_4$ (1.50 g, 39.4 mmol) in anhydrous THF (150 mL) was added a solution of crude **5** (5.00 g, 26.3 mmol) in anhydrous THF (50 mL) under argon slowly at 0 ℃. The mixture was warmed to room temperature and stirred for 1 h, then quenched with Na_2SO_4•$10H_2O$ and water carefully until no bubble occurred and the mixture turned white. The resulting mixture was filtered and the filtrate was diluted with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford light yellow oil, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 5/1, *V*/*V*) to afford the title compound as a colorless oil (3.10 g, 79% over 2 steps). b.p. 70 ℃/30 Pa; $[\alpha]_D^{27}$ +4.36 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.57 (s, 2H), 3.58 (t, J=6.5 Hz, 2H), 3.35−3.27 (m, 2H), 3.32 (s, 3H), 2.07 (s, 1H), 1.76−1.65 (m, 1H), 1.65−1.41 (m, 3H), 1.16 (m, 1H), 0.90 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.6 (CH_2), 73.2 (CH_2), 63.0 (CH_2), 55.2 (CH_3), 33.3 (CH), 30.2 (CH_2), 29.7 (CH_2), 17.1 (CH_3); IR (KBr) ν: 3406, 2933, 1466, 1385, 1216, 1150, 1111, 1047, 921 cm^{-1}; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_8H_{18}O_3$: 163.1329, found 163.1328. Anal. calcd for $C_8H_{18}O_3$: C 59.23, H 11.18; found C 59.45, H 11.37.

(*R*)-5-Iodo-1-(methoxymethoxy)-2-methylpentane (6)

To a solution of PPh_3 (14.6 g, 55.5 mmol) and imidazole (7.6 g, 111 mmol) in anhydrous dichloromethane (150 mL) was added iodine (14.1 g, 55.5 mol) slowly under argon at 0 ℃. After being stirred at 0 ℃ for 30 min, a solution of the alcoholic compound (3.00 g, 18.5 mmol) in anhydrous DCM (30 mL) was added. The mixture was allowed to warm to room temperature and stirred for 3 h and was quenched with water. The resulting mixture was evaporated under reduced pressure to remove most of the organic solvent and then diluted with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 80/1, *V*/*V*) to afford **6** (4.20 g, 84%) as acolorless oil. $[\alpha]_D^{27}$ +7.24 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.59 (s, 2H), 3.37−3.31 (m, 2H), 3.34 (s, 3H), 3.19−3.13 (m, 2H), 1.93−1.79 (m, 2H), 1.78−1.70 (m, 1H), 1.56−1.47 (m, 1H), 1.28−1.20 (m, 1H), 0.92 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.6 (CH_2), 72.9 (CH_2), 55.3 (CH_3), 34.7 (CH_2), 32.8 (CH), 31.3 (CH_2), 17.1 (CH_3), 7.2 (CH_2). IR (KBr) ν: 2929, 2881, 1463, 1387, 1214, 1175, 1151, 1111, 1046, 920 cm^{-1}; HRMS-EI (*m/z*): M^+ calcd for $C_8H_{17}O_2I$ 272.0273, found 272.0271.

(2*R*)-1-(Methoxymethoxy)-2,6-dimethyloctane (8)

