Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1375–1388

TETRAHEDRON: *ASYMMETRY*

A convenient synthesis of (+)-albicanol based on enzymatic function: total syntheses of (+)-albicanyl acetate, (–)-albicanyl 3,4-dihydroxycinnamate, (–)-drimenol, (–)-drimenin and (–)-ambrox

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Received 27 January 2000; accepted 21 February 2000

Abstract

By using lipase 'PL-266' from *Alcaligenes* sp. enantioselective acetylation of (±)-albicanol **4** with isopropenyl acetate gave the enantiomerically pure (+)-albicanyl acetate **3** and (+)-albicanol **4**. Deprotection of (+)-**3** afforded the natural (+)-albicanol **4** which was converted to the natural products (–)-albicanyl 3,4-dihydroxycinnamate **7**, (–)-drimenol **8**, (–)-drimenin **9** and (–)-ambrox **10**.

1. Introduction

The wide variety of biological activities of some drimane sesquiterpenes[1] has focused on the development of general synthetic routes to this class of compounds.[2] Due to the potent antifeedant activity of several members of these groups, including polygodial **1**, warburganal **2** and albicanyl acetate **3**, much attention has been paid to their synthesis both in racemic and optically active forms.[3] While some asymmetric syntheses of **1** and **2** have been achieved by the conversion of higher terpenes such as sclareol,[3] abietic acid[4] and mannol,[2] asymmetric syntheses of **3** and albicanol **4** were carried out by employing enantiomerically pure Wieland–Miescher ketone.[5] A short and efficient synthesis of **1** from **3** has been reported[3a] and drimenyl acetate **5** corresponding to the C_7–C_8 double bond isomer of **3** has been used in the preparation of **1**,[6] **2**[7] and ugandensidial **6**.[8] In this paper, enantioselective syntheses of (–)- and (+)-albicanols **4**, and (+)-albicanyl acetate **3**, based on the enzymatic preparation and application of (+)-**4** into the syntheses of (–)-albicanyl 3,4-dihydroxycinnamate **7**, (–)-drimenol **8**, (–)-drimenin **9** and (–)-ambrox **10**, are described (Scheme 1).

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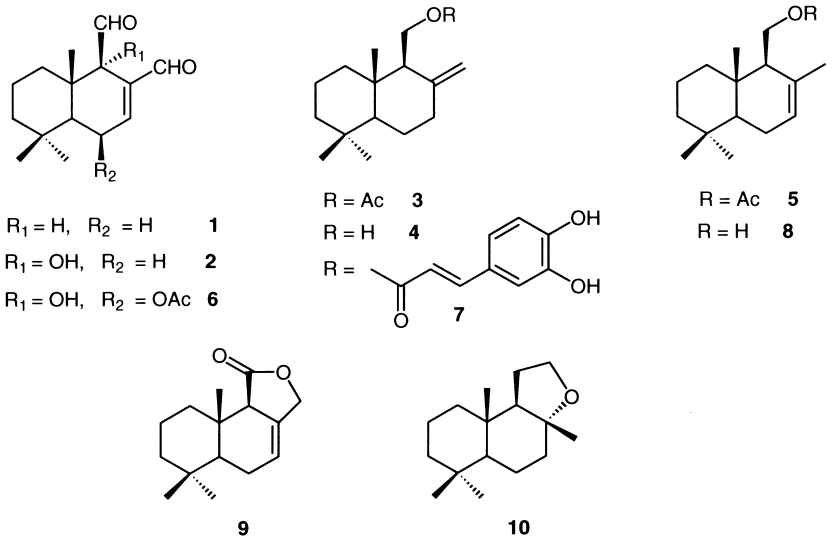
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00076-8

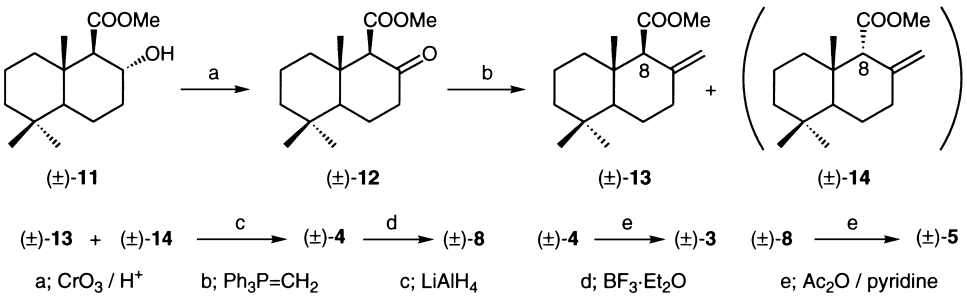


Scheme 1.

2. Results and discussion

2.1. Synthesis of the substrate for enzymatic resolution

Jones oxidation of the β-hydroxy ester (±)-**11**[9] gave the β-keto ester (±)-**12** in 96% yield. The Wittig reaction of **12** with $Ph_3P{=}CH_2$, by applying the reported procedure,[9] provided a 22:1 epimeric mixture of the 8β-methoxycarbonyl-7-methylene compound (±)-**13** and (±)-8α-**14** in 98% yield. The minor epimer (±)-**14** could not be separated by conventional chromatography. $LiAlH_4$ reduction of a 22:1 mixture of (±)-**13**, followed by chromatographic purification, afforded a 37:1 mixture of (±)-**4**, which was recrystallized to provide pure (±)-albicanol **4** in 87% overall yield. Conversion of (±)-**4** into (±)-drimenol **8** was carried out using $BF_3{\cdot}Et_2O$ to provide (±)-**8** in 93% yield (Scheme 2).



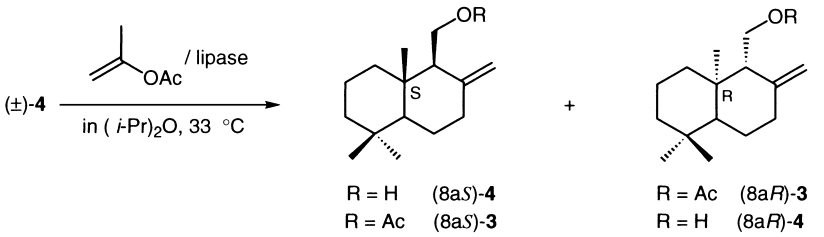
Scheme 2.

