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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 stereocenter¹ 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* family⁴ 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 alkaloids⁸ 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 hydroindole

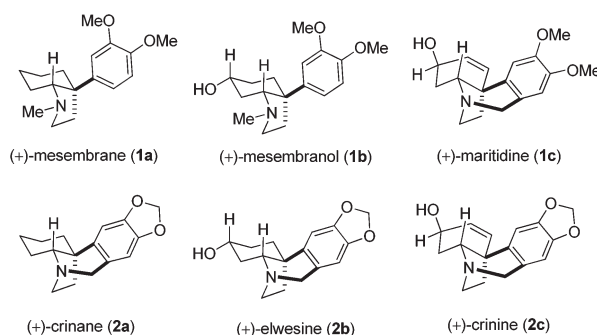


Fig. 1 The *Amaryllidaceae* alkaloids.

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

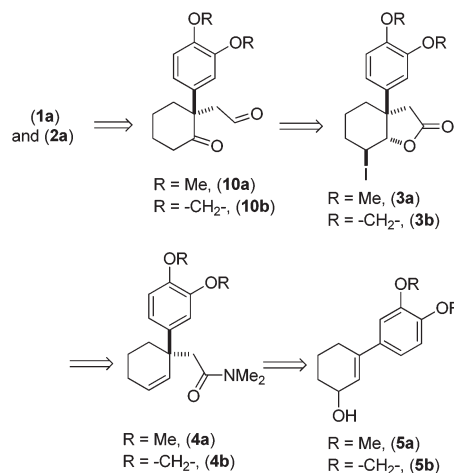
Moving forward with our proposed strategy, we performed the Stork–Danheiser sequence on compound **6** using arylmagnesium bromides to afford 3-aryl-2-cyclohexenones **7a, b** in 73–85% yields (Scheme 2). The latter were then reduced under Luche reduction¹³ to access allyl alcohols **5a, b** in 92–96% 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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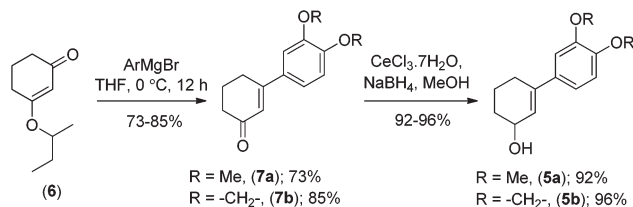
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. See DOI: 10.1039/c5ob00183h

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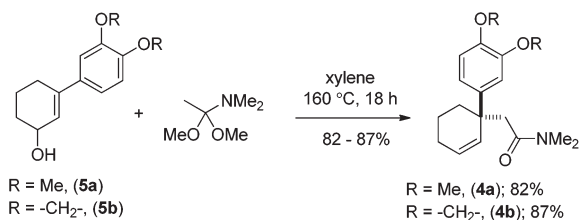




Scheme 1 Retrosynthetic analysis of (±)-1a and (±)-2a.

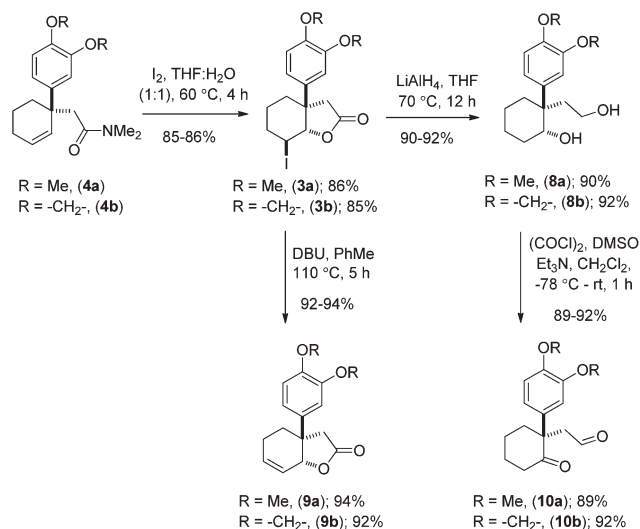


Scheme 2 Synthesis of 3-aryl-cyclohexenols (±)-5a, b.



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 crinine (**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 oxidation¹⁴ 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 cyanoborohydride 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^{a,b}

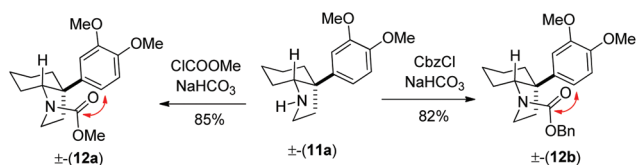
Entry	Acid	Solvent	Temp.	Time	Yield ^{a,b} (%)
1	TFA (1 equiv.)	MeOH	0–25 °C	12 h	72%
2	AcOH (1 equiv.)	MeOH	0–25 °C	12 h	75%
3	TFA (1 equiv.)	EtOH	0–25 °C	10 h	89%
4	AcOH (1 equiv.)	EtOH	0–25 °C	10 h	88%
5	TFA (1 equiv.)	THF	0–25 °C	18 h	35%
6	AcOH (1 equiv.)	THF	0–25 °C	18 h	32%
7	TFA (10 mol%)	EtOH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

^a 2.0 equiv. of NH₄OAc and 4.0 equiv. NaBH₃CN 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.

