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Radical mediated stereoselective synthesis of *meso*-7,11-dimethylheptadecane, a female sex pheromone component of the spring hemlock looper and the pitch pine looper

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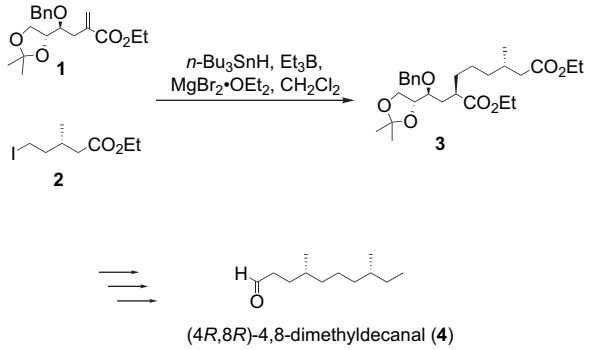
Abstract—*meso*-7,11-Dimethylheptadecane, a female sex pheromone component of the spring hemlock looper and the pitch pine looper, was synthesized from ethyl 2-(bromomethyl)propenoate in nine steps and 14% overall yield. The key step in the synthesis is the highly diastereoselective chelation-controlled radical reaction of diethyl 4-benzyloxy-2,6-dimethyleneheptanedioate with pentyl iodide performed in the presence of 6 equiv of $MgBr_2 \cdot OEt_2$.

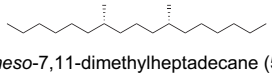
1. Introduction

The stereoselective construction of the 1,5-*syn*-dimethylalkyl motif is of particular interest because of the ubiquitous presence of the structural motif in many natural products such as tocopherols, insect pheromones and membrane lipids of archaebacteria.[1–3] Recently, we reported the stereoselective synthesis of (4*R*,8*R*)-4,8-dimethyldecanal (**4**), a common aggregation pheromone of *Tribolium* flour beetles (Scheme 1).[4] The key step in the synthesis is the highly diastereoselective chelation-controlled radical reaction of ethyl (4*S*,5*R*)-4-benzyloxy-5,6-(isopropylidenedioxy)-2-methylenehexanoate (**1**) with ethyl (*R*)-5-iodo-3-methylpentanoate (**2**) performed in the presence of 7 equiv of $MgBr_2 \cdot OEt_2$ (Scheme 1).[5] The highly *syn*-selective addition of alkyl iodide **2** yielding compound **3** is referred to the H-atom transfer to the outside face of radical centre in the sharply folded seven-membered chelate intermediate.[5c]

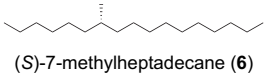


Scheme 1. Stereoselective synthesis of (4*R*,8*R*)-4,8-dimethyldecanal (**4**) via the chelation-controlled diastereoselective radical reaction of α-methylene-γ-oxycarboxylic acid ester **1** with alkyl iodide **2** yielding *syn*-adduct **3**.

7,11-Dimethylheptadecane and 7-methylheptadecane have been reported as female sex pheromone components of the spring hemlock looper (*Lambdina athasaria*) and the pitch pine looper (*Lambdina pellucidaria*), forest pests in northeastern America.[6] All the stereoisomers of the methylated heptadecanes were synthesized and a mixture of *meso*-7,11-dimethylheptadecane, that is (7*R*,11*S*)-7,11-dimethylheptadecane (**5**), and (*S*)-7-methylheptadecane (**6**) was identified as the pheromone of the loopers.[7]



meso-7,11-dimethylheptadecane (**5**)



(*S*)-7-methylheptadecane (**6**)

We now report the radical mediated stereoselective synthesis of *meso*-7,11-dimethylheptadecane (**5**).[8] The pheromone **5**

