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SHORT SYNTHESIS OF (+)-CYLINDRICINE C AND FORMAL TOTAL SYNTHESIS OF (–)-LEPADIFORMINE

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Abstract - A short synthesis of (+)-cylindricine C (**1c**) and a formal total synthesis of (–)-lepadiformine (**2**) were achieved. The key strategy for the syntheses was a catalytic asymmetric Michael reaction using a two-center organocatalyst (**11**) (TaDiAS: Tartrate-derived Di-Ammonium Salt) and tandem cyclization to construct the tricyclic ring system.

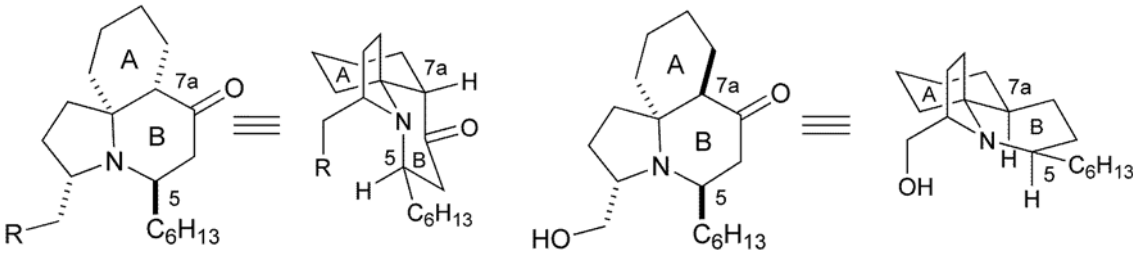
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

INTRODUCTION

Marine ascidians (Tunicate) are a rich source of a large variety of interesting bioactive alkaloids.[1] Alkaloids with a tricyclic ring system were discovered in the 1990s. Cylindricines A-K (Figure 1) were isolated from the marine ascidian *Clavelina cylindrica*, collected off the east coast of Tasmania by Blackman et al. from 1993 to 1995.[2] Lepadiformine (**2**) was obtained from the ascidian *Clavelina lepadiformis* collected in the Mediterranean[3a] near Tunisia and later isolated from *Clavelina moluccensis* obtained near the Djibouti coast in 1994.[3b] These structurally related alkaloids possess bioactivity that inhibits the growth of murine leukemia and human solid tumor cell lines.[4] Furthermore, lepadiformine exhibits antiarrhythmic properties *in vivo* and *in vitro*.[5] The structural features and biologic activities of those alkaloids have fascinated many research groups as a target of total synthesis.[6]

So far, several research groups have accomplished the total synthesis of (+)-cylindricine C (**1c**).[7] Stepwise strategies, requiring several steps (9~14 steps), have been used to construct the tricyclic ring system. For a more efficient synthesis, we planned to use tandem cyclization to construct the tricyclic ring system. Tandem reactions, which combine several transformations in a single procedure, might greatly decrease

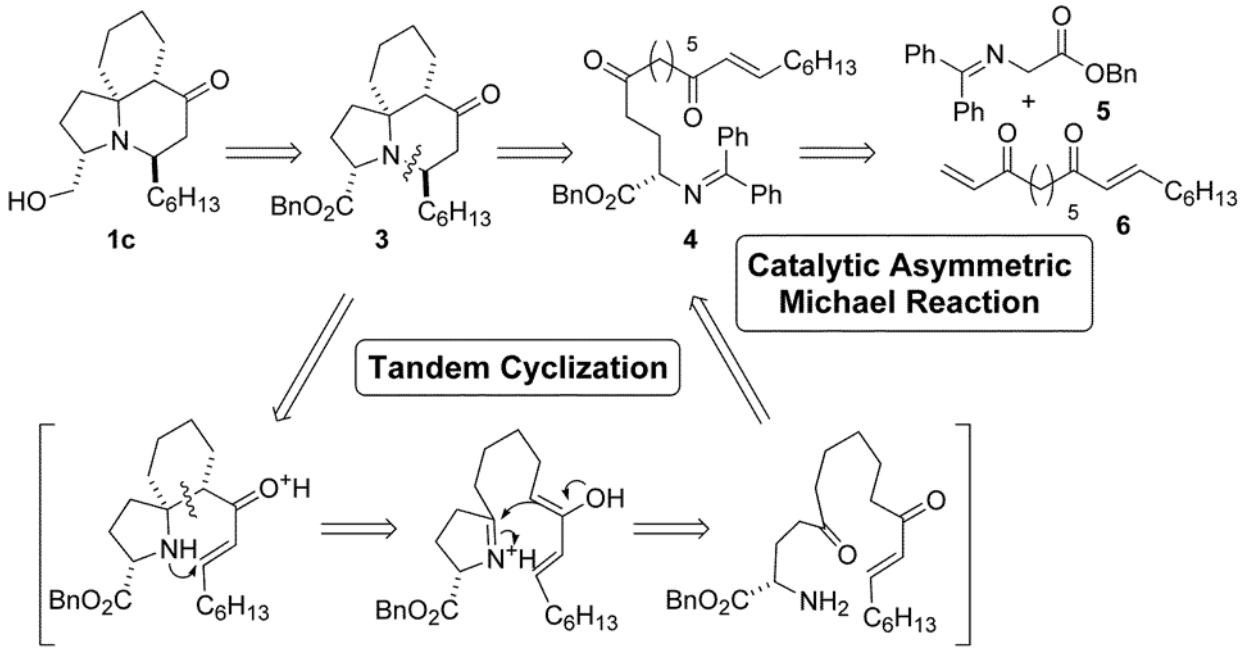
the number of synthetic steps required.[8] Scheme 1 shows our retrosynthetic analysis. The tricyclic ring system of **1c** would be constructed using tandem cyclization via imine formation, the Mannich reaction, and the aza-Michael reaction in a one-pot reaction from **4**. The required compound (**4**) is a highly functionalized α-amino acid derivative. Recently, we developed a catalytic asymmetric phase-transfer reaction using TaDiAS.[9] Using this asymmetric catalysis, various optically active α-amino acid derivatives can be synthesized. Thus, to construct the key intermediate (**4**), we planned to use a catalytic asymmetric Michael reaction of a glycine Schiff base[10,11] to dienone (**6**).



cylindricine A (**1a**) R = Cl
C (**1c**) R = OH
D (**1d**) R = OMe
E (**1e**) R = OAc
F (**1f**) R = SCN

lepadiformine (**2**)

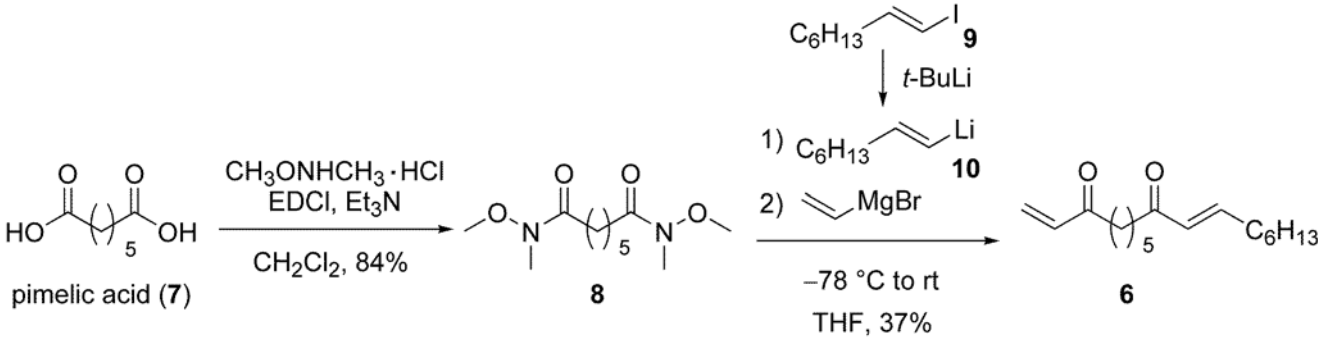
Figure 1. Tricyclic Marine Alkaloids, Cylindricines and Lepadiformine



