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# Enantioselective Acylation of Primary and Secondary Alcohols Catalyzed by Lipase QL from *Alcaligenes sp.*: A Predictive Active Site Model for Lipase QL to Identify which Enantiomer of an Alcohol Reacts Faster in this Acylation[1]

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**Abstract:** Lipase QL (from *Alcaligenes sp.*)-catalyzed acylation of alcohols using isopropenyl acetate as the acylating agent in diisopropyl ether converted preferentially primary alcohols with an *S* configuration and secondary alcohols with an *R* configuration into the corresponding homochiral acetates. On the basis of observed enantiomer selectivities, a predictive active site model for lipase QL is proposed for identifying which enantiomer of a primary or a secondary alcohol reacts faster in this acylation. Copyright © 1996 Published by Elsevier Science Ltd

Enzymes have become increasingly popular as chiral catalysts in organic synthesis for the preparation of homochiral compounds.[2] Lipases are especially attractive for this purpose because they are relatively inexpensive, can function in both organic and aqueous solutions, are simple to use and show high enantioselectivity for a broad range of substrates. However, there are the considerable differences in the substrate specificity between lipases and hence, in order for lipases to be widely used in organic synthesis, it is desirable to reveal the substrate specificity for each lipase. In this regard, some simple rules or active site models for lipases have been introduced for predicting which enantiomer of a substrate reacts predominantly.[3] For lipase from *Alcaligenes sp.* (lipase PLC), the active site cavity model has been reported by K. Kato and co-workers on the basis of the stereoselectivity of the acylation of 2,2,2-trifluoro-1-naphthylethanols.[4] We here report the stereoselectivity of the enantioselective acylation of primary and secondary alcohols mediated by lipase QL from *Alcaligenes sp.* and, on the basis of the observed enantiomer selectivities, propose a predictive active site model for this lipase as a rule of thumb to identify the primary and the secondary alcohols which can be accommodated in the active site and their faster-reacting enantiomer in this acylation.

## RESULTS AND DISCUSSION

Enantioselective transesterifications of primary and secondary alcohols with 5 mol equiv. of isopropenyl acetate were carried out in diisopropyl ether at 30 °C using lipase QL as a chiral catalyst. The progress of the reaction was monitored by GLC and the enantioselective reactions were terminated at, or close to, 50% conversion by removal of the enzyme by filtration. The products were purified by column and/or thin layer chromatography on silica gel. The enantiomeric excess (e.e.) values of the isolated acetates and alcohols having an aromatic moiety were directly determined by HPLC using a chiral column. In the cases of the products without a chromophore, HPLC analyses of their e.e.-values were performed after conversion of the alcohols into the corresponding phenyl carbamates.

Table 1. Lipase OL-catalyzed acylation of primary and secondary alcohols

| Entry | Substrate | Products | | | | | | E-value[a] |
|---|---|---|---|---|---|---|---|---|
| | | Alcohol | (yield %), | e.e.(%) | Acetate | (yield %), | e.e.(%) | |
| 1 | (±)-**1** | (+)-(*S*)-**1** | (37) | 44 | (-)-(*R*)-**2** | (34) | 40 | 3 |
| 2 | (±)-**3** | (+)-(*S*)-**3** | (39) | 22 | (-)-(*R*)-**4** | (40) | 27 | 2 |
| 3 | (±)-**5** | (+)-(*S*)-**5** | (28) | 63 | (-)-(*R*)-**6** | (38) | 85 | 24 |
| 4 | (±)-**7** | (-)-(*S*)-**7** | (45) | 84 | (+)-(*R*)-**8** | (40) | 84 | 30 |
| 5 | (±)-**9** | (-)-(*S*)-**9** | (46) | 83 | (+)-(*R*)-**10** | (48) | 72 | 16 |
| 6 | (±)-**11** | (-)-(*S*)-**11** | (51) | 49 | (+)-(*R*)-**12** | (30) | 76 | 12 |
| 7 | (±)-**13** | (-)-(*S*)-**13** | (61) | 46 | (+)-(*R*)-**14** | (31) | 94 | 51 |
| 8 | (±)-**15** | (+)-(*S*)-**15** | (56) | 41 | (-)-(*R*)-**16** | (42) | 51 | 5 |
| 9 | (±)-**17** | (-)-(*S*)-**17** | (42) | 55 | (+)-(*R*)-**18** | (39) | 62 | 7 |
| 10 | (±)-**19** | (-)-(*S*)-**19** | (57) | 45 | (+)-(*R*)-**20** | (32) | 94 | 77 |
| 11 | (±)-**21** | (-)-(*S*)-**21** | (57) | 59 | (+)-(*R*)-**22** | (33) | 93 | 50 |
| 12 | (±)-**23** | (-)-**23**[b] | (52) | 71 | (+)-**24**[b] | (34) | 98 | 200 |
| 13 | (±)-**25** | (-)-(*S*)-**25** | (43) | 66 | (+)-(*R*)-**26** | (37) | 99 | 400 |
| 14 | (±)-**27** | (-)-(*S*)-**27** | (56) | 64 | (+)-(*R*)-**28** | (42) | 84 | 22 |
| 15 | (±)-**29** | (-)-(*S*)-**29** | (59) | 55 | (-)-(*R*)-**30** | (37) | 94 | 56 |
| 16 | (±)-**31** | (-)-(*S*)-**31** | (57) | 70 | (+)-(*R*)-**32** | (38) | 99 | 400 |
| 17 | (±)-**33** | (-)-(*S*)-**33** | (54) | 67 | (+)-(*R*)-**34** | (37) | 98 | 200 |
| 18 | (±)-**35** | (-)-(*S*)-**35** | (57) | 55 | (+)-(*R*)-**36** | (30) | 94 | 56 |
| 19 | (±)-**37** | (-)-**37**[b] | (40) | 57 | (+)-**38**[b] | (37) | 91 | 38 |
| 20 | (±)-**39** | (-)-**39**[b] | (54) | 62 | (+)-**40**[b] | (39) | 91 | 41 |
| 21 | (±)-**41** | (-)-(*S*)-**41** | (57) | 62 | (+)-(*R*)-**42** | (35) | 97 | 120 |
| 22 | (±)-**43** | (-)-(*S*)-**43** | (66) | 39 | (+)-(*R*)-**44** | (28) | 96 | 72 |
| 23 | (±)-**45** | (-)-(*S*)-**45** | (57) | 75 | (+)-(*R*)-**46** | (42) | 97 | 150 |
| 24 | (±)-**47** | (-)-(*S*)-**47** | (54) | 50 | (+)-(*R*)-**48** | (29) | 93 | 45 |
| 25 | (±)-**49** | (+)-(*S*)-**49** | (62) | 52 | (-)-(*R*)-**50** | (33) | 92 | 40 |
| 26 | (±)-**51** | (+)-(*S*)-**51** | (39) | 75 | (-)-(*R*)-**52** | (38) | 80 | 48 |
| 27 | (±)-**53** | (+)-(1*S*,2*S*)-**53** | (54) | 38 | (-)-(1*R*,2*R*)-**54** | (27) | 52 | 5 |
| | | | | | (-)-(1*R*,2*R*)-**55** | (12) | 91 | |
| 28 | (±)-**56** | (+)-(1*R*,2*S*)-**56** | (57) | 63 | (-)-(1*S*,2*R*)-**57** | (40) | 98 | 190 |
| 29 | *meso*-**58** | | | | (-)-(1*S*,2*R*)-**59** | (98) | 34 | |
| 30 | (±)-**60** | (-)-(2*S*,6*S*)-**60** | (51) | 72 | (+)-(2*R*,6*R*)-**61** | (30) | 90 | 40 |
| | | | | | (+)-(2*R*,6*R*)-**62** | ( 4) | 55 | |
| 31 | (±)-**63** | (+)-(*R*)-**63** | (34) | 24 | (-)-(*S*)-**64** | (59) | 14 | 2 |
| 32 | (±)-**65** | (-)-(*R*)-**65** | (39) | 60 | (+)-(*S*)-**66** | (47) | 62 | 8 |
| 33 | (±)-**67** | (-)-(*R*)-**67** | (51) | 59 | (+)-(*S*)-**68** | (42) | 82 | 18 |
| 34 | (±)-**69** | (-)-(*R*)-**69** | (46) | 63 | (+)-(*S*)-**70** | (39) | 77 | 15 |
| 35 | (±)-**71** | (+)-(*R*)-**71** | (65) | 5 | (-)-(*S*)-**72** | (33) | 10 | 1.3 |
| 36 | (±)-**73** | (+)-(*R*)-**73** | (46) | 49 | (-)-(*S*)-**74** | (38) | 66 | 8 |
| 37 | (±)-**75** | (-)-(*R*)-**75** | (58) | 22 | (+)-(*S*)-**76** | (41) | 27 | 2 |

