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Complementary Lipase-Mediated Desymmetrization Processes of 3-Aryl-1,5-Disubstituted Fragments. Enantiopure Synthetic Valuable Carboxylic Acid Derivatives

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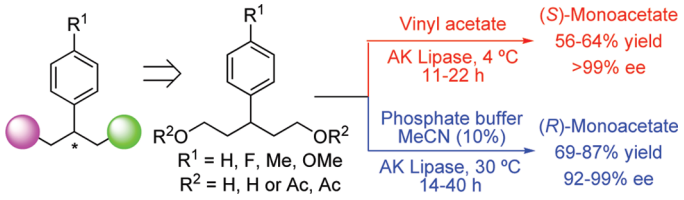
Received October 5, 2010



Desymmetrizaton enzymatic processes have been extensively studied searching for optimal methods of producing enantioenriched monoacetates from prochiral diols and diesters. AK lipase has been found as an excellent biocatalyst for the desymmetriaztion of a series of previously synthesized 3-arylpentane-1,5-diols derivatives. The access to (*S*)- or (*R*)-monoacetates in high optical purity (86−99% ee) has been possible by using acetylation or hydrolysis reactions, respectively, where the reaction parameters have been optimized in terms of source and amount of biocatalyst, temperature, solvent, and reaction time. The synthetic potential of enantiopure monoesters has been demonstrated by using these interesting chiral building blocks for the preparation of novel enantiopure carboxylic acid derivatives.

Introduction

Pentane-1,5-diol possesses a myriad of applications in different industrial sectors, for instance it is commonly employed as plasticizer in cellulose products, and additives, but also is widely used in brake fluid compositions, dental composites and as a percutaneous absorption enhancer.[1] Selective monoprotection of polyfunctional compounds has been intensified during recent years searching for adequate chemo-, regio-, or stereoselective synthetic methods.[2] These strategies are extremely useful specially if simple prochiral compounds can be used as starting materials, being enantioselective desymmetrization processes adequate tools for the introduction of chirality.[3] Enzymatic methods have gained major attention because of their mild reaction conditions,[4] allowing the selective modification of different motifs maintaining unaltered functional groups susceptible to react in more aggressive chemical conditions.[5]

From the enzymatic toolbox, hydrolases[6] and oxidoreductases[7] have been extensively employed in desymmetrization processes of *meso* or prochiral compounds. Among them, lipases have attracted the attention of a high number of

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DOI: 10.1021/jo101962v Published on Web 01/10/2011

scientific publications because of their action without cofactor requirements in aqueous media, organic solvents, or neoteric systems. Diols, cyclic anhydrides, or diesters have been shown as ideal substrates in these types of transformations mainly by acetylation,[8] esterification,[9] or aminolysis[10] reactions, respectively.

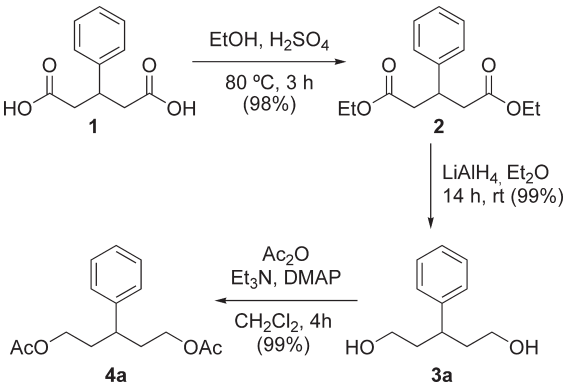
Meanwhile a large number of examples for the lipase-mediated desymmetrization of 1,3-diols have been reported in the literature,[4,11] asymmetric synthetic methodologies for the asymmetrization of 1,5-diols have been scarcely reported[12] in spite of their versatilities for the production of sesquiterpenoids as (−)-Heliannuol E[13] or (−)-Heliannuol C.[14] Unfortunately these approaches allow the production of the corresponding monoesters with high selectivity but low yields or vice versa. Alternatively, lipase-catalyzed dynamic kinetic asymmetric transformations of 1,5-diols have allowed the preparation of 1,5-diacetates in high diastereo- and enantioselectivities, applying them later for the production of optically active six-membered heterocycles.[15]

In our case we have tried to provide a clear understanding for the development of enzymatic desymmetrizations starting from diols or diacetates in acetylation or hydrolytic reactions, optimizing the experimental conditions for a good atom economy and the preparation of organic compounds in high optical purity. The complementary stereoselective actions of lipases have provide us the access to opposite enantiomers, which is a highly demanding task especially for the industrial pharmaceutical sector.[16]

Results and Discussion

We focused first on the chemical synthesis of a model substrate **3a** starting from commercially available 3-phenylpentanedioic acid (**1**). Esterification reaction with ethanol occurred in quantitative yield isolating the diethyl ester **2**, which was subsequently reduced to 3-phenylpentane-1,5-diol (**3a**) with lithium aluminum hydride in diethyl ether at room temperature (Scheme 1). To obtain standard samples

SCHEME 1. Chemical Synthesis of Diol 3a and Diacetate 4a



for all possible products involved in the enzymatic desymmetrization of **3a** using vinyl acetate (VinOAc, **5a**) or ethyl acetate (EtOAc, **5b**) as acyl donors, 3-phenylpentane-1,5-diol was reacted with acetic anhydride in the presence of triethylamine and DMAP to achieve the isolation of the corresponding monoacetate (±)-**6a** and the diacetate **4a**, the latest in quantitative yield when using an excess of acetic anhydride.

The enzymatic desymmetrization of prochiral diol **3a** was initially attempted with 1 equiv of VinOAc and a wide set of lipases (Table 1). Reaction without enzyme led to the formation of the racemic monoacetate **6a** in 18% conversion after 38 h (entry 1). For that reason and in order to minimize the chemical production of the racemic monoester **6a**, we decided to react diol **3a** in the presence of a panel of biocatalysts during a shorter reaction time (14 h). In all cases complex mixtures of diol, monoacetate, and diacetate were observed. Although preferentially the monoacylation was observed, conversions do not overcome 50% in the synthesis of the optically active monoacetate **6a** for porcine pancreas lipase (PPL, entry 2), *Candida rugosa* lipase (CRL, entry 3), *Pseudomonas cepacia* lipase (PSL-C I, entry 4), and *Candida antarctica* lipase B (CAL-B, entry 5). Close to 60% yield values in the chiral monoester were attained with *Rhizomoccus Miehei* lipase (RML, entry 7) and AK lipase (entry 6), with AK lipase being the one that exhibited the best stereopreference toward the formation of (*S*)-**6a** (68% ee). It must be mentioned that most of the lipases led to the formation of optically enriched (*S*)-**6a**, with CAL-B and RM lipase being the only biocatalysts that allowed the formation of the (*R*)-enantiomer. Alternatively we decided to employ other acyl donors such as a nonactivated ester as ethyl acetate (EtOAc, **5b**), which did not react in the absence of enzyme inclusively at 60 °C (entry 8). However, lower reaction rates and moderate selectivities were observed for all tested enzymes (entries 9−12).

After several unsuccessful attempts to find the more suitable experimental conditions for the desymmetrization of **3a**, we decided to use vinyl acetate as both acyl donor and solvent in the lipase AK mediated desymmetrization of diol **3a**. As can be seen in Figure 1, the diol **3a** was completely transformed into the acetate (*S*)-**6a** and diester **4a** both at 4 and 30 °C. In the reaction at 30 °C, the complete disappearance of diol **3a** was observed after 4 h, increasing the optical purity of **6a** from 4 to 6 h (92 to 95% ee) in detriment of the appearance of higher concentrations of diacetate **4a**

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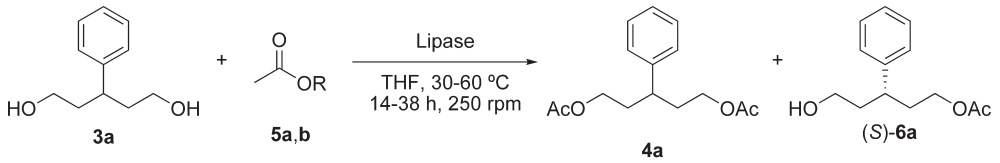
TABLE 1. Enzymatic Desymmetrization of Diol 3a Using Vinyl Acetate or Ethyl Acetate in THF As Solvent and 250 Revolutions Per Minute (rpm)



5a: R= $CH{=}CH_2$ (VinOAc); **5b**: R= CH_2CH_3 (EtOAc)

entry	acyl donor[a]	enzyme	T (°C)	t (h)	**3a** (%)[b]	**4a** (%)[b]	**6a** (%)[b]	ee_{6a} (%)[c]
1	**5a** (1 equiv)		30	38	82	0	18	0
2	**5a** (1 equiv)	PPL	30	14	82	7	11	13
3	**5a** (1 equiv)	CRL	30	14	76	1	23	42
4	**5a** (1 equiv)	PSL-C I	30	14	62	2	36	52
5[c]	**5a** (1 equiv)	CAL-B	30	14	42	8	50	8
6	**5a** (1 equiv)	AK	30	14	35	6	59	68
7[c]	**5a** (1 equiv)	RM	30	14	33	7	60	45
8	**5b** (3 equiv)		60	38	>99	0	0	
9	**5b** (3 equiv)	PPL	30	14	>99	0	0	
10	**5b** (3 equiv)	AK	30	14	90	0	10	40
11	**5b** (3 equiv)	PSL-C I	30	14	81	0	19	52
12	**5b** (3 equiv)	RM	30	14	82	0	18	54

[a]Equivalents of acyl donor in parentheses. [b]Determined by GC. [c]Determined by HPLC. In all cases (*S*)-**6a** was isolated except for the CAL-B and lipase RM catalyzed acetylations where the formation of (*R*)-**6a** was observed.

