Unified Synthesis of (–)-Folicanthine and (–)-Ditryptophenaline Enabled by a Room Temperature Nickel-Mediated Reductive Dimerization

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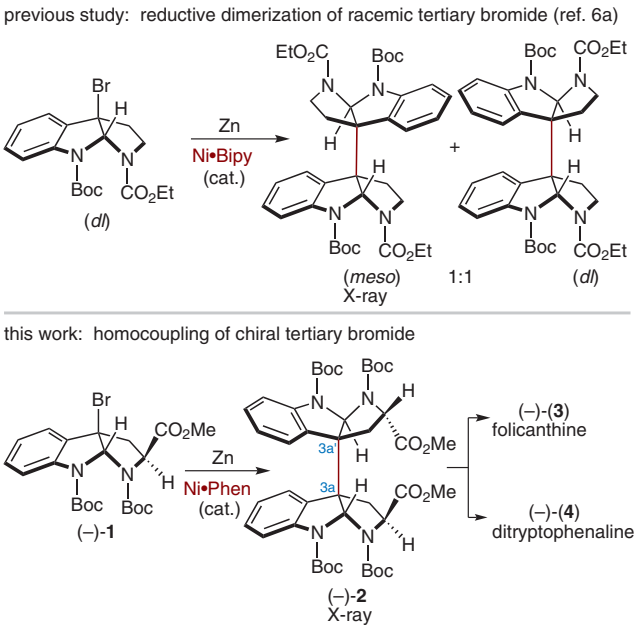
Received: 17.03.2014; Accepted after revision: 05.05.2014

Abstract: A Ni·Phen-mediated reductive homocoupling of an optically active tertiary bromide has been efficiently achieved after the systematic screen of reaction conditions including ligands. This key step establishes sterically hindered vicinal quaternary stereocenters embedded in natural bispyrrolo[2,3-*b*]indoline alkaloids, thus enabling to realize the first asymmetric total synthesis of (–)-folicanthine via the detailed investigation of a challenging double decarboxylation. Notably, the concise synthesis of diketopiperazine alkaloid (–)-ditryptophenaline was also completed from the common dimeric intermediate.

Key words: nickel catalysis, reductive homocoupling, dimeric alkaloids, total synthesis, vicinal quaternary stereocenters

Direct cross-coupling of halides has already emerged as a potentially advantageous method for the formation of C–C bond. It can avoid some problems associated with preformed organometallic reagents, therefore leading to generally excellent functional-group compatibility. A noteworthy advance is the nickel-catalyzed reductive coupling of the challenging alkyl halides.[1–5] Recently, Weix[1] and Gong[2] developed bi- and tridentate amine ligated nickel-complex-catalyzed transformations toward the facile construction of $C(sp^3)$–$C(sp^2)$ and $C(sp^3)$–$C(sp^3)$ bonds under reducing conditions. In particular, nickel/(*R*,*R*)-diphenyl-Box-catalyzed asymmetric reductive acyl cross-coupling with secondary benzyl chlorides has been reported by Reisman;[3] Ni/Cy_3P or Ni/Me_3P-catalyzed reductive carboxylation of benzyl (pseudo)halides with CO_2 has also been realized by Martin.[4] More importantly, Weix[1e] provided elegant mechanistic insight to this kind of cross-electrophile couplings, which would enable rational improvement and reliable application of this strategy. Independently, we[5] have disclosed intermolecular and unprecedented intramolecular reductive C–C and C–S bond-forming reactions catalyzed by some nickel complexes, which could be generated from bench stable and easy-to-handle materials.

However, the utility of these methods in the synthesis of complex natural products remains elusive. In line with our recent work on cross-coupling,[5] we have already realized the first Ni/Bipy-catalyzed reductive homocoupling of the challenging racemic tertiary bromide (Scheme 1, top),[6a] and further applied it to the versatile syntheses of both (±)-chimonanthine and (±)-folicanthine. Surprisingly, the total synthesis of (–)-folicanthine has not been reported yet,[7] although significant progress[8] has been made about asymmetric construction of sterically hindered vicinal quaternary stereocenters for the access to these two typical C3a–C3a′-bispyrrolo[2,3-*b*]indoline alkaloids.[9] Herein we have extended this powerful method to the dimerization of chiral tricyclic bromide (–)-**1** by means of analogous Ni·Phen catalysis in the presence of Zn dust as a stoichiometric reductant (Scheme 1, bottom), and the resulting hexacyclic diester (–)-**2** has been successfully converted into (–)-folicanthine (**3**). Starting from C_2-symmetric (–)-**2** as a common precursor, the expeditious synthesis of (–)-ditryptophenaline (**4**) that belongs to the dimeric diketopiperazine (DKP) alkaloid[10] is also accomplished. To the best of our knowledge, this is the first *catalytic* synthesis of (–)-(**4**) in terms of the construction of two all-carbon quaternary carbons.

