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Enzymatic Resolution of Acylates of Prochiral Phenolic 1-Aryl- and 1-Arylalkyl-1,2,3,4-tetrahydroisoquinolinols, which possess a Guaiacol-type Moiety, by use of Immobilized Lipase in Organic Solvent

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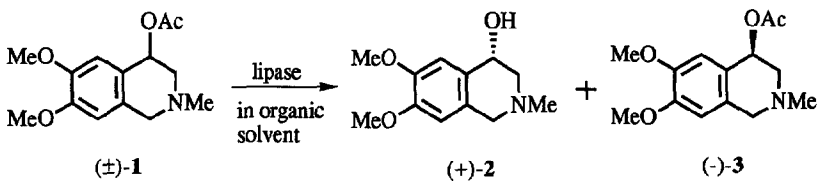
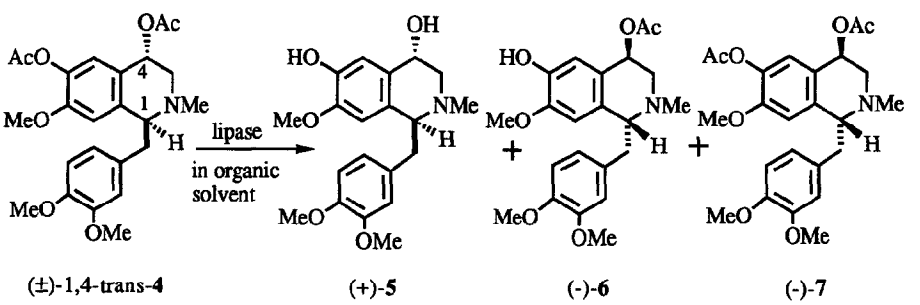
Abstract: Enzymatic resolution of acylates of prochiral phenolic 1-aryl- and 1-arylalkyl-1,2,3,4-tetrahydroisoquinolinols, which possess a guaiacol-type moiety by use of lipase immobilized with celite in water-saturated organic solvent gave the corresponding acylates and phenols in moderate optical yields.

Introduction

Application of biocatalysts[1] in organic synthesis has been well known to be a useful method for the synthesis of chiral building blocks. Recently, we have reported that reaction of (±)-4-acetoxytetrahydroisoquinoline (**1**) by using lipase immobilized with celite in water-saturated organic solvent gives (+)-alcohol (**2**) and (-)-acetate (**3**) in 40% (94% ee) and 44% (93% ee) yields, respectively.[2]





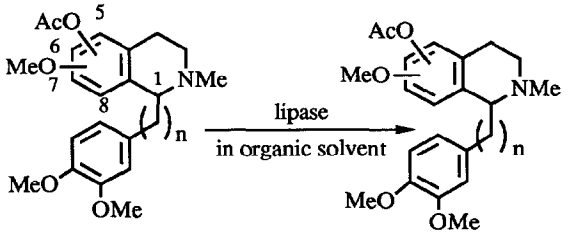
This method has been also applied to synthesis of (+)-roemecarine (**5**),[3] in which reaction of (±)-diacetate (**4**) under the similar conditions is found to afford (-)-monoacetate (**6**) and recovered (-)-diacetate (**7**) besides (+)-**5**, suggesting that enzymatic resolution of acetate of prochiral phenolic 1-substituted tetrahydroisoquinolinol took place. As for enzymatic hydrolysis of prochiral phenyl acetates using biocatalysts, there are only a few reports[4] on binaphthyl acylates. Therefore, the forementioned findings promoted us to attempt the enzymatic

reaction of acylates of prochiral phenolic 1-substituted tetrahydroisoquinolinols for exploring the resolution of prochiral phenolic derivatives.

In order to examine how the asymmetric hydrolysis with lipase can be effected by the distance between the acetoxyl group and a prochiral center at the 1-position in 1-substituted tetrahydroisoquinolines and also by bulkiness of 1-substituents, (±)-1-(3,4-dimethoxyphenyl)- (**17-19**), (±)-1-(3,4-dimethoxybenzyl)- (**20-22**), and (±)-1-(3,4-dimethoxyphenethyl)-tetrahydroisoquinolines (**23-25**) containing a guaiacol-type moiety in the tetrahydroisoquinoline ring, which possess an acetoxyl group at 5-, 6-, and 7-positions except for 8-position, were chosen because they are of useful precursors for synthesis of chiral isoquinoline alkaloids. Synthesis of **17-25** was performed by acetylation of (±)-tetrahydroisoquinolinols (**8**,[5] **9**, **10**,[6] **11**,[5] **12**,[6] **13**,[7] **14**,[5] **15**,[8] and **16**[9]) in the usual manner.