[a] E-values were calculated according to the equation described in the literature.[6]

[b] Absolute configuration is unknown.

The absolute configurations of the products were confirmed by comparison of their specific rotations

with those of known compounds reported in the literature and that of (-)-**19** was determined by application of Mosher's method[5] to the $^1$H n.m.r. data of the corresponding α-methoxy-α-trifluoromethylphenylacetate (MTPA). The absolute configurations of the faster-reacting enantiomers of secondary alcohols examined here are illustrated in Figure 1, but those of alcohols **23**, **37** and **39** and acetates **24**, **38** and **40** are unknown. E.e.-values and isolated yields of products together with E-values of the reactions are summarized in Table 1.

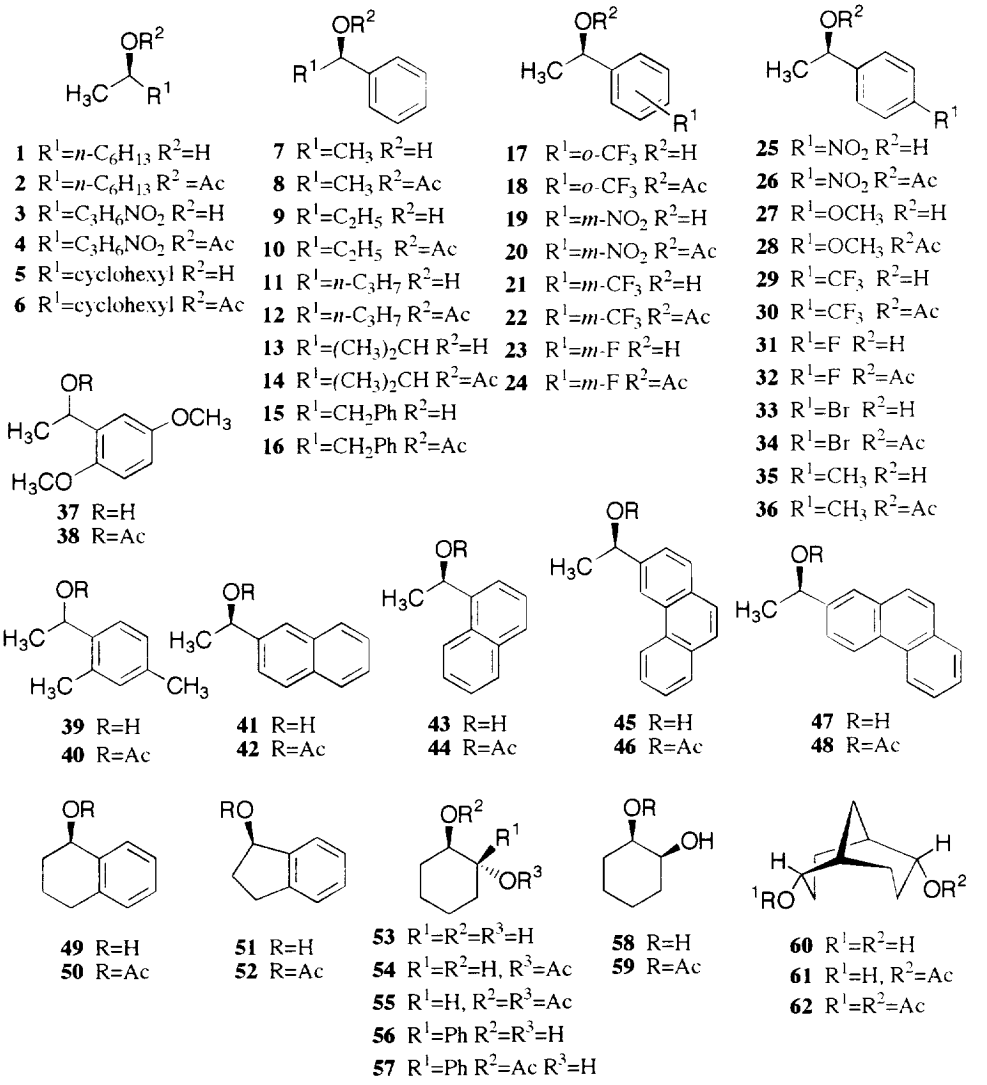
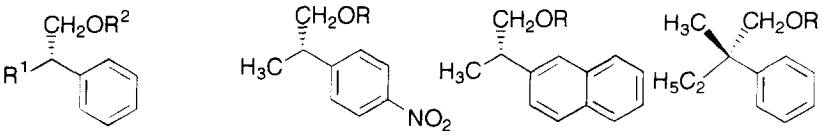



