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Synthesis of diversely functionalized pyrrolizidines and indolizidines using olefin ring-closing metathesis

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ABSTRACT

Various nitrogen-fused tricyclic compounds, having benzoindolizidine and benzopyrrolizidines ring systems were synthesized via ene–ene metathesis using the first and second-generation Grubbs catalyst. The ene–ene metathesis proceeded smoothly in refluxing CH_2Cl_2 with 3.0 mol % of **G_1**, giving good yields (78–86%) of the benzoindolizidine products **12a**,**b**. The benzopyrrolizidine **6** was prepared after optimization in 64% yield by using 5.0+5.0 mol % of **G_2**. The resulting olefin moiety of the indolizidine framework is a suitable precursor for polyhydroxy structures via the Sharpless process. The structures of the polyhydroxylated adducts were determined by ^{1}H NMR spectra and single-crystal X-ray analysis.

1. Introduction

During the two past decades, the transition metal-catalyzed metathesis reaction has emerged as one of the most powerful methods in synthetic organic chemistry.[1] The ring-closing metathesis (RCM) has been widely used for the construction of heterocyclic compounds bearing a nitrogen atom at one of the ring fused positions. In the majority of these syntheses the first and second-generation olefin metathesis catalysts **G_1** and **G_2** and the Hoveyda–Grubbs catalyst, **G_3**, have been employed (Fig. 1).

On the other hand, nitrogen-fused polycyclic alkaloids having indolizidine (**I**), and pyrrolizidine (**II**) ring systems, have been the targets of many synthetic efforts due to their wide range of biological and physiological properties (Fig. 2).

For example, indolizidines and pyrrolizidines such as castanospermine, crispine A, crotarecine and certain natural and synthetic analogues attracted special interest by virtue of their varied and pharmaceutically useful biological actions as potential antiviral, antitumor, specific inhibitors of protein kinases (Cdk4), and glycosidase inhibition agents.[2–4]

Unfortunately many of these compounds are also toxic to human cells. Nevertheless, there is a need to prepare new alkaloid analogues to allow a better understanding of the structure–activity

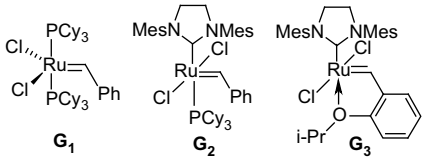

Figure 1. Ruthenium metathesis catalysts.

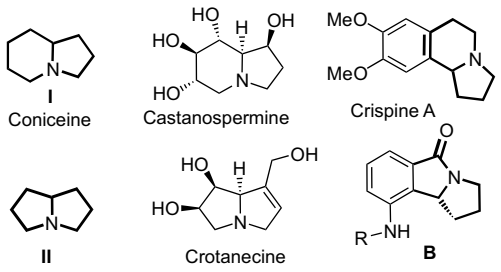

Figure 2.

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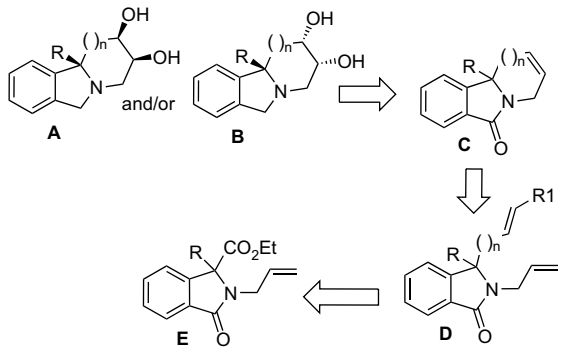


Scheme 1. Retrosynthetic approach.

relationship (SAR) and to develop more potent, selective, and less toxic drugs.

However, among these analogues, only a few structures contain a quaternary carbon at the α-position to the nitrogen at the ring junction and/or a benzene ring at the junction with the five(six)-membered ring.[5,6] Among the efforts in this area and in connection with our current research interests in the preparation of novel biologically relevant nitrogenated and oxygenated compounds,[7,8] we have recently delineated a convenient access to various new indolizidine and pyrrolizidine benzanalogs by using enyne ring-closing metathesis.[7b]

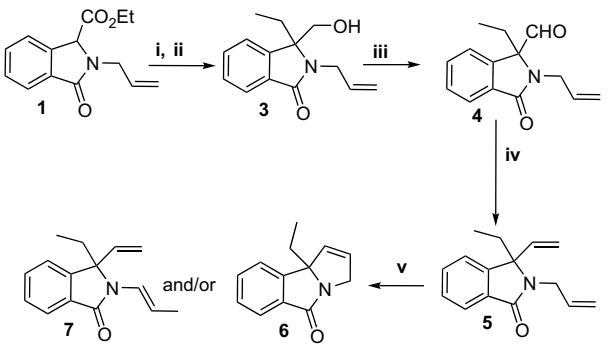
Pursuing our investigation on the synthesis of indolizidine and pyrrolizidines benzanalogs, we describe herein the efficient construction of new benzoindolizidines, benzopyrrolizidines, and their polyhydroxy derivatives via the ene–ene ring-closing metathesis reaction (RCM).

Our retrosynthetic strategy is outlined in Scheme 1. Benzoindolizidines (pyrrolizidines) of type **A** and/or **B** may arise from the *syn*-dihydroxylation of the unsaturated indolizidine (pyrrolizidine) precursor **C**, which itself can be readily prepared via a ruthenium catalyzed ring-closing metathesis (RCM) as the key step in our synthetic strategy from diolefinic phthalimidine **D**. The latter compound **D** is readily accessible from the well-known phthalimidine **E**.

2. Results and discussion

2.1. Synthesis of benzopyrrolizidine derivatives using RCM

As depicted in Scheme 2, we envisaged that ring-closing metathesis (RCM) of diolefinic phthalimidine **5** could provide a highly functionalized tricyclic lactam **6** that may serve as a valuable precursor for polyhydroxylated benzopyrrolizidine compounds of type



Scheme 2. Reagents and conditions: (i) Ethyl iodide, K_2CO_3, CH_3CN, reflux, 8 h, 78%; (ii) $LiBH_4$, THF, rt, 2 h, 82%; (iii) PCC, CH_2Cl_2, rt, 2 h, 93%; (iv) $Ph_3PCH_3Br/^tBuOK$, THF, rt, 2 h, 73%; (v) $\mathbf{G_1}$ or $\mathbf{G_2}$.

Table 1
Cyclization of derivative **5** produced via Scheme 2

Entry	Catalyst[a,b]	Solvent	Time (h)	**5** (%)	**6** (%)	**7** (%)
1	$\mathbf{G_1}$ (5 mol %)	CH_2Cl_2	24	40	20	—
2	$\mathbf{G_1}$ (5+5 mol %)	CH_2Cl_2	8+12	35	20	—
3	$\mathbf{G_1}$ or $\mathbf{G_2}$ (5 mol %)	$C_2H_4Cl_2$	24	10	30	20
4	$\mathbf{G_2}$ (5+5 mol %)	$C_2H_4Cl_2$	4+8	10	30	25
5	$\mathbf{G_3}$ (5 mol %)	$C_2H_4Cl_2$	24	Traces	34	20
6	$\mathbf{G_1}$ or $\mathbf{G_2}$ or $\mathbf{G_3}$ (5 mol %)	Toluene	24	—	—	70
7	$\mathbf{G_2}$ (5 mol %)	CH_2Cl_2	8	—	42	—
8	$\mathbf{G_2}$ (10 mol %)	CH_2Cl_2	8	—	40	—
9	$\mathbf{G_3}$ (5 mol %)	CH_2Cl_2	24	Traces	44	—
10	$\mathbf{G_2}$ (5+5 mol %)	CH_2Cl_2	4+8	—	64	—
11	$\mathbf{G_2}$ (5+5+5 mol %)	CH_2Cl_2	4+8+8	—	62	—
12	$\mathbf{G_3}$ (5+5 mol %)	CH_2Cl_2	4+8	—	60	—

[a] All the reactions were carried out under reflux and Argon.
[b] In this study, ethylene was not required.

