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LITHIUM BROMIDE-PROMOTED THREE-COMPONENT SYNTHESIS OF OXA-BRIDGED TETRACYCLIC TETRAHYDROISOQUINOLINES

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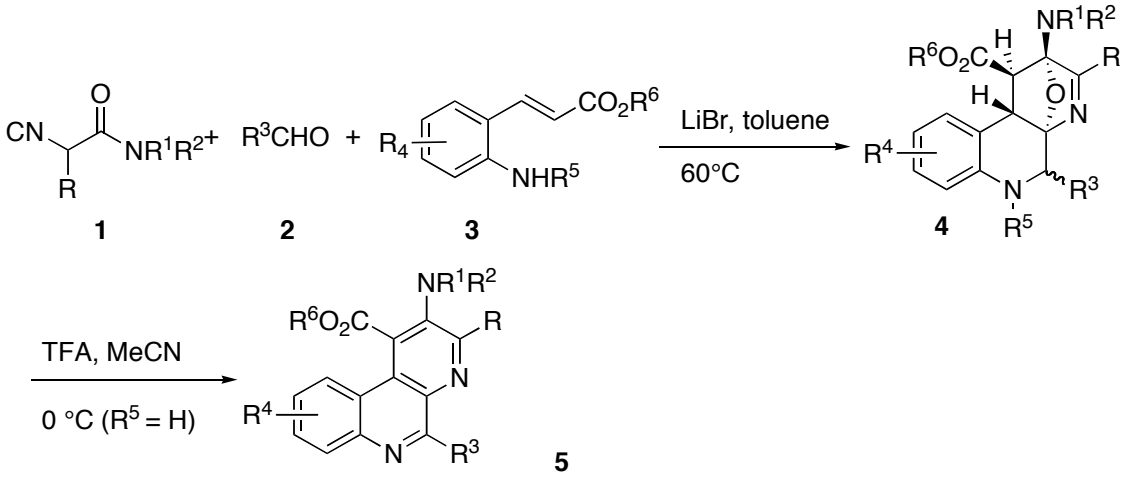
Abstract – Heating a toluene solution of an α-isocyanoacetamide (**1**), an aldehyde (**2**) and an aniline (**3**) in the presence of lithium bromide at 60 °C provides the oxa-bridged tetracyclic tetrahydroquinoline (**4**) in good to excellent yield as a mixture of two separable diastereoisomers. In this one-pot multicomponent reaction, one *C-N*, one *C-O* and three *C-C* bonds are formed with concomitant creation of five asymmetric centers and three heterocycles. Fragmentation of epoxy-tetrahydroquinoline (**4**) under mild acidic conditions affords 4,6-phenanthroline (**5**).

Dedicated to the memory of Professor Ivar Ugi

INTRODUCTION

By virtue of its inherent convergence, high productivity, its exploratory and complexity-generating power, multicomponent reaction (MCR) is being recognized as one of the most promising approaches in diversity oriented syntheses and is undoubtedly well suited for the drug discovery program.[1] Among named MCRs, the Ugi four-component reaction (Ugi-4CR) is without doubt one of the most powerful transformations.[2] Discovered in the late 1950's by Ugi,[3] this MCR has been extensively investigated for the past twenty years and has became a reference reaction for those working in the field of multicomponent reactions. Indeed, it belongs to a very rare family of truly four-component reaction in the sense that each input (carboxylic acid, aldehyde, amine and isocyanide) bearing an organic residue that can be varied systematically.[4] Inspired by Ugi's pioneering work, many variants have since been developed taking advantage of the unique carbene-like reactivity of isocyanide.[5]

We have been working on the chemistry of α-isocyano acetamide[6] as well as α-isocyano acetic acid[7] and have developed an efficient three-component synthesis of 5-aminooxazole by its reaction with an amine and an aldehyde. Taking advantage of the chemical reactivity of 5-aminooxazole and by fine tuning the structure of the starting materials, several new multicomponent reactions have subsequently been devised for the syntheses of a number of polyheterocycles[8] and macrocycles.[9] One of such reactions involving an α-isocyanoacetamide (**1**), an aldehyde (**2**) and an *o*-amino cinnamate (**3**) afforded the epoxy-tetrahydroquinoline (**4**) in excellent yield and good level of diastereoselectivity.[10] We report herein full details the development of this three-component reaction and the subsequent acid-promoted fragmentation of **4** to 4,6-phenanthroline (**5**) (Scheme 1).



1 **2** **3** **4** **5**

Scheme 1. Three-component synthesis of oxa-bridged polycycle and its fragmentation to diazaphenanthrene.

RESULTS AND DISCUSSION

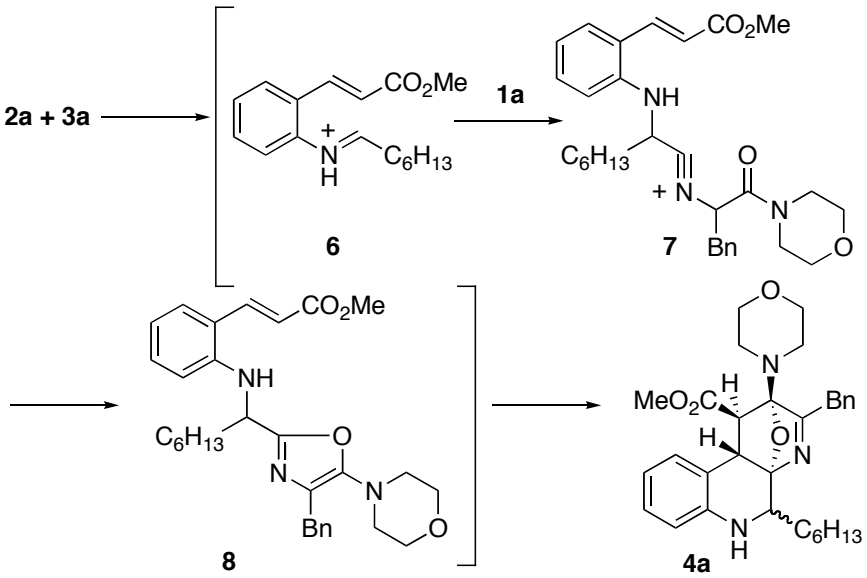
Using *N*-morpholinyl α-isocyano–α-benzyl acetamide (**1a**),[11] an heptanal (**2a**) and an *ortho*-amino methyl cinnamate (**3a**) as inputs (Scheme 2), we performed a survey of reaction conditions varying the solvents (MeOH, CF_3CH_2OH, benzene, toluene), the temperatures (room temperature to 110°C), and the promoters (LiBr, $BF_3.OEt_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $MgSO_4$).[12] Some representative results are summarized in Table 1. The optimized conditions we found for this three-component reaction consisted of heating a toluene solution of **2a**, **3a** and **1a** in the presence of LiBr (60 °C). Under these conditions, the tetracyclic tetrahydroquinoline **4a** (Scheme 2) was isolated in 94% yield as a mixture of two separable diastereomers. The presence of lithium bromide was of utmost importance for the success of this reaction. Indeed, in its absence, the adduct **4** was isolated in only 6% yield under otherwise identical conditions. LiBr may act as an activator for both the nucloephilic addition of isocyanide carbon to imine and the subsequent Diels-Alder reaction.

