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Dynamic kinetic resolution of racemic tropic acid ethyl ester and its derivatives

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Abstract—The dynamic kinetic resolution of racemic mixtures of tropic acid ethyl ester under substrate racemizing conditions was studied using lipase PS with a ruthenium catalyst. Isopropenyl acetate was used as an acyl donor, since it was found to be compatible with both catalysts; this resulted in an efficient dynamic kinetic resolution. With this process, a variety of racemic tropic acid ethyl esters were transformed to optically active acetoxy-2-arylpropionic acid ethyl esters with 60–88% yields and 53–92% ee.
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(*S*)-(−)-Tropic acid is an important building block for biologically active tropane alkaloids, such as hyoscyamine and scopolamine[1] (Fig. 1). The use of these alkaloids has its roots in ancient times and they continue to be valuable drugs in the pharmaceutical field. Scopolamine is used as an anesthetic during surgery, for treatment of mental illness and as a vomiting inhibitor.[2] Hyoscyamine is used to treat cardiacarythmia and also as an anesthetic.[3] Motofen,[4] which contains difenoxin hydrochloride and atropine sulfate, is used as adjunctive therapy in the management of acute diarrhea. Atrovent[5] is used to treat chronic bronchitis and emphysema. Furthermore, the presence of the two functional groups (alcohol and ester) in the tropic acid greatly aids in the further modification of the molecule, thus permitting several important derivatives to be made from this single chiral building block. Given there are many important uses for chiral tropic acid, an efficient method for synthesizing this compound is greatly desired.

Recently, we have reported the first lipase-catalyzed kinetic enzymatic resolution of tropic acid ethyl ester and its derivatives in high yield and with excellent % ee (Scheme 1).[6] Kinetic resolution is generally defined as a process, where the two enantiomers of the racemic mixture are transformed into products at different rates.[7,8] Therefore, in an efficient enzymatic resolution one of the enantiomers of the racemate is selectively transformed to product, whereas the other is left behind. During a kinetic resolution process, the maximum yield of the desired enantiomer (starting from a racemate)[7–9] is 50%. This aspect tends to make kinetic resolution a costly process since half of the material must be discarded or recycled. To overcome this limitation, the dynamic kinetic resolution (DKR) process allows for the complete transformation of a racemic mixture into a single enantiomer. Essentially, the DKR process comprises kinetic resolution with an additional feature: in situ racemization of the starting material, which is usually achieved via chemocatalaysis[8–11] As a result, it is possible to obtain the desired isomer in yields approaching 100%.

DKR is a well investigated area, in particular, with racemic secondary alcohols where the hydroxy group is bound to a stereogenic carbon center.[7–10] In this Letter, we report the first successful dynamic kinetic resolution of a racemic primary alcohol (tropic acid ethyl ester) and its derivatives via enzymatic acylation and catalytic racemization.

Since metal catalysts have been effectively used for racemization of enantiomers during kinetic resolution by enzymes, we decided to use this same approach in our DKR method. Thus we used the most effective complex hydrogen[7–9,11,12] transfer metal catalyst **1** (Scheme 2) for racemization of optically pure tropic acid ester. Catalyst **1** was readily synthesized by a known procedure.[8–13] Preliminary experiments indicated that chiral tropic acid ethyl ester **2a** undergoes complete racemization in 24 h by the metal catalyst (substrate to catalyst ratio is 50–1). Although the mechanistic details

