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Enantioselective Organocatalytic Reaction Cascades of Substituted Pyrroles and their Application in Complex Alkaloid Natural Product Synthesis

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Enantioselective Organocatalytic Reaction Cascades of Substituted Pyrroles and their Application in Complex Alkaloid Natural Product Synthesis

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(University of Oxford)

1. WORK PROGRESS AND ACHIEVEMENTS DURING THE PERIOD:

INTRODUCTION

Our proposal is based on the development of new, enantioselective cascade reactions towards the perhydroindole ring structure, a saturated 6,5-fused bicycle containing a nitrogen at the 1-position (Figure 1, in red). This chemical motif is present in several complex alkaloid natural products, such as daphniyunnine B (**1**) and daphniyunnine D (**2**), both members of the daphniyunnine family. Daphniyunnine B and D were first isolated in 2006 from *Daphniphyllum yunnanense*[1] and they show interesting anti-cancer properties. Despite the efforts of many research groups from all over the world, their synthesis still remains a major challenge for the synthetic organic community.

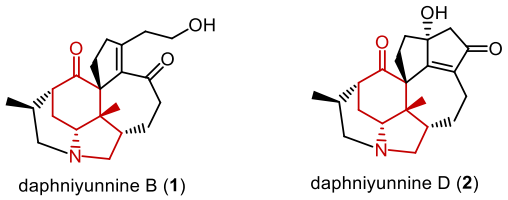


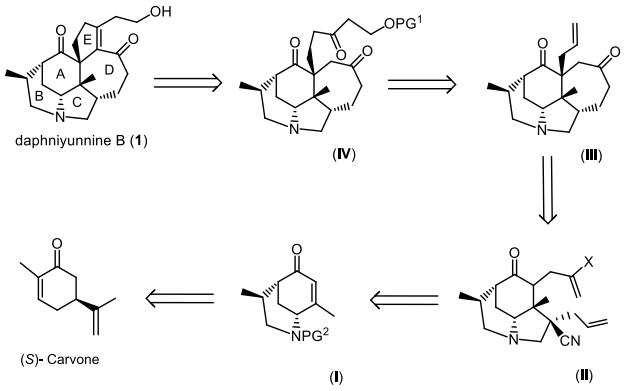
Figure 1. Representative examples of Daphniyunnine-alkaloids

Specifically, we wanted to develop a new asymmetric, organocatalysed Michael, Michael cyclisation cascades of substituted pyrrole substrates with α,β-unsaturated ketones to rapidly access the perhydroindole scaffold. However, our cascade design was partially covered by a report that appeared in the literature.[2] In view of this unexpected publication we envisioned a different approach for the synthesis of perhydroindole ring structure and focused our attention on the synthesis of daphniyunine B.

The retrosynthetic analysis for daphniyunnine B identified the tetracyclic core structure **III** (Scheme 1) as an advanced precursor, bearing all the stereocenters present in the target molecule. Further functionalization of the double bond could lead to substrates of type **IV** and subsequently formation of ring E could be achieved *via* intramolecular aldol condensation. On the other hand, ring D would be installed through intramolecular ring closing metathesis (RCM) from precursor **II** and the five-membered C ring through

[1] Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 553.
[2] Yang, J.; Huang H.; Jin Z.;Wu W.; Ye W. *Synthesis*, **2011**, 1984

intramolecular Michael addition using methodologies previously developed in our group. [3]

