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Lipase-Catalyzed Regioselective Monoacetylation of Unsymmetrical 1,5-Primary Diols

Camille Oger,[†] Zsuzsanna Marton,[‡] Yasmin Brinkmann,[†] Valérie Bultel-Poncé,[†] Thierry Durand,[†] Marianne Graber,[‡] and Jean-Marie Galano*,[†]

[†]*Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 CNRS, Université Montpellier I et II, Faculté de Pharmacie, 15 avenue Charles Flahault, BP 14491, 34093 Montpellier, Cedex 05, France, and* [‡]*Université de la Rochelle, Pôle Sciences-Bât. Marie Curie, UMR 6250 LIENSs CNRS-ULR, Avenue Michel Crépeau, 17042 La Rochelle, Cedex 01, France*

jgalano@univ-montp1.fr

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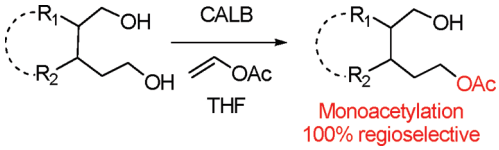


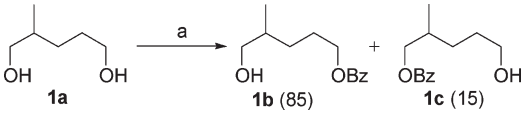
Lipase B from *Candida antarctica* (CALB) has been selected as the most suitable enzyme to catalyze the regioselective monoacetylation of 1,5-diol isoprostane intermediate, using vinyl acetate as an acyl transfer reagent in THF. We next applied this reaction on linear 2-substituted, 2,2′-disubstituted-1,5-pentanediols, and cyclic 2,3-disubstituted-1,5-pentanediols. To rationalize the regioselectivity observed, molecular docking simulations were performed.

Introduction

The selective monoprotection of two chemically equivalent primary hydroxyl groups constitutes a challenge in organic chemistry.[1] Protection of such compounds by chemical methods usually generates a mixture of unreacted and mono- and diprotected diols. Recently, Clarke described monoacylation of *meso* 1,3- and 1,4-diols, using cerium or ytterbium with modest regioselectivity.[2] The development of enzymatic protecting group techniques offers viable alternatives to classical chemical approaches. However, enzymatic protection techniques of hydroxyl groups was mainly developed on polyhydroxylated compounds such as mono- and oligosaccharides[3] and nucleosides[4] and therefore rarely applied to primary alcohols differentiation.[5] To the best of our knowledge, there is only one example for the selective monoprotection of primary non-*meso* 1,5-diols being furthermore enzymatic. Indeed, in 2003 Santaniello et al. reported the monobenzoylation of the 2-methyl-1,5-pentanediol **1a** (Scheme 1) using the *Mucor miehei* lipase (MML) and vinyl benzoate (VB) as an acyl transfer agent.[6] The monobenzoylated compound **1b** and its regioisomer **1c** were obtained in a 85:15 ratio.

We recently developed a new strategy[7] toward the synthesis of isoprostanes including a selective oxidation of **2a** using an iridium catalyst,[8] which allowed the introduction of the α chain (Scheme 2). A method that could differentiate

SCHEME 1. Lipase-Catalyzed Monobenzoylation of 1,5-Diol Developed by Santaniello et al.[a]



[a]Reagents: (a) MML, VB, *tert*-butyl methyl ether.

