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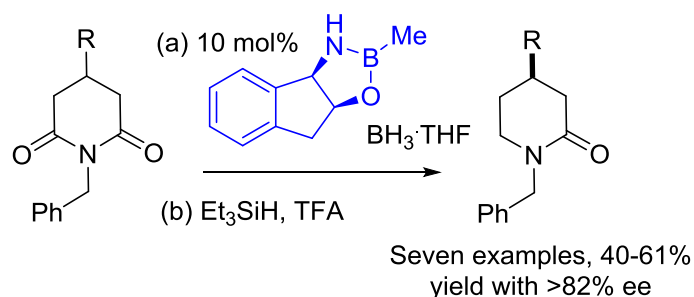
Enantioselective desymmetrization of glutarimides catalysed by oxazaborolidines derived from cis-1-amino-indan-2-ol

Ibrahim U. Kutama and Simon Jones*

Department of Chemistry, University of Sheffield, Dainton Building, Brook Hill, Sheffield, S3 7HF. UK.

E-mail: simon.jones@sheffield.ac.uk

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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

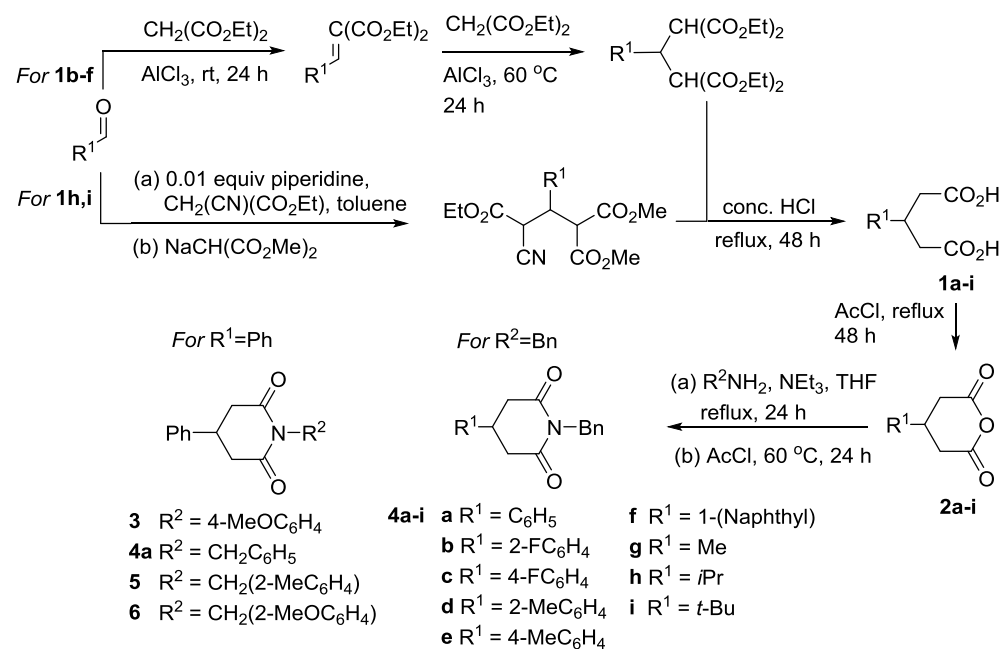
Desymmetrization to access chiral molecules is a popular strategy in organic synthesis, providing compounds with multiple stereogenic centers in one operation. The synthetic chemistry used in these strategies can be wide-ranging, for example, the addition of chiral alcohols to cyclic meso-anhydrides to yield diastereomerically-enriched mono esters,¹ 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.² 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.³⁻⁵ Strategies within this area of chemistry include the use of chiral auxiliaries,⁶ BINAL-H complexes,⁷ and thiazazincolidine complexes⁸ 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.^{9,10} 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,¹¹ with further studies demonstrating the crucial role of the nitrogen substituent in obtaining high selectivities.¹² The use of these catalysts for the kinetic resolution of racemic C-3 substituted imides has also been reported.¹³ 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.¹⁴

Although there has been much work on the desymmetrisation 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,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%).^{16, 17} Here we present the enantioselective desymmetrisation of 3-substituted glutarimides using oxazaborolidine catalysts derived from cis-1-amino-indan-2-ol.

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 tetraethyl propane tetracarboxylates through Knoevenegel condensation followed by Michael addition.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 AlCl₃ 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 sodiomalonate for the Michael addition (Scheme 1).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).¹⁶



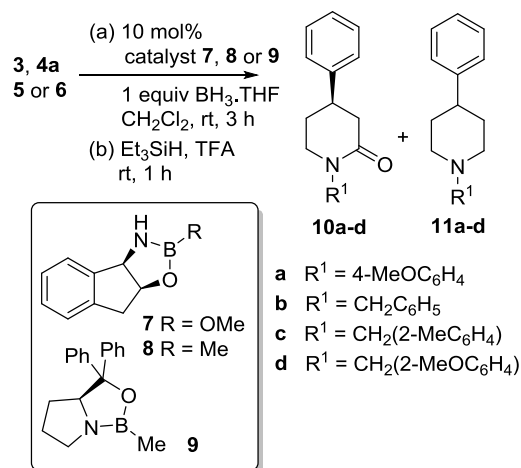
Scheme 1. Route to glutarimide substrates

