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An Ugi-intramolecular Diels–Alder route to highly substituted tetrahydroepoxyisoindole carboxamides

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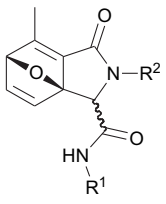
ABSTRACT

The four component Ugi reaction of 2-furaldehyde, an alkenoic acid (three examples), an isonitrile (eight examples) and an amine (eight examples) affords rapid access to a family of acetylenic furan analogues, which on heating undergo an intramolecular Diels–Alder (IMDA) reaction yielding highly substituted tricyclic lactams (17 examples) in good to excellent yields (38–72% two-steps). This Ugi-IMDA reaction proved to be highly substituent tolerant across both the isonitriles and amines examined. In one instance, with *N*,*N*-dimethylaminopropylamine, a second equivalent of alkynoic acid was required to afford a good yield of the desired tricyclic lactam.

1. Introduction

Our current medicinal chemistry programs targets novel inhibitors of protein phosphatases 1 and 2A,[1–4] and also the large GTPase, dynamin.[5–8] Within these programs we place rapid and robust access to focused compound libraries as a priority in our synthetic program. Accordingly we are keen to develop rapid entry points to rigid scaffolds that permit accurate placement of key pharmacophoric groups in previously unexplored chemical space, at least for the proteins we are examining. Our attention was thus drawn to a potential series of tricyclic lactams (**1**, Fig. 1).[9] In addition to containing a crucial oxabicyclo functionality, which we have previously noted is important in the inhibition of protein phosphatase 1 and 2A, the scaffold possesses features well suited to our medicinal chemistry program. That is, highly decorated molecules could be obtained using a simple two-step protocol affording molecules with a high level of structural rigidity. Furthermore, in the few examples thus far reported, high diastereoselectivities were noted (dr ~9:1).[9]



1

Fig. 1. The oxabicyclo[2.2.1]heptadiene scaffold.

2. Results and discussion

The value of a scaffold to a medicinal chemist is inexorably linked to its ease of synthesis and amenability to diverse functional group alterations. Previously, access to this tricyclic lactam scaffold was limited to simple substrates bearing hydrocarbon groups such as *tert*-butyl and benzyl, failing to provide the flexibility required for a medicinal chemistry scaffold.[9] Entry to the tricyclic lactam scaffold was available using a two-step procedure. First an acetylenic amide (**6**) was synthesized (Scheme 1) via an Ugi condensation of 2-furaldehyde (**5**), 2-butynoic acid (**4**), an isonitrile (**3**) and an amine (**2**).[9–15] A range of electron withdrawing, electron donating and aliphatic amines were investigated initially (see Table 1 for details). Final conversion to the oxabicyclo[2.2.1]heptadiene scaffold (**7**) via an intramolecular Diels–Alder (IMDA) reaction was effected smoothly under thermal conditions.

Pleasingly a diverse array of amines was tolerated including electron deficient anilines (**2a**–**c**), aliphatic (**2d**), functionalised (**2e**), electron donating (**2f**) and simple benzylic (**2g**) amines. Of all the amines examined, only *N*,*N*-dimethylaminopropylamine (**2h**) failed to afford significant amounts of the desired acetylenic amide Ugi product. Flash column chromatography (silica gel, ethyl

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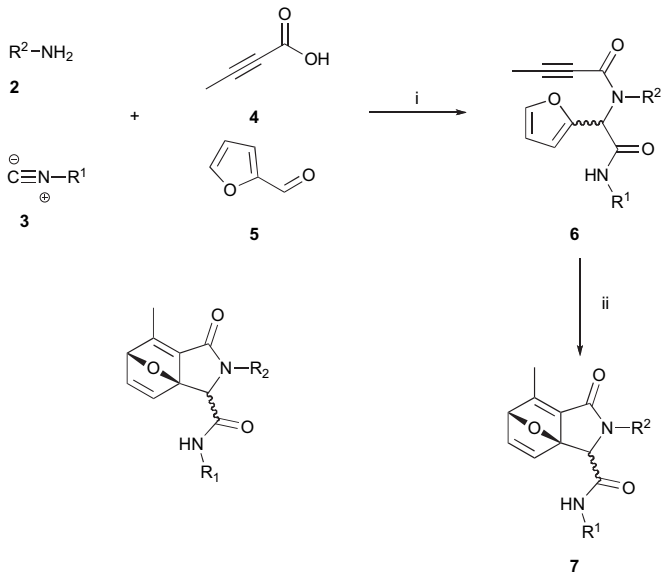
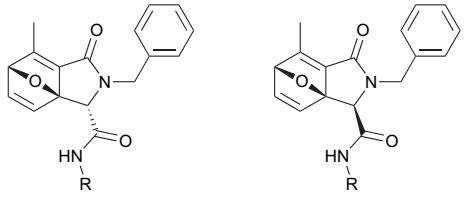


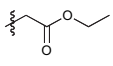
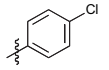
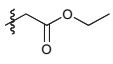
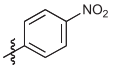
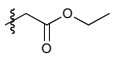
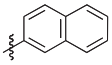
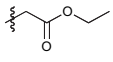
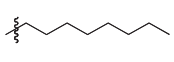
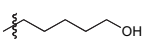
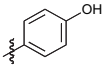
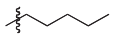
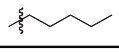
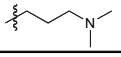
Scheme 1. Reagents and Conditions: (i) **2**, **3**, **4**, **5**, CH_3OH, room temperature, 30 min; (ii) $PhCH_3$, sealed tube 200 °C 36 h.

acetate/hexanes) allowed separation of two isomeric product that differed only in the relative orientation of the carboxamide substituent to the oxabicyclo bridgehead, either in a cis- or trans-arrangement (see Table 1).

Table 1
Oxabicyclo[2.2.1]heptadiene analogues prepared using a diverse array of amines and simple isonitriles. Two isomers were isolated and identified as either cis- or trans-configured relative to the oxabicyclo bridgehead



trans *cis*

Compound	R^1	R^2	trans:cis	Yield[a] (%)
7a			1:1.1	39
7b			1:1	38
7c			1:1.1	53
7d			1:1	63
7e			1:1.1	54
7f			1:1.1	68
7g			1:1.5	64
7h			1:1.1	72[b]

[a] Isolated yield for both.
[b] 2-Butynoic acid (2 equiv) used.

Whilst a number of mechanisms for the Ugi reaction have been proposed, there is consensus that the first step involves condensation of an aldehyde and amine, followed by protonation of the imine by a carboxylic acid to form an iminium ion (Fig. 2).[16,17] We believe that the poor yield of **7h** (17%) was a direct consequence of efficient proton scavenging (from 2-butynoic acid) by the *N*,*N*-dimethyl amino moiety of **2h**, effectively removing the key iminium intermediate from the reaction mixture. Consistent with this postulation, the inclusion of an additional equivalent of 2-butynoic acid saw a significant increase in isolated yield (17–72%) of **7h**.

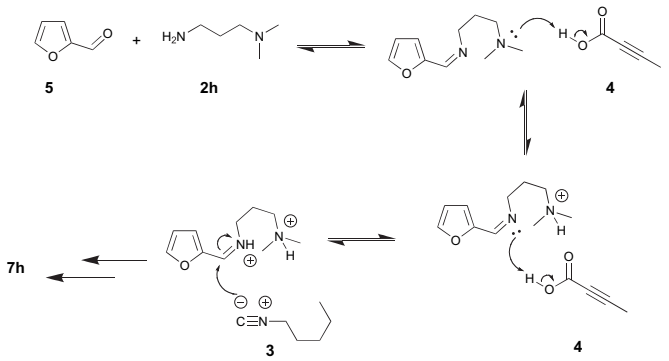
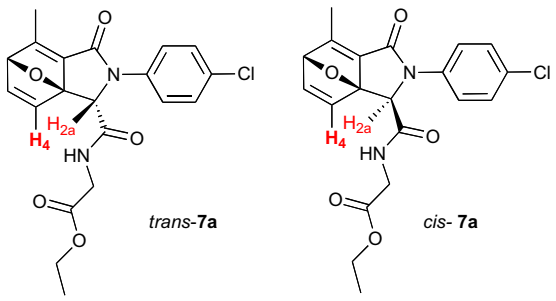


Fig. 2. Proposed mechanism of the initial steps in the Ugi reaction, and the effect of a second equivalent of 2-butynoic acid in the reaction with **2h**.

