Stereoselective Synthesis of Racemic Fragranol by an Intramolecular Ester Enolate Alkylation

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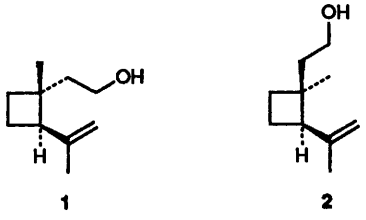
A highly stereoselective synthesis of (±)-fragranol **1** has been accomplished from the readily available homoallylic alcohol **3** in 11 steps in 10.5% overall yield utilizing an intramolecular ester enolate alkylation as the key step.

Fragranol **1** was isolated from the roots of *Artemisia fragranas* Willd by Bohlmann *et al.* in 1973.[1] Along with diastereoisomeric grandisol **2**,[2] a sex attractant of the male boll weevil, *Anthonomous grandis* Boheman, these cyclobutanes have served



1 **2**

as attractive targets for synthetic chemists to test new synthetic strategies for stereoselective construction of four-membered rings owing to their remarkable biological activity, coupled with their interesting molecular structures.[3,4]

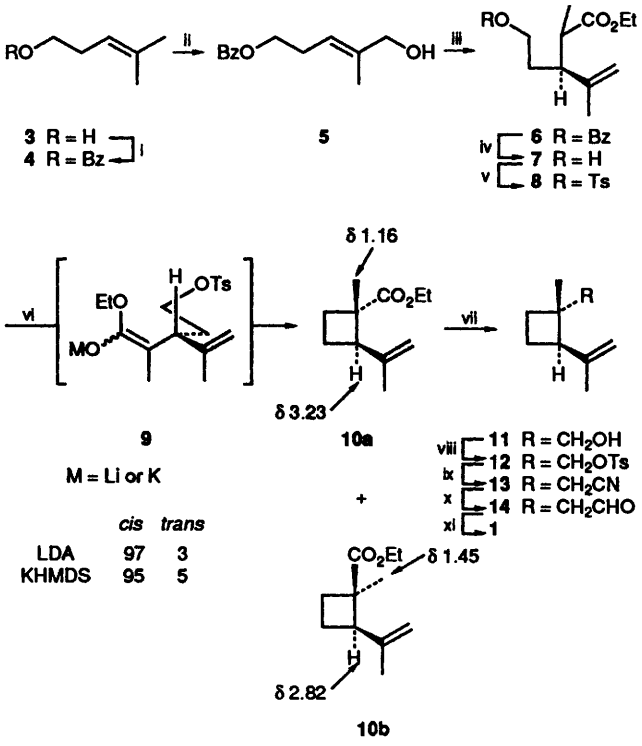
Described herein is a full account of a highly stereoselective synthesis of (±)-fragranol **1** based upon our intramolecular ester enolate alkylation methodology.[5]

Results and Discussion

Our synthetic plan for (±)-fragranol **1** involves the crucial intramolecular ester enolate alkylation of the tosylate **8** followed by a conventional one-carbon homologation of the resulting cyclobutanecarboxylate **10a** as indicated in Scheme 1.

The alkylation substrate **8** was prepared from the known homoallylic alcohol **3**[6] in a straightforward five-step sequence. Thus, protection of the primary hydroxy group of the alcohol **3** by treatment with benzoyl chloride in pyridine, followed by allylic oxidation of the olefin **4** with selenium dioxide under Sharpless conditions[7] yielded the (*E*)-allylic alcohol **5** after $NaBH_4$ reductive work-up in 64% yield. Upon being heated at 145–155 °C for 24 h in triethyl orthopropionate with a small amount of phenol as an acid catalyst, the allylic alcohol **5** underwent a smooth Johnson orthoester Claisen rearrangement[8] to give the γ,δ-unsaturated ester **6** as a 1:1 mixture of stereoisomers in 86% yield. Conversion of the ester **6** into the corresponding δ-hydroxy ester **7** was more problematic than we expected. For instance, attempted removal of the benzoate group under transesterification conditions such as potassium carbonate in absolute ethanol, was unsatisfactory. After some experimentation it was found that treatment of the ester **6** with 2 equiv. of Triton B followed by esterification of the resulting quaternary ammonium carboxylate with ethyl iodide in an S_N2 fashion afforded the desired δ-hydroxy ester **7** without contamination by the corresponding δ-lactone. It is worthwhile to mention that the corresponding silyl-protected ester, prepared in a similar fashion, afforded the δ-lactone as the major compound (56%) along with a small amount of the desired hydroxy ester (15%) upon treatment with tetrabutylammonium fluoride in THF. Finally, tosylation of the hydroxy ester **7** with TsCl in pyridine–$CHCl_3$[9] produced the key cyclization substrate **8** in 88% yield for the two steps.

