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Palladium catalyzed reductive Heck coupling and its application in total synthesis of (−)-17-nor-excelsinidine†

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Monoterpene indole alkaloids, bearing a highly substituted piperidine ring, are a structurally diverse class of bioactive natural products, found in various parts of the world. Herein, we reported the construction of the key piperidine ring *via* palladium catalyzed reductive Heck coupling with a good *syn* selective manner, avoiding the usage of stoichiometric, highly toxic, air sensitive and moisture sensitive Ni(COD)$_2$. To further showcase the value of this methodology, we realized the total synthesis of the structurally unique zwitterionic monoterpene indole alkaloid (−)-17-nor-excelsinidine in 9 steps, in which the key ammonium–acetate connection (N4–C16) of (−)-17-nor-excelsinidine was constructed *via* oxidative coupling in excellent yield and high regioselectivity under NBS/pyridine from the enolate of geissoschizine.

Monoterpene indole alkaloids are a structurally diverse class of bioactive natural products found in various parts of the world. Related biological investigations showed that these alkaloids have broad biological activities and medical properties, ranging from the treatment of headaches to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[1] Their characteristic biological activities and interesting architectures have stimulated synthetic efforts directed toward the total syntheses of which by many research groups.[2]

According to biosynthetic hypothesis, many of them can be accessed from geissoschizine (**1**) through oxidative cyclization with different interconnections.[3] Inspired by the biosynthetic hypothesis, several monoterpene indole alkaloids were synthesized *via* a bioinspired strategy. Baran and coworkers invented an intermolecular oxidative coupling strategy between indole and carbonyl enolates to assemble these natural products.[4] Ma and coworkers elaborate the core structure of communesin F *via* an intramolecular oxidative coupling reaction.[5] Using a similar intramolecular oxidative coupling between indole and malonate moieties, Ma's group also achieved the total synthesis of another akuammiline alkaloid aspidophylline A.[6] In all of these total synthesis of indole alkaloids, Ma,[5,6] Zhu[7] and co-workers constructed, at early stages, either the C7–C16 bond over the N1–C16 bond using LiHMDS/I$_2$ oxidative conditions.

So far, most of this interconnection transformation are not completely confirmed *via* total synthesis study for many reasons, such as the difficulties to control the regioselective oxidation due to the density of functional groups, to adjust the spatial distance of two functional groups, or to maintain the stability of the related products and strong oxidants. For example, Lounasmaa's group did many synthetic study base on "biogenetic-type cyclization" but not getting desired ring system.[8] So far, it's still quite difficult to explain these negative results.

Even today, synthetic approach towards these alkaloids *via* biosynthetic hypothesis is still quite challenging and demanding. In 2018, Vincent's group reported the first total synthesis of (−)-17-nor-excelsinidine *via* bioinspired oxidative cyclization strategy.[9] Due to the tolerance of the indole ring, the desired cyclization products were only obtained in 25% yield. According to reported biosynthetic hypothesis, from the key precursor geissoschizine (**1**), nature products such as marvacurin (**2**), strychnos (**3**), rhazimal (**4**), meloyine B (**5**), ajmalicine (**6**) and (−)-17-nor-excelsinidine (**7**) might be synthesized *via* connections of different atoms (Fig. 1). Based on these hypotheses, herein we reported the total synthesis of (−)-17-nor-excelsinidine *via* palladium catalyzed reductive heck coupling and NBS promoted oxidative cyclization with high overall yield.

From the skeleton of monoterpene indole alkaloids, most of them bear a highly substituted *syn*-piperidine ring. However, this key *syn*-piperidine ring was mainly synthesized through reductive heck coupling by using stoichiometric Ni(COD)$_2$.[6,9,10] Due to the highly toxic, air sensitive and moisty sensitive of Ni(COD)$_2$, this type of reactions has to be handled in a glove box, which further limited its application. Yet, efficient preparation of this highly substituted 2,4-*syn*-piperidine ring through other less toxic, catalytic, air and moisty stable transition metal catalyst with a stereo-control manner remains quite challenging.

