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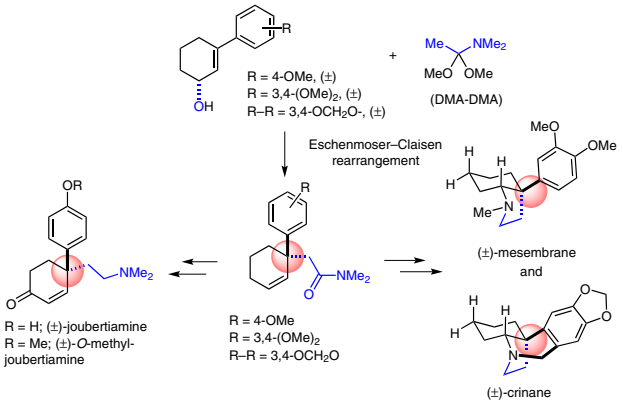
Concise Total Syntheses of (±)-Joubertiamine, (±)-*O*-Methyljoubertiamine, (±)-3′-Methoxy-4′-*O*-methyljoubertiamine, (±)-Mesembrane, and (±)-Crinane

Mrinal Kanti Das
Subhadip De
Shubhashish
Alakesh Bisai*

Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhauri, Bhopal 462 066, Madhya Pradesh, India
alakesh@iiserb.ac.in



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Abstract A method to access *cis*-3a-aryloctahydroindole alkaloids has been developed through a key strategy involving Eschenmoser–Claisen rearrangement of allylalcohol. This approach gives us an opportunity to access the all-carbon quaternary center required for *cis*-3a-aryloctahydroindole alkaloids. Subsequent simple allylic oxidation of Eschenmoser–Claisen products and synthetic elaborations (reductions/oxidations) enabled the total syntheses of the title compounds to be completed in good yields in a few steps. The strategic viability was further tested in the total syntheses of *Amaryllidaceae* alkaloids (±)-mesembrane and (±)-crinane. Towards this end, we synthesized advanced intermediate keto-aldehydes from Eschenmoser–Claisen rearrangement products through iodolactonization followed by elaboration involving reduction and oxidation steps.

Keywords Eschenmoser–Claisen rearrangement, all-carbon quaternary centers, allylic oxidation, alkaloids

Sceletium alkaloids[1] of the family *Aizoaceae* (**1a–d** and **2a–c**; Figure 1) represent an interesting class of alkaloids with an all-carbon quaternary stereocenter. Most of the bases that have been characterized belong to two different groups: *seco*-mesembrane alkaloids (**1**), such as joubertiamine (**1a**),[1] *O*-methyljoubertiamine (**1b**), 3′-methoxy-4′-*O*-methyljoubertiamine (**1c**), and dihydrojoubertiamine (**1d**), and *cis*-3a-aryloctahydroindole alkaloids (**2**)[2] such as mesembrane (**2a**), mesembranol (**2b**), mesembrine (**2c**).[2]

The common structural feature of these classes of alkaloids is the presence of an all-carbon quaternary stereocenter;[3] hence, it is quite reasonable to believe that they originated through a common biosynthetic pathway.[4] In addition to their interesting architecture, the *cis*-3a-aryloctahydroindole skeleton constitutes the core structure of many alkaloids with impressive diversity of biological activities.[4] Their biological potential was significantly manifested by their antiviral, antitumor, anticholinergic and anti-HIV properties.[5] Therefore, in recent years considerable effort has been directed toward the synthesis of *Sceletium* alkaloids.[1]

The alkaloids of the *Amaryllidaceae* family (Figure 2) also have interesting architecture with an all-carbon quaternary stereocenter.[6] These alkaloids drew the attention of the synthetic community because of their intriguing physiological activities.[7] Plants belonging to the *Amaryllidaceae* family are herbaceous perennials that grow from bulbs. The

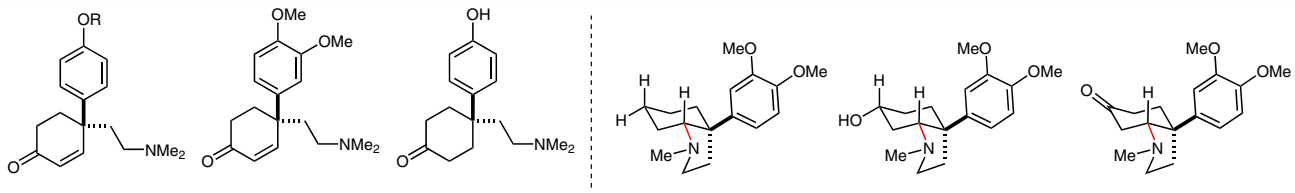


Figure 1 Selected *seco*-mesembrane **1a–d** and mesembrane **2a–c** alkaloids

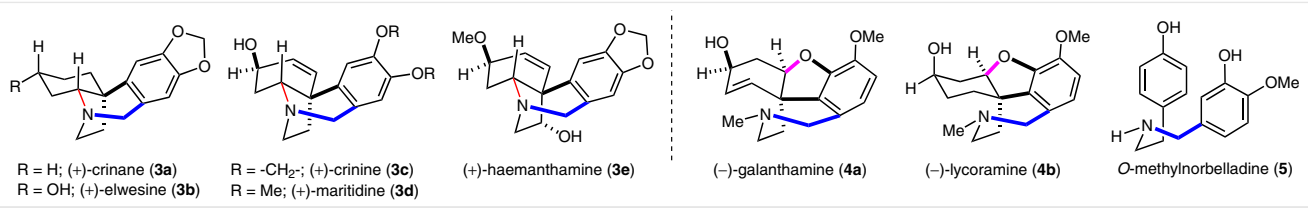


Figure 2 The *Amaryllidaceae* alkaloids **3a**–**e** and **4a**–**b**, and biosynthetic precursor, *O*-methylnorbelladine (**5**)

family consists of about 60 genera, whose 800 species are widely distributed in several countries around the world. They are also cultivated as ornamental plants for their beautiful flowers and for the production of volatile oil. Among all *Amaryllidaceae* alkaloids, the crinine-type alkaloids, which have the 5,10b-ethanophenanthridine skeleton as the core structure, represented by crinane **3a**, elwesine **3b**, crinine **3c**, martidine **3d**, and haemanthamine **3e**, have received considerable attention, since they have been reported to possess antiviral, and anticancer activities (Figure 2).[8] These activities, together with their intriguing structures, have brought a major impetus for synthetic exploration in this direction from organic chemists across the globe.

