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Concise Asymmetric Total Synthesis of *ent*-Ancistrocladinium A

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Abstract: An asymmetric total synthesis of *ent*-ancistrocladinium A was developed *via* chiral phosphoric acid-catalyzed asymmetric reductive amination of 1-aryl-2-propanone and naphthylamine followed by a Bischler–Napieralski reaction. Direct use of the naphthyl moiety in the amine as a key building block in the natural product allowed us to achieve the total synthesis of ancistrocladinium A in only three steps from the known starting materials.

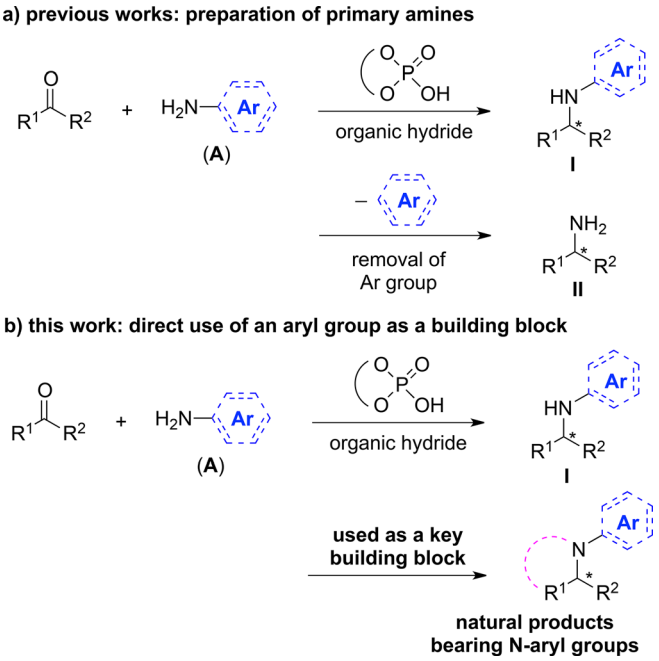
Keywords: ancistrocladinium A; chiral phosphoric acid catalysis; naphthylisoquinoline alkaloids; reductive amination; total synthesis

During the past decade, we have witnessed an increased interest in the chiral phosphoric acid-catalyzed asymmetric reduction of ketimines, derived from ketones and an aniline derivative **A**, using organic hydride sources such as Hantzsch ester and benzothiazolines.[1–4] Most of the previous approaches have focused on the preparation of chiral primary amines **II** by removing the aryl group from the resulting chiral secondary amines **I** (Scheme 1a). Since electron-rich aryl moieties are necessary for the deprotection from **I** under oxidative conditions, the use of amines **A** has been limited to electron-rich arylamines, particularly *para*-methoxyphenylamine, and other types of aniline derivatives have been rarely investigated in this asymmetric transformation.[5,6]

In contrast to the conventional approach, we envisaged that if an aryl group in amine **A** used in the chiral phosphoric acid-catalyzed asymmetric reductive amination of ketones could be directly utilized as a building block in chiral compounds rather than as a removable protecting group, the application of this asymmetric transformation could be significantly expanded to the synthesis of important chiral natural products, in particular ones bearing N-aryl moieties (Scheme 1b).

Although most of the naphthylisoquinoline alkaloids possess C,C-coupled linkages between the naphthalene and the isoquinoline fragments,[7] N,C-coupled alkaloids such as ancistrocladiniums A and B have been isolated recently (Figure 1).[8–10] Considering the fact that N,C-coupled naphthylisoquinoline alkaloids possess an N-aryl moiety, we envisioned that these alkaloids could be prepared *via* the chiral phosphoric acid-catalyzed reductive amination of a ketone with a naphthylamine carrying appropriate substituents, provided that the stereogenic center at the C-3 position in the dihydroisoquinoline ring could be controlled in this asymmetric protocol.

Herein, we present a new application of chiral phosphoric acid-catalyzed asymmetric reductive amination of 1-aryl-2-propanone **3** with naphthylamine **4** where the naphthyl moiety present in the amine was



Scheme 1. (a) Previous work: removal of an aryl group generating primary amines **II**. (b) Our work: utilization of an aryl group as a key building block.

