Tetrahedron: *Asymmetry* 23 (2012) 1410–1415

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective synthesis of the essential oil and pheromonal component *ar*-himachalene by a chiral pool and chirality induction approach

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ARTICLE INFO

Article history:
Received 11 August 2012
Accepted 12 September 2012

ABSTRACT

The enantioselective synthesis of both isomers of *ar*-himachalene has been achieved starting from enantiomerically pure citronellal and *p*-methyl α-methyl styrene as an application of a chiral pool and chirality induction approach, respectively. The key reactions involved in the synthesis include the Sharpless asymmetric dihydroxylation for the induction of chirality at benzylic carbon bearing the methyl group and the use of a hypervalent iodine reagent or trimethylsilyldiazomethane ($TMSCHN_2$) for the six to seven membered ring expansion.

1. Introduction

A large number of naturally occurring sesquiterpenes are known in the literature, which possess a broad range of applications in drugs, pharmaceuticals, rubber, paints, perfumery, agriculture, and so on. Many methods have been reported for the synthesis of this class of natural products. Himachalene is a structurally and biologically important class of the naturally occurring sesquiterpene hydrocarbons containing the synthetically challenging benzo[7]annulene ring system.[1] They are found as essential oil components in several cedar woods (Fig. 1), which include *Cedrus deodara* Loud, *Cedrus atlantica*, and *Cedrus libani*[2] found in Himalayan and Morroccon forests. The essential oil and different constituents of *C. deodara* account for the insecticidal and larvicidal action and therefore their use in pest management.[3] Himachalene was also isolated as a male specific aggregation pheromonal component of the flea beetles, *Aphthona flava* and *Phyllotreta cruciferae* (Fig. 1).[4] These aggregation pheromones, which are typically produced by only one sex but attract both sexes, have become important scientific tools for monitoring and managing economically important insects. However, only the (*R*)-enantiomer of *ar*-himachalene exhibits the desired pheromonal activity,[5] which intrinsically requires the compound to be used in enantiomerically pure form. Although (*R*)-*ar*-himachalene can be used under field experiments for the control of economically important insects, it constitutes only 0.5% of the total oil of *Aphthona flava*,[4] and this shows the need for the development of its chemical synthesis. In recent times, several himachalene type sesquiterpenes have gained attention because of the revision of absolute stereochemistry by Mori et al.[6] Several syntheses of himachalenes based on Friedel–Crafts acylation, and Robinson annulations, starting from citronellal as a chiral building block have been reported in the literature.[7]

The construction of a seven-membered ring fused to an aromatic ring, and the introduction of stereogenic center at the benzylic position and geminal dimethyl groups are the main tasks of an enantioselective total synthesis. Many chemical transformations of *ar*-himachalene are also known to afford other structurally important synthetic compounds.[8] These activities as well as interesting structural features gained our interest in its synthesis.

2. Results and discussion

As part of our ongoing program toward the synthesis of bioactive sesquiterpene natural products[9] we envisioned that enantiomerically pure citronellal **2** can be used as a chiral building block for the enantioselective synthesis of *ar*-himachalene. Based on the chemistry involving Sharpless asymmetric dihydroxylation and intramolecular ring expansion either by using a hypervalent iodine reagent or by using TMS diazomethane, we realized that *ar*-himachalene could be synthesized in enantiomerically pure form from *p*-methyl α-methyl styrene **3**. As per our proposed retrosynthetic plan (Scheme 1), (*S*)-*ar*-himachalene can be accessed from (*S*)-4-(*p*-tolyl)-pentanoic acid **8** by using a trifluoroacetic acid and trifluoroacetic anhydride mediated cyclization followed by a ring expansion reaction. Acid (*S*)-**8** can be obtained by two routes; (i) from (*S*)-citronellal **2** by a one-pot Michael addition, Robinson annulation, and decarboxylation, followed by aromatization and Jones oxidation reaction and (ii) from the *p*-methyl α-methyl styrene **3**, in which chirality at the benzylic position can be introduced using the Sharpless asymmetric dihydroxylation reaction as the key step.

