Prayogik Rasayan

Total Synthesis of Hapalindole Alkaloids via Cascade Prins-type Cyclization

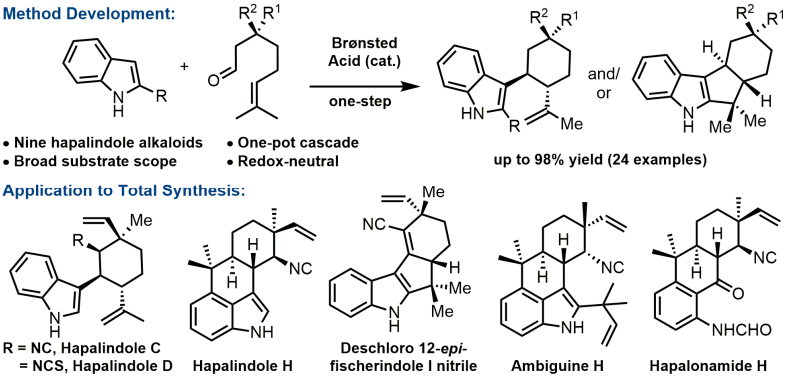
Samrat Sahu and Modhu Sudan Maji*

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur-721302, West Bengal, India.
Email: msm@chem.iitkgp.ac.in

Received: May 30, 2021 | Accepted: June 16, 2021 | Published online: August 14, 2021

Abstract

This brief highlight described about our recently reported method of cascade Prins-type cyclization method. Structural complexity and interesting biological activity made hapalindole alkaloid an attractive choice to the synthetic organic chemist over the past few decades. Keeping the importance of hapalindole scaffolds in mind, in this line, we recently disclosed a redox-neutral, biomimetic Prins-type cyclization between indole and an aldehyde bearing a terminal *ene*-promoter. The mild reaction protocol allows incorporation of several key functionalities in the products, and products were isolated with excellent yields and diastereoselectivities. Applying this strategy total synthesis of seven hapalindole alkaloids and formal synthesis of two more related alkaloids were accomplished in a stereodivergent manner in relatively fewer synthetic steps.



Keywords: *indole • Hapalindole • redox-neutral • Prins-cyclization*

1. Introduction

Hapalindoles are a unique class of indoleterpenoids with fascinating structural geometry isolated from prokariyotic organism cyanobacteria otherwise known as ´ ´ *blue green algae*´ ´ which generally thrives itself in costal area's fresh water. In 1984, Moore and his co-workers isolated its first congener Hapalindole A and B from *Hapalosiphonfontinalis*and*Anabaena oscillarioides.*[1-5]Since then, until now about 81 hapalindole alkaloids have been isolated from 18 different cyanobacteria strains of the order *Stigonematales*. These secondary metabolites are exclusive to *Stigonematales*and have not been found anywhere else. They display a wide range of bio-activities which might be interesting in medicinal chemistry.[6-11]Their structural analysis shows these are consisting of an indole ring connected to a densely functionalized cyclohexane ring with up to five contiguous stereocenters via C2/C3/C4 positions. The presence of a nitrile or isonitrile group at the C11 position and a quaternary vinyl group at the C12 position is notable. Further analysis shows that these natural products are based on a polycyclic ring system such as tricyclic, tetracyclic or pentacyclic*etc*. Based on the carbon skeletal backbone, hapalindoles can be classified into eight subgroups such as-fischerindoles, ambiguine, welwitindolinones, *etc.* (Figure 1).

