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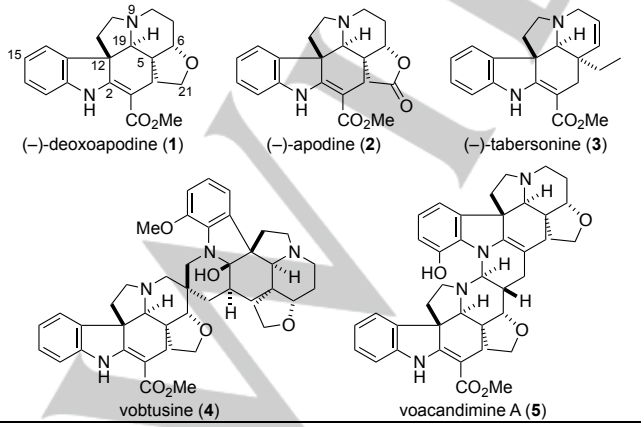
A Concise Enantioselective Total Synthesis of (–)-Deoxoapodine

Kei Yoshida,[+] Kosuke Okada,[+] Hirofumi Ueda, and Hidetoshi Tokuyama*

Abstract: We established a highly convergent 10-step route for total synthesis of (–)-deoxoapodine, which is a hexacyclic aspidosperma alkaloid. The quaternary carbon center at C5 on the characteristic tetrahydrofuran ring was constructed *via* a chiral phosphoric acid-catalyzed enantioselective bromocycloetherification in a 5-*endo* fashion and subsequent allylation by using Keck's protocol. The aspidosperma skeleton was constructed featuring the formation of 9-membered lactam by catalytic C–H palladation/alkylation cascade at the indole 2-position and the iron-catalyzed oxidative transannular reaction at the late-stage of synthesis.

Over the last decades, aspidosperma alkaloids possessing fused pentacyclic skeleton have attracted significant attention from the synthetic community[1] as this family of compounds displays remarkable structural diversity and constitutes clinically important antitumor bisindole alkaloids, such as vinblastine.[2] A several congeners, including (–)-deoxoapodine (**1**) and (–)-apodine (**2**), among these alkaloids, have oxygenated structure at the C21 position. (–)-Deoxoapodine (**1**), isolated first from *Tabernae armeniaca* and then from *Hazunta modesta*, has the characteristic tetrahydrofuran (THF) ring fused to aspidosperma skeleton.[3] Two bisindole alkaloids, vobtusine (**4**) and voacandimine A (**5**), isolated from *Voacanga africana* Stapf (*Apocynaceae*), are composed of two deoxoapodine segments with two different modes of connectivity (Figure 1).[4] An enantioenriched total synthesis[5] and two enantioselective total syntheses[6,7] have so far been reported after the first racemic total synthesis of **1** by Overman *et al.*[8] In this paper, we report a convergent 10-step total synthesis of **1** by featuring an enantioselective construction of contiguous C5 and C6 centers *via* a catalytic enantioselective 5-*endo* bromocycloetherification,[9] formation of a highly strained bridged 9-membered ring through Pd-catalyzed C–H activation/alkylation cascade at indole C2 position, and an iron-catalyzed oxidative transannular reaction to form an aspidosperma skeleton.