According to the retrosynthetic analysis, our synthesis started with the chiral building block (*S*)-citronellal **2**[10] to give acid (*S*)-**8**

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http://dx.doi.org/10.1016/j.tetasy.2012.09.008

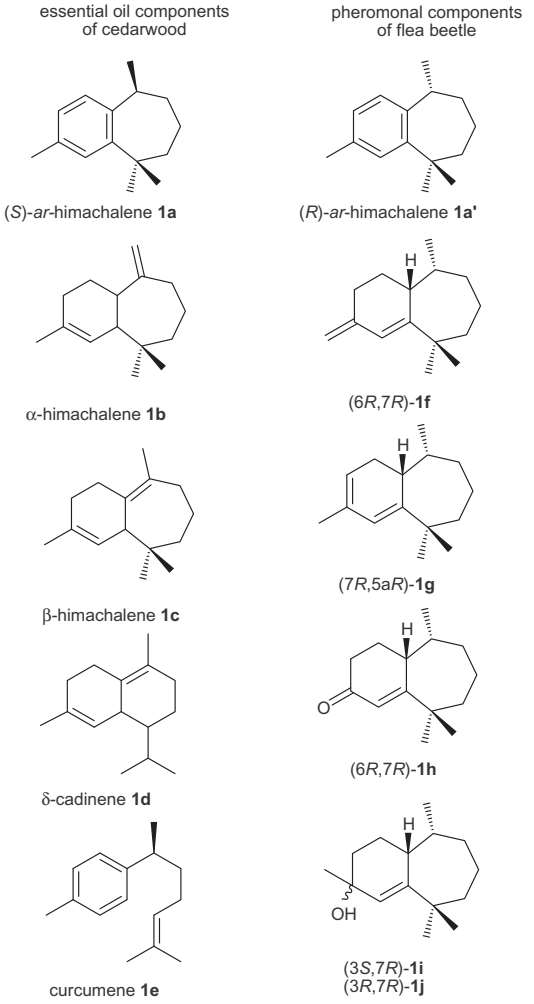
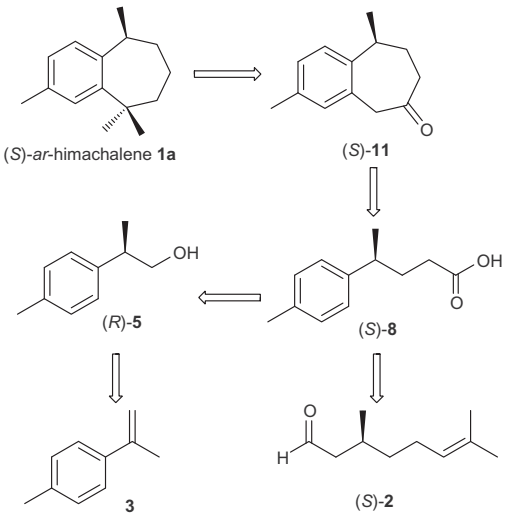
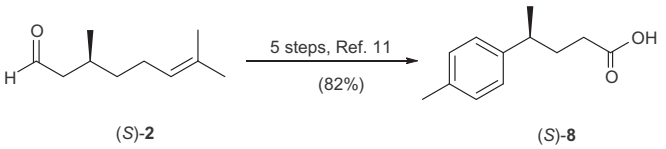


Figure 1. Natural sesquiterpenes isolated along with *ar*-himachalene.



Scheme 1. Retrosynthetic analysis for (*S*)-*ar*-himachalene.

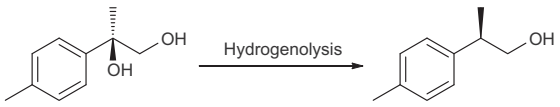
using the procedure reported earlier (Scheme 2).[11] Acid (*S*)-**8** could also be obtained from styrene derivative **3**. Sharpless asymmetric dihydroxylation of *p*-methyl α-methyl styrene **3** using AD-mix-β, furnished diol (*R*)-**4** in 89% yield and 99% ee (by chiral HPLC).[12] The diol (*R*)-**4** was then subjected to hydrogenolysis to obtain



Scheme 2. Preparation of (*S*)-4-(*p*-tolyl)pentanoic acid **8** from (*S*)-citronellal.

