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Enantioselective synthesis of a hindered furyl substituted allyl alcohol intermediate: a case study in asymmetric synthesis

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Abstract—In the course of the synthesis of the DEFG ring system of cneorin C **1**, we were faced with the task of preparing the furyl substituted allyl alcohol **5** enantioselectively. Several different methods starting from enantioselective zinc-mediated alkylations were attempted, but none of them proved entirely satisfactory. The solution turned out to be enzymatic kinetic resolution through a highly enantioselective ($E > 300$) acylation in the presence of *Candida antarctica* lipase A.

1. Introduction

Cneorin C **1** was originally isolated from the xerophytic shrub *Cneorum pulverulentum* native to the Canary Islands in the early 1970s.[1] Despite its intriguing structure, no efforts toward its synthesis have been reported. Due to lack of material from natural sources, the compound has not received proper pharmacological screening. We have been interested in copper-catalyzed intramolecular cyclopropanations of diazomalonates for a long time.[2–6] As evident from the retrosynthetic analysis shown in Figure 1, the DEFG ring system of cneorin C is an ideal candidate for the intramolecular cyclopropanation of diazomalonate **4**, which can be conveniently prepared from the furyl substituted allyl alcohol (*S*)-**5**. The preparation of enantiopure compounds is of crucial importance in modern organic synthesis, and chiral allylic alcohols provide a useful template for a variety of stereoselective transformations of olefins. The stereogenic center of the allylic alcohol can be used to direct, for example, epoxidations[7,8] and dihydroxylations.[9] In a recent example, Evans' syntheses of pectenotoxins-4 and -8 utilize a hydroxyl directed epoxidation twice in a highly diastereoselective manner.[10,11] A wide selection of

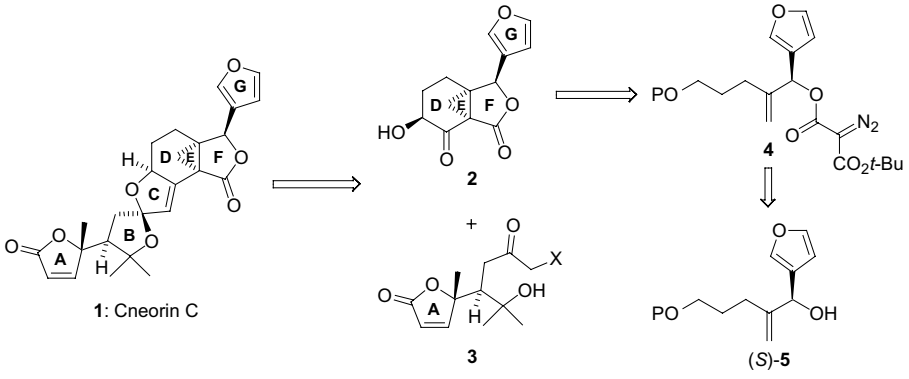

Figure 1. Retrosynthesis of cneorin C.

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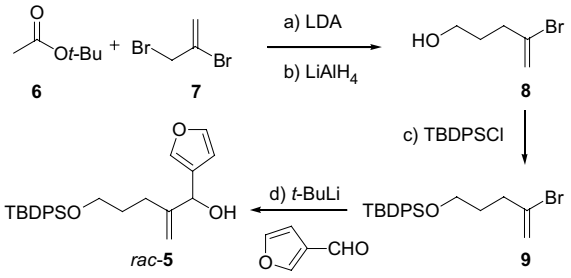
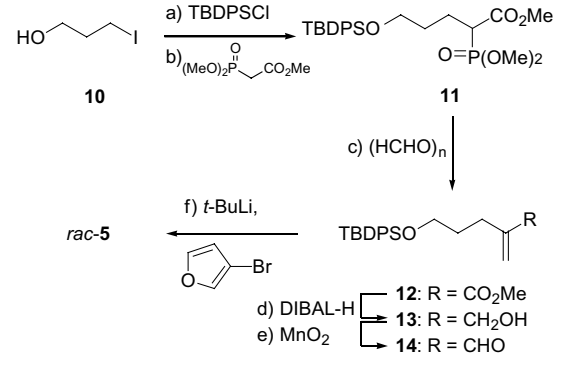
different chemical and enzymatic methods is available to produce either enantiomer of allylic alcohols. One such method is the use of hydrolytic enzymes in deacylations (hydrolysis or alcoholysis) of secondary alcohol esters or in acylations of secondary alcohols in an organic solvent.[12] Herein, we describe the successful application of a lipase-catalyzed kinetic resolution to access the sterically hindered furyl substituted allyl alcohol (*S*)-**5**.

