JOC The Journal of Organic Chemistry

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Ring Expansion of 2-Azido-2-phenyl-indan-1,3-dione for the Generation of Heterocyclic Scaffolds

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c01586 Read Online

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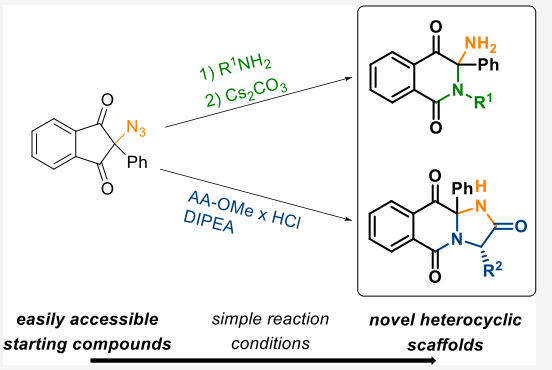
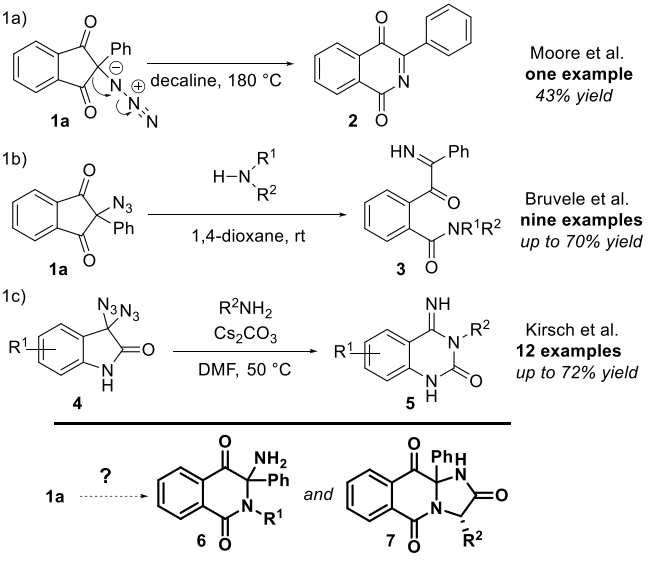
ABSTRACT: A novel ring expansion based on the readily available 2-azido-2-phenyl-indan-1,3-dione is described. Treatment with primary amines and cesium carbonate in a two-step sequence gives rise to 3-amino-2,3-dihydroisoquinoline-1,4-diones with an unprecedented substitution pattern. The corresponding conversion using amino acid methyl esters leads directly to a novel tricyclic 1,10a-dihydroimidazo-isoquinoline-2,5,10-trione scaffold, a structure that has never been reported before, to the best of our knowledge.



The use of ring enlargement reactions proved to be a highly efficient strategy for the generation of nitrogen-containing heterocycles as well as for the synthesis of numerous natural products and pharmacologically active substances.[1−5] To trigger the ring expansions, a range of features has been exploited, including ring strain,[6−9] radical stability,[10,11] and aromatization, among others.[1−5] For example, the classical Tiffeneau−Demjanov reaction of diazonium ions is primarily driven by the loss of dinitrogen.[12,13] Accordingly, organic azides[14,15] also became versatile starting points for ring expanding rearrangements, in most cases comprising a Schmidt[16,17] or Boyer[18] reaction where the dinitrogen formation is often accompanied by the creation of reactive nitrene intermediates prone to skeletal rearrangements.[19−22]

In 1975, Moore and coworkers reported the thermally induced ring expansion of 2-azido-2-phenyl-1,3-indandione **1a**, shown in Scheme 1a.[23,24] Upon refluxing in decalin at 180 °C, the dihydroisoquinoline-1,4-dione **2** was obtained in 43% yield. The reaction was proposed to proceed through a concerted rearrangement with release of nitrogen, similar to the Curtius reaction.[25] Surprisingly, this rearrangement remained of anecdotal nature, although the azanaphthoquinone core within reach appeared to be of some interest.[26] In the course of our recent studies on the reactivity of geminal diazides,[27−29] we then stumbled upon a report by Bruvele on how the azide **1a** undergoes ring-opening when treated with amines in 1,4-dioxane at room temperature; imine **3** was described to become the product of this carbon−carbon bond cleavage reaction (Scheme 1b).[30] Because this result is well-matched with our own findings that nucleophilic amines are capable of

Scheme 1. Ring Expansion and Fragmentation Reactions with Organic Azides



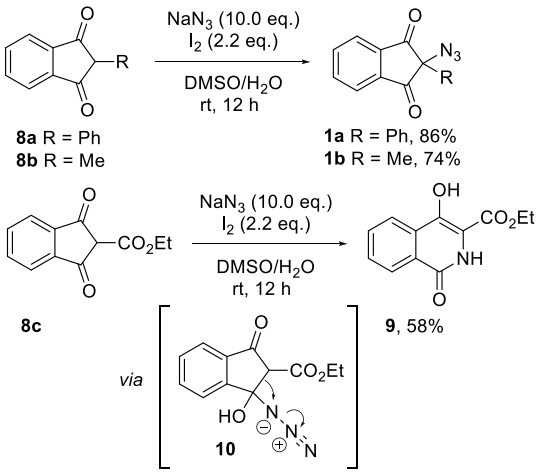
Received: July 3, 2020

provoking the fragmentation of certain 2-azido carbonyl systems,[31] we sought to use 2-azido-1,3-indandiones of type **1** for the new and general route toward 3-amino-2,3-dihydroisoquinoline-1,4-diones **6** outlined in Scheme 1. It was expected that the ring-opening of the azide **1** is initiated by the nucleophilic attack of the amine, and the resulting anion then decomposes with loss of dinitrogen, forming the Bruvele imine, which finally cyclizes by an intramolecular attack that results in a net ring expansion. A somewhat related ring expansion was recently disclosed by us for the synthesis of 4-imino-3,4-dihydroquinazolin-2-(1*H*)-ones **5** from diazides **4** upon simple treatment with primary amines (Scheme 1c).[32]

In this Note, we report the novel two-step ring expansion of 2-azido-1,3-indandiones **1**: through simple treatment with primary amines and bases, 3-amino-2,3-dihydroisoquinoline-1,4-diones **6** were easily generated, a class of heterocycles quite unique in that our literature search revealed no more than two substructures.[26] We also expanded this method to produce 1,10a-dihydroimidazo-isoquinoline-2,5,10-triones **7** from the 2-azido-1,3-indandiones **1** with amino acid methyl esters possessing, to our knowledge, an unprecedented tricyclic scaffold. Of note, the two uncommon heterocyclic structures that are themes of this Note have potential as versatile starting points for further functionalization, as we will show in future works.

We began our studies with the synthesis of 2-azido-indan-1,3-diones **1** with the goal of testing the potential ring expansion reaction to produce the lactams **6** (and **7**, *vide infra*). The two azides **1a** and **1b** having an aryl or alkyl group attached at 2-position were selected as archetypical 2-azido-indan-1,3-dione compounds (Scheme 2). The transformation

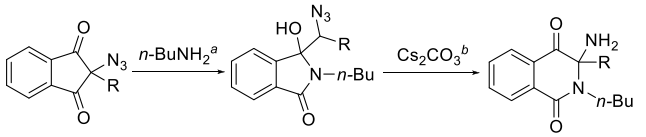
Scheme 2. Synthesis of 2-Azido-indan-1,3-diones 1a and 1b



of commercially available **8a** (R = Ph) and easily accessible **8b**[33] (R = Me) proceeded smoothly using our standard azidation conditions[34] (NaN_3, I_2, DMSO/H_2O, room temperature; Scheme 2). However, the conditions were unsuccessful for the conversion of ethyl ester **8c**,[38] providing the isoquinoline **9** in 58% yield instead of the desired 2-azido-indan-1,3-dione. This ring expansion most likely proceeds through a Schmidt reaction[16,17] via **10**. We note that iodine was required to make the transformation possible; in the absence of iodine, or when several standard acids were added, we never observed even traces of isoquinoline formation. Several attempts accessing the 2-azido-indan-1,3-dione with an ester group (R = CO_2Et) through alternative synthetic routes failed, unfortunately.

We then studied the amine-triggered ring-opening of the 2-azido-indan-1,3-diones **1a** and **1b**. To our disappointment, when azide **1a** was treated with *n*-butylamine in 1,4-dioxane at room temperature, as described in the Bruvele report,[30] we obtained an unidentified product mixture, and not even traces of the expected imine **3** (or its cyclized derivative **6**) were detected using mass spectrometer analysis. By simply switching from 1,4-dioxane to toluene as solvent, however, diastereomeric mixtures of the rearranged azides **11a** and **12** were formed in good yields, both of which show that the carbon−carbon bond was successfully cleaved by the amine nucleophile (Scheme 3). We then sought to prompt a further

Scheme 3. Nucleophilic Ring Expansion



[a]Conditions: *n*-$BuNH_2$ (1.0 equiv), toluene, rt, 12 h. [b]Conditions: Cs_2CO_3 (1.0 equiv), toluene, rt, 12 h.

fragmentation of **11a** and **12** under thermal, acidic, and basic conditions. While **12** (R = Me) produced complex product mixtures in all instances, the phenyl-substituted azide **11a** converted smoothly into the corresponding lactam **6** when treated with a base. In particular, with stoichiometric amounts of cesium carbonate in toluene at room temperature, 3-amino-2,3-dihydroisoquinoline-1,4-dione **6a** was obtained with an excellent isolated yield of 90%. Although the 2,3-dihydroisoquinoline-1,4-diones **6** consist of a quite familiar-looking core, the only reported alternative to generate the 3-amino-substituted 2,3-dihydroisoquinoline-1,4-diones **6** is by addition of ammonia to azanaphthoquinones: the seminal publication by Feiner and Schenker from 1969 included two examples, and substituents at the dihydroisoquinoline nitrogen were not accessible.[26] In 2015, the synthesis of N^2-substituted 3-hydroxy-derivatives of **6** was described by Zhao and coworkers using the intramolecular hypervalent iodine-mediated cyclization of ortho-(1-alkynyl)-benzamides and a subsequent oxidative hydroxylation.[35]

Because our ring-expanding method was obviously limited with regard to R, requiring an aromatic substituent, we further investigated the scope of this two-step sequence **1a** → **6** with a focus on the amine nucleophiles, as summarized in Table 1. To our delight, aliphatic amines were generally good nucleophiles that gave the rearranged azides **11a−g** in yields between 55 and 87% (and diastereoselectivities ranging from 69:31 to >95:5). Subsequent treatment of the azides **11a−g** with cesium carbonate then provided the corresponding 2-amino-2,3-dihydroisoquinoline-1,4-diones **6a−g** in 57−90% yield. The structure of **6f** was unequivocally proven by X-ray crystallography. Aniline derivatives were not reactive in this ring-opening reaction.

