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Ugi/Himbert Arene/Allene Diels–Alder Cycloaddition to Synthesize Strained Polycyclic Skeleton

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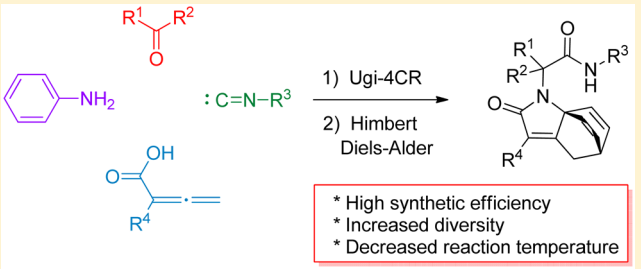
Supporting Information

ABSTRACT: The present work disclosed an efficient multicomponent reaction of isocyanide, allenic acid, aldehyde (ketone), and aniline. This protocol undergoes Ugi reaction followed by an intramolecular arene/allene Diels–Alder sequence, thus providing a rapid access to synthesize strained polycyclic skeletons.



Owing to their easy preparation and exceptional reactivity, isocyanides have found wide application in organic synthesis.[1−3] In particular, isocyanides have been considered as excellent partners in multicomponent reactions for a long history.[4] As such, isocyanide-based multicomponent reactions (IMCRs) have attracted considerable interest from the synthetic community.[5] Among the IMCR family, the Ugi reaction has been widely investigated in organic chemistry since its first discovery in 1959.[6] The classical Ugi-4CR gives rise to a linear peptide adduct, but its diversity and complexity can be significantly increased when bifunctional components are used.[7] For example, sequenced reactions including Ugi/Diels–Alder,[8] Ugi/Heck,[9] Ugi/aldol,[10] and Ugi/Buchwald–Hartwig[11] have been well documented. From the standpoint of organic synthesis, the conditional Ugi reaction has the ability to access molecular complexity and diversity in one step, which is of great significance for the construction of natural products and druglike compounds.[12] It is noteworthy that traditional Ugi/Diels–Alder reactions usually involve the use of furan and oxazole as the dienes and electron-deficient alkenes and alkynes as dienophiles. However, studies on the Ugi reaction followed by the intramolecular Diels–Alder reaction involving allene and unactivated arene have not been reported.

Since the first example reported in 1982,[13] the Himbert intramolecular arene/allene Diels–Alder sequence has been widely investigated for more than 30 years. Starting from allenecarboxanilide, this protocol provides an efficient and straightforward method to approach complex bridged polycyclic architectures. In the past decades, many efforts have been devoted to studies on different characters of this reaction. At an early stage, varying the substitution of carboxylic acid derivatives including amide, ester, and thioester has been widely investigated.[14] Recently, Vanderwal, Houk et al. have extended the substrate to benzyl allenyl ketones, thus giving rise to all-carbon-linked polycyclic architectures.[15] In addition, this strategy has also been applied to the synthesis of natural product like skeletons, and the reaction mechanism also drew attention from organic chemists.[16] Although many milestones have been reached, some issues in the Himbert reaction seem to be problematic and hence need to be overcome. For instance, several steps including *N*-alkylation of aniline and conversion of the acid to acyl chloride are indispensible for the preparation of the precursor allenecarboxanilides. In addition, this method usually required a high reaction temperature (toluene or xylene, higher than 100 °C), which limited its further application. Consequently, there is a continuous need to develop novel and efficient protocols to overcome the above-mentioned drawbacks.

In the past several years, we have focused our attention on isocyanide-based multicomponent reactions involving electron-deficient allenes. In 2011, we disclosed the first example in this field involving isocyanide and allenoate,[17] thus providing a rapid access to spirooxindole derivatives. Following this work, our multicomponent strategy has also been applied to synthesize other five-membered rings and structurally complex fused skeletons.[18] Furthermore, these successful examples with isocyanide and electron-deficient allene have also prompted us to try the multicomponent reaction with isocyanide and allenic acid. As a reasonable design, we assume that the incorporation of the Ugi reaction based on isocyanide and allenic acid with the Himbert reaction may be successful (Scheme 1). As a continuation, we report a novel multicomponent reaction of isocyanide, aldehyde (ketone), aniline, and allenic acid to produce the complex polycyclic skeleton with high efficiency. To the best of our knowledge, no such examples have been reported.

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Scheme 1. Ugi/Himbert Diels–Alder Reaction to Construct Polycyclic Architecture

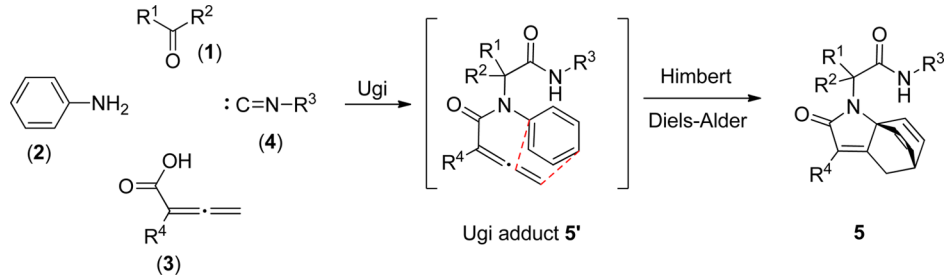
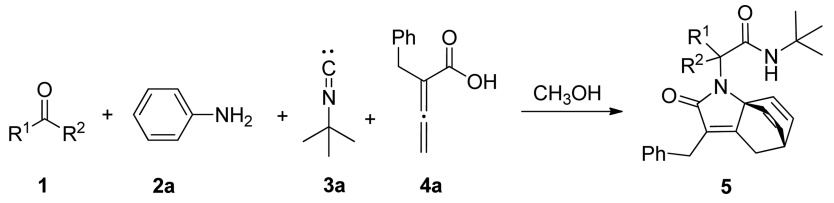
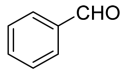
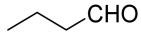
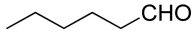
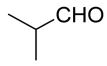
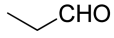
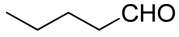
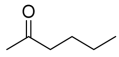


