Chem. Pharm. Bull. 45(5) 824—831 (1997) Vol. 45, No. 5

Simple Approach to Optically Active Drimane Sesquiterpenes Based on Enzymatic Resolution

Hiroyuki Akita,* Masako Nozawa, Yoshiko Futagami, Maiko Miyamoto, and Chikako Saotome

School of Pharmaceutical Science, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274, Japan.

Received November 28, 1996; accepted January 25, 1997

When the β-acyloxy esters (±)-10 and (±)-11 were exposed to the lipase OF-360 from *Candida rugosa* or immobilized lipase OF-360 in a water-saturated organic solvent, the hydrolyzed product (8a*S*)-6 was obtained in high chemical (40%) and optical (>99% ee) yields. The absolute structure of (8a*S*)-6 was confirmed by the fact that (8a*S*)-6 was converted into an authentic sample γ-keto nitrile (8a*S*)-17. Treatment of the diol (±)-12 with isopropenyl acetate in the presence of the lipase Godo E-4 from *Pseudomonas* sp. provided the unchanged (8a*R*)-12 (89% ee) in 42% yield.

Key words lipase; immobilized lipase; enantioselective hydrolysis; enantioselective acetylation; drimane sesquiterpene

The potent antifeedant activity of several drimane sesquiterpenes has focused attention on the development of chiral synthesis of such natural products.[1] Some asymmetric syntheses of compounds of this class have been achieved by the conversion of higher terpenes such as abietic acid[2] or enantiomerically pure Wieland-Miescher ketone[3] or by tedious optical resolution of the carboxylic acid[4] but baker's yeast-mediated asymmetric reduction of prochiral ketone has been employed as the chiral induction step.[5] In previous papers, we have reported a large-scale synthesis of (±)-confertifolin (**2**) and (±)-isodrimenin (**3**) starting from dihydro-β-ionone (**1**),[6] and subsequently, we accomplished total synthesis of (±)-warburganal (**4**) using (±)-**3**.[7] We now report a useful and practical synthesis of the chiral synthon (8a*S*)-**6** with the decahydro-5,5,8a-trimethylnaphthalene-1-carboxylate skeleton, based on enzymatic resolution. This compound should be convertible to more functionalized and more biologically active drimane sesquiterpenes such as warburganal (**4**) and polygodial (**5**).

Synthesis of the Substrates for Enzymatic Reaction The desired racemic β-hydroxy ester **6** was obtained by improvement of the reported procedure.[8] Heating linalool (**7**) and ethylvinyl ether in a sealed tube in the presence of phosphoric acid gave a crude reaction mixture, which was treated with 10% aqueous acetic acid to provide the aldehyde **8** as a mixture of Δ^4 *cis*- and *trans*-isomers. Wittig condensation of the aldehyde **8** with methyl (triphenylphosphoranylidene)acetate in benzene solution stereoselectively gave the methyl Δ^2 *trans*-dodecatrienoate **9**. Biomimetic cyclization of compound **9** in formic acid-sulfuric acid yielded the (±)-formate **10** and (±)-**6** in 30% and 8% overall yields from linalool, respectively. Saponification of (±)-**10** gave quantitatively the (±)-β-hydroxy ester **6**, which was treated with acetic anhydride in pyridine to provide the (±)-acetate **11**.

Lipase-Catalyzed Enantioselective Hydrolysis of (±)-10 and (±)-11 In a screening experiment, three kinds of lipases MY-30, OF-360, and Sigma type VII from the same microorganism, *Candida rugosa*, were found to be effective for the enantioselective hydrolysis of two kinds of β-acyloxy esters, (±)-**10** and (±)-**11**. The β-acyloxy esters were subjected to enzymatic hydrolysis using the above-mentioned lipases in water-saturated isooctane or isopropyl ether at 33 °C for a suitable time and selected data are shown in Table 1.

In every case, the configuration of the C_2-OH group liberated by lipase-catalyzed hydrolysis of the corresponding acylate was found to be *R* and that of the recovered C_2-acyloxyl group, *S*. The hydrolyzed substrate (1*R*,2*R*,

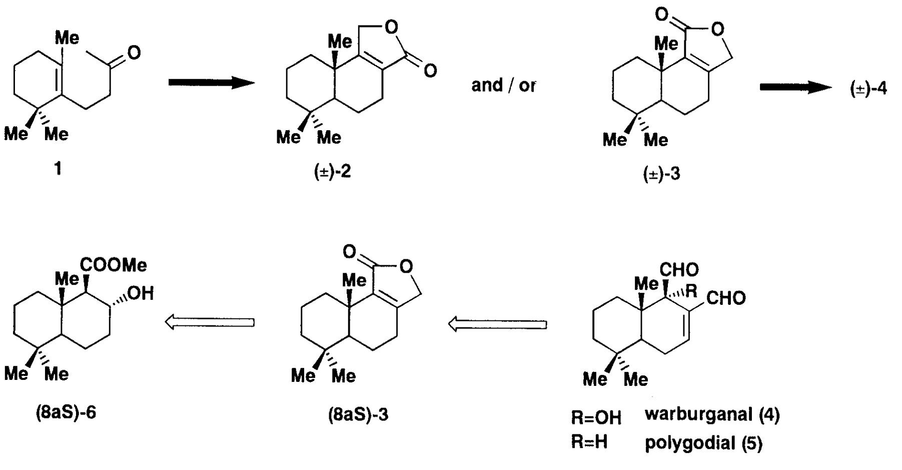


Chart 1

---

* To whom correspondence should be addressed.

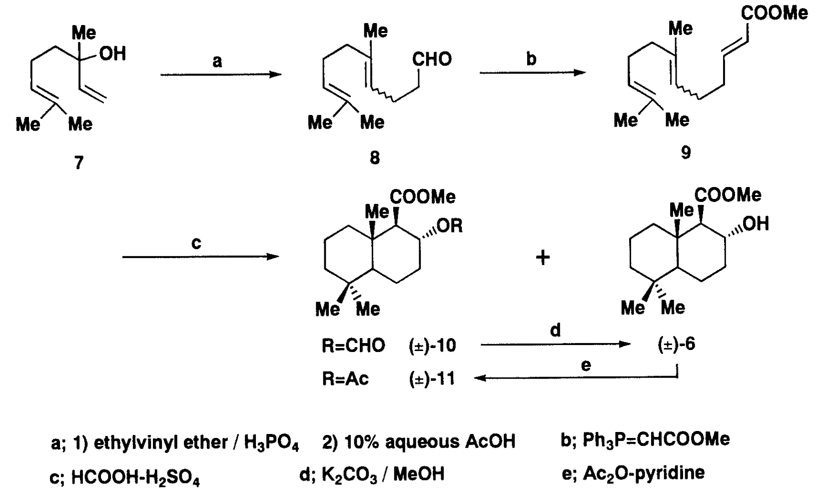
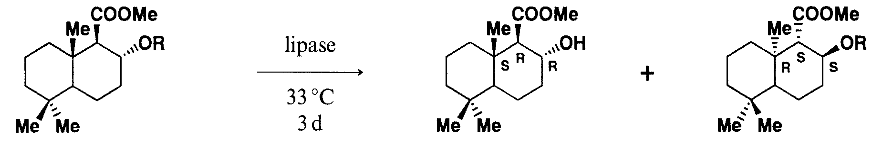


Chart 2

Table 1.



