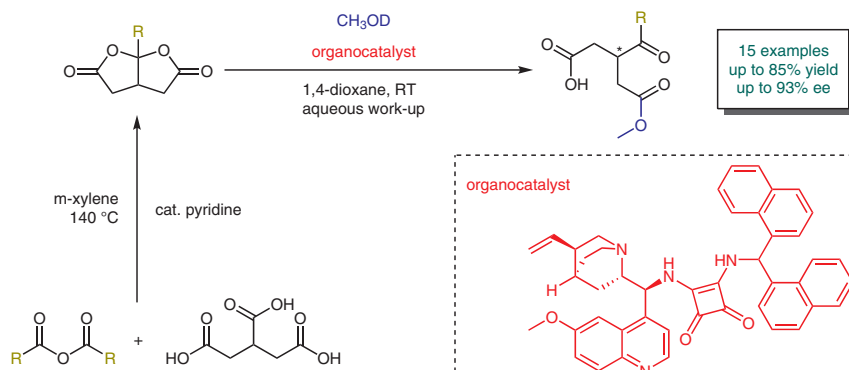


Organocatalytic Desymmetrisation of Fittig's Lactones: Deuterium as a Reporter Tag for Hidden Racemisation

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Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue



Received: 12.12.2018
 Accepted: 17.12.2018
 Published online: 24.01.2019
 DOI: 10.1055/s-0037-1611655; Art ID: ss-2018-z0845-op

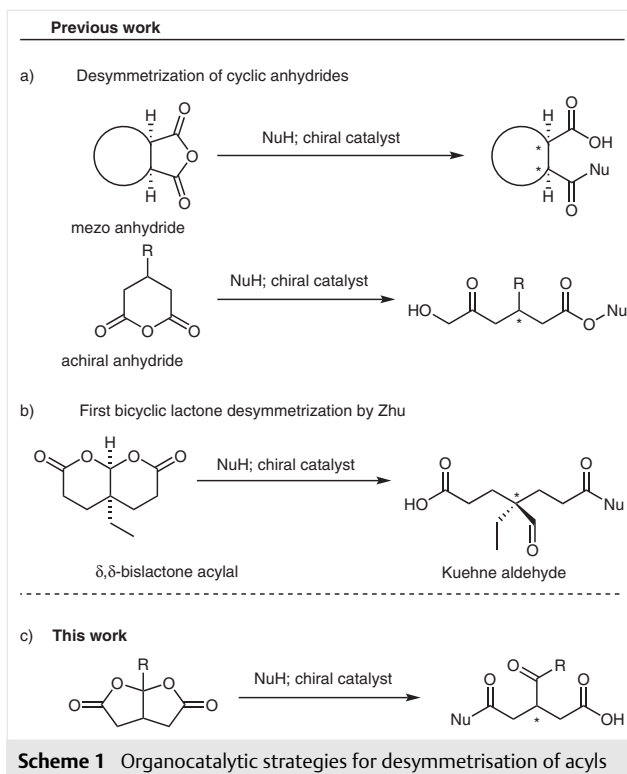
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Abstract Highly enantioselective desymmetrisation of Fittig's lactones with alcohols is promoted by bifunctional cinchona squaramides. The reactions were carried out with monodeuterated methanol to detect possible hidden racemisation of the stereogenic centre. Current evidence suggests that racemisation was not a relevant process for most substrates; partial erosion of enantioselectivity was only detected with *ortho*-substituted aryl derivatives. The resultant glutaric acid derivatives possess a scaffold that is common in natural products and the compounds are also useful chiral building blocks for further synthetic endeavours.

Key words Fittig's lactone, desymmetrization, bislactone acylal, bifunctional organocatalysis, racemization

Over the last decade, the field of enantioselective desymmetrisation mediated by organocatalysts has undergone widespread growth and significantly expanded access to valuable complex chiral molecules.¹ The influence of this synthetic platform reaches far beyond the domain of asymmetric methodology development; it has a profound impact on total synthesis because of its unique capacity to deliver multifunctional scaffolds tailored to meet the needs of synthetic brevity.² Major efforts in this field have been devoted toward the use of meso or achiral cyclic anhydrides as inexpensive and easily accessible feedstocks (Scheme 1).³ Despite the widespread success of these transformations, the substrate scope is limited to five- or six-membered cyclic anhydrides, a feature that can be attributed to both the aforementioned availability and their enhanced reactivity. As a notable exception, Zhu has recently disclosed that less electrophilic δ,δ -bislactone-acylals could be applied in analogous organocatalytic desymmetrisation.⁴

In a dual effort to extend the narrow breadth of acylal-based substrates and to investigate the synthetic limitation of the organocatalytic desymmetrisation platform, we became interested in developing the asymmetric organocatalytic desymmetrisation of the venerable Fittig's lactones. We envisioned that these easily available γ,γ -bislactone-acylals could be converted into ring-opened products through organocatalytic activation. Herein, we show that bifunc-



tional cinchona squaramides can be used to promote the cleavage of this bislactone in an enantioselective manner and to deliver multifunctional chiral building blocks.

The γ,δ - and γ,γ -bislactones are unusual structural elements of many natural products that display important biological activity (Figure 1).⁵ Their bislactone-acylal core shows high stability toward hydrolysis and their structural integrity is not affected by the presence of hydroxyl groups. Furthermore, data concerning the absorption, metabolism, and bioavailability of Bilobalide after oral administration have indicated that the γ,γ -bislactone moiety has a certain stability in biological environments.⁶

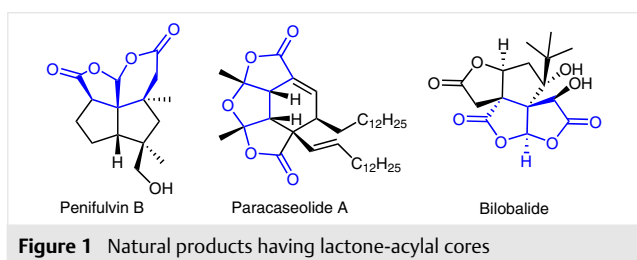


Figure 1 Natural products having lactone-acylal cores

The intrinsic hydrolytic stability of γ,γ -bislactone-acylals⁷ of natural products prompted us to study their simplified analogues, the Fittig's lactones, in organocatalytic desymmetrisation.⁸ Reported by Rudolf Fittig in 1901, these lactones can be synthesised from tricarballic acid in a Dakin–West type reaction. Given that they can be conveniently elaborated, this class of compound has found various uses in polymer chemistry⁹ and total synthesis.¹⁰ Given all of the above, it is surprising that catalytic desymmetrisation of these lactones as a means to deliver multifunctional chiral building blocks has not previously been exploited, especially in light of their easy accessibility and the current upheaval of desymmetrisation protocols.

Despite the lack of precedent, we postulated that the enantioselective ring opening of Fittig's lactone could be achieved through an organocatalysed, hydrogen-bond-assisted general-base activation strategy. We also recognised that the ability to deliver chiral ring-opened products would hinge on the identification of a catalyst that satisfies two critical requirements: (i) the enantiotopic acyl group discrimination capacity upon ring opening, and (ii) the inability to racemise the acidic α -position of the chiral ketone product.

