Revisiting the Urech Synthesis of Hydantoins: Direct Access to Enantiopure 1,5-Substituted Hydantoins using Cyanobenziodoxolone.

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ABSTRACT: A method for the synthesis of enantiopure 1,5-substituted hydantoins was developed using a hypervalent iodine cyanation reagent (Cyanobenziodoxolone, CBX) as a source of electrophilic carbon. Starting from inexpensive commercially available enantiopure protected amino acids, the method allowed the synthesis of various hydantoins without epimerization. Formation of hydantoins from dipeptides was also possible, but partial epimerization was observed in this case. This synthetic strategy is user-friendly as CBX is a bench-stable easy-to-handle crystalline reagent, and avoid conventional multistep protocols, thus allowing the facile synthesis of a library of chiral hydantoins.

Hydantoins (2,4-imidazolidinediones) are important heterocycles in organic chemistry. The most simple hydantoin has been isolated in 1861 by Adolf von Bayer through reduction of allantoin (**1**) (Figure 1).¹ Since then, tremendous efforts have been invested to synthesize and study this important family of five-membered heterocycles.² Among them, chiral 5-substituted hydantoins are broadly used as chiral ligands³ or auxiliaries, such as hydantoin **2** for enolate functionalization.⁴ Many of them are bioactive compounds, either natural such as **3** isolated from the Red Sea sponge *Hemimyscale arabica*,⁵ or synthetic, such as the clinical candidates HR22C16 **4** (antimitotic)⁶ and the BMS-564929 (**5**) (orally active and selective androgen receptor modulator).⁷ Compounds **1-5** are all derivatives of natural amino acids.

Figure 1 Important chiral 5-substituted hydantoins derived from α -amino-acids.

The synthesis of hydantoins is well-established.² Classical methods are the Bucherer-Bergs,⁸ the Biltz,⁹ the Read¹⁰ and the Urech¹¹ syntheses. The two firsts are based on carbonyl or dicarbonyl condensation, affording racemic hydantoins; whereas the Read and Urech's conditions involve a two-step enantioconservative condensation-cyclization of amino-acid derivatives in presence of isocyanates under harsh conditions (Scheme 1). These isocyanates are often not commercially available and their synthesis requires extra steps with often toxic reagents. Since then, efforts towards more environmental and user friendly approaches have been made, especially based on amino acid derivatives.¹² Using amino amides, Cuny and co-workers were able to obtain enantiopure hydantoins in presence of triphosgene.¹³ Amino amides were also used by Pan and co-work-

ers using triflic anhydride,¹⁴ while Fang and co-workers described a method using amino acid ureas under similar conditions of the Read/Urech cyclization step.¹⁵ The reaction of α -amino methyl ester hydrochlorides with carbamates to produce substituted hydantoins was recently developed by Gill and co-workers.¹⁶ However, these syntheses still required highly reactive reagents and pre-functionalization of the amino acids. Earlier this year, Gong and co-workers developed an elegant asymmetric synthesis of 5-substituted hydantoins using chiral Lewis base and copper cooperative catalysis.¹⁷

Scheme 1 Reported syntheses of chiral hydantoins starting from the chiral pool and our previous work on decarboxylative cyanation of amino acids.

Recently, our group has been interested in transformations of amino acids using hypervalent iodine reagents.¹⁸ We reported a room temperature decarboxylative cyanation of carboxylic acids using photoredox catalysis and cyanobenziodoxolone (CBX, **6**, Scheme 1).¹⁹ The synthesis of CBX (**6**) had been first

described by Zhdankin, who developed the cyanation of dialkylanilines.²⁰ Since then, several electrophilic cyanations using CBX reagents have been described.^{21,22} Herein, we report a new method for the one-step synthesis of 1,5-substituted enantiopure hydantoins, starting from chiral protected amino acids and CBX (**6**).

During our previous work on decarboxylative cyanation, screening of different amino acids was performed but the reaction was not always efficient. In fact, the desired transformation did not occur for tryptophan and cysteine. Instead, a hydantoin was formed, as confirmed by X-Ray analysis.²³ A control experiment on Boc-protected L-alanine **7a** in absence of light and photocatalyst led also to the formation of hydantoin **8a** (Scheme 2, 42% in the dark with 1.25 equiv CsOBz). This background reaction had not been observed before, as the photoredox mediated process was faster. Based on this unexpected result, different protecting groups on the nitrogen were first examined. Carbamates protecting groups were successful (products **8a-c**), and best results were obtained for Cbz (**8c**). In contrast, acetyl- and benzyl protected as well as unprotected amino acids **7** could not be used.

Scheme 2. Screening of N-substituents for the synthesis of hydantoins using CBX (**6**).

We continued our investigation with optimization of the synthesis of hydantoin **8b** from L-Cbz-Ala (**6b**) (Table 1). Even though conversion, yield and retention of enantiomeric excess were excellent (95% conversion, 83% isolated yield, 95% ee after 4 h, entry 1), we had solubility issues leading to lack of reproducibility. Two chromatography columns were required to separate the desired hydantoin from 2-iodobenzoic acid and benzoic acid. Both CBX and CsOBz are poorly soluble in THF, thus making a white slurry. Therefore, different solvents were tested to improve the solubility of the reaction mixture. Dioxane and ethyl acetate (entries 2 and 3) did not allow to enhance the solubility, while a slightly better solubility were observed with DCM and DMF (entries 4 and 5), albeit the yields obtained were lower than in THF. We then decided to screen the base. Neither sodium nor potassium benzoate were superior to cesium benzoate (50 and 60% yield, entries 6 and 7). Surprisingly cesium carbonate and cesium acetate did not promote the formation of hydantoin (entries 8 and 9). Organic bases such as pyridine and triethylamine gave moderate yields (60%, entries 10 and 11), while DMAP allowed a clean conversion, better reproducibility and excellent isolated yield (entry 12). When lowering concentration in THF to 0.05 M and 0.1 M (entries 13 and 14), the yield was slightly lower than at 0.2 M. The yield dropped to 80% when increasing the concentration to 0.3 M (entry 15). Screening of CBX derivatives and other cyanation reagents under optimized conditions have also been performed (results not shown, see SI). However, none of the examined reagents allowed to improve neither reactivity nor purification efficiency. Control experiments were performed with other cyanation reagents such as BrCN, ICN and 1-cyano-4-dimethylamino-pyridinium tetrafluoroborate (CDAP) instead of CBX (**6**). Using BrCN and ICN, hydantoin formation could be observed, albeit in lower yield (35% NMR yield compared to quantitative yield with CBX) while CDAP gave much lower yield (< 20%).

Table 1. Optimization of the synthesis of hydantoin **8b.^a**

entry	base	solvent	concentration (M)	NMR yield (%)
1	CsOBz	THF	0.2	>95, 83 ^b
2	CsOBz	dioxane	0.2	60
3	CsOBz	EtOAc	0.2	20
4	CsOBz	DCM	0.2	45
5	CsOBz	DMF	0.2	55
6	NaOBz	THF	0.2	50
7	KOBz	THF	0.2	60
8	Cs ₂ CO ₃	THF	0.2	<10
9	CsOAc	THF	0.2	<10
10	pyridine	THF	0.2	60
11	Et ₃ N	THF	0.2	60
12	DMAP	THF	0.2	>95, 75 ^b
13	DMAP	THF	0.05	90
14	DMAP	THF	0.1	90
15	DMAP	THF	0.3	80

^aReaction conditions: **7b** (67 mg, 0.30 mmol, 1 equiv), CBX **6** (123 mg, 0.450 mmol, 1.5 equiv), base (0.375 mmol, 1.25 equiv.) in the corresponding solvent (1.5 mL) for 4 h at RT under N₂. The NMR yield of **8b** is given.

^bIsolated yield (%) after two columns chromatography.

We then studied the scope of amino acids, running the reaction overnight at room temperature to ensure complete conversion for all substrates (Scheme 3). Under these conditions, Cbz protected L-alanine (**7b**) is fully converted to hydantoin **8b** with 85% isolated yield and 96% ee. Boc and Fmoc protected hydantoins **8a** and **8c** were obtained in better yields. 30% NMR yield could be observed for acetyl protected hydantoin **8d** and the benzyl protected hydantoin **8e**. Less than 5% NMR yield was observed when using benzamide as protecting group (result not shown). Amino acids bearing apolar side chains (valine, leucine, *iso*-leucine and phenylalanine) gave the corresponding hydantoins in good to excellent yields (55–85%, **8g-j**). Tyrosine is suitable for this transformation, but protection of the phenol moiety is required for efficient purification. Protected hydantoin **8k** was further crystallized and allowed unambiguously confirmation of the hydantoin core, with full retention of the stereochemistry of the amino acid.²² Both L-Cbz-tryptophan and D-Boc-tryptophan based hydantoins **8l** and **8m** were obtained in good yields. L-Methionine, L-S(Bn)-cysteine, L-N(Boc)-lysine, L-O(*t*Bu)-glutamic acid and L-O(*t*Bu)-asparagic acid and L-O(Bn)-serine were successfully converted to the corresponding hydantoins **8n-s** in good to excellent yields (54–82%). It is also possible to use unnatural amino acids. For example hydantoin **8t** with a cyclopropyl side chain was obtained in 65% yield. Surprisingly, although the nitrogen of L-proline is electron-rich, 62% of bicyclic hydantoin **8u** was isolated. Hydantoin **8v** was obtained from glycine in 88% yield. Hydantoin **8v** can be condensed with benzaldehyde derivatives to afford bioactive methylenehydantoins.^{5,24} Sterically hindered

hydantoin **8w** was obtained in 56% yield. Side chain unprotected asparagine, glutamine, threonine, histidine and cysteine were unsuccessful.

Scheme 3 Scope of amino acids.^a

^aReaction conditions: **7** (0.15 mmol, 1.0 equiv.), CBX (**6**) (61 mg, 0.23 mmol, 1.5 equiv.), DMAP (23 mg, 0.19 mmol, 1.25 equiv.) in THF (0.75 mL) for 16 h at RT under N₂. Isolated yield of **8** after purification by preparative TLC (Heptane/Et₂O) is given. ^bee was measured by chiral HPLC. ^cNMR yield.

To highlight the efficiency of this transformation, a gram scale synthesis was undertaken and 1.2 g of optically pure hydantoin **8b** was obtained (Scheme 4, equation 1), along with the recovery of 1.75 g of the precipitated salt **9**. Cbz deprotection of **8b** to give **10** was quantitative using 5 mol% of Pd(OH)₂/C in methanol (equation 2).

Scheme 4 Gram-scale synthesis and Cbz deprotection of hydantoin **8b**.^a

^aReaction conditions: (1) **7b** (1.0 g, 4.5 mmol, 1.0 equiv.), CBX (**6**) (1.84 g, 6.72 mmol, 1.5 equiv.), DMAP (0.68 g, 5.6 mmol, 1.25 equiv.) for 16 h at RT. Isolated yield of **8b** after filtration and column chromatography. (2) **8b** (30 mg, 0.12 mmol, 1.00 equiv.),

Pd(OH)₂/C (6.1 μmol, 5 mol %) in MeOH (6.0 mL) for 4 h at RT under H₂. Isolated yield of **10** after filtration over HPLC filter.