Figure 1. The absolute configurations of faster-reacting enantiomers of secondary alchohols are shown.

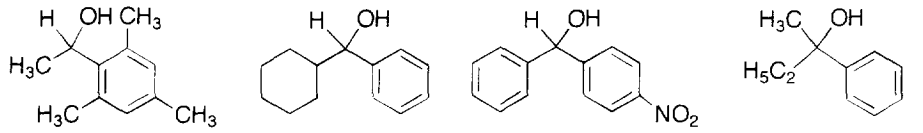
Much data on the stereoselectivity of lipase-catalyzed reactions of secondary alcohols have been reported, but there have been few results for primary alcohols. Therefore, we also examined the

enantioselective acylation of primary alcohols which have the same hydrohobic framework as the corresponding secondary alcohol except for substitution of a hydroxymethyl group for a hydroxy group and the absolute configurations of the faster-reacting enantiomers of primary alcohols are given in Figure 2.



**63** $R^1$=$CH_3$ $R^2$=H **67** $R^1$=*i*-$C_3H_7$ $R^2$=H **71** R=H **73** R=H **75** R=H
**64** $R^1$=$CH_3$ $R^2$=Ac **68** $R^1$=*i*-$C_3H_7$ $R^2$=Ac **72** R=Ac **74** R=Ac **76** R=Ac
**65** $R^1$=$C_2H_5$ $R^2$=H **69** $R^1$=*n*-$C_4H_9$ $R^2$=H
**66** $R^1$=$C_2H_5$ $R^2$=Ac **70** $R^1$=*n*-$C_4H_9$ $R^2$=Ac

Figure 2. The absolute configurations of faster-reacting enantiomers of primary alcohols are shown.



**77** **78** **79** **80**

Figure 3. The alcohols were not acylated by lipase QL-catalyzed reaction.

The alcohols **13**, **19**, **37**, **39**, **41** and **43** were inert in the acylation using lipase from *Pseudomonas fluorecens*.[7] However, lipase QL-catalyzed acylations of these substrates proceeded with a rather good E-value suggesting that the hydrophobic binding site of lipase QL is wider than that of lipase from *Pseudomonas fluorecens*. On the basis of observed enantiomer selectivities, we propose the active site model for this lipase for predicting the faster-reacting enantiomer of primary and secondary alcohols on the basis of the sizes of the two hydrophobic groups at the stereogenic center of the substrate.

For our model we use a working hypothesis that the hydroxy group being acylated is always positioned at the catalytic site and two hydrophobic groups at the stereogenic center are located at the back of the large hydrophobic binding site (HL pocket). In all cases of the present reactions, the secondary alcohols with an *R* configuration were preferentially acylated and a priority of the 'large' group of the all secondary alcohols examined here is higher than that of the 'small' hydrophobic group. From the results we infer that the right pocket of the large hydrophobic binding site ($H_{Lr}$) is wider than the left pocket ($H_{Ll}$) as shown in Fig. 4(a) where the large phenanthryl group and the small methyl group of the faster-reacting enantiomer (*R*)-**45** occupy the $H_{Lr}$ and the $H_{Ll}$ pockets, respectively.

In order to predict the substrate which can be accommodated in the active site of this lipase, we estimate approximately the sizes of the hydrophobic pockets on the basis of the sizes of the groups of secondary alcohols. The acylations of the substrates **45** and **47** proceeded smoothly with high E-value suggesting that the $H_{Lr}$ pocket is wide enough to accommodate at least the phenanthryl group as shown in Fig. 4(a) and 4(b), but the inert substrate **77** showed that the 2,4,6-trimethylphenyl group is a boundary substituent in terms of bulk [Fig. 4(d)]. The acylations of the alcohols **13**, **78** and **79** suggested that the $H_{Ll}$ pocket can accept the isopropyl group but not the cyclohexyl and the phenyl groups as shown in Fig.

4(c) and 4(e). The facts that the alcohols **9**, **65** and **75** were acylated but the tertiary alcohol **80** was inert led us to infer that the small hydrophobic binding site (HS pocket) can accept a hydrogen atom or a methylene group but a methyl group at the stereogenic center can not be accommodated in this site.

