▌**Total Synthesis**
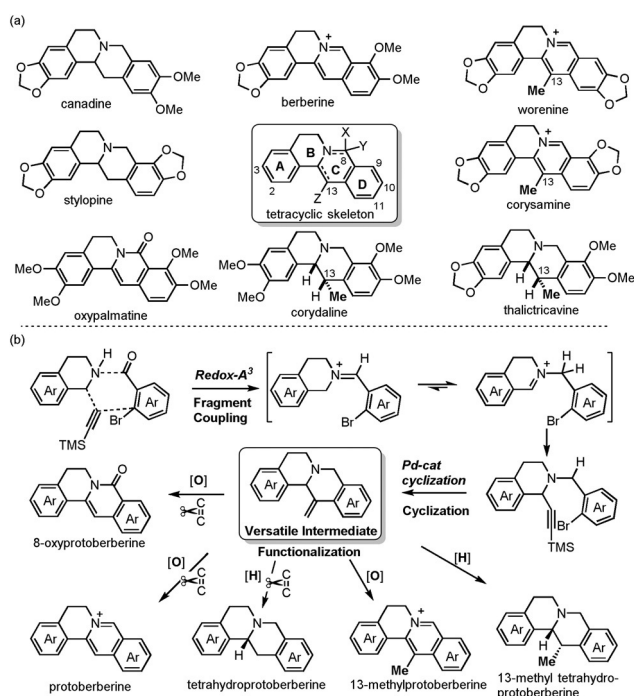
A General, Concise Strategy that Enables Collective Total Syntheses of over 50 Protoberberine and Five Aporhoeadane Alkaloids within Four to Eight Steps

Shiqiang Zhou and Rongbiao Tong*[a]

Abstract: A concise, catalytic, and general strategy that allowed efficient total syntheses of 22 natural 13-methylprotoberberines within four steps for each molecule is reported. This synthesis represents the most efficient and shortest route to date, featuring three catalytic processes: CuI-catalyzed redox-A^3 reaction, Pd-catalyzed reductive carbocyclization, and PtO$_2$-catalyzed hydrogenation. Importantly, this new strategy to the tetracyclic framework has also been applied to the collective concise syntheses of >30 natural protoberberines (without 13-methyl group) and five aporhoeadane alkaloids.

Protoberberine alkaloids such as canadine, berberine, stylopine, corysame, and corydaline (Figure 1a) are widely spread in the plant kingdom and over 150 members have been reported from these species.[1] They represent a pharmacologically important group of isoquinoline alkaloids for their broad and potent biological activities with diverse structures.[2] Three key structure-differentiating features among protoberberines are: 1) substituents of A/D rings (usually four substituents of hydroxy, methoxy, and/or methylenedioxy at positions of either C2, C3, C9, C10 or C2, C3, C10, C11); 2) oxidation state of the C ring; and 3) the presence/absence of a methyl group at C13 of the C ring. Tremendous prior synthetic efforts[3] have been predominantly devoted to the rapid construction of the tetracyclic backbone with desired aromatic substitutions (A/D rings) through regioselective cyclizations. These synthetic studies also led to identification of efficient methods for different oxidation states of the C ring.[4] Synthetic methods to access the tetracyclic skeleton with 13-methyl group, which features in a number of protoberberines (>20 isolated, e.g., thalictricavine, corydaline, corysamine, and worenine, Figure 1a), are rather underdeveloped.[5] The classical Bersch procedure, which involves 1) reduction of protoberberine salt with precisely one equivalent of NaBH$_4$ and 2) subsequent reaction with formalde-

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Figure 1. a) Representative protoberberine alkaloids. b) This work: our postulated synthetic strategy.

