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Enantioselective Desymmetrization of Glutarimides Catalyzed by Oxazaborolidines Derived from *cis*-1-Amino-indan-2-ol

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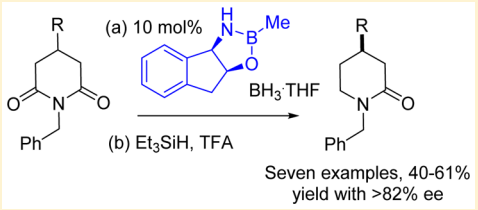
Supporting Information

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 C_3-symmetric zirconium(IV) and C_2-symmetric chromium(III) complexes to catalyze 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 complexes[8] for enantioselective reduction to affect such transformations. Oxazaborolidine mediated borane reduction, using catalysts derived from α,α-diphenylprolinol, has also been reported, but requires 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 desymmetrization 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 desymmetrization to give the corresponding hydroxyamides in excellent ee's (88−98%).[16,17] Here, we present the enantioselective desymmetrization of 3-substituted glutarimides using oxazaborolidine catalysts derived from *cis*-1-amino-indan-2-ol.

RESULTS AND DISCUSSION

The 3-aryl-substituted glutaric acids **1b−1f** required for preparing the glutarimides were synthesized from the corresponding aldehydes by adapting literature procedures. The aldehydes were first converted to the 2-substituted tetraethylpropane tetracarboxylates through Knoevenagel 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, dropwise addition of a solution of the aldehyde in toluene to a mixture of diethylmalonate and $AlCl_3$ in toluene in the Knoevenagel condensation step led to the required product. For the 3-alkyl glutaric acids **1h** and **1i**, the method of Theisen et al. gave better yields, which uses ethyl cyanoacetate in the Knoevenagel 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**, and **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]

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Scheme 1. Route to Glutarimide Substrates

