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Synthesis of Kainoids and C4 Derivatives

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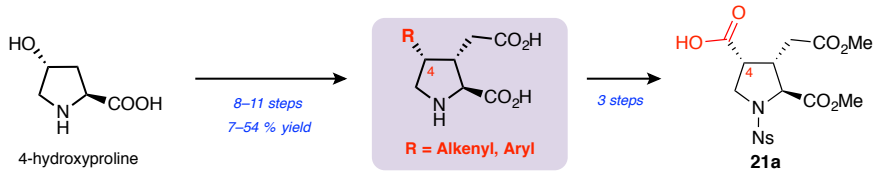
Supporting Information Placeholder



ABSTRACT: A unified stereoselective synthesis of 4-substituted kainoids is reported. Four kainic acid analogs were obtained in 8 to 11 steps with up to 54% overall yields. Starting from *trans*-4-hydroxy-*L*-proline, the sequence enables a late-stage modification of C4 substituents with of sp^2 nucleophiles. Stereoselective steps include a cerium-promoted nucleophilic addition and a palladium-catalyzed reduction. A 10-step route to acid **21a** was also established to enable ready functionalization of the C4 position.

Kainoids are a group of non-proteinogenic amino acids displaying strong neurological activity.[1] The title compound of the family, kainic acid (KA, **1**) and its epimer allokainic acid (**2**) were isolated from the marine algae *Digenea simplex* in 1953 (Figure 1).[2] The selectivity of **1** for a subset of ionotropic glutamate receptors even led to naming them as kainate receptors (GluK1-5).[3] Kainic acid is now commonly used in neurobiology research to study conditions such as epilepsy, Huntington's, Parkinson's and Alzheimer's diseases.[4] Biological testing of KA analogs revealed that the neuroactivity of KA is highly dependent on its C4 substituent. For instance, synthetic derivatives such as phenylkainic acid (**4**),[5] acromelic acid (**5**),[5] and thiazole analog **6**[6] all display equal or higher potency than kainic acid. Herein, we report a synthesis of kainoids that allows access to C4 derivatives via late-stage divergence.

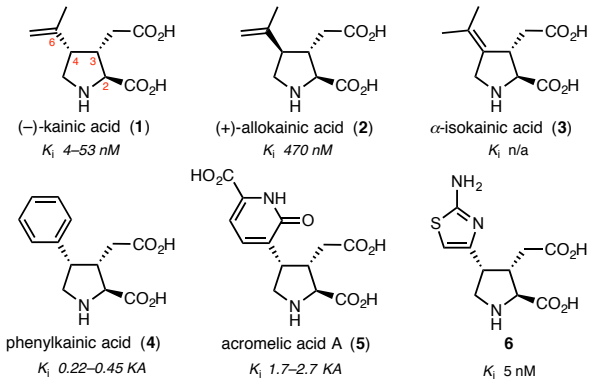


Figure 1. Naturally occurring (1–3, 5) and synthetic kainoids (4 and 6). Potency is indicated as absolute value or relative to kainic acid's.

Kainoids are a popular synthetic target: close to 70 syntheses of kainic acid, allokainic acid, isokainic acid, and phenylkainic acid have been reported.[1,2,7-9] The shortest synthesis of kainic acid was accomplished by Ohshima in six steps,[9] however, it does not allow for ready variation of the C4 position.

Structure-activity relationship studies have confirmed that the C4 substituent of kainoids is the only position that can be exploited to enhance the activity of kainic acid.[5,11] Compiling the biological studies conducted with kainic acid analogs over the past 30 years reveals that only sp^2-hybridized C4 substituents display a high affinity for GluK receptors.[12] As part of our research program in neuron-glia communication, we required a GluK chemical probe bearing a reporter tag at C4. We reasoned that an ideal approach would enable late-stage introduction of sp^2-hybridized nucleophiles at the C4 position. A route to phenylkainic acid reported by Baldwin in 1995 provided a potential framework that could be modified for our purpose.[10] Accordingly, we developed a pragmatic route that can deliver large amounts of C4 kainoid derivatives for cell and animal assays.[13]

The synthesis begins with a two-step protection of *trans*-4-hydroxy-*L*-proline, followed by a Swern oxidation to obtain pyrrolidinone **10** (Scheme 1).[14] The choice of protecting group for the amine is crucial for the subsequent C3 alkylation leading to **11**.[14b] Indeed, Lubell and Rapoport's phenylfluorenyl (Pf) protecting group [15,16] was unique in achieving enolate alkylation regioselectively at the more hindered *alpha* position of ketone **10**. Initial trials with Boc or Cbz were unproductive, leading to poor regioselectivity or stereoselectivity. While Pf's large steric bulk was essential to control selectivity, it later offered its share of challenges.

Alkylation of the C3 ester side chain to obtain the desired *trans* diester **11a** is highly sensitive to reactions conditions (Table 1). We selected a *tert*-butyl ester because it allowed us to unambiguously assign the stereochemistry of compounds

Scheme 1. Synthesis of pyrrolidin-4-one 11a

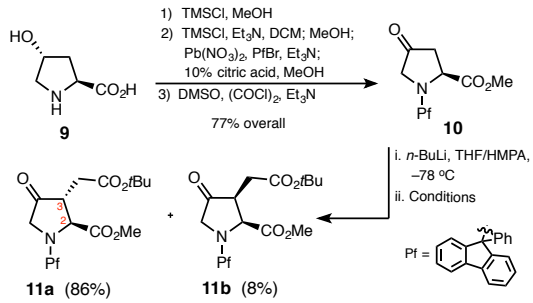


Table 1. Stereoselective alkylation of ketone 10

Entry	Halide	Conditions	Conversion (%)[a]	dr[a] 11a:11b
1[b]	$BrCH_2CO_2tBu$ (3.5 eq)	–41 °C, 3h	100	5:1
2[c]	ICH_2CO_2tBu (5.0 eq)	–41 °C, 5.5 h	100	9:1[d]
3[c]	ICH_2CO_2tBu (6.0 eq)	–78 °C, 5 h	60	10:1
4[c]	ICH_2CO_2tBu (3.5 eq)	–78 °C, 5 h	50	14:1

[a] Determined by ^{1}H NMR analysis of crude products. [b] Reaction conditions: 1:5 HMPA/THF; 0.5 equiv. NaI, halide (Method B in supp. info.). [c] 1:10 HMPA/THF; halide (Method A in supp. info.). [d] After purification, the ratio of isolated products was 10.8:1.

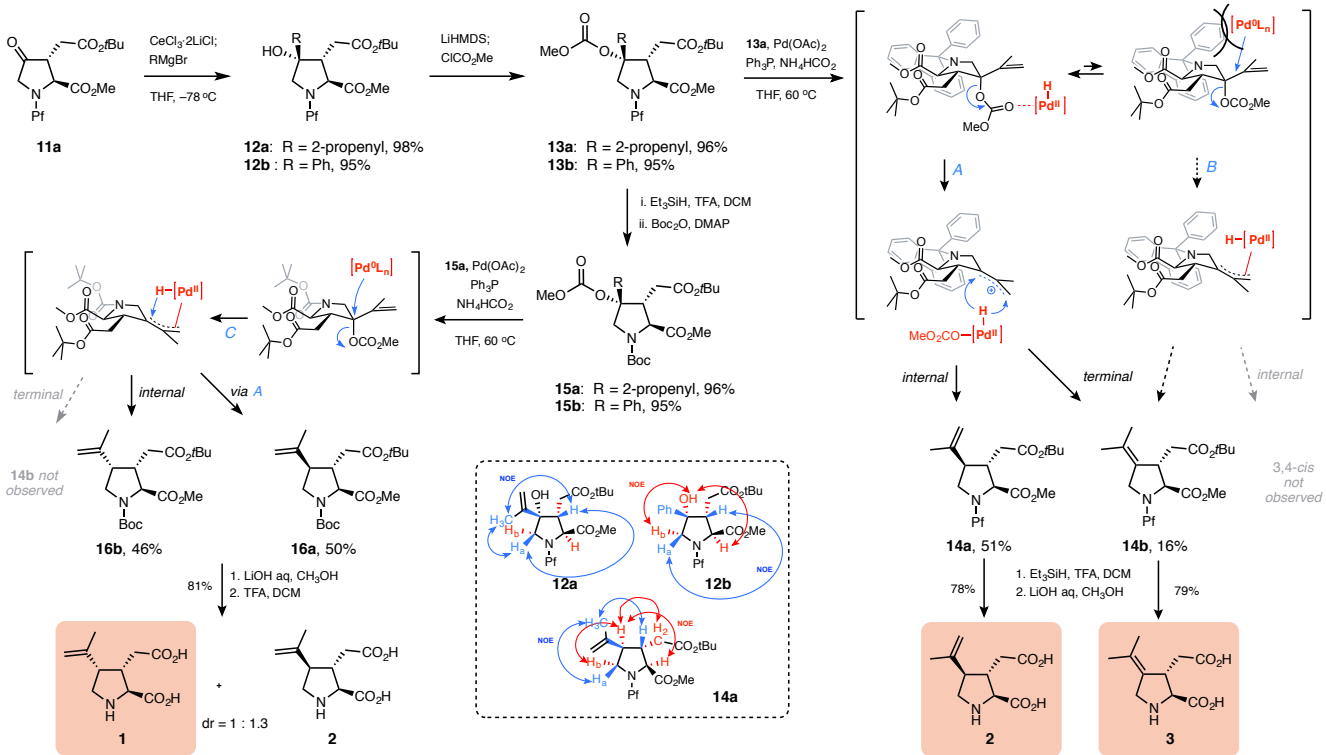
12–**14** (reduced conformational flexibility greatly enhances NOE). Adapting conditions for a related alkylation using a catalytic amount of NaI[14b,c] yielded a 5:1 ratio when the reaction was performed on >5 grams scale using $BrCH_2CO_2tBu$ (entry 1). Instead, using *tert*-butyl iodoacetate directly, the ratio was improved to 14:1, although the conversion was sluggish (entry 4). Increasing equivalents and temperature afforded an acceptable compromise in terms of conversion and selectivity (entries 2 and 3). The stereochemistry of **11a** and **11b** was determined by ^{1}H NMR analysis: the $J_{H2\text{-}3}$ value for the *trans* product **11a** is 6.1 Hz, and that of **11b** is 8.2 Hz.[14]

