Lipase-Catalyzed Domino Kinetic Resolution/Intramolecular Diels–Alder Reaction: One-Pot Synthesis of Optically Active 7-Oxabicyclo[2.2.1]heptenes from Furfuryl Alcohols and β-Substituted Acrylic Acids

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Abstract: The first lipase-catalyzed domino reaction is described in which the acyl moiety formed during the enzymatic kinetic resolution of furfuryl alcohols (±)-**3** with a 1-ethoxyvinyl ester **2** was utilized as a part of the constituent structure for the subsequent Diels–Alder reaction. The preparation of ester **2** from carboxylic acid **1** and the subsequent domino reaction were carried out in a one-pot reaction. Therefore, this procedure provides a convenient preparation of the optically active 7-oxabicyclo[2.2.1]heptene derivatives **5**, which has five chiral, non-racemic carbon centers, from achiral **1** and racemic **3**. The overall efficiency of this process was dependent on the substituent at the C-3 position of **3**, and the use of the 3-methylfurfuryl derivatives, (±)-**3b** and (±)-**3f**, exclusively produced diastereoselectivity with excellent enantioselectivity to give (2*R*)-*syn*-**5** (91–≥99% *ee*) and (*S*)-**3** (96–≥99% *ee*). Similar procedures starting from the 3-bromofurfuryl alcohols (±)-**3h–j** provided the cycloadducts (2*R*)-*syn*-**5j–q** (93–≥99% *ee*), in which the bromo group was utilized for the installation of bulky substituents to the 7-oxabicycloheptene core.

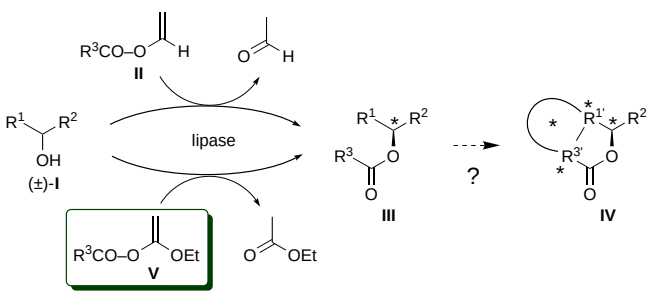
Keywords: asymmetric synthesis · cycloadditions · domino reactions · hydrolases · kinetic resolution

Introduction

The lipase-catalyzed enantioselective transesterification of racemic alcohols (±)-**I** with vinyl esters **II** in organic solvents has been widely employed to give optically active esters **III** (Scheme 1).[1] These reactions are more advantageous than the original enzymatic hydrolysis of esters in terms of their simple operation, the good solubility of the substrates, and the prevention of water dependent side reactions. In addition to the inherent nontoxicity of the lipases, recent studies on the efficient application of supercritical carbon dioxide[2] and ionic liquids[3] as a solvent have raised the potential of the lipase-catalyzed transesterification reaction as an environmentally benign asymmetric synthesis.

Although this reaction provides optically active **III**, the installed acyl moiety is usually removed during the subsequent transformations, therefore its effective use as a part of the constituent structure of the subsequent reactions has been limited.[4] In addition, all of the reported examples were carried out after isolation of **III**. If one can achieve a domino process,[5] namely, the enzymatic transesterification followed by an intramolecular cyclization reaction of R^1 and R^3 groups of **III**, such a reaction must be attractive because it provides optically active cyclic compounds **IV** with multichiral carbon centers in a one-pot reaction. The potential influence of the lipase on the intramolecular reaction of **III** might have a chance of improving the optical purity and the diastereoselectivity of the products. However, no examples have been reported probably due to the lack of the easy preparation of **II** having a reactive acyl moiety (Scheme 1).

Recently, we disclosed that 1-ethoxyvinyl esters **V** are highly effective acyl donors for the lipase-catalyzed kinetic resolution of racemic alcohols[6] and the desymmetrization of



Scheme 1. Transesterification of (±)-**I** with **II** or **V**.

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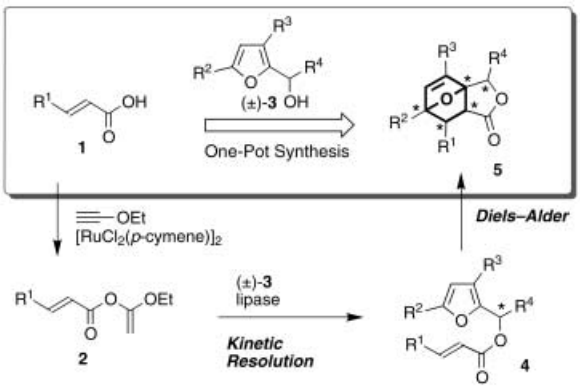
symmetrical diols.[7] Some remarkable advantages of **V** over **II** involve the generation of nonharmful, volatile ethyl acetate as a single co-product,[8] facile preparation of **V** with an acyl moiety of various kinds,[9] and its applicability for a one-pot enzymatic reaction following the preparation of **V**.[6b]

Utilizing these features, we briefly communicated the one-pot synthesis of the 7-oxabicyclo[2.2.1]heptenes, **5a** ($R^1 = CO_2Me$, $R^2 = R^3 = H$, $R^4 = Me$) and **5b** ($R^1 = CO_2Me$, $R^2 = H$, $R^3 = R^4 = Me$), from the carboxylic acid **1a** ($R^1 = CO_2Me$) and the racemic furfuryl alcohol derivatives, **3a** ($R^2 = R^3 = H$, $R^4 = Me$) and **3b** ($R^2 = H$, $R^3 = R^4 = Me$). In this process, the domino reaction, that is the lipase-catalyzed kinetic resolution of **3** using an in situ prepared ethoxyvinyl ester **2a** followed by an intramolecular Diels–Alder reaction of the resulting optically active ester **4**, was achieved for the first time (Scheme 2).[10] We now present details of these reactions with additional examples of the formation of **5** with up to ≥99% *ee* and some synthetic applications.

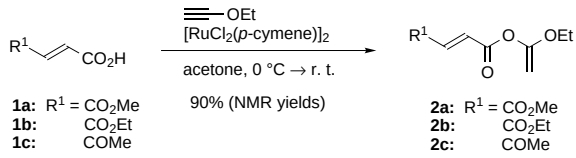


Scheme 2. The domino kinetic resolution/Diels–Alder reaction starting from **1** and (±)-**3**.

Results and Discussion

Enantiomerically pure 7-oxabicyclo[2.2.1]heptenes are highly useful as synthetic intermediates of various biologically important natural products.[11] Intensive efforts have been devoted to synthesize these structures, among which the intramolecular Diels–Alder reaction of the optically active furan derivatives is one of the most effective methods.[12] The intramolecular Diels–Alder reaction of furfuryl acrylate derivatives **4** under thermal or high-pressure conditions is a typical example.[12a] The requisite optically active esters **4** were prepared by esterification of the corresponding optically active furfuryl alcohols **3**, obtained by chemical[13] or enzymatic reactions.[14, 15] In contrast to these stepwise methods, we envisaged a highly effective, domino synthesis of optically active **5** via the lipase-catalyzed kinetic resolution of (±)-**3** with **2** followed by the intramolecular Diels–Alder reaction (Scheme 2). For the success of this plan, the easy preparation of the reagents **2** with a dienophilic moiety and their applicability in the enzymatic reaction were the pivotal issues to be investigated.

The preparation of new ethoxyvinyl esters **2** was examined by applying our method.[9] Thus, monomethyl fumarate (**1a**) was added to a mixture of ethoxyacetylene (1.5 equiv to **1a**) and $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol% to **1a**) in anhydrous acetone at 0 °C, and the reaction mixture was stirred at room temperature. The reaction was monitored by IR spectroscopy which found that **1a** was consumed within 3–5 h; the formation of **2a** was confirmed by the appearance of the characteristic absorption of its olefin (1676 cm^{-1} in $CHCl_3$). Concentration of the reaction mixture gave 90–95% pure **2a** (^1H NMR analysis) in quantitative yield. However, **2a** was not very stable, and purification by either silica gel flash column chromatography using a mixture of hexane/ethyl acetate/Et_3N as the eluent or distillation under reduced pressure caused partial decomposition. Although the crude **2a** was contaminated with a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$, we have already confirmed that the enzymatic transesterification of various alcohols was not affected by the presence of the ruthenium complex. Thus, the reaction using a crude ethoxyvinyl ester presented the same reactivity and same selectivity as that using the purified reagent.[6b] Therefore, the crude solution of **2a** in acetone was used for the subsequent enzymatic resolution. Similarly, the ethoxyvinyl esters **2b**, **c** having an electron-withdrawing group were prepared in ≥90% yields (^1H NMR analysis) (Scheme 3).



Scheme 3. Preparation of **2a–c** from **1a–c**.

Next, suitable enzymes for the kinetic resolution of (±)-**3a** were investigated using a crude solution of **2a** in acetone. We checked the reaction conversion and the optical purity of the ester **4a** prior to the formation of the cycloadduct **5a**. After screening a number of hydrolytic enzymes including lipases (Amano A-6, AK, AY, PPL, PS; Meito MY, OF; Toyobo LIP; Novo CHIRAZYME L-3) and pig liver esterase, lipases from the *Pseudomonas* species (LIP, AK, PS) were found to actively catalyze the kinetic resolution (Table 1). Especially Toyobo LIP, a lipase from *Pseudomonas aeruginosa* immobilized on Hyflo Super-Cell, gave the optically active (*R*)-**4a** (70% *ee*, 26% yield) along with the recovered alcohol (*S*)-**3a** (34% *ee*, 65% yield) after 10 h (entry 1).