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.
(2) Clarke, P. A. *Tetrahedron Lett.* **2002**, *43*, 4761.
(3) For seminal work see: (a) Riva, S.; Chopineau, J.; Kieboom, A. P. G.; Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 584. (b) Therisod, M.; Klibanov, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 3977. (c) Hennen, W. J.; Sweers, H. M.; Wang, Y. F.; Wong, C. H. *J. Org. Chem.* **1988**, *53*, 4939. For a review on enzymatic protective group techniques, see: (d) Kadereit, D.; Waldmann, H. *Chem. Rev.* **2001**, *101*, 3367.
(4) For seminal work see: (a) Wong, C. H.; Chen, S. T.; Hennen, W. J.; Bibbs, J. A.; Wang, Y. F.; Liu, J. L. C.; Pantoliano, M. W.; Whitlow, M.; Bryan, P. N. *J. Am. Chem. Soc.* **1990**, *112*, 945. (b) Moris, F.; Gotor, V. *J. Org. Chem.* **1992**, *57*, 2490.
(5) For nonsymmetric primary 1,3-diols see: (a) Hisano, T.; Onodera, K.; Toyabe, Y.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2005**, *46*, 6293. For primary 1,4-diols (acyclic α,ω-terpenediols) see: (b) Takabe, K.; Mase, N.; Hisano, T.; Yoda, H. *Tetrahedron Lett.* **2003**, *44*, 3267.
(6) Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron Lett.* **2003**, *44*, 3663.
(7) Oger, C.; Brinkmann, Y.; Bouazzaoui, S.; Durand, T.; Galano, J.-M. *Org. Lett.* **2008**, *10*, 5087.
(8) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361.

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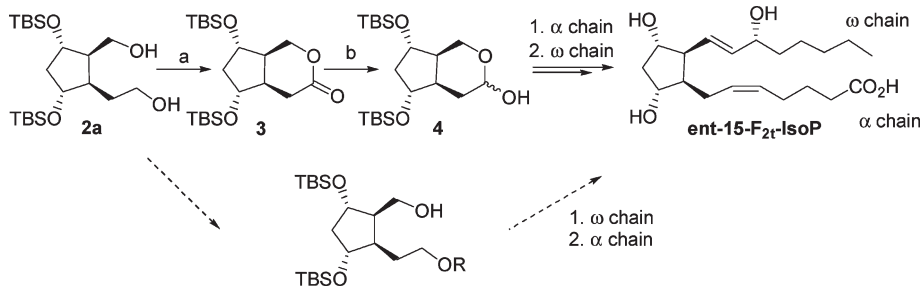
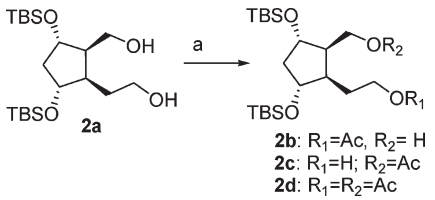
SCHEME 2. Functionalization of 2a-1,5-Diol[a]



[a]Reagents and conditions: (a) Cp*Ir[$OCH_2C(C_2H_5)_2NH$] 0.8 mol %, butanone, reflux, 91%; (b) DIBAL-H, CH_2Cl_2, −78°C, 89%.

SCHEME 3[a]



[a]Reagents: (a) lipase, vinyl acetate, solvent.

the two primary alcohol groups of the cyclic 2,3-disubstituted-1,5-pentanediol key intermediate **2a** would afford a complementary and more flexible strategy for the introduction of lateral chains.

Results and Discussion

We started our investigation by using a slight modification of the Santaniello et al. reaction conditions for the regioselective monoprotection of the diol **2a**, employing vinyl acetate instead of vinyl benzoate (Scheme 3). Unfortunately, a mixture of monoacetylated compounds **2b**/**2c** was obtained (Table 1, entry 1).

We then decided to screen various enzymes in order to study the regioselective monoacetylation of the diol **2a**. The results obtained are summarized in Table 1. No reaction occurs with the lipases from *Pseudomonas cepacia* (PCL), Amano AK, porcine pancreas (PPL), and *Candida rugosa* (entries 2−5). To our delight, full conversion and highly regioselective monoprotection of **2a** (entry 6) were obtained when the lipase B from *Candida antarctica* (CALB) was used. The desired monoacetylated compound **2b** was obtained as a sole product after 16 h in THF. We then studied the effect of vinyl acetate concentration with the aim to decrease the reaction time. Switching the ratio of solvent/vinyl acetate from 220:1 to 1:1 (v/v) still provided full conversion and a high regioselectivity with significantly reduced reaction time (entry 7). Similar result in terms of reaction rate was obtained when the reaction was carried out in neat vinyl acetate or *t*BuOMe albeit with a lower regioselectivity (90:10) (entries 8 and 9).[9] Finally, other solvents such as diethyl ether or dichloromethane did not improve the regiochemical outcome of the reaction (entries 10 and 11). It is important to note that similar results were obtained with the racemic form of diol **2a** and that no enantioselective discrimination was observed.