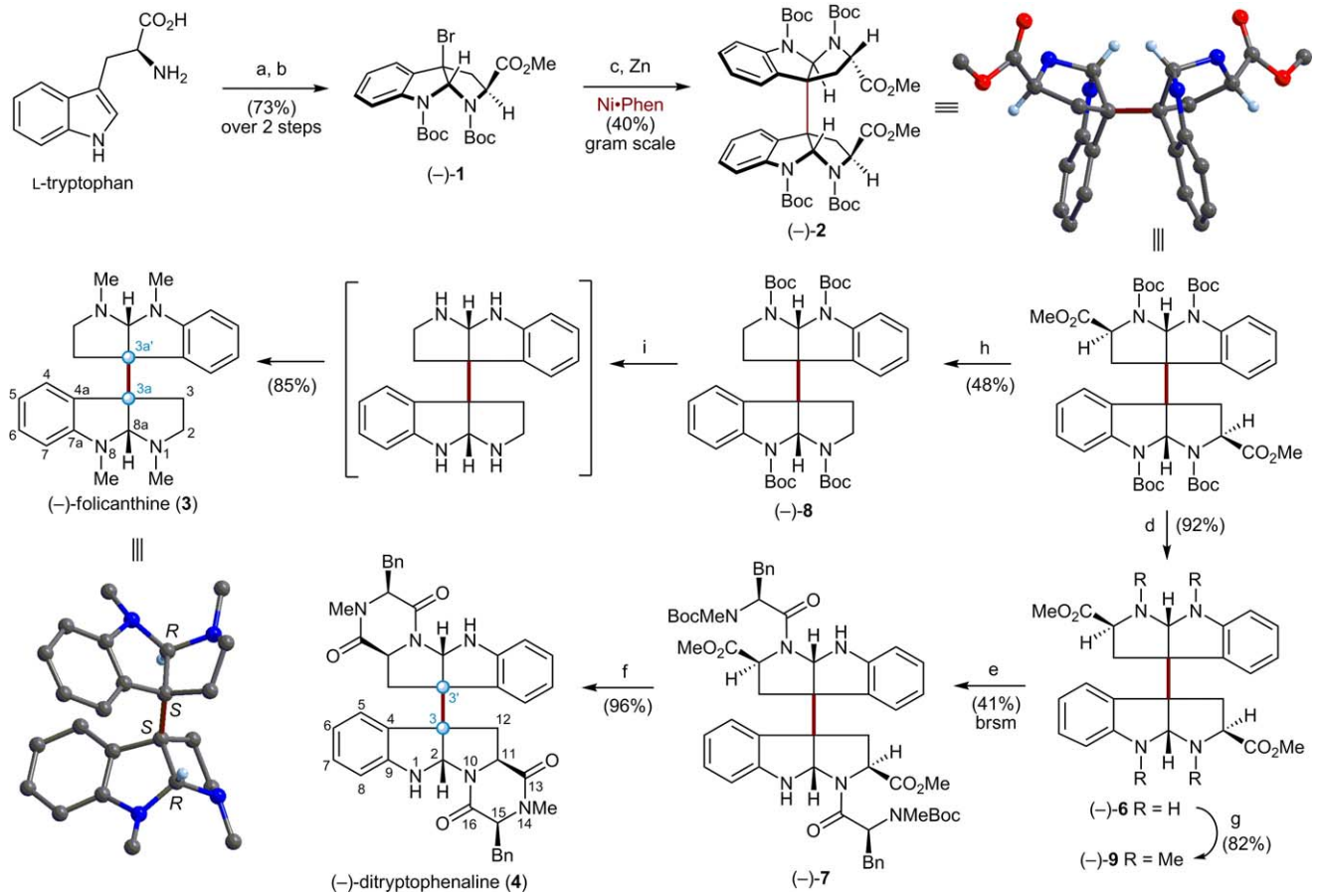


Scheme 1 Comparison of reductive homocoupling

Esterification of natural L-tryptophan followed by the double protection with di-*tert*-butyl dicarbonate provided the bis-Boc-tryptophan methyl ester (+)-**5** in 80% yield (Scheme 2 and the experimental section). According to the known protocol,[11] the desired chiral tertiary bromide (–)-**1** with hexahydropyrroloindole scaffold[12] can be prepared in 91% yield and decagram scale. The key reductive

SYNTHESIS 2014, 46, 1908–1916
Advanced online publication: 21.05.2014
DOI: 10.1055/s-0033-1339126; Art ID: ss-2014-c0189-st

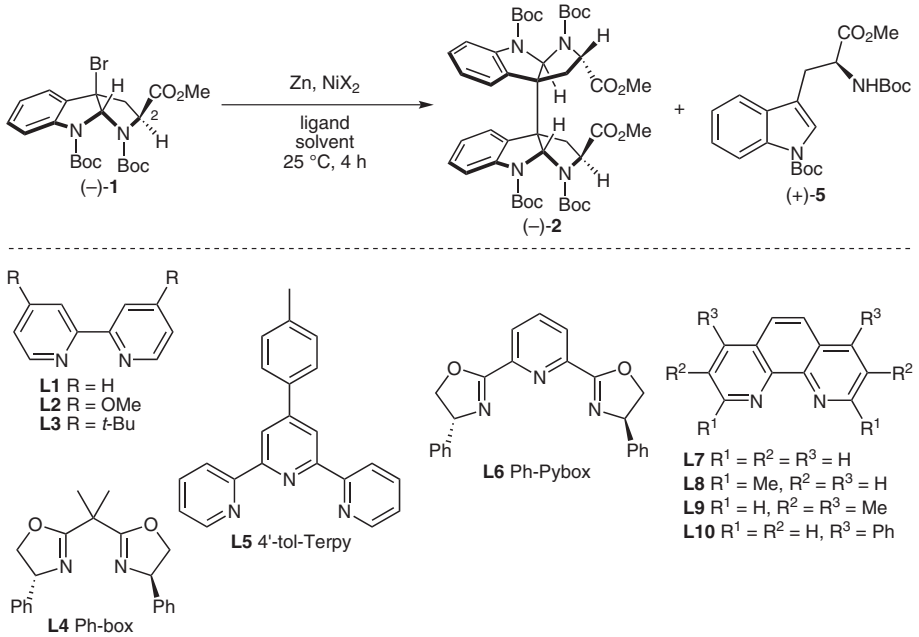
homocoupling was then investigated (Table 1), and the general procedure involved the subjection of (–)-**1** into the in situ generated nickel catalytic system at room temperature. Ligand-free condition (Table 1, entry 1) resulted in the almost exclusive formation of (+)-**5** along with a trace of (–)-**2**, whereas the absence of either Zn or $NiCl_2$ led to quantitative recovery of the starting (–)-**1** (not shown). These control experiments indicated that the described dimerization event is a ligand-controlled reductive homocoupling catalyzed by nickel. Thus, a series of ligands were next examined, and the 2,2′-bipyridine (**L1**) used successfully in the previous racemic setting[6a] was first evaluated in MeCN (entry 2). Disappointedly, only 24% yield of (–)-**2** was obtained although the *meso*-dimer that would arise from the homocoupling of *dl*-**1** could be excluded. The diminished dimer could be ascribed to the substantial formation of (+)-**5** that may have resulted from facile fragmentation of (–)-**1** with *exo*-methoxycarbonyl group at C2. Other 2,2′-bipyridines **L2** and **L3** did not bring any improvement (entries 3 and 4), whereas other bidentate ligands such as 2,2′-isopropylidenebis(4-phenyl-2-oxazoline) (**L4**) showed deleterious effect on the reaction outcome (entry 5). Inspired by the preceding utilization of tridentate nitrogen ligands in nickel-catalyzed homocoupling of primary and secondary bromides,[13] we checked analogous 4′-(4-tolyl)-2,2′:6′,2″-terpyridine (**L5**, entry 6) and 2,6-(4-phenyl-2-oxazolinyl)pyridine (**L6**, entry 7), and disappointedly found that even worse results were obtained. However, a little improvement was indeed observed when $NiCl_2$ was replaced by NiI_2 and DMA was employed as the solvent (entries 8 and 9). Once the determination of these two reaction parameters was completed, a screen of other bidentate ligands besides 2,2′-bipyridine was conducted, and planar phenanthrolines[14] proved to be beneficial (entries 10–16). When commercially available **L7**·H_2O was used directly, (–)-**2** was obtained in 38% yield; pleasingly, this dimer yield further increased to 50% when anhydrous **L7** participated in the homocoupling (entry 10 vs 11). Replacement of the ultimate reductant zinc by manganese resulted in



