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Stereospecific palladium(0)-catalyzed reduction of 2-cyclobutylidenepropyl esters. A versatile preparation of diastereomeric monoterpenoids: (±)-fragranol and (±)-grandisol

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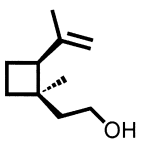
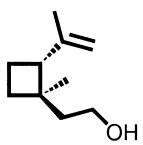
Abstract—Mixtures of (*E* and *Z*)-2-cyclobutylidenepropyl sulfonates, readily available from α,α-disubstituted cyclobutanones arising from suitable cyclopropane derivatives ring expansion, underwent regioselective and stereospecific reduction by formate anion to offer, through π-1,1-trimethyleneallylpalladium complexes formed upon treatment with palladium(0), a new and convenient entry to the diastereomeric four-membered ring monoterpenoids (±)-fragranol and (±)-grandisol.

The monoterpenoid grandisol **1** is the main constituent of the aggregation male-produced pheromone of the cotton boll weevil *Anthonomous grandis* Boheman[1] and of the sex pheromones of other pests responsible for conifer infestations in North America and Central Europe, like *Bark weevils*[2] and *Bark beetles*.[3] The diastereomeric monoterpenoid fragranol **2** was isolated from the roots *of Artemisia fragrans Willd*.[4] Due to the potential alternative to classical pesticides offered by such four-membered ring natural products involving environmentally friendly use, the total synthesis of these terpenes is a matter of current investigation.[5]



(±) - *Grandisol*-**1**



(±) - *Fragranol*-**2**

In most of the reported syntheses of grandisol **1** and fragranol **2**, formation of the cyclobutane ring arose from photochemically,[6] thermally[7] or $TiCl_4$[8] promoted [2+2] cycloadditions. Although when suitably substituted, cyclopropanes provided convenient precursors of cyclobutanones,[9] their use as intermediaries for the total synthesis of grandisol **1** has been scarcely exploited.[10]

We report herein our investigations to form readily these natural products from the regioselective and stereospecific palladium(0) induced reduction of the 2-cyclobutylidenepropyl esters **3a**,**b** (Y=O-*p*-An, CH_2OBn),[11] easily available from the cyclobutanones **4a**,**b**, arising from the ring expansions[9] of either the oxaspiropentane **5**[12] or the (1-phenylthiocyclopropyl)carbinol **6** (Scheme 1).

As a matter of fact, we have previously reported that 1-(1-alkenyl)cycloalkyl esters (acetate, tosylate, mesylate) **7** (*n*=1, 3, 4; R=H, alkyl, aryl, silyl) underwent palladium(0) catalyzed hydrogenolysis by sodium formate in the presence of crown ethers (15-C-5), or by *n*-butylzinc chloride as hydride sources, to provide either alkylidenecycloalkanes **9** or (1-alkenyl) cycloalkanes **10**, regioselectively.[11] This alternative to the Wittig olefination implied the intermediate formation of the π-1,1-(polymethylene)allylpalladium complexes **8** which underwent then, nucleophilic hydride substitution with a regioselectivity monitored by the nature of the hydride source, by ring strain, silyl substitution and by the steric effect of phosphorus ligands (Scheme 2).[11]

Our first approach towards the monoterpenoid alcohols **1**

Keywords: palladium and compounds; stereospecificity; cyclobutanes; natural products.

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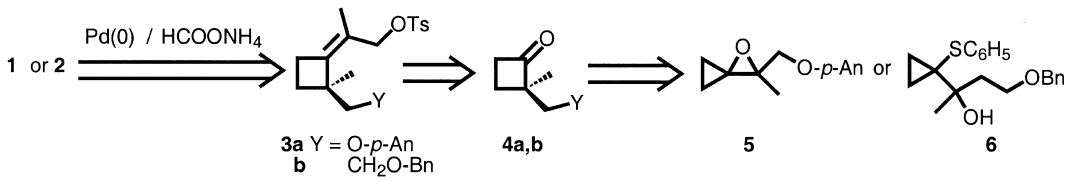
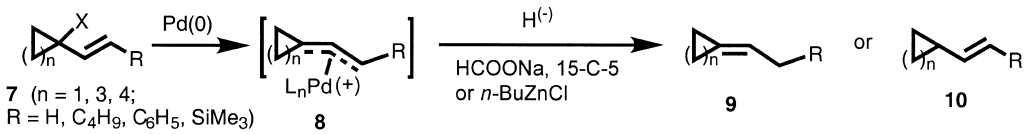


Scheme 1.



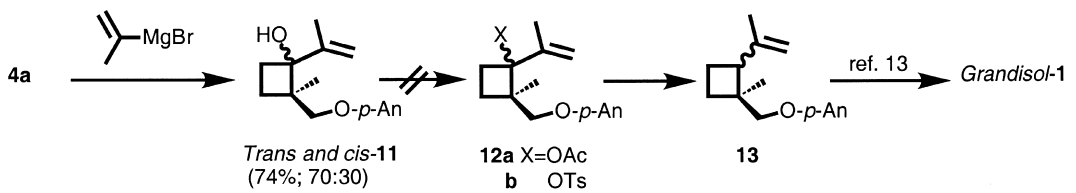
Scheme 2.

and **2** involved the reaction of isopropenyl magnesium bromide with the 2-(*p*-anisyloxymethyl)-2-methylcyclobutanone **4a**, previously obtained from oxaspiropentane **5**,[12] which furnished in 74% yield, a 70:30 mixture of *trans*- and *cis*-1-isopropenyl-2-(*p*-anisyloxymethyl)-2-methylcyclobutanols **11**. As reported with 1-ethenylcyclopropyl tosylates and mesylates **7** (n=1) and 1-ethenylcyclohexyl acetates **7** (n=4),[11] the palladium(0) catalyzed hydride reduction [$Pd(dba)_2$, $P(PPh_3)_2$] by sodium formate of the 1-isopropenylcyclobutylacetates **12** derived from cyclobutanols **11** could be expected to provide analogously the 1-(*p*-anisyloxymethyl)-2-isopropenyl-1-methylcyclobutane **13**, a convenient and known precursor of grandisol **1** (Scheme 3).[13] However, likely as result of steric hindrance or lability, the allylic tertiary acetates **12a** and the corresponding sulfonic esters **12b** were not obtained.

