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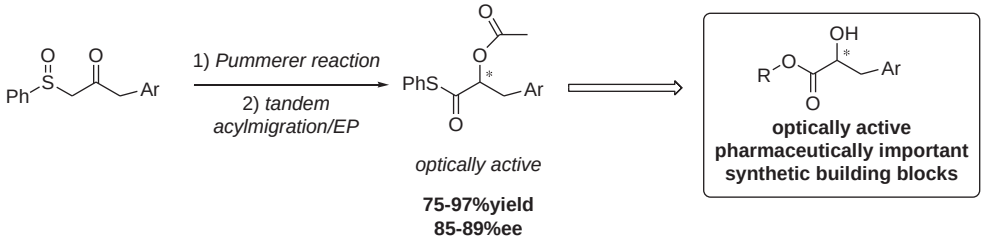
Dedicated to Professor Pier Paolo Piras on the occasion of his retirement

The organocatalytic synthesis of new α-acyloxy-3-arylpropionic thioesters has been accomplished providing some enantioenriched important aryllactic acid derivatives in good yield and enantioselectivities.



Keywords: asymmetric catalysis; protonation; rearrangement; sulfur; tandem reaction

1. Introduction

Optically active 3-phenyllactic acids and derivatives are a biologically and pharmaceutically relevant class of building blocks [1,2]: they have been targeted as intermediates for the total synthesis of bioactive peptides such as hirsutellide A,[3,4] cryptophycins [5–9] and cyclooctadepsipeptides PF1022A [10] and have been used as starting materials for the synthesis of anti-HIV natural products [11,12] and potential anti-diabetic agents.[13]

A certain number of methods are reported in the literature for their synthesis in non-racemic form that include strategies involving (Scheme 1): enzymatic and biomimetic methods;[14–16] reduction of α-keto esters;[17,18] Friedel–Crafts reactions;[19] Sharpless dihydroxylation of substituted cinnamate esters;[20] 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO)-mediated oxidation of optically active glycols [21] and the chiral pool approach, based on the diazotization

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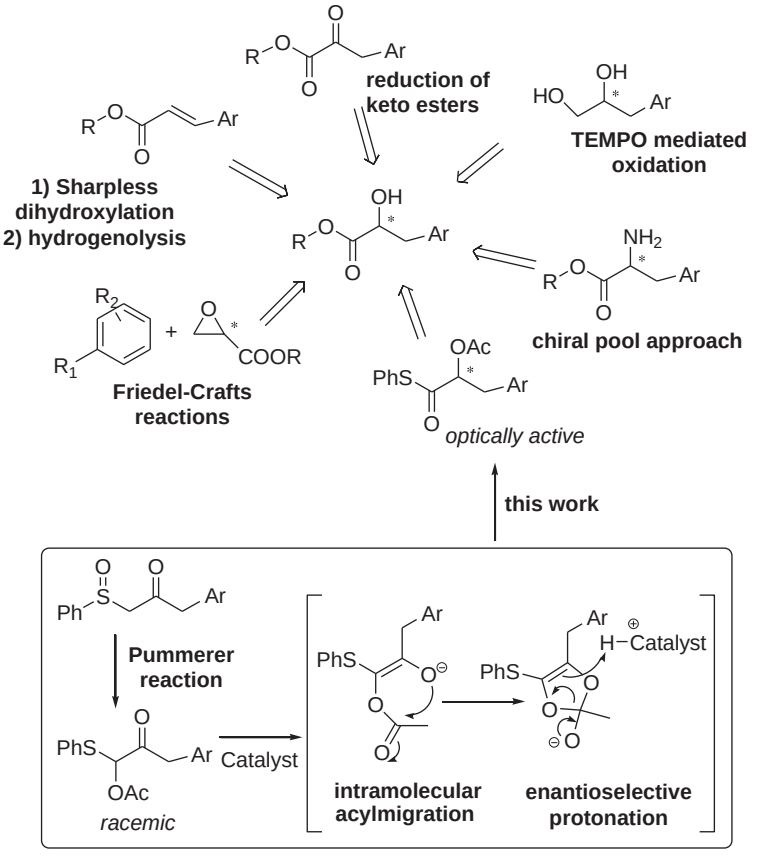
of the corresponding naturally occurring amino acid derivative.[22,23] In this context, an organocatalytic protocol (for a general review on asymmetric organocatalysis, see [24–30]) that provides for the efficient preparation of such products from readily available materials is highly desirable.



