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Asymmetric Total Synthesis of (−)-Leuconoxine via Chiral Phosphoric Acid Catalyzed Desymmetrization of a Prochiral Diester

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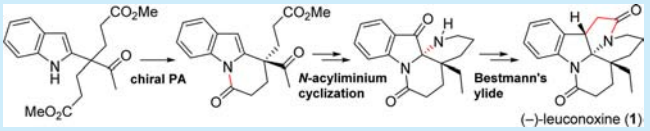
Supporting Information

ABSTRACT: The asymmetric total synthesis of (−)-leuconoxine has been achieved. The desymmetrization of a prochiral diester using a chiral phosphoric acid catalyst produced a highly enantioenriched lactam with excellent yield. The ring construction featuring an intramolecular *N*-acyliminium cyclization and the one-step pyrrolidone formation using Bestmann's ylide was successfully accomplished.



The plant apocynaceae produces various biologically important monoterpene indole alkaloids such as reserpine, ajmaline, and vinblastine. Therefore, it has attracted attention as a medicinal resource over the centuries.[1] Recently, compounds **1**−**4** were isolated from apocynaceae. These are attractive due to their complex structures, intriguing bioactivities, and biosynthetic relationship (Figure 1). Leuconoxine (**1**), isolated from stems and leaves of *Leuconotis eugenifolius* in Indonesia,[2] has the tetracyclic ring fused at the aminal carbon and the adjacent quaternary carbon center. We are interested in the inherent structure of **1** and planned the retrosynthesis of **1** as shown in Figure 1. Pyrrolidone ring formation using a phosphine ylide and subsequent hydrogenation of **2** in the last stage lead to **1**. Due to our ongoing program of the *N*-acyliminium mediated ring construction for alkaloid synthesis,[3,4] we are interested in the chemoselective cyclization of **6** toward seven-membered imine **4** or piperidine **5**. Compound **6** is derived from the oxidation of indole **7**. With the aim of synthesizing chiral **1**, we also planned the chiral phosphoric acid catalyzed desymmetrization of prochiral diester **8**. The desymmetrization of prochiral molecules to obtain chiral products with an enzyme and organocatalyst is a powerful tool in asymmetric syntheses. Chiral phosphoric acid catalysts[5] have recently attracted growing interest because of their easy tuning and applicability to a wide range of substrates. Particularly, the desymmetric ring opening reaction of acid anhydride[6a] and bicyclic bislactone,[6b] and the desymmetric lactonization of diesters[6c] have potential use in organic synthesis. However, there is no example of asymmetric amidation[7] by chiral phosphoric acid catalysts; thus, we undertook the challenge of desymmetric lactam cyclization of **8**.

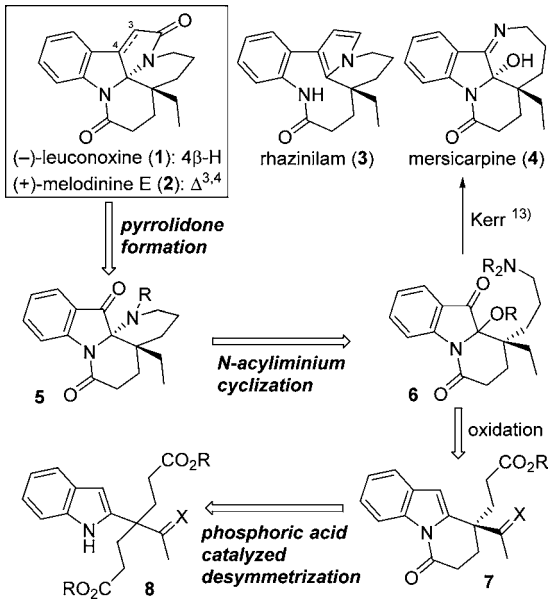


Figure 1. Leuconoxine (**1**) and retrosynthetic analysis.