Biogenetically, crinane (**3a**) type alkaloids are closely related to other major *Amaryllidaceae* family natural products, such as galanthamine **4a** and lycoramine **4b**, as they are all derived from the same precursor *O*-methylnorbelladine **5** (Figure 2).[9] These alkaloids display vicinal quaternary and tertiary carbon stereocenters[3] with a fused pyrrolidine ring, as common structural features, the stereochemical incorporation of which is indeed a challenge. Several approaches have been developed to synthesize this skeleton, which includes a quaternary carbon.[10] The incorporation of this sterically congested quaternary center is the critical element in the total synthesis of crinine-type alkaloids, and a number of synthetic approaches have emerged to solve this challenging problem.[11]

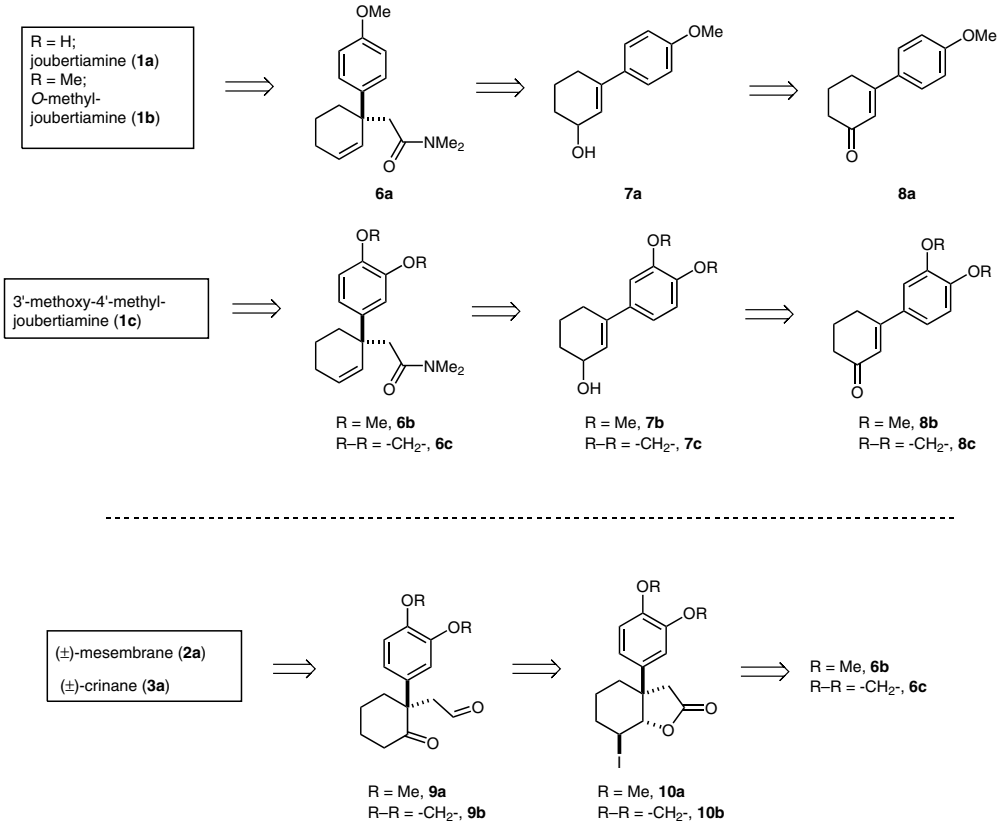
Recently, we envisaged a strategy to access alkaloids having the *cis*-3a-aryloctahydroindole skeleton with a sterically congested quaternary carbon center located at the hydroindolone bridgehead (C-3a) position.[12] Herein, we delineate a unified approach to the *seco*-mesembrane alkaloids **1a**–**c**, mesembrane alkaloids **2a**, and crinane alkaloids **3a** through a key Eschenmoser–Claisen rearrangement of allylic alcohol of type **7** (Scheme 1), which permits an iodolactonization process for the divergent introduction of a range of functionality to address the total synthesis of several congeners of this family.

Structurally, *Sceletium* alkaloids of *seco*-mesembrane and mesembrane classes of alkaloids (see **1** and **2**, Figure 1) have an interesting all-carbon quaternary stereocenter,[1,2] whereas *Amaryllidaceae* alkaloids, with a 5,10b-ethanophenanthridine skeleton (**3a**–**e**, Figure 2), possess a structure that may be regarded as a carbocyclic six-membered ring, an appended aryl substituent, and a five-membered, nitrogen-containing ring annulated onto a carbocyclic six-membered ring.

We hypothesized that an Eschenmoser–Claisen rearrangement of 3-(4-methoxyphenyl)cyclohex-2-enol (**7a**), 3-(3,4-dimethoxyphenyl)cyclohex-2-enol (**7b**), and 3-(3,4-methylenedioxyphenyl)cyclohex-2-enol (**7c**) could be an excellent strategic platform to install the all-carbon quaternary stereocenter required for a unified strategy for the construction of *Sceletium* and *Amaryllidaceae* alkaloids shown in Figure 1 and Figure 2. Our retrosynthetic analysis is shown in Scheme 1. A simple allylic oxidation of products from Eschenmoser–Claisen rearrangement (**6a**–**c**) can provide a simple route to the complete skeleton of *seco*-mesembrane alkaloids (Scheme 1).

Retrosynthetically, we also thought that the advanced intermediate ketoaldehydes **9a** and **9b** would lead to a unified pathway to access both mesembrane (**2a**) and crinane (**3a**) type alkaloids (Scheme 1). Ketoaldehydes **9a** and **9b** could be synthesized from a complete reduction of iodolactones **10a** and **10b**, respectively, which could be accessed from iodolactonization[13] of dimethylamides **6b** and **6c**. The latter can be accessed from Eschenmoser–Claisen rearrangement[14] of 3-(aryl)cyclohex-2-enols **7a**–**c** (Scheme 1). At this stage we hypothesized that, because [3,3]-sigmatropic rearrangements follow a completely stereospecific reaction, enantioenriched 3-(aryl)cyclohex-2-enols **7a**–**c** would easily allow our approach to be conducted in an asymmetric manner. Compounds **7a**–**c** can be obtained from the reduction of 3-aryl-2-cyclohexenones **8a**–**c**, which, in turn, can be obtained from vinylogous ester **11** through a well-known Stork–Danheiser sequence.[15]

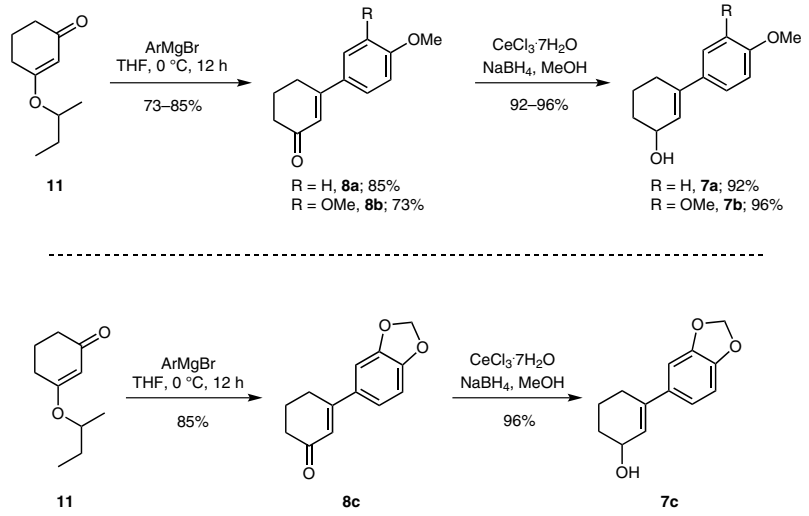
Moving forward with our proposed strategy, our first task was to synthesize 3-(aryl)cyclohex-2-enols (±)-**7a**–**c** required for the Eschenmoser–Claisen rearrangement. Towards this, we carried out the Stork–Danheiser sequence on compound **11** by using arylmagnesium bromides to afford 3-aryl-2-cyclohexenones **8a**–**c** in 73–85% yields (Scheme 2). The latter were then reduced under Luche reduction[16] to access 3-(aryl)cyclohex-2-enols (±)-**7a**–**c** in 92–96% yields. With allyl alcohols **7a**–**c** in hand, we sought conditions to effect the key [3,3]-sigmatropic rearrangement for the synthesis of 1-dimethylacetamide-1-aryl-2-cyclohexenes **6a**–**c** (Table 1), with an all-carbon quaternary stereocenter. Eschenmoser–Claisen rearrangement[17,18] of



Scheme 1 Retrosynthetic analysis of (±)-**1a–c**, (±)-**2a**, and (±)-**3a**

N,*O*-ketene acetals is a fundamental concerted process that yields γ,δ-unsaturated amides, which are of great use in natural product synthesis.[19] This process allows the formation of a carbon–carbon bond at the β-position to a nitrogen atom of *N*,*O*-ketene acetals.

