Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

CrossMark click for updates

Cite this: *Org. Biomol. Chem.*, 2015, **13**, 3585

Received 29th January 2015,
Accepted 10th February 2015

DOI: 10.1039/c5ob00183h

www.rsc.org/obc

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

Mrinal Kanti Das,‡ Subhadip De,‡ Shubhashish and Alakesh Bisai*

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.

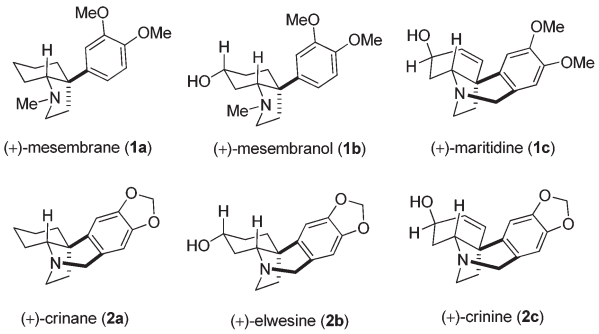


Fig. 1 The Amaryllidaceae alkaloids.

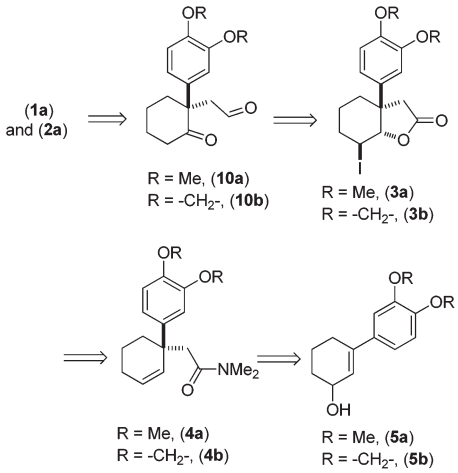
Retrosynthetically, we envisioned that the advanced intermediate ketoaldehydes **10a**, **b** would lead to a unified pathway to access both mesembrane (**1a**) and crinane (**2a**). The dimethylamides **4a**, **b** (Scheme 1) would afford **3a**, **b**,[10] *via* iodolactonization, which in turn can 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.

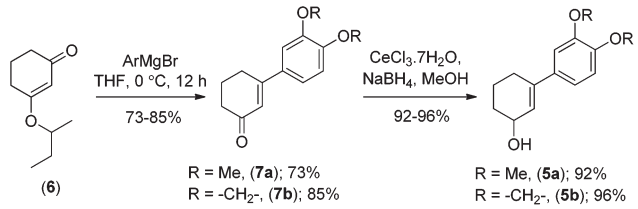
Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal, MP-462066, India. E-mail: alakesh@iiserb.ac.in

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. See DOI: 10.1039/c5ob00183h

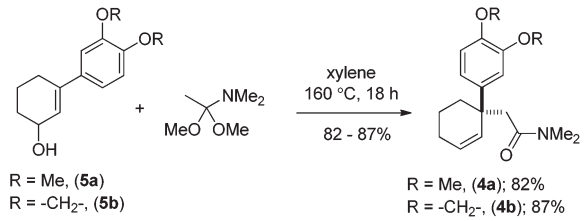
‡Both authors contributed equally.



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

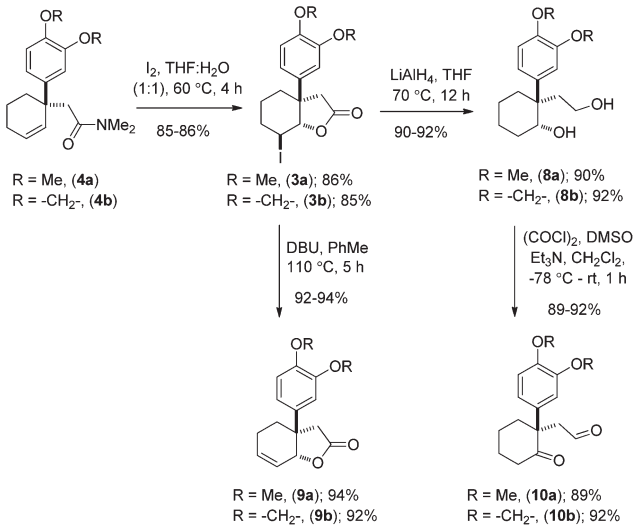


Scheme 2 Synthesis of 3-aryl-cyclohexenols (±)-**5a, b**.



