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Enantioselective desymmetrization of glutarimides catalysed by oxazaborolidines derived from cis-1-amino-indan-2-ol

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Abstract

Enantioselective reductive desymmetrization of glutarimides has been achieved employing an oxazaborolidine catalyst derived from cis-1-amino-indan-2-ol. The reaction was found to proceed through a stereoablative process that upgraded the enantioselectivity of an intermediate hydroxy-lactam. The reaction was generally tolerant of a number of substituents in the 4-position, giving enantiomeric excesses of greater than 82%.

Introduction
Desymmetrization to access chiral molecules is a popular strategy in organic synthesis, providing compounds with multiple stereogenic centers in one operation. The synthetic chemistry used in these strategies can be wide-ranging, for example, the addition of chiral alcohols to cyclic meso-anhydrides to yield diastereomERICally-enriched mono esters, or the use of chiral C₃-symmetric zirconium(IV) and C₂-symmetric chromium (III) complexes to catalyse the addition of azide nucleophiles to meso-epoxides. Desymmetrization of five-membered ring meso-imides is an important approach, as enantioselective reduction of one of the carbonyl groups leads to the chiral 5-hydroxy-2-pyrrolidinones, important intermediates in the synthesis of many natural products and other important heterocyclics. Strategies within this area of chemistry include the use of chiral auxiliaries, BINAL-H complexes, and thiazazincolidine complexes for enantioselective reduction to affect such transformations. Oxazaborolidine mediated borane reduction, using catalysts derived from α,α-diphenylprolinol have also been reported, but require as much as 50 mol% catalyst to obtain high yield and selectivity. Several reports from this research group have shown that alternative oxazaborolidine catalysts derived from cis-1-amino-indan-2-ol are very effective for this desymmetrization process, proceeding with good enantiomeric excess at significantly lower catalyst loadings compared to reactions using the prolinol-derived catalyst, with further studies demonstrating the crucial role of the nitrogen substituent in obtaining high selectivities. The use of these catalysts for the kinetic resolution of racemic C-3 substituted imides has also been reported. More recently, in attempting to accessing the target molecule pyrrolam A, we have disclosed a hitherto unreported stereoablative process that serves to upgrade the enantioselectivity of this process. Although there has been much work on the desymetrisation of five-membered ring meso-imides, the six-membered ring glutarimides have received little attention. There appear to be
only two strategies developed to desymmetrize glutarimides; the first by Simpkins and co-
workers using a chiral bis-lithium amide base to give chiral 3,4-disubstituted piperidin-2,5-
diones,\textsuperscript{15} and the second by Ikariya and co-workers using chiral Cp*Ru(PN) catalysts to affect
the enantioselective hydrogenative desymmetrisation to give the corresponding hydroxyamides
in excellent ee’s (88-98%).\textsuperscript{16, 17} Here we present the enantioselective desymmetrisation of 3-
substituted glutarimides using oxazaborolidine catalysts derived from cis-1-amino-indan-2-ol.

\textbf{Results and discussion}

The 3-arylsubstituted glutaric acids 1b–1f required for preparing the glutarimides, were
synthesised from the corresponding aldehydes by adapting literature procedures. The aldehydes
were first converted to the 2-substituted tetaethyl propane tetracarboxylates through
Knoevenegel condensation followed by Michael addition.\textsuperscript{18} In the case of p-substituted aromatic
aldehydes these solvent-free conditions do not give the required tetracarboxylates but instead
yield the corresponding benzoic acid. However, drop-wise addition of a solution of the aldehyde
in toluene to a mixture of diethylmalonate and AlCl$_3$ in toluene in the Knoevenegel condensation
step led to the required product. For the 3-alkyl glutaric acids 1h & 1i the method of Theisen et
al. gave better yields which uses ethyl cyanoacetate in the Knoevenegel step and dimethyl
dosiomalonate for the Michael addition (Scheme 1).\textsuperscript{19} The resultant dimalonates then underwent
acid hydrolysis and decarboxylation giving the corresponding glutaric acids in moderate yields
(Scheme 1). 3-Phenylglutaric acid 1a and 3-methylglutaric acid 1g are commercially available
and were used as purchased. The glutarimides 3, 4a-i, 5 & 6 were accessed in a procedure
developed by Ikariya et al. by transforming the glutaric acids 1a-i to the corresponding
anhydrides 2a-i which were subsequently converted to the imides (Scheme 1, Table 1).\textsuperscript{16}
Scheme 1. Route to glutarimide substrates

Table 1. Synthesis of 3-Substituted Glutaric acids, Anhydrides, and Glutarimides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>R^2</th>
<th>Yield</th>
<th>Glutaric acid^a</th>
<th>Anhydride</th>
<th>Imide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4-MeOC_6H_4</td>
<td></td>
<td>1a^b</td>
<td>2a 82%</td>
<td>3 80%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>CH_3C_6H_5</td>
<td></td>
<td>1a^b</td>
<td>2a 82%</td>
<td>4a 85%</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>CH_2(2-MeC_6H_4)</td>
<td></td>
<td>1a^b</td>
<td>2a 82%</td>
<td>5 71%</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>CH_2(2-MeOC_6H_4)</td>
<td></td>
<td>1a^b</td>
<td>2a 82%</td>
<td>6 60%</td>
</tr>
<tr>
<td>5</td>
<td>2-FC_6H_4</td>
<td>CH_3C_6H_5</td>
<td>1b 52%</td>
<td>2b 75%</td>
<td>4b 87%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4-FC_6H_4</td>
<td>CH_3C_6H_5</td>
<td>1c 57%</td>
<td>2c 93%</td>
<td>4c 71%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2-MeC_6H_4</td>
<td>CH_3C_6H_5</td>
<td>1d 51%</td>
<td>2d 73%</td>
<td>4d 60%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-MeC_6H_4</td>
<td>CH_3C_6H_5</td>
<td>1e 50%</td>
<td>3e 85%</td>
<td>4e 67%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1-Naphthyl</td>
<td>CH_3C_6H_5</td>
<td>1f 60%</td>
<td>3f 80%</td>
<td>4f 52%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>CH_3C_6H_5</td>
<td>1g^b</td>
<td>3g 79%</td>
<td>4g 68%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>iPr</td>
<td>CH_3C_6H_5</td>
<td>1h 35%</td>
<td>3h 79%</td>
<td>4h 70%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>t-Bu</td>
<td>CH_3C_6H_5</td>
<td>1i 58%</td>
<td>3i 70%</td>
<td>4i 89%</td>
<td></td>
</tr>
</tbody>
</table>

^a Refers to yield of isolated product after 3 step sequence; ^b Commercially available material so no yield reported.
The initial screening for the best desymmetrization conditions was first carried out on N-PMP protected 3-phenylglutarimide 3 using both B-OMe catalyst 7 and B-Me catalyst 8 employing BH\(_3\).THF as borane source. Two methods of preparing the catalysts were evaluated; the first involved preparing the stock solution of the catalyst in situ at room temperature and using it immediately, while the second involved repeated azeotropic distillations before the final stock solution of the catalyst was made. In all cases, monitoring of the reaction by TLC indicated an optimum conversion to product after 3 h, and therefore the reactions were stopped at this point and the crude mixture reduced with triethylsilane to convert the intermediate hydroxyl-lactam to the more stable 2-piperidinone 10a to aid analysis (Scheme 2, Table 2). In all cases, the presence of the piperidine 11a was observed, formed by over-reduction of the intermediate hydroxyl-lactam. This relatively rapid formation of the doubly reduced product was observed in earlier work on related N-PMP five membered imides.\(^\text{14}\)

Scheme 2. Reduction of meso-glutarimides 3, 4a, 5 and 6.
Table 2. Screening Catalysts for Desymmetrisation of glutarimides 3, 4a, 5 and 6.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Method</th>
<th>Product / yield (%)</th>
<th>10a-d ee (%)</th>
<th>10a-d ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>7</td>
<td>A</td>
<td>3a (20)</td>
<td>10a (48)</td>
<td>11a (21)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>7</td>
<td>B</td>
<td>3a (37)</td>
<td>10a (43)</td>
<td>11a (15)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>8</td>
<td>A</td>
<td>3a (66)</td>
<td>10a (18)</td>
<td>11a (10)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>8</td>
<td>B</td>
<td>3a (28)</td>
<td>10a (33)</td>
<td>11a (30)</td>
</tr>
<tr>
<td>5</td>
<td>4a</td>
<td>7</td>
<td>A</td>
<td>4a (60)</td>
<td>10b (34)</td>
<td>11b (5)</td>
</tr>
<tr>
<td>6</td>
<td>4a</td>
<td>7</td>
<td>B</td>
<td>4a (59)</td>
<td>10b (30)</td>
<td>11b (5)</td>
</tr>
<tr>
<td>7</td>
<td>4a</td>
<td>8</td>
<td>A</td>
<td>4a (62)</td>
<td>10b (20)</td>
<td>11b (9)</td>
</tr>
<tr>
<td>8</td>
<td>4a</td>
<td>8</td>
<td>B</td>
<td>4a (20)</td>
<td>10b (60)</td>
<td>11b (12)</td>
</tr>
<tr>
<td>10</td>
<td>4a</td>
<td>9</td>
<td>B</td>
<td>ND</td>
<td>10b (13)</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>8</td>
<td>B</td>
<td>ND</td>
<td>10c (25)</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>8</td>
<td>B</td>
<td>ND</td>
<td>10d (21)</td>
<td>ND</td>
</tr>
</tbody>
</table>

\(^a\) Reactions conducted by treating a solution of the glutarimide 3 in dry \(\text{CH}_2\text{Cl}_2\) with 10 mol% of the catalyst solution and 1 equiv BH\(_3\)·THF at rt for 3 h, followed work-up, dissolution into \(\text{CH}_2\text{Cl}_2\) and treatment with Et\(_3\)SiH / TFA for 1 h. \(^b\) Refers to isolated components after column chromatography. \(^c\) Determined by chiral phase HPLC. \(^d\) Catalyst prepared by mixing (1R, 2S)-cis-1-aminoindan-2-ol (1.00 mmol) and either trimethylborate (0.10 mL, 1.00 mmol) or trimethylboroxine (0.05 mL, 0.33 mmol) in THF (3 mL) and allowing to stir for 45 min, before dilution to 5 mL with THF. \(^e\) Catalyst prepared by reaction of (1R, 2S)-cis-amino-2-indanol (1.00 mmol) in dry toluene (3 mL) with either trimethylboroxine (0.33 mmol) or trimethylborate (1.00 mmol) and allowed to stir for 30 min before azeotropic distillation with dry toluene. Dry dichloromethane (5 mL) was added to give a stock solution of the catalyst. \(^f\) ND – not determined.

When using the N-PMP substrate 3 with the B-OMe catalyst, both methods of preparation gave excellent ee's of piperidinone 10a, however method A produced the 2-piperidinone 10a in a 48% yield and the undesired piperidine 11a in a 21% yield (Table 2, entry 1) while method B gave 43% yield of the desired product 10a and 15% of the undesired product 11b (Table 2, entry 2). For the B-Me catalyst, a significant difference in both yield and enantioselectivity was observed for the two methods of preparing the catalyst (Table 2, entries 3 and 4). Only 18% yield and 53% ee of the desired product was obtained when the catalyst was prepared in situ at room
temperature while for the method involving azeotropic distillation gave 33% yield of the desired product in 95% ee. The undesired over-reduced product was also increased from 10% to 30%.

The desymmetrisation of 3-phenyl N-benzyl glutarimide analogue 4a was also explored using both B-Me and B-OMe catalysts (Table 2, entries 5-8). The formation of the piperidine product 11b was significantly slower compared to N-PMP glutarimide 3 which allowed the reaction time to be extended to as long as 24 hours. As expected, a slight decrease in selectivity was observed with both catalysts showing consistency with observations from earlier work on five-membered meso-imides.12 As with the PMP substrates, the B-OMe catalyst gave rather disappointing results, but again, use of the repetitive azeotropic distillation protocol for the preparation of B-Me catalyst led to a significant increase in the yield of the desymmetrised product, from 33% (Table 2, entry 4) to 60% (Table 2, entry 8), with only a slight decrease in enantioselectivity. Thus, this was adopted as the optimum catalyst and procedure. For comparison purposes, desymmetrisation of N-benzyl-4-phenylpiperidin-2,5-dione 4a using these optimised conditions with a catalyst prepared in situ from (S)-(−)-α,α-diphenyl-2-pyrrolidinemethanol 9 gave only 13% yield and 14% ee of the lactam product 10b (Table 2, entry 10). This showed a remarkable superiority of oxazaborolidines derived from cis-1-amino-indan-2-ol over those derived from α,α-diphenyl prolinol with these substrates.

Since the change in nitrogen protecting group afforded a significant increase in yield, use of modified benzyl protecting groups (2-methylbenzyl and 2-methoxybenzyl) was probed, but this led to a significant fall in yield (25% and 21%, respectively) but kept the ee at excellent levels (Table 2, entries 11 & 12). This further reinforces the delicate nature of the N-protecting groups in influencing the yield and / or selectivity of the oxazaborolidine mediated desymmetrisation. Hence N-benzyl was chosen as the optimum protecting group for further exemplification.
Recently, we have reported the discovery of an in situ stereoablative process, partly responsible for the excellent ee observed for N-PMP anthracene-maleimide cyloaduct desymmetrisation.\textsuperscript{14} This was also investigated in this series, with the B-Me catalyst \textsuperscript{8}, employing the repeated distillation procedure since the highest yield of the over-reduced compound with a significant change in selectivity was observed (Scheme 3). The N-PMP glutarimide substrate \textsuperscript{3} was first reduced using both enantiomers of the B-Me catalyst \textsuperscript{8} separately under standard conditions but purifying the intermediate hydroxy-lactams by flash column chromatography. This led to isolation of the two enantiomers of the hydroxy-lactam \textsuperscript{12}, both as a 2:1 diastereomeric ratio, in 20% yield for (1R, 2S) catalyst and 27% yield for (1S, 2R) catalyst, respectively. A scalemic mixture of the two enantiomers of the hydroxy-lactam \textsuperscript{12} was then prepared by mixing these in a 2:1 ratio (1R, 2S:1S, 2R), and a portion of this quantitatively converted to the lactam to determine the ee. A sample of the scalemic hydroxyl-lactam mixture was then subjected to reduction with (1R, 2S) version of the B-Me catalyst followed by further reduction to the corresponding lactam. The same procedure was repeated with the (1S, 2R) version of the catalyst for comparison.

