Syntheses of Cyclobutane Derivatives: Total Synthesis of (+) and (–) Enantiomers of the Oleander Scale *Aspidiotus nerii* Sex Pheromone

François-Didier Boyer*[a] and Paul-Henri Ducrot[a]

Keywords: Pheromones / *Aspidiotus nerii* / Sex attractant / Cyclobutane / Enantiomeric purity

Synthesis of both enantiomers of the *Aspidiotus nerii* sex pheromone and their diastereomers has been achieved using, as a key step, an intramolecular ester enolate alkylation reaction for the formation of the cyclobutane ring with a good control of the relative configurations of the asymmetric centers. Stereoselective synthesis of a number of other trisubstituted cyclobutane derivatives also proves the versatility of the methodology used for the synthesis of the *Aspidiotus nerii* sex pheromone.

Aspidiotus nerii (Homoptera, Diaspididae) is an endemic pest in southern Europe. This highly polyphagous[1] scale insect attacks olive, citrus fruits, plum and various other trees, shrubs, low-growing and ornamental plants such as oleander. The life cycle of the insect has, in the case of the adult female, two nymphal instars before molt and, in the case of the adult male, four. The adult female is immobile, but the male has two wings and is therefore able to fly. The damage caused by this piercing and sucking insect consists of a weakening of the plant, leaf fall, drying of shoots and deformation of fruits. This scale insect usually has three generations per year. These consequences have led us to investigate the structure of the female sex pheromone produced by this species as it is a potentially decisive factor in survey and control strategies. The structure of the sex pheromone of *Aspidiotus nerii*[2][3] has been elucidated by ^{1}H- and ^{13}C-NMR experiments and mass spectrometry. However, these spectrometric methods did not allow the relative and absolute configurations of the two stereogenic centers of the molecule to be determined. A synthetic sample of the pheromone with a known absolute configuration would therefore be useful as a reference material in order to assign the absolute configuration of that occurring naturally. Accordingly, one must compare the synthetic sample with the natural pheromone by physical and/or biological methods. Hence the problem of synthesizing the four stereomers (1*S*,2*S*)- and (1*R*,2*R*)-**1** and (1*R*,2*S*)- and (1*S*,2*R*)-**2** (see Figure 1) was addressed. This work presents the studies required to obtain these four stereomers, involving stereoselective synthesis of various cyclobutane derivatives. This class of compounds is involved in many organic transformations,[4–6] their skeleton constituting the basic structure of several natural products[7–9] and the design of a versatile methodology for their synthesis is of topical interest.

The goal was to design an enantiospecific synthesis of all these diastereomers without having recourse to optical resolution and/or sophisticated reactions in order to be able to scale up the synthesis for biological field assays. An abundant monoterpene, carvone, commercially available either as a racemate or enantiomerically pure, was used as starting material. The initial strategy was based on alkylation of cyclobutane **A**, as K. Mori et al. described for the total synthesis of (+)-grandisol [(1*S*,2*R*)-(+)-2-isopropenyl-1-methylcyclobutaneethanol];[10] the pheromone component of the boll weevil *Anthonomus grandis* (see Scheme 1) and some other beetles.[11]

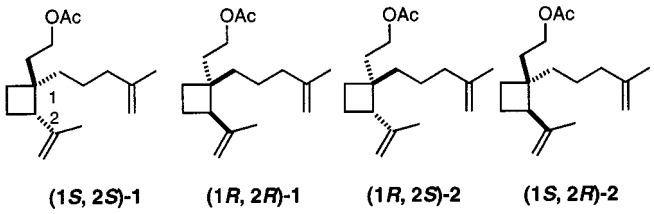
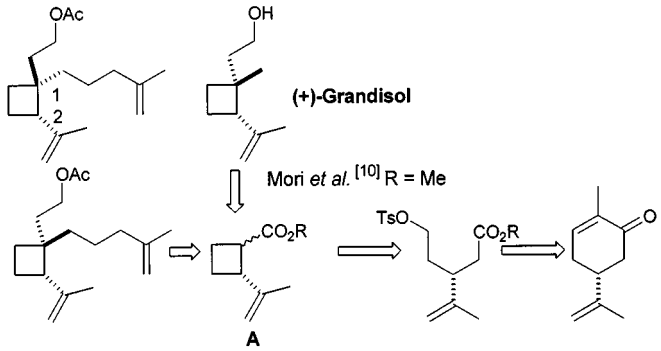


Figure 1. Four enantiomers of *Aspidiotus nerii* sex pheromone



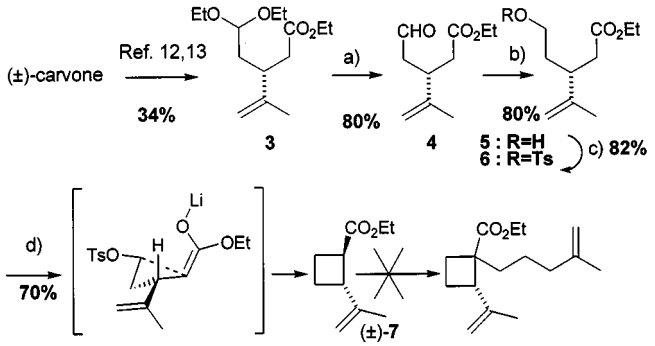
Scheme 1. Strategy based on alkylation of cyclobutane **A**

The starting ester **3** was synthesized from carvone in four steps according to a standard procedure[12,13] [34% overall yield (3 ×) in our hands]. Treatment of **3** with PTSA in a mixture acetone/water gave the formyl ester **4**, which was immediately reduced with sodium tetrahydridoborate to furnish the hydroxy ester **5** in an overall yield of 64%. Esterification of the hydroxy ester **5** under standard conditions led to the tosylate **6**. This substrate for the key cycli-

[a] Unité de Phytopharmacie et Médiateurs Chimiques, I.N.R.A., Route de Saint-Cyr, F-78026 Versailles, France.
Fax: (internat.) + 33-1/30833119
E-mail: boyer@versailles.inra.fr

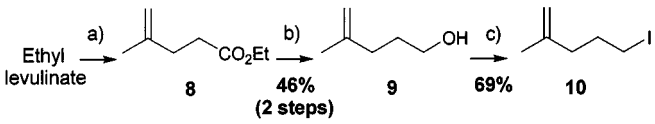
  1434–193X/99/0505–1201 $ 17.50+.50/0

zation reaction needed to be carefully purified by flash chromatography on silica gel in order to afford a high yield in the next step. After a number of attempts, the best yield for this intramolecular ester enolate alkylation was obtained with LiHMDS in THF/HMPA (85:15) at −10°C with high diastereoselectivity (> 95:5) (see Scheme 2). The observed high stereoselectivity can be explained by invoking the most stable "1-H-eclipsed" transition-state geometry as depicted in Scheme 2.[14][15][16]



Scheme 2. (a) PTSA, acetone/water, room temp., 48 h; (b) $NaBH_4$, EtOH, 0°C; (c) TsCl, pyridine, 0°C, 18 h; (d) LiHMDS, THF/HMPA, −10°C to room temp.

However, all attempts to perform the further alkylation of ethyl cyclobutanecarboxylate **7** with the iodide **10**[17][18] prepared, in our case, from commercially available ethyl levulinate by Wittig reaction involving the ketone function, reduction of the ester **8** and iodination of the resultant alcohol **9** (32% overall yield, see Scheme 3) failed. In all cases, the substrate **7** was recovered in a quantitative yield. It was therefore decided to introduce the 4-methyl-4-penten-1-yl side chain before cyclization into the cyclobutane derivative.

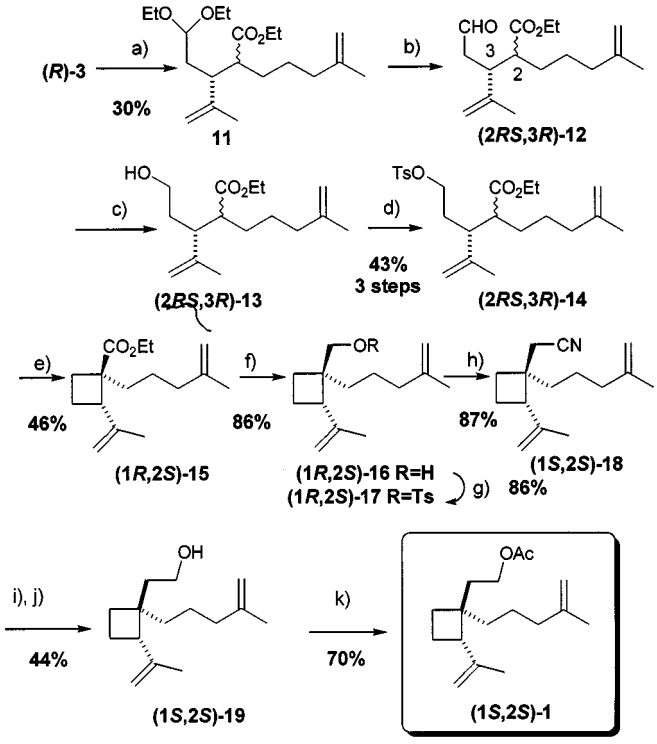


Scheme 3. (a) Ph_3PCH_3Br, BuLi, THF, −70°C to room temp., 24 h; (b) $LiAlH_4$, Et_2O, 0°C, 1 h; (c) I_2, Ph_3P, imidazole, benzene, 1 h, room temp.

The only problem which should arise from this choice of strategy would be that of the diastereoselectivity of the ester enolate alkylation reaction used for the formation of the cyclobutane ring. Indeed, one could argue that the "1-H-eclipsed" transition state advocated in the earlier reports in the literature as the explanation of the diastereoselectivity of the reaction would be disfavored when the side chain in the α position to the ester group experiences steric interactions with the isopropenyl substituent in the β position. It is of note that the only reports in the literature using this reaction with a substrate bearing an alkyl substituent at this position were aimed at the synthesis of fragranol[14] or grandisol,[16] the alkyl chain being a methyl group in both cases. Increasing the size of the side chain to a 4-methyl-4-penten-1-yl group should result in a decrease of the diastereoselectivity of the reaction.

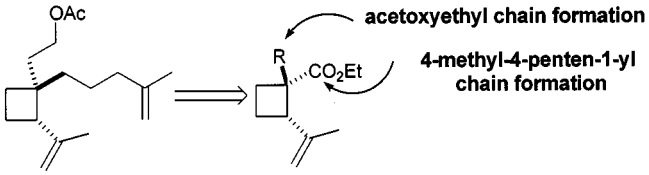
However, for the purposes of this study, the alkylation of ester **3** by treatment with KHMDS and iodide **10** in THF/HMPA (1:1) was performed and afforded the desired ester **11** as a mixture of inseparable diastereomers (73:27) in a yield of 30%, in addition to 50% of recovered starting material **3**. Modification of the experimental procedure did not increase the yield of alkylation (base, temperature, reaction time). The same conditions to form **6** from **3** were used to furnish the tosylate **14** in a yield of 43%. Intramolecular ester enolate alkylation was performed on **14** with LiHMDS in the presence of HMPA to afford the ethyl cyclobutanecarboxylate **15** in a yield of 46%. Surprisingly however, this reaction occurred with a similarly high diastereoselectivity as for **7** (> 95:5) in favour of the diastereomer having the configuration required for the synthesis of **1**.

In order to complete the synthesis, compound **15** was further converted into **1** through a six-step procedure using a conventional one-carbon homologation protocol.[14] Reduction of the ester **15** with lithium aluminium hydride in THF followed by tosylation in the presence of 4-DMAP gave the corresponding tosylate **17** in a yield of 70%. Substitution of the tosyloxy group of **15** by sodium cyanide in aqueous HMPA furnished the cyanide **18** in a yield of 87%. The crude aldehyde, obtained by DIBAL-H reduction of the cyanide **18** and careful acidic aqueous hydrolysis of the resultant imine, was immediately reduced to the alcohol **19** in an overall yield of 44%. Final acetylation of **19** furnished **1**.



Scheme 4. (a) KHMDS, THF, HMPA, 5-iodo-2-methyl-1-pentene (**10**), −20°C to 0°C; (b) PTSA, acetone, water, room temp., 48 h; (c) $NaBH_4$, EtOH, 0°C; (d) TsCl, pyridine, 0°C, 18 h; (e) LiHMDS, THF, HMPA, −10°C; (f) $LiAlH_4$, THF, 0°C to room temp., 3 h; (g) TsCl, 4-DMAP, CH_2Cl_2, 0°C, 18 h; (h) NaCN, aq. HMPA; (i) DIBAL-H, CH_2Cl_2, −20°C; (j) $NaBH_4$, EtOH, 0°C; (k) Ac_2O, pyridine

On the other hand, it was decided to synthesize **2** by taking advantage of the high diastereoselectivity observed in the formation of the cyclobutane ring by the reaction described above. It was thus necessary to form the 4-methyl-4-penten-1-yl chain from the ethoxycarbonyl side chain while the R group introduced in α position to the ester before the cyclization reaction was chosen as a good precursor of the acetoxyethyl moiety (see Scheme 5).