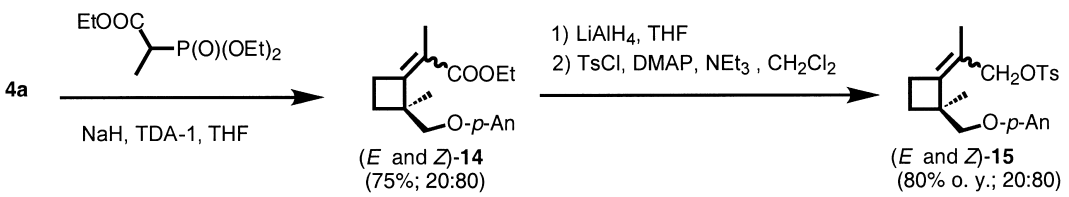
In order to overcome this failure, we have then prepared the isomeric allylic tosylates **15**. Thus, Wittig–Horner olefination of cyclobutanone **4a** by triethyl 2-phosphonopropionate (NaH, TDA-1, THF), provided an unseparable 20:80 mixture of (*E*)- and (*Z*)-2-[2-(*p*-anisyloxymethyl)-2-methylcyclobutylidene]propionates **14**. Their relative geometries were assigned on the basis of NOE experiments; effectively this effect was observed only between the vinylic methyl at δ 1.71 and the cyclobutanic allylic methylene at δ 2.76 ppm of (*Z*)-**14**. Then reduction ($LiAlH_4$, THF) of (*E* and *Z*)-**14**, followed by tosylation (TsCl, DMAP, NEt_3, CH_2Cl_2), led in 80% overall yield for these two steps, to an unseparable 20:80 mixture of (*E*)- and (*Z*)-allylic tosylates **15** (Scheme 4).

Palladium(0) [$Pd(dba)_2$, $2PPh_3$] treatment of the 20:80 mixture of allylic tosylates (*E* and *Z*)-**15** gave likely the π-1,1-trimethyleneallylpalladium complex **16**,[11] which then underwent nucleophilic addition of formate anion, when treated by sodium formate in the presence of [15]-crown-5-ether, to form the σ-1,1-trimethyleneallylpalladium formate complex **17**.[11] Decarboxylation of the formate ligand and attack of the resulting hydride, as well as S_{Ni} transfer of hydride to the cyclobutanic allylic end, led to a 20:80 mixture of *cis*- and *trans*-1,1,2-trisubstituted cyclobutanes **18** in 77% yield. Finally, cleavage of the *O*-protective group by ammonium cerium(IV) nitrate (CAN, CH_3CN, H_2O) gave in 74% yield, after chromatography the pure *trans*-2-isopropyl-1-methyl cyclobutylcarbinol **19**, a reported convenient precursor of (±)-fragranol **2** by homologation of the primary alcohol.[8]

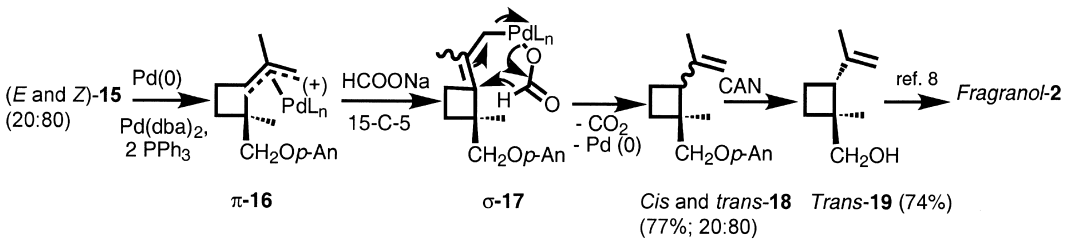
The regioselectivity of this Pd(0) catalyzed reduction likely resulted from the exclusive formation of the σ-1,1-trimethyleneallylpalladium complex **17**, where the palladium was positioned exclusively on the primary allylic end, contrary to the π-1,1-dimethyleneallylpalladium complexes **8** (n=1) arising from 1-ethenyl-1-tosyloxycyclopropanes derivatives,[14] for which the palladium was shown to be positioned on the allylic carbon bearing the least



Scheme 3.



Scheme 4.



Scheme 5.

pronounced positive charge, because of the intrinsic three-membered ring strain (Scheme 5).[11,14] The stereospecificity observed for this reaction, i.e. the formation of a 20:80 mixture of *cis*- and *trans*-**18** from the 20:80 mixture of allylic tosylates (*E* and *Z*)-**15** was also noteworthy.

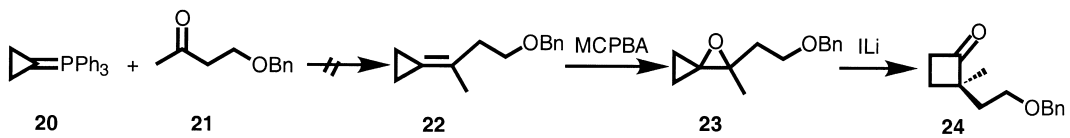
With the aim of synthesizing the diastereomeric monoterpenoid grandisol **1** with a reduced number of steps, we have then prepared the 2-(2-benzyloxyethyl)-2-methylcyclobutanone **24**. First of all, attempted reaction of the commercially available 4-benzyloxybutan-2-one **21** with the cyclopropylidenephosphorane **20** (arising from reaction of cyclopropyltriphenylphosphonium bromide[15] with base) failed to provide the cyclopropylidene derivative **22**, however potent precursor by peracid epoxidation (MCPBA)[16] of the oxaspiropentane **23**, which was expected to furnish then, by lithium iodide induced ring expansion the cyclobutanone **24** (Scheme 6).[9,16]

Formation of methyl vinyl ketone and benzyl alcohol indicated a competitive base-induced elimination of the benzyloxy group. Replacement of the *O*-protective group of **21** by a tetrahydropyranyloxy, led unexpectedly but nevertheless interestingly to the 5-cyclopropylidenepentan-1-ol **29** in 45% yield.[17] In fact **25** (prepared from commercially available 4-hydroxybutan-2-one and THP, PPTs) underwent likewise, elimination of the tetrahydropyranyloxy by the basic phosphorane **20**, with formation of the methyl vinyl ketone **26** and of the hemiacetal anion **27** in equilibrium with the 5-oxypentan-1-one anion **28**, which then underwent Wittig olefination by the ylide **20** (Scheme 7).[18]

