Enantiomerically Pure Highly Functionalized α-Amino Ketones from the Reaction of Chiral Cyclic *N*-(9-Phenylfluoren-9-yl) α-Amido Esters with Organolithium Reagents

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The reaction of methyl *N*-(9-phenylfluoren-9-yl)pyroglutamate with several organolithium reagents afforded the corresponding ketones in excellent yields and with complete retention of enantiomeric purity. The success of this transformation is due to the unusual stability of the tetrahedral intermediates **5**, which stems from two factors: the electron-withdrawing effect of the amide nitrogen and the lithium complexing ability of the fluorenyl ring of the 9-phenylfluoren-9-yl group. This ester-to-ketone transformation was also successfully applied to oxazolidinone **9** and imidazolidinone **20** and provided a ketone (**21b**) that was ultimately transformed into the urea-lactam **26** which incorporates the bicyclic core of streptolidine lactam, a component of the streptrothricin antibiotics.

Introduction

It is well-known that the reactions of organolithium and organomagnesium reagents with carboxylic acid esters initially lead to ketones which, being more electrophilic than the starting esters, undergo a second nucleophilic addition to give tertiary alcohols. In most cases it is not possible to stop these reactions at the ketone stage due to the instability of the tetrahedral intermediates resulting from the addition of the organometallic reagent to the carboxyl group.[1] In those instances where the tetrahedral alkoxide intermediate is stabilized by intramolecular complexation of the metal counterion (*N*-alkoxyamides),[2] or by the use of very poor leaving groups attached to the carbonyl group (lithium carboxylates),[3] or by electron-withdrawal from the carbonyl carbon (α-diesters[4] or α-polyhalo esters),[4,5] acylations of organolithium nucleophiles to give ketones can be carried out successfully. We report herein our serendipitous discovery that certain chiral cyclic *N*-(9-phenylfluoren-9-yl)-α-amido esters react with organolithium reagents to give the corresponding enantiomerically pure ketones in excellent yields.

Results and Discussion

We have recently reported that dimethyl *N*-(9-phenylfluoren-9-yl)aspartate can be selectively *N*-deprotonated with *n*-BuLi (100 mol %, THF, −78 °C) and that advantage could be taken of this behavior to stereoselectively prepare 3-hydroxyaspartate derivatives.[6] In an attempt to extend this methodology to the closely related *N*-Pf-glutamate system we treated dimethyl *N*-Pf-glutamate (**1**)[7] with *n*-BuLi under a variety of conditions. When 100 mol % of *n*-BuLi was used (THF, −78 °C, 2 h), methyl *N*-Pf-pyroglutamate **3a** was obtained as the major product (57%) along with recovered **1** (30%). Under more drastic conditions [*n*-BuLi (200 mol %), THF, −78 °C, 24 h], pyroglutamate **3a** (28%) and ketone **4d** (53%) were obtained as major products. Therefore, the abstraction of the NH in **1** was followed by amide attack to the ω-ester to give **3a**, which then would react through its remaining ester group with the excess organolithium reagent to give ketone **4d**. No traces of the corresponding tertiary alcohol were detected in the crude reaction product. Due to the surprising chemoselectivity of this process, we decided to study further the transformation of pyroglutamate **3a** into ketones **4**.

With this idea in mind, a more convenient method for furnishing the methyl *N*-Pf-pyroglutamate (**3a**) was explored. Thus, **3a** was readily prepared from **1** by selective hydrolysis of the ω-ester (LiOH, dioxane−H_2O, 0 °C) and cyclization of the resulting amino acid (**2**) with TsCl in pyridine (91% overall yield).[8] When **3a** was treated with several organolithium reagents (THF, −78 °C),[9] ketones **4a**−**c** were obtained in excellent yields; traces of the corresponding tertiary alcohols were isolated only from the reaction of **3a** with MeLi (Scheme 1).

The success of this transformation is due to the unusual stability of the tetrahedral intermediates **5**, which we attribute to two factors: the electron-withdrawing effect of the amide nitrogen and the lithium complexing ability of the fluorenyl ring of the 9-phenylfluoren-9-yl group.[10] Thus, when we studied the reactions of *N*-benzylpyroglutamate **3b** (poorer Li^+ coordinating ability) and *N*-Pf-proline methyl ester (lower electron-withdrawing effect) with MeLi, substantial

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(10) (a) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934. (b) Brooks, J. J.; Rhine, W.; Stucky, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 7339. (c) Taft, R. W.; Anvia, F.; Gal, J.-F.; Walsh, S.; Capon, M.; Holmes, M. C.; Hosn, K.; Oloumi, G.; Vasanwala, R.; Yazdani, S. *Pure Appl. Chem.* **1990**, *62*, 17. (d) Staley, R. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 5920.

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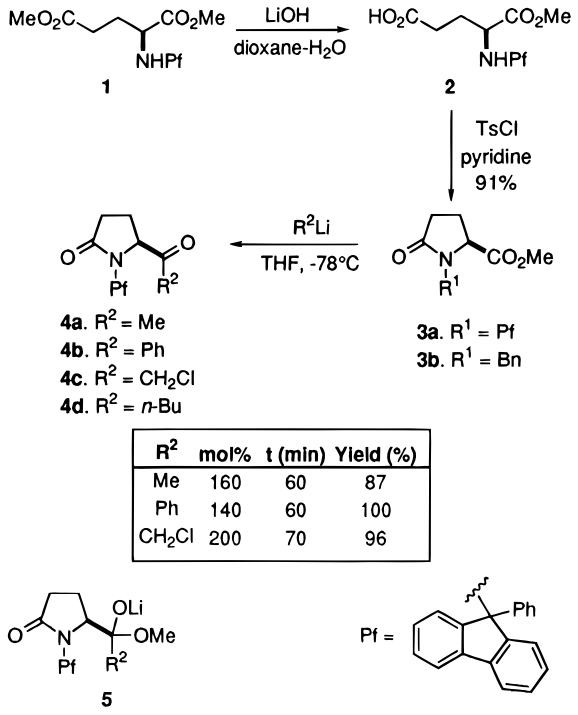
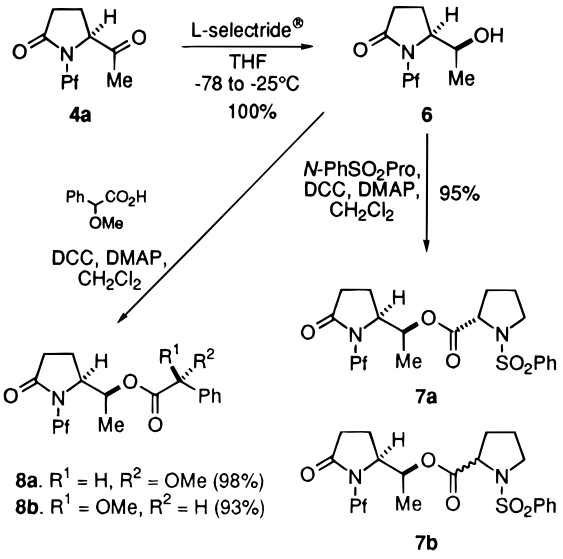
Scheme 1



Scheme 2



amounts (>20% yields at incomplete conversions) of the corresponding tertiary alcohols were isolated in both cases.[11]

A key point in the preparation of ketones **4a**−**c** is the question of the enantiomeric purity of the products. This question was addressed by stereoselective reduction of ketone **4a** with L-selectride (150 mol %, THF, −78 to −25 °C, quantitative)[12] and coupling of the resulting alcohol (**6**, only one stereoisomer detected) with both L- and D,L-*N*-benzenesulfonylproline (DCC, DMAP, CH_2Cl_2, 95%) to give esters **7a** and **7b** (mixture of diatereoisomers). ^{1}H NMR analysis of mixtures of **7a** and **7b** of known composition showed that **6**, and therefore **4a**, had a ratio of enantiomers (er) >99.5/0.5. The configuration of the newly created stereocenter in **6** was established by acylation of the OH group with both (*R*)- and (*S*)-methoxyphenylacetic acids. The diastereomeric esters **8a** and **8b** were obtained in 98% and 93% yields, respectively (Scheme 2). The application of the Trost−Mosher method for the determination of the absolute configuration of secondary alcohols to esters **8a** and **8b** led us to assign the *S* configuration to C1″ in **6**.[13,14]

In order to further study the generality of the above observations, and to provide access to heavily functionalized amino acid derivatives, we decided to study the behavior of more complex systems, such as oxazolidinone **9** and imidazolidinone **16**.[6] In these systems the electron-withdrawing X−CO (X = O, NR) group is α to the electrophile but, since we expected that the most exposed carboxylate (at C-5) would be preferentially attacked by the organolithium reagent, the *N*-Pf group would be *β* to the electrophile. Molecular models as well as semiempirical (MNDO) calculations on model systems showed that intramolecular Pf···Li complexation would still be possible in the tetrahedral adducts obtained from **9** and **16**. Thus, when oxazolidinone **9** was treated with several organolithium reagents[15,16] (THF, −78 °C), ketones **10a**−**d** were obtained in good to excellent yields. The corresponding tertiary alcohols were not detected in the crude products of these reactions; however it was very difficult to avoid the formation of small amounts of diketones **11**, resulting from the addition of the RLi to both ester groups of **9**. For example, when **9** was treated with an excess of PhLi (325 mol %), diketone **11** (R = Ph) was obtained as the major product in a **11** (R = Ph):**10c**, ratio of 4.5:1. Even in this instance no traces of the corresponding tertiary alcohols were detected in the crude product. The intermediate resulting from the addition of the organolithium reagent to the carboxylate at C-5 of **9** is apparently stable in the reaction medium, which allows the formation of the corresponding ketone as the only product even in this system where the reacting ester is *β* to the NPf group.

The chemoselectivity of the formation of ketones **10** was established by reduction of ketone **10d** with $LiBH_4$ (150 mol %, THF−*i*-PrOH, −78 to −30 °C) and analysis of the H-5 signal in the ^{1}H NMR spectra of the resulting pure alcohols, which is always at lower field than that of H-4. ^{1}H NMR (*δ*, mult, *J*) major isomer, H-5 (4.33, dd, *J* = 3.4 and 5.2 Hz), H-4 (3.90, d, *J* = 3.4 Hz); minor isomer, H-5 (4.35, t, *J* = 3.6 Hz), H-4 (4.10, d, *J* = 3.8 Hz).[17]

The higher electron-withdrawing effect of O *vs* N in **9** than in **3a**, or a possible intramolecular complexation Li···O (at C-5), is not responsible for the success of this

(11) Correa, J. F.; Fernández-Megía, E.; Sardina, F. J. Unpublished results.

(12) Other reducing agents tested were (diastereomeric ratio, reaction conversion in percent): $NaBH_4$ (80:20, 100), DIBAL-H (91:9, 70), K-Selectride (>99:1, 45), Super-Hydride (>99:1, 100), where **6** was always the major product.

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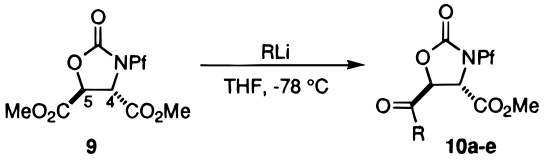
(15) [(Methoxymethoxy)methyl]lithium was prepared by following a literature procedure: Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131.