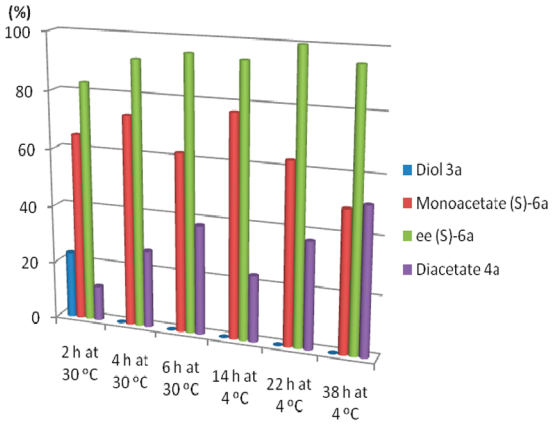


FIGURE 1. Time course of the lipase AK catalyzed desymmetrization of diol **3a**, using vinyl acetate as acyl donor and solvent at 4 and 30 °C at 250 rpm.

(27 to 38%). On the other hand, reaction at 4 °C occurred with an excellent degree of selectivity (Table 2); longer reaction times were needed for the disappearance of diol **3a**, obtaining the enantiopure monoacetate (*S*)-**6a** after 22 h in 63% yield (entry 1). When the enzymatic processes were left for more than 1 day there was a decrease in the optical purity of (*S*)-monoacetates and an increase in the formation of the diacetate **4a** (for more details see also Table S4 in the Supporting Information).

With the best results in hand for the enantioselective enzymatic desymmetrization of **3a**, we decided to test this methodology as a general and efficient manner to produce optically active compounds by synthesizing a novel family of 3-arylpropane-1,5-diols (Scheme 2). That was possible starting from commercially available aldehydes **7**−**11**, which were reacted with ethyl acetoacetate in the presence of piperidine and later with EtOH and NaOH leading to the corresponding diethyl-3-arylpentanedioates.[17] Subsequent reaction

TABLE 2. Enantioselective Desymmetrization of Diols 3a−f through AK Lipase-Mediated Acetylation in Vinyl Acetate at 4 °C and 250 rpm

entry	R	t (h)	**3a**−**d** (%)[a]	(*S*)-**6a**−**d** (%)[a,b]	**4a**−**d** (%)[a]
1	2,3,4-H	22	0	63 (>99)	37
2	4-F	11	0	61 (>99)	39
3	4-Me	11	0	56 (>99)	44
4	4-OMe	11	0	64 (>99)	36
5	3-OMe	11	0	62 (90)	38
6	2-OMe	72	24	43 (86)	33

[a]Percentages of compounds determined by GC. [b]Enantiomeric excess of (*S*)-**6a** in parentheses determined by HPLC.

with $LiAlH_4$ in dry diethyl ether led to the corresponding diols **3b**−**f** in good overall yield (54−80%), higher when the 4-substituted phenyl rings were considered (70−80%) instead of the 2- or 3-substituted rings (54−63%), obtaining the corresponding diacetates **4a**−**f** in quantitative yields by conventional chemical acetylation procedures.

Then we extended the best experimental conditions found for the lipase-mediated desymmetrization of **3a** to this new family of diols **3b**−**f** (Table 2). Different tendencies were observed in the AK lipase catalyzed acetylation reactions depending on the pattern substitution. For substrates substituted in the 4-position of the phenyl ring (**3b**−**d**), the enzyme initially preferred to monoacetylate the (*S*)-enantiomers providing the disappearance of all the starting diols after 8.5 h (see Table S4 in the Supporting Information for additional data). Enantiomericallly pure acetates (*S*)-**3b**−**d** were obtained after 11 h (56−64%, entries 2−4), showing in all cases the presence of the diacetylated compound **4b**−**d**

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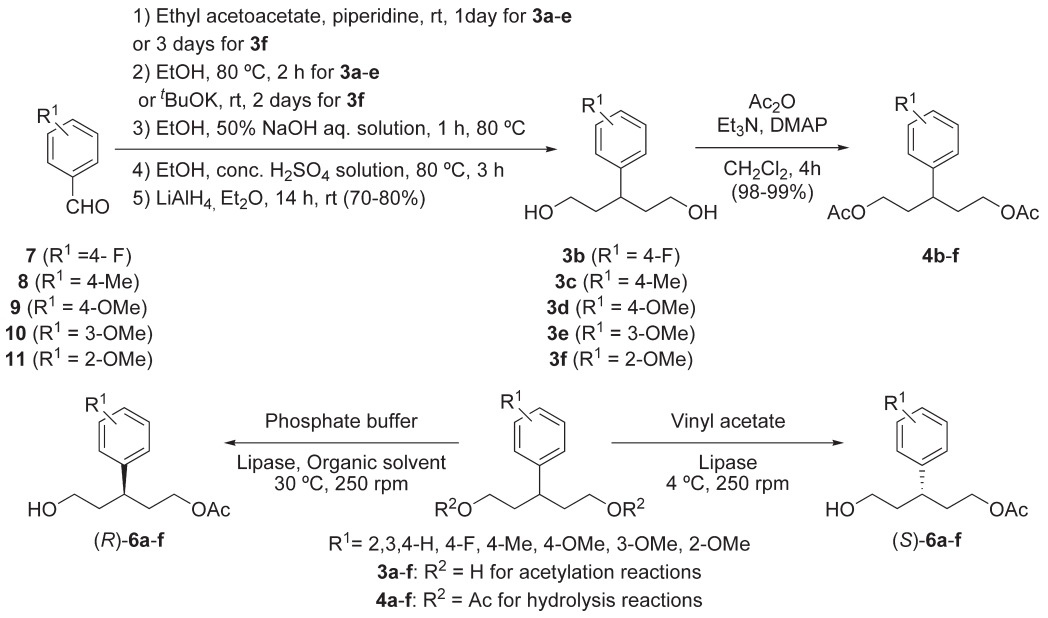
SCHEME 2. Chemical Synthesis of Diols 3b−f and Diacetates 4b−f Followed by Enzymatic Desymmetrization Reactions through Acetylation or Hydrolytic Procedures



that appeared in higher concentrations at longer reaction times (42−55% at 14 h, see Table S4 in the Supporting Information). The reactivity of substrates bearing the methoxy group in positions 2 or 3 in the aromatic ring was considered, noting a low stereopreference in the production of (*S*)-**6e** (62% yield and 90% ee after 11 h) and also a slow reaction rate for the acetylation of **3f**, yielding (*S*)-**6f** in 43% yield and 86% ee after 72 h.

Trying to obtain the (*R*)-monoacetates **3a**−**f** we took advantage of the complementary enzymatic activities of lipases in acetylation and hydrolytic reactions. Considering diacetate **4a** as a model substrate we observed a very low reactivity with different lipases using 5 equiv of water in organic solvents (data not shown). For that reason, we decided to study the hydrolytic processes in a biphasic system combining a 50 mM phosphate buffer pH (90%) with THF, dioxane, MeOH, or MeCN as organic cosolvent (10%) in order to facilitate the solubility of **4a**. Reactions were followed taking aliquots at 14, 40, and 64 h, and the most representative results have been summarized in Table 3.

In all the reactions carried out with THF except for CAL-B (entry 2), the presence of starting material **4a** was observed after 14 h, the monoacetate being found as the major compound in the reaction vessel. The reactions evolved toward the formation of optically active **6a** in low to high enantiomeric excesses (entries 1−5), reaching the highest stereoselectivities with AK lipase and PSL preparations for the production of (*R*)-**6a**. On the other hand CAL-B and lipase RM led to the appearance of the opposite enantiomer (*S*)-**6a**. Focusing on the optimization of the reaction conditions for the minimization of the formation of diol **3a** and the isolation of (*R*)-**6a** in high enantiomeric excess, different cosolvents were tested (dioxane, acetonitrile, and methanol, entries 6−17), finding the best results when using the AK lipase and MeCN as solvent with the isolation of the desired optically active final product in 77−85% yield and 90−92% ee (entries 16 and 17). Longer reaction times (64 h) led in all cases to a significant formation of the corresponding diol and a decreases in the optical purity of (*R*)-monoacetates.

