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Kinetic Resolution of Racemic 2-Hydroxy-γ-butyrolactones by Asymmetric Esterification Using Diphenylacetic Acid with Pivalic Anhydride and a Chiral Acyl-Transfer Catalyst

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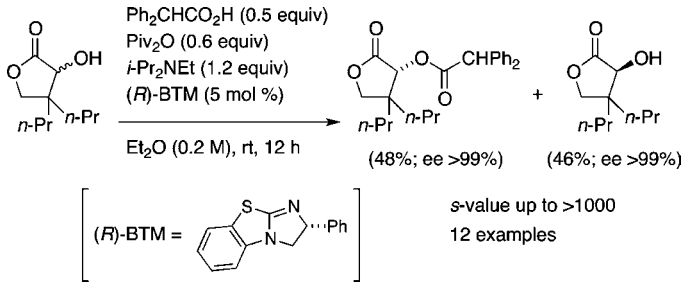
ABSTRACT



Various optically active 2-hydroxy-γ-butyrolactone derivatives are produced via the kinetic resolution of racemic 2-hydroxy-γ-butyrolactones with diphenylacetic acid using pivalic anhydride and (*R*)-benzotetramisole ((*R*)-BTM), a chiral acyl-transfer catalyst. Importantly, the substrate scope of this novel protocol is fairly broad (12 examples, *s*-value; up to over 1000). In addition, we succeeded in disclosing the reaction mechanism to afford high enantioselectivity using theoretical calculations and expounded on the substituent effects at the C-3 positions in 2-hydroxylactones.

Optically active 2-hydroxy-γ-butyrolactone derivatives, especially pantolactone (±)-**1a**, are useful chiral building blocks not only for the synthesis of natural products but also for the preparation of chiral auxiliaries. As a result, numerous efforts have been devoted to the development of efficient methods for the preparation of these compounds, including enzymatic and chemical transformations.[1] To the best of our knowledge, however, a general method for the kinetic resolution (KR) of racemic 2-hydroxy-γ-butyrolactones has not been reported until recently. A pioneering efficient KR of racemic 2-hydroxy-γ-butyrolactones was achieved by Ohkuma[2] using the Matsumura protocol,[3] which involves the asymmetric carbamoylation of racemic 2-hydroxy-γ-butyrolactones catalyzed by copper(II)−bis(oxazoline).[4] Previously, we demonstrated the first kinetic resolution of racemic alcohols with achiral carboxylic acids or racemic carboxylic acids with achiral alcohols by asymmetric esterification[5,6] via the in situ formation of a mixed anhydride using carboxylic

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(1) For a selected review, see: (a) Shimizu, S.; Morikawa, T.; Nitta, K.; Sakamoto, K.; Wada, K. *Nippon Kagaku Kaishi* **2002**, *1*, 1. (b) Camps, P.; Muñoz-Torrero, D. *Curr. Org. Chem.* **2004**, *8*, 1339 and references cited therein.

(2) Kurono, N.; Kondo, T.; Wakabayashi, M.; Ooka, H.; Inoue, T.; Tachikawa, H.; Ohkuma, T. *Chem. Asian. J.* **2008**, *3*, 1289 and references cited therein.

(3) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052.

(4) (a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure. Appl. Chem.* **1999**, *71*, 1407. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

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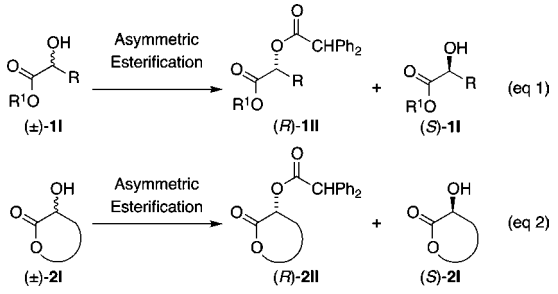
anhydrides as coupling reagents in combination with chiral acyl-transfer catalysts. In addition, we achieved the kinetic resolution of racemic 2-hydroxyalkanoates with diphenylacetic acid using pivalic anhydride in the presence of (*R*)-benzotetramisole ((*R*)-BTM) (Scheme 1, eq 1).[7] Thus, it was anticipated that this kinetic resolution method could be applied in the same manner to 2-hydroxy-γ-butyrolactones, which are corresponding cyclic analogs (Scheme 1, eq 2). In this paper, we report the novel kinetic resolution of various racemic 2-hydroxy-γ-butyrolactones using diphenylacetic acid promoted by pivalic anhydride and (*R*)-BTM via mixed-anhydride formation.