Results and Discussion

Screening of acetoxy-1-(3,4-dimethoxyphenyl)-tetrahydroisoquinolines (**17-19**) using eleven kinds of lipases (Amano A-6 from *Asperigillus niger*; Amano P from *Pseudomonas fluorescens*; Amano F-AP-15 from *Rhizopus javanicus*; Amano M-10 from *Mucol javanicus*; Lipase F from *Rhizopus javanicus*; Pancratin F from *Porcine Pancreas*; OF-360 from *Candida cylindracea*; C. C. Sigma from *Candida cylindracea*; Amano AY-30 from *Candida cylindracea*, Amano GC-20 from *Geotrichum candidum*; No. L-3001 from *Wheat Germ*) in a solution of water-saturated benzene-isooctane (1:4) was carried out according to the previously reported method.[2] Among these lipases, Amano A-6, OF-360, C. C. Sigma, Amano AY-30, Amano GC-20, and No. L-3001 showed to be effective for hydrolysis by monitoring on TLC. On the basis of the observation, hence, reaction of **17-19** with these lipases was performed. When spots of the starting material and product on TLC became approximately 1:1 ratio, the reaction was quenched. The reaction mixture was separated by silica gel or Sephadex column chromatography or preparative silica gel TLC to phenols (**8-10**) and acetates (**17-**



(RS)-**17**: n = 0, 5-OAc, 6-OMe	(R) or (S)-**17**	(S) or (R)-**8**: 5-OH, 6-OMe
(RS)-**18**: n = 0, 6-OAc, 7-OMe	(R) or (S)-**18**	(S) or (R)-**9**: 6-OH, 7-OMe
(RS)-**19**: n = 0, 7-OAc, 6-OMe	(R) or (S)-**19**	(S) or (R)-**10**: 7-OH, 6-OMe
(RS)-**20**: n = 1, 5-OAc, 6-OMe	(R) or (S)-**20**	(S) or (R)**11**: 5-OH, 6-OMe
(RS)-**21**: n = 1, 6-OAc, 7-OMe	(R) or (S)-**21**	(S) or (R)-**12**: 6-OH, 7-OMe
(RS)-**22**: n = 1, 7-OAc, 6-OMe	(R) or (S)-**22**	(S) or (R)-**13**: 7-OH, 6-OMe
(RS)-**23**: n = 2, 5-OAc, 6-OMe	(R) or (S)-**23**	(S) or (R)-**14**: 5-OH, 6-OMe
(RS)-**24**: n = 2, 6-OAc, 7-OMe	(R) or (S)-**24**	(S) or (R)-**15**: 6-OH, 7-OMe
(RS)-**25**: n = 2, 7-OAc, 6-OMe	(R) or (S)-**25**	(S) or (R)-**16**: 7-OH, 6-OMe

19), respectively. Enantiomeric excess (ee) of the products was estimated by HPLC analysis using chiralcel OJ or OC of the corresponding phenols or acetates (see Experimental), because ^{1}H-NMR spectral analysis of MTPA esters[10] of the (±)-phenols (**8-10**) was unsuccessful. The results are listed in Table 1.

Table 1. Reaction of Acetoxy-1-aryltetrahydroisoquinolines (**17-19**) with Lipases[1)]

Entry	(RS)-Acetates	Lipases[2)]	Reaction Time (h)	Yields % (ee)[3] Acetates		Phenols	Abs.Config. of Phenols
1		A	0.33	67 (21)[4)]		17 (30)[5)]	S
2	**17**	C	2.5	**17** 60 (31)	**8**	17 (31)	S
3		D	4.2	46 (38)		38 (55)	S
4		A	0.33	38 (90)[6)]		60 (59)[7)]	R
5	**18**	B	0.75	**18** 28 (11)	**9**	70 (6)	S
6		E	4.0	41 (59)		58 (38)[8)]	R
7		A	0.5	41 (9)		34 (44)	S
8	**19**	E	53.0	**19** 73 (18)	**10**	25 (42)	R
9		F	7.1	44 (20)[9)]		44 (46)[10)]	R

1) All reactions were carried out in benzene-isooctane (1:4) at 33° C.
2) A: Amano A-6; B: OF-360; C: C.C. Sigma; D: Amano AY-30; E: Amano GC-20; F: No. L-3001.
3) Values in parenthesis showed enantiomeric excess (ee) of each product.
4) $[\alpha]_D$ -8.59 (c=0.71). 5) $[\alpha]_D$ +13.9 (c=0.19). 6) $[\alpha]_D$ +7.5 (c=1.47). 7) $[\alpha]_D$ -11.9 (c=1.57).
8) $[\alpha]_D$ -6.1 (c=0.18). 9) $[\alpha]_D$ -3.0 (c=0.54). 10) $[\alpha]_D$ +7.6 (c=0.58)

Reactions with lipase Amano A-6, all proceeded in relatively short reaction time to give hydrolyzed products in moderate chemical and optical yields (entries 1, 4, and 7). Interestingly, 6-acetoxy-tetrahydroisoquinolines (**18**), in which an acetoxyl group is furthest from prochiral center, afforded fair to good optical yields of recovered acetates (**18**) (entries 4, 6).

Next, acetoxy-1-arylmethyl congeners (**20-22**) were examined under the similar conditions. The results are listed in Table 2. Reaction with lipase Amano A-6 as well as that of 1-aryltetrahydroisoquinolines (**17-19**), all took place in comparatively short reaction times and in moderate optical yields. In the reaction of 6-acetoxy derivative (**21**) with lipase Amano GC-20, recovered acetate (**21**) was obtained in the highest optical yield, although the prolonged reaction time was required (entry 10). However, reaction of **20** and **22** with lipase Amano GC-20 was unsuccessful. Enantiomeric excess (ee) of the products was estimated by ^{1}H-NMR spectral analysis of MTPA esters of the phenols (**11-13**)(after acetates were hydrolyzed to phenols).