hyde in acetic acid or methyl iodide/NaBH$_4$ reduction, is still employed despite moderate yields, a lack of generality (not applicable to other aldehydes), and dependence on availability of the corresponding intact protoberberine or its quaternary salt.[6] In 2014, Donohoe[7] et al. developed a short route for the synthesis of three protoberberines, which could allow subsequent regioselective methylation for the total synthesis of 13-methylprotoberberine dehydrocorydaline with 47% overall yield in eight steps. More recently, Seidel[8] reported a redox–Mannich reaction to access the tetrahydroprotoberberine core, which could be elaborated to the thalictricavine with 14.3% overall yield in a total of 11 steps. Nevertheless, the lack of a more efficient and general synthetic method for 13-methylprotoberberines coupled with the proven beneficial effects of 13-methyl (or 13-alkyl) on biological activities[9] prompted us to develop a de novo synthetic strategy. Here, we report a novel, concise, general strategy for the collective synthesis of 22 natural 13-methylprotoberberines within four steps, featuring CuI-catalyzed redox-A^3 reaction[10] and Pd-catalyzed reductive cyclization. Importantly, this strategy could be employed for truly

collective syntheses of more than 30 natural protoberberine alkaloids lacking a 13-methyl group and five aporhoeadane alkaloids within four to eight steps.

Strategically inspired by recent work on redox-A[3] reactions[10] by the research groups of Seidel,[11] Yu,[12] and Ma,[13] we conceived that a redox-A[3] reaction of a tetrahydroisoquinoline (THIQ), acetylene, and a 2-bromoaldehyde could be exploited to construct the key tetracyclic protoberberine skeleton with the C ring decorated with exo-alkene as the potential methyl group if the subsequent Pd-catalyzed reductive exo-selective carbocyclization[14] could be realized (Figure 1b). Furthermore, if the exo-methylene at C13 could be cleaved by a method such as $NaIO_4/RuCl_3$ or O_3/Me_2S and the oxidation state of the C ring could be manipulated after cleavage, it would be possible for us to access other members of protoberberine alkaloids lacking 13-methyl group. Optimistically, if this strategy is successfully implemented, a rapid assembly of a large collection of natural protoberberines and 13-methylprotoberberines and their analogues could be achieved efficiently. Additionally, the key redox-A[3] reaction employs a one-pot transformation of aldehyde, amine, alkyne (A[3])[15] and could be regarded as a multicomponent reaction, which will provide the most efficiency and flexibility.[16]