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

Entry	R^1	R^2	Yield		
			Glutaric acid ^a	Anhydride	Imide
1	Ph	4-MeOC ₆ H ₄	1a ^b	2a 82%	3 80%
2	Ph	CH ₂ C ₆ H ₅	1a ^b	2a 82%	4a 85%
3	Ph	CH ₂ (2-MeC ₆ H ₄)	1a ^b	2a 82%	5 71%
4	Ph	CH ₂ (2-MeOC ₆ H ₄)	1a ^b	2a 82%	6 60%
5	2-FC ₆ H ₄	CH ₂ C ₆ H ₅	1b 52%	2b 75%	4b 87%
6	4-FC ₆ H ₄	CH ₂ C ₆ H ₅	1c 57%	2c 93%	4c 71%
7	2-MeC ₆ H ₄	CH ₂ C ₆ H ₅	1d 51%	2d 73%	4d 60%
8	4-MeC ₆ H ₄	CH ₂ C ₆ H ₅	1e 50%	3e 85%	4e 67%
9	1-Naphthyl	CH ₂ C ₆ H ₅	1f 60%	3f 80%	4f 52%
10	Me	CH ₂ C ₆ H ₅	1g ^b	3g 79%	4g 68%
11	iPr	CH ₂ C ₆ H ₅	1h 35%	3h 79%	4h 70%
12	t-Bu	CH ₂ C ₆ H ₅	1i 58%	3i 70%	4i 89%

^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 BH₃.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.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

Entry	Substrate	Catalyst	Method	Product / yield (%) ^b			10a-d ee (%) ^c
1	3	7	A ^d	3a (20)	10a (48)	11a (21)	99
2	3	7	B ^e	3a (37)	10a (43)	11a (15)	99
3	3	8	A ^d	3a (66)	10a (18)	11a (10)	53
4	3	8	B ^e	3a (28)	10a (33)	11a (30)	95
5	4a	7	A ^d	4a (60)	10b (34)	11b (5)	85
6	4a	7	B ^e	4a (59)	10b (30)	11b (5)	92
7	4a	8	A ^d	4a (62)	10b (20)	11b (9)	80
8	4a	8	B ^e	4a (20)	10b (60)	11b (12)	90
10	4a	9	B ^e	ND ^f	10b (13)	ND ^f	14
11	5	8	B ^e	ND ^f	10c (25)	ND ^f	88
12	6	8	B ^e	ND ^f	10d (21)	ND ^f	90

^a Reactions conducted by treating a solution of the glutarimide **3** in dry CH₂Cl₂ with 10 mol% of the catalyst solution and 1 equiv BH₃.THF at rt for 3 h, followed work-up, dissolution into CH₂Cl₂ and treatment with Et₃SiH / 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.

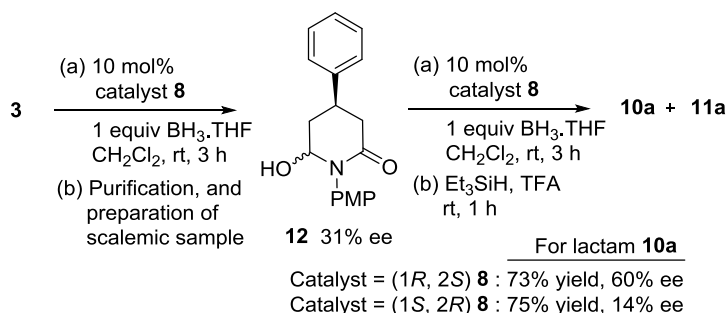
When using the N-PMP substrate **3** with the B-OMe catalyst, both methods of preparation gave excellent ee's of piperidinone **10a**, however method A produced the 2-piperidinone **10a** in a 48% yield and the undesired piperidine **11a** in a 21% yield (Table 2, entry 1) while method B gave 43% yield 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 cycloadduct desymmetrisation.¹⁴ This was also investigated in this series, with the B-Me catalyst **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 **3** was first reduced using both enantiomers of the B-Me catalyst **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 **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 **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.



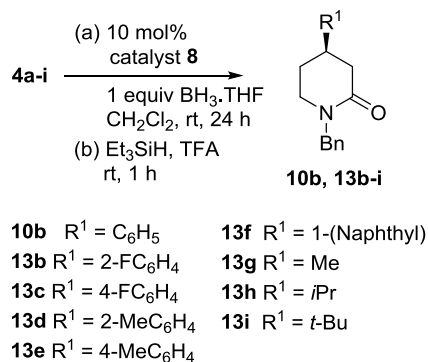
Scheme 3. Stereoablation experiment with N-PMP glutarimide **3**

When a representative sample from the scalemic hydroxy-lactam **12** (31% ee) was subjected to reduction with (1R, 2S) enantiomer of the B-Me catalyst **8** followed by subsequent reduction with Et₃SiH, 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 / 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 ^1H 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^a