Table 1. Multicomponent Reaction of Aldehyde (Ketone) 1, Aniline 2a, *tert*-Butyl Isocyanide 3a, and Allenic Acid 4a[a]



entry	substrate **1**	product	yield (%)[b]
1		**5a**	47
2		**5b**	35
3		**5c**	58
4		**5d**	43
5		**5e**	54
6		**5f**	41
7		**5g**	32
8		**5h**	44
9		**5i**	60
10		**5j**	37

[a]Reaction conditions: 0.5 mmol of carbonyl compound **1**, 0.5 mmol of aniline **2a**, 0.5 mmol of *tert*-butyl isocyanide **3a**, 0.5 mmol of allenic acid **4a** in 5 mL of methanol, reflux, 4 h. [b]Yields of product after silica gel chromatography.

In our initial experiment, benzaldehyde **1a**, aniline **2a**, *tert*-butyl isocyanide **3a**, and allenic acid **4a** were selected as model substrates. Simply heating the mixture in CH_3OH under reflux directly produced a polycyclic cycloadduct **5a** in 47% yield (Table 1, entry 1). The structure of compound **5a** was unambiguously confirmed by single-crystal X-ray analysis.[19] Various aldehydes were subsequently used to undergo the reflux conditions, thereby affording the corresponding complex skeletons **5** in satisfactory yields (Table 1, entries 2–6; see the Supporting Information for details). The experimental results revealed that ketones including cyclic ones could also be well tolerated, and no obvious steric hindrance is observed (Table 1, entries 7–10). The present method has several advantages worth clarification. First, this protocol provides a straightforward route to structurally complex skeletons in one step, which represents high synthetic efficiency. For instance, there is no requirement to isolate the reaction intermediate, which is directly converted to the final product upon heating. In contrast, the synthesis of precursor usually requires several synthetic procedures in the traditional Himbert cycloaddition. Second, aldehyde, aniline, and isocyanide as well as allenic acid are all readily available starting materials, which brings great convenience for the construction of the corresponding compound library.

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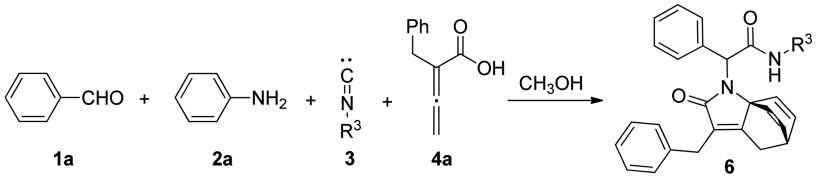
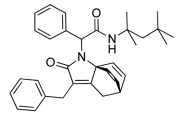
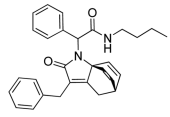
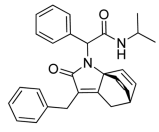
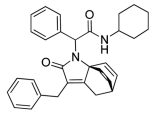
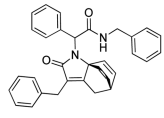
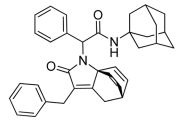
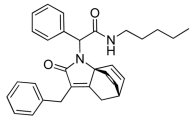
Table 2. Multicomponent Reaction of Benzaldehyde 1a, Aniline 2a, Isocyanide 3, and Allenic Acid 4a[a]



entry	R^3	product	yield (%)[b]
1	1,1,3,3-tetramethylbutyl	 **6a**	31
2	*n*-butyl	 **6b**	40
3	*i*-propyl	 **6c**	67
4	cyclohexyl	 **6d**	25
5	benzyl	 **6e**	58
6		 **6f**	41
7	*n*-pentyl	 **6g**	48

[a]Reaction conditions: 0.5 mmol of benzaldehyde **1a**, 0.5 mmol of aniline **2a**, 0.5 mmol of isocyanide **3**, 0.5 mmol of allenic acid **4a** in 5 mL of methanol, reflux, 4 h. [b]Yields of product after silica gel chromatography.

After a broad aldehyde scope had been established, we then turned our attention to the compatibility of substituted isocyanides. As shown in Table 2, sterically hindered 1,1,3,3-tetramethylbutyl isocyanide **3b** was first proven to proceed smoothly under the standard conditions (Table 2, entry 1). Other isocyanides including benzyl and admantyl isocyanides were subsequently employed to react with benzaldehyde **1a**, aniline **2a**, and allenic acid **4a** (Table 2, entries 2−7). To our delight, all these substrates were well tolerated to give the corresponding products **6** (see the Supporting Information for details).

To gain further insight into the present transformation, a series of substituted allenic acids **4** were examined with benzaldehyde **1a**, aniline **2a**, and *tert*-butyl isocyanide **3a**. As shown in Table 3, a variety of allenic acids **4** bearing electron-withdrawing (Table 3, entries 1 and 2) and -donating groups (Table 3, entries 3 and 4) on the aromatic ring of the benzyl group substituent were screened under the standard reaction conditions. Pleasingly, most of the substituents were well tolerated to give the corresponding products **7** (see the Supporting Information for details). Notably, substrate **4** containing γ-substituted substrate was aslo observed to react