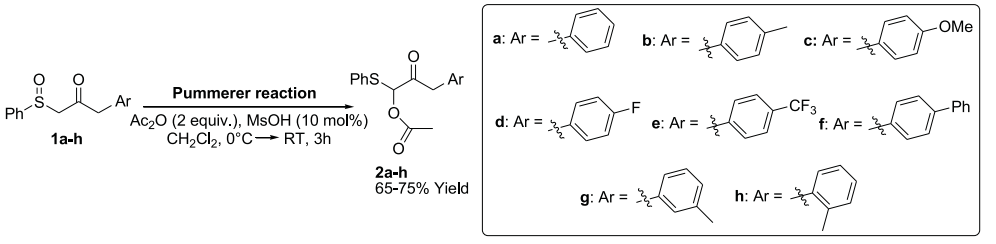
Scheme 1. Synthesis of optically active 3-phenyllactate and derivatives.

Recently, we developed an efficient synthesis of α-acyloxy thioesters from β-ketosulfoxides ([31]; for seminal studies on tandem processes involving enantioselective organocatalytic enol-keto tautomerisation, see [32]; for a diastereoselective approach, see [33,34]) through a Pummerer reaction [35,36] followed by an enantioselective organocatalytic tandem acyl migration/enantioselective protonation (for reviews on enantioselective protonation, see [37–42]; for personal research accounts, see [43–46]). This finding resulted in an operationally attractive method for the synthesis of such reaction products which could be easily transformed into sulfur-free derivatives without racemization. Thus, as part of an extension of our work, we planned the application of this methodology to the preparation of some chiral aryllactic acid derivatives.

2. Results and discussion

A selection of α-acyloxy-β-ketosulfides **2a**–**h** was prepared from the corresponding β-ketosulfoxides **1a**–**h** in reasonable overall yields by a Pummerer reaction (Scheme 2). Initially,

α-acyloxy-β-ketosulfide **2a** was selected as a model compound for catalyst screening and evaluation (Table 1). Pleasingly, the expected product **3a** was obtained with good chemical yield (84%) and enantioselectivity (85% ee) when quinidine (10 mol%) was used as catalyst at room temperature in 0.25 mL of toluene (Table 1, Entry 1).

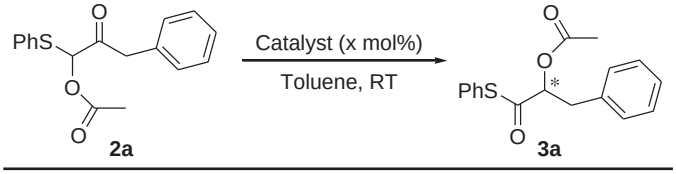


Scheme 2. Synthesis of α-acyloxy-β-ketosulfides **2a–h**.

In an effort to improve the stereoselectivity control, different cinchona alkaloids were evaluated. Hydroquinidine (Entry 3) gave results comparable with those of quinidine, while the reaction in the presence of β-isocupreidine (Entry 2) displayed excellent yield (98%) albeit with poor enantioselectivity (−32% ee). Unfortunately, the results obtained with biscinchona alkaloids $(DHQD)_2PHAL$, $(DHQD)_2AQN$ and $(DHQD)_2PYR$ did not bring any appreciable improvement of asymmetric induction (Entries 4–6). Further screening of reaction conditions, using different catalyst loading as well as substrate concentration (Entries 7–9), revealed that optimum yield and enantioselectivity of **3a** was obtained with 10 mol% of quinidine in 0.5 mL of toluene (Entry 7). However, it should be noted that the catalyst loading could be reduced to 5 mol% without any detrimental effect on the selectivity, although with concomitant increasing reaction time (Entry 8).

Next, the substituent tolerance in the phenyl ring was investigated in a series of rearrangement experiments (Scheme 3) using optimized reaction conditions for examining the substrate scope.