Scheme 2 Unified synthesis of (–)-folicanthine and (–)-ditryptophenaline. *Reagents and conditions*: (a) AcCl (3.5 equiv), MeOH, 0 °C to r.t. then 50 °C, 5 h; then NaOH (10.0 equiv), *n*-Bu_4NHSO_4 (0.1 equiv), CH_2Cl_2, r.t.; then $(Boc)_2O$ (3.5 equiv), 0 °C to r.t., 24 h, 80%; (b) NBS (1.0 equiv), PPTs (1.0 equiv), CH_2Cl_2, 0 °C, 30 min, 91%; (c) Zn (1.2 equiv), $NiCl_2$ (30 mol%), 1,10-phenanthroline (45 mol%), and pyridine–DMA, 25 °C, 10 h, 40%; (d) TMSI (8.0 equiv), MeCN, 0 °C to r.t., 30 min, 92%; (e) *N*-Boc-*N*-Me-L-Phe-OH (2.4 equiv), HATU (2.4 equiv), Et_3N (6.0 equiv), DMF, 0 °C, 77 h, 36% (41% brsm); (f) neat, 235 °C under vacuum, 30 min, 96%; (g) aq HCHO (6.0 equiv), $NaBH(OAc)_3$ (6.0 equiv), r.t., MeCN, 30 min, 82%; (h) 5 M aq KOH, MeOH–THF, 0 °C to r.t., 3.5 h, then 2-mercaptopyridine *N*-oxide (3.0 equiv), DMAP (0.1 equiv), TCFH (3.0 equiv), Et_3N (8.0 equiv), 6 h, then *t*-BuSH (24.0 equiv), *hv*, 2 h, 48%; (i) TMSOTf (20.0 equiv), 2,6-lutidine (20.0 equiv), CH_2Cl_2, 0 °C, 30 min, then aq HCHO (20.0 equiv), $NaBH(OAc)_3$ (20.0 equiv), r.t., MeCN, 1.5 h, 85%. HATU: *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; TFCH: Chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate.

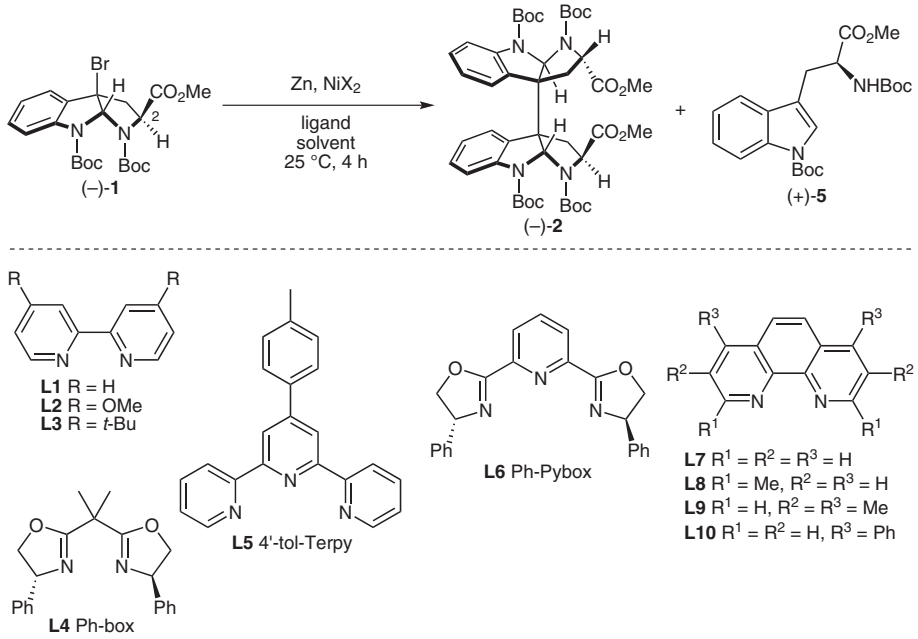
the almost identical dimerization yield (entry 12). The tertiary iodide, freshly prepared according to the procedure for (–)-**1**,[15] afforded a slight decrease of (–)-**2** (entry 13), presumably due to the labile nature of this tricyclic iodide. As shown in entry 14, the yield of (–)-**2** dropped by 14% when the protocol with slow addition of (–)-**1** in a dilute concentration was utilized. The comparison of solvents identified DMA still as the superior choice (entries 15 and 16). Some phenanthrolines with various substituents **L8**–**L10** were next surveyed (entries 17–19), and 2,9-dimethyl-1,10-phenanthroline (neocuproine, **L8**) was found to give similar result as that of parent ligand $\mathbf{L}_7$, whereas those ligands with substitution remote from the coordination center were detrimental to the dimerization. Finally, attempts to run this reductive homocoupling at large scale with lower nickel catalyst loading were carried out to see whether this dimerization reaction has applicable potential for practical synthesis or not. To our delight, dimerization with 10-fold scale relative to the standard procedure (Table 1, footnote a) still proceeded well, affording (–)-**2** in 45% yield, albeit at a lower reaction rate (entry 20). Slightly diminished yield of (–)-**2** could be observed when the dimerization reaction of (–)-**1** was further scaled up to 3.5 g (entry 21). NiI_2 loading can be lowered to 15 or 10 mol% without a significant loss of dimerization efficiency on gram scale (entries 22 and 23), but further lowering nickel catalyst did resulted in the erosion of the dimerization (entry 24). Nonetheless, the recovered (+)-**5** could be readily reconverted into (–)-**1** that in turn could be subjected to the next round of reductive homocoupling. With the above optimized conditions and recycle process in hand, the sufficient supply of (–)-**2** was then guaranteed.

Table 1 Optimization for Nickel-Catalyzed Reductive Dimerization[a]



Entry	NiX_2	Ligand (**L**)	Solvent	Yield (%)[b] (–)-**2**	(–)-**5**
1	$NiCl_2$	none	MeCN	trace	90
2	$NiCl_2$	**L1**	MeCN	24	61
3	$NiCl_2$	**L2**	MeCN	16	65
4	$NiCl_2$	**L3**	MeCN	18	62
5	$NiCl_2$	**L4**	MeCN	3	80
6	$NiCl_2$	**L5**	MeCN	12	71
7	$NiCl_2$	**L6**	MeCN	3	82
8	$NiCl_2$	**L1**	DMA	31	53
9	NiI_2	**L1**	DMA	36	48
10	NiI_2	**L7**·H_2O	DMA	38	47
11	NiI_2	**L7**	DMA	50	28

Table 1 Optimization for Nickel-Catalyzed Reductive Dimerization[a] (continued)



Entry	NiX_2	Ligand (**L**)	Solvent	Yield (%)[b]	
				(–)-**2**	(–)-**5**
12[c]	NiI_2	**L7**	DMA	50	34
13[d]	NiI_2	**L7**	DMA	42	38
14[e]	NiI_2	**L7**	DMA	36	45
15	NiI_2	**L7**	DMF	44	36
16	NiI_2	**L7**	MeCN	41	44
17	NiI_2	**L8**	DMA	45	43
18	NiI_2	**L9**	DMA	30	55
19	NiI_2	**L10**	DMA	32	46
20[f]	NiI_2	**L7**	DMA	45	39
21[g]	NiI_2	**L7**	DMA	37	40
22[h]	NiI_2	**L7**	DMA	39	45
23[i]	NiI_2	**L7**	DMA	37	47
24[j]	NiI_2	**L7**	DMA	27	48