The stereoselectivity of the asymmetric acylation of *meso*-substrate **58** is rationalized in terms of the binding orientation [Fig. 4(f)]. The acylation of the bicyclic compound **60** proceeded with moderate E-value to give the monoacetate (2*R*,6*R*)-**61** as the major product together with the diacetate (2*R*,6*R*)-**62** and the observed enantioselectivity was interpreted in terms of the binding orientations as shown in Fig. 4(h) and 4(i).

The reactions of secondary alcohols possessing the phenyl moiety having a polar group or an electronegative atom at its *para* or *meta*-position showed high E-value. The results demonstrated that the HLr pocket is more polar in character and these moieties fitted well into this pocket resulting in high enantiodiscrimination.

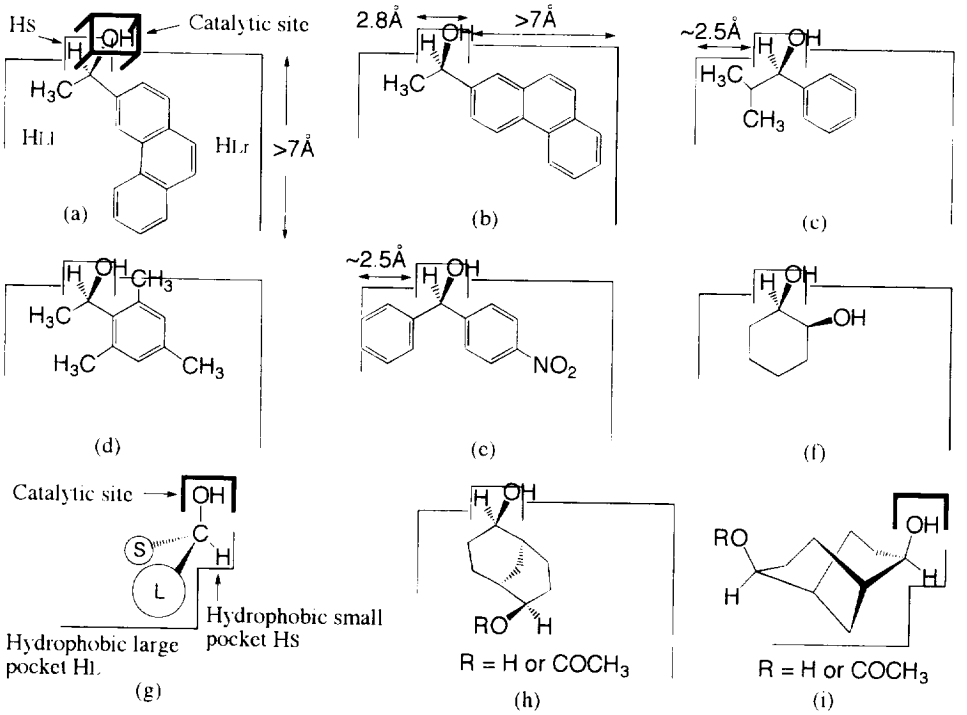
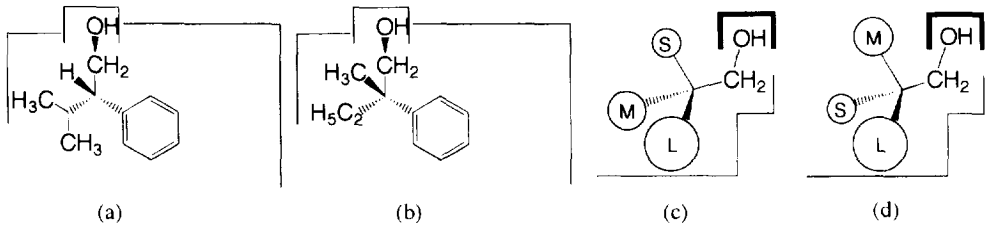



Figure 4. Top and side perspective view of the active site model. HLl and HLr: left and right pocket of large hydrophobic binding site, respectively; (a), (b) and (c) good fit of the secondary alcohols (*R*)-**45**, (*R*)-**47** and (*R*)-**13** into the active site; (d) and (e) the secondary alcohols **77** and **79** were not accommodated in the binding site; (f) good fit of *meso*-diol **58** giving predominantly (1*S*,2*R*)-2-acetoxy-1-cyclohexanol (**59**); (g) side perspective view of a favorable geometry of a secondary alcohol accommodated in the active site; (h) and (i) good fit of (2*R*,6*R*)-**60** into the active site.

All secondary alcohols with an *R* configuration reacted faster in lipase QL-catalyzed acylation, however, the acylations of the corresponding primary alcohols gave predominantly the acetates having an

acetoxymethyl group at the *S* stereogenic center. The observed stereoselectivity reversals are interpreted on the basis of the binding orientations [Fig. 5(a)-5(d)]. The binding orientation of (*S*)-**67** in which the 'large' group and the 'medium' group are located at the back of the HL*r* and the HL*l* pockets, respectively, gives better hydrophobic binding [Fig 5(a) and 5(c)] than that of (*R*)-**67** in which the 'medium' group; the isopropyl group is placed outside the HL pocket resulting in weak hydrophobic binding [Fig 5(d)]. For the 2,2-disubstituted 1-alkanol **75**, the observed selectivity is understandable from the binding orientations [Fig. 5(b), 5(c) and 5(d) (L = $C_6H_5$, M = $C_2H_5$ and S = $CH_3$)]. The binding orientation of (*S*)-**75** where the 'large' group and the 'medium' group occupy the back of the HL*r* and HL*l* pockets, respectively, is more favorable [Fig 5(b) and 5(c)] than that of (*R*)-**75** where the 'medium' group is placed outside the HL pocket [Fig 5(d)].




(a) (b) (c) (d)

Figure 5. (a) and (b) Good fit of (*S*)-**67** and (*S*)-**75** into the active site; (c) and (d) side perspective view of a favorable and an unfavorable geometry of a primary alcohol in the active site, respectively.