R=CHO (±)-**10** (8a*S*)-**6** R=CHO (8a*R*)-**10**
R=Ac (±)-**11** R=Ac (8a*R*)-**11**

Entry	Substrate (mg)	Lipase	Solvent	Product (%, %ee)	
1	(±)-**10** (100)	MY-30	H_2O–saturated (iso-Pr)$_2$O	(8a*S*)-**6** (7, >99)	(8a*R*)-**10** (90, 11)
2	(±)-**10** (100)	OF-360	H_2O–saturated (iso-Pr)$_2$O	(8a*S*)-**6** (16, >99)	(8a*R*)-**10** (76, 11)
3	(±)-**10** (100)	Sigma type VII	H_2O–saturated (iso-Pr)$_2$O	(8a*S*)-**6** (12, >99)	(8a*R*)-**10** (85, 8)
4	(±)-**10** (100)	MY-30	H_2O–saturated isooctane	(8a*S*)-**6** (9, >99)	(8a*R*)-**10** (80, 21)
5	(±)-**10** (100)	OF-360	H_2O–saturated isooctane	(8a*S*)-**6** (22, 84)	(8a*R*)-**10** (69, 27)
6	(±)-**10** (100)	Sigma type VII	H_2O–saturated isooctane	(8a*S*)-**6** (13, 98)	(8a*R*)-**10** (80, 15)
7	(±)-**11** (100)	MY-30	H_2O–saturated isooctane	(8a*S*)-**6** (44, 48)	(8a*R*)-**11** (48, 58)
8	(±)-**11** (100)	OF-360	H_2O–saturated isooctane	(8a*S*)-**6** (33, 65)	(8a*R*)-**11** (50, 76)

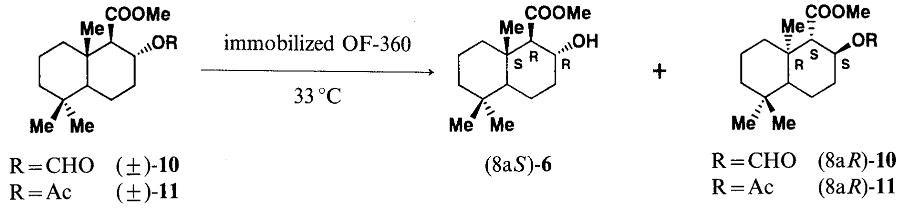
4a*S*,8a*S*)-**6** was obtained with a much higher optical purity than the unhydrolyzed compounds in most cases. In particular, when (±)-**10** was treated with OF-360 (entry 2 in Table 1), the optical purity of (+)-**6** ([α]$_D$ +13.4° (c=1.26, $CHCl_3$)) was found to be very high (>99% ee). For the purpose of improving the chemical yield of (+)-**6** or accelerating the enzymatic reaction rate, immobilized lipase OF-360 was prepared by illumination of a mixture of a photo-crosslinkable resin prepolymer ENTP-4000,[9] a photo-sensitizer, benzoin ethyl ether, and the crude lipase OF-360. When (±)-**10** was subjected to enantioselective hydrolysis using the immobilized lipase OF-360 for 17 d (entry 2 in Table 2), (8a*S*)-**6** was obtained in 40% yield with >99% ee.

The key feature of the present kinetic resolution using immobilized lipase is that both chemical and optical yields were much improved, compared to the previous cases where native lipases were used. The enantiomeric purity of the chiral compounds was determined by high-performance liquid chromatography (HPLC) on a Chiralcel OD (250×4.6 mm) column. In order to confirm the absolute structure of the present (+)-**6**, (+)-**6** was converted into the known γ-keto nitrile (8a*S*)-**17**[10] as shown in Chart 3. Reduction of (+)-**6** with $LiAlH_4$ gave a diol (−)-**12** ([α]$_D$ −2.26° (c=1.06, MeOH)), which was treated with 1 eq of pivaloyl chloride (*tert*-BuCOCl) to afford **13** (11% yield) and **14** (55% yield). Oxidation of **14** followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided an intermediary α,β-unsaturated ketone **16**, which was treated with cyanide ion to give the desired γ-keto nitrile **17** in 73% overall yield. Spectral data ([α]$_D$ −43.4° (c=1.00, $CHCl_3$), mp 74.5—75 °C, NMR) of the present **17** were identical with those ([α]$_D$ −45.6° (c=0.5, $CHCl_3$), mp 75—76 °C, NMR) of authentic (8a*S*)-**17**.[10] Consequently, the absolute configurations of (+)-**6** were found to be 1*R*, 2*R*, 4a*S* and 8a*S*.

Enantioselective Acetylation of (±)-6 with Immobilized Lipase OF-360 and Vinyl Acetate The β-hydroxy ester (±)-**6** was subjected to enantioselective acetylation using immobilized lipase OF-360 and vinyl acetate, and selected data are shown in Table 3.

In both cases, the acetylated products had (1*R*,2*R*,4a*S*, 8a*S*) configurations and the unchanged β-hydroxy ester had (1*S*,2*S*,4a*R*,8a*R*) configurations. No improvement in chemical and optical yields was observed.

Table 2.



Entry	Substrate (mg)	Solvent	Time (d)	Product (%, %ee)	
1	(±)-**10** (100)	A	3	(8a*S*)-**6** (15, >99)	(8a*R*)-**10** (82, 16)
2	(±)-**10** (100)	A	17	(8a*S*)-**6** (40, >99)	(8a*R*)-**10** (57, 68)
3	(±)-**10** (100)	A	21	(8a*S*)-**6** (44, 89)	(8a*R*)-**10** (49, 70)
4	(±)-**10** (100)	B	3	(8a*S*)-**6** (20, >99)	(8a*R*)-**10** (76, 11)
5	(±)-**11** (100)	A	3	(8a*S*)-**6** (17, 97)	(8a*R*)-**11** (74, 11)
6	(±)-**11** (100)	A	6	(8a*S*)-**6** (25, >99)	(8a*R*)-**11** (65, 29)
7	(±)-**11** (100)	A	21	(8a*S*)-**6** (27, >99)	(8a*R*)-**11** (69, 44)
8	(±)-**11** (100)	A	42	(8a*S*)-**6** (45, 93)	(8a*R*)-**11** (49, 74)
9	(±)-**11** (100)	B	3	(8a*S*)-**6** (10, 97)	(8a*R*)-**11** (77, 29)

A, H_2O–saturated isooctane; B, H_2O–saturated (iso-Pr)$_2$O.

