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Formal total synthesis of histrionicotoxin alkaloids *via* $Hg(OTf)_2$-catalyzed cycloisomerization and SmI_2-induced ring expansion†

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The efficient formal total synthesis of histrionicotoxin alkaloids was achieved. In this process, two key reactions were used to construct a core 1-azaspiro[5.5]undecane framework common to histrionicotoxins: a mercuric triflate ($Hg(OTf)_2$)-catalyzed cycloisomerization of a linear substrate, which was developed in our laboratory, and a samarium iodide (SmI_2)-mediated ring expansion.

Introduction

(−)-Histrionicotoxin 283A (HTX-283A, **1**, Fig. 1) is an azaspirocyclic histrionicotoxin alkaloid that was first isolated from skin extracts of the Colombian poison arrow frog *Dendrobates histrionicus* in 1971 by Witkop *et al.*[1] It exhibits highly selective inhibition of nicotinic acetylcholine receptors. Since Witkop *et al.* separated a mixture of six alkaloids including **1** from the skin extracts of 1110 frogs, other members of this alkaloid family have also been identified. In 1992, (−)-histrionicotoxin 235A (HTX-235A, **2**) was also isolated as a major constituent by Spande *et al.* from the other poison frog *Dendrobates auratus*.[2] The bioactivities have led to its use as important probes in neurophysiology. Establishing an efficient synthetic pathway for histrionicotoxin alkaloids is essential to investigate the development of new biological tools and the structure–activity relationships in more detail.

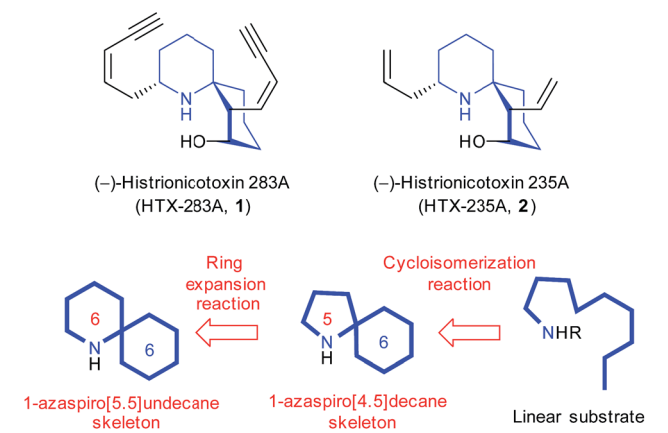

Fig. 1 Chemical structures of (−)-HTX-283A (**1**) and (−)-HTX-235A (**2**).

Regarding the structural features, compound **1** has a unique chemical structure characterized by a core spiropiperidine structure and two *cis*-enyne side chains. The core spirocyclic skeleton of **1** is conserved in **2**, but the two side *cis*-enyne groups are replaced by allylic and vinylic groups. The spirocyclic skeleton structure of histrionicotoxin alkaloids has prompted many synthetic organic chemists to promote the total syntheses so far.[3] In this contribution, we intended to realize the efficient construction of the core 1-azaspiro[5.5]undecane skeleton common to histrionicotoxin alkaloids based on ring expansion of a 1-azaspiro[4.5]decane one that could be formed in a stereoselective manner from a linear substrate by our original $Hg(OTf)_2$-catalyzed cycloisomerization reaction[4] (Fig. 1). In this letter, we report the formal synthesis of histrionicotoxins *via* two key steps: $Hg(OTf)_2$-catalyzed cycloisomerization and SmI_2-mediated ring expansion reactions.

Results and discussion

The retrosynthetic analysis of histrionicotoxin alkaloids is shown in Scheme 1. The spirocyclic ring compound **3** has been converted into histrionicotoxins *via* introduction of an allylic group by Tokuyama *et al.*[3i] Therefore, we planned to synthesize the 1-azaspiro[5.5]undecane skeleton **3** by applying a SmI_2-mediated ring expansion reaction, reported by Honda *et al.*,[5] to 1-azaspiro[4.5]decane skeleton **4**, which would be derived from spirocyclic compound **5**. Compound **5** would be constructed by the key $Hg(OTf)_2$-catalyzed cycloisomerization reaction of linear ynone **6**, which would be prepared through acylation of sulfone **8** with pyrrolidinone **7**, derived from L-glutamic acid according to the known method.[6] Compound **8**

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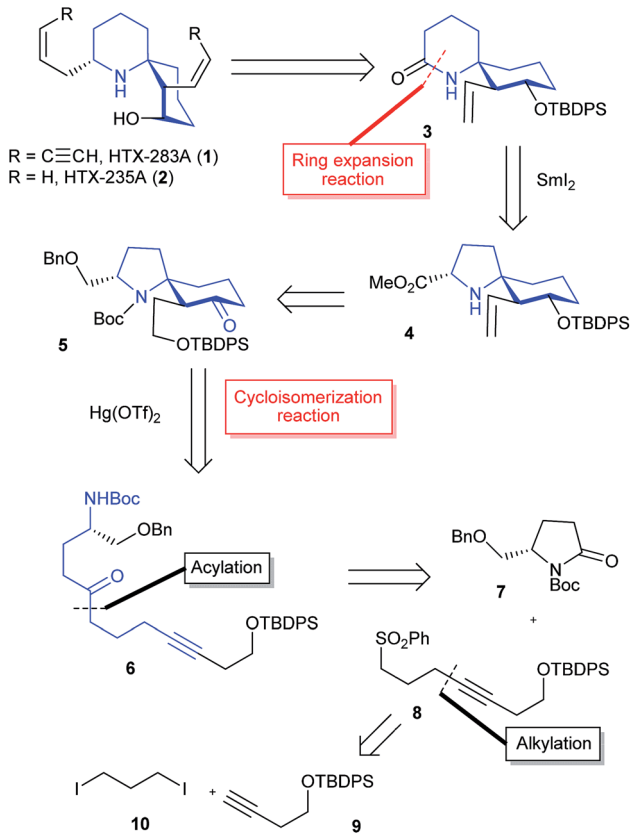
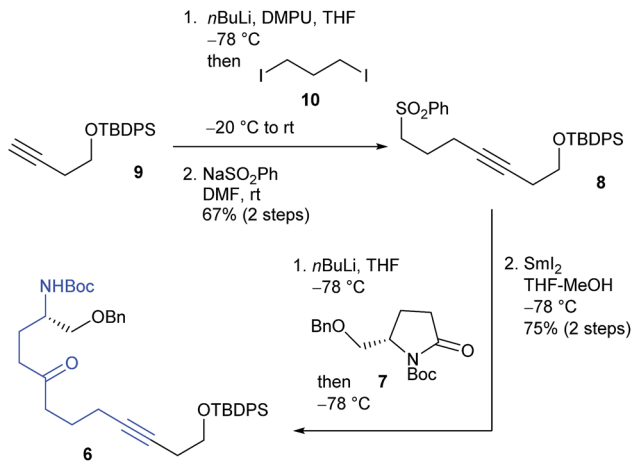


Scheme 1 Retrosynthetic analysis of histrionicotoxins.

would be synthesized by alkylation of a lithium acetylide of alkyne **9** with commercially available 1,3-diiodopropane (**10**).