Furthermore, reaction of acetoxy-1-(2-arylethyl) derivatives (**23-25**), in which a methylene unit of 1-substituent was longer by one unit than 1-arylmethyltetrahydroisoquinolines (**20-22**), was examined under the similar conditions. The results are listed in Table 3. In all cases as well as those of acetates of 1-aryl-(**17-19**) and 1-arylmethyl-tetrahydroisoquinolines (**20-22**), reaction with lipase Amano A-6 proceeded in relatively short reaction time to give hydrolyzed products (**14-16**) and recovered acetates (**23-25**) in moderate optical yield except for reaction of **24** with lipase OF-360 (entry 3). With lipase Amano GC-20 in benzene

Table 2. Reaction of Acetoxy-1-arylmethyltetrahydroisoquinolines (**20-22**) with Lipases[1)]

Entry	(RS)-Acetates	Lipases[2)]	Reaction Time (h)	Yields % (ee)[3)] Acetates		Phenols	Abs. Config. of Phenols
1		A	0.51	42 (50)[4)]		45 (32)[5)]	S
2		B	6.0	35 (34)		49 (30)[6)]	R
3	**20**	C	6.0	**20** 45 (32)	**11**	50 (24)	S
4		D	6.0	25 (73)[7)]		59 (32)[8)]	S
5		F	0.51	36 (50)		46 (45)[9)]	R
6		A	0.16	55 (8)		14 (28)	R
7		B	0.25	37 (44)		38 (35)	R
8		C	0.5	55 (44)		45 (36)	R
9	**21**	D	0.5	**21** 18 (32)	**12**	57 (29)	R
10		E	4.75	17 (96)[10)]		74 (15)[11)]	R
11		E[12)]	0.75	51 (57)		65 (21)	R
12		A	0.51	29 (51)[13)]		48 (29)[14)]	S
13	**22**	C	2.66	**22** 85 (2)	**13**	8 (57)	S
14		D	3.0	52 (25)		16 (70)	S

1) All reactions were carried out in benzene-isooctane (1:4) at 33° C, unless otherwise noted.
2) A: Amano A-6; B: OF-360; C: C.C. Sigma; D: Amano AY-30; E: Amano GC-20; F: No. L-3001.
3) Values in parenthesis showed enantiomeric excess (ee) of each product.
4) $[\alpha]_D$ -24.5 (c=2.21). 5) $[\alpha]_D$ +15.7 (c=1.74). 6) $[\alpha]_D$ -11.8 (c=1.77). 7) $[\alpha]_D$ -41.9 (c=1.37).
8) $[\alpha]_D$ +14.2 (c=1.66). 9) $[\alpha]_D$ -17.3 (c=1.48). 10) $[\alpha]_D$ +34.5 (c=0.49). 11) $[\alpha]_D$ -6.7 (c=1.07).
12) Benzene alone was used. 13) $[\alpha]_D$ -10.6 (c=1.87). 14) $[\alpha]_D$ +16.5 (c=2.17).

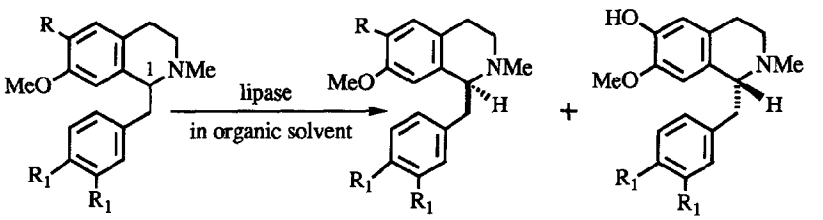
Table 3. Reaction of Acetoxy-1-(2-arylethyl)-tetrahydroisoquinolines (**23-25**) with Lipases[1)]

Entry	(RS)-Acetates	Lipases[2)]	Reaction Time (h)	Yields % (ee)[3)] Acetates		Phenols	Abs. Config. of Phenols
1	**23**	A	1.0	**23** 27 (42)[4)]	**14**	53 (34)[5)]	S
2		A	1.1	26 (32)		32 (20)	R
3	**24**	B	2.0	**24** 22 (4)	**15**	76 (5)	R
4		E	16.0	15 (21)		44 (48)	R
5		E[6)]	2.0	41 (88)[7)]		40 (18)[8)]	R
6		A	1.5	29 (33)[9)]		61 (17)[10)]	S
7	**25**	C	123.0	**25** 60 (23)	**16**	31 (49)	S
8		D	84.0	77 (14)		21 (56)[11)]	R
9		E	24.0	50 (13)		34 (20)	R

1) All reactions were carried out in benzene-isooctane (1:4) at 33° C, unless otherwise noted..
2) A: Amano A-6; B: OF-360; C: C.C. Sigma; D: Amano AY-30; E: Amano GC-20.
3) Values in parenthesis showed enantiomeric excess (ee) of each product.
4) $[\alpha]_D$ -5.6 (c=1.22). 5) $[\alpha]_D$ -1.0 (c=1.0). 6) Benzene alone was used. 7) $[\alpha]_D$ -12.1 (c=1.49).
8) $[\alpha]_D$ +5.9 (c=1.51). 9) $[\alpha]_D$ -4.3 (c=1.41). 10) $[\alpha]_D$ +3.3 (c=1.48). 11) $[\alpha]_D$ -13.5 (c=0.47).

alone, recovered acetate (**24**) was obtained in favorable chemical and optical yields (entry 5). Optical yield of the products was taken by HPLC analysis in the similar way as noted for 1-aryl derivatives (**17-19**).

