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Stereoselective synthesis of tetrahydroisoquinoline alkaloids: (−)-trolline, (+)-crispin A, (+)-oleracein E

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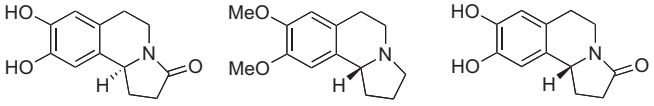
ABSTRACT

Tetrahydroisoquinoline alkaloids, (*S*)-(−)-trolline, (*R*)-(+)-crispin A, and (*R*)-(+)-oleracein E, have been synthesized stereoselectively from the both enantiomers of common intermediate (*S*)-**4** and (*R*)-**4**. The key step in the synthesis include a stereoselective $Bi(OTf)_3$-catalyzed intramolecular 1,3-chirality transfer reaction of chiral non-racemic amino allylic alcohols (*S*)-**6** and (*R*)-**6** to construct both enantiomers of (*E*)-1-propenyl tetrahydroisoquinoline **4**.

1. Introduction

Tetrahydroisoquinoline alkaloids, having a stereocenter at the C-1 carbon, exist widely in nature and are compounds of extensive interest due to their biological and pharmacological properties.[1] Representative tetrahydroisoquinoline alkaloids, such as (*S*)-(−)-trolline (**1**), (*R*)-(+)-crispine A (**2**), (*R*)-(+)-oleracein E (**3**), shown in Fig. 1, have the tricyclic hydropyrrolo[2,1-*a*]isoquinoline core structure with (*R*) and (*S*) configurations at the stereocenter. (−)-Trolline,[2] isolated from the flowers of *Trollius chinensis*, exhibits antibacterial activity against respiratory bacteria, such as *Staphylococcus aureus*, *Staphylcoccus pneumonia*, and *Klesiella pneumoniae*, as well as antiviral activity against influenza viruses A and B. (+)-Crispine A shows significant cytotoxic activity against SKOV3, KB, and HeLa human cancer lines.[3] (+)-Oleracein E (**3**),[4] the antipode of (−)-trolline, was isolated from *Portulaca oleracea L* and exhibits DPPH-radical scavenging activity. Accordingly, significant attention has been focused on the development of a general synthetic approach to obtaining these alkaloids. Although several asymmetric synthetic strategies have already been reported for the preparation of the tricyclic hydropyrrolo[2,1-*a*]isoquinoline core of the alkaloids,[5–7] including the elegant strategy utilizing the allylation of cyclic imines,[6e,f] the development of a stereoselective synthetic methodology for producing both enantiomers of the alkaloids remains an extremely important.



(*S*)-(−)-Trolline **1** (*R*)-(+)-Crispine A **2** (*R*)-(+)-Oleracein E **3**

Fig. 1. Tetrahydroisoquinoline alkaloids.

We have developed an intramolecular 1,3-chirality transfer reaction of the chiral non-racemic-amino allylic alcohol for the synthesis of chiral C-1 substituted tetrahydroisoquinolines.[8] The advantage of intramolecular 1,3-chirality transfer reaction has been considered as the stereoselective synthesis of both enantiomers from (*S*)- and (*R*)-chiral-amino allylic alcohols. In this paper, we describe the asymmetric synthesis of the tricyclic tetrahydroisoquinoline alkaloids (*S*)-(−)-trolline (**1**), (*R*)-(+)-crispine A (**2**), and (*R*)-(+)-oleracein E (**3**) by $Bi(OTf)_3$-catalyzed cyclization via 1,3-chirality transfer.

The retrosynthetic strategy for the synthesis of **1**, **2**, and **3** is outlined in Scheme 1. In our previous report, $Bi(OTf)_3$-catalyzed cyclizations for the oxygen-substituted tetrahydroisoquinoline at the 6 position afforded a high level of 1,3-chirality transfer by the replacement of the methoxy group with the pivaloyl ester. Therefore, the oxygen-functional group at the 6 position of the lactam **4** was selected as the pivaloyl ester. The construction of the tricyclic system utilizes the RCM reaction or the standard lactam formation from **5**. The key step involves the construction of the chiral 1-

