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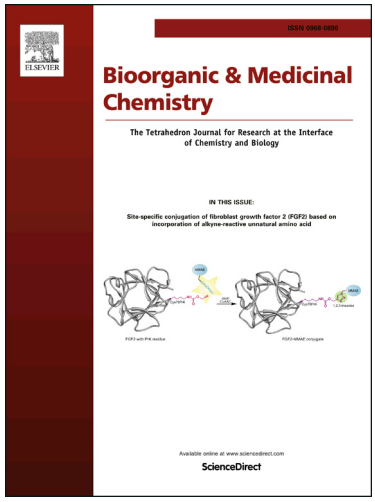

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Lipase-catalyzed asymmetric synthesis of naphtho[2,3-*c*]furan-1(3*H*)-one derivatives by a one-pot dynamic kinetic resolution/intramolecular Diels–Alder reaction: Total synthesis of (–)-himbacine

Koji Sugiyama[a], Shinji Kawanishi[a], Yasuhiro Oki[a], Marin Kamiya[b], Ryosuke Hanada[b], Masahiro Egi[b,c] and Shuji Akai[a,*]

[a] *Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita, Osaka 567-0871, Japan*
[b] *School of Pharmaceutical Sciences, University of Shizuoka, 52-1, Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan*
[c] *School of Food and Nutritional Sciences, University of Shizuoka, 52-1, Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan*

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ABSTRACT

One-pot sequential reactions using the acyl moieties installed by enzymatic dynamic kinetic resolution of alcohols have been little investigated. In this work, the acryloyl moiety installed via the lipase/oxovanadium combo-catalyzed dynamic kinetic resolution of a racemic dienol [4-(cyclohex-1-en-1-yl)but-3-en-2-ol or 1-(cyclohex-1-en-1-yl)but-2-en-1-ol] with a (*Z*)-3-(phenylsulfonyl)acrylate underwent an intramolecular Diels–Alder reaction in a one-pot procedure to produce an optically active naphtho[2,3-*c*]furan-1(3*H*)-one derivative (98% ee). This method was successfully applied to the asymmetric total synthesis of (–)-himbacine.

* Corresponding author. Tel.: +81-6-6879-8210; fax: +81-6-6879-8210; e-mail: akai@phs.osaka-u.ac.jp

1. Introduction

Hydrolase-catalyzed kinetic resolution (KR) of racemic secondary alcohols via enantioselective esterification in organic media has been extensively used for the preparation of optically active compounds because of its advantages over the hydrolytic KR in aqueous media, such as high solubility and stability of substrates in organic solvents, easy operation, and easy product purification.[1] However, KR has the inherent limitation of maximum 50% yield of the desired product. On the other hand, dynamic kinetic resolution (DKR), in which enzymatic KR is combined with rapid in situ racemization of slowly reacting enantiomers, provides the additional benefit of quantitative conversion of racemic substrates into optically pure compounds. A variety of DKRs of secondary alcohols have been developed based on the combination of hydrolases and racemization catalysts, mainly ruthenium complexes.[2] We recently reported a novel DKR process using a combination of lipases and racemization catalysts V-MPSs[3,4] in which oxovanadium moieties are covalently bound to the inner surface of mesoporous silica (MPS) with a pore diameter of 2–4 nm (Fig. 1a). The racemization proceeds via the 1,3-transposition of the hydroxyl group of allylic alcohols in the V-MPS pores generating a dynamic equilibrium between the two regioisomers [(±)-**I** and (±)-**II**], while lipase catalyzes the enantio- and chemoselective transesterification of alcohols with acyl donors outside the pores, producing quantitative yields of optically pure allyl esters (*R*)-**III** (Fig. 1b, the absolute stereochemistry of **I**–**III** is shown as representative examples). In this DKR, the two regioisomers (**I** and **II**) serve as equivalent substrates to afford the same product (*R*)-**III**, unlike the above-mentioned DKR based on the use of ruthenium complexes as racemization catalysts.

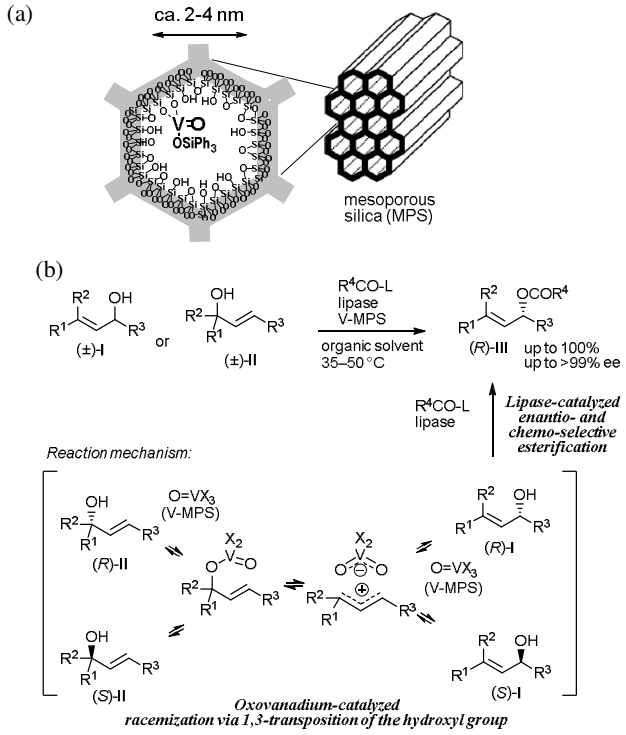


Fig. 1. (a) V-MPS structure; (b) Lipase/oxovanadium combo-catalyzed DKR of racemic allylic alcohols (**I** or **II**).

The combination of multiple reactions in a single operation is of particular interest because it minimizes the use of chemicals, waste production, number of steps, energy, and time.[5] The acyl groups introduced into alcohol substrates via KR or DKR are generally removed or replaced by other groups in subsequent transformations,[6] and only a few examples have been reported on the direct use of the installed acyl moieties in subsequent reactions.[7] Domino or one-pot sequential reactions using the installed acyl moiety, especially proceeding through intermediates that are too unstable to be isolated, provide a powerful synthetic tool. In this context, we reported the preparation of fused cyclic compounds by lipase-catalyzed domino KR (or DKR)/ intramolecular cyclization reactions.[8]

This paper presents advanced examples of such domino or one-pot sequential reactions in the synthesis of naphtho[2,3-*c*]furan-1(3*H*)-one derivatives **5** with several stereogenic carbon centers by lipase/oxovanadium combo-catalyzed DKR of a racemic dienol (**1** or **2**) with functionalized acyl donors **3** followed by intramolecular Diels–Alder (IMDA) reaction of thus generated optically active esters **4** (Fig. 2). This method was applied to the asymmetric synthesis of (–)-himbacine (98% ee), the opposite enantiomer of the natural product.[9]

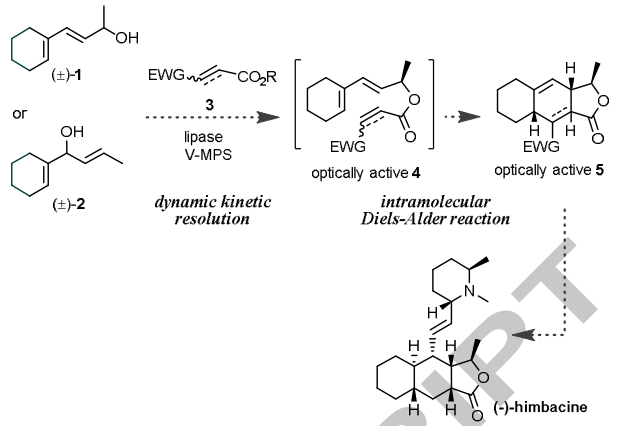


Fig. 2. A synthetic plan for optically active naphtho[2,3-*c*]furan-1(3*H*)-one derivatives **5** via a one-pot DKR/IMDA process and its application to the total synthesis of (–)-himbacine.

