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Lipase-mediated enantioselective acylation of alcohols with functionalized vinyl esters: acyl donor tolerance and applications

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ABSTRACT

Enzymatic acylation is commonly used for the kinetic resolution of alcohols and amines. The simple acyl group introduced during the enzymatic reaction is usually removed or replaced by another group. Retention of more complex acyl moieties as part of the target structures would be a more efficient strategy. We have studied the enantioselective acylation of a model alcohol substrate, 1-phenylethanol, with vinyl esters bearing various functionality on the acyl moieties in the presence of three lipases (*Candida antarctica*, *Candida rugosa* and *Burkholderia cepacia*) frequently used in organic synthesis. *C. antarctica* lipase is the most versatile lipase for this type of biotransformations. We applied this strategy to the synthesis of a protein kinase C ligand and a natural product, phoracantholide.

1. Introduction

Enzymatic acylation in organic media is commonly used for the kinetic resolution[1] or for the desymmetrization[2,3] of alcohols and amines.[4–8] Acylation by transesterification in organic media is an equilibrium reaction and must be shifted in the desired direction. The most common solution is the use of activated esters that ensure an irreversible reaction.[9] The most popular activated acyl donors are enol esters such as vinyl and isopropenyl acetate. The leaving group is an enol that immediately tautomerizes to a carbonyl compound (acetaldehyde or acetone) thereby driving the reaction to completion.

In most cases, the acyl moiety is an acetyl but sometimes acyl donors with longer saturated chains show higher enantioselectivity.[7] The simple acyl functional group introduced during the enzymatic esterifications are usually removed or replaced by other groups. Retention of more complex acyl moieties as part of the target structures would be a more efficient strategy (atom economy concept[10]). For example, Brenna et al. reported the synthesis of both enantiomers of verapamil, a calcium channel blocker, via an enantioselective enzymatic acetylation followed by an Ireland–Claisen rearrangement of the acetate.[11] More recently, the combination of lipase-catalyzed transesterification with unsaturated vinyl esters as acyl donors with ring-closing metathesis has been applied to the synthesis of goniothalamin[12,13] and γ-alkyl-γ-butenolides.[14] Most notable among the efforts to develop this strategy are the reports by Akai and Kita of lipase-catalyzed domino processes.[15–17] For example, they reported a concise asymmetric total synthesis of (−)-rosmarinecine, the base portion of several pyrrolizidine alkaloids; the domino reaction was an enzymatic dynamic kinetic resolution of a hydroxy nitrone with a functionalized acyl donor derived from maleic acid followed by an intramolecular cycloaddition.[18]

Herein, we report the enantioselective acylation of a model substrate, 1-phenylethanol, with various functionalized vinyl esters in the presence of three of the most useful lipases in organic synthesis. The overall objective was to determine their substrate tolerance with respect to the acyl moiety of the acyl donor. Application of this methodology to the enantioselective synthesis of a protein kinase C ligand and the natural product phoracantholide is also described.

2. Results and discussion

2.1. Lipase-catalyzed acylation of 1-phenylethanol with functionalized vinyl esters

Since the stereochemistry of 1-phenylethanol had been the subject of numerous previous investigations in asymmetric synthesis, we selected this compound as an alcohol model substrate. We used three of the most useful lipases for organic synthesis: *Candida antarctica* lipase B (CAL-B),[19–23] *Candida rugosa* lipase (CRL),[24,25] and *Burkholderia cepacia* lipase (BCL, formerly named *Pseudomonas cepacia* lipase).[6,7,26] Nine vinyl esters were evaluated as potential substrates for these three biocatalysts. Non-commercially available vinyl esters were synthesized according to Schneider's method.[27]

For a better comparison of the catalytic activity and enantioselectivity of the lipases considered, the resolutions were performed under the following standard conditions: racemic 1-phenylethanol **1** (1.5 equiv) was treated with vinyl esters **2a–i** (1.5 equiv) in the presence of the enzyme (1000 units) in diethyl ether at room

