Synthesis of Norpyrenophorin, Hydroxy β-Sanshool and ZP amide-I *via* Ru-Catalyzed C-H Activation

Objective:

This project demonstrate an ideal synthetic strategy for the synthesis of pharmaceutically valuable compounds using novel Ru-catalyzed carbon-carbon bond formation reaction as a key chemical transformation starting from inexpensive raw materials. Norpyrenophorin is a synthetic 16-membered macrolactone which has essentially the same physiological activity as the natural fungicide pyrenophorin and the antibiotic vermiculine. Hydroxy β-Sanahool and ZP amide-I are the pungent *Zanthoxylum* derived alkylamides possess significant academic and industrial interest due to the universal interest for both culinary and medicinal applications. Therefore, the development of highly atom-/step economical catalytic strategies using commercially available starting materials are desirable and their application to the synthesis of bioactive and natural products is highly encouraged. Hence we have developed novel methods for the carbon-carbon bond forming reaction via Ru-catalyzed C-H activation of allyl silanes/allyl acetates/allyl alcohols followed by cross coupling reaction with activated olefins and their synthetic utility has been demonstrated by the efficient and straightforward synthesis of norpyrenophorin, hydroxy β-sanahool and ZP amide-I.

Introduction:

Macrodiolides (macrocyclic dilactones) are well represented in nature as both homo- and heterodimers and offer a wide variety of skeletons, ring sizes, and functional groups. Molecules belonging to the medium and large size rings lactones have attracted considerable attention from synthetic chemists due to their interesting biological properties.[1] Particularly, natural products with macrodiolide frameworks are also known to exhibit a wide range of biological properties including antibiotic, antifungal, anthelmintic, phytotoxic, and antileukemic activities.[2] Norpyrenophorin **1** is a synthetic, unnatural 16-membered achiral macrolactone has a structural as well as physiological correlation with two simple natural, chiral macrocyclic dilactides such as pyrenophorin **2**, a good antifungal and herbicidal agent which has been isolated from *Pyrenophora avenae* and (-)-vermiculine **3**, a crystalline antibiotic substance, shows cytotoxic activity and isolated from *Penicillium vermiculatum* dangeard (figure 1).[3] These C2-symmetric

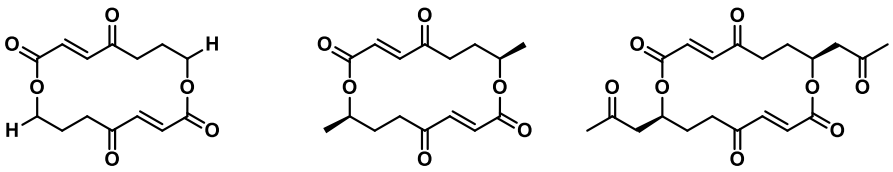


Figure 1: Structures of norpyrenophorin **1**, pyrenophorin **2** and (-)-vermiculine **3**

dilactones is derived by head to tail dimerization of two identical C8 units. The potent biological activities and interesting structural features made attractive targets for the total synthesis. A number of synthetic routes are reported toward the synthesis of these compounds.[2,3] Most of the reported methods associated with longest linear sequence, harsh reaction conditions and following protection-deprotection strategies, which diminishes atom- and step economy as well as practical efficiency of the synthetic method. To overcome the aforementioned problems associated with the above methods, we have developed a novel, straightforward and five step strategy for the synthesis of norpyrenophorin **1** via transition metal catalyzed C-H functionalization of small molecules.[4]

Similarly, the past decade has a witnessed remarkable enhancement in academic and industrial interest for pungent Zanthoxylum-derived alkylamides, due to the universal interest for both culinary and medicinal applications.[5] Since

there is a concomitant momentum in studies aimed for understanding the specific biochemical mechanisms behind several medically-relevant biological activities controlled by the natural products. Due to rapid increase in interest, there is a demand for developing synthetic routes for accessing these natural products and related analogs in multigram quantities. It is observed that the olefin geometry of long-chained polyunsaturated amides can dramatically alter both the degree and specific nature of the observed biological activities; thus, it is important to have diastereomerically pure compounds for all biological studies. Hence, many synthetic routes have been developed for the synthesis of different members of this family by following traditional functional group transformation strategies.[5a] Sanshools are the main isobutylhydroxyamides found in the pericarp of the fruit, Szechuan pepper (*Zanthoxylum piperitum*). Herein, we demonstrated shortest synthetic routes for two natural products, Hydroxy β-Sanshool **4** and ZP-Amide I **5**, in a highly diastereoselective manner via Ru-catalyzed C-H activation of allyl alcohols followed by oxidatively coupling with activated olefins (figure 2).[6]

Hydroxy β-Sanshool (4) ZP-amide I, (5)

Figure 2: Structures of Hydroxy β-Sanshool **4** and ZP-Amide I **5**

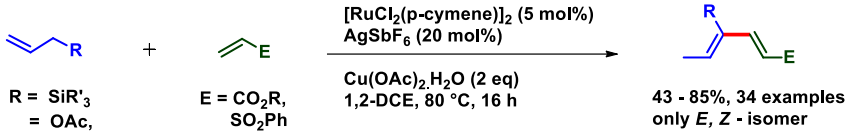
Development of novel approaches for the carbon−carbon bond formation is a continuous process in organic synthesis. So, several synthetic approaches for C-C bond forming reaction have been reported such as Wittig reaction, olefin metathesis, metal-catalyzed cross-coupling reactions, and many more.[7] However, many of these methods suffer from poor atom economy and use of toxic reagents. It is highly desirable to develop cheap, selective, and highly atom-economical reactions. To overcome aforementioned limitations, recently developed approaches rely on transition-metal-catalyzed alkenyl C−H bond coupling reactions, as these reactions are performed in a catalytic, atom- and step-economic manner.[4,6,8] Hence, we have focused on the development of novel C-C bond forming reactions and their application towards synthesis of biologically active compounds such as natural products and pharmaceutical targets.

Results and Discussion:

Past decade has witnessed a huge advancement in the field of metal-catalyzed C-H activation/functionalization and has become convenient and alternative tool to the traditional methods.[9] Transition metal catalyzed carbon-carbon and carbon-hetero bond formation reactions by directing group assisted inert C-H functionalization reactions have been reported. Although, a significant amount of work in the field of C(alkyl)-H and C(aryl)-H activation has been reported, C(alkenyl)−H activation has not been explored conspicuously, probably due to the complications caused by competitive reactivity of the alkene moiety, which can make chemoselectivity a significant challenge. Over the past few years, several different palladium-based protocols have been developed for C(alkenyl)−H functionalization, but the reactions are generally limited to employing conjugated alkenes, such as styrenes, acrylates/acrylamides, enamides, and enol esters /ethers.[10] To date, only a few reports have appeared in the literature for expanding this reactivity towards non-conjugated olefins, which can be exemplified by camphene dimerization[11], carboxylate-directed C(alkenyl)−H alkenylation of 1,4-cyclohexadienes.[12] From last three decades Trost *et al* have done pioneering work in this field and extensively studied the ruthenium-catalyzed alkynes-alkenes coupling reaction which is an atom-economic strategy for carbon−carbon bond formation.[13] Surprisingly, ruthenium-catalyzed alkene-alkene coupling reactions are underdeveloped. Particularly, Trost and coworkers reported an elegant method for highly chemoselective ruthenium-catalyzed redox-isomerization of allyl alcohols without affecting the primary and secondary alcohols and isolated double bonds.[14] Inspired by the potentiality of ruthenium for such isomerization of double bonds in allyl alcohols, we sought to identify a ruthenium-based catalytic system that can promote isomerization of olefin in allyl sources followed by *in*

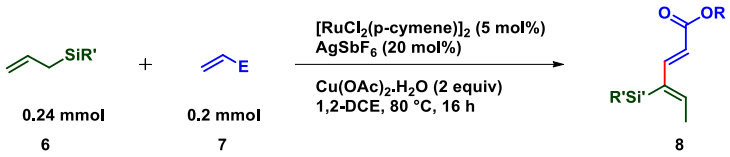
situ oxidative coupling with an activated olefin to form highly functionalized substituted 1,3-dienes (scheme 1).

