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Enantiocontrolled Total Synthesis of (−)-Mersicarpine

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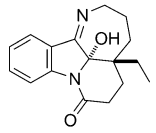
Abstract: A racemic synthesis of mersicarpine (**1**) was achieved by the Mizoroki–Heck reaction and a DIBALH-mediated reductive ring-expansion reaction. Based on a first-generation synthesis, a second-generation enantiocontrolled total synthesis of (−)-mersicarpine (**1**) was achieved by an 8-pot/11-step sequence in 21% overall yield from commercially available 2-ethylcyclohexanone. Subjection of a ketoester, which was prepared by an asymmetric Michael addition (according to the protocol by d'Angelo and Desmaële), and phenylhydrazine to modified Fischer indole conditions provided a six-membered tricyclic indole. Benzylic oxidation and subsequent oxime formation provided a ketoxime, which was treated with diisobutylaluminum hydride (DIBALH) to construct the characteristic azepinoindole skeleton in good yield. In the DIBALH-mediated reductive ring-expansion reaction, gradually increasing the reaction temperature and in situ-protection of the nitrogen in an oxygen-sensitive azepinoindole with a benzyloxycarbonyl (Cbz) group were crucial for the high-yielding process. With these methodologies, the short-step and efficient synthesis of (−)-mersicarpine was accomplished. Several synthetic efforts are also described.

Keywords: mersicarpine · natural products · ring expansion · synthetic methods · total synthesis

Introduction

Mersicarpine (**1**) was obtained from the stem-bark extracts of the *Kopsia fruticosa* and *Kopsia arborea* by Kam and co-workers in 2004,[1] which has a characteristic seven-membered cyclic imine fused with δ-lactam and indoline. This unique structure has received considerable attention by synthetic chemists.[2] The first total synthesis of (±)-mersicarpine (**1**) was reported by Kerr and co-workers in 2008,[3] in which they utilized a radical cyclization of malonic radical that was generated by malonate and $Mn(OAc)_3$ to form a key δ-lactam fused indoline intermediate (11% overall yield in 14 pots/14 steps from commercially available indoline). Zard and Biechy later accomplished the formal synthesis of (±)-**1** by using an intermolecular radical cascade reaction of a xanthate.[4] In 2010, Fukuyama and co-workers reported the first enantiocontrolled total synthesis of (−)-**1** featuring the formation of an indole with a chiral quaternary carbon center by a gold-catalyzed cyclization of the corresponding *o*-aminophenylacetylene derivative, which was assembled from a chiral acetylene by the Sonogashira cross-coupling reaction.[5] The formation of azepinoindole through diazocoupling and the subsequent autoxidation led to (−)-mersicarpine (**1**) (4.5% overall yield in 14 pots/16 steps from commercially available 2-ethylcyclohexanone including the enriching process of enantiometic excess of an intermediate). Very recently, Han and co-workers reported on an alternative synthetic route for the Kerr's intermediate, utilizing an $Al(OTf)_3$-catalyzed nucleophilic addition of a silyl enol ether to the carbocation species generated in situ from a tertiary alcohol.[6] Recently, we achieved a synthesis of (−)-mersicarpine (**1**)[7] utilizing the diisobutylaluminum hydride (DIBALH)-mediated reductive ring-expansion reaction established in our group (21% overall yield in 8 pots/11 steps from commercially available 2-ethylcyclohexanone).[8]



(−)-Mersicarpine (**1**)

A crucial synthetic challenge for this molecule should be the construction of a seven-membered α-hydroxy cyclic imine. Kerr and co-workers constructed a cyclic imine by using the intramolecular condensation of the primary amine and the carbonyl group, which was generated through oxidation of the indole **2** moiety by using dimethyl dioxirane, followed by the removal of the Boc group (Scheme 1).[3]

Fukuyama demonstrated that azepinoindole **4** was a precursor for the seven-membered α-hydroxy cyclic imine (Scheme 2).[5] Thus, the subjection of azepinoindole **4**, which was generated by the reduction of the phenylazo group in **5** and the subsequent cyclization of the resultant amine **6**, to aerobic conditions resulted in the autoxidation of the 2,3-position of an electron-rich azepinoindole to provide peroxide

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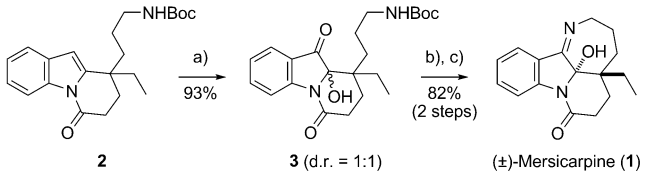
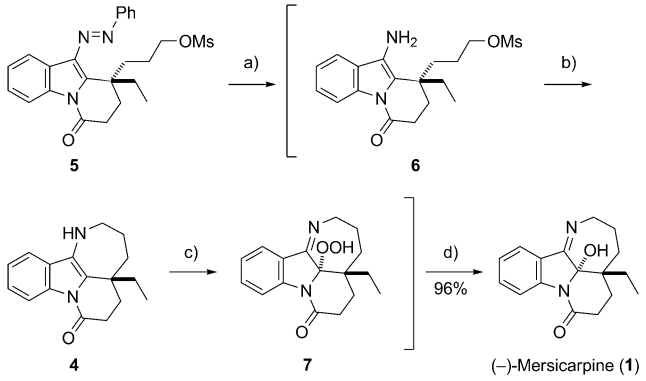
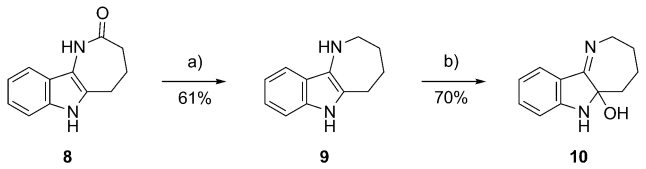


Scheme 1. Kerr's synthesis of (±)-mersicarpine.[3] Reagents and conditions: a) oxone, acetone, EDTA·Na_2, TBAS, MeCN, H_2O, 0 °C; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; c) TBAF, THF, RT. Abbreviations: EDTA·Na_2 = disodium ethylenediaminetetraacetic acid; TBAS = tetrabutylammonium hydrogen sulfate; TBS = *tert*-butyldimethylsilyl; TBAF = tetrabutylammonium fluoride; THF = tetrahydrofuran.



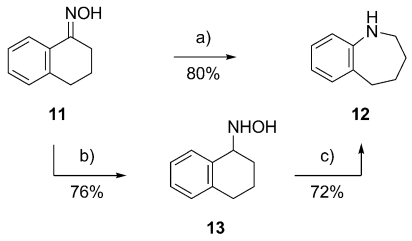
Scheme 2. Fukuyama's synthesis of (−)-mersicarpine.[5] Reagents and conditions: a) H_2, Pd/C, *i*PrOH/CH_2Cl_2, RT; b) $NaHCO_3$, then degassing, heat to reflux; c) air, RT; d) Me_2S, RT.

7. Reductive cleavage of the O–O bond gave (−)-mersicarpine (**1**). This aerobic oxidation of azepinoindole was also reported by Hester (Scheme 3).[9] Thus, the reduction of lactam **8** provided air-sensitive azepinoindole **9** that was easily oxidized to hemiaminal **10** fused with cyclic imine under aerobic conditions.



Scheme 3. Hester's synthesis of azepinoindole.[9] Reagents and conditions: a) $LiAlH_4$, THF, heat at reflux; b) EtOAc, RT.