To a solution of iodide **6** (4.00 g, 14.7 mmol) and *N*-methyl-2-pyrrolidone (NMP, 2.83 mL, 29.4 mmol) and Li_2CuCl_4 (14.7 mL, 0.1 mol/L in THF) in anhydrous THF (120 mL) was added *sec*-butylmagnesium bromide (**7**, 29.4 mL, 1.0 mol/L in THF) under argon at 0 ℃. The reactant solution was allowed to warm to room temperature and stirred for 1 h and was quenched with saturated aqueous solution of NH_4Cl and filtered. The filtrate was diluted with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford light yellow oil, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 80/1, *V*/*V*) to afford colorless oil **8** (2.80 g, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ: 4.57 (s, 2H), 3.38−3.26 (m, 2H), 3.31 (s, 3H), 1.72−1.64 (m, 1H), 1.38−1.19 (m, 6H), 1.14−1.01 (m, 3H), 0.89 (d, J=6.7 Hz, 3H), 0.82 (t, J=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.6 (CH_2), 73.4 (CH_2), 55.1 (CH_3), 37.0 (CH_2), 34.5 (CH), 34.1 (CH_2), 33.58 (CH), 29.6 (CH_2), 24.5 (CH_2), 19.3 (CH_3), 17.2 (CH_3), 11.5 (CH_3); IR (KBr) ν: 2958, 2923, 2876, 1464, 1378, 1215, 1152, 1112, 1049, 921 cm^{-1}; HRMS-ESI (*m/z*): $[M+NH_4]^+$ calcd for $C_{12}H_{26}O_2$: 220.2271, found 220.2270.

(2*R*)-2,6-Dimethyloctan-1-ol

To a solution of **8** (2.0 g, 9.9 mmol) in MeOH (80 mL) was added concentrated hydrochloric acid (2 mL). The solution was heated to reflux for 1 h, neutralized with the saturated solution of $NaHCO_3$, and filtered. The filtrate was evaporated under reduced pressure to remove most of the organic solvent and then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated

to afford light yellow oil, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 10/1, *V*/*V*) to afford the title compound (1.3 g, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51－3.47 (dd, J＝10.4, 5.8 Hz, 1H), 3.41－3.37 (dd, J＝10.5, 6.6 Hz, 1H), 1.68 (s, 1H), 1.64－1.56 (m, 1H), 1.39－1.21 (m, 6H), 1.16－1.02 (m, 3H), 0.90 (d, J＝6.7 Hz, 3H), 0.84 (t, J＝7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 68.5 (CH_2), 37.0 (CH_2), 35.9 (CH), 34.5 (CH), 33.6 (CH_2), 29.6 (CH_2), 24.5 (CH_2), 19.3 (CH_3), 16.7 (CH_3), 11.5 (CH_3); IR (KBr) *v*: 3332, 2926, 1463, 1378, 1230, 1125, 1038, 939, 769, 734 cm^{-1}; HRMS-ESI (*m/z*): $[M+NH_4]^+$ calcd for $C_{10}H_{22}O$: 176.2009, found 176.2009.

(2*R*)-1-Iodo-2,6-dimethyloctane (9)

To a solution of PPh_3 (5.0 g, 18.9 mmol) and imidazole (2.6 g, 37.8 mmol) in anhydrous dichloromethane (60 mL) was added iodine (4.8 g, 18.9 mmol) slowly under argon at 0 ℃. After being stirred at 0 ℃ for 30 min, a solution of (2*R*)-2,6-dimethyloctan-1-ol (1.00 g, 6.3 mmol) in anhydrous DCM (20 mL) was added. The reactant solution was stirred at room temperature for 3 h, quenched with water, evaporated under reduced pressure to remove most of the organic solvent, diluted with water, and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (petroleum ether) to afford **9** (1.40 g, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.23 (dd, J＝9.5, 4.4 Hz, 1H), 3.15 (dd, J＝9.5, 6.1 Hz, 1H), 1.51－1.40 (m, 1H), 1.39－1.05 (m, 9H), 0.97 (d, J＝6.5 Hz, 3H), 0.86 (t, J＝7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.9 (CH_2), 36.7 (CH_2), 34.9 (CH_2), 34.4 (CH), 29.6 (CH_2), 24.5 (CH_2), 20.8 (CH_3), 19.3 (CH_3), 18.2 (CH_2), 11.6 (CH_3); IR (KBr) *v*: 2959, 2926, 2872, 1460, 1425, 1378, 1324, 1234, 1193, 605, 586 cm^{-1}; HRMS-EI (*m/z*): M^+ calcd for $C_{10}H_{21}I$: 268.0688, found 268.0690.

