Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 4968–4974
Tetrahedron

A highly stereocontrolled formal total synthesis of (±)- and of (−)-grandisol by 1,4-conjugated addition of organocopper reagents to cyclobutylidene derivatives

Angela M. Bernard,[a] Angelo Frongia,[a] Jean Ollivier,[b,*] Pier Paolo Piras,[a,*] Francesco Secci[a] and Marco Spiga[a]

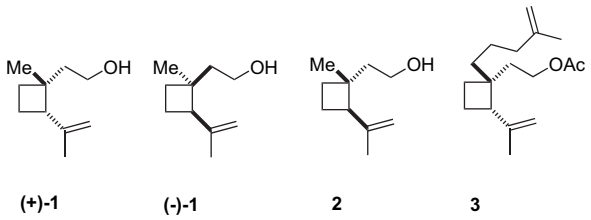
[a]*Dipartimento di Scienze Chimiche, Università degli Studi di Cagliari, 09042 Monserrato (Ca), Italy*
[b]*Laboratoire de Synthèse Organique et Méthodologie, Université de Paris-sud Bât 420, 91405 Orsay cedex, France*

Received 19 December 2006; revised 27 February 2007; accepted 22 March 2007
Available online 27 March 2007

Abstract—Starting from suitable cyclopropanes, a formal total synthesis of racemic grandisol and of the enantiopure (−)-grandisol is presented. The racemic synthesis of the grandisol precursor was accomplished in five steps. The synthesis of the chiral non-racemic precursor (1*S*,2*S*,2′*R*)-cis of this pheromone was realized in 10 steps, with an overall yield of 45%, using the enantiopure cyclobutanone (*R*,*S*), previously obtained by ring expansion of an optically pure oxaspiropentane. The key stereodefining step was the addition of lithium dimethylcuprate to a chiral α,β-unsaturated cyclobutylidene carbonyl derivative.

1. Introduction

Grandisol **1**, first isolated in 1967,[1] is one of the components of the male-produced pheromone of the cotton boll weevil *Anthonomus grandis* Boheman and of the sex pheromone of other pests responsible for conifer infestation in North America and Central Europe.[2] This product is present in nature in the two enantiomeric forms, (+)-**1** and (−)-**1**, both showing comparable biological activity.[3] One well-known geometric isomer of grandisol is fragranol **2**, a natural product isolated from the roots of *Artemisia fragrans* Willd.[4] Another interesting natural derivative, structurally related to grandisol is the pheromone **3** of the *Aspidiotus nerii*, a pest that causes damage to lemon and olive trees, and to ornamental plants like oleander[5] (Fig. 1). Due to their structural complexity, mainly related to the difficulty of constructing small-size rings with quaternary carbons, and the possibility of using **1** and **3** as an alternative to classical pesticides, these derivatives attracted the attention of many synthetic chemists.[6,7] In fact many racemic or enantioselective syntheses of **1**, **2** and **3** have been reported and for most of them the formation of the cyclobutane ring arose from photochemically, thermally or Lewis acid promoted [2+2] cycloadditions.[7]



(+)-1 (-)-1 2 3

Figure 1. (+)-Grandisol **1**, (−)-grandisol **1**, fragranol **2** and the *Aspidiotus nerii* pheromone **3**.

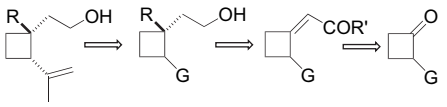
2. Results and discussion

We have recently reported a new approach to the stereoselective synthesis of racemic grandisol **1** and fragranol **2**, using the cyclobutanones obtained from suitable substituted cyclopropyl derivatives as intermediates.[8] Due to the similarity of the carbon skeleton of **1**, **2** and **3** it would be interesting to find a synthetic approach based on a common intermediate for all the three compounds. As a possible common approach, we envisaged the addition of organocopper reagents to a cyclobutylidene derivative according to the retrosynthetic analysis reported in Scheme 1.

In this paper we report the first results of this new method used for the synthesis of grandisol, where two goals have been pursued. First, the improvement of our previously[8] obtained stereoselection, in order to reduce the amounts of fragranol always present as an impurity in the syntheses of

Keywords: Carbocycles; Cuprates; Diastereoselectivity; Pheromones.
* Corresponding authors. Tel.: +39 070 6754410; fax: +39 070 6754388 (P.P.P.); e-mail: pppiras@unica.it

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.134



R = Me or 4-methyl-4-penten-1-yl-; R' = H, OMe
G = Synthetic equivalent of an isopropenyl group

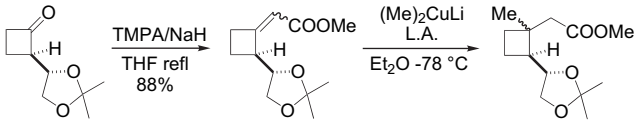
Scheme 1. Retrosynthetic analysis for the synthesis of the products **1**, **2** and **3**.

grandisol and the reduction of the number of steps; secondly to carry out a chiral non-racemic synthesis of grandisol.

Our reaction sequence for reaching the first goal is reported in Scheme 2. The cyclobutanone **4**[9] was prepared initially and submitted to a Horner–Emmons olefination with trimethylphosphonoacetate (TMPA) to give ester **5** as a (50:50) mixture of *E*-isomers. Due to the low reactivity of the α,β-unsaturated esters[10] towards organocopper (I) reagents, the reaction of **5** with $(Me)_2CuLi$ did not proceed, while $(Me)_2CuLi/BF_3$-OEt_2, $(Me)_2CuLi$/TMSCl and $(Me)_2CuLi$/TBDMSOTf led to the addition product in very low yields and stereoselectivity. For this reason we reduced **5** with DIBAL-H to obtain the allylic alcohol **6**, which was readily oxidized to the corresponding cyclobutylidene aldehyde **7**.[11] This compound reacted with $(Me)_2CuLi$ to give the corresponding addition product **8** as a 90:10 mixture of cis/trans stereomers.[12] After reduction of the carbonyl function, oxidation of the purified alcohol with *m*-chloroperbenzoic acid and final reflux in toluene/$CaCO_3$, as reported in the literature,[9] a 90:10 mixture of (±)-grandisol **1** and (±)-fragranol **2** was obtained in an overall yield of 42% (Scheme 2).