Scheme 1. Retrosynthetic Analysis

RESULTS AND DISCUSSION

Our synthesis began with the synthesis of dienone (**6**) (Scheme 2). Both carboxylic acid moieties of pimelic acid (**7**) were converted to a Weinreb-amide to afford diamide (**8**) in 84% yield using 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide. One Weinreb-amide of **8** was converted to a β-substituted enone by treatment with 1 equivalent of alkenyllithium reagent (**10**), which was prepared from alkenyl iodide (**9**) at –78 °C, and subsequent treatment with vinylmagnesium bromide gave dienone (**6**) in 37% yield.



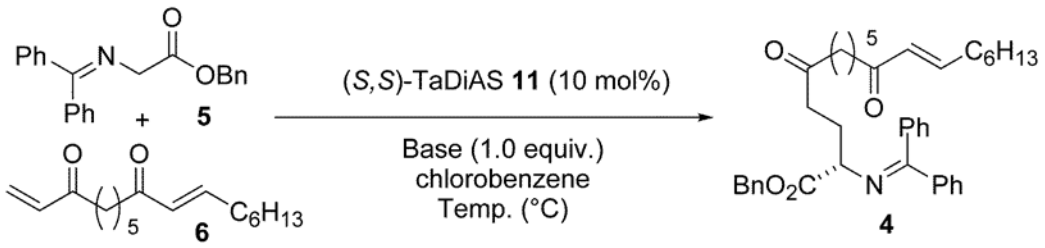
Scheme 2. Preparation of Dienone (**6**)

We then examined the catalytic asymmetric Michael reaction of the glycine Schiff base (**5**) to dienone (**6**) (Table 1). Based on previous results,[9a,b] the reaction was performed using 10 mol% of (*S,S*)-**11a**, the best catalyst for the Michael reaction of **5** to α,β-unsaturated esters. In contrast to the Michael reaction to α,β-unsaturated esters, the addition to α,β-unsaturated ketone (enone) proceeded with modest selectivity, although there was clean formation of the mono-addition product (Entry 1).[9a,9b] To improve the enantioselectivity, we examined the catalyst structure. Previous conformational analysis of **11a**[9c] suggested that the acetal moiety regulates the chiral-environment around the two ammonium cations. To more strongly affect the chiral-environment, we designed a new catalyst (**11b**) with a 2,6-disubstituted cyclohexane structure on the acetal moiety. Among the three diastereomers originating from relative stereochemistry in the acetal moiety, C_2-symmetric **11b** was the most effective catalyst for the reaction of **5** to **6** and enantioselectivity was improved to 63% ee (Entry 2). At a lower temperature (–30 °C), both reactivity and selectivity were decreased (Entry 3). Using Cs_2CO_3 as the base improved enantioselectivity to 74% ee (Entry 4). Further investigations revealed that using 1.5 equivalents of Cs_2CO_3 and 3-fluorotoluene as the solvent at –40 °C produced the Michael product (**4**) in 87% isolated yield and 82% ee (Entry 5).

Having achieved the catalytic asymmetric synthesis of **4** with high enantiomeric excess, we then focused on the tandem cyclization of **4** to **3** (Table 2). When **4** was treated with 3 equivalents of CSA in 1,2-dichloroethane at room temperature, the tricyclic compound (**3**) was obtained in 25% yield. NMR analysis indicated that three diastereomers resulted from the reaction and their stereochemistries were identified (Table 2). The NMR analysis revealed that **3a** possessed the *cis*-fused AB ring system and had

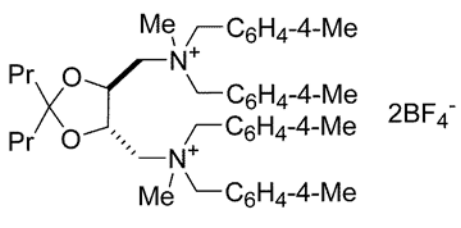
the same configuration as cylindricine C. Isomer (**3b**) had the *trans*-fused AB ring system, and isomer (**3c**) also possessed the *cis*-fused AB ring system, in which the hexyl group at C5 was at the *epi*-position of **3a**. To obtain the desired **3a** as a major product, we examined the reaction conditions.

Table 1. Catalytic Asymmetric Michael Reaction with (*S,S*)-**11**

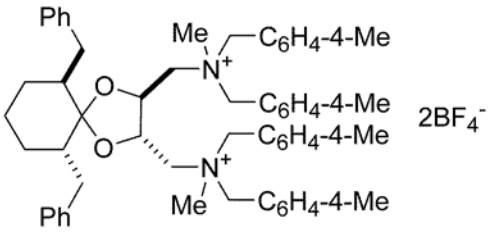


Entry	Catalyst	Base	Temp. (°C)	Time (h)	Yield(%)[a]	Ee(%)[b]
1	**11a**	K_2CO_3	4	14	96	48
2	**11b**	K_2CO_3	4	14	96	63
3	**11b**	K_2CO_3	–30	36	86	61
4	**11b**	Cs_2CO_3	–30	24	72	74
5[c,d]	**11b**	Cs_2CO_3	–40	96	87	82
6[c,d]	**11c**	Cs_2CO_3	–40	60	76	71
7[c,d]	**11d**	Cs_2CO_3	–40	72	55	55

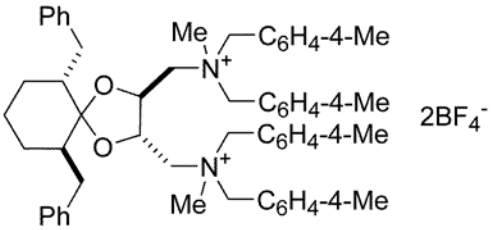
a) Yield of the isolated product. b) Determined by chiral stationary phase HPLC. c) 3-Fluorotoluene was used as the solvent. d) Cs_2CO_3: 1.5 equivalents.



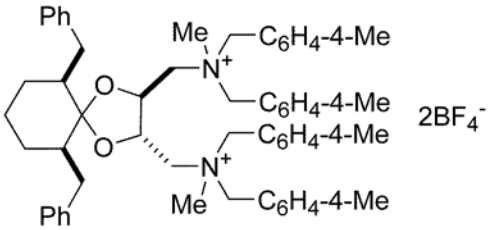
11a



11b



11c

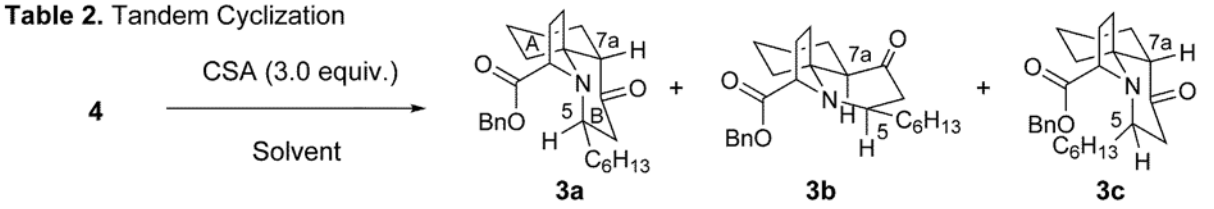


11d

When the reaction was performed at 50 °C, reactivity was improved (47%) and **3b** was obtained as the major product (Entry 2, **3a**:**3b**:**3c** = 33:63:4). We then examined the solvent effects at 50 °C. In polar solvents, the reactivity was further improved, but selectivity was decreased (Entries 4, 5). Under reflux conditions in toluene, the reaction became messy and very few tricyclic compounds were obtained (Entry 7).