(5*R*)-5,9-Dimethylundec-1-ene (10)

To a solution of **9** (1.00 g, 3.7 mmol) and CuI (106 mg, 0.6 mmol) in anhydrous THF (30 mL) was added allylmagnesium bromide (9.3 mL, 1.0 mol/L in ether) slowly under argon at −78 ℃. After the addition was complete, the reaction mixture was maintained at 0 ℃ for 2 h and quenched with saturated aqueous solution of NH_4Cl and filtered. The filtrate was diluted with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford light yellow oil, which was purified by flash column chromatography on silica gel (petroleum ether) to afford **10** (0.60 g, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88－5.75 (m, 1H), 4.97 (dd, J＝29.0, 13.6 Hz, 2H), 1.94－2.14 (m, 2H), 1.48－0.98 (m, 12H), 0.86 (t, J＝7.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.6 (CH), 114.1 (CH_2), 37.5 (CH_2), 37.2 (CH_2), 36.5 (CH_2), 34.6 (CH), 32.5 (CH), 31.6 (CH_2), 29.7(CH_2), 24.6 (CH_2), 19.7 (CH_3), 19.4 (CH_3), 11.6 (CH_3); IR (KBr) *v*: 3078, 2927, 1641, 1462, 1378, 992, 909 cm^{-1}; HRMS-EI (*m/z*): M^+ calcd for $C_{13}H_{26}$: 182.2035, found 182.2043.

(4*R*,8*S*/*R*)-4,8-Dimethyldecanal (1)

To a solution of compound **10** (0.500 g, 2.7 mmol) in MeOH (15 mL) and DCM (15 mL) was inlet ozone at −78 ℃ until the reactant solution turned blue. Then it was added Me_2S (1 mL, 13.5 mmol) at −78 ℃ and warmed to room temperature and stirred for 5 h. The resulting mixture was washed with water and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford light yellow oil, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 80/1, *V*/*V*) to afford (4*R*,8*S*/*R*)-4,8-dimethyldecanal as colorless oil (0.40 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (t, J＝1.80 Hz, 1H), 2.49－2.30 (m, 2H), 1.71－1.59 (m, 1H), 1.48－1.00 (m, 11H), 0.85 (dd, J＝14.1, 6.7 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.1 (CH), 41.8 (CH_2), 37.1 (CH_2), 36.9 (CH_2), 34.5 (CH), 32.5 (CH), 29.6 (CH_2), 29.0 (CH_2), 24.5 (CH_2), 19.5 (CH_3), 19.3 (CH_3), 11.5 (CH_3); IR (KBr) *v*: 2960, 2927, 2713, 1728, 1462, 1379, 733 cm^{-1}; HRMS-EI (*m/z*): M^+ calcd for $C_{12}H_{24}O$ 184.1827, found 184.1824.

(*R*)-Methyl-5-bromo-4-methylpentanoate (11)

Valerolactone **2** (16.1 g, 0.14 mmol) was dissolved in an acetic acid solution of HBr (33 wt%, 49 mL) and the resulting solution was stirred at 75 ℃ for 4 h. After cooling to room temperature, MeOH (75 mL) was added and the reaction was stirred overnight. The reaction solution was concentrated in vacuo and a saturated aqueous solution of $NaHCO_3$ (80 mL) was added, the mixture was extracted with Et_2O and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford **11** (24.3 g, 83%) as a yellow oil. Known compound. R_f＝0.63 (silica gel, EtOAc/hexane: 1/8); b.p. 42 ℃/10 Pa; $[\alpha]_D^{25}$ ＋2.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.65 (s, 1H), 3.28－3.40 (m, 2H), 2.32 (td, J＝8.2, 2.1 Hz, 2H), 1.74－1.87 (m, 2H), 1.50－1.62 (m, 1H), 1.00 (d, J＝6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 51.5, 40.5, 34.3, 31.4, 29.7, 18.4.; IR (KBr) *v*: 2957, 2876, 1740, 1459, 1437, 1380, 1329, 1234, 1199, 1117, 991,895 cm^{-1}. Anal. calcd for $C_7H_{13}O_2Br$: C 40.21, H 6.27; found C 40.13, H 6.29.