Since the synthesis of grandisol through this route appeared efficient, particularly the high stereoselectivity and the reduced number of steps, we decided to use this approach for the enantioselective formal total synthesis of grandisol using the enantiopure cyclobutanone **9**, which we have previously reported.[13]

The cyclobutanone **9** was transformed into the α,β-unsaturated methyl ester **10**. The *E*/*Z* (80:20) mixture of geometric isomers was readily separated by column chromatography and the stereochemistry of these compounds was confirmed by NOE experiments assigning the *E*-configuration to the major isomer of the mixture (Scheme 3). Despite the low yields obtained previously in the reaction of methyl cuprate with ester **5**, it was decided to screen a set of Lewis acids as activators of the α,β-unsaturated ester **10** towards nucleophilic attack of the cuprate.



(*R*,*S*)-**9** **10** (*E*/*Z*) = **80:20** (*cis*/*trans*)-**11**

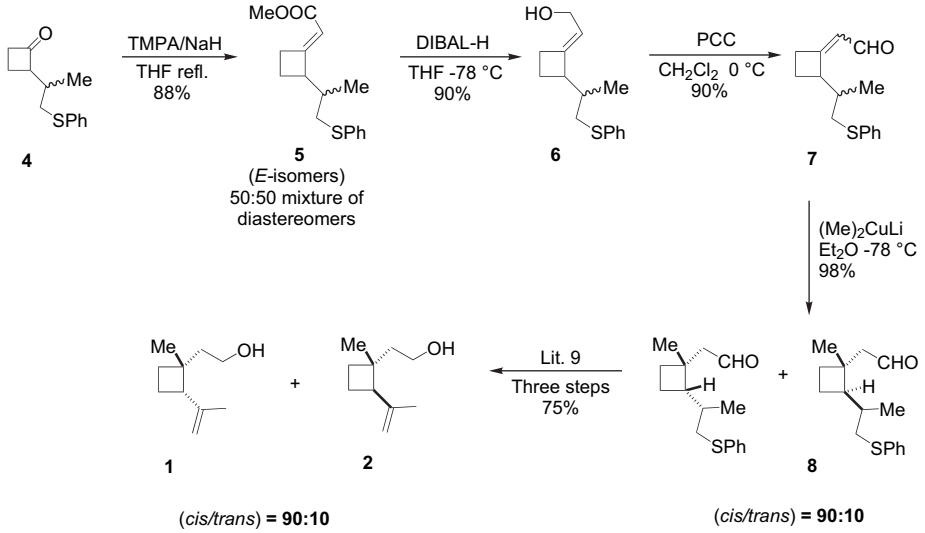
Scheme 3. Conjugated addition of $(Me)_2CuLi$-L.A. to the ester **10**.

As listed in Table 1, the reaction afforded the cyclobutyl esters **11** in good to high yields and varying cis/trans ratios. The best result was obtained using TBDMSOTf as Lewis acid, which afforded the addition product **11** in quantitative yield and with a cis/trans ratio of 95:5, determined by NOE experiments (Fig. 2). The stereoselectivity of the addition is clearly controlled by the steric effects of the activating Lewis acid and does not depend on the stereochemistry of the

Table 1. Conjugated addition of $(Me)_2CuLi$-L.A. to the ester **10**

Entry	(*E*/*Z*)-10	Lewis acid	(cis/trans)-**11** Ratio[a] %	Yield[b]
1	80:20	—	—	0
2	80:20	BF_3-OEt_2	—	0
3	80:20	TMSCl	70:30	57
4	80:20	TMSOTf	80:20	98
5	100:0	TMSOTf	80:20	97
6	0:100	TMSOTf	80:20	98
7	80:20	TBDMSOTf	95:5	>99
8	100:0	TBDMSOTf	95:5	>99

[a] Cis/trans ratios were determined by GC and ^1H NMR analysis of the crude reactions.
[b] Yields were calculated after chromatography purification.



(*cis*/*trans*) = **90:10** (*cis*/*trans*) = **90:10**

Scheme 2. Stereoselective synthesis of (±)-grandisol **1** through the 1,4-conjugated addition of $(Me)_2CuLi$ to the cyclobutylidene aldehyde **7**.

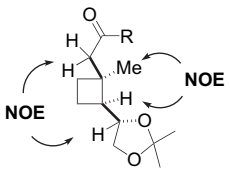


Figure 2. NOE experiments for the (cis)-ester **11** and the (cis)-aldehyde **14**.

double bond of the starting material. Thus, by avoiding the transformation of the ester function into the corresponding aldehyde, two reaction steps were gained in the synthetic plan.

In order to evaluate the possibility of further increasing the stereoselectivity of the organocopper addition, a sequence analogous to that reported in Scheme 2 was followed.

Thus the ester **10** was converted into the corresponding allylic alcohol **12** and subsequently oxidized to give the α,β-unsaturated cyclobutylidene aldehyde **13**.

We were pleased to find that in the reaction of this aldehyde with $(Me)_2CuLi$, the only detectable product was the diastereomerically pure *cis*-**14**; the stereochemistry was assigned by NOE experiments (Fig. 2).

This excellent stereoselectivity could very likely be attributed to the increased steric requirement of the oxadiolane ring in **13**, in comparison with the phenylthiopropyl group in **7** (Schemes 2 and 4).

Reduction of the derivative **14** afforded the alcohol **15**, whose hydroxyl group was protected to give the benzoyl ester **16**. Hydrolysis of the dioxolane group of **16** led to the cyclobutyldiol **17**. After purification, the diol was treated with DIAD/$P(Ph)_3$ in refluxing benzene to afford the epoxide **18**, which was treated with DIBAL-H to give the optically pure diol **19**, $[\alpha]_D^{27}$ −27.83 (*c* 1.60, CH_2Cl_2) (Scheme 4). Comparison of the optical rotation of **19** with the value reported by Narasaka for (+)-*cis* **19**,[14] $[\alpha]_D^{24}$ +27.3 (*c* 1.59, CH_2Cl_2) confirmed that the absolute configuration of the (−)-*cis* **19** diol, a direct precursor of (−)-**1**, was (1*S*,2*S*,2′*R*).

