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Multicatalytic Enantioselective Borrowing Hydrogen δ-Lactonization Strategy from β-Keto Esters and Allylic Alcohols

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Abstract  By combining an iron-catalyzed borrowing hydrogen of allylic alcohols with an enantioselective organocatalyzed Michael addition of β-keto esters followed by a subsequent DBU-promoted lactonization different enantioenriched δ-lactones have been synthesized with good enantiomeric ratios. The valuable building blocks, featuring in some cases challenging quaternary stereocenters, have been obtained with >90% ee.

Key words  organocatalysis, iron catalysis, lactone synthesis, borrowing hydrogen, multi-catalysis

The ability of organic chemists to synthesize rapidly original scaffolds is crucial for the future development of the pharmaceutical industry. In this context, the control of the stereochemistry of the newly formed molecular entities while taking into account eco-compatibility parameters such as the minimization of steps, time, or waste is crucial. To fulfill the above mentioned goal, recent developments in such as the minimization of steps, time, or waste is crucial. How- ever, the challenge of the enantioselective construction of otherwise poorly reactive substrates. However, the challenge of the enantioselective construction of chiral molecules through such reversible hydrogen transfer has only received limited attention as compared to the corresponding racemic or achiral techniques.

Substituted δ-lactones including spirocyclic congeners are common motifs represented in highly diversified families of natural products (Scheme 1, a). Given the interesting biological profiles associated with these skeletons, organic chemists have been pushed to develop creative methods to access these scaffolds. However, alternative methods decreasing time and waste for their preparation remain highly desirable to complete the toolbox available for synthetic chemists. We anticipated that a new enantioselective approach combining an iron-catalyzed borrowing hydrogen with an amino-catalyzed Michael addition should allow a rapid access to attractive δ-lactone frameworks (Scheme 1, b). By allowing the condensation of appropriate β-keto esters 1 with allylic alcohols 2, the resulting enantioenriched chiral alcohols 3 should then undergo a key cyclization affording the desired structures 4.

Our initial experiments conducted using a catalytic combination of iron cyclopentadienone complex [Fe] and CatI to control the stereochemistry indicated that the key lactone precursors 3a–c (2.3:1 ratio, equilibrium between

Scheme 1  Proposed multi-catalytic approach towards enantioenriched δ-lactones
open form and lactol) could be prepared with 79 to 86% ee from readily available cyclic β-keto esters 1a–c and crotyl alcohol (2a). In this reaction, the iron catalyst promotes a reversible hydrogen transfer from the alcohol to the aldehyde level while the organocatalyst controls the stereoselectivity of the Michael addition on the formed α,β-unsaturated aldehyde. From the obtained enantiomerically enriched alcohols isolated as single diastereomers, several spiro lactonization conditions were tested (Table 1).

These investigations revealed the relative sensitivity of the obtained alcohols, particularly recalcitrant to the ring closure. From 3b (R = Et, t-Bu), using thermal (Table 1, entries 1, 4), acidic (entry 2), or mildly basic conditions (entry 3), only degradation of the starting material was observed possibly through side reaction of the unprotected ketone. Interestingly, when turning to the use of the less sterically hindered compound 3a (R = Me), using TBAF in THF afforded after one hour around 50% of the expected spiro lactone 4 in combination with other undescribed side products (entry 7). Use of other bases such as Cs2CO3 or DBU in THF or toluene (entries 8, 9), resulted in better selectivity forming 4 in excellent 88–90% yield. Given the relative price of DBU versus Cs2CO3, we selected the conditions of entry 9 for the investigation of the scope of the lactonization.

Using the optimized conditions of Table 1, different cyclic keto esters and allylic alcohols combination were tested in the lactone formation (Scheme 2). Using aliphatic alcohols 2 (R = Me, n-Pr, CH2CH2Ph), different spiro-β-lactones 4–7 were formed in 25–37% yield over two steps with 73 to 90% ee. It is important to point out that the final lactones possessing a challenging quaternary stereocenter are isolated as single diastereomers, the minor one being separated by column chromatography after the first step of the process. Using the sterically hindered keto ester 1d possessing a gem-dimethyl substituent, the reaction worked equally well forming 7 in 38% yield over two steps with 80% ee.