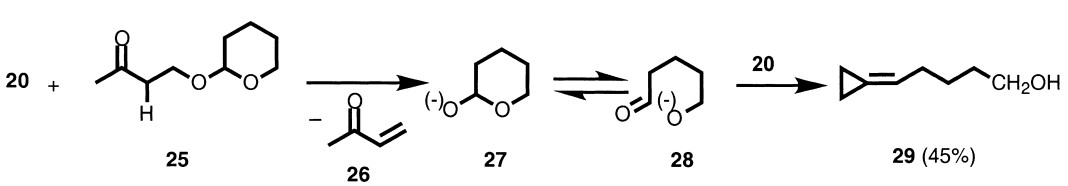
Finally, the expected cyclobutanone **24** was successfully obtained by reaction of the *O*-protected β-hydroxyketone **21** with the lithium salt of the cyclopropyl phenyl sulfide **30**,[19] (*n*-BuLi, THF, 0°C) which furnished the 1-(phenylthio cyclopropyl)carbinol **31** in 90% yield; then, **31** underwent acid catalyzed ring expansion[20] (PTSA, C_6H_6) to lead to the cyclobutanone **24** in 98% yield (Scheme 8).

Wittig–Horner reaction of **24** with triethyl 2-phosphonopropionate (60% NaH in oil, TDA-1, THF, reflux) provided in 78% yield an unseparable 30:70 mixture of ethyl (*E*)- and (*Z*)-2-[2-(benzyloxyethyl)-2-methyl cyclobutylidene]propionate **32**. Then, successive conjugated double bond (Mg, MeOH)[21] and ester function reductions ($LiAlH_4$, THF) of **32** followed by iodination of the resulting alcohol (I_2, PPh_3, imidazole, benzene) gave a diastereomeric mixture of the 2-cyclobutyl-1-iodopropane derivative **33** in 88% overall yield. Finally, dehydroiodination of **33** by silver fluoride in pyridine led in 80% yield to a 1:1 diastereomeric mixture of 2-isopropenylcyclobutane derivatives **34** and **35**. This lack of diastereoselectivity was pointed out from their ^1H NMR data, in particular by the occurrence of two aliphatic methyl signals, as well from glc-mass spectroscopy. Furthermore, after *O*-deprotection by cleavage of the *O*-benzyl bond with Li/NH_3 in dry diethyl ether, the mixture exhibited in its ^1H NMR two saturated methyl groups at δ 1.17 and 0.92 ppm, attributed to grandisol **1** and fragranol **2**,[8] respectively, which then readily separable by liquid chromatography, were obtained in 80% yield (Scheme 9).

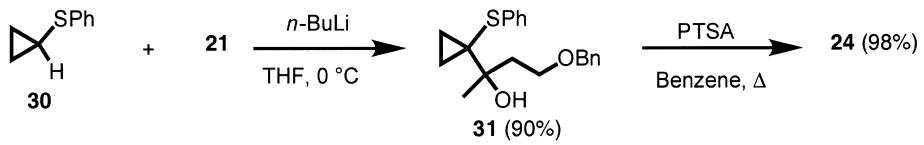
On the other hand, lithium aluminium hydride reduction of the unseparable 30:70 mixture of conjugated esters (*E* and *Z*)-**32** gave the corresponding allylic alcohols in 98% yield, which were transformed into the crude tosylates (*E* and *Z*)-**36** (TsCl, DMAP, NEt_3, CH_2Cl_2 at rt). Then, palladium(0) catalyzed reduction of (*E* and *Z*)-**36** by ammonium formate in THF, which most probably occurred through the σ-1,1-trimethyleneallylpalladium formate complexes **38**, analogous to the σ-complexes **17**, (see Scheme 5) led in 80% yield to a 70:30 mixture of *cis*-**34**, precursor of grandisol **1**, and of *trans*-**35** precursor of fragranol **2**, after *O*-deprotection (Li/NH_3) and chromatography. Obviously, contrary to



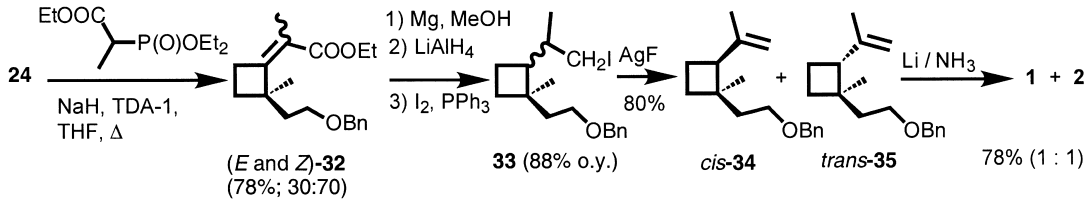
Scheme 6.



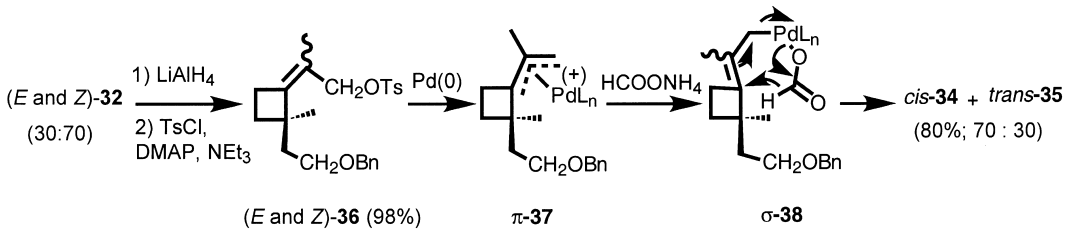
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

the sequence leading from the allylic tosylates (*E* and *Z*)-**15** to fragranol **2** as major product (80%), as reported on scheme 5, for the Pd(0)-catalyzed reduction of (*E* and *Z*)-**36** the more bulky 2-(2-benzyloxyethyl)substituent appeared to hamper one side of the palladium complexes π-**37** and/or σ-**38** and to entail the favored formation of the *cis*-2-isopropylidenecyclobutane **34** (70%), precursor of (±)-grandisol **1** after *O*-deprotection (Scheme 10).

