SYNTHESIS
Journal of
Synthetic Organic
Chemistry
REPRINT

With compliments of the Author

Thieme

Syntheses of Aggregation Pheromones of the Palm Weevils *Rhyncophorus vulneratus* and *R. phoenicis* and of (+)-*trans*-Whiskey Lactone

J. S. Yadav,*[a,b] C. Venkateshwar Rao,[a] A. R. Prasad,[a] Ahmad Al Khazim Al Ghamdi[b]

[a] Division of Organic Chemistry I, CSIR, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

[b] Engineer Abdullah Baqshan for Bee Research, King Saud University, Saudi Arabia
Fax +91(40)27160512; E-mail: yadav@iict.res.in

Received 6 August 2011; revised 20 September 2011

Abstract: (3*S*,4*S*)-3-Methyloctan-4-ol, (4*S*,5*S*)-4-methylnonan-5-ol, and (+)-*trans*-whiskey lactone [(4*S*,5*R*)-5-butyl-4-methyldihydrofuran-2(3*H*)-one] were synthesized stereoselectively by using a radical cyclization reaction as a key step. All three molecules were synthesized from a common cyclic acetal intermediate.

Key words: alcohols, pheromones, lactones, radical reactions, stereoselective synthesis

Insect pheromones play a major role in pest-control strategies and are considered to be potential useful tools in integrated pest management, an ecofriendly and environmentally safe agricultural technique that is practiced worldwide. Palm weevils are obnoxious pests of coconut and oil palm crops. Most species produce a single isomer of a methyl-branched secondary alcohol as an aggregation pheromone. Rochat and co-workers[1] isolated and identified (4*S*,5*S*)-4-methylnonan-5-ol (**1**; Figure 1) as the major component of the aggregation pheromone of the male *Rhynchophorus vulneratus,* the Asian palm weevil; the same compound is also a key component of the male pheromones of the taxonomically related *Metamasous hemipterus* (L.), a weevil of the genus Rhynchophornae. *R. phoenicis* (F.),[2] the African palm weevil, secretes (3*S*,4*S*)-3-methyloctan-4-ol (**2**), whereas *R. cruentatus* (F.),[3] the palmetto weevil, secretes (4*S*,5*S*)-5-methyloctan-4-ol. The absolute configuration of the naturally occurring stereoisomer of 4-methylnonan-5-ol (**1**) was established by Oehlschlager and co-workers[4] to be (4*S*,5*S*), and Mori and co-workers[5] synthesized the compound from an epoxy alcohol, whereas Gil and co-workers[6] prepared it by using chiral auxiliary units, according to Evans' method.

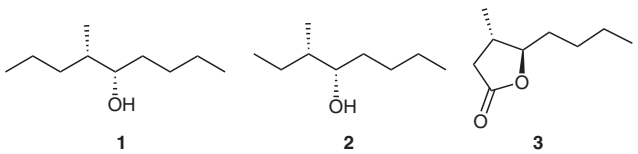
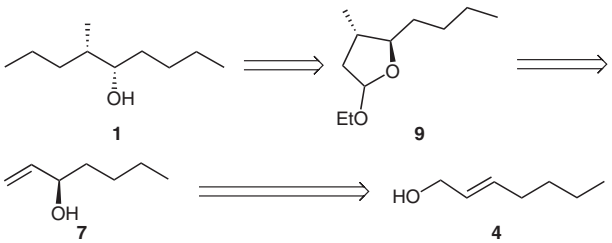


Figure 1 (4*S*,5*S*)-4-methylnonan-5-ol (**1**), (3*S*,4*S*)-3-methyloctan-4-ol (**2**), and (3) (+)-*trans*-whiskey lactone (**3**)

SYNTHESIS 2011, No. 23, pp 3894–3898
Advanced online publication: 27.10.2011
DOI: 10.1055/s-0031-1289579; Art ID: Z77911SS

