(R)-10-Methyl-2-tridecanone, the female sex pheromone of the southern corn rootworm (Diabrotica undecimpunctata howardi Barber), was synthesized in 9 steps from methyl (S)-3-hydroxy-2-methylpropanoate in a 15.7% overall yield. Olefin cross metathesis between (R)-6-methyl-1-nonene and 5-hexen-2-one employing Grubbs’ first-generation catalyst was the key step of the synthesis.

Key words: Diabrotica undecimpunctata howardi Barber; 10-methyl-2-tridecanone; Grignard coupling; metathesis; pheromone

The development of efficient synthetic methods for the pheromones of insect pests is a valuable task of chemists. Diabrotica undecimpunctata howardi Barber (Coleoptera: Chrysomelidae), known as the southern corn rootworm or cucumber beetle, is an economically important pest. Its female-produced pheromone was identified in 1983 as (R)-10-methyl-2-tridecanone (1) by Guss et al.,12 after examining the pheromone activity of both (R)- and (S)-1 of synthetic origin.3 A number of syntheses of (R)-1 have been reported13,14 since then, including our own.15 Chen and co-workers published in 2009 an asymmetric synthesis of (R)-1 employing a stoichiometric amount of a chiral auxiliary.16

This Note reports our new synthesis of (R)-1 by using olefin cross metathesis8,10 as the key step and employing the readily available chiral building block, methyl (S)-3-hydroxy-2-methylpropanoate (2) as the starting material. The present synthesis is more economical than Chen’s, because no chiral auxiliary is required.

Scheme 1 shows that the target pheromone (R)-1 could be prepared by olefin cross metathesis between (R)-6-methyl-1-nonene (A) and 5-hexen-2-one (B). The former (A) can be synthesized from readily available C (= 2), while the latter (B) is commercially available.

Scheme 2 summarizes the preparation procedure. Methyl (S)-3-hydroxy-2-methylpropanoate (2) was converted to known (S)-3 in a 73% yield as previously reported.11 Chain-extension of (S)-3 to (R)-4 was achieved with ethylmagnesium bromide in the presence of dilithium tetrachlorocuprate in THF under Schlosser conditions12 to give (R)-4 in a 63% yield. In this particular case, 2.8 equivalents of the Grignard reagent and 0.69 mol % of the catalyst were necessary to convert (S)-3 to (R)-4 in an acceptable yield of 63%, presumably due to steric congestion caused by methyl-branching at C-2 of (S)-3. Treatment of (R)-4 with acidic methanol gave alcohol (R)-5. The enantiomeric purity of (R)-5 was estimated as approximately 95% ee by a 1H-NMR analysis of the corresponding Mosher ester [α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)].13 Alcohol (R)-5 was tosylated to give (R)-6. The second chain-extension of (R)-6 with 3-butenyl bromide proceeded smoothly to give (R)-7 (= A) in an 83% yield, employing relatively large amounts of the bromide (2.8 equivalents) and the catalyst (2.0 mol %) based on our previous experience with the conversion of (S)-3.

Olef in cross metathesis between (R)-7 and 5-hexen-2-one (B) was best carried out using an excess (6.2 equivalents) of the latter to fully utilize (R)-7 to give the desired (R)-10-methyl-5-tridecen-2-one (8) as an E/Z-mixture (E/Z = 2 : 1) in a 73% yield based on (R)-7. Hydrogenation of (R)-8 over 10% palladium-charcoal in ethyl acetate finally yielded (R)-10-methyl-2-tridecane none (1) as an oil, [α]D23 = −1.39 (c 4.09, CHCl3) [ref. 5, [α]D20 = −1.4 (c 3.017, CHCl3)]. Its IR and NMR data were identical to those previously reported.2,5 Although direct estimation of the enantiomeric purity of (R)-1 could not be achieved by GC with a chiral stationary phase (Chirami x®), the purity would have been high enough to reflect the high enantiomeric purity of intermediate (R)-5.