primary alcohol (*R*)-**5**. We studied various reagents under different hydrogenation conditions for removal of the tertiary hydroxyl group and the introduction of chirality at the benzylic position (Table 1). As expected, in most cases an inversion of configuration was observed.[13] However, the use of freshly activated Raney Ni in refluxing ethanol gave (*S*)-**5** that is retention of configuration occurred with 78% yield with 86% ee. (by chiral HPLC) (entry 7). The use of Et_3SiH in the presence of a Lewis acid catalyst gave the product with very poor ee (entries 1 and 2), whereas, $Pd(OH)_2$ under room temperature as well as under refluxing conditions gave a moderate yield with good ee (entries 3 and 4).[14] Using $Pd(OH)_2$ in the presence of ammonium formate as a hydrogen source resulted in the decomposition of starting material (entry 8). The best result for inversion was observed when using 10% Pd/C under a hydrogen atmosphere of 60 psi to obtain product (*R*)-**5** with 72% yield and 97.5% ee (by chiral HPLC) (entry 5).[15] Alcohol (*R*)-**5** was then converted into its iodo derivative (*R*)-**6** by using triphenylphosphine, imidazole and iodine in 81% yield. The iodo compound (*R*)-**6** was further treated with diethyl malonate, sodium hydride, and tetrabutyl ammonium iodide (TBAI) as a phase transfer catalyst to obtain diester (*S*)-**7** in 88% yield. Diester (*S*)-**7** was then hydrolyzed under basic conditions to the corresponding diacid, which was used without further purification for thermal decarboxylation to furnish the desired chiral acid (*S*)-**8** in 83% yield with 96% ee (by chiral HPLC) (Scheme 3). Acid (*S*)-**8** was then subjected to a trifluoroacetic acid and trifluoroacetic anhydride mediated intramolecular acylation reaction[11] to obtain the (*S*)-trinorsesquiterpene **9** in 83% yield and with 96% ee (by chiral HPLC). It is worth mentioning that trinorsesquiterpene is a natural product which can be isolated from the Japanese species *J. truncate* as a 1:1 mixture of enantiomers.[16] Although, it is difficult to construct a seven membered ring fused to an aromatic ring, few references are known in the literature to make this framework.[1,17,18] We chose Koser's reagent and $TMSCHN_2$ for the six to seven membered ring expansion. One-carbon Wittig olefination of *p*-methyl-tetralone (*S*)-**9** gave compound (*S*)-**10** with an exocyclic methylene group in 60% yield and 35% of starting material was recovered. This compound upon treatment with Koser's reagent, [hydroxy(tosyloxy)iodo]benzene (HTIB), underwent facile ring expansion to furnish ketone (*S*)-**11** in 82% yield.[17] Ketone (*S*)-**11** was also obtained directly from *p*-methyl-tetralone (*S*)-**9** by insertion of the methylene group using trimethylsilyl diazomethane in 49% yield.[18] Dimethylation of compound (*S*)-**11** with excess methyl iodide using potassium *tert*-butoxide as a base furnished compound (*S*)-**12** in 87% yield which after Wolff–Kishner reduction of the carbonyl group furnished the (*S*)-*ar*-himachalene **1a** in 67% yield (Scheme 3).[19] We decided to check the enantiomeric purity of the final natural product (*S*)-**1a** by using a chiral HPLC method but all of our attempts to resolve a sample of (±)-*ar*-himachalene on suitable chiral HPLC columns were unsuccessful. Finally, we carried out chiral GC analysis and determined the enantiomeric excess as 94% for the final (*S*)-*ar*-himachalene **1a**.[20] Mori et al. reported (*R*)-*ar*-himachalene was dextrorotatory in *n*-hexane and levorotatory in chloroform.[6] We observed that (*S*)-*ar*-himachalene was dextrorotatory in chloroform while levorotatory in *n*-hexane.

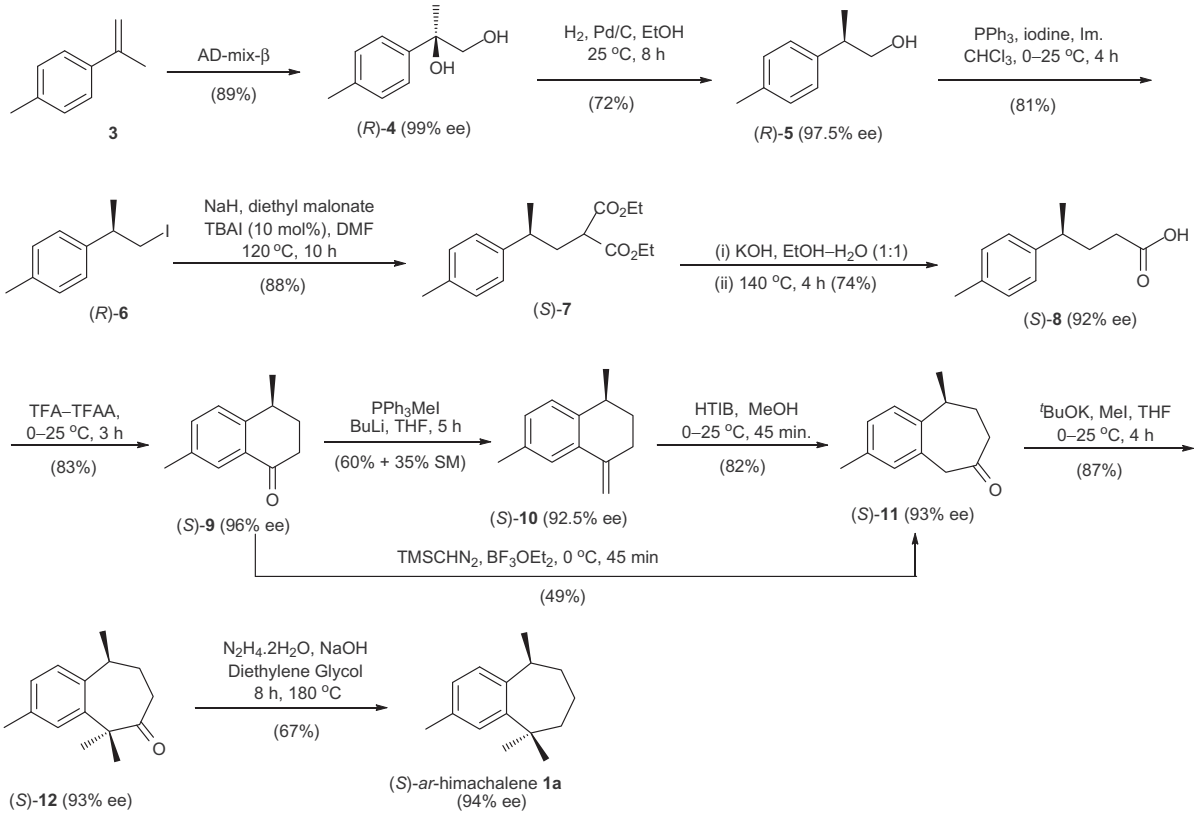
Table 1
Asymmetric hydrogenolysis of (*R*)-2-(*p*-tolyl)propane-1,2-diol **4**