Scheme 1: Highly Stereoselective Construction of 1,3-Dienes

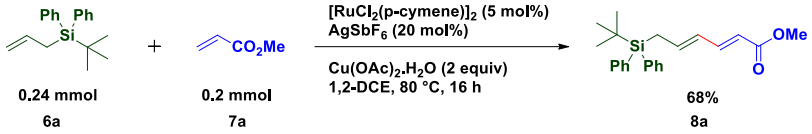


We initiated our studies by choosing trimethylallylsilane and methyl acrylate by using commercially available $[RuCl_2(p\text{-cymene})]_2$ catalyst in the presence $AgSbF_6$ as an additive and co-oxidant $Cu(OAc)_2$ in 1,2-DCE at 100 ^oC. The reaction successfully offered isomerization of trimethylallylsilane followed by regioselective cross-coupling reaction with methyl acrylate to give highly stereodefined 1,3-diene as a single isomer in 55% yield. This is likely that the reaction occurs by C(allyl)-H activation to π-allyl ruthenium complex followed by oxidative coupling with the acrylate and leaving the silyl group intact. π-allyl ruthenium complex formation may be highly favorable due to α-silyl effect which stabilizes the carbanion forming *in situ* in the reaction.[15a] Next, the regioselective C-H insertion of vinyl silanes could be controlled by stabilization of carbon-metal (C-M) bond in the α-position to silicon. This stability arises due to the overlapping of filled carbon-metal orbital with the d-orbitals on silicon or the antibonding orbitals of the methyl-silicon (Me-Si) bond.[15b] To quantify the C-H activation mediated coupling efficiency, an extensive optimization study was conducted by varying solvent, temperature and additives (see ref 4 and 6). After conducting the multiple experiments, the reaction yield was successfully increased to 82%. With the optimized conditions in hand, various allyl silanes **6** and activated olefins **7** has been tested and corresponding 1,3-dienes **8** obtained in very good yields with exclusive (*E,Z*)-stereoselectivity (scheme 2a). When *tert*-butyldiphenylallylsilane **6a** was subjected for coupling reaction with methyl acrylate **7a**, end-end coupling product **8a** was isolated in 68% yield. This may be attributed to the steric crowding offered by bulky groups on silicon which prevents allyl to vinyl isomerisation (scheme 2b).

Scheme 2a: Oxidative coupling of allylsilanes with acrylates and vinyl sulfones



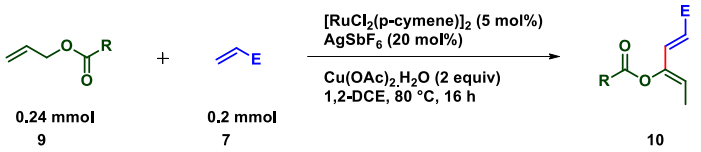
Scheme 2b: Oxidative coupling of *tert*-butyldiphenylallylsilane with methyl acrylates



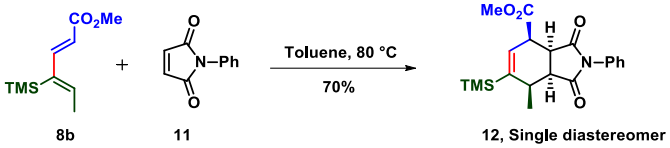
To extend the substrate scope of the reaction, we next examined the scope of allylesters by employing as the coupling partner (scheme 3). First, we carried out coupling reaction between heptadecylallyl ester and methyl acrylate under standard conditions. To our delight, a single isomer of acetate substituted (*2E,4Z*)-1,3-diene was isolated with a good yield (75%). This result may be extremely unusual due to the weak thermodynamic driving force for the double bond migration of allyl esters and tendency of many metal catalysts to insert into the C(allyl)-O bond to form the stable carboxylate complex.[16a] Even for unsubstituted allyl esters very few reports of double bond migrations exists.[16b-e] It is worth mentioning that unlike Tsuji-Trost reaction[16f-h], C(allyl)-O bond doesn't break to form π-allyl palladium complex as an electrophile, instead it forms a nucleophilic π-allylruthenium complex (Umpolung reactivity) keeping acetate group intact, which further reacts with an electrophile. Next we turned our attention to expand the scope of coupling reaction between various activated olefins **7** and allyl esters **9**. It was found that a variety of allyl esters **9** bearing alkyl substituents on the carbonyl carbon could provide moderate to good yields of the corresponding stereodefined (*2E,4Z*)-1,3,4-trisubstituted 1,3-dienes **10** successfully. It is

delightful to mention that diene **8b** successfully underwent Diels-Alder reaction with N-phenyl maleimide **11** in toluene at 80 ºC, to afford corresponding bicycle **12** as a single isomer in 70% yield which ensure the pragmatism of the method (scheme 4).

Scheme 3: oxidative coupling of various allyl esters with different acrylates and vinyl sulfones

