Lipase promoted asymmetric trans-esterification of 4-alkyl-, 3-alkyl- and 3,4-dialkyloxetan-2-ones with ring-opening

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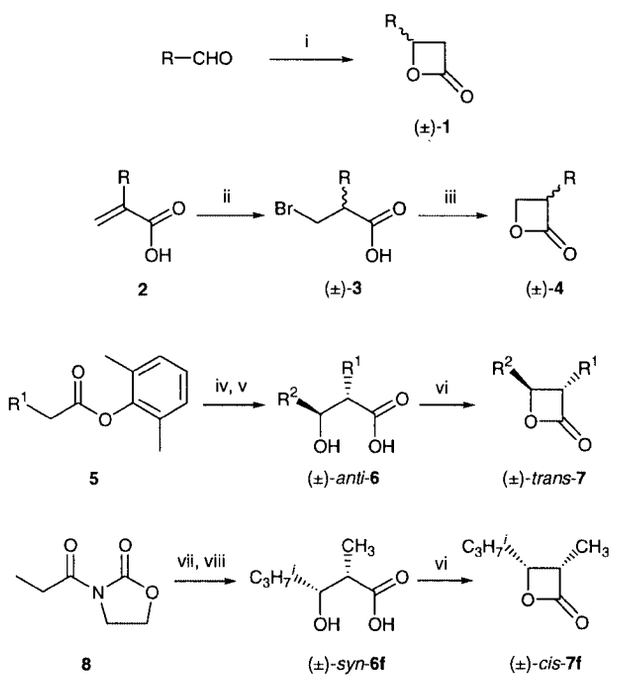
Kinetic resolution of (±)-4-substituted [(±)-**1**], 3-substituted [(±)-**4**] and 3,4-disubstituted oxetan-2-ones [(±)-**7**] was effected by the action of lipases in organic solvents. The substrates (±)-**1**, (±)-**4** and (±)-**7** were prepared by [2 + 2] cycloaddition of aldehydes with ketene, intramolecular substitution of 3-bromoalkanoic acids and the Adams cyclization of *anti*- and *syn*-3-hydroxyalkanoic acids, respectively. Lipase PS exhibited good activity towards all the oxetanones and was employed for the resolution experiments except with (±)-4-methyloxetan-2-one (±)-**1a** for which PPL was used. The stereoselectivity was satisfactory for obtaining oxetan-2-ones of high ee's except for a few cases. The configuration of new compounds was established by chemical correlation and CD spectroscopy.

Optically active oxetan-2-ones, β-lactones, have attracted much attention because they are found in many biologically active natural products[1,2] and have also been utilized as monomers in the preparation of biodegradable poly(hydroxyalkanoates).[3,4] Moreover, they can be employed as chiral building blocks having two centres that are reactive towards nucleophiles.[1] Optically active 4-substituted oxetan-2-ones have been synthesized from optically active 3-halo- and 3-hydroxyalkanoic acids. Asymmetric syntheses of these compounds have also been reported, including the stereoselective synthesis of 3,4-dialkyloxetan-2-one from optically active 3-methyloxetan-2-one,[5] the asymmetric hydrogenation of diketene[6] and the asymmetric cycloaddition of ketene and trichloroacetaldehyde.[7] These methods have afforded oxetan-2-ones in high ee's but their structure is restricted to 4-alkyl-3-methyl-, 4-methyl- and 4-trichloromethyloxetan-2-one, respectively. Recently, asymmetric cycloadditions were reported in which various aldehydes reacted with ketene[8] or trimethylsilylketene[9a] in the presence of chiral Lewis acids.[9b] However, the selectivity was moderate or low. In this context, we planned to develop an enzymatic procedure that would yield oxetan-2-ones in high ee's.

Lipase has been widely used for asymmetric synthesis and optical resolution.[10] Asymmetric hydrolysis of lactones which are 5-membered rings or bigger[11] and asymmetric lactonization of hydroxy esters[12] have been reported. Diketene (4-methyleneoxetan-2-one), having a similar structure, catalyzed by lipase has been employed for the resolution of alcohols with high stereoselectivity.[13] We have previously reported the facile optical resolution of 4-alkyloxetan-2-ones with lipase and alcohols in organic solvents. The reaction is promoted by releasing the strain in the 4-membered ring.[14] Recently, 4-alkyl-3-methyleneoxetan-2-ones[15] and 4-haloalkyloxetan-2-ones[16] were resolved by this procedure. Here, we describe the lipase promoted asymmetric trans-esterification of (±)-4-substituted [(±)-**1**], 3-substituted [(±)-**4**] and 3,4-disubstituted oxetan-2-ones [(±)-**7**] and aim to clarify the scope and limitation of this method.

The synthesis of racemic oxetan-2-ones is summarized in Scheme 1. 4-Alkyloxetan-2-ones (±)-**1** were prepared by the [2 + 2] cycloaddition of aldehydes with ketene, catalyzed by boron trifluoride (except for (±)-**1a** which was formed by hydrogenation of diketene).[17] By the action of aqueous sodium hydroxide, 3-alkyloxetan-2-ones (±)-**4** were prepared from 3-bromoalkanoic acids (±)-**3** which were derived from unsaturated acids **2**.[18] Stereoselective aldol reactions gave



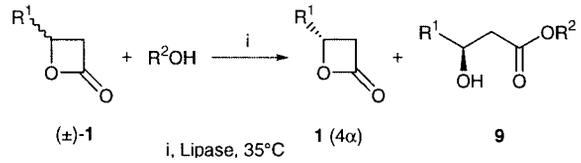
Scheme 1 *Reagents and conditions*: i, CH_2=C=O, BF_3; ii, HBr; iii, NaOH, iv, LDA, R^2CHO, −78 °C; v, KOH; vi, TsCl, pyridine, 0 °C; vii, $(C_4H_9^n)_2BOTf$, $(C_2H_5)_3N$, $C_3H_7^iCHO$, −78 °C; viii, H_2O_2, LiOH.

(±)-*anti*-**6a–e**[19] and (±)-*syn*-**6f**[20] from which (±)-*trans*-**7a–e** and (±)-*cis*-**7f** were afforded by Adams' cyclization.[21]

4-Methyloxetan-2-one **1a** was chosen for the initial optimization study and reacted with ethanol, butan-1-ol and benzyl alcohol to give alkyl 3-hydroxybutanoates in the presence of porcine pancreas lipase (PPL) and Lipase PS (*Pseudomonas* sp. lipase) in various organic solvents. The products are those expected from ordinary lipase promoted trans-esterification and are generated by acyl fission of **1a**, which is observed in basic hydrolysis of oxetan-2-ones (while acidic hydrolysis proceeds by alkyl fission).[22] By using the *E* value calculated from the ee of the remaining oxetanone (ee_s) and the reaction conversion [eqn. (1)],[23] we examined various combinations of lipases,

$$E = [\ln(1 - c)(1 - ee_s)]/[\ln(1 - c)(1 + ee_s)] \quad (1)$$

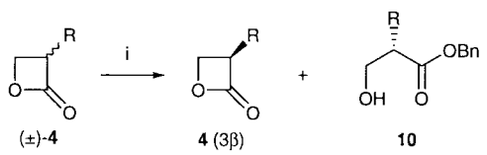
Table 1 Lipase promoted asymmetric trans-esterification of 4-alkyloxetan-2-ones