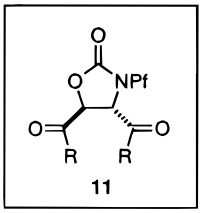
(16) [*p*-[(*tert*-Butyldimethylsilyl)oxy]phenyl]lithium was prepared following a literature procedure: Kurokawa, N.; Ohfune, Y. *Tetrahedron* **1993**, *49*, 6195.

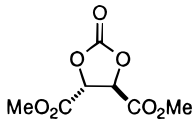
Scheme 3

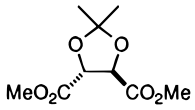


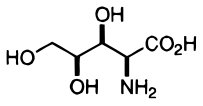
	R	mol%	t (min)	Yield (%)
10a	Me	120	30	99
10b	CH_2OMOM	140	30	66 (6)[a]
10c	Ph	150	30	84 (6)[a]
10d	*p*-PhOTBS	105	90	70 (6)[a]

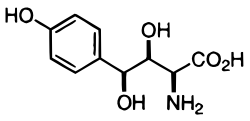
[a] Yields in brackets correspond to diketones **11**.









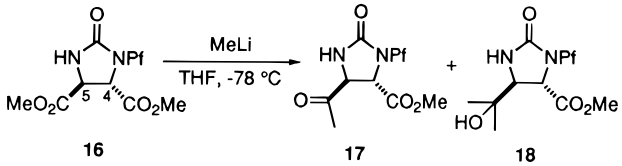


reaction, since when carbonate (**12**) or dimethyl acetal (**13**) derivatives (Scheme 3) were treated under similar conditions, the corresponding tertiary alcohols were detected along with other products.[18]

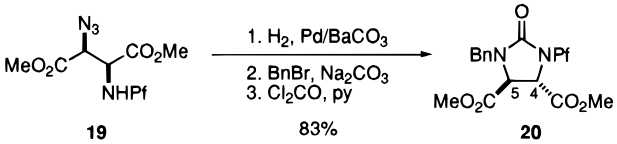
Dialkoxy ketone **10b** is an advanced intermediate in the synthesis of polioxamic acid (**14**), present as 5-*O*-carbamoylpolioxamic acid in the polioxins, a family of antifungal antibiotics widely used in agriculture;[19] while phenoxy ketone **10d** is a precursor of (2*S*,3*S*,4*R*)-3,4-dihydroxyhomotyrosine (**15**), a component of the cyclic hexapeptidic antibiotic Echinocandin B[20] and other related natural products,[16] which present a great activity against *Candida albicans*.[16,21]

Imidazolidinone **16** proved to be a more demanding system due to the presence of the acidic NH proton. We tried to optimize the formation of ketone **17** by using MeLi (THF, −78 °C) as the nucleophile (Scheme 4). Under all the reaction conditions tried, a ∼1:1 mixture

Scheme 4

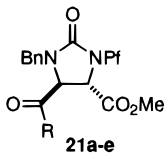


Scheme 5



	R	mol%	t (min)	T (°C)	Yield (%)
21a	Me	105	45	-78	92
21b	CH_2Cl	200	75	-78	100
21c	*n*-Bu	125	45	-78	61[a]
21d	Ph	125	45	-78	85
21e	≀—⟨ OEt	250	80	-78 to -55	78[b]

[a] Based on recovered **20**. [b] Not optimized conditions.



of the desired ketone **17** and the tertiary alcohol **18** was always obtained. We thought that **18** could result from either incomplete NH deprotonation prior to the addition of the organolithium reagent to the C-5 ester (resulting in the protonation of the intermediate by the residual NH) or to the instability of a doubly (N-Li and O-Li) lithiated intermediate.

To avoid this undesired side reaction we proceeded to synthesize the *N*-benzylimidazolidinone **20**. Due to the low yields of the direct benzylation of **16** (base, BnBr), we decided to prepare **20** by benzylation of the 3-aminoaspartate synthetic precursor of **16**.[22] Mild hydrogenation of **19** [H_2 (1 atm), $Pd/BaCO_3$], followed by *N*-monobenzylation (BnBr, Na_2CO_3, $CH_2Cl_2-H_2O$, reflux)[23] and cyclization of the resulting diamine with Cl_2CO (DMAP, pyridine, 70 °C),[6] provided **20** in 83% overall yield (Scheme 5).

When **20** was treated with several organolithium reagents[9,24] (THF, −78 °C), ketones **21a**−**e** were obtained in good to excellent yields. In no instances the corresponding tertiary alcohols were detected in the crude reaction products.[22] Therefore the protection of the NH had resulted in a stabilization of the intermediate resulting from the addition of the organolithium to the C-5 carboxylate of **20**, which allowed the formation of the corresponding ketone as the only product, as in the previous cases.

The highly functionalized ketone **21b** is an atractive advanced intermediate in the synthesis of the bicycle streptolidine lactam (**27**), a guanidinelactam which forms the core of the streptothricin antibiotics, a family of potent antibiotics isolated from microbial sources.[25−29]

(17) The chemical shift of the CO_2Me group α to the *N*-Pf always appears at higher field (∼0.4 ppm) than the one at position *β* in *N*-Pf aspartic acid diesters, due to the shielding effect of the fluorenyl ring: Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068 and ref 6. The disappearance of the lower field methoxyl singlet when **9** (*δ* 3.72 and 3.29 ppm) and **20** (*δ* 3.54 and 3.18 ppm) are transformed into the corresponding ketones [i.e., **10a**, *δ* 3.28 ppm; **10c**, *δ* 3.19 ppm; **21a**, *δ* 3.28 ppm; **21d**, *δ* 3.16 ppm) provides further proof of the regiochemistry of the reaction.

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(23) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.

(24) 1-Ethoxy-1-lithioethene was prepared by following a literature procedure: (a) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913. (b) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830.

(25) Carter, H. E.; Clark, R. K., Jr.; Kohn, P.; Rothrock, J. W.; Taylor, W. R.; West, C. A.; Whitfield, G. B.; Jackson, W. G. *J. Am. Chem. Soc.* **1954**, *76*, 566.

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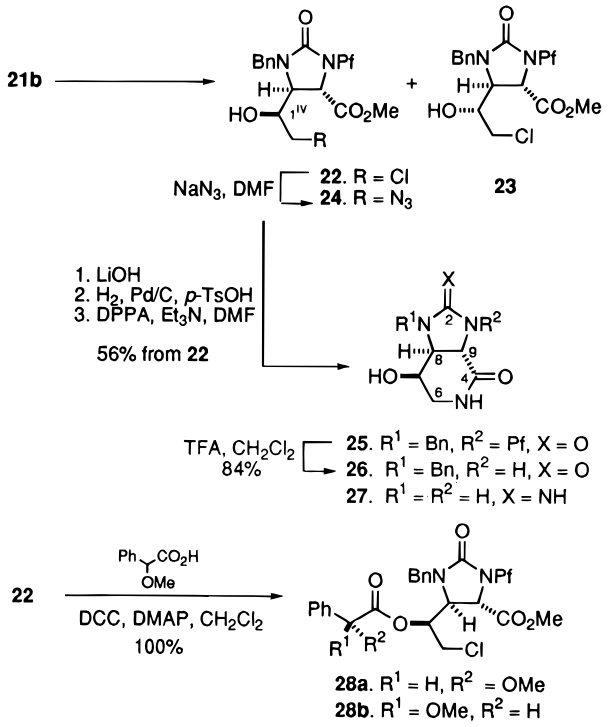
(27) Brockmann, H.; Musso, H. *Chem. Ber.* **1955**, *88*, 648.

Scheme 6



Several syntheses of **27** have been reported; all of them use carbohydrates as starting materials.[30−32] Thus, crude **21b** was directly reduced with $LiEt_3BH$ (THF, 3 Å molecular sieves, −78 °C)[33] to give a mixture of alcohols **22**/**23** in a 7:1 ratio (77% combined yield from **20**). Furthermore, alcohol **23** could be obtained as the major diastereoisomer by treatment with DIBAL-H (CH_2Cl_2−hexane, −78 °C) in a **22**/**23**, ratio of 1:10 (71% combined yield from **20**). The configuration of the newly created stereocenter in **22** was established, as above, by reaction with both (*R*)- and (*S*)-methoxyphenylacetic acids. The diastereomeric esters **28a** and **28b** were obtained quantitatively. The application of the Trost−Mosher method to esters **28a** and **28b** led us to assign the *S* configuration to $C1^{IV}$ in **22**.[13]

Chloride displacement by NaN_3 (DMF, 110 °C) converted **22** into azido alcohol **24**. The chemoselectivity of the formation of ketones **21** was established at this stage, since a strong NOE was observed between $H1^{IV}$ and the *N*-benzylic CH_2 group in the ^1H NMR spectrum of **24**.[17] Urea-lactam **25**, which contains the bicyclic system required for the synthesis of streptolidine lactam **27**, was prepared from crude **24** by ester hydrolysis ($LiOH·H_2O$, dioxane−H_2O) followed by azide reduction (H_2, Pd/C, *p*-$TsOH·H_2O$) and cyclization of the resulting amino acid with diphenyl phosphoryl azide (Et_3N, DMF, 0 °C to rt, 56% yield from **22**).[34,35] Treatment of **25** with TFA (CH_2Cl_2, rt)[36] led to the monoprotected urea-lactam **26** in a 84% yield. Studies to complete the synthesis of streptolidine lactam (**27**) and its epimer in the C-7 position (from alcohol **23**) are in progress.

Conclusion

We have described that certain *N*-Pf-α (or *β*)-amino esters react with organolithium reagents leading to the corresponding ketones in good to excellent yields. The resulting highly functionalized ketones are attractive synthetic precursors of interesting natural products; thus, ketone **19b** has been transfomed into the urealactam **26** which posesses the bicyclic structure present in streptolidine lactam (**27**). Studies to extend this methodology to other related cyclic and acyclic *N*-Pf-amino esters are in progress.

Experimental Section

General. All the reactions were carried out under an atmosphere of dry argon, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use; methylene chloride, triethylamine, CH_3CN, pyridine, DMF, and HCO_2Et were distilled from CaH_2; methanol was distilled from magnesium; and acetone was distilled from $CaCO_3$. Column chromatography was performed with 230−400 (low-pressure chromatography) mesh silica gel unless otherwise noted. Thin-layer chromatography (TLC) was done on silica 60/F-254 aluminum-backed plates (E. Merck). Melting points are uncorrected. ^1H NMR spectra were recorded on a Bruker WM-250 MHz or Bruker AMX-500 MHz spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in ppm (*δ* units) downfield from internal tetramethylsilane or the appropriate solvent signal [CD_2Cl_2, CD_3OD, or $(CD_3)_2CO$].

(2*S*)-5-Oxo-1-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl ester (3a): $LiOH·H_2O$ (4881 mg, 116.32 mmol) was added to a solution of **1** (3448 mg, 8.31 mmol) in dioxane (96 mL)/H_2O (70 mL, deoxygenated with Ar) at 0 °C. The resulting solution was stirred at 0 °C for 2 h 30 min and then acidified to pH = 2 with HCl (5%) and allowed to reach room temperature. The aqueous phase was extracted with EtOAc (2 × 250 mL), and the combined organic phase was washed with brine (250 mL), dried, and concentrated to give a residue that was dissolved (MeOH, 15 mL) and evaporated. This operation was repeated three times to remove traces of dioxane.

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(35) The use of $NaHCO_3$ as base instead of Et_3N lead to the formation of several byproducts.