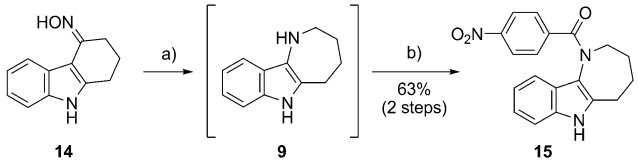
During the course of our studies on the synthesis of the secondary cyclic amine fused with an aromatic ring, we developed a DIBALH-mediated ring-expansion reaction of a cyclic ketoxime (Scheme 4).[8a,b] For instance, treatment of oxime **11** with DIBALH exclusively provided tetrahydrobenzazepine **12** in good yield. Unlike the classical Beckmann rearrangement,[10] the reaction proceeds through the hydroxylamine intermediate **13**, which was supported by the results that both the (*E*)- and (*Z*)-oxime were converted to



Scheme 4. Construction of tetrahydrobenzazepine using DIBALH-mediated reductive ring-expansion reaction. Reagents and conditions: a) DIBALH (6 equiv), CH_2Cl_2, 0 °C; b) $NaBH_3CN$, concd HCl, MeOH, 0 °C; c) DIBALH (5 equiv), CH_2Cl_2, 0 °C. DIBALH = diisobutylaluminum hydride.

the same tetrahydrobenzazepine and that the corresponding hydroxylamine **13** was also transformed to tetrahydrobenzazepine **12** under the same reaction conditions.

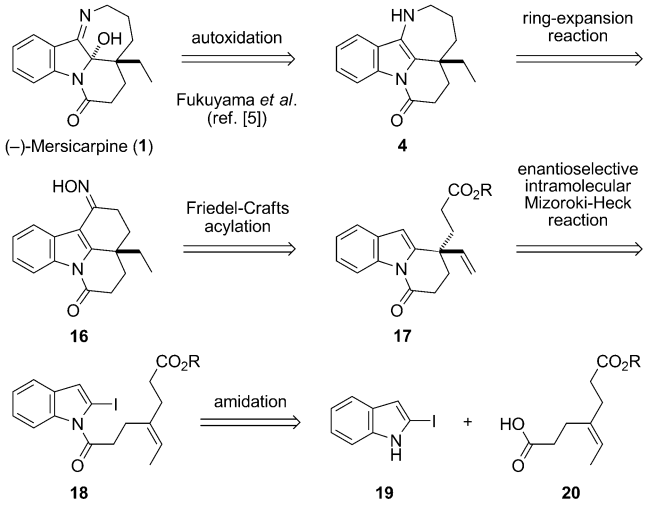
The reaction was successfully applied to the construction of the azepinoindole skeleton by using cyclic ketoxime **14** (Scheme 5). Since compound **9** was too unstable to be isolated due to the oxidation of the electron-rich indole,[5,9] azepinoindole **9** was isolated in 63% yield as *N*-benzoylazepinoindole **15** after subsequent acylation. Encouraged by these results, we considered the possibility that the reaction could be very useful for the formation of azepinoindole moiety and began synthetic studies toward mersicarpine by using the DIBALH-mediated ring-expansion reaction. In this paper, we describe the full details of our synthetic efforts on the enantiocontrolled efficient total synthesis of (−)-mersicarpine (**1**).



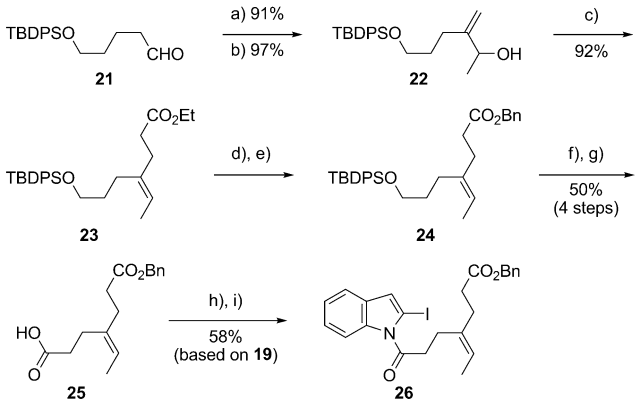
Scheme 5. Previous studies on construction of azepinoindole skeleton. Reagents and conditions: a) DIBALH (9 equiv), THF/CH_2Cl_2, 0 °C to RT; b) *p*-$NO_2C_6H_4COCl$, Et_3N, CH_2Cl_2, RT.

Results and Discussion

The preliminary report suggested that we utilize azepinoindole as a precursor of mersicarpine, which would be synthesized by the DIBALH-mediated reductive ring-expansion reaction (Scheme 6). Fukuyama's autoxidation[5] of tetracyclic azepinoindole **4** would lead to (−)-mersicarpine (**1**). We anticipated that the seven-membered azepine ring would be constructed from the tetracyclic six-membered oxime **16** by the reductive ring-expansion reaction. The oxime should be synthesized from the corresponding ketone that would be derived by Friedel–Crafts acylation of carboxylic acid **17**



Scheme 6. Retrosynthetic analysis of (−)-mersicarpine.



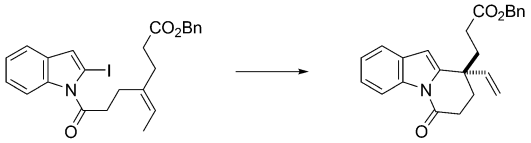
Scheme 7. Preparation of *N*-acyl-2-iodoindole. Reagents and conditions: a) HCHO (aq), pyrrolidine (10 mol%), $EtCO_2H$ (10 mol%), *i*PrOH, 45°C, 6 h; b) MeLi, Et_2O, 0°C, 0.5 h; c) $MeC(OEt)_3$, $EtCO_2H$ (5 mol%), 120°C, 7 h; d) 2 M NaOH (aq), MeOH/THF, RT, 5 h; e) BnBr, K_2CO_3, DMF, RT, 0.5 h; f) TBAF, THF, RT, 12 h; g) PDC, DMF, RT, 12 h; h) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0°C to RT, 1 h; i) 2-iodoindole (**19**), NaH, DMAP, THF, 0°C to RT, 1.5 h. Bn = benzyl; DMF = *N*,*N*-dimethylformamide; TBAF = tetra-*n*-butylammonium fluoride; PDC = pyridinium dichromate; DMAP = 4-dimethylaminopyridine.

(R = H) bearing a chiral quaternary carbon center. We planned to construct the lactam ring having the chiral center by an enantioselective Mizoroki–Heck reaction[11] of *N*-acyl-2-iodoindole **18**, which would be readily prepared by amidation of 2-iodoindole (**19**) and half ester **20**.

First, we prepared *N*-acyl-2-iodoindole **26** from the known aldehyde **21**[12] (Scheme 7). Stereoselective construction of the trisubstituted olefin **23** was performed according to the procedure by Trauner and Bowie[13] through the Johnson–Claisen rearrangement of allylic alcohol **22**, which was prepared from **21** over 2 steps. After the transformation of ethyl ester **23** to benzyl ester **24**, deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group and subsequent pyridinium dichromate (PDC) oxidation of the resulting alcohol provided half ester **25**, which was converted to *N*-acyl-2-iodoindole **26** through condensation with 2-iodoindole (**19**).[14]

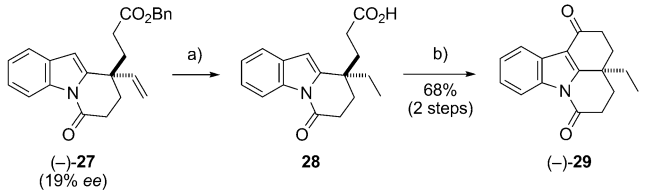
With substrate **26** in hand, we then examined the enantioselective intramolecular Mizoroki–Heck reaction (Table 1). First, we employed the Sodeoka and Shibasaki's conditions by using $[Pd_2(dba)_3{\cdot}CHCl_3]$ (DBA = dibenzylideneacetone) or $[Pd(OAc)_2]$ (OAc = acetyl) as a precatalyst, (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene ((*S*)-BINAP) as a chiral ligand, $CaCO_3$ as a base, and Ag_3PO_4 as a scavenger of HI in *N*-methyl-2-pyrrolidinone (NMP; Table 1, entries 1 and 2).[11a,b] Both conditions provided the desired product in low to moderate yields, although the enantiomeric excess (*ee*) was quite low. The use of the palladium precatalyst having a chiral ligand,[15] which was also proved to be effective in asymmetric intramolecular Mizoroki–Heck reaction by Sodeoka and Shibasaki,[11a,b] gave cyclic compound **27**[16] in better yield but low enantioselectivity (Table 1, entry 3). Then, we adopted the conditions reported by Overman and co-workers,[11c,d] using 1,2,2,6,6-pentamethylpiperidine (PMP) as a base. The reaction using $[Pd_2(dba)_3{\cdot}CHCl_3]$ at 100°C in DMF smoothly proceeded to give **27** in much