On examination of the ^1H and ^{13}C NMR spectra of our lactam analogues, we observed essentially no diastereoselectivity with isomer ratios of approximately 1:1.2, contradicting the previously reported 9:1 ratio.[9] This is not surprising as the C2′ stereocentre is remote from the tricyclic core, and as such the rigid tricyclic structure may have little or no effect on the control of the stereochemistry at this centre.

We assign the relative stereochemistry based on a combination of spectroscopic analysis (^1H and ^{13}C NMR) and molecular modelling. In the NMR analysis (Table 2), the chemical shift of the peaks assigned to the carboxamide side chain proton, the C2a carbon and proton and the C4 carbon and proton of **7a** differed significantly depending on the stereochemistry at that centre. While the change in shift noted in the ^{13}C NMR is relatively small, the corresponding ^1H NMR shift is substantial with shift of 0.22 ppm noted for both H_{2a} and H_4 signal. The amide proton also undergoes a large shift, in this instance of 0.20 ppm. These chemical shifts are consistent with

Table 2
NMR peak shifts of protons **2a** and **4** and amide NH of *cis*- and *trans*-**7a**



trans-**7a** *cis*- **7a**

Proton	*trans*-**7a** ^1H δ (ppm)	*cis*-**7a** ^1H δ (ppm)	Carbon	*trans*-**7a** ^{13}C δ (ppm)	*cis*-**7a** ^{13}C δ (ppm)
2a	5.29	5.51	2a	62.9	62.5
4	7.19	7.41	4	143.9	145.4
Amide NH	9.03	8.83			

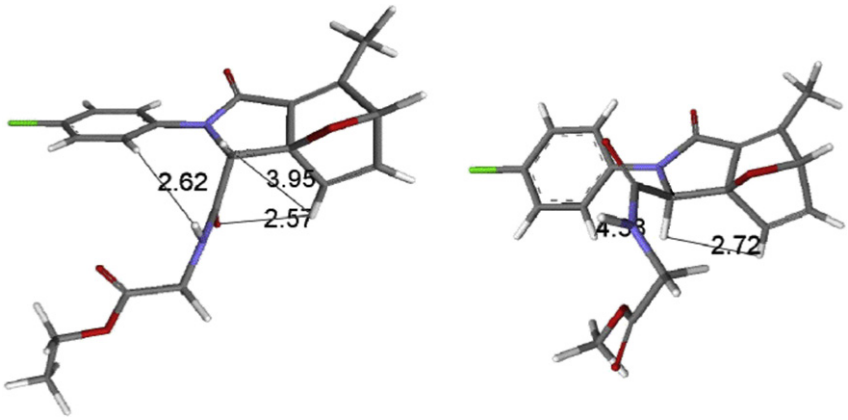
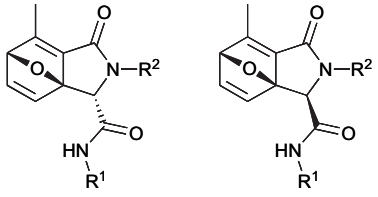


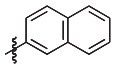
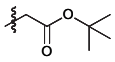
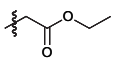
Fig. 3. Three dimensional representation of the two isomers of **7a** isolated in this work. Image (a) displays the equilibrium geometry of *cis*-**7a** and image (b) displays the equilibrium geometry of *trans*-**7a**. Both (a) and (b) were calculated using the Spartan molecular modelling suite at the AM1 level of theory. Distances highlighted between atoms are in Å.

the changes in deshielding effected by the 4-chlorophenyl group depending on the molecule adopting a cis-, or trans-orientation of the carboximide substituent relative to the oxabicyclo bridgehead. This is illustrated in Fig. 3, where the energy minimized molecular modelled structure of cis-**7a** places the carboxamide side chain in a conformation in which the amide proton was removed from the 4-chlorophenyl group by approximately 4.5 Å. In contrast, modelling of the trans isomer showed that the carboxamide amide proton adopted a conformation approximately 2.5 Å removed from the aromatic moiety thus deshielding the proton. The variations observed in the ^{1}H and ^{13}C NMR spectra of **7a** isomers were consistently observed for all analogues synthesized, consequently the relative configuration of the carboxamide side chain of the other adducts was assigned by analogy. Given the poor selectivity noted in these additions we did not pursue a single crystal structure determination.

Table 3
Oxabicyclo[2.2.1]heptadiene analogues prepared using an array of isonitriles



trans *cis*

Compound	R	trans:cis	Yield[a] (%)
8a		1:1.2	53
8b		1:1.7	53
8c		1:1.7	60
8d		1:1.1	59
8e		1:1.1	56
8f		1:1.2	52
8g		1:1.4	47

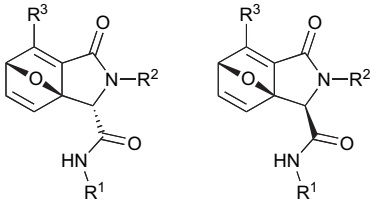
[a] Isolated yield for both steps.

We next examined the potential scope of isonitrile addition using aromatic (**8a** and **8h**), acyclic and cyclic aliphatic (**8b**, **8c** and **8f**) isonitriles and isonitrile esters (**8d** and **8e**). The desired oxabicyclo[2.2.1]heptadiene analogues were accessed as in Scheme 1 (see Table 3 for details).

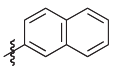
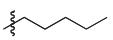
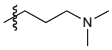
As can be seen from the data presented in Table 3, all modified isonitriles were smoothly accommodated in the two-step procedure affording the desired tricyclic lactams **8a**–**g** in modest to good yields (47–60%, two-steps). We also note that there was no change in the observed diastereoselectivity.

Presently, libraries of commercially available functionalised acetylenic dienophiles are limited, restricting investigations to 2-hexynoic acid and 2-octynoic acid. As illustrated in Table 4, both acids were tolerated affording the desired analogues (**9a** and **9b**). Furthermore, 3-phenyl-2-propynoic acid was reported to be tolerated, indicating that the C7 region of the scaffold is amenable to a number of structural variations.[9]

Table 4
Oxabicyclo[2.2.1]heptadiene analogues prepared using 2-hexynoic and 2-octynoic acid



trans *cis*

Compound	R^1	R^2	R^3	trans:cis	Yield %[a]
9a				1:1.2	53
9b				1:1.7	53

[a] Isolated yield for both steps.

3. Conclusions

The Ugi condensation of 2-furaldehyde, 2-butynoic acid, an isonitrile and an amine affords highly substituted acetylenic furan analogues, which, on heating, undergo an intramolecular Diels–Alder reaction to highly substituted tricyclic lactams. This sequence of reactions was highly substituent tolerant affording good yields of tricyclic lactams with a variety of isonitriles:aromatic,

acyclic and cyclic aliphatic and isonitrile esters; as well as a wide range of substituted amines—electron deficient anilines, aliphatic functionalised, electron donating and simple benzylic. Whilst the range of commercially available acetylenic dienophiles is limited, both 2-hexynoic and 2-octynoic acid were well tolerated.

In cases where the amine bears an additional amino moiety, e.g., *N*,*N*-dimethylaminopropylamine, an additional equivalent of the acetylenic acid is required to off set the proton scavenging ability of the dimethyl amino moiety. This is in keeping with the accepted mechanism of the initial Ugi reaction.