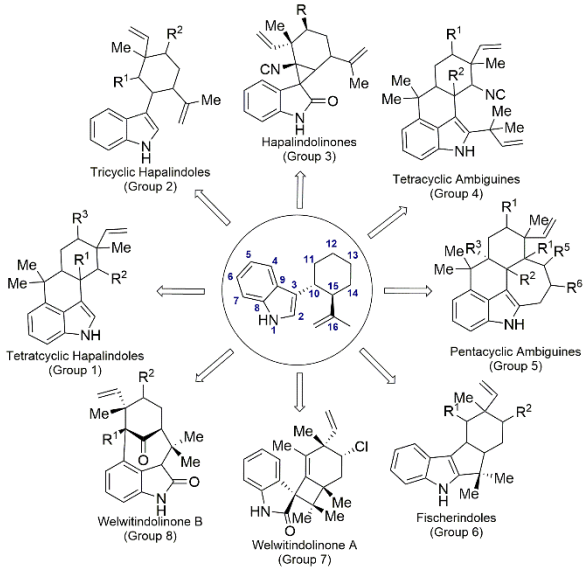
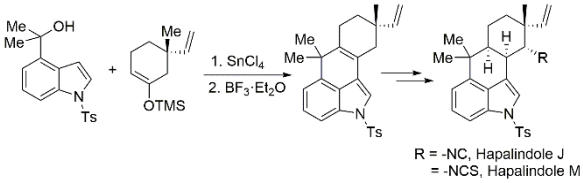


Figure1: Hapalindole alkaloids.

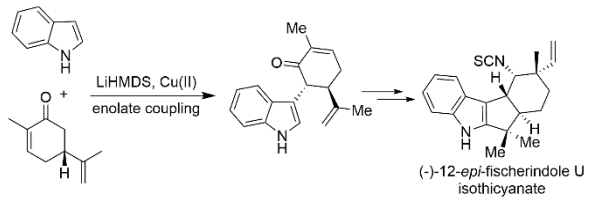
The inspiring molecular architectures of the hapalindoles along with their encouraging biological activities have

spawned many research programs directed toward the total syntheses of these molecules and consequently a number of total synthesis both in racemate[12-21] as well as asymmetric[22-29] form has been reported. In 1989, Natsume and co-workers reported total synthesis of hapalindole J, M, H, and U via a Lewis acid mediated coupling of tertiary benzylic alcohol and silylenol ether (Scheme 1).[12] This tetracyclic intermediate was later used as a common intermediate for all hapalindoles. The *cis*-geometry between C and D ring was accomplished through $LiAlH_4$ mediated alkene reduction.



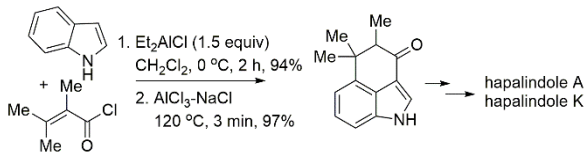
Scheme 1: Natsume's synthesis of hapalindoles J and M.

. In 2004, Baran*et al.* first reported protecting group free synthesis of Hapalindoles and Fischerindole in their pioneering work (Scheme 2).[25] The C-C bond formation between the indole ring and cyclohexane ring was achieved via Cu(II)-mediated oxidative enolate coupling of indole with (-)-carvone in presence of LiHMDS acting as a base for enolate generation.



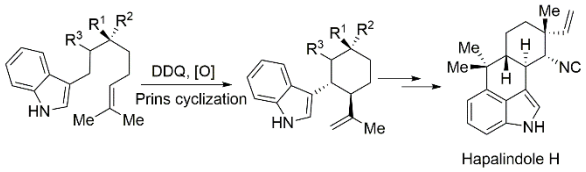
Scheme 2: Baran's total synthesis of hapalindole alkaloids.

In 2011, Johnston *et al.* reported total syntheses of hapalindole A and K and formal synthesis of hapalindole G.[19] The core structure was synthesized from indole via Et_2AlCl mediated acylation/alkylation with α-methyl tiglic acid chloride (Scheme 3). The generated 3-acylated indole was converted to 1,3-diene via $Pd(PPh_3)_4$catalyzed Heck coupling. Later it was coupled with (*E*)-4-chloro-3-methylbut-3-en-2-one via Diels-Alder reaction to access the core structure needed for hapalindole A and K.



Scheme 3: Johnston's synthesis of hapalindole alkaloids.