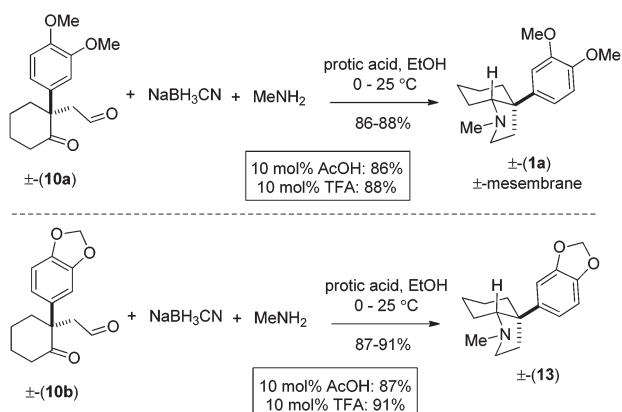


hydroindole **11a** could be obtained in 32–89% isolated yields (entries 1–6, Table 1).

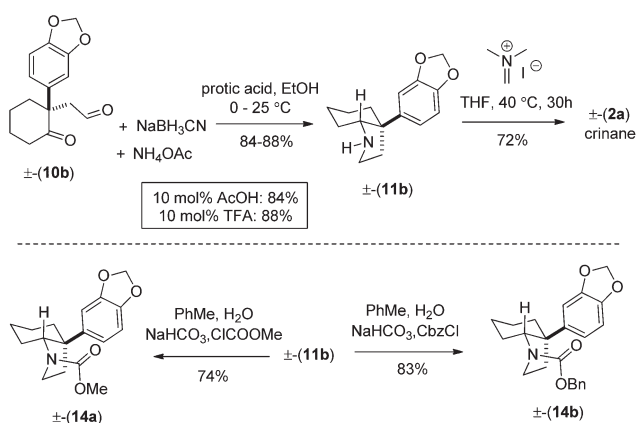
Following further optimization, we were pleased to find that secondary amine **11a** could be obtained in 83–85% yields when reductive amination was carried out in the presence of only 10 mol% of trifluoroacetic acid and acetic acid, respectively (entries 7 and 8, Table 1). Further, we synthesized carbamates **12a, b** in 82–85% yields from **11a** by treatment with chloromethylformate and benzyl chloroformate in the presence of NaHCO₃ (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



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



Scheme 6 Total synthesis of \pm -(**1a**).



Scheme 7 Total synthesis of \pm -(**2a**).

arrows) related to many *Amaryllidaceae* alkaloids (see, **2a, c**, Fig. 1) *via* a Bischler–Napieralski type process.¹⁵

For total synthesis of \pm -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 crinine (**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 \pm -crinine (**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 crinine (**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.

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Notes and references

- (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, Germany, 2005; (b) For numerous examples, see: K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, New York, 1st edn, 1996; (c) K. C. Nicolaou and S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, 1st edn, 2003. For reviews, see: (d) E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388; (e) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591; (f) B. M. Trost and C. H. Jiang, *Synthesis*, 2006, 369; (g) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473.
- (a) P. M. Jeffs, in *The Alkaloids*, ed. R. G. A. Rodrigo, Academic Press, New York, 1981, vol. 19, pp. 1–80; (b) S. F. Martin, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987, vol. 30, pp. 251–376; (c) P. M. Jeffs, in *MTP International Review of Science, Alkaloids, Organic*



