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Four-Step One-Pot Catalytic Asymmetric Synthesis of Polysubstituted Tricyclic Compounds: Lipase-Catalyzed Dynamic Kinetic Resolution Followed by an Intramolecular Diels–Alder Reaction

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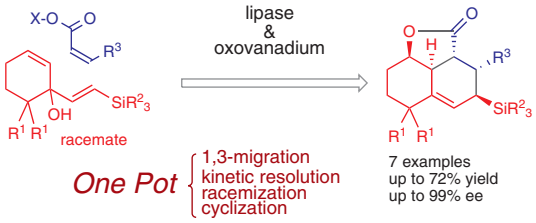

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Abstract Starting from readily available tertiary alcohols, four different reactions (a 1,3-migration of a hydroxy group, kinetic resolution, racemization, and an intramolecular Diels–Alder reaction) took place under co-catalysis by lipase and oxovanadium compounds in a one-pot process to produce polysubstituted tricyclic carbon frameworks in high yields and with high enantioselectivities. The key to the success of this process was the discovery that a silyl group attached to the terminal carbon of the vinyl moiety completely controls the direction of hydroxy group migration

Key words allylic alcohols, asymmetric synthesis, Diels–Alder reaction, dynamic kinetic resolution, lipase, one-pot reaction

Multistep one-pot processes represent a smart synthetic concept that increases the overall efficiency of a preparation by decreasing the number of isolation and purification steps in addition to allowing a reduction in the quantities of organic solvents and reagents required for each step.[1] Catalysis plays a central role in realizing such one-pot processes, because catalytic transformations can avoid the generation of stoichiometric byproducts. Therefore, the combined use of multiple catalysts, each of which conducts a different reaction, in a single flask should further improve the overall efficiency of a transformation. However, such multistep multicatalyst one-pot syntheses tend to involve more-challenging criteria in relation to catalyst and reaction design.

Chemoenzymatic dynamic kinetic resolution (DKR) is a successful example of a multistep, multicatalysis, one-pot asymmetric synthesis, in which enzymes such as lipases conduct the kinetic resolution (KR) of racemic substrates, while racemization catalysts generate a rapid equilibrium between two enantiomers.[2] A high compatibility between these two different catalysts permits the efficient transformation of racemic secondary alcohols or amines into optically pure compounds in up to quantitative yields with minimal material losses. Thus, transition-metal catalysts, such as those based on Ru,[3] Rh,[4] Pd,[5] and Fe,[6] have been found to catalyze racemization through a redox process, and have been widely combined with lipases in DKR processes. At the same time, we have independently developed the DKR of allylic alcohols by combining oxovanadium compounds with lipases.[7] In particular, oxovanadium compounds, unlike the aforementioned redox racemization catalysts, catalyze both the racemization and the 1,3-migration of an allylic hydroxy group. These vanadium catalysts generate a dynamic equilibrium between the two regioisomers (±)-**I** and (±)-**II** (Scheme 1a) while lipase catalyzes the chemo- and enantioselective esterification of (*R*)-**I** to achieve the DKR.

In these DKR processes, the acyl groups introduced into the alcoholic substrates are generally removed or replaced by other substituents in subsequent transformations,[8] and only a few examples involving the use of these installed acyl moieties have been reported.[7e,f,9] Domino or one-pot se-