Table 1. Three-component synthesis of **4a**, a survey of reaction conditions.[a]

Entry	Solvant	Time (h)	T (°C)	Additive	**4a** (%)
1	MeOH	24	25	-	-
2	toluene	24	25	-	-
3	MeOH	24	reflux	-	42[b]
4	toluene	24	reflux	-	6[c]
5	MeOH	20	reflux	LiBr	30[d]
6	toluene	24	60	LiBr	94[d]
7	benzene	8	reflux	LiBr	28[d]
8	toluene	15	60	$BF_3.Et_2O$	-
9	toluene	15	60	$Yb(OTf)_3$	20
10	toluene	15	60	$Sc(OTf)_3$	16

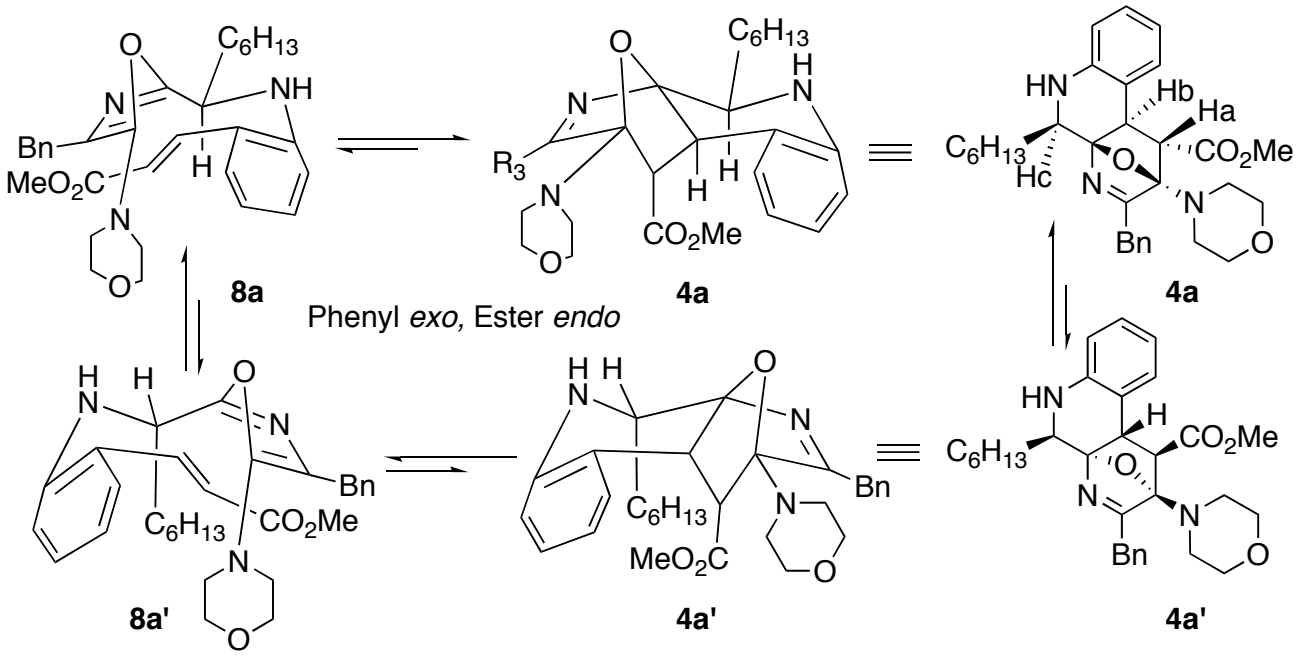
[a]General conditions: mole ratio: **1a**/**2a**/**3a** = 1/1.2/1.0, C = 0.15M ;
[b]diastereomeric ratio 5/1; [c]diastereomeric ratio 2/1; [d]diastereomeric ratio 3/1.

The sequence of events leading to the formation of **4** is outlined in Scheme 2. Reaction of an aniline, an aldehyde and an α-isocyano acetamide should give the aminooxazole via an iminium **6**, then a nitrilium ion **7** intermediate. Cycloaddition of oxazole **8** as an aza-diene with a properly predisposed dienophile produced then a bridged tetrahydroquinoline-containing polycycle **4**.[13,14] It is interesting to note that Ugi-type condensation is preferably performed in polar protic solvents such as methanol and trifluoroethanol, whereas in non-polar aprotic solvent, the Passerini-type reaction became competitive.[15] It is thus remarkable that the present multicomponent reaction worked so efficiently in toluene. Lithium bromide may activate the imine intermediate and thus facilitating the subsequent nucleophilic attack of the divalent carbon of isocyanide. In the presence of strong Lewis acids such as $BF_3.OEt_2$, degradation of the acid-sensitive 5-aminooxazole may occur decreasing consequently the overall reaction efficiency. It is worth noting that one *C-N*, one *C-O* and three *C-C* bonds were formed with the concomitant creation of five asymmetric centers in this one-pot process. The efficiency of this reaction was thus truly remarkable if one looks at the yield *per* bond formation.



Scheme 2. Reaction sequence of the three-component reaction.

Since five chiral centers were created in this 3CR, 16 pairs of diastereomers would theoretically be expected. However, only two of them were isolated in a ratio of 3 to 1. The stereochemistry of compound **4a** and **4a'** was deduced from both mechanistic consideration and NMR studies. The observed coupling constant between H_a and H_b ($J_{Ha\text{-}Hb}$ = 4.6 Hz for **4a** and 4.4 Hz for **4a'**) indicated a gauche relationship of these two protons in both compounds. For the inherent ring strain imposed by the connecting bridge, only the aryl-*exo*-ester *endo* mode of cycloaddition was possible leading to the observed compounds (Scheme 3). This model of ring formation is also indicative of a concerted rather than a stepwise process, since one could expect the formation of aryl-*exo*-ester-*exo* diastereomers if the latter mechanism was operating. The relative stereochemistry of the major adduct **4a** was deduced from the observation of a strong NOE cross peak between H_b and H_c in its NOESY spectrum and corroborated by X-ray analysis.[10]



Scheme 3. Stereochemistry of the three-component adduct.

Control experiments showed that the observed stereoselectivity was a thermodynamically controlled process. Indeed, re-submitting the diastereomerically pure compound **4a** to the reaction conditions led to the formation of a mixture of **4a** and **4a'** with the ratio identical to that resulting from the reaction mixture. The same is true for **4a'**. While the thermo-equilibrium can be interpreted by a sequence of heterocycloreversion/cycloaddition, the relatively high stability of compound **4** towards fragmentation and/or degradation was nevertheless intriguing.

