

Enantioselective Electrochemical Lactonization Using Chiral Iodoarenes as Mediators

Wen-Chao Gao¹

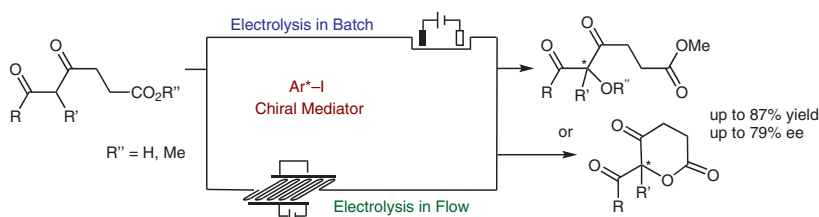
Zi-Yue Xiong

Shafiq Pirhaghani

Thomas Wirth* 

School of Chemistry, Cardiff University, Park Place, Cardiff,
CF10 3AT, UK
wirth@cf.ac.uk

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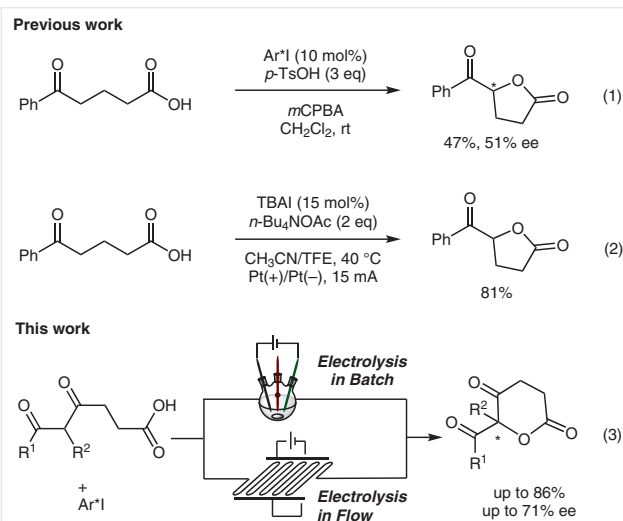
Abstract The enantioselective electrochemical lactonization of diketo acid derivatives using chiral iodoarenes as redox mediators is reported for the first time. Good to high stereoselectivities are observed in the lactonization and also in intermolecular α -alkoxylations of diketo ester derivatives. This enantioselective process was then adapted to an electrochemical flow microreactor where only small amounts of supporting electrolyte were necessary.

Key words electrolysis, flow microreactors, hypervalent iodine, lactonization, stereoselective synthesis

The utility of chiral hypervalent iodine compounds for enantioselective oxidative reactions represents an important and interesting area in organic chemistry.² Specifically, as a versatile and general oxidation system, the combination of *m*CPBA as the stoichiometric oxidant and chiral iodoarenes as catalysts has been successfully applied to various transformations, including the asymmetric difunctionalization of alkenes,³ the stereoselective dearomatization of phenol or naphthol derivatives,⁴ enantioselective oxidative rearrangement⁵ and the enantioselective synthesis of spirooxindole derivatives.⁶ Nevertheless, although enantioselective oxidative lactonization has been well developed via the dearomatization of phenol or naphthol derivatives using chiral iodoarenes in combination with *m*CPBA, direct lactone synthesis through oxidative cyclization of keto acids is underdeveloped, and only moderate enantioselectivities (<51% ee) were achieved (Scheme 1, eq. 1).⁷

As an efficient and environmentally friendly protocol for organic synthesis, electrochemical conversions have recently gained more attention as often an excess amount of conventional chemical oxidants and reducing reagents can be avoided.⁸ Although the electrochemical oxidative α -lac-

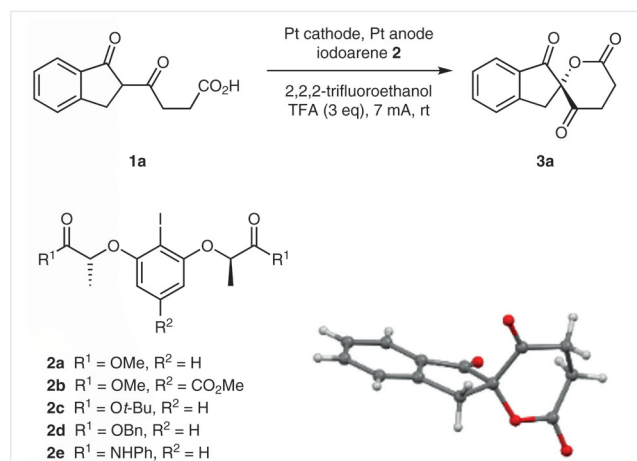
tonization of γ -keto acids has been reported using *n*-Bu₄NI as the mediator (Scheme 1, eq. 2),⁹ the enantioselective electrosynthesis of lactones is still unexplored.¹⁰ In organic electrochemistry, iodoarenes represent a versatile class of redox mediators, which can generate hypervalent iodine(III) reagents via anodic oxidation to accomplish various transformations without use of a stoichiometric oxidant such as *m*CPBA. The first electrolysis of iodoarenes described the synthesis of (difluoroiodo)benzene, by Schmidt and Meinert in 1960,¹¹ and subsequently Fuchigami has contributed to the development of different fluorination reactions in electrochemistry.¹² Recently, the anodic oxidation of iodoarenes in trifluoroethanol and hexafluoroisopropanol (HFIP) has been reported by Nishiyama and Francke and their co-workers, who accomplished C–N and C–O bond formations.¹³ Some reviews in this area have recently been published.¹⁴



Scheme 1 Different methods for oxidative lactonization

The anodic oxidation of chiral iodoarenes and subsequent enantioselective synthesis has never been reported, although there are many reported works on stereoselective oxidative functionalizations using hypervalent iodine reagents.¹⁵ Herein, we report the enantioselective electrochemical α -lactonization and α -alkoxylation of diketo acid derivatives with chiral iodoarenes as electron-transfer mediators.¹⁶ These asymmetric reactions have been performed in batch chemistry but can also proceed using an electrochemical flow reactor¹⁷ with lower amounts of electrolyte (Scheme 1, eq. 3).

Initial reactions were performed using diketo acid **1a** as a model substrate for the enantioselective lactonization with chiral iodoarene **2b** as redox mediator, and platinum as anode and cathode material, under galvanostatic conditions at 7 mA (Scheme 2). Since fluorinated solvents are known to stabilize iodine(III) reagents by the anodic oxidation of iodoarenes,¹⁴ 2,2,2-trifluoroethanol (TFE) was initially chosen as the solvent.



