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ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · FEBRUARY 2014

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A β-Enaminone-Initiated Multicomponent Domino Reaction for the Synthesis of Indoloquinolizines and Benzoquinolizines from Acyclic Precursors

Padmakar A. Suryavanshi,[a] Vellaisamy Sridharan,[a, b] and J. Carlos Menéndez*[a]

Abstract: The cerium(IV) ammonium nitrate (CAN)-catalyzed sequential multicomponent reaction between tryptamine, α,β-unsaturated aldehydes, and β-dicarbonyl compounds affords highly substituted indolo[2,3-*a*]quinolizines in a single synthetic operation. Two rings are generated through the creation of two C–C and two C–N bonds by a domino process comprising initial β-enaminone formation, followed by individual Michael addition, 6-*exo-trig* cyclization, iminium formation, and Pictet–Spengler steps. Furthermore, the reaction is diastereoselective and affords exclusively compounds with a *trans* relationship between the H-2 and H-12b protons. The use of amines bearing a less nucleophilic side chain aromatic ring (5-bromotryptamine, 3,4-dimethoxyphenylethylamine) prevents the Pictet–Spengler final step and leads to *N*-indolylethyl or *N*-phenylethyl-1,4-dihydropyridines, which are cyclized to the corresponding indolo[2,3-*a*]quinolizines or benzo[*a*]-quinolizines in the presence of HCl in methanol/water. Treatment of the fused quinolizine derivatives with sodium triacetoxyborohydride led to the corresponding indolo[2,3-*a*]quinolizidines or benzo[*a*]quinolizidines, possessing four stereogenic centers, as mixtures of two diastereomers.

Keywords: acyliminium cations · β-enaminones · domino reactions · multicomponent reactions · Pictet–Spengler reactions

Introduction

Contemporary organic synthesis aims at achieving the maximum efficiency with the minimum consumption of resources and generation of waste. One of the most useful approaches for achieving these goals relies on the invention and discovery of multibond-forming reactions,[1,2] especially domino[3] and multicomponent[4] reactions. According to Tietze, domino reactions can be defined as those for which each step takes place as a consequence of the generation of a functional group in the previous one, without addition of reagents or changes in the reaction conditions.[3j] On the other hand, multicomponent reactions (MCRs) combine three or more substrates in such a way that the final product contains significant portions of all the starting materials. MCRs in which all substrates are added simultaneously can be considered as domino processes; alternatively, MCRs can also be performed by the sequential addition of reactants, without isolation of intermediate species or a change of solvent.

β-Enaminones are very important intermediates in synthesis, especially in the preparation of heterocycles.[5] Since our discovery that cerium(IV) ammonium nitrate (CAN)[6] is an excellent catalyst that allows the very fast synthesis of β-enaminones from β-dicarbonyl compounds and primary amines,[7] we have described a number of CAN-catalyzed domino and multicomponent reactions initiated by the formation of a β-enaminone.[8] One of the methods thus discovered allowed the one-pot, efficient preparation of 1-alkyl-6-ethoxy-1,4,5,6-tetrahydropyridines from primary amines, β-dicarbonyl compounds, α,β-unsaturated aldehydes, and alcohols.[8j]

In this context, and in view of the importance of quinolizidines due to their prevalence as alkaloids and their varied pharmacological activities,[9] we sought to combine this tetrahydropyridine preparation with a Pictet–Spengler reaction, thus achieving a domino process leading to the direct, one-pot preparation of a variety of areno[*a*]quinolizidines from open-chain precursors. The process involves the generation of two C–C and two C–N bonds through generation of the iminium cation **I** from the initial tetrahydropyridine **II**, which in turn is derived from a formal aza[3+3] cycloaddition between a β-enaminone and an α,β-unsaturated aldehyde, followed by reaction of the resulting hemiaminal with ethanol (Scheme 1). A mechanistically unrelated, two-step method has been described for the synthesis of the same type of compounds that involves the preparation of a cyclic hemiacetal from a β-dicarbonyl compound and an α,β-unsaturated aldehyde. Subsequent reaction of this hemiacetal with tryptamine in the presence of a Brønsted acid affords

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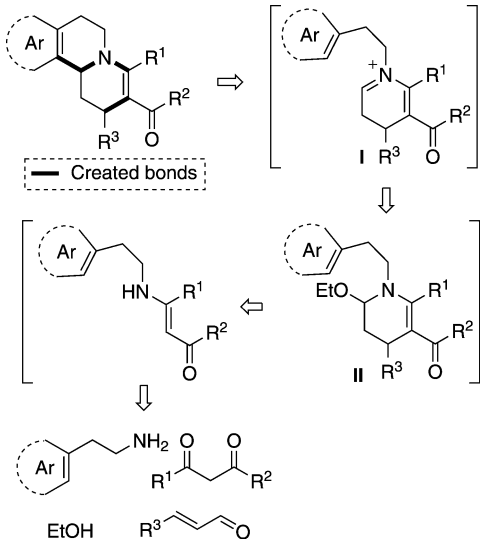
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204594.



Scheme 1. Planning of the synthesis of areno[*a*]quinolizines.

the target product, probably through a Pictet–Spengler reaction.[10] Although less directly related to our work, we also mention the reaction between β-amidoesters derived from tryptamine and α,β-unsaturated aldehydes, which affords lactams derived from the indolo[2,3-*a*]quinolizidin-4-one system.[11]

Results and Discussion

Our initial experiments involved tryptamine, ethyl acetoacetate, and acrolein ($R^3=H$). Initially, we aimed at isolating the corresponding tetrahydropyridine derivative **II**, which we hoped to cyclize in a second step via an intermediate iminium species. However, all of our attempts to cyclize compound **1** under acidic conditions led only to complex mixtures. We then examined the reaction involving cinnamaldehyde, and found that our usual conditions (CAN, acetonitrile, room temperature) gave the β-enaminone derived from tryptamine and ethyl acetoacetate, but the reaction did not progress to the tetrahydropyridine stage (Table 1, entry 1). The use of indium trichloride as the catalyst did not change this result (Table 1, entry 2). When the solvent was replaced by ethanol, some reaction was observed, but, most interestingly, instead of the expected tetrahydropyridine derivative (**1**), we obtained the target final product **2a** shown in Figure 1 (Table 1, entry 3). In spite of the low yield, this result was very encouraging in that it proved that it should be possible to effect the desired transformation in a single synthetic operation. Indeed, we found that simply by carrying out the reaction under reflux conditions we were able to isolate compound **2a** in 86% yield (Table 1, entry 4). The use of other alcohols (methanol, 2-propanol) as solvents was also examined, but we found no improvement (Table 1, entries 5 and 6). Results similar to those achieved with CAN were obtained by using indium trichloride

Table 1. Optimization of the synthesis of compound **2a**.

Entry	Solvent	Conditions	Yield [%]
1	CH_3CN	CAN (5%), RT, 1 h	0[a]
2	CH_3CN	$InCl_3$ (5%), RT, 1 h	0[a]
3	EtOH	CAN (5%), RT, 1 h	35[b]
4	EtOH	CAN (5%), reflux, 1.5 h	86
5	MeOH	CAN (5%), reflux, 1.5 h	35
6	*i*PrOH	CAN (5%), reflux, 1.5 h	75
7	EtOH	$InCl_3$ (5%), RT, 1 h	45
8	EtOH	$InCl_3$ (5%), reflux, 1 h	87

[a] The enaminone derived from tryptamine and ethyl acetoacetate was obtained. [b] The isolated enaminone was used as the starting material.

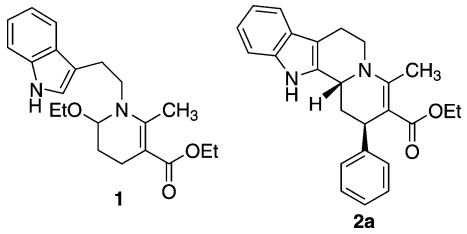
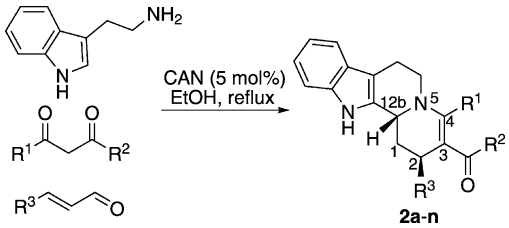


Figure 1. Structures relevant to the optimization study.

in ethanol (Table 1, entries 7 and 8), but we decided to employ the cerium catalyst for additional studies in view of its lower cost and better stability.