4. Experimental

4.1. General experimental

All starting materials were purchased from Aldrich Chemical Co. and Lancaster Synthesis. Solvents were bulk and distilled from glass prior to use. Reaction progress was monitored by TLC, on aluminium plates coated with silica gel with fluorescent indicator (Merck 60 F_{254}) and flash chromatography was conducted utilizing SNAP Biotage KP-SIL columns. ^{1}H and ^{13}C spectra were recorded on a Bruker Advance AMX 300 MHz spectrometer at 300.13 and 75.48 MHz, respectively. Chemical shifts are relative to TMS as internal standard. All compounds returned satisfactory mass spectra and were obtained using a micromass liquid chromatography *Z*-path (LCZ) platform spectrometer. Mass to charge ratios (*m*/*z*) are stated with their peak intensity as a percentage in parentheses. All mass spectra were obtained via the ES method thus fragmentation patterns were not observed. The University of Wollongong, Australia, Biomolecular Mass Spectrometry Laboratory, analyzed samples for HRMS. The spectra were run on a micromass QTof2 spectrometer using polyethylene glycol or polypropylene glycol as the internal standard.

Note: The vast majority of isonitriles are associated with a pungent stench thus preparation of the Ugi acetylenic amides was conducted in a fume hood and reactions proceeded under an atmosphere of nitrogen.

5. Chemistry

5.1. General procedure

A solution of amine (1 equiv, 1.2 mmol), 2-furaldehyde (1 equiv, 1.2 mmol) and anhydrous MeOH (10.0 mL) was stirred at room temperature for 0.5 h. 2-Butynoic acid (1.2 equiv, 1.4 mmol) was added and the resulting mixture was stirred for 0.5 h prior to the addition of an isocyanide (1 equiv, 1.2 mmol). The mixture was stirred at room temperature for 2 h, quenched with 1 M NaOH (100 mL), extracted with CH_2Cl_2 (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo. A sealed tube was charged with the crude mixture, toluene (80 mL), degassed and heated (250 °C) for 36 h. The resulting mixture was concentrated in vacuo and subjected to flash silica gel column chromatography.

*5.1.1. (3S,3aS,6R)-2-(4-Chlorophenyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7a**) and (3R,3aS,6R)-2-(4-chlorophenyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7a**).* Synthesized utilizing the general procedure, 4-chloroaniline (0.15 g, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol), and ethyl isocyanoacetate (0.13 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (4:1 EtOAc/hexanes) to afford *trans*-**7a** (0.09 g, 19%) as an off-white solid (mp 155–156 °C). HRMS calculated for: $C_{20}H_{19}ClN_2O_5$, 402.09825 found 402.09828. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.03 (1H, t, *J*=5.6 Hz), 7.58 (2H, d, *J*=9.0 Hz), 7.42 (2H, d, *J*=8.9 Hz), 7.24 (1H, dd, *J*=5.4, 2.1 Hz), 7.19 (1H, d, *J*=5.4 Hz), 5.55 (1H, d, *J*=2.0 Hz), 5.29 (3H, s), 4.07 (2H, q, *J*=7.1 Hz) 3.86 (2H, qd, *J*=17.4, 5.7 Hz), 2.19 (3H, s), 1.14 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.1, 167.5, 162.7, 161.8, 142.9, 142.4, 141.8, 137.2, 129.0, 128.4, 122.9, 92.0, 91.1, 62.9, 60.5, 40.8, 14.0, 13.9. IR (KBr) ν_{max}/cm^{-1} 3280 (NH), 3091, 2995 (CH), 1760 (CO), 1710 (CO), 1673 (CO), 824 (CCl).

Further elution (4:1 EtOAc/hexanes) afforded *cis*-**7a** (0.10 g, 19%) as a light brown solid (mp 165–167 °C). HRMS calculated for: $C_{20}H_{19}ClN_2O_5$, 402.09825 found 402.09833. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.83 (1H, t, *J*=5.3 Hz), 7.67 (2H, d, *J*=8.9 Hz), 7.43 (2H, d, *J*=8.9 Hz), 7.41 (1H, d, *J*=4.5 Hz), 7.23 (1H, dd, *J*=5.0, 1.7 Hz), 5.51 (1H, s), 5.51 (1H, d, *J*=1.3 Hz), 4.07 (2H, q, *J*=7.1 Hz), 3.84 (2H, dq, *J*=17.4, 5.7 Hz), 2.14 (3H, s), 1.14 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.2, 165.5, 162.5, 160.1, 145.4, 142.4, 142.0, 138.1, 128.5, 128.4, 121.8, 90.7, 90.4, 62.5, 60.4, 40.8, 14.0, 13.9. IR (KBr) ν_{max}/cm^{-1} 3301 (NH), 3098, 2995 (CH), 1758 (CO), 1691 (CO), 1672 (CO), 834 (CCl).

*5.1.2. (3S,3aS,6R)-2-(4-Nitrophenyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7b**) and (3R,3aS,6R)-2-(4-nitrophenyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7b**).* Synthesized utilizing the general procedure, 4-nitroaniline (0.16 g, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and ethyl isocyanoacetate (0.13 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:2 EtOAc/hexanes) to afford *cis*-**7b** (0.09 g, 18%) as an off-white solid (mp 141–143 °C). HRMS calculated for: $C_{20}H_{19}ClN_3O_7$, 413.12230 found 413.12239. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.18 (1H, t, *J*=5.7 Hz), 8.24 (2H, d, *J*=9.1 Hz), 7.83 (2H, d, *J*=9.1 Hz), 7.26 (1H, dd, *J*=5.4, 1.8 Hz), 7.20 (1H, d, *J*=5.4 Hz), 5.59 (1H, d, *J*=1.50 Hz), 5.43 (1H, s), 4.05 (2H, q, *J*=7.0 Hz), 3.87 (2H, qd, *J*=17.6, 5.7 Hz), 2.22 (3H, s), 1.13 (3H, t, *J*=7.0 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.2, 167.3, 165.2, 162.1, 144.3, 143.1, 142.8, 141.9, 141.8, 124.3, 120.3, 91.8, 91.1, 62.8, 60.6, 40.8, 14.2, 13.9. IR (KBr) ν_{max}/cm^{-1} 3284 (NH), 3102, 2998, 2937 (CH), 1751 (CO), 1711 (CO), 1656 (CO), 1514, 1325 (NO).

Further elution (4:1 EtOAc/hexanes) afforded *trans*-**7b** (0.10 g, 20%) as a light brown solid (mp 158–161 °C). HRMS calculated for: $C_{20}H_{19}ClN_3O_7$, 413.12230 found 413.12232. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.95 (1H, t, *J*=5.7 Hz), 8.24 (2H, d, *J*=9.2 Hz), 7.91 (2H, d, *J*=9.2 Hz), 7.41 (1H, d, *J*=5.2 Hz), 7.23 (1H, dd, *J*=5.2, 1.9 Hz), 5.67 (1H, s), 5.52 (1H, d, *J*=1.9 Hz), 4.07 (2H, q, *J*=7.1 Hz), 3.86 (1H, qd, *J*=17.4, 5.8 Hz), 2.18 (3H, s), 1.14 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.2, 165.2, 162.8, 145.4, 145.1, 142.7, 142.5, 142.0, 141.7, 124.3, 119.1, 90.8, 90.1, 62.3, 60.5, 40.8, 14.2, 13.9. IR (KBr) ν_{max}/cm^{-1} 3339 (NH), 3200, 3099, 2898 (CH), 1719 (CO), 1595, 1310 (NO).

*5.1.3. (3S,3aS,6R)-2-(2-Naphthyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7c**) and (3R,3aS,6R)-2-(2-naphthyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7c**).* Synthesized utilizing the general procedure, 1-aminonaphthalene (0.19 g, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and ethyl isocyanoacetate (0.13 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:1 EtOAc/hexanes) to afford *cis*-**7c** (0.13 g, 26%) as a brown solid (mp 152–153 °C). HRMS calculated for: $C_{24}H_{22}N_2O_5$, 418.15287 found 418.15292. ^{1}H NMR (300 MHz) (acetone-d_6): δ 7.92 (4H, m), 7.61 (1H, t, *J*=5.3 Hz), 7.52 (3H, m), 7.38 (1H, d, *J*=5.4 Hz), 7.25 (1H, dd, *J*=5.4, 2.1 Hz), 5.54 (1H, d, *J*=2.1 Hz), 4.18 (2H, qd, *J*=17.8, 4.9 Hz), 4.06 (1H, s), 3.41 (2H, q, *J*=7.1 Hz), 2.76 (3H, s), 1.25 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 178.3168.3, 167.3, 160.8, 142.8,

142.5, 141.2141.0, 135.7, 134.9, 134.0, 127.9, 127.8, 127.7, 127.7, 127.9, 125.6, 124.9, 91.2, 65.5, 60.0, 40.4, 12.9, 12.7. IR (KBr) ν_{max}/cm^{-1} 3283 (NH), 3076, 2982 (CH), 1744 (CO), 1690 (CO), 1675 (CO).

