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Enantiospecific total syntheses of (+)-Hapalindole H and (–)-12-*epi*-Hapalindole U

Dattatraya H. Dethe,*[a] Saikat Das,[a] Vijay Kumar B,[a] and Nisar A. Mir [a]

Dedication ((optional))

Abstract: Enantiospecific total syntheses of (+)-hapalindole H, (–)-12-*epi*-hapalindole U, formal synthesis of (+)-hapalindole Q and (+)-12-*epi*-fischerindole U isothiocyanate have been described. Key steps of our approach feature expedient, highly regio- and diastereoselective Lewis acid catalyzed Friedel-Crafts reaction of indole with cyclic allylic alcohols and intramolecular reductive Heck reaction. Efficiency of the synthetic route also relies on an alkynyl aluminate complex driven regioselective nucleophilic epoxide opening from sterically hindered site.

Hapalindoles and fisherindoles are two important classes of bioactive indole alkaloids derived from marine cyanobacteria belonging to Stigonemataceae family. Isolation of these marine indole alkaloids was first reported by Moore *et.al*. in 1984[1] which was followed by addition of more than eighty alkaloid members to this family.[2] Hapalindoles show prominent biological aspects such as insecticidal, anti algal, antimycotic or antibacterial activities along with the inhibitory activity against arginine vasopression binding. These natural products possess unique tri- or tetracyclic framework featuring indole moiety connected through its C3 position to highly functionalized cyclohexyl ring with an uncommon nitrile or isonitrile substituent. Owing to these fascinating biological activities along with their challenging structural features, developing new methods for total synthesis of hapalindoles has been a rousing task in recent years.[3]
So far, there are multiple approaches[4] towards synthesis of the natural products belonging to the class of hapalindoles and a few of them have succeeded in synthesizing the natural products both in racemic[5] or enantiomerically pure[6] form. First total synthesis of hapalindoles J, M, H, and U were reported by Natsume and coworkers.[5a-c] Albizati group synthesized (+)-hapalindole Q [6a] and subsequently Fukuyama and Natsume et al. independently described enantiospecific syntheses of (–)-hapalindoles G and O from (–)-carvone.[6b-c] Kerr group reported organocatalytic asymmetric Diels Alder reaction for the formation of (–)-hapalindole Q.[6d] Baran group achieved total synthesis of a number of hapalindole alkaloids by using copper mediated unique oxidative coupling protocol.[6e-h] Syntheses of hapalindole K, A and G were also achieved by Johnston group.[5e] Very recently Zhou *et. al.* reported total syntheses of (+)-hapalindole Q and (+)-12-*epi*-fischerindole U isothiocyanate using DKR method.[6n] Herein, we report a first enantiospecific total synthesis

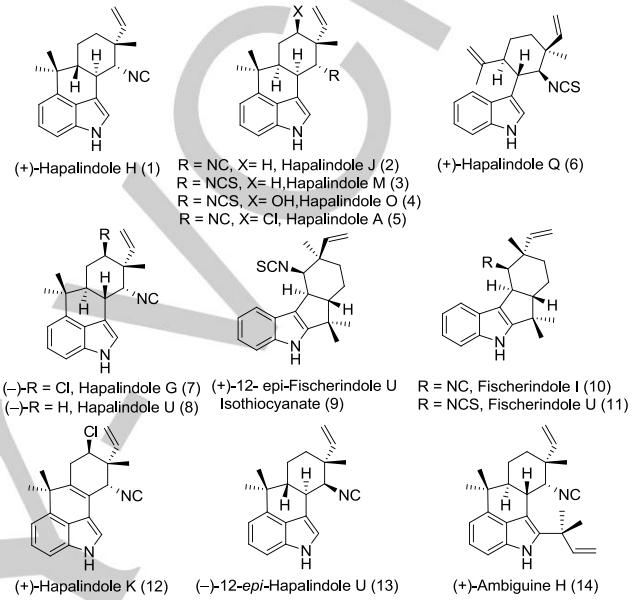

Figure 1. Selected examples of natural products of Hapalindole type alkaloids.