We then examined the effects of additives (Table 3). When 3 equivalents of $AlCl_3$ were added to the reaction, diastereoselectivity was dramatically improved, and **3a** was obtained as the major product (Entry 2, **3a**:**3b**:**3c** = 87:13:trace). The isolated yield of **3a**-**c**, however, remained at 47%. Although adding $La(OTf)_3$ improved the isolated yield of **3a**-**c** , it had almost no effect on selectivity (Entry 3). The addition of alkali and alkaline earth metal salts improved both the selectivity and isolated yield (Entries 4-6). Among them, $MgCl_2$ gave the best result (Entry 4, 66% yield, **3a**:**3b**:**3c** = 87:7:6).

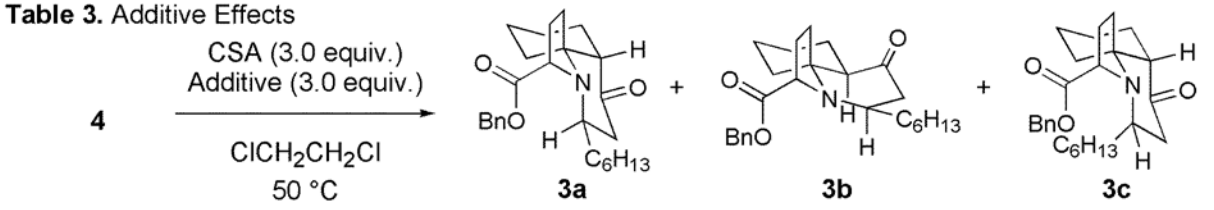
Table 2. Tandem Cyclization



Entry	Solvent	Temp. (°C)	Time (h)	dr (**3a** : **3b** : **3c**)[a]	Yield (%)[b]
1	$ClCH_2CH_2Cl$	rt	25	30 : 62 : 8	25
2	$ClCH_2CH_2Cl$	50	18	33 : 63 : 4	47
3	THF	50	26	35 : 59 : 6	48
4	DMSO	50	21	23 : 49 : 28	68
5	DMF	50	18	25 : 51 : 24	64
6	toluene	50	18	34 : 58 : 8	35
7	toluene	reflux	20	ND	trace

a) Determined by ^{1}H NMR spectroscopic analysis. b) Yield of the isolated product (**3a-c**).

Table 3. Additive Effects

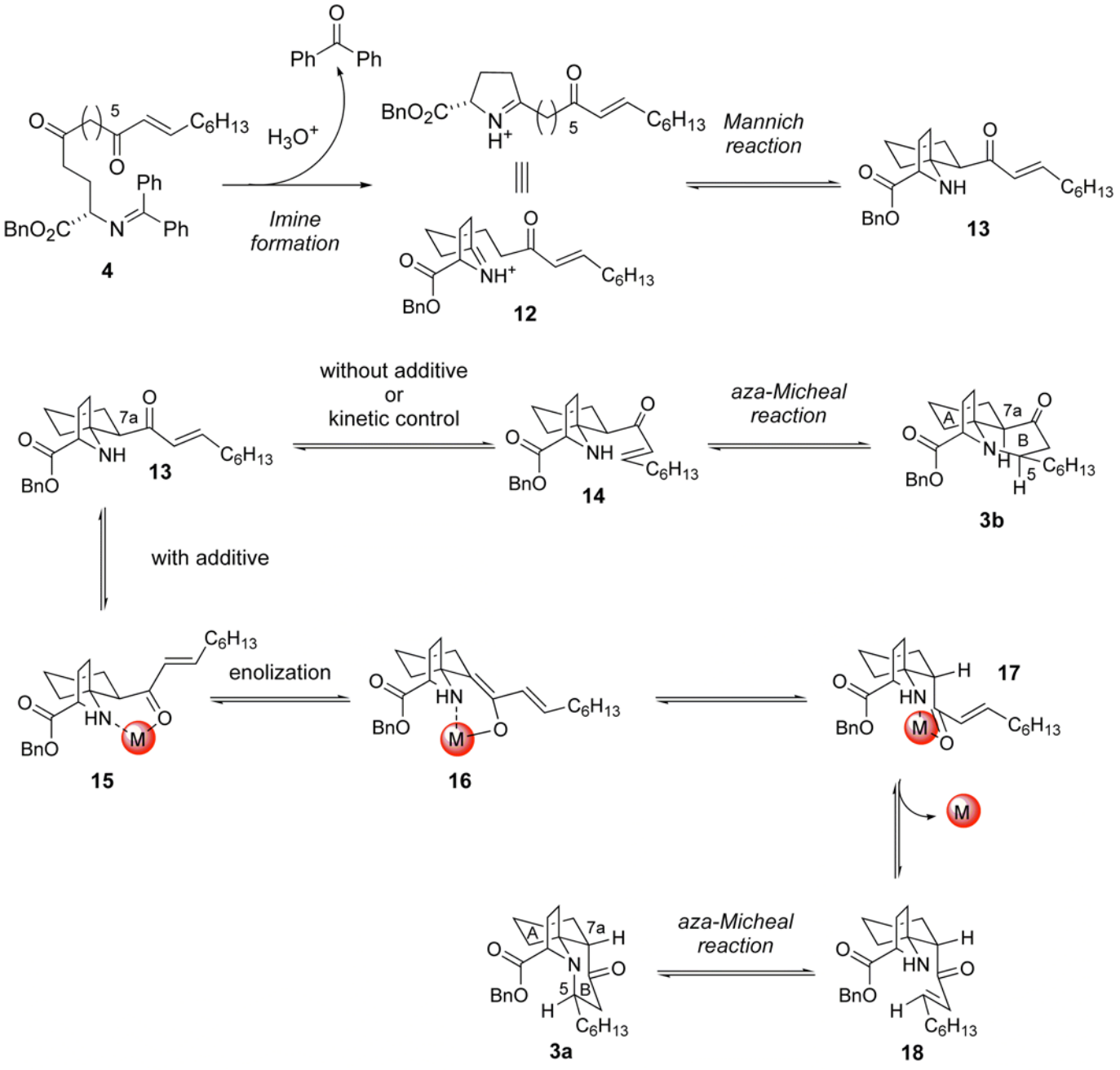


Entry	Additive	Time (h)	dr (**3a** : **3b** : **3c**)[a]	Yield (%)[b]
1	-	18	33 : 63 : 4	47
2	$AlCl_3$	24	87 : 13 : trace	47
3	$La(OTf)_3$	12	27 : 65 : 8	57
4	$MgCl_2$	18	87 : 7 : 6	66
5	$MgBr\cdot(Et_2O)_2$	18	82 : 13 : 5	61
6	LiCl	18	89 : 6 : 5	57

a) Determined by ^{1}H NMR spectroscopic analysis. b) Yield of the isolated product (**3a-c**).