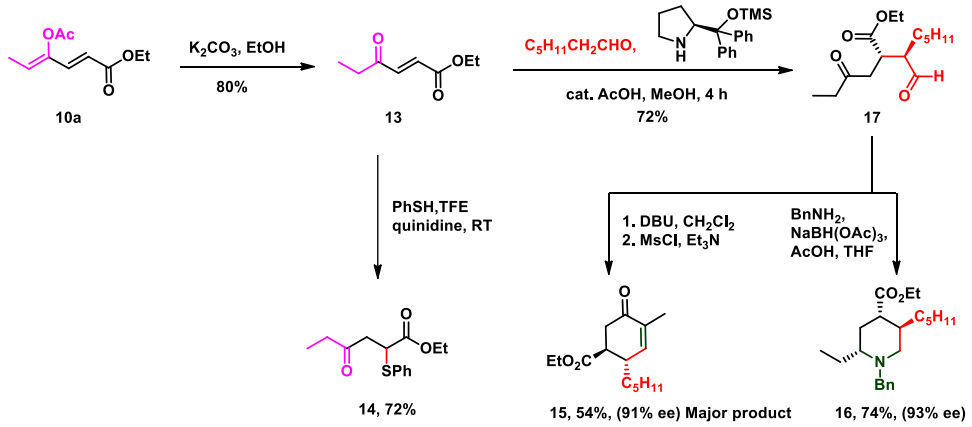


Scheme 4: Application to Diels-Alder reaction

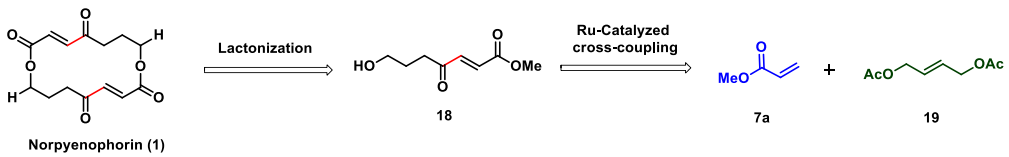


The unique power of this ruthenium-catalyzed C-H functionalization strategy is illustrated by the late-stage diversification of the diene **10a**, to a very reactive Michael acceptor **13** (conventional route for preparation of **13** requires *in situ* oxidation of α-hydroxyketones using 10 equiv. MnO_2 followed by Wittig reaction, which generates superstoichiometric amount of phosphine waste)[17] via selective hydrolysis of the acetate group, which is useful in the synthesis of ester-thiol **14**, cyclohexenone **15** and polysubstituted piperidine **16** (scheme 5). Thus, the Micheal acceptor **13** on reaction with thiophenol generated compound **14** in excellent yield and high regioselectivity. On the other hand compound **13** on reaction with heptanal in presence of Hayashi-Jørgensen's catalyst afforded the Michael adduct **17** in 72% yield and excellent diastereoselectivity.[6] Keto-aldehyde **17** was converted to highly substituted cyclohexenone **15** and piperidine **16**.

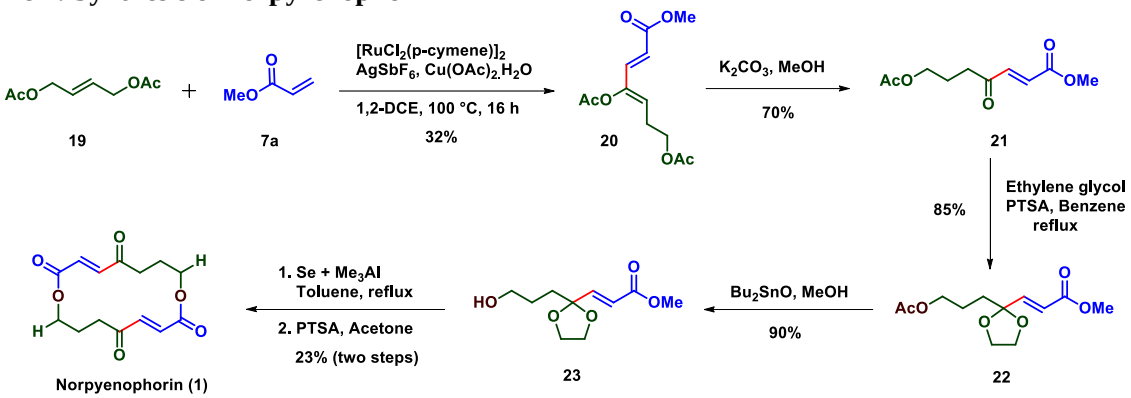
Scheme 5: Application to organocatalytic Michael addition reaction



Scheme 6: Retrosynthetic analysis for norpyrenophorin



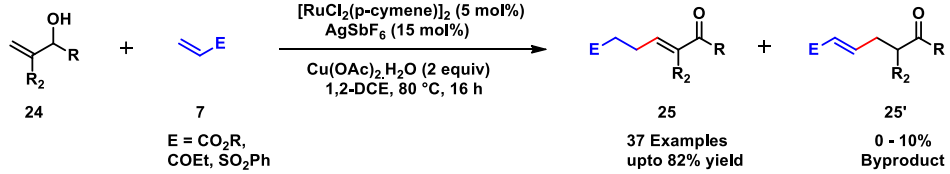
Scheme 7: Synthesis of norpyrenophorin



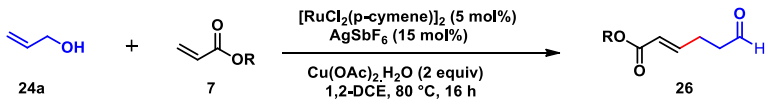
The potential of this Ru-catalysed reaction was further demonstrated by norpyrenophorin synthesis.[3] A brief retrosynthetic analysis revealed that the dimeric macrocycle **1** could be dissected into monomer **18** which could be easily accessed from oxidative coupling of **7a** with **19** using C-H activation reaction (Scheme 6). Ruthenium catalysed oxidative coupling of symmetric allylester **19** with **2a** generated the key intermediate **20** in 32% yield. Selective hydrolysis of acetyl enolate **20** was accomplished by the treatment with K_2CO_3 in methanol to provide **21** in 70% yield. In accordance with some previously reported literature, active ketone functionality of **21** was protected as ketal by treatment with ethylene glycol in refluxing benzene to afford substrate **22**. Selective hydrolysis of acetate was achieved using Bu_2SnO to generate alcohol **23** and finally, aluminium-selenium adduct mediated ring closing lactonization followed by deketalization ensured the completion of synthesis of **1** in 23% yield (two steps) (Scheme 7). A similar type of dimerization reaction could be envisioned to synthesize the natural products pyrenophorin **2** and vermiculin **3**.

Various C-C bond forming reactions have been reported via transition metal catalysed C-H activation. Particularly, ruthenium(II)-catalyzed directing group facilitated C−H bond activation/functionalization of aromatic compounds have been reported,[18] however, C−H bond activation/functionalization of alkene/alkane are less explored. From last three decades Trost *et al* have done pioneering work in this field and extensively studied the ruthenium-catalyzed alkynes-alkenes coupling reaction which is an atom-economic strategy for carbon-carbon bond formation.[19] Surprisingly, ruthenium-catalyzed alkene-alkene coupling reactions are underdeveloped. Based on the ruthenium reactivity towards isomerization of allyl alcohols, we planned to develop a new strategy by coupling of in situ generated enone with activated olefins. In this context, we have developed a highly atom/step-economical ruthenium catalyzed sp^2 C–H activation of allyl alcohols followed by cross coupling reaction with activated olefins (scheme 8a).

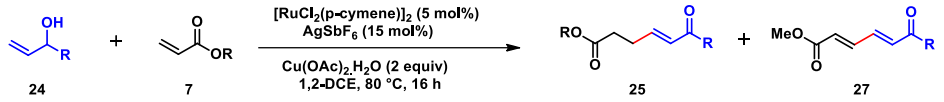
Scheme 8a: Dehydrogenative cross-coupling of allyl alcohols and acrylates



Scheme 8b: Dehydrogenative cross-coupling of primary allyl alcohol with acrylates

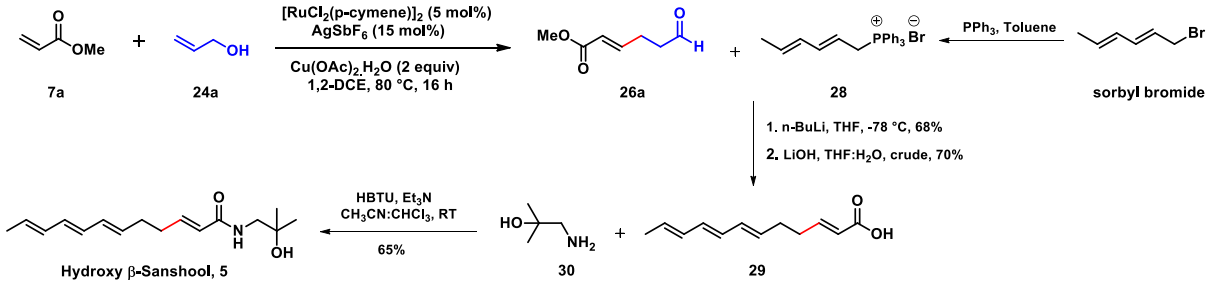


Scheme 8c: Dehydrogenative cross-coupling of secondary allyl alcohol with acrylates