Stereoselective Addition of *sp*² Nucleophiles. Next, we turned to the key installation of side chains at the C4 position of **11a** (Scheme 2). When ketone **11a** was treated with alkenyl or aromatic Grignard reagents, only starting material **11** epimerized at C3 was recovered. We explored less basic organocerium reagents to promote the addition. We found that using $CeCl_3$·2LiCl (1.3 equiv. for **12a**, 3.0 equiv. for **12b**) afforded alcohols **12** as single diastereomers with an almost quantitative yield.[17] The presence of LiCl is essential to full obtain conversion with **11a**, and the reaction worked equally well with *i*-Pr- and Ph- organometallic reagents. Baldwin *et al.* reported a similar strategy using *N*-Bz proline ketone with PhMgBr and $CeCl_3$ that afforded a 52% yield.[10] However, the more sterically demanding *N*-Pf protected **11a** led to poor conversion with $CeCl_3$. For instance, using *i*-PrMgBr/$CeCl_3$ gave only 5% yield, and PhMgBr/$CeCl_3$ gave **12b** in 16% yield with C3 epimerized. NOE experiments confirmed the stereochemistry of the C4 centers (Scheme 2).

Synthesis of Natural Kainoids. Deoxygenation of tertiary alcohols **12a** and **12b** posed a significant challenge of chemoselectivity. Traditional radical-based deoxygenation methods failed, so we examined the reactivity of the parent carbonates (Scheme 2). Allylic carbonate **13a** was reduced via a catalytic transfer hydrogenation using ammonium formate and palladium acetate[18] to afford a 3:1 regioisomeric mixture of allokainic acid precursor **14a** and isokainic acid precursor **14b**.[19]

The *cis*-C3,C4 diastereomer of **14** (precursor of kainic acid) was not observed under these reduction conditions. The steric bulk of the *N*-Pf protecting group likely prevents the catalyst from approaching the top face of the allylic carbonate (*viz.* path B, Scheme 2). We surmise that competing catalytic pathways take place. For instance, the sterically congested substrate **13** may slow the antiperiplanar addition of Pd(0) to the allylic system, and a Pd(II) complex may act as Lewis acid toward the carbonate group. The resulting transient allylic

Scheme 2. Synthesis of key intermediates



carbocation then gets reduced from the same face as the leaving group. To solve this problem, the amine's Pf protecting group was replaced by a less bulky Boc. Extensive optimization was needed to selectively cleave the Pf group without losing the *tert*-butyl ester or epimerizing C3. We found buffered reductive conditions that are compatible with: tertiary alcohols, allylic carbonates, *tert*-butyl carbonates, and esters (summarized in Table 2). We settled on using Et_3SiH with TFA in dichloromethane, which led to quantitative removal of *N*-Pf (entries 2 and 3). Alternatively, Et_3SiH with I_2 in acetonitrile was also efficient, but led to the loss of the *tert*-butyl group (entry 4). Using Rapoport's original conditions (excess TFA)[20] removed the Pf group, however the *tert*-butyl ester was quite prone to elimination and high yields were difficult to reproduce (entry 1). With **13** deprotected, the resulting pyrrolidine was directly subjected to standard Boc protection conditions to afford carbamates **15a** and **15b** in excellent yields. The catalytic hydrogenolysis of allylic carbonate **15a** with $Pd(OAc)_2$ and formate afforded **16a** and **16b** as a 1.1:1 mixture of C4 epimers. Improving the ratio for kainic acid precursor **16b** remained elusive, despite several attempts.

Table 2. Deprotection of *N*-phenylfluorenyl (*N*-Pf)

Cmpd	Conditions	Yield	Byproduct
12a/b	TFA (15 eq.), DCM, 1 h	90% [a]	PfOH
12a/b	Et_3SiH (3 eq.), TFA (5 eq.), DCM, 1 h	Quant.	PfH
13a/b	Et_3SiH (3 eq.), TFA (5 eq.), DCM, 1 h	Quant.	PfH
13a/b	Et_3SiH (2 eq.), I_2 (1 eq.), MeCN, 10 min.	Quant. [b]	PfH

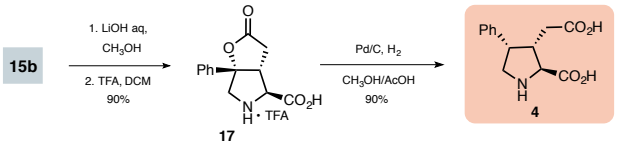
(a) ~10% *tert*-Butyl ester was converted to the parent acid.

(b) *tert*-Butyl ester was also deprotected under these conditions.

Kainic acid (**1**), allokainic acid (**2**), and isokainic acid (**3**) were obtained via global deprotection of **16b**, **14a** and **14b**, respectively (Scheme 2). A telescoped sequence was used for **14a** and **14b**: the reductive Pf deprotection was followed by a mildly alkaline hydrolysis. Natural products **2** and **3** were obtained in 78% and 79% yields, respectively, without epimerization of the C2 or C4 stereocenters. NMR spectra of **2** and **3** are consistent with reported data (Table S1, SI). The ~1:1 mixture of *N*-Boc protected diesters **16a** and **16b** was also deprotected with a telescoped sequence: alkaline hydrolysis followed by anhydrous TFA treatment led to kainic acid (**1**, 35%) and allokainic acid (**2**, 46%). Separation of **1** and **2** by crystallization and HPLC proved challenging. While it was possible to obtain analytically pure samples for characterization, the bulk of the products remained a mixture. Regardless, this **1**/**2** mixture is useful to us—and we expect to others—as it enables the gram-scale synthesis of thiazole **6** in four steps, currently the most potent GluK receptor agonist.[6]

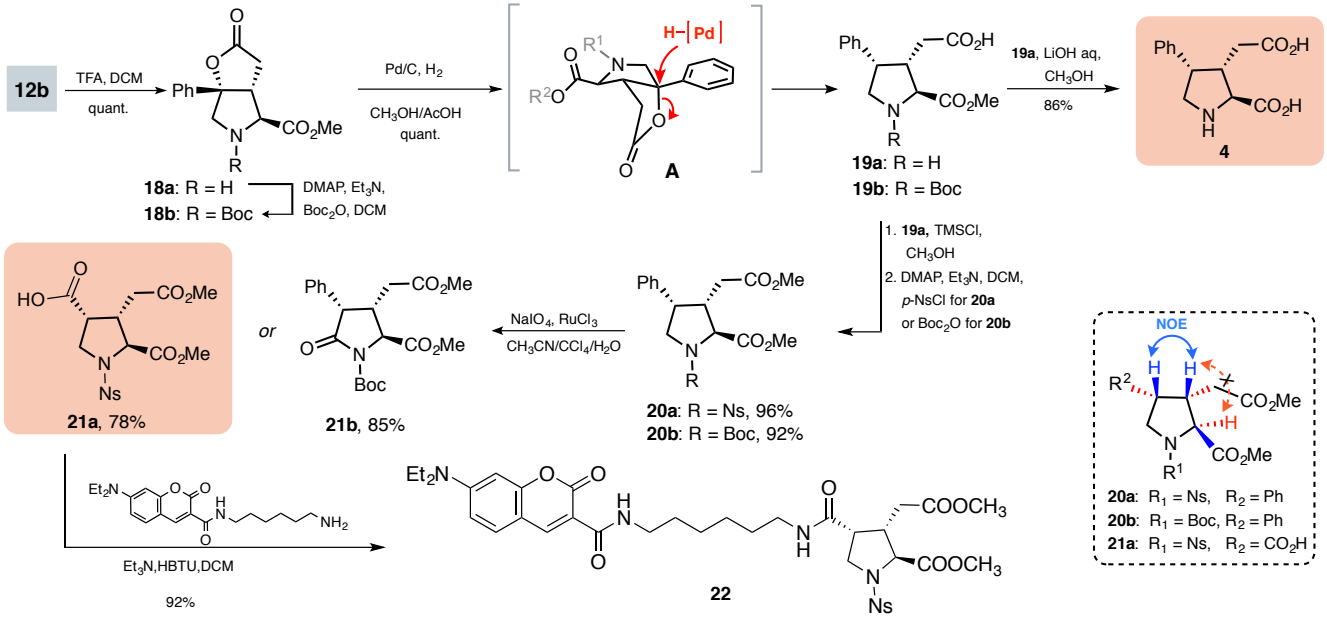
Synthesis of Non-natural Kainic Acid Derivatives. Inspired by the lactone hydrogenolysis reaction developed by Baldwin *et al.*,[10] we attempted to invert the C4 stereocenter with hydrogenation (Scheme 3). Upon full deprotection, carbonate **15b** spontaneously cyclized to lactone **17** (sparingly soluble in DMSO). This lactone was then ring-opened with inversion of stereochemistry under standard hydrogenation conditions using Pd/C. Phenylkainic acid (**4**) was obtained as a single diastereomer in 90% yield from **17**.