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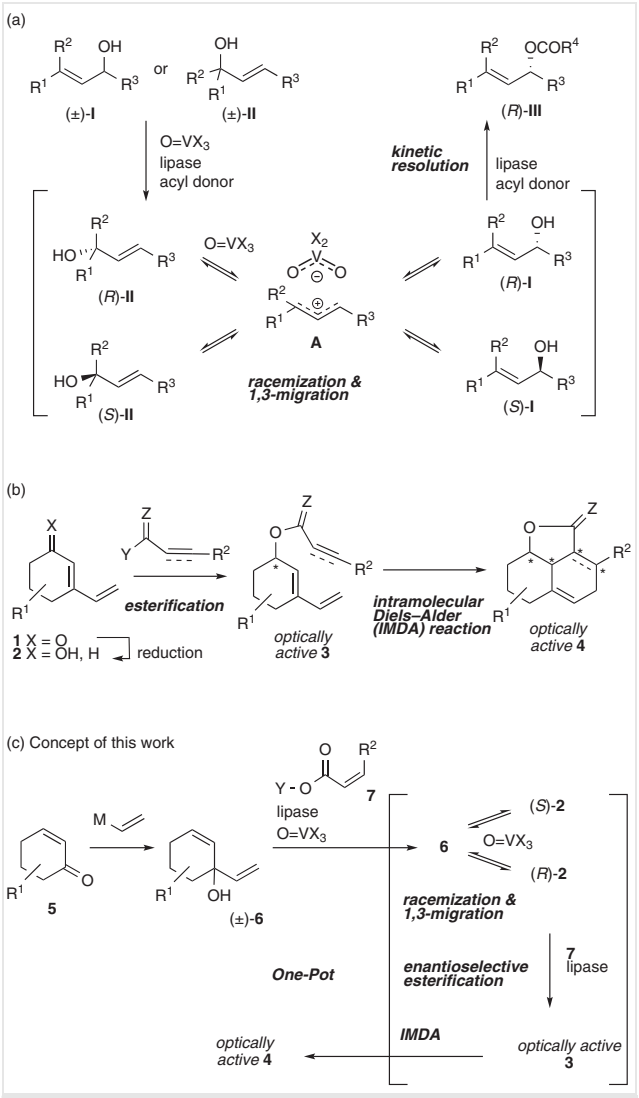


Scheme 1 (a) Lipase/oxovanadium co-catalyzed DKR of racemic allyl alcohols (**I** and **II**). (b) Approaches for constructing optically active polysubstituted tricyclic compounds **4**. (c) Lipase/oxovanadium co-catalyzed one-pot DKR/IMDA of *tert*-alcohols (±)-**6** for constructing optically active **4**.

quential reactions that utilize the acyl moiety for construction of a carbon framework can amplify the synthetic efficiency of the DKR. On this basis, we applied the aforementioned lipase/Ru co-catalyzed DKR of (±)-**2** with acylating reagents each bearing a dienophile moiety. More specifically, the DKR of (±)-**2** provided optically active esters **3**, which underwent an intramolecular Diels–Alder (IMDA) reaction to form optically active tricyclic molecules **4** (Scheme 1b).[10] In these reactions, ketones **1** (~10% yield) were obtained as byproducts of the in situ racemization. In their related work, Corey et al. prepared optically active allylic alcohols **2** by enantioselective reduction of dienones **1**, and they synthesized similar compounds **4** through an esterification reaction followed by an IMDA reaction.[11] In addition, Aso and co-workers obtained an optically active alcohol **2** through a lipase-catalyzed KR of (±)-**2**, and they synthesized optically active **4** by using similar esterification and IMDA reactions.[12] These polycyclic compounds **4** are pivotal synthetic intermediates for the enantioselective syntheses of such bioactive molecules as forskolin and mevastatin. However, the methods discussed above all employ relatively unstable conjugated dienols **2** as key intermediates.

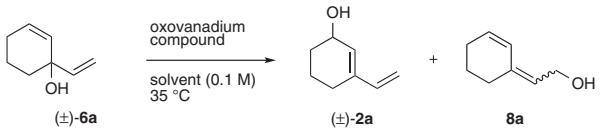
We report a challenging one-pot DKR/IMDA that uses a combination of lipase and oxovanadium catalysts, and in which more stable tertiary alcohols (±)-**6** are used as synthetic equivalents of (±)-**2** to produce products **4** in their optically active form through four different reactions: a 1,3-hydroxy migration from (±)-**6** to give (±)-**2**, the enantioselective esterification of (±)-**2**, the racemization of **2**, and the IMDA reaction of optically active **3** (Scheme 1c). This strategy is expected to be beneficial due to the ready availability of (±)-**6** through the 1,2-addition of a vinyl anion to enones **5**, some of which are commercially available, and also because it addresses the issue of instability of alcohols **2**.[13]