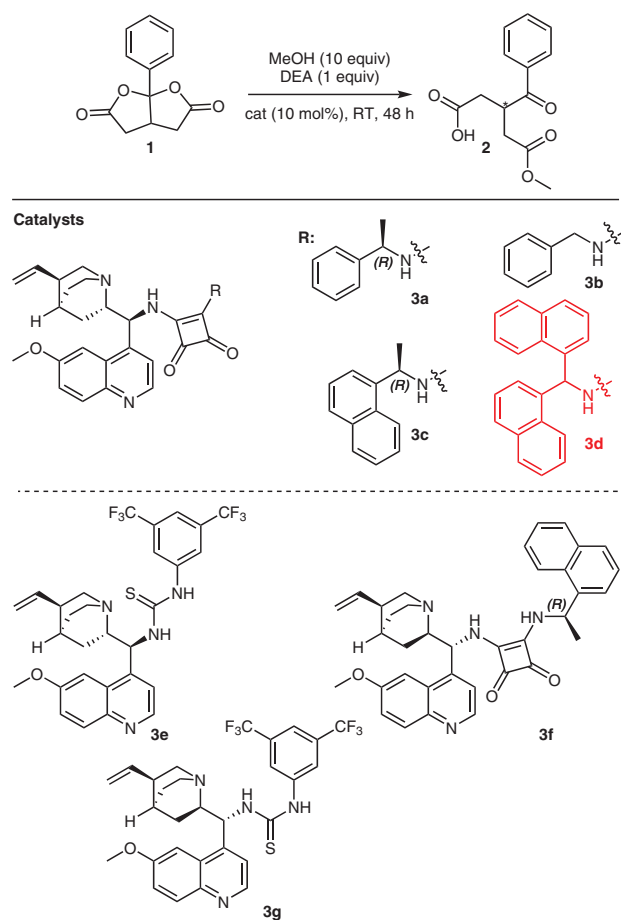
We began our study of the proposed organocatalytic desymmetrisation by examining whether Fittig's lactone was a suitable substrate for desymmetrisation with methanol. Gratifyingly, the bifunctional squaramide organocatalyst **3a** enabled the desired transformation of the phenyl-substituted Fittig's lactone **1** at room temperature (Table 1, entry 1). To increase the solubility of the applied catalyst, the use of 1 equivalent of *N,N*-diethylacetamide (DEA) was probed as an additive.¹¹ We then proceeded to investigate the influence of the applied solvent. This study revealed that etheral

type solvents resulted in higher enantioselectivities and that 1,4-dioxane was the best choice for the desymmetrisation process (entries 1–3). In contrast, neat methanol afforded product **2** with a diminished enantiomeric excess (entry 6), which might be the consequence of the solvent's capacity to disrupt the hydrogen-bond network of the catalyst. A broad range of bifunctional thiourea and squaramide organocatalysts was then evaluated in the model reaction (entries 7–12). The squaramide-type bifunctional organocatalysts¹² **3a–d** and **3f** were found to exert higher enantiocontrol than thiourea¹³ catalysts **3e** and **3g**. Moreover, installation of a binaphthyl element into the quinine squaramide provided the highest enantioselectivity in the series of benzyl-substituted catalysts (entry 9 vs. entries 3, 7, and 8). Importantly, this is in line with our previous findings on squaramide-promoted organocatalytic Robinson type annulation,¹⁴ and suggests a direct role of the π -system in the mechanism of stereoinduction. It is also worth mentioning that quinine-derived catalysts **3c** and **3e** always afforded higher enantioselectivities than their pseudo-enantiomeric quinidine-derived catalysts **3f** and **3g**.

A study was then undertaken to elucidate the racemisation capacity of the applied organocatalyst **3d** during the desymmetrisation process, because such a side-reaction might erode the enantioselectivity of the overall process. To identify such a hidden reactivity, we carried out the model reaction with monodeuterated methanol (CH_3OD) as a nucleophile and the possible H–D exchange was followed by ¹H NMR spectroscopy. Most importantly, the same enantioselectivity and no H–D exchange was observed in the presence of CH_3OD , which indicates that the applied catalyst does not racemise the stereogenic centre of **2**. Furthermore, the absence of a dependence of enantioselectivity and yield on the identity of nucleophiles (CH_3OH vs. CH_3OD) suggests that the kinetic isotope effect is close to 1 in this organocatalytic process.

We then intended to define the scope of this asymmetric ring-opening methodology; to this end, a variety of Fittig's lactones bearing aromatic, heteroaromatic and also aliphatic substituents were targeted. First, the appropriate Fittig's lactones were synthesised by using the previously reported reaction conditions (Scheme 2). Most of the decarboxylative acylation reactions took place smoothly at high temperature, providing products **4–15** with moderate to high yields. However, the sterically more crowded bislactones **16** and **18** formed in this reaction with only lower yields. Furthermore, several attempts under the reported conditions failed to deliver the *tert*-butyl or 2-thienyl derivatives **17** and **19**.

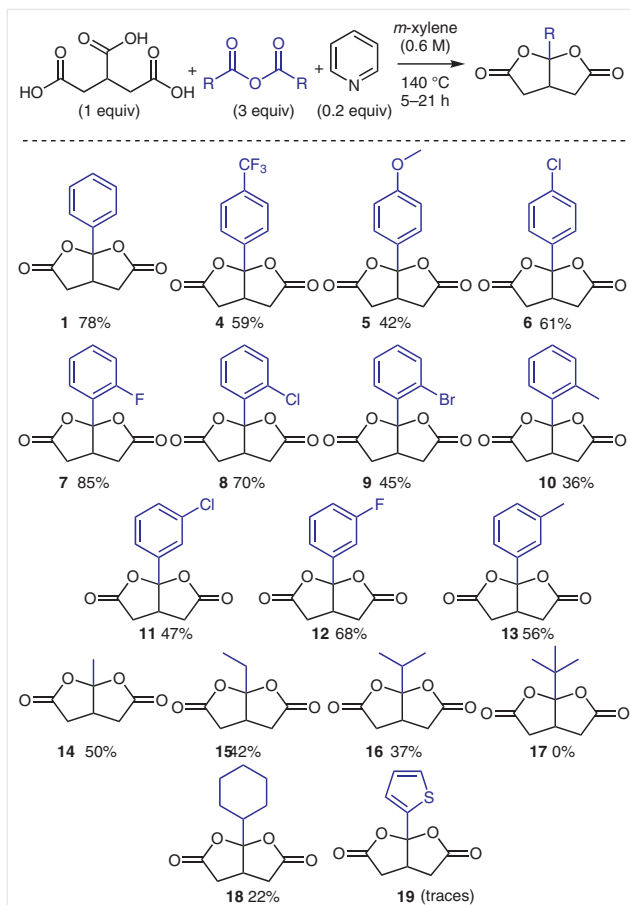
With an optimised desymmetrisation process and the appropriate set of Fittig's lactones in hand, we investigated the scope of the organocatalytic reaction. Notably, we used the relatively inexpensive CH_3OD as a nucleophile for ring opening to validate and monitor the previously mentioned