Scheme 3. First attempt of phenylkainic acid synthesis



Alternatively, we shortened the above path by directly cyclizing alcohol **12b** to lactone **18a** under excess of TFA. Lactone **18** was hydrogenolyzed to yield phenylkainic ester **19** as a single diastereomer (Scheme 4). Compared to Baldwin's synthesis of phenylkainic acid (9 steps, 11% overall yield),[10] the route presented herein compares favorably: **4** is obtained in 8 steps with an overall yield of 54%. Stereochemistry of the phenyl group in **4** was confirmed by ^1H NMR spectroscopic analyses and is consistent with literature data (Table S1, SI).[6b,21] The *cis*-C3,C4 stereochemistry was further confirmed by NOE analysis of the subsequent products **20a** and **20b** (Scheme 4).

Scheme 4 Synthesis and Functionalization of Phenylkainic Acid. (*p*-Ns = *p*-nitrobenzenesulfonyl)



Our need for kainic acid-based chemical probes motivated us to exploit our most efficient route: that leading to intermediate **19a** in 7 steps (Scheme 4). Chemoselective oxidation of the C4-phenyl group to a carboxylic acid would provide a versatile synthetic handle to append any side chain at a late stage. Accordingly, diester amine **19a** was converted to the *N*-Boc diester **20b** in two steps. However, when **20b** was presented to $RuCl_3$ and $NaIO_4$, the phenyl group remained untouched and only the C5 position of the pyrrolidine was oxidized to pyrrolidinone **21b**. Instead of Boc, a *p*-nitrobenzenesulfonyl (Ns) protecting group was selected for its ability to deactivate the *N-alpha* position and its mild deprotection condition (ArSH, K_2CO_3, DMF).[22] Thus **19a** was converted to the *N*-Ns amide **20a** in two steps and almost quantitative yield. The phenyl group of **20a** was oxidized selectively and afforded the desired acid **21a** in 78% yield without epimerization (stereochemistry confirmed by NOE analysis).

The C4-acid kainoid **21a** provides easy access to a variety of kainoid derivatives. It enables the synthesis of numbers of heteroaromatic kainoids.[23] In addition, our ongoing work toward kainoid-based GluK imaging probes confirms that **21a** can be readily coupled to fluorescent dyes, further studies will be reported in due course.

In summary, a unified diastereoselective route to 4-substituted kainoids was demonstrated from commercially available *trans*-4-hydroxy-*L*-proline. The sequence affords: kainic acid (**1**, 11 steps, 19%), allokainic acid (**2**, 9 steps, 24%), isokainic acid (**3**, 9 steps, 8%), and phenylkainic acid (**4**, 8 steps, 54%). In addition, a mild oxidaton step has been developed for C4 derivatization from **4**. The novel intermediate **21a** (10 steps, 47%) enables the rapid synthesis of a variety of non-natural kainoids via amide coupling. This report provides a general access to a range of biologically active 4-substituted kainoids.

EXPERIMENTAL SECTION

General Information. NMR spectra were acquired on a 400 MHz Varian NMR AS400 equiped with an ATB-400 probe at 25 °C. Infrared spectra (IR) were obtained using a Nicolet 6700 FT-IR spectrometer (compounds 9-16) as a neat film on a NaCl plate, or a Perkin-Elmer FT-IR Spectrum Two IR spectrometer. High resolution mass spectrometry analyses recorded with a HCTultra PTM Discovery System, or with a Waters Micromass LCT Premier TOF Mass Spectrometer. Melting points of solid samples were measured with a IA9200 melting point apparatus (Electrothermal). Column chromatography was carried on silica gel (230-400, Silicycle, Quebec). The mixture of kainic acid and allokainic acid was purified using a Varian ProStar HPLC system with a C18 column (Eclipse Plus C18, 4.6 × 250 mm, 5 μm, Agilent).

tert-Butyl iodoacetate. To a rigorously stirred solution of magnesium sulfate (52.0 g, 432 mmol) in dichloromethane (300 mL) were added concentrated sulfuric acid (3.8 mL, 72 mmol) slowly. After 10 mins, bromoacetic acid (20.0 g, 144 mmol) was added at r.t., followed by addition of *tert*-butyl alcohol (41.2 mL, 432 mmol). After 24 h, a second portion of tert-butyl alcohol (20.5 mL, 216 mmol) was added to take the reaction to completion in an additional 24 h. The insoluble matter in resulted reaction solution was removed by vacuum filtration. The filtrate was transferred to a separatory funnel, and washed with 200 mL water, 200 mL saturated sodium bicarbonate. The aqeous layer was extracted with dichloromethane (3×50 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude *tert*-butyl bromoacetate as a light-yellow liquid (26.9 g, 96%), which was used for the following reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 2H), 1.48 (s, 9H) ppm. ^{13}C NMR (101 MHz, CDCl3) δ 166.2, 82.9, 27.8, 27.7 ppm. *tert*-butyl iodoacetate was prepared according to a literature procedure from the above *tert*-butyl bromoacetate.[24] *tert*-butyl bromoacetate (25.2 g, 128 mmol) was added at r.t. to a suspension of NaI (23.1 g, 154 mmol) in acetone (200 mL) under a nitrogen atmosphere; the resulting suspension was stirred for 5 hours. The insoluble salt was removed by vacuum filtration. and the filtrate was concentrated under reduced pressure. The residue was redissolved in diethyl ether (150 mL) and washed with 100 mL basic Na_2S_2O3 aqueous solution (5% wt. in aqueous saturated sodium bicarbonate), brine (100 mL). The obtained organic layer was dried over $MgSO_4$, filtered under vacuum. The resulted solution was concentrated under reduced pressure to afford *tert*-butyl iodoacetate as a pale-yellow liquid (29.4 g, 95%). The crude product tert-butyl iodoacetate was dried over 4 Å molecular sieve to remove the trace water residue before use. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 2H), 1.46 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 82.3, 27.6, -2.6 ppm.

9-Bromo-9-phenylfluorene (**PfBr**). To a suspension of magnesium turnings (9.2 g, 382 mmol) in anhydrous THF (5 mL) under argon atmosphere, 0.5 mL bromobenzene was added neat at r.t. in one portion to initiate the reaction. The reaction vessel was cooled to 0 °C on an ice bath, followed by dropwise addition of a THF solution of bromobenzene (1.2 M, 270 mL) at 0 °C. The resulted reaction solution was allowed to r.t. and stirred vigorously for an additional 2 h. The exact concentration of the resulted phenyl magnesium bromide solution was determined by titration with salicylaldehyde phenylhydrazone.[25] This phenyl magnesium bromide solution (180 mL, 216 mmol) was transferred into a flame-dried single neck flask by a syringe. To this solution, $CeCl_3$·2LiCl (15 mL, 0.1 M) THF solution was added in one portion, 9-fluorenone (30.1 g, 186 mmol) was added by portions. 15 mins later, TLC analysis showed full conversion. The reaction was quenched with diluted hydrochloric acid (1.0 M, 100 mL) at 0 °C. The resulted solution was extracted with Et_2O (3×150 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and was concentrated under reduced pressure to yield **PfOH** as pale-yellow crystals (40.8 g, 95%). Mp 108-109 °C. FTIR (thin film): 3544, 3423, 3059, 1603, 1448, 774, 732, 701cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 2H), 7.53 – 7.41 (m, 4H), 7.34 (dq, J = 15.1, 7.5 Hz, 7H), 2.79 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 143.2, 139.5, 129.0, 128.4, 128.2, 127.2, 125.4, 124.8, 120.1, 83.6 ppm. **PfBr** was prepared according to the reported procedure.[26] The above **PfOH** (36.1 g, 140 mmol) was dissolved in toluene (150 mL) and aqueous HBr (48% w/w, 50 mL) was added at r.t.. This heterogeneous mixture was stirred vigorously at r.t. for 48 h, away from light. The mixture was then extracted with toluene (3 × 100 mL). The combined organic layer was washed with brine (6 × 150 mL), dried over $MgSO_4$, filtered, and was concentrated under reduced pressure to afford the crude product as a light-yellow solid. Recrystallization with hexane afforded pale-yellow crystals (40.2 g, 90%). Mp 100-101 °C. FTIR (thin film): 3056, 1603, 837, 738, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dt, J = 7.6, 0.9 Hz, 2H), 7.60 – 7.49 (m, 4H), 7.36 (td, J = 7.5, 1.2 Hz, 2H), 7.35 – 7.18 (m, 5H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 141.1, 138.1, 129.0, 128.5, 128.3, 128.0, 127.4, 126.1, 120.3, 67.5 ppm.

(2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid methyl ester hydrochloride (**9a**). *trans*-4-hydroxyl-*L*-proline (10.0 g, 76 mmol) was suspended in methanol (150 mL) under argon. The suspension was cooled to 0 ºC in an ice bath, followed by dropwise addition of chlorotrimethylsilane (33.9 mL, 267 mmol). After 30 min., it was allowed to warm up to r.t. and stirred overnight. The solvent was removed under reduced pressure, the residue was triturated with Et_2O (100 mL) and the ester **9a** was obtained as white crystals (13.1 g, 95%). ^{1}H NMR (400 MHz, D_2O) δ: 4.78–4.68 (m, 2H), 3.88 (s, 3H), 3.56 (dd, *J* = 12.6, 3.8 Hz, 1H), 3.44 (dt, *J* = 12.5, 1.6 Hz, 1H), 2.52 (ddt, *J* = 14.3, 7.8, 1.8 Hz, 1H), 2.32 (ddd, *J* = 14.5, 10.5, 4.3 Hz, 1H) ppm. ^{13}C NMR (101 MHz, D_2O) δ 170.2, 69.4, 58.1, 53.8, 53.4, 36.6 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_6H_{12}NO_3$ 146.0817; Found 146.0817.