At the outset, we started optimization of Eschenmoser–Claisen rearrangement by using 3-(3,4-dimethoxyphenyl)cyclohex-2-enol (**7b**) as a model substrate with the dimethyl acetal of dimethylacetamide (DMA-DMA) in different solvents under reflux; the results are summarized in Ta-

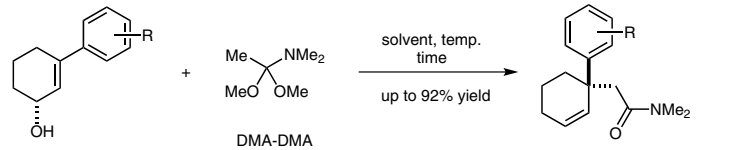


Scheme 2 Synthesis of 3-(aryl)cyclohex-2-enols (±)-**7a–c**

ble 1. Preliminary studies indicate that two equivalents of dimethylacetal of DMA-DMA in different solvents furnished product **6b** in only 26–49% yields (entries 1–3). After exhaustive optimization, it was observed that six equivalents of DMA-DMA was also not sufficient for optimal conditions (up to 53% of **6b** was obtained) when reactions were carried out in toluene, xylene, or mesitylene (entries 4–6). By increasing the amount of DMA-DMA to 10 equivalents, it was observed that **6b** could be obtained in maximum 73% yields in mesitylene heated to reflux (entries 7–9).

Gratifyingly, it was seen that Eschenmoser–Claisen rearrangement of **7b** could be effected smoothly at 180 °C without any solvent to give **6b** in 92% yield (Table 1, entry 10). Under these conditions, 3-(aryl)cyclohex-2-enols (±)-**7a** and (±)-**7c** also afforded products in 90 and 83% isolated yields, respectively (entries 11 and 12). However, use of an excess (10 equiv) of DMA-DMA in Eschenmoser–Claisen rearrangement of **7b** under heating led us to consider the use of a microwave-assisted reaction as an alternative method.

Table 1 Optimization of Eschenmoser–Claisen Rearrangement of 3-(3,4-Dimethoxy)cyclohex-2-enols (±)-**7b**[a]



R = 4-OMe, (±)-**7a**
R = 3,4-$(OMe)_2$, (±)-**7b**
R–R = 3,4-OCH_2O-, (±)-**7c**

R = 4-OMe, (±)-**6a**
R = 3,4-$(OMe)_2$, (±)-**6b**
R–R = 3,4-OCH_2O-, (±)-**6c**

Entry	7	DMA-DMA (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	**7b**	2	toluene	110	24	26 (**6b**)[c]
2	**7b**	2	xylene	130	24	42 (**6b**)[c]
3	**7b**	2	mesitylene	150	24	49 (**6b**)[c]
4	**7b**	6	toluene	110	16	47 (**6b**)[c]
5	**7b**	6	xylene	130	16	50 (**6b**)[c]
6	**7b**	6	mesitylene	150	16	53 (**6b**)
7	**7b**	10	toluene	110	12	61 (**6b**)
8	**7b**	10	xylene	130	12	66 (**6b**)
9	**7b**	10	mesitylene	150	12	73 (**6b**)
10	**7b**	10	–	180	12	92 (**6b**)
11	**7a**	10	–	180	12	90 (**6a**)
12	**7c**	10	–	180	12	83 (**6c**)
13	**7a**	5	toluene	110 (MW)	10 min	65 (**6a**)
14	**7a**	5	xylene	140 (MW)	20 min	81 (**6a**)
15	**7a**	5	mesitylene	170 (MW)	15 min	74 (**6a**)
16	**7a**	5	xylene	200 (MW)	10 min	92 (**6a**)
17	**7a**	5	mesitylene	200 (MW)	15 min	89 (**6a**)
18	**7a**	3	xylene	200 (MW)	15 min	72 (**6a**)
19	**7a**	3	mesitylene	200 (MW)	15 min	74 (**6a**)
20	**7a**	2	xylene	200 (MW)	30 min	63 (**6a**)
21	**7b**	5	xylene	200 (MW)	10 min	87 (**6b**)
22	**7c**	5	xylene	200 (MW)	10 min	89 (**6c**)
23	**7a**	5	xylene	200	2	71 (**6a**)
24	**7b**	5	xylene	200	2	74 (**6b**)
25	**7c**	5	xylene	200	2	69 (**6a**)

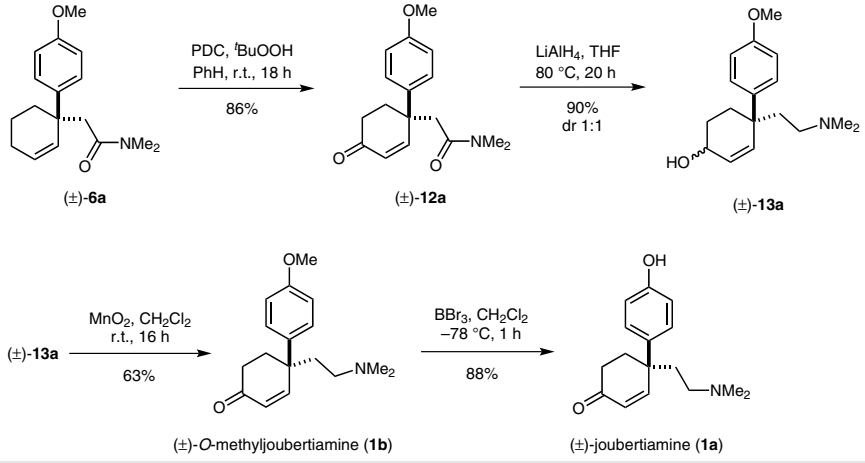
[a] Reaction was conducted with (±)-**7a–b** (0.25 mmol) and solvent (2 mL) unless noted otherwise.
[b] Isolated yield after column chromatography.
[c] (±)-**7b** was recovered in 28–37%.

Towards this, we continued our optimization of the Eschenmoser–Claisen rearrangement by using 3-(4-methoxyphenyl)cyclohex-2-enol (**7a**) as model substrate in a microwave-assisted process in different solvents (Table 1, entries 13–22). The use of five equivalents DMA-DMA was sufficient to afford **6a** in 92% yield in only 10 minutes at 200 °C in xylene (entries 13–17). However, it was observed that reducing the amount of DMA-DMA led to a drop in the isolated yield of **6a** to 74 and 63% when three and two equivalents of DMA-DMA, respectively, was used (entries 19 and 20). Under the optimized conditions, allylalcohols **7b** and **7c** afforded products **6b** and **6c**, respectively, in 87–89% yields (entries 21 and 22).