8. The synthesis of diolefinic phthalimidine **5** starts from the known bicyclic lactam **1**.[7b] Alkylation at the α-position relative to the nitrogen of the ring junction and subsequent reduction of the ester function under standard conditions afforded the phthalimidine **3** in 64% yield after the two steps. Oxidation of alcohol **3** by PCC in CH_2Cl_2 at room temperature produced the aldehyde **4** in 93% yield.[7b] The thus isolated crude aldehyde **4** was then converted into diolefinic **5** by using $PPh_3{=}CH_2$ ($Ph_3PCH_3Br/^tBuOK$) in 73% yield, as previously described by our group.[7b] With diolefinic phthalimidine **5** in hand, we were ready to test the ring-closing metathesis to form the pyrrolizidine derivative **6**.

RCM of **5** was investigated under various conditions (Table 1). The reaction of **5** under the catalysis of 5 mol % $\mathbf{G_1}$ in CH_2Cl_2 at reflux for 24 h gave **6** in a low yield of 20% along with the starting material **5** in 40% yield (Table 1, entry 1). A similar result was obtained when **5** was treated with 5 mol % $\mathbf{G_1}$ in CH_2Cl_2 for 8 h followed by the addition of another portion of 5 mol % $\mathbf{G_1}$ with continuous stirring for 12 h (Table 1, entry 2).

When CH_2Cl_2 was replaced by $C_2H_4Cl_2$, **6** was obtained in 30% yield along with a migrated double bond isomer **7** in 20% yield (Table 1, entry 3). Migration of the double bond is dependent on the temperature at which RCM was carried out. Increasing the temperature yielded an increasing amount of **7**. When toluene was used for 24 h at reflux, rearrangement product **7** was isolated in 70% yield, devoid of any sign of the expected benzopyrrolyzidine **6** (Table 1, entry 6). This isomerization seems to be catalyzed by a ruthenium degradation product, probably a ruthenium hydride species.[9]

In order to prevent the migration of the double bond, the use of additives in an RCM reaction has proved to be successful in several cases. This inspired us to investigate the role of some additives on the RCM reaction of **5**. The investigated additives were tricyclohexylphosphine oxide and 1,4-benzoquinone (Table 2). Tricyclohexylphosphine oxide is an additive, which has been reported by Prunet and co-workers[10] to prevent olefin migration of a specific substrate, did not prevent the isomerization of **5** (Table 2, entries 1

Table 2
Influence of additives on the product distribution

Entry[c]	Additive[b]	Solvent[a]	**5** (%)	**6** (%)	**7** (%)
1	Tricyclohexylphosphine oxide	Toluene	—	—	65
2	Tricyclohexylphosphine oxide	$C_2H_4Cl_2$	10	30	20
3	1,4-Benzoquinone	Toluene	60	<5	
4	1,4-Benzoquinone	$C_2H_4Cl_2$	28	36	—

[a] All the reactions were carried out at reflux under Argon.
[b] In this study, 0.1 equiv (relative to **5**) are used.
[c] The ratio of the different products was determined by integration of the ^1H NMR spectra of the crude reaction mixtures.

and 2). On the other hand, 1,4-benzoquinones, which are described by Grubbs and co-workers[11] to prevent olefin isomerization of a number of allylic ethers and long-chain aliphatic alkenes, work well in suppressing olefin migration during RCM reaction of substrate **5**, but without real improvement of the yield of the desired pyrrolizidine **6**. When **5** was reacted together with $\mathbf{G_2}$ (5 mol %) and 1,4-benzoquinone (10 mol %) in toluene, only trace amounts (<5%) of **6** were obtained (Table 2, entry 3). When toluene was replaced by $C_2H_4Cl_2$, the 1,4-benzoquinone additive is also effective to prevent the isomerization of **5** to **7** (Table 2, entry 4). Under these conditions, **6** was obtained in 36% yield along with the starting material **5** in 28% yield. Additional catalyst loading (10 mol %) did not improve the yield.

$\mathbf{G_2}$ and $\mathbf{G_3}$ were found to be superior catalysts for the reaction of **5** in CH_2Cl_2 at reflux; under these conditions **6** was isolated in 42 and 44% yields, respectively (Table 1, entries 7 and 9). Encouraged by the above results, and to improve the yield of the desired compound, the RCM reaction of **5** was carried out under various conditions. We reacted this compound with 10 mol % (entry 8), 2×5 mol % (entry 10) and 3×5 mol % (entry 11) of catalyst $\mathbf{G_2}$. We found that the reaction of **5**, catalyzed by 2×5 mol % of $\mathbf{G_2}$ afforded **6** in 64% yield after column chromatography. It should be noted that the use of the Hoveyda–Grubbs catalyst, $\mathbf{G_3}$ gave a similar result (entry 12). In all cases the use of ethylene gas gave no significant improvement.

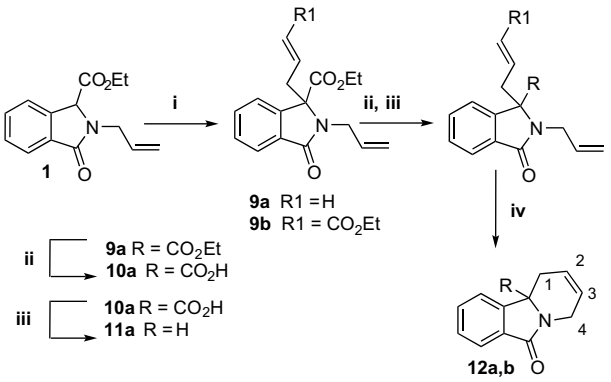
Having successfully achieved the conversion of diene **5** into pyrrolizidine **6**, the next step consisted in the *syn*-dihydroxylation of the olefin moiety of the pyrrolizidine framework. Submitted to hydroxylation conditions (osmium tetroxide (OsO_4)/*N*-methylmorpholine *N*-oxide (NMO)),[12] compound **6** gave a complex crude mixture, in which the expected dihydroxy pyrrolizidine **8** was only the minor product (<10%) and could not be isolated. Unfortunately, despite a variation of reaction times, solvent ratios, and temperatures, no improvement concerning the overall yield of compound **8** could be achieved (Scheme 3).

Since we were unable to obtain a chromatographically pure sample of the dihydroxy benzopyrrolizidine **8**, we turned our attention to the preparation of the polyhydroxy indolizidine benzoanalogs.

2.2. Synthesis of polyhydroxylated benzoindolizidine derivatives

The route we employed is shown in Scheme 4, where *N*-allyl phthalimidine ethyl ester **1** was α-alkylated with allyl bromide or with ethyl 4-bromocrotonate, using K_2CO_3 as base to gave the first precursors **9a**,**b** for the synthesis of the benzoindolizidines in 98 and 94% yields, respectively. Basic saponification of the ester function of **9a** under standard conditions followed by thermal decarboxylation[7b] of the resulting acid **10a**, gave the second precursor **11a** for the RCM reaction in 70% yield after the two steps.

RCM[13] was carried out on the substrate **11a**, which cyclized smoothly (1 h) at 40 °C in CH_2Cl_2 with 3 mol % of the first generation Grubbs catalyst $\mathbf{G_1}$ to afford the lactam **12a**. Silica gel column chromatography was used to remove the catalyst, yielding the pure tricyclic **12a** in isolated yield of 83%. Similarly, the same reaction



Scheme 4. Reagents and conditions: (i) Allyl bromide (ethyl 4-bromocrotonate), K_2CO_3, CH_3CN, reflux, 8 h, 98% (94%); (ii) NaOH, EtOH/H_2O, rt, 1 h, 85%; (iii) acetone, reflux, 8 h, 83%; (iv) $\mathbf{G_1}$, CH_2Cl_2, reflux, 1 h, **12a**, 83%, **12b**, 86 (78)%.

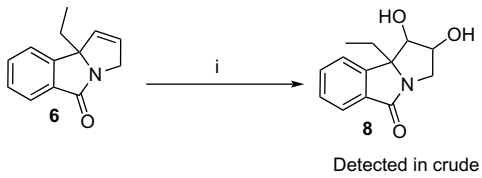
conditions applied to **9a** (1 h) and **9b** (1.5 h)[14] afforded the fused compound **12b** in 86 and 78% yields, respectively.

