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PERSPECTIVE

One-pot quadruple/triple reaction sequence: A useful tool for the synthesis of natural products

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Multiple reactions in one pot has always been a useful technique for synthetic organic chemists, as it can minimizes the solvent usage, time and the number of purification steps when compared to individual multi-step syntheses. In line with this, here in this perspective we discuss a one-pot quadruple/triple reaction sequence comprising an enyne ring-closing metathesis/cross-metathesis/Diels-Alder/aromatization for the synthesis of natural products setting.

Introduction

One pot reactions are a set of reactions where a sequence of chemical transformations performed in the same reaction flask. They are broadly classified into two categories: Domino/cascade reactions in which the starting substrates are designed to undergo several reactions without the additional reagents or catalysts. The second class is performing multiple reactions in a one-pot process in which additional reagents and catalysts are added at different time points. The first kind is extensively studied and was reviewed several times in the literature.[1] The second category is underexplored and recently started gaining momentum.[2] The concept "pot economy" was introduced by Clarke *et al.*,[2c] in which we need to complete as many sequential synthetic transformations in the same reaction pot without the need for work-up and product isolation between successive steps. This effort can dramatically reduce the amount of solvents used in reactions, in work-up during the product isolation and purification of intermediate products. Additional benefits are reduction of various materials used in chromatographic purification, contaminated aqueous waste generated while cleaning glassware, time required to do multiple operations *etc*. Recently, we and others have demonstrated the use of one-pot quadruple/triple reaction sequence comprising enyne ring-closing metathesis/cross-metathesis/Diels-Alder/aromatization

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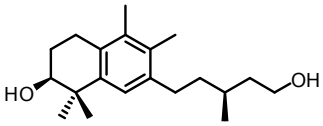
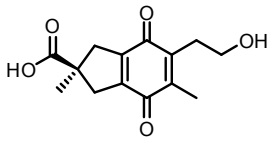
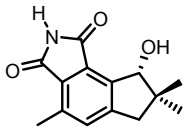


isofregenedadiol (**1**)



puraquinonic acid (**2**)



norsesquiterpene alkaloid (**3**)

Figure 1: Structures of natural products

D. Srinivasa Reddy received his Ph.D. in 2000, under the supervision of Professor Goverdhan Mehta from University of Hyderabad, Hyderabad, India. He was a postdoctoral research fellow at the University of Chicago (Prof. Sergey A. Kozmin), Chicago, USA (2000-2001), followed by at the University of Kansas (Prof. Jeffrey Aubé), USA (2001-2003). Later he moved back to India to work in Dr. Reddy's Laboratories followed by TATA Advinus (2003-2010). During the 7 years of stay in drug discovery pharma industry, he successfully led two drug discovery programs. One of the molecules he discovered is currently in human clinical trials (Phase-II). Then he moved to academics in the year 2011 and currently working in CSIR-National Chemical Laboratory, Pune, India. His main research interests are synthesis of biologically active natural products and medicinal chemistry. He is the recipient of CDRI Award 2013 for Excellence in Drug Discovery Research (Chemical Sciences) and NCL- Research Foundation Scientist of the Year Award 2013. He is an author of more than 55 scientific publications and inventor on 30 patents.

reactions during the total synthesis of natural products.[3-5] The metathesis and Diels-Alder reactions are well explored reactions in organic synthesis to form a carbon–carbon bond. The combination of these reactions were elegantly used by several groups to form different molecular frameworks either stepwise manner or in one-pot process.[3-7] Although, the combination of these reactions were used for the synthesis of different molecular architectures, their use in synthesis of natural products is very limited. In this perspective, we discuss the synthesis of three biologically interesting natural products isofregenedadiol,[3] puraquinonic acid[4] and a norsesquiterpene alkaloid[5] (Figure 1) using the one-pot quadruple/triple reaction sequence. This effort needs to be highlighted so as to encourage the use of greener practices in total synthesis of natural products.