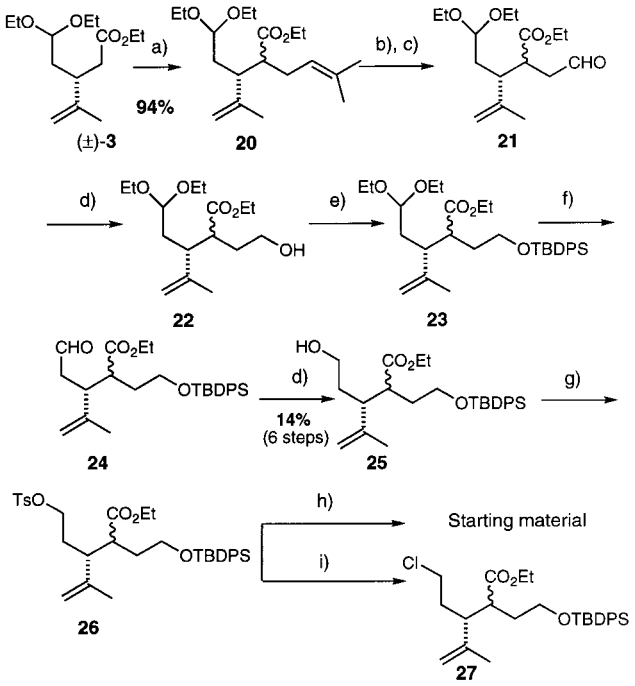


Scheme 5. Strategy based on trisubstituted cyclobutane ester

The first attempt used an alkenyl chain (allyl or 3,3-dimethylallyl) as a protected hydroxyethyl precursor before cyclization. Moreover, the use of an allyl bromide as the alkylating agent should enhance the efficiency of the alkylation step. Indeed, alkylation of **3** with 3,3-dimethylallyl bromide (KHMDS in a mixture THF/HMPA) gave the ester **20** in a yield of 94%.

Initially the transformation of this newly introduced alkenyl side chain into the desired hydroxyethyl substituent before cyclization was attempted. The selective osmylation of the more substituted double bond followed by the oxidative cleavage of the resultant vicinal diol afforded the aldehyde **21**, reduction of which afforded the alcohol **22** which could be then protected as its *tert*-butyldiphenylsilyl ether to yield **23**. The same sequence as described above furnished the hydroxy ester **25**. Tosylation under standard conditions gave the tosylate **26**. Disappointingly, all attempts to form the cyclobutane derivative from this substrate through the previously optimized procedure failed. The tosylate **26** was either recovered untouched or transformed into the chloro ester **27** upon hydrolysis with saturated aqueous ammonium chloride (see Scheme 6).

Nevertheless, an alternative route was to keep the alkenyl precursor of the acetoxyethyl side chain unchanged for the cyclization to form the four-membered ring. Therefore, **3** was transformed into the tosylate **30** (3 steps, yield 30%) (see Scheme 7). Intramolecular ester enolate alkylation performed on **30** gave, in this case, the cyclobutane derivative **31** in a yield of 50%, again with high diastereoselectivity (> 95:5). The stereochemistry of cyclobutane ester derivatives, at first assumed from mechanistic considerations, was unambiguously confirmed by NOE difference experiments performed on **31** and **32** (see Figure 2) and was in agreement with the literature.[14–16] In the same fashion, use of an allyl substituent instead of the 3,3-dimethyl did not affect the course of the reaction sequence and the cyclobutane **37** was synthesized from **35** in a good overall yield with the same diastereoselectivity. Noteworthy was the fact that, in all cases, the four-membered ring-formation reaction gave similar diastereoselection without being influenced by the nature and the bulkiness of the substituent in α position to the ester group. However, even if the nature of the side

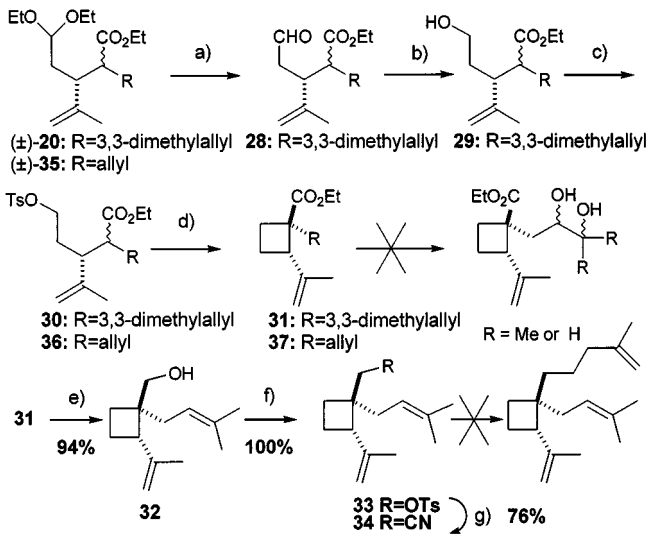


Scheme 6. (a) LiHMDS, THF, HMPA, 3,3-dimethylallyl bromide, −60°C to 0°C; (b) cat. OsO_4, NMO, acetone, water, room temp., 1 h; (c) $NaIO_4$, acetone/water, $NaHCO_3$, room temp., 1 h; (d) $NaBH_4$, EtOH, 0°C; (e) TBDPSCl, imidazole, DMF, room temp., 18 h; f) PTSA, acetone/water, room temp., 72 h; (g) TsCl, pyridine, 0°C, 18 h; (h) LiHMDS,THF/HMPA, 0°C, H_2O hydrolysis; (i) LiHMDS,THF/HMPA, 0°C, aq. NH_4Cl hydrolysis

chain did not seem to have any influence on the diastereoselectivity of the reaction, its increasing size induced a significant decrease in the chemical yield of the cyclobutane formation reaction (see Scheme 8). This work shows the versatility of the intramolecular enolate alkylation method developed by D. Kim and co-workers[14–16] to form various cyclobutane derivatives as summarized in Scheme 8. However, the inefficiency of this method when performed on a substrate bearing a protected hydroxyethyl side chain could be explained not only by steric considerations but also by an intramolecular chelation of the counterion by the oxygen atom of the side chain. It induces a folded conformation of the molecule which prevents the cyclization to occur.

The further elaboration of the two side chains of the molecule was then tried. Unfortunately, neither selective osmylation on compound **31** or **37**, nor alkylation on the tosylate **33** or the cyanide **34**, which would have allowed the formation of 4-methyl-4-penten-1-yl chain were possible, probably due to the steric hindrance of this part of the molecule (see Scheme 7).

So, it seemed essential to form the 4-methyl-4-penten-1-yl chain before cyclization to the four-membered ring. As the configuration of the target molecule **2** and the stereoselectivity observed in the four-membered ring formation were incompatible with this experimental feature, we were forced to adopt another synthetic strategy. Therefore, we decided to use compound **18** already obtained for synthesis of **1**. Indeed, the diastereomer **2** was finally synthesized by epimerization at C-2 of the cyclobutane as described below.



Scheme 7. (a) PTSA, acetone/water, room temp., 72 h; (b) $NaBH_4$, EtOH, 0°C; (c) TsCl, pyridine, 0°C, 18 h; (d) LiHMDS, THF/HMPA, 0°C; (e) $LiAlH_4$, Et_2O, 0°C; (f) TsCl, 4-DMAP, CH_2Cl_2, 0°C; (g) NaCN, aq. HMPA, 60°C

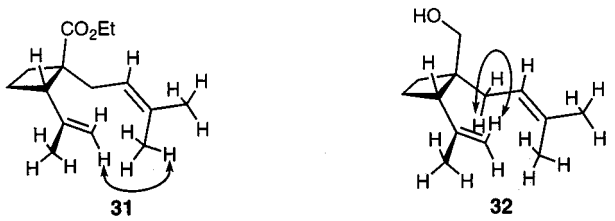
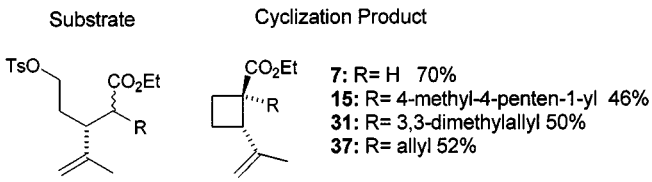


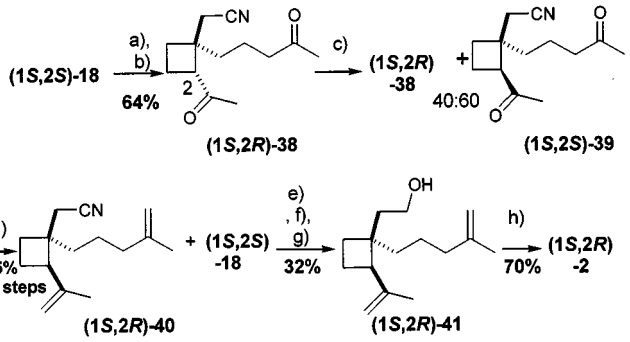
Figure 2. NOE for **31** and **32**



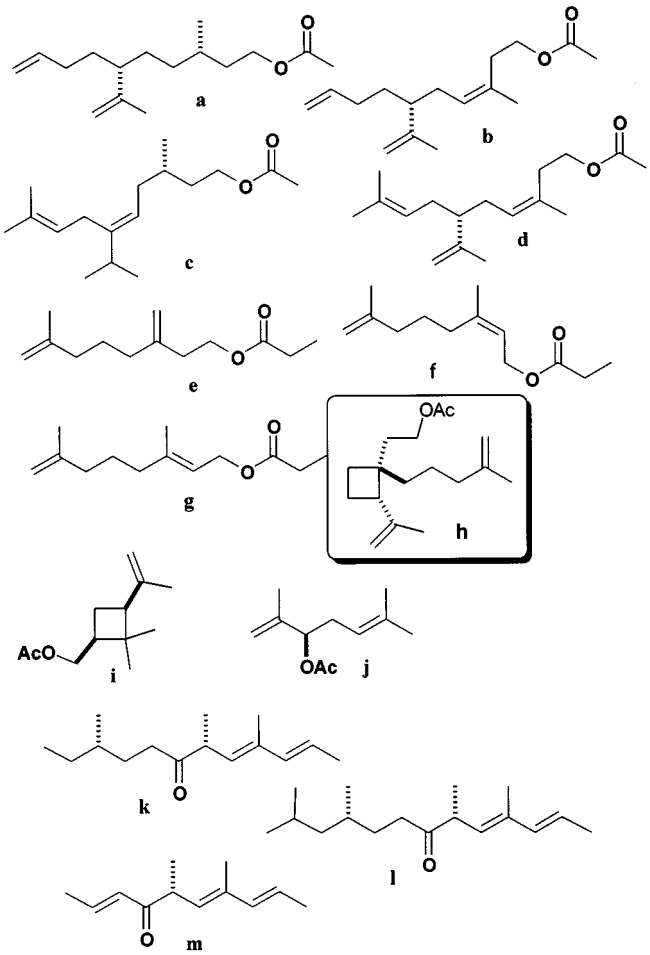
Scheme 8. Results of intramolecular ester enolate alkylation

Osmylation of **18** and oxidative cleavage of the resultant diol gave the diketone **38**. Epimerization at C-2 of **38** by treatment with base (DBU, benzene, 70°C, 18 h) yielded a 40:60 mixture of the diketones **38/39**. Double Wittig reaction performed on the diketone mixture **38/39** furnished the cyanides **18** and **40**. The same sequence as described for the preparation of **1** (see Scheme 9) completed the synthesis of **2**. Using either (*S*)-(+) or (*R*)-(−)-carvone as a starting material for the synthesis afforded (1*R*,2*R*)-(+)-**1** and (1*R*, 2*S*)-(−)-**2** $\{[\alpha]_D^{20} = -2.5$ (c = 1.1, n-hexane)$\}$ and (1*S*, 2*S*)-(−)-**1** and (1S, 2*R*)-(+)-**2** $\{[\alpha]_D^{20} = +2.4$ (c = 0.9, n-hexane)$\}$, respectively.