We then wondered if the reaction could be applied on peptides to access more complex hydantoins. Indeed, the formation of the hydantoin was feasible on Cbz protected Ala-Ala-OH and Gly-Phe-OH dipeptides **11a** and **11b** (Scheme 5), even though the reaction was slower. After 36 h at room temperature, hydantoins **12a** and **12b** were obtained in 80% and 64% isolated yield respectively. In contrast to amino acids, some epimerization occurred, leading to a decrease of diastereomeric/enantiomeric excess (**12a**, 72% de; **12b**, 44% ee). This may be due to the prolonged reaction time under basic conditions.

Scheme 5 C-terminal hydantoin formation on dipeptides **11**.^a

^aReaction conditions: **11** (0.15 mmol, 1.0 equiv.), CBX (**6**) (61 mg, 0.23 mmol, 1.5 equiv.), DMAP (23 mg, 0.19 mmol, 1.25 equiv.) in THF (0.75 mL) for 16 h at RT under N₂. Isolated yield of **12** after purification by preparative TLC (Heptane/Et₂O) is given. ^bMeasured by chiral HPLC.

A speculative mechanism is outlined in Scheme 6. We envisioned that deprotonation of amino acid **7** by DMAP will lead to carboxylate **7'**. Cyanation with CBX **6** gives then mixed anhydride intermediate **I** and salt **9**, which was indeed isolated at the end of the reaction. Cyclization of intermediate **I**, affording the corresponding 2-iminooxazolidin-5-one **II** appears highly probable.

Scheme 6 Speculative mechanism for hydantoin formation.

Subsequent rearrangement of **II** to more stable hydantoin **8** may be accelerated by DMAP as a nucleophilic catalyst, via intermediate **III**. A possible alternative inspired from Urech synthesis is a nucleophilic attack of DMAP on the activated car-

bonyl of **I** releasing in situ a cyanate anion, which after condensation on the amine would also give intermediate **III**. Concerning transfer of the cyanide group, several pathways can be proposed (See SI details). Based on our previous work on thiocyanation with CBX,^{19a} a concerted mechanism via a three-atom transition state could be considered, but a stepwise process cannot be excluded. Mechanisms involving a single electron transfer and subsequent formation of radical intermediates also constitute an alternative when considering the strong oxidizing properties of hypervalent iodine reagents.^{19,25}

In conclusion, we have developed an efficient and practical method for the synthesis of 1,5-substituted enantiopure hydantoins. Starting from chiral amino acids, the reaction proceeds at room temperature, using cyanobenziodoxolone (CBX, **6**) and DMAP. A broad range of hydantoins could be synthesized without epimerization starting from protected amino acids, whereas partial epimerization was observed in the case of dipeptides. The method is expected to be highly useful in synthetic and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENT

We thank the European Research Council (ERC Starting Grant 334840) and the Institute of Chemistry and Chemical Engineering at EPFL (Master grant for N. D.) for financial support. Dr Rosario Scopelliti, Dr Euro Solari and Dr Farzaneh Fadaei Tirani (ISIC, EPFL) are acknowledged for the X-ray study. Bastian Muriel from LCSO is acknowledged for the purification of hydantoin **8t**. Paola Caramenti and Phillip Greenwood from LCSO are acknowledged for their help with the HPLC analysis.

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(25) Only trace amount of nitrile resulting from decarboxylative cyanation of peptide **11a** was isolated and characterized by HRMS after 48 h at 50 °C. A SET pathway for hydantoin synthesis would be expected to lead to a higher extent of such side product.

Supporting Information for

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1,5-Substituted Hydantoins using Cyanobenziodoxolone.**

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1. General Methods

HPLC grade or freshly distilled solvents purchased from Sigma-Aldrich were used. All reagents and solvents were purchased from commercial sources ABCR, Acros, Sigma Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å. TLC was performed on Merck silica gel 60 F254 TLC glass plates and visualized with UV light, permanganate stain or phosphomolybdic acid stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^1H -NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in CDCl_3 , CD_2Cl_2 , DMSO- d_6 , CD_3OD ; all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal CD_2Cl_2 signal at 5.32 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet d = doublet t = triplet q = quadruplet quint = quintet m = multiplet or unresolved bs = broad signal, coupling constant(s) in Hz, integration, interpretation). ^{19}F -NMR spectra were recorded on a Bruker DPX-400 376 MHz spectrometer in CDCl_3 . ^{13}C -NMR spectra were recorded with ^1H -decoupling on a Bruker DPX-400 101 MHz spectrometer in CDCl_3 , CD_2Cl_2 , DMSO- d_6 , CD_3OD ; all signals are reported in ppm with the internal chloroform signal at 77.2 ppm, the internal CD_2Cl_2 signal at 54.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 or a Bruker Alpha-P spectrophotometer with an ATR device and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurements were done on a Agilent 1260 Infinity autosampler using a CHIRALPAK ID column from DAICEL Chemical. Samples were prepared in a 80/20 hexane/isopropanol mixture, before being submitted in chiral HPLC. Optical rotations were measured on a polarimeter using a 10 cm cell with a Na 589 nm filter. The specific solvents and concentrations (in g/100 mL) are indicated. All amino acids and peptides used in this work were commercially available and used as received.

2. Preparation of Reagents

The synthesis of reagents **6** and **6b-f** had already been described before by our group. The procedures are taken from the indicated publications to facilitate reproduction of the results by having all data in the same file.

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (**14**)

Following a reported procedure,^[1] NaIO₄ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (**13**) (8.00 g, 32.2 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (48 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 20 mL) and acetone (3 x 20 mL), and air-dried in the dark to give the pure product **14** (8.3 g, 31 mmol, 98%) as a colorless solid. ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1 H, Ar*H*); ¹³C NMR (100 MHz, (CD₃)₂SO) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4; IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m). The reported values correspond to the ones in literature.^[1]

1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (**15**)

^[1] a) Fernandez Gonzalez, D.; Brand, J. P.; Waser, J. *Chem. Eur. J.* **2010**, *16*, 9457. b) Kraszkiewicz, L.; Skulski, L. *Arkivoc.* **2003**, *6*, 120.

Following a reported procedure,^[2] 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**14**, 10.3 g, 39.1 mmol, 1.00 equiv.) was suspended in acetic anhydride (35 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried *in vacuo* affording **15** (10.8 g, 35.3 mmol, 90%) as a white solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.24 (dd, 1 H, *J* = 7.6, 1.6 Hz, Ar*H*), 8.00 (dd, 1 H, *J* = 8.3, 1.0 Hz, Ar*H*), 7.92 (ddd, 1 H, *J* = 8.4, 7.2, 1.6 Hz, Ar*H*), 7.71 (td, 1 H, *J* = 7.3, 1.1 Hz, Ar*H*), 2.25 (s, 3 H, COCH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.^[2]

1-Cyano-1,2-benziodoxol-3-(1*H*)-one (**6**)

Following a reported procedure,^[3] 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**15**, 11.8 g, 38.6 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (200 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 10 mL, 77 mmol, 2.00 eq.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 70 μL, 0.386 mmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **6** (10.3 g, 37.7 mmol, 98 %) as a white solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.29 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 8.13 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ar*H*), 8.06-7.97 (m, 1 H, Ar*H*), 7.88 (t, *J* = 7.3 Hz, 1 H, Ar*H*). ¹³C NMR (DMSO-*d*₆, 100 MHz): δ 166.7, 136.5, 132.0, 131.9, 130.2, 127.8, 117.5, 87.9. IR ν 3157 (w), 3093 (w), 2160 (w), 1629 (s), 1562 (m), 1439 (m), 1321 (s), 1298 (s), 1148 (m), 839 (m), 747 (s). The characterization data is in accordance with reported literature values.^[3]

^[2] Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579.

^[3] Chen, M.; Huang, Z. T.; Zheng, Q. Y. *Org. Biomol. Chem.* **2015**, *13*, 8812.

1-Acetoxy-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (**17**)

Following a reported procedure,^[2] 1-chloro-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole^[4] (**16**, 3.10 g, 10.5 mmol, 1.00 eq.) and silver acetate (1.83 g, 11.0 mmol, 1.05 eq.) were suspended under nitrogen in dry acetonitrile (30 mL). The mixture was stirred in the dark at room temperature for 15 hours. Filtration of the precipitated silver chloride followed by solvent removal *in vacuo* yielded compound **17** (2.98 g, 9.31 mmol, 89%) as a white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.79 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.52-7.41 (m, 2 H, Ar*H*), 7.17 (dd, *J* = 7.4, 1.6 Hz, 1 H, Ar*H*), 2.10 (s, 3 H, COCH₃), 1.52 (s, 6 H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 177.4, 149.4, 130.5, 130.0, 129.9, 126.3, 115.8, 84.6, 29.3, 21.6. The characterization data is in accordance with reported literature values.^[2]

1-Cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (**6b**)

To a solution consisting of 1-acetoxy-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (**17**, 2.00 g, 6.25 mmol, 1.00 equiv.) and dry dichloromethane (15 mL) was added dropwise trimethylsilyl cyanide (TMS-CN, 1.71 mL, 12.5 mmol, 2.00 eq.) at room temperature under nitrogen. The clear colorless solution was stirred at room temperature for 20 hours. Solvent removal afforded a white solid, which was suspended in pentane (10 mL), filtered and dried *in vacuo* affording pure compound **6b** (1.73 g, 6.03 mmol, 96%) as a white solid. *R_f* (pentane:EtOAc 7:3) = 0.54. ¹H NMR (CDCl₃, 400 MHz): δ 8.05 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 7.62 (t, *J* = 7.3 Hz, 1 H, Ar*H*), 7.58-7.49 (m, 1 H, Ar*H*), 7.33 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 1.48 (s, 6 H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 148.1, 131.7, 131.0, 128.3, 126.9, 111.6, 98.0, 80.4, 30.3. IR ν 2974 (w), 2925

^[4] This commercially available compound can also be synthesized following the practical procedure by Matousek, V.; Pietrasiak, E.; Schwenk, R.; Togni, A. *J. Org. Chem.* **2013**, 78, 6763.