3. Conclusions

In summary, we have reported two different approaches for a formal total synthesis of racemic grandisol and of the enantiopure (−)-grandisol **1** through the intermediary of cyclobutylidene derivatives. Moreover, as the other diastereoisomer of **9** has been prepared enantiomerically enriched,[13] both isomers of grandisol can be prepared using this synthetic approach. Research is now in progress to apply this method to the synthesis of fragranol and to the pheromone of the *A. nerii*.

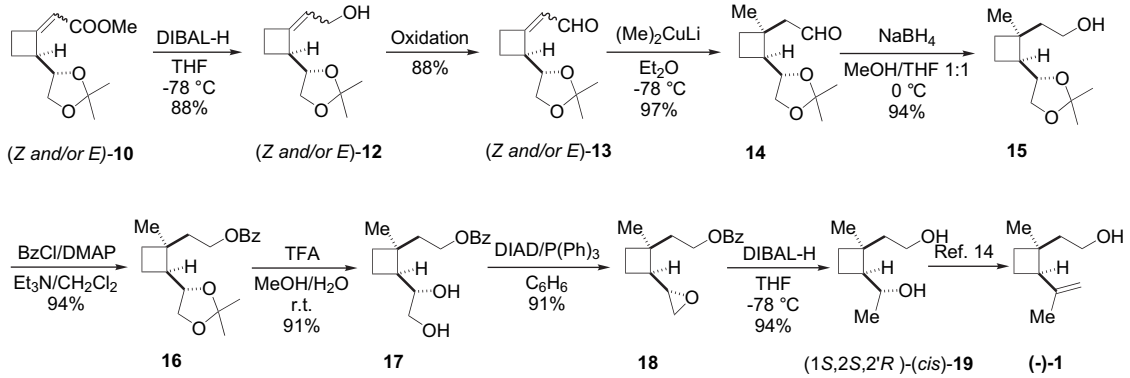
4. Experimental

4.1. General

^1H NMR spectra were recorded at 300 and 400 MHz VARIAN spectrometer at ambient temperature with $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra were recorded at 75 or 100 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. NMR data are reported as follows: chemical shifts, integration, multiplicity and coupling constants.

Infrared spectra were recorded on a Nicolet Nexus 670 FTIR spectrophotometer. Mass spectra analyses were recorded on Agilent 5973N (Cpsil 32m) and Nermag R10-10 (quartz-Cpsil 5.25m). (EI 70 eV; CI NH_3). The high-resolution mass analysis spectra were recorded on a electrospray Finningan MAT-95 (precision 5/1000).

The optical rotation values were measured at 25 °C with a Perkin–Elmer 241 and PolAAr 32. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200–400 mesh silica gel (Merk KGaA). Yields refer to chromatography and spectroscopically pure materials, unless otherwise stated. Diisopropylamine and triethylamine were distilled from calcium hydride and stored under argon. Methylene chloride and acetonitrile were freshly distilled from calcium hydride or P_2O_5. THF and diethyl ether were freshly distilled from sodium/benzophenone. Ethanol was dried over 2 Å molecular sieves. Methanol was dried on magnesium powder. Reactions requiring anhydrous conditions were performed in oven-dried glassware under argon atmosphere.



Scheme 4. Formal total synthesis of (−)-grandisol **1**.

4.1.1. Methyl 2-(2-(1-(phenylthio)propan-2-yl)cyclobutylidene)acetate (5). To a stirred suspension of pentane-washed NaH (364 mg, 9.1 mmol, 60% mineral oil dispersion) in THF (30 mL), trimethylphosphonoacetate (2.16 g, 9.1 mmol) was rapidly added and the mixture was stirred for 6 h under argon at 65 °C. Then a solution of cyclobutanone **4** (2 g, 9.1 mmol) and 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. After cooling, the solution was diluted with diethyl ether and washed with brine, dried on Na_2SO_4 and evaporated under vacuum. Chromatography of the residue on silica gel (light petroleum/diethyl ether 10:1) gave an inseparable 50:50 diastereomeric mixture of the (*E*)-derivatives **5**, 88% yield (2.41 g).

Yellow oil. First isomer: IR (neat): 3000, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (d, 3H, J=6.6 Hz), 1.77–1.95 (m, 2H), 1.97–2.18 (m, 2H), 2.78 (dd, 1H, J=7.5, 12.6 Hz), 2.97–3.02 (m, 2H), 3.26–3.29 (m, 1H), 3.69 (s, 3H), 5.63 (q, 1H, J=2.4 Hz), 7.12–7.36 (m, 5H). MS *m/z*: 276 (M^+ (30)), 248 (43), 234 (15), 216 (12), 199 (12), 167 (40), 150 (28), 135 (72), 123 (100), 121 (54), 109 (41), 107 (76), 93 (58), 79 (54), 77 (66), 65 (54), 45 (97).

Second isomer: IR (neat): 3000, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (d, 3H, J=6.6 Hz), 1.77–1.95 (m, 2H), 1.97–2.18 (m, 2H), 2.67 (dd, 1H, J=1.0, 12.6 Hz), 2.92–3.10 (m, 3H), 3.68 (s, 3H), 5.64 (q, 1H, J=2.4 Hz), 7.12–7.36 (m, 5H). MS *m/z*: 276 (M^+ (30)), 248 (43), 234 (15), 216 (12), 199 (12), 167 (40), 150 (28), 135 (72), 123 (100), 121 (54), 109 (41), 107 (76), 93 (58), 79 (54), 77 (66), 65 (54), 45 (97). Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29; S, 11.60. Found: C, 69.58; H, 7.35; S, 11.70.

