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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 allyl alcohol 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<sup>1</sup> constitute the core structure of many alkaloids with impressive diversity of biological activity.<sup>2</sup> Their biological potential is significantly manifested by their anti-viral, anti-tumor, anti-cholinergic and anti-HIV properties.<sup>3</sup> 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<sup>4</sup> and elicit continuing interest in the synthetic research community due to their intriguing physiological activities.<sup>5,6</sup> 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.<sup>7</sup> These *cis*-3a-aryloctahydroindole alkaloids<sup>8</sup> display vicinal quaternary and tertiary carbon stereocenters with a fused pyrrolidine ring whose stereochemical incorporation is indeed a challenge.<sup>9</sup> 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 hydroindole-

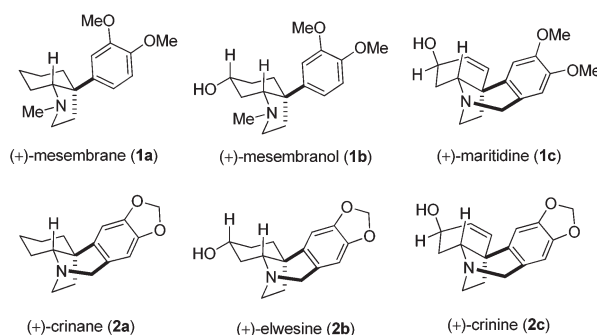


Fig. 1 The *Amaryllidaceae* alkaloids.

lone 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.

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**,<sup>10</sup> via iodolactonization, which in turn can be synthesized from allyl alcohols **5a, b** following Eschenmoser–Claisen rearrangement.<sup>11</sup> Allyl alcohols **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.<sup>12</sup>

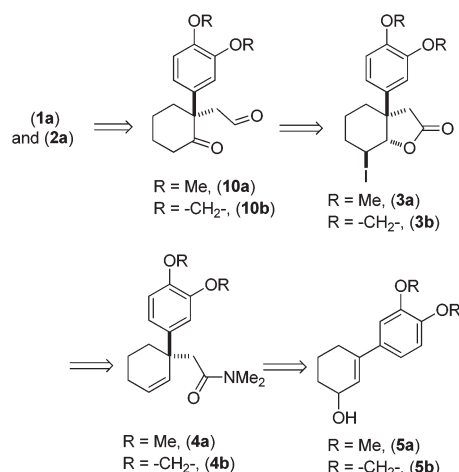
Moving forward with our proposed strategy, we performed the Stork–Danheiser sequence on compound **6** using aryl-magnesium bromides to afford 3-aryl-2-cyclohexenones **7a, b** in 73–85% yields (Scheme 2). The latter were then reduced under Luche reduction<sup>13</sup> to access allyl alcohols **5a, 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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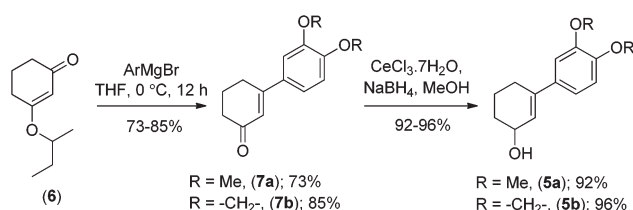
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. See DOI: 10.1039/c5ob00183h

‡Both authors contributed equally.

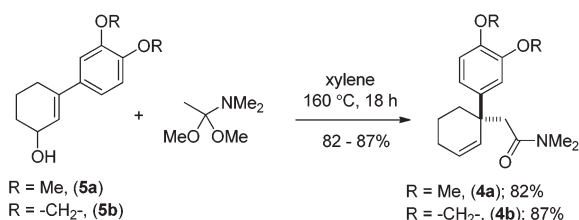




Scheme 1 Retrosynthetic analysis of (±)-1a and (±)-2a.