(w), 2139 (w), 1461 (m), 1436 (m), 1251 (m), 1160 (s), 1003 (w), 954 (s), 869 (m), 761 (s). The characterization data is in accordance with reported literature values.^[5]

4-*Tert*-butyl-2-iodobenzoic acid (**19**)

From a modification of known procedures^[2], to the solution of 4-*tert*-butyl-2-iodo-1-methylbenzene **18** (6.8 g, 25 mmol, 1 equiv) in H₂O/pyridine (85 ml : 106 ml), was added KMnO₄ (15.6 g, 99.0 mmol, 4 equiv) and *n*BuN₄I (137 mg, 0.371 mmol, 1.5 mol %). The purple mixture was heated to reflux for 4 days. It was then allowed to cool down to room temperature and the solids were filtered off through a pad of celite, which was then washed with aq. NaOH (2.0 M). Most of the pyridine was removed from the filtrate by evaporation under reduced pressure. The aqueous residue was washed with diethyl ether (3 x 100 mL) and it then acidified until pH < 2 by careful addition of aq. HCl (37% v/v). The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organic extracts were dried over MgSO₄, filtered and concentrated under vacuum to provide the 4-(*tert*-butyl)-2-iodobenzoic acid **19** (3.88 g, 12.8 mmol, 52%) as a yellowish solid. ¹H-NMR (400 MHz, CDCl₃): δ 8.04 (d, *J* = 1.8 Hz, 1H, Ar*H*), 7.97 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.45 (dd, *J* = 8.2, 1.8 Hz, 1H, Ar*H*), 1.31 (s, 9H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ 171.6, 158.0, 139.6, 132.3, 130.2, 125.5, 95.5, 35.1, 31.1. The characterization data is in accordance with reported literature values.^[3]

4-*Tert*-butyl -1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**20**)

Following a reported procedure,^[3] NaIO₄ (2.67 g, 12.5 mmol, 1.05 equiv) and 4-(*tert*-butyl)-2-iodobenzoic acid (**19**) (3.80 g, 12.5 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH

^[5]Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, 36, 7975.

(24 mL). The mixture was vigorously stirred and refluxed (140 °C) for 4 h. The reaction mixture was then allowed to cool to room temperature, protecting it from light. The bottom of the flask was scratched with a spatula in order to induce the crystallization. The flask was then cooled to -18 °C (by transferring it into a freezer) and kept at this temperature for 3 hours. The precipitated white crystalline solid was then collected by filtration and washed with several portions of pentane to provide **20** (3.47 g, 10.8 mmol, 87%) as a white solid. ¹H-NMR (400 MHz, DMSO): δ 8.00 (s, 1H, OH), 7.92 (d, *J* = 7.8 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.74 (d, *J* = 7.8 Hz, 1H, ArH), 1.35 (s, 9H, CH₃). ¹³C-NMR (100 MHz, DMSO): δ 168.6, 158.8, 131.8, 130.0, 128.8, 123.3, 121.5, 36.5, 31.8. The reported values correspond to the ones in literature.^[3]

4-*Tert*-butyl-1-acetoxy-1,2-benziodoxol-3-(1H)-one (**21**)

Following a reported procedure,^[2] 1-hydroxy-6-(*tert*-butyl)-1,2-benziodoxol-3-(1H)-one (**20**, 3.47 g, 10.8 mmol, 1.00 equiv.) was suspended in acetic anhydride (10 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 10 mL) and dried *in vacuo* affording **21** (2.95 g, 8.15 mmol, 75%) as a white solid. ¹H-NMR (400 MHz, CDCl₃): δ 8.14 (d, *J* = 8 Hz, 1H, ArH), 7.94 (d, *J* = 1.6 Hz, 1H, ArH), 7.71 (dd, *J* = 1.6, 8 Hz, 1H, ArH), 2.26 (s, 3H, OCOCH₃), 1.41 (s, 9H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ 176.4, 168.5, 161.2, 133.0, 129.1, 126.4, 125.8, 119.2, 36.4, 31.3, 20.5. The values of the NMR spectra are in accordance with reported literature data.^[3]

4-*Tert*-butyl-1-acetoxy-1,2-benziodoxol-3-(1H)-one (**6c**)

Following a reported procedure,^[3] 1-acetoxy-4-tert-butyl-1,2-benziodoxol-3-(1H)-one (**21**, 2.8 g, 7.7 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (77 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 1.93 mL, 15.4 mmol, 2.00 eq.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 14 μ L, 0.077 mmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with pentane (5 mL) before being filtered and the solid was washed with pentane (3 x 20 mL) and dried *in vacuo* affording **6c** (2.48 g, 7.53 mmol, 97%) as a white solid. ¹H-NMR (400 MHz, CDCl₃): δ 8.46 (s, 1H, ArH), 8.25 (d, J = 7.6 Hz, 1H, ArH), 7.84 (d, J = 8.0 Hz, 1H, ArH), 1.44 (s, 9H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ 168.7, 162.1, 132.9, 130.0, 127.5, 124.9, 117.4, 85.6, 36.7, 31.3. HRMS (ESI+) calcd for [C₁₂H₁₃O₂NI]⁺: 329.9986, found: 329.9982. The characterization data is in accordance with reported literature values.^[3]

2-Iodosyl-5-nitrobenzoic acid (**22**) and 2-iodosyl-3-nitrobenzoic acid (**23**)

Following a reported procedure,^[6] fuming nitric acid (3.3 mL) was added to 2-iodobenzoic acid (**13**) (5.0 g, 20 mmol, 1.0 equiv) in concentrated H₂SO₄ (6.7 mL). The reaction was equipped with a cooler and a nitrous vapor trap and was heated at 100 °C for 1 h. The reaction mixture was then poured in ice-water and filtered. The resulting solid was refluxed in water (50 mL) and filtered. A second crop of precipitate was filtered from the mother liquors. Both solids were combined, washed with acetone (10 mL) and dried under vacuum to afford **22** (2.19 g, 7.10 mmol, 36 %). The mother liquors were reduced to one third and then kept at 4 °C, the resulting precipitate was filtered, washed with acetone (10 mL) and dried under vacuum to afford **23** (630 mg, 2.04 mmol, 10 %). **22**: ¹H NMR (400 MHz, (CD₃)₂SO): δ 8.73 (dd, J = 8.8, 2.6 Hz, 1H, ArH), 8.58 (d, J = 2.4 Hz, 1H, ArH), 8.54 (br s, 1H, OH), 8.11 (d, J = 8.8 Hz, 1H, ArH). **23**: ¹H NMR (400 MHz, (CD₃)₂SO): δ 7.92 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 7.79 (m, 1H, ArH), 7.67 (m, 1H, ArH). The reported values correspond to the ones in literature.^[6]

^[6]Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 5655.

5-Nitro-1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (**24**)

Following a reported procedure,^[2] 5-nitro-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**22**, 6.55 g, 21.2 mmol, 1.00 eq.) was suspended in acetic anhydride (18 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried *in vacuo* affording **24** (5.88 g, 16.7 mmol, 79 %) as a white solid. ¹H NMR(400 MHz, Chloroform-*d*) δ 9.04 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.71 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 8.27 (d, *J* = 8.9 Hz, 1H, Ar*H*), 2.30 (s, 3H, OC(O)*Me*). The values of the NMR spectra are in accordance with reported literature data.^[2]

5-Nitro-1-Cyano-1,2-benziodoxol-3-(1*H*)-one (**6d**)

Following a reported procedure,^[3] 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**24**, 351 mg, 1.00 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (7.0 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 0.27 mL, 2.0 mmol, 2.00 eq.) over a five minute time period. then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 1.8 μL , 10 μmol , 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **6d** (273 mg, 0.859 mmol, 86 %) as a white solid. ¹H NMR(400 MHz, DMSO-*d*₆) δ 8.77 (dd, *J* = 8.9, 2.7 Hz, 1H, Ar*H*), 8.64 (d, *J* = 2.6 Hz, 1H, Ar*H*), 8.54 (d, *J* = 8.9 Hz, 1H, Ar*H*). The characterization data is in accordance with reported literature values.^[3]

5-Fluoro-1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (**26**)

Following a reported procedure,^[6] NaIO₄ (760 mg, 3.55 mmol, 1.05 equiv) and 5-fluoro-2-iodobenzoic acid (**25**) (900 mg, 3.38 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (1.8 mL) / H₂O (4.5 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product **26** (908 mg, 3.22 mmol, 95%) as a colorless solid. ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.25 (bs, 1 H, *OH*), 7.90 – 7.78 (m, 2 H, *ArH*), 7.75 (dd, *J* = 8.4, 2.5 Hz, 1 H, *ArH*). ¹³C NMR (100 MHz, (CD₃)₂SO) δ 166.7 (d, *J* = 2.6 Hz), 164.0 (d, *J* = 248.3 Hz), 134.2 (d, *J* = 7.5 Hz), 128.5 (d, *J* = 8.7 Hz), 121.98 (d, *J* = 23.9 Hz), 117.4 (d, *J* = 23.6 Hz), 114.4. The reported values correspond to the ones in literature.^[6]

5-Fluoro-1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (**27**)

Following a reported procedure,^[6] hypervalent iodine precursor **26** (800 mg, 2.84 mmol, 1.00 equiv.) was suspended in acetic anhydride (2.80 mL, 29.7 mmol, 10.5 equiv) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to cool down to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording the corresponding OAc hypervalent iodine reagent **27** (825 mg, 2.55 mmol, 90%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.93 (m, 2H, *ArH*), 7.64 (ddd, *J* = 9.1, 7.7, 2.9 Hz, 1H, *ArH*), 2.26 (s, 3H, OC(O)*Me*). ¹³C NMR (100 MHz, CDCl₃) δ 176.4, 166.7 (d, *J* = 2.9 Hz), 165.0 (d, *J* = 254.5 Hz), 131.7 (d, *J* = 8.0 Hz), 131.0 (d, *J* = 8.1 Hz), 123.7 (d,

$J = 24.0$ Hz), 120.0 (d, $J = 24.3$ Hz), 111.2 (d, $J = 2.3$ Hz), 20.2. The values of the NMR spectra are in accordance with reported literature data, with small differences in chemical shifts for several signals.^[7]

5-Fluoro-1-Cyano-1,2-benziodoxol-3-(1*H*)-one (**6e**)

Following a reported procedure,^[3] 5-Fluoro-1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**27**, 750 g, 2.31 mmol, 1.00 equiv.) was dissolved under nitrogen in dry dichloromethane (15 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 0.62 mL, 4.6 mmol, 2.0 equiv.), over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 4.2 μ L, 23 μ mol, 0.010 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **6e** (610 mg, 2.10 mmol, 91 %) as a white solid. Mp: 181.1 – 184.1°C (decomp). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (dd, $J = 8.9, 4.2$ Hz, 1H, Ar*H*), 7.99 – 7.75 (m, 2H, Ar*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.3 (d, $J = 2.4$ Hz), 164.6 (d, $J = 251.5$ Hz), 133.1 (d, $J = 7.7$ Hz), 130.1 (d, $J = 8.9$ Hz), 123.8 (d, $J = 24.5$ Hz), 118.4 (d, $J = 24.1$ Hz), 111.4, 87.4. IR (solid) 3870 (s), 3740 (s), 3686 (s), 3620 (m), 3435 (w), 3335 (w), 3227 (w), 3109 (w), 2988 (w), 2914 (w), 2360 (m), 2162 (w), 2005 (w), 1926 (w), 1865 (w), 1739 (m), 1702 (m), 1647 (m), 1518 (s), 1457 (m), 1419 (m), 1306 (m), 1141 (w), 1025 (s), 823 (w). HRMS (ESI) calcd for C₈H₄FINO₂⁺ [M+H]⁺ 291.9265; found 291.9270.

1-Hydroxy-1,2-naphthiodoxol-3-(1*H*) (**29**)

^[7]Iinuma, M.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* **2014**, 772.

