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One-pot enyne metathesis/Diels–Alder reaction for the construction of highly functionalized novel polycyclic aza-compounds

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Abstract

Various tricyclic dienes were synthesized via enyne metathesis using the first generation Grubbs catalyst. The enyne metathesis proceeded smoothly in refluxing CH_2Cl_2 with a low catalyst loading (3.0 mol %), giving good yields (72–89%) of the tricyclic products **6** and **16**. The resulting 1,3-dienes are suitable precursors of polycyclic structures via a Diels–Alder process. One-pot RCM/Diels–Alder reactions of the enyne products with dienophiles proceeded smoothly to afford polycyclic compounds as a single cycloadduct. The structures of the Diels–Alder adducts were determined by ^{1}H NMR spectra and X-ray analysis. The cycloadducts were formed via the approach of the dienophiles towards the diene in *endo* mode.
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Keywords: Enyne metathesis; Cycloaddition; Isoindole; Benzoindolizidine; Benzopyrrolizidine; One-pot procedure

1. Introduction

Transition metals have played an important role in recent synthetic organic chemistry and are now important tools for the synthesis of polyfunctional natural products and biologically active substances. Olefin metathesis, in particular ring-closing metathesis (RCM) is now regarded as a standard carbon–carbon bond forming reaction in modern organic chemistry.[1]

Intramolecular enyne metathesis is also attractive because it produces exocyclic 1,3-dienes,[2] which can be further converted to complex polycyclic molecules by a Diels–Alder reaction.[3] This protocol has been widely applied in organic synthesis to elegantly obtain numerous polycyclic systems such as perhydroindenes,[3e] tetrahydropyridines,[3b] hexahydroisoindoles,[3a] aza- and oxa-steroids,[3i] tricyclic and tetracyclic benzoxepin[3h] derivatives and polycyclic-β-lactams.[3k]

This programme can be accomplished either by the addition of all of the reagents at once or by the addition of the dienophile after the metathesis is completed. In the first case only electron deficient dienophiles can be used, in order to avoid cross-metathesis reactions.

Heterocyclic compounds containing pyrrolizidine or indolizidine skeletons are commonly observed structural units of many alkaloids, which display a large range of interesting biological activities, such as the inhibition of various glycosidases and in treatments for diabetes, cancer and viral infections.[4] Because of the importance of these products, the synthesis of their analogues has become an important goal for synthetic chemists in recent years.

In this context and in connection with our current research interests in the preparation of novel biologically relevant nitrogenated and oxygenated compounds,[5,6] we wish to now describe the use of isoindole enynes for the construction of highly functionalized benzoindolizidines and benzopyrrolizidines by using a one-pot enyne metathesis/Diels–Alder reaction from commercially available homophthalic acid.

Retrosynthetically, we envisaged that a phthalimidine of type **A** might serve as suitable precursor for the preparation, via enyne metathesis using the first generation Grubbs catalyst

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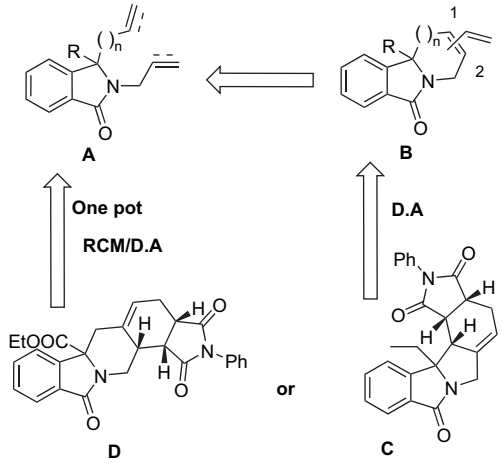
($\mathbf{G_1}$), of the corresponding ring systems **B** (benzoindolizidines and benzopyrrolizidines). The latter contain a butadiene moiety, allowing an intermolecular [4+2] cycloaddition reaction leading to the formation of fused polycyclic products of the type **C** or **D** in the one-pot protocol shown in Scheme 1.

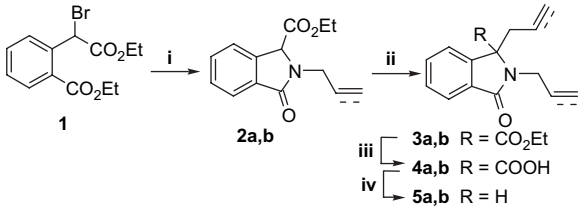


Scheme 1. Retrosynthetic approach.

2. Results and discussion

2.1. Synthesis of benzoindolizidine derivatives using RCM of enynes

To test our plan, various phthalimidines **3** and **5** were prepared as shown in Scheme 2. Diethyl α-bromohomophthalate **1**,[6] upon treatment with allylamine or propargylamine for 8 h in acetonitrile at room temperature, offered the phtalimidines **2a** and **b**, respectively, in good yield.

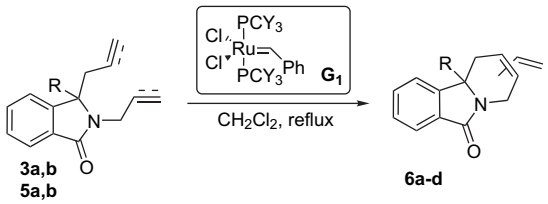


Scheme 2. Reagents and conditions: (i) allylamine (**2a**) or propargylamine (**2b**), CH_3CN, rt, 8 h; (ii) allyl bromide or propargyl bromide, K_2CO_3, CH_3CN, reflux, 8 h; (iii) NaOH, EtOH/H_2O, rt, 1 h; (iv) acetone, reflux, 8 h.

The 2-alkylated derivatives **3a**,**b**, were prepared by the deprotonation of phtalimidines **2** with potassium carbonate, followed by reaction of propargyl bromide (**3a**) or allyl bromide (**3b**). Compounds **3** were then transformed into the corresponding acids **4a**,**b** under basic saponification conditions.[7] Thermal decarboxylation of compounds **4a**,**b** gave the second precursors **5a**,**b** for the (RCM) reaction. Before exploring the one-pot procedure, we decided to test the feasibility of the enyne metathesis reaction.