With the optimized conditions in hand, we explored the scope of the reaction (Scheme 2 and Table 2). Although most experiments were performed on the dicarbonyl substrate having $R^1=Me$ because of its commercial availability, longer alkyl chains were also tolerated, albeit in diminished



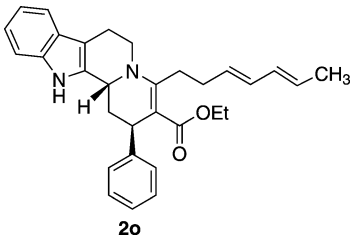
Scheme 2. Synthesis of indolo[2,3-*a*]quinolizines from tryptamine, α,β-unsaturated aldehydes, and β-dicarbonyl compounds.

yields. Thus, ethyl 3-oxohexanoate gave compound **2m** in 50% yield (Table 2, entry 13), and (*E*,*E*)-ethyl 3-oxo-6,8-decanedioate[12] gave compound **2o**, bearing a complex side chain containing a diene fragment, in 45% yield (Figure 2). As regards the carbonyl functionality, we successfully assayed esters (Table 2, entries 1–10, 12, and 13), thioesters (Table 2, entry 11), and ketones (Table 2, entries 14–16). Finally, the reaction tolerated a wide variety of aromatic R^3 substituents, including unsubstituted phenyl (Table 2, entries 1, 2, and 11–16), phenyl groups bearing electron-withdrawing (Table 2, entries 4 and 6) and electron-donating (Table 2, entry 5) substituents, 4-biphenyl (Table 2, entry 3),

Table 2. Yields obtained in the preparation of compounds **2**.

Entry		R^1	R^2	R^3	*t* [h]	Yield [%][a]
1	**2a**	Me	OEt	Ph	1.5	86
2	**2b**	Me	OMe	Ph	1	88
3	**2c**	Me	OEt	4-PhC_6H_4	1.5	86
4	**2d**	Me	OEt	4-ClC_6H_4	1.5	88
5	**2e**	Me	OEt	4-$MeOC_6H_4$	1.5	85
6	**2f**	Me	OEt	2-$NO_2C_6H_4$	1.5	28
7	**2g**	Me	OEt	2-furyl	1	77
8	**2h**	Me	OEt	2-naphthyl	1	92
9	**2i**	Me	OEt	Me	1	62
10	**2j**	Me	OEt	*n*Pr	1	40
11	**2k**	Me	S*t*Bu	Ph	1	70
12	**2l**	Me	O*t*Bu	Ph	1	68
13	**2m**	*n*Pr	OEt	Ph	1	50
14	**2n**	Me	Me	Ph	1.5	48
15	**2n**	Me	Me	Ph	12	72
16	**2n**	Me	Me	Ph	2	80[b]

[a] Yield of the isolated product. [b] CAN (15%) was used in this case.



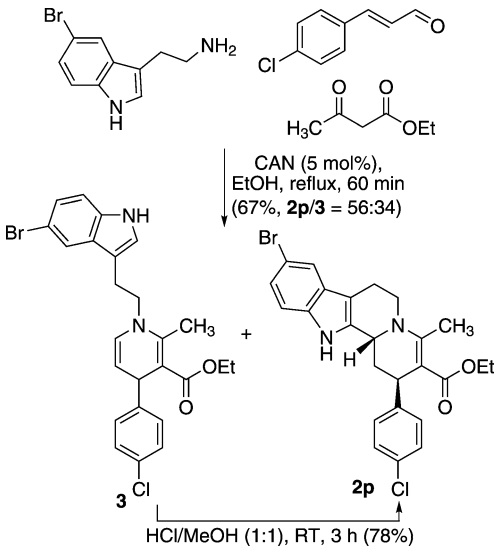
2o

Figure 2. Structure of compound **2o**.

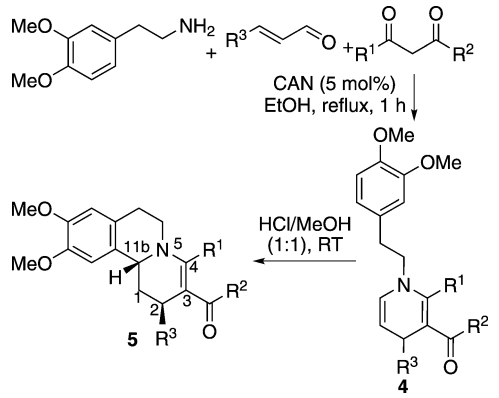
2-naphthyl (Table 2, entry 8), and 2-furyl (Table 2, entry 7). Alkyl substituents at R^3 were also well tolerated (Table 2, entries 9 and 10).

At this stage, we became interested in ascertaining whether the reaction would work in the presence of less electron-rich aromatic side chains on the tryptamine component. To this end, as shown in Scheme 3, we employed 5-bromotryptamine[13] as the starting material and found that its reaction with *para*-chlorocinnamaldehyde and ethyl acetoacetate afforded the desired compound **2p** as the major product together with dihydropyridine **3**, which revealed that in this case an elimination reaction competed with the final Pictet–Spengler step. Fortunately, exposure of **3** to a 1:1 mixture of 35% aqueous HCl and methanol led to its transformation into the desired compound **2p** in 78% yield.

Further explore the synthetic scope of our domino process, we briefly investigated its application to the synthesis of benzo[*a*]quinolizines by the use of 3,4-dimethoxyphenylethylamine as the amine component. As shown in Scheme 4, behavior similar to that described for 5-bromotryptamine was observed, and the reaction products were identified as dihydropyridine derivatives **4**. As in the previous case, these compounds could be cyclized to benzo[*a*]quinolizines **5** by treatment with a 1:1 mixture of 35% aqueous HCl and methanol (Scheme 4 and Table 3) with the exception of the *tert*-butyl ester **4b**, which, as expected, was unstable under the strongly acidic conditions.



Scheme 3. Products of a multicomponent reaction starting from 5-bromotryptamine.



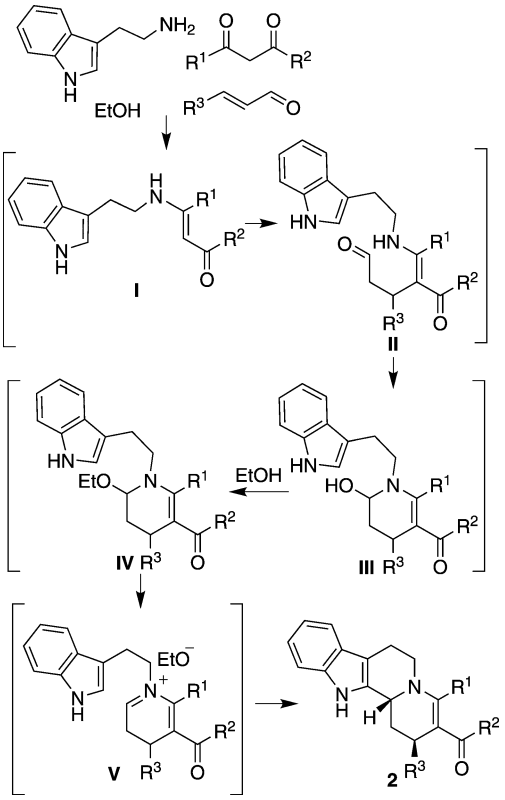
Scheme 4. Synthesis of benzo[*a*]quinolizines from 3,4-dimethoxyphenylethylamine, α,β-unsaturated aldehydes, and β-dicarbonyl compounds.

