ORGANIC LETTERS

2010
Vol. 12, No. 15
3498−3501

Straightforward Synthesis of Enantiopure 2,3-Dihydrobenzofurans by a Sequential Stereoselective Biotransformation and Chemical Intramolecular Cyclization

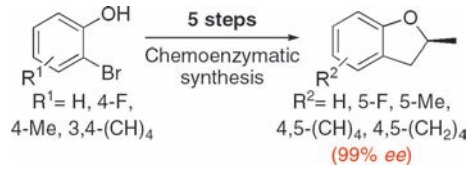
Juan Mangas-Sánchez, Eduardo Busto, Vicente Gotor-Fernández,* and Vicente Gotor*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo, E-33006 Spain

vicgotfer@uniovi.es; vgs@fq.uniovi.es

Received June 10, 2010

ABSTRACT



A new family of optically active 2,3-dihydrobenzofurans has been prepared by a simple chemoenzymatic asymmetric strategy. This synthetic approach is based on the combination of a lipase-mediated kinetic resolution of 1-aryl-2-propanols or bioreduction of the corresponding ketones followed by an intramolecular cyclization reaction. These novel compounds have been prepared in enantiopure form and in good overall yield through a straightforward route.

Furan derivatives constitute a versatile class of heterocycles because of their presence in many biologically active compounds and their applications in a wide range of chemical transformations.[1] Among them, 2,3-dihydrobenzofurans are an attractive type of oxygenated organic compound since its basic skeleton is present in serotobenine, darifenacin, corsifuran A, or (−)-ephedadrine A, substrates with remarkable biological properties. A series of nonstereoselective[2] and stereoselective chemical syntheses of this class of materials have been reported in the literature,[3] chemoenzymatic methods scarcely being reported for the preparation of 2,3-dihydrobenzofuran.[4]

Here we first report an exhaustive enzymatic study for the production of adequate alcohol intermediates in the synthesis of 2,3-dihydrobenzofurans, which will be later used in intramolecular cyclization reactions to obtain a wide family of enantiopure 2,3-dihydrobenzofurans.

(1) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Durani, N.; Jain, R.; Saeed, A.; Dikshit, D. K.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1989**, *32*, 1700. (c) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67. (d) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *33*, 3838.

(2) See for example: (a) Chow, Y. L.; Zhou, X.-M.; Gaitan, T. J.; Wu, Z.-Z. *J. Am. Chem. Soc.* **1989**, *111*, 3813. (b) Bernard, A. M.; Cocco, M. T.; Onnis, V.; Oiras, P. P. *Synthesis* **1997**, 41. (c) Zulfikar, F.; Kitazume, T. *Green Chem.* **2000**, *2*, 296. (d) Tsukada, N.; Yagura, Y.; Sato, T.; Inoue, Y. *Synlett* **2003**, 1431. (e) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (f) Reich, N. W.; Yang, C.-G.; Shi, Z; He, C. *Synlett* **2006**, 1278. (g) Ohta, T.; Kataoka, Y.; Miyoshi, A.; Oe, Y.; Furukawa, I.; Ito, Y. *J. Organomet. Chem.* **2007**, *692*, 671.

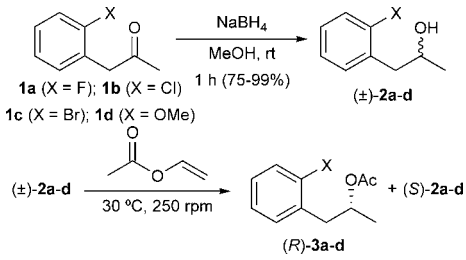
(3) See, for example: (a) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068. (b) Petit, F.; Furtoss, R. *Synthesis* **1995**, 1517. (c) Enders, D.; Vázquez, J.; Raabe, G. *J. Chem. Soc., Chem. Commun.* **1999**, 701. (d) Engler, T. A.; Letavic, M. A.; Iyengar, R.; La Tessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391. (e) Garzino, F.; Méou, A.; Brun, P. *Tetrahedron Lett.* **2000**, *41*, 9803. (f) Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202. (g) Garzino, F.; Méou, A.; Brun, P. *Eur. J. Org. Chem.* **2003**, 1410. (h) Kurosawa, W.; Kan, T.; Fukuyama, T. *Synlett* **2003**, 1028. (i) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194. (j) Chuang, C.-P.; Tsai, A.-I. *Synthesis* **2006**, 675. (k) Chuang, C.-P.; Chen, K.-P.; Hsu, Y.-L.; Tsai, A.-I.; Liu, S.-T. *Tetrahedron* **2008**, *64*, 7511. (l) Adams, H.; Gilmore, N. J.; Jones, S.; Muldowney, M. P.; von Reuss, S. H.; Vemula, R. *Org. Lett.* **2008**, *10*, 1457.