In their pioneering work on enyne metathesis, Castells and Mori[8] established that the first generation Grubbs catalyst $\mathbf{G_1}$ can be used to transform terminal alkyne derivatives into highly functionalized polycyclic systems in a rapid and completely atom-economical process.[9] Hence, we elected to use $\mathbf{G_1}$ to study the best reaction conditions. Compound **3a** was used as a model for our study. We reacted this compound with 1 mol %, 3 mol % and 5 mol % of $\mathbf{G_1}$ in CH_2Cl_2 at room temperature and at reflux. We found that the best conditions consisted of using 3 mol % of catalyst in refluxing CH_2Cl_2.

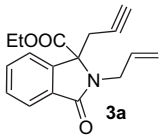
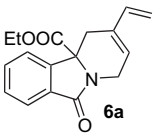
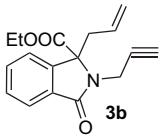
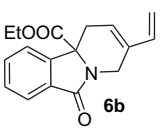
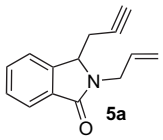
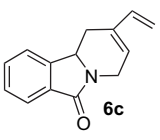
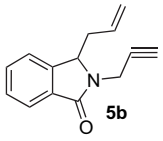
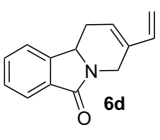
The above selected conditions were used with the rest of the substrates **3** and **5**, which cyclized (1.5 h) to afford the fused compounds **6a**–**d** (Scheme 3). Silica gel column chromatography was ultimately used to remove the catalyst, and the results are summarized in Table 1.



Scheme 3. Enyne metathesis of **3a**,**b** and **5a**,**b**.

It should be noted that both compounds **6b** and **6d** are much less stable than their regioisomers **6a** and **6c**. An NMR study of these compounds conducted a few hours after purification by column chromatography showed the appearance of

Table 1
Enyne metathesis produced via Scheme 3

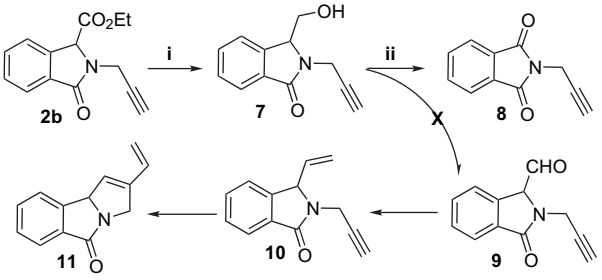
Entry[a,b,c]	Substrate	Product	Yield %
1			89
2			79
3			72
4			84

[a] All the reactions were conducted under inert atmosphere (argon).
[b] All the reactions were carried out using 3 mol % of the first-generation Grubbs catalyst.
[c] In this study, ethylene was not required.

decomposition peaks. These peaks rapidly became predominant and the signals corresponding to the initial expected products disappeared. Generally, reaction products purified by chromatography are contaminated by traces of ruthenium species. Sometimes, their stability is moderate and they can be degraded[10,11] by ROMP (Ring-Opening Metathesis) or ADMET (Acyclic Diene Metathesis Polymerization) processes. It is likely that **6b** and **6d** can be degraded by such processes, although a spontaneous decomposition may also occur. The use of the second generation Grubbs catalyst gave no significant improvement. As this catalyst and its by-products are less electrophilic than the ruthenium salts from the Grubbs first generation catalyst, this survey seems to indicate the spontaneous degradation of **6b** and **6d**. On the other hand, **6a** and **6c** were found to be more stable and thus less sensitive to the presence of residual ruthenium salts.

2.2. Synthesis of benzopyrrolizidine derivatives using RCM of enyne

Our initial efforts in the synthesis of benzopyrrolizidine **16** started from the phthalimidine-3-carboxylate derivative **2b**. Reduction of the ester function with $LiBH_4$ in THF[12] afforded **7** in 88% yield. However, subsequent oxidation of **7** to aldehyde **9** turned out to be problematic in our hands. Our attempts to prepare aldehyde **9** by the oxidation of alcohol **7** with various oxidizing agents (swern,[13] PCC[14]) were unsuccessful, affording just the imide **8** when PCC was used (Scheme 4).



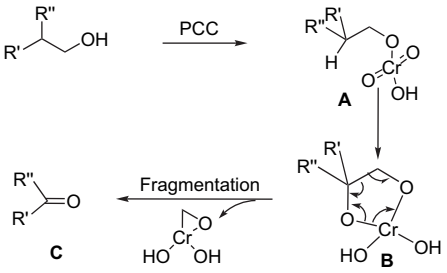
Scheme 4. Reagents and conditions: (i) $LiBH_4$, THF, rt, 2 h, 88%; (ii) PCC, CH_2Cl_2, rt, 2 h, 86%.

Two possible oxidation mechanisms leading to product **8** can be proposed.

The primary alcohol **7** reacts with PCC to furnish a chromic ester. Instead of following a classical oxidation mechanism, it undergoes an intramolecular metalloxidation of the activated C–H bond (benzilic position) to lead to the equivalent of the 1,3-dioxolane derivative **B** in which the anomeric atom of carbon is replaced with chromium (Fig. 1).[15]

This probably unstable species could directly supply phthalimide **8** by radicular fragmentation.[16]

A second pathway could consist in the decomposition of the intermediate **B** to give the exocyclic methylene lactam **C**, which leads to phthalimide **8**, after metathesis with the released chromium species, Figure 2.