The results demonstrated that lipase QL accepted a rather broad range of alcohols as a substrate and therefore can be widely used as the chiral catalyst for preparing homochiral alcohols. The active site model would serve as a rule of thumb for judging the absolute configuration of primary and secondary alcohols on the basis of the enantiomer selectivity of lipase QL-catalyzed acylation.

**Experimental**

*General Procedure* - Optical rotations were measured using a JASCO DIP-40 polarimeter at ambient temperature and $[\alpha]_D$-values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. HPLC analyses were performed on a Shimazu LC-6A chromatograph using a chiral column Opti-Pak AD (Waters), 250 mm ×4.6 mm column. GLC analyses were carried out on a Shimazu GS 8A chromatograph using an SE-52 on Uniport HP 2 m ×2.6 mm column. Lipase QL was supplied by Meito Sangyo and used without further purification. Isopropenyl acetate was commercially avairable and used without further purification. Diisopropyl ether was stocked on Molecular sieves 4A after drying on $CaCl_2$ followed by distillation.

*General Procedure for Lipase QL-catalyzed Acylation (Entry 23)* - A mixture of (±)-**45** (200 mg, 0.901 mmol), isopropenyl acetate (400 mg, 4.55 mmol) and lipase QL (90 mg) in diisopropyl ether (50 $cm^3$) was stirred at 30 °C and the progress of the reaction was monitored by GLC. After stirring for 3h, the enzyme was removed by filtration and the volatile materials were evaporated under reduced pressure. Silica gel chromatography of the residue (*n*-hexane-ethyl acetate 9:1 eluent) gave (-)-**45** (113 mg, 57% yield), $[\alpha]_D^{22}$ -25.7 (*c* 1.15, $CHCl_3$) and (+)-**46** (100 mg, 42% yield), $[\alpha]_D^{22}$ +82.6 (*c* 0.874, $CHCl_3$). A mixture of (+)-**46** (80 mg, 0.30 mmol) and $LiAlH_4$ (12 mg, 0.32 mmol) in dry diethyl ether (20 $cm^3$) was refluxed for 6 h. After a usual work-up, the products were separated by thin layer chromatography on silica gel to give (+)-**45** (57 mg, 85% yield), $[\alpha]_D^{23}$ +28.5 (*c* 0.633, $CHCl_3$). E.e.-values of (-)-**45**, (+)-**45** and (+)-**46** were determined by HPLC using the chiral column. The absolute configuration of **45** was confirmed by

comparison of its specific rotation with that reported in the literature.[8]

*General Procedure for the Preparation of the Phenyl Carbamate* - A mixture of (+)-**5** (40 mg, 0.28 mmol), phenyl isocyanate (36 mg, 0.30 mmol) and a few drops of dry pyridine was stirred for 3h at room temperature and then hydrochloric acid was added to the reaction mixture. It was extracted with benzene and the extract was washed with saturated aqueous solution of sodium hydrogen carbonate and water and dried ($MgSO_4$). After evaporation of the solvent, the phenyl carbamate was isolated by TLC on silica gel and its HPLC analysis was performed without further purification.

*Lipase QL-catalyzed Acylation of Alcohols*

*Entry 1* - Reaction for 2h followed by silica gel chromatography of the products gave (+)-(*S*)-**1**, $[\alpha]_D^{27}$ (*c* 1.54, MeOH)[9] and (-)-(*R*)-**2**, $[\alpha]_D^{23}$ (*c* 0.894, $CHCl_3$). Treatment of (-)-(*R*)-**2** with $LiAlH_4$ gave (-)-(*R*)-**1**, $[\alpha]_D^{27}$ (*c* 1.08, MeOH). The e.e. values of (+)-**1** and (-)-**1** were determined by HPLC analysis of the corresponding phenyl carbamates.

*Entry 2* - Reaction for 40 min followed by silica gel chromatography of the products gave (+)-(*S*)-**3**, $[\alpha]_D^{23}$ +4.49 (*c* 0.934, MeOH)[10] and (-)-(*R*)-**4**, $[\alpha]_D^{23}$ -1.57 (*c* 0.933, $CHCl_3$). Treatment of (-)-(*R*)-**4** with $LiAlH_4$ gave (-)-(*R*)-**3**, $[\alpha]_D^{22}$ -5.50 (*c* 1.08, MeOH). The e.e. values of (+)-**3** and (-)-**3** were determined by HPLC analysis of the corresponding phenyl carbamates.

*Ebtry 3* - Reaction for 2h followed by silica gel chromatography of the products gave (+)-(*S*)-**5**, $[\alpha]_D^{27}$ +2.78 (*c* 1.54, MeOH)[11] and (-)-(*R*)-**6**, $[\alpha]_D^{23}$ -6.57 (*c* 0.894, $CHCl_3$). Treatment of (-)-(*R*)-**6** with $LiAlH_4$ gave (-)-(*R*)-**5**, $[\alpha]_D^{27}$ -2.74 (*c* 1.08, MeOH). The e.e. values of (+)-**5** and (-)-**5** were determined by HPLC analysis of the corresponding phenyl carbamates.

*Entry 4* - Reaction for 6.5h followed by silica gel chromatography of the products gave (-)-(*S*)-**7**, $[\alpha]_D^{25}$ -36.1 (*c* 2.96, MeOH)[11] and (+)-(*R*)-**8**, $[\alpha]_D^{24}$ +105 (*c* 4.05, $CHCl_3$). Treatment of (+)-(*R*)-**8** with $LiAlH_4$ gave (+)-(*R*)-**7**, $[\alpha]_D^{23}$ +37.5 (*c* 0.823, MeOH).

*Entry 5* - Reaction for 40h followed by silica gel chromatography of the products gave (-)-(*S*)-**9**, $[\alpha]_D^{23}$ -27.7 (*c* 2.06, MeOH)[9] and (+)-(*R*)-**10**, $[\alpha]_D^{24}$ +91.7 (*c* 4.17, $CHCl_3$). Treatment of (+)-(*R*)-**10** with $LiAlH_4$ gave (+)-(*R*)-**9**, $[\alpha]_D^{25}$ +22.2 (*c* 1.29, MeOH).