In conclusion, the palladium(0) catalyzed reduction of 2-cyclobutylidenepropyl sulfonic esters by sodium formate, involving π-1,1-trimethyleneallylpalladium complexes, appeared completely regioselective and stereospecific. It opened a new and convenient entry to diastereomeric four-membered ring compounds; thus the allylic tosylates (*E* and *Z*)-**15** and (*E* and *Z*)-**36**, which were readily available from the cyclobutanones **4a** and **36**, bearing either a 2-*p*-anisyloxymethyl- or a 2-(2-benzyloxyethyl) substituents, and prepared by ring expansion of the oxaspiropentane **5**[12] or of the 2-(phenylthiocyclopropyl)carbinol **31**, respectively, afforded the pure (±)-fragranol **2** in 7 steps from **4a** with 25% overall yields and the pure (±)-grandisol **1** in 6 steps from the cyclopropylphenyl sulfide **30**, with 42% overall yields.

1. Experimental

1.1. General

IR spectra were recorded on a Perkin–Elmer 682 spectrophotometer using NaCl plates. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer with tetramethylsilane as internal reference. Mass spectra were recorded with a GC/MS spectrometer. TLC were carried out on precoated TLC plates with silica gel 60 F-254. For liquid chromatography silica gel 60 (230–4000 mesh) was used. Melting points were determined on a Tottoli apparatus and are incorrected. Microanalyses were carried out on a Carlo Erba 1106 Elemental Analyzer. The preparation of cyclobutanoned **4a** has been previously reported.[12]

1.1.1. *trans*- and *cis*-1-Isopropenyl-2-[(4-methoxyphenoxy)methyl]-2-methylcyclobutanol 11. To a stirred solution of cyclobutanone **4a** (1 g, 4.5 mmol) in THF (5 mL) was added at −20°C a solution of isopropenylmagnesium bromide [prepared as usual from magnesium turnings (432 mg, 18 mmol) and 2-bromo propene (1.6 mL, 18 mmol)] in THF (1 mL). The solution was allowed to gradually reach room temperature and stirring was continued for 20 h. The mixture was then quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. Then the separated organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give in 74% yield, a 70:30 mixture of *trans*- and *cis*-1-isopropenyl-2-[(4-methoxyphenoxy)methyl]-2-methyl cyclobutanol **11**, as exhibited from the ^{1}H NMR of the crude mixture.

Chromatography on a silica gel (eluent light petroleum/AcOEt 10:1) allowed to isolate the pure *trans*-isomer. *Trans*-**11**: IR (neat): 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.34 (3H, s), 1.62–1.82 (3H, m), 1.79 (3H, s), 2.45–2.54 (1H, m), 2.81 (1H, br s) 3.66, 3.71 (2H, AB q, *J*=8.7 Hz), 3.75 (3H, s), 4.91 (2H, s), 6.80 (4H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 18.40, 19.14, 24.96, 29.36, 46.65, 55.68, 73.35, 80.49, 111.32, 114.54, 115.23, 146.54, 153.47, 153.64; Mass spectrum (EI) *m/z* (rel. intensity): 262 (3, M^+), 178 (11), 163 (3), 124 (100), 109

(20); Elemental analysis Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.32; H, 8.58.

cis-**11**: IR (neat): 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): (data were determined from the diastereomeric mixture NMR spectra) 1.13 (3H, s), 1.62–2.02 (3H, m), 1.85 (3H, s), 2.45–2.54 (1H, m), 2.81 (br s, 1H), 3.77 (3H, s), 3.87, 4.15 (2H, AB q, J=9 Hz), 4.99 (1H, br s) and 5.02 (1H, br s), 6.80 (4H, m); Mass spectrum (EI) *m/z* (rel. intensity): 262 (3, M^+), 178 (11), 163 (3), 124 (100), 109 (20).

1.1.2. Ethyl (*E*)- and (*Z*)-2-{2-[(4-methoxyphenoxy)-methyl]2-methylcyclobutylidene}propanoate 14. 2.16 g of triethyl phosphonopropionate (9 mmol) was rapidly added to a stirred suspension of pentane-washed NaH (360 mg, 9 mmol, 60% in oil) in THF (30 mL) under Argon. After keeping the reaction mixture at 65°C for 6 h, a solution of cyclobutanone **4a** (2 g, 9 mmol) and the catalyst TDA-1 (2.3 μL, 0.9 mmol), was slowly added over about 30 min. The mixture was kept at the same temperature for 16 h. After cooling to room temperature, the solution was diluted with diethyl ether and washed with brine, dried (Na_2SO_4) and evaporated under vacuum to give 2.05 g (75% yield) of a 20:80 mixture of two (*E*)- and (*Z*)-diastereomers, which were separated by chromatography on silica gel (eluent light petroleum/diethyl ether, 10:1).

(*Z*)-**14**: Colourless oil: IR (neat): 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.25 (3H, t, J=9 Hz), 1.38 (3H, s), 1.71 (3H, s), 1.72–1.82 (1H, m), 2.26–2.36 (1H, m), 2.65 (2H, t, J=8.4 Hz), 3.74 (3H, s), 3.91, 4.20 (2H, AB q, J=9 Hz), 4.12 (2H, q, J=9 Hz), 6.82 (4H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 14.16, 14.18, 21.28, 26.09, 27.15, 49.06, 55.52, 59.80, 73.13, 114.37, 115.58, 121.11, 153.56, 153.69, 160.80, 166.56; Mass spectrum (EI) *m/z* (rel. intensity): 304 (5, M^+), 259 (3), 181 (48), 153 (18), 135 (24), 124 (100), 109 (22), 91 (12); Elemental analysis Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.14; H, 7.79.