									Oxetanone **1**			Ester **9**		
Entry	Substrate	R^1	R^2	Lipase	Solvent	*t*/h	Conv. (%)[a]	*E*[a]	Yield (%)	$[\alpha]_D^{25}/10^{-1}$ deg cm^2 g^{-1} (*c*, $CHCl_3$)	Ee (%)	Yield (%)	$[\alpha]_D^{25}/10^{-1}$ deg cm^2 g^{-1} (*c*, $CHCl_3$)	Ee (%)[b]
1	**1a**	CH_3	Bn	PPL	Acetone	144	54	39	36	+28.0 (4.3)	96[c]	51	+25.7 (1.1)	85
2	**1b**	$C_3H_7^n$	Bn	PS	Acetone	96	52	12	42	+32.8 (1.1)	75[d]	45	+14.1 (1.1)	69
3	**1c**	$C_3H_7^i$	Bn	PS	Acetone	288	51	70	41	+22.8 (1.1)	95[d]	43	+27.4 (1.0)	90
4	**1d**	$C_4H_9^n$	Bn	PS	Acetone	504	47	20	46	+26.0 (1.5)	71[d]	36	+16.1 (1.5)	81
5	**1d**	$C_4H_9^n$	$C_4H_9^n$	PS	$(C_3H_7^i)_2O$	44	57	16	30	+32.9 (1.5)	90[d]	40	+15.2 (1.4)	68
6	**1e**	$C_4H_9^t$	$C_4H_9^n$	PS	$(C_3H_7^i)_2O$	200	<1	—	—	—	—	—	—	—
7	**1f**	$C_{11}H_{23}^n$	Bn	PS	Acetone	216	48	16	27	+14.7 (1.2)	70[d]	25	+9.7 (1.1)	77
8	**1f**	$C_{11}H_{23}^n$	$C_4H_9^n$	PS	$(C_3H_7^i)_2O$	14	42	16	52	+12.0 (1.2)	57[d]	35	+14.1 (1.1)	80

[a] Calculated from eqns. (2) and (3). [b] Determined by ^1H NMR using $Eu(hfc)_3$. [c] Determined by method A. Finepak SIL; retention time [amide from (*R*)-**1a**] 23.6 min, [amide from (*S*)-**1a**] 25.5 min. The *R* configuration was assigned by optical rotation (ref. 6). [d] Determined by method B: methyl ester **13b** $[\alpha]_D^{25}$ −3.5 (*c* 2.5, EtOH) [(*S*)-isomer, $[\alpha]_D^{25}$ +4.6 (*c* 1.0, EtOH), 98% ee] (ref. 26); methyl ester **13c** $[\alpha]_D^{25}$ −25.3 (*c* 2.2, EtOH) [(*S*)-isomer, $[\alpha]_D^{25}$ −23.5 (*c* 5.0, EtOH), 80% ee] (ref. 27); methyl ester **13d** $[\alpha]_D^{25}$ −19.1 (*c* 1.6, $CHCl_3$) [(*S*)-isomer, $[\alpha]_D^{25}$ −27.1 (*c* 1.5, $CHCl_3$), >99% ee] (ref. 28); acid **14f** $[\alpha]_D^{25}$ −11.3 (*c* 1.2, $CHCl_3$) [(*R*)-isomer, $[\alpha]_D^{25}$ −16.2 (*c* 1.0, $CHCl_3$), >99% ee] (ref. 29).

Table 2 Lipase promoted asymmetric trans-esterification of 3-alkyloxetan-2-ones



						Oxetanone **4**			Ester **10**		
Entry	Substrate	R	*t*/h	Conv. (%)[a]	*E*[a]	Yield (%)	$[\alpha]_D^{25}/10^{-1}$ deg cm^2 g^{-1} (*c*, $CHCl_3$)	Ee (%)	Yield (%)	$[\alpha]_D^{25}/10^{-1}$ deg cm^2 g^{-1} (*c*, $CHCl_3$)	Ee (%)
1	**4a**	CH_3	9	49	13	38	+7.4 (9.4)	70[b]	24	+13.2 (10.0)	72[c]
2	**4b**	$C_3H_7^i$	192	<1	—	—	—	—	—	—	—
3	**4c**	$C_4H_9^n$	204	49	3	45	−8.6 (9.3)	32[d]	32	+1.8 (8.8)	36[e]

[a] Calculated from eqns. (2) and (3). [b] Based on the reported maximum rotation [(*R*)-isomer, $[\alpha]_D^{25}$ +10.5 (*c* 1.0, $CHCl_3$), >99% ee] (ref. 30). [c] Compared the rotation [$[\alpha]_D^{25}$ +9.1 (*c* 10.3, EtOH)] of hydroxy acid derived from **10a** by hydrogenolysis with the reported maximum rotation [(*S*)-isomer, $[\alpha]_D^{25}$ +12.7 (*c* 12.5, EtOH), >99% ee] (ref. 31). [d] Chiral GC, ASTEC CHIRALDEX B-PH; retention time [(3*R*)-**4a**] 20.6 min, [(3*S*)-**4a**] 21.0 min. [e] Determined by method C.

$$E = [\ln(1 - ee_s)(ee_s + ee_p)]/[\ln(1 + ee_s)(ee_s + ee_p)] \quad (2)$$

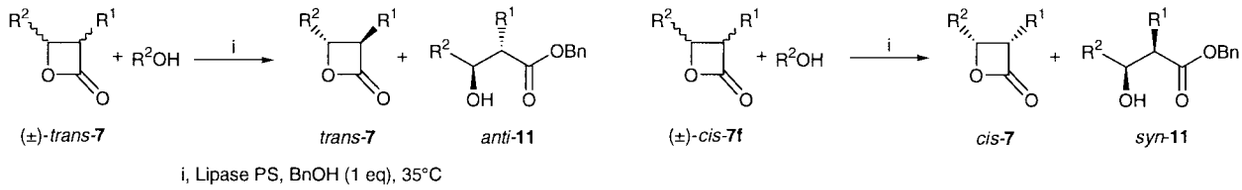
$$\text{Conversion} = \ln[ee_s/(ee_s + ee_p)] \quad (3)$$

alcohols and solvents. It turned out that the reaction proceeded with very high stereoselectivity when using PPL, benzyl alcohol and acetone. Based on this preliminary experiment, a preparative resolution was carried out to obtain (+)-**1a** (96% ee) and benzyl 3-hydroxybutanoate (+)-**9a** (85% ee) in good yields (Table 1, entry 1). From these values we calculated an *E* value of 39 [eqn. (2)] which is a more reliable method than eqn. (1).[24]