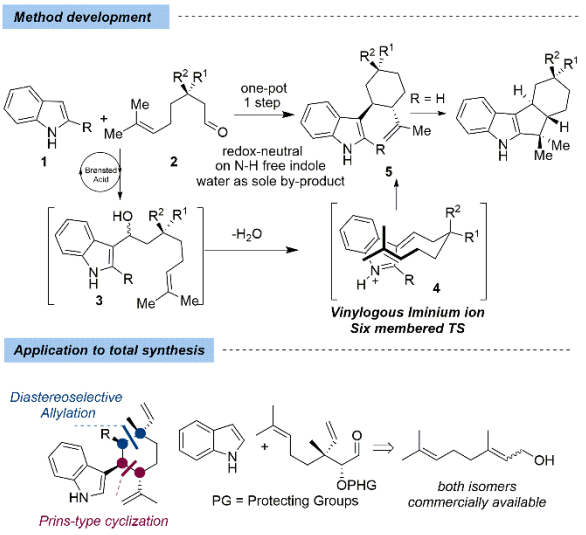
In 2014, Ang Li and co-workers reported core structure of hapalindole alkaloids via DDQ promoted Prins cyclization of 3-alkylated indoles (Scheme 4).[21] It requires considerable efforts for the synthesis of 3-alkylated indole, stoichiometric usage of oxidants, high temperature and corresponding indolyl ketone is formed as by-product.



Scheme 4: Ang Li's synthesis of hapalindole and fischerindoles.

2. Retrosynthesis and Work Plan

Despite numerous reports on the total synthesis of hapalindole alkaloids, direct access to these scaffolds from commercially available starting material is elusive and still a challenging task. There also remained few drawbacks for the existing methods. For example, Cu(II)-mediated oxidative coupling employs stoichiometric amount of indole, base, and oxidant. DDQ promoted benzylic oxidation as documented by Ang Li and co-workers requires tedious pre-functionalization of indoles (up to 7 steps to get the product), stoichiometric use of expensive Sc(III)-triflate Lewis acid an oxidizing agent, in addition, corresponding indolyl ketone is formed as a side product. Considering its synthetic and biological importance as discussed above it would be an efficient protocol if this scaffold can be synthesized in a single step. The proposed idea was based on a one-pot tandem reaction pathway (Scheme 5). First, *in situ* generated indolyl alcohol **3**, formed by reaction of indole**1** and aldehyde **2** in the presence of



Scheme 5: Working hypothesis.