Table 1. Asymmetric intramolecular Mizoroki–Heck reaction.[a]



Entry	Pd, Ligand ([mol%])	Solvent	Base ([equiv])	Additive ([equiv])	*T* [°C]	*t* [h]	Yield [%]	*ee* [%][b]
1[c]	$[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.5), (*S*)-BINAP (10)	NMP	$CaCO_3$ (2)	Ag_3PO_4 (2)	70 to 75	109	36	1.9
2[c]	$[Pd(OAc)_2]$ (10), (*S*)-BINAP (20)	NMP	$CaCO_3$ (2)	Ag_3PO_4 (2)	70 to 75	109	57	2.3
3	$[PdCl_2((S)\text{-BINAP})]$ (10)	NMP	$CaCO_3$ (2)	Ag_3PO_4 (2)	70	92	77	2.8
4[d]	$[Pd_2(dba)_3{\cdot}CHCl_3]$ (5), (*S*)-BINAP (20)	DMF	PMP (4)	none	100	1	90	0
5[c]	$[Pd(OAc)_2]$ (10), (*S*)-BINAP (20)	DMF	none	Ag_3PO_4 (2)	100	84	19	19

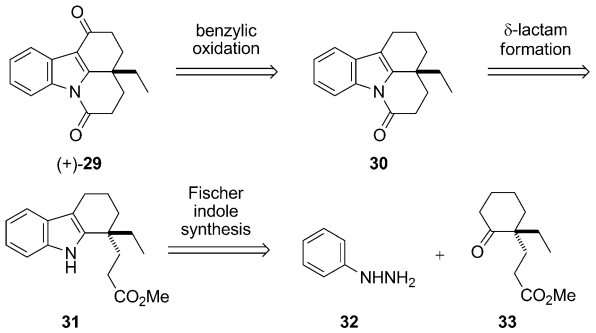
[a] Conditions: Pd catalysts (2.5–10 mol%), (*S*)-BINAP (10–20 mol%), base (2–4 equiv) or additive (2 equiv), solvent (0.05 M). [b] The enantiomeric excess was determined by HPLC analysis of **27** using a Chiralcel OJ-H column. [c] The precatalysts were stirred at room temperature for 0.5 h prior to addition of **26**, a base, and an additive. [d] The precatalysts were heated at 100°C for 12 h prior to addition of **26**, a base, and an additive. DBA = dibenzylideneacetone; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; NMP = *N*-methyl-2-pyrrolidinone; PMP = 1,2,2,6,6-pentamethylpiperidine.



Scheme 8. Synthesis of tetracyclic ketone **29**. Reagents and conditions: a) H_2 (1 atm), Pd/C (10 mol%), EtOAc/EtOH, RT, 5 h; b) P_2O_5, MsOH, 80°C, 20 min. Ms = methanesulfonyl.

higher yield, but in a racemic form (Table 1, entry 4). After extensive optimization, we found that the enantioselectivity improved to 19% when we performed the reaction without a base, in spite of the lower yield and prolonged reaction time (Table 1, entry 5). Unfortunately, further investigations did not provide us any satisfactory results regarding the enantiomeric excess, which led to this approach being abandoned. The absolute stereochemistry of the intramolecular Mizoroki–Heck reaction product was determined after Friedel–Crafts acylation[17] of corresponding carboxylic acid **28** to requisite cyclic ketone **29**, which was alternatively synthesized in the optically pure form (Scheme 8).

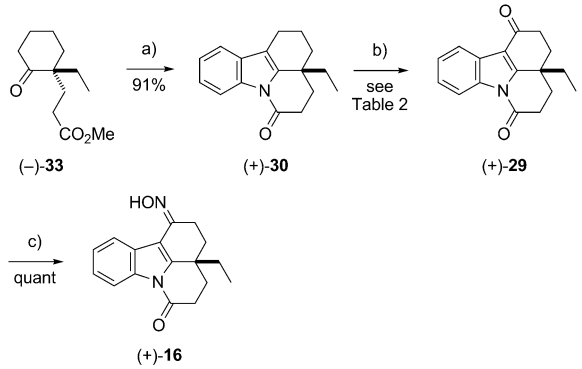
For the second-generation synthesis of cyclic ketone **29**, we planned a strategy featuring the Fischer indole synthesis by using an easily accessible optically active ketoester **33**[18] (Scheme 9). Ketone **29** would be prepared by benzylic oxidation[19] of carbazole derivative **30**. The δ-lactam ring of



Scheme 9. Our second synthetic strategy for optically active cyclic ketone **29**.

tetracyclic compound **30** would be formed by cyclization of indole ester **31**, which should be derived from phenylhydrazine (**32**) and an optically active ketoester **33** by Fischer indole synthesis.[20]

The investigation commenced with the Fischer indole synthesis using optically active ketoester **33** (Scheme 10). Ketoester **33**, prepared in 99% *ee* according to the protocol by d'Angelo and Desmaële,[18,21] was treated with phenylhydrazine hydrochloride in acetic acid at 120°C to give tetracyclic tetrahydrocarbazole **30** in high yield without isolation of the transient tricyclic tetrahydrocarbazole **31**. We then investigated the oxidation of **30** to ketone **29** (Table 2). Whereas



Scheme 10. Preparation of optically pure oxime **16** by Fischer indole synthesis followed by benzylic oxidation. Reagents and conditions: a) $PhNHNH_2$·HCl, AcOH, heat at reflux; b) benzylic oxidation; c) NH_2OH·HCl, pyridine, RT. Ac = acetyl.

2,3-dichloro-5,6-dicyanoquinone (DDQ) did not provide the desired compound at all (Table 2, entry 1), compound **30** was completely consumed to provide desired ketone **29** in 22% yield when using cerium(IV) ammonium nitrate (CAN; Table 2, entry 2). Considering that the low yield was

Table 2. Conditions for benzylic oxidation of **30**.[a]

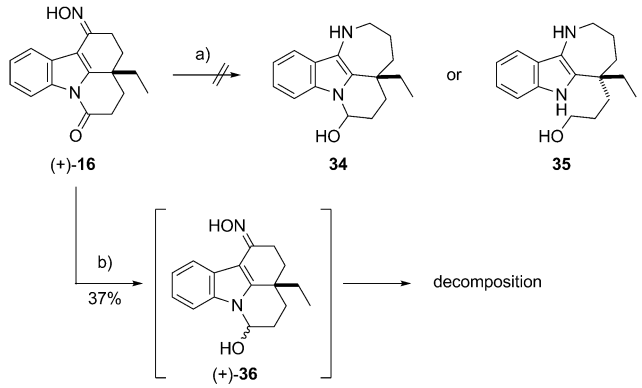
Entry	Reagents ([equiv])	Additive ([equiv])	*T* [°C]	*t* [h]	Yield [%]
1[b]	DDQ (3)	none	0 to reflux	–	N.R.
2	CAN (3)	none	0 to RT	1	22
3	CAN (4)	buffer (pH 6.86) [c]	0	2	45
4	CAN (7.5)	Et_3N (10)	0	1	66

[a] MeCN/H_2O (9:1 or 8:2) was used as a solvent. [b] THF/H_2O (9:1) was used as a solvent. [c] MeCN/buffer (pH 6.86) (9:1) was used as a solvent. DDQ = 2,3-dichloro-5,6-dicyanoquinone; CAN = cerium(IV) ammonium nitrate.

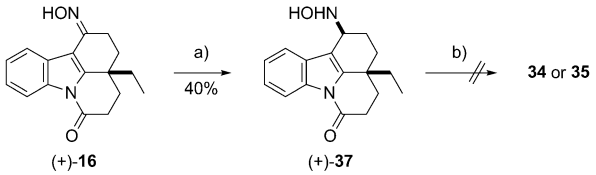
presumably caused by the strong acidity of CAN, we carried out the reaction in buffer (pH 6.86) to improve the yield of the product up to 45% even over a prolonged reaction time (Table 2, entry 3). Furthermore, the addition of triethylamine was found to be effective in providing **29** in 66% yield (Table 2, entry 4). Finally, the resultant ketone **29** was converted into oxime **16** in a quantitative yield.