Further elution (4:1 EtOAc/hexanes) afforded *trans*-**7c** (0.14 g, 28%) as a light brown solid (mp 162–163 °C). HRMS calculated for: $C_{24}H_{22}N_2O_5$, 418.15287 found 418.15299. ^{1}H NMR (300 MHz) (acetone-d_6): δ 7.83 (3H, m), 7.78 (1H, d, J=8.3 Hz), 7.63 (1H, d, J=7.3 Hz), 7.50 (1H, t, J=5.3 Hz), 7.46–7.34 (3H, m), 7.19 (1H, dd, J=5.2, 2.1 Hz), 5.33 (1H, d, J=2.1 Hz), 5.28 (1H, s), 3.90 (2H, q, J=7.1 Hz), 3.77 (2H, qd, J=17.8, 4.9 Hz), 2.02 (3H, s), 0.98 (3H, t, J=7.1 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 168.5, 165.5, 162.8, 157.6, 145.0, 142.4, 142.2, 141.9, 141.6, 134.0, 129.5, 127.6, 126.5, 126.3, 126.0, 125.5, 125.0, 91.8, 90.9, 65.3, 59.9, 40.6, 12.9, 12.7. IR (KBr) ν_{max}/cm^{-1} 3209 (NH), 3101, 3000 (CH), 1749 (CO), 1690 (CO), 1666 (CO).

*5.1.4. (3S,3aS,6R)-2-(Octyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7d**) and (3R,3aS,6R)-2-(octyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7d**).* Synthesized utilizing the general procedure, *n*-octylamine (0.19 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and ethyl isocyanoacetate (0.13 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:2 EtOAc/hexanes) to afford *cis*-**7d** (0.15 g, 31%) as an off-white solid (mp 72–73 °C). HRMS calculated for: $C_{22}H_{32}N_2O_5$, 404.23112 found 404.23119. ^{1}H NMR (300 MHz) (acetone-d_6): δ 8.44 (1H, t, J=5.2 Hz), 7.10 (1H, d, J=5.5 Hz), 7.02 (1H, dd, J=5.5, 2.1 Hz), 5.27 (1H, d, J=2.1 Hz), 5.22 (1H, s), 4.04 (2H, m), 4.01–3.92 (2H, m), 3.66 (2H, m), 2.87 (2H, m), 2.00 (3H, s), 1.54–1.31 (8H, m), 1.25–1.08 (4H, m), 0.75 (3H, t, J=6.7 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 168.7, 167.6, 157.8, 142.6, 141.2, 136.7, 130.6, 91.0, 62.0, 60.1, 41.0, 40.4, 31.1, 28.4, 26.4, 26.2, 26.1, 25.8, 21.8, 13.1, 12.9, 12.5. IR (KBr) ν_{max}/cm^{-1} 3417 (NH), 1651 (CO).

Further elution (4:1 EtOAc/hexanes) afforded *trans*-**7d** (0.16 g, 32%) as a brown solid (mp 79–81 °C). HRMS calculated for: $C_{22}H_{32}N_2O_5$, 404.23112 found 404.23120. ^{1}H NMR (300 MHz) (acetone-d_6): δ 7.64 (1H, t, J=5.4 Hz), 7.21 (1H, dd, J=5.5, 2.1 Hz), 7.0 (1H, d, J=5.5 Hz) 5.36 (1H, d, J=2.1 Hz), 4.99 (1H, s), 4.14 (1H, q, J=7.1 Hz), 3.95 (2H, m), 3.79 (2H, qd, J=14.0, 8.0 Hz), 3.00 (2H, ddd, J=13.7, 8.1, 5.4 Hz), 2.07 (3H, s), 1.60 (8H, m), 1.31 (4H, m), 1.24 (2H, m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 168.7, 165.3, 162.6, 155.9, 144.8, 141.9, 91.3, 90.8, 61.4, 60.0, 41.2, 40.4, 40.3, 31.1, 28.5, 28.4, 26.5, 26.2, 21.8, 13.0, 12.9, 12.5. IR (KBr) ν_{max}/cm^{-1} 3291 (NH), 3095, 2925, 2851 (CH), 1690 (CO), 1653 (CO).

*5.1.5. (3S,3aS,6R)-2-(5-Pentanol)-1,2,3,6-tetrahydro-7-propyl-1-oxo-N-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (S-**7e**) and (3R,3aS,6R)-2-(5-pentanol)-1,2,3,6-tetrahydro-7-propyl-1-oxo-N-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (R-**7e**).* Synthesized utilizing the general procedure, 5-pentanol (0.12 g, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol),and methyl isocyanoacetate (0.11 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (4:1 EtOAc/hexanes) to afford *S*-**7e** (0.13 g, 26%) as an off-white solid (mp 76–78 °C). HRMS calculated for: $C_{19}H_{26}N_2O_6$, 378.17909 found 378.17901. ^{1}H NMR (300 MHz) (acetone-d_6): δ 8.31 (1H, t, J=5.8 Hz), 7.08 (1H, d, J=5.4 Hz), 7.03 (1H, dd, J=5.4, 2.0 Hz), 5.29 (1H, d, J=2.0 Hz), 4.46 (1H, s), 4.07–3.87 (1H, m), 3.74–3.60 (1H, m), 3.57 (3H, s), 3.41 (1H, t, J=6.4 Hz), 2.89 (1H, ddd, J=13.7, 8.3, 5.2 Hz), 2.44 (1H, br s), 1.96 (3H, s), 1.49–1.32 (6H, m), 1.22 (2H, m); ^{13}C NMR (75 MHz) (acetone-d_6): δ 171.6, 170.1, 165.2, 160.5, 145.0, 144.9, 143.6, 95.2, 93.4, 64.4, 63.1, 53.3, 43.4, 42.5, 34.0, 28.3, 24.9, 15.0. IR (KBr) ν_{max}/cm^{-1} 3275 (NH), 1697 (CO), 1651 (CO).

Further elution (100%, EtOAc) afforded *R*-**7e** (0.14 g, 28%) as a brown solid (mp 85–87 °C). HRMS calculated for: $C_{19}H_{26}N_2O_6$, 378.17909 found 378.17916. ^{1}H NMR (300 MHz) (acetone-d_6): δ 7.55 (1H, t, J=5.1 Hz), 7.09 (1H, d, J=5.3 Hz), 7.06 (1H, dd, J=5.3, 1.9 Hz), 5.23 (1H, d, J=1.9 Hz), 4.87 (1H, s), 3.92–3.75 (2H, m), 3.66 (1H, td, J=14.0, 7.9 Hz), 3.55 (3H, s), 3.42 (2H, t, J=6.3 Hz), 2.88 (1H, ddd, J=13.6, 7.8, 5.5 Hz), 2.66 (1H, br s), 1.95 (3H, s), 1.59–1.35 (4H, m), 1.26 (2H, m); ^{13}C NMR (75 MHz) (acetone-d_6): δ 171.7, 167.9, 165.2, 158.3, 147.3, 145.1, 144.4, 93.8, 93.3, 63.8, 63.2, 53.2, 43.6, 42.6, 34.3, 28.8, 25.0, 15.0. IR (KBr) ν_{max}/cm^{-1} 3242 (NH), 1693 (CO), 1655 (CO).

