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An efficient enantioselective synthesis of an indane acetic acid derivative: methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]butanoate

Mingbao Zhang,* Lei Zhu and Xin Ma

Department of Chemistry Research, Bayer Research Center, West Haven, CT 06516, USA

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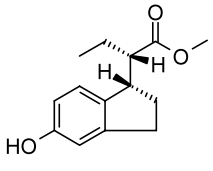
Abstract—We have developed a practical enantioselective synthesis of **1**, a novel indane acetic acid derivative with two contiguous stereogenic centers. The key indene acetic acid framework was constructed via a robust, unprecedented Reformatsky process. One stereogenic center was set via a resolution, and the other via a highly diastereoselective hydrogenation of the indene acetic acid.

1. Introduction

Indane-containing compounds have been of great interest as synthetic targets due to their biological and pharmacological properties.[1–9] Indane-derived chiral ligands have also found application in transition metal-catalyzed processes.[10] In connection to a drug discovery project, we required a large quantity of the indane acetic acid derivative **1** in enantiomerically pure form. Despite numerous synthetic methods for constructing functionalized indanes,[1,2,11–13] the two contiguous stereogenic centers in **1** presented a formidable synthetic challenge. Herein we describe an efficient enantioselective synthesis of **1** with both high de and ee.

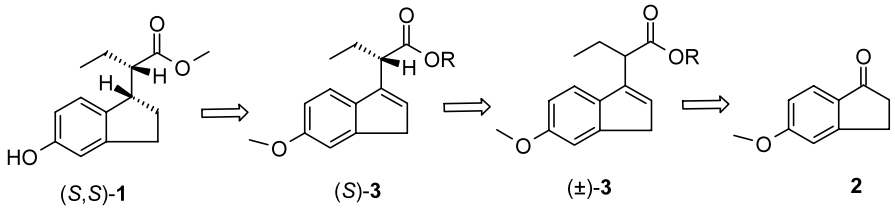


(*S*,*S*)-**1**

2. Results and discussion

2.1. Retrosynthetic analysis of 1

The retrosynthetic analysis of **1** is shown in Scheme 1. The benzylic stereogenic center could be derived from the prochiral C=C bond in the indene intermediate (*S*)-**3**. The chiral indene precursor could in turn be obtained by resolution of the corresponding racemate. We envisioned that racemic **3** could be obtained via the Reformatsky reaction[14] of 5-methoxy-1-indanone **2**, a commercially available starting material. The success of this strategy hinged on a robust Reformatsky process



3a: R = H
3b: R = Me

Scheme 1.

* Corresponding author. Tel.: (203) 812-5906; fax: (203) 812-2452; e-mail: mingbao.zhang.b@bayer.com

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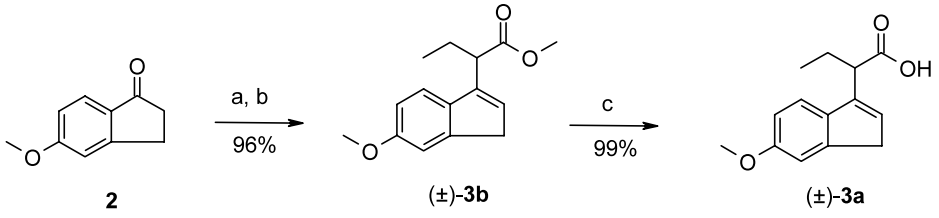
and the ability to perform a diastereoselective reduction of the indene precursor (*S*)-**3** that would set the benzylic carbon to the desired (*S*)-configuration.