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 crinane (**2a**) we required γ-keto aldehydes **10a, b** to be further charged under reductive amination conditions to afford *cis*-3a-

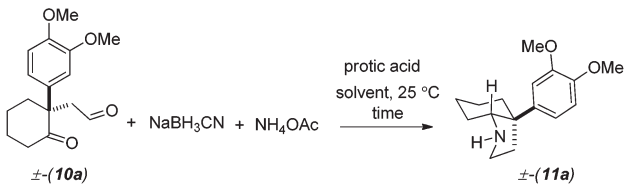


Scheme 4 Synthesis of ketoaldehydes (±)-**10a, b**.

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-arylocta-

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

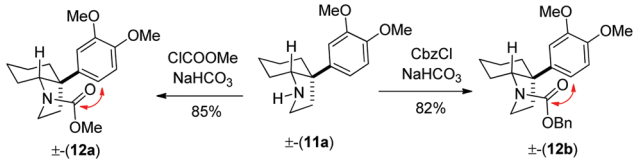


Entry	Acid	Solvent	Temp.	Time	Yield[a,b] (%)
1	TFA (1 equiv.)	MeOH	0–25 °C	12 h	72%
2	AcOH (1 equiv.)	MeOH	0–25 °C	12 h	75%
3	TFA (1 equiv.)	EtOH	0–25 °C	10 h	89%
4	AcOH (1 equiv.)	EtOH	0–25 °C	10 h	88%
5	TFA (1 equiv.)	THF	0–25 °C	18 h	35%
6	AcOH (1 equiv.)	THF	0–25 °C	18 h	32%
7	TFA (10 mol%)	EtOH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

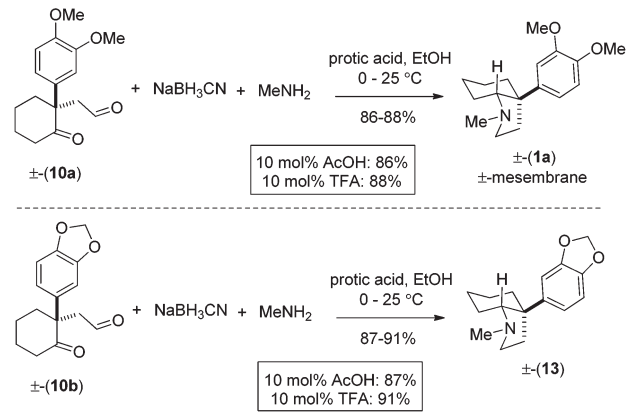
[a] 2.0 equiv. of NH_4OAc and 4.0 equiv. $NaBH_3CN$ were used in each case and all the reactions were performed on a 0.20 mmol of (±)-**10a** in 2 mL of the solvent under an inert atmosphere. [b] Isolated yields after column chromatography.

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

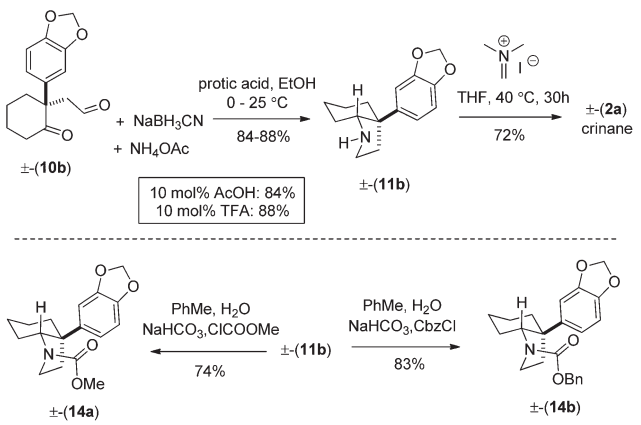
Following further optimization, we were pleased to find that secondary amine **11a** could be obtained in 83–85% yields when reductive amination was carried out in the presence of only 10 mol% of trifluoroacetic acid and acetic acid, respectively (entries 7 and 8, Table 1). Further, we synthesized carbamates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

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

1 (*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.

2 (*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*) (±)-Martidine (**1c**): G. Pandey, N. R. Gupta and T. M. Pimpalpalle, *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. Nieuwenhius, 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 crinane (**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.