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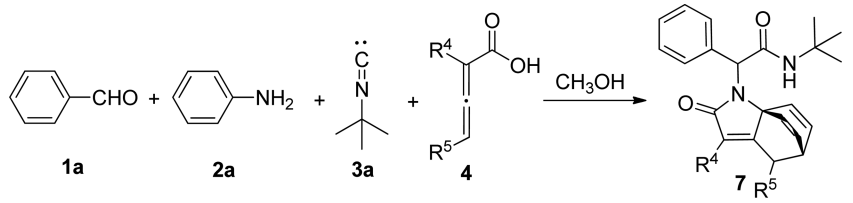
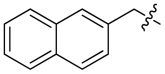
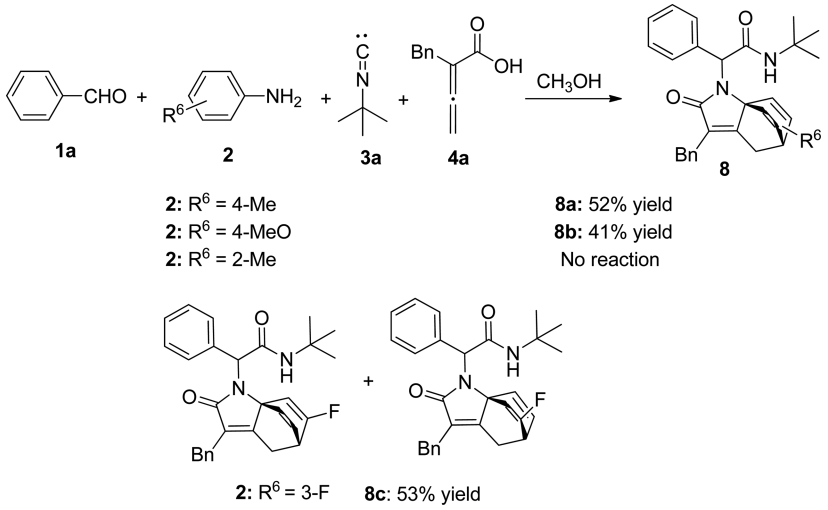
Table 3. Multicomponent Reaction of Benzaldehyde 1a, Aniline 2a, *tert*-Butyl Isocyanide 3a, and Substituted Allenic Acid 4[a]



entry	R^4	R^5	product	yield (%)[b]
1	3-chlorobenzyl	H	**7a**	40
2	4-bromobenzyl	H	**7b**	36
3	2-methylbenzyl	H	**7c**	44
4		H	**7d**	42
5	methyl	phenyl	**7e**	30
6	H	phenyl	-	ND

[a]Reaction conditions: 0.5 mmol of benzaldehyde **1a**, 0.5 mmol of aniline **2a**, 0.5 mmol of *tert*-butyl isocyanide **3a**, 0.5 mmol of allenic acid **4** in 5 mL of methanol, reflux, 4 h. [b]Yields of product after silica gel chromatography.

Scheme 2. Controlled Experiments



smoothly under the same conditions (Table 3, entry 5). Since the above-mentioned reactions all finished in a short amount of time, we thus deduced that the employment of protic solvent CH_3OH may also help accelerate the reaction rate.[20] However, no desired products were observed when other solvents such as DCM and toluene were used even under reflux.

Further experiments were also carried out with substituted anilines. As shown in Scheme 2, the reactions proceeded smoothly to give rise the corresponding product **8a** and **8b** when *para*-substituted anilines were used. In contrast, no reaction occurred when *ortho*-substituted aniline was used. The *meta*-substituted substrate was also examined and proven to be compatible.

In conclusion, we have described the multicomponent reaction of aldehyde (ketone), aniline, isocyanide, and allenic acid. This protocol represents the first example to incorporate a multicomponent reaction and the Himbert reaction, thus providing a quick access to the complex polycyclic skeleton with high efficiency.[21] The advantages of the present strategy can be summarized as follows: (1) the substrate scope has been expanded greatly since aldehyde and isocyanide components are easily varied, (2) the amine does not need to be protected, (3) the acid does not need to be transformed to acyl chloride,

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and (4) the reaction temperature is decreased dramatically. Given these advantages, the present reaction may find application in the synthesis of similar complex architectrues.

EXPERIMENTAL SECTION

General Information. The NMR spectra were recorded on a 500 MHz spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) with $CDCl_3$ as the solvent and TMS as internal reference. ^{1}H NMR spectral data were reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constant (Hz). ^{13}C NMR spectral data were reported in terms of the chemical shift. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. IR spectra were recorded on an FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an FTMS instrument in ESI mode and reported as m/z. Melting points were obtained on a digital melting point apparatus without correction. Unless otherwise stated, all reagents were commercially purchased and used without further purification. All substituted allenic acids **4** were synthesized according to procedures reported previously.[22]