TABLE 3. Lipase-Mediated Enantioselective Desymmetrization of Diacetate 4a in a Biphasic System Composed of a 50 mM Phosphate Buffer pH 7.0 and MeCN (90:10 v/v) at 30 °C and 250 rpm

entry	enzyme	cosolvent	*t* (h)	**4a** (%)[a]	**3a** (%)[a]	**6a** (%)[a]	ee_{6a} (%)[b]
1[c]	RM	THF	40	48	5	47	23
2[c]	CAL-B	THF	14	0	84	16	27
3	AK	THF	40	3	12	85	85
4	PSL SD	THF	40	2	29	69	90
5	PSL IM	THF	40	3	18	79	88
6	PSL IM	dioxane	14	0	16	84	88
7	PSL IM	dioxane	40	0	32	68	92
8	PSL IM	MeOH	14	2	17	81	84
9	PSL IM	MeOH	40	0	26	74	88
10	PSL IM	MeCN	14	5	9	86	84
11	PSL IM	MeCN	40	1	24	75	88
12	AK	dioxane	14	2	13	85	86
13	AK	dioxane	40	2	14	84	89
14	AK	MeOH	14	3	7	90	84
15	AK	MeOH	40	1	28	71	92
16	AK	MeCN	14	3	12	85	90
17	AK	MeCN	40	2	21	77	92

[a]Determined by GC. [b]Determined by HPLC. [c]In all cases (*R*)-**6a** was isolated except for the CAL-B and lipase RM catalyzed hydrolysis where the formation of (*S*)-**6a** was observed.

Then different amounts of acetonitrile were used in the enantioselective enzymatic desymmetrization of **4a** (Table 4), showing that by employing 5% (entries 1 and 2) or 20% of MeCN (entries 3 and 4) (*R*)-**6a** was isolated in good yield and enantiomeric excess as occurred previously with the 10% ratio, while higher amounts of MeCN (≥50%, entries 5 and 6) have a large negative effect in the enzyme action, leading to the complete inactivation of the enzyme.

The temperature influence was also analyzed, finding similar enantiomeric excesses for (*R*)-**6a** at 4 or 30 °C (entries 1−4 of Table 5), although at lower temperatures the starting diacetate was recovered instead of the diol. On the other hand, when increasing the temperature to 50 °C a

TABLE 4. Percentages of Diacetate 4a, Diol 3a, and Monoacetate (*R*)-6a in the Lipase AK Catalyzed Desymmetrization of 4a through Hydrolysis in a Biphasic System Composed of a 50 mM Phosphate Buffer pH 7.0 and MeCN at 30 °C and 250 rpm

entry	MeCN (%)	*t* (h)	**4a** (%)[a]	**3a** (%)[a]	(*R*)-**6a** (%)[a–c]
1	5	14	4	9	87 (89)
2	5	40	3	21	76 (92)
3	20	14	15	0	83 (85)
4	20	40	3	7	90 (88)
5	50	40	> 99	0	0
6	80	40	> 99	0	0

[a]Percentages determined by GC. [b]Enantiomeric excess of (*R*)-**6a** determined by HPLC. [c]Enantiomeric excess of monoacetate (*R*)-**6a** in parentheses.

TABLE 5. Percentages of Diacetate 4a, Diol 3a, and Monoacetate (*R*)-6a in the Lipase AK Catalyzed Desymmetrization of Diacetate 4a through Hydrolysis in a Biphasic System Composed of a 50 mM Phosphate Buffer pH 7.0 and MeCN (90:10 v/v) at 250 rpm

entry	*T* (°C)	*t* (h)	**4a** (%)[a]	**3a** (%)[a]	(*R*)-**6a** (%)[a,b,e]
1[c]	30	14	3	12	85 (90)
2[c]	30	40	2	21	77 (92)
3[c]	4	14	36	0	64 (88)
4[c]	4	40	14	0	86 (90)
5[c]	50	14	19	0	81 (78)
6[d]	30	14	7	0	93 (89)
7[d]	30	40	3	10	87 (92)

[a]Percentages determined by GC. [b]Enantiomeric excess of (*R*)-**6a** determined by HPLC. [c]Ratio AK lipase:**4a** (1:1) in weight. [d]Ratio AK lipase:**4a** (2:1) in weight. [e]Enantiomeric excess of monoacetate (*R*)-**6a** in parentheses.

significant loss of the optical purity of the final product was observed (entry 5). Finally the use of high loadings of catalyst has a notable effect on the stereopreference exhibited by the enzyme, recovering the (*R*)-monoacetate with the best yield and the highest enantiomeric excess (entries 6 and 7).

With the best results in hand shown in entries 1 and 2 of Table 6, we decided to extend these experimental conditions to other diacetates **4b**−**f** (Scheme 2), yielding the 4-fluoro-substituted **6b** (entries 3 and 4) and the 4-methoxy-substituted **6d** (entries 7 and 8) in enantiopure form with a good yield (72−74%) after 14 h, while for the 4-methyl-substituted **6c** high stereoselectivities were attained (92−95% ee, entries 5 and 6). As observed in the acetylation reactions, the 3-methoxy-substituted **6e** (entries 9 and 10) was recovered with lower selectivity (88% ee), while the formation of the 2-methoxy-substituted **6f** required longer reaction times (24−48 h) occurring with moderate steropreference (84−86% ee).

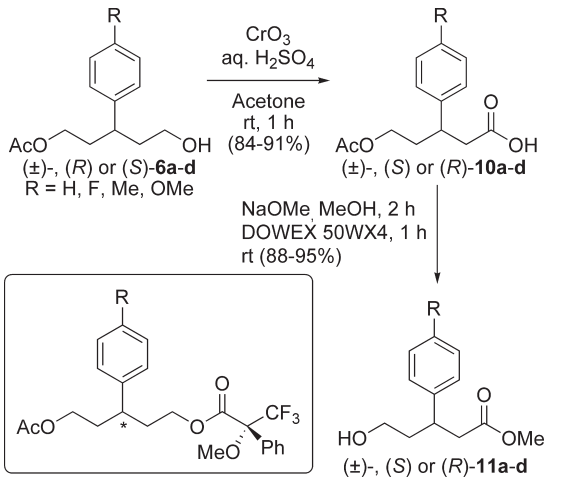
Once the chemoenzymatic routes to the racemates and both enantiomers of hydroxyesters **6a**−**d** were optimized, we took advantage of the selective enzymatic protection achieved in one of the hydroxyl groups present in these interesting building blocks. In this manner, their free alcohol residues were selective oxidized by using the Jones reagent in acetone at room temperature (Scheme 3). High yields (84−91%) were obtained in the isolation of **10a**−**d**,[18] (*R*)-**10a** being for instance an adequate intermediate for the preparation of monopyrroline-based HIV-1 protease inhibitors.[19] Transformation

TABLE 6. Percentages of Diacetates 4a−f, Diols 3a−f, and Monoacetates (*R*)-6a−f in the Lipase AK Catalyzed Desymmetrization of Diacetates 4a−f through Hydrolysis in a Biphasic System Composed of a 50 mM Phosphate Buffer pH 7.0 and MeCN (90:10 v/v) at 30 °C and 250 rpm

entry	**4a**−**d**[a]	*t* (h)	**4a**−**d** (%)[b]	**3a**−**d** (%)[b]	(*R*)-**6a**−**d** (%)[b–d]
1	**4a**	14	7	0	93 (89)
2	**4a**	40	3	10	87 (92)
3	**4b**	14	2	26	72 (> 99)
4	**4b**	18	0	38	62 (> 99)
5	**4c**	14	4	27	69 (95)
6	**4c**	18	4	31	65 (92)
7	**4d**	14	2	24	74 (> 99)
8	**4d**	18	2	33	65 (> 99)
9	**4e**	14	2	32	66 (88)
10	**4e**	18	0	42	58 (88)
11	**4f**	24	7	16	77 (84)
12	**4f**	48	0	30	70 (86)

[a]Enzyme:substrate ratio in weight (2:1). [b]Percentages determined by GC. [c]Enantiomeric excesses of (*R*)-**6a**−**f** were determined by HPLC. [d]Enantiomeric excesses of monoacetates (*R*)-**6a**−**f** in parentheses.