Table 1 Solvent and Catalyst Screen for Desymmetrisation Reaction of **1**^a

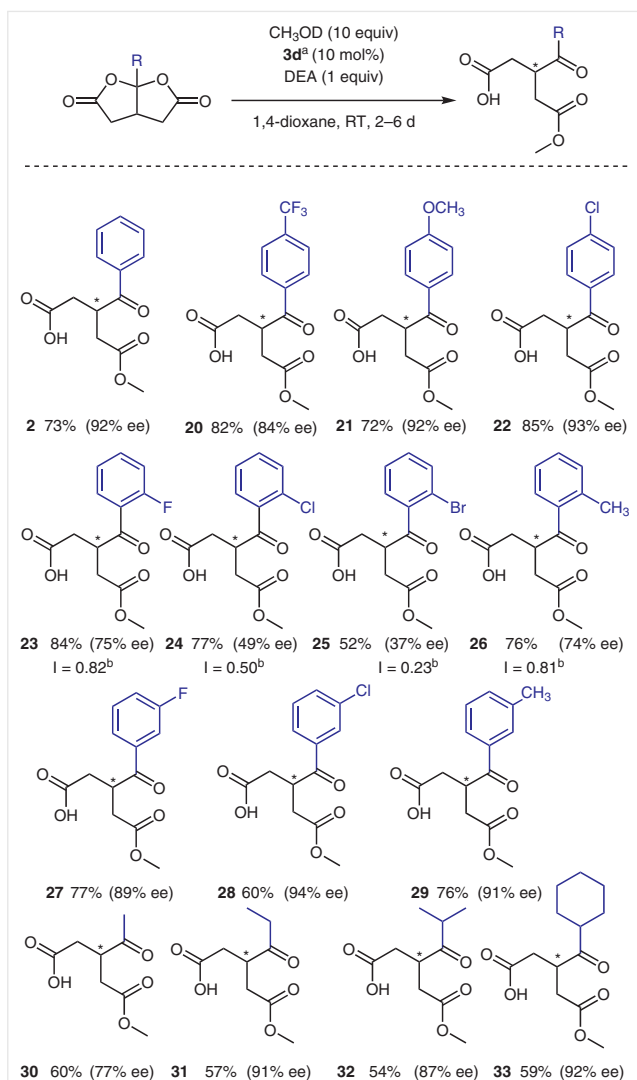
Entry	Solvent	Catalyst	ee (%) ^b
1	THF	3a	76
2	2-methyl-THF	3a	79
3	1,4-dioxane	3a	83
4	toluene	3a	50
5	CH ₂ Cl ₂	3a	56
6	MeOH	3a	21
7	1,4-dioxane	3b	74
8	1,4-dioxane	3c	83
9	1,4-dioxane	3d	92
10	1,4-dioxane	3e	67
11	1,4-dioxane	3f	-60
12	1,4-dioxane	3g	-58

^a Reactions were performed on 0.5 mmol scale and 0.2 M substrate concentration.

^b Determined by chiral HPLC.

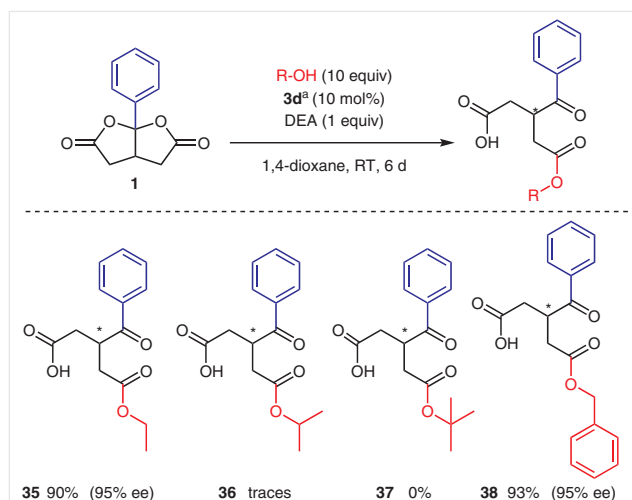
**Scheme 2** Substrate scope of Fittig's lactone formation

potential racemisation process of the stereogenic centre upon desymmetrisation (Scheme 3). Aromatic substrates bearing electron-withdrawing or electron-donating groups in the *para*- or *meta*-positions underwent smooth ring opening without any detectable H–D exchanges, and afforded the chiral 3-acyl-glutaric acid monomethyl ester derivatives with good yields and high enantioselectivities. In contrast, the desymmetrisation of *ortho*-substituted aromatic Fittig-lactones **7–10**, bearing either electron-withdrawing or electron-donating substituents, resulted in diminished enantioselectivities. The lower ee, however, seems to be the result of the racemisation of the stereogenic centre, because extensive H–D exchange was observed by ¹H NMR spectroscopy. Variation of aliphatic substituents on the Fittig's lactone backbone revealed that primary and secondary aliphatic substituents were also compatible reaction partners, and afforded the product with good to high enantioselectivities. Finally, we examined the generality of the organocatalytic desymmetrisation with respect to the nucleophilic reaction partner (Scheme 4). Whereas ethanol and benzyl alcohol were highly successful reaction partners, isopropanol and *tert*-butanol failed to deliver the desired products.



Scheme 3 Substrate scope of desymmetrisation reaction of Fittig's lactones. ^a Enantioselectivity was determined by chiral HPLC. ^b I = integer of the proton at the stereocentre in ¹H NMR spectra.

To better understand the mechanism of this organocatalytic process and the thermodynamic driving force of the transformation, we performed DFT calculations on the reaction of the methyl substituted Fittig's lactone **14**.¹⁵ The calculated free energy of the desymmetrisation process suggests that the ring opening reaction is only slightly exergonic and the actual yield was close to the theoretical yield of the chemical equilibrium of the methanolysis of **14** (Figure 2). Our theoretical calculations also revealed that γ,γ -bislactone acylal **14** is significantly more stable than its glutaric anhydride isomer **40**, which explains why this isomer could not be observed experimentally. The generally accepted mechanism of catalysis by cinchona alkaloids in cyclic anhydride desymmetrisation process is general base ac-



Scheme 4 Desymmetrisation of model Fittig's lactone **1** with different alcohols. ^a Enantioselectivity was determined by chiral HPLC.

tivation of the methanol by the quinuclidine nitrogen.¹⁶ Given the size and complexity of the applied catalytic system, we only performed calculations on possible covalent intermediates using a trimethylamine base to gain some insight into the mechanism. For the lactone ring opening, a B_{AC}2-like mechanism¹⁷ was envisioned, which occurs in two steps. In the first step, a methanol molecule attacks the carbonyl carbon in a base-assisted addition reaction that yields tetrahedral intermediates. As calculations revealed, attack of methanol from the convex face is preferred over the concave approach. These intermediates (**12a** and **12b**) are metastable and decompose in the second step to a more stable hemiacetal **39**.

Taken together, the data presented above indicate that the use of bifunctional squaramides has allowed the development of catalytic desymmetrisation of Fittig's lactones with high enantioselectivity. Thus, the currently narrow scope of bislactone acylal desymmetrisation can be expanded toward substrates having sluggish reactivity. To detect any hidden racemisation process at the stereogenic centre of the product, monodeuterated methanol was used as a nucleophile. We expect this synthetic method to be adopted in total synthesis developments as an efficient platform to generate complex chiral intermediates.