A common strategy was used to synthesize the main core of all the three natural products listed above and the strategy used for the synthesis is depicted in forward synthetic manner (Figure 2). An enyne can undergo ring closing enyne metathesis (RCEM) and/or cross metathesis (CM) to afford a diene which can be reacted with a dienophile followed by oxidation to furnish aromatic skeleton (Figure 2).

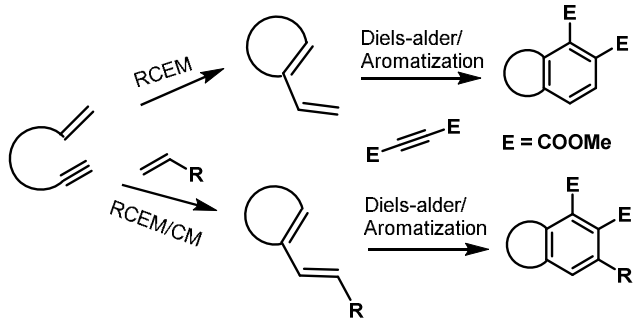
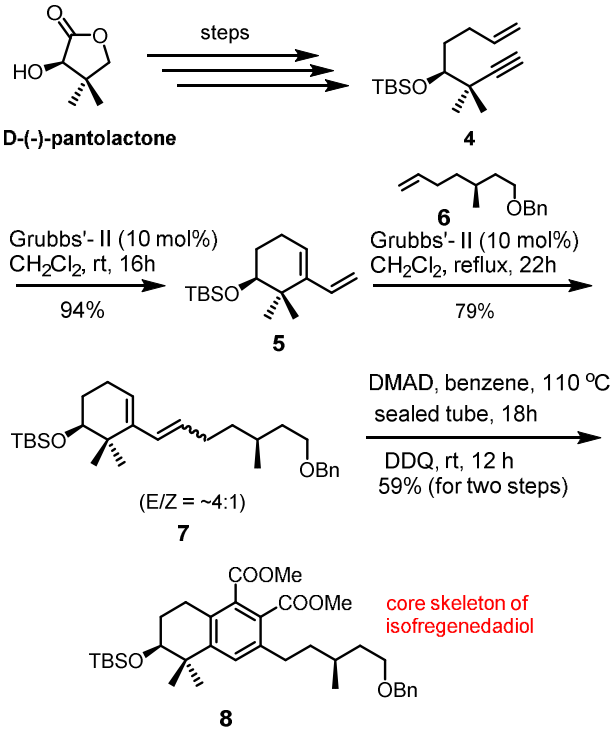


Figure 2: Common strategy followed to access the core skeleton of natural products.

