Total synthesis of (−)-himalensine A

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Supporting Information Placeholder

ABSTRACT: The first enantioselective synthesis of (−)-himalensine A has been achieved in 22 steps. The synthesis was enabled by a novel catalytic, enantioselective prototropic shift / furan Diels-Alder (IMDAF) cascade to construct the ACD tricyclic core. A reductive radical cyclization cascade was utilized to build the B ring, and end game manipulations featuring a molecular oxygen mediated γ-CH oxidation, a Stetter cyclization to access the pendant cyclopentenone and a highly chemoselective lactam reduction delivered the natural product target.

The complex polycyclic frameworks of the *Daphniphyllum* alkaloids and their extensive biological properties[1] have made this family of natural products much sought after within the total synthesis community.[2-4] It is not only the ability to access new potential lead structures for drug discovery[5] – which makes their synthesis relevant – but additionally the intricate and congested polycyclic architecture provide a perfect platform for the development of new chemical strategies and the discovery of new synthetic methodologies. This combination of target driven and methods driven synthesis has indeed led to intense effort to deliver natural products within this family, resulting in elegant syntheses of daphmanidine E,[6] calyciphylline N,[7] daphenylline[8] and most recently longeracinphyllin A[9] within the past decade.

Himalensine A, recently isolated in 2016,[10] features a trinorcalyciphylline A skeleton belonging to the calyciphylline A-type structural family. This sub-class of the *Daphniphyllum* family, first discovered in 2003, all possess a characteristic core consisting of four [6-6-5-7] fused rings. Due to the isolation of only limited amounts of the natural product from nature, a full biological evaluation of these alkaloids has yet to be performed, although promising cytotoxicity data towards a range of human cell lines has been demonstrated[2]. To date, intense synthetic efforts[11] within this family have yielded daphenylline (**2**)[8] and most recently, longeracinphyllin A (**3**)[9] as completed synthetic targets. Attracted by the biological potential of these alkaloids, and drawn by their architectural complexity, our aim was to devise a new, efficient and enantioselective route to access such compounds. Herein we report our findings, culminating in the first total synthesis of (−)-himalensine A (**1**).

Pivotal to our synthetic strategy was the enantioselective installation of the 5,6,7-tricyclic core early into the route. We recognized that an enantio- and diastereoselective intramolecular amidofuran Diels-Alder (IMDAF) reaction, would enable the construction of the ACD tricyclic core (**4**) in a single step and configure five stereogenic centres including two that were vicinal and quaternary within the carboskeleton (Figure 1). The amidofuran IMDAF reaction, pioneered and exploited by Padwa[12], has been used to access various target structures, including natural products minfiensine[13a] and dendrobine,[13b] however no catalytic enantioselective variant has been developed to date. In our planned IMDAF reaction, we envisaged asymmetry arising from the generation of the Diels-Alder dienophile **5** through a chiral Brønsted base-catalyzed prototropic shift reaction of an isomeric precursor **6**. Successful execution, with sufficient stereocontrol, would constitute the first example of a catalytic, enantioselective amidofuran Diels-Alder reaction and provide the foundation for an enantioselective total synthesis.