2. Results and discussion

Vinyl bromide **9** (Scheme 1) was prepared according to the literature[13] from *t*-butyl acetate and 2,3-dibromopropene. The vinyl bromide **9** was then converted to the corresponding vinyl lithium species by halogen metal exchange with *t*-BuLi and then treated with 3-furyl aldehyde as the electrophile to furnish the racemic furyl substituted allyl alcohol *rac*-**5**. An alternative preparation of the racemic alcohol *rac*-**5** was developed as follows: enal **14** was prepared from 3-iodopropanol via a Horner–Wadsworth–Emmons reaction of phosphonate **11** (Scheme 2).[14,15] The enal **14** was then alkylated with 3-furyl lithium yielding the racemic furyl substituted allyl alcohol *rac*-**5**. The route presented in Scheme 1 via vinyl bromide **9** turned out to be more convenient for obtaining alcohol *rac*-**5** than the route in Scheme 2.

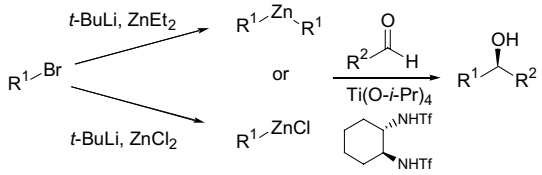


Scheme 1. Synthesis of furyl substituted allyl alcohol **5** via vinyl bromide **9**: (a) Ref. 13, LDA, THF, −78 °C, 62%; (b) Ref. 13, $LiAlH_4$, THF, 0 °C → rt, 90%; (c) TBDPSCl, imid., CH_2Cl_2, rt, 90%; (d) *t*-BuLi, 3-furylaldehyde, THF, −78 °C → rt, 74%.



Scheme 2. Synthesis of furyl substituted allyl alcohol **5** via enal **14**: (a) TBDPSCl, imid., CH_2Cl_2, rt, 88%; (b) Ref. 14, NaH, trimethyl phosphonoacetate, DMSO, rt, 71%; (c) Ref. 15, paraformaldehyde, K_2CO_3, THF, reflux, 71%; (d) DIBAL-H, THF, −78 °C, 99%; (e) MnO_2, CH_2Cl_2, rt, 94%; (f) 3-bromofuran, *t*-BuLi, THF, −78 °C, 87%.

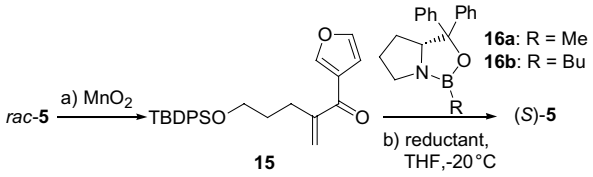
We were next faced with the task of preparing the furyl substituted allyl alcohol **5** in an enantioselective manner. When approaching this problem, the first solution was to use a catalytic enantioselective alkylation.[16] A vinyl bromide would be converted to a vinyl zinc species and added to an aldehyde in the presence of a chiral ligand in an enantioselective manner (Scheme 3). Two different routes were attempted: (1) alkylation of 3-furylaldehyde with the vinyl bromide **9** and (2) alkylation of enal **14** with 3-furylbromide. In the first case of vinyl bromide **9** and 3-furylaldehyde, the vinyl zinc species was never formed and only unreacted vinyl bromide was recovered. In the second case of enal **14** and 3-furylbromide, the corresponding furyl zinc species was not reactive enough to add to the aldehyde, which was recovered.



Scheme 3. Enantioselective alkylation.

Our second potential solution was to convert the furyl substituted allyl alcohol to an enone followed by enantioselective reduction. Thus, the alcohol *rac*-**5** was oxidized to ketone **15** with MnO_2.[17] The Corey–Bakshi–Shibata (CBS) reduction[18,19] is a widely established catalytic asymmetric reduction method. In this case, reduction of ketone **15** with $BH_3{\cdot}SMe_2$ in the presence of the chiral catalyst **16a**–**b** gave at its best the alcohol in 35% ee (Table 1). BINAL reduction[20,21] as well as DIP-chloride reduction[22–24] were also tried, but only the starting material was recovered.

Table 1. CBS reduction

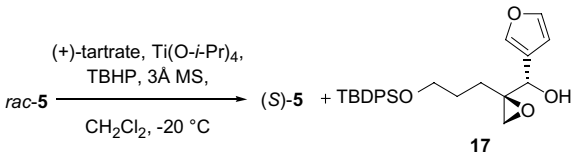


Entry	Reagents	% Ee	Time (h)
1	$BH_3{\cdot}SMe_2$, **16a**	35	114
2	$BH_3{\cdot}SMe_2$, **16b**	13	70
3	Catecholborane, **16b**	22	67

Yields were not determined.

