Utilization of Selenium-directed [2 + 2] Cycloadditions: Concise Synthesis of (±)-Fragranol

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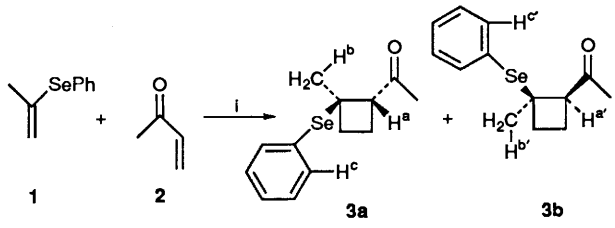
The reaction of 2-(phenylseleno)prop-1-ene **1** and methyl vinyl ketone **2** in the presence of $EtAlCl_2$ gave the [2 + 2] cycloadducts **3a** and **3b**. A radical substitution of the adducts **3a** and **3b** with allyltributyltin gave the allylated cyclobutane product, which was transformed into the cyclobutane natural product, (±)-fragranol. Stereoselective radical substitution using the ethylene glycol ketals of compounds **3a** and **3b** was also achieved.

Heteroatoms such as silicon, sulfur and tin have been extensively used recently as effective directing atoms in various kinds of synthetic reactions to control chemo-, regio- and stereoselectivities.[1] Although selenium has been recognized to be versatile for conversion of functional groups,[2] the use of selenium as a directing atom in organic synthesis is limited.[3]

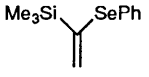
Recently, we reported selenium-directed stereoselective [2 + 2] cycloaddition of silyl vinyl selenides promoted by Lewis acids.[4] The phenylseleno group proved to be an excellent directing group for [2 + 2] cycloadditions and the resulting selenium- and silyl-substituted cycloadducts were demonstrated to be synthetically useful by a formal synthesis of (±)-junionone.[4] For further applications, we have investigated the [2 + 2] cycloadducts of alkyl vinyl selenides and the transformation of the selenium-substituted cycloadducts into the cyclobutane natural product (±)-fragranol **8a**, which is one of the constituents of *Artemisia fragrans willd.*[5] In this transformation, one of the versatile synthetic utilities of selenium, generation of a carbon-centred radical, has been utilized.

Aluminium-promoted [2 + 2] *Cycloadditions.*—Phenylseleno groups have been successfully used for radical carbon–carbon bond formation,[6] and selenium-substituted cyclobutanes can generate a radical on a cyclobutane ring. Hence, 2-acetyl-1-methyl-1-phenylselenocyclobutane **3** could be a versatile key intermediate for the synthesis of fragranol. In our previous report, attempted [2 + 2] cycloaddition of 2-phenylselenoprop-1-ene **1** and the methyl vinyl ketone **2** in the presence of $SnCl_4$ was unsuccessful.[4] Various kinds of Lewis acids were subsequently investigated, and we have now found that reaction of the propene **1** and excess of ketone **2** (3 mol equiv.) in the presence of $EtAlCl_2$ (0.9 mol equiv.) gave diastereoisomers **3a/b** (1.4:1) in 58% yield. Reaction of the propene **1** and excess of ketone **2** (3 mol equiv.) in the presence of $AlCl_3$ (1.0 mol equiv.) also gave products **3a/b** (1.5:1) in 44% yield. The two stereoisomers **3a** and **3b** were conveniently separated by column chromatography, and their relative stereochemistry was determined by 2D nuclear Overhauser (2D-NOESY) spectroscopy. In the major isomer **3a**, NOEs were observed between H^a (δ 3.30–3.34, m) and H^c (δ 7.66–7.68, m) and not between H^a and H^b (δ 1.45, s). On the other hand, in the minor isomer **3b**, NOEs were observed between $H^{a'}$ (δ 3.16–3.20, m) and $H^{b'}$ (δ 1.76, s), but not between $H^{a'}$ and $H^{c'}$ (δ 7.58–7.62, m) (see numbering of H-atoms in Scheme 1). Therefore, the stereochemistry of the major isomer **3a** was assigned as *trans* and that of the minor isomer **3b** was *cis*, with respect to the relationship between the phenylseleno and acetyl groups. Thus, this [2 + 2] cycloaddition is regioselective but relatively nonstereoselective, and slightly favoured to give the opposite diastereoisomer to that obtained by the $SnCl_4$, $AlCl_3$



Scheme 1 *Reagent and yield:* i, $EtAlCl_2$ (58%)

or $EtAlCl_2$-promoted [2 + 2] cycloaddition of 1-(phenylseleno)-1-(trimethylsilyl)ethene **4** and ketone **2**.[4]