TABLE 1. Lipase-Catalyzed Acetylation of 2a in Different Solvents

entry	enzymes	solvent (solvent, vinyl acetate)	time (h)	ratio **2b**/**2c**/**2d**	yield[d] (%)
1	MML[a]	*t*BuOMe (220:1)	16	90/10/0	49[e]
2	Amano AK[a]	*t*BuOMe (220:1)	16		
3	PCL[a]	*t*BuOMe (220:1)	16		
4	PPL[a]	*t*BuOMe (220:1)	16		
5	*Candida rugosa*[a]	*t*BuOMe (220:1)	16	70/30/0	31[e]
6	CALB[a]	THF (220:1)	16	100/0/0	96
7	CALB[b]	THF (1:1)	8	100/0/0	98
8	CALB[b]	vinyl acetate	8	90/0/10	90
9	CALB[b]	*t*BuOMe (1:1)	6	90/0/10	82
10	CALB[b]	CH_2Cl_2 (1:1)	8	100/0/0[c]	97
11	CALB[b]	Et_2O (1:1)	12	100/0/0[c]	97

[a]50 mg of **2a**, 10 mg of enzyme in 3 mL of solvent and 15 μL of vinyl acetate. [b]100 mg of **2a**, 30 mg of CALB in 10 mL of a mixture of solvent/vinyl acetate (1:1). [c]Diacetylated compound **2d** was not detected by ^{1}H NMR of the crude reaction, but traces were separated by column chromatography; [d]Yields refer to monoacetylated compounds isolated after flash chromatography. [e]Reaction was stopped after 16 h when unsatisfactory ratio was observed by TLC.

With these results in hand, we sought to examine the scope of the method. The above optimized conditions were then applied to an array of cyclic 2,3-disubstituted-1,5-pentanediols (compounds **5a**−**13a**, Figure 1).

The results are summarized in Table 2. In all cases full conversion was obtained. For isoprostanes precursors (**5a**−**8a**), complete regioselectivity in favor of monoacetylated compounds **5b**−**8b** (entries 1−5) was obtained, whereas 3% of bis-acetylated compound **9d** was observed with **9a**-diol (entry 6). Compound **10a**, a prostaglandins precursor, gave a similar result, providing exclusively the desired monoprotected compound **10b** (entry 7). Surprisingly, only the bis-protected compound **11d** was obtained when the reaction was run with the hydroxylpentan-1,5-diol **11a** (entry 8). Poor results were obtained with the naked cyclohexane **12a** (entry 9) with a ratio of bis-acetylated compound **12d**/monoacetylated product **12b** of 66:34. Finally, cyclopentane derivatives **13a** (entry 10) gave only the bis-acetylated adduct **13d**. It should be noted that the reaction could be run on gram scale on diols **2a** and **5a**−**9a**, with high yields (96−100%) and no loss of regioselectivity.

Encouraged by the above results and to further extend the scope of the reaction, we applied our optimized conditions to

(9) Solvent effects on enantioselectivities have been previously observed which could account for the lowering in regioselectivy, see: (a) Carrea, G.; D'Arrigo, P.; Piergianni, V.; Roncaglio, S.; Secundo, F.; Servi, S. *Biochim. Biophys. Acta* **1995**, *1255*, 273. (b) Wescott, C. R.; Klibanov, A. M. *Biochim. Biophys. Acta* **1994**, *1206*, 1.