(*E*)-**14**: Colourless oil: IR (neat): 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.28 (3H, t, J=6.9 Hz), 1.41 (3H, s), 1.75–1.85 (1H, m), 1.84 (3H, s), 2.08–2.18 (1H, m), 3.08 (2H, t, J=9 Hz), 3.76 (3H, s), 3.88, 3.96 (2H, AB q, J=9 Hz), 4.16 (2H, q, J=6.9 Hz), 6.83 (4H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 13.68, 14.32, 21.56, 28.14, 29.06, 48.35, 55.67, 59.89, 73.76, 114.56, 115.51, 121.16, 153.39, 153.84, 161.56, 168.17; Mass spectrum (EI) *m/z* (rel. intensity): 304 (6, M^+), 259 (2), 180 (8), 151 (11), 135 (10), 124 (100), 109 (20), 91 (10); Elemental analysis Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.28; H, 7.72.

1.1.3. 2-(2-[(4-Methoxyphenoxy)methyl]-2-methylcyclo-butylidene(propyl (4-methylbenzene) sulfonate 15. To a stirred solution of the diastereomeric mixture of (*E*,*Z*)-**14** (5.16 g, 0.017 mol) in 50 mL of dry THF at −20°C was added dropwise a 1.5 M solution of $LiAlH_4$ in THF (11.34 mL, 0.017 mol). After 2 h the mixture was treated with wet Na_2SO_4, then filtered on celite, dried (Na_2SO_4) and the solvent evaporated under vacuum. Flash chromatography of the residual oil (silica gel, pentane/diethyl ether 1:1) gave 3.74 g (84% yield) of a 20:80 mixture of the corresponding (*E*)- and (*Z*)-allylic alcohols.

(*Z*)-*Allylic alcohol*: IR (neat): 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.37 (3H, s), 1.61 (3H, s), 1.73–1.80 (1H, m), 1.86–1.92 (1H, m), 1.87 (1 H, br s), 2.55 (2H, t, J=8.1 Hz), 3.75 (3H, s), 3.81, 3.88 (2H, AB q, J=9 Hz), 3.95, 4.17 (2H, AB q, J=11.4 Hz), 6.85 (4H, m); ^{13}C ($CDCl_3$, 62.9 MHz) δ (ppm):15.61, 23.36, 24.15, 27.28, 47.03, 55.70, 62.89, 75.10, 114.67, 115.50, 128.89, 141.26, 153.24, 153.97; Mass spectrum (EI) *m/z* (rel. intensity): 262 (5, M^+), 124 (100), 109 (27), 81 (38), 55 (11), 43 (30); Elemental analysis Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.18; H, 8.58.

(*E*)-*Allylic alcohol*: IR (neat): 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.35 (3H, s), 1.71 (3H, s), 1.62–1.80 (1H, m), 1.96–2.08 (1H, m), 2.20 (1H, br s), 2.58 (2H, t, J=8.4 Hz), 3.73 (3H, s), 3.83, 3.91 (2H, q, J=9 Hz), 3.90 (2H, s), 6.78–6.86 (4H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 14.51, 22.13, 23.88, 27.34, 46.84, 55.53, 63.29, 74.38, 114.44, 115.44, 127.57, 140.45, 153.54, 153.58; Mass spectrum (EI) identical to (*Z*)-allylic alcohol; Elemental analysis Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.38; H, 8.32.

To a solution of 412 mg (1.57 mmol) of the 20:80 mixture of these (*E*, *Z*)-allylic alcohols in 10 mL of CH_2Cl_2 was added triethylamine (462 μL, 4.71 mmol) at 0°C, 19 mg of DMAP (0.15 mmol) and 598 mg of tosylchloride (3.14 mmol). The reaction mixture was maintained at 0°C for 6 h and then diluted with CH_2Cl_2. The organic layer was washed with brine and then dried (Na_2SO_4). Evaporation of the solvent afforded 650 mg (80% yield) of crude (4-methylbenzene)sulfonate **15**, which was used without further purification in the next step. Spectroscopic data of the crude mixture of (*E*,*Z*)-**15**: IR (neat): 1150 and 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.37 (3H, s), 1.41 (3H, s), 1.62 (3H, s), 1.63 (3H, s), 1.89–2.08 (4H, m), 2.48 (6H, s), 2.44–2.62 (4H, m), 3.75 (3H, s), 3.83, 3.88 (2H, AB q, J=8.1 Hz), 4.06, 4.29 (2H, AB q, J=10.8 Hz), 3.86–3.94 (2H, m), 4.20–4.25 (2H, m), 6.83–7.93 (8H, m).

1.1.4. 2-Isopropenyl-1-methyl-1-(4-methoxyphenoxy)cyclobutane 18. A solution of the crude tosylate (*E*,*Z*)-**15** (650 mg, 1.57 mmol) in 15 mL of dry CH_3CN was added to a stirred solution of 50.63 mg (78.5 μmol, 5 mol%) of $Pd(dba)_2$ and 41.13 mg (157 μmol, 10 mol%) of PPh_3 in 15 mL of dry CH_3CN. After 10 min to the mixture was added 320 mg of sodium formate (4.71 mmol) and 50 mg of [15]-crown-5 (0.4 mmol). The reaction mixture was stirred for 16 h at room temperature and then water was added. The aqueous phase was extracted with ether and the ether extracts were washed with brine, dried and evaporated. Chromatography of the residue on silica gel (eluent pentane/diethyl ether, 9:1) gave 297 mg (77% yield) of a 80:20 mixture of **18** as a yellow oil.

Major isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.05 (3H, s), 1.64 (3H, s), 1.70–2.12 (3H, m), 2.90 (2H, t), 3.71 (2H, s), 3.77 (3H, s), 4.67 (1H, s), 4.98 (1H, s), 6.87 (4H, s); Mass spectrum (EI) *m/z* (rel. intensity): 246 (1, M^+), 178 (1), 125 (8), 124 (100), 123 (28), 109 (21), 107 (5), 95 (14), 81 (22), 79 (10), 67 (14), 55 (14), 53 (8).

Minor isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.34 (3H, s). 1.73 (3H, s), 1.70-2.12 (3H, m), 2.65 (2H, t), 3.68

(2H, s), 3.75 (3H, s), 4.80 (1H, s), 4.98 (1H, s), 6.80 (4H, s); Mass spectrum (EI) *m/z* 246 (1, M^+), 178 (1), 125 (8), 67 (11), 55 (12), 53 (8).