The reactions of 4-alkyloxetan-2-ones (±)-**1** having primary alkyl groups, including those with long chains, and isopropyl groups were very sluggish with PPL but they were effectively catalyzed by Lipase PS to give the products (+)-**1** and (+)-**9** in high ee (Table 1). The best selectivity (*E* = 70) was attained with **1c**, which has a secondary alkyl group, whilst moderate *E*'s were obtained with oxetanones which have primary alkyl groups. The reaction of (±)-**1a** (R = CH_3) was catalyzed effectively by Lipase PS but the selectivity was low (*E* = 7). The *tert*-butyl derivative (±)-**1e** did not react under any conditions (Table 1, entry 6). The configurations of the remaining oxetanones (+)-**1** and esters (+)-**9** are *S* and *R*, respectively, except for **1c** and **9c**. This difference is due to the *R*,*S*-nomenclature and the spatial orientation at the stereogenic centre is the same. Because the *R*,*S*-notation could lead to serious confusion, the structure is given in Table 1 and we have used the terminology employed in steroid chemistry to identify the stereochemistry, *i.e.* α (below the plane of the paper) and β (above the plane). Accordingly, the 4-alkyloxetan-2-ones **1** have an α-4-alkyl group. The long reaction periods could be reduced by employing butan-1-ol and diisopropyl ether as the nucleophile and solvent, respectively, without lowering the stereoselectivity (Table 1, entries 5 and 8). In the case of the isopropyl derivative (±)-**1c**, the reaction periods were almost the same with benzyl alcohol–acetone and butan-1-ol–diisopropyl ether.

Based on the results of the 4-alkyloxetan-2-ones (±)-**1**, the asymmetric trans-esterification of 3-alkyloxetan-2-ones (±)-**4** was effected but the results were not as good (Table 2). In addition to ester **10**, dimers and trimers were found when an

Table 3 Lipase promoted asymmetric trans-esterification of 3,4-dialkyloxetan-2-ones



							Oxetanone **7**				Ester **11**			
Entry	Substrate	R^1	R^2	*t*/ day	Conv. (%)[a]	*E*[a]	Yield (%)	$[a]_D^{25}/10^{-1}$ deg cm^2 g^{-1} (*c*, $CHCl_3$)	Ee (%)	Config.	Yield (%)	$[a]_D^{25}/10^{-1}$ deg cm^2 g^{-1} (*c*, $CHCl_3$)	Ee (%)	Config.
1	*trans*-**7a**	CH_3	$C_3H_7^n$	11	51	50	50	+41.3 (1.1)	92[b]	3*R*,4*R* (3β,4α)	34	+1.3 (*c* 1.1)	87[d]	2*S*,3*S*
2	*trans*-**7b**	CH_3	$C_3H_7^i$	15	46	26	37	+34.6 (1.2)	72[c]	3*R*,4*R* (3β,4α)	41	+15.2 (1.2)	85[e]	2*S*,3*S*
3	*trans*-**7c**	CH_3	$C_4H_9^t$	14	<1	—	—	—	—	—	—	—	—	—
4	*trans*-**7d**	$C_3H_7^n$	CH_3	21	45	>99	16	+11.4 (0.92)	79[b]	3*R*,4*R* (3β,4α)	24	+4.4 (0.92)	98[f]	2*S*,3*S*
5	*trans*-**7e**	$C_3H_7^n$	$C_3H_7^i$	14	<1	—	—	—	—	—	—	—	—	—
6	*cis*-**7f**	CH_3	$C_3H_7^i$	20	50	32	13	−1.3 (2.3)[g]	85[h]	3*S*,4*R* (3α,4α)	39	+5.8 (0.40)	84[j]	2*R*,3*S*

[a] Calculated from eqns. (2) and (3). [b] Determined by method D. DAICEL CHIRALPAK AD. [c] Determined by method D. DAICEL CHIRALPAK OJ. [d] Determined by Chiral HPLC, CHIRALPAK AD; retention time [(2*S*,3*S*)-**11a**] 19.9 min, [(2*R*,3*R*)-**11a**] 18.8 min. [e] Determined by Chiral HPLC, CHIRALPAK OJ; retention time [(2*S*,3*S*)-**11b**] 20.5 min, [(2*R*,3*R*)-**11b**] 18.5 min. [f] Determined by Chiral HPLC, CHIRALPAK AD; retention time [(2*S*,3*S*)-**11d**] 12.9 min, [(2*R*,3*R*)-**11d**] 6.2 min. [g] 51% ee. [h] Chiral GC, ASTEC CHIRALDEX B-PH; retention time [(3*S*,4*R*)-**7f**] 12.5 min, [(3*R*,4*S*)-**7f**] 13.6 min. [j] Determined by method E.

equimolar amount of alcohol was employed. They were derived from acylation of **10** with oxetanone **4** and their formation was suppressed by using two equivalents of alcohol. The methyl derivative (±)-**4a** and the butyl derivative (±)-**4c** were resolved with moderate and low selectivity, respectively (Table 2, entries 1 and 3); they have the 3*R* configuration and a 3β-substituent. Oxetanone **4b**, which has an isopropyl group, did not react at all.

The reactions of 3,4-dialkyloxetan-2-ones (±)-**7** were slower than those of both 4-alkyl- and 3-alkyloxetanones (Table 3). Oxetanones (±)-*trans*-**7c**, having *tert*-butyl group, and (±)-*trans*-**7e**, having both 3-propyl and 4-isopropyl groups, did not react (Table 3, entries 3 and 5). The trans-esterification proceeded with a considerably high selectivity in the cases where one of the two substituents was a methyl group. Both the *trans* and *cis* forms of 3,4-dialkyloxetan-2-ones **7** have a 4α-substituent regardless of the orientation of the 3-substituents. This configuration is in accord with that expected from the more selective reaction of 4-alkyloxetan-2-ones **1** and the less selective reaction of 3-alkyloxetan-2-ones **4**. It can be concluded that the stereochemical course of the reaction is mainly directed by the 4-substituent.

The methods used to directly determine the ee and configuration of the compounds, **4a**, **4c**, *cis*-**7f**, **9a**–**d**, **9f**, **10a** and *anti*-**11a**, **11b**, are given as footnotes to the relevant Table. The methods of determining the ee's of the others are summarized in Scheme 2. The ee of oxetanone **1a** was assessed by HPLC after converting to a diastereomeric mixture of amide **12** (method A). The other 4-alkyloxetan-2-ones were converted to the corresponding acids or esters and the specific rotations were measured (method B). Ester **10c** was cyclized to oxetanone **4** and chiral GC analysis was performed (method C). After converting *trans*-**7a**, **7b** and **7d** to the corresponding benzyl esters, their ee's were assessed by chiral HPLC (method D). Ester *syn*-**11f** was cyclized to *cis*-**7f** on which chiral GC was carried out (method E).