A plausible mechanism accounting for the formation of **11** and **6** is proposed in Scheme 4. The first step starts with a nucleophilic attack of the amine onto a carbonyl group of **1a** followed by ring-opening substitution, affording intermediate

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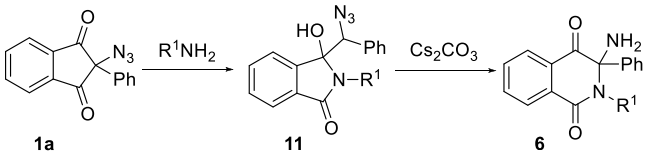
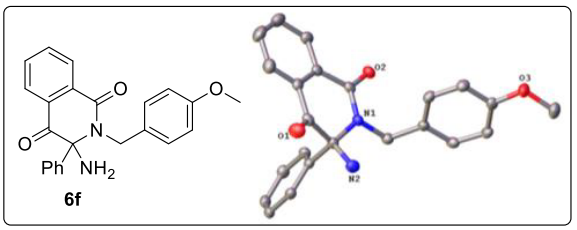
Table 1. Reaction Scope of Primary Amines

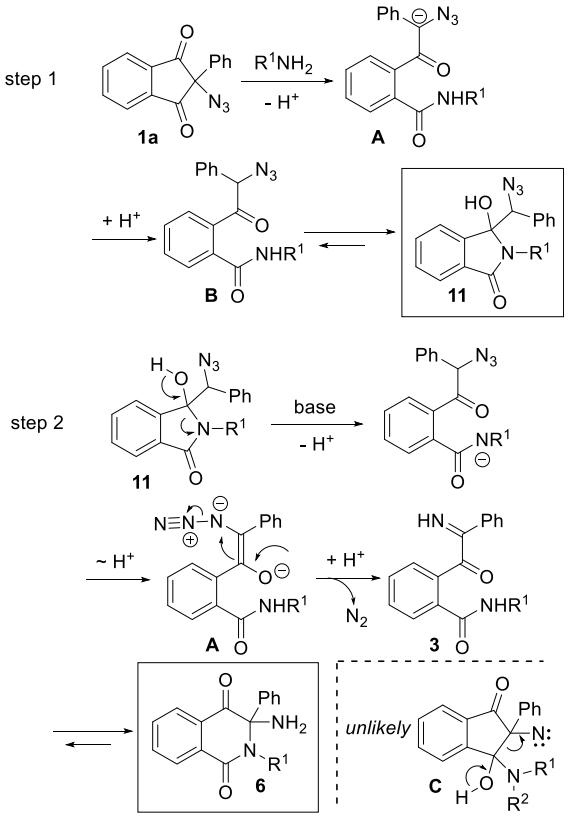




entry	R^1	yield of **11** (%)[a,b,c]	compd	yield of **6** (%)[a,d]
1	*n*-Bu	82[e]	**a**	90 (82)[f]
2	*n*-Hex	87	**b**	79
3	*n*-Oct	78	**c**	67
4	*i*-Bu	72	**d**	57(63)
5	Bn	55	**e**	78
6	4-MeO-C_6H_4-CH_2	50	**f**	70
7	3-Cl-C_6H_4-CH_2	57	**g**	89

[a]Isolated yields after column chromatography. [b]Conditions: 0.38 mmol of **1a**, amine (1.0 equiv), toluene, rt, 12 h. [c]Diastereomeric ratio: **11a**, 69:31; **11b**, 77:23; **11c**, 84:16; **11d**, 75:25; **11e** > 95:5; **11f**, 80:20; **11g** > 95:5. [d]Conditions: Cs_2CO_3 (1.0 equiv), toluene, rt, 12 h. [e]1.14 mmol of **1a**. [f]1.09 mmol of **11a**. X-ray structure: Ellipsoid is drawn at 50% probability; hydrogen atoms are omitted for clarity.

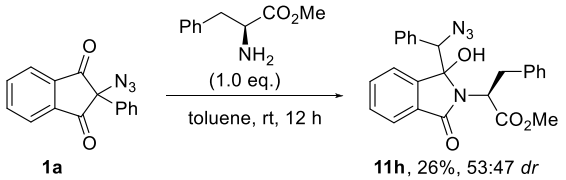
Scheme 4. Possible Mechanism for the Two-Step Ring Expansion



A. Due to the adjacent phenyl group, the azidated enolate anion is apparently of sufficient stability to become protonated from the close amide moiety (or from an external proton source), instead of undergoing the usual fragmentation under loss of dinitrogen one would expect from azide-bearing carbanions.[36] A similar observation by us on diazidated enolates that were relatively inert to fragmentation supports this hypothesis.[37] Intramolecular carbonyl addition with **B** then results in the formation of the *N*,*O*-acetal **11**. In the second step, treatment with the base forces the fragmentation of **A** that then provides the imine species **3** upon loss of dinitrogen. Cyclization finally gives the stable 2-amino-2,3-dihydroisoquinoline-1,4-dione target compounds **6**. We note that the amide nitrogen functions as nucleophile, and cyclization products provided by a nucleophilic carbonyl were not found. Based on our results, we can rule out a mechanism where the ring enlargement is accomplished through the rearrangement of a nitrene intermediate **C**, as proposed in the reports by Moore and Bruvele groups.[23,24,30]

We reasoned that the analogous reaction of azide **1a** with amino acid methyl esters may give rise to the unprecedented tricyclic scaffold **7** after lactamization of the initially formed 2-amino-2,3-dihydroisoquinoline-1,4-dione. To this end, we treated **1a** with L-phenylalanine methyl ester in toluene at room temperature. However, the intermediate **11h** was isolated in disappointingly low yields only (Scheme 5).

Scheme 5. Reaction of Azide 1a with L-Phenylalanine Methyl Ester



Next, we tested the reaction with the goal of providing the tricyclic heterocycle **7a** in a direct manner: **1a** was smoothly converted in toluene using L-phenylalanine methyl ester hydrochloride and supplementary base additives. Best results were obtained with four equivalents of DIPEA at 60 °C, and **7a** was formed in 60% overall yield. As summarized in Table 2, a series of dihydroimidazo-isoquinoline-2,5,10-triones **7a**–**g** could be obtained in overall yields between 59 and 88%, including scaffolds derived from valine (**7c**), methionine (**7f**), and tyrosine (**7g**). In all cases, the target heterocycles were formed as mixtures of diastereomers in a ratio of about 60:40. With the exception of **7e** and **7g**, it was easily possible to separate the two diastereomers by standard flash column chromatography. We analyzed the ^{1}H NMR spectra with respect to the anisotropy-related shielding of the protons at the *β*-carbon in the amino acid derived side chains R^2, and it was found that the mainly formed diastereomers are the ones where the phenyl group and the amino acid side chain are *cis*-configured. A single crystal of **7b** suitable for X-ray crystallography was evidence for the relative and thus absolute configuration of the major stereoisomer. In the case of **7e** and **7g**, we were not able to isolate the minor diastereomers in pure form.

In summary, we developed a new ring expansion reaction that relies on the uncommon fragmentation of 2-azido-2-phenyl-1,3-indandione. In the presence of simple amines or

https://dx.doi.org/10.1021/acs.joc.0c01586
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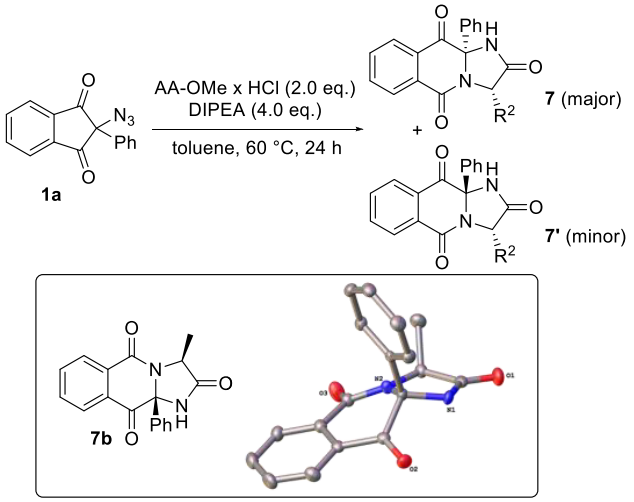
Table 2. Synthesis of 1,10a-Dihydroimidazo[1,2-*b*]isochinolin-2,5,10-(3*H*)-triones 7



entry	AA	R^2	compd	yield of 7/7′ (%)[a,b,c]
1	Phe	Bn	**a**	39/21
2	Ala	Me	**b**	52/34 (53/32)[d]
3	Val	*i*-Pr	**c**	56/32
4	Ile	(*S*)-2-methylbutyl	**d**	56/25
5	Tle	*t*-Bu	**e**	55/−
6	Met	$MeSCH_2CH_2$	**f**	56/27
7	Tyr	4-HO-C_6H_4-CH_2	**g**	33/−

[a]Isolated yield; diastereomers were separated by flash chromatography. [b]Conditions: 0.27 mmol of **1a**, AA-OMe × HCl (2.0 equiv), DIPEA (4.0 equiv), toluene, 60 °C, **1d**. [c]Diastereomeric ratio determined by ^{1}H NMR of the crude mixture 7/7′: **a**, 61:39; **b**, 60:40; **c**, 65:35; **d**, 65:35; **e**, nd; **f**, 61:39; **g**, nd. [d]1.14 mmol of **1a**. X-ray structure: Ellipsoid is drawn at 50% probability; hydrogen atoms are omitted for clarity.

amino acid methyl esters, the widely unknown bicyclic and tricyclic heterocycle scaffolds **6** and **7**, both of which may attract interest as building blocks for pharmaceuticals, are easily accessible under mild conditions. Results with amines bearing other functional groups will be reported in due course, extending this concept of how organic azides can be fragmented and rearranged through the action of nucleophiles.