Brønsted acid should undergo a rapid water elimination to

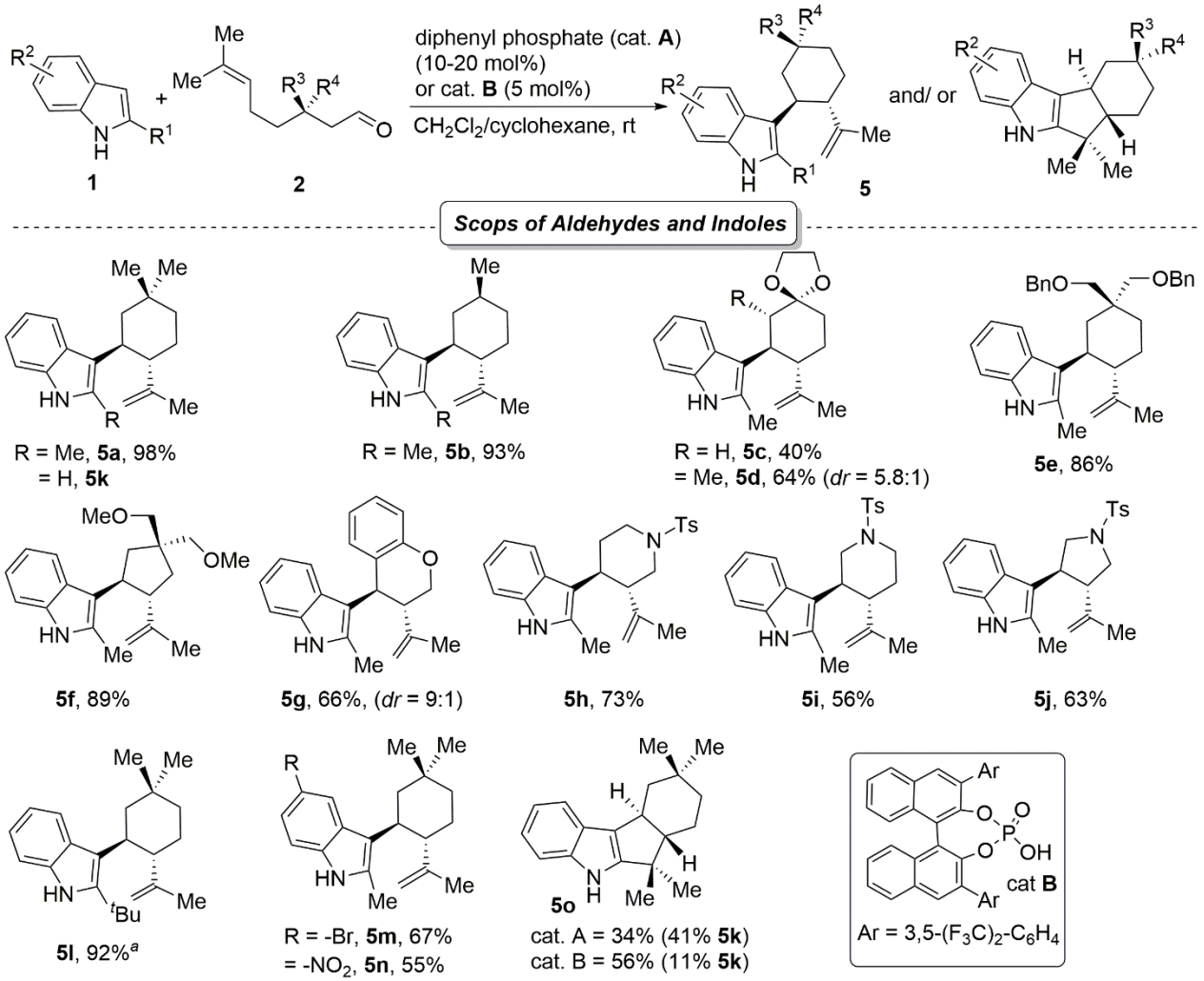
generate vinylogousiminium intermediate **4** which would undergo intramolecularPrins-type cyclization to provide the *trans*-1-indolyl-2-isopropenylcyclohexane scaffold **5** via an all-equatorial chair like TS.[31-32] The success of this strategy exclusively depends on the selectivity at which two competing reactions namely, (a) the generation of **3**, and (b) the intramolecularene reaction of **2** (a decomposition pathway) takes place.

Since, the hapalindole alkaloids are differentiated within themselves at the relative geometrical position, we applied the strategy towards total synthesis of these alkaloids. We hypothesized that C11-C12 geometry can be fixed with a diastereoselectiveallylationwhere as C10-C15 stereocenters can be achieved through the Prins-type cyclization.

3. Result and discussion:

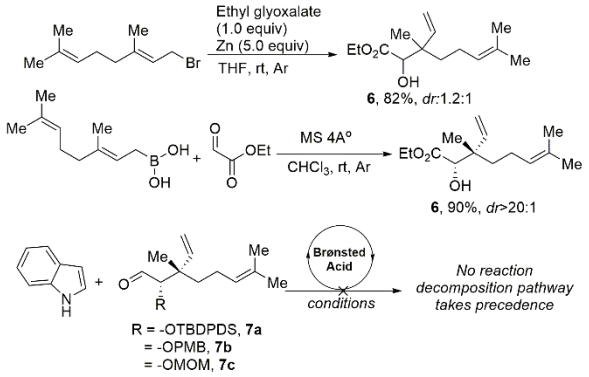
At the outset of this investigation, a brief optimization study shows that diphenyl phosphate is an excellent catalyst for these type of reactions in dichloromethane solvent. As depicted in Scheme 6, several indoles and aldehydes participated in the reaction. Products were isolated in excellent diastereoselectivities and good to excellent yields.Forindole having no C2-substitution, cyclohexane was found to be the solvent of choice. In the presence of BINOL-derived phosphoric acid catalyst B (5 mol%), we pleasingly found that fully cyclized product **5o** was the major product (56% yield) along with **5k** as the minor (11%).[24,29]