Figure 1. Aspidosperma Family Alkaloids



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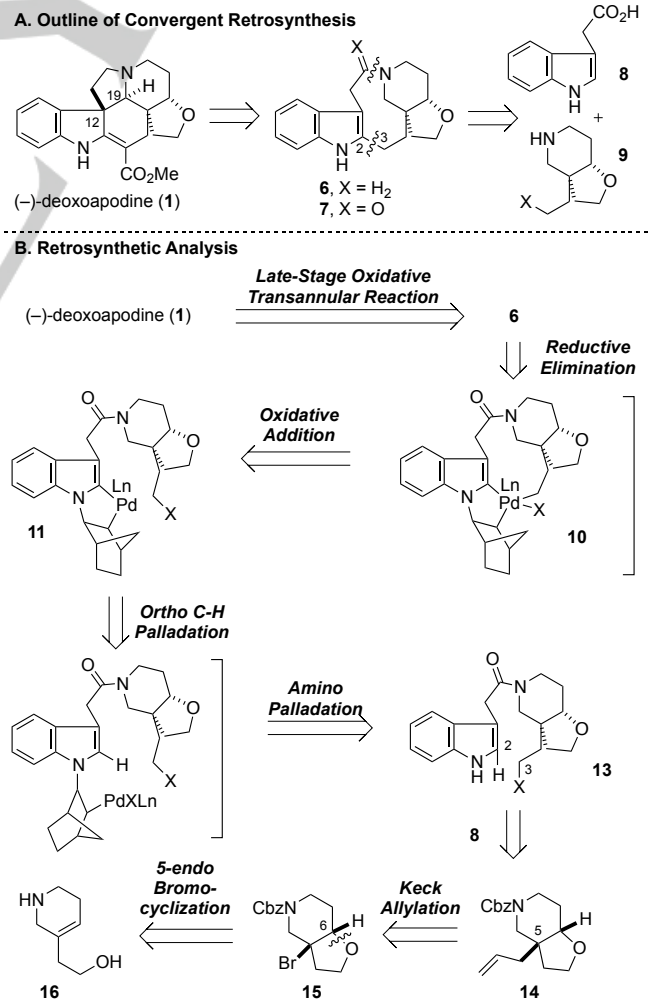
We designed a convergent route by dissecting **1** into two segments through a quebrachamine type precursor (**6** or **7**). During this process, disconnection of C12–C19 bond gave the quebrachamine analog (**6** or **7**). Then, this analog broke down into indole-3-acetic acid (**8**) and a bicyclic THF-fused piperidine segment **9** (Scheme 1A). To realize this highly convergent route to **1**, three major synthetic challenges should be addressed: oxidative transannular reaction to form C12–C19 bond,[10] assembly of the quebrachamine skeleton possessing highly strained bridged 9-membered ring,[11] and asymmetric synthesis of bicyclic THF-fused piperidine segment.

With these considerations in mind, we conducted a retrosynthetic analysis of **1** (Scheme 1B). To realize the oxidative transannular Mannich reaction at the indole C3 position of **6**, a broad range of oxidation protocols, such as the conditions of using a stoichiometric oxidant,[10,12a] recently developed photoredox reactions,[12b] and the reaction in presence of non-heme type iron catalyst,[13] were extensively screened. We designed a cascade process to connect indole C2 position and halogenated alkyl chain of substrate **13** for the formation of the

Scheme 1. Retrosynthetic Analysis.

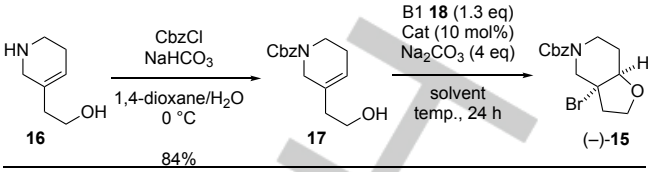


highly strained bridged 9-membered ring in the quebrachamine skeleton by applying Bach's intermolecular C–H alkylation condition of indole[14a] to the intramolecular version. This process would start from nitrogen-assisted norbornene mediated ortho C–H palladation at indole 2-position, followed by ring closure of the highly strained bridged 9-membered ring *via* less strained 10-membered palladacycle and subsequent reductive elimination. Substrate **13** would be assembled from indole-3-acetic acid (**8**) and THF-fused piperidine segment **14**. For an asymmetric synthesis of the THF-fused piperidine segment, we planned development of an enantioselective *5-endo* bromocycloetherification and subsequent quaternarization of C5 tertiary bromide by radical-mediated Keck allylation with retention of the configuration.[15]