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temperature (Scheme 1). The results of this screening are summarized in Tables 1–3. Conversion (c) and the enantiomeric excess (ee of the recovered substrate **1** and product **3**) were measured by HPLC on a chiral phase. The E values were determined using Sih's method.[28] On the basis of the data reported in the literature for 1-phenylethanol, we have attributed the (*S*)-configuration to the remaining substrate and the (*R*)-configuration to all corresponding esters **3a–i**. As can be seen from Tables 1–3, the rate and enantioselectivity varied largely with the acyl donor and the enzyme employed, while the stereochemical preference remained unchanged. All the reactions followed the empirical rule proposed by Kazlauskas[6] and in each case, the (*R*)-enantiomer was acylated faster by the enzymes. Among the three lipases tested, CAL-B showed efficiency and high enantioselectivity toward the range of acylation reactions (Table 1). Most E values were above 200 but reactions with vinyl 4-pentenoate, cinnamate, and *N*-Boc glycinate were slow. The CAL-B-mediated acylations were interrupted at about 50% conversion and acetates (*R*)-**3a–i** were separated from the unreacted alcohol (*S*)-**1** and purified by column chromatography (isolated yields). Table 2 summarizes the results obtained in the CRL-catalyzed acylations of (±)-**1**. Under the standard conditions, this lipase showed low activity or low enantioselectivity in these processes. The resolution of **1** in the presence of BCL proceeded with varying degrees of enantioselectivity (Table 3). Acylations with vinyl acetate and vinyl (phenylthio)acetate were fast and highly stereoselective. In other cases, BCL was inactive or the reaction was very slow. Under the standard conditions, CAL-B is the most versatile lipase due to its ability to react with a broad variety of acylation agents and give high enantioselectivity.

Table 1
Acylations of 1-phenylethanol **1** in the presence of *Candida antarctica* lipase B

Vinyl ester	c[a] (%)	Time (h)	Ester **3**		Alcohol **1**		E
			Yield[b] (%)	ee[a] (%)	Yield[b] (%)	ee[a] (%)	
Acetate **2a**	45	24	44	>98	48	>98	>200
Pivalate **2b**	52	90	44	92	42	86	66
4-Pentenoate **2c**	24	144	20	95	62	67	>200
Crotonate **2d**	50	30	50	>98	50	91	>200
Methacrylate **2e**	48	34	45	>98	52	91	>200
Benzoate **2f**	47	43	40	92	54	84	60
Cinnamate **2g**	50	144	43	>98	50	>98	>200
N-Boc Glycinate **2h**	49	140	36	>98	42	>98	>200
Phenyl(thio)acetate **2i**	50	4	48	94	49	>98	>200

[a] Determined by HPLC on a chiral phase.
[b] Isolated yields.

Table 2
Acylations of 1-phenylethanol **1** in the presence of *Candida rugosa* lipase

Vinyl ester	c[a] (%)	Time (h)	Ester **3** ee[a] (%)	Alcohol **1** ee[a] (%)	E
Acetate **2a**	30	40	21	50	4
Pivalate **2b**	4	144	34	2	2
4-pentenoate **2c**	4	144	>95	13	>200
Crotonate **2d**	51	30	44	49	4
Methacrylate **2e**	28	140	67	22	6
Benzoate **2f**	49	9	85	68	22
Cinnamate **2g**	30	144	40	8	3
N-Boc glycinate **2h**	0	144	—	—	—
(Phenylthio)acetate **2i**	51	8	30	78	10

[a] Determined by HPLC on a chiral phase.

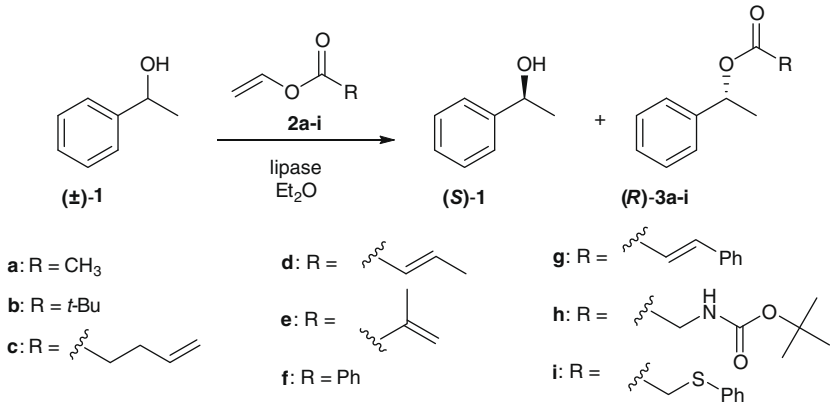
Table 3
Acylations of 1-phenylethanol **1** in the presence of *Burkholderia cepacia* lipase

Vinyl ester	c[a] (%)	Time (h)	Ester **3** ee[a] (%)	Alcohol **1** ee[a] (%)	E
Acetate **2a**	45	20	98	98	>200
Pivalate **2b**	10	144	66	7	5
4-Pentenoate **2c**	0	144	—	—	—
Crotonate **2d**	13	144	>98	8	100
Methacrylate **2e**	35	144	95	40	60
Benzoate **2f**	3	144	—	—	—
Cinnamate **2g**	2	144	>98	2	40
N-Boc glycinate **2h**	0	144	—	—	—
(Phenylthio)acetate **2i**	57	4	95	81	97