The domino reaction of (±)-**3a** was carried out by simply prolonging the reaction time of the above-mentioned kinetic resolution, and meanwhile, the gradual formation of (2*R*)-*syn*-**5a** and (2*R*)-*anti*-**5a** was observed (Scheme 4). The time-course of the reaction monitored by ^1H NMR analysis has revealed that the Diels–Alder reaction reached equilibrium[16] after 7–8 days (Figure 1). At this point, a 3:2 mixture of (2*R*)-*syn*-**5a** (78–79% *ee*) and (2*R*)-*anti*-**5a** (75–81% *ee*) was obtained in 25–36% yield after a few repeated runs.[17] (*R*)-**4a** (10–68% *ee*, 20–29% yield) and (*S*)-**3a** (73–79% *ee*, 35–46% yield) were also isolated. Quite interestingly, the optical purity of either the *syn*- or *anti*-**5a** was higher than that of the

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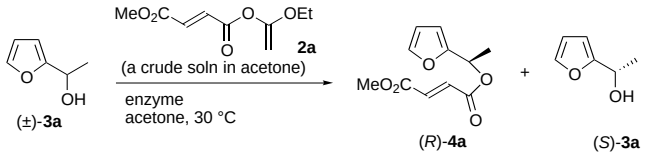
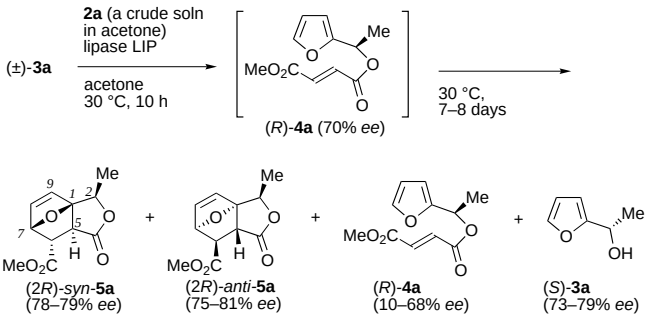
Table 1. Screening of suitable enzymes for the kinetic resolution of (±)-**3a** using **2a**.



Entry	enzyme[a]	Reaction time	(*R*)-**4a**		(*S*)-**3a**	
			ee [%][b]	Yield [%][c]	*ee* [%][d]	Yield [%][c]
1	LIP (*Pseudomonas aeruginosa*)	10 h	70	26	34	65
2	AK (*Pseudomonas* sp.)	1.5 d	≈10	49	8	36
3	PS (*Pseudomonas cepacia*)	1.5 d	≈10	44	6	38

[a] Unreactive enzymes (≤10% conversion after 10 d); A-6 (*Aspergillus niger*), AY (*Candida rugosa*), MY (*Candida rugosa*), OF (*Candida rugosa*), L-3 (*Candida rugosa*), porcine pancreas, and pig liver esterase. [b] Determined by the HPLC (Daicel CHIRALCEL OD) analysis. [c] Isolated yield. [d] Determined by the GC analysis using a chiral column (TCI CHIRALDEX G-TA).



Scheme 4. Lipase LIP-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-**3a** with **2a**.

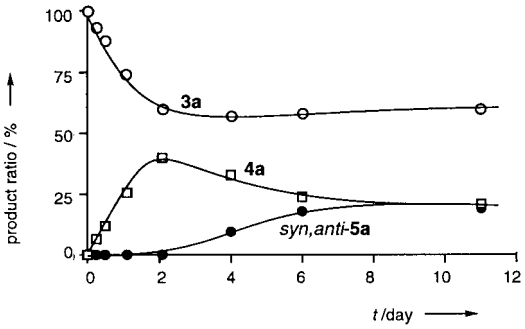


Figure 1. Time-course of the domino reaction of (±)-**3a** with **2a**.

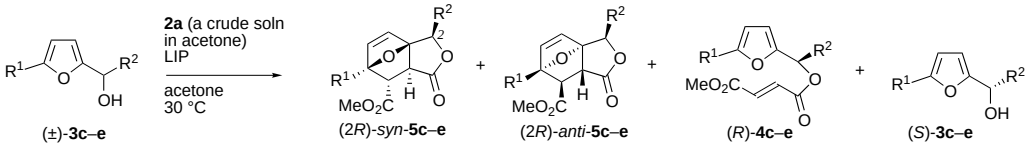
intermediate (*R*)-**4a** (70% *ee*) at 10 h, which suggested some catalytic effect of the lipase on the Diels–Alder reaction with increasing optical purity.[18]

Some other examples of the domino kinetic resolution/intramolecular Diels–Alder reaction of (±)-**3c–e** using crude **2a** are summarized in Table 2. All these reactions provided a mixture of (2*R*)-*syn*- and (2*R*)-*anti*-**5c–e** in favor of the *syn*-isomer. Especially, both *syn*- and *anti*-**5d**, **e** were obtained as a single enantiomer (entries 2 and 3). However, the equilibrium between **4** and **5** has hampered the improvement of the chemical yields of **5c–e**.

On the other hand, the domino reaction of the furfuryl alcohol (±)-**3b** having a methyl group at the C-3 position with **2a** gave much better results than those of **3a** and **3c–e**. Thus, the kinetic resolution at 30 °C reached 50% conversion within one day to provide (2*R*)-*syn*-**5b** (82% *ee*, 42% yield) as a single product along with the recovery of (*S*)-**3b** (71% *ee*, 44% yield) (Table 3, entry 1). The intramolecular Diels–Alder reaction instantaneously and completely proceeded, and formation of the ester **4b** was not detected by the ^{1}H NMR analysis of the crude product. A similar reaction proceeded at 20 °C with better enantioselectivity to give (2*R*)-*syn*-**5b** (91% *ee*, 34% yield) and (*S*)-**3b** (≥99% *ee*, 45% yield) (entry 2), whereas the reaction at 4 °C was tedious and no improvement was attained.

In a similar manner, the reaction of (±)-**3f** with **2a** at 20 °C accomplished perfect resolution to give (2*R*)-*syn*-**5f** (≥99% *ee*, 45% yield) and (*S*)-**3f** (≥99% *ee*, 50% yield) (entry 3). Similar reactions using the in situ prepared **2b**, **c** also provided the corresponding (2*R*)-*syn*-**5g**, **h** (95–≥99% *ee*) and (*S*)-**3f** (96–≥99% *ee*) (entries 4 and 5); however, the

Table 2. Domino kinetic resolution/Diels–Alder reaction of (±)-**3c–e** with **2a**.[a]



For **3–5**; **c:** R^1 = H, R^2 = Et, **d:** R^1 = R^2 = Me, **e:** R^1 = Me, R^2 = Et

Entry	**3**	R^1	R^2	Reaction time	(2*R*)-**5c–e**					(*R*)-**4c–e**		(*S*)-**3c–e**		
						ee [%][b]		Total yield [%][c]	*de* [%][d]		Yield [%][e]		*ee* [%][b]	Yield [%][c]
						syn	*anti*							
1	**3c**	H	Et	12 d	**5c**	77	78	50	46	**4c**	14	**3c**	86	32
2	**3d**	Me	Me	5 d	**5d**	≥99	≥99	31	24	**4d**	23	**3d**	98	46
3	**3e**	Me	Et	5 d	**5e**	≥99	≥99	27	42	**4e**	22	**3e**	≥99	51

[a] The reaction was run according to the typical procedure in the Experimental Section. [b] For determination of the enantiomeric excess of the products, see the general method of the experimental section. [c] Isolated yield. [d] Obtained in favor of *syn*-**5**. Diastereomeric excess was determined by the 500 MHz ^{1}H NMR analysis. [e] Yield based on the 500 MHz ^{1}H NMR analysis of the crude reaction mixture.

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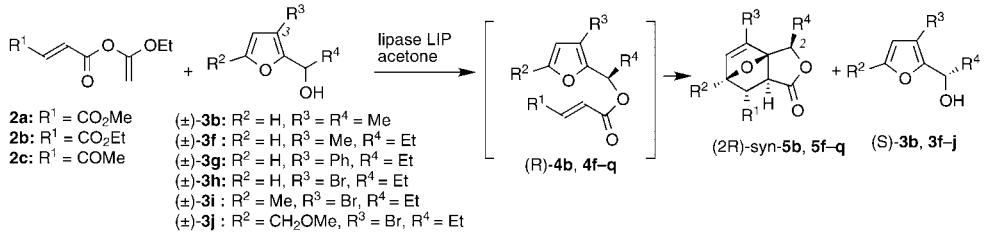
Table 3. Domino kinetic resolution/Diels–Alder reaction of (±)-**3b**, **3f–j** with **2a–c**.[a]



Entry	2	3	Reaction conditions	(2*R*)-*syn*-**5**[b]							(*S*)-**3**		
					R^1	R^2	R^3	R^4	*ee* [%][c]	Yield [%][d]		*ee* [%][c]	Yield [%][d]
1	**2a**	**3b**	30 °C, 1 d	**5b**	CO_2Me	H	Me	Me	82	42	(*S*)-**3b**	71	44
2	**2a**	**3b**	20 °C, 2 d	**5b**	CO_2Me	H	Me	Me	91	34	(*S*)-**3b**	≥99	45
3	**2a**	**3f**	20 °C, 2 d	**5f**	CO_2Me	H	Me	Et	≥99	45	(*S*)-**3f**	≥99	50
4	**2b**	**3f**	30 °C, 4 d	**5g**	CO_2Et	H	Me	Et	≥99	46	(*S*)-**3f**	96	43
5	**2c**	**3f**	30 °C, 4 d	**5h**	COMe	H	Me	Et	95	44	(*S*)-**3f**	≥99	47
6	**2b**	**3g**	30 °C, 7 d	**5i**	CO_2Et	H	Ph	Et	–	trace	**3g**	–	>95
7	**2b**	**3h**	30 °C, 6 d	**5j**	CO_2Et	H	Br	Et	96	43	(*S*)-**3h**	≥99	38
8	**2c**	**3h**	30 °C, 5 d	**5k**	COMe	H	Br	Et	≥99	40	(*S*)-**3h**	≥99	48
9[e]	**2a**	**3i**	30 °C, 2.5 d	**5l**	CO_2Me	Me	Br	Et	95	35	(*S*)-**3i**	82	54
10	**2b**	**3i**	30 °C, 2.5 d	**5m**	CO_2Et	Me	Br	Et	95	30	(*S*)-**3i**	≥99	45
11[e]	**2c**	**3i**	10 °C, 1 d	**5n**	COMe	Me	Br	Et	≥99	34[f]	(*S*)-**3i**	82	48
12	**2a**	**3j**	30 °C, 4.5 d	**5o**	CO_2Me	CH_2OMe	Br	Et	94	43	(*S*)-**3j**	≥99	44
13	**2b**	**3j**	30 °C, 4.5 d	**5p**	CO_2Et	CH_2OMe	Br	Et	96	45	(*S*)-**3j**	98	44
14	**2c**	**3j**	30 °C, 4.5 d	**5q**	COMe	CH_2OMe	Br	Et	93	36	(*S*)-**3j**	93	44