*5.1.6. (3S,3aS,6R)-2-(4-Phenol)-1,2,3,6-tetrahydro-7-propyl-1-oxo-N-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7f**) and (3R,3aS,6R)-2-(4-phenol)-1,2,3,6-tetrahydro-7-propyl-1-oxo-N-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7f**).* Synthesized utilizing the general procedure, 4-aminophenol (0.13 g, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and methyl isocyanoacetate (0.11 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (4:1 EtOAc/hexanes) to afford *cis*-**7f** (0.15 g, 34%) as an off-white solid (mp 147–148 °C). HRMS calculated for: $C_{19}H_{18}N_2O_6$, 370.11649 found 370.11659. ^{1}H NMR (300 MHz) (acetone-d_6): δ 9.32 (1H, br s) 9.03 (1H, t, J=5.6 Hz), 7.58 (2H, d, J=9.0 Hz), 7.42 (2H, d, J=8.9 Hz), 7.24 (1H, dd, J=5.4, 2.1 Hz), 7.19 (1H, d, J=5.4 Hz), 5.55 (1H, d, J=2.0 Hz), 5.29 (3H, s), 3.75 (2H, qd, J=17.4, 5.7 Hz), 3.51 (3H, s), 3.35 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.1, 167.5, 162.7, 161.8, 142.9, 142.4, 141.8, 137.2, 129.0, 128.4, 122.9, 92.0, 91.1, 62.9, 60.5, 40.8, 14.0, 13.9. IR (KBr) ν_{max}/cm^{-1} 3394 (NH), 3286 (OH), 2968 (CH), 1742 (CO), 1707 (CO), 1653 (CO).

Further elution (100% EtOAc) afforded *trans*-**7f** (0.16 g, 36%) as an off-white solid (mp 157–158 °C). HRMS calculated for: $C_{19}H_{18}N_2O_6$, 370.11649 found 370.11650. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.32 (1H br s), 8.83 (1H, t, J=5.3 Hz), 7.67 (2H, d, J=8.9 Hz), 7.43 (2H, d, J=8.9 Hz), 7.41 (1H, d, J=4.5 Hz), 7.23 (1H, dd, J=5.0, 1.7 Hz), 5.51 (1H, s), 5.49 (1H, d, J=1.3 Hz), 3.74 (2H, dq, J=17.4, 5.7 Hz), 3.51 (3H, s), 3.35 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 168.8, 165.4, 162.6, 156.0, 144.9, 142.6, 141.9, 122.7, 90.8, 61.2, 60.7, 60.0, 41.0, 40.3, 31.8, 26.7, 22.4, 13.0, 12.6. IR (KBr) ν_{max}/cm^{-1} 3394 (NH), 3286 (OH), 2968 (CH), 1742 (CO), 1707 (CO), 1653 (CO).

*5.1.7. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(pentyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7g**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(pentyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7g**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and 1-pentyl isocyanide (0.15 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (4:1 EtOAc/hexanes) to afford *cis*-**7g** (0.13 g, 30%) as an off-white solid (mp 76–77 °C). HRMS calculated for: $C_{22}H_{26}N_2O_3$, 366.19434 found 366.19438. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 7.57–6.85 (3H, m), 7.50–6.78 (1H, m), 7.00 (1H, dd, J=5.5, 1.9 Hz), 6.96 (1H, d, J=5.4 Hz), 6.63 (1H, t, J=5.7 Hz), 5.17 (1H, d, J=14.9 Hz), 5.17 (1H, d, J=1.8 Hz), 4.08 (3H, s), 3.93 (1H, d, J=14.9 Hz), 3.20 (2H, dp, J=13.1, 7.0 Hz), 2.11 (3H, s), 1.42 (2H, td, J=14.2, 7.2, Hz), 1.35–1.13 (4H, m), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (300 MHz) ($CDCl_3$): δ 166.4, 163.1, 158.1, 142.4, 142.0, 141.1, 135.0, 128.2, 128.1, 127.3, 92.9, 91.2, 61.4, 45.1, 39.1, 28.5, 28.4, 22.0, 13.7, 13.4. IR (KBr) ν_{max}/cm^{-1} 3299 (NH), 3089, 2956, 2871 (CH), 1693 (CO), 1666 (CO).

Further elution (4:1 EtOAc/hexanes) afforded *trans*-**7g** (0.15 g, 34%) as an off-white solid (mp 82–84 °C). HRMS calculated for: $C_{22}H_{26}N_2O_3$, 366.19434 found 366.19430. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.07 (1H, t, J=5.5 Hz), 7.40–7.26 (2H, m), 7.19 (1H, dd, J=5.6, 1.9 Hz), 7.08 (1H, d, J=5.3 Hz), 5.42 (1H, d, J=2.0 Hz), 5.02 (1H, d, J=15.4 Hz), 4.53 (1H, s), 3.72 (1H, d, J=15.4 Hz), 3.34 (3H, s), 3.21–2.83 (2H, m), 2.06 (3H, s), 1.43–1.28 (2H, m), 1.28–1.12 (4H,

m), 0.84 (3H, t, J=6.8 Hz); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 164.2, 163.2, 156.9, 145.3, 142.54, 142.51, 136.3, 128.7, 127.5, 127.4, 91.4, 90.7, 60.6, 44.8, 38.6, 28.5, 28.3, 21.7, 13.83, 13.78. IR (KBr) ν_{max}/cm^{-1} 3274 (NH), 3098, 2924, 2865 (CH), 1682 (CO), 1654 (CO).

*5.1.8. (3S,3aS,6R)-2-(4-N,N-Dimethylaminopropyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(pentyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**7h**) and (3R,3aS,6R)-2-(4-N,N-dimethylaminopropyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(pentyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**7h**).* Synthesized utilizing the general procedure, 3-(dimethylamino)-1-propylamine (0.30 mL, 2.4 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.10 g, 1.2 mmol) and 1-pentyl isocyanide (0.15 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (95:5 EtOAc/Et$_3$N) to afford *cis*-**7h** (0.15 g, 34%) as a yellow oil. HRMS calculated for: $C_{20}H_{31}N_3O_3$, 361.23654 found 361.23658. ^{1}H NMR (300 MHz) (acetone-d_6): δ 8.08 (1H, t, J=5.4 Hz), 6.51 (1H, dd, J=5.8, 1.8 Hz), 6.34 (1H, d, J=5.8 Hz), 5.22 (2H, dd, J=10.6, 1.1 Hz), 5.08 (1H, d, J=0.8 Hz), 4.38 (1H, s), 3.63–3.45 (1H, m), 3.32 (2H, q, J=6.8 Hz), 3.05 (1H, ddd, J=14.2, 7.9, 6.6 Hz), 2.21 (1H, ddd, J=13.4, 7.0, 5.5 Hz), 2.12 (7H, s), 1.77–1.51 (5H, m), 1.41–1.24 (5H, m), 0.89 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 170.8, 167.0, 141.6, 135.7, 132.3, 106.8, 91.2, 82.4, 63.0, 55.8, 50.2, 44.2, 39.6, 38.7, 28.5, 28.4, 24.7, 21.6, 13.0. IR (KBr) ν_{max}/cm^{-1} 3299 (NH), 3082, 2933, 2863 (CH), 1681 (CO), 1556 (CO).

Further elution (95:5 EtOAc/Et$_3$N) to afforded *trans*-**7h** (0.16 g, 37%) as a white solid (mp 67–68 °C). HRMS calculated for: $C_{20}H_{31}N_3O_3$, 361.23654 found 361.23660. ^{1}H NMR (300 MHz) (acetone-d_6): δ 7.12 (1H, t, J=5.4 Hz), 6.65 (1H, d, J=5.7 Hz), 6.48 (1H, dd, J=5.7, 1.8 Hz), 5.22 (2H, dd, J=10.6, 1.1 Hz), 5.07 (1H, d, J=0.8 Hz), 4.81 (1H, s), 3.75 (1H, ddd, J=14.2, 8.5, 7.2 Hz), 3.23 (2H, m), 3.08 (1H, ddd, J=13.9, 8.4, 5.7 Hz), 2.22 (2H, ddd, J=12.2, 9.9, 5.4 Hz), 2.13 (7H, s), 1.82–1.57 (2H, m), 1.51 (2H, m), 1.30 (4H, m), 0.87 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 170.7, 164.7, 141.6, 135.3, 133.5, 106.3, 90.3, 82.4, 61.4, 56.4, 50.9, 44.2, 39.7, 38.4, 38.2, 28.7, 24.1, 21.5, 12.9. IR (KBr) ν_{max}/cm^{-1} 3303 (NH), 3100, 2949, 2818 (CH), 1681 (CO), 1556 (CO).