(*R*)-**4** (*R*)-**5**

Entry	Catalyst	Reaction conditions	Yield (%)	$[\alpha]_D^{25}$[a]	ee (%)
1	CF_3COOH	Et_3SiH, 25 °C, 3 h	79	R[b]	—
2	$BF_3{\cdot}OEt_2$	Et_3SiH, 25 °C, 3 h	62	R[b]	—
3	$Pd(OH)_2$	H_2(60 psi), EtOH, 25 °C, 7 h	74	+16.8	93
4[c]	$Pd(OH)_2$	H_2, EtOH, reflux, 4 h	83	+13.9	84
5	Pd/C	H_2(60 psi), EtOH, 25 °C, 10 h	72	+17.4	97.5
6[c]	Pd/C	H_2, EtOH, reflux, 12 h	88	+16.2[d]	92
7	Raney Ni	EtOH, reflux, 3 h	78	−15.1	86
8	NH_4CO_2H, $Pd(OH)_2$	THF–MeOH (1:1), reflux, 5 h	D[e]	—	—

[a] Specific rotations measured at (*c* 1, $CHCl_3$).
[b] Product formed with racemization.
[c] Reaction was performed under balloon pressure hydrogen atmosphere.
[d] Product formed with retention of configuration.
[e] Decomposition of the starting material was observed.



Scheme 3. Total synthesis of (*S*)-*ar*-himachalene **1a**.

Thus, we have accomplished the enantioselective total synthesis of (*S*)-*ar*-himachalene starting from (*S*)-citronellal **2** and *p*-methyl α-methyl styrene **3** in 10 and 11 steps, respectively in 5% and 6% overall yields, respectively. We have also synthesized the opposite enantiomer (*R*)-*ar*-himachalene **1a**′ by following the same reaction sequence starting from (*R*)-citronellal by a chiral pool approach and also from *p*-methyl α-methyl styrene **3** followed by Sharpless asymmetric dihydroxylation, using AD-mix-α for the induction of chirality with equivalent overall yields.

3. Conclusion

In conclusion, we have accomplished the enantioselective synthesis of both isomers of *ar*-himachalene. The synthetic sequence involved a Sharpless asymmetric dihydroxylation reaction, hydrogenolysis, and the use of *TMSCHN*$_2$ or a hypervalent iodine reagent for the ring expansion. We believe this protocol could be of general interest and also useful for the synthesis of several complex bioactive natural and unnatural products.

4. Experimental

4.1. General

Optical rotations were recorded on a JASCO J-20C polarimeter. The ^{1}H NMR spectra were recorded on 200 MHz NMR spectrometer, 400 MHz NMR spectrometer, and 500 MHz NMR spectrometer using TMS as the internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz), and 500 NMR spectrometer (125 MHz). Mass spectra were taken on a MS-TOF mass spectrometer. The IR spectra were recorded on a FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120, 200–400 and 100–200 mesh). Commercially available $(DHQ)_2PHAL$, $(DHQD)_2PHAL$, OsO_4, Pd-C, $Pd(OH)_2$, HTIB, *t*-BuOK, and $TMSCHN_2$ were used.