4.1.2. 2-(2-(1-(Phenylthio)propan-2-yl)cyclobutylidene)ethanol (6). To a stirred solution of the diastereomeric mixture of **5** (300 mg, 1.2 mmol) in dry THF (30 mL), cooled at −78 °C, a 1.0 M solution of DIBAL-H (2.4 mL, 2.4 mmol) in toluene was added dropwise. After 8 h, the reaction mixture was treated with methanol (5 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/diethyl ether 5:1) to afford an inseparable 50:50 mixture of the alcohols **6** in 90% yield (267 mg). Colourless oil. IR (neat): 3437, 3000, 1615, 1201 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.02 (d, 3H, J=6.9 Hz), 1.10 (d, 3H, J=6.9 Hz), 1.22 (br s, 1H), 1.25 (br s, 1H), 1.32–2.11 (m, 7H), 2.54–2.61 (m, 4H), 2.66 (dd, 1H, J=7.8, 12.6 Hz), 2.90–3.04 (m, 4H), 3.92 (d, 4H, J=6.3 Hz), 5.26–5.34 (m, 2H), 7.03–7.26 (m, 10H). MS (same for all isomers) *m/z*: 248 (M^+ (30)), 234 (15), 216 (12), 199 (12), 167 (40), 150 (28), 135 (72), 123 (100), 121 (54), 109 (41), 107 (76), 93 (58), 79 (54), 77 (66), 65 (54), 45 (97). Anal. Calcd for $C_{15}H_{20}OS$: C, 72.54; H, 8.12; S, 12.91. Found: C, 72.67; H, 8.14; S, 13.01.

4.1.3. 2-(2-(1-(Phenylthio)propan-2-yl)cyclobutylidene)acetaldehyde (7). To a stirred suspension of PCC (300 mg, 1.2 mmol) in CH_2Cl_2 at 0 °C, a solution of the alcohol **6** in dichloromethane was added dropwise. The mixture was stirred for 6 h and after warming at room temperature, the solvent was evaporated and the residue was diluted in diethyl ether and filtered on Celite. The filtrate was washed twice with brine and the organic phase was dried on Na_2SO_4. After concentration, the resultant crude oil was used in the next step without further purification; 80:20 mixture of (*E*/*Z*)-isomers.[11] Colourless oil. IR (neat): 3000, 1680, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.04 (d, 3H, J=6.6 Hz), 1.12 (d, 3H, J=6.6 Hz), 1.84–2.29 (m, 8H), 2.69 (dd, 1H, J=8.7, 12.6 Hz), 2.81 (dd, 1H, J=6.9, 12.6 Hz), 2.94 (dd, 1H, J=5.7, 12.6 Hz), 3.01–3.08 (m, 3H), 3.17–3.27 (m, 1H), 3.38–3.47 (m, 1H), 5.85 (m, 2H), 7.15–7.63 (m, 10H), 9.56 (dd, 1H, J=3.0, 5.4 Hz), 9.65 (dd, 1H, J=1.8, 7.8 Hz). MS (same for all isomers) *m/z*: 246 (M^+ (18)), 217 (9), 176 (10), 150 (38), 135 (7), 123 (100), 118 (20), 95 (37), 81 (22), 77 (22), 65 (20), 55 (11), 45 (41). Anal. Calcd for $C_{15}H_{18}OS$: C, 73.13; H, 7.36; S, 13.01. Found: C, 73.21; H, 7.38; S, 13.11.

4.1.4. 2-(1-Methyl-2-(1-(phenylthio)propan-2-yl)cyclobutyl)acetaldehyde (8). To a stirred suspension of CuI (570 mg, 3.04 mmol) in dry diethyl ether (7 mL) under argon, cooled at −10 °C, a 1.6 M solution of methyllithium in THF (3.8 mL, 6.09 mmol) was added dropwise until the formation of a colourless solution. The reaction mixture was cooled at −78 °C and the aldehyde **7** (250 mg, 1.01 mmol) in diethyl ether (5 mL) was added in one portion. The reaction mixture was stirred for 15 min, quenched with some drops of acetic acid and warmed to room temperature. The mixture was diluted with diethyl ether and washed with a saturated solution of NH_4Cl. The separated organic layer was dried on Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by chromatography (light petroleum/diethyl ether 5:1) to provide a 90:10 mixture of the cis/trans derivatives **8**; 98% yield (253 mg). Colourless oil. IR (neat): 2730, 1715, 1579, 1475 cm^{-1}. cis-Isomer: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, 3H, J=6.6 Hz), 0.97 (d, 3H, J=6.3 Hz), 1.23 (s, 3H), 1.24 (s, 3H), 1.56–1.77 (m, 6H), 1.82–1.97 (m, 6H), 2.25 (dd, 1H, J=3.0, 15.3 Hz), 2.27 (dd, 1H, J=3.0, 15.3 Hz), 2.43–2.64 (m, 4H), 2.96 (dd, 2H, J=3.6, 12.6 Hz), 7.15–7.36 (m, 10H), 9.78 (t, 1H, J=3.0 Hz), 9.81 (t, 1H, J=3.0 Hz). MS *m/z* (same for the two cis-isomers): 262 (M+(33)), 219 (5), 178 (35), 150 (5), 123 (100), 110 (25), 95 (10), 77 (10), 69 (25), 55 (33), 45 (35), 41 (45). Minor trans-isomer: MS *m/z*: 262 (M^+ (40)), 219 (5), 178 (42), 150 (7), 123 (100), 110 (30), 95 (8), 77 (10), 69 (25), 55 (35), 45 (37), 41 (50). Anal. Calcd for $C_{16}H_{22}OS$: C, 73.23; H, 8.45; S, 12.22. Found: C, 73.31; H, 8.49; S, 12.20.

4.1.5. *cis* and *trans*-2-(1-Methyl-2-(prop-1-en-2-yl)cyclobutyl)ethanol (1) and (2). Derivative **8** was first reduced to the corresponding alcohol and then oxidized to the corresponding sulfoxides according to the literature.[9]

To a stirred solution of these sulfoxides (267 mg, 0.95 mmol) in dry toluene, $CaCO_3$ (190 mg, 1.90 mmol) was added and the mixture was refluxed for 4 h. After filtration and concentration under reduced pressure, the crude 90:10 mixture of (±)-**1** and (±)-**2** was easily separated by flash chromatography (light petroleum/diethyl ether 90:10). Overall yield 75% (113 mg).

4.1.5.1. (±)-Grandisol (1). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (s, 3H), 1.45 (m, 1H), 1.58 (br s, 1H), 1.67 (s, 3H), 1.75–2.04 (m, 4H), 2.54–2.59 (m, 1H), 3.66–3.73 (m, 2H), 4.65 (s, 1H), 4.84 (s, 1H). MS *m/z*: 154 (M^+ (0.2)), 139 (2), 121 (4), 109 (21), 93 (11), 91 (6), 79 (12), 68 (100), 67 (80).