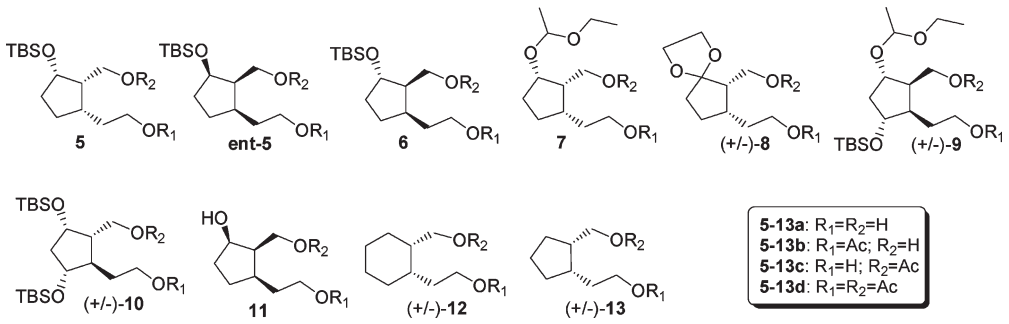


FIGURE 1. Structure of 2,3-disubstituted 1,5-diols and their acetates (compounds **5a**−**d** to **13a**−**d**).

TABLE 2. CALB-Catalyzed Acetylation of Diols 5a−13a

entry	diol[a]	time (h)	products	ratio[b] **b**/**c**/**d**	yield[c] (%)
1	**5a**	2	**5b**	100/0/0	88
2	**ent-5a**	2	**ent-5b**	100/0/0	88
3	**6a**	2	**6b**	100/0/0	88
4	**7a**	2	**7b**	100/0/0	83
5	**8a**	2	**8b**	100/0/0	94
6	**9a**	23	**9b/9d**	97/0/3	97
7	**10a**	24	**10b**	100/0/0	90
8	**11a**	2	**11d**	0/0/100	
9	**12a**	3.5	**12b/12d**	34/0/66	25
10	**13a**	24	**13d**	0/0/100	

[a]100 mg of diol, 30 mg of CALB in 10 mL of a mixture THF/ vinyl acetate (1/1). [b]Determined by ^{1}H NMR analysis of the crude reaction at full conversion. [c]Yields refer to monoacetylated compound isolated after flash chromatography.

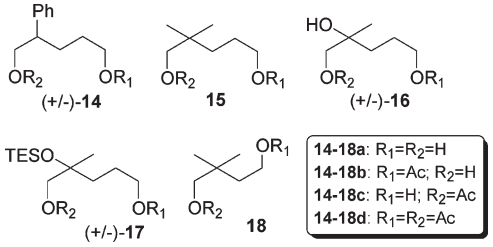


FIGURE 2. Structure of linear 2-substituted and 2,2′-substituted 1,5-diols and their acetate analogues (compounds **14a**−**d** to **18a**−**d**).

several linear 2-substituted diols (**14a**−**18a**, Figure 2). In all cases, regioselectivities observed were lower than those obtained for cyclic 2,3-disubstituted-1,5-pentane-diols compounds. Good results were obtained for compounds **14a** and **15a** with 79% yields in favor of the monoprotected compounds **14b** and **15b** (entries 1 and 2, Table 3). However, as observed for cyclic diol **11a**, the presence of a free hydroxyl group seems to have a deleterious effect on the regioselectivity.

Indeed, acetylation of compound **16a** bearing a free tertiary hydroxyl group produced exclusively the bis-acetylated product **16d**, whereas reaction of its silylated version (compound **17a**) gave a mixture of mono- and diacetate adducts (entries 3 and 4). Finally, as observed with the 1,5-diol **15a**, good regioselectivity was obtained for the 1,4-diol-**18a**, with 66% yield in favor of the monoacetylated compound **18b**. For all the substrates presented, monoprotected compounds **2c**−**18c** were never observed. The reaction was completely regioselective toward the alcohol with the longer chain.