The third approach was kinetic resolution of the furyl substituted allyl alcohols via Sharpless asymmetric epoxidation (SAE).[25,26] We tested both diethyl and diisopropyl tartrates, and two days of reaction at −20 °C yielded 50% conversion and 57% and 68% ee of the alcohol, respectively (Table 2). The enantiomeric purity of the corresponding epoxide **17** was very high with both tartrates. One reason to account for the ee difference of alcohol (*S*)-**5** with the two tartrates is that with a smaller tartrate the allylic double bond of the furan ring starts to epoxidize, thus causing the molecule to decompose faster.

Table 2. Sharpless asymmetric epoxidation



Entry	Tartrate	(*S*)-**5**		**17**	
		% Ee	Yield (%)	% Ee	Yield (%)
1	(+)-DET	57	38	96	36
2	(+)-DIPT	68	37	94	39

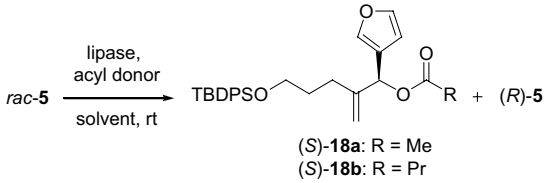
Conversion 50% according to NMR.

Eventually, a successful solution for the preparation of (*S*)-**5** was found through enzymatic kinetic resolution. The capacities of *Candida antarctica* lipase B (CAL-B) and the lipase from *Pseudomonas cepacia* (lipase PS) are well recognized for carrying out highly enantioselective acylations of racemic secondary alcohols.[12] Especially in the case of sterically hindered substrates, it is advisable to add the relatively rarely applied *Candida antarctica* lipase A (CAL-A) to the list of potential lipases.[27–32] Thus, the above lipases (CAL-A and lipase PS adsorbed on Celite® in the presence of sucrose[33] and commercially available CAL-B and lipase PS-C II immobilized on ceramic) were screened for the enantioselective acylation of *rac*-**5** with 2,2,2-trifluoroethyl butanoate in methyl *t*-butyl ether (MTBE) at room temperature (Table 3). CAL-B (entry 10) and the lipase PS preparations (entries 11 and 12) were hardly reactive under the reaction conditions while CAL-A led to a fast formation of (*S*)-butanoate **18b** (entry 7) in a highly enantioselective manner ($E > 300$). Solvent effects on reactivity (measured as the conversion reached after 1 h; entries 1–7) and easy evaporation were reasons to choose MTBE (boiling point 55.2 °C) for the gram-scale resolution of *rac*-**5**. After the usual workup, the (*S*)-butanoate **18b** (isolated yield 95% from the theoretical 50% yield, 96% ee) and (*R*)-alcohol **5** (isolated yield 83% from the theoretical 50% yield, 95% ee) were isolated by column chromatography at 50% conversion. The butanoate was finally reduced with DIBAL-H to furnish (*S*)-**5**.[24]

In the above acylation of *rac*-**5** in the presence of the CAL-A preparation, commercial vinyl butanoate (entry 8) or acetate (entry 9) can replace 2,2,2-trifluoroethyl butanoate as an acyl donor. The reaction with vinyl acetate was slow (5% conversion in 1 h, entry 9) compared to that with the butanoates, taking 27 h to reach 50% conversion. It is important to recognize that the butanoate (*S*)-**18b** (or the corresponding acetate) as an activated ester is easily hydrolyzed through enzymatic ester hydrolysis by the water present in the medium and in the enzyme preparation. Such a reaction (if it takes place) lowers the ee value of the alcohol enantiomer (*R*)-**5** and the yield of the ester product (*S*)-**18b**. In order to furnish fast enzymatic reaction in preparative resolution, the butanoate ester rather than acetate has been used as an acyl donor in dried organic solvents. On the other hand, sucrose in the CAL-A preparation apparently binds the water necessary for enzymatic activity in the seemingly dry enzyme preparation.

The enzymatic reactions were monitored by chiral HPLC. The absolute configurations of the reduction

Table 3. Lipase-catalyzed asymmetric acylation



Entry	Lipase	Acyl donor	Solvent	Time (h)	% Conv.	(*S*)-**18** % Ee	(*R*)-**5** % Ee	*E*
1	CAL-A	$PrCO_2CH_2CF_3$	Acetonitrile	1	44	99	79	>300
2	CAL-A	$PrCO_2CH_2CF_3$	*tert*-Amyl alcohol	1	17	>99	21	>300
3	CAL-A	$PrCO_2CH_2CH_3$	Ethyl butanoate	1	16	>99	19	>300
4	CAL-A	$PrCO_2CH_2CF_3$	Hexane	1	32	>99	47	>300
5	CAL-A	$PrCO_2CH_2CF_3$	Toluene	1	32	>99	47	>300
6	CAL-A	$PrCO_2CH_2CF_3$	DIPE	1	47	97	85	>300
7	CAL-A	$PrCO_2CH_2CF_3$	MTBE	1	45	99	80	>300
8	CAL-A	$PrCO_2CH{=}CH_2$	MTBE	1	46	98	83	>300
9	CAL-A	$MeCO_2CH{=}CH_2$	MTBE	1	5	99	5	>300
10	CAL-B	$PrCO_2CH_2CF_3$	MTBE	24	0.3	99	*rac*	—
11	Lipase PS-C II	$PrCO_2CH_2CF_3$	MTBE	24	2	38	0.7	2
12	Lipase PS	$PrCO_2CH_2CF_3$	MTBE	24	1	66	0.4	5