4.1.5.2. (±)-Fragranol (2). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (s, 3H), 1.42 (m, 1H), 1.65 (s, 1H), 1.58 (br s, 1H), 1.75–2.04 (m, 4H), 2.56–2.59 (m, 1H), 3.66–3.73 (m, 2H), 4.62 (s, 1H), 4.83 (q, 1H, J=1.5 Hz). MS *m/z*: 154 (M^+ (0.2)), 139 (2), 121 (3), 109 (17), 93 (11), 91 (6), 79 (12), 68 (100), 67 (82).

4.1.6. (*Z* and *E*)-Methyl 2-((*S*)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclobutylidene)acetate (10). To a stirred suspension of pentane-washed NaH (360 mg, 9.0 mmol, 60% in mineral oil dispersion) in THF (30 mL) under argon, trimethylphosphonoacetate (2.16 g, 8.9 mmol) was rapidly added. After keeping the reaction mixture at 65 °C for 6 h, a solution of the cyclobutanone **9**[11] (1.51 g, 8.9 mmol) and TDA-1 (2.76 μL, 0.9 mmol) was slowly added over about 30 min. The mixture was kept at the same temperature for 16 h. After cooling, the solution was diluted with diethyl ether and washed with brine. The separated organic phase was dried on Na_2SO_4 and evaporated under reduced pressure to give 2 g of a 80:20 mixture of two (*E*)- and (*Z*)-diastereomers, which were separated by chromatography on silica gel (eluent light petroleum/diethyl ether 5:1). Global yield 88% (1.77 g). (*E*)-isomer: IR (neat): 1713 cm^{-1}. $[\alpha]_D^{26}$ +130.7 (*c*, 0.3672, $CHCl_3$). Colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 3H), 1.40 (s, 3H), 2.04–2.12 (m, 1H), 2.14–2.25 (m, 1H), 2.64–2.85 (m, 2H), 3.68 (s, 3H), 3.74 (t, 1H, J=7.5 Hz), 3.78–3.81 (m, 1H), 3.97 (dd, 1H, J=7.8, 6.9 Hz), 4.73 (q, 1H, J=6.9 Hz), 5.66 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 18.9, 25.2, 26.3, 31.1, 46.4, 50.8, 65.9, 74.9, 108.4, 114.1, 164.8, 165.9. MS *m/z*: 211 (M^+−15 (7)), 195 (2), 169 (1), 151 (9), 137 (4), 125 (2), 119 (1), 107 (6), 101 (48), 91 (14), 77 (16), 65 (11), 59 (23), 43 (100). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.15. (*Z*)-isomer: IR (neat): 1715 cm^{-1}. $[\alpha]_D^{24.6}$ −31.4 (*c*, 0.6994, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 3H), 1.40 (s, 3H), 1.75–1.86 (m, 1H), 2.10–2.22 (m, 1H), 3.02–3.10 (m, 2H), 3.20–3.25 (m, 1H), 3.62 (dd, 1H, J=6.0, 8.1 Hz), 3.68 (s, 3H), 4.02 (dd, 1H, J=6.0, 8.1 Hz), 4.18 (dd, 1H, J=8.1, 6.0 Hz), 5.85 (q, 1H, J=2.4 Hz). ^{13}C NMR ($CDCl_3$): δ 19.7, 25.3, 26.7, 30.9, 46.9, 50.7, 67.1, 77.2, 109.2, 112.9, 166.3, 166.5. MS *m/z*: 211 (M^+−15 (15)), 195 (2), 168 (4), 151 (16), 137 (11), 125 (4), 119 (9), 107 (13), 101 (35), 91 (18), 77 (18), 65 (14), 59 (26), 43 (100). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.04.

4.1.7. Methyl 2-((1*S*,2*S*)-1-methyl-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclobutyl)acetate (11). To a stirred suspension of CuI (570 mg, 3.04 mmol) in dry diethyl ether (7 mL) at −10 °C, a 1.6 M solution of methyllithium in THF (3.8 mL, 6.09 mmol) was added dropwise until the formation of a colourless solution. The ester **10** (250 mg, 1.01 mmol), stirred at 0 °C with TBDMSOTf (1.01 mmol) in diethyl ether (5 mL) for 2 h, was added in one portion to the solution of $(Me)_2CuLi$ at −78 °C under argon. After 6 h, the reaction mixture was quenched with some drops of a saturated solution of $NaHCO_3$ and warmed to room temperature. The 95:5 diastereomeric mixture was diluted with diethyl ether (7 mL) and washed with a saturated solution of NH_4Cl. The organic layer was dried on Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by chromatography (light petroleum/diethyl ether 5:1) to provide **11** in 99% yield (253 mg). Major cis-isomer: colourless oil. $[\alpha]_D^{27}$ −16.5 (*c* 0.6225, $CHCl_3$). IR (neat): 2730, 1715, 1579, 1475 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (s, 3H), 1.28 (s, 3H), 1.34 (s, 3H), 1.37–1.50 (m, 1H), 1.63–1.79 (m, 1H), 1.81–1.89 (m, 1H), 2.02–2.12 (m, 2H), 2.55 (ABq, 2H, J=19.2 Hz), 3.40 (dd, 1H, J=8.8, 10.4 Hz), 3.62 (s, 3H), 3.94 (dd, 1H, J=10.4, 8.8 Hz), 4.08 (dt, 1H, J=8.4, 13.2 Hz). ^{13}C NMR ($CDCl_3$): δ 17.95, 25.68, 27.12, 30.05, 39.23, 40.09, 48.31, 51.17, 68.08, 76.64, 107.08, 173.13. MS *m/z*: 227 (M^+−15 (18)), 211 (13), 207 (9), 184 (3), 167 (7), 152 (4), 135 (9), 125 (7), 113 (16), 107 (34), 101 (10), 93 (26), 83 (21), 79 (25), 72 (26), 59 (44), 55 (24), 43 (100), 31 (12). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.43; H, 9.17. trans-Isomer (traces): MS *m/z*: 227 (M^+−15 (18)), 211 (13), 207 (12), 184 (3), 167 (9), 152 (4), 135 (12), 125 (7), 113 (18), 107 (32), 101 (10), 93 (26), 83 (21), 79 (25), 72 (21), 59 (44), 55 (24), 43 (100), 31 (14).