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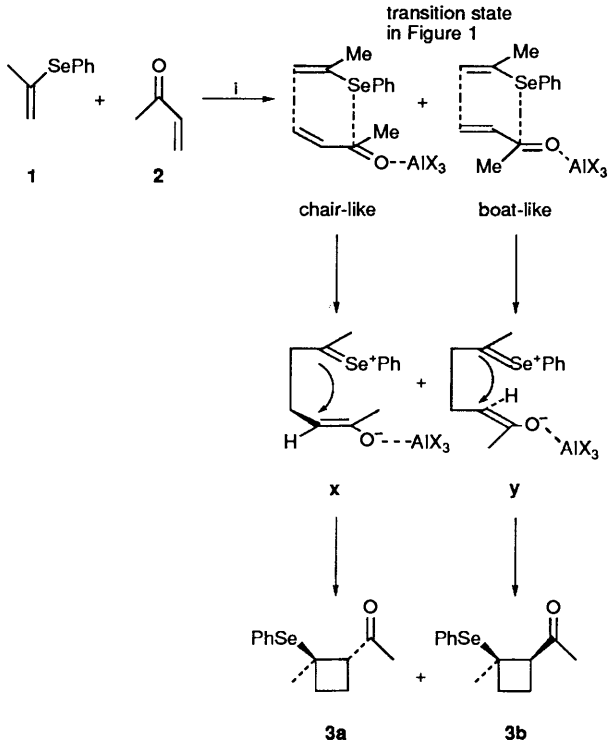
The observed regioselectivity with respect to selenium and the stereochemical outcome may be explained as follows.† Scheme 2 outlines the proposed course of the [2 + 2] cycloaddition process. In the first step, the nucleophilic vinyl selenide **1** attacks the electrophilic olefin **2** activated by a Lewis acid ($AlEtCl_2$ or $AlCl_3$) to give betaine intermediate **x** or **y**. The secondary-orbital interaction which was considered in the $SnCl_4$-promoted [2 + 2] reaction of the silyl analogue **4**[4] may occur in this first conjugate addition step (Fig. 1). The low stereoselectivity of the [2 + 2] cycloaddition of compounds **1** and **2** and slightly opposite preference to that of the silyl analogue **4** and ketone **2** is probably due to the smaller size of a methyl group compared with that of a trimethylsilyl group. Although a boat-like transition state was postulated in the [2 + 2] cycloaddition of the silyl analogue **4** because of the steric effect of the bulky $SiMe_3$ group, both a chair-like and a boat-like transition state would exist in this case because the steric hindrance between two Me groups of substrates **1** and **2** in a chair-like transition state is not so large compared with that of the silyl analogue **4** and ketone **2** (Fig. 2).

The low stereoselectivity of the [2 + 2] cycloaddition of compounds **1** and **2** was not troublesome since the phenylseleno

† Compounds **3a** and **3b** were separately treated with $EtAlCl_2$ (1 mol equiv.) in CH_2Cl_2 (−78 °C; 3 h), followed by Et_3N work-up at the same temperature. Compound **3a** gave the starting material with partial decomposition and formation of compound **3b** was not detected. Compound **3b** gave mainly the starting material with partial decomposition and a trace amount of compound **3a** was detected. Therefore, equilibrium of diastereoisomers of **3a** and **3b** under the reaction conditions is unlikely.

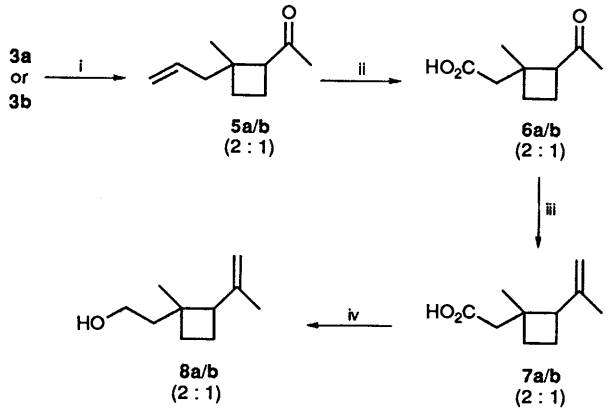


Scheme 2 *Reagents:* i, AlX_3 (X_3 = $EtCl_2$ or Cl_3)

group was planned to function as a latent radical for the synthesis of fragranol.

Synthesis of (±)-*Fragranol.*—The use of allyltin reagents to effect allyl transfer by a radical chain process is now well established.[1,6,9] A radical-substitution reaction of the phenylseleno group for stereoisomers **3a** and **3b** obtained as described above was attempted using allyltributyltin. When a mixture of compound **3a**, allylbutyltin (3 mol equiv.) and azoisobutyronitrile (AIBN) in benzene was heated at 80 °C for 4 h, allylated products **5a/b** (2:1), which could not be separated, were obtained in 86% yield. The same product mixture was obtained from the other diastereoisomer **3b** in 58% yield. The 2:1 mixture of compounds **5a/5b** obtained from selenides **3a** and **3b** was transformed by the following sequence (Scheme 3). Oxidation of alkenes **5a/b** by $NaIO_4$–$RuCl_3$·xH_2O and a neutral work-up gave acids **6a/b** (2:1) in 93% yield. Methylenation of the carbonyl group of acids **6a/b** by use of the modified Nozaki reagent, Zn–CH_2Br_2–$TiCl_4$,[10] gave **7a/b** (2:1) in 98% yield. The methylenated products **7a/b** were reduced with $LiAlH_4$ in diethyl ether to give a 2:1 mixture of (±)-fragranol **8a** and its diastereoisomer (±)-grandisol **8b**, respectively.[11] The spectral data of the mixture containing the alcohols **8a** and **8b** are in accord with the reported data. Fragranol **8a** was isolated after column chromatography. Separation of the diastereoisomers **5a/b**, **6a/b** and **7a/b** was not possible by column chromatography.