*Entry 6* - After reaction for 63h, silica gel chromatography of the products gave (-)-(*S*)-**11**, $[\alpha]_D^{25}$ -15.8 (*c* 2.02, MeOH)[12] and (+)-(*R*)-**12**, $[\alpha]_D^{25}$ +75.5 (*c* 2.29, $CHCl_3$). Treatment of (+)-(*R*)-**12** with $LiAlH_4$ gave (+)-(*R*)-**11**, $[\alpha]_D^{24}$ +27.7 (*c* 0.280, MeOH).

*Entry 7* - After reaction for 74h, silica gel chromatography of the products gave (-)-(*S*)-**13**, $[\alpha]_D^{28}$ -10.8 (*c* 3.23, MeOH)[13] and (+)-(*R*)-**14**, $[\alpha]_D^{28}$ +75.2 (*c* 2.17, $CHCl_3$). Treatment of (+)-(*R*)-**14** with $LiAlH_4$ gave (+)-(*R*)-**13**, $[\alpha]_D^{24}$ -21.2 (*c* 3.23, MeOH).

*Entry 8* - After reaction for 7 days, (+)-(*S*)-**15**, $[\alpha]_D^{22}$ +23.0 (*c* 1.34, MeOH)[14] and (-)-(*R*)-**16**, $[\alpha]_D^{24}$ -17.1 (*c* 2.04, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (-)-(*R*)-**16** with $LiAlH_4$ gave (-)-(*R*)-**15**, $[\alpha]_D^{22}$ -13.7 (*c* 1.28, MeOH).

*Entry 9* - After reaction for 21 days, (-)-(*S*)-**17**, $[\alpha]_D^{22}$ -23.0 (*c* 1.26, MeOH)[15] and (+)-(*R*)-**18**, $[\alpha]_D^{23}$ +48.5 (*c* 1.55, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-(*R*)-**18** with $LiAlH_4$ gave (+)-(*R*)-**17**, $[\alpha]_D^{22}$ +29.2 (*c* 0.795, MeOH).

*Entry 10* - After reaction for 16 days, (-)-(*S*)-**19**, $[\alpha]_D^{27}$ -17.2 (*c* 2.03, MeOH) and (+)-(*R*)-**20**, $[\alpha]_D^{28}$ +80.1 (*c* 1.85, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-(*R*)-**20** with $LiAlH_4$ gave (+)-(*R*)-**19**, $[\alpha]_D^{28}$ +33.2 (*c* 1.89, MeOH). Treatment of (-)-**19** with (*R*)- and (*S*)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride, 4-dimethylaminopyridine and 1,3-dicyclohexylcarbodiimide in $CH_2Cl_2$ followed by purification on silica gel TLC gave the diastereoisomers of MTPA and the absolute configuration of (-)-(*S*)-**19** was determined by application of Mosher's method to the $^1H$ n.m.r. data of the esters.

*Entry 11* - After reaction for 4h, (-)-(*S*)-**21**, $[\alpha]_D^{24}$ -17.1 (*c* 2.92, MeOH)[15] and (+)-(*R*)-**22**, $[\alpha]_D^{25}$ +70.7 (*c* 2.63, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-(*R*)-**22** with $LiAlH_4$ gave

(+)-(*R*)-**21**, $[\alpha]_D^{23}$ +26.9 (*c* 1.22, MeOH).

*Entry 12* - After reaction for 3h, (-)-**23**, $[\alpha]_D^{28}$ -27.8 (*c* 0.985, MeOH) and (+)-**24**, $[\alpha]_D^{25}$ +96.8 (*c* 1.03, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-**24** with $LiAlH_4$ gave (+)-(*R*)-**23**, $[\alpha]_D^{25}$ +38.5 (*c* 0.998, MeOH). Absolute configurations of these products are unknown.

*Entry 13* - After reaction for 10h, (-)-(*S*)-**25**, $[\alpha]_D^{25}$ -19.4 (*c* 1.96, MeOH)[16] and (+)-(*R*)-**26**, $[\alpha]_D^{26}$ +101 (*c* 2.13, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-(*R*)-**26** with $LiAlH_4$ gave (+)-(*R*)-**25**, $[\alpha]_D^{25}$ +28.1 (*c* 0.186, MeOH).

*Entry 14* - After reaction for 9h, (-)-(*S*)-**27**, $[\alpha]_D^{24}$ -26.2 (*c* 3.18, MeOH)[17] and (+)-(*R*)-**28**, $[\alpha]_D^{24}$ +114 (*c* 3.10, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-(*R*)-**28** with $LiAlH_4$ gave (+)-(*R*)-**27**, $[\alpha]_D^{28}$ +33.6 (*c* 0.831, MeOH).

*Entry 15* - After reaction for 3h, (-)-(*S*)-**29**, $[\alpha]_D^{29}$ -19.2 (*c* 3.79, MeOH)[18] and (+)-(*R*)-**30**, $[\alpha]_D^{29}$ +68.7 (*c* 3.11, $CHCl_3$) were isolated on silica gel chromatography. Treatment of (+)-(*R*)-**30** with $LiAlH_4$ gave (+)-(*R*)-**29**, $[\alpha]_D^{24}$ +38.5 (*c* 2.13, MeOH).

*Entry 16* - After reaction for 24h followed by silica gel chromatography of the products, (-)-(*S*)-**31**, $[\alpha]_D^{31}$ -23.1 (*c* 3.12, MeOH)[19] and (+)-(*R*)-**32**, $[\alpha]_D^{32}$ +92.8 (*c* 3.36, $CHCl_3$) were isolated. Reduction of (+)-(*R*)-**32** with $LiAlH_4$ gave (+)-(*R*)-**31**, $[\alpha]_D^{28}$ +30.7 (*c* 1.36, MeOH).

