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Lipase-mediated resolution of the hydroxy-cyclogeraniol isomers: application to the synthesis of the enantiomers of karahana lactone, karahana ether, crocusatin C and γ-cyclogeraniol

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ABSTRACT

A comprehensive study on the lipase PS-mediated resolution of different hydroxy-geraniol isomers is reported. A number of α-, β- and γ-isomers bearing a 2-, 3- or 4-hydroxy functional group were synthesised regioselectively and then submitted to the lipase-mediated kinetic acetylation. The latter experiments showed that the 2-hydroxy isomers **4**, **5** and **14** (α, γ and β, respectively) as well as *cis*-3-hydroxy α-cyclogeraniol **7** and *cis*-4-hydroxy γ-cyclogeraniol **10** could be easily resolved by this procedure. The enantiomeric purity of the main part of these compounds was increased by recrystallisation and the enantiopure diols obtained were used as building blocks for the synthesis of the natural terpenoids karahana lactone, karahana ether and crocusatin C and for the preparation of the synthetic intermediate γ-cyclogeraniol. The absolute configurations of the enantiomers of the diols **7**, **10**, **14** and **19** were determined by chemical correlation with the known compounds **40**, **41**, **39** and **41**, respectively.

1. Introduction

The cyclohexene ring of general structure **1** (Fig. 1) is a very common moiety belonging to the frameworks of a variety of natural products. The most relevant class of these compounds is that of the oxygenated carotenoids[1] bearing a polyenic side chain at the 6-position and a hydroxyl group on the cyclohexenic ring. In addition, a large number of biologically active terpenoids (often carotenoid derivatives) with shorter side chains and different degrees of functionalization have been isolated from natural sources. All these compounds share a difficult accessibility by the chemical synthesis of their single isomeric forms. Since the biological properties of these molecules depend on their stereochemistry, this aspect is especially demanding for compounds bearing at least one stereocentre. Due to the extensive industrial production of carotenoids/retinoics from inexpensive ionone isomers, the synthetic requirement was settled on the stereospecific preparation of oxygenated ionone derivatives.[2] Otherwise, for compounds with less than thirteen carbon atoms, there is not an exclusive pathway; these kinds of terpenoids were synthesised by a variety of stereospecific approaches. In this context, we envisaged that the enantioenriched diols of general structure **2** could be useful chiral building blocks for the synthesis of all compounds of type **1**.

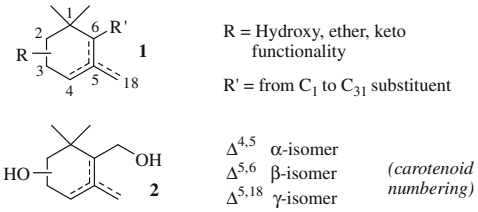

Figure 1. Structures and numbering of general framework **1** and of hydroxy-cyclogeraniol isomers **2**.

Since a number of racemic diol isomers **2** are easily available by chemical synthesis we set our study on the resolution approach. We have previously reported the enzyme-mediated resolution of different terpenic alcohols,[3] diols[4] and hydroxy-ionone derivatives.[5] By taking advantage of this acquired experience, we extended this method to the resolution of hydroxy-cyclogeraniol isomers. Herein, we report a comprehensive study on the lipase PS-mediated acetylation of the latter compounds. We found that the use of the aforementioned acetylation or its use in combination with fractional crystallisation of the obtained enantioenriched diols was an effective resolution protocol. By these means we prepared the enantiomers of the 2-hydroxy cyclogeraniol isomers **4**, **5** and **14** (α-, γ- and β-, respectively) as well as *cis*-3-hydroxy α-cyclogeraniol **7** and *cis*-4-hydroxy γ-cyclogeraniol **10**. The latter compounds are valuable chiral building blocks as demonstrated by their use in the synthesis of

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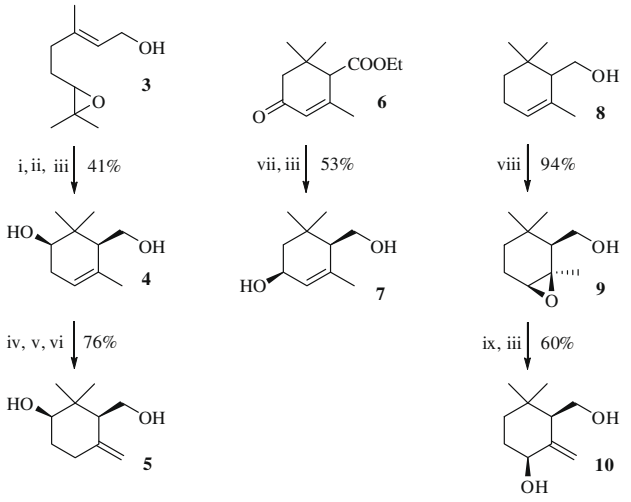
the natural terpenoids such as karahana lactone,[6] karahana ether and crocusatin C[7] and for the preparation of the relevant synthetic intermediate γ-cyclogeraniol.[8]

2. Results and discussion

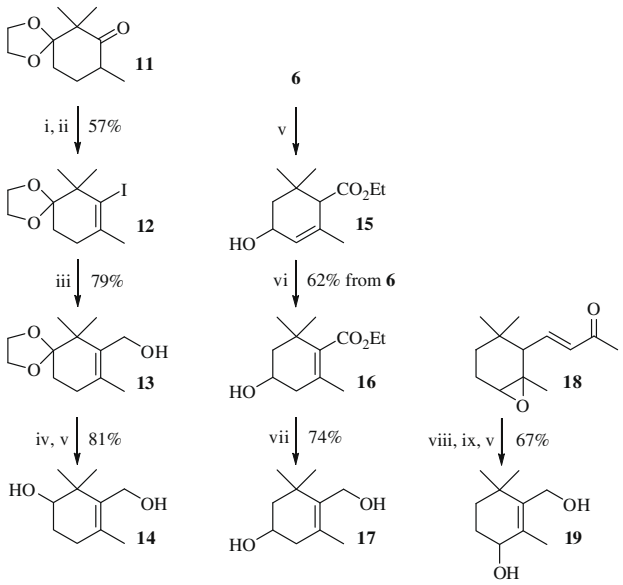
2.1. Preparation of the racemic diols

Diols of type **2**, showing a secondary hydroxy group at the 2-, 3- or 4-position and a double bond in one of the three different isomeric positions (α-, β- or γ-), could exist in overall 13 different isomeric forms. Our study on their resolutions first required a valuable amount of regioisomerically pure racemic starting materials. Indeed, it is mandatory to investigate both the enantioselectivity and the regioselectivity of the enzyme-mediated acetylation using a single isomeric form of each hydroxy-cyclogeraniol isomer. Therefore, we selected some synthetic methods that would allow their regiospecific preparation in a straightforward fashion and starting from easily available materials. According to these general requirements, seven representative diols were prepared as described below.

The α- and γ-*cis*-2-hydroxy-cyclogeraniol isomers **4** and **5**, respectively (Scheme 1), were synthesised from epoxygeraniol **3**, which in turn is obtainable on a multigram scale from geraniol by a hydrobromination-elimination protocol.[9] The $SnCl_4$-catalysed cyclisation[10] of the trimethylsilyl ether of **3** afforded a mixture of products from which the regioisomerically pure diol **4** was easily separated by crystallization. Otherwise, diol **5** was prepared from **4** by a photochemical double bond isomerization reaction previously developed by us.[11,5d,e] The *cis*-α-diol **4** was protected as a diacetate and then irradiated in an isopropanol/xylene solution with high-pressure Hg lamps light. Almost complete transformation was necessary since diol **5** is a liquid compound, and hence not purifiable by crystallisation, and was not separable from **4** by chromatography. Deprotection by saponification gave pure *cis*-γ-diols **5**. The 3,5,5-trimethyl-2-cyclohexen-1-one-4-carboxylic acid ethyl ester **6** is available in large scale by condensation of mesityl oxide with ethyl acetoacetate.[12] Its reduction with $LiAlH_4$ gave mainly *cis*-diol **7** that could be purified both by chromatography and by fractional crystallisation. Otherwise, α-cyclogeraniol **8** is the precursor of *cis*-γ-diol **10**. Oxidation of **8** with 3-chloroperbenzoic acid in CH_2Cl_2 gave epoxide **9** as a single isomer.[13] The following isomerisation of the oxirane ring to an allylic alcohol was performed using LDA as a strong, non-nucleophilic base.[5c] By these means, diol **10** was obtained in a satisfactory yield and, due to its crystalline nature, in a regioisomerically pure form. Concerning the β-hydroxycyclogeraniol isomers, they could exist in only three isomeric forms which we synthesised as described in Scheme 2.



Scheme 1. Synthesis of racemic diols **4**, **5**, **7** and **10**. Reagents and conditions: (i) Me_3SiCl, Et_3N; (ii) $SnCl_4$, toluene; (iii) crystallization from hexane/ether; (iv) Ac_2O, Py; (v) xylene, *i*-PrOH, high-pressure Hg lamp light; (vi) NaOH, MeOH; (vii) $LiAlH_4$, ether; (viii) MCPBA, CH_2Cl_2; (ix) LDA, THF, reflux.



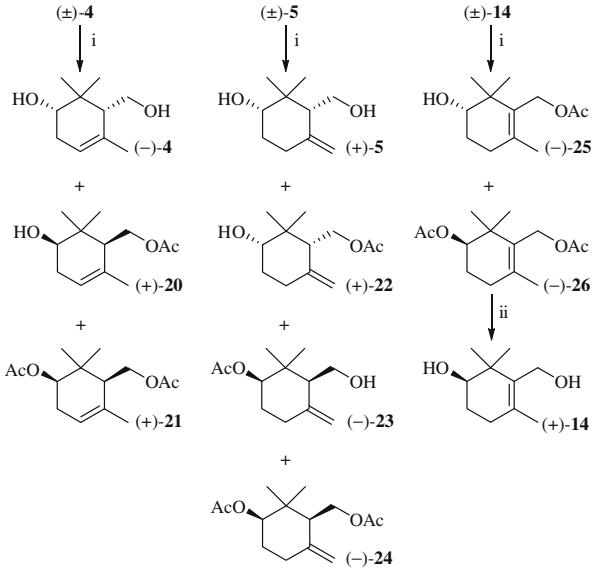
Scheme 2. Synthesis of racemic diols **14**, **17** and **19**. Reagents and conditions: (i) NH_2NH_2, Et_3N, EtOH, reflux; (ii) DBN, I_2, ether; (iii) BuLi, THF then formaldehyde; (iv) THF/H_2O, $HClO_4$ cat.; (v) $NaBH_4$, MeOH; (vi) NaOEt, EtOH, reflux; (vii) $LiAlH_4$, ether; (viii) O_3, CH_2Cl_2/MeOH, −78 °C then Ph_3P; (ix) DBU, CH_2Cl_2.