\textbf{Scheme 3. Stereoablation experiment with N-PMP glutarimide 3}

When a representative sample from the scalemic hydroxy-lactam \textsuperscript{12} (31% ee) was subjected to reduction with (1R, 2S) enantiomer of the B-Me catalyst \textsuperscript{8} followed by subsequent reduction with \textsubscript{3}SiH, the lactam was obtained in 73% yield and 60% ee. As observed in previous work
with the anthracene-maleimide, there was an upgrade in the ee of the scalemic hydroxy-lactam 12 from 31% to 60%, showing a stereoablative reduction of one enantiomer of the hydroxy-lactam by the (1R, 2S) catalyst (presumably the minor enantiomer) to the piperidine 11. On the other hand, when the reaction was repeated with (1S, 2R) version of the catalyst, a near identical yield of 75% of the lactam was obtained. However, unlike in the anthracene-maleimide case where the ee of the scalemic hydroxy-lactam remained the same with this version of the catalyst, the ee of the scalemic hydroxy-lactam in this case eroded to 14%. This shows that the (1S, 2R) catalyst selectively reduces the opposite enantiomer of the hydroxy-lactam, the major enantiomer in this case, thereby diminishing the ee of the scalemic hydroxy-lactam 12. Thus a double stereo-differentiation process is operative whereby matched and mismatched catalyst / substrate combinations are observed with the two versions of the B-Me catalyst. The near identical yields of the lactam products obtained (73% & 75%) under the same experimental conditions suggests similar reaction rates of the two catalyst in this stereoablation reaction. Further experiments probing the effect of the nitrogen protecting group on the stereoablative process are underway.

The optimum catalyst system (Table 2, entry 8) was then applied to the remainder of the N-benzyl glutarimides 4b-i over a 24 hour period in an attempt to maximise yield and/or selectivity. All 4-aryl substrates 4a-e furnished the chiral 2-piperidinones 13b–i in moderate yields (51–61%) and excellent enantioselectivities of 82–92% ee (Scheme 4 and Table 3, entries 1–4). However, a notable decrease in both yield and ee was observed when the aryl group was changed to 1-naphthyl (Table 3, entry 6). A change from 4-substituted aryls to 4-substituted alkyls 3g–i was well tolerated but a slight drop in the yield of the products was noticeable (Table 3, entries 6–8). As expected, residual starting material and over-reduced piperidine products were observed
in variable quantities in the $^1$H NMR spectrum of all unpurified reaction mixtures, but in these examples, only the 2-piperidinone was isolated and characterised.

Scheme 4. Desymmetrisation of N-Bn glutarimides using B-Me catalyst

Table 3. Desymmetrisation of N-benzyl-3-substituted glutarimides 4a-i using B-Me catalyst 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imide</th>
<th>Product / yield (%)$^b$</th>
<th>ee (%)$^c$</th>
<th>Measured [$\alpha$]$^{20}_D$</th>
<th>Literature [$\alpha$]$^{20}_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>10b (60)</td>
<td>90</td>
<td>+33.0 (c 1.1, CHCl$_3$)</td>
<td>+35.0 (c 1.1, CHCl$_3$)$^{20}$</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>13b (61)</td>
<td>86</td>
<td>+39.4 (c 0.3, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>13c (51)</td>
<td>88</td>
<td>+33.6 (c 1.1, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>13d (51)</td>
<td>82</td>
<td>+20.1 (c 2.1, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>13e (54)</td>
<td>92</td>
<td>+30.0 (c 1.1, CHCl$_3$)</td>
<td>+33.0 (c 1.1, CHCl$_3$)$^{20}$</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>13f (20)</td>
<td>54</td>
<td>-13.3 (c 0.5, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>13g (46)</td>
<td>90</td>
<td>+46.6 (c 3.3, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>13h (41)</td>
<td>86</td>
<td>+44.3 (c 1.9, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>13i (46)</td>
<td>87</td>
<td>+36.8 (c 1.4, CHCl$_3$)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

$^a$ Reactions conducted by treating a solution of the glutarimide 4a-i in dry CH$_2$Cl$_2$ with 10 mol% of the catalyst solution [prepared by reaction of (1R, 2S)-cis-amino-indan-2-ol (1.00 mmol) in dry toluene (3 mL) with trimethylboroxine (0.33 mmol) and allowing to stir for 30 min before azeotropic distillation with dry toluene. Dry dichloromethane (5 mL) was added to give a stock solution of the catalyst and 1 equiv BH$_3$.THF at rt for 24 h, followed work-up, dissolution into CH$_2$Cl$_2$ and treatment with Et$_3$SiH / TFA for 1 h. $^b$ Refers to isolated material after column chromatography. $^c$ Determined by chiral phase HPLC.
The absolute configuration was assigned as (4R) by comparison of the specific rotation with that of known compounds for the N-benzyl-4-phenyl lactam \(10b\) (Table 3, entry 1) and N-benzyl-4-(4-fluorophenyl) lactam \(13e\) (Table 3, entry 5). The remainder of the N-benzyl products have comparable values to these, with the exception of the 1-naphthyl system (Table 3, entry 6) which has an outlying negative value (Table 6, entry 10). For the N-PMP-phenyl lactam \(3\), the specific rotation \([+6.0 \, (c \, 1.3, \, CHCl_3)]\) closely matched that of a related known compound, N-PMP-4-(4-fluorophenyl)piperidin-2-one \([+8.0 \, (c \, 1.3, \, CHCl_3)^{21}]\).

To explain the stereochemical outcome, two possible pre-transition state intermediates involving the imide and the borane-activated oxazaborolidine catalyst can be imagined (Figure 1). The models are based on the assumption that the catalyst is co-ordinated to the least hindered carbonyl lone pair anti to the amide C-N bond. When placing the borane B-H bond in the correct orientation to affect reduction of the carbonyl group, interactions of the B-Me bond occur with the group at the 4-position of the glutarimide.

![Figure 1. Pre-transition state models for imide reduction](image)

In conclusion, an efficient strategy for the highly enantioselective desymmetrisation of glutarimides using oxazaborolidines has been developed, providing an efficient method to access important piperidine building blocks. This strategy appears to be heavily reliant on catalysts derived from cis-1-amino-indan-2-ol. Further evidence has also been accrued for a stereoablative
upgrade of enantioselectivity through a double stereo-differentiation process with N-PMP-3-phenyl glutarimide substrate, and more experiments probing this process are underway.

**Experimental Section**

**General experimental methods**

All solvents were obtained dry from a dry solvent system and glassware was flame dried and cooled under vacuum before use. All dry reactions were carried out under a nitrogen atmosphere. TLC was carried out using aluminium TLC sheets (silica gel 60 F254), and was performed using a UV lamp or by dipping in KMnO4 solution then exposure to heat. Flash column chromatography was carried out with silica gel 40-63µ 60Å. H and 13C NMR spectra were measured using CDCl3 as solvent unless otherwise stated. 13C NMR spectra were recorded using the JMOD method. Specific rotations were measured using the 589 nm (Na D-Line) at 20 °C unless otherwise stated, and are given in 10^-1 deg cm^2 g^-1. HPLC was carried out using a Chiralcel (4.8 mm × 250 mm) column with 10% or 20% iPrOH in hexane as the solvent. The flow rate was 1.00 mL per minute and the detector was set at 220 nm or 254 nm. All chemicals were used as received without further purification except (1R,2S)-cis-1-amino-2-indanol and (1S,2R)-cis-1-amino-2-indanol which were recrystallized from hot toluene prior to use. Borane-THF was used as a 1M solution in THF.

**General Procedure A for the synthesis of 3-(o-substituted phenyl) glutaric acids.**

AlCl3 (0.1 equiv.) was slowly added to a mixture of 2-substituted benzaldehyde (1 equiv.) and diethylmalonate (2 equiv.) and stirred at room temperature for 24 hrs. The mixture was poured into an ice-water / conc. HCl solution mixture (25 : 5 mL) and extracted with CH2Cl2 (3 × 15
mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation (130 °C, 9.5 × 10⁻¹ mbar) to give the crude diethyl o-substituted benzylidene malonate which was taken to next step without further purification. AlCl₃ (0.05 equiv.) was slowly added to a mixture of the crude benzylidene malonate (1 equiv.) and diethylmalonate (1 equiv.) and stirred at 60 °C for 24 h. Another portion of AlCl₃ (0.05 equiv.) was slowly added to the mixture, the reaction temperature was raised to 70 °C and further stirred for additional 24 h. The mixture was allowed to cool to room temperature, poured into an ice / conc. HCl solution mixture (25 : 5 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation (130 °C, 9.5 × 10⁻¹ mbar) to give the crude material as an oily residue which was taken to the next synthetic step without further purification. This material was dissolved in conc. HCl (10 mL) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 mL and fresh conc. HCl (10 mL) was added and further heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, the solid was filtered and recrystallized from EtOAc / petroleum ether (40–60).

**General Procedure B for the synthesis of 3-(p-substituted phenyl) glutaric acids.**¹⁸

A solution of p-substituted benzaldehyde (1 equiv.) in toluene (10 mL) was added drop-wise to a mixture of AlCl₃ (0.1 equiv.) and diethylmalonate (2 equiv.) in toluene (10 mL) and stirred at room temperature for 24 h. The mixture was poured into an ice-water / conc. HCl solution mixture (25 : 5 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation (130 °C, 9.5 × 10⁻¹ mbar) to give the crude diethyl p-
substituted benzylidene malonate as oily residue which was taken to next step without further purification. AlCl₃ (0.05 equiv.) was slowly added to a mixture of the crude benzylidene malonate (1 equiv.) and diethylmalonate (1 equiv.) and stirred at 60 °C for 24 h. Another portion of AlCl₃ (0.05 equiv.) was slowly added to the mixture, the reaction temperature was raised to 70 °C and further stirred for additional 24 h. The mixture was allowed to cool to room temperature, poured into an ice / conc. HCl solution mixture (25 : 5 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation (130 °C, 9.5 × 10⁻¹ mbar) to leave the crude tetraethyl 2-(ortho or para substituted phenyl)propane-1,1,3,3-tetracarboxylate as an oily residue which was taken to the next synthetic step without further purification. This material was dissolved in conc. HCl (10 mL) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 mL and fresh conc. HCl (10 mL) was added and further heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, the solid was filtered and recrystallized from EtOAc / petroleum ether (40–60).

**General Procedure C for the synthesis of 3-isopropyl & 3-tert-butyl glutaric acids**

A mixture of isobutyraldehyde or trimethylacetaldehyde (1.0 equiv.), ethylcyanoacetate (1.0 equiv.) and piperidine (0.01 equiv.) in toluene (40 mL) was heated at reflux for 4 hours and allowed to cool to room temperature. The solvent was removed in vacuo and the residue was dissolved in CH₂Cl₂ (30 mL), dried over MgSO₄ and filtered. The solvent was evaporated in vacuo to give an orange oily residue which was added to a solution of dimethylsodiomalonate [made from dimethylmalonate (1.0 equiv.) and sodium (0.1 equiv.) in dry MeOH (20 mL)]. The mixture was heated at reflux for 17 h, allowed to cool to room temperature and acidified with 1M HCl (15 mL). The mixture was then extracted with ether (5 × 60 mL) and the combined ethereal
fractions were washed with water (60 mL), dried over MgSO$_4$ and filtered. The ether was evaporated under reduced pressure to give the crude cyanotricarboxylate as orange oil. The crude cyanotricarboxylate in conc. HCl (10 mL) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 mL and fresh conc. HCl (10 mL) was added. The reaction mixture was again heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, poured in to ice / water mixture (50 mL) and extracted with ether (5 × 30 mL). The combined ethereal portions were washed with water (20 mL), dried over MgSO$_4$, filtered and solvent evaporated in vacuo to obtain a dark brown liquid which upon standing in fridge turned to brown solid, which was purified by recrystallisation from EtOAc / hexane.

