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A gold-triggered dearomative spirocarbocyclization/Diels–Alder reaction cascade towards diverse bridged N-heterocycles†

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A rapid approach for the diversity-oriented synthesis of complex bridged polycyclic N-heterocycles from readily available starting materials in two operational steps has been developed. This strategy firstly introduces molecular diversity by an Ugi four-component reaction, and then achieves these bridged N-heterocycles *via* an efficient gold-triggered chemo- and diastereoselective cascade non-oxidative *ortho*-dearomative spirocarbocyclization/Diels–Alder reaction sequence. The application of microwave irradiation for this cascade process efficiently shortens the reaction time to 10 minutes and improves the diastereoselectivity.

Introduction

Bridged polyheterocyclic cores are widely present in various natural products exhibiting impressive biological activities such as anti-inflammatory, anti-tumour, analgesic effects, and cardiovascular regulation (Fig. 1).[1] Not surprisingly, synthetic chemists have devised a number of strategies for their syntheses, frequently featuring intramolecular Diels–Alder (IMDA) reactions.[2] Notably, the cascade *ortho*-oxidative dearomatization of phenols/inter- or intramolecular Diels–Alder cycloaddition of *in situ* generated masked *o*-benzoquinones (MOBs)[3] with various dienophiles has served as a key step for the construction of bridged frameworks of natural products like diterpenoid alkaloids (Scheme 1a).[4] Despite these achievements, the development of a complementary approach that provides a rapid and large collection of diverse bridged heterocycles for high throughput screening of biological activities, is still highly desirable.[5]

During recent decades, the further transformations of skeletally diverse Ugi four-component reaction (Ugi-4CR)[6] adducts, facilitated by various transition metal catalysts such as gold and palladium, afforded numerous diversity-oriented access to complex heterocycles in two operational steps.[7]

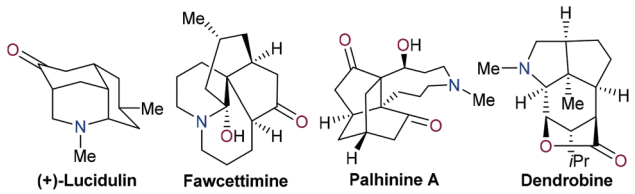
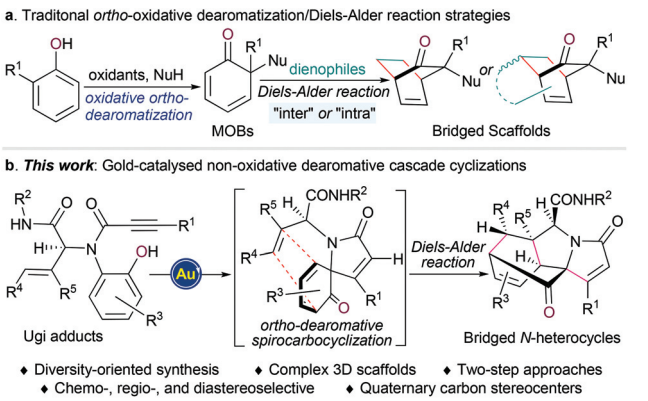


Fig. 1 Examples of bridged polycyclic natural products.



Scheme 1 Construction of bridged polycyclic scaffolds through *ortho*-dearomative cascade cyclization.

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Meanwhile, the past two decades have witnessed extraordinary advances in homogeneous gold catalysis.[8] The gold-catalysed dearomative spiro-cyclization of phenol and its derivatives attracted considerable attention due to its unique capacity to generate highly functionalized spirocarbocycles bearing 2,5-cyclohexadienones or 2,4-cyclohexadienones.[9] It is noteworthy that the spiro-annulated 2,4-cyclohexadienones contain the reactive MOB fragment, allowing various subsequent transformations such as Diels–Alder reaction. However, till date very few examples exploring this kind of gold-catalysed cascade strategies have been reported.[10]

Recently, our group developed an efficient gold-triggered cascade non-oxidative *ortho*-dearomative spirocarbocyclization of phenol moieties, and subsequent [4 + 2] cyclization of the indole moiety with the *in situ* formed spiro-fused 2,4-cyclohexadienones, leading to architecturally complex bridged indole alkaloid-like polyheterocycles.[10c] Mechanistic studies suggest that this [4 + 2] cyclization goes through a concerted pathway without involvement of the gold catalyst. Thus, it is conceivable that replacing the indole moiety with other dienophiles like simple alkenes, this cascade sequences should process smoothly, furnishing new diverse bridged polyheterocycles. Furthermore, the highly functionalized precursors bearing an *ortho*-phenol, an alkene and a propiolamide moiety, could be easily prepared through Ugi-4CR. Based on these findings, it is envisioned that a post-Ugi gold(I)-triggered diastereoselective cascade *ortho*-dearomative spiro-carbocyclization/Diels–Alder reaction sequence is quite promising for the synthesis of complex and diverse bridged polycyclic heterocycles (Scheme 1b).

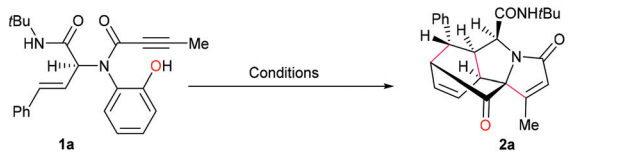
Results and discussion

Our exploratory studies of the envisaged cascade *ortho*-dearomative spirocyclization/Diels–Alder reaction process were conducted using the highly functionalized acyclic precursor **1a** as a model substrate, which was readily constructed through Ugi-4CR of *trans*-cinnamaldehyde, 2-aminophenol, *tert*-butyl isocyanide, and 2-butynoic acid. In the preliminary investigations, treating the Ugi adduct **1a** with cationic gold(I) catalyst [(IMes)Au][OTf] *in situ* generated from (IMes)AuCl and AgOTf using DCE as solvent at r.t. for 16 h, gave the desired bridged polycyclic compound **2a** in 45% yield with a diastereomeric ratio of 16 : 1 (Table 1, entry 1, see ESI† for optimization details). Performing the reaction at 115 °C led to an increased yield of 58% (Table 1, entry 2), and further prolonging the reaction time to 16 h delivered the desired bridged compound **2a** in a moderate yield of 68% (Table 1, entry 3).