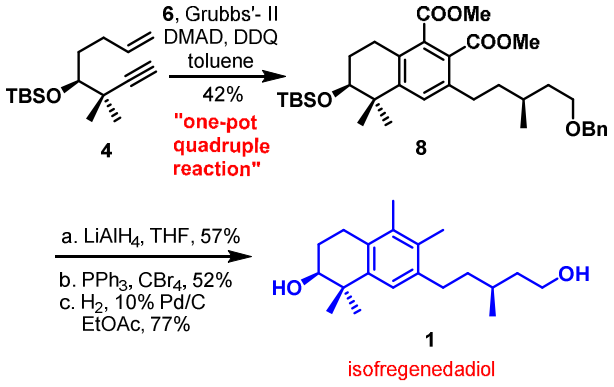
Total synthesis of isofregenedadiol

The first total synthesis of biogenetically interesting isofregenedadiol, a bicyclic diterpene, was reported by our group in 2011.[3] The synthesis commenced from a commercially available D-(-)-pantolactone, a favourite chiral building block for this group.[8] The D-(-)-pantolactone was converted into the desired enyne **4** by standard functional group transformations. Initially, we synthesized the desired tetrahydronapthalene skeleton in a sequential manner as shown in Scheme 1. Enyne **4** in the presence of Grubbs' second generation catalyst, underwent RCEM to produce diene **5** in 94% yield. Compound **5** on cross metathesis with olefin **6** afforded diene **7** in 79% yield, which on Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD), followed by aromatization using DDQ, furnished the desired tetrahydronaphthalene derivative **8** in 59% yield for two steps. Having established the route in sequential manner, we attempted the planned key one-pot quadruple reaction sequence. After a few trials, the planned one-pot sequence proceeded smoothly to furnish the desired tetrahydronaphthalene derivative **8** in 42% overall yield (Scheme 2). The reaction times were chosen



Scheme 1: Synthesis of isofregenedadiol skeleton through sequential manner

for the addition of subsequent reagents and catalysts based on thin-layer chromatography (tlc) monitoring at each step. Although, the obtained yield was moderate, it was very similar (44% *vs* 42%) to the overall yield obtained in 4 steps., By this process we could save time, solvent, materials required for chromatography at each step *etc*. Both carboxylic esters present in compound **8** were transformed to methyl groups and ultimately to the natural product isofregenedadiol **1** with the help of three additional steps ($LiAlH_4$ reduction, diol to dibromide and hydrogenation).

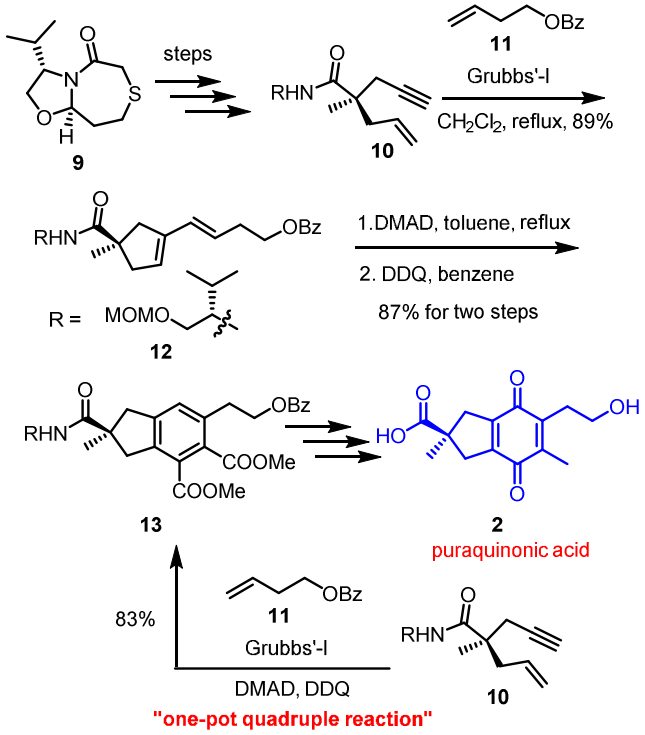


Scheme 2: Synthesis of isofregenedadiol through One-Pot quadruple reaction process

Total synthesis of puraquinonic acid

The same one pot quadruple reaction sequence strategy was used by Gleason *et al.* in the total synthesis of anti-cancer natural

