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Concise total syntheses of (±)-mesembrane and (±)-crinane†

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A straightforward and unified strategy to access *Amaryllidaceae* alkaloids comprising a *cis*-3a-aryloctahydroindole scaffold has been developed. The strategy features Eschenmoser–Claisen rearrangement of allylalcohol as a key step for the installation of all-carbon quaternary stereocenters present in these alkaloids. The consequent iodolactonization–reduction–oxidation sequence beautifully assembles the advanced intermediate keto-aldehyde 10a, b in synthetically viable yields. The methodology has been successfully applied in the efficient syntheses of (±)-mesembrane (1a) and (±)-crinane (2a).

The *cis*-3a-aryloctahydroindole alkaloids possessing an all-carbon quaternary stereocenter[1] constitute the core structure of many alkaloids with impressive diversity of biological activity.[2] Their biological potential is significantly manifested by their anti-viral, anti-tumor, anti-cholinergic and anti-HIV properties.[3] These activities together with their intriguing structures have brought a major impetus for synthetic exploration in this direction from organic chemists across the globe.

In particular, the *cis*-3a-aryloctahydroindole alkaloids **1** and **2** (Fig. 1) are found in plants of the *Amaryllidaceae* family[4] and elicit continuing interest in the synthetic research community due to their intriguing physiological activities.[5,6] Biogenetically, crinane (**2a**) and related alkaloids are closely related to other major *Amaryllidaceae* family natural products, lycorane- and galanthamine-type alkaloids as they all are derived from the same precursor norbelladine.[7] These *cis*-3a-aryloctahydroindole alkaloids[8] display vicinal quaternary and tertiary carbon stereocenters with a fused pyrrolidine ring whose stereochemical incorporation is indeed a challenge.[9] We envisaged a unified strategy to access all of these alkaloids having the *cis*-3a-aryloctahydroindole skeleton (Fig. 1) with a sterically congested quaternary carbon center located at the hydroindolone bridgehead (C-3a) position as a common structural feature. Herein, we report the development of a powerful strategy involving Eschenmoser–Claisen rearrangement followed by iodolactonization which would permit the late stage, divergent introduction of a range of functionality to address the total synthesis of several congeners of this family.

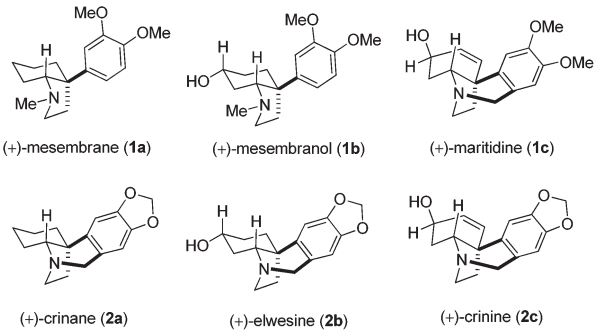

Fig. 1 The Amaryllidaceae alkaloids.

Retrosynthetically, we envisioned that the advanced intermediate ketoaldehydes **10a**, **b** would lead to a unified pathway to access both mesembrane (**1a**) and crinane (**2a**). The dimethylamides **4a**, **b** (Scheme 1) would afford **3a**, **b**,[10] *via* iodolactonization, which in turn can be synthesized from allylalcohols **5a**, **b** following Eschenmoser–Claisen rearrangement.[11] Allylalcohols **5a**, **b** can be accessed from 3-aryl-2-cyclohexenones **7a**, **b** (Scheme 2), and the latter could easily be obtained directly from vinylogous ester **6** *via* a well-known Stork–Danheiser sequence.[12]

Moving forward with our proposed strategy, we performed the Stork–Danheiser sequence on compound **6** using arylmagnesium bromides to afford 3-aryl-2-cyclohexenones **7a**, **b** in 73–85% yields (Scheme 2). The latter were then reduced under Luche reduction[13] to access allylalcohols **5a**, **b** in 92–96% yields. With allyl alcohols **5a**, **b** in hand, we sought after conditions to effect Eschenmoser–Claisen rearrangement for the synthesis of 1-alkyl-1-aryl-2-cyclohexenes **4a**, **b** (Scheme 3) having an all-carbon quaternary stereocenter.

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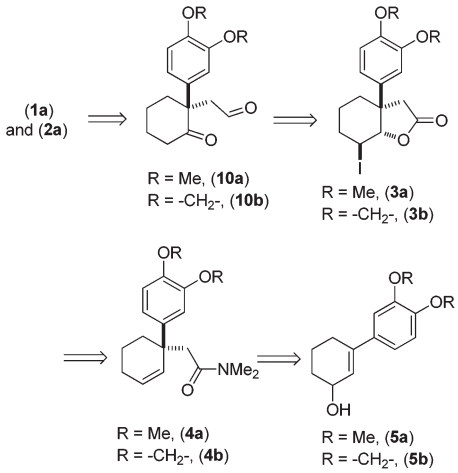
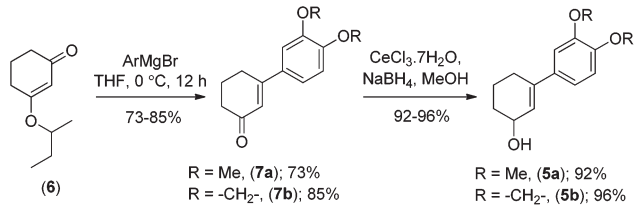
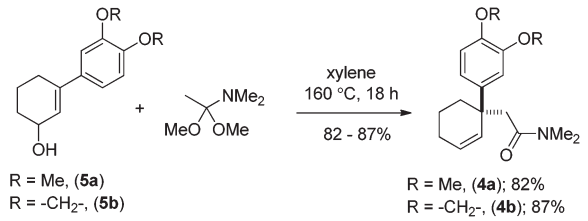