Entry	Imide	Product / yield (%) ^b	ee (%) ^c	Measured $[\alpha]_{\text{D}}^{20}$	Literature $[\alpha]_{\text{D}}^{20}$
1	4a	10b (60)	90	+33.0 (c 1.1, CHCl_3)	+35.0 (c 1.1, CHCl_3) ²⁰
2	4b	13b (61)	86	+39.4 (c 0.3, CHCl_3)	Unknown
3	4c	13c (51)	88	+ 33.6 (c 1.1, CHCl_3)	Unknown
4	4d	13d (51)	82	+ 20.1 (c 2.1, CHCl_3)	Unknown
5	4e	13e (54)	92	+30.0 (c 1.1, CHCl_3)	+33.0 (c 1.1, CHCl_3) ²⁰
6	4f	13f (20)	54	-13.3 (c 0.5, CHCl_3)	Unknown
7	4g	13g (46)	90	+ 46.6 (c 3.3, CHCl_3)	Unknown
8	4h	13h (41)	86	+ 44.3 (c 1.9, CHCl_3)	Unknown
9	4i	13i (46)	87	+ 36.8 (c 1.4, CHCl_3)	Unknown

^a Reactions conducted by treating a solution of the glutarimide **4a-i** in dry CH_2Cl_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 $\text{BH}_3\cdot\text{THF}$ at rt for 24 h, followed work-up, dissolution into CH_2Cl_2 and treatment with Et_3SiH / 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, CHCl₃)] closely matched that of a related known compound, N-PMP-4-(4-fluorophenyl)piperidin-2-one [+8.0 (c 1.3, CHCl₃)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.

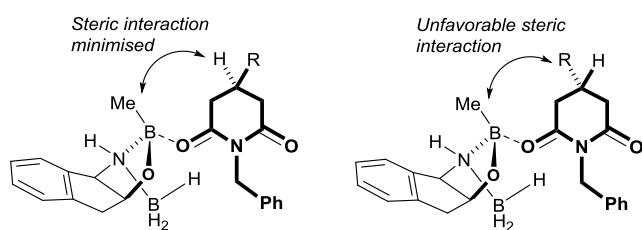


Figure 1. Pre-transition state models for imide reduction

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 40-63 μ 60Å. ¹H 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 cm² g⁻¹. HPLC was carried out using a Chiralcel (4.8 mm \times 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.¹⁸

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 \times 15

mL). The combined organic extracts were dried over MgSO_4 and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation ($130\text{ }^\circ\text{C}$, 9.5×10^{-1} mbar) to give the crude diethyl o-substituted benzylidenemalonate which was taken to next step without further purification. AlCl_3 (0.05 equiv.) was slowly added to a mixture of the crude benzylidene malonate (1 equiv.) and diethylmalonate (1 equiv.) and stirred at $60\text{ }^\circ\text{C}$ for 24 h. Another portion of AlCl_3 (0.05 equiv.) was slowly added to the mixture, the reaction temperature was raised to $70\text{ }^\circ\text{C}$ 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 CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over MgSO_4 and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation ($130\text{ }^\circ\text{C}$, 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 AlCl_3 (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 CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over MgSO_4 and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation ($130\text{ }^\circ\text{C}$, 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. AlCl_3 (0.05 equiv.) was slowly added to a mixture of the crude benzylidene malonate (1 equiv.) and diethylmalonate (1 equiv.) and stirred at $60\text{ }^\circ\text{C}$ for 24 h. Another portion of AlCl_3 (0.05 equiv.) was slowly added to the mixture, the reaction temperature was raised to $70\text{ }^\circ\text{C}$ 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 CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over MgSO_4 and filtered. The solvent was removed in vacuo and excess diethylmalonate was removed by vacuum distillation ($130\text{ }^\circ\text{C}$, 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 CH_2Cl_2 (30 mL), dried over MgSO_4 and filtered. The solvent was evaporated in vacuo to give an orange oily residue which was added to a solution of dimethylsodiummalonate [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 MgSO₄ 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 MgSO₄, 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: δ_{H} (400 MHz, CDCl₃) 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: δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 13.7 (2 × CH₃), 13.9 (2 × CH₃), 38.3 (CH), 54.4 (2 × CH), 61.4 (2 × CH₂), 61.7 (2 × CH₂), 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 C₁₁H₁₁FO₄: 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 × CH₂), 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⁺ TOF) m/z: 227 ([MH]⁺, 70%), 209 ([M - OH]⁺, 100%).

3-(4-Fluorophenyl)pentan-1,5-dioic acid 1c¹⁷

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, CDCl₃) 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, CDCl₃) 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.²² 146–147 °C); Anal. Calcd for C₁₁H₁₁FO₄: 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)₂, 2H], 7.31 [(AX)₂, 2H], 12.11 (2brd s, 2H); δ_C (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); δ_F (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; δ_H (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; δ_H (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; ν_{max} /cm⁻¹ (ATR) 2971 (brd, O-H), 1708 (s C=O) 1514 (w, Ar C=C); δ_H (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); δ_C (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 **1e²³**

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; δ_{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; δ_{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.²³ 118–121 °C); Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35. Found: C, 64.85; H, 6.13; ν_{max} / cm^{-1} (ATR) 2925 (brd, O-H), 1704 (s, C=O), 1515 (w, Ar C=C); δ_{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), 12.06 (s, 2H); δ_{C} (100 MHz, DMSO) 21.1 (CH_3), 38.0 (CH), 40.7 ($2 \times \text{CH}_2$), 127.8 ($2 \times \text{CH}$), 129.2 ($2 \times \text{CH}$), 135.8 (C), 140.8 (C), 173.3 ($2 \times \text{C}$); MS (ESI⁺ TOF) m/z: 223 ($[\text{MH}]^+$, 10%), 205 ($[\text{M} - \text{OH}]^+$, 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 **1f²⁴**