Among acetoxytetrahydroisoquinolines used, 6-acetoxy-1-arylmethyltetrahydroisoquinoline (**21**) was found to give recovered acetate (**21**) in good optical yield excluding reaction with lipaseAmano A-6.



(RS)-**27**: R = $OCO(CH_2)_4Ph$, R_1 = OMe — (R) or (S)-**27** — (S) or (R)-**12**: R_1 = OMe

(RS)-**28**: R = OAc, $R_1 + R_1 = OCH_2O$ — (R) or (S)-**28** — (S) or (R)-**26**: $R_1 + R_1 = OCH_2O$

Table 4. Reaction of Acyloxy-1-arylmethyltetrahydroisoquinolines (**27, 28**) with Lipases[1].

Entry	(RS)-Acetates	Lipases[2]	Reaction Time (h)	Yields % (ee)[3] Acetates		Phenols	Abs. Config. of Phenols
1	**27**	A	6.0	76 (29)	**27**	14 (72) **12**	R
2		B	3.0	35 (71)		57 (30)	R
3		C	2.5	47 (39)		35 (28)	R
4		D	6.0	41 (93)[4]		49 (42)[5]	R
5	**28**	D	1.0	29 (71)	**28**	52 (38) **26**	R
6		D[6]	1.0	47 (70)[7]		32 (67)[8]	R

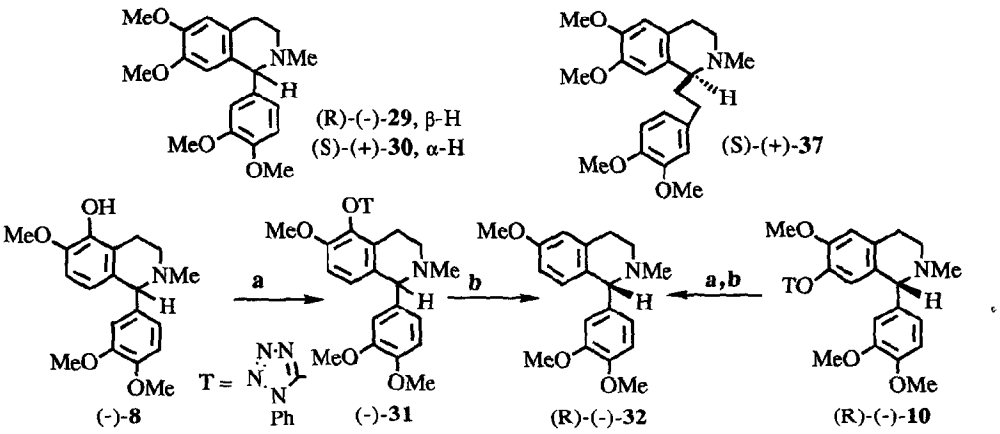
1) All reactions were carried out in benzene-isooctane (1:4) at 33° C, unless otherwise noted.
2) A: Amano A-6; B: C.C. Sigma; C: Amano AY-30; D: Amano GC-20.
3) Values in parenthesis showed enantiomeric excess (ee) of each product. 4) $[\alpha]_D$ +25.7 (c = 0.35).
5) $[\alpha]_D$ +17.9 (c = 0.84). 6) Benzene alone was used. 7) $[\alpha]_D$ +35.0 (c=1.77). 8) $[\alpha]_D$ -55.0 (c = 0.16).

In addition, to establish the synthetic utility in this method, the reaction of (±)-6-(5-phenylvaleroxy)-1-arylmethyltetrahydroisoquinoline (**27**) with the 5-phenylvaleryl group[11] instead of the acetyl group and of 6-acetoxy-1-(3,4-methylenedioxyphenylmethyl) congener (**28**) was performed under the similar conditions. Substrates (**27** and **28**) were prepared from phenols (**12** and **26**[12]) in the usual manner. The results are listed in Table 4.

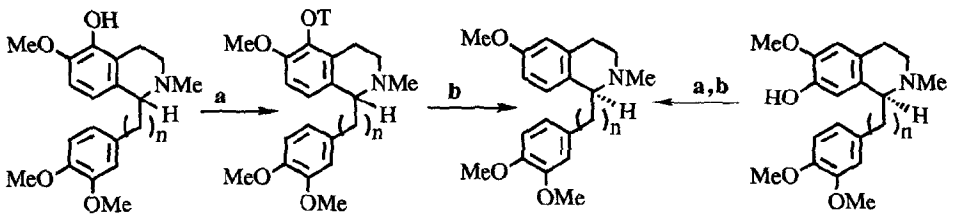
As expected, reaction with lipase Amano GC-20 in benzene-isooctane (1:4) or benzene alone afforded acceptable optical yields of recovered acylates (**27** and **28**) (entries 4-6). Optical yields of the products were estimated by HPLC analysis in the similar manner as noted for 1-aryl derivatives (**17-19**).