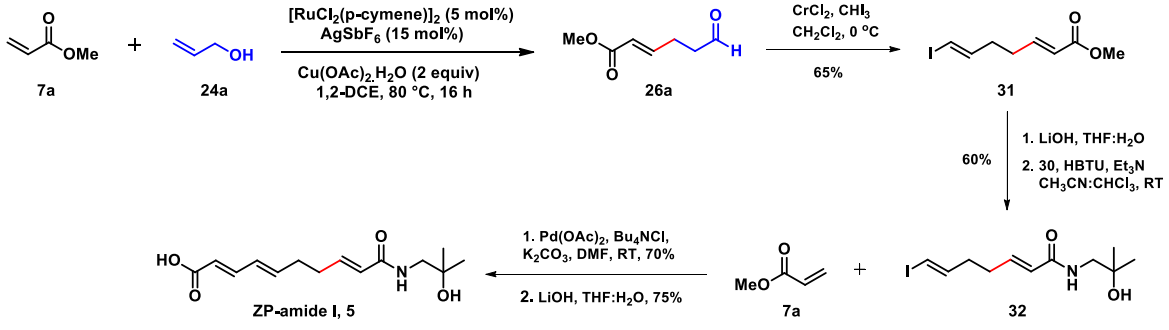


In this direction, we initiated our studies by choosing the C-H activation reaction between substituted allyl alcohol and cyclohexyl acrylate as a model reaction to optimize the reaction condition. The coupling reaction was carried out by varying different parameters such as catalysts, solvents, additives and temperature. To our delight, 82% yield of the cross-coupled product with a regioisomeric ratio 96:4 was isolated when reaction was performed using 5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ and 15 mol % of $AgSbF_6$ as additive in presence of 2.0 equiv. of $Cu(OAc)_2.H_2O$ as an oxidant in 1,2-dichoroethane at 80 ^oC for 16 hours. With an optimized conditions in hand, a variety of allyl alcohols **24** and activated olefins **7** bearing different functionality reacted well, providing the corresponding coupling products **25** in moderate to good yields with excellent stereoselectivity (scheme 8a). It is surprising that, when we used simple allyl alcohol **24a** as a coupling partner with methyl acrylate **7**, coupled product **26** was observed with double bond migration towards ester side (instead of towards aldehyde) which was confirmed by NMR analysis with the reported data (scheme 8b). To check the reproducibility of this product, we carried out coupling reaction with various acrylates which successfully generated similar products. It was delightful and interesting to observe that secondary allyl alcohols **24** without having any β-substitution underwent smooth reaction to afford coupling products **25.** Trace amount of corresponding diene was also observed as byproduct **27** which may be due to improper selectivity for β-hydride elimination in case of β-unsubstituted allyl alcohols. Similar reactivity was observed when reaction was carried out with different allyl alcohols (scheme 8c).

Scheme 8d: Total synthesis of hydroxy β-sanshool and ZP-amide I



Scheme 8e: Total synthesis of ZP-amide I



Synthetic utility of dehydrogenase cross-coupling reaction of allyl alcohols and acrylates was further demonstrated by the synthesis of bioactive natural products such as hydroxy-β-sanshool **4** and ZP-amide I **5**.[4,5] Several synthetic

reports have been developed for the synthesis of pungent polyunsaturated fatty acid amides.[5a] We have reported the application of our reaction by shortest synthesis of two natural products, hydroxy β-sanshool **4** and ZP-amide I **5** in a highly diastereoselective manner. We initiated synthesis of hydroxy-β-sanshool **4** by dehydrogenase cross-coupling reaction of allyl alcohol **24a** and methyl acrylate **7a** to get crucial intermediate ester-aldehyde **26a** in 60% yield. Wittig salt of sorbyl bromide **28** was subjected for base treatment using n-butyl lithium at -78 ^{o}C followed by reaction with ester-aldehyde **26a** provided unsaturated alkyl ester in 68% yield with approximate 3:1 *E*/*Z*-stereo selectivity and it was then converted into corresponding acid **29** using LiOH in 70% yield. Finally, coupling of **29** with commercially available hydroxy amine **30** using HBTU and Et_3N afforded Hydroxy-β-sanshool **4** in 65% yield with 31% overall yield making it an efficient and shortest synthesis to date (scheme 8d). It is graceful to demonstrate the first total synthesis of the other natural product called ZP-amide I **5**, an isobutylhydroxyamide isolated from Sichuan Pepper. Aldehyde **26a** was subjected for Takai olefination using $CrCl_2$ and iodoform providing corresponding vinyl iodide derivative **31** with 65% yield**.** Compound **31** could be utilized for many coupling reactions and other functional group transformations since it appears as a part natural product like Lactimidomycin.[20] LiOH mediated hydrolysis followed by coupling with hydroxy amine **30** using HBTU and Et_3N afforded corresponding amide **32** in 60% yield. Amide **32** on Heck reaction with methyl acrylate **7a** using palladium acetate generated ester-amide in 70% yield and its ester group was hydrolysed using LiOH provided natural product ZP-amide I **5** in 75% yield with a 21% overall yield (scheme 8e).

Conclusion:

We have developed a carbon-carbon bond forming reaction by Ru-catalyzed oxidative coupling of allylsilanes and allyl esters with activated olefins *via* isomerization followed by C(allyl)-H activation. This method provided efficient access to highly functionalized stereodefined 1,3-dienes in excellent yields. Mild reaction conditions, less expensive catalyst, excellent regio and diastereoselectivity ensure universality of the reaction. In addition, the unique power of this reaction was illustrated by performing Diels-Alder reaction, enantioselective synthesis of highly functionalized cyclohexenone, piperidine and finally synthetic utility was further demonstrated by the efficient synthesis of norpyrenophorin, an antifungal agent. Similarly, we also developed novel C-C bond forming reaction by ruthenium catalyzed hydroxy directed sp^2 C-H activation of allyl alcohols followed by oxidative coupling with activated olefins. The developed method provided efficient and direct access to synthetically useful α,β-unsaturated enone intermediates and its synthetic utility was further demonstrated by its application to synthesis of bioactive natural products such as hydroxy-β-sanshool and ZP-amide I in an highly diastereoselective manner. The application of C-H functionalization reactions in the field of natural products synthesis has become a trend in synthetic organic chemistry and has been successfully developed from our lab and described in this proposal.