3-(2-Fluorophenyl)pentan-1,5-dioic acid 1b

Using general procedure A starting with (8.250 g, 66.47 mmol) of 2-fluorobenzaldehyde and diethylmalonate (20.20 mL, 132.9 mmol), the crude diethyl 2-fluorobenzylidene malonate (17.00 g) was obtained as a yellow liquid which was not purified [selected data: $\delta_H$ (400 MHz, CDCl$_3$) 1.26 (t, $J = 6.6$ Hz, 6H), 4.23 (qd, $J = 7.1$, 1.2 Hz, 4H), 7.00–7.07 (m, 2H), 7.28–7.34 (m, 1H), 7.36–7.40 (m, 1H), 7.83 (s, 1H)]. This was taken onto the next step and the tetraethyl 2-(2-fluorophenyl)propane-1,1,3,3-tetracarboxylate (23.29 g) was obtained as a yellow liquid. [selected data: $\delta_H$ (400 MHz, CDCl$_3$) 0.90 (t, $J = 7.1$ Hz, 6H), 1.11 (t, $J = 7.1$ Hz, 6H), 3.82 (q, $J = 7.1$ Hz, 4H), 3.98–4.06 (m, 6H), 4.36 (t, $J = 9.4$ Hz, 1H), 6.83–6.88 (m, 1H), 6.90–6.94 (m, 1H), 7.07–7.12 (m, 1H), 7.28–7.32 (m, 1H); $\delta_C$ (100 MHz, CDCl$_3$) 13.7 (2 × CH$_3$), 13.9 (2 × CH$_3$), 38.3 (CH), 54.4 (2 × CH), 61.4 (2 × CH$_2$), 61.7 (2 × CH$_2$), 115.4 (d, $J_{C:F} = 22.9$ Hz, CH), 123.8 (d, $J_{C:F} = 3.3$ Hz, CH), 124.8 (d, $J_{C:F} = 14.6$ Hz, C), 129.5 (d, $J_{C:F} = 8.6$ Hz, CH), 131.6 (CH), 161.2 (d, $J_{C:F} = 248.0$ Hz, C), 167.4 (2 × C), 167.8 (2 × C). Final decarboxylation gave a brown solid that was purified by recrystallization from EtOAc / petroleum ether (40–60) to give
the title compound 1b as white crystals (7.66 g, 52% over 3 steps); mp = 140–142 °C; Anal. Calcd for C_{11}H_{11}FO_{4}: C, 58.41; H, 4.90. Found: C, 58.23; H, 4.96; ν_{max} /cm^{-1} (ATR) 2890 (brd, O-H), 1693 (s, C=O), 1489 (w, Ar C=C); δ_{H} (400 MHz, DMSO) 2.58 (dd, J = 15.9, 8.5 Hz, 2H), 2.66 (dd, J = 15.9, 6.6 Hz, 2H), 3.73 (quintet, J = 7.0 Hz, 1H), 7.09–7.15 (m, 2H), 7.21–7.27 (m, 1H), 7.37 (td, J = 7.7, 1.5 Hz, 1H), 12.16 (s, 2H); δ_{C} (100 MHz, DMSO) 31.8 (CH), 39.4 (2 × CH_{2}), 115.8 (d, J_{C-F} = 22.5 Hz, CH), 124.7 (d, J_{C-F} = 2.9 Hz, CH), 128.7 (d, J_{C-F} = 8.4 Hz, CH), 129.5 (d, J_{C-F} = 4.5 Hz, CH), 130.4 (d, J_{C-F} = 14.2 Hz, C), 160.7 (d, J_{C-F} = 244.0 Hz, C), 173.1 (2 × C); δ_{F} (235 MHz, DMSO) -117.9; MS (ESI\textsuperscript{+} TOF) m/z: 227 ([MH\textsuperscript{+}], 70%), 209 ([M - OH]\textsuperscript{+}, 100%).

3-(4-Fluorophenyl)pentan-1,5-dioic acid 1c\textsuperscript{17}

Using general procedure B starting with (10.00 g, 80.57 mmol) of 4-fluorobenzaldehyde and diethylmalonate (24.50 mL, 161.1 mmol), the crude diethyl 4-fluorobenzylidenemalonate (18.22 g) was obtained as a yellow liquid which was not purified (selected data: δ_{H} (400 MHz, CDCl_{3}) 0.90 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 4.16 (q, J = 7.1 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 6.82 [(AX)_2, 2H], 7.35 [(AX)_2, 2H], 7.56 (s, 1H)). This was taken onto the next step and the tetraethyl 2-(4-fluorophenyl)propane-1,1,3,3-tetracarboxylate (23.29 g) was obtained as a yellow liquid (selected data: δ_{H} (400 MHz, CDCl_{3}) 0.89 (t, J = 7.1 Hz, 6H), 1.08 (t, J = 7.1 Hz, 6H), 3.82 (q, J = 7.1 Hz, 4H), 3.94–4.02 (m, 7H), 6.80 (app t, J = 8.7 Hz, 2H), 7.24 [(AX)_2, 2H]). Final decarboxylation gave a brown solid that was purified by recrystallization from EtOAc / petroleum ether (40–60) to give the title compound 1c as white crystals (9.881 g, 55% over 3 steps); mp = 145–147 °C (lit.\textsuperscript{22} 146–147 °C); Anal. Calcd for C_{11}H_{11}FO_{4}: C, 58.41; H, 4.90. Found: C, 58.36; H, 4.65; ν_{max} /cm^{-1} (ATR) 2914 (brd, O-H), 1708 (s, C=O), 1604 (w, Ar C=C), 1509 (w, Ar C=C); δ_{H} (400 MHz, DMSO) 2.51 (dd, J = 15.8, 8.8 Hz, 2H), 2.65 (dd, J = 15.8, 6.2
Hz, 2H), 3.37–3.45 (m, 1H), 7.10 [(AX), 2H], 7.31 [(AX), 2H], 12.11 (2 brd s, 2H); δC (100 MHz, DMSO) 37.7 (CH), 40.6 (2 × CH₂), 115.3 (d, J_C-F = 21.0 Hz, 2 × CH), 129.8 (d, J_C-F = 7.8 Hz, 2 × CH), 140.0 (d, J_C-F = 2.6 Hz, C), 161.3 (d, J_C-F = 242.0 Hz, C), 173.2 (2 × C); δF (235 MHz, DMSO) -116.8; MS (ESI⁺ TOF) m/z: 250 ([MH + Na]⁺, 20%), 227 ([M + H]⁺, 30%), 209 ([M - OH]⁺, 100%). All data are in accordance with literature.

3-(2-Methylphenyl)pentan-1,5-dioic acid 1d

Using general procedure A starting with 2-methylbenzaldehyde (9.350 g, 77.82 mmol) and diethylmalonate (23.60 mL, 155.6 mmol), the crude diethyl 2-methylbenzylidene malonate (17.00 g) was obtained as a yellow liquid, which was not purified [selected data; δH (400 MHz, CDCl₃) 1.05 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 2.24 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 7.02–7.09 (m, 2H), 7.15 (app td, J = 7.5, 1.2 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.87 (s, 1H)]. This was taken onto the next step and the crude tetraethyl 2-(2-methylphenyl)propane-1,1,3,3-tetracarboxylate (15.90 g) was obtained as a yellow liquid [selected data; δH (400 MHz, CDCl₃) 0.89 (t, J = 7.1 Hz, 6H), 1.17 (t, J = 7.1 Hz, 6H), 2.42 (s, 3H), 3.80 (q, J = 7.1 Hz, 4H), 3.96 (d, J = 9.5 Hz, 2H), 4.03–4.11 (m, 4H), 4.51 (t, J = 9.5 Hz, 1H), 7.00–7.06 (m, 3H), 7.18 (d, J = 6.8 Hz, 1H)]. Final decarboxylation gave a brown solid that was purified by recrystallization from EtOAc / petroleum ether (40–60) giving the title compound 1d as white crystals (8.942 g, 52% over 3 steps); mp = 154–156 °C; Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.46; νmax /cm⁻¹ (ATR) 2971 (brd, O-H), 1708 (s, C=O) 1514 (w, Ar C=C); δH (400 MHz, DMSO) 2.37 (s, 3H), 2.49–2.63 (m, 4H), 3.69–3.76 (m, 1H), 7.04–7.16 (m, 3H), 7.27 (d, J = 7.6 Hz, 1H), 12.60 (s, 2H); δC (100 MHz, DMSO) 19.7 (CH₃), 33.2 (CH), 40.5 (2 × CH₂), 126.2 (CH), 126.4 (CH), 126.5 (CH), 130.5 (CH), 136.2 (C), 142.3 (C), 173.4 (2 × C); MS (ESI TOF) m/z: 221 ([M-H]⁻, 100%).
3-(4-Methylphenyl)pentan-1,5-dioic acid 1e\textsuperscript{23}

Using general procedure B starting with 4-methylbenzaldehyde (10.00 g, 83.23 mmol) and diethylmalonate (25.30 mL, 166.5 mmol), the crude diethyl 4-methylbenzylidenemalonate (17.23 g) was obtained as a yellow liquid, which was not purified [selected data; \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.20 (t, \(J = 7.2\) Hz, 3H), 1.21 (t, \(J = 7.1\) Hz, 3H), 2.24 (s, 3H), 4.18 (q, \(J = 7.2\) Hz, 2H), 4.24 (q, \(J = 7.1\) Hz, 2H), 7.07 (d, \(J = 8.1\) Hz, 1H), 7.25 (d, \(J = 8.1\) Hz, 1H), 7.60 (s, 1H)]. This was taken onto the next step and the crude tetraethyl 2-(4-methylphenyl)propane-1,1,3,3-tetracarboxylate (25.20 g) was obtained as a yellow liquid [selected data; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.98 (t, \(J = 7.1\) Hz, 6H), 1.18 (t, \(J = 7.1\) Hz, 6H), 2.22 (s, 3H), 3.90 (q, \(J = 7.1\) Hz, 4H), 4.02–4.15 (m, 7H), 7.00 (d, \(J = 8.0\) Hz, 2H), 7.17 (d, \(J = 8.0\) Hz, 2H)]. Final decarboxylation gave a brown solid that was purified by recrystallization from EtOAc / petroleum ether (40–60) to give the title compound 1e as white crystals (10.55 g, 57% over 3 steps); mp = 122–124 °C (lit.\textsuperscript{23} 118–121 °C); Anal. Calcd for C\(_{12}\)H\(_{14}\)O\(_4\): C, 64.85; H, 6.35. Found: C, 64.85; H, 6.13; \(v_{\text{max}}\) /cm\(^{-1}\) (ATR) 2925 (brd, O-H), 1704 (s, Ar C=O), 1515 (w, Ar C=O); \(\delta_H\) (400 MHz, DMSO) 2.25 (s, 3H), 2.48 (dd, \(J = 15.7, 8.7\) Hz, 2H), 2.62 (dd, \(J = 15.7, 6.3\) Hz, 2H), 3.34–3.41 (m, 1H), 7.07 (d, \(J = 8.0\) Hz, 2H), 7.14 (d, \(J = 8.0\) Hz, 2H), 7.12 (d, \(J = 8.0\) Hz, 2H); \(\delta_C\) (100 MHz, DMSO) 21.1 (CH\(_3\)), 38.0 (CH), 40.7 (2 × CH\(_2\)), 127.8 (2 × CH), 129.2 (2 × CH), 135.8 (C), 140.8 (C), 173.3 (2 × C); MS (ESI\(^+\) TOF) m/z: 223 ([MH\(^+\), 10%], 205 ([M - OH]\(^+\), 100%). Literature \(^{13}\)C NMR data is missing a signal at 40.7 otherwise all data are in accordance with literature.

3-(1-Naphthyl)pentan-1,5-dioic acid 1f\textsuperscript{24}
Using general procedure A starting with 1-naphthaldehyde (10.35 g, 66.27 mmol) and diethylmalonate (20.12 mL, 132.5 mmol), the crude diethyl 1-naphthylidenemalonate (19.25 g) was obtained as a pale yellow liquid, which was not purified [selected data; $\delta_H$ (400 MHz, CDCl$_3$) 1.06 (t, $J = 7.1$ Hz, 3H), 1.38 (t, $J = 7.1$ Hz, 3H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 7.42 (t, $J = 7.8$ Hz, 1H), 7.49–7.56 (m, 2H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.83–7.87 (m, 2H), 8.00 (d, $J = 7.8$ Hz, 1H), 8.50 (s, 1H)]; This was taken onto the next step and the crude tetraethyl 2-(1-naphthyl)propane-1,1,3,3-tetracarboxylate (32.56 g) was obtained as dark brown liquid [selected data; $\delta_H$ (400 MHz, CDCl$_3$) 0.73 (t, $J = 7.1$ Hz, 6H), 1.17 (t, $J = 7.1$ Hz, 6H), 3.67–3.76 (m, 4H), 4.06–4.14 (m, 4H), 4.24 (d, $J = 9.0$ Hz, 2H), 5.25 (t, $J = 9.0$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.51–7.56 (m, 2H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 8.41 (d, $J = 8.1$ Hz, 1H)]; ]. Final decarboxylation gave a brown solid that was purified by recrystallization from EtOAc / petroleum ether (40–60) giving the title compound 1f as white crystals (10.20 g, 60% over 3 steps); mp =185–187 °C (lit.$^{24}$ 181.5 °C); Anal. Calcd for C$_{15}$H$_{14}$O$_4$: C, 69.76; H, 5.46. Found: C, 69.64; H, 5.39; $\nu_{max}$/cm$^{-1}$ (ATR) 2904 (brd, O-H), 1707 (s, C=O), 1599 (w, C=C), 1511 (w, C=C); $\delta_H$ (400 MHz, DMSO) 2.76 (d, $J = 7.2$ Hz, 4H), 3.39 (quintet, $J = 7.2$ Hz, 1H), 7.46–7.62 (m, 4H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.93 (d, $J = 8.1$ Hz, 1H), 8.21 (d, $J = 8.6$ Hz, 1H), 12.17 (s, 2H); $\delta_C$ (100 MHz, DMSO) 38.0 (CH), 40.3 (2 × CH$_2$), 123.5 (CH), 123.7 (CH), 125.9 (CH), 126.0 (CH), 126.6 (CH), 127.3 (CH), 129.2 (CH), 131.5 (C), 134.0 (C), 140.0 (C), 173.4 (2 × C); MS (ESI TOF) m/z: 257 ([M-H]$^-$, 100%). Only melting point is reported in the literature.