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(37) Improved procedure for the preparation of **9**: dimethyl *N*-Pf-glutamate (3123 mg, 7.79 mmol) was treated with LHMDS (120 mol %, THF−HMPA, −50/−55 °C, 1 h). Then MoOPH was added (135 mol %, 1 h at −78 °C and 2 h from −78 to −62 °C) and the reaction was quenched, worked up, and purified as in ref 6. An 11:1 mixture of (3*S*)- and (3*R*)-dimethyl *N*-Pf-3-hydroxyaspartes was obtained (62%, 76% based on recovered starting material). A sample of this mixture (3302 mg, 7.92 mmol) was treated with Cl_2CO (500 mol %, DMAP, pyridine, 70 °C, 15 min) and then quenched and worked up as in ref 6. Recrystallization of the crude product (CH_2Cl_2/hexane) and purification of the mother liquors by column cromatography (conditions in ref 6) afforded **9** (93% combined yield) in a ratio of diastereomers 20:1.

(2*S*)-α-Methyl *N*-(9′-phenylfluoren-9′-yl)glutamate (2) was obtained pure as a white foam. (Recrystallization of the crude product from Et_2O/hexane afforded pure white crystals.) TsCl (2376 mg, 12.46 mmol) was added to a solution of the above residue in pyridine (28 mL) at room temperature. The resulting solution was stirred for 10 h and then partitioned between EtOAc (350 mL) and HCl (5%, 250 mL). The organic layer was washed with HCl (5%, 200 mL), saturated $NaHCO_3$ (150 mL), and brine (150 mL), dried, and concentrated to give a solid residue that was purified by short column chromatography (silica gel 70−230 mesh, 2/1 hexane/EtOAc with 0.2% pyridine) to afford **3a** (2895 mg, 91%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from EtOAc/hexane.

2: mp 148 °C; $[\alpha]^{20}_D$ −274.4° (*c* 1.04, $CHCl_3$); IR (KBr) 1737, 1710 cm^{-1}; ^1H NMR δ 7.68 (t, *J* = 7.9 Hz, 2H), 7.41−7.14 (m, 11H), 3.28 (s, 3H), 2.63 (dd, *J* = 4.6 Hz, *J* = 8.9 Hz, 1H), 2.42 (t, *J* = 6.9 Hz, 2H), 1.87−1.63 (m, 2H); ^{13}C NMR δ 178.3, 175.9, 148.5, 148.0, 143.8, 141.3, 140.1, 128.6, 128.5, 128.4, 128.2, 127.4, 126.3, 126.0, 125.4, 120.1, 120.0, 72.9, 55.0, 51.7, 31.0, 29.1. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.6; H, 5.7; N, 3.4.

3a: mp 200−202 °C; $[\alpha]^{20}_D$ −91.9° (*c* 0.57, $CHCl_3$); IR (KBr) 1740, 1690, 1207 cm^{-1}; ^1H NMR δ 7.65 (d, *J* = 7.4 Hz, 3H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.41−7.19 (m, 9H), 3.93 (d, *J* = 9.2 Hz, 1H), 3.28 (s, 3H), 2.69 (ddd, *J* = 9.3 Hz, *J* = 11.0 Hz, *J* = 16.0 Hz, 1H), 2.41−2.12 (m, 2H), 1.91−1.82 (m, 1H); ^{13}C NMR δ 176.5, 173.0, 147.0, 146.8, 141.0, 140.1, 129.1, 129.0, 128.3, 128.0, 127.9, 127.0, 126.8, 125.1, 119.8, 119.6, 73.2, 60.5, 51.8, 30.8, 24.3. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.3; H, 5.5; N, 3.7. Found: C, 78.6; H, 5.6; N, 3.5.

(5*S*)-5-Acetyl-1-(9′-phenylfluoren-9′-yl)pyrrolidin-2-one (4a). MeLi (0.509 mL, 0.836 mmol, 160 mol %, 1.64 M in Et_2O) was added dropwise to a stirred solution of **3a** (200 mg, 0.522 mmol) in THF (5.3 mL) at −78 °C. The resulting orange solution was stirred for 1 h at −78 °C, then HCO_2Et (0.211 mL, 2.611 mmol) was added and after 5 min the reaction was quenched with MeOH (1.5 mL). The reaction mixture was allowed to reach room temperature and was partitioned between CH_2Cl_2 (100 mL) and H_3PO_4 (1 M, 100 mL). The aqueous layer was washed with CH_2Cl_2 (100 mL), and the combined organic phase was washed with brine (100 mL), dried, and concentrated to give a residue that was purified by column chromatography (silica gel 70−230 mesh, hexane/EtOAc, 1.05/1) to give **4a** (167 mg, 87%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from CH_2Cl_2/hexane: mp 258−260 °C; $[\alpha]^{20}_D$ +71.6° (*c* 0.55, $CHCl_3$); IR (NaCl) 1720, 1689 cm^{-1}; ^1H NMR δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.47 (d, 7.6 Hz, 1H), 7.41−7.37 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.30−7.24 (m, 3H), 7.21−7.17 (m, 2H), 3.99 (dd, *J* = 1.5 Hz, *J* = 9.9 Hz, 1H), 2.59 (ddd, *J* = 9.1 Hz, *J* = 11.6 Hz, *J* = 16.5 Hz, 1H), 2.30 (ddd, *J* = 1.7 Hz, *J* = 9.3 Hz, *J* = 16.5 Hz, 1H), 2.15−2.06 (m, 1H), 1.71−1.66 (m, 1H), 1.55 (s, 3H); ^{13}C NMR δ 207.0, 176.3, 147.7, 147.3, 140.8, 140.3, 139.9, 129.2, 129.0, 128.5, 128.4, 128.1, 127.3, 127.0, 125.4, 119.9, 119.8, 73.2, 65.7, 30.6, 26.2, 23.1. Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.7; H, 5.8; N, 3.8. Found: C, 81.6; H, 5.7; N, 3.8.

(5*S*)-5-Benzoyl-1-(9′-phenylfluoren-9′-yl)pyrrolidin-2-one (4b). nBuLi (0.156 mL, 0.256 mmol, 140 mol %, 1.64 M in hexane) was added dropwise to a stirred solution of PhBr (0.029 mL, 0.274 mmol, 150 mol %) in THF (0.65 mL) at −78 °C. The resulting solution was stirred at −78 °C for 20 min and then cannulated dropwise at −78 °C to a precooled (−78 °C) solution of **3a** (70 mg, 0.183 mmol, 100 mol %) in THF (1.2 mL). The resulting orange solution was stirred for 1 h at −78 °C, then HCO_2Et (0.074 mL, 0.914 mmol) was added, and after 5 min the reaction was quenched with MeOH (1 mL). The reaction mixture was allowed to reach room temperature and was partitioned between CH_2Cl_2 (70 mL) and H_3PO_4 (1 M, 70 mL). The aqueous phase was washed with CH_2Cl_2 (50 mL), and the combined organic phase was washed with brine (100 mL), dried, and concentrated to give a residue that was purified by short column chromatography (silica gel 70−230 mesh, 1.65/1 hexane/EtOAc, with 0.2% of pyridine) to afford **4b** (78 mg, 100%) as a white crystalline solid. An analytical sample, as white microcrystals, was obtained by recrystallization from EtOAc/hexane: mp 170 °C dec; $[\alpha]^{20}_D$ +42.8° (*c* 2.85, $CHCl_3$); IR (NaCl) 1696 cm^{-1}; ^1H NMR δ 7.84 (dd, *J* = 1.6 Hz, *J* = 6.3 Hz, 1H), 7.58−7.09 (m, 16H), 6.84 (dt, *J* = 0.8 Hz, *J* = 8.4 Hz, 1H), 4.79 (d, *J* = 8.9 Hz, 1H), 2.72 (ddd, *J* = 9.0 Hz, *J* = 11.9 Hz, *J* = 16.2 Hz, 1H), 2.35−2.05 (m, 2H), 1.72 (dd, *J* = 9.2 Hz, *J* = 12.6 Hz, 1H); ^{13}C NMR δ 199.0, 176.8, 148.2, 147.1, 140.8, 140.3, 139.6, 134.5, 133.3, 129.0, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 127.2, 126.9, 125.6, 119.8, 119.6, 73.3, 61.3, 30.7, 24.5. Anal. Calcd for $C_{30}H_{23}NO_2 \cdot 0.25H_2O$: C, 83.0; H, 5.5; N, 3.2. Found: C, 82.9; H, 5.5; N, 3.2.

(5*S*)-5-(2″-Chloroacetyl)-1-(9′-phenylfluoren-9′-yl)pyrrolidin-2-one (4c). MeLi (0.714 mL, 1.149 mmol, 200 mol %, 1.61 M in Et_2O) was added dropwise to a stirred solution of **3a** (220 mg, 0.574 mmol), chloroiodomethane (0.091 mL, 1.246 mmol, 217 mol %), and LiBr (75 mg, 0.862 mmol, 150 mol %) in THF (5.6 mL) at −78 °C. The resulting yellow solution was stirred at −78 °C for 70 min, then HCO_2Et (0.232 mL, 2.872 mmol) was added, and after 5 min at −78 °C the reaction was quenched with MeOH (1 mL). The reaction mixture was allowed to reach room temperature and was partitioned between CH_2Cl_2 (75 mL) and H_3PO_4 (1 M, 50 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL), and the combined organic layer was washed with brine (75 mL), dried, and concentrated to give a residue that was purified by short column chromatography (silica gel 70−230 mesh, 1.3/1 hexane/EtOAc) to give **4c** (222 mg, 96%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from EtOAc/hexane: mp 170 °C dec; $[\alpha]^{20}_D$ +71.8° (*c* 2.72, $CHCl_3$); IR (KBr) 1740, 1690 cm^{-1}; ^1H NMR δ 7.66 (*c*, *J* = 7.7 Hz, 3H), 7.44−7.17 (m, 10H), 4.22 (d, *J* = 8.6 Hz, 1H), 3.41 (d, *J* = 16.1 Hz, 1H), 3.17 (d, *J* = 16.1 Hz, 1H), 2.70−2.55 (m, 1H), 2.36−2.26 (m, 1H), 2.21−2.06 (m, 1H), 1.78−1.69 (m, 1H); ^{13}C NMR δ 201.3, 176.2, 147.5, 147.2, 140.4, 140.3, 139.9, 129.4, 129.2, 128.6, 128.4, 128.2, 127.3, 127.1, 125.4, 120.0, 73.2, 62.7, 45.8, 30.5, 23.6. Anal. Calcd for $C_{25}H_{20}NO_2Cl$: C, 74.7; H, 5.0; N, 3.5. Found: C, 74.4; H, 5.0; N, 3.3.