To check the feasibility of this concept, we studied the 1,3-migration of (±)-**6a** [obtained from cyclohex-2-en-1-one (**5a**)] by using our original racemization catalyst V-MPS4, in which oxovanadium species are covalently bound to the inner surface of mesoporous silica (MPS) with a pore size of 4 nm.[7c,d] However, trials with V-MPS4 (1 mol%) in several solvents[14] gave the desired dienol (±)-**2a** in relatively low yields of 32–48%, together with a mixture of the *E*- and *Z*-isomers of primary alcohol **8a** (≤8% yield) (Table 1, entries 1–3). A more serious problem was that the total yields of these three regioisomers (**2a**, **6a**, and **8a**) were low (≤68%), indicating significant decomposition of the alcohols occurred under the migration conditions. We therefore examined the same reaction by using a less reactive oxovanadium compound, $O{=}V(OSiPh_3)_3$[7a] (10 mol%) and, fortunately, obtained **2a** in higher yields in acetone (63%) or dichloromethane (68%) (entries 4 and 6). In particular, dichloromethane was found to be the most suitable solvent, with no loss of the alcohols being observed; however, the yield of **8a** also increased.

With these results in hand, we conducted preliminary trials of the one-pot DKR/IMDA of (±)-**6a** in dichloromethane. A mixture of (±)-**6a**, functionalized acyl donor **7A**, the commercially available immobilized lipase *Candida antarctica* lipase B (CAL-B), $O{=}V(OSiPh_3)_3$, and 4Å molecular sieves (MS 4Å)[15] was stirred in dichloromethane at 35 °C for two days to give the tricyclic product **4aA** (92% ee) as a single diastereomer, albeit in a low yield of 34%. The main reason for this low yield was the formation of a mixture of (*E*)- and (*Z*)-**9a** in a 36% combined yield, derived from the undesired migration product **8a** (Scheme 2).

To improve the yield of **4aA**, we considered using the tertiary allyl alcohol (±)-**6b**, bearing a silyl group at the alkene terminal and we expected that the catalytic equilib-

Table 1 Oxovanadium-Catalyzed Isomerization of **6a**



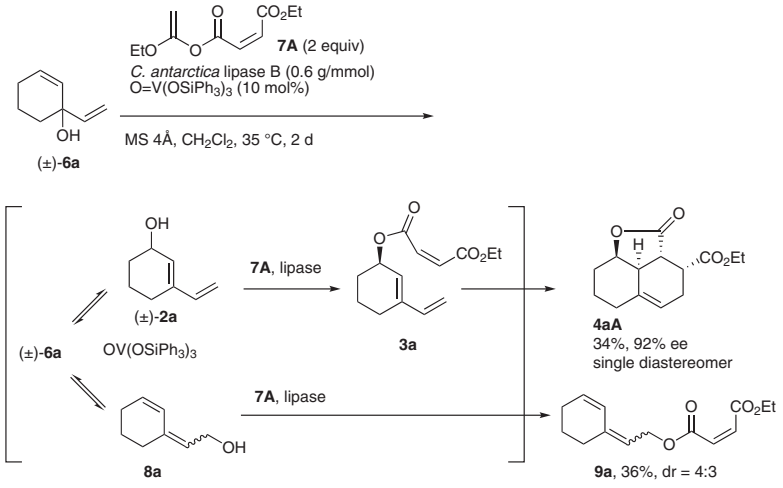
(±)-**6a** (±)-**2a** **8a**

Entry	Oxovanadium compound (mol%)	Solvent	Time (min)	Yield[a] (%)		
				2a	**8a**	**6a**
1	V-MPS4 (1)	acetone	40	32	3	33
2	V-MPS4 (1)	MeCN	40	48	8	10
3	V-MPS4 (1)	CH_2Cl_2	40	39	4	trace
4	$O=V(OSiPh_3)_3$ (10)	acetone	30	63	16	trace
5	$O=V(OSiPh_3)_3$ (10)	MeCN	30	18	4	trace
6	$O=V(OSiPh_3)_3$ (10)	CH_2Cl_2	30	68	24	8