4.2. Experimental procedures and tabulated spectroscopic data

4.2.1. 2-(*p*-Tolyl)propane-1,2-diol 4

To a stirred solution of potassium ferricyanide (22.3 g, 3.0 mmol) and potassium carbonate (9.4 g, 3.0 mmol) in water (150 mL) was added methane sulfonamide (2.2 g, 1.1 mmol) followed by *tert*-butanol (150 mL) and then allowed to stir until the suspension became clear. Next, ligand $(DHQD)_2PHAL$ [for the (*R*)-isomer] or $(DHQ)_2PHAL$ [for the (*S*)-isomer] (0.055 g, 4.0 mol %) followed by 1 M solution of osmium tetraoxide in *tert*-butanol (0.010 mL, 1.0 mol %) were added at 0 °C and the resulting suspension was stirred until an orange color was obtained. To this mixture was added *p*-methyl α-methyl styrene **3** (3.0 g, 1.0 mmol) in a dropwise manner. The resultant heterogeneous suspension was stirred vigorously at 0 °C until the reaction was complete, as monitored by TLC (24 h). Sodium sulfite (5 g) was added slowly to the reaction mixture and the resulting suspension stirred at room temperature for 1 h. The reaction mixture was transferred into a 100 mL separatory funnel and extracted with ethyl acetate (4 × 20 mL). The organic layer was washed with brine then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a residue. The residue obtained was purified by using 60–120 silica gel column chromatography, (30% ethyl acetate–petroleum ether) to furnish diol **4** as a colorless oil [3.36 g, 89%, 99% ee for the (*R*)-isomer, 97% ee for the (*S*)-isomer $[\alpha]_D^{25} = -10.7$ (*c* 1, $CHCl_3$)] for the (*R*)-isomer, $[\alpha]_D^{25} = +10.5$ (*c* 1, $CHCl_3$ for the (*S*)-isomer); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 3H), 2.33 (s, 3H), 2.80 (br s, 2H), 3.54 (d, *J* = 11 Hz, 1H), 3.71 (d, *J* = 11 Hz, 1H), 7.13 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 25.9, 70.8, 74.8, 125.0 (2 Carbons), 129.0 (2 Carbons), 136.5, 142.2; ESIMS (*m*/*z*) 189 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3448, 3049, 1216, 1040 cm^{-1}.

4.2.2. 2-(4-Methylphenyl)propanol 5

4.2.2.1. Method A: with Raney Ni. To a stirred solution of (*R*)-2-(*p*-tolyl)propane-1,2-diol **4** (0.850 g, 20 mmol) in ethanol (20 mL) was added freshly prepared Raney Ni (2 g, 80 mmol) at 25 °C and the reaction mixture was heated at reflux for 3 h. After completion of the reaction, it was allowed to cool at room temperature, the catalyst was filtered off through a bed of Celite and the residue was washed with ethanol (3 × 5 mL). The combined filtrate was evaporated under reduced pressure and the residue was purified using 60–120 silica gel column chromatography (5% ethyl acetate–petroleum ether) to afford alcohol (*S*)-**5** as a colorless oil (0.663 g, 78%, 86% ee). $[\alpha]_D^{25} = -15.1$ (*c* 1, $CHCl_3$).

4.2.2.2. Method B: with H_2, Pd/C. To a stirred solution of 2-(*p*-tolyl)propane-1,2-diol **4** (0.110 g, 20 mmol) in ethanol (5 mL) was added Pd/C (90 mg, 10 wt%). The reaction mixture was stirred under a hydrogen atmosphere at 25 °C and 60 psi pressure for 6 h. After completion of the reaction, the catalyst was filtered off and the residue washed with hot ethanol (3 × 5 mL). The combined filtrate was evaporated under reduced pressure and the residue obtained was purified using 60–120 silica gel column chromatography (5% ethyl acetate–petroleum ether) to furnish alcohol **5** as a colorless oil [0.075 g, 72%, 97.5% ee for the (*R*)-isomer, 93% for the (*S*)-isomer]. $[\alpha]_D^{25} = +17.4$ (*c* 1, $CHCl_3$) for the (*R*)-isomer, $[\alpha]_D^{25} = -16.7$ (*c* 1, $CHCl_3$) for the (*S*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (d, *J* = 8 Hz, 3H), 2.36 (s, 3H), 2.92 (sextet, *J* = 8 Hz, 1H), 3.67 (d, *J* = 6 Hz, 2H), 7.00–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.7, 21.0, 42.0, 68.6, 127.3 (2 Carbons), 129.3 (2 Carbons), 136.0, 140.6; ESIMS (*m*/*z*) 151 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3320, 1606, 1515 cm^{-1}.