In 2013, Zhu et al.[8] developed enantioselective total syntheses of (−)-**1** and (+)-**2** by controlling the nucleophilicity of amines within the α-diketone intermediate. In 2014, Tokuyama et al.[9] established powerful divergent syntheses of (±)-**1** and **3** by the oxidative cyclic aminal formation and diastereoselective ring closing metathesis. Here, we report the asymmetric total synthesis of (−)-leuconoxine (**1**) using chiral phosphoric acid catalyzed desymmetrization of prochiral diester and *N*-acyliminium cyclization.[10]

In order to examine the desymmetrization, we first synthesized prochiral diesters **8a** and **8b** (Scheme 1). Acylation of *tert*-butyl acetoacetate using an acid chloride of **9** under basic conditions afforded ester **10**. The *tert*-butoxy carbonyl group in **10** was removed by treatment with TFA to give β-diketone **11** in 68% yield in three steps.[11] Michael addition of **11** with methyl acrylate produced β-diketo diester **12** in 56% yield which was reduced under hydrogenation and cyclized into diester **8a** in 98% yield. Lactonization of **8a** in the presence of

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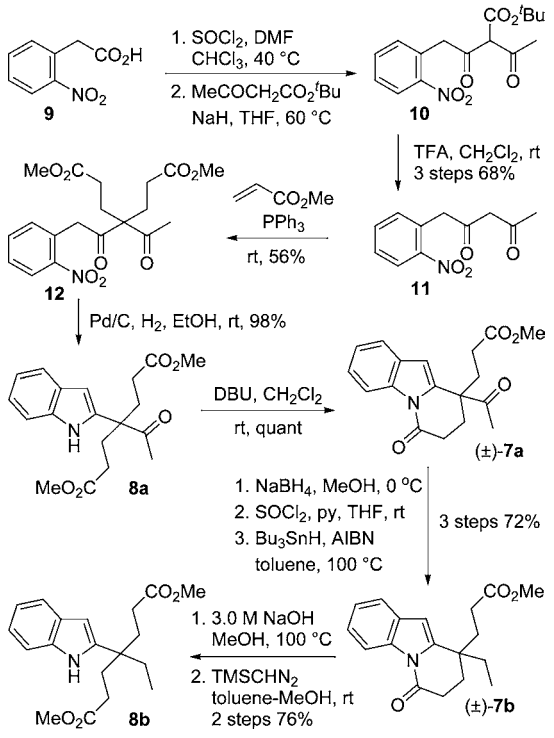
Scheme 1. Syntheses of Prochiral Diester 8a and 8b



DBU at rt afforded (±)-**7a**. The acetyl group in (±)-**7a** was converted into an ethyl group by successive $NaBH_4$ reduction of ketone, chlorination, and radical reduction to produce (±)-**7b**. Finally, hydrolysis and the subsequent methylation led to diester **8b** in 76% yield in two steps.

Next, using the chiral phosphoric acids **13a–l** (Figure 2), we studied the desymmetrization of diesters **8** as shown in Table 1.

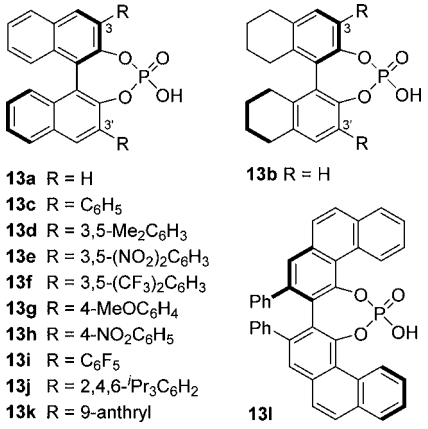
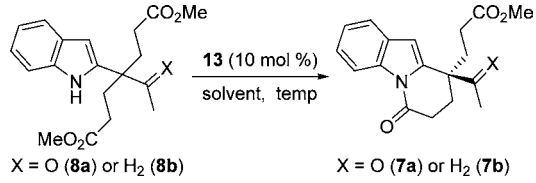


Figure 2. Chiral phosphoric acids.

A solution of diester **8** and 10 mol % chiral phosphoric acid (**13a–k**) in solvents was heated under reflux to give lactam **7** in good to excellent yields. The nonpolar and high-boiling solvent afforded a better product yield and enantiomer ratio (er) (entries 1–5). Using catalysts **13a** and **13b** (R = H) in toluene, the reaction gave (−)-**7a** in 38% ee and 34% ee, respectively (entries 5 and 6). The presence of **13c** (R = Ph) shortened the reaction time to 2 h and increased the ee value (entry 7). Upon use of 3,5-disubstituted (**13d–f**) and 4-substituted phenyl catalysts (**13g,h**), the electron-withdrawing substituents gave