2.2. Synthesis of 1

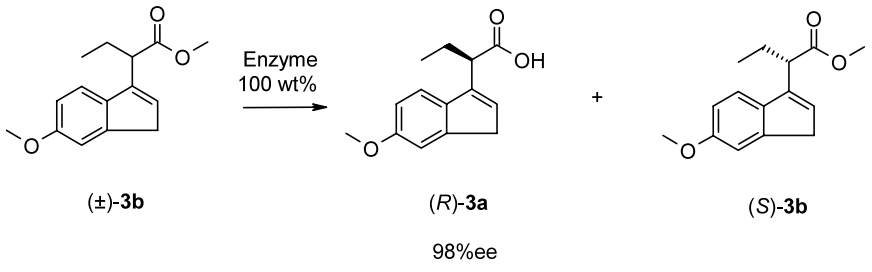
We previously reported a novel, carboxylate-directed, diastereoselective, homogeneous hydrogenation of cyclic β,γ-unsaturated carboxylic acids with Wilkinson's catalyst.[15] With this methodology, the racemic indene acetic acid **3a** was hydrogenated smoothly via its triethyl amine salt to yield the corresponding indane acetic acid in greater than 199:1 diastereoselectivity in favor of the desired racemic diastereomer **4**. We envisioned that hydrogenation of enantiomerically pure (*S*)-**3a** using this method would deliver the corresponding single diastereomer (*S*,*S*)-**4**.

2.2.1. Reformatsky reaction to construct the indene acetic acid framework. The requisite racemic indene acetic acid precursor **3a** was prepared by saponification of the indene ester **3b**. Synthesis of **3b** was achieved via the Reformatsky reaction of 5-methoxy-1-indanone **2** and methyl 2-bromobutyrate using 'Barbier-type' conditions in tetrahydrofuran (Scheme 2). During our initial work on the Reformatsky reaction, the reaction was not reproducible: under very similar reaction conditions, yields ranged from near quantitative to zero where the indanone starting material **2** was completely recovered. The predictability of the Reformatsky reaction has remained a major challenge for organic chemists since the reaction was first reported more than a century ago.[16,17] While it is generally accepted that activation of the zinc improves reliability, very few of the numerous literature procedures are universally effective.[18] Furthermore, most reported zinc activation methods require use of additional reagents which inevitably end up as impurities in the reaction.[14] Our initial results were also inconsistent. Thus, to enhance the success of our overall synthetic strategy for **1**, we needed to develop a robust process for the Reformatsky reaction. A pattern emerged from careful analysis of the results from our initial survey of the Reformatsky conditions. We observed that if a small amount of product was formed as detected by TLC, then the reaction always proceeded rapidly to completion. While the induction period for the reaction varied, production of the end product was consistent. This observation prompted us to investigate a 'seeding process'. A small-scale batch (typically 1–10 g of the indanone) was carried to completion, and this reaction mixture was used without workup as 'seed' for the next larger batch. As expected, the larger batch proceeded to completion rapidly after addition of the 'seed'. The bulk of the reaction mixture (ca. 90%) was then transferred to another vessel via a Teflon tube for workup. The reaction flask was subsequently charged with a new batch of starting material, and the reaction was repeated iteratively until the desired amount of product was produced. Interestingly, a tightly closed sample of the 'seed' was effective in promoting Reformatsky reaction of similar substrates after being kept for 5 months on the bench. While the nature of the catalytic cycle and of the catalyst itself is not clear at this point, we nevertheless believe that this observation could be generally valuable.

2.2.2. Resolution of the indene acetic acid 3a. With a process in hand for generating racemic **3b**, we next explored its resolution and resolution of its hydrolysis product, **3a**. Our initial focus was enzymatic hydrolysis[19,20] of the indene ester **3b** using the Altus screening kit ChiroScreen-EH (Scheme 3). An enzymatic resolution of the ester would highly be advantageous if the desired enantiomer undergoes hydrolysis selectively. Under this circumstance, the saponification of **3b** to **3a** would not be required prior to resolution. Among the numerous enzymes screened, Mucor meihei lipase showed high enantioselectivity. Even at 100 wt% enzyme loading, the hydrolysis stopped at ca. 50% conversion after overnight stirring. The acid was iso-



Scheme 2. *Conditions*: (a) zinc powder, methyl 2-bromobutyrate, THF, 60°C; (b) 1N HCl; (c) KOH (3 equiv.)/MeOH.