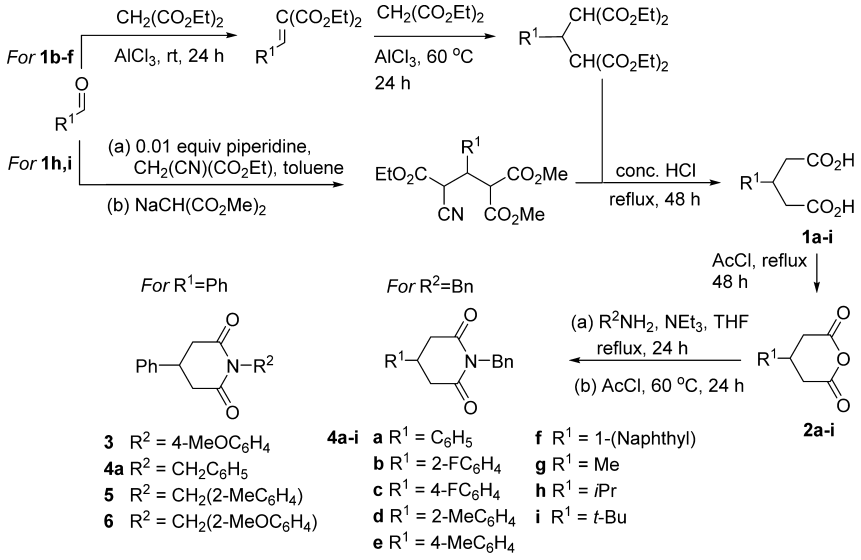


Table 1. Synthesis of 3-Substituted Glutaric Acids, Anhydrides, and Glutarimides

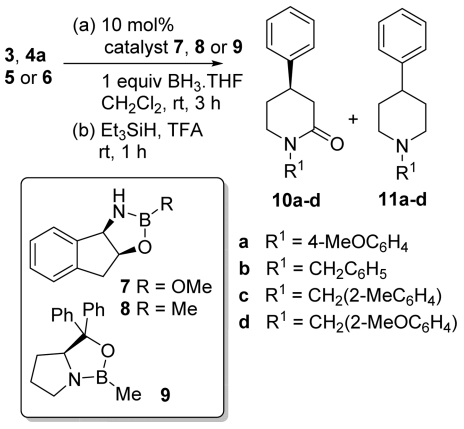
			yield		
entry	R^1	R^2	glutaric acid[a]	anhydride	imide
1	Ph	4-$MeOC_6H_4$	**1a**[b]	**2a** 82%	**3** 80%
2	Ph	$CH_2C_6H_5$	**1a**[b]	**2a** 82%	**4a** 85%
3	Ph	CH_2(2-MeC_6H_4)	**1a**[b]	**2a** 82%	**5** 71%
4	Ph	CH_2(2-$MeOC_6H_4$)	**1a**[b]	**2a** 82%	**6** 60%
5	2-FC_6H_4	$CH_2C_6H_5$	**1b** 52%	**2b** 75%	**4b** 87%
6	4-FC_6H_4	$CH_2C_6H_5$	**1c** 57%	**2c** 93%	**4c** 71%
7	2-MeC_6H_4	$CH_2C_6H_5$	**1d** 51%	**2d** 73%	**4d** 60%
8	4-MeC_6H_4	$CH_2C_6H_5$	**1e** 50%	**3e** 85%	**4e** 67%
9	1-naphthyl	$CH_2C_6H_5$	**1f** 60%	**3f** 80%	**4f** 52%
10	Me	$CH_2C_6H_5$	**1g**[b]	**3g** 79%	**4g** 68%
11	*i*Pr	$CH_2C_6H_5$	**1h** 35%	**3h** 79%	**4h** 70%
12	*t*-Bu	$CH_2C_6H_5$	**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 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 hydroxy-lactam. This relatively rapid formation of the doubly reduced product was observed in earlier work on related *N*-PMP five-membered imides.[14]

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

Scheme 2. Reduction of *meso*-Glutarimides 3, 4a, 5, and 6



(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 were

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Table 2. Screening Catalysts for Desymmetrization 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 CH_2Cl_2 with 10 mol % of the catalyst solution and 1 equiv of BH_3·THF at rt for 3 h, followed workup, dissolution into CH_2Cl_2 and treatment with Et_3SiH/TFA for 1 h. [b]Refers to isolated components after column chromatography. [c]Determined by chiral phase HPLC. [d]Catalyst prepared by mixing (1*R*,2*S*)-*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 (1*R*,2*S*)-*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.

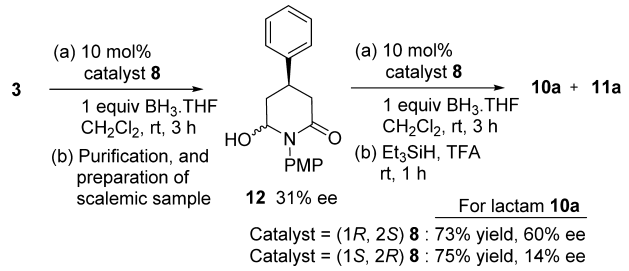
obtained when the catalyst was prepared *in situ* at room temperature, while the method involving azeotropic distillation gave 33% yield of the desired product in 95% ee. The undesired over-reduced product was also increased from 10% to 30%.

The desymmetrization 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 h. 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, desymmetrization of *N*-benzyl-4-phenylpiperidin-2,5-dione **4a** using these optimized 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 and 12). This further reinforces the delicate nature of the *N*-protecting groups in influencing the yield and/or selectivity of the oxazaborolidine mediated desymmetrization. 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 cyloadduct desymmetrization.[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

Scheme 3. Stereoablation Experiment with *N*-PMP Glutarimide 3



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 (1*R*,2*S*) catalyst and 27% yield for (1*S*,2*R*) 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 (1*R*,2*S*:1*S*,2*R*), 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 the (1*R*,2*S*) version of the *B*-Me catalyst, followed by further reduction to the corresponding lactam. The same procedure was repeated with the (1*S*,2*R*) version of the catalyst for comparison.

When a representative sample from the scalemic hydroxy-lactam **12** (31% ee) was subjected to reduction with the (1*R*,2*S*) enantiomer of the *B*-Me catalyst **8**, followed by subsequent reduction with Et_3SiH, 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 (1*R*,2*S*) catalyst (presumably the minor enantiomer) to the piperidine **11**. On the other hand, when

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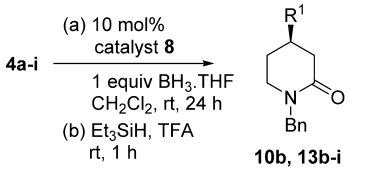
the reaction was repeated with the (1*S*,2*R*) version of the catalyst, a near identical yield of 75% of the lactam was obtained. However, unlike in the anthracene-maleimide case where the ee of the scalemic hydroxy-lactam remained the same with this version of the catalyst, the ee of the scalemic hydroxy-lactam in this case eroded to 14%. This shows that the (1*S*,2*R*) 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% and 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 h period in an attempt to maximize 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 ^{1}H NMR spectrum of all unpurified reaction mixtures, but in these examples, only the 2-piperidinone was isolated and characterized.