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; δ_{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; δ_{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 $\text{C}_{15}\text{H}_{14}\text{O}_4$: C, 69.76; H, 5.46. Found: C, 69.64; H, 5.39; ν_{max} / cm^{-1} (ATR) 2904 (brd, O-H), 1707 (s, C=O), 1599 (w, C=C), 1511 (w, C=C); δ_{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); δ_{C} (100 MHz, DMSO) 38.0 (CH), 40.3 ($2 \times \text{CH}_2$), 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 ($2 \times \text{C}$); MS (ESI TOF) m/z : 257 ($[\text{M-H}]^-$, 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.²⁵ 87.5–88.5 °C); Anal. Calcd for C₈H₁₄O₄: C, 55.16; H, 8.10. Found: C, 55.14; H, 8.16; ν_{\max} /cm⁻¹ (ATR) 2966 (brd, O-H), 1692 (s, C=O); δ_{H} (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); δ_{C} (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 **1i**²⁶

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.²⁶ 153–154 °C); ν_{\max} (ATR)/cm⁻¹ 2966 (brd, O-H), 1704 (s, C=O); δ_{H} (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); δ_{C} (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]⁺), 189.1127; 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 **2a**¹⁹

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_{\max} /cm⁻¹ (ATR) 1812 (s, C=O), 1752 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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_{C} (100 MHz, CDCl₃) 34.1 (CH), 37.2 (2 × CH₂), 126.2 (2 × CH), 128.2 (CH), 129.4 (2 × CH), 139.1 (C), 165.8 (C); MS (ESI⁺TOF) m/z: 191 ([MH]⁺, 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_{\max} /cm⁻¹ (ATR) 1812 (w), 1754 (s, C=O), 1710 (s, C=O), 1586 (w, C=C); δ_{H} (400 MHz, CDCl₃) 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), 7.11–7.21 (m, 3H), 7.33–7.38 (m, 1H); δ_{C} (100 MHz, CDCl₃) 28.9 (CH), 35.5 (2 × CH₂), 116.3 (d, J_{C-F} = 21.8 Hz, CH), 125.0 (d, J_{C-F} = 3.4 Hz, CH), 126.0 (d, J_{C-F} = 13.3 Hz, C), 127.2 (d, J_{C-F} = 3.8 Hz, CH), 129.9 (d, J_{C-F} = 8.5 Hz, CH), 160.7 (d, J_{C-F} = 246.6 Hz, C), 165.7 (2 × C); δ_{F} (235 MHz, CDCl₃) -117.0; MS (EI⁺) m/z: 208 ([M]⁺, 30%), 122 (100%), 96 (20%); HRMS (EI⁺): calcd for C₁₁H₉FO₃ ([M]⁺), 208.0536; found, 208.0544.

4-(4-Fluorophenyl)dihydropyran-2,6-dione **2c**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.²⁷ 98 °C); Anal. Calcd for C₁₁H₉FO₃: C, 63.46; H, 4.36. Found: C, 63.22; H, 4.08; ν_{\max} /cm⁻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 ($2 \times \text{CH}_2$), 116.4 (d, $J_{\text{C-F}} = 21.6$ Hz, $2 \times \text{CH}$), 127.9 (d, $J_{\text{C-F}} = 8.1$ Hz, $2 \times \text{CH}$), 134.8 (d, $J_{\text{C-F}} = 3.2$ Hz, C), 162.3 (d, $J_{\text{C-F}} = 248.5$ Hz, C), 165.6 ($2 \times \text{C}$); MS (EI^+) m/z : 208 ($[\text{M}]^+$, 40%), 123 (30%), 122 (100%). All data are in accordance with literature.

4-(2-Methylphenyl)dihydropyran-2,6-dione 2d^{28}

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); ν_{max} (ATR)/ 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 ($2 \times \text{CH}_2$), 124.1 (CH), 127.1 (CH), 127.9 (CH), 131.4 (CH), 135.6 (C), 137.2 (C), 166.1 ($2 \times \text{C}$); MS (EI^+) m/z : 204 ($[\text{MH}]^+$, 40%), 144 (60%), 118 (100%), 91 (45%); HRMS (EI^+): calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3$ ($[\text{MH}]^+$), 204.0786; found, 204.0792. All data are in accordance with literature.

4-(4-Methylphenyl)dihydropyran-2,6-dione 2e^{29}

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; ν_{max} / 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 ($2 \times \text{CH}_2$), 126.1 ($2 \times \text{CH}$), 130.0 ($2 \times \text{CH}$),

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; ν_{\max} /cm⁻¹ (ATR) 1808 (s, C=O), 1753 (s, C=O), 1599 (w, C=C); δ_{H} (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); δ_{C} (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 2g³⁰

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.³⁰ 45–46 °C); Anal. Calcd for C₆H₈O₃: C, 56.24; H, 6.29. Found: C, 56.27; H, 6.31; ν_{\max} /cm⁻¹ (ATR) 2977 (w, C-H), 1806 (s, C=O), 1757 (s, C=O), 1744 (s, C=O); δ_{H} (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); δ_{C} (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**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, 85×10^{-2} mbar, lit.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.¹⁹ 25.5–26.5 °C); ν_{\max} /cm⁻¹ (ATR) 2967 (m, C-H), 2878 (m, C-H), 1798 (s, C=O), 1757 (s, C=O), 1702 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 18.9 (2 × CH₃), 31.3 (CH), 34.0 (2 × CH₂), 35.0 (CH), 166.9 (2 × C); HRMS (ESI⁺TOF): calcd for C₈H₁₃O₃ ([MH]⁺), 157.0865; found, 157.0870. All data are in accordance with literature.