4.1.8. (*Z* and *E*)-2-((*S*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclobutylidene)ethanol (12). To a stirred solution of the diastereomeric mixture of the cyclobutylidene acetate **10** (1.4 g, 6.2 mmol) in dry THF (50 mL) at −78 °C, DIBAL-H (1 M in THF, 12 mL, 12 mmol) was added dropwise. The mixture was stirred at the same temperature for 2 h, diluted with diethyl ether and washed with a saturated $NaHCO_3$ solution. The organic layer was dried on Na_2SO_4 and the solvent removed under reduced pressure. Flash chromatography of the residual oil on silica gel (eluent pentane/diethyl ether 1:1) gave a 80:20 diastereomeric mixture of **12**. Colourless oil. Global yield 91% (1.11 g).

(*E*)-isomer: IR (neat): 3425 cm^{-1}. $[\alpha]_D^{17}$ +23.2 (*c*, 0.1577, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.46 (s, 3H), 2.14–2.24 (m, 2H), 2.50–2.62 (m, 1H), 273–2.82 (m, 1H), 3.12–3.18 (m, 1H), 3.62 (t, 1H, J=6.6 Hz), 3.92–4.09 (m, 3H), 4.14 (t, 1H, J=7.8 Hz), 4.19–4.26 (m, 1H), 5.51–5.56 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 19.5, 25.3, 26.4, 28.6, 45.7, 58.7, 68.1, 77.8, 109.6, 122.9, 143.6. MS *m/z*: 183 (M^+−15 (3)), 129 (3), 123 (3), 109 (5), 101 (84), 95 (23), 77 (14), 67 (17), 59 (15), 53 (15), 43 (100). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.63; H, 9.19. (*Z*)-isomer: IR (neat): 3430 cm^{-1}. $[\alpha]_D^{17}$ +14.7 (*c* 0.065, MeOH).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.41 (s, 3H), 1.66–1.78 (m, 2H), 1.98–2.37 (m, 3H), 2.65 (t, 1H, J=7.8 Hz), 3.13 (q, 1H, J=7.5 Hz), 3.63 (dd, 1H, J=6.6, 8.1 Hz), 4.02 (dd, 2H, J=1.2, 6.9 Hz), 4.07–4.10 (q, 1H, J=6.3 Hz), 5.52–5.58 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 19.1, 25.4, 26.6, 26.8, 45.6, 59.1, 66.9, 77.8, 109.0, 120.7, 144.1. MS *m/z*: 183 (M^+−15 (4)), 138 (3), 123 (3), 109 (2), 101 (72), 95 (14), 77 (14), 67 (15), 59 (10), 53 (14), 43 (100). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.59; H, 9.18.

4.1.9. (*Z* and *E*)-2-((*S*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclobutylidene)acetaldehyde (13). To a stirred solution of **12** (594 mg, 3.0 mmol) in 40 mL of methylene chloride at 0 °C, pyridinium chlorochromate (0.711 mg, 3.3 mmol) was added. The reaction mixture was stirred for 1 h, filtered on Celite and concentrated under reduced pressure. The residue was diluted with diethyl ether and filtered again on Celite. The obtained solution was washed twice with solutions of 2 M NaOH and saturated NH_4Cl. The organic phase was dried on Na_2SO_4 and concentrated under reduced pressure to give an oil, which was chromatographed with diethyl ether/light petroleum (1:1) to afford the aldehydes **13** in 88% yield (517 mg).

(*E*)-isomer: IR (neat) 1660 cm^{-1}. $[\alpha]_D^{17}$ +31.4 (*c* 0.315, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H), 1.41 (s, 3H), 1.85–1.94 (m, 1H), 2.20–2.32 (m, 2H), 3.03–3.34 (m, 2H), 3.58–3.73 (m, 1H), 4.01–4.06 (m, 1H), 4.08–4.25 (m, 1H), 6.07 (dd, 1H, *J*=2.1, 7.8 Hz), 9.66 (d, 1H, *J*=7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 15.16, 19.86, 26.80, 28.53, 29.60, 48.00, 65.73, 67.12, 109.52, 171.87, 190.21. MS *m/z*: 181 (M^+-15 (21)), 139 (5), 121 (18), 109 (12), 101 (18), 93 (20), 91 (17), 77 (23), 73 (21), 59 (20), 43 (100), 39 (40). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.54; H, 8.16.

(*Z*)-isomer: Spectral data were worked out from the *E*/*Z* mixture of the aldehydes **13**. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.37 (s, 3H), 1.68–179 (m, 1H), 2.15–2.30 (m, 2H), 2.93–3.00 (m, 1H), 3.47–3.56 (m, 1H), 4.07–4.13 (m, 1H), 4.14–4.32 (m, 1H), 4.25–4.32 (m, 1H), 5.87 (dd, 1H, *J*=2.1, 8.1 Hz), 9.66 (d, 1H, *J*=8.1 Hz). MS *m/z*: 181 (M^+-15 (23)), 139 (6), 121 (17), 109 (11), 101 (19), 93 (20), 91 (17), 77 (23), 73 (21), 43 (100), 39 (42).