2.2. Enantioselective acetylation of (±)-4 and (±)-8

At first, for the purpose of determining the enantiomeric excess (ee) of the enzymatic reaction products, two racemates [(±)-**4** and (±)-**8**] were treated with (*S*)-α-methoxy-α-trifluoromethyl-

phenylacetyl chloride [(*S*)-MTPACl][10] in pyridine to afford the corresponding (*R*)-MTPA esters. In every case, the signals due to C_8-methylene protons appeared in distinctly different fields [(*R*)-MTPA esters from (±)-**4**: δ 4.58 dd and 4.23 dd, δ 4.45 dd and 4.37 dd; (*R*)-MTPA esters from (±)-**8**: δ 4.22 dd and 4.55 dd, δ 4.17 dd and 4.63 dd] of the 400 MHz NMR spectrum. From a screening experiment using various kinds of lipase, the effective lipases were as follows: 'OF-360' from *Candida rugosa*, 'MY-30' from *Candida rugosa*, 'Amano P' from *Pseudomonas* sp. and 'PL-266' from *Alcaligenes* sp. Enzymatic acetylation of (±)-**4** in the presence of isopropenyl acetate was performed in diisopropyl ether at 33°C and selected data are shown in Table 1. In the cases of 'OF-360' and 'MY-30', (–)-acetate **3** and unchanged (+)-**4** were obtained (entries 1 and 2), while 'Amano P' and 'PL-266' afforded (+)-acetate **3** and unchanged (–)-**4** (entries 3–6). When the alcohol (±)-**4** was exposed to 'PL-266' in the presence of isopropenyl acetate, an acetate (+)-**3** (56%, 67% ee) and unchanged (–)-**4** (38%, >99% ee) were obtained (entry 5). Optically active (+)-**3** possessing 67% ee was reduced with $LiAlH_4$ to give an alcohol (+)-**4**, which was again subjected to the same enzymatic acetylation to afford the enantiomerically pure albicanyl acetate (+)-**3** ($[\alpha]_D$ +33.9 (*c* 1.34, $CHCl_3$)) in 53% yield (entry 6). The spectral data of synthetic (+)-**3** were identical with those ($[\alpha]_D$ +24.0 (*c* 0.5, $CHCl_3$)) of natural (8a*S*)-(+)-**3**.[11] The enantiomeric purity of the enzymatic reaction products was determined by NMR measurement of the corresponding (*R*)-MTPA ester derived from each enzymatic reaction product. The absolute configuration at the C_{8a}-position of (–)-**4** ($[\alpha]_D$ –12.7 (*c* 0.74, $CHCl_3$)) was determined to be *R* by direct comparison with the sign of the specific rotation of the natural (8a*S*)-(+)-albicanol **4** ($[\alpha]_D$ +13 (*c* 0.6, $CHCl_3$)).[11] The enantiomerically pure (+)-**3** was treated with $LiAlH_4$ to provide enantiomerically pure (+)-albicanol **4** (mp 70°C, $[\alpha]_D$ +12.8 (*c* 1.14, $CHCl_3$)) whose physical data were identical with those (mp 68–69°C,[12] $[\alpha]_D$) of the natural (8a*S*)-(+)-albicanol **4**. Then enantioselective acetylation of (±)-**8** was carried out and selected data are shown in Table 2. When alcohol (±)-**8** was exposed to 'PL-266' in the presence of isopropenyl acetate, acetate (+)-**5** (53%, 61% ee) and unchanged (+)-**8** (40%, 80% ee) were obtained (entry 2). The ee of (+)-**8**

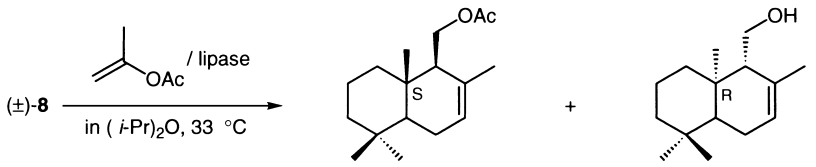
Table 1
Asymmetric acetylation of (±)-**4** with enzymes



entry	substrate (mg)	lipase	time (d)	product (%, % ee)	
1	(±)-**4** (100)	OF-360	0.5	(8a*S*)-(+)-**4** (46, 75)	(8a*R*)-(-)-**3** (50, 76)
2	(±)-**4** (700)	MY-30	1	(8a*S*)-(+)-**4** (50, 60)	(8a*R*)-(-)-**3** (43, 56)
3	(±)-**4** (231)	Amano P	12	(8a*R*)-(-)-**4** (57, 61)	(8a*S*)-(+)-**3** (42, 82)
4	(±)-**4** (233)	PL-266	1	(8a*R*)-(-)-**4** (40, >99)	(8a*S*)-(+)-**3** (58, 68)
5	(±)-**4** (2469)	PL-266	1	(8a*R*)-(-)-**4** (38, >99)	(8a*S*)-(+)-**3** (56, 67)
6	(+)-**4** (67% ee) [1)](1268)	PL-266	1	(8a*S*)-(+)-**4** (35, 19)	(8a*S*)-(+)-**3** (53, >99)

1) (8a*S*)-(+)-**4** (67% ee) was obtained by $LiAlH_4$ reduction of (8a*S*)-(+)-**3** (67% ee).

Table 2
Asymmetric acetylation of (±)-**8** with enzymes



(8a*S*)-**5** (8a*R*)-**8**

entry	substrate (mg)	lipase	time (d)	product (%, % ee)	
1	(±)-**8** (235)	PL-266	1	(8a*S*)-(+)-**5** (48, 72)	(8a*R*)-(+)-**8** (48, 73)
2	(±)-**8** (669)	PL-266	1	(8a*S*)-(+)-**5** (53, 61)	(8a*R*)-(+)-**8** (40, 80)
3	(+)-**8** (80% ee)(247)	PL-266	1	(8a*R*)-(-)-**5** (18, 57)	(8a*R*)-(+)-**8** (80, 88)
4	(-)-**8** (61% ee)[1)] (322)	PL-266	1	(8a*S*)-(+)-**5** (73, 85)	(±)-**8** (26, 0)
5	(±)-**8** (216)	Amano P	5.5	(8a*S*)-(+)-**5** (41, 88)	(8a*R*)-(+)-**8** (53, 68)

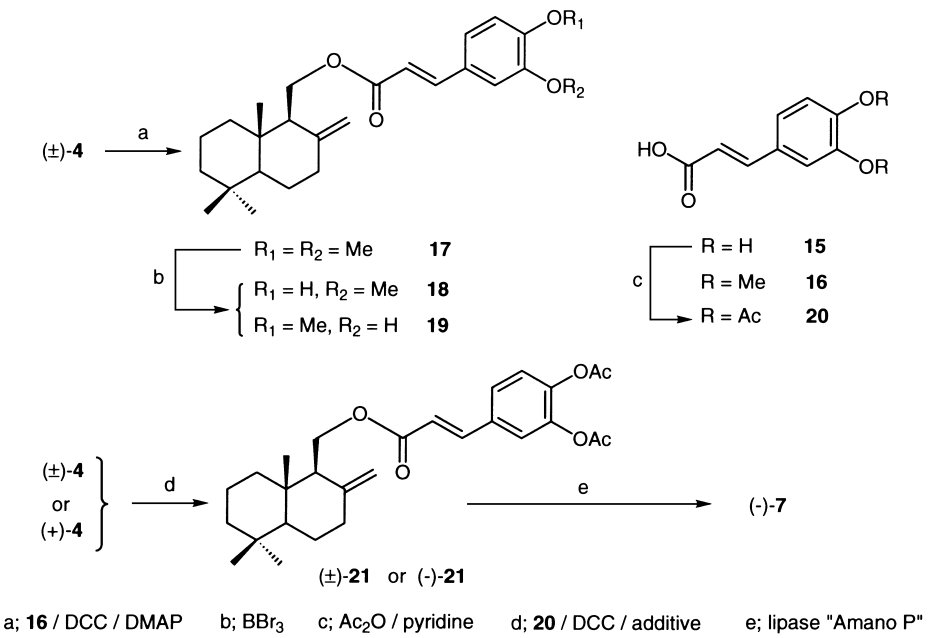
1) (-)-**8** (61% ee) was obtained by $LiAlH_4$ reduction of (+)-**5** (61% ee).