Following a reported procedure,^[3] NaIO₄ (1.9 g, 8.8 mmol, 1.05 equiv) and 3-iodo-2-naphthoic acid (**28**) (2.5 g, 8.4 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (27 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 8 mL) and acetone (3 x 8 mL), and air-dried in the dark to give the pure product **29** (2.2 g, 6.9 mmol, 82%) as a colorless solid. ¹H-NMR (400 MHz, DMSO): δ 8.67 (s, 1H, OH), 8.38 (s, 1H, ArH), 8.28 (d, *J* = 8.0 Hz, 1H, ArH), 8.18-8.20 (m, 2H, ArH), 7.71-7.78 (m, 2H, ArH). ¹³C-NMR (100 MHz, CDCl₃): δ 168.5, 136.6, 133.5, 132.5, 130.0, 129.6, 128.8, 128.7, 128.6, 127.1, 116.6. The reported values correspond to the ones in literature.^[3]

1-Acetoxy-1,2-naphthiodoxol-3-(1H)-one (**30**)

Following a reported procedure,^[3] 1-hydroxy-1,2-naphthiodoxol-3-(1H)-one (**29**, 1.57 g, 5.00 mmol, 1.00 equiv.) was suspended in acetic anhydride (5 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 5 mL) and dried *in vacuo* affording **30** (1.48 g, 4.17 mmol, 83%) as a white solid. ¹H-NMR (400 MHz, CDCl₃): δ 8.72 (s, 1H, ArH), 8.35 (s, 1H, ArH), 8.05 (d, *J* = 8.0 Hz, 1H, ArH), 7.96 (d, *J* = 8.0 Hz, 1H, ArH), 7.68-7.77 (m, 2H, ArH), 2.31 (s, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ 176.7, 168.6, 137.7, 134.5, 133.6, 130.0, 129.9, 129.8, 129.2, 128.4, 124.6, 112.7, 20.7. The values of the NMR spectra are in accordance with reported literature data.^[3]

1-Cyano-1,2-naphthiodoxol-3-(1H)-one (**6f**)

Following a reported procedure,^[3] 1-acetoxy-1,2-naphthiodoxol-3-(1H)-one (**30**, 500 mg, 1.40 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (14 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 0.35 mL, 2.8 mmol, 2.00 eq.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 2.5 μ L, 0.014 mmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **6f** (421 mg, 1.30 mmol, 93 %) as an off-white solid. ¹H-NMR (400 MHz, DMSO): δ 8.73 (d, J = 12.0 Hz, 2H, ArH), 8.27 (d, J = 7.6Hz, 1H, ArH), 8.19 (d, J = 7.6Hz, 1H, ArH), 7.75-7.82(m, 2H, ArH). ¹³C-NMR (100 MHz, DMSO): δ 167.4, 137.5, 134.3, 133.4, 130.3, 130.2, 129.6, 128.8, 128.3, 126.7, 113.8, 88.8. The characterization data is in accordance with reported literature values.^[3]

3. Hydantoin synthesis

Optimization of the reaction:

Dry THF (1.5 mL) was added in a flame dried 5 mL test tube containing a teflon coated stir bar, the commercially available amino acid **7b** (67 mg, 0.30 mmol, 1.0 equiv), CBX reagent (**6**) (123 mg, 0.450 mmol, 1.5 equiv) and CsOBz (95.0 mg, 0.375 mmol, 1.25 equiv) under N₂ (vacuum / N₂ exchange). The resulting mixture was stirred for 4 h at rt. After completion of the reaction, the reaction mixture concentrated under reduced pressure. Purification was performed by column chromatography (DCM/MeOH) affording the corresponding hydantoin **8b**.

Table S1. Optimization of the hydantoin formation.

entry	base	equiv.	solvent	concentration (M)	NMR yield (%)
1	CsOBz	1.25	THF	0.2	>95, 83 ^[b]
2	CsOBz	1.1	THF	0.2	53
3	CsOBz	0.2	THF	0.2	20
4	CsOBz	1.25	dioxane	0.2	60
5	CsOBz	1.25	MTBE	0.2	<10
6	CsOBz	1.25	EtOAc	0.2	20
7	CsOBz	1.25	DCM	0.2	45
8	CsOBz	1.25	DMF	0.2	55
9	Cs ₂ CO ₃	1.25	THF	0.2	<10
10	CsOAc	1.25	THF	0.2	<10
11	CsOBz-F ^[c]	1.25	THF	0.2	60
12	NaOBz	1.25	THF	0.2	50
13	KOBz	1.25	THF	0.2	60
14	pyridine	1.25	THF	0.2	60
15	Et ₃ N	1.25	THF	0.2	60
16	DMAP	1.25	THF	0.2	>95, 75 ^[b]
17	DMAP	0.2 ^[d]	THF	0.2	>95
18	DMAP	0.1 ^[d]	THF	0.2	>95
19	DMAP	1.25	THF	0.05	90
20	DMAP	1.25	THF	0.1	90
21	DMAP	1.25	THF	0.3	80

[a] Reaction conditions: 0.3 mmol **7b** (67 mg, 1 equiv), 0.45 mmol CBX **6** (123 mg, 1.5 equiv), 0.375 mmol base (1.25 equiv.) in the corresponding solvent (1.5 mL) for 4 h at RT under N₂. The NMR yield of **8b** is given. [b] Isolated yield (%) after two columns chromatography. [c] Cesium 4-fluorobenzoate. [d] Catalytic amount of DMAP allowed the complete conversion of the amino acid into the corresponding hydantoin, however the time of reaction is not reproducible.

A screening of the hypervalent iodine cyanating reagents was performed (Scheme S1). The structure of the reagent is important, particularly the core of the five membered ring: 1-cyano-3,3-dimethyl-1,2-benziodoxole (CDBX, **6b**) did not promote formation of the hydantoin, instead starting material was recovered. Substituents on the aromatic ring also have an effect on the reactivity. A weak electron donating *t*-Bu group in meta position to the iodine (**6c**) led to lower yields, as well as a strong electron withdrawing nitro group in para position to the iodine (**6d**). Same NMR yield as CBX (**6**) was observed with compound **6e**, bearing a fluorine group in para position, but a lower isolated yield was obtained. The reaction was not complete with **6f**, maybe due to the insolubility of this reagent.

Scheme S1. Reagents screening.

General procedure for hydantoin synthesis:

Dry THF (0.75 mL) was added in a flame dried 1 mL test tube containing a teflon coated stirring bar, the commercially available amino acid **7** (0.15 mmol, 1.0 equiv), CBX reagent (**6**) (61 mg, 0.23 mmol, 1.5 equiv) and DMAP (23.0 mg, 0.188 mmol, 1.25 equiv) under N₂ (vacuum / N₂ exchange). The resulting mixture was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. Purification was performed by preparative TLC (Heptane/ Et₂O) affording the corresponding hydantoin **8**.

(S)-*tert*-Butyl 5-methyl-2,4-dioxoimidazolidine-1-carboxylate (**8a**)

Starting from **7a** (28 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8a** as colorless sticky solid (27 mg, 0.13 mmol, 85%). R_f: 0.38 (Heptane/Et₂O = 25:75). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H, NH), 4.43 (q, *J* = 6.9 Hz, 1H, NCHCH₃), 1.60 (d, *J* = 6.9 Hz, 3H, CH₃), 1.56 (s, 9H, OC(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 151.4, 148.4, 84.7, 57.3, 28.2, 17.0. IR (ν_{max}, cm⁻¹) 3666 (m), 2988 (s), 2969 (s), 2901 (s), 2256 (w), 1936 (w), 1809 (w), 1761 (w), 1722 (w), 1477 (w), 1450 (w), 1404 (m), 1377 (m), 1347 (w), 1317 (w), 1251 (m), 1228 (m), 1196 (w), 1160 (w), 1073 (s), 1054 (s), 908 (m), 874 (w), 826 (w), 803 (w), 780 (w), 737 (m). HRMS (ESI) calcd for C₉H₁₄N₂NaO₄⁺ [M+Na]⁺ 237.0846; found 237.0852. [α]_D²⁰ = + 34.7 (c = 0.29, CHCl₃).

(S)-Benzyl 5-methyl-2,4-dioxoimidazolidine-1-carboxylate (**8b**)

Starting from **7b** (33 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8b** as white solid (33 mg, 0.13 mmol, 85%). R_f: 0.40

(Heptane/Et₂O = 25:75). M. p. 117 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H, *NH*), 7.46 - 7.34 (m, 5H, *ArH*), 5.33 (dd, *J* = 11.9 Hz, 2H, *CH*₂*Ar*), 4.50 (q, *J* = 6.9 Hz, 1H, *NCHCH*₃), 1.60 (d, *J* = 6.9 Hz, 3H, *CH*₃). ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 150.6, 149.6, 134.4, 128.6, 128.6, 128.2, 68.8, 57.1, 16.5. IR (ν_{max}, cm⁻¹) 3248 (w), 2751 (w), 2255 (w), 1816 (m), 1755 (s), 1626 (w), 1499 (w), 1453 (w), 1385 (s), 1340 (s), 1306 (s), 1268 (m), 1211 (m), 1189 (m), 1105 (m), 1062 (w), 1002 (m), 943 (w), 913 (m), 845 (w), 776 (m), 740 (m). HRMS (ESI) calcd for C₁₂H₁₂N₂NaO₄⁺ [M+Na]⁺ 271.0689; found 271.0693. [α]_D²⁰ = + 21.3 (c = 1.00, CHCl₃). Chiral HPLC conditions: ee = 96% ; Chiralpak ID 85:15 Hexane/iPrOH, 1.0 mL/min, 60 min. tr = 27.3 min, λ = 210 nm.

(S)-(9H-Fluoren-9-yl)methyl 5-methyl-2,4-dioximidazolidine-1-carboxylate (8c)

Starting from **7c** (46.7 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8c** as white sticky solid (27 mg, 80 μmol, 54%). R_f: 0.35 (Heptane/Et₂O = 25:75). ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H, *NH*), 7.78 (d, *J* = 7.5 Hz, 2H, *ArH*), 7.69 (dd, *J* = 7.5, 1.3 Hz, 2H, *ArH*), 7.42 (t, *J* = 7.4 Hz, 2H, *ArH*), 7.34 (t, *J* = 7.5 Hz, 2H, *ArH*), 4.72 – 4.57 (m, 2H, *CH*₂*Ar*), 4.35 – 4.23 (m, 2H, *NCHCH*₃, *CH* Fmoc), 1.38 (d, *J* = 6.9 Hz, 3H, *CH*₃). ¹³C NMR (101 MHz, CDCl₃) δ 171.7, 151.2, 150.0, 143.2, 141.5, 128.2, 127.5, 125.1, 120.2, 69.1, 57.4, 46.7, 16.4. IR (ν_{max}, cm⁻¹) 3666 (m), 2988 (s), 2902 (s), 2255 (w), 1934 (w), 1760 (w), 1719 (w), 1475 (w), 1450 (w), 1404 (m), 1388 (m), 1345 (w), 1313 (w), 1256 (m), 1230 (m), 1071 (s), 1050 (s), 909 (m), 872 (w), 733 (s). HRMS (ESI) calcd for C₁₉H₁₆N₂NaO₄⁺ [M+Na]⁺ 359.1002; found 359.1000. [α]_D²⁰ = + 18.3 (c = 1.00, CHCl₃).