[a] Determined by gas-chromatographic analysis of the crude product.

rium between **6b**, **2b**, and **8b** would be pushed in the direction of **2b** due to the steric and electronic effects of the silyl group. In fact, computational studies suggested that the relative stability of **2** compared with that of **8** should increase upon the introduction of a silyl group [see the Supporting Information (SI) for further details]. We also expected that **2b**, which presents the lowest steric hindrance, would react exclusively with lipase so that an equilibrium between **2b** and **8b** would favor the formation of **2b**, thereby leading to the complete transformation of all alcohols into a single product. As expected, the reaction of (±)-**6b** [prepared from **5a** and 2-(trimethylsilyl)vinyllithium] in the presence of $O=V(OSiPh_3)_3$ (10 mol%) in dichloromethane afforded (±)-**2b** in >90% yield (Scheme 3).[13] Similar good results were obtained in acetone and acetonitrile (Scheme 3).

Subsequently, the CAL-B-catalyzed KR of (±)-**2b** was examined by using **7A** at 35 °C in dichloromethane. Even with its bulky trimethylsilyl group, (±)-**2b** underwent enantioselective esterification to form a mixture of ester (*R*)-**3bA**, cyclic product **4bA**, and (*S*)-**2b**, with almost 50% conversion after two hours. To achieve complete conversion of **3bA** into **4bA**, toluene was added to the reaction solution, and the mixture was stirred at 80 °C for further two hours. The crude product mixture was found to contain only **4bA** and (*S*)-**2b**, both of which were optically pure. Thus, the KR proceeded with an extremely high enantioselectivity (*E* value[16] >200) (Table 2, entry 1). Similarly, the KR was carried out by using the same conditions and procedure in acetone, acetonitrile, and 1,2-dichloroethane, and gave excellent enantioselectivities (entries 2–4) (see the SI for additional results).



Scheme 2 Lipase/oxovanadium co-catalyzed one-pot DKR/IMDA of (±)-**6a**.

Overall, our results indicated that silylated alcohol **6b** can serve as an alternative substrate for the one-pot DKR/IMDA process.

A racemization study of the optically active secondary alcohol **2b** provided further insights into its DKR. The reaction of (*S*)-**2b** (99% ee) with O=V(OSiPh$_3$)$_3$ (10 mol%) in either dichloromethane or acetone at 35 °C for six hours caused neither racemization nor decomposition (Table 3, entries 1 and 2). In contrast, the racemization proceeded in dichloromethane in the presence of only 0.2 mol% V-MPS4, with no decomposition of **2b** being observed (entry 3). Similarly, racemization proceeded in 1,2-dichloroethane (DCE) (entry 6), but was unsuccessful in both acetone and acetonitrile (entries 5 and 6). Therefore, the use of V-MPS4 in either dichloromethane or DCE was considered suitable for the DKR, whereas that of O=V(OSiPh$_3$)$_3$ was suitable for the migration of **6b** to yield **2b**.

