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Unambiguous Characterization of the Sesquiterpene (7*R*,9*E*)-1,2,11-Trihydroxy-1,3,5,9-bisabolatetraene through Its Enantioselective Synthesis

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The bisabolane sesquiterpene (7*R*,9*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene previously extracted from *Commiphora kua* resins was prepared by enantioselective synthesis using an enzyme-mediated resolution procedure as the key step. Both the chemical structure and the absolute configuration were unambiguously assigned, although the comparison of the obtained analytical data with those previously reported for the isolated terpene indicated a possible error in the characterization of the natural product. A further study on the chemical stability of the aforementioned compound revealed that it is very unstable in an acidic environment, where it cyclizes readily to give the corresponding chromane derivatives.

Introduction

The phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources. They display a wide range of biological activities, which are strictly related to their chemical structures. In particular, minor modification of the molecular framework or switching of the absolute configuration might result in a dramatic change in their activity. Most of these compounds possess a benzylic asymmetric center whose stereoselective introduction is especially demanding from a synthetic point of view. Therefore, only a few of the reported synthetic approaches to these compounds are enantioselective,[1] and the assignment of the absolute configuration of a newly isolated natural product belonging to this class is often tricky, especially if a straightforward chemical conversion into a known compound is not available. To this end, circular dichroism (CD), biosynthetic considerations, or comparison of the sign of optical rotation with those of structurally similar terpenes might help with the tentative assignment of the configuration. Phenolic sesquiterpenes with the structural framework **1** (Figure 1) are quite rare, and to the best of our knowledge, their occurrence in nature is restricted to the three structures **1a**–**c**. Compounds **1a** were first isolated from the aerial part of the plants *Wedelia regis*[2] (angeloyl derivatives) and *Rutidosis murchisonii*[3] (senecioyl derivatives), whereas the bioactive diol parahigginol D[4] (**1b**) was isolated from a marine sponge *Parahigginsia* sp. All the aforementioned studies left the absolute configuration of the identified sesquiterpenes unassigned, as a reliable chemical conversion into a compound of known configuration was unavailable. More recently, 1,2,11-trihydroxy-1,3,5,9-bisabolatetraene[5] (**1c**) was isolated from the resins of the plant *Commiphora kua*, and its configuration was tentatively assigned as *R* on the basis of its CD spectrum. None of the sesquiterpenes described above have been prepared before by chemical synthesis. This means that both the confirmation of their chemical structure and the unambiguous assignment of their absolute configuration are still lacking.

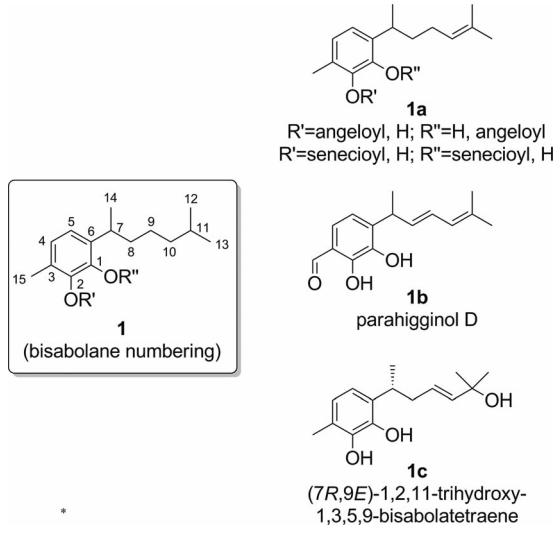

Figure 1. Structure and numbering of the phenolic 1,2-dihydroxy-bisabolane sesquiterpenes.