Structurally simple γ-butyrolactones are widespread naturally occurring substances that occur not only as sex pheromones,[7] but also as key flavor components.[8] The biological activity of these substances is strictly dependent on the absolute configuration of the chiral C-4 carbon atom attached to the lactone ring. (+)-*trans*-Whiskey lactone [(4*S*,5*R*)-5-butyl-4-methyldihydrofuran-2(3*H*)-one] and *cis*-whiskey lactone [(4*S*,5*S*)-5-butyl-4-methyldihydrofuran-2(3*H*)-one] were identified as key aroma components of oak-aged alcoholic beverages, such as whiskey, brandy, or wine.[9a] The two compounds, which are originally components of the oak used in barrels for the alcoholic beverages, are extracted slowly from the oak barrels into the alcoholic beverage during the maturing process. The absolute configuration of the natural *trans*- and *cis*-whiskey lactones were confirmed to be (4*S*,5*R*) and (4*S*,5*S*), respectively, by Masuda and Nashimura.[9b] Although several syntheses of optically active *trans*-whiskey lactone **3** have been reported, most use either a stoichiometric amount of a chiral source as a starting material[10] or require chiral auxiliaries.[11]

As a part of our ongoing work on the synthesis of pheromones,[12] we stereoselectively synthesized (+)-*trans*-whiskey lactone (**3**) and the palm weevil pheromones (3*S*,4*S*)-3-methyloctan-4-ol (**2**) and (4*S*,5*S*)-4-methylnonan-5-ol (**1**) through radical cyclization reactions. Our retrosynthetic analysis is shown in Scheme 1.



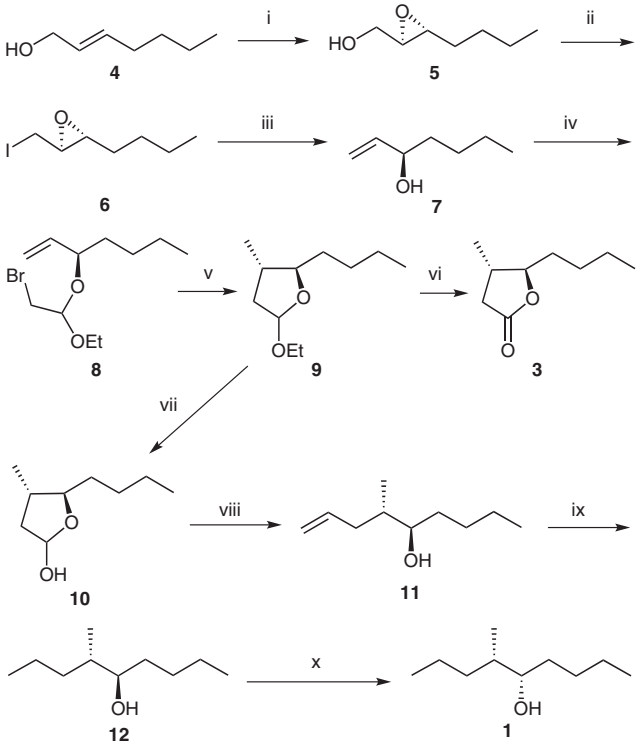
Scheme 1 Retrosynthetic strategy

Our synthesis of (4*S*,5*S*)-4-methylnonan-5-ol (**1**), (3*S*, 4*S*)-3-methyloctan-4-ol (**2**), and (+)-*trans*-whiskey lactone (**3**) began from the readily available allyl alcohol **4** (Scheme 2). Alcohol **4** gave the epoxy alcohol **5** when treated under Sharpless asymmetric epoxidation conditions.[13] Epoxy alcohol **5** was converted into the corresponding iodide **6** by treatment with diiodine, triphenylphosphine, and imidazole at 0 °C.[14] Dehydro-

iodination and ring cleavage of iodide **6** by treatment with zinc and sodium iodide in refluxing methanol gave the desired chiral allylic alcohol **7**.[15]

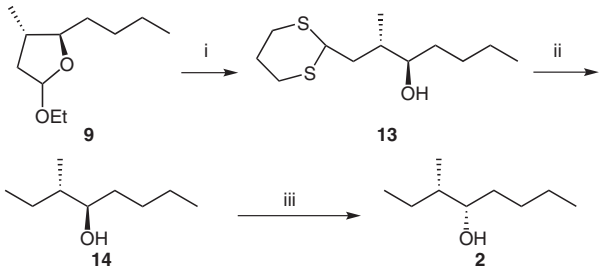
Treatment of allylic alcohol **7** with *N*-bromosuccinimide and ethyl vinyl ether in dichloromethane gave the required bromo acetal **8**.[16] As expected, on treatment with tributylstannane in refluxing toluene with 2,2′-azobis(isobutyronitrile) as the radical initiator, acetal **8** underwent a standard 5-*exo* trig cyclization to give the cyclic ethyl acetal **9** with a preferential *anti*-geometry of the resulting new stereogenic center.[17] The absolute stereochemistry of the new stereogenic center was confirmed by oxidizing the cyclic acetal with Jones reagent to give (+)-*trans*-whiskey lactone (**3**). The ^{1}H and ^{13}C NMR spectra and optical rotation of **3** matched the reported data for (+)-*trans*-whiskey lactone.[10g]