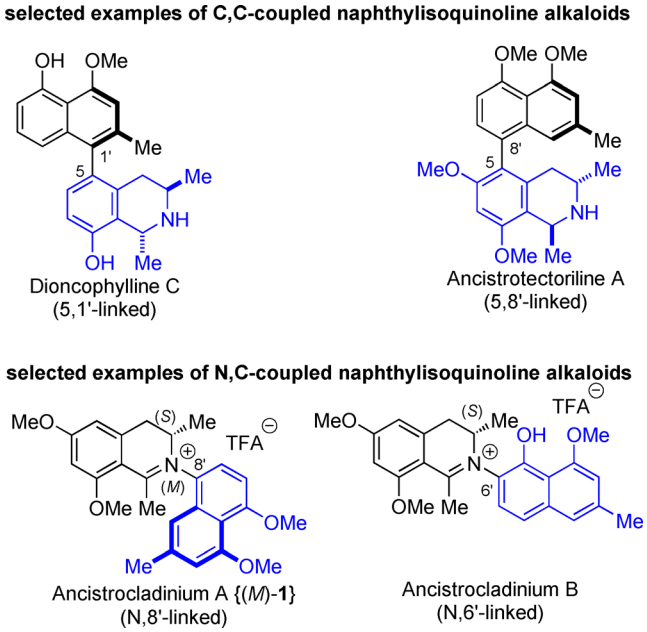
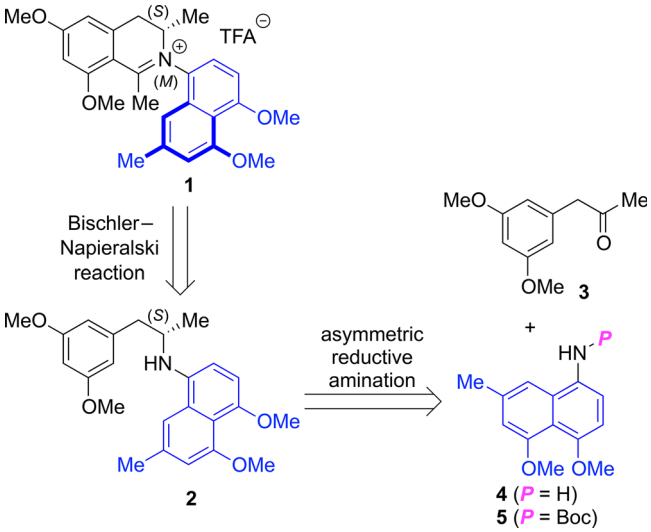


Figure 1. Representative examples of naphthylisoquinoline alkaloids with different coupling types.



Scheme 2. Retrosynthetic analysis for ancistrocladinium A (**1**).

directly utilized as a key building block of *ent*-ancistrocladinium A (*ent*-**1**) *via* chiral phosphoric acid-catalyzed asymmetric reductive amination followed by Bischler–Napieralski reaction. Direct use of the naphthalene moiety in the amine as a key building block in the natural product enabled us to complete the total synthesis of *ent*-**1** in only three steps from the known starting materials.

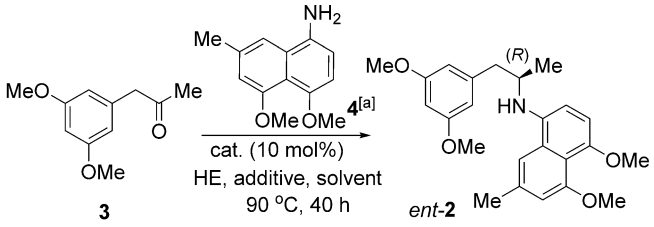
The first total synthesis of ancistrocladinium A (**1**) was reported by the Bringmann group in 2010.[9b] The N–C bond formation *via* the Buchwald–Hartwig amination of naphthyl bromide with (*S*)-1-aryl-2-propylamine, which was prepared from naturally occurring chiral L-alanine in five steps,[11] provided (*S*)-*N*-naphthyl-1-aryl-2-propylamine. Subsequent formation of the dihydroisoquinoline ring *via* Bischler–Napieralski reaction completed the synthesis of **1**. However, the previous synthesis started with a chiral pool (e.g., α-amino acid) to control the stereogenic center at the C-3 position in the dihydroisoquinoline moiety, and there have been no reports on the total synthesis of **1** *via* catalytic asymmetric transformations. Furthermore, although in the previous synthesis of **1**, the naturally predominant (*M*)-isomer of ancistrocladinium A, (*M*)-**1**, was obtained as the major atropo-isomer along with its atropo-epimer, (*P*)-**1**, as an inseparable mixture in a ratio of 2.5:1, no attempts to prepare (*P*)-**1** have been made and no general guidelines for the synthesis of (*P*)-**1** have been provided.