Diol **14** was prepared starting from ketone **11** that was obtained on a large scale by the regioselective ketalisation of 2,2,4-trimethylcyclohexane-1,3-dione.[14] The C1 unit was introduced by a two-step sequence. The reaction of **11** with hydrazine gave the corresponding hydrazone[15] which was converted into iodide **12** by treatment with iodine and DBN according to Barton's protocol.[16] The vinyl iodide was metallated with BuLi and the organo-lithium derivative obtained was quenched with formaldehyde to afford alcohol **13**. The hydrolysis of the ketal functionality followed by $NaBH_4$ reduction of the intermediate keto-alcohol gave diol **14**. The 3-hydroxycyclogeraniol isomer **17** was prepared starting from 3,5,5-trimethyl-2-cyclohexen-1-one-4-carboxylic acid ethyl ester **6**. The $NaBH_4$ reduction afforded hydroxy-ester **15** whose α double bond was isomerised at the β-position by NaOEt catalysis. The $LiAlH_4$ reduction of the obtained **16** gave diol **17**. Otherwise, 4-hydroxy-cyclogeraniol isomer **19** was prepared by degradation of epoxy-ionone **18**. Racemic α-ionone is an inexpensive starting material whose α-double bond could be selectively epoxidised. Thus, according to a reported procedure,[17] compound **18** was treated with ozone and the intermediate epoxy-aldehyde was isomerised to 4-hydroxy-β-cyclogeranial in the presence of catalytic DBU. The following $NaBH_4$ reduction afforded diol **19**.

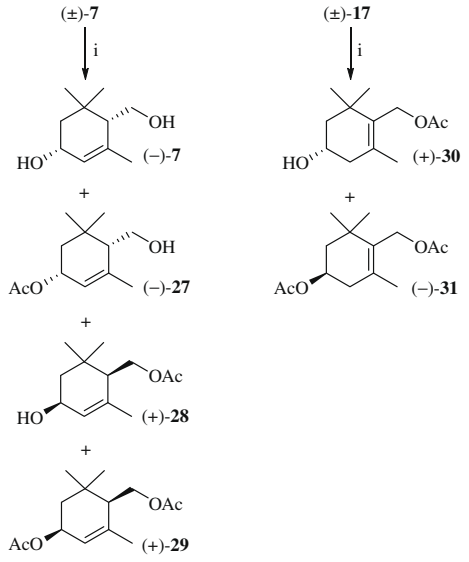
2.2. Enzyme-mediated acetylation of the obtained diols

To the best of our knowledge, no enzyme-mediated resolutions of hydroxy-geraniol isomers have been reported until now. Some studies have investigated the stereoselectivity of the lipase-catalysed acetylation of α-cyclogeraniol,[13,18] γ-cyclogeraniol,[19] 3-[5b] and 4-hydroxy-ionone[5a,c] derivatives. It should be noted that the enantioselectivities in the primary alcohol esterification were very low with the exception of the lipase PS-catalysed acetylation of α-cyclogeraniol.[13] Moreover, the enzyme-mediated resolution of

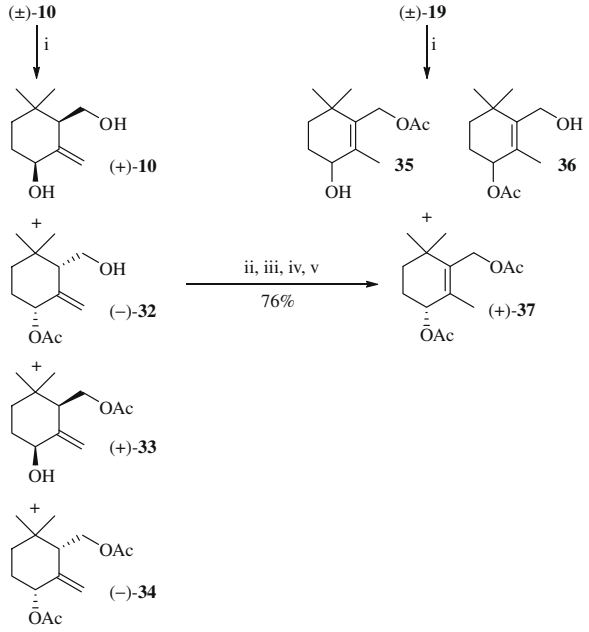
3- and 4-hydroxy-ionone derivatives was possible by using the same kind of lipase. Therefore, we settled on the employment of the lipase PS as the enzyme of choice for our study. Accordingly, we performed seven different acetylation experiments. Each diol was treated with vinyl acetate in *t*-butyl-methyl ether in the presence of the aforementioned enzyme. The reactions were interrupted when the wanted conversion was achieved; all the compounds were separated and characterised. The results are described in Schemes 3–5, and are summarised in Table 1. The first examined diols are the 2-hydroxy-cyclogeraniol isomers **4**, **5** and **14**. All of these compounds afforded 2-acetoxy derivatives with a high preference for the (2*R*)-configuration allowing the preparation of diacetates **21**, **24** and **26** with high enantiomeric purity (Scheme 3). Interestingly, both the enantioselectivity and the kinetic of the acetylation of the primary alcohol changed considerably shifting the double bond from the α- to γ-position. Indeed,



Scheme 3. Lipase PS-mediated acetylation of diols **4**, **5** and **14**. Reagents: (i) lipase PS, *t*-BuOMe, vinyl acetate; (ii) NaOH, MeOH.



Scheme 4. Lipase PS-mediated acetylation of diols **7** and **17**. Reagents: (i) lipase PS, *t*-BuOMe, vinyl acetate.



Scheme 5. Lipase PS-mediated acetylation of diols **10** and **19**. Reagents: (i) lipase PS, *t*-BuOMe, vinyl acetate; (ii) Dess–Martin periodinane, CH_2Cl_2; (iii) DBU, CH_2Cl_2; (iv) $NaBH_4$, MeOH; (v) Ac_2O, Py.

compound **4** was easily converted into (2*R*,6*S*)-monoacetate **20** with modest enantioselectivity and did not afford any 2-acetoxy-cyclogeraniol derivative, clearly indicating that the acetylation of the secondary alcohol is the rate-determining step. Otherwise, diol **5** gave both (6*R*)-monoacetate **22** and the (6*S*)-2-acetoxy-cyclogeraniol derivative **23** with modest and good enantioselectivity, respectively. This is likely due to the combination of two factors: the rate and the enantioselectivity of the acetylation of the two hydroxy groups. The acetylation rates of the two hydroxyl groups are very similar whereas the transformation of the secondary alcohol showed higher enantioselectivity.

Regarding the transformations of the 3-hydroxy-cyclogeraniol isomers **7** and **17**, we observed different behaviours (Scheme 4). Again, the acetylation of the two hydroxyl groups of diol **7** proceeded with similar ratios allowing the formation of both 3-acetoxy-cyclogeraniol **27** and 3-hydroxy-cyclogeraniol acetate **28** with very low and modest enantiomeric purity, respectively. This indicates a corresponding very low and modest enantioselectivity in the acetylation of the secondary and primary alcohol, respectively. Nevertheless, both diacetate **29** and the unreacted diol (−)-**7** showed high enantiomeric excesses. We can explain this effect by considering that the lipase catalyses the acetylation of the (6*R*) and (3*S*) primary and secondary alcohol functionalities of this diol, respectively. Since the relative configuration of *cis* diol **7** is (3*SR*,6*RS*), both acetylation steps must work in a 'matching' fashion to afford the diacetate and hence the unreacted diol with high ee. This hypothesis is also supported by two further observations. As described above, the α-diols **4** and **7** gave monoacetates **20** and **28** with the same stereochemical preference at C6, again the same as that described for the PS-mediated resolution of α-cyclogeraniol. In addition, the results obtained in the acetylation of 3-hydroxy-β-cyclogeraniol **17** confirmed that the enzyme catalyses this transformation with the same stereochemical preference at C3.

Indeed, racemic **17** was converted into diacetate **31** and monoacetate **30** having the (3*R*)- and (3*S*)-configurations, respectively, both with very low enantiomeric purity. At the reported conversion, only traces of diol and 2-acetoxy-cyclogeraniol derivative were detected in the reaction mixture, clearly indicating that the

Table 1
Results of the lipase PS-mediated acetylation of racemic diols **4**, **5**, **7**, **10**, **14**, **17** and **19**

Diol	Diacetate[a] (%) configuration (ee)	Monoacetate[a] (%) configuration (ee)		Unreacted diol[a] (%) configuration (ee)
		7-Acetoxy	7-Hydroxy	
(±)-**4**	(+)-**21** (10) (2*R*,6*S*) (96% ee)	(+)-**20** (51) (2*R*,6*S*) (37% ee)		(−)-**4** (39) (2*S*,6*R*) (57% ee)
(±)-**5**	(−)-**24** (7) (2*R*,6*S*) (99% ee)	(+)-**22** (15) (2*S*,6*R*) (32% ee)	(−)-**23** (18) (2*R*,6*S*) (89% ee)	(+)-**5** (60) (2*S*,6*R*) (22% ee)
(±)-**14**	(−)-**26** (24) (2*R*) (99% ee)	(−)-**25** (76) (2*S*) (30% ee)	Trace	
(±)-**7**	(+)-**29** (11) (3*S*,6*R*) (94% ee)	(+)-**28** (39) (3*S*,6*R*) (52% ee)	(−)-**27** (3) (3*R*,6*S*) (7% ee)	(−)-**7** (47) (3*R*,6*S*) (93% ee)
(±)-**17**	(−)-**31** (39) (3*R*) (27% ee)	(+)-**30** (61) (3*S*) (10% ee)	Trace	Trace
(±)-**10**	(−)-**34** (12) (4*R*,6*S*) (92% ee)	(+)-**33** (10) (4*S*,6*R*) (90% ee)	(−)-**32** (46) (4*R*,6*S*) (76% ee)	(+)-**10** (32) (4*S*,6*R*) (>99% ee)
(±)-**19**	(+)-**37** (39) (4*R*) (19% ee)	**35** + **36** (61)		

[a] Molar percentage of the compound in the reaction mixture.

acetylation of the primary alcohol proceeds much faster than that of the secondary one.