NMR spectra were acquired with a Varian INOVA spectrometer, running at 500 MHz and 125 MHz for ¹H and ¹³C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (¹H, CHCl₃: δ = 7.26 ppm, DMSO: δ = 2.50 ppm; ¹³C: CHCl₃: δ = 77.16 ppm, DMSO: δ = 39.52 ppm). The following abbreviations are used to indicate the multiplicity in spectra: s, singlet; d, doublet; t, triplet; quint., quintet; m, multiplet. ¹³C NMR spectra were acquired in broad-band continuous decoupled mode. HRMS was performed with a Q Exactive quadrupole-orbitrap mass spectrometer (Thermo Fischer Scientific, Bremen, Germany). Positive and negative electrospray ionisation

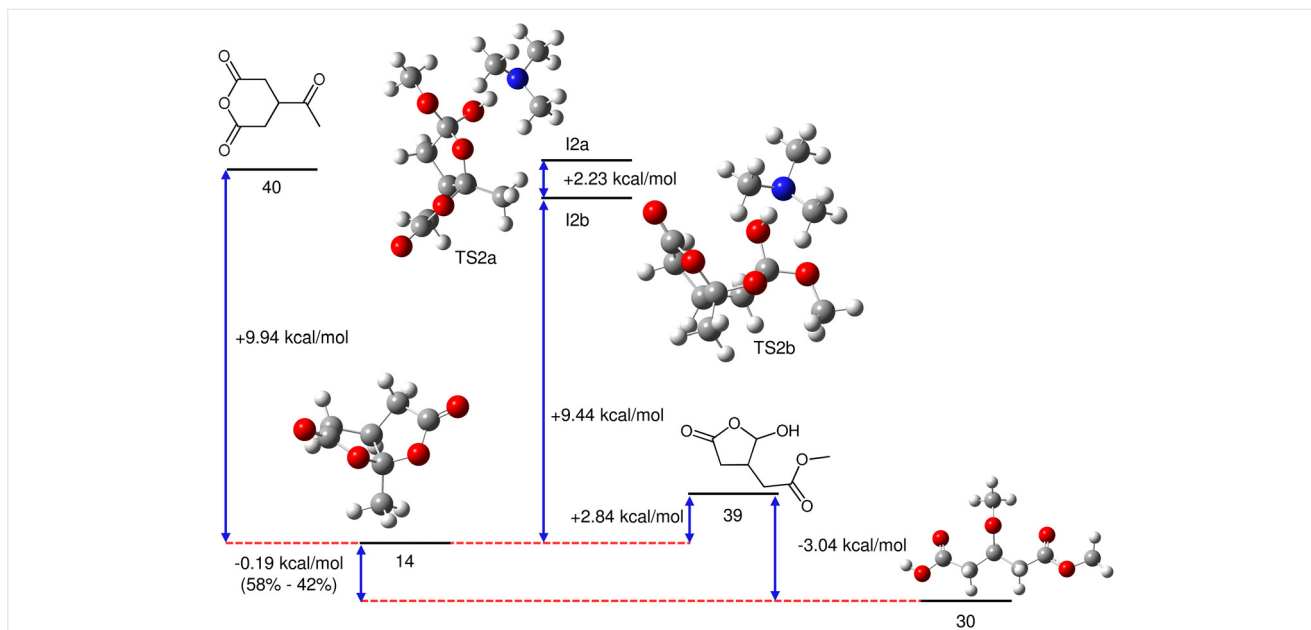


Figure 2 Relevant intermediates of the desymmetrisation of Fittig's lactone **14** with trimethylamine

mass spectra were acquired by flow injection analysis using 1:1 acetonitrile/water solvent mixture containing 0.1% formic acid (v/v). GC-MS analysis was conducted with a Shimadzu GC-2010 Plus Ultra instrument. Melting points were determined with a SRS MPA100 apparatus and are uncorrected. Column chromatography was carried out with a Teledyne ISCO CombiFlash Rf200 UV/VIS system, using RediSep Rf Gold® Normal-phase Silica. The enantiomeric excess of the products were determined with a Jasco ChromPass Chromatography Data System and Waters™ 600E Multisolvant Delivery System, using chiral stationary phase. Commercially available materials were purchased from Sigma-Aldrich and Fluorochem; all were used without further purification. Ether type solvents and toluene were freshly distilled from sodium/benzophenone.

The conformational analysis involved an initial Monte Carlo sampling using the OPLS_2005 force field as implemented in Schrödinger Maestro. The DFT calculations were carried out with the dispersion corrected, range-separated hybrid ω B97X-D exchange-correlation functional, along with the AUG-cc-pVDZ double- ζ basis set, as implemented in the Gaussian16 package.¹⁸ For each located structure, single-point energies were calculated as well with the larger, AUG-cc-pVTZ triple- ζ basis set. In all DFT calculations, the ultrafine integration grid was employed to warrant the accuracy of numerical integration. The thermal and entropic contributions were estimated within the ideal gas-rigid rotor-harmonic oscillator approximation for $T = 298.15$ K and $c = 1$ mol/dm³ conditions. The solvent effects were taken into account as well by computing the solvation free energies (at the ω B97X-D/AUG-cc-pVDZ level) via the integral equation formalism variant of the polarisable continuum model (IEFPCM).²⁴ calculations were those of the SMD solvation model.

Preparation of Aromatic Anhydrides; General Procedure

Step 1

In a three-necked 100 mL flask under N₂-atmosphere, the corresponding benzoic acid (32 mmol) was suspended in anhydrous toluene (21 mL, 1.5 M). A few drops of anhydrous DMF (126 μ L, 1.6 mmol, 0.05 equiv) and SOCl₂ (3.0 mL, 41.5 mmol, 1.3 equiv) were added at r.t. sequentially. The mixture was heated to 70 °C and stirred at this temperature for 1 hour, then cooled to r.t. and the excess SOCl₂ was purged from the system by flushing with N₂ for 15 min. The solution of the benzoyl chloride was used without purification in the next step.

Step 2

In a three-necked flask under N₂-atmosphere, the corresponding benzoic acid (32 mmol, 1.0 equiv) was suspended in anhydrous toluene (21 mL, 1.5 M). Anhydrous pyridine (3.1 mL, 38.3 mmol, 1.2 equiv) was added to the mixture and the resulting solution was cooled to 0 °C. A solution of the corresponding benzoyl chloride from *Step 1* was added at such rate that the temperature was kept under 20 °C, while a white precipitate formed. The resulting suspension was heated at reflux for 2 h then cooled to r.t. The precipitate (Pyr-HCl) was filtered, washed with toluene, and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂ (100 mL), washed with 10% HCl (10 mL) then washed with cc. NaHCO₃ (3 \times 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to dryness. Pure anhydrides were obtained in 91–98% yield; NMR data were consistent with the reported values.

Preparation of Fittig's Lactones; General Procedure

Into a one-necked 25 mL flask, tricarballic acid (518 mg, 2.95 mmol, 1.0 equiv) and the appropriate anhydride (8.83 mmol, 3 equiv) were suspended in *m*-xylene (5 mL, 0.6 M). Pyridine was added (47 μ L, 0.59 mmol, 0.2 equiv) in one portion, then the mixture was heated to 140 °C and stirred until the completion of the reaction was indicated by GC-MS (5–21 h). After cooling to r.t., CH₂Cl₂ (100 mL) was added

and the mixture was passed through a short pad of Celite to remove insoluble side-products. The solution was washed with saturated Na₂CO₃ solution (2 × 10 mL) then with brine (10 mL). The organic phase was dried over Na₂SO₄, filtered, and evaporated to dryness. Purification by flash chromatography (hexanes/EtOAc) afforded the pure Fittig lactone.

6a-Phenyldihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (1)

Yield: 502 mg (78%); off-white solid; mp 136–138 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.48–7.45 (m, 5 H), 3.36 (tt, *J* = 9.3, 4.7 Hz, 1 H), 3.10 (dd, *J* = 18.4, 9.3 Hz, 2 H), 2.66 (dd, *J* = 18.4, 4.7 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.5, 136.3, 130.2, 129.04, 124.9, 112.8, 41.4, 35.2.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₁O₄: 219.0657; found: 219.0644.