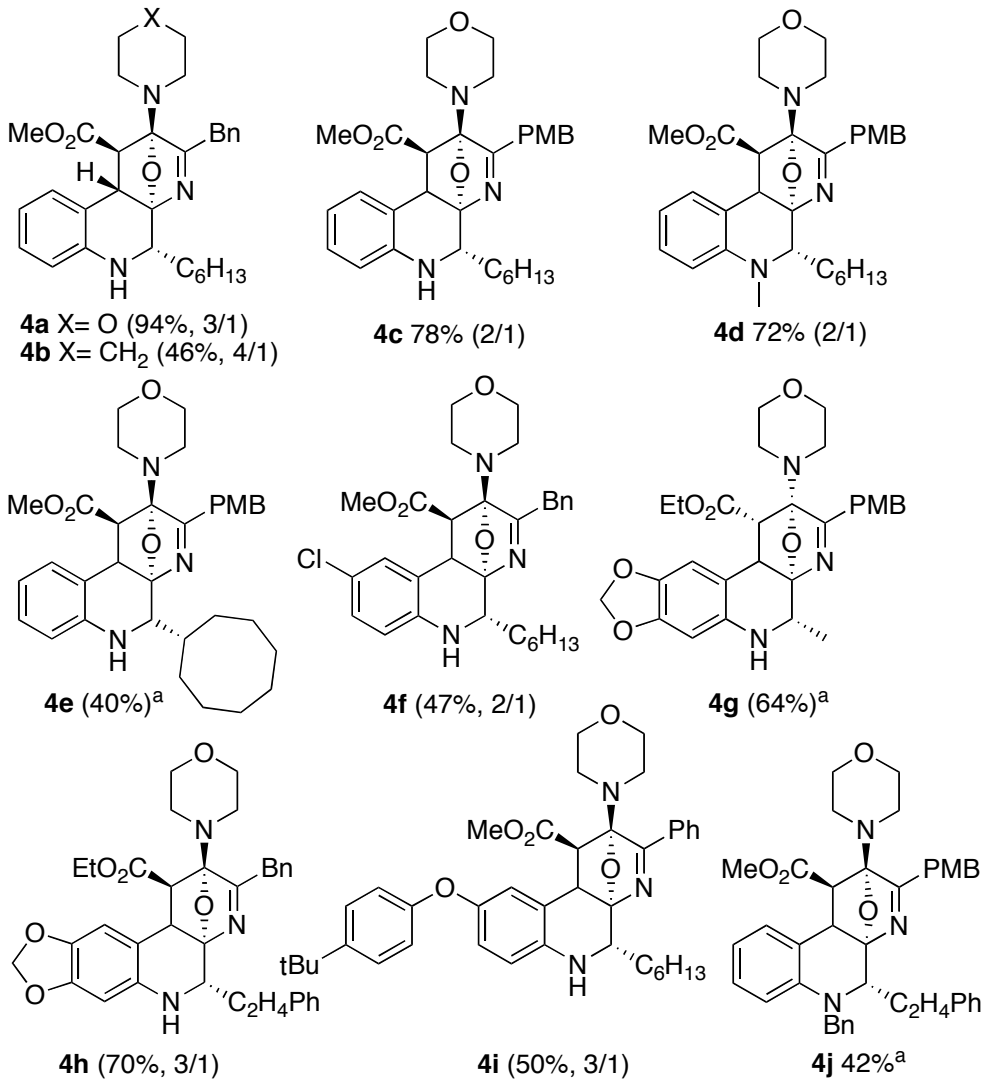
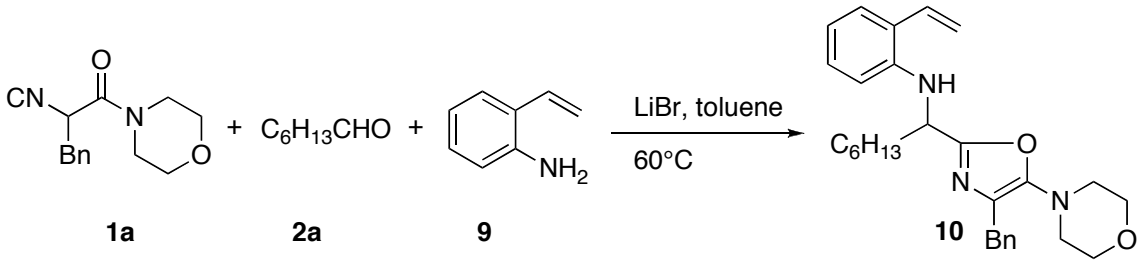


Figure 1. Representative structure of oxa-bridged tetrahydroquinoline **4**; [a]only one diastereoisomer was isolated. Abbreviations: Bn = benzyl; PMB = *para*-methoxy benzyl.

The scope of this MCR was examined and compounds synthesized are listed in Figure 1. The reaction conditions have not been individually optimized. As is seen, all substituents at the peripheral of the tetracyclic ring system can be varied. The α-branched aldehydes, as well as the α-alkyl and α-aryl substituted α-isocyano acetamides can took part in this reaction. When cyclooctyl aldehyde was used, a single diastereomer was isolated. Since the nitrogen bearing asymmetric center was the one that controlled the facial selectivity of the subsequent aza-Diels-Alder cycloaddition, the observation is thus understandable. However, aromatic aldehyde failed to enter the reaction cascade under these conditions. The *ortho*-amino cinnamate having either electron donating or electron withdrawing group at the aromatic ring participated in the reaction, as did the *N*-alkylated derivatives. However, the presence of an ester function was required for the Diels-Alder reaction. Using *o*-amino styrene **9** as amine input, the oxazole **10** was isolated in 64% yield. Intramolecular cycloaddition did not take place even at refluxing

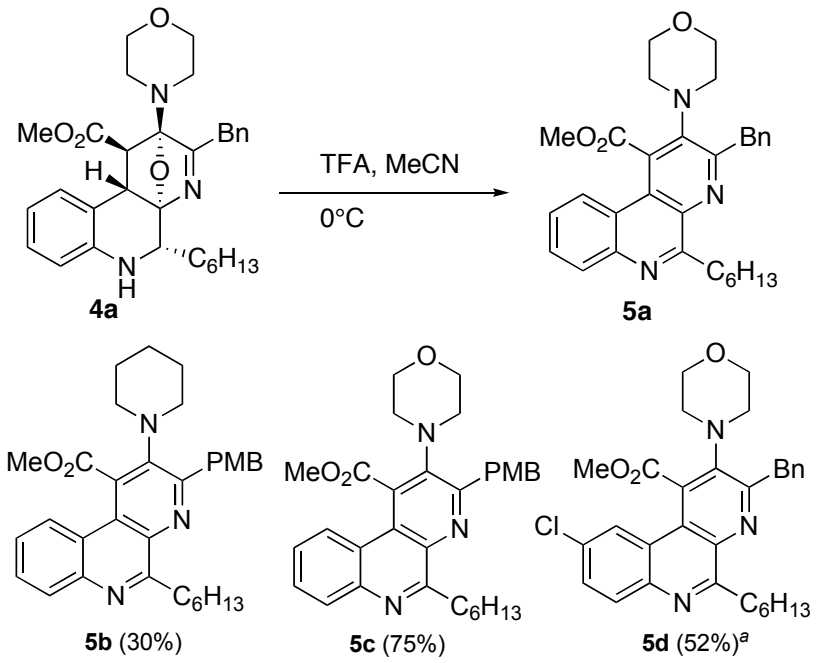
temperatrure of toluene (Scheme 4). This result validated on the other hand the reaction sequence that we proposed for this three-component reaction.



Scheme 4. Three-component synthesis of 5-amino oxazole.

As expected for Ugi type reaction, racemic tetrahydroquinoline was obtained even when enantiomerically pure isonitrile **1** (R = Bn, or phenyl) was used as input.

Fragmentation of **4** by breaking the aminal function should in principle afford the 4,6-phenanthroline after oxidative aromatization.[16] Two fragmentation pathways are possible leading to amino-substituted and hydroxylated phenanthroline, respectively. However, under carefully controlled conditions (TFA, 0°C), the oxa-bridge tetracycle **4a** was cleanly converted to 4,6-phenanthroline **5a** in 71% yield (Scheme 5). Three other phenanthrolines synthesized were listed in the Scheme 5.



Scheme 5. Fragmentation of **4a** to **5** [a] Fragmentation was performed at -30°C.

In conclusion, we have developed a novel multicomponent reaction for the synthesis of complex heterocycles from simple and readily accessible precursors. Besides its synthetic efficiency and potential application in diversity-oriented synthesis, we demonstrated that Ugi-type condensation can be performed in toluene in the presence of LiBr without concurrent occurrence of a Passerini-type reaction. Only one molecule of water was lost in this MCR that leads to the formation of five chemical bonds with current creation of five asymmetric centers and three heterocycles.

EXPERIMENTAL

General procedure for the three-component synthesis of oxa-bridged tetrahydroquinolines (4)

A solution of aniline (**3**) (1.0 equiv) and aldehyde (**2**) (1.2 equiv) in dry toluene (0.15 M) with α-isocyanoacetamide (**1**) (1.0 equiv) and LiBr (1.0 equiv) was stirred at 60 °C. The reaction was monitored by TLC (5-20 h). The solvent was removed under reduced pressure and after dilution with water, the product was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated to dryness. Purification of the crude product by either preparative TLC (silica gel, eluent heptane/AcOEt) or flash chromatography (silica gel, eluent: heptane/AcOEt) afforded the title compound.