(S)-1-Acetyl-5-isopropylimidazolidine-2,4-dione (8d)

Starting from **7d** (20 mg, 0.15 mmol), 30% NMR yield could be observed for acetyl protected hydantoin **8d**. The crude product could not be purified.

(S)-1-benzyl-5-methylimidazolidine-2,4-dione (8e)

Starting from **7e** (27 mg, 0.15 mmol), 30% NMR yield could be observed for benzyl protected hydantoin **8e**. The crude product could not be purified.

(S)-Benzyl 5-isopropyl-2,4-dioxoimidazolidine-1-carboxylate (8g)

Starting from **7g** (37.7 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8g** as colorless sticky solid (31 mg, 0.11 mmol, 75%). R_f: 0.50 (Heptane/Et₂O = 25:75). ¹H NMR (400 MHz, CDCl₃) δ 8.56 (s, 1H, *NH*), 7.46 – 7.32 (m, 5H, *ArH*), 5.39 – 5.25 (m, 2H, *CH*₂*Ar*), 4.39 (d, *J* = 3.4 Hz, 1H, *NCHCH*(CH₃)₂), 2.49 (ddh, *J* = 10.9, 7.0, 3.4 Hz, 1H, *NCHCH*(CH₃)₂), 1.17 (d, *J* = 7.0 Hz, 3H, *CH*₃), 0.91 (d, *J* = 6.9 Hz, 3H, *CH*₃). ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 151.5, 149.8, 134.5, 128.5, 128.4, 128.0, 68.7, 65.4, 29.5, 17.7, 15.4. IR (ν_{max}, cm⁻¹) 3671 (m), 2983 (s), 2972 (s), 2901 (s), 2256 (w), 1927 (w), 1795 (w), 1745 (w), 1450 (w), 1388 (m), 1310 (w), 1249 (m), 1228 (m), 1070 (s), 1052 (s), 908 (s), 872 (w), 735 (s). HRMS (ESI) calcd for C₁₄H₁₆N₂NaO₄⁺ [*M*+Na]⁺ 299.1002; found 299.1007. [α]_D²⁰ = + 26.5 (c = 1.00, CHCl₃).

(S)-Benzyl 5-isobutyl-2,4-dioxoimidazolidine-1-carboxylate (8h)

Starting from **7h** (40 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8h** as colorless sticky solid (24 mg, 83 μmol, 55%). R_f: 0.45 (Heptane/Et₂O = 25:75). ¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H, *NH*), 7.50 – 7.31 (m, 5H, *ArH*), 5.42 – 5.21 (m, 2H, *CH*₂*Ar*), 4.47 (dd, *J* = 7.3, 3.8 Hz, 1H, *NCHCH*₂), 1.95 – 1.76 (m,

3H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.88 (dd, $J = 8.9, 5.9$ Hz, 3H, CH_3), 0.87 (d, $J = 9$ Hz, 3H, CH_3).. ^{13}C NMR (101 MHz, CDCl_3) δ 171.6, 151.6, 149.9, 134.7, 128.9, 128.8, 128.6, 69.0, 59.9, 39.2, 24.1, 23.4, 22.1. IR (ν_{max} , cm^{-1}) 3257 (w), 2962 (w), 2254 (w), 1815 (m), 1745 (m), 1498 (w), 1463 (w), 1386 (m), 1333 (w), 1304 (m), 1269 (w), 1210 (w), 1112 (w), 1029 (w), 910 (s), 776 (w), 735 (s). HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$ 313.1159; found 313.1160. $[\alpha]_{\text{D}}^{20} = +39.3$ ($c = 1.00$, CHCl_3).

(2S,3S)-2-(((Benzyloxy)carbonyl)amino)-3-methylpentanoic acid (8i)

Starting from **7i** (39.8 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/ $\text{Et}_2\text{O} = 20:80$) to afford **8i** as colorless sticky solid (34.7 mg, 0.120 mmol, 80 %). Rf: 0.60 (Heptane/ $\text{Et}_2\text{O} = 20:80$). ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.31 (m, 5H, ArH), 5.41 – 5.25 (m, 2H, CH_2Ar), 4.50 (dd, $J = 3.3, 2.2$ Hz, 1H, NCHCH), 2.30 – 2.15 (m, 1H, $\text{CHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1.68 (dp, $J = 14.4, 7.3$ Hz, 1H, $\text{CHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1.54 (dq, $J = 14.3, 7.5$ Hz, 1H, $\text{CHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 0.95 (t, $J = 7.4$ Hz, 3H, $\text{CHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 0.89 (dd, $J = 7.0, 1.3$ Hz, 3H, $\text{CHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$). ^{13}C NMR (101 MHz, CDCl_3) δ 169.9, 151.6, 150.0, 134.7, 128.9, 128.9, 128.4, 69.1, 64.4, 36.4, 25.3, 13.1, 12.0. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 291.1339; found 291.1340. IR (ν_{max} , cm^{-1}) 3668 (w), 3251 (w), 2979 (w), 2915 (w), 1802 (w), 1745 (w), 1479 (w), 1467 (w), 1391 (w), 1309 (w), 1245 (w), 1150 (w), 1100 (w), 1068 (w), 910 (s), 840 (w), 771 (w), 746 (s), 657 (w). $[\alpha]_{\text{D}}^{20} = +28.7$ ($c = 1.00$, CHCl_3).

(S)-Benzyl 5-benzyl-2,4-dioximidazolidine-1-carboxylate (8j)

Starting from **7j** (45 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/ $\text{Et}_2\text{O} = 25:75$) to afford **8j** as yellowish sticky solid (41 mg, 0.13 mmol, 85%). Rf: 0.52 (Heptane/ $\text{Et}_2\text{O} = 25:75$). ^1H NMR (400 MHz, CDCl_3) δ 7.61 (s, 1H, NH), 7.50 – 7.46 (m, 2H, ArH), 7.45 – 7.38 (m, 3H, ArH), 7.22 – 7.15 (m, 3H, ArH), 6.95 – 6.85 (m, 2H, ArH), 5.38 (s, 2H, CH_2Ar), 4.73 (dd, $J = 5.6, 2.6$ Hz, 1H, NCHCH_2Ar), 3.44 (dd, $J = 14.1, 5.6$ Hz, 1H,

NCHCH₂Ar), 3.26 (dd, $J = 14.1, 2.7$ Hz, 1H, NCHCH₂Ar). ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 150.6, 150.1, 134.8, 133.0, 129.7, 129.0, 128.9, 128.9, 128.8, 127.8, 69.1, 61.9, 35.0. IR ($\nu_{\max}$, cm⁻¹) 3669 (m), 2983 (s), 2901 (s), 2256 (w), 1936 (w), 1815 (w), 1751 (w), 1479 (w), 1447 (w), 1388 (m), 1310 (w), 1253 (m), 1230 (m), 1070 (s), 908 (m), 869 (w), 735 (m). HRMS (ESI) calcd for C₁₈H₁₆N₂NaO₄⁺ [M+Na]⁺ 347.1002; found 347.1006. $[\alpha]_D^{20} = +91.5$ ($c = 1.00$, CHCl₃).

(S)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-((2,6-dichlorobenzyl)oxy)phenyl)propanoic acid (8k)

Starting from **7k** (66 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 20:80) to afford **8k** as white solid (63.0 mg, 0.135 mmol, 90 %). R_f: 0.58 (Heptane/Et₂O = 20:80). ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.33 (m, 2H, ArH), 7.25 – 7.21 (m, 1H, ArH), 7.08 – 7.00 (m, 2H, ArH), 6.97 – 6.89 (m, 2H, ArH), 5.23 (d, $J = 0.8$ Hz, 2H, ArOCH₂Ar), 4.67 (dd, $J = 5.5, 2.7$ Hz, 1H, NCHCH₂), 3.44 (dd, $J = 14.2, 5.5$ Hz, 1H, NCHCH₂), 3.25 (dd, $J = 14.2, 2.7$ Hz, 1H, NCHCH₂), 1.62 (s, 9H, O(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.0, 158.5, 150.8, 148.6, 137.2, 132.2, 130.9, 130.6, 128.6, 125.9, 115.4, 84.8, 65.3, 62.1, 34.5, 28.2. HRMS (ESI) calcd for C₂₂H₂₂Cl₂N₂NaO₅⁺ [M+Na]⁺ 487.0798; found 487.0800. IR ($\nu_{\max}$, cm⁻¹) 3668 (w), 3251 (w), 2985 (w), 2878 (w), 1821 (w), 1745 (w), 1606 (w), 1511 (w), 1378 (w), 1321 (w), 1245 (w), 1163 (w), 1081 (w), 1011 (w), 910 (s), 840 (w), 746 (s), 657 (w). $[\alpha]_D^{20} = +67.0$ ($c = 1.00$, CHCl₃).

(S)-Benzyl 5-((1H-indol-3-yl)methyl)-2,4-dioxoimidazolidine-1-carboxylate (8l)

Starting from **7l** (50.8 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8l** as yellow sticky solid (36 mg, 99 μ mol, 66%). R_f: 0.30

(Heptane/Et₂O = 25:75). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H, NH), 7.76 (s, 1H, NH), 7.51 – 7.39 (m, 6H, ArH), 7.28 (s, 1H, ArH), 7.19 – 7.09 (m, 1H, ArH), 7.01 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, ArH), 6.71 (d, *J* = 2.4 Hz, 1H, ArH), 5.45 – 5.33 (m, 2H, CH₂Ar), 4.73 (dd, *J* = 5.4, 2.6 Hz, 1H, NCHCH₂Ar), 3.61 (dd, *J* = 15.0, 5.4 Hz, 1H, NCHCH₂Ar), 3.49 (dd, *J* = 15.0, 2.6 Hz, 1H, NCHCH₂Ar). ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 151.0, 150.2, 136.0, 134.9, 129.0, 128.9, 128.9, 127.5, 124.0, 122.4, 120.1, 118.7, 111.3, 107.1, 69.1, 61.8, 25.3. HRMS (ESI) calcd for C₂₀H₁₇N₃NaO₄⁺ [M+Na]⁺ 386.1111; found 386.1105. IR (ν_{max}, cm⁻¹) 3669 (m), 2983 (s), 2972 (s), 2901 (s), 2252 (w), 1932 (w), 1799 (w), 1735 (w), 1454 (w), 1402 (m), 1386 (m), 1315 (w), 1251 (m), 1228 (m), 1073 (s), 1054 (s), 908 (m), 872 (w), 735 (m). [α]_D²⁰ = + 20.2 (c = 1.00, CHCl₃).