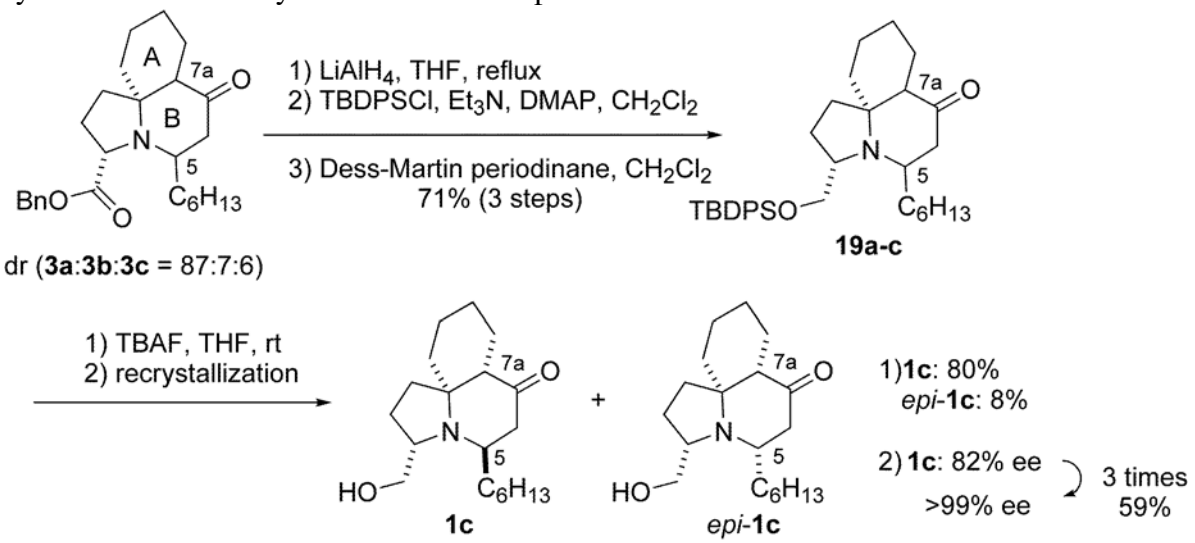
The proposed mechanism of this tandem cyclization and additive effects, as shown in Scheme 3, is described below. First, the diphenylmethylene group of **4** is removed under acidic conditions. The resulting amine then reacts with ketone to form iminium cation (**12**) and the following Mannich-type

reaction gives **13**. In the absence of metal salt, intramolecular attack of the amine moiety of **13** to the β-position of the enone (aza-Michael reaction) proceeds to give the *cis*-fused tricyclic compound (**3b**) predominantly. On the other hand, in the presence of a metal salt such as $MgCl_2$ the carbonyl group at the C7 position of **13** is activated by chelation to the metal (**13** to **15**), which then induces epimerization at the C7a position (**15** to **18**) through enolization of the enone. Although the side chain of **17** possesses a thermodynamically unfavorable axial position, this conformation is stabilized by chelation of the carbonyl group to the metal. Finally, after dissociation of the metal (**17** to **18**), aza-Michael addition proceeds and the configuration of the side chain is maintained as in **18** to afford the *cis*-fused tricyclic compound (**3a**).



Scheme 3. Proposed Mechanism of Tandem Cyclization

The obtained tricyclic compounds (**3a**-**c**) (Table 2, Entry 4) were transformed to (+)-**1c** (Scheme 4). First, both the ester and ketone functionalities of **3a**-**c** were reduced by $LiAlH_4$, and the resulting primary hydroxyl group was protected with a TBDPS group. Oxidation of the remaining secondary hydroxyl group with Dess-Martin periodinane afforded **19a**-**c** (3 steps 71%). After treatment of **19a-c** with TBAF, cylindricine C (**1c**) and 5-*epi*-cylindricine C (*epi*-**1c**)[12] were obtained in 80% and 8% yield, respectively. The *trans*-fused AB ring of **19b** was isomerized at the C7a position to the desired *cis*-fused AB ring under basic conditions. Computational studies supported this result (vide infra). Optically pure **1c** was obtained in 59% yield after three recrystallizations of the picric acid salt of **1c** from EtOH.



Scheme 4. Synthesis of (+)-Cylindricine C

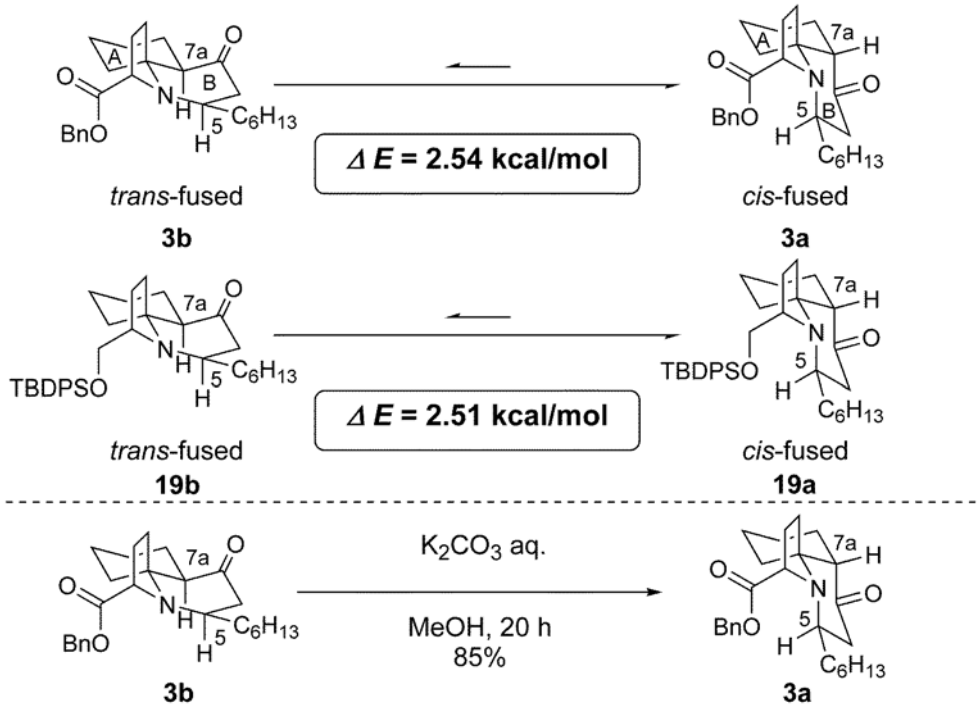
Thus, we succeeded in the synthesis of enantiomerically pure **1c** from pimelic acid in 9 steps, including the recrystallization process. The number of synthetic steps required to obtain **1c** was further decreased by using a mixed anhydride reduction process (Scheme 5).[13] Thereby, **1c** was obtained in two steps from **3a** (total 6 steps)

Scheme. 5 Shorter Approach to (+)-Cylindricine C from **3a**

To find a possible explanation of isomerization from a *trans*-fused AB ring system to a *cis*-fused AB ring system under basic conditions,[7f,g] we performed several computational studies (Scheme 6). First, conformational analysis was performed for all isomers (**3a**, **3b**, **19a**, and **19b**) using CONFLEX5/MMFF94s.[14] All the geometries of the global minimum (lowest energy structure) were further optimized with Gaussian03[15] at the B3LYP[16]/6-31G(d) level followed by frequency calculations