SCHEME 3. Chemical Synthesis of Carboxylic Acid Derivatives 10a−d and Hydroxyesters 11a−d As Racemates and Both Single Enantiomers[a]



[a]The structures of related Mosher derivatives are shown in the box.

of **10a**−**d** into hydroxyesters **11a**−**d** occurred with very high to excellent yields by deprotection of the acetyl group by using sodium methoxide, which simultaneously favored the esterification of the carboxylic acid residue. A careful evaporation of the solvent is critical for the success of the reaction as the intramolecular cyclization of the **11a**−**d** can be favored by heating the reaction mixture. In this manner, this synthetic approach has allowed us to obtain a family of racemic and enantiopure hydroxyesters, which possess interesting synthetic possibilities for the synthesis of compounds with medicinal applications such as (±)-**11a** used as precursor for the synthesis of brain penetration macrocyclic tertiary carbinamine BACE-1 inhibitors,[20] or the selective serotonin reuptake inhibitor (−)-Paroxetine hydrochloride from (*S*)-**11b**.[17b,21]

(18) It must be noticed that (*R*)-**10a**−**d** were obtained from (*S*)-**6a**−**d** due to CIP priority rules. In the same manner (*S*)-**10a**−**d** were prepared from (*R*)-**6a**−**d**.

(19) Smith, A. B., III; Cantin, L.-D.; Pasternak, A.; Guise-Zawacki, L.; Yao, W.; Charnley, A. K.; Barbosa, J.; Sprengeler, P. A.; Hirschmann, R.; Munshi, S.; Olsen, D. B.; Schleif, W. A.; Kuo, L. C. *J. Med. Chem.* **2003**, *46*, 1831–1844.

(20) Moore, K. P.; Zhu, H.; Rajapakse, H. A.; McGaughey, G. B.; Colussi, D.; Price, E. A.; Sankaranarayanan, S.; Simon, A. J.; Pudvah, N. T.; Hochman, J. H.; Allison, T.; Munshi, S. K.; Graham, S. L.; Vacca, J. P.; Nantermet, P. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5831–5835.

(21) De Risi, C.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron: Asymmetry* **2008**, *19*, 131–155.

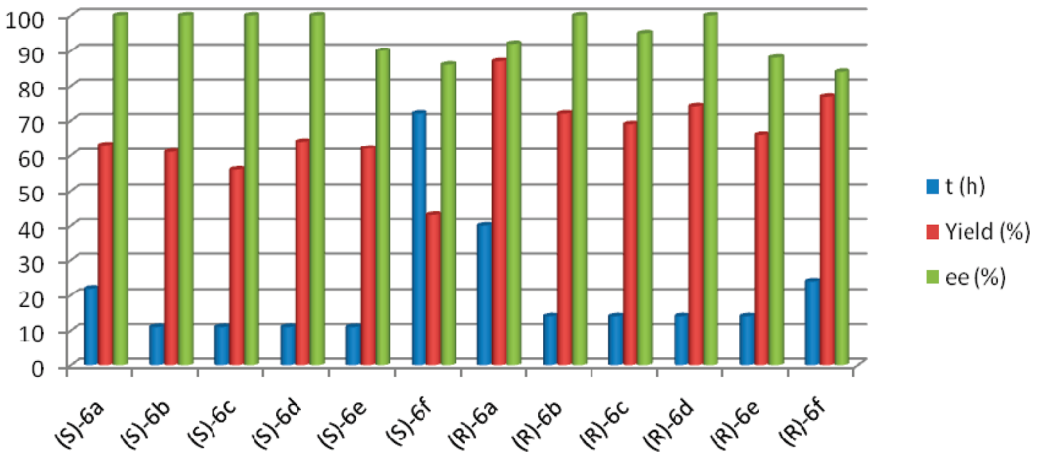


FIGURE 2. Summary of the best synthetic processes found with AK lipase for the production of optically active monoacetates, acetylation processes being used for the production of (*S*)-**6a**−**f**, and hydrolytic reaction for the (*R*)-enantiomers.

Absolute configuration for hydroxyester (*R*)-**11a** was assigned comparing its optical rotation with the one previously described in the literature.[22] After the synthesis of the corresponding Mosher derivatives depicted in Scheme 3, the assignment was confirmed. We also observed for all compounds the same tendency in the stereopreference shown by lipases, which means the production of the (*S*)-monoacetates **6a**−**d** through acetylation processes, and the isolation of opposite (*R*)-enantiomers by hydrolytic reactions.[23] These results are also in agreement with the stereopreference showed by *Pseudomonas cepacia lipase*[13b] and AK lipase[14] in the monoacetylation of 3-arylpentane-1,5-diols reported by Shisido and co-workers.

Conclusions

In summary, a new family of 3-arylpentane-1,5-diols have been prepared in a straightforward manner starting from commercially available aldehydes or carboxylic acids, studying later the enzymatic desymmetrization of these diols and their corresponding acetates. Thus, stereoselective monoprotection methods have been developed, the access to both optically active (*S*)- and (*R*)-monoacetates being possible in excellent enantiomeric excesses by using complementary biocatalyzed acetylation or hydrolysis reactions. AK lipase has been responsible for the introduction of chirality with a high degree of reactivity under very mild reaction conditions, achieving the isolation of the corresponding optically active monoacetates generally in good to high yields (Figure 2). Finally, selected (*S*)- and (*R*)-monoacetates have been effectively transformed into enantiopure acid derivatives, some of them presenting high importance as synthetic precursors for compounds with remarkable biological properties.

Experimental Section

Synthesis of Diethyl 3-Phenylpentanedioate (2). To a solution of diacid **1** (1.00 g, 4.80 mmol) in EtOH (48 mL) were added 6 drops of concd H_2SO_4 and the solution was stirred for 3 h at 80 °C. After this time the solvent was evaporated under reduced pressure and the resulting crude purified by flash chromatography on silica gel (50% EtOAc/hexane) yielding 1.24 g of **2** as a colorless oil (98%). R_f (50% EtOAc/hexane) 0.26; IR (NaCl) ν 2982, 1734, 1454, 1373, 1262, 1180, 1149, 1030, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.13 (t, 6H, J = 7.0 Hz), 2.58−2.75 (m, 4H), 3.59−3.69 (m, 1H), 4.03 (q, 4H, J = 7.0 Hz), 7.17−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.9 (2C), 38.3, 40.6 (2C), 60.2 (2C), 126.8, 127.2 (2C), 128.4 (2C), 142.4, 171.4 (2C); MS (APCI$^+$, m/z) 265 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{15}H_{20}NaO_4$ [(M + Na)$^+$] 287.1259, found 287.1261.

Synthesis of 3-Phenylpentane-1,5-diol (3a). A solution of diester **2** (1.24 g, 4.70 mmol) in dry Et_2O (17 mL) was cooled to 0 °C and $LiAlH_4$ (728 mg, 19.20 mmol) was carefully added during 15 min under nitrogen atmosphere. The resulting solution was stirred for 14 h at room temperature and then the reaction was quenched with water (1.7 mL) at 0 °C. Salts were filtered off through Celite, and the filtrate was washed with Et_2O (6 × 8 mL). Organic phases were combined and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (50% EtOAc/hexane), affording 837 mg of **3a** as a white solid (99%). R_f (50% EtOAc/hexane) 0.13; mp 30−32 °C; IR (KBr) ν 3325, 2933, 2881, 1498, 1453, 1046, 763, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.75−2.00 (m, 6H), 2.87−2.98 (m, 1H), 3.42−3.60 (m, 4H), 7.18−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.9, 38.8 (2C), 59.8 (2C), 126.0, 127.8 (2C), 128.2 (2C), 144.4; MS (APCI$^+$, m/z) 181 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{11}H_{16}NaO_2$ [(M + Na)$^+$] 203.1048, found 203.1046.

General Procedure for the Synthesis of Diols 3b−e.[17] A solution of the corresponding aldehyde **7**−**10** (10.0 mmol), ethyl acetoacetate (2.53 mL, 20.0 mmol), and piperidine (136 μL, 0.001 mmol) was stirred for 3 days at room temperature. After this time EtOH (1.08 mL) was added and the mixture was refluxed for 2 h. The solution was slowly cooled to room temperature and the resulting crystalline product was filtered off, washed with Et_2O (4 × 10 mL), and dried in vacuo. This solid was dissolved in EtOH (39 mL) and a solution of NaOH (39.0 g, 0.98 mmol) in water (39 mL) and refluxed for 1 h. Then the organic solvent was evaporated under reduce pressure, and the aqueous phase acidified to pH 1 with an HCl 37% solution and extracted with EtOAc (3 × 40 mL). The organic phases were combined and dried over Na_2SO_4, then the organic solvent was evaporated under reduce pressure. The resulting diacid was dissolved in EtOH (40 mL) and 10 drops of a concentrated

(22) Optical rotation for (*R*)-**11a**: $[\alpha]^{20}_D$ +13.0 (*c* 1.0, EtOH) or $[\alpha]^{20}_D$ +12.2 (*c* 0.9, $CHCl_3$) in comparison with previously described $[\alpha]^{20}_D$ +12.8 (*c* 0.9, $CHCl_3$) in ref 16.