Next, in order to obtain stereoselectivity in the radical substitution step, ketals of compounds **3a** and **3b** were examined (Scheme 4). Ketalization of compound **3a** with ethylene glycol in the presence of *p*-TsOH in refluxing benzene for 4.5 h gave a ~4:1 mixture of *trans* and *cis* ketals **9a/b** in 87% yield. Ketalization of the stereoisomer **3b** with ethylene glycol also gave a ~4:1 mixture of ketals **9a/b** in 80% yield. The stereochemistry of ketals **9a/b** obtained under these thermodynamic conditions was assigned by steric considerations. When the mixture of ketals **9a/b** (4:1), allyltributyltin (3 mol equiv.) and AIBN in benzene was heated at 80 °C for 4h,



Scheme 3 *Reagents and yields:* i, CH_2=$CHCH_2SnBu_3$, AIBN (86% from **3a**, 58% from **3b**); ii, $NaIO_4$, $RuCl_3$·xH_2O (93%); iii, Zn–CH_2Br_2–$TiCl_4$ (98%); iv, $LiAlH_4$ (65%)

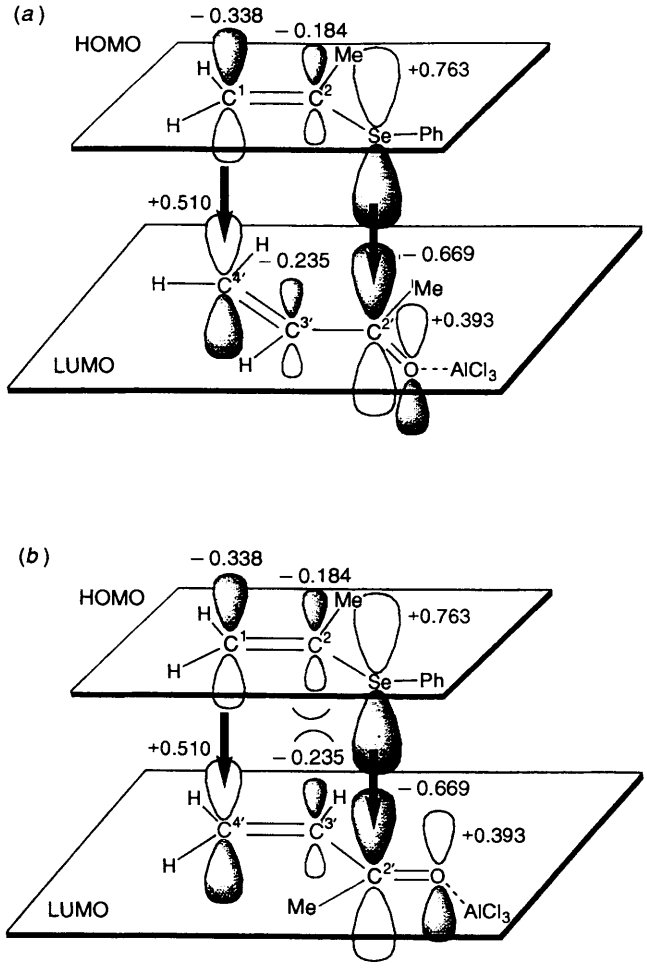


Fig. 1 Frontier orbital coefficients of the HOMO of selenide **1** and LUMO of $AlCl_3$-coordinated methyl vinyl ketone **2** are shown. These coefficients are of PM3[7] in MOPAC ver. 6.[8] (*a*) The HOMO ⟶ LUMO charge-transfer interaction in the chair-like alignment. (*b*) The HOMO ⟶ LUMO charge-transfer interaction in the boat-like alignment. The boat-like alignment is unfavourable because of C^2–$C^{3'}$ orbital cancellation.

allylated product **10a/b** (diastereoisomeric ratio 9:1) was obtained in 48% yield. Although the product yield decreased compared with that from direct allylation of seleno ketone **3a** or **3b** by ketalic protection, compounds **10a/b** were obtained with high stereoselectivity. Thus, the generated four-membered