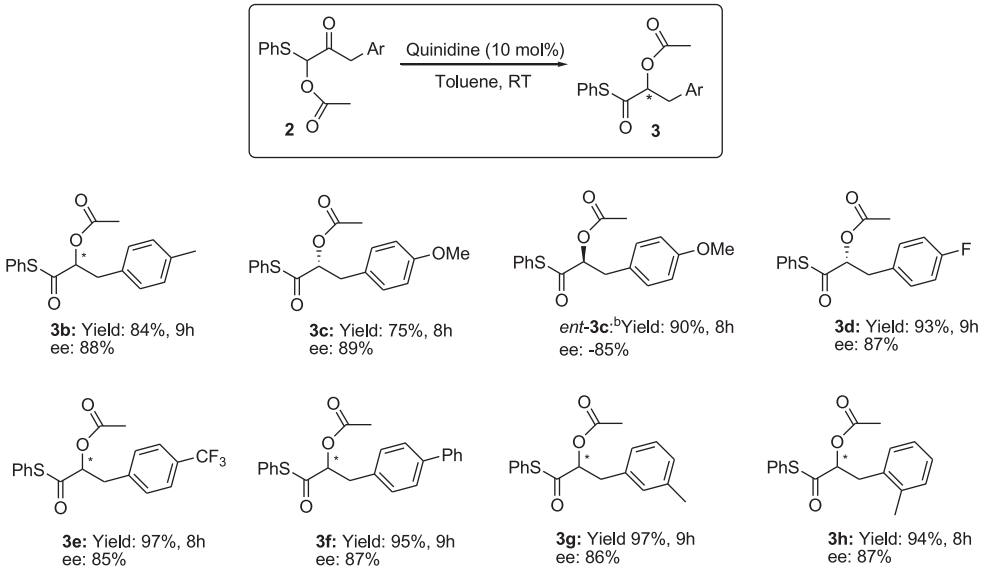
Table 1. Optimization of reaction conditions[a].



Entry	Catalyst (*x* mol%)	Time (h)	Yield(%)[b]	Ee (%)[c]
1	Quinidine (10)	4	84	85
2	β-isocupreidine (10)	20	98	−32
3	Hydroquinidine (10)	5	85	83
4	$(DHQD)_2PHAL$ (10)	18	67	−82
5	$(DHQD)_2AQN$ (10)	24	95	Racemic
6	$(DHQD)_2PYR$ (10)	9	99	−68
7[d]	Quinidine (10)	8	90	87
8[d]	Quinidine (5)	48	93	87
9[d]	Quinidine (20)	4	93	80

[a]*Reaction conditions*: **2a** (0.0675 mmol), catalyst (x mol%) in toluene (0.25 mL) at room temperature.
[b]Isolated yield after chromatography.
[c]Determined by HPLC analysis using a chiral stationary column.
[d]0.5 mL of toluene was used.

Gratifyingly, the reactions of **2b**–**h** proceeded with uniform chemical yields and enantioselectivities, regardless of the steric and electronic properties of the substituents on the phenyl ring, to give the desired α-acyloxy thioester adducts **3b**–**h** in good to high yields and enantioselectivities.