EXPERIMENTAL SECTION

General Remarks. All commercial reagents and solvents were used as purchased. In all reactions with elevated temperatures, an oil bath was used as a heat source. Thin layer chromatography (TLC) was conducted with precoated glass-backed plates (silica gel 60 F_{254}) and visualized by exposure to UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$) and subsequent heating. Flash column chromatography was performed on silica gel (40−60 μm), and the used eluent is reported in the respective experiments. Abbreviations of solvents are as follows: CH: cyclohexane, EA: ethyl acetate, DCM: dichloromethane, MeOH: methanol, DIPEA: diisopropylethylamine. IR spectra were measured using ATR-technique in the range of 400−4000 cm^{-1}. ^{1}H NMR spectra were recorded at 400 or 600 MHz, and ^{13}C NMR spectra at 101 or 151 MHz. Chemical shifts are reported in ppm relative to the solvent signal, coupling constants *J* in Hz. Multiplicities were defined by standard abbreviations. Low-resolution mass spectra (LRMS) were recorded using a LC/MS-combination (ESI). High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive) on a Bruker micrOTOF or FD ionization on a JEOL-TOF. Caution: Azides are potentially hazardous and should be handled with care.

General Procedures. *General Procedure A for the Synthesis of 3-(Azido(phenyl)methyl)-3-hydroxyiso-indolin-1-ones **11**.* The 2-azido-indene-1,3-dione **1a** (1.0 equiv) was dissolved in toluene (0.3 M), and the respective amine (1.0 equiv) was added. The solution was stirred at room temperature for 12 h. Evaporation of the solvent in vacuo and flash chromatography on silica gel afforded the corresponding isoindolinones.

*General Procedure B for the Synthesis of 3-Amino-3-phenyl-2,3-dihydroisoquinoline-1,4-diones **6**.* The respective isoindolinone **11** (1.0 equiv) was dissolved in toluene (0.1 M), and cesium carbonate (1.0 equiv) was added. The reaction mixture was stirred at room temperature for 12 h. Evaporation of the solvent in vacuo and flash-chromatography on silica gel afforded the corresponding isoquinolines.

*General Procedure C for the Synthesis of Dihydroimidazo[1,2-b]isoquinoline-2,5,10(3H)-triones **7**.* The respective amino acid methyl ester hydrochlorides (2.0 equiv) were dissolved in toluene (0.36 M). Following the addition of DIPEA (2.0 equiv), the solution was allowed to stir for 5 min. 2-Azido-indene-1,3-dione **1a** (1.0 equiv) and DIPEA (2.0 equiv) were added consecutively, and the solution was stirred at 60 °C for 24 h. Evaporation of the solvent *in vacuo* and flash-chromatography on silica gel afforded the corresponding isoquinolines.

*2-Methyl-1H-indene-1,3(2H)-dione (**8b**).* To a solution of dimethyl phthalate (6.18 g, 31.8 mmol, 1.1 equiv) in toluene (19 mL) was added pentan-3-one (2.49 g, 28.9 mmol, 1.0 equiv). Following the addition of sodium hydride (1.16 g, 28.9 mmol, 1.0 equiv, 60% dispersion in mineral oil), the reaction mixture was heated at 110 °C for 16 h. The residue was then filtered off and washed with toluene. The solid was absorbed in water and acidified dropwise with concentrated hydrochloric acid (pH = 3). The aqueous layer was then extracted with dichloromethane, and the combined organic layers dried with sodium sulfate. Evaporation of the solvent *in vacuo* and flash chromatography on silica gel afforded product **8b** as a yellow solid (2.81 g, 17.5 mmol, 61%). TLC: R_f = 0.31 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.92 (m, 2H), 7.87−7.77 (m, 2H), 3.04 (q, *J* = 7.7 Hz, 1H), 1.41 (d, *J* = 7.7 Hz, 3*H*). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 201.0, 142.1, 135.8, 123.4, 48.9, 10.6. The analytical data are in agreement with previously reported one.[3]

*Ethyl-1,3-dioxo-2,3-dihydro-1H-indene-2-carboxylate (**8c**).* To diethyl phthalate (10.0 g, 51.5 mmol, 1.0 equiv) was added sodium (1.99 g, 86.5 mmol, 1.7 equiv). The suspension was heated to 115 °C and 10 mL ethyl acetate was added dropwise. The mixture was stirred at 90 °C for 7 h. Following the addition of 15 mL ethanol the solution was stirred again until the resulting solid was completely dissolved at 90 °C. After cooling the reaction to room temperature, the resulting solid was filtered off and washed with ethanol. The sodium salt obtained was dissolved in hot water and acidified with diluted hydrochloric acid (1 M) (pH = 3). The residue was filtered off to give product **8c** as a yellow solid (1.34 g, 6.14 mmol, 12%). TLC: R_f = 0.18 (DCM/MeOH 95:5) (UV). ^{1}H NMR (600 MHz, CD_3OD) δ 7.52−7.47 (m, 4H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3*H*). ^{13}C{^{1}H} NMR (151 MHz, CD_3OD): δ 194.3, 167.8, 140.4, 132.5, 120.6, 99.2, 59.2, 15.1. The analytical data are in agreement with previously reported one.3[8]

*2-Azido-2-phenyl-1H-indene-1,3(2H)-dione (**1a**).* To a solution of 2-phenyl-1*H*-indene-(1,3)-(2*H*)-dione **8a** (1.00 g, 4.90 mmol, 2.0 equiv) in DMSO/water (45 mL, 2:1) were added sodium azide (2.94 g, 45.0 mmol, 10 equiv) and iodine (2.54 g, 9.90 mmol, 2.2 equiv) consecutively. The reaction mixture was stirred at room temperature for 18 h. A saturated aqueous solution of sodium thiosulfate was added, and the solution was extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate. Evaporation of the solvent *in vacuo* and flash chromatography on silica gel afforded product **1a** as a white solid (1.02 g, 3.87 mmol, 86%). TLC: R_f = 0.28 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 5.7, 3.1 Hz, 1H), 7.93 (dd, *J* = 5.7, 3.1 Hz, 1H), 7.57−7.46 (m, 1H), 7.45−7.38 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.8, 140.7, 137.1, 132.3, 129.9, 129.5, 127.6, 124.6, 70.9. IR (ATR): $\tilde{\nu}$ = 2096, 1791, 1764, 1735, 1713, 1592, 1578, 1488, 1464, 1445, 1351,

https://dx.doi.org/10.1021/acs.joc.0c01586
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1331, 1248, 1235, 1182, 1156, 1104, 1085, 1000, 973, 956, 879, 849, 764, 722, 697, 657, 557, 534, 510, 417 (cm^{-1}). LRMS (ESI) *m/z*: 281.1 [M + NH_4^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{15}H_9N_3NaO_2$: 286.0587; found 286.0586.

*2-Azido-2-methyl-1H-indene-1,3(2H)-dione (**1b**).* To a solution of 2-methyl-*1H*-indene-(1,3)-(2*H*)-dione **8b** (2.00 g, 12.5 mmol, 1.0 equiv) in DMSO/water (125 mL, 2:1) were added sodium azide (8.16 g, 124 mmol, 10 equiv) and iodine (7.04 g, 27.5 mmol, 2.2 equiv) consecutively. The reaction mixture was stirred at room temperature for 18 h. A saturated aqueous solution of sodium thiosulfate was added, and the solution was extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate. Evaporation of the solvent *in vacuo* and flash chromatography on silica gel afforded product **1b** as a white solid (1.85 g, 9.20 mmol, 74%). TLC: R_f = 0.29 (CH/EA 6:4) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 5.7, 3.1 Hz, 1H), 7.94 (dd, *J* = 5.7, 3.1 Hz, 1H), 1.65 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 196.5, 139.8, 137.1, 124.6, 64.3, 17.4. IR (ATR): $\tilde{\nu}$ = 2116, 2091, 1752, 1712, 1596, 1466, 1445, 1372, 1350, 1332, 1278, 1239, 1180, 1154, 1069, 1016, 981, 941, 891, 866, 835, 792, 728, 711, 638, 549, 527, 478, 419 (cm^{-1}). LRMS (ESI) *m/z*: 219.1 [M + NH_4^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{10}H_7N_3NaO_2$: 224.0430; found 224.0430.

*Ethyl-4-hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxy-late (**9**).* To a solution of ethyl-1,3-dioxo-2,3-dihydro-1*H*-indene-2-carboxylate **8c** (50 mg, 0.23 mmol, 1.0 equiv) in DMSO/water (2.2 mL, 2:1) were added sodium azide (149 mg, 2.29 mmol, 10 equiv) and iodine (129 mg, 0.500 mmol, 2.2 equiv) consecutively. The reaction mixture was stirred at room temperature for 18 h. A saturated aqueous solution of sodium thiosulfate was added, and the solution was extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate. Evaporation of the solvent *in vacuo* and flash chromatography on silica gel afforded product **9** as a white solid (31 mg, 0.13 mmol, 58%). TLC: R_f = 0.19 (CH/EA 8:2) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.68 (s, 1H), 8.57−8.24 (m, 1H), 8.32−8.01 (m, 1H), 7.81 (ddd, *J* = 8.1, 7.3, 1.3 Hz, 1H), 7.72 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 165.0, 159.1, 147.7, 132.9, 131.3, 130.9, 129.4, 128.1, 123.8, 107.0, 62.8, 14.4. IR (ATR): $\tilde{\nu}$ = 3143, 3119, 3009, 2995, 2925, 2852, 1637, 1594, 1562, 1465, 1410, 1368, 1325, 1275, 1254, 1170, 1158, 1129, 1112, 1085, 1021, 965, 949, 883, 871, 826, 783, 740, 706, 680, 666, 594, 517, 468, 451, 426, 410 (cm^{-1}). LRMS (ESI) *m/z*: 234.1 [M + H$^+$]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{12}H_{11}NNaO_4$: 256.0580; found 256.0591.