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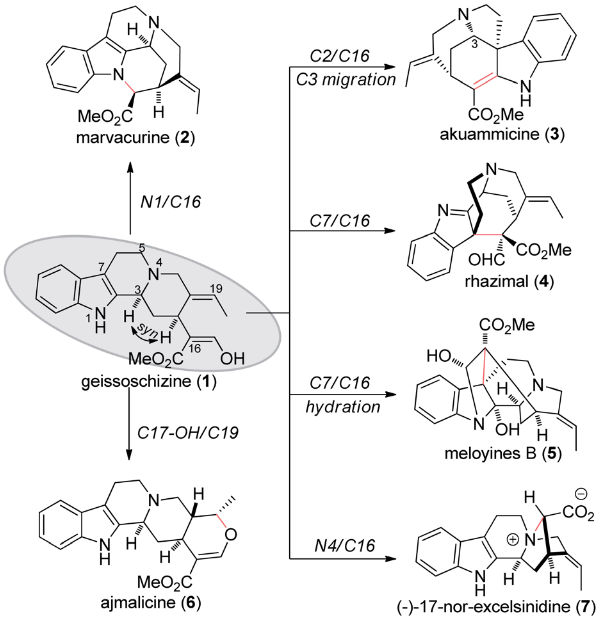
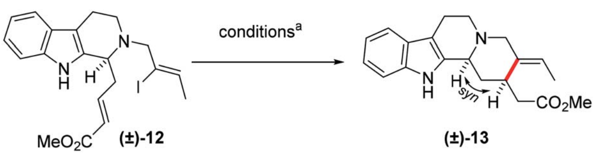


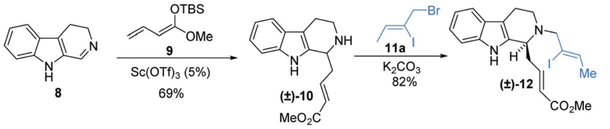
Fig. 1 Postulated biosynthetic transformation of selected monoterpene indole alkaloids.

Table 1 Optimization of the reductive Heck coupling[a]



Entry	Catalysts	Reductants	Additives	Yield[b]
1[c]	$Pd(OAc)_2$	HCO_2Na	n-Bu_4NCI	10%
2	$Pd_2(dba)_3CHCI_3$	HCO_2Na	—	0
3	$Pd(OAc)_2/PPh_3$	HCO_2H	Et_3N	0
4	$Pd(OAc)_2/PPh_3$	HCO_2H	DIPEA	0
5	$Pd(OAc)_2/PPh_3$	HCO_2Na	—	0
6	$Pd_2(dba)_3CHCI_3$	HCO_2H	DIPEA	0
7	$Pd_2(dba)_3CHCI_3$/DPPE	HCO_2H	DIPEA	0
8	$Pd(OAc)_2$	HCO_2H	Et_3N	0
9	$Pd(OAc)_2$	HCO_2H	PMP	0
10[d]	$Pd(OAc)_2$	HCO_2Na	$nBu_4NCI/LiCI$	47%
11[e]	$Pd(OAc)_2$	HCO_2Na	n-$Bu_4NCI/LiBr$	55%
12[f]	$Pd(OAc)_2$	HCO_2Na	n-$Bu_4NCI/LiBr$	51%
13[g,h]	$Pd(OAc)_2$	HCO_2Na	n-$Bu_4NCI/LiBr$	56%