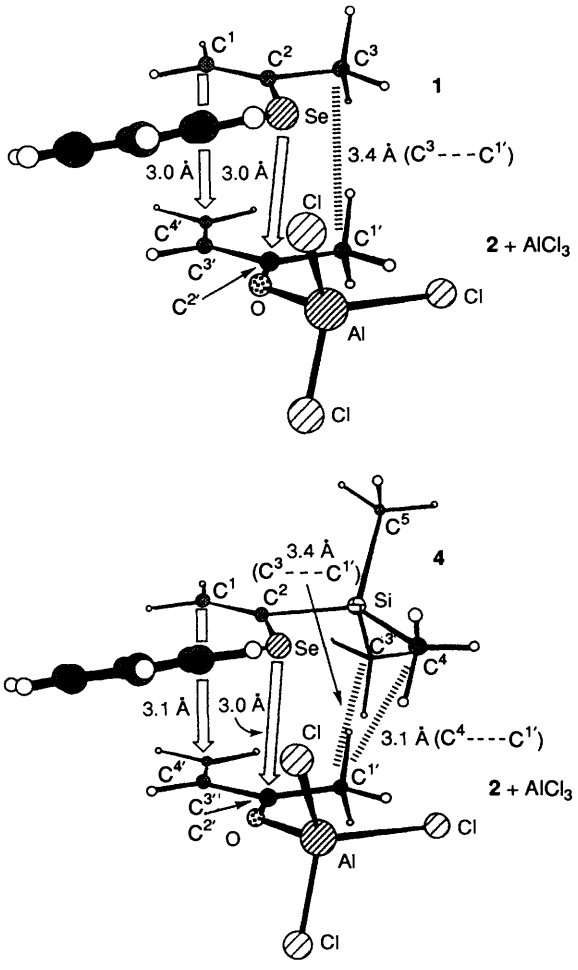
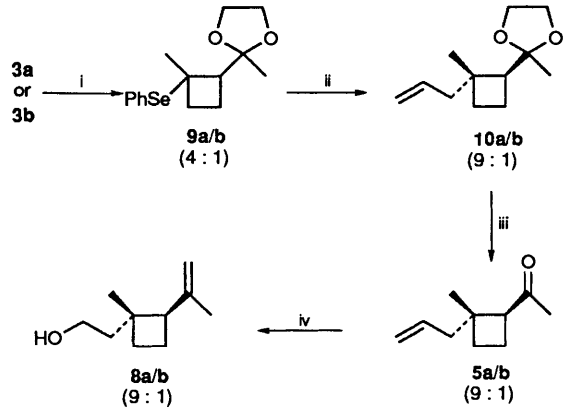


Fig. 2 Each reactant geometry is that optimized (PM3) at the isolated state. When the Se ··· C$^{2'}$ distance is set to 3.0 Å, a C^{1} ··· C$^{4'}$ distance of ~ 3.0 Å is obtained between **1** and **2** + $AlCl_3$ and between **4** and **2** + $AlCl_3$. These molecular-model figures demonstrate that steric hindrance between the two methyl groups of **1** and **2** in a chair-like transition state is not as large as that between the Me of **2** and the Me_3Si group of **4**.

cyclic radical from seleno ketals **9a/b** reacted with allyltributyltin from the *anti* side of the ketal group and the attempted stereoselective radical substitution was successful. The ketal group of compounds of **10a/b** (9:1) was removed by oxidative cleavage (Ph_3C^+ BF_4^-)[12] to give ketones **5a/b** (9:1) in 70% yield. Ketones **5a/b** (9:1) were transformed into (±)-fragranol **8a** *via* the intermediates with high diastereoisomeric ratios (9:1) by the method already described (Scheme 4).



Scheme 4 *Reagents and yields:* i, ethylene glycol, *p*-TsOH (87% from **3a**, 80% from **3b**); ii, CH_2=$CH_2CH_2SnBu_3$, AIBN (48%); iii, Ph_3C^+ BF_4^- (70%); iv, $NaIO_4$, $RuCl_3$·xH_2O; then Zn–CH_2Br_2–$TiCl_4$; then $LiAlH_4$

Experimental

General Methods.—IR spectra were recorded with a JASCO FT-IR 5000 spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a JEOL FX-200 or JEOL JNM-GSX400 spectrometer. For the ^1H and ^{13}C spectra, Me_4Si was used as internal reference. *J* Values are given in Hz. Mass spectra were determined on a JMS-SX102 spectrometer. Gas chromatography (GLC) was performed on a Yanaco G6800 chromatograph fitted with a flame ionization detecter and using a fused silica capillary column (carrier gas He, 1.0 kg cm^{-2}). All reactions were carried out under nitrogen.