(R)-2-((*tert*-Butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoic acid (8m)

Starting from **7m** (45.7 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 10:90) to afford **8m** as greenish sticky solid (42.5 mg, 0.129 mmol, 86 %). R_f: 0.63 (Heptane/Et₂O = 10:90). ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H, NH), 7.61 – 7.52 (m, 1H, ArH), 7.39 – 7.29 (m, 1H, ArH), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, ArH), 7.10 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, ArH), 6.95 (d, *J* = 2.4 Hz, 1H, ArH), 4.70 (dd, *J* = 5.3, 2.7 Hz, 1H, NCHCH₂), 3.64 (dd, *J* = 15.0, 5.2 Hz, 1H, NCHCH₂), 3.51 (dd, *J* = 14.9, 2.7 Hz, 1H, NCHCH₂), 1.63 (s, 9H, O(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.9, 151.3, 148.8, 136.0, 127.7, 123.8, 122.4, 120.0, 118.9, 111.3, 107.4, 84.7, 61.8, 28.2, 25.4. HRMS (ESI) calcd for C₁₇H₁₉N₃NaO₄⁺ [M+Na]⁺ 352.1268; found 352.1262. IR (ν_{max}, cm⁻¹) 2979 (w), 2896 (w), 1827 (w), 1751 (w), 1372 (w), 1321 (w), 1226 (w), 1163 (w), 1068 (w), 1011 (w), 914 (s), 841 (w), 747 (s), 644 (w). [α]_D²⁰ = - 55.0 (c = 1.00, CHCl₃).

Benzyl (R)-5-((benzylthio)methyl)-2,4-dioxoimidazolidine-1-carboxylate (8n)

Starting from **7n** (52 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8n** as yellowish sticky solid (31 mg, 83 μ mol, 55%). Rf: 0.45 (Heptane/Et₂O = 25:75). ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H, NH), 7.48 – 7.21 (m, 10H, ArH), 5.31 (s, 2H, CH₂Ar), 4.69 (dd, *J* = 4.5, 2.3 Hz, 1H, NCHCH₂), 3.72 – 3.53 (m, 2H, SCH₂Ar), 3.25 (dd, *J* = 14.6, 4.5 Hz, 1H, NCHCH₂), 3.06 (dd, *J* = 14.7, 2.4 Hz, 1H, NCHCH₂). ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 151.5, 149.9, 137.4, 134.6, 129.1, 128.9, 128.9, 128.7, 128.5, 127.5, 69.2, 61.4, 37.5, 30.7. IR ($\nu_{\max}$, cm⁻¹) 3669 (m), 2988 (s), 2908 (m), 2259 (w), 1824 (w), 1754 (w), 1450 (w), 1409 (m), 1390 (m), 1310 (w), 1253 (m), 1228 (m), 1070 (s), 910 (s), 867 (w), 735 (s). HRMS (ESI) calcd for C₁₉H₁₈N₂NaO₄S⁺ [M+Na]⁺ 393.0879; found 393.0885. [α]_D²⁰ = + 10.2 (c = 1.00, CHCl₃).

(S)-Benzyl 5-(2-(methylthio)ethyl)-2,4-dioximidazolidine-1-carboxylate (8o)

Starting from **7o** (43 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 10:90) to afford **8o** as white sticky solid (31 mg, 0.10 mmol, 67 %). Rf: 0.46 (Heptane/Et₂O = 10:90). ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H, NH), 7.42 – 7.23 (m, 5H, ArH), 5.36 – 5.13 (m, 2H, CH₂Ar), 4.54 (dd, *J* = 6.3, 3.8 Hz, 1H, NCHCH₂), 2.59 – 2.37 (m, 2H, CH₂CH₂S), 2.33 – 2.20 (m, 2H, CH₂CH₂S), 1.94 (s, 3H, SCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 151.4, 150.0, 134.6, 128.9, 128.9, 128.6, 69.2, 59.9, 28.7, 28.4, 15.3. HRMS (ESI) calcd for C₁₄H₁₆N₂NaO₄S⁺ [M+Na]⁺ 331.0723; found 331.0730. IR ($\nu_{\max}$, cm⁻¹) 3225 (w), 2979 (w), 2909 (w), 1821 (w), 1745 (m), 1498 (w), 1460 (w), 1378 (m), 1353 (w), 1302 (m), 1264 (w), 1195 (w), 1150 (w), 1106 (w), 1075 (w), 916 (s), 859 (w), 746 (s), 695 (w), 657 (w). [α]_D²⁰ = + 44.5 (c = 1.00, CHCl₃).

2-(((Benzyloxy)carbonyl)amino)-6-((tert-butoxycarbonyl)amino)hexanoic acid (8p)

Starting from **7p** (57 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 10:90) to afford **8p** as colorless sticky solid (50 mg, 0.12 mmol, 82 %). R_f: 0.58 (Heptane/Et₂O = 10:90). ¹H NMR (400 MHz, CDCl₃) δ 8.86 (s, 1H, *NH*), 7.46 – 7.31 (m, 5H, *ArH*), 5.41 – 5.24 (m, 2H, *CH*₂*Ar*), 4.55 (s, 1H, *NH*), 4.49 (dd, *J* = 6.2, 3.2 Hz, 1H, *NCHCH*₂), 3.05 (q, *J* = 6.5 Hz, 2H, *CH*₂*NHBoc*), 2.15 – 1.90 (m, 2H, *NCHCH*₂), 1.43 (m, 13H, *NCHCH*₂*CH*₂*CH*₂, *O*(*CH*₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 171.0, 156.1, 151.7, 150.0, 134.8, 128.9, 128.9, 128.6, 79.5, 69.0, 61.0, 40.3, 29.7, 29.5, 28.5, 20.4. HRMS (ESI) calcd for C₂₀H₂₇N₃NaO₆⁺ [*M*+*Na*]⁺ 428.1792; found 428.1795. IR (ν_{max}, cm⁻¹) 2985 (w), 2896 (w), 1808 (w), 1764 (w), 1511 (w), 1454 (w), 1391 (w), 1296 (w), 1252 (w), 1176 (w), 1100 (w), 1068 (w), 980 (w), 910 (s), 853 (w), 739 (s), 651 (w). [α]_D²⁰ = + 34.3 (c = 1.00, CHCl₃).

(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-(tert-butoxy)-5-oxopentanoic acid (8q)

Starting from **7q** (63.8 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 20:80) to afford **8q** as colorless sticky solid (36.5 mg, 81.0 μmol, 54 %). R_f: 0.46 (Heptane/Et₂O = 20:80). ¹H NMR (400 MHz, CDCl₃) δ 7.85 (s, 1H, *NH*), 7.81 – 7.68 (m, 4H, *ArH*), 7.46 – 7.30 (m, 4H, *ArH*), 4.71 – 4.57 (m, 2H, *OCH*₂*CH*), 4.44 – 4.27 (m, 2H, *NCHCH*₂, *OCH*₂*CH*), 2.37 – 2.06 (m, 4H, *NCHCH*₂*CH*₂), 1.43 (s, 9H, *OC*(*CH*₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 170.2, 150.7, 150.0, 143.3, 143.2, 141.5, 141.4, 128.2, 127.5, 125.3, 125.2, 120.3, 120.2, 81.2, 69.3, 60.3, 46.7, 29.5, 28.2, 25.0. HRMS (ESI) calcd for C₂₅H₂₆N₂NaO₆⁺ [*M*+*Na*]⁺ 473.1683; found 473.1686. IR (ν_{max}, cm⁻¹) 3253 (w), 2959 (w), 1807 (w), 1749 (m), 1474 (w), 1448 (w), 1384 (m), 1372 (m), 1308 (m), 1244 (w), 1212 (w), 1161 (w), 1109 (w), 1071 (w), 1045 (w), 975 (w), 956 (w), 917 (s), 841 (w), 745 (s), 693 (w), 655 (m), 623 (m). [α]_D²⁰ = + 10.2 (c = 1.00, CHCl₃).

(S)-Benzyl 5-(2-(tert-butoxy)-2-oxoethyl)-2,4-dioxoimidazolidine-1-carboxylate (8r)

Starting from **7r** (48.5 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 10:90) to afford **8r** as white sticky solid (37.6 mg, 0.108 mmol, 72 %). R_f: 0.55 (Heptane/Et₂O = 10:90). ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H, *NH*), 7.52 – 7.31 (m, 5H, *ArH*), 5.42 – 5.24 (m, 2H, *CH*₂*Ar*), 4.53 (dd, *J* = 5.2, 2.9 Hz, 1H, *NCHCH*₂*CO*), 3.15 (dd, *J* = 17.1, 5.2 Hz, 1H, *NCHCH*₂*CO*), 3.01 (dd, *J* = 17.1, 2.9 Hz, 1H, *NCHCH*₂*CO*), 1.38 (s, 9H, *OC(CH*₃*)*₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.4, 167.9, 151.6, 150.1, 134.8, 128.8, 128.8, 128.4, 82.7, 69.1, 57.7, 35.1, 28.0. HRMS (ESI) calcd for C₁₇H₂₀N₂NaO₆⁺ [M+Na]⁺ 371.1214; found 371.1218. IR (ν_{max}, cm⁻¹) 3263 (w), 2979 (w), 2903 (w), 1815 (w), 1751 (m), 1460 (w), 1372 (w), 1359 (w), 1309 (w), 1150 (w), 1106 (w), 1049 (w), 992 (w), 910 (s), 916 (s), 834 (w), 739 (s), 695 (w), 651 (w). [α]_D²⁰ = + 28.7 (c = 1.00, Ethanol).

(S)-tert-Butyl 5-((benzyloxy)methyl)-2,4-dioxoimidazolidine-1-carboxylate (8s)

Starting from **7s** (53.5 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 20:80) to afford **8s** as colorless sticky solid (36 mg, 95 μmol, 64 %). R_f: 0.60 (Heptane/Et₂O = 20:80). ¹H NMR (400 MHz, CDCl₃) δ 7.60 (s, 1H, *NH*), 7.39 – 7.19 (m, 5H, *ArH*), 4.60 – 4.42 (m, 3H, *NCHCH*₂*OCH*₂), 4.03 (dd, *J* = 10.0, 2.7 Hz, 1H, *NCHCH*₂), 3.90 (dd, *J* = 10.0, 1.8 Hz, 1H, *NCHCH*₂), 1.49 (s, 9H, *OC(CH*₃*)*₃). ¹³C NMR (101 MHz, CDCl₃) δ 169.1, 151.3, 148.2, 137.1, 128.5, 128.0, 127.6, 84.5, 73.5, 66.0, 61.8, 28.0. HRMS (ESI) calcd for C₁₆H₂₀N₂NaO₅⁺ [M+Na]⁺ 343.1264; found 343.1266. IR (ν_{max}, cm⁻¹) 3661 (w), 3236 (w), 2985 (w), 2903 (w), 2760 (w), 1812 (w), 1751 (m), 1611 (w), 1514 (w), 1453 (w), 1369 (m), 1317 (w), 1280 (w), 1245 (w), 1216 (w), 1155 (w), 1104 (w), 1076 (w), 1052 (w), 994 (w), 914 (s), 848 (w), 745 (s), 703 (w), 670 (w), 651 (w), 618 (w). [α]_D²⁰ = + 4.0 (c = 1.00, CHCl₃).