(5*S*,1″*S*)-5-(1-Hydroxyethyl)-1-(9′-phenylfluoren-9′-yl)pyrrolidin-2-one (6). L-Selectride (0.331 mL, 0.331 mmol, 150 mol %, 1 M in THF) was added dropwise to a stirred solution of **4a** (81 mg, 0.221 mmol) in THF (4.25 mL) at −78 °C. The resulting solution was stirred from −78 °C to −25 °C for 2 h and then quenched with AcOH (0.038 mL, 0.662 mmol). After 5 min of stirring at −25 °C the reaction was allowed to reach room temperature. $LiOH \cdot H_2O$ (46 mg, 1.104 mmol) and H_2O_2 (30%, 1 mL) were added, and the resulting mixture was stirred for 30 min and then partitioned between CH_2Cl_2 (35 mL) and H_3PO_4 (1 M, 40 mL). The aqueous phase was washed with CH_2Cl_2 (35 mL), and the combined organic phase was washed with brine (40 mL), dried, and concentrated to give a residue that was purified by short column chromatography (silica gel 70−230 mesh, 1/1.5 hexane/EtOAc) to give **6** (81 mg, 100%) as a white crystalline solid. An analytical sample, as white microcrystals, was obtained by recrystallization from CH_2Cl_2/hexane: mp 216−218 °C; $[\alpha]^{20}_D$ −576.3° (*c* 1.12, $CHCl_3$); IR (KBr) 3377, 1686, 1664 cm^{-1}; ^1H NMR δ 8.17 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.35−7.10 (m, 9H), 3.95 (dd, *J* = 3.4 Hz, *J* = 7.7 Hz, 1H), 2.98 (dc, *J* = 3.8 Hz, *J* = 6.3 Hz, 1H), 2.41−2.28 (m, 2H), 2.20−1.95 (m, 2H), 1.74 (bs, 1H), 0.42 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR δ 176.2, 148.6, 145.6, 142.3, 140.0, 139.4, 129.1, 128.7, 128.4, 128.3, 127.5, 126.9, 126.7, 124.4, 120.1, 119.7, 72.6, 66.8, 63.5, 31.7, 18.0, 15.1. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.3; H, 6.3; N, 3.8. Found: C, 81.2; H, 6.3; N, 3.6.

(2*S*,1″*S*,2‴*S*)-1′-[5‴-Oxo-1‴-(9^{IV}-phenylfluoren-9^{IV}-yl)pyrrolidin-2‴-yl]ethyl 1-(Benzenesulfonyl)pyrrolidine-2-carboxylate (7a). L-*N*-(Benzenesulfonyl)proline (26 mg, 0.101 mmol), DMAP (1 mg, 0.008 mmol), and DCC (21 mg, 0.101 mmol) were added to a solution of **6** (25 mg, 0.068 mmol) in CH_2Cl_2 (0.7 mL). The resulting cloudy solution was stirred at room temperature for 1 h. HCl (5%, 1 mL) was then added, and after 10 min of stirring, the mixture was partitioned

between CH_2Cl_2 (30 mL) and HCl (5%, 30 mL). The aqueous phase was washed with CH_2Cl_2 (20 mL), and the combined organic phase was washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried, and concentrated to give a residue that was filtered (through a cotton plug) and purified by column chromatography (1/1 hexane/EtOAc) to give **7a** (39 mg, 95%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from CH_2Cl_2/hexane: mp 218−220 °C; $[\alpha]^{20}_D$ −490.9° (*c* 0.5, $CHCl_3$); IR (NaCl) 1753, 1691 cm^{-1}; ^1H NMR δ 8.22 (d, J = 7.6 Hz, 1H), 7.79−7.69 (m, 4H), 7.61−7.43 (m, 4H), 7.37−7.31 (m, 3H), 7.25−7.15 (m, 6H), 4.17−4.04 (m, 2H), 3.94 (dd, J = 3.8 Hz, J = 8.0 Hz, 1H), 3.48−3.40 (m, 1H), 3.18−3.09 (m, 1H), 2.54−2.47 (m, 2H), 2.39−2.26 (m, 1H), 2.22−2.10 (m, 1H), 1.86−1.55 (m, 4H), 0.58 (d, J = 6.4 Hz, 3H); ^{13}C NMR (CD_2Cl_2) δ 176.4, 170.5, 148.9, 145.8, 143.2, 140.9, 139.9, 138.6, 133.2, 129.7, 129.5, 129.3, 129.1, 128.7, 128.6, 128.1, 127.6, 127.2, 127.1, 125.1, 121.0, 120.5, 73.0, 70.8, 60.9, 60.8, 48.8, 32.0, 31.2, 24.7, 19.2, 12.4. Anal. Calcd for $C_{36}H_{34}N_2O_5S$: C, 71.3; H, 5.7; N, 4.6. Found: C, 71.0; H, 5.6; N, 4.5.

(2*R*,1′*S*,2″*S*)-1′-[5″-Oxo-1″-(9‴-phenylfluoren-9‴-yl)-pyrrolidin-2″-yl]ethyl Methoxyphenylacetate (8a). DMAP (1 mg, 0.009 mmol), (*R*)-methoxyphenylacetic acid (31 mg, 0.187 mmol), and DCC (39 mg, 0.187 mmol) were added to a solution of **6** (46 mg, 0.124 mmol) in CH_2Cl_2 (1.2 mL). The resulting cloudy solution was stirred for 2 h at room temperature. Then HCl (5%, 1 mL) was added, and after 10 min of stirring, the mixture was filtered (through a cotton plug) and partitioned between EtOAc (20 mL) and HCl (5%, 15 mL). The aqueous phase was washed with EtOAc (15 mL), and the combined organic phase was washed with HCl (5%, 15 mL), saturated $NaHCO_3$ (15 mL), and brine (20 mL), dried, and concentrated to give a residue that was dissolved in CH_2Cl_2, filtered (through a cotton plug), and purified by column chromatography (1.5/1 hexane/EtOAc) to give **8a** (63 mg, 98%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from CH_2Cl_2/hexane: mp 220−230 °C sublimes; $[\alpha]^{20}_D$ −253.2° (*c* 0.43, $CHCl_3$); ^1H NMR (CD_2Cl_2) δ 8.09 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.35−7.12 (m, 14H), 4.47 (s, 1H), 4.01 (d, J = 6.4 Hz, 2H), 3.20 (s, 3H), 2.43−2.36 (m, 2H), 2.29−2.15 (m, 1H), 2.01−1.93 (m,1H), 0.40 (d, J = 5.0 Hz, 3H); ^{13}C NMR (CD_2Cl_2) δ 176.3, 169.1, 148.8, 145.8, 143.1, 140.9, 139.9, 136.8, 129.7, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.1, 127.3, 127.2, 127.0, 125.1, 121.1, 120.5, 82.6, 73.1, 70.5, 61.1, 57.4, 31.9, 19.2, 12.1. Anal. Calcd for $C_{34}H_{31}NO_4 \cdot 0.5H_2O$: C, 77.5; H, 6.1; N, 2.7. Found: C, 77.7; H, 5.8; N, 2.6.

(2*S*,1′*S*,2″*S*)-1′-[5″-Oxo-1″-(9‴-phenylfluoren-9‴-yl)pyrrolidin-2″-yl]ethyl Methoxyphenylacetate (8b). Same procedure as above. From **6** (46 mg, 0.124 mmol), DMAP (1 mg, 0.009 mmol), (*S*)-methoxyphenylacetic acid (31 mg, 0.187 mmol), and DCC (39 mg, 0.187 mmol), after purification by column chromatography in the same conditions as above, was obtained **8b** (60 mg, 93%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from EtOAc/hexane: mp 180−182 °C; $[\alpha]^{20}_D$ −507.2° (*c* 0.86, $CHCl_3$); IR (NaCl) 1746, 1690 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 8.13 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.39−7.32 (m, 6H), 7.20−7.09 (m, 8H), 4.49 (s, 1H), 4.03 (dc, J = 3.7 Hz, J = 6.5 Hz, 1H), 3.75 (dd, J = 3.6 Hz, J = 7.6 Hz, 1H), 3.23 (s, 3H), 2.40−2.34 (m, 2H), 1.95−1.72,(m, 2H), 0.55 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CD_2Cl_2) δ 176.2, 169.1, 148.8, 145.6, 143.0, 140.9, 139.8, 137.0, 129.7, 129.4, 129.1, 129.0, 128.9, 128.7, 128.6, 128.1, 127.5, 127.1, 126.9, 125.0, 121.0, 120.5, 82.5, 72.9, 70.3 , 60.7, 57.4, 31.8, 18.7, 12.3. Anal. Calcd for $C_{34}H_{31}NO_4$: C, 78.9; H, 6.0; N, 2.7. Found: C, 79.0; H, 5.9; N, 2.6.

(4*S*,5*S*)-5-Acetyl-2-oxo-3-(9′-phenylfluoren-9′-yl)oxazolidine-4-carboxylic Acid Methyl Ester (10a). MeLi (0.040 mL, 0.111 mmol, 120 mol %, 2.78 M in Et_2O) was added dropwise to a solution of **9** (41 mg, 0.092 mmol, 100 mol %) in THF (1 mL) at −78 °C. The resulting colorless solution was stirred at −78 °C for 30 min, then acetone (0.068 mL, 0.924 mmol) was added, and stirring was continued for 3 min at −78 °C. H_3PO_4 (1 M, 1 mL) was added, and the reaction was allowed to reach room temperature. The resulting mixture was partitioned between CH_2Cl_2 (20 mL) and H_3PO_4 (1 M, 20 mL). The aqueous phase was washed with CH_2Cl_2 (15 mL), and the combined organic phase was washed with brine (20 mL), dried, and concentrated to give a residue that was purified by short column chromatography (70−230 mesh, 2.2/1 hexane/EtOAc) to give **10a** [39 mg, 99% yield, in a 35:1 ratio with the diketone **11** (R = Me)] as a white crystalline solid that could be recrystallized from EtOAc/hexane: mp 168−170 °C; $[\alpha]^{20}_D$ −90.3° (*c* 0.66, $CHCl_3$); IR (KBr) 1770, 1741, 1734 cm^{-1}; ^1H NMR δ 7.66 (d, J = 7.2 Hz, 3H), 7.54 (d, J = 7.4 Hz, 1H), 7.41−7.24 (m, 9H), 4.45 (d, J = 2.9 Hz, 1H), 4.20 (d, J = 2.9 Hz, 1H), 3.28 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ 203.1, 169.8, 155.8, 145.8, 145.6, 140.1 (2 × C), 140.0, 129.8, 129.4, 128.6, 128.5, 128.1, 127.8, 127.6, 126.2, 125.4, 120.2, 120.0, 78.4, 72.8, 59,2, 52.5, 26.1. Anal. Calcd for $C_{26}H_{21}NO_5 \cdot 0.5H_2O$: C, 71.5; H, 5.1; N, 3.2. Found: C, 71.3; H, 5.0; N, 3.3.