In order to determine the configuration of disubstituted oxetanone *cis*-**7f**, it was independently synthesized by Evans' asymmetric aldol reaction followed by Adams' cyclization (Scheme 3). On chiral GC analysis, the retention time of the major isomer derived from the asymmetric synthesis coincided with that from the present enzymatic reaction, the 3*S*,4*R* configuration (3α-methyl and 4α-isopropyl) having been assigned to the latter. Epimerization of (3*S*,4*R*)-*cis*-**7f** at position 3 with LDA gave four base-line separated peaks on the chiral GC. The major peak observed is assigned to (3*R*,4*R*)-*trans*-**7b** (3β-methyl and 4α-isopropyl) whose retention time coincided with that from the present enzymatic reaction of (±)-*trans*-**7b**. The 3β,4α orientation of the alkyl groups of the other 3,4-dialkyloxetan-2-ones *trans*-**7a**,**d** was confirmed by the comparison of their CD spectra (Table 4). The 3*R* configuration of **4c** (R = Bu^n) was also established by this method, and by comparing it with (3*R*)-**4a** (R = Me). All the compounds showed a negative maximum at 214–217 nm.

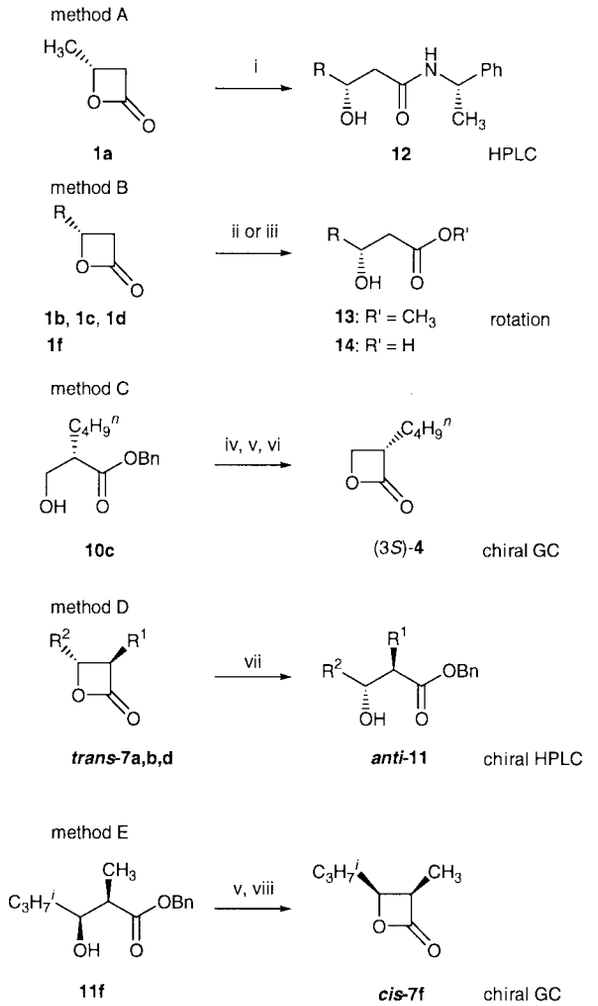
Table 4 CD spectra of oxetan-2-ones

Oxetanone	Ee (%)	θ^a (λ/nm)	Configuration
(+)-**4a**	75	−1100 (214)	3*R* (3β) known
(−)-**4c**	32	−1600 (214)	3*R* (3β)
(+)-*trans*-**7a**	92	−2200 (217)	3*R*,4*R* (3β,4α)
(+)-*trans*-**7b**	72	−1860 (216)	3*R*,4*R* (3β,4α) known
(+)-*trans*-**7d**	79	−1700 (216)	3*R*,4*R* (3β,4α)

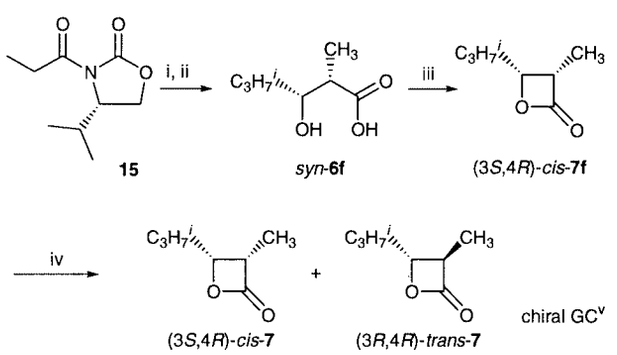
[a] deg cm^2 dmol^{-1}, in hexane.

In conclusion, this report describes a methodology for the preparation of optically active oxetan-2-ones of moderate to high ee's, and the substrate structure which permits the lipase promoted trans-esterification.

Moreover, the orientation of the ring substituents, which directs the stereochemistry of the reaction has been identified. The resolution of 4-alkyloxetan-2-ones **1** is especially efficient in the enzymatic preparation methods discussed here. Oxetan-2-ones **1** and 3-hydroxyalkanoates, readily derived from **1**, are useful chiral building blocks. In addition, it is very interesting that natural products containing the oxetan-2-one moiety are potent inhibitors of some lipases, including PPL.[25] The results from this work and further application of these methods to oxetan-2-ones with long alkyl substituents should help to identify the catalysis and inhibition mechanisms. The reasons for the inhibition towards PPL hydrolysis and trans-esterification by the oxetan-2-ones resolved by Lipase PS are currently under investigation.



Scheme 2 Determination of ee; *reagents and conditions*: i, (*S*)-1-phenylethylamine, 130 °C; ii, CH_3OH, reflux; iii, NaOH, rt; iv, MsCl, $(C_2H_5)_3N$, 0 °C; v, H_2/Pd–C, vi, NaOH, vii, BnOH, NaH; viii, TsCl, pyridine, 0 °C.



Scheme 3 *Reagents and conditions*: i, $(C_4H_9^n)_2BOTf$, $(C_2H_5)_3N$, 0 °C, then $C_3H_7^iCHO$, −78 °C; ii, TsCl, pyridine; iv, LDA then CH_3CO_2H; v, Chiral GC ASTEC CHIRALDEX B-PH; rt [(3*S*,4*R*)-*cis*-**7f**] 12.5 min (major), rt [(3*R*,4*S*)-*cis*-**7f**] 13.6 min (minor), rt [(3*R*,4*R*)-*trans*-**7f**] 6.9 min (major), rt [(3*S*,4*S*)-*trans*-**7f**] 7.1 min (minor).

Experimental

^1H NMR and ^{13}C NMR spectra were recorded with a JEOL-JNM-EX-270 spectrometer (at 270 MHz for ^1H, 68 MHz for ^{13}C). *J* Values are given in Hz. IR spectra were recorded with a SHIMADZU FTIR-8600PC spectrophotometer. Optical rotation was measured with a JASCO DIP-1000 polarimeter (with a 10 cm cell). [*a*] values are given as 10^{-1} deg cm^2 g^{-1}. HPLC analyses were run on a JASCO 880-PU chromatographic system with an 875-UV detector (220 nm) and a silica gel column (FINPAK SIL, 4 mm × 25 cm). Chiral HPLC analyses were run with DAICEL CHIRALPAK AD and OJ. Chiral GC-mass analyses were done on a Shimadzu GC-17A with ASTEC CHIRALDEX B-PH. High resolution mass spectra (HRMS) were recorded with a JEOL JMS DX-300 spectrometer. CD spectra were measured with a JASCO J-720 CD spectrometer (with a 0.1 cm cell). The elemental analyses were performed by Kyoto University elemental analysis center.