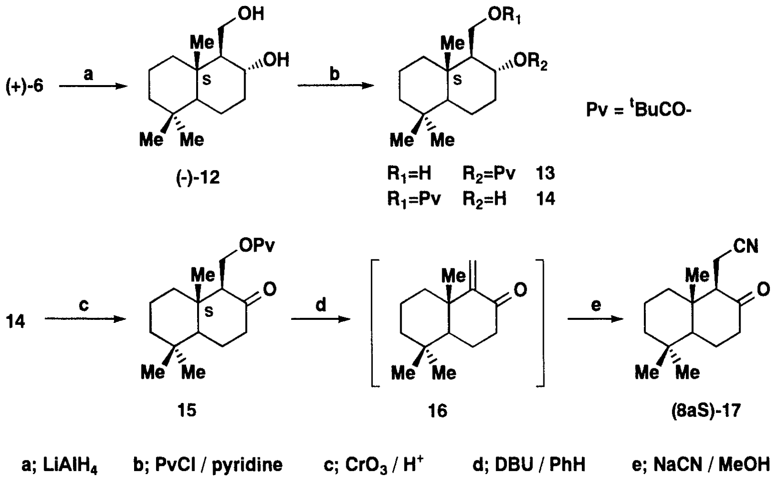
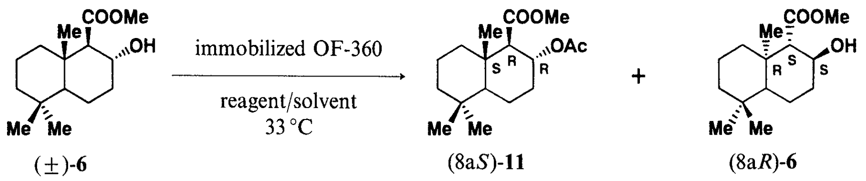


Chart 3

Table 3.

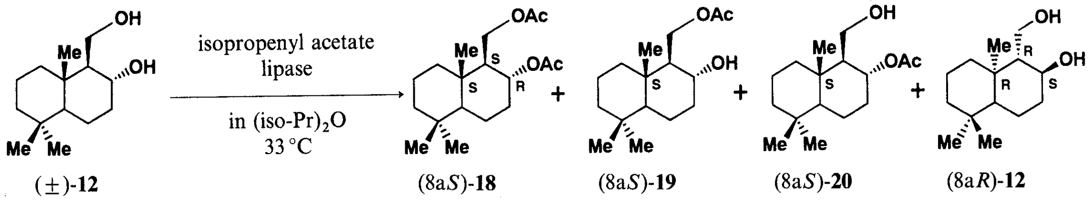


Entry	Substrate (mg)	Solvent/solvent	Time (h)	Products (%, %ee)	
1	(±)-**6** (100)	Vinyl acetate	91	(8a*S*)-**11** (9, 89)	(8a*R*)-**6** (87, 7)
2	(±)-**6** (100)	Vinyl acetate/ (iso-Pr)$_2$O	72	(8a*S*)-**11** (6, 69)	(8a*R*)-**6** (93, 4)

Enantioselective Acetylation of the Diol (±)-12 with Lipases and Isopropenyl Acetate In the case of the enantioselective hydrolysis of the β-acyloxy esters (±)-**10** and (±)-**11** with lipase, the enzymatic reaction rate was found to be slow, and the conversion yield was consequently low. Therefore, enantioselective acetylation of the diol (±)-**12** obtained by $LiAlH_4$ reduction of (±)-**10** with lipase and isopropenyl acetate as the acylating reagent was carried out. From a screening experiment, four kinds of lipases (OF-360, MY-30, Sigma type VII, and Amano AY-30) from the same microorganism, *Candida rugosa*, and a lipase Godo E-4 from *Pseudomonas* sp. were chosen for enantioselective acetylation; selected data are shown in Table 4.

In particular, when (±)-**12** was subjected to enantioselective acetylation with the lipase Godo E-4 and

Table 4.



Entry	Lipase	(8a*S*)-**18**		(8a*S*)-**19** + (8a*S*)-**20**				(8a*R*)-**12**	
		Yield (%)	(%ee)	Yield (%)	(**19**:**20**)	**19** (%ee)	**20** (%ee)	Yield (%)	(%ee)
1	OF-360			54	(3.6:1)	48	51	40	54
2	MY-30			36	(4.2:1)	45	43	58	35
3	Sigma type VII	4	81	70	(4.7:1)	26	28	23	67
4	Amano AY-30	2	51	46	(4.8:1)	43	40	50	39
5	Godo E-4	2	94	53	(5.8:1)	75	78	42	89

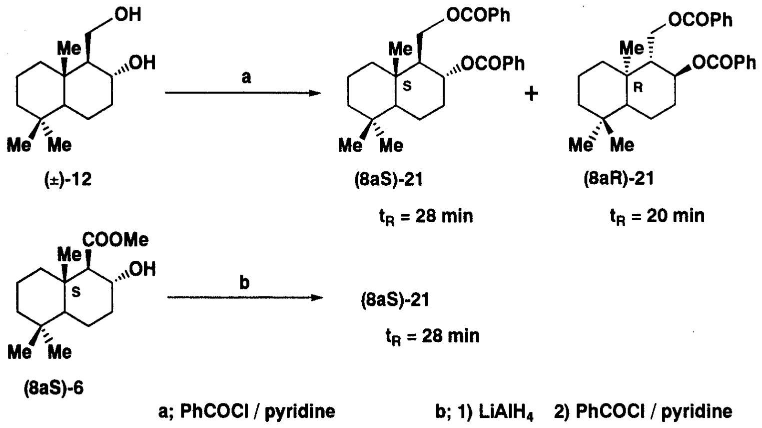


Chart 4

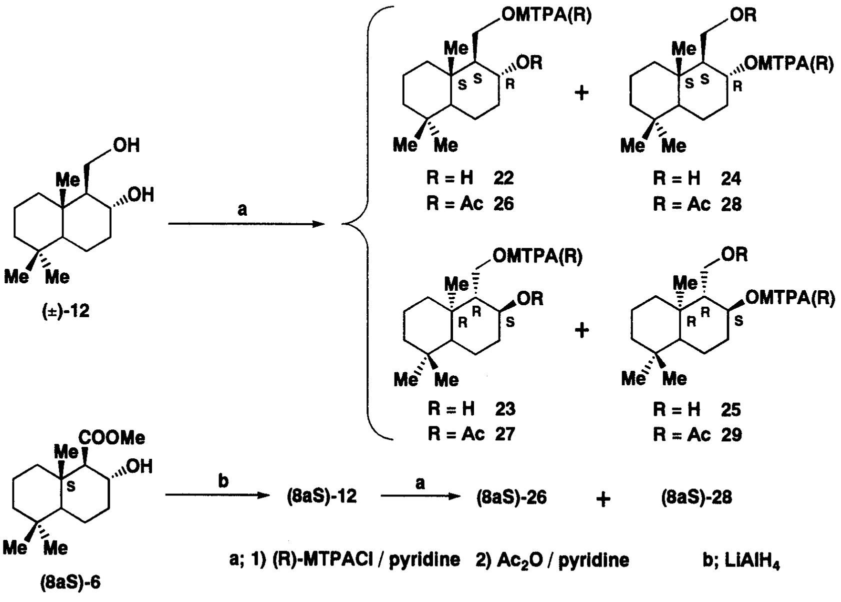


Chart 5

isopropenyl acetate (entry 5), the chemical yield (42%) and optical purity (89% ee) of (8a*R*)-**12** were found to be rather high. In every case, the reaction time was shortened and three or four kinds of products were obtained. The ratio of the monoacetates (8a*S*)-**19** and (8a*S*)-**20** was calculated by means of nuclear magnetic resonance (NMR) analysis as described below, because chromatographic separation of the monoacetates **19** and **20** was difficult. In every case, the configuration of the C_{8a}-angular methyl group of the acetylated products (**18**, **19**, and **20**) was found to be *S*. In order to determine the optical purity and absolute structure of the enzymatic reaction products, chiral authentic samples were synthesized. First, we will describe the determinations of the diacetate **18** and the unchanged diol **12**. The racemic **12** was converted to the corresponding (±)-dibenzoate **21** ((8a*S*)-**21** and (8a*R*)-**21**). In HPLC analysis using a chiral column (Chiralcel OD 4.6×250 mm), the racemate **21** gave two well separated peaks ($t_R = 20$ and 28 min), while the retention time of the dibenzoate (8a*S*)-**21** derived from the above-mentioned (8a*S*)-**6** (>99% ee) was 28 min. Therefore, derivations of the diacetate **18** and the unchanged diol **12** into the dibenzoates **21**, respectively, made it possible to determine the optical purity and the absolute structure; the results are shown in Table 4.