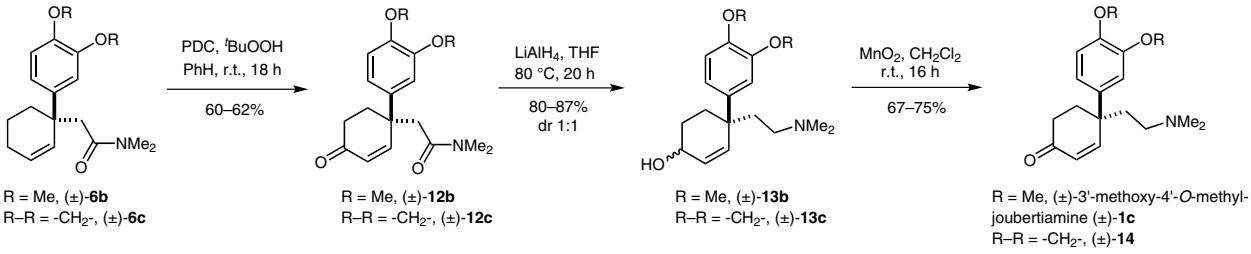
Having accomplished the synthesis of (±)-**6a**–**c**, we attempted to manipulate the cyclohexene double bond toward the synthesis of more decorated cyclohexenones (Scheme 3). For this purpose, we carried out allylic oxidations of the intermediate (±)-**6a** with pyridinium dichromate (PDC) in the presence of *tert*-butyl hydroperoxide to afford enone (±)-**12a** in 86% yield, which, on subsequent lithium aluminum hydride mediated reduction, provided (±)-**13a** in 90% yield with approximately 1:1 diastereomeric ratio.[20] Manganese dioxide mediated oxidation of allylalcohol (±)-**13a** completed the total synthesis of (±)-*O*-methyljoubertiamine (±)-**1b** in 63% yield, from which the total synthesis of (±)-joubertiamine (±)-**1a** was accomplished in 88% yield by treatment with BBr_3 (Scheme 3).

Along similar lines, PDC oxidation[21] of (±)-**6b**,**c** afforded enones (±)-**12b**,**c** in 60–62% yield, which, on subsequent reduction using lithium aluminum hydride provided allylalcohols (±)-**13b**,**c** in 80–87% yield with approximately 1:1 dr (Scheme 4). The latter were then oxidized with MnO_2 to complete the total synthesis of 3′-methoxy-4′-*O*-methyljoubertiamine (±)-**1c** and related structure (±)-**14** in 67–75% yields.

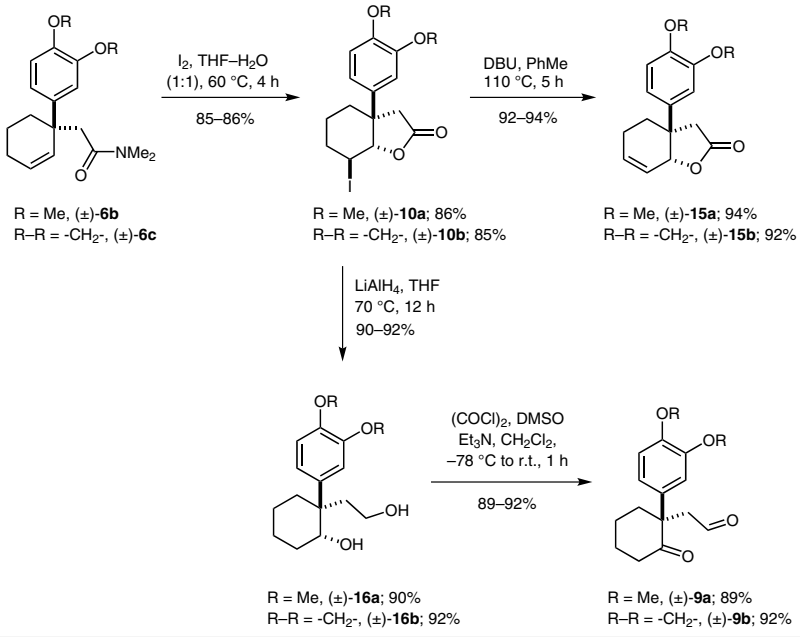
We then turned our attention to the total syntheses of (±)-mesembrane (±)-**2a** and (±)-crinane (±)-**3a**; for these it was required to functionalize the 2-position of the cyclohexene ring of (±)-**6b**,**c**. Towards this end, iodolactonization of 1-dimethylacetamido-1-aryl cyclohexenes (±)-**6b**,**c** in the presence of iodine in a mixture of THF and water provided iodolactone intermediates (±)-**10a**,**b** in 85–86% yield (Scheme 5). Iodolactones (±)-**10a**,**b**, upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base, furnished alkenes (±)-**15a**,**b** in excellent yields. The latter could be used as advanced intermediates for the synthesis of a variety of *Amaryllidaceae* alkaloids. However, for the total synthesis of (±)-mesembrane (**2a**) and (±)-crinane (**3a**), γ-keto aldehydes (±)-**9a**,**b** were required. Towards this end, iodolactones (±)-**10a**,**b** were reduced in the presence of



Scheme 3 Total synthesis of (±)-*O*-methyljoubertiamine (**1b**) and (±)-joubertiamine (**1a**)



Scheme 4 Total syntheses of 3′-methoxy-4′-*O*-methyljoubertiamine (**1c**) and related structure **14**

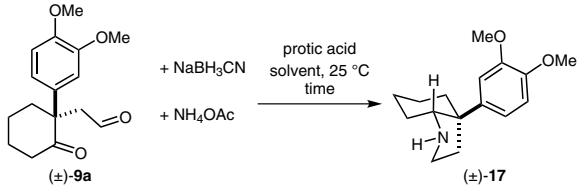


Scheme 5 Synthesis of keto aldehydes (±)-**9a**,**b**

$LiAlH_4$ to afford 1,4-diols (±)-**16a**,**b** in quantitative yield (Scheme 5). Among various oxidation procedures investigated to synthesize γ-keto aldehydes (±)-**9a**,**b**, we found that Swern oxidation[22] of 1,4-diols (±)-**16a**,**b** afforded (±)-**9a**,**b** in the highest yield (89–92%; Scheme 5). Optimization studies were further conducted to carry out reductive amination of model γ-keto aldehyde (±)-**9a** to complete the total synthesis of (±)-mesembrane (**2a**). The optimization studies are summarized in Table 2. Initially, reductive amination of (±)-**9a** was carried out in the presence of two equivalents of ammonium acetate and four equivalents of sodium cyanoborohydride in solvents such as MeOH, EtOH, and THF in the presence of one equivalent of trifluoroacetic acid and acetic acid.