(4) Itoh, T.; Kawai, K.; Hayase, S.; Ohara, H. *Tetrahedron Lett.* **2003**, *44*, 4081.

10.1021/ol101336y
Published on Web 07/15/2010

Taking advantage of the high stereodiscrimination shown by enzymes[5] and the fact that resolution of racemic mixtures is probably the most common technique used in the industrial sector for the preparation of enantiomerically pure compounds,[6] we have considered the kinetic resolution of (±)-**2a**−**d**, compounds easily prepared by chemical reduction of commercially available ketones **1a**−**d** using sodium borohydride in MeOH (Scheme 1). The chemical reduction processes proceed smoothly obtaining the racemic 1-aryl-2-propanols **2a**−**d** in good to excellent yields after 1 h. This simple chemical reaction is a more efficient alternative than the previous synthesis reported for this family of alcohols.[3f,7]

Scheme 1. Chemical Synthesis and Lipase-Mediated Kinetic Resolution of Racemic Alcohols **2a**−**d**



Then, after a preliminary screening of enzymatic activity, we found *Pseudomonas cepacia* lipase (PSL-C I), also known as *Burkholderia cepacia* lipase, as the most efficient biocatalyst for the asymmetric preparation of (*R*)-acetates **3a**−**d** and (*S*)-alcohols **2a**−**d** (Table 1). In the lipase-mediated acetylation, stereochemistries were in accordance with Kazlauskas' rule[8] and previous enzymatic studies carried out with **2d**.[9] Vinyl acetate was used as adequate irreversible acyl donor, observing moderate enantioselectivity values when halogen atoms were present in the 2-position of the phenyl ring (F, Cl, and Br). PSL-C I allowed the recovery of the (*R*)-acetates **3a**−**d** up to 89% ee in all cases (entries 1, 2, 4, and 6), obtaining the best results with the methoxy derivative **2d**. In general, CAL-B showed lower stereopreference values, although in the case of compounds **2b**,**c** (X = Cl and Br, entries 3 and 5) made possible the recovery of the (*S*)-alcohols in nearly enantiopure form (96−99% ee).

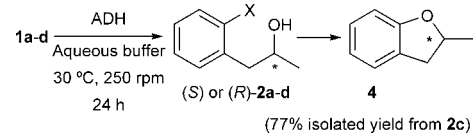
Table 1. Lipase-Mediated Kinetic Resolutions of Alcohols (±)-**2a**−**d** Using 3 equiv of Vinyl Acetate in THF at 30 °C and 250 rpm

entry	lipase	X	t (h)	ee_P (%)[a]	ee_S (%)[a]	c (%)[b]	E[c]
1	PSL-C I	F	6	89	95	52	61
2	PSL-C I	Cl	4	95	55	37	72
3	CAL-B	Cl	8	71	96	58	22
4	PSL-C I	Br	8	89	95	51.5	65
5	CAL-B	Br	8	67	>99	60	36
6	PSL-C I	OMe	9	95	>99	51.5	>200

[a] Determined by HPLC. [b] $c = ee_S/(ee_S + ee_P)$. [c] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.[10]

Additionally, bioreduction processes offer a new alternative for the production of enantiopure alcohols, particularly substituted 1-phenylpropan-2-ols.[7,11] To examine the scope of this methodology, ketones **1a**−**d** were stereoselectively reduced using a set of alcohol dehydrogenases (ADH): T, LB, CP, PR2, RS1, and A (Scheme 2). The best results are summarized in Table 2.

Scheme 2. Bioreduction of Ketones **1a**−**d** Followed by Intramolecular Cyclization to Afford 2,3-Dihydrobenzofuran **4**



From all of the ADH tested, T, CP, RS1, and A led to the production of the (*S*)-alcohols; meanwhile, LB and PR2 allowed the isolation of the complementary (*R*)-alcohols (see also Table S4 in the Supporting Information). In general, ADH CP and ADH A acted with higher levels of stereopreference toward the formation of (*S*)-**2a**−**d**, observing slightly higher activity values for ADH A. Comparing both lipase-catalyzed and bioreduction processes we can conclude that meanwhile the classical kinetic resolution of alcohols (±)-**2a**−**d** allows the recovery of both alcohol and acetate of opposite configurations in good to excellent optical purities, and these biotransformations are limited to a maximum 50% isolated yield. In contrast, the bioreductions have led to the isolation of the (*S*)-alcohols in enantiopure form and quantitative yield, although any of the ADH tested has allowed the recovery of enantiopure (*R*)-alcohols up to 43% yield (see Table S4 in the Supporting Information). For all the above reasons, bioreduction and lipase-catalyzed resolutions can be considered as ideal complementary tools for the production of enantiomerically pure compounds.