1.1.5. *trans*-2-Isopropenyl-1-methylcyclobutanemethanol 19. Ammonium cerium(IV) nitrate (169.3 mg, 0.33 mmol) dissolved in 5 mL of water was added to a cooled (−10°C) solution of the 20:80 mixture of **18** (36.8 mg, 015 mmol) in 10 mL of CH_3CN. The reaction mixture was stirred for 2 h and then diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$, dried and evaporated under reduced pressure. Purification of the residue by liquid chromatography on silica gel (eluent pentane/ether, 9:1) gave 16 mg (74% yield) of pure (*E*)-**19**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.95 (3H, s), 1.14–2.20 (5H, m), 1.65 (3H, s), 2.74 (1H, t, *J*=9.2 Hz), 3.49 (2H, br s), 4.67 (1H, br s), 4.85 (1H, br s).[22]

1.1.6. 5-Cyclopropylidenepentan-1-ol 29. 50.73 g of (3-bromopropyl)triphenylphosphonium bromide (0.109 mol) rapidly added to a stirred suspension of pentane washed NaH (8.72 g, 0.218 mol, 60% in oil) in dry THF (150 mL) under Argon was stirred at 65°C for 6 h. Then a solution of 4-(tetrahydropyran-2-yloxy)butan-2-one **25** (9.4 g, 0.054 mol) and the catalyst TDA-1 (1.73 mL, 5.4 mmol) in THF (30 mL) was slowly added. The mixture was kept at same temperature for 16 h and after cooling to room temperature the solution was diluted with diethyl ether and washed with brine, dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residue on silica gel (eluent light petroleum/diethyl acetate, 1:1) gave 3.10 g (45% yield) of known 5-cyclopropylidenepentan-1-ol **29**, with spectral data in complete agreement with the literature.[17]

1.1.7. 4-(Benzyloxy)-2-[1-(phenylthio)cyclopropyl]butan-2-ol 31. A 1.5 M solution of *n*-BuLi (13 mL, 0.02 mol) in hexane was added to a stirred solution of cyclopropyl phenyl sulfide (3 g, 0.02 mol) in THF (50 mL) at 0°C. The resulting solution was stirred for 5 h at room temperature and then 4-(benzyloxy)butan-2-one **21** (3.6 g, 0.02 mol) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Then, brine and diethyl ether were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), evaporated in vacuum and the crude product was purified by liquid chromatography on silica gel (eluent diethyl ether/light petroleum, 1:10) to provide 5.9 g (90% yield) of **31** as yellow oil. IR (neat): 3484 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.90 (4H, m), 1.26 (3H, s), 1.96–2.05 (2H, m), 2.26–2.19 (2H, m), 3.78 (1H, br s), 3.61–3.68 (1H, m), 3.74–3.81 (1H, m), 4.46 (2H, s), 7.26–7.46 (10H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 11.09, 13.15, 26.83, 38.37, 67.92, 73.50, 126.15, 127.81, 127.86, 128.44, 128.53, 129.88, 137.02, 137.31, 178.19; Mass spectrum (EI) *m/z* (rel. intensity): 328 (0.5, M^+), 221 (1), 204 (3), 179 (13) 150 (7), 135 (6), 117 (12), 91 (100); Elemental analysis Calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36; S, 9.76. Found: C, 73.24; H, 7.42; S, 9.62.

1.1.8. 2-[2-(Benzyloxy)ethyl]-2-methylcyclobutanone 24. A mixture of cyclopropylcarbinol **31** (4.5 g, 13.6 mmol) and 2.2 g (13.6 mmol) of *p*-toluensulfonic acid in 80 mL of water-saturated benzene was refluxed for 4 h. After cooling to room temperature, the benzene solution was washed twice with saturated aqueous sodium bicarbonate solution (20 mL) and with brine (20 mL). After drying (Na_2SO_4) and concentration in vacuum, chromatography of the residue (eluent diethyl ether/light petroleum, 1:5) gave 2.91 g (yield 98%) of cyclobutanone **24**: IR (neat): 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): ^{1}H NMR ($CDCl_3$) 1.86 (3H, s), 1.64–1.79 (2H, m), 1.93–2.01 (2H, m), 2.98 (2H, t, *J*=9.6 Hz), 3.56 (2H, t, *J*=6.3 Hz), 4.40–4.46 (2H, AB q, *J*=11.7 Hz), 7.30 (5H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm) 21.30, 23.87, 35.32, 42.32, 62.22, 66.66, 72.85, 127.41, 128.22, 138.13, 214.821; Mass spectrum (EI) *m/z* (rel. intensity): 218 (0.5, M^+), 127 (12), 97 (11), 91 (100), 41 (38); Elemental analysis Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.24; H, 8.42.

1.1.9. Ethyl 2-(2-[2-(benzyloxy)ethyl]-2-methylcyclobutylidene(propanoate 32. To a stirred suspension of pentane-washed NaH (364 mg, 9.1 mmol, 60% in oil) in THF (30 mL) was rapidly added 2.16 g (9.1 mmol) of triethylphosphonopropionate and the mixture was stirred under argon at 65°C for 6 h. Then a solution of cyclobutanone **24** (2 g, 9.1 mmol) and of tris-(3,6-dioxa heptyl)amine (TDA-1) (290 μL, 0.91 mmol) in THF (10 mL) was slowly added within 30 min. The mixture was stirred at the same temperature for 16 h and after cooling to room temperature, the solution was diluted with diethyl ether and washed with brine, dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residue on silica gel (eluent light petroleum/diethyl ether, 10:1) gave 2.14 g (78% yield) of a 30:70 (*E*,*Z*) diastereomeric mixture of **32**.

(*Z*)-**32**: (spectroscopic data were worked out from pure (*Z*)-**32**, isolated by chromatography): IR (neat): 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.22 (3H, t, *J*=6.8 Hz), 1.24 (3H, s), 1.60 (3H, s), 1.63–1.68 (1H, m), 1.85–2.05 (3H, m), 2.42–2.59 (2H, m), 3.40–3.52 (2H, m), 4.08 (2H, q, *J*=6.8 Hz), 4.40 (2H, s), 7.25 (5H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm) 14.28, 25.01, 25.89, 29.07, 29.70, 37.25, 47.58, 59.91, 67.96, 72.88, 120.16, 127.45, 128.26, 138.67, 138.67, 163.59, 166.89; Mass spectrum (EI) *m/z* (rel. intensity): 302 (1.6, M^+), 256 (13), 216 (10), 168 (28), 153 (16), 139 (25), 91 (100); Elemental analysis Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.28; H, 8.52.