- Chemistry, Series One*, ed. D. H. Hey and K. F. Wiesner, Butterworth, London, 1973, vol. 9, pp. 273–318.
- 3 L.-Z. Lin, S.-F. Hu, H.-B. Chai, T. Pengsuparp, J. M. Pezzuto, G. A. Cordell and N. Ruangrungsi, *Phytochemistry*, 1995, **40**, 1295.
 - 4 For reviews on Amaryllidaceae alkaloids, see: (a) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 363 and references cited therein; (b) J. R. Lewis, *Nat. Prod. Rep.*, 2002, **19**, 223; (c) Z. Jin, Z. Li and R. Huang, *Nat. Prod. Rep.*, 2002, **19**, 454.
 - 5 (a) R. Lebeuf, F. Robert, K. Schenk and Y. Landais, *Org. Lett.*, 2006, **8**, 4755; (b) F.-M. Zhang, Y.-Q. Tu, J.-D. Liu, X.-H. Fan, L. Shi, X.-D. Hu, S.-H. Wang and Y.-Q. Zhang, *Tetrahedron*, 2006, **62**, 9446; (c) W. H. Pearson and F. E. Lovering, *J. Org. Chem.*, 1998, **63**, 3607; (d) S. F. Martin and C. L. Campbell, *J. Org. Chem.*, 1988, **53**, 3184; (e) L. E. Overman and L. T. Mendelson, *J. Am. Chem. Soc.*, 1981, **103**, 5579.
 - 6 J. McNulty, J. J. Nair, C. Codina, J. Bastida, S. Pandey, J. Gerasimoff and C. Griffin, *Phytochemistry*, 2007, **68**, 1068.
 - 7 P. W. Jeffs, H. F. Campbell, D. S. Farrier, G. Ganguli, N. H. Martin and G. Molina, *Phytochemistry*, 1974, **13**, 933.
 - 8 Approaches to *cis*-3a-aryloctahydroindole alkaloids, see: (a) (\pm)-Martidine (**1c**): G. Pandey, N. R. Gupta and T. M. Pimpalalle, *Org. Lett.*, 2009, **11**, 2547; (b) (–)-Mesembranol (*ent*-**1b**): N. Chida, K. Sugihara, S. Amano and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1997, 275; (c) M. Asaoka, N. Fuji and H. Takei, *Chem. Lett.*, 1988, **17**, 1655; (d) J. J. Nieuwenhuis, H. F. Strauss and A. Wiechers, *J. Chem. Soc., Perkin Trans. 1*, 1981, 284; (e) H. F. Strauss and A. Wiechers, *Tetrahedron Lett.*, 1979, **20**, 4495; (f) K. Psotta and A. Wiechers, *Tetrahedron*, 1979, **35**, 255; (g) H. F. Strauss and A. Wiechers, *Tetrahedron*, 1978, **34**, 127; (h) G. Schwenker and G. Metz, *Arch. Pharm.*, 1968, **301**, 592.
 - 9 For total synthesis of crinine (**2a**), see: (a) T. Kano, Y. Hayashi and K. Maruoka, *J. Am. Chem. Soc.*, 2013, **135**, 7134; (b) A. Padwa, M. A. Brodney, M. Dimitroff, B. Liu and T. H. Wu, *J. Org. Chem.*, 2001, **66**, 3119; (c) J. M. Schkeryantz and W. H. Pearson, *Tetrahedron*, 1996, **52**, 3107; (d) G. E. Keck and R. R. Webb, *J. Am. Chem. Soc.*, 1981, **103**, 3173; (e) G. E. Keck and R. R. Webb II, *J. Org. Chem.*, 1982, **47**, 1302. For total synthesis of mesembrane (**1a**), see: (f) D. F. Taber and T. D. Neubert, *J. Org. Chem.*, 2001, **66**, 143; (g) J. H. Rigby and W. Dong, *Org. Lett.*, 2000, **2**, 1673; (h) K. Ogasawara and O. Tamada, *Tetrahedron Lett.*, 1998, **39**, 7747; (i) M. Mori, S. Kuroda, C. Zhang and Y. Sato, *J. Org. Chem.*, 1997, **62**, 3263; (j) S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1997, **62**, 1675; (k) S. F. Martin, T. A. Puckette and J. A. Colapret, *J. Org. Chem.*, 1979, **44**, 3391.
 - 10 Iodolactonization of Eschenmoser–Claisen products, see: (a) V. Bisai and R. Sarpong, *Org. Lett.*, 2010, **12**, 2551; (b) L. Zhu, J. Luo and R. Hong, *Org. Lett.*, 2014, **16**, 2162.
 - 11 (a) K. Hayashi, H. Tanimoto, H. Zhang, T. Morimoto, Y. Nishiyama and K. Kakiuchi, *Org. Lett.*, 2012, **14**, 5728; (b) M. Asaoka, N. Fuji and H. Takei, *Chem. Lett.*, 1988, **17**, 1655; (c) V. H. Bruderer and K. Bernauer, *Helv. Chim. Acta.*, 1983, **66**, 570; (d) A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta.*, 1964, **47**, 2425; (e) For a review, see: A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939.
 - 12 (a) G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38**, 1775. For recent examples, see: (b) A. Bisai, S. P. West and R. Sarpong, *J. Am. Chem. Soc.*, 2008, **130**, 7222; (c) N. B. Bennett, A. Y. Hong, A. M. Harned and B. M. Stoltz, *Org. Biomol. Chem.*, 2012, **10**, 56; (d) B. N. Kakde, S. Bhunia and A. Bisai, *Tetrahedron Lett.*, 2013, **54**, 1436.
 - 13 (a) J. L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226; (b) G. A. Molander, *Chem. Rev.*, 1992, **92**, 29; (c) S. P. West, A. Bisai, A. D. Lim, R. R. Narayan and R. Sarpong, *J. Am. Chem. Soc.*, 2009, **131**, 11187.
 - 14 (a) K. Omura and D. Swern, *Tetrahedron*, 1978, **36**, 1651; (b) G. Tojo and M. I. Fernandez, *Oxidation of Alcohols to Aldehyde and Ketones: A Guide to Current Common Practice*, Springer, New York, 2006.
 - 15 For a Bischler–Napieralski reaction of carbamate for a synthesis of *trans*-dihydronarciclasine, see: N. T. Tam and C.-G. Cho, *Org. Lett.*, 2008, **10**, 601.
 - 16 (a) E. J. Corey, R. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 7925; (b) E. J. Corey and J. O. Link, *J. Am. Chem. Soc.*, 1992, **114**, 1906.