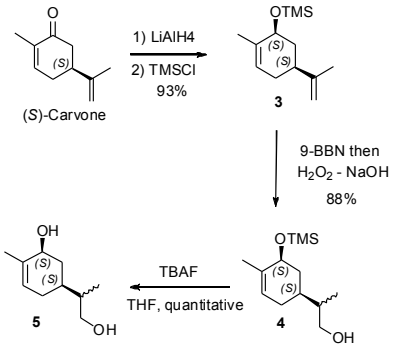


Scheme 1 Retrosynthetic analysis for daphniyunnine B

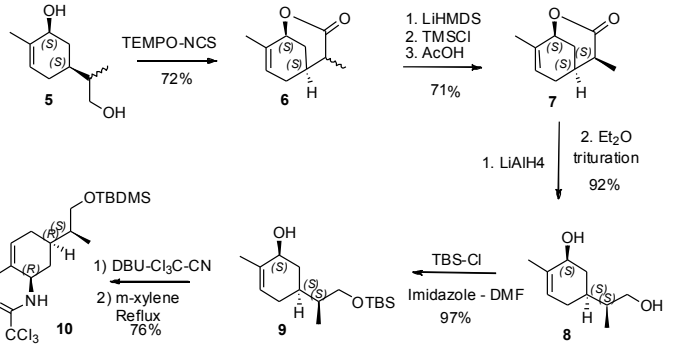
Results and discussion:

A) Optimisation and scale up of a synthetic route towards the tetracycle III

The route started with the reduction of (*S*)-carvone followed by TMS-protection of the resulting secondary alcohol in a two-step sequence without any need for purification and in 93% overall yield. This protocol was efficiently performed in 20 g scale. Hydroboration and oxidative cleavage of the double bond leading to the mixture of diastereomers **4** proceeded smoothly and proved to be an easily scalable reaction. The subsequent cleavage of the silyl ether with TBAF/THF afforded the desirable diol **5** quantitatively. Some epimerization was observed when the removal of the silyl group was tried under slightly acidic conditions, i.e., PPTS/MeOH.



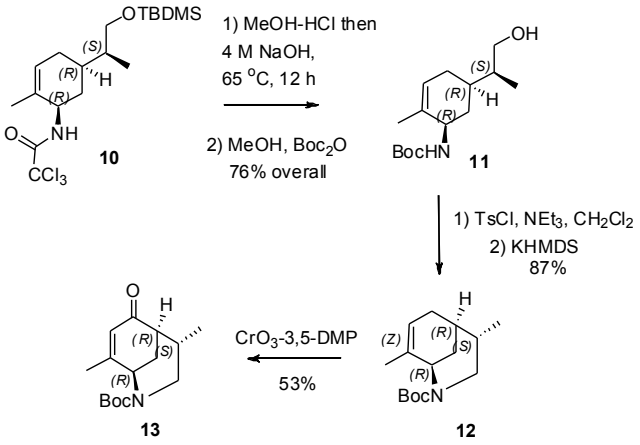
Submission of the diol **5** to standard conditions for TEMPO oxidation led to the selective oxidation of the primary alcohol to the aldehyde followed by an intramolecular nucleophilic attack of the secondary alcohol to render a cyclic hemiacetal. The subsequent oxidation of this specie afforded the epimeric lactones **6**. Pleasingly, the product was obtained in one-pot procedure in 72% yield. Conversion of the diatereomeric mixture to the optically pure lactone **7** was performed under kinetic control. Reduction of the obtained product with $LiAlH_4$ afforded the crystalline diol **8** in quantitative yield. The spectroscopic data and



[3] Sladojevich, F.; Michaelides I. N.; Benjamin B.; Ward, J. W.; Dixon, D. J. *Org. Lett*. **2011**, *13*, 5132.

optical rotation of compound **8** perfectly matched those reported in the literature.[4] Selective TBS-protection of the primary alcohol was accomplished in excellent yields. Interestingly, attempts to form the analogous TBDPS-derivative was unsuccessfully tried. The key Overman rearrangement for the introduction of the amino functionality with the required stereochemistry was performed as reported previously for a similar system and afforded the formation of the trichlororoacetamide **10** in good yield.[5] The imidate, which is an intermediate in this procedure proved to be extremely sensitive to silica gel and its purification through flash column chromatography should be performed very quick in order to get the best overall yields.