(4*S*,5*S*)-5-(2‴-(Methoxymethoxy)acetyl)-2-oxo-3-(9′-phenylfluoren-9′-yl)oxazolidine-4-carboxylic Acid Methyl Ester (10b). nBuLi (0.655 mL, 0.865 mmol, 140 mol %, 1.32 M in hexane) was added dropwise to a solution of ((methoxymethoxy)methyl)tributylstannane (315 mg, 0.865 mmol, 140 mol %) in THF (2.6 mL) at −78 °C. The resulting solution was stirred at −78 °C for 9 min and then was cannulated at −78 °C dropwise for 5 min to a solution of **9**[37] (274 mg, 0.618 mmol, 100 mol %) in THF (6 mL) at −78 °C. The resulting yellow solution was stirred at −78 °C for 30 min, then acetone (0.091 mL, 1.236 mmol) was added, and stirring was continued for 3 min at −78 °C. Saturated NH_4Cl (4 mL) was added. The resulting mixture was allowed to reach room temperature and was partitioned between EtOAc (140 mL) and saturated NH_4Cl (140 mL). The aqueous phase was washed with EtOAc (100 mL), and the combined organic phase was washed with H_2O (100 mL) and brine (100 mL), dried, and concentrated to give a residue that was purified by column chromatography (70−230 mesh, 1/1.35 hexane/EtOAc) to give **10b** (198 mg, 66%) as a white foam and the diketone **11** (R = CH_2OMOM) in a 6% yield. An analytical sample of **10b** as white crystals was obtained by recrystallization from Et_2O/EtOAc/hexane: mp 59 °C dec; $[\alpha]^{20}_D$ −161° (*c* 1.52, $CHCl_3$); IR (KBr) 2951, 1746, 1450, 1383 cm^{-1}; ^1H NMR δ 7.79−7.20 (m, 13H), 4.77 (d, J = 2.7 Hz, 1H), 4.64 (d, J = 1.6 Hz, 2H), 4.41 (d, J = 5.9 Hz, 2H), 4.32 (d, J = 2.7 Hz, 1H), 3.36 (s, 3H), 3.24 (s, 3H); ^{13}C NMR δ 201.4, 169.2, 155.6, 145.8, 145.2, 140.1, 140.0, 139.9, 129.7, 129.4, 128.5, 128.2, 127.8, 127.6, 126.1, 125.3, 120.2, 119.8, 96.6, 76.4, 72.6, 69.9, 59.0, 55.8, 52.4. Anal. Calcd for $C_{28}H_{25}NO_7 \cdot 0.5H_2O$: C, 67.7; H, 5.3; N, 2.8. Found: C, 67.5; H, 5.3; N, 2.7.

(4*S*,5*S*)-5-Benzoyl-2-oxo-3-(9′-phenylfluoren-9′-yl)oxazolidine-4-carboxylic Acid Methyl Ester (10c). nBuLi (0.215 mL, 0.271 mmol, 150 mol %, 1.26 M in hexane) was added dropwise to a stirred solution of PhBr (0.031 mL, 0.298 mmol, 165 mol %) in THF (0.75 mL) at −78 °C. The resulting solution was stirred at −78 °C for 20 min and then cannulated dropwise at −78 °C to a precooled (−78 °C) solution of **9**[37] (80 mg, 0.180 mmol, 100 mol %) in THF (1.8 mL). The resulting colorless solution was stirred for 30 min at −78 °C, then acetone (0.150 mL) was added, and, after 2 min the reaction was quenched with H_3PO_4 (1 M, 1 mL). The reaction mixture was allowed to reach room temperature and was partitioned between CH_2Cl_2 (70 mL) and H_3PO_4 (1 M, 50 mL). The aqueous phase was washed with CH_2Cl_2 (40 mL), and the combined organic phase was washed with brine (70 mL), dried, and concentrated to give a residue [ratio **10c**:diketone **11** (R = Ph) 15:1] that was purified by column chromatography (2.8/1 hexane/EtOAc) to afford pure **10c** (74 mg, 84%) as a white foam and **11** (R = Ph) (6 mg, 6%) as a white foam. Both **10c** and **11** (R = Ph) partially epimerize after 1 day in $CDCl_3$.

10c: $[\alpha]^{20}_D$ −158.0° (*c* 0.89, $CHCl_3$); IR (NaCl) 1774, 1693 cm^{-1}; ^1H NMR δ 8.00 (d, J = 7.4 Hz, 2H), 7.94 (d, J = 7.6 Hz, 1H), 7.70−7.22 (m, 15H), 5.43 (d, J = 2.3 Hz, 1H), 4.76 (d, J = 2.3 Hz, 1H), 3.19 (s, 3H); ^{13}C NMR δ 191.3, 169.8, 155.6, 146.6, 145.2, 140.4, 140.3, 139.8, 134.6, 133.1, 129.5, 129.4, 129.2, 129.0, 128.5, 128.3, 128.0, 127.5, 126.5, 125.3, 120.1, 119.6, 75.4, 72.5, 59.0, 52.4. Anal. Calcd for $C_{31}H_{23}NO_5 \cdot 0.5H_2O$: C, 74.7; H, 4.9; N, 2.8. Found: C, 74.3; H, 4.7; N, 2.8.

11 (R = Ph): $[\alpha]^{20}_D$ −24.6° (*c* 1.45, CH_2Cl_2); IR (NaCl) 1774, 1735, 1690 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.90−7.87 (m, 2H), 7.71−7.13 (m, 21H), 5.76 (d, *J* = 2.6 Hz, 1H), 5.22 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ 195.6, 192.6, 156.5, 147.1, 146.4, 141.1, 140.7, 140.4, 135.1, 134.5, 134.1, 133.8, 130.0, 129.9, 129.7, 129.4, 129.1, 128.9, 128.8, 128.5, 128.4, 127.9, 126.8, 126.1, 120.8, 120.3, 76.4, 72.9, 59.3. Anal. Calcd for $C_{36}H_{25}NO_4 \cdot 0.75H_2O$: C, 78.7; H, 4.9; N, 2.6. Found: C, 78.8; H, 4.8; N, 2.6.

(4*S*,5*S*)-5-(4^{IV}-((*tert*-Butyldimethylsilyl)oxy)benzoyl)-2-oxo-3-(9′-phenylfluoren-9′-yl)oxazolidine-4-carboxylic Acid Methyl Ester (10d). nBuLi (1.39 mL, 1.475 mmol, 105 mol %, 1.06 M in hexane) was added dropwise to a solution of *O*-(*tert*-butyldimethylsilyl)-4-bromophenol (444 mg, 1.545 mmol, 110 mol %) in THF (7.5 mL) at −78 °C. The resulting solution was stirred for 90 min at −78 °C and then cannulated at −78 °C, dropwise for 15 min, over a solution of **9**[37] (623 mg, 1.405 mmol, 100 mol %, ratio of stereoisomers 20:1) in THF (11.5 mL) at −78 °C. The resulting yellow solution was stirred for 90 min at −78 °C, then acetone (0.619 mL, 8.428 mmol) was added, and stirring was continued for 3 min at −78 °C. HCl (5%, 2 mL) was added, and the mixture was allowed to reach room temperature and partitioned between CH_2Cl_2 (200 mL) and HCl (5%, 150 mL). The aqueous phase was washed with CH_2Cl_2 (150 mL), and the combined organic phase was washed with brine (200 mL), dried, and evaporated to give a residue that was purified by column chromatography (70−230 mesh, 4.75/1 hexane/EtOAc) to give **10d** (609 mg, 70%) as a white foam and the diketone **11** (R = *p*-PhOTBS) in 6% yield. An analytical sample of **10d** as white crystals was obtained by recrystallization from Et_2O/hexane: mp 85 °C dec; $[\alpha]^{20}_D$ −90° (*c* 1,86, $CHCl_3$); IR (KBr) 2953, 2929, 2857, 1775, 1682, 1596 cm^{-1}; ^1H NMR δ 7.96 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.46−7.20 (m, 9H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.37 (d, *J* = 1.7 Hz, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 3.19 (s, 3H), 0.99 (s, 9H), 0.25 (s, 6H); ^{13}C NMR δ 189.6, 169.9, 161.7, 155.7, 146.7, 145.2, 140.5, 140.3, 139.8, 131.8, 129.5, 129.2, 128.5, 128.3, 128.0, 127.5, 126.6, 126.5, 125.3, 120.4, 120.0, 119.6, 75.4, 72.5, 59.1, 52.3, 25.4, 18.1, −4.5. Anal. Calcd for $C_{37}H_{37}NO_6Si \cdot H_2O$: C, 69.7; H, 6.2; N, 2.2. Found: C, 69.8; H, 6.0; N, 2.1.

(4*S*,5*S*)-5-Acetyl-2-oxo-3-(9′-phenylfluoren-9′-yl)imidazolidine-4-carboxylic Acid Methyl Ester (17). When **16** was treated with MeLi (200−1000 mol %) in THF at −78 °C under different reaction conditions, approximately 1:1 mixtures of ketone **17** and tertiary alcohol **(4*S*,5*S*)-5-(1-hydroxy-1-methylethyl)-2-oxo-3-(9′-phenylfluoren-9′-yl)imidazolidine-4-carboxylic acid methyl ester (18)** were always obtained. **17** and **18** were easily separated by column chromatography (1/1.8 hexane/EtOAc).

17: white foam that was recrystallized from EtOAc/hexane to give white crystals: mp 94 °C dec; $[\alpha]^{20}_D$ −15.2° (*c* 1.57, $CHCl_3$); IR (KBr) 1708, 1454, 1407, 1210 cm^{-1}; ^1H NMR δ 7.64 (d, *J* = 6.7 Hz, 3H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.38−7.19 (m, 9H), 6.56 (s, 1H), 3.99 (d, *J* = 2.6 Hz, 1H), 3.79 (s, 1H), 3.30 (s, 3H), 1.97 (s, 3H); ^{13}C NMR δ 204.6, 171.0, 161.1, 146.8, 146.1, 141.7, 140.2, 139.9, 129.3, 129.0, 128.5, 128.2, 128.0, 127.9, 127.1, 126.5, 125.4, 120.0, 119.8, 72.7, 61.2, 59.4, 52.3, 25.4.

18: white foam that was recrystallized from Et_2O/hexane to give white crystals: mp 114 °C dec; $[\alpha]^{20}_D$ +48.9° (*c* 0.65, $CHCl_3$); IR (KBr) 3397, 1745, 1703, 1444, 1205 cm^{-1}; ^1H NMR δ 7.70−7.63 (m, 3H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.46−7.16 (m, 9H), 6.01 (s, 1H), 3.73 (d, *J* = 3.7 Hz, 1H), 3.32 (s, 3H), 3.17 (d, *J* = 3.3 Hz, 1H), 2.41 (s, 1H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 172.4, 161.6, 147.0, 146.4, 142.0, 140.5, 140.0, 129.2, 128.9, 128.4, 128.2, 128.0, 127.7, 126.9, 125.6, 119.8 (2 × C), 72.8, 71.2, 62.0, 59.8, 52.0, 25.0, 23.4. Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.3; H, 5.9; N, 6.3. Found: C, 73.3; H, 6.1; N, 6.0.

(4*S*,5*S*)-1-Benzyl-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4,5-dicarboxylic Acid Dimethyl Ester (20). A suspension of **19** (1050 mg, 2.373 mmol) and Pd/$BaCO_3$ (210 mg, 5%) in MeOH (30 mL, deoxygenated with Ar) was stirred under 1 atm of H_2 for 3 h. The reaction mixture was filtered (Celite), the filter cake was washed with 1/1 CH_2Cl_2/MeOH, and the combined filtrate was concentrated to give a white foam that was dissolved in CH_2Cl_2 (4 mL). A solution of Na_2CO_3 (503 mg, 4.746 mmol) in H_2O (1.7 mL, deoxygenated with Ar) and BrBn (0.310 mL, 2.610 mmol) were added to the above solution. The resulting mixture was heated at reflux for 54 h and then partitioned between Et_2O (150 mL) and H_2O (150 mL). The aqueous phase was washed with Et_2O (2 × 80 mL), and the combined organic phase was washed with brine (150 mL), dried, and concentrated to give **dimethyl (2*S*,3*S*)-*N*-(9′-phenylfluoren-9′-yl)-3-(benzylamino)aspartate** as a white foam. [Purification of the crude product by column chromatography (6.5/1 hexane/EtOAc) led to the pure compound that could be recrystallized from hexane to give white crystals.] Cl_2CO (4.3 mL, 8.3 mmol, 1.93 M in toluene) was slowly added to a stirred solution of the above foam and DMAP (29 mg, 0.237 mmol) in pyridine (14 mL) at 70 °C. After 20 min of stirring the brown mixture was cooled in an ice-water bath and MeOH (4 mL) was added. The resulting mixture was partitioned between CH_2Cl_2 (150 mL) and H_3PO_4 (1 M, 150 mL), the aqueous phase was washed with CH_2Cl_2 (2 × 100 mL), and the combined organic phase was washed with H_3PO_4 (1 M, 3 × 100 mL) and brine (100 mL), dried, and concentrated to give a residue that was triturated in hot hexane (2 × 30 mL) and Et_2O (20 mL) to give **20** (1003 mg, 79%) as a white crystalline solid that was recrystallized from EtOAc/hexane to give white microcrystals. Purification of the mother liquors by short column chromatography (70−230 mesh, 3.25/1 hexane/EtOAc) afforded **20** (45 mg, 83% combined yield).