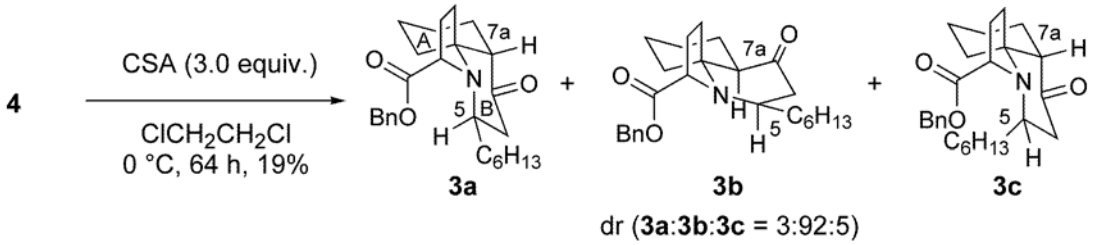
to determine the nature of the stationary points. The energies shown below include zero-point energy corrections at the same level of the geometry (B3LYP/6-31G(d)) scaled by 0.9806.[17]

The computational results suggested that *cis*-fused isomers (**3a** and **19a**) were thermodynamically more stable than *trans*-fused isomers (**3b** and **19b**). In fact, almost all of **3b** was isomerized to **3a** when **3b** was treated with aqueous K_2CO_3 in MeOH.[7f]



Scheme 6. Computational Analysis and Isomerization

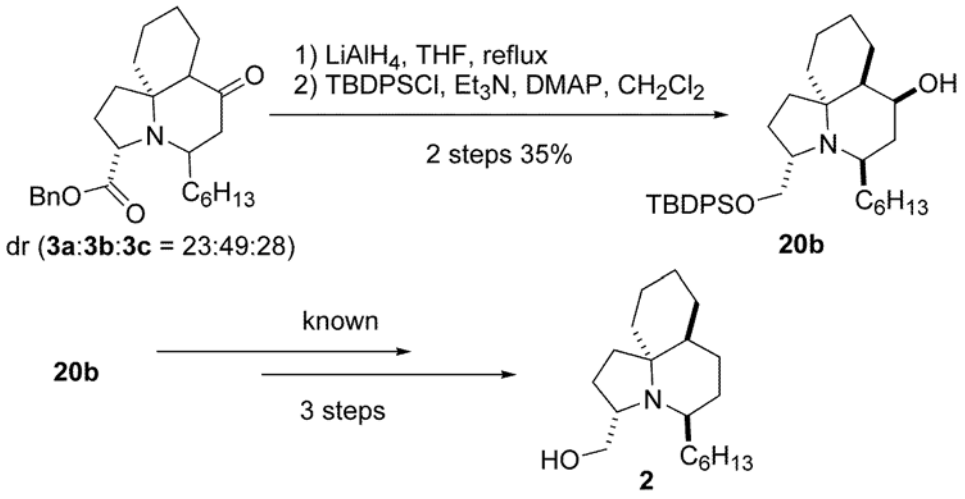
Next, we planned to synthesize (–)-lepadiformine (**2**),[18] which has a *trans*-fused AB ring system. As **3b** has the same configuration as **2**, we turned our attention to the selective synthesis of **3b**. Based on our experimental results and computational studies, **3b** should be the kinetic product in a tandem cyclization reaction. To examine this hypothesis, tandem cyclization was performed at 0 °C with 3 equivalents of CSA. As expected, **3b** was obtained with higher selectivity (**3a**:**3b**:**3c** = 3:92:5) (Scheme 7). In this condition, however, the chemical yield of the tricyclic compounds was relatively low (19%). Although we examined several reaction conditions, reactivity was not improved.



Scheme 7. Tandem Cyclization at 0 °C

The conditions shown in Table 2, Entry 4 (**3a**:**3b**:**3c** = 23:49:28, 68% yield) were used to construct the tricyclic products (Scheme 8). The obtained tricyclic compounds were treated with $LiAlH_4$ and the resulting primary hydroxyl group was protected by a TBDPS group, and the remaining secondary

hydroxyl group was exclusively β. The obtained diastereomixture (**20a**-**c**) was separated by silica gel column chromatography to give pure **20b** in 35% yield as a single diastereomer. The synthetic route from **20b** to (–)-lepadiformine (**2**) was established by Hsung et al.[7g] Thus, the formal synthesis of (–)-lepadiformine (**2**) was accomplished.



Scheme 8. Formal Synthesis of Lepadiformine

In summary, we accomplished a short synthesis of (+)-cylindricine C (6 steps) and a formal synthesis of (–)-lepadiformine using a combination of the catalytic asymmetric Michael reaction with TaDiAS and tandem cyclization under acidic conditions. Further improvement of each step and the expansion of current strategies are in progress.

EXPERIMENTAL

NMR spectra were measured on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H, and 126 MHz for ^{13}C. For ^{1}H and ^{13}C NMR, chemical shifts are reported in ppm on the δ scale relative to TMS (d = 0 for ^{1}H NMR) or residual solvent as an internal reference. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier transform infrared spectrophotometer. ESI mass spectra were measured on a Waters-ZQ4000. FAB mass spectra were measured on a JEOL JMS-700V. Optical rotations were measured on a JASCO P-1010 polarimeter. The enantiomeric excess was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU980; detector; UVIDEC-100-IV, measured at 254 nm; column, DAICEL CHIRALPAK AD-H, AS-H, and DAICEL CHIRALCEL OD-H; mobile phase, hexane–2-propanol. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). The reactions were performed in dry solvents under an argon atmosphere, unless otherwise noted.

N,N'-Dimethoxy-*N,N'*-dimethylheptanediamide (8)

A mixture of pimelic acid (**7**) (4.80 g, 30 mmol), *N,O*-dimethylhydroxylamine hydrochloride (6.40 g, 66 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (12.6 g, 66 mmol), triethylamine (12.6 mL, 90

mmol), and CH_2Cl_2 (75 mL) was stirred for 22 h. The reaction mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc) to yield **8** (6.17 g, 84%) as a colorless oil; R_f = 0.31 (silica gel, EtOAc); FT-IR (neat) ν_{max} 2934, 1665, 1415, 1385, 1178, 1117, 999 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (s, 6H), 3.17 (s, 6H), 2.42 (t, *J* = 7.3 Hz, 4H), 1.66 (m, 4H), 1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.6, 61.2, 32.1, 31.7, 29.1, 24.3; LR-MS [ESI(+)] *m/z* 269 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{11}H_{23}N_2O_4^+$ $[M+H]^+$: 247.1652. Found 247.1652.