We first concentrated on identification of redox-A[3] reaction conditions for THIQ (1a), aldehyde 2a, and acetylene (3a) because none of them has been employed in the previous examples of redox-A[3] reaction. After preliminary examinations of the redox-A[3] reaction conditions reported previously,[11–13] we were delighted to find that the redox-A[3] reaction of 1a, 2a, and 3 under a slightly modified condition (addition of catalytic amount of benzoic acid using CuI as the catalyst without the phosphine ligand) gave an excellent yield of 4a on both milligram and gram scales after subsequent desilylation with K_2CO_3 in methanol (Scheme 1). Remarkably, the addition of benzoic acid (0.1 equiv) greatly accelerated the conversion, improved the yield (from < 5% to 81%) and reproducibility, and expanded the THIQ scope for the redox-A[3] reaction. This exciting result was in sharp contrast to the observation by Yu and Seidel. We speculated that the favorable steric effects of ortho-substituents of 2-bromo-5,6,-dimethoxybenzaldehyde might mitigate the unfavorable electronic effects of THIQ (observed
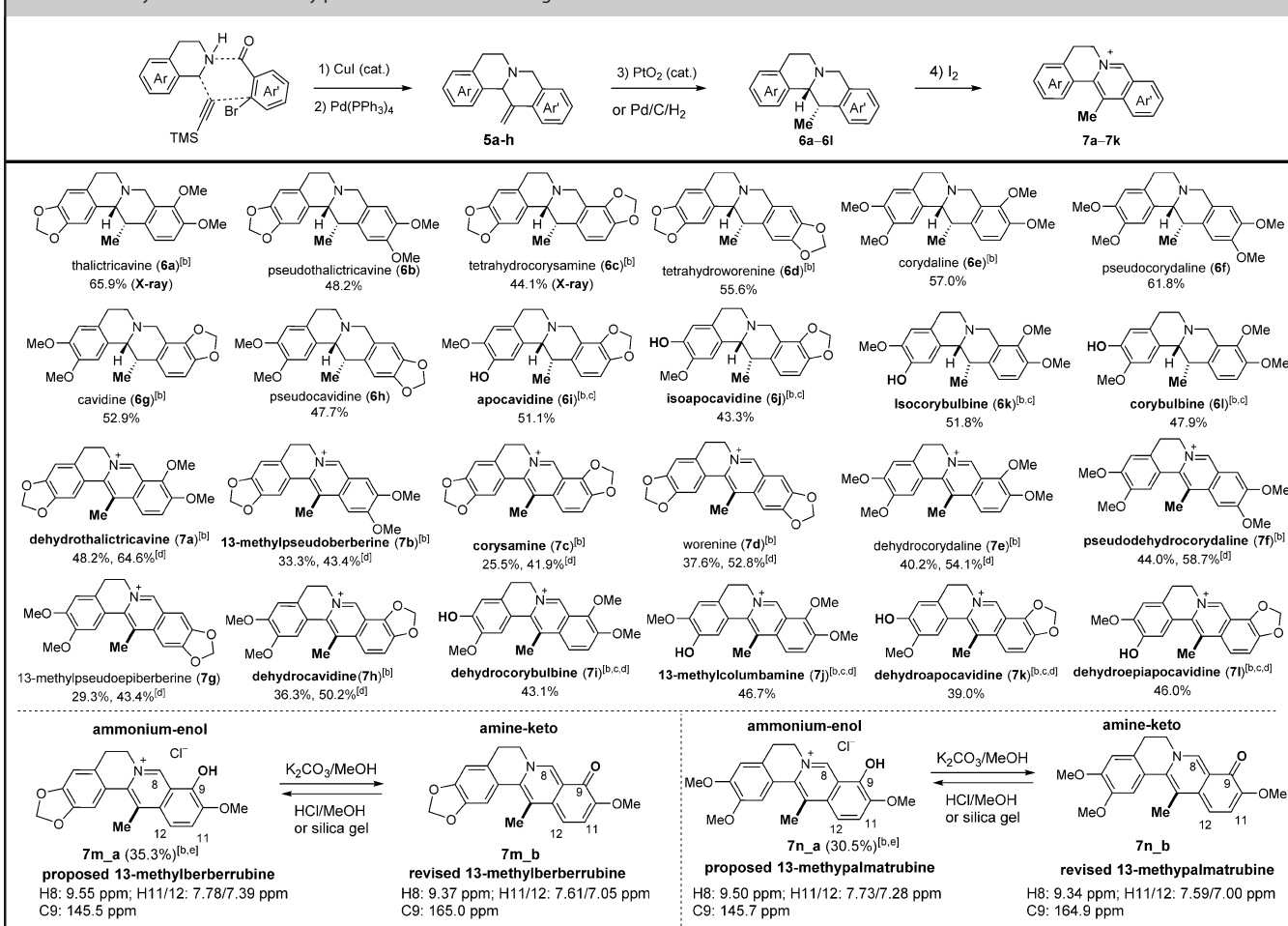
by Yu). Next, we explored the exo-carbocyclization reaction of 4a to construct the tetracyclic framework, corresponding to the protoberberine core. After unsuccessful attempts on the radical cyclization using either $AIBN/Bu_3SnH$ or SmI_2, we then examined the possibility of Pd-catalyzed reductive carbocyclization of 4a. Among all protocols examined, including $Pd(PPh_3)_4/Et_3SiH$, $Pd(PPh_3)_4/Bu_3SnH$, $Pd(PPh_3)_4/HCO_2H/Et_3N$, $Pd(OAc)_2/PPh_3/HCO_2Na$, and $Pd(PPh_3)_4$ and HCO_2Na, we fortunately found that the combination of $Pd(PPh_3)_4$ and HCO_2Na in DMF at 100 °C effected the reductive exo-carbocyclization to provide the desired tetracyclic protoberberine framework 5a in 79% yield. It was noted that longer reaction time (e.g., overnight) caused a significant decomposition of the product 5a. Next, we attempted the catalytic hydrogenation of the exo-methylene of 5a for the synthesis of 13-methylprotoberberine. After examination of many conditions, including $Pd/C/H_2$ in MeOH (EtOAc, or toluene), $Pd(OH)_2/C/H_2$ in MeOH, and PtO_2/H_2 in MeOH under various temperatures, PtO_2/H_2 (1 atm) in acetic acid was found to be the only condition that could effectively promote the hydrogenation, which furnished (±)-thalictricavine[17] (6a) as the single diastereomer in a nearly quantitative yield. The structure of our synthetic thalictricavine (6a) was further confirmed by X-ray diffraction analysis and the NMR data of our synthetic thalictricavine were in good agreement with those reported for thalictricavine. To date, this constitutes the most efficient and shortest synthesis (69.5% overall yield in three steps). Oxidation of thalictricavine with iodine in ethanol completed the synthesis of the quaternary 13-methylprotoberberine salt dehydrothalictricavine[18] (7a, also known as 13-methylberberine) in 99% yield, which is, to date, the first de novo synthesis. We recognized that this two-step protocol (5a→6a→7a) provides a reliable and high-yielding access to the family of the quaternary 13-methylprotoberberines, but it was not redox-economical[19] for employment of the reduction and subsequent oxidation. Therefore, we were interested in the idea of isomerization and concomitant oxidation (5a→8a→7a) in a single operation. After some experimentation, we found that the $RhCl_3$-catalyzed isomerization[20] of 5a occurred with concomitant oxidation under air atmosphere (open flask) to produce the corresponding quaternary dehydrothalictricavine (7a) in a single step but with only 65% yield. Notably, direct oxidation of 5a with iodine in ethanol resulted in a 1:1 inseparable mixture of 7a and an unknown compound.