Scheme 1 Retrosynthetic analysis of (±)-**1a** and (±)-**2a**.

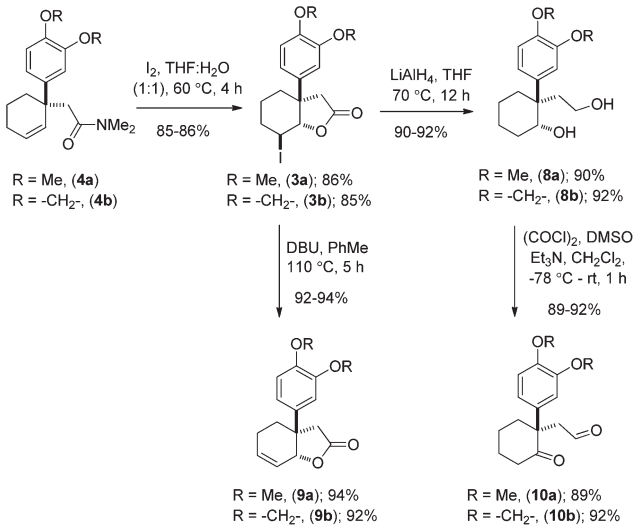


Scheme 2 Synthesis of 3-aryl-cyclohexenols (±)-**5a, b**.



Scheme 3 Eschenmoser–Claisen rearrangement of (±)-**5a, b**.

Preliminary studies indicate that 2–6 equiv. of dimethylacetal of *N*,*N*-dimethylacetamide (DMA–DMA) in different solvents furnished product **4a** only in 26–53% yields. After exhaustive optimization, it was found that 7 equiv. of DMA–DMA under heating at 160 °C led to the formation of the desired product in 82% yield (Scheme 3). Under optimized conditions, **5b** afforded product **4b** in 87% isolated yield (Scheme 3). We then turned our attention to functionalize the 2-position of the cyclohexene ring. Iodolactonization of 1-alkyl-1-aryl substituted cyclohexenes **4a, b** in the presence of iodine in the THF and water mixture provided iodolactone intermediates **3a, b** in 85–86% yield (Scheme 4). The iodolactones **3a, b** upon treatment with DBU furnished alkenes **9a, b** in excellent yields, which can in turn be utilized as advanced intermediates for the synthesis of various *Amaryllidaceae* alkaloids. However, for total synthesis of mesembrane (**1a**) and crinane (**2a**) we required γ-keto aldehydes **10a, b** to be further charged under reductive amination conditions to afford *cis*-3a-

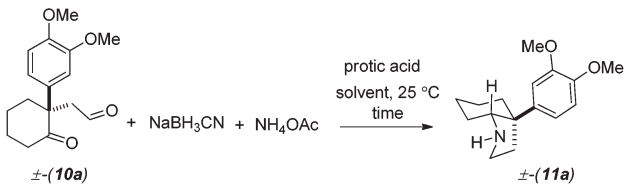


Scheme 4 Synthesis of ketoaldehydes (±)-**10a, b**.

aryloctahydroindole. To synthesize γ-keto aldehydes **10a, b**, we reduced **3a, b** in the presence of lithium aluminum hydride to afford 1,4-diols **8a, b** in quantitative yield (Scheme 4). Among the various oxidation procedures tried to synthesize γ-keto aldehydes **10a, b**, we found that the Swern oxidation[14] afforded **10a, b** in 89–92% yields (Scheme 4).

Optimization studies were further conducted to achieve reductive amination of compound **10a** in order to complete the total synthesis of mesembrane (**1a**) (Table 1). Initially, we carried out reductive amination of **10a** in the presence of 2 equiv. of ammonium acetate and 4 equiv. of sodium cyano borohydride in different solvents such as MeOH, EtOH, and THF in the presence of 1 equiv. of trifluoroacetic acid and acetic acid. To our delight, we found that *cis*-3a-aryloctahydroindole

Table 1 Optimization of reductive amination of (±)-**10a**[a,b]