Our retrosynthetic analysis for ancistrocladinium A (**1**) is depicted in Scheme 2. Ancistrocladinium A (**1**) could be prepared from chiral amine **2** through the formation of the dihydroisoquinoline ring *via* a Bischler–Napieralski reaction. Chiral amine **2** could be synthesized *via* the chiral phosphoric acid-catalyzed asymmetric reductive amination of ketone **3** and naphthylamine **4**.[12,13]

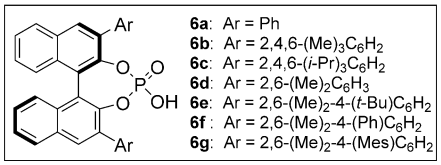
However, a few concerns were raised at the initial stages of our synthesis. Although a PMP amine has been widely utilized in the chiral phosphoric acid-catalyzed asymmetric reductive amination of ketones leading to the corresponding chiral amines in high enantioselectivity, there have been no reports on the chiral phosphoric acid-catalyzed asymmetric reductive amination of ketones with a naphthylamine. Thus, both the reactivity and the enantioselectivity in the chiral phosphoric acid-catalyzed reductive amination of ketone **3** with naphthylamine **4** were potential major concerns. In addition, since naphthylamine **4** was reported to be unstable and undergo decomposition under ambient conditions,[8a] the stability of **4** presented another concern. Furthermore, since the atropo-epimer of ancistrocladinium A, (*P*)-**1**, was not prepared as the major product in the previous synthesis, althouth (*P*)-**1** was obtained as the minor atropoisomer along with (*M*)-1 as an inseparable mixture, our third concern was whether we could prepared both (*M*)-**1** and (*P*)-**1**, respectively.

Keeping these anticipated challenges in mind, we began the total synthesis of ancistrocladinium A (**1**) by optimizing the chiral phosphoric acid-catalyzed asymmetric reductive amination of ketone **3** with naphthylamine **4** (Table 1). Since naphthylamine **4** was reported to be unstable, and *N*-Boc-protected naphthylamine **5** was reported to be stable,[9a] we first attempted to utilize **5** as a precursor for **4**. Particularly, if the Boc group in **5** could be removed by a relatively strong chiral phosphoric acid, naphthylamine **4** could be generated *in situ* from **5**, and be directly

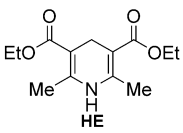
Table 1. Investigation of the reaction parameters.



Entry	Cat.	Additive	Solvent	Yield [%][b]	*ee*[c]
1[d]	**6a**	4 Å MS	toluene	N.R.[e]	N.D.[f]
2	**6a**	4 Å MS	toluene	62	16
3	**6b**	4 Å MS	toluene	68	46
4	**6c**	4 Å MS	toluene	45	5 (–)[g]
5	**6d**	4 Å MS	toluene	68	28
6	**6e**	4 Å MS	toluene	66	42
7	**6f**	4 Å MS	toluene	73	45
8	**6g**	4 Å MS	toluene	68	57
9	**6g**	5 Å MS	toluene	78	63
10[h]	**6g**	5 Å MS	TBME	76	78
11[i]	**6g**	5 Å MS	TBME	69	80
12[i,j]	**6g**	5 Å MS	TBME	66	82
13[i,j,k]	**6g**	5 Å MS	TBME	76	85



6a: Ar = Ph
6b: Ar = 2,4,6-$(Me)_3C_6H_2$
6c: Ar = 2,4,6-$(i\text{-}Pr)_3C_6H_2$
6d: Ar = 2,6-$(Me)_2C_6H_3$
6e: Ar = 2,6-$(Me)_2$-4-$(t\text{-}Bu)C_6H_2$
6f: Ar = 2,6-$(Me)_2$-4-$(Ph)C_6H_2$
6g: Ar = 2,6-$(Me)_2$-4-$(Mes)C_6H_2$