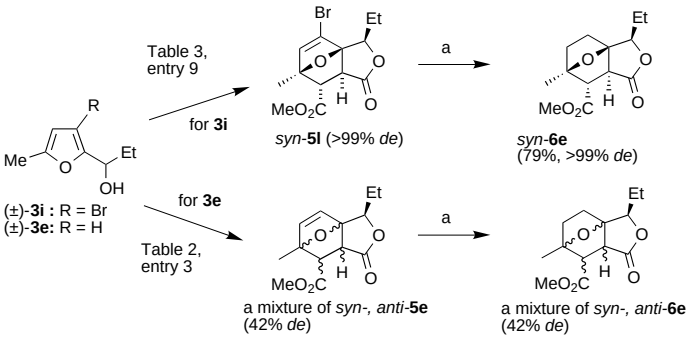
[a] The reaction was run according to the typical procedure in the Experimental Section. [b] *syn*:*anti* >99:1 based on the ^{1}H NMR analysis of the crude reaction mixture. [c] For determination of the enantiomeric excess of the products, see the methods of the Experimental Section. [d] Isolated yield. [e] Formation of the ester **4** was observed based on the ^{1}H NMR analysis of the crude product; 6% for entry 9, 11% for entry 11. [f] Contaminated with 12% of the corresponding ester **4n** due to the retro-Diels–Alder reaction of **5n** during the silica gel column chromatography.

application of this method to (±)-**3g** having a phenyl group at the C-3 position resulted in no reaction (entry 6).

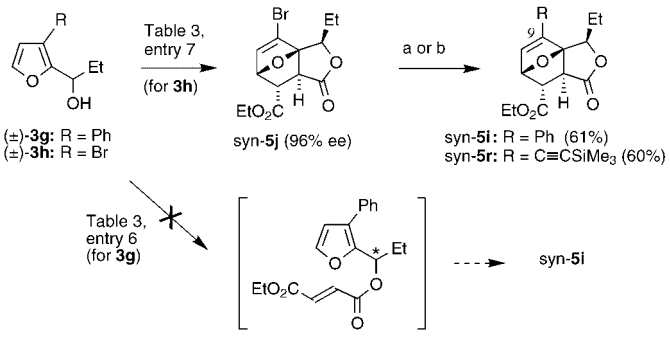
As mentioned above, some problems have been uncovered for the C-3 unsubstituted furfuryl alcohols **3a**, **3c–e** and the C-3 phenyl substituted one **3g**: The low yield and the low diastereoselectivity for **3a**, **3c–e** and the limited applicability for the sterically congested alcohols such as **3g**. Aiming at the solution of these problems at once, we next investigated the domino reaction of the furfuryl alcohol (±)-**3h** having a key bromo group at the C-3 position.[19] To our delight, the reaction of the 3-bromofuryl alcohol (±)-**3h** with **2b** at 30 °C gradually gave the cycloadduct, (2*R*)-*syn*-**5j**. After six days, the Diels–Alder reaction reached completion, and (2*R*)-*syn*-**5j** (96% *ee*, 43% yield) and (*S*)-**3h** (≥99% *ee*, 38% yield) were isolated (entry 7). The exclusive diastereoselectivity was confirmed by the ^{1}H NMR analysis of the crude product. Likewise, (±)-**3h–j** and **2a–c** were subjected to similar reaction conditions to produce the diastereoselective preparation of (2*R*)-*syn*-**5k–q** with 93–≥99% *ee* (entries 8–14). In most cases, the Diels–Alder reaction was brought to completion; however, the reaction of **2c** and **3i** suffered from an incomplete Diels–Alder reaction and also the retro-Diels–Alder reaction during the silica gel chromatography (entry 11).

The hydrogenation of *syn*-**5l** afforded *syn*-**6e** (>99% *de*) in 79% yield. On the contrary, the same sequence from **3e** resulted in the formation of a hardly separable mixture of *syn*- and *anti*-**6e** (Scheme 5).

The application of the Suzuki coupling[20] to *syn*-**5j** enabled us to obtain *syn*-**5i** (61% yield) which could not be prepared from **3g** (Table 3, entry 6). Similarly, by the Sonogashira coupling,[21] *syn*-**5r** having a (trimethylsilyl)ethynyl group was prepared in 60% yield (Scheme 6). This protocol will open a



Scheme 5. Preparation of *syn*-**6e**. a) Pd/C, H_2, MeOH, room temperature.



Scheme 6. Preparation of *syn*-**5i** and **5r** having a bulky substituent. a) $PhB(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, THF, 65 °C; b) (trimethylsilyl)acetylene, $Pd(PPh_3)_4$, CuI, Et_2NH, DMF, 50 °C.

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new approach towards the asymmetric synthesis of some biologically interesting natural products such as viridin[22] and himbacine.[23]

The absolute configuration of **3a–e** recovered in the enzymatic reactions was determined to be (*S*) based on the comparison of their specific rotation values with those of the reported values. The product *syn*-**6e** from either **3e** or **3i** was identical, and therefore, the absolute stereochemistry of (2*R*)-**5l** and (*S*)-**3i** was determined. The absolute configuration of all the new alcohols **3f**,**h**, **j** was deduced to be (*S*) based on the similarity of their specific rotational values to those of **3a–e** and **3i**. Consequently, the absolute configuration of all the Diels–Alder adducts **5a–q** is (*R*) at the C-2 position. The relative stereochemistry of the adducts, *syn*-**5a**, *anti*-**5a**, *syn*-**5b**, *syn*-**5c**, and *anti*-**5c**, was determined by the comparison of their ^{1}H NMR data with those of the reported data.[12a] The others were deduced to be the same by the similarity of their ^{1}H and ^{13}C NMR data to those of **5a–c**.

Conclusion

The first lipase-catalyzed domino reaction was developed in which the acyl moiety installed during the enzymatic kinetic resolution was utilized as a part of the constituent structure for the subsequent Diels–Alder reaction. Coupled with the in situ preparation of **2**, this reaction has achieved a one-pot synthesis of optically active 7-oxabicyclo[2.2.1]heptene derivatives **5** having five chiral, non-racemic carbon centers from an achiral carboxylic acid **1** and a racemic alcohol **3** (Scheme 2). It also takes advantages of the atom efficiency and the environmentally acceptable nature of the lipases, and therefore, is attractive as a new environmentally benign protocol. We believe wide applicability of this concept to a finely designed process that starts from a carboxylic acid with a reactive functional group and an alcohol with a reactive counterpart.[24]

On the other hand, the potential catalytic effect of the lipase LIP on the Diels–Alder reaction offers an interesting topic because the natural-enzyme-catalyzed Diels–Alder reactions have recently been receiving increasing attention.[25] A detailed evaluation of the lipase effect is currently under progress in our laboratory.

Experimental Section

Methods: The ^{1}H NMR spectra were measured at 300 or 500 MHz with tetramethylsilane (TMS) as the internal standard at 20–25 °C. The ^{13}C NMR spectra were measured at 75 or 125 MHz with TMS as the internal standard at 20–25 °C. The IR spectra were recorded by a diffuse reflectance measurement of samples dispersed in KBr powder or as a $CHCl_3$ solution. Flash column chromatography was done using silica gel BW-300 (200–400 mesh, Fuji Silysia Chemical Co., Ltd., Japan). Yields refer to isolated material of ≥95% purity as determined by ^{1}H NMR unless otherwise noted. The diastereoselectivity of the *syn*- and *anti*-**5** was determined based on the ^{1}H NMR (300 or 500 MHz) data of the crude product. The determination of the optical purity of the products was performed by the following methods: **3a–f**, chiral GC analysis using TCI CHIRALDEX G-TA (10 m × 0.125 mm, 0.125 μm film thickness); **3h–j**, **4a**, **5k–n**, chiral HPLC analysis using a Daicel CHIRALCEL OD or OD-H column (250 mm × 4.6 mm); **4j**, **5j**, **p**, chiral HPLC analysis using a Daicel CHIRALPAK AD-H column (250 mm × 4.6 mm); **5a–c**, **f**, **o**, chiral HPLC analysis using a Daicel CHIRALCEL OJ column (250 mm × 4.6 mm); **5q**, chiral HPLC analysis using a Daicel CHIRALPAK AS column (250 mm × 4.6 mm); **5a**, **d**, **e**, **g**,**h**, chiral GC analysis (TCI CHIRALDEX G-TA) of its derivative obtained by hydrogenation of the mixture of *syn*- and *anti*-**5** (for details, see the hydrogenation of **5d**). A mixture of hexane-iPrOH was used as the eluent for the HPLC analysis.

Materials: Lipases AK (*Pseudomonas* sp.), PS (*Pseudomonas cepacia*), A-6 (*Aspergillus niger*), AY (*Candida rugosa*), porcine pancreas, and pig liver esterase were gifts from Amano Enzyme Inc. (Japan). Lipase MY (*Candida rugosa*) and OF (*Candida rugosa*) were gifts from Meito Sangyo Co., Ltd. (Japan). CHIRAZYME L-3 (*Candida rugosa*) was a gift from Roche Diagnostics (Japan). Lipases LIP (*Pseudomonas aeruginosa*) was a gift from Toyobo Co., Ltd. (Japan). Enzymes except for LIP were dried (1 mm Hg, room temperature, overnight) prior to use, and LIP was used without prior treatment. Anhydrous acetone (H_2O ≤0.005%) used for the preparation of **2** and the subsequent enzymatic reaction was purchased from Kanto Chemical Co., Inc. (Japan), and kept under a nitrogen atmosphere before use. Known compounds [**1a**,[26] **1b**,[26, 27] **1c**,[28] (±)-**3a-c**,[12a] (±)-**3d**,[29] (±)-**3e**,[29] and (±)-**4a**[12a]] were prepared according to their reported methods. Unknown compounds (±)-**3f–j** were prepared as follows. The others are commercially available.