*5.1.9. (3S,3aS,6R)-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-naphthyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8a**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-naphthyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8a**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and 2-naphthyl isocyanide (0.18 g, 1.2 mmol). The resulting crude material was purified via flash silica gel chromatography (1:1 EtOAC/hexanes) to afford *cis*-**8a** (0.13 g, 25%) as an off-white solid (mp 163–165 °C). HRMS calculated for: $C_{27}H_{22}N_2O_3$, 422.16304 found 422.16311. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 10.37 (1H, s), 7.85–7.78 (2H, m), 7.52–7.19 (12H, m), 5.44 (1H, d, J=1.8 Hz,), 5.09 (1H, d, J=15.4 Hz), 4.87 (1H, s), 3.91 (1H, d, J=15.4 Hz), 2.10 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 163.8, 163.3, 157.1, 145.0, 142.6, 142.2, 136.4, 136.0, 133.2, 129.8, 128.7, 128.3, 127.6, 127.3, 127.2, 126.4, 124.7, 119.7, 115.4, 91.6, 90.9, 61.1, 59.6, 45.0, 13.8. IR (KBr) ν_{max}/cm^{-1} 3294 (NH), 3101, 3059, 2914 (CH), 1693 (CO), 1663 (CO).

Further elution (1:1 EtOAC/hexanes) afforded *trans*-**8a** (0.15 g, 28%) as an off-white solid (mp 161–162 °C). HRMS calculated for: $C_{27}H_{22}N_2O_3$, 422.16304 found 422.16315. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.22 (1H, s), 7.85–7.78 (2H, m), 7.52–7.19 (12H, m), 5.44 (1H, d, J=1.8 Hz), 5.09 (1H, d, J=15.4 Hz), 4.87 (1H, s), 3.91 (1H, d, J=15.4 Hz), 2.10 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 163.8, 163.3, 157.1, 145.0, 142.6, 142.2, 136.4, 136.0, 133.2, 129.8, 128.7, 128.3, 127.6, 127.3, 127.2, 126.4, 124.7, 119.7, 115.4, 91.6, 90.9, 61.1, 59.6, 45.0, 13.8. IR (KBr) ν_{max}/cm^{-1} 3252 (NH), 3103, 3063, 2986 (CH), 1697 (CO), 1655 (CO).

*5.1.10. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-tert-butoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8b**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-tert-butoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8b**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and *tert*-butyl isocyanoacetate (0.17 mL, 1.2 mmol). The resulting crude material was purified via flash silica gel chromatography (2:1 EtOAc/hexanes) to afford *cis*-**8b** (0.12 g, 24%) as an off-white solid (mp 193–194 °C). HRMS calculated for: $C_{23}H_{26}N_2O_5$, 410.18417 found 410.18418. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.04 (1H, t, J=5.5 Hz), 7.51–7.27 (3H, m), 7.21 (3H, m), 7.07 (1H, d, J=5.4 Hz), 5.45 (1H, d, J=1.8 Hz), 5.06 (1H, d, J=15.0 Hz), 4.20 (1H, s), 3.89 (2H, m), 3.81 (1H, d, J=15.0 Hz), 2.13 (3H, s), 1.44 (9H, s); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 168.5, 167.5, 162.6, 159.5, 142.7, 142.4, 142.0, 135.9, 128.7, 128.0, 127.5, 92.8, 91.0, 80.9, 61.2, 44.7, 41.6, 27.6, 13.9. IR (KBr) ν_{max}/cm^{-1} 3250 (NH), 3069, 2974, 2936 (CH), 1740 (CO), 1690 (CO), 1663 (CO).

Further elution (9:1 EtOAc/hexanes) afforded *trans*-**8b** (0.14 g, 28%) as an off-white solid (mp 169–170 °C). HRMS calculated for: $C_{23}H_{26}N_2O_5$, 410.18417 found 410.18422. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.57 (1H, t, J=5.6 Hz), 7.48–7.27 (3H, m), 7.23 (2H, d, J=7.2 Hz), 7.19 (1H, dd, J=7.3, 1.73 Hz), 7.10 (1H, d, J=5.2 Hz), 5.44 (1H, d, J=1.8 Hz), 5.06 (1H, d, J=15.3 Hz), 4.68 (1H, s), 3.76 (1H, d, J=15.3 Hz), 3.88–3.59 (2H, m), 2.08 (3H, s), 1.42 (9H, s); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 168.5, 165.1, 163.0, 157.4, 145.4, 142.4, 142.3, 136.3, 128.7, 127.6, 127.4, 91.3, 90.7, 80.7, 60.5, 44.7, 41.6, 27.6, 13.8. IR (KBr) ν_{max}/cm^{-1} 3226 (NH), 3052, 2979, 2931 (CH), 1750 (CO), 1695 (CO), 1648 (CO).

*5.1.11. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(cyclohexyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8c**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(cyclohexyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8c**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and cyclohexyl isocyanide (0.15 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:2 EtOAc/hexanes) to afford *cis*-**8c** (0.63 g, 27%) as an off-white solid (mp 178–179 °C). HRMS calculated for: $C_{23}H_{26}N_2O_3$, 378.19434 found 378.19436. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 7.46–7.16 (5H, m), 7.08 (1H, dd, J=5.4, 1.8 Hz), 7.02 (1H, d, J=5.5 Hz), 5.65 (1H, s), 5.28 (2H, d, J=15.2 Hz), 4.04 (1H, d, J=15.2 Hz), 4.01 (1H, s), 3.86 (1H, m), 2.20 (3H, s), 2.02–1.80 (2H, m), 1.68 (2H, m), 1.50–1.27 (4H, m), 1.11 (2H, m); ^{13}C NMR (300 MHz) ($CDCl_3$): δ 165.3, 163.1, 158.1, 142.3, 142.1, 141.2, 135.1, 128.3, 128.2, 127.3, 92.9, 91.3, 61.6, 48.1, 45.3, 32.5, 32.4, 24.8, 24.3, 24.2, 13.8. IR (KBr) ν_{max}/cm^{-1} 3251 (NH), 3093, 2914, 2851 (CH), 1698 (CO), 1654 (CO).

Further elution (2:1 EtOAc/hexanes) afforded *trans*-**8c** (0.74 g, 33%) as a brown solid (mp 209–211 °C); HRMS calculated for:- $C_{23}H_{26}N_2O_3$, 378.19434 found 378.19437. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 7.98 (1H, d, J=7.7 Hz), 7.34 (3H, m), 7.20 (3H, d, J=7.0 Hz), 7.08 (1H, d, J=5.2 Hz), 5.43 (1H, d, J=5.5 Hz), 5.01 (1H, d, J=15.3 Hz), 4.55 (1H, s), 3.72 (1H, d, J=15.3 Hz), 3.61–3.41 (1H, m), 2.07 (3H, s), 1.84–1.41 (6H, m), 1.15 (4H, m); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 163.3, 156.7, 145.3, 142.6, 142.5, 136.4, 128.7, 127.5, 127.4, 91.4, 90.7, 60.5, 47.8, 44.8, 32.24, 32.19, 25.0, 24.3, 24.2, 13.8. IR (KBr) ν_{max}/cm^{-1} 3270 (NH), 3058, 2928, 2850 (CH), 1685 (CO), 1655 (CO).