(23) Further explanations related to the absolute configuration assignments and also copy of ^1H NMR for the Mosher derivatives are given in the Supporting Information.

H_2SO_4 aqueous solution was carefully added, refluxing the solution for 3 h. After this time, EtOH was evaporated under reduced pressure, and the resulting crude was dissolved in water (20 mL), extracting the aqueous phase with EtOAc (3 × 20 mL). A solution of the corresponding diester (8.77 mmol) in dry Et_2O (30 mL) was cooled to 0 °C, and $LiAlH_4$ (1.33 g, 35.08 mmol) was carefully added during 15 min. The resulting solution was stirred for 14 h at room temperature and then the reaction was quenched with water (3.1 mL) at 0 °C. Salts were filtered off through Celite, and the filtrate was washed with Et_2O (6 × 8 mL). Organic phases were combined and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (50% EtOAc/hexane), affording the corresponding diol **3b−d** (70−80%). **3b** (76% yield): R_f (50% EtOAc/hexane) 0.08; mp 79−81 °C; IR (KBr) ν 3296, 2942, 2860, 1603, 1509, 1422, 1266, 1223, 1040, 863 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.64−1.98 (m, 6H), 2.89−2.99 (m, 1H), 3.40−3.59 (m, 4H), 6.89 (t, 2H, J = 8.8 Hz), 7.11−7.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.2, 38.9 (2C), 59.9 (2C), 115.1 (d, 2C, J = 21 Hz), 128.7 (d, 2C, J = 8 Hz), 140.1, 161.3 (d, J = 244 Hz); MS (APCI$^+$, m/z) 199 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{11}H_{15}FNaO_2$ [(M + Na)$^+$] 221.0954, found 221.0951. **3c** (70% yield): R_f (50% EtOAc/hexane) 0.12; IR (NaCl) ν 3361, 2933, 2882, 1513, 1433, 1265, 1042, 818, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.72−1.96 (m, 4H), 2.31 (s, 3H), 2.63 (brs, 2H), 2.82−2.92 (m, 1H), 3.39−3.57 (m, 4H), 7.04−7.11 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.9, 37.9, 39.0 (2C), 60.4 (2C), 127.4 (2C), 129.1 (2C), 135.7, 141.4; MS (APCI$^+$, m/z) 195 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{12}H_{18}NaO_2$ [(M + Na)$^+$] 217.1204, found 217.1207. **3d** (80% yield): R_f (50% EtOAc/hexane) 0.11; IR (NaCl) ν 3349, 2934, 1611, 1512, 1464, 1302, 1247, 1178, 1034, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.67−1.91 (m, 4H), 2.79−2.99 (m, 3H), 3.36−3.54 (m, 4H), 3.76 (s, 3H), 6.80 (A′B′ system, J = 8.7 Hz, 2H), 7.06 (A′B′ system, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.3, 39.2 (2C), 55.1, 60.3 (2C), 113.8 (2C), 128.3 (2C), 136.5, 157.8; MS (APCI$^+$, m/z) 211 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{12}H_{18}NaO_3$ [(M + Na)$^+$] 233.1148, found 233.1142. **3e** (63% yield): R_f (100% EtOAc) 0.39; IR (NaCl) ν 3335, 2936, 1600, 1485, 1257, 1158, 1042, 1001, 883, 783, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.71−1.94 (m, 4H), 2.73−2.94 (m, 3H), 3.37−3.47 (m, 2H), 3.48−3.58 (m, 2H), 3.76 (s, 3H), 6.70−6.80 (m, 3H) 7.19 (t, $^3J_{HH}$ = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 38.2, 38.9 (2C), 55.0, 60.3 (2C), 111.1, 113.5, 119.9, 129.4, 146.3, 159.5; MS (APCI$^+$, m/z) 211 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{12}H_{18}NaO_3$ [(M + Na)$^+$] 233.1148, found 233.1144.

Synthesis of 3-(2-Methoxyphenyl)Pentane-1,5-diol (3f). A solution of the corresponding aldehyde **11** (10.0 mmol), ethyl acetoacetate (2.53 mL, 20.0 mmol), and piperidine (136 μL, 0.001 mmol) was stirred for 1 day at room temperature. After this time potassium *tert*-butoxide (170 mg, 1.5 mmol) was added, and the mixture was stirred for an additional 2 days. The resulting solid was filtered off, washed with cold Et_2O (4 × 10 mL), and dried in vacuo. This solid was dissolved in EtOH (39 mL) and a solution of NaOH (39.0 g, 0.98 mmol) in water (39 mL) and refluxed for 1 h. Then the organic solvent was evaporated under reduced pressure, and the aqueous phase was acidified to pH 1 with an HCl 37% solution and extracted with EtOAc (3 × 40 mL). The organic phases were combined and dried over Na_2SO_4, then the organic solvent was evaporated under reduce pressure. The resulting diacid was dissolved in EtOH (40 mL) and 10 drops of a concentrated H_2SO_4 aqueous solution was carefully added, refluxing the solution for 3 h. After this time, EtOH was evaporated under reduced pressure, and the resulting crude was dissolved in water (20 mL), extracting the aqueous phase with EtOAc (3 × 20 mL). A solution of the corresponding diester (8.77 mmol) in dry Et_2O (30 mL) was cooled to 0 °C, and $LiAlH_4$ (1.33 g, 35.08 mmol) was carefully added during 15 min. The resulting solution was stirred for 14 h at room temperature and then the reaction was quenched with water (3.1 mL) at 0 °C. Salts were filtered off through Celite, and the filtrate was washed with Et_2O (6 × 8 mL). Organic phases were combined and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (50% EtOAc/hexane), affording the diol **3f** (54% yield): R_f (100% EtOAc) 0.40; mp 109−111 °C; IR (NaCl) ν 3337, 2935, 1603, 1483, 1467, 1256, 1162, 1040, 1010, 882, 782, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.70−1.87 (m, 2H), 1.89−2.15 (m, 4H), 3.34−3.47 (m, 3H) 3.48−3.60 (m, 2H), 3.83 (s, 3H), 6.87 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 6.96 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 7.12−7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.7, 38.7 (2C), 55.6, 60.8 (2C), 110.7, 121.4, 127.2, 127.4, 131.9, 157.2; MS (APCI$^+$, m/z) 211 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{12}H_{18}NaO_3$ [(M + Na)$^+$] 233.1148, found 233.1156.

