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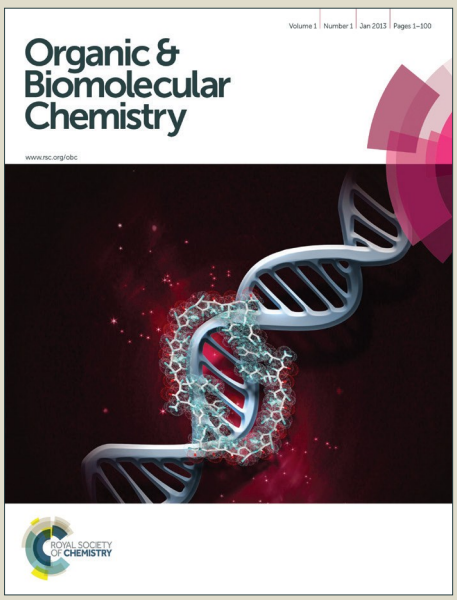

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Concise Total Syntheses of (±)-Mesembrane and (±)-Crinane

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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A straightforward and unified strategy to access *Amarylidaceae* alkaloids comprising *cis*-3a-aryloctahydroindole scaffold has been developed. The strategy features Eschenmoser-Claisen rearrangement of allylalcohol as key step for the installation of all-carbon quaternary stereocenters present in these alkaloids. 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.

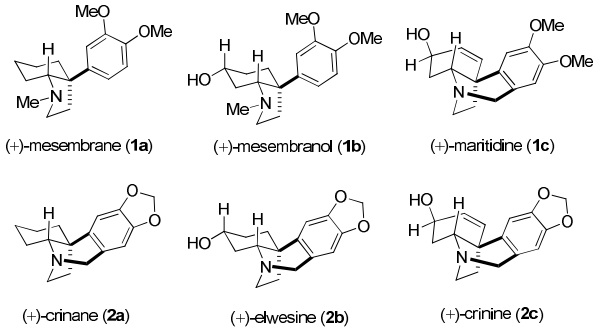
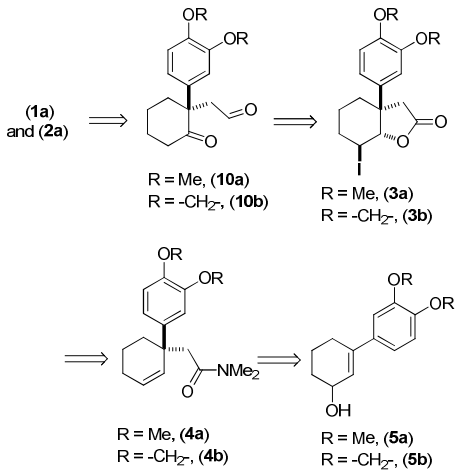


Figure 1. The *Amarylidaceae* alkaloids.

Especially, the *cis*-3a-aryloctahydroindole alkaloids **1** and **2** (Figure 1) are found in plants of *Amaryllidaceae* family[4] and elicit continuing interest in the synthetic community due to their intriguing physiological acitivities.[5-6] Biogenetically, crinane (**2a**) and related alkaloids are closely related with other major *Amarylidaceae* 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 (Figure 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 total synthesis of several congeners of this family.



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

Retrosynthetically, we envisioned that the advanced intermediate ketoaldehyde **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

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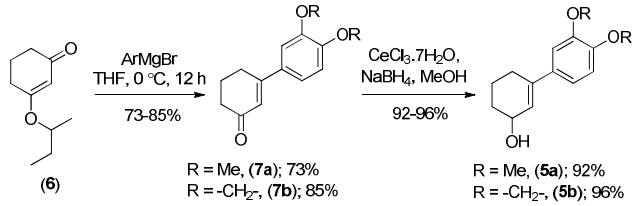
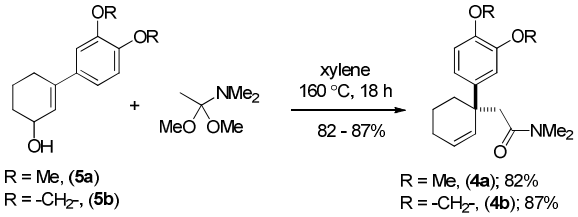
be obtained directly from vinylogous ester **6** via a well-known Stork-Danheiser sequence.[12]



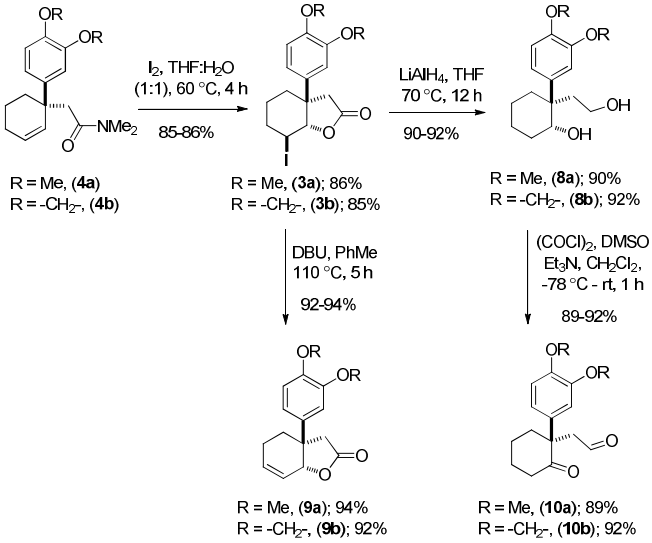
Scheme 2. Synthesis of 3-Aryl-cyclohexenol (±)-**5a-b**.