(4*S*,8*R*/*S*)-Methyl-4,8-dimethyldecanoate (13)

Preparation of 3-methylpentylmagnesium bromide (**12**): 3-Methylpentyl bromide (1.816 g, 11 mmol) was dissolved in anhydrous THF (7 mL). To a suspension of magnesium turnings (600 mg, 25 mmol) in anhydrous THF (2 mL) at room temperature were added an iodine pellet and 0.5 mL of the above-mentioned solution. After the reaction was initiated, the residual solution was

added dropwise over 20 min at 50 ℃. The resulting suspension was stirred for 2 h at the same temperature and used directly.

To a solution of bromoester **11** (1.165 g, 5.5 mmol) in anhydrous THF (7 mL) were added Li_2CuCl_4 (0.1 mol/L in THF, 3 mL, 0.3 mmol) and NMP (2 mL, 20 mmol) at room temperature. Then, the freshly prepared **12** (11 mmol) was added dropwise over 30 min and the solution was stirred for another 20 min. Diluted with Et_2O (30 mL), the reaction solution was quenched by saturated NH_4Cl solution. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel to afford **13** (1.043 g, 87%), a mixture of C8-epimers, as a colorless oil. R_f=0.79 (silica gel, EtOAc/hexane: 1/8); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.64 (s, 3H), 2.22−2.36 (m, 2H), 1.62−1.68 (m, 1H), 1.39−1.46 (m, 2H), 1.24−1.32 (m, 6H), 1.02−1.15 (m, 3H), 0.81−0.88 (m, 9H, $3CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 51.6, 37.1, 37.0, 34.5, 32.5, 32.1, 29.7, 29.6, 24.5, 19.4, 19.3, 11.5; IR (KBr) ν: 2958, 2928, 2873, 1743, 1462, 1436, 1378, 1256, 1195, 1170 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 214 (10.37), 157 (64.15), 141 (38.86), 87 (100); HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{13}H_{26}O_2$: 214.1933, found 214.1937.

(4*S*,8*R/S*)-4,8-Dimethyldecan-1-ol

To a suspension of $LiAlH_4$ (246 mg, 6.5 mmol) in dry Et_2O (5 mL) at 0 ℃ was added slowly a solution of **13** (1.40 g, 6.5 mmol) in dry Et_2O (10 mL). After stirred at room temperature for 1 h, the reaction mixture was quenched carefully with Na_2SO_4•$10H_2O$ and water successively, and filtered through celite. The filtrate was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel to afford the title compound (1.14 g, 94%), a mixture of C8-epimers, as a light yellow oil. R_f=0.33 (silica gel, EtOAc/hexane: 1/8); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.59 (t, J=6.7 Hz, 2H), 1.82−1.91 (br, 1H, OH), 1.45−1.63 (m, 2H), 1.22−1.40 (m, 8H), 1.02−1.17 (m, 4H), 0.79−0.89 (m, 9H, $3CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.4, 37.4, 37.1, 34.5, 33.1, 32.8, 30.4, 29.7, 24.6, 19.8, 19.4, 11.5; IR (KBr) ν: 3331, 2927, 1462, 1377, 1058 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 186 (0.2), 140 (56.11), 111 (42.71), 83 (50.89), 69 (100); HRMS-EI (*m/z*): $[M-H_2O]^+$ calcd for $C_{12}H_{26}O$: 168.1878, found 168.1879.

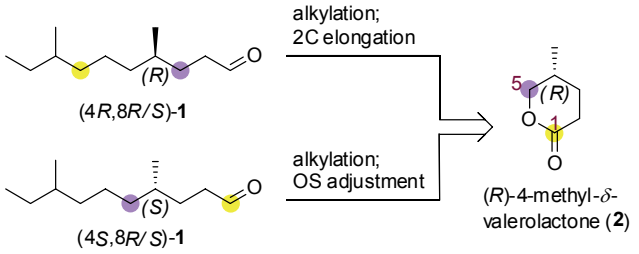
(4*S*,8*R/S*)-4,8-Dimethyldecanal (1)

