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.
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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, epoxidations7,8 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.
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. 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 from t-butyll 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-isopropanol via a Horner–Wadsworth–Emmons reaction of phosphonate 11 (Scheme 2). 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, LiAlH4, THF, 0 °C→rt, 90%; (c) TBDPSCI, imid., CH2Cl2, rt, 90%; (d) t-BuLi, 3-furylaldehyde, THF, -78 °C→rt, 74%.

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 MnO2. The Corey–Bakshi–Shibata (CBS) reduction is a widely established catalytic asymmetric reduction method. In this case, reduction of ketone 15 with BH3·SMe2 in the presence of the chiral catalyst 16a gave at its best the alcohol in 35% ee (Table 1). BINAL reduction as well as DIP-chloride reduction were also tried, but only the starting material was recovered.

Table 1. CBS reduction

<table>
<thead>
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<th>Entry</th>
<th>Reagents</th>
<th>% Ee</th>
<th>Time (h)</th>
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<tr>
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<td>BH3·SMe2, 16a</td>
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<tr>
<td>2</td>
<td>BH3·SMe2, 16b</td>
<td>13</td>
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<tr>
<td>3</td>
<td>Catecholborane, 16b</td>
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Yields were not determined.

The third approach was kinetic resolution of the furyl substituted allyl alcohols via Sharpless asymmetric epoxidation (SAE). 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.
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. 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. Thus, the above lipases (CAL-A and lipase PS adsorbed on Celite in the presence of sucrose 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 (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.

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>
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<th>Entry</th>
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<th>Solvent</th>
<th>Time (h)</th>
<th>% Conv.</th>
<th>(S)-18 % Ee</th>
<th>(R)-5 % Ee</th>
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<td>66</td>
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and epoxidation products [(S)-5 and 17] and resolution products [(R)-5 and (S)-18b] are based on Mosher ester analysis14-36 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 CaCl₂ and distilled from CaH₂. All other solvents were distilled from CaH₂. 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. ¹H NMR spectra and ¹³C NMR spectra were recorded in CDCl₃ on a spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.26 ppm in ¹H NMR spectra and 77.0 ppm in ¹³C 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 Pharmaceutica. 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-Trifluoro-ethyl butanoate was prepared from the acid chloride and 2,2,2-trifluoroethanol. Equation $E = \ln[(1 - eeS)/(1 + eeS/eeP)]/\ln[(1 - eeS)/(1 + eeS/eeP)]$ with $c = eeS/(eeS + eeP)$ gave the $E$ (enantiomeric ratio)37 values and conversion.

4.2. 5-(tert-Butyl-diphenyl-silylanoxy)-1-furan-3-yl-2-methylene-pentan-1-ol rac-5
To a stirred solution of vinyl bromide 98 (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 NH₄Cl 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); ¹H NMR (400 MHz, CDCl₃) $\delta$ 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); ¹³C NMR (100 MHz, CDCl₃) $\delta$ 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) $v_{\text{max}}$ 3385, 1649, 1586, 1427 cm⁻¹; HRMS (ES+) $m/z$ 443.2034 (MNa⁺, calcd for C₂₆H₂₃O₃NaSi 443.2011).

4.3. 5-(tert-Butyl-diphenyl-silylanoxy)-2-(dimethoxyphosphoryl)-pentanioic acid methyl ester 114
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-proproxy)-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 Et₂O. The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0–2% MeOH in CH₂Cl₂) provided phosphonate 11 as a clear oil (3.20 g, 71%). TLC $R_f = 0.37$ (silica, 2% MeOH); ¹H NMR (400 MHz, CDCl₃) $\delta$ 7.70–6.63 (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 (dd, $J = 22.8$, 10.6, 4.5 Hz, 1H), 2.14–1.93 (m, 2H), 1.71–1.49 (m, 2H), 1.05 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) $\delta$ 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) $v_{\text{max}}$ 1738 cm⁻¹; HRMS (ES+) $m/z$ 501.1844 (MNa⁺, calcd for C₃₀H₃₀O₇NaSiP 501.1838).

4.4. 5-(tert-Butyl-diphenyl-silylanoxy)-2-methylene-pentanioic acid methyl ester 1215
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 K₂CO₃ (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 Rf = 0.68 (silica, 50% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 129.9, 127.6, 124.9, 63.1, 51.7, 31.2, 28.3, 26.8, 19.2; IR (film) vmax 2994, 2942, 1645 cm−1; HRMS (ES+) m/z 405.1888 (MNa+, calculated for C21H30O3NaSi 405.1862).