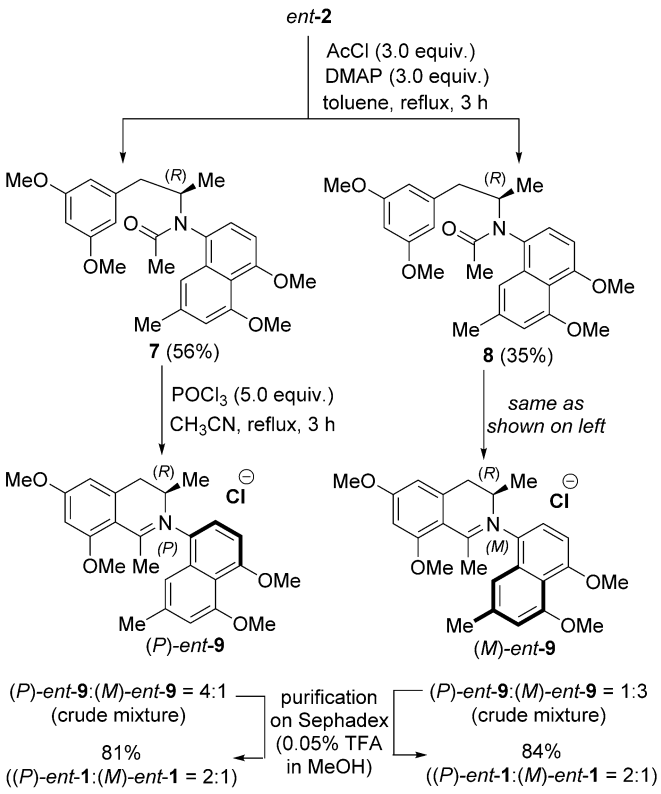
[a] **4** was prepared by the treatment of **5** with TFA, followed by basification with NaOH, extraction with dichloromethane, and concentration. The crude mixture of **4** was used directly in the reductive amination.
[b] Isolated yield.
[c] Enantiomeric excess (*ee*) was determined by HPLC analysis using a chiral AS-H column.
[d] Boc-protected naphthylamine **5** was used.
[e] No reaction.
[f] Not determined.
[g] The other enantiomer was obtained as the major product.
[h] At 50 °C.
[i] At 40 °C.
[j] Concentration of 0.050 M.
[k] 1.0 mmol scale.

used in the reductive amination reaction. With this expectation in mind, we first directly applied compound **5** to asymmetric reductive amination with ketone **3**. However, no reaction was observed under these conditions, and **5** remained intact even after a long reaction time (entry 1).

Since this result implied that a chiral phosphoric acid is not acidic enough to deprotect the Boc-group in **5**, we attempted to isolate naphthylamine **4** after removal of the Boc group from **5** with trifluoroacetic acid (TFA). When **5** was treated with TFA, the cleavage of the Boc group in **5** was evident in the ^{1}H NMR analysis of a crude mixture, but **4** underwent decomposition during the purification process, preventing us from isolating free amine **4** in a pure form. Thus, we decided to directly subject the resulting free amine **4** to the asymmetric reductive amination without further purification.[13] When the crude sample of **4** was directly subjected to the asymmetric reductive amination of ketone **3** using Hantzsch ester as an organic hydride source with phosphoric acid **6a**, to our delight, the formation of amine **2** was observed at 90 °C after 40 h, albeit in a moderate yield and with low enantioselectivity (entry 2). With this result in hand, we then investigated several chiral phosphoric acids **6** derived from chiral BINOL derivatives bearing different aryl substituents at the 3,3′-positions on the BINOL framework (entries 2–8). Among the phosphoric acids **6** tested, **6g** bearing 4-mesityl-2,6-dimethylphenyl substituents at the 3,3′-positions was chosen for further investigation since **6g** provided the desired amine **2** with the highest enantioselectivity (57% *ee*, entry 8).

With **6g** as the optimal catalyst, we further investigated the effect of a dehydration agent in this asymmetric amination reaction. Changing a dehydration agent from 4 Å molecular sieves into 5 Å molecular sieves slightly improved the enantioselectivity (entries 8 and 9). The reaction medium turned out to strongly affect the outcome of this transformation; the reaction performed in *tert*-butyl methyl ether (TBME) provided the desired product **2** in a much better enantioselectivity than that carried out in toluene (entry 10). Lowering the reaction temperatures had a slightly beneficial influence on the enantioselectivity to provide **2** in 80% *ee* at 40 °C (entry 11). Finally, reaction in a dilute concentration (0.050 M) slightly improved the enantioselectivity, affording **2** in 82% *ee* (entry 12). Under these optimized conditions,[14] this transformation could be carried out on a 1.0 mmol scale to provide **2** in 76% yield in 85% *ee* (entry 13). The absolute stereochemistry of the resulting amine **2** was assigned as the (*R*)-configuration by comparing the optical rotation of amine **2** with the reported value.[15]