2. Results and Discussion

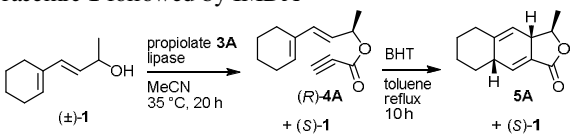
2.1. Asymmetric synthesis of naphtho[2,3-c]furan-1(3H)-one derivatives by one-pot DKR/IMDA reactions

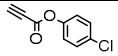
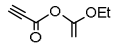
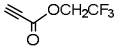
First, we examined the feasibility of the lipase-catalyzed KR of dienol (±)-**1** using different propiolates **3A** as acyl donors (Table 1). Screening of commercially available immobilized lipases at 35 °C in MeCN revealed that *Burkholderia cepacia* lipase (Amano PS-IM) and *Candida antarctica* lipase B (Novozym 435) were most effective in forming ester **4A**; however, **4A** was very unstable during chromatographic purification on silica gel, which caused decomposition and partial hydrolysis with regeneration of **1**. To overcome this problem, the crude mixture was filtered through a Celite pad and concentrated. Then, a solution of the residue and 5.0 mol% 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) in toluene was gradually heated to reflux and kept at that temperature for 10 h to produce an IMDA product **5A** as a single diastereomer. The effect of various parameters on this two-step synthesis was investigated, and some representative results are summarized in Table 1.

Firstly, the leaving group of propiolate **3A** was found to significantly affect both yield and enantiomeric excess of the product. *p*-Chlorophenyl propiolate (**3Aa**) was reactive in the PS-IM-catalyzed KR of (±)-**1**, but the enantiomeric excess of **5A** was very low (Table 1, entry 1). This result was probably due to to acid-catalyzed racemization of **4A** by the *p*-chlorophenol generated from **3Aa**. Although 1-ethyxvinyl esters have been found to be effective for lipase-catalyzed KR of racemic alcohols,[10] the use of 1-ethoxyvinyl propiolate (**3Ab**) for the KR of (±)-**1** resulted in the formation of racemic **5A** (entry 2). In this case, highly reactive **3Ab** caused non-enzymatic esterification of (±)-**1** (Some experimental evidences are given in the Supplementary Information). Whereas methyl propiolate (**3Ac**) was less reactive (entry 3), the reaction using 2,2,2-trifluoroethyl propiolate (**3Ad**) proceeded smoothly to give **5A** (63% ee) in 37% NMR yield (entry 4).[11]

In the screening of lipases, Novozym 435 exhibited higher reactivity than PS-IM, and similar enantioselectivity was observed (entry 5). Moreover, lowering the reaction temperature (25 °C) improved the enantioselectivity (entry 6).

Table 1. Screening of propiolates and lipases for the KR of racemic **1** followed by IMDA[a]



entry	propiolate **3A**	lipase	**5A**	
			yield (%)[b]	ee (%)
1	 **3Aa**	PS-IM	44	2
2	 **3Ab**	PS-IM	41	0
3	 **3Ac**	PS-IM	13	75
4	 **3Ad**	PS-IM	37	63
5	**3Ad**	Novozym 435	43	52
6[c]	**3Ad**	Novozym 435	36	71
7[c,d]	**3Ad**	Novozym 435	46[e]	91
8[c,d,f]	**3Ad**	Novozym 435	22	92

[a]The KR was conducted with **3A** (2.0 equiv) and lipase (1.5 w/w) in MeCN (80 mM) at 35 °C for 20 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. Toluene (5 mM) and BHT (5.0 mol%) were added to the residue, the mixture was gradually heated to reflux, and heating was continued for 10 h. PS-IM: *Burkholderia cepacia* lipase from Amano Enzyme; Novozym 435: *Candida antarctica* lipase B from Novozymes .

[b]Determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as the internal standard.

[c]The KR was conducted at 25 °C for 20 h.

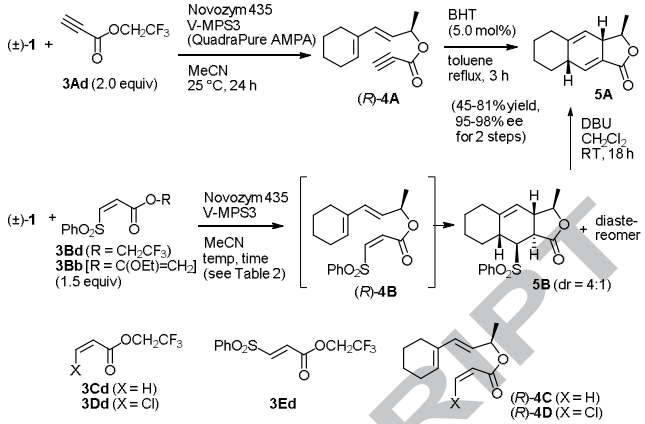
[d]The IMDA reaction was conducted by heating a solution of crude KR products in toluene in an oil bath preheated at 120 °C for 3 h.

[e]Isolated yield by silica gel column chromatography.

[f]The IMDA reaction was conducted without BHT.

In addition, rapid heating of the crude mixture containing **4A** was found to be critical to minimize hydrolysis and decomposition of **4A**. Thus, a solution of crude (*R*)-**4A** in toluene was placed in an oil bath preheated at 120 °C and kept at the same temperature for 3 h to give **5A** in 46% isolated yield and with 91% ee (entry 7). On the other hand, gradual heating from room temperature to reflux followed by heating at the same temperature for 10 h produced **5A** in a lower yield (36%) and with lower enantiomeric excess (71% ee) (entry 6). The use of BHT was also important in suppressing the decomposition of **4A** (entry 8).

We next focused our attention on the DKR of (±)-**1** with **3Ad** and V-MPS3[12] followed by IMDA. The DKR was performed in MeCN at 25 °C for 24 h, and the reaction mixture was concentrated in vacuo (Scheme 1). Toluene and BHT (5.0 mol%) were added to the residue, and the flask was placed in an oil bath preheated at 120 °C for 3 h to produce the IMDA product **5A** with higher enantioselectivity (95% ee) than that achieved with the KR/IMDA process (Table 1, entry 7), but no improvement in the isolated yield (45%) was observed. In order to increase the yield of **5A**, a variety of additives and solvents were screened, and the addition of QuadraPure AMPA (1.0 w/w) significantly improved the yield of **5A** to up to 81%. However, the yield of **5A** varied in the range of 50–80% depending on the reaction scale, probably because of partial decomposition of **4A** during heating of the toluene solution of the crude mixture.



Scheme 1. DKR/IMDA reaction of (±)-**1** using different acyl donors (**3A**–**3E**).

Table 2. Optimization of the DKR/IMDA reaction of (±)-**1** using **3Bd** or **3Bb**[a]

entry	**3B**	conditions	**5B**	
			yield (%)[b]	ee (%)[c]
1	**3Bd**	35 °C, 4 days	84	70
2	**3Bd**	25 °C, 4 days then reflux, 2 h	78	77
3	**3Bd**	15 °C, 4 days then reflux, 2 h	72	90
4	**3Bb**	35 °C, 4 days	84	81
5[d]	**3Bb**	25 °C, 36 h then reflux, 2 h	72	98

[a]The DKR was conducted with acyl donor **3Bd** or **3Bb** (1.5 equiv; unless otherwise noted), Novozym 435 (3.0 w/w), and V-MPS3 (1.0 mol%) in MeCN (80 mM) at the temperature and for the time given in the table.