This extremely short and highly efficient route to 13-methylprotoberberines were further demonstrated in the collective total synthesis of additional 20 natural 13-methylprotoberberines[21] and four analogues in excellent overall yields with only three or four steps (Table 1). In particular, we accomplished the first de novo total synthesis of the following 15 natural products (names highlighted in bold in Table 1): 6i–l, 7a–c, 7f, and 7h–n. When compared with previous total syntheses[22] of 6a, 6c, 6d, 6e, 6g, 7d, and 7e, our syntheses were shorter and more efficient with a single flexible and catalytic strategy. It is noteworthy that hydrogenation and debenzylation could be accomplished by palladium catalysis in a single step with excellent yields to provide otherwise poorly accessible 2- or 3-de-
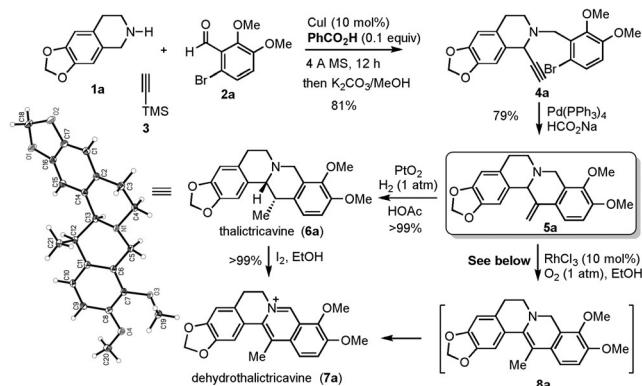
Scheme 1. Synthesis of thalictricavine and 13-methylprotoberberine through redox-A[3] reaction and Pd-catalyzed reductive carbocyclization.