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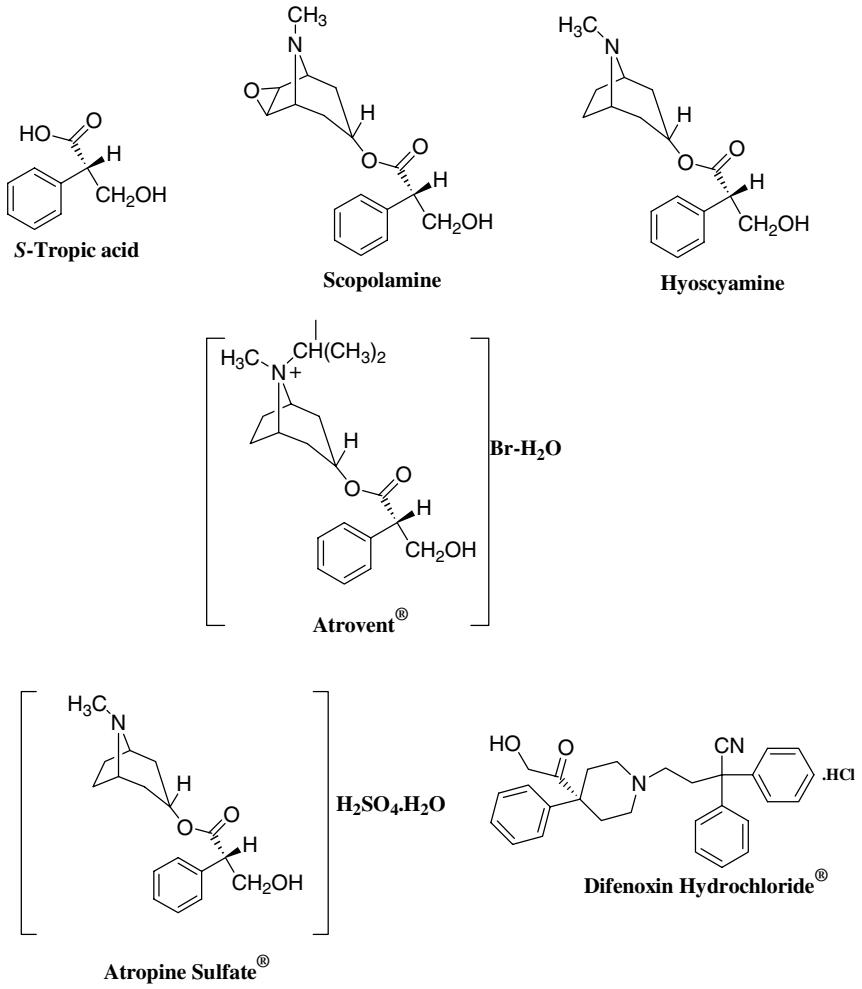
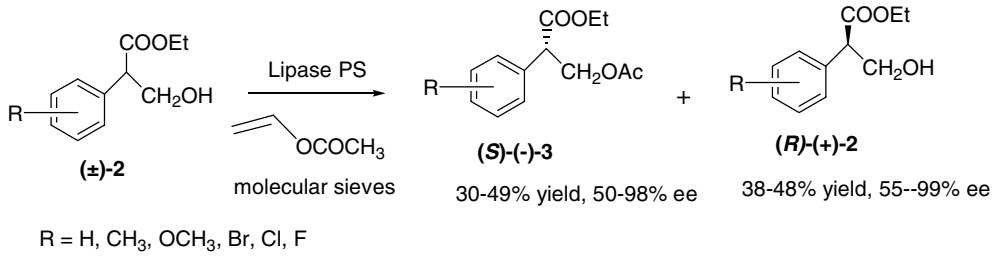


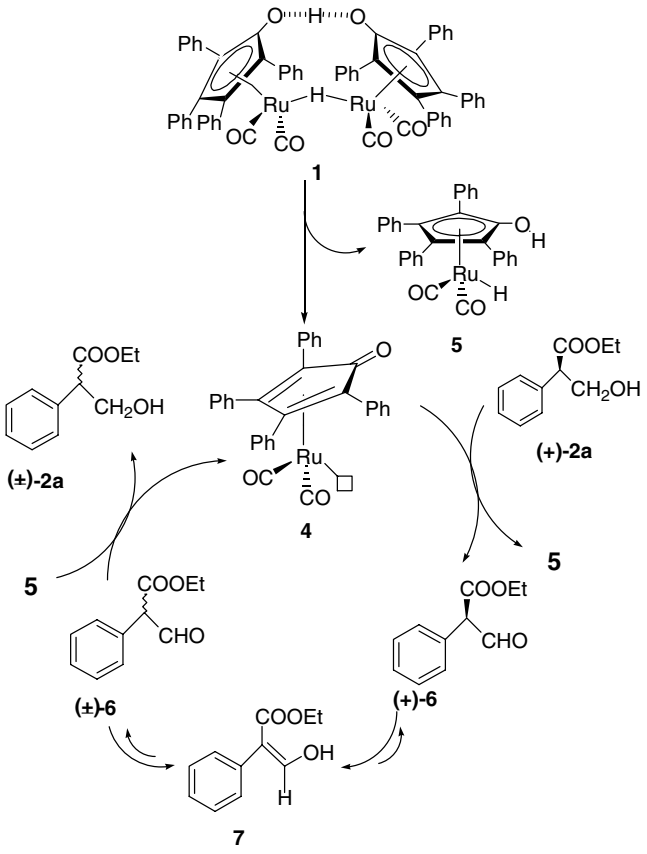
Figure 1.