The structures of indolizidines **12** were determined by the ^1H and ^{13}C NMR spectra, including DEPT programs and elemental analyses. For example, the ^1H NMR spectrum of **12b** displayed the methylene group of the –N–CH_2-function as an AB system due to the diastereotopy with a coupling constant of J=13.2 Hz characteristic of *gem* protons. More interestingly, the ^{13}C NMR spectrum showed the disappearance of two peaks corresponding to the methylene carbons (–CH_2– in the allyl groups) in **9a** at δ=117 and 120 ppm, and revealed the presence of two tertiary carbons (–CH–) corresponding to C2 and C3 of the olefin moiety in the indolizidine framework of **12b** at δ=122 ppm.

The next stage for our synthesis strategy was the diastereoselective dihydroxylation of the olefin moiety of the indolizidine framework. Introduction of cis-dihydroxylation on **12a** was carried out using osmium tetroxide (OsO_4, NMO) to give a mixture of the corresponding diol derivatives **13** and **14** in 78% yield. Since this mixture of diastereomers could not be separated by column chromatography, the mixture was converted into the corresponding acetonide derivatives **15** and **16** using 2,2-dimetoxypropane and APTS under conventional conditions.[15] Column chromatography of the resulting mixture provided **15** and **16** (**15**/**16**∼1:2) in 77% yield.

The stereochemical assignments of the relative configurations of the bishydroxylated products **13** and **14** were deduced from the ^1H NMR coupling constants of their derivatives **15** and **16**. For example, the ^1H NMR spectra of the most abundant diastereomer (less polar) **16** reveals a doublet of doublets of doublets for the axial proton H_{1ax} (δ=1.48 ppm, J_{gem}=14.0 Hz, $J_{H1ax\text{-}H10b}$=11.7 Hz, $J_{H1ax\text{-}H2}$=3.1 Hz) and a doublet of doublets of doublets for the equatorial proton H_{1eq} (δ=2.65 ppm, J_{gem}=14.0 Hz, $J_{H1eq\text{-}H10b}$=3.1 Hz, $J_{Heq\text{-}H2}$=2.3 Hz). The different coupling constants support the proposed structure in which the dihydroxylation occurred mainly from the face of the double bond in a cis relationship with regard to H_{10b} (Fig. 3).

In the same manner, the ^1H NMR spectrum of **15** exhibits a doublet of doublets of doublets for the axial proton H_{1ax}



Scheme 3. Reagents and conditions: (i) OsO_4 cat, NMO, acetone:H_2O 1:1, rt, 6 h.

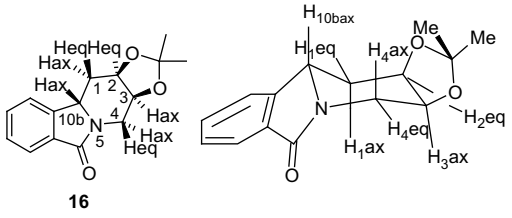


Figure 3.

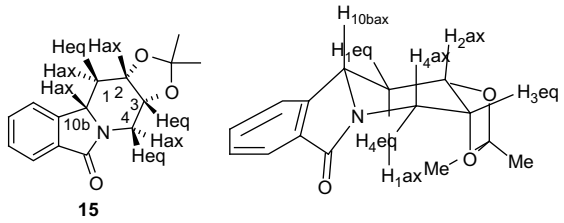
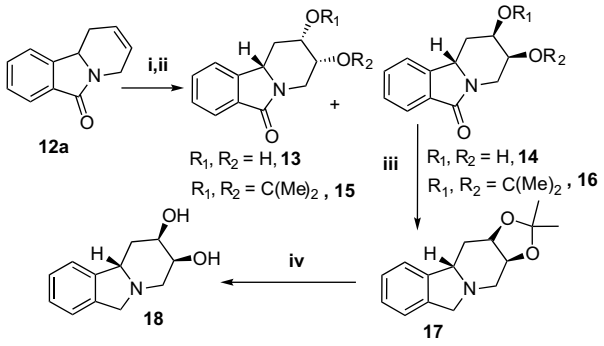


Figure 4.

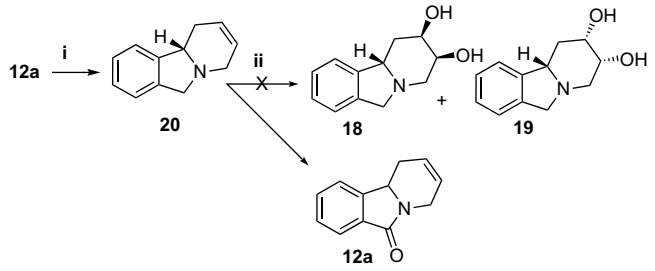


Scheme 5. Reagents and conditions: (i) OsO_4 cat, NMO, acetone:H_2O 1:1, rt, 6 h, 78%; (ii) DMP, PTSA cat, CH_2Cl_2, rt, 2 h, **15** 25%, **16** 52%; (iii) $LiAlH_4$, THF, rt, 1 h, 45%; (iv) HCl, EtOH, rt, 12 h.

(δ=1.45 ppm, J_{gem}=13.3 Hz, $J_{H1ax\text{-}H10b}$=9.3 Hz, $J_{H1ax\text{-}H2}$=10.1 Hz). The proton H_{1eq} also appears as a doublet of doublet of doublet (δ=2.44 ppm, J_{gem}=13.3 Hz, $J_{H1eq\text{-}H10b}$=3.9 Hz, $J_{Heq\text{-}H2}$=5.4 Hz). These observations allow us to assign an axial relationship between H_2 and H_{10b} (H_{2ax} and H_{10bax}) (Fig. 4).

The following step involved the reduction of the lactam carbonyl. Although the reduction of amide to amine has been disclosed several times, some of these reported procedures ($BH_3 \cdot Me_2S$)[16] were not reproducible in our hands. The best reagent to obtain **17** was $LiAlH_4$ in THF according to the protocol developed by Greene and co-workers;[17] which gave the target molecule in a moderate yield of 45% (Scheme 5). Finally, removal of the protecting group[18] failed. The desired benzoindolizidine **18** could only be detected spectroscopically in the highly complex spectrum of the crude mixture. These reaction products decomposed after few minutes at room temperature. Therefore, all attempts to isolate **18** were unsuccessful.

We have also investigated an alternative route leading to the polyhydroxylated indolizidines, starting from **12a**. The pathways of these transformations are summarized in Scheme 6. We thought that the dihydroxyindolizidines **18** and **19** could be derived from indolizidine **20** by cis-dihydroxylation and, in turn, **20** could be prepared from **12a** by $LiAlH_4$ reduction. Thus, treatment of **12a** by the same methodology reported for the reduction of **17** gave **20** in moderate yield of 55%.



Scheme 6. Reagents and conditions: (i) $LiAlH_4$, THF, rt, 1 h, 55%; (ii) OsO_4 cat, NMO, acetone:H_2O 1:1, rt, 6 h, 52%.

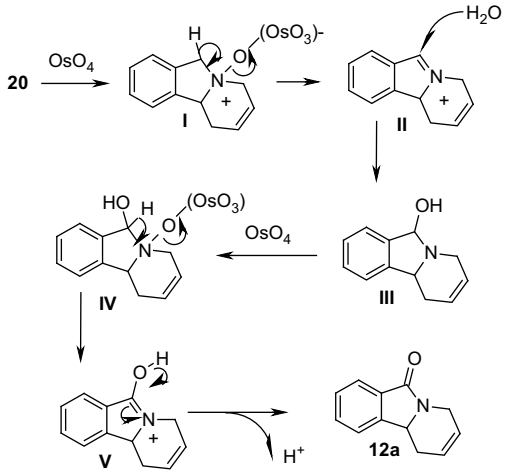


Figure 5. First plausible mechanism for the formation of **12a**.

Compound **20**, under dihydroxylation conditions (OsO_4, NMO), did not yield the desired dihydroxyindolizidines **18** and **19**. Instead, and unexpectedly, the compound formed in the reaction was assigned the benzoindolizidone structure **12a** on the basis of elemental analyses and NMR spectra.

It is interesting to note that oxidation of tertiary amines to amides and lactams is well-known for reagents such as RuO_4,[19] (batho)$_2$-Cu,[20] MnO_2,[21] $KMnO_4$,[22] $Hg(OAc)_2$,[23] and recently by OsO_4.[24]

Two different mechanistic scenarios can be proposed to explain the formation of **12a**. First, the mechanism of this oxidation (Fig. 5) is based on the mechanistic proposals for oxidation of amines by OsO_4 recently reported by Liotta and Sletten.[24]

In an alternative scenario, the mechanism for this oxidation is based on the proposals for the action of chiral ligands (AD-mix-α or AD-mix-β) in asymmetric oxidation. For example, the action of AD-mix-α is based on a coordination of the nitrogen atom of the quinuclidine core on the metal center followed by an asymmetrical oxidation of the double bond by effect of proximity.