A plausible mechanistic pathway for the domino transformation is summarized in Scheme 5. We propose that the first step involves the formation of β-enaminone **I**, on the basis that 1) CAN is an excellent catalyst for β-enaminone synthesis[7] and 2) in the synthesis of **2a**, the use of the isolated β-enaminone arising from reaction of tryptamine and ethyl acetoacetate as the starting material, together with cin-

Table 3. Conditions and yields for the benzo[*a*]quinolizine synthesis.

Entry		R^1	R^2	R^3	**4** [%][a]	**5** *t* [h]	Yield [%][a]
1	**4a**, **5a**	Me	OEt	Ph	70	2	75
2	**4b**, **5b**	Me	O*t*Bu	Ph	72	2	0[b]
3	**4c**, **5c**	Me	OEt	4-ClC_6H_4	68	2	76
4	**4d**, **5d**	Me	OEt	4-$MeOC_6H_4$	65	4	77
5	**4e**, **5e**	Me	OEt	Me	62	8	63
6	**4f**, **5f**	*n*Pr	OEt	Ph	60	2	60

[a] Yield of the isolated product. [b] Decomposition was observed in this case.

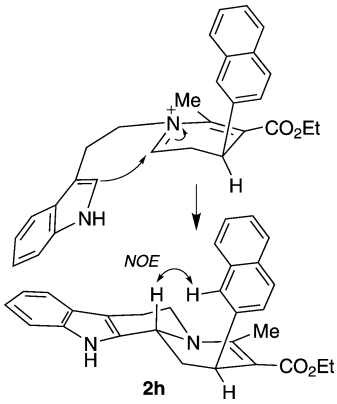


Scheme 5. Mechanistic proposal accounting for the domino process that leads to the formation of compounds **2**.

namaldehyde, led to an identical result as the multicomponent process under the same reaction conditions (84% yield in the presence of 5% CAN in ethanol, after 1 h reflux). Subsequent steps include a Michael addition of **I** to the unsaturated aldehyde to give **II**, which would then undergo a 6-*exo-trig* cyclization to a cyclic hemiaminal **III**. According to our experience,[8j] this intermediate is unstable and reacts with the ethanol present in the reaction medium to afford **IV**, which would be in equilibrium with species **V**, a vinylogous acyliminium cation. Finally, a Pictet–Spengler reaction would afford the observed products **2**.

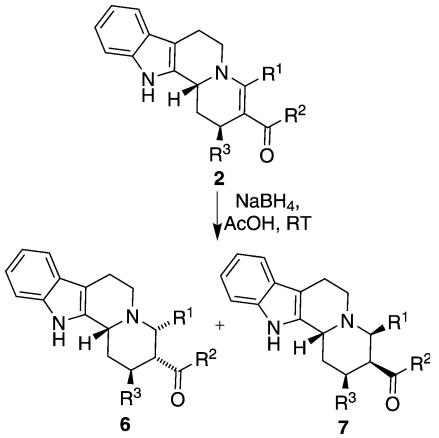
The stereochemistry of compounds **2** was deduced from NOE studies on **2h**, and also from the structures of their reduced derivatives (see below). As shown in Scheme 6, an NOE between the angular indoloquinolizine proton and H-2 at the naphthyl substituent proves their *cis* relationship. This product arises from attack of the indole on the vinylogous acyliminium intermediate opposite to the naphthyl substituent.

Finally, we examined the transformation of compounds **2** and **5** into indolo[2,3-*a*]quinolizidines and benzo[*a*]quinolizidines, respectively, by reduction of their conjugated double bond in the presence of sodium triacetoxyborohydride, generated in situ from sodium borohydride and acetic acid.[14] This reagent is known to deliver two *cis* hydrogen atoms to double bonds belonging to vinylogous amide systems, such as those present in our substrates.[14,15] The reduction of **2** in



Scheme 6. Pictet–Spengler cyclization step and key NOE effect allowing the stereochemical assignment of compound **2h**.

this way proceeded in good to excellent yields and afforded mixtures of compounds **6** and **7** in ratios of around 40:60 (Scheme 7 and Table 4). The major products were identified as compounds **7**, arising from reduction opposite to the R^3 substituent.



Scheme 7. Reduction of compounds **2** to indolo[2,3-*a*]quinolizidines.

The relative configurations of compounds **6** and **7** were established from spectroscopic evidence, as summarized below for the representative case of **6a** and **7a**. Arenoquinolizidines pose an interesting conformational problem owing to the presence of a bridgehead nitrogen atom that can be inverted, which complicates their stereochemical assignment.[9] The nitrogen lone pair and the proton at the quinolizidine ring fusion point can be in *cis* and *trans* arrangements, which can be distinguished by several spectral criteria. Thus, compounds with a *trans* ring junction often show a characteristic series of IR bands between 2700 and 2800 cm^{-1} known as Bohlmann bands, which are absent in the spectra of *cis* compounds and may be attributed to the stretching vibrations of the two C–H bonds antiperiplanar to the nitrogen lone pair.[16] These bands were present in the IR spectrum of the minor compound **6a** (2799 cm^{-1}), but

Table 4. Conditions and yields for the reduction of compounds **2**.

Entry		R^1	R^2	R^3	*t* [h]	Yield [%][a]	**6**/**7**[b]
1	**6a**, **7a**	Me	OEt	Ph	2	86	40:60
2	**6b**, **7b**	Me	OEt	4-PhC_6H_4	5	85	46:54
3	**6c**, **7c**	Me	OEt	4-ClC_6H_4	2	89	40:60
4	**6d**, **7d**	Me	OEt	4-$MeOC_6H_4$	2	90	39:61
5	**6e**, **7e**	Me	Me	Ph	3	73[c]	47:53
6	**6f**, **7f**	Me	OEt	2-furyl	3	80[c]	39:61
7	**6g**, **7g**	Me	S*t*Bu	Ph	1.3	85	39:61
8	**6h**, **7h**	Me	O*t*Bu	Ph	1.3	80	48:52
9	**6i**, **7i**	Me	OEt	2-naphthyl	72[d]	58[c]	33:57
10	**6j**, **7j**	Me	OEt	Me	2	60[c]	42:58
11	**6k**, **7k**	Me	OEt	*n*Pr	2	68[c]	40:60
12	**6l**, **7l**	*n*Pr	OEt	Ph	36[e]	65[c]	35:65

[a] Yield of the isolated product. [b] Ratio calculated from ^{1}H NMR spectra of the crude product. [c] Only one isomer could be isolated in pure form. [d] Starting material **2i** (18%) was recovered. [e] Starting material **2l** (22%) was recovered.

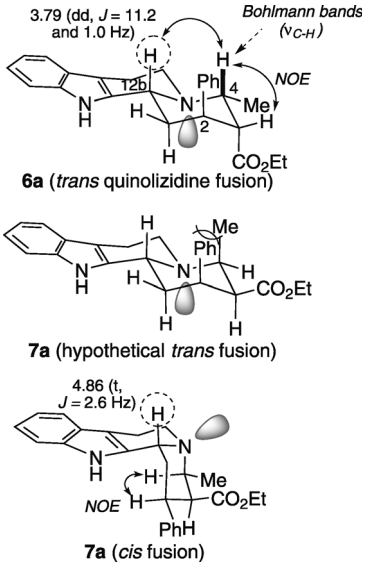
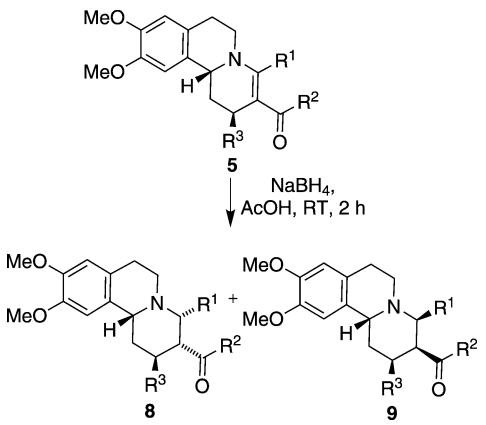


Figure 3. Stereochemical study of compounds **6** and **7**.

