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Formal Synthesis of (−)-Cephalotaxine Based on a Tandem Hydroamination/Semipinacol Rearrangement Reaction

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(−)-Cephalotaxine **1** was first isolated from *Cephalotaxus drupacea* and *C. fortunei* as a major alkaloid among a series of its ester derivatives in 1963.[1] Much attention has been paid towards the studies of cephalotaxine due to the unique pentacyclic structure and antileukemic activity of its derivatives.[2] As a classic target for organic chemists, the syntheses of cephalotaxine have been continuing since the pioneering work of Weinreb and Semmelheck in 1972.[3–5] Among the various strategies reported, the establishment of the 1-azaspiro[4.4]nonane ring system **2** followed by benzazepine formation were most frequently introduced (Figure 1). Thus, an effective construction of this unit would be of great importance in the synthesis of cephalotaxine and other structurally related alkaloids such as serratine and stemonamine.[6]

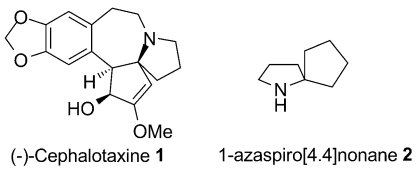
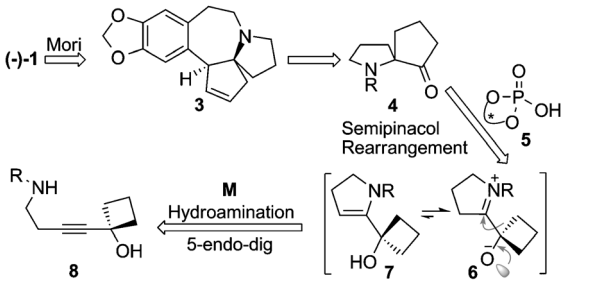


Figure 1. (−)-Cephalotaxine and the key 1-azaspiro[4.4]nonane unit.

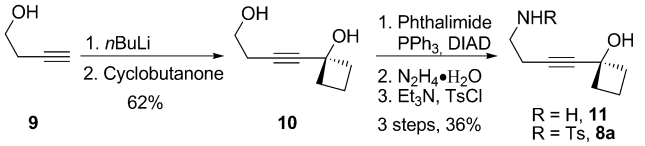
Azaspiro[4.4]nonane **2**-type azaspirocycles have long been recognized as useful building blocks and recently been selected as templates for pharmaceutical investigations.[7] A number of methods have been developed to construct this structural unit in the context of total synthesis. However, these methods often require multiple manipulations, installing the aza-quaternary carbon center and each of the spiro rings in separate steps.[7–8] Additionally, chiral syntheses of this unit are mainly based either on chiral auxiliaries or chiral starting materials. As far as we are aware, catalytic asymmetric synthesis of this kind of azaspirocycles has not been reported. In connection with our longstanding works on the semipinacol rearrangement reaction and its application in total synthesis of polycyclic alkaloids,[9] we intended to develop a highly efficient catalytic asymmetric formal synthesis of (−)-**1**, taking advantage of the tandem hydroamination/semipinacol rearrangement reaction.[10–11]

As shown in Scheme 1, according to the procedure by Isono and Mori, (−)-cephalotaxine **1** could be obtained in four steps from **3**, which has generally been introduced as an advanced intermediate in the formal synthesis of (−)-**1**.[5a] We envisioned that **3** could be derived from the useful building block 1-azaspirocycle **4**. As the key step, we proposed that upon the catalysis of transition metal **M** and chiral phosphoric acid **5**, alkyne **8** would first undergo *5-endo-dig* intramolecular hydroamination[10] to form the corresponding enamine followed by proton exchange to produce the iminium ion **6**. Intermediate **6** would then undergo an enantioselective ring expansion-type semipinacol rearrangement to furnish the relevant azaspirocycle **4**.[11]



Scheme 1. Retrosythetic analysis of (−)-cephalotaxine.

To check our hypothesis regarding the key reaction, we performed a divergent strategy that would enable the synthesis of **8** with different protecting groups (Scheme 2). The 1, 2-addition of the lithium reagent derived from homopropargylic alcohol **9** to cyclobutanone afforded diol **10** in 62 %



Scheme 2. Synthesis of model substrate **8a**.