Scheme 4. Desymmetrization of *N*-Bn Glutarimides Using *B*-Me Catalyst



10b $R^1 = C_6H_5$ **13f** R^1 = 1-(Naphthyl)
13b R^1 = 2-FC_6H_4 **13g** R^1 = Me
13c R^1 = 4-FC_6H_4 **13h** R^1 = *i*Pr
13d R^1 = 2-MeC_6H_4 **13i** R^1 = *t*-Bu
13e R^1 = 4-MeC_6H_4

The absolute configuration was assigned as (4*R*) 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. 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 coordinated 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.

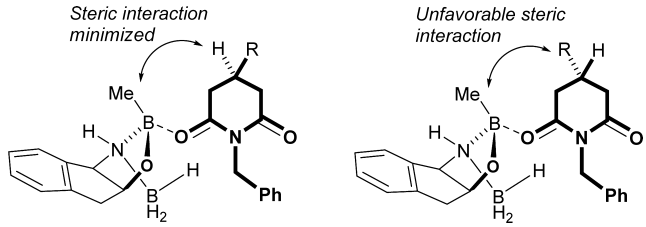


Figure 1. Pre-transition state models for imide reduction.

In conclusion, an efficient strategy for the highly enantioselective desymmetrization 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 the *N*-PMP-3-phenyl

Table 3. Desymmetrization of *N*-Benzyl-3-Substituted Glutarimides 4a–i Using *B*-Me Catalyst 8[a]

entry	imide	product/yield (%)[b]	ee (%)[c]	measured $[\alpha]_D^{20}$	literature $[\alpha]_D^{20}$
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 (1*R*,2*S*)-*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 of BH_3·THF at rt for 24 h, followed workup, 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.

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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 aluminum TLC sheets (silica gel 60 F_{254}) and was performed using a UV lamp or by dipping in $KMnO_4$ solution, then exposure to heat. Flash column chromatography was carried out with silica gel 40−63 μ, 60 Å. ^1H and ^{13}C NMR spectra were measured using $CDCl_3$ as solvent unless otherwise stated. ^{13}C 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 4.6 mm × 250 mm chiral column with conditions as described in individual experiments. The flow rate was 1.00 mL/min, and the detector was set at 220 or 254 nm. All chemicals were used as received without further purification except (1*R*,2*S*)-*cis*-1-amino-2-indanol and (1*S*,2*R*)-*cis*-1-amino-2-indanol, which were recrystallized from hot toluene prior to use. Borane−THF was used as a 1 M solution in THF.

General Procedure A for the Synthesis of 3-(*o*-Substituted Phenyl) Glutaric Acids.[18] $AlCl_3$ (0.1 equiv) was slowly added to a mixture of 2-substituted benzaldehyde (1 equiv) and diethylmalonate (2 equiv), and the mixture was 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 × 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 °C, 9.5 × 10^{-1} mbar) to give the crude diethyl *o*-substituted benzylidenemalonate, which was taken to the 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 the mixture was stirred at 60 °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 °C, and the mixture was further stirred for an 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 °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) and 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, and 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 dropwise to a mixture of $AlCl_3$ (0.1 equiv) and diethylmalonate (2 equiv) in toluene (10 mL), and the mixture was 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 °C, 9.5 × 10^{-1} mbar) to give the crude diethyl *p*-substituted benzylidene malonate as an oily residue, which was taken to the 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 the mixture was stirred at 60 °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 °C, and the mixture was further stirred for an 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 °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) and 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, and the solid was filtered and recrystallized from EtOAc/petroleum ether (40−60).