Compound 4a, yield: 94%, *dr* = 3/1. **Major isomer:** Yellow crystalline solid, 192-193 °C; IR ($CHCl_3$) ν 3008, 2956, 2926, 2857, 1733, 1628, 1606, 1586, 1495, 1486, 1454, 1437, 1381, 1351, 1302, 1272, 1232, 1168, 1118, 1071, 1047, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*= 7.0 Hz, 3H), 1.20-1.64 (m, 9H), 1.83-1.94 (m, 1H), 2.60 (ddd, *J*= 3.2, 5.9, 11.7 Hz, 2H), 2.90 (ddd, *J*= 3.2, 6.6, 11.9 Hz, 2H), 3.16 (d, *J*= 4.6 Hz, 1H), 3.31 (d, *J*= 4.6 Hz, 1H), 3.60-3.70 (m, 4H), 3.65 (d, *J*= 16.5 Hz, 1H), 3.80 (s, 3H), 3.82 (d, *J*= 16.5 Hz, 1H), 3.89 (dd, *J*= 3.7, 8.8 Hz, 1H), 3.94 (br s, 1H, NH), 6.62 (dd, *J*= 1.2, 8.1 Hz, 1H), 6.72 (dt, *J*= 1.2, 7.5 Hz, 1H), 6.96 (td, *J*= 1.2, 7.7 Hz), 7.02 (dt, *J*= 1.2, 7.5 Hz, 1H), 7.20-7.40 (m, *5*H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 26.2, 29.5, 29.8, 31.9, 35.8, 47.3, 48.4, 52.0, 52.6, 53.2, 67.1, 97.8, 106.4, 115.6, 119.1, 123.0, 126.9, 127.4, 128.6, 129.3, 129.8, 135.9, 142.7, 171.1, 178.0; MS (ESI) *m/z* 556 [M+K^+], 540 [M+Na^+], 518 [M+1]; HRMS (CI) *m/z calcd. for:* $[M+1]^+$ 518.30186, *m/z found for:* $[M+1]^+$ 518.30170. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3020, 2956, 2929, 2859, 1729, 1676, 1655, 1603, 1494, 1455, 1437, 1379, 1345, 1319, 1302, 1274, 1226, 1218, 1205, 1175, 1116, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J*= 6.9 Hz, 3H), 1.25-1.62 (m, 9H), 2.09-2.21 (m, 1H), 2.58 (ddd, *J*= 3.3, 6.4, 9.7 Hz, 2H), 2.90 (ddd, *J*= 2.8, 6.4, 9.7 Hz, 2H), 3.15 (d, *J*= 4.4 Hz, 1H), 3.28 (d, *J*= 4.4 Hz, 1H), 3.60-3.70 (m, 5H), 3.65 (d, *J*= 15.1 Hz, 1H), 3.78 (s, 3H), 3.79 (d, *J*= 15.1 Hz, 1H), 4.18 (d, *J*= 2.0 Hz, 1H, NH), 6.60 (dd, *J*= 1.2, 8.0 Hz, 1H), 6.72 (dt, *J*= 1.2, 7.5 Hz, 1H), 6.95 (dt, *J*= 1.2, 7.5 Hz), 7.03 (dt, *J*= 1.2, 7.5 Hz, 1H), 7.20-7.40 (m, *5*H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 26.4, 29.2, 29.9, 32.0, 35.7, 44.6, 48.4, 51.6, 52.6, 53.4, 67.2, 98.5, 106.2, 116.1, 118.8, 122.8, 126.9, 127.7, 128.5, 129.5, 129.7, 135.8, 140.7, 171.1, 178.3; MS (IE) *m/z*; MS (ESI) *m/z* 556 [M+K^+], 540 [M+Na^+], 518 [M+1]; HRMS (CI) *m/z calcd. for:* $[M+1]^+$ 518.30186, *m/z found for:* $[M+1]^+$ 518.30170.

Compound 4b, yield: 46%, *dr* = 4/1. **Major isomer:** Yellow oil; IR ($CHCl_3$) ν 3020, 2938, 2854, 1732, 1606, 1496, 1348, 1224, 1210, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 3H), 1.25-1.57 (m, 15H), 1.87 (m, 1H), 2.58 (m, 2H), 2.92 (m, 2H), 3,16 (d, *J*= 4.6 Hz, 1H), 3.28 (d, *J* = 4.6 Hz, 1H), 3.74 (m, 2H), 3.80 (s, 3H), 3.84 (dd, *J* = 9.1, 3.8 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 1H), 6.96-7.04 (m, 2H), 7.24-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 24.5, 26.1, 26.3 (2C),

29.4, 29.7, 31.8, 35.6, 47.4, 48.9 (2C), 52.2, 52.4, 53.2, 97.3, 107.3, 115.5, 118.9, 126.6, 127.2, 128.4, 128.2, 129.3, 129.7, 136.3, 142.7, 171.4, 178.8; MS (IE) *m/z* 430 $[M\text{-}C_6H_{13}]^+$, 515 $[M]^+$. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3019, 2933, 2854, 1732, 1606, 1218, 1224, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (m, 3H), 1.25-1.57 (m, 15H), 2.15 (m, 1H), 2,57 (m, 2H), 2.92 (m, 2H), 3.21 (d, *J*= 4.6 Hz, 1H), 3.25 (d, *J*= 4.6 Hz, 1H), 3.61 (dd, *J*=9.1, 3.8 Hz, 1H), 3.66 (d, *J*= 16.0 Hz, 1H), 3.76 (s, 3H), 3.77 (d, *J*= 16.0 Hz, 1H), 6.61 (d, *J*= 8.1Hz, 1H), 6.74 (t, *J*= 7.6 Hz, 1H), 6.94-7.04 (m, 2H), 7.21-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.9, 24.8, 26.6, 26.4, 29.4, 30.0, 32.2, 35.6, 44.9, 49.3, 51.9, 52.6, 53.6, 98.2, 107.3, 116.2, 118.8, 123.3, 126.8, 127.6, 128.5, 129.6, 129.9, 140.9, 136.4, 171.6, 179.3; MS (EI) *m/z* 515 $[M]^+$.