(1)

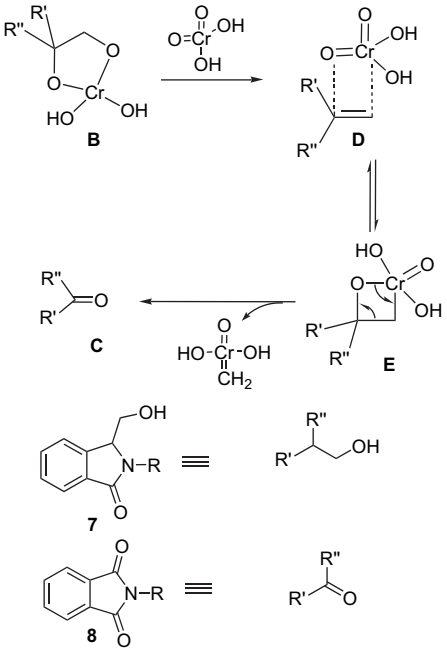
Figure 1. First plausible mechanism for the formation of **8**.

In order to avoid the formation of imide **8**, we have substituted the hydrogen atom in the α position of the ester function with an ethyl group. We should remark that the alkylation of this position by a group, which can be removed after the reaction such as TMS (Me_3Si) has failed.[17]

Thus, the derivative **12** has been prepared from compound **2b** by a procedure similar to that used for the synthesis of **3b**. Reduction of **12** with $LiBH_4$ under standard conditions followed by PCC oxidation of the resulting alcohol **13**, gave the aldehyde **14** in 71% yield after the two steps. Wittig olefination[18] of **14** with $Ph_3P{=}CH_2$ (Ph_3PCH_3Br/*t*-BuOK) gave the desired component **15** in 57% yield. Enyne metathesis of **15** under the conditions described above (see Section 2.1) produced **16** in 73% yield (Scheme 5).

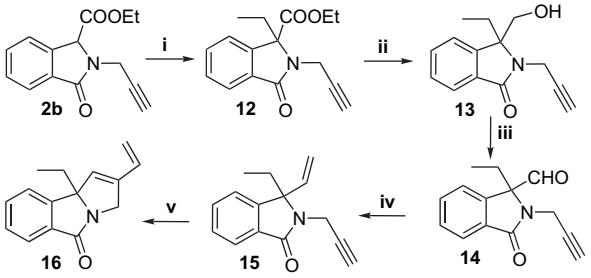
2.3. One-pot enyne metathesis/Diels–Alder reaction

Next, we turned our attention to the synthesis of polycyclic compounds using Diels–Alder reaction of some of these cyclized products. As a model we performed the cyclization of compounds **6a** and **16** with *N*-phenylmaleimide **17**. When



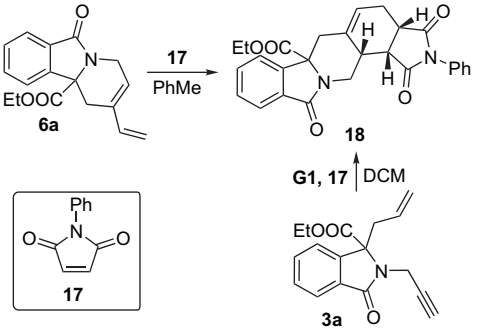
(2)

Figure 2. Second possible mechanism for the formation of **8**.



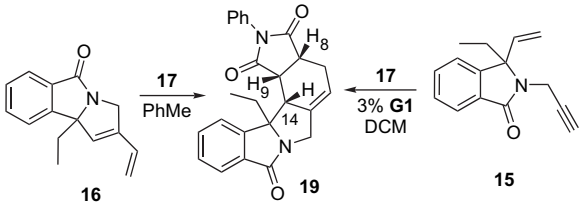
Scheme 5. Reagents and conditions: (i) EtI, K_2CO_3, CH_3CN, reflux, 8 h, 72%; (ii) $LiBH_4$, THF, rt, 2 h, 84%; (iii) PCC, CH_2Cl_2, rt, 1 h, 93%; (iv) Ph_3PCH_3Br/*t*-BuOK, THF, rt, 2 h, 57%; (v) **G_1**, CH_2Cl_2, reflux, 2 h, 73%.

a mixture of **6a** and **17** in toluene was stirred at 60–70 °C for 24 h, the reaction proceeded cleanly to give the pentacyclic compound **18** as a single stereoisomer in 86% yield (Scheme 6).



Scheme 6. One-pot enyne metathesis/Diels–Alder reaction of **3a**.

Similarly, the same reaction conditions applied to **16** afforded the fused polycyclic compound **19** as a single stereoisomer (*endo* adduct) in 73% yield (Scheme 7).



Scheme 7. One-pot enyne metathesis/Diels–Alder reaction of **15**.

Encouraged by the easy diastereoselective formation of the polycyclic compounds, we tried to obtain the adducts from enynes **3a** and **15** by adding the dienophile to the metathesis reaction mixture in one pot.

We were happy to find that the reaction of **3a** and **15**, which has been catalyzed by 3 mol % of **G_1** in the presence of 2 equiv of *N*-phenylmaleimide **17** gave **18** (Scheme 6) with a 82% yield and **19** (Scheme 7) with a 90% yield, respectively. The reaction was complete after 48 h in refluxing dichloromethane, the total conversion of the enyne having been verified by TLC.

The yield of the two-step one-pot reaction of enyne **3a** shows a possible beneficial action of the ruthenium complex in the Diels–Alder reaction.[19] The relative stereochemistry of **19** was unambiguously determined by usual spectrometric methods (IR, ^1H, 2D and ^{13}C NMR) and X-ray crystallography analysis (Fig. 3).[20]

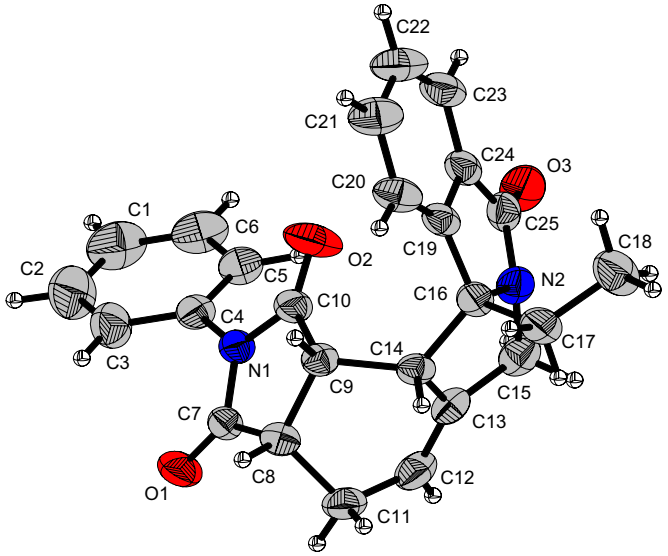


Figure 3. ORTEP drawing of structure **19**.