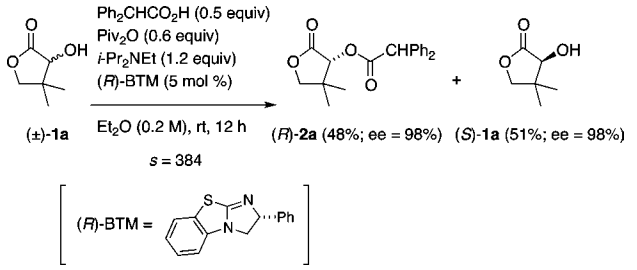
Scheme 1. Previous Results (eq 1) and Working Hypothesis for This Study (eq 2)



The KR of racemic pantolactone ((±)-**1a**) was first examined with diphenylacetic acid using pivalic anhydride and (*R*)-BTM in Et_2O at room temperature for 12 h, which were optimized reaction conditions established in the previous study (Scheme 2).[7] Fortunately, it was observed that the reaction conditions are applicable to the lactone (±)-**1a** as well as the acyclic esters. The KR of (±)-**1a** smoothly proceeded to afford the corresponding ester (*R*)-**2a** (48%, 98% ee) and the recovered alcohol (*S*)-**1a** (51%, 98% ee) with a high *s*-value[8] ($s = 384$).

This successful result encouraged us to explore the substrate scope for the reaction. Therefore, various racemic 2-hydroxy-γ-butyrolactone derivatives[9] ((±)-**1b**–**e**, (±)-*cis*-**1f**, (±)-*trans*-**1f**, (±)-*endo*-**1g** and **1h**, and (±)-*exo*-**1g** and **1h**), including spiro and fused compounds (Table 1), were examined. When the KR of **1b**–**d** bearing dialkyl substituents at the C-3 position was carried out under the above conditions, high *s*-values were obtained in all cases;

Scheme 2. Kinetic Resolution of Racemic Pantolactone ((±)-**1a**)



notably, the reaction of (±)-**1c** afforded perfect selectivity (Table 1, entries 1–3). On the other hand, the reaction of (±)-**1e** bearing substituents at the C-4 position had a diminished *s*-value (Table 1, entry 4). To clarify the effect of the substituent groups, both (±)-*cis*-**1f** and (±)-*trans*-**1f** were subjected to the same reaction, and it was revealed that a higher selectivity was achieved by the reaction of (±)-*cis*-**1f** than that achieved by the reaction of (±)-*trans*-**1f** (Table 1, entry 5; $s = 228$ vs entry 6; $s = 49$, respectively). Thus, it was concluded that the *cis*-configuration of the substrate plays an important role in attaining high selectivity. The broad generality of the reaction was established when the successful reaction of fused substrates was demonstrated (Table 1, entries 7–10). It is worth mentioning that these fused ones were frequently used as effective chiral building blocks for the synthesis of various natural products, such as brefeldin A.[10] In these reactions, it was observed that *endo* compounds exhibited a tendency to show higher selectivities than the corresponding *exo* isomers, regardless of the number of carbons in the fused rings (entries 7, 9 vs 8, 10). Furthermore, fused five-membered ring compounds gave better results than the corresponding six-membered fused systems (Table 1, entries 7, 8 vs 9, 10).

Unfortunately, not all substrates investigated provided such good results. Specifically, during the course of our investigation, we encountered difficulty with the racemic unsubstituted 2-hydroxy-γ-butyrolactone (±)-**1i** (Scheme 3). When treated under the optimized conditions, both the carboxylic ester (*R*)-**2i** and the recovered alcohol (*S*)-**1i** were obtained; however, pivalate **3** was also produced in 9% yield as a byproduct (eq 1). To avoid generation of **3**, the asymmetric acylation of (±)-**1i** with diphenylacetic anhydride (DPHAA)[11] was attempted instead of employing the dehydration condensation of (±)-**1i** with diphenylacetic acid. As a result, it was found that the

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(7) Shiina, I.; Nakata, K.; Ono, K.; Sugimoto, M.; Sekiguchi, A. *Chem.—Eur. J.* **2010**, *16*, 167.