Alkylative cyclization of the tosylate **8** with lithium diisopropylamide in THF at −78 °C to room temperature gave



Scheme 1. *Reagents and conditions:* i, PhCOCl, DMAP, pyridine, methylene dichloride, room temp., 5 h (98%); ii, SeO_2, Bu'OOH, methylene dichloride, room temp., 24 h, then $NaBH_4$, EtOH, 0 °C, 30 min (65%); iii, $MeCH_2C(OEt)_3$, phenol, 145–155 °C, 24 h (86%); iv, Triton B, THF, reflux, 1 h, then EtI, reflux, 5 h (91%); v, TsCl, pyridine, chloroform, 0 °C, 3 h (97%); vi, KHMDS, THF, −78 to 0 °C, 2 h (85%); vii, LAH, THF, room temp., 2 h (81%); viii, TsCl, pyridine, chloroform, 0 °C, 5 h (77%); ix, NaCN, HMPA, 80–90 °C, 5 h (76%); x, DIBAL, methylene dichloride, −20–0 °C, 1.5 h; xi, $NaBH_4$, EtOH, room temp., 5 min (54% for 2 steps).

a 97:3 mixture of the cyclobutanecarboxylates **10a** and **10b** in 45% total yield. Alternatively, the corresponding potassium enolate, generated by treatment of **8** with potassium hexamethyldisilazide,[10] afforded a 95:5 mixture of **10a** and **10b** in 85% optimized yield.

The ratio of stereoisomers of **10** was determined by capillary GC analysis. The chemical shift values of the quaternary methyl and methine protons in **10a** and **10b** were quite diagnostic for the stereochemistry as shown in Scheme 1 due to the shielding and deshielding effects of the adjacent isopropenyl and ester groups, respectively. The minor isomer **10b** was also independently synthesized from the authentic parent acid corresponding to **10b** by successive treatment with Triton B and ethyl iodide.

The observed high stereoselectivity of the intramolecular ester enolate alkylation can best be rationalized by invoking the most stable 'H-eclipsed' transition state geometry as depicted in **9**.[5,11]

The *cis* isomer **10a** was converted into the natural product in five steps by a conventional one-carbon homologation protocol *via* the cyanide **13**. Thus, reduction of the ester **10a** with LAH in THF followed by tosylation gave rise to the corresponding tosylate **12** in 62% overall yield. Treatment of the tosylate **12** with NaCN in HMPA at 80–90 °C for 5 h furnished the corresponding cyanide **13** in 76% yield. The aldehyde **14**, obtained by DIBAL reduction of the cyanide **13**, was reduced with $NaBH_4$ without purification to give racemic fragranol in 54% yield for the final two steps.

In conclusion, racemic fragranol has been synthesized from the readily available homoallylic alcohol **3** in 11 steps in 10.5% overall yield in a highly stereoselective manner based upon an intramolecular ester enolate alkylation strategy.

Experimental

NMR spectra were recorded on a Bruker 80 or 270 AM spectrometer. IR spectra were measured on a Perkin-Elmer 1710 FT-IR spectrometer. MS data were obtained from a Finnigan Mat. TSQ-70 instrument with electron or chemical ionization. Capillary GC analysis was performed on a Shimadzu GC-9A instrument. Elemental analyses were carried out at the Research Institute of Pharmacal Sciences of Seoul National University. Analytical TLC was performed on glass pre-coated silica gel plates (Merck F-254). Column chromatography was performed by using E. Merck Silica Gel (70–230 mesh). All reactions were performed under an atmosphere of dry nitrogen.

4-Methylpent-3-enyl Benzoate **4**.—To a solution of the homoallylic alcohol **3** (2.6 g, 24 mmol), 4-dimethylaminopyridine (0.29 g, 0.24 mmol), and dry pyridine (3.9 ml, 48 mmol) in anhydrous CH_2Cl_2 (30 ml) was slowly added benzoyl chloride (3.32 ml, 28.8 mmol) at 0 °C. The solution was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (30 ml) and water (30 ml). The organic layer was washed successively with 2M HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes–ethyl acetate, 30:1) to yield the benzoate **4** (4.76 g, 98%) as an oil: ν_{max}(neat): 1 720 cm^{-1}; δ_H(80 MHz, $CDCl_3$): 8.10–7.26 (m, 5 H), 5.20 (t, *J* 7 Hz, 1 H), 4.29 (t, *J* 7 Hz, 2 H), 2.45 (q, *J* 7 Hz, 2 H), 1.73 (s, 3 H) and 1.67 (s 3, H); δ_C(20.15 MHz, $CDCl_3$): 166.36, 134.40, 132.56, 130.46, 129.38, 128.10, 119.20, 64.42, 27.65, 25.50 and 17.60 (Found: C, 76.5; H, 7.8. $C_{12}H_{16}O_2$ requires C, 76.44; H, 7.89%).