Keywords: Pheromone; *meso*-7,11-Dimethylheptadecane; Radical reaction; 1,3-Asymmetric induction.
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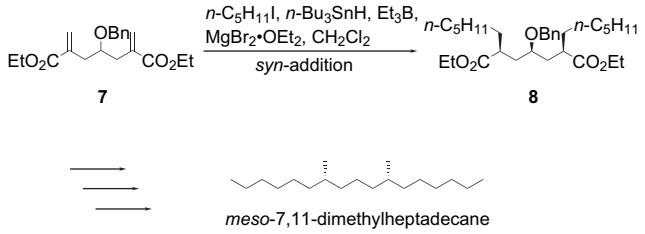
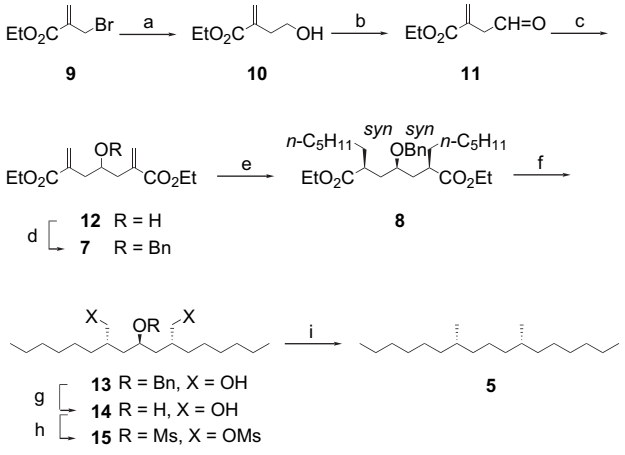
possessing a 1,5-dimethylalkyl motif would be synthesized by using the radical addition of pentyl iodide to diester **7** followed by the reduction of the oxygen functional groups in the radical adduct **8** (Scheme 2). Both the two newly formed hexyl chains located at the positions α to the ethoxy carbonyl groups in **8** are expected to be *syn* to the benzyloxy group.[9,10]



Scheme 2. Synthetic plan of *meso*-7,11-dimethylheptadecane (**5**).

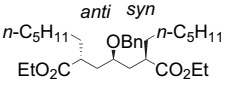
2. Results and discussion

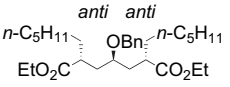
The substrate **7** for the key radical reaction mentioned above was prepared as follows. The Reformatsky reaction of bromomethacrylate **9**[11] and formaldehyde using indium gave alcohol **10**[12] in 79% yield. The oxidation of **10** with pyridinium chlorochromate yielding the corresponding aldehyde **11**, followed by the Reformatsky reaction with bromide **9**, gave hydroxy ester **12** (54% yield for two steps). Treatment of **12** with benzyl 2,2,2-trichloroacetimidate (2 equiv) and trifluoromethanesulfonic acid (0.2 equiv) gave the corresponding benzyl ether **7** in 70% yield (Scheme 3).



Scheme 3. Synthesis of *meso*-7,11-dimethylheptadecane (**5**). Reagents: (a) HCH=O, In, H_2O–EtOH (1:1), 79%; (b) PCC, AcONa, CH_2Cl_2; (c) **9**, Zn, aq NH_4Cl, 54% yield from **10**; (d) BnC(=NH)CCl_3, TfOH, cyclohexane–CH_2Cl_2 (2:1), 70%; (e) *n*-$C_5H_{11}I$, *n*-Bu_3SnH, Et_3B, $MgBr_2\cdot OEt_2$, CH_2Cl_2, −60 °C, 59%, **8**:**16**=>50:1; (f) DIBAL-H, CH_2Cl_2, 91%; (g) H_2, Pd–C, ethanol, 100%; (h) MsCl, pyridine, CH_2Cl_2, 96% and (i) $LiAlH_4$, diethyl ether; 88%.

The radical reaction of **7** with pentyl iodide in the presence of $MgBr_2\cdot OEt_2$ (3 equiv) at 0 °C gave an inseparable diastereomeric mixture of **8** and **16** in 55% yield with a ratio of 11:1.[5] The diastereomeric ratio was determined on the basis of the integration of ^1H NMR signals of benzyl methylene groups [δ 4.43 (major product **8**) and 4.46 (minor product **16**)]. When the amount of the Lewis acid was increased to 6 equiv, the diastereomeric ratio increased to 20:1. Furthermore, when the reaction of **7** using 6 equiv of $MgBr_2\cdot OEt_2$ was performed at −60 °C, adduct **8** was obtained exclusively in 59% yield.