r-2-*Acetyl*-c-1-*methyl*-t-1-(*phenylseleno*)*cyclobutane* **3a** *and* r-2-*Acetyl*-t-2-*methyl*-c-2-(*phenylseleno*)*cyclobutane* **3b**.—To a mixture of 0.95 mol dm^{-3} $EtAlCl_2$ in hexane (1.69 cm^3, 1.61 mmol) and dichloromethane (3.4 cm^3), cooled to −78 °C, was added selenide **1** (353 mg, 1.78 mmol), followed by methyl vinyl ketone **2** (374 mg, 5.34 mmol). The mixture was stirred at −78 °C for 3 h. The reaction mixture was quenched by triethylamine (1.51 cm^3, 10.9 mmol), and then saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel and eluted with hexane–diethyl ether (2:1) to give compound **3a** (162 mg, 34%) (R_f 0.5) and compound **3b** (112 mg, 24%) (R_f 0.3). Compound **3a**: pale yellow oil; δ_H(400 MHz; $CDCl_3$) 1.45 (3 H, s, Me), 1.61–1.70 (1 H, m), 1.78–1.86 (1 H, m), 2.11 (3 H, s, COMe), 2.27–2.38 (2 H, m), 3.30–3.34 (1 H, m, C*H*COMe), 7.35–7.44 (3 H, m, *m*-, *p*-H of SePh) and 7.66–7.68 (2 H, m, *o*-H of SePh). NOEs were observed between δ 3.30–3.34 and δ 7.66–7.68 by 2D-NOESY; δ_C(100.4 MHz; $CDCl_3$) 17.02 (CH_2), 23.03 (CH_3), 29.80 (CO*Me*), 33.57 (CH_2), 48.60 (C), 55.13 (CH), 128.0 (C), 129.0 (CH), 129.2 (CH), 137.7 (CH) and 206.7 (C). ^{13}C Multiplicities were determined by ^{13}C–^1H 2D homonuclear chemical-shift correlation (COSY) and intensive nuclei enhancement by polarization transfer (INEPT) spectroscopy; ν_{max}(neat)/cm^{-1} 2960, 1711, 1437, 1359, 1181, 743 and 694; MS (70 eV) *m/z* (relative intensity) 268 (7), 157 (16), 111 (100) and 43 (63) (Found: M^+, 268.0354. Calc. for $C_{13}H_{16}O^{80}Se$: M, 268.0366) (Found: M^+, 266.0354. Calc. for $C_{13}H_{16}O^{78}Se$: M, 266.0374). Compound **3b**: pale yellow oil; δ_H(400 MHz; $CDCl_3$) 1.76 (3 H, s, Me), 1.85–1.97 (2 H, m), 2.05–2.15 (1 H, m), 2.11 (3 H, s, COMe), 2.42–2.52 (1 H, m), 3.16–3.20 (1 H, m, C*H*COMe), 7.24–7.36 (3 H, m, *m*-, *p*-H of SePh) and 7.58–7.62 (2 H, m, *o*-H of SePh). NOEs were observed between δ 1.76 and δ 3.16–3.20 by 2D-NOESY; δ_C(50.1 MHz; $CDCl_3$) 18.71 (CH_2), 29.42 (CH_3), 32.08 (CH_3), 33.57 (CH_2), 50.00 (C), 58.65 (CH), 127.5 (C), 128.6 (CH), 128.8 (CH), 137.6 (CH) and 206.6 (C). ^{13}C Multiplicities were determined by INEPT; ν_{max}(neat)/cm^{-1} 2954, 1709, 1437, 1359, 1183, 743 and 694; MS (70 eV) *m/z* (rel. int.) 268 (24), 158 (14), 111 (100) and 43 (42) (Found: M^+, 268.0350. Calc. for $C_{13}H_{16}OSe$: M, 268.0366).

Reaction of Compounds **1** *and* **2** *in the Presence of* $AlCl_3$.—To a mixture of $AlCl_3$ (166 mg, 1.25 mmol) and dichloromethane (1 cm^3), cooled to −78 °C, was added a solution of selenide **1** (197 mg, 1.0 mmol) in dichloromethane (1 cm^3), followed by methyl vinyl ketone **2** (211 mg, 3.0 mmol). The mixture was stirred at −78 °C for 3 h before being quenched by triethylamine (0.261 cm^3, 1.88 mmol), and then saturated aq. $NaHCO_3$ was added to the mixture. The mixture was extracted

with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel and eluted with hexane–diethyl ether (2:1) to give compounds **3a** (71 mg, 27%) and **3b** (46 mg, 17%).

r-2-*Acetyl*-t- *and* c-1-*allyl*-1-*methylcyclobutane* **5a**/**b**.[13]—A mixture of compound **3a** (157 mg, 0.59 mmol), allyltributyltin (586 mg, 1.77 mmol) and AIBN (21 mg, 0.13 mmol) in benzene (1.3 cm^3) was refluxed for 4 h. After cooling the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel and eluted with hexane–diethyl ether (4 : 1) to give compounds **5a**/**b** (diastereoisomeric ratio 2:1 determined by ^1H NMR spectroscopy) (77 mg, 86%) (R_f 0.5).

When compound **3b** (164 mg, 0.615 mmol) was used as the starting material, compounds **5a**/**b** (2:1) (54.5 mg, 58%) were obtained. Compounds **5a**/**b**: oil; b.p. 60–65 °C/19 mmHg; δ_H(200 MHz; $CDCl_3$) peaks for **5a**: 0.995 (3 H, s, Me), 1.44–1.54 (1 H, m), 1.66–1.91 (2 H, m), 2.04 (3 H, s, COMe), 2.24–2.39 (1 H, m), 2.30 (2 H, d, *J* 7.3), 3.06 (1 H, t-like, *J* 8.3), 5.12 (1 H, d, *J* 15.9), 5.13 (1 H, d, *J* 12.0) and 5.74–5.95 (1 H, m); peaks for **5b**: 1.28 (3 H, s, Me), 1.61–2.02 (3 H, m), 2.07 (3 H, s, COMe), 2.12–2.23 (3 H, m), 2.98–3.06 (1 H, m), 4.99–5.10 (2 H, m) and 5.58–5.75 (1 H, m); δ_C(50.1 MHz; $CDCl_3$) peaks for **5a**: 16.08, 21.25, 29.51, 30.21, 43.32, 47.52, 53.39, 117.83, 134.4 and 208.5; peaks for **5b**: 15.93, 27.84, 29.10, 30.70, 39.96, 43.23, 56.11, 117.77, 134.0 and 208.5; ν_{max}(neat)/cm^{-1} 2958, 1707, 1361, 1180 and 917; MS (70 eV) *m*/*z* (rel. int.) 152 (8), 111 (58), 110 (55), 94 (63), 82 (70), 71 (84), 67 (100) and 43 (83) (Found: C, 78.8; H, 10.7%. M^+, 152.1213. Calc. for $C_{10}H_{16}O$: M, 152.1201. C, 78.90; H, 10.59%).