*3-(Azido(phenyl)methyl)-2-butyl-3-hydroxyiso-indolin-1-one (**11a**).* According to the general procedure A using **1a** (300 mg, 1.14 mmol, 1.0 equiv) and *n*-butylamine (83 mg, 1.14 mmol, 1.0 equiv) product **11a** (313 mg, 930 μmol, 82%, dr 69:31) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.29 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ major diastereomer 7.80 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.64−7.46 (m, 3*H*), 7.22−7.10 (m, 1H), 7.10−6.97 (m, 2H), 6.78−6.66 (m, 2H), 5.11 (s, 1H), 3.73−3.59 (m, 1H), 3.53 (s, 1H), 3.35−3.22 (m, 1H), 1.86−1.62 (m, 2H), 1.48−1.31 (m, 2H), 1.05−0.92 (m, 3*H*); minor diastereomer 7.63−7.60 (m, 1H), 7.52−7.37 (m, 3*H*), 7.23−7.14 (m, 2H), 7.13−7.02 (m, 2H), 6.93−6.85 (m, 1H), 5.17 (s, 1H), 3.82−3.73 (m, 1H), 3.49−3.42 (m, 1H), 3.38 (s, 1H), 1.72−1.68 (m, 2H), 1.45−1.35 (m, 2H), 1.05−0.92 (m, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 167.4, 166.8, 143.4, 143.4, 134.1, 133.6, 132.6, 132.4, 131.8, 131.4, 130.3, 130.2, 129.1, 128.9, 128.8, 128.2, 128.2, 127.6, 92.4, 91.7, 70.1, 69.7, 40.4, 40.2, 31.6, 31.5, 20.8, 20.7, 14.0, 13.9.. IR (ATR): $\tilde{\nu}$ = 3203, 2956, 2926, 2871, 2857, 2100, 1686, 1672, 1615, 1600, 1469, 1452, 1436, 1412, 1371, 1325, 1302, 1276, 1262, 1182, 1118, 1074, 1018, 1001, 956, 929, 912, 874, 848, 780, 753, 712, 694, 656, 624, 613, 591, 541, 513 (cm^{-1}). LRMS (ESI) *m/z*: 337.2 [M + H$^+$]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{19}H_{20}N_4NaO_2$: 359.1478; found 359.1487.

*3-(Azido(phenyl)methyl)-2-hexyl-3-hydroxyiso-indolin-1-one (**11b**).* According to the general procedure A using **1a** (100 mg, 0.38 mmol, 1.0 equiv) and *n*-hexylamine (38 mg, 0.38 mmol, 1.0 equiv) product **11b** (121 mg, 332 μmol, 87%, dr 77:23) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.32 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ major diastereomer 7.81 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.58−7.28 (m, 3*H*), 7.33−7.28 (m, 1H), 7.22−7.12 (m, 2H), 7.10−6.63 (m, 2H), 5.11 (s, 1H), 3.66 (ddd, *J* = 13.6, 10.2, 5.4 Hz, 1H), 3.39 (s, 1H), 3.29 (ddd, *J* = 13.6, 10.2, 5.8 Hz, 1H), 1.85−1.63 (m, 2H), 1.42−1.22 (m, 6H), 0.96−0.88 (m, 3*H*); minor diastereomer 7.66−7.61 (m, 1H), 7.53−7.37 (m, 5H), 7.22−7.15 (m, 2H), 6.93−6.87 (m, 1H), 5.17 (s, 1H), 3.82−3.72 (m, 1H), 3.51−3.42 (m, 1H), 3.24 (s, 1H), 1.75−1.65 (m, 2H), 1.42−1.22 (m, 6H), 0.99−0.88 (m, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 167.4, 166.7, 143.4, 143.3, 134.1, 133.6, 132.6, 132.5, 131.4, 130.3, 130.3, 129.6, 129.1, 128.9, 128.8, 128.2, 127.6, 124.0, 123.3, 123.3, 123.1, 92.4, 91.6, 70.1, 69.7, 40.7, 40.4, 31.7, 31.7, 29.5, 29.4, 27.3, 27.2, 22.8, 22.8, 14.2, 14.2. IR (ATR): $\tilde{\nu}$ = 3272, 3063, 3033, 2958, 2914, 2871, 2849, 2232, 2102, 1689, 1672, 1617, 1600, 1491, 1467, 1454, 1436, 1411, 1372, 1348, 1326, 1259, 1223, 1170, 1114, 1075, 1017, 971, 949, 872, 780, 769, 754, 712, 693, 663, 625, 610, 531, 512 (cm^{-1}). LRMS (ESI) *m/z*: 365.3 [M + H$^+$]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{21}H_{24}N_4O_2$: 387.1791; found 387.1798.

*3-(Azido(phenyl)methyl)-2-octyl-3-hydroxyiso-indolin-1-one (**11c**).* According to the general procedure A using **1a** (100 mg, 0.38 mmol, 1.0 equiv) and *n*-hexylamine (50 mg, 0.38 mmol, 1.0 equiv) product **11c** (116 mg, 295 μmol, 78%, dr 84:16) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.33 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ major diastereomer 7.82−7.80 (m, 1H), 7.60−7.38 (m, 3*H*), 7.22−7.14 (m, 1H), 7.11−7.05 (m, 2H), 6.81−6.64 (m, 2H), 5.10 (s, 1H), 3.64 (ddd, *J* = 13.6, 10.2, 5.4 Hz, 1H), 3.57 (s, 1H), 3.27 (ddd, *J* = 13.6, 10.2, 5.8 Hz, 1H), 1.84−1.59 (m, 2H), 1.43−1.18 (m, 10H), 1.05−0.87 (m, 3*H*); minor diastereomer 7.63−7.59 (m, 1H), 7.52−7.38 (m, 5H), 7.23−7.14 (m, 2H), 6.92−6.87 (m, 1H), 5.17 (s, 1H), 3.79−3.71 (m, 1H), 3.48−3.37 (m, 2H), 1.86−1.58 (m, 2H), 1.46−1.17 (m, 10H), 1.01−0.87 (m, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 166.7, 143.4, 134.1, 133.6, 132.6, 132.5, 131.8, 131.4, 130.3, 130.3, 129.1, 128.8, 128.2, 128.2, 127.6, 124.0, 123.3, 123.3, 123.1, 92.4, 77.2, 70.2, 40.7, 40.5, 32.0, 29.5, 29.5, 29.4, 29.4, 29.4, 27.7, 27.6, 22.8, 14.2; not all signals of the two diastereomers are resolved. IR (ATR): $\tilde{\nu}$ = 3268, 3065, 3033, 2955, 2921, 2852, 2104, 1692, 1674, 1616, 1600, 1492, 1468, 1453, 1437, 1409, 1372, 1345, 1328, 1310, 1282, 1256, 1212, 1182, 1156, 1117, 1076, 1017, 1002, 973, 948, 910, 872, 781, 754, 716, 695, 664, 626, 609, 592, 544, 516 (cm^{-1}). LRMS (ESI) *m/z*: 393.3 [M + H$^+$]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{23}H_{28}N_4NaO_2$: 415.2104; found 415.2112.

*3-(Azido(phenyl)methyl)-3-hydroxy-2-isobutyliso-indolin-1-one (**11d**).* According to the general procedure A using **1a** (100 mg, 0.38 mmol, 1.0 equiv) and isobutylamine (28 mg, 0.38 mmol, 1.0 equiv) product **11d** (92 mg, 0.27 mmol, 72%, dr 75:25) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.30 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ major diastereomer 7.86 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.64−7.43 (m, 2H), 7.23−7.13 (m, 2H), 7.10−7.03 (m, 2H), 6.77−6.64 (m, 2H), 5.13 (s, 1H), 3.56 (dd, *J* = 13.6, 7.7 Hz, 1H), 3.39 (s, 1H), 3.11 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.43−2.30 (m, 1H), 0.92 (d, *J* = 5.3 Hz, 6H); minor diastereomer 7.66 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.44−7.37 (m, 5H), 7.22−7.13 (m, 1H), 7.13−7.01 (m, 1H), 6.84 (dt, *J* = 7.3, 1.0 Hz, 1H), 5.20 (s, 1H), 3.69 (dd, *J* = 13.9, 7.7 Hz, 1H), 3.25 (dd, *J* = 13.9, 7.7 Hz, 1H), 3.16 (s, 1H), 2.43−2.30 (m, 1H), 0.97 (d, *J* = 3.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 167.6, 166.9, 143.2, 143.1, 134.1, 133.5, 131.9, 131.4, 130.3, 130.3, 129.1, 128.9, 128.8, 128.2, 128.2, 127.6, 127.6, 124.0, 123.4, 123.3, 123.1, 92.5, 91.7, 77.2, 70.2, 69.7, 47.9, 47.8, 27.9, 27.7, 20.9, 20.8, 20.7, 20.6. IR (ATR): $\tilde{\nu}$ = 3242, 2958, 2925, 2869, 2103, 1669, 1615, 1601, 1468, 1452, 1435, 1408, 1385, 1368, 1345, 1299, 1281, 1254, 1212, 1192, 1119, 1071,1017, 1001, 967, 889, 876, 849, 821, 780, 756, 715, 695, 662, 628,612, 591, 541, 513, 466, 437, 417 (cm^{-1}). LRMS (ESI) *m/z*: 337.2 [M + H$^+$]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{19}H_{20}N_4NaO_2$: 359.1478; found 359.1490.

https://dx.doi.org/10.1021/acs.joc.0c01586
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*3-(Azido(phenyl)methyl)-2-benzyl-3-hydroxyiso-indolin-1-one (**11e**).* According to the general procedure A using **1a** (30 mg, 0.11 mmol, 1.0 equiv) and benzylamine (12 mg, 0.11 mmol, 1.0 equiv) product **11e** (23 mg, 62 μmol, 55%, dr > 95:5) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.30 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ major diastereomer 7.79 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.68−7.56 (m, 2H), 7.56−7.42 (m, 3*H*), 7.37−7.26 (m, 3*H*), 7.24−7.15 (m, 1H), 7.14−6.94 (m, 2H), 6.70−6.58 (m, 2H), 5.11 (s, 1H), 4.87 (d, *J* = 15.1 Hz, 1H), 4.59 (d, *J* = 15.1 Hz, 1H), 3.12 (s, 1H); minor diastereomer 8.10−6.55 (m, 14H), 5.06 (s, 1H), 4.88 (d, *J* = 15.1 Hz, 1H), 4.34 (d, *J* = 15.1 Hz, 1H), 2.94 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.2, 143.6, 138.3, 133.5, 132.1, 132.0, 131.7, 130.4, 129.1, 128.8, 128.8, 128.6, 128.2, 127.9, 127.6, 124.2, 123.4, 92.4, 70.5, 43.6; not all signals of the two diastereomers are resolved. IR (ATR): $\tilde{\nu}$ = 3254, 3062, 3030, 2921, 2852, 2103, 1671, 1601, 1494, 1468, 1453, 1430, 1401, 1353, 1255, 1129, 1071, 1018, 967, 932, 907, 874, 782, 756, 694, 605, 570, 538, 519, 451 (cm^{-1}). LRMS (ESI) *m*/*z*: 371.2 [M + H^+]. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{22}H_{18}N_4NaO_2$: 393.1322; found 359.1329.