Cleavage of the TBS group and basic hydrolysis of the trichoroacetamide amide **10** followed by Boc-protection afforded the alcohol **11** in 76% overall yield. The exhaustive extraction of the amino-alcohol from the aqueous mixture after the basic hydrolysis determines the yield of this three-step sequence. Introduction of the tosyl group followed by an intramolecular cyclization under basic conditions led to the formation of bicycle **12** with retention of stereochemistry. The important allylic oxidation of substrate **12** was first tried using several methodologies based on *tert*-butyl hydroperoxide (TBHP) as the oxidant and in combination with a metal catalyst such as copper iodide,[6] dirhodium caprolactamate,[7,8,9,10,11] chromium compounds,[12] palladium(II) salts[13] or manganese(III) acetate.[14] Unfortunately, the desired product **8** was either obtained in very low yield and with the formation of several side products, or no reactivity was observed at all. Alternatively, the oxidation of the more reactive allylic position to the alcohol was attempted by with SeO_2 either in catalytic or stoichiometric amounts.[15,16] None of these methods showed selectivity in the oxidation and undesirable side products were obtained. Lack of selectivity was also observed when NBS was tried for the allylic oxidation.[17] The best results for the selective allylic oxidation of substrate **12** were obtained by the use of CrO_3 and 3,5-DMP in CH_2Cl_2. However, the high toxicity associated to Cr (VI) compounds constitutes a drawback of this methodology.



[4] Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Org. Chem*. **2009**, *74*, 5458.
[5] Chen, X.; Zheng, L.; Huifei, W.; Zhang, Z.; Xiang, Z.; Hao, X.; Wang, Z. W. *Org. Lett*. **2011**, *13*, 1812.
[6] Salvador, J. A. R.; Sa e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett*. **1997**, *38*, 119.
[7] Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc*. **2004**, *126*, 13622.
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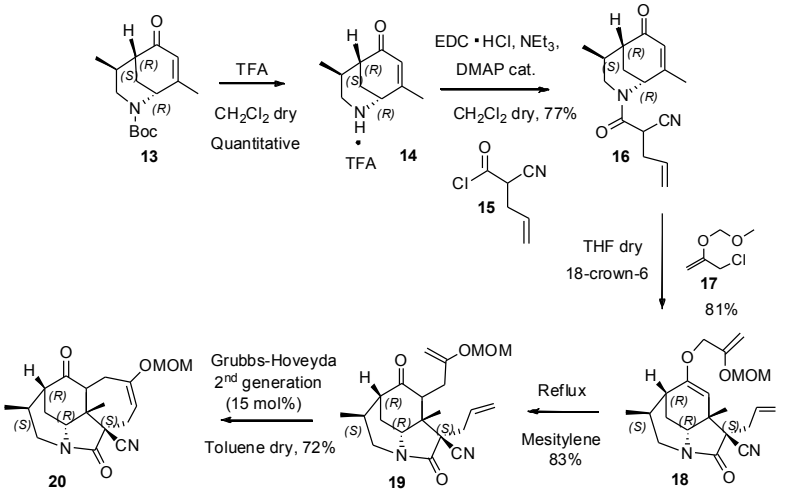
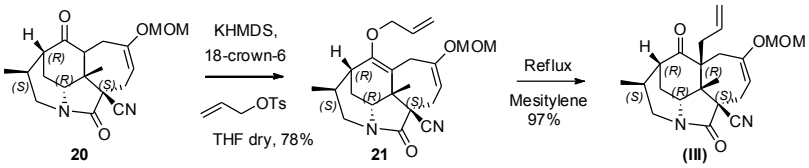
[9] Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett*. **2005**, *7*, 5167.
[10] McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem*. **2009**, *74*, 730.
[11] McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317.
[12] Muzart, J. *Chem. Rev.* **1992**, *92*, 113.
[13] Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232.
[14] Shing, T. K. M.; Yeung, Y.-Y.; SU, P. L. *Org. Lett*. **2006**, *8*, 3149.
[15] Umbreit, M. A.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
[16] Hirai, S.; Nakada, M. *Tetrahedron*. **2011**, *67*, 518.
[17] Ziegler, F. E.; Sobolov, S. B. *J. Am. Chem. Soc.* **1990**, *112*, 2749.