Table 1. Desymmetric Lactamization Using Chiral Phosphoric Acids



entry	8	13	solvent	temp (°C)	time	yield of 7 (%)	er[a]
1	a	a	DCM	reflux	1 d	no reaction	–
2	a	a	THF	reflux	1 d	a 44	53:47
3	a	a	MeCN	reflux	10 d	a 52	59:41
4	a	a	DCE	reflux	4 d	a 99	67:33
5	a	a	toluene	reflux	8 h	a 96	69:31
6	a	b	toluene	reflux	8 h	a 95	67:33
7	a	c	toluene	reflux	2 h	a quant	26:74
8	a	d	toluene	reflux	15 h	a 98	30:70
9	a	e	toluene	reflux	20 h	a 99	25:75
10	a	f	toluene	reflux	1 h	a 96	22:78
11	a	g	toluene	reflux	7 h	a 97	30:70
12	a	h	toluene	reflux	1 h	a quant	21:79
13	a	i	toluene	reflux	0.8 h	a 96	20:80
14	a	i	toluene	rt	6 d	a 89	17:83
15	a	j	toluene	reflux	1.5 h	a quant	31:69
16	a	k	toluene	reflux	0.8 h	a quant	43:57
17	b	f	toluene	reflux	0.8 h	b quant	40:60
18	b	h	toluene	reflux	0.3 h	b 96	42:58
19	a	l	toluene	reflux	11 h	a quant	83:17
20	a	l	toluene	80	4 d	a 94	87:13

[a]Enantiomer ratios (er's) were determined by HPLC.

better ee's (entries 8–12). Using the pentafluorophenyl group **13i** at rt instead of toluene–reflux temperature enhanced the ee but prolonged the reaction time significantly (entries 13 and 14). In addition, the effect of a sterically bulky group, such as triisopropyl **13j** and 9-anthryl **13k** groups, resulted in low ee's (entries 15 and 16). In order to investigate the influence of the acetyl carbonyl group in substrate **8a**, the ethyl derivative **8b** was used and resulted in a substantial decline of ee's (entries 17 and 18). This result suggests the importance of hydrogen bonding between the phosphate and acetyl carbonyl group of **8a** in the cyclization process.

Consequently, a desymmetrization using VAPOL (**13l**)[12] at 80 °C and after stirring for 4 days provided the best enantioselectivity (74% ee, entry 20). Optimized conditions in hand, we continued the next transformation.

We next performed the transformation of **7a** (75% ee) to Kerr's intermediate **17**[13] (Scheme 2). The conversion of an acetyl derivative of **7a** to an ethyl group in **7b** was carried out according to the same procedure as that shown in Scheme 1. Ester **7b** was reduced to alcohol **15** by sequential hydrolysis, mixed-anhydride formation, and $NaBH_4$ reduction in 83% yield in three steps. After azidation of **15** using DPPA, NaN_3, and DBU,[14] Staudinger reduction and subsequent Boc-protection gave **16** in 87% yield in three steps. Then, the oxidation of indole **16** to **17** resulted in the best yield (83%) using OXONE according to Kerr's method.[13]

Then, we studied *N*-acyliminium cyclization using (±)-**17** to tetracyclic compound **5** which has an aminal moiety next to the quaternary carbon center (Table 2). In the presence of PPTS under refluxing toluene for 24 h, sequential Boc group removal

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Scheme 2. Synthesis of 2-Hydroxy Indolinone 17

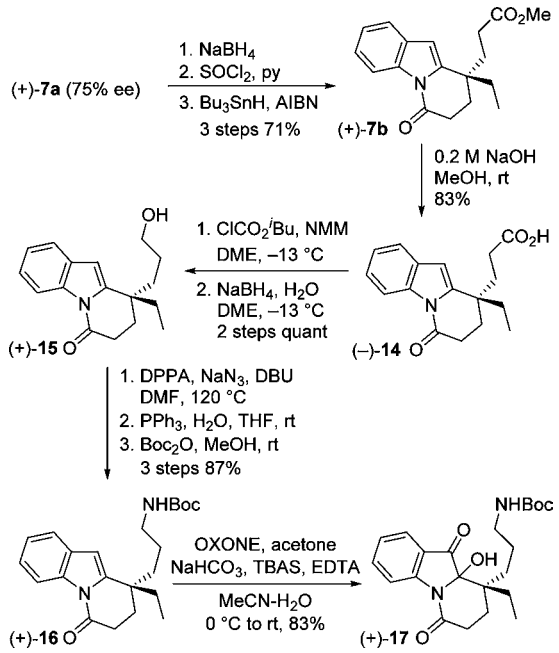
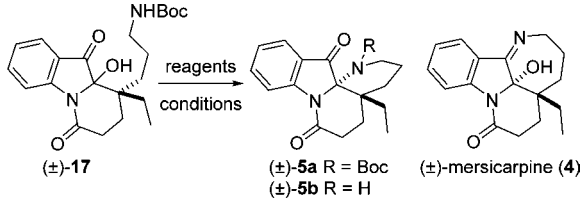