General Procedure for the Formation of Products 5−8. Isocyanide **3** (0.5 mmol) was added to a solution of allenic acid **4** (0.5 mmol), aldehyde (ketone) **1** (0.5 mmol), and aniline **2** (0.5 mmol) in 5 mL of methanol. The stirred mixture was heated under reflux for 4 h, and the progress was monitored using TLC detection. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (silica: 200−300; eluant: petroleum ether/ethyl acetate) to afford the desired products **5**−**8**.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-phenylacetamide (**5a**).* 102.9 mg, 47% yield. White solid. Mp: 194−195 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, J = 6.5 Hz, 2H), 7.37−7.32 (m, 3H), 7.23 (t, J = 7. 0 Hz, 2H), 7.18−7.14 (m, 3H), 6.69 (s, 1H), 6.50 (d, J = 7.0 Hz, 1H), 6.32 (t, J = 7. 0 Hz, 1H), 6.16 (t, J = 6.5 Hz, 1H), 5.81 (d, J = 7.0 Hz, 1H), 5.55 (s, 1H), 3.87 (s, 1H), 3.57 (d, J = 17.0 Hz, 1H), 3.54 (d, J = 17.0 Hz, 1H), 1.86 (s, 2H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0, 169.5, 155.3, 138.8, 135.0, 133.5, 132.9, 131.6, 130.9, 128.9, 128.7, 128.6, 128.3, 126.1, 125.2, 74.1, 63.7, 51.5, 39.0, 31.2, 29.9, 28.6. IR (film): 3326, 2966, 1686, 697 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{30}N_2NaO_2$ [M + Na]$^+$ 461.2205, found 461.2183.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butylpentanamide (**5b**).* 70.7 mg, 35% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (s, 1H), 7.22 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.37−6.33 (m, 3H), 6.26 (dd, J = 7.5, 1.5 Hz, 1H), 4.24 (t, J = 8.0 Hz, 1H), 3.94−3.93 (m, 1H), 3.52 (s, 2H), 2.22−2.08 (m, 2H), 1.92 (s, 2H), 1.46−1.41 (m, 2H), 1.29 (s, 9H), 0.98 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 171.4, 155.3, 138.8, 134.1, 133.9, 131.6, 130.3, 128.7, 128.4, 126.1, 125.5, 74.3, 61.1, 51.0, 39.1, 31.3, 30.9, 29.9, 28.6, 20.3, 13.9. IR (film): 3327, 2963, 1675, 1362 cm^{-1}. HRMS (ESI): calcd for $C_{26}H_{32}N_2NaO_2$ [M + Na]$^+$ 427.2361, found 427.2352.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butylheptanamide (**5c**).* 125.3 mg, 58% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.22 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.37−6.33 (m, 3H), 6.26 (dd, J = 7.5, 1.5 Hz, 1H), 4.24 (t, J = 7.5 Hz, 1H), 3.94−3.93 (m, 1H), 3.52 (s, 2H), 2.23−2.07 (m, 2H), 1.94 (d, J = 17.0 Hz, 1H), 1.90 (d, J = 17.0 Hz, 1H), 1.42−1.33 (m, 14H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3): δ = 174.8, 171.4, 155.3, 138. 8, 134.1, 133.9, 131.6, 130.3, 128.7, 128.3, 126.1, 125.5, 74.3, 61.4, 50.9, 39.1, 31.6, 30.9, 29.9, 29.1, 28.6, 26.6, 22.5, 14.0. IR (film): 3328, 2960, 1672, 1363 cm^{-1}. HRMS (ESI): calcd for $C_{28}H_{36}N_2NaO_2$ [M + Na]$^+$ 455.2674, found 455.2668.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-3-methylbutanamide (**5d**).* 86.9 mg, 43% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.21 (d, J = 7.5 Hz, 2H), 7.15 (t, J = 7.0 Hz, 1H), 7.10 (d, J = 7.0 Hz, 2H), 6.39 (dd, J = 7.5, 6.0 Hz, 1H), 6.34 (d, J = 4.0 Hz, 1H), 6.22 (dd, J = 7.5, 1.0 Hz, 1H), 3.95−3.93 (m, 1H), 3.51−3.46 (m, 3H), 3.13−3.06 (m, 1H), 1.93 (t, J = 1.0 Hz 1H), 1.30 (s, 9H), 1.04 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 171.7, 155.0, 138.8, 134.7, 134.2, 130.8, 130.7, 128.6, 128.4, 126.1, 125.8, 75.2, 71.4, 50.8, 39.3, 30.9, 30.2, 28.6, 27.7, 20.8, 19.5. IR (film): 3306, 2966, 1677, 705 cm^{-1}. HRMS (ESI): calcd for $C_{26}H_{32}N_2O_2$ [M + Na]$^+$ 427.2361, found 427.2356.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butylbutanamide (**5e**).* 105.3 mg, 54% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (s, 1H), 7.24−7.11 (m, 5H), 6.38−6.34 (m, 3H), 6.27 (dd, J = 7.0, 1.5 Hz, 1H), 4.14 (t, J = 8.0 Hz, 1H), 3.96−3.92 (m, 1H), 3.53 (s, 2H), 2.28−2.13 (m, 2H), 1.96−1.88 (m, 2H), 1.29 (s, 9H), 1.04 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 171.2, 155.3, 138.8, 134.1, 133.9, 131.5, 130.4, 128.7, 128.4, 126.1, 125.4, 74.3, 62.9, 51.0, 39.1, 30.9, 29.9, 28.6, 22.5, 11.6. IR (film): 3326, 2967, 1671 cm^{-1}. HRMS (ESI): calcd for $C_{25}H_{30}N_2NaO_2$ [M + Na]$^+$ 413.2205, found 413.2199.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butylhexanamide (**5f**).* 85.7 mg, 41% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (s, 1H), 7.21 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.0 Hz, 1H), 7.11 (d, J = 7.0 Hz, 2H), 6.37−6.33 (m, 3H), 6.25 (dd, J = 7.5, 1.0 Hz, 1H), 4.22 (t, J = 8.0 Hz, 1H), 3.94−3.93 (m, 1H), 3.52 (s, 2H), 2.22−2.10 (m, 2H), 1.92 (s, 2H), 1.39−1.38 (m, 4H), 1.29 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 171.4, 155.3, 138.8, 134.1, 133.9, 131.5, 130.3, 128.7, 128.4, 126.1, 125.4, 74.2, 61.34, 50.8, 39.1, 30.9, 29.9, 29.2, 28.9, 28.6, 22.6, 13.9. IR (film): 3326, 2961, 1660, 1364 cm^{-1}. HRMS (ESI): calcd for $C_{27}H_{34}N_2NaO_2$ [M + Na]$^+$ 441.2518, found441.2514.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-methylpropanamide (**5g**).* 62.4 mg, 32% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 7.0 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.75 (s, 1H), 6.36 (dd, J = 7.0, 1.5 Hz, 2H), 6.29 (t, J = 6.5 Hz, 2H), 3.92−3.90 (m, 1H), 3.49 (s, 2H), 1.87 (t, J = 1.0 Hz, 2H), 1.74 (s, 6H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 174.0, 154.4, 138.9, 132.2, 132.1, 128. 8, 128.3, 126.1, 126.0, 73.3, 61.5, 50.9, 38.4, 31.0, 29.6, 28.6, 25.2. IR (film): 3363, 2968, 1654, 1526 cm^{-1}. HRMS (ESI): calcd for $C_{25}H_{30}N_2NaO_2$ [M + Na]$^+$ 413.2205, found 413.2197.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-methylbutanamide (**5h**).* 88.9 mg, 44% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23−7.11 (m, 6H), 6.39 (dd, J = 7.5, 1.0 Hz, 1H), 6.32−6.25 (m, 3H), 3.92−3.90 (m, 1H), 3.52 (d, J = 16.5 Hz, 1H), 3.45 (d, J = 16.5 Hz, 1H), 2.66−2062 (m, 1H), 2.17−2.10 (m, 1H), 1.90 (d, J = 2.1 Hz, 1H), 1.88 (d, J = 2.1 Hz, 1H), 1.56 (s, 3H), 1.27 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.3, 173.7, 154.5, 139.0, 133.4, 132.0, 131.4, 131.2, 128.7, 128.3, 126.1, 126.0, 73.6, 65.8, 50.9, 38.4, 31.0, 29.7, 29.6, 28.5, 20.3, 8.9. IR (film): 3306, 2967, 1676, 700 cm^{-1}. HRMS (ESI): calcd for $C_{26}H_{32}N_2NaO_2$ [M + Na]$^+$ 427.2361, found 427.2343.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-methylhexanamide (**5i**).* 129.6 mg, 60% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (s, 1H), 7.24 (t, J = 7.0 Hz, 2H), 7.19−7.13 (m, 3H), 6.42−6.40 (m, 1H), 6.34−6.28 (m, 3H), 3.95−3.93 (m, 1H), 3.56 (d, J = 15.0 Hz, 1H), 3.48 (d, J = 15.0 Hz, 1H), 2.65−2.60 (m, 1H), 2.16−2.11 (m, 1H), 1.93 (d, J = 1.5 Hz, 1H), 1.92 (d, J = 1.5 Hz, 1H), 1.60 (s, 3H), 1.42−1.38 (m, 4H), 1.29 (s, 9H), 0.94 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4, 173.8, 154.5, 139.0, 133.4, 132.0, 131.4, 131.2, 128.7, 128.3, 125.1, 125.1, 73.6, 65.4, 50.9, 38.4, 36.6, 31.0, 29.7, 28.5, 26.6, 22.9, 21.0, 14.1. IR (film): 2961, 1673, 1357, 698 cm^{-1}. HRMS (ESI): calcd for $C_{28}H_{37}N_2O_2$ [M + H]$^+$ 433.2855, found 433.2848