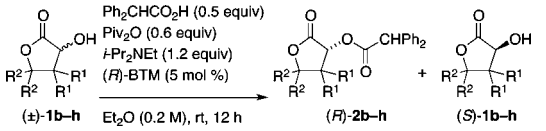
(8) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

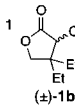
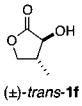
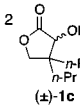
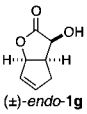
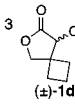
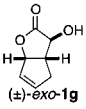
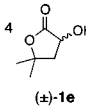
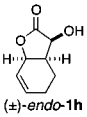
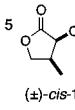
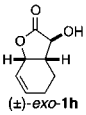
(9) Racemic compounds were prepared as follows: (a) Lubineau, A.; Augé, J.; Lubin, N. *Tetrahedron Lett.* **1991**, *32*, 7529. (b) Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* **1994**, *50*, 10265. (c) Effenberger, F.; Eichhorn, J.; Roos, J. *Tetrahedron: Asymmetry* **1995**, *6*, 271.

(10) (a) Grieco, P. A.; Henry, K. J.; Nunes, J. J.; Matt, J. E., Jr. *J. Chem. Soc. Chem. Commun.* **1992**, 368. (b) Carnell, A. J.; Casy, G.; Gorins, G.; Kompany-Saeid, A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3431. (c) Hibbs, D. E.; Hursthouse, M. B.; Knutsen, L. J. S.; Malik, K. M. A.; Olivo, H. F.; Roberts, S. M.; Varley, D. R.; Xiong, H. *Acta Chem. Scand.* **1995**, *49*, 122. (d) Olivo, H. F.; Yu, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3785. (e) Burlina, F.; Favre, A.; Fourrey, J.-L.; Thomas, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 247.

(11) Nakata, K.; Sekiguchi, A.; Shiina, I. *Tetrahedron: Asymmetry* **2011**, *22*, 1610.

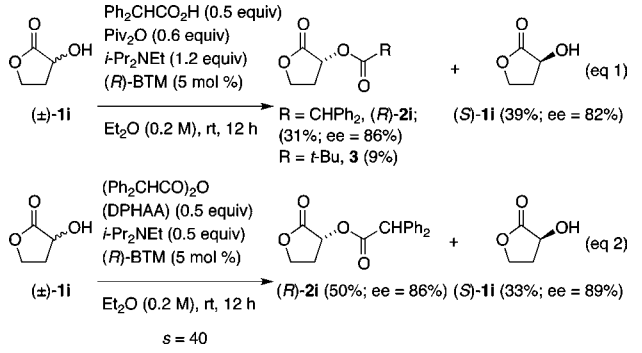
Table 1. Kinetic Resolution of 2-Hydroxylactones (±)-**1b**−**e**, (±)-*cis*, *trans*-**1f**, and (±)-*endo*, *exo*-**1g** and **h**



1	 (±)-**1b**	(*R*)-**2b** (50%; ee = 98%) (*S*)-**1b** (46%; ee = 99%) *s* = 552	6[a]	 (±)-*trans*-**1f**	(*R*)-*trans*-**2f** (43%; ee = 83%) (*S*)-*trans*-**1f** (48%; ee = 98%) *s* = 49
2	 (±)-**1c**	(*R*)-**2c** (48%; ee = >99%) (*S*)-**1c** (46%; ee = >99%) *s* = >1000	7	 (±)-*endo*-**1g**	(*R*)-*endo*-**2g** (40%; ee = 89%) (*S*)-*endo*-**1g** (41%; ee = 99%) *s* = 85
3	 (±)-**1d**	(*R*)-**2d** (44%; ee = 97%) (*S*)-**1d** (55%; ee = 96%) *s* = 313	8	 (±)-*exo*-**1g**	(*R*)-*exo*-**2g** (48%; ee = 85%) (*S*)-*exo*-**1g** (36%; ee = 95%) *s* = 45
4	 (±)-**1e**	(*R*)-**2e** (50%; ee = 87%) (*S*)-**1e** (50%; ee = 93%) *s* = 49	9	 (±)-*endo*-**1h**	(*R*)-*endo*-**2h** (40%; ee = 90%) (*S*)-*endo*-**1h** (52%; ee = 89%) *s* = 54
5	 (±)-*cis*-**1f**	(*R*)-*cis*-**2f** (45%; ee = 97%) (*S*)-*cis*-**1f** (38%; ee = 90%) *s* = 228	10	 (±)-*exo*-**1h**	(*R*)-*exo*-**2h** (45%; ee = 81%) (*S*)-*exo*-**1h** (52%; ee = 84%) *s* = 24

[a] Corresponding pivalate was obtained in ca. 6% yield.