*3-(Azido(phenyl)methyl)-3-hydroxy-2-(4-methoxy-benzyl)-isoindolin-1-one (**11f**).* According to the general procedure A using **1a** (100 mg, 0.38 mmol, 1.0 equiv) and 4-methoxybenzylamine (52 mg, 0.38 mmol, 1.0 equiv) product **11f** (76 mg, 0.19 mmol, 50%, dr 80:20) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.28 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ major diastereomer 7.79−7.77 (m, 1H), 7.61−7.51 (m, 1H), 7.50−7.42 (m, 2H), 7.39−7.33 (m, 2H), 7.20−7.12 (m, 1H), 7.04 (dd, *J* = 8.4, 7.1 Hz, 2H), 6.81−6.73 (m, 2H), 6.64−6.53 (m, 2H), 5.13 (s, 1H), 4.80 (d, *J* = 14.7 Hz, 1H), 4.51 (d, *J* = 14.7 Hz, 1H), 3.75 (s, 3*H*), 3.49 (s, 1H); minor diastereomer 7.68−7.62 (m, 1H), 7.33−7.26 (m, 5H), 7.20−6.99 (m, 2H), 6.90 (dt, *J* = 6.8, 1.0 Hz, 1H), 6.86−6.81 (m, 2H), 6.81−6.74 (m, 2H), 5.06 (s, 1H), 4.87−4.75 (m, 1H), 4.51 (d, *J* = 14.9 Hz, 1H), 3.76 (s, 3*H*), 3.32 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.5, 167.2, 159.1, 159.0, 143.7, 143.6, 134.2, 133.5, 132.2, 132.1, 132.0, 131.6, 130.5, 130.4, 130.3, 130.3, 130.2, 130.1, 128.9, 127.9, 124.2, 123.5, 123.3, 123.3, 114.2, 114.1, 92.5, 91.9, 70.4, 69.5, 55.4, 43.0, 42.7. IR (ATR): $\tilde{\nu}$ = 3288, 3061, 3034, 2997, 2955, 2925, 2852, 2834, 2103, 1673, 1611, 1585, 1510, 1467, 1452, 1428, 1404, 1352, 1328, 1302, 1281, 1241, 1175, 1132, 1111, 1072, 1030, 970, 847, 807, 780, 755, 715, 696, 662, 625, 597, 552, 539, 523, 505, 444 (cm^{-1}). LRMS (ESI) *m*/*z*: 401.2 [M + H^+]. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{23}H_{20}N_4NaO_3$: 423.1428; found 423.1426.

*3-(Azido(phenyl)methyl)-2-(3-chlorobenzyl)-3-hydroxy-isoindolin-1-one (**11g**).* According to the general procedure A using **1a** (100 mg, 0.38 mmol, 1.0 equiv) and 3-chlorobenzylamine (54 mg, 0.38 mmol, 1.0 equiv) product **11g** (87 mg, 0.21 mmol, 57%, dr > 95:5) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.27 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.65−7.58 (m, 2H), 7.52 (td, *J* = 7.5, 1.0 Hz, 1H), 7.41−7.40 (m, 1H), 7.32 (ddd, *J* = 6.1, 2.5, 1.7 Hz, 1H), 7.27−7.23 (m, 2H), 7.24−7.18 (m, 1H), 7.12−7.06 (m, 2H), 6.68−6.63 (m, 2H), 5.06 (s, 1H), 4.80 (d, *J* = 15.3 Hz, 1H), 4.56 (d, *J* = 15.3 Hz, 1H), 3.27 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.4, 143.6, 140.2, 134.6, 133.4, 132.3, 131.8, 130.5, 129.9, 129.2, 128.8, 128.3, 127.9, 127.8, 126.8, 124.3, 123.5, 92.3, 70.6, 43.1; not all signals of the two diastereomers are resolved. IR (ATR): $\tilde{\nu}$ = 3252, 3085, 3063, 3031, 2920, 2104, 1672, 1615, 1597, 1574, 1491, 1469, 1429, 1400, 1345, 1306, 1253, 1204, 1158, 1131, 1114, 1018, 1001, 969, 930, 914, 874, 851, 820, 779, 757, 716, 696, 679, 635, 606, 570, 552, 539, 525, 485, 429, 412 (cm^{-1}). LRMS (ESI) *m*/*z*: 405.1 [M + H^+]. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{22}H_{17}ClN_4NaO_2$: 427.0932; found 427.0951.

*(2R)-2-(1-(Azido(phenyl)methyl)-1-hydroxy-3-oxo-iso-indolin-2-yl)-3-phenylpropanoate (**11h**).* According to the general procedure A using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-phenylalanine methyl ester (48 mg, 0.27 mmol, 1.0 equiv) product **11h** (31 mg, 70 μmol, 26%, dr 53:47) was obtained after chromatography (CH/EA 9:1 → 7:3) as a yellow oil. TLC: R_f = 0.20 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ major diastereomer 7.80 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.51 (td, *J* = 7.5, 1.0 Hz, 1H), 7.46−7.27 (m, 5H), 7.26−7.08 (m, 6H), 6.11 (dt, *J* = 7.6, 0.9 Hz, 1H), 5.03 (dd, *J* = 11.8, 4.4 Hz, 1H), 4.56 (s, 1H), 3.89 (s, 3*H*), 3.81−3.70 (m, 1H), 3.57−3.39 (m, 1H); minor diastereomer 7.74 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.45−7.29 (m, 6H), 7.24−7.09 (m, 6H), 6.89 (dt, *J* = 7.5, 0.9 Hz, 1H), 4.79 (s, 1H), 4.40 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.86 (s, 3*H*), 3.86−3.70 (m, 1H), 3.57−3.39 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 171.1, 170.5, 167.3, 166.8, 143.8, 143.8, 139.0, 138.5, 135.1, 134.5, 131.9, 131.7, 131.6, 131.4, 130.2, 130.2, 129.6, 129.5, 129.4, 129.0, 128.8, 128.8, 128.3, 128.1, 127.2, 127.1, 124.6, 123.9, 123.3, 123.3, 90.6, 89.8, 72.5, 69.3, 57.9, 56.6, 53.2, 53.0, 34.6, 34.5. IR (ATR): $\tilde{\nu}$ = 3524, 3281, 3062, 3029, 2951, 2926, 2851, 2249, 2105, 1743, 1676, 1614, 1601, 1494, 1468, 1453, 1401, 1341, 1264, 1250, 1227, 1217, 1124, 1075, 1029, 973, 907, 875, 840, 828, 808, 755, 725, 697, 646, 621, 605, 566, 553, 536, 487 (cm^{-1}). LRMS (ESI) *m*/*z*: 443.2 [M + H^+]. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{25}H_{22}N_4NaO_4$: 465.1533; found 465.1551.

*3-Amino-2-butyl-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**6a**).* According to the general procedure B using **11a** (40 mg, 0.12 mmol, 1.0 equiv) and cesium carbonate (39 mg, 0.12 mmol, 1.0 equiv) product **6a** (33 mg, 0.11 mmol, 90%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.31 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42−8.21 (m, 1H), 7.91 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.78 (td, *J* = 7.6, 1.3 Hz, 1H), 7.61 (td, *J* = 7.6, 1.3 Hz, 1H), 7.37−7.25 (m, 5H), 3.95 (ddd, *J* = 13.0, 10.5, 5.2 Hz, 1H), 3.24−2.93 (m, 1H), 2.67 (s, 2H), 1.84−1.55 (m, 2H), 1.46−1.19 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3*H*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.2, 162.0, 140.2, 135.4, 132.7, 132.6, 129.6, 129.2, 129.0, 128.7, 126.9, 126.1, 81.2, 45.1, 31.8, 20.8, 13.9. IR (ATR): $\tilde{\nu}$ = 3368, 3294, 3065, 3027, 2957, 2931, 2871, 1693, 1642, 1597, 1580, 1487, 1465, 1445, 1405, 1369, 1323, 1286, 1251, 1184, 1158, 1099, 1078, 1029, 992, 908, 843, 795, 784, 729, 708, 646, 606, 526, 504, 450 (cm^{-1}). HRMS (ESI-TOF) *m*/*z*: [M − NH_3]$^+$ calculated for $C_{19}H_{18}NO_2^+$: 292.1380; found 292.1369.

*3-Amino-2-hexyl-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**6b**).* According to the general procedure B using **11b** (40 mg, 0.11 mmol, 1.0 equiv) and cesium carbonate (36 mg, 0.11 mmol, 1.0 equiv) product **6b** (29 mg, 86 μmol, 79%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.33 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (ddd, *J* = 7.9, 1.2, 0.5 Hz, 1H), 7.91 (ddd, *J* = 7.7, 1.3, 0.5 Hz, 1H), 7.78 (td, *J* = 7.6, 1.4 Hz, 1H), 7.61 (td, *J* = 7.6, 1.3 Hz, 1H), 7.37−7.26 (m, 5H), 3.93 (ddd, *J* = 13.0, 10.7, 5.1 Hz, 1H), 3.13 (ddd, *J* = 13.0, 10.8, 5.5 Hz, 1H), 2.66 (s, 2H), 1.83−1.60 (m, 2H), 1.39−1.14 (m, 6H), 0.97−0.67 (m, 3*H*). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.2, 162.0, 140.2, 135.4, 132.7, 132.6, 129.6, 129.2, 129.0, 128.7, 126.9, 126.1, 81.2, 45.3, 31.6, 29.6, 27.1, 22.7, 14.2. IR (ATR): $\tilde{\nu}$ = 3392, 3367, 3294, 3065, 3027, 2952, 2923, 2851, 1694, 1645, 1597, 1580, 1489, 1464, 1446, 1404, 1370, 1322, 1285, 1245, 1177, 1158, 1105, 1079, 1029, 999, 972, 945, 927, 904, 840, 794, 784, 753, 708, 697, 657, 611, 512, 495, 445 (cm^{-1}). HRMS (ESI-TOF) *m*/*z*: [M + H^+]$^+$ calculated for $C_{21}H_{25}N_2O_2$: 337.1911; found 337.1910.