6a-(4-(Trifluoromethyl)phenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (4)

Yield: 498 mg (59%); off-white solid; decomposition at 128–132 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.73 (d, *J* = 8.0 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 3.38–3.32 (m, 1 H), 3.12 (dd, *J* = 18.5, 9.5 Hz, 2 H), 2.70 (dd, *J* = 18.5, 4.2 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.0, 140.1, 132.5 (q, *J* = 33.0 Hz), 126.1 (q, *J* = 3.64 Hz), 123.5 (q, *J* = 272.6 Hz), 111.8, 41.4, 35.1.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₃H₁₀F₃O₄: 287.0531; found: 287.0521

6a-(4-Methoxyphenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (5)

Yield: 307 mg (42%); off-white solid; decomposition at 128–136 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.37 (d, *J* = 8.9 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H), 3.34 (tt, *J* = 9.3, 4.7 Hz, 1 H), 3.08 (dd, *J* = 18.4, 9.3 Hz, 2 H), 2.64 (dd, *J* = 18.4, 4.6 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.4, 126.4, 114.3, 55.4, 41.4, 35.3.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₃H₁₃O₅: 249.0763; found: 249.0747.

6a-(4-Chlorophenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (6)

Yield: 453 (61%); off-white solid; mp 127–135 °C.

¹H NMR (500 MHz, DMSO-*d*₆): δ = 7.60–7.49 (m, 4 H), 3.45 (m, 1 H), 3.17 (dd, *J* = 18.5, 9.8 Hz, 2 H), 2.84 (dd, *J* = 18.5, 3.8 Hz, 2 H).

¹³C NMR (125 MHz, DMSO): δ = 174.3, 136.7, 135.0, 129.2, 127.7, 112.4, 40.9, 35.0.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₀ClO₄: 253.0268; found: 253.0252.

6a-(2-Fluorophenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (7)

Yield: 592 mg (85%); off-white solid; decomposition at 100–110 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.61 (td, *J* = 7.9, 1.8 Hz, 1 H), 7.45 (tdd, *J* = 7.4, 5.2, 1.8 Hz, 1 H), 7.25–7.05 (m, 2 H), 3.54 (ttd, *J* = 10.2, 4.4, 1.5 Hz, 1 H), 3.16 (dd, *J* = 18.7, 10.2 Hz, 2 H), 2.65 (ddd, *J* = 18.8, 4.4, 1.5 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.3, 159.8 (d, *J* = 248.3 Hz), 132.4 (d, *J* = 9.1 Hz), 127.1 (d, *J* = 2.1 Hz), 124.5 (d, *J* = 3.8 Hz), 124.3 (d, *J* = 10.5 Hz), 116.5 (d, *J* = 21.2 Hz), 110.7 (d, *J* = 1.4 Hz), 39.9 (d, *J* = 2.8 Hz), 35.6 (d, *J* = 1.9 Hz).

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₀FO₄: 237.0563; found: 237.5559.

6a-(2-Chlorophenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (8)

Yield: 522 mg (70%); off-white solid; decomposition at 134–142 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.71 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.50 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.43 (td, *J* = 7.6, 1.7 Hz, 1 H), 7.37 (td, *J* = 7.6, 1.4 Hz, 1 H), 3.76 (tt, *J* = 10.0, 4.3 Hz, 1 H), 3.11 (dd, *J* = 18.6, 9.9 Hz, 2 H), 2.66 (dd, *J* = 18.7, 4.4 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.4, 133.2, 132.0, 131.7, 131.6, 127.7, 127.3, 111.8, 39.0, 35.4.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₀ClO₄: 253.0268; found: 253.0261.

6a-(2-Bromophenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (9)

Yield: 393 mg (45%); off-white solid; mp 162–165 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.72 (dd, *J* = 3.3, 1.6 Hz, 1 H), 7.70 (dd, *J* = 3.4, 1.5 Hz, 1 H), 7.41 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.33 (td, *J* = 7.7, 1.7 Hz, 1 H), 3.80 (tt, *J* = 9.9, 4.4 Hz, 1 H), 3.09 (dd, *J* = 18.6, 9.9 Hz, 2 H), 2.65 (dd, *J* = 18.6, 4.3 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.5, 135.1, 134.3, 131.9, 128.1, 127.8, 120.9, 112.2, 39.1, 35.4.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₀BrO₄: 296.9762; found: 296.9755.

6a-(*o*-Tolyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (10)

Yield: 246 mg (36%); off-white solid; decomposition at 90–109 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.43 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.35 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.30–7.19 (m, 2 H), 3.55 (dq, *J* = 9.3, 4.7 Hz, 1 H), 3.03 (dd, *J* = 18.5, 9.3 Hz, 2 H), 2.65 (dd, *J* = 18.5, 4.6 Hz, 2 H), 2.41 (s, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.4, 136.1, 133.1, 132.9, 130.4, 126.2, 125.2, 113.6, 39.4, 35.1, 20.8.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₃H₁₃O₄: 233.0814; found: 233.0807.

6a-(3-Chlorophenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (11)

Yield: 349 mg (47%); off-white solid; decomposition at 125–130 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.47–7.36 (m, 3 H), 7.35–7.31 (m, 1 H), 3.35 (tt, *J* = 9.5, 4.6 Hz, 1 H), 3.11 (dd, *J* = 18.6, 9.5 Hz, 2 H), 2.67 (dd, *J* = 18.6, 4.6 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 172.1, 138.3, 135.2, 130.4, 130.4, 125.3, 111.9, 123.1, 41.4, 35.1.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₀ClO₄: 253.0268; found: 253.0261.

6a-(3-Fluorophenyl)dihydrofuro[2,3-b]furan-2,5(3H,6aH)-dione (12)

Yield: 473 mg (68%); off-white solid; decomposition at 151–157 °C.

^1H NMR (500 MHz, CDCl_3): δ = 7.45 (td, J = 7.9, 5.6 Hz, 2 H), 7.25–7.13 (m, 3 H), 3.34 (tt, J = 9.3, 4.6 Hz, 1 H), 3.11 (dd, J = 18.5, 9.5 Hz, 2 H), 2.67 (dd, J = 18.5, 4.6 Hz, 2 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 172.0, 162.9 (d, J = 248.6 Hz), 138.7 (d, J = 7.3 Hz), 130.9 (d, J = 8.1 Hz), 120.5 (d, J = 3.3 Hz), 117.3 (d, J = 21.1 Hz), 112.5 (d, J = 24.0 Hz), 41.4, 35.1.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{12}\text{H}_{10}\text{FO}_4$: 237.0563; found: 237.0556.

6a-(*m*-Tolyl)dihydrofuro[2,3-*b*]furan-2,5(3*H*,6*aH*)-dione (13)

Yield: 383 mg (56%); off-white solid; decomposition at 92–96 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 7.51–7.15 (m, 4 H), 3.44 (tt, J = 9.5, 4.3 Hz, 1 H), 3.17 (dd, J = 18.6, 9.8 Hz, 2 H), 2.84 (dd, J = 18.6, 4.3 Hz, 2 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): δ = 174.4, 138.7, 137.8, 130.8, 129.1, 126.0, 122.6, 113.0, 40.9, 35.1, 21.4.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{O}_4$: 233.0814; found: 233.0808.