Comparison of the sprectroscopic data and coinjection with a sample of the natural pheromone led us to conclude that the pheromone has the relative configuration of **2**. GC separation of the enantiomers of **2** on chiral stationary phases failed. However, biological activity in greenhouse bioassays and field tests of these synthetic enantiomers (+)-**2** and (−)-**2** allowed unambiguous attribution of the absolute configuration of the active enantiomeric form of *Aspidiotus nerii* pheromone as (1*R*,2*S*)-(−)-**2**.[2] This confirms the high diversity of structures of known sex pheromones in the Superfamilia Coccoidea[19][20] (see Scheme 10). Insect



Scheme 9. (a) OsO_4, NMO, acetone/water, 18 h, room temp.; (b) $NaIO_4$, MeOH/water, 18 h, room temp.; (c) DBU, benzene, 80°C, 18 h; (d) $Ph_3P^+CH_2^-$, THF, −70°C to room temp.; (e) DIBAL-H, CH_2Cl_2, −20°C, then 5% H_2SO_4, H_2O; (f) $NaBH_4$, EtOH, 0°C; (g) careful separation on silica gel; (h) Ac_2O, pyridine



Scheme 10. Diaspididae: *Aonidiella aurantii* (**a**, **b**), *Aonidiella citrina* (**c**), *Pseudaulacapsis pentagona* (**d**), *Quadraspidiotus perniciosus* (**e**, **f**, **g**), *Aspidiotus nerii* (**h**), Pseudococcidae: *Planococcus citri* (**i**), *Pseudococcus comstocki* (**j**), Margarodidae: *Matsucoccus resinosae* (**k**), *Matsucoccus thunbergianae* (**k**), *Matsucoccus matsumurae* (**k**), *Matsucoccus feytaudi* (**l**), *Matsucoccus josephi* (**m**)

pheromones and/or attractants containing a cyclobutane function are relatively uncommon.[11] The sesquiterpene skeleton of the pheromone of *Aspidiotus nerii* is similar to that of the monoterpenic pheromone grandisol, with an additional isoprenic unit branched on the methyl group of grandisol.

In connection with the synthesis of this pheromone, we have investigated the scope and the limitations of the ester enolate alkylation methodology developed for the synthesis of cyclobutane derivatives. The usefulness of this methodology has been proven for the diastereoselective formation of various cyclobutane derivatives having two adjacent stereocenters bearing alkyl or alkenyl side chains, with an almost complete control of the configuration of the quaternary center formed in the course of the reaction.

Experimental Section

General: Melting points: Büchi 510, uncorrected values. − NMR (^{1}H: 300 MHz; ^{13}C: 75.5 MHz): VARIAN Gemini 300 instrument, in deuteriochloroform ($CDCl_3$), $CHCl_3$ ($CDCl_3$) as internal reference: δ = 7.27 for ^{1}H (δ = 77.14 for ^{13}C). − MS: Nermag R10−10C linked to a Varian 3300 GC, ionization obtained either by electronic impact (EI) or chemical ionization with ammonia (CI, NH_3). − IR: Perkin Elmer FT 1600 instrument or Perkin−Elmer 397 instrument using either NaCl salt plates (thin film) or NaCl cell (in the specified solvent). − Optical rotations: Perkin−Elmer 241 polarimeter in a 1-dm cell. − All reactions were monitored by thin layer chromatography (TLC): E. Merck Ref. 5554 precoated silica-gel 60F 254 plates, visualization accomplished with UV light then 7−10% ethanolic phosphomolybdic acid solution or $KMnO_4$ solution followed by heating were used as developing agents. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2) and dimethylformamide (DMF) from calcium hydride.

Ethyl 5,5-Diethoxy-3-isopropenylpentanoate (3): $Pb(OAc)_4$ (58.1 g, 262.4 mmol) was added to a solution of a mixture of diastereomeric *trans*-diol obtained from carvone[12][13] (12.08 g, 65.6 mmol, 0 °C) in a mixture benzene/ethanol (1:1, 140 mL). The reaction mixture was stirred for 2 h at room temp. and filtered through Celite. The solid was washed with ether and the filtrate washed with water, satd. aqueous sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was diluted with EtOH (250 mL) and triethyl orthoformate (37 mL) and PTSA (0.5 g, 2.6 mmol) were then added to this solution. The reaction mixture was stirred overnight at room temp. and concentrated under reduced pressure. The residue was dissolved in ether and the solution washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 30:70) and distillation (115−120 °C, 0.1 Torr) to give 14.1 g (84%) of **3** as a pale yellow liquid. (3*R*)-**3** from (*R*)-carvone, $[\alpha]_D^{20}$ = +2.7 (*c* = 1.51, CH_2Cl_2), (3*S*)-**3** from (*S*)-carvone, $[\alpha]_D^{20}$ = −2.5 (*c* = 2.61, CH_2Cl_2). − ^{1}H NMR: δ = 4.77 (m, 2 H), 4.43 (dd, 1 H, *J* = 7 Hz, *J* = 4 Hz), 4.08 (q, 2 H, *J* = 7 Hz), 3.70−3.40 (m, 4 H), 2.74 (m, 1 H), 2.44−2.34 (m, 2 H), 1.68 (m, 1 H), 1.67 (s, 3 H), 1.24−1.15 (m, 9 H). − ^{13}C NMR: δ = 172.4 (s), 145.9 (s), 112.5 (t), 101.3 (d), 61.1 (t), 60.3 (t), 40.0 (t), 39.3 (t), 36.9 (t), 18.8 (q), 15.5 (2 C, q), 14.3 (q). − Capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 100−300 °C, 10 °C/min), retention time 8.75 min. − EI MS; *m*/*z* (%): 257 (1), 212 (4), 187 (2), 185 (4), 167 (18), 139 (4), 121 (10), 103 (80), 93 (100), 75 (65), 67 (25), 47 (95). − IR (neat): $\tilde{\nu}$ = 3060 cm^{-1}, 2970, 2920, 1735, 1640.

Ethyl 3-Isopropenyl-5-oxopentanoate (4): PTSA (450 mg, 2.36 mmol) was added to a solution of **3** (1.7 g, 6.58 mmol) in acetone/water (2:1, 135 mL). The resultant mixture was stirred for 48 h at room temp. and acetone was removed by distillation under reduced pressure. The aqueous phase was extracted with ether (3 × 75 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 0.96 g (80%, 2 steps) of the product **4** as a colourless liquid. − ^{1}H NMR: δ = 9.63 (br. s), 4.77 (br. s, 2 H), 4.05 (q, 2 H, *J* = 7 Hz), 3.10 (m, 1 H), 2.50−2.37 (m, 4 H), 1.68 (s, 3 H), 1.19 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 201.2 (d), 171.7 (s), 145.2 (s), 112.4 (t), 60.5 (t), 46.7 (d), 38.4 (t), 37.6 (t), 19.7 (q), 14.2 (q). − GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 120 °C), retention time 2.90 min. − EI MS; *m*/*z* (%): 184 (1), 166 (4), 156 (4), 143 (6), 139 (10), 110 (10), 95 (25), 82 (45), 69 (70), 60 (15), 55 (30), 43 (25), 41 (100). − IR (CCl_4): $\tilde{\nu}$ = 3049 cm^{-1}, 2980, 2921, 2840, 1735, 1715, 1637.

Ethyl 5-Hydroxy-3-isopropenylpentanoate (5): $NaBH_4$ (146 mg, 3.66 mmol) was added to a solution of aldehyde **4** (368 mg, 2 mmol, 0 °C) in EtOH (18 mL). The reaction mixture was stirred for 10 min at 0 °C, then 0.5 N HCl (10 mL) and water (10 mL) added. The aqueous phase was extracted with ether (3 × 30 mL), the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 20:80) to give 297 mg (80%) of the product **5** as a colourless liquid. − ^{1}H NMR: δ = 4.75 (br. s, 2 H), 4.06 (q, 2 H, *J* = 7 Hz), 3.55 (m, 2 H), 2.71 (m, 1 H), 2.36 (m, 3 H), 2.25 (m, 2 H), 1.65 (s, 3 H), 1.19 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 172.7 (s), 146.2 (s), 112.3 (t), 60.7 (t), 60.4 (t), 40.5 (d), 39.1 (t), 35.7 (t), 18.7 (q), 14.2 (q). − GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 120 °C), retention time 4.52 min. − EI MS; *m*/*z* (%): 168 (3), 156 (8), 143 (10), 141 (14), 154 (6), 122 (6), 110 (14), 97 (28), 95 (25), 83 (42), 79 (25), 69 (100), 67 (70), 55 (45), 53 (34), 43 (42), 41 (91). − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1}, 3050, 2920, 2860, 1720, 1630.

Ethyl 3-Isopropenyl-5-(tosyloxy)pentanoate (6): TsCl (2.12 g, 11.1 mmol) was added to a solution of alcohol **5** (1 g, 5.37 mmol, 0 °C) in pyridine (8 mL). The reaction mixture was stirred overnight at 0 °C under argon and poured into a mixture of water and ice (40 mL). The aqueous phase was extracted with ether (3 × 40 mL), the combined organic layers washed with 2 N HCl, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 30:70) to give 1.53 g (82%) of the product **6** as a colourless liquid. − ^{1}H NMR: δ = 7.65 (d, 2 H, *J* = 8 Hz), 7.21 (d, 2 H, *J* = 8 Hz), 4.61 (br. s, 1 H), 4.53 (br. s, 1 H), 3.97−3.79 (m, 4 H), 2.52 (m, 1 H), 2.32 (s, 3 H), 2.26−2.14 (m, 2 H), 1.65−1.53 (m, 2 H), 1.47 (s, 3 H), 1.10 (t, 3 H, *J* = 7.0 Hz). − ^{13}C NMR: δ = 171.8 (s), 144.8 (s), 144.2 (s), 133.0 (s), 129.8 (d), 127.9 (d), 113.4 (t), 68.4 (t), 60.5 (t), 40.0 (d), 38.9 (t), 31.6 (t), 21.7 (q), 18.4 (q), 14.3 (q).

Ethyl *trans*-2-Isopropenylcyclobutanecarboxylate (7): A solution of LiHMDS (23.4 mL, 23.4 mmol, 1 M solution in THF) was added dropwise under argon to a solution of tosylate **6** (4.0 g, 11.7 mmol, −10 °C) in THF/HMPA (90 mL/15 mL). The reaction mixture was stirred for 10 min at −10 °C and for 2 h at 0 °C, then quenched with satd. aqueous ammonium chloride solution (100 mL) at 0 °C. The aqueous phase was extracted with ether (3 × 150 mL) and the combined organic layers washed with water (150 mL), brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The

crude product (diastereoselectivity > 95:5) was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 1.38 g (70%) of the product **7** as a colourless oil. − ^{1}H NMR: δ = 4.75 (br. s, 1 H), 4.71 (br. s, 1 H), 4.12 (q, 2 H, *J* = 7 Hz), 3.10 (dd, 1 H, *J* = 9 Hz, *J* = 18 Hz), 2.94 (dt, 1 H, *J* = 9 Hz, *J* = 18 Hz), 2.20−1.70 (m, 4 H), 1.66 (s, 3 H), 1.24 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 174.6 (s), 146.8 (s), 108.9 (t), 60.4 (t), 45.1 (s), 43.4 (d), 23.5 (t), 21.1 (t), 20.2 (q), 14.3 (q). − Capillary GC analysis (BPX-5-MS, 0.32 mm i.d. × 30 m, 80°C), retention time 6.35 min. − EI MS; *m*/*z* (%): 168 (5), 140 (5), 165 (1), 111 (5), 95 (40), 79 (20), 68 (100), 67 (80), 55 (50), 53 (30), 41 (40).

Ethyl 4-Methyl-4-penten-1-oate (8):[17] *n*-Butyllithium (96 mL, 201.6 mmol, 2.1 M solution in hexane) was added dropwise to a solution of methyltriphenylphosphonium bromide (66 g, 183 mmol, −60°C) in THF (250 mL) under argon. The solution of ylide was stirred for 1 h at 0°C. A solution of ethyl levulinate (20.7 mL, 144 mmol) in THF (150 mL) was added to the solution of ylide (−60°C). The resultant reaction mixture was heated at room temp., stirred overnight and quenched with water. The aqueous phase was extracted with cyclohexane (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in pentane and stirred for 1 h at room temp. The solution was filtered and the solvent removed under reduced pressure to give 9.2 g of the crude product **8** used in the next step without further purification. − ^{1}H NMR: δ = 4.65 (br. s, 1 H), 4.55 (br. s, 1 H), 4.10 (q, 2 H, *J* = 7.5 Hz), 2.42 (t, 2 H, *J* = 8 Hz), 2.33 (t, 2 H, *J* = 8 Hz), 1.73 (s, 3 H), 1.25 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 173.3 (s), 144.1 (s), 110.3 (t), 60.3 (t), 32.72 (t), 32.68 (t), 22.5 (q), 14.3 (q). − GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 100°C), retention time 0.60 min. − EI MS; *m*/*z* (%): 142 (10), 96 (18), 97 (19), 81 (4), 69 (100), 55 (12), 53 (14), 41 (36). − IR (neat): $\tilde{\nu}$ = 3090 cm^{-1}, 3000, 2940, 2880, 1740, 1650.