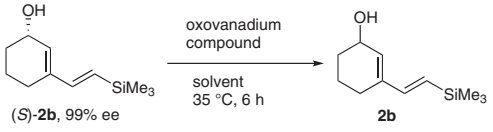
After these studies, the one-pot DKR/IMDA was investigated by treatment of (±)-**6b** with **7A** in the presence of CAL-B, O=V(OSiPh$_3$)$_3$, and MS4Å in dichloromethane, followed by the addition of V-MPS4. Under these conditions, the migration and enantioselective esterification proceeded to give (*R*)-**3bA** and (*S*)-**2b**, whereas the subsequent addition of V-MPS4 promoted the racemization of (*S*)-**2b** to complete the DKR, while the IMDA proceeded in parallel to give **4bA**. Optimization of the conditions was carried out by varying the quantities of **7A**, CAL-B, and V-MPS4, as well as the concentration of **6b**, the reaction temperature, the solvent, and the reaction time (see the SI for further details). One of the best procedures was as follows. (±)-**6b** was initially treated with **7A** (2 equiv), CAL-B (0.6 g/mmol), and O=V(OSiPh$_3$)$_3$ (10 mol%) in dichloromethane (0.05 M of **6b**) at 35 °C for two hours, then V-MPS4 (2 mol%) was added and the resulting mixture was stirred at 35 °C for two days to obtain **4bA** as a single diastereomer (93% ee) in a 72% isolated yield (Method I) (Scheme 4).[17] This method was then applied to (±)-**6c** bearing a *tert*-butyl(dimethyl)silyl group to afford **4cA** (98% ee) in 70% yield. Another acyl donor **7B**, bearing a sulfonyl group was also suitable for this one-pot DKR/IMDA, giving **4bB** and **4cB**. In these cases, esterification with **7B** proceeded more slowly than the correspond-

Table 2 CAL-B-Catalyzed Kinetic Resolution of (±)-**2b** followed by IMDA

Entry	Solvent	Conversion[a] (%)	ee (%)		*E* value[16]
			4b[b]	(*S*)-**2b**[c]	
1	CH_2Cl_2	50	98	99	>200
2	acetone	50	99	99	>200
3	MeCN	51	97	99	>200
4	DCE	50	96	94	175

[a] Calculated[16] based on the optical purities of **4bA** and (*S*)-**2b**.
[b] Determined by HPLC analysis on a Daicel CHIRALPAK AD-3 column.
[c] Determined by HPLC analysis on a Daicel CHIRALCEL OD-3 column.

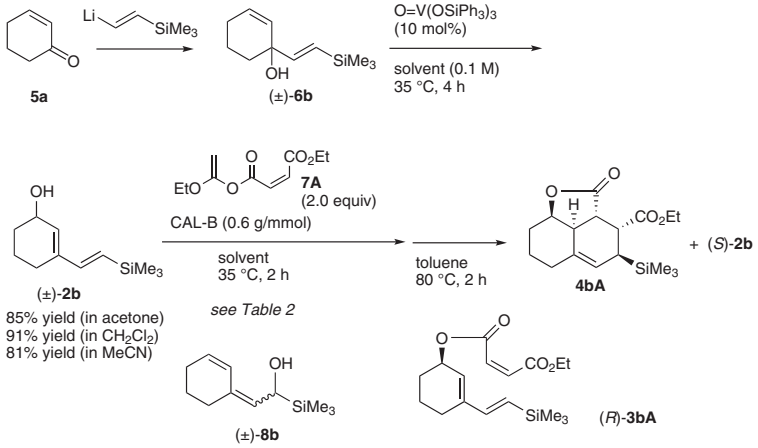
Table 3 Oxovanadium-Catalyzed Racemization of Optically Pure (*S*)-**2b**



(*S*)-**2b**, 99% ee — **2b**

Entry	Oxovanadium compound (mol%)	Solvent	**2b**	
			Yield[a] (%)	ee[b] (%)
1	O=V(OSiPh$_3$)$_3$ (10)	CH_2Cl_2	100	97
2	O=V(OSiPh$_3$)$_3$ (10)	acetone	84	99
3	V-MPS4 (0.2)	CH_2Cl_2	95	37
4	V-MPS4 (0.2)	acetone	80	99
5	V-MPS4 (0.2)	MeCN	84	99
6	V-MPS4 (0.2)	DCE	70	49