(80%) was improved to 88% by repeating enzymatic acetylation (entry 3). On the other hand, the ee of (+)-**5** (61%) was improved to 85% by repeating enzymatic acetylation of (–)-**8** (61% ee) prepared by $LiAlH_4$ reduction of (+)-**5** (61% ee) (entry 4). The enantiomeric purity of the enzymatic reaction products was determined by NMR measurement of the corresponding (*R*)-MTPA esters derived from enzymatic reaction products. The absolute configuration at the C_{8a}-position of (+)-**8** (entry 3; $[\alpha]_D$ +15.8 (*c* 1.2, benzene); corresponds to 88% ee) was confirmed to be *R* by direct comparison with the sign of the specific rotation ($[\alpha]_D$ –18 (*c* 3.55, benzene)) of the natural (8a*S*)-(–)-drimenol **8**.[13] When using 'Amano P', 88% ee of (+)-**5** was obtained in 41% yield (entry 5). Finally, enantiomerically pure (–)-drimenol **8** ($[\alpha]_D$ –18.2 (*c* 1.19, benzene)) was obtained in 90% yield by treatment of the above-mentioned enantiomerically pure (+)-albicanol **4** with $BF_3{\cdot}Et_2O$. The physical data ($[\alpha]_D$ and NMR) of the synthetic (–)-**5** were identical with those ($[\alpha]_D$ and NMR) of the natural (–)-drimenol **8**.[13]

2.3. Synthesis of (–)-albicanyl 3,4-dihydroxycinnamate 7

Albicanyl 3,4-dihydroxycinnamate **7** was isolated from *Bazzania japonica* and *Bazzania pompeana* as the major component.[14] Attempts to synthesize it directly by the reaction of (±)-**4** and 3,4-dihydroxycinnamic acid **15** in the presence of dicyclohexylcarbodiimide (DCC)-4-dimethylaminopyridine (DMAP) were unsuccessful. The reaction of (±)-**4** and 3,4-dimethoxycinnamic acid **16** in the presence of DCC–DMAP gave (±)-albicanyl 3,4-dimethoxycinnamate **17** in 94% yield, whose spectra (^1H NMR) were identical with those reported for **17**.[14] Treatment of (±)-**17** with BBr_3 provided an inseparable 1:1 mixture of 3-hydroxy-4-methoxycinnamate **18** and the 4-hydroxy-3-methoxycinnamate **19** in 62% yield (Scheme 3).

Then esterification of (±)-**4** and 3,4-diacetoxycinnamic acid **20** was carried out. Acetylation of **15** gave the desired acid **20** in 93% yield, which was subjected to the esterification of (+)-**4** under the following reaction conditions (the results are shown in Table 3). When using DCC without an additive, the *trans*-acetylation product, (±)-albicanyl acetate **3**, was obtained in 26% yield along



Scheme 3.

Table 3
The reaction of (±)- or (–)-**4** and **20**

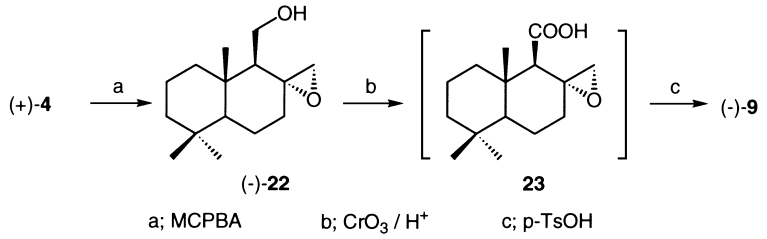
entry	substrate	additive	product (%)	
1	(±)-**4**	none		(±)-**3** (26)
2	(±)-**4**	DMAP (2.5 eq)	(±)-**21** (1)	(±)-**3** (78)
3	(±)-**4**	DMAP (2.5 eq) / (+)-CSA (2.5 eq)	(±)-**21** (49)	(±)-**3** (34)
4	(+)-**4**	DMAP (2.5 eq) / (+)-CSA (2.5 eq)	(-)-**21** (50)	(-)-**3** (8)

with the starting material (±)-**4** (60%) (entry 1). The same reaction as for entry 1 was carried out in the presence of DMAP to afford (±)-**3** (78%) and the desired (±)-3,4-diacetoxycinnamate **21** (1%) (entry 2). Surprisingly, the same reaction as for entry 2 in the presence of (+)-camphorsulfonic acid ((+)-CSA) furnished (±)-**21** (49%) and (±)-**3** (34%). This reaction condition was applied for the reaction of (+)-**4** and **20**, and (–)-albicanyl 3,4-diacetoxycinnamate **21** ($[\alpha]_D$ –5.6 (*c* 1.18, $CHCl_3$)) was obtained in 50% yield. Finally, enzymatic hydrolysis of (–)-**21** using the lipase 'Amano P' in water-saturated isopropyl ether provided the (–)-albicanyl-3,4-dihydroxycinnamate (**7**; mp 179–180°C, $[\alpha]_D$ –29.3 (*c* 0.89, MeOH)) quantitatively, which was consistent with the natural **7** with respect to the physico-chemical data (mp 179–180°C, $[\alpha]_D$ –18.3 (*c* 3.2, MeOH) and ^{13}C NMR).[14]

2.4. Synthesis of (–)-drimenin 9

(–)-Drimenin **9** was isolated from the stem bark of the South American *Drimys* species,[15] and (–)-**9** was converted to potent antifeedants such as polygodial **1** and warburganal **2**.[2] Epoxidation of (+)-albicanol **4** gave the diastereomerically pure epoxide **22** (mp 60.5–61°C, $[\alpha]_D$ –24.4 (*c* 1.24, $CHCl_3$)) in 99% yield. Jones oxidation of **22** provided an epoxy acid **23** followed by treatment

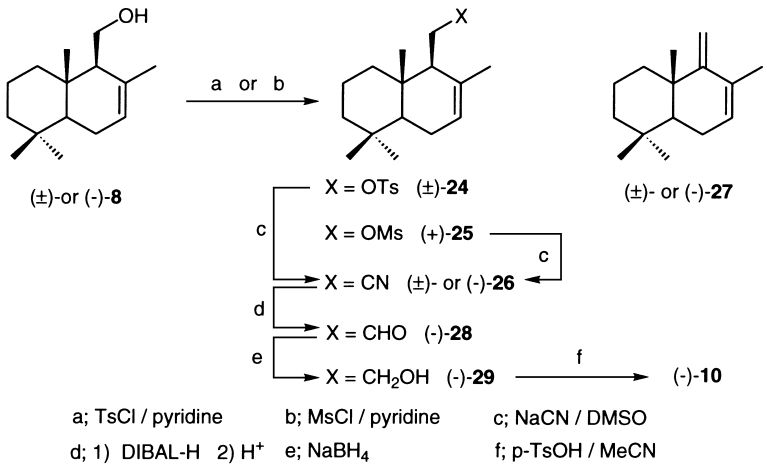
with *p*-toluenesulfonic acid to yield (–)-drimenin **9** (mp 128.5–129°C, $[\alpha]_D$ –58.6 (*c* 0.85, benzene)) in an overall 46% yield from (–)-**22** (Scheme 4). The spectral data of the synthetic (–)-**9** were identical with those (mp 129–130°C, $[\alpha]_D$ –54.5 (*c* 1, benzene)) of the natural (–)-**9**.[12]



Scheme 4.