4-tert-Butyldihydropyran-2,6-dione **2i**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, 16×10^{-2} mbar, lit.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.¹⁹ 63.5–64.5 °C); ν_{\max} /cm⁻¹ (ATR) 2967 (m, C-H), 1808 (s, C=O), 1748 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 26.4 (3 × CH₃), 32.0 (C), 32.3 (2 × CH₂), 38.7 (CH), 167.2 (C); HRMS (ESI⁺TOF): calcd for C₉H₁₅O₃ ([MH]⁺), 171.1021; found, 171.1024. All data are in accordance with literature.

General Procedure E for the synthesis of glutarimides.¹⁶

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 MgSO₄ 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 C₁₈H₁₇NO₃: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.00; H, 5.52; N, 4.66; ν_{\max} /cm⁻¹ (ATR) 1731 (m, C=O), 1672 (s, C=O), 1610 (s), 1511 (s); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 34.7 (CH), 40.1 (2 × CH₂), 55.4 (CH₃), 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); ν_{\max} /cm⁻¹ (ATR) 3031 (w, C-H), 1726 (m, C=O), 1668 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 34.6 (CH), 39.9 (2 × CH₂), 42.9 (CH₂), 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 ¹H 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 C₁₈H₁₆FNO₂: C, 72.71; H, 5.42; N, 4.71. Found: C, 72.38; H, 5.26; N, 4.57; ν_{\max} /cm⁻¹ (ATR) 3068 (w, C-H), 1728 (m, C=O), 1672 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 29.1 (CH), 38.3 (2 × CH₂), 43.0 (CH₂), 116.1 (d, J_{C-F} = 22.1 Hz, CH), 124.7 (d, J_{C-F} = 3.3 Hz, CH), 127.2 (d, J_{C-F} = 4.0 Hz, CH), 127.4 (d, J_{C-F} = 14.4 Hz, C), 127.6 (CH), 128.5 (2 × CH), 129.0 (2 × CH), 129.3 (d, J_{C-F} = 8.5 Hz, CH), 137.1 (C), 160.8 (d, J_{C-F} = 246.6 Hz, C), 171.4 (2 × C); δ_{F} (235 MHz, CDCl₃) -117.4; MS (TOF MS ES⁺) m/z: 298 ([MH]⁺, 100%).

1-(Phenylmethyl)-4-(4-fluorophenyl)piperidin-2,6-dione **4c**¹⁷

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 C₁₈H₁₆FNO₂: C, 72.71; H, 5.42; N, 4.71. Found: C, 72.47; H, 5.31; N, 4.67; ν_{\max} /cm⁻¹ (ATR) 2955 (w, C-H), 1718 (m, C=O), 1672 (s, C=O), 1604 (m), 1512 (s); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 33.9 (CH), 40.0 (2 × CH₂), 42.9 (CH₂), 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); δ_{F} (235 MHz, CDCl₃) -114.7; HRMS (ESI⁺TOF): calcd for C₁₈H₁₇FNO₂ ([MH]⁺), 298.1243; found, 298.1233. Only ¹H NMR data was reported in the literature.¹⁷

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; ν_{\max} /cm⁻¹ (ATR) 3017 (w, C-H), 1728 (m, C=O), 1670 (s, C=O), 1605 (w); δ_{H} (400 MHz, CDCl₃) 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_C (100 MHz, CDCl_3) 19.3 (CH_3), 30.7 (CH), 39.3 ($2 \times \text{CH}_2$), 43.0 (CH_2), 124.5 (CH), 126.8 (CH), 127.4 (CH), 127.6 (CH), 128.5 ($2 \times \text{CH}$), 129.1 ($2 \times \text{CH}$), 131.1 (CH), 135.6 (C), 137.1 (C), 138.7 (C), 171.9 ($2 \times \text{C}$); HRMS (ESI⁺TOF): calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ ($[\text{MH}]^+$), 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; ν_{max} / cm^{-1} (ATR) 2955 (w, C-H), 1727 (m, C=O), 1669 (s, C=O); δ_H (400 MHz, CDCl_3) 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_C (100 MHz, CDCl_3) 21.0 (CH_3), 34.2 (CH), 40.1 ($2 \times \text{CH}_2$), 42.9 (CH_2), 126.2 ($2 \times \text{CH}$), 127.5 (CH), 128.4 ($2 \times \text{CH}$), 128.9 ($2 \times \text{CH}$), 129.7 ($2 \times \text{CH}$), 137.1 (C), 137.3 (C), 138.6 (C), 171.7 ($2 \times \text{C}$); HRMS (ESI⁺TOF): calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ ($[\text{MH}]^+$), 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; ν_{max} / cm^{-1} (ATR) 3052 (w, C-H), 2964 (w, C-H), 1723 (m, C=O), 1672 (s, C=O), 1598 (m); δ_H (400 MHz, CDCl_3) 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, CDCl₃) 30.0 (CH), 39.5 (2 × CH₂), 43.1 (CH₂), 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 C₂₂H₂₀NO₂ ([MH]⁺), 330.1494; found, 330.1504.