4.2.3. 1-Iodo-2-(4-methylphenyl) propane 6

To a stirred solution of alcohol **5** (3.9 g, 26 mmol) together with triphenyl phosphine (8.86 g, 33.8 mmol) and imidazole (2.30 g, 33.8 mmol) in methylene dichloride (40 mL), iodine (8.59 g, 33.8 mmol) was added in three equal portions at 10 °C and the solution was allowed to warm at 25 °C and stirred for 4 h. After completion of the reaction, petroleum ether (40 mL) was added to the reaction mixture and then filtered through Celite and washed with petroleum ether–ethyl acetate (10:1 mL). The combined filtrate was evaporated under reduced pressure and the residue obtained was purified using 60–120 silica gel column chromatography (petroleum ether) to obtain compound **6** as a thick oil (5.4 g, 82%). $[\alpha]_D^{25} = +30.1$ (*c* 1, $CHCl_3$) for the (*R*)-isomer, $[\alpha]_D^{25} = -29.7$ (*c* 1, $CHCl_3$) for the (*S*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (d, *J* = 8 Hz, 3H), 2.36 (s, 3H), 3.03 (sextet, *J* = 8 Hz, 1H), 3.23–3.50 (m, 2H), 7.05–7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.9, 21.2, 21.7, 42.1, 126.6 (2 Carbons), 129.3 (2 Carbons), 136.3, 141.3; ESIMS (*m*/*z*) 301 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3012, 2925, 1514, 668 cm^{-1}.

4.2.4. Diethyl 2-(2-(*p*-tolyl)propyl)malonate 7

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.12 g, 28 mmol) in anhydrous DMF (10 mL) at 0 °C was added diethyl malonate (4.25 mL, 28 mmol) in a dropwise manner. After 30 min, iodo compound **6** (5.2 g, 20 mmol) in anhydrous DMF (5 mL) was added dropwise over a period of 10 min followed by a catalytic amount of tetrabutyl ammonium iodide (10 mol %) after which the reaction mixture was heated at 120 °C for 10 h. The reaction mixture was then allowed to cool to room temperature and diluted with ethyl acetate. The organic layer was washed with brine then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a residue. The residue obtained was then purified by flash column chromatography using 60–120 silica gel (5% ethyl acetate–petroleum ether) to furnish the diester compound **7** as a viscous oil (5.19 g, 88%). $[\alpha]_D^{25} = +22.4$ (*c* 1, $CHCl_3$) for the (*S*)-isomer, $[\alpha]_D^{25} = -22.2$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05–1.43 (m, 9H), 2.00–2.27 (m, 2H), 2.33 (s, 3H), 2.54–2.81 (m, 1H), 3.14 (dd, *J* = 10 and 6 Hz, 1H), 4.00–4.30 (m, 4H), 6.95–7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 21.0, 22.6, 29.7, 37.0, 37.4, 50.3, 61.2, 127.0 (2 Carbons), 129.2 (2 Carbons), 135.8, 142.3, 169.3; ESIMS (*m*/*z*) 315 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3021, 1744, 1724 cm^{-1}, HRMS (EI) calculated for $C_{17}H_{25}O_4$ $[M+H]^+$ 293.1752, found 293.1747.

4.2.5. 4-(*p*-Tolyl)pentanoic acid 8

To a solution of diester compound **7** (5 g 17.1 mmol) in water (20 mL) and ethanol (20 mL) was added solution of KOH (3.83 g, 68.4 mmol) in 10 mL of water and the reaction mixture was stirred for 2–3 h at room temperature until the emulsion became clear.

The ethanol was removed under reduced pressure and the aqueous solution was neutralized with 10% HCl, extracted with diethyl ether (3 × 10 mL), dried over anhydrous sodium sulfate, and filtered. Removal of the solvent under reduced pressure afforded the diacid. This crude product was used as such for further decarboxylation, and was heated at 140 °C for 4 h. The residue was dissolved in DCM (2.5 mL) and passed through silica gel flash column chromatography (10% ethyl acetate–petroleum ether) to furnish acid **8** as a viscous oil [2.52 g, 78%, 92% ee for the (*S*)-isomer, 97% ee for the (*R*)-isomer]. $[\alpha]_D^{25} = +14.2$ (*c* 1, $CHCl_3$) for the (*S*)-isomer, $[\alpha]_D^{25} = -14.5$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (d, *J* = 6 Hz, 3H), 1.77–2.13 (m, 2H), 2.26 (t, *J* = 8 Hz, 2H), 2.36 (s, 3H), 2.59–2.86 (m, 1H), 6.95–7.30 (m, 4H), 10.4 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 22.3, 32.3, 32.9, 38.8, 126.8 (2 Carbons), 129.2 (2 Carbons), 135.7, 143.0, 180.1; ESIMS (*m*/*z*) 263 $[M+K+MeOH]^+$; IR ($CHCl_3$) ν_{max} 1707, 1217 cm^{-1}.