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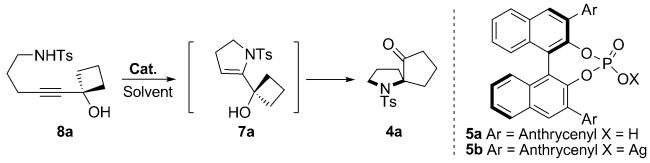
yield. Mitsunobu reaction of **10** followed by replacing the protecting group with tosyl group furnished the model substrate **8a** in 22% overall yield from **9**.

With **8a** in hand, the aforementioned tandem reaction was then extensively examined, as shown in Table 1. Initially

Table 1. Optimization for the formation of **4a**.[a]



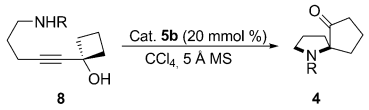
Entry	Catalyst (10%)	Solvent	t	Yield [%][b]	ee[c]
1	$[Ph_3PAuCl]$[d]/*p*-TsOH	CH_2Cl_2	24 h	37	–
2	$[Ph_3PAuOTf]$[d]/*p*-TsOH	CH_2Cl_2	4 h	90	–
3	$[Ph_3PAuOTf]$[d]/**5a**	CH_2Cl_2	4 h	95	10
4	$[Ph_3PAugOTf]$[d]/**5a**	CCl_4	4 h	93	50
5	$[Ph_3PAuOTf]$[d]/**5b**	CCl_4	36 h	99	81
6	**5b**	CCl_4	36 h	99	81
7	**5b**	Mesitylene	8 h	99	78
8	**5b**(recycled)	CCl_4	36 h	99	81
9	**5b**[e]	CCl_4	24 h	99	81

[a] Conditions: 0.04 mmol **8a**, 10 mol% cat., and 40 mg 5 Å molecular sieve in 0.4 mL solvent stirred in the dark at 25°C. [b] Isolated yield. [c] Determined by chiral-HPLC analysis. [d] 5% catalyst was added. [e] 20% catalyst was added. For further conditions screened, see the Supporting Information. *p*-TsOH = p-toluenesulfonic acid. Ts = *p*-toluenesulfonyl.

we examined the cooperative gold and Brønsted acid catalysis.[12–13] When $[Ph_3PAuCl]$ (5 mol%) and p-toluenesulfonic acid (*p*-TsOH, 10 mol%) were stirred in CH_2Cl_2, **4a** could be obtained in 37% yield within 24 hours (entry 1). A 90% yield was observed when $[Ph_3PAuOTf]$ (5 mol%) obtained from $[Ph_3PAuCl]$ and AgOTf, was used in the presence of *p*-TsOH (entry 2). Compound **4a** could also be obtained in high yield (95%) with low enantioselectivity (10% *ee*) under the catalysis of $[Ph_3PAuOTf]$ and phosphoric acid **5a** in CH_2Cl_2 (entry 3). A better result (50% *ee*, 93% yield) was observed with the same catalyst in the nonpolar solvent carbon tetrachloride (CCl_4, entry 4). The enantiomeric excess could be further improved to 81% when the chiral silver phosphate **5b** was used instead of phosphoric acid (entry 5).[11g] In all cases in which $[Ph_3PAuOTf]$ served as the transition metal catalyst, the intermediate **7a** could be detected by TLC (entries 2–5, Tables S1 and S2 in the Supporting Information)

Next, a series of cyclobutanols **8** differing in the amino protecting group were synthesized and tested under the optimized conditions to potentially find a better substrate. When **8a** was subjected to the reaction conditions (Table 2, entry 1), the enantiomeric excess slightly increased to 82% with excellent yield. Other arylsulfonyl protected compounds **8** were then used as substrates and all proceeded well, resulting in 90–99% yield and 55–82% *ee* (entries 2–13). The enantiomeric excess of **4h** could be increased to 93% after one recrystallization (75% yield) and the absolute configuration of **4h** was determined to be *S* by X-ray analysis (see the Supporting Information).[16] Due to the potential bioactivities of the azaspirocycles, these compounds could serve as candidates for medicinal evaluations.