Then, the optical purity and the absolute structures of the monoacetates **19** and **20** were determined.

The racemic diol (±)-**12** was treated with one equivalent of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride ((*R*)-(+)-MTPACl)[11] in pyridine to give two diastereomeric mixtures, which were separated into a diasteromeric mixture (34% yield) of the 2-hydroxy-(*R*)-MTPA esters **22** and **23**, and the other diasteromeric mixture (4% yield) of the 1-hydroxylmethyl-(*R*)-MTPA esters **24** and **25**. The diasteromeric mixture of **22** and **23** was converted into a diasteromeric mixture of the 2-acetoxy-(*R*)-MTPA esters **26** and **27**, in which the signal of the acetoxyl group appeared as singlets at δ 1.90 and 1.89 in the 500 MHz NMR spectrum. The acetoxyl group of the diasteromeric mixture of the 1-acetoxylmethyl-(*R*)-MTPA esters **28** and **29** derived from the diasteromeric mixture of **24** and **25** also gave two singlet signals at δ 1.95 and 1.91. In order to distinguish between the four singlets due to acetoxyl groups, authentic samples of (8a*S*)-(2*R*)-acetoxy-(*R*)-MTPA ester **26** and (8a*S*)-(1*S*)-acetoxylmethyl-(*R*)-MTPA ester **28** were synthesized from (2*R*)-hydroxy-(*R*)-MTPA ester (**22**; 32% yield from (8a*S*)-**12**) and (1*S*)-hydroxylmethyl-(*R*)-MTPA ester (**24**; 5% yield from (8a*S*)-**12**), respectively. The signals of the acetoxyl groups of (8a*S*)-**26** and (8a*S*)-**28** appeared at δ 1.90 and 1.95, each as a singlet, respectively. When the acetoxyl group (δ 1.90, s) and C_2-hydrogen (δ 4.88, m) of **26** were irradiated at the same time by applying the long-range selective proton decoupling (LSPD) technique, the acetoxyl carbonyl signal appeared as a singlet at δ 170.8 ppm in the ^{13}C-NMR spectrum. This means that the acetoxyl group of **26** is located at the C_2-position. Consequently, the signals at δ 1.89 and 1.91 could be assigned to the acetoxyl group of **27** and that of **29**, respectively. Therefore, the relationship between the signals of the four kinds of acetoxyl groups and the absolute structures of the four acetates (**26**—**29**) was confirmed, and the derivations of monoacetate mixtures of **19** and **20** into (*R*)-MTPA esters made it possible to determine the optical purity, the absolute structure, and the ratio of **19** and **20**. The results are shown in Table 4. In the case of treatment of the diol (±)-**12** with isopropenyl acetate in the presence of the lipase Godo E-4 from *Pseudomonas* sp., the enantiomer (8a*R*)-**12** (89% ee) of the desired compound (8a*S*)-**12** for the synthesis of target molecules was obtained in 42% yield. This *ent*-type compound (8a*R*)-**12** should be a versatile chiral intermediate for the synthesis of biologically active marine natural products such as zonarol, isozonarol and zonaroic acid.[12)]

Further improvement of the enzymatic reaction conditions and application of the products to natural products synthesis are being undertaken.

Experimental

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR-300 instrument. NMR spectra were measured on a JEOL EX 4000 instrument. Spectra were taken for 5—10% (w/v) solutions in $CDCl_3$ with Me_4Si as an internal reference (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Fast atom bombardment mass spectra (FAB-MS) were obtained with a JEOL JMS-DX 303 spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). All organic solvent extracts were washed with saturated brine and dried over anhydrous magnesium sulfate ($MgSO_4$). All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

(±)-Methyl (1β,2α,4aα,8aβ)-2-Formyloxy-decahydro-5,5,8a-trimethylnaphthalene-1-carboxylate (10) and (±)-Methyl (1β,2α,4aα,8aβ)-2-Hydroxydecahydro-5,5,8a-trimethylnaphthalene-1-carboxylate (6) A mixture of linalool (**7**; 0.1 mol, 15.4 g), ethyl vinyl ether (0.2 mol, 14.4 g), and H_3PO_4 (0.06 ml) was heated in a sealed tube at 140 °C for 8 h. The reaction mixture was treated with triethylamine (0.1 ml) and was diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was refluxed in 10% aqueous AcOH (AcOH; 18 ml, H_2O; 2 ml) with stirring for 1 h. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine, dried over $MgSO_4$, and evaporated to give a crude aldehyde **8**. A mixture of crude **8**, methyl(triphenylphosphoranylidene) acetate (0.1 mol, 33.4 g), and benzene (100 ml) was refluxed with stirring for 12 h. The reaction mixture was directly subjected to chromatography on silica gel (150 g) to give a homogeneous oil **9** (17.06 g) from the *n*-hexane–ethyl acetate (20 : 1) eluate. The triene methyl ester (**9**) was added slowly during 1 h to a cold solution of HCOOH (320 ml) and H_2SO_4 (32 ml). The reaction mixture was stirred for 2 h at room temperature, then diluted with H_2O and extracted with ether. The ether layer was diluted with H_2O, neutralized with solid Na_2CO_3 (*ca.* 440 g), and dried over $MgSO_4$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (150 g) to afford (±)-**10** from the *n*-hexane–ethyl acetate (20 : 1) eluate and (±)-**6** from the *n*-hexane–ethyl acetate (5 : 1) eluate. Crystallization of (±)-**10** from *n*-hexane–ethyl acetate gave colorless needles (8.34 g, 30% overall yield from **7**). (±)-**10**: mp 111.0—111.3 °C. *Anal.* Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.22; H, 9.32. IR (Nujol): 1731 cm^{-1}. NMR δ: 0.84, 0.89, 1.03 (each 3H, s, Me), 1.15—1.74 (11H, m, methylene and 4a-H), 2.32 (1H, d, J=11.7 Hz, 1-H), 3.66 (3H, s, COOMe), 5.27 (1H, dt, J=5.1, 11.2 Hz, 2-H), 7.96 (1H, s, CHO). Crystallization of (±)-**6** from *n*-hexane gave colorless plates (2.11 g, 8% overall yield from **7**). (±)-**6**: mp 90.5—90.8 °C. *Anal.* Calcd for $C_{15}H_{26}O_3$: C, 70.83, H, 10.30. Found: C, 70.68; H, 10.23. IR (Nujol): 3525, 1722 cm^{-1}. NMR δ: 0.82, 0.89, 0.97 (each 3H, s, Me), 1.01—1.75 (11H, m, methylene and 4a-H), 2.08 (1H, d, J=10.7 Hz, 1-H), 3.68 (3H, s, COOMe), 4.02—4.13 (1H, m, 2-H).