2.5. Synthesis of (–)-ambrox *10*

Ambergris is a metabolite product found in the gut of some blue sperm whales and used in perfumery as a valuable ingredient of many fine fragrances. (–)-Ambrox **10** is one of the constituents of the *ambergris* tincture and possesses a powerful amber-type aroma. In order to achieve homologation of the primary alcohol group of (–)-**8**, the following synthetic sequence was developed (Scheme 5). Tosylation of (±)-**8** in pyridine gave the tosylate (±)-**24** (88%), while mesylation of (–)-**8** in pyridine provided the mesylate (+)-**25** ($[\alpha]_D$ +12.0 (*c* 1.26, $CHCl_3$)) quantitatively. Treatment of (±)-**24** with NaCN in DMSO gave the nitrile compound (±)-**26** (53%) and *exo*-olefin (±)-**27** (34%), while the reaction of (+)-**25** and NaCN in DMSO furnished (–)-**26** (45%, $[\alpha]_D$ –7.5 (*c* 1.14, $CHCl_3$)) and (–)-**27** (37%, $[\alpha]_D$ –185.4 (*c* 0.22, $CHCl_3$)). Reduction of (–)-**26** with diisobutylaluminum hydride (DIBAL-H) in toluene furnished an aldehyde (–)-**28** ($[\alpha]_D$ –27.4 (*c* 0.55, $CHCl_3$)) in 81% yield. $NaBH_4$ reduction of (–)-**28** provided the alcohol (–)-**29** ($[\alpha]_D$ –9.6 (*c* 1.51, $CHCl_3$)) in quantitative yield. Treatment of (–)-**29** with *p*-TsOH in acetonitrile gave (–)-ambrox **10** ($[\alpha]_D$ –23.8 (*c* 1.13, $CHCl_3$)) in 55% yield, which was consistent with the reported (–)-**10** ($[\alpha]_D$ –22.3 (*c* 1.30, $CHCl_3$)).[16]



Scheme 5.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-DX 303 spectrometer. IR spectra were recorded using a JASCO FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

3.2. (±)-Methyl (1R*,4aS*,8aS*)-decahydro-5,5,8a-trimethyl-2-oxonaphthalene-1-carboxylate **12**

Jones reagent (6 ml) was added to a solution of (±)-**11** (3.75 g, 14.7 mmol) in acetone (30 ml) at 0°C and the reaction mixture was stirred at room temperature for 90 min. After *iso*-PrOH (6 ml) was added to the reaction mixture, the whole was condensed and diluted with H_2O, and extracted with ether. The ether layer was washed in brine and dried over $MgSO_4$. The ether layer was evaporated to give a crude residue, which was chromatographed on silica gel (50 g, *n*-hexane:AcOEt = 20:1) to give (±)-**12** (3.58 g, 96%). Crystallization of (±)-**12** from *n*-hexane provided colorless plates: mp 84.5–85°C; IR (KBr): 1747, 1708 cm^{-1} (COOMe, ketone); ^{1}H NMR: δ 0.90 (3H, s), 0.97 (3H, s), 1.16 (3H, s), 1.19–1.30 (2H, m), 1.43 (1H, dd, J = 3, 13 Hz), 1.45–1.69 (4H, m), 1.75 (1H, dddd, J = 5.5, 13, 14, 14 Hz), 2.03 (1H, dddd, J = 2, 3, 7, 14 Hz), 2.33 (1H, ddd, J = 7, 14, 14 Hz), 2.51 (1H, ddd, J = 2, 2.5, 14 Hz), 3.22 (1H, s), 3.69 (3H, s). ^{13}C NMR: δ 14.8 (q), 18.6 (t), 21.7 (q), 23.0 (t), 33.5 (q), 33.6 (s), 39.2 (t), 41.3 (t), 41.9 (t), 42.0 (s), 51.4 (q), 53.3 (d), 70.0 (d), 168.7 (s), 205.6 (s). Anal. found: C, 71.67; H, 9.35. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%. EI MS m/z: 252 (M^+).

3.3. (±)-Albicanol **4**

(1) A solution of $Ph_3P^+MeBr^-$ (9.45 g, 26.5 mmol) and $NaNH_2$ (972 mg, 24.9 mmol) in toluene (100 ml) was heated under reflux for 6 h under argon. After the suspension had settled, the decanted yellow solution ($Ph_3P{=}CH_2$) was poured into (±)-**12** (1.32 g, 5.23 mmol) at 0°C. The whole was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed in brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (60 g, *n*-hexane:AcOEt = 50:1) to give a 22:1 mixture (1.288 g, 98%) of (±)-**13** and (±)-**14**. Compound (±)-**13**: IR (neat): 1737 cm^{-1} (COOMe); ^{1}H NMR: δ 0.84 (3H, s), 0.87 (3H, s), 1.05 (3H, s), 1.06–1.73 (9H, m), 2.02–2.12 (1H, m), 2.42 (1H, ddd, J = 2, 5, 13 Hz), 2.80 (1H, s), 3.65 (3H, s), 4.64 (1H, d, J = 1.5 Hz), 4.83 (1H, d, J = 1.5 Hz). EI MS m/z: 250 (M^+). (2) To a solution of the above mixture (1.236 g, 4.97 mmol) in Et_2O (20 ml) at 0°C was added $LiAlH_4$ (256 mg, 6.76 mmol) and the whole was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed in brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue. This was chromatographed

on silica gel (50 g, *n*-hexane:AcOEt = 5:1) to give a colorless oil which was crystallized from *n*-hexane to provide colorless needles (±)-**4** (953 mg, 87%): mp 67–68°C; IR (KBr): 3358 cm^{-1} (OH); ^1H NMR: δ 0.72 (3H, s), 0.80 (3H, s), 0.88 (3H, s), 1.11–2.45 (12H, m), 3.75 (1H, dd, J = 9.5, 11 Hz), 3.82 (1H, dd, J = 4, 11 Hz), 4.64 (1H, d, J = 1.5 Hz), 4.93 (1H, d, J = 1.5 Hz). ^{13}C NMR: δ 15.4 (q), 19.4 (t), 21.9 (q), 24.3 (t), 33.6 (s), 33.7 (q), 38.0 (t), 39.0 (s), 39.1 (t), 42.1 (t), 55.2 (d), 58.8 (t), 59.2 (d), 106.2 (t), 147.7 (s). Anal. found: C, 81.19; H, 11.97. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%. EI MS m/z: 222 (M^+).

3.4. (±)-Albicanyl acetate (±)-3

A solution of (±)-**4** (1.013 g, 4.56 mmol) in pyridine (20 ml) and 4-dimethylaminopyridine (50 mg, 0.42 mmol) was treated with Ac_2O (0.66 ml, 6.47 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 30:1) to give (±)-**3** as a colorless oil (1.161 g, 96%): IR (neat): 1738 cm^{-1} (OAc); ^1H NMR: δ 0.73 (3H, s), 0.80 (3H, s), 0.86 (3H, s), 1.10–2.41 (12H, m), 2.00 (3H, s), 4.17 (1H, dd, J = 9, 11 Hz), 4.32 (1H, dd, J = 4, 11 Hz), 4.49 (1H, d, J = 1 Hz), 4.83 (1H, d, J = 1 Hz). ^{13}C NMR: δ 15.3 (q), 19.3 (t), 21.3 (q), 21.9 (q), 24.0 (t), 33.6 (s), 33.7 (q), 37.7 (t), 39.1 (s), 39.2 (t), 42.0 (t), 54.8 (d), 55.1 (d), 61.6 (t), 107.1 (t), 146.7 (s), 171.1 (s). Anal. found: C, 77.51; H, 10.69. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%. FAB MS m/z: 265 (M^++1).