*Entry 17* - After reaction for 22h followed by silica gel chromatography of the products, (-)-(*S*)-**33**, $[\alpha]_D^{27}$ -21.6 (*c* 1.93, MeOH)[19] and (+)-(*R*)-**34**, $[\alpha]_D^{28}$ +92.4 (*c* 2.49, $CHCl_3$) were isolated. Reduction of (+)-(*R*)-**34** with $LiAlH_4$ gave (+)-(*R*)-**33**, $[\alpha]_D^{28}$ +31.3 (*c* 1.16, MeOH).

*Entry 18* - After reaction for 72h followed by silica gel chromatography of the products, (-)-(*S*)-**35**, $[\alpha]_D^{27}$ -22.3 (*c* 3.79, MeOH)[16] and (+)-(*R*)-**36**, $[\alpha]_D^{27}$ +116 (*c* 1.68, $CHCl_3$) were isolared. Reduction of (+)-(*R*)-**36** with $LiAlH_4$ gave (+)-(*R*)-**35**, $[\alpha]_D^{28}$ +38.5 (*c* 1.09, MeOH).

*Entry 19* - Reaction for 7 days followed by silica gel chromatography of the products gave (-)-**37**, $[\alpha]_D^{27}$ -30.6 (*c* 0.780, MeOH) and (+)-**38**, $[\alpha]_D^{27}$ +64.6 (*c* 1.54, $CHCl_3$). Reduction of (+)-**38** with $LiAlH_4$ gave (+)-**37**, $[\alpha]_D^{27}$ +48.2 (*c* 0.578, MeOH). Absolute configurations of these products are unknown.

*Entry 20* - Reaction for 74h followed by silica gel chromatography of the products gave (-)-**39**, $[\alpha]_D^{28}$ -33.6 (*c* 3.07, MeOH) and (+)-**40**, $[\alpha]_D^{29}$ +75.1 (*c* 3.48, $CHCl_3$). Reduction of (+)-**40** with $LiAlH_4$ gave (+)-**39**, $[\alpha]_D^{29}$ +46.3 (*c* 1.57, MeOH). Absolute configurations of these products are unknown.

*Entry 21* - Reaction for 64h followed by silica gel chromatography of the products gave (-)-(*S*)-**41**, $[\alpha]_D^{28}$ -23.0 (*c* 4.55, MeOH)[8] and (+)-(*R*)-**42**, $[\alpha]_D^{28}$ +109 (*c* 1.83, $CHCl_3$). Reduction of (+)-(*R*)-**42** with $LiAlH_4$ gave (+)-(*R*)-**41**, $[\alpha]_D^{28}$ +36.5 (*c* 1.92, MeOH).

*Entry 22* - Reaction for 90h followed by silica gel chromatography of the products gave (-)-(*S*)-**43**, $[\alpha]_D^{29}$ -26.2 (*c* 1.32, MeOH)[8] and (+)-(*R*)-**44**, $[\alpha]_D^{29}$ +48.1 (*c* 1.36, $CHCl_3$). Reduction of (+)-(*R*)-**44** with $LiAlH_4$ gave (+)-(*R*)-**43**, $[\alpha]_D^{28}$ +66.7 (*c* 0.307, MeOH).

*Entry 24* - After reaction for 3h, (-)-(*S*)-**47**, $[\alpha]_D^{24}$ -25.1 (*c* 1.27, $CHCl_3$)[8] and (+)-(*R*)-**48**, $[\alpha]_D^{23}$ +116 (*c* 1.05, $CHCl_3$) were obtained on silica gel chromatography. Reduction of (+)-(*R*)-**48** with $LiAlH_4$ gave (+)-(*R*)-**47**, $[\alpha]_D^{22}$ +38.1 (*c* 1.11, $CHCl_3$).

*Entry 25* - Reaction for 24h followed by silica gel chromatography of the products gave (+)-(*S*)-**49**, $[\alpha]_D^{28}$ +14.8 (*c* 3.23, MeOH)[20] and (+)-(*R*)-**50**, $[\alpha]_D^{24}$ +105 (*c* 0.984, $CHCl_3$). Reduction of (+)-**50** with $LiAlH_4$ gave (-)-(*R*)-**49**, $[\alpha]_D^{24}$ -21.3 (*c* 0.583, MeOH).

*Entry 26* - Reaction for 4.5h followed by silica gel chromatography of the products gave (+)-(*S*)-**51**, $[\alpha]_D^{24}$ +13.6 (*c* 2.02, MeOH)[21] and (+)-(*R*)-**52**, $[\alpha]_D^{22}$ +84.4 (*c* 2.47, $CHCl_3$). Reduction of (+)-(*R*)-**52** with $LiAlH_4$ gave (-)-(*R*)-**51**, $[\alpha]_D^{24}$ -14.6 (*c* 0.597, MeOH).

*Entry 27* - After reaction for 1h, silica gel chromatography of the products gave (+)-(1*S*,2*S*)-**53**, $[\alpha]_D^{23}$ +15.9 (*c* 0.510, $CHCl_3$), (-)-(1*R*,2*R*)-**54**, $[\alpha]_D^{23}$ -27.6 (*c* 1.24, $CHCl_3$)[22] and (-)-(1*R*,2*R*)-**55**, $[\alpha]_D^{23}$ -12.1 (*c* 1.36, $CHCl_3$). Treatment of (-)-(1*R*,2*R*)-**54** and (-)-(1*R*,2*R*)-**55** with $LiAlH_4$ gave (-)-(1*R*,2*R*)-**53**, $[\alpha]_D^{23}$

-21.9 (*c* 0.406, $CHCl_3$) and (-)-(1*R*,2*R*)-**53**, $[\alpha]_D^{23}$ -38.1 (*c* 0.410, $CHCl_3$), respectively, and the e.e. values of (-)-**53** and (+)-**53** were determined by HPLC analysis of the corresponding phenyl carbamates.