Taking advantage of our previous experience[6–10] in the enantioselective synthesis of phenolic sesquiterpenes, we decided to investigate a synthetic approach to **1c**, which seems

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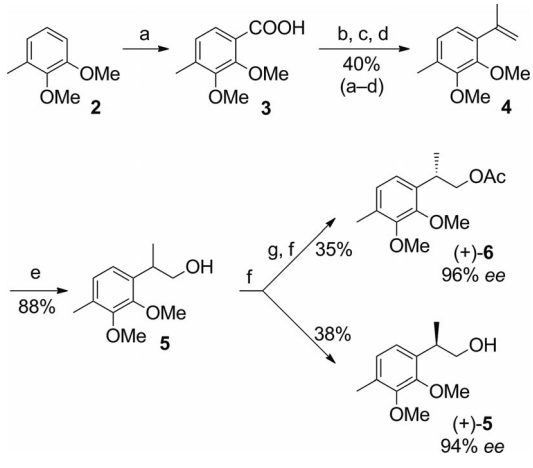
to be the most well-characterized compound among the aforementioned class of terpenes. In this paper, we describe the accomplishment of this plan by reporting the first enantioselective synthesis of (–)-**1c**. The comparison of the analytical data obtained with those previously reported indicated a possible error in the characterization of the natural product. A further study involving degradation of the sesquiterpene was thus undertaken. This revealed that **1c** is very unstable in an acidic environment, cyclizing readily to give chromane derivative **12**, whose analytical data could account for some of the discrepancies observed.

Results and Discussion

A reliable synthesis of a natural product to be used in structural determination should give the desired compound as a single isomer. For **1c**, two challenging aspects of the synthesis are the enantioselective preparation of the *R*-configured benzylic stereocenter, and the avoidance of the formation of other isomers (regioisomers and/or geometrical isomers) during the construction of the molecular framework. Recently, we developed a chemo-enzymatic process[10] that allows the resolution of 2-arylpropanols. The key step of the method is the irreversible lipase-mediated acetylation of the primary alcohol, and the enantioselectivity of this step is strongly dependent on the substitution pattern of the aromatic ring. We found porcine pancreatic lipase (PPL) to be the most enantioselective catalyst suitable for this purpose, preferentially acetylating the *S* enantiomers. Substituents in the position *para* to the aliphatic chain and methoxy substituents both greatly increased the selectivity of the enzyme. We envisaged that 2-arylpropanol **5** (Scheme 1) could be efficiently resolved by this protocol, since its aromatic substitution pattern fulfills all the requirements described above.

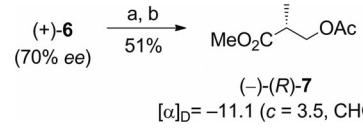


Scheme 1. Synthesis and enzyme-mediated resolution of 2-(2,3-dimethoxy-4-methylphenyl)propan-1-ol. Reagents and conditions: (a) BuLi, TMEDA, hexane, r.t., 24 h, then CO_2, –78 °C; (b) MeOH, conc. H_2SO_4, reflux, 4 h; (c) MeMgBr, THF; (d) cat. PTSA, benzene, reflux; (e) $BH_3{\cdot}SMe_2$, THF, r.t., 2 h, then $NaOH/H_2O_2$; (f) PPL, vinyl acetate, *t*BuOMe, then chromatographic separation; (g) NaOH, MeOH, reflux.

Thus, we devised a large-scale preparation of racemic **5** starting from commercially available 1,2-dimethoxy-3-methylbenzene (**2**). Dimethyl ether **2** was metalated[11] regioselectively at position 6 of the aromatic ring by reaction with butyllithium and tetramethylethylenediamine (TMEDA) in hexane at room temperature. The aryllithium derivative was then quenched with CO_2 at low temperature, and the resulting benzoic acid (i.e., **3**) was converted in the corresponding methyl ester by treatment with methanol and concentrated H_2SO_4. The ester was treated with excess methylmagnesium bromide, and the resulting crude dimethyl alcohol was dehydrated by heating in refluxing benzene in the presence of a catalytic amount of *para*-toluenesulfonic acid (PTSA). The resulting styrene derivative **4** was hydroborated by reaction with $BH_3{\cdot}SMe_2$. The organoborane intermediate was then oxidized in situ with H_2O_2 in the presence of NaOH to give alcohol **5** in very good yield and with almost complete regioselectivity.