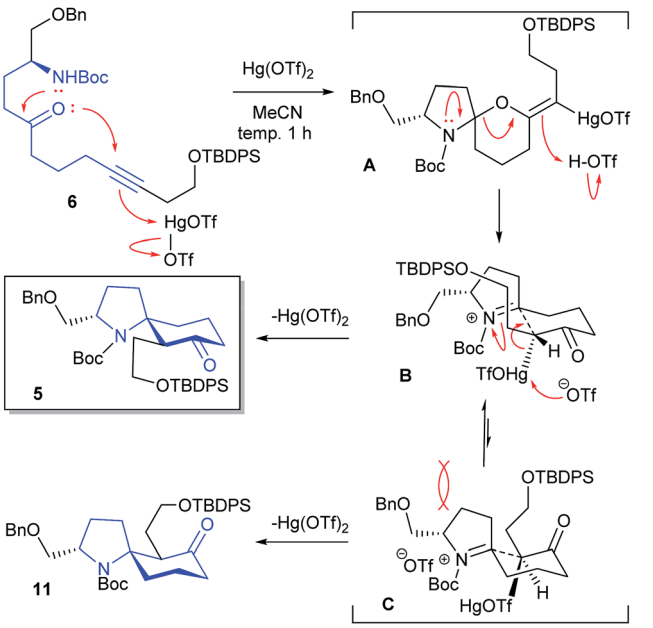
The total synthesis commenced with the known silyl ether **9**, derived from commercially available 3-butyn-1-ol (Scheme 2).[7] Alkylation of a lithium acetylide of **9** with 1,3-diiodopropane (**10**) followed by sulfonylation of the iodo moiety gave sulfone **8**. After acylation of an α-anion of **8** with the known pyrrolidinone **7**, the cyclization precursor **6** was prepared through SmI_2-mediated desulfonylation.[8]



Scheme 2 Synthesis of the cyclization precursor **6**.

We examined the $Hg(OTf)_2$-catalyzed cycloisomerization reaction of precursor **6** as the first key reaction (Table 1). As expected, the reaction proceeded in a stereoselective manner to provide the desired spirocyclic product **5** in an isolated yield of 58%, along with a minor diastereomer **11** (11% and 12%), when **6** was allowed to react with $Hg(OTf)_2$ (5 and 10 mol%) in MeCN at 0 °C (entries 1 and 2, respectively). Increasing the catalyst loading to 20 mol% afforded a better yield (67%) of **5** (entry 3). When the catalyst loading was increased to 30 and 50 mol%, the yield of **5** decreased to 52% and 38%, respectively (entries 4 and 5). The reaction at −20 °C resulted in a decrease in the yield of **11** (trace) (entry 6). When the reaction solution was gradually warmed to room temperature from −20 °C, the result was the same as that in entry 3 (entry 7). Finally, the effect of reaction temperature was examined (entries 8–10). Entry 9 showed the best conditions (cat. 20 mol%, −30 °C) in terms of the yield of **5**. Lowering the temperature resulted in a gradual decrease in the

Table 1 Optimization of the cycloisomerization of cyclization precursor **6**



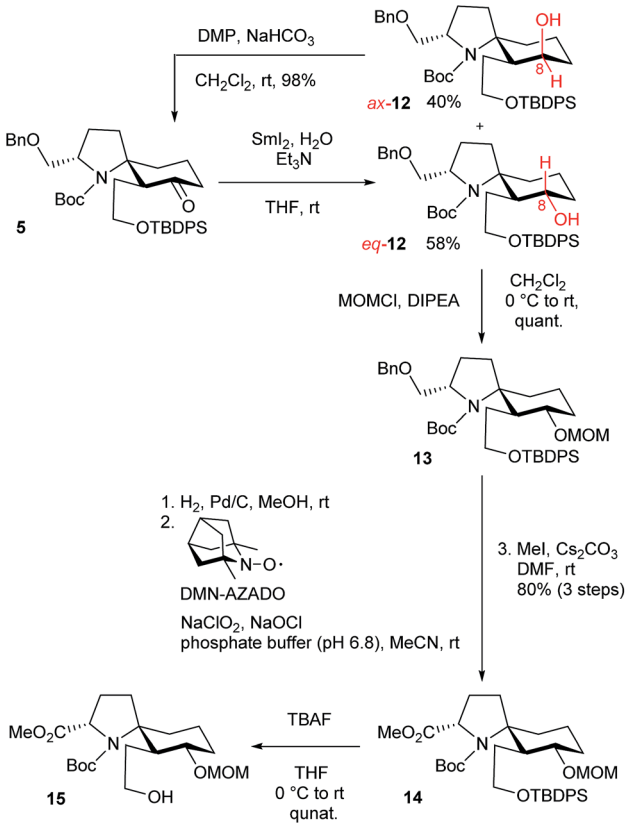
Entry	$Hg(OTf)_2$ (mol%)	Temp. (°C)	Yield[a] (%) 5	11
1	5	0	58	11
2	10	0	58	12
3	20	0	67	11
4	30	0	52	11
5	50	0	38	17
6	10	−20	67	Trace
7	20	−20 to 0	69	17
8	20	−20	73	7
9	20	−30	77	6
10	20	−40	53	3

[a] Isolated yield.

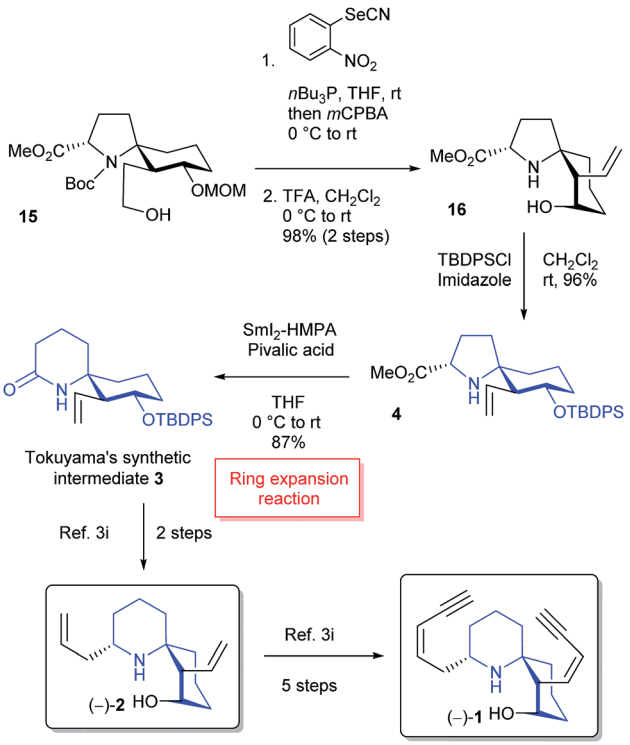
yield of **11**. Stereochemical assignments of **5** and **11** were achieved by their NOESY spectra; see (ESI†). The reaction mechanism, which we propose at present, is shown in Table 1.

