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Oxidative Homologation of Aldehydes to α-Ketoaldehydes by using Iodoform, *o*-Iodoxybenzoic Acid, and Dimethyl Sulfoxide

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Keywords: Homologation / Aldehydes / Oxidation / Synthetic methods

An efficient three-step synthetic route to α-ketoaldehydes starting from aryl aldehydes is reported. The aldehydes were treated with *i*PrMgCl and iodoform to obtain β-diiodoalcohols, which were then oxidized with *o*-iodoxybenzoic acid at room temperature to the corresponding β-diiodoketones. Subsequent reaction of the β-diiodoketone to the α-ketoaldehyde occurred under oxygen transfer from dimethyl sulfoxide. These sensitive products were in situ cyclized with *o*-phenylenediamine to form the stable monosubstituted quinoxalines, which could be characterized and isolated easily.

Introduction

α-Ketoaldehydes are a versatile, highly reactive moiety for the synthesis of heterocyclic compounds.[1] Cyclization of α-ketoaldehydes has been utilized in the design of peptidyl α-ketoaldehydes, which inhibit the 20 S proteasome,[2] and various synthetic approaches to such desirable peptidic α-ketoaldehydes have been established. A frequently employed method, the oxidation of α-diazoketones by using dimethyldioxirane (DMD), imposes a potential hazard in the scale up of the synthesis.[3] Another versatile method, recently developed by Rademann et al., starts with the C-acylation of polymer-supported 2-phosphoranylidene acetates linked to protected amino acids, which is followed by saponification of the ester, decarboxylation, and oxidation with DMD.[4]

The majority of the documented syntheses of α-ketoaldehydes rely on the oxidation of acetophenone by SeO_2.[5] The alternative iodination of acetophenone under acidic conditions and subsequent oxidation of the phenacyl iodides with dimethyl sulfoxide has distinct merits.[6] However, all these methods are unfavorable with respect to reagent toxicity, or require harsh reaction conditions or suffer from insufficient yields. An alternative approach to non-peptidic aldehydes utilizes dihalide compounds and dimethyl sulfoxide under mild conditions.[7] Motivated by this method, we investigated the transformation of aldehydes into α-ketoaldehydes via β-diiodoketone intermediates and finally applied the procedure to the synthesis of peptidic substrates.

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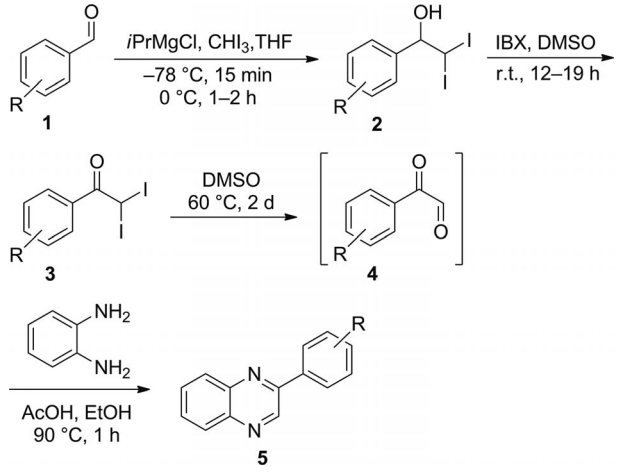
Results and Discussion

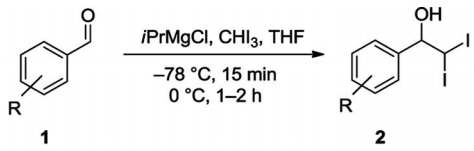
Here we report the efficient three-step synthetic route to α-ketoaldehydes starting from aryl aldehydes. Initially, the aldehydes were treated with *i*PrMgCl and iodoform to obtain desired β-diiodoalcohols **2**, which were then oxidized with *o*-iodoxybenzoic acid (IBX) at room temperature to the corresponding β-diiodoketones **3**. Compounds **3** are a valuable reactive species on there own. Subsequent reaction of β-diiodoketones **3** with α-ketoaldehydes **4** occurred under oxygen transfer from dimethyl sulfoxide. These sensitive products were then cyclized in situ with *o*-phenylenediamine to form stable monosubstituted quinoxalines **5**, which could be characterized and isolated easily (Scheme 1).



Scheme 1. Synthesis route to α-ketoaldehydes/quinoxalines.

The synthesis of β-diiodoalcohols from simple aromatic aldehydes was described by Braun et al.[8] and was extended to substituted benzaldehydes. A diverse array of commercial, substituted benzaldehydes **1** was subjected to the reaction conditions, and the corresponding products were iso-

Table 1. Scope of the reaction.[a]



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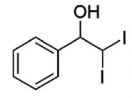
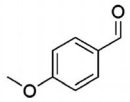
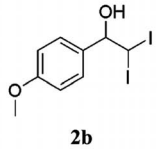
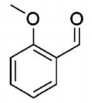
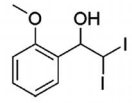
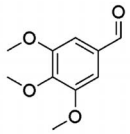
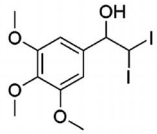
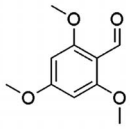
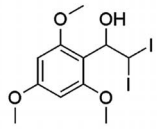
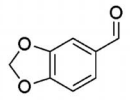
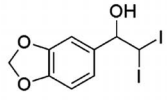
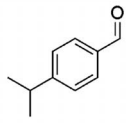
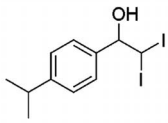
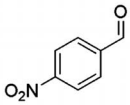
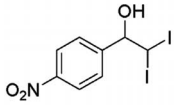
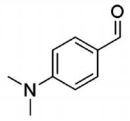
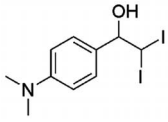
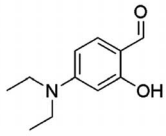
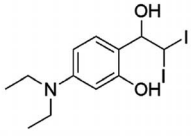
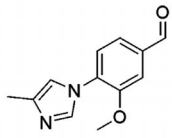
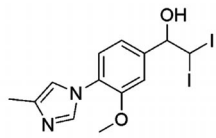
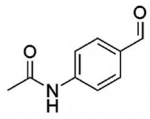
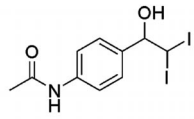
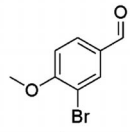
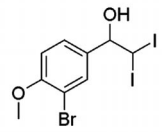
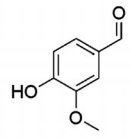
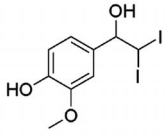
1	 1a	 2a	79
2	 1b	 2b	96
3	 1c	 2c	73
4	 1d	 2d	67
5	 1e	 2e	99
6	 1f	 2f	82
7	 1g	 2g	71
8	 1h	 2h	73
9	 1i	 2i	no product
10	 1j	 2j	no reaction

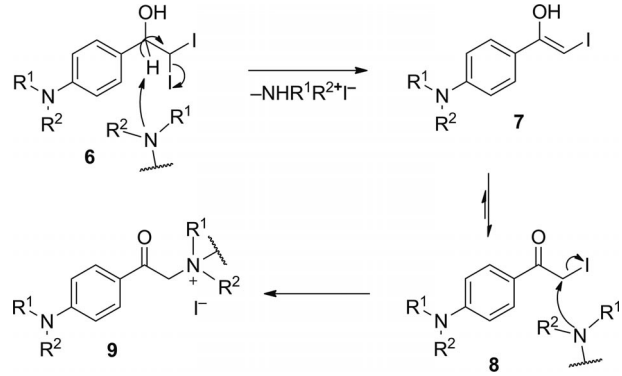
Table 1. *(Continued)*

Entry	Substrate	Product	Yield [%][b]
11	 1k	 2k	76
12	 1l	 2l	76
13	 1m	 2m	94
14	 1n	 2n	67