Hydrolysis of ethyl acetal **9** in refluxing 80% acetic acid gave the lactol **10**, which on one-carbon Wittig olefination afforded the homologated derivative **11** in 85% yield. The ^{13}C NMR spectrum and HPLC data confirmed the homogeneity of the new stereogenic center created during the free-radical cyclization. The double bond was reduced in the presence of palladium(II) hydroxide under a hydrogen atmosphere to give the alcohol **12**. Mitsunobu inversion[18] of the free alcohol **12** gave the desired pheromone **1**. The ^{1}H and ^{13}C NMR spectra and the optical rotation of this compound were in complete agreement with those of the natural product.[5a]



Scheme 2 *Reagents and conditions*: (i) D-(–)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –20 °C; (ii) I_2, Ph_3P, imidazole, MeCN–Et_2O (1:3); (iii) Zn, NaI, MeOH, reflux; (iv) NBS, CH_2=CHOEt, CH_2Cl_2; (v) Bu_3SnH, toluene, AIBN, 80 °C; (vi) Jones's reagent, acetone; (vii) 80% acetic acid, reflux; (viii) $Ph_3P^+Me\ I^-$, THF, BuLi, –78 °C; (ix) $Pd(OH)_2$, H_2, MeOH; (x) DEAD, Ph_3P, 4-nitrobenzoic acid, then K_2CO_3, MeOH.

Treatment of the cyclic acetal **9** with propane-1,3-dithiol and boron trifluoride etherate[19] at 0 °C gave the cyclic thioacetal **13**, which on treatment with activated Raney nickel[20] in refluxing methanol gave alcohol **14** in 80% yield. Mitsunobu inversion of the free hydroxyl group by using diethyl azodicarboxylate, triphenylphosphine, and 4-nitrobenzoic acid gave the target molecule (3*S*,4*S*)-3-methyloctan-4-ol (**2**). The spectral data and rotation values matched those of the natural compound.[2] The two pheromones **1** and **2** exhibited excellent electrophysical activities in electroactinographic studies.



Scheme 3 *Reagents and conditions*: (i) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (ii) Raney Ni, MeOH, reflux; (iii) DEAD, Ph_3P, 4-nitrobenzoic acid, THF, then K_2CO_3, MeOH.

To summarize, we have successfully developed a concise, efficient, and highly stereoselective synthesis of the pheromones (4*S*,5*S*) 4-methylnonan-5-ol (**1**) and (3*S*,4*S*) 3-methyloctan-4-ol (**2**) and of (+)-*trans*-whiskey lactone (**3**) by using radical cyclization as the key step. The two pheromones **1** and **2** exhibited excellent electrophysiological activity in electroactinographic studies, and further field trials are in progress.

Optical rotations were measured with a Jasco DIP-360 polarimeter at 20 °C, and IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H NMR spectra were recorded using a Varian Gemini (200 MHz), a Varian Inova (500 MHz), or a Bruker Avance (300 MHz) spectrometer with TMS as an internal standard in $CDCl_3$. EI mass spectra were recorded on Micromass VG-7070 H. High-resolution mass spectra were recorded on a VG-7070 H spectrometer. Elemental analyses were performed on a Vario EL analyzer. Electroactinographic equipment was obtained from Syntech GmbH (Kirchzarten, Germany). GC-MS studies were performed on an Agilent Technologies System 6890N. The progress of all the reactions was monitored by TLC on glass plates precoated with silica gel 60 F_{254} to a thickness of 0.5 mm (Merck). Column chromatography was on columns of silica gel 60–120 mesh with EtOAc–hexane as the eluent. All reactions were carried out under an inert atmosphere unless stated otherwise, following standard syringe–septa techniques. All the solvents were dried by using the standard procedures.