[b]Isolated yield after column chromatography. A 4:1 mixture of two diastereomers was obtained.

[c]Optical purity of each diastereomer determined by HPLC using a chiral column.

[d]The DKR was conducted with acyl donor **3Bb** (0.90 equiv), Novozym 435 (3.0 w/w), and V-MPS3 (1.0 mol%) in MeCN (80 mM) at 25 °C. **3Bb** (0.90 equiv) was added portionwise in three equal batches at an interval of 12 h, and the reaction mixture was stirred for another 12 h (total reaction time: 36 h) at 25 °C. The mixture was heated at reflux in an oil bath for 2 h to produce **5B**, whose yield was based on (±)-**1**.

The applicability of other acyl donors **3B**–**3E** bearing different dienophile moieties to the Novozym 435-catalyzed DKR/IMDA process was then examined,[13] and the use of (*Z*)-3-(phenylsulfonyl)acrylates (**3Bd** and **3Bb**) was found to produce the corresponding cycloadduct **5B** even at 35 °C. Based on this finding, we have devised a more reliable method for this transformation. Thus, the treatment of (±)-**1** with **3Bd** (1.5 equiv), Novozym 435 (3.0 w/w), and V-MPS3 (1.0 mol%) in MeCN at 35 °C resulted in the generation of ester (*R*)-**4B** followed by gradual IMDA cyclization under the same reaction conditions. After 4 days at 35 °C, a 4:1 diastereomeric mixture of tricyclic **5B** was isolated in a total yield of 84% and with 70% ee for both diastereomers (Table 2, entry 1). Next, we attempted to improve the enantiomeric excess of the products by performing the DKR at a lower temperature, namely 25 °C and 15 °C; however, the IMDA reaction was sluggish under these conditions. Thus, after 4 days at 25 °C or 15 °C, the crude mixture was heated at reflux for 2 h to drive the IMDA reaction to completion, and a 4:1 diastereomeric mixture of **5B** was obtained with 77% ee (entry 2) or 90% ee (entry 3), respectively.

In other attempts to increase the enantioselectivity, the more reactive 1-ethoxyvinyl ester **3Bb** was used. The DKR using **3Bb** (1.5 equiv) at 35 °C for 4 days provided **5B** (81% ee) in 84% yield (entry 4). A more dramatic improvement was achieved by portionwise addition of **3Bb** (0.90 equiv) in three equal batches every 12 h at 25 °C followed by heating at reflux for 2 h, which afforded **5B** (a 4:1 mixture of two diastereomers, each with 98% ee) in 72% isolated yield (entry 5). The absolute structure of its major isomer is shown in Scheme 1 (for the determination of its stereochemistry, see: Supplementary Information). Notably, this method gave reproducible results regardless of the reaction scale. Although **5B** was always obtained as a 4:1 mixture of two diastereomers, this diastereomeric mixture quantitatively afforded **5A** (98% ee) as a single stereoisomer by treatment with 1 equiv of DBU in CH_2Cl_2 at room temperature (Scheme 1).[14]

2.2. Asymmetric total synthesis of (–)-himbacine

With these results in hand, we applied our DKR/IMDA strategy to the asymmetric total synthesis of himbacine,[9] a tetracyclic piperidine alkaloid isolated from the bark of the Australian pine tree of *Galbulimima* species. Himbacine is an interesting natural product with strong selective affinity for M_2 muscarinic receptor subtypes[15] and potential medicinal applications such as in the treatment of Alzheimer's disease.[16] The total syntheses of himbacine reported to date are based on the construction of the optically active naphtho[2,3-*c*]furan-1(3*H*)-one ring system by intra- or intermolecular Diels–Alder reaction of optically active compounds with an (*S*)-stereogenic center at the C3 position (the numbering refers to the naphtho[2,3-*c*]furan-1(3*H*)-one skeleton) (Fig. 3),[17-23] in which more than five steps are required to prepare the substrates for the IMDA reactions.

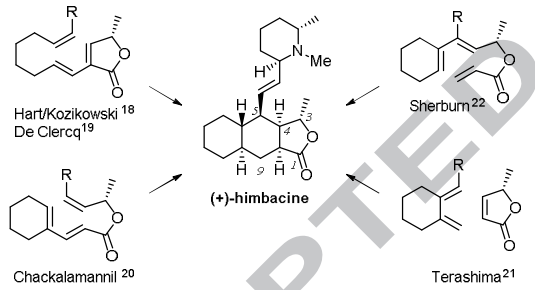


Fig. 3. Reported syntheses of (+)-himbacine.

In contrast, application of our DKR/IMDA reaction to the total synthesis of himbacine is particularly attractive because it allows the use of racemic alcohols (**1** or **2**) as substrates, which are readily prepared from commercially available compounds in only one or two steps.

As above-mentioned, compound **5A** (72% yield, 98% ee) was prepared from (±)-**1**, which was synthesized from enyne **6** in two steps and 94% overall yield (Scheme 2). A similar one-pot DKR/IMDA reaction was performed on the regioisomer (±)-**2** (a 1:1 mixture of *E*- and *Z*-isomers), obtained in quantitative yield from commercially available aldehyde **7** and the Grignard reagent **8** (*E*/*Z* mixture). Treatment of (±)-**2** with **3Bb** (0.30 equiv × 3) in the presence of Novozym 435 (3.0 w/w) and V-MPS3 (1.0 mol%) in MeCN at 25 °C for 36 h followed by refluxing for 2 h afforded **5B** in 73% isolated yield as a 4:1 mixture of diastereomers (98% ee for both diastereomers) (Scheme 2). The latter results have proved that V-MPS3 catalyzed the 1,3-migration of the hydroxyl group along with *Z*-to-*E* isomerization and racemization via the allyl cation intermediate as shown in Fig. 1b.

The diastereomeric mixture of **5B** was treated with 1 equiv of DBU to give **5A**, which was then subjected to the olefin-selective reduction with Mg in MeOH to afford **9** in quantitative yield.[24] The lactone was protected as its acetal **10** (4:1 diastereomeric mixture), and the olefin moiety was then converted into secondary alcohol **11** (a mixture of four diastereomers) by the standard hydroboration/oxidation protocol. Dess–Martin periodinane (DMP)-oxidation followed by DBU-mediated epimerization quantitatively produced ketone **12**. Notably, these transformations converted the mixture of four diastereomers of **11** into **12** as a single stereoisomer. The spectroscopic data (^{1}H NMR, ^{13}C NMR, and IR), melting point, and specific optical rotation of **12** were in agreement with those of the compound synthesized by Terashima et al.[21c]; thus, the absolute structure of **12** was unambiguously determined as shown in Scheme 2. Next, homologation of the carbonyl of **12** into sulfone **15** was achieved by Wittig olefination, hydroboration/oxidation, Mitsunobu reaction with PhSH, and oxidation. The spectroscopic data of **15** were in agreement with those of its enantiomer, the key synthetic intermediate of (+)-himbacine reported by Hart/Kozikowski[18] and Terashima.[21c] Specific optical rotation of **15** was identical with that of the same compound reported by Terashima.[21c]