The stereochemistry of the products was assigned on the basis of chemical shift values of the methine protons α to the ester carbonyl groups. The methine proton of *syn*-adduct resonates in lower field than that of *anti*-adduct.[4,5] The signal at δ 2.58 was thus assigned to both the two methine protons in *syn*,*syn*-adduct **8** (major product) and one of the methine protons of *syn*,*anti*-adduct **16** (minor product), while the signal at δ 2.41 was assigned to the other methine proton of *syn*,*anti*-adduct **16**. In this case, *syn*,*syn*, *syn*,*anti* and *anti*,*anti* denote the stereochemical relations between the two hexyl groups and the benzyloxy group. The comparison of the *syn*/*anti* ratio of methine protons with the integration ratio of benzyl methylene signals suggested the formation of two diastereomers **8** and **16**, but not *anti*,*anti*-adduct **17** bearing two hexyl groups *anti* to the benzyloxy group. Furthermore, the ^{13}C NMR spectrum supported the formation of the two diastereomers **8** and **16** (δ 176.1, 75.7, 60.0, 41.6, 37.1, 33.2 for **8** and δ 176.0, 75.6, 60.1, 42.1, 37.0, 33.0 for **16**).

In our previous work,[4,5c] we confirmed the seven-membered chelate ring formation of the starting material **1** by the complexation experiment with $MgBr_2\cdot OEt_2$ in $CDCl_3$. The large difference of chemical shift increments, Δδ values [δ_H (substrate+$MgBr_2\cdot OEt_2$)−δ_H (substrate)] between the diastereotopic β-methylene protons suggests the formation of bidentate complexation. However, in the complexation experiment of **6** with 3 equiv of $MgBr_2\cdot OEt_2$, only slight chemical shift increments were observed. The large $\Delta\delta_H$ values as shown in Figure 1 suggest that the addition of 6 equiv of Lewis acid is required to achieve the chelate

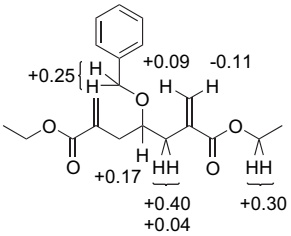


Figure 1. $\Delta\delta_H$ values (ppm) for the substrate **7**. $\Delta\delta_H=\delta_H$ (substrate **7**+6 equiv of $MgBr_2\cdot OEt_2$)−δ_H (substrate **7**). The δ_H values were obtained after sonication of **7** with $MgBr_2\cdot OEt_2$ in $CDCl_3$.

ring formation and the highly diastetreoselective radical addition reaction.

The transformation of diester **8** into the pheromone **5** was performed as follows. The reduction of **8** with diisobutylaluminium hydride (DIBAL-H) gave diol **13** in 90% yield. The hydrogenolysis of the diol over Pd–C gave triol **14** quantitatively. Finally, mesylate **15** derived from the triol in 96% yield was reduced with lithium aluminium hydride to give *meso*-7,11-dimethylheptadecane (**5**) in 88% yield. The ^{1}H and ^{13}C NMR and MS spectral data of the synthetic hydrocarbon **5** were identical with those reported in the literatures.[8]

3. Conclusion

meso-7,11-Dimethylheptadecane, a female sex pheromone component of the spring hemlock looper and the pitch pine looper, has been synthesized from ethyl 2-(bromomethyl)propenoate in nine steps and 14% overall yield. The key step in the synthesis is the highly diastereoselective chelation-controlled radical reaction of diethyl 4-benzyloxy-2,6-dimethyleneheptanedioate with pentyl iodide performed in the presence of 6 equiv of $MgBr_2 \cdot OEt_2$.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a JEOL GSX-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the instrument operating at 100.5 MHz with $CDCl_3$ as the solvent and internal standard (δ 77.0). Mass spectra (EI^+) were obtained on a JEOL JMS-700 mass spectrometer. Precoated Merck Kieselgel 60 F_{254} and Kanto silica gel 60 (spherical neutral) were used for thin layer chromatography and column chromatography, respectively.

4.1.1. Ethyl 2-(2-hydroxyethyl)propenoate (10). To a solution of bromide **9** (200 mg, 1.0 mmol) in a mixture of ethanol–H_2O (1:1; 2 ml) were added formalin (0.18 ml, 1.8 mmol) and indium powder (131 mg, 1.1 mmol), and the mixture was stirred at room temperature for 22 h. Dilute HCl (1 mol/dm^3; 5 ml) was then added. The mixture was stirred for 15 min, and then the product was extracted with ethyl acetate. The organic layer was washed with satd aq $NaHCO_3$ and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel [eluent: AcOEt] to afford ethyl 2-(2-hydroxyethyl)propenoate (**10**) (117 mg, 79% yield) as an oil; ^{1}H NMR δ 6.25 (1H, d, J=1.5 Hz, C=C*H*H), 5.67 (1H, d, J=1.5 Hz, C=CH*H*), 4.23 (2H, q, J=6.8 Hz, C*H*$_2$CH$_3$), 3.75 (2H, q, J=6.3 Hz, C*H*$_2$OH), 2.59 (2H, t, J=6.3 Hz, CH$_2$C*H*$_2$OH), 1.31 (3H, t, J=6.8 Hz, C*H*$_3$); ^{13}C NMR δ 167.2, 137.4, 126.9, 61.5, 60.9, 35.5, 14.1; MS: *m*/*z* 144 (M^+, 1), 114 (100), 99 (36), 86 (66), 68 (33).