TABLE 3. CALB-Catalyzed Acetylation of Diols 14a−18a

entry	diol[a]	time (h)	products	ratio[b] **b/c/d**	yield[c] (%)
1	**14a**	1	**14b**/**14d**	87/0/13	79
2	**15a**	42	**15b**/**15d**	78/0/22	78
3	**16a**	0.5	**16d**	0/0/100	
4	**17a**	3	**17b/17d**	36/0/64	30
5	**18a**	3	**18b**/**18d**	90/0/10	66

[a]100 mg of diol, 30 mg of CALB in 10 mL of a mixture of THF/vinyl acetate (1:1). [b]Determined by ^{1}H NMR analysis of the crude reaction at full conversion. [c]Yields refer to monoacetylated product isolated after flash chromatography.

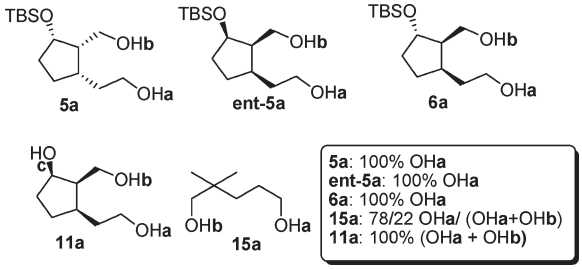


FIGURE 3. Structure of the docked 1,5-diols and summary of the regioselectivities observed.

Molecular Modeling Study

Recently, computer-based modeling methodology has been used to understand the regioselectivity in acylation of complex substrate including several hydroxyl groups catalyzed by enzymes.[10] In order to explain the regioselectivity obtained with the same enzyme during our study, docking simulations were performed on five substrates with good regioselectivities (**5a**, **ent-5a** and **6a**; Figure 3), modest regioselectivity (**15a**; Figure 3), and without selectivity (**11a**; Figure 3).

Molecular docking experiments of compounds **5a**, **ent-5a**, **6a**, **11a**, and **15a** into the active site of the CALB were performed using the CHARMm force field[11] based docking

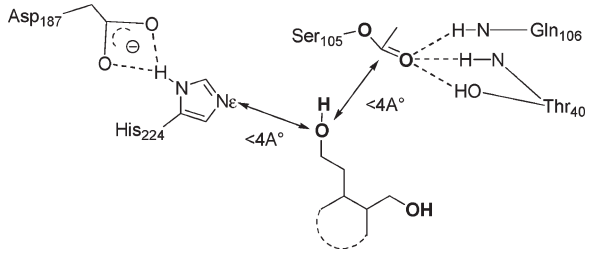
(10) (a) De Oliveira, E. B.; Humeau, C.; Chebil, L.; Maia, E. R.; Dehez, F.; Maigret, B.; Ghoul, M.; Engasser, J.-M. *J. Mol. Catal. B: Enzym.* **2009**, *59*, 96. (b) Pieraccini, S.; Sironi, M.; Colombo, G. *Chem. Phys. Lett.* **2006**, *418*, 373–376. (c) Colombo, G.; Riva, S.; Danieli, B. *Tetrahedron* **2004**, *60*, 741. (d) Fuentes, G.; Cruces, M. A.; Plou, F. J.; Ballesteros, A.; Verma, C. S. *ChemBioChem* **2002**, *3*, 907. (e) Rich, J. O.; Bedell, B. A.; Dordick, J. S. *Biotechnol. Bioeng.* **1995**, *45*, 426.

(11) MacKerell, A. D., Jr.; Bashford, D.; Bellott, M.; Dunbrack, R. L., Jr.; Evanseck, J.; Field, M. J.; Fischer, S.; Gao, J.; Guo, H.; Ha, S.; Joseph, D.; Kuchnir, L.; Kuczera, K.; Lau, F. T. K.; Mattos, C.; Michnick, S.; Ngo, T.; Nguyen, D. T.; Prodhom, B.; Reiher, I., W. E.; Roux, B.; Schlenkrich, M.; Smith, J.; Stote, R.; Straub, J.; Watanabe, M.; Wiorkiewicz-Kuczera, J.; Yin, D.; Karplus, M. *J. Phys. Chem. B.* **1998**, *102*, 3586.