The reactivity of this substrate in the PPL-mediated irreversible acetylation was tested by treatment of the alcohol with vinyl acetate in *tert*-butyl methyl ether in the presence of the enzyme at room temperature. In a preliminary experiment, the reaction was interrupted at a conversion of about 50%, and the acetate product had 76%*ee*. This data allowed the calculation of the enantiomeric ratio (*E*)[12] of the reaction, and the value of 17 is in good agreement with results previously obtained with structurally analogous substrates.

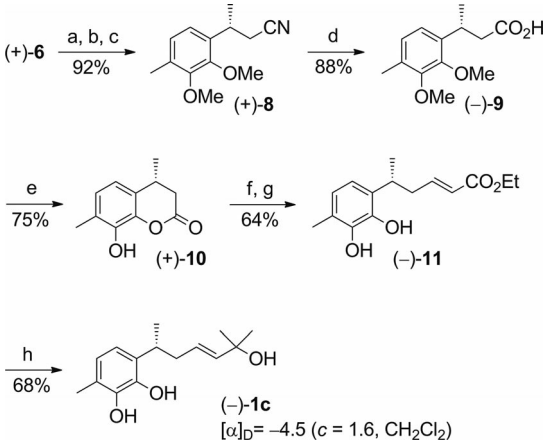
In order to obtain both enantiomeric forms of **5** in high *ee*, we prolonged the reaction time until the acetylation reached about 60% conversion. The unreacted alcohol [i.e., (+)-**5**, 94%*ee*, 38% yield] was separated by chromatography. Acetate (+)-**6** was hydrolyzed and the resulting enantiomerically enriched alcohol was submitted again to the PPL-mediated acetylation process until a conversion of about 60% was reached. Chromatographic separation gave (+)-**6** (96%*ee*, 35% yield). By this protocol, we obtained both the isomeric forms of **5** in high enantiomeric purity. Even though PPL usually catalyzes the acetylation of *S*-configured 2-aryl propanols, the absolute configuration of acetate (+)-**6** had to be unambiguously assigned. Thus, we degraded acetate (+)-**6** into methyl 3-acetoxy-2-methylpropanoate (–)-**7** (Scheme 2). A sample of (+)-**6** (70%*ee*) was oxidized with sodium periodate in the presence of a catalytic amount of ruthenium trichloride,[13,14] and the re-



Scheme 2. Chemical degradation of acetate (+)-**6** into (–)-(*R*)-3-acetoxy-2-methylpropanoate (**7**). Reagents and conditions: (a) $NaIO_4$, CH_3CN/CCl_4, H_2O, cat. $RuCl_3{\cdot}nH_2O$, 48 h; (b) CH_2N_2, Et_2O, 0 °C, 1 h.

sulting acid was treated with diazomethane. This degradative procedure afforded (–)-**7** of known[15] *R* absolute configuration, thus confirming our assumption about the lipase enantioselectivity.

As a result, we used (+)-**6** as a chiral building block for the synthesis of **1c** (Scheme 3). The acetate was homologated to acid (–)-**9** by a four-step process. Compound (+)-**6** was hydrolyzed, and the resulting alcohol was converted into the corresponding tosylate. This was heated with NaCN in DMSO, and the nucleophilic substitution reaction afforded cyano derivative (+)-**8**, which was hydrolyzed with NaOH in diethylene glycol/water at reflux. The resulting acid [i.e., (–)-**9**] was treated with boron tribromide in dichloromethane, which allowed the deprotection of the two methyl ether groups, and simultaneous lactone ring closure gave (+)-**10** in good yield. This compound was reduced with diisobutylaluminum hydride (DIBALH; 2 equiv.) at low temperature (–78 °C) to give the corresponding lactol. This intermediate was not isolated, but was treated with an excess of (carbethoxymethylene)triphenylphosphorane to give ester (–)-**11** as an inseparable 9:1 mixture of *E*/*Z* isomers. Since the natural terpene consists of the *E* isomer only, we had to remove the unwanted compound (*Z*)-**11**. Luckily, we found that chromatographic purification of the crude target compound obtained in the following step allowed the isolation of **1c** in isomerically pure form. Therefore, we treated impure (–)-**11** with an excess of methyllithium, and then proceeded with the chromatographic procedure to obtain pure (–)-**1c** in good yield. The chemical structure of the resulting compound was confirmed by ^{1}H- and ^{13}C NMR spectroscopic analysis, whose complete spectral assignment was performed by HSQC and HMBC experiments (see Table 1).