[(2*R*,3*R*)-3-Butyloxiran-2-yl]methanol (5)

A freshly flame-dried, double-necked, round-bottomed flask was charged with activated 4-Å MS (~5 g) and anhyd CH_2Cl_2 (150 mL) at –20 °C. Ti(O-*i*-Pr)$_4$ (0.358 g, 1.26 mmol) and D-(–)-DIPT (0.355 g, 1.51 mmol) were added and the mixture was stirred for 20 min. A soln of allylic alcohol **4** (2.88 g, 25.2 mmol) in CH_2Cl_2 (20 mL)

was added, followed after an interval of 20 min by a 3.7 M soln of *t*-BuOOH in toluene (13.6 g, 50.5 mmol). Stirring was continued until the reaction was complete (4 h). The mixture was then warmed to 0 °C, quenched with H_2O (20 mL), and stirred vigorously for 30 min. It was then filtered through a sintered funnel, and the filtrate was stirred with 20% aq NaOH (5 mL) saturated with solid NaCl. The biphasic soln was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a crude residue that was purified by column chromatography to give a colorless oil; yield: 2.7 g (85%); $[\alpha]_D^{25}$ +26.87 (*c* 0.9, $CHCl_3$).

IR (neat): 3550, 2929, 2860, 1602, 1453, 1276, 1096, 912, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.95 (t, *J* = 6.7 Hz, 3 H), 1.10–1.50 (m, 6 H), 2.80–3.00 (m, 2 H), 3.50–4.00 (m, 2 H).

MS (EI): *m/z* = 130 [M^+].

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84; Found: C, 64.56; H, 10.81.

(2*R*,3*S*)-2-Butyl-3-(iodomethyl)oxirane (6)

Imidazole (3.27 g, 51.9 mmol), I_2 (10.5 g, 41.5 mmol), and Ph_3P (10.88 g, 41.5 mmol) were added successively to a soln of alcohol **5** (2.7 g, 20.7 mmol) in 1:3 MeCN–Et_2O (100 mL) at 0 °C under N_2, and the mixture was stirred for 20 min. The resulting soln was diluted with cool Et_2O (200 mL) and filtered through a sintered funnel. The residue was washed with anhyd Et_2O (2 × 25 mL) and the combined filtrates were concentrated under reduced pressure. The crude product was passed through a pad of silica gel to give a colorless liquid; yield: 4.56 g (92%); $[\alpha]_D^{25}$ +6.5 (*c* 1.5, $CHCl_3$).

IR (neat): 3087, 2921, 1496, 1455, 1092, 1027, 894 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.95 (t, *J* = 6.7 Hz, 3 H), 1.10–1.50 (m, 6 H), 2.80–3.00 (m, 2 H), 3.50–4.00 (m, 2 H).

MS (EI): *m/z* = 240 [M^+].

Anal. Calcd for $C_7H_{13}IO$: C, 35.02; H, 5.46; Found: C, 35.00; H, 5.45.

(3*R*)-Hept-1-en-3-ol (7)

A mixture of iodo compound **6** (4.5 g, 18.8 mmol), NaI (5.64 g, 37.6 mmol), and freshly activated Zn (2.98 g, 47.0 mmol) in anhyd MeOH (30 mL) was refluxed for 8 h under N_2. The soln was filtered and the residue was washed with MeOH (2 × 15 mL). The filtrates were combined and concentrated. The residue was taken up in EtOAc (30 mL), washed successively with H_2O (2 × 10 mL) and brine (1 × 10 mL), and then dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified by column chromatography to give a colorless liquid; yield: 1.93 g (90%); $[\alpha]_D^{25}$ –21.5 (*c* 1.04, EtOH) {Lit.[21] $[\alpha]_D^{21}$ –21.6 (*c* 1.02)}.

IR (neat): 3440, 3031, 2862, 1954, 1602, 1493, 1207, 1091 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.94 (t, *J* = 6.7 Hz, 3 H), 1.20–1.41 (m, 4 H), 1.40–1.55 (m, 2 H), 4.05 (q, *J* = 3.0, 9.3 Hz, 1 H), 5.10–5.25 (dd, *J* = 8.2, 14.5 Hz, 2 H), 5.80–5.91 (m, 1 H).

MS (EI): *m/z* = 114 [M^+].

GC-MS: *m/z* = 115 [M + H]$^+$.

(3*R*)-3-(2-Bromo-1-ethoxyethoxy)hept-1-ene (8)

NBS (4.34 g, 24.1 mmol) was added to a stirred soln of CH_2=CHOEt (3.15 g, 43.8 mmol) and allyl alcohol **7** (2.5 g, 21.9 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C, and the mixture was stirred until the reaction was complete (8–9 h). The mixture was washed with successively with H_2O (2 × 30 mL) and brine (1 × 30 mL) then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography to give a colorless liquid; yield: 4.7 g (81%).