3.5. (±)Drimenol (±)-8

To a solution of (±)-**4** (2.125 g, 9.39 mmol) in CH_2Cl_2 (20 ml) was added $BF_3{\cdot}Et_2O$ (3.3 ml, 11 mmol) at –20°C. The whole was stirred for 30 min at 0°C and allowed to stand for 12 h in a refrigerator. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (45 g, *n*-hexane:AcOEt = 20:1) to give a homogeneous oil (±)-**8** (1.983 g, 93%): IR (KBr): 3335 cm^{-1} (OH); ^1H NMR: δ 0.79 (3H, s), 0.80 (3H, s), 0.82 (3H, s), 0.94–1.18 (3H, m), 1.32–1.56 (3H, m), 1.71 (3H, br s), 1.74–1.97 (4H, m), 3.66 (1H, dd, J = 5, 11.5 Hz), 3.79 (1H, dd, J = 3, 11.5 Hz), 5.46–5.48 (1H, m). ^{13}C NMR: δ 14.9 (q), 18.8 (t), 22.0 (q), 22.1 (q), 23.6 (t), 32.9 (s), 33.4 (q), 36.1 (s), 39.9 (t), 42.2 (t), 49.9 (d), 57.3 (d), 60.9 (t), 124.1 (d), 132.9 (s). Anal. found: C, 80.77; H, 11.86. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%. EI MS m/z: 222 (M^+).

3.6. (±)-Drimenyl acetate (±)-5

A solution of (±)-**8** (743 mg, 3.28 mmol) in pyridine (5 ml) and 4-dimethylaminopyridine (30 mg, 0.2 mmol) was treated with Ac_2O (0.64 ml, 6.75 mmol) and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane:AcOEt = 50:1) to give (±)-**5** as a colorless oil (840 mg, 95%): IR (neat): 1740 cm^{-1} (OAc); ^1H NMR: δ 0.82 (3H, s), 0.86 (3H, s), 0.89 (3H, s), 1.09 (1H, dt,

$J=4$, 13 Hz), 1.13–1.23 (2H, m), 1.39–1.58 (3H, m), 1.67 (3H, br s), 1.82–2.01 (4H, m), 2.04 (3H, s), 4.09 (1H, dd, $J=6.5$, 12 Hz), 4.25 (1H, dd, $J=3$, 12 Hz), 5.50 (1H, br s). ^{13}C NMR: δ 14.6 (q), 18.9 (t), 21.4 (q), 21.8 (q), 22.1 (q), 23.7 (t), 33.1 (s), 33.4 (q), 36.1 (s), 39.6 (t), 42.2 (t), 49.9 (d),53.4 (d), 63.2 (t), 123.5 (d), 132.3 (s), 170.9 (s). Anal. found: C, 77.02; H, 10.67. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%. FAB MS m/z: 265 (M^++1).

3.7. (R)-MTPA ester formation from (±)-albicanol **4**

To a stirred solution of (±)-**4** (51 mg, 0.23 mmol) in pyridine (2 ml) was added (*S*)-MTPACl (65 mg, 0.25 mmol) and the whole was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to give a diastereomeric mixture of (8a*S*)-(*R*)- and (8a*R*)-(*R*)-MTPA esters (100 mg, 99%): ^{1}H NMR: δ 4.37 (1H, dd, $J=9$, 11 Hz) and 4.45 (1H, dd, $J=4$, 11 Hz), δ 4.22 (1H, dd, $J=9.5$, 11 Hz) and 4.58 (1H, dd, $J=3.5$, 11 Hz). FAB MS m/z: 439 (M^++1).

3.8. (R)-MTPA ester formation from (±)-drimenol **8**

To a stirred solution of (±)-**8** (120 mg, 0.54 mmol) in pyridine (1 ml) was added (*S*)-MTPACl (160 mg, 0.64 mmol) and the whole was stirred for 12 h at room temperature. The reaction mixture was worked up in the same way as in Section 3.7 to afford a diastereomeric mixture of (8a*S*)-(*R*)- and (8a*R*)-(*R*)-MTPA esters (237 mg, 99%): ^{1}H NMR: δ 4.17 (1H, dd, $J=6$, 11.5 Hz) and 4.63 (1H, dd, $J=3$, 11.5 Hz), δ 4.22 (1H, dd, $J=6.5$, 11.5 Hz) and 4.55 (1H, dd, $J=3$, 11.5 Hz). FAB MS m/z: 439 (M^++1).

3.9. Enantioselective acetylation of (±)-**4**

(1) Table 1, entry 1: A suspension of (±)-**4** (100 mg), isopropenyl acetate (100 mg) and lipase OF-360 (100 mg) in diisopropyl ether (10 ml) was incubated at 33°C for 0.5 day. After the reaction mixture was filtered, the precipitate was washed with diisopropyl ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g) to give (–)-**3** (59 mg, 50%, 76% ee) from *n*-hexane:AcOEt = 50:1 eluate and (+)-**4** (46 mg, 46%, 75% ee) from *n*-hexane:EtOAc = 20:1 eluate, respectively. (2) Table 1, entry 2: A suspension of (±)-**4** (700 mg), isopropenyl acetate (700 mg) and lipase MY-30 (700 mg) in diisopropyl ether (70 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1 to give (–)-**3** (358 mg, 43%, 56% ee) and (+)-**4** (350 mg, 50%, 60% ee). (3) Table 1, entry 3: A suspension of (±)-**4** (231 mg), isopropenyl acetate (230 mg) and lipase Amano-P (200 mg) in diisopropyl ether (40 ml) was incubated at 33°C for 12 days. The reaction mixture was worked up in the same way as for entry 1 to give (+)-**3** (115 mg, 42%, 82% ee) and (–)-**4** (132 mg, 57%, 61% ee). (4) Table 1, entry 4: A suspension of (±)-**4** (233 mg), isopropenyl acetate (230 mg) and lipas PL-266 (200 mg) in diisopropyl ether (40 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1 to give (+)-**3** (161 mg, 58%, 68% ee) and (–)-**4** (93 mg, 40%, >99% ee). (5) Table 1, entry 5: A suspension of (±)-**4** (2.469 g), isopropenyl acetate (2.5 g) and lipase PL-266 (2.5 g) in diisopropyl ether (100 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1

to give (+)-**3** (1.647 g, 56%, 67% ee) and (–)-**4** (938 mg, 38%, $[\alpha]_D^{24}$ –12.7 (*c* 0.74, $CHCl_3$); corresponds to >99% ee). (6) Table 1, entry 6: $LiAlH_4$ (372 mg) reduction of (+)-**3** (67% ee, 1.647 g) in Et_2O (20 ml) gave (+)-**4** (1.33 g, 96%, 67% ee) in the same way as that in Section 3.3. A suspension of (+)-**4** (67% ee, 1.268 g), isopropenyl acetate (1.26 g) and lipase PL-266 (1.26 g) in diisopropyl ether (150 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1 to give (+)-**3** (799 mg, 53%, $[\alpha]_D^{21}$ +33.9 (*c* 1.34, $CHCl_3$); corresponds to >99% ee) and (+)-**4** (449 mg, 35%, 19% ee).