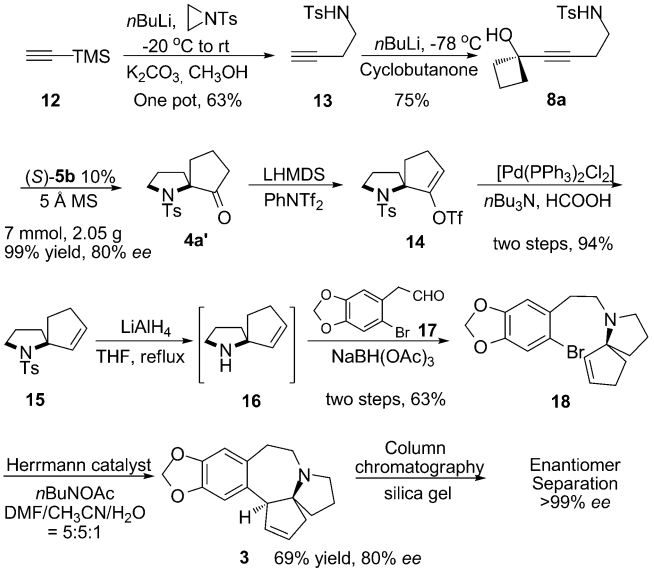
Table 2. Tandem intramolecular hydroamination/asymmetric semipinacol rearrangement.[a]



Entry	R	**8**	**4**	Yield[b]	ee[c]
1	Ts	**8a**	**4a**	99	82
2	$C_6H_5SO_2$	**8b**	**4b**	90	67
3	2-$MeC_6H_4SO_2$	**8c**	**4c**	96	62
4	3-$MeC_6H_4SO_2$	**8d**	**4d**	99	66
5[f]	4-$BrC_6H_4SO_2$	**8e**	**4e**	96	79
6[f]	4-$ClC_6H_4SO_2$	**8f**	**4f**	92	82
7[f]	4-$FC_6H_4SO_2$	**8g**	**4g**	98	70
8[f]	4-$IC_6H_4SO_2$	**8h**	**4h**	99(75)[d]	78(93)[e]
9	4-*t*Bu$C_6H_4SO_2$	**8l**	**4l**	94	71
10	4-$CF_3C_6H_4SO_2$	**8j**	**4j**	98	72
11	4-$OMeC_6H_4SO_2$	**8k**	**4k**	99	65
12	1- $C_{10}H_7SO_2$	**8l**	**4l**	92	55
13	2- $C_{10}H_7SO_2$	**8m**	**4m**	90	66

[a] Conditions: 0.1 mmol **8**, 20 mol% (*R*)-**5b**, and 100 mg 5 Å molecular sieve in 1.0 mL CCl_4 stirred in the dark at 25°C for 24 h. [b] Isolated yield. [c] Determined by chiral-HPLC analysis. [d] Yield after recrystallization. [e] *ee* of mother liquid after recrystallization. [f] 36 h was needed.

Based on the results of Table 2, **4a′** with same configuration as natural (−)-cephalotaxine could be easily obtained through **8a** with (*S*)-**5b** as catalyst. Thus, a concise and facile strategy for **8a** was developed. As shown in Scheme 3, trimethylsilylacetylene **12** was lithiated by *n*BuLi and trapped with tosylaziridine followed by deprotection of the TMS group to afford the tosyl homopropargyl amine **13** in one pot with 63% yield. The tandem reaction substrate **8a**



Scheme 3. Formal synthesis of (−)-cephalotaxine.

was delivered in 75% yield (97% based on recovered **13**) through 1, 2-addition of lithiated **13** to cyclobutanone. The key reaction was readily performed to give spirocycle **4a′** in 99% yield and 80% *ee* in gram-scale quantity (7 mmol, 2.05 g). Subsequently, **4a′** was transformed into triflate **14** by enolization with lithium hexamethyldisilazide (LHMDS) and captured with $PhNTf_2$. Reduction of **14** under the catalysis of $[Pd(PPh_3)_2Cl_2]$ with formic acid as hydrogen source afforded **15**, a key intermediate in the racemic synthesis of cephalotaxine reported by Stoltz and coworkers.[5h] Following elimination of the tosyl group and reductive amination with aldehyde **17**, amine **18** was obtained in 63% yield.[5h,17] Finally, pentacyclic compound **3** was obtained in 69% yield through a Heck reaction performed under previously reported conditions[5d], and the enantiomeric excess was determined to be 80% by chiral high-performance liquid chromatography (chiral HPLC).