Now the stage was set for testing the reductive ring-expansion reaction of tetracyclic oxime **16** (Scheme 11). Disappointingly, treatment of **16** with DIBALH gave neither azepinoindole **34** nor **35**, but provided hemiaminal **36** in low yield, which gradually decomposed upon prolonged reaction time. The lactam carbonyl group in oxime **16** was more reactive than oxime toward DIBALH, and the treatment of the resulting hemiaminal **36** with excess DIBALH gave a deteriorated mixture, which indicated that oxime **16** was an unsuitable substrate for the reductive ring-expansion reaction.

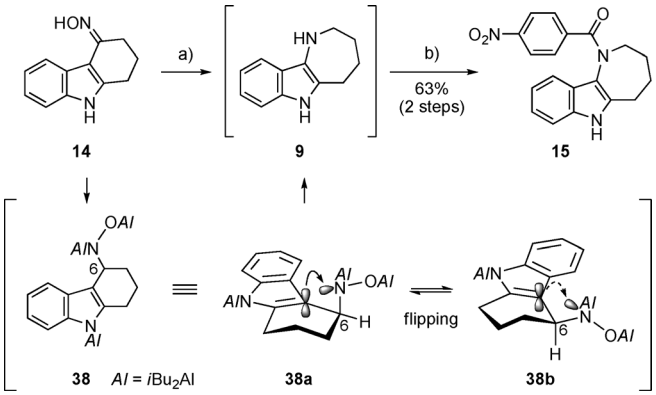
Next, we attempted the reductive ring-expansion reaction of hydroxylamine, which was proved to be the intermediate of the reaction of oxime with DIBALH (Scheme 12).[8b,c] Oxime **16** was reduced with sodium cyanoborohydride to



Scheme 11. Unsuccessful ring-expansion reaction of oxime **16**. Reagents and conditions: a) DIBALH (6–12 equiv), CH_2Cl_2, 0 °C to RT; b) DIBALH (4.5 equiv), CH_2Cl_2, 0 °C to RT.



Scheme 12. Unsuccessful ring-expansion reaction of hydroxylamine **37**. Reagents and conditions: a) $NaBH_3CN$, AcOH, RT; b) DIBALH (6 equiv), CH_2Cl_2, 0 °C to RT.



Scheme 13. Conformational restriction in the reductive ring-expansion reaction.

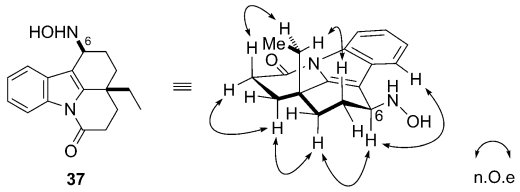
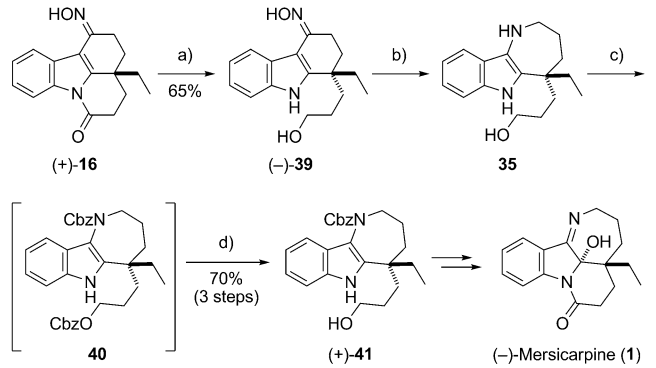


Figure 1. Selected nuclear Overhauser effect (NOE) interactions observed in hydroxylamine **37**.

afford hydroxylamine **37** in 40% yield as a single diastereomer. Unfortunately, the subjection of **37** to the ring-expansion reaction also did not provide azepinoindoles **34** or **35**.

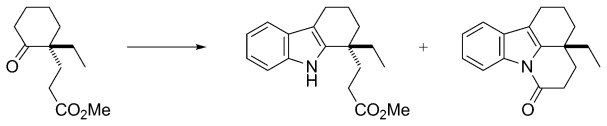
These unsuccessful results are rationalized by taking into consideration a conformational property of the hydroxylamino group. Our previous mechanistic studies using DFT calculation revealed that the ring-expansion reaction is initiated by elongation of the N–O bond, which is promoted by the donation of the π-electron of the aromatic ring to the σ^*_{N-O} orbital. In this event the hydroxylamine on the cyclohexene ring should occupy the pseudoaxial position to enable proper overlapping of the π-orbital of the aromatic ring with the σ^*_{N-O} orbital of the hydroxyamino group.[8b] In the successful ring-expansion reaction using cyclic ketoxime **14** as a substrate, the resultant hydroxylamine intermediate **38** would exist in two conformers, **38a** and **38b**. Between them, the subsequent cleavage of the N–O bond should take place through conformer **38a** having the hydroxylamino group at the pseudoaxial position (Scheme 13). In contrast to the conformationally flexible tricyclic hydroxylamine intermediate **38**, tetracyclic hydroxylamine **37** has the rigid fused skeleton and thus should exist in a stacked conformation. The observed NOE correlations of hydroxylamine **37** suggested that the cyclohexene ring existed in a twist-chair conformation with a pseudoequatorial hydroxyamino group (Figure 1). Therefore, the conformational restriction, due to the lactam ring, prevents the flipping of the cyclohexene ring to locate the hydroxylamino group in a pseudoaxial position, which is necessary for the ring-expansion reaction.

The conformational analysis of tetracyclic hydroxylamine **37** prompted us to carry out the reductive ring-expansion reaction using a more flexible tricyclic oxime (Scheme 14). Treatment of **16** with sodium borohydride in THF/MeOH chemoselectively reduced lactam to alcohol **39**. Gratifyingly, upon subjection of **39** to the reductive ring-expansion reaction (10 equiv of DIBALH in CH_2Cl_2 at 0 °C), the desired azepinoindole **35** was obtained as expected. Due to the air-sensitive nature of the unprotected azepinoindole **35**, the



Scheme 14. Successful ring expansion. Reagents and conditions: a) $NaBH_4$ (excess), MeOH/THF, 0 °C to RT, 1 h; b) DIBALH (10 equiv), CH_2Cl_2, 0 °C to RT, 1 h; c) CbzCl, pyridine, CH_2Cl_2, 0 °C, 15 min, then evaporation; then d) 2 M NaOH (aq), MeOH/THF, 0 °C, 1 h. Cbz = benzyloxycarbonyl.

Table 3. Fischer indole synthesis.[a]



Entry	Hydrazine ([equiv])	MsOH [equiv]	Solvent	T [°C]	t [h]	**31** [%]	**30** [%]
1	$PhNHNH_2$·HCl (1.5)	none	AcOH	120	13	0	91
2	$PhNHNH_2$·HCl (1.5)	none	MeOH	reflux	18	82	18
3	$PhNHNH_2$ (2.0)	1.8	MeOH	reflux	70	80	7
4	$PhNHNH_2$ (2.0)	1.9	MeOH	reflux	24	84	7
5	$PhNHNH_2$ (2.0)	2.0	MeOH	reflux	22	72	18

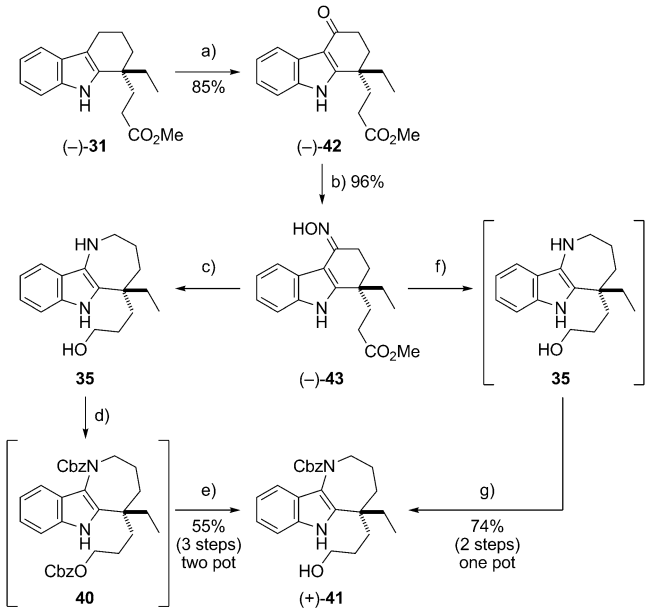
[a] Reaction conditions: the reaction mixture was heated at reflux. Ms = methanesulfonyl.

crude **35** was immediately treated with CbzCl and pyridine and the resultant Cbz carbonate **40** was hydrolyzed to provide Cbz carbamate **41**. As described later, the carbamate **41** serves as a key intermediate to synthesize (−)-mersicarpine (**1**). However, we decided at this point to improve this synthetic route to exclude the inefficient sequence involving construction, reductive opening, and reconstruction of the lactam ring.