To examine the synthetic possibilities of the resulting enantiopure alcohols, (*S*)-**2a**−**d** were reacted in different

(5) (a) *Asymmetric Organic Synthesis with Enzymes*; Gotor, V., Alfonso, I., García-Urdiales, E., Eds.; Willey-VCH: Weinheim, 2008. (b) *Organic Synthesis with Enzymes in Non-Aqueous Medium*; Carrea, G., Riva, S., Eds.; Willey-VCH: Weinheim, 2008. (c) Fessner, W.-D.; Anthonsen, T. *Modern Biocatalysis. Stereoselective and Environmentally Friendly Reactions*; Wiley-VCH: Weinheim, 2009. (d) Hudlicky, T.; Reed, J. W. *Chem. Soc. Rev.* **2009**, *38*, 3117.

(6) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kebeler, M; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.

(7) (a) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Harwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (b) Shimizu, H.; Saito, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2003**, *345*, 185. (c) Erdélyi, B.; Szabó, A.; Seres, G.; Birincsik, L.; Ivanics, J.; Szatzker, G.; Poppe, L. *Tetrahedron: Asymmetry* **2006**, *17*, 268.

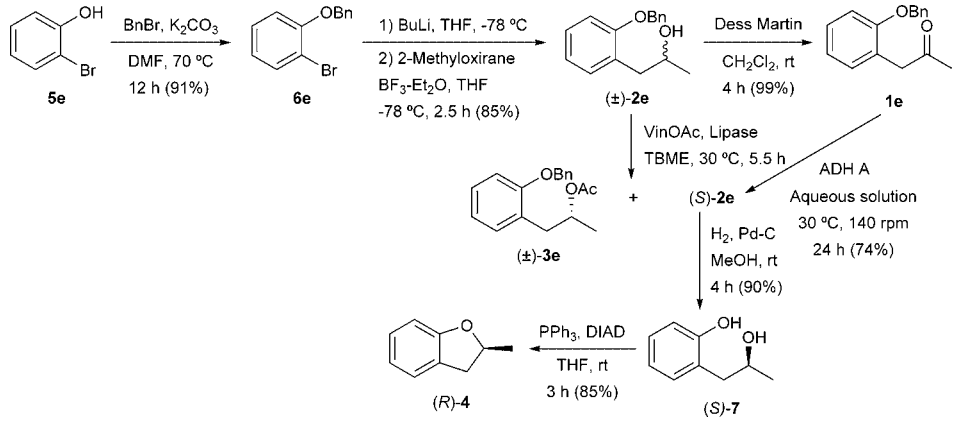
(8) Kazlauskas, R. J.; Weissfoch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.

(9) Ema, T.; Yoshii, M.; Korenaga, T.; Sakai, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1223.

(10) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

(11) Schubert, T.; Kula, M.-R.; Müller, M. *Synthesis* **1999**, 2045.

Scheme 3. Chemoenzymatic Synthesis of 2,3-Dihydrobenzofuran (*R*)-**4a** from Commercially Available 2-Bromophenol (**5e**)



conditions to obtain the corresponding (*S*)-2-methyl-2,3-dihydro-1-benzofuran (**4**).[12] It must be mentioned that for (*S*)-**2d** a previous deprotection of the methoxy group is needed for the intramolecular coupling. Unfortunately, in all the experimental conditions tested, racemization occurred in a high extension. The best results were obtained when using the brominated derivative (*S*)-**2c** and a combination of sodium hydride and copper(I) chloride in refluxing toluene, yielding a complete conversion into the desired benzofuran in 77% isolated yield without any loss of the optical purity.[13] Unfortunately, the lack of access to valuable precursors for the preparation of substituted 1-(2-bromophenyl)propan-2-ols made us focus on an alternative synthetic route.