Table 2. *N*-Acyliminium Cyclization

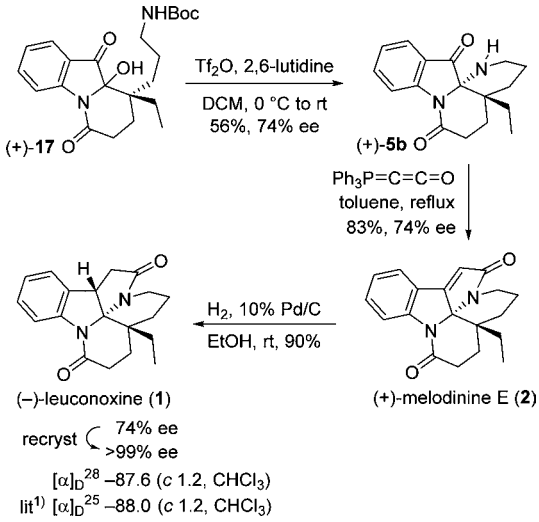


entry	reagents (equiv)	solvent	temp (°C)	time (h)	yields (%)
1	PPTS (1.0)	toluene	reflux	24	**4** quant
2	PPTS (1.0), $HC(OMe)_3$ (10)	MeOH	reflux	30	**4** 62
3	Tf_2O (1.5), TEA (2.0)	CH_2Cl_2	−78 to 0	1	**17** 63, **5a** 11, **5b** 9
4	Tf_2O (1.5), TEA (2.0)	CH_2Cl_2	0 to rt	1	**5b** 50
5	Tf_2O (1.5), DIEA (2.0)	CH_2Cl_2	0 to rt	1	**5b** 62
6	Tf_2O (1.5), DBU (2.0)	CH_2Cl_2	0 to rt	1	**5b** 50
7	Tf_2O (1.5), 2,6-lutidine (2.0)	CH_2Cl_2	0 to rt	2	**5b** 67

and condensation with ketone provided mersicarpine (**4**) in quantitative yield (entry 1). The addition of $HC(OMe)_3$[15] did not give the desired product **5** (entry 2). In order to accelerate the elimination of the hydroxyl group, the application of acid anhydride was tested. When Tf_2O and TEA were added at −78 °C and the reaction mixture was stirred at 0 °C for 1 h, the desired acyliminium formation and intramolecular cyclization occurred to generate compounds **5a** and **5b** in 11% and 9% yield, respectively, along with recovered **17** (63% yield) (entry 3). When these reagents were added at 0 °C and the mixture was stirred at rt, the reaction afforded **5b** as a sole product in 50% yield without diastereomer formation (entry 4). An evaluation of other bases (entries 5−7) revealed that 2,6-lutidine produced a good yield in this transformation (entry 7).

Finally, the total synthesis of (−)-leuconoxine (**1**) was completed as shown in Scheme 3. Under the optimized

Scheme 3. Asymmetric Total Synthesis of (−)-Leuconoxine (1)



cyclization conditions (Table 2), (+)-**17** was converted to (+)-**5b** in 56% yield without loss of chirality. The one-step formation of γ-butyrolactam was accomplished by the treatment of indolinone **5b** using Bestmann's ylide[16] to give (+)-melodinine E[17] (**2**, 83% yield, 74% ee). The hydrogenation of **2** took place from the convex face of (+)-**2** to afford (−)-leuconoxine (**1**) (90% yield, 74% ee), which was recrystallized into its optically pure form (>99% ee). Synthetic (−)-**1** displayed physical and spectroscopic data identical in all respects to those reported for the natural product.[2]

In conclusion, we have accomplished the asymmetric total synthesis of (−)-leuconoxine (**1**). In the presence of a chiral phosphoric acid catalyst, the desymmetrization of a prochiral diester produced a highly enantioenriched lactam in excellent yield. Ring construction steps featuring the *N*-acyliminium mediated intramolecular piperidine cyclization and the one-step pyrrolidone formation using Bestmann's ylide were achieved successfully. Application of this methodology to the synthesis of more complicated natural products is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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