4.2.6. 4,7-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (trinorsesquiterpene) 9

Acid **8** (2.4 g, 12.5 mmol) was dissolved in the minimum amount of freshly distilled trifluoroacetic acid (8 mL) in a 25 ml round bottom flask under a nitrogen atmosphere. To this solution, freshly distilled trifluoroacetic anhydride (10.6 g, 15 mmol) was added dropwise at 0 °C with constant stirring. The reaction mixture was then allowed to warm to room temperature and stirred for 3 h. After completion of the reaction, it was neutralized with the saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated under reduced pressure to obtain a residue. The residue obtained was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to furnish the trinorsesquiterpene **9** as a viscous oil [1.75 g, 83%, 96% ee for the (*S*)-isomer, 93% ee for the (*R*)-isomer]. $[\alpha]_D^{25} = -10.0$ (*c* 1, $CHCl_3$) for the (*S*)-isomer, $[\alpha]_D^{25} = +9.4$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, *J* = 8 Hz, 3H), 1.77–1.99 (m, 1H), 2.14–2.34 (m, 1H), 2.36 (s, 3H), 2.45–2.88 (m, 2H), 2.95–3.17 (m, 1H), 7.15–7.37 (m, 2H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8 (2 Carbons), 30.8, 32.5, 36.4, 127.3, 127.5, 131.7, 134.5, 136.0, 145.9, 198.1; ESIMS (*m*/*z*) 197 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1683, 1611 cm^{-1}.

4.2.7. 1,6-Dimethyl-4-methylene-1,2,3,4-tetrahydronaphthalene 10

To a mechanically stirred mixture of methyltriphenylphosphonium iodide (7.67 g, 19 mmol) in dry THF (50 mL) at 0 °C was slowly added a 1.6 M THF solution of *n*-BuLi (11. 9 mL, 19 mmol) under an argon atmosphere and the solution was stirred vigorously for 20 min. A solution of tetralone **9** (1.32 g, 7.60 mmol) in dry THF (20 mL) was then added dropwise to the reaction mixture over a period of 5 min. The color of the mixture gradually changed from yellow to orange. After 5 h, the reaction was quenched by the addition of a saturated solution of NH_4Cl and the resulting precipitate was filtered off through a bed of Celite, and washed thoroughly with diethyl ether (3 × 30 mL). The combined filtrate was washed with water, brine, dried over anhydrous sodium sulfate, and filtered. The solvent was concentrated under vacuum to obtain a residue. The residue obtained was purified by using 60–120 silica gel column chromatography, eluted with petroleum ether to furnish compound **10** as a colorless oil [0.78 g, 60%, 92.5% ee for the (*S*)-isomer, 93.4% ee for the (*R*)-isomer]. $[\alpha]_D^{25} = +3.2$ (*c* 1, $CHCl_3$) the (*S*)-isomer, $[\alpha]_D^{25} = -3.6$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (d, *J* = 8 Hz, 3H), 1.60–1.75 (m, 1H), 1.98–2.13 (m, 1H), 2.38 (s, 3H), 2.45–2.56 (m, 1H), 2.62–2.75(m, 1H), 2.91–3.57 (m, 1H), 4.96 (d, *J* = 2 Hz, 1H), 5.48 (s, 1H), 7.07 (d, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 22.4, 30.3, 31.8, 33.0, 107.6, 124.8, 128.0, 128.8, 134.1, 135.0, 139.2, 143.9; ESIMS (*m*/*z*) 227 $[M+ Na+MeOH]^+$; IR ($CHCl_3$) ν_{max} 1629, 1217 cm^{-1}.

4.2.8. 3,9-Dimethyl-8,9-dihydro-5*H*-benzo[7]annulen-6(7*H*)-one 11

4.2.8.1. Method A. Compound **9** (1.20 g, 33.6 mmol) was suspended in Et_2O (34 mL) and cooled to 0 °C under a nitrogen atmosphere. Next, $BF_3.OEt_2$ (4.70 mL, 37.1 mmol) was added followed by the dropwise addition of $TMSCHN_2$ (18.5 mL, 37.0 mmol). The mixture was stirred at 0 °C for 45 min after which saturated aq. $NaHCO_3$ (100 mL) was added carefully. The two layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a yellow oil, which was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to give compound **11** as a light yellow oil (0.635 g, 49%).