Scheme 2 Sample reaction for the development of electrochemical reaction conditions and X-ray structure of (S)-**3a**

Several commonly used electrolytes were investigated in the electrochemical reaction shown in Scheme 2 (Table 1, entries 1–3); the use of $n\text{-Bu}_4\text{NBF}_4$ as the electrolyte gave lactone **3a** in good yield (70%) and enantioselectivity (71% ee) (entry 3). Although the reaction does proceed in the absence of trifluoroacetic acid (TFA), both the efficiency and enantioselectivity were decreased (Table 1, entry 4). For this electrochemical process, the solvent HFIP is not a good choice and only results in moderate yield and lower enantioselectivity (Table 1, entry 5); no product was detected using acetonitrile as the solvent. There is also no product formed in the absence of either electrolyte or chiral iodoarene, and with catalytic amounts of **2b** only traces of the product were observed (Table 1, entries 6–8). A decrease in the reaction temperature to -10°C did not improve the enantioselectivity, but only resulted in a lower yield of **3a** (Table 1, entry 9).

Table 1 Enantioselective Electrochemical Lactonization of **1a** to **3a** Using Chiral Iodoarenes^a

Entry	Electrolyte	3a	
		Yield (%)	ee ^b (%)
1	2b (1.2 eq), LiClO_4	30	67
2	2b (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NClO}_4$	61	65
3	2b (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$	70	71
4	2b (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$, no TFA added	51	61
5	2b (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$, HFIP instead of TFE	50	29
6	2b (1.2 eq)	0	–
7	no iodoarene, 0.05 M LiClO_4	0	–
8	2b (0.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$	<5	–
9 ^c	2b (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$	41	70
10	2a (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$	54	67
11	2c (1.2 eq), 0.05 M $n\text{-Bu}_4\text{NBF}_4$	15	68

^a Reaction conditions: Pt cathode, Pt anode, **1a** (0.025 M), **2** (0.03 M), electrolyte (0.05 M), TFA (0.075 M), solvent (4 mL), undivided cell (charge passed: 2.6 F).

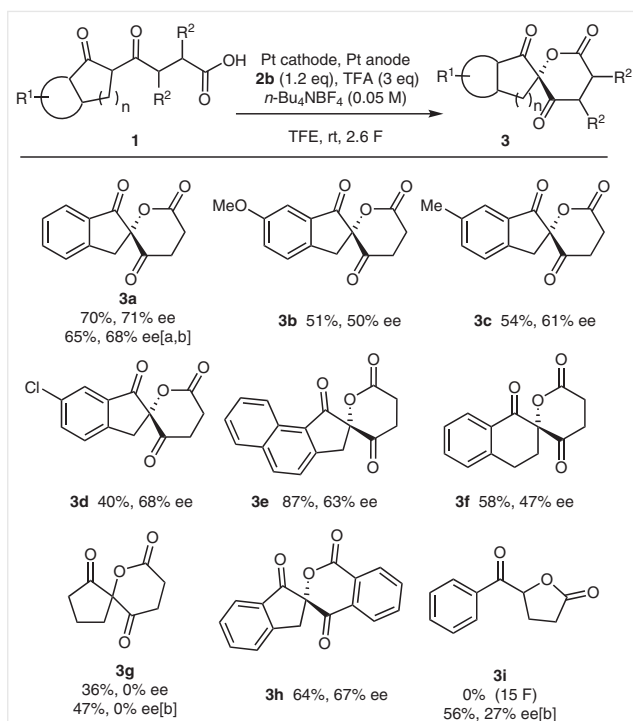
^b Determined by HPLC.

^c The reaction was performed at -10°C .

The absolute configuration of the major isomer of **3a** was shown to be (S) via X-ray crystallographic analysis (Scheme 2).¹⁸ Other lactate-based 2-iodoresorcinol derivatives were also employed as potential electron-transfer mediators, including iodoarenes that have previously found applications in the enantioselective oxidative dearomatization of naphthols.⁴ Neither **2a** nor **2c** gave better results than **2b** (Table 1, entries 10 and 11) while the chiral iodoarenes **2d** and **2e** containing benzyl ester and amide functionalities decomposed after several minutes under the electrochemical reaction conditions.¹⁹

To explore the generality and the substrate scope of this electrochemical reaction, some diketo acid derivatives **1** were subjected to the electrolysis conditions (Scheme 3). The electrolysis of substrates bearing electron-rich or -poor groups on the indanone moiety gave the corresponding lactones **3b–3d** in moderate yields with reasonable enantioselectivities. For the naphthyl-substituted substrate **1e**, the reaction proceeded in high yield leading to the product **3e** in 63% ee. Also, tetralone derivatives such as **1f** led to the cyclized product **3f** in 58% yield and 47% ee, while lactone **3g** without an aryl moiety was only formed in 36% yield as a racemate.

When the carbonyl group and carboxylic acid were both fixed to an aromatic ring as **3h**, the reaction proceeded well with good selectivity. Unfortunately, the attempted cyclization of the monocarbonyl substrate 5-oxo-5-phenylpentanoic acid (**1i**) failed to give any desired product **3i**, which was previously reported in high yield under electrochemical conditions with $n\text{-Bu}_4\text{NI}$ as the mediator.⁹

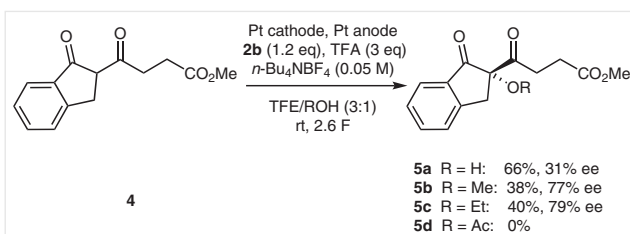


Scheme 3 Scope and limitations for enantioselective electrochemical spirolactonization using **2b**. *Reagents and conditions:* Pt cathode, Pt anode, **1** (0.025 M), **2b** (0.03 M), $n\text{-Bu}_4\text{NBF}_4$ (0.05 M), TFA (0.075 M), TFE (4 mL), undivided cell (charge passed: 2.6 F). [a] Current efficiency: 54%. [b] *Reagents and conditions:* $m\text{CPBA}$ (1.5 eq), **2b** (15 mol%), TFA (3 eq), TFE (2 mL), rt, 24 h.