Statistical Analysis:

The developed methodologies allows facile construction of 1,3-dienes and olefins in highly stereoselective manner which are of great importance in organic synthesis. At present, many of the reported methods for accessing these targets follows the Wittig/Horner−Wadsworth−Emmons reactions or transition-metal-catalyzed cross-coupling reactions. Although robust, these routes possess disadvantages, that they require prefunctionalized starting materials, generate stoichiometric by-products and in some cases deliver *E/Z* product mixtures, which is a major deleterious problem to be circumvented. Therefore, novel and highly atom-economical method for the stereoselective synthesis of alkenes utilizing cheap and easily available starting materials that is susceptible to large scale production is highly desirable. Also, application of developed methodologies towards synthesis of bioactive compounds is at high demand. We have confirmed all the compounds synthesized by our method using ^{1}H NMR, ^{13}C NMR, HRMS and IR. Also, synthetic data was compared with that of previous reports. Moreover, we have published both these results in the peer-reviewed journal and supporting information is available (see references).

References:

1. Dethe, D. H.; Nagabhushana, C. B.; Das, S.; Nirpal, A. K. Ruthenium-catalyzed formal sp^3 C–H activation of allylsilanes/esters with olefins: efficient access to functionalized 1,3-dienes. *Chem. Sci.*, **2021**, *12*, 4367-4372.

2. Dethe, D. H.; Nagabhushana, C. B. Ruthenium-Catalyzed Direct Dehydrogenative Cross-Coupling of Allyl Alcohols and Acrylates: Application to Total Synthesis of Hydroxy β-Sanshool, ZP-Amide I, and Chondrillin. *Org. Lett.* ***2020***, *22*, 1618-1623.

Impact of Research:

The above described methods have been developed based on the metal catalyzed reactions, particularly functionalization of inert C-H bonds under catalytic methods. The application of catalytic methods towards generation of useful synthetic intermediates and their utility in the synthesis of biologically important and complex natural products always holds a great importance in synthetic organic chemistry. The synthesis of same products using traditional transformations requires multiple steps, more than equivalent amount of desired reagents, lower yields and leads to the generation of organic waste during this process. Hence, the developed inert C-H bond functionalization reactions under catalytic conditions are beneficially to research community by associating with crucial parameters such as use of inexpensive materials, avoid of multiple steps, no use of equivalent amount reagents and oxidants and by avoiding organic waste. Moreover, the synthetic utility of these reactions have been further explored by developing shortest synthetic route towards natural products synthesis such as norpyrenophorin, hydroxy β-sanshool and ZP-amide I and which are found as a shortest and efficient synthesis reported in the literature so far. Similarly, the developed novel synthetic routes can be utilized for the synthesis of natural products of the same family and others. Hence, we believe that the above described reactions will be useful methods in carbon-carbon bond formation, holding great promise for wide use in organic and medicinal chemistry fields.

Material and Methods:

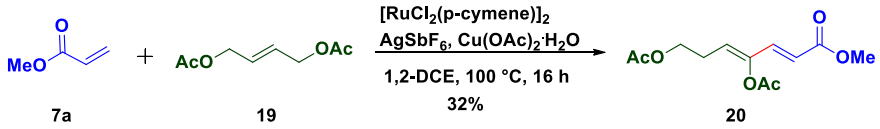
Please find the below the reaction conditions and reagents used in the C-H functionalization reactions and detailed procedure has been provided. Only experimentation related to natural products syntheses have been given below and for more details like experimentation and corresponding supporting information will be available in online (references mentioned above).

General procedure for the oxidative coupling reaction of allylsilanes/esters with activated olefins for the synthesis of highly functionalized 1,3-dienes

A 8 mL screw-cap vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol, 5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (80 mg, 0.4 mmol, 2.0 equiv), $AgSbF_6$ (14 mg, 0.04 mmol, 20 mol%) and 1,2-dichloroethane (2.0 mL). Then acrylate/vinyl sulfone (0.2 mmol, 1.0 equiv) and allylsilane or allyl ester (0.24 mmol, 1.2 equiv) were added into the solution in sequence. The vial was sealed under N_2 and heated to 80 °C with stirring for 16 h. After cooling down, the mixture was diluted with ethyl acetate, filtrated and concentrated to give the crude compound which was directly purified by column chromatography.

Part 1: Synthesis of norpyrenophorin 1

Synthesis of compound diene 20

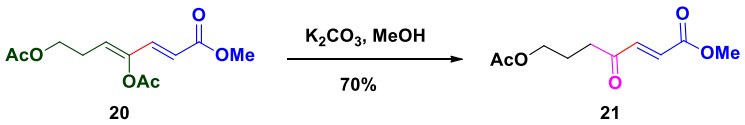


7a 19 20

By following the general procedure, A 50 mL seal tube was charged with $[RuCl_2(p\text{-cymene})]_2$ (179 mg, 5.83 mmol, 5.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.32 g, 11.6 mmol, 2.0 equiv), $AgSbF_6$ (400 mg, 2.0 mmol, 20 mol%) and 1,2-dichloroethane (20 mL). Then methyl acrylate **7a** (250mg, 0.255ml, 2.90 mmol, 0.5equiv) and diacetate **19** (1.0 g,5.83 mmol, 1.0 equiv) were added into the solution in sequence. Then vial was sealed under N_2 and heated to 100 ^oC with stirring for 16 h. After cooling down, the mixture was diluted with ethyl acetate, filtrated and concentrated to give the crude compound which was directly purified by column chromatography (3:1:: Pet ether : EtOAc) to give **20** (477 mg, 1.86 mmol, 32%).

(3Z,5E)-7-methoxy-7-oxohepta-3,5-diene-1,4-diyl diacetate (20)
^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 15.9 Hz, 1 H), 5.83 - 5.73 (m, 2 H), 4.13 (t, *J* = 6.7 Hz, 2 H), 3.75 (s, 3 H), 2.42 (q, *J* = 6.9 Hz, 2 H), 2.28 (s, 3 H), 2.05 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 167.8, 166.7, 146.0, 138.7, 125.9, 117.7, 62.3, 51.8, 26.4, 20.9, 20.3. HRMS (ESI) m/z calcd. for $C_{12}H_{16}O_6$ $[M+NH_4]^+$ 274.1291; found 274.1296. IR (neat): ν_{max}/cm^{-1} 2954, 2849, 1765, 1738, 1652, 1627, 1435, 1368, 1309, 1238, 1198, 1172, 1037.

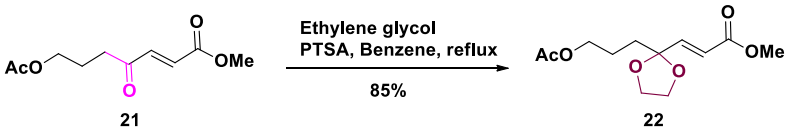
Synthesis of compound 21



To a solution of **20** (450 mg, 1.75 mmol, 1.0 equiv) in methanol, added potassium carbonate (218 mg, 1.58 mmol, 0.9 equiv) in four portions over 5 min and reaction mixture was allowed to stirred for 40 minutes at room temperature. Then reaction mixture was quenched with water and extracted with ethyl acetate (15ml X 3), washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (3 : 1.5 :: Pet ether : EtOAc) furnishing the compound **21** (262mg, 1.22mmol, 70%).