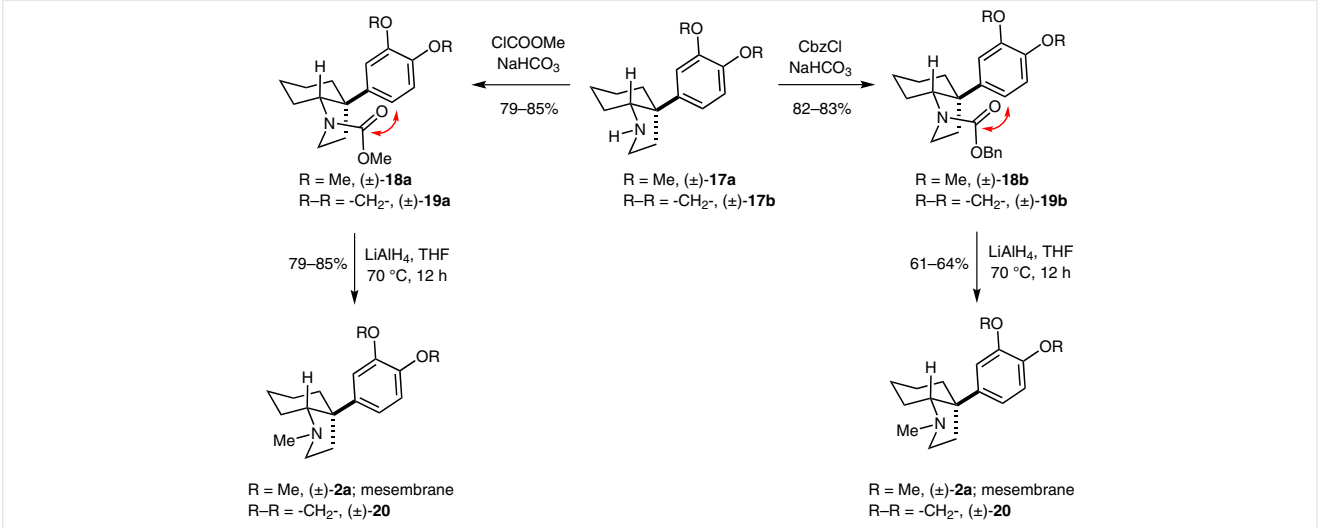
To our delight, we found that *cis*-3a-aryloctahydroindole (±)-**17a** could be obtained in 32–89% isolated yields (Table 2,). Following further optimization, we were pleased to find that secondary amine (±)-**17a** could be obtained in 83–85% yields when reductive amination was carried out in the presence of only 10 mol% of each trifluoroacetic acid (TFA) and acetic acid (AcOH) (entries 7 and 8). Gratifyingly, on further reducing the amount of catalyst to 5 mol%, we found that *cis*-3a-aryloctahydroindole (±)-**17a** could be obtained in 82–84% in the presence of 5 mol% of each TFA and AcOH, respectively (entries 9 and 10), whereas, 2 mol% of each TFA and AcOH afforded *cis*-3a-aryloctahydroindole (±)-**17a** in 69–71% in one day (entries 11 and 12).

Table 2 Optimization of Reductive Amination of (±)-**9a**[a]



Entry	Acid	Solvent	Time (h)	Yield (%)[b]
1	TFA (1 equiv)	MeOH	12	72
2	AcOH (1 equiv)	MeOH	12	75
3	TFA (1 equiv)	EtOH	10	89
4	AcOH (1 equiv)	MeOH	10	88
5	TFA (1 equiv)	THF	18	35
6	AcOH (1 equiv)	THF	18	32
7	TFA (10 mol%)	EtOH	16	83
8	AcOH (10 mol%)	EtOH	16	85
9	TFA (5 mol%)	EtOH	19	84
10	AcOH (5 mol%)	EtOH	19	82
11	TFA (2 mol%)	EtOH	24	69
12	AcOH (2 mol%)	EtOH	24	71

[a] Reaction conditions: (±)-**9a** (0.20 mmol), NH_4OAc (2.0 equiv), $NaBH_3CN$ (4.0 equiv), solvent (2 mL), 0–25 °C, inert atmosphere.
[b] Isolated yield after column chromatography.

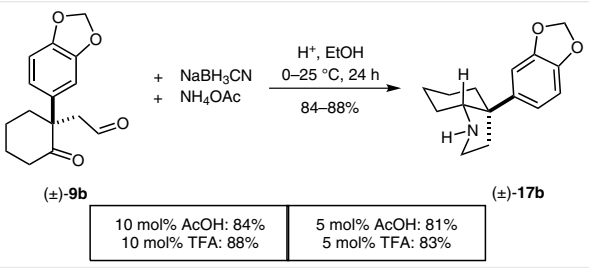


Scheme 6 Total synthesis of (±)-mesembrane (**2a**)

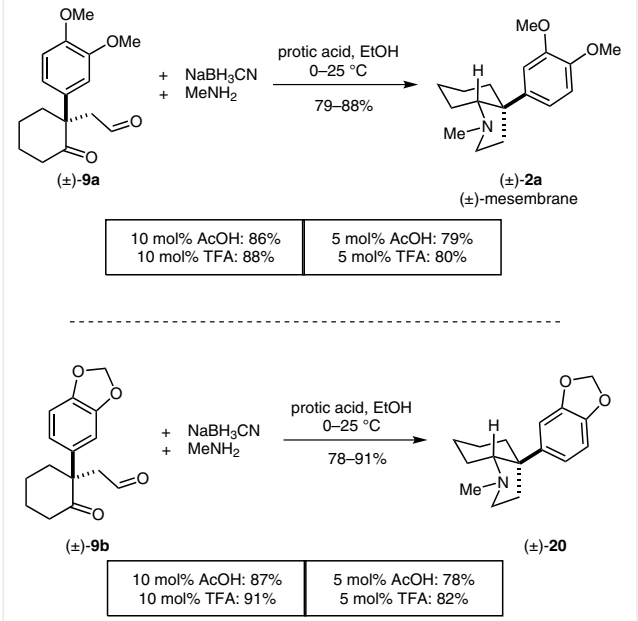
Continuing our studies, carbamates (±)-**18a**,**b** were synthesized in 82–85% yields from *cis*-3a-aryloctahydroindole (±)-**17a** by treatment with chloromethylformate and benzyl chloroformate in the presence of $NaHCO_3$ (Scheme 6).

In fact, carbamates (±)-**18a**,**b** could serve as potential precursors for the synthesis of the tricyclic core with additional amide functionality (see Scheme 6, red arrows) related to many *Amaryllidaceae* alkaloids (**3a**–**c**; Figure 2) through a Bischler–Napieralski type process.[23] For the total synthesis of (±)-mesembrane (±)-**2a**, we then carried out $LiAlH_4$-mediated reduction of carbamates (±)-**18a**,**b** to afford (±)-**2a** in 64–79% yield (Scheme 6).

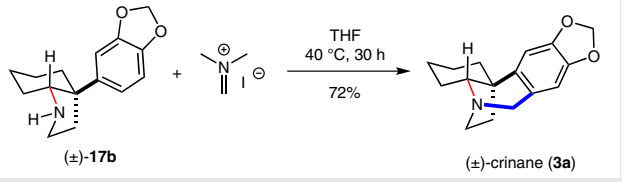
A similar reductive amination was carried out with γ-keto aldehyde (±)-**9b** in the presence of 10 mol% of each TFA and AcOH, which afforded *cis*-3a-aryloctahydroindole (±)-**17b** in 84–88% yield in 24 hours (Scheme 7). As found for the earlier case, reductive amination of γ-keto aldehyde (±)-**9b** also afforded (±)-**17b** in 84–88% yield in 24 hours only in the presence of 5 mol% of each TFA and AcOH (Scheme 7). Similar to carbamates (±)-**18a**,**b**, carbamates (±)-**19a**,**b** were also synthesized in 79–83% yields from (±)-**17b** by treatment with chloromethylformate and benzyl chloroformate in the presence of $NaHCO_3$, which, on reduction using $LiAlH_4$, afforded *cis*-3a-aryloctahydroindole (±)-**20** in 61–85% (Scheme 6). However, for a direct total synthesis of (±)-mesembrane **2a** from γ-keto aldehyde (±)-**9a**, reductive amination was carried out using methylamine with sodium cyanoborohydride ($NaBH_3CN$) in the presence of protic acids such as TFA and AcOH. Thus, the total synthesis of (±)-mesembrane (±)-**2a** was accomplished in 79–88% yield (Scheme 8). Along similar lines, we also synthesized *cis*-3a-aryloctahydroindole (±)-**20** in 78–91% isolated yields.