[a] Reagents and conditions: **1** (1.0 mmol), *i*PrMgCl (2 M in THF, 3.0 mmol), CHI_3 (3.0 mmol) in THF at –78 °C for 15 min, then at 0 °C for 1–2 h. [b] Yield of isolated product.

lated in moderate to good yields with excellent functional group tolerance (Table 1, Entries 1–8, 11–14). The formation of the β-diiodoalcohols was achieved in a single step from the aldehyde and avoids expensive or sensitive reagents such as diazomethane and SmI_2.[5a]

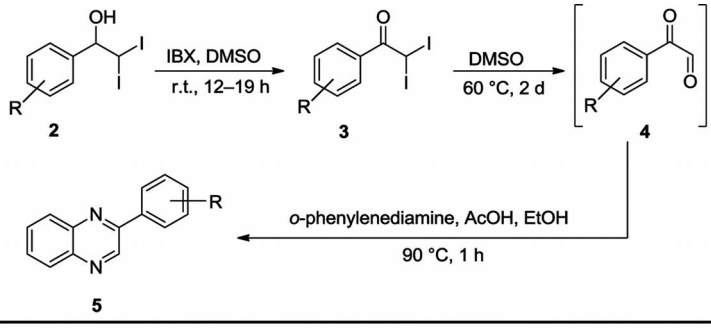
In general, it was observed that aldehydes containing either electron-withdrawing or electron-donating groups reacted smoothly to give the corresponding β-diiodoalcohols in good yields. These transformations occurred readily when the benzaldehyde was substitted in the *ortho*, *meta*, and *para* positions with a variety of substituents including methoxy, alkoxy, alkyl, hydroxy, and nitro groups (compounds **2b**, **2c**, **2g**, **2h**, **2m**, **2n**; Table 1). However, the reaction of aldehyde **1i** did not provide the desired product



Scheme 2. Reaction of amines with β-diiodoalcohols.

upon workup. Desired product **2i** formed in the course of the reaction as monitored by HPLC–MS, but disintegrated during removal of the solvent to leave a complex product mixture. A reason for the decomposition may be the strong nucleophilicity and basicity of tertiary amines, producing conjugated enol **7** by deprotection at Cα and elimination of

Table 2. Scope of the reaction.[a,b]



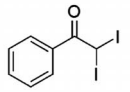
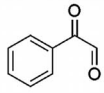
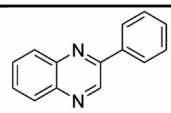
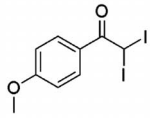
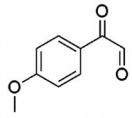
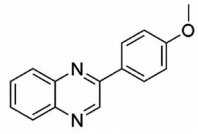
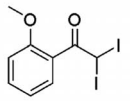
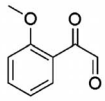
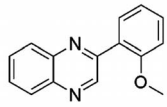
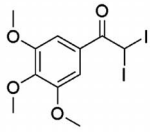
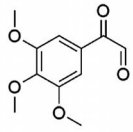
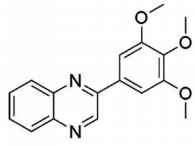
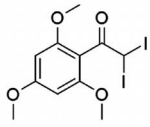
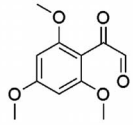
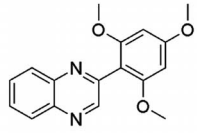
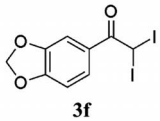
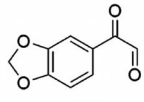
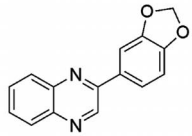
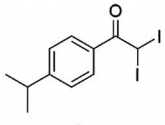
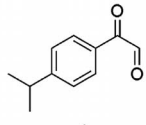
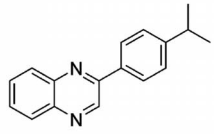
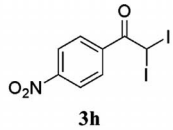
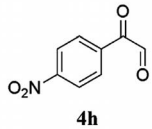
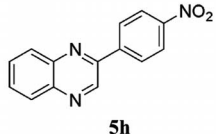
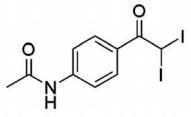
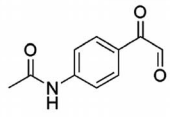
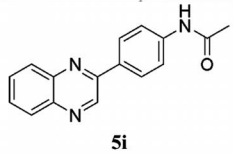
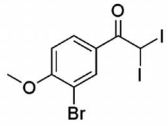
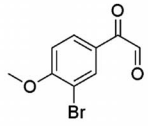
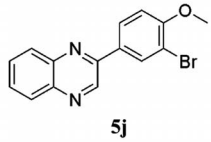
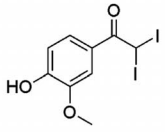
β-Diiodoketone	Yield [%][c]	α-Ketoaldehyde[d]	Quinoxaline	Yield [%][c]
 **3a**	82	 **4a**	 **5a**	81
 **3b**	93	 **4b**	 **5b**	84
 **3c**	64	 **4c**	 **5c**	88
 **3d**	71	 **4d**	 **5d**	81
 **3e**	88	 **4e**	 **5e**	84
 **3f**	84	 **4f**	 **5f**	90
 **3g**	56	 **4g**	 **5g**	81
 **3h**	not isolated	 **4h**	 **5h**	93

Table 2. *(Continued)*

β-Diiodoketone	Yield [%][c]	α-Ketoaldehyde[d]	Quinoxaline	Yield [%][c]
 **3i**	not isolated	 **4i**	 **5i**	83
 **3j**	94	 **4j**	 **5j**	90
 **3k**	reaction mixture			

[a] Reagents and conditions: **2** (1.0 mmol), IBX (2.0 mmol) in DMSO at room temperature for 12–19 h. [b] Compound **3** (1.0 mmol) in DMSO at 60 °C for 2 d, then AcOH, *o*-phenylenediamine (1.0 mmol) in EtOH at 90 °C for 1 h. [c] Yield of isolated product. [d] Detected by HPLC; in situ cyclization with *o*-phenylenediamine.