(±)-4-Methyloxetan-2-one (±)-1a

The desired oxetan-2-one (±)-**1a** (86%) was yielded by hydrogenation of diketene.[17]

General method for the preparation of (±)-4-alkyloxetan-2-ones

Ketene gas was passed into a solution of $BF_3{\cdot}Et_2O$ (0.1 eq.) in dry ether (50 cm^3) at 0 °C for 5 min. Then, aldehyde (1.0 eq.) in dry ether (50 cm^3) was added dropwise over 3 h to this solution at 10 °C during which the introduction of ketene gas was continued. After adding 50% aq. NaOH (2 cm^3), the mixture was washed with 10% aq. citric acid (20 cm^3 × 2) and saturated NaCl (20 cm^3). Then the organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by distillation or silica gel flash chromatography.

4-Propyloxetan-2-one (±)-1b. Distillation gave (±)-**1b** (80%); bp 84 °C (25 mmHg).

4-Isopropyloxetan-2-one (±)-1c. Distillation gave (±)-**1c** (88%); bp 80 °C (20 mmHg).

4-Butyloxetan-2-one (±)-1d. Distillation gave (±)-**1d** (80%); bp 100 °C (20 mmHg).

4-*tert*-Butyloxetan-2-one (±)-1e. Distillation gave (±)-**1e** (75%); bp 100 °C (25 mmHg); $\delta_H(CDCl_3)$ 1.00 (s, 9H, $CH(CH_3)_3$), 3.15 (dd, *J* 4.6, 11.1, 1H, $COCHH$), 3.32 (dd, *J* 6.2, 11.1, 1H, $COCHH$), 4.2–4.3 (m, 1H, $CHC_4H_9^t$); δ_C ($CDCl_3$) 24.0, 32.8, 38.2, 77.9, 168.3.

4-Undecyloxetan-2-one (±)-1f. Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave (±)-**1f** (65%); bp 100 °C (0.1 mmHg).

General method for preparation of 3-alkyloxetan-2-ones

To a solution of HBr in CH_3CO_2H (25%, 1.1 eq.), acid **2** was added dropwise at 0 °C. After stirring overnight, the solution was evaporated. The residue was purified by distillation to give bromo acid (±)-**3**. A solution of NaOH (1 M, 1.0 eq.) was added to (±)-**3** slowly. After adding $CHCl_3$, the mixture was stirred vigorously. The organic layer was separated and $CHCl_3$ was added to the aqueous layer. The mixture was stirred for 2 h and the organic layer was separated. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by distillation or silica gel flash chromatography.

3-Methyloxetan-2-one (±)-4a. Distillation gave (±)-**4a** (42%); bp 76 °C (27 mmHg).

3-Isopropyloxetan-2-one (±)-4b. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-**4b** (23%, overall yield from **2**); bp 67 °C (9 mmHg) (Found: C, 62.62; H, 9.05. Calcd. for $C_6H_{12}O_2$: C, 63.14; H, 8.83%); $\delta_H(CDCl_3)$ 1.02 (d, *J* 7.0, 3H, $CH(CH_3)CH_3$), 1.10 (d, *J* 6.7, 3H, $CH(CH_3)CH_3$), 2.03–2.16 (m, 1H, $CH(CH)_3$), 3.5–3.6 (m, 1H, $CHC_3H_7^i$), 4.06 (dd, *J* 5.4, 5.4, 1H, $OCHH$), 4.31 (dd, *J* 5.4, 6.2, 1H, $OCHCH$); $\delta_C(CDCl_3)$ 19.6, 20.2, 27.8, 58.9, 63.2, 171.6; IR (neat): 1820 cm^{-1}.

3-Butyloxetan-2-one (±)-4c. Distillation gave (±)-**4c** (46%, overall yield from **2**); bp 63 °C (0.6 mmHg).

General method for preparation of *trans*- and *cis*-3,4-disubstituted oxetan-2-ones

The desired products (±)-*trans*-**7a**–**e** and (±)-*cis*-**7f** were prepared according to Heathcock[19] and Evans[20] and their co-workers respectively, followed by Adams' cyclization.[21]

(±)-*trans*-3-Methyl-4-propyloxetan-2-one (±)-*trans*-7a. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-*trans*-**7a** (35%, overall yield from **5**), containing the *cis* isomer (18%).

(±)-*trans*-4-Isopropyl-3-methyloxetan-2-one (±)-*trans*-7b. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-*trans*-**7b** (40%, overall yield from **5**).

(±)-*trans*-4-*tert*-Butyl-3-methyloxetan-2-one (±)-*trans*-7c. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-*trans*-**7c** (59%, overall yield from **5**); bp 70 °C (18 mmHg) (Found: C, 67.49; H, 9.95. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92%); $\delta_H(CDCl_3)$ 0.99 (s, 9H, $C(CH_3)_3$), 1.38 (d, *J* 7.3, 3H, $CHCH_3$), 3.35 (dq, *J* 4.3, 7.4, 1H, $CHCH_3$), 3.86 (d, 1H, *J* 4.3, $CHC_4H_9^t$); $\delta_C(CDCl_3)$ 13.1, 24.2, 32.8, 45.5, 86.6, 172.0; IR (neat): 1820 cm^{-1}.

(±)-*trans*-4-Methyl-3-propyloxetan-2-one (±)-7d. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-*trans*-**7d** (21%, overall yield from **5**), containing the *cis* isomer (19%).

(±)-*trans*-4-Isopropyl-3-propyloxetan-2-one (±)-7e. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-*trans*-**7e** (30%, overall yield from **5**); bp 86 °C (22 mmHg) (Found: C, 68.89; H, 10.12. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32%); $\delta_H(CDCl_3)$ 0.96 (d, *J* 6.8, 3H, $CH(CH_3)CH_3$), 0.97 (t, *J* 7.3, 3H, $(CH_2)_2CH_3$), 1.04 (d, *J* 6.5, 3H, $CH(CH_3)CH_3$), 1.4–1.5 (m, 2H, $CH_2CH_2CH_3$), 1.7–1.8 (m, 2H, $CH_2CH_2CH_3$), 1.8–2.0 (m, 1H, $CH(CH_3)_2$), 3.22 (ddd, *J* 4.0, 6.8, 8.5, 1H, $CHC_3H_7^n$), 3.86 (dd, *J* 4.0, 8.0, 1H, $CHC_3H_7^i$); $\delta_C(CDCl_3)$ 13.8, 16.9, 18.0, 20.3, 30.3, 32.3, 53.9, 82.8, 172.2; IR (neat): 1821 cm^{-1}.

(±)-*cis*-4-Isopropyl-3-methyloxetan-2-one (±)-*cis*-7f. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave (±)-*cis*-**7f** (29%, overall yield from **8**).

General method for asymmetric trans-esterification of oxetan-2-ones

A mixture of oxetan-2-one (58 mmol), alcohol (46 mmol), lipase (5.0 g) and solvent (50 cm^3) was stirred at 35 °C during which the reaction conversion was assessed by ^1H NMR. When the conversion reached *ca.* 50%, the lipase was filtered off and washed with ether (20 cm^3) and the combined filtrate and washings were evaporated. Oxetan-2-one and ester were separated from the residue by fractional distillation or silica gel column chromatography.