Our research commenced with studies on the asymmetric bromocycloetherification using homoallylic alcohol **17**. In general, asymmetric halocycloetherification is difficult and rare because coordination of alcohols to chiral Lewis bases by formation of hydrogen bonding or ion pairing is relatively poorer than that of carboxylic acids.[16] Moreover, almost all the cases are using activated olefin such as a styrene derivative as substrate and there are few examples of using a non-activated olefin. Upon selection of a catalytic system, we focused on the Toste's chiral anion concept in phase-transfer catalytic reactions and its application to bromocyclization of tryptophol by Ma and Xie *et al*.[17] Thus, we treated substrate **17**, which was derived from the commercially available alcohol **16**, with chiral anion bromonium ion complex generated from a combination of (*R*)-binaphthyl-phosphoric acid (*R*)-Cat 1 and B1 (**18**) as a bromonium ion source in toluene at 0 °C (Table 1, entry 1). While the desired *5-endo* bromocycloetherification product (–)-**15** was obtained, the yield and enantiomeric excess (ee) were low. Cat 2-4 having bulky substituents at 3 and 3′ positions, were not effective (entries 2–4). On the other hand, both chemical yield and ee were dramatically improved by using Cat 5 and Cat 6 having bulkier 2,4,6-trisubstituted phenyl groups (entries 5 and 6) and were further improved by using Cat 7 having linear alkyl chains at 6 and 6′ positions to afford **15** in 75% yield and 70% ee (entry 7). Cat 8, having different scaffold than BINOL motif, gave parallel result with that obtained with Cat 7 (entry 8). On the other hand, Cat 9, which has a (*R*)-1,1′-spirobiindane skeleton, provided (+)-**15** with the opposite stereochemistry (entry 9). Given the best result with Cat 7, further optimizations on solvent and reaction temperature were carried out (entries 10–14). Eventually, the desired bicyclic bromoether **15** was obtained at best in 71% yield and 84% ee by the reaction in a 1:1 (v/v) mixture of fluorobenzene and heptane at −30 °C (entry 15). Conversion of (–)-**15** into the final deoxoapodine revealed that the absolute stereochemistry of (–)-**15** was determined to be opposite to that required for the synthesis of natural (–)-deoxoapodine (**1**). Finally, reliability and scalability of this catalytic enantioselective process was proved by a two-gram scale reaction with excellent reproducibility (entry 16). Moreover, we can recover Cat 7 in 90% yield and reuse without losing its enantioselectivity.[18]

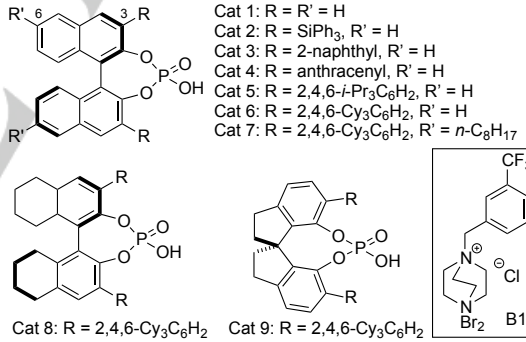
Having established the catalytic enantioselective 5-*endo* bromocycloetherification of non-activated olefin, we then assembled the substrates **21** and **22** for testing the palladium-