In our case, it is probable that the tertiary amine of the substrate **20** coordinates to osmium tetroxide and that the transitory species **A** resulting from this complexation uses a process of insertion of an oxygen on the adjacent benzylic CH_2 to form the OH group **B**, which will be oxidized on a carbonyl function in the last step (Fig. 6).[25]

To complete our study, and in order to obtain polyhydroxy indolizidines with a quaternary carbon at the α-position to the nitrogen at the ring junction, cis-hydroxylation of **12b** was

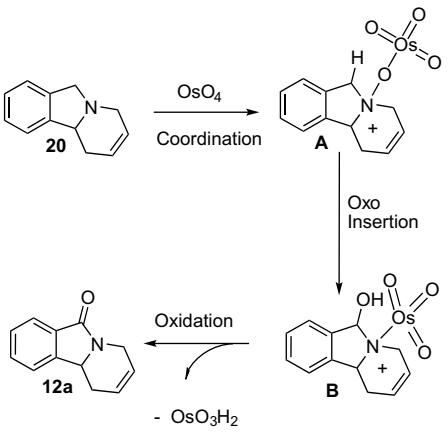
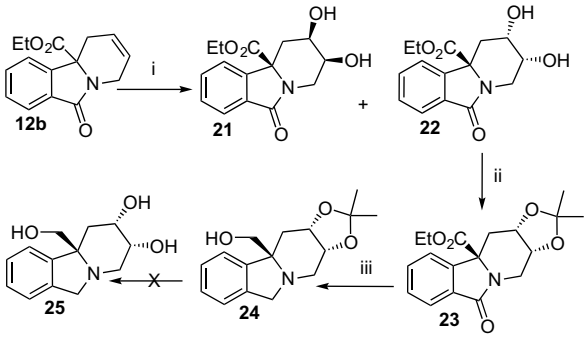


Figure 6. Second plausible mechanism for the formation of **12a**.



Scheme 7. Reagents and conditions: (i) OsO_4 cat, NMO, acetone:H_2O 1:1, rt, 6 h, 83%; (ii) DMP, PTSA cat, CH_2Cl_2, rt, 2 h, **23** 73%; (iii) $LiAlH_4$, THF, rt, 1 h, 39%.

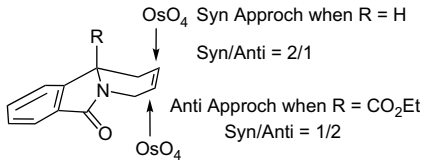


Figure 7.

performed under the same above conditions and yielded a chromatographically separable mixture of two diastereoisomers **21** and **22** in 83% yield and again in modest diastereoselectivity (ds=33%) (Scheme 7).

Interestingly, the stereoselectivity of the *syn*-dihydroxylation of the indolizidines **12** with OsO_4 proved to be dependent on the nature of the group at C10b (H in **12a** and CO_2Et in **12b**). Thus, whereas the dihydroxylation of **12a** occurred mainly from the face of the double bond in a *syn* relationship with regard to H10b (Fig. 7), leading to a 25:50 mixture of the **15**/**16** diastereomeric diols, the same reaction from the indolizidine **12b** was also poorly diastereoselective and in favor of the dihydroxylation *anti* to the bulky ethyl ester group at the carbon C10b, providing a 25:50 mixture of diols **21**/**22** (Fig. 7).

To confirm this result, a single crystal of the minor diastereomer **21** was subjected to an X-ray diffraction analysis.[26] This structural analysis depicted in Figure 8 confirms a cis disposition between the ester function and the two hydroxyl groups on carbon atoms C(6) and C(7), the torsion angle O(4)–C(7)–C(6)–O(3) being 60.27°.

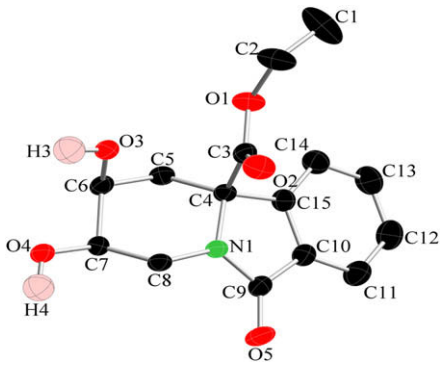
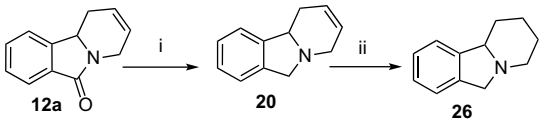


Figure 8. Thermal ellipsoid plot of the molecular structure of **21**. Only one of two independent molecules in the asymmetric unit is shown. Except of H_4 and H_3 the H atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: C(4)–N(1) 1.463(2), C(4)–C(15) 1.520(3), C(15)–C(10) 1.387(3), C(10)–C(9) 1.475(3), C(9)–O(5) 1.235(2), C(9)–N(1) 1.354(2), N(1)–C(8) 1.448(2), C(8)–C(7) 1.527(3), C(7)–C(6) 1.5229(2), C(6)–C(5) 1.522(3), C(5)–C(4) 1.541(3), C(4)–C(5)–C(6) 111.80(15), C(5)–C(4)–N(1) 108.84(14), C(4)–N(1)–C(8) 119.84(14), C(4)–N(1)–C(9) 113.97(15), N(1)–C(9)–C(10) 106.53(15), N(1)–C(9)–O(5) 124.60(18), C(10)–C(15)–C(4) 109.13(16).



Scheme 8. Reagents and conditions: (i) $LiAlH_4$, THF, rt, 1 h, 55%; (ii) H_2, Pd/C, MeOH, rt, 6 h, 65%.

It should be noted that in both cases a similar poor diastereofacial selectivity (ds=33%) was also observed when asymmetric oxidation was employed (AD-mix-α or AD-mix-β),[12] which demonstrates control of the structure of the substrate for the dihydroxylation reaction. It should also be noted that the reduction of the unprotected diol **22** gave a complex mixture of products was from which the expected polyhydroxy indolizidine **25** could not be isolated.

Next, and after protection of the major (less polar) diastereomer diol **22** as acetonide **23**, the lactam and the ester functions were reduced by treatment with $LiAlH_4$ to afford the desired compound **24** in 39% yield. As previously observed, removal of protecting group failed to give us the desired benzoindolizidine **25**.

Our final aim in this series was now the synthesis of the benzoindolizidine **26** analogue of crispine A. This alkaloid has been isolated in 2002 from , a common invasive plant occurring in Asia and Europe. It is of interest to note that this indolizidine alkaloid was found to exhibit superior antitumor activity against SKOV3, KB, and HeLa human cancer lines.[27] Because of its potent antitumor activity, and in order to understand the structure–activity relationship (SAR) as well as to improve the efficacy of this novel anticancer agent, various analogues of crispine A were synthesized.

The route employed is outlined in Scheme 8, where the amide **12a** was reduced to the amine **20** according to the method reported previously. Next, catalytic hydrogenolysis[28] of **20** efficiently afforded the benzoindolizidine derivative **26** in 65% yield. The spectropic data of **26** hydrochloride salt were in excellent agreement with those already reported.[29]

3. Conclusion

In summary, the results reported herein demonstrate that nitrogen-heterocycles such as benzoindolizidines or benzopyrrolizidines can easily be synthesized by using ene–ene ring-closing metathesis. Under *syn*-dihydroxylation reaction conditions they lead to a variety of interesting polyhydroxy systems. Furthermore the synthetic strategy presented constitutes an efficient route to new polyhydroxy benzoindolizidines bearing a quaternary hydroxymethyl group. All these attributes make this strategy very interesting and quite attractive for the design and synthesis of a wide variety of polyhydroxylated indolizidines including alkaloids comprising different substituents and stereochemistry with promising pharmacological profiles.