3. Conclusion

In summary, the results reported herein indicate that nitrogen-heterocycles such as benzoindolizidines or benzopyrrolizidines having a 1,3-diene moiety can easily be synthesized by using enyne ring-closing metathesis. Under Diels–Alder reaction conditions they lead to variable interesting polycyclic systems. Furthermore the tandem RCM/Diels–Alder reaction in a one-pot procedure was tested successfully. Further studies along these lines are currently in progress.

4. Experimental part

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded, respectively, at 200 and 50 MHz. The infrared spectra were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. Thin-layer chromatography (TLC) was performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230–400 mesh) was used for flash chromatography separations. Gas chromatography–mass spectrometry (GC–MS) was performed with a GC apparatus equipped with a 25 m capillary column, at 90 °C for 2 min, then 10 °C/min up to 290 °C. Some reactions were performed under an inert atmosphere. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France. Abbreviations: dd=doublet

of doublets, m=multiplet, s=singlet, d=doublet, q=quartet, t=triplet, sl=large singlet, DCM=dichloromethane. Grubbs catalysts 1 and 2 were purchased from Sigma–Aldrich. Tetrahydrofuran was dried by distillation from sodium/benzophenone. Dichloromethane was dried by distillation from calcium hydride, toluene was distilled from sodium and acetonitrile was dried by distillation from P_2O_5.

4.2. Typical procedure of primary amine condensation

To an ice chilled solution of diethyl α-bromophthalate **1** (2 g, 6.34 mmol) in dry acetonitrile (50 mL) was added under argon, allylamine or propargylamine (12.7 mol) diluted in 10 mL of acetonitrile. The mixture was stirred at room temperature for 8 h. The salt that formed was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (dichloromethane/acetone 90:10).

4.2.1. Ethyl-3-oxo-2-(prop-2-enyl)isoindoline-1-carboxylate (*2a*)

Colourless oil; yield: 86%; IR (ν, cm^{-1}, $CHCl_3$) 1747.9, 1695.9; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.23 (t, J=7.0 Hz, 3H), 3.76 (dd, J=7.8, 15.6 Hz, 1H), 4.05–4.32 (m, 2H), 4.71 (dd, J=4.7, 15.6 Hz, 1H), 5.05–5.23 (m, 3H), 5.77–5.91 (m, 1H), 7.37–7.61 (m, 3H), 7.82 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.4 (CH_3), 44.2 (CH_2), 61.8 (CH), 62.3 (CH_2), 119.1 (CH_2), 122.9 (CH), 124.2 (CH), 129.5 (CH), 132.0 (Cq), 132.1 (CH), 132.8 (CH), 139.6 (Cq), 168.3 (C=O), 168.5 (C=O); LRMS *m/z* 245 ($M^{+\bullet}$, 25), 172 (base), 130 (18). Anal. Calcd for $C_{14}H_{15}NO_3$ (245.28): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.94; H, 6.42; N, 5.95.

4.2.2. Ethyl-3-oxo-2-(prop-2-ynyl)isoindoline-1-carboxylate (*2b*)

Yellow solid; yield: 84%; mp 73–75 °C; IR (ν, cm^{-1}, $CHCl_3$) 1747.8, 1698.5; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.28 (t, J=8.61 Hz, 3H), 2.27 (t, J=2.35 Hz, 1H), 4.05 (dd, J=2.3, 18.0 Hz, 1H), 4.14–4.34 (m, 2H), 4.96 (dd, J=2.3, 18.0 Hz, 1H), 5.35 (s, 1H), 7.38–7.69 (m, 3H), 7.82 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.4 (CH_3), 31.2 (CH_2), 61.4 (CH), 62.5 (CH_2), 73.1 (CH), 73.7 (Cq), 123.2 (CH), 124.3 (CH), 129.6 (CH), 131.4 (Cq), 132.5 (CH), 139.5 (Cq), 168.1 (C=O), 168.2 (C=O); LRMS *m/z* 243 ($M^{+\bullet}$, 30), 215 (31), 170 (base). Anal. Calcd for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.47; H, 5.64; N, 6.02.

4.3. Alkylation with propargyl bromide or allyl bromide

To a mixture of **2** (8.23 mmol), potassium carbonate (1.25 g, 9.05 mmol) and 50 mL of acetonitrile was added propargyl bromide (allyl bromide) (9.87 mmol). The reaction mixture was refluxed 8 h. The cooled resulting suspension was filtered off. The filtrate was concentrated in vacuo, diluted with water, and extracted with dichloromethane (3×30 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 75:25) to give the phthalimidines **3a**,**b**.

4.3.1. Ethyl-2-allyl-3-oxo-1-(prop-2-ynyl)isoindoline-1-carboxylate (*3a*)

Yellow solid; yield: 95%; mp 138–140 °C; IR (ν, cm^{-1}, $CHCl_3$) 1712.1, 1738.4 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.13 (t, J=7.0 Hz, 3H), 1.74 (t, J=2.3 Hz, 1H), 3.13 (dd, J=2.3, 17.2 Hz, 1H), 3.25 (dd, J=2.3, 17.2 Hz, 1H), 3.97–4.25 (m, 4H), 5.09–5.37 (m, 2H), 5.84–6.08 (m, 1H), 7.43–7.59 (m, 3H), 7.84 (d, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.0 (CH_3), 25.3 (CH_2), 44.1 (CH_2), 62.6 (CH_2), 70.2 (Cq), 72.3 (Cq+CH), 118.0 (CH_2), 121.5 (CH), 123.9 (CH), 129.6 (CH), 132.0 (Cq), 132.3 (CH), 132.6 (CH), 143.3 (Cq), 168.9 (C=O), 169.6 (C=O); LRMS *m/z* 283 ($M^{+\bullet}$, 1), 244 (98), 210 (base). Anal. Calcd for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.45; H, 6.36; N, 5.32.