(*R*)-4-Methyloxetan-2-one 1a. Distillation gave **1a** (36%); bp 66 °C (22 mmHg) (Found: C, 55.11; H, 6.97. Calcd. for $C_4H_6O_2$: C, 55.81; H, 7.02%); 96% ee; $[\alpha]_D^{25}$ +28.0 (*c* 4.3, $CHCl_3$); $\delta_H(CDCl_3)$ 1.58 (d, *J* 6.2, 3H, CH_3), 3.07 (dd, *J* 4.3, 16, 1H, CHH), 3.57 (dd, *J* 5.9, 16, 1H, CHH), 4.6–4.8 (m, 1H, $CHCH_3$); $\delta_C(CDCl_3)$ 20.5, 44.2, 67.8, 168.2.

(*S*)-Benzyl 3-hydroxybutanoate 9a. Distillation gave **9a** (51%); bp 105 °C (10 mmHg) (Found: C, 67.86; H, 7.45. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26%); 85% ee; $[\alpha]_D^{25}$ +25.7 (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 1.20 (d, *J* 6.2, 3H, CH_3), 2.4–2.6 (m, 2H, CH_2CO), 3.3 (br s, 1H, OH), 4.1–4.3 (m, 1H, CHOH), 5.15 (s, 2H, CH_2Ph), 7.35 (s, 5H, *Ph*); $\delta_C(CDCl_3)$ 22.4, 42.8, 64.2, 66.4, 128.1, 128.3, 128.5, 135.5, 172.5.

(*R*)-4-Propyloxetan-2-one 1b. Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave **1b** (42%); bp 84 °C (25 mmHg) (Found: C, 62.94; H, 8.30. Calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83%); 75% ee; $[\alpha]_D^{25}$ +32.8 (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 0.97 (d, *J* 7.3, 3H, CH_3), 1.3–1.6 (m, 2H, CH_2CH_3), 1.7–1.9 (m, 2H, $CH_2CH_2CH_3$), 3.05 (dd, *J* 4.3, 16, 1H, CHH), 3.50 (dd, *J* 5.9, 16, 1H, CHH), 4.5–4.6 (m, 1H, $CHC_3H_7^n$); $\delta_C(CDCl_3)$ 13.5, 18.2, 36.6, 42.8, 71.1, 168.3.

(*S*)-Benzyl 3-hydroxyhexanoate 9b. Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave **9b** (45%) (Found: C, 69.98; H, 8.18. Calcd. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%); 69% ee; $[\alpha]_D^{25}$ +14.1 (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 0.92 (d, *J* 7.0, 3H, CH_3), 1.3–1.6 (m, 4H, $CH_2CH_2CH_3$), 2.41–2.59 (m, CH_2CO, 2H), 2.9 (br s, 1H, OH), 4.0–4.1 (m, 1H, CHOH), 5.15 (s, 2H, CH_2Ph), 7.35 (s, 5H, *Ph*); $\delta_C(CDCl_3)$ 13.9, 18.6, 38.6, 41.3, 66.4, 67.7, 128.2, 128.3, 128.6, 135.6, 172.8.

(*S*)-4-Isopropyloxetan-2-one 1c. Purification by silica gel flash chromatography (EtOAc–hexane 15:85) gave **1c** (41%); bp 80 °C (20 mmHg) (Found: C, 63.09; H, 8.91. Calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83%); 95% ee; $[\alpha]_D^{25}$ +22.8 (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 0.94 (d, *J* 7.0, 3H, $CH(CH_3)CH_3$), 1.03 (d, *J* 6.8, 3H, $CH(CH_3)CH_3$), 1.9–2.0 (m, 1H, $CH(CH_3)_2$), 3.06 (dd, *J* 4.3, 16, 1H, CHH), 3.41 (dd, *J* 5.7, 16, 1H, CHH), 4.2–4.3 (m, 1H, $CHC_3H_7^i$); δ_C ($CDCl_3$) 16.7, 17.6, 32.4, 40.8, 75.7, 168.3.

(*R*)-Benzyl 3-hydroxy-4-methylpentanoate 9c. Purification by silica gel flash chromatography (EtOAc–hexane 15:85) gave **9c** (43%) (Found: C, 70.05; H, 8.11. Calcd. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%); 90% ee; $[\alpha]_D^{25}$ +27.4 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$) 0.87 (d, *J* 7.3, 3H, $CH(CH_3)CH_3$), 0.89 (d, *J* 7.3, 3H, $CH(CH_3)CH_3$), 1.6–1.8 (m, 1H, $CH(CH_3)_2$), 2.4–2.6 (m, 2H, CH_2CO), 2.6–3.1 (br s, 1H, OH), 3.8–3.9 (m, 1H, CHOH), 5.15 (s, 2H, CH_2Ph), 7.36 (s, 5H, *Ph*); $\delta_C(CDCl_3)$ 17.6, 18.3, 33.1, 38.5, 66.4, 72.6, 128.2, 128.3, 128.5, 135.6, 173.1.

(*R*)-4-Butyloxetan-2-one 1d. Purification by silica gel flash chromatography (EtOAc–hexane 1:19) gave **1d** (46%); bp 100 °C (25 mmHg) (Found: C, 65.22; H, 9.28. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44%); 71% ee; $[\alpha]_D^{25}$ +26.0 (*c* 1.5, $CHCl_3$); $\delta_H(CDCl_3)$ 0.93 (t, *J* 6.8, 3H, CH_3), 1.4–1.5 (m, 4H, $CH_2CH_2CH_3$), 1.7–1.9 (m, 2H, $OCHCH_2$), 3.06 (dd, *J* 4.3, 11.9, 1H, $CHHCO$), 3.51 (dd, *J* 5.7, 11.9, 1H, $CHHCO$), 4.5–4.6 (m, 1H, $OCHCH_2$); δ_C ($CDCl_3$) 13.8, 22.2, 27.0, 34.3, 42.9, 71.3, 168.3.

(*S*)-Benzyl 3-hydroxyheptanoate 9d (R^2 = Bn). Purification by silica gel flash chromatography (EtOAc–hexane 1:19) gave **9d** (36%); bp 80 °C (0.3 mmHg) (Found: C, 70.69; H, 8.57. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%); 81% ee; $[\alpha]_D^{25}$ +16.1 (*c* 1.5, $CHCl_3$); $\delta_H(CDCl_3)$ 0.90 (t, *J* 6.9, 3H, CH_3), 1.3–1.6 (m, 6H, $(CH_2)_3CH_3$), 2.4–2.6 (m, 2H, CH_2CO), 2.9 (br s, 1H, OH), 4.0–4.1 (m, 1H, CHOH), 5.16 (s, 2H, CH_2Ph), 7.37 (s, 5H, *Ph*); $\delta_C(CDCl_3)$ 14.0, 22.6, 36.7, 43.8, 68.8, 120.0, 124.4, 129.0, 137.6, 170.5.