Conversion of (±)-10 into (±)-6 A mixture of (±)-**10** (11.5 mmol, 3.25 g), K_2CO_3 (17.3 mmol, 2.4 g), and MeOH (20 ml) was stirred at room temperature for 30 min. The reaction mixture was concentrated, diluted with H_2O, and extracted with ether. The ether layer was washed with saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (45 g) to provide (±)-**6** (2.92 g, 99% yield) from the *n*-hexane–ethyl acetate (5 : 1) eluate.

(±)-Methyl (1β,2α,4aα,8aβ)-2-Acetoxy-decahydro-5,5,8a-trimethylnaphthalene-1-carboxylate (11) A mixture of (±)-**6** (10 mmol, 2.53 g), Ac_2O (43 mmol, 4.36 g), dimethylaminopyridine (10 mg), and pyridine (15 ml) was stirred at room temperature for 4 h. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (50 g) to provide (±)-**11** from the *n*-hexane–ethyl acetate (10 : 1) eluate. Crystallization of (±)-**11** from *n*-hexane gave colorless plates (8.34 g, 83% yield). (±)-**11**: mp 82 °C. *Anal.* Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.91; H, 9.62. IR (Nujol): 1784, 1732 cm^{-1}. NMR δ: 0.82, 0.89, 1.03 (each 3H, s, Me), 0.87—1.73 (11H, m, methylene and 4a-H), 1.96 (3H, s, $OCOCH_3$), 2.28 (1H, d, J=11.2 Hz, 1-H), 3.65 (3H, s, COOMe), 5.15 (1H, dt, J=5.1, 11.2 Hz, 2-H).

HPLC Analysis of Three Racemates ((±)-6, (±)-10 and (±)-11) by Using a Chiral Column Three kinds of racemates were analyzed individually to provide well separated peaks ((±)-**6**, 8 and 21 min; (±)-**10**, 19 and 23 min; (±)-**11**, 20 and 26 min) of each enantiomer under the following analytical conditions: for (±)-**6** (column, Chiralcel OD (4.6 × 250 mm); eluent, *n*-hexane–EtOH–iso-PrOH (600 : 10 : 10); detection, UV at 240 nm; flow rate, 1.0 ml/min), for (±)-**10** and (±)-**11** (column, Chiralcel OD (4.6 × 250 mm); eluent, *n*-hexane–EtOH (1000 : 1); detection, UV at 240 nm; flow rate, 1.0 ml/min).

General Procedure of Enantioselective Hydrolysis of (±)-10 and (±)-11 A mixture of substrate (0.34—0.35 mmol, 100 mg) and a commercial lipase (100 mg) in a water-saturated organic solvent was shaken at 33 °C for 3 d. The reaction mixture was filtered with the aid of Celite and the Celite pad was washed with ethyl acetate. The combined organic solution was dried over $MgSO_4$ and evaporated to give an oily product, which was subjected to silica gel (10 g) column chromatography to afford the unchanged esters (8a*R*)-**10** or (8a*R*)-**11** and the hydrolyzed product (8a*S*)-**6**. The resulting alcohol and esters were directly analyzed by HPLC and the results are shown in Table 1. The $[\alpha]_D$ values and retention times (t_R) of all reaction products were as follows: (+)-(1*R*,2*R*,4a*S*,8a*S*)-**6**, $[\alpha]_D^{25}$ +13.4° (c=1.26, $CHCl_3$) corresponds to >99% ee, 8 min; (1*S*,2*S*,4a*R*,8a*R*)-**10**, 27% ee, t_R=19 min (36%) and 23 min (64%); (1*S*,2*S*,4a*R*,8a*R*)-**11**, 76% ee, t_R=20 min (12%) and 26 min (88%).

Immobilization of Lipase OF-360 with Photo-crosslinkable Prepolymer (ENTP 4000) One gram of ENTP 4000 was mixed with 10 mg of a photosensitizer, benzoin ethyl ether. The mixture was melted completely at 60 °C. The powdered lipase (100 mg) OF-360 was added to the molten mixture under continuous mixing. The prepolymer-lipase mixture was layered on a framed sheet of transparent polyester film (thickness, *ca.* 0.5 mm). The layer was covered with transparent thin film and then illuminated with chemical lamps (wavelength range, 300—400 nm) for 3 min. The gel film thus formed was cut into small pieces (0.5 × 5 × 5 mm) and used for biochemical reactions.

General Procedure of Enantioselective Hydrolysis of (±)-10 and (±)-11 Using Immobilized Lipase OF-360 A mixture of substrate (0.34—0.35 mmol, 100 mg), the above-mentioned immobilized lipase OF-360, and water-saturated organic solvent was shaken at 33 °C for a suitable time. The reaction mixture was worked up in the same manner as in the case of enantioselective hydrolysis. The results are shown in Table 2.

General Procedure of Enantioselective Esterification of (±)-6 Using Immobilized Lipase OF-360 A mixture of substrate (0.39 mmol, 100 mg), the above-mentioned immobilized lipase OF-360, and vinyl acetate (10 g) or vinyl acetate (100 mg)–isopropyl ether (20 ml) was incubated at 33 °C for a suitable time. The reaction mixture was worked up in the same manner as in the case of enantioselective hydrolysis. The results are shown in Table 3.

(−)-(1*S*,2*R*,4a*S*,8a*S*)-2-Hydroxy-decahydro-5,5,8a-trimethyl-1-naphthylmethanol (12) A solution of (8a*S*)-**6** (1.48 mmol, 375 mg) in dry tetrahydrofuran (THF, 15 ml) was added to a suspension of $LiAlH_4$ (2.29 mmol, 87 mg) in dry THF (15 ml) at 0 °C. The whole mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O, then extracted with ethyl acetate and the organic solution was dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (30 g) to provide (8a*S*)-**12** from the *n*-hexane–ethyl acetate (1 : 1) eluate. Crystallization from *n*-hexane–ethyl acetate provided a colorless (8a*S*)-**12** (324 mg, 97% yield). (8a*S*)-**12**: mp 65 °C. *Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.14; H, 11.56. $[\alpha]_D^{27}$ −2.26° (c=1.06, MeOH). IR (Nujol): 3313, 3209 cm^{-1}. NMR δ: 0.79, 0.80, 0.88 (each 3H, s, Me), 0.84—2.11 (12H, m, methylene, 1-H, and 4a-H), 2.47, 2.95 (each 1H, br s, OH), 3.72 (2H, dd, J=8.8, 10.8 Hz, $\underline{CH}_2OH$), 3.84—3.95 (1H, m, 2-H).