[a] The reaction was conducted on a 0.3 mmol scale. A mixture of Zn (1.2 equiv), NiX_2 (30 mol%), ligand (1.5 equiv relative to Ni), and pyridine (1.0 mL) were employed for the generation of Ni·L at 55 °C, and then a solution of (–)-**1** in solvent (1.0 mL) was added to the above nickel complex dropwise at 25 °C. The resulting reaction mixture was stirred for 4 h, and subjected to the workup procedure.
[b] The yields were estimated by ^{1}H NMR spectroscopic analysis with diethyl phthalate as an internal standard. Another by-product (ca. 10%) resulted from direct reduction at C3a within (–)-**1**.
[c] Mn as the ultimate reductant.
[d] The corresponding tertiary iodide was employed.
[e] A solution of (–)-**1** in solvent (3.0 mL) was added dropwise over a 3 h period.
[f] Scale: 3.0 mmol (1.5 g), DMA (3.0 mL), 10 h.
[g] Scale: 7.0 mmol (3.5 g), DMA (7.0 mL), 24 h.
[h] Scale: 3.0 mmol, NiI_2 (15 mol%), 24 h.
[i] Scale: 1.5 mmol, NiI_2 (10 mol%), 24 h.
[j] Scale: 1.5 mmol, NiI_2 (5 mol%), 24 h.

Interestingly, Danishefsky and co-workers[16] reported the isolation of (–)-**2**, albeit as a by-product (10–15% yield) during their synthetic studies towards amauromine, and its dimeric structure has been deduced by variable temperature NMR experiments. In our hands, the expected C_2-symmetry was unambiguously confirmed by its single crystal X-ray analysis[17] (Scheme 2 inset; selected H atoms and Boc groups have been omitted for clarity). The sufficient amount of (–)-**2** with the correct connection of vicinal quaternary stereocenters paved the way for its subsequent elaboration for the unified syntheses of (–)-ditryptophenaline (**4**) and (–)-folicanthine (**3**).

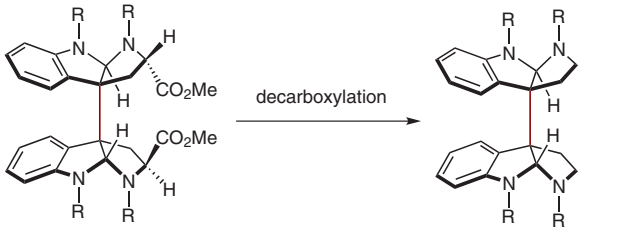
As a typical member of DKP alkaloid family, (–)-**4** was isolated from *Aspergillus flavus* cultures by Büchi and co-workers[18a] and the absolute configuration of all eight chiral centers in this molecule was determined as *S*.[18b,c] This secondary metabolite was later identified as a weak inhibitor for the human neurokinin 1 receptor.[18d] Although the pioneering[18b] (ca. 3% yield) and later some elegant synthesis[19a–c] of (–)-**4** has been reported, herein our approach featured the *catalytic* stereoselective construction of vicinal quaternary stereocenters C3 and C3′. As shown in Scheme 2 (bottom), the present end-game to (–)-**4** is straightforward: global cleavage of Boc protecting groups in (–)-**2** using iodotrimethylsilane delivered bis-ester (–)-**6** in 92% yield, which set the stage for the stepwise peptide coupling for the formation of DKP moiety.[10c] Accordingly, regioselective condensation of (–)-**6** and L-phenylanaline derivative followed by the pyrolysis of the resulting amide (–)-**7** under vacuum,[19c] eventually furnished (–)-ditryptophenaline (**4**). Spectroscopic data of synthetic (–)-**4** {$[\alpha]_D^{20}$ –286 (*c* 1.0, CH_2Cl_2); Lit.[19b] $[\alpha]_D^{20}$ –292 (*c* 0.97, CH_2Cl_2)} are consistent with those published in the previous syntheses.[19a–c] It is noteworthy that the late-stage formation of DKP is a beneficial route for the preservation of stereochemical integrity at C11 and C15 since this cyclodipeptide moiety was found to be sensitive toward base-promoted epimerization and autoxidative decomposition, which has been accounted in the distinct preassembly strategy before dimerization by Movassaghi.[19b]

The pursuit of (–)-folicanthine (**3**) that was isolated from the leaves of *Calycanthus floridus* L. and *C. occidentalis*,[20] was then put on the agenda. However, the seemingly simple and routine double decarboxylation[21] of (–)-**2** en route to (–)-**3**, proved to be a challenging task. As shown in Table 2, initial saponification of (–)-**2** with aqueous KOH and the ensuing Barton radical decarboxylation[22] of the resulting dicarboxylic acid failed to give any of *N*-Boc carbamate (–)-**8** (Table 2, entry 1). The omission of sensitive dicarboxylic acid chloride intermediate, and therefore the direct formation of thiohydroxamate ester by neutral 2-mercaptopyridine *N*-oxide and dicarboxylic acid, indeed provided (–)-**8**, albeit in only 8% yield under the irradiation of 450 W Hg lamp (entry 2). It was hypothesized that the overall efficiency of decarboxylation sequence could be hampered by the steric hindrance of proximal Boc groups. We thus explored the feasibility of (–)-**9** as a precursor that was conveniently available in 82% yield through permethylation of (–)-**6** using formalin and sodium triacetoxyborohydride (Scheme 2). Subjection of (–)-**9** into thermal or photochemical decarboxylation condition led to better yields (up to 16%, entries 3 and 4 vs 1) of (–)-folicanthine (**3**). The first synthetic sample of (–)-**3** {$[\alpha]_D^{20}$ –331 (*c* 1.0, MeOH); Lit.[20a] $[\alpha]_D^{21.5}$ –364.4 (*c* 2.043, MeOH)} demonstrated matched spectroscopic data with those published in the previous syntheses for *dl* and (+)-**3**.[6,8a–c] Its structure was also unambiguously confirmed by X-ray crystallographic analysis[17] using Cu-Kα radiation, and the absolute configuration was accordingly assigned as 3a*S*,8a*R*,3a′*S*,8a′*R* (Scheme 2 inset; selected H atoms have been omitted for clarity). A two-fold increase in the yield is still not satisfactory, thus the optimization investigation was continued. While the direct decarboxylation via dicarboxylic acid chloride[23] proved to be unfruitful (entry 5), the protocol utilized in the related monodecarboxylation step by Baran and co-workers[24] provided (–)-**3** in 30% yield (entry 6). The simplified procedure with TCFH[25] gave the almost identical result (entry 7). Any further improvement was not obtained, since the dicarboxylic acid derived from (–)-**9** is somewhat soluble in water and therefore the loss of some material is inevitable during the aqueous workup. Gratifyingly, this procedure with TCFH can be successfully applied to (–)-**2**, affording (–)-**8** in 48% overall yield that is fairly good as an essential three-step transformation (78% per step, entry 8 and Scheme 2). Eventually, TMSOTf-mediated removal[26] of all the Boc groups in (–)-**8** followed by reductive amination of unisolated *N*-demethylfolicanthine completed the total synthesis of (–)-folicanthine (**3**) ultimately in a more efficient route than that from (–)-**6** mentioned above.