(10*E*)-1,10-Heptadecadiene-3,9-dione (6)

t-BuLi (1.46 M in pentane, 2.74 mL, 4.0 mmol) was added to a solution of *trans*-1-iodo-1-octene (**9**) (476 mg, 2.0 mmol) in THF (10 mL) at –78 °C. After stirring for 2 h at the same temperature, the reaction mixture was added to a solution of **8** (492 mg, 2.0 mmol) in THF (10 mL) at –78 °C. The reaction mixture was stirred for 2 h at the same temperature, and then vinylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol) was added. After the mixture was allowed to warm to room temperature, the reaction mixture was stirred for 12 h. The mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (30 mL x 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to yield **6** (195.5 mg, 37%) as a pale yellow oil; R_f = 0.55 (silica gel, 25% EtOAc in hexane); FT-IR (neat) ν_{max} 2929, 2857, 1680, 1677, 1628, 1403, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (dt, *J* = 15.9, 7.0 Hz, 1H), 6.34 (dd, *J* = 17.7, 10.7 Hz, 1H), 6.21 (dd, *J* = 17.7, 1.2 Hz, 1H), 6.08 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.81 (dd, *J* = 10.7, 1.2 Hz, 1H), 2.59 (t, *J* = 7.4 Hz, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.20 (dd, *J* = 14.7, 1.6 Hz, 2H) 1.67-1.60 (m, 4H), 1.46 (dt, *J* = 15.0, 7.6 Hz, 2H), 1.37-1.26 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.8, 200.7, 147.5, 136.5, 130.2, 128.0, 39.7, 39.3, 32.4, 31.5, 28.82, 28.77, 28.0, 23.9, 23.6, 22.5, 14.0; LR-MS [ESI(+)] *m/z* 287 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{17}H_{29}O_2^+$ $[M+H]^+$: 265.2162. Found 265.2162.

(2*S*,12*E*)-2-(Diphenylmethylene)amino-5,11-dioxo-12-nonadecenoic acid benzyl ester (4)

A mixture of **5** (35.2 mg, 0.107 mmol), **6** (33.9 mg 0.128 mmol), and (*S*,*S*)-TaDiAS (**11b**) (10.7 mg, 0.0107 mmol) in 3-fluorotoluene (0.71 mL) was stirred for 1 h at –40 °C, and then Cs_2CO_3 (52.1 mg, 0.160 mmol) was added. The mixture was stirred vigorously for 96 h at the same temperature. The reaction was quenched with water (2 mL) and extracted with Et_2O (5 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to yield **4** (55.4 mg, 87%) as a pale yellow oil; R_f = 0.29 (silica gel, 25% EtOAc in hexane); $[\alpha]^{23}_D$ –44.1 (*c* 1.62, $CHCl_3$, 82% ee); FT-IR (neat) ν_{max}

2929, 2857, 1739, 1713, 1626, 1173, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61 (m, 2H), 7.41-7.24 (m, 11H), 7.09 (m, 2H), 6.81 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.07 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.17 (d, *J* = 12.6 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 4.12 (t, *J* = 6.1 Hz, 1H), 2.51-2.33 (m, 6H), 2.19 (m, 4H), 1.60-1.42 (m, 6H), 1.34-1.22 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 210.0, 200.6, 171.6, 171.0, 147.4, 139.3, 136.1, 135.8, 130.4, 130.2, 128.8, 128.7, 128.51, 128.46, 128.2, 128.1, 128.0, 127.6, 66.5, 64.1, 42.5, 39.7, 38.6, 32.4, 31.5, 28.8, 28.7, 28.0, 27.6, 23.9, 23.4, 22.5, 14.0; LR-MS[ESI(+)] *m/z* 616 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{39}H_{48}NO_4^+$ $[M+H]^+$: 594.3578. Found 594.3575.; HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9/1, 1.0 mL/min) t_R: 14.9 min ((*R*)-isomer minor) and 16.6 min ((*S*)-isomer major).

Tricyclic compound (3)

CSA (126.1 mg, 0.543 mmol) was added to solution of **4** (107.4 mg, 0.181 mmol) in 1,2-dichloroethane (4.5 mL). After the mixture was stirred for 1 h at room temperature, $MgCl_2$ (51.7 mg, 0.543 mmol) was added, and the mixture was warmed to 50 °C and stirred for 18 h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to yield a mixture of diastereomers **3** (49.1 mg, 66%, **3a**:**3b**:**3c** = 87:7:6) as a pale yellow oil. **3a**-**c** were used for the following reaction without further purification. To determine the conformations of the diastereomixtures, **3a**-**c** were separated by HPLC. HPLC separation was performed on JASCO HPLC systems [(PU-2086 Plus Pump, UV-2075-Plus Detector, 254 nm, DAICEL CHIRALPAK AS-H, hexane/2-propanol = 50/1, 20 mL/min), t_R 11.5 min (**3c** major), 12.5 min (**3a** major), 13.0 min (**3c** minor), 13.0 min (**3a** minor), 15.0 min (**3b** minor)], and after 20 min the solvent was changed to hexane/2-propanol = 4/1, 20 mL/min, t_R 10 min (**3b** major).

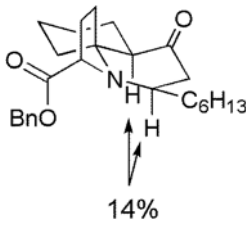
(3*S*,5*R*,7a*S*,11a*S*)-5-Hexyldecahydro-pyrrolo-1*H*-[2,1-*j*]quinoline-7-oxo-3-carboxylic acid benzyl ester (3a)

R_f = 0.55 (silica gel, 10% Et_2O in toluene); FT-IR (neat) ν_{max} 2931, 2859, 1747, 1706, 1455, 1145, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.32 (m, 5H), 5.21 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 3.99 (dd, *J* = 10.7, 2.7 Hz, 1H), 3.34 (m, 1H), 2.29-2.10 (m, 6H), 1.93-1.86 (m, 2H), 1.70 (m, 1H), 1.62-1.14 (m, 16H), 0.86, (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 210.5, 176.1, 135.9, 128.5, 128.33, 128.27, 69.5, 66.4, 58.4, 54.1, 50.9, 42.6, 35.6, 34.6, 34.4, 31.7, 29.2, 27.6, 26.4, 24.3, 23.0, 22.5, 21.6, 14.0; LR-MS [ESI(+)] *m/z* 434 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{26}H_{38}NO_3^+$ $[M+H]^+$: 412.2846. Found: 412.2851.

(3*S*,5*R*,7a*R*,11a*S*)-5-Hexyldecahydro-pyrrolo-1*H*-[2,1-*j*]quinoline-7-oxo-3-carboxylic acid benzyl ester (3b)

R_f = 0.43 (silica gel, 10% Et_2O in toluene); FT-IR (neat) ν_{max} 2930, 2857, 1749, 1715, 1454, 1152, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.29 (m, 5H), 5.23 (d, *J* = 12.3 Hz, 1H), 5.l4 (dd, *J* = 12.3 Hz, 1H), 3.73-3.66 (m, 2H), 2.70 (dd, *J* = 11.0, 2.8 Hz, 1H), 2.24 (t, *J* = 5.1 Hz, 2H), 2.07-1.97 (m, 2H), 1.92 (d, *J* = 8.9 Hz, 1H), 1.82-1.70 (m, 4H), 1.62 (dt, *J* = 13.3, 2.8 Hz, 1H), 1.53 (m, 1H), 1.38-1.05 (m, 13H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 212.3, 176.3, 135.9, 128.5, 128.3, 128.2, 68.3, 66.4, 61.5, 54.9, 53.9, 40.9, 39.2, 32.9, 31.9, 31.7, 29.3, 28.8, 27.0, 24.8, 24.1, 22.5, 22.4, 14.0; LR-MS [ESI(+)] *m/z* 434 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{26}H_{38}NO_3^+$ $[M+H]^+$: 412.2846. Found: 412.2849.

Based on NOE measurement, **3b** had a *trans*-fused AB ring, and A ring had a boat-type conformation.