3-Isopropylpentan-1,5-dioic acid 1h$^{25}$

Using general procedure C starting with isobutyraldehyde (10.00 g, 138.7 mmol), the title compound 1h was obtained as white crystals by recrystallization from EtOAc / petroleum ether
(40–60) (8.211 g, 34% over 3 steps); mp = 94–96 °C (lit. 87.5–88.5 °C); Anal. Calcd for C₈H₁₄O₄: C, 55.16; H, 8.10. Found: C, 55.14; H, 8.16; νmax/cm⁻¹ (ATR) 2966 (brd, O-H), 1692 (s, C=O); δH (400 MHz, DMSO) 0.82 (d, J = 6.9 Hz, 6H), 1.70 (pent d, J = 6.9, 3.4 Hz, 1H), 2.10–2.15 (m, 3H), 2.19–2.26 (m, 2H), 12.10 (brd s, 2H); δC (100 MHz, DMSO) 19.2 (2 × CH₃), 29.9 (CH), 35.9 (2 × CH₂), 37.5 (CH), 174.5 (2 × C); MS (ESI⁺ TOF) m/z: 198 ([M + Na]⁺, 40%), 175 ([MH]⁺, 30%), 157 ([M-OH]⁺, 100%). Only melting point is given in literature.

3-tert-Butylpentan-1,5-dioic acid 1i²⁶

Using general procedure C starting with trimethylacetaldehyde (10.00 g, 116.3 mmol), the title compound 1i was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (12.76 g, 58% over 3 steps); mp = 146–148 °C (lit. 153–154 °C); νmax (ATR)/cm⁻¹ 2966 (brd, O-H), 1704 (s, C=O); δH (400 MHz, CDCl₃) 0.96 (s, 9H), 2.15–2.22 (m, 2H), 2.32 (tt, J = 9.7, 1.8 Hz, 1H), 2.66 (dd, J = 14.2, 1.8 Hz, 2H), 12.36 (brd s, 2H); δC (100 MHz, CDCl₃) 27.3 (3 × CH₃), 33.1 (C), 36.1 (2 × CH₂), 42.4 (CH), 180.9 (2 × C); MS (ESI⁺TOF) m/z: 230 ([MH+Na]⁺, 30%), 212 ([MH]⁺, 55%), 189 ([M-OH]⁺, 100%), 171 (70%); HRMS (ESI⁺TOF): calcd for C₉H₁₇O₄ ([MH]⁺), 1891127; found, 189.1130. Only melting point and ¹H NMR were reported in the literature.

**General Procedure D for the synthesis of glutaric anhydrides.**¹⁶

A mixture of glutaric acid in acetyl chloride (30 mL) was heated at reflux for 48 h. The mixture was cooled to room temperature and the acetyl chloride was removed in vacuo to give brown liquid which was purified by recrystallisation.

**4-Phenyldihydropyran-2,6-dione 2a¹⁹**
Using general procedure D starting with commercially available 3-phenylglutaric acid (4.10 g, 0.02 mol), the title compound 2a was obtained as white crystals by recrystallization from EtOAc / hexane (3.22 g, 84%); mp = 104–106 °C (lit. 19 104–105 °C); ν\textsubscript{max} / cm\textsuperscript{-1} (ATR) 1812 (s, C=O), 1752 (s, C=O); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.90 (dd, J = 17.5, 11.5 Hz, 2H), 3.11 (dd, J = 17.5, 4.3 Hz, 2H), 3.42 (tt, J = 11.5, 4.3 Hz, 1H), 7.21–7.24 (m, 2H), 7.34–7.45 (m, 3H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 34.1 (CH), 37.2 (2 × CH\textsubscript{2}), 126.2 (2 × CH), 128.2 (CH), 129.4 (2 × CH), 139.1 (C), 165.8 (C); MS (ESI\textsuperscript{+}TOF) m/z: 191 ([MH]\textsuperscript{+}, 100%). All data in accordance with the literature.

4-(2-Fluorophenyl)dihydropyran-2,6-dione 2b

Using general procedure D starting with glutaric acid 1b (3.00 g, 13.3 mmol), the title compound 2b was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (2.00 g, 73%); mp 84–86 °C; ν\textsubscript{max} / cm\textsuperscript{-1} (ATR) 1812 (w), 1754 (s, C=O), 1710 (s, C=O), 1586 (w, C=C); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.99 (dd, J = 17.2, 11.2 Hz, 2H), 3.13 (dd, J = 17.2, 4.2 Hz, 2H), 3.66–3.73 (m, 1H), 6.11–7.21 (m, 3H), 7.33–7.38 (m, 1H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 28.9 (CH), 28.9 (CH), 116.3 (d, J\textsubscript{C,F} = 21.8 Hz, CH), 125.0 (d, J\textsubscript{C,F} = 3.4 Hz, CH), 126.0 (d, J\textsubscript{C,F} = 13.3 Hz, C), 127.2 (d, J\textsubscript{C,F} = 3.8 Hz, CH), 129.9 (d, J\textsubscript{C,F} = 8.5 Hz, CH), 160.7 (d, J\textsubscript{C,F} = 246.6 Hz, C), 165.7 (2 × C); δ\textsubscript{F} (235 MHz, CDCl\textsubscript{3}) -117.0; MS (EI\textsuperscript{+}) m/z: 208 ([M]\textsuperscript{+}, 30%), 122 (100%), 96 (20%); HRMS (EI\textsuperscript{+}): calcd for C\textsubscript{11}H\textsubscript{8}FO\textsubscript{3} ([M]\textsuperscript{+}), 208.0536; found, 208.0544.

4-(4-Fluorophenyl)dihydropyran-2,6-dione 2c\textsuperscript{27}

Using general procedure D starting with glutaric acid 1c (2.50 g, 11.1 mmol), the title compound 2c was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (1.96 g, 85%); mp = 84 – 86 °C (lit.\textsuperscript{27} 98 °C); Anal. Calcd for C\textsubscript{11}H\textsubscript{8}FO\textsubscript{3}: C, 63.46; H, 4.36. Found: C, 63.22; H, 4.08; ν\textsubscript{max} / cm\textsuperscript{-1} (ATR) 1806 (s, C=O), 1755 (s, C=O), 1717 (m, C=O), 1606
(w, C=C), 1512 (s, C=C); δ_H (400 MHz, CDCl_3) 2.86 (dd, J = 17.4, 11.4 Hz, 2H), 3.13 (dd, J = 17.4, 4.4 Hz, 2H), 3.45 (tt, J = 11.4, 4.4 Hz, 1H), 7.09–7.14 (m, 2H), 7.18–7.23 (m, 2H); δ_C (100 MHz, CDCl_3) 33.5 (CH), 37.3 (2 × CH_2), 116.4 (d, J_C-F = 21.6 Hz, 2 × CH), 127.9 (d, J_C-F = 8.1 Hz, 2 × CH), 134.8 (d, J_C-F = 3.2 Hz, C), 162.3 (d, J_C-F = 248.5 Hz, C), 165.6 (2 × C); MS (EI^+) m/z: 208 ([M]^+, 40%), 123 (30%), 122 (100%). All data are in accordance with literature.

**4-(2-Methylphenyl)dihydropyran-2,6-dione 2d**

Using general procedure D starting with glutaric acid 1d (3.00 g, 13.5 mmol), the title compound 2d was obtained as white crystals by recrystallization from EtOAc / hexane (2.07 g, 75%); mp = 103–105 °C (lit. 28 106–109 °C); \nu_{\text{max}} (ATR)/\text{cm}^{-1} 1808 (s, C=O), 1749 (s, C=O), 1712 (s, C=O); δ_H (400 MHz, CDCl_3) 2.39 (s, 3H), 2.86 (dd, J = 17.4, 11.6 Hz, 2H), 3.08 (dd, J = 17.4, 4.4 Hz, 2H), 3.65 (tt, J = 11.6, 4.4 Hz, 1H), 7.13 (d, J = 6.9 Hz, 1H), 7.24–7.31 (m, 3H); δ_C (100 MHz, CDCl_3) 19.3 (CH_3), 30.1 (CH), 36.6 (2 × CH_2), 124.1 (CH), 127.1 (CH), 127.9 (CH), 131.4 (CH), 135.6 (C), 137.2 (C), 166.1 (2 × C); MS (EI^+) m/z: 204 ([MH]^+, 40%), 144 (60%), 118 (100%), 91 (45%); HRMS (EI^+): calcd for C_{12}H_{12}O_3 ([MH]^+), 204.0786; found, 204.0792. All data are in accordance with literature.

**4-(4-Methylphenyl)dihydropyran-2,6-dione 2e**

Using general procedure D starting with glutaric acid 1e (7.00 g, 31.5 mmol), the title compound 2e was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (6.00 g, 93%); mp = 136–138 °C; \nu_{\text{max}} /\text{cm}^{-1} (ATR) 1806 (s, C=O), 1753 (s, C=O), 1518 (w, C=C); δ_H (400 MHz, CDCl_3) 2.37 (s, 3H), 2.87 (dd, J = 17.4, 11.4 Hz, 2H), 3.12 (dd, J = 17.4, 4.5 Hz, 2H), 3.41 (tt, J = 11.4, 4.5 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H); δ_C (100 MHz, CDCl_3) 21.0 (CH_3), 33.7 (CH), 37.3 (2 × CH_2), 126.1 (2 × CH), 130.0 (2 × CH),

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136.1 (C), 138.0 (C), 165.9 (2 × C); MS (EI+) m/z: 204 ([M]+, 40%), 118 (100%), 91 (20%); HRMS (EI+): calcd for C₁₂H₁₂O₃ ([M]+), 204.0786; found, 204.0796. No analytical data was given for the compound in the literature.

4-(1-Naphthyl)dihydropyran-2,6-dione 2f

Using general procedure D starting with glutaric acid 1f (3.00 g, 0.01 mol), the title compound 2f was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (2.24 g, 80%); mp = 148–150 °C; Anal. Calcd for C₁₅H₁₂O₃: C, 74.99; H, 5.03. Found: C, 74.64; H, 4.68; νmax/cm⁻¹ (ATR) 1808 (s, C=O), 1753 (s, C=O), 1599 (w, C=C); δH (400 MHz, CDCl₃) 3.05 (dd, J = 17.3, 10.5 Hz, 2H), 3.31 (dd, J = 17.3, 4.5 Hz, 2H), 4.28 (tt, J = 10.5, 4.5 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.49–7.53 (m, 1H), 7.57–7.66 (m, 2H), 7.87 (d, J = 8.2 Hz, 1H), 7.94–7.98 (m, 2H); δC (100 MHz, CDCl₃) 29.5 (CH), 36.8 (2 × CH₂), 121.8 (CH), 122.0 (CH), 125.5 (CH), 126.3 (CH), 127.1 (CH), 128.9 (CH), 129.5 (CH), 130.6 (C), 134.1 (C), 134.8 (C), 166.0 (2 × C); MS (TOF MS ES⁺) m/z: 241 ([MH]⁺, 100%).

4-Methyldihydropyran-2,6-dione 2g

Using general procedure D starting with commercially available 3-methylglutaric acid (10.0 g, 63.5 mmol), the title compound 2g was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (6.89 g, 79%); mp = 44–46 °C (lit. 45–46 °C); Anal. Calcd for C₆H₈O₃: C, 56.24; H, 6.29. Found: C, 56.27; H, 6.31; νmax/cm⁻¹ (ATR) 2977 (w, C-H), 1806 (s, C=O), 1757 (s, C=O), 1744 (s, C=O); δH (400 MHz, CDCl₃) 1.16 (d, J = 6.4 Hz, 3H), 2.29–2.37 (m, 1H), 2.39–2.46 (m, 2H), 2.88 (dd, J = 17.1, 4.2 Hz, 2H); δC (100 MHz, CDCl₃) 20.0 (CH₃), 24.0 (CH), 37.7 (2 × CH₂), 166.4 (2 × C); MS (TOF MS ES⁺) m/z: 129 ([MH]⁺, 100%). Only a melting point and a copy of the ¹H NMR spectrum are recorded in the literature.
4-Isopropyldihydropyran-2,6-dione 2h\textsuperscript{19}

Using general procedure D starting with glutaric acid 1h (5.74 g, 33.0 mmol), a brown liquid was obtained. This was vacuum distilled (bp = 110 °C, 85 \times 10^{-2} mbar, lit.\textsuperscript{19} 138 °C, 0.5 Torr) to give a colourless liquid which solidified upon standing. This was recrystallized from hexane to give the title compound 2h as white crystals (3.93 g, 76%); mp = 25–26 °C (lit.\textsuperscript{19} 25.5–26.5 °C); \(\nu_{\text{max}}/\text{cm}^{-1}\) (ATR) 2967 (m, C-H), 2878 (m, C-H), 1798 (s, C=O), 1757 (s, C=O), 1702 (s, C=O); \(\delta_{\text{H}}\) (400 MHz, CDCl\textsubscript{3}) 0.97 (d, J = 6.8 Hz, 6H), 1.62 (octet, J = 6.8 Hz, 1H), 1.94 (dtt, J = 6.8, 11.5, 4.4 Hz, 1H), 2.43 (dd, J = 17.3, 11.5 Hz, 2H), 2.88 (dd, J = 17.3, 4.4 Hz, 2H); \(\delta_{\text{C}}\) (100 MHz, CDCl\textsubscript{3}) 18.9 (2 \times CH\textsubscript{3}), 31.3 (CH), 34.0 (2 \times CH\textsubscript{2}), 35.0 (CH), 166.9 (2 \times C); HRMS (ESI\textsuperscript{+}TOF): calcd for C\textsubscript{8}H\textsubscript{13}O\textsubscript{3} ([MH\textsuperscript{+}]), 157.0865; found, 157.0870. All data are in accordance with literature.