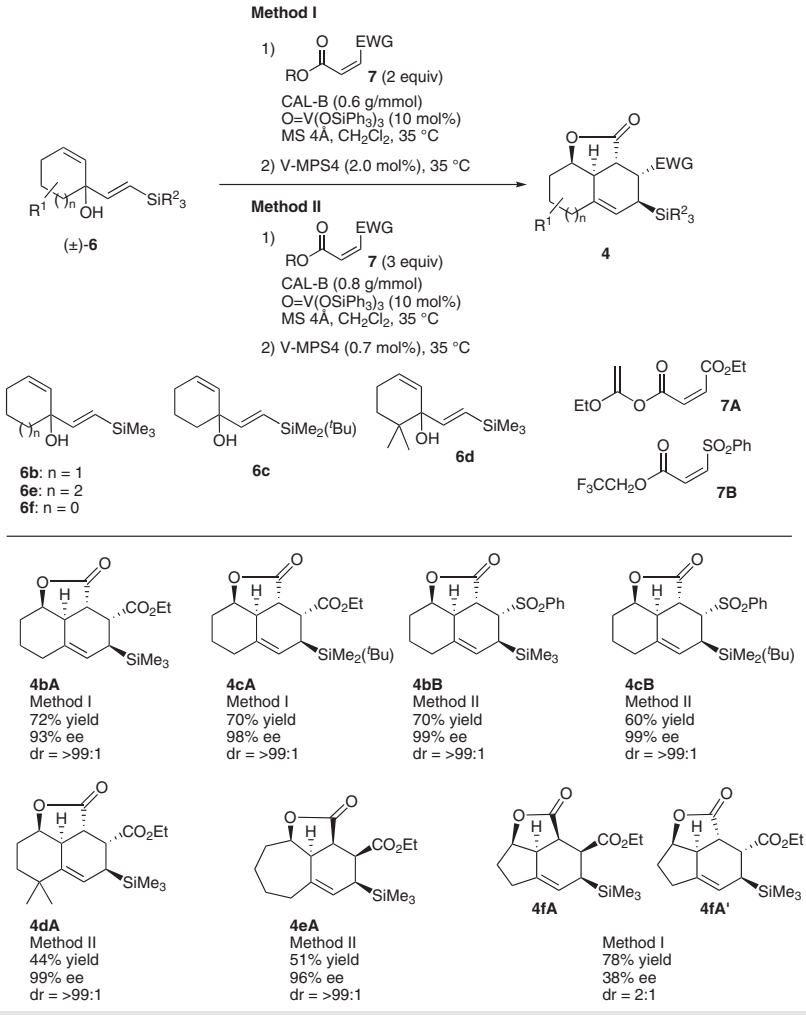
[a] Determined by HPLC analysis of the crude product.
[b] Determined by HPLC analysis on a chiral column (CHIRALCEL OD-3).



Scheme 3 Oxovanadium-catalyzed isomerization of (±)-**6b** into (±)-**2b** and CAL-B-catalyzed kinetic resolution followed by IMDA.

ing reaction with **7A**, and higher yields of the products, **4bB** (70% yield, 99% ee) and **4cB** (60% yield, 99% ee), were obtained by a stepwise addition of V-MPS4 (Method II) (see the SI for details). Moreover, **6d**, which contains two methyl groups, gave optically pure **4dA** (99% ee) in 44% yield. In addition, **6e**, bearing a seven-membered ring, could also be used in this reaction, giving **4eA** (96% ee) in 51% yield. In contrast, **6f**, which contains a five-membered ring, provided two diastereomers, **4fA** and **4fA′**, with an optical purity of 38% ee and a total yield of 78% (for determination of the stereochemistry of all products, see the SI).[13] Further optimization is therefore required to improve the yields, optical purities, and diastereoselectivities of **4dA**, **4eA**, and **4fA**.