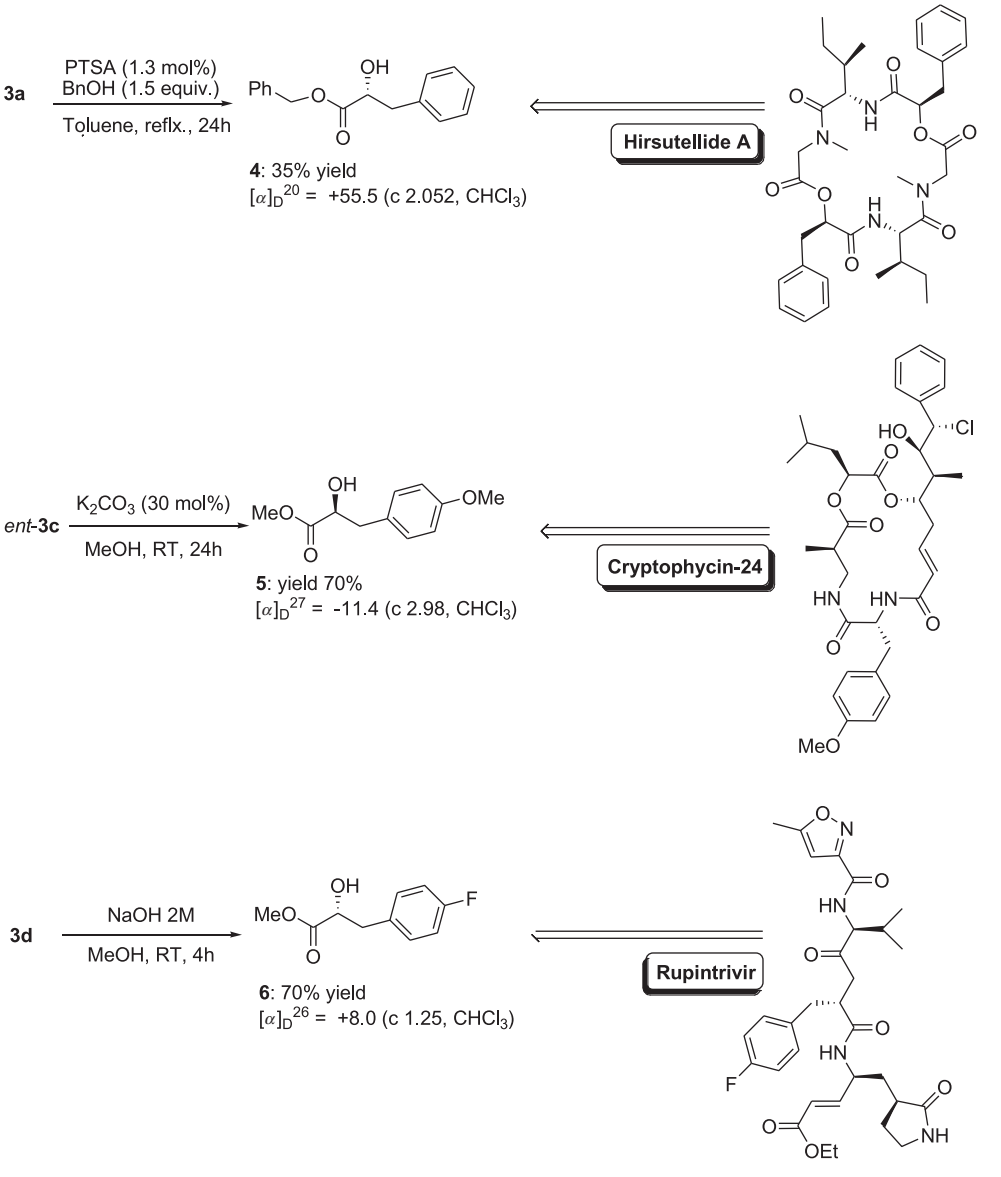


Scheme 3. Scope of the reaction. [a]*Reaction conditions*: **2** (0.0675 mmol), quinidine (10 mol%) in toluene (0.5 mL) at room temperature. Yields are given for isolated materials after column chromatography. [b]Quinine was used as catalyst.

Preliminary studies on the application of our methodology were carried out to accomplish the asymmetric synthesis of derivatives **4**–**6** (Scheme 4). (*R*)-2-hydroxy-3-phenylpropanoic acid benzyl ester **4**, a key precursor of hirsutellide A (antimycobacterial cyclohexadepsipeptide),[3,4] was obtained from **3a**, by treatment with benzyl alcohol, in 35% non-optimized yield. On the other hand, α-hydroxy methylester **5**, an important fragment (unit-B) of cryptophycin-24 [5–9] (tumor selective cytotoxin), was synthesized with the *S* configuration, from *ent*-**3c** in 70% yield by using K_2CO_3 in methanol at room temperature. Meanwhile, using the method described in Scheme 4, we were also able to prepare (*R*)-methyl 3-(4-fluorophenyl)-2-hydroxypropanoate **6** that is a key building block for the synthesis of various human rhinovirus 3C protease (3CP) inhibitors [47–49] such as rupintrivir (AG7088).

3. Conclusions

In conclusion, we have developed an efficient and simple route to α-acyloxy-3-arylpropionic thioester derivatives, which can be transformed into the corresponding optically active aryllactic acid derivatives. This method provides a new entry to this class of α-hydroxy acid derivatives (for selected recent general stereoselective synthesis of α-hydroxy acids and their derivatives, see [50–55]; also of interest in this respect is [32]) from easily available materials; and moreover, it has been demonstrated to be applicable to the synthesis of biologically and pharmaceutically important synthetic building blocks, such as derivatives **4**–**6**, in good yield and enantioselectivities.



Scheme 4. Synthesis of aryllactic acid derivatives **4**–**6**.