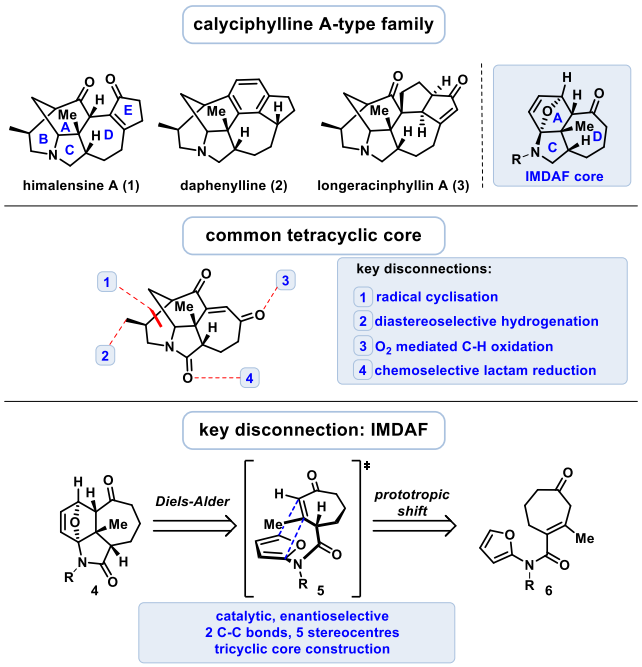


Figure 1. Synthetic strategy towards the caliciphylline A-type alkaloids *via* a common tetracyclic core.

N-Boc protected furan **7** was selected as the ideal model to develop the enantioselective IMDAF reaction whilst possessing the right functionality to continue synthetic efforts. This was synthesized on decagram scale via a 7-step sequence from ethyl-2-oxocyclopentanecarboxylate[14] and was investigated for performance in the DABCO-catalyzed prototropic shift / IMDAF reaction. Pleasingly at 50 °C, using 20 mol% DABCO, IMDAF cascade product (±)-**8** was afforded in 95% yield, in 92:8 dr after 24 hours, thus demonstrating feasibility of the key catalytic step.