The aminoketal **A** would be formed through a 6-*exo*-dig intramolecular oxymercuration to the alkyne π-electron activated by coordination of $Hg(OTf)_2$ followed by nucleophilic addition of the nitrogen function. The intermediate **A** could be cleaved by protonation with the generated TfOH to give an iminium ion intermediate **B** or **C**. The construction of a carbocycle *via* Ferrier-type cyclization would provide the desired spirocyclic product **5** with regeneration of the catalyst. Considering the chair-like transition states **B** and **C**, the desired **5** would be diastereoselectively obtained by way of the more stable transition state **B** without steric repulsion with a benzyloxymethyl group as outlined in Table 1. The by-product **11** would be produced through **C**.[9]

According to Procter's conditions,[10] treatment of spirocyclic product **5** with SmI_2 in the presence of H_2O and triethylamine afforded the desired *eq*-alcohol **12** as a major diastereomer (58%), along with *ax*-alcohol **12** (40%) (Scheme 3).[11] The undesired *ax*-**12** was oxidized with Dess–Martin periodinane (DMP) for the recycling use.[12] After MOM protection of a hydroxy group in *eq*-**12**, a benzylic group was removed by hydrogenolysis using Pd/C. After a hydroxy group was converted into a carboxylic acid through one-pot oxidation using 1,5-dimethyl-nor-AZADO (DMN-AZADO) and $NaClO_2$,[13] the esterification using MeI and Cs_2CO_3 afforded ester **14**. Deprotection of a TBDPS group using tetrabutylammonium fluoride (TBAF) provided the desired alcohol **15**.



Scheme 3 Synthesis of alcohol **15**.



Scheme 4 Formal synthesis of histrionicotoxin alkaloids.

The formal total syntheses of histrionicotoxins were completed from **15** as outlined in Scheme 4. After a vinylic group was constructed by Nishizawa–Grieco elimination,[3i,14] deprotection of MOM and Boc groups afforded vinyl alcohol **16**. The conformation of the spirocycle in **16** was assigned based on the NOESY spectra; see ESI.† The TBDPS protection of a hydroxy group in **16** provided silyl ether **4**. Compound **4** was further converted into 1-azaspiro[5.5]undecane **3** in high yield through the key SmI_2-mediated ring expansion reaction in the presence of HMPA and pivalic acid.[5] It is the first example that the SmI_2-mediated radical ring expansion was applied for constructing such a complex system as a 1-azaspiro[5.5]undecane skeleton of histrionicotoxins. Compound **3** is a key intermediate in the total synthesis of histrionicotoxin alkaloids, (−)-HTX-283A (**1**) and (−)-HTX-235A (**2**), by Tokuyama's group.[3i] The spectral data (^{1}H- and ^{13}C-NMR) and the optical rotation of our synthetic **3** were consistent with those reported for the previous synthetic compound.[3i] It has been reported that compound **3** can be transformed to (−)-**1** *via* (−)-**2**.[3i]

Conclusions

In summary, the combination of $Hg(OTf)_2$-catalyzed cycloisomerization and SmI_2-mediated ring expansion reactions made it possible to efficiently construct a 1-azaspiro[5.5]undecane framework of histrionicotoxin alkaloids. The synthetic efficiency of key intermediate **3** (15% overall yield and 15 steps based on the known silyl ether **9**) was demonstrated in

comparison with Tokuyama's method[3i] (5% overall yield and 14 steps based on the readily available ketodiester and benzylamine). Our synthetic method will be useful to synthesize HTXs and the derivatives as biological probes.

Experimental

General procedures

^{1}H-NMR spectra were recorded in deuteriochloroform on Bruker Biospin Avance 300 nanobay (300 MHz), JEOL JNM-ECZ400S or Bruker Biospin Avance III HD 400 (400 MHz), and Bruker Biospin Avance III HD 600 (600 MHz) spectrometers. ^{13}C-NMR spectra were measured in deuteriochloroform on Bruker Biospin Avance 300 nanobay (75 MHz), JEOL JNM-ECZ400S or Bruker Biospin Avance III HD 400 (100 MHz), and Bruker Biospin Avance III HD 600 (150 MHz) spectrometers. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm for ^{1}H-NMR, 77.0 ppm for ^{13}C-NMR). Splitting patterns were designated as "s, d, t, q, and m" to indicate "singlet, doublet, triplet, quartet, and multiplet," respectively. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer by the attenuated total reflection (ATR) method, unless otherwise noted. High-resolution mass spectra were obtained on a JEOL AccuTOF LC-plus JMS-T100LP (DART). Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Mp are uncorrected and were recorded on a Yanagimoto micro melting point apparatus. Analytical TLC was carried out by precoated silica gel (Merck TLC plates silica gel 60 F254). Flash column chromatography was performed with Merck silica gel 60 (particle size 63–200 μm), Wakogel® 60N (particle size 38–100 μm), and KANTO silica gel 60N (particle size 40–50 μm). All reactions were performed in oven-dried glassware. Tetrahydrofuran (THF) was distilled over sodium metal/benzophenone ketyl. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2), and triethylamine (Et_3N) were distilled over calcium hydride. Hexamethylphosphoric triamide (HMPA), *N*,*N*′-dimethylpropyleneurea (DMPU), and *N*,*N*-dimethylformamide (DMF) were distilled over calcium hydride under reduced pressure. Methanol (MeOH) was distilled from $Mg(OMe)_2$.

Experimental procedures

Sulfone 8. To a solution of **9** (ref. 7) (2.10 g, 6.81 mmol) in THF (14 mL) was added dropwise *n*BuLi (8.86 mL, 5.68 mmol, 1.56 M in hexane) at −78 °C under a nitrogen atmosphere, and the solution was stirred for 30 min. After DMPU (1.60 mL, 13.3 mmol) was added to the solution, the mixture was stirred for 15 min. To the solution of a lithium acetylide of **9** in THF was added a solution of 1,3-diiodopropane (**10**) (8.07 g, 27.3 mmol) in THF (14 mL) at −20 °C, and the solution was allowed to warm to room temperature and stirred for 10 h. After the reaction was quenched with a saturated aqueous solution of NH_4Cl, the resulting mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (toluene/hexane, 10 : 90) on silica gel to give a mixture including a desired mono-iodide, which was used in the next reaction without further purification.