*1-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butylcyclopentanecarboxamide (**5j**).* 77.0 mg, 37% yield. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (s, 1H), 7.21 (t, J = 7.5 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.37 (d, J = 7.0 Hz, 2H), 6.30 (d, J = 7.0 Hz, 2H), 3.95−3.92 (m, 1H), 3.49 (s, 2H), 2.67−2.65 (m, 2H), 2.24−2.22 (m, 2H), 1.93 (d, J = 1.0 Hz, 2H), 1.76−1.73 (m, 5H), 1.24 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7, 173.5, 154.8, 139.0, 132.3, 131.8, 128.7, 128.3, 126.1, 126.0,

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74.0, 71.4, 50.8, 38.6, 35.4, 31.0, 29.7, 28.5, 23.9. IR (film): 3309, 2962, 1671, 1359 cm^{-1}. HRMS (ESI): calcd for $C_{27}H_{32}N_2NaO_2$ $[M + Na]^+$ 439.2361, found 439.2359.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenyl-N-(2,4,4-trimethylpentan-2-yl)acetamide (**6a**).* 76.6 mg, 31% yield. Yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, J = 7.0 Hz, 2H), 7.37−7.32 (m, 3H), 7.25−7.22 (m, 2H), 7.18−7.14 (m, 3H), 6.81 (s, 1H), 6.42 (d, J = 7.5 Hz, 1H), 6.32 (d, J = 7.0 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 5.93 (d, J = 7.0 Hz, 1H), 5.48 (s, 1H), 3.87 (s, 1H), 3.58 (d, J = 16.0 Hz, 1H), 3.54 (d, J = 16.0 Hz, 1H), 1.84 (s, 2H), 1.73 (d, J = 15.0, 3H), 1.61 (d, J = 15.0, 3H), 1.40 (s, 6H), 0.88 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0, 168.8, 155.1, 138.8, 135.2, 133.7, 133.1, 131.6, 130.9, 129.0, 128.8, 128.5, 128.3, 128.2, 126.1, 125.3, 74.3, 64.3, 55.5, 52.2, 39.1, 31.5, 31.4, 31.2, 30.0, 28.1. IR (film): 3288, 2967, 1651, 700 cm^{-1}. HRMS (ESI): calcd for $C_{33}H_{38}N_2NaO_2$ $[M + Na]^+$ 517.2831, found 517.2819.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-butyl-2-phenylacetamide (**6b**).* 87.6 mg, 40% yield. Yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, J = 6.0 Hz, 2H), 7.38−7.33 (m, 3H), 7.25−7.14 (m, 5H), 6.94 (s, 1H), 6.44 (d, J = 6.5 Hz, 1H), 6.32 (t, J = 6.5 Hz, 1H), 6.22 (t, J = 7.0 Hz, 1H), 5.93 (d, J = 7.0 Hz, 1H), 5.60 (d, J = 4.5 Hz, 1H), 3.89−3.87 (m, 1H), 3.56 (s, 2H), 3.29 (q, J = 7.0 Hz, 2H), 1.84 (s, 2H), 1.49−1.43 (m, 2H), 1.30−1.26 (m, 2H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 170.2, 155.4, 138.7, 135.0, 133.8, 133.2, 131.5, 130.8, 129.0, 128.8, 128.4, 128.3, 126.2, 125.2, 74.3, 63.4, 39.6, 39.1, 31.4, 31.2, 30.0, 20.0, 13.7. IR (film): 3307, 2951, 1655, 700 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{30}N_2NaO_2$ $[M + Na]^+$ 461.2205, found 461.2197.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-isopropyl-2-phenylacetamide (**6c**).* 142.0 mg, 67% yield. White solid. Mp: 114−115 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, J = 1.5 Hz, 2H), 7.36−7.34 (m, 3H), 7.25−7.14 (m, 5H), 6.66 (d, J = 6.5 Hz, 1H), 6.47 (d, J = 7.0 Hz, 1H), 6.32 (t, J = 6.5 Hz, 1H), 6.18 (t, J = 7.0 Hz, 1H), 5.87 (d, J = 7.5 Hz, 1H), 5.59 (s, 1H), 4.14−4.07 (m, 1H), 3.89−3.86 (m, 1H), 3.58 (d, J = 16.5 Hz, 1H), 3.54 (d, J = 16.5 Hz, 1H), 1.85 (s, 2H), 1.13 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 169.4, 155.4, 138.8, 135.0, 133.7, 133.1, 131.5, 130.9, 128.9, 128.8, 128.6, 128.4, 128.4, 126.1, 125.2, 74.2, 63.2, 41.9, 39.1, 31.1, 30.0, 22.5, 22.4. IR (film): 3301, 1677, 702 cm^{-1}. HRMS (ESI): calcd for $C_{28}H_{28}N_2NaO_2$ $[M + Na]^+$ 447.2048, found 447.2050.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-cyclohexyl-2-phenylacetamide (**6d**).* 58.0 mg, 25% yield. White solid. Mp: 184−185 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50−7.49 (m, 2H), 7.37−7.30 (m, 3H), 7.25−7.14 (m, 5H), 6.81 (d, J = 7.0 Hz, 1H), 6.47 (d, J = 7.5 Hz, 1H), 6.33 (t, J = 7.0 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 5.90 (d, J = 7.0 Hz, 1H), 5.59 (s, 1H), 3.88−3.81 (m, 2H), 3.57 (d, J = 16.5 Hz, 1H), 3.53 (d, J = 16.5 Hz, 1H), 1.89−1.84 (m, 4H), 1.62−1.53 (m, 3H), 1.36−1.29 (m, 2H), 1.18−1.11 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 169.4, 155.4, 138.8, 135.0, 133.7, 133.1, 131.5, 130.8, 128.9, 128.8, 128.5, 128.4, 128.3, 126.1, 125.3, 74.3, 63.3, 48.5, 39.1, 32.6, 32.5, 31.1, 30.0, 25.5, 24.6. IR (film): 3293, 2926, 1680, 701 cm^{-1}. HRMS (ESI): calcd for $C_{31}H_{33}N_2O_2$ $[M + H]^+$ 465.2542, found 465.2535.