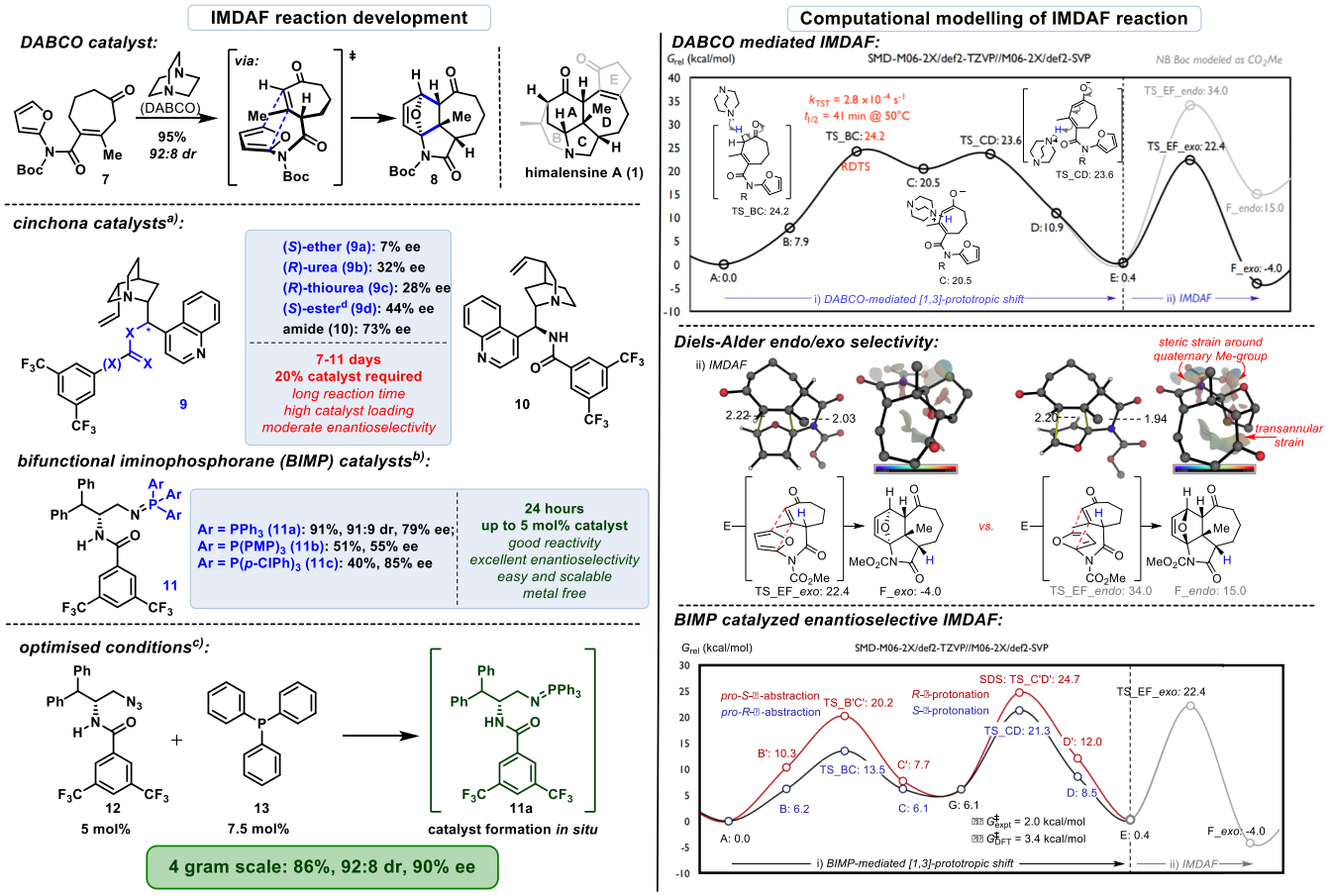


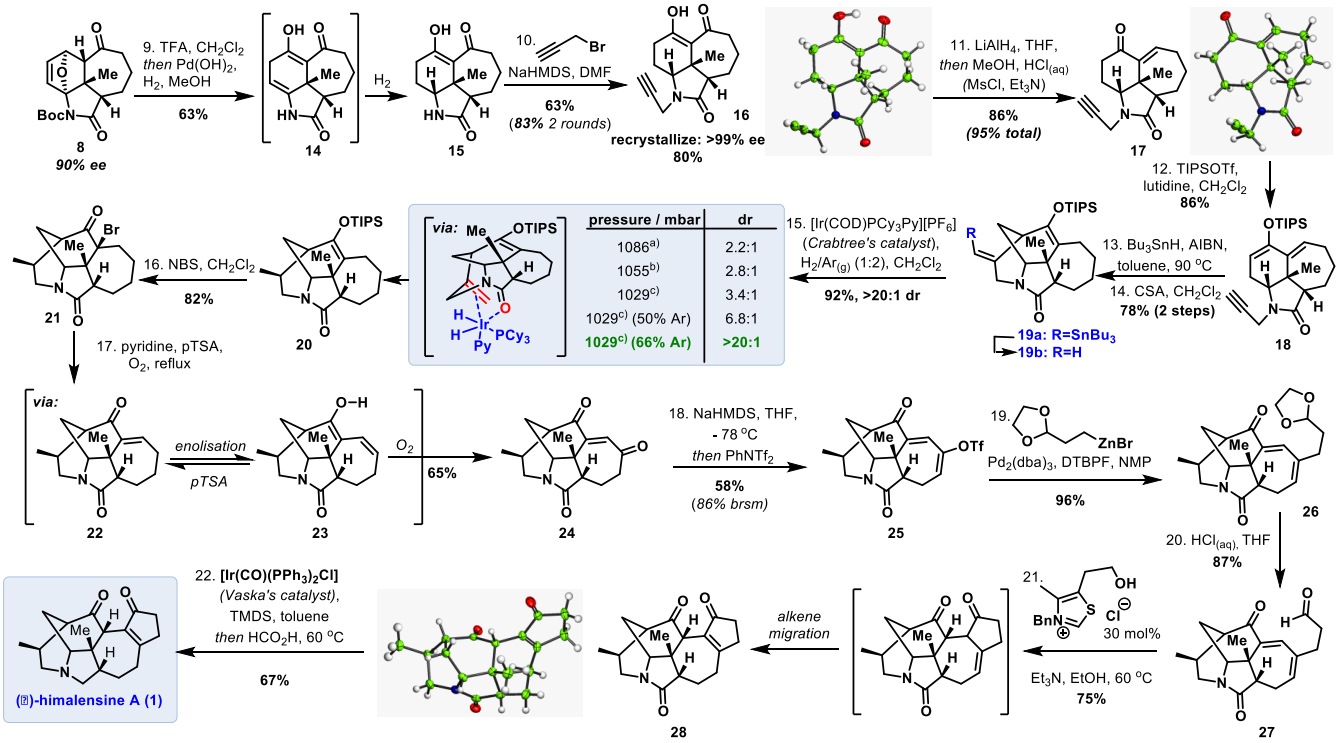
Figure 2. Development of the key enantioselective IMDAF reaction and rationalization by computation calculations. a) cinchona catalysts screening conditions: 20 mol% catalyst, toluene, 7 days, 60 °C. b) bifunctional iminophosphorane catalyst screening conditions: 20 mol% catalyst, toluene, 24 h, 60 °C. c) optimized conditions: 5 mol% catalyst, toluene, 0.06 M, 24 h, 60 °C. d) 6-hydroxy-quinoline derivative.