Towards synthesis of hapalindoles total synthesis, at first, Zn-mediated allylation of ethyl glyoxalate with geranyl bromide failed to provide desired homoallylic alcohol in any diastereoselectivity(Scheme 7). Next, we move towards more Lewis acidic geranylboronic acid, and to our joy it furnished the homoallylic alcohol **6** in >20:1 *dr* and 90% yield.[33-34] Next, we protected the hydroxyl; group with several protecting groups such as *p*-methoxybenzyl, MOM, and silyl ethers (TBDPS); and converted the ester group to aldehydes (**7a-7c**) via reduction-oxidation sequence. However, under the standard reaction conditions, none of the aldehyde furnished any cyclized products after extensive optimization. In every case, we only observed the decomposition of aldehyde. We hypothesized that, this might be due to the steric bulk adjacent to the aldehyde, which is retarding the initial attack of indole. As a result, decomposition pathway



Scheme 6: Scope of the Aldehydes and Indoles. [a]Batchwise addition of aldehyde at 60 °C. *dr* = diastereomeric ratio.

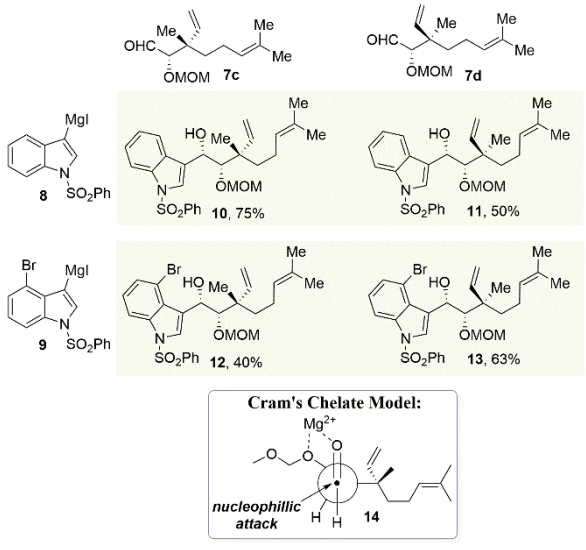
(intramolecularene reaction) is operative rather than nucleophilic addition of indole nucleus to the aldehyde. To overcome this, we introduced the indole-nucleophile while erasing the possibility of ene reaction by introducing a Grignard reagent. We have chosen MOM-protected aldehyde **7c** as our optimal aldehyde due to its moderate steric bulk as well as its ability to get deprotectedunder acidic conditions.[35]



Scheme 7: Initial approaches to hapalindole alkaloids

3.1 Total Synthesis of Deschloro 12-*epi* Fischerindole W Nitrile and Hapalindole Q

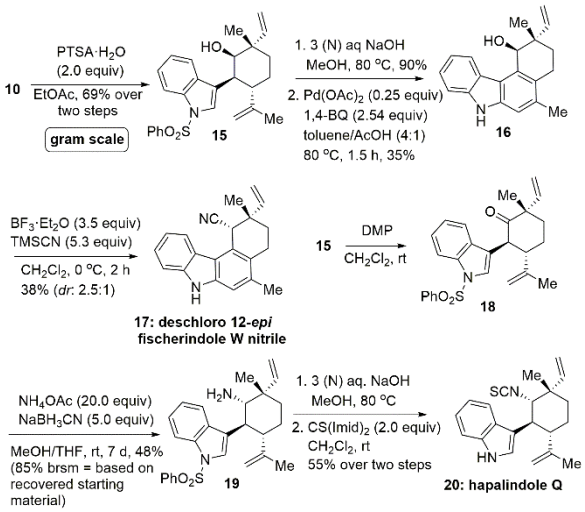
In order to get all the isomeric hapalindoles from the same common intermediate using a stereodivergent strategy we synthesized these four diastereomeric alcohols by coupling MOM protected aldehyde **7c** and **7d** was reacted with Grignard generated from **8** and **9** using iodine-magnesium exchange carbazole alcohol **16** in 35% yield.[21,35] Total synthesis of deschloro 12-*epi*-fischerindole W nitrile **17** was accomplished in 38% overall yield as major diastereomer (*dr*: 2.5:1) by treatment of **16** with TMSCN in the presence of $BF_3{\cdot}Et_2O$.[21] To synthesize hapalindole Q, **15**was oxidized to the corresponding ketone **18** using Dess-Martin-Periodinane oxidant. The resulting ketone was then converted to amine **19** in 48% yield (85% brsm) through reductive amination using NH_4OAc and $NaBH_3CN$.[29] Removal of the protecting group followed by isothiocyanate formation using $CS(Imid)_2$ gave hapalindole Q **20** in 55% yield over two steps.[35]