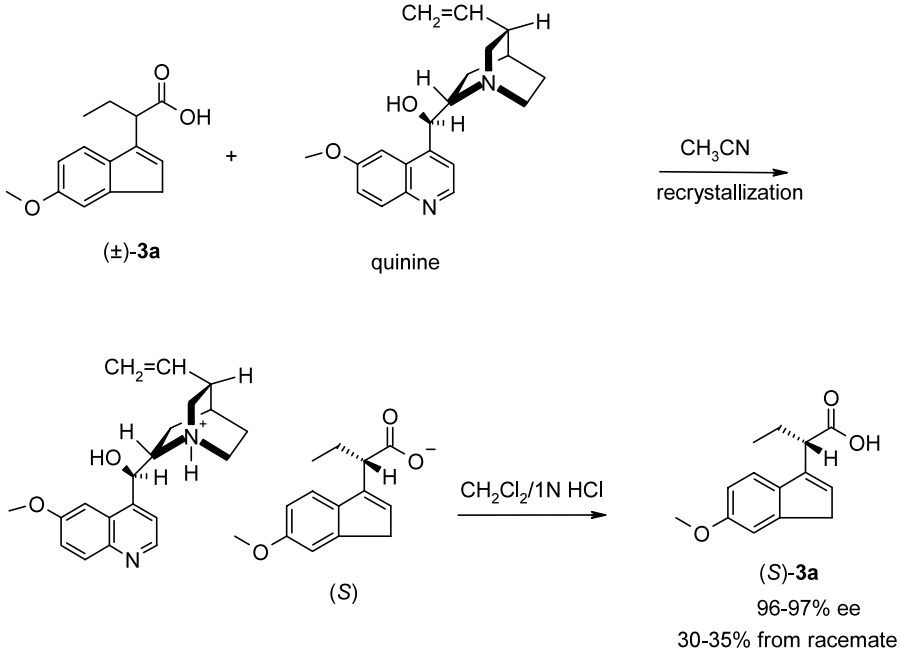


Scheme 3.

lated with 98% ee. Unfortunately, these conditions afforded the undesired (*R*)-**3a** enantiomer, as indicated by chiral HPLC. It is important to note that this chiral acid would no longer undergo hydrogenation under our diastereoselective, homogeneous hydrogenation conditions with Wilkinson's catalyst, presumably due to residual enzyme impurities that poisoned the catalyst. The chiral ester (*S*)-**3b**, recovered from the enzymatic resolution racemized when we tried to hydrolyze it to the corresponding acid (*S*)-**3a**. Based on these results, we abandoned the enzymatic resolution approach.

Chemical resolution of the indene acid (±)-**3a** was carried out with quinine in acetonitrile (Scheme 4). In this case, the desired (*S*)-enantiomer formed a less soluble diastereomeric salt with quinine and was conveniently isolated and purified by recrystallization. The salt was then dissolved in dichloromethane and washed with 1 M HCl to liberate the free (*S*)-indene acid **3**. The results are summarized in Table 1. Several points are worth noting. Lower mole ratios of quinine:**3a** resulted in higher ee, but lower yields (entries 1–5). At a stoichiometric ratio (1:1), a substantial amount of the undesired (*R*)-enantiomer crystallized (entry 6). The optimal ratio of quinine:**3a** was set at 0.77 for the large-scale runs. Under these conditions, reproducibly high ee and yields were obtained from a single recrystallization (entries 8 and 9).

2.2.3. Diastereoselective hydrogenation. Carboxylate-directed hydrogenation[15] of (*S*)-**3a** with Wilkinson's catalyst in ethanol/tetrahydrofuran (9:1) at 60 psi hydrogen pressure afforded the (*S*,*S*)-indane acid intermediate **4** in >99% de and no loss of ee. At this point, the stereoselective elaboration of the target was complete (Scheme 5).