4. Experimental part

4.1. General

All melting points were measured on a Boetius micro hotstage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded, respectively, at 200 and 50 MHz on a Brucker AC-200. The infrared spectra were recorded on a Perkin–Elmer FT-IR paragon 1000 spectrometer. Thin-layer chromatography (TLC) was performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexane 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, ddd=doublet of doublet of doublet, m=multiplet, s=singlet, d=doublet, q=quartet, t=triplet, br s=broad singlet. Grubbs catalysts **G1**, **G2**, and **G3** were purchased from Sigma–Aldrich. Tetrahydrofuran was dried by distillation from sodium/benzophenone. Dichloromethane and dichloroethane were dried by distillation from calcium hydride, toluene was distilled from sodium, and acetonitrile was dried by distillation from P_2O_5.

4.2. Preparation of benzopyrrolizidines

*4.2.1. 2-Allyl-1-ethyl-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**2**)*

This product was prepared according to our previous work.[7b]

Viscous liquid; yield: 78%; IR (ν, cm^{-1}, $CHCl_3$) 1732.4, 1688.3; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.39 (t, J=7.0 Hz, 3H), 1.14 (t, J=7.0 Hz, 3H), 2.23 (dq, J=7.8, 15.8 Hz, 1H), 2.45 (dq, J=7.8, 15.8 Hz, 1H), 3.91–4.23 (m, 4H), 5.08–5.31 (m, 2H), 5.82–6.06 (m, 1H), 7.36–7.59 (m, 3H), 7.81 (d, J=6.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 6.9 (CH_3), 14.2 (CH_3), 25.9 (CH_2), 44.3 (CH_2), 62.2 (CH_2), 72.6 (Cq), 118.1 (CH_2), 121.7 (CH), 124.0 (CH), 129.2 (CH), 132.2 (CH), 133.6 (CH), 143.8 (2Cq), 169.3 (C=O), 171.2 (C=O); LRMS m/z 273 ($M^{+\bullet}$−29, 1), 201 (18), 200 (Base). Anal. Calcd for $C_{16}H_{19}NO_3$ (273.33): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.69; H, 7.32; N, 5.39.

*4.2.2. 2-Allyl-3-ethyl-3-hydroxymethyl-2,3-dihydro-1H-isoindol-1-one (**3**)*

This product was prepared according to our previous work.[7b]

White solid; yield: 82%; mp 88–90 °C; IR (ν, cm^{-1}, $CHCl_3$) 3426.8, 1680.1; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.36 (t, J=7.0 Hz, 3H), 1.81–1.97 (m, 2H), 2.32–2.49 (m, 1H), 3.73–3.91 (m, 3H), 4.22–4.36 (m, 1H), 5.10–5.35 (m, 2H), 5.88–6.11 (m, 1H), 7.28–7.58 (m, 3H), 7.73 (d, J=7.83 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 6.9 (CH_3), 25.0 (CH_2), 42.4 (CH_2), 66.6 (CH_2), 71.2 (Cq), 117.8 (CH_2), 121.3 (CH), 123.8 (CH), 128.6 (CH), 132.0 (CH), 133.0 (Cq), 134.4 (CH), 146.4 (Cq), 169.4 (C=O); LRMS m/z 231 ($M^{+\bullet}$, 2.5), 202 (13), 200 (Base). Anal. Calcd for $C_{14}H_{17}NO_2$ (231.30): C, 72.70; H, 7.41; N, 6.06. Found: C, 73.12; H, 7.69; N, 6.34.

*4.2.3. 2-Allyl-1-ethyl-3-oxo-2,3-dihydro-1H-isoindole-1-carbaldehyde (**4**)*

This product was prepared according to our previous work.[7b]

Viscous liquid; yield: 93%; IR (ν, cm^{-1}, $CHCl_3$) 1732.3, 1692.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.36 (t, J=7.0 Hz, 3H), 1.91–2.48 (m, 2H), 3.66 (dd, J=7.8, 14.8 Hz, 1H), 4.46–4.65 (m, 1H), 5.08–5.32 (m, 2H), 5.67–5.94 (m, 1H), 7.18 (d, J=7.0 Hz, 1H), 7.38–7.60 (m, 2H), 7.81 (d, J=7.0 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 6.2 (CH_3), 22.0 (CH_2), 43.1 (CH_2), 77.7 (Cq), 120.3 (CH_2), 122.7 (CH), 124.3 (CH), 129.9 (CH), 132.8 (CH), 133.0 (CH), 133.1 (Cq), 139.6 (Cq), 169.2 (C=O), 196.6 (C=O); LRMS m/z 229 ($M^{+\bullet}$, <1), 200 (Base), 199 (85). Anal. Calcd for $C_{14}H_{15}NO_2$ (229.28): C, 73.37; H, 6.59; N, 6.11. Found: C, 73.75; H, 6.88; N, 6.38.

*4.2.4. 2-Allyl-3-ethyl-3-vinyl-2,3-dihydro-1H-isoindol-1-one (**5**)*

This product was prepared according to our previous work.[7b]

Colorless oil; yield: 73%; IR (ν, cm^{-1}, $CHCl_3$) 1678.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.39 (t, J=7.0 Hz, 3H), 2.10 (q, J=7.0 Hz, 2H), 3.92 (dd, J=6.2, 14.8 Hz, 1H), 4.04 (dd, J=6.2, 14.8 Hz, 1H), 5.05–5.41 (m, 4H), 5.68 (dd, J=10.1, 17.2 Hz, 1H), 5.82–6.30 (m, 1H), 7.19 (d, J=7.0 Hz, 1H), 7.33–7.57 (m, 2H), 7.80 (d, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 7.2 (CH_3), 26.3 (CH_2), 42.9 (CH_2), 70.2 (Cq), 116.5 (CH_2), 117.7 (CH_2), 122.0 (CH), 123.8 (CH), 128.4 (CH), 132.0 (CH), 132.3 (Cq), 134.0 (CH), 139.8 (CH), 147.8 (Cq), 168.8 (C=O); LRMS m/z 227 ($M^{+\bullet}$, 5), 199 (16), 198 (Base). Anal. Calcd for $C_{15}H_{17}NO$ (227.31): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.68; H, 7.82; N, 6.45.

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

To a solution of **5** (68 mg, 0.3 mmol) in dichloromethane (5 mL) was added **G2** (12.7 mg, 5 mol %) under argon. After the mixture was stirred under reflux for 4 h, another portion of **G2** (12.7 mg, 5 mol %) was added followed by continuous stirring (8 h); the resulting solution was concentrated and purified by flash-column chromatography on silica gel (cyclohexane/ACOEt 75:25) to give the benzopyrrolizidine **6**.

*4.3.1. 9b-Ethyl-2,3,9b-dihydro-pyrrolo[2,1-a]isoindol-5-one (**6**)*

Yellow liquid; yield: 64%; IR (ν, cm^{-1}, $CHCl_3$) 1681.7; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.77 (t, J=7.8 Hz, 3H), 1.86 (q, J=7.8 Hz, 2H), 3.94 (dt, J=2.3, 15.6 Hz, 1H), 4.55 (dt, J=2.3, 15.6 Hz, 1H), 5.86 (dt, J=2.3, 6.2 Hz, 1H), 6.03 (dt, J=2.3, 6.2 Hz, 1H), 7.32–7.61 (m, 3H), 7.78 (d, J=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 8.7 (CH_3), 31.9 (CH_2), 51.7 (CH_2), 80.2 (Cq), 121.9 (CH), 124.8 (CH), 128.5 (CH), 129.9 (CH), 132.6 (2CH), 132.8 (Cq), 150.9 (Cq), 176.0 (C=O); LRMS m/z 199 ($M^{+\bullet}$, 3), 170 (86), 115 (Base). Anal. Calcd for $C_{13}H_{13}NO$ (199.25): C, 78.36; H, 6.58; N, 7.03. Found: C, 78.81; H, 6.90; N, 7.35.