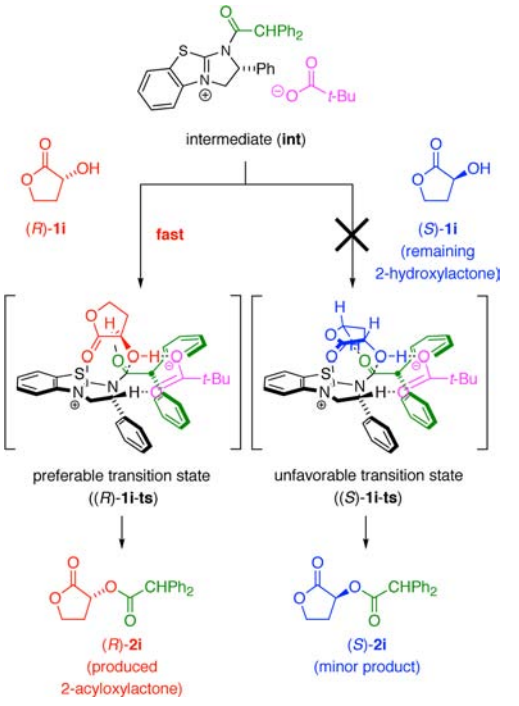
Scheme 3. Kinetic Resolution of Racemic 2-Hydroxy-γ-butyrolactone (±)-**1i** via Asymmetric Esterification (eq 1) and Acylation (eq 2)



chiral acylation system was useful for obtaining a good *s*-value ($s = 40$) without the production of pivalate **3** (eq 2).

Determination of the transition state forming the optically active 2-acyloxylactone (*R*)-**2i** from (*R*)-**1i** with the key intermediate (**int**) was carried out by using density functional theory (DFT) calculations at the B3LYP/6-31G*//B3LYP/6-31G* level according to the method previously reported (Scheme 4).[7,6b] The most stable transition state that produces (*R*)- or (*S*)-2-acyloxylactone is depicted in Figure 1.[12] It was found that the high selectivity

Scheme 4. Calculated Transition States of the Kinetic Resolution of (±)-**1i**



attained in the present kinetic resolution can be explained by the rapid transformation of (*R*)-**1i** into (*R*)-**2i** through the stabilized transition state (*R*)-**1i-ts**, which consists of (*R*)-**1i** and the dihydroimidazolium salt derived from the mixed anhydride and (*R*)-BTM. The distance of the forming C−O bond (between carbonyl carbon of the acid component and oxygen of hydroxy) is 2.159 Å, accompanied by the coordination of oxygen in the carbonyl moiety onto the hydrogen at the C-2 position of 2-hydroxylactone at a distance of 2.286 Å, as shown in Figure 1. It is further observed that the distance of the cleaved O−H bond (between oxygen and hydrogen in hydroxy) is 1.376 Å. A frequency analysis of (*R*)-**1i-ts** revealed that the nucleophilic attack of the alcohol to carbonyl group and the deprotonation of the hydroxyl group with the pivalate anion proceeded under the concerted reaction mechanism because the C−O bond-forming step and the O−H bond-cleaving process occurred synchronously. The lactone moiety has a rigid structure in which the conformation is restricted by the attractive interaction between oxygen in the ester carbonyl group and the positive electronic charge on the face of the dihydroimidazolium salt as well as the coordination of oxygens in the pivalate anion onto hydrogen in hydroxy (1.096 Å) and hydrogen at C-2 of the dihydroimidazolium salt (2.124 Å). On the other hand, complexation of the dihydroimidazolium salt with (*S*)-2-hydroxy-γ-butyrolactone ((*S*)-**1i**), an enantiomer of (*R*)-2-hydroxy-γ-butyrolactone ((*R*)-**1i**), produced an unstable structure, (*S*)-**1i-ts**, that has

(12) All calculations were performed with the program package Spartan '10 1.1.0 of Wavefunction Inc. (http://www.wavefun.com). Cartesian coordinates are included in the Supporting Information.