absent in that of **7a**. The chemical shift of the ring junction proton in the ^{1}H NMR spectrum of quinolizidines also has diagnostic relevance, since its value depends on the dihedral angle between the C–H bond and the lone pair. A significant upfield shift has been found for the *trans*-fused systems ($\delta \approx 3.5$ ppm in the case of arenoquinolizidines) in comparison with their *cis* counterparts ($\delta > 4$ ppm). In the case of compound **6a**, the signal of this proton was observed at $\delta =$ 3.79 ppm, which confirms the *trans* structure suggested by the IR data. Furthermore, the coupling constants for the angular proton ($J = 11.2$ and 1.0 Hz) are only compatible with a *trans*-fused system, which leads to a large diaxial coupling. The ^{1}H NMR spectrum of compound **7a** showed the signal of the relevant proton H-12b at $\delta = 4.86$ ppm as a triplet with $J = 2.6$ Hz, which is consistent with a *cis* quinolizidine structure. NOE data were used to confirm the proposed relative configurations (Figure 3), which were also supported by the coupling constants for the H1–H4 protons. Usually, *trans*-arenoquinolizidines are considered to be thermodynamically more stable than their *cis* counterparts because of their all-equatorial framework. However, the tendency of compound **7a** to exist in the *cis* form can be easily explained by the repulsion between the phenyl and methyl substituents in a hypothetical *trans* compound, which would become *cis* by chair flipping accompanied by inversion of the angular nitrogen atom. Interestingly, the *cis* fusion in compounds **7** is associated with a much higher polarity in comparison with their isomers **6**, which can be explained in terms of better accessibility of the nitrogen lone pair.

Next, we studied the reduction of compounds **5** and found that benzo[*a*]quinolizidines **8** and **9** were obtained under similar conditions as in the case of indoloquinolizines. Again, the major products were compounds **9**, arising from reduction opposite the R^3 substituent (Scheme 8 and Table 5).

Although compounds **8a–d** and **9a–d** showed the same spectral characteristics as the corresponding indoloquinolizidines, it is interesting to note that the benzo[*a*]quinolizidines



Scheme 8. Reduction of compounds **5** to benzo[*a*]quinolizidines.

bearing a methyl substituent at C-2 (compounds **e**) showed peculiar conformational behavior. Thus, in this case, the major product **9e** can be assumed to have a *trans* quinolizidine fusion, since the signal of the angular proton 11b is hidden inside a multiplet at $\delta \approx 3.8$ ppm instead of appearing at $\delta \approx 4.6$ ppm, as in the case of compounds **7** and **9a–d** (Figure 4). This difference can be ascribed to a less unfavor-

Table 5. Conditions and yields for the reduction of compounds **5**.

Entry		R^1	R^2	R^3	Yield [%][a]	**8**/**9**[b]
1	**8a**, **9a**	Me	OEt	Ph	90[c]	38:62
2	**8b**, **9b**	Me	OEt	*p*-ClC_6H_4	92	35:65
3	**8c**, **9c**	Me	OEt	*p*-$MeOC_6H_4$	82[c]	32:68
4	**8d**, **9d**	*n*Pr	OEt	Ph	78[d]	35:65
5	**8e**, **9e**	Me	OEt	Me	79[c]	35:65

[a] Yield of the isolated product. [b] Ratio calculated from ^{1}H NMR spectra of the crude product. [c] Only one isomer could be isolated in pure form. [d] Reaction time was 3 h in this case.

able 1,3-diaxial interaction between the two methyl substituents at C-2 and C-4 in **9e**, in comparison with that between a methyl and an aryl substituent in all other cases.

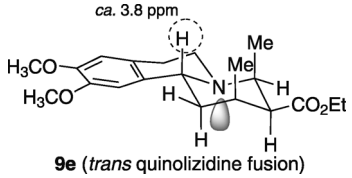


Figure 4. Stereochemistry of compound **9e**.

Conclusion

We have developed a multicomponent reaction leading to indolo[2,3-*a*]quinolizines from tryptamine, α,β-unsaturated aldehydes, and β-dicarbonyl compounds. This reaction creates two rings in a single operation by generating two carbon–carbon and two carbon–nitrogen bonds, and is proposed to take place through a domino process that involves at least five individual reactions, including the initial formation of an enamine from tryptamine and the β-dicarbonyl component, its Michael addition to the α,β-unsaturated aldehyde, and a subsequent 6-*exo*-*trig* cyclization followed by the formation of a vinylogous acyliminium cation, and, finally, a Pictet–Spengler reaction. This domino reaction is diastereoselective and leads exclusively to compounds having a *trans* relationship between the H-2 and H-12b protons. Less nucleophilic arylethylamines (5-bromotryptamine, 3,4-dimethoxyphenylethylamine) did not give the final Pictet–Spengler step directly and led instead to the isolation of *N*-indolylethyl or *N*-phenylethyl-1,4-dihydropyridines, which were efficiently cyclized to the desired indolo[2,3-*a*]quinolizines or benzo[*a*]quinolizines in the presence of HCl in methanol/water. Finally, reduction of the arenoquinolizine derivatives with sodium triacetoxyborohydride afforded the corresponding fused quinolizidines, having four stereocenters, as mixtures of two diastereomers.

Experimental Section

General experimental information: All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin-layer chromatography on aluminum plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm). Melting points were measured on a Reichert 723 hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FTIR spectrophotometer, with all compounds examined as thin films on NaCl disks. NMR spectra were obtained on Bruker Avance 250 and 500 spectrometers operating at 250 or 500 MHz for ^{1}H and 63 or 125 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined at the CAI de Microanálisis Elemental, Universidad Complutense, by using a Leco 932 CHNS combustion microanalyzer.

General procedure for the synthesis of indolo[2,3-*a*]quinolizines (2) and 1-(3-indolylethyl)-1,4-dihydropyridine (3): The requisite β-dicarbonyl compound (1 mmol) and CAN (5 mol%) were added to a stirred solution of the requisite primary amine (1 mmol) in ethanol (3 mL). Stirring was continued for 30 min under reflux, after which the requisite unsaturated aldehyde (1 mmol) was added and the mixture was heated at reflux for a further 30 min. After completion of the reaction, as monitored by TLC, the mixture was diluted with dichloromethane (20 mL) and washed with water (3×5 mL). The organic phase was dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The residue was purified by flash column chromatography eluting with a petroleum ether/ethyl acetate mixture (85:15, v/v). Characterization data for representative compounds are given below. For the full data, see the Supporting Information.

(±)-(2*S,12b*S**)-Ethyl 4-methyl-2-phenyl-1,2,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine-3-carboxylate (2a)**: Yellow solid; m.p. 175–176 °C; IR (neat): $\tilde{\nu}$ = 3314, 1556, 1454, 1305, 1212, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.80 (t, J = 7.1 Hz, 3H), 1.86 (td, J = 12.4, 5.3 Hz, 1H), 2.11 (ddd, J = 12.8, 3.5, 2.5 Hz, 1H), 2.46 (s, 3H), 2.51–2.74 (m, 2H), 2.96 (ddd, J = 15.0, 10.9, 4.1 Hz, 1H), 3.75 (q, J = 7.1 Hz, 2H), 4.06–4.17 (m, 3H), 6.89–6.95 (m, 3H), 7.01–7.15 (m, 5H), 7.27–7.30 (m, 1H), 7.58 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.6, 17.9, 22.8, 36.3, 38.5, 45.2, 49.9, 59.3, 97.2, 109.4, 111.3, 118.4, 120.0, 122.1, 126.4, 127.2, 128.2, 128.6, 134.4, 136.4, 147.4, 155.2, 169.4 ppm; elemental analysis calcd (%) for $C_{25}H_{26}N_2O_2$: C 77.69, H 6.78, N 7.25; found: C 77.53, H 6.63, N 6.99.