General Procedure C for the Synthesis of 3-Isopropyl and 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 h 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 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 1 M 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 an 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 an additional 24 h. The mixture was allowed to cool to room temperature, poured into an ice/water mixture (50 mL), and extracted with ether (5 × 30 mL). The combined ethereal portions were washed with water (20 mL), dried over $MgSO_4$, and filtered, and solvent was evaporated *in vacuo* to obtain a dark brown liquid, which, upon standing in a fridge, turned to a brown solid, which was purified by recrystallization 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, $CDCl_3$) 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: δ_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); δ_C (100 MHz, $CDCl_3$) 13.7 (2 × CH_3), 13.9 (2 × CH_3), 38.3 (*C*H), 54.4 (2 × *C*H), 61.4 (2 × CH_2), 61.7 (2 × CH_2), 115.4 (d, $J_{C\text{-}F}$ = 22.9 Hz, *C*H), 123.8 (d, $J_{C\text{-}F}$ = 3.3 Hz, *C*H), 124.8 (d, $J_{C\text{-}F}$ = 14.6 Hz, *C*), 129.5 (d, $J_{C\text{-}F}$ = 8.6 Hz, *C*H), 131.6 (*C*H), 161.2 (d, $J_{C\text{-}F}$ = 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 (*C*H), 39.4 (2 × CH_2), 115.8 (d, $J_{C\text{-}F}$ = 22.5 Hz, *C*H), 124.7 (d, $J_{C\text{-}F}$ = 2.9 Hz, *C*H), 128.7 (d, $J_{C\text{-}F}$ = 8.4 Hz, *C*H), 129.5 (d, $J_{C\text{-}F}$ = 4.5 Hz, *C*H), 130.4 (d, $J_{C\text{-}F}$ = 14.2 Hz, *C*), 160.7 (d, $J_{C\text{-}F}$ = 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 ***1c***.[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

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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.[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; υ_{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 (*C*H), 40.6 (2 × CH_2), 115.3 (d, $J_{C\text{-}F}$ = 21.0 Hz, 2 × *C*H), 129.8 (d, $J_{C\text{-}F}$ = 7.8 Hz, 2 × *C*H), 140.0 (d, $J_{C\text{-}F}$ = 2.6 Hz, *C*), 161.3 (d, $J_{C\text{-}F}$ = 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 the 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, $CDCl_3$) 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, $CDCl_3$) 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 $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.46; υ_{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 (CH_3), 33.2 (*C*H), 40.5 (2 × CH_2), 126.2 (*C*H), 126.4 (*C*H), 126.5 (*C*H), 130.5 (*C*H), 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.***[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; 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 $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.85; H, 6.13; υ_{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 (*C*H), 40.7 (2 × CH_2), 127.8 (2 × *C*H), 129.2 (2 × *C*H), 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 are missing a signal at 40.7; otherwise, all data are in accordance with the literature.

3-(1-Naphthyl)pentan-1,5-dioic Acid ***1f.***[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; 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 a 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 $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.64; H, 5.39; υ_{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 (*C*H), 40.3 (2 × CH_2), 123.5 (*C*H), 123.7 (*C*H), 125.9 (*C*H), 126.0 (*C*H), 126.6 (*C*H), 127.3 (*C*H), 129.2 (*C*H), 131.5 (*C*), 134.0 (*C*), 140.0 (*C*), 173.4 (2 × *C*); MS (ESI$^-$ TOF) m/z: 257 ([M − H]$^-$, 100%). Only a 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 $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.14; H, 8.16; υ_{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 × CH_3), 29.9 (*C*H), 35.9 (2 × CH_2), 37.5 (*C*H), 174.5 (2 × *C*); MS (ESI$^+$ TOF) m/z: 198 ([M + Na]$^+$, 40%), 175 ([MH]$^+$, 30%), 157 ([M − OH]$^+$, 100%). Only a melting point is given in the 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); υ_{max} (ATR)/cm^{-1} 2966 (brd, O-H), 1704 (s, C=O); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 27.3 (3 × CH_3), 33.1 (*C*), 36.1 (2 × CH_2), 42.4 (*C*H), 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 $C_9H_{17}O_4$ ([MH]$^+$), 1891127; found, 189.1130. Only a 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 a brown liquid, which was purified by recrystallization.