(3*S*,5*S*,7a*S*,11a*S*)-5-Hexyldecahydro-pyrrolo-1*H*-[2,1-*j*]quinoline-7-oxo-3-carboxylic acid benzyl ester (3c)

R_f = 0.55 (silica gel, 10% Et_2O in toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.31 (m, 5H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 3.67 (t, *J* = 7.5 Hz, 1H), 3.18 (m, 1H), 2.50 (dd, *J* = 17.4, 3.7 Hz, 1H), 2.48 (m, 1H), 2.30-2.14 (m, 4H), 1.95 (m, 1H), 1.78 (dd, *J* = 12.2, 6.7 Hz, 1H), 1.75 (d, *J* = 11.9 Hz, 1H), 1.47-1.41 (m, 2H), 1.37-1.07 (m, 14H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.8, 175.9, 136.1, 128.6, 128.3, 128.2, 67.8, 67.0, 66.5, 57.9, 52.6, 43.4, 39.6, 36.7, 36.1, 31.9, 29.4, 28.8, 25.2, 24.3, 23.0, 22.7, 21.4, 14.2; LR-MS [ESI(+)] *m/z* 434 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{26}H_{38}NO_3^+$ $[M+H]^+$: 412.2846. Found: 412.2849.

Tricyclic compound (19)

A solution of diastereomixture of **3** (48.9 mg, 0.0824 mmol, **3a**:**3b**:**3c** = 87:7:6) in THF (0.8 mL) was added to lithium aluminum hydride (6.3 mg, 0.165 mmol) in THF (0.8 mL) at 0 °C. The mixture was refluxed for 2 h. The mixture was cooled to 0 °C and H_2O (6.3 μL), 4 N NaOH (6.3 μL), and H_2O (18.9 μL) were added at 0 °C. The mixture was warmed to room temperature, stirred for 8 h, diluted with water (3 mL), then extracted with 20% MeOH in CH_2Cl_2 (5 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the residue, which was dissolved in CH_2Cl_2 (0.8 mL). TBDPSCl (64.3 μL, 0.247 mmol), triethylamine (41.4 μL, 0.297 mmol), and DMAP (1.0 mg, 0.00824 mmol) were added to the mixture and stirred for 6 h. The reaction was quenched with water (3 mL) and extracted with CH_2Cl_2 (3 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the residue, which was dissolved in CH_2Cl_2 (0.8 mL). Dess-Martin periodinane (69.9 mg, 0.165 mmol) was added to the mixture. The reaction mixture was

stirred for 12 h and then quenched with water (3 mL) and extracted with CH_2Cl_2 (5 mL x 3). The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 7.5% to 10% EtOAc in hexane) to yield a diastereomixture of **19** (32 mg, 71%, **19a**:**19b**:**19c** = 90:3:7) as a brown oil.

(3*S*,5*R*,7a*S*,11a*S*)-3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-hexyloctahydro-1*H*-pyrrolo[2,1,*j*]quinoline-7(7a*H*)-one (19a)

R_f = 0.71 (silica gel, 25% EtOAc in hexane); $[\alpha]^{20}_D$ +8.5 (*c* 0.71, $CHCl_3$, 78% ee); FT-IR (neat) ν_{max} 2930, 2856, 1707, 1427, 1111, 702, 505 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70-7.66 (m, 4H), 7.43-7.35 (m, 6H), 3.61 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.33 (m,1H), 3.29 (dd, *J* = 18.5, 9.3 Hz, 1H), 3.08 (m, 1H), 2.27 (m, 1H), 2.22-2.05 (m, 6H), 1.62-1.45 (m, 4H), 1.32-1.18 (m, 9H), 1.07 (s, 9H), 1.07-1.03 (m, 5H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.4, 135.6, 133.9, 129.6, 127.6, 70.2, 68.4, 57.8, 55.3, 51.0, 43.0, 35.9, 34.9, 34.8, 31.7, 29.1, 27.0, 26.9, 25.9, 24.4, 22.9, 22.5, 21.9, 19.3, 14.0; LR-MS [ESI(+)] *m*/*z* 568 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{35}H_{52}NO_2Si^+$ $[M+H]^+$: 546.3762. Found: 546.3771.

(3*S*,5*R*,7a*R*,11a*S*)-3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-hexyloctahydro-1*H*-pyrrolo[2,1,*j*]quinoline-7(7a*H*)-one (19b)

R_f = 0.67 (silica gel, 25% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71-7.63 (m, 4H), 7.43-7.27 (m, 6H), 3.73 (dd, *J* = 9.6, 4.1 Hz, 1H), 3.46 (m, 1H), 3.28 (t, *J* = 9.2 Hz, 1H), 3.18 (m, 1H), 2.61 (dd, *J* = 11.6, 3.1 Hz, 1H), 2.15 (d, *J* = 8.0 Hz, 2H), 1.95-1.89 (m, 2H), 1.81-1.75 (m, 2H), 1.72-1.51 (m, 5H), 1.41 (m, 1H), 1.32-1.06 (m, 12H), 1.04 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 213.5, 135.6, 134.0, 129.6, 127.6, 70.4, 68.3, 60.2, 54.7, 54.0, 41.5, 40.7, 33.3, 31.8, 31.5, 29.7, 28.3, 27.3, 26.9, 24.9, 24.1, 22.6, 22.5, 19.2, 14.0; LR-MS [ESI(+)] *m*/*z* 568 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{35}H_{52}NO_2Si^+$ $[M+H]^+$: 546.3762. Found: 546.3770.

(3*S*,5*S*,7a*S*,11a*S*)-3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-hexyloctahydro-1*H*-pyrrolo[2,1,*j*]quinoline-7(7a*H*)-one (19c)

R_f = 0.71 (silica gel, 25% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69-7.63 (m, 4H), 7.44-7.35 (m, 6H), 3.57 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.40 (t, *J* = 9.5 Hz, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 2.48 (dd, *J* = 15.4, 5.4 Hz, 1H), 2.43 (m, 1H), 2.23 (m, 1H), 2.07 (dd, *J* = 15.4, 7.0 Hz, 1H), 2.00 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 15.2 (m, 1H), 1.43-1.39 (m, 4H), 1.38-1.05 (m, 12H), 1.04 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 212.5, 135.6, 133.9, 129.6, 127.6, 68.1, 66.2, 58.6, 50.9, 43.1, 40.5, 36.9, 36.2, 31.8, 29.7, 29.2, 26.9, 26.0, 25.7, 24.3, 23.1, 22.6, 21.7, 19.2, 14.0; LR-MS [ESI(+)] *m*/*z* 568 $[M+Na]^+$; HR-MS [FAB(+)] Calcd for $C_{35}H_{52}NO_2Si^+$ $[M+H]^+$: 546.3762. Found: 546.3772.

(+)-Cylindricine C (1c)

TBAF (1.0 M in THF, 90 μL, 0.0897 mmol) was added to solution of diastereomixture of **19** (16.9 mg, 0.0299 mmol, **19a**:**19b**:**19c** = 90:3:7) in THF (1.5 mL) at 0 °C. The mixture was stirred for 6 h at room temperature. The reaction was quenched with water (3 mL) and extracted with CH_2Cl_2 (5 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 7.5% to 10% EtOAc in hexane) to give **1c** (7.4 mg, 0.024 mmol, 80%) and *epi*-**1c** (0.73 mg, 0.0023 mmol, 8%) as a pale yellow oil, respectively.