1-(Phenylmethyl)-4-methylpiperidin-2,6-dione 4g¹⁷

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 C₁₃H₁₅NO₂: 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, CDCl₃) 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, CDCl₃) 20.3 (CH₃), 24.5 (CH), 40.7 (2 × CH₂), 42.7 (CH₂), 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.¹⁷

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

°C; Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.24; H, 7.75; N, 5.53; ν_{\max} /cm⁻¹ (ATR) 2960 (w), 2874 (w), 1724 (m, C=O), 1668 (s, C=O); δ_{H} (400 MHz, CDCl₃) 0.95 (d, J = 6.7 Hz, 6H), 1.57 (octet, J = 6.7 Hz, 1H), 1.81–1.91 (m, 1H), 2.35 (dd, J = 17.1, 12.3 Hz, 2H), 2.82 (dd, J = 17.1, 4.0 Hz, 2H), 4.96 (s, 2H), 7.23–7.32 (m, 3H), 7.39 [(AX)₂, 2H]; δ_{C} (100 MHz, CDCl₃) 19.2 (2 × CH₃), 31.4 (CH), 35.5 (CH), 36.9 (2 × CH₂), 42.8 (CH₂), 127.4 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 137.2 (C), 172.6 (2 × C); HRMS (ESI⁺TOF): calcd for C₁₅H₂₀NO₂ ([MH]⁺), 246.1494; found, 246.1504.

1-(Phenylmethyl)-4-tert-butylpiperidin-2,6-dione 4i

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; ν_{\max} /cm⁻¹ (ATR) 2951 (w, C-H), 2874 (w, C-H), 1719 (m, C=O), 1666 (s, C=O); δ_{H} (400 MHz, CDCl₃) 0.93 (s, 9H), 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); δ_{C} (100 MHz, CDCl₃) 26.5 (3 × CH₃), 31.8 (C), 35.0 (2 × CH₂), 39.2 (CH), 42.8 (CH₂), 127.5 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 137.2 (C), 172.9 (2 × C); HRMS (ESI⁺TOF): calcd for C₁₆H₂₂NO₂ ([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 C₁₉H₁₉NO₂: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.53; H, 6.51; N, 4.76; ν_{\max} /cm⁻¹ (ATR) 2973 (w, C-H), 1727 (m, C=O), 1667 (s, C=O); δ_{H} (250 MHz, CDCl₃) 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 = 11.5, 4.4 Hz, 1H), 5.01 (s, 2H), 6.96 [(AX)₂, 1H], 7.08–7.18 (m, 3H), 7.23–7.27 (m, 2H), 7.32–7.44 (m, 3H); δ_{C} (100 MHz, CDCl₃) 19.4 (CH₃), 34.6 (CH), 39.9 (2 × CH₂), 40.4 (CH₂), 126.0 (CH), 126.0 (CH), 126.4 (2 × CH), 127.1 (CH), 127.7 (CH), 129.1 (2 × CH), 130.3 (CH), 134.7 (C), 135.8 (C), 140.5 (C), 171.7 (2 × C); MS (TOF MS ES⁺) m/z: 294 ([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 C₁₉H₁₉NO₃: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.50; H, 6.06; N, 4.44; ν_{\max} /cm⁻¹ (ATR) 2960 (w, C-H), 1728 (m, C=O), 1671 (s, C=O), 1603 (m); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 34.6 (CH), 38.5 (2 × CH₂), 39.9 (CH₂), 55.4 (CH₃), 110.4 (CH), 120.3 (2 × CH), 124.8 (C), 126.5 (2 × CH), 127.0 (CH), 127.6 (CH), 128.2 (CH), 129.1 (CH), 140.7 (C), 157.1 (C), 171.5 (2 × C); HRMS (ESI⁺TOF): calcd for C₁₉H₂₀NO₃ ([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 BH₃.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 CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was removed in vacuo to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH₂Cl₂ (25 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 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 $\text{BH}_3\cdot\text{THF}$ (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_2Cl_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_2Cl_2 (30 mL) and treated with TFA (1 mL) and triethylsilane (1 mL) in CH_2Cl_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_2Cl_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 $\text{BH}_3\cdot\text{THF}$ (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; $[\alpha]_{\text{D}}^{20}$ + 6.0 (c 1.3, CHCl₃; 95% ee); ν_{max} / cm⁻¹ (ATR) 2940 (w, C-H), 1640 (s, C=O), 1620 (m, C=O), 1605 (m, C=O), 1506 (s, C=C); δ_{H} (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 (ddd, J = 17.5, 5.3 Hz, 1.9 Hz, 1H), 3.29 (tdd, J = 10.8, 5.3 Hz, 3.4 Hz, 1H), 3.65 (ddd, 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); δ_{C} (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

(C), 158.3 (C), 169.6 (C); HRMS (ESI⁺TOF): calcd for C₁₈H₂₀NO₂ ([MH]⁺), 282.1494; found, 282.1493.