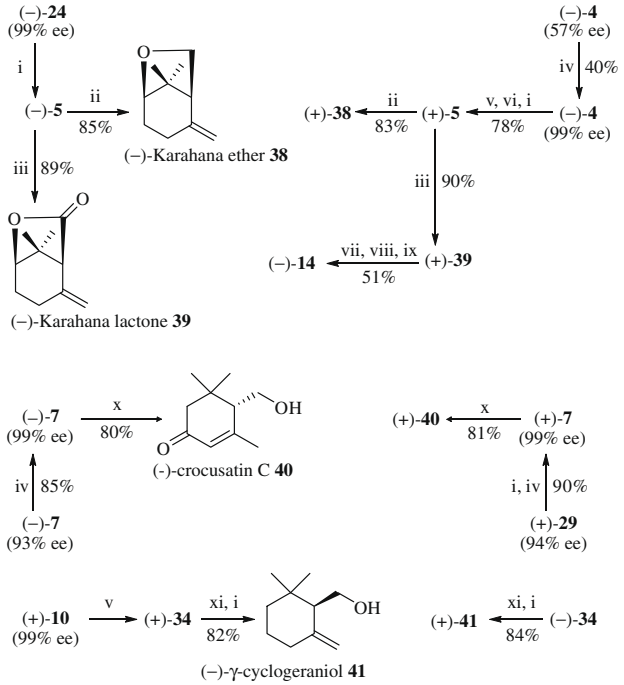
The transformations of the 4-hydroxy-cyclogeraniol isomers **10** and **19** showed further interesting insights (Scheme 5). The acetylation of the two hydroxy groups of the diol **10** proceeds with similar ratios allowing the formation of both 4-acetoxy-cyclogeraniol **32** and 4-hydroxy-cyclogeraniol acetate **33**. Moreover, both the diacetate **34** and the unreacted diol (+)-**10** showed good and very good enantiomeric purity, respectively. These results, seen to demonstrate that the enzyme catalyses the acetylation of the hydroxide groups of the isomers showing (4*R*)- and (6*S*)-configuration with high and low enantioselectivity, respectively. At the reported conversion, the (4*R*,6*S*)-diol was completely transformed and the unreacted diol (+)-**10** was isolated in its enantiopure form. Otherwise, the low enantioselectivity in the acetylation of primary alcohols allowed the formation of the (6*R*)-acetate **33** whose configuration and enantiomeric purity arose from the conversion of the remaining (4*S*,6*R*)-diol. Interestingly, the acetylation of the diol **19** showed a preference for the (4*R*)-enantiomer as demonstrated by chemical correlation of the obtained diacetate **37** with compound (−)-**32**.

Indeed, the latter compound was oxidised with Dess–Martin periodinane[20] and the obtained aldehyde was treated with DBU in order to achieve γ–β double bond isomerisation. Next, $NaBH_4$ reduction followed by acetylation gave (+)-**37** showing the same configuration and higher enantiomeric purity than the material obtained by enzymic acetylation of **19**. In the latter instance, the recorded enantio- and regioselectivity were very low. Indeed, the diacetate **37** showed only 19% ee (*c* 0.39), whereas monoacetylated derivatives were obtained as an inseparable mixture of compounds **35** and **36**.

2.3. Resolution of diols 4, 5, 14, 7 and 10, assignation of their absolute configuration and evaluation of their synthetic utility

Although the enzymic transformations described above ever afforded enantioenriched compounds, not all are suitable for large-scale preparation of the enantiopure hydroxy-cyclogeraniol isomers. This is the case for diols **17**[21] and **19**[22] whose lipase PS-mediated acetylation afforded diacetate derivatives with a very low enantiomeric purities. In contrast, the transformations of diols **4**, **5**, **14**, **7** and **10** afforded derivatives with high enantiomeric excess that could be considered, useful chiral building blocks. In addition, both the racemates and the single enantiomeric forms of the diols **4**,[10,23] **14**,[22] **7**[22] and **10**[24] are crystalline compounds whose enantiomeric purity could be increased by fractional crystallisation. Moreover, the enantiomers of liquid diol **5** were obtained without any racemisation starting from enantiopure (+)- and (−)-**4** by the photoisomerization procedure described above. We have experimentally verified these aspects by carrying out the large-scale preparation of the enantiomeric forms of all these diols.

It should be noted that the enantioselective synthesis of diols **4** and **5** and their use in the preparation of natural terpenoids such as α- and γ-ionones, α- and γ-damascone, karahana ether and karahana lactone have been already described.[6a,b,23] As a demonstration of the usefulness of our resolution protocol, we report here (Scheme 6) a further preparation of karahana ether and a new short synthesis of karahana lactone that is itself a relevant chiral building block for the synthesis of several natural compounds.[25] Accordingly, we converted diacetate (−)-**24** into diol (−)-**5** which



Scheme 6. Synthesis of the enantiomeric forms of karahana ether, karahana lactone, crocusatin C and γ-cyclogeraniol. Reagents and conditions: (i) NaOH, MeOH; (ii) TsCl, Py; (iii) BAIB, TEMPO cat., CH_2Cl_2; (iv) crystallisation from hexane/ether; (v) Ac_2O, Py; (vi) xylene, *i*-PrOH, high-pressure Hg lamp light; (vii) DIBAH, toluene, −78 °C; (viii) NaOMe, MeOH; (ix) $NaBH_4$, MeOH; (x) MnO_2, CH_2Cl_2; (xi) Et_3N, HCO_2H, $(Ph_3P)_2PdCl_2$ cat., Ph_3P cat., THF, reflux.

was treated with TsCl and an excess of pyridine to give (−)-karahana ether **38**. Then, oxidation of the same diol with bis-acetoxyiodobenzene (BAIB) in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidinooxy (TEMPO)[26] gave directly (−)-karahana lactone **39** in good yield. The opposite enantiomers of the latter compounds were prepared starting from diol (−)-**4** (57% ee) whose enantiomeric purity was easily increased to 99% ee by fractional crystallisation. The diol obtained was then converted into enantiopure (+)-**5** by means of protection as a diacetate, photoisomerization and saponification. Next, this diol was transformed into the (+)-karahana ether and the (+)-karahana lactone following the methods described above. It should be noted that (+)-karahana lactone was also employed for the determination of the absolute configuration of the enantiomers of diol **14** which were unknown until now. The reduction of (+)-**39** with DIBAH at low temperature afforded the corresponding lactol which was treated with sodium methylate in order to achieve double bond isomerisation from the γ- to the β-position. Next, the $NaBH_4$ reduction gave enantiopure (−)-**14** whose configuration was unambiguous (2*S*). Subsequently, we exploited the use of diols **7** and **10** for the preparation of additional natural compounds. The enantiomeric purity of diols (−)- and (+)-**7** was increased to 99% by crystallisation. Then, the following MnO_2 oxidation of the secondary alcohol functionality gave (−)- and (+)-crocusatin **40**,[7] respectively, whose enantiospecific syntheses have not been reported before. The latter compound is a natural monoterpenoid that can be found either free or as β-D-glucoside[27] in the pollen of *Crocus sativus* and in the fruit of *Gardenia jasminoides*. Since the absolute configuration of natural (−)-crocusatin was described as (6*S*) by mean of a circular dichroism study,[27b] we assigned the (3*R*,6*S*) configuration to diol (−)-**7**. Similarly, the configuration of the enantiomers of diol **10**, also still unknown, was assigned by chemical correlation. Accordingly, we submitted diacetate (+)- and (−)-**34** to reductive elimination of the allylic acetate group by treatment with triethylammoniun formate in the presence of catalytic $(Ph_3P)_2PdCl_2$. We obtained (−)-(*R*)- and (+)-(*S*)-γ-cyclogeraniol, respectively, with very good regioselectivity and without any racemisation. These transformations are noteworthy since γ-cyclogeraniol isomers are suitable starting materials for the preparation of relevant fragrances such as γ-ionone and γ-damascone[6a,8b] and for the synthesis of the triterpene ambrein.[8a] Moreover, by these means we assigned the absolute configuration of diol (+)- and (−)-**10** as (4*S*,6*R*) and (4*R*,6*S*), respectively. In addition, since acetate (−)-**32** was chemically correlated with diacetate (+)-**37** (Scheme 5), the latter compound is the (4*R*)-enantiomer.

3. Conclusions

The study described above is a comprehensive investigation on the lipase PS-mediated resolution of hydroxy-cyclogeraniol isomers. Some representative members of this class of compounds were synthesised regioselectively and the following experiments showed many relevant results. We found that the 2-hydroxy isomers **4**, **5** and **14** (α, γ and β, respectively) as well as *cis* 3-hydroxy α-cyclogeraniol **7** and *cis*-4-hydroxy γ-cyclogeraniol **10** can be easily resolved by a straightforward procedure consisting of a combination of a lipase-mediated kinetic acetylation with a fractional crystallisation. The enantiopure diols obtained are suitable building blocks for the synthesis of many natural terpenoids such as karahana lactone, karahana ether and crocusatin C and for the preparation of the synthetic intermediate γ-cyclogeraniol. Further studies on the use of the latter enantiopure diols as starting materials for the preparation of hydroxylated carotenoids are still in progress and will be reported in due course.

4. Experimental

4.1. General experimental

All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. The photoisomerization experiments were carried out using a Rayonet photochemical reactor equipped with 12 × 8 W high pressure mercury (Hg) lamps. Geraniol epoxide **3** was prepared by hydrobromination of geraniol acetate with NBS/H_2O followed by NaOH treatment of the obtained bromohydrin.[9] Keto-ester **6** was prepared by zinc chloride-catalysed condensation of mesityl oxide with ethyl acetoacetate.[12] α-Cyclogeraniol **8** was prepared by $LiAlH_4$ reduction of ethyl α-cyclogeraniate in turn obtained by $SnCl_4$-catalysed cyclization[28] of 3,7-dimethyl-octa-2,6-dienoic acid ethyl ester. Iodide **12**[15] was prepared via I_2/DBN-[16] mediated decomposition of the hydrazone of mono ethylene glycol ketal **11**. The latter compound was obtained by the regioselective ketalisation of 2,2,4-trimethylcyclohexane-1,3-dione, which in turn was synthesised by the condensation of 3-pentanone with ethyl acrylate followed by iodomethane alkylation.[14] Epoxy-α-ionone **18** was obtained as a 4:1 mixture of *cis*/*trans* isomers, respectively, by means of MCPBA treatment of the commercially available α-ionone. Lipase from *Pseudomonas cepacia* (PS), *Amano Pharmaceuticals Co.*, Japan, 30 units/mg was employed in this work. TLC: *Merk* Silica Gel *60 F_{254}* plates. Column chromatography (CC): silica gel. GC–MS analyses: *HP-6890* gas chromatograph equipped with a 5973 mass detector, using a *HP-5MS* column (30 m × 0.25 mm, 0.25 μm firm thickness; *Hewlett Packard*) with the following temp. program: 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); carrier gas, He; constant flow 1 ml/min; split ratio, 1/30; t_R given in min: t_R(**4**) 16.75, t_R(**5**) 16.42, t_R(**7**) 15.54, t_R(**9**) 12.79, t_R(**10**) 16.11, t_R(**13**) 19.97, t_R(**14**) 16.58, t_R(**15**) 17.17 and 17.74, t_R(**16**) 16.22, t_R(**17**) 14.39, t_R(**19**) 15.92, t_R(**20**) 18.77, t_R(**21**) 20.37, t_R(**22**) 18.84, t_R(**23**) 18.24, t_R(**24**) 19.92, t_R(**25**) 19.25 t_R(**26**) 20.73, t_R(**27**) 18.58, t_R(**28**) 18.21, t_R(**29**) 19.16, t_R(**30**) 17.12, t_R(**31**) 19.24, t_R(**32**) 18.19, t_R(**33**) 18.47, t_R(**34**) 20.10, t_R(**35**) 16.83, t_R(**36**) 16.72, t_R(**37**) 20.32, t_R(**38**) 8.98, t_R(**39**) 14.12, t_R(**40**) 17.82, t_R(**41**) 11.05; mass spectra: *m*/*z* (rel.%). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a CHIRASIL DEX CB-Column with the following temp. program: compound **24**: 70° (1 min)–2°/min–100° (0 min)–0.3°/min–105° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((+)-**24**) 28.7, t_R((−)-**24**) 29.2; compound **26**: 65° (0 min)–1°/min–94° (0 min)–0.3°/min–110° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((+)-**26**) 50.9, t_R((−)-**26**) 51.5; compound **29**: 80° (0 min)–1°/min–100° (0 min)–0.5°/min–115° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((+)-**29**) 28.8, t_R((−)-**29**) 29.6; compounds **31** and **37**: 60° (2 min)–1°/min–95° (0 min)–0.5°/min–120° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((+)-**31**) 62.3, t_R((−)-**31**) 63.7, t_R((+)-**37**) 57.9, t_R((−)-**37**) 58.4; compound **34**: 80° (0 min)–1°/min–100° (1 min)–0.3°/min–105° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((−)-**34**) 29.2, t_R((+)-**34**) 29.7; compound **39**: 70° (1 min)–1.5°/min–90° (1 min)–0.5°/min–95° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((+)-**39**) 17.8, t_R((−)-**39**) 18.6. Enantiomer excesses of compounds **4**, **20** and **21** were determined by measurement of the specific rotation value of the corresponding diols and comparison with that of enantiopure **4**. Optical rotations: *Jasco-DIP-181* digital polarimeter. ^1H and ^{13}C Spectra: $CDCl_3$ solns. at rt; *Bruker-AC-400* spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm rel to internal $SiMe_4$ (=0 ppm), *J* values in hertz. IR spectra were recorded on a *Perkin-Elmer 2000 FT-IR* spectrometer; *ν* in cm^{-1}. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected.