4.1.2. Ethyl 2-(formylmethyl)propenoate (11). To a solution of alcohol **10** (760 mg, 5.3 mmol) in dry CH_2Cl_2 (25 ml) were added pyridinium chlorochromate (1.7 g, 7.9 mmol) and sodium acetate (130 mg, 1.6 mmol) at room temperature and the mixture was stirred at room temperature for 4.5 h. The reaction mixture was passed through a short pad of Florisil, and the eluate was concentrated in vacuo until ca. 5 ml. The product containing **11** was used for the next step without further purification.

4.1.3. Diethyl 4-hydroxy-2,6-dimethyleneheptanedioate (12). To a solution of the above aldehyde **11** in THF–satd aq NH_4Cl (1:3; 40 ml) was added bromide **9** (1.49 g, 10.5 mmol) at room temperature. To the suspension cooled to 0 °C was added activated zinc powder (345 mg, 10.5 mmol). After stirring at 0 °C for 10 h, the mixture was extracted with diethyl ether and the organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel [eluent: hexane–AcOEt (1:1)] to afford diethyl 4-hydroxy-2,6-dimethyleneheptanedioate (**12**) (739 mg, 55% yield from alcohol **10**) as an oil; ^{1}H NMR δ 6.27 (2H, d, J=1.5 Hz, =C*H*H×2), 5.68 (2H, d, J=1.5 Hz, =CH*H*×2), 4.22 (4H, q, J=7.3 Hz, CO$_2$CH$_2$×2), 3.95 (1H, m, C*H*OH), 2.64 (1H, d, J=4.2 Hz, OH), 2.58 (2H, dd, J=14.1, 3.9 Hz, C*H*HC=C×2), 2.42 (2H, dd, J=14.1, 8.3 Hz, CH*H*C=C×2), 1.31 (6H, t, J=7.3 Hz, CH$_2$C*H*$_3$×2); ^{13}C NMR δ 167.3, 137.3, 127.5, 69.3, 60.9, 39.9, 14.2; MS *m*/*z* 239 (M^+−OH, 1.4), 211 (M^+−OEt, 5.5), 165 (25), 143 (86), 97 (100), 86 (50).

4.1.4. Diethyl 4-benzyloxy-2,6-dimethyleneheptanedioate (7). To a solution of alcohol **12** (119 mg, 0.47 mmol) in cyclohexane–CH_2Cl_2 (2:1; 4.5 ml) were added benzyl 2,2,2-trichloroacetimidate (0.18 ml, 0.94 mmol) and trifluoromethanesulfonic acid (8 μl, 0.09 mmol) at 0 °C. The solution was stirred at 0 °C for 2.5 h. The product was extracted with diethyl ether and the organic layer was washed with satd aq $NaHCO_3$ and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel [eluent: hexane–AcOEt (10:1)] to afford diethyl 4-benzyloxy-2,6-dimethyleneheptanedioate (**7**) (113 mg, 70% yield) as an oil; ^{1}H NMR δ 7.32–7.22 (5H, m, C$_6$H$_5$), 6.22 (2H, d, J=1.8 Hz, =C*H*H×2), 5.64 (2H, d, J=1.8 Hz, =CH*H*×2), 4.51 (2H, s, C*H*$_2$C$_6$H$_5$), 4.16 (4H, q, J=7.3 Hz, CO$_2$CH$_2$×2), 3.80 (1H, m, OCH), 2.58 (2H, dd, J=13.7, 7.0 Hz, =CH$_2$C*H*H×2), 2.52 (2H, dd, J=13.7, 5.5 Hz, =CH$_2$CH*H*×2), 1.27 (6H, t, J=7.3 Hz, CH$_2$C*H*$_3$×2); ^{13}C NMR δ 166.9, 138.4, 137.3, 128.1, 127.7, 127.3, 76.20, 71.4, 60.7, 37.1, 14.2; MS *m*/*z* 347 (M^++H, 1.7), 254 (9), 239 (19), 233 (47), 91 (100); HRMS calcd for $C_{20}H_{27}O_5$ [M^++H] 347.1858, found 347.1819.