*4.3.2. 2-(Prop-1-enyl)-3-ethyl-3-vinyl-2,3-dihydro-1H-isoindol-1-one (**7**)*

Yellow solid; yield: 70%; mp 87–89 °C; IR (ν, cm^{-1}, $CHCl_3$) 1685.3; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.28 (t, J=7.0 Hz, 3H), 1.71 (dd, J=1.5, 6.2 Hz, 3H), 1.97–2.43 (m, 2H), 5.21 (dd, J=3.1, 10.9 Hz, 1H), 5.30 (dd, J=3.1, 18.0 Hz, 1H), 5.53 (dq, J=6.2, 14.8 Hz, 1H), 5.79 (dd, J=10.9, 18.0 Hz, 1H), 6.68 (dd, J=1.5, 14.8 Hz, 1H), 7.12–7.28 (m, 1H), 7.31–7.53 (m, 2H), 7.78 (d, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 6.7 (CH_3), 16.5 (CH_3), 26.6 (CH_2), 70.2 (Cq), 110.4 (CH), 115.9 (CH_2), 121.8 (CH), 122.1 (CH), 123.9 (CH), 128.5 (CH), 132.6 (CH), 140.1 (CH), 148.0 (2Cq), 166.9 (C=O); LRMS m/z 227 ($M^{+\bullet}$, <1), 132 (Base). Anal. Calcd for $C_{15}H_{17}NO$ (227.31): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.69; H, 7.84; N, 6.44.

4.4. Preparation of benzoindolizidines

*4.4.1. 1,2-Diallyl-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**9a**)*

This product was prepared according to our previous work.[7b]

Yellow oil; yield: 98%; IR (ν, cm^{-1}, $CHCl_3$) 1732.5, 1690.2; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.09 (t, J=7.0 Hz, 3H), 3.96 (dd, J=6.2, 14.8 Hz, 1H), 3.12 (dd, J=6.2, 14.8 Hz, 1H), 3.92–4.23 (m, 4H), 4.78–5.29 (m, 5H), 5.78–6.61 (m, 1H), 7.33–7.53 (m, 3H), 7.76 (d, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, CDCl3, 25 °C) δ 13.8 (CH_3), 37.2 (CH_2), 44.1 (CH_2), 62.0 (CH_2), 71.2 (Cq), 117.7 (CH_2), 120.1 (CH_2), 121.7 (CH), 123.6 (CH), 129.0 (CH), 129.9 (CH), 131.7 (Cq), 132.0 (CH), 133.4 (CH), 143.5 (Cq), 168.7 (C=O), 170.1 (C=O); LRMS m/z 285 ($M^{+\bullet}$, 10), 244 (98), 212 (Base). Anal. Calcd for $C_{17}H_{19}NO_3$ (285.35): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.95; H, 6.99; N, 5.20.

*4.4.2. 2-Allyl-1-((E)-3-ethoxycarbonyl-allyl)-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**9b**)*

This product was prepared according to our previous work.[7b]

Colorless liquid; yield: 94%; IR (ν, cm^{-1}, $CHCl_3$) 1733.4, 1698.1, 1691.3; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.04–1.26 (m, 6H), 3.12 (dd, J=7.0, 15.6 Hz, 1H), 3.30 (ddd, J=1.5, 7.0, 15.6 Hz, 1H), 3.94–4.16 (m, 6H), 5.09–5.35 (m, 2H), 5.67–5.79 (d, J=15.6 Hz, 1H), 5.80–6.31 (m, 1H), 6.19 (dt, J=7.0, 15.6 Hz, 1H), 7.38–7.58 (m, 3H), 7.80–7.84 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.1 (CH_3), 14.4 (CH_3),

36.1 (CH_2), 44.5 (CH_2), 60.7 (CH_2), 62.7 (CH_2), 71.1 (Cq), 118.4 (CH_2), 121.8 (CH), 124.5 (CH), 126.4 (CH), 129.8 (CH), 131.9 (Cq), 132.6 (CH), 133.6 (CH), 140.2 (CH), 143.2 (Cq), 165.6 (C=O), 169.0 (C=O), 170.3 (C=O); LRMS *m/z* 357 ($M^{+\bullet}$, 10), 284 (58), 244 (Base). Anal. Calcd for $C_{20}H_{23}NO_5$ (357.41): C, 67.21; H, 6.49; N, 3.92. Found: C, 67.49; H, 6.78; N, 4.20.

*4.4.3. 1,2-Diallyl-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid (**10a**)*

This product was prepared according to our previous work.[7b]

White solid; yield: 85%; mp 138–140 °C; IR (ν, cm^{-1}, $CHCl_3$) 2979.2, 1727.9, 1689.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.09 (dd, *J*=6.2, 14.8 Hz, 1H), 3.18 (dd, *J*=4.7, 14.8 Hz, 1H), 4.10 (dd, *J*=6.2, 15.6 Hz), 4.20 (dd, *J*=6.2, 15.6 Hz, 1H), 4.84–5.27 (m, 5H), 5.82–6.02 (m, 1H), 7.37–7.58 (m, 3H), 7.76 (d, *J*=7.0 Hz, 1H), 11.07 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 37.4 (CH_2), 44.9 (CH_2), 72.1 (Cq), 118.5 (CH_2), 120.7 (CH_2), 122.4 (CH), 124.4 (CH), 129.6 (CH), 130.0 (CH), 131.7 (Cq), 132.6 (CH), 133.3 (CH), 143.6 (Cq), 169.9 (C=O), 173.6 (C=O); LRMS *m/z* 212 ($M^{+\bullet}$−45, 2), 173 (Base), 131 (52). Anal. Calcd for $C_{15}H_{15}NO_3$ (257.29): C, 70.02; H, 5.88; N, 5.44. Found: C, 70.4; H, 6.16; N, 5.73.

*4.4.4. 2,3-Diallyl-2,3-dihydro-isoindol-1-one (**11a**)*

This product was prepared according to our previous work.[7b]

Yellow oil; yield: 85%; IR (ν, cm^{-1}, $CHCl_3$) 1677.2; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.42–2.90 (m, 2H), 3.70 (dd, *J*=7.8, 15.6 Hz, 1H), 4.52–4.80 (m, 2H), 4.87–5.51 (m, 5H), 5.70–5.90 (m, 1H), 7.32–7.60 (m, 3H), 7.82 (dd, *J*=2.4, 9.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 29.9 (CH_2), 35.4 (CH_2), 43.0 (CH), 118.1 (CH_2), 119.5 (CH_2), 122.6 (CH), 123.8 (CH), 128.4 (CH), 131.5 (2CH), 132.5 (Cq), 133.5 (CH), 145.1 (Cq), 168.4 (C=O); LRMS *m/z* 213 ($M^{+\bullet}$, 4), 172 (Base), 132 (37). Anal. Calcd for $C_{14}H_{15}NO$ (213.28): C, 78.84; H, 7.09; N, 6.57. Found: C, 79.22; H, 7.38; N, 6.85.

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

To 1 mmol of **9a**,**b** or **11a** 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 (≈1 h). Evaporation of the solvent and purification by column chromatography (cyclohexane/EtOAc 75:25) yielded the corresponding diene.

*4.5.1. 1,10b-Dihydro-4H-pyrido[2,1-a]isoindol-6-one (**12a**)*

Colorless solid, yield: 83%; mp 86–88 °C; IR (ν, cm^{-1}, $CHCl_3$) 1673; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ 1.89 (m, 1H), 2.67–2.79 (m, 1H), 3.82 (dd, *J*=3.1, 18.0 Hz, 1H), 4.42 (dd, *J*=4.7, 10.9 Hz, 1H), 4.61 (dd, *J*=3.1, 18.0 Hz, 1H), 5.81–5.93 (m, 2H), 7.40–7.56 (m, 3H), 7.85 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 30.9 (CH_2), 40.5 (CH_2), 55.4 (CH), 122.7 (CH), 123.7 (CH), 124.4 (CH), 124.7 (CH), 129.0 (CH), 132.1 (CH), 133.3 (C), 146.8 (C), 167.7 (C=O). Anal. Calcd for $C_{12}H_{11}NO$ (185.23): C, 77.81; H, 5.99; N, 7.65. Found: C, 79.23; H, 6.27; N, 7.92.