Dimethyl (2*S*,3*S*)-*N*-(9′-phenylfluoren-9′-yl)-3-(benzylamino)aspartate: mp 91 °C; $[\alpha]^{20}_D$ −268.4° (*c* 2.12, $CHCl_3$); IR (KBr) 3349, 1740 cm^{-1}; ^1H NMR δ 7.64 (t, *J* = 6.6 Hz, 2H), 7.38−7.21 (m, 16H), 3.91 (d, *J* = 13.6 Hz, 1H), 3.49 (d, *J* = 14.0 Hz, 1H), 3.43 (s, 3H), 3.28 (s, 3H), 3.23 (bs, 1H), 2.99 (bs, 1H), 2.40 (bs, 1H); ^{13}C NMR δ 173.5, 172.4, 148.9, 147.8, 144.4, 141.0, 140.0, 139.8, 128.4, 128.3, 128.2, 127.8, 127.3, 127.2, 127.0, 126.9, 126.1, 125.7, 119.8, 119.7, 72.6, 62.6, 57.9, 51.9, 51.7 (2 × C). Anal. Calcd for $C_{32}H_{30}N_2O_4 \cdot 0.5H_2O$: C, 74.5; H, 6.1; N, 5.4. Found: C, 74.3; H, 5.8; N, 5.3.

20: mp 194 °C; $[\alpha]^{20}_D$ −45.7° (*c* 1.15, $CHCl_3$); IR (KBr) 1737, 1710 cm^{-1}; ^1H NMR δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.46−7.18 (m, 14H), 4.88 (d, *J* = 15.2 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.93 (d, *J* = 2.8 Hz, 1H), 3.68 (d, *J* = 2.8 Hz, 1H), 3.54 (s, 3H), 3.18 (s, 3H); ^{13}C NMR δ 170.4, 169.7, 158.8, 146.9, 146.1, 141.8, 140.2, 140.0, 136.1, 129.1, 128.9, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.1, 126.6, 125.5, 119.9, 119.7, 72.9, 58.4, 57.8, 52.5, 52.0, 46.5. Anal. Calcd for $C_{33}H_{28}N_2O_5$: C, 74.4; H, 5.3; N, 5.3. Found: C, 74.3; H, 5.3; N, 5.1.

(4*S*,5*S*)-5-Acetyl-1-benzyl-2-oxo-3-(9′-phenylfluoren-9′-yl)imidazolidine-4-carboxylic Acid Methyl Ester (21a). MeLi (1.41 mL, 1.972 mmol, 105 mol %, 1.4 M in Et_2O) was added dropwise to a stirred solution of **20** (1000 mg, 1.878 mmol, 100 mol %) in THF (19.5 mL) at −78 °C. The resulting orange solution was stirred at −78 °C for 45 min, then acetone (0.55 mL, 7.512 mmol) was added, and after 5 min of stirring at −78 °C the reaction was quenched with HCl (5%, 3 mL). The resulting mixture was allowed to warm to room temperature and was partitioned between CH_2Cl_2 (100 mL) and HCl (5%, 80 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 70 mL), and the combined organic phase was washed with brine (100 mL), dried, and concentrated to give a residue that was purified by short column chromatography (70−230 mesh, 3/1 hexane/EtOAc) to give **21a** (892 mg, 92%) as a white crystalline solid that was recrystallized from EtOAc/hexane to give white microcrystals: mp 188 °C; $[\alpha]^{20}_D$ +93.5° (*c* 1.57, $CHCl_3$); IR (KBr) 1746, 1717 cm^{-1}; ^1H NMR δ 7.68−7.58 (m, 4H), 7.48−7.16 (m, 14H), 4.80 (d, *J* = 15.1 Hz, 1H), 4.03 (d, *J* = 15.1 Hz, 1H), 3.55 (d, *J* = 3.9 Hz, 1H), 3.50 (d, *J* = 3.9 Hz, 1H), 3.28 (s, 3H), 1.64 (s, 3H); ^{13}C NMR δ 204.2, 170.9, 159.5, 146.4, 146.2, 141.4, 140.5, 139.9, 135.9, 129.5, 129.1, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 127.3, 126.6, 125.7, 120.0, 119.9, 73.3, 63.9, 57.3, 52.3, 47.0, 24.7. Anal. Calcd for $C_{33}H_{28}N_2O_4$: C, 76.7; H, 5.5; N, 5.4. Found: C, 76.6; H, 5.6; N, 5.2.

(4*S*,5*S*)-1-Benzyl-2-oxo-5-pentanoyl-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic Acid Methyl Ester (21c). nBuLi (0.255 mL, 0.293 mmol, 125 mol %, 1.15 M in hexane) was added dropwise to a stirred solution of **20** (125 mg, 0.235 mmol) in THF (2.3 mL) at −78 °C. The resulting orange solution was stirred at −78 °C for 45 min, then HCO_2Et (0.038 mL, 0.469 mmol) was added, and after 3 min of stirring at −78 °C the reaction was quenched with H_3PO_4 (1 M, 1 mL). The resulting mixture was allowed to warm to room temperature and was partitioned between CH_2Cl_2 (50 mL) and H_3PO_4 (1 M, 40 mL). The aqueous phase was washed with CH_2Cl_2 (40 mL), and the combined organic phase was washed with brine (50 mL), dried, and concentrated to give a residue that was purified by column chromatography (6/1 hexane/EtOAc) to afford 23 mg (18%) of recovered **20** and 70 mg of a white crystalline solid, unseparable mixture of **21c** (50%, 61% based on recovered **20**) and a product of unknown structure in a ratio of 14:1. Pure **21c** as white crystals was obtained by recrystallization from EtOAc/hexane: mp 139 °C; $[\alpha]^{20}_D$ +73.1° (*c* 1.02, $CHCl_3$); IR (KBr) 1751, 1705 cm^{-1}; ^1H NMR δ 7.67−7.15 (m, 18H), 4.82 (d, J = 15.1 Hz, 1H), 3.99 (d, J = 15.1 Hz, 1H), 3.57 (d, J = 3.5 Hz, 1H), 3.49 (d, J = 3.5 Hz, 1H), 3.28 (s, 3H), 2.02 (dt, J = 7.4 Hz, J = 17.7 Hz, 1H), 1.81 (dt, J = 6.9 Hz, J = 17.6 Hz, 1H), 1.24 (quint, J = 6.9 Hz, 2H), 1.03 (sext, J = 7.3 Hz, 2H), 0.78 (t, J = 7.04 Hz, 3H); ^{13}C NMR δ 206.2, 171.0, 159.5, 146.6, 146.2, 141.5, 140.4, 139.9, 136.0, 129.4, 129.0, 128.7, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.2, 126.7, 125.7, 119.9, 119.8, 73.2, 63.4, 57.4, 52.3, 47.0, 37.4, 25.0, 21.9, 13.6. Anal. Calcd for $C_{36}H_{34}N_2O_4 \cdot 0.75\ H_2O$: C, 75.6; H, 6.3; N, 4.9. Found: C, 75.6; H, 6.1; N, 5.1.

(4*S*,5*S*)-5-Benzoyl-1-benzyl-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic Acid Methyl Ester (21d). nBuLi (0.255 mL, 0.293 mmol, 125 mol %, 1.15 M in hexane) was added dropwise to a stirred solution of PhBr (0.035 mL, 0.329 mmol, 140 mol %) in THF (1 mL) at −78 °C. The resulting solution was stirred at −78 °C for 22 min and then cannulated dropwise at −78 °C to a precooled (−78 °C) solution of **20** (125 mg, 0.235 mmol, 100 mol %) in THF (1.3 mL). The resulting pale orange solution was stirred at −78 °C for 45 min, then HCO_2Et (0.038 mL, 0.469 mmol) was added, and after 3 min the reaction was quenched with H_3PO_4 (1 M, 1 mL). The reaction mixture was allowed to reach room temperature and was partitioned between CH_2Cl_2 (50 mL) and H_3PO_4 (1 M, 50 mL). The aqueous phase was washed with CH_2Cl_2 (50 mL), and the combined organic phase was washed with brine (50 mL), dried, and concentrated to give a residue that was purified by column chromatography (3.7/1 hexane/EtOAc) to afford 124 mg of a white foam, unseparable mixture of **21d** (85%) and a product of unknown structure in a ratio of 14:1. Pure **21d** (85 mg, 63%) as white crystals was obtained by recrystallization from Et_2O/hexane: mp 189−191 °C; $[\alpha]^{20}_D$ −145.6° (*c* 1.08, $CHCl_3$); IR (KBr) 1750, 1718, 1683 cm^{-1}; ^1H NMR δ 7.95 (d, J = 6.9 Hz, 1H), 7.71−7.51 (m, 5H), 7.44−7.12 (m, 17H), 5.07 (d, J = 15.4 Hz, 1H), 4.57 (d, J = 2.4 Hz, 1H), 3.95 (d, J = 2.5 Hz, 1H), 3.85 (d, J = 15.4 Hz, 1H), 3.16 (s, 3H); ^{13}C NMR δ 194.6, 170.6, 159.2, 147.4, 145.9, 142.1, 140.1, 139.9, 136.4, 134.1, 133.8, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.5, 127.1, 126.6, 125.4, 119.9, 119.4, 72.7, 59.6, 58.9, 52.1, 46.3. Anal. Calcd for $C_{38}H_{30}N_2O_4$: C, 78.9; H, 5.2; N, 4.8. Found: C, 78.8; H, 5.2; N, 4.7.