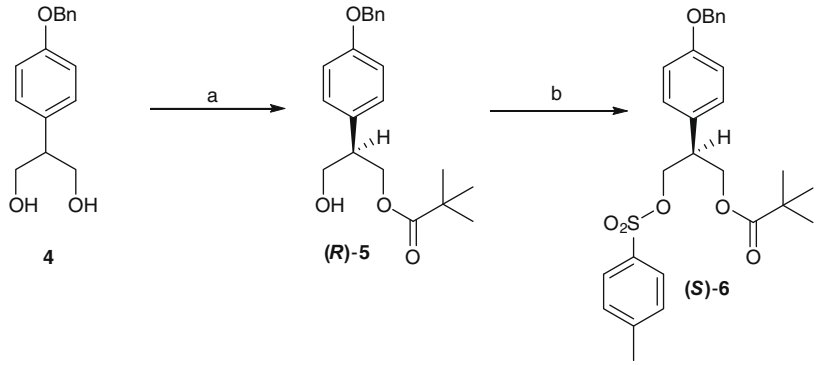
[a] Determined by HPLC on a chiral phase.

2.2. Synthetic applications

To demonstrate the usefulness of the described biocatalytic transformations we synthesized compound **5** via the enzymatic desymmetrization of *meso* arylpropanediol **4** (Scheme 2). Compound **5** is a 1,2-diacylglycerol (DAG) surrogate and a protein kinase C (PKC) ligand.[29] DAGs are intracellular second messengers and their target is a family of PKC isoenzymes playing a pivotal role in cellular signal transduction that regulates cell growth, differentiation, apoptosis, and tumor promotion. Diol **4** was prepared according to the procedure reported by Lee et al.[29] Acylation of meso-**4** with vinyl pivalate in ether in the presence of CAL-B or *Pseudomonas fluorescens* (PFL) provided monoester **5** in good yield and moderate enantioselectivity, whereas CRL and BCL were not active (Table 4). The funnel-like active site of CAL-B is known to be sterically restricted[30] and accordingly the enzyme is not very efficient with two bulky substrates such as diol **4** and vinyl pivalate



Scheme 1. Lipase-mediated resolution of 1-phenylethanol **1** with various acyl donors.



Scheme 2. Reagents and conditions: (a) vinyl pivalate, ANL, Et_2O, 96%, ee >98%; (b) tosyl chloride, Et_3N.

Table 4
Enzymatic acylation of diol **4** with vinyl pivalate

Enzyme	Time (h)	Monopivalate (*R*)-**5**	
		Yield[f] (%)	ee[g] (%)
CRL[a]		No reaction	
BCL[b]		No reaction	
CAL-B[c]	216	78	30
PFL[d]	230	98	60
ANL[e]	312	96	⩾98

[a] *Candida rugosa* lipase.
[b] *Burkholderia cepacia* lipase.
[c] *Candida antarctica* lipase.
[d] *Pseudomonas fluorescens* lipase.
[e] *Aspergillus niger* lipase.
[f] Isolated yield.
[g] Determined by HPLC analysis using a Chiralcel OD-H or AD-H column.

2b. The lipase from *Aspergillus niger* (ANL) proved to be the optimal biocatalyst in the desymmetrization of **4** (yield = 96%, ee ⩾ 98%) but the reaction was very slow. The absolute configuration of **5** was determined to be (*R*) by X-ray crystallographic analysis of the tosylate derivative (*S*)-**6** (Fig. 1).[31]

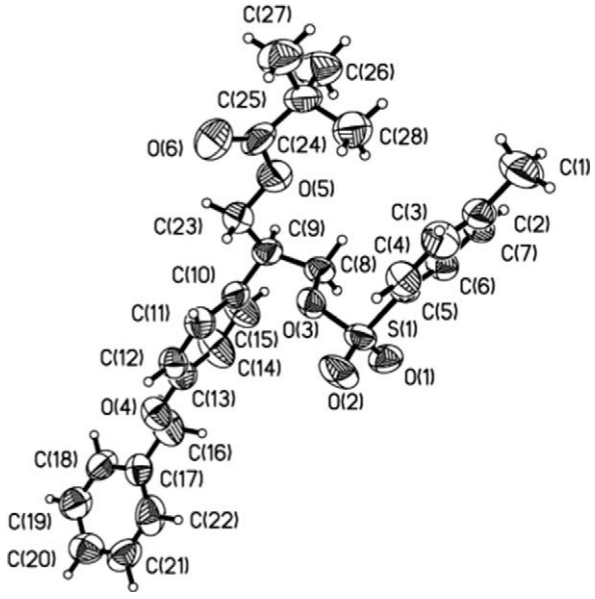


Figure 1. X-ray structure of compound (*S*)-**6**.