3.10. (8*a*S)-(+)-Albicanol **4**

$LiAlH_4$ (241 mg, 6.3 mmol) reduction of (+)-**3** (>99% ee, 799 mg, 3 mmol) in Et_2O (20 ml) gave (+)-**4** (638 mg, 95%) in the same way as in Section 3.3. Recrystallization of (+)-**4** from *n*-hexane afforded colorless needles: mp 70°C; $[\alpha]_D^{26}$ +12.8 (*c* 1.14, $CHCl_3$). Physical data of (+)-**4** were identical with those of (±)-**4**.

3.11. Enantioselective acetylation of (±)-**8**

(1) Table 2, entry 1: A suspension of (±)-**8** (235 mg), isopropenyl acetate (200 mg) and lipase PL-266 (200 mg) in diisopropyl ether (40 ml) was incubated at 33°C for 1 day. After the reaction mixture was filtered, the precipitate was washed with diisopropyl ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g) to give (+)-**5** (134 mg, 48%, 72% ee) from *n*-hexane:AcOEt = 50:1 eluate and (+)-**8** (113 mg, 48%, 73% ee) from *n*-hexane:AcOEt = 20:1 eluate, respectively. (2) Table 2, entry 2: A suspension of (±)-**4** (669 mg), isopropenyl acetate (670 mg) and lipase PL-266 (670 mg) in diisopropyl ether (80 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1 to give (+)-**5** (422 mg, 53%, 61% ee) and (+)-**8** (267 mg, 40%, 80% ee). (3) Table 2, entry 3: A suspension of (+)-**8** (247 mg, 80% ee), isopropenyl acetate (240 mg) and lipase PL-266 (200 mg) in diisopropyl ether (60 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1 to give (–)-**5** (53 mg, 18%, 57% ee) and (+)-**8** (198 mg, 80%, $[\alpha]_D^{26}$ +15.8 (*c* 1.2, benzene); corresponds to 88% ee). (4) Table 2, entry 4: $LiAlH_4$ (122 mg) reduction of (+)-**5** (61% ee, 442 mg) in Et_2O (10 ml) gave (–)-**8** (356 mg, 96%, $[\alpha]_D^{25}$ –10.8 (*c* 1.09, benzene); corresponds to 61% ee) in the same way as in Section 3.3. A suspension of (–)-**8** (61% ee, 322 mg), isopropenyl acetate (320 mg) and lipase PL-266 (320) in diisopropyl ether (60 ml) was incubated at 33°C for 1 day. The reaction mixture was worked up in the same way as for entry 1 to give (+)-**5** (278 mg, 73%, $[\alpha]_D^{26}$ +8.7 (*c* 1.88, $CHCl_3$); corresponds to 85% ee) and (±)-**8** (83 mg, 26%). (5) Table 2, entry 5: A suspension of (±)-**8** (216 mg), isopropenyl acetate (200 mg) and lipase PL-266 (200 mg) in diisopropyl ether (40 ml) was incubated at 33°C for 5.5 days. The reaction mixture was worked up in the same way as for entry 1 to give (+)-**5** (107 mg, 41%, 88% ee) and (+)-**8** (115 mg, 53%, 68 ee).

3.12. General procedure of (R)-MTPA ester formation from enzymatic reaction products (alcohol and acetate)

(1) To a stirred solution of alcohol (ca. 10 mg) in pyridine (0.5 ml) was added (*S*)-MTPACl (ca. 30 mg), and the whole was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as in Section 3.7 to give the corresponding (*R*)-MTPA ester quantitatively.

The ee of the resulting (*R*)-MTPA ester was determined by NMR analysis. (2) $LiAlH_4$ (10–16 mg) reduction of acetate (59–100 mg) in Et_2O (15 ml) gave the corresponding alcohol quantitatively. To a stirred solution of the resulting alcohol (ca. 10 mg) in pyridine (0.5 ml) was added (*S*)-MTPACl (ca. 30 mg), and the whole was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as in (1) to give the corresponding (R)-MTPA ester quantitatively. The ee of the resulting (*R*)-MTPA ester was determined by NMR analysis.

3.13. Conversion of (+)-albicanol **4** into (–)-drimenol **8**

To a solution of (+)-**4** (1.418 g, 6.38 mmol) in CH_2Cl_2 (15 ml) was added $BF_3{\cdot}Et_2O$ (2.4 ml, 8.24 mmol) at –20°C, and the whole was stirred for 12 h at 0°C. The reaction mixture was worked up in the same way as in Section 3.5 to give (–)-**8** (1.278 g, 90%). Recrystallization of (–)-**8** from *n*-hexane afforded colorless needles: mp 86°C; $[\alpha]_D^{24}$ –18.2 (*c* 1.19, benzene). Physical data of (–)-**8** were identical with those of (±)-**8**.

3.14. (±)-Albicanyl 3,4-dimethoxycinnamate **17**

A mixture of (±)-**4** (48 mg, 0.22 mmol), 3,4-dimethoxycinnamic acid **16** (111 mg, 0.54 mmol), DCC (108 mg, 0.52 mmol) and DMAP (64 mg, 0.53 mmol) in CH_2Cl_2 (1 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 10:1) to provide crystals (±)-**17** (84 mg, 94%). Recrystallization of (±)-**17** from *n*-hexane–AcOEt gave colorless (±)-**17**: mp 118.5°C; IR (KBr): 1710 cm^{-1} (ester); ^1H NMR data of (±)-**17** were identical with those of the reported **17**.[14] ^{13}C NMR: δ 15.3 (q), 19.3 (t), 21.9 (q), 24.0 (t), 33.6 (s), 33.7 (q), 37.7 (t), 39.1 (s), 39.2 (t), 42.0 (t), 55.0 (d), 55.2 (d), 55.9 (q), 56.0 (q), 61.5 (t), 107.2 (t), 109.5 (d), 110.9 (d), 115.9 (d), 122.5 (d), 127.3 (s), 144.3 (d), 146.7 (s), 149.0 (s), 150.8 (s), 167.2 (s). Anal. found: C, 75.82; H, 8.32. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80%. EI MS *m*/*z*: 412 (M^+).

3.15. 3,4-Diacetoxycinnamic acid **20**

A solution of caffeic acid **15** (1.0 g, 5.5 mmol) in pyridine (10 ml) was treated with Ac_2O (2.83 g, 27.7 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl and saturated brine, and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 1:1) to give crystals **20** (1.368 g, 93%). Recrystallization of **20** from MeOH gave a colorless powder: mp 206–207°C; IR (KBr): 1763, 1683, 1682 cm^{-1} (OAc, C=C–COOH); ^1H NMR (DMSO-d_6): δ 2.28 (3H, s), 2.29 (3H, s), 6.53 (1H, d, J = 16 Hz), 7.31 (1H, d, J = 8 Hz), 7.58 (1H, d, J = 16 Hz), 7.63 (1H, dd, J = 2, 8 Hz), 7.66 (1H, d, J = 2 Hz), 12.45 (1H, br s). Anal. found: C, 58.81; H, 4.61. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58%. EI MS *m*/*z*: 264 (M^+).