4.2. Procedures for the preparation of racemic diols

4.2.1. cis-2-Hydroxy α-cyclogeraniol 4

Chlorotrimethylsilane (56 mL, 441 mmol) was added dropwise to a cooled (0 °C) solution of geraniol epoxide **3** (50 g, 294 mmol) in ether (500 mL) and triethylamine (90 mL, 646 mmol). The reaction was stirred for 4 h at rt, the precipitated salt was removed by filtration and the filtrate was washed with brine. The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was diluted with toluene (350 mL) and cooled (0 °C). Tin tetrachloride (1 M in toluene, 150 mL) was added dropwise and the reaction was stirred for 2 h followed by quenching with a saturated solution of NH_4Cl aq (300 mL). The mixture was extracted with ether (300 mL) and the organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed with hexane/diethyl ether (9:1–2:1) as eluent to give **4** contaminated with the corresponding γ isomers. Crystallisation of the latter oil (hexane/diethyl ether, −20 °C) afforded pure **4** (20.4 g, 41%, 99% of chemical purity by GC), mp 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (s, 1H), 4.45 (br s, 2H), 3.79–3.71 (m, 2H), 3.37 (d, J = 4.5 Hz, 1H), 2.36 (dm, J = 18.3 Hz, 1H), 2.11 (d, J = 18.3 Hz, 1H), 1.75 (s, 3H), 1.71 (br s, 1H), 1.10 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (100 MHz) δ 131.5, 120.3, 71.3, 58.7, 51.0, 37.0, 32.1, 28.5, 24.1, 22.4. IR (nujol, cm^{-1}) 3221, 1490, 1374, 1318, 1163, 1085, 1032, 974, 909. GC–MS *m/z* (rel intensity) 152 (M^+−H_2O, 6), 140 (4), 122 (52), 107 (100), 91 (16), 81 (17), 72 (9), 55 (8), 43 (12).

4.2.2. cis-2-Hydroxy γ-cyclogeraniol 5

A sample of diol **4** (5 g, 29.4 mmol) was treated with pyridine (20 mL) and Ac_2O (10 mL) and set aside at rt until acetylation was complete (12 h). The mixture was concentrated under reduced pressure and the residue was dissolved in isopropanol (320 mL) and xylene (80 mL). The obtained solution was flushed with nitrogen, sealed in quartz vessels and irradiated in a Rayonet photochemical reactor equipped with 12 8-W high-pressure Hg lamps. The reaction was monitored by GC analysis and the irradiation was interrupted until starting compound became less than 1% of the mixture (10 days). The solution was then concentrated under reduced pressure to afford oil that was dissolved in methanol (50 mL) and treated with a solution of NaOH (4 g, 100 mmol) in methanol (50 mL). The mixture was stirred at rt until no more starting acetate was detected by TLC analysis, then was diluted with water (200 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography eluting with hexane/diethyl ether (9:1–2:1) as eluent to give **5** (3.8 g, 76%, 97% of chemical purity by GC) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.73 (s, 1H), 3.92 (dd, J = 10.8, 7.0 Hz, 1H), 3.68 (dd, J = 10.8, 3.4 Hz, 1H), 3.44 (dd, J = 5.4, 3.4 Hz, 1H), 2.93 (br s, 2H), 2.55–2.45 (m, 1H), 2.08 (dt, J = 13.7, 5.4 Hz, 1H), 2.01–1.95 (m, 1H), 1.91–1.79 (m, 1H), 1.64 (dq, J = 13.7, 5.4 Hz, 1H), 1.00 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz) δ 147.8, 110.3, 74.6, 62.3, 55.0, 38.8, 30.8, 29.3, 27.5, 20.8. IR (film, cm^{-1}) 3291, 1646, 1445, 1386, 1365, 1160, 1087, 1013, 991, 956, 890. GC–MS *m/z* (rel intensity) 170 (M^+, 1), 152 (M^+ −H_2O, 7), 134 (4), 122 (89), 107 (100), 93 (33), 79 (38), 67 (27), 55 (21), 43 (29).

4.2.3. *cis*-3-Hydroxy α-cyclogeraniol 7

A solution of 3,5,5-trimethyl-2cyclohexen-1-one-4-carboxylic acid ethyl ester **6** (50 g, 238 mmol) in dry ether (200 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (10 g, 263 mmol) in dry ether (250 mL). The mixture was heated at reflux for 2 h, then cooled (0 °C) and quenched by dropwise addition of water (10 mL) and a 20% aqueous solution of NaOH (50 mL). The ether layer was separated, washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was chromatographed with hexane/diethyl ether (9:1–2:1) as eluent to give **7** contaminated with *trans* isomers. Crystallisation of the latter oil (hexane/diethyl ether, −20 °C) afforded pure **7** (21.5 g, 53%, 98% of chemical purity by GC), mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (s, 1H), 4.20–4.11 (m, 1H), 3.81–3.71 (m, 2H), 2.65 (br s, 1H), 2.23 (br s, 1H), 1.77 (t, J = 1.3 Hz, 3H), 1.62 (d, J = 8.4 Hz, 2H), 1.55 (s, 1H), 1.05 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (100 MHz) δ 135.0, 128.0, 66.2, 60.9, 51.9, 42.2, 34.0, 28.3, 28.1, 22.4. IR (nujol, cm^{-1}) 3355, 1039, 1007, 987, 828. GC–MS *m/z* (rel intensity) 170 (M^+, 1), 155 (26), 152 (17), 137 (37), 121 (48), 107 (100), 96 (88), 91 (56), 81 (31), 69 (31), 55 (12), 41 (19).

4.2.4. *cis*-4-Hydroxy γ-cyclogeraniol 10

A solution of α-cyclogeraniol **8** (35 g, 227 mmol) in CH_2Cl_2 (350 mL) was treated with MCPBA (43 g, 249 mmol) stirring at 0 °C until no more starting **8** was detected by TLC analysis (2 h). The MCBA was eliminated by filtration and the solution was washed in turn with saturated $NaHCO_3$ solution (100 mL) and 5% aq Na_2SO_3 (100 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue was chromatographed with hexane/ethyl acetate (9:1–2:1) as eluent to give pure **9** (36.5 g, 94%, 96% of chemical purity by GC) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (dd, J = 11.3, 3.8 Hz, 1H), 3.80 (dd, J = 11.3, 6.2 Hz, 1H), 3.01 (s, 1H), 2.61 (br s, 1H), 1.98 (ddt, J = 15.4, 6.2, 1.7 Hz, 1H), 1.92–1.82 (m, 1H), 1.63–1.52 (m, 1H), 1.50–1.44 (m, 1H), 1.40 (s, 3H), 0.98–0.88 (m, 1H), 0.95 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz) δ 62.2, 60.4, 59.6, 47.6, 30.5, 28.6, 28.2, 26.9, 25.4, 21.7. IR (film, cm^{-1}) 3447, 1448, 1366, 1090, 1049, 902. GC–MS *m/z* (rel intensity): 170 (M^+, 1), 155 (93), 137 (35), 125 (21), 109 (27), 95 (28), 87 (100), 81 (30), 69 (35), 55 (40), 43 (72).

BuLi (45 ml of a 10 M solution in hexane) was added dropwise to a cooled (−78 °C) solution of *i*Pr_2NH (50 g, 494 mol) in dry THF (350 mL) under nitrogen. The mixture was stirred at this temperature for 30 min, then a solution of the epoxy-α-cyclogeraniol **9** (34 g, 200 mmol) in dry THF (80 ml) was added dropwise. The reaction was gradually warmed to rt (1 h) and then heated at reflux until no more starting epoxide was detected by TLC analysis (3 h). After cooling to rt, the mixture was poured into a mixture of crushed ice and 10% HCl soln (500 ml) and extracted with EtOAc (2 × 300 mL). The organic phase was successively washed with satd aq NH_4Cl soln (100 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed with hexane/ethyl acetate (4:1–1:1) as eluent and the obtained diol was further purified by crystallisation (hexane/ether) to give pure **10** (20.5 g, 60%, 99% of chemical purity by GC), mp 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 4.88 (s, 1H), 4.12 (dd, J = 5.9, 4.5 Hz, 1H), 3.89 (dd, J = 10.7, 8.7 Hz, 1H), 3.73 (dd, J = 10.7, 3.9 Hz, 1H), 2.90 (br s, 1H), 2.58 (br s, 1H), 2.03 (dd, J = 8.7, 3.9 Hz, 1H), 1.90–1.80 (m, 1H), 1.75–1.66 (m, 1H), 1.65–1.55 (m, 1H), 1.26 (ddd, J = 13.5, 7.6, 4.5 Hz, 1H), 0.95 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100 MHz) δ 149.2, 110.7, 72.2, 61.7, 54.1, 34.5, 34.1, 31.4, 28.7, 24.3. IR (nujol, cm^{-1}) 3365, 1653, 1368, 1350, 1114, 1066, 1024, 901, 869. GC–MS *m/z* (rel intensity) 170 (M^+, 1), 152 (M^+−H_2O, 5), 139 (30), 122 (82), 107 (100), 93 (52), 79 (40), 70 (22), 55 (34), 41 (24).