4. Experimental

4.1. *General methods*

^{1}H NMR spectra were recorded at 500 and 400 MHz at ambient temperature with $CDCl_3$ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity, coupling constants and integration. ^{13}C NMR spectra were recorded operating, respectively, at 125 or 100 MHz at ambient temperature with $CDCl_3$ as solvent. Infrared (IR) spectra were recorded on an FT-IR spectrophotometer. Low resolution mass spectral analyses were recorded in electron impact ionization (70 eV) mode. Relative intensities are given in parentheses. The high resolution mass

spectrometry (HRMS) analyses were performed using a Bruker micro-TOF QII mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode. The sample solutions (CH_3OH) were introduced by continuous infusion with a syringe pump at a flow rate of 180 μL min^{-1}. The instrument was operated with end-plate offset and capillary voltages set to -500 and -4500 V, respectively. The nebulizer pressure was 0.4 bar (N_2), and the drying gas (N_2) flow rate was 4.0 L min^{-1}. The capillary exit and skimmer voltages were 90 and 30 V, respectively. The drying gas temperature was set at 180°C. The calibration was carried out with a sodium formate solution (10 mM NaOH in isopropanol/water 1:1 (+0.2% HCOOH)) and the software used for the simulations was Bruker Daltonics DataAnalysis (version 4.0). Enantiomeric excesses of α-acyloxy thioester were determined by HPLC, using a Chiralpak AD-H or Chiralcel OJ analytical column with *i*-PrOH/hexane as eluent, using authentic racemic samples for reference comparison. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 230–400 mesh silica gel 60 (0.040–0.063 mm). Yields refer to chromatographically pure materials. All spectroscopic data of compounds **4**, **5**, **6** matched those reported previously in the literature.

4.2. *General procedure for the synthesis of α-acyloxy-β-ketosulfides (2a–h)*

Acetic anhydride (0.504 mmol) is added followed by methanesulfonic acid (0.0252 mmol) to a stirred solution of β-ketosulfoxide **1a**–**h** (0.252 mmol) in dichloromethane (2 mL) at 0°C and stirring is continued at the same temperature for 1 h and then at room temperature for 2 h. The reaction mixture is washed successively with saturated $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution, and dried over anhydrous Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue chromatographed on silica gel (mixture of hexane/ether) to give the corresponding α-acyloxy-β-ketosulfide **2a**–**h** (65–75% yield).

4.2.1. *2-Oxo-3-phenyl-1-(phenylthio)propyl acetate (**2a**)*

Pale yellow oil. IR (neat): 3032, 1737, 1439, 1213 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.86 (s, 2H), 6.26 (s, 1H), 7.13 (d, $J = 10.0$ Hz, 2H), 7.24–7.32 (m, 6H), 7.45 (d, $J = 10.0$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8, 45.8, 81.2, 127.3, 128.7, 129.2, 129.3, 129.7, 130.0, 132.9, 133.6, 169.8, 197.0. MS (m/z): 191 (M^+-109 (31)), 163 (40), 109 (38), 91 (35), 65 (26), 43 (100).

4.2.2. *2-Oxo-1-(phenylthio)-3-(p-tolyl)propyl acetate (**2b**)*

Pale yellow oil. IR (neat): 2922, 1737, 1520, 1222 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 2.30 (s, 3H), 3.82 (s, 2H), 6.26 (s, 1H), 7.05 (dd, $J = 35.0$, 10.0 Hz, 4H), 7.30–7.32 (m, 3H), 7.45 (dd, $J = 10.0$, 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8, 21.1, 45.5, 81.2, 129.1, 129.3, 129.4, 129.6, 133.6, 136.9, 169.7, 197.2. MS (m/z): 254 (M^+-60 (35)), 226 (38), 193 (20), 178 (12), 149 (100), 134 (27), 123 (31), 117 (82), 109 (41), 105 (61), 91 (39), 77 (51), 39 (31).

4.2.3. *3-(4-Methoxyphenyl)-2-oxo-1-(phenylthio)propyl acetate (**2c**)*

Yellow oil. IR (neat): 2934, 1737, 1511, 1252 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 3.77 (s, 3H), 3.80 (s, 2H), 6.26 (s, 1H), 6.82 (d, $J = 5.0$ Hz, 2H), 7.05 (d, $J = 10.0$ Hz, 2H), 7.25–7.34 (m, 3H), 7.45–7.46 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8, 45.0, 55.3, 81.2,

114.2, 124.9, 129.2, 129.3, 130.1, 130.8, 133.6, 158.9, 169.8, 197.4. MS (m/z): 330 (M^+ (3)), 221 (85), 193 (100), 161 (30), 152 (28), 121 (82), 101 (23), 91 (10), 77 (12), 65 (12), 43 (60).