TABLE 4. Distances between the Hydroxyl Group, Acetate Carbonyl, and His224-Nε Atom, after Optimization for Diols 5a, ent-5a, 6a, and 15a

entry	complex	buried OH	distance from ACE (Å)	distance from His224 (Å)
1	**5a-I**	OH**a**	3.3	3.7
		OH**b**	6.5	6.0
2	**5a-II**	OH**a**	3.5	3.3
		OH**b**	7.9	7.0
3	**ent-5a-I**	OH**a**	3.7	3.0
		OH**b**	6.6	8.1
4	**ent-5a-II**	OH**a**	3.8	3.1
		OH**b**	4.6	5.8
5	**6a-I**	OH**a**	3.3	3.8
		OH**b**	4.4	5.8
6	**6a-II**	OH**a**	3.4	3.8
		OH**b**	6.5	7.6
7	**15a-I**	OH**a**	3.4	4.1
		OH**b**	5.8	7.6
8	**15a-II**	OH**a**	3.9	4.4
		OH**b**	5.8	7.6

SCHEME 4. Structural Requirements the Substrate Must Satisfy To Be Considered Reactive



tool CDOCKER[12] of Discovery Studio 2.1 (Accelrys Inc., San Diego, CA). The study was composed of the following steps: preparation of the starting enzyme structure and modeling of the acetyl-enzyme; docking of the 1,5-primary diol substrates; scoring; optimization and structural analysis of the best poses; verification of the reliability of the final models. After scoring, poses with a good consensus score and with a good orientation of the hydroxyl groups toward the active site were retained and were submitted to further optimizations. Three criteria have to be combined for the complex to be considered as a productive binding mode, in order to conclude that the acetylation reaction is able to take place. First, the root-mean-square deviation (rmsd) value between the initial crystal structure and the final optimized structure must be small. As found by Valliki et al. for prostaglandins acetylation, a rmsd value of <3 Å was chosen, as a limit.[13] Then, the complex must form a minimum of two of the three hydrogen bond interactions between the acetate oxygen and the hydrogen of the Thr40 and Gln106 residues. Finally, the hydroxyl group of the 1,5-diol must be placed simultaneously at <4 Å from the sp^2 carbon of the acetyl and the Nε atom of His224 to be considered as a productive complex (Scheme 4).

In Table 4 are summarized the transacetylation distances for structures having the best potential energy after optimizations, for the diols **5a** and its enantiomer **6a** and **15a**.

(12) Wu, G.; Robertson, D. H.; Brooks, C. L. III; Veith, M. *J. Comput. Chem.* **2003**, *24*, 1549.
(13) Valliki, I.; Fransson, L.; Hult, K.; Järving, I.; Pehk, T.; Samel, N.; Tõugu, V.; Villo, O.; Parve, J. *J. Mol. Catal. B: Enzym.* **2005**, *35*, 62.