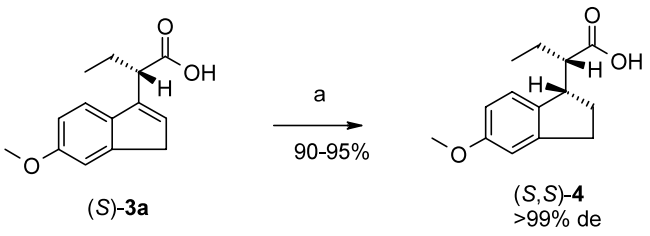


Scheme 4.

Table 1. Chemical resolution of (±)-**3a** using quinine

Entry	Quinine:**3a** (mole ratio)	**3a** conc. (M)	Agitation	Ee (%)	Yield (%)[g]
1[a]	0.50	0.29	Magnetic	97.3	25.0
2[a]	0.50	0.57	Magnetic	98.5	22.7
3[a]	0.58	0.29	Magnetic	92.9	35.9
4[a]	0.64	0.29	Magnetic	93.0	40.9
5[b]	0.50	0.29	Mechanical	92.8	23.4
6[b]	1.0	0.29	Mechanical	67.6	58.0
7[c,f]	0.71	0.29	Mechanical	98.1	27.8
8[d,f]	0.77	0.27	Mechanical	97.4	35.4
9[e,f]	0.77	0.28	Mechanical	96.4	32.2

[a] Resolution was carried out on 4.9 mmol scale.
[b] Resolution was carried out on 9.8 mmol scale.
[c] Resolution was carried out on 0.245 mol scale.
[d] Resolution was carried out on 1.29 mol scale.
[e] Resolution was carried out on 1.64 mol scale.
[f] After one recrystallization.
[g] Isolated yield (based on racemate).



Scheme 5. *Conditions*: (a): $ClRh(PPh_3)_3$, 5 mol%, Et_3N (1.5 equiv.), EtOH/THF (9:1), 60 psi H_2.

We also investigated carboxylate-directed hydrogenation of racemic indene acid (±)-**3a**. Using the same conditions, we obtained the corresponding racemic indane acid **4** in >99% de. Chemical resolution of racemic **4** with (*R*)-α-methyl benzylamine afforded the desired (*S*,*S*)-enantiomer in 96% ee and 25% yield (from racemate).[15]

While both routes produced the intermediate **4** in high ee, the former method is superior because it provides an opportunity to recycle the undesired enantiomer. For example, using a previously reported method,[21] enantiomerically enriched (*R*)-**3a** was readily converted to the racemate in 80% yield.

2.2.4. Esterification and selective de-methylation. With the enantiomerically pure indane acid precursor (*S*,*S*)-**4** in hand,[22] we are set to complete the synthesis of the target compound (*S*,*S*)-**1**. Esterification of the carboxyl group of (*S*,*S*)-**4** with iodomethane and sodium bicarbonate in DMF afforded the intermediate (*S*,*S*)-**5** with no loss of enantiomeric excess.[23] Selective removal of the arylmethyl ether[24] of (*S*,*S*)-**5** was achieved using ethanethiol in the presence of aluminum trichloride to afford the desired target, (*S*,*S*)-**1**, again with no loss of enantiomeric excess (Scheme 6).[23]

3. Conclusions

We have developed an efficient enantioselective synthesis of **1**, a novel indane acetic acid derivative. The key steps of the synthesis consist of a robust Reformatsky process for constructing the indene acetic acid framework followed by efficient chiral resolution and diastereoselective homogeneous hydrogenation.