[a] Unless otherwise noted, the reaction of (±)-**12** (0.1 mmol, 1.0 equiv.) was carried out using a catalytic of palladium (0.1 equiv.) under Ar atmosphere in the presence of reductant and an additive in DMF (2.0 mL) at 40 °C for 12 h. [b] Isolated yields. [c] HCO_2Na (5.0 equiv.), n-Bu_4NCl (7.5 equiv.). [d] HCO_2Na (10.0 equiv.), n-Bu_4NCl (15.0 equiv.) and LiCl (5.0 equiv.). [e] HCO_2Na (10.0 equiv.), n-Bu_4NCl (15.0 equiv.) and LiBr (5.0 equiv.). [f] HCO_2Na (15.0 equiv.), n-Bu_4NCl (22.5 equiv.) and LiBr (5.0 equiv.). [g] HCO_2Na (15.0 equiv.), n-Bu_4NCl (22.5 equiv.). [h] Gram-scale: (±)-**12** (3.16 mmol, 1.42 g), 45% yield. DMF: *N*,*N*′-dimethylformamide; DIPEA: *N*,*N*-diisopropylethylamine; PMP: 1,2,2,6,6-pentamethylpiperidine.

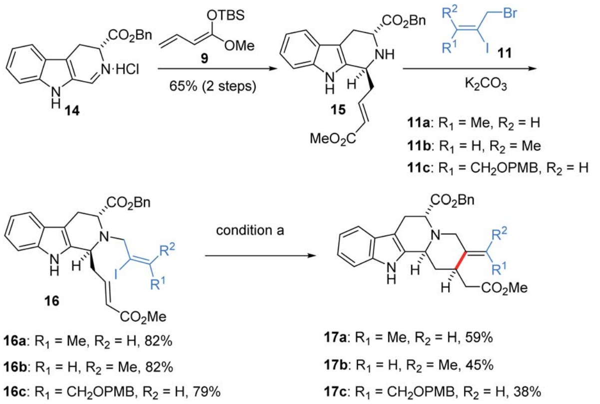


Scheme 1 Synthesis of the starting materials for reductive Heck-coupling.

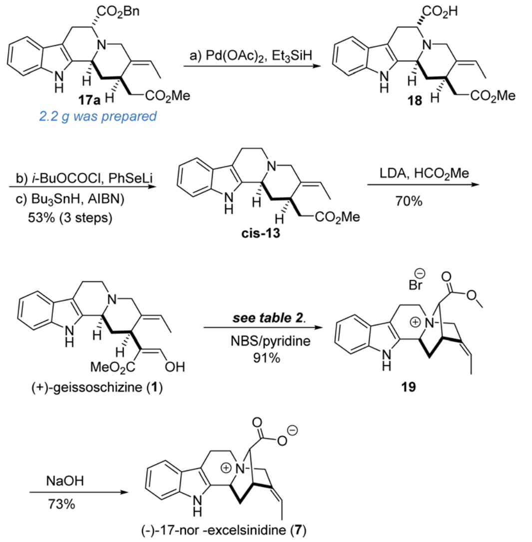
As is known to us, palladium-catalyzed reductive Heck coupling involves intercepting the alkylpalladium intermediate generated upon migratory insertion with a hydride source. This transformation has been investigated since the early 1980s, and pioneering work by Cacchi[11] and others during that period led to effective strategies with several classes of C–C–π-bond-containing substrates that lack β-H atoms or that form stabilized π-allyl/π-benzyl/enolate intermediates.[12] In contrast, application of this mode of reactivity to alkenes is comparatively underdeveloped, likely due to the rapid velocity of the aforementioned β-H elimination step with such substrates.

To circumvent this issue and test the validity of this proposal, the precursors for reductive Heck coupling was synthesized *via* Mannich addition and *N*-alkylation as shown in Scheme 1 as the known protocol. Iodo (±)-**12**[10c] was smoothly generated from imine **8**[13a] and enolate **9**.