Considering the advantages of microwave-assisted organic synthesis such as drastic acceleration of sluggish transformations, enhanced yields, and cleaner reactions,[11] we next optimized the reaction conditions under microwave irradiation. First, the reaction of **1a** was performed at 115 °C for 10 min under microwave irradiation using dichloroethane as solvent with 10 mol% of (IMes)AuOTf, yielding the bridged polycyclic compound **2a** in an increased yield of 73% with a satisfactory dr of 36.5 : 1 (Table 1, entry 4). The screening of cationic gold catalysts *in situ* generated from different ligand-supported gold (I) chloride salts with AgOTf, showed that the combination of IPrAuCl and AgOTf gave **2a** in the highest isolated yield of 85% with an excellent diasteroselectivity (Table 1, entries 5–9). While combining IPrAuCl with different chloride scavengers such as AgOAc, $AgBF_4$, $AgNTf_2$, and Ag_2SO_4, no improvement was observed (Table 1, entries 10–13). Employing IPrAuCl or AgOTf separately led to almost no conversion (Table 1, entries 14 and 15). Further examination of different Lewis acids such as $AlCl_3$, $ZnCl_2$, $InCl_3$ and $Sc(OTf)_3$ failed to generate the desired heterocycle **2a** (Table 1, entries 16–19). A lower catalyst loading of 5 mol% furnished **2a** in a lower yield of 76% (Table 1, entry 20). The control experiment indicated that the application of the cationic gold complex was necessary to ensure the occurrence of this cascade process (Table 1, entry 21).

To evaluate the generality of this microwave-promoted gold-catalysed cascade dearomative cyclizations, a wide range of substituted Ugi adducts **1** was prepared and subjected to the

Table 1 Optimization of the reaction conditions[a]



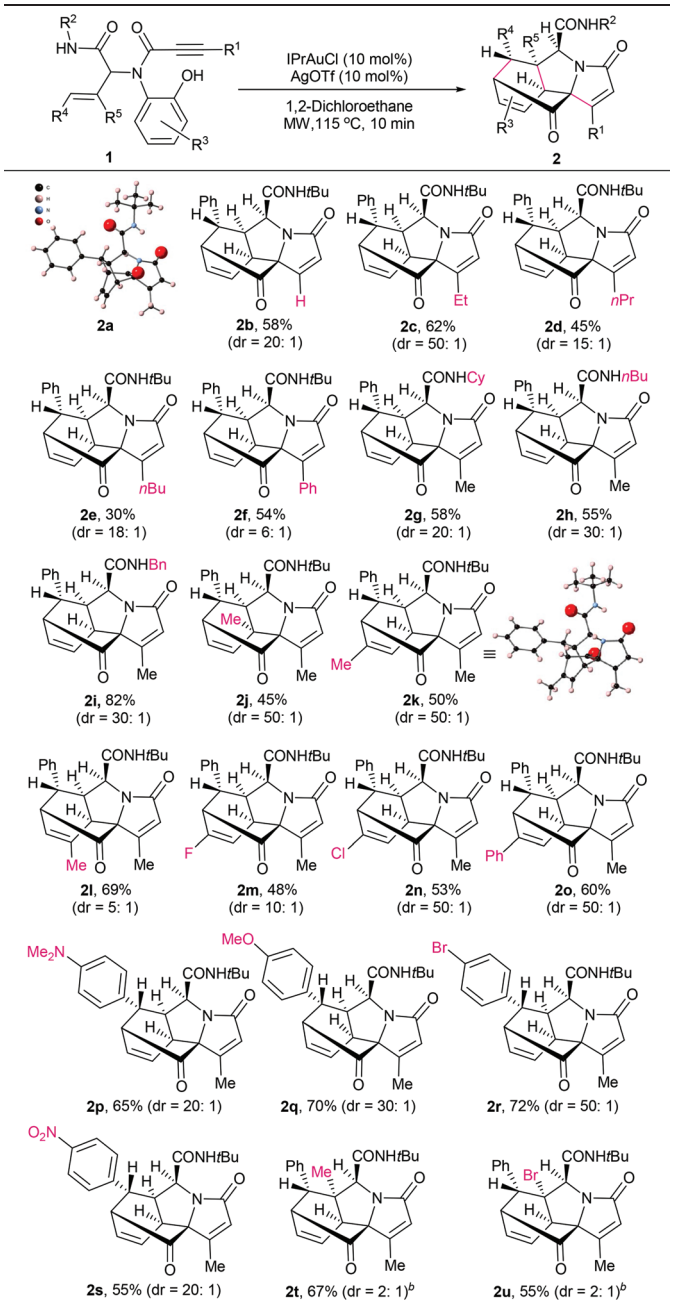
Entry	Catalysts	T/°C	Time/min	Yield[b] of (±)-**2a**/%	dr[c]
1	(IMes)AuCl/AgOTf	r.t.	960	45	16 : 1
2	(IMes)AuCl/AgOTf	115[d]	10	58	8 : 1
3	(IMes)AuCl/AgOTf	115[d]	960	68	8 : 1
4	(IMes)AuCl/AgOTf	115	10	73	36.5 : 1
5	**IPrAuCl/AgOTf**	**115**	**10**	**92(85[e])**	**46 : 1**
6	XPhosAuCl/AgOTf	115	10	55	3.9 : 1
7	CyJohnPhosAuCl/AgOTf	115	10	77	20 : 1
8	Me_2SAuCl/AgOTf	115	10	81	14 : 1
9	$(Ph_3P)AuCl$/AgOTf	115	10	87	30 : 1
10	IPrAuCl/AgOAc	115	10	36	2 : 1
11	IPrAuCl/$AgBF_4$	115	10	57	4.5 : 1
12	IPrAuCl/$AgNTf_2$	115	10	84	6.5 : 1
13	IPrAuCl/Ag_2SO_4	115	10	68	3.6 : 1
14	IPrAuCl	115	10	0	_
15	AgOTf	115	10	Trace	_
16	$AlCl_3$	115	10	0	_
17	$ZnCl_2$	115	10	Trace	_
18	$InCl_3$	115	10	0	_
19	$Sc(OTf)_3$	115	10	0	_
20[f]	IPrAuCl/AgOTf	115	10	85(76[e])	40 : 1
21	—	115	10	0	_