In summary, the reductive homodimerization of chiral tertiary bromide (–)-**1** mediated by a nickel complex ligated to 1,10-phenanthroline could be secured in gram scale. The resulting C_2 symmetric hexacycle (–)-**2** bearing sterically hindered vicinal all-carbon quaternary stereocenters, can be served as a common intermediate for the unified syntheses of (–)-ditryptophenaline (**4**) and (–)-folicanthine (**3**) via the preservation of methoxycarbonyl group or not. Notably, these endeavors represent the first catalytic stereoselective syntheses of these two natural product molecules.

For product purification by flash column chromatography, silica gel (200–300 mesh) and petroleum ether (PE; bp 60–90 °C) were used. All solvents were purified and dried by standard techniques, and distilled prior to use. Organic extracts were dried over Na_2SO_4 or $MgSO_4$, unless otherwise noted. Experiments were conducted under an argon or N_2 atmosphere in oven-dried or flame-dried glassware with magnetic stirring, unless otherwise specified. NMR spectra were recorded on 300 and 400 MHz instruments at r.t. All ^{1}H chemical shifts (δ) are reported relative to residual protic solvent ($CHCl_3$: δ = 7.26 ppm) or internal TMS (TMS: δ = 0.00 ppm), and all ^{13}C chemical shifts (δ) are reported relative to the solvent ($CHCl_3$: δ = 77.00 ppm). High-resolution mass spectral data were measured with electrospray ionization (ESI). IR spectra were recorded on an FT-IR spectrophotometer. The X-ray diffraction studies were carried out on a Bruker SMART Apex CCD area detector diffractometer

Table 2 Double Decarboxylation Optimization



Entry	Substrate	Conditions	Yield (%)[a]
1	(–)-**2**	5 M aq KOH, MeOH, 0 °C to r.t., 5 h; $(COCl)_2$ (4 equiv), DMF (1 drop), CH_2Cl_2, 0 °C to r.t., 2.5 h; 2-mercaptopyridine *N*-oxide sodium salt (3 equiv), $(TMS)_3SiH$ (10 equiv), AIBN (0.5 equiv), toluene, 80 °C, 1.5 h	0
2	(–)-**2**	5 M aq KOH, MeOH, 0 °C to r.t., 2.5 h; 2-mercaptopyridine *N*-oxide (4 equiv), DCC (3 equiv), DMAP (0.15 equiv), CH_2Cl_2, 0 °C to r.t., dark, 9 h; *t*-BuSH (10 equiv), *hν* (450 W high-pressure Hg lamp), r.t., 3 h	8
3	(–)-**9**	5 M aq KOH, MeOH, 0 °C to r.t., 2.5 h; $(COCl)_2$ (4 equiv), DMF (1 drop), CH_2Cl_2, 0 °C to r.t., 2 h; 2-mercaptopyridine *N*-oxide sodium salt (5 equiv), $(TMS)_3SiH$ (8 equiv), AIBN (0.5 equiv), toluene, 80 °C, 3 h	16
4	(–)-**9**	5 M aq KOH, MeOH, 0 °C to r.t., 1.5 h; 2-mercaptopyridine *N*-oxide (3 equiv), DCC (3.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C to r.t., dark, 9 h; *t*-BuSH (40 equiv), *hν* (7 W LED), r.t., 10 h	13
5	(–)-**9**	5 M aq KOH, MeOH, 0 °C to r.t., 2 h; $(COCl)_2$ (10 equiv), DMF (1 drop), CH_2Cl_2, 0 °C to r.t., 2 h; $(TMS)_3SiH$ (3 × 10 equiv), AIBN (3 × 1.5 equiv), toluene, 80 °C, 3 h	0
6	(–)-**9**	5 M aq KOH, MeOH, 0 °C to r.t., 1.5 h; $(COCl)_2$ (3.5 equiv), DMF (1 drop), CH_2Cl_2, 0 °C to r.t., 40 min; 2-mercaptopyridine *N*-oxide sodium salt (2.4 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to r.t., dark, 0.5 h; *t*-BuSH (40 equiv), *hν* (450 W high-pressure Hg lamp), r.t., 3 h	30
7	(–)-**9**	5 M aq KOH, MeOH, 0 °C to r.t., 2.5 h; 2-mercaptopyridine *N*-oxide (3 equiv), DMAP (0.2 equiv), TCFH (2.8 equiv), Et_3N (8 equiv), THF, 0 °C, dark, 5 h; *t*-BuSH (20 equiv), *hν* (450 W high-pressure Hg lamp), r.t., 3 h	31
8	(–)-**2**	5 M aq KOH, MeOH, 0 °C to r.t., 3.5 h; 2-mercaptopyridine *N*-oxide (3 equiv), DMAP (0.1 equiv), TCFH (3 equiv), Et_3N (8 equiv), THF, 0 °C, dark, 6 h; *t*-BuSH (20 equiv), *hν* (450 W high-pressure Hg lamp), r.t., 2 h	48

[a] Yield of isolated (–)-**3** or (–)-**8**.

equipped with graphite-monochromated Cu-Kα radiation source (λ = 1.54184 Å).

***tert*-Butyl (+)-(*S*)-3-[2-(*tert*-Butoxycarbonylamino)-3-methoxy-3-oxopropyl]-1*H*-indole-1-carboxylate (5)**[16]

AcCl (24.3 mL, 343 mmol, 3.5 equiv) was added dropwise to MeOH (250 mL) under stirring at 0 °C. The stirring was continued for 15 min followed by the addition of L-tryptophan (20 g, 98 mmol) portionwise at 0 °C. The reaction mixture was allowed to warm to r.t. slowly, then heated to 50 °C and stirred for 5 h. After the evaporation of MeOH, the residue was diluted with CH_2Cl_2 (150 mL) and poured into a separatory funnel. The combined organic layers were washed with aq NH_3 (28%, 20 mL), H_2O (20 mL) and brine (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting pale yellow L-tryptophan methyl ester (18.8 g) could be used directly in the next step. To a stirred solution of the above L-tryptophan methyl ester (2.18 g, 10 mmol) in CH_2Cl_2 (40 mL) were added NaOH (4.0 g, 100 mmol, 10.0 equiv) and *n*-Bu_4NHSO_4 (344 mg, 1 mmol, 0.1 equiv) portionwise at r.t. The reaction system was cooled to 0 °C, and $(Boc)_2O$ (7.63 g, 35 mmol, 3.5 equiv) was added portionwise. The resulting mixture was then allowed to warm to r.t. and stirred for 24 h. Eventually, the mixture was diluted with CH_2Cl_2 (100 mL) and poured into a separatory funnel that contained H_2O (10 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting L-N_α-Boc-N_β-Boc-tryptophan methyl ester (+)-**5** (3.8 g, 80%) could be used directly for further reactions; brown oil; R_f = 0.58 (PE–EtOAc, 2:1); $[\alpha]_D^{21}$ +45 (*c* 2.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (br, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.40 (s, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.23 (t, *J* = 7.6 Hz, 1