4.2.5. 2-Hydroxy β-cyclogeraniol 14

BuLi (13 mL of a 10 M solution in hexane) was added dropwise to a cooled (−78 °C) solution of iodide **12** (35 g, 114 mmol) in dry THF (200 mL) under nitrogen. The mixture was stirred at this temperature for 20 min., then the cooling bath was removed and a stream of formaldehyde (obtained by thermal depolymerisation of solid formaldehyde) was bubbled into the solution. The reaction

mixture was diluted with ether (300 mL) and quenched by the addition of saturated NH_4Cl (200 mL). The layers were separated and the organic phase was concentrated. The residue was chromatographed eluting with hexane/diethyl ether (8:1–2:1) as eluent to give **13** (19.1 g, 79%, 95% of chemical purity by GC), as a thick oil; ^{1}H NMR (250 MHz, $CDCl_3$) 4.15 (br s, 2H), 4.05–3.94 (m, 4H), 2.24–2.12 (m, 2H), 1.84–1.68 (m, 2H), 1.78 (s, 3H), 1.11 (s, 6H). ^{13}C NMR (62.8 MHz) δ 136.8, 132.3, 89.2, 65.0, 59.1, 42.5, 30.7, 26.7, 22.8, 19.2. GC–MS *m/z* (rel intensity) 212 (M^+, 5), 194 (M^+-H_2O, 3), 179 (3), 169 (3), 151 (2), 137 (2), 121 (4), 107 (8), 99 (10), 93 (19), 86 (100), 79 (6), 67 (4), 55 (7). Compound **13** (15 g, 70.6 mmol) was dissolved in THF (80 mL) and stirred at rt with water (20 mL) and 70% $HClO_4$ (0.5 mL). After complete hydrolysis of the ketal functionality (TLC analysis), the mixture was partitioned between a saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL). The organic phase was concentrated under reduced pressure and the residue, dissolved in MeOH (100 mL), was treated at 0 °C with $NaBH_4$ (1.4 g, 37 mmol). The reaction was then quenched by addition of 1 M aq HCl solution (200 mL) and ethyl acetate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (100 mL). The organic layers were concentrated and the residue was purified by chromatography (hexane/Et_2O 2:1) and crystallisation (hexane/ether) to afford pure diol **14** (9.8 g, 81%, 97% of chemical purity by GC), mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 4.20–4.10 (m, 2H), 3.52 (dd, J = 9.0, 3.1 Hz, 1H), 2.19–2.02 (m, 2H), 1.87–1.77 (m, 1H), 1.76 (s, 3H), 1.76–1.65 (m, 1H), 1.57 (br s, 2H), 1.12 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz) δ 135.9, 132.8, 75.6, 58.9, 39.1, 29.8, 26.5, 26.3, 21.7, 19.3. IR (film, cm^{-1}) 3287, 1313, 1196, 1145, 1075, 1039, 1012, 995. GC–MS *m/z* (rel intensity) 170 (M^+, 3), 152 (M^+-H_2O, 50), 137 (32), 123 (50), 109 (84), 93 (100), 81 (32), 67 (34), 55 (29), 43 (26).

4.2.6. 3-Hydroxy β-cyclogeraniol 17

A cooled (0 °C) solution of 3,5,5-trimethyl-2cyclohexen-1-one-4-carboxylic acid ethyl ester **6** (40 g, 190 mmol) in MeOH (200 mL) was treated under stirring with $NaBH_4$ (3.6 g, 95 mmol). Until complete reduction of the starting ketone (1 h), the reaction mixture was then partitioned between 1 M aq HCl solution (500 mL) and ethyl acetate (400 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude **15** as a 3:2 mixture of diastereoisomers. The latter oil was dissolved in ethanol (250 mL) and treated with NaOEt (14 g, 206 mmol) stirring at reflux for 24 h. The mixture was then cooled, poured into a mixture of crushed ice and 5% HCl soln (250 mL) and extracted with ethyl acetate (2 × 200 ml). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed with hexane/ethyl acetate (5:1–2:1) as eluent to give pure **16** (25.1 g, 62%, 95% chemical purity by GC) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28–4.18 (m, 2H), 4.10–3.99 (m, 1H), 2.36 (ddd, J = 17.1, 5.8, 1.3 Hz, 1H), 2.00 (ddd, J = 17.1, 9.6, 1.1 Hz, 1H), 1.74 (ddd, J = 12.0, 3.7, 1.7 Hz, 1H), 1.70 (s, 3H), 1.68 (br s, 1H), 1.46 (t, J = 12.0 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.22 (s, 3H), 1.08 (s, 3H). GC–MS *m/z* (rel intensity) 212 (M^+, 14), 197 (26), 179 (34), 167 (59), 151 (100), 139 (33), 121 (75), 107 (32), 95 (21), 79 (18), 67 (12), 55 (13), 43 (13). The latter compound was then reduced with $LiAlH_4$ (9 g, 237 mmol) using the same conditions described for the preparation of **7**. The crude diol obtained was chromatographed with hexane/diethyl ether (8:1–2:1) as eluent to give **17** as a thick oil (14.8 g, 74%, 97% of chemical purity by GC) that crystallised on standing, mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, J = 11.6 Hz, 1H), 4.09 (d, J = 11.6 Hz, 1H), 4.01–3.91 (m, 1H), 2.33 (ddd, J = 16.8, 5.5, 1.7 Hz, 1H), 2.02 (dd, J = 16.8, 9.6 Hz, 1H), 1.78 (s, 3H), 1.74 (ddd, J = 12.0, 3.5, 2.1 Hz, 1H), 1.46 (t, J = 12.0 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz) δ 137.4, 130.7, 64.9, 58.2, 48.2, 42.2, 36.8, 29.3, 28.6, 19.4. IR (nujol, cm^{-1}) 3291, 1657, 1373, 1363, 1074, 1039, 1020, 998. GC–MS *m/z* (rel intensity) 170 (M^+, 12), 152 ((M^+-H_2O, 45), 137 (53), 119 (100), 109 (59), 95 (50), 81 (28), 67 (46), 55 (30), 41 (36).

4.2.7. 4-Hydroxy β-cyclogeraniol 19

A solution of the epoxy-α-ionone **18** (30 g, 144 mmol) in CH_2Cl_2 (200 mL) and MeOH (50 mL) was treated with a stream of ozone at −78 °C until the appearance of a persistent blue colour. Nitrogen was then bubbled through the solution until it turned colourless and the reaction was treated with a solution of Ph_3P (42 g, 160 mmol) in CH_2Cl_2 (100 mL). The obtained solution was gradually warmed at rt and then concentrated at reduced pressure. The residue was diluted with CH_2Cl_2 (300 mL) and washed with water (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to a final volume of about 100 mL. The solution was then treated with DBU (4.4 g, 28.9 mmol) stirring at rt until complete isomerisation to the β-isomer (12 h, TLC analysis). The reaction was then quenched by addition of 1 M aq HCl solution (100 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic layers were concentrated under reduced pressure and the residue was dissolved in MeOH (100 mL) and treated with $NaBH_4$ (2.7 g, 71.4 mmol). The reaction mixture was then partitioned between a 1 M aq HCl solution (300 mL) and ethyl acetate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (100 mL). The organic layers were concentrated, the residue was chromatographed with hexane/ethyl acetate (4:1–1:1) as eluent and the obtained diol was further purified by crystallisation (hexane/$CHCl_3$) to give pure **19** (16.6 g, 67%, 98% chemical purity by GC), mp 112–113 °C, Ref. 17b mp 109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19–4.09 (m, 2H), 3.95 (brt, J = 4.8 Hz, 1H), 1.95–1.83 (m, 2H), 1.88 (s, 3H), 1.72–1.59 (m, 2H), 1.44 (br s, 1H), 1.43–1.35 (m, 1H), 1.10 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz) δ 141.2, 134.3, 69.9, 58.7, 34.5, 28.6, 28.1, 27.2, 16.4. IR (nujol, cm^{-1}) 3269, 1377, 1150, 1044, 1032, 1001, 971. GC–MS *m/z* (rel intensity) 152 (M^+-H_2O, 48), 139 (100), 123 (28), 109 (61), 95 (46), 81 (46), 67 (37), 55 (24), 43 (43).

4.3. Lipase PS-mediated diols resolution

4.3.1. General procedure

A solution of the suitable hydroxy-cyclogeraniol (5 g, 29.4 mmol), lipase PS (5 g), vinyl acetate (15 mL) and *t*-BuOMe (60 mL) was stirred at rt and the formation of the acetylated compounds was monitored by TLC analysis. The reaction was stopped at the reported conversion (see Table 1) by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was then purified by chromatography using hexane–diethyl ether (95:5–2:1) as eluent.

4.3.2. Resolution of cis 2-hydroxy α-cyclogeraniol 4

The general procedure afforded:

Diacetate (+)-**21**: colourless oil, $[\alpha]_D^{20} = +8.5$ (*c* 2.5, $CHCl_3$), 98% chemical purity by GC, 96% ee, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38–5.32 (m, 1H), 4.71 (t, J = 5.5 Hz, 1H), 4.44 (dd, J = 11.6, 4.9 Hz, 1H), 4.15 (dd, J = 11.6, 5.3 Hz, 1H), 2.32 (dm, J = 18.5 Hz, 1H), 2.13–1.98 (m, 2H), 2.05 (s, 6H), 1.75 (br s, 3H), 0.99 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz) δ 170.8, 170.4, 133.5, 119.3, 75.6, 64.1, 48.6, 35.7, 28.6, 25.8, 22.4, 21.0, 21.0, 19.6. IR (film, cm^{-1}) 1739, 1661, 1372, 1238, 1049. GC–MS *m/z* (rel intensity) 151 (<1), 134 (99), 119 (100), 107 (13), 91 (10), 81 (7), 72 (6), 55 (3).

Monoacetate (+)-**20**: colourless oil, $[\alpha]_D^{20} = +26.1$ (*c* 2, $CHCl_3$), 97% chemical purity by GC, 37% ee, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43–5.36 (m, 1H), 4.45 (dd, J = 11.7, 4.1 Hz, 1H), 4.15 (dd,

J = 11.7, 4.4 Hz, 1H), 3.49–3.40 (m, 1H), 2.32 (dm, J = 17.7 Hz, 1H), 2.10–1.96 (m, 3H), 2.04 (s, 3H), 1.72 (br s, 3H), 1.02 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz) δ 170.6, 132.6, 120.4, 73.4, 63.3, 48.4, 37.1, 31.8, 26.6, 22.2, 21.0, 19.2. IR (film, cm^{-1}) 3447, 1738, 1438, 1386, 1366, 1243, 1030, 971, 909. GC–MS *m/z* (rel intensity) 152 (M$^+$–AcOH, 98), 137 (38), 123 (43), 119 (44), 107 (100), 91 (30), 81 (72), 72 (23), 55 (15).

Diol (−)-**4**: colourless crystals, $[\alpha]_D^{20} = -31.5$ (c 2, CH_2Cl_2), 97% chemical purity by GC, 57% ee, ^{1}H NMR, ^{13}C NMR, IR and MS: in accordance with those of racemic diol. The diol (−)-**4** was recrystallised twice from hexane/ether and its specific rotation value increased to $[\alpha]_D^{20} = -57.4$ (c 2, CH_2Cl_2), mp 120–122 °C; Ref. 23 $[\alpha]_D^{20} = -51.7$ (c 2, CH_2Cl_2), mp 131–132 °C.