IR (neat): 2932, 1423, 1114, 1026, 927, 675 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.95 (t, *J* = 6.7 Hz, 3 H), 1.15–1.60 (m, 9 H), 3.30 (d, *J* = 4.9 Hz, 2 H), 3.60 (m, 2 H), 3.95 (m, 1 H), 4.70 (m, 1 H), 5.20 (m, 2 H), 5.60–5.80 (m, 1 H).

MS (EI): *m/z* = 267 [M + 2 H]$^+$.

Anal. Calcd for $C_{11}H_{21}BrO_2$: C, 49.82; H, 7.98; Found: C, 49.30; H, 8.22.

(2*R*,3*S*)-2-Butyl-5-ethoxy-3-methyltetrahydrofuran (9)

A soln of Bu_3SnH (4.92 g, 16.9 mmol) and a catalytic amount of AIBN in toluene (5 mL) was added to a soln of bromoacetal **8** (4.5 g, 16.9 mmol) in refluxing anhyd toluene (35 mL) under N_2. After 2 h, the soln was cooled to r.t. and passed through a column of silica gel column to give a colorless oil; yield: 2.82 g (90%).

IR (neat): 2929, 2870, 1606, 1455, 1372, 1097, 991, 795, 697 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (t, *J* = 6.7 Hz, 3 H), 1.05 (d, *J* = 6.0 Hz, 3 H), 1.19 (t, *J* = 6.7 Hz, 3 H), 1.25–1.62 (m, 8 H), 2.10 (m, 1 H), 3.28–3.49 (m, 2 H), 3.70 (m, 1 H), 4.90–5.09 (m, 1 H).

MS (EI): *m/z* = 188 [M^+].

(4*S*,5*R*)-5-Butyl-4-methyldihydrofuran-2(3*H*)-one [(+)-*trans*-Whiskey Lactone] (3)

Jones's reagent was added dropwise to an ice-cooled soln of cyclic acetal **9** (400 mg) in acetone (20 mL) at 0 °C until the color of the reagent persisted. The mixture was then stirred for 1 h at r.t., then concentrated under reduced pressure to remove acetone. The resulting residue was diluted with H_2O (10 mL) and extracted with Et_2O (2 × 20 mL). The extracts were dried (Na_2SO_4), concentrated, and purified by column chromatography to give a colorless oil; yield: 240 mg (80%); $[\alpha]_D^{25}$ +76.8 (*c* 1.01, MeOH), {Lit.[10g] $[\alpha]_D^{19}$ +79 (*c* 1.04, MeOH)}.

IR (neat): 2933, 1781, 1458, 1211, 1171, 985, 476 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (t, *J* = 6.7 Hz, 3 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.30–1.75 (m, 6 H), 2.20 (m, 2 H), 2.55–2.62 (m, 1 H), 3.99 (dt, *J* = 4.0, 7.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.89, 17.65, 22.55, 28.01, 33.5, 36.19, 37.21, 87.56, 176.56.

MS (EI): *m/z* = 156 [M^+].

HRMS (EI): *m/z* calcd for $C_9H_{16}O_2$: 156.2265; found: 156.2267.

(4*S*,5*R*)-5-Butyl-4-methyltetrahydrofuran-2-ol (10)

A soln of ethyl acetal **9** (1.5 g, 7.5 mmol) in 80% aq AcOH (15 mL) was refluxed for 4 h then cooled to 0 °C, neutralized with solid $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed successively with H_2O (2 × 10 mL) and brine (1 × 10 mL) then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography to give a colorless liquid; yield: 0.96 (76%).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.95 (d, *J* = 6.0 Hz, 3 H), 1.06 (t, *J* = 6.7 Hz, 3 H), 1.24–1.62 (m, 6 H), 1.70 (m, 1 H), 2.10–2.40 (m, 2 H), 3.45 (m, 1 H), 3.92 (br s, 1 H), 4.85–4.99 (m, 1 H).

MS (EI): *m/z* = 158 [M^+].

(4*S*,5*R*)-4-Methylnon-1-en-5-ol (11)

t-BuOK (1.41g, 12.6 mmol) was added to $Ph_3P^+Me\ I^-$ (6.12 g, 15.1 mmol) in anhyd THF (40 mL) under N_2 at –78 °C. After 30 min, a soln of furanol **11** (0.8 g, 5.0 mmol) in anhyd THF (5 mL) was added from a cannula to the orange-yellow turbid mixture, and the resulting mixture was stirred for 8 h while the temperature increased to 0 °C. The reaction was then quenched with sat. aq NH_4Cl (15 mL). The mixture was filtered through a sintered funnel and the residue was washed with Et_2O (3 × 15 mL). The combined organic filtrates were washed successively with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and filtered. The residue was purified by col-

umn chromatography to give a colorless liquid; yield: 0.59 g (76.2%); $[\alpha]_D^{25}$ +18.1 (*c* 1.3, MeOH).