H), 5.14 (d, J = 7.2 Hz, 1 H), 4.65 (d, J = 7.2 Hz, 1 H), 3.69 (s, 3 H), 3.27 (dd, J = 5.2, 14.8 Hz, 1 H), 3.18 (dd, J = 5.2, 14.8 Hz, 1 H), 1.67 (s, 9 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 155.0, 149.5, 135.3, 130.5, 124.4, 124.0, 122.5, 118.8, 115.2, 115.0, 83.6, 76.9, 53.6, 52.3, 28.2 (3 C), 28.1 (3 C), 27.7.

ESI-MS: m/z = 419.2 $[M + H]^+$.

1,8-Di-*tert*-butyl 2-Methyl (–)-(2*S*,3a*R*,8a*R*)-3a-Bromo-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1)[27]

To a stirred solution of the above (+)-**5** (2.09 g, 5 mmol) in CH_2Cl_2 (60 mL) were added NBS (890 mg, 5 mmol, 1.0 equiv) and PPTs (1.26 g, 5 mmol, 1.0 equiv) portionwise at 0 °C. After vigorous stirring for 30 min, the resulting mixture was diluted with CH_2Cl_2 (100 mL) and poured into a separatory funnel containing H_2O (10 mL). The combined organic layers were washed with sat. aq $Na_2S_2O_3$ (20 mL), H_2O (3 × 15 mL), and brine (3 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE–EtOAc, 16:1) on silica gel (basified with Et_3N) to afford the desired tertiary benzylic bromide (–)-**1** (2.26 g, 91%) as a brown oil; R_f = 0.50 (PE–EtOAc, 4:1); $[\alpha]_D^{20}$ –148 (*c* 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (br, 1 H), 7.36 (d, J = 7.6 Hz, 1 H), 7.32 (t, J = 7.6 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 6.40 (s, 1 H), 3.89 (dd, J = 6.4, 10.4 Hz, 1 H), 3.75 (s, 3 H), 3.21 (dd, J = 6.4, 12.4 Hz, 1 H), 2.82 (dd, J = 10.4, 12.4 Hz, 1 H), 1.59 (s, 9 H), 1.40 (br, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (rotamers) = 171.4, 152.1 (2 C), 141.4, 132.8 (br), 130.5, 124.3 (br), 123.8, 118.6 (br), 83.7, 82.2, 81.4 (br), 59.6, 59.4, 52.3, 41.9 (br), 28.1 (6 C).

ESI-MS: m/z = 497.1 $[M + H]^+$.

1,1′,8,8′-Tetra-*tert*-butyl 2,2′-Dimethyl (–)-(2*S*,2′*S*,3a*S*,3′a*S*,8a*R*,8′a*R*)-2,2′,3,3′-Tetrahydro-1*H*,1′*H*-3a,3′a-bipyrrolo[2,3-*b*]indole-1,1′,2,2′,8,8′(8a*H*,8′a*H*)-hexacarboxylate (2)[16]

To a stirred slurry of Zn powder (234 mg, 3.6 mmol, 1.2 equiv) and NiI_2 (281 mg, 0.9 mmol, 0.3 equiv) in pyridine (2 mL) was added 1,10-phenanthroline (267 mg, 1.35 mmol, 0.45 equiv) at r.t. The temperature then rose to 55 °C, and vigorous stirring was continued for 15 min. The resulting black nickel(0) complex was cooled to r.t., and a solution of the bromide (–)-**1** (1.5 g, 3 mmol) in degassed DMA (3 mL) was added dropwise. After 10 h, the mixture was filtered with a short plug of silica gel (elution with 50 mL of EtOAc), and the combined organic layers were washed with H_2O (3 × 15 mL) and brine (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was carefully purified by flash column chromatography (PE–EtOAc, 16:1) on silica gel (basified with Et_3N) to afford 496 mg (40%) of (–)-**2** as a white solid and 401 mg (32%) of (–)-**5**. Product (–)-**2** was dissolved in hexane–EtOAc (1:1) and after 4 days, colorless single crystals were obtained by slow evaporation of the solvent at r.t.; mp 194–195 °C; R_f = 0.21 (PE–EtOAc, 4:1); $[\alpha]_D^{19}$ –138 (*c* 0.5, CH_2Cl_2).

IR (film): 2982, 2933, 1759, 1715, 1631, 1482, 1460, 1396, 1366, 1335, 1258, 1159, 1015, 908, 854, 791, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (br, 2 H), 7.10 (t, J = 7.6 Hz, 2 H), 7.05 (d, J = 6.0 Hz, 2 H), 6.86 (t, J = 7.6 Hz, 2 H), 6.39 (br, 2 H), 3.79 (t, J = 8.0 Hz, 2 H), 3.71 (s, 6 H), 2.50 (br, 2 H), 2.38 (t, J = 11.2 Hz, 2 H), 1.61 (s, 18 H), 1.37 (br, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (rotamers) = 172.4 (br, 2 C), 151.8 (4 C), 142.0 (2 C), 130.7 (br, 2 C), 129.2 (2 C), 124.0 (br, 2 C), 122.8 (br, 2 C), 116.8 (br, 2 C), 81.8 (2 C), 80.8 (br, 2 C), 79.0 (br, 2 C), 58.8 (2 C), 57.9 (br, 2 C), 52.1 (2 C), 35.5 (2 C), 28.3 (6 C), 28.1 (6 C).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{44}H_{59}N_4O_{12}$: 835.4124; found: 835.4094.