General Procedure for the Synthesis of Diacetates 4a−f. To a solution of the corresponding diol **3a−d** (1.39 mmol) in dry CH_2Cl_2 (13.9 mL) were successively added under nitrogen atmosphere Et_3N (1.17 mL, 8.31 mmol), DMAP (111 mg, 0.92 mmol), and Ac_2O (0.52 mL, 5.54 mmol). The reaction was stirred at room temperature during 4 h until complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was finally purified by flash chromatography on silica gel (10−30% EtOAc/hexane), yielding the corresponding diacetate **4a−d** as an oil (98−99%). **4a** (99% yield): R_f (10% EtOAc/hexane) 0.12; IR (NaCl) ν 3028, 2958, 1738, 1454, 1386, 1367, 1241, 1041, 762, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.85−2.06 (m, 10H), 2.73−2.83 (m, 1H), 3.82−3.99 (m, 4H), 7.11−7.16 (m, 2H), 7.17−7.23 (m, 1H), 7.24−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.5 (2C), 35.0 (2C), 39.2, 62.2 (2C), 126.4, 127.2 (2C), 128.4 (2C), 142.7, 170.5 (2C); MS (APCI$^+$, m/z) 265 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{15}H_{20}NaO_4$ [(M + Na)$^+$] 287.1259, found 287.1260. **4b** (98% yield): R_f (10% EtOAc/hexane) 0.11; IR (NaCl) ν 2959, 1739, 1604, 1510, 1388, 1367, 1242, 1160, 1041, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.76−2.04 (m, 10H), 2.72−2.82 (m, 1H), 3.79−3.98 (m, 4H), 6.97 (t, J = 8.6 Hz, 2H), 7.06−7.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7 (2C), 35.4 (2C), 38.7, 62.3 (2C), 115.3 (d, 2C, J = 85 Hz), 128.8 (d, 2C, J = 32 Hz), 138.5 (d, J = 3 Hz), 161.4 (d, J = 245 Hz), 170.8 (2C); MS (APCI$^+$, m/z) 283 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{15}H_{19}FNaO_4$ [(M + Na)$^+$] 305.1165, found 305.1167. **4c** (98% yield): R_f (10% EtOAc/hexane) 0.13; IR (NaCl) ν 2957, 1740, 1514, 1367, 1241, 1040, 915, 817, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.77−2.04 (m, 10H), 2.30 (s, 3H), 2.69−2.79 (m, 1H), 3.81−3.98 (m, 4H), 7.01 (A′B′ system, J = 8.1 Hz, 2H), 7.09 (A′B′ system, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.8 (3C), 35.3 (2C), 38.8, 62.6 (2C), 127.2 (2C), 129.3 (2C), 136.1, 139.7, 170.9 (2C); MS (APCI$^+$, m/z) 279 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{16}H_{22}NaO_4$ [(M + Na)$^+$] 301.1416, found 301.1415. **4d** (99% yield): R_f (10% EtOAc/hexane) 0.11; IR (NaCl) ν 2957, 2837, 1738, 1611, 1513, 1367, 1246, 1179, 1036, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.75−2.02 (m, 10H), 2.68−2.76 (m, 1H), 3.74−4.00 (m, 7H), 6.82 (A′B′ system, J = 7.5 Hz, 2H), 7.03 (A′B′ system, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.8 (2C), 35.4 (2C), 38.4, 55.1, 62.5 (2C), 113.9 (2C), 128.2 (2C), 134.7, 158.2, 170.8 (2C); MS (APCI$^+$, m/z) 295 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{16}H_{22}NaO_5$ [(M + Na)$^+$] 317.1357, found 317.1359. **4e** (98% yield): R_f (10% EtOAc/hexane) 0.10; IR (NaCl) ν 2958, 1738, 1602, 1487, 1456, 1437, 1367, 1242, 1158, 1042, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 1.78−1.94 (m, 4H), 1.96 (s, 6H), 2.67−2.80 (m, 1H), 3.75 (s, 3H), 3.78−3.98 (m, 4H), 6.63−6.75 (m, 3H) 7.18 (t, $^3J_{HH}$ = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$,

75.5 MHz) δ 20.6 (2C), 35.1 (2C), 39.3, 54.9, 62.4 (2C), 111.3, 113.4, 119.7, 129.5, 144.5, 159.7, 170.7; MS (APCI$^+$, m/z) 295 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{16}H_{22}NaO_5$ [(M + Na)$^+$] 317.1356, found 317.1359. **4f** (99% yield): R_f (10% EtOAc/hexane) 0.11; IR (NaCl) ν 2959, 1738, 1599, 1493, 1466, 1439, 1367, 1242, 1038, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.90−2.13 (m, 10H), 3.16−3.32 (m, 1H), 3.75 (m, 3H), 3.89 (t, $^3J_{HH}$ = 7.0 Hz, 4H), 6.80 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 6.87 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 7.05−7.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.6 (2C), 32.6, 33.8 (2C), 55.0, 62.8 (2C), 110.5, 120.5, 127.3, 127.7, 130.7, 157.3, 170.7; MS (APCI$^+$, m/z) 295 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{16}H_{22}NaO_5$ [(M + Na)$^+$] 317.1375, found 317.1359.

General Procedure for the Chemical Synthesis of Racemic Monoacetates 6a−f. To a solution of diol **3a−d** (0.56 mmol) in dry CH_2Cl_2 (5.6 mL) were added under nitrogen atmosphere Et_3N (24 μL, 1.68 mmol) and DMAP (22 mg, 0.18 mmol). After the mixture was stirred for a couple of minutes, Ac_2O (53 μL, 0.56 mmol) was added in portions, and the solution was stirred for an additional 4 h at room temperature. After this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (10% EtOAc/hexane to 50% EtOAc/hexane) affording the monoacetate (±)-**6a−d** as a colorless oil (42−51%). **6a** (44% yield): R_f (50% EtOAc/hexane) 0.34; IR (NaCl) ν 3417, 2935, 1738, 1454, 1367, 1245, 1042, 762, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.73−2.05 (m, 8H), 2.79−2.89 (m, 1H), 3.38−3.54 (m, 2H), 3.80−3.99 (m, 2H), 7.13−7.21 (m, 3H), 7.26−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7, 35.3, 38.9, 39.3, 60.5, 62.7, 126.5, 127.4 (2C), 125.5 (2C), 143.5, 171.0; MS (APCI$^+$, m/z) 223 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{13}H_{18}NaO_3$ [(M + Na)$^+$] 245.1154, found 245.1157. **6b** (51% yield): R_f (50% EtOAc/hexane) 0.32; IR (NaCl) ν 3423, 2937, 1737, 1509, 1367, 1245, 1042, 836, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.69−2.03 (m, 8H), 2.79−2.89 (m, 1H), 3.34−3.52 (m, 2H), 3.77−3.97 (m, 2H), 6.95 (t, J = 8.6 Hz, 2H), 7.08−7.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7, 35.3, 38.1, 39.3, 60.2, 62.5, 115.3 (d, J = 85 Hz, 2C), 128.7 (d, J = 30 Hz, 2C), 139.1, 161.4 (d, J = 245 Hz), 171.0; MS (APCI$^+$, m/z) 240 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{13}H_{17}FNaO_3$ [(M + Na)$^+$] 263.1059, found 263.1059. **6c** (49% yield): R_f (50% EtOAc/hexane) 0.33; IR (NaCl) ν 3437, 2935, 1733, 1514, 1367, 1249, 1043, 910, 818, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.30 (1H, brs, OH), 1.75−2.05 (m, 7H), 2.31 (m, 3H), 2.76−2.86 (m, 1H), 3.41−3.57 (m, 2H), 3.81−3.99 (m, 2H), 7.03−7.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.9 (2C), 35.4, 38.6, 39.4, 60.8, 62.7, 127.3 (2C), 129.3 (2C), 136.0, 140.3, 171.0; MS (APCI$^+$, m/z) 237 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{14}H_{20}NaO_3$ [(M + Na)$^+$] 259.1310, found 259.1312. **6d** (42% yield): R_f (50% EtOAc/hexane) 0.39; IR (NaCl) ν 3429, 2935, 1734, 1513, 1464, 1367, 1248, 1178, 1036, 831, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.44 (brs, 1H), 1.72−1.99 (m, 4H), 2.03 (s, 3H), 2.74−2.84 (m, 1H), 3.39−3.55 (m, 2H), 3.74−4.01 (m, 5H), 6.83 (A′B′ system, J = 8.5 Hz, 2H), 7.06 (A′B′ system, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.8, 35.5, 38.1, 39.4, 55.1, 60.7, 62.7, 114.0 (2C), 128.3 (2C), 135.4, 158.1, 171.0; MS (APCI$^+$, m/z) 253 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{14}H_{20}NaO_4$ [(M + Na)$^+$] 275.1254, found 275.1258. **6e** (66% yield): R_f (50% EtOAc/hexane) 0.36; IR (NaCl) ν 3427, 2938, 1737, 1602, 1487, 1437, 1367, 1256, 1156, 1042, 782, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.65−1.89 (m, 4H), 1.90 (s, 3H), 2.51 (brs, 1H), 2.69−2.82 (m, 1H), 3.27−3.48 (m, 2H), 3.71 (s, 3H), 3.73−3.95 (m, 2H), 6.62−6.72 (m, 3H), 7.13 (t, $^3J_{HH}$ = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.5, 34.9, 38.7, 39.0, 54.7, 59.9, 62.5, 111.1, 113.2, 119.6, 129.2, 145.1, 159.4, 170.8 (C_{12}); MS (APCI$^+$, m/z) 253 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{14}H_{20}NaO_4$ [(M + Na)$^+$] 275.1254, found 275.1261. **6f** (47% yield): R_f (50% EtOAc/hexane) 0.37; IR (NaCl) ν 3432, 2940, 1737, 1599, 1493, 1465, 1439, 1390, 1366, 1342, 1041, 755, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.67−1.80 (m, 1H), 1.84−1.91 (m, 1H), 1.92 (s, 3H), 1.93−2.04 (m, 2H), 2.34 (brs, 1H), 3.24−3.38 (m, 2H), 3.39−3.49 (m, H), 3.76 (s, 3H), 3.89 (t, $^3J_{HH}$ = 6.8 Hz, 2H), 6.81 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 6.89 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 7.06−7.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.6, 31.0, 33.9, 38.6, 55.2, 60.4, 62.8, 110.5, 120.9, 127.0, 127.4, 131.2, 157.2, 170.8; MS (APCI$^+$, m/z) 253 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{14}H_{20}NaO_4$ [(M + Na)$^+$] 275.1254, found 275.1254.