and epoxidation products [(*S*)-**5** and **17**] and resolution products [(*R*)-**5** and (*S*)-**18b**] are based on Mosher ester analysis[34–36] of (*S*)-**5** (see experimental section for details) and then on comparison with the corresponding peaks on the chromatogram.

3. Conclusion

Preparation of the sterically hindered furyl substituted allyl alcohol (*S*)-**5** has been achieved in quantities reasonable for a planned total synthesis of the natural product cneorin C. Four different methods were tested for their ability to produce alcohol (*S*)-**5**. Direct addition reactions between an organozinc species and aldehyde failed completely. Reduction of an enone (CBS and other reduction protocols) and kinetic resolution via the Sharpless epoxidation gave alcohol (*S*)-**5** with only low enantiopurity (68% ee or lower). These methods failing, enzymatic kinetic resolution of alcohol *rac*-**5** by acylation in the presence of CAL-A proved to be highly (*S*)-enantioselective with $E > 300$. The gram-scale resolution produced (*S*)-ester with 96% ee and (*R*)-alcohol with 95% ee at 50% conversion and the following reduction of the (*S*)-ester with DIBAL-H finally gave the alcohol (*S*)-**5**, an intermediate for the total synthesis of cneorin C **1**.

4. Experimental section

4.1. General

Tetrahydrofuran was distilled from Na/benzophenone. Dichloromethane was pre-dried with $CaCl_2$ and distilled from CaH_2. All other solvents were distilled from CaH_2. Unless otherwise noted, all experiments were performed under Ar-atmosphere using oven-dried glassware. Silica gel (230–400 mesh) for column chromatography as well as the corresponding TLC plates were purchased from Merck. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.26 ppm in ^{1}H NMR spectra and 77.0 ppm in ^{13}C NMR spectra). Enantiomeric excesses were determined by HPLC analysis using Chiralcel OD columns 0.46×5 and 0.46×25 cm. CAL-A (*Candida antarctica* lipase A, Chirazyme L5, lyo.) and CAL-B (*Candida antarctica* lipase B, Chirazyme L2) were purchased from Roche and lipase PS and lipase PS-C II (*Pseudomonas cepacia*) from Amano Pharmaceuticals. Before use, CAL-A and lipase PS were adsorbed on Celite® (17 g) by dissolving the enzyme (5 g) and sucrose (3 g) in Tris–HCl buffer (250 mL, 20 mM, pH = 7.9) as described previously, the final preparation containing 20% (w/w) of the lipase.[33] 2,2,2-Trifluoroethyl butanoate was prepared from the acid chloride and 2,2,2-trifluoroethanol. Equation $E = \ln[(1 - ee_S)/(1 + ee_S/ee_P)]/\ln[(1 + ee_S)/(1 + ee_S/ee_P)]$ with $c = ee_S/(ee_S + ee_P)$ gave the E (enantiomeric ratio)[37] values and conversion.

4.2. 5-(*tert*-Butyl-diphenyl-silanyloxy)-1-furan-3-yl-2-methylene-pentan-1-ol *rac*-5

To a stirred solution of vinyl bromide **9**[38] (4.00 g, 9.91 mmol, 100 mol%) in THF (50 mL) at −78 °C was added *t*-BuLi (17.7 mL, 24.8 mmol, 250 mol%) dropwise over 10 min. After 30 min, 3-furylaldehyde (1.24 mL, 14.9 mmol, 150 mol%) was added dropwise. After stirring overnight at rt, satd aq NH_4Cl was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5–15% EtOAc in hexanes) provided alcohol *rac*-**5** as a clear oil (2.91 g, 70%). TLC $R_f = 0.38$ (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.62 (m, 4H), 7.46–7.33 (m, 8H), 6.33–6.30 (m, 1H), 5.22 (br s, 1H), 5.11 (br d, $J = 3.8$ Hz, 1H), 4.94 (br s, 1H), 3.66 (t, $J = 6.2$ Hz, 2H), 2.10–1.98 (m, 2H), 1.96 (d, $J = 3.8$ Hz, 1H), 1.77–1.65 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 143.2, 139.9, 135.6, 133.9, 129.6, 127.6, 121.3, 110.1, 109.0, 70.4, 63.5, 30.9, 28.0, 26.8, 19.2; IR (film) ν_{max} 3385, 1649, 1586, 1427 cm^{-1}; HRMS (ES+) *m/z* 443.2034 (MNa^+, calcd for $C_{26}H_{32}O_3NaSi$ 443.2011).