Moving forward with our proposed strategy, we carried out 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 all-carbon quaternary stereocenter.



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

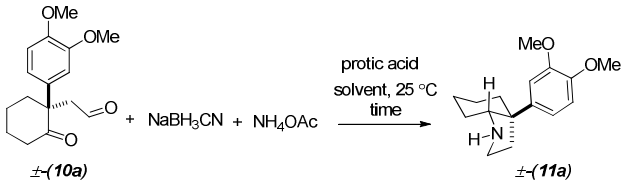
Preliminary studies indicate that 2-6 equiv. of dimethylacetal of *N*,*N*-dimethylacetamide (DMA-DMA) in different solvents furnished product **4a** only in 26-53% yields. After exhaustive optimization, it was found that 7 equiv. of DMA-DMA under heating at 160 ˚C led to the formation of desired product in 82% yield (Scheme 3). Under optimized condition, **5b** afforded product **4b** in 87% isolated yield (Scheme 3). We then turned our attention to functionalize 2-position of cyclohexene ring. Iodolactonization of 1-alkyl-1-aryl substituted cyclohexenes **4a-b** in presence of iodine in THF and water mixture provided iodolactone intermediates **3a-b** without event 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 *Amarylidaceae* 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-aryloctahydroindole. To synthesize γ-keto aldehyde **10a-b**, we reduced **3a-b** in presence of lithium aluminum hydride to afford 1,4-diols **8a-b** in quantitative yield (Scheme 4). Among 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).



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

Optimization studies were further conducted to carry out reductive amination of compound **10a** in order to complete total synthesis of mesembrane (**1a**) (Table 1). Initially, we carried out reductive amination of **10a** in presence of 2 equiv. of ammonium acetate and 4 equiv. of sodium cyano borohydride in different solvent such as MeOH, EtOH, and THF in presence of 1 equiv. of trifluoroacetic acid and acetic acid. To our delight, we found that *cis*-3a-aryloctahydroindole **11a** could be obtained in 32-89% isolated yields (entries 1-6, Table 1).

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 solvent under inert atmosphere. [b]isolated yields after column chromatography.

Following further optimization, we were pleased to find that secondary amine **11a** could be obtained in 83-85% yields when reduction amination were carried out in 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%

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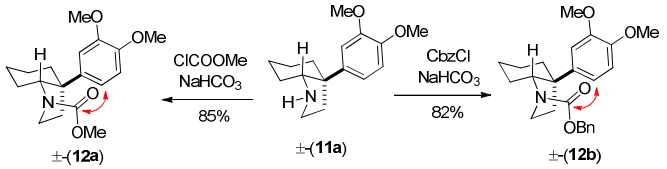
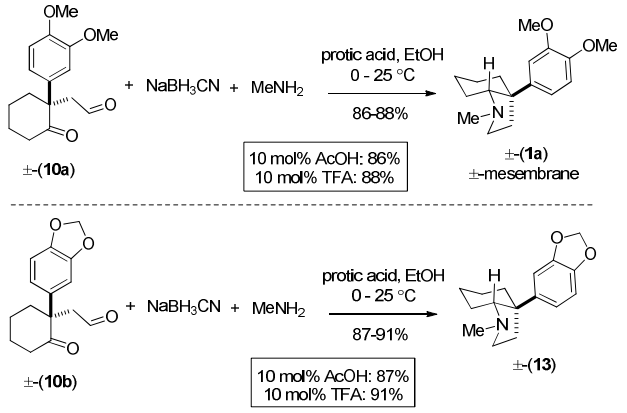
yields from **11a** by treatment with chloromethylformate and benzyl chloroformate in presence of $NaHCO_3$ (Scheme 5). In fact, we strongly feel that **12a-b** could serve as potential precursors for the synthesis of tricyclic core with additional amide functionality (see red arrows) related to many *amarylidaceae* alkaloids (see, **2a-c**, Figure 1) via a Bischler-Napieralski type process.[15]



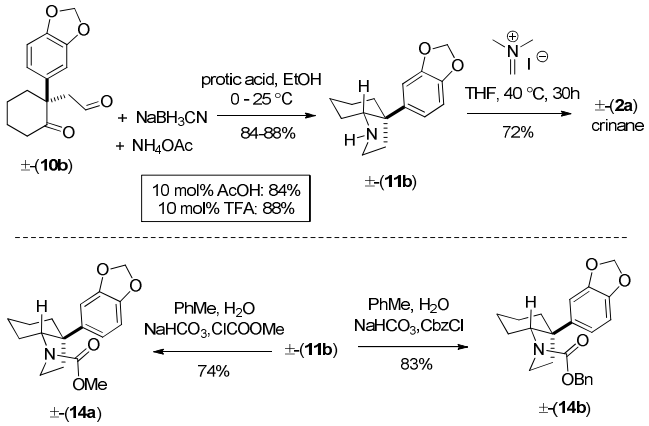
Scheme 5. Synthesis of *cis*-3a-aryloctahydroindole derivatives (**12a-b**).

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



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

Next, we shifted our attention for a concise 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 total synthesis of (±)-crinane (**2a**). Following our optimized conditions shown in scheme 7, we have also synthesized **14a-b** in 74-83% yields.



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

Conclusions

In conclusion, total synthesis of *Amarylidaceae* alkaloids mesembrane (**1a**) and crinane (**2a**) has been demonstrated. The strategy features the Eschemoser-Claisen rearrangement as the key step to install all carbon quaternary stereocenter. As allylic alcohols of the type **5a-b** could easily be accessed in entioenriched form either using resolution or employing CBS reduction,[16] 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 infrastructure.

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, NMR spectra, See DOI: 10.1039/b000000x/

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