*N-**b**enzyl-2-((5r,7ar)-3-benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenylacetamide (**6e**).* 136.9 mg, 58% yield. White solid. Mp: 146−147 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53−7.51 (m, 2H), 7.36−7.13 (m, 13H), 6.46 (d, J = 7.5 Hz, 1H), 6.31 (t, J = 7.0 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 5.88 (d, J = 7.0 Hz, 1H), 5.70 (s, 1H), 4.51 (d, J = 5.5 Hz, 2H), 3.88−3.86 (m, 1H), 3.58 (t, J = 17.0 Hz, 1H), 3.54 (t, J = 17.0 Hz, 1H), 1.83 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 170.3, 155.6, 138.7, 138.2, 134.8, 133.6, 133.1, 131.4, 130.9, 129.0, 128.7, 128.6, 128.4, 127.4, 127.2, 126.2, 125.1, 74.2, 63.1, 43.7, 39.1, 31.2, 30.0. IR (film): 3278, 1652, 1380, 705 cm^{-1}. HRMS (ESI): calcd for $C_{32}H_{28}N_2NaO_2$ $[M + Na]^+$ 495.2048, found 495.2044.

*N-((3S,5S,7S)-Adamantan-1-yl)-2-((5R,7ar)-3-benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenylacetamide (**6f**).* 105.8 mg, 41% yield. Colorless transparent liquid. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52−7.50 (m, 2H), 7.36−7.30 (m, 3H), 7.24−7.14 (m, 5H), 6.52 (d, J = 6.5 Hz, 2H), 6.31 (t, J = 7.0 Hz, 1H), 6.15 (t, J = 7.0 Hz, 1H), 5.80 (d, J = 7.0 Hz, 1H), 5.56 (s, 1H), 3.87−3.85 (m, 1H), 3.58 (d, J = 16.0 Hz, 1H), 3.54 (d, J = 16.0 Hz, 1H), 2.04 (s, 3H), 1.98 (d, J = 2.5 Hz, 6H), 1.85 (s, 2H), 1.65 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0, 169.2, 155.3, 138.9, 135.1, 133.4, 132.8, 131.6, 131.0, 129.0, 128.8, 128.7, 128.3, 128.3, 126.1, 125.2, 74.0, 63.5, 52.2, 41.3, 39.0, 36.4, 31.2, 29.9, 29.4. IR (film): 3445, 2907, 1656 cm^{-1}. HRMS (ESI): calcd for $C_{35}H_{37}N_2O_2$ $[M + H]^+$ 517.2855, found 517.2850.

*2-((5r,7ar)-3-Benzyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-pentyl-2-phenylacetamide (**6g**).* 108.5 mg, 48% yield. White solid. Mp: 164−165 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53−7.47 (m, 2H), 7.35−7.13 (m, 8H), 7.00 (d, J = 10.0 Hz, 1H), 6.47 (d, J = 7.0 Hz, 1H), 6.32 (t, J = 7.0 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 5.91 (d, J = 7.5 Hz, 1H), 5.63 (s, 1H), 3.88−3.86 (m, 1H), 3.58 (d, J = 16.5 Hz, 1H), 3.54 (d, J = 16.5 Hz, 1H), 3.29−3.25 (m, 2H), 1.83 (s, 2H), 1.50−1.44 (m, 2H), 1.30−1.21 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 170.2, 155.4, 138.7, 135.0, 133.7, 133.2, 131.5, 130.8, 129.0, 128.8, 126.2, 125.2, 74.3, 63.4, 39.8, 39.1, 31.2 30.0, 29.0, 22.3, 14.0. IR (film): 3309, 2926, 1655, 1388, 709 cm^{-1}. HRMS (ESI): calcd for $C_{30}H_{33}N_2O_2$ $[M + H]^+$ 453.2542, found 453.2544.