(E)-methyl 7-acetoxy-4-oxohept-2-enoate (21)
^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 16.0 Hz, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 4.10 (t, *J* = 6.3 Hz, 2 H), 3.82 (s, 3 H), 2.74 (t, *J* = 6.9 Hz, 2 H), 2.04 (s, 3 H), 2.02 - 1.97 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.5, 171.1, 166.0, 139.3, 130.6, 63.4, 52.5, 38.0, 22.7, 21.0. HRMS (ESI) m/z calcd. for $C_{10}H_{14}O_5$ $[M+Na]^+$ 237.0739; found 237.0730. IR (neat): ν_{max}/cm^{-1} 2956, 2853, 1737, 1731, 1703, 1643, 1437, 1366, 1305, 1241, 1176, 1040.

Synthesis of compound 22

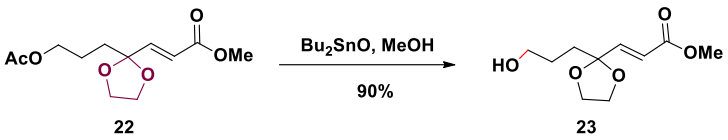


Using a Dean-Stark trap, ethylene glycol (1.3 ml, 23.36 mmol, 30 equiv.) was refluxed in benzene (5 mL) for 1 hour. Upon cooling, compound **21** (250 mg, 1.16 mmol) in benzene (2 mL) and p-toluene sulfonic acid (10 mg, 0.046 mmol, 0.04 equiv.) were added to the solution and the resulting mixture was heated to reflux under a condenser for 1.5 hours (heating for more than 1.5 hours resulted in decomposition of product). The solution was then cooled and quenched with $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL), washed with water (80 mL) and brine (80 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (3 : 1.5:: Pet ether : EtOAc) to obtain of the pure ketal **22** (254 mg, 0.986 mmol, 85% yield) as a yellow liquid.

(E)-methyl 3-(2-(3-acetoxypropyl)-1,3-dioxolan-2-yl)acrylate (22)
^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, *J* = 15.6 Hz, 1 H), 6.09 (d, *J* = 15.8 Hz, 1 H), 4.07 (t, *J* = 6.4 Hz, 2 H), 4.00 - 3.95 (m, 2 H), 3.90 - 3.85 (m, 2 H), 3.76 (s, 3 H), 2.04 (s, 3 H), 1.85 - 1.78 (m, 2 H), 1.78 - 1.70 (m, 2 H). ^{13}C NMR

(101 MHz, $CDCl_3$): δ 171.4, 166.9, 146.6, 121.9, 108.2, 65.3 (2C), 64.5, 52.1, 34.4, 22.8, 21.3. HRMS (ESI) m/z calcd. for $C_{12}H_{18}O_6$ $[M+Na]^+$ 281.1001; found 281.1000. IR (neat): ν_{max}/cm^{-1}2955, 2895, 1731 (br.), 1663, 1436, 1387, 1365, 1305, 1243, 1197, 1169, 1036.

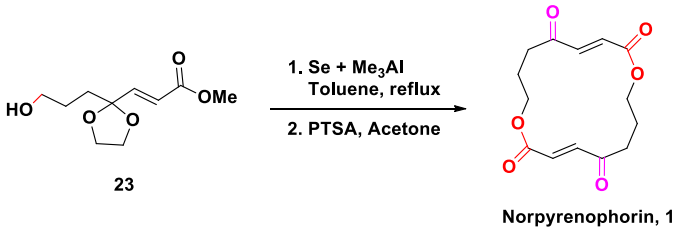
Synthesis of compound 23



To a solution of **22** (240 mg, 0.930 mmol, 1.0 equiv) in methanol (8 ml), added dibutyl tin oxide (2.31 g, 5.9 mmol, 0.9 equiv) in one portion and reaction mixture was refluxed for 2 hours. Upon cooling the reaction mixture, concentrated *in vacuo*, solid was removed by filtration, residue washed with ethyl acetate and filterarte was concentrated, purified by column chromatography (3 : 2 :: Pet ether : EtOAc) furnishing the product **23** (216 mg, 0.93 mmol, 90%) as a pale brownish liquid.

(E)-methyl 3-(2-(3-hydroxypropyl)-1,3-dioxolan-2-yl)acrylate (23)
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, *J* = 15.4 Hz, 1 H), 6.07 (d, *J* = 15.4 Hz, 1 H), 4.00 - 3.96 (m, 2 H), 3.89 - 3.85 (m, 2 H), 3.74 (s, 3 H), 3.63 (t, *J* = 5.9 Hz, 2 H), 2.03 (br. s., 1 H), 1.87 - 1.82 (m, 2 H), 1.69 - 1.64 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 146.3, 121.5, 108.1, 64.9 (2C), 62.5, 51.8, 34.1, 26.2. HRMS (ESI) m/z calcd. for $C_{10}H_{16}O_5$ $[M+Na]^+$ 239.0895; found 239.0894. IR (neat): ν_{max}/cm^{-1} 3400 (br.), 2954, 2849, 1765, 1738, 1652, 1627, 1435, 1368, 1309, 1238, 1198, 1172, 1037.

Synthesis of norpyrenophorin 1



Trimethylaluminium (0.925 mL of a 2 M solution, 1.85 mmol, 10 equiv) in toluene was added to a 5 mL side-arm flask containing selenium powder (150 mg, 1.924 mmol, 10.4 equiv) at 0 °C and refluxed till the selenium powder had reacted completely, the resulting mixture was cooled to room temperature. An aliquot of $Me_2SeAlMe$ (10 µl, 1.1 mmol) was transferred by syringe to a solution containing compound **23** (40 mg, 0.185 mmol) in toluene (1.2 mL) at 0 °C. After 28 h of heating at reflux, the yellow solution was warmed to room temperature over a period of 30 min and treated with sodium sulfate. The solution was then diluted with dichloromethane, washed with water six times and treated with sodium hydrogen carbonate. The solution was then dried with brine and anhydrous magnesium sulfate. The solvent was removed under vacuum from the yellow solution and the residue wasdissolved in acetone (0.75 ml), added p-toluene sulfonic acid (3 mg, 0.0081 mmol, 0.1 equiv) at 0 °C and stirred for 4 hours at room temperature. then reaction mixture was quenched with $NaHCO_3$ solution and extracted with EtOAc, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (1:1 :: Pet ether : EtOAc) furnishing the **norpyrenophorin 1** (6 mg, 0.0214 mmol, 23% in two steps).

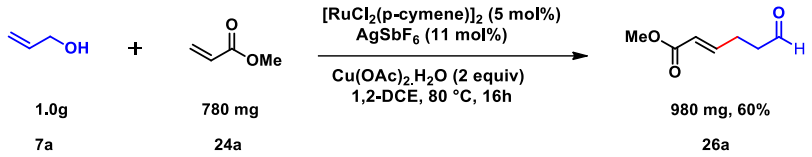
Norpyrenophorin (14)
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 16.3 Hz, 1 H), 6.68 (d, *J* = 16.2 Hz, 1 H), 4.31 (t, *J* = 5.9 Hz, 2 H), 2.85 (t, *J* = 7.0 Hz, 2 H), 2.13 - 2.07 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.5, 165.4, 140.2, 131.2, 64.6, 37.2, 22.4. HRMS (ESI) m/z calcd. for $C_{14}H_{17}O_6$ $[M+H]^+$ 281.1025; found 281.1025. IR (neat): ν_{max}/cm^{-1} 2923, 2852, 1728, 1428, 1258.