Scheme 1.

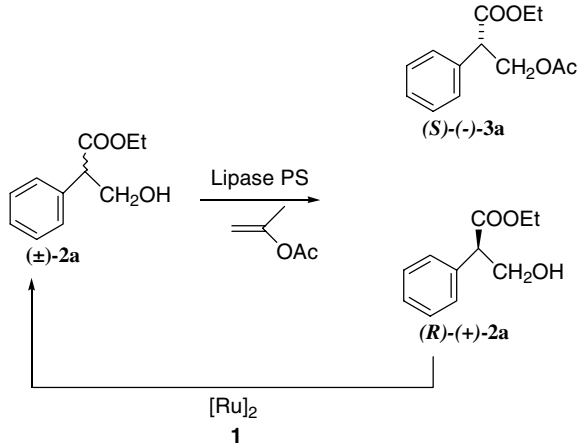
concerning the racemization of tropic acid ethyl ester are not fully studied, based on studies done by Casey,[13] Bäckvall[10e] and Shvo[12a] on hydrogen transfer reactions involving catalyst **1**, we propose the mechanism outlined in Scheme 2. We think, first catalyst **1** dissociates to form the active catalyst **4** and ruthenium hydride complex **5**. The active catalyst **4** then dehydrogenates the tropic acid ethyl ester to form **6**, which readily undergoes tautomerization to give 3-hydroxy acrylate **7**. Acrylate **7** undergoes reduction (via aldehyde) by metal complex **5** to give the racemic tropic acid ethyl ester and regenerates catalyst **4** (Scheme 2).

After screening several acylating reagents,[8,14,15] we have chosen isopropenyl acetate as an acyl donor since it gave the best results. The common acylating agent, vinyl acetate inhibits the activity of the metal catalyst by forming acetaldehyde during the acylation step which unfortunately competes with the oxidized substrate during hydrogenation.[7,14] Whereas the use of isopropenyl acetate from which acetone is formed in the acylation step[7,14] showed a similar trend, but to a much lower extent than vinyl acetate. Finally, the combination of catalyst **1** with the lipase PS and isopropenyl acetate as an acyl donor was selected for the DKR of the tropic acid



Scheme 2.

ethyl ester. Under these conditions, the racemic tropic acid ethyl ester is resolved to (*S*)-3-acetoxy-2-phenyl-propionic acid ethyl ester **3a** and (*R*)-tropic acid ethyl ester **2a**. At the same time, (*R*)-**2a** enantiomer undergoes racemization by catalyst **1** (Scheme 3) and is subsequently resolved again until all the remaining tropic acid ethyl ester is consumed. To a solution of (±)-**2a** (58.274 mg, 0.30 mmol) in dry toluene (6 mL) under argon, ruthenium catalyst **1** (24.5 mg, .018 mmol) and lipase PS (65 mg) on celite support (10 mg) were added along with isopropenyl acetate (120 mg, 1.20 mmol.). The resulting reaction mixture was bubbled with argon



Scheme 3.

for 5 min and stirred at 40–45 °C for 24 h under argon. The enzyme was then filtered off and washed with toluene (3 × 5 mL). The toluene phases were combined and the solvent was removed under reduced pressure, and the product was purified by flash chromatography (pentane/ethyl acetate, 95/5) to yield 62.37 mg, 0.264 mmol (88% yield) of 3-acetoxy-2-phenyl propionic acid ethyl ester **3a** (90% ee) (Table 1, entry 1).