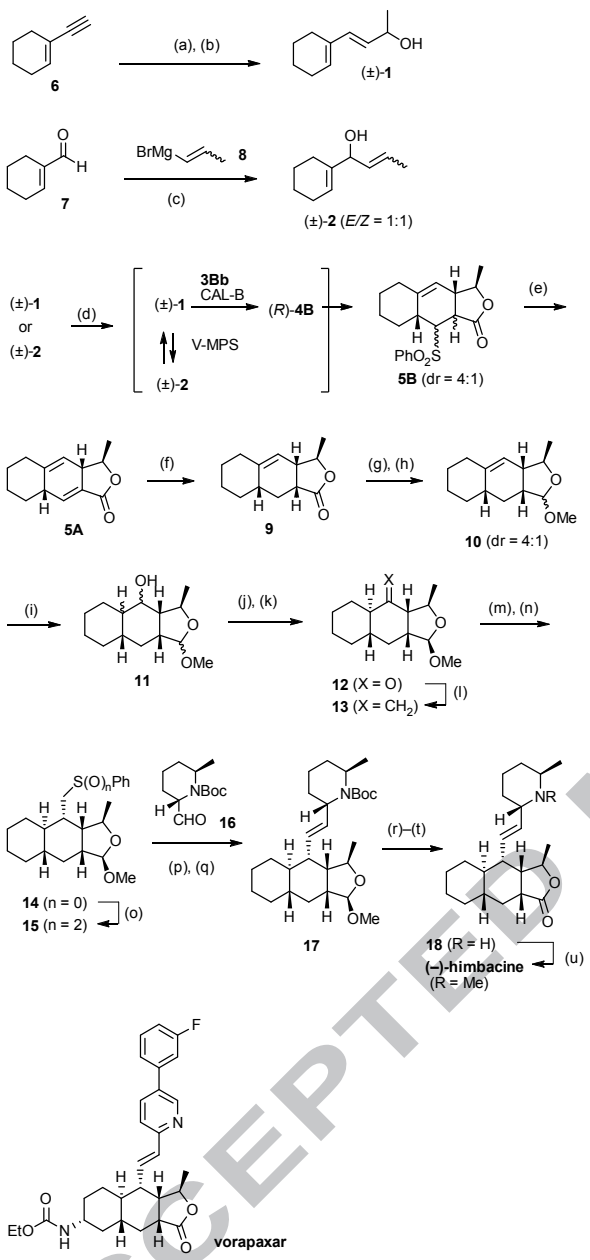
The final part of the total synthesis was carried out according to the method of Hart and Kozikowski.[18] The anion generated from **15** was coupled with optically pure **16**,[21c,25] prepared from (*S*)-piperidine-2-carboxylic acid according to the method reported for *ent*-**16**,[18] and the resulting diastereomeric mixture was treated with sodium amalgam and Na_2HPO_4 in MeOH to afford olefin **17**. Hydrolysis of **17** followed by oxidation and Boc deprotection produced (–)-himbeline **18**, and final *N*-methylation gave (–)-himbacine (Scheme 2). The spectroscopic data (^{1}H NMR, ^{13}C NMR, and IR) and melting point of the product were identical to the reported values,[18b] and the specific optical rotation was in good agreement with that of (+)-himbacine[18b] and (–)-himbacine.[21c] Hence, the use of commercial lipases in our DKR/IMDA strategy led to the formation of (–)-himbacine, the opposite enantiomer of the natural product. Notably, the core tricyclic structure with the same absolute stereochemistry is found in the FDA-approved thrombin receptor antagonist, vorapaxar (Scheme 2).[26]

3. Conclusion

In contrast to the extensively developed lipase-catalyzed DKR of racemic secondary alcohols, effective use of the acyl group installed during KR or DKR, as part of the constituent structure for subsequent reactions has been little investigated so far. In this study, highly enantioselective DKR was achieved by suitable choice of acyl donors and lipases, which was then directly followed by IMDA reaction of the installed acyl moiety to produce tricyclic products with up to 98% ee in a one-pot procedure.

The practical effectiveness of our DKR/IMDA strategy was demonstrated in the asymmetric synthesis of himbacine, using commercial lipases. As most lipases exhibit catalytic activity toward the (*R*)-enantiomers of secondary alcohols to produce (*R*)-esters, our strategy led to the synthesis of (–)-himbacine, the opposite enantiomer of the natural product. Notably, the (–)-himbacine scaffold is found in vorapaxar (Scheme 2), a thrombin receptor antagonist recently approved by the FDA for reducing the risk of cardiovascular events.[26] The (*S*)-selective DKR process can be performed using other hydrolases, such as subtilisin Carlsberg,[27,28] *Candida antarctica* lipase A,[29] and a Novozym 435 mutant.[30] Hence, the synthesis of both (*R*)- and (*S*)-esters from racemic secondary alcohols can be achieved by the choice of suitable enzymes, and the obtained compounds can

be used in the construction of fused cyclic compounds by the one-pot DKR/IMDA process.



Scheme 2. Total synthesis of (–)-himbacine. Reagents and conditions: (a) *n*BuLi then MeCHO. (b) $LiAlH_4$, 94% yield over two steps. (c) **8** then H_3O^+, 99% yield (1:1 mixture of *E*- and *Z*-isomers). (d) **3Bb** (0.30 equiv × 3), Novozym 435 (3.0 w/w), V-MPS3 (1.0 mol%), MeCN, 25 °C, 36 h then reflux 2 h, 72% yield, 98% ee, dr = 4:1 from **1**, 73% yield 98% ee, dr = 4:1 from **2**. (e) DBU. (f) Mg, MeOH, quant. over two steps. (g) DIBAL-H. (h) BF_3•Et_2O, MeOH, 84% yield over two steps (dr = 4:1). (i) BH_3•Me_2S then H_2O_2, NaOH, 89% yield (a mixture of four diastereomers). (j) DMP. (k) DBU, quant. over two steps. (l) $Ph_3P{=}CH_2$, 81% yield. (m) 9-BBN, then H_2O_2, NaOH. (n) PhSH, DEAD, Ph_3P, 86% yield over two steps. (o) *m*CPBA, 97% yield. (p) *n*BuLi, **16**. (q) Na(Hg), 33% yield (84% yield based on recovery of **15**) over two steps. (r) 10% aq. HCl, (s) PDC, (t) CF_3CO_2H, 67% yield over three steps. (u) $NaBH_3CN$, HCHO, 82% yield.

The oxovanadium-catalyzed DKR offers the possibility to use regioisomeric allylic alcohols as equivalent substrates, which makes the overall transformation shorter and more effective, and represents an important advantage over the well-known DKR requiring redox catalysts for the racemization.[2] Our findings will pave the way for a broader application of enzymatic DKR in the production of optically active fused cyclic compounds. Further application of the oxovanadium/hydrolase combo-catalyzed DKR/intramolecular cyclization process is currently under investigation in our group.

4. Experimental

4.1. General considerations

Melting points were determined on BUCHI Melting Point M-565 and Yanagimoto melting point apparatuses were uncorrected. Infrared (IR) absorption spectra were recorded on SHIMADZU FTIR-8400S and SHIMADZU IRAffinity-1S spectrophotometers. ^1H and ^{13}C NMR spectra were measured on JEOL JNM-ECA500 (^1H: 500 MHz, ^{13}C: 125 MHz), JEOL AL-400 (^1H: 400 MHz, ^{13}C: 100 MHz), and JEOL AL-300 (^1H: 300 MHz, ^{13}C: 75 MHz) instruments with chemical shifts reported in ppm relative to the residual deuterated solvent. The mass spectra (MS) were measured on JEOL JMS-S3000 (MALDI), Bruker Daltonics micrOTOF (ESI), and JEOL JMS-700 (FAB) instruments. Yield refers to the isolated yield of a compound greater than 95% purity as determined by ^1H NMR analysis. ^1H NMR and melting points (where applicable) of all known compounds were taken. All new products were further characterized by ^{13}C NMR, IR and high resolution mass spectrum (HRMS). HPLC analyses were carried out using a JASCO LC-2000Plus system (HPLC pump: PU-2080, UV detectors: MD-2018 and MD-4017) equipped with a Daicel CHIRALPAK AD-3 column. All optically active compounds are detected by 254 nm wavelength absorption unless otherwise noted. Optical rotations were measured on a JASCO P-1020 polarimeter.