(E)-5-Benzoyloxy-2-methylpent-2-en-1-ol **5**.—To a stirred solution of selenium dioxide (1.1 g, 9.78 mmol) and 70% t-butyl hydroperoxide (5.4 ml, 39.6 mmol) in CH_2Cl_2 (35 ml) was slowly added a solution of the benzoate **4** (4 g, 19.78 mmol) in CH_2Cl_2 (5 ml) at room temperature. After the mixture had been stirred for 24 h at room temperature methyl sulphide (3 ml, 40 mmol) was added and stirring was continued for 30 min. To the ice-cooled mixture was added ethanol (3 ml) followed by $NaBH_4$ (0.76 g, 20 mmol) and the mixture was stirred at 0 °C for 30 min. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography (hexanes–ethyl acetate, 3:1) to afford the desired oily allylic alcohol **5** (2.8 g, 65%); ν_{max}(neat): 3426 and 1719 cm^{-1}; δ_H(80 MHz, $CDCl_3$): 8.09–7.25 (m, 5 H), 5.50 (t, *J* 7 Hz, 1 H), 4.33 (t, *J* 7 Hz, 2 H), 4.02 (s, 2 H), 2.52 (q, *J* 7 Hz, 2 H), 1.71 (s, 3 H) and 1.63 (s, 1 H, exchangeable); δ_C(20.15 MHz, $CDCl_3$): 166.46, 137.68, 132.63, 130.07, 129.26, 128.07, 119.87, 67.83, 64.09, 27.08 and 13.44 (Found: C, 70.95; H, 7.2. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%).

Ethyl 5-Benzoyloxy-3-isopropenyl-2-methylpentanoate **6**.—A solution of the allylic alcohol **5** (1.3 g, 5.96 mmol), triethyl orthopropionate (25 ml, 120 mmol) and phenol (43 mg, 0.6 mmol) was heated at 145–155 °C for 24 h with distillative removal of ethanol. The excess of triethyl orthopropionate was removed under reduced pressure and the residue was column chromatographed on silica gel (hexanes–ethyl acetate, 15:1) to furnish the desired Claisen rearrangement product **6** (1.56 g, 86%); ν_{max}(neat): 1723 cm^{-1}; δ_H(80 MHz, $CDCl_3$) 8.09–7.25 (m, 5 H), 4.84 (m, 2 H), 4.31–3.96 (m, 4 H), 2.57–2.46 (m, 2 H), 1.73–1.58 (m, 5 H) and 1.35–1.04 (m, 6 H); *m/z* (CI) 305 (*M* + 1).

Ethyl 5-Hydroxy-3-isopropenyl-2-methylpentanoate **7**.—A mixture of benzyltrimethylammonium hydroxide (1.1 g, 6.57 mmol), the ester **6** (1.0 g, 3.29 mmol), THF (10 ml), and water (1 ml) was stirred at room temperature for 30 min in the presence of phenolphthalein solution (1 drop) as an indicator. To the mixture was added ethyl acetate (3 ml) and the mixture was refluxed until the pink colour disappeared. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in THF (8 ml). To this solution was added ethyl iodide (1.3 ml, 16.43 mmol) and the solution was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was purified on silica gel (hexanes–ethyl acetate, 2.5:1) to afford the desired product **7** 0.6 g, 91%); ν_{max}(neat): 3439 and 1734 cm^{-1}; δ_H(80 MHz, $CDCl_3$) 4.87–4.78 (m, 2 H), 4.29–4.04 (m, 2 H), 3.56 (t, *J* 7 Hz, 2 H), 2.53–2.36 (m, 2 H), 1.71–1.54 (m, 5 H), 1.37–1.01 (m, 6 H).