To a solution of (4*S*)-4,8-dimethyldecan-1-ol (602 mg, 3.2 mmol) in dry DCM (8 mL) were added $PhI(OAc)_2$ (1.25 g, 3.9 mmol) and TEMPO (51 mg, 0.32 mmol) at room temperature. The reaction was stirred for 2.5 h and quenched with saturated $Na_2S_2O_3$ solution. The mixture was extracted with DCM and the combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography to afford (4*S*,8*R/S*)-**1** (590 mg, 99%), a mixture of C8-epimers, as a colorless oil. R_f=0.73 (silica gel, EtOAc/hexane: 1/8); ^{1}H NMR (100 MHz, $CDCl_3$) δ: 9.75 (t, J=1.80 Hz, 1H), 2.49−2.30 (m, 2H), 1.71−1.59 (m, 1H), 1.48−1.00 (m, 11H), 0.85 (dd, J=14.1, 6.7 Hz, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 203.1, 41.8, 37.1, 36.9, 34.5, 32.5, 29.6, 29.0, 24.5, 19.5, 19.5, 19.3, 11.5; IR (KBr) ν: 2959, 2927, 2873, 2713, 1728, 1462, 1378, 733 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 184 (1.97), 111 (66.39), 95 (93.16), 85 (88.87), 55 (100). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{12}H_{24}O$: 184.1827, found 184.1830.

Results and Discussion

As depicted in Scheme 1, our synthesis of **1** started from (*R*)-4-methyl-δ-valerolactone (**2**). For (4*R*,8*R/S*)-**1**, we needed to introduce a *sec*-butyl group at C1 and an acetaldehyde unit at C5, and for (4*R*,8*R/S*)-**1**, we needed to introduce a 3-methylpentyl group at C5 and then adjust the oxidative state of C1. Mixing (4*R*,8*R/S*)-**1** and (4*S*,8*R/S*)-**1** gave tribolure.

Scheme 1 Synthetic plan for tribolure



Scheme 2 summarizes the synthesis of (4*R*,8*R/S*)-**1**. Lactone **2** was prepared according to the reported procedure.[6] We envisioned that an addition of **2** with *sec*-butylmetallic reagent followed by a Clemmensen reduction would give **4** directly. Disappointingly, the reaction of **2** was slow with *sec*-butylmagnesium chloride at low temperature and complex at higher temperature. Using *sec*-butyllithium as nucleophile also failed to give a usable yield of **3**.

We then adopted a less direct approach. By stirring **2** in an acidified dimethoxymethane solution, its lactone ring was opened to afford **5**, which was transformed into iodide **6** through reduction ($LiAlH_4$) and iodination (PPh_3/I_2). A Li_2CuCl_4-catalyzed alkylation[7] of **6** with **7** successfully installed the *sec*-butyl group, giving **8** in 94% yield. The C5 side was treated likewise. Removing the MOM ether on **8** and iodinating the resultant hydroxyl group afforded **9** in good yield. Upon treating with allylmagnesium bromide (**7**) in the presence of copper(I) iodide,[8] **9** was transformed into **11**. Ozonolysis cleaved its double bond to provide (4*R*,8*R/S*)-**1** as an inseparable mixture.