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); υ_{max}/cm^{-1} (ATR) 1812 (s, C=O), 1752 (s, C=O); δ_H (400 MHz, $CDCl_3$) 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_C (100 MHz, $CDCl_3$) 34.1 (*C*H), 37.2 (2 × CH_2), 126.2 (2 × *C*H), 128.2 (*C*H), 129.4 (2 × *C*H), 139.1 (*C*),

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165.8 (C); MS (ESI+ TOF) *m/z*: 191 ([MH]+, 100%). All data are 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; υ_{max}/cm^{-1} (ATR) 1812 (w), 1754 (s, C=O), 1710 (s, C=O), 1586 (w, C=C); δ_H (400 MHz, $CDCl_3$) 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), 7.11−7.21 (m, 3H), 7.33−7.38 (m, 1H); δ_C (100 MHz, $CDCl_3$) 28.9 (CH), 35.5 (2 × CH_2), 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, $CDCl_3$) −117.0; MS (EI+) *m/z*: 208 ([M]+, 30%), 122 (100%), 96 (20%); HRMS (EI+): calcd for $C_{11}H_9FO_3$ ([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 $C_{11}H_9FO_3$: C, 63.46; H, 4.36. Found: C, 63.22; H, 4.08; υ_{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 × 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 the 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); υ_{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 × 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 the 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; υ_{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 × CH_2), 126.1 (2 × CH), 130.0 (2 × 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 $C_{12}H_{12}O_3$ ([M]+), 204.0786; found, 204.0796. No analytical data were 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 $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.64; H, 4.68; υ_{max}/cm^{-1} (ATR) 1808 (s, C=O), 1753 (s, C=O), 1599 (w, C=C); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 29.5 (CH), 36.8 (2 × CH_2), 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**.[30] 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 $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.27; H, 6.31; υ_{max}/cm^{-1} (ATR) 2977 (w, C-H), 1806 (s, C=O), 1757 (s, C=O), 1744 (s, C=O); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 20.0 (CH_3), 24.0 (CH), 37.7 (2 × CH_2), 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 colorless 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); υ_{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, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 18.9 (2 × CH_3), 31.3 (CH), 34.0 (2 × CH_2), 35.0 (CH), 166.9 (2 × C); HRMS (ESI+ TOF): calcd for $C_8H_{13}O_3$ ([MH]+), 157.0865; found, 157.0870. All data are in accordance with the 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 colorless 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); υ_{max}/cm^{-1} (ATR) 2967 (m, C-H), 1808 (s, C=O), 1748 (s, C=O); δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 26.4 (3 × CH_3), 32.0 (C), 32.3 (2 × CH_2), 38.7 (CH), 167.2 (C); HRMS (ESI+ TOF): calcd for $C_9H_{15}O_3$ ([MH]+), 171.1021; found, 171.1024. All data are in accordance with the 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 1 M 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; υ_{max}/cm^{-1} (ATR) 1731 (m, C=O), 1672 (s, C=O), 1610 (s), 1511 (s); δ_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); δ_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); υ_{max}/cm^{-1} (ATR) 3031 (w, C-H), 1726 (m, C=O), 1668 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.85

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(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, $CDCl_3$) 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 a 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 a 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; υ_{max}/cm^{-1} (ATR) 3068 (w, C-H), 1728 (m, C═O), 1672 (s, C═O); δ_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); δ_C (100 MHz, $CDCl_3$) 29.1 (CH), 38.3 (2 × CH_2), 43.0 (CH_2), 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, $CDCl_3$) −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 a 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; υ_{max}/cm^{-1} (ATR) 2955 (w, C-H), 1718 (m, C═O), 1672 (s, C═O), 1604 (m), 1512 (s); δ_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); δ_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); δ_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 were 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 a white powder by recrystallization from EtOAc/petroleum ether (40−60) (1.88 g, 87%); mp = 138−140 °C; υ_{max}/cm^{-1} (ATR) 3017 (w, C-H), 1728 (m, C═O), 1670 (s, C═O), 1605 (w); δ_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_C (100 MHz, $CDCl_3$) 19.3 (CH_3), 30.7 (CH), 39.3 (2 × CH_2), 43.0 (CH_2), 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 $C_{19}H_{20}NO_2$ ([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 a white powder by recrystallization from EtOAc/petroleum ether (40−60) (5.10 g, 71%); mp = 106−108 °C; υ_{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 × CH_2), 42.9 (CH_2), 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 $C_{19}H_{20}NO_2$ ([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 a white powder by recrystallization from EtOAc/petroluem ether (40−60) (1.42 g, 52%); mp = 116−118 °C; υ_{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, $CDCl_3$) 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**.[17] 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 a white powder by recrystallization from 50% EtOAc/hexane (4.13 g, 70%); mp = 68−70 °C; Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.74; H, 6.87; N, 6.46; υ_{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 ^{1}H NMR was cited in the 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 a colorless liquid, which turned to a white solid upon standing (2.10 g, 67%); mp = 45−46 °C; Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.24; H, 7.75; N, 5.53; υ_{max}/cm^{-1} (ATR) 2960 (w), 2874 (w), 1724 (m, C═O), 1668 (s, C═O); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 19.2 (2 × CH_3), 31.4 (CH), 35.5 (CH), 36.9 (2 × CH_2), 42.8 (CH_2), 127.4 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 137.2 (C), 172.6 (2 × C); HRMS (ESI$^+$ TOF): calcd for $C_{15}H_{20}NO_2$ ([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 a colorless liquid, which turned to a white solid upon standing (1.12 g, 57%); mp = 44−46 °C; υ_{max}/cm^{-1} (ATR) 2951 (w, C-H), 2874 (w, C-H), 1719 (m, C═O), 1666 (s, C═O); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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