Table 1. Studies on Asymmetric Bromocyclization



Entry	Catalyst	Solvent	Temp. (°C)	Yield[a] (%)	ee (%)
1	(*R*)-Cat 1	PhMe	0	14	–9
2	(*R*)-Cat 2	PhMe	0	24	31
3	(*R*)-Cat 3	PhMe	0	22	–14
4	(*R*)-Cat 4	PhMe	0	14	–3
5	(*R*)-Cat 5	PhMe	0	77	52
6	(*R*)-Cat 6	PhMe	0	59	64
7	(*R*)-Cat 7	PhMe	0	75	70
8	(*R*)-Cat 8	PhMe	0	72	65
9	(*R*)-Cat 9	PhMe	0	46	–70
10	(*R*)-Cat 7	PhCl	0	61	74
11	(*R*)-Cat 7	PhF	0	62	74
12	(*R*)-Cat 7	PhF/*n*-hexane	0	52	79
13	(*R*)-Cat 7	PhF/*n*-hexane	–20	57	80
14	(*R*)-Cat 7	PhF/*n*-heptane	–20	64	81
15[b]	(*R*)-Cat 7	PhF/*n*-heptane	–30	71	84
16[c]	(*S*)-Cat 7	PhF/*n*-heptane	–30	76	–86

[a] Isolated yield. [b] Reaction time was 72 h. [c] The reaction was conducted in a two gram-scale and the reaction time was 120 h. Cbz = benzyloxycarbonyl.



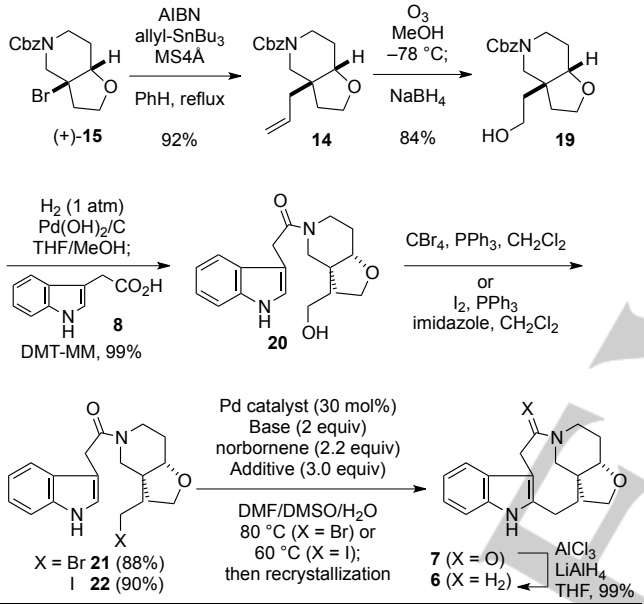
mediated C–H activation/cyclization cascade. First, bromoether (+)-**15**, which was obtained under the established optimal conditions using (*S*)-Cat 7, was subjected to Keck's allylation condition[15] (Scheme 2). Desired allylation reaction proceeded uneventfully with the retention of the configuration to produce **14** possessing the C5 quaternary carbon center. Ozonolysis of the terminal alkene, followed by a reductive treatment, afforded primary alcohol **19**. After removal of benzyloxycarbonyl (Cbz) group, the resultant secondary amine was condensed with indole-3-acetic acid (**8**) produced amide **20**. Finally, the desired bromide **21** and iodide **22** were obtained by the corresponding Appel reaction of primary alcohol **20**.

With the indole substrate in hand, we examined the formation of the highly strained bridged 9-membered lactam ring by palladium catalyzed C–H activation/intramolecular alkylation cascade (Scheme 2). First, bromide **21** was subjected to the Bach's intermolecular alkylation condition with $PdCl_2$ and K_2CO_3 in the presence of norbornene at 80 °C.[14] Gratifyingly, the