[a] Unless otherwise stated, the reactions were run with **1a** (0.05 mmol) and a mixture of the corresponding gold catalyst (10 mol%) and silver catalyst (10 mol%) in a screw-cap vial with 1,2-dichloroethane (1 mL) under microwave irradiation (100 W). [b] Yields based on ^{1}H NMR analysis using 2,4,6-trimethoxybenzaldehyde as internal standard. [c] The dr values were determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Conventional heating. [e] Isolated yields. [f] 5 mol% of catalysts. OTf = trifluoromethanesulfonate, IPr = 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, XPhos = 2-dicyclohexylphosph-ino-2′,4′,6′-triisopropylbiphenyl, CyJohnPhos = 2-(dicyclohexylphosphino)biphenyl.

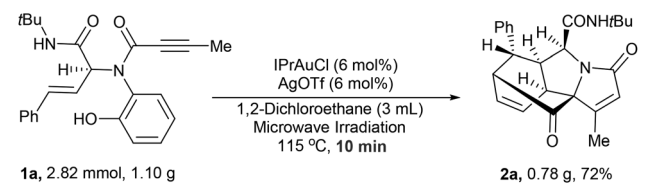
optimized reaction conditions (Table 1, entry 3). As illustrated in Table 2, the influences of the R^1-substituent on the propiolamide was first investigated. The reaction gives moderate to good yields with hydrogen (**2b**), and various alkyl groups including ethyl, *n*-propyl and *n*-butyl (**2c–e**), as well as a phenyl group (**2f**). Secondly, the examination of the R^2-substituent of the secondary amide reveals that the reaction runs satisfactory well with a cyclohexyl, an *n*-butyl, and a benzyl group (Table 2, **2g–i**). The reactions of substrates with a methyl group on various positions of the *ortho*-phenol moiety also proceeded sufficiently well, affording the bridged polycyclic compounds **2j–l** in moderate isolated yields of 45–69% with an excellent diasteroselectivity. Halogens like F and Cl installed in the *meta*-position of the *ortho*-phenol moiety were compatible in this cascade process, furnishing the bridged heterocycles **2m** and **2n** in yields of 48 and 53%, respectively. To our delight, a good yield was observed in the case of a *meta*-phenyl-substituted *ortho*-phenol moiety, indicating that steric effects did not affect the domino process (Table 2, **2o**). Finally, the effect of the R^4- and R^5-substituents on the alkene fragment was investigated. *Para*-substituted phenyl rings with electron donating (NMe_2 and OMe) and electron withdrawing (Br and NO_2) substituents were well tolerated, affording the desired bridged compounds **2p–s** in moderate-to-good yield of 55–72%. However, substituents on alkenes bearing a methyl or a bromide group gave **2t** and **2u** in yields of 67% and 55%, respectively, with a lower diasteromeric ratio of 2 : 1. In addition, the absolute structures of bridged products **2a** and **2k** were unequivocally confirmed by X-ray crystallographic analysis.[12]

To test the practical utility of this gold-catalysed cascade approach, a preparative, gram-scale reaction of **2a** was conducted. Only 6 mol% of IPrAuOTf was employed to accomplish the cascade cyclizations at 115 °C for 10 min under microwave irradiation, affording the bridged polyheterocycle **2a** in 72% yield (Scheme 2).

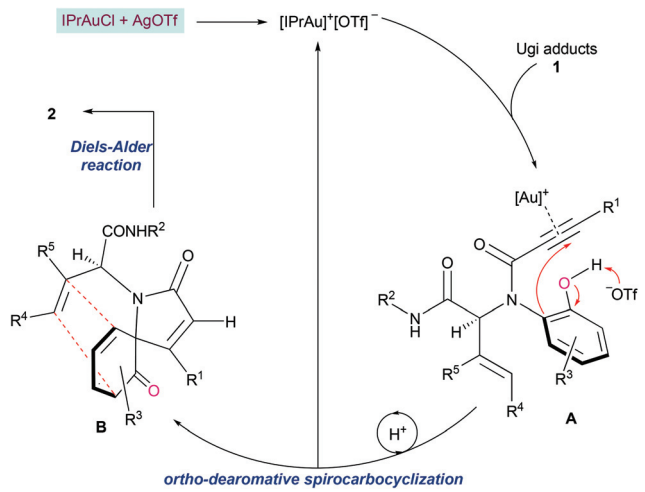
Table 2 Scope of our gold-catalysed cascade *ortho*-dearomative spirocyclization/Diels–Alder reaction sequence[a]



[a] All reactions were conducted with **1** (0.20 mmol) and a mixture of IPrAuCl (10 mol%) and AgOTf (10 mol%) dissolved in 1,2-dichloroethane (1 mL) in a 10 mL sealed tube under microwave irradiation (100 W, 115 °C for 10 min), all yields are isolated yields. [b] Calculated based on ^{1}HNMR analysis, inseparable mixture of diastereoisomers.