Then, we applied the same strategy to the synthesis of phoracantholides I **10** and J **11** (Scheme 3). These natural products are components of the highly odoriferous defense secretion of the Australian longicorn beetle *Phoracantha synonyma*.[32] Several syntheses of phoracantholides in the racemic and the enantiopure forms have been reported.[33] Our methodology is based upon an enzymatic kinetic resolution of (±)-hept-6-en-2-ol **7**[34] with an unsaturated acyl donor for the control of the sole stereogenic center followed by a ring-closing metathesis for the formation of the 10-membered lactone. Of the enzymes and conditions studied, the esterification of (±)-**7** with vinyl ester **2c** in toluene in the presence of CAL-B gave the best result and provided ester (*R*)-**9** (ee ⩾ 98%) and the remaining alcohol substrate (*S*)-**7**. After column chromatography, product **7** was still contaminated with trace amount of **2c** and this acyl donor was replaced by ethoxyvinyl ester **8**. At 50% conversion, this resolution provided ester (*R*)-**9** (yield = 44%, ee ⩾ 95%) and the alcohol (*S*)-**7** (yield = 46%, ee = 98%). The reactions were monitored by gas chromatography on a chiral phase column allowing simultaneous determination of conversion (*c*) and enantiomeric excesses of both product and remaining substrate. The absolute configurations were determined by comparison of the sign of the specific rotation of the remaining alcohol **7** with the reported values and further confirmed by the transformation of **9** into phoracantholides **10** and **11** of known absolute configuration. Ring-closing metathesis of the diene ester (*R*)-**9** in the presence of 10 mol % of the second-generation Grubbs catalyst gave lactone (*R*)-**10** as a mixture of *cis* and *trans* isomers (*Z*/*E* = 13) which was directly reduced with H_2/Pd–C to provide the natural enantiomer of phoracantholide (*R*)-**11**.

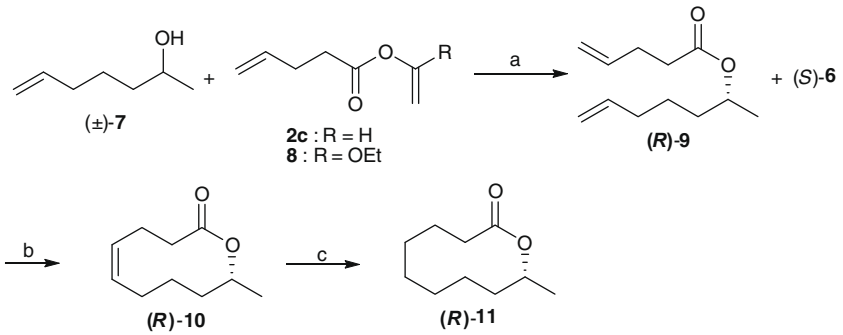
3. Conclusion

Herein, we have shown that lipases tolerate a range of functionalized vinyl esters as acyl donors in the enantioselective acylations of alcohols. *C. antarctica* lipase is the most versatile biocatalyst for this type of reactions. This substrate tolerance allows the introduction and retention of diverse acyl moieties as part of the final target structures. We applied this strategy to the enantioselective synthesis of a protein kinase ligand and a natural product (phoracantholide).

4. Experimental

4.1. General

NMR spectra were recorded on a Varian Inova AS400 spectrometer (400 MHz). Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter (*c* as gram of compounds per 100 mL). High resolution mass spectra (HRMS) of new compounds were recorded on an Agilent MSTOF-6210 (electrospray) spectrometer.



Scheme 3. Reagents and conditions: (a) CAL-B, toluene, 44%, ee = 95%; (b) Grubb's second-generation catalyst, CH_2Cl_2, reflux, 34%; (c) H_2, Pd–C, EtOAc–EtOH (3:1), 24 h, 73%.

Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. The enantiomeric excesses (ees) were determined by chiral HPLC analysis on a Chiralcel OD-H, OJ-H, or AD-H columns and by chiral GC analysis on a Chiraldex B-DM column, using racemic compounds as references. *C. antarctica* lipase B (Chirazyme L2, CAL-B) was obtained from Boehringer Mannheim. *C. rugosa* lipase (CRL), *P. fluorescens* lipase (PFL), and *B. cepacia* lipase (BCL) were from Sigma–Aldrich. *A. niger* lipase (ANL) was from Amano International Enzyme. Vinyl esters (acetate **2a**, pivalate **2b**, crotonate **2d**, methacrylate **2e**, benzoate **2f**, and cinnamate **2g**) and both enantiomers of 1-phenylethanol **1** are commercially available (Aldrich).