4.3.2. Ethyl-1-allyl-3-oxo-2-(prop-2-ynyl)isoindoline-1-carboxylate (*3b*)

Yellow solid; yield: 89%; mp 74–76 °C; IR (ν, cm^{-1}, $CHCl_3$) 1734.5, 1697.9; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.16 (t, J=7.0 Hz, 3H), 2.21–2.24 (t, J=7.0 Hz, 1H), 3.19 (d, J=7.0 Hz, 2H), 4.04–4.18 (m, 2H), 4.35 (dd, J=2.3, 18.0 Hz, 1H), 4.45 (dd, J=2.3, 18.0 Hz, 1H), 4.86–5.06 (m, 2H), 5.14–5.34 (m, 1H), 7.42–7.59 (m, 3H), 7.76–7.85 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.2 (CH_3), 30.6 (CH_2), 38.0 (CH_2), 62.6 (CH_2), 71.5 (Cq), 72.6 (CH), 78.4 (Cq), 120.6 (CH_2), 122.2 (CH), 124.2 (CH), 129.5 (CH), 130.5 (CH), 131.5 (Cq), 132.6 (CH), 143.8 (Cq), 168.6 (C=O), 170.4 (C=O); LRMS *m/z* 244 ($M^{+\bullet}$–39, 1), 242 (98), 210 (base). Anal. Calcd for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.45; H, 6.33; N, 5.23.

4.4. Preparation of acids *4a*,*b*

To an ice chilled solution of the esters **3a**,**b** (4 mmol) in 20 mL of ethanol was added sodium hydroxide solution (0.32 g, 8 mmol in 5 mL of water). The reaction mixture was stirred for 15 min concentrated in vacuo, diluted with water, and washed with dichloromethane. The aqueous layer was acidified with 10% hydrochloric acid solution to pH=1. The aqueous layer was extracted with dichloromethane (3×30 mL). The organic phase was dried over $MgSO_4$, filtered then concentrated under reduced pressure to give the corresponding acids **4a**,**b**, which were used without purification in the following steps.

4.4.1. 2-Allyl-3-oxo-1-(prop-2-ynyl)-isoindoline-1-carboxylic acid (*4a*)

White solid; yield: 84%; mp 114–115 °C; IR (ν, cm^{-1}, $CHCl_3$) 3423.8, 1709.2, 1693.3; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.69 (t, J=2.3 Hz, 1H), 3.12 (dd, J=2.3, 17.2 Hz, 1H), 3.24 (dd, J=2.3, 17.2 Hz, 1H), 4.09 (dd, J=6.2,

15.6 Hz, 1H), 4.28 (dd, *J*=6.2, 15.6 Hz, 1H), 5.03–5.32 (m, 2H), 5.81–6.04 (m, 1H), 6.33 (sl, 1H), 7.38–7.59 (m, 3H), 7.65 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 25.4 (CH_2), 44.7 (CH_2), 66.5 (Cq), 70.7 (CH), 72.7 (Cq), 118.6 (CH_2), 121.9 (CH), 124.3 (CH), 130.0 (CH), 131.9 (Cq), 132.8 (CH), 133.4 (CH), 143.2 (Cq), 168.8 (C=O), 172.4 (C=O); LRMS *m/z* 210 ($M^{+\bullet}$–45, 1), 170 (base), 169 (27). Anal. Calcd for $C_{15}H_{13}NO_3$ (255.28): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.97; H, 5.41; N, 5.78.

4.4.2. 1-Allyl-3-oxo-2-(prop-2-ynyl) isoindoline-1-carboxylic acid (**4b**)

White solid; yield: 85%; mp 109–111 °C; IR (ν, cm^{-1}, $CHCl_3$) 3429.9, 1693.8, 1641.6; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.21 (t, *J*=2.2 Hz, 1H), 3.14–3.29 (m, 2H), 3.69 (sl, 1H), 4.33 (dd, *J*=2.2, 18.0 Hz, 1H), 4.53 (dd, *J*=2.2, 18.0 Hz, 1H), 4.89–5.04 (m, 2H), 5.20–5.33 (m, 1H), 7.45–7.60 (m, 3H), 7.82 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 30.8 (CH_2), 37.9 (CH_2), 73.0 (CH), 78.1 (2Cq), 120.9 (CH_2), 122.5 (CH), 124.4 (CH), 125.4 (Cq), 129.8 (CH), 130.2 (CH), 132.8 (CH), 143.2 (Cq), 169.4 (C=O), 170.0 (C=O); LRMS *m/z* 210 ($M^{+\bullet}$–45, <1), 171 (71), 170 (base). Anal. Calcd for $C_{15}H_{13}NO_3$ (255.28): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.96; H, 5.41; N, 5.78.

4.5. Decarboxylation of acids **4a**,**b**

A mixture of acid **4a**,**b** and 50 mL of acetone was refluxed for 6 h (monitored by TLC). The reaction mixture was concentrated under reduced pressure to give **5a**,**b**. These compounds were pure enough to be used without any purification.