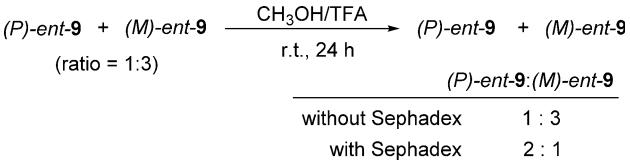
With *ent*-**2** in hand, we attempted to complete the total synthesis of *ent*-ancistrocladinium A (*ent*-**1**). Since the atropo-epimer of ancistrocladinium A (*P*)-**1** has not been prepared in the previous synthesis, we were particularly interested in the preparation of both of the atropo-diastereomers of *ent*-ancistrocladinium A if possible (Scheme 3). When *ent*-**2** was subjected to acylation with acetyl chloride in the presence of DMAP, to our delight, tertiary amide **7** and its rotamer **8** were obtained in 56% and 35% yields, respectively, after column chromatography on silica.[16]



Scheme 3. Total synthesis of *ent*-ancistrocladinium A (*ent*-**1**).

When compound **7** was treated with $POCl_3$, *ent*-ancistrocladinium A [(*P*)-*ent*-**9**], carrying chloride as a counter anion, was obtained as the major product along with its atropo-epimer [(*M*)-*ent*-**9**] in a 4:1 ratio in the crude mixture.[17–19] Rather unexpectedly, erosion of atropo-purity was observed during the purification process with Sephadex to afford a mixture of (*P*)-*ent*-**1** and (*M*)-*ent*-**1** with a ratio of 2:1 in 81% yield, which is similar to the ratio reported by the Bringmann group.[9b] An even more unexpected, but disappointing, result was observed in the Bischler–Napieralski cyclization of compound **8**. Bischler–Napieralski reaction of **8** provided the atropo-epimer of *ent*-ancistrocladinium A, (*M*)-*ent*-**9**, as the major product along with (*P*)-*ent*-**9** in a ratio of around 3:1 in the crude mixture. Unfortunately, however, significant atropo-epimerization occurred during the purification with Sephadex to provide a mixture of (*P*)-*ent*-**1** and (*M*)-*ent*-**1** in a ratio of 2:1 after the purification with Sephadex, which was a similar ratio as that from the reaction with compound **7**.

With these unexpected results in hand, we explored several reaction parameters to influence the atropo-epimerization in ancistrocladinium A during the purification process with Sephadex. First, the effect of a mixture of MeOH and TFA, used as an eluent during the purification on Sephadex, on the axial epimerization was investigated. When a mixture of (*P*)-*ent*-**9** and (*M*)-*ent*-**9** with a ratio of 1:3 was treated with a solution of TFA in MeOH, the ratio of the two atropo-diastereomers remained unchanged even after 24 h. However, when the same mixture was subjected to the similar conditions in the presence of Sephadex, the axial epimerization gradually took place to provide a mixture of (*P*)-*ent*-**9** and (*M*)-*ent*-**9** with a 2:1 ratio, respectively. Although the chiral axis in ancistrocladinium A is known to be configurationally stable,[9b] this result strongly suggested that the atropo-epimerization could take place during the purification with Sephadex and thus, a new purification protocol must be designed for the better preparation of both atropo-diastereomers of ancistrocladinium A.[14]



(*P*)-*ent*-**9**:(*M*)-*ent*-**9**	
without Sephadex	1 : 3
with Sephadex	2 : 1

In conclusion, we have developed a new protocol of chiral phosphoric acid-catalyzed reductive amination of ketone with arylamine where the aryl moiety was utilized as a key building block in natural products bearing an N-aryl moiety. The utility of this approach was successfully demonstrated in the asymmetric total synthesis of *ent*-ancistrocladinium A (*ent*-**1**) *via* the chiral phosphoric acid-catalyzed asymmetric reductive amination of ketone **3** and naphthylamine **4** and subsequent Bischler–Napieralski reaction. Direct use of the naththyl moiety in arylamine **4** as a key building block in the synthesis of *ent*-**1** allowed us to complete this total synthesis in only three steps from the reported starting materials. Furthermore, we described an unexpected atropo-epimerization along the N,C-axis in *ent*-**1** during the purification process with Sephadex, which led to a mixture of the naturally occurring atropo-isomer and its atropo-epimer in the ratio of 2:1 regardless of the atropo-purity of the starting materials. Further applications of this protocol to the asymmetric syntheses of other natural products bearing N-aryl groups are currently underway in our laboratory and will be reported in due course.