3-Isopropenyl-2-methyl-3-(toluene-p-sulphonyloxy)-pentanoate **8**.—To an ice-cooled solution of alcohol **7** (1 g, 5.0 mmol) in chloroform (8 ml) was added pyridine (0.9 ml, 10.0 mmol) followed by toluene-*p*-sulphonyl chloride (1.43 g, 7.5 mmol) in small portions with constant stirring. The reaction was complete in 3 h (TLC). To the reaction mixture was added ethyl acetate (30 ml) and water (3 ml) and the organic layer was washed successively with 2M HCl, 5% $NaHCO_3$, and water and then dried ($MgSO_4$). The solvent was purified under reduced pressure and the crude product was purified on silica gel (hexanes–ethyl acetate, 10:1) to give the tosylate **8** (1.72 g, 97%); ν_{max}(neat): 1 729 cm^{-1}; δ_H(80 MHz, $CDCl_3$): 7.77 (d, *J* 8 Hz, 2 H), 7.31 (d, *J* 8 Hz, 2 H), 4.82–4.61 (m, 2 H), 4.17–3.82 (m, 4 H), 2.44 (s, 3 H), 2.32 (m, 2 H), 1.90–1.52 (m, 5 H) and 1.33–0.98 (m, 6 H).

Ethyl trans-*2-Isopropenyl-1-methylcyclobutanecarboxylate* **10a**.—To a solution of 1M KHMDS in THF (6.8 ml, 6.8 mmol) in anhydrous THF (3 ml) was slowly added a solution of the tosylate **8** (0.8 g, 2.26 mmol) in THF (12 ml) with vigorous

stirring at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, gradually warmed to 0 °C over 1 h, quenched with saturated aqueous NH_4Cl, and then extracted with ethyl acetate (30 ml). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes–ethyl acetate, 15:1) to afford a 95:5 mixture of **10a** and **10b** (0.39 g, 85%). The ratio of stereoisomers was determined by capillary GC analysis (0.2 mm i.d. × 50 m; CBP-1); ν_{max}(neat): 1729 cm^{-1}; δ_H(80 MHz, $CDCl_3$): 4.90 (br s, 1 H), 4.69 (br s, 1 H), 4.16 (q, *J* 7 Hz, 2 H), 3.23 (t, *J* 7 Hz, 1 H), 2.45–1.78 (m, 4 H), 1.65 (s, 3 H), 1.26 (t, *J* 7 Hz, 3 H) and 1.16 (s, 3 H); δ_C(20.15 MHz, $CDCl_3$): 176.96, 144.21, 110.95, 60.19, 46.61, 46.21, 28.27, 21.84, 19.01, 16.66 and 14.12; *m/z* 137 (M^+ − OEt).

Ethyl cis-2-*Isopropenyl*-1-*methylcyclobutanecarboxylate* **10b**.—A solution of the acid corresponding to ester **10b** (10 mg, 0.065 mmol), benzyltrimethylammonium hydroxide (10.9 mg, 0.065 mmol), and ethyl iodide (13 μl, 0.16 mmol) in THF (1 ml) was refluxed for 1 h. The mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexanes–ethyl acetate, 15:1) to afford authentic ester **10b** (9 mg, 83%); ν_{max}(neat): 1725 cm^{-1}; δ_H(80 MHz, $CDCl_3$): δ 4.78 (br s, 1 H), 4.67 (br s, 1 H), 4.09 (q, *J* 7 Hz, 2 H), 2.82 (t, *J* 9 Hz, 1 H), 1.71 (s, 3 H), 1.45 (s, 3 H) and 1.23 (t, *J* 7 Hz, 3 H); δ_C(20.15 MHz, $CDCl_3$): 175.20, 144.94, 109.81, 60.00, 52.46, 50.50, 28.26, 25.79, 22.06, 20.23 and 14.18.

trans-2-*Isopropenyl*-1-*methylcyclobutylmethanol* **11**.—To a suspension of $LiAlH_4$ (10.4 mg, 0.27 mmol) in dry THF (1 ml) was added dropwise a solution of the ester **10a** (50 mg, 0.27 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by successive addition of water (11 μl), 15% NaOH (11 μl) and water (33 μl) and the mixture was stirred at room temperature for 10 min. The precipitate was filtered through a pad of Celite. The filtrate was dried ($MgSO_4$) and evaporated to dryness. The residue was purified on silica gel (hexanes–ethyl acetate, 6:1) to afford the desired product **11** (31 mg, 81%); ν_{max}(neat): 3345 and 1646 cm^{-1}; δ_H(80 MHz, $CDCl_3$): 4.85 (br s, 1 H), 4.66 (br s, 1 H), 3.47 (br s, 2 H), 2.74 (t, *J* 9.2 Hz, 1 H), 1.64 (s, 3 H), 2.20–1.15 (m, 5 H), 0.94 (s, 3 H); δ_C(20.15 MHz, $CDCl_3$): 145.30, 109.82, 71.31, 45.11, 43.98, 26.47, 22.91, 18.84 and 17.16 (Found: C, 77.15; H, 11.4. $C_9H_{16}O$ requires C, 77.09; H, 11.59%).