(4R)-1-(Phenylmethyl)-4-phenylpiperidin-2-one 10b²⁰

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 3 μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{major} = 23.5 min, t_{minor} = 26.1 min); mp = 80–82 °C (lit.³² 88–90 °C); $[\alpha]_{\text{D}}^{20}$ + 33.0 (c 1.1, CHCl₃; 90% ee), lit.²⁰ $[\alpha]_{\text{D}}^{20}$ + 35.0 (c 1.1, CHCl₃, 92.5% ee); ν_{max} /cm⁻¹ (ATR) 1619 (s, C=O), 1494 (m, C=C); δ_{H} (400 MHz, CDCl₃) 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_{C} (100 MHz, CDCl₃) 30.3 (CH₂), 38.7 (CH), 39.5 (CH₂), 46.4 (CH₂), 50.0 (CH₂), 126.5 (2 \times CH), 126.8 (CH), 127.5 (CH), 128.2 (2 \times CH), 128.6 (2 \times CH), 128.8 (2 \times CH), 137.1 (C), 143.4 (C), 169.3 (C); MS (EI⁺) m/z: 265 ([M]⁺, 100%), 174 (12), 131 (32), 104 (230), 131 (32), 91 (70). All data are in accordance with literature.^{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 3 μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{major} = 20.6 min, t_{minor} = 22.3 min); mp = 72–74 °C; $[\alpha]_{\text{D}}^{20}$ + 26.6 (c 0.8, CHCl₃; 88% ee); Anal. Calcd for C₁₉H₂₁NO: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.81; H, 7.82; N, 4.85; ν_{max} /cm⁻¹ (ATR) 3024 (w, C-H), 2915 (w, C-H), 1627 (s, C=O), 1605 (m, C=C); δ_{H} (400 MHz, CDCl₃) 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); δ_C (100 MHz, $CDCl_3$) 19.25 (CH_3), 30.3 (CH_2), 38.7 (CH), 39.5 (CH_2), 46.3 (CH_2), 47.7 (CH_2), 126.1 (CH), 126.5 ($2 \times$ CH), 126.8 (CH), 127.5 (CH), 128.1 (CH), 128.8 ($2 \times$ CH), 130.5 (CH), 134.5 (C), 136.6 (C), 143.4 (C), 169.2 (C); HRMS (ESI⁺TOF): calcd for $C_{19}H_{22}NO$ ($[MH]^+$), 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 3 μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, $t_{major} = 21.3$ min, $t_{minor} = 23.6$ min); mp = 80–82 °C; $[\alpha]_D^{20} + 21.7$ (c 1.0, $CHCl_3$; 90% ee); ν_{max} / cm^{-1} (ATR) 2940 (w, C-H), 1636 (s, C=O); δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 30.4 (CH_2), 38.7 (CH), 39.5 (CH_2), 44.5 (CH_2), 46.8 (CH_2), 55.4 (CH_3), 110.3 (CH), 120.7 (CH), 125.1 (C), 126.6 ($2 \times$ CH), 126.8 (CH), 128.5 (CH), 128.7 ($2 \times$ CH), 129.1 (CH), 143.6 (C), 157.6 (C), 169.4 (C); HRMS (EI⁺): calcd for $C_{19}H_{21}NO_2$ (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

C₁₈H₂₁NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.74; H, 7.91; N, 5.12; ν_{\max} / cm⁻¹ (ATR) 2953 (w, C-H), 2938 (m, C-H), 2917 (m, C-H), 2810 (m, C-H), 1508 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 33.6 (2 × CH₂), 42.4 (CH), 52.2 (2 × CH₂), 55.6 (CH₃), 114.4 (2 × CH), 118.9 (2 × CH), 126.3 (CH), 126.9 (2 × CH), 128.5 (2 × CH), 146.2 (C), 146.4 (C), 153.8 (C); HRMS (ESI⁺TOF): calcd for C₁₈H₂₂NO ([MH⁺]), 268.1701; found, 268.1693. Only ¹H NMR and low resolution mass spectrometry data were provided in the literature. The literature ¹H NMR data is mis-assigned.³⁴

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); ν_{\max} / cm⁻¹ (ATR) 3026 (w, C-H), 2933 (m, C-H), 2798 (m, C-H), 2754 (m, C-H), 1493 (m, C=O); δ_{H} (250 MHz, CDCl₃) 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); δ_{C} (75 MHz, CDCl₃) 33.6 (2 × CH₂), 42.8 (CH), 54.3 (2 × CH₂), 63.5 (CH₂), 126.1 (CH), 126.9 (2 × CH), 127.0 (CH), 128.2 (2 × CH), 128.4 (2 × CH), 129.2 (2 × CH), 138.6 (C), 146.6 (C); HRMS (ESI⁺TOF): calcd for C₁₈H₂₂N ([MH⁺]), 252.1752; found, 252.1764. All data are in accordance with literature.³⁵