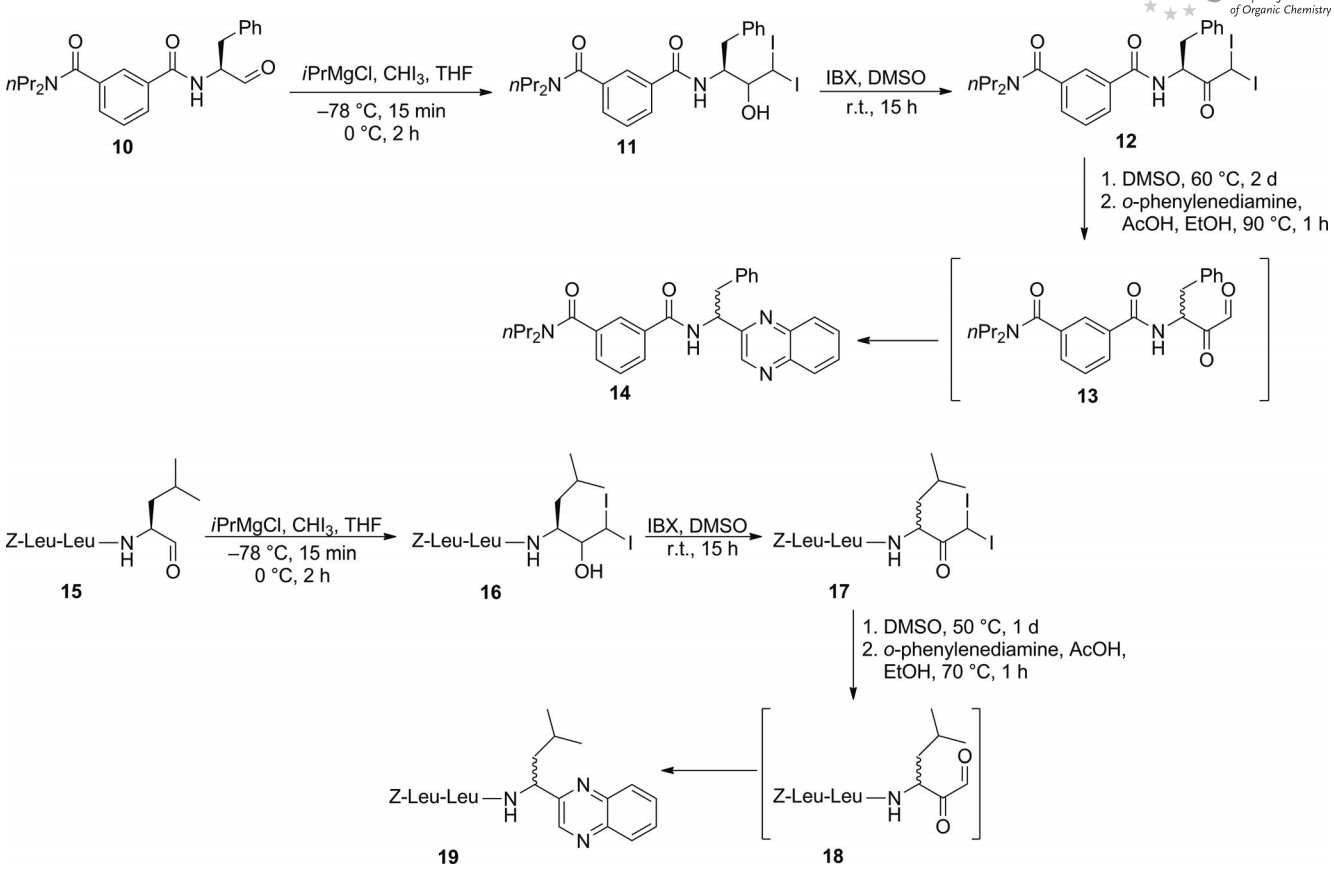
iodide. Enol **7** is in tautomeric equilibrium with β-diiodoketone **8**, which generates stable quaternary ammonium salt **9** by nucleophilic substitution (Scheme 2).

Phenolic precursor **1j** did not participate in the reaction and was recovered upon workup of the reaction mixture. Reduced acidity and nucleophilicity, which is realized in imidazole **1k** and amide **1l**, result in good to excellent yield, which supports the proposed hypothesis, illustrated in Scheme 2.

Subsequent oxidation of β-diiodoalcohols with 2-iodoxybenzoic acid (IBX)[9] delivered the desired β-diiodoketones (Table 2). IBX is a selective and mild oxidizing agent for primary and secondary alcohols and has been applied to the oxidation of peptidic substrates previously.[10]

The β-diiodoalcohols were oxidized with IBX (2 equiv.) in DMSO at room temperature within 12–19 h. Most β-diiodoalcohols reacted smoothly irrespective of the electronic nature of the groups in the *ortho*, *meta*, and *para* positions or multiple substitutions to provide the β-diiodoketones in good yields (56–94%, **3b**–**g**, **3j**; Table 2) except for *p*-phenol **2n**. This substrate was consumed rapidly as monitored by HPLC–MS, but gave a complex reaction mixture. This observation was rationalized by the ability to give a cyclohexadienone intermediate and the known IBX-mediated demethylation of 2-methoxyphenol.[11] The oxidation of alcohols **2h** and **2l** proceeded so fast that resulting ketones **3h** and **3i** could not be isolated because they immediately reacted further to the corresponding α-ketoaldehydes **4h** and **4i**. These were then cyclized with *o*-phenylenediamine in situ to provide quinoxalines **5h** and **5i** as the final products. Isolated β-diiodoketones **3a**–**g** and **3j** were converted into desired α-ketoaldehydes **4** by DMSO at 60 °C. The reaction progress was monitored by HPLC until complete. The targeted, labile α-ketoaldehydes form hydrates and ketals easily and thus give rise to errors in yield determination. Thus, in a one-pot reaction the α-ketoaldehydes were treated with *o*-phenylenediamine to give stable quinoxalines **5**, which facilitate yield comparison (Table 2). The transformation of *gem*-dihalomethylarenes into aldehydes by dimethyl sulfoxide as an oxygen donor was described to occur under neutral conditions for bromine and chlorine derivatives.[7] Wei Li et al. proposed that the conversion proceeds via an alkoxysulfonium species, which undergoes 1,2-elimination to give the desired product and a halodimethylsulfonium halide as a byproduct. Therefore, we assumed that the reaction of the α-diiodoketones to afford the corresponding α-ketoaldehydes involved such an oxygen transfer from DMSO. This reaction mechanism was confirmed for substrate **3a** by NMR spectroscopy in [D_6]-DMSO. The ^{1}H NMR spectrum included a significant signal of the resulting aldehyde at $\delta \approx 9.55$ ppm and the ^{13}C NMR spectrum showed signals at $\delta \approx 196$ and 189 ppm, typical for carbonyl groups of ketoaldehydes. The ^{13}C NMR signal of the diiodinated carbon atom at $\delta \approx -22.4$ ppm disappeared at the same speed as the new signals arose.

We tested the potential and general applicability of this method by synthesizing peptidic and peptidomimetic α-ketoaldehydes **13** and **18**, which are versatile intermediates and may be used in protease inhibition (Scheme 3). Peptide aldehydes **10** and **15** were converted into peptidyl β-diiodoalcohols **11** und **16** in analogy to the aryl aldehydes, and this process was reported to occur without epimerization of the α-carbon.[8] Subsequent oxidation by IBX provided peptidyl β-diiodoketones **12** and **17**. Reaction to peptidyl α-ketoaldehydes **13** and **18** was carried out in DMSO at 50 °C and was monitored by HPLC–MS. A structurally related analogue of ketoaldehyde **18** was identified recently as a potent inhibitor of the 20 S proteasome with a novel mode of action.[2] Cyclocondensation with *o*-phenylenediamine at



Scheme 3. Synthesis route to peptidyl quinoxalines.

70 °C afforded peptidyl quinoxalines **14** and **19** in good yields. Compound **19** was isolated as a single diastereomer with >95% *dr* as assigned by ^{1}H NMR spectroscopic analysis of the quinolyl 3H, which gave one signal only (see spectrum 19 in the Supporting Information).

Conclusions

In summary, we have developed a simple and mild synthetic method to transform aldehydes into the corresponding α-ketoaldehydes via β-diiodoketones. This is the first example involving the use of DMSO as a single reagent/solvent to convert β-diiodoketones into α-ketoaldehydes. The synthetic route was applied to the straightforward synthesis of peptidyl α-ketoaldehydes from peptidic β-diiodoketones, which are versatile intermediates that can lead to structures for protease inhibition.

Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 300 (300 MHz) and AC 500 (500 MHz) spectrometer. Chemical shifts are reported in δ (ppm) adjusted to the central line of the deuterated solvent (MeOD, $CDCl_3$, [D_6]DMSO). Mass spectrometry was performed with a Bruker-Franzen Esquire LC mass spectrometer (ESI) and a double-focused MAT 95 (EI). HPLC analysis was performed with an Agilent 1100 system. The purity of the final compounds was determined by using UV detection (λ = 254 nm). The chromatographic method employed the following: column Zorbax Eclipse XDB-C18; 4.6×150 mm; mobile phase A H_2O (0.1% TFA), mobile phase B acetonitrile, flow rate 1 mL/min, gradient elution 30 to 100% B over 15 min. According to these methods the purities for all compounds were ≥95% if not indicated otherwise in the experimental details. Thin-layer chromatography (TLC) was carried out by using aluminum sheets precoated with silica gel 60 F254 (0.2 mm; E. Merck). Chromatographic spots were visualized by UV and/or by spraying with a methanolic solution of vanillin/H_2SO_4 or aq. $KMNO_4$ solution followed by heating. Silica gel chromatography was carried out by using Merck silica gel 60 (0.063–0.2 mm). Melting points were determined with a Mettler FP 51 melting point apparatus. All reagents and solvents (THF, DMF, CH_2Cl_2, ethyl acetate, MeOH, DMSO) were purchased from ABCR, Acros and Alfa Aesar, TCI, Sigma Aldrich, and VWR.

