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Desymmetrization of Glycerol Derivatives with Peptide-Based Acylation Catalysts

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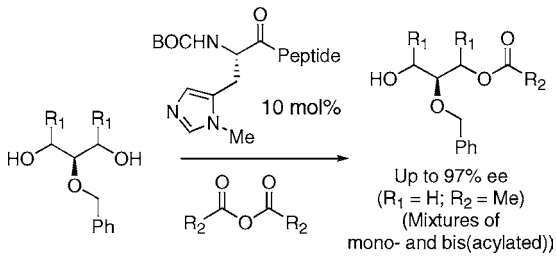
ABSTRACT



Nucleophile-loaded peptides have been evaluated as catalysts for the desymmetrization of glycerol derivatives through an enantioselective acylation process. Enantiomeric excesses of up to 97% have been obtained for the monoacylated products. A range of other substrates have been examined that shed light on the mechanistic basis of the desymmetrizations.

Glycerol appears in a myriad of forms in biomolecules, including as membrane constituents and various natural products. Among the many forms of glycerol, many appear such that the two enantiotopic, primary hydroxyl groups are differentially functionalized (Figure 1).[1] As part of an investigation of site-selective functionalization of complex molecules, we report herein a study of the desymmetrization reactions of glycerol derivatives based on asymmetric acylation reactions.[2] The catalysts we employ are peptide-based nucleophilic catalysts. The results constitute steps toward highly efficient, nonenzymatic acylation reactions of primary alcohols, including glycerol derivatives.[3−5] The results employing small-molecule peptide-based catalysts—

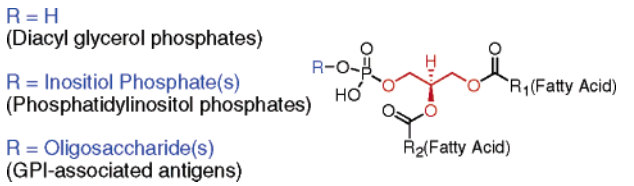


Figure 1. Representative chiral glycerol derivatives.

in terms of enantioselectivity—are intriguing in comparison to the results obtained when certain enzymes are used as catalysts.[6,7]

Among the most successful demonstrations of enzymatic catalysts as tools for enantioselective catalysis in preparative

(1) Takano, S. *Pure Appl. Chem.* **1987**, *59*, 353−362.

(2) For a recent review of enantioselective desymmetrization, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784.

(3) For a key example of nonenzymatic desymmetrization of 1,3-propanediols, inter alia, see: Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410−2411. Glycerols are not presented in this study.

(4) In the field of nonenzymatic asymmetric acylation reactions, many of the successful examples involve secondary alcohols. For reviews, see: (a) Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Org. Prepr. Proc. Int.* **2000**, *32*, 331−365. (b) Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.: Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 43.

(5) For a case of nonenzymatic asymmetric acylation of tertiary alcohols, see: Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522−5527.

(6) Garcia-Urdíales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313−354.

(7) For an alternative approach to nonenzymatic glycerol desymmetrization, see: Boons, G. J.; Entwistle, D. A.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1993**, *34*, 5649−5652.

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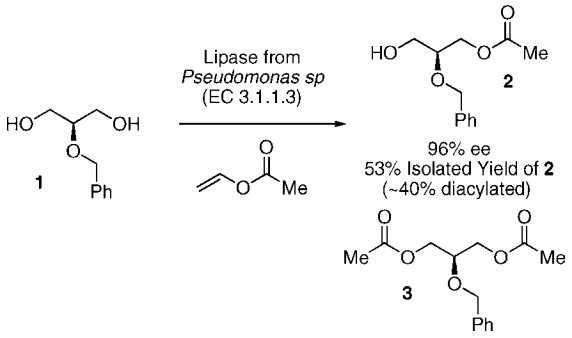
organic synthesis are the desymmetrization reactions mediated by lipases such as that from *Pseudomonas sp*.[8,9] When the reaction is performed with acylating agents such as vinyl acetate, glycerol derivative **1** may be converted to the chiral mono(acetate) **2** with excellent enantiopurity (96% ee, Scheme 1). Notably, **2** is obtained in 53% isolated yield,

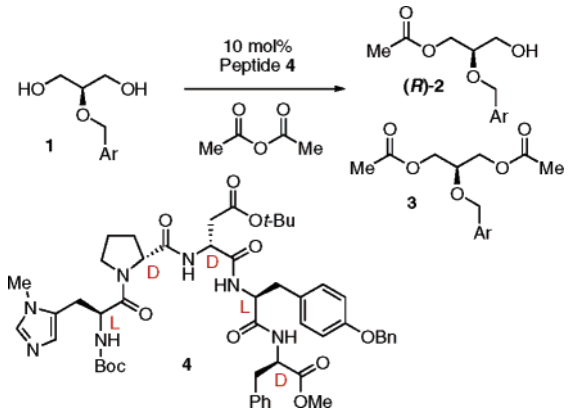
Scheme 1



along with ~40% conversion to bis(acetate) **3**, through the well-known secondary kinetic resolution associated with the desymmetrization.[10,11]