(±)-(2*S,12b*S**)-Ethyl 2-(4-chlorophenyl)-4-methyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (2d)**: Orange solid; m.p. 118–119 °C; IR (neat): $\tilde{\nu}$ = 2923, 1556, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.03 (t, J = 7.1 Hz, 3H), 2.09 (td, J = 12.3, 5.2 Hz, 1H), 2.30 (dt, J = 12.8, 2.5 Hz, 1H), 2.68 (s, 3H), 2.77–2.96 (m, 2H), 3.22 (td, J = 10.7, 4.1 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 4.26–4.39 (m, 3H), 7.09–7.22 (m, 4H), 7.28–7.32 (m, 3H), 7.51 (d, J = 7.0 Hz, 1H), 7.72 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.7, 17.9, 22.7, 36.3, 38.0, 45.2, 49.8, 59.4, 96.7, 109.5, 111.3, 118.4, 120.1, 122.3, 127.1, 128.7, 129.6, 132.0, 134.1, 136.4, 146.0, 155.4, 169.2 ppm; elemental analysis calcd (%) for $C_{25}H_{25}ClN_2O_2$: C 71.33, H 5.99, N 6.66; found: C 71.02, H 5.76, N 6.32.

(±)-(2*S,12b*S**)-Ethyl 4-methyl-2-(2-nitrophenyl)-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (2f)**: Pale-brown solid; m.p. 135–136 °C; IR (neat): $\tilde{\nu}$ = 3290, 2979, 1731, 1651, 1555, 1434, 1353, 1305, 1216, 1124, 1097, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.90 (t, J = 7.0 Hz, 3H), 2.15–2.29 (m, 1H), 2.54–2.98 (m, 6H), 2.79–2.98 (m, 4H), 3.24–3.34 (m, 1H), 3.83 (q, J = 6.9 Hz, 2H), 4.41–4.56 (m, 2H), 4.65 (d, J = 3.6 Hz, 1H), 7.10–7.21 (m, 3H), 7.29–7.57 (m, 4H), 7.85 (d, J = 7.8 Hz, 1H), 8.02 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14, 17, 22, 34, 34.5, 45, 50, 59, 97, 109, 111, 118, 120, 122, 124, 127, 127.3, 130, 132, 133, 136, 142, 150, 156, 168 ppm; elemental analysis calcd (%) for $C_{25}H_{25}N_3O_4$: C 69.59, H 5.84, N 9.74; found: C 69.25, H 5.59, N 9.50.

(±)-(2*S,12b*S**)-*S*-*tert*-Butyl 4-methyl-2-phenyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carbothioate (2k)**: Yellow solid; m.p. 139–140 °C; IR (neat): $\tilde{\nu}$ = 3310, 2923, 1614, 1519, 1453, 1350, 1304, 1161, 1054, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.40 (s, 9H), 2.11 (td, J = 12.5, 4.7 Hz, 1H), 2.37–2.42 (m, 1H), 2.60 (s, 3H), 2.75–2.93 (m, 2H), 3.18 (td, J = 13.5, 3.8 Hz, 1H), 4.21–4.44 (m, 3H), 7.09–7.20 (m, 2H), 7.27–7.40 (m, 6H), 7.50 (d, J = 7.0 Hz, 1H), 7.67 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 18.5, 22.7, 30.6, 36.6, 39.1, 45.4, 47.1, 50.1, 106.4, 109.5, 111.3, 118.4, 120.1, 122.3, 126.6, 127.1, 128.4, 128.8, 134.0, 136.4, 145.8, 153.1, 192.1 ppm; elemental analysis calcd (%) for $C_{27}H_{30}N_2OS$: C 75.31, H 7.02, N 6.51, S 7.45; found: C 75.10, H 7.02, N 6.47, S 7.49.

(±)-(2*S,12b*S**)-1-(4-Methyl-2-phenyl-1,2,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizin-3-yl)ethanone (2n)**: Orange solid; m.p. 115–116 °C; IR (neat): $\tilde{\nu}$ = 2925, 1505, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.02 (s, 3H), 2.13 (td, J = 12.5, 4.8 Hz, 1H), 2.45 (dt, J = 12.5, 3.4 Hz, 1H), 2.72 (s, 3H), 2.75–2.97 (m, 2H), 3.20 (td, J = 11.2, 4.4 Hz, 1H), 4.18 (s, 1H), 4.29 (dd, J = 12.0, 1.6 Hz, 1H), 4.41 (dd, J = 13.1, 2.0 Hz, 1H), 7.09–7.20 (m, 3H), 7.25–7.28 (m, 3H), 7.34–7.40 (m, 2H), 7.49–7.52 (m, 1H), 8.00 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 18.5, 22.7, 29.9, 36.6, 40.0, 45.5, 50.3, 106.4, 109.2, 111.4, 118.4, 119.9, 122.1, 126.9, 127.0, 128.4, 129.0,

134.2, 136.5, 146.0, 156.3, 197.4 ppm; elemental analysis calcd (%) for $C_{24}H_{24}N_2O$: C 80.87, H 6.79, N 7.86; found: C 80.55, H 6.93, N 7.53.

(±)-Ethyl 1-[2-(5-bromo-1*H*-indol-3-yl)ethyl]-4-(4-chlorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (3): Orange solid; m.p. 132–133 °C; IR (neat): $\tilde{\nu}$ = 2927, 1728, 1651, 1462, 1366, 1269, 1220, 1170, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.13 (t, J = 7.0 Hz, 3H), 2.43 (s, 3H), 3.00 (t, J = 7.3 Hz, 2H), 3.59 (quint., J = 7.4 Hz, 1H), 3.78 (quint., J = 7.4 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 4.60 (d, J = 5.5 Hz, 1H), 4.90 (dd, J = 7.6, 5.5 Hz, 1H), 5.89 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 7.15–7.31 (m, 6H), 7.71 (d, J = 1.5 Hz, 1H), 8.16 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.6, 16.1, 26.4, 40.0, 50.9, 59.7, 99.9, 107.9, 112.2, 113.2, 113.3, 121.4, 123.9, 125.6, 128.6, 129.1, 129.2, 129.3, 135.2, 147.9, 149.1, 150.1, 169.2 ppm; elemental analysis calcd (%) for $C_{25}H_{24}BrClN_2O_2$: C 60.07, H 4.84, N 5.60; found: C 59.81, H 4.79, N 5.57.

Cyclization of 1-(3-indolylethyl)-1,4-dihydropyridine 3 to form indoloquinolizidine (2p): Compound **3** (0.5 mmol) was added to a stirred solution of aqueous HCl (37%)/MeOH (1:1, 2 mL). Stirring was continued for 3 h at room temperature, whereupon completion of the reaction was indicated by TLC analysis. Dichloromethane (20 mL) was then added to the reaction mixture, and the resulting mixture was washed with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the residue by chromatography on silica gel, eluting with petroleum ether/EtOAc (85:15, v/v), gave compound **2p** in 78% yield.

General procedure for the synthesis of 1-(2-phenylethyl)-1,4-dihydropyridine derivatives (4): A solution of the requisite primary amine (1 mmol), the requisite β-dicarbonyl compound (1 mmol), and CAN (5 mol%) in ethanol (3 mL) was heated at reflux for 30 min. The requisite unsaturated aldehyde (1 mmol) was then added and reflux was maintained for a further 30 min. After completion of the reaction, as monitored by TLC, the reaction mixture was poured onto dichloromethane (20 mL), and the organic phase was washed with water (5 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the residue by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (85:15, v/v), afforded compounds **4**.

(±)-Ethyl 1-(3,4-dimethoxyphenylethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4a): Pale-brown viscous liquid; IR (neat): $\tilde{\nu}$ = 2935, 1681, 1621, 1516, 1453, 1418, 1368, 1263, 1238, 1157, 1097, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.11 (t, J = 7.1 Hz, 3H), 2.45 (s, 3H), 2.85 (t, J = 7.6 Hz, 2H), 3.51 (quint., J = 7.7 Hz, 1H), 3.71 (quint., J = 7.6 Hz, 1H), 3.07–3.09 (m, 6H), 4.00 (q, J = 7.1 Hz, 2H), 4.61 (d, J = 5.4 Hz, 1H), 4.96 (dd, J = 7.6, 5.4 Hz, 1H), 5.90 (d, J = 7.6 Hz, 1H), 6.71–6.85 (m, 3H), 7.17–7.32 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 13.1, 14.6, 35.2, 39.2, 50.9, 54.8, 58.2, 98.9, 107.0, 110.3, 110.9, 119.7, 124.9, 126.3, 127.1, 127.4, 129.5, 146.8, 147.3, 147.8, 147.9, 168.0 ppm; elemental analysis calcd (%) for $C_{25}H_{29}NO_4$: C 73.68, H 7.17, N 3.44; found: C 73.39, H 6.93, N 3.25.