Scheme 8: Synthesis of diastereomeric alcohols via Grignard addition

3.2 Total Synthesis of 12-*epi*-Hapalindole Q Isonitrile, Hapalindole C, and Hapalindole D:

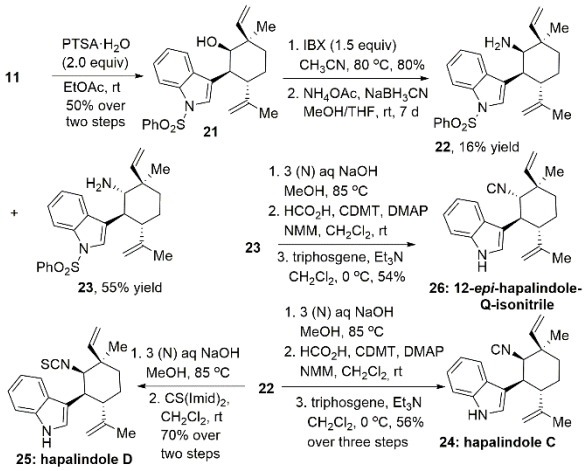
In a similar fashion, other diastereomericalcohol **11**, obtained from nerylboronic acid, was treatedwith $PTSA{\cdot}H_2O$ and it proceeded as anticipated, providing **21** in 50% yield over two steps (Scheme 10). Alcohol functionality was converted to ketone using IBX oxidation and the resulting ketone was then subjected to reductive amination. Unlike previous case, it gives two isomeric *cis*- and *trans*- amines **22** and **23** in 16% and 55% yields, respectively.[29]Desulfonylation of **23** followed by isocyanide formation gave 12-*epi*hapalindole-Q-isonitrile**26** in 54% yield over three steps using Baran′ s protocol.[25] Similarly, desulfonylation of another isomeric amine **22** followed by isothiocyanate formation using $CS(Imid)_2$ gave **25**hapalindole D. The same amine was subjected to isocyanate formation according to Baran′ s protocol which provided hapalindole C **24** in 56% yield over three steps.[35]



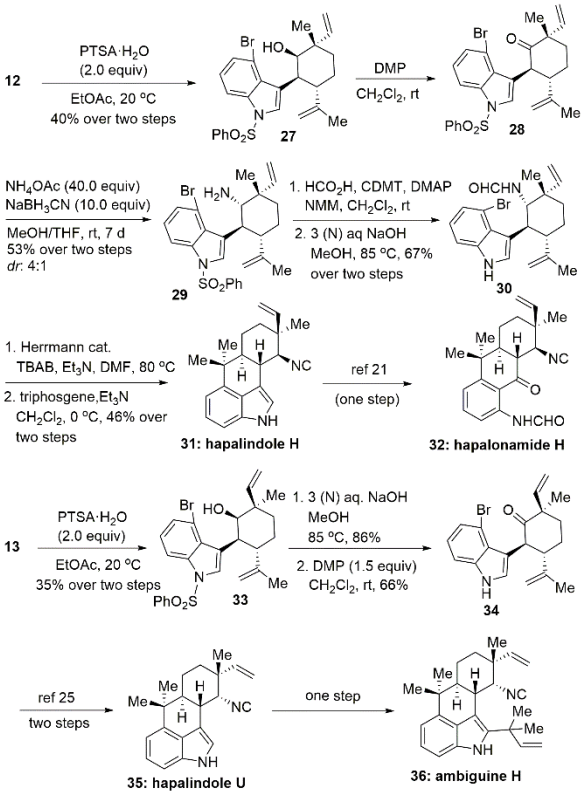
Scheme 9:Total synthesis of Deschloro 12-*epi* Fischerindole W Nitrile and hapalindole Q.