4.3. 5-(*tert*-Butyl-diphenyl-silanyloxy)-2-(dimethoxy-phosphoryl)-pentanoic acid methyl ester 11[14]

To a stirred suspension of NaH (60% suspension in mineral oil, 1.37 g, 34.2 mmol, 360 mol%) in DMSO (25 mL) at rt was added trimethyl phosphonoacetate (4.10 mL, 28.5 mmol, 300 mol%) dropwise over 30 min. After 70 min, *tert*-butyl-(3-iodo-propoxy)-diphenylsilane (4.03 g, 9.50 mmol, 100 mol%) in DMSO (15 mL) was added. After 2 h 40 min, HCl (0.1 M, 15 mL) was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0–2% MeOH in CH_2Cl_2) provided phosphonate **11** as a clear oil (3.20 g, 71%). TLC $R_f = 0.37$ (silica, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.63 (m, 4H), 7.47–7.35 (m, 6H), 3.80 (d, $J = 8.1$ Hz, 3H), 3.77 (d, $J = 7.6$ Hz, 3H), 3.70 (s, 3H), 3.66 (t, $J = 6.1$ Hz, 2H), 3.05 (ddd, $J = 22.8$, 10.6, 4.5 Hz, 1H), 2.14–1.93 (m, 2H), 1.71–1.49 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.5, 133.7, 129.6, 127.6, 63.0, 53.3 (d, $J = 15.1$ Hz), 53.2 (d, $J = 15.1$ Hz), 52.5, 44.8 (d, $J = 131$ Hz), 31.0 (d, $J = 14.3$ Hz), 26.8, 23.6 (d, $J = 4.8$ Hz), 19.1; IR (film) ν_{max} 1738 cm^{-1}; HRMS (ES+) *m/z* 501.1844 (MNa^+, calcd for $C_{24}H_{35}O_6NaSiP$ 501.1838).

4.4. 5-(*tert*-Butyl-diphenyl-silanyloxy)-2-methylene-pentanoic acid methyl ester 12[15]

To a stirred solution of phosphonate **11** (3.20 g, 6.69 mmol, 100 mol%) in THF (10 mL) at rt were added paraformaldehyde (0.402 g, 13.39 mmol, 200 mol%) and K_2CO_3 (1.86 g, 13.39 mmol, 200 mol%). After 6 h of refluxing, the reaction mixture was cooled down, water was added and the aqueous layer was extracted with

hexanes. The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5% EtOAc in hexanes) provided methyl ester **12** as a clear oil (1.80 g, 71%). TLC $R_f = 0.68$ (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4H), 7.47–7.35 (m, 6H), 6.14 (s, 1H), 5.52 (s, 1H), 3.75 (s, 3H), 3.70 (t, $J = 6.3$ Hz, 2H), 2.43 (t, $J = 7.6$ Hz, 2H), 1.77–1.71 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 140.3, 135.6, 134.0, 129.5, 127.6, 124.9, 63.1, 51.7, 31.2, 28.3, 26.8, 19.2; IR (film) ν_{max} 1720, 1627 cm^{-1}; HRMS (ES+) *m/z* 405.1888 (MNa^+, calcd for $C_{23}H_{30}O_3NaSi$ 405.1862).

4.5. 5-(*tert*-Butyl-diphenyl-silanyloxy)-2-methylene-pentan-1-ol 13[38]

To a stirred solution of methyl ester **12** (1.19 g, 3.10 mmol, 100 mol %) in THF (16 mL) at −78 °C was added DIBAL-H (1 M in toluene, 9.3 mL, 9.30 mmol, 300 mol %) dropwise. After 30 min, MeOH (3.1 mL) was added, the solution was allowed to warm to 0 °C and HCl (1 M, 30 mL) was added. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried, filtered and concentrated. Alcohol **13** was isolated as a yellowish oil (1.10 g, 99%). TLC $R_f = 0.59$ (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4H), 7.47–7.35 (m, 6H), 5.02 (br s, 1H), 4.86 (br s, 1H), 4.06 (s, 2H), 3.69 (t, $J = 6.2$ Hz, 2H), 2.16 (t, $J = 7.8$ Hz, 2H), 1.78–1.68 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 135.6, 134.0, 129.6, 127.6, 109.3, 66.0, 63.4, 30.7, 29.2, 26.9, 19.2.