(−)-(1*S*,2*R*,4a*S*,8a*S*)-2-Pivaloyloxy-decahydro-5,5,8a-trimethyl-1-naphthylmethanol (13) and (+)-(1*S*,2*R*,4a*S*,8a*S*)-2-Hydroxy-1-pivaloyloxymethyl-decahydro-5,5,8a-trimethyl-naphthalene (14) A mixture of (8a*S*)-**12** (5.28 mmol, 1.194 g), pivaloyl chloride (*tert*-BuCOCl, 4.22 mmol, 508 mg), and pyridine (15 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (50 g) to provide (8a*S*)-**13** (185 mg, 11% yield) from the *n*-hexane–ethyl acetate (20 : 1) eluate, (8a*S*)-**14** (904 mg, 55% yield) from the *n*-hexane–ethyl acetate (5 : 1) eluate, and recovered (8a*S*)-**12** (387 mg, 32% yield) from the *n*-hexane–ethyl acetate (1:1) eluate. (8a*S*)-**13**: a colorless oil, FAB-MS *m*/*z*: 311 (M^++1) (Calcd for $C_{19}H_{34}O_3$: 310). $[\alpha]_D^{26}$ −13.1° (c=1.63, $CHCl_3$). IR (neat): 3446, 1726 cm^{-1}. NMR δ: 0.81, 0.87, 0.89 (each 3H, s, Me), 1.19 (9H, s, *tert*-Bu), 0.96—2.17 (12H, m, methylene, 1-H and 4a-H), 3.58—3.67 (1H, m, 2-H), 4.19 (1H, dd, J=12, 3.7 Hz, $\underline{CH}_2OCOBu^t$), 4.49 (1H, dd, J=12, 4.1 Hz, $\underline{CH}_2OCOBu^t$). (8a*S*)-**14**: a colorless oil, FAB-MS *m*/*z*: 311 (M^++1) (Calcd for $C_{19}H_{34}O_3$: 310). $[\alpha]_D^{22}$ +23.3° (c=1.07, $CHCl_3$). IR (neat): 3443, 1725 cm^{-1}. NMR δ: 0.82, 0.88, 0.90 (each 3H, s, Me), 1.20 (9H, s, *tert*-Bu), 1.13—2.16 (12H, m, methylene, 1-H and 4a-H), 3.60—3.70 (1H, m, 2-H), 4.19 (1H, dd, J=12, 3.9 Hz, $\underline{CH}_2OCOBu^t$), 4.51 (1H, dd, J=12, 3.9 Hz, $\underline{CH}_2OCOBu^t$).

(−)-(1*S*,4a*S*,8a*S*)-2-Oxo-1-pivaloyloxymethyl-decahydro-5,5,8a-trimethyl-naphthalene (15) Jones reagent (0.8 ml) was added to a solution of (8a*S*)-**14** (3.9 mmol, 1.211 g) in acetone (20 ml) at 0 °C and the reaction mixture was stirred at room temperature for 1h. Then iso-PrOH (1 ml) was added to the reaction mixture, and the whole was concentrated, diluted with H_2O, and extracted with ether. The ether layer was washed with saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (30 g) to provide a colorless oil (8a*S*)-**15** (1.14 g, 94% yield) from the *n*-hexane–ethyl acetate (20 : 1) eluate. (8a*S*)-**15**: FAB-MS *m*/*z*: 309 (M^++1) (Calcd for $C_{19}H_{32}O_3$: 308). $[\alpha]_D^{22}$ −22.3° (c=1.03, $CHCl_3$). IR (neat): 1727 cm^{-1}. NMR δ: 0.79, 0.86, 0.98 (each 3H, s, Me), 1.15 (9H, s, *tert*-Bu), 1.23—2.48 (12H, m, methylene, 1-H and 4a-H), 4.14 (1H, dd, J=11.2, 4 Hz, $\underline{CH}_2OCOBu^t$), 4.41 (1H, dd, J=11.2, 7.3 Hz, $\underline{CH}_2OCOBu^t$).

(−)-(1*R*,4a*S*,8a*S*)-2-Oxo-decahydro-5,5,8a-trimethyl-1-naphthalene-acetonitrile (17) A mixture of (8a*S*)-**15** (3.70 mmol, 1.142 g), DBU (19.1 mmol, 2.913 g), and benzene (20 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O, and extracted with ether. The ether layer was washed with saturated brine, dried over $MgSO_4$, and evaporated to give a crude α,β-unsaturated ketone (**16**). Without further purification of **16**, a mixture of **16**, NaCN (6.1 mmol, 299 mg), and MeOH (18 ml) was refluxed with stirring for 1 h. The reaction mixture was diluted with saturated brine and extracted with ether. The ether layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (30 g) to provide (8a*S*)-**17** from the *n*-hexane–ethyl acetate (10 : 1) eluate. Crystallization of (8a*S*)-**17** from *n*-hexane gave colorless needles (8a*S*)-**17** (665 mg, 77% yield). (8a*S*)-**17**: mp 74.5—75 °C. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.36, H, 9.81, N, 6.00. $[\alpha]_D^{23}$ −43.4° (c=1.00, $CHCl_3$). IR (KBr): 2242, 1712 cm^{-1}. NMR δ: 0.72, 0.87, 1.00 (each 3H, s, Me), 1.23—2.60 (12H, m, methylene, 1-H and 4a-H), 2.24 (1H, dd, J=16.6, 4.4 Hz, $\underline{CH}_2CN$), 2.72 (1H, dd, J=16.6, 8.3 Hz, $\underline{CH}_2CN$).

(±)-(1β,2α,4aα,8aβ)-2-Hydroxy-decahydro-5,5,8a-trimethyl-1-naphthylmethanol (12) A solution of (±)-**10** (5.58 mmol, 1.65 g) in dry ether (50 ml) was added to a suspension of $LiAlH_4$ (15.1 mmol, 574 mg) in dry ether (10 ml) at 0 °C. The reaction mixture was stirred for 4 h at room temperature, then diluted with H_2O and extracted with ethyl acetate. The organic solution was dried over $MgSO_4$. Removal of the solvent gave a residue, which was crystallized from *n*-hexane–ethyl acetate to provide colorless plates (±)-**12** (1.30 g, 98% yield). (±)-**12**: mp 97.5—98 °C. Spectral data of (±)-**12** were identical with those (IR and NMR) of (8a*S*)-**12**.

(±)-(1β,2α,4aα,8aβ)-2-Benzoyloxy-1-benzoyloxymethyl-decahydro-5,5,8a-trimethylnaphthylene (21) A mixture of (±)-**12** (13 mg) and benzoyl chloride (31 mg) in pyridine (0.5 ml) was stirred at room temperature for 8 h. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 N aqueous HCl and saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (10 g) to provide (±)-**21** from the *n*-hexane–ethyl acetate (19 : 1) eluate. Crystallization of (±)-**21** from *n*-hexane–ethyl acetate gave colorless needles (25 mg, 99% yield). (±)-**21**: mp 108.5—109 °C. *Anal.* Calcd for $C_{28}H_{34}O_4$: C, 77.39; H, 7.89. Found: C, 77.39; H, 7.81. IR (Nujol): 1784, 1732 cm^{-1}. NMR δ: 0.87, 0.92, 1.04 (each 3H, s, Me), 1.17—1.97 (11H, m, methylene and 4a-H), 2.34—2.38 (1H, m, 1-H), 4.41 (1H, dd, $J=11.7$, 3.7 Hz, $\underline{CH_2}OCOPh$), 4.53 (1H, dd, $J=11.7$, 4.4 Hz, $\underline{CH_2}OCOPh$), 5.31—5.38 (1H, m, 2-H), 7.28—7.36 (4H, m, aromatic-H), 7.45—7.52 (2H, m, aromatic-H), 7.89—7.98 (4H, m, aromatic-H).

HPLC Analysis of the Racemate (±)-21 by Using a Chiral Column The dibenzoate (±)-**21** was analyzed to provide well separated peaks (20 and 28 min) of each enantiomer under the following analytical conditions: column, Chiralcel OD (4.6 × 250 mm); eluent, *n*-hexane–EtOH (500 : 1); detection, UV at 254 nm; flow rate, 1.0 ml/min).