4-Methyl-4-penten-1-ol (9):[17] A solution of the crude product **8** (9.2 g) in THF (150 mL) was added to a solution of $LiAlH_4$ (8.0 g, 216 mmol, 0°C) in THF (200 mL). The reaction mixture was stirred at 0°C for 1 h, quenched with water (8 mL), NaOH (15%) (8 mL), water (24 mL) and stirred for 1 h at room temp. The resultant mixture was filtered and solvent removed under reduced pressure. The residue was purified by distillation (78−79°C, 20 Torr) to give 6.8 g (46%) of **9** as a colourless liquid. − ^{1}H NMR: δ = 4.77 (br. s, 2 H), 3.65 (t, 2 H, *J* = 7.5 Hz), 2.50−1.60 (m, 5 H), 1.75 (s, 3 H). − ^{13}C NMR: δ = 145.5 (s), 110.2 (t), 62.6 (t), 34.1 (t), 30.5 (t), 22.4 (q). − GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 80°C), retention time 0.98 min. − EI MS; *m*/*z* (%): 100 (2), 81 (10), 72 (15), 67 (100), 56 (70), 41 (90). − IR (neat): $\tilde{\nu}$ = 3350 cm^{-1}, 3090, 3000, 2940, 2880, 1655.

5-Iodo-2-methyl-1-pentene (10):[18] Triphenylphosphane (22.2 g, 84.2 mmol), imidazole (11.1 g, 163.5 mmol) and I_2 (20.1 g, 79.7 mmol) were added to a solution of **9** (5.8 g, 58 mmol, 0°C) in benzene (330 mL). The reaction mixture was stirred for 1 h at room temp. and filtered. The solid was washed with pentane and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane) to give 8.46 g (69%) of product **10** as a colourless liquid. − ^{1}H NMR: δ = 4.77, 4.73 (2 br. s, 2 H), 3.19 (t, 2 H, *J* = 7 Hz), 2.13 (t, 2 H, *J* = 7 Hz), 1.97 (m, 2 H), 1.73 (s, 3 H). − ^{13}C NMR: δ = 143.8 (s), 111.2 (t), 38.4 (t), 31.4 (t), 22.4 (q), 6.5 (t). − GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 100°C), retention time 1.41 min. − EI MS; *m*/*z* (%): 210 (5), 182 (3), 155 (2), 127 (2), 83 (36), 67 (7), 55 (100), 41 (26).

Ethyl 5,5-Diethoxy-3-isopropenyl-2-(4′-methyl-4′-penten-1′-yl)pentanoate (11): A solution of **3** (3.34 g, 12.9 mmol) in THF/HMPA (36 mL 1:1) was added dropwise under argon to a solution of KHMDS (54 mL, 27 mmol, 0.5 M solution in toluene, −20°C) in THF (16 mL). The reaction mixture was stirred for 1 h at −20°C, then added a solution of **10** (5.5 g, 26 mmol) in THF/HMPA (36 mL 1:1), warmed to 0°C, stirred for 3.5 h and quenched with satd. aqueous ammonium chloride solution (75 mL). The aqueous phase was extracted with ether (3 × 100 mL) and the combined organic layers washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product **11** (2.3 g) which was used in the next step without further purification. For pure product, flash chromatography (100 cyclohexane then AcOEt/cyclohexane, 5:95). − Major isomer: ^{1}H NMR: δ = 4.87 (br. s, 1 H), 4.83 (br. s, 1 H), 4.68 (br. s, 1 H), 4.63 (br. s, 1 H), 4.37 (dd, 1 H, *J* = 6.5 Hz, *J* = 6 Hz), 4.15 (m, 2 H), 3.60 (m, 2 H), 3.44 (m, 2 H), 2.51−2.20 (m, 2 H), 2.1−1.3 (m, 8 H), 1.60 (s, 3 H), 1.55 (s, 3 H), 1.25−1.15 (m, 9 H). − ^{13}C NMR: δ = 175.7 (s), 145.6 (s), 143.8 (s), 114.9 (t), 110.1 (t), 101.0 (d), 61.5 (t), 60.1 (t), 60.0 (t), 48.8 (d), 46.1 (d), 37.6 (t), 34.0 (t), 30.3 (t), 25.4 (t), 22.4 (q), 18.2 (q), 15.5 (2 C, q), 14.5 (q). − The ratio of stereomers was determined by capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 7.40 min (73%), 7.56 min (27%). − EI MS; *m*/*z* (%): 340 (1), 295 (2), 249 (2), 203 (3), 175 (12), 116 (24), 103 (100), 75 (36), 47 (41). − IR (neat): $\tilde{\nu}$ = 3073 cm^{-1}, 2974, 2931, 1732, 1646, 1373, 1058.

Ethyl 3-Isopropenyl-2-(4′-methyl-4′-penten-1′-yl)-5-oxopentanoate (12): Prepared from the crude product **11** by the same procedure as for **4** (20%, 2 steps). Colourless oil. (2*RS*, 3*R*)-**12** from (3*R*)-**3**: $[\alpha]_D^{20}$ = −33.0 (*c* = 1.47, CH_2Cl_2), (2*RS*, 3*S*)-**12** from (3*S*)-**3**: $[\alpha]_D^{20}$ = +30.0 (*c* = 2.55, CH_2Cl_2). − Major isomer: ^{1}H NMR: δ = 9.53 (dd, 1 H, *J* = 3 Hz, *J* = 1.5 Hz), 4.85 (br. s, 1 H), 4.83 (br. s, 1 H), 4.65 (br. s, 1 H), 4.60 (br. s, 1 H), 4.11 (q, 2 H, *J* = 7 Hz), 2.88 (m, 1 H), 2.50−2.30 (m, 3 H), 2.00−1.90 (m, 2 H), 1.65 (s, 3 H), 1.61 (s, 3 H), 1.60−1.20 (m, 4 H), 1.23 (t, 3 H, *J* = 7 Hz). ^{13}C NMR: δ = 201.2 (d), 175.0 (s), 145.2 (s), 143.4 (s), 115.0 (t), 110.2 (t), 60.5 (t), 48.1 (d), 45.1 (t), 44.2 (d), 37.4 (t), 30.2 (t), 25.1 (t), 22.2 (q), 18.6 (q), 14.3 (q). − The ratio of stereomers was determined by capillary GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 7.33 min (73%), 7.45 min (27%). − EI MS; *m*/*z* (%): 223 (2), 205 (2), 197 (8), 175 (6), 169 (6), 156 (8), 133 (4), 123 (6), 110 (10), 101 (16), 95 (40), 82 (42), 69 (50), 55 (56), 41 (100). − IR (neat): $\tilde{\nu}$ = 3050 cm^{-1}, 2960, 2920, 2840, 2820, 2705, 1715, 1635. − HRMS; $C_{16}H_{27}O_3$ [MH$^+$]: calcd. 267.1950; found 267.1958.

Ethyl 5-Hydroxy-3-isopropenyl-2-(4′-methyl-4′-penten-1′-yl)pentanoate (13): Prepared from **12** by the same procedure as for **5** (84%). Colourless oil. (2*RS*, 3*R*)-**13** from (2*RS*, 3*R*)-**12**: $[\alpha]_D^{20}$ = −10.3 (*c* = 1.18, CH_2Cl_2), (2*RS*, 3*S*)-**13** from (2*RS*, 3*S*)-**12**: $[\alpha]_D^{20}$ = +11.6 (*c* = 1.29, CH_2Cl_2). − Major isomer: ^{1}H NMR: δ = 4.85 (br. s, 1 H), 4.80 (br. s, 1 H), 4.70 (br. s, 1 H), 4.60 (br. s, 1 H), 4.20 (m, 2 H), 3.50 (m, 2 H), 2.50−2.30 (m, 2 H), 2.10−1.90 (m, 3 H), 1.61 (s, 3 H), 1.55 (s, 3 H), 1.4 (m, 6 H), 1.20 (t, 3 H, *J* = 7.5 Hz). − ^{13}C NMR: δ = 176.0 (s), 145.5 (s), 144.2 (s), 114.8 (t), 110.0 (t), 61.1 (t), 60.4 (t), 48.6 (d), 47.0 (d), 37.4 (t), 33.8 (t), 30.5 (t), 25.2 (t), 22.3 (q), 17.7 (q), 14.4 (q). − The ratio of stereomers was determined by capillary GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 8.25 min (73%), 8.35 min (27%). − EI MS; *m*/*z* (%): 223 (4), 198 (6), 181 (2), 169 (4), 154 (6), 142 (10), 121 (4), 107 (8), 95 (30), 81 (24), 69 (30), 55 (34), 41 (100). − IR (neat): $\tilde{\nu}$ = 3420 cm^{-1}, 3080, 2980, 2940, 1730, 1645.

Ethyl 3-Isopropenyl-2-(4′-methyl-4′-penten-1′-yl)-5-(tosyloxy)pentanoate (14): Prepared from **13** by the same procedure as for **6**

(79%). Colourless oil. – Major isomer: ^{1}H NMR: δ = 7.76 (d, 2 H, *J* = 8 Hz), 7.33 (d, 2 H, *J* = 8 Hz), 4.80 (br. s, 1 H), 4.67 (br. s, 2 H), 4.62 (br. s, 1 H), 4.16–3.80 (m, 4 H), 2.45 (s, 3 H), 2.35 (m, 2 H), 2.00–1.90 (m, 9 H), 1.66 (s, 3 H), 1.40 (s, 3 H), 1.26 (t, 3 H, *J* = 7.1 Hz). – ^{13}C NMR: δ = 175.3 (s), 145.4 (s), 144.7 (s), 133.2 (s), 129.8 (d), 128.0 (d), 115.0 (t), 110.2 (t), 68.6 (t), 60.5 (t), 48.5 (d), 46.3 (d), 37.5 (t), 30.5 (t), 29.8 (t), 25.2 (t), 22.4 (q), 21.7 (q), 17.6 (q), 14.4 (q). – IR (neat): $\tilde{\nu}$ = 3074 cm^{-1}, 2918, 2854, 1716, 1645, 1598, 1363, 1174.

Ethyl *trans*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutanecarboxylate (15): A solution of LiHMDS (6.6 mL, 6.6 mmol, 1 M solution in THF) was added dropwise under argon to a solution of tosylate **14** (920 mg, 2.18 mmol, –10°C) in THF/HMPA (17 mL:3.2 mL). The reaction mixture was stirred for 15 min at –10°C and for 1 h at room temp., then quenched with satd. aqueous ammonium chloride solution (15 mL) at 0°C. The aqueous phase was extracted with ether (3 × 30 mL) and the combined organic layers washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (diastereoselectivity > 95:5) was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 255 mg (46%) of the product **15** as a colourless oil. (1*R*, 2*S*)-**15** from (2*RS*, 3*R*)-**13**: $[\alpha]_D^{20}$ = –13.4 (*c* = 2.07, CH_2Cl_2), (1*S*, 2*R*)-**15** from (2*RS*, 3*S*)-**13**: $[\alpha]_D^{20}$ = +13.5 (*c* = 2.34, CH_2Cl_2). – ^{1}H NMR: δ = 4.93 (br. s, 1 H), 4.71 (br. s, 1 H), 4.67 (br. s, 1 H), 4.64 (br. s, 1 H), 4.15 (q, 2 H, *J* = 7 Hz), 3.04 (br. t, 1 H, *J* = 9 Hz), 2.41 (ddd, 1 H, *J* = 20 Hz, *J* = 10 Hz, *J* = 1 Hz), 2.05–1.30 (m, 9 H), 1.73 (s, 3 H), 1.67 (s, 3 H), 1.26 (t, 3 H, *J* = 7 Hz). – ^{13}C NMR: δ = 176.7 (s), 145.7 (s), 144.0 (s), 111.6 (t), 109.9 (t), 60.3 (t), 51.0 (s), 48.1 (d), 38.2 (t), 30.3 (t), 24.6 (t), 23.0 (q), 22.4 (t), 22.4 (q), 19.3 (t), 14.3 (q). – Capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m), retention time 4.40 min. – EI MS; *m*/*z* (%): 250 (0.5), 235 (2), 222 (2), 177 (8), 168 (10), 139 (8), 121 (25), 109 (25), 93 (25), 91 (10), 81 (25), 69 (80), 68 (100), 67 (60), 55 (30), 53 (25), 41 (60). IR (neat): $\tilde{\nu}$ = 3060 cm^{-1}, 2960, 2920, 2840, 1715, 1635. – HRMS; $C_{16}H_{27}O_2$ [MH^+]: calcd. 251.2004; found 251.2019.