Compound 4c, yield: 78%, *dr* = 2/1. **Major isomer:** Yellow oil; IR ($CHCl_3$) ν 3007, 2957, 2929, 2859, 1734, 1655, 1608, 1512, 1487, 1457, 1302, 1249, 1176, 1118, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J*= 7.2 Hz, 3H), 1.20-1.66 (m, 9H), 1.83-1.93 (m, 1H), 2.61 (ddd, *J*= 3.4, 5.9, 10.2 Hz, 2H), 2.96 (ddd, *J*= 3.4, 5.9, 11.5 Hz, 2H), 3.11 (d, *J*= 4.3 Hz, 1H), 3.30 (d, *J*= 4.7 Hz, 1H), 3.61 (d, *J*= 14.7 Hz, 1H), 3.64-3.69 (m, 4H), 3.75 (d, *J*= 14.7 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.89 (dd, *J*= 3.4, 8.5 Hz, 1H), 3.95 (br s, 1H, NH), 6.63 (d, *J*= 8.1 Hz, 1H), 6.72 (t, *J*= 7.5 Hz, 1H), 6.86 (d, *J*= 8.7 Hz, 2H), 6.95 (d, *J*= 7.7 Hz, 1H), 7.02 (t, *J*= 7.5 Hz, 1H), 7.27 (d, *J*= 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 26.2, 29.4, 29.1, 31.9, 34.9, 47.3, 48.4, 52.0, 52.6, 53.2, 55.3, 67.1, 97.7, 106.4, 114.0, 115.6, 119.0, 123.1, 127.4, 127.9, 129.8, 130.3, 142.7, 171.1, 178.2; MS (IE) *m/z* 547 $[M]^+$. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3008, 2957, 2930, 2860, 1697, 1632, 1602, 1511, 1460, 1436, 1320, 1303, 1250, 1170, 1115, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J*= 6.4 Hz), 1.23-1.60 (m, 9H), 2.03-2.20 (m, 1H), 2.59 (ddd, 2H, *J*= 3.4, 5.6, 11.9 Hz), 2.96 (ddd, 2H, *J*= 3.4, 4.7, 11.9 Hz), 3.14 (d, 1H, *J*= 4.3 Hz), 3.27 (d, 1H, *J*= 4.3 Hz), 3.58 (d, 1H, *J*= 16.5 Hz), 3.61 (d, 1H, *J*= 3.0 Hz), 3.64-3.69 (m, 4H), 3.68 (d, 1H, *J*= 16.5 Hz), 3.76 (d, 1H, *J*= 4.3 Hz, NH), 3.79 (s, 3H), 3.80 (s, 3H), 6.60 (d, 1H, *J*= 8.1 Hz), 6.71 (t, 1H, *J*= 7.5 Hz), 6.85 (d, 2H, *J*= 8.7 Hz), 6.94 (d, 1H, *J*= 7.7 Hz), 7.03 (t, 1H, *J*= 7.7 Hz), 7.30 (d, 2H, *J*= 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 29.2, 29.8, 32.0, 34.8, 44.6, 48.5, 51.6, 52.6, 53.4, 55.4, 67.2, 98.5, 106.2, 113.9, 114.0, 116.1, 118.8, 122.8, 127.7, 127.8, 129.7, 130.4, 140.7, 171.1, 178.6; MS (IE) *m/z* 547 $[M]^+$.

Compound 4d, yield: 72%, *dr* = 2/1. **Major isomer:** Yellow oil; IR ($CHCl_3$) ν 3009, 2957, 2929, 2859, 1729, 1604, 1512, 1456, 1438, 1333, 1304, 1253, 1175, 1118, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J*= 6.5 Hz, 3H), 1.25-1.35 (m, 6H), 1.47-1.67 (m, 3H), 2.13-2.18 (m, 1H), 2.19-2.27 (m, 2H), 2.72-2.78 (m, 2H), 3.08 (s, 3H), 3.15 (d, *J*= 4.3 Hz, 1H), 3.26 (d, *J*= 4.3 Hz, 1H), 3.40-3.50 (m, 4H), 3.62-3.66 (m, 1H), 3.72-3.77 (m, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 6.62 (d, *J*= 8.1 Hz, 1H), 6.69 (t, *J*= 7.4 Hz, 1H), 6.88 (d, *J*= 8.6 Hz, 2H), 6.94 (d, *J*= 7.2 Hz, 1H), 7.14 (t, *J*= 7.2 Hz, 1H), 7.42 (d, *J*= 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.8, 27.91, 29.6, 30.1, 32.0, 40.4, 45.5, 48.7, 52.6, 53.03, 55.4,

61.8, 66.9, 71.1, 99.0, 105.8, 112.8, 114.1, 117.2, 123.0, 128.0, 129.5, 129.8, 131.2, 142.7, 160.0, 172.1, 181.3. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3004, 2956, 2928, 2859, 1732, 1603, 1511, 1456, 1437, 1339, 1333, 1303, 1273, 1254, 1177, 1119, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J*= 6.7 Hz, 3H), 1.18-1.28 (m, 6H), 1.42-1.67 (m, 3H), 2.02-2.11 (m, 1H), 2.54-2.61 (m, 2H), 2.87-2.96 (m, 2H), 3.07 (s, 3H), 3.11 (d, *J*= 4.4 Hz, 1H), 3.28 (d, *J*= 4.4 Hz, 1H), 3.54-3.71 (m, 7H), 3.78 (s, 3H), 3.80 (s, 3H), 6.61 (d, *J*= 8.3 Hz, 1H), 6.68 (t, *J*= 7.5 Hz, 1H), 6.84 (d, *J*= 8.8 Hz, 2H), 6.94 (d, *J*= 7.3 Hz, 1H), 7.13 (t, *J*= 7.3 Hz, 1H), 7.30 (d, *J*= 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 27.8, 29.6, 30.0, 31.9, 34.7, 40.3, 45.0, 48.4, 52.1, 52.5, 55.3, 61.9, 67.1, 98.2, 105.9, 112.6, 113.8, 117.1, 123.5, 127.8, 127.9, 129.5, 130.4, 142.8, 158.5, 171.2, 178.3; MS (IE) *m/z* 561$[M]^+$; HRMS (IC) *m/z calcd. for:* $[M+1]^+$ 562.3279, *m/z found for:* $[M+1]^+$ 562.3280.

Compound 4e, yield: 40%, *one diastereomer*. Yellow oil; IR ($CHCl_3$) ν 3008, 2922, 2857, 2360, 1733, 1671, 1608, 1511, 1486, 1456, 1382, 1355, 1302, 1272, 1248, 1176, 1118, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23-1.30 (m, 4H), 1.49-1.77 (m, 9H), 2.06-2.13 (m, 1H), 2.40-2.44 (br s, 1H), 2.45-2.56 (m, 2H), 2.83-2.93 (m, 2H), 3.09 (d, 1H, *J*= 4.3 Hz), 3.31 (d, 1H, *J*= 4.3 Hz), 3.57-3.65 (m, 4H), 3.67 (d, 1H, *J*= 11.5 Hz), 3.76 (br s, 1H), 3.79 (s, 3H), 3.82 (s, 4H), 3.84 (d, 1H, *J*= 11.5 Hz), 6.64 (d, 1H, *J*= 8.1 Hz), 6.71 (t, 1H, *J*= 7.5 Hz), 6.83 (d, 2H, *J*= 8.5 Hz), 6.96 (d, 1H, *J*= 7.7 Hz), 7.03 (t, 1H, *J*= 7.5 Hz), 7.29 (d, 2H, *J*= 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.8, 26.6, 26.9, 27.0, 27.2, 27.6, 33.9, 34.8, 36.2, 48.5, 48.6, 52.1, 52.6, 55.4, 59.4, 67.1, 97.9, 106.7, 114.0, 114.0, 115.7, 118.8, 123.0, 127.4, 128.0, 129.9, 130.1, 143.4, 158.6, 171.3, 178.0; MS (IE) *m/z* 573 $[M]^+$; HRMS *m/z calcd. for:* $[M+1]^+$ 574.3280, *m/z found for:* $[M+1]^+$ 574.3262.

Compound 4f, yield: 47%, *dr* = 2/1. **Major isomer:** Yellow solid, 120-122°C; IR ($CHCl_3$) ν 3020, 2974, 2928, 2959, 1735, 1603, 1522, 1493, 1437, 1219, 1118, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.20-1.57 (m, 9H), 1.87 (m, 1H), 2.60 (m, 2H), 2.96 (m, 2H), 3.09 (d, *J*= 4.6 Hz, 1H), 3.25 (d, *J*= 4.6 Hz, 1H), 3.60-3.86 (m, 7H), 3.81 (s, 3H), 6.55 (d, *J*= 8.5 Hz, 1H), 6.93 (d, *J*= 2.5 Hz, 1H), 6.96 (dd, *J*= 8.5, 2.5 Hz, 1H), 7.23-7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 26.0, 29.3, 29.6, 31.7, 35.7, 46.9, 48.2 (2C), 51.8, 52.6, 53.0, 67.0 (2C), 97.2, 106.3, 116.7, 123.2, 124.4, 126.8, 127.4, 128.5 (2C), 129.2 (3CH), 135.7, 141.3, 170.1, 178. 8; MS (IC) *m/z* 552 $[M]^+$. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3019, 2956, 2928, 2858, 1734, 1493, 1455, 1218, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (m, 3H), 1.14-1.59 (m, 9H), 2.16 (m, 1H), 2.58 (m, 2H), 2.92 (m, 2H), 3.12 (d, *J*= 4.6 Hz, 1H), 3.23 (d, *J*= 4.6 Hz, 1H), 3.60-3.83 (m, 7H), 3.78 (s, 3H), 6.52 (d, *J*= 8.5 Hz, 1H), 6.91 (d, *J*= 2.5 Hz, 1H), 6.97 (dd, *J*= 8.5, 2.5 Hz, 1H), 7.23-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 26.4, 29.2, 29.8, 32.0, 35.7, 46.3, 48.5 (2C), 51.5, 52.7, 53.3, 67.1 (2C,), 98.1, 106.2, 117.2, 123.0, 124.3, 126.9, 127.8, 128.5 (2C), 129.3, 129.5, 135.7, 139.4, 170.7, 178.6.