*N-tert-Butyl-2-((5r,7ar)-3-(3-chlorobenzyl)-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenylacetamide (**7a**).* 94.4 mg, 40% yield; white solid: mp 166−167 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, J = 7.0 Hz, 2H), 7.35−7.34 (m, 3H), 7.15−7.03 (m, 4H), 6.64 (s, 1H), 6.52 (d, J = 7.0 Hz, 1H), 6.34 (t, J = 6.5 Hz, 1H), 6.18 (t, J = 7.0 Hz, 1H), 5.81 (d, J = 7.5 Hz, 1H), 5.55 (s, 1H), 3.92−3.90 (m, 1H), 3.54 (d, J = 15.5 Hz, 1H), 3.50 (d, J = 15.5 Hz, 1H), 1.92 (s, 2H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 169.4, 155.8, 140.9, 134.9, 134.1, 133.6, 133.0, 131.5, 130.9, 129.6, 128.9, 128.8, 128.6, 128.4, 127.1, 125.4, 124.5, 74.1, 63.7, 51.5, 39.0, 30.8, 30.0, 28.6. IR (film): 3305, 1649, 701 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{29}ClN_2NaO_2$ $[M + Na]^+$ 495.1815, found 495.1805.

*2-((5r,7ar)-3-(4-Bromobenzyl)-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-phenylacetamide (**7b**).* 92.9 mg, 36% yield. White solid. Mp: 225−226 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49−7.47 (m, 2H), 7.36−7.34 (m, 5H), 7.03 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.32 (t, J = 7.0 Hz, 1H), 6.17 (t, J = 7.0 Hz, 1H), 5.79 (d, J = 7.5 Hz, 1H), 5.54 (s, 1H), 3.90 (s, 1H), 3.52 (d, J = 16.0 Hz, 1H), 3.48 (d, J = 16.0 Hz, 1H), 1.88 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 169.3, 155.6, 137.9, 134.9, 133.5, 132.9, 131.5, 131.4, 131.0, 130.6, 128.8, 128.7, 128.4, 124.7, 120.0, 74.1, 63.6, 51.5, 39.0, 30.6, 30.0, 28.6. IR (film): 3306, 1652, 703 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{29}BrN_2NaO_2$ $[M + Na]^+$ 539.1310, found 539.1303.

*N-tert-Butyl-2-((5r,7ar)-3-(2-methylbenzyl)-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenylacetamide (**7c**).* 99.4 mg, 44% yield. White solid. Mp: 238−240 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, J = 7.0 Hz, 2H), 7.36−7.35 (m, 3H), 7.09−7.06 (m, 1H), 6.75 (s, 1H), 6.47 (d, J = 7.5 Hz, 1H), 6.28 (t, J = 6.5 Hz, 1H), 6.13 (t, J = 6.5 Hz, 1H), 5.82 (d, J = 7.0 Hz, 1H), 5.56 (s, 1H), 3.79 (s, 1H), 3.56 (s, 2H), 2.15 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 155.1, 136.8, 136.7, 135.1, 133.6, 133.0, 131.3, 130.7, 123.0, 129.8, 128.8, 128.6, 128.3, 125.5, 125.8, 124.3, 74.2, 63.7, 51.4, 39.1, 29.8, 29.3, 28.6, 19.4. IR (film): 3433, 1652, 1378 cm^{-1}. HRMS (ESI): calcd for $C_{30}H_{32}N_2NaO_2$ $[M + Na]^+$ 475.2361, found 475.2352.

*N-tert-Butyl-2-((5r,7ar)-3-(naphthalen-2-ylmethyl)-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenylacetamide (**7d**).* 102.5 mg, 42% yield. White solid. Mp: 195−196 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82−7.74 (m, 3H), 7.63 (s, 1H), 7.55−7.53 (m, 2H), 7.48−7.32 (m, 6H), 6.75 (s, 1H), 6.55−6.54 (m, 1H), 6.34−6.21 (m, 1H), 6.18−6.15 (m, 1H), 5.85 (d, J = 7.0 Hz, 1H), 5.61 (s, 1H), 3.86−3.84 (m, 1H), 3.76−3.75 (m, 2H), 1.86 (s, 2H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 169.5, 155.6, 136.4, 135.1, 133.6, 133.5, 132.9, 132.1, 131.5, 130.9, 128.8, 128.6, 128.4, 127.9, 127.7, 127.6, 127.5, 127.1, 125.9, 125.4, 125.2, 74.2, 63.7, 51.5, 39.1, 31.4, 30.0, 28.7, 28.6. IR (film): 3312, 1653, 1376 cm^{-1}. HRMS (ESI): calcd for $C_{33}H_{32}N_2NaO_2$ $[M + Na]^+$ 511.2361, found 511.2357.

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*N-tert-Butyl-2-((5r,7ar)-3-methyl-2-oxo-4-phenyl-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-2-phenylacetamide (**7e**).* 65.7 mg, 30% yield. White solid. Mp: 161−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, J = 6.5 Hz, 2H), 7.40−7.35 (m, 3H), 7.25−6.99 (m, 5H), 6.70 (d, J = 7.0 Hz, 0.65H), 6.64 (d, J = 7.0 Hz, 0.35H), 6.63−6.47 (m, 1H), 6.37 (s, 0.35H), 6.32 (t, J = 7.0 Hz, 0.65H), 6.07−6.04 (m, 1H), 5.90−5.88 (m, 1H), 5.62−5.61 (m, 1H), 3.89−3.86 (m, 1H), 3.67 (s, 1H), 1.47−1.46 (m, 3H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 169.3, 169.2, 155.2, 155.1, 140.3, 140.2, 135.3, 135.2, 133.9, 133.5, 132.6, 132.2, 131.4, 131.3, 131.0, 130.8, 130.2, 130.1, 129.1, 128.9, 128.8, 128.6, 128.5, 128.42, 128.41, 128.3, 128.2, 127.6, 127.0, 123.8, 123.7, 74.2, 74.1, 63.7, 63.3, 51.6, 51.6, 48.2, 48.1, 47.5, 47.4, 28.7, 28.6, 9.9, 9.8. IR (film): 3441, 1661, 1461 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{31}N_2O_2$ $[M + H]^+$ 439.2386, found 439.2357.