It has been reported that oxidative lactonization can be achieved with a combination of chiral iodoarenes and $m\text{CPBA}$ as stoichiometric oxidant.⁷ Therefore, the combination of **2b** and $m\text{CPBA}$ was compared to the electrochemical reaction conditions, leading to products **3a**, **3g** and **3i**. Compounds **3a** and **3g** were obtained with similar yields and selectivities, while **3i** could be isolated in moderate yield and low enantioselectivity only using the combination of **2b** and $m\text{CPBA}$ (Scheme 3).

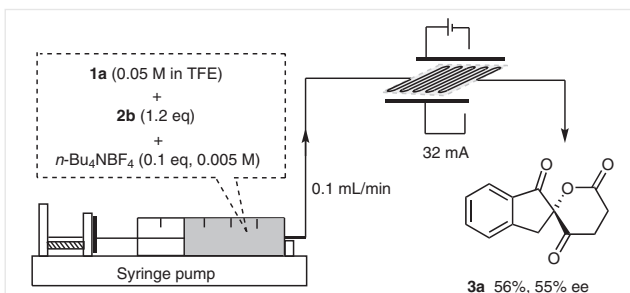
With chiral iodoarene **2b**, intermolecular C–O bond functionalization was also investigated using ester **4** as a substrate under the standard electrochemical conditions (Scheme 4). Protic solvents such as water, alcohols and acetic acid were chosen, together with TFE, due to their conductivity and nucleophilicity.

Pleasingly, the electrochemical reaction of ester **4** in a mixture of TFE/ H_2O (3:1) with **2b** as the chiral mediator gave the desired α -hydroxy product **5a** in moderate yield with 31% ee. Although the reaction efficiency was reduced in solvent mixtures of TFE with methanol or ethanol, high enantioselectivities (up to 79% ee) were observed (**5b** and **5c**). However, when the electrolysis was attempted in the solvent TFE/ AcOH (3:1), the desired α -acetoxy product **5d** was not detected. The absolute configuration of compounds **5** was assigned by analogy to compound **3a**.



Scheme 4 Intermolecular enantioselective electrosynthesis. *Reagents and conditions:* Pt cathode, Pt anode, **4** (0.1 mmol), **2b** (0.12 mmol), $n\text{-Bu}_4\text{NBF}_4$ (0.05 M), TFA (0.075 M), TFE/ROH (3:1 v/v, 4 mL), undivided cell (charge passed: 2.6 F).

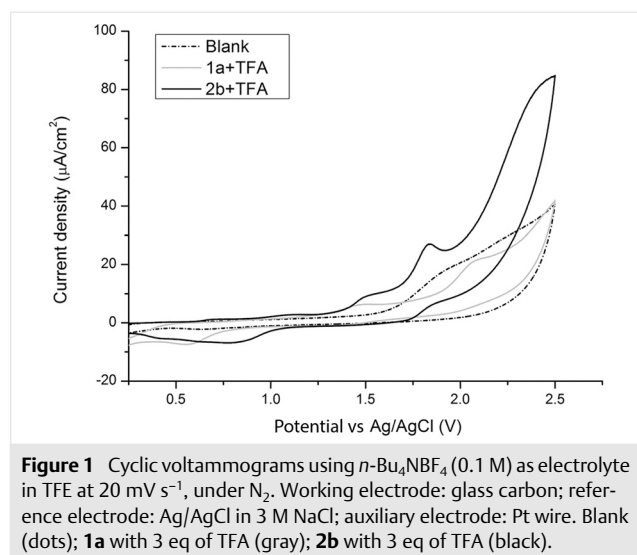
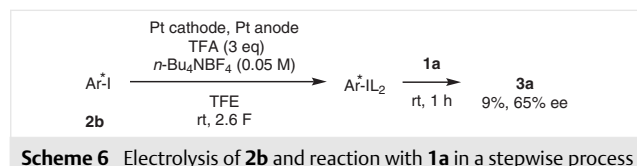
Compared with batch processes for electrochemical reactions, continuous flow reactors can reduce the amount or avoid the use of electrolytes because of the close distance of the electrodes.²⁰ We have reported electrochemical flow microreactors for several oxidative transformations.¹⁷ Pleasingly, the present enantioselective lactonization could also be successfully accomplished using an electrochemical flow microreactor with a lower concentration of $n\text{-Bu}_4\text{NBF}_4$ (5 mM) (Scheme 5), despite a slight decrease in the efficiency and enantioselectivity. There is no conversion without catalytic amounts of electrolyte and the conversion decreases when the platinum cathode is replaced by graphite. To the best of our knowledge, this is the first enantioselective reaction with iodine(III) reagents generated in an electrochemical flow microreactor.



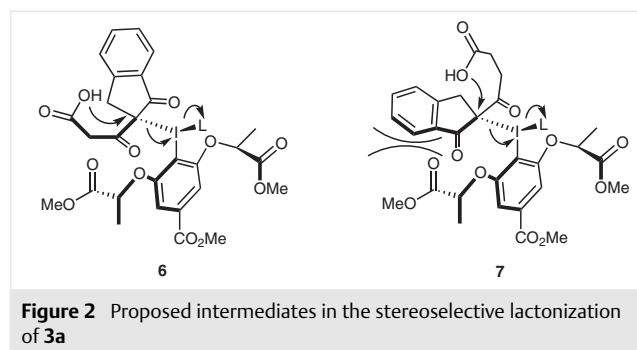
Scheme 5 Enantioselective electrochemical lactonization of **1a** to **3a** in a flow microreactor

Additional experiments were carried out to further explore the mechanism of this enantioselective electrolytic lactonization. Initially, a stepwise batch process was performed. After the anodic oxidation of mediator **2b**, substrate **1a** was added to the reaction mixture. However, this stepwise protocol only led to the desired product **3a** in 9% yield (65% ee) (Scheme 6). In the ^1H NMR spectra of the electrolyzed **2b** in TFE, a downfield peak at around 7.24 ppm was observed indicating the formation of an iodine(III) species, but this peak disappeared after several hours or after removal of the solvent (see the Supporting Information). This indicates the formation of an unstable iodine(III) species $\text{Ar}^*\text{-IL}_2$ by electrolysis of iodoarene **2b**. In addition, cy-

cyclic voltammetry in TFE showed a lower potential (1.83 V, vs Ag/AgCl) for **2b** than for **1a** (2.07 V, vs Ag/AgCl) indicating that **2b** is easier oxidized than **1a** in the one-pot electrolysis (Figure 1).^{8c}



Based on the investigations from Muñiz, Ishihara and co-workers,^{3e} two structures for a possible explanation of the observed stereoselectivities are shown in Figure 2. These structures show the intermediates after the reaction of the substrate enolates with the iodine(III) reagent. Due to the steric hindrance between the indanone moiety and the lactate ester, intramolecular cyclization favorably proceeds through intermediate **6** rather than through intermediate **7**.