We recently reported that the addition of a soft Lewis acid such as Cu(acac)2 could be beneficial to improve both reactivity and enantioselectivity in multi-catalyzed borrowing hydrogen. We thus decided to verify the efficiency of a triple iron-, copper-, organocatalytic system towards spiro lactone formation (Scheme 3). Gratifyingly, adding 5 mol% of Cu(acac)2 to the system and performing the reaction at 10 °C, the first step worked better providing after DBU promoted lactonization, the expected spiro-β-lactones with significantly improved ee. Using this two-step protocol, all spiro-β-lactones were formed in ≥90% ee in 21 to 51% yield.

In order to simplify our approach, we subsequently wondered about applying a one-pot procedure where the intermediate lactol would not be isolated prior to spiro lactonization limiting the number of operations necessary to access the key spiro lactones. Interestingly, directly adding DBU after completion of the borrowing hydrogen, the expected lactone could be formed (Scheme 4). It is important to point out that a kinetic resolution of the intermediate lactol was observed here. Indeed, only the major diastere-
mer of intermediate 3a reacted forming 4 in 48% yield and 92% ee while the minor diastereomer 3a remained untouched.

Besides from spirolactones, we also wondered about the formation of simple stereodefined monocyclic lactones 11 starting from more challenging acyclic non-substituted β-keto esters such as methyl acetooctate (9) (Table 2). In this case, other possible reactivity issues at various stages of the sequence could replace the difficulty associated with the formation of a quaternary stereocenter. Indeed, the potential formation of a unproductive Knoevenagel adduct can inhibit the overall transformation, while the possible evolution of the transient Michael adduct 10 by a competitive retro-Dieckmann type fragmentation can produce the undesired acyclic ketone 12. However, gratifyingly the triple-catalytic enantioslective sequence proved to be efficient with 9 and crotyl alcohol (2a) leading to the expected reduced Michael adduct 10 as its hemiacetal form in 60% yield and 90% ee.

From here, initial lactonization attempt using the same conditions as for spirolactones (Table 2) failed and virtually no conversion of 10 was observed (Table 2, entry 1). When forcing the conditions by increasing the temperature to 60 or 80 °C (entries 2, 3), a partial conversion, a mixture of

\[ \begin{align*}
\text{1a, } X &= \text{Me} \\
\text{1b, } X &= \text{OCH}_3
\end{align*} \]

\[ \begin{align*}
\text{2a-c} \\
\text{2a} \\
\text{3a} & \text{ 48% yield}^a \\
\text{3a} \text{ unreacted minor diastereomer}
\end{align*} \]

\[ \begin{align*}
\text{4, 51% yield}^a \\
\text{5, 25% yield}^a \\
\text{6, 49% yield}^a \\
\text{7, 21% yield}^a
\end{align*} \]

\[ \begin{align*}
\text{Scheme 3 Scope of the triple-catalytic approach to enantiorenergic spiro-δ-lactones 4–7. a Isolated pure diastereomer.}
\end{align*} \]

\[ \begin{align*}
\text{One-pot process:} \\
\text{[Fe] (6.5 mol%)} \\
\text{MeNO·2H}_2\text{O (8 mol%)} \\
\text{Cat 1 (13 mol%)} \\
\text{Cu(acac)}_2 (5 mol%) \\
xylanes, 10 °C, 64 h \\
\text{then DBU, r.t., 2 h}
\end{align*} \]

\[ \begin{align*}
\text{1a} \\
\text{2a} \\
\text{1b} \\
\text{2b} \\
\text{3a} & \text{ 92% ee}
\end{align*} \]

\[ \begin{align*}
\text{Scheme 4 One-pot synthesis of spiro-δ-lactone 4. a Isolated pure diastereomer.}
\end{align*} \]