Scheme 3. Stereoselective synthesis of sesquiterpene (–)-(7*R*,9*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene (**1c**). Reagents and conditions: (a) NaOH, MeOH, reflux; (b) TsCl, Py, CH_2Cl_2; (c) NaCN, DMSO, 80 °C, 3 h; (d) NaOH, diethylene glycol, H_2O, reflux, 2 h; (e) BBr_3, CH_2Cl_2, r.t., 3 h; (f) DIBALH, toluene, –78 °C then 0 °C, 1 h; (g) Ph_3PCHCO_2Et, CH_2Cl_2, reflux 3 h; (h) MeLi, diethyl ether, 0 °C then r.t., 2 h.

Thus, our chemical synthesis unambiguously assigns the *R* absolute configuration to (–)-(*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene **1c**, confirming the previously reported results based on CD study. In spite of this fact, we have to report a number of discrepancies between our analytical data and those recorded in the natural product study. First of all, we measured an optical rotation value of –4.5 (c = 1.6, CH_2Cl_2) for a sample of **1c** with 96%*ee*, whereas the isolated natural compound had an optical rotation value of –35 (c = 1.0, CH_2Cl_2). In addition, although our NMR spectroscopic data were, for the most part, in good agreement with those reported for the natural product, there are three ^{13}C NMR signals described in the latter study (Table 1) that do not match our data, and neither do they match the data from a simulated ^{13}C NMR spectrum.

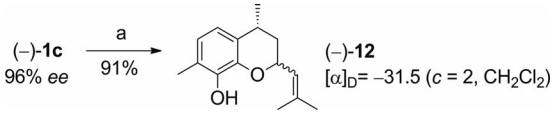
These signals are due to carbons 7, 8 and 15 of the bisabolane framework, and are all in allylic or benzylic positions. This points to the possibility of a 1,3-allylic transposition of the oxygen atom and thus of the formation of a

Table 1. NMR spectroscopic data of synthetic and natural (–)-(7*R*,9*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene (**1c**) and cyclized compound **12**.

Position[a]	Synthetic **1c** δ_C ($CDCl_3$) 125 MHz	δ_H ([D$_6$]benzene) 400 MHz	Natural **1c**[b] δ_C ($CDCl_3$) 100 MHz	δ_H ([D$_6$]benzene) 400 MHz	**12**[c] δ_C ($CDCl_3$) 125 MHz
1	141.6	5.76 and 5.50	141.4	7.20 (s, 2 H)	141.5
2	142.2	(2 br. s, OH)	142.0		143.0
3	122.0		122.0		121.5
4	122.2	6.66 (s, 2 H)	123.5	6.85 (d, J = 7.5 Hz, 1 H)	122.0
5	118.2		118.2	7.02 (d, J = 7.5 Hz, 1 H)	117.2
6	131.3		131.4		124.8
7	32.9	3.26–3.12 (m, 1 H)	39.3	2.70 (tq, J = 6.9, 6.9 Hz, 1 H)	29.5
8	40.1	2.38–2.18 (m, 2 H)	37.5	not reported	38.2
9	126.0	5.57 (dt, J = 15.6, 7.1 Hz, 1 H)	124.7	5.50 (ddd, J = 15.5, 6.5, 6 Hz, 1 H)	74.0
10	139.2	5.44 (br. d, J = 15.6 Hz, 1 H)	138.2	5.46 (br. d, J = 15.5 Hz, 1 H)	124.9
11	71.2		72.6		137.3
12	29.6[d]	1.12 and 1.08 (2s, 3 H each)	29.4	1.20 (s, 6 H)	25.8
13	29.7[d]		30.1		18.5
14	20.4	1.25 (d, J = 7.0 Hz, 3 H)	22.0	1.25 (d, J = 6.6 Hz, 3 H)	20.3
15	15.6	2.09 (s, 3 H)	18.7	2.10 (s, 3 H)	15.3

[a] Bisabolane numbering. [b] Data reported in ref.[5] [c] Data of the major diastereoisomer. [d] These NMR signals could be switched.

degradation product during acquisition of the ^{13}C NMR spectra. In order to test our theory, we checked the acid-catalyzed degradation of **1c**. A sample of (–)-**1c** was dissolved in $CHCl_3$ and treated at room temperature with a catalytic amount of PTSA (Scheme 4).