*3-Amino-2-octyl-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**6c**).* According to the general procedure B using **11c** (40 mg, 0.10 mmol, 1.0 equiv) and cesium carbonate (33 mg, 0.10 mmol, 1.0 equiv) product **6c** (25 mg, 69 μmol, 67%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.34 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (ddd, *J* = 7.9, 1.2, 0.5 Hz, 1H), 7.95−7.86 (m, 1H), 7.78 (td, *J* = 7.6, 1.4 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38−7.25 (m, 5H), 3.93 (ddd, *J* = 13.0, 10.7, 5.1 Hz, 1H), 3.13 (ddd, *J* = 13.0, 10.8, 5.5 Hz, 1H), 2.66 (s, 2H), 1.81−1.60 (m, 2H), 1.37−1.09 (m, 10H), 1.00−0.33 (m, 3*H*). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.2, 162.0, 140.2, 135.4, 132.7, 132.6, 129.6, 129.2, 129.0, 128.7, 126.9, 126.1, 81.2, 45.3, 32.0, 29.7, 29.4, 29.4, 27.6, 22.8, 14.2. IR (ATR): $\tilde{\nu}$ = 3369, 3293, 3064, 3027, 2952, 2922, 2852, 1735, 1694, 1645, 1597, 1580, 1488, 1464, 1445, 1436, 1404, 1379, 1323, 1285, 1248, 1178, 1158, 1108, 1079, 1046, 1029, 990, 941, 906, 839, 794, 784, 753, 708, 609, 525, 500, 447

https://dx.doi.org/10.1021/acs.joc.0c01586
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(cm^{-1}). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{23}H_{28}N_2NaO_2$: 387.2043; found 387.2051.

*3-Amino-2-isobutyl-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**6d**).* According to the general procedure B using **11d** (40 mg, 0.12 mmol, 1.0 equiv) and cesium carbonate (39 mg, 0.12 mmol, 1.0 equiv) product **6d** (23 mg, 75 μmol, 63%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.25 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36−8.29 (m, 1H), 7.93−7.86 (m, 1H), 7.76 (td, *J* = 7.7, 1.3 Hz, 1H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H), 7.33−7.25 (m, 5H), 3.97 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.03 (dd, *J* = 13.2, 7.3 Hz, 1H), 2.67 (s, 2H), 2.37−2.17 (m, 1H), 0.95 (t, *J* = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.2, 163.5, 140.7, 135.3, 132.7, 132.6, 129.7, 129.3, 128.9, 128.8, 126.8, 126.0, 81.7, 51.6, 28.8, 20.9, 20.8. IR (ATR): $\tilde{\nu}$ = 3398, 3306, 3064, 3026, 2958, 2927, 2869, 1733, 1698, 1646, 1597, 1581, 1490, 1464, 1445, 1433, 1400, 1382, 1355, 1284, 1241, 1194, 1078, 1044, 1033, 997, 973, 934, 910, 875, 847, 826, 817, 795, 783, 753, 708, 695, 659, 613, 519, 491, 448 (cm^{-1}). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{19}H_{20}N_2NaO_2$: 331.1417; found 331.1418.

*3-Amino-2-benzyl-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**6e**).* According to the general procedure B using **11e** (50 mg, 0.13 mmol, 1.0 equiv) and cesium carbonate (44 mg, 0.13 mmol, 1.0 equiv) product **6e** (36 mg, 0.11 mmol, 78%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.30 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.45−8.29 (m, 1H), 7.93 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.79 (td, *J* = 7.7, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43−7.36 (m, 4H), 7.35−7.25 (m, 5H), 7.24−7.16 (m, 1H), 5.39 (d, *J* = 14.9 Hz, 1H), 4.36 (d, *J* = 14.9 Hz, 1H), 2.61 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.9, 163.0, 139.9, 139.0, 135.4, 133.0, 132.3, 130.4, 129.8, 129.3, 129.1, 129.0, 128.5, 127.8, 127.7, 127.0, 127.0, 126.0, 81.9, 47.7. IR (ATR): $\tilde{\nu}$ = 3388, 3303, 3062, 3029, 2980, 2926, 2853, 2125, 1777, 1733, 1697, 1648, 1596, 1581, 1493, 1445, 1426, 1396, 1372, 1355, 1284, 1239, 1167, 1075, 1043, 999, 941, 913, 845, 793, 784, 754, 732, 695, 657, 619, 594, 539, 519, 499, 454 (cm^{-1}). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{22}H_{18}N_2NaO_2$: 365.1260; found 365.1264.

*3-Amino-2-(4-methoxybenzyl)-3-phenyl-2,3-dihydroiso-quinoline-1,4-dione (**6f**).* According to the general procedure B using **11f** (40 mg, 0.10 mmol, 1.0 equiv) and cesium carbonate (33 mg, 0.10 mmol, 1.0 equiv) product **6f** (26 mg, 70 μmol, 70%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.27 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53−8.22 (m, 1H), 7.94−7.88 (m, 1H), 7.78 (td, *J* = 7.7, 1.3 Hz, 1H), 7.63 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41−7.35 (m, 4H), 7.34−7.27 (m, 3*H*), 6.86−6.77 (m, 2H), 5.30 (d, *J* = 14.6 Hz, 1H), 4.30 (d, *J* = 14.6 Hz, 1H), 3.76 (s, 3*H*), 2.64 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.0, 162.9, 158.7, 140.0, 135.4, 132.9, 132.4, 131.1, 130.4, 129.7, 129.6, 129.3, 129.0, 129.0, 126.9, 126.1, 113.9, 81.8, 55.4, 47.2. IR (ATR): $\tilde{\nu}$ = 3409, 3382, 3062, 2953, 2922, 2852, 1731, 1698, 1650, 1596, 1580, 1510, 1491, 1462, 1444, 1428, 1396, 1353, 1326, 1283, 1242, 1175, 1106, 1030, 999, 971, 949, 927, 915, 849, 807, 782, 753, 707, 696, 633, 613, 564, 518, 495, 446, 436, 413 (cm^{-1}). HRMS (ESI) m/z: $[M + Na]^+$ calculated for $C_{23}H_{20}N_2NaO_3$: 395.1366; found 395.1378.

*3-Amino-2-(3-chlorobenzyl)-3-phenyl-2,3-dihydroiso-quinoline-1,4-dione (**6g**).* According to the general procedure B using **11g** (40 mg, 0.10 mmol, 1.0 equiv) and cesium carbonate (33 mg, 0.10 mmol, 1.0 equiv) product **6g** (33 mg, 88 μmol, 89%) was obtained after chromatography (CH/EA 9:1 → 7:3) as a white solid. TLC: R_f = 0.26 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39−8.36 (m, 1H), 8.01−7.88 (m, 1H), 7.80 (td, *J* = 7.7, 1.3 Hz, 1H), 7.65 (td, *J* = 7.6, 1.2 Hz, 1H), 7.42−7.27 (m, 7H), 7.24−7.14 (m, 2H), 5.29 (d, *J* = 15.0 Hz, 1H), 4.37 (d, *J* = 15.0 Hz, 1H), 2.65 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.8, 163.0, 141.1, 139.7, 135.5, 134.3, 133.1, 132.1, 129.7, 129.6, 129.4, 129.2, 129.0, 128.1, 127.2, 127.0, 126.3, 126.0, 81.9, 47.3. IR (ATR): $\tilde{\nu}$ = 3385, 3303, 3063, 3025, 2979, 2929, 2849, 1776, 1731, 1695, 1647, 1596, 1580, 1474, 1445, 1424, 1393, 1347, 1284, 1241, 1202, 1178, 1159, 1093, 1076, 1043, 998, 972, 942, 896, 844, 830, 774, 753, 714, 696, 682, 622, 576, 524, 493, 447, 430 (cm^{-1}). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{22}H_{17}ClN_2NaO_2$: 399.0871; found 399.0882.

*3-(1-Azidoethyl)-2-butyl-3-hydroxyisoindolin-1one (**12**).* According to the general procedure A using **1b** (70 mg, 0.35 mmol, 1.0 equiv) and *n*-butylamine (25 mg, 0.35 mmol, 1.0 equiv) 41 mg (0.15 mmol, 43%) of the major diastereomer and 18 mg (0.07 mmol, 19%) of the minor diastereomer of product **12** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless oils (total yield: 62%, 59 mg, 0.22 mmol, dr 69:31). Major diastereomer: TLC: R_f = 0.27 (CH/EA 7:3) (UV). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.62 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 7.5, 1.0 Hz, 1H), 4.13 (q, *J* = 6.8 Hz, 1H), 3.88 (s, 1H), 3.43 (ddd, *J* = 14.1, 10.5, 5.5 Hz, 1H), 3.03 (ddd, *J* = 14.1, 10.5, 5.6 Hz, 1H), 1.73−1.46 (m, 2H), 1.36−1.30 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3*H*), 0.70 (d, *J* = 6.8 Hz, 3*H*). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.8, 143.6, 132.3, 131.9, 130.2, 123.9, 123.3, 92.8, 61.5, 39.2, 31.3, 20.7, 14.7, 13.9. IR (ATR): $\tilde{\nu}$ = 3239, 2960, 2933, 2873, 2133, 2109, 2088, 1671, 1671, 1615, 1600, 1469, 1439, 1408, 1377, 1314, 1257, 1181, 1121, 1064, 1044, 945, 910, 880, 867, 839, 801, 764, 730, 697, 645, 589, 550, 537, 478, 460, 429 (cm^{-1}). HRMS (ESI) m/z: $[M + Na]^+$ calculated for $C_{14}H_{18}N_4NaO_2$: 297.1322; found 297.1320; minor diastereomer: TLC: R_f = 0.22 (CH/EA 7:3) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.59−7.41 (m, 3*H*), 4.14 (q, *J* = 6.7 Hz, 1H), 3.84 (s, 1H), 3.57−3.34 (m, 1H), 3.25−3.00 (m, 1H), 1.78−1.54 (m, 1H), 1.39−1.26 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3*H*), 0.93 (t, *J* = 7.4 Hz, 3*H*). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.0, 144.4, 132.2, 132.0, 130.3, 123.6, 122.2, 92.1, 61.8, 39.9, 31.1, 20.7, 14.5, 13.9. IR (ATR): $\tilde{\nu}$ = 3250, 2965, 2953, 2925, 2871, 2857, 2143, 2091, 1667, 1614, 1601, 1469, 1455, 1441, 1413, 1370, 1350, 1323, 1306, 1276, 1254, 1196, 1181, 1159, 1126, 1078, 1044, 1012, 972, 955, 946, 918, 899, 885, 854, 801,764, 730, 682, 643, 600, 587, 568, 554, 537, 514, 455, 433 (cm^{-1}). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{14}H_{18}N_4NaO_2$: 297.1322; found 297.1323.