\[ \begin{align*}
\text{1a} & \text{ DBU, toluene, r.t., 2 h} \\
\text{2a} & \text{ DBU, toluene, 60 °C, 12 h} \\
\text{3a} & \text{ DBU, toluene, 80 °C, 14 h} \\
\text{4} & \text{ DBU, toluene, 80 °C, 48 h} \\
\text{5} & \text{ DBU, toluene, 60 °C, MW, 10 min} \\
\text{6} & \text{ DBU, toluene, 80 °C, MW, 90 min} \\
\text{7} & \text{ DBU, toluene, 100 °C, MW, 20 min} \\
\text{8} & \text{ DBU, toluene, 60 °C, MW, 30 min}
\end{align*} \]

\[ \begin{align*}
\text{Table 2 Selected Optimization for Formation of δ-Lactones 11}
\end{align*} \]

\[ \begin{align*}
\text{Entry} & \text{ Lactonization conditions} & \text{Ratio}^a \text{ Yield}^a \text{ of 11} \\
1 & \text{DBU, toluene, r.t., 2 h} & 99:1:1 & – \\
2 & \text{DBU, toluene, 60 °C, 12 h} & 76:99:1 & \text{nd} \\
3 & \text{DBU, toluene, 80 °C, 14 h} & 1.3:1:1.6 & \text{nd} \\
4 & \text{DBU, toluene, 80 °C, 48 h} & 1.2:1:5.4 & \text{nd} \\
5 & \text{DBU, toluene, 60 °C, MW, 10 min} & 99:24:1 & \text{nd} \\
6 & \text{DBU, toluene, 80 °C, MW, 90 min} & 40:99:1 & 28 \\
7 & \text{DBU, toluene, 100 °C, MW, 20 min} & 32:99:1 & 30 \\
8 & \text{DBU, toluene, 60 °C, MW, 30 min} & 52:99:1 & 52 (71, brsm)
\end{align*} \]

\[ \begin{align*}
^a \text{Determined by } ^1\text{H NMR spectroscopy.} \\
^b \text{Isolated yield; nd = not determined.}
\end{align*} \]
In conclusion, we have shown that combining a cooperative multiple catalytic enantioselective sequence with a DBU-promoted lactonization allowed the formation of valuable \( \delta \)-lactones starting from simple \( \beta \)-keto esters and allylic alcohols. Thanks to the cooperative role of the different catalysts, these lactones were formed in >90% ee. In addition, spirilocactones were synthesized with the controlled formation of challenging quaternary stereocenters.

Finally, this two-step sequence could be combined in one pot, reducing the required operations to access these building blocks, which should ensure a rapid application of this strategy.

NMR spectra were recorded on a Bruker AC 300 (300 MHz) or a Bruker AC 400 (400 MHz) spectrometer in CDC\(_3\). Chemical shifts are given in ppm, using as internal standards the residual CHCl\(_3\) signal for \(^1\)H NMR (\( \delta = 7.26 \)) and the deuterated solvent signal for \(^13\)C NMR (\( \delta = 77.0 \)). Data for \(^13\)C NMR are reported as follows: chemical shift (multiplicity), coupling constant \( J \) in hertz (Hz), integration. Anhyd toluene was obtained from a Solvent Purification System M Braun SPS-800. Unless specified, all other solvents were used in their commercial form without further purification. TLC analyses were conducted on Merck 60 F254 silica gel plates and on Alugram ALOX N/UV254 and revealed under UV lamp (\( \lambda = 254 \) nm) and with universal stain: p-anisaldehyde (prepared from 5 mL of p-anisaldehyde with 30 g of ice, 60 mL of EtOH, 5 mL of H\(_2\)SO\(_4\)), and 0.5 mL of ACOH). Flash Chromatography was performed following the method of Still on 40–63 \( \mu \)m silica gel or 63–200 \( \mu \)m Al\(_2\)O\(_3\), 90 active basic eluted with the specified eluent.

High-resolution mass spectra (HRMS) were performed on a QStar Elite (Applied Biosystems SCIEX) spectrometer equipped with pneumatically assisted atmospheric pressure ionization source (APPI). Samples were ionized by positive electrospray mode as follow: electro-spray tension (ISV): 5500 V; opening tension (OR): 50 V; nebulization gas pressure (air): 20 psi.