Drawing from Deng's pioneering studies in the field of asymmetric proton transfer catalysis,[15] cinchona alkaloid derivatives were then investigated for their ability to impart enantiocontrol. These privileged scaffolds have been widely used as bifunctional Brønsted base / H-bond donor catalysts where multipoint-binding allows the catalyst to arrange the substrate within a chiral environment and effect enantioselective deprotonation / reprotonation reactions. A preliminary screen of these catalysts identified **10** as the best which gave IMDAF cascade product **8** in quantitative yield and 73% ee. Although encouraging, attempts to improve enantioselectivity failed and the long reaction time of 7 days and high catalyst loading of 20 mol% severely limited the scalability of the reaction. Accordingly, an alternative chiral catalyst class was sought. Linking low reactivity to the weakly basic nitrogen atom of the quinuclidine moiety, we investigated the bifunctional iminophosphorane (BIMP) class of chiral superbase organocatalysts developed recently in our group as alternatives.[16] The use of these high pK_a organic super-bases in place of tertiary amines has been shown to enhance reactivity and allow reduction to both the reaction times and catalyst loadings in sluggish acid / base reactions.[16] Pleasingly, exploration of the BIMP family allowed identification of **11** as the optimal catalyst scaffold, allowing good conversion to the product in 24h with as low as 5 mol% catalyst. Tuning the iminophosphorane basicity by varying the substituents of the triaryl phosphine moiety, showed a substantial effect on both reactivity and enantioselectivity. After optimization and scale up using catalyst **11a** — generated in situ from azide **12** and triphenylphosphine **13** — the IMDAF cascade product 8 was delivered in 86% yield, 92:8 dr and 90% ee on multigram scale.

To further understand the nature of this reaction, the prototropic shift / IMDAF reaction sequence was investigated using DFT calculations.[17] With DABCO as catalyst, the transition structures (TSs) for α-deprotonation and subsequent γ-reprotonation are 24.2 and 23.6 kcal/mol, a feasible process at 50 °C. The IMDAF reaction is more facile (22.4 kcal/mol) and highly exo-diastereoselective (by more than 10 kcal/mol). Isomerization with BIMP catalyst **11a** proceeds with a more facile proton abstraction due to its greater basicity than DABCO, ensuring that reprotonation is the overall rate-limiting and stereo-determining step. The bifunctional catalyst engages the substrate with a dual H-bonding interaction from both amide N-H and aryl C-H bonds. One of the CF_3 groups comes into close contact with a substrate CH_2 group in this binding mode forming the major (S)-enantiomer: in the minor pathway, a methyl group must be accommodated in this position which results in substantial reorganization and longer (i.e. weaker) H-bonds to the catalyst. The minor reprotonation TS is disfavoured by 3.4 kcal/mol.