Typical Procedure (TP I) for the Synthesis of β-Diiodoalcohols from Aldehydes: *i*PrMgCl (2.0 M in THF, 1.5 mL, 3.0 mmol) was added dropwise to a solution of iodoform (1.18 g, 3.0 mmol) in THF (10 mL, abs.) at –78 °C under an argon atmosphere. A solution of aldehyde **1** (1.00 mmol) in THF (1 mL, abs.) was added, and the resulting mixture was stirred at the same temperature for 15 min and at 0 °C for 1–2 h. The mixture was quenched with aqueous NH_4Cl (10 mL, sat.) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Crude product **2** was purified by LC.

Typical Procedure (TP II) for the Oxidation of β-Diiodoalcohols with IBX: To a solution of β-diiodoalcohol **2** (1.0 mmol) in DMSO (5 mL) was added IBX (0.56 g, 2.0 mmol), and the mixture was stirred at room temperature for 19 h. The reaction mixture was

quenched with water (50 mL) and CH_2Cl_2 (70 mL) was added. The precipitate was filtered off, and the organic layer was extracted with water (2 × 50 mL), washed with $NaHCO_3$ (50 mL, sat.), dried with Na_2SO_4, and concentrated in vacuo. Crude product **3** was purified by LC.

Typical Procedure (TP III): Synthesis of Quinoxalines from β-Diiodoketones over α-Ketoaldehydes: β-Diiodoketone **3** (0.25 mmol) was dissolved in DMSO (2.5 mL) and stirred at 60 °C for 40 h (HPLC control). Glacial acetic acid (0.6 mL) and a solution of *o*-phenylenediamine (27 mg, 0.25 mmol) in EtOH (1.5 mL) was added to the reaction mixture, which was stirred at 90 °C for 1 h. After cooling, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with water (2 × 30 mL), dried with Na_2SO_4, and concentrated in vacuo. Crude product **5** was purified by LC.

2-Iodoxybenzoic Acid: 2-Iodobenzoic acid (4.0 g, 16.13 mmol) was added all at once to a solution of oxone (12.9 g, 20.97 mmol) in water (52 mL). The reaction mixture was warmed slowly to 73 °C and stirred at this temperature for 3 h. The suspension was than cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The mixture was filtered, and the solid was repeatedly rinsed with water (3 × 15 mL) and acetone (20 mL). The white, crystalline solid (4.26 g, 94%) was dried under reduced pressure. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.01 (m), 8.42 (s) ppm.^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.5, 146.6, 133.3, 132.9, 131.4, 130.1, 125.0 ppm.

2,2-Diiodo-1-phenylethanol (2a): According to typical procedure TP I, benzaldehyde (**1a**; 0.30 g, 2.83 mmol), CHI_3 (3.34 g, 8.48 mmol), and *i*PrMgCl (4.2 mL, 8.48 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 834 mg (79%) of **2a** as a brown oil. R_f ($CHCl_3$) = 0.67. HPLC: t_R = 6.52 min (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.36 (m, 5 H), 5.35 (d, *J* = 3.6, 2.0 Hz, 1 H), 4.71 (t, *J* = 3.9 Hz, 1 H), 2.85 (d, *J* = 3.8 Hz, 1 H, -OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.1, 128.8, 128.6, 126.5, 79.7, –10.8 ppm. MS (EI): *m*/*z* = 374 [M]$^+$.

2,2-Diiodo-1-(4-methoxyphenyl)ethanol(2b): According to typical procedure TP I, anisaldehyde (**1b**; 0.272 g, 2.0 mmol), CHI_3 (2.36 g, 6.0 mmol), and *i*PrMgCl (3.0 mL, 6.0 mmol).The crude product was purified by LC ($CHCl_3$). Yield: 775 mg (96%) of **2b** as a brown oil. R_f ($CHCl_3$) = 0.59. HPLC: t_R = 6.42 min (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 2 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 5.28 (d, *J* = 4.7 Hz, 1 H), 4.65 (d, *J* = 4.4 Hz, 1 H), 3.82 (s, 3 H), 2.88 (s, 1 H, -OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 131.2, 127.8, 113.9, 79.3, 55.3, –9.5 ppm. MS (EI): *m*/*z* = 404 [M]$^+$.

2,2-Diiodo-1-(2-methoxyphenyl)ethanol (2c): According to typical procedure TP I, *o*-methoxybenzaldehyde (**1c**; 0.30 g, 2.2 mmol), CHI_3 (2.60 g, 6.6 mmol), and *i*PrMgCl (3.3 mL, 6.6 mmol). The crude product was purified by LC (CH/$CHCl_3$, 1:1). Yield: 654 mg (73%) of **2c** as a brown oil. R_f (CH/$CHCl_3$, 1:1) = 0.55. HPLC: t_R = 6.982 min (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 1 H), 7.39–7.33 (m, 1 H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.88 (dd, *J* = 8.3, 0.9 Hz, 1 H), 5.66 (d, *J* = 3.8 Hz, 1 H), 4.51 (d, *J* = 3.6 Hz, 1 H), 3.88 (s, 3 H), 4.04 (s, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 129.6, 128.6, 127.5, 120.7, 110.5, 76.3, 55.5, –11.0 ppm. MS (EI): *m*/*z* = 404 [M]$^+$.

2,2-Diiodo-1-(3,4,5-trimethoxyphenyl)ethanol (2d): According to typical procedure TP I, 3,4,5-trimethoxybenzaldehyde (**1d**; 0.35 g, 1.78 mmol), CHI_3 (2.1 g, 5.34 mmol), and *i*PrMgCl (2.7 mL, 5.4 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 550 mg (67%) of **2d** as a brown-orange oil. R_f ($CHCl_3$) = 0.14. HPLC: t_R = 5.90 min (99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.63 (s, 2 H), 5.30 (d, *J* = 4.4 Hz, 1 H), 4.62 (t, *J* = 4.1 Hz, 1 H), 3.88 (s, 6 H), 3.85 (s, 3 H), 2.95 (d, *J* = 4.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz,$CDCl_3$): δ = 153.3, 138.2, 134.5, 103.8, 79.7, 60.8, 56.3, –11.2 ppm. MS (EI): *m*/*z* = 464 [M]$^+$.

2,2-Diiodo-1-(2,4,6-trimethoxyphenyl)ethanol (2e): According to typical procedure TP I, 2,4,6-trimethoxybenzaldehyde (**1e**; 0.30 g, 1.53 mmol), CHI_3 (1.8 g, 4.59 mmol), and *i*PrMgCl (2.3 mL, 4.59 mmol). Yield: 700 mg (99%) of **2e** as a brown solid. R_f ($CHCl_3$) = 0.50. HPLC: t_R = 7.20 min (93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.06 (s, 2 H), 5.46 (d, *J* = 7.8 Hz, 1 H), 5.19 (t, *J* = 8.4 Hz, 1 H), 4.83 (s, 1 H), 3.79 (s, 6 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (75 MHz,$CDCl_3$): δ = 161.4, 158.7, 107.2, 91.1, 75.0, 55.9, 55.4, –11.2 ppm. MS (EI): *m*/*z* = 464 [M]$^+$.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-diiodoethanol (2f): According to typical procedure TP I, piperonal (**1f**; 0.30 g, 2.0 mmol), CHI_3 (2.36 g, 5.99 mmol), and *i*PrMgCl (3.0 mL, 5.99 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 683 mg (82%) of **2f** as a brown oil. R_f ($CHCl_3$) = 0.71. HPLC: t_R = 6.53 min (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–6.86 (m, 2 H), 6.79 (d, *J* = 8 Hz, 1 H), 5.99 (m, 2 H), 5.25 (d, *J* = 4.7 Hz, 1 H), 4.61 (d, *J* = 4.6 Hz, 1 H), 2.89 (s, -OH) ppm. ^{13}C NMR (75 MHz,$CDCl_3$): δ = 147.8, 133, 120.5, 108.2, 106.9, 101.3, 79.4, –10.3 ppm. MS (EI): *m*/*z* = 418 [M]$^+$.