In conclusion, female pheromone (R)-1 of the southern corn rootworm was synthesized in nine steps with a 15.7% overall yield, starting from readily available chiral building block (S)-2. The present Note provides another example of the usefulness of the olefin cross metathesis reaction in pheromone synthesis.11,14,15

\[ \text{Scheme 1. Retrosynthetic Analysis of (R)-1.} \]

\[ \text{Scheme 2. Preparation of (R)-1.} \]

\[ \text{Scheme 3. Preparation of (S)-3.} \]
Experimental

All boiling point (bp) data are uncorrected values. Refractive indices (nD) were measured with an Atago DR-M2 refractometer, and optical rotation values were measured with a Jasco P-1020 polarimeter. IR spectra were measured with a Jasco FT/IR-410 spectrometer, and 1H-NMR spectra (400 MHz, TMS at δ = 0.00 as the internal standard) and 13C-NMR spectra (100 MHz, CDCl₃ at δ = 77.0 as the internal standard) were recorded by a Jeol JNM-AL 400 spectrometer. GC-MS data were measured with an Agilent Technologies 5975 Inert XL instrument, and HRMS data were recorded on an Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS instrument. Column chromatography was carried out on Merck Kiesel gel 60 Ar 1.07734.

(R)-2-Methyl-1-pentanol THP ether (4). A solution of 3 (20.0 g, 60.9 mmol) in dry THF (60 mL) was added dropwise to a stirred and cooled solution of ethylmagnesium bromide in Et₂O (2.04 g, 10.7 mmol) in dry THF (80 mL) at −60° to −40° C in an Ar atmosphere. The mixture was poured into an ice-cooled dil. HCl mixture and extracted with Et₂O. The combined Et₂O solution was successively washed with water and brine, dried (MgSO₄), and concentrated in vacuo. The residue (20.2 g) was chromatographed over SiO₂ (150 g). Elution with hexane/EtOAc (15:1) gave 7.09 g (63%) of 4 as an oil, nD₂⁻¹ 1.4385; [α]D₂⁻¹ +0.05 c (3.94, Et₂O); IR νmax (cm⁻¹): 1128 (m, C–O–C), 1080 (m, C–O–C), 1063 (m, C–O–C), 1032 (s, C–O–C); 1H-NMR (CDCl₃, 400 MHz): 0.88–0.94 (6H, m, CH₂ × 2), 1.04–1.14 (1H, m), 1.23–1.45 (3H, m), 1.49–1.62 (4H, m), 1.67–1.78 (2H, m), 1.78–1.88 (1H, m), 3.11–3.26 (1H, m), 3.47–3.63 (2H, m), 3.83–3.90 (1H, m), 4.55–4.58 (1H, m); GC-MS (HP-5MS column, 5% phenylmethylsiloxane, 30.0 × 0.25 mm i.d., 60.7 kPa pressure; 70–230°C + 10°C/min temperature): [α]D = 9.06 min (33.5%) and 9.07 min (65.6%), the diastereomer resulting from stereochirality of the protective group. MS of 4 (former peak, 70 eV, EI): m/z: 185 (0.4) [M⁺ – 1], C₇H₁₄O₂, 115 (8), 101 (9), 85 (100), 56 (18), 43 (24). MS of the latter peak was indistinguishable from that of the former.

(R)-2-Methyl-1-pentanol (5). p-Toluene sulfonic acid monohydrate (2.04 g, 10.7 mmol) was added to a solution of 4 (17.3 g, 92.9 mmol) in methanol (170 mL). The solution was stirred and heated at reflux for 5 h, before being diluted with water and extracted with Et₂O. The combined Et₂O solution was successively washed with NaHCO₃ solution and brine, dried (MgSO₄), and concentrated under atmospheric pressure. The residue (21.2 g) was chromatographed over SiO₂ (190 g), elution with pentane/EtOAc (10:1–3:1) giving 6.78 g (71%) of 5 as a colorless oil. A portion of this oil was distilled to give an analytical sample, bp 91–92°C at 98 Torr. nD₂⁻¹ 1.4153; [α]D₂⁻¹ +13.3 c (4.08, Et₂O); IR νmax (cm⁻¹): 3336 (s, O–H), 3040 (m, C–H), 2960 (m, C–H), 1606 (s, C=O), 1599 ± 10° C at 98 Torr, 1.65–1.67 (1H, m), 1.25–1.44 (4H, m), 1.57–1.67 (1H, m), 3.38–3.54 (2H, m, CH₂OH); GC-MS [same conditions as those for 4]: [M]+ 2.9 min (99.4%). MS of 5 (70 eV, EI): m/z: 101 (1) (M⁺ – 1), C₄H₈O₄, 84 (17), 71 (50), 55 (34), 43 (100). HRMS of 5 [APCI ionization; positive polarity; 6 μA corona current; N₂ (50 psi) nebulizer; N₂ (5 L/min), 350°C) drying gas; 350°C vaporizer; 3500 V capillary current; 0.01 m HCOH₄aq/Methanol (10/90) eluant]: calc. for C₄H₈O₄ [M⁺ + H⁺]: 103.1117; found, 103.1117. The enatiomeric purity of 5 was determined by comparing the 1H-NMR spectrum of the corresponding (R)-MTPA ester (4.5 ± 1.4 ppm, CH₂OMTPA) with that of the (S)-MTPA ester (4.0–4.09 and 4.22–4.26 ppm, CH₂OMTPA). Neither spectrum exhibited any signals from the other isomer, indicating the enantiomeric purity of 5 to be over 95% ee.