In summary, we have developed a one-pot synthesis of optically active (or, in some cases, optically pure) polysubstituted tricyclic skeletons in good-to-high overall yields from readily available tertiary alcohols. This one-pot transformation involves four different steps: an oxovanadium-catalyzed 1,3-migration of the hydroxy group, a racemization, a lipase-catalyzed enantioselective esterification, and an intramolecular Diels–Alder reaction. It was successfully achieved by using a combination of lipase and an oxovanadium compound in a single environment. Another key to the success of this process was the discovery of the effect of the silyl group, which completely controls the direction of hydroxy group migration. Because these tertiary alcohols are readily available from cyclic enones, this work provides a proof-of-concept for a two-step enantioselective assembly of enones, vinyl anions, and acyl donors, and features excellent pot (or step), atom, and redox economies for the asymmetric synthesis of highly functionalized polycyclic carbon skeletons that could serve as useful synthetic intermediates for biologically important compounds such as mevastatin and forskolin. Studies into further transformations of the products by using available functional groups, such as the allylsilane moiety, to synthesize these molecules are now underway in our laboratory, and the results will be reported in due course. Because of the inherent enantioselec-



Scheme 4 Lipase/oxovanadium co-catalyzed one-pot DKR/IMDA of (±)-**6**.

tivities of natural lipases, the stereochemistries of the products obtained in this study were antipodes of mevastatin and forskolin. We are therefore also investigating the manipulation of natural lipases to create mutants for the production of enantiomers of the resulting products.[18,19]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1344-8713.

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(13) The conjugated dienol **2a** is prone to decompose even when stored under argon atmosphere in a refrigerator, whereas the unconjugated alcohol **6a** is stable and no decomposition was observed during storage in a refrigerator for more than six months. Similarly, the silylated dienols **2b** and **2c** decomposed in a refrigerator, whereas the unconjugated alcohols **6b**–**f** were all stable.

(14) Because the lipase-catalyzed KR of (±)-**2a** proceeded with high enantioselectivity in acetone, CH_2Cl_2, and acetonitrile in our previous study,[10] these solvents were chosen for a preliminary study of the migration to find suitable conditions for the DKR.

(15) Although the results of KR of (±)-**2a** in CH_2Cl_2 fluctuated, we found that the addition of MS4Å under the KR conditions dramatically improved their reproducibility. We are now investigating the effect of MS4Å.

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(17) **Ethyl (2a*S*,3*R*,4*S*,8a*R*,8b*S*)-2-Oxo-4-(trimethylsilyl)-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-3-carboxylate (4bA); Typical Procedure** (**Method I in Scheme 4**)
To a solution of (±)-**6b** (20 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) at rt were added **7A** (43 mg, 0.20 mmol), MS4Å (40 mg), immobilized CAL-B (60 mg) and O=V($OSiPh_3$)$_3$ (8.9 mg, 0.010 mmol).

The mixture was stirred at 35 °C for 2 h, and then V-MPS4 (10 mg, 0.0020 mmol) was added at the same temperature. The mixture was stirred at 35 °C for 2 d then filtered through a Celite pad, that was washed with Et_2O. The combined filtrates were concentrated under reduced pressure, and the residue was purified by column chromatography [silica gel, EtOAc–hexane (1:10)] to give a colorless oil; yield: 24 mg (72%, 93% ee); $[\alpha]_D^{22}$ = 45.5 (*c* 1.0, $CHCl_3$).

IR (neat): 1730, 1786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.32–5.30 (m, 1 H), 4.65 (ddd, *J* = 4.5, 8.5, 13.0 Hz, 1 H), 4.22–4.10 (m, 2 H), 3.21–3.17 (m, 1 H), 3.12 (dd, *J* = 1.0, 4.0 Hz, 1 H), 2.31–2.23 (m, 3 H), 2.15 (d, *J* = 1.0 Hz, 1 H), 1.97–1.93 (m, 1 H), 1.91–1.89 (m, 1 H), 1.70–1.61 (m, 1 H), 1.43–1.33 (m, 1 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 0.09 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6, 173.5, 137.0, 121.1, 77.9, 61.3, 42.6, 37.4, 36.6, 30.6, 26.2, 24.3, 19.4, 14.2, –2.9. HRMS (EI): *m/z* [M^+] calcd for $C_{17}H_{26}O_4Si$: 322.1600; found: 322.1599

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