(S)-tert-Butyl 5-cyclopropyl-2,4-dioxoimidazolidine-1-carboxylate (8t)

Starting from **7t** (32.3 mg, 0.150 mmol), the crude product was purified by preparative TLC (DCM/EtOAc = 80:20) to afford **8t** as colorless solid (23.5 mg, 98.0 μ mol, 65 %). R_f = 0.30 (DCM/EtOAc: 4/1) M.p. 145-146 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (bs, 1H, NH), 4.19 (d, *J* = 7.0 Hz, 1H, NCHCO), 1.57 (s, 9H, Boc), 1.30 – 1.23 (m, 1H, CH(CH₂)₂), 0.80 – 0.70 (m, 1H, CH₂), 0.70 – 0.63 (m, 2H, CH₂), 0.63 – 0.52 (m, 1H, CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 169.8, 151.5, 148.6, 84.7, 63.0, 28.2, 12.8, 3.7, 1.8. IR (v_{max}, cm⁻¹) 3262 (m), 2983 (m), 1808 (s), 1751 (s), 1370 (s), 1332 (s), 1155 (s), 1098 (s), 1028 (m), 913 (m), 850 (m), 767 (m), 736 (s), 666 (m), 654 (m). HRMS (ESI) calcd for C₁₁H₁₆N₂NaO₄⁺ [M+Na]⁺ 263.1002; found 263.1007. [α]_D²⁰ = + 24.2 (c = 0.4, CHCl₃).

(S)-Tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (8u)

Starting from **7u** (17.3 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 20:80) to afford **8u** as white solid (13 mg, 93 μ mol, 62 %). R_f: 0.13 (Heptane/Et₂O = 20:80). ¹H NMR (400 MHz, DMSO-d₆) δ 10.75 (s, 1H, NH), 4.11 (dd, *J* = 9.0, 7.5 Hz, 1H, NCH), 3.46 (dt, *J* = 10.8, 7.6 Hz, 1H, NCH₂), 3.04 (ddd, *J* = 10.8, 7.9, 4.8 Hz, 1H, NCH₂), 2.10 – 2.01 (m, 1H, NCH₂CH₂CH₂), 2.00 – 1.85 (m, 2H, NCH₂CH₂CH₂), 1.71 – 1.58 (m, 1H, NCH₂CH₂CH₂). ¹³C NMR (101 MHz, DMSO-d₆) δ 175.4, 161.0, 64.0, 44.9, 26.7, 26.6. HRMS (ESI) calcd for C₄H₇N₂O₂⁺ [M+H]⁺ 115.0502; found 115.0499. [α]_D²⁰ = - 118.11 (c = 0.51, Ethanol). The characterization data is in accordance with reported literature values.^[8]

Benzyl 2,4-dioxoimidazolidine-1-carboxylate (8v)

Starting from **7v** (31.4 mg, 0.150 mmol), the crude product was purified by preparative TLC (DCM/MeOH = 90:10) to afford **8v** as white sticky solid (31 mg, 0.13 mmol, 88 %). R_f: 0.69 (DCM/MeOH = 90:10). ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.35 (m, 5H, ArH), 5.32 (s, 2H, OCH₂Ar), 4.32 (s, 2H, NCH₂). ¹³C NMR (101 MHz, CDCl₃) δ 166.8, 150.8, 149.6, 134.5,

^[8] Kumar, V.; Rana, H.; Sankolli, R.; Kaushik, M. P. *Tetrahedron Lett.* **2011**, 52, 6148.

128.9, 128.8, 128.5, 69.1, 49.9. HRMS (ESI) calcd for $C_{11}H_{10}N_2NaO_4^+$ $[M+Na]^+$ 257.0533; found 257.0540. IR (ν_{max} , cm^{-1}) 3244 (w), 2998 (w), 2903 (w), 1815 (w), 1764 (m), 1435 (w), 1391 (w), 1353 (w), 1290 (w), 1201 (w), 1106 (w), 1056 (w), 973 (w), 916 (s), 834 (w), 746 (s), 651 (w), 632 (w).

***Tert*-butyl 5,5-dimethyl-2,4-dioxoimidazolidine-1-carboxylate (**8w**)**

Starting from **7w** (30.5 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 25:75) to afford **8w** as white solid (19.0 mg, 83.0 μ mol, 56 %). R_f = 0.45 (Heptane/Et₂O = 25:75) M.p. 157-159 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.94 (bs, 1H, NH), 1.64 (s, 6H, NCH(CH₃)₂), 1.57 (s, 9H, C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 174.9, 151.3, 148.5, 84.5, 64.7, 28.2, 23.2. IR (ν_{max} , cm^{-1}) 3669 (w), 3245 (w), 2983 (s), 2906 (m), 1813 (m), 1752 (s), 1459 (w), 1388 (m), 1369 (s), 1330 (s), 1255 (m), 1228 (m), 1163 (m), 1078 (s), 1073 (s), 1063 (s), 940 (w), 909 (w), 845 (w). HRMS (ESI/QTOF) m/z : $[M+Na]^+$ Calcd for $C_{10}H_{16}N_2NaO_4^+$ 251.1002; Found 251.1005.

Hydantoin hydrogenolysis deprotection:

A flame dried 50 mL flask containing palladium hydroxide on carbon (4.3 mg, 6.1 μ mol, 5 mol%) and equipped with a teflon coated stirring bar, was placed under nitrogen atmosphere (vacuum / N₂ exchange). A solution of the hydantoin **8b** (30 mg, 0.12 mmol, 1 equiv) in dry MeOH (6.0 mL, 0.02 M) was added. The flask was then placed under hydrogen atmosphere (vacuum / H₂ cycles) and the solution was stirred at room temperature for 4 h. The solution was then filtrated over a hplc filter and concentrated under reduced pressure to provide the (S)-5-methylimidazolidine-2,4-dione **10** (14 mg, 0.12 mmol, 100 % yield) as a white solid.

(S)-5-Methylimidazolidine-2,4-dione (**10**)

¹H NMR (400 MHz, DMSO-d₆) δ 10.57 (s, 1H, NH), 7.87 (s, 1H, NH), 4.02 (qd, J = 6.9, 1.2 Hz, 1H, NCHCH₃), 1.21 (d, J = 6.9 Hz, 3H, NCHCH₃). ¹³C NMR (101 MHz, DMSO-d₆) δ 176.8, 157.1, 53.3, 17.2. HRMS (ESI) calcd for C₄H₇N₂O₂⁺ [M+H]⁺ 115.0502; found 115.0501. $[\alpha]_D^{20}$ = - 30.7 (c = 0.43, Ethanol). The characterization data is in accordance with reported literature values.^[9]

^[9] Konnert, L.; Reneaud, B.; Marcia de Figueiredo, R.; Campagne, J. M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2014**, 79, 10132.

Procedure for hydantoin gram scale synthesis:

In a flame dried 50 mL balloon containing a teflon coated stirring bar were added **7b** (1.0 g, 4.5 mmol, 1 equiv), CBX **6** (1.84 g, 6.72 mmol, 1.5 equiv) and N,N-dimethylpyridin-4-amine (0.68 g, 5.6 mmol, 1.25 equiv). Then, the test tube was evacuated and backfilled 3 times with N₂. Then dry THF (22.4 mL) was added, and the resulting white mixture was stirred for 16 h. Addition of 20 mL of pentane to the reaction mixture lead to full precipitation of salt **8**. Then, the mixture was filtrated over a plug of celite to remove the main part of the salt formed. The celite plug was washed with 2x20 mL of THF:pentane (1:1) and the filtrate was evaporated to give the crude hydantoin in 70% purity. The pad was then washed with 50 mL of DCM, and after concentration under reduced pressure salt **9** was recovered (1.75 g, 4.73 mmol, 84%). The crude material was then purified by column (full DCM to DCM/Ethyl acetate 80:20) to provide the (S)-benzyl 5-methyl-2,4-dioxoimidazolidine-1-carboxylate **8b** (1.2 g, 4.5 mmol, 100 % yield) with 93 % purity.

General procedure for hydantoin synthesis from peptides:

Dry THF (1.5 mL) was added in a flame dried 1 mL test tube containing a teflon coated stirring bar, the peptide **11** (0.15 mmol, 1.0 equiv), CBX reagent (**6**) (61 mg, 0.23 mmol, 1.5 equiv) and DMAP (23.0 mg, 0.188 mmol, 1.25 equiv) under N₂ (vacuum / N₂ exchange). The resulting mixture was stirred for 36 h at room temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. Purification was performed by preparative TLC (Heptane/ Et₂O) affording the corresponding hydantoin **12**.

Benzyl ((S)-1-((S)-5-methyl-2,4-dioxoimidazolidin-1-yl)-1-oxopropan-2-yl)carbamate (**12a**)

Starting from **11a** (44 mg, 0.15 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 10:90) to afford **12a** as white sticky solid (38 mg, 0.12 mmol, 80 %). R_f: 0.5 (Heptane/Et₂O = 10:90). ¹H NMR (400 MHz, CDCl₃, mixture of rotamers not fully resolved, only the major rotamer is described) δ 8.24 (s, 1H, NH), 7.40 – 7.28 (m, 5H, ArH), 5.52 – 5.26 (m, 2H, OCH₂Ar), 5.17 – 5.04 (m, 2H, NCHCH₃), 4.68 – 4.45 (m, 1H, NH), 1.74 – 1.51 (m, 3H, CH₃), 1.51 – 1.38 (m, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃, mixture of rotamers not fully resolved, only the major rotamer is described) δ 172.9, 171.7, 155.8, 152.0, 136.3, 128.7, 128.4, 128.2, 67.2, 57.2, 50.8, 18.2, 16.2. HRMS (ESI) calcd for C₁₅H₁₇N₃NaO₅⁺ [M+Na]⁺ 342.1060; found 342.1062. IR (ν_{max}, cm⁻¹) 3658 (w), 3349 (w), 2976 (m), 2919 (w), 2894 (m), 1918 (w), 1810 (w), 1747 (w), 1695 (w), 1643 (w), 1456 (w), 1385 (w), 1329 (w), 1275 (w), 1240 (w), 1155 (w), 1087 (m), 1048 (m), 914 (s), 883 (w), 839 (w), 750 (s), 682 (w), 653 (w), 632 (w). [α]_D²⁰ = - 9.7 (c = 1.00, CHCl₃). Chiral HPLC conditions: de = 72% ; Chiralpak ID 80:20 Hexane/iPrOH, 1.0 mL/min, 60 min. tr = 27.1 min, λ = 210 nm.