of (+)-hapalindole H and (–)-12-*epi*-hapalindole U (**13**).[7] Hapalindole H (**1**) has unique structure accommodating a *trans* fused decalin ring junction with quaternary axial vinyl group at C12 position and an equatorial isonitrile group at C11 position. Hapalindole H (**1**) acts as a fungicide and also inhibits growth of *Staphylococcus aureus, Staphylococcus epidermidis* and *Staphylococcus pyogenes.*[8] Till date, only two total syntheses of (±)-hapalindole H are reported in literature.[5c,5g] The first total synthesis was achieved by Natsume and coworkers in 1990 and recently Li group reported another synthesis using bioinspired oxidative cyclization reaction. But so far, the total synthesis of enantiomerically pure hapalindole H is not reported. Thus, the absolute configuration of the hapalindole H is still unknown.

Friedel-Crafts reaction is one of the most powerful synthetic methods in organic chemistry as it directly constructs carbon-carbon bond in an atom economical manner and provides advanced intermediates for total synthesis of natural products.[9a-i] In particular, enantio- and diastereoselective Friedel-Crafts reaction has been a fascinating and perplexing exercise as the carbocation intermediate involved in the reaction would bring about racemic and diastereomeric mixture or it would undergo a carbocationic rearrangement giving rise to regioisomers. Grieco and coworkers have also developed a Friedel-Crafts reaction of indole nucleophile with allylic alcohols using lithium perchlorate-diethyl ether and a catalytic amount of Bronsted acid. Their strategy was limited to allylic alcohols with β,β-disubstitution. Diastereoselectivities and wide substrate scope remained unexplored or unexplained.[10a] Herein, we report a highly regio- and diastereoselective Friedel-Crafts reaction between indole

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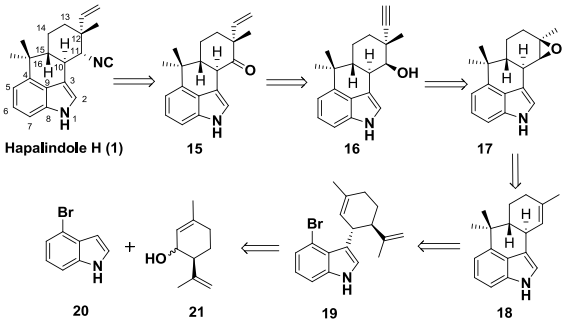
derivatives and chiral allylic alcohols which was then practiced in an enantiospecific synthesis of the two natural products (+)-hapalindole H (**1**) and (–)-12-*epi*-hapalindole U (**13**).



Scheme 1. Retrosynthetic analysis for hapalindole H (1).

It was envisioned that hapalindole H (**1**) could be obtained from the tetracyclic keto compound **15** by a functional group switch from ketone to isonitrile group. The required vinyl group could be introduced by applying a two step hydrogenation and oxidation protocol on compound **16**. All-carbon quaternary centre at C12 could be installed by regioselective nucleophilic epoxide ring opening of compound **17** by TMS-acetylene. Epoxide **17** could be prepared easily from the corresponding olefin. Tetracyclic core **18** of hapalindole could be constructed using a two step protocol constituting a highly regio- and diastereoselective Friedel-Crafts reaction between 4-Bromo indole (**20**) and sec-allylic alcohol (**21**), followed by an intramolecular reductive Heck reaction.

To quickly check the viability of our hypothesis, Lewis acid catalysed Friedel-Crafts reaction of indole and diastereomeric mixture (4:1) of sec-allylic alcohols (**21)** (prepared by CrO_3 mediated allylic oxidation of (*R*)-limonene followed by reduction with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$)[9a] was attempted. To our delight, after screening various Lewis and Brønsted acids, the mixture of indole and sec allylic alcohol (**21**), on treatment with 20 mol% $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 30 min, afforded coupling product **19a** with 68% yield in a highly regio- and diastereoselective manner (dr ≥19:1, confirmed by crude ^1H NMR) (**Table 1**) having water as only by product of the reaction. It is worth mentioning that, LAH reduction of the enone obtained by CrO_3 mediated allylic oxidation of (*R*)-limonene prodcued 2:3 diastereomeric mixture of allylic alcohols (21).[9j] Interestingly, Friedel-Crafts reaction of indole and alcohols (21) obtained by LAH reduction generated product **19a** in 65% yield with more than 19:1 diastereomeric ratio. This result further supports that, the reaction proceeds via S_N1 pathway. Bulky isopropenyl group present nearby the reactive site in allylic alcohol **21** is indeed responsible for the observed excellent diastereoselectivity by constraining indole nucleophile to take a path of attack selectively from the opposite side to furnish the *trans* isomer. This result encouraged us to generalize Friedel-Crafts reaction with various indole derivatives as well as allylic alcohols to generate diverse optically active indoloterpene derivatives in a single step as depicted in **Table 2**. It is worth mentioning that scope of the reaction was broadened to the indoles having substitution not just on the benzene moiety but also at C2 position. Reaction worked with equal efficiency when an ester functional group was placed at C2 position. A couple of these indoloterpene derivatives were further converted into tetra- cyclic core of fischerindole (**22** and **22a**) in good yields