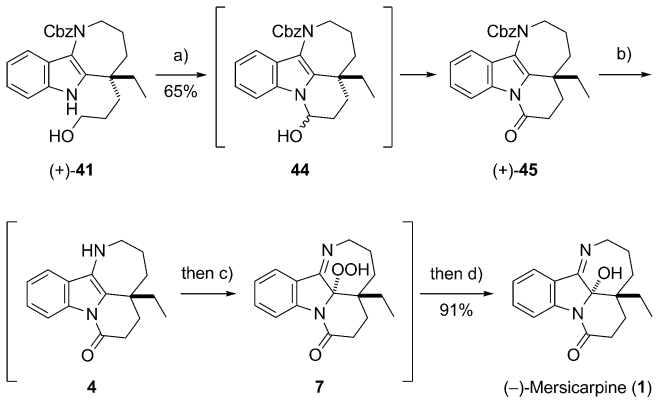
First we explored the reaction conditions of Fischer indole synthesis, which gives tricyclic tetrahydrocarbazole **31** without the formation of the lactam ring (Table 3). Based on the initial observation that the reaction in MeOH instead of AcOH using phenylhydrazine hydrochloride selectively gave the desired tricyclic tetrahydrocarbazole **31** (Table 3, entry 2), we carefully investigated the effects of acid on the ratio of **30** to **31**. To this end, it was found that methanesulfonic acid (MsOH) was an appropriate acid to selectively promote the Fischer indole synthesis and, more importantly, that the product ratio was highly sensitive to the amount of acid used. Thus, the reaction using 2.0 equiv of phenylhydrazine and 1.9 equiv of MsOH gave **31** in highest yield and selectivity (Table 3, entry 4). The reaction using 1.8 equiv of MsOH suppressed the formation of **30**, but a longer reaction time was needed (Table 3, entry 3). On the other hand, the reaction in the presence of 2.0 equiv of MsOH did not suppress the undesired lactamization to give **30** (Table 3, entry 5).

Second, we examined transformation of tetrahydrocarbazole **31** into Cbz carbamate **41** through a reductive ring-expansion reaction (Scheme 15). Oxidation of **31** with DDQ[19] in THF/H_2O provided ketone **42** in high yield, which was converted to oxime **43** by using hydroxylamine hydrochloride in pyridine. In the key ring-expansion reaction of **43** with a reactive methyl ester toward DIBALH, extensive optimization suggested that an initial reaction temperature should be −78 °C for the smooth conversion. Thus, general reaction conditions established in our previous studies (0 °C to RT, Scheme 4) provided the desired product in 25–33 % yield. On the other hand, control of the reaction temperature from −78 to 0 °C significantly improved the yield of the product up to 55 %. We then modified the protocol for a one-pot transformation of oxime **43** to azepinoindole **41** without the isolation of unstable azepinoindole **35**. Following the consumption of oxime **43** by TLC analysis, the resultant unprotected azepinoindole **35** was protected as a Cbz carbamate **41** under Schotten–Baumann conditions[22] in 74 % yield.

The remaining tasks for the completion of the total synthesis of (−)-mersicarpine (**1**) from azepinoindole **41** included the construction of the δ-lactam and the oxidation of the indole moiety (Scheme 16). We found that a combination of tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[23] was effective for one-pot lactam formation, presumably through the hemiaminal intermediate **44**. According to Fukuyama's protocol,[5] the reductive removal of the Cbz group of **45** and the subsequent treatment with air generated hydroperoxide **7**, which was reduced by dimethyl sulfide to provide (−)-mersicarpine (**1**) in 91 % yield from **45**.



Scheme 15. Reductive ring-expansion reaction. Reaction conditions: a) DDQ, THF/H_2O, 0 °C; b) NH_2OH·HCl, pyridine, RT; c) DIBALH (10 equiv), CH_2Cl_2, −78 to 0 °C, 2 h, then 0 °C to RT, 1 h; d) CbzCl (2 equiv), pyridine, CH_2Cl_2, 0 °C, then evaporation; then e) 2 M NaOH (aq), MeOH/THF, 0 °C, f) DIBALH (8 equiv), CH_2Cl_2, −78 to 0 °C, 1 h, then 0 °C to RT, 1 h; then g) 2 M NaOH (aq), 0 °C, 20 min, then CbzCl (1.5 equiv), 0 °C, 30 min.



Scheme 16. Total synthesis of (−)-mersicarpine (**1**): a) TPAP (5 mol%), NMO (6 equiv), MeCN, RT, 1 h; b) H_2 (1 atm), Pd/C (10 mol%), EtOAc, RT, 3 h; then c) air, RT, 3 h; then d) Me_2S (5 equiv), RT, 2 h. TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide.

Conclusion

We have achieved a highly efficient enantiocontrolled total synthesis of (−)-mersicarpine (**1**), which features a fine-tuned Fischer indole synthesis and a reductive ring-expansion reaction with DIBAL. The efficiency of this synthetic strategy has been proven by the facile access to the azepinoindole skeleton and the total synthesis of (−)-**1** in 21% overall yield in 8 pots/11 steps from commercially available 2-ethylcyclohexanone. The reductive ring-expansion reaction strategy should be useful not only for mersicarpine but also for nitrogen-containing heterocycles fused to aromatic rings.

Experimental Section

General remarks: Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Anhydrous THF and dichloromethane were purchased from Kanto Chemical Co. Inc. Anhydrous toluene, DMF, and MeCN were purchased from Wako Pure Chemical Industries. Anhydrous EtOAc, MeOH, and EtOH were dried and distilled according to the standard protocols. Column chromatography was performed on silica gel 60N (Kanto, spherical neutral, 63–210 μm) and flash column chromatography was performed on silica gel 60N (Kanto, spherical neutral, 40–50 μm) using the indicated eluent. Preparative TLC and analytical TLC were performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured on a SHIMADZU FTIR-8300 spectrometer or a JASCO FT/IR-4100 spectrometer. NMR spectra were recorded on a JEOL-ECA600, a GX500 spectrometer and JNM-AL400 spectrometer. For ^{1}H NMR spectra, chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ($\delta = 0$ ppm) or relative internal $CHCl_3$ ($\delta = 7.26$ ppm), or [D_5]acetone ($\delta = 2.04$ ppm). For ^{13}C NMR spectra, chemical shifts are expressed in ppm downfield from relative internal $CDCl_3$ ($\delta = 77.0$ ppm) or [D_6]acetone ($\delta = 29.8$ ppm). Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer (EI), a JMS-T100GC spectrometer (EI), or a Bruker micrOTOF II (ESI). Optical rotations were measured on a Horiba SEPA-300 high sensitive polarimeter. Elemental analyses were performed by a Yanaco CHN CORDER MT-5. Compound data of **1**, **31**, **33**, **41**, **42**, **43**, and **45** were reported in reference [7].