After successfully resolving the tropic acid ethyl ester in high yield and high ee, various tropic acid ethyl ester

Table 1. Kinetic resolution of (±)-**2** tropic acid ethyl esters (primary alcohol) with Lipase PS on Celite support coupled with ruthenium-catalyzed racemization

Substrate	Product	Yield (%)	% ee of (*S*)-(−)
2a	**3a**	88	90[a]
2b	**3b**	75	92[a]
2c	**3c**	75	95[a]
2d	**3d**	73	80[a]
2e	**3e**	84	61[b]
2f	**3f**	70	81[a]
2g	**3g**	60	53[b]
2h	**3h**	68	72[b]

[a] The % ee was determined by analysis of the ^{1}H NMR spectrum of its (*R*)-(−)-α-methoxyphenyl acetic acid derivative as described in our earlier paper.[6]

[b] % ee was determined from optical rotation using known reported values.[6]

derivatives **2b**–**h**[6] were subjected to the DKR reaction conditions in order to investigate the scope of this process (Table 1). In all cases, racemic substrates **2b**–**h** were completely consumed, and chiral products were isolated in good to high yields (Table 1). In addition, the enantioselectivities for the product were generally high and similar to those reported from our kinetic resolution process.[6]

It is noteworthy to mention that our process is simple; no external hydrogen source is needed for very good to excellent yields and ee %. In most DKR methods involving chiral secondary alcohols, an external hydrogen source is used to enhance yields and enantioselectivies.[10,12] In addition, most of these the DKR proceses were carried out at higher temperatures (60–80 °C) to speed up the racemization step.[10,12] Our DKR process eliminates the need for an external hydrogen source or higher temperature to obtain very good yields of products. One reason for the overall simplicity of our DKR process may lie in the use of a more reactive primary alcohol (easier to dehydrogenate than secondary alcohol) and formation of an aldehyde (easier to hydrogenate than ketone). Further studies using different hydrogen donors at different temperatures in order to optimize yields and enatioselectivities of this DKR process are underway.

In conclusion, we have demonstrated that a ruthenium catalyst in combination with enzymatic acylation, results in racemization and a full transformation of tropic acid ester (primary alcohol) **2a**–**i** to 3-acetoxy-2-phenyl propionic acid ethyl ester **3a**–**i** in good yield and good % ee. Currently, we are working to convert these chiral 3-acetoxy-2-phenyl propionic acid esters into chiral 2-aryl propionic acids. Many of these chiral 2-aryl propanoic acids such as ibuprofen and naproxen are important non-steroidal anti-inflamatory drugs (NSAIDs).[16]