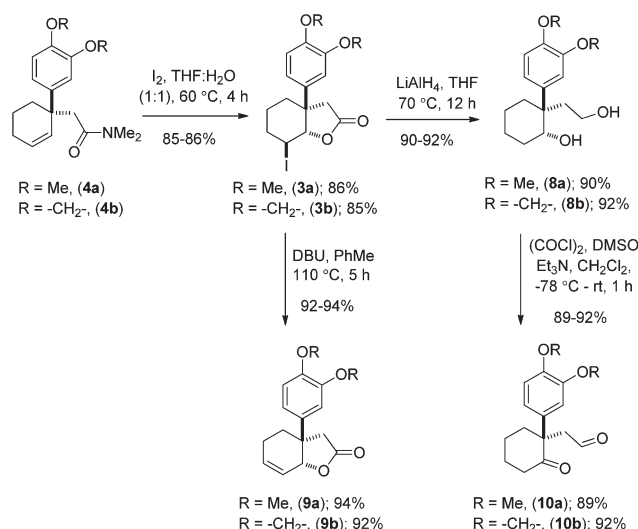


Scheme 2 Synthesis of 3-aryl-cyclohexenols (±)-5a, b.



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 crinine (2a) we required  $\gamma$ -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  $\gamma$ -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  $\gamma$ -keto aldehydes 10a, b, we found that the Swern oxidation<sup>14</sup> 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-

Table 1 Optimization of reductive amination of (±)-10a<sup>a,b</sup>

Entry	Acid	Solvent	Temp.	Time	Yield <sup>a,b</sup> (%)
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%

<sup>a</sup> 2.0 equiv. of NH<sub>4</sub>OAc and 4.0 equiv. NaBH<sub>3</sub>CN 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. <sup>b</sup> 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<sub>3</sub> (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.<sup>15</sup>

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  $\gamma$ -keto aldehyde **10b**, affording *cis*-3a-aryloctahydroindole **11b** in 84–88% isolated yields (Scheme 7). Finally, **11b** was treated with Eschenmoser's salt,<sup>9d</sup> 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

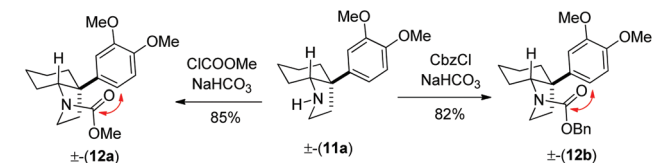
In conclusion, total synthesis of the *Amaryllidaceae* alkaloids mesembrane (**1a**) and crinane (**2a**) has been demonstrated. The strategy features the Eschenmoser–Claisen rearrangement as the key step to install an all carbon quaternary stereocenter. As allylic alcohols of the type **5a, b** could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

## Acknowledgements

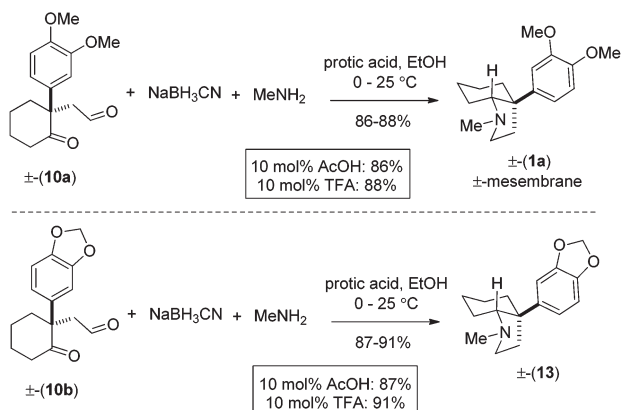
A.B. thanks the DST, SERB, India, for a research grant through FAST-TRACK scheme (SB/FT/CS-54/2011). M.K.D. and S.D. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for predoctoral fellowships. We thank the Department of Chemistry, IISER Bhopal for the infrastructure.

## Notes and references

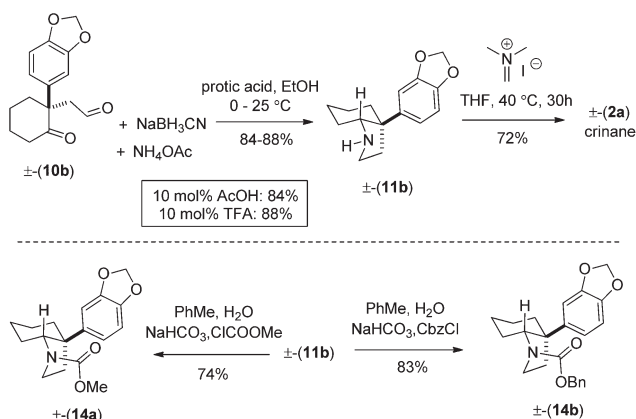
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Scheme 5 Synthesis of *cis*-3a-aryloctahydroindole derivatives (**12a, b**).



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



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



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