Cyclization

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Short Synthesis of (+)-Cylindricine C by Using a Catalytic Asymmetric Michael Reaction with a Two-Center Organocatalyst**

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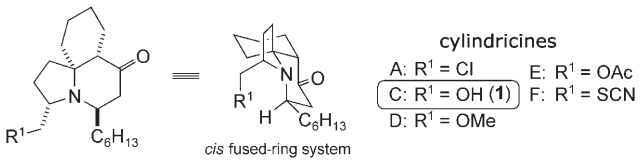
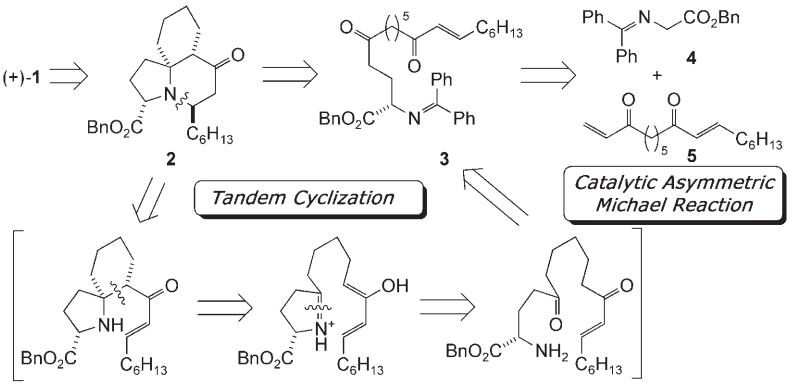


Scheme 1. Structure of the cylindricines.

Present syntheses of natural products and medicinally relevant compounds require high efficiency in terms of the number of synthetic steps. Tandem reactions that combine several transformations in a single procedural step are powerful tools for minimizing synthetic steps.[1] In addition to time–cost benefits, they can allow selective reactions of unstable species and side reactions to be minimized by the rapid successive formation and consumption of intermediates. Catalytic asymmetric reactions have also enabled more efficient syntheses of various highly versatile chiral compounds that allow for the development of new or more practical retrosynthetic analyses of complex natural products.[2] The combination of tandem reactions and catalytic asymmetric reactions leads to more efficient synthetic routes. Herein, we report a short total synthesis of (+)-cylindricine C by a tandem cyclization and catalytic asymmetric Michael reaction with a newly designed two-center organocatalyst.

The cylindricines were isolated from the marine ascidian *Clavelina cylindrica* by Blackman et al. between 1993 and 1995.[3] These structurally related compounds exhibit bioactivity against a DNA-repair-deficient yeast strain[4] and also inhibit the growth of murine leukemia and human solid-tumor cell lines.[5] Their tricyclic ring system (see Scheme 1) is comprised of a spirocyclic amine that makes them an attractive target for total synthesis.[6]

The first total synthesis of optically active cylindricine C was reported by Molander and Ronn,[7a] and several groups also succeeded in its total synthesis.[7b–e] Because they used stepwise strategies to construct the tricyclic ring system, their synthesis required several steps (9–14 steps). We planned to construct a tricyclic ring system from **3** in a one-pot reaction by using tandem cyclization through imine formation, the Mannich reaction, and the aza-Michael reaction (Scheme 2). The required compound **3** is a highly functionalized α-amino acid derivative. Recently, we developed a two-center organocatalyst **6** (TaDiAS; tartrate-derived diammonium salt) that efficiently catalyzes phase-transfer alkylation,[8a,b] Michael reactions,[8a,b] and Mannich-type reactions of the glycine Schiff base.[8c] We planned to synthesize **3** by using a catalytic asymmetric Michael reaction[9,10] with TaDiAS.



Scheme 2. Retrosynthetic analysis of (+)-cylindricine C. Bn = benzyl.