(±)-*tert*-Butyl 1-(3,4-dimethoxyphenylethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4b): Pale-brown viscous liquid; IR (neat): $\tilde{\nu}$ = 2932, 1714, 1681, 1651, 1591, 1516, 1454, 1418, 1392, 1368, 1263, 1157, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.27 (s, 9H), 2.42 (s, 3H), 2.84 (t, J = 7.5 Hz, 2H), 3.49 (quint., J = 7.6 Hz, 1H), 3.67 (quint., J = 7.6 Hz, 1H), 3.87–3.90 (m, 6H), 4.59 (d, J = 5.0 Hz, 1H), 4.90 (dd, J = 7.6, 5.1 Hz, 1H), 5.84 (d, J = 7.7 Hz, 1H), 6.72–6.86 (m, 3H), 7.18–7.33 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 16.0, 28.5, 36.7, 41.4, 52.3, 56.3, 79.2, 102.1, 108.2, 111.7, 112.4, 121.1, 126.2, 127.8, 128.5, 128.7, 131.1, 147.5, 148.2, 149.4, 149.7, 169.0 ppm; elemental analysis calcd (%) for $C_{27}H_{33}NO_4$: C 74.45, H 7.64, N 3.22; found: C 74.20, H 7.42, N 2.96.

(±)-Ethyl 1-(3,4-dimethoxyphenylethyl)-4-phenyl-2-propyl-1,4-dihydropyridine-3-carboxylate (4f): Orange syrup; IR (neat): $\tilde{\nu}$ = 2961, 2934, 2872, 1682, 1591, 1516, 1454, 1418, 1367, 1263, 1238, 1158, 1101, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.02–1.15 (m, 6H), 1.59–1.69 (m, 2H), 2.81–2.90 (m, 4H), 3.46 (quint., J = 7.0 Hz, 1H), 3.66 (quint., J = 7.1 Hz, 1H), 3.87–3.90 (m, 6H), 4.01 (q, J = 7.0 Hz, 2H), 4.62 (d, J = 5.5 Hz, 1H), 4.99 (dd, J = 7.6, 5.6 Hz, 1H), 5.91 (d, J = 7.6 Hz, 1H), 6.72–6.86 (m, 3H), 7.16–7.29 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 14.7, 22.9, 30.7, 37.0, 40.5, 52.1, 56.2, 56.3, 59.5, 99.7, 108.7, 111.8, 112.3, 121.0, 126.3, 127.7, 128.6, 128.9, 130.9, 148.2, 149.4, 149.5, 152.9, 168.8 ppm; elemental analysis calcd (%) for $C_{27}H_{33}NO_4$: C 74.45, H 7.64, N 3.22; found: C 74.22, H 7.41, N 2.98.

General procedure for the synthesis of benzo[*a*]quinolizines (pyrido[2,1-*a*]isoquinolines) (5): The requisite compound **4** (0.5 mmol) was added to a stirred solution of aqueous HCl (37%)/MeOH (1:1, 2 mL). Stirring was continued at room temperature for the times specified in Table 3, with completion of the reactions being monitored by TLC. Dichloromethane (20 mL) was added to the reaction mixture, and the resulting mixture was washed with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the residue by chromatography on silica gel, eluting with petroleum ether/EtOAc (85:15, v/v), gave compounds **5**.

(±)-(2*S,11b*S**)-Ethyl 9,10-dimethoxy-4-methyl-2-phenyl-2,6,7,11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (5a)**: Pale-brown syrup; IR (neat): $\tilde{\nu}$ = 2931, 2836, 1728, 1673, 1563, 1513, 1433, 1362, 1290, 1215, 1120, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.11 (t, J = 7.0 Hz, 3H), 2.10 (td, J = 12.6, 5.3 Hz, 1H), 2.48 (dt, J = 12.9, 2.6 Hz, 1H), 2.77–2.82 (m, 4H), 3.04 (td, J = 15.2, 3.7 Hz, 1H), 3.28 (td, J = 13.8, 2.6 Hz, 1H), 3.91–4.12 (m, 8H), 4.26–4.38 (m, 3H), 6.54 (s, 1H), 6.72 (s, 1H), 7.28–7.48 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.6, 17.7, 30.2, 38.5, 39.1, 44.5, 52.4, 56.2, 56.5, 59.1, 97.1, 109.2, 111.5, 126.1, 127.5, 128.3, 128.5, 129.9, 147.8, 147.9, 148.0, 154.9, 169.5 ppm; elemental analysis calcd (%) for $C_{25}H_{29}NO_4$: C 73.68, H 7.17, N 3.44; found: C 73.49, H 6.91, N 3.29.

(±)-(2*S,11b*S**)-Ethyl 2-(4-chlorophenyl)-9,10-dimethoxy-4-methyl-2,6,7,11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (5c)**: Pale-brown syrup; IR (neat): $\tilde{\nu}$ = 2930, 1672, 1557, 1513, 1488, 1433, 1362, 1256, 1215, 1121, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.01 (t, J = 7.0 Hz, 3H), 1.97 (td, J = 12.8, 5.4 Hz, 1H), 2.27 (dt, J = 13.0, 3.1 Hz, 1H), 2.64–2.71 (m, 4H), 2.92 (td, J = 15.2, 3.8 Hz, 1H), 3.16 (td, J = 11.4, 3.0 Hz, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 3.96 (q, J = 7.0 Hz, 2H), 4.09–4.23 (m, 3H), 6.39 (s, 1H), 6.61 (s, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.28–7.32 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.6, 17.7, 30.1, 38.5, 38.7, 44.4, 52.3, 56.2, 56.5, 59.2, 96.7, 109.2, 111.5, 127.5, 128.6, 129.6, 129.7, 131.7, 146.7, 147.9, 148.0, 155.2, 169.3 ppm; elemental analysis calcd (%) for $C_{25}H_{28}ClNO_4$: C 67.94, H 6.39, N 3.17; found: C 67.67, H 6.15, N 2.97.

(±)-Ethyl 9,10-dimethoxy-2,4-dimethyl-2,6,7,11b-tetrahydro-1*H*-pyrido-[2,1-*a*]isoquinoline-3-carboxylate (5e): Pale-brown solid; m.p. 73–74 °C; IR (neat): $\tilde{\nu}$ = 2926, 1728, 1604, 1514, 1463, 1254, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.19 (d, J = 6.7 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.70 (td, J = 12.3, 5.2 Hz, 1H), 2.07 (ddd, J = 13.0, 5.4, 2.0 Hz, 1H), 2.47 (s, 3H), 2.68 (dt, J = 18.1, 2.5 Hz, 1H), 2.90 (td, J = 15.4, 4.2 Hz, 1H), 3.02–3.19 (m, 2H), 3.89–3.91 (m, 6H), 4.02–4.25 (m, 3H), 4.37 (dd, J = 11.9, 2.9 Hz, 1H), 6.63 (s, 1H), 6.68 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.0, 17.8, 23.0, 27.5, 30.2, 37.6, 44.2, 52.5, 56.2, 56.5, 59.2, 101.5, 109.2, 111.5, 127.5, 130.3, 147.8, 148.0, 153.3, 170.0 ppm; elemental analysis calcd (%) for $C_{20}H_{27}NO_4$: C 69.54, H 7.88, N 4.05; found: C 68.51, H 6.93, N 3.75.