To a solution of the mixture including a desired mono-iodide in DMF (68 mL) was added $NaSO_2Ph$ (1.68 g, 10.2 mmol) at room temperature under a nitrogen atmosphere, and the solution was stirred for 5 h. After the reaction was quenched with H_2O, the resulting mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 30 : 70) on silica gel to give **8** (2.24 g, 4.56 mmol, 67% in 2 steps) as a colorless oil: R_f = 0.58 (EtOAc/hexane, 30 : 70); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91–7.85 (2H, m), 7.70–7.58 (5H, m), 7.56–7.48 (2H, m), 7.47–7.34 (6H, m), 3.69 (2H, t, J = 7.1 Hz), 3.22–3.12 (2H, m), 2.42–2.33 (2H, m), 2.28–2.19 (2H, m), 1.85 (2H, quintet, J = 7.3 Hz), 1.03 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.0, 135.5, 133.7, 133.6, 129.7, 129.3, 128.0, 127.7, 79.0, 78.6, 62.6, 55.2, 26.7, 22.8, 22.1, 19.2, 17.6; IR (ATR) 3070, 3051, 2997, 2956, 2931, 2857, 1769, 1588, 1508, 1472, 1447, 1428, 1388, 1362, 1308, 1261, 1152, 1111, 1089, 1059, 1025, 915, 822, 800 cm^{-1}; DART-HRMS calcd for $C_{29}H_{35}O_3SSi$ [$(M + H)^+$] 491.2076, found 491.2078.

Preparation of a THF solution of SmI_2. To a slurry of Sm metal powder (1.50 g, 9.98 mmol) in THF (50 mL) was added CH_2I_2 (450 μL, 5.60 mmol) at room temperature under a nitrogen atmosphere, and the mixture was stirred for 5 h. The resulting solution was directly used to effect the following reductive reactions.

Ynone 6 (ref. 8). To a solution of **8** (252 mg, 826 μmol) in THF (6.1 mL) at −78 °C was added dropwise *n*BuLi (1.60 M in hexane, 862 μL, 1.38 mmol) under a nitrogen atmosphere, and the solution was stirred for 30 min. A solution of **7** (ref. 6) (749 mg, 1.53 mmol) in THF (1.7 mL) was added to the solution, and the solution was stirred at −78 °C for 35 h. After the reaction was quenched with a saturated aqueous solution of NH_4Cl, the resulting mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/hexane, 10 : 90) on silica gel to afford a mixture including a desired sulfone, which was used in the next reaction without further purification.

To a solution of the mixture including a desired sulfone in THF (6.0 mL) and MeOH (4.0 mL) was added SmI_2 (15.0 mL, 1.50 mmol, 0.100 M in THF) at −78 °C under a nitrogen atmosphere, and the solution was stirred for 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 30 : 70) on silica gel to provide **6** (404 mg, 617 μmol, 75% in 2 steps) as a colorless oil: R_f = 0.37 (EtOAc/hexane, 30 : 70); $[\alpha]_D^{25}$ −12.3 (*c* 2.31, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72–7.64 (4H, m), 7.46–7.26 (11H, m), 4.74 (1H, br d, J = 11.3 Hz), 4.52 (1H, d, J = 11.9 Hz), 4.46 (1H, d, J = 12.0 Hz), 3.73 (2H, t,

J = 7.1 Hz), 3.71 (1H, m), 3.44 (2H, d, J = 4.0 Hz), 2.52–2.36 (6H, m), 2.14 (2H, td, J = 7.0, 2.3 Hz), 1.92–1.61 (4H, m), 1.42 (9H, s), 1.05 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 210.1, 155.7, 138.0, 135.5, 133.6, 129.6, 128.4, 127.64, 127.61, 127.57, 80.4, 79.2, 77.7, 77.2, 73.1, 72.2, 62.8, 49.9, 41.5, 39.3, 28.3, 26.7, 26.1, 22.9, 22.8, 19.2, 18.1; IR (ATR) 3371, 3070, 3049, 3031, 2956, 2932, 2894, 2858, 1712, 1589, 1499, 1473, 1453, 1428, 1389, 1365, 1246, 1221, 1171, 1111, 1059, 1028, 915, 823 cm^{-1}; DART-HRMS calcd for $C_{40}H_{54}NO_5Si$ [(M + H)$^+$] 656.3771, found 656.3789.

Spiroketone 5 and its diastereomer 11 (Table 1, entry 9).[4] To a solution of **6** (42.7 mg, 65.2 μmol) in MeCN (1.3 mL) was added a solution of $Hg(OTf)_2$ (6.5 mg, 13.0 μmol) in MeCN (650 μL) at −30 °C under a nitrogen atmosphere, and the solution was stirred for 1 h at −30 °C. After the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, the mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 10 : 90) on silica gel to give **5** (32.8 mg, 50.0 μmol, 77%) and **11** (2.6 mg, 3.97 μmol, 6%) as each colorless oil. **5**: R_f = 0.58 (EtOAc/hexane, 30 : 70); $[\alpha]_D^{26}$ −15.9 (*c* 0.34, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C, two rotamers in a 4 : 1 ratio) δ 7.68–7.61 (4H, m), 7.42–7.21 (11H, m), 4.55 (0.2H, d, J = 12.0 Hz), 4.51 (1.6H, s), 4.49 (0.2H, d, J = 12.0 Hz), 4.20 (0.2H, br s), 4.01 (0.8H, br s), 3.84 (0.8H, dd, J = 10.2, 1.8 Hz), 3.69 (1H, td, J = 9.2, 4.6 Hz), 3.55 (0.2H, d, J = 4.7 Hz), 3.53–3.44 (2H, m), 3.36 (0.8H, dd, J = 8.9, 7.5 Hz), 3.30 (0.2H, d, J = 9.8 Hz), 2.96 (0.8H, td, J = 13.6, 4.2 Hz), 2.62 (0.2H, td, J = 13.4, 4.2 Hz), 2.36–2.22 (1.8H, m), 2.21–1.99 (1.2H, m), 1.93–1.63 (5.2H, m), 1.61–1.53 (0.8H, m), 1.52–1.38 (2H, m), 1.38 and 1.36 (total 9H, each s), 1.03 (9H, s); ^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C, two rotamers in a 4 : 1 ratio) δ 210.9, 210.0, 153.3, 152.9, 138.5, 138.2, 135.49, 135.45, 134.1, 133.9, 133.84, 133.82, 129.43, 129.42, 129.36, 129.3, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 80.2, 79.4, 73.0, 71.2, 70.8, 70.3, 69.4, 63.2, 62.8, 59.7, 59.1, 54.3, 52.4, 42.0, 41.8, 37.7, 36.8, 33.7, 32.4, 28.5, 28.4, 27.0, 26.84, 26.80, 26.6, 26.3, 25.8, 21.5, 19.1; IR (ATR) 3070, 3048, 3032, 2956, 2929, 2858, 1712, 1688, 1589, 1541, 1472, 1455, 1428, 1388, 1364, 1317, 1298, 1254, 1219, 1171, 1111, 1072, 1029, 999, 973, 941, 909, 886, 866, 823, 772 cm^{-1}; DART-HRMS calcd for $C_{40}H_{54}NO_5Si$ [(M + H)$^+$] 656.3771, found 656.3773. **11**: R_f = 0.53 (EtOAc/hexane, 30 : 70); $[\alpha]_D^{24}$ −8.0 (*c* 0.87, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C, two rotamers in a 5 : 1 ratio) δ 7.68–7.60 (4H, m), 7.42–7.25 (11H, m), 4.56 (0.83H, d, J = 12.1 Hz), 4.53, 4.51 (each 0.17H, d, J = 12.1 Hz), 4.50 (0.83H, d, J = 12.1 Hz), 4.15 (0.17H, br s), 3.98 (0.83H, br t, J = 7.0 Hz), 3.91 (0.83H, d, J = 9.7 Hz), 3.87 (0.17H, dd, J = 10.1, 2.1 Hz), 3.69 (0.17H, m), 3.67–3.55 (1.83H, m), 3.55–3.44 (1H, m), 3.37 (0.17H, m), 3.25 (0.83H, t, J = 8.9 Hz), 3.02 (0.17H, td, J = 13.5, 4.3 Hz), 2.73 (0.83H, td, J = 13.3, 4.0 Hz), 2.42–2.17 (2.17H, m), 2.15–2.02 (0.83H, m), 1.97–1.33 (8H, m), 1.42 and 1.37 (total 9H, each s), 1.03 (1.53H, s), 1.02 (7.47H, s); ^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C, two rotamers in a 5 : 1 ratio) δ 210.5, 209.5, 153.2, 152.9, 138.3, 138.1, 135.54, 135.52, 134.13, 134.10, 134.07, 133.9, 129.6, 129.4, 128.4, 128.3, 127.7, 127.64, 127.59, 127.53, 127.50, 80.2, 79.6, 73.2, 71.0, 70.7, 70.5, 70.4, 62.83, 62.75, 58.2, 57.8, 52.4, 52.1, 41.5, 41.4, 32.2, 30.6, 28.4, 26.9, 26.8, 25.7, 25.3, 24.5, 23.8, 21.9, 21.4, 19.18, 19.16; IR (ATR) 3069, 3049, 3030, 2959, 2931, 2857, 1712, 1688, 1588, 1473, 1455, 1428, 1366, 1306, 1256, 1169, 1110, 1026, 975, 955, 908, 854, 823, 804 cm^{-1}; DART-HRMS calcd for $C_{40}H_{54}NO_5Si$ [(M + H)$^+$] 656.3771, found 656.3771.