Scheme 7 Reductive amination of (±)-**9b**



Scheme 8 Total synthesis of (±)-mesembrane (**2a**)



Scheme 9 Total synthesis of (±)-crinane (±)-**3a**

We then shifted our attention to developing a concise synthesis of (±)-crinane (±)-**3a**. Towards this end, a variety of conditions were investigated to affect Pictet–Spengler reactions with formalin, paraformaldehyde, and 1,3,5-trioxane without success. Finally, *cis*-3a-aryloctahydroindole (±)-**17b** was reacted with Eschenmoser's salt (*N*,*N*-dimethylmethyleneammonium iodide),[11d] in THF at 40 °C for 30 hours to complete the total synthesis of (±)-crinane (±)-**3a** (Scheme 9).

In conclusion, we have described a general approach to a number of *Sceletium* alkaloids of the family *Aizoaceae* and the *Amaryllidaceae* alkaloids, featuring an Eschenmoser–Claisen rearrangement as the key step to install the all-carbon quaternary stereocenter. By utilizing the aforementioned strategy, we have demonstrated the total syntheses of (±)-joubertiamine (**1a**), (±)-*O*-methyljoubertiamine (**1b**), and (±)-3′-methoxy-4′-*O*-methyljoubertiamine (**1c**), and *Amaryllidaceae* alkaloids mesembrane (**2a**) and crinane (**3a**). We believe that this method could be extended to other structural types of *Amaryllidaceae* alkaloids. Importantly, as allylic alcohols of type **7a**–**c** could easily be accessed in entioenriched form through either resolution or by employing CBS (Corey–Bakshi–Shibata) reduction,[24] our strategy could also be adapted to an enantioselective version. Further application of the methodology described herein is under investigation in our laboratories and will be reported in due course.

Chemicals and reagents were purchased from commercial sources and used without further purification. Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under an inert atmosphere and were stirred with Teflon-coated magnetic stirring bars. THF and toluene were distilled over sodium/benzophenone ketyl. Dichloromethane, chloroform, and dichloroethane were distilled over calcium hydride. All other solvents such as DMF, MeCN, and MeOH were used as received. Thin-layer chromatography was performed using Silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain, and other stains. Silicagel of particle size 100–200 mesh was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded with 400, 500 MHz spectrometers (Bruker) with ^{13}C operating frequencies of 100, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent ($CDCl_3$) signal (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogen). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded with a FT-IR system (Spectrum BX) and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-resolution mass spectrometry (HRMS) data were recorded with a MicrOTOF-Q-II (Bruker) mass spectrometer using MeOH as solvent.

Stork–Danheiser Sequence Followed by Luche Reduction of Vinylogous Esters; General Procedure

A flame-dried round-bottom flask was charged with vinylogous ester **11** (20.0 mmol, 1.0 equiv) and anhydrous THF (30 mL) and cooled to 0 °C. To this solution, aryl magnesium bromide (24.0 mmol, 1.2 equiv) in anhydrous THF (20 mL) was added dropwise over 10 min by using a syringe. After stirring for 6–8 h at r.t., the reaction was quenched by the addition of 1 M HCl (20 mL) at 0 °C. The reaction mixture was stirred and warmed to r.t. over 3 h, then neutralized by the addition of sat. aq $NaHCO_3$. The resulting mixture was extracted with EtOAc (4 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (hexanes–EtOAc) to give 3-arylcyclohexenone **8**.

In a round-bottom flask, 3-aryl-cyclohexenone **8** (20.0 mmol, 1.0 equiv) was dissolved in MeOH (40 mL), and $CeCl_3{\cdot}7\,H_2O$ (8.94 g, 24.0 mmol, 1.2 equiv) was added. The reaction mixture was stirred at r.t. for 15 min and then cooled to 0 °C. $NaBH_4$ (912 mg, 24.0 mmol, 1.2 equiv) was then added over 15 min and the reaction mixture was stirred. Upon completion (TLC, ca. 30 min) the reaction was quenched with sat. aq NH_4Cl (10 mL). After stirring vigorously for 30 min, the solvent was removed under reduced pressure, H_2O (20 mL) was added and the crude reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with sat. aq NaCl (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide allylic alcohol **7**.

4′-Methoxy-3,4,5,6-tetrahydro-[1,1′-biphenyl]-3-ol [(±)-7a]

Yield: 3.2 g (78% yield over two steps); white solid; mp 59–60 °C; R_f = 0.35 (EtOAc–hexane, 30%).

IR (film): 3390, 3035, 2999, 2933, 2051, 1887, 1606, 1574, 1505, 1454, 1343, 1279, 1250, 1181, 1037, 911 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.03–6.02 (m, 1 H), 4.33 (d, *J* = 3.5 Hz, 1 H), 3.75 (m, 3 H), 2.77 (br s, 1 H), 2.39–2.25 (m, 2 H), 1.92–1.84 (m, 2 H), 1.70–1.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 139.0, 133.9, 126.4, 125.2, 113.7, 66.3, 55.2, 31.7, 27.5, 19.6.

Microwave-Assisted Eschenmoser–Claisen Rearrangement; General Procedure

Alcohol (±)-**7** (generally in 0.25 mmol scale, 1.0 equiv) was charged with *N*,*N*-dimethylacetamide dimethyl acetal (183 µL, 1.25 mmol, 5.0 equiv) and *p*-xylene (2 mL) in a sealed tube at r.t. After sealing, the reaction mixture was heated under microwave irradiation for 10 min (power = 300 W, ramp time = 6 min, ramp to temperature = 200 °C, hold time = 4 min, stirring high). After 10 min, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to give amide **6**.

2-(4′-Methoxy-1,2,3,4-tetrahydro-[1,1′-biphenyl]-1-yl)-*N*,*N*-dimethylacetamide [(±)-6a]

Yield: 63 mg (92%); yellow gel; R_f = 0.25 (EtOAc–hexane, 50%).

IR (film): 2930, 2835, 2056, 1888, 1634, 1502, 1394, 1249, 1183, 1139, 1035, 982, 827, 745 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.8 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 6.13 (dd, *J* = 1.9, 10.3 Hz, 1 H), 5.83 (td, *J* = 3.5, 10.2 Hz, 1 H), 3.72 (s, 3 H), 2.77 (s, 3 H), 2.70 (s, 3 H), 2.64 (t, *J* = 11.0 Hz, 1 H), 2.04–1.86 (m, 4 H), 1.57–1.49 (m, 1 H), 1.37–1.27 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 157.5, 139.6, 133.3, 127.8, 127.7, 113.3, 55.1, 45.0, 41.5, 37.7, 36.6, 35.3, 25.2, 18.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{23}NO_2 + H]^+$: 274.1802; found: 274.1829.

Allylic Oxidation; General Procedure

In an oven-dried round-bottom flask, amide **6a–c** (0.731 mmol, 1.0 equiv) was dissolved in anhydrous benzene (6 mL). To this solution, oven-dried Celite was added and the mixture was stirred vigorously. Pyridinium dichromate (3.66 mmol, 5.0 equiv) and *tert*-butylhydroperoxide solution (6.0 M in decane, 3.66 mmol, 5.0 equiv) were added to the reaction mixture at r.t. and stirring was continued for 18 h. Celite and black tar was filtered out and washed continuously with CH_2Cl_2 (50 mL) and the crude product was purified by flash chromatography to afford enone **12a–c**.

2-(4′-Methoxy-4-oxo-1,2,3,4-tetrahydro-[1,1′-biphenyl]-1-yl)-*N*,*N*-dimethylacetamide [(±)-12a]

Yield: 180 mg (86%); yellowish gel; R_f = 0.20 (EtOAc–hexane, 75%).