4.6. 5-(*tert*-Butyl-diphenyl-silanyloxy)-2-methylene-pentanal 14[38]

To a stirred solution of alcohol **13** (0.529 g, 1.49 mmol, 100 mol %) in CH_2Cl_2 (15 mL) was added MnO_2[17] (0.649 g, 7.46 mmol, 500 mol %). After 17 h, more MnO_2 (0.130 g, 1.49 mmol, 100 mol %) was added. After 21 h, the mixture was filtered through a pad of Celite® and concentrated. Enal **14** was isolated as a clear oil (0.495 g, 94%). TLC $R_f = 0.57$ (silica, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.70–7.65 (m, 4H), 7.47–7.35 (m, 6H), 6.21 (br s, 1H), 5.97 (br s, 1H), 3.67 (t, $J = 6.2$ Hz, 2H), 2.36 (t, $J = 7.8$ Hz, 2H), 1.70–1.67 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 149.9, 135.6, 134.0, 133.9, 129.6, 127.6, 63.1, 30.5, 26.8, 24.3, 19.2.

4.7. Alcohol *rac*-5 from enal 14

To a stirred solution of 3-bromofuran (0.510 mL, 5.67 mmol, 200 mol %) in THF (12 mL) at −78 °C was added *t*-BuLi (7.59 mL, 9.94 mmol, 350 mol %) dropwise. After 40 min, aldehyde **14** (1.00 g, 2.84 mmol, 100 mol%) in THF (3 mL) was added. After 2 h 10 min, satd aq NH_4Cl was added, the mixture was allowed to warm to rt and the aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 7.5–15% EtOAc in hexanes) provided alcohol *rac*-**5** as a clear oil (1.04 g, 87%).

4.8. 5-(*tert*-Butyl-diphenyl-silanyloxy)-1-furan-3-yl-2-methylene-pentan-1-one 15

To a stirred solution of alcohol *rac*-**5** (0.250 g, 0.594 mmol, 100 mol %) in CH_2Cl_2 (6.0 mL) was added MnO_2[17] (0.258 g, 2.97 mmol, 500 mol %). After 4 h, more CH_2Cl_2 (6.0 mL) and MnO_2 (0.258 g, 2.97 mmol, 500 mol %) were added. After 22 h, a third portion of MnO_2 (0.258 g, 2.97 mmol, 500 mol %) was added. After 27 h, the reaction mixture was filtered through a pad of Celite® and concentrated. Flash column chromatography (silica, 5–15% EtOAc in hexanes) provided ketone **15** as a clear oil (0.148 g, 83% based on recovered starting material (0.071 g)). TLC $R_f = 0.5$ (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.76 (m, 1H), 7.71–7.65 (m, 4H), 7.47–7.35 (m, 7H), 6.81–6.77 (m, 1H), 5.76 (br s, 1H), 5.67 (br d, $J = 0.92$ Hz, 1H), 3.69 (t, $J = 6.3$ Hz, 2H), 2.55 (br t, $J = 7.5$ Hz, 2H), 1.80–1.71 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 149.4, 147.8, 143.9, 135.5, 133.9, 129.5, 127.6, 126.5, 122.9, 109.9, 63.1, 30.8, 28.5, 26.8, 19.2; IR (film) ν_{max} 1646 cm^{-1}; HRMS (ES+) *m/z* 441.1884 (MNa^+, calcd for $C_{26}H_{30}O_3NaSi$ 441.1862).

4.9. General procedure for the CBS reduction

To a stirred solution of ketone **15** (54.9 μmol, 100 mol %) in THF (0.5 mL) at rt was added the catalyst **16a**–**b** (1M in toluene, 11.0 μmol, 20 mol %). The solution was cooled to −20 °C and $BH_3{\cdot}SMe_2$ (32.9 μmol, 60 mol %) or catecholborane (165 μmol, 300 mol %) was added. After the time shown in Table 1 at −20 °C, methanol (0.5 mL) and satd aq $NaHCO_3$ (1 mL) were added. The phases were separated, the aqueous phase was extracted with EtOAc and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5–7.5% EtOAc in hexanes) provided alcohol (*S*)-**5** as a clear oil. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD): 1% *i*-PrOH in hexanes, 0.4 mL/min, $t_S = 69$ min, $t_R = 73$ min.

4.10. Sharpless asymmetric epoxidation

To a stirred mixture of powdered and activated 3 Å molecular sieves (0.300 g, 30 wt %), alcohol *rac*-**5** (1.00 g, 2.38 mmol, 100 mol %) and (+)-DIPT (76 μL, 0.357 mmol, 15 mol%) in CH_2Cl_2 (10 mL) at −20 °C was added $Ti(O\text{-}i\text{-}Pr)_4$ (71 μL, 0.238 mmol, 10 mol %). After 80 min, *t*-butyl hydroperoxide[26] (5 M in isooctane, 0.286 mL, 1.43 mmol) was added. After 47 h at −20 °C, water (1.36 mL) was added. After another 30 min, 30% NaOH in brine (0.35 mL) was added. After stirring for 30 min, the mixture was filtered through a cotton plug, the phases were separated and the aqueous phase was

extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5–50% EtOAc in hexanes) provided alcohol (*S*)-**5** as a clear oil (0.367 g, 37%, 68% ee) and epoxide **17** as a clear oil (0.405 g, 39%, 94% ee). The ee of **17** was determined by chiral HPLC (Chiralcel OD): 0.5% *i*-PrOH in hexanes, 1.0 mL/min, t_{RR}(major) = 53 min, t_{SS}(minor) = 62 min. **Epoxide 17:** TLC $R_f = 0.15$ (silica, 20% EtOAc in hexanes); $[\alpha]_D^{20} = +20.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.61 (m, 4H), 7.47–7.34 (m, 8H), 6.41–6.38 (m, 1H), 4.76 (br s, 1H), 3.70–3.58 (m, 2H), 3.04 (d, $J = 4.7$ Hz, 1H), 2.68 (d, $J = 4.7$ Hz, 1H), 2.43 (app d, $J = 1.5$ Hz, 1H), 1.85–1.76 (m, 1H), 1.73–1.49 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.6, 135.5, 133.8, 129.6, 127.6, 124.3, 109.0, 65.8, 63.5, 61.5, 48.5, 27.3, 27.0, 26.8, 19.2; IR (film) ν_{max} 3468 cm^{-1}; HRMS (ES+) *m*/*z* 459.1961 (MNa^+, calcd for $C_{26}H_{32}O_4NaSi$ 459.1968).

4.11. Lipase-catalyzed acylation

The reactions were typically performed as small-scale experiments at room temperature (22–24 °C) where an acyl donor (0.1 M) was added into the solution (0.05 M) of *rac*-**5** in an organic solvent and one of the enzyme preparations (25 mg/mL) was added in order to start the reaction. The progress of enzymatic reactions and the ee values of the unreacted (*R*)-**5** and the formed (*S*)-**18b** were followed by taking samples (0.1 mL) at intervals and analyzing them by HPLC on Chiracel OD-column (220 nm) eluting with isopropanol in hexanes (0.3% for the alcohol ($t_R = 96$ min, $t_S = 104$ min); 0.1% for the acetate ($t_S = 33$ min, $t_R = 37$ min) and butanoate ($t_S = 28$ min, $t_R = 33$ min)).

In a gram-scale experiment, 2,2,2-trifluoroethyl butanoate (0.36 mL, 2.38 mmol) and CAL-A preparation (0.59 g, 25 mg/mL) were added to a solution of *rac*-**5** (0.50 g, 1.19 mmol) in MTBE (23.8 mL). After 5 h, the enzyme was filtered off at 50% conversion. Purification by column chromatography (silica, 10% EtOAc in hexanes) yielded (*S*)-**18b** (0.28 g, 0.57 mmol, 96% ee) and (*R*)-**5** (0.21 g, 0.49 mmol, 95% ee, $[\alpha]_D^{20} = +5.1$ (*c* 1.0, $CHCl_3$)). **Butanoate (*S*)-18b**: TLC $R_f = 0.50$ (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4H), 7.45–7.33 (m, 8H), 6.33–6.31 (m, 1H), 6.20 (br s, 1H), 5.17 (br s, 1H), 4.97 (br s, 1H), 3.66 (t, $J = 6.2$ Hz, 2H), 2.32 (t, $J = 7.4$ Hz, 2H), 2.20–2.03 (m, 2H), 1.77–1.60 (m, 4H), 1.04 (s, 9H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 146.6, 143.2, 140.8, 135.5, 133.9, 129.5, 127.6, 123.8, 111.1, 109.4, 70.5, 63.3, 36.4, 30.6, 28.5, 26.8, 19.2, 18.4, 13.6; IR (film) ν_{max} 1737, 1652, 1588, 1427 cm^{-1}; HRMS (ES+) *m*/*z* 513.2456 (MNa^+, calcd for $C_{30}H_{38}O_4NaSi$ 513.2437).

4.12. Hydrolysis of butanoate (*S*)-18b

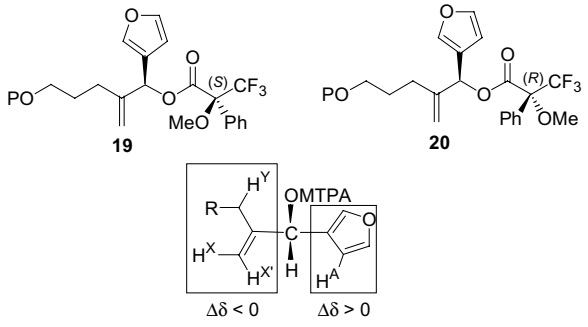
To a solution of (*S*)-**18b** (72 mg, 0.147 mmol) in CH_2Cl_2 (0.8 mL) at −78 °C was added DIBAL-H (1 M in CH_2Cl_2, 0.293 mL, 0.293 mmol) dropwise. After 30 min, 1 M HCl was added and the solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc and the organic extracts were washed with brine, dried, filtered and concentrated. Furyl substituted allyl alcohol (*S*)-**5** was isolated as a clear oil (61 mg, 98%, 96% ee). $[\alpha]_D^{20} = -6.2$ (*c* 1.0, $CHCl_3$).