To compare the results employing lipases to those obtained with simple peptides, we began our study of glycerol desymmetrizations using peptide catalysts armed with the π-methyl-histidine substructure. Our previous studies of enantioselective "group transfer" with peptide-based catalysts have led to effective asymmetric acylations of a substantial scope of secondary alcohols,[12] several desymmetrizations through asymmetric phosphorylation,[13] and also cases of enantioselective sulfinylation.[14] We therefore began our studies of asymmetric acylation of glycerol with catalyst libraries that we had prepared previously in the context of these studies. After a series of screens, described in the Supporting Information, we arrived at catalyst **4** as the lead catalyst for the desymmetrization of **1** (Scheme 2).

Scheme 2



The performance of pentapeptide **4** for the desymmetrization of compound **1** (Ar = Ph) is presented in Table 1.

Table 1. Desymmetrization of Compound **1** under the Influence of Catalyst **4**[a]

entry	amt of Ac_2O, equiv	ee	isolated yield (*R*)-**2**, %	mono (**2**):bis (**3**)
1	1.5	86	52	59:41
2	1.6	92	42	46:54
3	1.7	90	38	42:58
4	1.8	91	37	39:61
5	1.9	94	36	39:61
6	2.0	97	27	29:71

[a] All reactions were conducted at −55 °C in the presence of 2 equiv of Hunig's base. Isolated yields are after silica gel chromatography. The mono to bis ratio was determined by comparing isolated yields of **2** and **3**. All reactions proceeded to >90% conversion within 24−36 h, as judged by TLC. ee's were determined by chiral HPLC.

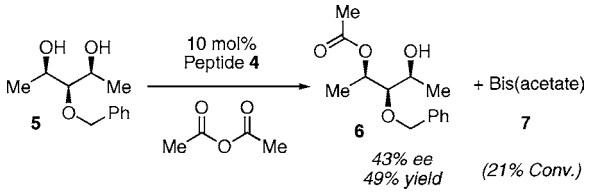
When the substrate is dissolved in $PhCH_3/CH_2Cl_2$ (12:1) at −55 °C, on exposure to Ac_2O and peptide **4** (10 mol %), an asymmetric acylation occurs to form (*R*)-**2**.[15] The relative quantities of mono(acetate) **2** and bis(acetate) **3** may be regulated as a function of anhydride stoichiometry. As shown in entry 1, when 1.5 equiv of Ac_2O is employed, (*R*)-**2** is obtained in 52% isolated yield as a 93:7 mixture of enantiomers (86% ee). Under these conditions, a 59:41 ratio of mono(acetate) **2** to bis(acetate) **3** is observed. As the quantity of acetic anhydride is increased, the overall ee of **2** is also increased, at the expense of isolated yield. For example, when 1.6−1.9 equiv of anhydride is employed, (*R*)-**2** is obtained with >90% ee, with isolated yields from 36% to 42% (entries 2−5). Compound (*R*)-**2** is isolated with 97% ee when 2.0 equiv of Ac_2O is used in the reaction, with an isolated yield of 27% (**2**:**3**, 29:71; entry 6). Under the conditions of the experiment, racemization through acyl migration is not observed.

We also examined a number of glycerol analogues with the hope of uncovering the factors that impact reaction selectivity. At this stage, we wondered if the inherently higher reactvity of the primary alcohols might imply that meso secondary 1,3-diols analogous to glycerol might be inherently better substrates for catalyst **4**. We therefore prepared diols **5** (Scheme 3) and **8** (Scheme 4) and studied them under analogous desymmetrization conditions. Not surprisingly, each is of lower reactivity than the analogous glycerol derivative **1**, necessitating that reactions be run at

(8) Wang, Y. F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127−3129.
(9) For glycerol desymmetrization employing a kinase, see: Chenault, H. K.; Chafin, L. F.; Liehr, S. *J. Org. Chem.* **1998**, *63*, 4039−4045.
(10) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529.
(11) For a glycerol desymmetrization with a different lipase that reports higher recovery of monoacetate under different conditions, see: Terao, Y.; Murata, M.; Achiwa, K. *Tetrahedron Lett.* **1988**, *29*, 5173−5176.
(12) (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496−6502. (b) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643.
(13) (a) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653−11656. (b) Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125−10126. (c) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *Chem. Commun.* **2003**, 1781−1785.
(14) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134−8135.