(*E*)-**32**: (spectroscopic data were worked out from spectra of (*E*,*Z*) mixture of **32**); IR (neat): 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.20 (3H, t, *J*=7.6 Hz), 1.22 (3H, s), 1.57–1.66 (1H, m), 1.68 (3H, s), 1.80–1.99 (3H, m), 2.80–2.89 (2H, m), 3.42–3.54 (2H, m), 4.07 (2H, q, *J*=7.6 Hz), 4.42 (2H, s), 7.25 (m, 5H); Mass spectrum (EI) *m/z* (rel. intensity): 302 (1.6, M^+), 256 (10), 216 (16), 168 (33), 153 (20), 139 (33), 91 (100).

1.1.10. 2-[2-(2-Benzyloxy)ethyl-2-methylcyclobutyl]-1-iodopropane 33. To a stirred solution of cyclobutylidene propanoate (*E*,*Z*)-**32** (1.5 g, 4.9 mmol) in dry methanol (15 mL) Mg turning (935 mg, 39 mmol) was added. After stirring for 24 h, the mixture was diluted with diethyl ether, treated with few drops of acetic acid and washed with saturated solution of NH_4Cl. After evaporation of the

solvent in vacuum, the crude oil was purified by flash chromatography on silica gel (eluent light petroleum/diethyl ether 5:1) to afford 1.29 g (87% yield) of a diastereomeric mixture of four corresponding 2-cyclobutylpropanoates: IR (neat): 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.98 (3H, t, J=7.2 Hz), 1.07, 1.03, 1.05, 1.07 (s, 3H), 1.75–1.24 (3H, doublets), 1.38–2.52 (6H, m), 3.43–3.63 (2H, m), 4.02 (2H, m), 4.45 (2H, br s), 4.48 (2H, br s), 7.22–7.32 (5H, m); Mass spectrum (EI) m/z (rel. intensity): (*first diastereomer*: 43%): 276 (1, M^+-28), 259 (3), 196 (7) 176 (14), 167 (4), 161 (8) 129 (8), 107 (18) 91 (100); (*second diastereomer*: 32%): 259 (1, M^+-45), 176 (10), 161 (7), 131 (4), 107 (16), 91 (100); (*third diastereomer*: 13%) :259 (3, M^+-45), 196 (4), 176 (7), 167 (5), 161 (5), 129 (6), 107 (13), 91 (100); (*fourth diastereomer*: 12%): 276 (1, M^+-28), 259 (3), 196 (7) 176 (14), 167 (4), 161 (8) 129 (8), 107 (18) 91 (100).

To a stirred solution of this diastereomeric mixture of propanoates (5.16 g, 1.7 mmol) in dry THF (50 mL) at −20°C was added dropwise a 1.5 M solution of $LiAlH_4$ (11.34 mL, 0.017 mol) in THF. After 2 h the mixture was treated with wet Na_2SO_4, then filtered on celite, dried (Na_2SO_4) and the solvent evaporated under vacuum. Flash chromatography of the residual oil on silica gel, (eluent pentane/diethyl ether 10:1) gave 3.43 g (77% yield) of a diastereomeric mixture of 2-cyclobutyl propanols. IR (neat): 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.05 (3H, s), 1.07 (3H, s), 0.8–2.00 (6H, m), 3.24–3.59 (3H, m), 4.47 (4H, s), 4.50 (2H, s), 7.20–7.31 (5H, m); Mass spectrum (EI) m/z (rel. intensity): 262 (0.5, M^+), 228 (0.3), 197 (0.7), 176 (15), 161 (18), 153 (3), 131 (5), 113 (2); 107 (17), 91 (100).

To a stirred solution of triphenylphosphine (1.99 g, 7.6 mmol) in benzene (50 mL), were added imidazole (1.15 g, 17 mmol), the previously obtained 2-cyclobutyl propanol (1 g, 3.8 mmol) and iodine (0.96 g, 7.6 mmol); the mixture was stirred at room temperature for 1 h. Then, it was diluted with pentane and quenched with an aqueous solution of 2.5% sodium thiosulfate (20 mL). The organic layer was separated, dried and concentrated under vacuum to provide 1.34 g [in 88% yield from (*E*,*Z*)-**32**] of a mixture of *cis*- and *trans*-crude iodopropanes **33**, which were used without further purification in the next step.

1.1.11. *cis*- and *trans*-1-(2-Benzyloxyethyl)-2-isopropenyl-1-methylcyclobutanes 34 and 35 from iodides 33. To a stirred solution of 1.4 g (3.8 mmol) of crude iodopropanes *cis*- and *trans*-**33** (3.8 mmol) in dry pyridine (10 mL) was added under argon silver fluoride (0.96 g, 7.6 mmol). The reaction mixture was stirred at room temperature for 12 h, and then diluted with diethyl ether. The separated organic layer was successively washed with a saturated solution of $CuSO_4$, with brine, then dried (Na_2SO_4) and concentrated under vacuum. Chromatography of the residual oil on silica gel (eluent pentane/diethyl ether 10:1) gave 700 mg (80% yield) of an unseparable 1:1 mixture of cyclobutanes *cis*-**34** and *trans*-**35** as a colourless oil.

cis-**34**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.15 (3H, s), 1.41–1.96 (6H, m), 1.65 (3H, s), 2.45–2.62 (1H, m), 3.45–3.54 (2H, m), 4.48 (2H, s), 4.63 (1H, br s), 4.81 (1H, br s), 7.31 (5H, m); Mass spectrum (EI) m/z (rel. intensity): 244 (0.5, M^+), 229 (0.5), 153 (3), 135 (8), 107 (25), 91 (100).

trans-**35**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.92 (3H, s), 1.41–1.96 (6H, m), 1.63 (3H, s), 2.45–2.62 (1H, m), 3.45–3.54 (2H, m), 4.47 (2H, s), 4.60 (1H, br s), 4.81 (1H, br s), 7.31 (5H, m); Mass spectrum (EI) m/z (rel. intensity): 244 (0.5, M^+), 229 (0.5), 153 (3), 135 (8), 107 (25), 91 (100).