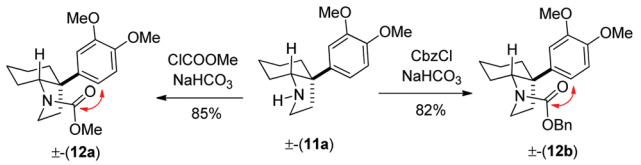


Entry	Acid	Solvent	Temp.	Time	Yield[a,b] (%)
1	TFA (1 equiv.)	MeOH	0–25 °C	12 h	72%
2	AcOH (1 equiv.)	MeOH	0–25 °C	12 h	75%
3	TFA (1 equiv.)	EtOH	0–25 °C	10 h	89%
4	AcOH (1 equiv.)	EtOH	0–25 °C	10 h	88%
5	TFA (1 equiv.)	THF	0–25 °C	18 h	35%
6	AcOH (1 equiv.)	THF	0–25 °C	18 h	32%
7	TFA (10 mol%)	EtOH	0–25 °C	16 h	83%
8	AcOH (10 mol%)	EtOH	0–25 °C	16 h	85%

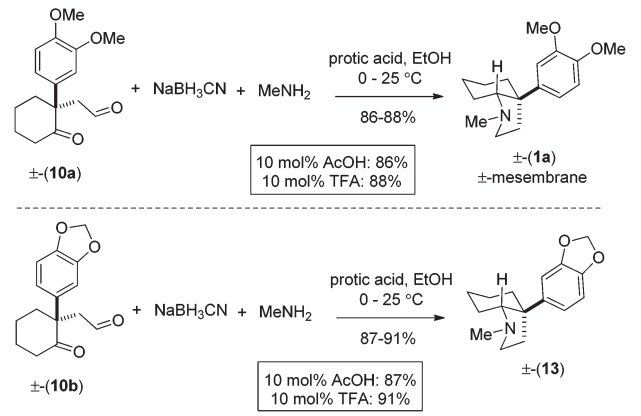
[a] 2.0 equiv. of NH_4OAc and 4.0 equiv. $NaBH_3CN$ were used in each case and all the reactions were performed on a 0.20 mmol of (±)-**10a** in 2 mL of the solvent under an inert atmosphere. [b] Isolated yields after column chromatography.

hydroindole **11a** could be obtained in 32–89% isolated yields (entries 1–6, Table 1).

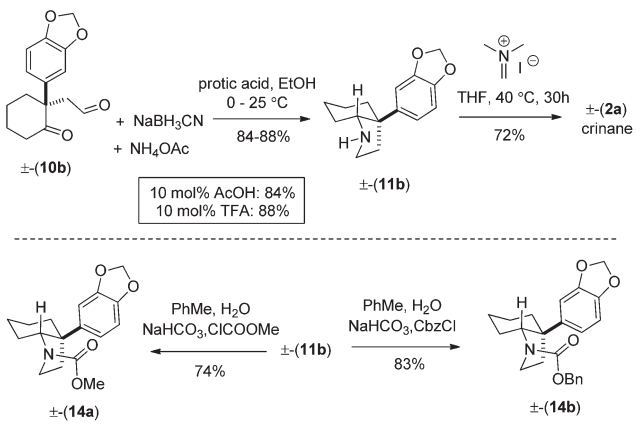
Following further optimization, we were pleased to find that secondary amine **11a** could be obtained in 83–85% yields when reductive amination was carried out in the presence of only 10 mol% of trifluoroacetic acid and acetic acid, respectively (entries 7 and 8, Table 1). Further, we synthesized carbamates **12a**, **b** in 82–85% yields from **11a** by treatment with chloromethylformate and benzyl chloroformate in the presence of $NaHCO_3$ (Scheme 5). In fact, we strongly feel that **12a**, **b** could serve as potential precursors for the synthesis of a tricyclic core with additional amide functionality (see red arrows) related to many *Amaryllidaceae* alkaloids (see, **2a**, **c**, Fig. 1) *via* a Bischler–Napieralski type process.[15]



Scheme 5 Synthesis of *cis*-3a-aryloctahydroindole derivatives (**12a**, **b**).



Scheme 6 Total synthesis of (±)-mesembrane (**1a**).



Scheme 7 Total synthesis of (±)-crinane (**2a**).

For total synthesis of (±)-mesembrane **1a**, we then carried out reductive amination using methylamine under optimized conditions, which in turn provided **1a** in 86–88% yields (Scheme 6). Along similar lines, we have also synthesized **13** in 87–91% isolated yields (Scheme 6).

Next, we shifted our attention for a concise total synthesis of crinane (**2a**). Towards this end, we carried out the reductive amination of γ-keto aldehyde **10b**, affording *cis*-3a-aryloctahydroindole **11b** in 84–88% isolated yields (Scheme 7). Finally, **11b** was treated with Eschenmoser's salt,[9d] to complete the total synthesis of (±)-crinane (**2a**). Following our optimized conditions shown in Scheme 7, we have also synthesized **14a**, **b** in 74–83% yields.

Conclusions

In conclusion, total synthesis of the *Amaryllidaceae* alkaloids mesembrane (**1a**) and crinane (**2a**) has been demonstrated. The strategy features the Eschenmoser–Claisen rearrangement as the key step to install an all carbon quaternary stereocenter. As allylic alcohols of the type **5a**, **b** could easily be accessed in an enantioenriched form either using resolution or employing CBS reduction,[16] our strategy could be nicely adopted to an enantioselective version as well.

Acknowledgements

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