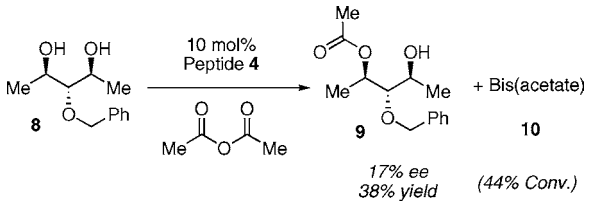
(15) We did not observe an appreciable background rate of acylation of the substrate under these conditions.

Scheme 3



25 °C to proceed at an appreciable rate. At the same time, each affords products that are of substantially lower ee in the desymmetrization reaction. The all-*syn* compound **5**

Scheme 4



delivers mono(acetate) **6** with 43% ee (49% isolated yield, 21% conversion) to bis(acetate) **7**. The *anti* derivative **8** affords compound **9** with only 17% ee (38% isolated yield). As with glycerol derivative **2**, compounds **6** and **9** did not exhibit a significant racemization rate upon standing at room temperature in solution.

The basis of the lower degree of selectivity observed for compounds **5** and **8** is not fully understood at this time. However, it is tempting to suggest that these secondary alcohols may be disfavored from adopting a putative reactive conformation of glycerol derivative **1** that may be favorable for enantioselective catalysis. For example, if **1** were to react in a *gauche*−*gauche* conformation as shown in Figure 2

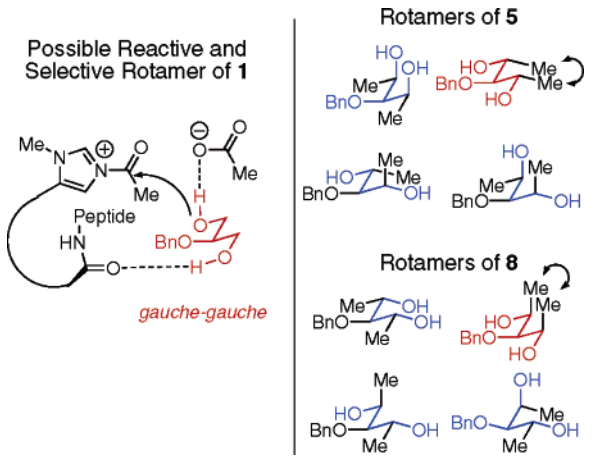
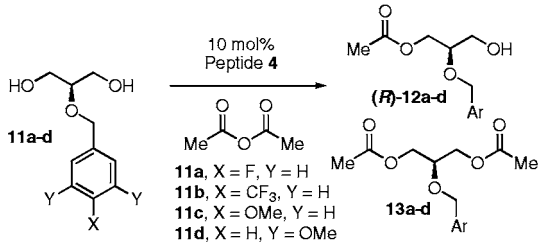


Figure 2. Sample of representative conformations of glycerol analogues and their relationship to glycerol analogue **1**.

(perhaps to maximize a favorable H bond to the catalyst),[16] then the analogous conformations in **5** and **8** would be disfavored by destabilizing *syn*-pentane-type interactions.

We then turned our attention to the possibility of a pK_a effect that might influence reaction selectivity. We found, for example, remote *para* substitution on the 2-*O*-benzyl group has a modest effect on reaction selectivity (Table 2). When electron-withdrawing groups are introduced in the *para* position, the selectivity appears to decrease slightly. For example, when the *p*-fluorophenyl substrate **11a** is employed, **12a** is obtained with 68% ee (40% isolated yield, entry 1); *p*-CF_3 substitution leads to isolation of **12b** with 73% ee (37% yield, entry 2). On the other hand, when the electron-rich PMB derivative **11c** is employed as a substrate, mono-(acetate) **12c** is isolated in 48% yield with 88% ee (Table 2,

Table 2. Desymmetrization of Compounds **11a**−**d** under the Influence of Catalyst **4**[a]



entry	compd	amt of Ac_2O, equiv	ee	isolated yield (*R*)-**12**, %	mono (**12**):bis (**13**)
1	**11a**	1.8	68	40	50:50
2	**11b**	1.8	73	37	43:57
3	**11c**	1.8	88	48	51:49
4	**11d**	1.8	95	34	37:63

entry 3). Bis(methoxy)benzyl ether **11d** is also a more selective substrate, delivering mono(acetate) **12d** in 95% ee with 34% isolated yield. While we do not have a definitive explanation for this remote effect, it appears that a lower pK_a for the reacting hydroxyl group may lead to a slightly less selective substrate for the desymmetrizations.

In summary, we have illustrated that a pentapeptide catalyst may lead to effective desymmetrization of simple glycerol derivatives with enantioselectivity which is comparable to that exhibited by the lipase *Pseudomonas sp*. The extension of this observation to hydroxyl group differentiation in more complex settings, with a range of catalytic reactions, is now the current focus of this research.

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Supporting Information Available: Experimental procedures and product characterization data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Vasbinder, M. M.; Jarvo, E. J.; Miller, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2824−2827.