7-(Benzyloxy)-4-eth-(*E*)-ylidene-7-oxoheptanoic acid (25): A 300 mL round-bottomed flask equipped with a magnetic stirring bar was charged with ester **23** (5.31 g, 12.1 mmol), MeOH (20 mL), and THF (20 mL). Aqueous NaOH (2 M; 30 mL) was added to the solution at 0 °C. After the reaction mixture was stirred at 0 °C for 5 min, the mixture was allowed to warm to room temperature and the solution was stirred for 5 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **23**. The reaction was quenched with 2 M aqueous HCl at 0 °C, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford a crude carboxylic acid as a colorless oil, which was used to the next reaction without further purification. A 300 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the crude carboxylic acid, K_2CO_3 (5.03 g, 36.4 mmol), and DMF (40 mL). BnBr (2.20 mL, 18.5 mmol) was added to the suspension at room temperature. The suspension was stirred for 0.5 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of the carboxylic acid. The reaction was quenched with 1 M aqueous HCl at 0 °C, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford a crude benzyl ester **24** as a colorless oil, which was used to the next reaction without further purification. A 500 mL round-bottomed flask equipped with a magnetic stirring bar was charged with benzyl ester **24** and THF (24 mL). TBAF (1.0 M in THF, 24 mL, 24 mmol) was added to the solution at 0 °C. After the reaction mixture was stirred at 0 °C for 5 min, the mixture was allowed to warm to room temperature and the solution was stirred for 12 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **24**. The reaction was quenched with brine, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 3:2) to afford the corresponding alcohol (3.20 g) as a colorless oil. A 500 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the alcohol and DMF (24 mL). To the solution was added PDC (22.8 g, 60.6 mmol) at room temperature. The solution was stirred for 12 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of the alcohol. The reaction was quenched with water, and the mixture was extracted with diethyl ether five times. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 1:1) to afford half ester **25** (1.68 g, 6.08 mmol, 50% for 4 steps) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.50$–7.28 (m, 5H), 5.28 (q, $J = 6.6$ Hz, 1H), 5.11 (s, 2H), 2.55–2.23 (m, 8H), 1.57 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.5$, 173.1, 135.99, 135.95, 128.5, 128.24, 128.21, 121.35, 66.2, 33.1, 32.4, 31.4, 24.9, 13.2 ppm; IR (neat): $\tilde{\nu} = 3034$, 2925, 1737, 1709, 1161, 751, 698 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{19}O_4$: 275.1289 [$M-H^-$]; found: 275.1265.

7-(Benzyloxy)-4-eth-(*Z*)-ylidene-7-oxoheptanoyl chloride: A two-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged with carboxylic acid **25** (1.30 g, 4.69 mmol) and dry dichloromethane (2.0 mL). To the solution were added $(COCl)_2$ (0.80 mL, 9.3 mmol) and DMF (36 μL, 0.46 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 5 min, the mixture was allowed to warm to room temperature and the solution was stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford a crude acid chloride as a pale-yellow oil, which was used to the next reaction without further purification.

Benzyl 4-eth-(*E*)-ylidene-7-(2-iodo-1*H*-indol-1-yl)-7-oxoheptanoate (26): A two-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 2-iodoindole (**19**) (754 mg, 3.10 mmol) and

dry THF (10 mL). NaH (186 mg, 60% in mineral oil, 4.65 mmol) was added to the solution at 0°C. The solution was stirred for 30 min at the same temperature. To the reaction mixture were added DMAP (75.7 mg, 0.620 mmol) and the acid chloride in THF (6.0 mL). The solution was stirred for 0.5 h, after which time TLC (hexanes/EtOAc = 17:3) indicated complete consumption of **19**. The reaction was quenched with saturated aqueous NH_4Cl at 0°C and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 19:1 to 9:1) to afford amide **26** (903 mg, 1.80 mmol, 58%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.40–7.28 (m, 5H), 7.28–7.18 (m, 2H), 7.02 (s, 1H), 5.31 (q, J = 6.8 Hz, 1H), 5.10 (s, 2H), 3.22 (t, J = 8.0 Hz, 2H), 2.62–2.35 (m, 6H), 1.58 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 172.7, 137.9, 135.60, 135.95, 131.1, 128.5, 128.21, 128.17, 124.7, 123.5, 123.2, 121.6, 119.6, 114.8, 73.2, 66.2, 38.5, 33.1, 31.6, 25.3, 13.3 ppm; IR (neat): $\tilde{\nu}$ = 2922, 2860, 1733, 1438, 1355, 1282, 1163, 747, 698 cm^{-1}; MS (EI): m/z: 501 [M^+]; HRMS (EI): m/z calcd for $C_{24}H_{24}INO_3$: 501.0801 [M^+]; found: 501.0807.

Benzyl 2-(6-oxo-9-vinyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-9-yl)propionate (27): (see Table 1, entry 4): A 10 mL screw-top test tube equipped with a magnetic stirring bar was charged with [$Pd_2(dba)_3$·$CHCl_3$] (2.2 mg, 2.1 μmol), (*S*)-BINAP (2.9 mg, 4.7 μmol), and degassed DMF (0.3 mL). The solution was heated at 100°C for 12 h. To the solution were added *N*-acyl-2-iodoindole **26** (10.8 mg, 0.0215 mmol) in DMF (0.1 mL) and 1,2,2,6,6-pentamethylpiperidine (20 μL, 0.11 mmol) at room temperature. The solution was stirred for 1 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **26**. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexanes/EtOAc = 3:1) to afford lactam **27** (7.2 mg, 0.019 mmol, 90%) as a pale-yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 8.5, 8.5 Hz, 1H), 7.36–7.25 (m, 7H), 6.43 (s, 1H), 5.88 (dd, J = 17.5, 10.5 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 5.10 (s, 2H), 4.83 (d, J = 17.5 Hz, 1H), 2.82 (ddd, J = 17.5, 11.0, 5.0 Hz, 1H), 2.75 (ddd, J = 17.5, 5.0, 5.0 Hz, 1H), 2.50 (ddd, J = 16.0, 9.0, 7.0 Hz, 1H), 2.46 (ddd, J = 16.0, 9.0, 7.5 Hz, 1H), 2.26 (ddd, J = 16.0, 9.0, 7.5 Hz, 1H), 2.23 (ddd, J = 15.0, 9.0, 7.0 Hz, 1H), 2.06 (ddd, J = 13.5, 11.0, 5.0 Hz, 1H), 1.94 ppm (ddd, J = 13.5, 5.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 168.7, 141.6, 140.9, 135.7, 135.2, 129.2, 128.6, 128.31, 128.28, 124.6, 124.0, 120.1, 116.7, 116.5, 106.3, 66.5, 42.0, 33.7, 30.8, 30.2, 29.5 ppm; IR (neat): $\tilde{\nu}$ = 1732, 1705, 1456, 1350, 1180, 754 cm^{-1}; MS (EI): m/z 373 [M^+]; HRMS (EI): m/z calcd for $C_{24}H_{23}NO_3$: 373.1678 [M^+]; found: 373.1675.

(*S*)-(−)-Benzyl 2-(6-oxo-9-vinyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-9-yl)propionate (27): (see Table 1, entry 5): A two-necked 30 mL round-bottomed flask equipped with a magnetic stirring bar was charged with [$Pd(OAc)_2$] (4.5 mg, 20 μmol), (*S*)-BINAP (25.0 mg, 40.1 μmol), and degassed DMF (2.0 mL). The solution was stirred at room temperature for 0.5 h. To the solution were added *N*-acyl-2-iodoindole **26** (102 mg, 0.203 mmol) in DMF (2.0 mL) and Ag_3PO_4 (167 mg, 0.400 mmol) at room temperature. The solution was heated at 100°C for 84 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **26**. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 17:3) to afford lactam **27** (14.8 mg, 0.0396 mmol, 19%, 19% *ee*) as a pale-yellow oil. The enantiomeric excess of **27** was determined by HPLC (DAICEL-CHIRALCEL-OJ-H, hexane/*i*PrOH = 80:20, flow rate = 0.5 mL min^{-1}, t_+ = 65.8 min, t_- = 76.4 min). $[\alpha]_D^{29} = -6.8$ (c = 0.34, $CHCl_3$).