(±)-1-(3-Methyl-2-furyl)propanol (3f): Under a nitrogen atmosphere, EtMgBr (1.0 M in THF, 17 mL, 17 mmol) was added to an ice-cooled solution of 3-methyl-2-furfural[12a] (1.6 g, 14 mmol) in anhydrous THF (15 mL). The reaction mixture was stirred at 0 °C for 30 min and quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 1:1) gave (±)-**3f** (1.1 g, 56%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.5$ Hz, 3H), 1.74 (d, $J = 5.5$ Hz, 1H), 1.82–1.98 (m, 2H), 2.04 (s, 3H), 4.61 (dt, $J = 5.0$, 7.0 Hz, 1H), 6.19 (d, $J = 2.0$ Hz, 1H), 7.28 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.6$, 10.0, 28.8, 67.5, 112.9, 116.3, 140.9, 150.6; IR (KBr): $\tilde{\nu} = 3603$, 1587 cm^{-1}; elemental analysis calcd (%) for $C_8H_{12}O_2$ (140.2): C 68.54, H 8.63; found: C 68.31, H 8.60.

(±)-1-(3-Phenyl-2-furyl)propanol (3g): Under a nitrogen atmosphere, $PhB(OH)_2$ (160 mg, 1.25 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol), and 2 M aqueous Na_2CO_3 (2.0 mL, 4.0 mmol) were successively added to a solution of (±)-**3g** (100 mg, 0.50 mmol) in THF (10 mL). The reaction mixture was stirred at refluxing temperature for 12 h. After cooling, the reaction was quenched with water, and the product was extracted with EtOAc twice. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by Japan Analytical Industry Co., Ltd. Recycling preparative HPLC LC-928 equipped with gel permeation chromatography columns, JAIGEL 1H and 2H (each 600 mm × 20 mm) (eluent: $CHCl_3$) to give **3g** (24 mg, 24%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.5$ Hz, 3H), 1.91–2.01 (m, 2H), 4.72 (dd, $J = 7.0$, 12.5 Hz, 1H), 6.51 (d, $J = 2.0$ Hz, 1H), 7.27–7.56 (m, 6H); IR (KBr): $\tilde{\nu} = 3342$, 1612, 1512 cm^{-1}; HRMS: calcd for $C_{13}H_{14}O_2$ [M^+]: 202.0994; found: 202.1001.

(±)-1-(3-Bromo-2-furyl)propanol (3h): According to the reported method,[30] a solution of 3-bromo-2-lithiofuran in anhydrous THF was prepared from 3-bromofuran (0.90 mL, 10 mmol), *i*Pr_2NH (1.4 mL, 10 mmol), and *n*BuLi (1.6 M in hexane, 6.4 mL, 10 mmol). A solution of propanal (0.80 mL, 11 mmol) in anhydrous THF (15 mL) was added to it at −78 °C, and the reaction mixture was stirred at −78 °C for 15 min and quenched with saturated aqueous NH_4Cl (125 mL). The product was extracted with Et_2O three times, and the combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (hexane/Et_2O 19:1 → 3:1) gave (±)-**3h** (1.5 g, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.5$ Hz, 3H), 1.82–1.98 (m, 2H), 2.21 (s, 1H), 4.71 (t, $J = 7.5$ Hz, 1H), 6.39 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.8$, 28.3, 67.2, 97.4, 113.7, 142.2, 152.2; IR (KBr): $\tilde{\nu} = 3342$, 1574 cm^{-1}; elemental analysis calcd (%) for $C_7H_9BrO_2$ (205.0): C 41.00, H 4.42; found: C 40.95, H 4.37.

(±)-1-(3-Bromo-5-methyl-2-furyl)propanol (3i): Prepared according to the reported method for the synthesis of similar compounds.[31] Under a nitrogen atmosphere, *i*Pr_2NH (3.4 mL, 24 mmol) and *n*BuLi (1.6 M in

hexane, 15.6 mL, 24 mmol) were successively added to a mixture of KO(*t*Bu) (2.7 g, 24 mmol) and anhydrous THF (50 mL), and the reaction mixture was stirred at −78 °C for 1 h. A solution of 2-bromo-5-methylfuran (3.3 g, 20 mmol) in anhydrous THF (10 mL) was added to the above reaction mixture over a period of 5 min, and the mixture was gradually allowed to warm up to −20 °C over a period of 1 h with stirring. After 1 h at −20 °C, propanal (2.3 mL, 32.6 mmol) was added to the reaction mixture over a period of 10 min, and the whole mixture was stirred at −20 °C for 2 h and then at 0 °C for 4 h. The reaction mixture was poured onto a 1:1 mixture of saturated aqueous NH_4Cl and ice. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/Et_2O 5:1 → 3:1) to give **3i** (0.57 g, 13 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.5$ Hz, 3H), 1.82–1.94 (m, 2H), 2.26 (d, $J = 1.0$ Hz, 3H), 4.65 (dt, $J = 5.5$, 7.5 Hz, 1H), 5.97 (q, $J = 1.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.9$, 13.7, 28.4, 67.3, 97.8, 109.6, 150.3, 152.1; IR (KBr): $\tilde{\nu} = 3340$, 1568 cm^{-1}; elemental analysis calcd (%) for $C_8H_{11}BrO_2$(219.1): C 43.86, H 5.06; found: C 44.17, H 5.14.

(±)-1-(3-Bromo-5-methoxymethyl-2-furyl)propanol (3j): Methyl 4,5-dibromofuran-2-carboxylate[32] was converted to 2,3-dibromo-5-(methoxymethyl)furan by standard methods: Reduction using diisobutylaluminum hydride in THF followed by O-methylation using NaH and MOMCl in THF. Under a nitrogen atmosphere, a solution of 2,3-dibromo-5-(methoxymethyl)furan (0.20 g, 0.74 mmol) in anhydrous THF (2 mL) was cooled to −78 °C, and *n*BuLi (1.6 M in hexane, 0.48 mL, 0.74 mmol) was added. After stirring the reaction mixture at −78 °C for 20 min, a solution of propanal (47 mg, 0.82 mmol) in anhydrous THF (3 mL) was added over 1 min. The reaction mixture was stirred for 5 min and quenched with saturated aqueous NH_4Cl. Similar work-up and column chromatography (hexane/Et_2O 49:1 → 1:1) as described for the preparation of **3h** gave (±)-**3j** (46 mg, 25 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.5$ Hz, 3H), 1.83–2.04 (m, 2H), 2.01 (s, 1H), 3.35 (s, 3H), 4.35 (s, 2H), 4.67–4.74 (m, 1H), 6.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.8$, 28.4, 57.9, 66.1, 67.3, 97.6, 113.0, 151.2, 152.4; IR (KBr): $\tilde{\nu} = 3396$, 1601 cm^{-1}; elemental analysis calcd (%) for $C_9H_{13}BrO_3$ (249.1): C 43.39, H 5.26; found: C 43.08, H 5.11.

1-Ethoxyvinyl methyl fumarate (2a)—A Typical procedure for the preparation of 2: Under a nitrogen atmosphere, **1a** (98 mg, 0.75 mmol) was portionwise added to an ice-cooled solution of ethoxyacetylene[7e] (79 mg, 1.1 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (4.5 mg, 0.0075 mmol) in anhydrous acetone (3.0 mL) over a period of 30 min. The reaction mixture was stirred at room temperature for 5 h. An aliquot was concentrated in vacuo and was subject to ^{1}H NMR and IR analyses. Usually **1a** was consumed at this point. In the case of incomplete reaction, the stirring was continued for another 5 h. The reaction mixture was used for the following enzymatic reaction as such. Concentration of the reaction mixture in vacuo gave **2a** (160 mg, quant.) with 90–95 % purity based on the ^{1}H NMR analysis. Similar reaction was run from **1a** (1.0 g, 7.7 mmol) and the crude product was purified by either flash column chromatography (hexane/EtOAc/Et_3N 83:17:1) or distillation [b.p. 120–130 °C at 2.0 mmHg (bath temp.)] to give analytically pure **2a** as a colorless oil (0.47 g, 31 % or 0.80 g, 52 %, respectively). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (t, $J = 7.0$ Hz, 3H), 3.81 (d, $J = 3.5$ Hz, 1H), 3.82 (s, 3H), 3.88 (d, $J = 3.5$ Hz, 1H), 3.90 (q, $J = 7.0$ Hz, 2H), 6.88 (d, $J = 16.0$ Hz, 1H), 6.97 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 52.5, 65.2, 72.2, 132.4, 135.1, 156.7, 162.1, 165.0; IR ($CHCl_3$): $\tilde{\nu} = 1755$, 1732, 1676 cm^{-1}; elemental analysis calcd (%) for $C_9H_{12}O_5$ (200.2): C 54.00, H 6.04; found: C 54.04, H 6.02.

1-Ethoxyvinyl ethyl fumarate (2b): Similarly to the preparation of **2a**, **2b** (5.3 g, quant., approx. 95 % purity by ^{1}H NMR analysis) was obtained from **1b** (3.6 g, 25 mmol) and was used for the following enzymatic reaction as such. Distillation of the crude product gave analytically pure **2b** (1.6 g, 30 %) as a colorless oil. B.p. 105–107 °C at 2.5 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (t, $J = 7.0$ Hz, 3H), 1.35 (t, $J = 7.0$ Hz, 3H), 3.83 (d, $J = 4.0$ Hz, 1H), 3.91 (d, $J = 4.0$ Hz, 1H), 3.93 (q, $J = 7.0$ Hz, 2H), 4.28 (q, $J = 7.0$ Hz, 2H), 6.88 (d, $J = 16.0$ Hz, 1H), 6.97 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$, 61.4, 65.0, 72.0, 132.0, 135.6, 156.7, 162.1, 164.4; IR ($CHCl_3$): $\tilde{\nu} = 1751$, 1724, 1676 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{14}O_5$ (214.2): C 56.07, H 6.59; found: C 55.53, H 6.50.