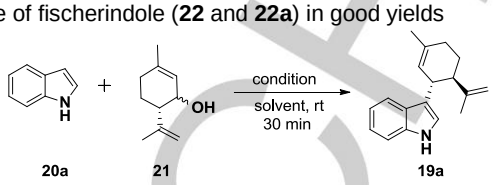


Table 1. Optimization of Friedel-Crafts reaction condition. [a]

Entry	mol %	catalyst	solvent	yield[%][b]	*dr*
1	20	$Cu(OTf)_2$	CH_2Cl_2	32	(19:1)
2	20	$Sc(OTf)_2$	CH_2Cl_2	47	(17:1)
3	20	$SnCl_4$	CH_2Cl_2	43	(9:1)
4	20	$TiCl_3$	CH_2Cl_2	26	(10:1)
5	20	TMSOTf	CH_2Cl_2	56	(15:1)
6	20	*p*-TSA	CH_2Cl_2	38	(8:1)
7	20	$AlCl_3$	CH_2Cl_2	35	(12:1)
8	20	$BF_3{\cdot}OEt_2$	CH_2Cl_2	68	(>19:1)
9	10	$BF_3{\cdot}OEt_2$	CH_2Cl_2	62	(>19:1)
10	20	$BF_3{\cdot}OEt_2$	toluene	44	(10:1)

[a] Reaction conditions: **20a** (1.08 mmol), **21** (0.98 mmol), CH_2Cl_2 (5 mL). [b] Isolated yields.

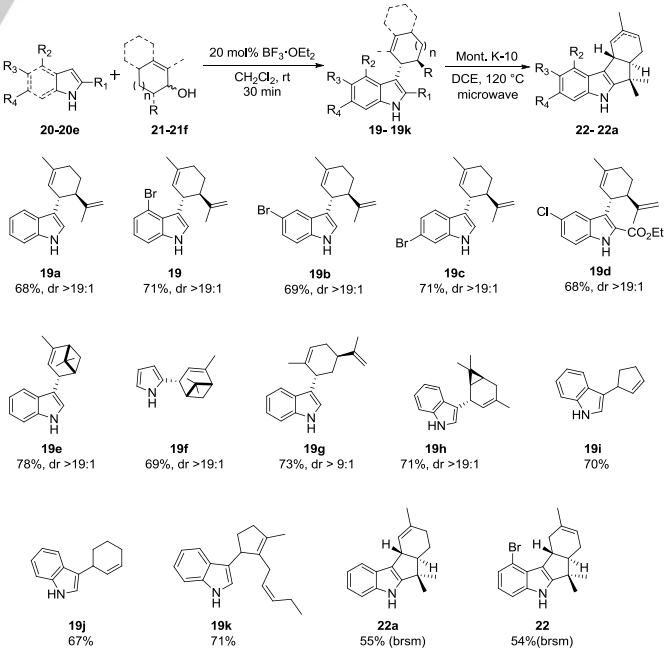
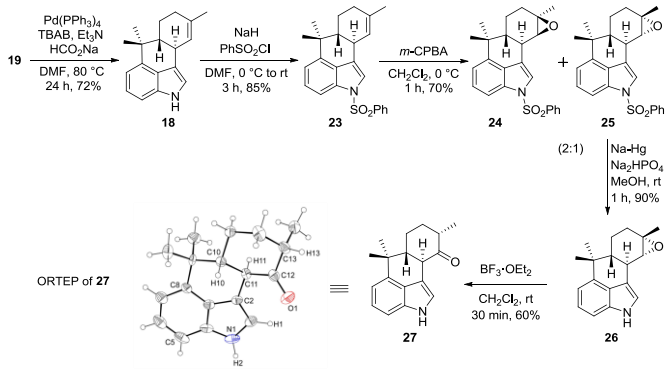