*2-((5r,7ar)-3-Benzyl-5-methyl-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-phenylacetamide (**8a**).* 117.5 mg, 52% yield. White solid. Mp: 194−195 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50−7.48 (m, 2H), 7.36−7.32 (m, 3H), 7.24−7.14 (m, 5H), 6.69 (s, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H), 5.88 (d, J = 7.5 Hz, 1H), 5.75 (d, J = 7.5 Hz, 1H), 5.57 (s, 1H), 3.56 (d, J = 16.0 Hz, 1H), 3.52 (d, J = 16.0 Hz, 1H), 1.79 (s, 2H), 1.53 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0, 169.5, 157.3, 138.9, 138.8, 138.3, 135.0, 131.5, 131.0, 128.8, 128.8, 128.7, 128.4, 126.1, 124.5, 74.4, 63.5, 51.4, 44.6, 37.4, 31.1, 28.6, 21.6. IR (film): 3319, 1662, 1370, 706 cm^{-1}. HRMS (ESI): calcd for $C_{30}H_{33}N_2O_2$ $[M + H]^+$ 453.2542, found 453.2535.

*2-((5s,7as)-3-Benzyl-5-methoxy-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-phenylacetamide (**8b**).* 95.9 mg, 41% yield. Brown solid. Mp: 158−159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49−7.47 (m, 2H), 7.36−7.33 (m, 3H), 7.22 (t, J = 7.5 Hz, 2H), 7.18−7.13 (m, 3H), 6.76−6.70 (m, 1H), 6.63 (dd, J = 7.0, 2.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.48 (s, 1H), 6.39 (d, J = 8.0 Hz, 1H), 6.20 (d, J = 8.0 Hz, 1H), 5.63 (d, J = 7.5 Hz, 1H), 5.60 (s, 1H), 3.55−3.54 (m, 2H), 3.48 (s, 3H), 2.04 (d, J = 16.0 Hz, 1H), 2.01 (d, J = 16.0 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6, 169.2, 153.8, 152.8, 140.0, 138.4, 134.8, 134.4, 134.0 129.8, 129.5, 128.9, 128.8, 128.6, 128.4, 126.3, 125.0, 116.4, 114.8, 85.1, 72.9, 63.1, 55.7, 53.7, 51.6, 34.7, 31.2, 28.5. IR (film): 3447, 3304, 1659, 1366, 705 cm^{-1}. HRMS (ESI): calcd for $C_{30}H_{33}N_2O_3$ $[M + H]^+$ 469.2491, found 469.2485.

*2-((5R,7aR)-3-Benzyl-6-fluoro-2-oxo-4,5-dihydro-5,7a-ethenoindol-1(2H)-yl)-N-tert-butyl-2-phenylacetamide (**8c**).* 120.8 mg, 53% yield. White solid. Mp: 161−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49−7.48 (m, 2H), 7.37−7.34 (m, 3H), 7.25−7.15 (m, 5H), 6.61 (d, J = 7.5 Hz, 0.4H), 6.36 (s, 0.4H), 6.34−6.31 (m, 1H), 6.16−6.13 (m, 0.6H), 5.78−5.53 (m, 1H), 4.92−4.91 (m, 1H), 3.63−3.58 (m, 1H), 3.55 (s, 2H), 2.13−2.10 (m, 1H), 1.88−1.85 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 173.6, 169.0, 163.2, 155.1, 138.5, 134.7, 134.0, 133.7, 131.8, 131.2, 129.1, 129.0, 128.9, 128.8, 128.6, 128.4, 126.3, 125.7, 122.1, 118.9, 111.1, 103.4, 103.1, 103.0, 72.0, 63.2, 63.1, 51.6, 41.4, 40.2, 40.1, 31.3, 29.7, 28.5, 27.9, 24.2. IR (film): 3309, 2966, 1651, 1551 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{30}FN_2O_2$ $[M + H]^+$ 457.2291, found 457.2277.

General Procedure for the Formation of Intermediate 5′. Isocyanide **3** (0.5 mmol) was added to a solution of allenic acid **4** (0.5 mmol), benzaldehyde **1** (0.5 mmol), and aniline **2** (0.5 mmol) in 5 mL of methanol. The mixture was stirred at room temperature for 2 h, and the progress was monitored using TLC detection. After completion of the present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (silica: 200−300; eluant: petroleum ether/ethyl acetate) to afford the desired product **5′**.

*2-Benzyl-N-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-N-phenylbuta-2,3-dienamide (**5a′**).* 179.6 mg, 82% yield. White solid. Mp: 141−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (d, J = 7.0 Hz, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.20−7.13 (m, 7H), 7.25−6.95 (m, 12H), 7.12−7.08 (m, 1H), 7.04 (t, J = 7.5 Hz, 2H), 6.82−6.64 (m, 2H), 6.07 (s, 1H), 6.07 (s, 1H), 5.80 (s, 1H), 4.28 (d, J = 12.5 Hz, 1H), 4.20 (d, J = 12.5 Hz, 1H), 3.60 (d, J = 14.5 Hz, 1H), 3.54 (d, J = 14.5 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.7, 168.6, 167.6, 141.3, 138.7, 134.9, 130.2, 129.6, 129.3, 128.2, 128.2, 128.1, 127.3, 126.5, 100.8, 68.0, 51.5, 37.3, 28.6. IR (film): 3326, 1941, 1686, 700 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{30}N_2NaO_2$ $[M + Na]^+$ 461.2205, found 461.2183.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01724.

Copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds (PDF)

X-ray crystallographic file for **5a** (CIF)

X-ray crystallographic file for **5a′** (CIF)

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Notes

The authors declare no competing financial interest.

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