(1*S*,2*R*,4a*S*,8a*S*)-2-Benzoyloxy-1-benzoyloxymethyl-decahydro-5,5,8a-trimethyl-naphthylene (21) A mixture of (8a*S*)-**12** (5 mg) and benzoyl chloride (30 mg) in pyridine (0.5 ml) was stirred at room temperature for 8 h. The reaction mixture was worked up in the same way as in the case of (±)-**21** to afford (8a*S*)-**21** (9 mg). Retention time of (8a*S*)-**21** by HPLC analysis: $t_R=28$ min.

General Procedure of Enantioselective Esterification of (±)-12 A mixture of substrate (0.44 mmol, 100 mg) and a commercial lipase (100 mg) in isopropyl ether (20 ml) was shaken at 33 °C for a suitable time. The experiment was carried out twice on the same scale in every case. Each reaction mixture was worked up in the same manner as in the case of enantioselective hydrolysis of (±)-**10** to afford an oily product, which was chromatographed on silica gel (10 g) to provide the (8a*S*)-diacetate **18** from the *n*-hexane–ethyl acetate (20 : 1) eluate, a mixture of (8a*S*)-monoacetates (**19** and **20**) from the *n*-hexane–ethyl acetate (10 : 1) eluate, and the (8a*R*)-diol **12** from the *n*-hexane–ethyl acetate (1 : 1) eluate. The results are shown in Table 4. (8a*S*)-**18** (Table 4, entry 3): FAB-MS *m/z*: 311 ($M^+ + 1$) (Calcd for $C_{18}H_{30}O_4$: 310). IR (KBr): 1749, 1274 cm^{-1}. NMR δ: 0.83, 0.88, 0.93 (each 3H, s, Me), 1.07—1.81 (11H, m, methylene and 4a-H), 2.007, 2.009 (each 3H, s, $OCOCH_3$), 2.13—2.18 (1H, m, 1-H), 4.00 (1H, dd, $J=3.4$, 11.7 Hz, $\underline{CH_2}OAc$), 4.29 (1H, dd, $J=4.4$, 11.7 Hz, $\underline{CH_2}OAc$), 4.97 (1H, dt, $J=5.4$, 11.2, 11.7 Hz, 2-H). Mixture of (8a*S*)-monoacetates (**19** and **20**) (Table 4, entry 3): FAB-MS *m/z*: 269 ($M^+ + 1$) (Calcd for $C_{16}H_{28}O_3$: 268). IR (neat): 3442, 1739, 1244 cm^{-1}. NMR δ: 2.06, 2.08 (each 3H, s, $OCOCH_3$). A part of each (8a*R*)-**12** (*ca.* 10 mg) was converted into the corresponding (8a*R*)-dibenzoate **21** in the same way as described for the preparation of (±)-**21**, and the product was directly analyzed by means of HPLC. A part of the (8a*S*)-diacetate **18** (*ca.* 5 mg) was treated with K_2CO_3 (10 mg) in MeOH (0.5 ml) to give crude (8a*S*)-**12**, which was converted to the corresponding (8a*S*)-benzoate **21**. The optical yield and absolute structure of (8a*S*)-**21** were confirmed by means of HPLC analysis. A mixture (*ca.* 10 mg) of (8a*S*)-monoacetates **19** and **20** was converted to the corresponding mixture of (8a*S*,1*S*)-1-acetoxymethyl-(*R*)-MTPA ester **28** and (8a*S*,2*R*)-2-acetoxy-(*R*)-MTPA ester **26** in the manner described below. Optical yield, absolute structure and the ratio of (8a*S*,1*S*)-**28** and (8a*S*,2*R*)-**26** were confirmed by means of NMR analysis.

Preparation of the Diastereomeric Mixture of 2-Hydroxy-(*R*)-MTPA Esters 22 and 23, and the Diastereomeric Mixture of 1-Hydroxymethyl-(*R*)-MTPA Esters 24 and 25 A mixture of (±)-**12** (0.62 mmol, 141 mg) and (*R*)-(+)-MTPACl (0.62 mmol, 156 mg) in pyridine (3 ml) was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (50 g) to provide a diasteromeric mixture (17 mg, 4% yield) of **24** and **25** from the *n*-hexane–ethyl acetate (10 : 1) eluate, a diasteromeric mixture (152 mg, 34% yield) of **22** and **23** from the *n*-hexane–ethyl acetate (5 : 1) eluate, and (±)-**12** (42 mg, 30% yield) from the *n*-hexane–ethyl acetate (1 : 1) eluate. Mixture of (8a*S*)-**22** and (8a*R*)-**23**: FAB-MS *m/z*: 443 ($M^+ + 1$) (Calcd for $C_{24}H_{33}F_3O_4$: 442). IR (neat): 3544, 3432, 1747 cm^{-1}. NMR δ: 0.78, 0.858, 0.862, 0.88 (each 3H, s, Me), 0.79 (6H, s, Me × 2), 0.9—2.15 (24H, m, methylene, 1-H and 4a-H), 3.540, 3.545 (each 3H, OMe), 3.50—3.67 (2H, m, 2-H), 4.39—4.66 (4H, m, $\underline{CH_2}OMTPA$), 7.38—7.53 (10H, m, aromatic-H). Mixture of (8a*S*)-**24** and (8a*R*)-**25**: FAB-MS *m/z*: 443($M^+ + 1$) (Calcd for $C_{24}H_{33}O_4F_3$: 442). IR (neat): 3581, 3470, 1745 cm^{-1}. NMR δ: 0.81, 0.91 (each 6H, s, Me × 2), 0.86, 0.87 (each 3H, s, Me), 0.94—2.39 (24H, m, methylene, 1-H and 4a-H), 3.49, 3.58 (each 3H, s, OMe), 3.35—3.72 (2H, m, 2-H), 5.08—5.17 (2H, m, 2-H), 7.40—7.57 (10H, m, aromatic-H).

Preparation of a Diastereomeric Mixture of (8a*S*,2*R*)-2-Acetoxy-(*R*)-MTPA Ester 26 and (8a*R*,2*S*)-2-Acetoxy-(*R*)-MTPA Ester 27 A mixture (152 mg) of (8a*S*)-**22** and (8a*R*)-**23**, Ac_2O (0.5 ml) in pyridine (1 ml) was stirred at room temperature for 2 h. The reaction mixture was worked up in the same way as in the case of the preparation of (±)-**11** to afford an oily product, which was chromatographed on silica gel (10 g) to provide a diastereomeric mixture (156 mg) of (8a*S*,2*R*)-(*R*)-MTPA ester **26** and (8a*R*,2*S*)-(*R*)-MTPA ester **27** from the *n*-hexane–ethyl acetate (20 : 1) eluate. NMR δ: 1.89, 1.90 (each 3H, s, 2-OAc), 3.52, 3.53 (each 3H, s, OMe).