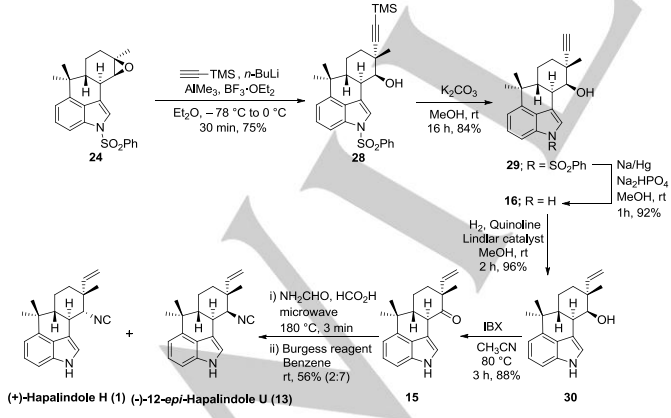
Table 2. Substrates scope of the Friedel-Crafts reaction.

using Mont. K-10 in microwave irradiation at 120 °C. After finding appropriate condition for Friedel-Crafts reaction and C-2 cyclization of indole derivatives, we next directed our attention towards our eventual task, enantiospecific total synthesis of

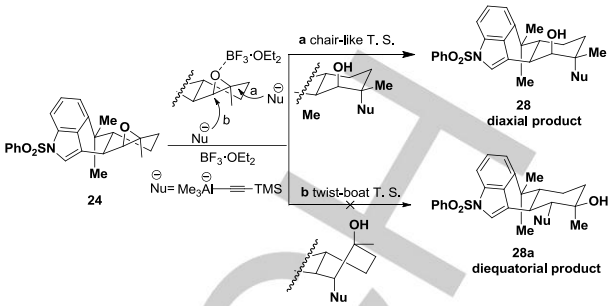


Scheme 2. Synthesis of compound (-)-27

hapalindole H (**1**) which was commenced by a reductive Heck reaction on compound **19** using 10 mol% [$Pd(PPh_3)_4$] in presence of sodium formate to furnish compound **18** (72% yield) generating the tetracyclic carbon skeleton of hapalindoles.[6g] Epoxidation of the olefin using various oxidizing reagents such as *m*-CPBA and DMDO led to decomposition of the starting material probably due to free -NH group of the indole. To overcome this problem, indole-nitrogen of compound **18** was protected by reaction with NaH and benzenesulfonyl chloride in DMF. Epoxidation of olefin **23** using *m*-CPBA in CH_2Cl_2 at 0 °C then generated 2:1 mixture of diastereomers **24** and **25** in 70% combined yield which were readily separated by silica gel column chromatography. Our attempts to get single crystal of **24** or **25** for the confirmation of stereostructure of epoxides were not successful. However, structure and stereochemistry of compound **25** was established unambiguously by single crystal X-ray diffraction analysis[11] of **27** generated from **26** by semipinacol rearrangement[12] (Scheme 2).



Scheme 3. Synthesis of (+)-hapalindole H (1) and (-)-12-*epi*-hapalindole U (13)