3.16. (–)-Abicanyl 3,3-dihydroxycinnamate **7**

(1) To a solution of (+)-**4** (226 mg, 1.02 mmol) in CH_2Cl_2 (15 ml) was added **20** (506 mg, 1.92 mmol), DCC (494 mg, 2.4 mmol), DMAP (282 mg, 2.31 mmol) and (+)-CSA (229 mg, 1.88 mmol)

at 0°C, and the whole was stirred for 12 h at ambient temperature. The reaction mixture was directly filtered with the aid of Celite and the filtrate was condensed. The residue was subjected to chromatography on silica gel (30 g) to give (–)-**3** (22 mg, 8%) from *n*-hexane:AcOEt = 50:1 eluate and (–)-albicanyl 3,4-diacetoxycinnamate **21** (240 mg, 50%) from *n*-hexane:AcOEt = 5:1 eluate. Recrystallization of **21** from *n*-hexane–AcOEt gave a colorless powder **21**. (–)-**21**: mp 103°C; IR (KBr): 1768, 1702 cm^{-1} (OAc, C=C–COOR); $[\alpha]_D^{27}$ –5.6 (*c* 1.18, $CHCl_3$); ^1H NMR: δ 0.79 (3H, s), 0.83 (3H, s), 0.89 (3H, s), 1.14–2.15 (11H, m), 2.29 (3H, s), 2.30 (3H, s), 2.40–2.46 (1H, m), 4.31 (1H, dd, J = 9, 11.5 Hz), 4.50 (1H, dd, J = 3, 11.5 Hz), 4.57 (1H, d, J = 1.5 Hz), 4.88 (1H, d, J = 1.5 Hz), 6.36 (1H, d, J = 16 Hz), 7.21 (1H, d, J = 8.5 Hz), 7.35 (1H, d, J = 2.5 Hz), 7.39 (1H, dd, J = 2.5, 8.5 Hz), 7.58 (1H, d, J = 16 Hz). ^{13}C NMR: δ 15.2 (q), 19.2 (t), 20.6 (q), 20.6 (q), 21.8 (q), 23.9 (t), 33.5 (s), 33.6 (s), 37.6 (t), 39.0 (s), 39.1 (t), 42.0 (t), 54.9 (d), 55.1 (d), 61.8 (t), 107.3 (t), 119.6 (d), 122.7 (d), 123.9 (d), 126.4 (d), 133.4 (s), 142.4 (s), 142.6 (d), 143.4 (s), 146.8 (s), 166.8 (s), 167.9 (s), 168.0 (s). Anal. found: C, 71.70; H, 7.88. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74%. FAB MS m/z: 469 (M^++1). (2) A suspension of (–)-**21** (105 mg, 0.22 mmol) and Amano P (100 mg) in H_2O saturated isopropyl ether (10 ml) was stirred for 1 h at 35°C and the reaction mixture was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 2:1) to give (–)-**7** (85 mg, 99%). Recrystallization of (–)-**7** from AcOEt afforded colorless needles: mp 179–180°C; IR ($CHCl_3$): 1696 cm^{-1} (C=C–COOR); $[\alpha]_D^{23}$ –29.3 (*c* 0.89, MeOH); ^1H NMR and ^{13}C NMR data of (–)-**7** were identical with those of the reported (–)-**7**.[14] Anal. found: C, 75.32; H, 8.42. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39%.

3.17. (–)-Drimenin **9**

(1) A mixture of (+)-**4** (473 mg, 2.13 mmol) and MCPBA (444 mg, 2.58 mmol) in CH_2Cl_2 (8 ml) was stirred for 20 min at room temperature. The reaction mixture was diluted with ether and the organic layer was washed with 10% aqueous $Na_2S_2O_3$, 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 50:1) to give (–)-**22** (507 mg, 99%). Recrystallization of (–)-**22** from *n*-hexane provided colorless plates (–)-**22**: mp 60.5–61°C; IR (KBr): 3514 cm^{-1} (OH); $[\alpha]_D^{24}$ –24.4 (*c* 1.24, $CHCl_3$); ^1H NMR: δ 0.83 (3H, s), 0.85 (3H, s), 0.91 (3H, s), 1.07 (1H, dd, J = 2, 12 Hz), 1.17–2.02 (11H, m), 2.72 (1H, d, J = 4 Hz), 3.11 (1H, d, J = 10.5 Hz, disappeared with D_2O, OH), 3.41 (1H, dd, J = 10, 10.5 Hz), 3.63 (1H, dd, J = 3, 10.5 Hz). ^{13}C NMR: δ 15.6 (q), 18.6 (t), 21.6 (q), 21.6 (t), 33.3 (s), 33.5 (q), 36.2 (t), 38.8 (t), 39.1 (s), 41.7 (t), 51.8 (t), 54.3 (d), 54.6 (d), 58.8 (t), 61.7 (s). Anal. found: C, 75.67; H, 11.03. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%. FAB MS m/z: 239 (M^++1). (2) Jones reagent (0.65 ml) was added to a solution of (–)-**22** (322 mg, 1.35 mmol) in acetone (10 ml) at 0°C and the reaction mixture was stirred for 1 h at room temperature. After *iso*-PrOH (0.5 ml) was added to the reaction mixture, the whole was condensed and diluted with H_2O, and extracted with ether. The ether layer was washed in brine and dried over $MgSO_4$. The ether layer was evaporated to give a crude residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 1:1) to give **23** as a colorless oil (311 mg, 91%): IR (neat): 1711 cm^{-1} (COOH); ^1H NMR: δ 0.86 (3H, s), 0.91 (3H, s), 1.03 (1H, dd, J = 2.5, 12 Hz), 1.14 (3H, s), 1.12–1.97 (10H, m), 2.62 (1H, d, J = 5 Hz), 2.69 (1H, s), 3.37 (1H, dd, J = 2, 5 Hz). FAB MS m/z: 253 (M^++1). (3) A mixture of **23** (160 mg, 0.63 mmol) and $TsOH \cdot H_2O$ (13 mg, 0.07 mmol) in $CHCl_3$ (5 ml) was stirred for 1 h at reflux. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent

gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 20:1) to give (–)-**9** (69 mg, 46%). Recrystallization of (–)-**9** from MeOH provided colorless plates: mp 128.5–129°C; IR (KBr): 1762 cm^{-1} (lactone); $[\alpha]_D^{24}$ –58.6 (*c* 0.85, benzene); ^1H NMR: δ 0.87 (3H, s), 0.89 (3H, s), 0.91 (3H, s), 1.17–1.29 (2H, m), 1.36 (1H, dd, *J* = 5, 11.5 Hz), 1.46–1.65 (3H, m), 1.93–2.04 (1H, m), 2.16–2.25 (1H, m), 2.50 (1H, *J* = 3.5, 5, 13.5 Hz), 2.78 (1H, br s), 4.61–4.71 (2H, m), 5.73 (1H, br s). ^{13}C NMR: δ 14.0 (q), 18.3 (t), 21.4 (q), 23.4 (t), 33.0 (q), 33.1 (s), 34.4 (s), 38.5 (t), 42.4 (t), 49.7 (d), 53.7 (d), 69.8 (t), 121.2 (d), 129.9 (s), 175.3 (s). Anal. found: C, 76.84; H, 9.53. Calcd for $C_{15}H_{22}O_2$: C, 76.84; H, 9.46%. EI MS *m*/*z*: 234 (M^++1).