4.2. General procedure for the synthesis of vinyl esters

A mixture of carboxylic acid (10 mmol), palladium acetate (1.6 mmol), and potassium hydroxide (1 mmol) in vinyl acetate (25 mL) was stirred overnight at room temperature. The reaction mixture was filtered (Celite) and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography.

4.2.1. Vinyl pent-4-enoate 2c

Eluent: hexanes–diethyl ether, 6:1; 40% yield; IR (neat) 3084–2924, 1757, 1714, 1417, 1156, 918 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.46 (m, 2H), 2.54 (m, 2H), 4.62 (dd, J = 1.0 and 6.2 Hz, 1H), 4.92 (dd, J = 1.0 and 14.0 Hz, 1H), 5.07 (m, 2H), 5.86 (m, 1H), 7.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 33.4, 97.9, 116.1, 136.5, 141.4, 170.4; HRMS (ES) calcd for $C_7H_{11}O_2$ $(M+H)^+$: 127.0754. Found: 127.0753.

4.2.2. Vinyl 2-(*tert*-butoxycarbonylamino)acetate 2h

Eluent: hexanes–EtOAc, 2:1; 72% yield; IR (neat) 3376, 3094–2935, 1714, 1517, 1169, 947 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 4.00 (d, J = 5.5 Hz, 2H), 4.64 (dd, J = 1.3 and 6.1 Hz, 1H), 4.94 (dd, J = 1.3 and 12.0 Hz, 1H), 5.03 (br s, 1H), 7.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 42.4, 80.5, 98.9, 141.0, 167.9; HRMS (ES) calcd for $C_9H_{15}NO_4Na$ $(M+Na)^+$: 224.0893. Found: 224.0901.

4.2.3. Vinyl 2-(phenylthio)acetate 2i

Eluent: hexanes–EtOAc, 5:1; 44% yield; IR (neat) 3090–2921, 1751, 1645, 1258, 1138 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 2H), 4.62 (dd, J = 1.8 and 6.0 Hz, 1H), 4.91 (dd, J = 1.8 and 13.8 Hz, 1H), 7.21–7.36 (m, 4H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.7, 98.6, 127.4, 129.2, 130.6, 134.4, 141.2, 166.8; HRMS (ES) calcd for $C_{10}H_{11}O_2S$ $(M+H)^+$: 195.0474. Found 195.0481.

4.3. General procedure for enzymatic acylations

The selected enzyme (1000 units) was added to a solution of racemic 1-phenylethanol (250 mg, 2 mmol) and the vinyl ester (1.5 equiv) in diethyl ether (5 mL), and the mixture was stirred at room temperature. The reaction course was monitored by HPLC and stopped by filtration of the enzyme on Celite at 50% conversion. The solvent was removed under reduced pressure. The enantioenriched (*S*)-1-phenylethanol and the corresponding (*R*)-ester were isolated by flash chromatography.

4.3.1. (*R*)-1-Phenylethyl acetate 3a

Eluent: hexanes–EtOAc, 10:1; $[\alpha]_D^{23} = +43$ (c 2.1, $CHCl_3$), ee ⩾ 98% (HPLC, Chiralcel OD-H, hexanes–2% isopropyl alcohol); IR (neat) 3087–2872, 1742, 1371, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (d, J = 6.6 Hz, 3H), 2.08 (s, 3H), 5.89 (q, J = 6.6 Hz, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 22.5, 72.6, 126.3, 128.1, 128.7, 141.9, 170.6.

4.3.2. (*R*)-1-Phenylethyl pivaloate 3b

Eluent: hexanes–EtOAc, 10:1; $[\alpha]_D^{23} = -5.8$ (c 0.5, $CHCl_3$), ee = 92% (HPLC, Chiralcel AD-H, hexanes–2% isopropyl alcohol); IR (neat) 3065–2872, 1730, 1480, 1281, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (s, 9H), 1.52 (d, J = 6.6 Hz, 3H), 5.85 (q, J = 6.6 Hz, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 27.3, 38.9, 72.6, 126.0, 127.8, 142.4, 170.6.