4-tert-Butyldihydropyran-2,6-dione 2i\textsuperscript{19}

Using general procedure D starting with glutaric acid 1i (5.00 g, 26.6 mmol), a brown liquid was obtained that was vacuum distilled (bp = 120 °C, 16 \times 10^{-2} mbar, lit.\textsuperscript{19} 146–148 °C, 0.5 Torr), to give a colourless liquid which solidified upon standing to give the title compound 2i as a white solid (3.15 g, 70%); mp = 62–64 °C (lit.\textsuperscript{19} 63.5–64.5 °C); \(\nu_{\text{max}}/\text{cm}^{-1}\) (ATR) 2967 (m, C-H), 1808 (s, C=O), 1748 (s, C=O); \(\delta_{\text{H}}\) (400 MHz, CDCl\textsubscript{3}) 0.96 (s, 9H), 1.94 (tt, J = 12.9, 4.1 Hz, 1H), 2.35–2.43 (m, 2H), 2.90 (dd, J = 17.2, 4.1 Hz, 2H); \(\delta_{\text{C}}\) (100 MHz, CDCl\textsubscript{3}) 26.4 (3 × CH\textsubscript{3}), 32.0 (C), 32.3 (2 × CH\textsubscript{2}), 38.7 (CH), 167.2 (C); HRMS (ESI\textsuperscript{+}TOF): calcd for C\textsubscript{9}H\textsubscript{15}O\textsubscript{3} ([MH\textsuperscript{+}]), 171.1021; found, 171.1024. All data are in accordance with literature.
**General Procedure E for the synthesis of glutarimides.**

The corresponding amine (1.0 equiv) was slowly added to a solution of the glutaric anhydride (1.0 equiv) and triethylamine (1.0 equiv) in dry THF (30 mL). The mixture was heated at reflux for 48 h, cooled to room temperature and concentrated under reduced pressure. Dichloromethane (15 mL) was added and the resulting solution was washed with 1M HCl (5 mL) and brine (5 mL), dried over MgSO$_4$ and filtered. The solvent was removed in vacuo and the residue was dissolved in acetyl chloride (30 mL), heated at 60 °C for 48 h and cooled to room temperature. The solvent was removed in vacuo to give a brown solid which was purified by recrystallization.

**N-(4-Methoxyphenyl)-4-phenylpiperidin-2,6-dione 3**

Using general procedure E starting with 3-phenylglutaric anhydride 2a (1.00 g, 5.26 mmol), p-anisidine (0.65 g, 5.26 mmol) and triethylamine (0.70 mL, 5.26 mmol), the title compound 3 was obtained as white crystals by recrystallization from EtOAc (1.23 g, 80%); mp = 248–250 °C; Anal. Calcd for C$_{18}$H$_{17}$NO$_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.00; H, 5.52; N, 4.66; $\nu_{\text{max}}$/cm$^{-1}$ (ATR) 1731 (m, C=O), 1672 (s, C=O), 1610 (s), 1511 (s); $\delta$$_{\text{H}}$ (400 MHz, CDCl$_3$) 3.02 (dd, $J$ = 17.2, 11.4 Hz, 2H), 3.18 (dd, $J$ = 17.2, 4.4 Hz, 2H), 3.58 (tt, $J$ = 11.4, 4.4 Hz, 1H), 3.85 (s, 3H), 6.99–7.06 (m, 4H), 7.28–7.45 (m, 5H); $\delta$$_{\text{C}}$ (100 MHz, CDCl$_3$) 34.7 (CH), 40.1 (2 × CH$_2$), 55.4 (CH$_3$), 114.7 (2 × CH), 126.4 (2 × CH), 127.3 (C), 127.7 (CH), 129.2 (2 × CH), 129.3 (2 × CH), 140.5 (C) 159.5 (C), 172.0 (2 × C); MS (TOF MS ES$^+$) m/z: 296 ([MH]$^+$, 100%), 270 (10%), 249 (40%), 241 (8%).

**1-(Phenylmethyl)-4-phenylpiperidin-2,6-dione 4a**
Using general procedure E starting with 3-phenylglutaric anhydride 2a (1.50 g, 7.89 mmol), benzylamine (0.85 g, 7.89 mmol) and triethylamine (1.10 mL, 7.89 mmol), the title compound 4a was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (1.87 g, 85%); mp = 100–102 °C (lit.31 94–96 °C); $\nu_{\text{max}}$ / cm$^{-1}$ (ATR) 3031 (w, C-H), 1726 (m, C=O), 1668 (s, C=O); $\delta_H$ (400 MHz, CDCl$_3$) 2.85 (dd, J = 17.2, 11.8 Hz, 2H), 3.05 (dd, J = 17.2, 4.3 Hz, 2H), 3.38 (tt, J = 11.8, 4.3 Hz, 1H), 5.02 (s, 2H), 7.18–7.22 (m, 2H), 7.28–7.42 (m, 8H); $\delta_C$ (100 MHz, CDCl$_3$) 34.6 (CH), 39.9 (2 × CH$_2$), 42.9 (CH$_2$), 126.3 (2 × CH), 127.5 (CH), 127.6 (CH), 128.4 (2 × CH), 128.9 (2 × CH), 129.1 (2 × CH), 137.1 (C) 140.6 (C), 171.6 (2 × C); MS (TOF MS ES$^+$) m/z: 280 ([MH]$^+$, 100%). Only melting point and $^1$H NMR were cited in the literature.17,31

**1-(Phenylmethyl)-4-(2-fluorophenyl)piperidin-2,6-dione 4b**

Using general procedure E starting with glutaric anhydride 2b (2.00 g, 9.62 mmol), benzylamine (1.10 mL, 9.62 mmol) and triethylamine (1.34 mL, 9.62 mmol), the title compound 4b was obtained as white powder by recrystallization from EtOAc / petroleum ether (40–60) (1.7 g, 60%); mp = 76–78 °C; Anal. Calcd for C$_{18}$H$_{16}$FNO$_2$: C, 72.71; H, 5.42; N, 4.71. Found: C, 72.38; H, 5.26; N, 4.57; $\nu_{\text{max}}$ / cm$^{-1}$ (ATR) 3068 (w, C-H), 1728 (m, C=O), 1672 (s, C=O) $\delta_H$ (400 MHz, CDCl$_3$) 2.91 (dd, J = 16.9, 11.4 Hz, 2H), 3.04 (dd, J = 16.9, 4.0 Hz, 2H), 3.61–3.68 (m, 1H), 5.02 (s, 2H), 7.07–7.13 (m, 3H), 7.27–7.34 (m, 4H), 7.42 (d, J = 7.0 Hz, 2H); $\delta_C$ (100 MHz, CDCl$_3$) 29.1 (CH), 38.3 (2 × CH$_2$), 43.0 (CH$_2$), 116.1 (d, J$_{C\text{-F}}$ = 22.1 Hz, CH), 124.7 (d, J$_{C\text{-F}}$ = 3.3 Hz, CH), 127.2 (d, J$_{C\text{-F}}$ = 4.0 Hz, CH), 127.4 (d, J$_{C\text{-F}}$ = 14.4 Hz, C), 127.6 (CH), 128.5 (2 × CH), 129.0 (2 × CH), 129.3 (d, J$_{C\text{-F}}$ = 8.5 Hz, CH), 137.1 (C), 160.8 (d, J$_{C\text{-F}}$ = 246.6 Hz, C), 171.4 (2 × C); $\delta_F$ (235 MHz, CDCl$_3$) -117.4; MS (TOF MS ES$^+$) m/z: 298 ([MH]$^+$, 100%).
1-(Phenylmethyl)-4-(4-fluorophenyl)piperidin-2,6-dione 4c

Using general procedure E starting with glutaric anhydride 2c (4.00 g, 19.20 mmol), benzylamine (2.10 mL, 19.2 mmol) and triethylamine (2.60 mL, 19.20 mmol), the title compound 4c was obtained as white powder by recrystallization from EtOAc / petroleum ether (40–60) (1.20 g, 67%); mp = 120–122 °C; Anal. Calcd for C$_{18}$H$_{16}$FNO$_2$: C, 72.71; H, 5.42; N, 4.71. Found: C, 72.47; H, 5.31; N, 4.67; $\nu_{\text{max}}$/cm$^{-1}$ (ATR) 2955 (w, C-H), 1718 (m, C=O), 1672 (s, C=O), 1604 (m), 1512 (s); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.81 (dd, J = 17.1, 11.5 Hz, 2H), 3.00 (dd, J = 17.1, 4.3 Hz, 2H), 3.37 (tt, J = 11.5, 4.3 Hz, 1H), 5.01 (s, 2H), 7.02–7.07 (m, 2H), 7.13–7.17 (m, 2H), 7.28–7.32 (m, 3H), 7.38–7.41 (m, 2H); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 33.9 (CH), 40.0 (2 × CH$_2$), 42.9 (CH$_2$), 115.9 (d, J C-F = 21.5 Hz, 2 × CH), 127.6 (CH), 127.9 (d, J C-F = 7.0 Hz, 2 × CH), 128.4 (2 × CH), 128.9 (2 × CH), 136.3 (d, J C-F = 3.0 Hz, C), 137.0 (C), 162.0 (d, J C-F = 246.6 Hz, C), 171.3 (2 × C); $\delta_{\text{F}}$ (235 MHz, CDCl$_3$) -114.7; HRMS (ESI$^+$TOF): calcd for C$_{18}$H$_{17}$FNO$_2$ ([MH]$^+$), 298.1243; found, 298.1233. Only $^1$H NMR data was reported in the literature.

1-(Phenylmethyl)-4-(2-methylphenyl)piperidin-2,6-dione 4d

Using general procedure E starting with glutaric anhydride 2d (1.50 g, 7.35 mmol), benzylamine (0.81 mL, 7.35 mmol) and triethylamine (1.02 mL, 7.35 mmol), the title compound 4d was obtained as white powder by recrystallization from EtOAc / petroleum ether (40–60) (1.88 g, 87%); mp = 138–140 °C; $\nu_{\text{max}}$/cm$^{-1}$ (ATR) 3017 (w, C-H), 1728 (m, C=O), 1670 (s, C=O), 1605 (w); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.37 (s, 3H), 2.81 (dd, J = 17.2, 11.8 Hz, 2H), 2.98 (dd, J = 17.2, 4.3
Hz, 2H), 3.58 (tt, J = 11.8, 4.3 Hz, 1H), 5.04 (s, 2H), 7.09–7.12 (m, 1H), 7.20–7.23 (m, 3H), 7.27–7.37 (m, 3H), 7.43–7.46 (m, 2H); δ (100 MHz, CDCl₃) 19.3 (CH₃), 30.7 (CH), 39.3 (2 × CH₂), 43.0 (CH₂), 124.5 (CH), 126.8 (CH), 127.4 (CH), 127.6 (CH), 128.5 (2 × CH), 129.1 (2 × CH), 131.1 (CH), 135.6 (C), 137.1 (C), 138.7 (C), 171.9 (2 × C); HRMS (ESI⁺TOF): calcd for C₁₉H₂₀NO₂ ([MH]+), 294.1494; found, 294.1485.

1-(Phenylmethyl)-4-(4-methylphenyl)piperidin-2,6-dione 4e

Using general procedure E starting with glutaric anhydride 2e (5.00 g, 24.5 mmol), benzylamine (2.67 mL, 24.5 mmol) and triethylamine (3.40 mL, 24.5 mmol), the title compound 4e was obtained as white powder by recrystallization from EtOAc / petroleum ether (40–60) (5.10 g, 71%); mp = 106–108 °C; vₚₑₘₐₓ /cm⁻¹ (ATR) 2955 (w, C-H), 1727 (m, C=O), 1669 (s, C=O); δ (400 MHz, CDCl₃) 2.36 (s, 3H), 2.82 (dd, J = 17.1, 11.8 Hz, 2H), 3.03 (dd, J = 17.1, 4.2 Hz, 2H), 3.34 (tt, J = 11.8, 4.2 Hz, 1H), 5.02 (s, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.26–7.35 (m, 3H), 7.39–7.52 (m, 2H); δ (100 MHz, CDCl₃) 21.0 (CH₃), 34.2 (CH), 40.1 (2 × CH₂), 42.9 (CH₂), 126.2 (2 × CH), 127.5 (CH), 128.4 (2 × CH), 128.9 (2 × CH), 129.7 (2 × CH), 137.1 (C), 137.3 (C), 138.6 (C), 171.7 (2 × C); HRMS (ESI⁺TOF): calcd for C₁₉H₂₀NO₂ ([MH]+), 294.1494; found, 294.1504.

1-(Phenylmethyl)-4-(1-naphthyl)piperidin-2,6-dione 4f

Using general procedure E starting with glutaric anhydride 2f (2.00 g, 8.33 mmol), benzylamine (0.90 mL, 8.33 mmol) and triethylamine (1.16 mL, 8.33 mmol), the title compound 4f was obtained as white powder by recrystallization from EtOAc / petroleum ether (40–60) (1.42 g, 52%); mp = 116–118 °C; vₚₑₘₐₓ /cm⁻¹ (ATR) 3052 (w, C-H), 2964 (w, C-H), 1723 (m, C=O), 1672 (s, C=O), 1598 (m); δ (400 MHz, CDCl₃) 2.98 (dd, J = 16.9, 10.8 Hz, 2H), 3.21 (dd, J = 16.9,
3.8 Hz, 2H), 4.15–4.22 (m, 1H), 5.08 (s, 2H), 7.23–7.38 (m, 4H), 7.40–7.48 (m, 3H), 7.53–7.61 (m, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H); δ_C (100 MHz, CDCl_3) 30.0 (CH), 39.5 (2 × CH_2), 43.1 (CH_2), 122.2 (CH), 122.3 (CH), 125.5 (CH), 126.1 (CH), 126.8 (CH), 127.6 (CH), 128.3 (CH), 128.5 (2 × CH), 129.1 (2 × CH), 129.3 (CH), 130.8 (C), 134.1 (C), 136.3 (C), 137.1 (C), 171.8 (2 × C); HRMS (ESI^+TOF): calcd for C_{22}H_{20}NO_2 ([MH]^+), 330.1494; found, 330.1504.