In summary, we have developed an electrochemical method for enantioselective lactonization using chiral lactate-based iodoarenes as redox mediators. This protocol was also applied to the intermolecular α -alkoxylation of diketo esters with good enantioselectivities. Furthermore, it was demonstrated that this enantioselective transformation could be adapted to an electrochemical flow microreactor with lower supporting electrolyte concentration. Further studies on stereoselective electrosynthesis using chiral iodoarenes are currently in progress.

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. All commercial reagents were used as received. ¹H NMR spectra were recorded at 400 or 500 MHz on Bruker DPX 400 or DPX 500 spectrometers. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS (δ 0.00). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). ¹³C NMR spectra were recorded at 100 or 125 MHz. Mass spectra were obtained using a Waters Xevo G2-S ESI mass spectrometers. IR spectra were recorded as neat on a Shimadzu FTIR Affinity-1S spectrophotometer. Melting points were determined using a Gallenkamp hot-stage apparatus and are uncorrected. Optical rotations were measured using a 10.0 mL cell with a 1.0 dm path length on a SCHMIDT + HAENSCH UniPol L polarimeter apparatus and are reported as $[\alpha]$ (c in g per 100 mL, solvent) at 20 °C.

Methyl 4-Oxo-4-(1-oxo-2,3-dihydro-1H-inden-2-yl)butanoate (**4**)

To a solution of diisopropylamine (1.6 g, 15.8 mmol) in THF (40 mL) was added 2.5 M *n*-BuLi in hexane (6.9 mL, 17.4 mmol) at -78 °C. The resulting solution was stirred at -78 °C for 30 min and then at room temperature for an additional 30 min. The solution was cooled to -78 °C, and to this solution was added dropwise a solution of 1-indanone (1 g, 8 mmol) in THF (10 mL). After 1 h at -78 °C, to the solution was added dropwise methyl-4-chloro-4-oxobutanoate (1.36 mL, 11 mmol) in THF (5 mL). The resulting solution was warmed to room temperature over 2 h, and then quenched with saturated NH₄Cl solution. The organic phase was separated, and the water phase was extracted with Et₂O (3 $\times$ 20 mL). The combined organic layers were dried, concentrated and purified by chromatography (petroleum ether/EtOAc, 5:1) to give **4** as a colorless solid; yield: 1.01 g (51%); mp 57–59 °C.

IR (neat): 3025, 1734, 1628, 1545, 1221, 1167, 1038, 779, 731 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.78 (d, *J* = 8.0 Hz, 1 H), 7.55–7.48 (m, 2 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 3.70 (s, 3 H), 3.64 (s, 2 H), 2.82 (t, *J* = 6.0 Hz, 2 H), 2.75 (t, *J* = 6.0 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 187.5, 182.4, 173.0, 146.8, 137.7, 132.4, 127.3, 125.6, 122.8, 110.6, 51.9, 30.5, 30.4, 28.9.

HRMS (ESI): *m/z* calcd for C₁₄H₁₅O₄ [M + H]⁺: 247.0965; found: 247.0968.

4-Oxo-4-(1-oxo-2,3-dihydro-1H-inden-2-yl)butanoic Acid (**1a**)

Compound **4** (1.2 g, 5 mmol) was dissolved in THF/MeOH/water (3:1:1 v/v/v, 20 mL). To this mixture 1 M LiOH in water (10 mL) was added and the resulting solution stirred overnight. After removal of organic solvent in vacuo, the aqueous phase was acidified with HCl until pH 3. The mixture was extracted with EtOAc (3 $\times$ 20 mL). The combined organic fractions were dried with sodium sulfate and con-

centrated in vacuo to give the crude acid **1a**, which was recrystallized from EtOAc to give **1a** as a white solid; yield: 1.03 g (89%); mp 119–121 °C.

IR (neat): 3025, 1699, 1624, 1549, 1404, 1067, 972, 775 cm⁻¹.

¹H NMR (500 MHz, CD₃OD): δ (two isomers) = 7.70 (d, *J* = 7.5 Hz, 0.77 H) (major), 7.68–7.60 (m, 1 H), 7.57–7.52 (m, 2 H), 7.44–7.35 (m, 1.23 H), 3.66 (s, 1.54 H) (major), 3.60 (d, *J* = 16.5 Hz, 0.46 H), 3.28–3.25 (m, 0.23 H), 3.19 (d, *J* = 16.5 Hz, 0.46 H), 2.98–2.90 (m, 0.46 H), 2.83 (t, *J* = 6.5 Hz, 1.54 H) (major), 2.70 (t, *J* = 6.5 Hz, 1.63 H) (major), 2.63–2.50 (m, 0.77 H).

¹³C NMR (125 MHz, CD₃OD): δ = 204.4, 202.1, 176.3, 156.2, 148.7, 139.1, 136.8, 136.5, 133.7, 128.9, 128.5, 128.0, 127.0, 125.3, 123.6, 112.3, 38.6, 31.6, 31.5, 29.9, 29.3, 28.8.

HRMS (ESI): *m/z* calcd for C₁₃H₁₁O₄ [M – H]⁻: 231.0663; found: 231.0665.

4-(6-Methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)-4-oxobutanoic Acid (**1b**)

Yield: 406 mg (31%); white solid; mp 132–134 °C.

IR (neat): 3003, 1718, 1647, 1576, 1492, 1375, 1024, 877, 786 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ (two isomers) = 12.2 (br s, 1 H), 7.52 (d, *J* = 8.4 Hz, 0.40 H), 7.48 (d, *J* = 8.4 Hz, 0.60 H) (major), 7.29 (dd, *J* = 8.4, 2.8 Hz, 0.40 H), 7.25–7.20 (m, 0.60 H) (major), 7.15 (dd, *J* = 8.4, 2.8 Hz, 0.60 H) (major), 7.09 (d, *J* = 2.8 Hz, 0.40 H), 4.25 (dd, *J* = 8.0, 2.8 Hz, 0.60 H) (major), 3.81 (s, 2 H), 3.79 (s, 1 H), 3.56 (br s, 1.40 H), 3.37 (dd, *J* = 13.2, 2.8 Hz, 0.60 H) (major), 3.20–3.07 (m, 1 H), 2.92–2.80 (m, 1.60 H) (major), 2.56 (t, *J* = 2.8 Hz, 1.40 H), 2.43 (t, *J* = 6.8 Hz, 0.60 H) (major).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 202.8, 199.8, 173.7, 173.6, 159.2, 158.9, 147.0, 136.1, 127.7, 126.6, 124.3, 119.6, 112.5, 105.4, 105.1, 61.4, 55.6, 55.4, 37.1, 31.6, 30.1, 28.4, 27.6, 27.4.