(3a*S*)-(−)-1,2,3,3a,4,5-Hexahydro-3a-ethyl-6*H*-pyrido[3,2,1-*jk*]-carbazol-1,6-dione (29): A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with benzyl ester **27** (12.4 mg, 0.0332 mmol, 19% *ee*) prepared in the enantioselective Mizoroki–Heck reaction (Table 1, entry 5), 10% Pd/C (3.5 mg, 3.3 μmol), EtOAc (0.17 mL), and EtOH (0.17 mL). To the flask was charged with hydrogen gas (1 atm). The resulting suspension was vigorously stirred for 5 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **27**. The reaction mixture was filtered through celite pad. The filter cake was washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford a crude acid **28** as a colorless oil, which was used to the next reaction without further purification. A 10 mL screw-top test tube equipped with a magnetic stirring bar was charged with the crude acid **28**. To the test tube was added Eaton's reagent, which was prepared from P_2O_5 (57.5 mg, 0.405 mmol) and MsOH (0.40 mL) at 80°C for 0.5 h. After the solution was stirred for 20 min at 80°C, the reaction mixture was poured into ice-water and extracted with $CHCl_3$ three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexanes/EtOAc = 1:1) to afford ketone **29** (5.88 mg, 0.0220 mmol, 68% for 2 steps, 16% *ee*) as a yellow oil. $[\alpha]_D^{26} = -13.9$ (c = 0.588, $CHCl_3$).

(3a*R*)-(+)-1,2,3,3a,4,5-Hexahydro-3a-ethyl-6*H*-pyrido[3,2,1-*jk*]-carbazol-6-one (30): A two-necked 20 mL round-bottomed flask equipped with a magnetic stirring bar was charged with ketoester **33** (162.2 mg, 0.764 mmol), phenylhydrazine hydrogen chloride salt (168.3 mg, 1.16 mmol), and acetic acid (2.5 mL). The reaction mixture was heated at 120°C for 13 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **33**. The reaction was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 17:3) to afford indole **30** (177.0 mg, 0.699 mmol, 91%) as an orange oil. $[\alpha]_D^{25} = +74.6$ (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.38 (dd, J = 7.2, 1.2 Hz, 1H), 7.39 (dd, J = 7.2, 1.2 Hz, 1H), 7.29 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.26 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 2.87 (ddd, J = 18.6, 13.8, 5.4 Hz, 1H), 2.78–2.72 (m, 1H), 2.70 (ddd, J = 18.6, 4.8, 1.8 Hz, 1H), 2.55 (ddd, J = 16.8, 10.2, 7.8 Hz, 1H), 2.13 (ddd, J = 13.2, 5.4, 1.8 Hz, 1H), 2.10 (ddd, J = 13.2, 3.6, 3.6 Hz, 1H), 2.04–1.94 (m, 2H), 1.75 (dq, J = 15.6, 7.8 Hz, 1H), 1.71 (dq, J = 15.6, 7.8 Hz, 1H), 1.65 (ddd, J = 13.8, 13.2, 4.8 Hz, 1H), 1.34 (ddd, J = 13.2, 12.6, 5.4 Hz, 1H), 0.92 ppm (dd, J = 7.8, 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 141.1, 135.0, 130.0, 124.1, 123.6, 117.9, 116.2, 113.3, 33.2, 31.7, 30.9, 30.6, 26.3, 19.8, 18.3, 8.1 ppm; IR (neat): $\tilde{\nu}$ = 2937, 1697, 1631, 1454, 1368, 1331, 1314, 1187, 1156, 750 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{19}NO$: 253.1467 [M^+]; found: 253.1462.

(3a*R*)-(+)-1,2,3,3a,4,5-Hexahydro-3a-ethyl-6*H*-pyrido[3,2,1-*jk*]-carbazol-1,6-dione (29): A 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged with indole **30** (206.3 mg, 0.814 mmol), triethylamine (1.1 mL, 7.9 mmol), acetonitrile (6.4 mL) and water (1.6 mL). The solution was cooled to 0°C and ceric ammonium nitrate (2.11 g, 3.85 mmol) at 0°C, and the resulting mixture was stirred at 0°C for 15 min. Cerium(IV) ammonium nitrate (1.04 g, 1.90 mmol) was added to the mixture at 0°C, and the resulting mixture was stirred at 0°C for 45 min, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **30**. The reaction was quenched with water. The resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by using silica gel column chromatography (hexanes/EtOAc = 1:1 to 1:3) to afford ketone **29** (143.0 mg, 0.535 mmol, 66%) as a colorless oil. $[\alpha]_D^{26} = +86.8$ (c = 1.00, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.41–8.38 (m, 1H), 8.20–8.16 (m, 1H), 7.40–7.35 (m, 2H), 2.98 (ddd, J = 19.2, 13.8, 5.4 Hz, 1H), 2.87 (ddd, J = 19.2, 4.8, 2.4 Hz, 1H), 2.80 (ddd, J = 18.0, 13.8, 4.8 Hz, 1H), 2.61 (ddd, J = 18.0, 4.8, 2.4 Hz, 1H), 2.34 (ddd, J = 13.8, 4.8, 2.4 Hz, 1H), 2.26 (ddd, J = 13.8, 5.4, 2.4 Hz, 1H), 1.95 (dddd, J = 13.8, 13.8, 4.8, 1.2 Hz, 1H), 1.93–1.81 (m, 3H), 1.06 ppm (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 168.1, 157.5, 134.8, 125.5, 125.4, 125.3, 121.3, 115.9, 113.8, 34.7, 34.1, 32.5, 30.5, 29.6, 25.2, 8.6 ppm; IR (neat-ATR): $\tilde{\nu}$ = 2945, 1714, 1659, 1572, 1479, 1451, 1363, 1305, 1165, 1134, 1098, 770, 757 cm^{-1}; HRMS (EI): m/z calcd for $C_{17}H_{17}NO_2$: 267.1259 [M^+]; found: 267.1266.

(3a*R*)-(+)-1,2,3,3a,4,5-Hexahydro-3a-ethyl-6*H*-pyrido[3,2,1-*jk*]-carbazol-1,6-dione oxime (16): A 10 mL test tube equipped with a magnetic stirring bar was charged with ketone **29** (26.8 mg, 0.100 mmol) and pyridine (0.25 mL). Hydroxylamine hydrogen chloride salt (32.6 mg, 0.469 mmol) was added to the solution at room temperature, and the solution was stirred for 17 h, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **29**. The reaction was quenched with water. The resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude oxime **16** (28.5 mg) as a pale-yellow solid as a single diastereomer, which was used to the next reaction without further purification. M.p. 251–253 °C (recrystallized from MeOH and EtOAc); $[\alpha]_D^{27} = +53.0$ ($c = 0.150$, MeOH); ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 10.02$ (s, 1H), 8.34 (dd, $J = 6.8$, 2.0 Hz, 1H), 8.02 (dd, $J = 6.8$, 2.0 Hz, 1H), 7.29 (ddd, $J = 6.8$, 6.8, 2.0 Hz, 1H), 7.26 (ddd, $J = 6.8$, 6.8, 2.0 Hz, 1H), 3.26 (ddd, $J = 18.4$, 5.2, 2.0 Hz, 1H), 3.03 (ddd, $J = 18.4$, 14.0, 5.2 Hz, 1H), 2.72 (ddd, $J = 18.4$, 5.2, 2.0 Hz, 1H), 2.52 (ddd, $J = 18.4$, 14.0, 5.2 Hz, 1H), 2.30–2.18 (m, 2H), 1.95–1.82 (m, 2H), 1.78–1.66 (m, 1H), 1.59 (dddd, $J = 14.0$, 14.0, 5.2, 1.6 Hz, 1H), 1.00 ppm (dd, $J = 7.6$, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 169.0$, 152.1, 148.2, 136.2, 127.4, 125.2, 124.9, 123.0, 116.5, 110.9, 34.7, 31.7, 31.3, 30.5, 25.9, 20.5, 8.6 ppm; IR (neat-ATR): $\tilde{\nu} = 3334$, 2955, 1674, 1468, 1455, 1373, 1322, 1308, 946, 846, 759, 698, 681 cm^{-1}; HRMS (EI): m/z calcd for $C_{17}H_{18}N_2O_2$: 282.1368 [M^+]; found: 282.1366; elemental analysis calcd (%) for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92; found: C 72.13, H 6.50, N 9.93.