***trans*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutanemethanol (16):** A solution of ester **15** (250 mg, 1 mmol) in THF (4.5 mL) was added under argon to a suspension of $LiAlH_4$ (46 mg, 1.2 mmol, 0°C) in THF (4.5 mL). The reaction mixture was stirred for 3 h at room temp., then diluted with ether (20 mL) and quenched with 6 drops of water at 0°C. The organic phase was washed with water (5 mL), the aqueous phase reextracted with ether (2 × 20 mL) and the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (180 mg, 86%) **16** was used in the next step without further purification. (1*R*, 2*S*)-**16** from (1*R*, 2*S*)-**15**: $[\alpha]_D^{20}$ = +13.6 (*c* = 0.85, CH_2Cl_2), (1*S*, 2*R*)-**16** from (1*S*, 2*R*)-**15**: $[\alpha]_D^{20}$ = –14.4 (*c* = 2.71, CH_2Cl_2). – ^{1}H NMR: δ = 4.87 (br. s, 1 H), 4.69 (br. s, 2 H), 4.65 (br. s, 1 H), 3.54 (AB, 2 H, *J* = 11 Hz), 2.82 (br. t, 1 H, *J* = 9 Hz), 2.05–1.30 (m, 11 H), 1.70 (s, 6 H). – ^{13}C NMR: δ = 146.1 (s), 145.2 (s), 110.3 (t), 109.8 (t), 68.9 (t), 47.1 (s), 46.3 (d), 38.7 (t), 29.8 (t), 23.5 (t), 21.8 (t), 19.2 (t), 23.7 (q), 22.6 (q). – Capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140–240°C, 10°C/min), retention time 5.03 min. – EI MS; *m*/*z* (%): 193 (0.5), 177 (11), 165 (1), 147 (6), 134 (6), 121 (51), 109 (40), 108 (12), 107 (41), 95 (38), 93 (52), 91 (23), 82 (37), 81 (36), 79 (43), 70 (43), 69 (60), 68 (96), 67 (100), 55 (67), 53 (37), 43 (33), 41 (88). – IR (neat): $\tilde{\nu}$ = 3350 cm^{-1}, 3070, 2970, 2930, 2860, 1640, 1445, 1360. – HRMS $C_{14}H_{25}O$ (MH^+): calcd. 209.1899; found 209.1901. – HRMS; $C_{14}H_{23}$ [$MH^+ - H_2O$]: calcd. 191.1794; found 191.1798.

***trans*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutanemethyl *p*-Toluenesulfonate (17):** TsCl (120 mg, 0.57 mmol) and 4-DMAP (138 mg, 1.13 mmol) were added to a solution of crude alcohol **16** (120 mg, 0.57 mmol, 0°C) in CH_2Cl_2 (1.2 mL) The reaction mixture was stirred overnight at 0°C under argon, and then poured into a mixture of water and ice (20 mL). The aqueous phase was extracted with ether (3 × 15 mL), the combined organic layers washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 168 mg (81%) of the product **17** as a colourless oil. – ^{1}H NMR: δ = 7.75 (d, 2 H, *J* = 7.5 Hz), 7.35 (d, 2 H, *J* = 7.5 Hz), 4.84 (br. s, 1 H), 4.64 (br. s, 2 H), 4.56 (br. s, 1 H), 3.88 (AB, 2 H, *J* = 11 Hz), 2.72 (br. t, 1 H, *J* = 9 Hz), 2.43 (s, 3 H), 2.00–1.10 (m, 10 H), 1.63 (s, 3 H), 1.57 (s, 3 H). – ^{13}C NMR: δ = 145.6 (s), 144.8 (s), 144.1 (s), 132.9 (s), 129.9 (d), 128.0 (d), 110.9 (t), 109.9 (t), 75.4 (t), 46.9 (d), 44.7 (s), 38.3 (t), 29.3 (t), 23.8 (t), 21.3 (t), 19.1 (t), 23.5 (q), 22.5 (q), 21.7 (q).

***trans*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneacetonitrile (18):** Three drops of water and NaCN (34 mg, 0.69 mmol) were added to a solution of tosylate **17** (168 mg, 0.46 mmol) in HMPA (1 mL). The reaction mixture was stirred for 3 h at 80–90°C, cooled to room temp. and diluted in a mixture of AcOEt/cyclohexane (5:95). The organic layer was washed with water (10 mL), brine (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane to AcOEt/cyclohexane, 10:90) to give 87 mg (87%) of the product **18** as a colourless oil. (1*S*, 2*S*)-**18** from (1*R*, 2*S*)-**16**: $[\alpha]_D^{20}$ = –2.6 (*c* = 1.17, CH_2Cl_2), (1*R*, 2*R*)-**18** from (1*S*, 2*R*)-**16**: $[\alpha]_D^{20}$ = +3.0 (*c* = 5.01, CH_2Cl_2). – ^{1}H NMR: δ = 4.92 (br. s, 1 H), 4.71 (br. s, 2 H), 4.67 (br. s, 1 H), 2.87 (br. t, 1 H, 9.5 Hz), 2.48 (AB, 2 H, *J* = 17 Hz), 2.10–1.26 (m, 10 H), 1.72, 1.71 (2s, 6 H). – ^{13}C NMR: δ = 145.5 (s), 143.5 (s), 118.6 (s), 111.4 (t), 110.2 (t), 49.2 (d), 43.0 (d), 38.3 (t), 32.0 (t), 28.6 (t), 26.7 (t), 21.7 (t), 19.3 (t), 23.6 (q), 22.5 (q). – Capillary GC analysis (BPX-70-MS, 0.32 mm i.d. × 30 m, 125–275°C, 10°C/min), retention time 5.25 min. – EI MS; *m*/*z* (%): 217 (0.1), 216 (1), 202 (3), 177 (5), 161 (1), 146 (2), 134 (3), 121 (10), 109 (15), 93 (12), 79 (14), 69 (15), 68 (100), 67 (50), 56 (13), 53 (17), 41 (41). – IR (neat): $\tilde{\nu}$ = 3085 cm^{-1}, 2840, 2760, 2250, 1650, 1450, 1360, 890. – HRMS; $C_{15}H_{24}N$ [MH^+]: calcd. 218.1903; found 218.1909.

***trans*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneethanol (19):** Diisobutylaluminium hydride (0.1 mL, 0.1 mmol, 1 M solution in toluene) was added dropwise under argon to a solution of **18** (13 mg, 0.059 mmol, –20°C) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 2 h at –20°C and 0.5 h at room temp. then water (0.1 mL) and 5% H_2SO_4 (0.3 mL) added. The mixture was stirred for 1 h at 0°C, the aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with satd. aqueous sodium bicarbonate solution (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the aldehyde used in the next step without further purification. $NaBH_4$ (5 mg, 0.13 mmol) was added to a solution of this aldehyde in EtOH (0.5 mL, 0°C). The reaction mixture was stirred for 15 min at 0°C and hydrolyzed with 9 drops of acetone. The resultant solution was stirred for 30 min at room temp. and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 7 mg (44%) of **19** as a colourless oil. – ^{1}H NMR: δ = 4.88 (br. s, 1 H), 4.72 (br. s, 2 H), 4.69 (br. s, 1 H), 3.61 (m, 2 H), 2.64 (br. t, 1 H, *J* = 9 Hz), 2.05–1.25 (m, 12 H), 1.72 (s, 3 H), 1.70 (s, 3 H). – ^{13}C NMR: δ = 145.9 (s), 145.5 (s), 110.5 (t), 110.1 (t), 59.7 (t), 49.3 (d), 44.8 (s), 40.1 (t), 38.5 (t), 36.2 (t), 28.0 (t), 24.0 (q), 22.6 (t), 22.5 (q), 19.5 (t). – Capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 150–225°C, 10°C/min), retention time 6.46 min. – EI

MS; *m/z* (%): 208 (1), 191 (1), 177 (5), 149 (3), 139 (22), 135 (5), 121 (20), 119 (16), 109 (16), 107 (18), 95 (23), 93 (35), 81 (45), 79 (30), 77 (13), 69 (66), 68 (100), 67 (70), 55 (38), 53 (30), 43 (11), 41 (71), 40 (15). − IR (CCl_4): $\tilde{\nu}$ = 3632 cm^{-1}, 3078, 2931, 2853, 1645, 1449, 1373, 1226, 1042.

***trans*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneethanol Acetate (1):** A solution of alcohol **19** (5 mg, 0.22 mmol) in pyridine (0.15 mL) with Ac_2O (0.05 mL) was stirred overnight at room temp. The reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 4 mg (70%) of **1** as colourless oil. (1*S*, 2*S*)-**1** from (1*S*, 2*S*)-**18**: $[\alpha]_D^{20}$ = −3.1 (*c* = 0.6, *n*-hexane), (1*R*, 2*R*)-**1** from (1*R*, 2*R*)-**18**: $[\alpha]_D^{20}$ = +2.9 (*c* = 1.0, CH_2Cl_2). − ^{1}H NMR: δ = 4.86 (br. s, 1 H), 4.70 (br. s, 2 H), 4.66 (br. s, 1 H), 4.13 (m, 2 H), 2.66 (br. t, 1 H, *J* = 8 Hz), 2.2−1.2 (m, 12 H), 2.04 (s, 3 H), 1.70 (s, 6 H). − ^{13}C NMR: δ = 171.2 (s), 146.1 (s), 145.2 (s), 110.6 (t), 109.9 (t), 62.0 (t), 49.5 (d), 44.5 (s), 38.8 (t), 38.2 (t), 33.1 (t), 23.9 (t), 22.0 (t), 19.8 (t), 22.5 (q), 22.3 (q), 21.2 (q). − Capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 120−300°C, 10°C/min), retention time 9.66 min. − EI MS; *m/z* (%): 204 (1), 189 (6), 175 (5), 161 (12), 148 (7), 133 (12), 121 (43), 119 (14), 107 (27), 105 (15), 93 (63), 91 (20), 81 (33), 79 (42), 77 (13), 69 (58), 68 (74), 67 (43), 55 (22), 53 (20), 43 (100), 41 (64). − CI/NH_3 MS; *m/z* (%): 282 (100), 265 (8), 205 (67), 183 (3), 149 (30), 135 (13), 123 (13), 121 (18), 109 (18), 95 (18), 81 (10). − IR (CCl_4): $\tilde{\nu}$ = 3079 cm^{-1}, 2933, 2856, 1741, 1647, 1453, 1365, 1238. − HRMS; $C_{17}H_{29}O_2$ [MH^+]: calcd. 265.2160; found 265.2178. − HRMS; $C_{15}H_{25}$ [MH^+ − AcOH]: calcd. 205.1950; found 205.1939.

Ethyl 5,5-Diethoxy-2-(3′,3′-dimethylallyl)-3-isopropenylpentanoate (20): A solution of **3** (1.0 g, 3.87 mmol) in THF/HMPA (1:1, 12 mL) was added dropwise under argon to a solution of LiHMDS (11.6 mL, 11.6 mmol, 1 M solution in THF, −60°C) in THF (6 mL). The reaction mixture was stirred for 45 min at −60°C, then a solution of 4-bromo-2-methyl-2-butene (2.2 mL, 19.35 mmol) in HMPA (6 mL) was added. It was then stirred for 1 h at −40°C, warmed to 0°C and quenched with satd. aqueous ammonium chloride solution (15 mL) at −20°C. The aqueous phase was extracted with ether (3 × 60 mL) and the combined organic layers were washed with water (60 mL), brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 1.19 g (94%) of the product **20** as a colourless oil. − Two isomers: ^{13}C NMR: δ = 175.3 (s), 174.6 (s), 144.8 (s), 143.7 (s), 135.5 (s), 133.4 (s), 121.1 (d), 115.0 (t), 114.0 (t), 101.4 (d), 101.0 (d), 61.4 (t), 61.3 (t), 60.2 (t), 60.1 (t), 59.9 (t), 59.8 (t), 49.9 (d), 49.3 (d), 45.7 (d), 34.6 (t), 33.8 (t), 29.7 (t), 28.6 (t), 25.8 (d), 18.9 (q), 18.1 (q), 18.0 (q), 17.8 (q), 17.7 (q), 15.5 (q), 14.4 (q), 14.3 (q). − The ratio of stereomers was determined by capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 12.30 min (73%), 12.36 min (27%). − EI MS; *m/z* (%): 326 (0.03), 280 (2), 265 (0.5), 234 (14), 161 (18), 139 (15), 125 (19), 103 (100), 75 (77), 69 (49), 55 (18), 47 (69), 43 (28), 41 (42). − IR (neat): $\tilde{\nu}$ = 3080 cm^{-1}, 2980, 2940, 1735, 1645.