trans-2-*Isopropenyl*-1-*methylcyclobutylmethyl Toluene*-p-*sulphonate* **12**.—To an ice-cooled solution of the alcohol **11** (0.3 g, 2.14 mmol) in chloroform (3 ml) was added dry pyridine (0.35 ml) followed by toluene-*p*-sulphonyl chloride (0.49 mg, 2.57 mmol) in small portions with constant stirring. The reaction was complete (TLC) in 5 h. To the reaction mixture was added ethyl acetate (20 ml) and water (2 ml). The organic layer was separated and washed successively with 2M HCl, 5% $NaHCO_3$ and water and then dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified on silica gel (hexanes–ethyl acetate, 20:1) to give the title product **12** (487 mg, 77%); δ_H(80 MHz, $CDCl_3$): 7.80 (d, *J* 8.2 Hz, 2 H), 7.34 (d, *J* 8.2 Hz, 2 H), 4.84 (br s, 1 H), 4.63 (br s, 1 H), 3.85 (s, 2 H), 2.71 (t, *J* 7.2 Hz, 1 H), 2.45 (s, 3 H), 2.17–1.12 (m, 4 H), 1.53 (s, 3 H) and 0.90 (s, 3 H); δ_C(25.15 MHz, $CDCl_3$): 144.17, 143.66, 132.74, 129.31, 127.35, 110.20, 76.99, 44.95, 41.20, 26.23, 22.23, 21.04, 18.37 and 16.56.

trans-2-*Isopropenyl*-1-*methylcyclobutylacetonitrile* **13**.—A mixture of the tosylate **12** (50 mg, 0.17 mmol), NaCN (12.5 mg, 0.19 mmol), water (2 drops) and HMPA (0.7 ml) was heated at 80–90 °C for 5 h with stirring. The mixture was partitioned between a 20:1 mixture of hexanes–ethyl acetate (20 ml) and water (4 ml). The organic layer was washed with brine (× 3), dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (2 g, hexanes–ethyl acetate, 20:1) to give the title nitrile **13** (19 mg, 76%); ν_{max}(neat): 2247 and 1647 cm^{-1}; δ_H(200 MHz, $CDCl_3$): 4.88 (m, 1 H), 2.73 (t, 1 H), 2.42 (s, 2 H), 1.64 (s, 3 H) and 1.04 (s, 3 H); δ_C(50 MHz, $CDCl_3$): 143.72, 118.13, 111.01, 48.53, 39.82, 31.17, 29.37, 22.75, 19.79 and 18.97.

Racemic Fragranol **1**.—To a solution of the nitrile **13** (43 mg, 0.29 mmol) in dry methylene dichloride (1 ml) was slowly added a solution of 1M DIBAL in toluene (0.29 ml, 0.29 mmol) at −20 °C. The resulting solution was stirred at −20 °C for 1 h and then gradually warmed to room temperature over 30 min. The reaction mixture was diluted with water (0.2 ml) followed by 5% (w/v) H_2SO_4 (0.5 ml) and the mixture was then stirred for 30 min. The mixture was extracted with ether (2 × 20 ml) and the organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. This was used for the next reaction without further purification.

To a solution the crude aldehyde in ethanol (1 ml) was added $NaBH_4$ (5 mg, 0.13 mmol) and the mixture was stirred for 5 min at room temperature. The reaction mixture was quenched by addition of acetone (2 drops). The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2.5 g, hexanes–ethyl acetate, 4:1) to give fragranol **1** (24 mg, 54% for two steps); ν_{max}(neat): 3335 and 1646 cm^{-1}; δ_H(200 MHz, $CDCl_3$) 4.82 (br s, 1 H), 4.60 (s, 1 H), 3.69 (m, 2 H), 2.56 (t, *J* 8.6 Hz), 1.64 (s, 3 H) and 0.93 (s, 3 H); δ_C(50 MHz, $CDCl_3$): 145.56, 109.77, 59.91, 50.50, 46.66, 40.94, 30.25, 22.99, 19.74 and 19.46; *m/z* 154 (M^+) (Found: M^+, 154.1347. $C_{10}H_{18}O$ requires 154.1358).

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