General Procedure for the Lipase-Mediated Desymmetrization of Diols 3a−f by Acetylation Processes, Using Vinyl Acetate. A suspension of the corresponding diol **3a−f** (0.56 mmol) and AK lipase (ratio 1:1 in weight relative to **3a−f**) in vinyl acetate (5.6 mL) was shaken at 4 °C and 250 rpm under nitrogen atmosphere. The reaction time course was followed by GC (compound ratios) and HPLC [enantiomeric excess of (*S*)-**6a−f**]. The reaction was stopped and the enzyme filtered off, washing it with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated under reduced pressure and the reaction crude was purified by flash chromatography on silica gel (10% to 50% EtOAc/hexane), affording the corresponding optically enriched monoacetate (*S*)-**6a−f**. (*S*)-**6a**: $[\alpha]^{20}_D$ +20.5 (*c* 1.0, EtOH) for >99% ee. (*S*)-**6b**: $[\alpha]^{20}_D$ +14.0 (*c* 1.0, EtOH) for >99% ee. (*S*)-**6c**: $[\alpha]^{20}_D$ +10.4 (*c* 1.0, EtOH) for >99% ee. (*S*)-**6d**: $[\alpha]^{20}_D$ +21.0 (*c* 1.0, EtOH) for >99% ee. (*S*)-**6e**: $[\alpha]^{20}_D$ +13.0 (*c* 1.0, EtOH) for 92% ee. (*S*)-**6f**: $[\alpha]^{20}_D$ +3.3 (*c* 1.0, EtOH) for (*S*)-**6f** in 81% ee.

General Procedure for the Lipase-Mediated Desymmetrization of Diacetates 4a−f by Hydrolytic Processes. A suspension of diacetate **4a−f** (0.38 mmol) and AK lipase (ratio 2:1 in weight relative to **4a−f**) in a 3.8 mL system composed of 50 mM phosphate buffer pH 7:MeCN (90:10) was shaken at 30 °C and 250 rpm. The reaction time course was followed by GC (compound ratios) and HPLC [enantiomeric excess of (*R*)-**6a−f**]. The reaction was stopped and the enzyme filtered off, washing it with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated under reduced pressure and the reaction crude was purified by flash chromatography on silica gel (10% to 50% EtOAc/hexane), affording the corresponding optically enriched monoacetate (*R*)-**6a−f**.

General Procedure for the Chemical Synthesis of Racemic or Optically Active 5-(Acetyloxy)-3-arylpentanoic Acid (10a−d). To a solution of the corresponding racemic or optically active monoacetate **6a−d** (0.38 mmol) in acetone (3.8 mL) was added Jones reagent (0.91 mL). The resulting solution was stirred for 1 h at room temperature and after this time the reaction was quenched with 2-propanol (0.91 mL) to precipate the chromium salts. The mixture was diluted with Et_2O (20 mL) and the corresponding salts were filtered off through Celite, washing the solid with Et_2O (3 × 10 mL). The organic solvent from the filtrate was evaporated under reduced pressure, obtaining a reaction crude that was purified by a quick filtration on silica gel (80% EtOAc/hexane), affording **10a−d** as a colorless oil (84−91%). (*R*)-**10a** (84% yield): R_f (50% EtOAc/hexane) 0.25; IR (NaCl) ν 3167, 3030, 2961, 1729, 1712, 1454, 1393, 1369, 1241, 1162, 1043, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.86−2.11 (m, 5H), 2.68 (d, J = 7.2 Hz, 2H), 3.18−3.28 (m, 1H), 3.80−3.89 (m, 1H), 3.94−4.02 (m, 1H), 7.15−7.33 (m, 5H), 9.65 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7, 34.5, 38.5, 41.1, 62.3, 126.8, 127.2 (2C), 128.6 (2C), 142.3, 171.1, 177.7; MS (ESI$^+$, m/z) 259 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{13}H_{16}NaO_4$ [(M + Na)$^+$] 259.0941, found 259.0941. $[\alpha]^{20}_D$ +13.0 (*c* 1.0, EtOH) for >99% ee. (*R*)-**10b** (88% yield): R_f (50% EtOAc/hexane) 0.22; IR (NaCl) ν 3178, 2962, 1738, 1712, 1604, 1511, 1371, 1241, 1180, 1045, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.77−1.92 (m, 1H), 1.94−2.08 (m, 4H), 2.56−2.72 (m, 2H), 3.15−3.26 (m, 1H), 3.78−3.87 (m, 1H), 3.94−4.01

(m, 1H), 6.97 (t, J = 8.6 Hz, 2H), 7.09−7.18 (m, 2H), 11.68 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7, 34.8, 37.8, 41.1, 62.3, 115.3 (d, J = 21 Hz, 2C), 128.7 (d, J = 7 Hz, 2C), 137.9, 161.0 (d, J = 245 Hz), 171.6, 177.7; MS (ESI$^+$, m/z) 277 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{13}H_{15}FNaO_4$ [(M + Na)$^+$] 277.0847, found 277.0838. $[\alpha]^{20}_D$ +14.2 (c 1.0, EtOH) for >99% ee. (*R*)-**10c** (91% yield): R_f (50% EtOAc/hexane) 0.30; IR (NaCl) ν 3220, 3023, 2961, 1740, 1711, 1515, 1370, 1241, 1161, 1043, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.77−2.10 (m, 5H), 2.31 (s, 3H), 2.65 (d, J = 7.2 Hz, 2H), 3.13−3.28 (m, 1H), 3.79−3.88 (m, 1H), 3.94−4.01 (m, 1H), 7.05−7.12 (m, 4H), 9.84 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7, 20.8, 34.5, 38.0, 41.1, 62.3, 127.1 (2C), 129.2 (2C), 136.3, 139.2, 171.1, 177.7; MS (ESI$^+$, m/z) 273 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{14}H_{18}NaO_4$ [(M + Na)$^+$] 273.1103, found 273.1104. $[\alpha]^{20}_D$ +16.5 (c 1.0, EtOH) for >99% ee. (*R*)-**10d** (89% yield): R_f (50% EtOAc/hexane) 0.28; IR (NaCl) ν 2957, 2935, 2836, 1733, 1711, 1611, 1513, 1369, 1249, 1180, 1036, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.75−1.93 (m, 1H), 1.95−2.13 (m, 4H), 2.55−2.68 (m, 2H), 3.12−3.23 (m, 1H), 3.72−3.86 (m, 4H), 3.91−3.99 (m, 1H), 6.81 (A′B′ system, J = 8.7 Hz, 2H), 7.08 (A′B′ system, J = 8.7 Hz, 2H), 9.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7, 34.6, 37.7, 41.3, 55.0, 62.3, 113.9 (2C), 128.1 (2C), 134.2, 158.2, 171.1, 177.6; MS (ESI$^+$, m/z) 289 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{14}H_{18}NaO_5$ [(M + Na)$^+$] 289.1046, found 289.1048. $[\alpha]^{20}_D$ +17.0 (c 1.0, EtOH) for >99% ee.