Experimental Section

Procedure

To a solution of **5** (0.63 g, 2.0 mmol, 2.0 equiv.) in dichloromethane (5.0 mL) was added TFA (0.40 mL) and the reaction mixture was stirred at room temperature and monitored by TLC. After the complete consumption of **5**, 1.0 N NaOH solution was slowly added to the reaction mixture until the pH value of the crude mixture reached 11. The crude mixture was extracted with dichloromethane. The organic layers

were combined, dried over $MgSO_4$ and concentrated to afford the crude product – naphthylamine **4** as dark brown oil; yield: 0.27 g (1.2 mmol, 64%). The crude product of **4** was used for the chiral phosphoric acid-catalyzed asymmetric reductive amination without further purification.

To a 50-mL round-bottom flask equipped with a stirring bar were added ketone **3** (0.19 g, 1.0 mmol), Hantzsch ester (0.37 g, 1.5 mmol), catalyst **6g** (0.080 g, 0.10 mmol) and 5 Å molecular sieves (1.0 g). Then, a solution of naphthylamine **4** in *tert*-butyl methyl ether (TBME) was added to the above test tube. The reaction mixture was allowed to stir at 40 °C and monitored by TLC. After all the ketone **3** was completely consumed, the reaction mixture was cooled to room temperature, and filtered to remove molecular sieves. The filtrate was concentrated and purified by column chromatography on silica gel using hexanes/ethyl acetate (6:1) as an eluent to provide the desired product **2** as light yellow oil; yield: 0.31 g (0.78 mmol, 78%); 85% *ee*.

Acknowledgements

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[13] An asymmetric reductive amination strategy has been utilized several times in the total synthesis of naphthylisoquinoline alkaloids. However, all previous reports relied on the preparation of chiral amines *via* the diastereoselective reductive amination of ketone **3** with chiral phenethylamine followed by the removal of the chiral auxiliary from the reductive amination products;

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[14] For details, see the Supporting Information.

[15] The optical rotation ($[\alpha]_D^{20}$) value of **2** was found to be −74 ($c = 0.13$, CH_3OH). Since this value has the opposite sign to the reference value of (*S*)-**2** {+51 ($c = 0.13$, CH_3OH)}, we assigned the absolute stereochemistry of **2** as the (*R*)-configuration, despite the difference in measured $[\alpha]_D^{20}$ value in comparison to the literature value. For the reported $[\alpha]_D^{20}$ value of **2**, see: ref.[8b]).

[16] The N,C-axes in tertiary amides **7** and **8** are configurationally stable at temperatures below 50 °C. However, they undergo isomerization at temperatures above 50 °C. For example, treatment of each amide (either **7** or **8**) in toluene at 100 °C for 6 h led to a mixture of **7** and **8** with a ratio of 1.4:1, regardless of the starting amide. For details, please see the Supporting Information.

[17] In order to check whether interconversion between initially formed atropisomers, (*P*)-*ent*-**9** and (*M*)-*ent*-**9**, might take place under the reaction conditions, a mixture of the isolated atropisomers with a ratio of 4:1 was re-subjected to the reaction conditions. However, under such conditions, no interconversion of the two atropisomers was observed and the ratio of the two isomers mixture remained constant even after 12 h. For details, please see the Supporting Information.

[18] We also investigated the possibility of interconversion of two atropisomers during the Bischler–Napieralski reaction. However, there was no interconversion of the two atropisomers during the reaction and the ratio of two atropisomers did not change throughout the Bischler–Napieralski reaction. For details, please see the Supporting Information.

[19] The N,C-axes in the resulting atropisomers, (*P*)-*ent*-**9** and (*M*)-*ent*-**9**, were configurationally stable at temperatures below 100 °C. When a mixture of the isolated two atropisomers with a ratio of 4:1 was treated at 100 °C for 12 h, no change in the ratio of the two isomers was observed. For details, please see the Supporting Information.

Concise Asymmetric Total Synthesis of *ent*-Ancistrocladinium A

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