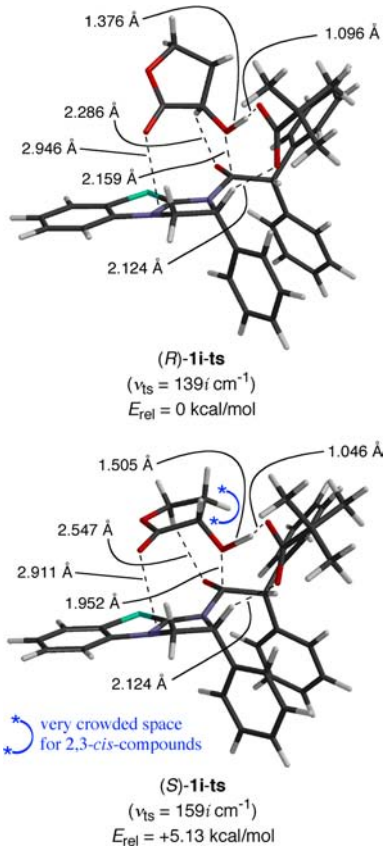


Figure 1. Three-dimensional structures of the calculated transition states ((*R*)-**1i-ts** and (*S*)-**1i-ts**).

a higher energy. The distance of the forming C−O bond is 1.952 Å (later transition state compared with (*R*)-**1i-ts**), accompanied by the coordination of oxygen in the carbonyl moiety onto the hydrogen at the C-4 position of 2-hydroxylactone at a distance of 2.547 Å, as shown in Figure 1. On the basis of theoretical calculations, it is certain that the desired chiral 2-acyloxylactone (*R*)-**2i** was selectively obtained by the rapid transformation of (*R*)-**1i** through the most stable transition state (*R*)-**1i-ts**, while the esterification of (*S*)-**1i** via (*S*)-**1i-ts** proceeded very slowly according to the energy gap of 5.13 kcal/mol.

It is assumed that very unfavorable transition states will be formed by the interaction of the dihydroimidazolium salt with (*S*)-**1a**, (*S*)-**1b**, (*S*)-**1c**, (*S*)-**1d**, (*S*)-*cis*-**1f**, (*S*)-*endo*-**1g**, and (*S*)-*endo*-**1h**, which have substituted groups at the C-3 positions with 2,3-*cis* configuration, to form the corresponding (*S*)-2,3-*cis*-2-acyloxylactones ((*S*)-**2a**, (*S*)-**2b**, (*S*)-**2c**, (*S*)-**2d**, (*S*)-*cis*-**2f**, (*S*)-*endo*-**2g**, and (*S*)-*endo*-**2h**) because of higher energies derived from steric repulsion between the alkyl substituents at the C-3 position with 2,3-*cis* configuration in (*S*)-2-hydroxylactones and one of the phenyl groups of diphenylacetic acid moiety of the dihydroimidazolium salt (see (*S*)-**1i-ts** in Figure 1). Therefore, the desired (*R*)-2,3-*cis*-2-acyloxylactones ((*R*)-**2a**, (*R*)-**2b**, (*R*)-**2c**, (*R*)-**2d**, (*R*)-*cis*-**2f**, (*R*)-*endo*-**2g**, and (*R*)-*endo*-**2h**) were predominantly obtained by the rapid transformation of (*R*)-2,3-*cis*-2-hydroxylactones into (*R*)-2,3-*cis*-2-acyloxylactones with excellent *s*-values ($s = 384$ for (±)-**1a**, $s = 552$ for (±)-**1b**, $s = >1000$ for (±)-**1c**, $s = 313$ for (±)-**1d**, $s = 228$ for (±)-*cis*-**1f**, $s = 85$ for (±)-*endo*-**1g**, and $s = 54$ for (±)-*endo*-**1h**) through the preferable transition states similar to (*R*)-**1i-ts**.

In summary, we have developed an efficient method for producing optically active 2-hydroxy-γ-butyrolactone derivatives via the kinetic resolution of racemic 2-hydroxy-γ-butyrolactones with diphenylacetic acid using pivalic anhydride and (*R*)-benzotetramisole ((*R*)-BTM) as a nucleophilic chiral acyl-transfer catalyst. Further studies of the present method, including application of this novel protocol for the production of other chiral materials, are currently in progress in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.