The synthesis of (4*R*,8*R/S*)-**1** was shown in Scheme

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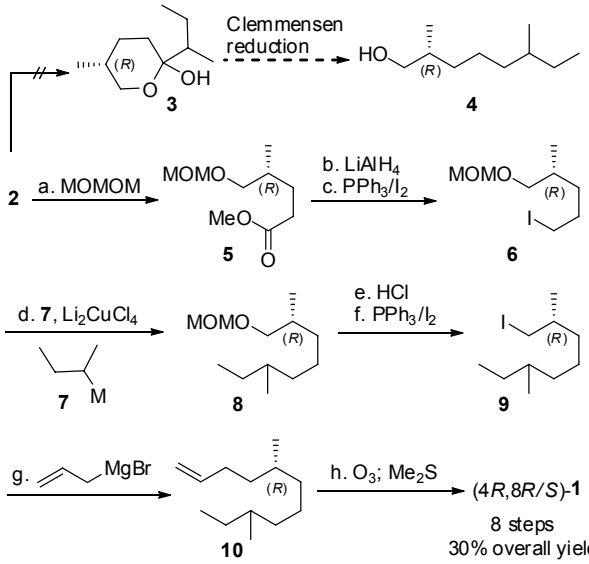
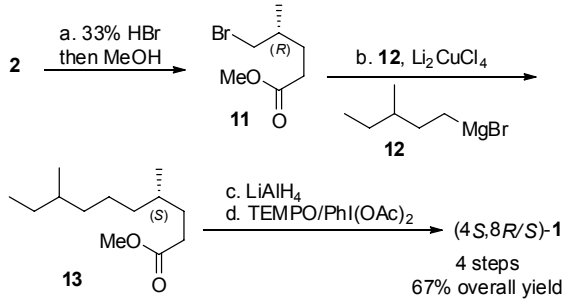
Scheme 2 Synthesis of (4*R*,8*R*/*S*)-tribolure



Conditions and reagents: (a) MOMOM, H_2SO_4, r.t., 5 h; (b) $LiAlH_4$, THF, 0 ℃ to r.t., 1 h, 79% from **2**; (c) PPh_3, I_2, imidazole, CH_2Cl_2, 0 ℃ to r.t., 3 h, 84%; (d) **7**, Li_2CuCl_4, NMP, THF, 0 ℃ to r.t., 1 h, 94%; (e) HCl, MeOH, reflux, 1 h, 83%; (f) PPh_3, I_2, imidazole, CH_2Cl_2, 0 ℃ to r.t., 3 h, 84%; (g) allyl-MgBr, CuI, −78 ℃ to 0 ℃, 2 h, 88%; (h) O_3, MeOH/DCM, −78 ℃, Me_2S, r.t., 5 h, 80%.

Scheme 3 Synthesis of (4*S*,8*R*/*S*)-tribolure



Conditions and reagents: (a) 33% HBr/HOAc, 75 ℃, 4 h, then MeOH, r.t., overnight, 83%; (b) **12**, Li_2CuCl_4, NMP, THF, 0 ℃ to r.t., 4 h, 87%; (c) $LiAlH_4$, THF, 0 ℃ to r.t., 1 h, 94%; (d) TEMPO, $PhI(OAc)_2$, DCM, r.t., 2.5 h, 99%.

3. Upon treating with HBr/HOAc and quenching with MeOH,[9] lactone **2** was converted into bromoester **11** in 83% yield. A chemoselective Cu(I)-catalyzed alkylation[7] of **11** with 3-methylpentylmagnesium bromide (**12**) provided **13** in good yield. Then, **13** underwent an oxidation-reduction process to deliver (4*S*,8*R*/*S*)-**1** as an inseparable mixture.

The analytic data of (4*R*,8*R*/*S*)-**1** and (4*S*,8*R*/*S*)-**1** were virtually identical and matched those of stereoisomers reported by Mori. Although Mori reported that the ^{13}C NMR spectra of the C8-epimers were identical because the stereogenic center was far separated from functional groups, we observed slight differences in the chemical shifts on the ^{13}C NMRs of our samples. Nine peaks were accompanied by twin peaks with similar intensities, indicating a 1/1 ratio of the epimers although the intensities of the peaks on ^{13}C NMR do not strictly reflect the proportions of carbons. Combining (4*R*,8*R*/*S*)-**1** and (4*S*,8*R*/*S*)-**1** in a ratio of 4/1 provided the natural tribolure.

Conclusions

We have accomplished a synthesis of the natural tribolure, the common aggregation pheromone of four *Tribolium* flour beetles. Two remarkable features of our strategy include merging the four isomers of **1** into two synthetic targets and creating both the required C4 stereocenters from (*R*)-4-methyl-*δ*-valerolactone. Not requiring the establishment of the C8 stereocenters, our strategy made the synthesis of the natural tribolure much easier. Syntheses of other natural products containing chiral methyl units are ongoing in this laboratory.