Preparation of a Diastereomeric Mixture of (8a*S*,1*S*)-1-Acetoxylmethyl-(*R*)-MTPA Ester 28 and (8a*R*,1*R*)-1-Acetoxylmethyl-(*R*)-MTPA Ester 29 A mixture (17 mg) of (8a*S*)-**24** and (8a*R*)-**25**, Ac_2O (60 mg) in pyridine (1 ml) was stirred at room temperature for 2 h. The reaction mixture was worked up in the same way as in the case of the preparation of (±)-**11** to afford an oily product, which was chromatographed on silica gel (3 g) to provide a diastereomeric mixture (17 mg) of (8a*S*,1*S*)-(*R*)-MTPA ester **28** and (8a*R*,1*R*)-(*R*)-MTPA ester **29** from the *n*-hexane–ethyl acetate (20 : 1) eluate. NMR δ: 1.91, 1.95 (each 3H, s, 2-OAc), 3.49, 3.54 (each 3H, s, OMe).

Preparation of (2*R*,8a*S*)-2-Hydroxy-(*R*)-MTPA Ester 22 and (1*S*,8a*S*)-1-Hydroxymethyl-(*R*)-MTPA Esters 24 A mixture of (8a*S*)-**12** (0.64 mmol, 146 mg), (*R*)-(+)-MTPACl (0.58 mmol, 145 mg) in pyridine (2 ml) was stirred for 12 h at room temperature. The reaction mixture was worked up in the same way as in the case of the preparation of **22**—**25** to afford (8a*S*)-**24** (14 mg, 5% yield), (8a*S*)-**22** (93 mg, 32% yield), and (8a*S*)-**12** (72 mg, 49% yield).

Preparation of (8a*S*,2*R*)-2-Acetoxy-(*R*)-MTPA Ester 26 A mixture of (8a*S*)-**22** (93 mg) and Ac_2O (200 mg) in pyridine (1 ml) was stirred at room temperature for 2 h. The reaction mixture was worked up in the same way as in the case of the preparation of the diastereomeric mixture of (8a*S*,2*R*)-**26** and (8a*R*,2*S*)-**27** to afford (8a*S*,2*R*)-2-acetoxy-(*R*)-MTPA ester **26** (96 mg). FAB-MS *m/z*: 485 ($M^+ + 1$) (Calcd for $C_{26}H_{35}F_3O_5$: 484). IR (neat): 1746 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 0.79, 0.80, 0.86 (each 3H, s, Me), 1.90 (3H, s, 2-OAc), 0.88—2.21 (12H, m, methylene, 1-H and 4a-H), 3.53 (3H, s, OMe), 4.18 (1H, dd, $J=11.7$, 3.5 Hz, $\underline{CH_2}OMTPA$), 4.51 (1H, dd, $J=11.7$, 3.7 Hz, $\underline{CH_2}OMTPA$), 4.88 (1H, dt, $J=5.1$, 11.2 Hz, 2-H), 7.38—7.53 (5H, m, aromatic-H). ^{13}C-NMR δ: 15.14 (q), 18.33 (t), 20.43 (t), 21.07 (q), 21.63 (q), 32.55 (t), 33.19 (s), 33.52 (q), 38.24 (s), 38.99 (t), 41.69 (t), 54.28 (d), 54.40 (d), 55.46 (q), 63.87 (t), 71.85 (d), 127.36 (d), 128.39 (d), 129.55 (d), 132.40 (s), 166.54 (s), 170.79 (s).

Preparation of (8a*S*,1*S*)-1-Acetoxylmethyl-(*R*)-MTPA Ester 28 A mixture of (8a*S*)-**24** (14 mg) and Ac_2O (60 mg) in pyridine (0.5 ml) was stirred at room temperature for 3 h. The reaction mixture was worked up in the same way as in the case of the preparation of the diastereomeric mixture of (8a*S*,1*S*)-**28** and (8a*R*,1*R*)-**29** to afford (8a*S*,1*S*)-1-acetoxylmethyl-(*R*)-MTPA ester **28** (13 mg). FAB-MS *m/z*: 485 ($M^+ + 1$) (Calcd for $C_{26}H_{35}F_3O_5$: 484). IR (neat): 1745 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 0.83, 0.86, 0.94 (each 3H, s, Me), 1.95 (3H, s, 2-OAc), 0.96—2.34 (12H, m, methylene, 1-H and 4a-H), 3.49 (3H, s, OMe), 4.08 (1H, dd, $J=12.0$, 4.4 Hz, $\underline{CH_2}OMTPA$), 4.15 (1H, dd, $J=12.0$, 2.4 Hz, $\underline{CH_2}OMTPA$), 5.25 (1H, dt, $J=5.1$, 11.2 Hz, 2-H), 7.35—7.49 (5H, m, aromatic-H).

Acknowledgement This work was supported by a grant for the “Biodesign Research Program” from The Institute of Physical and Chemical Research (RIKEN, Japan) to H. A.

References and Notes

1) Jansen B. J. M., De Groot A., *Nat. Prod. Rep.*, 319—337, **1991** and references cited therein.

2) *a*) Akita H., Mori K., Tahara A. (deceased), *Chem. Pharm. Bull.*, **25**, 974—980 (1977); *b*) Akita H., Oishi T., *Tetrahedron Lett.*, **1978**, 3733—3736; *c*) *Idem*, *Chem. Pharm. Bull.*, **29**, 1567—1579 (1981); *d*) *Idem*, *Chem. Pharm. Bull.*, **29**, 1580—1587 (1981); *e*) *Idem ibid.*, **29**, 1588—1593 (1981).

3) *a*) Shishido K., Tokunaga Y., Omachi N., Hiroya K., Fukumoto K., Kametani T., *J. Chem. Soc. Chem. Commun.*, **1989**, 1093—1094; *b*) *Idem*, *J. Chem. Soc.*, *Perkin Trans. 1*, **1990**, 2481—2486.

4) Ragoussis V., Liapis M., *J. Chem. Soc.*, *Perkin Trans. 1*, **1987**, 987—992.

5) Mori K., Watanabe H., *Tetrahedron*, **42**, 273—281 (1986).

6) *a*) Akita H., Naito T., Oishi T., *Chemistry Lett.*, **1979**, 1365—1368; *b*) *Idem*, *Chem. Pharm. Bull.*, **28**, 2166—2171 (1980).

7) *a*) Nakata T., Akita H., Naito T., Oishi T., *J. Am. Chem. Soc.*, **101**, 4400—4401 (1979); *b*) *Idem*, *Chem. Pharm. Bull.*, **28**, 2172—2177 (1980); *c*) Naito T., Nakata T., Akita H., Oishi T.,

Chemistry Lett., **1980**, 445—446.

8) Liapis M., Ragoussis V., *J. Chem. Soc.*, *Perkin Trans. 1*, **1985**, 815—817.

9) Fukui S., Tanaka A., *Advances in Biochem. Engineering/Biotech.*, **29**, 1—33 (1984).

10) Mori K., Tamura H., *Liebigs Ann. Chem.*, **1990**, 361—368.

11) *a*) Dale J. A., Dull D. L., Mosher H. S., *J. Org. Chem.*, **34**, 2543—2549 (1969); *b*) Dale J. A., Mosher H. S., *J. Am. Chem. Soc.*, **95**, 512—519 (1973).

12) *a*) Fenical W., Sims J. J., Squatrito D., Wing R. M., Radlick P., *J. Org. Chem.*, **38**, 2383—2386 (1973); *b*) Ochi M., Kotsuki H., Muraoka K., Tokoroyama T., *Bull. Chem. Soc. Jpn.*, **52**, 629—630 (1979).