(S)-Benzyl (2-(5-benzyl-2,4-dioxoimidazolidin-1-yl)-2-oxoethyl)carbamate (12b)

Starting from **11b** (53.5 mg, 0.150 mmol), the crude product was purified by preparative TLC (Heptane/Et₂O = 10:90) to afford **12b** as white sticky solid (36 mg, 95 μ mol, 64 %). R_f: 0.65 (Heptane/Et₂O = 10:90). ¹H NMR (400 MHz, CDCl₃) δ 7.49 – 6.88 (m, 10H, ArH), 5.55 – 5.40 (m, 1H, NH), 5.17 (s, 2H, OCH₂Ar), 4.82 (ddd, *J* = 5.7, 4.5, 2.5 Hz, 1H, NCHCH₂), 4.54 (ddd, *J* = 19.3, 8.4, 5.9 Hz, 1H, NCH₂CO), 4.40 – 4.23 (m, 1H, NCH₂CO), 3.53 (ddd, *J* = 14.2, 5.8, 1.8 Hz, 1H, NCHCH₂Ar), 3.29 (dd, *J* = 14.0, 2.5 Hz, 1H, NCHCH₂Ar). ¹³C NMR (101 MHz, CDCl₃) δ 170.4, 168.9, 156.6, 152.3, 136.2, 133.1, 129.7, 129.0, 128.7, 128.5, 128.3, 127.9, 67.5, 61.4, 46.4, 34.3. HRMS (ESI) calcd for C₂₀H₁₉N₃NaO₅⁺ [M+Na]⁺ 404.1217; found 404.1221. IR (ν_{max} , cm⁻¹) 3670 (w), 2985 (w), 2901 (w), 1801 (w), 1740 (w), 1711 (w), 1615 (w), 1510 (w), 1456 (w), 1388 (w), 1268 (w), 1245 (w), 1174 (w), 1134 (w), 1059 (w), 989 (w), 916 (s), 843 (w), 743 (s), 700 (w), 656 (w), 632 (w). [α]_D²⁰ = + 42.1 (*c* = 0.52, CHCl₃). Chiral HPLC conditions: ee = 44% ; Chiralpak ID 80:20 Hexane/iPrOH, 1.0 mL/min, 60 min. tr = 40.7 min, λ = 210 cm⁻¹.

4. Possible transition states for cyanation

Concerning transfer of the cyanide group, several pathways can be proposed (Scheme 2). A first possibility would be nucleophilic attack on the carbon of the cyanide group, however when considering that the most electrophilic position is usually on the iodine for this type of reagent, this mechanism is less probable.^[10] Consequently, attack on the iodine atom, followed by reductive elimination on iodine, appears more feasible. Mechanisms involving a single electron transfer and subsequent formation of radical intermediates also constitute an alternative when considering the strong oxidizing properties of hypervalent iodine reagents. Finally, as recently demonstrated by our group,^[11] a concerted mechanism via a three-atom transition state is also possible. Further computational studies could be done to better highlight the transition state involved.

Scheme 2. Speculative transition states for the cyanide group transfer.

¹⁰ Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. *Angew. Chem. Int. Ed.* **2016**, 55, 4436.

¹¹ Frei, R.; Courant, T.; Wodrich, M. D.; Waser, J. *Chem. Eur. J.* **2015**, 21, 2662.

5. Spectra of New Compounds

^1H -NMR (400 MHz, CDCl_3) of compound **8a**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8a**

IR of compound 8a

^1H -NMR (400 MHz, CDCl_3) of compound **8b**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8b**

IR of compound 8b

HPLC of compound 8b

Chiralpak ID 85:15 Hexane/iPrOH, 1.0 mL/min, 60 min.

Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.893	BV	0.6697	4287.84912	91.66563	1.9051
2	27.249	VB	1.9500	2.20787e5	1442.20618	98.0949

Totals : 2.25075e5 1533.87180

HPLC of racemic compound 8b

Chiralpak ID 85:15 Hexane/iPrOH, 1.0 mL/min, 60 min.

Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.976	BB	1.4454	2.71847e5	2289.29443	46.3703
2	25.251	BBA	1.8384	3.14404e5	2102.80762	53.6297

Totals : 5.86251e5 4392.10205

^1H -NMR (400 MHz, CDCl_3) of compound **8c**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8c**

IR of compound 8c

¹H-NMR (400 MHz, CDCl₃) crude of compound **8d**

¹H-NMR (400 MHz, CDCl₃) crude of compound **8e**

^1H -NMR (400 MHz, CDCl_3) of compound **8g**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8g**

IR of compound 8g

^1H -NMR (400 MHz, CDCl_3) of compound **8h**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8h**

IR of compound 8h

¹H-NMR (400 MHz, CDCl₃) of compound **8i**

¹³C-NMR (100 MHz, CDCl₃) of compound **8i**

IR of compound 8i

¹H NMR spectrum (400 MHz, CDCl₃) of (S)-1-benzyl-2-((benzyloxy)carbonyl)imidazole. The spectrum shows peaks in the aromatic region (7.1-7.6 ppm), a methylene singlet (4.7 ppm), a methoxy singlet (3.4 ppm), and a benzyl methylene doublet (2.9 ppm). Integration values are provided for several peaks.

Chemical structure: O=C1NC(=O)[C@H](Cc2ccccc2)N1C(=O)OCc3ccccc3

Peak list (ppm): 7.61, 7.49, 7.48, 7.48, 7.47, 7.47, 7.44, 7.43, 7.43, 7.42, 7.41, 7.41, 7.40, 7.40, 7.39, 7.38, 7.38, 7.22, 7.20, 7.20, 7.19, 7.19, 7.16, 7.16, 7.15, 7.15, 6.92, 6.92, 6.91, 6.90, 6.88, 6.88, 4.74, 4.73, 4.72, 3.47, 3.45, 3.43, 3.42, 3.39, 3.38, 3.24, 3.23, 3.28, 3.27, 3.24, 3.23.

Integration values: 0.97, 2.00, 3.03, 3.01, 2.00, 2.06, 1.00, 1.03, 1.04.

Chemical structure: O=C1NC(=O)[C@H](Cc2ccccc2)N1C(=O)OCc3ccccc3

¹³C NMR spectrum (ppm):

- 169.95
- 150.58
- 150.08
- 134.82
- 132.00
- 129.05
- 129.02
- 128.91
- 128.80
- 127.83
- 69.14
- 61.96
- 35.00

IR of compound **8j**

^1H -NMR (400 MHz, CDCl_3) of compound **8k**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8k**

IR of compound **8k**

^1H -NMR (400 MHz, CDCl_3) of compound **81**

^{13}C -NMR (100 MHz, CDCl_3) of compound **81**

IR of compound 8l

¹H-NMR (400 MHz, CDCl₃) of compound 8m

¹³C-NMR (100 MHz, CDCl₃) of compound 8m

IR of compound **8m**

^1H -NMR (400 MHz, CDCl_3) of compound **8n**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8n**

IR of compound **8n**

^1H -NMR (400 MHz, CDCl_3) of compound **8o**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8o**

IR of compound 8o

^1H -NMR (400 MHz, CDCl_3) of compound **8p**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8p**

IR of compound 8p

^1H -NMR (400 MHz, CDCl_3) of compound **8q**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8q**

IR of compound 8q

Chemical structure: CC(C)(C)OC(=O)C[C@@H](C(=O)OCc1ccccc1)C(=O)N

¹H NMR spectrum (CDCl₃) data:

Chemical Shift (ppm)	Integration
1.38	9.00
3.00 - 3.18	1.00
4.52 - 4.54	1.00
5.31 - 5.37	2.13
7.33 - 7.43	5.00
8.58	0.04

The image displays the ¹³C NMR spectrum of a chemical compound, with the chemical structure shown above the spectrum. The x-axis represents the chemical shift in ppm, ranging from -10 to 210. The spectrum shows several peaks, with the following chemical shifts assigned to specific carbon atoms in the structure:

- 170.42 ppm: Carbonyl carbon of the benzyl carbamate group.
- 167.91 ppm: Carbonyl carbon of the benzyl carbamate group.
- 151.63 ppm: Carbonyl carbon of the benzyl carbamate group.
- 150.11 ppm: Carbonyl carbon of the benzyl carbamate group.
- 134.75 ppm: Aromatic carbon of the benzyl group.
- 128.84 ppm: Aromatic carbon of the benzyl group.
- 128.82 ppm: Aromatic carbon of the benzyl group.
- 128.42 ppm: Aromatic carbon of the benzyl group.
- 82.73 ppm: Aromatic carbon of the benzyl group.
- 69.07 ppm: Aromatic carbon of the benzyl group.
- 57.73 ppm: Aromatic carbon of the benzyl group.
- 35.05 ppm: Aromatic carbon of the benzyl group.
- 28.01 ppm: Aromatic carbon of the benzyl group.

The chemical structure is a benzyl carbamate derivative, specifically a benzyl (2-((tert-butoxycarbonyl)amino)acrylate). The structure shows a benzyl group attached to a carbamate group, which is further attached to a tert-butoxycarbonyl group.

IR of compound 8r

^1H -NMR (400 MHz, CDCl_3) of compound **8s**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8s**

IR of compound 8s

^1H -NMR (400 MHz, CDCl_3) of compound **8t**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8t**

IR of compound 8t

¹H-NMR (400 MHz, DMSO-*d*₆) of compound **8u**

¹³C-NMR (100 MHz, DMSO-*d*₆) of compound **8u**

^1H -NMR (400 MHz, CDCl_3) of compound **8v**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8v**

IR of compound 8v

^1H -NMR (400 MHz, CDCl_3) of compound **8w**

^{13}C -NMR (100 MHz, CDCl_3) of compound **8w**

IR of compound 8w

^1H -NMR (400 MHz, $\text{DMSO-}d_6$) of compound **10**

^{13}C -NMR (100 MHz, $\text{DMSO-}d_6$) of compound **10**

^1H -NMR (400 MHz, CDCl_3) of compound **12a**

^{13}C -NMR (100 MHz, CDCl_3) of compound **12a**

IR of compound **12a**

HPLC of compound **12a**

Chiralpak ID 80:20 Hexane/iPrOH, 1.0 mL/min, 60 min.

Signal 2: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.876	MF	1.3271	1266.51709	15.90585	13.9515
2	27.116	FM	1.9772	7811.45410	65.84715	86.0485

Totals : 9077.97119 81.75299

HPLC of diastereoisomers of compound **12a**

Chiralpak ID 80:20 Hexane/iPrOH, 1.0 mL/min, 60 min.

Signal 2: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.963	BV	1.2255	1.44973e4	173.73763	33.3365
2	27.333	VB	1.9882	2.89905e4	197.30777	66.6635

Totals : 4.34878e4 371.04539

Signal 2: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.963	MM	1.1682	1.09927e4	156.83369	42.5651
2	27.350	MM	1.7280	1.48330e4	143.06259	57.4349

Totals : 2.58257e4 299.89629

^1H -NMR (400 MHz, CDCl_3) of compound **12b**

^{13}C -NMR (100 MHz, CDCl_3) of compound **12b**

IR of compound **12b**

HPLC of compound **12b**

Chiralpak ID 80:20 Hexane/iPrOH, 1.0 mL/min, 60 min.

Signal 2: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.345	BB	1.6992	4627.91846	36.11084	28.0741
2	40.697	BB	3.0536	1.18567e4	45.68857	71.9259

Totals : 1.64846e4 81.79942

HPLC of racemate of compound **12b**

Chiralpak ID 80:20 Hexane/iPrOH, 1.0 mL/min, 60 min.

Signal 2: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.833	BB	1.3789	4.23652e4	422.83505	50.6460
2	37.785	BB	2.5987	4.12845e4	206.12225	49.3540

Totals : 8.36497e4 628.95731