1-(Phenylmethyl)-4-methylpiperidin-2,6-dione 4g

Using general procedure E starting with glutaric anhydride 2g (3.50 g, 27.3 mmol), benzylamine (2.93 g, 27.3 mmol) and triethylamine (3.82 mL, 27.3 mmol), the title compound 4g was obtained as white powder by recrystallization from 50% EtOAc / hexane (4.13 g, 70%); mp = 68–70 °C; Anal. Calcd for C_{13}H_{15}NO: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.74; H, 6.87; N, 6.46; ν_{max} /cm^{-1} (ATR) 2961 (w, C-H), 1721 (m, C=O), 1665 (s, C=O); δ_H (400 MHz, CDCl_3) 1.08 (d, J = 6.4 Hz, 3H), 2.17–2.29 (m, 1H), 2.31–2.37 (m, 2H), 2.80 (dd, J = 16.7, 3.8 Hz, 2H), 4.97 (s, 2H), 7.24–7.32 (m, 3H), 7.37–7.39 (m, 2H); δ_C (100 MHz, CDCl_3) 20.3 (CH_3), 24.5 (CH), 40.7 (2 × CH_2), 42.7 (CH_2), 127.4 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 137.3 (C), 172.1 (2 × C); MS (TOF MS ES^+) m/z: 218 ([MH]^+, 100%). Only ^1H NMR was cited in literature.

1-(Phenylmethyl)-4-isopropylpiperidin-2,6-dione 4h

Using general procedure E starting with glutaric anhydride 2h (2.00 g, 12.8 mmol), benzylamine (1.37 g, 12.8 mmol) and triethylamine (1.80 mL, 12.8 mmol), a yellowish liquid was obtained that turned to a yellowish solid upon standing. The solid was purified via flash column chromatography eluting with EtOAc / petroleum ether (40–60) (3:7) to afford the title compound 4h as colourless liquid which turned to a white solid upon standing (2.10 g, 67%); mp = 45–46
Using general procedure E starting with glutaric anhydride 2i (1.30 g, 7.65 mmol), benzylamine (0.89 g, 7.65 mmol) and triethylamine (1.10 mL, 7.65 mmol), a yellowish solid was obtained. The solid was purified via flash column chromatography eluting with EtOAc : petroleum ether (40–60) (3:7) to afford the title compound 4i as colourless liquid which turned to a white solid upon standing (1.12 g, 57%); mp = 44–46 °C; $\nu_{\text{max}}$ /cm$^{-1}$ (ATR) 2951 (w, C-H), 2874 (w, C-H), 1719 (m, C=O), 1666 (s, C=O); $\delta_H$ (400 MHz, CDCl$_3$) 1.86 (tt, J = 13.5, 3.8 Hz, 1H), 2.30–2.37 (m, 2H), 2.83 (dd, J = 17.0, 3.8 Hz, 2H), 4.96 (s, 2H), 7.24–7.33 (m, 3H), 7.37–7.40 (m, 2H); $\delta_C$ (100 MHz, CDCl$_3$) 26.5 (3 × CH$_3$), 31.8 (C), 35.0 (2 × CH$_2$), 39.2 (CH), 42.8 (CH$_2$), 127.5 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 137.2 (C), 172.9 (2 × C); HRMS (ESI$^+$TOF): calcd for C$_{16}$H$_{22}$NO$_2$ ([MH]$^+$), 260.1651; found, 260.1650.

1-(2-Methylphenylmethyl)-4-phenylpiperidin-2,6-dione 5

Using general procedure E starting with 3-phenylglutaric anhydride 2a (1.70 g, 8.95 mmol), 2-methylbenzylamine (1.09 g, 8.95 mmol) and triethylamine (1.25 mL, 8.95 mmol), the title compound 5 was obtained as white crystals by recrystallization from EtOAc / petroleum ether...
(40–60) (1.87 g, 71%); mp = 123–125 °C; Anal. Calcd for C_{19}H_{19}NO_2: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.53; H, 6.51; N, 4.76; \nu_{\text{max}} / \text{cm}^{-1} (\text{ATR}) 2973 (\text{w, C-H}), 1727 (\text{m, C=O}), 1667 (s, C=O); \delta_{\text{H}} (250 \text{ MHz, CDCl}_3) 2.44 (s, 3H), 2.91 (dd, J = 17.0, 11.5 Hz, 2H), 3.10 (dd, J = 17.0, 4.4 Hz, 2H), 3.46 (tt, J = 17.0, 4.4 Hz, 1H), 5.01 (s, 2H), 6.96 ([\text{AX}], 1H), 7.08–7.18 (m, 3H), 7.23–7.27 (m, 2H), 7.32–7.44 (m, 3H); \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 19.4 (\text{CH}_3), 34.6 (\text{CH}), 39.9 (2 \times \text{CH}_2), 40.4 (\text{CH}_2), 126.0 (\text{CH}), 126.0 (\text{CH}), 126.4 (2 \times \text{CH}), 127.1 (\text{CH}), 127.7 (\text{CH}), 129.1 (2 \times \text{CH}), 130.3 (\text{CH}), 134.7 (\text{C}), 135.8 (\text{C}), 140.5 (\text{C}), 171.7 (2 \times \text{C}); MS (\text{TOF MS ESI}^+) m/z: 294 ([\text{MH}]^+, 100%).

1-(2-Methoxyphenylmethyl)-4-phenylpiperidin-2,6-dione 6

Using general procedure E starting with 3-phenylglutaric anhydride 2a (2.00 g, 10.5 mmol), 2-methoxybenzylamine (1.37 mL, 10.5 mmol) and triethylamine (1.47 mL, 10.5 mmol), the title compound 6 was obtained as white crystals by recrystallization from EtOAc / petroleum ether (40–60) (1.97 g, 60%); mp = 98–100 °C; Anal. Calcd for C_{19}H_{20}NO_3: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.50; H, 6.06; N, 4.44; \nu_{\text{max}} / \text{cm}^{-1} (\text{ATR}) 2960 (\text{w, C-H}), 1728 (\text{m, C=O}), 1671 (s, C=O), 1603 (m); \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) 2.91 (dd, J = 17.1, 11.5 Hz, 2H), 3.08 (dd, J = 17.1, 4.3 Hz, 2H), 3.44 (tt, J = 11.5, 4.3 Hz, 1H), 3.86 (s, 3H), 5.08 (s, 2H), 6.88–6.96 (m, 3H), 7.22–7.28 (m, 3H), 7.31–7.35 (m, 1H), 7.38–7.40 (m, 2H); \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 34.6 (\text{CH}), 38.5 (2 \times \text{CH}_2), 55.4 (\text{CH}_3), 110.4 (\text{CH}), 120.3 (2 \times \text{CH}), 124.8 (\text{C}), 126.5 (2 \times \text{CH}), 127.0 (\text{CH}), 127.6 (\text{CH}), 128.2 (\text{CH}), 129.1 (\text{CH}), 140.7 (\text{C}) 157.1 (\text{C}), 171.5 (2 \times \text{C}); HRMS (ESI^+TOF): calcd for C_{19}H_{20}NO_3 ([\text{MH}]^+), 310.1443; found, 310.1451.

General Procedure F for the asymmetric reduction of 4-phenylglutarimides using B-OMe catalyst 7 followed by conversion to the corresponding lactam
A solution of (1R, 2S)-cis-1-amino-indan-2-ol (0.15 g, 1.00 mmol) in THF (3 mL) was treated with trimethylborate (0.10 mL, 1.00 mmol) and allowed to stir for 45 min. The solution was then diluted to 5 mL by further addition of THF, to give the catalyst 7 as a stock solution. The glutarimide (1.00 mmol) was dissolved in dry DCM (30 mL) under a nitrogen atmosphere and this solution was treated with the catalyst stock solution (0.50 mL, 10 mol%) then a drop-wise addition of BH$_3$·THF (1.00 mL, 1.00 mmol), and allowed to stir at rt for 3 h (for N-PMP glutarimide) or 24 h (for N-Bn glutarimide). The reaction was quenched by the addition of MeOH (5 mL) and 1M HCl (5 mL), and extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extracts were dried over MgSO$_4$ and filtered. The solvent was removed in vacuo to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH$_2$Cl$_2$ (25 mL) and treated with TFA (1 mL) and triethylsilane (1 mL) in CH$_2$Cl$_2$ (5 mL). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 mL) followed by extraction with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extracts were washed with saturated NaHCO$_3$ (15 mL), dried over MgSO$_4$ and filtered. The solvent was removed in vacuo to give a white solid, which was purified via flash column chromatography.

**General Procedure G for the asymmetric reduction of glutarimides using B-Me catalyst 8 followed by conversion to the corresponding lactam**

A suspension of (1R, 2S)-cis-amino-2-indanol (0.15 g, 1.00 mmol) in dry toluene (3 mL) was treated with trimethylboroxine (0.05 mL, 0.33 mmol) and allowed to stir under nitrogen for 30 min. Dry toluene (5 mL) was added and the reaction distilled until approximately 2 mL of solvent remained. This procedure was repeated twice after which the final volume of toluene was removed under pressure to give a yellow solid. Dry dichloromethane (5 mL) was added to give a stock solution of the B-Me catalyst 8. The catalyst (0.5 mL, 10 mol %) was added to the solution
of the glutarimide substrate (1.00 mmol) in dry dichloromethane (30 mL) followed by a drop-wise addition of BH$_3$.THF (1 mL, 1.00 mmol). The solution was then allowed to stir at room temperature for 3 h (for N-PMP glutarimide) or 24 h (for N-Bn glutarimides). The reaction was finally quenched by addition of MeOH (2 mL) and 1M HCl (2 mL), extracted with CH$_2$Cl$_2$ (3 × 15 mL), dried over MgSO$_4$ and filtered. The solvent was evaporated in vacuo to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH$_2$Cl$_2$ (30 mL) and treated with TFA (1 mL) and triethylsilane (1 mL) in CH$_2$Cl$_2$ (5 mL). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 mL) followed by extraction with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extracts were washed with saturated NaHCO$_3$ (3 × 15 mL), dried over MgSO$_4$ and filtered. The solvent was removed in vacuo to give a crude white solid, which was purified via flash column chromatography eluting with EtOAc / petroleum ether (40–60) (7:3).

**Procedure for the asymmetric reduction of N-(benzyl)-4-phenylpiperidin-2,6-dione 4a using catalyst 9 followed by conversion to the corresponding lactam 10b**

A suspension of (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (0.25 g, 1.00 mmol) in dry toluene (3 mL) was treated with trimethylboroxine (0.05 mL, 0.33 mmol) and allowed to stir under nitrogen for 30 min. Dry toluene (5 mL) was added and the reaction distilled until approximately 2 mL of solvent remained. This procedure was repeated twice after which the final volume of toluene was removed under pressure to give a yellow solid. Dry dichloromethane (5 mL) was added to give a stock solution of the B-Me CBS catalyst. The catalyst (0.50 mL, 10 mol %) was added to the solution of the glutarimide substrate 4a (0.28 g, 1.00 mmol) in dry dichloromethane (30 mL) followed by a drop-wise addition of BH$_3$.THF (1 mL, 1.00 mmol). The solution was then allowed to stir at room temperature for 24 h. The reaction was finally quenched by addition
of MeOH (2 mL) and 1M HCl (2 mL), extracted with CH₂Cl₂ (3 × 15 mL), dried over MgSO₄ and filtered. The solvent was evaporated in vacuo to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH₂Cl₂ (30 mL) and treated with TFA (1 mL) and triethylsilane (1 mL) in CH₂Cl₂ (5 mL). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 mL) followed by extraction with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were washed with saturated NaHCO₃ (15 mL), dried over MgSO₄ and filtered. The solvent was removed in vacuo to give a crude white solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40–60) (7:3) to afford the corresponding lactam as white solid (0.03 g, 13% over 2 steps, 14% ee determined by HPLC on a Lux 3u Cellulose-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_minor = 21.1 min, t_major = 23.1 min); All analytical data corresponds to those reported for compound 10b.