General procedure for the reduction of compounds 2 to form 6 and 7 and of compounds 5 to form 8 and 9: Sodium borohydride (6 mmol) was added to stirred glacial acetic acid (3 mL) in three portions, keeping the temperature between 15 and 20 °C, so as to prepare sodium triacetoxyborohydride ($NaBH(OAc)_3$). After hydrogen evolution had ceased (10 min), the requisite compound **2** or **5** (1 mmol) was added in one portion and the reaction mixture was stirred for the time indicated in Table 4 for compounds **2** or for 2 h for compounds **5**. After completion the reaction, as monitored by TLC, the reaction mixture was diluted with water (10 mL), neutralized with saturated sodium hydrogencarbonate solution, and extracted twice with dichloromethane (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (gradient from 90:10 to 80:20, v/v). Characterization data for the diastereomers that could be isolated in a pure state are given below.

(±)-(2*R,3*S**,4*S**,12b*S**)-Ethyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (6a)**: Pale-red solid; m.p.

95–96 °C; IR (neat): $\tilde{\nu}$ = 3364, 2964, 2928, 2846, 1721, 1453, 1384, 1313, 1262, 1174, 1129, 1028, 909 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.00 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 2.06 (td, J = 13.1, 4.5 Hz, 1H), 2.28–2.41 (m, 2H), 2.57 (dd, J = 15.2, 1.7 Hz, 1H), 2.70–2.82 (m, 1H), 2.96 (quint., J = 6.4 Hz, 1H), 3.13 (t, J = 5.4 Hz, 1H), 3.22 (ddd, J = 11.3, 5.3, 3.3 Hz, 1H), 3.39 (q, J = 7.2 Hz, 1H), 3.78 (dd, J = 11.2, 1.0 Hz, 1H), 3.84–3.98 (m, 2H), 6.90–7.20 (m, 8H), 7.30–7.34 (m, 1H), 7.6 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 18.5, 22.5, 34.9, 37.0. 48.6, 49.7, 54.4, 56.0, 60.6, 109.0, 111.1, 118.5, 119.7, 121.7, 126.6, 127.5, 127.9, 128.9, 135.7, 136.5, 145.0, 173.0 ppm; elemental analysis calcd (%) for $C_{25}H_{28}N_2O_2$: C 77.29, H 7.26, N 7.21; found: C 77.05, H 7.02, N 6.90.

(±)-(2*R,3*R**,4*R**,12b*S**)-Ethyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (7a)**: Orange solid; m.p. 177–178 °C; IR (neat): $\tilde{\nu}$ = 3381, 2977, 2929, 2845, 2799, 1723, 1601, 1494, 1452, 1383, 1175, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.96 (t, J = 7.1 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 2.17 (dd, J = 13.7, 1.6 Hz, 1H), 2.57 (dd, J = 14.8, 3.0 Hz, 1H), 2.73 (t, J = 3.6 Hz, 1H), 2.90 (td, J = 13.7, 3.7 Hz, 1H), 3.03 (ddd, J = 15.8, 5.1, 2.4 Hz, 1H), 3.21–3.34 (m, 2H), 3.48 (td, J = 13.7, 5.4 Hz, 1H), 3.71 (dd, J = 14.2, 4.9 Hz, 1H), 3.83–3.99 (m, 2H), 4.86 (t, J = 2.6 Hz, 1H), 7.11–7.37 (m, 8H), 7.52–7.55 (m, 1H), 7.83 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.4, 16.4, 19.0, 27.1, 39.9, 48.0, 49.6, 53.3, 55.9, 59.9, 109.7, 111.4, 118.3, 119.9, 121.9, 127.1, 127.8, 128.1, 128.7, 133.5, 135.8, 142.5, 171.7 ppm; elemental analysis calcd (%) for $C_{25}H_{28}N_2O_2$: C 77.29, H 7.26, N 7.21; found: C 76.94, H 6.99, N 7.02.

(±)-(2*R,3*S**,4*S**,12b*S**)-Ethyl 2-(4-chlorophenyl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (6c)**: Pale-red solid; m.p. 120–121 °C; IR (neat): $\tilde{\nu}$ = 2927, 1731, 1622, 1531, 1493, 1470, 1372, 1328, 1290, 1233, 1176, 1091, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.19 (t, J = 7.1 Hz, 3H), 1.31 (d, J = 6.5 Hz, 3H), 2.11–2.23 (m, 1H), 2.44–2.58 (m, 2H), 2.75 (dd, J = 13.4, 1.8 Hz, 1H), 2.88–3.01 (m, 1H), 3.13 (quint., J = 6.3 Hz, 1H), 3.27 (dd, J = 7.7, 5.6 Hz, 1H), 3.40 (ddd, J = 11.2, 5.2, 2.0 Hz, 1H), 3.50–3.59 (m, 1H), 3.98–4.15 (m, 3H), 7.08–7.18 (m, 2H), 7.23–7.35 (m, 5H), 7.48–7.51 (m, 1H), 7.69 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 18.3, 22.5, 35.3, 36.4, 48.8, 49.5, 54.1, 56.1, 60.8, 109.1, 111.1, 118.5, 119.8, 121.8, 127.5, 129.0, 129.3, 132.3, 135.5, 136.5. 143.7, 172.7 ppm; elemental analysis calcd (%) for $C_{25}H_{27}ClN_2O_2$: C 70.99, H 6.43, N 6.62; found: C 70.66, H 6.22, N 6.39.

(±)-(2*R,3*R**,4*R**,12b*S**)-Ethyl 2-(4-chlorophenyl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (7c)**: Orange solid; m.p. 245–246 °C; IR (neat): $\tilde{\nu}$ = 3370, 3054, 2977, 2934, 2845, 1715, 1491, 1453, 1406, 1314, 1262, 1173, 1067, 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.02 (t, J = 7.1 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 2.14 (d, J = 14.8 Hz, 1H), 2.57 (dd, J = 16.0, 3.8 Hz, 1H), 2.69 (t, J = 3.8 Hz, 1H), 2.86 (dt, J = 13.7, 3.8 Hz, 1H), 2.94–3.07 (m, 1H), 3.21–3.33 (m, 2H), 3.45 (td, J = 13.6, 5.0 Hz, 1H), 3.70 (dd, J = 14.1, 5.0 Hz, 1H), 3.91 (q, J = 7.1 Hz, 2H), 4.85 (s, 1H), 7.12–7.22 (m, 4H), 7.27–7.36 (m, 3H), 7.52–7.55 (m, 1H), 7.80 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 16.4, 19.1, 27.2, 39.4, 48.0, 49.6, 53.1, 55.8, 60.1, 109.8, 111.4, 118.4, 120.0, 121.9, 128.0, 128.8, 129.2, 132.9, 133.3, 135.8, 141.1, 171.6 ppm; elemental analysis calcd (%) for $C_{25}H_{27}ClN_2O_2$: C 70.99, H 6.43, N 6.62; found: C 70.72, H 6.32, N 6.83.

(±)-(2*R,3*S**,4*S**,12b*S**)-*S*-*tert*-Butyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carbothioate (6g)**: Pale-brown solid; m.p. 125–126 °C; IR (neat): $\tilde{\nu}$ = 2923, 1673, 1454, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.29–1.39 (m, 12H), 2.16–2.23 (m, 1H), 2.39–2.58 (m, 2H), 2.75 (d, J = 15.3 Hz, 1H), 2.91–3.03 (m, 1H), 3.11–3.18 (m, 1H), 3.39–3.56 (m, 3H), 3.97 (d, J = 9.0 Hz, 1H), 7.07–7.14 (m, 2H), 7.24–7.36 (m, 6H), 7.49 (d, J = 6.8 Hz, 1H), 7.68 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 17.8, 22.5, 29.9, 35.8, 37.2, 48.6, 49.1, 53.7, 56.8, 57.6, 109.1, 111.0, 118.5, 119.7, 121.7, 126.7, 127.6, 127.9, 128.9, 135.6, 136.5, 144.7, 199.5 ppm; elemental analysis calcd (%) for $C_{27}H_{32}N_2OS$: C 74.96, H 7.46, N 6.48, S 7.41; found: C 74.67, H 7.21, N 6.21.