*5.1.12. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8d**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8d**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL,

1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and ethyl isocyanoacetate (0.13 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:2 EtOAc/hexanes) to afford *cis*-**8d** (0.13 g, 28%) as an off-white solid (mp 156–157 °C). HRMS calculated for: $C_{21}H_{22}N_2O_5$, 382.15287 found 382.15295. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.12 (1H, t, J=5.7 Hz), 7.43–7.26 (3H, m), 7.21 (2H, d, J=7.7 Hz), 7.19 (1H, dd, J=5.7, 1.6 Hz), 7.06 (1H, d, J=5.4 Hz), 5.46 (1H, d, J=1.6 Hz), 5.07 (1H, d, J=15.0 Hz), 4.21 (1H, s), 4.15 (2H, q, J=7.1 Hz), 3.97 (2H, qt, J=23.4, 5.8 Hz), 3.81 (1H, d, J=15.0 Hz), 2.13 (3H, s), 1.22 (3H, t, J=7.1 Hz); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 169.4, 167.7, 162.6, 159.5, 142.7, 142.4, 142.1, 135.9, 128.7, 128.1, 127.6, 92.7, 91.0, 61.1, 60.6, 44.6, 40.9, 14.0, 13.9. IR (KBr) ν_{max}/cm^{-1} 3223 (NH), 3049 (CH), 1740 (CO), 1690 (CO), 1659 (CO).

Further elution (9:1 EtOAc/hexanes) afforded *trans*-**8d** (0.14 g, 30%) as an off-white solid (mp 161–162 °C). HRMS calculated for: $C_{21}H_{22}N_2O_5$, 382.15287 found 382.15289. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.65 (1H, t, J=5.8 Hz), 7.43–7.27 (3H, m), 7.23 (2H, d, J=6.9 Hz), 7.19 (1H, dd, J=5.3, 2.1 Hz), 7.09 (1H, d, J=5.3 Hz), 5.43 (1H, d, J=2.0 Hz), 5.06 (1H, d, J=15.3 Hz), 4.66 (1H, s), 4.11 (2H, q, J=7.1 Hz), 3.83 (2H, dq, J=17.5, 5.9 Hz), 3.74 (1H, d, J=15.3 Hz), 2.07 (3H, s), 1.19 (3H, t, J=7.1 Hz); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 169.3, 165.3, 163.0, 157.4, 145.2, 142.4, 142.3, 136.2, 128.7, 127.7, 127.5, 91.2, 90.8, 60.5, 60.4, 44.7, 40.8, 14.0, 13.8. IR (KBr) ν_{max}/cm^{-1} 3316 (NH), 3020 (CH), 1738 (CO), 1697 (CO), 1670 (CO).

*5.1.13. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8e**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8e**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and methyl isocyanoacetate (0.11 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:2 EtOAc/hexanes) to afford *cis*-**8e** (0.12 g, 27%) as an off-white solid (mp 151–153 °C). HRMS calculated for: $C_{20}H_{20}N_2O_5$, 368.13722 found 368.13730. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.17 (1H, t, J=5.7 Hz), 7.36 (3H, m), 7.26 (2H, d, J=6.6 Hz), 7.21 (1H, dd, J=5.4, 2.0 Hz), 7.10 (1H, d, J=5.4 Hz), 5.47 (1H, d, J=1.9 Hz), 5.13 (1H, d, J=15.0 Hz), 4.26 (1H, s), 4.02 (2H, dq, J=17.5, 5.9 Hz), 3.86 (1H, d, J=15.0 Hz), 3.70 (3H, s), 2.15 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.9, 167.4, 162.7, 159.5, 142.7, 142.4, 142.0, 135.9, 128.7, 128.1, 127.6, 92.8, 91.1, 61.1, 51.8, 44.7, 40.7, 13.8. IR (KBr) ν_{max}/cm^{-1} 3221 (NH), 3049, 2951 (CH), 1747 (CO), 1686 (CO), 1659 (CO).

Further elution (9:1 EtOAc/hexanes) afforded *trans*-**8e** (1.3 g, 29%) as an off-white solid (mp 133–135 °C). HRMS calculated for: $C_{20}H_{20}N_2O_5$, 368.13722 found 368.13726. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.68 (1H, t, J=5.8 Hz), 7.47–7.29 (3H, m), 7.26 (2H, d, J=6.9 Hz), 7.20 (1H, dd, J=5.2, 2.1 Hz), 7.11 (1H, d, J=5.3 Hz), 5.45 (1H, d, J=1.9 Hz), 5.09 (1H, d, J=15.3 Hz), 4.69 (1H, s), 3.88 (2H, dq, J=22.9, 6.6 Hz), 3.77 (1H, d, J=15.3 Hz), 3.37 (3H, s), 2.09 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.9, 165.4, 163.0, 157.5, 145.2, 142.4, 142.3, 136.2, 128.72, 127.70, 127.5, 91.2, 90.8, 60.4, 51.7, 44.7, 40.6, 13.8. IR (KBr) ν_{max}/cm^{-1} 3227 (NH), 3076, 2945 (CH), 1745 (CO), 1693 (CO), 1655 (CO).

*5.1.14. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(butyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8f**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(butyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8f**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and 1-butyl isocyanide (0.12 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (3:2 EtOAc/hexanes) to afford *cis*-**8f** (0.10 g, 24%) as an off-white solid (mp 84–85 °C). HRMS calculated for: $C_{21}H_{24}N_2O_3$, 352.17869 found 352.17876. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.57 (1H, t, J=5.6 Hz), 7.51–7.24 (3H, m), 7.20 (1H, dd, J=5.4, 2.1 Hz), 7.18–7.13 (2H, m), 6.87 (1H, d, J=5.4 Hz), 5.46 (1H, d, J=2.1 Hz), 5.06 (1H, d, J=15.1 Hz), 4.16 (1H, s), 3.74 (1H, d, J=15.1 Hz), 3.17 (2H, qd, J=13.0, 6.5 Hz), 2.13 (3H, s), 1.50–1.16 (4H, m), 0.88 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 166.5, 162.7, 159.0, 142.5, 142.4, 135.9, 128.7, 127.9, 127.5, 92.9, 91.1, 61.1, 44.6, 38.3, 30.8, 19.3, 13.8, 13.5. IR (KBr) ν_{max}/cm^{-1} 3283 (NH), 3110, 3957, 2932, 2872 (CH), 1688 (CO), 1662 (CO).

Further elution (9:1 EtOAc/hexanes) afforded *trans*-**8f** (1.2 g, 28%) as an off-white solid (mp 79–80 °C). HRMS calculated for: $C_{21}H_{24}N_2O_3$, 352.17869 found 352.17877. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.08 (1H, t, J=5.5 Hz), 7.43–7.26 (3H, m), 7.20 (3H, d, J=7.0 Hz), 7.10 (1H, d, J=5.3 Hz), 5.44 (1H, d, J=1.9 Hz), 5.04 (1H, d, J=15.4 Hz), 4.55 (1H, s), 3.74 (1H, d, J=15.4 Hz), 3.03 (2H, qd, J=13.0, 6.5 Hz), 2.08 (3H, s), 1.48–1.10 (4H, m), 0.85 (3H, t, J=7.1 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 164.2, 163.2, 156.9, 145.3, 142.5, 136.3, 128.7, 127.5, 127.4, 91.4, 90.7, 60.6, 44.9, 38.3, 30.9, 19.3, 13.8, 13.5. IR (KBr) ν_{max}/cm^{-1} 3281 (NH), 3077, 2961, 2930, 2872 (CH), 1686 (CO), 1655 (CO).

*5.1.15. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-toly)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**8g**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-N-(2-toly)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**8g**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol) and 2-tolylisocyanide (0.14 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (1:1 EtOAc/hexanes) to afford *cis*-**8g** (0.09 g, 19%) as an off-white solid (mp 161–163 °C). HRMS calculated for: $C_{24}H_{22}N_2O_3$, 386.16304 found 386.16307. ^{1}H NMR (300 MHz) (acetone-d_6): δ 9.50 (s, 1H), 7.48–7.17 (11H, m), 5.48 (1H, d, J=1.9 Hz), 5.47 (1H, d, J=15.0 Hz), 4.90 (1H, s), 4.02 (1H, d, J=15.0 Hz), 3.92 (3H, s), 2.33 (3H, s); ^{13}C NMR (300 MHz) (acetone-d_6): δ 165.6, 158.8, 142.3, 141.8, 137.8, 136.2, 135.9, 132.3, 131.5, 128.6, 128.5, 128.3, 128.2, 127.9, 127.6, 127.1, 126.2, 91.1, 60.5, 44.7, 17.9, 12.7. IR (KBr) ν_{max}/cm^{-1} 3279 (NH), 3050, 2955 (CH), 1706 (CO), 1690 (CO).