4.13. Analysis of stereochemistry by the Mosher ester method

For determination of stereochemistry, alcohol (*S*)-**5** was converted to (*S*)- and (*R*)-MTPA esters according to the procedure of Kobayashi et al.[34] The NMR signals were assigned with reference to two dimensional correlation spectra (HMQC and HMBC). The chemical shift differences ($\Delta\delta$) between (*R*) and (*S*) isomers were calculated (Table 4) and the results were compared against the Mosher configuration model.[36] The stereochemistry of the alcohol was assigned to be (*S*).

4.13.1. 3,3,3-Trifluoro-(2*S*)-methoxy-2-phenyl-propionic acid 5-(*tert*-butyl-diphenyl-silanyloxy)-(1*S*)-furan-3-yl-2-methylene-pentyl ester 19. To a stirred solution of alcohol (*S*)-**5** (16 mg, 38.0 μmol, 100 mol%) in CH_2Cl_2 (0.1 mL) were added (*S*)-MTPA (18 mg, 76.1 μmol, 200 mol%), DMAP (2.3 mg, 19.0 μmol, 50 mol%) and DCC (16 mg, 76.1 μmol, 200 mol%). After 3 h, the mixture was filtered, washed twice with HCl (0.5 M) and satd aq $NaHCO_3$ and once with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0–2% EtOAc in hexanes) provided the (*S*)-MTPA ester **19** as a clear oil (17 mg, 70%). TLC $R_f = 0.50$ (silica, 20% EtOAc in hexanes); $[\alpha]_D^{20} = -32.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.61 (m, 4H), 7.47–7.29 (m, 13H), 6.40 (br s, 1H), 6.33 (br d, $J = 1.6$ Hz, 1H), 5.09 (br s, 1H), 4.96 (br s, 1H), 3.59 (dt, $J = 6.2$, 2.0 Hz, 2H), 3.50 (s, 3H), 2.02 (dd, $J = 8.4$, 7.1 Hz, 2H), 1.70–1.60 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

Table 4. Mosher ester analysis



	$\delta(S)$	$\delta(R)$	$\Delta\delta^a$
H^X	5.09	5.25	−0.16
$H^{X'}$	4.96	5.04	−0.08
H^Y	2.02	2.11	−0.09
H^A	6.33	6.21	0.12

[a] $\Delta\delta = \delta(S) - \delta(R)$.

δ 165.5, 145.1, 143.5, 141.5, 135.5, 133.9, 132.3, 129.6, 129.5, 128.3, 127.6, 127.3, 126.7 (q, $J = 395$ Hz), 122.6, 112.3, 109.4, 84.4 (q, $J = 28$ Hz), 72.8, 63.2, 55.4, 30.4, 28.4, 26.8, 19.2; IR (film) ν_{max} 1748, 1427 cm^{-1}; HRMS (ES+) *m/z* 659.2408 (MNa^+, calcd for $C_{36}H_{39}O_5F_3NaSi$ 659.2417).

4.13.2. 3,3,3-Trifluoro-(2*R*)-methoxy-2-phenyl-propionic acid 5-(*tert*-butyl-diphenyl-silanyloxy)-(1*S*)-furan-3-yl-2-methylene-pentyl ester 20. Prepared as **19**. $[\alpha]_D^{20} = +6.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4H), 7.48–7.30 (m, 13H), 6.40 (br s, 1H), 6.21 (br d, $J = 0.9$ Hz, 1H), 5.25 (br s, 1H), 5.04 (br s, 1H), 3.63 (t, $J = 6.2$ Hz, 2H), 3.50 (s, 3H), 2.11 (dd, $J = 9.1$, 6.6 Hz, 2H), 1.75–1.66 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 145.3, 143.3, 141.1, 135.5, 133.9, 132.2, 129.6, 129.5, 128.3, 127.6, 127.4, 126.7 (q, $J = 391$ Hz), 122.6, 112.9, 109.2, 84.6 (q, $J = 27$ Hz), 73.4, 63.2, 55.4, 30.5, 28.3, 26.8, 19.2; IR (film) ν_{max} 1748, 1427 cm^{-1}; HRMS (ES+) *m/z* 659.2393 (MNa^+, calcd for $C_{36}H_{39}O_5F_3NaSi$ 659.2417).

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