4.5.1. 2-Allyl-3-(prop-2-ynyl)-isoindolin-1-one (**5a**)

Yellow oil; yield: 84%; IR (ν, cm^{-1}, $CHCl_3$) 1686.0; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.95 (t, *J*=2.3 Hz, 1H), 2.62 (ddd, *J*=2.3, 6.2, 17.2 Hz, 1H), 2.85 (ddd, *J*=2.3, 6.2, 17.2 Hz, 1H), 3.82 (dd, *J*=7.8, 16.4 Hz, 1H), 4.71 (m, 2H), 5.15–5.33 (m, 2H), 5.62–5.94 (m, 1H), 7.43–7.57 (m, 3H), 7.83 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 21.3 (CH_2), 41.8 (CH_2), 56.4 (CH), 70.8 (Cq), 77.2 (CH), 117.0 (CH_2), 121.4 (CH), 122.5 (CH), 127.5 (CH), 130.6 (CH), 131.0 (Cq), 132.0 (CH), 143.2 (Cq), 167.1 (C=O); LRMS *m/z* 211 ($M^{+\bullet}$, 10), 131 (20), 172 (base). Anal. Calcd for $C_{14}H_{13}NO$ (211.27): C, 79.59; H, 6.20; N, 6.63. Found: C, 79.98; H, 6.48; N, 6.91.

4.5.2. 3-Allyl-2-(prop-2-ynyl)-2,3-dihydro-isoindolin-1-one (**5b**)

Yellow oil; yield: 85%; IR (ν, cm^{-1}, $CHCl_3$) 1687.3; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.24 (t, *J*=2.3 Hz, 1H), 2.65–2.89 (m, 2H), 3.93 (dd, *J*=2.3, 18.0 Hz, 1H), 4.78–4.98 (m, 3H), 5.08 (dd, *J*=2.3, 18.0 Hz, 1H), 5.25–5.53 (m, 1H), 7.40–7.57 (m, 3H), 7.79–7.83 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 30.0 (CH_2), 35.6 (CH_2), 58.6 (CH), 72.6 (Cq), 78.2 (CH), 119.5 (CH_2), 122.6 (CH), 123.9 (CH), 128.5 (CH), 131.5 (CH), 131.9 (CH), 144.9 (2Cq), 168.1 (C=O); LRMS *m/z* 211 ($M^{+\bullet}$, 1), 172 (base), 171 (16). Anal. Calcd for $C_{14}H_{13}NO$ (211.27): C, 79.59; H, 6.20; N, 6.63. Found: C, 79.93; H, 6.48; N, 6.87.

4.6. Preparation of benzoindolizines

4.6.1. General procedure used for the ring-closing metathesis reaction

To 1 mmol of **3a**,**b** or **5a**,**b** dissolved in 5 mL of dry dichloromethane under argon, was added 3 mol % of the Grubbs first generation catalyst, $\mathbf{G_1}$. The mixture was refluxed until completion (TLC). Evaporation of the solvent and purification by column chromatography (cyclohexane/EtOAc 75:25) yielded the corresponding diene.

4.6.2. Ethyl-6-oxo-2-vinyl-1,4-dihydro-6H-pyrido[2,1-a]-isoindole-10b-carboxylate (**6a**)

Yellow solid; yield: 89%; mp 80–82 °C; IR (ν, cm^{-1}, $CHCl_3$) 1735.3, 1691.1; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.18 (t, *J*=7.0 Hz, 3H), 2.16 (d, *J*=15.6 Hz, 1H), 3.61 (d, *J*=15.6 Hz, 1H), 3.96–4.22 (m, 3H), 4.69–4.79 (m, 1H), 5.03–5.25 (m, 2H), 5.85 (d, *J*=3.1 Hz, 1H), 6.43 (dd, *J*=10.9, 18.0 Hz, 1H), 7.47–7.66 (m, 3H), 7.88 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.3 (CH_3), 32.5 (CH_2), 39.4 (CH_2), 62.6 (CH_2), 66.4 (Cq), 113.1 (CH_2), 122.2 (CH), 124.2 (CH), 124.4 (CH), 129.7 (CH), 132.0 (Cq), 132.1 (Cq), 132.2 (CH), 137.6 (CH), 144.7 (Cq), 167.1 (C=O), 170.0 (C=O); LRMS *m/z* 283 ($M^{+\bullet}$, 9), 182 (13), 210 (base). Anal. Calcd for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.48; H, 6.36; N, 5.13.

4.6.3. 2-Vinyl-1,10b-dihydro-4H-pyrido[2,1-a]-isoindol-6-one (**6c**)

The eluent used for the flash chromatography was a mixture dichloromethane/acetone (95:5). Viscous liquid; yield: 72%; IR (ν, cm^{-1}, $CHCl_3$) 1682.5; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.86–2.01 (m, 1H), 2.92–3.02 (m, 1H), 3.93 (m, 1H), 4.46 (dd, *J*=4.7, 10.9 Hz, 1H), 4.72 (dt, *J*=3.1, 18.3 Hz, 1H), 5.03–5.26 (m, 2H), 5.82–5.89 (m, 1H), 6.46 (dd, *J*=10.9, 18.0 Hz, 1H), 7.42–7.59 (m, 3H), 7.86 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 29.2 (CH_2), 39.9 (CH_2), 55.0 (CH), 112.6 (CH_2), 122.2 (CH), 124.0 (CH), 124.5 (CH), 128.6 (CH), 131.6 (CH), 132.7 (Cq), 132.9 (Cq), 138.0 (CH), 146.1 (Cq), 167.1 (C=O); LRMS *m/z* 211 ($M^{+\bullet}$, 30), 182 (17), 79 (base). Anal. Calcd for $C_{14}H_{13}NO$ (211.27): C, 79.59; H, 6.20; N, 6.63. Found: C, 80.01; H, 6.52; N, 6.92.