Methyl (2S)-4-oxo-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (**10**). **10** was prepared according to reported procedures from **9a** by two steps with an overall yield of 81%.[19a] FTIR (thin film): 3060, 2949, 2838, 1758, 1739, 745, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.62 (m, 2H), 7.49 – 7.40 (m, 3H), 7.44 – 7.35 (m, 3H), 7.35 – 7.16 (m, 5H), 3.76 (d, *J* = 17.8 Hz, 1H), 3.76 (dd, *J* = 8.6, 2.9 Hz, 1H), 3.48 (dt, *J* = 17.8, 1.2 Hz, 1H), 3.20 (s, 3H), 2.44 (dd, *J* = 18.1, 8.6 Hz, 1H), 2.29 (dd, J = 18.1, 2.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.9, 173.1, 146.5, 145.3, 141.8, 140.9, 140.3, 128.9, 128.9, 128.6, 128.0, 127.7, 127.6, 127.0, 126.9, 125.5, 120.3, 120.1, 76.0, 58.2, 55.2, 51.5, 51.5, 41.6 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{25}H_{22}NO_3$ 384.1600; Found 384.1602.

Methyl (2S,3R)-3-[2-tert-butoxy]-2-oxoethyl]-4-oxo-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (**11a**) *and Methyl (2S,3S)-3-[2-(tert-butoxy)-2-oxoethyl]-4-oxo-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2carboxylate* (**11b**).

Method A: Ketone 10 (6.0 g, 16 mmol) was dissolved in THF (41.0 mL) and anhydrous HMPA (4.1 mL) in a single-neck flask, and under an Ar atmosphere. The solution was cooled to –78 ºC on a dry ice/acetone bath, followed by a dropwise addition of n-butyllithium (2.1 M in cyclohexane, 7.8 mL, 16 mmol). After 30 mins, *tert*-butyl iodoacetate (18.9 g, 79 mmol) was added dropwise to the reaction. The solution was allowed to wamr up to -41 ºC (dry ice/acetonitrile bath) and stirred for an additional 5.5 h. The reaction was quenched at -41 °C by a quick addition of phosphoric acid (10% wt., 15 mL) and allowed warm up to r.t. Water (50 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvents were evaporated under reduced pressure to yield the alkylated products **11a** and **11b**. The diastereomeric ratio was determined with ^{1}H NMR of the crude product; dr = 9:1 with ketones **11a** as the major isomer. The crude products from method A were retaken in MeOH (5 mL) and stored at –20 ºC overnight in a freezer. The white solid formed was filtered and washed with cold methanol (5 mL) to yield **11a** as white solid (6.2 g). The mother liquor's solvents were removed, and the residue was purified by column chromatography on silica gel (15-25% EtOAc/hexane as elution gradient) to yield **11a** (525 mg) and **11b** (621 mg, 8%) as white foam-like solid.

Method B: Adapted from a reported procedure[14]; $BrCH_2COOtBu$ (3.5 eq) /NaI (0.5 eq). The alkylated ketones **11a** and **11b** were recovered with a dr = 5:1 (^{1}H NMR analysis of the crude).

trans-Ketodiester **11a** (major: 6.725 g, 86%): FTIR (thin film): 2974, 1758, 1730, 742, 698 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 1.0 Hz, 2H), 7.50 (dt, *J* = 7.6, 1.6 Hz, 3H), 7.43 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.32 – 7.21 (m, 5H), 3.78 (d, *J* = 17.6 Hz, 1H), 3.45 (d, *J* = 17.6 Hz, 1H), 3.44 (d, *J* = 6.1 Hz, 1H), 3.10 (s, 3H), 2.82 (dd, *J* = 12.4, 6.2 Hz, 1H), 2.45 – 2.38 (m, 2H), 1.31 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8, 172.9, 169.6, 146.0, 144.4, 141.4, 141.1, 140.4, 128.9, 128.5, 127.9, 127.8, 127.7, 127.3, 127.0, 126.0, 120.2, 120.0, 81.4, 75.8, 63.7, 55.7, 51.5, 49.2, 34.2, 27.9 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{31}H_{32}NO_5$ 498.2280; Found 498.2278.

cis-Ketodiester **11b** (minor, 621 mg, 8%):FTIR (thin film): 2974, 1758, 1727, 748, 694 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.41 (ddt, *J* = 9.0, 5.1, 1.6 Hz, 5H), 7.33 (dtd, *J* = 17.9, 7.4, 1.1 Hz, 3H), 7.24 (dt, *J* = 7.0, 1.1 Hz, 3H), 4.02 (d, *J* = 8.2 Hz, 1H), 3.80 (d, *J* = 17.6 Hz, 1H), 3.58 (dd, *J* = 17.6, 1.1 Hz, 1H), 3.15 (s, 3H), 3.11 – 3.01 (m, 1H), 2.57 (dd, *J* = 17.4, 5.2 Hz, 1H), 1.84 (dd, *J* = 17.4, 8.9 Hz, 1H), 1.34 (s, 9H) ppm. ^{13} C NMR (101 MHz, $CDCl_3$) δ 212.2, 171.7, 170.3, 146.9, 145.3, 141.7, 141.3, 139.8, 128.9, 128.8, 128.6, 128.1, 127.7, 127.6, 126.8, 126.7, 125.4, 120.1, 81.1, 75.4, 61.9, 53.7, 51.1, 48.0, 31.1, 28.0 ppm. HRMS (ESI-TOF) m/z $(M+H)^+$ Calcd for $C_{31}H_{32}NO_5$ 498.2280; Found 498.2275.

Methyl (2S,3R,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-hydroxy-1-(9-phenyl-9H-fluoren-9-yl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylate (**12a**). A single-neck flask was charged with magnesium turnings (322 mg, 13.1 mmol) and dry THF (20 mL) under argon atmosphere, followed by dropwise addition of 2-bromopropene (1.10 mL, 12.4 mmol) at rt. The suspension was stirred for 2 h, a gradually turned to a pale-yellow solution. The resulting isopropenyl magnesium bromide solution was titrated using salicylaldehyde phenylhydrazone.[26]

Into a single-neck flask, ketone **11a** (4.105 g, 8.25 mmol) was loaded, purged with argon, and a $CeCl_3$·2LiCl solution in THF (107 mL, 0.1 M) was added via syringe at r.t. The clear solution was cooled to –78 ºC and stirred for 15 mins. The *i*-PrMgBr solution (19.5 mL, 0.55 M) was added dropwise at –78 ºC. After 2 h, the reaction was quenched at –78 ºC with a diluted 0.1 M HCl aqueous solution (10 mL). The biphasic mixture was extracted with Et_2O (2 × 100 mL), washed with brine, dried over MgSO4 and filtered. The solvent was evaporated under reduced pressure to afford tertiary alcohol **12a** as a white foam-like solid (4.305 g, 98%), which was used without further purification. FTIR (thin film): 3510, 3060, 2978, 2949, 2885, 1715, 1706, 788, 745, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (d, J = 7.6 Hz, 1H), 7.67–7.50 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.39–7.28 (m, 5H), 7.23–7.09 (m, 2H), 5.13 (s, 1H), 4.91 (s, 1H), 3.72 (d, *J* = 12.1 Hz, 1H), 3.18 (s, 3H), 3.07 (d, *J* = 3.9 Hz, 1H), 3.06 (d, *J* = 17.7 Hz, 1H), 2.85 (dt, *J* = 9.7, 6.2 Hz, 1H), 2.22 (dd, *J* = 16.3, 5.4 Hz, 1H), 1.99 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.82 (s, 3H), 1.78 (s, 1H), 1.30 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.9, 171.5, 146.8, 146.4, 144.6, 142.8, 141.7, 139.7, 129.0, 128.4, 128.3, 127.9, 127.7, 127.4, 127.3, 127.0, 126.2, 120.1, 119.7, 113.0, 81.9, 80.6, 66.3, 61.2, 51.3, 47.0, 32.3, 29.7, 27.9, 19.6 ppm. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{34}H_{38}NO_5$ 540.2744; Found 540.2730.

Methyl (2S,3R,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-hydroxy-4-phenyl-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (**12b**). Proceeded as described for **12a** with the following modifications: **11a** (2.530 g, 5.08 mmol), phenyl magnesium bromide (12 mL, 1.1 M), and $CeCl_3$·2LiCl (127 mL, 0.1 M). The crude product was purified by silica-gel chromatography with ethyl acetate/hexanes as eluent (15-25%

gradient). Alcohol **12b** was recovered as a white foam-like solid (2.780 g, 95%). FTIR (thin film): 3506, 3059, 2977, 2946, 2879, 1729, 742, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75 (ddd, *J* = 7.5, 1.2, 0.6 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.59 – 7.53 (m, 4H), 7.45 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.40–7.36 (m, 2H), 7.35–7.28 (m, 4H), 7.25–7.24 (m, 1H), 7.24 – 7.22 (m, 1H), 7.22–7.19 (m, 1H), 7.19–7.16 (m, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.35 (d, *J* = 12.1 Hz, 1H), 3.22 (d, *J* = 12.0 Hz), 3.20 (s, 3H), 3.09–3.01 (m, 1H), 2.20 (dd, *J* = 16.3, 5.6 Hz, 1H), 2.08 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.18 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.9, 171.4, 146.7, 146.5, 142.8, 141.8, 141.6, 139.8, 129.0, 128.5, 128.4, 128.2, 127.9, 127.8, 127.4, 127.3, 127.1, 127.1, 126.1, 125.6, 120.2, 119.8, 81.1, 80.7, 66.4, 65.3, 51.4, 51.1, 32.5, 27.7 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{37}H_{38}NO_5$ 576.2744; Found 576.2738.