HRMS (ESI): *m/z* calcd for C₁₄H₁₃O₅ [M – H]⁻: 261.0768; found: 261.0770.

4-(6-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl)-4-oxobutanoic Acid (**1c**)

Yield: 677 mg (55%); white solid; mp 138–140 °C.

IR (neat): 2950, 1703, 1614, 1544, 1207, 1165, 1111, 1031 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ (two isomers) = 12.1 (br s, 1 H), 7.57–7.37 (m, 3 H), 4.23 (dd, *J* = 8.0, 3.2 Hz, 0.40 H), 3.60 (s, 1.3 H) (major), 3.43 (dd, *J* = 17.6, 3.2 Hz, 0.40 H), 3.24–3.10 (m, 1 H), 2.95–2.75 (m, 1.60 H) (major), 2.57 (t, *J* = 6.4 Hz, 1.40 H), 2.44 (t, *J* = 6.4 Hz, 1 H), 2.39 (m, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 202.9, 199.9, 173.7, 173.6, 151.7, 137.3, 136.6, 135.0, 126.5, 125.5, 123.6, 122.0, 61.0, 37.1, 31.5, 30.4, 27.7, 27.6, 20.9, 20.5.

HRMS (ESI): *m/z* calcd for C₁₄H₁₃O₄ [M – H]⁻: 245.0819; found: 245.0822.

4-(6-Chloro-1-oxo-2,3-dihydro-1*H*-inden-2-yl)-4-oxobutanoic Acid (**1d**)

Yield: 373 mg (28%); white solid; mp 134–136 °C.

IR (neat): 2950, 1701, 1626, 1541, 1217, 1078, 813, 748 cm⁻¹.

¹H NMR (500 MHz, CD₃OD): δ (two isomers) = 7.70–7.63 (m, 3 H), 3.67 (s, 1.50 H) (major), 3.60 (d, *J* = 18.0 Hz, 0.30 H), 3.30–3.24 (m, 0.30 H), 3.18 (d, *J* = 18 Hz, 0.30 H), 3.00–2.90 (m, 0.30 H), 2.90–2.82 (m, 1.50 H) (major), 2.71 (t, *J* = 7.0 Hz, 1.50 H) (major), 2.60–2.54 (m, 0.30 H).

¹³C NMR (125 MHz, CD₃OD): δ = 203.9, 200.7, 176.4, 176.3, 154.4, 146.4, 140.8, 138.2, 136.5, 134.7, 133.2, 129.5, 128.4, 124.7, 123.1, 113.3, 38.5, 32.3, 31.6, 29.7, 28.9, 28.8.

HRMS (ESI): *m/z* calcd for C₁₃H₁₀ClO₄ [M – H]⁻: 265.0273, 267.0243; found: 265.0273, 267.0244.

4-Oxo-4-(1-oxo-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-2-yl)butanoic Acid (**1e**)

Yield: 1.01 g (71%); white solid; mp 164–166 °C.

IR (neat): 3010, 1710, 1591, 1541, 1340, 1219, 1062, 870, 783 cm⁻¹.

¹H NMR (500 MHz, DMSO-*d*₆): δ (two isomers) = 12.2 (br s, 1 H), 8.97 (d, *J* = 8.5 Hz, 0.45 H), 8.92 (d, *J* = 8.5 Hz, 0.55 H) (major), 8.27 (d, *J* = 7.0 Hz, 0.55 H) (major), 8.20 (d, *J* = 7.5 Hz, 0.45 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.77–7.67 (m, 2 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 4.34 (tt, *J* = 7.5, 2.5 Hz, 0.45 H), 3.59–3.52 (m, 0.55 H) (major), 3.35–3.16 (m, 1.45 H), 3.00–2.90 (m, 0.55 H) (major), 2.78 (t, *J* = 7.5 Hz, 1 H), 2.48–2.44 (m, 2 H).

¹³C NMR (125 MHz, DMSO-*d*₆): δ = 203.1, 200.4, 190.6, 173.5, 173.4, 158.4, 149.7, 136.5, 133.8, 132.3, 131.2, 128.7, 128.2, 126.5, 124.3, 123.8, 123.2, 122.7, 111.0, 61.1, 37.1, 30.3, 29.6, 29.0, 28.6, 27.6.

HRMS (ESI): *m/z* calcd for C₁₇H₁₃O₄ [M – H]⁻: 281.0819; found: 281.0820.

4-Oxo-4-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)butanoic Acid (**1f**)

Yield: 627 mg (51%); white solid; mp 102–104 °C.

IR (neat): 2934, 1697, 1614, 1558, 1410, 1153, 935, 781, 737 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ (two isomers) = 8.02 (dd, *J* = 8.0, 1.0 Hz, 0.10 H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 0.90 H) (major), 7.49 (td, *J* = 9.0, 1.5 Hz, 0.10 H), 7.38 (td, *J* = 7.5, 1.5 Hz, 0.90 H) (major), 7.34–7.28 (m, 1 H), 7.25 (d, *J* = 7.5 Hz, 0.10 H), 7.19 (d, *J* = 7.5 Hz, 0.90 H) (major), 2.92–2.84 (m, 4 H), 2.75 (t, *J* = 6.5 Hz, 2 H), 2.67–2.62 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 197.4, 178.3, 173.0, 140.3, 131.7, 130.4, 127.5, 126.8, 125.6, 105.5, 31.9, 28.2, 28.0, 21.8.

HRMS (ESI): *m/z* calcd for C₁₄H₁₃O₄ [M – H]⁻: 245.0819; found: 245.0821.

2-(1-Oxo-2,3-dihydro-1*H*-inden-2-ylcarbonyl)benzoic Acid (**1h**)

Yield: 1.08 g (77%); white solid; mp 142–144 °C.

IR (neat): 2893, 1699, 1647, 1568, 1361, 1205, 1091, 999, 849, 781 cm⁻¹.

¹H NMR (500 MHz, CD₃OD): δ (two isomers) = 8.00 (dd, *J* = 7.5, 1.0 Hz, 0.5 H), 7.82 (br s, 0.5 H), 7.76 (d, *J* = 8.0 Hz, 0.55 H) (major), 7.74–7.52 (m, 5 H), 7.48 (d, *J* = 7.5 Hz, 0.55 H) (major), 7.43 (t, *J* = 7.5 Hz, 0.55 H) (major), 7.36 (t, *J* = 8.0 Hz, 0.55 H) (major), 3.46–3.15 (m, 2 H).