4.2.4. *3-(4-Fluorophenyl)-2-oxo-1-(phenylthio)propyl acetate (**2d**)*

Yellow oil. IR (neat): 3062, 2926, 1737, 1511, 1226 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H), 3.85 (q, $J = 16.0$ Hz, 2H), 6.27 (s, 1H), 6.95–7.00 (m, 2H), 7.07–7.10 (m, 2H), 7.32–7.35 (m, 3H), 7.46–7.48 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.7, 44.7, 81.2, 115.3, 115.5, 128.5, 129.2, 129.3, 129.8, 131.2, 131.3, 133.5, 163.3, 169.8, 196.8. MS (m/z): 209 (M^+-109 (49)), 181 (44), 149 (2), 110 (42), 101 (4), 83 (6), 65 (8), 43 (100), 39 (3).

4.2.5. *2-Oxo-1-(phenylthio)-3-(4-(trifluoromethyl)phenyl)propyl acetate (**2e**)*

Yellow oil. IR (neat): 3066, 2922, 1754, 1729, 1328 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.19 (s, 3H), 3.93 (ABq, $J = 16.0$, 44.0 Hz, 2H), 6.25 (s, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.29–7.35 (m, 3H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 45.2, 81.5, 125.4, 125.53, 125.57, 125.6, 129.40, 129.44, 130.1, 133.6, 136.9, 169.9, 196.1. MS (m/z): 259 (M^+-109 (22)), 231 (18), 159 (11), 109 (44), 91 (5), 77 (5), 65 (15), 43 (100).

4.2.6. *3-([1,1′-Biphenyl]-4-yl)-2-oxo-1-(phenylthio)propyl acetate (**2f**)*

Pale yellow oil. IR (neat): 3032, 1754, 1733, 1486, 1226 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.19 (s, 3H), 3.92 (d, $J = 4.0$ Hz, 2H), 6.30 (s, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.31–7.35 (m, 3H), 7.40–7.48 (m, 5H), 7.54 (dd, $J = 16.0$, 8.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 45.4, 81.4, 127.1, 127.42, 127.46, 128.8, 129.2, 129.4, 130.0, 130.2, 131.9, 133.6, 140.3, 140.8, 169.9, 197.0. MS (m/z): 318 (M^+-58 (17)), 209 (37), 191 (5), 167 (100), 152 (26), 123 (37), 109 (10), 77 (14), 65 (10), 45 (19), 39 (6).

4.2.7. *2-Oxo-1-(phenylthio)-3-(m-tolyl)propyl acetate (**2g**)*

Pale yellow oil. IR (neat): 3028, 2922, 1750, 1729, 1213 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 2.29 (s, 3H), 3.83 (s, 2H), 6.27 (s, 1H), 6.92–7.19 (m, 4H), 7.31–7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.7, 21.3, 45.6, 81.1, 126.7, 127.9, 128.4, 129.0, 129.2, 130.4, 132.7, 133.5, 134.5, 138.1, 169.6, 197.0. MS (m/z): 254 (M^+-60 (51)), 226 (7), 193 (3), 145 (7), 117 (100), 109 (28), 91 (27), 77 (19), 65 (28), 58 (15), 39 (15).

4.2.8. *2-Oxo-1-(phenylthio)-3-(o-tolyl)propyl acetate (**2h**)*

Yellow oil. IR (neat): 3020, 1759, 1703, 1448, 1443, 1222 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.17 (s, 6H), 3.90 (s, 2H), 6.25 (s, 1H), 7.05–7.17 (m, 4H), 7.32–7.48 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 20.8, 44.1, 81.4, 126.2, 127.7, 129.1, 129.2, 129.4, 130.5, 130.7, 131.7, 133.4, 137.4, 169.9, 197.0. MS (m/z): 254 (M^+-60 (59)), 226 (29), 193 (9), 178 (5), 149 (86), 117 (100), 115 (98), 109 (37), 91 (40), 87 (41), 65 (43), 49 (28), 39 (24).

4.3. *General procedure for the synthesis of optically active α-acyloxy thioester 3a–h*

To a solution of **2a**–**h** (0.0675 mmol) in toluene (0.5 mL) was added quinidine (2.17 mg, 0.00675 mmol), and the mixture was stirred for 8–9 h at room temperature. The crude reaction

mixture was directly loaded on silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of hexane/ether).