designed cascade reaction proceeded to provide 9-membered lactam **7** in 9% yield along with a formation of bromo-chloro substitution product (entry 1). Use of $PdBr_2$ was effective to suppress the substitution reaction and significantly accelerate the reaction to provide **7** in higher yield (entry 2). Switching K_2CO_3 to K_3PO_4 further accelerated conversion of **21** (entry 3). Afterwards, we found that iodide **22** was better substrate and the reaction of **22** with PdI_2 proceeded at 60 °C to give **7** in 38% yield (entry 5). Extensive optimization led us to find that halide scavengers, such as NaOTf,[19] $NaNTf_2$, and $KNTf_2$, were crucial or high yielding reaction (entries 6–8). Thus, the yield of **7** was dramatically improved up to 67% when iodide **22** was treated with PdI_2, K_3PO_4, $KNTf_2$, and norbornene at 60 °C.[20] A control experiment without norbornene did not gave the desired product **7** (entry 9), supporting that this reaction started from a norbornene-induced amino palladation as shown in Scheme 1. At this stage, the optical purity of lactam **7** was improved up to >99% ee by recrystallization. Finally, reduction of lactam **7** by alane furnished pentacyclic **6** possessing the THF-fused quebrachamine skeleton.

We then focused our attention on the oxidative transannular reaction. First, Kutney's conditions[10] by using $Hg(OAc)_2$ was tested. However, the reaction only gave a complex mixture and the expected aspidosperma skeleton was not formed (Table 2, entry 1). Stephenson's photoredox condition[12b] by using Ru catalyst and bromomalonate resulted in a decomposition of the starting material **6** (entry 2). The reaction with iodine and sodium bicarbonate in acetonitrile[12a]

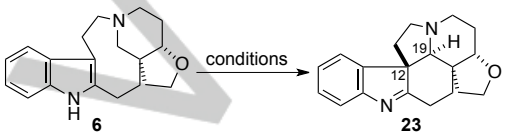
Scheme 2. Synthesis of 9-Membered Tertiary Amine



Entry	X	Pd catalyst	Base	Additive	Time (h)	Yield[a] (%)
1	Br	$PdCl_2$	K_2CO_3	–	120	9
2	Br	$PdBr_2$	K_2CO_3	–	28	28
3	Br	$PdBr_2$	K_3PO_4	–	20	27
4[b]	I	$PdBr_2$	K_3PO_4	–	23	31
5[b]	I	PdI_2	K_3PO_4	–	17	38
6[b]	I	PdI_2	K_3PO_4	NaOTf	48	48
7[b]	I	PdI_2	K_3PO_4	$NaNTf_2$	48	55
8[b]	I	PdI_2	K_3PO_4	$KNTf_2$	10	67
9[b,c]	I	PdI_2	K_3PO_4	$KNTf_2$	10	0[d]

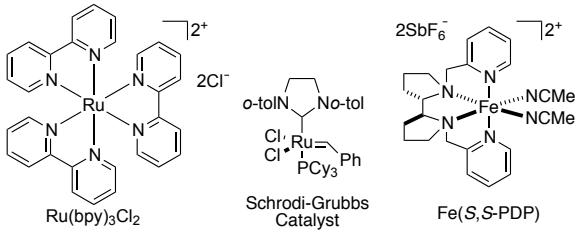
[a] Isolated yield. [b] DMA was used instead of DMF. [c] Norbornene was not used. [d] The starting material **22** was recovered in 61% yield. AIBN = azobisisobutyronitrile, MS = molecular sieves, DMT-MM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide, Tf = trifluoromethanesulfonyl, DMA = *N,N*-dimethylacetamide.