Burkholderia cepacia lipases PS-IM immobilized on diatomaceous earth, supplied by Amano Enzyme Inc., Japan, and *Candida antarctica* lipase B (Novozym 435) immobilized on a support (commercial name: Chirazyme L-2 C4), purchased from Novozymes, were used as received without further purification. V-MPS3 was prepared according to the report.[4a] Silica gel 60N purchased from Kanto Chemical Co., Inc., Japan was used for column chromatography. All reagents were of reagent grade unless otherwise stated. In general, the reactions were carried out in commercial anhydrous solvents.

*4.2 Preparation of racemic alcohols (**1** and **2**)*

Racemic alcohols (**1** and **2**) were prepared from the commercially available compounds (**6** and **7**) as shown in Scheme 2.

*4.2.1. (E)-4-(1-Cyclohexenyl)-3-buten-2-ol (**1**)*

Under an argon atmosphere, *n*-BuLi (2.6 M in hexanes, 57 mL, 0.148 mol) was added into a solution of 1-ethynylcyclohexene (**6**) (15.0 g, 0.141 mol) in THF (0.23 L) at –78 °C. The mixture was stirred at the same temperature for an additional 15 min before a solution of acetaldehyde (11.9 mL, 0.21 mol) in THF (20 mL) was added. After being stirred at the same temperature for 30 min, the reaction mixture was warmed up to 0 °C and then quenched with sat. aq. NH_4Cl. The product was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc = 2:1) to give 4-(cyclohex-1-en-1-yl)but-3-yn-2-ol (21 g, 0.140 mol) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.46 (t, *J* = 6.5 Hz, 3H), 1.53–1.67 (m, 4H),

1.76 (d, *J* = 3.5 Hz, 1H), 2.03–2.14 (m, 4H), 4.60–4.68 (m, 1H), 6.07–6.13 (m, 1H).

Under an an argon atmosphere, a solution of 4-(cyclohex-1-en-1-yl)but-3-yn-2-ol (21 g, 0.140 mol) in THF (50 mL) was dropwise added to an ice-cold suspension of $LiAlH_4$ (16 g, 0.42 mol) in THF (0.65 L). After being stirring at the same temperature for 1 h, the reaction mixture was quenched with 15% aq. NaOH, and the whole mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes/EtOAc = 1:2) to give **1** (20.2 g, 94% yield over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (d, *J* = 6.0 Hz, 3H), 1.54–1.73 (m, 4H), 2.07–2.15 (m, 4H), 4.31–4.39 (m, 1H), 5.59 (dd, *J* = 16.0, 7.0 Hz, 1H), 5.73–5.78 (m, 1H), 6.18 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.4, 22.5, 23.5, 24.5, 25.8, 69.2, 129.4, 130.1, 133.4, 135.0; IR ($CHCl_3$) ν: 3607 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274. Found; 153.1279.

*4.2.2. 1-(1-Cyclohexenyl)-2-buten-1-ol (**2**)*

Under an argon atmosphere, 1-propenylmagnesium bromide **8** (a mixture of *E*- and *Z*-isomers, 0.5 M in THF, 1.1 mL, 0.54 mmol) was added to a solution of **7** (50 mg, 0.45 mmol) in THF (2 mL) at –78 °C. After being stirred at the same temperature for 5 min, the reaction mixture was warmed up to 0 °C, quenched with sat. aq. NH_4Cl, and extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc = 3:1) to give **2** (69 mg, 99% yield) as a 1:1 mixture of *E*- and *Z*-**2**. A colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.43-1.50 (m, 1H), 1.52-1.68 (m, 5H), 1.705 (t, *J* = 6.0 Hz, 1.5H), 1.707 (t, *J* = 6.0 Hz, 1.5H),1.90-2.08 (m, 4H),4.40 (d, *J* = 7.0 Hz, 0.5H), 4.82 (d, *J* = 8.5 Hz, 0.5H),5.42-5.55 (m, 0.5H), (qdd, *J* = 1.5, 7.0, 8.5 Hz, 0.5H), 5.57-5.64 (m, 0.5H), 5.66-5.76 (m, 1.5H);^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.3, 17.7, 22.5, 22.6, 24.2, 24.3, 25.0, 71.5, 122.1, 122.5, 126.5, 127.2, 131.6, 132.2, 139.3, 139.4; IR ($CHCl_3$) ν: 3350, 2930 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274. Found; 153.1276.

*4.3. (3R,3aS,8aR,9S,9aS)-3-Methyl-9-(phenylsulfonyl)-3a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-c]furan-1(3H)-one and its diastereomer (**5B**)*

*4.3.1. From (±)-**1**:*

Under an argon atmosphere immobilized *Candida antarctica* lipase B (Novozym 435) (300 mg, 3.0 w/w), V-MPS3 (33 mg, vanadium component: 6.6 μmol) and **3Bb** (56 mg, 0.197 mmol) were added to a solution of (±)-**1** (100 mg, 0.66 mmol) in MeCN (8 mL, 0.08 M). The reaction mixture was stirred at 25 °C for 12 h, and another **3Bb** (56 mg, 0.197 mmol) was added, and the reaction mixture was stirred at 25 °C for 12 h. This procedure was repeated one more time (the reaction mixure was stirred for totally 36 h), and then the mixture was heated at reflux temperature for 2 h. After cooling, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc = 10:1) to give **5B** (164 mg, 72% yield) as a 4:1 mixture of **(3*R*,3a*S*,8a*R*,9*S*,9a*S*)-3-methyl-9-(phenylsulfonyl)-3a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one** (98% ee) and its diastereomer (98% ee). A white solid. The enantiomeric excess of each diastereomer was determined by HPLC analysis at 20 °C using a Daicel CHIRALCPAK AD-3 column (hexanes/2-propanol = 95:5, 1.0 mL/min. Retention times; major isomer: 16.5 (*R*), 18.3 min (*S*), minor isomer: 20.5 (*R*), 22.4 min (*S*)). $[\alpha]_D^{28}$ = − 36.2 (*c* 0.82, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.18–1.39 (m, 2H) , 1.49–1.61 (m, 4H) , 1.63–1.70 (m, 1H) , 1.80–1.89 (m, 2H), 2.19–2.21 (m, 1H) , 2.28–2.37 (m, 1H), 2.62 (dd, *J* = 14.0, 3.0 Hz, 0.8H), 2.69 (dd, *J* = 14.0, 3.5 Hz, 0.2H) , 2.92–3.00 (m, 1H), 3.24–3.32 (m, 0.8H), 3.51–3.56 (m, 1H), 3.84–3.92 (m, 0.2H) , 4.07–4.15 (m, 0.8H), 4.87–4.94 (m, 0.2H), 5.56 (d, *J* = 2.0 Hz, 0.2H), 5.60 (d, *J* = 2.0 Hz, 0.8H), 7.56–7.61 (m, 2H), 7.71–7.66 (m, 1H), 7.97–7.93 (m, 2H). IR (neat) ν: 1778 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NaO_4S$ $[M+Na]^+$: 369.1132. Found: 369.1131.