Compound 4g, yield: 64%, *one diastereomer*. Yellow oil; IR ($CHCl_3$) ν 3395, 3032, 3008, 2897, 2860, 1734, 1630, 1611, 1512, 1484, 1455, 1380, 1353, 1301, 1272, 1249, 1176, 1118, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J*= 76.4 Hz), 2.61-2.69 (m, 2H), 2.92-3.01 (m, 2H), 3.05 (d, 1H, *J*= 4.7 Hz), 3.19 (d, 1H, *J*= 4.7 Hz), 3.61 (d, 1H, *J*= 16.8 Hz), 3.63-3.72 (m, 5H), 3.72 (d, 1H, *J*= 16.8 Hz), 3.77 (d, 1H, *J*= 5.1 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 5.84 (dd, 2H, *J*= 1.3, 3.3 Hz), 6.17 (s, 1H), 6.45 (s, 1H), 6.86 (d, 2H, *J*= 8.7 Hz), 7.25 (d, 2H, *J*= 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 35.0, 47.4, 48.3, 49.3, 52.0, 52.6, 55.3, 67.1, 97.4, 97.6, 100.7, 106.2, 108.6, 112.5, 113.9, 114.0, 115.0, 127.8, 130.3, 130.4, 137.6, 141.2, 146.9, 158.5, 171.0, 178.8; MS (IE) *m/z* 521 $[M]^+$; HRMS (EI) *m/z calcd. for:* $[M+1]^+$ 521.21618, *m/z found for:* $[M+1]^+$ 521.21721.

Compound 4h, yield: 70%, *dr* = 3/1. **Major isomer:** Yellow oil; IR ($CHCl_3$) ν 3391, 3032, 3009, 2921, 2859, 1728, 1631, 1602, 1505, 1483, 1455, 1372, 1336, 1302, 1272, 1256, 1236, 1179, 1118, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J*= 7.4 Hz), 1.83-1.96 (m, 1H), 2.19-2.29 (m, 1H), 2.58-2.66 (m, 2H), 2.85 (t, 2H, *J*= 8.1 Hz), 2.93-3.01 (m, 2H), 3.03 (d, 1H, *J*= 4.4 Hz), 3.23 (d, 1H, *J*= 4.4 Hz), 3.56-3.73 (m, 4H), 3.38 (d, 1H, *J*= 16.2 Hz), 3.78 (d, 1H, *J*= 5.1 Hz), 3.83 (d, 1H, *J*= 16.2 Hz), 3.88 (dd, 1H, *J*= 3.7, 8.8 Hz), 4.16-4.39 (m, 2H), 5.84 (d, 2H, *J*= 2.9 Hz), 6.06 (s, 1H), 6.45 (s, 1H), 7.22-7.34 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 33.7, 33.0, 36.0, 47.4, 48.4, 52.0, 53.6, 61.5, 67.1, 97.7, 97.6, 100.7, 106.3, 108.5, 114.9, 126.3, 126.9, 128.4, 128.6, 128.7, 129.4, 135.9, 137.4, 141.2, 141.7, 146.9, 170.5, 178.3; MS (IC) *m/z* 594 $[M-H]^+$. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3397, 3032, 3009, 2922, 2859, 1728, 1631, 1602, 1505, 1483, 1455, 1372, 1329, 1304, 1272, 1256, 1236, 1176, 1118, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J*= 7.1 Hz), 1.80-1.95 (m, 1H), 2.45-2.53 (m, 1H), 2.55-2.64 (m, 2H), 2.82 (t, 2H, *J*= 8.1 Hz), 2.92-3.00 (m, 2H), 3.05 (d, 1H, *J*= 4.6 Hz), 3.16 (d, 1H, *J*= 4.6 Hz), 3.58-3.73 (m, 6H), 3.64 (d, 1H, *J*= 16.4 Hz), 3.80 (d, 1H, *J*= 16.4 Hz), 4.08-4.35 (m, 2H), 5.84 (s, 2H), 5.97 (s, 1H), 6.43 (s, 1H), 7.18-7.37 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 30.7, 33,1, 35.8, 44.7, 48.4, 51.4, 53.1, 61.5, 67.2, 98.1, 98.4, 100.7, 106.0, 108.5, 114.7, 126.1, 126.8, 128.5, 128.6, 128.7, 129.5, 135.1, 135.8, 141.0, 141.7, 147.0, 170.5, 178.3; MS (IE) *m/z* 595 $[M]^+$.

Compound 4i, yield: 50%, *dr* = 3/1. **Major isomer:** Yellow oil; IR ($CHCl_3$) ν 3024, 2958, 2928, 2858,1735, 1496, 1265, 1228, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (m, 3H), 1.31-1.74 (m, 18H), 2.01 (m, 1H), 2.76 (m, 2H), 3.15 (m, 2H), 3.31 (d, *J*= 4.4 Hz, 1H), 3.49 (s, 3H), 3.52 (d, *J*= 4.4 Hz, 1H), 3.72 (m, 4H), 4.01 (dd, *J*= 8.8, 3.0 Hz, 1H), 6.66 (d, *J*= 8.6 Hz, 1H), 6.70 (d, *J*= 3.1 Hz, 1H), 6.77 (dd, *J*= 8.7, 2.6 Hz, 1H), 6.85 (d, *J*= 8.9 Hz, 2H), 7.30 (d, *J*= 8.8 Hz, 2H), 7.38-7.46 (m, 3H), 8.19 (dd, *J*= 8.1, 1.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.1, 29.3, 29.7, 31.5 (3C), 31.7, 34.2, 46.4, 47.9, 51.8, 52.1, 53.4, 66.9 (2C), 97.0, 106.5, 116.5, 116.6 (2C), 119.4, 121.1, 124.3, 126.3 (2C), 127. (2C), 128.3 (2C), 131.3, 131.8, 139.0, 144.9, 148.8, 156.3, 169.8, 171.5; MS (ESI) *m/z* 566 $[M-C_4H_8NO]^+$, 567 $[M-C_6H_{13}]^+$, 651 $[M]^+$, 652 $[M+H]^+$. **Minor isomer:** Yellow oil; IR ($CHCl_3$) ν 3009, 2961, 2928,

2858,1736, 1497, 1271, 1251, 1232, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.20-1.61 (m, 18H), 2.30 (m, 1H), 2.75 (m, 2H), 3.12 (m, 2H), 3.34 (d, *J*= 4.3 Hz, 1H), 3.47 (d, *J*= 4.3 Hz, 1H), 3.61-3.82 (m, 4H), 3.78 (s, 3H), 4.26 (m, 1H), 6.60 (d, *J*= 8.6 Hz, 1H), 6.66 (d, *J*= 2.6 Hz, 1H), 6.75 (dd, *J*= 8.0, 2.6 Hz, 1H), 6.85-6.91 (m, 2H), 7.27-7.46 (m, 4H), 7.94 (d, *J*= 8.2 Hz, 1H), 8.19 (d, *J*= 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 25.1, 26.4, 27.3, 28.1, 29.2, 31.6, 31.9, 34.3, 35.5, 48.1, 50.5, 52.3, 56.6, 63.4, 65.1, 67.0, 72.5, 94.6, 94.8, 101.3, 106.3, 108.2, 116.8, 119.5, 126.0, 126.4, 127.3, 128.4, 131.4, 131.9, 141.5, 147.8, 152.3, 169.9, 172.0.