Absolute configuration of hydrolyzed products (**8, 11, 14, 15,** and **16**) except for (-)-**12**[13], (-)-**26**[12], and (+)-**13**[14] was determined as follows. Methylation of (-)-**9** with diazomethane gave (R)-(-)-cryptostyline II (**29**), whereas that of (R)-(+)-**10** led to (S)-(+)-cryptostyline II (**30**).[15] (-)-Phenol (**8**) was converted to (R)-

(-)-6-methoxy compound (**32**) via (-)-tetrazolyloxy derivative (**31**). (-)-**32** was identical with authentic sample derived from (R)-(-)-**10**. Thus, absolute configuration of (+)-**8** was confirmed to be S.



a: 5-chloro-1-phenyltetrazole, K_2CO_3, acetone, Δ ; b: 10% Pd-C, benzene, HCO_2H, aq. EtOH, Δ



(+)-**11**, n = 1 (+)-**33**, n = 1 (S)-(+)-**34**, n = 1 (S)-(+)-**13**, n = 1
(-)-**14**, n = 2 (+)-**35**, n = 2 (S)-(+)-**36**, n = 2 (S)-(+)-**16**, n = 2

a: 5-chloro-1-phenyltetrazole, K_2CO_3, acetone, Δ ; b: 10% Pd-C, AcOH, H_2 (70-75 psi)

(+)-Phenol (**11**) and (-)-phenol (**14**) were transformed to (+)-**34** and (+)-**36**, respectively, via (+)-**33** and (+)-**35** by the similar methodology as noted for (-)-**8**. Identity of (+)-**34** and (+)-**36** with the corresponding authentic samples derived from (S)-(+)-**13** and (S)-(+)-**16** proved their S configuration. Moreover, S configuration of both (-)-**15** and (+)-**16** were confirmed by their conversion to (S)-(+)-homolaudanosine (**37**)[16] by methylation with diazomethane.

Conclusion

Enzymatic resolution of acylates of prochiral phenolic acyloxy-1-aryl- and 1-arylalkyl-tetrahydroisoquinolines (**17-25**, **27**, and **28**) using lipase in organic solvent was proved to be effective for 6-acyloxy-1-arylmethyltetrahydroisoquinolines (**21**, **27**, and **28**), in which acyloxy groups existed the farest distance to prochiral center, although the reaction conditions were not always optimilized. 5- and 7-Acetoxy derivatives (**17**, **20**, **23** and **19**, **22**, **25**), where a relationship between acetoxy group and prochiral center are similar,

appeared to show similar chemical behaviour in enzymatic hydrolysis. Furthermore, bulkiness of 1-substituents seemed to somewhat retard the reaction, although the optical yield of the phenols inceased slightly. Interestingly, hydrolysis of 6-acyloxy-1-arylmethyl derivatives (**18**, **21**, **27**, and **28**) with these lipases except that of **18** with lipase OF-360 produced (R)-enantiomers (**9**, **12**, and **26**). In addition, it was noticable that reaction of 6-acetoxy derivatives (**21**, **24**, and **28**) using lipase Amano GC-20 even in benzene alone smoothly proceeded to give recovered acetates (**21** and **28**) in fair to good chemical and optical yields and that 5-phenylvaleroxyl group was also effective for reaction with lipase Amano GC-20.

Experimental

All meting points were measured on a Büchi melting point measuring apparatus and are uncorrected. ^{1}H-NMR spectra were taken with a JEOL FX-100 (100 MHz) or JEOL GSX-500 (500 MHz) spectrometer in $CDCl_3$ solution using TMS as internal standard. IR spectra were run with a Hitachi 260-10 infrared spectrometer in $CHCl_3$ solution. Mass spectra were measured with a Hitachi RMU-7M mas spectrometer. Specific rotation was run on Nippon Bunko DIP-360 polarimeter in $CHCl_3$ solution, unless otherwise noted. HPLC was carried out with a Shenshu Kagaku instrument equipped with UV detector 3000A-II using chiralcel OJ or OC (Daicel Chemicals). Preparative TLC was run on Kieselgel F-254 (Merck) and column chromatography was performed using Wakogel C-200 (Wako Pure Chemicals) and Sephadex LH-20 (Pharmacia Fine Chemicals).

Analysis.--- Enantiomeric excess (ee) of the products was estimated by HPLC analysis (chiralcel OJ or OC) of acylates and phenols or on the basis of the peak due to NMe or OMe group, or 8-H in ^{1}H-NMR (500 MHz) spectrum of MTPA esters of the phenols (**11-13**), which were prepared from phenols and (-)-MTPA-Cl in the usual manner. Acetates were hydrolyzed with 5% methanolic KOH at room temperature to give the corresponding phenols for measuring the ^{1}H-NMR (500 MHz) spectrum of MTPA esters or HPLC analysis, whereas the phenols were converted with Ac_2O in pyridine to acetates for HPLC analysis.

(±)-**17**: HPLC (EtOH: hexane / 1:1, chiralcel OJ) of acetates: Rt (min): 20 for (-)-**17**; 25 for (+)-**17**.

(±)-**18**: HPLC (EtOH: hexane / 9:1; chiralcel OJ) of phenols: Rt (min): 9 for (+)-**9**; 23 for (-)-**9**.

(±)-**19**: HPLC (EtOH: hexane / 1:1; chiralcel OJ) of acetates and phenols: Rt (min): 15 for (+)-**19**; 30 for (-)-**19**; 12 for (+)-**10**; 15 for (-)-**10**.