Following the above described synthetic path, 2.5 g of the bicyclic product **13** were prepared in 10% overall yield.

Boc deprotection of the bicycle **13** led to the trifluoroacetate salt **14,** which smoothly reacted with acid chloride **15** to provide amide **16** as a mixture of two inseparable diastereomers. When amide **16** was treated with KHMDS in THF, it was cleanly converted to the expected Michael addition product with complete stereocontrol. A more convenient approach is to perform a tandem enolate allylation reaction through sequential addition of KHMDS followed by **17** and catalytic 18-crown-6 ether. This protocol allowed the isolation of enol ether **18** in 81% yield, as a single diastereomer, starting from precursor **16**. Heating enol ether **18** in refluxing mesitylene rendered the Claisen product **19** which was perfectly poised for the subsequent RCM step. Refluxing **19** in dry CH_2Cl_2 with 15 mol% of Grubbs-Hoveyda II catalyst furnished the tetracyclic core **20** in good yield. Allyltosylate and catalytic 18-crown-6 furnished the *O*-alkylated product **21** upon reaction with **20** in excellent yield and with complete regioselectivity. Subsequent Claisen rearrangement afforded the carbon allylated product in 78% yield. Overall, the preparation of the tetracycle **III** could be accomplished in 21 steps from commercially available materials through a synthetic route that proved to be scaleable.



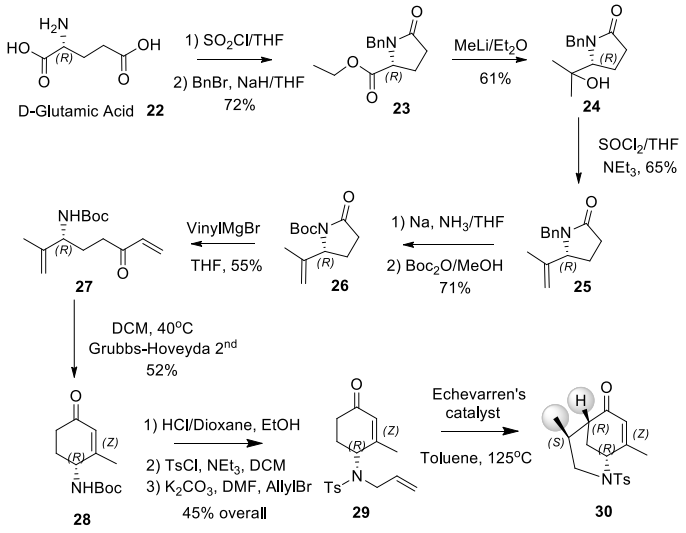


B) An attempt to synthesise a bicycle of type I *via* a gold-catalysed cyclisation as the key step.

As highlighted above, compounds of type I (Scheme 1) are extremely important in our synthetic design. Although bicycle **13** was prepared on a multi-gram scale, we were still in need of a more straightforward pathway towards its synthesis. Consequently, we envisioned a new synthetic route involving a late stage gold-catalyzed cyclization as the key step (shown below).

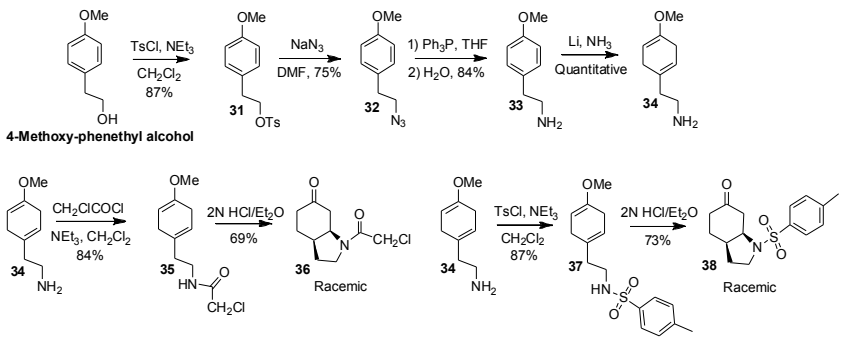
Our synthetic path started with the one-pot esterification and intramolecular cyclization of commercially available D-glutamic acid to render (*R*)-Pyroglutamic ethyl ester in quantitative yields. Amide bond alkylation proceeded smoothly under standard conditions to give the functionalized lactam **23**. As expected, a chemoselective double addition of methyl lithium on this substrate led to the desired secondary alcohol **24** in 61% yield. Gratifyingly, formation of alkene **25** was promoted by activation of the