Alcohols *eq*-12 and *ax*-12 (SmI_2-mediated reduction).[10] To a solution of **5** (133 mg, 203 μmol) in THF (2.0 mL) were added H_2O (66.0 μL, 3.66 mmol) and Et_3N (510 μL, 3.66 mmol). After SmI_2 (12.0 mL, 1.20 mmol, 0.100 M in THF) was added to the solution at room temperature under a nitrogen atmosphere, the mixture was stirred for 6 h. After the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, the resulting mixture was extracted with EtOAc (×3). The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 10 : 90) on silica gel to provide *eq*-**12** (77.4 mg, 118 μmol, 58%) and *ax*-**12** (54.1 mg, 82.2 μmol, 40%) as each colorless oil: *eq*-**12**: R_f = 0.54 (EtOAc/hexane, 30 : 70); $[\alpha]_D^{26}$ −15.1 (*c* 1.40, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C, two rotamers in a 2 : 1 ratio) δ 7.71–7.63 (4H, m), 7.46–7.36 (6H, m), 7.36–7.23 (5H, m), 4.75 (0.33H, br s), 4.54 (0.67H, d, J = 13.0 Hz), 4.49 (0.67H, d, J = 11.6 Hz), 4.47 (0.33H, d, J = 12.0 Hz), 4.46 (0.33H, d, J = 12.1 Hz), 4.23 (0.67H, d, J = 3.1 Hz), 4.10 (0.33H, m), 3.91 (0.67H, m), 3.77 (0.33H, dt, J = 10.2, 4.1 Hz), 3.72–3.65 (0.67H, m), 3.61 (0.67H, td, J = 10.0, 3.7 Hz), 3.57 (0.33H, m), 3.56 (0.33H, td, J = 9.3, 2.5 Hz), 3.49 (0.67H, dd, J = 8.9, 3.1 Hz), 3.45 (0.33H, dd, J = 8.9, 7.7 Hz), 3.43–3.32 (1H, m), 3.29 (0.67H, t, J = 8.5 Hz), 2.77 (0.67H, br t, J = 7.4 Hz), 2.39 (0.67H, td, J = 13.2, 4.2 Hz), 2.37 (0.33H, m), 2.16 (0.33H, td, J = 12.9, 3.6 Hz), 2.10–1.99 (1H, m), 1.99–1.88 (1H, m), 1.88–1.53 (7H, m), 1.45–1.16 (2H, m), 1.38 (3H, s), 1.26 (6H, s), 1.07 (3H, s), 1.04 (6H, s); ^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C, two rotamers in a 2 : 1 ratio) δ 153.5, 152.6, 138.6, 138.3, 135.64, 135.59, 135.56, 133.0, 132.6, 132.5, 129.94, 129.90, 129.72, 129.67, 128.4, 128.3, 127.8, 127.7, 127.6, 127.44, 127.39, 79.9, 79.0, 73.11, 73.06, 73.0, 71.5, 70.7, 68.9, 68.3, 65.1, 64.6, 59.0, 58.6, 50.0, 47.3, 37.9, 36.8, 35.1, 35.0, 33.4, 31.8, 31.4, 31.1, 28.5, 28.3, 26.8, 26.7, 26.0, 20.58, 20.56, 19.0, 18.9; IR (ATR) 3435, 3070, 3048, 3032, 2956, 2929, 2858, 1688, 1589, 1541, 1472, 1455, 1428, 1388, 1364, 1317, 1298, 1254, 1219, 1171, 1111, 1072, 1029, 999, 973, 941, 909, 886, 866, 823, 772, 736, 700 cm^{-1}; DART-HRMS calcd for $C_{40}H_{56}NO_5Si$ [(M + H)$^+$] 658.3928, found 658.3935. *ax*-**12**: R_f = 0.67 (EtOAc/hexane, 30 : 70); $[\alpha]_D^{27}$ −26.3 (*c* 0.82, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C, two rotamers in a 3 : 1 ratio) δ 7.70–7.62 (4H, m), 7.47–7.22 (11H, m), 4.57 (0.25H, d, J = 12.0 Hz), 4.53 (0.75H, d, J = 12.1 Hz), 4.48 (0.25H, d, J = 12.0 Hz), 4.50 (0.75H, d, J = 11.9 Hz), 4.18 (1H, br d, J = 2.4 Hz), 4.12 (0.25H, m), 3.94 (0.75H, m), 3.82–3.71 (1H, m), 3.71–3.60 (1H, m), 3.60 (0.25H, dd, J = 9.0, 3.3 Hz), 3.50 (0.75H, dd, J = 8.8, 3.1 Hz), 3.39 (0.25H, t, J = 8.5 Hz), 3.24 (0.75H, t, J = 8.8 Hz), 2.81 (1H, m), 2.49 (0.75H, td, J = 13.0, 3.2 Hz), 2.44 (0.25H, m), 2.25 (0.75H, br s), 2.10 (0.25H, br s), 1.89–1.75 (3H, m), 1.75–1.53 (5H, m), 1.53–1.28 (2H, m), 1.39 (2.25H, s), 1.32 (6.75H, s), 1.05 (2.25H, s), 1.04 (6.75H, s); ^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C, two rotamers in a 3 : 1 ratio) δ 153.7, 152.8, 138.7, 138.4, 135.6, 135.5, 133.3, 133.2, 129.80, 129.78, 129.74, 129.71, 128.4, 128.3, 127.8, 127.73, 127.71, 127.6, 127.5, 127.4, 127.3, 79.5, 78.8,