Scheme 4. Acid-catalyzed cyclization of (–)-(7*R*,9*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene (**1c**). Reagents and conditions: (a) cat. PTSA, $CHCl_3$, r.t., 30 min.

We observed the rapid and quantitative formation of bicyclic ether (–)-**12** as a 2:1 mixture of diastereoisomers. This experiment confirms the chemical instability of **1c** in an acidic environment. Even though the ^{13}C NMR spectrum of compound **12** (Table 1) does not account for the misleading signals described for the natural product, we measured an optical rotation value of –31.5 (c = 2, CH_2Cl_2) for the mixture of diastereoisomers of **12** that might explain the difference between our data and that previously reported for **1c**. It is possible that the isolated natural sample was impure (thus explaining the misleading signals), and it may have slowly degraded after the NMR spectroscopic analysis had been performed. Nevertheless, none of these sensible considerations can allow a definitive statement on the chemical and optical purity of the natural compounds whose unambiguous determination requires further investigation.

Conclusions

We report here the first enantioselective synthesis of (–)-(*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene (**1c**) and the unambiguous assignment of its absolute configuration as *R*. Careful comparison of the obtained analytical data with those reported for the isolated terpene indicated a possible error in the characterization of the natural product. Studying the acid-catalyzed degradation of synthetic **1c** revealed that this sesquiterpene is very unstable, cyclizing readily to give chromane derivative **12**, whose analytical data could account for some of the discrepancies observed.

Experimental Section

General Methods: All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. Lipase from porcine pancreas (PPL) type II, Sigma, 147 units/mg was used in this work. TLC: Merck silica gel 60 F_{254} plates. Column chromatography: silica gel. GC–MS analysis: HP-6890 gas chromatograph equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm, 0.25 μm film thickness; Hewlett–Packard) with the following temperature program: 60 °C (1 min), then 6 °C/min to 150 °C (1 min), then 12 °C/min to 280 °C (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1:30; t_R given in min: t_R (**3**) = 20.11, t_R (**4**) = 13.64, t_R (**5**) = 18.70, t_R (**6**) = 20.60, t_R (**7**) = 8.06, t_R (**8**) = 20.49, t_R (**9**) = 21.53, t_R (**10**) = 20.51, t_R (**11**) = 24.46, t_R (**12**) = 23.40 (minor diastereoisomer) and 23.67 (major diastereoisomer); mass spectra: *m/z* (%); Mass spectrum of compound **1c** was recorded with a Bruker ESQUIRE 3000 PLUS spectrometer (ESI ionization). Chiral HPLC analysis: Merck–Hitachi L-7100 equipped with a Merck–Hitachi L-4250 UV/Vis detector, constant flow, detector 210 nm, t_R given in min; with the following elution conditions: compound **6**: flow 1 mL/min, eluent hexane/*i*PrOH, 99:1 t_R [(*S*)-(**+**)-**6**] = 8.6, t_R [(*R*)-(–)-**6**] = 9.2. Optical rotations: Jasco-DI-181 digital polarimeter. ^1H and ^{13}C NMR spectra: recorded at room temperature; Bruker AC-400 spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm relative to internal $SiMe_4$ (0 ppm), J values in Hz. The complete ^{13}C NMR signal assignment for compounds **1c** and **12** was performed by HSQC (heteronuclear single quantum coherence) and HMBC (heteronuclear multiple-bond correlation) experiments using a Bruker AC-500 spectrometer at 500 and 125 MHz. Melting points were measured with a Reichert apparatus, equipped with a Reichert microscope.