4.3.1. *1-Oxo-3-phenyl-1-(phenylthio)propan-2-yl acetate (**3a**)*

Yield 90%; pale yellow oil. IR (neat): 3037, 1759, 1703, 1443, 1217 cm^{-1}. $[\alpha]_D^{20} = +114.5$ (*c* 1.45, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 3.12 (ddd, $J = 20.0, 15.0, 5.0$ Hz, 2H), 5.47 (dd, $J = 10.0, 5.0$ Hz, 1H), 7.15–7.34 (m, 10 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8, 38.3, 78.7, 126.4, 127.2, 128.6, 129.4, 129.6, 129.7, 134.8, 135.5, 169.8, 196.8. MS (*m*/*z*): 191 (M^+-109 (43)), 163 (47), 121 (3), 110 (38), 101 (7), 91 (23), 77 (9), 65 (17), 43 (100). The ee was determined to be 87% ee by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 254$ nm): t_R(major) = 53.46 min, t_R(minor) = 47.58 min. HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{16}O_3SNa$ 323.0712; found 323.0725.

4.3.2. *1-Oxo-1-(phenylthio)-3-(p-tolyl)propan-2-yl acetate (**3b**)*

Yield 84%; white solid; mp: 53–55°C. IR (nujol): 3024, 1754, 1699, 1217 cm^{-1}. $[\alpha]_D^{27} = +135.3$ (*c* 0.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H), 2.33 (s, 3H), 3.05–3.24 (m, 2H), 5.51 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.11 (s, 4H) 7.35–7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 21.2, 37.9, 78.8, 126.4, 129.3, 129.43, 129.48, 129.7, 132.4, 134.9, 136.8, 169.9, 196.9. MS (*m*/*z*): 205 (M^+-109 (36)), 177 (46), 145 (4), 135 (10), 109 (34), 91 (11), 77 (17), 65 (11), 43 (100), 39 (7). The ee was determined to be 88% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 254$ nm): t_R(major) = 7.90 min, t_R(minor) = 6.65 min. HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}O_3SNa$ 337.0869; found 337.0883.

4.3.3. *3-(4-Methoxyphenyl)-1-oxo-1-(phenylthio)propan-2-yl acetate (**3c**)*

Yield 75%; pale yellow oil. IR (neat): 2951, 1754, 1707, 1516, 1252 cm^{-1}. $[\alpha]_D^{24} = +120.0$ (*c* 1.65, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 3.13 (ddd, $J = 20.0, 15.0, 5.0$ Hz, 2H), 3.79 (s, 3H), 5.50 (dd, $J = 10.0, 5.0$ Hz, 1H), 6.84 (d, $J = 10.0$ Hz, 2H), 7.14 (d, $J = 10.0$ Hz, 2H), 7.36–7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8, 45.0, 55.3, 81.2, 114.2, 124.9, 129.2, 129.3, 130.1, 130.8, 133.6, 158.9, 169.8, 197.4. MS (*m*/*z*): 221 (M^+-109 (38)), 193 (61), 179 (3), 161 (22), 151 (24), 121 (88), 109 (32), 91 (13), 77 (17), 65 (18), 43 (100), 39 (6) .The ee was determined to be 89% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 254$ nm): t_R(major) = 12.71 min, t_R(minor) = 10.14 min. (*ent*-**3c**): Yield 90%; $[\alpha]_D^{24} = -86.0$ (*c* 1.00, $CHCl_3$). The ee was determined to be −85% ee. HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}O_4SNa$ 353.0818; found 353.0833.

4.3.4. *3-(4-Fluorophenyl)-1-oxo-1-(phenylthio)propan-2-yl acetate (**3d**)*

Yield 93%; pale yellow oil. IR (neat): 2964, 1767, 1465, 1379 cm^{-1}. $[\alpha]_D^{26} = +125.7$ (*c* 3.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 3.16 (ddd, $J = 16.0, 12.0, 4.0$ Hz, 2H), 5.52 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.00 (t, $J = 8.0$ Hz, 2H), 7.17–7.20 (m, 2H), 7.35–7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.7, 37.4, 78.5, 115.3, 115.5, 126.2, 129.4, 129.8, 131.11, 131.19, 134.8, 163.3, 169.7, 196.8. MS (*m*/*z*): 209 (M^+-109 (53)), 181 (52), 149 (2), 121 (5), 109 (62), 101 (6), 83 (10), 65 (13), 43 (100), 39 (5). The ee was determined to be 87% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min,

$\lambda = 254$ nm): t_R(major) = 8.97 min, t_R(minor) = 7.01 min. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{15}FO_3SNa$ 341.0618; found 341.0627.