Ethyl 5,5-Diethoxy-2-(2′-hydroxyethyl)-3-isopropenylpentanoate (22): *N*-methylmorpholine *N*-oxide (385 mg, 3.0 mmol) and a solution of OsO_4 (1 mL, 2.5% solution in 2-methyl-2-propanol) was added to a solution of **20** (1.0 g, 3.0 mmol, 0°C) in acetone/water (9:1, 2.5 mL). This was then stirred for 1 h at 0°C, treated with $Na_2S_2O_3$ (2.3 g, 14.5 mmol) for 2 h at room temp. and diluted with dichloromethane (50 mL). The mixture was filtered through Celite, the solid washed with AcOEt and the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. $NaHCO_3$ (500 mg) and $NaIO_4$ (3.45 g, 16 mmol) were added to a solution of the residue in acetone/water (1:1, 30 mL) and the resultant mixture stirred for 1.5 h at room temp. Acetone was removed under reduced pressure and the aqueous phase extracted with dichloromethane (30 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the aldehyde **21** (850 mg, 94%) as a crude product. To a solution of the aldehyde **21** (850 mg, 0°C) in ethanol (25 mL) was added $NaBH_4$ (175 mg, 4.6 mmol). The reaction mixture was stirred for 10 min at 0°C and quenched with 0.5 N HCl (5 mL), water (5 mL). The aqueous phase was extracted with ether (3 × 30 mL), the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 50:50) to give 320 mg (35%) of the product **22**. − Major isomer: ^{1}H NMR: δ = 4.89 (br. s, 1 H), 4.84 (br. s, 1 H), 4.38 (dd, 1 H, *J* = 7.5 Hz, *J* = 7 Hz), 4.17 (m, 2 H), 3.60 (m, 4 H), 3.44 (m, 2 H), 2.48 (m, 2 H), 1.70 (m, 2 H), 1.62 (s, 3 H), 1.27 (t, 3 H, *J* = 7 Hz), 1.19 (m, 6 H). − ^{13}C NMR: δ = 175.8 (s), 143.6 (s), 115.4 (t), 101.0 (d), 61.5 (t), 61.1 (t), 60.7 (t), 60.1 (t), 45.8 (d), 34.6 (t), 33.7 (t), 18.2 (q), 15.5 (2 C, q), 14.4 (q). − The ratio of stereomers was determined by capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140−280°C, 10°C/min), retention time 8.55 min (71%), 8.72 min (29%). − IR (neat): $\tilde{\nu}$ = 3450 cm^{-1}, 3050, 2960, 2910, 2860, 1720, 1635.

Ethyl 2-{2′-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-3-isopropenyl-5-oxopentanoate (24): Imidazole (100 mg, 1.5 mmol) and TBDPSCl (0.305 mL, 1.16 mmol) were added to a solution of the alcohol **22** (320 mg, 1 mmol) in DMF (1 mL). The reaction mixture was stirred overnight at room temp. and diluted with dichloromethane (50 mL), washed with water (20 mL), HCl (0.5 N, 20 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product **23** (660 mg). The crude product **23** was diluted in acetone/water (6.5 mL:3.5 mL) and PTSA (84 mg, 0.44 mmol) added to the resultant mixture. The reaction mixture was stirred for 72 h at room temp. The aqueous phase was extracted with ether (3 × 30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 20:80) to give 302 mg (64%) of the product **24** as a colourless oil. The ratio of stereomers was determined by capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 160−300°C, 10°C/min), retention time 15.35 min (71%), 15.64 min (29%). − EI MS; *m/z* 466, 421, 421, 409, 363, 335, 227, 199, 183, 165, 139, 105, 77, 55, 41. − IR (neat): $\tilde{\nu}$ = 3480 cm^{-1}, 3060, 3040, 2950, 2920, 2890, 2850, 2730, 1730, 1710, 1640, 1580.

Ethyl 2-{2′-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-5-hydroxy-3-isopropenylpentanoate (25): $NaBH_4$ (30 mg, 0.79 mmol) was added to a solution of the aldehyde **24** (302 mg, 0.65 mmol, 0°C) in EtOH (6 mL). The reaction mixture was stirred for 10 min at 0°C, then 0.5 N HCl (4 mL) and water (4 mL) added. The aqueous phase was extracted with ether (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 50:50) to give 163 mg (53%) of the product **25** as a colourless oil. − ^{1}H NMR: δ = 7.60 (m, 5 H), 7.39 (m, 5 H), 4.90 (br. s, 1 H), 4.85 (br. s, 1 H), 4.11 (m, 2 H), 3.58 (m, 4 H), 2.64 (dt, 1 H, *J* = 11 Hz, *J* = 4 Hz), 2.46 (dt, 1 H, *J* = 11 Hz, *J* = 4 Hz), 1.8−1.4 (m, 5 H), 1.64 (s, 3 H), 1.22 (t, 3 H, *J* = 7 Hz), 1.05 (s, 9 H). − ^{13}C NMR: δ = 175.8 (s), 144.6 (s), 135.7 (d), 133.9 (s), 129.7 (d), 127.7 (d), 115.0 (t), 62.0 (t), 61.4 (t), 60.4 (t), 47.2 (d), 45.5 (d), 33.9 (2 C, t), 27.0 (q), 19.3 (s), 17.9 (q), 14.4 (q). − GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 160−300°C, 10°C/min), retention time 16.87 min. − EI MS; *m/z* (%): 366 (20), 365 (69), 287 (4), 251 (5),

225 (6), 199 (100), 183 (28), 135 (30), 121 (27),105 (41), 91 (34), 77 (49), 67 (44), 55 (30), 41 (39). − IR (neat): $\tilde{\nu}$ = 3450 cm^{-1}, 3050, 2960, 2910, 2860, 1720, 1635.

Ethyl 2-{2′-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-3-isopropenyl-5-(tosyloxy)pentanoate (26): Prepared from **25** by the same procedure as for **6** (93%). Colourless oil. − ^{1}H NMR: δ = 7.77 (d, 2 H, *J* = 8 Hz), 7.65 (m, 5 H), 7.40 (m, 7 H), 4.83 (br. s, 1 H), 4.69 (br. s, 1 H), 4.08 (q, 2 H, *J* = 7 Hz), 4.05−3.88 (m, 2 H), 3.59 (m, 2 H), 2.60 (m, 1 H), 2.45 (s, 3 H), 2.35 (m, 1 H), 1.71 (m, 3 H), 1.61 (s, 3 H), 1.21 (t, 3 H, *J* = 7 Hz), 1.08 (m, 9 H). − ^{13}C NMR: δ = 175.2 (s), 144.7 (s), 144.4 (s), 135.6 (d), 133.6 (s), 129.8 (d), 129.7 (d), 127.9 (d), 127.7 (d), 116.0 (t), 68.6 (t), 61.7 (t), 60.5 (t), 46.3 (d), 45.4 (d), 33.8 (t), 29.6 (t), 26.8 (q), 21.7 (q), 19.1 (s), 17.5 (q), 14.5 (q).

Ethyl 2-{2′-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-5-chloro-3-isopropenylpentanoate (27): A solution of LiHMDS (1 mL, 1 mmol, 1 M solution in THF) was added dropwise under argon to a solution of the tosylate **26** (189 mg, 0.31 mmol, −20°C) in THF/HMPA (5:1, 6 mL). The reaction mixture was stirred for 1 h at 0°C and for 1 h at room temp., then quenched with satd. aqueous ammonium chloride solution (10 mL) at 0°C. The aqueous phase was extracted with ether (3 × 15 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 120 mg (80%) of the product **27** as a colourless oil. − Major isomer: ^{1}H NMR: δ = 7.60 (m, 5 H), 7.39 (m, 5 H), 4.95 (br. s, 1 H), 4.88 (br. s, 1 H), 4.13 (q, 2 H, *J* = 7 Hz), 3.67−3.20 (m, 4 H), 2.66 (m, 1 H), 2.55 (dt, 1 H, *J* = 11 Hz, *J* = 3.5 Hz), 1.8−1.6 (m, 4 H), 1.62 (s, 3 H), 1.22 (t, 3 H, *J* = 7 Hz), 1.05 (s, 9 H). − ^{13}C NMR: δ = 175.4 (s), 142.6 (s), 135.6 (d), 133,7 (s), 129.7 (d), 127.7 (d), 116.1 (t), 61.8 (t), 60.5 (t), 47.5 (d), 45.2 (d), 42.8 (t), 33.8 (t), 33.6 (t), 26.9 (q), 19.3 (s), 17.6 (q), 14.4 (q). − GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 160−300°C, 10°C/min), retention time 16.20 min. − CI/NH_3 MS; *m/z* (%): 489 (60), 488 (50), 487 (100), 429 (20), 409 (25), 371 (15). − IR (neat): $\tilde{\nu}$ = 3070 cm^{-1}, 3020, 2960, 2910, 2860, 1725, 1640.

Ethyl 2-(3′,3′-Dimethylallyl)-3-isopropenyl-5-oxopentanoate (28): Prepared from **20** by the same procedure as for **4** (60%). Colourless oil. − ^{1}H NMR: δ = 9.54 (dd, 1 H, *J* = 3 Hz, *J* = 2 Hz), 4.99 (tt, 1 H, *J* = 7.5 Hz, *J* = 1.5 Hz), 4.87 (t, 1 H, *J* = 1.5 Hz), 4.85 (br. s, 1 H), 4.08 (m, 2 H), 2.92 (dt, 1 H, *J* = 10 Hz, *J* = 5 Hz), 2.50−2.13 (m, 4 H), 1.63 (s, 6 H), 1.54 (s, 3 H), 1.21 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 201.3 (s), 174.6 (s), 143.3 (s), 133.9 (s), 120.4 (d), 115.0 (t), 60.5 (t), 48.5 (d), 45.0 (t), 43.8 (d), 29.4 (t), 25.8 (q), 18.6 (q), 17.7 (2 C, q), 14.3 (q). − Capillary GC analysis (BPX-5, 0.32 mm i.d. × 30 m, 120−300°C, 10°C/min), retention time 7.89 min. − EI MS; *m/z* (%): 237 (1), 234 (1), 209 (3), 208 (9), 206 (8), 191 (1), 179 (5), 169 (9), 155 (9), 139 (17), 135 (14), 111 (15), 109 (40), 107 (11), 95 (16), 93 (34), 91 (12), 81 (79), 80 (22), 69 (52), 67 (23), 55 (21), 53 (19), 43 (29), 41 (100). − IR (neat): $\tilde{\nu}$ = 3070 cm^{-1}, 2970, 2920, 2720, 1725, 1640.

Ethyl 2-(3′,3′-Dimethylallyl)-5-hydroxy-3-isopropenylpentanoate (29): Prepared from **28** by the same procedure as for **5** (80%). Colourless oil. − ^{1}H NMR: δ = 5.00 (t, 1 H, *J* = 7 Hz), 4.88 (br. s, 1 H), 4.86 (br. s, 1 H), 4.12 (m, 2 H), 3.52 (m, 2 H), 2.46 (dt, 1 H, *J* = 11 Hz, *J* = 4 Hz), 2.33 (ddd, 1 H, *J* = 11 Hz, *J* = 9 Hz, *J* = 5.5 Hz), 2.10 (m, 2 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.54 (s, 3 H), 1.23 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 175.6 (s), 144.3 (s), 140.9 (s), 133.5 (s), 120.9 (d), 115.0 (t), 61.2 (t), 60.3 (t), 49.2 (d), 46.8 (d), 33.8 (t), 29.8 (t), 25.8 (q), 17.7 (q), 14.4 (q). − GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 6.77 min. − EI MS; *m/z* (%): 249 (1), 208 (2), 180 (2), 165 (1), 140 (8), 126 (8), 125 (8), 111 (18), 82 (69), 81 (40), 67 (100), 55 (15), 41 (52). − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1}, 3040, 2940, 2900, 1710, 1630.