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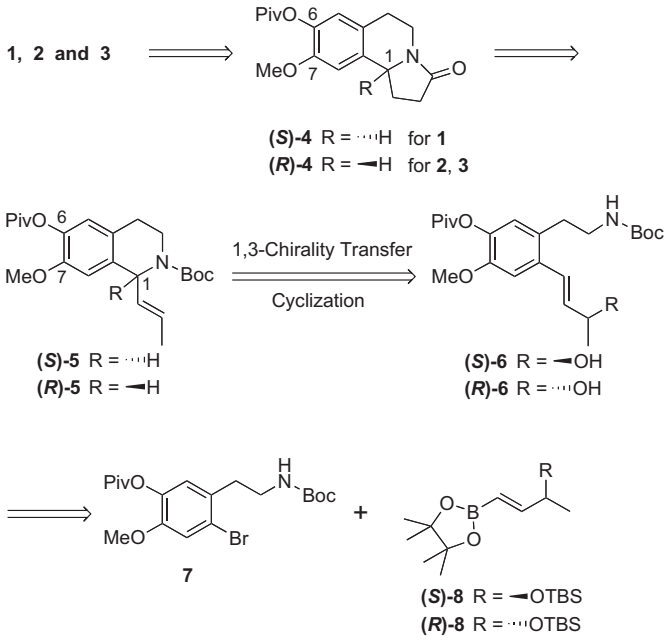
propenyl tetrahydroisoquinolines (*S*)-**5** and (*R*)-**5** from (*S*)-**6** and (*R*)-**6**, respectively, by the $Bi(OTf)_3$-catalyzed 1,3-chirality transfer reaction. The precursors (*S*)-**6** and (*R*)-**6** can be derived by the Suzuki–Miyaura cross coupling of **7** with chiral (*E*)-alkenyl boronates (*S*)-**8**,[9a] (*R*)-**8**,[9b] which are readily prepared from the corresponding alkyne by the hydroboration.



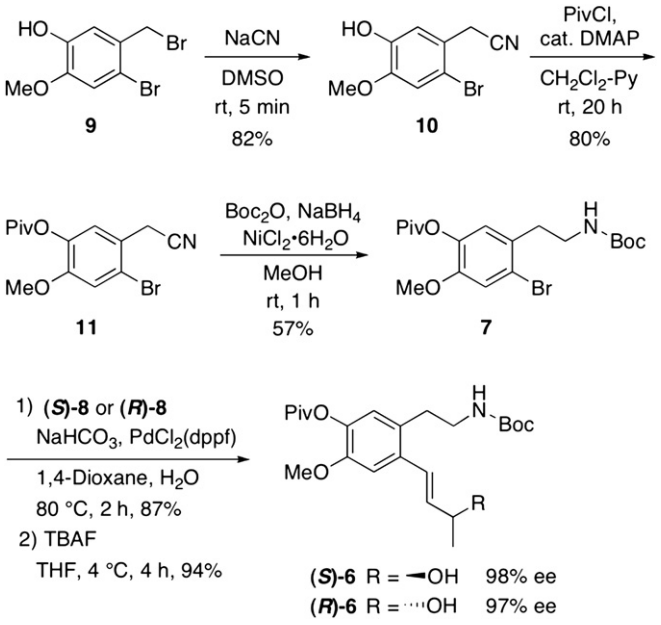
Scheme 1. Retrosynthesis of alkaloids.

2. Results and discussion

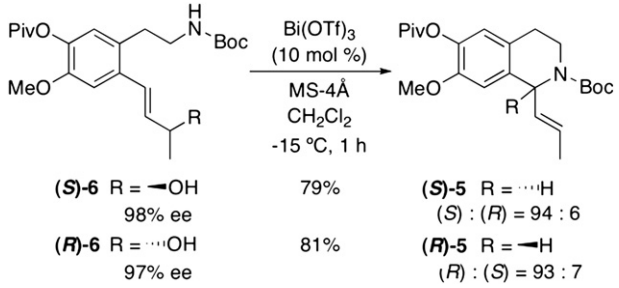
The synthesis of **7**, shown in Scheme 2, was initiated using the bromide **9**,[10] readily prepared from a veratraldehyde in four steps. Cyanation of **9** with NaCN in DMSO afforded **10** in 82% yield. The hydroxy group of **10** was protected as the pivaloyl ester **11** in 80% yield. Reduction of the nitrile with $NaBH_4$ and a catalytic amount of $NiCl_2$ in MeOH followed by protection of the resultant amine with Boc_2O afforded **7** in 57% yield. The $PdCl_2$(dppf)-catalyzed Suzuki–Miyaura cross coupling reaction of **7** and (*S*)-**8** and (*R*)-**8** in aqueous solution at 80 °C provided the corresponding products in 87% yield. Deprotection of the silyl ether by TBAF in THF at 4 °C afforded the corresponding alcohols (*S*)-**6** and (*R*)-**6** in 94% yield.[11]