*(S)-3-Benzyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]iso-quinoline-2,5,10(3H)-trione (**7a**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-phenylalanine methyl ester hydrochloride (115 mg, 531 μmol, 2.0 equiv), 40 mg (0.10 mmol, 39%) of the major diastereomer and 21 mg (0.06 mmol, 21%) of the minor diastereomer of product **7a** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 60%, 61 mg, 0.16 mmol, dr 61:39).

(3S,10aS)-3-Benzyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10(3H)-trione (Major Diastereomer). TLC: R_f = 0.18 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: −18.2 (*c* = 1.14, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33−8.18 (m, 1H), 7.94 (s, 1H), 7.86−7.74 (m, 1H), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H), 7.26−7.01 (m, 10H), 5.00 (dd, *J* = 6.9, 5.3 Hz, 1H), 3.35−3.03 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 190.4, 171.5, 161.0, 137.1, 136.1, 135.8, 133.5, 132.4, 129.9, 129.8, 129.3, 129.2, 128.8, 128.4, 127.2, 127.1, 125.3, 81.2, 62.3, 37.7. IR (ATR): $\tilde{\nu}$ = 3140, 3065, 3028, 2957, 2922, 2852, 1706, 1654, 1597, 1577, 1492, 1480, 1466, 1452, 1435, 1398, 1356, 1343, 1324, 1288, 1270, 1255, 1212, 1181, 1171, 1149, 1086, 1074, 1059, 1040, 1027, 1016, 992, 971, 953, 906, 880, 791, 762, 724, 693, 673, 637, 615, 566, 518, 496, 449, 426 (cm^{-1}). LRMS (ESI) m/z: 383.1 $[M + H^+]$. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{24}H_{18}N_2NaO_3$: 405.1210; found 405.1213.

(3S,10aR)-3-Benzyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10-(3H)-trione (Minor Diastereomer). TLC: R_f = 0.20 (CH/EA 7:3) (UV). $[\alpha]_D^{20}$: −273.5 (*c* = 0.910, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.07 (m, 1H), 7.76−7.64 (m, 2H), 7.57 (td, *J* = 7.5, 1.2 Hz, 1H), 7.49 (s, 1H), 7.32−7.21 (m, 5H), 7.12−7.03 (m, 3*H*), 7.02−6.91 (m, 2H), 4.94 (dd, *J* = 5.3, 2.2 Hz, 1H), 4.00 (dd, *J* = 13.9, 5.3 Hz, 1H), 3.38 (dd, *J* = 13.9, 2.1 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 189.5, 170.7, 161.7, 138.9, 135.1, 134.3, 133.4, 132.3, 130.0, 129.9, 129.9, 129.8, 128.4, 128.3, 127.2, 126.5, 124.3, 81.1, 61.1, 33.0. IR (ATR): $\tilde{\nu}$ = 3175, 3068, 3055, 3029, 2930, 2835, 1713, 1666, 1600, 1579, 1487, 1479, 1464, 1445, 1394, 1364, 1340, 1281, 1253, 1242, 1212, 1178, 1154, 1110, 1087, 1078, 1059, 1026,

https://dx.doi.org/10.1021/acs.joc.0c01586
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999, 973, 930, 914, 902, 888, 876, 848, 799, 780, 760, 729, 715, 677, 667, 634, 615, 583, 534, 504, 466, 418 (cm^{-1}). LRMS (ESI) *m/z*: 383.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{24}H_{18}N_2NaO_3$: 405.1210; found 405.1225.

*(S)-3-Methyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]iso-quinoline-2,5,10(3H)-trione (**7b**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-alanine methyl ester hydrochloride (74 mg, 0.53 mmol, 2.0 equiv) 43 mg (0.14 mmol, 52%) of the major diastereomer and 27 mg (0.09 mmol, 34%) of the minor diastereomer of product **7b** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 86%, 70 mg, 0.23 mmol, dr 60:40).

(3S,10aS)-3-Methyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10(3H)-trione (Major Diastereomer). TLC: R_f = 0.17 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: −27.9 (*c* = 1.00, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26−8.17 (m, 1H), 7.91−7.84 (m, 2H), 7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36−7.27 (m, 5H), 4.53 (q, *J* = 6.7 Hz, 1H), 1.84 (d, *J* = 6.7 Hz, 3*H*). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 190.2, 173.1, 160.3, 137.7, 135.7, 133.5, 132.2, 129.9, 129.7, 129.4, 128.7, 127.1, 125.4, 81.3, 56.4, 16.8. IR (ATR): $\tilde{\nu}$ = 3212, 3063, 2923, 2850, 1712, 1661, 1651, 1597, 1577, 1478, 1464, 1447, 1428, 1391, 1333, 1284, 1247, 1202, 1178, 1145, 1097, 1086, 1071, 1054, 1032, 1001, 970, 907, 877, 825, 790, 757, 735, 709, 696, 679, 633, 618, 519, 495, 443 (cm^{-1}). LRMS (ESI) *m/z*: 307.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{18}H_{14}N_2NaO_3$: 329.0897; found 329.0905.

(3S,10aR)-3-Methyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10-(3H)-trione (Minor Diastereomer). TLC: R_f = 0.19 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: 143.9 (*c* = 1.04, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.34−8.16 (m, 1H), 7.87−7.72 (m, 2H), 7.64 (td, *J* = 7.4, 1.2 Hz, 1H), 7.49−7.37 (m, 2H), 7.35−7.27 (m, 3*H*), 4.82 (q, *J* = 7.1 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 190.1, 172.4, 160.8, 138.3, 135.5, 133.5, 132.4, 130.0, 129.9, 129.8, 129.1, 128.6, 126.9, 126.3, 124.6, 81.3, 56.2, 15.6. IR (ATR): $\tilde{\nu}$ = 3220, 3069, 2981, 2935, 2872, 1714, 1670, 1651, 1596, 1577, 1463, 1445, 1429, 1386, 1371, 1334, 1312, 1283, 1240, 1206, 1184, 1173, 1150, 1097, 1057, 1043, 1003, 909, 880, 846, 824, 787, 759, 725, 714, 697, 618, 530, 489, 464, 406 (cm^{-1}). [M + H^+]. LRMS (ESI) *m/z*: 307.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{18}H_{14}N_2NaO_3$: 329.0897; found 329.0904.

*(S)-3-Isopropyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10(3H)-trione (**7c**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-valine methyl ester hydrochloride (89 mg, 0.53 mmol, 2.0 equiv) 50 mg (0.15 mmol, 56%) of the major diastereomer and 28 mg (0.08 mmol, 32%) of the minor diastereomer of product **7c** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 88%, 78 mg, 0.23 mmol, dr 65:35).

(3S,10aS)-3-Isopropyl-10a-phenyl-1,10a-dihydroimidazo-[1,2-b]isoquinoline-2,5,10(3H)-trione (Major Diastereomer). TLC: R_f = 0.20 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: −9.5 (*c* = 1.11, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.32 (d, *J* = 9.4 Hz, 1H), 7.85 (td, *J* = 7.6, 1.3 Hz, 1H), 7.81−7.74 (m, 1H), 7.66 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40−7.33 (m, 2H), 7.33−7.27 (m, 3*H*), 4.58 (d, *J* = 7.3 Hz, 1H), 2.07−1.86 (m, 1H), 0.99 (dd, *J* = 6.8, 2.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 190.3, 172.0, 161.1, 137.6, 136.0, 133.4, 132.7, 129.7, 129.6, 129.2, 129.0, 127.2, 125.6, 81.3, 66.1, 31.7, 20.3, 18.9. IR (ATR): $\tilde{\nu}$ = 3232, 3068, 2963, 2927, 2875, 2852, 1709, 1663, 1598, 1579, 1463, 1446, 1426, 1383, 1284, 1253, 1189, 1145, 1094, 1079, 1050, 1030, 992, 969, 948, 907, 876, 849, 823, 792, 755, 708, 693, 671, 641, 617, 542, 514, 499, 472, 439 (cm^{-1}). LRMS (ESI) *m/z*: 335.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calculated for $C_{20}H_{19}N_2O_3$: 335.1390; found 335.1393.

(3S,10aR)-3-Isopropyl-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10-(3H)-trione (Minor Diastereomer). TLC: R_f = 0.23 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: 188.6 (*c* = 1.00, DCM) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19−8.13 (m, 1H), 7.91−7.84 (m, 1H), 7.72 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H), 7.32−7.27 (m, 5H), 7.25 (s, 1H), 4.57 (d, *J* = 3.2 Hz, 1H), 3.31−3.11 (m, 1H), 1.28 (d, *J* = 7.2 Hz, 3*H*), 0.87 (d, *J* = 6.9 Hz, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 190.6, 170.4, 161.2, 139.2, 135.4, 133.5, 132.3, 130.3, 129.9, 129.8, 128.6, 126.8, 124.3, 81.2, 64.3, 26.0, 18.1, 15.9. IR (ATR): $\tilde{\nu}$ = 3233, 3065, 2960, 2930, 2875, 1714, 1667, 1651, 1597, 1578, 1462, 1446, 1384, 1282, 1247, 1196, 1182, 1151, 1084, 1050, 1030, 1000, 986, 913, 881, 854, 794, 760, 732, 697, 675, 637, 617, 531, 506, 477, 449, 439, 423 (cm^{-1}). LRMS (ESI) *m/z*: 335.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calculated for $C_{20}H_{19}N_2O_3$: 335.1390; found 335.1392.

*(S)-3-((S)-sec-Butyl)-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10(3H)-trione (**7d**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-isoleucine methyl ester hydrochloride (96 mg, 0.53 mmol, 2.0 equiv) 52 mg (0.15 mmol, 56%) of the major diastereomer and 23 mg (0.06 mmol, 25%) of the minor diastereomer of product **7d** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 81%, 75 mg, 0.22 mmol, dr 65:35).