Scheme 2 Gram-scale reaction.



Scheme 3 Proposed mechanism.

Based on previous reports,[8,9,13] a mechanism for this gold(I)-catalysed cascade *ortho*-dearomative spirocyclization/Diels–Alder reaction sequence is proposed in Scheme 3. The *in situ* generated cationic gold(I) species activates the triple bond of the Ugi adduct (±)-**1**. This is followed by a nucleophilic attack of the C-2 position of the phenol facilitated by concomitant deprotonation by OTf^- anion. This was in a 5-*endo-dig* fashion, directly yielding a spiro-fused 2,4-cyclohexadienone intermediate **B**. Subsequently, a formal [4 + 2] intramolecular cycloaddition of the substituted alkene with the *in situ* generated 2,4-cyclohexadienone moiety take places in a concerted pathway,[14] producing the bridged heterocycles (±)-**2**.

Conclusions

In summary, we have developed an efficient protocol for the construction of highly functionalized bridged N-heterocyclic frameworks *via* a gold(I)-catalysed post-Ugi cascade *ortho*-dearomative spirocarbocyclization/Diels–Alder reaction sequence under microwave irradiation. The first step, Ugi-4CR, generates the structural diversity of the target molecules from easily available starting materials. The operational simplicity together with the capability of reaction scale-up will be beneficial for the potential synthetic application of this approach.

Experimental section

General procedure to bridged N-heterocyclic scaffolds 2a–u *via* gold-catalysed cascade dearomative spirocyclization/ Diels–Alder reaction sequence

The cationic gold catalyst IPrAuOTf was first generated *in situ* by mixing of (IPr)AuCl (10 mol%) and AgOTf (10 mol%) along with dichloroethane (2 mL) in a 10 mL microwave vial loaded with a stirring bar and kept stirring for 5 min and used without filtration. To this vial Ugi products **1a–u** (0.20 mmol) was subsequently loaded and the reaction vessel was sealed and irradiated in the cavity of a CEM-Discover microwave reactor for 10 min at the set temperature of 115 °C. After completion, the reaction mixture was diluted with dichloromethane and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/heptane = 1 : 1) to afford the bridged compounds **2a–u**.

***N*-(*tert*-Butyl)-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2a).** Pale yellow solid, yield 85%, melting point: 185–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, J = 14.6 Hz, 2H), 7.22–7.17 (m, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.68 (s, 1H), 6.51 (t, J = 7.3 Hz, 1H), 6.26 (t, J = 7.3 Hz, 1H), 5.94 (d, J = 1.8 Hz, 1H), 4.26 (d, J = 5.2 Hz, 1H), 3.65–3.58 (m, 1H), 3.47–3.42 (m, 1H), 3.39 (s, 1H), 3.04 (t, J = 5.4 Hz, 1H), 1.87 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.8, 178.1, 167.9, 162.4, 141.3, 129.6, 129.5, 128.5, 128.1, 126.9, 125.7, 65.4, 54.3, 51.5, 50.3, 46.4, 42.2, 28.6, 14.1. HRMS (ESI) calculated for $C_{24}H_{27}N_2O_3^+$ ($[M + H]^+$): 391.2021, found 391.2025.

***N*-(*tert*-Butyl)-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2b).** Pale yellow solid, yield 58%, melting point: 185–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, J = 14.6 Hz, 2H), 7.14 (d, J = 7.4 Hz, 2H), 6.99 (d, J = 5.9 Hz, 1H), 6.58 (s, 1H), 6.46 (t, J = 7.3 Hz, 1H), 6.33–6.24 (m, 2H), 4.29 (d, J = 5.4 Hz, 1H), 3.60 (dd, J = 6.7, 2.9 Hz, 1H), 3.48 (t, J = 4.4 Hz, 1H), 3.41–3.34 (m, 1H), 3.05 (t, J = 4.4 Hz, 2H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.6, 177.3, 167.7, 149.3, 141.1, 130.7, 129.9, 129.1, 128.5, 128.1, 127.0, 75.7, 65.2, 53.8, 51.6, 50.6, 46.7, 42.2, 28.7. HRMS (ESI) calculated for $C_{23}H_{25}N_2O_3^+$ ($[M + H]^+$): 377.1865, found 377.1860.

***N*-(*tert*-Butyl)-1-ethyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo [2,1-*a*]isoindole-5-carboxamide (2c).** Pale yellow solid, yield 62%, melting point: 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30–7.23 (m, 2H), 7.21 (d, J = 6.9 Hz, 1H), 7.17–7.10 (m, 2H), 6.68 (s, 1H), 6.50 (ddd, J = 8.0, 6.4, 1.3 Hz, 1H), 6.25 (ddd, J = 8.2, 6.6, 1.8 Hz, 1H), 5.94 (t, J = 1.9 Hz, 1H), 4.26 (d, J = 5.1 Hz, 1H), 3.61 (ddd, J = 6.7, 3.0, 1.3 Hz, 1H), 3.49–3.41 (m, 1H), 3.41–3.37 (m, 1H), 3.03 (ddd, J = 6.2, 4.0, 1.8 Hz, 1H), 2.20–1.93 (m, 2H), 1.37 (s, 9H), 1.17 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.7, 177.9, 168.3, 168.0, 141.5, 129.7, 128.5, 128.3, 127.0, 123.6, 65.6, 54.6, 51.6, 50.5, 46.8, 42.6, 28.8, 21.5, 11.0. HRMS (ESI) calculated for $C_{25}H_{29}N_2O_3^+$ ($[M + H]^+$): 405.2178, found 405.2177.