4.3.3. (*R*)-1-Phenylethyl pent-4-enoate 3c

Eluent: hexanes–EtOAc, 7:1; $[\alpha]_D^{23} = +64$ (c 2.4, $CHCl_3$), ee = 95% (HPLC, Chiralcel AD-H, hexanes–2% isopropyl alcohol); IR (neat) 3065–2932, 1735, 1451, 1171, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (m, 3H), 2.41 (m, 4H), 5.01 (dd, J = 10.3 and 17.9 Hz, 2H), 5.82 (m, 1H), 5.90 (q, J = 7.0 Hz, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 29.1, 34.0, 72.5, 115.7, 126.3, 128.1, 128.7, 136.9, 141.9, 172.5; HRMS (ES) calcd for $C_{13}H_{20}NO_2$ $(M+NH_4)^+$: 222.1489. Found 222.1486.

4.3.4. (*R*,*E*)-1-Phenylethyl but-2-enoate 3d

Eluent: hexanes–EtOAc, 7:1; $[\alpha]_D^{23} = +11$ (c 1.2, $CHCl_3$), ee ⩾ 98% (HPLC, Chiralcel OD-H, hexanes–2% isopropyl alcohol); IR (neat) 3088–2871, 1718, 1445, 1264, 1185 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (d, J = 6.6 Hz, 3H), 1.87 (dd, J = 1.5 and 6.9 Hz, 3H), 5.89 (dd, J = 1.5 and 15.5 Hz, 1H), 5.95 (q, J = 6.6 Hz, 1H), 7.00 (m, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 22.5, 72.2, 123.1, 126.3, 128.0, 128.7, 142.1, 145.1, 166.0.

4.3.5. (*R*)-1-Phenylethyl methacrylate 3e

Eluent: hexanes–EtOAc, 5:1; $[\alpha]_D^{23} = +50$ (c 0.88, $CHCl_3$), ee ⩾ 98% (HPLC, Chiralcel OD-H, hexanes–0.5% isopropyl alcohol); IR (neat) 3034–2930, 1717, 1452, 1292, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57 (d, J = 6.6 Hz, 3H), 1.97 (s, 3H), 5.58 (m, 1H), 5.94 (q, J = 6.6 Hz, 1H), 6.17 (s, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5, 22.6, 72.8, 125.7, 126.2, 128.0, 128.7, 136.8, 142.1, 166.8.

4.3.6. (*R*)-1-Phenylethyl benzoate 3f

Eluent: hexanes–EtOAc, 7:1; $[\alpha]_D^{23} = -23$ (*c* 1.2, EtOH), ee = 92% (HPLC, Chiralcel OD-H, hexanes–0.5% isopropyl alcohol); IR (neat) 3090–2933, 1734, 1645, 1452, 1268, 1139, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69 (d, *J* = 6.5 Hz, 3H), 6.15 (q, *J* = 6.6 Hz, 1H), 7.29–7.59 (m, 8H), 8.10 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 73.1, 126.3, 128.1, 128.6, 128.8, 129.9, 130.7, 133.1, 166.1.

4.3.7. (*R*)-1-Phenylethyl cinnamate 3g

Eluent: hexanes–EtOAc, 7:1; $[\alpha]_D^{23} = -39$ (*c* 1.5, $CHCl_3$), ee ⩾ 98% (HPLC, Chiralcel OD-H, hexanes–1% isopropyl alcohol); IR (neat) 3062–2932, 1711, 1449, 1304, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.63 (d, *J* = 6.5 Hz, 3H), 6.03 (q, *J* = 6.5 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 7.30–7.44 (m, 8H), 7.52–7.55 (m, 2H), 7.71 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 72.2, 118.6, 126.3, 128.1, 128.3, 128.7, 129.1, 130.5, 134.6, 141.9, 145.1, 166.4.

4.3.8. (*R*)-1-Phenylethyl 2-(*tert*-butoxycarbonylamino)acetate 3h

Eluent: hexanes–EtOAc, 5:1; $[\alpha]_D^{23} = +15.0$ (*c* 1.15, $CHCl_3$), ee ⩾ 98% (HPLC, Chiralcel OD-H, hexanes–2% isopropyl alcohol); IR (neat) 3415, 3085, 2873, 1700, 1452, 1203, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 1.50 (d, *J* = 6.5 Hz, 3H), 3.84 (dq, *J* = 18.0 and 5.8 Hz, 2H), 5.29 (m, 1H), 5.88 (q, *J* = 6.5 Hz, 1H), 7.22–7.27 (m, 5H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 28.5, 42.8, 73.5, 79.8, 126.3, 128.2, 128.7, 141.3, 156.0, 169.9; HRMS (ES) calcd for $C_{15}H_{21}NO_4Na$ $(M+Na)^+$: 302.1363. Found 302.1401.