The diacetate (+)-**21** was saponified with NaOH in methanol. The product was purified by chromatography and crystallisation from hexane/ether to give diol (+)-**4**: colourless crystals, $[\alpha]_D^{20} = +57.8$ (c 2, CH_2Cl_2), mp 122–123 °C; Ref. 10 $[\alpha]_D^{20} = +45.8$ (c 1.93, $CHCl_3$), mp 113–114 °C.

4.3.3. Resolution of cis-2-hydroxy γ-cyclogeraniol 5

The general procedure afforded:

Diacetate (−)-**24**: colourless oil, $[\alpha]_D^{20} = -20.1$ (c 1, $CHCl_3$), 96% chemical purity by GC, 99% ee by chiral GC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.70 (dd, J = 7.1, 3.7 Hz, 1H), 4.67 (s, 1H), 4.40 (dd, J = 11.2, 9.8 Hz, 1H), 4.30 (dd, J = 11.2, 4.1 Hz, 1H), 2.42–2.31 (m, 1H), 2.20 (dd, J = 9.8, 4.1 Hz, 1H), 2.14–2.00 (m, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.90–1.79 (m, 1H), 1.72–1.57 (m, 1H), 1.01 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz) δ 171.0, 170.3, 144.9, 110.9, 77.5, 62.3, 51.3, 38.0, 29.5, 27.9, 26.3, 21.2, 21.0, 19.6. IR (film, cm^{-1}) 1739, 1649, 1442, 1369, 1236, 1026, 960, 895. GC–MS *m/z* (rel intensity) 212 (<1), 194 (M$^+$–AcOH, 2), 152 (2), 134 (100), 119 (78), 107 (27), 93 (18), 79 (14), 71 (15), 55 (6).

Mono acetate (+)-**22**: colourless oil, $[\alpha]_D^{20} = +2.5$ (c 2, $CHCl_3$), 98% chemical purity by GC, 32% ee by chiral GC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 1H), 4.63 (s, 1H), 4.39 (dd, J = 11.3, 9.3 Hz, 1H), 4.33 (dd, J = 11.3, 4.2 Hz, 1H), 3.45 (dd, J = 8.4, 3.8 Hz, 1H), 2.41 (dt, J = 13.6, 5.8 Hz, 1H), 2.13 (dd, J = 9.3, 4.2 Hz, 1H), 2.11–1.98 (m, 1H), 2.02 (s, 3H), 1.91–1.81 (m, 1H), 1.62–1.50 (m, 2H), 1.07 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (100 MHz) δ 171.1, 145.6, 109.8, 76.1, 62.6, 50.7, 39.2, 31.4, 30.9, 26.0, 21.0, 17.4. IR (film, cm^{-1}) 3464, 1736, 1649, 1443, 1384, 1367, 1252, 1078, 1025, 892. GC–MS *m/z* (rel intensity) 152 (M$^+$–AcOH, 51), 134 (77), 119 (100), 110 (67), 107 (68), 93 (61), 81 (56), 71 (36), 67 (43), 55 (25).

Mono acetate (−)-**23**: colourless oil, $[\alpha]_D^{20} = -52.5$ (c 2, $CHCl_3$), 98% of chemical purity by GC, 89% ee by chiral GC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.81 (s, 1H), 4.70 (dd, J = 5.8, 3.5 Hz, 1H), 3.86 (t, J = 10.8 Hz, 1H), 3.74 (dd, J = 10.8, 3.9 Hz, 1H), 2.40–2.30 (m, 1H), 2.15–2.04 (m, 2H), 2.06 (s, 3H), 1.91–1.80 (m, 1H), 1.69 (dq, J = 13.8, 5.8 Hz, 1H), 1.48 (br s, 1H), 1.01 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (100 MHz) δ 170.2, 145.8, 111.8, 77.1, 59.9, 55.8, 37.7, 28.2, 27.7, 26.9, 21.2, 20.7. IR (film, cm^{-1}) 3446, 1736, 1649, 1443, 1373, 1240, 1053, 1023, 896. GC–MS *m/z* (rel intensity) 212 (M$^+$ <1), 195 (<1), 152 (M$^+$–AcOH, 8), 134 (8), 121 (100), 107 (62), 93 (23), 81 (20), 79 (20), 67 (13), 55 (10).

Diol (+)-**5**: colourless oil, $[\alpha]_D^{20} = +19.9$ (c 1.5, $CHCl_3$), 99% of chemical purity by GC, 22% ee by chiral GC, ^{1}H NMR, ^{13}C NMR, IR and MS: in accordance with those of racemic diol.

The diacetate (−)-**24** was saponified with NaOH in methanol. The product was purified by chromatography to give diol (−)-**5**: colourless oil, $[\alpha]_D^{20} = -47.2$ (c 2, $CHCl_3$); Ref. 6b $[\alpha]_D^{20} = -54.0$ (c 1, $CHCl_3$).

4.3.4. Resolution of 2-hydroxy β-cyclogeraniol 14

The general procedure afforded:

Diacetate (−)-**26**: colourless oil, $[\alpha]_D^{20} = -2.9$ (c 2.5, $CHCl_3$), 96% of chemical purity by GC, 99% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) 4.78 (dd, J = 8.9, 3.3 Hz, 1H), 4.66–4.55 (m, 2H), 2.17–2.10 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 1.89–1.69 (m, 2H), 1.70 (s, 3H), 1.02 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz) δ 171.2, 170.8, 135.4, 130.5, 77.4, 60.8, 37.9, 29.9, 25.8, 23.4, 22.3, 21.2, 21.0, 19.5. IR (film, cm^{-1}) 1738, 1368, 1242, 1021, 954. GC–MS *m/z* (rel intensity) 194 (M$^+$–AcOH, 1), 151 (2), 134 (68), 119 (100), 105 (11), 93 (17), 79 (6), 67 (4), 55 (4).

Acetate (−)-**25**: colourless oil, $[\alpha]_D^{20} = -8.9$ (c 2, $CHCl_3$), 96% of chemical purity by GC, 30% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65–4.57 (m, 2H), 3.53 (dd, J = 8.9, 3.1 Hz, 1H), 2.22–2.07 (m, 2H), 2.04 (s, 3H), 1.89–1.79 (m, 1H), 1.79–1.66 (m, 1H), 1.70 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz) δ 170.8, 134.9, 130.0, 74.9, 60.5, 38.6, 29.4, 25.8, 25.4, 21.1, 20.6, 19.0. GC–MS *m/z* (rel intensity) 194 (M$^+$–H_2O, <1), 152 (M$^+$–AcOH, 55), 137 (34), 123 (44), 119 (50), 109 (72), 93 (100), 81 (26), 67 (23), 55 (15).

Diacetate (−)-**26** was saponified with NaOH in methanol. The product was purified by chromatography and crystallisation from hexane/ether to give diol (+)-**14**: colourless crystals, $[\alpha]_D^{20} = +23.8$ (c 1, $CHCl_3$); mp 126–127 °C.

4.3.5. Resolution of cis 3-hydroxy α-cyclogeraniol 7

The general procedure afforded:

Diacetate (+)-**29**: colourless oil, $[\alpha]_D^{20} = +17.9$ (c 2, $CHCl_3$), 97% of chemical purity by GC, 94% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 5.33–5.24 (m, 1H), 4.29 (dd, J = 11.8, 5.5 Hz, 1H), 4.08 (dd, J = 11.8, 3.4 Hz, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.83–177 (m, 1H), 1.80 (t, J = 1.6 Hz, 3H), 1.69 (dd, J = 13.1, 7.2 Hz, 1H), 1.58 (dd, J = 13.1, 9.3 Hz, 1H), 1.01 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz) δ 170.8, 170.7, 137.8, 122.6, 69.4, 63.2, 49.1, 37.1, 33.8, 27.9, 27.7, 22.6, 21.3, 21.0. IR (film, cm^{-1}) 1736, 1445, 1366, 1238, 1022, 975, 932, 836. GC–MS *m/z* (rel intensity) 194 (M$^+$–AcOH, 10), 169 (9), 152 (53), 137 (77), 119 (100), 109 (40), 96 (47), 91 (29), 79 (11), 69 (6), 55 (4).

Mono acetate (−)-**27**: colourless oil, $[\alpha]_D^{20} = -8$ (c 2, $CHCl_3$), 94% of chemical purity by GC, 7% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (s, 1H), 5.33–5.24 (m, 1H), 3.83–3.73 (m, 2H), 2.03 (s, 3H), 1.86–1.62 (m, 4H), 1.80 (t, J = 1.6 Hz, 3H), 1.08 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz) δ 170.9, 137.7, 123.6, 69.8, 61.2, 52.0, 37.7, 33.8, 28.1, 28.1, 22.5, 21.3. IR (film, cm^{-1}) 3449, 1735, 1649, 1376, 1243, 1023. GC–MS *m/z* (rel intensity) 212 (M$^+$, <1), 194 (M$^+$–H_2O, <1), 170 (6), 152 (17), 137 (23), 121 (74), 107 (100), 96 (66), 91 (42), 81 (21), 67 (9), 60 (7), 53 (6).

Mono acetate (+)-**28**: colourless oil, $[\alpha]_D^{20} = +49.6$ (c 2, $CHCl_3$), 98% of chemical purity by GC, 52% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (br s, 1H), 4.22 (dd, J = 11.8, 5.7 Hz, 1H), 4.21–4.13 (m, 1H), 4.09 (dd, J = 11.8, 3.3 Hz, 1H), 2.04 (s, 3H), 1.79 (t, J = 1.6 Hz, 3H), 1.80–1.69 (m, 2H), 1.65 (ddt, J = 12.8, 6.9, 1.4 Hz, 1H), 1.44 (dd, J = 12.8, 9.7 Hz, 1H), 1.00 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz) δ 170.8, 135.5, 127.0, 66.2, 63.6, 49.1, 41.4, 33.9, 28.1, 27.5, 22.6, 21.0. IR (film, cm^{-1}) 3402, 1740, 1672, 1471, 1447, 1382, 1366, 1235, 1026, 941, 838. GC–MS *m/z* (rel intensity) 169 (3), 152 (M$^+$–AcOH, 10), 137 (100), 119 (25), 109 (51), 96 (45), 84 (10), 77 (7), 69 (21), 55 (6), 43 (34).

Diol (−)-**7**: $[\alpha]_D^{20} = -70.6$ (c 2, $CHCl_3$), 98% chemical purity by GC, 93% ee by chiral GC, ^{1}H NMR, ^{13}C NMR, IR and MS: in accordance with those of racemic diol. The diol (−)-**7** was recrystallised from hexane/ether and its specific rotation value increased to: $[\alpha]_D^{20} = -76.1$ (c 2, $CHCl_3$), 99% ee by chiral GC.

Diacetate (+)-**29** was saponified with NaOH in methanol. The product was purified by chromatography and crystallised from

hexane/ether to give diol (+)-**7**: $[\alpha]_D^{20} = +77.1$ (*c* 2, $CHCl_3$), 99% ee by chiral GC.