Methyl (2S,3R,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-((methoxycarbonyl)oxy)-1-(9-phenyl-9H-fluoren-9-yl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylate (**13a**). Allylic alcohol **12a** (3.8 g, 7.0 mmol) was dissolved in THF (40 mL) under an argon atmosphere, cooled to –78 ºC. Lithium bis(trimethylsilyl)-amide solution (8.5 mL, 1.0 M) was added dropwise, and the reaction was stirred for 20 min. Methyl chloroformate (1.6 mL, 21.1 mmol) was added slowly and allowed to react for 2 h. The reaction was quenched at –78 ºC with saturated ammonium chloride aqueous solution (20 mL), extracted with Et_2O (2 × 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to obtain carbonate **13a** as a white foam-like solid. (4.1 g, 95%). Purity of the crude product was excellent, and **13a** was used as is for the next step. FTIR (thin film): 2978, 2950, 1753, 1731, 786, 745, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.57–7.49 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.41–7.34 (m, 2H), 7.33–7.26 (m, 1H), 7.24–7.09 (m, 5H), 4.96 (s, 1H), 4.87 (s, 1H), 3.98 (d, *J* = 12.9 Hz, 1H), 3.68 (s, 3H), 3.65–3.68 (m, 1H), 3.18 (d, *J* = 8.5 Hz, 1H), 3.15 (s, 3H), 2.80 (dt, *J* = 8.1, 4.7 Hz, 1H), 2.42 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.07 (dd, *J* = 16.9, 7.8 Hz, 1H), 1.90 (s, 3H), 1.31 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.0, 170.8, 153.6, 146.2, 146.1, 142.5, 141.9, 141.1, 140.1, 128.6, 128.4, 128.3, 128.1, 127.4, 127.4, 127.3, 126.9, 126.0, 120.0, 119.7, 90.1, 80.5, 66.0, 55.6, 54.4, 51.3, 48.2, 32.5, 27.9, 20.4 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{36}H_{40}NO_7$ 598.2805; Found 598.2797.

Methyl (2S,3R,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-((methoxycarbonyl)oxy)-4-phenyl-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (**13b**). Proceeded as described for **13a**. Allylic alcohol (450 mg, 0.782 mmol) afforded carbonate **13b** (472 mg, 95%) as a foam-like solid. FTIR (thin film): 3060, 2977, 2952, 1749, 1733, 742, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (ddd, *J* = 7.6, 1.1, 0.6 Hz, 1H), 7.65–7.58 (m, 3H), 7.52–7.48 (m, 1H), 7.45–7.30 (m, 7H), 7.30–7.24 (m, 4H), 7.24–7.15 (m, 2H), 4.34 (d, *J* = 13.0 Hz, 1H), 3.92 (d, *J* = 13.0 Hz, 1H), 3.67 (s, 3H), 3.28 (d, J = 8.2 Hz, 1H), 3.12 (s, 3H), 2.87 (dt, *J* = 8.0, 5.0 Hz, 1H), 2.38 (dd, *J* = 16.8, 5.0 Hz, 1H), 2.13 (dd, *J* = 16.8, 7.9 Hz, 1H), 1.22 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.8, 170.3, 153.7, 146.2, 146.0, 142.4, 141.3, 140.1, 139.2, 128.7, 128.5, 128.4, 128.4, 128.1, 127.6, 127.5, 127.4, 127.3, 126.9, 126.1, 125.0, 120.1, 119.7, 89.5, 80.4, 66.4, 57.8, 54.5, 52.7, 51.3, 32.5, 27.9 ppm. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{39}H_{40}NO_7$ 634.2799; Found 634.2802.

Methyl (2S,3S,4R)-3-(2-(tert-butoxy)-2-oxoethyl)-1-(9-phenyl-9H-fluoren-9-yl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylate (**14a**) and *methyl (2S,3S)-3-(2-(tert-butoxy)-2-oxoethyl)-1-(9-phenyl-9H-fluoren-9-yl)-4-(propan-2-ylidene)pyrrolidine-2-carboxylate* (**14b**). Allylic carbonate **13a** (621 mg, 1.36 mmol), palladium acetate (15 mg, 0.066 mmol), triphenyl phosphine (71 mg, 0.27 mmol), and ammonium formate (427 mg, 6.78 mmol) and THF (10 mL) were charged into a single-neck flask equipped with a condenser. The flask was purged with three vaccum/argon cycles. The reaction vessel was heated at 60 ºC with stirring until full conversion was obsered by TLC (~5 h). The reaction mixture was filtered on a Celite pad and washed with Et_2O (20 mL). The filtrate was concentrated under reduced pressure to a brown oil. The crude oil was purified by silica-gel chromatography with methyl *tert*-butyl ether/hexane as eluent (15-25% gradient). The reduced diesters were recovered as white foam-like solids: **14a** (263 mg, 51%), and **14b** (82 mg, 16%). Diester **14a**: FTIR (thin film): 3059, 2977, 2930, 2855, 1728, 741, 702, 638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.58–7.48 (m, 3H), 7.44 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.37–7.27 (m, 2H), 7.25–7.17 (m, 2H), 7.11 (dt, *J* = 7.5, 1.1 Hz, 1H), 4.75 (s, 2H), 3.43 (t, *J* = 11.1 Hz, 1H), 3.38–3.29 (m, 1H), 3.22 (s, 3H), 2.73–2.67 (m, 1H), 2.60 (dddd, *J* = 14.3, 8.9, 7.0, 5.2 Hz, 1H), 2.27 (dt, *J* = 11.0, 7.9 Hz, 1H), 2.07 (dd, *J* = 16.1, 5.2 Hz, 1H), 1.96 (dd, *J* = 16.1, 7.0 Hz, 1H), 1.69 (s, 3H), 1.29 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.4, 170.7, 147.6, 146.8, 143.9, 142.7, 142.1, 139.3, 128.7, 128.3, 128.2, 128.0, 127.3, 127.2, 127.2, 127.1, 125.7, 120.0, 119.7, 113.5, 80.3, 67.5, 55.1, 52.2, 51.3, 43.9, 37.3, 27.9, 19.0 ppm. HRMS (ESI) m/z $(M+H)^+$ Calcd. for $C_{34}H_{38}NO_4$ 524.2801; Found 524.2805. Diester **14b**: FTIR (thin film): 3061, 2978, 2934, 2867, 1732, 782, 738, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, J = 12.5, 7.5 Hz, 2H), 7.53-7.42 (m, 3H), 7.42-7.27 (m, 4H), 7.25–7.16 (m, 5H), 4.01 (d, J = 12.5 Hz, 1H), 3.76 (d, J = 12.5 Hz, 1H), 3.38–3.25 (m, 1H), 3.02 (s, 3H), 2.93–2.81 (m, 1H), 2.44–2.23 (m, 2H), 1.62 (s, 3H), 1.57 (s, 3H), 1.33 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.9, 171.2, 147.8, 146.1, 142.7, 140.9, 139.8, 133.2, 128.4, 128.3, 128.2, 127.7, 127.4, 127.3, 127.1, 126.9, 125.6, 123.4, 119.9, 119.7, 80.6, 65.0, 50.7, 49.2, 43.0, 40.1, 27.9, 21.3, 20.4 ppm. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{34}H_{38}NO_4$ 524.2801; Found 524.2809.

1-(tert-butyl) 2-methyl (2S,3R,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-((methoxycarbonyl)oxy)-4-(prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate (**15a**). *N*-Pf protected allylic carbonate **13a** (3.010 g, 5.04 mmol) was dissolved in dichloromethane (50 mL) at rt under argon. Triethyl silane (2.4 mL, 15 mmol) was added, followed by the dropwise addition of trifluoroacetic acid (1.9 mL, 25 mmol). The reaction was stirred at rt for 1 h. Solvents were evaporated *in vacuo*; the TFA ammonium salt was recovered as a light yellow waxy solid. The residue was retaken in dichloromethane (50 mL). Di-*tert*-butyl dicarbonate (1.8 g, 8.1 mmol) and 4-dimethylaminopyridine (1.5 g, 10 mmol) were added sequentially, and the reaction was allowed to stir at rt overnight. The reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexanes as eluent (15-25% gradient). *N*-Boc carbonate **15a** was recovered as a colorless oil (2.226 g, 97%). FTIR (thin film): 2979, 1758, 1730, 1707, 850, 791, 770 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, two rotamers) δ: 5.03 (s, 1H), 4.88 (s, 1H), 4.44 (d, *J* = 13.2 Hz, 1H), 4.00 (dd, *J* = 26.5, 9.6 Hz, 1H), 3.87–3.79 (m, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 2.84–2.73 (m, 1H), 2.62 (dd, *J* = 17.5, 4.3 Hz, 1H), 2.39 (ddd, *J* = 17.6, 14.9, 7.6 Hz, 1H), 1.81 (s, 3H), 1.46–1.29 (m, 19H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, two rotamers) δ: 172.5, 172.4, 170.7, 170.6, 154.2, 153.5, 153.4, 153.3, 139.5, 139.4, 114.1, 90.5,

89.7, 81.0, 80.7, 63.5, 63.0, 54.8, 54.7, 52.5, 52.3, 52.2, 52.1, 47.2, 46.6, 31.9, 31.6, 28.3, 28.1, 20.5, 20.4 ppm. HRMS (ESI-TOF) m/z $[M+Na]^+$ Calcd for $C_{22}H_{35}NO_9Na$ 480.2204; Found 480.2221.