Dimethyl (–)-(2*S*,2′*S*,3a*S*,3′a*S*,8a*R*,8′a*R*)-2,2′,3,3′,8,8a,8′,8′a-Octahydro-1*H*,1′*H*-3a,3′a-bipyrrolo[2,3-*b*]indole-2,2′-dicarboxylate (6)

To a stirred solution of (–)-**2** (928 mg, 1.11 mmol) in MeCN (8 mL) was added TMSI (1.3 mL, 8.8 mmol, 8.0 equiv) dropwise at 0 °C over a 5 min period. The resulting mixture was allowed to warm to r.t., stirred for 30 min, and then quenched with aq $NaHCO_3$ (5 mL). The mixture was diluted with $CHCl_3$ (25 mL) and the combined organic layers were washed with H_2O (3 × 5 mL), and brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE–acetone, 1:2) on silica gel (basified with Et_3N) to afford the desired (–)-**6** (443 mg, 92%) as a colorless solid; mp 181–182 °C; R_f = 0.20 (PE–acetone, 1:1); $[\alpha]_D^{20}$ –204 (*c* 0.5, CH_2Cl_2).

IR (film): 3434, 2252, 2126, 1658, 1053, 1027, 1007, 824, 762, 624 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 7.6 Hz, 2 H), 7.09 (t, J = 7.6 Hz, 2 H), 6.75 (t, J = 7.6 Hz, 2 H), 6.60 (d, J = 7.6 Hz, 2 H), 4.84 (s, 2 H), 3.68 (s, 6 H), 3.56 (dd, J = 7.2, 9.2 Hz, 2 H), 2.41 (s, 2 H), 2.39 (d, J = 2.0 Hz, 2 H). Signal for NH was not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (2 C), 151.1 (2 C), 129.3 (2 C), 129.0 (2 C), 124.9 (2 C), 118.7 (2 C), 109.4 (2 C), 80.9 (2 C), 63.9 (2 C), 59.5 (2 C), 52.1 (2 C), 42.1 (2 C).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{27}N_4O_4$: 435.2027; found: 435.2031.

Dimethyl (–)-(2*S*,2′*S*,3a*S*,3′a*S*,8a*S*,8′a*S*)-1,1′-Bis{(*S*)-2-[*tert*-butoxycarbonyl(methyl)amino]-3-phenylpropanoyl}-2,2′,3,3′,8,8a,8′,8′a-octahydro-1*H*,1′*H*-3a,3′a-bipyrrolo[2,3-*b*]indole-2,2′-dicarboxylate (7)

To a stirred solution of (–)-**6** (36 mg, 0.081 mmol) in DMF (2.5 mL) were added *N*-Boc-*N*-Me-L-Phe-OH[28] (54 mg, 0.194 mmol, 2.4 equiv) and Et_3N (68 μL, 0.486 mmol, 6.0 equiv) successively at 0 °C. After 10 min, HATU (76 mg, 0.194 mmol, 2.4 equiv) was added slowly, and the resulting mixture was stirred for 80 h at 0 °C. Then, the reaction mixture was carefully quenched with aq NH_3 (28%, 2 mL), and the aqueous layer was extracted with $CHCl_3$ (50 mL). The combined organic layers were washed with H_2O (3 × 8 mL) and brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (PE–acetone, 2:1) on silica gel (basified with Et_3N) to afford the desired (–)-**7** (28 mg, 36%) as a pale yellow solid and the recovered (–)-**6** (4 mg, 11%); mp 202–203 °C; R_f = 0.67 (PE–acetone, 1:2); $[\alpha]_D^{20}$ –222 (*c* 0.5, CH_2Cl_2).

IR (film): 3284, 2926, 2854, 1746, 1663, 1608, 1479, 1453, 1382, 1367, 1320, 1257, 1201, 1158, 913, 857, 738, 623 cm^{-1}.

NMR spectra showed complex rotamers mixture that were difficult to characterize.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{54}H_{64}N_6O_{10}$ + Na: 979.4576; found: 979.4585.

(–)-Ditryptophenaline (4)

A 5 mL pear-shaped flask was charged with (–)-**7** (9.0 mg, 0.0094 mmol), set-up under vacuum (6.7×10^{-2} Pa), and immersed in an oil bath preheated to 235 °C for 30 min. The residue was cooled to r.t., then directly purified by flash column chromatography (PE–EtOAc, 1:5) on silica gel (basified with Et_3N) to afford the desired (–)-ditryptophenaline (**4**; 6.3 mg, 96%) as white crystals; mp 198–199 °C; R_f = 0.35 (EtOAc); $[\alpha]_D^{20}$ –286 (*c* 1.0, CH_2Cl_2).

IR (film): 3344, 2924, 2853, 1732, 1658, 1606, 1454, 1401, 1317, 1243, 1211, 1113, 1077, 745, 704, 619 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (t, J = 7.2 Hz, 4 H), 7.50 (t, J = 7.2 Hz, 2 H), 7.13 (d, J = 6.8 Hz, 4 H), 7.06 (td, J = 0.8, 7.6 Hz, 2 H), 6.96 (d, J = 7.2 Hz, 2 H), 6.69 (t, J = 7.2 Hz, 2 H), 6.55 (d, J = 8.0 Hz, 2 H), 4.80 (s, 2 H), 4.68 (br s, 2 H, NH), 4.26 (br s, 2 H), 3.66 (dd, J = 4.0, 12.0 Hz, 2 H), 3.52 (dd, J = 3.2, 14.4 Hz, 2 H),

3.24 (dd, J = 4.4, 14.4 Hz, 2 H), 3.02 (s, 6 H), 2.01 (dd, J = 4.8, 12.4 Hz, 2 H), 1.56 (t, J = 12.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4 (2 C), 163.9 (2 C), 150.1 (2 C), 134.5 (2 C), 129.6 (2 C), 129.4 (4 C), 129.3 (4 C), 127.9 (2 C), 126.4 (2 C), 125.7 (2 C), 118.9 (2 C), 109.6 (2 C), 78.6 (2 C), 63.1 (2 C), 58.9 (2 C), 58.5 (2 C), 36.2 (2 C), 36.0 (2 C), 32.6 (2 C).

ESI-MS: m/z = 715.4 $[M+ Na]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{42}H_{41}N_6O_4$: 693.3184; found: 693.3192.

Dimethyl (–)-(2*S*,2′*S*,3a*S*,3′a*S*,8a*R*,8′a*R*)-1,1′,8,8′-Tetramethyl-2,2′,3,3′,8,8a,8′,8′a-octahydro-1*H*,1′*H*-3a,3′a-bipyrrolo[2,3-*b*]indole-2,2′-dicarboxylate (9)

To a stirred solution of (–)-**6** (222 mg, 0.51 mmol) in MeCN (10 mL) were added HCHO (0.25 mL, 37% in H_2O, 3.06 mmol, 6.0 equiv) and $NaBH(OAc)_3$ (649 mg, 3.06 mmol, 6.0 equiv) sequentially at r.t. The reaction mixture was stirred for 30 min, then quenched with aq NH_3 (28%, 20 mL). The mixture was diluted with $CHCl_3$ (15 mL) and the combined organic layers were washed with H_2O (3 × 5 mL) and brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (PE–acetone, 1:1) on silica gel (basified with Et_3N) to afford the desired (–)-**9** (204 mg, 82%) as colorless crystals; mp 211–213 °C; R_f = 0.40 (PE–acetone, 2:1); $[\alpha]_D^{20}$ –282 (*c* 0.5, CH_2Cl_2).