6a-Methyldihydrofuro[2,3-*b*]furan-2,5(3*H*,6*aH*)-dione (14)

Yield: 230 mg (50%); off-white solid; mp 93–95 °C.

^1H NMR (500 MHz, CDCl_3): δ = 3.12–3.06 (m, 1 H), 3.05–2.98 (m, 2 H), 2.60–2.50 (m, 2 H), 1.80 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 172.6, 113.1, 38.9, 35.4, 23.8.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_7\text{H}_9\text{O}_4$: 157.0501; found: 157.0490.

6a-Ethyldihydrofuro[2,3-*b*]furan-2,5(3*H*,6*aH*)-dione (15)

Yield: 210 mg (42%); off-white solid; mp 60–61 °C.

^1H NMR (500 MHz, CDCl_3): δ = 3.16–3.07 (m, 1 H), 2.96 (dd, J = 18.6, 9.6 Hz, 2 H), 2.53 (dd, J = 18.6, 4.5 Hz, 2 H), 2.01 (q, J = 7.5 Hz, 2 H), 1.04 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 172.73, 115.31, 36.76, 35.64, 30.28, 7.13.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_7\text{H}_{11}\text{O}_4$: 171.0657; found: 171.0651.

6a-Isopropyldihydrofuro[2,3-*b*]furan-2,5(3*H*,6*aH*)-dione (16)

Yield: 201 mg (37%); off-white solid; mp 88–89 °C.

^1H NMR (500 MHz, CDCl_3): δ = 3.17 (tt, J = 9.1, 4.3 Hz, 1 H), 2.97 (dd, J = 18.7, 10.0 Hz, 2 H), 2.54 (dd, J = 18.7, 4.4 Hz, 2 H), 2.22 (hept, J = 6.8 Hz, 1 H), 1.06 (d, J = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 172.7, 117.2, 36.2, 35.1, 34.9, 16.0.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_8\text{H}_{13}\text{O}_4$: 185.0814; found: 185.0802.

6a-Cyclohexyldihydrofuro[2,3-*b*]furan-2,5(3*H*,6*aH*)-dione (18)

Yield: 145 mg (22%); off-white solid; mp 143–145 °C.

^1H NMR (500 MHz, CDCl_3): δ = 3.18 (tt, J = 9.5, 4.5 Hz, 1 H), 2.95 (dd, J = 18.6, 10.0 Hz, 2 H), 2.52 (dd, J = 18.7, 4.4 Hz, 2 H), 1.96–1.67 (m, 6 H), 1.34–1.04 (m, 5 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 172.67, 116.68, 44.52, 36.06, 34.96, 25.97, 25.76, 25.40.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{12}\text{H}_{17}\text{O}_4$: 225.1127; found: 225.1120.

Desymmetrization of Fittig Lactones; General Procedure

All substrates were prepared in racemic form by using this procedure, except when 20 mol% DMAP was used instead of chiral catalyst.

In a 25 mL one-necked flask, organocatalyst **3d** (68 mg, 0.1 mmol, 0.1 equiv) was suspended in anhydrous dioxane (5 mL, 0.2 M for the substrate), and *N,N*-diethylacetamide (125 μL , 1.0 mmol, 1.0 equiv) was added to the flask. The corresponding Fittig lactone (1.0 mmol, 1.0 equiv) and alcohol (10 mmol, 10 equiv) were added sequentially and the mixture was stirred at r.t. Upon completion of the reaction as indicated by GC-MS or TLC (2–6 days), the solvent was evaporated and the residue was taken up in CH_2Cl_2 (15 mL) and washed with 10% citric acid (2 \times 5 mL). The inorganic phase was extracted with CH_2Cl_2 (3 \times 5 mL), the combined organic phase was dried over Na_2SO_4 , filtered and evaporated to dryness. Isolation by flash chromatography with a short column (hexanes/EtOAc, 1% AcOH) afforded the pure product. Determination of ee data is summarised in the section 'Derivatisation for chiral HPLC analysis'.

3-Benzoyl-5-methoxy-5-oxopentanoic Acid (2)

Yield: 182 mg (73%); white solid; ee: 92%; t_R = 13.3 (minor), 23.5 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; λ = 247 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 8.02–7.92 (m, 2 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.47 (t, J = 7.7 Hz, 2 H), 4.28 (quint., J = 6.9 Hz, 1 H), 3.63 (d, J = 2.1 Hz, 3 H), 2.86 (ddd, J = 29.0, 16.8, 7.0 Hz, 2 H), 2.54 (td, J = 16.5, 6.8 Hz, 2 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 200.5, 177.3, 171.8, 135.4, 133.4, 128.8, 128.5, 51.9, 38.6, 35.6, 35.4.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{O}_5$: 251.0919; found: 251.0903.

5-Methoxy-5-oxo-3-[4-(trifluoromethyl)benzoyl]pentanoic Acid (20)

Yield: 260 mg (82%); colourless oil; ee: 84%; t_R = 9.0 (major), 10.0 (minor) min (Chiralpak IB; 85% hexane/15% EtOH; 1 mL/min; 20 °C; λ = 247 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 8.08 (d, J = 8.1 Hz, 2 H), 7.74 (d, J = 8.2 Hz, 2 H), 4.25 (quint., J = 6.8 Hz, 1 H), 3.63 (s, 3 H), 2.85 (ddd, J = 34.3, 17.0, 7.3 Hz, 2 H), 2.57 (ddd, J = 21.4, 16.9, 6.6 Hz, 2 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 199.9, 176.9, 171.6, 138.4, 134.6 (q, J = 32.7 Hz), 128.9, 125.8 (q, J = 3.8 Hz), 123.5 (q, J = 272.8 Hz), 52.1, 38.8, 35.6, 35.3.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{O}_5$: 319.0793; found: 319.0786.

5-Methoxy-3-(4-methoxybenzoyl)-5-oxopentanoic Acid (21)

Yield: 202 mg (72%); colourless oil; ee: 92%; t_R = 13.0 (major), 15.5 (minor) min (Chiralpak IB; 85% hexane/15% EtOH; 1 mL/min; 20 °C; λ = 271 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 7.98 (d, J = 8.7 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 4.25 (quint., J = 7.0 Hz, 1 H), 3.87 (s, 3 H), 3.64 (s, 3 H), 2.85 (ddd, J = 28.2, 16.7, 6.9 Hz, 2 H), 2.54 (td, J = 16.4, 6.9 Hz, 2 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 198.9, 176.7, 171.9, 163.9, 130.9, 128.3, 114.0, 55.5, 51.9, 38.2, 35.8, 35.5.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{O}_6$: 281.1025; found: 281.1016.

3-(4-Chlorobenzoyl)-5-methoxy-5-oxopentanoic Acid (22)

Yield: 241 mg (85%); colourless oil; ee: 93%; $t_R = 9.0$ (major), 10.0 (minor) min (Chiralpak IB; 85% hexane/15% EtOH; 1 mL/min; 20 °C; $\lambda = 256$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 7.91$ (d, $J = 8.7$ Hz, 2 H), 7.43 (d, $J = 8.6$ Hz, 2 H), 4.20 (quint., $J = 6.9$ Hz, 1 H), 3.61 (s, 3 H), 2.82 (ddd, $J = 31.5, 16.8, 7.2$ Hz, 2 H), 2.53 (td, $J = 17.2, 6.6$ Hz, 2 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 199.5, 177.1, 171.7, 139.9, 133.9, 130.0, 129.1, 52.0, 38.5, 35.7, 35.4$.