73.02, 72.98, 71.3, 70.7, 68.9, 68.6, 67.1, 66.7, 63.7, 63.5, 58.5, 58.1, 43.1, 41.1, 39.3, 38.4, 34.2, 33.1, 33.0, 32.6, 29.3, 29.0, 28.6, 28.5, 26.9, 26.81, 26.79, 26.2, 19.03, 19.01, 18.7, 18.6; IR (ATR) 3485, 3070, 3049, 3031, 2957, 2929, 2858, 1673, 1473, 1454, 1428, 1388, 1364, 1322, 1253, 1219, 1169, 1108, 1081, 1028, 996, 940, 908, 858, 823, 805, 772, 735, 700 cm^{-1}; DART-HRMS calcd for $C_{40}H_{56}NO_5Si$ $[(M + H)^+]$ 658.3928, found 658.3942.

Alcohols *eq*-12 and *ax*-12 ($NaBH_4$ reduction). To a solution of **5** (15.7 mg, 24.0 μmol) in MeOH (480 μL) was added $NaBH_4$ (9.1 mg, 240 μmol) at 0 °C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature over 2 h. After the reaction was quenched with H_2O, the resulting mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 10 : 90) on silica gel to provide *eq*-**12** (2.8 mg, 3.96 μmol, 16%) and *ax*-**12** (9.8 mg, 14.9 μmol, 62%) as each colorless oil.

Spiroketone 5 from alcohol *ax*-12. To a solution of *ax*-**12** (75.8 mg, 115 μmol) in CH_2Cl_2 (1.2 mL) were added $NaHCO_3$ (92.2 mg, 1.10 mmol) and DMP (146 mg, 345 μmol) at room temperature under a nitrogen atmosphere. After the solution was stirred for 50 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the resulting mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (EtOAc/hexane, 10 : 90) on silica gel to give **5** (74.0 mg, 113 μmol, 98%) as a colorless oil.

Methoxymethyl ether 13. To a solution of *eq*-**12** (105 mg, 160 μmol) in CH_2Cl_2 (3.2 mL) were added DIPEA (264 μL, 1.60 mmol) and MOMCl (121 μL, 1.60 mmol) at 0 °C under a nitrogen atmosphere. After the mixture was allowed to warm to room temperature, the solution was stirred for 17 h. After the reaction was quenched with a saturated aqueous solution of NH_4Cl, the resulting mixture was extracted with CH_2Cl_2 (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 10 : 90) on silica gel to afford **13** (112 mg, 160 μmol, quant.) as a colorless oil: $R_f = 0.62$ (EtOAc/hexane, 30 : 70); $[\alpha]_D^{23}$ −27.6 (*c* 0.66, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, two rotamers in a 2 : 1 ratio) δ 7.69–7.60 (4H, m), 7.43–7.25 (11H, m), 4.57 (0.67H, d, $J = 7.0$ Hz), 4.53 (0.33H, d, $J = 7.3$ Hz), 4.50 (2H, s), 4.46 (0.67H, d, $J = 6.8$ Hz), 4.44 (0.33H, d, $J = 7.3$ Hz), 4.10 (0.33H, br s), 3.95–3.76 (1.67H, m), 3.66–3.51 (1.33H, m), 3.51–3.40 (1H, m), 3.30 (3H, s), 3.25 (0.67H, m), 3.16 (1H, td, $J = 10.2$, 4.4 Hz), 2.50 (0.67H, quintet, $J = 5.3$ Hz), 2.37 (0.67H, td, $J = 12.7$, 3.5 Hz), 2.20–2.03 (0.66H, m), 2.03–1.50 (8H, m), 1.45–1.08 (3H, m), 1.34 (3H, s), 1.23 (6H, s), 1.022 (3H, s), 1.015 (6H, s); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, two rotamers in a 2 : 1 ratio) δ 153.3, 152.6, 138.7, 138.4, 135.5, 134.3, 134.20, 134.18, 129.4, 129.3, 128.4, 128.3, 127.6, 127.53, 127.50, 127.4, 95.6, 95.4, 80.8, 80.5, 79.7, 78.9, 73.0, 71.5, 70.7, 68.3, 67.7, 64.82, 64.77, 59.1, 58.5, 55.5, 55.4, 44.7, 42.8, 37.8, 36.9, 33.5, 32.7, 32.10, 32.07, 32.04, 32.02, 28.5, 28.3, 26.91, 26.88, 26.6, 26.1, 20.5, 20.4, 19.2; IR (ATR) 3069, 3046, 3030, 2954, 2929, 2883, 2858, 2822, 1688, 1636, 1589, 1541, 1473, 1455, 1428, 1388, 1371, 1364, 1318, 1300, 1254, 1172, 1143, 1105, 1078, 1038, 998, 939, 915, 884, 863, 823, 805 cm^{-1}; DART-HRMS calcd for $C_{42}H_{60}NO_6Si$ $[(M + H)^+]$ 702.4190, found 702.4196.

Ester 14 (ref. 13). To a solution of **13** (40.6 mg, 57.8 μmol) in MeOH (1.2 mL) was added 10% Pd/C (200 mg, 493 wt%) at room temperature under a hydrogen atmosphere, and the solution was stirred for 4 h. After the mixture was filtered with a pad of Celite, the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to afford a mixture including a desired alcohol, which was used in the next reaction without further purification.

DMN-AZADO (9.2 mg, 55.3 μmol), $NaClO_2$ (81.9 mg, 906 μmol), and NaOCl (5.2 mg, 69.9 μmol) were added to a solution of the mixture including a desired alcohol in MeCN (600 μL) and phosphate buffer (pH 6.8, 190 μL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 22 h, and the reaction was quenched with H_2O. After the resulting mixture was extracted with $CHCl_3$, the organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. A mixture including a desired carboxylic acid was directly used in the following reaction.