A pure major isomer of **5B** was obtained by recrystalization of the abovementioned 4:1 diastereomixture of **5B** and its stereochemistry was determined by ^{1}H HMR and NOESY analyses (in detail, see: Supplementary Information). $[\alpha]_D^{19}$ = +31.8 (*c* 1.00, $CHCl_3$). Mp 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (tq, *J* = 4.0, 13.0 Hz, 1H), 1.34 (dq, *J* = 3.0, 12.5 Hz, 1H), 1.48–1.62 (m, 1H), 1.54 (d, *J* = 6.0 Hz, 3H), 1.63–1.70 (m, 1H), 1.80–1.90 (m, 2H), 2.10–2.22 (m, 1H), 2.27–2.35 (m, 1H), 2.63 (dd, *J* = 3.0, 14.0 Hz, 1H), 2.93–3.01 (m, 1H), 3.24–3.33 (m, 1H), 3.53 (d, *J* = 3.0 Hz, 1H), 4.11 (qd, *J* = 6.0, 10.5 Hz, 1H), 5.58–5.62 (m, 1H), 7.56–7.62 (m, 2H), 7.65–7.72 (m, 1H), 7.93–7.97 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.5, 26.6, 28.0, 35.6, 36.1, 40.0, 43.1, 44.2, 63.4, 80.4, 116.4, 128.5, 129.5, 134.3, 139.7, 143.6, 172.3.

*4.3.2. From (±)-**2**:*

Similarly to the preparation of **5B** from (±)-**1**, **5B** (165 mg, 73% yield), a 4:1 mixture of **(3*R*,3a*S*,8a*R*,9*S*,9a*S*)-3-methyl-9-(phenylsulfonyl)-3a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one** (98% ee) and its diastereomer (98% ee), was obtained from (±)-**2** (100 mg, 0.66 mmol), Novozym 435 (300 mg, 3.0 w/w), V-MPS3 (33 mg, vanadium component: 6.6 μmol) and **3Bb** (56 mg x 3, 0.20 mmol x 3). The spectroscopic data of the obtained product **5B** were in good agreement with **5B** obtained from (±)-**1**.

*4.4. (3R,3aS,8aS)-3-Methyl-3a,5,6,7,8,8a-hexahydronaphtho[2,3-c]furan-1(3H)-one (**5A**)*

To an ice-cold solution of **5B** (a 4:1 mixture of two diastereomer, 0.20 g, 0.58 mmol) in $CHCl_3$ (2 mL) was added DBU (86 μl, 0.58 mmol). The reaction mixture was stirred at room temperature for 1.5 h and was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc = 5:1) to afford **5A** (198 mg, quant., 98% ee) as a white solid. The enantiomeric excess was determined by HPLC analysis at 20 °C, using a CHIRALCPAK AD-3 column (hexanes/2-propanol = 97.5:2.5, 1.0 mL/min; retention times 10.7 (*R*), 13.9 min (*S*)). $[\alpha]_D^{20}$ = 7.90 (*c* 0.95, $CHCl_3$). Mp 84–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (qd, *J* = 13.0, 3.5 Hz, 1H), 1.23 (qt, *J* = 13.0, 4.0 Hz, 1H) , 1.55–1.44 (m, 1H), 1.53 (d, *J* = 6.5 Hz, 3H) , 1.77–1.87 (m, 2H) , 2.02–2.10 (m, 2H) , 2.34–2.40 (m, 1H), 2.85–2.77 (m, 1H), 3.07–3.00 (m, 1H), 4.11 (dq, *J* = 10.0, 6.5 Hz, 1H), 5.41 (dd, *J* = 2.5, 4.5 Hz, 1H), 6.50 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.2, 26.0, 26.9, 34.3, 34.9, 38.7, 45.8, 80.6, 113.5, 128.4, 136.2, 141.3, 169.8; IR (neat) ν: 1744 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1222. Found: 205.1223.

*4.5. (3R,3aS,8aS,9aR)-3-Methyl-3a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-c]furan-1(3H)-one (**9**)*

Under an argon atmosphere, magnesium (0.20 g, 8.3 mmol) was added to an ice-cold solution of **5A** (0.85 g, 4.2 mmol) in MeOH (21 mL). The reaction mixture was stirred at room temperature for 1 h and then filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure. To the residue was added CH_2Cl_2, and the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes/EtOAc = 10:1) to give **9** (0.86 g, quant.) as a white solid. $[\alpha]_D^{18}$ = 15.3 (*c* 1.01, $CHCl_3$). Mp 75–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (qd, *J* = 12.0, 3.5 Hz, 1H), 1.22 (qt, *J* = 13.0, 3.5 Hz, 1H), 1.31–1.45 (m, 2H) , 1.45 (d, *J* = 6.5 Hz, 3H), 1.73–1.80 (m, 2H), 1.89–2.08 (m, 4H), 2.27 (ddq, *J* = 14.5, 4.0, 2.0 Hz, 1H), 2.47–2.53 (m, 1H), 2.59–2.67 (m, 1H), 4.27 (dq, *J* = 9.0, 5.5 Hz, 1H), 5.29 (qd, *J* = 2.5, 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.2, 25.8, 27.0, 29.0, 34.7, 34.9, 35.8, 39.3,

43.7, 81.4, 114.8, 144.0, 178.9; IR (neat) ν: 1770 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{13}H_{19}O_2$ $[M+H]^+$: 207.1382. Found: 207.1380.

*4.6. (1R,3S,3aR,4aS,9aS)-3-Methoxy-1-methyl-1,3,3a,4,4a,5,6,7,8,9a-decahydronaphtho[2,3-c]furan (**10**)*

Under an argon atmosphere, DIBAL-H (1.0 M in hexane, 0.72 mL, 0.72 mmol) was dropwise added to a solution of **9** (99 mg, 0.49 mmol) in Et_2O (5.0 mL) at –78 °C. After being stirred at the same temperature for 10 min, the reaction mixture was quenched with MeOH (0.1 mL) and filtered through a silica gel pad. The pad was washed with EtOAc, and the combined filtrates were concentrated under reduced pressure. To the residue was added EtOAc, and the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (5.0 mL), and BF_3•Et_2O (3 μL, 14 μmol) was added at 0 °C. The mixture was warmed to room temperature over a period of 3 h and filtered through a silica gel pad. The pad was washed with EtOAc, and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 20:1) to give **10** (89 mg, 84% yield) as a 4:1 mixture of two diastereomers. A colorless oil. $[\alpha]_D^{19}$ = 33.4 (*c* 1.01, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90 (qd, *J* = 12.5, 3.5 Hz, 1H) , 1.08–1.36 (m, 3H) , 1.27 (d, *J* = 5.5 Hz, 0.6H), 1.33 (d, *J* = 5.5 Hz, 2.4H) , 1.70–1.77 (m, 3H), 1.83–2.04 (m, 3H) , 2.12–2.27 (m, 2H) , 2.33–2.40 (m, 1H), 3.33 (s, 2.4H), 3.44 (s, 0.6H), 3.78 (dq, *J* = 10.0, 6.0 Hz, 0.2H), 3.89 (dq, *J* = 9.0, 6.0 Hz, 0.8H), 4.61 (s, *J* = 0.8H), 5.10 (d, *J* = 5.5 Hz, 0.2H), 5.20–5.23 (m, 0.2H), 5.31–5.34 (m, 0.8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.8, 21.2, 26.0, 27.0, 27.2, 28.0, 31.1, 34.7, 34.8, 35.1, 35.2, 36.1, 36.6, 40.8, 44.2, 44.4, 47.4, 54.2, 56.5, 77.7, 82.1, 06.4, 109.5, 116.1, 117.2, 141.7, 143.3; IR (neat) ν: 1069 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NaO_2$ $[M+Na]^+$: 245.1503. Found: 245.1512.