With iodo (±)-**12** in hand, we chose palladium as the transition metal source, which was frequently used for reductive heck coupling.[12] After extension study of palladium systems, we can obtain the desired *syn*- (±)-**13** in 10% yield with other inseparable *anti* and elimination mixture while using $Pd(OAc)_2$ (0.01 equiv.) as catalyst, HCO_2Na (5.0 equiv.) as the hydride source and n-Bu_4NCl as the phase transfer reagent additive in DMF. The yield was considerably diminished under other reductants, additives or different palladium catalysts (entries 2–9). To our delight, the reaction yield was significant boosted while using halogen additive and increase the equivalent of HCO_2Na (entries 10–13). After examination of different equivalents of the hydride sources and additives, we finally got the desired *syn*-(±)-**13**[14] in 56% yield in 0.1 mmol scale of (±)-**12**. By comparing with previous work,[15] the intermediate **13** was generated in 53% yield while using 3.0 equivalent of $Ni(COD)_2$.



Scheme 2 Substrate synthesis and the scope of reductive heck coupling.



Scheme 3 The synthesis of (−)-17-nor-excelsinidine *via* NBS oxidation.

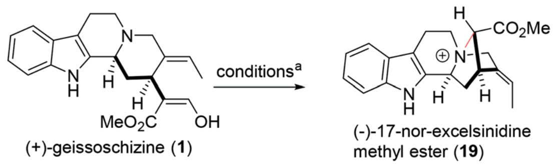
To further test the application of this reductive Heck coupling, gram-scale synthesis of *syn*-(±)-**13** was then achieved with an acceptable yield (Table 1).

Encouraged by this result, the scope with respect to the configuration and substitution of alkene was evaluated, as shown in Scheme 2, iodo **16a**[10c] was smoothly generated from imine **14**[13b] and enolate **9** *via* Mannich addition and *N*-alkylation. **16b** and **16c** bearing different configurations of alkene and substitutions were also obtained *via* a similar synthetic route. We found that both *Z* and *E* configuration are suitable in this reaction system to obtain **17a** and **17b** with acceptable yield. Other substitution of alkene is also well-tolerated in this reaction, giving desire *syn*-**17c** in 38% yield. Benzyloxycarbonyl substituent at C5 position increased the yield of reductive products in gram-scale. Therefore, starting from enantiopure tryptophan instead of tryptamine would allow us to perform an asymmetric synthesis of this series of natural products. Thus more than two-gram of ester **17a** was prepared as the protocol in Scheme 2.

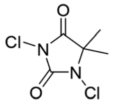
Subsequently, the benzyl ester was removed in a classical sequence,[10c] namely debenzylation into acid **18**, then comes the formation of phenylselenoester, and decarboxylation under reductive radical conditions, to yield enantiopure **13**. After the formylation of **13** under LDA/HCO$_2$Me, geissoschizine (**1**) was synthesized as expected in seven steps in the longest linear sequence (Scheme 3).

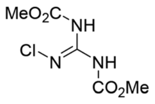
With geissoschizine (**1**) in hand and inspired by biosynthetic hypothesis as highlighted in Fig. 1, we investigated the potential transformation to yield natural products *via* different atom connections with C16. As shown in Fig. 1, ajmalicine (**6**) can be obtained through hydroxyl 1,4-addition to the imine intermediate. 17-nor-Excelsinidine can be accessed *via* carbon selective addition to the *in situ* generated ammonia salt and other types

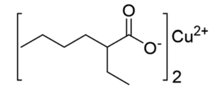
Table 2 Optimization of the oxidative coupling[a]