(4*S*,5*S*)-5-(2^{IV}-Ethoxyacryloyl)-1-benzyl-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic Acid Methyl Ester (21e). Ethyl vinyl ether (0.054 mL, 0.563 mmol, 300 mol %) was added to THF (0.65 mL) at −78 °C. Then *t*-BuLi (0.226 mL, 0.469 mmol, 250 mol %, 2.08 M in pentane) was added dropwise, and the resulting yellow solution was allowed to reach 0 °C for 2 h 5 min and then was stirred at this temperature for an additional 45 min. The 1-ethoxy-1-lithioethene colorless solution was cooled to −78 °C and then cannulated dropwise at −78 °C over a solution of **20** (100 mg, 0.188 mmol) in THF (1.4 mL) at −78 °C. The resulting yellow solution was stirred from −78 to −55 °C for 45 min and then at −55 °C for 35 min. The reaction was quenched with HCO_2Et (0.076 mL, 0.939 mmol), and after 3 min at −55 °C, H_3PO_4 (1 M, 1 mL) was added and the reaction was allowed to reach room temperature and was distributed between CH_2Cl_2 (20 mL) and H_3PO_4 (1 M, 15 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 20 mL), and the combined organic phase was washed with brine (40 mL), dried, and concentrated to give a residue that was purified by short column chromatography (70−230 mesh, 3.7/1 hexane/EtOAc with 0.2% of Et_3N) to give **21e** (84 mg, 78%) as a white crystalline solid that was recrystallized from EtOAc/hexane to give white crystals: mp 152−157 °C; $[\alpha]^{20}_D$ −202.4° (*c* 0.99, $CHCl_3$); IR (KBr) 1709 cm^{-1}; ^1H NMR δ 8.00 (dd, J = 1.4 Hz, J = 6.3 Hz, 1H), 7.62 (t, J = 8.6 Hz, 2H), 7.42−7.16 (m, 15H), 5.23 (d, J = 2.7 Hz, 1H), 5.06 (d, J = 15.6 Hz, 1H), 4.44 (d, J = 2.7 Hz, 1H), 4.36 (d, J = 2.1 Hz, 1H), 3.92−3.86 (m, 2H), 3.66 (*c*, J = 7.0 Hz, 2H), 3.06 (s, 3H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 192.1, 169.9, 159.1, 155.5, 147.5, 145.9, 142.2, 140.3, 139.9, 136.9, 129.0, 128.8, 128.4, 128.3, 128.0, 127.3, 127.1, 126.4, 125.3, 120.0, 119.4, 93.0, 72.5, 63.9, 59.1, 58.1, 51.7, 46.1, 13.6. Anal. Calcd for $C_{36}H_{32}N_2O_5$: C, 75.5; H, 5.6; N, 4.9. Found: C, 75.5; H, 5.7; N, 4.7.

(4*S*,5*S*,1^{IV}*S*)-1-Benzyl-5-(1^{IV}-hydroxy-2^{IV}-chloroethyl)-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic Acid Methyl Ester (22). MeLi (1.88 mL, 3.756 mmol, 200 mol %, 2.0 M in Et_2O) was added dropwise to a stirred solution of **20** (1000 mg, 1.878 mmol), chloroiodomethane (0.297 mL, 4.075 mmol, 217 mol %), and LiBr (245 mg, 2.817 mmol, 150 mol %) in THF (19 mL) at −78 °C. The resulting yellow solution was stirred at −78 °C for 75 min, then HCO_2Et (0.607 mL, 7.512 mmol) was added, and after 3 min of stirring, the reaction was quenched with H_3PO_4 (1 M, 2 mL). The resulting mixture was allowed to warm to room temperature and was partitioned between CH_2Cl_2 (100 mL) and H_3PO_4 (1 M, 75 mL). The aqueous phase was washed with CH_2Cl_2 (75 mL), and the combined organic phase was washed with saturated $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried, and concentrated to give pure **(4*S*,5*S*)-1-benzyl-5-(2^{IV}-chloroacetyl)-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic acid methyl ester (21b)** as a white foam (recrystallization of the crude product from EtOAc/hexane led to white crystals). The above crude was divided in four flasks which were dried under vacuum for 16 h at 65 °C; then aliquots of THF (16.4 mL in total) were added and the solutions were stirred in the presence of 3 Å molecular sieves for 2 h 15 min at room temperature. After each solution was cooled at −78 °C, aliquots of $LiEt_3BH$ (4.42 mL in total, 3.756 mmol, 200 mol %, 0.85 M in THF) were added dropwise. The resulting yellow solutions were stirred at −78 °C for 2 h and then were quenched with AcOH (0.376 mL in total, 6.573 mmol, deoxygenated with Ar), stirred for 3 min at −78 °C, and warmed to −15 °C. $LiOH \cdot H_2O$ (473 mg in total, 11.268 mmol) and H_2O_2 (30%, deoxygenated with Ar, 2 mL in total) were added, and after 20 min of stirring at −15 °C H_3PO_4 (1 M, 4 mL in total) was added. The resulting mixtures were allowed to warm to room temperature, combined, and partitioned between CH_2Cl_2 (125 mL) and H_3PO_4 (1 M, 75 mL). The aqueous phase was washed with CH_2Cl_2 (100 mL) and the combined organic phase was washed with brine (75 mL), dried, and concentrated to give a residue (ratio of isomers 7:1) that was recrystallized twice from EtOAc/hexane to give a first (484 mg, 47%) and a second crop (102 mg, 10%) of pure **22** as white crystals. The mother liquours were purified by column chromatography (2.2/1 hexane/EtOAc) to give a mixture of isomers **22**:**23**, 1:1 (210 mg, 20%), as a white crystalline solid, that could be recrystallized twice from EtOAc/hexane to give pure **22**.

21b: mp 174−176 °C; $[\alpha]^{20}_D$ +34.6° (*c* 2.84, $CHCl_3$); IR (KBr) 1744, 1708 cm^{-1}; ^1H NMR δ 7.67 (d, J = 6.3 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.47−7.16 (m, 14H), 4.74 (d, J = 15.1 Hz, 1H), 4.07 (d, J = 15.0 Hz, 1H), 3.85 (d, J = 3.6 Hz, 1H), 3.63 (d, J = 16.1 Hz, 1H), 3.58 (d, J = 3.6 Hz, 1H), 3.50 (d, J = 16.0 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR δ 197.9, 170.4, 159.2, 146.6, 146.0, 141.3, 140.4, 140.0, 135.7, 129.6, 129.1, 128.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.3, 126.5, 125.7, 120.1, 119.9, 73.4, 61.7, 57.6, 52.3, 47.4, 44.5. Anal. Calcd for $C_{33}H_{27}N_2O_4Cl \cdot 0.25\ H_2O$: C, 71.3; H, 5.0; N, 5.0. Found: C, 71.4; H, 4.9; N, 5.1.

22: mp 210 °C; $[\alpha]^{20}_D$ +39.2° (*c* 1.17, $CHCl_3$); IR (KBr) 3392, 1737, 1690, 1450 cm^{-1}; ^1H NMR δ 7.71−7.61 (m, 4H), 7.49 (d,

J = 7.0 Hz, 2H), 7.43−7.18 (m, 12H), 4.65 (d, J = 15.3 Hz, 1H), 4.20 (d, J = 15.4 Hz, 1H), 3.68−3.63 (m, 2H), 3.38 (t, J = 2.1 Hz, 1H), 3.26 (dd, J = 7.2 Hz, J = 11.5 Hz, 1H), 3.21 (s, 3H), 3.07 (dd, J = 6.0 Hz, J = 11.4 Hz, 1H), 2,11 (bs, 1H); ^{13}C NMR δ 172.0, 160.1, 146.8, 146.2, 141.9, 140.6, 140.0, 137.0, 129.4, 128.9, 128.8, 128.4, 128.3, 128.0, 127.8, 127.7, 127.1, 126.5, 125.6, 120.0, 119.9, 73.4, 70.1, 58.3, 55.7, 52.1, 46.7, 43.7.

(4*S*,5*S*,1^{IV}*R*)-1-Benzyl-5-(1^{IV}-hydroxy-2^{IV}-chloroethyl)-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic Acid Methyl Ester (23). Same procedure as above. From **20** (205 mg, 0.385 mmol), chloroiodomethane (0.061 mL, 0.835 mmol, 217 mol %), LiBr (50 mg, 0.577 mmol, 150 mol %), and MeLi (0.467 mL, 0.770 mmol, 200 mol %, 1.65 M in Et_2O), a residue of pure **21b** was obtained as a foam. DIBAL-H (0.577 mL, 0.577 mmol, 1 M in hexane) was added dropwise to a solution of the above crude in CH_2Cl_2 (4.9 mL) at −78 °C. The mixture was stirred for 70 min at −78 °C and then was quenched with EtOAc (1 mL). The resulting mixture was stirred for 3 min at −78 °C and then was allowed to reach room temperature and was concentrated to give a residue that was dissolved in $CHCl_3$ (4 mL). Saturated K_2CO_3 (3 drops) was added, and the residue was stirred until turbidness was seen. Then, KH_2PO_4 (500 mg) and Na_2SO_4 were added and after 3 min of stirring the residue was filtered and concentrated to give a crude product (ratio of isomers **22**:**23** = 1:5.4) that was purified by column chromatography (70−230 mesh, 2.5/1 hexane/EtOAc) to give **23** (152 mg; ratio of isomers **22**:**23** = 1:10; 71% overall yield) as a white foam. An analytical sample of pure **23** (ratio of isomers = 1:40), as white crystals, was obtained by recystallizing twice from EtOAc/hexane; this mixture was used for the caracterization of **23** (**23** partially epimerizes in $CDCl_3$ after 1 day): mp 200−205 °C; $[\alpha]^{20}_D$ +90.2° (*c* 0.59, $CHCl_3$); ^{1}H NMR δ 7.73−7.63 (m, 4H), 7.54−7.16 (m, 14H), 4.80 (d, J = 15.3 Hz, 1H), 4.08 (d, J = 15.3 Hz, 1H), 3.60−3.55 (m, 1H), 3.51 (d, J = 3.7 Hz, 1H), 3.38 (t, J = 4.0 Hz, 1H), 3.24 (s, 3H), 3.16 (dd, J = 3.8 Hz, J = 11.4 Hz, 1H), 2.82 (dd, J = 8.7 Hz, J = 11.3 Hz, 1H), 2.24 (d, J = 5.3 Hz, 1H); ^{13}C NMR δ 171.8, 160.2, 146.52, 146.49, 141.5, 140.5, 139.8, 136.5, 129.4, 129.1, 128.7, 128.3, 128.2, 127.8, 127.7, 127.2, 126.4, 125.6, 120.0, 73.4, 72.2, 57.7, 57.0, 52.1, 47.8, 44.8. Anal. Calcd for $C_{33}H_{29}N_2O_4Cl$: C, 71.7; H, 5.3; N, 5.1. Found: C, 71.6; H, 5.3; N, 5.1.

Lactam 25. A solution of **22** (152 mg, 0.275 mmol) and NaN_3 (54 mg, 0.825 mmol) in DMF (1.1 mL) was heated at 110 °C for 6 h 30 min, then allowed to reach room temperature, and partitioned between EtOAc (40 mL) and H_2O (30 mL). The organic phase was washed with H_2O (30 mL) and the combined aqueous phase, with EtOAc (40 mL). The combined organic phase was washed with brine (50 mL), dried, and concentrated to give a residue of **(4*S*,5*S*,1^{IV}*R*)-1-benzyl-5-(1^{IV}-hydroxy-2^{IV}-azidoethyl)-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic acid methyl ester (24)** [purification of the crude product by short column chromatography (70−230 mesh, 2.5/1 hexane/EtOAc) afforded pure **24** (90%) as a white crystalline solid that could be recrystallized from EtOAc/hexane to give white crystals]. A solution of the above crude **24** and LiOH·H_2O (161 mg, 3.848 mmol) in dioxane (1.5 mL)−H_2O (0.75 mL) was stirred at room temperature for 14 h. Then HCl (5%) was added until pH = 2 and the mixture was extracted with EtOAc (2 × 65 mL). The combined organic phase was washed with brine (80 mL), dried, and concentrated to give **(4*S*,5*S*,1^{IV}*R*)-1-benzyl-5-(1^{IV}-hydroxy-2^{IV}-azidoethyl)-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic acid** as a white solid (an analytical sample, as white crystals, was obtained by recrystallization of the crude product from EtOAc/hexane). A mixture of the above crude product, *p*-TsOH·H_2O (57 mg, 0.302 mmol, 110 mol %), and Pd/C (10%, 34 mg) in MeOH (deoxygenated with Ar, 3.1 mL) was hydrogenated (1 atm) for 75 min and then filtered (Celite) and concentrated to give a residue that was dissolved in DMF (6.0 mL). Et_3N (0.096 mL, 0.687 mmol, 250 mol %) was added, and the resulting solution was cooled to 0 °C. DPPA (0.080 mL, 0.371 mmol, 135 mol %) was added, and stirring was continued at 0 °C for 5.5 h; then the reaction was allowed to reach room temperature. After 22 h of total reaction time, the reaction mixture was partitioned between EtOAc (65 mL) and H_2O (65 mL). The organic phase was washed with H_2O (65 mL) and the combined aqueous phase with EtOAc (65 mL). The combined organic phase was washed with brine (100 mL), dried, and concentrated to give a residue that was purified by column cromatography [70−230 mesh, CH_2Cl_2/MeOH (2%)/Et_3N (0.1%)] to give pure **25** (77 mg, 56% overall yield) as a white crystalline solid that could be recrystallized from EtOAc/hexane to give white crystals (**25** after 1 day in $CDCl_3$ partially descomposes to give another product, probably the *cis*-fused bicycle).