¹³C NMR (125 MHz, CD₃OD): δ = 189.7, 169.8, 155.4, 139.1, 138.7, 136.7, 134.0, 133.4, 131.1, 129.8, 128.6, 127.9, 127.0, 124.8, 123.7, 112.8, 32.4, 30.5.

HRMS (ESI): *m/z* calcd for C₁₇H₁₁O₄ [M – H]⁻: 279.0663; found: 279.0665.

4-Oxo-4-(2-oxocyclopentyl)butanoic Acid (**1g**)

A mixture of cyclopentanone (2.6 mL, 30 mmol) and pyrrolidine (3.0 mL, 36 mmol) in benzene (12 mL) was refluxed using a Dean–Stark apparatus overnight. The solvents and excess pyrrolidine were removed in vacuo. The crude enamine and dry triethylamine (4.6 mL, 33 mmol) were dissolved in benzene (10 mL), and to this solution was added dropwise methyl-4-chloro-4-oxobutyrate (3 mL, 33 mmol). The reaction mixture was then heated at reflux for 8 h, cooled to room temperature and filtered through Celite. The filtrate was concentrated in vacuo to give the acylated enamine which was used without further purification. The acylated enamine was dissolved in water (7.5 mL), acetic acid (7.5 mL) and THF (15 mL), and the resultant dark-brown solution stirred at room temperature for 24 h. The reaction mixture was then added to water (20 mL) and chloroform (50 mL), the phases were separated, and the aqueous phase was extracted with chloroform. The combined organic extracts were dried, the solvent was removed and the remainder was purified by chromatography using petroleum ether/ethyl acetate 4:1 as eluent to give **1g** as a yellow oil; yield: 2.85 g (48%).

IR (neat): 2981, 2864, 1697, 1631, 1589, 1240, 928 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ (two isomers) = 3.40 (t, *J* = 8.0 Hz, 1 H), 3.18 (dd, *J* = 7.0, 5.5 Hz, 0.44 H), 3.14 (dd, *J* = 7.0, 5.5 Hz, 0.55 H) (major), 2.84–2.75 (m, 1 H), 2.73–2.65 (m, 2.7 H) (major), 2.63–2.54 (m, 4 H), 2.50–2.39 (m, 2.7 H) (major), 2.37–2.20 (m, 2.44 H), 2.12–2.00 (m, 2 H), 1.96–1.80 (m, 2.55 H) (major).

¹³C NMR (125 MHz, CDCl₃): δ = 212.8, 202.5, 199.5, 181.5, 178.0, 109.8, 61.9, 38.7, 37.2, 35.8, 30.1, 28.6, 27.7, 25.8, 25.1, 20.7, 20.1.

HRMS (ESI): *m/z* calcd for C₉H₁₁O₄ [*M* – H][–]: 183.0663; found: 183.0666.

Dimethyl (2*R*,2'*R*)-2,2'-(2-Iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy)dipropionate (**2b**)

Diisopropyl azodicarboxylate (10 mL, 50 mmol, 2.5 eq) was added dropwise via syringe over 30 min to a stirred suspension of methyl 3,5-dihydroxy-4-iodobenzoate (5.9 g, 20.0 mmol), triphenylphosphine (13 g, 50 mmol, 2.5 eq) and methyl (S)–(–)-lactate (4.85 mL, 50 mmol, 2.5 eq) in THF (100 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The resultant residue was purified by column chromatography (petroleum ether/EtOAc, 3:1) to give **2b** as a white solid; yield: 6.62 g (71%); mp 92–94 °C.

[α]_D²⁰ +11 (c 0.73, CHCl₃).

IR (neat): 2949, 1743, 1712, 1573, 1417, 1240, 1132, 1072, 1008, 966, 854 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.01 (s, 2 H), 4.88 (q, *J* = 7.0 Hz, 2 H), 3.88 (s, 3 H), 3.76 (s, 6 H), 1.71 (d, *J* = 7.0 Hz, 6 H).

¹³C NMR (125 MHz, CDCl₃): δ = 171.6, 166.1, 158.2, 131.7, 107.2, 87.3, 74.1, 55.4, 18.5.

HRMS (ESI): *m/z* calcd for C₁₆H₂₀IO₈ [*M* + H]⁺: 467.0197; found: 467.0194.

(S)-4',5'-Dihydrospiro[indene-2,2'-pyran]-1,3',6'(3H)-trione (**3a**); Typical Procedure for the Electrochemical Lactonization of **1**

A 10-mL three-necked round-bottomed flask was equipped with a magnetic stirrer, and platinum plate (1 cm²) electrode as the working electrode and counter electrode. The substrate **1a** (23 mg, 0.1 mmol), chiral iodobenzene **2b** (56 mg, 0.12 mmol), TFA (34 mg, 0.3 mmol) and supporting electrolyte *n*-Bu₄NBF₄ (66 mg, 0.2 mmol) were added

to the solvent TFE (4 mL). The resulting mixture was stirred and electrolyzed under galvanostatic conditions (7 mA/cm²) at room temperature for 1 h. The solvent was removed in vacuo and the residue purified by column chromatography (petroleum ether/EtOAc, 3:1) to give **3a** as a white solid; yield: 16 mg (70%); mp 162–164 °C; 71% ee (determined by HPLC).

[α]_D²⁰ +27 (c 0.4, CHCl₃).

IR (neat): 2922, 1749, 1707, 1606, 1411, 1271, 1215, 1090, 972, 768 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.75 (d, *J* = 7.5 Hz, 1 H), 7.70 (t, *J* = 6.0 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 7.0 Hz, 1 H), 3.77 (d, *J* = 17.0 Hz, 1 H), 3.73–3.63 (m, 1 H), 3.32 (d, *J* = 17.0 Hz, 1 H), 3.01 (dt, *J* = 17.5, 4.0 Hz, 1 H), 2.83 (dt, *J* = 10.0, 2.5 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 201.8, 197.3, 169.0, 151.9, 137.0, 132.4, 128.6, 126.2, 125.7, 92.7, 38.6, 33.4, 27.1.

HRMS (ESI): *m/z* calcd for C₁₃H₁₁O₄ [*M* + H]⁺: 231.0652; found: 231.0653.

HPLC (YMC Chiral Amylose-C S-5 μm (25 cm), hexane/*i*-PrOH, 90:10, 0.8 mL/min, 20 °C, 254 nm): *t*_R (minor) = 34.5 min, *t*_R (major) = 39.8 min.