General procedure for the oxidative coupling reaction of allyl alcohols with activated olefins

A 8 mL screw-cap vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (6.3 mg, 0.01 mmol, 5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (80 mg, 0.4 mmol, 2.0 equiv), $AgSbF_6$ (10.29 mg, 0.03 mmol, 15 mol%) and 1,2-dichloroethane (3 mL). The catalytic system was stirred at room temperature under nitrogen atmosphere for 10 minutes. To this allyl alcohol (0.22 mmol, 1.1 equiv) followed by acrylate (0.20 mmol, 1.0 equiv) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 80 ºC (using oil bath) with stirring for 16h. After cooling down, the mixture was diluted with ethyl acetate, filtrated and concentrated to give the crude compound which was directly purified by column chromatography.

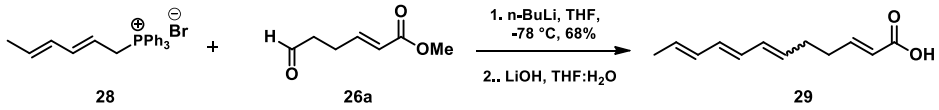
<u>Part 2: Synthesis of hydroxy β-sanshool 4 and ZP-amide I</u>

Gram scale Synthesis of 26a



26a was synthesized by following the general procedure, A 100 mL seal tube was charged with $[RuCl_2(p\text{-cymene})]_2$ (528 mg, 0.86 mmol, 5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (6.9 g, 34.5 mmol, 2.0 equiv), $AgSbF_6$ (707 mg, 2 mmol, 12 mol%) and 1,2- dichloroethane (35 mL). Then catalytic system was stirred at room temperature under nitrogen atmosphere for 10 minutes. To this allyl alcohol **7a** (1.17 g, 1.35 ml, 19 mmol, 1.1 equiv) and methyl acrylate **24a** (1.5 g, 1.53 ml, 17.25 mmol, 1.0 equiv) were added into the solution in sequence. Then vial was sealed under N2 and heated to 80 ºC with stirring for 16h. After cooling down, the mixture was diluted with ethyl acetate, filtrated and concentrated to give the crude compound which was directly purified by column chromatography to give **26a** as a colourless oil (1.47 mg, 10.35 mmol, 60%)(EtOAc : Pet ether = 2.5:7.5).

Synthesis of compound 29

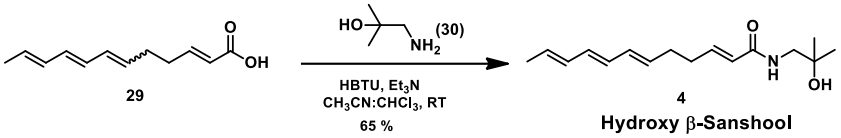


Wittig salt of sorbyl bromide **28** was prepared by refluxing with PPh_3 in toluene using literature procedure. To a suspension of (*2E,4E*)-hexa-2,4-dien-1-yltriphenylphosphonium bromide (1.78 g, 2.0 mmol) in THF (15 mL) was added dropwise n-BuLi (2.7 mL, 48.7 mmol, 1.6 M in hexane) via syringe at -78 ºC. The mixture was stirred for 1 hour at -60 ºC then re-cooled to -78 ºC and the liquid Wittig solution was transferred via cannula, slowly dropwise to a solution of aldehyde **26a** (300 mg, 2.11 mmol) in THF (6 mL) at -78 ºC. Then reaction mixture was slowly allowed room temperature and stirred for 3h. After completion, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL), diluted with diethyl ether (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified through neutral alumina column chromatography (9:1:: hexane : EtOAc) to yield polyene (295 mg, 1.43 mmol, 68%) as a pale yellow oil as an inseparable *E/Z* isomeric mixture (*E:Z* = ca. 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (dq, *J* = 15.5, 6.6 Hz, 1H), 6.23 – 5.94 (m, 4H), 5.83 (ddd, *J* = 14.6, 6.1, 3.3 Hz, 1H), 5.77 – 5.54 (m, 2H), 3.71 (s, 3H), 2.35 – 2.22 (m, 4H), 1.76 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.08, 148.61, 133.67, 131.72, 130.10, 129.47, 121.43, 51.47, 32.06, 31.23, 18.31. HRMS (ESI) m/z calcd. for

$C_{13}H_{18}O_2$ $[M+H]^+$ 207.1385; found 207.1383. IR (neat): ν_{max}/cm^{-1} 2989, 2945, 2931, 2898, 2863, 1720, 1685, 1678, 1643, 1520, 1189, 1163, 1012.

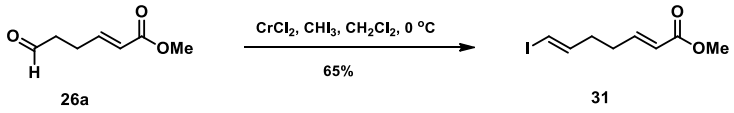
Polyene (200 mg, 0.97 mmol, 1.0 equiv) and LiOH (60 mg, 2.9 mmol, 3.0 equiv) in THF : H_2O, (1:1) 8 ml was stirred at room temperature for 3 h. The reaction mixture was acidified with aqueous HCl, extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a crude acid **29** as a white solid (130 mg, 0.67 mmol, 70%). Without purification, the crude product with inseparable *E/Z* mixture was used for next step.

Synthesis of Hydroxy β-sanshool, 4



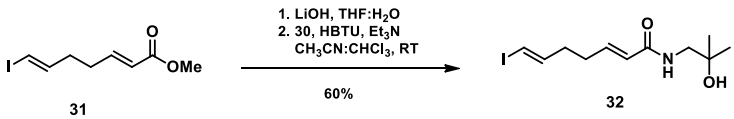
To a mixture of crude acid **29** (100 mg, 0.52 mmol, 1 equiv), **30** (69 mg , 0.78 mmol, 1.5 equiv) and triethylamine (0.13 mL, 1.0 mmol, 2.0 equiv) in MeCN (5 mL) and $CHCl_3$ (3 mL), was added HBTU (295 mg, 0.78 mmol, 1.5 equiv). After 1h, the reaction was judged to be complete by TLC analysis (EA:hexane =1:1). The reaction mixture was diluted with ethyl acetate (30 mL), and washed with brine, 1N HCl, water, 5% $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated and after careful purification through neutral alumina column chromatography using EtOAc in hexane (65:35) to afford single pure product **4** as a colorless solid (88 mg, 0.33 mmol, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 – 6.78 (m, 1H), 6.37 – 6.28 (m, 1H), 6.17 – 6.00 (m, 4H), 5.86 (d, *J* = 15.3 Hz, 1H), 5.68 (dtd, *J* = 20.0, 13.1, 6.9 Hz, 2H), 3.33 (d, *J* = 5.8 Hz, 2H), 2.27 (dd, *J* = 9.1, 4.8 Hz, 4H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.23 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.99, 144.30, 131.97, 131.58, 131.52, 131.37, 130.01, 129.34, 123.66, 70.91, 50.40, 31.85, 31.33, 27.21 (2C), 18.23. HRMS (ESI) m/z calcd. for $C_{16}H_{25}NO_2$ $[M+H]^+$ 264.1964; found 264.1969. IR (neat): ν_{max}/cm^{-1} 2993, 2952, 2929, 2883, 2833, 1732, 1663, 1644, 1638, 1565, 1178, 1123, 1039.