4. Experimental

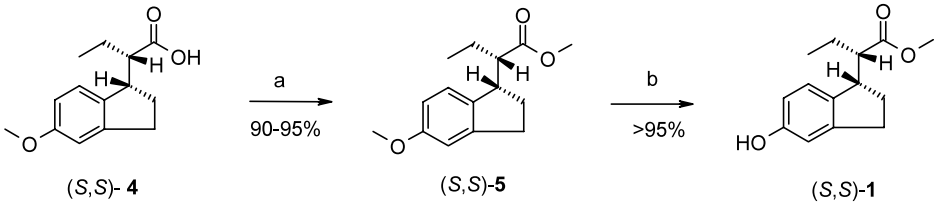
4.1. General

Starting materials **2**, as well as all other reagents used in this synthesis were purchased commercially and used without purification. Enantiomeric excess of intermediates (*R*)-**3a** and (*S*)-**3a**, and (*S*,*S*)-**4** was determined by chiral HPLC analysis using a Chiracel AD analytical column. NMR spectroscopic data were recorded on a Varian (300 MHz) NMR spectrometer. Coupling constants are reported in hertz (Hz). Optical rotation and IR measurements, and elemental analyses were performed by Robertson Microlit labs. Melting point was recorded on a Mel-Temp II uncorrected.

4.2. Synthesis of 2-(6-methoxy-1*H*-inden-3-yl)butanoic acid 3a

An oven dried, 5-L, four-necked, round-bottomed flask was fitted with a thermometer, a condenser, an addition funnel and a mechanic stirrer. Under argon protection, a suspension of 5-methoxy-1-indanone **2** (40.5 g, 250 mmol), zinc powder from Lancaster (28.1 g, 433 mmol) in 1.25 L of anhydrous THF was stirred at 60°C (internal temperature), while a solution of methyl 2-bromobutyrate (67.9 g, 375 mmol) in 250 mL of anhydrous THF was added slowly through an addition funnel. After completion of the addition, the reaction mixture was stirred at 60°C (internal temperature). The reaction was followed by TLC analysis of aliquots after 1N aqueous HCl work-up, which showed no reaction after 4 h.

A smaller batch [(indanone **2** (1.62 g, 10 mmol), Zn (1.13 g, 17.3 mmol), methyl 2-bromobutyrate (2.72 g, 15 mmol), THF (60 mL)] was then conducted which went to completion in 3 h. The reaction mixture (without workup) was then transferred to the larger batch mentioned above which caused its completion in 10 min at 60°C. After being cooled to room temperature, the bulk of the reaction mixture was transferred to a separate holding vessel for later on work up. The reaction flask was then recharged with 40 g of the indanone **2** and the appropriate amount of other reagents and re-heated to 60°C. The reaction went to completion in ca. 10 min after the addition. This step was repeated with 80g of **2**. The combined reaction mixture was cooled in an ice-water bath followed by slow addition of 3 L of 1N HCl solution. The pot temperature was kept below 15°C. The mixture was then extracted with ethyl acetate twice (4 and 2 L, respectively). The com-



Scheme 6. *Conditions*: (a) $NaHCO_3$, MeI, DMF, room temperature; (b) EtSH, $AlCl_3$, <10°C, CH_2Cl_2.

bined organic layer was washed with water until pH 6.0–7.0 (4×3L) and then dried over anhydrous Na_2SO_4. The methyl ester **3b** was obtained as a yellow oil (240 g, >99%) after solvent removal and drying under vacuum. The crude ester exhibited satisfactory ^1H and ^{13}C NMR spectra and was used directly for saponification: ^1H NMR (DMSO-d_6) δ 7.28 (d, $J=8.3$, 1H), 7.05 (d, $J=2.1$, 1H), 6.82 (dd, $J=8.3$, $J=2.5$, 1H), 6.22 (s, 1H), 3.72 (s, 3H), 3.60 (m, 1H), 3.58 (s, 3H), 3.28 (s, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 0.88 (t, $J=7.4$, 3H); ^{13}C NMR (DMSO-d_6) δ 173.52, 157.92, 146.30, 141.12, 137.09, 128.38, 120.15, 112.42, 110.90, 56.28, 52.74, 46.99, 38.51, 25.35, 13.43. HRMS (ES) m/z 247.1328 ([M+H]$^+$, calcd. for [$C_{15}H_{18}O_3$+H], 247.1329.