1-(tert-Butyl) 2-methyl (2S,3R,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-((methoxycarbonyl)oxy)-4-phenylpyrrolidine-1,2-dicarboxylate (**15b**). Proceeded as described for **15a**. Allylic carbonate **13b** (451 mg, 0.712 mmol) afforded *N*-Boc carbonate **15b** as a colorless liquid (331 mg, 94%). FTIR (thin film): 2974, 1755, 1727, 1705, 843,764, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.35 (m, 2H), 7.34–7.28 (m, 3H), 4.66 (d, J = 13.3 Hz, 1H), 4.27 (t, J = 13.0 Hz, 1H), 4.16 (dd, J = 23.4, 9.5 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 2.89 (ddd, J = 9.6, 7.8, 4.3 Hz, 1H), 2.61–2.43 (m, 2H), 1.45 (s, 9H), 1.31 (s, 9H) ppm.^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.3, 172.2, 170.1, 170.0, 154.1, 153.5, 153.4, 153.3, 136.2, 128.8, 128.8, 128.2, 128.2, 124.7, 124.7, 90.0, 89.3, 80.9, 80.9, 80.7, 80.6, 64.0, 63.5, 54.8, 54.7, 53.9, 53.6, 52.4, 52.2, 52.0, 51.4, 31.7, 31.4, 30.9, 28.3, 28.2, 28.0, 27.9 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd. for $C_{25}H_{36}NO_9$ 494.2385; Found 494.2408.

1-(tert-Butyl) 2-methyl (2S,3S,4R)-3-(2-(tert-butoxy)-2-oxoethyl)-4-(prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate (**16a**) and *1-(tert-Butyl) 2-methyl (2S,3S,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-4-(prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate* (**16b**). Proceeded as described for **14a** and **14b**. Allylic carbonate **15a** (2.010 g, 4.84 mmol) afforded a crude oil which was purified by silica-gel chromatography with ethyl acetate/hexane as eluent (15-25% gradient). Diesters **16a** and **16b** were recovered as an inseparable mixture: cololess oil (1.592 g, 96%). The combined diastereomers were used as is for the next step. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{20}H_{33}NO_6Na$ 406.2200; Found 406.2232.

Allokainic acid (**2**). *N*-Pf protected diester **14a** (103 mg, 0.197 mmol) was dissolved in dichloromethane (1 mL) at rt under argon. Triethyl silane (0.30 mL, 2.0 mmol) was added, followed by trifluoroacetic acid (0.19 mL, 3.0 mmol). The reaction was stirred at rt for 3 h, at which point a second portion of triethyl silane (0.63 mL, 3.9 mmol) and trifluoroacetic acid (0.39 mL, 5.9 mmol) was added. TLC showed full deprotection of the *N*-Pf group after an additional 4 h. The reaction was evaporated to dryness under reduced pressure. The residue was retaken in methanol (3 mL), LiOH aqueous solution (1 mL, 2.5 M) was added, and the reaction was stirred at rt overnight. The reaction was then neutralized at 0 ºC with 1.0 M HCl aqueous solution, and the mixture was diluted with water (20 mL). The Pf-H byproduct was removed by extraction with petroleum ether (2 × 50 mL). The aqueous layer was concentrated to dryness under high vacuum. The residue was retaken in water (5 mL) and purified by ion-exchange chromatography: ion-exchange resin Dowex 50WX4 100-200, eluting with 0.5 N aqueous ammonia. The eluting fractions were collected, and analyzed by TLC for presence of the desired product (TLC plates were dried gently with a heatgun before being stained with ninhydrin; further heating revealed the presence of the amino acid **2** as yellow spots). The fractions containing the product were combined, flash frozen, and the solvents were removed by lyophilization to yield a pale yellow solid. This product was recrystallized with aqueous ethanol (The product was dissolved with minimal water, followed by dropwise addition of ethanol until the crystal formed. It was then left standing at 0 ºC, and allokainic acid was recovered after tirtuation as a white crystalline solid (33 mg, 78%). MP 239–242 ºC. FTIR (thin film): 3451, 2971, 1578 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ: 4.95 (bs, 1H), 4.94 (m, 1H), 3.92 (d, *J* = 8.1 Hz, 1H), 3.51 (dd, *J* = 11.8, 7.8 Hz, 1H), 3.33 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.86 (dt, *J* = 10.5, 8.5 Hz, 1H), 2.72–2.59 (m, 2H), 2.41–2.32 (m, 1H), 1.73 (bs, 3H) ppm. ^{13}C NMR (101 MHz, D_2O) δ: 179.3, 173.7, 140.6, 114.6, 64.9, 51.5, 48.2, 42.6, 39.7, 17.7 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{10}H_{16}NO_4$ 214.1074; Found 214.1074.

Isokainic acid (**3**). Proceeded as described for **2**. Diester **14b** (50 mg, 0.95 mmol) was fully deprotected to afford isokainic **3** acid as a white crystalline solid (16 mg, 79%). MP 241–244 ºC. FTIR (thin film): 3421, 3182, 2920, 1732，1554, 706 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ: 4.16 (d, *J* = 1.6 Hz, 1H), 4.07 (d, *J* = 14.6, 1H), 3.96 (dd, *J* = 14.6, 1.9 Hz, 1H), 3.55 (t, *J* = 6.9 Hz, 1H), 2.51 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.44 (dd, *J* = 14.6, 6.9 Hz, 1H), 1.74 (bs, 3H), 1.65 (bs, 3H) ppm. 13C NMR (101 MHz, D_2O) δ: 179.7, 173.7, 129.8, 125.7, 66.4, 46.7, 42.1, 41.2, 20.4, 20.3 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{10}H_{16}NO_4$ 214.1074; Found 214.1075.

Kainic acid (**1**) and *allo-Kainic acid* (**2**). The diastereomeric mixture of **16a** and **16b** (605 mg, 1.46 mmol) was dissolved in methanol (20 mL), and a LiOH aqueous solution (2.5 N, 9.4 mL) was added and stirred at rt for 5 h. The reaction was neutralized at 0 ºC with diluted 1.0 N HCl aqueous solution, extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over $MgSO_4$, and filtered. The solvents were evaporated under reduced pressure to obtain a colorless oil. The crude oil was retaken in dichloromethane (5.0 mL) under Ar atmosphere, and trifluoroacetic acid (3.0 mL) was added at rt. The solution was stirred for 3 h, then was concentrated to dryness under reduced pressure to afford a light-yellow fluid oil. This crude product was purified and recrystallized as described above for **2**. The product was recovered as a white powder (273 mg, 81%), and consisted of kainic acid (**1**, 43%) and *allo*-kainic acid (**2**, 57%), as determined by ^1H NMR. The mixture of diastereomers proved inseparable with HPLC. Kainic acid (**1**): ^1H NMR (400 MHz, D_2O) δ: 5.08 (bs, 1H), 4.78 (bs, 1H), 4.18 (d, *J* = 3.5 Hz, 1H), 3.67 (dd, *J* = 11.9, 7.3 Hz, 1H), 3.46 (t, *J* = 11.4 Hz, 1H), 3.18–3.00 (m, 2H), 2.53 (dd, *J* = 16.9, 6.3 Hz, 1H), 2.44 (dd, *J* = 16.8, 8.2 Hz, 1H), 1.78 (s, 3H) ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{10}H_{16}NO_4$ 214.1074; Found: 214.1076. MS analysis was conducted with the mixture of **1** and **2**.

(3R,4S,6S)-4-carboxy-2-oxo-6a-phenyl-5-(2,2,2-trifluoroacetyl)hexahydro-2H-furo[2,3-c]pyrrol-5-ium (**17**). Benzylic carbonate **15b** (205 mg, 0.356 mmol) was dissolved in methanol (5 mL), a LiOH aqueous solution (1 mL, 2.5 N) was added at rt and was stirred for 6 h. The reaction was neutralized at 0 ºC with diluted 1.0 N HCl aqueous solution, and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, and filtered. The solvents were evaporated under reduced pressure. This residue was retaken in dichloromethane (5 mL) under argon atmosphere, trifluoroacetic acid (1 mL) was added, and the solution was stirred at rt for 3 h. The reaction mixture was concentrated to dryness under reduced pressure to obtain a light yellow solid. This crude product was triturated with acetone (5 mL) and afforded lactone **17** as a white powder (90 mg, 90%). The solubility of lactone **17** is extremely poor in either H_2O, acetone, chloroform, or DMSO. FTIR (thin film): 3521, 3017, 2983, 1783, 1605, 754, 705 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ: 7.59–7.46 (m, 5H), 4.36 (d, *J* = 4.8 Hz, 1H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.92 (d, *J* = 13.7 Hz, 1H), 3.76–3.64 (m, 1H), 3.21 (dd, *J* = 19.1, 8.7 Hz, 1H), 2.98 (d, *J* = 19.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 175.5, 171.6, 139.5, 128.7, 128.2, 124.7, 95.0, 67.6, 58.1, 49.5, 34.7 ppm. ^{19}F NMR (376 MHz,

DMSO-d_6) δ: -73.45 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{13}H_{14}NO_4$ 248.0917; Found 248.0912.