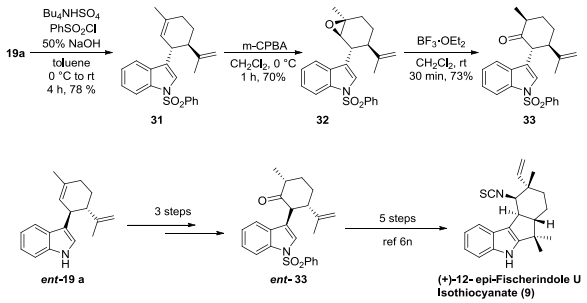


Scheme 4. Mechanism of epoxide 24 opening with alkynyl aluminate reagent

Our next focus was opening of β-epoxide by acetylide followed by Lindlar hydrogenation of triple bond to obtain the desired alcohol **30**. As per our assumption, treating epoxide **24** with TMS- acetylene in presence of $AlMe_3$ and $BF_3{\cdot}OEt_2$ afforded highly regio- and diastereoselective opening of corresponding epoxide to furnish compound **28** in 75% yield.[13] Excellent regioselectivity was observed for opening of epoxide **24** which is apparently due to preferential axial attack of alkynyl aluminate reagent on quaternary carbon of epoxide in compound **24** (path-a) to furnish compound **28** via chair like transition state. On the other hand, equatorial attack through path b would give diequatorial product **28a** via an energetically less favourable twist-boat transition state (Scheme 4). Subsequent removal of TMS and benzenesulfonyl groups furnished alcohol **16** in excellent yield. Hydrogenation of alkyne moiety of **16** assisted by H_2/Lindlar catalyst in presence of quinoline yielded compound **30** in 96% yield. Oxidation of the sec-alcohol by IBX in CH_3CN under reflux condition afforded corresponding ketone **15** in 88% yield. Microwave aided reductive amination[14] of ketone 15 at 180 °C for 3 min followed by subsequent dehydration by Burgess reagent furnished **1** and **13** in 2:7 diastereomeric ratio. Formation of diastereomers, **1** and **13**, in an uneven ratio can be rationalized by selective equatorial attack of hydride ion onto the iminium ion during reductive amination step. Because hydride ion, if takes the axial approach, would have strong 1,3 diaxial interactions with cyclohexane ring hydrogens. This completes the first enantiospecific total synthesis of (+)-hapalindole-H (**1**) and (–)-12-*epi*-hapalindole U (**13**). Spectral data (IR, ^1H, ^{13}C NMR and HRMS) and optical rotation of synthetic **1** and **13** were identical with those of isolated molecules.[1b,7]

We also became interested to showcase utility of indoloterpene **19a** and *ent*-**19a** for the synthesis of (+)-hapalindole Q and (+)-12-*epi*-fischerindole U isothiocyanate. Towards this goal, nitrogen of indole terpenoid **19a** was protected using benzenesulfonyl chloride.[15] Regio- and diastereoselective epoxidation of electron rich endocyclic olefin **31** using *m*-CPBA, generated compound **32**. Stereochemistry of epoxide of compound **32** was directed by bulky indole moiety by hindering one face of the olefin. Semi-pinacol rearrangement of epoxide using $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature furnished ketone **33** in 73 % yield.[12] Ent-ketone **33** was prepared using same synthetic sequence starting from (S)-limonene. Ketone **33** and its enantiomer were converted in five steps to (+)-hapalindole Q (**6**) and (+)-12-*epi*-fischerindole U isothiocyanate (**9**)

respectively by Zhou and coworkers.[6n] Thus, this constitutes the formal synthesis of these two natural products.



Scheme 5. Synthesis of compound (+)-33 and *ent*-33

In summary, a highly regio- and diastereoselective Friedel-Crafts reaction between secondary allylic alcohol and indole was developed. The potential of this methodology has been amply demonstrated by the total synthesis of (+)-hapalindole H (**1**), (–)-12-*epi*-hapalindole U (**13**) which involves 11 steps in the longest linear sequence starting from readily available *R*-(+) limonene. This method is fairly general and amenable to synthesis of other natural products of this class as well as their analogues.

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Keywords: Total Synthesis • Hapalindoles • Friedel-Crafts • Natural Products

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[11] (CCDC 1017680) (-)-**27** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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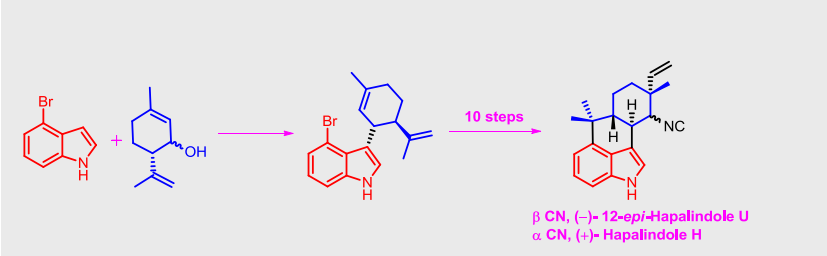

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