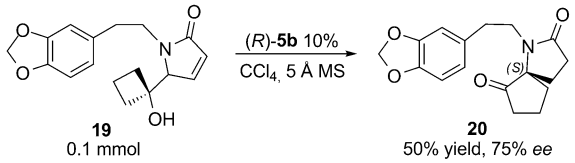
During the purification of **3** by column chromatography on silica gel using ethyl acetate as eluant, we found that the two fractions of purified **3** showed different enantiomeric excess values (89% and 65% *ee*, respectively). We are aware that the phenomenon of enantiomer separation probably resulted from different affinities of aggregates of compound **3** on silica gel.[20] Thus, further validation of this finding was carried out by column chromatography on silica gel of the first fraction with 89% *ee* (9.0 mg). As shown in Table 3, the first two fractions had increased *ee* values while those of the last three fractions were decreased. Significantly, the first fraction could be obtained in 35.5% yield with >99% *ee*, thus providing a practical method for the preparation of enantiopure **3** from enantiomer-enriched material simply by column chromatography. To our knowledge, this is the first such example discovered in the synthesis of a natural product and it could be anticipated that this phenomenon also exists in more complex compounds which should attract more attention.[20g]

Table 3. Enantiomer separation of **3** on silica gel.[a]

Fraction	1	2	3	4	5
Weight [%][b]	35.5	27.2	16.8	4.7	15.8
ee [%][b]	>99	96	82	76	68

[a] See the Supporting Information. [b] Calculated from HPLC analysis.

To further validate the feasibility of the enantioselective semipinacol rearrangement reaction for other types of substrate, we performed the catalytic asymmetric reaction with **19**. The chiral auxiliary-controlled diastereoselective semipinacol rearrangement of **19** has been reported by the group of Royer in the elegant total synthesis of (−)-cephalotaxine. Using the optimized conditions, this reaction also proceeded well to give the desired product **20**. (Scheme 4) The absolute configuration was determined to be *S* by comparing the optical rotation with that previously reported[21]; this indicates that enantiocontrol in the semipinacol rearrangement involves a similar mechanism as that in the tandem reaction.[11g]



Scheme 4. Catalytic asymmetric semipinacol rearrangement for the synthesis of spirolactam.

Based on these results, we propose the following mechanism for the stereocontrol of the catalytic asymmetric semipinacol rearrangement reaction (Figure 2): First, upon the catalysis of **5b**, the in situ generated **7** or lactam alcohol **19** would undergo isomerization to afford the zwitterionic intermediate forming an intimate counterion pair. Next, the Ag^I from catalyst **5b** (H^+ for **5a**) would bind with the cyclobutanol unit; simultaneously, the P=O group stabilizes the iminium ion and shields the *Si* face of the azacycle. Enantioselective ring expansion of the cyclobutanol would yield the product with *S* configuration. However, the mechanism suggested by List and Èorić might also be operative.[22–23]

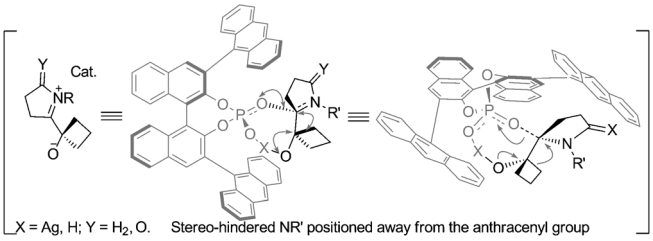


Figure 2. Rationalization of the absolute configuration obtained in the semipinacol rearrangement reaction.

In conclusion, the catalytic asymmetric formal synthesis of (−)-cephalotaxine has been accomplished using a highly efficient tandem intramolecular hydroamination/asymmetric semipinacol rearrangement reaction under mild conditions. We also found that the generally employed intermediate exhibits the enantiomer separation phenomenon on silica gel.

Experimental Section

Typical procedure for the tandem reaction: Substrate **8** (0.1 mmol), catalyst (*R*)-**5b** (0.02 mmol), 5 Å molecular sieve (100 mg), and solvent (1.0 mL) were added to a Schlenk tube and stirred in the dark at 25 °C for the indicated time. The reaction mixture was then directly subjected to column chromatography on silica gel (petroleum ether/EtOAc 4:1).

Acknowledgements

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Keywords: azaspirocycle · cephalotaxine · enantiomer separation · hydroamination · organocatalysis

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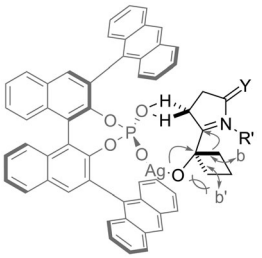

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