(±)-(2*R,3*R**,4*R**,12b*S**)-*S*-*tert*-Butyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carbothioate (7g)**: Orange solid; m.p. 148–149 °C; IR (neat): $\tilde{\nu}$ = 2924, 1667, 1454, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.27 (s, 9H), 1.37 (d, J = 6.5 Hz, 3H), 2.14–2.20 (m, 1H), 2.56 (dd, J = 15.1, 2.6 Hz, 1H), 2.79–2.74 (m, 1H), 2.84–3.03 (m, 2H), 3.24–3.43 (m, 3H), 3.72 (dd, J = 13.9, 4.7 Hz, 1H), 4.89 (br s, 1H), 7.11–7.19 (m, 3H), 7.25–7.35 (m, 5H), 7.51–7.54 (m, 1H), 7.79 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 16.3, 19.0, 27.8, 29.6, 41.0, 48.0, 48.5, 50.2, 55.8, 60.8, 109.8, 111.3, 118.4, 120.0, 121.9, 127.2, 128.1, 128.7, 133.4, 135.8, 141.9. 199.9 ppm (the signal of one quaternary carbon atom was merged with that of another); elemental analysis calcd (%) for $C_{27}H_{32}N_2OS$: C 74.96, H 7.46, N 6.48, S 7.41; found: C 74.73, H 7.72, N 6.17, S 6.89.

(±)-(2*R,3*S**,4*S**,11b*S**)-Ethyl 2-(4-chlorophenyl)-9,10-dimethoxy-4-methyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (8b)**: Yellow solid; m.p. 87–88 °C; IR (neat): $\tilde{\nu}$ = 2919, 1731, 1254, 1091, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.16 (t, J = 7.1 Hz, 3H), 1.25 (d, J = 6.4 Hz, 3H), 2.28–2.34 (m, 2H), 2.45 (td, J = 11.5, 2.3 Hz, 1H), 2.65 (d, J = 15.9 Hz, 1H), 2.94–3.08 (m, 2H), 3.22–3.28 (m, 2H), 3.51 (q, J = 7.2 Hz, 1H), 3.83–3.90 (m, 7H), 3.99–4.13 (m, 2H), 6.57–6.59 (m, 2H), 7.26–7.35 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 17.7, 30.0, 36.8, 37.9, 47.8, 49.1, 56.2, 56.4, 56.5, 57.0, 60.7, 108.7, 111.4, 127.1, 129.0, 129.3, 131.2, 132.2, 144.2, 147.7, 147.8, 172.9 ppm; elemental analysis calcd (%) for $C_{25}H_{30}ClNO_4$: C 67.63, H 6.81, N 3.15; found: C 67.55, H 6.68, N 3.04.

(±)-(2*R,3*R**,4*R**,11b*S**)-Ethyl 2-(4-chlorophenyl)-9,10-dimethoxy-4-methyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (9b)**: Pale-brown solid; m.p. 68–69 °C; IR (neat): $\tilde{\nu}$ = 2925, 2854, 2358, 1732, 1607, 1513, 1493, 1463, 1256, 1208, 1174, 1101, 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.01 (t, J = 7.1 Hz, 3H), 1.26 (d, J = 6.7 Hz, 3H), 2.35–2.49 (m, 2H), 2.70 (t, J = 4.2 Hz, 1H), 2.93 (dt, J = 13.4, 4.6 Hz, 1H), 3.00–3.09 (m, 1H), 3.15 (dd, J = 6.3, 4.2 Hz, 1H), 3.22–3.30 (m, 1H), 3.36 (dd, J = 13.5, 4.9 Hz, 1H), 3.57 (dd, J = 14.1, 5.7 Hz, 1H), 3.78 (s, 3H), 3.83–4.02 (m, 5H), 4.62 (br s, 1H), 6.65 (s, 1H), 6.70 (s, 1H), 7.17–7.20 (m, 2H), 7.26–7.30 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 18.6, 22.2, 27.1, 38.6, 47.6, 49.3, 53.1, 53.8, 56.2, 56.5, 58.3, 60.0, 77.6, 108.9, 112.4, 128.8, 129.2, 132.7, 141.5, 147.9, 148.0, 171.5 ppm; elemental analysis calcd (%) for $C_{25}H_{30}ClNO_4$: C 67.63, H 6.81, N 3.15; found: C 67.45, H 6.67, N 2.98.

(±)-(2*R,3*S**,4*S**,11b*S**)-Ethyl 9,10-dimethoxy-2-phenyl-4-propyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (8d)**: Pale-brown solid; m.p. 78–79 °C; IR (neat): $\tilde{\nu}$ = 2959, 1728, 1650, 1602, 1516, 1464, 1377, 1275, 1174, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.93 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.35–1.47 (m, 2H), 1.67–1.79 (m, 2H), 2.23 (dt, J = 14.2, 3.5 Hz, 1H), 2.46–2.59 (m, 1H), 2.70–2.90 (m, 4H), 3.08–3.18 (m, 3H), 3.63–3.69 (m, 1H), 3.81–3.97 (m, 6H), 4.17 (q, J = 7.1 Hz, 2H), 6.56–6.62 (m, 2H), 7.24–7.29 (m, 2H), 7.36–7.44 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.5, 14.6, 20.6, 30.3, 33.1, 34.6, 38.3, 43.4, 46.4, 56.2, 56.5, 56.9, 60.1, 60.7, 109.4, 111.7, 126.5, 127.4, 127.9, 129.0, 147.5, 147.8, 174.4 ppm; elemental analysis calcd (%) for $C_{27}H_{35}NO_4$: C 74.11, H 8.06, N 3.20; found: C 73.90, H 7.99, N 3.06.

(±)-(2*R,3*R**,4*R**,11b*S**)-Ethyl 9,10-dimethoxy-2-phenyl-4-propyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (9d)**: Pale-brown syrup; IR (neat): $\tilde{\nu}$ = 2927, 1732, 1514, 1463, 1256, 1161, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.90–0.96 (m, 6H), 1.22–1.37 (m, 2H), 1.79–1.94 (m, 1H), 2.37–2.48 (m, 2H), 2.87–3.06 (m, 4H), 3.21–3.40 (m, 2H), 3.66 (dd, J = 14.3, 5.6 Hz, 1H), 3.75–3.99 (m, 9H), 4.64 (br s, 1H), 6.66 (s, 1H), 6.72 (s, 1H), 7.23–7.35 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.3, 14.9, 19.4, 22.6, 26.9, 33.7, 39.2, 47.7, 49.7, 54.3, 56.2, 56.6, 58.8, 59.7, 109.2, 112.4, 127.0, 127.8, 128.3, 128.5, 128.7, 143.3, 147.8, 148.0, 171.6 ppm; elemental analysis calcd (%) for $C_{27}H_{35}NO_4$: C 74.11, H 8.06, N 3.20; found: C 73.97, H 8.19, N 2.98.

Acknowledgements

Financial support from the Ministerio de Economía y Competitividad, MINECO (grant CTQ2012–33272-BQU) and the Agencia Española para la Cooperación Internacional y el Desarrollo, AECID (predoctoral fellowship to PAS) is gratefully acknowledged.

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Received: December 26, 2012
Revised: June 27, 2013
Published online: ■■ ■■, 0000

Heterocycle Synthesis

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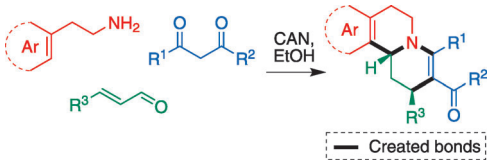
A β-Enaminone-Initiated Multicomponent Domino Reaction for the Synthesis of Indoloquinolizines and Benzoquinolizines from Acyclic Precursors



One operation, four bonds: The cerium(IV) ammonium nitrate (CAN)-catalyzed reaction between tryptamine, α,β-unsaturated aldehydes, and β-dicarbonyl compounds affords indolo[2,3-*a*]quinolizines in a single operation (see scheme). This multicomponent reaction creates two rings by generating two C–C and two C–N bonds, and is proposed to take place through a domino process that involves at least five individual reactions.