2,2-Diiodo-1-(4-isopropylphenyl)ethanol (2 g): According to typical procedure TP I, 4-isopropylbenzaldehyde (**1g**; 0.30 g, 2.02 mmol), CHI_3 (2.39 g, 6.06 mmol), and *i*PrMgCl (3.0 mL, 6.06 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 590 mg (71%) of **2g** as orange oil. R_f (CH/CHC,l$_3$1:1) = 0.21. HPLC: t_R = 7.91 min (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.22 (dd, *J* = 31.8, 8.2 Hz, 4 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.69 (d, *J* = 4.5 Hz, 1 H), 2.92 (hept., *J* = 6.3 Hz, 1 H), 2.81 (s, 1 H, -OH), 1.26 (d, *J* = 6.9 Hz, 6 H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 136.4, 126.6, 126.5, 79.7, 33.9, 23.8, –10.4 ppm. MS (EI): *m*/*z* = 416 [M]$^+$.

2,2-Diiodo-1-(4-nitrophenyl)ethanol (2h): According to typical procedure TP I, 4-nitrobenzaldehyde (**1h**; 0.27 g, 1.79 mmol), CHI_3 (2.12 g, 5.38 mmol), and *i*PrMgCl (2.7 mL, 5.38 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 609 mg (73%) of **2h** as a yellow solid. R_f ($CHCl_3$) = 0.42. HPLC: t_R = 6.76 min (95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18–8.14 (m, 2 H), 7.57–7.54 (m, 2 H), 5.28 (d, *J* = 4.1 Hz, 1 H), 4.76 (d, *J* = 4.1 Hz, 1 H), 2.96 (s, 1 H, -OH) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 145.8, 127.7, 123.7, 78.6, –14.2 ppm. MS (EI): *m*/*z* = 419 [M]$^+$.

***N*-[4-(1-Hydroxy-2,2-diiodoethyl)phenyl]acetamide (2l):** According to typical procedure TP I, 4-acetamidobenzaldehyde (**1l**; 0.30 g, 1.84 mmol), CHI_3 (2.17 g, 5.51 mmol), and *i*PrMgCl (2.8 mL, 5.51 mmol). The crude product was purified by LC ($CHCl_3$/MeOH, 20:1). Yield: 604 mg (76%) of **2l** as a yellow solid. R_f ($CHCl_3$/MeOH, 20:1) = 0.28. HPLC: t_R = 4.262 min (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 43.5, 8.6 Hz, 4 H), 5.03 (d, *J* = 4.4 Hz, 2 H), 4.3 (d, *J* = 4.4 Hz, 1 H), 4.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 137.9, 135.8, 126.7, 119.1, 78.3, 22.8, –12.3 ppm. MS (EI): *m*/*z* = 431 [M]$^+$.

1-(3-Bromo-4-methoxyphenyl)-2,2-diiodoethanol (2m): According to typical procedure TP I, 3-bromo-4-methoxybenzaldehyde (**1m**; 0.30 g, 1.40 mmol), CHI_3 (1.65 g, 4.19 mmol), and *i*PrMgCl (2.1 mL, 4.19 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 633 mg (94%) of **2m** as a brown oil. R_f ($CHCl_3$) = 0.51. HPLC: t_R = 7.317 min (95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 2.2 Hz, 1 H), 7.34 (ddd, *J* = 8.5, 2.2, 0.5 Hz, 1 H),

6.88 (d, J = 8.5 Hz, 1 H), 5.26 (d, J = 4.5 Hz, 1 H), 4.62 (d, J = 4.2 Hz, 1 H), 3.91 (s, 3 H), 2.89 (s, 1 H, -OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1, 132.5, 131.5, 126.9, 117.8, 111.6, 78.6, 56.3, –10.7 ppm. MS (EI): m/z = 482 $[M]^+$.

4-(1-Hydroxy-2,2-diiodoethyl)-2-methoxyphenol (2n): According to typical procedure TP I, 4-hydroxy-3-methoxybenzaldehyde (**1n**; 0.30 g, 1.97 mmol), CHI_3 (2.33 g, 5.91 mmol), and *i*PrMgCl (3.0 mL, 6.0 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 555 mg (67%) of **2m** as a brown oil. R_f ($CHCl_3$) = 0.18. HPLC: t_R = 4.89 min (100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.9 (d, J = 2 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 6.79 (dd, J = 8, 2 Hz, 1 H), 5.6 (s, 1 H), 5.2 (d, J = 4.5 Hz, 1 H), 4.55 (t, J = 4.0 Hz, 1 H), 3.85 (s, 3 H), 2.76 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 145.9, 130.9, 119.9, 114.3, 109.0, 79.51, 56.1, –9.67 ppm. MS (EI): m/z = 420 $[M]^+$.

2,2-Diiodo-1-phenylethanone (3a): According to typical procedure TP II, 2,2-diiodo-1-phenylethanol (**2a**; 0.57 g, 1.51 mmol) and IBX (0.85 g, 3.03 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 460 mg (82%) of **3a** as a brown oil. HPLC: t_R = 7.486 min (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–8.00 (m, 2 H), 7.67–7.58 (m, 1 H), 7.53–7.44 (m, 2 H), 6.52 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.3, 134.1, 129.5, 129.0, 128.7, –28.9 ppm. MS (EI): m/z = 372 $[M]^+$.

2,2-Diiodo-1-(4-methoxyphenyl)ethanone (3b): According to typical procedure TP II, 2,2-diiodo-1-(4-methoxyphenyl)ethanol (**2b**; 0.19 g, 0.47 mmol) and IBX (0.26 g, 0.94 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 176 mg (93%) of **3b** as a brown solid. R_f ($CHCl_3$) = 0.65. HPLC: t_R = 7.55 min (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 9.1 Hz, 2 H), 6.88 (d, J = 9.1 Hz, 2 H), 6.40 (s, 1 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.9, 164.3, 132.0, 121.0, 114.3, 55.6, –28.6 ppm. MS (EI): m/z = 402 $[M]^+$. HRMS (EI): calcd. for $C_9H_8O_2I_2$ $[M]^+$ 401.8605; found 401.8612.

2,2-Diiodo-1-(2-methoxyphenyl)ethanone (3c): According to typical procedure TP II, 2,2-diiodo-1-(2-methoxyphenyl)ethanol (**2c**; 0.65 g, 1.62 mmol) and IBX (0.91 g, 3.24 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 415 mg (64%) of **3c** as a brown solid. HPLC: t_R = 7.75 min (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.83 (m, 1 H), 7.52 (ddd, J = 8.4, 7.3, 1.8 Hz, 1 H), 7.07–6.99 (m, 2 H), 6.78 (s, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.1, 158.1, 134.8, 132.9, 121.4, 119.9, 111.6, 56.0, –20.1 ppm. MS (EI): m/z = 402 $[M]^+$. HRMS (EI): calcd. for $C_9H_8O_2I_2$ $[M]^+$ 401.8606; found 401.8612.

2,2-Diiodo-1-(3,4,5-trimethoxyphenyl)ethanone (3d): According to typical procedure TP II, 2,2-diiodo-1-(3,4,5-trimethoxyphenyl)ethanol (**2d**; 0.35 g, 0.75 mmol) and IBX (0.42 g, 1.51 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 250 mg (71%) of **3d** as a brown solid. R_f ($CHCl_3$) = 0.65. HPLC: t_R = 7.41 min (92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (s, 2 H), 6.39 (s, 1 H),3.88 (s, 3 H), 3.85 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2, 153.1, 143.7, 123.3, 107.4, 61.1, 56.4, –29.7 ppm. MS (EI): m/z = 462 $[M]^+$.