To overcome these limitations and try to increase the isolated yields, we move forward to the development of the synthesis and enzymatic kinetic resolution of a more versatile racemic intermediate, 1-2-(benzyloxy)phenyl-propan-2-ol (**2e**). To achieve this aim, 2-bromophenol (**5e**) was smoothly protected in the presence of benzyl bromide and potassium carbonate yielding **6e**,[14] which was subsequently reacted with BuLi and 2-methyloxirane in the presence of a Lewis acid, obtaining the desired (±)-**2e** in high overall yield (Scheme 3). Two different approaches were considered for the production of enantiopure (*S*)-**2e**: (a) lipase-mediated acetylation of its free hydroxyl group, which occurred with an excellent selectivity when PSL was used as biocatalyst (the results will be analyzed later in the manuscript, see Table 3) and (b) bioreduction of ketone **1e**, obtained by chemical oxidation of alcohol **2e** using the Dess−Martin reagent, which procceded with an excellent stereopreference with ADH A toward the production of (*S*)-**2e** in 74% yield (see Table S4 in the Supporting Information).

Cleavage of the benzyl group by palladium-catalyzed hydrogenation reaction of (*S*)-**2e** in MeOH led to diol (*S*)-**7** in 92% isolated yield. Then, final intramolecular cyclization in Mitsunobu conditions[15] using triphenylphosphine and diisopropyl azodicarboxylate (DIAD) allowed the recovery of the benzofuran (*R*)-**4** in enantiopure form and with good overall yield.

Table 2. Bioreduction of Ketones **1a**−**d** at 30 °C and 250 rpm during 24 h Using ADH CP and ADH A[a]

entry	ADH	X	*c* (%)[b]	ee$_P$ (%)[c]
1	CP	F	99	>99
2	A	F	99	>99
3	CP	Cl	97	>99
4	A	Cl	99	>99
5	CP	Br	92	>99
6	A	Br	99	>99
7	CP	OMe	95	>99
8	A	OMe	98	>99

[a] See Supporting Information for individual conditions. [b] Conversion value determined by GC of the reaction crude. [c] (*S*)-Alcohols **2a**−**d** were obtained. The ee was determined by HPLC or GC.

To examine the scope of this synthetic methodology, we decided to extend these studies toward the stereoselective preparation of a set of optically active benzofurans from conveniently substituted benzene derivatives. This general synthetic strategy has been outlined in Scheme 4 and is based on the preparation of the corresponding benzylic alcohols **2f**−**h** that could be enzymatically resolved and later transformed into the desired benzofurans (*R*)-**13**−**15**.

Initially, the starting methoxy compounds **8f**−**h** were chemically deprotected using boron tribromide in dichloromethane to afford phenols **5f**−**h** in quantitative yield, protecting next their free hydroxyl group with benzyl

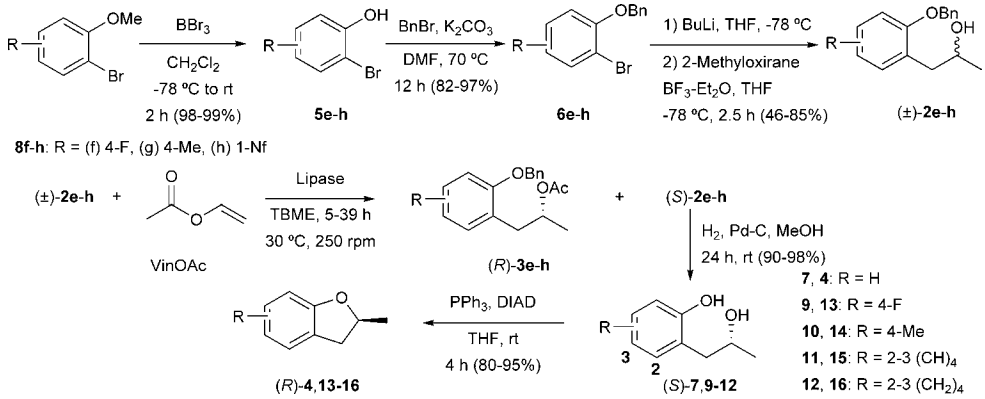
(12) (a) Grundon, M. F.; Stewart, D.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1973**, 573. (b) Saiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194. (c) Zhang, L.; Zhang, W.; Liu, J.; Hu, J. *J. Org. Chem.* **2009**, *74*, 2850.

(13) To assure that no racemization occurred during the process, the racemic furan derivative **4** was also prepared. Both optically active and racemic **4** were injected in the HPLC using a chiral column, finding clear evidence of no racemization during the proccess as it is shown in the Supporting Information.

(14) Thede, K.; Diedrichs, N.; Ragot, J. P. *Org. Lett.* **2004**, *6*, 4595.

(15) Prakash, G. K, S.; Do, C.; Wang, F.; Mathew, T.; Olah, G. A. *Synthesis* **2010**, 1891.