(S)-6-Methoxy-4',5'-dihydrospiro[indene-2,2'-pyran]-1,3',6'(3H)-trione (**3b**)

Yield: 13 mg (51%); white solid; mp 109–111 °C; 50% ee (determined by HPLC).

[α]_D²⁰ +30 (c 0.28, CHCl₃).

IR (neat): 1743, 1734, 1701, 1275, 1028, 983, 748 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.39 (d, *J* = 8.5 Hz, 1 H), 7.29 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.13 (d, *J* = 3.0 Hz, 1 H), 3.83 (s, 3 H), 3.71–3.61 (m, 2 H), 3.23 (d, *J* = 16.5 Hz, 1 H), 3.03–2.96 (m, 1 H), 2.85–2.81 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 201.8, 197.2, 169.0, 160.1, 145.0, 133.5, 126.9, 126.5, 106.5, 93.3, 55.7, 38.3, 33.4, 27.1.

HRMS (ESI): *m/z* calcd for C₁₄H₁₃O₅ [*M* + H]⁺: 261.0757; found: 261.0761.

HPLC (YMC Chiral Amylose-C S-5 μm (25 cm), hexane/*i*-PrOH, 90:10, 0.8 mL/min, 10 °C, 254 nm): *t*_R (minor) = 65.4 min, *t*_R (major) = 70.4 min.

(S)-6-Methyl-4',5'-dihydrospiro[indene-2,2'-pyran]-1,3',6'(3H)-trione (**3c**)

Yield: 13 mg (54%); white solid; mp 166–168 °C; 61% ee (determined by HPLC).

[α]_D²⁰ +18 (c 0.21, CHCl₃).

IR (neat): 2924, 1701, 1616, 1575, 1494, 1220, 1097, 831, 748 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.54 (s, 1 H), 7.52 (d, *J* = 7.5 Hz, 1 H), 7.39 (d, *J* = 7.5 Hz, 1 H), 3.74–3.64 (m, 2 H), 3.25 (d, *J* = 16.5 Hz, 1 H), 3.03–2.96 (m, 1 H), 2.85–2.80 (m, 2 H), 2.41 (s, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 201.9, 197.3, 169.1, 149.4, 138.8, 138.3, 132.6, 125.9, 125.5, 93.1, 38.6, 33.4, 27.1, 21.1.

HRMS (ESI): *m/z* calcd for C₁₄H₁₃O₄ [*M* + H]⁺: 245.0808; found: 245.0811.

HPLC (YMC Chiral Amylose-C S-5 μm (25 cm), hexane/*i*-PrOH, 85:15, 0.8 mL/min, 20 °C, 254 nm): *t*_R (minor) = 33.5 min, *t*_R (major) = 37.1 min.

(S)-6-Chloro-4',5'-dihydrospiro[indene-2,2'-pyran]-1,3',6'(3H)-trione (3d)

Yield: 10 mg (40%); white solid; mp 172–174 °C; 68% ee (determined by HPLC).

$[\alpha]_D^{20} +14$ (c 0.24, CHCl₃).

IR (neat): 2924, 2360, 1763, 1715, 1425, 1254, 1105, 982, 752 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.71 (d, J = 2.0 Hz, 1 H), 7.66 (dd, J = 8.5, 2.0 Hz, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 3.73 (d, J = 16.5 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.27 (d, J = 17.0 Hz, 1 H), 3.01 (dt, J = 17.0, 4.5 Hz, 1 H), 2.86–2.82 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 201.4, 196.2, 168.6, 145.0, 137.0, 135.1, 133.6, 127.4, 125.3, 92.8, 38.4, 33.3, 27.0.

HRMS (ESI): m/z calcd for C₁₃H₁₀ClO₄ [M + H]⁺: 265.0262, 267.0233; found: 265.0266, 267.0237.

HPLC (YMC Chiral Amylose-C S-5 μ m (25 cm), hexane/*i*-PrOH, 90:10, 1.0 mL/min, 20 °C, 254 nm): t_R (minor) = 28.8 min, t_R (major) = 38.1 min.

(S)-4',5'-Dihydrospiro[cyclopenta[*a*]naphthalene-2,2'-pyran]-1,3',6'(3H)-trione (3e)

Yield: 24 mg (87%); white solid; mp 200–202 °C; 63% ee (determined by HPLC).

$[\alpha]_D^{20} -26$ (c 0.14, CHCl₃).

IR (neat): 2920, 1699, 1573, 1517, 1417, 1312, 1180, 1155, 989, 826 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 8.85 (d, J = 8.5 Hz, 1 H), 8.16 (d, J = 8.5 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 1 H), 7.70 (td, J = 8.0, 1.0 Hz, 1 H), 7.60 (td, J = 8.0, 1.0 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 3.85 (d, J = 17.0 Hz, 1 H), 3.84–3.76 (m, 1 H), 3.42 (d, J = 17.0 Hz, 1 H), 3.07–3.01 (m, 1 H), 2.89–2.85 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 201.9, 197.1, 169.2, 155.9, 138.4, 133.0, 129.9, 129.5, 128.6, 127.4, 126.9, 123.8, 123.0, 92.9, 39.1, 33.5, 27.2.

HRMS (ESI): m/z calcd for C₁₇H₁₃O₄ [M + H]⁺: 281.0808; found: 281.0812.

HPLC (YMC Chiral Amylose-C S-5 μ m (25 cm), hexane/*i*-PrOH, 90:10, 1.0 mL/min, 20 °C, 254 nm): t_R (minor) = 28.8 min, t_R (major) = 38.1 min.

(S)-3,4,4',5'-Tetrahydro-1H-spiro[naphthalene-2,2'-pyran]-1,3',6'-trione (3f)

Yield: 14 mg (58%); white solid; mp 96–98 °C; 47% ee (determined by HPLC).

$[\alpha]_D^{20} +11$ (c 0.17, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ = 7.98 (dd, J = 7.6, 1.2 Hz, 1 H), 7.57 (td, J = 7.6, 1.2 Hz, 1 H), 7.35 (t, J = 7.6 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 3.40–3.32 (m, 1 H), 3.28–3.14 (m, 2 H), 3.00–2.83 (m, 2 H), 2.75–2.63 (m, 2 H), 2.49–2.41 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 203.5, 191.1, 169.3, 144.1, 135.1, 129.4, 128.9, 128.7, 127.2, 88.2, 34.1, 31.6, 27.7, 24.7.

HRMS (ESI): m/z calcd for C₁₄H₁₃O₄ [M + H]⁺: 245.0808; found: 245.0811.