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{14}\text{ClO}_5$: 285.0530; found: 285.0522.

3-(2-Fluorobenzoyl)-5-methoxy-5-oxopentanoic Acid (23)

Yield: 225 mg (84%); colourless oil; ee: 75%; $t_R = 12.3$ (minor), 17.3 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 239$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 7.81$ (td, $J = 7.6, 1.8$ Hz, 1 H), 7.51 (dddd, $J = 8.6, 7.1, 5.0, 1.8$ Hz, 1 H), 7.22 (td, $J = 7.6, 1.1$ Hz, 1 H), 7.12 (ddd, $J = 11.2, 8.3, 1.0$ Hz, 1 H), 4.08 (quint., $J = 6.7$ Hz, 1 H), 3.63 (s, 3 H), 2.88 (dddd, $J = 22.5, 16.7, 6.8, 1.4$ Hz, 2 H), 2.63–2.48 (m, 2 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 198.6, 177.2, 171.8, 161.2$ (d, $J = 254.1$ Hz), 134.7 (d, $J = 9.2$ Hz), 131.2 (d, $J = 2.4$ Hz), 124.7 (d, $J = 3.2$ Hz), 124.7 (d, $J = 13.9$ Hz), 116.6 (d, $J = 23.9$ Hz), 51.9, 43.2 (d, $J = 6.6$ Hz), 34.8 (d, $J = 16.7$ Hz).

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{14}\text{FO}_5$: 269.0825; found: 269.0817.

3-(2-Chlorobenzoyl)-5-methoxy-5-oxopentanoic Acid (24)

Yield: 219 mg (77%); colourless oil; ee: 49%; $t_R = 12.2$ (minor), 23.5 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 263$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 10.15$ (s, 1 H), 7.69–7.51 (m, 1 H), 7.42–7.30 (m, 3 H), 4.06 (quint., $J = 6.8, 6.0$ Hz, 1 H), 3.64 (s, 3 H), 2.94–2.79 (m, 2 H), 2.66–2.53 (m, 2 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 202.0, 177.0, 171.7, 137.7, 131.9, 131.1, 130.5, 129.5, 127.0, 52.0, 43.1, 34.3, 34.2$.

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{14}\text{ClO}_5$: 285.0530; found: 285.0521.

3-(2-Bromobenzoyl)-5-methoxy-5-oxopentanoic Acid (25)

Yield: 183 mg (56%); colourless oil; ee: 37%; $t_R = 13.1$ (minor), 25.5 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 247$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 10.19$ (s, 1 H), 7.59 (ddd, $J = 7.6, 5.1, 1.4$ Hz, 2 H), 7.37 (td, $J = 7.5, 1.1$ Hz, 1 H), 7.29 (td, $J = 7.7, 1.7$ Hz, 1 H), 4.05 (quint., $J = 6.7$ Hz, 1 H), 3.63 (s, 3 H), 2.85 (ddd, $J = 31.8, 17.0, 6.6$ Hz, 2 H), 2.58 (ddd, $J = 18.8, 17.0, 6.8$ Hz, 2 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 202.6, 177.2, 171.7, 139.7, 133.8, 131.9, 129.3, 127.4, 119.3, 52.0, 43.0, 34.2, 34.2$.

HRMS (ESI): m/z [M – H][–] calcd for $\text{C}_{13}\text{H}_{12}\text{BrO}_5$: 326.9868; found: 326.9874

5-Methoxy-3-(2-methylbenzoyl)-5-oxopentanoic Acid (26)

Yield: 201 mg (76%); colourless oil; ee: 74%; $t_R = 10.4$ (minor), 23.2 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 247$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 7.74$ –7.69 (m, 1 H), 7.40–7.34 (m, 1 H), 7.29–7.22 (m, 2 H), 4.09 (quint., $J = 6.8$ Hz, 1 H), 3.62 (s, 3 H), 2.81 (ddd, $J = 33.8, 16.8, 6.9$ Hz, 2 H), 2.54 (ddd, $J = 19.7, 16.8, 6.6$ Hz, 2 H), 2.42 (s, 3 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 203.7, 177.3, 171.8, 138.6, 136.6, 131.8, 131.4, 128.3, 125.8, 51.9, 41.8, 34.9, 34.8, 20.6$.

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{14}\text{H}_{17}\text{ClO}_5$: 265.1076; found: 265.1068.

3-(3-Fluorobenzoyl)-5-methoxy-5-oxopentanoic Acid (27)

Yield: 206 mg (77%); colourless oil; ee: 89%; $t_R = 18.5$ (minor), 23.5 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 244$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 10.28$ (s, 1 H), 7.73 (d, $J = 7.8$ Hz, 1 H), 7.62 (d, $J = 9.4$ Hz, 1 H), 7.42 (td, $J = 7.9, 5.3$ Hz, 1 H), 7.24 (ddd, $J = 10.8, 6.6, 2.5$ Hz, 1 H), 4.17 (t, $J = 6.9$ Hz, 1 H), 3.59 (s, 3 H), 2.80 (ddd, $J = 16.6, 12.9, 6.9$ Hz, 2 H), 2.51 (dd, $J = 16.9, 6.6$ Hz, 2 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 199.7, 177.0, 171.8, 162.9$ (d, $J = 247.9$ Hz), 137.7 (d, $J = 6.2$ Hz), 130.4 (d, $J = 7.6$ Hz), 124.2 (d, $J = 3.1$ Hz), 120.4 (d, $J = 21.4$ Hz), 115.3 (d, $J = 22.5$ Hz), 52.0, 38.9, 35.6, 35.5.

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{14}\text{FO}_5$: 269.0825; found: 269.08177.

3-(3-Chlorobenzoyl)-5-methoxy-5-oxopentanoic Acid (28)

Yield: 170 mg (60%); colourless oil; ee: 94%; $t_R = 19.5$ (minor), 25.5 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 243$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 7.93$ (s, 1 H), 7.85 (dt, $J = 7.8, 1.4$ Hz, 1 H), 7.61–7.50 (m, 1 H), 7.41 (t, $J = 7.9$ Hz, 1 H), 4.20 (quint., $J = 7.0$ Hz, 1 H), 3.63 (s, 3 H), 2.83 (ddd, $J = 28.7, 16.9, 7.1$ Hz, 2 H), 2.64–2.48 (m, 2 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 199.5, 176.9, 171.6, 137.2, 135.2, 133.3, 130.1, 128.6, 126.6, 52.0, 38.7, 35.6, 35.4$.

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{14}\text{ClO}_5$: 285.0530; found: 285.0522.

5-Methoxy-3-(3-methylbenzoyl)-5-oxopentanoic Acid (29)

Yield: 200 mg (76%); colourless oil; ee: 91%; $t_R = 18.5$ (minor), 25.5 (major) min (Chiralpak AD; 50% hexane/50% IPA; 1 mL/min; 20 °C; $\lambda = 254$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 7.78$ (d, $J = 6.2$ Hz, 2 H), 7.45–7.32 (m, 2 H), 4.27 (quint., $J = 7.0$ Hz, 1 H), 3.64 (s, 3 H), 2.86 (ddd, $J = 27.5, 16.8, 6.9$ Hz, 2 H), 2.54 (td, $J = 16.3, 6.9$ Hz, 2 H), 2.41 (s, 3 H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 200.6, 177.0, 171.8, 138.7, 135.4, 134.2, 129.0, 128.7, 125.7, 51.9, 38.7, 35.6, 35.3, 21.3$.