4.3.5. *1-Oxo-1-(phenylthio)-3-(4-(trifluoromethyl)phenyl)propan-2-yl acetate (**3e**)*

Yield 97%; pale yellow oil. IR (neat): 375, 2930, 1759, 1699, 1328 cm^{-1}. $[\alpha]_D^{22} = +96.1$ (*c* 0.66, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 3.25 (ddd, $J = 16.0, 12.0, 4.0$ Hz, 2H), 5.58 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.34–7.44 (m, 7H), 7.58 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 37.9, 78.7, 127.1, 127.3, 127.4, 128.9, 129.4, 129.8, 130.0, 134.9, 140.1, 140.8, 169.9, 196.9. MS (m/z): 259 (M^+-109 (28)), 231 (17), 159 (4), 110 (31), 91 (2), 65 (7), 43 (100), 39 (3). The ee was determined to be 85% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 254$ nm): t_R(major) = 7.79 min, t_R(minor) = 6.44 min. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{15}F_3O_3SNa$ 391.0586; found 391.0597.

4.3.6. *3-([1,1′-Biphenyl]-4-yl)-1-oxo-1-(phenylthio)propan-2-yl acetate (**3f**)*

Yield 95% (33.9 g); white solid; mp: 117–121°C. IR (nujol): 2960, 1764, 1716, 1465, 1371 cm^{-1}. $[\alpha]_D^{26} = +98.1$ (*c* 1.06, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 3.24 (ddd, $J = 20.0$, 16.0, 4.0 Hz, 2H), 5.58 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.29–7.45 (m, 10H), 7.57 (dd, $J = 16.0, 8.0$ Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 37.9, 78.7, 126.3, 127.1, 127.3, 127.4, 128.9, 129.4, 129.8, 130.0, 134.6, 134.9, 140.1, 140.8, 169.9, 196.9. MS (m/z): 267 (M^+-109 (35)), 239 (40), 207 (8), 179 (10), 167 (72), 152 (19), 109 (32), 65 (11), 43 (100), 39 (4). The ee was determined to be 87% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 254$ nm): t_R(major) = 10.52 min, t_R(minor) = 8.51 min. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{20}O_3SNa$ 399.1025; found 399.1045.

4.3.7. *1-Oxo-1-(phenylthio)-3-(m-tolyl)propan-2-yl acetate (**3g**)*

Yield 97%; pale yellow oil. IR (neat): 2968, 1759, 1707, 1465, 1379 cm^{-1}. $[\alpha]_D^{26} = +117.5$ (*c* 1.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H), 2.34 (s, 3H), 3.21 (ddd, $J = 8.0, 16.0$, 20.0 Hz, 2H), 5.52 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.02–7.08 (m, 3H), 7.18–7.21 (m, 1H), 7.36–7.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 21.5, 38.2, 78.8, 126.4, 126.6, 127.9, 128.4, 129.4, 129.8, 130.3, 134.9, 135.4, 138.2, 169.9, 196.9. MS (m/z): 205 (M^+-109 (68)), 177 (47), 163 (22), 135 (11), 110 (38), 91 (10), 77 (12), 65 (13), 43 (100), 39 (5). The ee was determined to be 86% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 254$ nm): t_R(major) = 6.70 min, t_R(minor) = 5.71 min. HRMS (ESI-TOF) m/z $[M + K]^+$ calcd for $C_{18}H_{18}O_3SK$ 353.0608; found 353.0622.

4.3.8. *1-Oxo-1-(phenylthio)-3-(o-tolyl)propan-2-yl acetate (**3h**)*

Yield 94%; pale yellow oil. IR (neat): 3034, 1750, 1729, 1439, 1367, 1226 cm^{-1}. $[\alpha]_D^{26} = +100.0$ (*c* 1.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.10 (s, 3H), 2.37 (s, 3H), 3.20 (ddd, $J = 20.0$, 10.0, 5.0 Hz, 2H), 5.52 (dd, $J = 10.0, 5.0$, 1H), 7.15–7.17 (m, 4H), 7.38–7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.6, 20.7, 35.6, 78.2, 126.1, 126.4, 127.4, 129.4, 129.8, 130.3, 130.6, 134.0, 134.8, 136.8, 169.8, 196.9. MS (m/z): 205 (M^+-109 (49)), 177 (36), 163 (10), 135 (8), 110 (29), 93 (5), 77 (8), 65 (8), 43 (100), 39 (4). The ee was determined to be 87% ee by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda =$

254 nm): t_R(major) = 6.72 min, t_R(minor) = 5.46 min. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{18}O_3SNa$ 337.0869; found 337.0878.

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Supplemental data

Supplemental data for this article can be accessed at 10.1080/17415993.2014.946506.

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