With the successful development of an expedient and enantioselective synthesis of the tricyclic core, synthetic efforts continued towards the natural product target. The enantioenriched IMDAF tricyclic product **8** was treated with trifluoroacetic acid to effect a ring opening isomerization of the aminal bridge, giving an enamide product **14** from which subsequent diastereoselective hydrogenation with Pearlman's catalyst gave **15**. Propargylation

of this material then yielded **16** in 83% yield over 2 rounds, and at this juncture, the enantiomeric purity of the product was upgraded to >99% ee by recrystallisation.



Scheme 1. Synthetic route to (−)-himalensine A from IMDAF cascade product 8. a) quad-skin balloon pressure. b) double-skin balloon pressure. c) single-skin balloon pressure. 9. TFA, CH_2Cl_2, then $Pd(OH)_2$, MeOH, H_2, 63%. 10. NaHMDS (2 equiv.), DMF, then propargyl bromide, 0 °C, 83%. 11. $LiAlH_4$, THF, -10 °C, then MeOH, HCl_{aq}, to separated β-hydroxyl, MsCl, Et_3N, CH_2Cl_2, 95% total. 12. TIPSOTf, lutidine, CH_2Cl_2, 86%. 13. Bu_3SnH and AIBN slow addition, toluene, 90 °C, 80%. 14. CSA, CH_2Cl_2, 0 °C, 97%. 15. Crabtree's catalyst (20 mol%), H_2:Ar [1:2, single-skin balloon pressure], CH_2Cl_2, 92%, >20:1 dr. 16. NBS, CH_2Cl_2, 82%. 17. pyridine, PTSA (excess), O_2, reflux, 65%. 18. NaHMDS, THF, then $PhNTf_2$, 58% (86% brsm). 19. $Pd_2(dba)_3$, DTBPF (1,1'-bis(di-*tert*-butylphosphino)ferrocene), NMP then alkylzinc bromide, 96%. 20. HCl_{aq}, THF, 87%. 21. thiazolium catalyst (30 mol%), Et_3N, EtOH, 60 °C, 75%. 22. Vaska's catalyst (10 mol%), TMDS (1,1,3,3-tetramethyldisiloxane), toluene, then MeOH, formic acid, 60 °C, 67%.

NMR and X-ray analysis of this product revealed the 1,3-diketone moiety existed completely in the ketoenol form with the hexanone carbonyl exclusively enolized. Exploiting this asymmetry, the heptanone carbonyl was selectively reduced using lithium aluminium hydride via *in situ* protection of the hexanone ketone as its enolate. Aqueous HCl work-up conveniently facilitated elimination of water affording the desired enone product **17** in good yield. The structure of **17** was confirmed by single crystal X-ray analysis.

Despite enone **17** possessing the necessary functionality for a ketone / alkyne cycloisomerization,[18] we found successful C-C bond formation was only possible via a reductive radical cyclization approach;[11b, 19] the first of its kind to construct a morphan core. The substrate required for this reaction was synthesized by treatment of enone **17** with TIPSOTf to give TIPS protected product **18** in high yield. This key precursor was then treated with tributyltin hydride and AIBN to effect a radical addition / cyclization / reduction sequence to construct the B ring. Due to steric crowding of the TIPS group, the tributyltin radical underwent selective addition to the terminal alkyne, triggering the cyclization /reduction cascade, giving **19a**. The accessory tributyl tin group was subsequently removed by protodemetallation using camphor sulfonic acid to forge tetracycle **19b** in 78% over two steps.