4.1.10. 2-((1*S*,2*S*)-1-Methyl-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclobutyl)acetaldehyde (14). Copper(I) iodide (1.07 g, 5.6 mmol) in dry diethyl ether (4 mL) was treated dropwise at 0 °C with methyllithium (5.87 mL, 9.4 mmol, 1.6 M in diethyl ether) and stirred for 1 h. Then, the formed $(Me)_2CuLi$ solution was cooled at −78 °C and the aldehyde **13** (370 mg, 1.88 mmol) dissolved in dry THF (4 mL) was injected in one portion. The resulting reaction mixture was stirred for 2 h, diluted with diethyl ether (15 mL) and quenched with a saturated NH_4Cl solution. The organic layer was dried on Na_2SO_4 and concentrated under reduced pressure to afford the aldehyde **14**, which was purified by flash chromatography (pentane/diethyl ether 5:1); 97% yield (387 mg). Colourless oil. $[\alpha]_D^{17}$ +44.3 (*c* 0.3613, MeOH). IR (neat) 1700 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 6H), 1.37 (s, 3H), 1.50–1.82 (m, 2H), 1.89–1.99 (m, 2H), 2.11–2.19 (m, 1H), 2.60 (dq, 1H, *J*=2.7, 15.6 Hz), 3.45 (t, 1H, *J*=7.5 Hz), 4.00 (dd, 1H, *J*=7.8, 6.2 Hz), 4.11–4.18 (m, 1H), 9.83 (t, 1H, *J*=2.7 Hz). ^{13}C NMR ($CDCl_3$): δ 18.2, 25.7, 27.1, 28.1, 30.8, 38.7, 48.3, 49.6, 68.1, 76.6, 109.3, 203.7. MS *m/z*: 197 (M^+-15 (18)), 136 (2), 119 (8), 109 (16), 93 (23), 81 (15), 67 (25), 59 (23), 43 (100). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.91; H, 9.49.

4.1.11. 2-((1*S*,2*S*)-1-Methyl-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclobutyl)ethanol (15). To a stirred solution of **14** (350 mg, 1.65 mmol) in MeOH/THF (20 mL, 1:1) at −20 °C, $NaBH_4$ (62 mg, 1.4 mmol) was added. After 2 h, the reaction mixture was filtered and evaporated. The residue was diluted with diethyl ether and washed twice with brine. After flash chromatography (light petroleum/ethyl acetate 5:1), the alcohol **15** was obtained with 94% yield (331 mg). $[\alpha]_D^{25}$ +13.92 (*c* 0.43, $CHCl_3$). IR (neat): 3485, 2987, 1364 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (s, 3H), 1.34–1.44 (m, 2H), 1.35 (s, 3H), 1.38 (s, 3H), 1.57–1.69 (m, 2H), 1.72–1.78 (m, 1H), 1.91–2.06 (m, 3H), 3.45 (dd, 1H, *J*=8.1, 6.9 Hz), 3.57–3.75 (m, 2H), 4.03 (dd, 1H, *J*=8.1, 6.0 Hz), 4.25–4.33 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 18.51, 25.73, 26.65, 26.95, 30.65, 31.38, 38.55, 48.44, 59.64, 68.37, 76.56, 109.29. MS *m/z*: 214 (M^+ (1)), 199 (9), 169 (2), 139 (5), 129 (12), 113 (10), 93 (19), 79 (21), 67 (24), 59 (24), 43 (100). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.28; H, 10.33.

4.1.12. 2-((1*S*,2*S*)-1-Methyl-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclobutyl)ethyl benzoate (16). To a stirred solution of the alcohol **15** (160 mg, 0.74 mmol) in CH_2Cl_2 (5 mL) at 0 °C, triethylamine (104 μL, 0.82 mmol), DMAP (100 mg, 0.82 mmol) and benzoylchloride (114 mg, 0.82 mmol) were added dropwise. The reaction mixture was kept at 0 °C for 6 h and then diluted with CH_2Cl_2. The organic layer was washed with brine and then dried on Na_2SO_4. Evaporation of the solvent afforded 184 mg of a crude oil, which was purified by flash chromatography (light petroleum/ethyl acetate 5:1) to afford the benzoyl derivative **16**; 94% yield (221 mg). Colourless oil. $[\alpha]_D^{27}$ −15.5 (*c* 0.5314, $CHCl_3$). IR (neat) 3018, 2989, 1715, 1648, 1612, 1548, 1220 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (s, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 1.43–1.55 (m, 1H), 1.61–1.73 (m, 1H), 1.82–1.91 (m, 2H), 2.03–2.18 (m, 3H), 3.45 (dd, 1H, *J*=5.3, 8.1 Hz), 3.98 (dd, 1H, *J*=6, 8.1 Hz), 4.15–4.25 (m, 1H), 4.31–4.50 (m, 2H), 7.41–7.58 (m, 3H), 8.04 (d, 2H, *J*=8.7 Hz). ^{13}C NMR ($CDCl_3$): δ 18.04, 25.75, 27.17, 27.58, 30.46, 34.00, 39.12, 45.45, 48.60, 62.49, 68.04, 76.57, 109.08, 128.26, 129.47, 132.73, 166.64. MS *m/z*: 318 (M^+ (1)), 303 (10), 290 (1), 260 (2), 243 (2), 231 (1), 190 (4), 181 (4), 153 (3), 138 (15), 121 (31), 105 (100), 93 (36), 77 (78), 68 (66), 55 (21), 43 (52). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.71; H, 8.24.

4.1.13. 2-((1*S*,2*S*)-2-((*S*)-1,2-Dihydroxyethyl)-1-methylcyclobutyl)ethyl benzoate (17). To a stirred solution of **16** (160 mg, 0.74 mmol) in MeOH (5 mL) and H_2O (5 mL), trifluoroacetic acid (104 μL, 0.82 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. After concentration under reduced pressure, the residue was purified by chromatography (hexane/EtOAc 1:1) to give the diol **17**; 91% yield (127 mg). Colourless oil. $[\alpha]_D^{27}$ −9.45 (*c* 0.501, $CHCl_3$). IR (neat) 3445, 2989, 1715, 1658, 1612, 1548, 1220 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.21 (s, 3H), 1.55–1.70 (m, 2H), 1.73–1.93 (m, 3H), 2.07 (t, 2H, *J*=7.5 Hz), 3.22 (br s, 2H exchange with D_2O), 3.33 (dd, 1H, *J*=6.9, 11.1 Hz), 3.60 (dd, 1H, *J*=2.1, 11.1 Hz), 3.77–3.83 (m, 1H), 4.36 (t, 1H, *J*=7.5 Hz), 4.46–4.54 (m, 1H), 7.41–7.55 (m, 3H), 8.03 (d, 2H, *J*=8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 18.67, 28.08, 30.41, 33.36, 39.33, 47.37, 62.62, 64.61, 74.93, 128.32, 129.51, 130.27, 132.91, 166.98. MS *m/z*: 278 (M^+ (3)), 215 (3), 202 (2), 188 (4), 175 (14), 167 (3), 157 (11), 145 (27), 132 (100), 117 (83), 105 (31), 91

(37), 77 (18), 66 (7), 55 (17). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.03; H, 8.00.