HRMS (ESI): m/z [M + H]⁺ calcd for $\text{C}_{14}\text{H}_{17}\text{O}_5$: 265.1076; found: 265.1069.

3-Acetyl-5-methoxy-5-oxopentanoic Acid (30)

Yield: 112 mg (60%); white crystals; decomposition at 89–96 °C; ee: 78%; $t_R = 51.0$ (minor), 57.5 (major) min (Chiralpak OJ; 70% hexane/30% IPA; 1 mL/min; 20 °C; $\lambda = 265$ nm; 20 μ L).

$^1\text{H NMR}$ (500 MHz, $\text{DMSO}-d_6$): $\delta = 3.56$ (s, 3 H), 3.12 (t, $J = 6.8$ Hz, 1 H), 2.60 (ddd, $J = 30.6, 16.8, 7.5$ Hz, 2 H), 2.42 (ddd, $J = 25.6, 16.8, 5.9$ Hz, 2 H), 2.15 (s, 3 H).

^{13}C NMR (125 MHz, DMSO- d_6): δ = 209.0, 173.2, 172.3, 51.9, 44.3, 35.1, 34.7, 28.9.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_8\text{H}_{13}\text{O}_5$: 189.0763; found: 189.0756.

3-(2-Methoxy-2-oxoethyl)-4-oxohexanoic Acid (31)

Yield: 115 mg (57%); colourless oil; ee: 88%; t_R = 29.5 (minor), 36.5 (major) min (Chiralpak OJ); 70% hexane/30% IPA; 1 mL/min; 20 °C; λ = 265 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 3.64 (s, 3 H), 3.29 (quint., J = 6.8 Hz, 1 H), 2.70 (ddd, J = 23.6, 16.9, 7.6 Hz, 2 H), 2.58 (q, J = 7.0 Hz, 2 H), 2.45 (ddd, J = 16.8, 11.7, 6.2 Hz, 2 H), 1.02 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 211.5, 177.1, 171.9, 52.0, 42.8, 35.2, 35.1, 35.0, 7.5.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_9\text{H}_{15}\text{O}_5$: 203.0919; found: 203.0912.

3-(2-Methoxy-2-oxoethyl)-5-methyl-4-oxohexanoic Acid (32)

Yield: 116 mg (54%); colourless oil; ee: 88%; t_R = 36.5 (minor), 40.5 (major) min (Chiralpak OJ); 85% hexane/15% IPA; 1 mL/min; 20 °C; λ = 264 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 3.65 (s, 3 H), 3.48 (quint., J = 6.6 Hz, 1 H), 2.83 (hept, J = 7.0, 5.8 Hz, 1 H), 2.71 (ddd, J = 23.2, 16.8, 6.9 Hz, 2 H), 2.43 (ddd, J = 16.8, 11.4, 6.7 Hz, 2 H), 1.10 (d, J = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 214.2, 177.2, 171.8, 51.9, 41.7, 39.4, 35.0, 34.9, 18.4, 18.3.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{O}_5$: 217.1076; found: 217.1068.

3-(Cyclohexanecarbonyl)-5-methoxy-5-oxopentanoic Acid (33)

Yield: 150 mg (59%); colourless oil; ee: 92%; t_R = 22.5 (minor), 26.5 (major) min (Chiralpak OJ); 85% hexane/15% IPA; 1 mL/min; 20 °C; λ = 265 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 3.67 (s, 3 H), 3.52–3.45 (m, 1 H), 2.72 (ddd, J = 20.5, 16.8, 6.9 Hz, 2 H), 2.57 (tt, J = 11.0, 3.0 Hz, 1 H), 2.43 (ddd, J = 16.8, 11.0, 6.9 Hz, 2 H), 1.94–1.09 (m, 10 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 213.3, 177.1, 171.8, 51.9, 49.5, 41.7, 34.9, 34.8, 28.7, 28.5, 25.7, 25.7, 25.6.

HRMS (ESI): m/z [M – H] $^-$ calcd for $\text{C}_{13}\text{H}_{19}\text{O}_5$: 255.1232; found: 255.1235.

3-Benzoyl-5-ethoxy-5-oxopentanoic Acid (34)

Yield: 237 mg (90%); colourless oil; ee: 95%; t_R = 13.0 (minor), 22.6 (major) min (Chiralpak AD); 50% hexane/50% IPA; 1 mL/min; 20 °C; λ = 247 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 10.09 (s, 1 H), 7.97 (dt, J = 7.2, 1.3 Hz, 2 H), 7.61–7.52 (m, 1 H), 7.46 (dd, J = 8.4, 7.1 Hz, 2 H), 4.27 (quint., J = 6.9 Hz, 1 H), 4.07 (qd, J = 7.1, 2.5 Hz, 2 H), 2.84 (ddd, J = 33.8, 16.7, 7.1 Hz, 2 H), 2.53 (ddd, J = 19.2, 16.7, 6.8 Hz, 2 H), 1.17 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 200.6, 177.2, 171.3, 135.5, 133.4, 128.8, 128.5, 61.0, 38.6, 35.9, 35.4, 14.0.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{O}_5$: 265.1076; found: 265.1071.

3-Benzoyl-5-(benzyloxy)-5-oxopentanoic Acid (38)

Yield: 303 mg (93%); colourless oil; ee: 95%; t_R = 18.8 (minor), 26.9 (major) min (Chiralpak AD); 50% hexane/50% IPA; 1 mL/min; 20 °C; λ = 247 nm; 20 μL).

^1H NMR (500 MHz, CDCl_3): δ = 10.29 (s, 1 H), 8.01–7.95 (m, 2 H), 7.60–7.53 (m, 1 H), 7.46 (t, J = 7.8 Hz, 2 H), 7.37–7.24 (m, 5 H), 5.12–5.03 (m, 2 H), 4.31 (quint., J = 6.9 Hz, 1 H), 2.89 (ddd, J = 17.0, 7.1, 5.1 Hz, 2 H), 2.58 (ddd, J = 17.8, 16.8, 6.8 Hz, 2 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 200.5, 177.2, 171.2, 135.5, 133.4, 128.80, 128.58, 128.56, 128.33, 128.25, 66.8, 38.7, 35.8, 35.4.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{19}\text{H}_{18}\text{O}_5$: 327.1232; found: 327.1226.

Derivatisation for Chiral HPLC Analysis

In a screw-capped 4 mL vial, 4-dimethylaminopyridine (3 mg, 0.025 mmol, 0.05 equiv), the corresponding 5-methoxy-5-oxopentanoic acid (0.5 mmol, 1.0 equiv) and 2-nitrophenol (56 mg, 0.45 mmol, 0.9 equiv) were added sequentially. CH_2Cl_2 was added as solvent (2.5 mL, 0.2 M) and then DCC (63 mg, 0.45 mmol, 0.9 equiv) was added in one portion. The resulting yellow solution turned cloudy in a couple of minutes due to the formation of *N,N'*-dicyclohexylurea. The suspension was stirred at r.t. overnight. The product was separated by TLC then dissolved from the plate with 200 μL HPLC ethanol, diluted to 1 mL with HPLC hexane and introduced to the HPLC system.

Funding Information

We are grateful for the financial support from NKFIH (K116150).

Acknowledgment

The authors thank Gitta Schlosser for HRMS measurements.

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