(*R*)-4-Undecyloxetan-2-one 1f. Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave **1f** (27%) (Found: C, 74.09; H, 11.62. Calcd. for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58%); 70% ee; $[\alpha]_D^{25}$ +14.7 (*c* 1.2, $CHCl_3$); $\delta_H(CDCl_3)$ 0.9–1.0 (m, 3H, CH_3), 1.2–1.5 (m, 18H, $(CH_2)_9CH_3$), 1.7–1.9 (m, 2H, $CH_2(CH_2)_9CH_3$), 3.05 (dd, *J* 4.3, 11.9, 1H, $CHHCO$), 3.51 (dd, *J* 6.8, 11.9, 1H, $CHHCO$), 4.5–4.6 (m, 1H, OCH); $\delta_C(CDCl_3)$ 14.1, 22.6, 24.9, 29.1, 29.3, 29.36, 29.42, 29.5, 31.8, 34.6, 42.8, 71.3, 168.3.

(*S*)-Benzyl 3-hydroxytetradecanoate 9f (R^2 = Bn). Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave **9f** (25%); mp 34 °C (Found: C, 75.01; H, 10.25. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.24%); 77% ee; $[\alpha]_D^{25}$ +9.7 (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 0.88 (t, *J* 6.8, 3H, CH_3), 1.2–1.6 (m, 20H,

(CH_2)$_{10}CH_3$), 2.4–2.6 (m, 2H, CH_2CO), 2.82 (d, *J* 4.1, 1H, OH), 4.0–4.1 (m, 1H, C*H*OH), 5.16 (s, 2H, CH_2Ph), 7.40 (s, 5H, *Ph*); δ_C($CDCl_3$) 14.1, 22.7, 29.3, 29.5, 29.6, 31.9, 36.5, 41.3, 66.5, 68.0, 128.2, 128.4, 128.6, 135.6, 172.8.

(*R*)-3-Methyloxetan-2-one 4a. Distillation gave **4a** (38%); bp 76 °C (27 mmHg) (Found: C, 55.16; H, 7.02. Calcd. for $C_4H_6O_2$: C, 55.81; H, 7.02%); 70% ee; $[\alpha]_D^{25}$ +7.4 (*c* 9.4, $CHCl_3$); δ_H($CDCl_3$) 1.42 (d, *J* 7.6, 3H, CH_3), 3.7–3.8 (m, 1H, C*H*CH_3), 3.97 (dd, *J* 4.8, 4.8, 1H, OC*H*H), 4.40 (dd, *J* 6.0, 6.0, 1H, OC*H*H); δ_C($CDCl_3$) 12.9, 46.7, 66.4, 172.3.

(*S*)-Benzyl 3-hydoxy-2-methylpropanoate 10a. Distillation gave **10a** (24%); bp 120 °C (0.6 mmHg) (Found: C, 68.16; H, 7.34. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26%); 72% ee; $[\alpha]_D^{25}$ +13.2 (*c* 10.0, EtOH); δ_H($CDCl_3$) 1.19 (d, *J* 7.3, 3H, CH_3), 2.3 (br s, 1H, O*H*), 2.7–2.8 (m, 1H, C*H*CH_3), 3.7 (br s, 2H, CH_2OH), 5.16 (s, 2H, CH_2Ph), 7.35 (s, 5H, *Ph*); δ_C($CDCl_3$) 13.4, 47.8, 64.5, 66.4, 128.0, 128.2, 128.6, 135.8, 175.4.

(*R*)-3-Butyloxetan-2-one 4c. Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave **4c** (45%); bp 63–64 °C (0.6 mmHg) (Found: C, 64.92; H, 9.49. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44%); 32% ee, $[\alpha]_D^{25}$ −8.6 (*c* 9.3, $CHCl_3$); δ_H($CDCl_3$) 0.92 (t, *J* 7.0, 3H, CH_3), 1.3–1.5 (m, 4H, (CH_2)$_2$-CH_3), 1.7–1.9 (m, 2H, CH_2(CH_2)$_2CH_3$), 3.7–3.8 (m, 1H, C*H*-$C_4H_9^n$), 4.02 (dd, *J* 4.7, 4.7, 1H, OCH*H*), 4.38 (dd, *J* 5.7, 5.7, 1H, OCH*H*); δ_C($CDCl_3$) 13.9, 22.4, 27.9, 29.0, 52.1, 65.0, 171.6; IR (neat): 1825 cm^{-1}.

(*S*)-Benzyl 2-hydroxymethylhexanoate 10c. Purification by silica gel flash chromatography (EtOAc–hexane 1:4) gave **10c** (32%); bp 90 °C (20 mmHg) 36% ee; $[\alpha]_D^{25}$ +1.8 (*c* 8.8, $CHCl_3$); δ_H($CDCl_3$) 0.89 (t, *J* 6.8, 3H, CH_3), 1.2–1.5 (m, 4H, (CH_2)$_2$-CH_3), 1.5–1.9 (m, 2H, CH_2(CH_2)$_2CH_3$), 2.5–2.7 (m, 1H, C*H*$C_4H_7^n$), 2.7–3.0 (br s, 1H, CH_2O*H*), 3.7–3.8 (m, 2H, CH_2OH), 5.15 (s, 2H, CH_2Ph), 7.34 (s, 5H, *Ph*); δ_C($CDCl_3$) 13.8, 22.5, 28.2, 29.2, 47.8, 63.0, 66.2, 127.9, 128.0, 128.3, 135.7, 175.1; (HRMS (M^+) Calcd. for $C_{14}H_{20}O_3$: 236.1413. Found: *M*, 236.1418).

(3*R*,4*R*)-*trans*-3-Methyl-4-propyloxetan-2-one 7a. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *trans*-**7a** (50%); bp 70 °C (7 mmHg) (Found: C, 65.87; H, 9.62. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44%); 92% ee; $[\alpha]_D^{25}$ +41.3 (*c* 1.0, $CHCl_3$); δ_H($CDCl_3$) 0.99 (t, *J* 7.0, 3H, (CH_2)$_2$CH_3), 1.39 (d, *J* 7.5, 3H, CHCH_3), 1.4–1.5 (m, 2H, CH_2C$H_2$$CH_3$), 1.7–1.8 (m, 2H, C$H_2$$CH_2CH_3$), 3.22 (dq, *J* 4.3, 7.5, 1H, C*H*CH_3), 3.86 (dt, *J* 4.3, 7.0, 1H, OC*H*$C_3H_7^n$); δ_C($CDCl_3$) 12.5, 13.7, 18.3, 36.1, 50.7, 79.4, 172.1; IR (neat): 1825 cm^{-1}.