IR (neat): 3417, 2958, 2932, 2862, 1467, 1233, 1023, 878, 755, 640 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (d, *J* = 6.7 Hz, 3 H), 0.95 (t, *J* = 6.7 Hz, 3 H), 1.23–1.49 (m, 6 H), 1.6 (m, 1 H), 1.92 (m, 1 H), 2.30 (m, 1 H), 3.38 (m, 1 H), 4.90–5.50 (m, 2 H), 5.68–5.83 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.06, 15.41, 22.75, 28.09, 33.37, 36.78, 38.64, 75.62, 115.85, 137.57.

MS (EI): *m/z* = 155 $[M - H]^+$.

GC-MS: *m/z* = 155 $[M - H]^+$.

(4*S*,5*R*)-4-Methylnonan-5-ol (12)

10% $Pd(OH)_2$ (50 mg) was added to a soln of enol **11** (500 mg) in anhyd EtOAc (5 mL), and the mixture was stirred under H_2 until the starting material was completely consumed. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure at low temperature to give a colorless oil; yield: 470 mg (92.8%); $[\alpha]_D^{25}$ +9.6 (*c* 0.60, EtO_2).

IR (neat): 3417, 2958, 2932, 2862, 1467, 1233, 1023, 878, 755, 640 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, *J* = 6.7 Hz, 3 H), 0.90 (t, *J* = 7.1 Hz, 3 H), 0.92 (t, *J* = 7.1 Hz, 3 H), 1.16–1.52 (m, 11 H), 1.55 (br s, 1 H), 3.35 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.08, 14.40, 15.2, 20.4, 22.8, 28.3, 33.05, 34.1, 38.55, 75.2.

MS (EI): *m/z* = 157 $[M - H]^+$.

GC-MS: *m/z* = 157 $[M - H]^+$.

(4*S*,5*S*)-4-Methylnonan-5-ol (1)

A soln of Ph_3P (1.32 g, 5.0 mmol) and DEAD (0.90 g, 5.1 mmol) in anhyd THF (7 mL) was added to a soln of alcohol **12** (400 mg, 2.5 mmol) in anhyd THF (7 mL) at 0 °C. After 30 min, 4-$O_2NC_6H_4CO_2H$ (0.42 g, 5.05 mmol) was added and the mixture was stirred until the reaction was complete. The mixture was then washed with H_2O (2 × 20 mL), extracted with EtOAc (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash column chromatography, and the resulting ester was deprotected by treatment with K_2CO_3 (0.698 mg, 5.06 mmol) in MeOH (10 mL) at 20 °C for 3 h to give the free alcohol. Residual solid K_2CO_3 was filtered off, and the filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography to give a colorless liquid; yield: 250 mg (62.5%); $[\alpha]_D^{25}$ –25.4 (*c* 1.25, Et_2O) {Lit.[5a] $[\alpha]_D^{19}$ –26.5 (*c* 88, Et_2O)}.

IR (KBr): 3380, 2980, 2932, 2875, 1461, 1118, 1001, 643 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.86 (d, *J* = 6.0 Hz, 3 H), 0.90 (t, *J* = 6.78 Hz, 3 H), 0.92 (t, *J* = 6.72 Hz, 3 H), 1.25–1.42 (m, 10 H), 1.42–1.46 (m, 1 H), 1.55 (br s, 1 H, OH), 3.50 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.8, 14.1, 14.2, 20.5, 22.85, 28.5, 34.1, 35.8, 38.0, 75.2.

MS (EI): *m/z* = 158 $[M^+]$.

GC-MS: *m/z* = 158 $[M^+]$.

Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01; Found: C, 75.91; H, 14.08.