To a solution of the methyl ester **3b** (200.0 g, 813 mmol) in 2 L of methanol, was added a solution of potassium hydroxide (91.0 g, 1.63 mol) in 200 mL of water. The reaction mixture was stirred at 60°C (pot temperature) for 2 h. TLC analysis showed 70% conversion. Additional solution of potassium hydroxide (45.0 g, 0.81 mol) in 100 mL of water was then added slowly to the pot. The reaction was completed in an hour. After the reaction mixture was cooled to room temperature, solvents were removed in vacuo. The residue was dissolved in 3 L of water and washed with ethyl acetate (2×1 L). The aqueous layer was cooled in an ice-water bath and acidified with concentrated HCl to pH<3.0. The product was extracted into 3 L of CH_2Cl_2, washed with water (2×1 L), and dried over Na_2SO_4. The title compound (±)-**3a** was obtained as a light brown solid (175 g, 93%) after solvent removal and vacuum drying: ^1H NMR (DMSO-d_6) δ 12.30 (s, 1H), 7.30 (d, $J=8.4$, 1H), 7.06 (d, $J=2.3$, 1H), 6.82 (dd, $J=8.4$, $J=2.4$, 1H), 6.22 (s, 1H), 3.75 (s, 3H), 3.45 (t, $J=7.3$, 1H), 3.30 (s, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 0.90 (t, $J=7.3$, 3H); ^{13}C NMR (DMSO-d_6) δ 174.56, 157.83, 146.28, 141.70, 137.38, 127.99, 120.35, 112.35, 110.80, 56.29, 47.38, 38.48, 25.27, 13.61. HRMS (ES) m/z 231.1021 ([M−H]$^-$, calcd for [$C_{14}H_{16}O_3$−H], 231.1026.

4.3. Screening for enzymatic resolution conditions for the methyl ester (±)-3b

A ChiroScreen™-EH enzyme kit, purchased from Altus Biologics, Inc. (Cambridge, Massachusetts, USA) was used to identify a potential enzyme catalyst for the resolution of (±)-**3b**. The kit contained 30 enzyme samples (20 mg each) in reaction vials marked with Altus catalog number. Following instructions provided by the vendor, each reaction vial was added (±)-**3b** (20 mg), 2.0 mL of pH 7 phosphate buffer. Two drops of acetone were also added to increase substrate solubility. The vials were then stirred at room temperature overnight. About 50% conversion, as shown by TLC, was observed in vial #8 containing Mucor meihei lipase. The acid product was isolated and shown to be (*R*)-**3a** with 98% ee by chiral HPLC.[22]