4.7. Typical procedure of the Diels–Alder reaction

To a solution of ester **6a** (283 mg, 1 mmol) in 5 mL of toluene was added (860 mg, 5 mmol) *N*-phenylmaleimide **17**. The mixture was refluxed for 24 h and the solvent was evaporated. The resulting crude material was purified by column chromatography eluting with cyclohexane/EtOAc (50:50) to give **19**. White solid; yield: 86%; mp 226–228 °C; IR (ν, cm^{-1}, $CHCl_3$) 1739.3, 1711.0, 1684.5, 1683.2; ^{1}H NMR

(200 MHz, $CDCl_3$, 25 °C) δ 1.19 (t, J=7.0 Hz, 3H), 2.24–2.35 (m, 2H), 2.80–2.98 (m, 2H), 3.28–3.47 (m, 3H), 4.04–4.21 (m, 3H), 4.79 (dd, J=9.3, 13.3 Hz, 1H), 5.82–5.98 (m, 1H), 7.04–7.11 (m, 2H), 7.29–7.63 (m, 6H), 7.81–7.85 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.4 (CH_3), 25.6 (CH_2), 32.1 (CH), 39.7 (CH_2), 40.2 (CH), 40.4 (CH_2), 43.2 (CH), 62.5 (CH_2), 68.6 (Cq), 122.6 (CH), 124.1 (2CH), 126.6 (2CH), 128.9 (CH), 129.3 (2CH), 129.7 (CH), 31.8 (Cq), 132.1 (CH), 135.1 (2Cq), 143.9 (Cq), 168.8 (C=O), 170.8 (C=O), 176.6 (C=O), 178.5 (C=O); LRMS *m/z* 283 ($M^{+\bullet}$–173, 9), 210 (base), 182 (13). Anal. Calcd for $C_{27}H_{24}N_2O_5$ (456.50): C, 71.04; H, 5.30; N, 6.14. Found: C, 71.46; H, 5.63; N, 6.43.

4.8. Preparation of benzopyrrolizidines

4.8.1. Ethyl-1-ethyl-3-oxo-2-(prop-2-ynyl)isoindoline-1-carboxyate (12)

To a solution of **2b** (2 g, 8.23 mmol) in 100 mL of acetonitrile was added potassium carbonate (K_2CO_3) (1.36 g, 8.87 mmol) followed by 3.9 mL of ethyliodide (EtI) (48.96 mmol), and the reaction mixture was stirred at reflux for 8 h. When the reaction was finished, the solution was filtrated through Celite, evaporated, washed with water then extracted with dichloromethane (3×30 mL), dried over $MgSO_4$ and evaporated under reduced pressure, then purified by chromatography on silica gel with a mixture of dichloromethane/acetone (95:5) to give **12**. Viscous liquid; yield: 72%; IR (ν, cm^{-1}, $CHCl_3$) 1734.2, 1689.8; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.49 (t, J=7.43 Hz, 3H), 1.15 (t, J=7.43 Hz, 3H), 2.15–2.25 (t, J=2.3 Hz, 1H), 2.38–2.54 (m, 2H), 4.04–4.35 (m, 3H), 4.52 (dd, J=2.3, 18.0 Hz, 1H), 7.41–7.55 (m, 3H), 7.77–7.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 7.3 (CH_3), 14.5 (CH_3), 26.6 (CH_2), 30.3 (CH_2), 62.4 (CH_2), 72.0 (CH), 72.8 (Cq), 72.9 (CH), 122.0 (CH), 124.2 (CH), 129.4 (CH), 131.8 (Cq), 132.6 (CH), 143.7 (Cq), 168.8 (C=O), 170.8 (C=O); LRMS *m/z* 241 ($M^{+\bullet}$–30, 3), 198 (12), 186 (base). Anal. Calcd for $C_{16}H_{17}NO_3$ (271.32): C, 70.83; H, 6.32; N, 5.16. Found: C, 71.19; H, 6.58; N, 5.36.

4.9. 3-Ethyl-3-(hydroxymethyl)-2-(prop-2-ynyl)-isoindolin-1-one (13)

To a solution of **12** (271 mg, 1 mmol) placed in 10 mL of anhydrous THF, was added dropwise, under argon, 0.7 mL of $LiBH_4$ (solution 2 M in THF) (30.50 mg, 1.4 mmol). The reaction mixture was stirred at room temperature for 1 h (monitored by TLC) washed with water, extracted with dichloromethane (3×20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **13**. The compound was pure enough to be used without any purification. Yield: 84%; mp 87–89 °C; IR (ν, cm^{-1}, $CHCl_3$) 3305.4, 1690.0; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.38 (t, J=7.0 Hz, 3H), 1.80–2.04 (m, 2H), 2.20–2.22 (t, J=2.35 Hz, 1H), 3.85 (dd, J=2.35, 18.0 Hz, 1H), 3.89 (d, J=12.5 Hz, 1H), 4.04 (d, J=12.5 Hz, 1H), 4.68 (dd, J=2.35, 18.0 Hz, 1H), 5.10 (sl, 1H), 7.53–7.30 (m, 3H), 7.89 (d, J=7.05 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 7.0 (CH_3), 26.2 (CH_2), 30.0 (CH_2), 62.1 (CH_2), 71.7 (Cq), 72.5 (Cq), 78.0 (CH), 121.7 (CH), 123.9 (CH), 129.1 (CH), 131.5 (Cq), 132.3 (CH), 143.4 (Cq), 168.5 (C=O); LRMS *m/z* 229 ($M^{+\bullet}$, 3), 198 (base), 170 (30). Anal. Calcd for $C_{14}H_{15}NO_2$ (229.28): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.69; H, 6.87; N, 6.38.