HPLC (YMC Chiral Amylose-C S-5 μ m (25 cm), hexane/*i*-PrOH, 90:10, 0.8 mL/min, 20 °C, 254 nm): t_R (major) = 34.2 min, t_R (minor) = 41.4 min.

6-Oxaspiro[4.5]decane-1,7,10-trione (3g)

Yield: 7 mg (36%); yellow oil; 0% ee (determined by HPLC).

IR (neat): 2924, 1743, 1713, 1456, 1265, 1142, 1103, 1051, 1009, 970, 872 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.34–3.25 (m, 1 H), 2.94–2.87 (m, 1 H), 2.80–2.68 (m, 2 H), 2.65–2.57 (m, 1 H), 2.55–2.40 (m, 2 H), 2.30–2.07 (m, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 209.9, 203.2, 168.9, 91.7, 35.8, 34.3, 33.8, 27.0, 18.2.

HRMS (ESI): m/z calcd for C₉H₁₁O₄ [M + H]⁺: 183.0652; found: 183.0651.

HPLC (YMC Chiral Amylose-C S-5 μ m (25 cm), hexane/*i*-PrOH, 90:10, 1.0 mL/min, 20 °C, 221 nm): t_R (1) = 14.2 min, t_R (2) = 21.3 min.

(R)-Spiro[indene-2,3'-isochroman]-1,1',4'(3H)-trione (3h)

Yield: 18 mg (64%); white solid; mp 140–142 °C; 67% ee (determined by HPLC).

$[\alpha]_D^{20} -34$ (c 0.51, CHCl₃).

IR (neat): 1738, 1690, 1595, 1421, 1263, 1213, 1101, 1006, 935, 851 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 8.38 (dd, J = 8.0, 1.0 Hz, 1 H), 8.00 (dd, J = 7.5, 1.0 Hz, 1 H), 7.91 (td, J = 7.5, 1.0 Hz, 1 H), 7.80 (td, J = 8.0, 1.0 Hz, 1 H), 7.75–7.69 (m, 2 H), 7.59 (dt, J = 8.0, 1.0 Hz, 1 H), 7.44 (t, J = 8.0 Hz, 1 H), 4.20 (d, J = 16.5 Hz, 1 H), 3.47 (d, J = 16.5 Hz, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 195.5, 187.9, 161.6, 152.2, 137.0, 135.9, 134.2, 131.5, 130.9, 130.5, 129.5, 128.6, 126.6, 126.4, 126.0, 94.0, 37.4.

HRMS (ESI): m/z calcd for C₁₇H₁₁O₄ [M + H]⁺: 279.0652; found: 279.0655.

HPLC (YMC Chiral Amylose-C S-5 μ m (25 cm), hexane/*i*-PrOH, 90:10, 0.8 mL/min, 20 °C, 254 nm): t_R (major) = 32.2 min, t_R (minor) = 35.3 min.

(S)-Methyl 4-(2-Hydroxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-4-oxobutanoate (5a)

Yield: 17 mg (66%); colorless oil; 31% ee (determined by HPLC).

$[\alpha]_D^{20} +19$ (c 0.32, CHCl₃).

IR (neat): 1726, 1705, 1609, 1211, 1092, 733 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.82 (d, J = 9.0 Hz, 1 H), 7.70 (t, J = 7.5 Hz, 1 H), 7.55 (d, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 4.42 (s, 1 H), 3.82 (d, J = 17.5 Hz, 1 H), 3.65 (s, 3 H), 3.24 (d, J = 17.5 Hz, 1 H), 2.82–2.66 (m, 2 H), 2.54–2.43 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 205.1, 201.5, 172.7, 152.2, 136.5, 134.3, 128.5, 126.8, 125.3, 87.1, 52.0, 38.9, 31.3, 27.5.

HRMS (ESI): m/z calcd for C₁₄H₁₅O₅ [M + H]⁺: 263.0914; found: 263.0916.

HPLC (YMC Chiral Amylose-C S-5 μ m (25 cm), hexane/*i*-PrOH, 90:10, 0.8 mL/min, 20 °C, 254 nm): t_R (minor) = 22.6 min, t_R (major) = 27.3 min.

(S)-Methyl 4-(2-Methoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-4-oxobutanoate (5b)

Yield: 10 mg (38%); colorless oil; 77% ee (determined by HPLC).

$[\alpha]_D^{20} +26$ (c 0.45, CHCl₃).

IR (neat): 2953, 2926, 1730, 1707, 1609, 1458, 1209, 1132, 1101, 1020, 771 cm⁻¹.

^1H NMR (500 MHz, CDCl_3): δ = 7.73 (d, J = 7.5 Hz, 1 H), 7.64 (t, J = 7.5 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 3.68 (d, J = 17.0 Hz, 1 H), 3.64 (s, 3 H), 3.41 (s, 3 H), 3.23–3.08 (m, 3 H), 2.62–2.46 (m, 2 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 205.8, 199.5, 173.0, 152.5, 136.2, 134.1, 128.0, 126.5, 124.8, 93.7, 53.6, 51.7, 33.6, 32.6, 27.5.

HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{17}\text{O}_5$ [$\text{M} + \text{H}$] $^+$: 277.1071; found: 277.1075.

HPLC (Daicel Chiralcel OD-H column (25 cm), hexane/*i*-PrOH, 95:5, 1.0 mL/min, 20 °C, 254 nm): t_R (minor) = 20.3 min, t_R (major) = 24.1 min.

(S)-Methyl 4-(2-Ethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-4-oxobutanoate (5c)

Yield: 12 mg (40%); colorless oil; 79% ee (determined by HPLC).

$[\alpha]_D^{20} +31$ (c 0.70, CHCl_3).

IR (neat): 2924, 1728, 1707, 1609, 1437, 1213, 1161, 1105, 1038, 772 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.72 (d, J = 7.6 Hz, 1 H), 7.63 (t, J = 8.0 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 3.70 (d, J = 17.2 Hz, 1 H), 3.64 (s, 3 H), 3.60–3.45 (m, 2 H), 3.24–3.10 (m, 3 H), 2.62–2.45 (m, 2 H), 1.30 (t, J = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 206.1, 199.7, 173.1, 152.6, 136.1, 134.0, 128.0, 126.4, 124.8, 93.4, 61.7, 51.7, 34.3, 32.6, 27.5, 15.6.

HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{18}\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 313.1052; found: 313.1061.

HPLC (Daicel Chiralcel OB-H column (25 cm), hexane/*i*-PrOH, 90:10, 1.0 mL/min, 20 °C, 254 nm): t_R (major) = 22.2 min, t_R (minor) = 36.8 min.

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Supporting Information

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