(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; $[\alpha]_{\text{D}}^{20}$ + 18.2 (c 1.7, CHCl₃); ν_{\max} /cm⁻¹ (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); δ_{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); δ_{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 ($2 \times \text{CH}$), 126.7 ($2 \times \text{CH}$), 127.4 (CH), 128.8 ($2 \times \text{CH}$), 129.2 ($2 \times \text{CH}$), 133.4 (C), 143.1 (C), 158.9 (C), 170.0 (C); HRMS (ESI⁺TOF): calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3$ ($[\text{MH}]^+$), 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 μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{major} = 16.4 min, t_{minor} = 18.2 min); mp = 60–62 °C; $[\alpha]_{\text{D}}^{20}$ +20.1 (c 2.1, CHCl_3 ; 86% ee); ν_{max} / cm^{-1} (ATR) 2925 (w, C-H), 1616 (s, C=O), 1580 (m, C=C); δ_{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); δ_{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 ($2 \times \text{CH}$), 128.3 (d, $J_{\text{C-F}}$ = 8.4 Hz, CH), 128.7 ($2 \times \text{CH}$), 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); δ_{F} (235 MHz, CDCl_3) -118.6; HRMS (EI⁺): calcd for $\text{C}_{18}\text{H}_{18}\text{FNO}$ (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, $t_{\text{minor}} = 38.2$ min, $t_{\text{major}} = 40.0$ min); mp = 114–116 °C; $[\alpha]_{\text{D}}^{20} +30.0$ (c 1.1, CHCl₃; 88% ee, lit.²⁰ $[\alpha]_{\text{D}}^{20} + 33.0$ (c 1.07, CHCl₃); $\nu_{\text{max}} / \text{cm}^{-1}$ (ATR) 3071 (w, C-H), 1625 (s, C=O), 1601 (m, C=C); δ_{H} (400 MHz, CDCl₃) 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, CDCl₃) 30.3 (CH₂), 38.0 (CH), 39.6 (CH₂), 46.2 (CH₂), 50.0 (CH₂), 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, CDCl₃) -116.0; HRMS (ESI⁺TOF): calcd for C₁₈H₁₉FNO ([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 3 μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, $t_{\text{minor}} = 15.3$ min, $t_{\text{major}} = 18.3$ min); mp = 68–70 °C; $[\alpha]_{\text{D}}^{20} +39.4$ (c 0.3, CHCl₃; 82% ee); $\nu_{\text{max}} / \text{cm}^{-1}$ (ATR) 2925 (w, C-H), 1626 (s, C=O), 1587 (m, C=C); δ_{H} (400 MHz, CDCl₃) 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, CDCl₃) 19.3 (CH₃), 29.3 (CH₂), 34.6 (CH), 39.0 (CH₂), 46.5 (CH₂), 50.1 (CH₂), 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 C₁₉H₂₂NO ([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; [α]_D²⁰ +33.6 (c 1.1, CHCl₃; 92% ee); Anal. Calcd for C₁₉H₂₁NO: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.58; H, 7.54; N, 4.90; ν_{max} / cm⁻¹ (ATR) 2924 (w, C-H), 1625 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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); δ_{C} (100 MHz, CDCl₃) 21.0 (CH₃), 30.4 (CH₂), 38.3 (CH), 39.6 (CH₂), 46.4 (CH₂), 50.0 (CH₂), 126.4 (2 × CH), 127.4 (CH), 128.2 (2 × CH), 128.6 (2 × CH), 129.4 (2 × CH), 136.4 (C), 137.2 (C), 140.5 (C) 169.4 (C); HRMS (ESI⁺TOF): calcd for C₁₉H₂₂NO ([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; [α]_D²⁰ -13.3 (c 0.5, CHCl₃; 54% ee); ν_{max} / cm⁻¹ (ATR) 2950 (w, C-H), 1636 (s, C=O), 1624 (s, C=O); δ_{H} (400 MHz, CDCl₃) 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, CDCl₃) 29.6 (CH₂), 33.8 (CH), 39.3 (CH₂), 46.2 (CH₂), 50.2 (CH₂), 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 C₂₂H₂₂NO ([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) : Et₃N (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 3 μ CELLULOSE-2 column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 13.2 min, t_{major} = 14.1 min); $[\alpha]_D^{20}$ + 46.6 (c 3.3, CHCl₃; 90% ee); ν_{max} / cm⁻¹ (ATR) 2953 (w, C-H), 1634 (s, C=O); δ_H (400 MHz, CDCl₃) 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, CDCl₃) 21.0 (CH₃), 28.0 (CH), 30.9 (CH₂), 40.5 (CH₂), 46.3 (CH₂), 50.0 (CH₂), 127.3 (CH), 128.0 (2 × CH), 128.6 (2 × CH), 137.3 (C), 169.7 (C); HRMS (ESI⁺TOF): calcd for C₁₃H₁₈NO ([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 : CH₂Cl₂ :

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 3 μ CELLULOSE-2 column (hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, t_{minor} = 47.1 min, t_{major} = 49.0 min); $[\alpha]_{\text{D}}^{20}$ + 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); δ_{C} (100 MHz, CDCl₃) 19.3 (CH₃), 19.6 (CH₃), 26.6 (CH₂), 31.9 (CH), 36.3 (CH₂), 39.4 (CH), 46.8 (CH₂), 49.9 (CH₂), 127.3 (CH), 128.0 (2 \times CH), 128.6 (2 \times 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 3 μ CELLULOSE-2 column (hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, t_{minor} = 11.3 min, t_{major} = 12.4 min); $[\alpha]_{\text{D}}^{20}$ + 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 \times CH₃), 32.0 (C), 34.3 (CH₂), 43.2 (CH), 47.1 (CH₂), 49.9 (CH₂), 127.3 (CH), 128.1 (2 \times CH), 128.6 (2 \times CH), 137.2 (C), 170.5 (C); HRMS (ESI⁺TOF): calcd for C₁₆H₂₄NO ([MH⁺]), 246.1858; found, 246.1861.

Associated content

Supporting Information

^1H 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>.

Author Information

Corresponding Author

*E-mail: simon.jones@sheffield.ac.uk

Notes

The authors declare no competing financial interest.

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