Chiral HPLC analyses were performed at the Chiral Chromatography Laboratory of Aix Marseille University (Sm2, plateforme de Chromatographie Chirale et de Stéréochimie Dynamique). The screening of chiral stationary phases was performed on two chromatographic units: 1) Merck-Lachrom unit: Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7200 autosampler, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, with EZChrom Elite software. 2) Lachrom-Elite unit: L-2130 pump, L-2220 autosampler, L-2350 oven and D-2455 detector. The samples were also detected by detectors of chirality: Jasco OR-1590 polarimeter or Jasco CD-1595 detector. Hexane, i-ProH and EtoH, HPLC grade, from Hipersolv Chromanorm (VWR), were degassed and filtered on a 0.45 \( \mu \)m millipore membrane before use. Retention time \( \text{Rt, abbreviated as } t_R \text{ in the experimental part} \) in min, retention factor \( \text{ki} = (\text{Rt-R0})/R0 \) and enantioselectivity factor \( a_R = k_R/k_L \) are given. R0 was determined by injection of tri-tert-butylbenzene.

The different analytical columns (250 × 46 mm)\(^a\) tested are Chiralcel OD-3, QJ-H, Chiralpak® AS-H, AD-H, AZ-H, IA, IB, and IC columns from Chiral Technology Europa (Illkirch, France), Lux-Amylese-2, Lux-Cellulose-2, and Lux-Cellulose-4, from Phenomenex and Whelk-O1 (SS) and Ulmo (SS) from Regis Technologies (Morton Grove, USA). Chiral GC analysis were performed on a HP 4890 using 6 bar argon as vector. Column: Hydrodex-\( \beta \), Lipodex-\( \epsilon \) from Macherey-Nagel (25 m/0.25 mm) and Cyclodisil-\( \beta \) from Agilent (18 m/0.25 mm). Chromatogram was analyzed with ChromNav software.

Iron-, Organocatalytic Catalytic Enantioselective Borrowing Hydrogen; General Procedure (GP1)

To a solution of \( \beta \)-keto ester 1 (0.3 mmol, 1 equiv) in anhyd toluene (0.9 mL) was successively added Cat 1 (12.5 mg, 0.039 mmol, 13 mol%) and allylic alcohol 2 (0.45 mmol, 1.5 equiv). [Fe] complex (8.2 mg, 0.0195 mmol, 6.5 mol%) and Me\(_2\)NO (1.8 mg, 0.024 mmol, 8 mol%) were then added at once. Argon was immediately passed through the vial for 20 seconds, the vial was closed, and the contents were stirred at rt. (20–22 °C) for the indicated time. Sat. aq NH\(_4\)Cl (1.5 mL) was then added, the aqueous layer extracted with Et\(_2\)O (3 × 2 mL), the combined organic layers dried (Na\(_2\)SO\(_4\)), filtered, and the solvent evaporated. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected functionalized alcohol in equilibrium between open and closed form.

Triple Catalytic Enantioselective Borrowing Hydrogen; General Procedure (GP2)

To a solution of \( \beta \)-keto ester 1 (0.2 mmol, 1 equiv) in anhyd xylene (0.6 mL) were added successively, allylic alcohol 2 (0.4 mmol, 2 equiv), Cu(acac)\(_2\) (2.4 mg, 0.01 mmol, 5 mol%), and Cat 1 (9.4 mg, 0.026 mmol, 13 mol%). [Fe] complex (3.4 mg, 0.013 mmol, 6.5 mol%) and Me\(_2\)NO/2H\(_2\)O (1.8 mg, 0.016 mmol, 8 mol%) were added all at once. Argon was immediately passed through the vial for 20 seconds, the vial was closed, and the contents were stirred at 10 °C for the indicated time. Sat. aq NH\(_4\)Cl (1.5 mL) was added and the aqueous layer extracted with Et\(_2\)O (3 × 2 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\)) and the solvent was removed under vacuum. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected functionalized alcohol in equilibrium between open and closed forms.