1-Ethoxyvinyl 4-oxo-2-pentenoate (2c): Similarly to the preparation of **2a**, **2c** (2.4 g, quant., approx. 90 % purity by ^{1}H NMR analysis) was obtained from **1c** (1.37 g, 12 mmol) and was used for the following enzymatic reaction as such. Distillation of the crude product gave analytically pure **2c** (0.11 g, 5 %) as a pale yellow oil. B.p. 70–80 °C at 2.0 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.0$ Hz, 3H), 2.38 (s, 3H), 3.83 (d, $J = 3.5$ Hz, 1H), 3.907 (q, $J = 7.0$ Hz, 2H), 3.912 (d, $J = 3.5$ Hz, 1H), 6.68 (d, $J = 16.0$ Hz, 1H), 7.12 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 28.3, 65.1, 72.1, 129.9, 141.5, 156.7, 162.6, 197.0; IR ($CHCl_3$): $\tilde{\nu} = 1751$, 1703, 1676 cm^{-1}; elemental analysis calcd (%) for $C_9H_{12}O_4$ (184.2): C 58.69, H 6.57; found: C 58.23, H 6.65.

Lipase-catalyzed kinetic resolution of (±)-3a with 2a: A solution of **2a** (0.75 mmol) in acetone (3.0 mL), prepared as above-described, was placed in a resealable tube. (±)-**3a** (56 mg, 0.50 mmol) and lipase LIP (0.10 g) were added, and the tube was sealed. The reaction mixture was stirred at 30 °C for 10 h and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (hexane/Et_2O 3:1) to give (*S*)-**3a** (36 mg, 65 %, 34 % *ee*) and (*R*)-**4a** (29 mg, 26 %, 70 % *ee*).

(*S*)-3a (34 % *ee*): Colorless oil. $[\alpha]_D^{28} = -5.8$ (*c* = 1.0, $CHCl_3$). [lit.[13f] $[\alpha]_D^{24} = -20.1$ (*c* = 1.0, $CHCl_3$)].

(*R*)-1-(2-Furyl)ethyl methyl fumarate [(*R*)-4a] (70 % *ee*): Colorless oil. $[\alpha]_D^{27} = +6.2$ (*c* = 1.4, CH_2Cl_2) [lit.[12a] $[\alpha]_D^{25} = -8.8$ (*c* = 4.6, CH_2Cl_2) for (*S*)-**4a**]. Spectroscopic data of **4a** were identical with the reported data.[12a]

Lipase-catalyzed domino kinetic resolution/Diels–Alder Reaction of (±)-3a with 2a—A typical procedure: A solution of **2a** (0.75 mmol) in acetone (3.0 mL), prepared as above-described, was placed in a resealable tube. (±)-**3a** (56 mg, 0.50 mmol) and lipase LIP (0.10 g) were added, and the tube was sealed. The reaction mixture was stirred at 30 °C for 8 d and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (hexane/Et_2O/Et_3N 16:4:1)[33] to give (*S*)-**3a** (20 mg, 35 %, 73 % *ee*), (*R*)-**4a** (22 mg, 20 %, 10 % *ee*), and a 63:37 mixture of (2*R*)-*syn*- and (2*R*)-*anti*-**5a** (40 mg, 36 %, 79 % *ee* for *syn*-**5a**, 81 % *ee* for *anti*-**5a**). ^{1}H NMR ($CDCl_3$) and IR data for *syn*- and *anti*-**5a** were identical with the reported data.[12a]

Methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-2-methyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5a): ^{1}H NMR (500 MHz, [D$_6$]acetone[33]): $\delta = 1.36$ (d, $J = 6.5$ Hz, 3H), 3.17 (d, $J = 3.5$ Hz, 1H), 3.40–3.43 (m, 1H), 3.65 (s, 3H), 5.29 (q, $J = 6.5$ Hz, 1H), 5.32 (dd, $J = 1.5$, 4.5 Hz, 1H), 6.40 (dd, $J = 1.5$, 6.0 Hz, 1H), 6.70 (d, $J = 6.0$ Hz, 1H).

(1*S*,2*R*,5*R*,6*R*,7*R*)-Diastereomer (*anti*-5a): ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.64$ (d, $J = 6.5$ Hz, 3H), 3.15 (d, $J = 3.5$ Hz, 1H), 3.40–3.43 (m, 1H), 3.65 (s, 3H), 4.82 (q, $J = 6.5$ Hz, 1H), 5.28–5.30 (m, 1H), 6.43 (dd, $J = 1.5$, 6.0 Hz, 1H), 6.74 (d, $J = 6.0$ Hz, 1H).

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3c with 2a: Similarly to the typical procedure, a mixture of **2a** (0.75 mmol), (±)-**3c** (63 mg, 0.50 mmol), and lipase LIP (0.10 g) was stirred at 30 °C for 12 d to give (*S*)-**3c** (20 mg, 32 %, 86 % *ee*), (*R*)-**4c** (14 %, NMR yield), and a 73:27 mixture of (2*R*)-*syn*- and (2*R*)-*anti*-**5c** (60 mg, 50 %, 77 % *ee* for *syn*-**5c**, 78 % *ee* for *anti*-**5c**). ^{1}H NMR ($CDCl_3$) and IR data for (*S*)-**3c**, (*R*)-**4c**, *syn*-**5c**, and *anti*-**5c** were identical with the reported data.[12a] The optical rotation power of (*R*)-**4c** could not be obtained due to contamination of small amount of impurity hardly separable by flash column chromatography.

(*S*)-3c (86 % *ee*): Colorless oil. $[\alpha]_D^{23} = -9.7$ (*c* = 0.5, $CHCl_3$) [lit.[13b] $[\alpha]_D^{25} = +12.6$ (*c* = 2.1, $CHCl_3$) for 95 % *ee* of (*R*)-form].

Methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5c) and its (1*S*,2*R*,5*R*,6*R*,7*R*)-diastereomer (*anti*-5c): A 73:27 mixture of *syn*- and *anti*-**5c**; colorless crystals; IR (KBr): $\tilde{\nu} = 1779$, 1738, 1734 cm^{-1}.

***syn*-5c** (77 % *ee*): ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.00$ (t, $J = 7.5$ Hz, 3H), 1.68–1.86 (m, 2H), 3.16 (d, $J = 3.0$ Hz, 1H), 3.39–3.42 (m, 1H), 3.69 (s, 3H), 5.05 (t, $J = 7.5$ Hz, 1H), 5.31 (dd, $J = 2.0$, 5.0 Hz, 1H), 6.38 (dd, $J = 2.0$, 6.0 Hz, 1H), 6.72 (d, $J = 6.0$ Hz, 1H).

***anti*-5c** (78 % *ee*): ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.12$ (t, $J = 7.5$ Hz, 3H), 1.86–2.11 (m, 2H), 3.07 (d, $J = 3.0$ Hz, 1H), 3.39–3.42 (m, 1H), 3.64 (s, 3H), 4.59 (dd, $J = 4.5$, 9.0 Hz, 1H), 5.28 (dd, $J = 2.0$, 5.0 Hz, 1H), 6.43 (dd, $J = 2.0$, 6.0 Hz, 1H), 6.74 (d, $J = 6.0$ Hz, 1H).

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3d with 2a: Similarly to the typical procedure, a mixture of **2a** (3.0 mmol), (±)-**3d** (0.25 g, 2.0 mmol), and lipase LIP (0.40 g) was stirred at 30 °C for

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5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 75:25:1) to give (*S*)-**3d** (116 mg, 46%, 98% *ee*), (*R*)-**4d** (23%, NMR yield), and a 62:38 mixture of (2*R*)-*syn*- and (2*R*)-*anti*-**5d** (148 mg, 31%, ≥99% *ee* for both *syn*- and *anti*-**5d**). Analytically pure (2*R*)-*syn*-**5d** was obtained by the second flash column chromatography (hexane/Et_2O/Et_3N 75:25:1) of the mixture of *syn*- and *anti*-**5d**. The optical rotation power of (*R*)-**4d** could not be obtained due to contamination of small amount of impurity hardly separable by flash column chromatography. Elemental analysis calcd (%) for a mixture of *syn*- and *anti*-**5d**: $C_{12}H_{14}O_5$ (238.2): C 60.50, H 5.92; found: C 60.28, H 5.87.

(*S*)-3d (98% *ee*): Colorless oil; $[\alpha]_D^{25} = -10.5$ (*c* = 0.35, $CHCl_3$) [lit.[15] $[\alpha]_D = +8.5$ (*c* = 2.2, $CHCl_3$) for 95% *ee* of (*R*)-form].

Methyl (*R*)-1-(5-methyl-2-furyl)ethyl fumarate (*R*)-4d: Colorless oil; ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 1.58$ (d, *J* = 6.5 Hz, 3H), 2.24 (d, *J* = 1.0 Hz, 3H), 3.76 (s, 3H), 5.94–6.01 (m, 2H), 6.33 (d, *J* = 3.0 Hz, 1H), 6.76 (br s, 2H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 13.4$, 18.3, 52.5, 66.9, 107.2, 110.1, 134.1, 134.3, 152.0, 153.1, 164.5, 165.6; IR (KBr): $\tilde{\nu} = 1780$, 1724, 1647, 1562 cm^{-1}; HRMS: calcd for $C_{12}H_{14}O_5$ [M^+]: 238.0841; found: 238.0841.

Methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-2,7-dimethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]-dec-8-ene-6-carboxylate (*syn*-5d) (≥99% *ee*): Colorless oil; $[\alpha]_D^{27} = -16.1$ (*c* = 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 1.35$ (d, *J* = 6.5 Hz, 3H), 1.74 (s, 3H), 3.06 (d, *J* = 3.5 Hz, 1H), 3.28 (d, *J* = 3.5 Hz, 1H), 3.66 (s, 3H), 5.23 (q, *J* = 6.5 Hz, 1H), 6.25 (d, *J* = 5.5 Hz, 1H), 6.66 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 14.5$, 18.6, 52.5, 54.1, 54.3, 60.4, 76.7, 110.9, 135.2, 139.1, 170.8, 206.1; IR (KBr): $\tilde{\nu} = 1774$, 1732 cm^{-1}; HRMS: calcd for $C_{12}H_{14}O_5$ [M^+]: 238.0841; found: 238.0851.