Compound 4j, yield: 42%, *one diastereomer*. Yellow oil; IR ($CHCl_3$) ν 3065, 3032, 3009, 2956, 2860, 2360, 1733, 1602, 1512, 1498, 1454, 1382, 1355, 1272, 1249, 1177, 1118, 1071, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85-2.07 (m, 2H), 2.43-2.55 (m, 1H), 2.57-2.68 (m, 2H), 2.80-2.87 (m, 1H), 2.92-3.01 (m, 2H), 3.16 (d, 1H, *J*= 4.3 Hz), 3.38 (d, 1H, *J*= 4.3 Hz), 3.58 (d, 1H, *J*= 16.7 Hz), 3.67-3.75 (m, 8H), 3.80 (s, 3H), 3.81 (d, 1H, *J*= 16.7 Hz), 4.39 (d, 1H, *J*= 16.2 Hz), 4.77 (d, 1H, *J*= 16.2 Hz), 6.57 (d, 1H, *J*= 8.1 Hz), 6.67 (t, 1H, *J*= 7.2 Hz), 6.86 (d, 2H, *J*= 8.7 Hz), 6.96 (d, 1H, *J*= 7.2 Hz), 7.00 (t, 1H, *J*= 7.6 Hz), 7.13-7.27 (m, 8H), 7.30 (d, 2H, *J*= 8.7 Hz) 7.40 (d, 2H, *J*= 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 31.7, 33.3, 34.8, 34.8, 45.1, 48.9, 52.2, 52.6, 55.3, 56.5, 60.3, 67.0, 98.7, 105.9, 113.8, 114.3, 117.6, 124.1, 125.9, 127.0, 127.4, 127.7, 128.4, 128.5, 128.5, 129.6, 130.5, 139.0, 141.5, 141.9, 158.5, 171.1, 178.4; MS (ESI) *m/z* 658 $[M+H]^+$, 680 $[M+Na]^+$.

Compound 10, yield: 64%. Yellow oil; IR ($CHCl_3$) ν 3016, 2960, 2929, 2860, 1602, 1508, 1454, 1234, 1225, 1114cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J*= 7.1 Hz, 3H), 1.24 (m, 8H), 1.95 (q, *J*= 6.6 Hz, 2H), 2.92 (t, *J*= 4.4 Hz, 4H), 3.70 (t, *J*= 4.4 Hz, 4H), 3.82 (s, 2H), 4.52 (t, *J*= 6.6 Hz, 1H), 5.36 (dd, *J*= 11.0, 2.0 Hz, 1H), 5.63 (dd, *J*= 17.6, 2.0 Hz, 1H), 6.75 (m, 2H), 6.84 (dd, *J*= 17.6, 11.0 Hz, 1H), 6.75 (m, 2H), 7.11-7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.8, 29.0, 31.7 (2C), 34.7, 51.1 (2C), 53.1, 66.9 (2C), 112.5, 116.6, 118.3, 124.5, 125.2, 126.2, 127.6, 128.4 (4C), 128.9, 133.0, 139.5, 144.1, 151.9, 159.9; MS (IE) *m/z* 459 $[M]^+$, 460 $[M+H]^+$.

General procedure for the synthesis of 4,6-diazaphenanthrene (5): A solution of epoxy-tetrahydroquinoline (**4**) (15.0 mg, 0.029 mmol, 1.0 equiv.) in MeCN (0.30 mL) was cold at 0 °C then TFA (2.0 μL, 0.029 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 0°C for 2 h to 3h. After dilution with saturated aqueous solution of $NaHCO_3$, the product was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by preparative TLC (silica gel, eluent heptane/AcOEt).

Compound 5a. Yellow solid; 216-217 °C; yield: 71%; IR ($CHCl_3$) ν 2956, 2930, 2858, 1732, 1603, 1454, 1435, 1380, 1265, 1146, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J*= 7.0 Hz), 1.26-1.33 (m, 4H), 1.40 (q, 2H, *J*= 8.1 Hz), 1.74 (q, 2H, *J*= 8.1 Hz), 2.99 (m, 2H), 3.30 (m, 2H), 3.40 (t, 2H, *J*= 8.1 Hz), 3.69 (m, 2H), 3.83 (m, 2H), 4.14 (s, 3H), 4.48 (s, 2H), 7.23 (m, 5H), 7.55 (ddd, 1H, *J*= 1.4, 7.0, 8.5 Hz),

7.72 (ddd, 1H, *J*= 1.4, 7.2, 8.1 Hz), 8.09 (dd, 1H, *J*= 1.0, 7.6 Hz), 8.14 (dd, 1H, *J*= 1.0, 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 29.8, 29.8, 31.9, 35.6, 41.5, 51.1, 53.2, 67.9, 121.7, 123.3, 123.6, 126.6, 126.6, 128.5, 129.3, 129.4, 130.3, 138.7, 138.8, 139.0, 143.2, 144.5, 160.3, 165.1, 169.8; MS (IE) *m/z* 497 $[M]^+$, 498 $[M+H]^+$.

Compound 5b. Yellow solid, 123-126 °C; yield: 30%; IR ($CHCl_3$) ν 3020, 2933, 2855, 1731, 1512, 1453, 1434, 1265, 1247, 1231, 1214, 1201 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*= 6.7 Hz, 3H), 1.26-1.40 (m, 6H), 1.62-1.73 (m, 6H), 2.37 (m, 2H), 3.10 (m, 4H), 3.42 (t, *J*= 7.8 Hz, 2H), 3.80 (s, 3H), 4.11 (s, 3H), 4.37 (s, 2H), 6.86 (d, *J*= 10.0 Hz, 2H), 7.26 (d, *J*= 10.0 Hz, 2H), 7.54 (t, *J*= 7.7 Hz, 1H), 7.71 (t, *J*= 7.7 Hz, 1H), 8.11 (m, 2H); MS (ESI) *m/z* 526 $[M+H]^+$.

Compound 5c. Yellow solid, 153-154 ˚C; yield: 75%; IR ($CHCl_3$) ν 2956, 2931, 2858, 1732, 1603, 1511, 1455, 1435, 1380, 1265, 1248, 1177, 1111, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J*= 6.7 Hz), 1.27-1.32 (m, 4H), 1.42 (q, 2H, *J*= 7.7 Hz), 1.76 (q, 2H, *J*= 7.8 Hz), 2.98 (m, 2H), 3.33 (m, 2H), 3.42 (t, 2H, *J*= 7.9 Hz), 3.71 (m, 2H), 3.79 (s, 3H), 3.85 (m, 2H), 4.13 (s, 3H), 4.41 (s, 2H), 6.86 (d, 2H, *J*= 8.3 Hz), 7.22 (d, 2H, *J*= 8.3 Hz), 7.55 (t, 1H, *J*= 7.1 Hz), 7.72 (t, 1H, *J*= 6.9 Hz), 8.08 (d, 1H, *J*= 8.1 Hz), 8.14 (d, 1H, *J*= 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.27, 22.79, 29.81, 29.93, 31.98, 35.65, 40.64, 51.10, 53.18, 55.38, 68.00, 113.89, 121.78, 123.69, 126.69, 128.75, 129.29, 130.36, 130.73, 133.89, 138.83, 139.11, 139.18, 143.14, 144.54, 160.66, 165.10, 169.87; MS (ESI) *m/z* 528 $[M+H]^+$; HRMS (IC) *m/z calcd. for:* $[M+1]^+$ 528.2854, *m/z found for:* $[M+1]^+$ 528.2862.