Table 1. Total syntheses of 13-methylprotoberberines and analogues.[a]

Reaction scheme: starting material (with Ar, Ar', TMS, Br, H, O) → 1) CuI (cat.); 2) Pd(PPh$_3$)$_4$ → **5a–h** → 3) PtO$_2$ (cat.) or Pd/C/H$_2$ → **6a–6l** → 4) I$_2$ → **7a–7k**

Row 1 compounds (6a–6f):
- thalictricavine (**6a**)[b] 65.9% (X-ray)
- pseudothalictricavine (**6b**) 48.2%
- tetrahydrocorysamine (**6c**)[b] 44.1% (X-ray)
- tetrahydroworenine (**6d**)[b] 55.6%
- corydaline (**6e**)[b] 57.0%
- pseudocorydaline (**6f**) 61.8%

Row 2 compounds (6g–6l):
- cavidine (**6g**)[b] 52.9%
- pseudocavidine (**6h**) 47.7%
- apocavidine (**6i**)[b,c] 51.1%
- isoapocavidine (**6j**)[b,c] 43.3%
- Isocorybulbine (**6k**)[b,c] 51.8%
- corybulbine (**6l**)[b,c] 47.9%

Row 3 compounds (7a–7f):
- dehydrothalictricavine (**7a**)[b] 48.2%, 64.6%[d]
- 13-methylpseudoberberine (**7b**)[b] 33.3%, 43.4%[d]
- corysamine (**7c**)[b] 25.5%, 41.9%[d]
- worenine (**7d**)[b] 37.6%, 52.8%[d]
- dehydrocorydaline (**7e**)[b] 40.2%, 54.1%[d]
- pseudodehydrocorydaline (**7f**)[b] 44.0%, 58.7%[d]

Row 4 compounds (7g–7l):
- 13-methylpseudoepiberberine (**7g**) 29.3%, 43.4%[d]
- dehydrocavidine (**7h**)[b] 36.3%, 50.2%[d]
- dehydrocorybulbine (**7i**)[b,c,d] 43.1%
- 13-methylcolumbamine (**7j**)[b,c,d] 46.7%
- dehydroapocavidine (**7k**)[b,c,d] 39.0%
- dehydroepiapocavidine (**7l**)[b,c,d] 46.0%

Bottom interconversion schemes:

Left:
- ammonium-enol: **7m_a** (35.3%)[b,e] proposed 13-methylberberrubine; H8: 9.55 ppm; H11/12: 7.78/7.39 ppm; C9: 145.5 ppm
- K$_2$CO$_3$/MeOH ⇌ HCl/MeOH or silica gel
- amine-keto: **7m_b** revised 13-methylberberrubine; H8: 9.37 ppm; H11/12: 7.61/7.05 ppm; C9: 165.0 ppm

Right:
- ammonium-enol: **7n_a** (30.5%)[b,e] proposed 13-methylpalmatrubine; H8: 9.50 ppm; H11/12: 7.73/7.28 ppm; C9: 145.7 ppm
- K$_2$CO$_3$/MeOH ⇌ HCl/MeOH or silica gel
- amine-keto: **7n_b** revised 13-methylpalmatrubine; H8: 9.34 ppm; H11/12: 7.59/7.00 ppm; C9: 164.9 ppm

[a] Isolated yields over three/four steps. [b] Naturally occurring substance. [c] Pd/C was used as the catalyst for hydrogenation of alkene and debenzylation. [d] One equivalent of I$_2$ was used as oxidant for synthesis of quaternary ammonium salt. [e] 2 N HCl was used for deprotection of MOM ether.

methyl protoberberines including **6i–l** and **7i–n**. Most NMR data of our synthetic 13-methylprotoberberines perfectly matched those reported for the authentic samples, except for 13-methylberberrubine[23] (**7m**) and 13-methylpalmatrubine[24] (**7n**). On the basis of careful NMR analysis, we concluded that **7m** and **7n** may undergo rapid interconversions[25] between its ammonium-enol and amine-keto forms depending on the basic (K$_2$CO$_3$) or acidic (2N HCl or silica gel) conditions (**7m_a**⇌**7m_b** and **7n_a**⇌**7n_b**, Table 1). The characteristic resonance of the C9 at 165 ppm in the ^{13}C NMR suggests the amine-keto form, whereas its ammonium-enol resonates around 145 ppm. In light of these new findings and NMR comparison, we proposed that the structure for 13-methylberberrubine and 13-methylpalmatrubine should be revised as its amine-keto forms, **7m_b** and **7n_b**, respectively.