IR (film): 3091, 2959, 2910, 1818, 1700, 1635, 1431, 1400, 1199, 1041, 811, 714 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 1.3, 10.3 Hz, 1 H), 7.21 (d, *J* = 8.9 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.13 (d, *J* = 10.3 Hz, 1 H), 3.77 (s, 3 H), 2.84 (d, *J* = 5.1 Hz, 6 H), 2.80–2.66 (m, 2 H), 2.43–2.20 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 169.6, 158.3, 156.4, 135.1, 128.7, 127.5, 114.0, 55.3, 44.1, 42.5, 37.6, 36.0, 35.4, 34.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $[C_{17}H_{21}NO_3 + Na]^+$: 310.1414; found: 310.1427.

2-(3′,4′-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-[1,1′-biphenyl]-1-yl)-*N*,*N*-dimethylacetamide [(±)-12b]

Yield: 201 mg (60%); yellow oil; R_f = 0.24 (EtOAc).

IR (film): 3444, 2935, 1644, 1519, 1463, 1410, 1257, 1177, 1146, 1025, 901, 857, 809 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 1.1, 10.3 Hz, 1 H), 6.85–6.79 (m, 3 H), 6.13 (d, *J* = 10.3 Hz, 1 H), 3.84 (d, *J* = 1.4 Hz, 6 H), 2.84 (s, 6 H), 2.46–2.18 (m, 4 H), 1.26–1.21 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 169.6, 156.2, 148.9, 147.9, 135.6, 128.7, 118.7, 111.1, 110.1, 56.0, 55.9, 44.1, 42.7, 37.6, 36.0, 35.4, 34.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $[C_{18}H_{23}NO_4 + Na]^+$: 340.1519; found: 340.1546.

2-{1-(benzo[*d*][1,3]dioxol-5-yl)-4-oxocyclohex-2-en-1-yl}-*N*,*N*-dimethylacetamide [(±)-12c]

Yield: 219 mg (62%); yellow gel; R_f = 0.28 (EtOAc–hexane, 75%).

IR (film): 3054, 2927, 1837, 1675, 1641, 1488, 1434, 1400, 1240, 1040, 934, 814 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 1.0, 10.3 Hz, 1 H), 6.78 (s, 1 H), 6.73 (s, 2 H), 6.12 (d, *J* = 10.3 Hz, 1 H), 5.92 (s, 2 H), 2.90 (s, 3 H), 2.84 (s, 3 H), 2.40–2.30 (m, 2 H), 2.28–2.14 (m, 2 H), 1.52–1.43 (m, 1 H), 1.40–1.37 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 169.5, 156.1, 148.0, 146.3, 137.1, 128.8, 119.7, 108.2, 106.9, 101.2, 44.0, 42.9, 37.6, 36.3, 35.5, 34.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{19}NO_4 + H]^+$: 302.1387; found: 302.1396.

Synthesis of Amines (±)-13a–c; General Procedure

To a suspension of $LiAlH_4$ (327 mg, 8.63 mmol, 4.0 equiv) in THF (40 mL) at 0 °C was added a solution of enone **12a–c** (2.16 mmol, 1.0 equiv) in THF (20 mL). The reaction mixture was allowed to warm to r.t., and the flask was fitted with a water condenser, heated to 80 °C and heated to reflux for 20 h. The mixture was cooled to r.t., then to 0 °C and the reaction was quenched with EtOAc, basified with 4N NaOH solution and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with sat. aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide amines **13a–c**.

1-(2-(Dimethylamino)ethyl)-4′-methoxy-1,2,3,4-tetrahydro-[1,1′-biphenyl]-4-ol (13a)

Yield: 559 mg (90%); colorless oil; R_f = 0.10 (EtOAc with one drop Et_3N).

IR (film): 3361, 2940, 2862, 2824, 2779, 1608, 1511, 1436, 1245, 1249, 1182, 1035, 948, 831, 709 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.7 Hz, 1 H), 7.16 (d, *J* = 8.7 Hz, 1 H), 6.81 (dd, *J* = 2.3, 8.8 Hz, 2 H), 5.95 (s, 1 H), 5.86 (s, 1 H), 4.22–4.10 (m, 1 H), 3.76 (s, 3 H), 2.13 (s, 6 H), 2.10–1.96 (m, 2 H), 1.94–1.70 (m, 5 H), 1.62–1.57 (m, 1 H), 1.40–1.22 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 157.7, 138.6, 138.3, 136.3, 134.8, 131.5, 129.8, 127.9, 127.6, 113.6, 113.5, 67.1, 64.3, 55.2, 55.2, 55.1, 45.5, 45.5, 41.6, 39.9, 39.4, 35.0, 32.7, 28.9, 28.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{25}NO_2 + H]^+$: 276.1958; found: 276.1982.

4-(Benzo[*d*][1,3]dioxol-5-yl)-4-[2-(dimethylamino)ethyl]cyclohex-2-enol (13c)

Yield: 203 mg (80%); colorless oil; R_f = 0.10 (MeOH–CH_2Cl_2, 10%).

IR (film): 3391, 2939, 2863, 2826, 1644, 1503, 1487, 1432, 1238, 1039, 936, 813, 735 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 1.2 Hz, 1 H), 6.75–6.70 (m, 2 H), 5.90 (s, 2 H), 5.90–5.81 (m, 2 H), 4.20 (d, *J* = 6.0 Hz, 1 H), 2.13 (s, 6 H), 2.11–1.96 (m, 4 H), 1.90–1.68 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 145.6, 140.6, 134.6, 131.7, 120.2, 107.7, 107.4, 100.9, 67.2, 55.1, 45.5, 42.1, 40.0, 35.2, 28.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{23}NO_3 + H]^+$: 290.1751; found: 290.1757.

Procedure for Selective Reduction[20]

In an oven-dried round-bottle flask compound (±)-**12a** (60 mg, 0.208 mmol, 1.0 equiv) in anhydrous THF (4 mL) was charged with reducing agent ($LiBH_4$ or $LiEt_3BH$; 0.46 mmol, 2.2 equiv] at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 1–2 h at the same temperature, then the reaction was quenched with sat. aq NH_4Cl and the mixture was diluted with EtOAc (10 mL). The combined organic

layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude material was purified by flash chromatography.

2-(4-Hydroxy-4′-methoxy-1,2,3,4-tetrahydro-[1,1′-biphenyl]-1-yl)-*N*,*N*-dimethylacetamide (13d)

Yield: 49 mg (82%); colorless gel; R_f = 0.15 (EtOAc–hexane, 75%).

IR (film): 3393, 2929, 2883, 1622, 1515, 1478, 1398, 1248, 1059, 912 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 2 H), 6.81–6.78 (m, 2 H), 6.21 (d, *J* = 10.2 Hz, 1 H), 5.85 (d, *J* = 10.2 Hz, 1 H), 4.22 (br s, 1 H), 3.74 (s, 3 H), 2.78 (s, 3 H), 2.74 (s, 3 H), 2.68–2.59 (m, 2 H), 2.04–1.94 (m, 4 H), 1.82 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 157.7, 138.5, 135.2, 131.2, 127.6, 113.5, 67.0, 55.2, 44.6, 41.8, 37.8, 35.4, 34.4, 28.8.

General Procedure for Allylic Oxidation

MnO_2 (6.91 mmol, 20.0 equiv) was added to a stirred solution of allylic alcohol (0.345 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (5 mL) in Celite (200 mg) at r.t. under an argon atmosphere. The reaction mixture was stirred at r.t. for 16 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was filtered with CH_2Cl_2 and purified by flash chromatography to provide enone **1** and **14**.

1-[2-(Dimethylamino)ethyl]-4′-methoxy-2,3-dihydro-[1,1′-biphenyl]-4(1*H*)-one [(±)-1b]

Yield: 59 mg (63%); colorless gel; R_f = 0.15 (EtOAc with one drop Et_3N).