***N*-(*tert*-Butyl)-3,10-dioxo-6-phenyl-1-propyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2d).** Pale yellow solid, yield 45%, melting point: 155–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30–7.23 (m, 2H), 7.23–7.19 (m, 1H), 7.17–7.09 (m, 2H), 6.68 (s, 1H), 6.51 (ddd, J = 7.9, 6.5, 1.3 Hz, 1H), 6.25 (ddd, J = 8.3, 6.5, 1.8 Hz, 1H), 5.93 (t, J = 1.8 Hz, 1H), 4.25 (d, J = 5.1 Hz, 1H), 3.61 (ddd, J = 6.7, 3.0, 1.3 Hz, 1H), 3.48–3.41 (m, 1H), 3.39 (t, J = 2.7 Hz, 1H), 3.03 (ddd, J = 6.2, 4.0, 1.8 Hz, 1H), 2.09–1.94 (m, 2H), 1.67–1.50 (m, 2H), 1.37 (s, 9H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.7, 178.0, 168.1, 166.9, 141.5, 129.7, 129.6, 128.5, 128.3, 126.9, 124.1, 65.6, 54.6, 51.6, 50.5, 46.8, 42.6, 30.3, 28.8, 20.1, 13.7. HRMS (ESI) calculated for $C_{26}H_{31}N_2O_3^+$ ($[M + H]^+$): 419.2334, found 419.2336.

***N*-(*tert*-Butyl)-1-butyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2e).** Pale yellow solid, yield 30%, melting point: 68–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30–7.23 (m, 2H), 7.23–7.19 (m, 1H), 7.17–7.07 (m, 2H), 6.68 (s, 1H), 6.50 (ddd, J = 7.9, 6.6, 1.3 Hz, 1H), 6.33–6.20 (m, 1H), 5.93 (t, J = 1.8 Hz, 1H), 4.25 (d, J = 5.1 Hz, 1H), 3.77–3.55 (m, 1H), 3.46–3.41 (m, 1H), 3.39 (t, J = 2.7 Hz, 1H), 3.02 (ddd, J = 6.1, 4.0, 1.8 Hz, 1H), 2.04 (ddd, J = 8.8, 6.4, 1.8 Hz, 2H), 1.61–1.46 (m, 2H), 1.37 (s, 9H), 1.36–1.28 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.7, 178.0, 168.1, 167.1, 141.5, 129.7, 129.6, 128.5, 128.3, 127.0, 124.1, 65.6, 54.6, 51.6, 50.6, 46.9, 42.7, 28.9, 28.8, 27.9, 22.3, 13.7. HRMS (ESI) calculated for $C_{27}H_{33}N_2O_3^+$ ($[M + H]^+$): 433.2491, found 433.2485.

***N*-(*tert*-Butyl)-3,10-dioxo-1,6-diphenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2f).** Pale yellow solid, yield 54%, melting point: 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41–7.22 (m, 6H), 7.19–6.99 (m, 4H), 6.79 (s, 1H), 6.41 (s, 1H), 6.33 (ddd, J = 8.0, 6.4, 1.5 Hz, 1H), 6.28–6.21 (m, 1H), 4.34 (d, J = 4.9 Hz, 1H), 3.74–3.64 (m, 1H), 3.52–3.41 (m, 2H), 3.20 (ddd, J = 6.1, 3.9, 1.9 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.8, 177.1, 167.9, 163.3, 141.4, 131.2, 130.7, 130.3, 129.2, 129.0, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.0, 126.9, 125.7, 65.7, 54.8, 52.1, 51.7, 50.5, 46.9, 43.1, 34.2, 28.8, 28.7, 28.6, 22.3, 14.0. HRMS (ESI) calculated for $C_{29}H_{29}N_2O_3^+$ ($[M + H]^+$): 453.2178, found 453.2178.

***N*-Cyclohexyl-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2g).** Pale yellow solid, yield 58%, melting point: 81–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.24 (m, 2H), 7.23–7.20 (m, 1H), 7.19–7.11 (m, 2H), 6.78 (d, J = 8.1 Hz, 1H), 6.50 (t, J = 7.3 Hz, 1H), 6.29 (ddd, J = 8.3, 6.6, 1.8 Hz, 1H), 5.95 (s, 1H), 4.33 (d, J = 6.0 Hz, 1H), 3.90–3.70 (m, 1H), 3.64 (dd, J = 6.6, 3.0 Hz, 1H), 3.52–3.43 (m, 1H), 3.39 (t, J = 2.8 Hz, 1H), 3.05 (ddd, J = 6.3, 4.1, 1.7 Hz, 1H), 1.98–1.89 (m, 1H), 1.88 (s, 3H), 1.75–1.52 (m, 4H), 1.44–1.10 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.4, 178.0, 167.8, 162.4, 141.4, 129.9, 129.5, 128.6, 128.5, 128.3, 126.9, 125.8, 65.4, 54.3, 50.4, 48.4, 46.8, 42.5, 33.2, 32.5, 25.7, 24.6, 24.6, 14.0. HRMS (ESI) calculated for $C_{26}H_{29}N_2O_3^+$ ($[M + H]^+$): 417.2178, found 417.2176.