Scheme 4. Chemoenzymatic Synthesis of 2,3-Dihydrobenzofurans (*R*)-**13**−**16** from Commercially Available **8f**−**g**



bromide in the presence of potassium carbonate, to afford **6f**−**h** in good to excellent yield.[16] These compounds were subsequently reacted with BuLi and 2-methyloxirane obtaining the racemic alcohols **2f**−**h** in moderate to good yields, substrates used in the subsequent lipase-mediated kinetic resolution experiments. The best results have been summarized in Table 3, and it is important to stress that in all cases alcohols (*S*)-**2e**−**h** or acetates (*R*)-**3e**−**h** have been obtained in enantiopure form by using CAL-B or PSL-C I as biocatalyst in TBME as solvent, 3 equiv of vinyl acetate as acyl donor, and 30 °C. Depending on the reactivity of each individual substrate, we have modified the amount of enzyme aiming to stop the reactions closer to 50% conversion value, yielding both substrate and product in excellent enantiomeric excesses.

PSL-C I showed an excellent selectivity toward alcohol **2e**, achieving the best stereocontrol when using a substrate:enzyme ratio of 1:0.5 to achieve in 9 h the isolation of both alcohol and acetate in up to 96% ee (entry 4). However, the introduction of substituents in the phenyl ring has led to a dramatic decrease in the reaction rate (for **2f**,**g**, entries 7, 8, and 11) or in the enantioselectivity (for **2h**, entry 13) shown by PSL-C I. The best results for alcohols **2f**−**h** were found with CAL-B by using a substrate:enzyme ratio of 1:0.5 for **2f**,**g** (entries 6 and 10); meanwhile, **2h** which possesses a more hindered substitution need longer reaction rates and higher loading of biocatalyst (entry 12).

Finally, the alcohols (*S*)-**2f**−**h** were reacted under the previously optimized reaction conditions for (*S*)-**2e**; that means palladium-catalyzed hydrogenation to remove the benzyl group affording (*S*)-**9**-**11**, which was subjected to an intramolecular cyclization reaction under Mitsunobu conditions to isolate optically active 2,3-dihydrobenzofurans (*R*)-**13**−**15** in good overall yield. It must be mentioned that at higher palladium loading the hydrogenation of the benzofusionated phenyl ring of (*S*)-**2h** was observed, leading to the formation of diol (*S*)-**12**, an adequate precursor for the syntheis of benzofuran (*S*)-**16**. Thus, a general chemoenzymatic strategy has been developed for the synthesis of a wide family of 2,3-dihydrobenzofurans.

Table 3. Lipase-Mediated Kinetic Resolution of (±)-**2e**−**h** in TBME Using 3 equiv of VinOAc at 30 °C and 250 rpm

entry	**2e**−**h**	lipase	*t* (h)	ee$_P$ (%)[a]	ee$_S$ (%)[a]	*c* (%)[b]	*E*[c]
1	**2e**	CAL-B[d]	5.5	81	94	56	33
2	**2e**	CAL-B[e]	5	92	91	50	70
3	**2e**	PSL-C I[d]	5.5	97	81	48	176
4	**2e**	PSL-C I[e]	9	96	>99	50	>200
5	**2f**	CAL-B[d]	3	98	95	49	>200
6	**2f**	CAL-B[e]	5	97	>99	50	>200
7	**2f**	PSL-C I[d]	5	>99	25	20	>200
8	**2f**	PSL-C I[e]	7	>99	24	19	>200
9	**2g**	CAL-B[d]	15	92	>99	52	179
10	**2g**	CAL-B[e]	5.5	99	>99	50	>200
11	**2g**	PSL-C I[d]	15	99	32	24	>200
12	**2h**	CAL-B[d]	39	99	>99	50	>200
13	**2h**	PSL-C I[d]	15	97	9	9	72

[a] Determined by HPLC. [b] Conversion value: $c = ee_S/(ee_S + ee_P)$. [c] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.[10] [d] Ratio substrate:enzyme (1:1). [e] Ratio substrate:enzyme (1:0.5).

In summary, we have developed a new access to a novel family of enantiomerically pure benzofurans by means of an asymmetric enzymatic process followed by an intramolecular chemical cyclization reaction. This system here developed opens a new window of research for the synthesis of related oxygenated and nitrogenated heterocyclic compounds in a stereoselective fashion.

Acknowledgment. This work has been supported by the Spanish Ministry of Science and Innovation (MICINN, CTQ 2007-61126). V. G.-F. (Ramón y Cajal Program) and J. M.-S. (FPU fellowship) thank also MICINN for personal funding.

Supporting Information Available: General methods, experimental procedures, characterization data for new compounds, and copies of ^{1}H, ^{13}C, and DEPT NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101336Y

(16) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430.