t- *and* c-2-*Acetyl*-1-*methy*-r-1-*cyclobutaneacetic Acid* **6a**/**b**.—A flask was charged with CCl_4 (7.2 cm^3), MeCN (7.2 cm^3), water (7.2 cm^3), compounds **5a**/**b** (2:1) (206 mg, 1.35 mmol) and $NaIO_4$ (1.35 g, 6.3 mmol). To the mixture was added ruthenium trichloride hydrate (25 mg, ~0.12 mmol), and the reaction mixture was stirred vigorously for 1 h at room temperature. Water was added, and the mixture was extracted three times with CH_2Cl_2. The combined organic extracts were dried ($NaSO_4$) and concentrated. The resulting residue was diluted with diethyl ether, filtered through a Celite pad, and concentrated to give acids **6a**/**b** (diastereoisomeric ratio 2:1 determined by ^1H NMR spectroscopy) (212 mg, 93%). Acids **6a**/**b**: oil; b.p. 100–120 °C/1 mmHg; δ_H(200 MHz; $CDCl_3$) peaks for **6a**: 1.14 (3 H, s, Me), 1.62–2.04 (3 H, m), 2.09 (3 H, s, COMe), 2.26–2.45 (1 H, m), 2.605–2.612 (2 H, m, CH_2CO_2H), 3.23 (1 H, t-like, *J* 8.3, C*H*COMe) and 9.70 (1 H, br s, CO_2H); peaks for **6b**: 1.41 (3 H, s, Me), 1.61–2.40 (4 H, m), 2.12 (3 H, s, COMe), 2.50–2.52 (2 H, m, CH_2CO_2H) 3.10 (1 H, t-like, *J* 8.2, C*H*COMe) and 9.70 (1 H, br s, CO_2H); δ_C(50.1 MHz; $CDCl_3$) peaks for **6a**: 16.78, 21.27, 30.15, 30.53, 41.19, 46.76, 53.48, 177.6 and 208.6; peaks for **6b**: 17.57, 27.72, 30.53, 30.94, 39.76, 41.27, 55.00, 178.3 and 209.6; ν_{max}(neat)/cm^{-1} 3200, 2940, 1700, 1363 and 1185; MS (70 eV) *m*/*z* (rel. int.) 170 (10), 124 (34), 111 (45), 71 (100) and 43 (84) (Found: M^+, 170.0934. Calc. for $C_9H_{14}O_3$: M, 170.0943). The spectral data for acid **6b** are in accord with the reported data.[11c–e]

t- *and* c-2-*Isopropenyl*-1-*methyl*-r-1-*cyclobutaneacetic Acid* **7a**/**b**.—Ice-cold Zn–CH_2Br_2–$TiCl_4$ reagent (~0.58 mol dm^{-3}; 9.3 cm^3, 5.4 mmol), which was prepared according to the literature procedure,[10c] was added portionwise to a stirred solution of keto acids **6a**/**b** (2:1) (157 mg, 0.92 mmol) in dichloromethane (8.2 cm^3) at room temperature. The mixture was stirred for 1 h before being poured into a mixture of sodium hydrogen carbonate (24 g), water (55 cm^3) and diethyl ether (55 cm^3). The mixture was extracted with diethyl ether (~110 cm^3). The organic phase was washed with water and dried ($MgSO_4$). Removal of the solvent gave the crude product **7a**/**b** (diastereoisomeric ratio 2:1 determined by ^1H NMR spectroscopy) (151 mg, 98%). The crude product can be used for the next reaction without further purification. Pure acids **7a**/**b** were obtained by column chromatography over silica gel and elution with hexane–diethyl ether (1:1) (R_f 0.5). Compounds **7a**/**b**: oil; δ_H(200 MHz; $CDCl_3$) peaks for **7a**; 1.04 (3 H, s), 1.65 (3 H, s), 1.82–2.03 (4 H, m), 2.50 (2 H, d, *J* 2.0), 2.57–2.71 (1 H, m), 4.61 (1 H, br s), 4.86 (1 H, br s) and 10.8 (1 H, br s); peaks for **7b**: 1.33 (3 H, s), 1.66 (3 H, s), 1.74–2.08 (4 H, m), 2.50–2.52 (2 H, m), 2.59 (1 H, m), 4.65 (1 H, br s), 4.87 (1 H, br s) and 10.8 (1 H, br s); δ_C(50.1 MHz; $CDCl_3$) peaks for **7a**: 19.61, 22.94, 30.15, 40.46, 47.79, 49.83, 110.4, 144.9 and 178.8; peaks for **7b**: 18.91, 23.17, 28.10, 29.16, 38.76, 41.36, 52.08, 110.5, 144.5 and 180.0; ν_{max}(neat)/cm^{-1} 3084, 2970, 2874, 1711, 1649, 1444, 1408, 1379 and 890; MS (70 eV) *m*/*z* (rel. int.) 168 (15), 153 (9), 125 (60), 108 (100) and 93 (49) (Found: M^+, 168.1106. Calc. for $C_{10}H_{16}O_2$: M, 168.1150). The spectral data for acid **7b** are in accord with the reported data.[11c–e]