Further elution (4:1 EtOAc/hexanes) afforded *trans*-**8g** (1.3 g, 28%) as an off-white solid (mp 175–177 °C). HRMS calculated for: $C_{24}H_{22}N_2O_3$, 386.16304 found 386.16309. ^{1}H NMR (300 MHz) (acetone-d_6): δ 9.11 (s, 1H), 7.40–7.17 (10H, m), 7.09 (1H, d, J=5.3 Hz), 5.48 (1H, d, J=1.9 Hz), 5.46 (1H, d, J=15.3 Hz), 5.28 (1H, s), 3.98 (1H, d, J=15.3 Hz), 2.93 (3H, s), 2.13 (3H, s); ^{13}C NMR (75 MHz) (acetone-d_6): δ 163.1, 157.3, 144.6, 142.1, 141.8, 138.3, 137.8, 136.2, 132.7, 131.5, 128.6, 128.2, 127.9, 127.7, 127.5, 127.1, 126.7, 91.2, 61.0, 44.4, 17.8, 12.7. IR (KBr) ν_{max}/cm^{-1} 3289 (NH), 3063, 2952 (CH), 1706 (CO), 1648 (CO).

*5.1.16. (3S,3aS,6R)-2-(Benzyl)-1,2,3,6-tetrahydro-7-propyl-1-oxo-N-(2-naphthyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**9a**) and (3R,3aS,6R)-2-(benzyl)-1,2,3,6-tetrahydro-7-propyl-1-oxo-N-(2-naphthyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (trans-**9a**).* Synthesized utilizing the general procedure, benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-hexynoic acid (0.16 mL, 1.4 mmol) and 2-naphthyl isocyanide (0.18 g, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (1:2 EtOAc/hexanes) to afford *cis*-**9a** (0.09 g, 17%) as an off-white solid (mp 157–160 °C). HRMS calculated for: $C_{29}H_{26}N_2O_3$, 450.19434 found 450.19441. ^{1}H NMR (300 MHz) (DMSO-d_6): δ 10.70 (1H, s), 8.34 (1H, s), 7.89 (2H, t, J=9.2 Hz), 7.62 (1H, dd, J=8.6, 1.2 Hz), 7.55–7.48 (2H, m), 7.47–7.41 (2H, m), 7.36 (2H, d, J=7.6 Hz), 7.34 (2H, m), 6.98 (1H, d, J=5.4 Hz), 7.22 (1H, d, J=6.8 Hz), 5.61 (1H, d, J=1.44 Hz), 5.14 (1H, d, J=15.2 Hz), 4.50 (1H, s), 3.95 (1H, d, J=15.2 Hz), 2.71–2.40 (2H, m), 1.73–1.47 (2H, m), 0.87 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 166.0, 163.2, 162.7, 143.2, 142.4, 142.2, 135.9, 135.5, 133.1, 130.1, 128.7, 128.5, 127.9, 127.6, 127.4, 127.4, 126.5, 125.0, 120.0, 116.2, 93.2, 90.4, 61.8, 44.9, 30.1,

19.7, 13.6. IR (KBr) ν_{max}/cm^{-1} 3301 (NH), 3060, 2965, 2953, 2871 (CH), 1704 (CO), 1651 (CO).

Further elution (1:2 EtOAc/hexanes) afforded *trans*-**9a** (0.09 g, 17%) as a brown solid (mp 167–168 °C). HRMS calculated for: $C_{29}H_{26}N_2O_3$, 450.19434 found 450.19439. ^1H NMR (300 MHz) (DMSO-d_6): δ 10.39 (1H, s), 8.25 (1H, s), 7.90–7.77 (4H, m), 7.57–7.35 (4H, m), 7.35–7.20 (5H, m), 5.54 (1H, d, J=1.3 Hz), 5.11 (1H, d, J=15.5 Hz), 4.87 (1H, s), 3.92 (1H, d, J=15.5 Hz), 2.48 (2H, qd, J=15.3, 7.2 Hz), 1.71–1.40 (2H, m), 0.87 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 163.8, 163.2, 161.1, 145.0, 142.8, 142.3, 136.5, 136.4, 136.0, 133.2, 129.8, 128.7, 128.3, 127.6, 127.4, 127.2, 126.4, 124.7, 119.6, 115.3, 91.8, 90.0, 61.1, 45.0, 30.3, 19.7, 13.7. IR (KBr) ν_{max}/cm^{-1} 3289 (NH), 3092, 2959, 2942, 2868 (CH), 1690 (CO), 1653 (CO).

*5.1.17. (3S,3aS,6R)-2-(4-N,N-Dimethylaminopropyl)-1,2,3,6-tetrahydro-7-pentyl-1-oxo-N-(pentyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**9b**) and (3R,3aS,6R)-2-(4-N,N-dimethylaminopropyl)-1,2,3,6-tetrahydro-7-pentyl-1-oxo-N-(pentyl)-3a,6-epoxy-3aH-isoindole-3-carboxamide (cis-**9b**).* Synthesized utilizing the general procedure, 3-(dimethylamino)-1-propylamine (0.30 mL, 2.4 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-octynoic acid (0.17 g, 1.2 mmol) and 1-pentyl isocyanide (0.15 mL, 1.2 mmol). The crude material was subjected to flash silica gel column chromatography (95:5 EtOAc/Et_3N) to afford *cis*-**9b** (0.17 g, 34%) as a yellow oil. HRMS calculated for: $C_{23}H_{37}N_2O_3$, 403.28349 found 403.28355. ^1H NMR (300 MHz) (acetone-d_6): δ 8.08 (1H, t, J=5.4 Hz), 6.51 (1H, dd, J=5.8, 1.8 Hz), 6.34 (1H, d, J=5.8 Hz), 5.22 (2H, dd, J=10.6, 1.1 Hz), 5.08 (1H, d, J=0.8 Hz), 4.38 (1H, s), 3.63–3.45 (3H, m), 3.32 (2H, q, J=6.8 Hz), 3.05 (3H, m), 2.21 (1H, ddd, J=13.4, 7.0, 5.5 Hz), 2.12 (9H, s), 1.77–1.51 (10H, m), 1.41–1.24 (5H, m), 0.89 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 170.8, 167.0, 141.6, 135.7, 132.3, 106.8, 91.2, 82.4, 63.0, 55.8, 50.2, 44.2, 39.6, 38.7, 30.1, 28.5, 28.4, 28.2, 24.7, 24.1, 21.6, 19.7, 13.0. IR (KBr) ν_{max}/cm^{-1} 3281 (NH), 2928, 2856 (CH), 1672 (CO), 1651 (CO).

Further elution (95:5 EtOAc/Et_3N) to afforded *trans*-**9b** (0.17 g, 34%) as a white solid (mp 67–68 °C). HRMS calculated for: $C_{23}H_{37}N_2O_3$, 403.28349 found 403.28352. ^1H NMR (300 MHz) (acetone-d_6): δ 7.12 (1H, t, J=5.4 Hz), 6.65 (1H, d, J=5.7 Hz), 6.48 (1H, dd, J=5.7, 1.8 Hz), 5.22 (2H, dd, J=10.6, 1.1 Hz), 5.07 (1H, d, J=0.8 Hz), 4.81 (1H, s), 3.75 (3H, m), 3.23 (2H, m), 3.08 (3H, m), 2.22 (4H, m), 2.13 (6H, s), 1.82–1.57 (4H, m), 1.51 (2H, m), 1.30 (4H, m), 0.87 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz) (acetone-d_6): δ 170.7, 164.7, 141.6, 135.3, 133.5, 106.3, 90.3, 82.4, 61.4, 56.4, 50.9, 44.8, 44.2, 39.7, 38.4, 38.2, 30.1, 28.7, 24.1, 21.5, 19.7, 13.6, 12.9. IR (KBr) ν_{max}/cm^{-1} 3389 (NH), 2956, 2931, 2860 (CH), 1681 (CO), 1651 (CO).

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