(3R,4S,6S)-4-(Methoxycarbonyl)-2-oxo-6a-phenyl-5-(2,2,2-trifluoroacetyl)hexahydro-2H-furo[2,3-c]pyrrol-5-ium (**18a**). To a stirred solution of allylic alcohol **12b** (2.268 g, 3.94 mmol) in dichloromethane (25 mL) was added trifluoroacetic acid (9.2 mL, 0.12 mol). After 3 h, a TLC showed the full conversion. The reaction mixture was concentrated to dryness under reduced pressure. The residue was triturated in methanol (20 mL), and the insoluble byproduct (PfOH) was removed by filtration. The filtrate was concentrated to afford the trifluoroacetate salt of **18a** as a pale-yellow oil (1.465 g, 99%) which was used as is for the next step. FTIR (thin film): 2955, 2914, 2847, 1777，1733 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 7.27–7.21 (m, 4H), 7.21–7.15 (m, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.69 (d, *J* = 13.5 Hz, 1H), 3.69 (s, 3H), 3.48 (ddd, *J* = 8.3, 7.1, 1.9 Hz 1H), 2.74 (dd, *J* = 18.7, 7.5 Hz, 1H), 2.67 (dd, *J* = 18.7, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ: 175.0, 169.0, 137.3, 130.5, 130.3, 126.0, 94.4, 65.5, 57.6, 54.4, 50.4, 49.6, 49.4, 49.2, 49.0, 49.0, 48.6, 48.4, 34.2. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd. for $C_{14}H_{16}NO_4$ 262.1079; Found 262.1070.

5-(tert-Butyl) 4-methyl (3R,4S,6S)-2-oxo-6a-phenylhexahydro-5H-furo[2,3-c]pyrrole-4,5-dicarboxylate (**18b**). To a solution of **18a** (TFA salt, 215 mg, 0.573 mmol) in dichloromethane (2 mL) was added DMAP (7 mg, 0.06 mmol), triethylamine (145 μL, 1.43 mmol) and Boc_2O (188 mg, 0.859 mmol). After 6 h, the reaction mixture was concentrated to dryness under reduced pressure. The crude residue was purified by column chromatography using dichloromethane/methanol as eluent (10-20% gradient). **18b** was recovered as a colorless oil (192 mg, 93%). FTIR (thin film): 2974, 2917, 1793, 1749, 1698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, two rotamers) δ: 7.41 (m, 7.42–7.40, 4H), 7.39–7.33 (m, 4H), 4.41 (d, *J* = 4.6 Hz, 0.5H), 4.33–4.25 (m, 4H), 4.25–4.21 (m, 0.5H), 3.89 (dd, *J* = 13.0, 9.0 Hz, 1H), 3.83 (s, 3H), 3.23–3.17 (m, 1H), 2.90–2.62 (m, 2H), 1.44 and 1.46 (2s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, two rotamers) δ: 174.2, 172.1, 172.0, 154.0, 153.0, 137.5, 137.2, 129.0, 128.9, 128.8, 124.8, 94.4, 93.4, 81.3, 81.2, 77.4, 77.2, 77.0, 76.7, 65.9, 65.8, 59.2, 58.6, 52.8, 52.6, 51.4, 50.5, 35.1, 34.9, 28.3, 28.2. HRMS (ESI-TOF) m/z $[M+Na]^+$ Calcd for $C_{19}H_{23}NO_6Na$ 384.1423; Found 384.1455.

(2S,3S,4S)-1-Acetyl-3-(carboxymethyl)-2-(methoxycarbonyl)-4-phenylpyrrolidin-1-ium (**19a**). To a solution of **18a** (TFA salt, 1.126 g, 2.97 mmol) in methanol (30 mL) was added acetic acid (0.71 mL) and Pd/C (56 mg). The reaction mixture was stirred under a hydrogen atmosphere (balloon) for 24 h. The resulted reaction mixture was filtered over a Celite pad. The filtrate was evaporated to dryness under reduced pressure and then high vaccum to afford the acetate salt of **19a** as a pale-yellow powder (956 mg, 99%). FTIR (thin film): 3390, 2521, 1739, 1673, 1635 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 7.42–7.31 (m, 4H), 7.29–7.22 (m, 2H), 4.59 (d, *J* = 6.2 Hz, 1H), 4.01–3.93 (m, 1H), 3.91 (s, 3H), 3.88–3.82 (m, 1H), 3.84–3.75 (m, 1H), 3.30–3.19 (m, 1H), 2.33 (ddd, *J* = 17.0, 7.8, 1.2 Hz, 1H), 2.22 (dd, *J* = 16.9, 6.1 Hz, 1H), 1.98 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 173.8, 172.9, 168.9, 134.4, 128.6, 128.2, 127.7, 68.2, 58.1, 53.4, 53.1, 48.2, 48.0, 47.8, 47.6, 47.4, 47.2, 46.9, 43.9, 42.5, 33.0. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{14}H_{18}NO_4$ 264.1236; Found 264.1257.

2-((2S,3S,4S)-1-(tert-Butoxycarbonyl)-2-(methoxycarbonyl)-4-phenylpyrrolidin-3-yl)acetic acid (**19b**). To a solution of **18b** (175 mg, 0.484 mmol) in methanol (20 mL) was added Pd/C (25 mg). The reaction mixture was stirred under a hydrogen atmosphere (balloon) for 24 h. The resulted reaction solution was filtered over a Celite pad. The filtrate was concentrated to dryness to under reduced pressure and afford **19b** as a colorless oil (174 mg, 99%). FTIR (thin film): 2977, 2917, 1742, 1698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, two rotamers) δ: 7.33–7.27 (m, 3H), 7.09–7.05 (m, 2H), 4.14 (d, *J* = 6.6 Hz, 0.4H), 4.02 (d, *J* = 6.7 Hz, 0.6H), 3.94 (ddd, J = 15.7, 10.9, 6.9 Hz, 1H), 3.84 (dd, *J* = 11.0, 4.7 Hz, 0.6H), 3.77 (d, *J* = 3.1 Hz, 3H), 3.74–3.73 (m, 0.4H), 3.71–3.65 (m, 1H), 2.99 (dt, *J* = 10.7, 6.9 Hz, 1H), 2.30 (ddd, *J* = 17.4, 14.7, 7.1 Hz, 1H), 2.14–2.02 (m, 1H), 1.45 and 1.49 (2s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.8, 172.8, 172.5, 154.3, 153.5, 138.5, 138.4, 128.9, 127.7, 127.7, 127.4, 80.7, 80.6, 77.3, 77.0, 76.7, 63.3, 63.0, 52.5, 52.3, 50.8, 50.4, 45.2, 44.3, 44.1, 43.3, 33.1, 28.4, 28.3. HRMS (ESI-TOF) m/z $[M+Na]^+$ Calcd. for $C_{19}H_{25}NO_6Na$ 386.1580; Found 386.1556.

Phenyl kainic acid (**4**). Synthetic route from **17**: To a solution of lactone **17** (50 mg, 0.21 mmol), acetic acid (1 mL) and methanol (5 mL) was added Pd/C (5 mg). This reaction mixture was stirred under a hydrogen atmosphere (balloon) for 24 h. The resulted reaction mixture was filtered over a Celite pad, and the filtrate was concentrated to dryness under reduced pressure. The residual acetic acid was removed under high vacuum. The crude product was purified and recrystallized as described above **2**. Phenylkainic acid (**4**) was recovered as a white crystalline solid (45 mg, 90%).

Synthetic route from **18a**: To a solution of methyl ester **18** (386 mg, 1.21 mmol) in methanol (15 mL) was added a LiOH aqueous solution (8 mL, 2.5 N). Full conversion was observed after 4 h. The reaction was neutralized at 0 ºC with 1.0 N aqueous HCl. The solvents were evaporated under high vaccum. The resulted residue was purified and recrystallized as described above **2**. Phenylkainic acid (**4**) was recovered as a white crystalline solid (256 mg, 86%). MP 255–257 ºC. FTIR (thin film): 3429, 3185, 3042, 2920, 1736, 765, 699 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ: 7.49–7.34 (m, 3H), 7.27–7.18 (m, 2H), 4.05 (d, *J* = 7.3 Hz, 1H), 3.94 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.87 (q, *J* = 7.8 Hz，1H), 3.72 (dd, *J* = 11.4, 8.1 Hz, 1H), 3.15 (q, *J* = 7.2 Hz, 1H), 2.38 (dd, *J* = 16.3, 6.5 Hz, 1H), 2.02 (dd, *J* = 16.3, 8.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, D_2O) δ: 178.5, 173.3, 136.2, 128.8, 128.2, 127.6, 65.1, 48.0, 44.8, 44.0, 35.7 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd. for $C_{13}H_{16}NO_4$ 250.1074; Found 250.1086.