***N*-Butyl-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2h).** Pale yellow solid, yield 55%, melting point: 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.24 (m, 2H), 7.23–7.20 (m, 1H), 7.20–7.13 (m, 2H), 6.89 (t, J = 5.3 Hz, 1H), 6.50 (ddd, J = 8.0, 6.4, 1.3 Hz, 1H), 6.29 (ddd, J = 8.3, 6.4, 1.8 Hz, 1H), 5.95 (q, J = 1.5 Hz, 1H), 4.35 (d, J = 5.2 Hz, 1H), 3.64 (ddd, J = 6.6, 3.1, 1.3 Hz, 1H), 3.54–3.43 (m, 1H), 3.37 (t, J = 2.7 Hz, 1H), 3.34–3.23 (m, 2H), 3.06 (ddd, J = 6.2, 4.1, 1.8 Hz, 1H), 1.88 (d, J = 1.5 Hz, 3H), 1.58–1.45 (m, 2H), 1.43–1.30 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.3, 178.1, 168.7, 162.6, 141.3, 129.9, 129.5, 128.6, 128.3, 127.0, 125.7, 65.4, 54.4, 50.4, 46.8, 42.6, 39.4, 31.7, 20.1, 14.0, 13.7. HRMS (ESI) calculated for $C_{24}H_{27}N_2O_3^+$ ($[M + H]^+$): 391.2021, found 391.2028.

***N*-Benzyl-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2i).** Pale yellow solid, yield 82%, melting point: 185–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.29 (m, 5H), 7.27–7.15 (m, 4H), 7.04 (d, J = 7.3 Hz, 2H), 6.50 (t, J = 7.3 Hz, 1H), 6.25 (t, J = 7.8 Hz, 1H), 5.94 (s, 1H), 4.50 (s, 1H), 4.49 (s, 1H), 4.41 (d, J = 5.2 Hz, 1H), 3.57 (dd, J = 6.9, 2.9 Hz, 1H), 3.51–3.46 (m, 1H), 3.32 (s, 1H), 3.07 (t, J = 5.2 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.5, 178.2, 168.7, 162.8, 140.9, 138.0, 129.6, 129.4, 128.7, 128.4, 128.2, 127.6, 127.4, 126.9, 125.6, 65.0, 54.2, 50.2, 46.4, 43.4, 42.2, 29.7, 14.1. HRMS (ESI) calculated for $C_{27}H_{25}N_2O_3^+$ ($[M + H]^+$): 425.1865, found 425.1869.

***N*-(*tert*-Butyl)-1,9a-dimethyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2j).** Pale yellow solid, yield 45%, melting point: 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.76 (s, 1H), 7.32–7.27 (m, 2H), 7.25–7.22 (m, 1H), 7.15–7.05 (m, 2H), 6.25 (dd, J = 8.1, 1.3 Hz, 1H), 6.13–6.10 (m, 1H), 6.09–6.02 (m, 1H), 4.33 (s, 1H), 3.85 (s, 1H), 3.68–3.52 (m, 1H), 3.33 (t, J = 2.5 Hz, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.34 (s, 9H), 1.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.9, 171.9, 167.2, 156.7, 140.5, 135.7, 130.6, 128.4, 127.4, 127.1, 81.6, 68.3, 54.4, 54.2, 51.5, 50.2, 46.1, 28.4, 17.2, 13.6. HRMS (ESI) calculated for $C_{25}H_{29}N_2O_3^+$ ($[M + H]^+$): 405.2178, found 418.2183.

***N*-(*tert*-Butyl)-1,8-dimethyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2k).** Pale yellow solid, yield 50%, melting point: 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.16 (m, 3H), 7.12–7.01 (m, 2H), 6.71 (s, 1H), 6.12 (dq, J = 6.5, 1.7 Hz, 1H), 5.92 (q, J = 1.5 Hz, 1H), 4.24 (d, J = 5.2 Hz, 1H), 3.50–3.40 (m, 1H), 3.36 (t, J = 2.7 Hz, 1H), 3.26 (dd, J = 3.1, 1.7 Hz, 1H), 2.98 (dd, J = 6.6, 4.0 Hz, 1H), 1.86 (d, J = 1.5 Hz, 3H), 1.55 (d, J = 1.7 Hz, 3H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.3, 178.1, 168.1, 162.6, 141.3, 139.0, 128.6, 127.7, 127.0, 125.6, 121.7, 65.6, 61.0, 51.6, 49.6, 46.2, 42.6, 28.8, 21.5, 13.8. HRMS (ESI) calculated for $C_{25}H_{29}N_2O_3^+$ ($[M + H]^+$): 405.2178, found 405.2169.

***N*-(*tert*-Butyl)-1,9-dimethyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3H,5H-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2l).** Pale yellow solid, yield 69%, melting point: 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.24 (m, 2H), 7.23–7.18 (m, 1H), 7.06 (dd, J = 8.0, 1.6 Hz, 2H), 6.64 (s, 1H), 5.94 (q, J = 1.5 Hz, 1H), 5.86 (dt, J = 6.7, 2.0 Hz, 1H), 4.24 (d, J = 5.1 Hz, 1H), 3.48 (dd, J = 6.7, 2.9 Hz, 1H), 3.45–3.40 (m, 1H), 3.36–3.32 (m, 1H), 2.81 (dd, J = 4.1, 2.3 Hz, 1H), 2.05 (d, J = 1.6 Hz, 3H), 1.86 (d, J = 1.5 Hz, 3H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.8, 178.0, 167.9, 162.4, 141.5, 139.0, 128.5, 128.2, 128.0, 126.8, 125.8, 121.4, 65.3, 54.0, 51.6, 51.5, 50.1, 42.8, 28.6, 28.5, 21.3, 14.0. HRMS (ESI) calculated for $C_{25}H_{29}N_2O_3^+$ ($[M + H]^+$): 405.2178, found 405.2178.