***anti*-5d** (≥99% *ee*): ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 1.59$ (d, *J* = 7.0 Hz, 3H), 1.73 (s, 3H), 3.04 (d, *J* = 3.5 Hz, 1H), 3.26 (d, *J* = 3.5 Hz, 1H), 3.66 (s, 3H), 4.78 (q, *J* = 7.0 Hz, 1H), 6.28 (d, *J* = 6.0 Hz, 1H), 6.69 (d, *J* = 6.0 Hz, 1H).

Hydrogenation of a mixture of (2*R*)-*syn*- and (2*R*)-*anti*-5d: A mixture of a 62:38 mixture of (2*R*)-*syn*- and (2*R*)-*anti*-**5d** (10 mg) and 10% Pd/C (10 mg) in MeOH (1.5 mL) was stirred at room temperature under atmospheric pressure of hydrogen overnight. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo to give a 58:42 mixture of methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-2,7-dimethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]decane-6-carboxylate (*syn*-**6d**) and its (1*S*,2*R*,5*R*,6*R*,7*R*)-diastereomer (*anti*-**6d**). This crude product was subjected to GC (CHIRALDEX G-TA) analysis to determine their optical purity. Some characteristic ^{1}H NMR data (300 MHz, [D$_6$]acetone): *syn*-**6d** $\delta = 1.37$ (d, *J* = 6.5 Hz, 3H), 1.58 (s, 3H), 3.74 (s, 3H), 4.86 (q, *J* = 6.5 Hz, 1H). *anti*-**6d** $\delta = 1.41$ (d, *J* = 7.0 Hz, 3H), 1.56 (s, 3H), 3.74 (s, 3H), 4.73 (q, *J* = 7.0 Hz, 1H).

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3e with 2a: Similarly to the typical procedure, a mixture of **2a** (3.0 mmol), (±)-**3e** (0.28 g, 2.0 mmol), and lipase LIP (0.40 g) was stirred at 30 °C for 5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 100:50:1) to give (*S*)-**3e** (143 mg, 51%, ≥99% *ee*), (*R*)-**4e** (22%, NMR yield), and a 71:29 mixture of (2*R*)-*syn*- and (2*R*)-*anti*-**5e** (136 mg, 27%, ≥99% *ee* for both *syn*- and *anti*-**5e**). The optical rotation power of (*R*)-**4e** could not be obtained due to contamination of small amount of impurity hardly separable by flash column chromatography.

(*S*)-3e (≥99% *ee*): Colorless oil; $[\alpha]_D^{25} = -11.3$ (*c* = 1.4, $CHCl_3$) [lit.[13d] $[\alpha]_D^{20} = +7.6$ (*c* = 1.0, $CHCl_3$) for 70% *ee* of (*R*)-form].

(*R*)-4e: Colorless oil; ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 0.90$ (t, *J* = 7.5 Hz, 3H), 1.99 (quint, *J* = 7.5 Hz, 1H), 2.24 (s, 3H), 3.77 (s, 3H), 5.78 (t, *J* = 7.0 Hz, 1H), 5.98 (br s, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 6.78 (s, 2H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 10.1$, 13.4, 26.3, 52.5, 71.8, 107.1, 110.7, 134.1, 134.2, 151.1, 153.1, 164.5, 165.6; IR (KBr): $\tilde{\nu} = 1782$, 1726, 1645, 1562 cm^{-1}; HRMS: calcd for $C_{13}H_{16}O_5$ [M^+]: 252.0998; found: 252.1021.

Methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-7-methyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5e) and its (1*S*,2*R*,5*R*,6*R*,7*R*)-diastereomer (*anti*-5e): A 71:29 mixture of *syn*- and *anti*-**5e**: Colorless oil; IR (KBr): $\tilde{\nu} = 1776$, 1769, 1735, 1730 cm^{-1}; HRMS: calcd for $C_{13}H_{16}O_5$ [M^+]: 252.0998; found: 252.1002.

***syn*-5e** (≥99% *ee*): ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.00$ (t, *J* = 7.5 Hz, 3H), 1.67–2.08 (m, 2H), 1.75 (s, 3H), 3.04 (d, *J* = 3.5 Hz, 1H), 3.27 (d, *J* = 3.5 Hz, 1H), 3.66 (s, 3H), 4.99 (t, *J* = 7.5 Hz, 1H), 6.23 (d, *J* = 6.0 Hz, 1H), 6.69 (d, *J* = 6.0 Hz, 1H).

***anti*-5e** (≥99% *ee*): ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.11$ (t, *J* = 7.5 Hz, 3H), 1.67–2.08 (m, 2H), 1.73 (s, 3H), 3.04 (d, *J* = 3.5 Hz, 1H), 3.19 (d, *J* = 3.5 Hz, 1H), 3.66 (s, 3H), 4.55 (dd, *J* = 4.0, 9.5 Hz, 1H), 6.28 (d, *J* = 6.0 Hz, 1H), 6.70 (d, *J* = 6.0 Hz, 1H).

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3b with 2a: Similarly to the typical procedure, a mixture of **2a** (1.5 mmol), (±)-**3b** (128 mg, 1.0 mmol), and lipase LIP (0.20 g) was stirred at 20 °C for 2 days followed by flash column chromatography (hexane/Et_2O/Et_3N 100:50:1) to give (*S*)-**3b** (58 mg, 45%, ≥99% *ee*) and (2*R*)-*syn*-**5b** (81 mg, 34%, 91% *ee*).

(*S*)-3b (≥99% *ee*): Colorless oil; $[\alpha]_D^{20} = -47.9$ (*c* = 1.1, $CHCl_3$) [lit.[12a] $[\alpha]_D^{20} = +34.6$ (*c* = 2.27, $CHCl_3$) for 85% *ee* of (*R*)-form].

Methyl (1*S*,2*R*,5*S*,6*S*,7*S*)-2,9-dimethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]-dec-8-ene-6-carboxylate (*syn*-5b): Colorless crystals (91% *ee*); m.p. 94–96 °C [lit.[12a] m.p. 98–100 °C (MeOH)]; $[\alpha]_D^{17} = -56.0$ (*c* = 0.81, $CHCl_3$). ^{1}H NMR ($CDCl_3$) and IR data were identical with the reported ones.[12a]

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3f with 2a: Similarly to the typical procedure, a mixture of **2a** (0.75 mmol), (±)-**3f** (70 mg, 0.50 mmol), and lipase LIP (0.20 g) was stirred at 20 °C for 2 d followed by flash column chromatography (hexane/Et_2O/Et_3N 100:50:1) to give (*S*)-**3f** (35 mg, 50%, ≥99% *ee*) and (2*R*)-*syn*-**5f** (57 mg, 45%, ≥99% *ee*).

(*S*)-3f (≥99% *ee*): Colorless oil; $[\alpha]_D^{20} = -35.3$ (*c* = 0.65, $CHCl_3$).

Methyl (1*S*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-9-methyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5f): Colorless crystals (≥99% *ee*); m.p. 115–116 °C (MeOH); $[\alpha]_D^{18} = -55.2$ (*c* = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.04$ (t, *J* = 7.5 Hz, 3H), 1.68–2.03 (m, 2H), 1.91 (d, *J* = 1.5 Hz, 3H), 3.05 (d, *J* = 3.5 Hz, 1H), 3.53 (dd, *J* = 3.5, 4.0 Hz, 1H), 3.68 (s, 3H), 4.79 (t, *J* = 7.5 Hz, 1H), 5.20 (br d, *J* = 4.0 Hz, 1H), 5.88 (quint, *J* = 1.5 Hz, 1H); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 1.02$ (t, *J* = 7.5 Hz, 3H), 1.65–1.92 (m, 2H), 1.95 (d, *J* = 1.5 Hz, 3H), 3.19 (d, *J* = 3.5 Hz, 1H), 3.40 (dd, *J* = 3.5, 4.0 Hz, 1H), 3.66 (s, 3H), 5.02 (t, *J* = 7.5 Hz, 1H), 5.20 (br d, *J* = 4.0 Hz, 1H), 5.94 (quint, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 9.8$, 12.0, 23.2, 50.5, 50.7, 52.4, 80.3, 80.8, 96.4, 128.6, 145.6, 171.0, 174.9; IR (KBr): $\tilde{\nu} = 1778$, 1744–1732 cm^{-1}; HRMS: calcd for $C_{13}H_{16}O_5$ [M^+]: 252.0998; found: 252.1004; elemental analysis calcd (%) for $C_{13}H_{16}O_5$ (252.3): C 61.90, H 6.39; found: C 61.64, H 6.38.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3f with 2b: Similarly to the typical procedure, a mixture of **2b** (3.0 mmol), (±)-**3f** (0.28 g, 2.0 mmol), and lipase LIP (0.40 g) was stirred at 30 °C for 4 d followed by flash column chromatography (hexane/Et_2O/Et_3N 100:50:1) to give (*S*)-**3f** (120 mg, 43%, 96% *ee*) and (2*R*)-*syn*-**5g** (0.24 g, 46%, ≥99% *ee*).

Ethyl (1*S*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-9-methyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5g): Colorless oil (≥99% *ee*); $[\alpha]_D^{27} = -64.9$ (*c* = 0.66, $CHCl_3$); ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.01$ (t, *J* = 7.5 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.67–1.76 (m, 1H), 1.79–1.88 (m, 1H), 1.94 (d, *J* = 2.0 Hz, 3H), 3.18 (d, *J* = 3.0 Hz, 1H), 3.37 (dd, *J* = 3.0, 4.5 Hz, 1H), 4.10 (q, *J* = 7.5 Hz, 2H), 5.00 (t, *J* = 7.5 Hz, 1H), 5.18 (d, *J* = 4.5 Hz, 1H), 5.93–5.95 (m, 1H); ^{13}C NMR (125 MHz, [D$_6$]acetone): $\delta = 9.9$, 12.0, 14.4, 23.2, 50.7, 50.8, 61.6, 80.3, 81.0, 96.5, 128.7, 145.7, 170.5, 175.0; IR (KBr): $\tilde{\nu} = 1781$, 1738–1732 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{18}O_5$ (266.3): C 63.15, H 6.81; found: C 62.90, H 6.79.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3f with 2c: Similarly to the typical procedure, a mixture of **2c** (0.75 mmol), (±)-**3f** (63 mg, 0.45 mmol), and lipase LIP (0.10 g) was stirred at 30 °C for 4 d followed by flash column chromatography (hexane/Et_2O/Et_3N 100:50:1) to give (*S*)-**3f** (30 mg, 47%, ≥99% *ee*) and (2*R*)-*syn*-**5h** (47 mg, 44%, 95% *ee*).