*Entry 28* - After reaction for 7 days, (+)-(1*R*,2*S*)-**56**, $[\alpha]_D^{23}$ +31.9 (*c* 0.938, benzene)[23] and (-)-(1*S*,2*R*)-**57**, $[\alpha]_D^{23}$ -29.9 (*c* 0.778, benzene) were obtained on silica gel chromatography. Treatment of (-)-(1*S*,2*R*)-**57** with $LiAlH_4$ gave (-)-(1*S*,2*R*)-**56**, $[\alpha]_D^{23}$ -41.3 (*c* 0.881, benzene).

*Entry 29* - After reaction for 3h, (-)-(1*S*,2*R*)-**59**, $[\alpha]_D^{24}$ -1.72 (*c* 1.43, $CHCl_3$)[24] was isolated in 98% yield on silica gel chromatography. Its e.e. value was determined by HPLC analysis of the corresponding phenyl carbamate.

*Entry 30* - After reaction for 31h, silica gel chromatography of the products gave (-)-(2*S*,6*S*)-**60**, $[\alpha]_D^{22}$ -46.5 (*c* 1.02, EtOH), (+)-(2*R*,6*R*)-**61**, $[\alpha]_D^{21}$ +58.8 (*c* 1.32, $CHCl_3$) and (+)-(2*R*,6*R*)-**62**, $[\alpha]_D^{21}$ +43.7 (*c* 0.542, $CHCl_3$). The e.e. values of the products were confirmed by comparison of their specific rotations with those reported in the literature.[25]

*Entry 31* - After reaction for 20 min, silica gel chromatography of the products gave (+)-(*R*)-**63**, $[\alpha]_D^{19}$ +1.87 (*c* 1.39, MeOH)[9] and (-)-(*S*)-**64**, $[\alpha]_D^{19}$ -0.35 (*c* 1.69, $CHCl_3$). Treatment of (-)-(*S*)-**64** with $LiAlH_4$ gave (-)-(*S*)-**63**, $[\alpha]_D^{20}$ -1.10 (*c* 1.20, MeOH).

*Entry 32* - After reaction for 50 min, silica gel chromatography of the products gave (-)-(*R*)-**65**, $[\alpha]_D^{22}$ -12.6 (*c* 1.20, MeOH)[26] and (+)-(*S*)-**66**, $[\alpha]_D^{24}$ +10.3 (*c* 1.08, $CHCl_3$). Treatment of (+)-(*S*)-**66** with $LiAlH_4$ gave (+)-(*S*)-**65**, $[\alpha]_D^{24}$ +13.1 (*c* 1.21, MeOH).

*Entry 33* - Reaction for 2h followed by silica gel chromatography of the products gave (-)-(*R*)-**67**, $[\alpha]_D^{25}$ -4.43 (*c* 1.26, MeOH) and (+)-(*S*)-**68**, $[\alpha]_D^{24}$ +12.6 (*c* 1.08, $CHCl_3$). Treatment of (+)-(*S*)-**68** with $LiAlH_4$ gave (+)-(*S*)-**67**, $[\alpha]_D^{25}$ +5.86 (*c* 1.21, MeOH). The absolute configuration of (-)-**67** was determined by comparison of the sign of specific rotation of the resulting carboxylic acid[27] after oxidation of (-)-**67** with Jones' reagent.

*Entry 34* - Reaction for 50 min followed by silica gel chromatography of the products gave (-)-(*R*)-**69**, $[\alpha]_D^{23}$ -16.3 (*c* 1.21, MeOH)[28] and (+)-(*S*)-**70**, $[\alpha]_D^{21}$ +13.7 (*c* 0.958, $CHCl_3$). Treatment of (+)-(*S*)-**70** with $LiAlH_4$ gave (+)-(*S*)-**69**, $[\alpha]_D^{23}$ +20.8 (*c* 1.21, MeOH).

*Entry 35* - Reaction for 20 min followed by silica gel chromatography of the products gave (+)-(*R*)-**71**, $[\alpha]_D^{23}$ +1.27 (*c* 1.11, $CHCl_3$) and (-)-(*S*)-**72**, $[\alpha]_D^{23}$ -2.57 (*c* 1.91, $CHCl_3$). Treatment of (-)-(*S*)-**72** with $LiAlH_4$ gave (-)-(*S*)-**71**, $[\alpha]_D^{23}$ -2.36 (*c* 1.03, $CHCl_3$). The absolute configuration of (+)-**71** was determined by comparison of the sign of specific rotation of the corresponding (-)-carboxylic acid[29] obtained by oxidation of (+)-**71** with Jones' reagent.

*Entry 36* - Reaction for 80 min followed by silica gel chromatography of the products gave (+)-(*R*)-**73**, $[\alpha]_D^{22}$ +19.0 (*c* 1.05, MeOH) and (-)-(*S*)-**74**, $[\alpha]_D^{22}$ -22.8 (*c* 1.83, $CHCl_3$). Treatment of (-)-(*S*)-**74** with $LiAlH_4$ gave (-)-(*S*)-**73**, $[\alpha]_D^{23}$ -23.4 (*c* 1.03, MeOH). The absolute configuration of (+)-**73** was determined by comparison of the sign of specific rotation of the corresponding (-)-carboxylic acid[30] obtained by oxidation of (+)-**73** with Jones' reagent.

*Entry 37* - Reaction for 68h followed by silica gel chromatography of the products gave (-)-(*R*)-**75**, $[\alpha]_D^{22}$ -0.85 (*c* 1.03, MeOH)[31] and (+)-(*S*)-**76**, $[\alpha]_D^{22}$ +5.36 (*c* 1.38, $CHCl_3$). Treatment of (+)-(*S*)-**76** with $LiAlH_4$ gave (+)-(*S*)-**75**, $[\alpha]_D^{23}$ +1.05 (*c* 1.03, MeOH).

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