Next, we turned our attention to explore the oxidative/reductive cleavage of the "extra" exo-methylene group, which were expected to allow the collective synthesis of the other three major types of protoberberines from the common tetracyclic framework of type **5a**. To this end, we had attempted to

cut off this "extra" carbon by oxidative cleavage of the exo-methylene using a variety of oxidation conditions including m-CPBA, O$_3$-Me$_2$S, RuCl$_3$-NaIO$_4$, and OsO$_4$-NaIO$_4$ under neutral or acidic conditions (Scheme 2). Unfortunately, prechilenine (**9a**) was consistently obtained as the only isolable product with moderate yield (15–71%). The capricious reactivity of **9a** under various reduction conditions discouraged us to make any further efforts on its conversion to protoberberines. Instead, we decided to cleave the extra carbon by hydroboration, oxidation, and decarbonylation (method A, Scheme 2). Gratifyingly, hydroboration/oxidation of **5a** followed by Swern[26] oxidation gave **14a** in 34% yield over two steps. Reductive decarbonylation with stoichiometric Wilkinson's catalyst[27] furnished tetrahydroprotoberberine (**12a**, also known as canadine) in 56% yield. Careful examination of the decarbonylation reaction by TLC led us to identify the formation of the quaternary salt protoberberine (**13a**) as the minor product, which might be derived from oxidation of canadine in the course of decarbonylation if oxygen was not strictly excluded. In fact, we found that decarbonylation with Wilkinson's catalyst
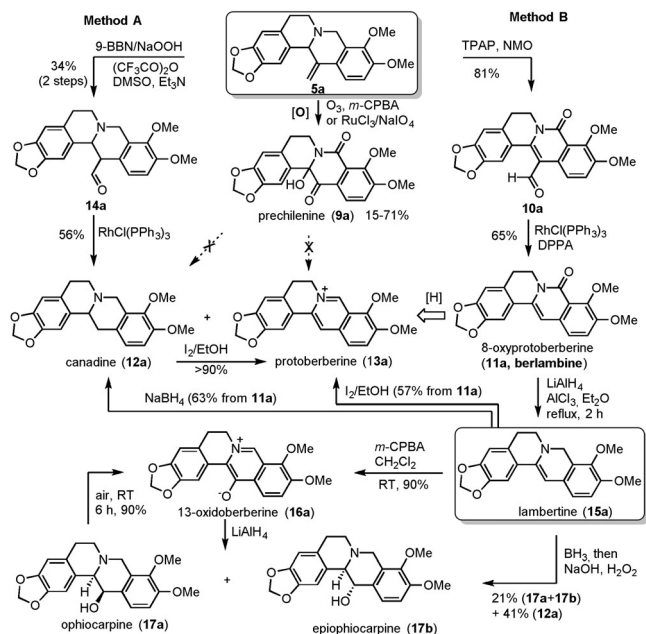
Scheme 2. Functionalizations of tetracyclic framework **5a** to canadine, protoberberine, 8-oxyberberine, lambertine, ophiocarpine, and epiophiocarpine.

Table 2. Total syntheses of 8-oxoprotoberberines, tetrahydroprotoberberines, protoberberines, and analogues.

under open flask condition occurred smoothly and provided the quaternary protoberberine salt in a good overall yield (50–70%).