3.18. (–)-Ambrox **10**

(1) To a solution of (–)-**8** (1.051 g, 1.02 mmol) in pyridine (10 ml) was added a solution of MsCl (795 mg, 1.92 mmol) in pyridine (5 ml), and the whole was stirred for 1 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 20:1) to give (+)-**25** as a colorless oil (1.406 g, 99%): IR (neat): 1354 cm^{-1}; $[\alpha]_D^{24}$ +12.0 (*c* 1.26, $CHCl_3$); ^1H NMR: δ 0.84 (3H, s), 0.87 (3H, s), 0.89 (3H, s), 1.09–2.13 (10H, m), 1.73 (3H, br s), 3.00 (3H, s), 4.23 (1H, dd, *J* = 6, 10 Hz), 4.42 (1H, dd, *J* = 3, 10 Hz), 5.54 (1H, br s). ^{13}C NMR: δ 14.6 (q), 18.6 (t), 21.6 (q), 21.9 (q), 23.4 (t), 32.9 (s), 33.2 (s), 36.0 (s), 37.4 (q), 41.8 (t), 49.6 (d), 53.6 (d), 67.9 (t), 124.3 (d), 130.8 (s). EI MS *m*/*z*: 204 (M^+–OMs). (2) A mixture of (+)-**25** (443 mg, 1.48 mmol) and NaCN (382 mg, 7.8 mmol) in DMSO (6 ml) was stirred for 12 h at room temperature, and the reaction mixture was dried over $MgSO_4$. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g) to give (–)-**27** as a colorless oil (106 mg, 37%) from *n*-hexane eluate and (–)-**26** as a colorless oil (155 mg, 45%) from *n*-hexane:AcOEt = 100:1 eluate. Compound (–)-**26**: IR (neat): 2243 cm^{-1} (CN); $[\alpha]_D^{24}$ –7.5 (*c* 1.14, $CHCl_3$); ^1H NMR: δ 0.84 (3H, s), 0.87 (3H, s), 0.89 (3H, s), 1.04–2.19 (10H, m), 1.79 (3H, br s), 2.24 (1H, dd, *J* = 7, 17 Hz), 2.48 (1H, dd, *J* = 4, 17 Hz), 5.56 (1H, br s). ^{13}C NMR: δ 13.8 (q), 15.0 (t), 18.6 (t), 21.6 (q), 21.9 (q), 23.5 (t), 32.9 (s), 33.2 (q), 36.5 (s), 39.6 (t), 41.9 (t), 49.7 (d), 51.6 (d), 121.0 (s), 125.0 (d), 131.2 (s). Anal. found: C, 83.07; H, 11.08; N, 5.91. Calcd for $C_{16}H_{25}N$: C, 83.05; H, 10.89; N, 6.05%. FAB MS *m*/*z*: 232 (M^++1). Compound (–)-**27**: IR (neat): 1601 cm^{-1}; $[\alpha]_D^{20}$ –185.4 (*c* 0.22, $CHCl_3$); ^1H NMR: δ 0.87 (3H, s), 0.93 (3H, s), 0.97 (3H, s), 1.18–2.19 (9H, m), 1.80 (3H, br s), 4.80 (1H, br s), 4.84 (1H, br s), 5.65 (1H, br s). ^{13}C NMR: δ 19.1 (t), 20.6 (q), 21.1 (q), 22.1 (q), 24.3 (t), 32.9 (q), 33.4 (s), 37.7 (t), 37.8 (s), 42.2 (t), 48.7 (d), 103.7 (t), 126.5 (d), 131.2 (s), 158.2 (s). Anal. found: C, 88.60; H, 12.02. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84%. EI MS *m*/*z*: 204 (M^+). (3) To a solution of (–)-**26** (390 mg, 1.69 mmol) in toluene (10 ml) was added 1 M DIBAL in toluene (3.7 ml, 3.7 mmol) at –78°C, and the whole was stirred for 30 min at the same temperature. After addition of acetone (0.5 ml), the reaction mixture was diluted with 2 M aqueous HCl and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 50:1) to afford (–)-**28** as a colorless oil (322 mg, 81%): IR (neat): 1724 cm^{-1} (CHO); $[\alpha]_D^{24}$ –27.4 (*c* 0.55, $CHCl_3$); ^1H NMR: δ 0.77 (3H, s), 0.88 (3H, s), 0.89 (3H, s), 1.52 (3H, br s), 1.03–2.06 (9H, m), 2.35–2.46 (2H, m), 2.53 (1H, br s), 5.43 (1H, br s), 9.85 (1H, *J* = 1.5, 2 Hz). ^{13}C NMR: δ 14.2 (q), 18.7 (t), 21.8 (q), 22.5 (q), 23.7 (t), 32.9 (s), 33.2 (q), 36.0 (s), 39.5 (t), 42.1 (t), 42.4 (t), 48.6 (d), 49.8 (d), 123.4

(d), 132.9 (s), 203.5 (d). Anal. found: C, 81.85; H, 11.20. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18%. (4) To a solution of (–)-**28** (298 mg, 1.27 mmol) in MeOH (4 ml) was added $NaBH_4$ (69 mg, 1.8 mmol) at 0°C, and the whole was stirred for 30 min at the same temperature. After addition of acetone (0.3 ml), the reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 10:1) to afford (–)-**29** as a colorless oil (300 mg, 99%): IR (neat): 3324 cm^{-1} (OH); $[\alpha]_D^{23}$ –9.6 (*c* 1.51, $CHCl_3$); ^1H NMR: δ 0.76 (3H, s), 0.85 (3H, s), 0.88 (3H, s), 0.96–2.02 (12H, m), 1.67 (3H, br s), 3.53–3.60 (1H, m), 3.76–3.83 (1H, m), 5.42 (1H, br s). ^{13}C NMR: δ 13.6 (q), 18.8 (t), 21.8 (q), 22.1 (q), 23.8 (t), 30.5 (s), 33.0 (t), 33.2 (q), 36.5 (s), 39.2 (t), 42.3 (t), 50.1 (d), 50.8 (d), 64.4 (t), 122.7 (d), 134.6 (s). Anal. found: C, 81.27; H, 12.04. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94%. FAB MS *m*/*z*: 237 (M^++1). (5) To a solution of (–)-**29** (300 mg, 1.27 mmol) in MeCN (8 ml) was added a solution of *p*-$TsOH \cdot H_2O$ in MeCN (2 ml) at 0°C, and the whole was stirred for 12 h at ambient temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 50:1) to afford (–)-**10** as a colorless oil (165 mg, 55%): $[\alpha]_D^{25}$ –23.8 (*c* 1.13, $CHCl_3$). FAB MS *m*/*z*: 342 (M^+). Spectral data (^1H NMR and ^{13}C NMR) were identical with those ($[\alpha]_D^{23}$ –22.3 (*c* 1.3, $CHCl_3$)) of reported (–)-**10**.[16]

Acknowledgements

This work was supported by a grant for the Biodesign Research Program from the Institute of Physical and Chemical Research (RIKEN) to H.A. and a Grant-in-Aid for Scientific Research (No. 10672002) from the Ministry of Education, Science and Culture of Japan to H.A.

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