2,2-Diiodo-1-(2,4,6-trimethoxyphenyl)ethanone (3e): According to typical procedure TP II, 2,2-diiodo-1-(2,4,6-trimethoxyphenyl)ethanol (**2e**; 1.00 g, 2.15 mmol) and IBX (1.20 g, 4.40 mmol). The crude product was purified by LC ($CHCl_3$/CH, 2:1). Yield: 813 mg (88%) of **3e** as a yellow solid. R_f ($CHCl_3$/CH) = 0.49. HPLC: t_R = 7.49 min (94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 6.12 (s, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.3, 163.9, 159.8, 104.3, 90.7, 56.0, 55.5, –17.8 ppm. MS (EI): m/z = 462 $[M]^+$. HRMS (EI): calcd. for $C_{11}H_{12}O_4I_2$ $[M]^+$ 461.8796; found 461.8823.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-diiodoethanone (3f): According to typical procedure TP II, 1-(benzo[*d*][1,3]dioxol-5-yl)-2,2-diiodoethanol (**2f**; 0.62 g, 1.49 mmol) and IBX (0.84 g, 2.98 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 523 mg (84%) of **3f** as a brown solid. HPLC: t_R = 7.51 min (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (dd, J = 8.3, 1.8 Hz, 1 H), 7.49 (d, J = 1.8 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 6.45 (s, 1 H), 6.08 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.3, 151.3, 147.1, 124.5, 121.3, 107.9, 106.8, 100.8, –29.3 ppm. MS (EI): m/z = 416 $[M]^+$. HRMS (EI): calcd. for $C_9H_6O_3I_2$ $[M]^+$ 415.8405; found 415.8404

2,2-Diiodo-1-(4-isopropylphenyl)ethanone (3g): According to typical procedure TP II, 2,2-diiodo-1-(4-isopropylphenyl)ethanol (**2g**; 0.59 g, 1.27 mmol) and IBX (0.71 g, 2.54 mmol). Yield: 330 mg (56%) of **3g** as a brown oil. R_f (CH/$CHCl_3$, 1:1) = 0.56. HPLC: t_R = 8.69 min (61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.3 Hz, 2 H), 6.43 (s, 1 H), 2.91 (hept., J = 6.3 Hz, 1 H), 1.20 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 156.0, 129.8, 127.2, 126.3, 34.4, 23.6, –28.5 ppm. MS (EI): m/z = 414 $[M]^+$.

1-(3-Bromo-4-methoxyphenyl)-2,2-diiodoethanone (3j): According to typical procedure TP II, 1-(3-bromo-4-methoxyphenyl)-2,2-diiodoethanol (**2m**; 0.19 g, 0.39 mmol) and IBX (0.22 g, 0.79 mmol). Yield: 178 mg (94%) of **3j** as a brown oil. HPLC: t_R = 8.28 min (60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, J = 2.2 Hz, 1 H), 8.02 (dd, J = 8.7, 2.3 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 6.42 (s, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.9, 159.0, 133.5, 129.9, 120.9, 111.5, 111.3, 55.5, –29.7 ppm. MS (EI): m/z = 480 $[M]^+$.

2-Phenylquinoxaline (5a): According to typical procedure TP III, 2,2-diiodo-1-phenylethanone (**3a**; 66 mg, 0.18 mmol) and *o*-phenylenediamine (19 mg, 0.18 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 30 mg (81%) of **5a** as a white solid. R_f ($CHCl_3$) = 0.41. HPLC: t_R = 6.67 min (99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.34 (s, 1 H), 8.14–8.10 (m, 4 H), 7.82–7.72 (m, 2 H), 7.61–7.50 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 143.4, 142.3, 141.6, 136.8, 130.0, 130.2, 129.7, 129.6, 129.2, 127.6 ppm.

2-(4-Methoxyphenyl)quinoxaline (5b): According to typical procedure TP III, 2,2-diiodo-1-(4-methoxyphenyl)ethanone (**3b**; 85 mg, 0.21 mmol) and *o*-phenylenediamine (23 mg, 0.21 mmol). The crude product was purified by LC (CH/$CHCl_3$, 1:1). Yield: 42 mg (84%) of **5b** as a brown solid. R_f (Cy/$CHCl_3$ = 1:1) = 0.23. HPLC: t_R = 6.81 min (93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 8.17 (m, 4 H), 7.76 (m, 2 H), 7.09 (m, 2 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 151.5, 143.1, 142.3, 141.2, 133.9, 130.2, 129.4, 129.1, 114.6, 113.9, 55.4 ppm. MS (EI): m/z = 236 $[M]^+$.

2-(2-Methoxyphenyl)quinoxaline (5c): According to typical procedure TP III, 2,2-diiodo-1-(2-methoxyphenyl)ethanone (**3c**; 100 mg, 0.25 mmol) and *o*-phenylenediamine (27 mg, 0.25 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 52 mg (88%) of **5c** as a yellow solid. HPLC: t_R = 6.56 min (99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.05–8.04 (m, 2 H), 7.84–7.82 (dd, J = 7.6, 1.8 Hz, 2 H), 7.70–7.65 (m, 2 H), 7.42–7.39 (ddd, J = 8.3, 7.4, 1.8 Hz, 1 H), 7.10–7.00 (td, J = 7.1, 1.0 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4, 152.2, 147.3, 142.7, 141.0, 131.6, 131.4, 129.8, 129.6, 129.4, 129.1, 126.6, 121.6, 111.5, 55.7 ppm. MS (EI): m/z = 236 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{12}N_2O$ $[M]^+$ 236.0931; found 236.0950.

2-(3,4,5-Trimethoxyphenyl)quinoxaline (5d): According to typical procedure TP III, 2,2-diiodo-1-(3,4,5-trimethoxyphenyl)ethanone

(**3d**; 250 mg, 0.54 mmol) and *o*-phenylenediamine (59 mg, 0.54 mmol). The crude product was purified by LC ($CHCl_3$/MeOH, 50:1). Yield: 130 mg (81%) of **5d** as a brown solid. R_f ($CHCl_3$/MeOH = 50:1) = 0.67. HPLC: t_R = 6.30 min (76%). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 8.14–8.10 (m, 2 H),7.81–7.71 (m, 2 H), 7.43 (s, 2 H), 4.01 (s, 6 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 151.4, 143.2, 142.2, 141.5, 140.2, 132.2, 130.3, 129.5, 129.1,104.8, 61.0, 56.4 ppm. MS (EI): *m*/*z* = 296 $[M]^+$.

2-(2,4,6-Trimethoxyphenyl)quinoxaline (5e): According to typical procedure TP III, 2,2-diiodo-1-(2,4,6-trimethoxyphenyl)ethanone (**3e**; 120 mg, 0.26 mmol) and *o*-phenylenediamine (28 mg, 0.26 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 65 mg (84%) of **5e** as a yellow solid. HPLC: t = 5.89 min (89%). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.85 (s, 1 H), 8.30–8.08 (m, 2 H), 7.82–7.71 (m, 2 H), 6.27 (s, 2 H), 3.90 (s, 3 H), 3.76 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 159.5, 148.6, 140.8, 129.7, 129.4, 129.0, 91.0, 55.9, 55.5 ppm.