IR (film): 3036, 2946, 2832, 2771, 2860, 2054, 1684, 1609, 1580, 1463, 1386, 1250, 1184, 1097, 895, 831 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 10.3 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.13 (d, *J* = 10.3 Hz, 1 H), 3.78 (s, 3 H), 2.36–2.19 (m, 4 H), 2.15 (s, 6 H), 2.12–1.93 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 158.3, 155.5, 135.1, 129.3, 127.7, 114.0, 55.3, 55.2, 45.6, 42.7, 39.4, 36.4, 34.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{23}NO_2 + H]^+$: 274.1802; found: 274.1802.

1-[2-(Dimethylamino)ethyl]-3′,4′-dimethoxy-2,3-dihydro-[1,1′-biphenyl]-4(1*H*)-one [(±)-1c]

Yield: 70 mg (67% over two steps); colorless oil; R_f = 0.30 (MeOH–CH_2Cl_2, 10%).

IR (film): 2945, 2861, 2832, 1681, 1606, 1514, 1463, 1203, 1180, 1149, 833, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, *J* = 4.1, 10.2 Hz, 1 H), 6.86 (dt, *J* = 3.4, 5.2 Hz, 1 H), 6.82–6.76 (m, 2 H), 6.17–6.12 (m, 1 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 2.34–2.18 (m, 4 H), 2.16 (d, *J* = 4.2 Hz, 6 H), 2.12–1.97 (m, 4 H).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{18}H_{25}NO_3 + H]^+$: 304.1907; found: 304.1929.

4-(Benzo[*d*][1,3]dioxol-5-yl)-4-[2-(dimethylamino)ethyl]cyclohex-2-enone [(±)-14]

Yield: 75 mg (75%); yellow oil; R_f = 0.12 (EtOAc with one drop Et_3N).

IR (film): 2946, 2820, 2773, 2052, 1850, 1681, 1612, 1485, 1388, 1238, 1171, 1097, 1038, 934, 813 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 10.3 Hz, 1 H), 6.75 (s, 1 H), 6.68 (q, *J* = 8.1 Hz, 2 H), 6.08 (d, *J* = 10.2 Hz, 1 H), 5.90 (s, 2 H), 2.32–2.16 (m, 5 H), 2.12 (s, 6 H), 2.10–2.02 (m, 1 H), 1.99–1.86 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 155.1, 148.1, 146.3, 137.0, 129.4, 120.0, 108.0, 107.0, 101.1, 55.1, 45.5, 43.1, 39.4, 36.5, 34.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{21}NO_3 + H]^+$: 288.1594; found: 288.1623.

Total Synthesis of (±)-Joubertiamine (1a)

In an oven-dried, long-neck, round-bottle flask, BBr_3 (307 μL, 0.307 mmol, 3.5 equiv) was added to a solution of (±)-**1b** (24 mg, 0.088 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.5 mL) at –78 °C under a N_2 atmosphere. The reaction mixture was stirred for 1 h at the same temperature, then the reaction was quenched with water at 0 °C and the mixture was diluted with CH_2Cl_2 (5 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude material was purified by flash chromatography to afford (±)-**1a**.

1-[2-(Dimethylamino)ethyl]-4′-hydroxy-2,3-dihydro-[1,1′-biphenyl]-4(1*H*)-one [(±)-1a]

Yield: 20 mg (88%); white solid; mp 158–160 °C; R_f = 0.1 (MeOH–CH_2Cl_2, 10%).

IR (film): 3382, 2999, 2860, 1681, 1608, 1511, 1463, 1386, 1250, 1184, 1097, 1034, 894, 830 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (t, *J* = 10.1 Hz, 3 H), 6.45 (d, *J* = 8.2 Hz, 2 H), 6.10 (d, *J* = 10.2 Hz, 1 H), 2.34–2.03 (m, 14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 155.9, 155.0, 132.8, 129.2, 127.7, 115.9, 54.3, 44.8, 42.6, 39.0, 36.3, 34.5, 29.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{21}NO_2 + H]^+$: 260.1645; found: 260.1666.

3a-(3,4-Dimethoxyphenyl)-1-methyloctahydro-1*H*-indole [Mesembrane; (±)-2a]

Yield: 17 mg (88%); colorless gel; R_f = 0.45 (1 mL MeOH + 30 mL CH_2Cl_2 + 1 mL Et_3N).

IR (film): 2932, 2856, 1589, 1519, 1464, 1410, 1326, 1257, 1148, 1030, 805 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.94–6.90 (m, 2 H), 6.84–6.81 (m, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.28–3.23 (m, 1 H), 2.59 (br s, 1 H), 2.33 (s, 3 H), 2.32–2.29 (m, 1 H), 1.96–1.80 (m, 4 H), 1.67–1.65 (m, 3 H), 1.50–1.45 (m, 2 H), 1.39–1.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 146.8, 140.3, 118.9, 110.7, 110.6, 68.7, 55.9, 55.8, 54.4, 47.5, 41.0, 40.7, 36.1, 23.7, 22.9, 20.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{25}NO_2 + H]^+$: 276.1958; found: 276.1965.

2,3,4,4a-Tetrahydro-1*H*,6*H*-5,11b-ethano[1,3]dioxolo[4,5-*j*]phenanthridine [Crinane; (±)-3a]

An oven-dried, round-bottom flask was charged with (±)-**11b** (21 mg, 0.082 mmol, 1.0 equiv) in anhydrous THF (7 mL). To the reaction mixture, Eschenmoser's salt (23 mg, 0.124 mmol, 1.5 equiv) was added and the reaction mixture was heated at 40 °C for 30 h. Upon completion of the reaction (monitored by TLC), THF was removed under vacuum and EtOAc (10 mL) and 1 M NaOH was added until the solution became basic. The organic phases were combined and dried over an-

hydrous K_2CO_3 and concentrated under vacuum. The crude product was purified by flash chromatography with basic alumina to give amine **3a**.

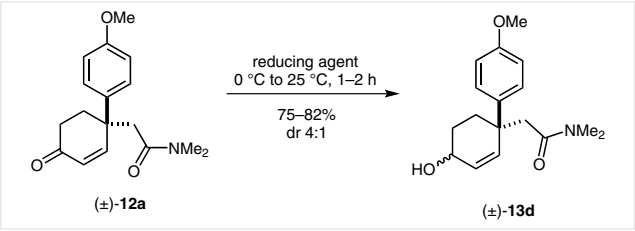
Yield: 16 mg (72%); light-yellow gel; R_f = 0.40 (MeOH–CH_2Cl_2, 10%).

IR (film): 2929, 2916, 2881, 1649, 1484, 1454, 1238, 1040, 935, 867 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.69 (s, 1 H), 6.43 (s, 1 H), 5.86 (s, 2 H), 4.31 (d, *J* = 16.8 Hz, 1 H), 3.72 (d, *J* = 16.8 Hz, 1 H), 3.27–3.34 (m, 1 H), 2.74–2.83 (m, 2 H), 2.31–2.34 (m, 1 H), 2.15–2.22 (m, 1 H), 1.70–1.84 (m, 6 H), 1.56–1.61 (m, 1 H), 1.47–1.51 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 145.5, 142.3, 126.2, 106.2, 103.3, 100.6, 57.3, 62.1, 51.9, 42.8, 37.9, 29.0, 27.6, 24.4, 21.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{19}NO_2 + H]^+$: 258.1489; found: 258.1497.



Scheme 10

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561583.

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