(±)-**20**: ^{1}H-NMR (500 MHz) δ: 2.46 (NMe) for (+)-**11**; 2.49 (NMe) for (-)-**11**.

(±)-**21**: ^{1}H-NMR (500 MHz) δ: 3.70 (OMe) for (+)-**12**; 3.72 (OMe) for (-)-**12**.

(±)-**22**: ^{1}H-NMR (500 MHz) δ: 6.15 (8-H) for (+)-**13**; 6.24 (8-H) for (-)-**13**.

(±)-**23**: HPLC (EtOH: hexane / 1:1; chiralcel OJ) of acetates; Rt (min): 16 for (+)-**23**; 20 for (-)-**23**.

(±)-**24**: HPLC (EtOH: hexane / 1:1; chiralcel OJ) of phenols: Rt (min): 17 for (-)-**15**; 25 for (+)-**15**.

(±)-**25**: HPLC (EtOH: hexane / 1:1; chiralcel OJ) of acetates and phenols: Rt (min): 14 for (+)-**25**; 17 for (-)-**25**; 13 for (+)-**16**; 17 for (-)-**16**.

(±)-**27**: HPLC (EtOH: hexane / 1:1; chiralcel OC) of phenylvalerates and phenols: Rt (min): 23 for (+)-**27**; 42 for (-)-**27** and 20 for (+)-**12**; 26 for (-)-**12**.

(±)-**28**: HPLC (EtOH: hexane / 9:1; chiralcel OJ) of acetates: Rt (min): 13 for (-)-**28**; 19 for (+)-**28**.

(±)-6-Hydroxy-1-(3,4-dimethoxyphenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (9)--- A solution of dimethoxybenzamide (mp 144-145° C)(20 g, 47.3 mmol) and $POCl_3$ (40 ml) in CH_2Cl_2 (130 ml) was refluxed for 6 h. Usual work-up of the reaction mixture produced 3,4-dihy-

droisoquinoline (15.8 g, 83%; mp 122-123° C). A mixture of 3,4-dihydroisoquinoline (4.6 g, 11.4 mmol) and $NaBH_4$ (1.5 g, 3.5 eq.) in MeOH (800 ml) was stirred at room temperature for 4.5 h. Work-up of the reaction mixture as usual gave tetrahydroisoquinoline (4.4 g, 98%, mp 104-105° C). A solution of tetrahydroisoquinoline (4.4 g, 10.6 mmol) and 35% formalin (4.7 g, 5 eq.) in MeOH (200 ml)-$CHCl_3$ (50 ml) was stirred at room temperature for 1 h. $NaBH_4$ (2.1 g, 5 eq.) was added to the reaction mixture under cooling and the whole was stirred at room temperature for 2.5 h. Usual work-up of the reaction mixture gave 2-methyl-1,2,3,4-tetrahydroisoquinoline (3.9 g, 85.7%, mp 116.5-117° C). A mixture of 2-methyl-1,2,3,4-tetrahydroisoquinoline (3.0 g, 7.2 mmol), 2% aq. $PdCl_2$ (3 ml) and charcoal (0.7 g) in MeOH (150 ml) was shaken with H_2 at room temperature for 2.5 h. Usual work-up of the reaction mixture left (±)-**9** (1.7 g, 72%); mp 62-67° C; ^{1}H-NMR δ 2.25 (3H, s, NMe), 3.58, 3.80, 3.88 (9H, each s, 3 x OMe), 4.17 (1H, s, 1-H), 6.07-6.78 (5H, m, 5 x arom.-H); IRν: 3550 (ArOAc) cm^{-1}; HRMS *m/z* Calcd for $C_{19}H_{23}NO_4$ (M^+):329.1625. Found: 329.1625.

General Procedure for Preparation of (±)-Acyloxy-1,2,3,4-tetrahydroisoquinolines (17-25, 27, and 28)----Tetrahydroisoquinolinols (**8**,[5] **9**, **10**,[6] **11**,[5] **12**,[6] **13**,[7] **14**,[5] **15**,[8] **16**[9] and **26**[12]) were treated with acetic anhydride (1.5 eq.) in pyridine containing 4-dimethylaminopyridine (DMAP)(0.5 eq.) was stirred at room temperature for 2-24 h. After the usual work-up the reaction mixture was purified by column chromatography. 5-Phenylvalerate (**27**) was synthesized by reaction of **12** with 5-phenylvaleryl chloride in CH_2Cl_2 containing Et_3N and DMAP.

(±)-**17**: mp 119-120° C (acetone-hexane): ^{1}H-NMR δ 2.21 (3H, s, NMe), 2.36 (3H, s, OAc), 3.76, 3.82, 3.88 (9H, each s, 3 x OMe), 4.09 (1H, s, 1-H), 6.41-6.78 (5H, m, 5 x arom.-H); IRν: 1775 (ArOAc) cm^{-1}. Anal Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.90; H, 6.86; N, 3.75.

(±)-**18**: mp 100-101° C (acetone-hexane): ^{1}H-NMR δ 2.22 (3H, s, NMe), 2.28 (3H, s, OAc), 3.52, 3.81, 3.87 (9H, each s, 3 x OMe), 4.11 (1H, s, 1-H), 6.19-6.78 (5H, m, 5 x arom.-H); IRν: 1765 (ArOAc) cm^{-1}. Anal Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.83; H, 6.79; N, 3.79.