4.3.9. (*R*)-1-Phenylethyl 2-(phenylthio)acetate 3i

Eluent: hexanes–EtOAc, 10:1; $[\alpha]_D^{23} = +49$ (*c* 3, $CHCl_3$), ee = 94% (HPLC, Chiralcel OD-H, hexanes–2% isopropyl alcohol); IR (neat) 3061–2931, 1731, 1270, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50 (d, *J* = 6.6 Hz, 3H), 3.65 (d, *J* = 1.8 Hz, 2H), 5.88 (q, *J* = 6.6 Hz, 1H), 7.21–7.37 (m, 10H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 37.2, 73.8, 126.4, 127.2, 128.2, 128.7, 129.2, 130.3, 135.1, 141.2, 169.2.

4.4. (2*R*)-2-(4-(Benzyloxy)phenyl)-3-hydroxypropyl pivalate (*R*)-5

To a solution of **4** (200 mg, 0.825 mmol) and vinyl pivalate (0.125 mL, 1.03 mmol) in diethyl ether (10 mL) was added *A. niger* lipase (1000 units) and the mixture was stirred at room temperature. The progress of the reaction was monitored by HPLC. The reaction was quenched by filtration of the enzyme and the volatiles evaporated. The crude product was purified by flash chromatography (hexanes–EtOAc, 2:1) to give (*S*)-**5** (261 mg, 96%) as a white solid: mp 51–53 °C, lit.[29] 57 °C; $[\alpha]_D^{23} = +12.9$ (*c* 0.64, $CHCl_3$), ee ⩾ 98% (HPLC, Chiralcel OD-H, hexanes–10% isopropyl alcohol); IR (neat) 3429, 3033–2872, 1725, 1512, 1242, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9H), 2.02 (br s, 1H), 3.13 (m, 1H), 3.81 (m, 2H), 4.34 (m, 2H), 5.06 (s, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.33–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 39.1, 46.9, 64.1, 65.2, 70.3, 115.3, 127.7, 128.2, 128.8, 129.4, 131.4, 137.2, 158.2, 179.1.

4.5. (2*S*)-2-(4-Benzyloxy)phenyl)-3-(tosyloxy)propyl pivalate (*S*)-6

To a solution of **5** (300 mg, 0.875 mmol) and triethylamine (2 mL) in CH_2Cl_2 (40 mL) was added tosyl chloride (185 mg, 0.960 mmol) and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. The volatiles were evaporated and the crude product was recrystallized in toluene–hexane for the X-ray diffraction analysis. IR (NaCl) 3065–2872, 1727, 1611, 1513, 1363, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 2.43 (s, 3H), 3.27 (quint, *J* = 6.5 Hz, 1H), 4.25 (m, 4H), 5.05 (s, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 7.33–7.45 (m, 7H); 7.69 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 27.2, 38.9, 43.5, 64.3, 70.2, 70.5, 115.3, 127.7, 128.2, 128.3, 128.9, 129.3, 129.6, 130.1, 132.9, 137.1, 145.1, 158.4, 178.3; HRMS (ES) calcd for $C_{28}H_{36}NO_6S$ $(M+H)^+$: 496.1919. Found: 496.1914.

4.6. Synthesis of phoracantholides I (*R*)-10 and J (*R*)-11

4.6.1. 1-Ethoxyvinyl pent-4-enoate 8

To a solution of 4-pentenoic acid (3.51 g, 35 mmol) and Bennett's ruthenium complex ($[RuCl_2(p\text{-cymene})]_2$) (0.117 g, 0.18 mmol) in anhydrous diethyl ether (230 mL) at 0 °C under an argon atmosphere, was added dropwise a solution of ethoxy acetylene (4.00 g, 57.1 mmol) in anhydrous diethyl ether. The mixture was stirred for 24 h at room temperature and the solvent was evaporated. The crude product was purified by distillation (bp 100 °C, 1 mm Hg) to yield **7** (3.57 g, 60%) as a colorless oil. IR (neat) 3081, 2984, 2934, 1773, 1674, 1240, 1132, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 8.0 Hz, 3H), 2.34–2.41 (m, 2H), 2.47–2.53 (m, 2H), 3.72 (dd, *J* = 4.0 and 20.0 Hz, 2H), 3.83 (q, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 28.7, 33.4, 65.0, 71.9, 116.1, 136.4, 157.4, 170.5; HMRS (ES) calcd for $C_9H_{18}NO_3$ $(M+NH_4)^+$: 188.12812. Found 188.12782.