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J. Org. Chem. 2015, 80, 11468−11479

$C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.53; H, 6.51; N, 4.76; υ_{max}/cm^{-1} (ATR) 2973 (w, C-H), 1727 (m, C═O), 1667 (s, C═O); δ_H (250 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 = 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, $CDCl_3$) 19.4 (CH_3), 34.6 (CH), 39.9 (2 × CH_2), 40.4 (CH_2), 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 $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.50; H, 6.06; N, 4.44; υ_{max}/cm^{-1} (ATR) 2960 (w, C-H), 1728 (m, C═O), 1671 (s, C═O), 1603 (m); δ_H (400 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); δ_C (100 MHz, $CDCl_3$) 34.6 (CH), 38.5 (2 × CH_2), 39.9 (CH_2), 55.4 (CH_3), 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 $C_{19}H_{20}NO_3$ ([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 (1*R*,2*S*)-*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 dropwise 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 1 M HCl (5 mL), and extracted with CH_2Cl_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 redissolved in CH_2Cl_2 (25 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 $NaHCO_3$ (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 (1*R*,2*S*)-*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 dropwise 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 1 M 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 redissolved 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 dropwise 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 1 M 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 redissolved 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 $NaHCO_3$ (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) to afford the corresponding lactam as a white solid (0.03 g, 13% over 2 steps, 14% 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} = 21.1 min, t_{major} = 23.1 min). All analytical data correspond 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; $[\alpha]_D^{20}$ + 6.0 (*c* 1.3, $CHCl_3$; 95% ee); υ_{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, $CDCl_3$) 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, $CDCl_3$) 30.7 (CH_2), 38.8 (CH), 39.8 (CH_2), 51.0 (CH_2), 55.5 (CH_3), 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 $C_{18}H_{20}NO_2$ ([MH]$^+$), 282.1494; found, 282.1493.

(4R)-1-(Phenylmethyl)-4-phenylpiperidin-2-one ***10b***.[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 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); $[\alpha]_D^{20}$ + 33.0 (*c* 1.1, $CHCl_3$; 90% ee), lit.[20] $[\alpha]_D^{20}$ + 35.0 (*c* 1.1, $CHCl_3$, 92.5% ee); υ_{max}/cm^{-1} (ATR) 1619 (s, C═O), 1494 (m, C═C); δ_H (400 MHz, $CDCl_3$) 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_C (100 MHz, $CDCl_3$) 30.3 (CH_2), 38.7 (CH), 39.5 (CH_2), 46.4 (CH_2),