(3S,10aS)-3-((S)-sec-Butyl)-10a-phenyl-1,10a-dihydro-imidazo-[1,2-b]isoquinoline-2,5,10(3H)-trione (Major Diastereomer). TLC: R_f = 0.21 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: −6.1 (*c* = 0.955, DCM) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.39−8.20 (m, 1H), 7.84 (td, *J* = 7.7, 1.3 Hz, 1H), 7.81−7.72 (m, 1H), 7.65 (td, *J* = 7.6, 1.2 Hz, 1H), 7.39−7.33 (m, 2H), 7.32−7.27 (m, 3*H*), 4.64 (d, *J* = 6.8 Hz, 1H), 1.84−1.58 (m, 2H), 1.42−1.23 (m, 1H), 0.98−0.73 (m, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 190.4, 172.0, 161.1, 137.5, 135.9, 133.4, 132.7, 129.7, 129.5, 129.2, 128.9, 127.2, 125.7, 81.3, 65.2, 38.1, 26.8, 15.0, 11.7. IR (ATR): $\tilde{\nu}$ = 3207, 3067, 2962, 2926, 2874, 2851, 1708, 1664, 1597, 1578, 1478, 1461, 1446, 1427, 1379, 1338, 1284, 1248, 1188, 1145, 1052, 1023, 1001, 979, 932, 910, 876, 792, 755, 727, 694, 671, 640, 618, 552, 522, 499, 466, 440 (cm^{-1}). LRMS (ESI) *m/z*: 349.2 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{21}H_{20}N_2NaO_3$: 371.1366; found 371.1381.

(3S,10aR)-3-((S)-sec-Butyl)-10a-phenyl-1,10a-dihydro-imidazo-[1,2-b]isoquinoline-2,5,10-(3H)-trione (Minor Diastereomer). TLC: R_f = 0.24 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: 86.7 (*c* = 1.12, DCM) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.89 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.73 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64 (td, *J* = 7.5, 1.2 Hz, 1H), 7.33−7.28 (m, 5H), 7.01 (s, 1H), 4.66 (d, *J* = 3.1 Hz, 1H), 3.04−2.82 (m, 1H), 1.84−1.70 (m, 1H), 1.71−1.52 (m, 1H), 1.04 (t, *J* = 7.4 Hz, 3*H*), 0.83 (d, *J* = 6.9 Hz, 3*H*). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 190.6, 170.3, 161.1, 139.2, 135.4, 133.5, 132.3, 130.3, 129.9, 129.7, 128.6, 126.8, 124.3, 81.2, 63.3, 32.7, 25.3, 13.5, 12.5. IR (ATR): $\tilde{\nu}$ = 3216, 3163, 3124, 3076, 2966, 2956, 2925, 2873, 1730, 1709, 1673, 1642, 1595, 1575, 1477, 1433, 1392, 1378, 1351, 1327, 1280, 1246, 1196, 1181, 1151, 1082, 1049, 1018, 1000, 975, 966, 909, 880, 797, 791, 734, 717, 680, 636, 612, 531, 517, 503, 490, 447 (cm^{-1}). LRMS (ESI) *m/z*: 349.2 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{21}H_{20}N_2NaO_3$: 371.1366; found 371.1376.

*(S)-3-(tert-Butyl)-10a-phenyl-1,10a-dihydroimidazo[1,2-b]-isoquinoline-2,5,10(3H)-trione (**7e**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-*tert*-leucine methyl ester hydrochloride (96 mg, 0.53 mmol, 2.0 equiv) 51 mg (0.15 mmol, 55%) of the major diastereomer and 4 mg (0.01 mmol, 4%) of the minor diastereomer of product **7e** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 59%, 55 mg, 0.16 mmol).

(3S,10aS)-3-(tert-Butyl)-10a-phenyl-1,10a-dihydro-imidazo[1,2-b]isoquinoline-2,5,10(3H)-trione (major diastereomer). TLC: R_f = 0.19 (CH/EA 1:1) (UV). $[\alpha]_D^{20}$: −13.3 (*c* = 1.11, DCM) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 7.85 (td, *J* = 7.7, 1.2 Hz, 1H), 7.77−7.69 (m, 1H), 7.63 (td, *J* = 7.6, 1.1 Hz, 1H), 7.36−7.31 (m, 2H), 7.32−7.27 (m, 3*H*), 4.63 (s, 1H), 0.94 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 190.7, 171.9, 162.0, 137.6, 135.9, 133.4, 133.0, 129.5, 129.4, 129.2, 129.1, 127.0, 126.0, 81.6, 69.5, 36.1, 27.5. IR (ATR): $\tilde{\nu}$ = 3207, 3067, 2954, 2924, 2870, 2852, 1707, 1666, 1598, 1580, 1477, 1462, 1447, 1428, 1396, 1366, 1339, 1285, 1238, 1189, 1168, 1094, 1080, 1051, 1027, 1001, 968, 947, 907, 876, 866, 792, 755, 728, 709, 693, 672, 642, 617, 596, 538, 519, 503,

https://dx.doi.org/10.1021/acs.joc.0c01586
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469, 434 (cm^{-1}). LRMS (ESI) *m/z*: 349.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{21}H_{20}N_2NaO_3$: 371.1366; found 371.1367.

*(S)-3-(2-(Methylthio)ethyl)-10a-phenyl-1,10a-dihydro-imidazo-[1,2-b]isoquinoline-2,5,10(3H)-trione (**7f**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and L-methionine methyl ester hydrochloride (106 mg, 531 μmol, 2.0 equiv) 56 mg (0.15 mmol, 57%) of the major diastereomer and 27 mg (0.07 mmol, 28%) of the minor diastereomer of product **7f** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 85%, 83 mg, 0.23 mmol, dr 61:39).

(3S,10aS)-3-(2-(Methylthio)ethyl)-10a-phenyl-1,10a-dihydroimidazo[1,2-b]isoquinoline-2,5,10(3H)-trione (Major Diastereomer). TLC: R_f = 0.21 (CH/EA 6:4) (UV). $[\alpha]_D^{20}$: −27.9 (*c* = 1.00, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.35−8.19 (m, 1H), 7.86−7.75 (m, 2H), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H), 7.44−7.35 (m, 2H), 7.33−7.27 (m, 3*H*), 4.91 (dd, *J* = 7.6, 6.5 Hz, 1H), 2.87−2.55 (m, 2H), 2.15−1.80 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 189.9, 172.4, 160.6, 137.5, 135.8, 133.6, 132.1, 129.8, 129.8, 129.4, 128.8, 127.2, 125.3, 81.5, 59.6, 31.9, 30.6, 15.3. IR (ATR): $\tilde{\nu}$ = 3213, 3067, 2964, 2916, 2852, 2836, 1708, 1661, 1597, 1578, 1479, 1463, 1425, 1386, 1340, 1284, 1246, 1175, 1145, 1096, 1064, 1047, 1001, 967, 907, 875, 847, 792, 726, 707, 674, 645, 635, 617, 543, 519, 499, 451, 440 (cm^{-1}). LRMS (ESI) *m/z*: 367.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{20}H_{18}N_2NaO_3S$: 389.0930; found 389.0939.

(3S,10aR)-3-(2-(Methylthio)ethyl)-10a-phenyl-1,10a-dihydroimidazo[1,2-b]isoquinoline-2,5,10-(3H)-trione (Minor Diastereomer). TLC: R_f = 0.23 (CH/EA 6:4) (UV). $[\alpha]_D^{20}$: 151.5 (*c* = 1.04, DCM) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.28−8.11 (m, 1H), 7.94−7.84 (m, 1H), 7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 7.70−7.60 (m, 2H), 7.35−7.27 (m, 5H), 4.70 (dd, *J* = 5.6, 2.3 Hz, 1H), 2.98−2.81 (m, 1H), 2.58−2.38 (m, 3*H*), 2.06 (s, 3*H*). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 190.1, 171.2, 160.9, 138.4, 135.5, 133.6, 132.1, 130.1, 129.9, 129.9, 129.3, 128.7, 126.9, 125.9, 124.5, 81.4, 59.1, 28.7, 26.7, 15.4. IR (ATR): $\tilde{\nu}$ = 3213, 3068, 2917, 2871, 1708, 1662, 1597, 1578, 1479, 1463, 1426, 1387, 1339, 1285, 1247, 1175, 1159, 1096, 1082, 1063, 1048, 1030, 1001, 950, 907, 876, 793, 728, 708, 695, 674, 635, 617, 544, 519, 499, 451, 440 (cm^{-1}). LRMS (ESI) *m/z*: 367.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{20}H_{18}N_2NaO_3S$: 389.0930; found 389.0939.

*(S)-3-(4-Hydroxybenzyl)-10a-phenyl-1,10a-dihydro-imidazo[1,2-b]isoquinoline-2,5,10(3H)-trione (**7g**).* According to the general procedure C using **1a** (70 mg, 0.27 mmol, 1.0 equiv) and *L*-tyrosine methyl ester hydrochloride (123 mg, 531 μmol, 2.0 equiv) 35 mg (0.09 mmol, 33%) of the major diastereomer and 22 mg (0.05 mmol, 21%) of the minor diastereomer of product **7g** were obtained following chromatographic separation (CH/EA 9:1 → 7:3) as colorless solids (total yield: 54%, 57 mg, 0.14 mmol). Instead of toluene, dichloromethane (0.36 M) was used as solvent in this case.

(3S,10aS)-3-(4-Hydroxybenzyl)-10a-phenyl-1,10a-dihydro-imidazo[1,2-b]isoquinoline-2,5,10(3H)-trione (Major Diastereomer). TLC: R_f = 0.24 (CH/EA 4:6) (UV). $[\alpha]_D^{20}$: 8.1 (*c* = 0.942, DCM) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.33−8.14 (m, 1H), 7.85−7.70 (m, 2H), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24−7.08 (m, 5H), 7.04−6.86 (m, 2H), 6.53−6.36 (m, 2H), 5.69 (s, 1H), 4.98 (dd, *J* = 6.5, 4.8 Hz, 1H), 3.37−2.91 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 190.3, 172.0, 161.3, 154.7, 136.9, 135.9, 133.6, 132.4, 131.0, 129.9, 129.1, 129.1, 128.8, 127.6, 127.3, 125.3, 115.4, 81.4, 62.9, 36.6. IR (ATR): $\tilde{\nu}$ = 3213, 3067, 2964, 2916, 2852, 2836, 1708, 1661, 1597, 1578, 1479, 1463, 1425, 1386, 1340, 1284, 1246, 1175, 1145, 1096, 1064, 1047, 1001, 967, 907, 875, 847, 792, 726, 707, 674, 645, 635, 617, 543, 519, 499, 451, 440 (cm^{-1}). LRMS (ESI) *m/z*: 399.1 [M + H^+]. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calculated for $C_{24}H_{18}N_2NaO_4$: 421.1159; found 421.1161.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01586.

Experimental and spectral details for all new compounds and all reactions (PDF)

Crystallographic information for **6f** (CIF)

Crystallographic information for **7b** (CIF)

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Notes

The authors declare no competing financial interest.

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https://dx.doi.org/10.1021/acs.joc.0c01586
J. Org. Chem. XXXX, XXX, XXX−XXX