1.1.12. 2-[2-(2-Benzyloxy)ethyl-2-methylcyclobutylidene]propyl (4-methylbenzene)sulfonate 36. To a solution of the diastereomeric mixture (*E*,*Z*)-**32** (1 g, 3.3 mmol) in dry THF (30 mL) stirred at −20°C, was added dropwise a 1.5 M solution of $LiAlH_4$ (2.2 mL, 3.3 mmol) in THF. After stirring for 2 h, the mixture was treated with wet Na_2SO_4, filtered on celite, dried (Na_2SO_4) and the solvent evaporated under vacuum. Flash chromatography of the residual oil on silica gel (eluent pentane/diethyl ether 5:1) gave 0.84 g (98% yield) of a 30:70 mixture of the corresponding 2-cyclobutylidenepropan-1-ols: IR (neat): 3380 cm^{-1}; *major isolated isomer*: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.22 (3H, s), 1.55 (3H, br s), 1.72–1.98 (4H, m), 2.22 (1H, br s), 2.37–2.52 (2H, m), 3.56 (2H, t, J=6.9 Hz), 3.81–4.05 (2H, m), 4.45–4.51 (2H, AB q, J=11.4 Hz), 7.25–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm) 15.08, 23.66, 27.38, 28.52, 38.50, 39.72, 45.21, 62.25, 63.54, 67.69, 73.02, 127.68, 128.26, 138.02, 144.11; Mass spectrum (EI) m/z (rel. intensity): 260 (0.1, M^+), 177 (10), 159 (8), 131 (6), 107 (11), 91 (100), 84 (24);); Elemental analysis Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.28; H, 9.42: *minor isomer* (spectroscopic data worked out from mixture spectra): ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.24, (3H, s), 1.63 (3H, br s), 1.71–1.98 (4H, m), 2.22 (1H, br s), 2.37–2.52 (2H, m), 3.56 (2H, t, J=6.9 Hz), 3.81–4.05 (2H, m), 4.49 (3H, s), 7.25–7.36 (5H, m); Mass spectrum (EI) m/z (rel. intensity): 260 (0.1, M^+), 177 (10), 159 (8), 131 (6), 107 (11), 91 (100), 84 (24).

To a solution of these 2-cyclobutylidenepropan-1-ols (290 mg, 1.1 mmol) in dichloromethane (10 mL) were added at 0°C triethylamine (462 μL, 3.34 mmol), DMAP (13 mg, 0.1 mmol) and tosylchloride (212 mg, 1.1 mmol). The reaction mixture was maintained at 0°C for 6 h and then diluted with dichloromethane. The separated organic layer was washed with brine and then dried (Na_2SO_4). Evaporation of the solvent in vacuum afforded 455 mg of the crude tosylate **36** which was used without further purification in the next step.

1.1.13. *cis*- and *trans*-1-(2-Benzyloxyethyl)-2-isopropenyl-1-methylcyclobutanes 34 and 35 from tosylate 36. A solution of tosylate **36** (455 mg, 1.1 mmol) in dry CH_3CN (15 mL) was added to a stirred solution of $Pd(dba)_2$ (45.5 mg, μmol,) and of PPh_3 (43.6 mg, 173 μmol) in dry CH_3CN (7 mL). After 10 min the mixture had turned orange and was added to ammonium formate (205 mg, 3.3 mmol). The reaction mixture was stirred for 16 h at room temperature and then diethyl ether (20 mL) was added. The separated organic solution was washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuum. Chromatography of the residue on silica gel (eluent pentane/ether 9:1) gave 215 mg (80% yield) of a 70:30 mixture of

cyclobutanes *cis*-**34** and *trans*-**35**, as a colourless oil, with spectral data analogous to the data reported above for *cis*-**34** and *trans*-**35**, obtained from iodide **33**.

1.1.14. *cis*-2-(2-Isopropenyl-1-methylcyclobutyl)ethan-1-ol or grandisol 1 and *trans*-2-(2-isopropenyl-1-methylcyclobutyl)ethan-1-ol or fragranol 2. To a dark blue solution of Li (33 mg, 4.8 mmol) in liquid NH_3 (ca. 40 mL) at −78°C was added under argon a 1:1 mixture of *cis*-**34** and *trans*-**35** (300 mg, 1.2 mmol) in dry ether (3 mL) all at once. The mixture was stirred for 10 min and quenched rapidly with methanol (10 mL). The solution was warmed to room temperature, treated with saturated aqueous NH_4Cl and extracted with diethyl ether. The extract dried (Na_2SO_4) and concentrated in vacuum afforded 200 mg (78%) of a 1:1 mixture of grandisol **1** and fragranol **2** which were isolated by chromatography on silica gel (eluent hexane/ethyl acetate, 7:3). Analogously, treatment of a 70:30 mixture of *cis*-**34** and *trans*-**35** led to a 70:30 mixture of grandisol **1** and fragranol **2**.

Grandisol **1**: Yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.17 (3H, s), 1.45 (1H, m), 1.58 (1H, br s),1.67 (3H, s), 1.75–2.04 (4H, m), 2.54–2.59 (1H, m), 3.66–3.73 (2H, m), 4.65 (1H, s), 4.84 (1H, s); Mass spectrum (EI) *m*/*z* (rel. intensity): 154 (0.2, M^+), 139 (2), 121 (4), 109 (21), 93 (11), 91 (6), 79 (12), 68 (100), 67 (80); in accordance with reported spectral data.[5]

Fragranol **2**: Yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.93 (3H, s), 1.42 (1H, m), 1.65 (3H, s),1.58 (1H, br s), 1.75–2.04 (4H, m), 2.56 (1H, m), 3.66–3.73 (2H, m), 4.62 (1H, s), 4.83 (1H, q, J=1.5 Hz); Mass spectrum (EI) *m*/*z* (rel. intensity): 154 (0.2, M^+), 139 (2), 121 (3), 109 (17), 93 (11), 91 (6), 79 (12), 68 (100), 67 (80); in accordance with reported spectral data.[8]

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