Methyl (R)-(\(\pm\)R)-4-Hydroxybutan-2-yl]-2-oxocyclopentane-1-carboxylate (3a)

Prepared according to the general triple catalytic procedure (GP2) starting from \( \beta \)-keto ester 1a (28.4 mg, 0.2 mmol) and allylic alcohol 2a (28.8 mg, 0.4 mmol), and purified by chromatography over silica gel (PE/EtOAc 9:1 to 8:2). The product was isolated as a pale yellow oil with >95:5 dr: yield: 23 mg (55%, 0.101 mmol); 90% ee.

The product was obtained as a mixture of open A and closed B forms in a 2:3:1 ratio; \( R_\beta = 0.11 \) (PE/EtOAc, 7:3); [\( \alpha \)]\(_{D, \text{cyc}}^20\) = –9.3 (CHCl\(_3\), c = 0.41, 84% ee sample).

HPLC determination of the enantiomeric excess on the corresponding benzoyl protected alcohol prepared according to procedure C as reported in our earlier work.\(^1\) Lux-Amylese-2, hexane/EtOH (90:10), 1 mL/min, UV 220 nm: \( t_i \) (major) = 15.8 min, \( t_{i, \text{minor}} \) = 23.8 min.

\(^1\) H NMR (400 MHz, CDCl\(_3\)), \( \delta = 0.84 \) (d, J = 6.8 Hz, CH\(_{3}\) A), 1.00 (d, J = 6.8 Hz, CH\(_{3}\) B), 1.20–2.18 (m, 7 H, A + B + OH A), 2.38–2.56 (m, 2 H, A + B), 3.50–3.73 (m, 4 H, A + B + 1 H of CH\(_2\) B), 4.08 (ddd, J = 4.4, 3.6, 3.4 Hz, 1 H of CH\(_2\) B), 4.26 (br s, OH, B).
with 95:5 (32.4 mg, 0.45 mmol). The product was isolated as a pale yellow oil with >95% dr; yield: 38.9 mg (57%, 0.171 mmol); 86% ee.

The product was obtained as a mixture of open A and closed B forms in a 2.3:1 ratio; \( \delta \) = 0.17 (PE/ESI/MS, 7:3); \([\alpha]_D^{20} = -7.10 \) (CHCl₃, c = 0.45, 98% ee sample).

**Ethyl (R)-1-[((R)-4-Hydroxybutan-2-yl)-2-oxocyclopentane-1-carboxylate (3b)**

Prepared according to the general bi-catalytic procedure (GP1) starting from \( \beta \)-keto ester \( 1b \) (46.7 mg, 0.33 mmol) and allylic alcohol \( 2b \) (R = Pr; 40 mg, 0.4 mmol), Purification over silica gel (PE/EOAc 9:1 to 8:2). The product was isolated as a pale yellow oil; yield: 13 mg (28%, 0.048 mmol). The ee was determined in the next step; \( R_f = 0.42 \) (PE/ESI/MS, 7:3).

** tert-Butyl (R)-1-[((R)-4-Hydroxybutan-2-yl)-2-oxocyclopentane-1-carboxylate (3c)**

Prepared according to the general bi-catalytic procedure (GP1) starting from \( \beta \)-keto ester \( 1c \) (55.1 mg, 0.33 mmol) and allylic alcohol \( 2c \) (32.4 mg, 0.45 mmol). The product was isolated as a pale yellow oil with 95:5 dr; yield: 41.9 mg (54%, 0.163 mmol); 73% ee.

The product was obtained as a mixture of open A and closed B forms in a 2.3:1 ratio; \( \delta \) = 0.21 (PE/ESI/MS, 7:3); \([\alpha]_D^{20} = -5.9 \) (CHCl₃, c = 0.57, 79% ee sample).