4.4. Resolution to obtain (S)-3a

To a solution of (±)-**3a** (300 g, 1.29 mol) in 4.5 L of CH_3CN, was added quinine (324 g, 0.99 mol) at room temperature. The mixture became a solution after 1 h of stirring. A small amount of insoluble particles was removed by filtration through a microfiber filter under vacuum. The filtrate was then mechanically stirred under argon overnight. Analysis of a small sample of solid, taken after 24 h, showed 76.2% ee. Agitation was continued for two days prior to isolating the suspension by filtration. The filter cake was washed with CH_3CN (3×200 mL) and then dried under vacuum at 40°C for 3 h before it was re-dissolved in 4.5 L of CH_3CN at 70°C. The solution was cooled slowly under agitation to room temperature to effect crystallization. Stirring was continued for one day prior to isolating the suspension by filtration. The filter cake was washed with CH_3CN (3×250 mL) and then dried under vacuum at 40°C for 24 h to afford the quinine salt as a white solid (254.6 g, 35.4% yield). An analytical sample was obtained by a second recrystallization. ^1H NMR (DMSO-d_6) δ 8.66 (d, $J=4.4$, 1H), 7.90 (d, $J=9.3$, 1H), 7.50 (d, $J=4.5$, 1H), 7.48 (d, $J=2.7$, 1H), 7.37 (dd, $J=9.1$, $J=2.8$, 1H), 7.33 (d, $J=8.4$, 1H), 7.06 (d, $J=1.9$, 1H), 6.82 (dd, $J=8.5$, $J=2.7$, 1H), 6.21 (s, 1H), 5.83 (m, 1H), 5.32 (d, $J=6.4$, 1H), 5.00 (s, 1H), 4.94 (t, $J=8.6$, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.44 (t, $J=7.4$, 1H), 3.30 (m, 3H), 3.11 (q, $J=7.3$, 1H), 2.91 (m, 1H), 2.50 (m, 4H), 2.25 (m, 1H), 1.94 (m, 1H), 1.74 (m, 5H), 1.45 (m, 1H), 0.92 (t, $J=7.5$, 3H). ^{13}C NMR (DMSO-d_6) δ 175.28, 157.76, 157.29, 148.97, 147.85, 146.28, 144.27, 142.45, 142.36, 137.70, 131.67, 127.50, 127.33, 121.72, 120.48, 119.69, 115.04, 112.27, 110.74, 102.94, 70.91, 61.16, 56.66, 56.27, 48.23, 43.05, 38.46, 28.61, 28.06, 25.52, 24.16, 24.12, 13.81. IR (KBr): 3542, 3454, 2937, 1620, 1556, 1508, 1476, 1385, 1333, 1240 cm^{-1}. $[\alpha]_D^{20}=-64.4$ (c 1.02, CH_2Cl_2). Anal. calcd for $C_{34}H_{40}N_2O_5$: C, 73.36; H, 7.24; N, 5.03. Found: C, 73.24; H, 7.07; N, 4.84.

The quinine salt (544.3 g, 0.98 mol, combined from two lots) was dissolved in 4.0 L of CH_2Cl_2 to obtain a clear solution. It was stirred vigorously with 4.0 L of 2N HCl solution in a 22-L round-bottomed flask with a bottom valve. After 30 min, the biphasic mixture was allowed to settle. The bottom layer was separated and top aqueous layer was extracted with 1 L of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water (3×2.0 L) and then dried over Na_2SO_4. The intermediate (*S*)-**3a** was obtained as a thick orange oil after solvent removal and vacuum drying (230.8 g, 99% yield). Its ee was determined to be 96.8% by chiral HPLC.[22] Its spectroscopic characteristics match those of (±)-**3a**. $[\alpha]_D^{20}=+51.8$ (c 1.05, $CHCl_3$).

4.5. Synthesis of (2S)-2-[(1S)-5-methoxy-2,3-dihydro-1H-inden-1-yl]butanoic acid (S,S)-4

A solution of (*S*)-**3a** (105 g, 453 mmol), $ClRh(PPh_3)_3$ (21.0 g, 5% equiv.) and triethylamine (68.8 g, 679.5 mmol) in a mixture of EtOH (945 mL) and THF (105 mL) was shaken in a 2-L pressure bottle under hydrogen (60 psi) for 16 h. Volatile components were removed at reduced pressure. The residue was partitioned between 1N HCl (1.5 L) and CH_2Cl_2 (1.5 L). The organic layer was separated and the aqueous layer

was extracted with CH_2Cl_2 (2×250 mL). The combined CH_2Cl_2 layers were first washed with 1 L of 1N HCl and then stirred with 1 L of 1N NaOH solution. The biphasic mixture was allowed to settle. The aqueous layer was separated. The organic layer was extracted with 1N NaOH solution (2×0.5 L). The combined aqueous layers were washed with CH_2Cl_2 (2×250 mL) and acidified at <15°C to pH 2.0–3.0 by slowly adding concentrated HCl solution. The resultant mixture was extracted with CH_2Cl_2 (2×1.5 L), and the combined organic layers were washed with water (2×0.5 L), brine and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure to afford the title compound (*S*,*S*)-**4** as a light-yellow oil (101.0 g, 95% yield). Its ee was determined to be 96.8% by chiral HPLC.[22] It exhibited identical spectroscopic data to that of the racemate.[15] IR (thin film): 2963 (broad), 1704, 1607, 1492, 1462 cm^{-1}; $[\alpha]_D^{20}=+24.4$ (*c* 1.07, $CHCl_3$).