2-(Benzo[*d*][1,3]dioxol-5-yl)quinoxaline (5f): According to typical procedure TP III, 1-(benzo[*d*][1,3]dioxol-5-yl)-2,2-diiodoethanone (105 mg, 0.25 mmol) and *o*-phenylenediamine (27 mg, 0.25 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 57 mg (90%) of **5f** as a white solid. HPLC: t_R = 6.85 min (95%). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.17 (s, 1 H), 8.03–8.00 (m, 2 H), 7.70–7.61 (m, 4 H), 6.91 (d, *J* = 8.1 Hz, 1 H), 5.99 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.2, 148.6, 147.7, 142.0, 141.2, 140.3, 130.1, 129.2, 128.4, 128.2, 128.0, 121.0, 107.8, 106.7, 100.6 ppm. MS (EI): *m*/*z* = 250 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{10}N_2O_2$ $[M]^+$ 250.0722; found 250.0742.

2-(4-isopropylphenyl)quinoxaline (5g): According to typical procedure TP III, 2,2-diiodo-1-(4-isopropylphenyl)ethanone (**3g**; 110 mg, 0.54 mmol) and *o*-phenylenediamine (58.5 mg, 0.54 mmol). The crude product was purified by LC ($CHCl_3$/MeOH, 50:1). Yield: 130 mg (81%) of **5g** as a brown solid. R_f (CH/CHC,$l_3$1:1) = 0.36. HPLC: t = 8.26 min (81%). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.07–8.01 (m, 4 H), 7.71–7.35 (m, 2 H), 7.35–7.31 (m, 2 H), 2.92 (hept., *J* = 6.3 Hz, 1 H), 1.23 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 151.4, 143.4, 142.4, 141.4, 134.4, 131.5, 130.2, 129.6, 129.3, 129.1, 127.6, 127.3, 34.1, 23.9 ppm. MS (EI): *m*/*z* = 248 $[M]^+$.

2-(4-Nitrophenyl)quinoxaline (5h): According to typical procedure TP II and TP III (one pot), 2,2-diiodo-1-(4-nitrophenyl)ethanol (**2h**; 100 mg, 0.24 mmol), IBX (134 mg, 0.48 mmol), and *o*-phenylenediamine (26.0 mg, 0.24 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 56 mg (93%) of **5h** as a brown solid. R_f ($CHCl_3$) = 0.66. HPLC: t_R = 7.19 min (90%). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 8.42 (s, 4 H), 8.14–8.08 (m, 2 H), 7.80–7.73 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.3,148.7, 142.8, 142.6, 142.2, 142.1, 130.9, 130.7, 129.9, 129.3, 128.4, 124.3 ppm. MS (EI): *m*/*z* = 251 $[M]^+$. HRMS (EI): calcd. for $C_{14}H_9N_3O_2$ $[M]^+$ 251.0685; found 251.0695.

***N*-[4-(Quinoxalin-2-yl)phenyl]acetamide (5i):** According to typical procedure TP II and TP III (one pot), *N*-[4-(1-hydroxy-2,2-diiodoethyl)phenyl]acetamide (**2l**; 200 mg, 0.46 mmol), IBX (260 mg, 0.93 mmol), and *o*-phenylenediamine (50.0 mg, 0.47 mmol). The crude product was purified by LC ($CHCl_3$/MeOH, 20:1). Yield: 102 mg (83%) of **5i** as a white solid. HPLC: t_R = 4.60 min (97%). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 8.20 (d, *J* = 8.6 Hz, 2 H), 8.16–8.08 (m, 2 H), 7.81–7.69 (m, 4 H), 7.39 (s, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 151.1, 143.0, 142.3, 141.4, 139.9, 132.4, 130.4, 129.5, 129.4, 129.1, 128.4, 120.0, 24.8 ppm. MS (EI): *m*/*z* = 263 $[M]^+$.

2-(3-Bromo-4-methoxyphenyl)quinoxaline (5j): According to typical procedure TP III, 1-(3-bromo-4-methoxyphenyl)-2,2-diiodoethanone (**3j**; 95 mg, 0.20 mmol) and *o*-phenylenediamine (21.0 mg, 0.20 mmol). The crude product was purified by LC ($CHCl_3$). Yield: 56 mg (90%) of **5j** as a white solid. R_f ($CHCl_3$) = 0.455. HPLC: t_R = 7.84 min (99%). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.26 (s, 1 H), 8.47 (d, *J* = 2.2 Hz, 1 H), 8.15–8.07 (m, 3 H), 7.82–7.68 (m, 2 H), 7.05 (d, *J* = 8.6 Hz, 1 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 150.0, 142.6, 142.2, 141.4, 132.5, 130.5, 130.4, 129.4, 129.1, 127.7, 112.8, 112.0, 56.4 ppm. MS (EI): *m*/*z* = 314 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{11}N_2OBr$ $[M]^+$ 314.00243; found 314.0055.

***N*^{1}-[(2*S*)-3-Hydroxy-4,4-diiodo-1-phenylbutan-2-yl]-*N*^{3},*N*^{3}-dipropylisophthalamide (11):** *i*PrMgCl (2.0 M in THF, 2.50 mL, 5.05 mmol) was added dropwise to a solution of iodoform (1988 mg, 5.05 mmol) in THF (25 mL, abs.) at –78 °C under an argon atmosphere. A solution of aldehyde **10** (358 mg, 1.01 mmol) in THF (5 mL, abs.) was added, and the resulting mixture was stirred at the same temperature for 15 min and at 0 °C for 2 h. The mixture was quenched with aqueous NH_4Cl (30 mL, sat.) and extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by LC ($CHCl_3$) to give β-diiodoalcohol **11** (470 mg, 77%) as a yellow solid. R_f ($CHCl_3$) = 0.31. HPLC: t_R = 7.62 min (98%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (td, *J* = 7.0, 1.9 Hz, 1 H), 7.62–7.61 (m, 1 H), 7.44–7.35 (m, 2 H), 7.28–7.18 (m, 5 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 5.02 (d, *J* = 8.5 Hz, 1 H), 4.87 (dq, *J* = 7.9, 2.2 Hz, 1 H), 3.72 (dd, *J* = 8.5, 2.6 Hz, 1 H), 3.55–3.37 (m, 2 H), 3.12–3.06 (m, 2 H), 2.98–2.01 (m, 2 H), 1.68–1.49 (m, 4 H), 1.09–0.84 (m, 3 H), 0.83–0.59 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 167.5, 137.3, 137.2, 134.5, 129.5, 129.3, 128.8, 128.7, 128.2, 126.8, 125.1, 76.8, 52.8, 50.9, 46.7, 39.0, 21.9, 20.8, 11.5, 11.1, –17.0 ppm. MS (ESI): *m*/*z* = 649 $[M + H]^+$.

(*S*)-*N*^{1}-(4,4-Diiodo-3-oxo-1-phenylbutan-2-yl)-*N*^{3},*N*^{3}-dipropylisophthalamide (12): To a solution of β-diiodoalcohol **11** (94 mg, 0.14 mmol) in DMSO (5 mL) was added IBX (78 mg, 0.28 mmol), and the mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water (50 mL) and MTBE (methyl *tert*-butyl ether) (70 mL) was added. The precipitate was filtered off, and the organic layer were extracted with water (2 × 50 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by LC [cyclohexane (CH)/ethyl acetate (EE), 1:1] to give β-diiodoketone **12** (86 mg, 91%) as a yellow solid. R_f (CH/EE, 1:1) = 0.68. HPLC: t_R = 8.26 min (95%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.64 (m, 2 H), 7.47–7.38 (m, 2 H), 7.35–7.24 (m, 5 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 5.68 (s, 1 H), 5.46 (q, *J* = 7.3 Hz, 1 H), 3.55–3.38 (m, 2 H), 3.24 (dd, *J* = 7.2, 1.4 Hz, 2 H), 3.18–3.03 (m, 2 H), 1.82–1.61 (m, 2 H), 1.60–1.41 (m, 2 H), 1.06–0.89 (m, 3 H), 0.83–0.61 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.9, 170.8, 166.5, 137.6, 135.7, 133.6, 129.9, 129.2, 129.1, 128.9, 127.9, 127.5, 125.2, 53.3, 50.8, 46.6, 38.9, 21.9, 20.8, 11.5, 11.1, –26.2 ppm. MS (EI): *m*/*z* = 647 $[M + Na]^+$.