Lipase-Mediated Resolution of Racemic 2-(2,3-Dimethoxy-4-methylphenyl)propan-1-ol (5): A solution of racemic 2-(2,3-dimethoxy-4-methylphenyl)propan-1-ol (6.3 g, 30 mmol), PPL (5 g), vinyl acetate (15 mL), and *t*BuOMe (60 mL) was stirred at room temperature, and the formation of acetylated compounds was monitored by TLC analysis. The reaction was stopped when the acetylation had reached a conversion of about 65% (GC analysis), by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was then purified by chromatography using hexane/diethyl ether (95:5–3:1) as eluent. The resulting alcohol (*R*)-(+)-**5** (2.40 g, 38%) gave the following analytical data: 97% purity by GC, 94%*ee* by chiral HPLC. $[a]_D^{20}$ = +14.8 (c = 2.2, $CHCl_3$). The resulting acetate (+)-**6** was treated with NaOH (2 g, 50 mol) in MeOH (40 mL) at reflux for 1 h. After work-up, the resulting alcohol was submitted again to the resolution procedure, allowing the acetylation reaction to reach a conversion of about 60%. The resulting acetate (*S*)-(+)-**6** (2.65 g, 35%) gave the following analytical data: 99% purity by GC, 96%*ee* by chiral HPLC; colorless oil. $[a]_D^{20}$ = +24.9 (c = 2.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 (dd, J = 8.0, 0.4 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 4.19–4.09 (m, 2 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.54–3.43 (m, 1 H), 2.24 (d, J = 0.4 Hz, 3 H), 2.00 (s, 3 H), 1.25 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 151.4, 151.1, 134.8, 130.5, 125.6, 121.7, 69.0, 60.6, 59.8, 31.8, 20.8, 17.8, 15.6 ppm. GC–MS (EI): *m/z* (%) = 252 (16) $[M]^+$, 192 (39), 179 (90), 177 (100), 164 (65), 149 (21), 135 (5), 119 (10), 105 (5), 91 (14), 77 (7).

Hydrolysis of (+)-**6** (using NaOH in MeOH) afforded (–)-**5**, which gave the following analytical data: 99% purity by GC, 96%*ee* by chiral HPLC; colorless oil. $[a]_D^{20}$ = –15.4 (c = 3.8, $CHCl_3$).

(*R*)-3-(2,3-Dimethoxy-4-methylphenyl)butanenitrile (8): A solution of *p*-toluenesulfonyl chloride (3 g, 15.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of alcohol (–)-**5** {$[a]_D^{20}$ = –15.4 (c = 3.8, $CHCl_3$), 98%*ee*, 2.6 g, 12.4 mmol} in pyridine (5 mL). After 4 h, the mixture was diluted with diethyl ether (100 mL), and washed in turn with 1 N aq. HCl solution (100 mL), saturated $NaHCO_3$ solution (50 mL) and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in dry DMSO (40 mL) and treated with NaCN (3.1 g, 63.3 mmol), stirring at 80–90 °C until the starting tosylate could no longer be detected by TLC analysis (3 h). The mixture was diluted with diethyl ether (100 mL), and washed in turn with water and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was then purified by chromatography eluting

with n-hexane/diethyl ether (95:5–8:2) to afford pure (+)-**8** (2.49 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ = +25.7 (*c* = 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.56–3.44 (m, 1 H), 2.63 (dd, *J* = 16.6, 6.1 Hz, 1 H), 2.53 (dd, *J* = 16.6, 7.8 Hz, 1 H), 2.24 (s, 3 H), 1.40 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 150.6, 134.4, 131.4, 125.8, 121.1, 118.8, 60.6, 59.8, 30.0, 25.3, 19.9, 15.6 ppm. GC–MS (EI): *m*/*z* (%) = 219 (41) $[M]^+$, 179 (100), 164 (39), 149 (9), 136 (2), 119 (6), 103 (2), 91 (10), 77 (6).