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References and notes

1. (a) Leete, E. *J. Am. Chem. Soc.* **1960**, *82*, 612; (b) Hamon, N. W.; Eyolfson, J. L. *J. Pharm. Sci.* **1972**, *61*, 2006; (c) Leete, E.; Kowanko, N.; Newmark, A. R. *J. Am. Chem. Soc.* **1975**, *97*, 6826.
2. Glasby, J. S. In *Encyclopedia of the Alkaloids*; Plenum: New York, 1975; Vol. 1, p 731.
3. (a) Conklin, M. E. In *Genetic and Biochemical Aspects of the Development of Datura*; Karger S: London, 1976; Vols. 1–3, p 118; (b) Roberts, M. F.; Wink, M. In *Alkaloids: Biochemistry, Ecology and Medicinal Applications*; Plenum: New York, 1998; Vol. 117, p 145.
4. *Physician's Desk Reference*, 56th ed.; 2002; p 1993.
5. *Physician's Desk Reference*, 56th ed.; 2002; p 1030.
6. Atuu, M. R.; Mahmood, S. J.; Laib, F.; Hossain, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3091.
7. (a) Serra, S.; Brenna, E.; Fuganti, C.; Maggioni, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3313; (b) Kawanami, Y.; Itoh, K. *Chem. Lett.* **2005**, *34*, 682; (c) Ferraboschi, P.; Rezaelahi, S.; Verza, E.; Santaniello, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2193; (d) Balint, J.; Kiss, V.; Egri, G.; Kalai, T.; Demeter, A.; Balog, M.; Fogassy, E.; Hideg, K. *Tetrahedron: Asymmetry* **2004**, *15*, 671; (e) Morrone, R.; Piatttelli, M.; Nocolosi, G. *Eur. J. Org. Chem.* **2001**, 1444; (f) Levy, L. M.; Dehli, J. R.; Gotor, V. *Tetrahedron: Asymmetry* **2003**, *14*, 2053.
8. (a) Kiebasiñski, P.; Omelanczuk, J.; Mikolaczyk, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3283; (b) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249; (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5; (d) Choi, Y.-K.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373; (e) Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M. J. *J. Org. Chem.* **1999**, *64*, 8423; (f) Morgan, B.; Bydlinky, G.; Dodds, D. R. *Tetrahedron: Asymmetry* **1995**, *6*, 1765; (g) Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *121*, 1645; (h) Kirchner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072; (i) Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 107.
9. (a) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *10*, 1021; (b) Koh, H. J.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545; (c) Garcia, M.; del Campo, C.; Llama, E. F.; Sanchez-Montero, J. M.; Sinisterra, J. V. *Tetrahedron* **1993**, *49*, 8433; (d) Lee, D.; Huh, E. A.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 2377; (e) Huerta, F.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 1209; (f) Chowdbury, R. L.; Bäckvall, J.-E. *Chem. Commun.* **1991**, 1063.
10. (a) Almeida, M. L. S.; Kocovsky, P.; Bäckvall, J.-E. *J. Org. Chem.* **1996**, *61*, 6587; (b) Pàmies, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130; (c) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1261; (d) Larsson, A. L. E.; Persson, B. A.; Ray, M. L.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **1997**, *36*, 1211; (e) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 9006; (f) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 2487.
11. (a) Sorgedrager, M. J.; Malpique, R.; Rantwijk, F. V.; Sheldon, R. *Tetrahedron: Asymmetry* **2004**, *15*, 1295; (b) Ji, A.; Wolberg, M.; Hummel, W.; Wandrey, C.; Muller, M. *Chem. Commun.* **2001**, 57.
12. (a) Shvo, Y.; Czarkie, D.; Rahamin, Y.; Chodosh, D. F. *J. Am. Chem. Soc.* **1986**, *108*, 7400; (b) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885; (c) Kim, M. J.; Choi, Y. K.; Choi, M. Y.; Park, J. *J. Org. Chem.* **2001**, *66*, 4736; (d) Riermeier, T. H.; Gross, P.; Monsees, A.; Hoff, M.; Trauthwein, H. *Tetrahedron Lett.* **2005**, *46*, 3403.
13. Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090.
14. (a) Veum, L.; Hanefeld, U. *Tetrahedron: Asymmetry* **2004**, *15*, 3707; (b) Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695; (c) Wang, Y. W.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200.
15. (a) Verzijl, G. K. M.; de Vries, J. G.; Broxterman, Q. B. *Tetrahedron: Asymmetry* **2005**, *16*, 1603; (b) Choi, J. H.; Kim, M.-J.; Nam, S. H.; Shin, S. T.; Kim, Y. H.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373.
16. (a) Sehgal, A. C.; Kelly, R. M. *Biotechnol. Prog.* **2003**, *19*, 1410; (b) Chang, C.-S.; Tsai, S.-W.; Lin, C.-N. *Tetrahedron: Asymmetry* **1998**, *9*, 2799; (c) Kumar, I.; Manju, K.; Jolly, R. S. *Tetrahedron: Asymmetry* **2001**, *12*, 1431; (d) Giordano, C.; Castaldi, G.; Uggeri, F. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413; (e) Shen, T. Y. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 460.