Entry	Conditions	Yield (**19**)[b]
1	LiHMDS (2.2 equiv.), I$_2$ (1.1 equiv.) THF, −78 °C	<10% (**19**)
2	LiHMDS (2.2 equiv.), Cu(II) (2.2 equiv.) THF, −78 °C	Trace (**19**)
3	LiHMDS (2.2 equiv.), Fe(acac)$_3$ (2.2 equiv.) THF, −78 °C	Trace (**19**)
4	K$_2$CO$_3$ (20 equiv.), NBS (1.0 equiv.) THF/H$_2$O, rt	<10% (**19**)
5	Mn(OAc)$_3$ (2.0 equiv.) CH$_3$CO$_2$H, 60 °C	NR
6	TFA (1.1 equiv.), *t*-BuOCI (1.4 equiv.) CHCI$_3$, 0 °C-rt	Decomp.
7	TfNH$_2$ (1.0 equiv.), *t*-BuOCI (2.0 equiv.) CH$_2$CI$_2$, 0 °C-rt	Decomp.
8	TFA (1.1 equiv.), DCDMH (1.2 equiv.) CHCI$_3$, 0 °C-rt	Decomp.
9	TFA (1.1 equiv.), CBMG (1.2 equiv.) CHCI$_3$, 0 °C-rt	Decomp.
10	TFA (1.5 equiv.), DMDO (1.2 equiv.) CH$_2$CI$_2$, 0 °C	Decomp.
11[c]	Ir(ppy)$_3$ (0.05 equiv.), RBr (3 equiv.), *hν*, DMF, rt	Decomp.
12	Ru(bpy)$_3$CI$_2$ (0.05 equiv.), O$_2$, *hν*, MeCN, rt	Decomp.
13[d]	**NBS (1.0 equiv.), pyridine/CH$_2$CI$_2$ (1/1), −40 °C**	**91%**


DCDMH


CBMG


copper(II) 2-ethylhexanoate

[a] Unless otherwise noted, geissoschizine (**1**) (5.0 mg, 0.014 mmol, 1.0 equiv.) was used for optimization of the oxidative coupling. [b] Isolated yields. [c] RBr: dimethyl 2-bromomalonate. [d] Geissoschizine (**1**) (20.0 mg, 0.057 mmol, 1.0 equiv.) was used.

of monoterpene alkaloids *via* different connections. Initially, we use LiHMDS/I$_2$ as oxidative conditions to forehead the synthesis of 17-nor-excelsinidine (entry 1). To our disappointment, less than 10% of 17-nor-excelsinidine was obtained with other inseparable decomposed mixture through this reaction system. Inspired by Baran's work, we screened other oxidants, such as Cu(II), Fe(III) and other organic oxidants as shown in Table 2 (entries 2–4). These oxidative condition only afforded a very complex mixture. The main reason might come from the intolerance of geissoschizine (**1**) under these oxidation conditions. The skeleton of natural product might be obtained by introducing acidic environment to reduce the activity of tertiary amine. With this propose in mind, we tested other acidic oxidation system (entries 5–10). We can only recovery the starting material while using Mn(OAc)$_3$ system. While using *t*-BuOCl, DCDMH, CBMG[16a] and other similar oxidants,[16b] the starting material disappeared very quickly, yielding a complex reaction mixture. As photoredox oxidation catalysis[17] system usually have a good functional group tolerance, we wondered whether the imine intermediate might be generated under this photoredox system. However, in our reaction system, the starting material was totally decomposed *via* previous conditions. Without getting positive results, we further screened basic oxidative system, and to our delight, 17-nor-excelsinidine precursor (**19**) was generated smoothly under NBS/pyridine system in 91% yield. The high yield is likely due to complete conversion and the region-selectivity of this coupling resulted from the inherent nucleophilicity of the lone pair electrons of the N-4 position. Methyl ester **19** was then saponified to afford (−)-17-nor-excelsinidine in 73% yield. The analytical and spectral data of synthetic (−)-17-nor-excelsinidine was in good agreement with previously reported.

Conclusions

In conclusion, we successfully constructed the key piperidine ring *via* a palladium catalyzed reductive Heck coupling with a good *syn* selective manner, avoiding the usage of stoichiometric, highly toxic, air and moisty sensitive Ni(COD)$_2$. From the key intermediate, we further built the key ammonium–acetate connection (N4–C16) of (−)-17-nor-excelsinidine *via* oxidative coupling in excellent yield and high regioselective under NBS/pyridine from the enolate of geissoschizine. Finally, racemic 17-nor-excelsinidine was synthesized in six steps with 11.8% overall yield, while the asymmetric synthesis was achieved in nine steps with 6.7% overall yield. Choosing a suitable oxidative system for realizing the selective oxidative coupling base on the biosynthetic route is still undergoing in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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