(*R*)-3-(2,3-Dimethoxy-4-methylphenyl)butanoic Acid (9): Nitrile (+)-**8** (1.1 g, 5 mmol) was heated with NaOH (2 g, 50 mmol) in diethylene glycol/water, 2:1 (30 mL) at reflux for 2 h. After cooling, the mixture was diluted with water and extracted with diethyl ether. The organic phase was discarded, and the aqueous phase was acidified with 5 N aq. HCl solution and then extracted with CH_2Cl_2. Removal of the solvent in vacuo left a thick oil, which was purified by chromatography, eluting with n-hexane/ethyl acetate (9:1–7:3) to afford pure acid (–)-**9** (1.05 g, 88%). $[\alpha]_D^{20}$ = –14.0 (*c* = 3.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 8.0 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.67–3.56 (m, 1 H), 2.67 (dd, *J* = 15.5, 6.5 Hz, 1 H), 2.54 (dd, *J* = 15.5, 8.4 Hz, 1 H), 2.23 (s, 3 H), 1.27 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 151.4, 150.6, 137.0, 130.4, 125.6, 121.3, 60.5, 59.8, 41.6, 29.6, 21.3, 15.6 ppm. GC–MS (EI): *m*/*z* (%) = 238 (56) $[M]^+$, 205 (6), 192 (4), 179 (100), 164 (39), 149 (10), 135 (5), 119 (8), 105 (4), 91 (14), 77 (6).

(*R*)-8-Hydroxy-4,7-dimethylchroman-2-one (10): Acid (–)-**9** (0.72 g, 3 mmol) was dissolved in dry dichloromethane (40 mL) at 0 °C, and BBr_3 (1.7 g, 6.8 mmol) was added under a nitrogen atmosphere. The reaction mixture was allowed to warm to ambient temperature, and stirred for further 3 h. The reaction was quenched by the addition of water (100 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/diethyl ether (9:1–2:1) to afford pure (+)-**10** (0.43 g, 75%), which solidified on standing. Colorless crystals; m.p. 83–85 °C. $[\alpha]_D^{20}$ = +20.1 (*c* = 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, *J* = 7.8 Hz, 1 H), 6.65 (d, *J* = 7.8 Hz, 1 H), 5.60 (s, 1 H), 3.21–3.10 (m, 1 H), 2.84 (dd, *J* = 15.8, 5.4 Hz, 1 H), 2.57 (dd, *J* = 15.8, 7.5 Hz, 1 H), 2.25 (s, 3 H), 1.32 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 141.9, 138.4, 126.1, 125.6, 124.4, 116.4, 37.0, 29.5, 19.8, 15.3 ppm. GC–MS (EI): *m*/*z* (%) = 192 (45) $[M]^+$, 177 (4), 164 (3), 150 (100), 131 (6), 121 (5), 107 (4), 91 (6), 77 (7).

(*R*)-Ethyl 5-(2,3-Dihydroxy-4-methylphenyl)hex-2-enoate (11): DIBALH (1.7 M in toluene, 3.1 mL) was added dropwise under nitrogen to a stirred solution of lactone (+)-**10** (0.9 g, 4.7 mmol) in dry toluene (20 mL) at –78 °C. The reaction mixture was stirred at 0 °C for 1 h, then diluted with diethyl ether (40 mL), and quenched with a saturated aqueous solution of NH_4Cl (50 mL). The mixture was extracted with diethyl ether (2 × 100 mL), and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), and treated with Ph_3PCHCO_2Et (3 g, 8.6 mmol), stirring at reflux for 3 h. The solvent was removed under reduced pressure, and the residue was then purified by chromatography eluting with n-hexane/diethyl ether (95:5–8:2) to afford (–)-**11** (0.8 g, 64%) as a colorless oil, with an *E*/*Z* ratio of 9:1 (by NMR spectroscopic analysis). $[\alpha]_D^{20}$ = –2.9 (*c* = 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (ddd, *J* = 15.6, 7.7, 6.9 Hz, 1 H), 6.63 (s, 2 H), 5.81 (dt, *J* = 15.6, 1.5 Hz, 1 H), 5.49, 5.12 (two br. s, each 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.26–3.15 (m, 1 H), 2.61–2.51 (m, 1 H), 2.46–2.34 (m, 1 H), 2.21 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.25 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 147.9, 141.8, 141.5, 130.2, 122.4, 121.8, 121.7, 118.3, 60.2, 39.5, 32.1, 20.2, 15.3, 14.2 ppm. GC–MS (EI): *m*/*z* (%) = 264 (98) $[M]^+$, 218 (8), 203 (15), 190 (7), 175 (50), 161 (45), 150 (100), 133 (7), 121 (9), 105 (4), 91 (10), 77 (11).