(1*S*,2*R*,5*S*,6*S*,7*S*)-6-Acetyl-2-ethyl-9-methyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]dec-8-ene (*syn*-5h): Pale yellow oil (95% *ee*); $[\alpha]_D^{26} = -34.2$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 1.01$ (t, *J* = 7.5 Hz, 3H), 1.66–1.90 (m, 2H), 1.92 (s, 3H), 2.21 (s, 3H), 3.23 (d, *J* = 3.5 Hz, 1H), 3.58 (t, *J* = 4.0 Hz, 1H), 4.98 (t, *J* = 7.0 Hz, 1H), 5.38 (br d, *J* = 3.5 Hz, 1H), 5.93 (quint, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 9.9$, 11.9, 23.2, 49.0, 59.5, 80.3, 80.8, 96.6, 128.0, 145.4, 175.5, 203.4; IR (KBr): $\tilde{\nu} =$

1774, 1713, 1624 cm^{-1}; HRMS: calcd for $C_{13}H_{16}O_4$ [M^+]: 236.1048; found: 236.1007.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3h with 2b: Similarly to the typical procedure, a mixture of **2b** (1.13 mmol), (±)-**3h** (154 mg, 0.75 mmol), and lipase LIP (0.30 g) was stirred at 30 °C for 6 d followed by flash column chromatography (hexane/Et_2O/Et_3N 93:2:5 → 85:10:5) to give (*S*)-**3h** (58 mg, 38%, ≥99% *ee*) and (2*R*)-*syn*-**5j** (106 mg, 43%, 96% *ee*).

(*S*)-3h (≥99% *ee*): Pale yellow oil; $[\alpha]_D^{24} = -1.6$ (*c* = 1.0, $CHCl_3$).

Ethyl (1*R*,2*R*,5*S*,6*S*,7*S*)-9-bromo-2-ethyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5j): Pale yellow oil (96% *ee*); $[\alpha]_D^{24} = -42.7$ (*c* = 1.2, MeOH); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.04 (t, *J* = 7.5 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.64–1.95 (m, 2H), 3.36 (d, *J* = 3.5 Hz, 1H), 3.50 (dd, *J* = 3.5, 4.5 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 5.03 (t, *J* = 7.5 Hz, 1H), 5.41 (dd, *J* = 2.0, 4.5 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, [D_6]acetone): δ = 9.7, 14.3, 22.9, 50.0, 50.8, 62.0, 79.7, 82.5, 96.6, 125.0, 135.4, 169.9, 173.6; IR (KBr): $\tilde{\nu}$ = 1788, 1730, 1570 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{15}BrO_5$ (331.2): C 47.15, H 4.57; found: C 47.32, H 4.62.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3h with 2c: Similarly to the typical procedure, a mixture of **2c** (1.13 mmol), (±)-**3h** (154 mg, 0.75 mmol), and lipase LIP (0.15 g) was stirred at 30 °C for 5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 92:3:5 → 20:75:5) to give (*S*)-**3h** (74 mg, 48%, ≥99% *ee*) and (2*R*)-*syn*-**5k** (90 mg, 40%, ≥99% *ee*).

(1*R*,2*R*,5*S*,6*S*,7*S*)-6-Acetyl-9-bromo-2-ethyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]dec-8-ene (*syn*-5k): Pale yellow oil (≥99% *ee*); $[\alpha]_D^{25} = -14.4$ (*c* = 1.1, MeOH); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.04 (t, *J* = 7.5 Hz, 3H), 1.64–1.97 (m, 2H), 2.27 (s, 3H), 3.39 (d, *J* = 4.0 Hz, 1H), 3.69–3.71 (m, 1H), 5.01 (t, *J* = 7.5 Hz, 1H), 5.56 (dd, *J* = 2.0, 4.5 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, [D_6]acetone): δ = 9.7, 22.9, 49.3, 58.6, 79.8, 82.5, 96.8, 124.7, 134.9, 174.2, 203.1; IR (KBr): $\tilde{\nu}$ = 1778, 1713, 1570 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{13}BrO_4$ (301.1): C 47.86, H 4.35; found: C 47.85, H 4.35.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3i with 2a: Similarly to the typical procedure, a mixture of **2a** (0.75 mmol), (±)-**3i** (110 mg, 0.50 mmol), and lipase LIP (0.10 g) was stirred at 30 °C for 2.5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 100:10:1 → 100:30:1) to give (*S*)-**3i** (59 mg, 54%, 82% *ee*) and (2*R*)-*syn*-**5l** (61 mg, 35%, 95% *ee*).

(*S*)-3i (82% *ee*): Colorless oil; $[\alpha]_D^{20} = -5.8$ (*c* = 1.0, $CHCl_3$).

Methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-9-bromo-2-ethyl-7-methyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5l): Colorless crystals (95% *ee*); m.p. 64–66 °C (AcOEt); $[\alpha]_D^{20} = -6.8$ (*c* = 0.81, MeOH); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.03 (t, *J* = 7.5 Hz, 3H), 1.65–1.74 (m, 1H), 1.77 (s, 3H), 1.80–1.90 (m, 1H), 3.14 (d, *J* = 4.0 Hz, 1H), 3.45 (d, *J* = 4.0 Hz, 1H), 3.69 (s, 3H), 4.97 (t, *J* = 7.0 Hz, 1H), 6.50 (s, 1H); ^{13}C NMR (125 MHz, [D_6]acetone): δ = 9.8, 18.6, 23.0, 52.7, 53.9, 54.8, 80.0, 92.1, 95.8, 124.9, 138.3, 170.7, 173.6; IR (KBr): $\tilde{\nu}$ = 1782, 1732 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{15}BrO_5$ (331.2): C 47.15, H 4.57; found: C 47.33, H 4.57.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3i with 2b: Similarly to the typical procedure, a mixture of **2b** (0.75 mmol), (±)-**3i** (110 mg, 0.50 mmol), and lipase LIP (0.10 g) was stirred at 30 °C for 2.5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 100:30:1 → 100:100:1) to give (*S*)-**3i** (50 mg, 45%, ≥99% *ee*) and (2*R*)-*syn*-**5m** (50 mg, 30%, 95% *ee*).

Ethyl (1*R*,2*R*,5*S*,6*S*,7*S*)-9-bromo-2-ethyl-7-methyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5m) (95% *ee*): Colorless oil (95% *ee*); $[\alpha]_D^{20} = -9.3$ (*c* = 1.7, MeOH); ^{1}H NMR (500 MHz, [D_6]acetone): δ = 1.03 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.66–1.74 (m, 1H), 1.78 (s, 3H), 1.81–1.91 (m, 1H), 3.12 (d, *J* = 4.0 Hz, 1H), 3.44 (d, *J* = 4.0 Hz, 1H), 4.10–4.17 (m, 2H), 4.97 (t, *J* = 7.5 Hz, 1H), 6.50 (s, 1H); ^{13}C NMR (125 MHz, [D_6]acetone): δ = 9.8, 14.4, 18.8, 23.0, 53.8, 55.0, 62.0, 80.0, 92.2, 95.8, 124.9, 138.2, 170.0, 173.7; IR (KBr): $\tilde{\nu}$ = 1784, 1736 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{17}BrO_5$ (345.2): C 48.71, H 4.96; found: C 49.00, H 4.98.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3i with 2c: Similarly to the typical procedure, a mixture of (±)-**3i** (110 mg, 0.50 mmol), **2c** (0.75 mmol), and lipase LIP (0.10 g) was stirred at 10 °C for 24 h followed by flash column chromatography (hexane/Et_2O/Et_3N 100:10:1 → 100:30:1) to give (*S*)-**3i** (53 mg, 48%, 82% *ee*) and (2*R*)-*syn*-**5n** (53 mg, 34%, ≥99% *ee*).

(1*R*,2*R*,5*S*,6*S*,7*S*)-6-Acetyl-9-bromo-2-ethyl-7-methyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene (*syn*-5n): Pale yellow oil (≥99% *ee*); $[\alpha]_D^{20} = +20.7$ (*c* = 1.4, MeOH); ^{1}H NMR (500 MHz, [D_6]acetone): δ = 1.02 (t, *J* = 7.5 Hz, 3H), 1.65–1.76 (m, 1H), 1.77 (s, 3H), 1.80–1.89 (m, 1H), 2.25 (s, 3H), 3.36 (d, *J* = 4.0 Hz, 1H), 3.39 (d, *J* = 4.0 Hz, 1H), 4.93 (t, *J* = 7.5 Hz, 1H), 6.49 (s, 1H); ^{13}C NMR (125 MHz, [D_6]acetone) δ = 9.8, 18.9, 23.0, 26.4, 53.3, 63.2, 80.1, 91.7, 95.5, 123.9, 138.9, 174.2, 204.5; IR (KBr): $\tilde{\nu}$ = 1778, 1713 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{15}BrO_4$ (315.2): C 49.54, H 4.80; found: C 49.72, H 4.80.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3j with 2a: Similarly to the typical procedure, a mixture of **2a** (0.75 mmol), (±)-**3j** (125 mg, 0.50 mmol), and lipase LIP (0.20 g) was stirred at 30 °C for 4.5 days followed by flash column chromatography (hexane/Et_2O/Et_3N 93:2:5 → 85:10:5) to give (*S*)-**3j** (55 mg, 44%, ≥99% *ee*) and (2*R*)-*syn*-**5o** (78 mg, 43%, 94% *ee*).

(*S*)-3j (≥99% *ee*): Pale yellow oil. $[\alpha]_D^{25} = -4.6$ (*c* = 1.0, $CHCl_3$).