*4.5.2. 6-Oxo-1,4-dihydro-6H-pyrido[2,1-a]isoindole-10b-carboxylic ethyl ester (**12b**)*

Yellow solid; yield: 86%; mp 91–93 °C; IR (ν, cm^{-1}, $CHCl_3$) 1732.6, 1689.9; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.16 (t, *J*=7.0 Hz, 3H), 2.08–2.25 (m, 1H), 3.27–3.43 (m, 1H), 3.83–3.99 (m, 1H), 4.02–4.29 (m, 2H), 4.52–4.69 (m, 1H), 5.72–5.92 (m, 2H), 7.43–7.61 (m, 3H), 7.74 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (50 MHz, CDCl3, 25 °C) δ 14.3 (CH_3), 33.5 (CH_2), 39.5 (CH_2), 62.5 (CH_2), 66.1 (Cq), 122.0 (2CH), 124.1 (CH), 124.5 (CH), 129.5 (CH), 131.8 (Cq), 132.1 (CH), 144.6 (Cq), 167.2 (C=O), 170.3 (C=O); LRMS *m/z* 257 ($M^{+\bullet}$, 9), 184 (Base), 156 (31). Anal. Calcd for $C_{15}H_{15}NO_3$ (257.29): C, 70.02; H, 5.88; N, 5.44. Found: C, 70.41; H, 6.16; N, 5.71.

4.6. Dihydroxylation of indolizidine 12a,b

To a solution of the enamide **12a**,**b** (1 mmol) in a mixture (1:1) of acetone and water (6 mL) was added dropwise a commercially available aqueous solution (4%) of osmium tetroxide (0.3 mL), immediately followed by addition of NMO (0.14 g, 3.2 mmol). The mixture was stirred at room temperature until total disappearance of starting material was observed. $Na_2S_2O_4$ (0.2 g, 1.1 mmol) was then added and the mixture was stirred for 15 min. Acetone was removed and the aqueous phase was extracted five times with EtOAc. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash-column chromatography on silica gel (cyclohexane/EtOAc 40:60) to give the diols **13** and **14** or **21** and **22**.

*4.6.1. 2,3-Dihydroxy-1,3,4,10b-tetrahydro-2H-pyrido[2,1-a]-isoindol-6-one (**13**) and (**14**)*

Viscous liquid; yield: 78%; IR (ν, cm^{-1}, $CHCl_3$) 3390.0, 1675.4; ^1H NMR (200 MHz, $CDCl^3$, 25 °C) δ 1.24 (dd, *J*=11.4, 13.1 Hz, 1H), 2.34 (dt, *J*=3.5, 4.1, 13.1 Hz, 1H), 2.94–3.06 (m, 1H), 3.38 (br s, 1H), 3.87–3.95 (m, 2H), 4.18 (dd, *J*=5.4, 11.7 Hz, 1H), 4.35–4.04 (m, 1H), 4.54 (dd, *J*=3.1, 11.7 Hz, 1H), 7.21–7.34 (m, 3H), 7.61 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 35.9 (CH_2), 39.1 (CH_2), 52.6 (CH), 67.3 (CH), 68.3 (CH), 121.8 (CH), 123.4 (CH), 127.9 (CH), 131.1 (CH), 132.2 (Cq), 145.6 (Cq), 166.1 (C=O); LRMS m/z 219 ($M^{+\bullet}$, 45), 182 (31), 103 (Base). Anal., Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 66.16; H, 6.29; N, 6.69.

*4.6.2. 2,3-Dihydroxy-6-oxo-1,2,3,4-tetrahydro-6H-pyrido [2,1-a]isoindole-10b-carboxylic acid ethyl ester (**21**)*

White solid; yield 27%; mp 183–185 °C; IR (ν, cm^{-1}, $CHCl_3$) 3428.7, 1738.6, 1690.1; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.22 (t, *J*=7.0 Hz, 3H), 1.68–1.80 (m, 1H), 2.88 (dd, *J*=3.9, 12.5 Hz, 1H), 3.28 (dd, *J*=2.3, 14.8 Hz, 1H), 3.52 (br s, 1H), 3.81–3.86 (m, 1H), 4.06–4.27 (m, 3H), 4.53 (dd, *J*=2.3, 14.8 Hz, 1H), 7.41–7.54 (m, 3H), 7.77 (d, *J*=8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.4 (CH_3), 36.2 (CH_2), 43.2 (CH_2), 62.9 (CH_2), 67.2 (CH), 68.4 (CH), 68.7 (Cq), 122.1 (CH), 124.4 (CH), 129.6 (CH), 131.0 (CH), 132.5 (Cq), 144.3 (Cq), 168.5 (C=O), 169.8 (C=O); LRMS *m/z* 219 ($M^{+\bullet}$−72, 14), 200 (Base), 103 (78). Anal. Calcd for $C_{15}H_{17}NO_5$ (291.31): C, 61.85; H, 5.88; N, 4.81. Found: C, 62.23; H, 6.19; N, 5.13.

*4.6.3. 2,3-Dihydroxy-6-oxo-1,2,3,4-tetrahydro-6H-pyrido-[2,1-a]isoindole-10b-carboxylic acid ethyl ester (**22**)*

White solid; yield: 56%; mp 177–178 °C; IR (ν, cm^{-1}, $CHCl_3$) 3448.2, 1734.0, 1689.5; ^1H RMN (200 MHz, $CDCl_3$, 25 °C) δ 1.23 (t, *J*=7.0 Hz, 3H), 1.54 (d, *J*=14.0 Hz, 1H), 2.28 (br s, 1H), 3.23 (br s, 1H), 3.25 (dd, *J*=3.1, 14.0 Hz, 1H), 3.42 (t, *J*=12.5 Hz, 1H), 3.62–3.76 (m, 1H), 4.01–4.31 (m, 3H), 4.44 (dd, *J*=6.2, 12.5 Hz, 1H), 7.43–7.65 (m, 3H), 7.78 (dd, *J*=1.5, 6.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.2 (CH_3), 39.1 (CH_2), 39.3 (CH_2), 62.5 (CH_2), 65.0 (Cq), 67.8 (CH), 68.5 (CH), 122.7 (CH), 124.3 (CH), 129.6 (CH), 131.0 (Cq), 132.5 (CH), 144.7 (Cq), 167.3 (C=O), 170.4 (C=O); LRMS *m/z* 219 ($M^{+\bullet}$−73, 14), 200 (Base), 103 (78). Anal. Calcd for $C_{15}H_{17}NO_5$ (291.31): C, 61.85; H, 5.88; N, 4.81. Found: C, 62.17; H, 6.15; N, 5.04.

4.7. Acetonidation of diols 13, 14, and 21

To a solution of a mixture of diols (**13** and **14**) or **21** (1 mmol) in dichloromethane (10 mL), was added DMP (0.5 mL, 4 mmol) and APTS (0.04 g, 0.2 mmol). After the total disappearance of starting material was observed, the organic solution was washed twice with water, dried over $MgSO_4$, and concentrated. The crude product was purified by flash-column chromatography using cyclohexanes/EtOAc (60:40) to give the acetonides **15**, **16**, and **23**.

*4.7.1. 2,2-Dimethyl-4,4a,10,10a-tetrahydro-3aH-1,3-dioxa-9a-aza-cyclopenta[b]fluoren-9-one (**16**)*

White solid, yield: 52%; mp 104–106 °C; IR (ν, cm^{-1}, $CHCl_3$) 1682.6; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.42 (s, 3H), 1.48 (ddd, J=3.1, 11.7, 14.0 Hz, 1H, H_{1ax}), 1.57 (s, 3H, CH_3), 2.65 (ddd, J=2.3, 3.1, 14.0 Hz, 1H, H_{1eq}), 3.42 (dd, J_1=9.4 Hz, J_2=16.4 Hz, 1H, H_{4ax}), 4.31 (ddd, J=6.2, 6.2, 9.4 Hz, 1H, H_{3ax}), 4.35 (dd, J=6.2, 16.4 Hz, 1H, H_{4eq}), 4.42 (ddd, J=2.3, 3.1, 6.2 Hz, 1H, H_{2eq}), 4.64 (dd, J=3.1, 11.7 Hz, 1H, H_{10bax}), 7.38–7.55 (m, 3H), 7.84 (d, J=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 25.9 (CH_3), 28.2 (CH_3), 33.2 (CH_2), 41.1 (CH_2), 52.9 (CH), 71.1 (CH), 72.2 (CH), 109.5 (Cq), 122.2 (CH), 124.2 (CH), 128.6 (CH), 131.7 (CH), 132.6 (Cq), 145.9 (Cq), 167.4 (C═O); LRMS m/z 259 ($M^{+\bullet}$, 26), 245 (57), 244 (Base). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.31): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.91; H, 6.94; N, 5.73.