(2*S*,3*R*)-1-(1,3-Dithian-2-yl)-2-methylheptan-3-ol (13)

A soln of cyclic acetal **9** (600 mg, 3.2 mmol), in anhyd CH_2Cl_2 was combined with an equimolar amount of propane-1,3-dithiol (0.348 g, 3.2 mmol) at r.t. The mixture was immediately cooled in an ice bath and then $BF_3{\cdot}OEt_2$ (0.045 g, 32 mmol) was added. The mixture was then allowed to warm to r.t. and, when the reaction was complete, washed successively with H_2O (2 × 10 mL), 10% aq KOH (15 mL), and H_2O (2 × 10mL) then dried (K_2CO_3). Evaporation of the solvent and purification by column chromatography gave a colorless liquid product; yield: 500 mg (62.5%); $[\alpha]_D^{25}$ –10.2 (*c* 1.01, MeOH).

IR (neat): 3446, 2931, 1457, 1274, 983, 475 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (t, *J* = 6.69 Hz, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 1.25–1.65 (m, 8 H), 1.80–1.95 (m, 3 H), 2.08–2.19 (m, 1 H), 2.75–2.85 (m, 4 H), 3.40 (m, 1 H), 4.00–4.11 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.01, 15.8, 22.6, 25.99, 28.1, 30.13, 30.5, 33.4, 35.5, 37.4, 45.64, 75.7.

GC-MS: *m/z* 248 $[M]^+$.

HRMS: *m/z* calcd for $C_{12}H_{24}S_2O$: 248.4525, found: 248.4521.

(3*S*,4*R*)-3-Methyloctan-4-ol (14)

A soln of thioacetal **13** (450 mg 1.8 mmol) in EtOH (15 mL) was added to activated Raney Ni (900 mg) in EtOH (15 mL), and the mixture was refluxed under N_2 until the starting material was consumed. The mixture was then cooled to r.t., filtered, and purified by column chromatography to give a colorless liquid; yield: 300 mg (76.9%); $[\alpha]_D^{25}$ +10.2 (*c* 1.02, EtO_2).

IR (neat): 3370, 2960, 1461, 1317, 1001, 643 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.80–1.10 (m, 9 H), 1.20–1.82 (m, 9 H), 3.42 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.01, 14.2, 14.89, 22.91, 24.91, 28.6, 33.2, 39.5 and 75.9.

GC-MS: *m/z* = 143 $[M- H]^+$.

Anal. Calcd for $C_9H_{20}O$: C, 74.93; H, 13.97; Found: C, 74.85; H, 13.99.

(3*S*,4*S*)-3-Methyloctan-4-ol (2)

A soln of Ph_3P (0.72 g, 2.7 mmol) and DEAD (0.48 g, 2.7 mmol) in anhyd THF (7 mL) was added to a soln of alcohol **14** (200 mg, 1.3 mmol) in anhyd THF (7 mL) at 0 °C. After 30 min, 4-$O_2NC_6H_4CO_2H$ (0.46 g, 2.7 mmol) was added and the mixture was stirred until the reaction was complete. The mixture was then washed with H_2O (2 × 15 mL) and extracted with EtOAc (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash column chromatography, and the resulting ester was deprotected by treatment with K_2CO_3 (0.38 g, 2.77 mmol) in MeOH (10 mL) at 20 °C for 3 h to give the free alcohol. Residual solid K_2CO_3 was filtered off, and the filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography to give a colorless liquid; yield: 120 mg (60%); $[\alpha]_D^{25}$ –20.2 (*c* 1.1, Et_2O) {Lit.[2] $[\alpha]_D^{19}$ –20.7 (*c* 1.01, Et_2O)}.

IR (neat): 3380, 2980, 2932, 2875, 1461, 1118, 643 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.86 (d, *J* = 6.08 Hz, 3 H), 0.90 (t, *J* = 6.78 Hz, 3 H), 0.92 (t, *J* = 6.72 Hz, 3 H), 1.00–1.16 (m, 1 H), 1.25–1.42 (m, 8 H), 1.55 (br s, 1 H), 3.50 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.9, 13.2, 14.1, 22.8, 26.1, 28.5, 34.3, 40.0, 74.9.

MS (EI): *m/z* = 144 $[M^+]$.

GC-MS: *m/z* = 143 $[M + 1]^+$.

Anal. Calcd for $C_9H_{20}O$: C, 74.93; H, 13.97; Found: C, 74.88; H, 14.03.

Acknowledgment

C.V.R. thanks CSIR, New Delhi for the award of a fellowship. The authors acknowledge partial support from King Saud University for Global Research Network for Organic Synthesis (GRNOS).