(±)-**19**: oil; ^{1}H-NMR δ 2.16 (3H, s, NMe), 2.19 (3H, s, OAc), 3.78, 3.80, 3.86 (9H, each s, 3 x OMe), 4.09 (1H, s, 1-H), 6.25-6.78 (5H, m, 5 x arom.-H); IRν: 1755 (ArOAc) cm^{-1}; HRMS *m/z* Calcd for $C_{21}H_{25}NO_5$ (M^+): 371.1730. Found: 371.1711.

(±)-**20**: oil; ^{1}H-NMR δ 2.32 (3H, s, OAc), 2.47 (3H, s, NMe), 3.67 (6H, each s, 2 x OMe), 3.84 (3H, s, OMe), 6.44-6.80 (5H, m, 5 x arom.-H); IRν: 1760 (ArOAc) cm^{-1}; MS *m/z* 234 (M^+-151).

(±)-**21**: oil; ^{1}H-NMR δ 2.28 (3H, s, OAc), 2.52 (3H, s, NMe), 3.76, 3.77, 3.84 (9H, each s, 3 x OMe), 6.44-6.80 (5H, m, 5 x arom.-H); IR ν: 1750 (ArOAc) cm^{-1}; MS *m/z* 234 (M^+-151).

(±)-**22**: oil; ^{1}H-NMR δ 2.24 (3H, s, OAc), 2.51 (3H, s, NMe), 3.76, 3.77, 3.84 (9H, each s, 3 x OMe), 6.40-6.80 (5H, m, 5 x arom.-H); IRν: 1755 (ArOAc) cm^{-1}; MS *m/z* (M^+-151).

(±)-**23**: oil; ^{1}H-NMR δ 2.32 (3H, s, OAc), 2.46 (3H, s, NMe), 3.80, 3.84, 3.86 (9H, each s, 3 x OMe), 6.73-6.88 (5H, m, 5 x arom.-H); IRν: 1760 (ArOAc) cm^{-1}; HRMS *m/z* Calcd for $C_{23}H_{29}NO_5$ (M^+): 399.2043. Found: 399.2041.

(±)-**24**: oil; ^{1}H-NMR δ 2.28 (3H, s, OAc), 2.47 (3H, s, NMe), 3.75, 3.84, 3.85 (9H, each s, 3 x OMe), 6.56-6.77 (5H, m, 5 x arom.-H); IRν: 1760 (ArOAc) cm^{-1}; HRMS *m/z* Calcd for $C_{23}H_{29}NO_5$ (M^+): 399.2043. Found: 399.2043.

(±)-**25**: oil; ^{1}H-NMR δ 2.29 (3H, s, OAc), 2.53 (3H, s, NMe), 3.80, 3.83, 3.85 (9H, each s, 3 x OMe), 6.66-6.74 (5H, m, 5 x arom.-H); IRν: 1760 (ArOAc) cm^{-1}; HRMS *m/z* Calcd for $C_{23}H_{29}NO_5$ (M^+):

399.2043. Found: 399.2040. (±)-**27**: oil; ^{1}H-NMR δ 2.56 (3H, s, NMe), 3.44 (3H, s, 7-OMe), 3.76, 3.83 (6H, each s, 2 x OMe), 6.52-6.72 (3H, m, 3 x arom.-H), 7.19-7.25 (6H, m, 6 x arom.-H); IRν: 1760 ($ArOCOCH_2$) cm^{-1}; HRMS *m/z* Calcd for $C_{31}H_{37}NO_5$ (M^+): 503.2966. Found: 503.2664.

(±)-**28**: mp 131-132° C (benzene-hexane): ^{1}H-NMR δ 2.28 (3H, s, OAc), 2.48 (3H, s, NMe), 3.56 (3H, s, OMe), 5.88 (2H, s, OCH_2O), 6.20 (1H, s, arom.-H), 6.48-6.72 (4H, m, 4 x arom.-H); IRν: 1760 (ArOAc) cm^{-1}. Anal Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.50; H, 6.40; N, 3.75.

General Procedure for Enzymatic Reaction of 17-25, 27, and 28 in Organic Solvent.----A mixture of substrates (**17-25**, **27**, and **28**)(100 mg) and lipase immobilized with celite, which was prepared from lipase (100 mg) and celite (300 mg) containing water (0.15 ml) according to the previously reported method,[2] was incubated at 33° C for appropriate reaction time. After filtation of celite by suction filter, the filter bed was washed with a mixture of $CHCl_3$ and MeOH. The combined filtrates were dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue. Separation of the residue by column chromatography ($CHCl_3$-MeOH or benzene-MeOH) and/or preparative TLC ($CHCl_3$-MeOH or benzene-AcOEt-MeOH) afforded recovered acylates and phenols, respectively. The results are summarized in Tables 1-4.