24: mp 155−158 °C; $[\alpha]^{20}_D$ +44.9° (*c* 0.94, $CHCl_3$); IR (KBr) 3391, 2101, 1744, 1688 cm^{-1}; ^{1}H NMR δ 7.73 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.44−7.19 (m, 12H), 4.60 (d, J = 15.4 Hz, 1H), 4.26 (d, J = 15.4 Hz, 1H), 3.63 (d, J = 4.6 Hz, 1H), 3.56−3.53 (m, 1H), 3.26 (s, 3H), 3.23 (dd, J = 1.9 Hz, J = 4.5 Hz, 1H), 3.13 (dd, J = 7.8 Hz, J = 12.5 Hz, 1H), 2.78 (dd, J = 5.1 Hz, J = 12.6 Hz, 1H), 1.69 (d, J = 3.2 Hz, 1H); ^{13}C NMR δ 172.0, 160.1, 146.8, 146.2, 141.8, 140.6, 139.9, 137.0, 129.4, 128.9, 128.8, 128.4, 128.3, 127.9, 127.8, 127.1, 126.6, 125.6, 120.0, 119.9, 73.4, 68.8, 58.6, 55.8, 52.1, 51.4, 46.6. Anal. Calcd for $C_{33}H_{29}N_5O_4$: C, 70.8; H, 5.2; N, 12.5. Found: C, 70.6; H, 5.2; N, 12.4.

(4*S*,5*S*,1^{IV}*R*)-1-Benzyl-5-(1^{IV}-hydroxy-2^{IV}-azidoethyl)-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic acid: mp 230−231 °C dec; $[\alpha]^{20}_D$ +38.4° (*c* 0.75, CH_3OH); IR (KBr) 3503, 2115, 1735, 1685 cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$] δ 7.79−7.70 (m, 4H), 7.52−7.48 (m, 2H), 7.43−7.11 (m, 12H), 4.83 (d, J = 15.7 Hz, 1H), 4.14 (d, J = 15.7 Hz, 1H), 3.92−3.86 (m, 2H), 3.37 (dd, J = 1.9 Hz, J = 4.1 Hz, 1H), 3.19 (dd, J = 8.0 Hz, J = 12.8 Hz, 1H), 2.87 (dd, J = 4.6 Hz, J = 12.8 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$] δ 173.5, 160.5, 148.7, 148.0, 144.5, 141.7, 141.1, 138.5, 129.9, 129.6, 129.4, 129.1, 128.8, 128.7, 128.6, 128.1, 127.4, 126.7, 120.8, 120.6, 74.1, 69.9, 60.0, 56.8, 52.9, 46.2. Anal. Calcd for $C_{32}H_{27}N_5O_4$·0.25 H_2O: C, 69.9; H, 5.0; N, 12.7. Found: C, 69.9; H, 5.0; N, 12.9.

25: mp ≈240−260 °C dec; $[\alpha]^{20}_D$ −109.4° (*c* 1.42, Cl_3CH); IR (KBr) 3377, 1700 cm^{-1}; ^{1}H NMR δ 7.98 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.35−7.17 (m, 14H), 4.99 (d, J = 4.9 Hz, 1H), 4.78 (d, J = 14.7 Hz, 1H), 4.09 (d, J = 12.2 Hz, 1H), 3.95−3.84, m, 2H), 3.45−3.34 (m, 1H), 3.05 (dd, J = 3.0 Hz, J = 12.0 Hz, 1H), 2.90 (d, J = 13.4 Hz, 1H), 1.22 (s, 1H); ^{13}C NMR δ 170.4, 163.3, 147.4, 145.9, 143.2, 141.7, 139.9, 137.1, 129.7, 129.3, 128.8, 128.6, 128.3, 128.2, 127.5, 127.4, 126.8, 126.5, 125.3, 119.7, 119.1, 74.2, 61.8, 60.9, 54.5, 48.4, 47.0. Anal. Calcd for $C_{32}H_{27}N_3O_3$: C, 76.6; H, 5.4; N, 8.4. Found: C, 76.5; H, 5.4; N, 8.2.

Lactam 26. TFA (0.070 mL) was added to a solution of **25** (16 mg, 0.032 mmol) in CH_2Cl_2 (0.350 mL). The resulting red solution was stirred at room temperature for 90 min and then concentrated. The residue was washed with Et_2O (4 × 7 mL) to give pure **26** (7 mg, 84%) as a white crystalline solid that could be recrystallized from CH_2Cl_2/MeOH/Et_2O to give white crystals: mp ≈ 226−260 °C dec; $[\alpha]^{20}_D$ −87.6° (*c* 0.29, CH_3OH); IR (KBr) 3370, 3328, 3298, 3250, 1710, 1683, 1668 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.34 (s, 5H), 4.78 (d, J = 15.2 Hz, 1H), 4.37−4.34 (m, 1H), 4.30 (d, J = 13.3 Hz, 1H), 4.17 (d, J = 15.2 Hz, 1H), 3.53 (dd, J = 5.3 Hz, J = 14.1 Hz, 1H), 3.28 -3.17 (m, 2H); ^{13}C NMR (CD_3OD) δ 172.1, 166.0, 137.5, 129.9, 129.6, 128.9, 61.8, 61.5, 51.3, 50.5, 47.0. Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.7; H, 5.8; N, 16.1. Found: C, 59.3; H, 5.8; N, 16.5.

(4*S*,5*S*,1^{IV}*S*,2^{V}*R*)-1-Benzyl-5-[2^{IV}-chloro-1^{IV}-(methoxyphenylacetoxy)ethyl]-2-oxo-3-(9″-phenylfluoren-9″-yl)-imidazolidine-4-carboxylic Acid Methyl Ester (28a). A solution of **22** (37 mg, 0.067 mmol), (*R*)-methoxyphenylacetic acid (17 mg, 0.100 mmol), DCC (21 mg, 0.100 mmol), and DMAP (1 mg, 0.008 mmol) in CH_2Cl_2 (0.7 mL) was stirred at room temperature for 90 min. H_3PO_4 (1 M, 1 mL) was then added, and after 10 min of stirring, the mixture was partitioned between Et_2O (20 mL) and H_3PO_4 (1 M, 20 mL). The organic phase was washed with H_3PO_4 (1 M, 20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL), filtered (through a cotton plug), dried, and concentrated to give a residue that was purified by short column chromatography (5/1 hexane/EtOAc)

to give **28a** (47 mg, 100%) as a white crystalline solid. An analytical sample, as white crystals, was obtained by recrystallization from EtOAc/hexane: mp 165 °C; $[\alpha]^{20}_D$ +45.0° (*c* 1.0, $CHCl_3$); IR (KBr) 1766, 1751, 1705 cm^{-1}; ^1H NMR δ 7.71−7.70 (m, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.47−7.45 (m, 2H), 7.41−7.19 (m, 15H), 7.10−7.08 (m, 2H), 4.89 (dt, J = 3.5 Hz, J = 5.7 Hz, 1H), 4.77 (d, J = 15.3 Hz, 1H), 4.68 (s, 1H), 3.73 (d, J = 15.3 Hz, 1H), 3.54 (d J = 4.5 Hz, 1H), 3.44 (t, J = 3.9 Hz, 1H), 3.36 (s, 3H), 3.34 (dd, J = 6.2 Hz, J = 11.9 Hz, 1H), 3.08 (s, 3H), 3.10−3.07 (m, 1H); ^{13}C NMR δ 171.0, 170.0, 159.7, 146.6, 146.2, 141.6, 140.4, 140.0, 136.0, 135.4, 129.4, 129.1, 128.9, 128.6, 128.5, 128.3, 127.8, 127.7, 127.2, 127.1, 126.7, 125.6, 120.0, 119.9, 82.4, 73.1, 73.0, 57.3, 57.2, 55.9, 52.1, 46.7, 40.3. Anal. Calcd for $C_{42}H_{37}N_2O_6Cl$: C, 71.9; H, 5.3; N, 4.0. Found: C, 71.9; H, 5.3; N, 4.2.

(4*S*,5*S*,1^{IV}*S*,2^{V}*S*)-1-Benzyl-5-[2^{IV}-chloro-1^{IV}-(methoxyphenylacetoxy)ethyl]-2-oxo-3-(9″-phenylfluoren-9″-yl)imidazolidine-4-carboxylic Acid Methyl Ester (28b). Same procedure as above. From **22** (33 mg, 0.060 mmol), (*S*)-methoxyphenylacetic acid (15 mg, 0.090 mmol), DCC (18 mg, 0.090 mmol), and DMAP (1 mg, 0.008 mmol) was obtained a residue that was purified by short column chromatography (4/1 hexane/EtOAc) to give **28b** (42 mg, 100%) as a white foam. An analytical sample, as white crystals, was obtained by recrystallization from Et_2O/hexane: mp 146−149 °C; $[\alpha]^{20}_D$ +181.1° (*c* 1.05, $CHCl_3$); ^1H NMR δ 7.78 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.50−7.43 (m, 5H), 7.36−7.23 (m, 14H), 7.19 (t, J = 7.6 Hz, 1H), 5.06 (dt, J = 1.2 Hz, J = 6.8 Hz, 1H), 4.93 (d, J = 15.5 Hz, 1H), 4.35 (s, 1H), 3.98 (d, J = 15.4 Hz, 1H), 3.56 (d, J = 5.1 Hz, 1H), 3.51−3.49 (m, 1H), 3.37 (s, 3H), 3.23 (s, 3H), 3.00 (dd, J = 6.4 Hz, J = 11.8 Hz, 1H), 2.91 (dd, J = 6.8 Hz, J = 11.7 Hz, 1H); ^{13}C NMR δ 171.7, 169.6, 159.7, 146.6, 146.4, 141.7, 140.9, 139.9, 135.8, 135.5, 129.4, 129.1, 129.0, 128.73, 128.70, 128.3, 128.2, 127.8, 127.7, 127.2, 125.5, 120.02, 119.96, 81.4, 73.3, 70.6, 57.1, 56.3, 55.7, 52.3, 46.2, 39.7. Anal. Calcd for $C_{42}H_{37}N_2O_6Cl$: C, 71.9; H, 5.3; N, 4.0. Found: C, 71.6; H, 5.3; N, 4.1.

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