*4.7. (1S,3R,3aR,8aS,9aR)-1-Methoxy-3-methyldodecahydro-naphtho[2,3-c]furan-4-ol and its diastereomers (**11**)*

Under an argon atmosphere, BH_3•Me_2S (1.0 g, 12.0 mmol) was added to an ice-cold solution of **10** (0.90 g, 4.0 mmol) in THF (20 mL). After being stirred at 30 °C for 1 h, the reaction mixture was cooled to 0 °C, and then 1 N aq. NaOH (20 mL) and 30% aq. H_2O_2 (2.3 mL) were added. After being stirred at 0 °C for 30 min, the reaction mixture was poured into saturated aq. NH_4Cl and extracted with Et_2O three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 5:1) to give **11** (0.87 g, 89% yield) as a mixture of four diastereomers. A colorless oil. The spectroscopic data (^{1}H NMR and IR) of one component of this mixture was in good agreement with those of **(1*S*,3*R*,3a*R*,8a*S*,9a*R*)-1-methoxy-3-methyldodecahydronaphtho[2,3-*c*]furan-4-ol** reported in the literature.[21c]

*4.8. (1S,3R,3aS,4aR,8aS,9aR)-1-methoxy-3-methyldecahydro-naphtho[2,3-c]furan-4(1H)-one (**12**)*

Dess–Martin periodinane (1.6 g, 3.8 mmol) was added to a solution of **11** (0.62 g, 2.6 mmol) in CH_2Cl_2 (60 mL). After being stirred at room temperature for 0.5 h, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/Et_2O = 5:1) to give a ketone (0.61 g, quant.) as a colorless oil. The ketone (0.60 g, 2.5 mmol) was dissolved in $CHCl_3$ (20 mL), and DBU (0.38 mL, 2.5 mmol) was added at room temperature. After being stirred at reflux temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 10:1) to give **12** (0.60 g, quant.) as a single compound. A white solid. $[\alpha]_D^{20}$ = –167 (*c* 0.53, $CHCl_3$) (lit.[21c] $[\alpha]_D^{21}$ = –165 (*c* 0.41, $CHCl_3$)). Mp 87–88 °C (lit.[21c] Mp 86–87 °C). The spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) of the obtained product **12** were in good agreement with those of *ent*-**12** reported in the literature.[21c]

*4.9. (1S,3R,3aR,4aR,8aS,9aR)-1-Methoxy-3-methyl-4-methylene-dodecahydronaphtho[2,3-c]furan (**13**)*

Under an argon atmosphere, *n*-butyl lithium (1.6 M in hexane, 2.4 mL, 4.0 mmol) was dropwise added to a suspension of methyl-triphenylphosphonium iodide (1.7 g, 4.2 mmol) in THF (10 mL) at –78 °C. The reaction mixture was stirred at 0 °C for 30 min and cooled down to –78 °C, to which a solution of **12** (0.40 g, 2.1 mmol) in THF (5 mL) was added. The reaction mixture was warmed up to room temperature, stirred at the same temperature for 1.5 h, quenched with saturated aq. NH_4Cl, and extracted with Et_2O three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 20:1) to give **13** (0.16 g, 81% yield) as a colorless oil. $[\alpha]_D^{20}$ = –65.5 (*c* 0.49, $CHCl_3$) (lit.[21c] $[\alpha]_D^{23}$ = –58 (*c* 0.29, $CHCl_3$)). The spectroscopic data of the obtained product **13** (^{1}H NMR, ^{13}C NMR and IR) were in good agreement with those of *ent*-**13** reported in the literature.[21c]

*4.10. (1S,3R,3aR,4S,4aR,8aS,9aR)-1-Methoxy-3-methyl-4-((phenylthio)methyl)dodecahydronaphtho[2,3-c]furan (**14**)*

Under an argon atmosphere, 9-BBN (0.5 M in THF, 10.4 mL, 5.2 mmol) was dropwise added to an ice-cold solution of **13** (0.41 g, 1.73 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 15 h and cooled to 0 °C. Then, 1 N aq. NaOH (8.7 mL) and 35% aq. H_2O_2 (0.84 mL) were added. The reaction mixture was stirred at 0 °C for 15 min and extracted with Et_2O three times. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 5:1) to afford the primary alcohol (0.40 g, 91% yield) as single isomer. The obtained alcohol (0.35 g) was dissolved in CH_2Cl_2 (0.3 mL), and diethyl azodicarboxylate (40%, 1.2 g, 2.8 mmol), Ph_3P (0.72 g, 2.8 mmol) and thiophenol (0.28 mL, 2.8 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 12 h, quenched with saturated aq. NH_4Cl, and extracted with Et_2O three times. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 40:1 to 4:1) to give **14** (0.45 g, 86% yield over 2 steps) as a white solid. $[\alpha]_D^{20}$ = –165 (*c* 0.50, $CHCl_3$) (lit.[21c] $[\alpha]_D^{25}$ = –140 (*c* 0.15, $CHCl_3$) for **14**, lit.[18b] $[\alpha]_D^{20}$ +138.5 (c 0.73, $CHCl_3$) for *ent*-**14**). Mp 51 °C (lit.[21c] 42–43°C for *ent*-**14**). The spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) of the obtained product **14** were in good agreement with those of *ent*-**14** reported in the literature.[18b,21c]

*4.11. (1S,3R,3aR,4S,4aR,8aS,9aR)-1-Methoxy-3-methyl-4-((phenylsulfonyl)methyl)dodecahydronaphtho[2,3-c]furan (**15**)*

To an ice-cold suspension of **14** (0.45 g, 1.30 mmol) and $NaHCO_3$ (0.55 g, 6.5 mmol) in CH_2Cl_2 (50 mL) was portionwise added *m*CPBA (77% pure, 0.78 g, 3.2 mmol). The reaction mixture was stirred at 0 °C for 1 h, diluted with Et_2O, and washed with aq. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 6:1 to 2:1) to give **15** (0.48 g, 97% yield) as a white solid. $[\alpha]_D^{20}$ = –103 (*c* 0.98, $CHCl_3$) (lit.[21c] $[\alpha]_D^{22}$ = –104 (*c* 0.35, $CHCl_3$)). Mp 132 °C (lit.[21c] 129–130 °C). The spectroscopic data (^{1}H NMR and ^{13}C NMR) of the obtained product **15** were in good agreement with those of *ent*-**15** reported in the literature.[18b,21c]

*4.12. tert-Butyl (2S,6R)-2-((E)-2-((1R,3R,3aS,4S,4aR,8aS,9aR)-1-methoxy-3-methyldodecahydronaphtha[2,3-c]furan-4-yl)vinyl)-6-methylpiperidine-1-carboxylate (**17**)*

Under an argon atmosphere, *n*-butyl lithium (2.6 M in hexane, 100 µL, 0.26 mmol) was dropwise added to a solution of **15** (100 mg, 0.26 mmol) in THF (2.0 mL) at –78 °C. The reaction mixture was stirred at –50 °C for 30 min, and a solution of **16** (90 mg, 0.40 mmol) in THF (1.0 mL) was added. The reaction mixture was stirred at –60 °C for 2 h, quenched with H_2O, and extracted with Et_2O three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (hexanes/EtOAc = 5:1) to give the coupling product (59 mg, 40% yield) as a white solid along with the recovery of **15** (60 mg, 60% yield). To a solution of thus obtained coupling product (59 mg) in MeOH (5 mL) were added 6% sodium amalgam (2.1 g) and disodium hydrogen phosphate (0.44 g) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with H_2O, and filtered through a Celite pad. The filtrate was extracted with Et_2O three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 9:1) to give **17** [39 mg, 33% yield (84% yield based on recovery of **15**) over 2 steps] as a white solid. $[\alpha]_D^{19}$ = –96.3 (*c* 0.39, $CHCl_3$) (lit.[21c] $[\alpha]_D^{23}$ = –88 (*c* 0.35, $CHCl_3$), lit.[18b] $[\alpha]_D^{20}$ = +90.5 (*c* 0.38, $CHCl_3$) for *ent*-**17**). Mp 92 °C (lit.[21c] 90–92 °C, lit.[18b] 92–93 °C for *ent*-**17**). The spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) of the obtained product **17** were in good agreement with those for *ent*-**17** reported in the literature.[18b,21c]