4.1.14. 2-((1*S*,2*S*)-2-((*S*)-1-Hydroxyethyl)-1-methylcyclobutyl)ethanol (19). To a stirred solution of the diol **17** (120 mg, 0.43 mmol) in dry benzene (7 mL) under argon, triphenylphosphine (123 mg, 0.47 mmol) was added. After reaching the complete solubilization, DIAD (94 mg, 0.47 mmol) was injected dropwise. The reaction mixture was stirred overnight and then concentrated under reduced pressure. The crude benzoyloxirane **18**, obtained as an oil, was filtered on Celite and used for the next step without further purification. IR (neat) 2987, 1794, 1728, 1457, 1250 cm^{-1}. MS *m*/*z*: 260 (M^+ (1)), 259 (2), 244 (3), 233 (2), 215 (4), 198 (2), 191 (7), 173 (25), 158 (12), 149 (24), 131 (32), 113 (7), 105 (12), 88 (15), 70 (12), 59 (10), 43 (100), 31 (4).

A stirred solution of the crude benzoyloxirane **18** (120 mg, 0.46 mmol) was diluted with dry THF (20 mL) and cooled at −78 °C under argon. To this solution, DIBAL-H (1 M in THF, 1.38 mL, 1.2 mmol) was added dropwise. The mixture was stirred for 14 h, diluted with diethyl ether and washed with a saturated $NaHCO_3$ solution. The organic layer was dried on Na_2SO_4 and concentrated under reduced pressure. The product was purified by chromatography (hexane/EtOAc 1:1) to give the diol **19** as a colourless oil. Overall yield 94% (67.9 mg). $[\alpha]_D^{27}$ −27.83 (*c* 0.7314, CH_2Cl_2). IR (neat) 3450, 2986, 1220, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (s, 3H), 1.06 (d, 3H, *J*=4.5 Hz), 1.41–1.53 (m, 1H), 1.56–1.68 (m, 2H), 1.71–1.80 (m, 1H), 1.86 (t, 1H, *J*=6 Hz), 1.90–1.94 (m, 2H), 2.56 (br s, 2H), 3.62–3.70 (m, 2H), 3.76–3.82 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 19.12, 22.68, 27.85, 29.95, 37.16, 46.20, 53.08, 59.77, 68.29. MS *m*/*z*: 158 (M^+ (1)), 141 (2), 124 (4), 113 (5), 109 (4), 99 (24), 95 (11), 81 (74), 77 (12), 67 (77), 57 (71), 53 (68), 41 (89), 39 (100), 31 (22). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.29; H, 11.44.

Acknowledgements

Financial support from the MIUR, Rome, and by the University of Cagliari (National Project 'Stereoselezione in Sintesi Organica Metodologie ed applicazioni') and from CINMPIS is gratefully acknowledged.

References and notes

1. (a) Tumlinson, J. R.; Gueldner, R. C.; Hardee, D. D.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *J. Org. Chem.* **1971**, *36*, 2616; (b) Hedin, P. A. *Chemtech* **1976**, 444.
2. (a) Boot, D. C.; Philips, T. W.; Claesson, A.; Silverstein, R. M.; Lanier, G. N. *J. Chem. Ecol.* **1983**, *9*, 1; (b) Philips, T. W.; West, J. R.; Foltz, J. L.; Silverstein, R. M.; Lanier, G. N. *J. Chem. Ecol.* **1984**, *10*, 1417.
3. Francke, W.; Pan, M. L.; Koenig, W. A.; Mori, K.; Puapoomchaeron, P.; Heuer, H.; Vite, J. P. *Naturwissenschaften* **1987**, *74*, 343.
4. Bohlmann, F.; Zdero, C.; Faass, U. *Chem. Ber.* **1973**, *106*, 2904.
5. Boyer, F. D.; Ducrot, P. H. *Eur. J. Org. Chem.* **1999**, *5*, 1201.
6. (a) Mori, K. *Tetrahedron* **1978**, *34*, 915; (b) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306; (c) Hamon, D. P. G.; Tuck, K. L. *Tetrahedron Lett.* **1999**, *40*, 7569; (d) Hamon, D. P. G.; Tuck, K. L. *J. Org. Chem.* **2000**, *65*, 7839; (e) March, P.; de Figueredo, M.; Font, J.; Raya, J. *Org. Lett.* **2000**, *2*, 163; (f) Petschen, I.; Bosch, M. P.; Guerrero, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1691.
7. (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449; (b) Alibes, R.; Bourdelande, J. L.; Font, J.; Parella, T. *Tetrahedron* **1996**, 1279; (c) Knolker, H. J.; Baum, G.; Schmitt, O.; Wanzl, G. *Chem. Commun.* **1999**, 1737; Sarkar, N.; Nayek, A.; Ghosh, S. *Org. Lett.* **2004**, *12*, 1903.
8. Bernard, A. M.; Frongia, A.; Secci, F.; Delogu, G.; Ollivier, J.; Piras, P. P.; Salläun, J. *Tetrahedron* **2003**, *59*, 9433.
9. (a) Trost, B. M.; Keeley, D. E. *J. Org. Chem.* **1975**, *40*, 2013; (b) Trost, B. M.; Keeley, D. E.; Arndt, H.; Mitchell, J.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088.
10. (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485; (b) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393.
11. During the oxidation reaction of the alcohols **6** and **12** we observed an acid-promoted isomerization of the aldehydes (*E* and *Z*)-**7** and -**13**. This process occurs without loss of optical purity of the obtained products in the case of the aldehyde **13**.
12. (a) Magnin, D. R.; Robl, J. A.; Sulsky, R. B.; Augeri, D. J.; Huang, Y.; Simpkins, L. M.; Taunk, P. C.; Betebenner, D. A.; Robertson, J. G.; Abboa-Offei, B. E.; Wang, A. *J. Med. Chem.* **2004**, *10*, 2587; (b) Montero, H. J.; Stefani, H. A. *Eur. J. Org. Chem.* **2001**, *14*, 2659.
13. Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. *Org. Lett.* **2003**, *5*, 2923.
14. Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471.