**Ethyl (R)-1-[((R)-3-Hydroxypentan-2-yl)-2-oxocyclopentane-1-carboxylate (3d)**

Prepared according to the general bi-catalytic procedure (GP1) starting from \( \beta \)-keto ester \( 1d \) (28.5 mg, 0.17 mmol) and allylic alcohol \( 2d \) (R = Pr; 25 mg, 0.34 mmol). The product was purified by chromatography over silica gel (PE/EOAc 8:2) and isolated as a pale yellow oil; yield: 9 mg (23%, 0.038 mmol). The ee was determined in the next step; \( R_f = 0.23 \) (PE/ESI/MS, 7:3).
Methyl (4R)-2-Hydroxy-2,4-dimethyltetrahydro-2H-pyran-3-carboxylate (10)

Prepared according to the triple-catalysis general procedure (GP2) using Cat2, β-keto ester 9 (24.6 mg, 0.21 mmol), and allylic alcohol 2a (30 mg, 0.42 mmol), and purified by chromatography over silica gel (PE/EtOAc 9:1). The product was isolated as a yellow oil; yield: 24 mg (60%, 0.128 mmol); HRMS-ESI: \( [M + H]\) 132.0905 (calcd 132.0897); \( \Delta m = 0.37 \) (PE/EtOAc 7:3); \( \Delta m = 0.7 \) (EtOAc). GC enantiomeric excess determination: Hydrodex, method: 0 min at 90 °C then 1 °C/min to 225 °C, \( t_\text{R} \) (minor) = 19.47 min. 3\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 4.12–4.00 \) (m, 1 H of CH\(_2\)), 2.30–2.07 (m, 2 H), 1.66–1.53 (1 H of CH\(_2\)), 1.47–1.20 (m, 4 H, CH\(_2\)), 1.17–1.10 (m, 1 H of CH\(_2\)), 0.90 (d, \( J = 5.9 \) Hz, CH\(_3\), 3 H). 3\(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 175.5 \) (COOR), 154.0 (C=O), 80.4 (CH\(_2\)), 75.6 (CH\(_2\)), 60.9 (CH\(_2\)), 32.7 (CH\(_2\)), 29.2 (CH\(_2\)), 28.8 (CH\(_2\)), 20.2 (CH\(_3\)).

HRMS-ESI: \( m/z [M + H]^+ \) calcd for C\(_6\)H\(_{10}\)O\(_3\): 193.1179; found: 193.1177.

Spirolactone Formation; General Procedure

To the solution of the corresponding cascade adduct in anhyd toluene (0.17 M) was added DBU (1.9 equiv). The mixture was then stirred at r.t. (22–25 °C) for 2 h. Then, aq 1 M HCl (1.5 mL) was added. The aqueous layer was extracted with Et\(_2\)O (3 × 2 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\)) and the solvent was removed under vacuum. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected lactone.

One-Pot Spirolactonization; (SR,10R)-10-Methyl-7-oxaspiro[4.5]decane-1,6-dione (4)

Prepared according to the general procedure starting from 3a (23 mg, 0.17 mmol) and purified by chromatography over silica gel (PE/EtOAc 9:1). The product was separated as a pale yellow oil; yield: 18 mg (92%, 0.099 mmol); \( \% \text{ ee} \); \( R_\text{R} = 0.37 \) (PE/EtOAc 7:3); \( \Delta m = 11.5 \) (CHCl\(_3\), c = 1 ml, 1 H) 99:1 dr, 93% ee. GC enantiomeric excess determination: Hydrodex, method: 0 min at 90 °C then 1 °C/min to 220 °C, \( t_\text{R} \) = 57.023 min, \( t_\text{R} \) = 57.825 min, \( t_\text{R} \) = 61.5 min, \( t_\text{R} \) = 62.4 min. 3\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 4.50–4.27 \) (m, 2 H), 2.70–2.54 (m, 1 H of CH\(_2\)), 2.52–2.43 (m, 1 H of CH\(_2\)), 2.34–2.20 (m, 4 H), 2.04–1.86 (m, 2 H), 1.75–1.64 (m, 1 H), 0.94 (d, \( J = 6.8 \) Hz, 3 H). 3\(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 217.3 \) (CO), 171.8 (COOR), 67.5 (CH\(_3\)), 61.2 (Quat), 37.6 (CH\(_2\)), 29.6 (CH\(_2\)), 26.7 (CH\(_2\)), 20.1 (CH\(_3\)), 16.5 (CH\(_2\)), 14.8 (CH\(_3\)).