*4.13. (3R,3aS,4S,4aR,8aS,9aR)-4-((E)-2-((2S,6R)-1,6-dimethylpiperidin-2-yl)vinyl)-3-methyldecahydronaphtho[2,3-c]furan-1(3H)-one (**18**, ent-himbeline)*

To an ice-cold solution of **17** (55 mg, 0.123 mmol) in acetone (4.0 mL) was added 10% aq. HCl (2.0 mL). The reaction mixture was stirred at room temperature for 30 min, quenched with aq. $NaHCO_3$, and extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a hemiacetal (51 mg). To a solution of thus obtained hemiacetal (51 mg) in CH_2Cl_2 (2.0 mL) were added pyridinium dichromate (90 mg, 0.24 mmol) and molecular sieves 4A (0.55 g). The reaction mixture was stirred at 30 °C for 1 h, diluted with a 3:1 mixture of hexanes and EtOAc, and filtered through a silica gel pad. The pad was washed with a 3:1 mixture of hexanes and EtOAc, and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 4:1) to give ***tert*-butyl (2*R*,6*S*)-2-methyl-6-((*E*)-2-((3*R*,3a*S*,4*S*,4a*R*,8a*S*,9a*R*)-3-methyl-1-oxododecahydronaphtho[2,3-c]furan-4-yl)vinyl)piperidine-1-carboxylate** (43 mg, 81% yield over 2 steps) as a colorless oil. $[\alpha]_D^{28}$ = –50.2 (*c* 0.14, $CHCl_3$) (lit.[21c] $[\alpha]_D^{25}$ = –63 (*c* 0.50, $CHCl_3$), lit.[18b] $[\alpha]_D^{20}$ = +60.6 (*c* 0.55, $CHCl_3$) for *ent*-isomer). ^{1}H NMR data of the obtained product were in good agreement with those for its enantiomer reported in the literature.[18b,21c]

Trifluoroacetic acid (0.5 mL) was added to a solution of thus obtained compound (30 mg, 38 µmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at room temperature for 30 min, quenched with 6N aq. NaOH, and extracted with CH_2Cl_2 three times. The combined organic phases were dried over K_2CO_3, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/MeOH = 3:1) to give **18 (*ent*-himbeline)** (9.2 mg, 83% yield) as a colorless oil. $[\alpha]_D^{19}$ = –20 (*c* 0.17, $CHCl_3$) (lit.[21c] $[\alpha]_D^{22}$ = –15 (*c* 0.44, $CHCl_3$) for *ent*-himbeline), lit.[18b] $[\alpha]_D^{20}$ = +17.1 (*c* 0.56, $CHCl_3$) for himbeline). The spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) of the obtained product were in good agreement with those for its enantiomer reported in the literature.[18b,21c]

4.14. (–)-Himbacine

Sodium cyanoborohydride (7.5 mg, 0.119 mmol) was added to a mixture of **18** (18 mg, 54 µmol) and 37 wt% aq. formaldehyde (40 µL, 0.54 mmol) in MeCN (1.0 mL). The reaction mixture was stirred at room temperature for 30 min, and acetic acid was added dropwise to make the reaction mixture neutral (pH 7). The resulting mixture was stirred at same temperature for an additional 1.5 h and cooled to 0 °C. 15% aq. NaOH (2 mL) was added, and the mixture was extracted with Et_2O three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/MeOH = 1:3) to give **(–)-himbacine** (15.3 mg, 82%) as a white solid. $[\alpha]_D^{19}$ = –59.8 (*c* 0.70, $CHCl_3$) (lit.[21c] $[\alpha]_D^{23}$ = –59 (*c* 0.29, $CHCl_3$) for (–)-himbacine), lit.[18b] $[\alpha]_D^{20}$ = +51.4 (*c* 1.01, $CHCl_3$) for (+)-himbacine). Mp 130-131 °C (lit.[21c] 128–130 °C for (–)-himbacine, lit.[18b] 129–130 °C for (+)-himbacine). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.65-0.83 (m, 1H), 0.89-1.06 (m, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.08–1.32 (m, 3H), 1.35-1.48 (m, 2H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.48–1.60 (m, 2H), 1.60–1.81 (m, 6H), 1.86 (dd, *J* = 6.5, 12.5 Hz, 1H), 2.04-2.16 (m, 1H), 2.18–2.29 (m, 1H), 2.21 (s, 3H), 2.61 (td, *J* = 6.5, 13.5 Hz, 1H), 2.78–2.90 (m, 1H), 2.97–3.09 (m, 1H), 4.62 (qd, *J* = 6.0, 11.0 Hz, 1H), 5.25 (dd, *J* = 10.0, 15.0 Hz, 1H), 5.57 (dd, *J* = 9.5, 15.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 18.9, 22.2, 26.1, 26.4, 31.4, 32.0, 32.5, 33.2, 33.6, 39.9, 41.1, 41.5, 42.2, 45.7, 49.1, 53.4, 61.3, 76.8, 133.4, 133.5, 178.3; IR (neat) ν: 1778, 1454 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{22}H_{36}NO_2$ $[M+H]^+$: 346.2741. Found: 346.2746. The abovementioned spectroscopic data were in good agreement with those for natural (+)-himbacine reported in the literature.[18b,21c]

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11. The absolute stereochemistries of **4A** and **5A** were tentatively assigned as shown in Table 1 according to general tendency of the enantioselectivity of PS-IM and Novozym 435, which preferentially catalyze esterification of (*R*)-alcohols. Later, the absolute stereochemistry of **12**, derived from **5A**, was confirmed by the comparison with the known compound (vide infra).
12. V-MPS3, prepared from MPS with a pore diameter of 3 nm, was mainly used in this work. We also have found that V-MPS4,[4b] which is now commercially available from Wako Pure Chemical Industries, Ltd. produces similar results.
13. The use of acrylate **3Cd** and (*Z*)-3-chloroacrylate **3Dd** afforded the corresponding esters (*R*)-**4C** (89% isolated yield, 95% ee) and (*R*)-**4D** (92% isolated yield, 97% ee), respectively, under the DKR conditions at 35 °C for 24 h. However, the subsequent IMDA reaction did not proceed in refluxing toluene. Other trials on the IMDA of **4C** in refluxing toluene in the presence of acid catalysts, such as BF_3•Et_2O, $InCl_3$ and montmorillonite K-10, resulted in no reaction or formation of a complex mixture. The use of (*E*)-3-(phenylsulfonyl)acrylate **3Ed** caused the formation of a complex mixture.
14. The use of 1 equiv of DBU was found to be crucial for the quantitavive formation of **5A** with high reproducibility**.** When more than one equivalent of DBU was used, the yield of **5A** dramatically decreased due to the formation of side products, among which an olefin-migration product was observed as a major component.
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24. The reductive removal of the sulfonyl group from **5B** was intensively examined to directly produce **9**. Some examples include the treatment of **5B** with Mg (5 equiv) in MeOH to produce **10** (28% yield) along with the recovery of **5B** (66% yield). The use of Me_3SiOK in MeCN followed by quenching with 20% aq HCl solution produced **9** (30% yield) along with the aromatized compound, 3-methyl-5,6,7,8-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (70% yield).
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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at xxxxxxxxxxxxx.

Graphical Abstract

Lipase-catalyzed asymmetric synthesis of naphtho-[2,3-*c*]furan-1(3*H*)-one derivatives by a one-pot dynamic kinetic resolution/intramolecular Diels–Alder reaction: Total synthesis of (–)-himbacine

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