(R)-2-Methylpentyl tosylate (6). Toluene chloride (6.08 g, 31.9 mmol) was added portionwise to a stirred and ice-cooled solution of 5 (2.52 g, 25.0 mmol) in dry pyridine (25 mL) at −50° C. After stirring for 3 h at 3−10° C, water was added to the mixture until the precipitate had dissolved, and stirring was continued for 5 min. It was then stirred with an ice-dil. HCl mixture and extracted with Et₂O. The combined Et₂O solution was successively washed with water, a dil. CuSO₄ solution, water, an NaHCO₃ solution and brine, dried (MgSO₄), and concentrated in vacuo. The residue (5.89 g) was chromatographed over SiO₂ (90 g). Elution with hexane/EtOAc (15:1) gave 5.67 g (89%) of 6 as an oil, nD₂⁻¹ 1.4957; [α]D₂⁻¹ +1.91 c (4.09, Et₂O); IR νmax (cm⁻¹): 1599 (m, arom. C=O), 1360 (s, SO₂), 1178 (s, SO₂), 1097 (m, C–O–C), 968 (s), 941 (m), 839 (m), 814 (m), 667 (s), 555 (s); 1H-NMR νH (400 MHz, CDCl₃): 0.84 (3H, t, J = 7.0 Hz, CH₃CH₂), 0.88 (3H, d, J = 6.8 Hz, CH₃CH₂), 1.05–1.35 (4H, m), 1.74–1.83 (1H, m), 2.45 (3H, s, CH₃CH₂), 3.78–3.90 (2H, m, CH₂O(Ts)), 7.34 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.4 Hz).

(R)-6-Methyl-1-nonene (7). A solution of the Grignard reagent (2.8 eq.) was prepared from 3-butenyl bromide (3.27 g, 24.2 mmol) and Mg (0.65 g, 27 mmol) in dry THF (9 mL) in an Ar atmosphere. This was then stirred with pentane/EtOAc (89 mL), and the solution added dropwise to a stirred and cooled solution of 6 (2.22 g, 8.66 mmol) in dry THF (10 mL) at −60° to −40° C in an Ar atmosphere. A solution of Li₂CuCl₄ in THF (1.92 g, 1.37 mmol) was added to a stirred solution of 7; H₂, 10% Pd–C, EtOAc (89%). The combined Et₂O solution was successively washed with water and
brine, dried (MgSO₄), and concentrated under atmospheric pressure. The residue (3.12 g) was chromatographed over SiO₂ (24 g), elution with pentane giving 1.00 g (83%) of 7 as an oil. A portion of this oil was distilled to give an analytical sample, bp 98 °C at 3 Torr; nD₂₀ 1.4387; [α]D²⁰ -1.39 (c 4.09, CHCl₃), ref. 5: [α]D²⁰ -1.4 (c 3.017, CHCl₃); IR νmax (film) cm⁻¹: 1720 (s, C=O), 1466 (m), 1360 (m), 1163 (m), 719 (w); ¹H-NMR δH (400 MHz, CDCl₃): 0.83 (3H, d, J = 6.4 Hz, CH₃); 0.87 (3H, t, J = 6.8 Hz, CH₂CH₃), 1.01–1.14 (2H, m), 1.15–1.43 (13H, m), 1.52–1.62 (2H, t-like), 2.13 (3H, s, COCH₃), 2.42 (2H, t, J = 7.2 Hz, COCH₃); ¹³C-NMR δC (100 MHz, CDCl₃): 14.4, 19.6, 20.1, 23.9, 27.0, 29.2, 29.4, 29.79, 31.2, 34.7, 39.4, 43.8, 209.1 (C=O); GC-MS [same conditions as those for 4]: tR 13.0 min (98.7%). MS of I (70 eV, EI) m/z: 212 (8) [M⁺, C₄H₈O₂], 194 (7), 151 (4), 123 (7), 110 (17), 96 (14), 85 (22), 71 (60), 58 (100), 43 (81). HRMS of I [same conditions as those for 5]: calcd. for C₄H₈O₂ [(M + H)+]: 213.2213; found: 213.2211.

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References