First, we examined the catalytic asymmetric Michael reaction of glycine Schiff base **4** to dienone **5**, which was prepared from pimelic acid in two steps (Table 1). Based on our previous results,[8a,b] the reaction was performed with 10 mol% of (*S*,*S*)-**6a** (the best catalyst for the Michael reaction to α,β-unsaturated esters). In contrast to the Michael reaction to α,β-unsaturated esters, the addition of **4** to α,β-unsaturated ketones (enone) proceeds with more modest selectivity.[8a,b] As expected from previous work, the reaction with **5** was only moderately enantioselective (entry 1). Nevertheless, we were pleased to observe clean formation of the monoaddition product. Next we examined the catalyst structure to improve the enantioselectivity. Previous conformational analysis of **6a**[8c] suggested that the acetal moiety regulates the chiral environment around the two ammonium cations. We designed a new catalyst **6b** that has a 2,6-disubstituted cyclohexane structure at the acetal moiety to affect the chiral environment more strongly. Among the three diastereomers that originate from the relative stereochemistry of the acetal moiety, C_2-symmetric **6b** was found to be most effective in the preceding investigations (see the Supporting Information). When **6b** was applied to the reaction of **4** with **5**, enantioselectivity was improved to 63% *ee* (entry 2). At lower temperature (−30°C) both reactivity and selectivity

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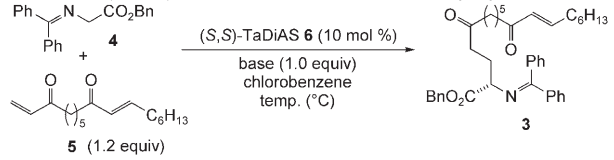
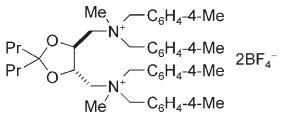
Table 1: Catalytic asymmetric Michael reaction with (*S*,*S*)-**6**.

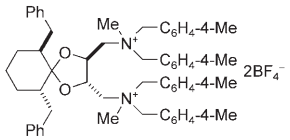


Entry	Catalyst	Base	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**6a**	K_2CO_3	4	14	96	48
2	**6b**	K_2CO_3	4	14	96	63
3	**6b**	K_2CO_3	−30	36	86	61
4	**6b**	Cs_2CO_3	−30	24	72	74
5[c,d]	**6b**	Cs_2CO_3	−40	66	84	82

[a] Yield of the isolated product. [b] Determined by chiral stationary phase HPLC. [c] 3-Fluorotoluene was used as the solvent. [d] Cs_2CO_3: 1.5 equivalents.



6a

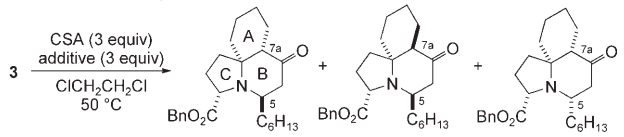


6b

were lowered (entry 3). Enantioselectivity was improved to 74% *ee* by using Cs_2CO_3 as the base (entry 4). Further investigations revealed that the use of 1.5 equivalents of Cs_2CO_3 and 3-fluorotoluene as the solvent at −40°C **3** could be obtained in 84% yield of isolated product and 82% *ee* (entry 5).

We next examined tandem cyclization (Table 2). Tricyclic compound **2** was obtained when **3** was treated with 3 equivalents of camphorsulfonic acid (CSA) in 1,2-dichloroethane. The reaction provided three diastereomers (**2a**–**c**), as determined by NMR spectroscopic analysis, whose configurations were identified as shown in Table 2 (**2a**: desired *cis* fused AB ring; **2b**: *trans*-fused AB ring; **2c**: *cis* fused AB ring and *epi* C5 position). Under these conditions, the chemical yield was moderate (47%) and **2b** was obtained as the major product (entry 1, **2a**/**2b**/**2c** = 33:63:4). Several different solvents and acids were examined, but the reactivity and diastereoselectivity were insignificantly affected. When $AlCl_3$ was used as an additive, the diastereoselectivity was greatly improved, thus selectively

Table 2: Tandem cyclization and additive effects.