IR (film): 3355, 2923, 2853, 1745, 1602, 1461, 1371, 1264, 1111, 1065, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (br s, 2 H), 6.88 (br s, 2 H), 6.51 (br s, 2 H), 6.28 (br s, 2 H), 5.00 (s, 2 H), 3.68 (s, 6 H), 3.17 (dd, J = 5.6, 10.8 Hz, 2 H), 3.04 (s, 6 H), 2.46 (s, 6 H), 2.23 (br s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (2 C), 153.3 (2 C), 130.8 (2 C), 128.6 (2 C), 123.3 (br, 2 C), 117.0 (2 C), 106.5 (2 C), 91.2 (2 C), 63.6 (2 C), 60.9 (2 C), 51.8 (2 C), 40.6 (2 C), 36.8 (2 C), 34.1 (2 C).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{34}N_4$ + Na: 513.2472; found: 513.2478.

Tetra-*tert*-butyl (–)-(3a*S*,3′a*S*,8a*R*,8′a*R*)-2,2′,3,3′-Tetrahydro-1*H*,1′*H*-3a,3′a-bipyrrolo[2,3-*b*]indole-1,1′,8,8′(8a*H*,8′a*H*)-tetracarboxylate (8)

To a stirred solution of (–)-**2** (140 mg, 0.167 mmol) in MeOH (2 mL) and THF (1 mL) was added aq 5 M KOH (2 mL) at 0 °C, and the vigorous stirring was continued for 5 min. The reaction mixture was then stirred at r.t. for 3.5 h, then acidified with aq 1 M HCl to pH 2 at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic layers were washed with brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting pale yellow carboxylic acid (almost quantitative yield) could be used directly for the next step. Thus, 2-mercaptopyridine *N*-oxide[29] (65 mg, 0.51 mmol, 3.0 equiv), DMAP (2 mg, 0.017 mmol, 0.1 equiv), and TCFH (143 mg, 0.51 mmol, 3.0 equiv) were sequentially added to a solution of the above carboxylic acid in degassed THF (2 mL) at 0 °C. The reaction flask was then removed from the ice bath, covered in aluminum foil, and Et_3N (137 mg, 1.36 mmol, 8.0 equiv) was added while re-cooling the mixture back to 0 °C. After stirring for 6 h in the dark, *t*-BuSH (0.38 mL, 3.4 mmol, 20 equiv) was added, and the aluminum foil was removed. The resulting suspension was warmed to r.t. and irradiated with a 450 W Hg lamp for 2 h. The mixture was diluted with CH_2Cl_2 (15 mL), and the combined organic layers were washed with H_2O (3 × 8 mL) and brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (PE–EtOAc, 15:1) on silica gel (basified with Et_3N) to afford the desired (–)-**8** (59 mg, 48%) as a white solid; mp 225–226 °C; R_f = 0.76 (PE–EtOAc, 4:1); $[\alpha]_D^{20}$ –213 (*c* 2.0, MeOH).

IR (film): 3046, 2959, 2928, 2858, 2792, 1602, 1492, 1463, 1427, 1380, 1347, 1325, 1299, 1254, 1211, 1159, 1124, 1040, 1022, 1021, 965, 927, 743, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (br, 2 H), 7.05 (t, J = 7.6 Hz, 2 H), 7.02 (d, J = 7.6 Hz, 2 H), 6.79 (t, J = 7.2 Hz, 2 H), 6.46 (br s, 2 H), 3.76 (dd, J = 7.6, 10.4 Hz, 2 H), 2.74 (td, J = 5.6, 10.8 Hz, 2 H), 2.25–2.11 (m, 4 H), 1.59 (s, 18 H), 1.50 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (2 C), 152.0 (2 C), 142.8 (2 C), 131.6 (2 C), 128.6 (2 C), 123.3 (2 C), 122.7 (2 C), 116.3 (br, 2 C), 81.5 (2 C), 80.4 (2 C), 78.4 (2 C), 60.5 (2 C), 45.0 (2 C), 33.8 (br, 2 C), 28.39 (6 C), 28.38 (6 C).

ESI-MS: m/z = 741.3 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{40}H_{54}N_4O_8$ + Na: 741.3834; found: 741.3859.

(–)-Folicanthine (3)

To a stirred solution of (–)-**8** (45 mg, 0.0627 mmol) in CH_2Cl_2 (2.5 mL) were added TMSOTf (0.23 mL, 1.25 mmol, 20 equiv) and 2,6-lutidine (0.14 mL, 1.25 mmol, 20 equiv) successively at 0 °C. The reaction mixture was stirred for 30 min and then carefully quenched with aq NH_3 (28%, 1 mL). The mixture was diluted with CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting white *N*-demethylfolicanthine could be used directly for the next step. Thus, HCHO (95 μL, 37% in H_2O, 20 equiv) and $NaBH(OAc)_3$ (265 mg, 1.25 mmol, 20 equiv) were sequentially added to a stirred solution of the above tetraamine in MeCN (5 mL) at r.t. The reaction mixture was stirred for 1.5 h, and then carefully quenched with aq NH_3 (28%, 3 mL) at 0 °C. The mixture was diluted with CH_2Cl_2 (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (acetone–PE–Et_3N, 4:1:0.1) on silica gel to afford the desired (–)-folicanthine (**3**; 20 mg, 85%) as colorless crystals. Product (–)-**3** was dissolved in EtOAc and after 3 days, colorless single crystals were obtained by slow evaporation of the solvent at r.t.; mp 178–179 °C; R_f = 0.45 (acetone–PE–Et_3N, 4:1:0.1); $[\alpha]_D^{20}$ –331 (*c* 1.0, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97 (t, J = 7.2 Hz, 2 H), 6.91 (br s, 2 H), 6.49 (t, J = 6.9 Hz, 2 H), 6.26 (d, J = 7.5 Hz, 2 H), 4.40 (br s, 2 H), 3.00 (s, 6 H), 2.64 (br s, 2 H), 2.48–2.39 (m, 4 H), 2.41 (s, 6 H), 2.01–1.93 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8 (2 C), 132.7 (2 C), 128.0 (2 C), 123.6 (2 C), 116.6 (2 C), 105.8 (2 C), 91.9 (2 C), 62.6 (2 C), 52.6 (2 C), 37.8 (2 C), 35.4 (2 C), 35.2 (2 C).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{31}N_4$: 375.2543; found: 375.2540.

Acknowledgment

This work was supported by NSFC (Nos. 21172096 and J1103307), the Fundamental Research Funds for the Central Universities (lzujbky-2013-ct02 and lzujbky-2014-59), Program for Changjiang Scholars and Innovative Research Team in University (IRT1138), and the '111' Project of MoE.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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