(t-2-*Isopropenyl*-1-*methyl*-r-*cyclobutyl*)*ethanol* [(±)-*Fragranol*] **8a**.—Lithium aluminium hydride (71 mg, 1.84 mmol) was suspended in anhydrous diethyl ether (7.0 cm^3). A solution of acids **7a**/**b** (2:1) (192 mg, 1.4 mmol) in anhydrous diethyl ether (3.9 cm^3) was slowly added to the stirred mixture, which was then stirred overnight at room temprature. Water was added to the stirred and ice-cooled mixture. The mixture was extracted with diethyl ether and the organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue (141 mg, 65%) was a (±)-fragranol **8a**[5] and (±)-grandisol **8b**[11] (2:1) mixture by ^1H NMR spectroscopy. Compounds **8a**/**b**: oil; δ_H(200 MHz; $CDCl_3$) peaks for **8a**: 0.934 (3 H, s), 1.36–1.46 (2 H, m), 1.65 (3 H, d, *J* 0.7), 1.75–2.04 (5 H, m), 2.53–2.62 (1 H, m), 3.69 (2 H, t-like, *J* 7.6, 2-H), 4.62 (1 H, br s) and 4.83 (1 H, br s); peaks for **8b**: 1.17 (3 H, s), 1.26–2.04 (7 H, m), 1.67 (3 H, s), 2.53 (1 H, m), 3.67 (2 H, m), 4.65 (1 H, br s) and 4.84 (1 H, br s). After column chromatography [silica gel; hexane–diethyl ether (1:1)] compound **8a** (32 mg) was isolated (**8a**: R_f 0.45, **8b**: R_f 0.5). Compound **8a**: oil; δ_C(50.1 MHz; $CDCl_3$) 19.58, 19.84, 23.11, 30.35, 41.04, 46.73, 50.62, 59.96, 109.9 and 145.7; ν_{max}(neat)/cm^{-1} 3302, 2962, 1647, 1456, 1377, 1054 and 886; MS (70 eV) *m*/*z* (rel. int.) 154 (4), 139 (18), 121 (67), 109 (100) and 93 (100).

r-2-*Acetyl*-r-1-*methyl*-t- *and* -c-1-(*phenylseleno*)*cyclobutane Ethylene Ketal* **9a**/**b**.—A solution of compound **3a** (1.40 g, 5.25 mmol), ethylene glycol (756 mg, 12.2 mmol), benzene (58 cm^3), and toluene-*p*-sulfonic acid (5.3 mg) was refluxed for 4.5 h in a round-bottomed flask equipped with a Dean–Stark trap and a condenser. The solution was cooled to room temperature, washed with saturated aq. $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel with hexane–diethyl ether (2:1) as eluent to give a 4:1 (determined by ^1H NMR spectroscopy) isomeric mixture of ketals **9a**/**b** (1.41 g, 87%, R_f 0.6).

When compound **3b** (927 mg, 3.48 mmol) was used as the starting material, ketals **9a**/**b** (4:1) (858 mg, 80%) were obtained.

Ketals **9a**/**b**: pale yellow oil; δ_C(200 MHz; $CDCl_3$) (peaks for the major isomer **9a**) 1.32 (3 H, s), 1.64 (3 H, s), 1.72–2.00 (3 H, m), 2.13–2.23 (1 H, m), 2.72 (1 H, t, *J* 9.0), 3.78–4.14 (4 H, m), 7.26–7.35 (3 H, m) and 7.60–7.64 (2 H, m); δ_C(50.1 MHz; $CDCl_3$) (peaks for the major isomer **9a**) 18.82, 23.17, 23.40, 34.50, 48.22, 51.35, 63.84, 65.68, 109.7, 128.4, 128.5, 128.9 and 137.6; ν_{max}(neat)/cm^{-1} 2982, 2882, 1578, 1477, 1437, 1373, 1044, 741 and 694; MS (70 eV) *m*/*z* (rel. int.) 312 (100), 269 (8), 235 (9), 225 (10), 198 (51), 157 (34), 111 (35) and

87 (100) (Found: M^+, 312.0594. Calc. for $C_{15}H_{20}O_2Se$: M, 312.0629).