4.3.6. Lipase-mediated acetylation of 3-hydroxy β-cyclogeraniol 17

The general procedure afforded:

Diacetate (−)-**31**: colourless oil, $[\alpha]_D^{20} = -20.8$ (*c* 1, MeOH), Ref. 21a $[\alpha]_D^{20} = -50.0$ (*c* 1.02, MeOH); 97% of chemical purity by GC, 27% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09–4.99 (m, 1H), 4.57 (s, 2H), 2.44 (dd, *J* = 17.1, 5.5 Hz, 1H), 2.12 (dd, *J* = 17.1, 9.6 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.76 (ddd, *J* = 12.3, 3.5, 2.1 Hz, 1H), 1.70 (s, 3H), 1.59 (t, *J* = 12.3 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz) δ 171.1, 170.6, 132.7, 132.2, 68.1, 60.2, 43.8, 38.3, 36.3, 28.8, 28.2, 21.3, 20.9, 19.5. IR (film, cm^{-1}) 1736, 1365, 1240, 1024, 957. GC–MS *m/z* (rel intensity) 194 (M^+−AcOH, 13), 152 (3), 134 (34), 119 (100), 105 (10), 91 (10), 79 (4), 67 (3), 55 (3).

Mono acetate (+)-**30**: colourless oil, $[\alpha]_D^{20} = +15.6$ (*c* 0.5, $CHCl_3$), 98% chemical purity by GC, 10% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 2H), 4.04–3.93 (m, 1H), 2.36 (ddd, *J* = 16.8, 5.5, 1.7 Hz, 1H), 2.09–2.00 (m, 1H), 2.04 (s, 3H), 1.75 (ddd, *J* = 12.1, 3.5, 2.1 Hz, 1H), 1.70 (s, 3H), 1.60 (br s, 1H), 1.48 (t, *J* = 12.1 Hz, 1H), 1.06 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (100 MHz) δ 171.3, 133.3, 132.1, 64.8, 60.3, 48.1, 42.3, 36.8, 29.0, 28.5, 21.0, 19.6. IR (film, cm^{-1}) 3391, 1736, 1365, 1233, 1023, 955. GC–MS *m/z* (rel intensity) 152 (M^+−AcOH, 93), 137 (55), 119 (100), 109 (45), 93 (34), 81 (15), 67 (26), 55 (14).

4.3.7. Resolution of cis 4-hydroxy γ-cyclogeraniol 10

The general procedure afforded:

Diacetate (−)-**34**: colourless oil, $[\alpha]_D^{20} = -16.7$ (*c* 2, $CHCl_3$), 97% chemical purity by GC, 92% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (dd, *J* = 8.6, 4.7 Hz, 1H), 5.13 (s, 1H), 4.80 (s, 1H), 4.32 (dd, *J* = 10.9, 4.7 Hz, 1H), 4.21 (dd, *J* = 10.9, 9.4 Hz, 1H), 2.25 (dd, *J* = 9.4, 4.7 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.93–1.79 (m, 1H), 1.70–1.55 (m, 2H), 1.47–1.36 (m, 1H), 1.02 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (100 MHz) δ 171.0, 169.8, 143.3, 110.5, 73.9, 62.7, 50.3, 35.7, 34.1, 28.8, 28.6, 23.2, 21.2, 20.9. IR (film, cm^{-1}) 1743, 1651, 1369, 1238, 1040, 970, 903. GC–MS *m/z* (rel intensity) 194 (M^+−AcOH, 10), 179 (2), 152 (68), 134 (100), 119 (77), 107 (28), 91 (29), 79 (19), 67 (7), 55 (9).

Mono acetate (+)-**33**: colourless oil, $[\alpha]_D^{20} = +28.1$ (*c* 2, $CHCl_3$), 96% of chemical purity by GC, 90% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (br s, 1H), 4.76 (br s, 1H), 4.38 (dd, *J* = 11.1, 9.4 Hz, 1H), 4.29 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.06 (dd, *J* = 8.3, 4.5 Hz, 1H), 2.15 (dd, *J* = 9.4, 4.5 Hz, 1H), 2.06 (br s, 1H), 2.02 (s, 3H), 1.93–1.83 (m, 1H), 1.62–1.49 (m, 2H), 1.44–1.31 (m, 1H), 1.01 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz) δ 171.3, 148.5, 107.9, 72.7, 63.1, 50.4, 36.7, 34.5, 31.9, 28.9, 22.7, 21.0. IR (film, cm^{-1}) 3452, 1733, 1368, 1239, 1036, 903. GC–MS *m/z* (rel intensity) 194 (M^+−H_2O, 4), 152 (M^+−AcOH, 90), 137 (61), 123 (40), 119 (50), 109 (73), 96 (52), 91 (38), 83 (100), 70 (42), 55 (47).

Mono acetate (−)-**32**: colourless oil, $[\alpha]_D^{20} = -14.9$ (*c* 2, $CHCl_3$), 98% of chemical purity by GC, 76% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (br s, 1H), 5.21 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.96 (br s, 1H), 3.81–3.75 (m, 2H), 2.15–2.07 (m, 1H), 2.08 (s, 3H), 1.92–1.81 (m, 1H), 1.74–1.64 (m, 1H), 1.65–1.55 (m, 1H), 1.48 (br s, 1H), 1.34 (ddd, *J* = 13.8, 7.9, 4.5 Hz, 1H), 0.99 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (100 MHz) δ 169.9, 143.9, 112.8, 74.3, 60.5, 54.6, 34.6, 33.9, 28.5, 24.1, 21.3. IR (film, cm^{-1}) 3446, 1743, 1652, 1368, 1243, 1043, 901. GC–MS *m/z* (rel intensity) 182 (3), 152 (M^+−AcOH, 5), 139 (30), 122 (100), 107 (91), 93 (47), 79 (28), 67 (10), 55 (11).

Diol (+)-**10**: $[\alpha]_D^{20} = +29.7$ (*c* 2, $CHCl_3$), mp 116–117; 98% of chemical purity by GC, >99% ee by chiral GC, ^{1}H NMR, ^{13}C NMR, IR and MS: in accordance with those of racemic diol.

Diacetate (−)-**34** was saponified with NaOH in methanol. The product was purified by chromatography and crystallisation from hexane/ether to give diol (−)-**10**: colourless crystals, $[\alpha]_D^{20} = -28.9$ (*c* 2, CH_2Cl_2); mp 114–116 °C, 99% ee by chiral GC.

4.3.8. Lipase-mediated acetylation of 4-hydroxy β-cyclogeraniol 19

The general procedure afforded:

Diacetate (+)-**37**: colourless oil, $[\alpha]_D^{20} = +18.6$ (*c* 2, $CHCl_3$), 98% of chemical purity by GC, 19% ee by chiral GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (t, *J* = 5.1 Hz, 1H), 4.65–4.56 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 1.97–1.87 (m, 1H), 1.78–1.55 (m, 2H), 1.66 (s, 3H), 1.48–1.39 (m, 1H), 1.06 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (100 MHz) δ 171.1, 170.8, 138.4, 133.1, 72.1, 60.5, 34.7, 34.4, 27.7, 26.8, 25.3, 21.2, 20.9, 16.2. IR (film, cm^{-1}) 1736, 1370, 1230, 1023, 964, 870. GC–MS *m/z* (rel intensity) 194 (M^+−AcOH, 4), 152 (100), 137 (18), 119 (25), 109 (11), 91 (9), 79 (5), 67 (3), 55 (3).

A mixture of monoacetate **35** and **36** (6:4 ratio, respectively); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (t, *J* = 5.0 Hz, 1H), 4.63–4.54 (m, 2H), 4.20–4.14 (m, 2H), 3.98 (t, *J* = 5.0 Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 1.96–1.84 (m, 2H), 1.80 (s, 3H), 1.75 (s, 3H), 1.76–1.57 (m, 6H), 1.46–1.37 (m, 2H), 1.12 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H). GC–MS *m/z* (rel intensity):

t_R(**36**) 16.72: 194 (M^+−H_2O, 1), 152 (100), 139 (22), 121 (27), 107 (32), 95 (16), 81 (12), 67 (9), 55 (7), 43 (28).

t_R(**35**) 16.83: 194 (M^+−H_2O, 1), 152 (100), 137 (59), 124 (41), 109 (60), 96 (37), 81 (21), 67 (23), 55 (16), 43 (55).

4.4. Conversion of enantiopure diol 4 into enantiopure diol 5

The photoisomerization procedure described for the conversion of racemic **4** into racemic **5** was used also for the transformation of the corresponding enantiopure compounds. Accordingly, diol (−)-**4** ($[\alpha]_D^{20} = -57.4$ (*c* 2, CH_2Cl_2)) gave diol (+)-**5** (yield 78%, $[\alpha]_D^{20} = +46.9$ (*c* 2, $CHCl_3$)) and diol (+)-**4** ($[\alpha]_D^{20} = +57.8$ (*c* 2, CH_2Cl_2)) gave diol (−)-**5** (yield 75%, $[\alpha]_D^{20} = -48.1$ (*c* 2, $CHCl_3$)); Ref. 6a $[\alpha]_D^{20} = +46.6$ (*c* 1.02, CH_2Cl_2), Ref. 6b $[\alpha]_D^{20} = -54.0$ (*c* 1, $CHCl_3$).

4.5. Synthesis of karahana ether and karahana lactone

p-Toluenesulphonyl chloride (0.92 g, 4.8 mmol) was added portion-wise to a stirred solution of diol (−)-**5** ($[\alpha]_D^{20} = -47.2$ (*c* 2, $CHCl_3$), 99% ee by chiral GC, 0.8 g, 4.7 mmol) in pyridine (20 mL). After 5 h, the mixture was diluted with ether (100 mL) and washed in turn with 1 N aq HCl solution (200 mL), saturated $NaHCO_3$ solution (50 mL) and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was bulb-to-bulb distilled to give pure (−)-**38** (0.61 g, 85%), $[\alpha]_D^{20} = -79.9$ (*c* 0.6, CH_2Cl_2), Ref. 6b $[\alpha]_D^{20} = -68.0$ (*c* 1, pentane), 97% chemical purity by GC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (t, *J* = 2.2 Hz, 1H), 4.55 (t, *J* = 2.2 Hz, 1H), 4.02 (dd, *J* = 8.2, 4.6 Hz, 1H), 3.80 (d, *J* = 8.2 Hz, 1H), 3.75 (d, *J* = 3.9 Hz, 1H), 2.48–2.35 (m, 1H), 2.31 (d, *J* = 4.6 Hz, 1H), 2.12 (dd, *J* = 15.5, 6.9 Hz, 1H), 1.79–1.70 (m, 1H), 1.70–1.59 (m, 1H), 1.08 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz) δ 149.0, 107.4, 82.4, 71.1, 54.0, 42.2, 28.6, 25.8, 25.4, 20.8. IR (film, cm^{-1}) 3072, 1646, 1446, 1388, 1368, 1240, 1066, 1035, 979, 911, 885, 874. GC–MS *m/z* (rel intensity) 152 (M^+, 3), 134 (4), 121 (57), 107 (100), 95 (15), 93 (22), 91 (24), 81 (17), 79 (35), 67 (18), 53 (10), 41 (17).