3.3 Total Synthesis of Hapalindole H, Hapalonamide H, Hapalindole U and Ambiguine H:

Having achieved tricyclic hapalindoles, we next concentrated our attention toward tetracyclic sub-class having*trans*-fuseddecalin ring system with a quaternary vinyl group at the C12-position and isonitrile group at the C11-position (Scheme 11). To achieve this, we took 4-bromo-*N*-benzenesulfonyl-3-iodoindole **9** as an indole coupling partner. On the reaction of aldehyde **7c**, provided the secondary alcohol **12** as a single diastereomer in 72% yield. Treatment of **12** with 2.0 equiv of PTSA·H_2O at a lower temperature (~20 °C) proceeded as hypothesized to give **27** in 40% overall yield over two steps. It is important to maintain the temperature at around 20 °C for optimal yield. Dess Martin Periodinane (DMP) oxidation of alcohol **27** gave the ketone **28**. Similar reductive amination as mentioned before proceeded smoothly to give amine **29** as a mixture of inseparable diastereomers (*dr*: 4:1) in 53% combined yield. In the next step, amine functionality was converted to the formamide functionality and the benzenesulfonyl group was deprotected. During this, major diastereomer**30** was separated and obtained in 67% yield. Formamide**30** was subjected to reductive Heck annulation and successive dehydration using triphosgene gave hapalindole H **31** in 46% yield over two steps. Hapalindole H has been used as an advanced intermediate for the synthesis of hapalonamide H **32** by Ang Li *et al.*[21] Thus, the formal synthesis of hapalonamide H **32** was also achieved.The other isomeric alcohol **13**, was similarly treated with PTSA·H_2O to obtain **33**in 35% yield. Desulfonylation followed by DMP oxidation gave ketone **34** which has been used as synthetic intermediate for the synthesis of hapalindole U and ambiguine H **36**, thus completing their formal synthesis.[25,35]



Scheme 10: Total Synthesis of 12-*epi*-hapalindole Q isonitrile, hapalindole C and hapalindole D.



Scheme 11*:* Total Synthesis of hapalindole H, hapalonamide H, hapalindole U and ambiguine H.

4. Conclusions

In conclusion, we have highlighted the work published recently on the synthesis of diversely functionalized *trans*-1-indolyl-2-isopropenylcyclohexane scaffolds via Brønsted acid catalyzed one-pot cascade protocol.[35] Simplicity and mild conditions significantly enhance the appeal of this method toward other systems. To show the applicability, hapalindoles-type nine alkaloids were synthesized in a stereodivergent manner. Out of four contiguous stereocenters, diastereoselective allylation using allylboronic acids fixed two adjacent stereocenters, whereas PTSA mediated deprotection-cyclization cascade sealed the other two.

5. Acknowledgements

M.S.M. gratefully acknowledge SERB, Department of Science and Technology, India (Sanction No. CRG/2018/000317) for funding. SS thanks CSIR, India for fellowships.