4.10. 1-Ethyl-3-oxo-2-(prop-2-ynyl)-isoindoline-1-carbaldehyde (14)

To a solution of PCC (147 mg, 0.682 mmol) and molecular sieves (4 Å) (68 mg) in anhydrous dichloromethane (5 mL), was added under argon 78 mg of alcohol **13** (0.34 mmol). The reaction mixture was stirred at room temperature, the evolution of the reaction was followed by TLC in dichloromethane/acetone (90:10). The crude solution was filtered through Celite, evaporated then purified by chromatography on silica with the mixture dichloromethane/acetone (95:5) to give **14**. White solid; yield: 93%; mp 84–86 °C; IR (ν, cm^{-1}, $CHCl_3$) 1733.4, 1698.3; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.48 (t, J=7.83 Hz, 3H), 2.10–2.35 (m, 2H), 2.52 (septuplet, J=7.8, 15.6 Hz, 1H), 3.89 (dd, J=2.3, 18.0 Hz, 1H), 4.92 (dd, J=2.3, 18.0 Hz, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.50–7.65 (m, 2H), 7.91 (d, J=7.0 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 6.5 (CH_3), 21.8 (CH_2), 29.3 (CH_2), 74.1 (2Cq), 79.0 (CH), 122.8 (CH), 124.5 (CH), 130.0 (CH), 132.5 (Cq), 133.1 (CH), 139.5 (Cq), 168.6 (C=O), 196.8 (C=O); LRMS *m/z* 199 ($M^{+\bullet}$–28, 15), 198 (base), 132 (16).

4.11. 3-Ethyl-2-(prop-2-ynyl)-3-vinylisoindolin-1-one (15)

To a solution of methyltriphenylphosphonium bromide (2.34 g, 6.54 mmol) in 100 mL of THF was added potassium tertiobutylate (586.9 mg, 5.23 mmol). The mixture was stirred for 30 min, and then a solution of aldehyde **14** (981 mg, 4.36 mmol) in 30 mL THF was added dropwise. The reaction mixture was stirred at room temperature for 2 h (monitored by TLC), washed with water, extracted with the dichloromethane (3×50 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (dichloromethane/acetone 95:5) to give **15**. White solid; yield: 57%; mp 111–113 °C; IR (ν, cm^{-1}, $CHCl_3$) 1687.6; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.46 (t, J=7.0 Hz, 3H), 2.01–2.35 (m, 3H), 3.95 (dd, J=2.3, 18.0 Hz, 1H), 4.38 (dd, J=2.3, 18.0 Hz, 1H), 5.20–5.48 (m, 2H), 5.71 (dd, J=10.1, 18.0 Hz, 1H), 7.21 (d, J=7.0 Hz, 1H), 7.35–7.61 (m, 2H), 7.81 (d, J=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 7.5 (CH_3), 26.3 (CH_2), 28.6 (CH_2), 70.2 (Cq), 71.2 (Cq), 79.0 (CH), 117.3 (CH_2), 122.0 (CH), 124.0 (CH), 128.5 (CH), 131.8 (Cq), 132.4 (CH), 139.0 (CH), 151.6 (Cq), 168.4 (C=O); LRMS *m/z* 225 ($M^{+\bullet}$, 2), 198 (5), 196 (base). Anal. Calcd for $C_{15}H_{15}NO$ (225.29): C, 79.97; H, 6.71; N, 6.22. Found: C, 81.38; H, 7.03; N, 6.49.

4.12. 9b-Ethyl-2-vinyl-3,9b-dihydropyrrolo[2,1-a]-isoindol-5-one (**16**)

We have used the same protocol, which was described in the preparation of **6a–d**. The eluent used for the flash chromatography was dichloromethane/acetone (95:5). Yellow solid; yield: 73%; mp 72–74 °C; IR (ν, cm^{-1}, $CHCl_3$) 1689.8; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.74 (t, J=7.8 Hz, 3H), 1.90 (q, J=7.8 Hz, 2H), 4.02 (dd, J=2.3, 14.8 Hz, 1H), 4.71 (d, J=14.8 Hz, 1H), 5.24–5.12 (m, 2H), 5.94 (s, 1H), 6.43 (dd, J=10.9, 18.0 Hz, 1H), 7.33–7.58 (m, 3H), 7.78 (d, J=7.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 9.4 (CH_3), 32.7 (CH_2), 51.1 (CH_2), 80.9 (Cq), 118.3 (CH_2), 122.5 (CH), 125.4 (CH), 129.2 (CH), 130.5 (CH), 131.4 (CH), 133.3 (CH), 142.6 (2Cq), 151.3 (Cq), 176.2 (C=O); LRMS *m/z* 225 ($M^{+\bullet}$, 2), 197 (96), 196 (base). Anal. Calcd for $C_{15}H_{15}NO$ (225.29): C, 79.97; H, 6.71; N, 6.22. Found: C, 80.39; H, 7.03; N, 6.55.

4.13. Diels–Alder adduct (**19**)

We have used the same protocol, which was described in the preparation of **18**. The eluent used for the flash chromatography was the mixture of cyclohexane/EtOAc (30:70). White solid; yield: 73%; mp 232–234 °C; IR (ν, cm^{-1}, $CHCl_3$) 1686.1, 1686.8, 1683.3; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.57 (t, J=7.0 Hz, 3H), 1.90–2.05 (m, 2H), 2.21–2.45 (m, 1H), 2.65–2.72 (m, 1H), 2.76 (dd, J=15.65, J=7.83 Hz, 1H), 3.23 (t, J=8.61 Hz, 1H), 3.46 (dd, J=3.91, 8.61 Hz, 1H), 3.98 (dt, J=2.3, 16.4 Hz, 1H), 4.61 (dt, J=2.3, 16.4 Hz, 1H), 5.78–5.81 (m, 1H), 6.87–7.03 (m, 2H), 7.61–7.12 (m, 6H), 7.82 (d, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 8.2 (CH_3), 27.2 (CH_2), 35.1 (CH_2), 40.6 (CH), 43.1 (CH), 44.4 (CH_2), 47.7 (CH), 74.2 (Cq), 117.7 (CH), 121.4 (CH), 124.4 (CH), 126.5 (2CH), 128.5 (CH), 128.6 (CH), 129.2 (2CH), 131.5 (CH), 131.7 (Cq), 136.8 (Cq), 146.6 (Cq), 147.3 (Cq), 170.3 (C=O), 174.1 (C=O), 178.4 (C=O). Anal. Calcd for $C_{25}H_{22}N_2O_3$ (398.47): C, 75.36; H, 5.75; N, 7.03. Found: C, 75.73; H, 6.03; N, 7.32.

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References and notes

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