Table 2. Examination of Oxidative Transannular Mannich Reaction



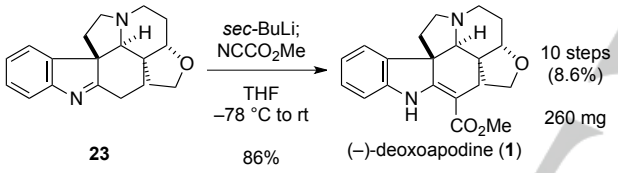
Entry	Reagent (equiv)	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	$Hg(OAc)_2$ (2.2)	AcOH	rt to reflux	24	0
2	$Ru(bpy)_3Cl_2$ (0.10) bromomalonate (3.0)	DMF	50	24	0
3	I_2 (3.0) sat. aq. $NaHCO_3$	MeCN	0	0.5	6
4	$K_3Fe(CN)_6$ (10)	*t*-BuOH /H_2O	0	2	6
5	*n*-Bu_4NBF_4 2.5 F/mol, 30 mA	MeOH	rt	1	0
6	Schrodi-Grubbs Catalyst (0.10)	EtOAc	70	24	0
7	AcOH (10), O_2 (1 atm)	DCE	60	2	13
8	Fe(*R,R*-PDP) (0.15) H_2O_2 (3.6)	*t*-BuOH	rt	3	22
9	Fe(*S,S*-PDP) (0.15) H_2O_2 (3.6)	*t*-BuOH	rt	0.3	38
10	Fe(*S,S*-PDP) (0.03) H_2O_2 (3.0)	*t*-AmOH	rt	3	35 (42)[b]
11	Fe(*S,S*-PDP) (0.03) TBHP (3.0)	*t*-AmOH	rt	0.5	33

[a] Isolated yield. [b] Based on recovered **6** (16%). bpy = bipyridine, DCE = 1,2-dichloroethane, PDP = bis(2-pyridinylmethyl)-2,2'-bipyrrolidine.



and oxidation conditions by using potassium ferricyanide[21] gave the desired product **23**, although the yield was only 6% (entries 3 and 4). Next, an electrochemical condition[22] and the aerobic oxidation with Grubbs catalyst developed by our group[23] were examined. In both cases, the starting material **6** was completely consumed, however, the desired product **23** was not obtained (entries 5 and 6). Interestingly, acetic acid-promoted aerobic oxidation of **6** provided **23** in 13% yield (entry 7).[24] Furthermore, non-heme type iron catalyst, such as Fe(*R*,*R*-PDP) and H_2O_2, as oxidant was effective to promote the oxidative intramolecular Mannich reaction to provide aspidosperma skeleton **23** in 22% yield (entry 8).[25] Interestingly, we observed the match–mismatch combination between substrate and catalyst. Thus, Fe(*S*,*S*-PDP) improved the yield of **23** up to 38% and substantially shortened the reaction time (entry 9). The catalyst loading of Fe(*S*,*S*-PDP) could be reduced to 3 mol% by using *t*-AmOH as solvent without losing the chemical yield of **23** (entry 10). Use of *tert*-butyl hydroperoxide (TBHP) instead of H_2O_2 accelerated the reaction (entry 11). The established optimal conditions (entry 10) were applicable to a half gram-scale reaction.[26] Finally, methoxy carbonyl group was introduced *via* a metalloenamine as intermediate to afford a sub-gram quantity (260 mg) of (–)-deoxoapodine (**1**) (Scheme 3).

Scheme 3. Total Synthesis of (–)-Deoxoapodine



synthetic **1**: $[\alpha]_D^{26}$ = –497 (*c* = 0.56, $CHCl_3$)
natural **1**: $[\alpha]_D^{25}$ = –432 (*c* = 0.76, $CHCl_3$)[Ref. 3]

In summary, we accomplished a concise total synthesis of (–)-deoxoapodine (**1**) in overall 10 steps[26] and with 8.6% yield. This successful synthesis relied on the design of a highly convergent route by utilizing direct formation of C12–C19 bond and C2–C3 bond based on the development of two C–H functionalization protocols and the early-stage construction of the right-hand bicyclic THF-fused piperidine segment by developing catalytic enantioselective 5-*endo* bromocycloetherification of non-activated olefin. The convergent synthetic design based on C–H functionalization was effective to reduce chemical steps and to eliminate protection/deprotection sequence. Over the entire synthetic route, we used only one protecting group. Efficiency and scalability of the synthesis of monomer unit is expected to expedite the synthetic research on the series of structurally intriguing dimeric compounds.