HRMS-ESI: \( m/z [M + H]^+ \) calcd for C\(_{13}\)H\(_{20}\)O\(_3\): 318.1012; found: 318.1012.

(SR,10R)-10-Propyl-7-oxaspiro[4.5]decane-1,6-dione (5)

Prepared according to the general procedure starting from the corresponding cascade adduct (12 mg, 0.048 mmol) and purified by chromatography over silica gel (PE/EtOAc 9:1 to 8:2). The product was isolated as a pale yellow oil; yield: 20 mg (90%, 0.046 mmol); \( \% \text{ ee} \); \( R_\text{R} = 0.42 \) (PE/EtOAc 7:3); \( \Delta m = 67.5 \) (CHCl\(_3\), c = 0.9 ml, 99:1 dr, 93% ee). GC enantiomeric excess determination: Hydrodex, method: 0 min at 90 °C then, 1 °C/min to 225 °C, \( t_\text{R} \) (major) = 75.23 min, \( t_\text{R} \) (minor) = 74.83 min. 3\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 4.45–4.38 \) (m, 2 H), 2.63–2.55 (m, 2 H), 2.39–2.07 (m, 4 H), 1.93–1.77 (m, 2 H), 1.70–1.63 (m, 1 H, 1.61–1.19 (m, 4 H), 0.89 (m, 3 H). 3\(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 215.6 \) (CO), 171.5 (COOR), 69.3 (CH\(_3\)), 60.2 (Quat), 39.06 (CH\(_2\)), 36.6 (CH\(_2\)), 32.7 (CH\(_2\)), 30.5 (CH\(_2\)), 24.9 (CH\(_3\)), 20.5 (CH\(_2\)), 19.4 (CH\(_3\)), 14.0 (CH\(_3\)).

HRMS-ESI: \( m/z [M + H]^+ \) calcd for C\(_{13}\)H\(_{21}\)O\(_3\): 211.1327; found: 211.1324.

(SR,10R)-10-Phenethyl-7-oxaspiro[4.5]decane-1,6-dione (6)

Prepared according to the general procedure starting from the corresponding cascade adduct (35 mg, 0.115 mmol) and purified by chromatography over silica gel (PE/EtOAc 9:1). The product was isolated as a pale yellow oil; yield: 27 mg (86%, 0.099 mmol); \( \% \text{ ee} \); \( R_\text{R} = 0.47 \) (PE/EtOAc 7:3); \( \Delta m = 14 \) (CHCl\(_3\), c = 0.7 ml, 99:1 dr, 93% ee). HPLC enantiomeric excess determination: Lux-Cellulose-4, heptane/EtOH (80:20), 1 mL/min, \( t_\text{R} \) (minor) = 11.46 min, \( t_\text{R} \) (major) = 12.55 min. 3\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.33–7.26 \) (m, 2 H), 7.24–7.17 (m, 1 H), 7.16–7.12 (m, 2 H), 4.50–4.44 (m, 1 H of CH\(_2\)), 4.40–4.32 (m, 1 H of CH\(_2\)), 2.78–2.49 (m, 3 H), 2.44–2.33 (m, 1 H), 2.33–2.07 (m, 5 H), 1.95–1.87 (m, 1 H), 1.78–1.66 (m, 1 H), 1.60–1.37 (m, 2 H).

3\(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 215.4 \) (CO), 171.3 (COOR), 141.0 (CO), 128.6 (CH\(_{2\text{ax}}\)), 128.2 (CH\(_{2\text{ax}}\)), 126.3 (CH\(_{2\text{ax}}\)), 69.2 (CH\(_3\)), 60.3 (Quat), 38.9 (CH\(_3\)), 36.7 (CH\(_2\)), 33.8 (CH\(_3\)), 32.6 (CH\(_3\)), 30.5 (CH\(_2\)), 24.9 (CH\(_3\)), 19.4 (CH\(_3\)).

HRMS-ESI: \( m/z [M + H]^+ \) calcd for C\(_{16}\)H\(_{21}\)O\(_3\): 273.1478; found: 273.1480.
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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588547.

**References**


(11) We are not aware of such challenging lactonization on non-substituted keto esters.