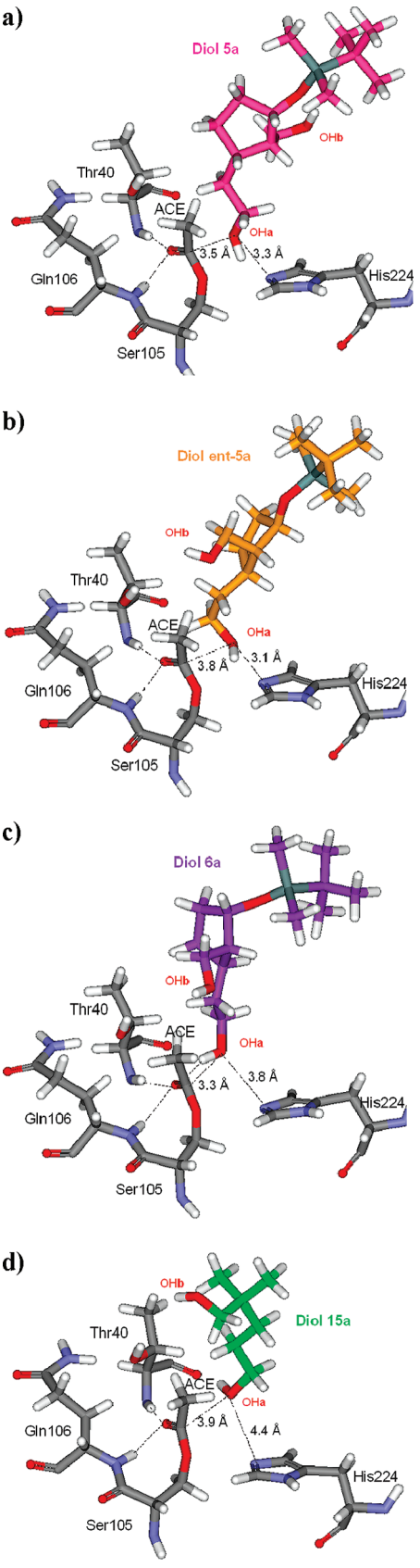


FIGURE 4. Orientations and hydrogen bond interactions (dashed lines) of the best structures obtained with diols: (a) **5a** (pink), (b) **ent-5a** (orange), (c) **6a** (purple), and (d) **15a** (green). For clarity, only the residues useful for discussion are shown (gray).

TABLE 5. Distances between the Hydroxyl Group, Acetate Carbonyl, and His224-Nε Atom, after Optimization for Diol 11a

entry	complex	buried OH	distance from ACE (Å)	distance from His224 (Å)
1	**11a-I**	OH**a**	5.7	4.8
		OH**b**	3.2	3.9
2	**11a-II**	OH**a**	7.6	7.0
		OH**b**	3.2	3.8
3	**11a-III**	OH**a**	4.1	4.3
		OH**b**	7.1	8.7
4	**11a-IV**	OH**a**	3.9	4.1
		OH**b**	9.2	9.2

TABLE 6. Distances between the Hydroxyl Group, Acetate Carbonyl, and His224-Nε Atom, after Optimization for Compounds 11b and 11c

entry	complex	buried OH	distance from ACE (Å)	distance from His224 (Å)
1	**11b-I**	OH**b**	3.3	4.5
2	**11b-II**	OH**b**	3.2	4.4
3	**11c-I**	OH**a**	4.0	4.8
4	**11c-II**	OH**a**	3.6	4.4

In all cases, the different complexes obtained with diols **5a**, **ent-5a**, and **6a** (entries 1−6, Table 4) adopted the acetylation distances criterion, with distances between the OH**a** hydroxyl, the acetate carbon, and the His224:Nε nitrogen <4 Å. For the diol **15a** (entries 7 and 8), the distance between the hydroxyl group OH**a** and the His224:Nε nitrogen is slightly larger than the fixed criteria. However, the OH**b** hydroxyl is too far from the catalytic residues with distances from 4.4 to 7.9 Å. The superimposition of the protein structure in the complex and the crystal structure showed minor displacements (rmsd values about 0.7 Å). Finally, two hydrogen bond interactions between oxyanion hole residues and OH**a** were formed for each complex.

The docking experiments of diols **5a**, **ent-5a**, **6a**, and **15a** showed that the substrates are preferentially orientated to form productive complexes with the OH**a** hydroxyl rather than the OH**b** (Figure 4). Those results are in accordance with the experimental acetylation of the OH**a** hydroxyl.

Encouraged by the above results, we applied this docking procedure to the diol **11a**. In this case, both hydroxyl OH**a** and OH**b** were acetylated during the experimental procedure, to form the bis-acetylated compound **11d**. Our first investigation led us to consider an effect of the free alcohol OH**c** even though the mechanism of this contribution is presently unclear. In 50% of the poses obtained after the docking experiment, the OH**a** hydroxyl was orientated in order to form a productive binding mode with the catalytic site, and the other 50% were orientated toward the OH**b** hydroxyl. After optimization, four complexes were then retained: two in favor of OH**a** and two in favor of OH**b** (Table 5).