Synthesis of compound 31



The compound **26a** (500 mg, 3.5 mmol) was subjected for Takai olefination using reported procedure[2] to afford corresponding vinyl iodide **31** as a brown liquid (606 mg, 2.2 mmol, 65%) (EtOAc : Pet ether = 1:9). ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 10.2, 8.2, 4.1 Hz, 1H), 6.48 (dt, *J* = 13.9, 6.2 Hz, 1H), 6.12 – 6.01 (d, *J* = 14.2, 1H), 5.82 (d, *J* = 15.6, 1H), 3.71 (d, *J* = 1.7 Hz, 3H), 2.32 – 2.26 (m, 2H), 2.20 (dd, *J* = 13.8, 6.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.87, 147.38, 144.57, 121.96, 76.04, 51.56, 34.41, 30.93. HRMS (ESI) m/z calcd. for $C_8H_{11}IO_2$ $[M+H]^+$ 266.9882; found 266.9879. IR (neat): ν_{max}/cm^{-1} 2975, 2923, 2810, 1723, 1612, 1580, 1432, 1323, 1210, 1112, 1010.

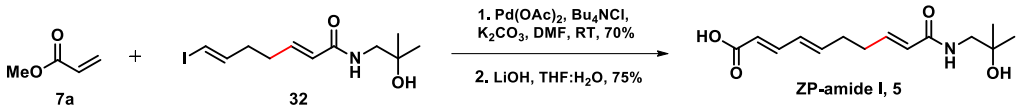
Synthesis of compound 32



A mixture of **31** (600 mg, 2.2 mmol, 1.0 equiv) and LiOH (160 mg, 6.6 mmol, 3.0 equiv) in THF : H_2O, (1:1) 15 mL was stirred at room temperature for 3 h. The reaction mixture was acidified with aqueous HCl, extracted with ethyl

acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a acid (450 mg). Without purification, the crude product was used for next step.
To a mixture of crude acid (450 mg, 1.8 mmol, 1 equiv), **30** (240 mg , 2.7 mmol, 1.5 equiv) and triethylamine (0.46 mL, 3.6 mmol, 2.0 equiv) in MeCN (5 mL) and $CHCl_3$ (3 mL), was added HBTU (1.0 g, 2.7 mmol, 1.5 equiv). After 2h, the reaction was judged to be complete by TLC analysis (EA:hexane =3:1.2). The reaction mixture was diluted with ethyl acetate (30 mL), and washed with brine, 1N HCl, water, 5% NaHCO3, and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated and after careful purification through neutral alumina column chromatography using EtOAc in hexane (75:25) to afford pure product **32** as a yellow solid (348 mg, 1.08 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 14.7, 9.5 Hz, 1H), 6.46 (dt, *J* = 13.9, 8.4 Hz, 2H, N-H), 6.03 (d, *J* = 14.3 Hz, 1H), 5.85 (d, *J* = 15.2 Hz, 1H), 3.28 (d, *J* = 5.1 Hz, 2H), 3.16 (s, 1H), 2.24 (dd, *J* = 12.7, 5.0 Hz, 2H), 2.17 (dd, *J* = 13.6, 6.7 Hz, 2H), 1.18 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.80, 144.79, 143.23, 124.36, 75.95, 71.00, 50.51, 34.63, 30.86, 27.37 (2C). HRMS (ESI) m/z calcd. for $C_{11}H_{18}INO_2$ $[M+H]^+$ 324.0460; found 324.0468. IR (neat): ν_{max}/cm^{-1} 2930, 2912, 2838, 1712, 1645, 1403, 1310, 1201, 1107, 1010.

Synthesis of compound 13



The round bottom flask was charged with compound **32** (320 mg, 1.0 mmol, 1.0 equiv), **7a** (0.28 mL, 3.0 mmol, 3.0 equiv), $Pd(OAc)_2$ (16mg, 0.05 mmol, 0.05 equiv), Bu_4NCl (300 mg, 1.1 mmol, 1.1 equiv) and K_2CO_3 (345 mg, 2.5 mmol, 2.5 equiv). To this, 3 mL of dry DMF was added and stirred for 24h under nitrogen atmosphere at room temperature. The reaction completion was determined by TLC using 80% EtOAc in hexane. The reaction mixture was diluted with ethyl acetate (30 mL), and washed with brine and ice water. The organic layer was separated, dried over $MgSO_4$, filtered, concentrated and purified by neutral alumina column chromatography using EtOAc in hexane (85:15) to afford pure coupling product as a colourless solid (196 mg, 0.7 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 15.3, 10.7 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.24 (br.. 1H, N-H), 6.17 (dd, *J* = 15.0, 10.9 Hz, 1H), 6.07 (dd, *J* = 13.6, 7.6 Hz, 1H), 5.81 (dd, *J* = 28.4, 15.4 Hz, 2H), 3.71 (d, *J* = 1.4 Hz, 3H), 3.29 (d, *J* = 5.9 Hz, 2H), 2.30 (m, *J* = 2.9 Hz, 4H), 1.20 (s, *J* = 1.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.71 (s), 166.77 (s), 144.85 (s), 143.69 (s), 142.46 (s), 129.29 (s), 124.15 (s), 119.62 (s), 71.07 (s), 51.60 (s), 50.47 (s), 31.37 (d, *J* = 34.1 Hz), 31.15 – 30.73 (m), 27.38 (s). HRMS (ESI) m/z calcd. for $C_{15}H_{23}NO_4$ $[M+H]^+$ 282.1705; found 282.1701. IR (neat): ν_{max}/cm^{-1} 2965, 2930, 2895, 2860, 1728, 1678, 1632, 1590, 1410, 1271, 1213, 1172, 1115, 1042.

A mixture of Heck product (150 mg, 0.53 mmol, 1.0 equiv) and LiOH (38 mg, 1.6 mmol, 3.0 equiv) in THF:H_2O, (1:1) 6 mL was stirred at room temperature for 3h. The reaction mixture was acidified with aqueous HCl, extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by neutral alumina column chromatography using 100 % EtOAc to afford pure product **5** as a colourless solid (106 mg, 0.39 mmol, 75%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.22 (dd, *J* = 15.1, 10.8 Hz, 1H), 6.76 (dt, *J* = 15.2, 6.6 Hz, 1H), 6.27 (dd, *J* = 15.1, 10.7 Hz, 1H), 6.16 (dd, *J* = 14.1, 7.4 Hz, 1H), 6.01 (d, *J* = 15.3 Hz, 1H), 5.82 (d, *J* = 14.2 Hz, 1H), 3.23 (s, 2H), 2.38 – 2.25 (m, 4H), 1.15 (s, 6H). ^{13}C NMR (100MHz, CD_3OD) δ = 169.0, 146.8, 144.6, 144.0, 130.6, 125.4, 121.9, 71.7, 51.1, 32.6, 32.2, 27.3. HRMS (ESI) m/z calcd. for $C_{14}H_{21}NO_4$ $[M+H]^+$ 268.1549; found 268.1548. IR (neat): ν_{max}/cm^{-1} 2932, 2915, 2862, 2815, 1712, 1665, 1610, 1575, 1412, 1213, 1145, 1125, 1010.

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