(4R)-1-(4-Methoxyphenyl)-4-phenylpiperidin-2-one 10a

Using glutarimide 3 (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure G (0.07 g, 33% over 2 steps, 95% ee determined by HPLC on a CELLULOSE-1 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_minor = 27.3 min, t_major = 29.9 min); mp = 204–206 °C; [α]D²⁰ + 6.0 (c 1.3, CHCl₃; 95% ee); νmax / cm⁻¹ (ATR) 2940 (w, C-H), 1640 (s, C=O), 1620 (m, C=O), 1506 (m, C=O), 1260 (s, C=C); δH (400 MHz, CDCl₃) 2.11–2.21 (m, 1H), 2.23–2.30 (m, 1H), 2.73 (dd, J = 17.5, 10.8 Hz, 1H), 2.92 (dddd, J = 17.5, 10.8, 5.3, 3.4 Hz, 1H), 3.29 (tdd, J = 10.8, 5.3, 3.4 Hz, 1H), 3.65 (dddd, J = 10.8, 5.3, 3.4 Hz, 1H), 3.74–3.81 (m, 1H), 3.84 (s, 3H), 6.96 [(AX)₂, 2H], 7.22 [(AX)₂, 2H], 7.28–7.32 (m, 3H), 7.38–7.42 (m, 2H); δC (100 MHz, CDCl₃) 30.7 (CH₂), 38.8 (CH), 39.8 (CH₂), 51.0 (CH₂), 55.5 (CH₃), 114.6 (2 × CH), 126.6 (2 × CH), 126.9 (CH), 127.4 (2 × CH), 128.8 (2 × CH), 135.9 (C), 143.4
(4R)-1-(Phenylmethyl)-4-phenylpiperidin-2-one 10b\textsuperscript{20}

Using glutarimide 4a (0.30 g, 1.00 mmol) the title compound 10b was obtained as a white solid using general procedure G (0.16 g, 60% over 2 steps, 90% ee determined by HPLC on a Lux 3µ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t\textsubscript{major} = 23.5 min, t\textsubscript{minor} = 26.1 min); mp = 80–82 °C (lit.\textsuperscript{32} 88–90 °C; [α]\textsubscript{D}\textsuperscript{20} + 33.0 (c 1.1, CHCl\textsubscript{3}; 90% ee), lit.\textsuperscript{20} [α]\textsubscript{D}\textsuperscript{20} + 35.0 (c 1.1, CHCl\textsubscript{3}, 92.5% ee); v\textsubscript{max}/cm\textsuperscript{-1} (ATR) 1619 (s, C=O), 1494 (m, C=C); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.97 (dtd, J = 13.2, 10.8, 6.0 Hz, 1H), 2.07–2.14 (m, 1H), 2.63 (dd, J = 17.5, 11.0 Hz, 1H), 2.83 (ddd, J = 17.5, 5.2, 2.0 Hz, 1H), 3.13 (tdd, J = 11.0, 5.2, 3.1 Hz, 1H), 3.26–3.37 (m, 2H), 4.59 (d, J = 14.5 Hz, 1H), 4.77 (d, J = 14.5 Hz, 1H), 7.21–7.39 (m, 10H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 30.3 (CH\textsubscript{2}), 38.7 (CH), 39.5 (CH\textsubscript{2}), 46.4 (CH\textsubscript{2}), 50.0 (CH\textsubscript{2}), 126.5 (2 × CH), 126.8 (CH), 127.5 (CH), 128.2 (2 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 137.1 (C), 143.4 (C), 169.3 (C); MS (EI\textsuperscript{+}) m/z: 265 ([M]\textsuperscript{+}, 100%), 174 (12), 131 (32), 104 (230), 131 (32), 91 (70). All data are in accordance with literature.\textsuperscript{20,32,33}

(4R)-1-(2-Methylbenzyl)-4-phenylpiperidin-2-one 10c

Using glutarimide 5 (0.30 g, 1.00 mmol) the title compound 10c was obtained as a white solid using general procedure G (0.07 g, 25% over 2 steps, 88% ee determined by HPLC on a Lux 3µ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t\textsubscript{major} = 20.6 min, t\textsubscript{minor} = 22.3 min); mp = 72–74 °C; [α]\textsubscript{D}\textsuperscript{20} + 26.6 (c 0.8, CHCl\textsubscript{3}; 88% ee); Anal. Calcd for C\textsubscript{19}H\textsubscript{21}NO: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.81; H, 7.82; N, 4.85; v\textsubscript{max}/cm\textsuperscript{-1} (ATR) 3024 (w, C-H), 2915 (w, C-H), 1627 (s, C=O), 1605 (m, C=C); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.93–2.03 (m,
1H), 2.09–2.15 (m, 1H), 2.34 (s, 3H), 2.64 (dd, J = 17.5, 11.1 Hz, 1H), 2.88 (ddd, J = 17.5, 5.2, 2.1 Hz, 1H), 3.15 (tdd, J = 11.1, 5.2, 3.1 Hz, 1H), 3.22–3.31 (m, 2H), 4.63 (d, J = 15.1 Hz, 1H), 4.81 (d, J = 15.1 Hz, 1H), 7.17–7.29 (m, 7H), 7.35–7.39 (m, 2H); δC (100 MHz, CDCl3) 19.25 (CH3), 30.3 (CH2), 38.7 (CH), 39.5 (CH2), 46.3 (CH2), 47.7 (CH2), 126.1 (CH), 126.5 (2 × CH), 126.8 (CH), 127.5 (CH), 128.1 (CH), 128.8 (2 × CH), 130.5 (CH), 134.5 (C), 136.6 (C), 143.4 (C), 169.2 (C); HRMS (ESI+TOF): calcd for C19H22NO ([MH]+), 280.1701; found, 280.1713.

(4R)-1-(2-Methoxybenzyl)-4-phenylpiperidin-2-one 10d

Using glutarimide 6 (0.30 g, 1.00 mmol) the title compound 10d was obtained as a white solid using general procedure G (0.06 g, 21% over 2 steps, 90% ee determined by HPLC on a Lux 3µ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, tmajor = 21.3 min, tminor = 23.6 min); mp = 80–82 °C; [α]D 20 + 21.7 (c 1.0, CHCl3; 90% ee); νmax / cm⁻¹ (ATR) 2940 (w, C-H), 1636 (s, C=O); δH (400 MHz, CDCl3) 1.95–2.03 (m, 1H), 2.09–2.13 (m, 1H), 2.62 (dd, J = 17.5, 11.1 Hz, 1H), 2.84 (ddd, J = 17.5 Hz, 5.3, 2.0 Hz, 1H), 3.15 (tdd, J = 11.1, 5.3, 3.2 Hz, 1H), 3.31–3.37 (m, 2H), 3.86 (s, 3H), 4.65 (d, J = 15.1 Hz, 1H), 4.77 (d, J = 15.1 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.97 (td, J = 7.5, 0.9 Hz, 1H), 7.23–7.30 (m, 5H), 7.34–7.38 (m, 2H); δC (100 MHz, CDCl3) 30.4 (CH2), 38.7 (CH), 39.5 (CH2), 44.5 (CH2), 46.8 (CH2), 55.4 (CH3), 110.3 (CH), 120.7 (CH), 125.1 (C), 126.6 (2 × CH), 126.8 (CH), 128.5 (CH), 128.7 (2 × CH), 129.1 (CH), 143.6 (C), 157.6 (C), 169.4 (C); HRMS (EI+): calcd for C19H21NO2 (M+), 295.1572; found, 295.1563; MS (EI+) m/z: 295 (M+, 100%), 264 (50), 176 (27), 149 (35), 121 (60), 91 (85).

1-(4-Methoxyphenyl)-4-phenylpiperidine 11a

Using general procedure G and glutarimide 3 (0.30 g, 1.00 mmol) the title compound 11a was obtained as white crystals (0.08 g, 30% over 2 steps); mp = 150–152 °C; Anal. Calcd for
C_{18}H_{21}NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.74; H, 7.91; N, 5.12; \nu_{\text{max}} / \text{cm}^{-1} (\text{ATR}) 2953 (w, C-H), 2938 (m, C-H), 2917 (m, C-H), 2810 (m, C-H), 1508 (s, C=O); \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) 1.95–1.96 (m, 4H), 2.61–2.69 (m, 1H), 2.75–2.82 (m, 2H), 3.65–3.69 (m, 2H), 3.81 (s, 3H), 6.90 [(AX)2, 2H], 7.00 [(AX)2, 2H], 7.24–7.38 (m, 5H); \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 33.6 (2 \times \text{CH}_2), 42.4 (\text{CH}), 52.2 (2 \times \text{CH}_2), 55.6 (\text{CH}_3), 114.4 (2 \times \text{CH}), 118.9 (2 \times \text{CH}), 126.3 (\text{CH}), 126.9 (2 \times \text{CH}), 128.5 (2 \times \text{CH}), 146.2 (\text{C}), 146.4 (\text{C}), 153.8 (\text{C}); \text{HRMS (ESI}^+\text{TOF): calcd for C}_{18}\text{H}_{22}\text{NO ([MH}^+]\)), 268.1701; found, 268.1693. Only \textsuperscript{1}H NMR and low resolution mass spectrometry data were provided in the literature. The literature \textsuperscript{1}H NMR data is mis-assigned.\textsuperscript{34}

\textbf{1-(Phenylmethyl)-4-phenylpiperidine 11b}

Using general procedure G and glutarimide 3 (0.30 g, 1.00 mmol) the title compound 11b was obtained as an undesired product as yellow oil (0.03 g, 12% over 2 steps); \nu_{\text{max}} / \text{cm}^{-1} (\text{ATR}) 3026 (w, C-H), 2933 (m, C-H), 2798 (m, C-H), 2754 (m, C-H), 1493 (m, C=O); \delta_{\text{H}} (250 \text{ MHz, CDCl}_3) 1.75–1.95 (m, 4H), 2.05–2.21 (m, 2H), 2.48–2.60 (m, 1H), 3.03–3.10 (m, 2H), 3.60 (s, 2H), 7.20–7.40 (m, 10H); \delta_{\text{C}} (75 \text{ MHz, CDCl}_3) 33.6 (2 \times \text{CH}_2), 42.8 (\text{CH}), 54.3 (2 \times \text{CH}_2), 63.5 (\text{CH}_2), 126.1 (\text{CH}), 126.9 (2 \times \text{CH}), 127.0 (\text{CH}), 128.2 (2 \times \text{CH}), 128.4 (2 \times \text{CH}), 129.2 (2 \times \text{CH}), 138.6 (\text{C}), 146.6 (\text{C}); \text{HRMS (ESI}^+\text{TOF): calcd for C}_{18}\text{H}_{22}\text{N ([MH}^+]\)), 252.1752; found, 252.1764. All data are in accordance with literature.\textsuperscript{35}

\textbf{(6R) and (6S)-(4R)-5-Hydroxy-1-(4-methoxyphenyl)-4-phenylpiperidin-2-one 12}

Using general procedure G with glutarimide 3 (0.30 g, 1.00 mmol) but halting the reaction and purifying the crude hydroxy-lactam before conversion to the N-PMP lactam gave the title compound 12 as a white powder in a 2:1 diastereomeric ratio (0.06 g, 20%); mp = 156–158 °C; \([\alpha]_D^{20} + 18.2 \text{ (c 1.7, CHCl}_3\)); \nu_{\text{max}} /\text{cm}^{-1} (\text{ATR}) 3188 (w, O-H), 2935 (w, C-H), 1644 (m, C=O),
1620 (s, C=O), 1602 (s, C=O), 1507 (s, C=C); \( ^{1}H\) (400 MHz, CDCl\(_3\)) major diastereoisomer 2.60–2.74 (m, 2H), 2.86–2.96 (m, 2H), 3.21–3.31 (m, 2H), 3.84 (s, 3H), 5.30–5.34 (m, 1H), 6.96–6.98 (m, 3H), 7.28–7.30 (m, 6H); \( ^{13}C\) (100 MHz, CDCl\(_3\)) major diastereoisomer 30.7 (CH\(_2\)), 33.1 (CH), 51.0 (CH\(_2\)), 55.5 (CH\(_3\)), 81.9 (CH), 114.8 (2 \times CH), 126.7 (2 \times CH), 127.4 (CH), 128.8 (2 \times CH), 129.2 (2 \times CH), 133.4 (C), 143.1 (C), 158.9 (C), 170.0 (C); HRMS (ESI\(^{+}\)TOF): calcd for C\(_{18}\)H\(_{19}\)NO\(_3\) ([MH]\(^{+}\)), 298.1443; found, 298.1446.

**(4R)-1-(Phenylmethyl)-4-(2-fluorophenyl)piperidin-2-one 13b**

Using glutarimide 4b (0.30 g, 1.00 mmol) the title compound 13b was obtained as a white solid using general procedure G (0.17 g, 61% over 2 steps, 86% ee determined by HPLC on a Lux 3\(\mu\) CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, \(t_{\text{major}}\) = 16.4 min, \(t_{\text{minor}}\) = 18.2 min); mp = 60–62 °C; [\(\alpha\)]\(^{20}\)_D +20.1 (c 2.1, CHCl\(_3\); 86% ee); \(\nu_{\text{max}}\) / cm\(^{-1}\) (ATR) 2925 (w, C-H), 1616 (s, C=O), 1580 (m, C=C); \( ^{1}H\) (400 MHz, CDCl\(_3\)) 1.98–2.10 (m, 2H), 2.64 (dd, J = 17.4, 10.8 Hz, 1H), 2.85 (ddd, J = 17.4, 5.3 Hz, 1.9 Hz, 1H), 3.25–3.38 (m, 2H), 3.45 (td, J = 10.8, 5.3, 3.9 Hz, 1H), 4.58 (d, J = 14.6 Hz, 1H), 4.76 (d, J = 14.6 Hz, 1H), 7.03–7.36 (m, 9H); \( ^{13}C\) (100 MHz, CDCl\(_3\)) 28.9 (CH\(_2\)), 32.2 (d, J\(_{\text{C-F}}\) = 1.5 Hz, CH), 38.0 (CH\(_2\)), 46.3 (CH\(_2\)), 50.1 (CH\(_2\)), 115.6 (d, J\(_{\text{C-F}}\) = 22.4 Hz, CH), 124.4 (d, J\(_{\text{C-F}}\) = 3.5 Hz, CH), 127.3 (d, J\(_{\text{C-F}}\) = 4.6 Hz, CH), 127.5 (CH), 128.2 (2 \times CH), 128.3 (d, J\(_{\text{C-F}}\) = 8.4 Hz, CH), 128.7 (2 \times CH), 130.1 (d, J\(_{\text{C-F}}\) = 14.2 Hz, C), 137.0 (C), 160.6 (d, J\(_{\text{C-F}}\) = 245.8 Hz, C), 169.1 (C); \( ^{19}F\) (235 MHz, CDCl\(_3\)) -118.6; HRMS (EI\(^{+}\)): calcd for C\(_{18}\)H\(_{19}\)FNO (M\(^{+}\)), 283.1372; found, 283.1382; MS (EI\(^{+}\)) m/z: 283 (M\(^{+}\), 100%), 149 (50), 109 (25), 103 (58) 105 (93), 91 (95), 77 (98).