Absolute Configuration of Hydrolyzed Products.-----(S)-(+)-**8**: A mixture of (-)-**8** (150 mg, 0.30 mmol, $[\alpha]_D$ -33.3 , c =1.1) (derived from (-)-**17** by hydrolysis with 5% KOH-MeOH) and 5-chloro-1-phenyltetrazole (121.5mg, 1.5 eq.) in acetone (10 ml) containing K_2CO_3 (183.5 mg, 3 eq.) was refluxed for 25 h. Usual work-up of the reaction mixture followed by column chromatography (CH_2Cl_2 : MeOH / 100 : 1) gave an oil (**31**)(104 mg, 79%); $[\alpha]_D$ -50 (c = 0.5); oil; ^{1}H-NMR δ 2.21 (3H, s, NMe), 3.68, 3.83, 3.88 (9H, each s, 3 x OMe), 4.11 (1H, s, 1-H), 6.56-6.84 (5H, m, 5 x arom.-H), 7.44-7.93 (5H, m, 5 x arom.-H); MS *m/z* :473 (M^+). A mixture of tetrazolyloxy compound (**31**)(67.4 mg, 0.14 mmol), 10% palladium on charcoal (100 mg) in a mixture[18] of benzene (10 ml), formic acid (1 ml), EtOH (4.5 ml) and water (3 ml) was refluxed for 54 h. After filtration of the calalyst, oily residue obtained by the usual work-up was purified by preparative TLC (benzene : AcOEt : MeOH / 4:4:1) to give (R)-(-)-**32** (4.0 mg, 9%); oil; $[\alpha]_D$ -15.7 (c = 0.27); ^{1}H-NMR δ 2.23 (3H, s, NMe), 3.75, 3.80, 3.88 (9H, each s, 3 x OMe), 6.52-6.80 (6H, m, 6 x arom.-H); HRMS *m/z* Calcd for $C_{19}H_{23}NO$ (M^+): 313.1677. Found: 313.1682. The ^{1}H-NMR spectrum and sign of $[\alpha]_D$ were identical with those of authentic sample ($[\alpha]_D$ -6.4, c = 0.96) obtained from (R)-(-)-**10** in the similar manner as noted for (-)-**8**. Thus, (+)-**8** was determined to be (S)-enantiomer.

(R)-(-)-**9**: (-)-**9** (23.5 mg, 0.07 mmol; $[\alpha]_D$ -11.9 , c = 1.57) was treated with diazomethane-ether (12 ml) in MeOH (12 ml) to give (R)-(-)-crytastyline II (**29**)(11.1 mg, 45%); mp 98-99° C, $[\alpha]_D$ -30.8 (c = 0.74); HRMS *m/z* Calcd for $C_{20}H_{25}NO_4$ (M^+): 343.1781. Found: 343.1784.

(S)-(+)-**10**: (+)-**10** (15 mg, 0.05 mmol; $[\alpha]_D$ +15.2, c = 1.35) was methylated with diazomethane-ether (10 ml) in MeOH (10 ml) to give (S)-(+)-crytastyline II[15] (**30**)(8.7 mg, 56%); oil; $[\alpha]_D$ +7.9 (c = 0.58); HRMS *m/z* Calcd for $C_{20}H_{25}NO_4$ (M^+): 343.1781. Found: 343.1766.

(S)-(+)-**11**: (+)-**11** (58.2 mg, 0.17 mmol; $[\alpha]_D$ +11.8, c = 0.88) was converted in the similar manner as noted for (-)-**8** to (+)-tetrazolyloxy derivative (**33**)(64,6 mg, 74%); $[\alpha]_D$ +25.0, c = 0.4), which was treated with H_2 (70-75 psi) over 10% palladium on charcoal (60 mg) in AcOH (6 ml) to afford after purification of the reaction mixture by preparative TLC ($CHCl_3$: MeOH / 8:1) (S)-(+)-**34** (5.3 mg, 13%); oil; $[\alpha]_D$ +23.9 (c = 0.36); HRMS *m/z* Calcd for $C_{20}H_{25}NO_3$ (M^+): 327.1832. Found: 327.1820. This was identical with authentic sample ($[\alpha]_D$ +22.4, c = 1.0) obtained from (S)-(+)-**12** in the similar manner as noted for (-)-**9**.

(S)-(-)-**14**: (-)-**14** (135.4 mg, 0.38 mmol; $[\alpha]_D$ -0.7, c = 0.21) was converted to (S)-(+)-**36** (3.9 mg; $[\alpha]_D$ +1.9, c = 0.20) via (+)-**35** in the similar manner as noted for (-)-**9**. This was identical with authentic sample ($[\alpha]_D$ +0.5, c = 0.26) from (S)-(+)-**16**.

(S)-(+)-**15**: (-)-**15** (12.9 mg, 0.04 mmol; $[\alpha]_D$ -3.5, c = 0.86) was treated with diazomethane-ether (12 ml) in MeOH (12 ml) to give after preparative TLC (benzene : AcOEt : MeOH / 10:10:3) (S)-(+)-homo-laudanosine (**37**)[17] (5.3 mg, 46%; $[\alpha]_D$ +2.0, c = 0.35); HRMS *m/z* Calcd for $C_{22}H_{29}NO_4$ (M^+): 371.2095. Found: 371.2098.

(S)-(+)-**16**: (+)-**16** (10 mg, 0.03 mmol; $[\alpha]_D$ +3.3, c = 1.48) was treated with diazomethane-ether (10 ml) in MeOH (10 ml) to give after preparative TLC (benzene : AcOEt : MeOH / 10:10:3) (S)-(+)-homo-laudanosine (**37**)[17] (7.6 mg, 67%; $[\alpha]_D$ +3.3, c = 0.39); HRMS *m/z* Calcd for $C_{22}H_{29}NO_4$ (M^+): 371.2095. Found: 371.2107.

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