General Procedure for the Chemical Synthesis of Racemic or Optically Active Methyl 5-Hydroxy-3-arylpentanoate (11a−d). To a solution of racemic or optically active compound **10a−d** (0.26 mmol) in MeOH (2.6 mL) was added sodium methoxide (83 mg, 1.53 mmol). The resulting solution was stirred for 2 h at room temperature and then ion-exchange resin DOWEX 50WX4 (200−400 mesh) was added until almost saturation of the organic solution. The mixture was stirred for 1 h, and then the resin was filtered off and washed with MeOH (2 mL). The filtrate was dried over anhydrous Na_2SO_4 and filtered, then the solvent was carefully evaporated under reduced pressure to prevent the formation of intramolecular cyclization products, affording **11a−d** as a colorless oil (88−95%). (*R*)-**11a** (94% yield): R_f (50% EtOAc/hexane) 0.26; IR (NaCl) ν 3423, 2953, 1731, 1648, 1446, 1441, 1259, 1158, 1024, 763 cm^{-1}; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.90−2.14 (m, 2H), 2.71−2.89 (m, 2H), 3.35−3.60 (m, 3H), 3.68 (s, 3H), 7.30−7.51 (m, 5H); ^{13}C NMR (MeOD, 75.5 MHz) δ 40.1, 40.3, 42.6, 52.2, 60.9, 127.9, 128.8 (2C), 129.8 (2C), 145.1, 174.7; MS (ESI$^+$, m/z) 231 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{12}H_{16}NaO_3$ [(M + Na)$^+$] 231.0992, found 231.0986. $[\alpha]^{20}_D$ −5.9 (c 1.0, EtOH) for >99% ee. (*R*)-**11b** (95% yield): R_f (50% EtOAc/hexane) 0.28; IR (NaCl) ν 3451, 3055, 2936, 1733, 1510, 1266, 1244, 1159, 734 cm^{-1}; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.88−2.14 (m, 2H), 2.69−2.89 (m, 2H), 3.37−3.61 (m, 3H), 3.68 (s, 3H), 7.15 (t, J = 9.0 Hz, 2H), 7.36−7.41 (m, 2H); ^{13}C NMR (MeOD, 75.5 MHz) δ 39.5, 40.1, 42.6, 52.3, 60.7, 116.2 (d, J = 21 Hz, 2C), 130.5 (d, J = 7 Hz, 2C), 141.0, 163.2 (d, J = 243 Hz), 174.6; MS (ESI$^+$, m/z) 249 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{12}H_{15}FNaO_3$ [(M + Na)$^+$] 249.0897, found 249.0894. $[\alpha]^{20}_D$ −2.7 (c 1.0, EtOH) for >99% ee. (*R*)-**11c** (91% yield): R_f (50% EtOAc/hexane) 0.48; IR (NaCl) ν 3419, 2952, 1730, 1649, 1445, 1441, 1260, 1158, 1025 cm^{-1}; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.92−2.14 (m, 2H), 2.47 (s, 3H), 2.72−2.90 (m, 2H), 3.34−3.45 (m, 1H), 3.52−3.63 (m, 2H), 3.77 (s, 3H), 7.28 (s, 4H); ^{13}C NMR (MeOD, 75.5 MHz) δ 21.3, 39.9, 40.2, 42.7, 52.2, 60.9, 128.7, 130.4 (2C), 137.5, 141.9, 174.8; MS (ESI$^+$, m/z) 245 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{13}H_{18}NaO_3$ [(M + Na)$^+$] 245.1154, found 245.1152. $[\alpha]^{20}_D$ −8.9 (c 1.0, EtOH) for >99% ee. (*R*)-**11d** (88% yield): R_f (50% EtOAc/hexane) 0.29; IR (NaCl) ν 3432, 2951, 1734, 1612, 1514, 1439, 1249, 1179, 1033, 832 cm^{-1}; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.90−2.13 (m, 2H), 2.70−2.89 (m, 2H), 3.31−3.44 (m, 1H), 3.52−3.64 (m, 2H), 3.72 (s, 3H), 3.94 (s, 3H), 7.02 (A′B′ system, J = 8.4 Hz, 2H), 7.31 (A′B′ system, J = 8.4 Hz, 2H); ^{13}C NMR (MeOD, 75.5 MHz) δ 39.5, 40.3, 42.8, 52.2, 55.9, 61.0, 115.2 (2C), 129.8 (2C), 136.9, 160.1, 174.8; MS (ESI$^+$, m/z) 261 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$) calcd for $C_{13}H_{18}NaO_4$ [(M + Na)$^+$] 261.1097, found 261.1100. $[\alpha]^{20}_D$ −12.7 (c 1.0, EtOH) for >99% ee.

General Procedure for the Chemical Synthesis of Racemic or Optically Active Mosher Derivatives. To a solution of racemic or enantiopure **6a−d** (0.04 mmol) in dry CH_2Cl_2 (400 μL) were successively added under nitrogen atmosphere DMAP (8 mg, 0.08 mmol) and (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride (8 μL, 0.044 mmol). The mixture was stirred for 2 h at room temperature and after this time the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography on silica gel (20% EtOAc/hexane) yielding the corresponding Mosher derivatives as colorless oils (97−99%). R = H (98% yield): R_f (20% EtOAc/hexane) 0.18; ^{1}H NMR ($CDCl_3$, 600.13 MHz) δ 1.84−2.01 [6H, m, $2H_6$ + $3H_9$ [isomer (*R*,*R*) + (*S*,*R*)] + $1H_{10}$], 2.05−2.12 (1H, m, $1H_{10}$), 2.72−2.79 (1H, m, H_5), 3.53 [3H, 2s, $3H_{13}$ isomer (*R*,*R*) + (*S*,*R*)], 3.77−3.83 (1H, m, $1H_7$), 3.90−3.95 (1H, m, $1H_7$), 3.97−4.07(1H, m, $1H_{11}$), 4.17−4.22 (1H, m, $1H_{11}$ isomer *SR*), 4.25−4.31 (1H, m, $1H_{11}$ isomer *RR*), 7.06 (2H, 2d, $^3J_{HH}$ = 7.1 Hz, $2H_3$), 7.19−7.24 (1H, m, H_1), 7.27−7.32 (2H, m, $2H_2$), 7.39−7.45 (3H, m, $2H_{17}$ + H_{19}), 7.48−7.52 (2H, m, $2H_{18}$). R = F (99% yield): R_f (20% EtOAc/hexane) 0.19; ^{1}H NMR ($CDCl_3$, 600.13 MHz) δ 1.80−1.95 (3H, m, $2H_6$ + $1H_{10}$), 1.96−1.97 [3H, 2s, $3H_9$ isomer (*R*,*R*) + (*S*,*R*)], 2.04−2.12 (1H, m, $1H_{10}$), 2.72−2.79 (1H, m, H_5), 3.52−3.53 [3H, 2s, $3H_{13}$ isomer (*R*,*R*) + (*S*,*R*)], 3.75−3.81 (1H, m, $1H_7$), 3.89−4.04 (2H, m, $1H_7$ + $1H_{11}$), 4.17−4.22 (1H, m, $1H_{11}$ isomer *SR*), 4.27−4.32 (1H, m, $1H_{11}$ isomer *RR*), 6.95−7.07 (4H, m, $2H_2$ + $2H_3$), 7.39−7.45 (3H, m, $2H_{17}$ + H_{19}), 7.47−7.51 (2H, m, $2H_{18}$). R = Me (97% yield): R_f (20% EtOAc/hexane) 0.18; ^{1}H NMR ($CDCl_3$, 600.13 MHz) δ 1.81−1.95 (3H, m, $2H_6$ + $1H_{10}$), 1.96−1.99 [3H, 2s, $3H_9$ isomer (*R*,*R*) + (*S*,*R*)], 2.02−2.10 (1H, m, $1H_{10}$), 2.31−2.32 [3H, 2s, $3H_{20}$ isomer (*R*,*R*) + (*S*,*R*)], 2.69−2.76 (1H, m, H_5), 3.52−3.54 [3H, 2s, $3H_{13}$ isomer (*R*,*R*) + (*S*,*R*)], 3.77−3.83 (1H, m, $1H_7$), 3.89−3.95 (1H, m, $1H_7$), 3.98−4.07(1H, m, $1H_{11}$), 4.17−4.22 (1H, m, $1H_{11}$ isomer *SR*), 4.25−4.30 (1H, m, $1H_{11}$ isomer *RR*), 6.95 (2H, 2d, $^3J_{HH}$ = 8.1 Hz, $2H_2$), 7.09 (2H, t, $^3J_{HH}$ = 8.1 Hz, $2H_3$), 7.39−7.45 (3H, m, $2H_{17}$ + H_{19}), 7.49−7.51 (2H, m, $2H_{18}$). R = OMe (99% yield): R_f (20% EtOAc/hexane) 0.16; ^{1}H NMR ($CDCl_3$, 600.13 MHz) δ 1.78−1.95 (3H, m, $2H_6$ + $1H_{10}$), 1.96−1.99 [3H, 2s, $3H_9$ isomer (*R*,*R*) + (*S*,*R*)], 2.01−2.10 (1H, m, $1H_{10}$), 2.67−2.75 (1H, m, H_5), 3.52 [3H, 2s, $3H_{13}$ isomer (*R*,*R*) + (*S*,*R*)], 3.76−3.83 (4H, m, $1H_7$ + $3H_{20}$), 3.89−3.95 (1H, m, $1H_7$), 3.98−4.07 (1H, m, $1H_{11}$), 4.17−4.22 (1H, m, $1H_{11}$ isomer *SR*), 4.25−4.30 (1H, m, $1H_{11}$ isomer *RR*), 6.83 (2H, t, $^3J_{HH}$ = 8.7 Hz, $2H_2$), 6.98 (2H, d, $^3J_{HH}$ = 8.7 Hz, $2H_3$), 7.38−7.44 (3H, m, $2H_{17}$ + H_{19}), 7.47−7.53 (2H, m, $2H_{18}$).

Acknowledgment. We thank Novo Nordisk Co. for the generous gift of CAL-B (Novozyme 435) and Amano Europe for providing us PSL-IM and PSL-SD. This work was supported by the Spanish Ministerio de Educación y Ciencia (Projects CTQ 2007-61126) V.G.-F. thanks the Spanish Ministerio de Ciencia e Innovación (MICINN) for a personal grant (Ramón y Cajal Program). N.R.-L. thanks Gobierno regional de Asturias (FICYT) for a predoctoral grant (Severo Ochoa Program)

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