Recrystallization of picric acid salt of 1c

Picric acid (31.1 mg, 0.136 mmol) was added to a solution of **1c** (41.6 mg, 0.136 mmol, 82% ee) in EtOH (1.0 mL). After the picric acid was completely dissolved, the solvent was removed in vacuo and a yellow solid was obtained. This solid was recrystallized from EtOH (3 times, 43.0 mg, 59%).

This solid was dissolved in EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (5 mL x 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. After the solvent was evaporated, the residue was purified by flash column chromatography (silica gel, 7.5% to 10% EtOAc in hexane) to yield optically pure **1c** (>99% ee) as a pale yellow oil; R_f = 0.53 (silica gel, 50% EtOAc in hexane); $[\alpha]^{21}_D$ +63.6 (*c* 0.44, CH_2Cl_2, >99% ee); FT-IR (neat) ν_{max} 3425, 2931, 2859, 1704, 1448, 1078, 407 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.50-3.55 (m, 2H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.28 (m, 1H), 2.91 (br, 1H), 2.30 (t, *J* = 12.4 Hz, 2H), 2.23 (dd, *J* = 13.1, 1.9 Hz, 2H), 2.12 (dd, *J* = 12.2, 8.0 Hz, 1H), 1.83 (m, 1H), 1.71-1.60 (m, 5H), 1.48 (m, 1H), 1.43-1.26 (m, 13H), 0.87 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 210.6, 70.7, 66.4, 56.5, 55.3, 50.2, 42.5, 36.4, 35.9, 35.2, 31.7, 29.3, 28.7, 27.1, 24.2, 22.7, 22.6, 21.8, 14.0; LR-MS [ESI(+)] *m*/*z* 308 $[M+H]^+$; HR-MS [FAB(+)] Calcd for $C_{19}H_{34}NO_2^+$ $[M+H]^+$: 308.2584. Found 308.2591.; HPLC (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 50/1, 1.0 mL/min) t_R: 16.8 min ((−)-**1c** minor) and 18.9 min ((+)-**1c** major).

5-*epi*-Cylindricine C (*epi*-1c)

Pale yellow oil; R_f = 0.40 (silica gel, 50% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.56 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.34 (dd, *J* = 10.7, 2.8 Hz, 1H), 3.31 (m, 1H), 3.22 (m, 1H), 2.80 (m, 1H), 2.66 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.52 (m, 1H), 2.26 (m, 1H), 2.16 (dd, *J* = 15.6, 6.1 Hz, 1H), 2.07- 2.02 (m, 2H), 1.83-1.25 (m, 19H), 0.87 (t, *J* = 6.9 Hz, 3H); LR-MS [ESI(+)] *m*/*z* 308 $[M+H]^+$; HR-MS [FAB(+)] Calcd for $C_{19}H_{34}NO_2^+$ $[M+H]^+$: 308.2584. Found: 308.2585.

A shorter approach to (+)-cylindricine C from 3a

Pd on charcoal (10%, 4.4 mg, 0.0042 mmol) was added a solution of **3a** (17.2 mg, 0.0418 mmol) in MeOH (0.42 mL) at room temperature. The reaction mixture was stirred at room temperature under H_2 atmosphere for 12 h. Pd and charcoal were filtered through Celite® eluting MeOH and concentrated.

The obtained residue was dissolved in THF (0.42 mL). *N*-methyl morpholine (4.6 μL, 0.0418 mmol) and ethyl chloroformate (4.0 μL, 0.0418 mmol) were added to this solution at −10 °C and stirred at the same temperature for 2 h. $NaBH_4$ (4.7 mg, 0.125 mmol) and MeOH (0.42 mL) were then added and stirred for 2 h at room temperature. The reaction mixture was quenched with 1 N HCl (9.4 μL), washed with saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with CH_2Cl_2 (5 mL x 3). The combined organic layer was washed with brine and dried over Na_2SO_4. After the solvent evaporated, the residue was purified by flash column chromatography (silica gel, 7.5% to 10% EtOAc in hexane) to give **1c** (4.0 mg, 0.013 mmol, 31% from **3a**) as a pale yellow oil.

Isomerization of 3b to 3a

Saturated aqueous K_2CO_3 solution (0.7 mL) was added to a solution of **3b** (42.1 mg, 0.102 mmol) in MeOH (1.4 mL), and the mixture was stirred for 20 h at room temperature. The reaction mixture was quenched with H_2O (3 mL), and extracted with EtOAc (3mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to yield **3a** (35.5 mg, 85%) as a pale yellow oil.

Synthesis of tricyclic compound 3 in the absence of metal salts (3b selective synthesis)

CSA (185.2 mg, 0.797 mmol) was added to a solution of **4** (157.7 mg, 0.266 mmol) in DMSO (1.8 mL). The mixture was warmed to 50 °C and stirred for 21 h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to yield diastereomixture of **3** (74.4 mg, 68%, **3a**:**3b**:**3c** = 23:49:28) as a pale yellow oil. **3a-c** were used for the following reaction without further purification.

(3*S*,5*R*,7a*R*,11a*S*)-3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-hexyldecahydro-1*H*-pyrrolo[2,1,*j*]quinoline-7-ol (20b)

A solution of diastereomixture of **3** (59.0 mg, 0.143 mmol, **3a**:**3b**:**3c** = 23:49:28) in THF (1.6 mL) was added to lithium aluminum hydride (24.8 mg, 0.752 mmol) in THF (1.6 mL) at 0 °C. The mixture was refluxed, and stirred for 4 h. H_2O (24.8 μL), 4 N NaOH (24.8 μL), and H_2O (74.4 μL) were added to the mixture at 0 °C. The mixture was warmed to room temperature, stirred 8 h, diluted with water (6 mL), and extracted with 20% MeOH in CH_2Cl_2 (10 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained residue was dissolved in CH_2Cl_2 (1.4 mL) and TBDPSCl (111.6 μL, 0.429 mmol), then triethylamine (72.3 μL, 0.515 mmol), and DMAP (1.7 mg, 0.0143 mmol) were added and the mixture was stirred for 5 h. The reaction was quenched with water (6 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel,

20% to 50% EtOAc in hexane) to yield **20b** (27.6 mg, 35 %) as a brown oil; R_f = 0.33 (silica gel, 25% MeOH in EtOAc); $[\alpha]^{23}_{D}$ –7.4 (*c* 0.68, $CHCl_3$, 77% ee); FT-IR (neat) ν_{max} 3382, 3070, 2928, 2857, 1589, 1463, 1427, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68-7.64 (m, 4H), 7.42-7.33 (m, 6H), 4.01 (m, 1H), 3.76 (dd, *J* = 8.9, 4.0 Hz, 1H), 3.27 (m, 2H), 2.84 (m, 2H), 2.18 (m, 1H), 2.02 (m, 2H), 1.77 (m, 2H), 1.68-1.54 (m, 5H), 1.50-1.36 (m, 4H), 1.33-1.23 (m, 5H), 1.17-1.07 (m, 5H), 1.05 (s, 9H), 0.96 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.6, 134.1, 129.5, 127.5, 71.2, 70.1, 67.2, 60.0, 53.2, 43.6, 41.6, 33.4, 31.8, 30.5, 29.6 29.4, 28.9, 27.6, 26.9, 26.5, 26.0, 24.4, 22.6, 19.3, 14.0; LR-MS [ESI(+)] *m/z* 548 $[M+H]^+$; HR-MS [FAB(+)] Calcd for $C_{35}H_{54}NO_2Si^+$ $[M+H]^+$: 548.3918. Found: 548.3909.

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