6. Notes and References

1. Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456.
2. Dixit, R. B.; Suseela, M. R. *Antonie van Leeuwenhoek.* **2013**, *103*, 947.
3. Ibelings, B. W.; Backer, L. C.; Kardinaal, W. E. A.; Chorus, I. *Harmful Algae.* **2014**, *40*, 63.
4. Hohlman, R. M.; Newmister, S. A.; Sanders, J. N.; Khatri, Y.; Li, S.; Keramati, N. R.; Lowell, A. N.; Houk, K. N.; Sherman, D. H. *ACS Catal.* **2021**, *11*, 4670–4681.
5. Hohlman, R. M.; Sherman, D. H. *Nat. Prod. Rep.* **2021**, 16–18.
6. Bhat, V.; Dave, A.; MacKay, J. A.; Rawal, V. H. *The Alkaloids: Chemistry and Biology*; Elsevier Inc., **2014**; Vol. 73, pp 65-160.
7. Walton, K.; Berry, J. P. *Mar. Drugs* **2016**, *14*, 73.
8. Moore, R. E.; Cheuk, C.; Yang, X. Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036.
9. Becher, P. G.; Keller, S.; Jung, G.; Süssmuth, R. D.; Jüttner, F. *Phytochemistry* **2007**, *68*, 2493.
10. Kim, H.; Lantvit, D.; Hwang, C. H.; Kroll, D. J.; Swanson, S. M.; Franzblau, S. G.; Orjala, J. *Bioorg. Med. Chem.***2012**, *20*, 5290.
11. Koodkaew, I.; Sunohara, Y.; Matsuyama, S.; Matsumoto, H. *Plant Growth Regul.***2012**, *68*, 141.
12. Muratake, H.; Natsume, M. *Tetrahedron Lett.***1989**, *30*, 1815.
13. Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron***1990**, *46*, 6351.
14. Natsume, M.; Muratake, H. *Tetrahedron Lett.* **1990**, *46*, 6331.
15. Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6343.
16. Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2000**, *2*, 3517.
17. Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983.
18. Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189.
19. Chandra, A.; Johnston, J. N. *Angew. Chem. Int. Ed* .**2011**, *50*, 7641.
20. Rafferty, R. J.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 519.
21. Lu, Z.; Yang, M.; Chen, P.; Xiong, X.; Li, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 13840.
22. Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.***1993**, *115*, 3499.
23. Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.
24. Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.
25. Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
26. Gademann, K.; Bonazzi, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 5656.
27. Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.***2008**, *130*, 17938.
28. Maimone, T. J.; Ishihara, Y.; Baran, P. S. *Tetrahedron* **2015**, *71*, 3652.
29. Liu, Y.; Cheng, L. J.; Yue, H. T.; Che, W.; Xie, J. H.; Zhou, Q. L. *Chem. Sci.* **2016**, *7*, 4725.
30. Dethe, D. H.; Das, S.; Kumar, V. B.; Mir, N. A. *Chem. - Eur. J.* **2018**, *24*, 8980.
31. Rasvan Khan, P.; Charan, P. H. K.; Rao, M. B. *Synth. Commun.* **2020**, *50*, 432–437.
32. Padmaja, P.; Reddy, P. N.; Subba Reddy, B. V. *Org. Biomol. Chem.* **2020**, *18*, 7514–7532.
33. Raducan, M.; Alam, R.; Szabó, K. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 13050.
34. Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. *J. Am. Chem. Soc.***2015**, *137*, 11262.
35. S. Sahu, B. Das and M. S. Maji, *Org. Lett.* **2018**, *20*, 6485-6489.

7. About the author(s)

Samrat Sahu received his B.Sc. in chemistry from University of Calcutta in 2011. Then he completed his master thesis work under the guidance of Prof. Govindasamy Sekar at Indian Institute of Technology Madras in 2013. From July 2014 onwards he is pursuing his Ph.D. under the guidance of Dr. Modhu Sudan Maji at Indian Institute of Technology Kharagpur. His research interest focuses on the cascade functionalization of indoles and total synthesis of complex indole alkaloids.

Modhu Sudan Maji was born in 1982 and did his schooling from his native place Howrah, India. He completed BSc in Chemistry (honors) from Ramakrishna Mission Residential College Narendrapur, University of Calcutta in 2003, and MS from Indian Institute of Science Bangalore in 2006 (master thesis work under Prof. Goverdhan Mehta). In 2009, he completed his Ph.D. under the guidance of Prof. Armido Studer from University of Muenster, Germany. Following this, he received Alexander von Humboldt Fellowship and completed three years of post-doctoral research with Prof. Magnus Rueping of RWTH Aachen University, Germany. After another short post-doctoral research stay with Prof. Martin Oestreich of Technical University Berlin, Germany, he joined the Department of Chemistry of IIT Kharagpur as an Assistant Professor in December 2013; where he is currently working as an associate professor since August 2019. His broad research interest includes the development of new reaction methods for the synthesis of alkaloids and conjugated organic materials.

Article Note: A collection of invited papers based on *Award Lecture* presentations in the 3rd CRS® International Symposium *'Rasyan 3'* held at Raja Narendra Lal Khan Women's College, Midnapore, West Bengal, India held on November 03, 2018.