Methyl (1*R*,2*R*,5*S*,6*S*,7*R*)-9-bromo-2-ethyl-7-methoxymethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5o): Pale yellow oil (94% *ee*); $[\alpha]_D^{24} = +7.8$ (*c* = 1.0, MeOH); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.05 (t, *J* = 7.5 Hz, 3H), 1.65–1.95 (m, 2H), 3.39 (s, 3H), 3.45–3.48 (m, 2H), 3.70 (s, 3H), 3.99 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 5.01 (t, *J* = 7.5 Hz, 1H), 6.57 (s, 1H); ^{13}C NMR (75 MHz, [D_6]acetone): δ = 9.8, 22.9, 49.6, 52.8, 52.9, 59.6, 70.6, 79.8, 94.9, 96.1, 124.9, 135.9, 170.5, 173.5; IR (KBr): $\tilde{\nu}$ = 1788, 1738, 1574 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{17}BrO_6$ (361.2): C 46.56, H 4.74; found: C 46.56, H 4.72.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3j with 2b: Similarly to the typical procedure, a mixture of **2b** (0.75 mmol), (±)-**3j** (125 mg, 0.50 mmol), and lipase LIP (0.20 g) was stirred at 30 °C for 4.5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 93:2:5 → 85:10:5) to give (*S*)-**3j** (55 mg, 44%, 98% *ee*) and *syn*-**5p** (84 mg, 45%, 96% *ee*).

Ethyl (1*R*,2*R*,5*S*,6*S*,7*R*)-9-bromo-2-ethyl-7-methoxymethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5p): Pale yellow oil (96% *ee*); $[\alpha]_D^{25} = +0.8$ (*c* = 1.3, MeOH); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.05 (t, *J* = 7.5 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.65–1.92 (m, 2H), 3.39 (s, 3H), 3.44–3.45 (m, 2H), 3.99 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 12.0 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 5.01 (t, *J* = 7.5 Hz, 1H), 6.57 (s, 1H); ^{13}C NMR (75 MHz, [D_6]acetone): δ = 9.8, 14.3, 22.9, 49.8, 52.8, 59.6, 62.1, 70.7, 79.8, 94.9, 96.1, 124.9, 135.9, 169.9, 173.5; IR (KBr): $\tilde{\nu}$ = 1782, 1730, 1574 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{19}BrO_6$ (375.2): C 48.02, H 5.10; found: C 48.05, H 5.08.

Lipase-catalyzed domino kinetic resolution/Diels–Alder reaction of (±)-3j with 2c: Similarly to the typical procedure, a mixture of **2c** (0.75 mmol), (±)-**3j** (125 mg, 0.50 mmol), and lipase LIP (0.20 g) was stirred at 30 °C for 4.5 d followed by flash column chromatography (hexane/Et_2O/Et_3N 93:2:5 → 85:10:5) to give (*S*)-**3j** (55 mg, 44%, 93% *ee*) and (2*R*)-*syn*-**5q** (62 mg, 36%, 93% *ee*).

(1*R*,2*R*,5*S*,6*S*,7*R*)-6-Acetyl-9-bromo-2-ethyl-7-methoxymethyl-3,10-dioxa-4-oxotricyclo[5.2.1.0^{1,5}]dec-8-ene (*syn*-5q): Pale yellow oil (93% *ee*); $[\alpha]_D^{25} = +21.7$ (*c* = 1.2, MeOH); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.04 (t, *J* = 7.5 Hz, 3H), 1.67–1.92 (m, 2H), 2.25 (s, 3H), 3.40 (d, *J* = 4.0 Hz, 1H), 3.41 (s, 3H), 3.66 (d, *J* = 4.0 Hz, 1H), 3.95 (d, *J* = 12.0 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 4.97 (t, *J* = 7.5 Hz, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, [D_6]acetone): δ = 9.8, 22.9, 52.5, 57.9, 59.6, 71.0, 79.9, 94.6, 96.0, 124.1, 136.2, 174.0, 204.5; IR (KBr): $\tilde{\nu}$ = 1778, 1713, 1574 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{17}BrO_5$ (345.2): C 48.71, H 4.96; found: C 48.80, H 4.96.

Methyl (1*R*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-7-methyl-3,10-dioxa-4-oxotricyclo-[5.2.1.0^{1,5}]decane-6-carboxylate (*syn*-6e): Similarly to the hydrogenation of **5d**, (2*R*)-*syn*-**6e** (6.0 mg, 79%) was obtained from (2*R*)-*syn*-**5l** (95% *ee*, 10 mg, 0.030 mmol) after flash column chromatography (hexane/Et_2O 1:1 → 1:2) as colorless crystals. M.p. 74–76 °C; $[\alpha]_D^{25} = +12.8$ (*c* = 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.11 (t, *J* = 7.0 Hz, 3H), 1.57 (s, 3H), 1.74–1.90 (m, 6H), 3.05 (m, 1H), 3.36 (d, *J* = 4.5 Hz, 1H), 3.73 (s, 3H), 4.47 (dd, *J* = 4.5, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.6, 20.5, 21.9, 28.8, 31.8, 52.4, 54.3, 57.0, 82.0, 87.3, 91.0, 171.0, 175.8; IR (KBr):

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$\tilde{\nu}$ = 1776, 1732 cm^{-1}; HRMS: calcd for $C_{13}H_{18}O_5$ [M^+]: 254.1163; found: 254.1154.

Hydrolysis of a mixture of (2*R*)-*syn*-5e and (2*R*)-*anti*-5e: Similarly to the hydrogenation of **5d**, a 67:33 mixture of (2*R*)-*syn*-**6e** and (2*R*)-*anti*-**6e** (16.6 mg, 97%) was obtained from a 70:30 mixture of (2*R*)-*syn*-**5e** and (2*R*)-*anti*-**5e** (17.0 mg, 0.067 mmol) after flash column chromatography as a colorless oil. ^{1}H NMR data of the major isomer, *syn*-**6e**, was identical with those of (2*R*)-*syn*-**6e** obtained above. Typical ^{1}H NMR (300 MHz, $CDCl_3$) data for *anti*-**6c**: δ = 1.10 (t, J = 7.0 Hz, 3H), 1.62 (s, 3H), 3.35 (d, J = 4.0 Hz, 1H), 3.76 (s, 3H), 4.57 (dd, J = 4.0, 10.0 Hz, 1H).

Ethyl (1*S*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-3,10-dioxa-4-oxo-9-phenyltricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5i): Under a nitrogen atmosphere, $PhB(OH)_2$ (11 mg, 0.090 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol), and 2M aqueous Na_2CO_3 (0.12 mL, 0.24 mmol) were successively added to a solution of (2*R*)-*syn*-**5i** (96% *ee*, 20 mg, 0.060 mmol) in THF (1 mL). The reaction mixture was stirred at refluxing temperature for 26 h. After cooling, the reaction was quenched by water, and the product was extracted with Et_2O three times. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/Et_2O 10:1 → 1:1) to give *syn*-**5i** (12 mg, 61%) as a colorless gum. $[\alpha]_D^{20} = -61.1$ (*c* = 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.82–2.00 (m, 2H), 3.30 (d, J = 3.0 Hz, 1H), 3.60 (dd, J = 3.0, 5.0 Hz, 1H), 4.08–4.27 (m, 2H), 5.10 (dd, J = 5.5, 8.0 Hz, 1H), 5.35 (dd, J = 2.0, 5.0 Hz, 1H), 6.28 (d, J = 2.0 Hz, 1H), 7.22–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.1, 14.2, 22.8, 49.7, 50.8, 61.5, 80.3, 80.4, 106.9, 126.9, 128.8, 129.0, 129.9, 132.1, 148.2, 169.7, 174.2; IR (KBr): $\tilde{\nu}$ = 1780, 1734 cm^{-1}; HRMS: calcd for $C_{19}H_{20}O_5$ [M^+]: 328.1294; found: 328.1310.

Ethyl (1*S*,2*R*,5*S*,6*S*,7*S*)-2-ethyl-3,10-dioxa-4-oxo-9-[(trimethylsilyl)ethynyl]tricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (*syn*-5r): Under a nitrogen atmosphere, Et_2NH (0.015 mL, 0.14 mmol) and CuI (0.5 mg, 2.4 μmol) and $Pd(PPh_3)_4$ (1.4 mg, 1.2 μmol) were successively added to a solution of (2*R*)-*syn*-**5i** (96% *ee*, 20 mg, 0.060 mmol) and (trimethylsilyl)acetylene (0.017 mL, 0.12 mmol) in anhydrous DMF (0.1 mL). The reaction mixture was stirred at 50 °C for 45 min, cooled to room temperature, and concentrated in vacuo. The residue was purified by preparative TLC (hexane/Et_2O 1:1) to give *syn*-**5r** (12.6 mg, 60%) as a pale yellow gum. $[\alpha]_D^{23} = -133$ (*c* = 0.85, MeOH); ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.23 (s, 9H), 1.05 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.72–2.01 (m, 2H), 3.20 (d, J = 4.0 Hz, 1H), 3.58 (dd, J = 4.0, 5.0 Hz, 1H), 4.10–4.21 (m, 2H), 4.91 (dd, J = 7.0, 9.0 Hz, 1H), 5.34 (dd, J = 2.0, 5.0 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = −0.3, 9.7, 14.4, 22.9, 49.7, 51.0, 61.9, 80.0, 81.5, 95.8, 96.2, 106.9, 131.2, 139.0, 170.0, 174.0; IR (KBr): $\tilde{\nu}$ = 1788, 1738, 1578 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{24}O_5Si$ (348.5): C 62.04, H 6.94; found: C 61.85, H 6.92.

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[18] To evaluate of the potential effect of the lipase on the Diels–Alder reaction, the reaction of a mixture of (±)-**4a** and LIP in acetone was examined with or without $[RuCl_2(p\text{-cymene})]_2$ at 30 °C for 4–6 days. In several repeated trials, optically enriched products, (*S*)-**4a** (7–9% *ee*), (2*R*)-*syn*-**5a** (0–8% *ee*), and (2*R*)-*anti*-**5a** (0–23% *ee*) were obtained; however, the degree of the optical purity was small and varied. Further investigation is now being continued.
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