References

(1) Rochat, D.; Malosse, C.; Lettere, M.; Ramirez-Lucas, P.; Einhorn, J.; Zagatti, P. *C. R. Acad. Sci., Ser. II* **1993**, *316*, 1737.
(2) Mori, K.; Kiyota, H.; Rochat, D. *Liebigs Ann. Chem.* **1993**, 865.
(3) Weissling, T. J.; Giblin-Davis, R. M.; Gries, G.; Perez, A. L.; Pierce, H. D. Jr.; Oehlschlager, A. C. *J. Chem. Ecol.* **1994**, *20*, 505.
(4) Perez A. L., Gries R., Gries G., Hallett R. H., Oehlschlager A. C., Pierce H. D. Jr., Gonzalez L. M., Borden J. H., Giblin-Davis R. M.; In *Abstracts of Papers*, Tenth Annual Meeting of the International Society of Chemical Ecology, Tampa, FL (USA), July 31–August 4, 1993; p. 54.
(5) (a) Mori, K.; Kiyota, H.; Malosse, C.; Rochat, D. *Liebigs Ann. Chem.* **1993**, 1201. (b) Mori, K.; Murata, N. *Liebigs Ann.* **1995**, 697.
(6) Odriozola, M. J.; Garcia, M. J.; González, A.; Gil, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4627.
(7) (a) Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 431. (b) Ho, T.-l. *Synth. Commun.* **1983**, *13*, 341.
(8) (a) Brand, J. M.; Young, J. C.; Silverstein, R. M. *Fortschr. Chem. Org. Naturst.* **1979**, *37*, 1. (b) Mori, K.; Ebata, T.; Takechi, S. *Tetrahedron* **1984**, *40*, 1761.
(9) (a) Otsuka, K.; Zenibayashi, Y.; Itoh, M.; Totsuka, A. *Agric. Biol. Chem.* **1974**, *50*, 485; and references cited therein. (b) Masuda, M.; Nishimura, K. *Chem. Lett.* **1981**, 1333.
(10) (a) Marino, J. P.; de la Pradilla, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381. (b) Gunther, C.; Mosandl, A. *Liebigs Ann. Chem.* **1986**, *12*, 2112. (c) Beckmann, M.; Hildebrandt, H.; Winterfeldt, E. *Tetrahedron: Asymmetry* **1990**, *1*, 335. (d) Sharma, G. V.; Vepachedu, S. R.; Chandrasekhar, S. *Synth. Commun.* **1990**, *20*, 3403. (e) Miata, O.; Shinada, T.; Kawakami, N.; Taji, K.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K. *Chem. Pharm. Bull.* **1992**, *40*, 2579. (f) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (g) Ebata, T.; Matsumoto, K.; Yoshikoshi, H.; Koseki, K.; Kawakami, H.; Okano, K.; Matsushita, H. *Heterocycles* **1993**, *36*, 1017. (h) Katsuji, I.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905. (i) Hisashi, N.; Katsuji, I.; Tsutomu, K. *Tetrahedron: Asymmetry* **1998**, *9*, 1165.
(11) (a) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603. (b) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004. (c) Pai, Y.-C.; Fang, J.-M.; Wu, S.-H. *J. Org. Chem.* **1994**, *59*, 6018. (d) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123. (e) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628.
(12) (a) Yadav, J. S.; Jagan Reddy, E.; Ramalingam, T. *New J. Chem.* **2001**, *25*, 223. (b) Yadav, J. S.; Valli, M. Y.; Prasad, A. R. *Tetrahedron* **1998**, *54*, 7551. (c) Yadav, J. S.; Reddy, K. V.; Chandrashekar, S. *Synth. Commun.* **1998**, *28*, 4249. (d) Yadav, J. S.; Deshpande, P. K. *Tetrahedron* **1992**, *48*, 4465. (e) Yadav, J. S.; Rao, E. S. *Synth. Commun.* **1989**, *19*, 705. (f) Yadav, J. S.; Deshpande, P. K.; Reddy, E. R. *Synth. Commun.* **1989**, *19*, 125.
(13) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc* **1987**, *109*, 5765.
(14) Garegg, P. J.; Samuelson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
(15) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okwara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351.
(16) Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, J. *Tetrahedron Lett.* **1984**, *25*, 2069.
(17) (a) Yadav, J. S.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, *23*, 1824. (b) Stork, G.; Mook, R. Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(18) Mitsunobu, O. *Synthesis* **1981**, 1.
(19) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.
(20) Fujisawa, T.; Mobele, I. B.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 5567.
(21) Suzuki, H.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1987**, 3369.