***N*-(*tert*-Butyl)-9-fluoro-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2m).** Pale yellow solid, yield 48%, melting point: 69–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33–7.27 (m, 2H), 7.25–7.20 (m, 1H), 7.17–6.98 (m, 2H), 6.68 (s, 1H), 5.98 (q, J = 1.6 Hz, 1H), 5.48 (ddd, J = 7.9, 5.0, 3.1 Hz, 1H), 4.27 (d, J = 5.2 Hz, 1H), 3.66 (td, J = 4.6, 2.2 Hz, 1H), 3.53 (ddd, J = 7.5, 4.2, 3.1 Hz, 1H), 3.38 (q, J = 2.6 Hz, 1H), 3.05 (ddd, J = 13.3, 4.2, 3.1 Hz, 1H), 1.95 (d, J = 1.6 Hz, 3H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.6, 177.5, 167.5, 161.6, 161.0, 157.3, 140.8, 128.9, 128.8, 128.3, 128.1, 127.6, 127.3, 126.2, 100.3, 100.2, 65.3, 65.3, 52.9, 52.2, 52.1, 51.8, 51.1, 47.8, 47.5, 43.0, 43.0, 28.8, 28.7, 22.3, 14.0, 13.7. HRMS (ESI) calculated for $C_{24}H_{26}FN_2O_3^+$ ($[M + H]^+$): 409.1927, found 409.1924.

***N*-(*tert*-Butyl)-8-chloro-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2n).** Pale yellow solid, yield 53%, melting point: 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38–7.23 (m, 3H), 7.22–7.12 (m, 2H), 6.70 (s, 1H), 6.43 (dd, J = 7.2, 2.2 Hz, 1H), 5.96 (q, J = 1.6 Hz, 1H), 4.26 (d, J = 5.2 Hz, 1H), 3.64–3.57 (m, 1H), 3.53–3.48 (m, 1H), 3.47–3.41 (m, 1H), 3.11 (dd, J = 7.2, 4.0 Hz, 1H), 1.90 (d, J = 1.6 Hz, 3H), 1.37 (s, 9H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ = 199.7, 177.6, 167.7, 161.6, 140.1, 131.9, 128.9, 127.8, 127.5, 126.0, 123.6, 65.3, 62.6, 51.7, 50.1, 47.0, 43.4, 28.8, 13.8. HRMS (ESI) calculated for $C_{24}H_{26}ClN_2O_3^+$ ([M + H]$^+$): 425.1631, found 425.1637.

***N*-(*tert*-Butyl)-1-methyl-3,10-dioxo-6,9-diphenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2o).** Pale yellow solid, yield 60%, melting point: 157–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51–7.36 (m, 5H), 7.28–7.17 (m, 3H), 7.06 (dd, *J* = 7.7, 1.7 Hz, 2H), 6.70 (s, 1H), 6.40 (dd, *J* = 6.9, 2.3 Hz, 1H), 5.96 (q, *J* = 1.4 Hz, 1H), 4.36 (d, *J* = 5.1 Hz, 1H), 3.70 (dd, *J* = 6.9, 2.9 Hz, 1H), 3.62–3.54 (m, 1H), 3.53–3.48 (m, 1H), 3.47 (t, *J* = 2.7 Hz, 1H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 201.9, 177.8, 167.9, 162.4, 141.6, 141.3, 136.9, 129.3, 129.0, 128.6, 128.1, 127.0, 126.0, 125.2, 121.8, 65.7, 55.2, 51.7, 50.8, 49.7, 43.3, 28.9, 14.0. HRMS (ESI) calculated for $C_{30}H_{31}N_2O_3^+$ ([M + H]$^+$): 467.2334, found 467.2332.

***N*-(*tert*-Butyl)-6-(4-(dimethylamino)phenyl)-1-methyl-3,10-dioxo-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2p).** Pale yellow solid, yield 65%, melting point: 244–246 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.01 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 2H), 6.60 (s, 1H), 6.47 (t, *J* = 7.3 Hz, 1H), 6.29 (t, *J* = 7.3 Hz, 1H), 5.92 (s, 1H), 4.23 (d, *J* = 5.2 Hz, 1H), 3.60 (dd, *J* = 6.7, 2.9 Hz, 1H), 3.42–3.36 (m, 1H), 3.31 (s, 1H), 3.06–2.98 (m, 1H), 2.90 (s, 6H), 1.86 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.4, 178.0, 168.0, 162.5, 149.5, 129.7, 129.3, 129.0, 128.7, 125.6, 112.6, 65.4, 54.5, 51.5, 50.6, 46.5, 41.3, 40.6, 28.7, 14.1. HRMS (ESI) calculated for $C_{26}H_{32}N_3O_3^+$ ([M + H]$^+$): 434.2443, found 434.2442.

***N*-(*tert*-Butyl)-6-(4-methoxyphenyl)-1-methyl-3,10-dioxo-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2q).** Pale yellow solid, yield 70%, melting point: 191–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 6.50 (t, *J* = 7.3 Hz, 1H), 6.27 (t, *J* = 7.3 Hz, 1H), 5.93 (s, 1H), 4.25 (d, *J* = 5.0 Hz, 1H), 3.77 (s, 3H), 3.59 (dd, *J* = 6.9, 2.8 Hz, 1H), 3.40–3.36 (m, 1H), 3.34 (s, 1H), 3.02 (t, *J* = 5.0 Hz, 1H), 1.87 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.0, 178.1, 168.0, 162.4, 158.5, 133.4, 129.5, 129.5, 129.1, 125.6, 113.9, 65.4, 55.2, 54.5, 51.5, 50.6, 46.4, 41.5, 28.6, 14.1. HRMS (ESI) calculated for $C_{25}H_{29}N_2O_4^+$ ([M + H]$^+$): 421.2127, found 421.2129.