Alternatively, the protoberberine salt could be obtained in > 90% yield by I$_2$ oxidation of **12a**. Several drawbacks of this functionalization route (method A) were encountered: 1) the low overall yields of hydroboration/oxidation and Swern oxidation and 2) the substrate-dependence of decarbonylation. Particularly, our subsequent studies showed that some substrates (2,3,9,10-tetramethoxy- and 2,3-dimethoxyl-10,11-methylenedioxy-) failed to undergo decarbonylation with various catalysts (Pd, Ir, Rh, etc.) under known conditions.[28] To overcome these problems, we set out to develop a more efficient and robust route (method B, Scheme 2). During the screenings of oxidation of **5a** for the oxidative cleavage of the extra methylene, we unexpectedly discovered that Ley oxidation[29] (TPAP/NMO) produced cleanly **10a** (81% yield), which upon reductive decarbonylation with either catalytic RhCl(PPh$_3$)$_3$ (10 mol%) in combination with diphenyl phosphoryl azide (DPPA)[30] or catalytic [Ir(COD)$_2$Cl]$_2$ provided 8-oxyprotoberberine (berlambine, **11a**) in 65% yield. This two-step sequence for the cleavage of the "extra" carbon proved to be a better choice with respect to the substrate scope (see Table 2) and overall yields.

Next, we concentrated our efforts on further elaboration of 8-oxyprotoberberine to other protoberberine natural products. AlCl$_3$-mediated LiAlH$_4$ reduction of 8-oxyprotoberberine furnished lambertine (**15a**) as an unstable intermediate, which without isolation (purification) could be easily reduced with NaBH$_4$ to canadine (**12a**, 63% yield over two steps) or oxidized by iodine to protoberberine (**13a**, 57% yield over two steps) in a one-pot fashion. Direct BH$_3$ reduction of **15a** produced a mixture of compounds, including ophiocarpine[31] (**17a**), epiophiocarpine[31] (**17b**), 13-oxidoberberine (**16a**) and canadine (**12a**).
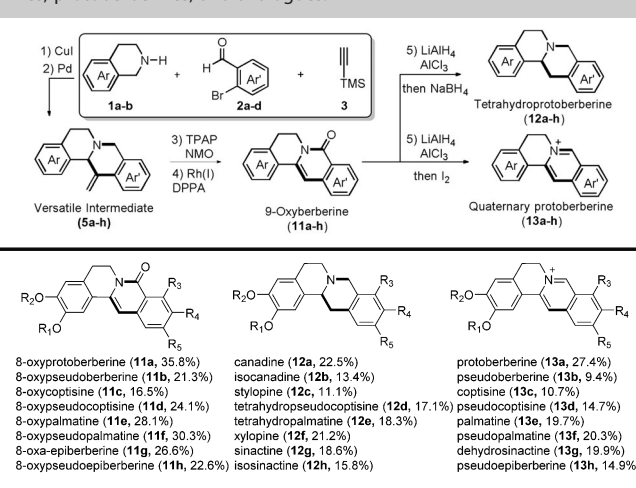
A two-step procedure, *m*-CPBA oxidation of **15a** to 13-oxidoberberine (**16a**) and LiAlH$_4$ reduction; however, could reproducibly and cleanly provide **17a** and **17b** as a 1:1 separable mixture in 62% combined yield. It was noted that both **17a** and **17b** could be readily oxidized by air and meticulous care should be taken in the course of workup and purification. In short, seven natural protoberberine alkaloids could be synthesized from the versatile tetracyclic framework **5a** within five steps.