**(4R)-1-(Phenylmethyl)-4-(4-fluorophenyl)piperidin-2-one 13c**
Using glutarimide 4c (0.30 g, 1.00 mmol) the title compound 13c was obtained as a white solid using general procedure G (0.15 g, 54% over 2 steps, 88% ee determined by HPLC on a CHIRALPAK IA column (hexane/2-propanol = 93/7, flow rate = 1.0 mL/min, t_{minor} = 38.2 min, t_{major} = 40.0 min); mp = 114–116 °C; [α]_D^{20} +30.0 (c 1.1, CHCl_3; 88% ee, lit. [20] [α]_D^{20} + 33.0 (c 1.07, CHCl_3); ν_{max} / cm^{-1} (ATR) 3071 (w, C-H), 1625 (s, C=O), 1601 (m, C=C); δ_H (400 MHz, CDCl_3) 1.87–1.97 (m, 1H), 2.07–2.10 (m, 1H), 2.57 (dd, J = 17.4, 11.0 Hz, 1H), 2.83 (dd, J = 17.4, 3.4 Hz, 1H), 3.09–3.14 (m, 1H), 3.25–3.36 (m, 2H), 4.57 (d, J = 14.5 Hz, 1H), 4.77 (d, J = 14.5 Hz, 1H), 7.03 [(AX)\_2, 2H], 7.18 [(AX)\_2, 2H], 7.28–7.38 (m, 5H); δ_C (100 MHz, CDCl_3) 30.3 (CH\_2), 38.0 (CH), 39.6 (CH\_2), 46.2 (CH\_2), 50.0 (CH\_2), 115.5 (d, J_{C-F} = 21.2 Hz, 2 × CH), 127.5 (CH), 128.0 (d, J_{C-F} = 7.8 Hz, 2 × CH), 128.2 (2 × CH), 128.7 (2 × CH), 137.1 (C), 139.1 (d, J_{C-F} = 3.0 Hz, C), 161.7 (d, J_{C-F} = 245.0 Hz, C), 169.1 (C); δ_F (235 MHz, CDCl_3) -116.0; HRMS (ESI^+TOF): calcd for C\_{18}H\_{19}FNO ([MH^+]), 284.1451; found, 284.1437. All data are in accordance with literature. [20,33,36]

(4R)-1-(Phenylmethyl)-4-(2-methylphenyl)piperidin-2-one 13d

Using glutarimide 4d (0.30 g, 1.00 mmol) the title compound 13d was obtained as a white solid using general procedure G (0.14 g, 51% over 2 steps, 82% ee determined by HPLC on a Lux 3μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 15.3 min, t_{major} = 18.3 min); mp = 68–70 °C; [α]_D^{20} +39.4 (c 0.3, CHCl_3; 82% ee); ν_{max} / cm^{-1} (ATR) 2925 (w, C-H), 1626 (s, C=O), 1587 (m, C=C); δ_H (400 MHz, CDCl_3) 2.01–2.04 (m, 2H), 2.37 (s, 3H), 2.56 (dd, J = 17.5, 11.0 Hz, 1H), 2.81 (ddd, J = 17.5, 5.2, 1.9 Hz, 1H), 3.28–3.37 (m, 3H), 4.55 (d, J = 14.5 Hz, 1H), 4.85 (d, J = 14.5 Hz, 1H), 7.16–7.22 (m, 4H), 7.33–7.40 (m, 5H); δ_C (100 MHz, CDCl_3) 19.3 (CH\_3), 29.3 (CH\_2), 34.6 (CH), 39.0 (CH\_2), 46.5 (CH\_2), 50.1 (CH\_2), 125.0 (CH), 126.5 (CH), 126.6 (CH), 127.5 (CH), 128.3 (2 × CH), 128.7 (2 × CH), 130.7 (CH), 135.3
(C), 137.2 (C), 141.5 (C) 169.6 (C); HRMS (ESI^+TOF): calcd for C_{19}H_{22}NO ([MH^+]), 280.1701; found, 280.1710.

(4R)-1-(Phenylmethyl)-4-(4-methylphenyl)piperidin-2-one 13e

Using glutarimide 4e (0.30 g, 1.00 mmol) the title compound 13e was obtained as a white solid using general procedure G (0.14 g, 54% over 2 steps, 92% ee determined by HPLC on a CHIRALPAK IA column (hexane/2-propanol = 92/7, flow rate = 1.0 mL/min, t_{minor} = 31.3 min, t_{major} = 32.9 min); mp = 105–106 °C; [a]_{D}^{20} +33.6 (c 1.1, CHCl_3; 92% ee); Anal. Calcd for C_{19}H_{21}NO: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.58; H, 7.54; N, 4.90; \nu_{max} / \text{cm}^{-1} (ATR) 2924 (w, C-H), 1625 (s, C=O) ; \delta_{H} (400 MHz, CDCl_3) 1.89–1.99 (m, 1H), 2.05–2.12 (m, 1H), 2.36 (s, 3H), 2.60 (dd, J = 17.5, 11.1 Hz, 1H), 2.83 (ddd, J = 17.5, 5.2, 2.0 Hz, 1H), 3.10 (tdd, J = 11.1, 5.2, 3.1 Hz, 1H), 3.25–3.36 (m, 2H), 4.59 (d, J = 14.6 Hz, 1H), 4.76 (d, J = 14.6 Hz, 1H), 7.13 [(AX)_{2}, 2H], 7.17 [(AX)_{2}, 2H], 7.28–7.39 (m, 5H); \delta_{C} (100 MHz, CDCl_3) 21.0 (CH_{3}), 30.4 (CH_{2}), 38.3 (CH), 39.6 (CH_{2}), 46.4 (CH_{2}), 50.0 (CH_{2}), 126.4 (2 \times CH), 127.4 (CH), 128.2 (2 \times CH), 128.6 (2 \times CH), 129.4 (2 \times CH), 136.4 (C), 137.2 (C), 140.5 (C) 169.4 (C); HRMS (ESI^+TOF): calcd for C_{19}H_{22}NO ([MH^+]), 280.1701; found, 280.1692.

(4R)-1-(Phenylmethyl)-4-(1-naphthyl)piperidin-2-one 13f

Using glutarimide 4f (0.33 g, 1.00 mmol) the title compound 13f was obtained as a white solid using general procedure G (0.06 g, 20% over 2 steps, 54% ee determined by HPLC on a CHIRALPAK IA column (hexane/2-propanol = 92/7, flow rate = 1.0 mL/min, t_{major} = 41.3 min, t_{minor} = 44.9 min); mp = 122–124 °C; [a]_{D}^{20} -13.3 (c 0.5, CHCl_3; 54% ee); \nu_{max} / \text{cm}^{-1} (ATR) 2950 (w, C-H), 1636 (s, C=O), 1624 (s, C=O); \delta_{H} (400 MHz, CDCl_3) 2.10–2.20 (m, 1H), 2.25–2.28 (m, 1H), 2.74 (dd, J = 17.5, 10.1 Hz, 1H), 3.05 (dd, J = 17.5, 3.6 Hz, 1H), 3.10 (dt, J = 10.1, 4.7
Hz, 1H), 3.38–3.45 (m, 1H), 3.95–3.99 (m, 1H), 4.61 (d, J = 14.5 Hz, 1H), 4.84 (d, J = 14.5 Hz, 1H), 7.31–7.41 (m, 6H), 7.44–7.57 (m, 3H), 7.78 (d, J = 8.2 Hz, 1H), 7.90 (dd, J = 7.7, 1.5 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H);  δ_C (100 MHz, CDCl_3) 29.6 (CH_2), 33.8 (CH), 39.3 (CH_2), 46.2 (CH_2), 50.2 (CH_2), 122.4 (CH), 122.7 (CH), 125.6 (CH), 125.7 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 128.3 (2 × CH), 128.7 (2 × CH), 129.1 (CH), 131.0 (C), 134.0 (C), 137.1 (C), 138.9 (C), 169.5 (C); HRMS (ESI^+TOF): calcd for C_{22}H_{22}NO ([MH^+]), 316.1701; found, 316.1689.

(4R)-1-(Phenylmethyl)-4-methylpiperidin-2-one 13g

Using general procedure G and glutarimide 4g (0.22 g, 1.00 mmol) a crude oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40–60 : Et_3N (2:8:0.05) to afford the title compound 13g as pale yellow oil (0.09 g, 46% over 2 steps, 90% ee determined by HPLC on a Lux 3µ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 13.2 min, t_{major} = 14.1 min); [α]^2_0 + 46.6 (c 3.3, CHCl_3; 90% ee); ν_{max} / cm^{-1} (ATR) 2953 (w, C-H), 1634 (s, C=O); δ_H (400 MHz, CDCl_3) 1.01 (d, J = 6.5 Hz, 3H), 1.39–1.47 (m, 1H), 1.78–1.85 (m, 1H), 1.90–2.00 (m, 1H), 2.07 (dd, J = 17.2, 10.7 Hz, 1H), 2.58 (ddd, J = 17.2, 4.9, 2.1 Hz, 1H), 3.18–3.22 (m, 2H), 4.48 (d, J = 14.7 Hz, 1H), 4.72 (d, J = 14.7 Hz, 1H), 7.24–7.34 (m, 5H); δ_C (100 MHz, CDCl_3) 21.0 (CH_3), 28.0 (CH), 30.9 (CH_2), 40.5 (CH_2), 46.3 (CH_2), 50.0 (CH_2), 127.3 (CH), 128.0 (2 × CH), 128.6 (2 × CH), 137.3 (C), 169.7 (C); HRMS (ESI^+TOF): calcd for C_{13}H_{18}NO ([MH^+]), 204.1388; found, 204.1394.

(4R)-1-(Phenylmethyl)-4-isopropylpiperidin-2-one 13h

Using general procedure G and glutarimide 4h (0.22 g, 1.00 mmol) a crude oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : CH_2Cl_2 :
petroleum ether (40–60) (3:1:6) to afford the title compound 13h as yellow oil (0.09 g, 41% over 2 steps, 86% ee determined by HPLC on a Lux 3μ CELLULOSE-2 column (hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, t_{minor} = 47.1 min, t_{major} = 49.0 min); [α]_{D}^{20} + 44.3 (c 1.9, CHCl₃; 86% ee); ν_{max} / cm⁻¹ (ATR) 2957 (m, C-H), 2871 (m, C-H), 1676 (m, C=O), 1638 (s, C=O); δ_{H} (400 MHz, CDCl₃) 0.92 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.40–1.60 (m, 3H), 1.85–1.90 (m, 1H), 2.17 (dd, J = 17.5, 11.6 Hz, 1H), 2.61 (ddd, J = 17.5, 4.9, 2.3 Hz, 1H), 3.15–3.27 (m, 2H), 4.53 (d, J = 14.6 Hz, 1H), 4.71 (d, J = 14.6 Hz, 1H), 7.25–7.36 (m, 5H);

į{H} (400 MHz, CDCl₃) 0.90 (s, 9H), 1.40 (qd, J = 12.5, 5.5 Hz, 1H), 1.57 (tdd, J = 12.5, 4.8, 2.3 Hz, 1H), 1.86–1.90 (m, 1H), 2.21 (dd, J = 17.3, 12.5 Hz, 1H), 2.59 (ddd, J = 17.3, 4.8, 2.3 Hz, 1H), 3.17 (td, J = 12.6, 4.8 Hz, 1H), 3.26 (ddd, J = 12.6, 5.5, 2.3 Hz, 1H), 4.53 (d, J = 14.6 Hz, 1H), 4.71 (d, J = 14.6 Hz, 1H), 7.26–7.36 (m, 5H); δ_{C} (100 MHz, CDCl₃) 24.6 (CH₂), 26.8 (3 × CH₃), 32.0 (C), 34.3 (CH₂), 43.2 (CH), 47.1 (CH₂), 49.9 (CH₂), 127.3 (CH), 128.1 (2 × CH), 128.6 (2 × CH), 137.2 (C), 170.3 (C); HRMS (ESI⁺TOF): calcd for C₁₅H₂₂NO ([MH⁺]), 232.1701; found, 232.1709.

(4R)-1-(Phenylmethyl)-4-tert-butylpiperidin-2-one 13i

Using general procedure F and glutarimide 4i (0.26 g, 1.00 mmol) an oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : CH₂Cl₂ : petroleum ether (40–60) (3:1:6) to afford the title compound 12i as yellow oil (0.11 g, 46% over 2 steps, 87% ee determined by HPLC on a Lux 3μ CELLULOSE-2 column (hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, t_{minor} = 11.3 min, t_{major} = 12.4 min); [α]_{D}^{20} + 36.8 (c 1.4, CHCl₃; 87% ee); ν_{max} / cm⁻¹ (ATR) 2957 (s, C-H), 2867 (s, C-H), 1636 (s, C=O); δ_{H} (400 MHz, CDCl₃) 0.90 (s, 9H), 1.40 (qd, J = 12.5, 5.5 Hz, 1H), 1.57 (tdd, J = 12.5, 4.8, 2.3 Hz, 1H), 1.86–1.90 (m, 1H), 2.21 (dd, J = 17.3, 12.5 Hz, 1H), 2.59 (ddd, J = 17.3, 4.8, 2.3 Hz, 1H), 3.17 (td, J = 12.6, 4.8 Hz, 1H), 3.26 (ddd, J = 12.6, 5.5, 2.3 Hz, 1H), 4.53 (d, J = 14.6 Hz, 1H), 4.71 (d, J = 14.6 Hz, 1H), 7.26–7.36 (m, 5H); δ_{C} (100 MHz, CDCl₃) 24.6 (CH₂), 26.8 (3 × CH₃), 32.0 (C), 34.3 (CH₂), 43.2 (CH), 47.1 (CH₂), 49.9 (CH₂), 127.3 (CH), 128.1 (2 × CH), 128.6 (2 × CH), 137.2 (C), 170.5 (C); HRMS (ESI⁺TOF): calcd for C₁₆H₂₄NO ([MH⁺]), 246.1858; found, 246.1861.
Associated content

Supporting Information

\(^1\)H and \(^{13}\)C NMR spectra of all compounds, HPLC of lactam products 10a-d, 13b-13i. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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