References

[1] (a) Suzuki, T. *Agric. Biol. Chem.* **1980**, *44*, 2519; (b) Suzuki, T. *Agric. Biol. Chem.* **1981**, *45*, 1357; (c) Suzuki, T. *Agric. Biol. Chem.* **1981**, *45*, 2641; (d) Suzuki, T.; Nakakita, H.; Kuwahara, Y. *Appl. Entomol. Zool.* **1987**, *22*, 340.

[2] Arnaud, L.; Lognay, G.; Verscheure, M.; Leenaers, L.; Gaspar, C.; Haubruge, E. *J. Chem. Ecol.* **2002**, *28*, 523.

[3] (a) Mori, K.; Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39*, 2439; (b) Suzuki, T.; Ozaki, J.; Sugawara, R. *Agric. Biol. Chem.* **1983**, *47*, 869; (c) Suzuki, T.; Kozaki, J.; Sugawara, R.; Mori, K. *Appl. Entomol. Zool.* **1984**, *19*, 15; (d) Mori, K.; Kato, M.; Kuwahara, S. *Liebigs Ann. Chem.* **1985**, *1985*, 861; (e) Akhaev, N. S.; Zakladnoy, G. A.; Mavrov, M. V.; Moiseenkov, A. M.; Hao, N. C.; Serebryakov, E. P.; Czeskis, B. A. *Bioorg. Khim.* **1988**, *14*, 243; (f) Cheskis, B. A.; Lebedeva, K. V.; Moiseenkov, A. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1988**, *37*, 745; (g) Mori, K.; Takikawa, H. *Liebigs Ann. Chem.* **1991**, *1991*, 497; (h) Kameda, Y.; Nagano, H. *Tetrahedron* **2006**, *62*, 9751; (i) Santangelo, E. M.; Corrêa, A. G.; Zarbin, P. H. G. *Tetrahedron Lett.* **2006**, *47*, 5135.

[4] (a) Akasaka, K.; Tamogami, S.; Beeman, R. W.; Mori, K. *Tetrahedron* **2011**, *67*, 201; (b) Lu, Y.; Beeman, R.; Campbell, J.; Park, Y.; Aikins, M.; Mori, K.; Akasaka, K.; Tamogami, S.; Phillips, T. *Naturwissenschaften* **2011**, *98*, 755; (c) Mori, K. *Proc. Jpn. Acad. Ser. B* **2014**, *90*, 373.

[5] (a) Tian, W.-S.; Shi, Y. *Prog. Chem.* **2010**, *22*, 538; (b) Huang, X.-G.; Li, T.; Lin, J.-R.; Jin, R.-H.; Tian, W.-S. *Chin. J. Org. Chem.* **2007**, *27*, 428; (c) Li, T.; Huang, X.-G.; Lin, J.-R.; Jin, R.-H.; Tian, W. S. *Acta Chim. Sinica* **2007**, *65*, 1165; (d) Wang, Z.-K.; Tian, W.-S.; Pan, X.-F. *Acta Chim. Sinica* **2007**, *65*, 705; (e) Wang, Z.-K.; Xu, Q.-H.; Tian, W.-S.; Pan, X.-F. *Tetrahedron Lett.* **2007**, *48*, 7549; (f) Wang, Z.-K.; Tian, W.-S.; Pan, X.-F. *Chin. J. Org. Chem.* **2007**, *27*, 866; (g) Song, Z.-J.; Shi, Y.; Jin, R.-H.; Lin, J.-R.; Tian, W.-S. *Chin. J. Chem.* **2012**, *30*, 2595.

[6] Tian, W.-S. *CN1146457* (*A*), **1996** [*Chem. Abstr.* **1998**, *128*, 167599].

[7] Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733.

[8] Wang, Y.; Dong, X.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 3090.

[9] Wolfe, S.; Wilson, M.-C.; Cheng, M.-H.; Shustov, G. V.; Akuche, C. I. *Can. J. Chem.* **2003**, *81*, 937.

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