To further expand the synthetic utility of this strategy, we set out to undertake the collective total synthesis of 22 natural protoberberine alkaloids[21] and four analogues using method B for cleavage of the *exo*-methylene at C13 (Table 2). This highly efficient assembly of tetrahydroisoquinolines (THIQs, **1a–b**), 2-bromobenzaldehydes (**2a–d**) and trimethylsilylacetylene (**3**) through the redox-A^3 reaction and palladium-catalyzed reductive carbocyclization allowed an expedient access to the tetracyclic framework (**5a–h**) for elaboration to three major types of protoberberine alkaloids (e.g., 8-oxyberberines, tetrahydroprotoberberines, and quaternary protoberberine salts) within four or five steps. Notably, our unified general strategy was superior to most prior routes tailored for specific protoberberines of potent biological activity and intensive synthetic interest, for example, stylopine,[32] coptisine,[33] xylopine,[34] sinactine,[32] and palmatine.[35]

Finally, we would like to explore the possibility of synthesis of aporheoeadane natural products by taking advantage of the isolated prechilenine (**9a**) from oxidation of **5a**, as depicted in Scheme 3. This idea was primarily inspired by the biogenetic connection of chilenine with protoberberine (**13a**) via prechilenine (**9a**) (Scheme 3a).[36] We conceived that the ready accessible **9a** from **5a** would be a good access to the aporheoeadane family of natural products if functional group transformations would be identified (Scheme 3b).[37]

Fortunately, Shamma[38] translactamization of **9a** occurred smoothly under mild basic conditions to furnish chilenine (**18**), which could be reduced by Clemmensen reduction to provide dihydrolennoxamine (**19**) and lennoxamine (**20**) as a mixture in
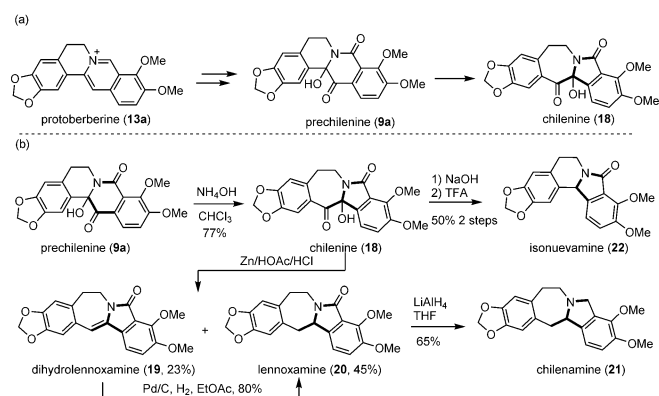
Scheme 3. a) Proposed biosynthesis of chilenine from berberine via prechilenine. b) Our work: total syntheses of chilenine, dihydrolennoxamine, lennoxamine, chilenamine, and isonuevamine from prechilenine.

68% yield. Hydrogenation[39] of **19** with Pd/C/H$_2$ (1 atm) gave **20**[40] in 80% yield, while LiAlH$_4$ reduction of **20** furnished chilenamine (**21**, 65% yield). In addition, upon treatment with NaOH **18** could undergo decarboxylative ring opening and subsequent intramolecular Friedel–Crafts alkylation, which completed the total synthesis of isonuevamine[41] (**22**) in 50% yield over two steps. Successful implementation of these transformations greatly expanded our newly-developed synthetic strategy for natural product synthesis through highly efficient CuI-catalyzed three-component redox-A^3 reaction and palladium-catalyzed reductive *exo*-carbocyclization.

In summary, we have developed a general and concise strategy for the collective total synthesis of more than **50** protoberberine alkaloids and five aporhoeadane alkaloids with four to eight steps. In particular, it represents the most efficient and shortest synthetic route (three to four steps that all are catalytic) to the 13-methylprotoberberines, most of which were synthesized for the first time. Our synthesis featured and was enabled by strategic exploitation of transition metal-catalyzed reactions: CuI-catalyzed redox-A^3 reaction, palladium-catalyzed reductive *exo*-carbocyclization, PtO$_2$-catalyzed hydrogenation (13-methyltetrahydroprotoberberines), Rh^{III}-catalyzed olefin isomerization/oxidation (13-methylprotoberberines), ruthenium-catalyzed oxidation (Ley oxidation), and Rh^I-catalyzed reductive decarbonylation. To date, it is the largest collection of natural products prepared by total synthesis with a single strategy. In principle, all protoberberines could be prepared by this unified strategy.

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