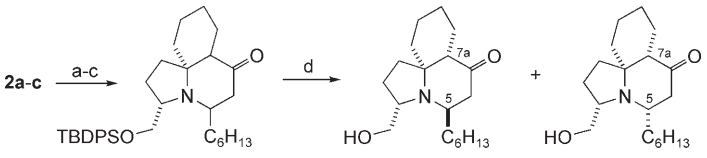
2a **2b** **2c**

Entry	Additive	*t* [h]	d.r. [**2a**/**2b**/**2c**][a]	Yield [%][b]
1	–	18	33:63:4	47
2	$AlCl_3$	24	87:13:trace	47
3	$[La(OTf)_3]$	12	27:65:8	57
4	$MgCl_2$	12	84:9:7	65
5	$MgBr_2 \cdot (Et_2O)_2$	18	82:13:5	61
6	LiCl	18	89:6:5	57

[a] Determined by ^1H NMR spectroscopic analysis. [b] Yield of the isolated product.

affording the desired **2a** (entry 2, **2a**/**2b**/**2c** = 87:13:trace). Several other additives were examined under the optimized conditions (entries 3–6). The reaction with $[La(OTf)_3]$ (OTf = triflate) afforded **2b** as the major product (entry 3), whereas $MgCl_2$, $MgBr_2 \cdot (Et_2O)_2$, and LiCl gave better reactivity and **2a** as the major product (entries 4–6). The mechanism of the additive effects is unclear, but we assume that additives operate as Lewis acids and organize the reacting centers through chelation.[11]

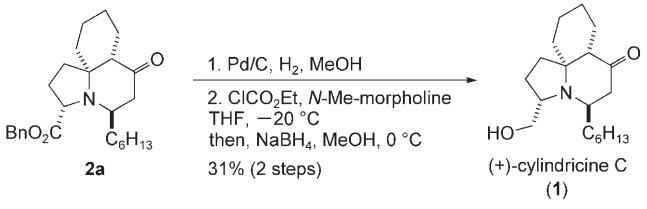
The obtained tricyclic compounds **2a**–**c** were transformed into (+)-cylindricine C (Scheme 3). The product mixture from entry 4 in Table 2 (**2a**/**2b**/**2c** = 84:9:7) was converted into **7a**–**c** in three steps. Cylindricine C (**1**) and 5-*epi*-cylindricine C (*epi*-**1**)[7c,11] were obtained in 80 and 8% yield, respectively, after treatment of **7a**–**c** with tetrabutylammonium fluoride (TBAF). The *trans*-fused AB ring of **7b** was isomerized at the C7a position to the desired *cis* fused AB ring under basic conditions.[7d,e] Computational studies also supported this result.[11] Optically pure **1** was obtained in 59% yield after three recrystallizations of the picric acid salt of **1** from EtOH.



7a-c **1** ***epi*-1**

Scheme 3. Synthesis of (+)-cylindricine C. Reagents and conditions: a) $LiAlH_4$, THF, reflux; b) *tert*-butyldiphenylsilyl chloride (TBDPSCl), Et_3N, CH_2Cl_2; c) Dess–Martin periodinane, CH_2Cl_2 (71%; 3 steps); d) TBAF, THF, RT (**1**: 80%; *epi*-**1**: 8%).

Thus, we succeeded in the synthesis of enantiomerically pure **1** from pimelic acid in nine steps, including the recrystallization process. The number of synthetic steps required to obtain **1** could be further decreased by using a mixed anhydride reduction process.[12] Thereby, **1** was obtained in two steps from **2a** (Scheme 4; total 6 steps).



2a

Scheme 4. Shorter approach to (+)-cylindricine C from **2a**.

In conclusion, we have achieved a short synthesis of (+)-cylindricine C (6 steps) using a catalytic asymmetric Michael reaction of a glycine Schiff base and subsequent tandem cyclization. Further improvement of each step and the expansion of current strategies are in progress.

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