The results summarized in Table 5 hold with those aforementioned and tend to corroborate the experience. Indeed, complexes **11a-I** and **11a-II** are able to form productive binding modes with the OH**b** alcohol (entries 1 and 2). Acetylating distances OH**b**-ACE and OH**b**-His224:Nε fit the distance criterion. In the same way, productive binding modes are formed with the OH**a** alcohol in complexes **11a-III** and **11a-IV** (entries 3 and 4) with distances OH**a**-ACE and OH**a**-His224:Nε close to 4 Å. In fact, diol **11a** is able to form two productive binding modes with the active site of the CALB, in order to acetylate both hydroxyls.

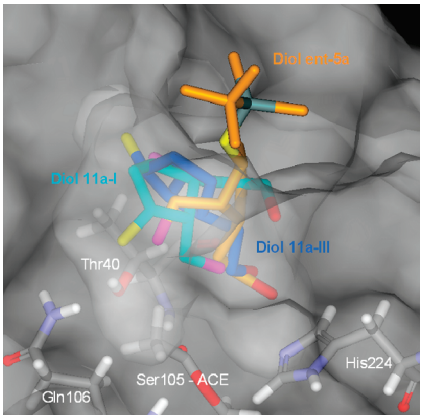


FIGURE 5. Orientations for diols **11a-I** (cyan) and **11a-III** (blue) compared to the protected diol **5a** (orange). For clarity, only the residues useful for discussion are shown (gray). Connolly surface of the enzyme is represented in white. OH**b** in pink and OH**c** in yellow.

To complete this study, one more docking experience was performed, replacing one hydroxyl with an acetate, to prove that a second acetylation reaction could be done thereafter. In Table 6 are summarized the results of the docking with monoacetylated products **11b** and **11c**. For these molecules, the free alcohols (OH**b** and OH**a**, respectively) were orientated toward Ser105 and His224 residues. After optimizations, the distances between the non-acetylated hydroxyl group (OH**a** or OH**b**) and the acetate were <4 Å. The distances between the Nε atom of His224 and the same free alcohol were ranged from 4.4 to 4.8 Å. The two other criteria (rmsd value and at least two hydrogen bonds with the oxyanion hole) were also respected. This suggests that after a first acetylation reaction, the residual hydroxyl group (OH**a** or OH**b**) could be acetylated.

It is important to note that after optimization, the secondary alcohol (OH**c**) of the diol **11a** was placed into the cavity of the enzyme. However, in the case of the diol **5a**, where the same secondary alcohol was protected, the protecting group stands outside the cavity (Figure 5).

Conclusion

In conclusion, we have developed for the first time a highly regioselective monoacetylation of unsymmetrical 1,5-diols substituted at the C_2 or C_2/C_3 carbons. This reaction, useful for the synthesis of isoprostanes derivatives, could also be extended to other derivatives, as shown with linear structures.

Docking experiments were used to study CALB-catalyzed acetylation of four 1,5-diols, and all substrates tested were able to dock with the CALB active site, in order to produce reactive complexes. The docking results corroborate with the regioselectivities observed experimentally and lead consideration of the use of docking experiments as a predictive tool.

Experimental Section

General Procedure for Regioselective Enzymatic Acetylation. To a solution of the diol (**1a**−**18a**, 100 mg), in 10 mL of a mixture THF/vinyl acetate (1:1, v/v) was added the *Candida antarctica* lipase B (30 mg). The mixtures were stirred with a rotavapor and followed by TLC for the appropriate time (see tables), then filtered, and rinsed with diethyl ether, and the solvents were

evaporated under reduced pressure. The ratio of acetate products was checked by NMR of the crude before purification by flash chromatography.

Computational Methods. Molecular dynamics calculations and docking simulations were performed with CHARMm force field, using the 2.1 version of Discovery Studio (Accelrys Inc.). MD simulations were carried out by adopting a 12 Å nonbound spherical cutoff, using the isothermal-isochoric ensemble (NVT)[14] and with distance-dependent dielectric implicit solvent model.

(14) Berendsen, H. J. C.; Postma, J. P. M.; Van Gunsteren, W. F.; Dinola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

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Supporting Information Available: Additional experimental details, NMR data of all compounds, and molecular dynamics calculations and docking simulations details. This material is available free of charge via the Internet at http://pubs.acs.org.