Acknowledgements

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Keywords: total synthesis · alkaloid · haloetherification · C-H functionalization · oxidation

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[10] For construction of aspidosperma skeleton by transannular Mannich reaction via oxidation of C12 position was only limited to Kutney's protocol using highly toxic $Hg(OAc)_2$, which resulted in a low yield and Ziegler's preliminary experiment (Ref. 1d) using Pt/O_2 (yield not reported). No alternative method has been developed over the half

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[11] Our model studies on the formation of the 9-membered ring in quebrachamine skeleton did not give the desired product except Bach's C-H alkylation of indole C2 position giving the desired product in only 11%, indicating difficulty of constructing this structure possibly due to the highly strained nature (see, the Supporting Information). See, also: a) B. Bajtos, B. L. Pagenkopf, *Eur. J. Org. Chem.* **2009**, 1072–1077; For a direct construction of quebrachamine structure by forming C2-C3 bond of 9-membered ring, see: b) F. E. Ziegler, G. B. Bennett, *Tetrahedron Lett.* **1970**, *11*, 2545–2547; For a selected example of formation of 9-membered ring of quebrachamine skeleton by reductive or nucleophilic cleavage of quaternary salt of tetrahydro-β-carboline derivative, see: c) J. Harley-Mason, A. Rahman, *Chem. Commun.* **1967**, 1048–1049.

[12] Iodine-mediated reaction or photoredox catalysis for the oxidative transannular reactions were recently reported although these cases only limited to construction of pseudoaspidosperma compounds without ethyl group at the C-5 position. a) C. Leitner, T. Gaichi, *Chem. Commun.* **2017**, *53*, 7451–7453; b) J. W. Beatty, C. R. J. Stephenson, *Acc. Chem. Res.* **2015**, *48*, 1474–1484. We also failed to apply this protocol for construction of aspidosperma skeleton.

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[20] When the reaction was conducted on a gram scale, the yield was decreased to a modest yield, see the Supporting Information.

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[25] Reaction using Fe-PDP only gave an unidentifiable complex mixture besides the desired product. Other oxidation conditions gave trace amount of side products due to oxidation of indole skeleton of the substrate and over-oxidation of the *tertiary* amine moiety or indole moiety of the desired product. These observations indicated that Fe-PDP conditions promoted further oxidative degradations triggered by these side reactions.

[26] See, the Supporting Information.

[27] The efficiencies of our total synthesis (10 total steps: 10 steps in longest linear sequence (LLS)) could be recognizable by comparison with those in the previous total syntheses, i.e., Overman's synthesis (24 total steps: 21 steps in LLS), Boger's synthesis (23 total steps: 19 steps in LLS), Movassaghi's synthesis (22 total steps: 17 steps in LLS), Peng's synthesis (17 total steps: 17 steps in LLS).

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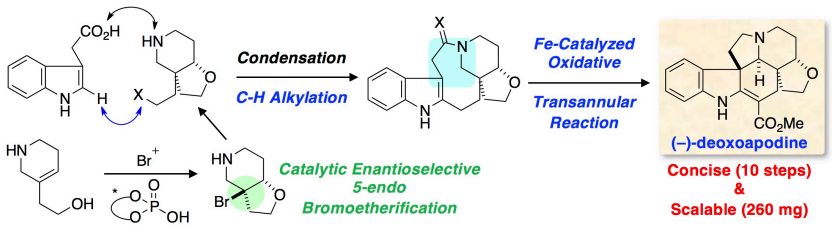

A highly convergent 10-step route for total synthesis of (–)-deoxoapodine was established. The quaternary carbon center at C5 on the characteristic tetrahydrofuran ring was constructed *via* a chiral phosphoric acid-catalyzed enantioselective bromocycloetherification in a 5-*endo* fashion and subsequent allylation by using Keck's protocol. The aspidosperma skeleton was constructed featuring the formation of 9-membered lactam by catalytic C–H palladation/alkylation cascade at the indole 2-position and the iron-catalyzed oxidative transannular reaction at the late-stage of the synthesis.

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