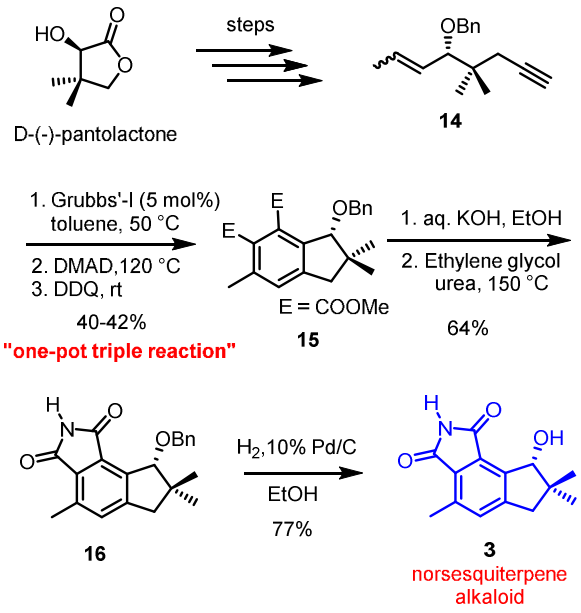
product puraquinonic acid in 2013.[4] The synthesis started from the conversion of **9** to enyne **10** in five steps. Initially they attempted ring-closing enyne/diene–ene cross metathesis of **10** with 3-buten-1-ol using Grubbs first/second-generation catalyst afforded only intramolecular enyne metathesis product and the homodimer of 3-buten-1-ol with no desired cross-metathesis products. However, replacement of 3-buten-1-ol with its benzoate ester **11** in the same metathesis conditions, afforded the desired cross metathesis product **12** in 89% yield as a single *E* isomer. Compound **12** on Diels–Alder reaction with DMAD followed by DDQ oxidation furnished the desired indane skeleton **13** in 87% yield. After having **13** in hand, they have attempted one pot quadruple reaction sequence, where they have performed enyne/cross metathesis in dichloromethane solvent followed by switching of solvent to the toluene for Diels-Alder and DDQ oxidation to afford the densely functionalized indane **13** in 83% yield. Compound **13** was used for the completion of the total synthesis of natural product puraquinonic acid (Scheme 3).



Scheme 3: Utilization of one-pot quadruple reaction strategy in total synthesis of puraquinonic acid.

Total synthesis of norsesquiterpene alkaloid

Very recently, the first total synthesis of an anticancer norsesquiterpene alkaloid (*R*)-8-hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]isoindole-1,3(*2H,6H*)-dione, in both racemic and enantiomeric pure forms, was accomplished by our group.[5] The synthesis features a one-pot, three-step reaction sequence comprising an enyne RCM/Diels-Alder/aromatization to construct the desired indane skeleton present in the natural product **3** (Scheme 4). The synthesis began with the preparation of key enyne intermediate **14** from D-(-)-pantolactone. Enyne **14** upon RCM using Grubbs' 1st generation catalyst followed by Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) and subsequent treatment with DDQ, provided the aromatized compound **15** in moderate yield (~40%). The indane derivative **15** on ester hydrolysis, heating with urea in ethylene glycol followed by benzyl deprotection furnished the norsesquiterpene alkaloid.



Scheme 4: Enantiospecific total synthesis of norsesquiterpene alkaloid using one-pot triple reaction strategy

Conclusion

Organic synthesis is continuously evolving to cater to the needs of a changing society. One of such advancements in that direction is implementing green chemistry practices wherever possible during the course of target molecule synthesis. This effort led to an increase in the use of tandem reactions, which combine multiple reactions in a one-pot process, for the synthesis of complex molecules, in particular, in total synthesis of natural products. In that direction, recently, our own research group was able to demonstrate the use of a one-pot quadruple/triple reaction sequence comprising of enyne ring-closing metathesis/cross-metathesis/Diels-Alder/aromatization for the synthesis of natural products like isofregenedadiol and a norsesquiterpene alkaloid. The same one-pot quadruple reaction sequence strategy was used by Gleason *et al*. in their synthesis of puraquinonic acid. This clearly suggests that the one-pot process that combines several reactions is feasible in the synthesis of natural products. We do understand that there are some limitations where we can only combine certain types of reactions. As we all are striving for making better processes for a better society, more efforts in this direction will certainly overcome these limitations by altering reaction conditions, by choosing appropriate solvents/reagents/catalysts, by using appropriate devices, *etc*. At this stage, these efforts may look small and only incremental, we are confident that in the future these practices will have significant impact and efforts in this direction will be appreciated and rewarded.

Acknowledgement

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