(7*R*,9*E*)-1,2,11-Trihydroxy-1,3,5,9-bisabolatetraene or (*R*,*E*)-3-(6-hydroxy-6-methylhept-4-en-2-yl)-6-methylbenzene-1,2-diol (1c): MeLi (4 mL of 1.6 M solution in diethyl ether) was added dropwise under nitrogen to a vigorously stirred solution of (–)-**11** (0.6 g, 2.3 mmol) in dry diethyl ether (20 mL). The reaction mixture was kept cool (0 °C) until complete addition of the reagents, after which it was left to reach room temperature, and stirring was continued for a further 2 h. The mixture then was poured onto crushed ice and a saturated aqueous solution of NH_4Cl (40 mL). The pH was adjusted to 6.5 by addition of dilute HCl, and the mixture was extracted with EtOAc (3 × 60 mL). The organic phase was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/EtOAc (9:1–7:3) to afford pure **1c** (0.39 g, 68%) as a colorless oil. $[\alpha]_D^{20}$ = –4.5 (*c* = 1.6, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR spectroscopic data are reported in Table 1. MS (ESI): *m*/*z* = 273.2 $[M + Na]^+$.

(4*R*)-4,7-Dimethyl-2-(2-methylprop-1-enyl)chroman-8-ol (12): A sample of (–)-**1c** (0.1 g, 0.4 mmol) was dissolved in $CHCl_3$ (5 mL) and treated with *p*-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol). After 30 min, the solvent was removed under reduced pressure, and the residue was purified by chromatography eluting with hexane/diethyl ether (95:5–8:2) to afford pure **12** (85 mg, 91%). Colorless oil, 2:1 mixture of diastereoisomers (by GC analysis). $[\alpha]_D^{20}$ = –31.5 (*c* = 2, CH_2Cl_2). Data for the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72–6.62 (m, 2 H), 5.62 (br. s, 1 H), 5.34 (double m, *J* = 8.3 Hz, 1 H), 4.76 (ddd, *J* = 11.4, 8.3, 1.9 Hz, 1 H), 3.08–2.97 (m, 1 H), 2.21 (s, 3 H), 2.00–1.91 (m, 1 H), 1.80 (d, *J* = 1.4 Hz, 3 H), 1.73 (d, *J* = 1.4 Hz, 3 H), 1.70–1.53 (m, 1 H), 1.30 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR spectroscopic data are reported in Table 1. GC–MS (EI): *m*/*z* (%) = 232 (25) $[M]^+$, 217 (6), 199 (2), 189 (4), 175 (7), 163 (7), 150 (100), 131 (5), 121 (3), 107 (5), 91 (9), 77 (13), 67 (12).

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **3**–**5** and **7**, and copies of the ^{1}H NMR and ^{13}C NMR spectra for compounds **4**–**12** and **1c**.

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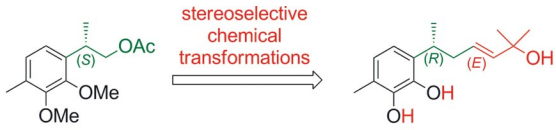

96% *ee*
by lipase-mediated resolution

(7*R*,9*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene
from ***Commiphora kua*** resin

The enantioselective synthesis of the bisabolane sesquiterpene (7*R*,9*E*)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene was accomplished using an enzyme-mediated resolution procedure and a number of stereoselective chemical reactions. Both the chemical structure and the absolute configuration of the natural product were thus unambiguously assigned.

Keywords: Natural products / Terpenoids / Configuration determination / Chiral resolution / Enzymes