4.1.5. Diethyl (2*R,4*R**,6*S**)-4-benzyloxy-2,6-dihexylheptanedioate (8).** To a solution of ester **7** (173 mg, 0.5 mmol) in dry CH_2Cl_2 (8 ml) was added $MgBr_2 \cdot OEt_2$ (774 mg, 3.0 mmol) and the mixture was stirred at room temperature for 15 min. To the suspension cooled to −60 °C were added pentyl iodide (541 μl, 3.0 mmol), *n*-Bu_3SnH (540 μl, 2.0 mmol) and Et_3B (980 μl, 1.0 mmol). The mixture was stirred at −60 °C for 12 h. KF and water were added and the mixture was stirred at room temperature for 24 h. After filtration, the solvent was evaporated in vacuo and the residue was purified by chromatography on silica

gel [eluent: hexane–AcOEt (20:1)] to afford diethyl (2*R**,4*R**,6*S**)-4-benzyloxy-2,6-dihexylheptanedioate (**8**) (146 mg, 59% yield; diastereomeric ratio: >50:1) as an oil; ^{1}H NMR δ 7.35–7.25 (5H, m, C_6H_5), 4.44 (2H, s, $CH_2C_6H_5$), 4.20–4.10 (4H, m, $CO_2CH_2\times2$), 3.37 (1H, m, OCH), 2.58 (2H, m, $CHCO_2\times2$), 1.87 (2H, ddd, J=14.1, 10.2, 3.9 Hz, OCHC*H*H×2), 1.69–1.54 (4H, m, $C_5H_{11}CHH\times2$, OCHCH*H*×2), 1.45–1.35 (2H, m, $C_5H_{11}CHH\times2$), 1.35–1.20 (16H, m, $C_4H_8CH_3\times2$), 1.21 (6H, t, J=6.8 Hz, $CH_3\times2$), 0.87 (6H, t, J=7.3 Hz, $CH_3\times2$); ^{13}C NMR δ 176.1, 138.4, 128.1, 127.9, 127.3, 75.7, 71.7, 60.0, 41.6, 37.1, 33.2, 31.6, 29.1, 27.1, 22.5, 14.3, 14.1; MS *m*/*z* 491 (M^++H, 0.5), 445 (7), 384 (12), 353 (7), 305 (8), 279 (10), 213 (65), 172 (67), 101 (19), 91 (100); HRMS calcd for $C_{30}H_{51}O_5$ [M^++H] 491.3737, found 491.3714.

4.1.6. (2*R,4*R**,6*S**)-4-Benzyloxy-2,6-dihexylheptane-1,7-diol (13).** To a solution of ester **8** (42.2 mg, 0.086 mmol) in dry CH_2Cl_2 (4 ml) was added DIBAL-H (0.93 mol/dm^3 in hexane; 0.74 ml, 0.69 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. Aq NaOH (10% w/v in water) was added. The product was extracted with diethyl ether and the organic layer was washed with aq NaOH (10% w/v in water) and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel [eluent: hexane–AcOEt (3:1)] to afford (2*R**,4*R**,6*S**)-4-benzyloxy-2,6-dihexylheptane-1,7-diol (**13**) (31.6 mg, 91% yield) as an oil; ^{1}H NMR δ 7.38–7.28 (5H, m, C_6H_5), 4.54 (2H, s, $PhCH_2$), 3.70 (1H, m, OCH), 3.53 (2H, dd, J=11.0, 3.9 Hz, C*H*HOH×2), 3.43 (2H, dd, J=11.0, 6.4 Hz, CH*H*OH×2), 2.39 (2H, br s, OH×2), 1.74–1.64 (4H, m, $OCHCH_2\times2$), 1.64–1.54 (2H, m, $CHCH_2OH\times2$), 1.27 (20H, m, $C_5H_{10}\times2$), 0.88 (6H, t, J=6.8 Hz, $CH_3\times2$); ^{13}C NMR δ 137.5, 128.3, 128.0, 127.8, 75.5, 70.7, 66.1, 37.1, 35.9, 31.84, 31.79, 29.6, 26.9, 22.7, 14.1; MS *m*/*z* 407 (M^++H, 0.1), 297 (12), 252 (9), 155 (61), 91 (100); HRMS calcd for $C_{26}H_{47}O_3$ [M^++H] 407.35.27, found 407.3520.