4.2.8.2. Method B. To a stirred solution of **10** (1.43 g, 11.0 mmol) in methanol (40 mL) was added crystalline HTIB (3.92 g, 10.0 mmol). The solid dissolved rapidly to give a colorless solution. The solution was stirred at room temperature for 30 min and the solvent was then removed to obtain an oily mixture. This mixture was then partitioned between CH_2Cl_2 (50 mL) and H_2O (25 mL) and transferred to a separatory funnel. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a bright yellow oil, which was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to give tetralone **11** as a light yellow oil [0.720 g, 82%, 93% ee for the (*S*)-isomer, 93.3% ee for the (*R*)-isomer]. $[\alpha]_D^{25} = +69.2$ (*c* 1, $CHCl_3$) for the (*S*)-isomer, $[\alpha]_D^{25} = -69.4$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (d, *J* = 8 Hz, 3H), 1.46–1.74 (m, 1H), 1.98–2.22 (m,1H), 2.22–2.62 (m, 2H), 2.32 (s, 3H), 3.00–3.25 (m, 1H), 3.48 (d, *J* = 18 Hz, 1H), 3.85 (d, *J* = 18 Hz, 1H), 6.94 (s, 1H), 7.02–7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.5, 20.8, 34.1, 34.2, 41.3, 49.5, 125.1, 128.2, 130.4, 133.8, 136.1, 140.0, 210.2; ESIMS (*m*/*z*) 197 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1705, 1216 cm^{-1}.

4.2.9. 3,5,5,9-Tetramethyl-8,9-dihydro-5H- benzo[7]annulen-6(7H)-one 12

To a magnetically stirred solution of **11** (0.6 g, 3.2 mmol) and methyl iodide (2.7 g, 19.2 mmol) in anhydrous THF (5 mL) under a nitrogen atmosphere, was added potassium *tert*-butoxide (1.07 g, 9.6 mmol) in three equal portions over a period of 30 min. The reaction mixture was stirred at room temperature for 4 h, poured into an ice-water slurry and extracted with diethyl ether (3 × 50 mL). The combined organic layer was washed with a saturated sodium bicarbonate solution (2 × 10 mL) followed by brine (2 × 10 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure. The residue obtained was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to furnish the ketone **12** as a colorless oil [0.602 g, 87%, 93% ee for the (*S*)-isomer, 93.3% ee for the (*R*)-isomer]. $[\alpha]_D^{25} = +32.1$(*c* 1, $CHCl_3$) for the (*S*)-isomer, $[\alpha]_D^{25} = -32.3$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26–1.43 (m, 6H), 1.50 (s, 3H), 2.03–2.29 (m, 2H), 2.38 (s, 3H), 2.57–2.80 (m,1H), 2.80–3.04 (m,1H), 7.05–7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.3, 21.3, 25.8, 26.5, 32.5, 35.9, 36.9, 52.6, 124.8, 126.0, 127.9, 136.0, 137.8, 143.9, 217.5; ESIMS (*m*/*z*) 238 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1702, 1216 cm^{-1}.

4.2.10. 2,5,9,9-Tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene 1a

A mixture of **12** (0.4 g, 1.85 mmol), anhydrous hydrazine hydrate (0.360 g, 360 μl, 7.4 mmol), and sodium hydroxide (0.296 g, 7.4 mmol) in a freshly distilled diethylene glycol (5 mL) was heated at 150 °C. After 1 h, the excess hydrazine hydrate was removed and the bath temperature was allowed to rise to 180 °C. Refluxing was then continued for an additional hour. The cooled reaction mixture was poured into ice and extracted with ether (3 × 50 mL). The combined organic layer was washed with a saturated sodium bicarbonate solution (2 × 10 mL) followed by brine (2 × 10 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product obtained was purified by using 60–120 silica gel column chromatography, (petroleum ether only) to furnish *ar*-himachalene **1** [0.242 g, 64%, 94% ee for the (*S*)-isomer,[20] 97% ee for the (*R*)-isomer[6]]. $[\alpha]_D^{25} = +2.9$ (*c* 1, $CHCl_3$) for the (*S*)-isomer $[\alpha]_D^{25} = -2.1$ (*c* 1, $CHCl_3$) for the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36–1.46 (m, 6H), 1.50 (s, 3H), 1.55–1.95 (m, 4H), 2.38 (s, 3H), 3.22–3.44 (m, 1H), 7.03 (d, J = 8 Hz, 1H), 7.17 (d, J = 8 Hz, 1H), 7.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 21.3, 24.1, 29.8, 34.1, 34.5, 36.6, 39.5, 41.2, 125.4, 126.6, 127.5, 134.9, 141.1, 147.6; ESIMS (*m*/*z*) 203 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3008, 2961, 1456, 1216 cm^{-1}.

Acknowledgements

H.S.K. thanks CSIR, New Delhi, for the award of a research fellowship and Dr U.R. Kalkate for helpful discussions. S.P.C. thanks NCL in-house project for financial support. We thank the Takasango International Company, Japan for the generous gift of chiral citronellal, Dr Kenji Mori for providing us with GC data for (*R*)-*ar*-himachalene and (Mrs.) S. S. Kunte from NCL, Pune, for the HPLC data.

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