4.6.2. Resolution of (±)-7: (*R*)-hept-6-en-yl pent-4-enoate (*R*)-9 and (*S*)-hept-6-en-2-ol (*S*)-7

To a solution of (±)-**7** (0.246 g, 2.16 mmol) in toluene (6 mL) were added 1-ethoxyvinyl pent-4-enoate (0.367 g, 2.16 mmol) and lipase B from *C. antarctica* (CAL-B, 35 mg). The kinetic resolution was monitored by chiral GC. At the 50% completion point, the mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2, 0–10% EtOAc) to give pure (*R*)-**9** (0.188 g, 44%, ee = 95%) and (*S*)-**7** (0.113 g, 46%, ee = 98%) as colorless oils. (*S*)-**7**: $[\alpha]_D^{23} = +10.2$ (*c* 1.2, $CHCl_3$); lit.[35a] $[\alpha]_D^{20} = +10.4$ (*c* 0.79, $CHCl_3$); lit.[35b] $[\alpha]_D^{23} = -10.8$ (*c* 0.82, $CHCl_3$) for the (*R*)-enantiomer. (*R*)-**9**: $[\alpha]_D^{23} = -5.5$ (*c* 2.06, $CHCl_3$); IR (neat) 3079, 2978, 2936, 2863, 1733, 1641, 1256, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.0 Hz, 3H), 1.32–1.57 (m, 4H), 1.98–2.04 (m, 2H), 2.32–2.35 (m, 4H), 4.85–5.04 (m, 5H), 5.69–5.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 24.8, 29.2, 33.6, 34.0, 35.5, 70.9, 114.9, 115.6, 136.9, 138.6, 172.8; HRMS (ES) calcd for $C_{12}H_{20}O_2Na$ $(M+Na)^+$: 219.13555. Found 219.13427.

4.6.3. (*R*,*Z*)-10-Methyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one: phoracantholide J (*R*)-10

In an oven and flame-dried round-bottomed flask equipped with a condenser containing second-generation Grubb's catalyst (81.5 mg, 10 mol %) were added methylene chloride (420 mL) and compound **9** (0.1882 g, 0.96 mmol). The mixture was heated at reflux and monitored by TLC. When all the starting material was consumed (3 days), the mixture was cooled to room temperature and the methylene chloride was evaporated. The crude product was immediately purified by flash chromatography (hexanes with 5% AcOEt) to yield (*R*)-phoracantholide J **9** as a yellowish oil (0.0548 g, 34%) and as the *Z* isomer. $[\alpha]_D^{23} = -32$ (*c* 1.09, $CHCl_3$); lit.[33f] $[\alpha]_D^{22.2} = -36.8$ (*c* 1.77, $CHCl_3$); lit.[33a] $[\alpha]_D^{23} = -40.3$ (*c* 2.40, $CHCl_3$); IR (neat) 2973, 2930, 2856, 1731, 1443, 1377, 1254, 1175, 1089, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, *J* = 6.8 Hz, 3H), 1.32–1.46 (m, 2H), 1.84–1.96 (m, 4H), 2.17–2.25 (m, 1H), 2.52 (dt, *J* = 4.0 and 14.4 Hz, 1H), 2.62–2.82 (m, 2H), 5.05–5.12 (m, 1H), 5.35 (td, *J* = 4.0 and 11.2 Hz, 1H), 5.41–5.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.53, 25.82, 28.75, 32.17, 35.29, 35.49, 70.97, 129.81, 130.30, 173.13.

4.6.4. (*R*)-10-Methyloxecan-2-one: (*R*)-phoracantholide I ((*R*)-11

A solution of (*R*)-**10** (54.8 mg, 0.33 mmol) in 1:1 EtOH–EtOAc (15 mL) was stirred at room temperature with 10% Pd–C (150 mg) under hydrogen (60 psi) overnight. The catalyst was then removed by filtration and the solvent evaporated. The crude product was purified by flash chromatography (hexanes–EtOAc, 9:1) to give (*R*)-**11** (40.2 mg, 73%) as a yellow oil. $[\alpha]_D^{20} = -33.5$ (*c* 0.8, $CHCl_3$); lit.[33f] $[\alpha]_D^{22.2} = -35.1$ (*c* 1.15, $CHCl_3$); lit.[33c] $[\alpha]_D^{23} = -32.4$ (*c* 0.7, $CHCl_3$); IR (neat) 2955, 2925, 2854, 1733, 1463, 1256, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02–1.08 (m, 1H), 1.25 (d, $J = 6.8$ Hz, 3H), 1.37–1.57 (m, 8H), 1.69–1.79 (m, 1H), 1.89–2.07 (m, 2H), 2.16 (qd, $J = 2.8$ and 11.8 Hz, 1H), 2.47 (qd, $J = 3$ and 6 Hz, 1H), 4.99 (qd, $J = 3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.65, 20.85, 23.63, 24.19, 24.43, 27.36, 31.55, 35.41, 72.82, 174.19.

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