To a solution of the mixture including a desired carboxylic acid in DMF (1.2 mL) were added Cs_2CO_3 (13.3 mg, 40.8 μmol) and MeI (4.3 μL, 69.0 μmol) at room temperature under a nitrogen atmosphere. After the solution was stirred for 9 h, the reaction was quenched with a saturated aqueous solution of Na_2CO_3. After the resulting mixture was extracted with EtOAc (×3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash silica gel column chromatography (EtOAc/hexane, 5 : 95) afforded **14** (29.7 mg, 46.4 μmol, 80% in 3 steps) as a colorless oil: $R_f = 0.41$ (EtOAc/hexane, 30 : 70); $[\alpha]_D^{23}$ −21.7 (*c* 0.45, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, two rotamers in a 3 : 1 ratio) δ 7.68–7.61 (4H, m), 7.45–7.30 (6H, m), 4.55 (0.75H, d, $J = 7.0$ Hz), 4.51 (0.25H, d, $J = 7.1$ Hz), 4.44 (1H, d, $J = 7.1$ Hz), 4.28 (0.25H, dd, $J = 8.5$, 4.6 Hz), 4.11 (0.75H, dd, $J = 7.9$, 6.3 Hz), 3.90 (1H, m), 3.71 (0.75H, s), 3.70 (2.25H, s), 3.58 (1H, m), 3.29 (0.75H, s), 3.28 (2.25H, m), 3.12 (1H, m), 2.78–2.63 (0.5H, m), 2.49 (0.75H, ddd, $J = 10.1$, 6.2, 3.1 Hz), 2.27 (0.75H, td, $J = 13.5$, 5.0 Hz), 2.16–1.86 (2H, m), 1.83–1.45 (6H, m), 1.37–1.14 (3H, m), 1.34 (2.25H, s), 1.25 (6.75H, s), 1.03 (2.25H, s), 1.02 (6.75H, s); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, two rotamers in a 3 : 1 ratio) δ 174.0, 173.9, 153.6, 152.2, 135.49, 135.47, 134.5, 134.3, 134.2, 134.1, 129.44, 129.41, 129.39, 129.36, 127.6, 127.52, 127.50, 127.47, 95.5, 95.2, 80.5, 80.4, 80.1, 79.6, 69.3, 68.4, 64.82, 64.80, 61.64, 61.59, 55.5, 55.4, 52.0, 51.8, 44.9, 43.1, 35.0, 33.3, 32.6, 32.2, 32.12, 32.06, 31.9, 30.3, 28.4, 28.0, 27.4, 27.3, 26.9, 26.6, 20.6, 19.2, 19.1; IR (ATR) 3071, 3051, 2950, 2931, 2888, 2859, 2822, 1749, 1701, 1685, 1624, 1590, 1577, 1569, 1558, 1541, 1522, 1507, 1497, 1489, 1473, 1457, 1429, 1389, 1376, 1364, 1327, 1297, 1272, 1257, 1197, 1177, 1146, 1133, 1110, 1082, 1040, 1008, 999, 941, 915, 881, 857, 824, 805 cm^{-1}; DART-HRMS calcd for $C_{36}H_{54}NO_7Si$ $[(M + H)^+]$ 640.3670, found 640.3657.

Alcohol 15. To a solution of **14** (36.1 mg, 56.4 μmol) in THF (282 μL) was added TBAF (63.2 μL, 63.2 μmol, 1.00 M in THF) at 0 °C under a nitrogen atmosphere. After the mixture was

allowed to warm to room temperature, the mixture was stirred for 23 h. After the reaction was quenched with a saturated aqueous solution of NH_4Cl, the resulting mixture was extracted with EtOAc (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 70 : 30) on silica gel to afford **15** (22.6 mg, 56.3 μmol, quant.) as a colorless oil: $R_f = 0.19$ (EtOAc/hexane, 50 : 50); $[\alpha]_D^{24}$ −29.7 (*c* 0.58, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, two rotamers in a 4 : 1 ratio) δ 4.81 (0.2H, d, $J = 7.1$ Hz), 4.78 (0.8H, d, $J = 7.1$ Hz), 4.62 (0.2H, d, $J = 7.2$ Hz), 4.59 (0.8H, d, $J = 7.1$ Hz), 4.39 (0.2H, m), 4.26 (0.8H, m), 3.72 (3H, s), 3.62 (1H, br s), 3.42 (0.6H, s), 3.38 (2.4H, s), 3.23 (1H, m), 3.04 (1H, br s), 2.86 (0.8H, ddd, $J = 8.4$, 6.1, 2.3 Hz), 2.50 (0.2H, ddd, $J = 8.8$, 6.0, 2.2 Hz), 2.27 (0.8H, td, $J = 13.0$, 3.7 Hz), 2.21–2.03 (2.2H, m), 1.94–1.65 (6H, m), 1.65–1.45 (2H, m), 1.31 (1H, m), 1.38 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, two rotamers in a 4 : 1 ratio) δ 173.9, 173.7, 153.8, 152.8, 95.00, 94.97, 81.1, 80.3, 79.8, 79.5, 69.9, 69.0, 63.0, 62.9, 61.9, 61.8, 56.1, 55.9, 52.0, 51.9, 46.8, 45.2, 34.5, 32.8, 32.0, 31.8, 31.7, 31.6, 31.3, 29.8, 28.5, 28.2, 27.1, 26.6, 20.6; IR (ATR) 3463, 2975, 2950, 2931, 2887, 2868, 2824, 1748, 1700, 1684, 1559, 1541, 1520, 1507, 1474, 1456, 1437, 1391, 1365, 1328, 1295, 1276, 1255, 1198, 1175, 1146, 1131, 1120, 1101, 1037, 942, 916, 879, 854, 792 cm^{-1}; DART-HRMS calcd for $C_{20}H_{36}NO_7$ $[(M + H)^+]$ 402.2492, found 402.2501.

Olefin 16 (ref. 14). To a solution of **15** (15.5 mg, 38.6 μmol) in THF (800 μL) were added nBu$_3$P (48.0 μL, 195 μmol) and 2-nitrophenylselenocyanate (43.4 mg, 191 μmol) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 12 h, *m*CPBA (77%, 71.0 mg, 317 μmol) was added to the solution at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$, and the resulting mixture was extracted with $CHCl_3$. The organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford a mixture including a desired olefin, which was used in the next reaction without further purification.