1-(tert-Butyl) 2-methyl (2S,3S,4S)-3-(2-methoxy-2-oxoethyl)-4-phenylpyrrolidine-1,2-dicarboxylate (**20b**). To a solution of **19a** (acetate salt, 136 mg, 0.421 mmol) in methanol (2.5 mL) was added TMSCl (0.1 mL, 1 mmol) at r.t. After 6 h, the reaction was concentrated to dryness to afford the methyl ester a white solid residue. This residue was retaken in dichloromethane (3 mL), and trimethylamine (150 μL, 1.08 mmol) was added, followed by DMAP (5 mg, 0.04 mmol) and Boc_2O (138 mg, 0.631 mmol). The white suspension was stirred overnight at rt. The solvent was evaporated under reduced pressure. The resulted residue was purified by column chromatography using ethyl acetate/hexane as eluent (10-20% gradient) to afford Boc-protected diester **20b** as a colorless oil (146 mg, 92%). FTIR (thin film): 2917, 2854, 1742, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, two rotamers) δ: 7.37–7.20 (m, 3H), 7.06 (dd, *J* = 7.9, 3.6 Hz, 2H), 4.07 (dd, *J* = 39.4, 6.4 Hz, 1H), 3.99–3.89 (m, 1H), 3.87–3.80 (m, 1H), 3.80–3.75 (m, 3H), 3.69 (q, *J* = 5.8 Hz, 1H), 3.65–3.58 (m, 3H), 3.01 (h, *J* = 7.2 Hz, 1H), 2.27 (dt, *J* = 17.7, 7.2 Hz, 1H), 2.04 (ddd, *J* = 17.2, 7.8, 4.9 Hz, 1H), 1.43 and 1.45 (2s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, two rotamers) δ: 172.8, 172.5, 172.1, 172.1, 154.2, 153.5, 138.6, 138.4, 128.8, 127.7, 127.7, 127.3, 80.5,

77.3, 77.0, 76.7, 63.4, 63.1, 52.4, 52.2, 51.8, 51.7, 50.7, 50.2, 45.2, 44.3, 44.3, 43.5, 33.3, 33.2, 28.4, 28.3. HRMS (ESI-TOF) m/z $[M+Na]^+$ Calcd. for $C_{20}H_{27}NO_6Na$ 400.1736; Found 400.1717.

Methyl (2S,3S,4S)-3-(2-methoxy-2-oxoethyl)-1-((4-nitrophenyl)sulfonyl)-4-phenylpyrrolidine-2-carboxylate (**20a**). To a solution of **19a** (acetate salt, 696 mg, 2.15 mmol) in methanol (5.0 mL) was added TMSCl (690 µL, 5.39 mmol). The solution was stirred at rt for 6 h. The reaction mixture was concentrated to dryness to afford the methyl ester as a white solid. This residue was retaken in dichloromethane (10 mL), and trimethylamine (746 µL, 5.39 mmol) was added, followed by DMAP (26 mg, 0.22 mmol) and *p*-NsCl (716 mg, 3.23 mmol). The reaction was stirred at rt overnight. The reaction concentrated to dryness. The resulted residue was purified by column chromatography using ethyl acetate/hexane as eluent (10-30% gradient). *N*-Ns-protected diester **20a** was recovered as a white foam-like solid (953 mg, 96%). FTIR (thin film): 3100, 2952, 1736, 1527 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.40 (d, J = 9.0 Hz, 1H), 8.13 (d, J = 9.1 Hz, 1H), 7.35–7.27 (m, 3H), 7.09–6.99 (m, 2H), 4.43 (d, J = 4.5 Hz, 1H), 3.81–3.78 (m, 3H), 3.78 (s, 3H), 3.60 (s, 3H), 3.10–2.99 (m, 1H), 2.02 (d, J = 1.8 Hz, 1H), 2.00 (d, J = 3.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.6, 171.4, 150.2, 144.5, 136.4, 129.0, 128.8, 127.7, 127.7, 124.2, 77.4, 77.0, 76.7, 65.2, 52.9, 51.9, 50.7, 45.2, 44.4, 32.5. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_8S$ 463.1175; Found 463.1174.

1-(tert-Butyl) 2-methyl (2S,3S,4S)-3-(2-(tert-butoxy)-2-oxoethyl)-5-oxo-4-phenylpyrrolidine-1,2-dicarboxylate (**21b**). *N*-Boc protected diester **20b** (52 mg, 0.14 mmol) was dissolved in a solvent mixture composed of: acetonitrile (0.5 mL), carbon tetratchloride (0.5 mL), and water (1 mL). Sodium metaperiodate (471 mg, 2.20 mmol) was added, followed by ruthenium trichloride monohydrate (2 mg, 0.009 mmol). After 8 h, TLC analysis showed only partial conversion. A second portion of metaperiodate (118 mg, 0.552 mmol) and ruthenium trichloride (1 mg, 0.04 mmol) was added. After an additoinal 24 h of reaction, the mixture was diluted with ethyl acetate (30 mL). The organic layer was washed with 0.5 N HCl aqueous solution (5 mL), brine (20 mL). It was then dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The resulted residue was purified by column chromatography using ethyl acetate/hexane as eluent (10-30% gradient). *N*-Boc pyrrolidin-5-one **21b** was recovered as a colorless oil (45 mg, 86%). FTIR (thin film): 2950, 2912, 2851, 1796, 1743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.29 (m, 3H), 7.17–7.10 (m, 2H), 4.43 (d, J = 3.3 Hz, 1H), 4.22 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.57 (s, 3H), 3.08 (m, 1H), 2.30 (dd, J = 16.9, 8.8 Hz, 1H), 2.09 (dd, J = 16.9, 6.4 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.9, 171.3, 170.9, 149.5, 133.2, 129.5, 128.8, 127.9, 84.2, 62.0, 52.9, 51.9, 51.4, 37.0, 34.4, 27.9. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{20}H_{25}NO_7Na$ 414.1529; Found 414.1492.

(3R,4S,5S)-4-(2-Methoxy-2-oxoethyl)-5-(methoxycarbonyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-3-carboxylic acid **(21a).** Proceeded according to the procedure described for **21b**, and started with **20a** (901 mg, 1.95 mmol). The resulted reaction mixture was acidified with 0.5 N aqueous HCl solution at 0 °C until the pH ~ 2. The resulted mixture was extracted with ethyl acetate (2 × 20 mL), followed by washing with brine (50 mL). The combined organic layers were then extracted with saturated aqueous sodium bicarbonate solution (3 × 20 mL), the desired product was thus extracted to the aqueous layers. The aqueous layers were combined and extracted with diethyl ether (3 × 20 mL) to remove impurities. The resulted aqueous layer was then acidified with 0.5 N aqueous HCl solution at 0 °C until the pH ~ 2. It was then reextracted with ethyl acetate (3 × 30 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography using methanol/dichloromethane as eluent (5-10% gradient) to afford **21a** (652 mg, 78%) as a white foamy solid. FTIR (thin film): 2914, 2851, 1723, 1591, 1524 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 9.1 Hz, 1H), 8.05 (d, J = 9.1 Hz, 1H), 4.14 (d, J = 7.0 Hz, 1H), 3.81 (s, 3H), 3.79-3.74 (m, 1H), 3.69 (s, 3H), 3.67 -3.64 (m, 1H), 3.37-3.32 (m, 1H), 3.06 – 2.98 (m, 1H), 2.47 (dd, J = 17.0, 7.4 Hz, 1H), 2.36 (dd, J = 17.0, 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 170.9, 170.8, 150.3, 143.3, 128.8, 124.2, 64.6, 53.1, 52.2, 49.2, 44.9, 42.0, 32.3. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd. for $C_{16}H_{19}N_2O_{10}S$ 431.0676; Found 431.0648.

Methyl (2S,3S,4R)-4-((6-(7-(diethylamino)-2-oxo-2H-chromene-3-carboxamido)hexyl)carbamoyl)-3-(2-methoxy-2-oxoethyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (**22**). To a stirred solution of **21a** (26 mg, 0.060 mmol) in dichloromethane (1 mL) was added triethylamine (13 µL, 0.090 mmol), HBTU (25 mg, 0.071 mmol) and the coumarin amine (33 mg, 0.091 mmol). After 1 h, **21a** was fully converted to **22**. The reaction mixture was poured into water and extracted with diethyl ether (3×15 mL). The combined ether layer was then washed with ammonium chloride aqueous solution, sodium bicarbonate aqueous solution and brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The resulted residue was purified by column chromatography on silica gel (10-35% EtOAc/hexane as elution gradient) to yield **22** (43 mg, 92%) as a yellow solid. FTIR (thin film): 3452, 3338, 2923, 2851, 1672, 1616, 1581, 1533, 1515, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (t, J = 6.0 Hz, 1H), 8.68 (s, 1H), 8.37 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.9 Hz, 1H), 6.66 (dd, J = 9.0, 2.5 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.24 (t, J = 5.6 Hz, 1H), 4.22 (d, J = 6.4 Hz, 1H), 3.74-3.78 (m, 4H), 3.68 (t, J = 4.9 Hz, 1H), 3.65 (s, 3H), 3.50 – 3.39 (m, 6H), 3.28 (td, J = 7.1, 5.2 Hz, 1H), 3.08 (dt, J = 15.0, 6.7 Hz, 2H), 3.03 – 2.95 (m, 1H), 2.42 (dd, J = 17.2, 8.2 Hz, 1H), 2.26 (dd, J = 17.2, 6.8 Hz, 1H), 1.60 (t, J = 6.7 Hz, 2H), 1.40 (d, J = 6.3 Hz, 2H), 1.37 – 1.30 (m, 4H), 1.25 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.3, 169.3, 163.3, 162.9, 152.6, 150.2, 148.1, 143.4, 131.2, 129.0, 124.2, 110.0, 108.4, 96.5, 65.3, 52.9, 52.0, 50.0, 45.8, 45.1, 42.8, 38.7, 38.7, 32.3, 29.3, 28.8, 25.7, 25.6, 12.4 ppm. HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd. for $C_{36}H_{46}N_5O_{12}S$ 772.2864; Found 772.2876.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic data for all compounds, spectra of $^1H/^{13}C$/2D NMR analyses. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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