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50.0 (CH_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$^+$) m/z: 265 ([M]$^+$, 100%), 174 (12), 131 (32), 104 (230), 131 (32), 91 (70). All data are in accordance with the 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; $[\alpha]_D^{20}$ + 26.6 (c 0.8, $CHCl_3$; 88% ee); Anal. Calcd for $C_{19}H_{21}NO$: 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, $CDCl_3$) 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); 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 × 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 $C_{19}H_{22}NO$ ([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 × 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 $C_{19}H_{21}NO_2$ (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 $C_{18}H_{21}NO$: 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, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 33.6 (2 × CH_2), 42.4 (CH), 52.2 (2 × CH_2), 55.6 (CH_3), 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 $C_{18}H_{22}NO$ ([MH$^+$]), 268.1701; found, 268.1693. Only ^{1}H NMR and low resolution mass spectrometry data were provided in the literature. The literature ^{1}H NMR data are 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 a 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, $CDCl_3$) 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); δ_C (75 MHz, $CDCl_3$) 33.6 (2 × CH_2), 42.8 (CH), 54.3 (2 × CH_2), 63.5 (CH_2), 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 $C_{18}H_{22}N$ ([MH$^+$]), 252.1752; found, 252.1764. All data are in accordance with the 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; $[\alpha]_D^{20}$ + 18.2 (c 1.7, $CHCl_3$); 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 × CH), 126.7 (2 × CH), 127.4 (CH), 128.8 (2 × CH), 129.2 (2 × 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 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; $[\alpha]_D^{20}$ + 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, $J_{C\text{-}F}$ = 1.5 Hz, CH), 38.0 (CH_2), 46.3 (CH_2), 50.1 (CH_2), 115.6 (d, $J_{C\text{-}F}$ = 22.4 Hz, CH), 124.4 (d, $J_{C\text{-}F}$ = 3.5 Hz, CH), 127.3 (d, $J_{C\text{-}F}$ = 4.6 Hz, CH), 127.5 (CH), 128.2 (2 × CH), 128.3 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH), 128.7 (2 × CH), 130.1 (d, $J_{C\text{-}F}$ = 14.2 Hz, C), 137.0 (C), 160.6 (d, $J_{C\text{-}F}$ = 245.8 Hz, C), 169.1 (C); δ_F (235 MHz, $CDCl_3$) −118.6; HRMS (EI$^+$): calcd for $C_{18}H_{18}FNO$ (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; $[\alpha]_D^{20}$ + 30.0 (c 1.1, $CHCl_3$; 88% ee, lit.[20] $[\alpha]_D^{20}$ + 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, $J_{C\text{-}F}$ = 21.2 Hz, 2 × CH), 127.5 (CH), 128.0 (d, $J_{C\text{-}F}$ = 7.8 Hz, 2 × CH), 128.2 (2 × CH), 128.7 (2× CH), 137.1 (C), 139.1 (d, $J_{C\text{-}F}$ = 3.0 Hz, C), 161.7 (d, $J_{C\text{-}F}$ = 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 the 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_{minor} = 15.3 min, t_{major} = 18.3 min); mp = 68−70 °C; $[\alpha]_D^{20}$ + 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%

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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; $[\alpha]_D^{20}$ + 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; ν_{max}/cm^{-1} (ATR) 2924 (w, C-H), 1625 (s, C═O); δ_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); δ_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 × 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 $C_{19}H_{22}NO$ ([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; $[\alpha]_D^{20}$ −13.3 (*c* 0.5, $CHCl_3$; 54% ee); ν_{max}/cm^{-1} (ATR) 2950 (w, C-H), 1636 (s, C═O), 1624 (s, C═O); δ_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 a 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, $CHCl_3$; 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 a 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); $[\alpha]_D^{20}$ + 44.3 (*c* 1.9, $CHCl_3$; 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, $CDCl_3$) 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, $CDCl_3$) 19.3 (CH_3), 19.6 (CH_3), 26.6 (CH_2), 31.9 (CH), 36.3 (CH_2), 39.4 (CH), 46.8 (CH_2), 49.9 (CH_2), 127.3 (CH), 128.0 (2 × CH), 128.6 (2 × CH), 137.2 (*C*), 170.3 (*C*); HRMS (ESI$^+$ TOF): calcd for $C_{15}H_{22}NO$ ([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:CH_2Cl_2:petroleum ether (40−60) (3:1:6) to afford the title compound **12i** as a 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); $[\alpha]_D^{20}$ + 36.8 (*c* 1.4, $CHCl_3$; 87% ee); ν_{max}/cm^{-1} (ATR) 2957 (s, C-H), 2867 (s, C-H), 1636 (s, C═O); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 24.6 (CH_2), 26.8 (3 × CH_3), 32.0 (*C*), 34.3 (CH_2), 43.2 (CH), 47.1 (CH_2), 49.9 (CH_2), 127.3 (CH), 128.1 (2 × CH), 128.6 (2 × CH), 137.2 (*C*), 170.5 (*C*); HRMS (ESI$^+$ TOF): calcd for $C_{16}H_{24}NO$ ([MH^+]), 246.1858; found, 246.1861.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02177.

^1H and ^{13}C NMR spectra of all compounds, HPLC of lactam products **10a−d**, **13b−13i** (PDF)

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Notes

The authors declare no competing financial interest.

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