To set the stereogenic center bearing the methyl group on the piperidine ring, a highly diastereoselective hydrogenation of the 1,1'-disubstituted alkene functionality from the concave face of the tetracycle was required. With heterogeneous catalysts such as Pd/C or Raney nickel, hydrogenation occurred exclusively from the convex face of the molecule, giving the undesired diastereomeric product. To deliver hydrogen from the concave interior, we envisaged using the lactam carbonyl as a Lewis basic directing group. Inspired by Li in his synthesis of daphenylline and more recent work,[8a, 11d] we turned to Crabtree's catalyst, and more promising results, with good yield and 7:3 dr favouring the desired diastereomer, were obtained at 1086 mbar hydrogen pressure. This encouraging but imperfect diastereoselectivity showed delivery of hydrogen from the convex face was still in operation, and binding of hydrogen to the catalyst in preference to the 'directing' lactam carbonyl was implicated. Accordingly, the hydrogenation was investigated at reduced partial pressure of hydrogen, and pleasingly optimal results were obtained using a 1:2 H_2/Ar gas mixture at 1029 mbar pressure, which yielded the desired product **20** in 92% yield and in excellent diastereoselectivity. Subsequent bromination of the resulting enol silane afforded bromide **21** in 82% yield.

Treatment of **21** with excess pTSA in refluxing pyridine under an oxygen atmosphere smoothly facilitated an E2 elimination of hydrogen bromide followed by aerobic γ-oxidation of the resulting enone **22**, affording enedione **24** in 65% yield. This novel reaction is the first report of an α-bromoketone to enedione transformation, and conveniently installs in the ketone functionality required to construct the final E ring. Originally, we aimed to perform the elimination and oxidation in two separate steps,[20] but the serendipitous discovery of the oxidation product in trace amounts (<5%) from refluxing bromide **21** in pyridine led us to develop the tandem process. Our investigations showed addition

of Brønsted acid was necessary for smooth conversion to oxidized enedione **24**, without which the reaction would stall at the enone stage. This observation, pointed to the oxidation mechanism proceeding through hydrogen atom abstraction of the extended enol **23**, followed by γ-radical combination with oxygen and Kornblum DeLaMare rearrangement.[21]

With enedione **24** in hand, we entered the final stage of the synthesis. Strategically, if the heptenone ketone moiety could be converted into the vinyl triflate, then the final 3 carbon atoms – required to complete the 5th and final ring through a Stetter cyclization – could be brought in through a coupling reaction, whilst maintaining the redox level required for the final natural product. Along these lines, treatment of **24** with NaHMDS and enolate quench with $PhNTf_2$ gave vinyl triflate **25** which was subjected to a palladium catalyzed sp^2-sp^3 Negishi coupling reaction to give **26** in excellent yield and subsequent aqueous acid deprotection of the acetal group gave aldehyde **27**. A Stetter cyclization and concomitant base induced double bond isomerism to the thermodynamically preferred conjugated enone **28**, completed the construction of the total carbon skeleton in 75% yield. The structure of **28** was confirmed by single crystal X-ray analysis.

The final transformation — the highly chemoselective reduction of the lactam carbonyl group — was then realized using Vaska's catalyst $[IrCl(CO)(PPh_3)_2]$ at 10 mol% loading and TMDS as the terminal reductant, without competitive reduction of the two sensitive ketone functionalities and alkene moiety.[22-23] The amide functionality was carried through the synthesis from the start, acting as a protecting group for the sensitive bridgehead amine, which may otherwise have interfered with metal catalyzed and oxidation reactions. By titrating TMDS into the reaction against conversion of starting material, a chemoselective reduction of the lactam amide was readily performed. The intermediate hemiaminal species formed from initial Vaska reduction was further reduced in hot formic acid to deliver (−)-himalensine A (**1**) in 67% and thus complete the 22-step synthetic sequence.

In conclusion, we report the first enantioselective total synthesis of (−)-himalensine A in 22 steps. This synthesis was enabled by the development of new synthetic methodologies, such as the catalytic, enantioselective prototropic shift / IMDAF cascade reaction for the construction of the ACD ring system and a sulfonic acid catalyzed oxygen mediated γ-CH oxidation of a conjugated enone. These new methods have not only made possible the first total synthesis of (−)-himalensine A, but will likely find great appeal and utility within the wider synthetic community.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, analytical data (^1H, ^{13}C NMR, MS) for all new compounds and computational calculations (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interests.

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