*4.7.2. 2,2-Dimethyl-4,4a,10,10a-tetrahydro-3aH-1,3-dioxa-9a-aza-cyclopenta[b]fluoren-9-one (**15**)*

White solid; yield: 25%; mp 182–184 °C; IR (ν, cm^{-1}, $CHCl_3$) 1683.9; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.34 (s, 6H), 1.45 (ddd, J=9.3, 10.1, 13.3 Hz, 1H, H_{1ax}), 2.44 (ddd, J=3.9, 5.4, 13.3 Hz, 1H, H_{1eq}), 3.38 (dd, J=3.1, 14.8 Hz, 1H, H_{4ax}), 4.22 (dd, J=3.1, 5.4 Hz, 1H, H_{3eq}), 4.24–4.30 (m, 1H, H_{10bax}), 4.44 (quintet, J=5.4, 10.1 Hz, 1H, H_{2ax}), 4.76 (d, J=14.8 Hz, 1H, H_{4eq}), 7.36–7.56 (m, 3H), 7.85 (d, J=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 26.4 (CH_3), 28.4 (CH_3), 34.8 (CH_2), 39.5 (CH_2), 55.7 (CH), 71.6 (CH), 72.8 (CH), 109.4 (Cq), 122.0 (CH), 124.3 (CH), 128.7 (CH), 131.8 (CH), 132.5 (Cq), 145.3 (Cq), 167.4 (C═O); LRMS m/z 259 ($M^{+\bullet}$, 26), 245 (57), 244 (Base). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.31): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.91; H, 6.94; N, 5.73.

*4.7.3. 2,2-Dimethyl-9-oxo-3a,4,10,10a-tetrahydro-9H-1,3-dioxa-9a-aza-cyclopenta[b]fluorene-4a-carboxylic acid ethyl ester (**23**)*

White solid; yield: 73%; mp 172–174 °C; IR (ν, cm^{-1}, $CHCl_3$) 1740.0, 1693.1; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.18 (t, J=7.0 Hz, 3H), 1.29 (s, 6H), 1.58 (dd, J=10.1, 13.3 Hz, 1H), 2.89 (dd, J=5.4, 13.3 Hz, 1H), 3.49 (dd, J=3.9, 15.6 Hz, 1H), 4.02–4.38 (m, 4H), 4.76 (d, J=15.6 Hz, 1H), 7.43–7.61 (m, 3H), 7.78–7.84 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.3 (CH_3), 26.3 (CH_3), 28.3 (CH_3), 36.9 (CH_2), 38.3 (CH_2), 62.7 (CH2), 67.0 (Cq), 71.1 (CH), 71.4 (CH), 109.3 (Cq), 122.0 (CH), 124.5 (CH), 129.6 (CH), 131.4 (Cq), 132.3 (CH), 144.4 (Cq), 167.4 (C═O), 169.6 (C═O); LRMS m/z 331 ($M^{+\bullet}$, 12), 316 (22), 258 (Base). Anal. Calcd for $C_{18}H_{21}NO_5$ (331.37): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.66; H, 6.71; N, 4.51.

4.8. Reduction of the amide function

Lithium aluminum hydride (38 mg, 1 mmol) was added to a solution of amides **16** or **23** (1.5 mmol) in dry THF (5 mL) at room temperature and the mixture was stirred for 1 h. The resulting mixture was cooled and water added cautiously until the lithium complex was destroyed. The mixture was then diluted with water (5 mL) and dichloromethane (10 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2×10 mL). The combined extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue. The crude product was purified by flash-column chromatography using cyclohexanes/EtOAc (70:30) to give pure amines **17** and **24**.

*4.8.1. 2,2-Dimethyl-3a,4,4a,9,10,10a-hexahydro-1,3-dioxa-9a-aza-cyclopenta[b]fluorene (**17**)*

Viscous liquid; yield: 45%; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.38 (s, 3H), 1.54 (s, 3H), 1.85 (septet, J=3.1, 10.9, 14.0 Hz, 1H, H_{1ax}), 2.57 (ddd, J=2.3, 3.1, 14.0 Hz, 1H, H_{1eq}), 2.73 (t, J=10.9 Hz, 1H, H_{4ax}), 3.17 (dd, J=5.4, 10.9 Hz, 1H, H_{4eq}), 3.72–3.84 (m, 2H, H_{10bax}+H_{6ax}), 4.00 (d, J=11.7 Hz, 1H, H_{6eq}), 4.35 (quintet, J=5.4, 10.9 Hz, 1H, H_{3ax}), 4.39–4.50 (m, 1H, H_{2eq}), 7.08–7.31 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 26.2 (CH_3), 28.3 (CH_3), 31.6 (CH_2), 54.0 (CH_2), 58.3 (CH_2), 61.2 (CH), 72.5 (CH), 73.1 (CH), 108.8 (Cq), 121.3 (CH), 122.7 (CH), 127.2 (2CH), 140.2 (Cq), 143.1 (Cq); LRMS m/z 245 ($M^{+\bullet}$, 48), 170 (82), 118 (Base). Anal. Calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.86; H, 8.14; N, 5.99.

*4.8.2. 2,2-Dimethyl-3a,4,10,10a-tetrahydro-9H-1,3-dioxa-9a-aza-cyclopenta[b]fluorene-4a-carboxylic acid ethyl ester (**24**)*

Viscous liquid; yield: 39%; IR (ν, cm^{-1}, $CHCl_3$) 3428.8; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.26 (s, 3H, CH_3), 1.48 (s, 3H), 1.99 (dd, J=8.6, 14.0 Hz, 1H), 2.15 (dd, J=5.4, 14.0 Hz, 1H), 2.91 (br s, 1H), 2.92 (dd, J=9.4, 14.0 Hz, 1H), 3.24 (dd, J=5.4, 14.0 Hz, 1H), 3.50 (d, J=10.9 Hz, 1H), 3.60 (d, J=10.9 Hz, 1H), 3.94–4.08 (m, 1H), 4.1 (d, J=14.8 Hz, 1H), 4.20–4.31 (m, 1H), 4.47 (d, J=14.8 Hz, 1H), 7.15–7.26 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 25.0 (CH_3), 27.5 (CH_3), 32.8 (CH_2), 49.9 (CH_2), 58.8 (CH_2), 68.5 (CH_2), 69.5 (CH), 70.2 (Cq), 71.3 (CH), 108.5 (Cq), 122.3 (CH), 122.6 (CH), 127.8 (CH), 128.1 (CH), 139.3 (Cq), 143.6 (Cq); LRMS m/z 260 ($M^{+\bullet}$−15), 245 ($M^{+\bullet}$−30), 244 (Base). Anal. Calcd for $C_{16}H_{21}NO_3$ (275.35): C, 69.79; H, 7.69; N, 5.09. Found: C, 70.22; H, 8.02; N, 5.35.

*4.8.3. 1,4,6,10b-Tetrahydro-pyrido[2,1-a]-isoindole (**20**)*

Viscous liquid; yield: 55%; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.10–2.32 (m, 1H), 2.52–2.65 (m, 1H), 3.11–3.22 (m, 1H), 3.42–3.59 (m, 3H), 4.19 (d, J=11.7 Hz, 1H), 5.73–5.86 (m, 2H), 7.08–7.22 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 30.5 (CH_2), 51.5 (CH_2), 58.0 (CH_2), 63.3 (CH_2), 121.1 (CH), 122.5 (CH), 125.4 (CH), 126.7 (CH), 126.8 (CH), 127.0 (CH), 140.0 (Cq), 143.5 (Cq); LRMS m/z 171 ($M^{+\bullet}$, 58), 117 (Base), 90 (72). Anal. Calcd for $C_{12}H_{13}N$ (172.24): C, 84.17; H, 7.65; N, 8.18. Found: C, 84.22; H, 7.62; N, 8.35.

4.9. Preparation of benzoindolizidine 26

To a solution of **20** (250 mg, 1.5 mmol) in MeOH (10 mL) was added a catalytic quantity of 10% palladium-on-carbon. The solution was stirred at room temperature under an atmosphere of hydrogen for a period of 6 h. The mixture was filtered over Celite and rinsed with MeOH (3×5 mL), and the solvent was removed by evaporation to give the amine **26**. The ^1H NMR and ^{13}C NMR spectra of the hydrochloride salt of **26** conform with the reported literature data.[29]

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