Ethyl 2-(3′,3′-Dimethylallyl)-3-isopropenyl-5-(tosyloxy)pentanoate (30): Prepared from **29** by the same procedure as for **6** (70%). Colourless oil. − ^{1}H NMR: δ = 7.75 (d, 2 H, *J* = 8 Hz), 7.32 (d, 2 H, *J* = 8 Hz), 4.95 (t, 1 H, *J* = 7 Hz), 4.82 (br. s, 1 H), 4.70 (br. s, 1 H), 4.17−3.80 (m, 4 H), 2.44 (s, 3 H), 2.40−2.14 (m, 2 H), 2.14−2.00 (m, 4 H), 1.63 (s, 3 H), 1.6−1.7 (m, 2 H), 1.53 (s, 6 H), 1.22 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 174.9 (s), 144.7 (s), 142.3 (s), 138.0 (s), 133.1 (s), 129.8 (d), 128.0 (d), 120.7 (d), 115.9 (t), 68.6 (t), 60.4 (t), 49.0 (d), 45.9 (d), 29.76 (t), 29.71 (t), 25.8 (q), 21.7 (q), 17.77 (q), 17.63 (q), 14.4 (q).

Ethyl *trans*-1-(3′,3′-Dimethylallyl)-2-isopropenylcyclobutanecarboxylate (31): A solution of LiHMDS (1.41 mL, 1.41 mmol, 1 M solution in THF) was added dropwise under argon to a solution of tosylate **30** (194 mg, 2.05 mmol, −20°C) in THF/HMPA (3.7 mL:0.6 mL). The reaction mixture was stirred for 1 h at 0°C and for 1 h at room temp., then quenched with satd. aqueous ammonium chloride solution (10 mL) at 0°C. The aqueous phase was extracted with ether (3 × 15 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product {diastereoselectivity > 95:5; the ratio of stereomers was determined by capillary GC analysis [DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 4.40 min (< 5%), 4.51 (> 95%)} was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 58 mg (50%) of the product **31** as a colourless oil. − ^{1}H NMR: δ = 4.98 (t, 1 H, *J* = 5 Hz), 4.95 (br. s, 1 H), 4.74 (br. s, 1 H), 4.14 (m, 2 H), 3.06 (t, 1 H, *J* = 9 Hz), 2.40−1.74 (m, 6 H), 1.74 (s, 3 H), 1.65 (s, 3 H), 1.60 (s, 3 H), 1.25 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 176.5 (s), 144.2 (s), 133.9 (s), 119.6 (d), 111.6 (t), 60.4 (t), 50.9 (s), 47.9 (d), 28.9 (t), 26.0 (q), 24.1 (t), 22.9 (q), 19.2 (t), 18.1 (q), 14.3 (q). − EI MS; *m/z* (%): 221 (1), 208 (1), 207 (1), 191 (5), 190 (2), 180 (2), 175 (2), 153 (26), 139 (9), 125 (32), 111 (18), 107 (39), 95 (96), 94 (58), 93 (100), 81 (32), 79 (67), 77 (40), 67 (45), 55 (41), 55 (67), 53 (41), 43 (37), 41 (95).

***trans*-1-(3′,3′-Dimethylallyl)-2-isopropenylcyclobutanemethanol (32):** A solution of ester **31** (195 mg, 0.82 mmol) in Et_2O (6 mL) was added under argon to a suspension of $LiAlH_4$ (40 mg, 1.0 mmol, 0°C) in Et_2O (6 mL). The reaction mixture was stirred for 1 h at 0°C, then quenched at 0°C with water (0.04 mL), 15% NaOH (0.12 mL), water (0.04 mL) and stirred for 30 min at room temp. The resultant mixture was filtered, the solid washed with and the combined organic layers were concentrated under reduced pressure to give the crude product **32** (150 mg, 94%) used in the next step without further purification. − ^{1}H NMR: δ = 5.13 (td, 1 H, *J* = 7 Hz, *J* = 1 Hz), 4.89 (br. s, 1 H), 4.71 (br. s, 1 H), 3.53 (AB, 2 H, *J* = 11 Hz), 2.81 (t, 1 H, *J* = 7 Hz), 2.20−1.50 (m, 6 H), 1.71 (s, 3 H), 1.69 (s, 3 H), 1.63 (s, 3 H). − ^{13}C NMR: δ = 145.3 (s), 133.7 (s), 120.5 (d), 110.4 (t), 69.8 (t), 47.7 (s), 46.5 (d), 28.7 (t), 26.1 (q), 23.7 (q), 23.4 (t), 19.1 (t), 18.0 (q). − GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 120−300°C, 10°C/min), retention time 5.92 min. − EI MS; *m/z* (%): 179 (1), 163 (6), 147 (1), 138 (1), 133 (4), 125 (4), 123 (4), 111 (5), 108 (26), 107 (20), 105 (10), 97 (6), 95 (29), 93 (98), 91 (21), 81 (16), 79 (24), 71 (16), 69 (53), 67 (37), 65 (8), 57 (19), 55 (41), 53 (27), 43 (39), 41 (100).

***trans*-1-(3′,3′-Dimethylallyl)-2-isopropenylcyclobutanemethyl *p*-Toluenesulfonate (33):** 4-DMAP (117 mg, 0.96 mmol) and TsCl (95 mg, 0.66 mmol) were added to a solution of crude alcohol **32** (93 mg, 0.47 mmol, 0°C) in dichloromethane (1 mL) . The reaction mixture was stirred for 36 h at 0°C under argon, poured into water

and ice (5 mL). The aqueous phase was extracted with ether (3 × 5 mL), the combined organic layers were washed with satd. aqueous copper(II) sulfate solution (3 × 5 mL), water (5 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product **33** (160 mg, 100%) was used in the next step without further purification. − ^{1}H NMR: δ = 7.79 (d, 2 H, *J* = 8 Hz), 7.35 (d, 2 H, *J* = 8 Hz), 4.88 (br. s, 1 H), 4.86 (m, 1 H), 4.68 (br. s, 1 H), 3.86 (AB, 2 H, *J* = 9.5 Hz), 2.77 (br. t, 1 H, *J* = 9 Hz), 2.45 (s, 3 H), 2.2−1.5 (m, 6 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.55 (s, 3 H). − ^{13}C NMR: δ = 144.7 (s), 144.3 (s), 134.5 (s), 133.1 (s), 129.8 (d), 128.0 (d), 118.8 (d), 109.9 (t), 75.3 (t), 46.4 (d), 45.3 (s), 27.8 (t), 26.0 (q), 23.5 (q), 23.4 (t), 21.7 (q), 19.0 (t), 18.1 (q).

***trans*-1-(3′,3′-Dimethylallyl)-2-isopropenylcyclobutaneacetonitrile (34):** NaCN (34 mg, 0.7 mmol) was added to a solution of crude tosylate **33** (160 mg, 0.47 mmol) in HMPA (1 mL) with 3 drops of water. The reaction mixture was warmed at 60°C overnight, cooled to room temp., diluted with AcOEt/cyclohexane (5:95, 40 mL), washed with water (10 mL), brine (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 73 mg (76%) of the product **34** as a colourless oil. − ^{1}H NMR: δ = 5.03 (br. t, 1 H, *J* = 5 Hz), 4.92 (br. s, 1 H), 4.73 (br. s, 1 H), 2.91 (br. t, 1 H, *J* = 8 Hz), 2.43 (AB, 2 H, *J* = 17 Hz), 2.25 (dd, 1 H, *J* = 6.5 Hz, *J* = 15 Hz), 2.10−1.75 (m, 5 H), 1.73, 1.71 (2s, 6 H), 1.62 (s, 3 H). − ^{13}C NMR: δ = 143.6 (s), 135.4 (s), 118.8 (s), 118.7 (d), 111.4 (t), 48.6 (d), 43.7 (s), 30.6 (t), 28.3 (t), 26.3 (t), 26.1 (q), 23.5 (q), 19.2 (t), 18.1 (q). − GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 4.95 min. − EI MS; *m*/*z* (%): 203 (3), 188 (3), 160 (7), 148 (3), 134 (21), 120 (40), 107 (14), 105 (14), 95 (60), 93 (60), 69 (62), 68 (100), 67 (70), 53 (40), 41 (80). − IR (neat): $\tilde{\nu}$ = 3080 cm^{-1}, 2916, 2848, 2244, 1646, 1462, 1377.

Ethyl 2-Allyl-5,5-diethoxy-3-isopropenylpentanoate (35): A solution of **3** (410 mg, 1.57 mmol) in THF/HMPA (1:1, 4 mL) was added dropwise under argon to a solution of LiHMDS (4.7 mL, 4.7 mmol, 1 M solution in THF, −60°C) in THF (2 mL). The reaction mixture was stirred for 1 h at −60°C, then added a solution of freshly distilled allyl bromide (2 mL, 23.5 mmol) in HMPA (2 mL), warmed to room temp. and quenched with satd. aqueous ammonium chloride solution (15 mL) at −20°C. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic layers were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 447 mg (90%) of the product **35** as a colourless oil. − Major isomer: ^{1}H NMR: δ = 5.69 (m, 1 H), 5.04−4.75 (m, 3 H), 4.38 (dd, 1 H, *J* = 7.5 Hz, *J* = 4 Hz), 4.13 (m, 2 H), 3.60 (m, 2 H), 3.44 (m, 2 H), 2.51−2.13 (m, 5 H), 1.63 (m, 1 H), 1.62 (s, 3 H), 1.25−1.15 (m, 9 H). − ^{13}C NMR: δ = 174.9 (s), 143.5 (s), 135.5 (d), 116.7 (t), 115.3 (t), 101.0 (d), 61.5 (t), 60.4 (t), 60.0 (t), 48.8 (d), 45.8 (d), 35.4 (t), 34.7 (t), 18.2 (q), 15.5 (2 C, q), 14.4 (q). − The ratio of stereomers was determined by capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 7.40 min (73%), 7.56 min (27%). − EI MS; *m*/*z* (%): 269 (1), 253 (2), 180 (4), 133 (30), 116 (28), 103 (100), 89 (28), 75 (88), 55 (15), 47 (68), 43 (30), 41 (30).

2-Allyl-3-isopropenyl-5-(tosyloxy)pentanoate (36): Prepared from **35** by the same procedure as for **14** (76%), colourless oil. − Major isomer: ^{1}H NMR: δ = 7.74 (d, 2 H, *J* = 8 Hz), 7.31 (d, 2 H, *J* = 8 Hz), 5.66 (m, 1 H), 4.97 (m, 2 H), 4.81 (br. s, 1 H), 4.68 (br. s, 1 H), 4.13−3.81 (m, 4 H), 2.43 (s, 3 H), 2.37−2.14 (m, 2 H), 2.14−2.11 (m, 2 H), 1.67−1.60 (m, 2 H), 1.51 (s, 3 H), 1.22 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 174.4 (s), 144.7 (s), 142.2 (s), 135.0 (d), 133.3 (s), 129.8 (d), 127.9 (d), 116.8 (t), 116.0 (t), 68.5 (t), 60.4 (t), 48.5 (d), 45.9 (d), 35.2 (t), 29.8 (t), 21.6 (q), 17.6 (q), 14.4 (q).

Ethyl *trans*-1-Allyl-2-isopropenylcyclobutanecarboxylate (37): Prepared from **36** by the same procedure as for **15** (52%), colourless oil. Diastereoselectivity > 95:5 − ^{1}H NMR: δ = 5.66 (m, 1 H), 5.07−4.94 (m, 3 H), 4.74 (s, 1 H), 4.15 (q, 2 H, *J* = 7 Hz), 3.09 (t, 1 H, *J* = 9 Hz), 2.41−2.34 (m, 2 H), 2.21 (ddd, 1 H, *J* = 14 Hz, *J* = 6.5 Hz, *J* = 1 Hz), 2.05 (m, 1 H), 1.85 (m, 1 H), 1.73 (s, 3 H), 1.67 (m, 1 H), 1.27 (t, 3 H, *J* = 7 Hz). − ^{13}C NMR: δ = 176.2 (s), 143.8 (s), 134.1 (d), 117.7 (t), 111.8 (t), 60.5 (t), 50.3 (s), 47.9 (d), 34.9 (t), 23.8 (t), 19.0 (t), 22.9 (q), 14.4 (q). − The ratio of stereomers was determined by capillary GC analysis of the crude product (DB5-MS, 0.32 mm i.d. × 30 m, 140−300°C, 10°C/min), retention time 3.28 min (< 5%), 3.43 (> 95%). − EI MS; *m*/*z* (%): 193 (0.5), 177 (11), 165 (1), 147 (6), 134 (6), 121 (51), 109 (40), 108 (12), 107 (41), 95 (38), 93 (52), 91 (23), 82 (37), 81 (36), 79 (43), 70 (43), 69 (60), 68 (96), 67 (100), 55 (67), 53 (37), 43 (33), 41 (88). − IR (CCl_4): $\tilde{\nu}$ = 3080 cm^{-1}, 2927, 2855, 1726, 1641.