To a solution of the mixture including a desired olefin in CH_2Cl_2 (800 μL) was slowly added TFA (200 μL) at 0 °C under a nitrogen atmosphere. After the mixture was allowed to warm to room temperature, the solution was stirred for 12 h. After the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, the resulting mixture was extracted with $CHCl_3$ (×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash silica gel column chromatography (MeOH/$CHCl_3$, 10 : 90) afforded **16** (9.0 mg, 37.6 μmol, 98% in 2 steps) as a colorless oil: $R_f = 0.50$ (MeOH/$CHCl_3$, 10 : 90); $[\alpha]_D^{27}$ −49.3 (*c* 0.90, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.73 (1H, dt, $J = 16.9$, 10.0 Hz), 5.17 (1H, dd, $J = 17.0$, 1.4 Hz), 5.16 (1H, dd, $J = 10.1$, 1.7 Hz), 3.85 (1H, dd, $J = 8.8$, 5.6 Hz), 3.80 (1H, m), 3.75 (3H, s), 2.38 (1H, dd, $J = 9.1$, 2.7 Hz), 2.19 (1H, m), 1.94 (1H, m), 1.88–1.78 (3H, m), 1.73–1.61 (2H, m), 1.56 (1H, dt, $J = 13.5$, 4.3 Hz), 1.46 (1H, dt, $J = 14.0$, 3.8 Hz), 1.25 (1H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 175.2, 136.7, 118.8, 72.4, 65.8, 58.7, 52.4, 51.7, 36.0, 34.4, 30.3, 28.9, 18.0; IR (ATR) 3282, 3074, 3005, 2930, 2856, 1736, 1699, 1635, 1507, 1456, 1438, 1356, 1339, 1327, 1284, 1260, 1232, 1206, 1153, 1117, 1092, 1074, 1032, 996, 968, 921, 901, 869, 856, 808 cm^{-1}; DART-HRMS calcd for $C_{13}H_{22}NO_3$ $[(M + H)^+]$ 240.1600, found 240.1560.

Silyl ether 4. To a solution of **16** (18.6 mg, 77.7 μmol) in CH_2Cl_2 (1.6 mL) were added TBDPSCl (200 μL, 769 μmol) and imidazole (48.6 mg, 714 μmol) at room temperature under a nitrogen atmosphere. After the solution was stirred for 17.5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl. After the resulting mixture was extracted with MeOH/$CHCl_3$ (10 : 90) (×3), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH/$CHCl_3$, 2 : 98) on silica gel to afford **4** (35.8 mg, 74.9 μmol, 96%) as a colorless oil: $R_f = 0.44$ (MeOH/$CHCl_3$, 2 : 98); $[\alpha]_D^{26}$ −35.1 (*c* 0.40, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.72–7.64 (4H, m), 7.46–7.33 (6H, m), 5.50 (1H, dt, $J = 17.0$, 10.0 Hz), 5.07 (1H, dd, $J = 10.2$, 2.0 Hz), 5.02 (1H, d, $J = 16.8$ Hz), 3.76 (1H, t, $J = 7.5$ Hz), 3.70 (1H, m), 3.68 (3H, s), 2.20 (1H, t, $J = 8.2$ Hz), 1.94 (1H, m), 1.87 (1H, m), 1.74 (1H, m), 1.60–1.43 (3H, m), 1.43–1.12 (4H, m), 1.05 (9H, s); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 175.4, 137.3, 136.02, 135.97, 135.5, 134.5, 134.0, 129.6, 129.5, 127.5, 127.4, 118.8, 74.0, 64.5, 59.1, 51.9, 57.3, 37.4, 33.0, 32.3, 28.8, 27.0, 19.5, 19.2; IR (ATR) 3373, 3071, 3050, 2998, 2932, 2892, 2858, 1737, 1639, 1540, 1523, 1510, 1458, 1429, 1361, 1311, 1282, 1254, 1200, 1158, 1109, 1086, 1029, 1002, 919, 885, 822, 793 cm^{-1}; DART-HRMS calcd for $C_{29}H_{40}NO_3Si$ $[(M + H)^+]$ 478.2777, found 478.2811.

Lactam 3 (ref. 3*i*). To a solution of **4** (13.4 mg, 28.0 μmol) in THF (560 μL) were HMPA (98.0 μL, 563 μmol) and pivalic acid (14.2 mg, 139 μmol). After the solution was cooled to 0 °C, SmI_2 (1.40 mL, 140 μmol, 0.100 M in THF) was added to the solution under a nitrogen atmosphere, and the solution was allowed to warm to room temperature over 2.5 h. After the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, the resulting mixture was extracted with $CHCl_3$ (×3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 50 : 50) on silica gel to give **3** (10.9 mg, 24.3 μmol, 87%) as a colorless oil: $R_f = 0.25$ (MeOH/$CHCl_3$, 2 : 98); $[\alpha]_D^{28}$ −57.1 (*c* 0.55, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74–7.64 (4H, m), 7.47–7.34 (6H, m), 5.47 (1H, dt, $J = 16.9$, 10.1 Hz), 4.97 (1H, dd, $J = 10.2$, 1.8 Hz), 4.83 (1H, dd, $J = 16.8$, 1.4 Hz), 3.88 (1H, br s), 2.40–2.15 (3H, m), 1.93 (1H, m), 1.82–1.56 (3H, m), 1.56–1.22 (7H, m), 1.14 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.9, 136.0, 135.9, 135.1, 133.5, 133.3, 129.9, 129.7, 127.64, 127.60, 118.7, 74.3, 56.7, 55.7, 34.2, 33.2, 31.0, 29.1, 27.1, 19.0, 16.5, 16.0; IR (ATR) 3358, 3207, 3071, 3048, 2932, 2857, 1659, 1589, 1463, 1428, 1406, 1391, 1363, 1335, 1283, 1220, 1184, 1165, 1110, 1084, 1071, 1025, 994, 957, 936, 919, 875, 841, 822, 795 cm^{-1}; DART-HRMS calcd for $C_{28}H_{38}NO_2Si$ $[(M + H)^+]$ 448.2672, found 448.2682.

Conflicts of interest

There are no conflicts to declare.

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11 The reduction of a carbonyl moiety in spirocyclic product **5** was performed using various reduction methods. When compound **5** was allowed to react with $NaBH_4$, the undesired *ax*-**12** was obtained as a major isomer (62%), along with the desired *eq*-**12** (16%). The use of Super-Hydride® (lithium triethylborohydride) also gave *ax*-**12** (76%). In the borohydride reduction of **5**, an equatorial hydride attack could predominate as a result of avoiding the axial alkyl group. In the ^{1}H NMR spectrum of a major rotamer of *ax*-**12**, the coupling pattern of C8-H at 4.18 ppm was observed as a doublet with $J = 2.4$ Hz, showing an equatorial proton. When using Bouveault–Blanc reduction, compound *eq*-**12** was stereoselectively obtained, but the yield was very low (22%). The reduction of **5** under Birch conditions afforded a debenzylated compound of *eq*-**12** in low yield (<30%). The Corey–Bakshi–Shibata (CBS) asymmetric reduction resulted in the recovery of the starting material. The Luche reduction gave *eq*-**12** as a major product (59%, *ax*-**12**: 30%).

12 Compound **5** could be recovered by DMP oxidation and again submitted to the SmI_2-mediated reduction, and after one cycle, the desired *eq*-**12** was obtained in 81% overall yield based on initial loading of the compound **5**. Two cycles gave *eq*-**12** with 90% overall yield.

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