r-2-*Acetyl*-t- *and* -c-1-*allyl*-1-*methylcyclobutane Ethylene Ketal* **10a/b** (9:1).—The mixture of selenides **9a/b** (4:1) (465 mg, 1.5 mmol), allyltributyltin (1.49 g, 4.5 mmol) and AIBN (51 mg, 0.3 mmol) in benzene (3.0 cm^3) was refluxed for 4 h. After cooling, the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel and eluted with hexane–diethyl ether (4:1) to give ketals **10a/b** (diastereoisomeric ratio 9:1 determined by ^1H NMR spectroscopy) (141 mg, 48%) [R_f 0.75 (hexane–diethyl ether, 2:1)]. Ketals **10a/b**: oil; δ_H(200 MHz; $CDCl_3$) peaks for the major isomer **10a**: 1.14 (3 H, s), 1.22 (3 H, s), 1.37–1.48 (1 H, m), 1.63–1.98 (3 H, m), 2.14 (2 H, d, *J* 7.7), 2.33 (1 H, t-like, *J* 9.0), 3.82–4.02 (4 H, m), 5.01 (1 H, d, *J* 18.7), 5.03 (1 H, d, *J* 9.4) and 5.79 (1 H, tdd, *J* 7.7, 9.4 and 18.7); δ_C(50.1 MHz; $CDCl_3$) peaks for the major isomer **10a**: 17.74, 20.89, 23.67, 30.00, 41.25, 48.46, 49.65, 63.73, 65.39, 110.4, 116.7 and 135.5; ν_{max}(neat)/cm^{-1} 2980, 2958, 2880, 1640, 1371, 1046 and 913; MS (70 eV) *m/z* (rel. int.) 196 (4), 181 (41), 153 (95), 127 (26), 115 (38) and 99 (100) (Found: M^+, 196.1478. Calc. for $C_{12}H_{20}O_2$: M, 196.1463).

Alternative Preparation of Ketones **5a/b** (9:1).—A solution of ketals **10a/b** (9:1) (113 mg, 0.577 mmol) in dry dichloromethane (5.7 cm^3) was treated with trityl tetrafluoroborate (224 mg, 0.663 mmol) at 0 °C. After 30 min at 0 °C the mixture was treated with aq. sodium hydrogen carbonate and was stirred for 10 min. The dichloromethane layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography over silica gel and eluted with hexane–diethyl ether (4:1) to give ketones **5a/b** (9:1 determined by ^1H NMR spectroscopy) (61 mg, 70%).

Alternative Preparation of Keto Acids **6a/b** (9:1).—A flask was charged with CCl_4 (3 cm^3), MeCN (3 cm^3), water (3 cm^3), ketones **5a/b** (9:1) (88 mg, 0.58 mmol) and $NaIO_4$ (783 mg, 3.7 mmol). To this mixture was added ruthenium trichloride hydrate (11 mg, ~0.052 mmol) and the reaction mixture was stirred vigorously for 1 h at room temperature. Water was then added, and the mixture was extracted three times with CH_2Cl_2. The combined extracts were dried ($NaSO_4$) and concentrated. The resulting residue was diluted with diethyl ether, filtered through a Celite pad, and concentrated to give keto acids **6a/b** (9:1 determined by ^1H NMR spectroscopy) (98 mg, 99%).

Alternative Preparation of Acids **7a/b** (9:1).—Ice-cold Zn–CH_2Br_2–$TiCl_4$ reagent (~0.58 mol dm^{-3}; 5.8 cm^3, 3.3 mmol) was added portionwise to a stirred solution of keto acids **6a/b** (9:1) (98 mg, 0.58 mmol) in dichloromethane (5.5 cm^3) at room temperature. The mixture was stirred for 1 h and was then poured into a mixture of sodium hydrogen carbonate (16 g), water (37 cm^3) and diethyl ether (37 cm^3). The mixture was extracted with diethyl ether (~74 cm^3). The organic phase was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography over silica gel and eluted with hexane–diethyl ether (1:1) to give acids **7a/b** (9:1 determined by ^1H NMR spectroscopy) (67 mg, 69%).

Alternative Preparation of Alcohols **8a/b** (9:1).—$LiAlH_4$–Et_2O suspension (~1 mol dm^{-3}; 2 cm^3, 2 mmol) was slowly added to a stirred solution of acids **7a/b** (9:1) (66 mg, 0.392 mmol) in anhydrous diethyl ether (1.1 cm^3). The mixture was stirred overnight at room temperature. Water was added to the stirred, ice-cooled mixture. The mixture was extracted with diethyl ether and the organic phase was dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography [silica gel; hexane–diethyl ether (1:1)] of the residue gave (±)-fragranol **8a** and (±)-grandisol **8b** (diastereoisomeric ratio 9:1 determined by GLC) as a mixture (48 mg, 75%). GLC column [SUPELCOWAX-10 (0.25 mm × 30 m)], column temp. 50–250 °C, 10 °C min^{-1}; **8a** t_R 14.1 min, **8b** t_R 14.0 min.

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