***trans*-2-(1′-Oxoethyl)-1-(4′-oxopent-1′-yl)cyclobutaneacetonitrile (38):** 4-Methylmorpholine *N*-oxide (344 mg, 2.9 mmol) and a solution of OsO_4 (0.75 mL, 2.5% in 2-methyl-2-propanol) were added dropwise under argon to a solution of nitrile **18** (290 mg, 1.33 mmol) in an acetone/water mixture (9:1). The reaction mixture was stirred at room temp. for 15 h, then $Na_2S_2O_3$ (1.6 g, 10.1 mmol) was added . The resultant mixture was stirred for 1 h, diluted with CH_2Cl_2 (20 mL) filtered through Celite and concentrated under reduced pressure to give the crude product as an orange oil. To a solution of this crude product in a mixture of MeOH/water (1:1, 12 mL) was added $NaHCO_3$ (480 mg) and $NaIO_4$ (1.25 g, 5.85 mmol). The resultant white suspension was stirred for 18 h at room temp. and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (40 mL) and the organic layer washed with water (10 mL), brine (10 mL) dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/cyclohexane, 40:60) to give 190 mg (64%) of the product **38** as a colourless oil. (1*S*, 2*R*)-**38** from (1*S*, 2*S*)-**18**: $[\alpha]_D^{20}$ = −33.7 (*c* = 2.1, CH_2Cl_2), (1*R*, 2*S*)-**38** from (1*R*, 2*R*)-**18**: $[\alpha]_D^{20}$ = +30.3 (*c* = 2.7, CH_2Cl_2). − ^{1}H NMR: δ = 3.27 (t, 1 H, *J* = 8 Hz), 2.61 (AB, 2 H, *J* = 17 Hz), 2.5−1.4 (m, 10 H), 2.15, 2.12 (2s, 6 H). − ^{13}C NMR: δ = 207.9 (s), 207.4 (s), 118.0 (s), 53.1 (d), 43.9 (s), 43.3 (t), 32.5 (t), 30.9 (q), 30.1 (q), 28.1 (t), 27.0 (t), 17.4 (t), 16.7 (t). − Capillary GC analysis (BPX-70-MS, 0.32 mm i.d. × 30 m, 125−270°C, 10°C/min), retention time 14.13 min. − EI MS; *m*/*z* (%): 178 (4), 164 (4), 151 (12), 136 (5), 133 (7), 120 (5), 108 (30), 94 (12), 91 (6), 79 (8), 71 (77), 58 (38), 55 (14), 43 (100). − IR (CCl_4): $\tilde{\nu}$ = 2958 cm^{-1}, 1719, 1708, 1359, 1260, 1163, 1097.

***cis*-2-(1′-Oxoethyl)-1-(4′-oxopent-1′-yl)cyclobutaneacetonitrile (39):** 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.43 mL, 2.57 mmol) was added to a solution of ketone **38** (190 mg, 0.85 mmol) in benzene (9 mL). The resultant mixture was stirred overnight at 80°C then cooled to room temp., and diluted with Et_2O (30 mL). The mixture was washed with HCl (0.5 M, 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give 190 mg of unseparable **39/38** (60:40) as crude product. − **39**: ^{1}H NMR: δ = 3.15 (t, 1 H, *J* = 9 Hz), 2.59 (AB, 2 H, *J* = 17 Hz), 2.5−1.4 (m, 10 H), 2.15, 2.14 (2s, 6 H). − ^{13}C NMR: δ = 208.5 (s), 208.2 (s), 118.2 (s), 51.8 (d), 44.4 (s), 43.2 (t), 39.5 (t), 30.2 (2 C, q), 28.3 (t), 22.7 (t), 18.3 (t), 18.2 (t). Capillary GC analysis (BPX-70-MS, 0.32 mm i.d. × 30 m, 125−270°C, 10°C/min), retention time 13.84 min. − EI MS; *m*/*z* (%): 203 (1), 178 (7), 164 (5), 151 (10),

136 (7), 133 (4), 120 (5), 108 (15), 94 (10), 91 (5), 79 (8), 71 (60), 58 (30), 55 (12), 43 (100).

***cis*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneacetonitrile (40):** *n*-Butyllithium (2.1 mL, 3.36 mmol, 1.6 M solution in hexane) was added dropwise under argon to a solution of methyltriphenylphosphonium bromide (1.2 g, 3.4 mmol, −60°C) in THF (17 mL). The ylide solution was stirred for 1 h to 0°C. A solution of a mixture of the crude diastereomers **38** and **39** (190 mg, 0.85 mmol) in THF (17 mL) was added to the ylide solution (−60°C). The resultant reaction mixture was warmed at room temp. overnight and quenched with water. The aqueous phase was extracted with cyclohexane (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in pentane (50 mL) and stirred for 1 h at room temp. The solution was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (AcOEt/cyclohexane, 5:95) to give 140 mg (75%) of a mixture of unseparable diastereomers **18** and **40** as a colourless oil. − **40**: ^{1}H NMR: δ = 4.98 (br. s, 1 H), 4.76 (br. s, 1 H), 4.74 (br. s, 1 H), 4.72 (1 br. s, 1 H), 2.75 (br. t, 1 H, *J* = 7 Hz), 2.37 (AB, 2 H, *J* = 17 Hz), 2.10−1.26 (m, 10 H), 1.72, 1.71 (2s, 6 H). − ^{13}C NMR: δ = 145.4 (s), 143.9 (s), 118.9 (s), 111.9 (t), 110.4 (t), 48.3 (d), 44.5 (s), 39.9 (t), 38.1 (t), 27.5 (t), 23.9 (q), 22.6 (t), 22.5 (q), 22.4 (t), 18.9 (t). − GC analysis (BPX-70-MS, 0.32 mm i.d. × 30 m, 125−275°C, 10°C/min), retention time 5.42 min. − EI MS; *m*/*z* (%): 217 (0.1), 216 (1), 202 (3), 177 (5), 161 (1), 146 (2), 134 (3), 121 (10), 109 (15), 93 (12), 79 (14), 69 (15), 68 (100), 67 (50), 56 (13), 53 (17), 41 (41).

***cis*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneethanol (41):** Diisobutylaluminium hydride (0.425 mL, 0.425 mmol, 1 M solution in toluene) was added dropwise under argon to a solution of diastereomers **18** and **40** (40 mg, 0.18 mmol, −20°C) in CH_2Cl_2 (1.6 mL) The reaction mixture was stirred for 2 h at −20°C, then water (0.3 mL) and 5% H_2SO_4 (0.9 mL) were added. The mixture was stirred for 1 h at 0°C, the aqueous phase was separated and extracted with Et_2O (2 × 25 mL). The combined organic layers were washed with satd. aqueous sodium bicarbonate solution (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of aldehydes used in the next step without further purification. $NaBH_4$ (15 mg, 0.39 mmol) was added to a solution of these aldehydes in EtOH (1.5 mL, 0°C) The reaction mixture was stirred for 15 min at 0°C and quenched with 9 drops of acetone. The resultant solution was stirred for 30 min at room temp. and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 13 mg (32%) of **41** and 4 mg of **19** (10%) as colourless oils. − **41**: ^{1}H NMR: δ = 4.85 (br. s, 1 H), 4.69 (br. s, 2 H), 4.66 (br. s, 1 H), 3.74 (m, 2 H), 2.67 (br. t, 1 H, *J* = 9 Hz), 2.05−1.25 (m, 12 H), 1.71 (s, 6 H). − ^{13}C NMR: δ = 146.2 (s), 145.4 (s), 110.4 (t), 109.8 (t), 60.1 (t), 49.5 (d), 44.4 (s), 42.7 (t), 38.8 (t), 33.0 (t), 28.1 (t), 24.0 (q), 22.6 (q), 21.9 (t), 19.8 (t). − Capillary GC analysis (DB5-MS, 0.32 mm i.d. × 30 m, 150−225°C, 10°C/min), retention time 6.31 min. − EI MS; *m*/*z* (%): 208 (1), 191 (1), 177 (5), 149 (3), 139 (22), 135 (5), 121 (20), 119 (16), 109 (16), 107 (18), 95 (23), 93 (35), 81 (45), 79 (30), 77 (13), 69 (66), 68 (100), 67 (70), 55 (38), 53 (30), 43 (11), 41 (71), 40 (15). − IR (CCl_4): $\tilde{\nu}$ = 3632 cm^{-1}, 3078, 2931, 2853, 1645, 1449, 1373, 1226, 1042.

***cis*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneethanol Acetate (2):** A solution of alcohol **41** (12 mg, 0.54 mmol) in pyridine (0.3 mL) with Ac_2O (0.1 mL) was stirred overnight at room temp. The reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography (AcOEt/cyclohexane, 10:90) to give 9.3 mg (70%) of **2** as colourless oil. (1*S*, 2*R*)-**2** from (1*S*, 2*R*)-**41**: $[\alpha]_D^{20}$ = +2.4 (*c* = 0.9, *n*-hexane), (1*R*, 2*S*)-**2** from (1*R*, 2*S*)-**41**: $[\alpha]_D^{20}$ = −2.5 (*c* = 1.1, *n*-hexane). ^{1}H-, ^{13}C-NMR spectra and mass data are identical to those of the natural sample.[2]

Acknowledgments

The authors wish to thank C. Malosse and L. Kerhoas (I. N. R. A. Versailles) for mass spectra and GC analysis and P. Toullec for technical assistance.

[1] J. W. Beardsley, R. H. González, *Annu. Rev. Entomol.* **1975**, *20*, 47−73 .
[2] J. Einhorn, A. Guerrero, P. H. Ducrot, F. D. Boyer, M. Gieselmann, W. Roelofs, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9867−9872.
[3] F. D. Boyer, P. H. Ducrot, *C. R. Acad. Sci., Sect. IIc* **1999**, 29−33 .
[4] D. Bellus, B. Ernst, *Angew. Chem. Int. Ed. Eng.* **1988**, *27*, 797−827.
[5] W. Oppolzer, *Acc. Chem. Res.* **1982**, *15*, 135−141.
[6] B. M. Trost, *Top. Curr. Chem.* **1986**; *133*, 3−82.
[7] A. F. Thomas,Y. Bessière, *The Synthesis of Monoterpenes, 1980−1986* in *The Total Synthesis of Natural Products* (Ed.: J. ApSimon), John Wiley & Sons, New York, **1988**, vol. 7, pp. 328−336.
[8] S. J. Bloor, *Tetrahedron Lett.* **1993**, *34*, 5617−5620.
[9] S. F. R. Hinkley, N. B. Perry, R. T. Weavers, *Tetrahedron Lett.* **1994**, *35*, 3775−3776.
[10] K. Mori, K. Fukamatsu, *Liebigs Ann. Chem.* **1992**, 489−493.
[11] K. Mori, *The Synthesis of Insect Pheromones, 1979−1989* in *The Total Synthesis of Natural Products* (Ed.: J. ApSimon), John Wiley & Sons, New York, **1992**, vol. 9, pp. 303−334.
[12] W. Roelofs, M. Gieselmann, A. Cardé, H. Tashiro, D. S. Moreno, C. A. Hennick, R. J. Anderson, *J. Chem. Ecol.* **1978**, *4*, 211−224.
[13] K. Tanida, K. Mori, *Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)* **1981**, 635−637.
[14] D. Kim, Y. K. Lee, Y. M. Jang, I. O. Kim, W. P. Sang, *J. Chem. Soc., Perkin Trans. 1* **1990**, 3221−3224.
[15] D. Kim, Y. K. Lee, *Tetrahedron Lett.* **1991**, *47*, 6885−6886.
[16] D. Kim, Y. S. Kwak, K. J. Shin, *Tetrahedron Lett.* **1994**, *49*, 9211−9212.
[17] P. H. Mazzocchi, P. Wilson, F. Khachik, L. Klinger, S. Minamikawa, *J. Org. Chem.* **1983**, *48*, 2981−2989.
[18] E. A. Mash, J. A. Fryling, *J. Org. Chem.* **1991**, *56*, 1094−1098.
[19] M. J. Gieselmann, *Armored Scale Insects; their Biology Natural Enemies and Control* in *World Crop Pests*, Elsevier, Amsterdam, New York, **1990**, vol. B (Ed.: D. Rosen), pp. 225−231.
[20] B. S. Fletcher, T. E. Bellas, in *CRC Handbook of Natural Pesticides*, **1988**, vol. IV-B, pp. 207−215.

Received November 16, 1998
[O98515]