4.5. 5-(tert-Butyl-diphenyl-silyloxy)-2-methylene-pentan-1-ol 13

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, 93.0 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 Rf = 0.59 (silica, 50% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3) δ 7.72–7.65 (m, 4H), 7.47–7.35 (m, 6H), 6.02 (br s, 1H), 4.86 (br s, 1H), 4.06 (s, 2H), 3.67 (t, J = 6.2 Hz, 2H), 2.16 (t, J = 7.8 Hz, 2H), 1.78–1.68 (m, 2H), 1.06 (s, 9H); 13C NMR (100 MHz, CDCl3) 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-silyloxy)-2-methylene-pentanal 14

To a stirred solution of alcohol 13 (0.529 g, 1.49 mmol, 100 mol %) in CH2Cl2 (15 mL) was added MnO2 (0.649 g, 7.46 mmol, 500 mol %). After 17 h, more MnO2 (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 (1.80 g, 71%). TLC Rf = 0.57 (silica, 25% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3) δ 7.72–7.65 (m, 4H), 7.47–7.35 (m, 6H), 3.67 (t, J = 6.2 Hz, 2H), 3.26 (t, J = 7.8 Hz, 2H), 1.70–1.67 (m, 2H), 1.05 (s, 9H); 13C NMR (100 MHz, CDCl3) 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, the mixture was added 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-silyloxy)-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 CH2Cl2 (6.0 mL) was added MnO2 (0.258 g, 2.97 mmol, 500 mol %). After 4 h, more CH2Cl2 (6.0 mL) and MnO2 (0.258 g, 2.97 mmol, 500 mol %) were added. After 22 h, a third portion of MnO2 (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 Rf = 0.5 (silica, 20% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3) 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), 1.80–1.70 (m, 2H), 1.07 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 190.9, 149.4, 147.8, 143.9, 135.5, 133.9, 129.5, 126.5, 122.9, 109.9, 63.1, 30.8, 28.5, 26.8, 19.2; IR (film) νmax 2920, 1720, 1627 cm−1; HRMS (ES+) m/z 441.1884 (MNa+, calculated for C26H30O3NaSi 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 (1 M in toluene, 11.0 µmol, 20 mol %). The solution was cooled to −20 °C and BH3·SMes2 (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 NaHCO3 (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 (Chiralel OD): 1% i-PrOH in hexanes, 0.4 mL/min, tR = 69 min, tR = 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 CH2Cl2 (10 mL) at −20 °C was added Ti(O-i-Pr)4 (71 µL, 0.238 mmol, 10 mol %). After 80 min, t-butyldihydroperoxide26 (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 CH₂Cl₂. 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); \( \delta_{1}^{1} = +20.6 \) (c 1.0, CHCl₃); \(^{1}H\) NMR (400 MHz, CDCl₃) 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, \( J = 61.5, 48.5, 27.3, 27.0, 26.8, 19.2 \)); IR (film) \( \nu_{max} \) 140.6, 135.5, 133.8, 129.6, 127.6, 124.3, 109.0, 65.8, 63.5, 70.5, 63.3, 36.4, 30.6, 28.5, 26.8, 19.2, 18.4, 13.6; IR (film) \( \nu_{max} \) 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) \( \nu_{max} \) 1737, 1652, 1588, 1427 cm⁻¹; HRMS (ES⁺) \( m/z \) 513.2456 (MNa⁺, calcld for C₂₃H₂₆O₂NaSi 513.2437).

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 Chiralcel OD-column (220 mm) eluting with isopropanol in hexanes (0.3%) for the alcohol \( t_{R} = 96 \) min, \( t_{S} = 104 \) min; 0.1% for the acetate \( t_{R} = 28 \) min, \( t_{S} = 33 \) 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 (0.21 g, 0.49 mmol, 95% ee) and \( \alpha \)-t-butyl-diphenyl-silanyloxy)-1,2,3-trimethylenepentyl ester 19. To a stirred solution of alcohol (0.28 g, 0.57 mmol, 96% ee) and DMAP (2.3 mg, 19.0 mol %) in CH₂Cl₂, 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. Furfyl substituted allyl alcohol (S)-5 was isolated as a clear oil (61 mg, 98%, 96% ee). \( [\alpha]_{D}^{20} = -6.2 \) (c 1.0, CHCl₃).

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 (HMCO 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-(2S)-methoxy-2-phenyl-propionic acid 5-(tert-butyldiphenylsilanylxy)-(1S)-furan-3-yl-2-methylene-pentyl ester 19. To a stirred solution of alcohol (S)-5 (16 mg, 38.0 µmol, 100 mol %) in CH₂Cl₂ (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 sat aq NaHCO₃ 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, CHCl₃); \(^{1}H\) NMR (400 MHz, CDCl₃) 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, CDCl₃)

Table 4. Mosher ester analysis

<table>
<thead>
<tr>
<th></th>
<th>( \Delta \delta )</th>
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<tbody>
<tr>
<td>H²</td>
<td>5.09</td>
</tr>
<tr>
<td>H²⁺</td>
<td>4.96</td>
</tr>
<tr>
<td>H³</td>
<td>2.02</td>
</tr>
<tr>
<td>H⁴</td>
<td>6.33</td>
</tr>
</tbody>
</table>

\( \Delta \delta = \delta(S) - \delta(R) \).
δ 165.5, 145.1, 143.5, 141.5, 135.5, 133.9, 132.3, 129.6, 129.5, 128.3, 127.6, 127.4, 126.7, 28.4, 26.8, 19.2; IR (film) ν max 1748, 1427 cm⁻¹; HRMS (ES⁺) m/z 659.2408 (MNa⁺, calcd for C₃₆H₃₉O₅F₃NaSi 659.2417).

4.13.2. 3,3,3-Trifluoro-(2R)-methoxy-2-phenyl-propionic acid 5-(tert-butyl-diphenyl-silylonyoxy)-(1S)-furan-3-yl-2-methylene-pentyl ester 20. Prepared as 19. [α]D²⁰ = +6.4 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₆H₃₉O₅F₃NaSi 659.2417).

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References and notes