4.1.7. (2*R,4*R**,6*S**)-2,6-Dihexylheptane-1,4,7-triol (14).** To a solution of diol **13** (172 mg, 0.43 mmol) in dry ethanol (8 ml) was added Pd–C (113 mg). After hydrogenation at room temperature for 24 h, the mixture was filtered through a pad of Celite. The filtrate was evaporated in vacuo to afford (2*R**,4*R**,6*R**)-2,6-dihexylheptane-1,4,7-triol (**14**) (145 mg, quant.) as an oil. The product was used in the next step without further purification. ^{1}H NMR δ 3.99 (1H, m, C*H*OH), 3.66 (2H, dd, J=10.5, 3.2 Hz, C*H*HOH×2), 3.56 (2H, dd, J=10.5, 6.8 Hz, CH*H*OH×2), 1.77 (2H, m, $CHCH_2OH\times2$), 1.66–1.43 (4H, m, $CH_2CHOH\times2$), 1.40–1.20 (20H, m, $C_5H_{10}\times2$), 0.88 (6H, t, J=7.3 Hz, $CH_3\times2$); ^{13}C NMR δ 66.2, 65.2, 40.9, 37.2, 31.9, 31.3, 29.6, 27.3, 22.7, 14.2; MS *m*/*z* 299 (M^+-OH, 7), 173 (23), 155 (100); HRMS calcd for $C_{29}H_{39}O_2$ [M^+-OH] 299.2960, found 299.2953.

4.1.8. (2*R,4*R**,6*S**)-2-Hexyl-4-methanesulfonyloxy-6-(methanesulfonyloxymethyl)dodecyl methanesulfonate (15).** To a solution of triol **14** (32.1 mg, 0.10 mmol) in dry CH_2Cl_2 (1 ml) was added Et_3N (47 μl, 0.33 mmol) at 0 °C. To the mixture was added dropwise methanesulfonyl chloride (26 μl, 0.33 mmol) over 5 min. The resulting mixture was stirred at room temperature for 24 h. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel [eluent: hexane–AcOEt (1:1)] to afford (2*R**,4*R**,6*S**)-2-hexyl-4-methanesulfonyloxy-6-(methanesulfonyloxymethyl)dodecyl methanesulfonate (**15**) (53.1 mg, 96% yield) as an oil; ^{1}H NMR δ 5.01 (1H, m, C*H*OMs), 4.32 (2H, dd, J=10.2, 4.2 Hz, C*H*HOMs), 4.18 (2H, dd, J=10.2, 4.9 Hz, CH*H*OMs), 3.06 (3H, s, OSO_2CH_3), 3.04 (6H, s, $OSO_2CH_3\times2$), 1.95 (2H, m, $CHCH_2OMs\times2$), 1.74 (4H, m, $CH_2COMs\times2$), 1.35–1.22 (20H, m, $C_5H_{10}\times2$), 0.89 (6H, t, J=6.8 Hz, $CH_3\times3$); ^{13}C NMR δ 78.5, 71.3, 38.9, 37.2, 36.9, 34.2, 31.7, 31.5, 29.3, 26.6, 22.6, 14.1.

4.1.9. *meso*-7,11-Dimethylheptadecane (5). To a suspension of lithium aluminium hydride (18.9 mg, 0.46 mmol) in dry ether (0.5 ml) was added a solution of mesylate **15** (28 mg, 0.051 mmol) in dry diethyl ether (1.5 ml) at 0 °C. The mixture was stirred at room temperature, and then water was added. After filtration through a pad of Celite, the filtrate was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo to afford *meso*-7,11-dimethylheptadecane (**5**) (12 mg, 88% yield) as an oil; ^{1}H NMR δ 1.40–1.02 (28H, m), 0.88 (6H, t, J=6.8 Hz, $CH_3\times2$), 0.85 (6H, d, J=6.8 Hz, $CH_3\times2$); ^{13}C NMR δ 37.5, 37.1, 32.8, 32.0, 29.7, 27.1, 24.5, 22.8, 19.8, 14.2; MS *m*/*z* 268 (M^+, 3.5), 266 (5), 253 (3), 239 (3.5), 225 (2), 211 (3), 197 (2), 183 (42), 112 (35), 85 (44), 71 (100); HRMS calcd for $C_{19}H_{40}$ [M^+] 268.3130, found 268.3085.

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