alcohol moiety of precursor **24** with thionyl chloride followed by slow addition of triethylamine. Notably, under these conditions the desired regioisomer was only obtained. The internal, more substituted alkene was the major product when other standard elimination reagents were tried. At this stage, ring-opening of the lactam **25** was unsuccessfully attempted. Alternatively, cleavage of the benzyl group followed by introduction of the Boc-protecting group to give carbamate **26** was accomplished in 71% yield over the two steps. Pleasingly, vinyl addition proceeded then under mild conditions but in moderate yields. RCM on diene **27** with Grubbs-Hoveyda II catalyst led to the enantiomerically pure cyclohexenone **28**. The optical purity of this compound was determined by HPLC analysis, in comparison with its racemic counterpart. Completion of the synthesis was accomplished by taking advantage of a gold-catalysed cyclisation from the *N*-tosylate amine **29**. This precursor proved to be very reactive towards the cyclisation reaction, whereas the *N*-Boc protected analog appeared to be inert under the same reaction conditions. Unfortunately, the desired compound **30** was only obtained as the minor product of the gold-catalysed cyclisation reaction and with the *trans*- diastereomer (i.e. in regard to the relative stereochemistry of the methyl group and the hydrogen on the newly generated stereogenic centers) as the favoured product. A wide range of catalysts and reaction conditions were tried in order to tune the diastereoselectivity of this cyclisation. Unfortunately, from sulfonamide **29,** the best results only afforded the bicycle **30** in a synthetically useless diastereomeric ratio of 1:7 (i.e favouring the wrong diastereomer). To overcome this issue several alternative strategies are currently ongoing in the Dixon research group.



C) Development of a reaction cascade towards the perhydroindole ring structure.

Initial studies focused on the development of a new reaction cascade towards the perhydroindole ring structure were performed. The proposed synthetic path relies on the Birch reduction of 4-methoxyphenethyl amine **33** which was prepared through a three step sequence and from commercially available 4-methoxyphenethyl alcohol. A reaction cascade starting from either **35** or **37** was discovered. Enol ether hydrolysis, double bond migration and an intramolecular Michael addition rapidly occurred under anhydrous acidic conditions leading to the formation of a saturated 6,5-fused bicycle containing a



nitrogen at the 1-position. The reaction cascade tolerates different types of substitution at the amino functionality. As expected, the single formation of the *cis*-diastereomer was observed. Studies oriented towards the development of an enantioselective variant of this kind of cyclisation are in progress.

2) Summary of the progress of the research training

2-1) Attendance to seminars and conferences

During my fellowship, I have had the opportunity to attend research seminars held by the Department of Chemistry in many aspects of chemistry given by leading academic visiting lecturers. I have also attended Oxford University training courses in career management and intellectual property rights and the 2012 Bristol Synthesis Meeting.

2-2) Research Skills and techniques:

This Marie Curie fellowship has allowed me to develop new skills that complement those that I already possessed. During this period I have acquired knowledge related to the field of total synthesis. Thus, the development of this project has provided me with an opportunity to learn and develop state-of-the-art methods available in this field.

2-3) Communication skills:

Results, progress and the work plan for the near future have been discussed on a weekly basis, and the presentation of results to the group have been made every week following the group's usual timetable. Weekly group meetings offered the opportunity for in-depth discussions involving all post-doctoral and post-graduate workers. In addition, weekly one-to-one meetings with Prof. Dixon have been regularly used to discuss progress, strategy and the direction of my research.