4.6. Synthesis of methyl (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoate (*S*,*S*)-5

A suspension of (*S*,*S*)-**4** (220.0 g, 0.94 mol), $NaHCO_3$ (237.0 g, 2.82 mol) and CH_3I (200 g, 1.41 mol) in 2.0 L of DMF was stirred under argon at room temperature for 18 h. ^1H NMR analysis showed 95% conversion. The reaction was complete after adding more CH_3I (100 g) and stirring for an additional 24 h. The reaction mixture was poured into 4.0 L of water and extracted with EtOAc (2×2 L). The combined organic layers were washed respectively with water (2×1 L), 1 M NaOH solution (1 L), again water (2×1 L), brine (500 mL) and dried over Na_2SO_4. Solvent removal and vacuum drying produced the title compound (*S*,*S*)-**5** as a light yellow oil (233 g, 99%):[23] IR (KBr): 2962, 1732 (C=O), 1492, 1461, 1434 cm^{-1}. ^1H NMR (DMSO-d_6) δ 6.90 (d, $J=8.4$, 1H), 6.78 (d, $J=2.6$, 1H), 6.66 (dd, $J=8.7$, $J=2.8$, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.20 (q, $J=6.3$, 1H), 2.80 (m, 2H), 2.40 (m, 1H), 2.08 (m, 1H), 1.80 (m, 1H), 1.58 (m, 1H), 1.40 (m, 1H), 0.80 (t, $J=7.4$, 3H). ^{13}C NMR (DMSO-d_6) δ 174.16, 157.71, 144.61, 135.50, 123.50, 111.59, 109.16, 54.93, 51.11, 50.76, 45.67, 30.95, 28.94, 22.28, 12.20. $[\alpha]_D^{20}=+29.3$ (*c* 1.01, $CHCl_3$). Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.76; H, 8.09.

4.7. Synthesis of methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]butanoate (*S*,*S*)-1

To a cold solution (<10°C) of (*S*,*S*)-**5** (233 g, 0.94 mol) in 2.5 L of CH_2Cl_2 was added slowly $AlCl_3$ (630 g, 4.7mol) under argon. Cooling was applied to keep pot temperature below 20°C. The reaction mixture turned purple. To the reaction was then added slowly EtSH (345 mL, 4.7mol) via an addition funnel while keeping the pot temperature below 15°C. After stirring for 2 h at 20°C, the reaction was complete by ^1H NMR analysis. The mixture was poured slowly into 2.5 L of ice-water with a strong agitation. The organic layer was separated and the aqueous layer was extracted with 1 L of CH_2Cl_2. The combined organic layers were washed with water to remove completely residual acid (4×1 L) and dried over Na_2SO_4. The title compound **1** was obtained as a white solid (216 g, 98%) after solvent removal and vacuum drying: mp 105.9–106.6°C.[23] IR (KBr): 3297 (br, OH), 2968, 1700 (C=O), 1617, 1585, 1494, 1463 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.10 (s, 1H), 6.78 (d, $J=8.2$, 1H), 6.58 (d, $J=2.3$, 1H), 6.50 (dd, $J=8.1$, $J=2.3$, 1H), 3.60 (s, 3H), 3.20 (q, $J=6.3$, 1H), 2.70 (m, 2H), 2.40 (m, 1H), 2.08 (m, 1H), 1.80 (m, 1H), 1.50 (m, 2H), 0.80 (t, $J=7.6$, 3H); ^{13}C NMR (DMSO-d_6) δ 174.22, 155.60, 144.40, 133.75, 123.41, 112.62, 110.66, 51.07, 50.92, 45.66, 30.83, 28.94, 22.29, 12.22. $[\alpha]_D^{20}=+29.3$ (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.52; H, 7.78.

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