Compound 5d. Yellow solid; 120-122 °C; yield: 52%; IR ($CHCl_3$) ν 3014, 2958, 2929, 2858, 1734, 1452, 1434, 1265, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.8 Hz, 3H), 1.15-1.29 (m, 4H), 1.34-1.38 (m, 2H), 1.68 (q, *J* = 7.8 Hz, 2H), 2.97 (m, 2H), 3.23 (m, 2H), 3.33 (t, *J*= 7.8 Hz, 2H), 3.71-3.77 (m, 4H), 4.12 (s, 3H), 4.43 (s, 2H), 7.22-7.28 (m, 5H), 7.62 (dd, *J*= 8.5, 2.0 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 29.6, 29.8, 31.9, 35.5, 41.5, 51.1 (2C), 53.3, 67.9 (2C), 122.4, 122.7, 123.5, 126.6, 128.5 (2C), 129.4 (2C), 129.7, 131.6, 132.4, 138.5, 138.6, 139.0, 143.0, 143.4, 161.2, 165.4, 169.4; MS (ESI) *m/z* 532 $[M]^+$.

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REFERENCES AND NOTES

1. J. Zhu and H. Bienaymé, 'Multicomponent Reactions', Wiley-VCH, Weiheim, 2005.
2. A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.,* 2000, **39**, 3168.
3. I. Ugi and R. Meyr, *Angew. Chem.*, 1958, **70**, 702; I. Ugi, R. Meyr and C. Steinbrückner, *Angew.*

Chem., 1959, **71**, 386.

4. H. Bienaymé, C. Hulme, G. Oddon, and P. Schmitt, *Chem. Eur. J.,* 2000, **6**, 3321; C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51; R. V. A. Orru and M. De Greef, *Synthesis,* 2003, 1471; A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, and M. Beller, *Chem. Eur. J.*, 2003, **9**, 4286; V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, and L. Balagopal, *Acc. Chem. Res.*, 2003, **36**, 899; G. Balme, E. Bossharth, and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101; C. Simon, T. Constantieux, and J. Rodriguez, *Eur. J. Org. Chem.*, 2004, 4957; P. Tempest, *Curr. Opin. in Drug Disc and Develop.,* 2005, **8**, 776; L. A. Wessjohann and E. Rüijter, *Top. Curr. Chem.,* 2005, **243**, 137; D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev.*, 2007, **36**, 1095.
5. J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133; A. Dömling, *Chem. Rev.*, 2006, **106**, 17 **.**
6. X. Sun, P. Janvier, G. Zhao, H. Bienaymé, and J. Zhu, *Org. Lett.*, 2001, **3**, 877; P. Janvier, X. Sun, H. Bienaymé, and J. Zhu, *J. Am. Chem. Soc.*, 2002, **124**, 2560; G. S. Tron and J. Zhu, *Synlett,* 2005, 532.
7. D. Bonne, M. Dekhane, and J. Zhu, *Org. Lett.* 2004, **6**, 4771; D. Bonne, M. Dekhane, and J. Zhu, *J. Am. Chem. Soc.*, 2005, **127**, 6926.
8. R. Gámez-Montaño and J. Zhu, *J. Chem. Soc., Chem. Commun.*, 2002, 2448; A. Fayol and J. Zhu, *Angew. Chem. Int. Ed.*, 2002, **41**, 3633; P. Janvier, H. Bienaymé, and J. Zhu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4291; A. Fayol and J. Zhu, *Org. Lett.*, 2005, **7**, 239; D. Bonne, M. Dekhane, and J. Zhu, *Org. Lett.*, 2005, **7**, 5285; D. Bonne, M. Dekhane, and J. Zhu, *Angew. Chem. Int. Ed.*, 2007, **46**, 2485.
9. G. Zhao, X. Sun, H. Bienaymé, and J. Zhu, *J. Am. Chem. Soc.*, 2001, **123**, 6700; P. Janvier, M. Bois-Choussy, H. Bienaymé, and J. Zhu, *Angew. Chem. Int. Ed.*, 2003, **42**, 811; T. Pirali, G. C. Tron, and J. Zhu, *Org. Lett.,* 2006, **8**, 4145; C. Bughin, G. Zhao, H. Bienaymé, and J. Zhu, *Chem. Eur J.*, 2006, **12**, 1174; C. Bughin, G. Masson, and J. Zhu, *J. Org. Chem.*, 2007, **72**, 1826.
10. E. González-Zamora, A. Fayol, M. Bois-Choussy, A. Chiaroni, and J. Zhu, *J. Chem. Soc., Chem. Commun.*, 2001, 1684.
11. A. Fayol, C. Housseman, X. Sun, P. Janvier, H. Bienaymé, and J. Zhu, *Synthesis,* 2005, 161; C. Housseman and J. Zhu, *Synlett*, 2006, 1777; A. Dömling, B. Beck, T. Fuchs, and A. Yazbak, *J. Comb. Chem.*, 2006, **8**, 872.
12. For a recent comprehensive survey on the Lewis acid-catalyzed α-addition of isocyanoacetamide to aldehyde, see: S. X. Wang, M.-X. Wang, D.-X. Wang, and J. Zhu, *Eur. J. Org. Chem.*, 2007, 4076; S. X. Wang, M.-X. Wang, D.-X. Wang, and J. Zhu, *Org. Lett.,* 2007, **9**, 3615.
13. For selected intramolecular cycloaddition of oxazole, see: J. I. Levin and S. M. Weinreb, *J. Org.*

Chem., 1984, **49**, 4325; M. E. Jung and L. J. Street, *J. Am. Chem. Soc*., 1984, **106**, 8327; C. Subramanyam, M. Noguchi, and S. M. Weinreb, *J. Org. Chem*., 1989, **54**, 5580; E. Vedejs, D. W. Piotrowski, and F. C. Tucci, *J. Org. Chem*., 2000, **65**, 5498; A. Padwa, M. Dimitroff, and B. Liu, *Org. Lett.,* 2000, **2**, 3233; L. A. Paquette and I. Efremov, *J. Am. Chem. Soc*., 2001, **123**, 4492; M. Ohba, I. Natsutani, and T. Sakuma, *Tetrahedron Lett*., 2004, **45**, 6471; For reviews, see: M. Y. Karpeiskii and V. L. Florent'ev, *Russ. Chem. Rev.,* 1969, **38**, 540; P. A. Jacobi, in *Adv. in Heterocyclic Nat. Prod. Syn*. (ed. by W. H. Pearson), 1992, Vol. 2, pp. 251-298.

14. For the domino Ugi 4CR/Intramolecular Diels-Alder cycloaddition of furan, see: K. Paulvannan, *Tetrahedron Lett*., 1999, **40**, 1851; K. Paulvannan, T. Chen, and J. W. Jacobs, *Synlett,* 1999, 1609; D. Lee, J. K. Sello, and S. L. Schreiber, *Org. Lett*., 2000, **2**, 709; D. L. Wright, C. V. Robotham, and K. Aboud, *Tetrahedron Lett*., 2002, **43**, 943; Ugi 4CR/Intramolecular Diels-Alder cycloaddition of pyrrole, see: Paulvannan, K. *J. Org. Chem*., 2004, **69**, 1207.
15. L. Banfi and R. Riva, "*Org. React."* Vol. 65, ed. by A. B. Charette, John Wiley & Sons Inc., 2005, pp. 1-140.
16. R. Gámez-Montaño, E. González-Zamora, P. Potier, and J. Zhu, *Tetrahedron,* 2002, **58**, 6351; A. Fayol and J. Zhu, *Tetrahedron,* 2005, **61**, 11511.