Benzyl (2*S*,3*S*)-2-methyl-3-hydroxyhexanoate 11a. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *anti*-**11a** (34%); bp 93 °C (0.4 mmHg) (Found: C, 71.34; H, 8.88. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%); 87% ee; $[\alpha]_D^{25}$ +1.3 (*c* 1.1, $CHCl_3$); δ_H($CDCl_3$) 0.91 (t, 3H, *J* 7.0, CH_2CH_3), 1.2–1.5 (m, 4H, (CH_2)$_2CH_3$), 1.22 (d, 3H, *J* 7.3, CHCH_3), 2.5–2.6 (m, 1H, C*H*CH_3), 3.6–3.8 (m, 1H, C*H*OH), 5.15 (s, 2H, CH_2Ph), 7.35 (s, 5H, *Ph*); δ_C($CDCl_3$) 14.0, 14.3, 18.7, 36.9, 45.3, 66.3, 73.1, 128.1, 128.3, 128.6, 135.8, 175.8; IR (neat): 1719 cm^{-1}.

(3*R*,4*R*)-*trans*-4-Isopropyl-3-methyloxetan-2-one *trans*-7b. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *anti*-**7b** (37%); bp 67 °C (18 mmHg) (Found: C, 65.78; H, 9.68. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44%); 72% ee; $[\alpha]_D^{25}$ +34.6 (*c* 1.2, $CHCl_3$); δ_H($CDCl_3$) 0.96 (d, *J* 7.0, 3H, CH(CH_3)CH_3), 1.05 (d, *J* 6.8, 3H, CH(CH_3)CH_3), 1.39 (d, *J* 7.4, 3H, CHCH_3), 1.9–2.0 (m, 1H, C*H*(CH_3)$_2$), 3.26 (dq, *J* 4.0, 7.4, 1H, C*H*CH_3), 3.86 (dd, *J* 4.0, 8.5, 1H, C*H*$C_3H_7^i$); δ_C($CDCl_3$) 12.7, 16.7, 17.9, 32.3, 46.7, 84.1, 171.9; IR (neat): 1825 cm^{-1}.

Benzyl (2*S*,3*S*)-2,4-dimethyl-3-hydroxypentanoate 11b. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *trans*-**11b** (41%); bp 93 °C (0.6 mmHg) (Found: C, 70.82; H, 8.56. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%); 85% ee; $[\alpha]_D^{25}$ +15.2 (*c* 1.2, $CHCl_3$); δ_H($CDCl_3$) 0.92 (d, 3H, *J* 6.5, CH(CH_3)CH_3), 0.95 (d, 3H, *J* 6.5, CH(CH_3)CH_3), 1.22 (d, 3H, *J* 7.3, CH_3), 1.7–1.8 (m, 1H, C*H*(CH_3)$_2$), 2.5 (br s, 1H, O*H*), 2.7–2.8 (m, 1H, C*H*CH_3), 3.39–3.42 (m, 1H, C*H*OH), 5.15 (s, 2H, CH_2Ph), 7.35 (s, 5H, *Ph*); δ_C($CDCl_3$) 14.8, 16.4, 19.8, 31.0, 42.7, 66.4, 78.2, 128.1, 128.3, 128.6, 135.7, 176.2; IR (neat): 1732 cm^{-1}.

(3*R*,4*R*)-*trans*-4-Methyl-3-propyloxetan-2-one 7d. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *trans*-**7d** (16%); bp 85 °C (20 mmHg) (Found: C, 65.74; H, 9.68. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44%); 79% ee; $[\alpha]_D^{25}$ +11.4 (*c* 0.92, $CHCl_3$); δ_H($CDCl_3$) 0.96 (t, *J* 7.3, 3H, CH_2CH_3), 1.4–1.5 (m, 2H, C$H_2$$CH_3$), 1.56 (d, *J* 5.9, 3H, CHCH_3), 1.6–1.9 (m, 2H, C$H_2C_2H_5$), 3.18 (ddd, *J* 4.0, 6.6, 8.9, 1H, C*H*$C_3H_7^n$), 3.86 (dq, *J* 4.0, 5.9, 1H, C*H*CH_3); δ_C($CDCl_3$) 13.7, 20.1, 20.3, 29.7, 57.4, 74.6, 171.3; IR (neat): 1817 cm^{-1}.

Benzyl (2*S*,3*S*)-2-methyl-3-hydroxyhexanoate 11d. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *anti*-**11d** (24%); bp 70 °C (0.5 mmHg) (Found: C, 71.17; H, 8.79. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%); 98% ee; $[\alpha]_D^{25}$ +4.4 (*c* 0.92, $CHCl_3$); δ_H($CDCl_3$) 0.89 (t, *J* 7.0, 3H, CH_2CH_3), 1.19 (d, *J* 4.3, 3H, CHCH_3), 1.2–1.4 (m, 2H, C$H_2$$CH_3$), 1.5–1.7 (m, 2H, C$H_2C_2H_5$), 2.4–2.5 (m, 2H, C*H*$C_3H_7^n$, OH), 3.9–4.0 (m, 1H, C*H*OH), 5.16 (s, 2H, CH_2Ph), 7.37 (s, 5H, *Ph*); δ_C($CDCl_3$) 13.9, 20.5, 21.6, 31.6, 52.6, 66.3, 68.5, 127.0, 128.3, 128.5, 135.8, 175.3; IR (neat): 1732 cm^{-1}.

(3*S*,4*R*)-*cis*-4-Isopropyl-3-methyloxetan-2-one 7f. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *cis*-**7f** (13%); bp 80 °C (23 mmHg) (Found: C, 65.66; H, 9.69. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44%); 85% ee; δ_H($CDCl_3$) 0.92 (d, *J* 6.8, 3H, CH(CH_3)CH_3), 1.07 (d, *J* 6.8, 3H, CH(CH_3)CH_3), 1.39 (d, *J* 7.5, 3H, CHCH_3), 1.9–2.0 (m, 1H, C*H*(CH_3)$_2$), 3.26 (dq, *J* 6.8, 7.4, 1H, C*H*CH_3), 3.86 (dd, *J* 6.8, 7.8, 1H, C*H*$C_3H_7^i$); δ_C($CDCl_3$) 8.5, 17.7, 19.0, 28.5, 46.7, 80.5, 172.8; IR (neat): 1823 cm^{-1}.

Benzyl (2*S*,3*S*)-2,4-dimethyl-3-hydroxypentanoate 11f. Purification by silica gel flash chromatography (EtOAc–hexane 1:9) gave *syn*-**11f** (39%); 84% ee; $[\alpha]_D^{25}$ +5.8 (*c* 0.40, $CHCl_3$); δ_H($CDCl_3$) 0.84 (d, *J* 6.5, 3H, CH(CH_3)CH_3), 0.99 (d, *J* 6.5, 3H, CH(CH_3)CH_3), 1.23 (d, 3H, COCHCH_3), 1.6–1.7 (m, 1H, C*H*(CH_3)$_2$), 2.4–2.6 (br s, 1H, OH), 2.6–2.7 (m, 1H, COC*H*), 3.5–3.6 (m, 1H, C*H*OH), 5.16 (s, 2H, CH_2Ph), 7.35 (s, 5H, *Ph*); δ_C($CDCl_3$) 13.9, 20.5, 21.6, 31.6, 52.6, 66.3, 68.5, 127.0, 128.3, 128.5, 135.8, 175.3 (HRMS (M^+) Calcd. for $C_{14}H_{20}O_3$: 236.1413. Found: *M*, 236.1418).

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