(*S*)-*N*^{1}-[2-Phenyl-1-(quinoxalin-2-yl)ethyl]-*N*^{3},*N*^{3}-dipropylisophthalamide (14): β-Diiodoketone **12** (65 mg, 0.11 mmol) was dissolved in DMSO (2.5 mL) and stirred at 60 °C for 2 d (HPLC control). Glacial acetic acid (1.0 mL) and a solution of *o*-phenylenediamine (12 mg, 0.11 mmol) in EtOH (2.0 mL) was added to the reaction mixture, which was stirred at 90 °C for 1 h. After cooling, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with water (2 × 30 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by LC (EE/CH, 1:2) to give compound

14 (22 mg, 45%) as a brown solid. R_f (CH/EE, 1:1) = 0.38. HPLC: t_R = 7.61 min (96%);^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.17–8.08 (m, 2 H), 7.85–7.73 (m, 4 H), 7.60–7.45 (m, 3 H), 7.42–7.35 (m, 1 H), 7.21–7.16 (m, 2 H), 7.43–7.35 (m, 2 H), 5.80 (td, J = 7.9, 5.8 Hz, 1 H), 3.54 (dd, J = 13.4, 5.7 Hz, 1 H), 3.51–3.42 (m, 2 H), 3.30 (dd, J = 13.4, 8.2 Hz, 1 H), 3.24–3.09 (m, 2 H), 1.87–1.48 (m, 4 H),1.01–0.89 (m, 3 H), 0.84–0.65 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 165.3, 153.1, 143.6, 142.2, 141.9, 137.9, 136.1, 134.6, 130.7, 130.1, 129.5, 129.3, 129.2, 128.9, 128.8, 128.6, 127.8, 127.1, 125.2, 54.1, 46.5, 42.2, 21.9, 20.7, 11.5, 11.1 ppm. MS (EI): m/z = 480 $[M]^+$. HRMS (EI): calcd. for $C_{30}H_{32}N_4O_2$ $[M]^+$ 480.2526; found 480.2486.

Benzyl (2*S*)-1-{(2*S*)-1-[(3*S*)-2-Hydroxy-1,1-diiodo-5-methylhexan-3-ylamino]-4-methyl-1-oxopentan-2-ylamino}-4-methyl-1-oxopentan-2-ylcarbamate (16): *i*PrMgCl (2.0 M in THF, 1.05 mL, 2.11 mmol) was added dropwise to a solution of iodoform (829 mg, 2.11 mmol) in THF (10 mL, abs.) at –78 °C under an argon atmosphere. A solution of aldehyde **15** (200 mg, 0.42 mmol) in THF (1 mL, abs.) was added, and the resulting mixture was stirred at the same temperature for 15 min and at 0 °C for 1 h. The mixture was quenched with aqueous NH_4Cl (10 mL, sat.) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by LC ($CHCl_3$/MeOH, 20:1) to give peptidic β-diiodoalcohol **16** (249 mg, 80%) as a yellow solid. R_f ($CHCl_3$/MeOH, 20:1) = 0.60. HPLC: t_R = 8.30 min (9%), 8.60 min (70%). Diastereomeric mixture: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5 H, H^{phenyl}), 6.95–6.92 (m, 1 H, NH), 6.72 (d, J = 6.5 Hz, 1 H, NH), 5.53 (d, J = 7.3 Hz, 1 H, NH), 5.04 (m, 2 H), 4.95 (d, J = 8.3 Hz, 1 H), 4.40–4.35 (m, 2 H), 4.13 (m, 1 H), 3.61–3.59 (m, 1 H),1.86 (s, OH), 1.56–1.18 (m, 9 H), 0.94–0.83 (m, 18 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.7, 127.6, 156.4, 136.0, 128.6, 128.3, 128.1, 79.1, 78.9, 67.4, 67.3, 53.8, 52.4, 52.1, 49.2, 41.6, 41.3, 40.6, 40.5, 25.0, 24.8, 24.7, 22.9, 22.9, 22.7, 22.4, 22.1, 21.4, –16.5 ppm. MS (ESI): m/z = 766 $[M + Na]^+$.

Benzyl (*S*)-1-{(*S*)-1-[(*S*)-1,1-Diiodo-5-methyl-2-oxohexan-3-ylamino]-4-methyl-1-oxopentan-2-ylamino}-4-methyl-1-oxopentan-2-ylcarbamate (17): To a solution of β-diiodoalcohol **16** (60 mg, 0.08 mmol) in DMSO (5 mL) was added IBX (45 mg, 0.16 mmol), and the mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water (50 mL) and MTBE (70 mL) was added. The precipitate was filtered off, and the organic layer was extracted with water (2 × 50 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by LC (CH/EE, 1:1) to give peptidic β-diiodoketone **17** (52 mg, 87%) as a yellow solid. HPLC: t_R = 8.90 min (70%), 9.18 min (20%). Diastereomeric mixture: ^{1}H NMR (500 MHz, MeOD): δ = 7.37–7.31 (m, 6 H), 5.19–5.02 (m, 2 H), 5.00–4.88 (m, 1 H), 4.49–4.28 (m, 2 H),4.27–4.00 (m, 1 H), 1.81–1.51 (m, 9 H), 1.05–0.80 (m, 18 H) ppm. ^{13}C-NMR (125 MHz, MeOD): δ = 199.4, 199.1, 175.4, 175.3, 174.7, 158.6, 138.2, 129.5, 129.0, 128.8, 67.7, 55.4, 55.2, 54.9, 53.1, 51.3, 42.5, 42.1, 42.0, 41.7, 41.5, 41.2, 26.1, 26.0, 25.9, 25.7, 25.2, 23.7, 23.6, 23.5, 23.4, –29.2 ppm.

Benzyl (*S*)-4-Methyl-1-{(*S*)-4-methyl-1-[(*S*)-3-methyl-1-(quinoxalin-2-yl)butylamino]-1-oxopentan-2-ylamino}-1-oxopentan-2-ylcarbamate (19): β-Diiodoketone **17** (80 mg, 0.11 mmol) was dissolved in DMSO (2.5 mL) and stirred at 50 °C for 24 h (HPLC control). Glacial acetic acid (1.0 mL) and a solution of *o*-phenylenediamine (12 mg, 0.11 mmol) in EtOH (2.0 mL) was added to the reaction mixture, which was stirred at 70 °C for 1 h. After cooling, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with water (2 × 30 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by LC (EE/CH, 1:2) to give compound **19** (51 mg, 82%) as a yellow solid. R_f (EE/CH = 1:2) = 0.21. HPLC: t_R = 8.301 min (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.83 (s, 1 H), 8.11–8.07 (m, 1 H), 8.06–8.04 (m, 1 H), 7.79–7.70 (m, 2 H), 7.38–7.26 (m, 5 H, H^{phenyl}), 7.14 (d, J = 7.7 Hz, 1 H, NH), 6.53 (d, J = 7.3 Hz, 1 H, NH), 5.45–5.31 (m, 1 H), 5.26 (d, J = 7.6 Hz, 1 H, NH), 5.11 (s, 2 H), 4.61–4.44 (m, 1 H), 4.23–4.01 (m, 1 H), 1.94–1.45 (m, 9 H), 1.05–0.86 (m, 18 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 171.2, 156.3, 156.0, 144.4, 142.0, 141.8, 136.1, 130.2, 129.7, 129.3, 129.0, 128.6, 128.3, 128.1, 67.2, 53.6, 51.9, 51.1, 45.2, 41.4, 40.9, 29.7, 25.0, 24.7, 23.0, 22.9, 22.8, 22.7, 22.3, 22.2, 22.0 ppm. MS (EI): m/z = 575 $[M]^+$. HRMS (EI): calcd. for $C_{33}H_{45}N_5O_4$ $[M]^+$ 575.3472; found 575.3382.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra.

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