A solution of the above described diol (−)-**5** (0.9 g, 5.3 mmol) in CH_2Cl_2 (50 mL) was treated with bis-acetoxyiodobenzene (BAIB, 5 g, 15.5 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 0.2 g, 1.3 mmol) and stirred at rt until no more starting material was detected by TLC analysis (4 h). The mixture was then poured in ice (100 g), treated with satd aq $Na_2S_2O_3$ soln (100 mL) and

extracted with Et_2O (2 × 150 mL). The combined organic phases were washed with satd aq $NaHCO_3$ soln (100 mL) and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ether (95:5–4:1) as eluent to afford pure (−)-**39** (0.78 g, 89%) as a colourless oil that crystallised on standing, $[\alpha]_D^{20} = -288.1$ (*c* 1, $CHCl_3$), mp 55–56 °C, 98% ee by chiral GC; Ref. 6b $[\alpha]_D^{20} = -295.0$ (*c* 1, $CHCl_3$), mp 57.5–58.5 °C, 98% chemical purity by GC, ^{1}H NMR (400 MHz, CDCl3) δ 4.90 (br s, 1H), 4.83 (br s, 1H), 4.33 (d, *J* = 4.0 Hz, 1H), 2.75 (s, 1H), 2.46–2.32 (m, 1H), 2.32 (dd, *J* = 15.8, 7.5 Hz, 1H), 2.04–1.94 (m, 1H), 1.87–1.75 (m, 1H), 1.17 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (100 MHz) δ 176.6, 139.8, 112.6, 85.2, 59.3, 42.4, 25.5, 25.1, 24.5, 20.0. IR (film, cm^{-1}) 1781, 1653, 1394, 1374, 1340, 1293, 1253, 1137, 1035, 945. GC–MS *m/z* (rel intensity) 166 (M^+, 1), 137 (2), 122 (24), 107 (100), 91 (35), 79 (39), 67 (8), 53 (5), 41 (7), 38 (8).

Following the procedures described above, diol (+)-**5** ($[\alpha]_D^{20} = +46.9$ (*c* 2, $CHCl_3$), 99% ee by chiral GC) was converted into (+)-karahana ether **38** (yield 83%, $[\alpha]_D^{20} = +78.1$ (*c* 1, CH_2Cl_2), Ref. 6a $[\alpha]_D^{20} = +76.6$ (*c* 0.88, CH_2Cl_2)) and into (+)-karahana lactone **39** (yield 90%, $[\alpha]_D^{20} = +277.5$ (*c* 1, $CHCl_3$), Ref. 6a $[\alpha]_D^{20} = +260.5$ (*c* 0.9, CH_2Cl_2)).

4.6. Synthesis of crocusatin C

A sample of diol (−)-**7** ($[\alpha]_D^{20} = -76.1$ (*c* 2, $CHCl_3$), 99% ee by chiral GC, 0.4 g, 2.3 mmol) was dissolved in CH_2Cl_2 (25 mL) and treated with MnO_2 (2 g, 23 mmol) stirring at rt for 4 h. The mixture was then filtered, the organic phase concentrated under reduced pressure and the residue was purified by chromatography (hexane/Et_2O from 9:1 to 2:1) to afford pure (−)-crocusatin C **40** (0.31 g, 80%) as a thick oil that crystallised on standing, mp 78–80 °C, $[\alpha]_D^{20} = -99.1$ (*c* 1, MeOH), Ref. 7 $[\alpha]_D^{20} = -63$ (*c* 0.06, MeOH), 98% of chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 3.99–3.85 (m, 2H), 2.63 (d, *J* = 17.1 Hz, 1H), 2.11 (dd, *J* = 6.6, 4.5 Hz, 1H), 2.04 (d, *J* = 1.2 Hz, 3H), 2.03 (d, *J* = 17.1 Hz, 1H), 2.00 (br t, *J* = 3.8 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (100 MHz) δ 199.9, 161.4, 127.3, 61.4, 53.6, 48.5, 35.3, 29.2, 27.0, 23.9. IR (nujol, cm^{-1}) 3335, 1640, 1377, 1364, 1276, 1068, 889. GC–MS *m/z* (rel intensity) 168 (M^+, 39), 153 (8), 138 (12), 123 (100), 111 (46), 97 (23), 91 (8), 82 (16), 67 (20), 55 (12).

The diol (+)-**7** ($[\alpha]_D^{20} = +77.1$ (*c* 2, $CHCl_3$), 99% ee by chiral GC) was oxidised as described above to give pure (+)-crocusatin C **40**, mp 78–80 °C; $[\alpha]_D^{20} = +99.8$ (*c* 1, MeOH).

4.7. Chemical correlation of 10 with γ-cyclogeraniol

A sample of diol (+)-**10** ($[\alpha]_D^{20} = +29.7$ (*c* 2, $CHCl_3$), 99% ee by chiral GC, 0.9 g, 5.3 mmol) was treated with pyridine (20 mL) and Ac_2O (10 mL) and set aside at rt until acetylation was complete (8 h). The mixture was concentrated under reduced pressure and the residue was dissolved in dry THF (30 mL). The solution obtained was refluxed under a static nitrogen atmosphere in the presence of formic acid (0.75 g, 16.3 mmol), Et_3N (1.65 g, 16.3 mmol), $(PPh_3)_2PdCl_2$ (140 mg, 0.2 mmol) and triphenylphosphine (0.25 g, 0.9 mmol). After the reaction was complete (6 h, TLC analysis), the mixture was diluted with ether (100 mL) and washed with water (50 mL), 5% HCl soln (50 mL), satd aq $NaHCO_3$ soln (50 mL) and brine. The organic phase was concentrated under reduced pressure. The obtained acetate was then dissolved in methanol (10 mL) and treated with NaOH (2 g, 50 mmol) in methanol (10 mL) stirring at rt until no more starting material was detected by TLC analysis. The mixture was diluted with water (60 mL) and extracted with diethyl ether (3 × 50 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography (hexane/Et_2O 9:1) and bulb-to-bulb distillation to give (−)-**41** as a cyclogeraniol isomeric mixture (0.67 g, 82%, 98% of chemical purity) with the following composition: ratio γ/α/β = 97/ 2.9/0.1; $[\alpha]_D^{20} = -21.3$ (*c* 2, $CHCl_3$), Ref. 8b $[\alpha]_D^{20} = -25.0$ (*c* 0.017, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 4.95 (br s, 1H), 4.75 (br s, 1H), 3.76–3.67 (m, 1H), 3.62 (t, *J* = 10.7 Hz, 1H), 2.12 (t, *J* = 6.5 Hz, 2H), 2.04 (dd, *J* = 10.7, 4.6 Hz, 1H), 1.65–1.49 (m, 2H), 1.47–1.38 (m, 1H), 1.37 (br s, 1H), 1.27 (dt, *J* = 13.5, 4.6 Hz, 1H), 0.96 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100 MHz) δ 147.5, 111.5, 59.6, 56.4, 36.4, 33.9, 31.9, 28.5, 26.4, 23.1. IR (film, cm^{-1}) 3371, 1648, 1441, 1029, 889. GC–MS *m/z* (rel intensity) 154 (M^+, 1), 136 (46), 121 (80), 109 (53), 93 (100), 81 (72), 69 (99), 55 (28), 41 (44).

The diacetate (−)-**34** ($[\alpha]_D^{20} = -16.7$ (*c* 2, $CHCl_3$)) was reduced as described above to give (+)-**41** as a cyclogeraniol isomeric mixture (84% yield, 98% of chemical purity) with the following composition: ratio γ/α/β = 96.6/ 3.3/0.1; $[\alpha]_D^{20} = +20.1$ (*c* 2, $CHCl_3$), Ref. 8a $[\alpha]_D^{20} = +23.7$ (*c* 0.31, $CHCl_3$).

4.8. Chemical correlation of 32 with 37

A solution of monoacetate diol (−)-**32** {$[\alpha]_D^{20} = -14.9$ (*c* 2, $CHCl_3$)}, 76% ee by chiral GC, 0.12 g, 0.56 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of Dess–Martin periodinane (0.36 g, 0.85 mmol) in CH_2Cl_2 (10 mL). After complete oxidation (30 min), the reaction mixture was diluted with ether (80 mL) and treated with 10% $Na_2S_2O_3$ solution (50 mL) and saturated $NaHCO_3$ solution (50 mL) stirring vigorously for 15 min. The layers were separated and the organic phase was washed with saturated $NaHCO_3$ and brine then was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and stirred at rt with DBU (0.1 g, 0.66 mmol). After complete isomerization (6 h, TLC analysis), the reaction was diluted with further CH_2Cl_2 (60 mL) and washed with water. The organic layer was concentrated and the residue was dissolved in MeOH (10 mL). The obtained solution was cooled (0 °C) and treated with $NaBH_4$ (25 mg, 0.66 mmol). The reaction mixture was then partitioned between a 1 M aq HCl solution (50 mL) and ethyl acetate (50 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (30 mL). The organic layers were concentrated and the residue, dissolved in pyridine (10 mL) and acetic anhydride (5 mL), was set aside at rt for 12 h. The solvent was then removed in vacuo and the obtained diacetate was purified by chromatography (hexane/Et_2O 9:1) and bulb-to-bulb distillation to afford pure (+)-**37** {$[\alpha]_D^{20} = +62.4$ (*c* 2, $CHCl_3$)}, 97% chemical purity by GC, 0.11 g, 76%) as a colourless oil.

4.9. Chemical correlation of karahana lactone with 14

Diisobutylaluminium hydride (2.3 mL of 1.2 M solution in toluene, 2.76 mmol) was added dropwise under nitrogen to a cooled (−78 °C) solution of (+)-karahana lactone {$[\alpha]_D^{20} = +286.6$ (*c* 1, $CHCl_3$)}, 0.4 g, 2.41 mmol) in toluene (30 mL). The reaction mixture was stirred for 1 h at this temperature, quenched by addition of 1 M aq HCl solution (50 mL) and diluted with ether (100 mL). The layers were separated and the organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in MeOH (40 mL) and stirred at rt in the presence of NaOMe (390 mg, 7.22 mmol). After 2 h, the isomerization reaction was cooled (0 °C) and quenched by dropwise addition of 1 N aq. HCl solution (7.2 mL). To the resulting mixture, $NaBH_4$ (100 mg, 2.64 mmol) was added portion-wise stirring at 0 °C for further 1 h. The reaction was then poured into a mixture of crushed ice and 5% HCl soln (50 mL) and extracted with EtOAc (2 × 100 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed with hexane/ethyl acetate (3:1–1:1) as

eluent and the obtained diol was further purified by crystallisation from hexane/acetate to give pure **14** (0.21 g, 51%, 99% of chemical purity by GC), mp 126–128 °C; $[\alpha]_D^{20} = -24.3$ (*c* 1, $CHCl_3$), ^1H NMR, ^{13}C NMR, IR and MS: in accordance with those of the racemic diol.

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