(3a*R*)-(+)-3a-Ethyl-6-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-pyrido[3,2,1-*jk*]carbazol-1-one oxime (36): A two-necked 10 mL round-bottomed flask equipped with a magnetic stirring bar was charged with oxime **16** (24.7 mg, 0.0875 mmol) and dry dichloromethane (0.9 mL). To the solution was added DIBALH (1.03 M in hexane, 255 μL, 0.262 mmol) at 0 °C. The solution was stirred for 20 min at the same temperature. To the solution was added DIBALH (1.03 M in hexane, 130 μL, 0.134 mmol) at 0 °C. The solution was stirred for 10 min, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of **16**. The reaction mixture was diluted with diethyl ether. The reaction was quenched with MeOH and 2 M aqueous NaOH, and the mixture was extracted with diethyl ether three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexanes/EtOAc = 3:1) to afford hemiaminal **36** (9.1 mg, 0.032 mmol, 37%) as a yellow oil as a mixture of diastereomers; $[\alpha]_D^{27} = +53.3$ ($c = 0.640$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.07$–7.97 (m, 1H), 7.74–7.64 (m, 0.36H), 7.46–7.36 (m, 1H), 7.25–7.19 (m, 1.64H), 6.04 (d, $J = 1.8$ Hz, 0.64H), 5.67 (dd, $J = 7.8$, 6.6 Hz, 0.36H), 3.32–3.18 (m, 1H), 2.66–2.53 (m, 1H), 2.50–2.37 (m, 1H), 2.22–2.11 (m, 2H), 2.11–2.02 (m, 1H), 1.96 (ddd, $J = 9.2$, 2.0, 2.0 Hz, 0.64H), 1.90–1.52 (m, 3.36H), 1.50–1.34 (m, 1H), 1.01–0.87 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 154.4$, 154.2, 148.8, 148.2, 137.6, 136.1, 125.7, 125.1, 122.42, 122.38, 122.2, 122.0, 121.9, 121.7, 111.6, 109.6, 105.4, 104.9, 78.4, 74.2, 34.2, 31.6, 31.3, 30.2, 29.1, 26.7, 26.5, 26.3, 23.9, 20.3, 20.1, 8.54, 8.50 ppm (complexity due to diastereomers); IR (neat): $\tilde{\nu} = 3320$, 2942, 2875, 1608, 1560, 1455, 978, 752 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{21}N_2O_2$: 285.1598 [$M+H^+$]; found: 285.1598.

(1*S*,3a*R*)-(+)-3a-Ethyl-1-(hydroxyamino)-3,3a,4,5-tetrahydro-1*H*-pyrido-[3,2,1-*jk*]carbazol-6(2*H*)-one (37): A two-necked 10 mL round-bottomed flask equipped with a magnetic stirring bar was charged with oxime **16** (54.5 mg, 0.193 mmol) and acetic acid (2.0 mL). Sodium cyanoborohydride (221 mg, 3.50 mmol) was added to the solution at room temperature. The solution was stirred for 4 h, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **16**. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 1:1) to afford hydroxylamine **37** (21.7 mg, 0.0763 mmol, 40%) as a pale-yellow oil; $[\alpha]_D^{26} = +33.6$ ($c = 0.805$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.42 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.73 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.34–7.22 (m, 2H), 5.13 (brs, 1H), 4.38 (dd, $J = 8.8$, 7.6 Hz, 1H), 2.89 (ddd, $J = 18.4$, 13.6, 4.8 Hz, 1H), 2.72 (ddd, $J = 18.4$, 4.8, 2.0 Hz, 1H), 2.26–2.03 (m, 4H), 1.89–1.71 (m, 2H), 1.65 (ddd, $J = 13.6$, 13.6, 4.8 Hz, 1H), 1.43 (ddd, $J = 13.6$, 13.6, 4.8 Hz, 1H), 0.94 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.8$, 144.5, 135.1, 129.0, 124.4, 124.0, 119.5, 116.3, 112.4, 56.6, 33.6, 31.6, 30.9, 30.3, 26.2, 24.4, 8.3 ppm; IR (neat): $\tilde{\nu} = 3262$, 2943, 2874, 1702, 1622, 1460, 1370, 1314, 752 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{18}NO$: 252.1383 [$M-NHOH^+$]; found: 252.1398.

(*R*)-(−)-1-Ethyl-1-(3-hydroxypropyl)-2,3-dihydro-1*H*-carbazol-4(9*H*)-one oxime (39): A 10 mL screw-top test tube equipped with a magnetic stirring bar was charged with oxime **16** (18.6 mg, 0.0659 mmol), THF (0.16 mL), and MeOH (0.16 mL). Sodium borohydride (25.7 mg, 0.679 mmol) was added to the solution at 0 °C. After the reaction mixture was stirred at 0 °C for 5 min, the mixture was allowed to warm to room temperature and the solution was stirred for 0.5 h, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **16**. The reaction mixture was cooled to 0 °C. The reaction was quenched with water and 2 M aqueous HCl, and the mixture was extracted with diethyl ether twice and EtOAc twice. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexanes/EtOAc = 1:1) to afford alcohol **39** (12.3 mg, 0.0430 mmol, 65%) as a colorless solid as a single diastereomer; $[\alpha]_D^{27} = -19.4$ ($c = 0.615$, MeOH); ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 10.25$ (brs, 1H), 9.40 (brs, 1H), 8.03 (d, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.06 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.01 (dd, $J = 7.6$, 7.6 Hz, 1H), 3.58–3.40 (m, 2H), 2.86 (dd, $J = 6.4$, 1.6 Hz, 2H), 2.82 (brs, 1H), 1.96–1.74 (m, 6H), 1.57–1.42 (m, 2H), 0.87 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 153.8$, 147.4, 137.5, 125.7, 122.9, 122.3, 120.6, 111.6, 108.0, 63.0, 38.9, 34.8, 32.1, 31.3, 28.7, 20.4, 9.0 ppm; IR (neat-ATR): $\tilde{\nu} = 3272$, 2937, 2875, 1615, 1475, 1455, 1427, 1052, 898, 747, 730 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{23}N_2O_2$: 287.1754 [$M+H^+$]; found: 287.1756.

(*R*)-(+)-1-Benzyloxycarbonyl-4-ethyl-4-hydroxyethyl-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole (41): A 10 mL screw-top test tube equipped with a magnetic stirring bar was charged with the crude oxime **39** (2.0 mg, 0.0070 mmol) and dry dichloromethane (0.07 mL). DIBALH (1.03 M in hexane, 70 μL, 0.072 mmol) was added to the solution at 0 °C. After the reaction mixture was stirred at 0 °C for 5 min, the mixture was allowed to warm to room temperature and the solution was stirred for 1 h, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **39**. The reaction mixture was cooled to 0 °C and then diluted with diethyl ether. The reaction was quenched with MeOH and 2 M aqueous NaOH, and the mixture was extracted with diethyl ether three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford a crude azepinoindole **35** as pale-yellow oil, which was used to the next reaction without further purification. A screw-top test tube equipped with a magnetic stirring bar was charged with the crude azepinoindole **35**, pyridine (3.0 μL, 0.037 mmol), and dry dichloromethane (0.07 mL). Benzyl chloroformate (2.0 μL, 0.014 mmol) was added to the solution at 0 °C. The solution was stirred for 15 min, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **35**. The reaction mixture was concentrated under reduced pressure. MeOH (0.07 mL), THF (0.07 mL), and 2 M aqueous NaOH (0.1 mL) were added to the residue at 0 °C. The solution was stirred for 1 h, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of **40**. The mixture was extracted with diethyl ether three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexanes/EtOAc = 1:1) to afford carbamate **41** (2.0 mg, 0.0049 mmol, 70%) as a colorless oil. The physical data of compound **41** were identical to those reported in reference [7].

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