6-(4-Bromophenyl)-*N*-(*tert*-butyl)-1-methyl-3,10-dioxo-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2r). Pale yellow solid, yield 72%, melting point: 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.76 (s, 1H), 6.51 (ddd, *J* = 8.0, 6.5, 1.3 Hz, 1H), 6.26 (ddd, *J* = 8.3, 6.5, 1.7 Hz, 1H), 5.94 (q, *J* = 1.5 Hz, 1H), 4.26 (d, *J* = 4.9 Hz, 1H), 3.61–3.54 (m, 1H), 3.39–3.30 (m, 2H), 3.04 (ddd, *J* = 6.1, 4.0, 1.7 Hz, 1H), 1.86 (d, *J* = 1.5 Hz, 3H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 201.7, 177.8, 167.8, 162.1, 140.5, 131.5, 129.8, 129.7, 129.4, 125.7, 120.9, 65.5, 54.0, 51.5, 50.4, 46.5, 42.0, 28.6, 13.8. HRMS (ESI) calculated for $C_{24}H_{26}BrN_2O_3^+$ ([M + H]$^+$): 469.1126, found 469.1125.

***N*-(*tert*-Butyl)-1-methyl-6-(4-nitrophenyl)-3,10-dioxo-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2s).** Pale yellow solid, yield 55%, melting point: 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.88 (s, 1H), 6.62 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 6.11 (ddd, *J* = 8.3, 6.6, 1.9 Hz, 1H), 5.99 (q, *J* = 1.6 Hz, 1H), 4.20–3.99 (m, 2H), 3.61–3.50 (m, 1H), 3.26 (t, *J* = 2.4 Hz, 1H), 2.95 (dd, *J* = 4.3, 1.9 Hz, 1H), 1.91 (d, *J* = 1.6 Hz, 3H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.1, 174.8, 168.1, 160.3, 148.8, 147.4, 131.2, 129.1, 128.6, 127.5, 123.5, 66.6, 60.1, 54.6, 52.0, 51.8, 47.6, 42.4, 28.5, 14.1, 13.7. HRMS (ESI) calculated for $C_{24}H_{26}N_3O_5^+$ ([M + H]$^+$): 436.1872, found 436.1877.

***N*-(*tert*-Butyl)-1,5a-dimethyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2t).** Yellow solid, yield 67% (dr = 2 : 1), melting point: 196–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.12 (m, 5H), 6.74 (t, *J* = 7.2 Hz, 0.70H), 6.68 (t, *J* = 7.2 Hz, 0.30H), 6.61 (s, 0.72H), 6.50 (t, *J* = 7.3 Hz, 0.66H), 6.45 (t, *J* = 7.3 Hz, 0.27H), 6.36 (s, 0.29H), 6.05 (s, 0.26H), 5.94 (s, 0.68H), 4.10 (s, 0.28H), 3.85 (s, 0.68H), 3.79 (dd, *J* = 6.9, 1.8 Hz, 0.29H), 3.68 (dd, *J* = 6.6, 2.0 Hz, 0.70H), 3.60 (d, *J* = 6.6 Hz, 0.29H), 3.50 (d, *J* = 2.2 Hz, 0.74H), 3.29 (d, *J* = 2.0 Hz, 0.29H), 2.73 (dd, *J* = 6.5, 1.7 Hz, 0.73H), 1.87 (s, 2H), 1.86 (s, 1H), 1.44 (s, 6H), 1.33 (s, 3H), 1.09 (s, 2H), 0.72 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.4, 202.1, 178.1, 176.8, 168.3, 167.9, 162.7, 161.4, 139.4, 139.0, 130.5, 130.1, 129.8, 129.3, 129.1, 128.4, 128.1, 127.4, 127.3, 127.0, 125.4, 75.7, 75.6, 72.8, 70.9, 56.0, 55.9, 54.2, 53.9, 53.6, 52.8, 52.0, 51.5, 47.0, 46.1, 28.8, 28.5, 24.5, 19.9, 14.1, 14.0. HRMS (ESI) calculated for $C_{25}H_{29}N_2O_3^+$ ([M + H]$^+$): 405.2178, found 405.2185.

5a-Bromo-*N*-(*tert*-butyl)-1-methyl-3,10-dioxo-6-phenyl-5a,6,7,9a-tetrahydro-3*H*,5*H*-7,9b-methanopyrrolo[2,1-*a*]isoindole-5-carboxamide (2u). Yellow solid, yield 55% (dr = 2 : 1), melting point: 249–251 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43–7.09 (m, 5.51H), 6.83 (m, 0.53H), 6.83–6.69 (m, 1H), 6.61 (t, *J* = 7.2 Hz, 0.61H), 6.54 (t, *J* = 7.2 Hz, 0.38H), 6.10 (s, 0.30H), 6.01 (s, 0.69H), 4.51 (s, 0.74H), 4.28 (s, 0.33H), 3.82 (d, *J* = 2.1 Hz, 0.68H), 3.72–3.57 (m, 1H), 3.47 (d, *J* = 1.8 Hz, 0.34H), 3.42 (dd, *J* = 6.3, 1.8 Hz, 0.63H), 3.35 (d, *J* = 4.8 Hz, 0.29H), 1.89 (s, 2H), 1.87 (s, 1H), 1.44 (s, 6H), 1.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.4, 200.2, 177.7, 176.4, 166.2, 166.0, 162.2, 160.6, 140.7, 140.6, 131.1, 130.4, 130.0, 129.3, 128.4, 128.2, 128.0, 127.6, 127.5, 125.6, 74.9, 74.3, 73.6, 72.5, 69.6, 67.1, 56.9, 54.2, 53.9, 53.5, 52.6, 51.8, 49.6, 47.5, 28.7, 28.5, 14.1, 14.0. HRMS (ESI) calculated for $C_{24}H_{26}BrN_2O_3^+$ ([M + H]$^+$): 469.1126, found 469.1133.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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