With amino-alcohols (*S*)-**6** and (*R*)-**6** in hand, $Bi(OTf)_3$-catalyzed cyclization was executed, as shown in Scheme 3. Treatment of (*S*)-**6** with 10 mol % of $Bi(OTf)_3$ in the presence of MS-4 Å, at −15 °C, in CH_2Cl_2, afforded the desired (*E*)-1-propenyl tetrahydroisoquinoline in 79% yield. The optical purity of (*S*)-**5** was determined by chiral stationary phase HPLC analysis to be (*S*)/(*R*)=94:6 by comparison with the corresponding racemates, which was prepared by the same route from racemic boronate **8**. In a similar manner, (*R*)-**5** was obtained with a ratio of (*R*)/(*S*)=93:7.

The initial strategy to construct the pyrrolidinone ring or pyrrolidine ring utilized an RCM reaction, as shown in Scheme 4. Deprotection of the *N*-Boc group of (*S*)-**5** with TMSCl and NaI gave the amine **12** in 91% yield. Conversion of the amine **12** to the acryl amide under the standard conditions was followed by execution of the RCM reaction under several conditions employing Grubbs catalysts; however, no reaction took place. On the other hand, the RCM reaction of the bis-allyl amine that was prepared from the amine **12** proceeded in the presence of 10 mol % of second generation Grubbs catalyst in CH_2Cl_2. However, the pyrrole **14**, which might have been

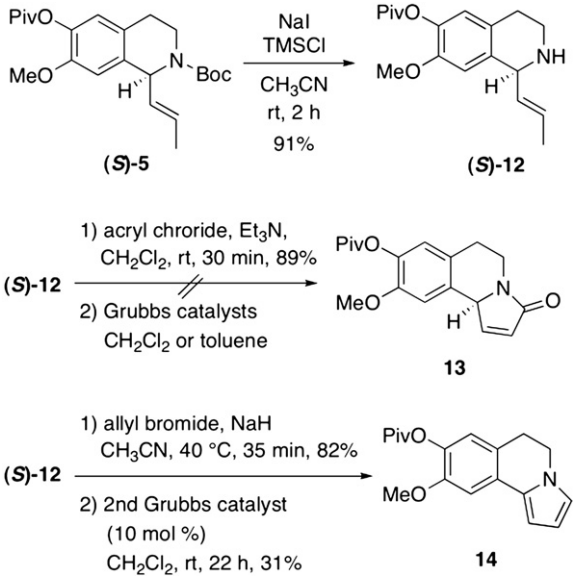


Scheme 2. Synthesis of precursors (*S*)-**6** and (*R*)-**6**.



Scheme 3. $Bi(OTf)_3$-catalyzed cyclization.

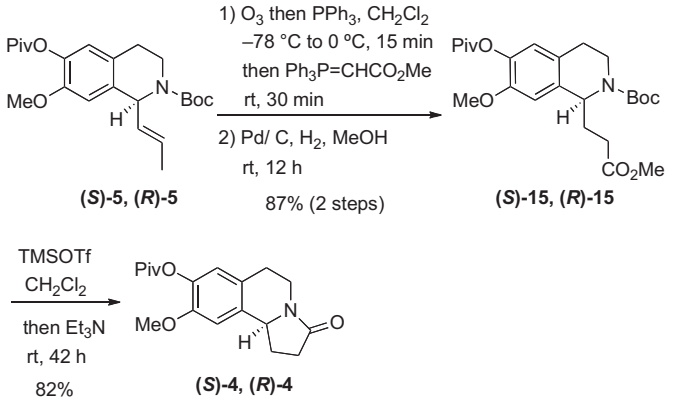
formed from the desired product by oxidation, was obtained in 31% yield instead of 3-pyrroline.[12] The additive effect of $Ti(OiPr)_4$[13] or 1,4-benzoquinone[14] in the reaction did not prevent the oxidation to



Scheme 4. RCM reaction.

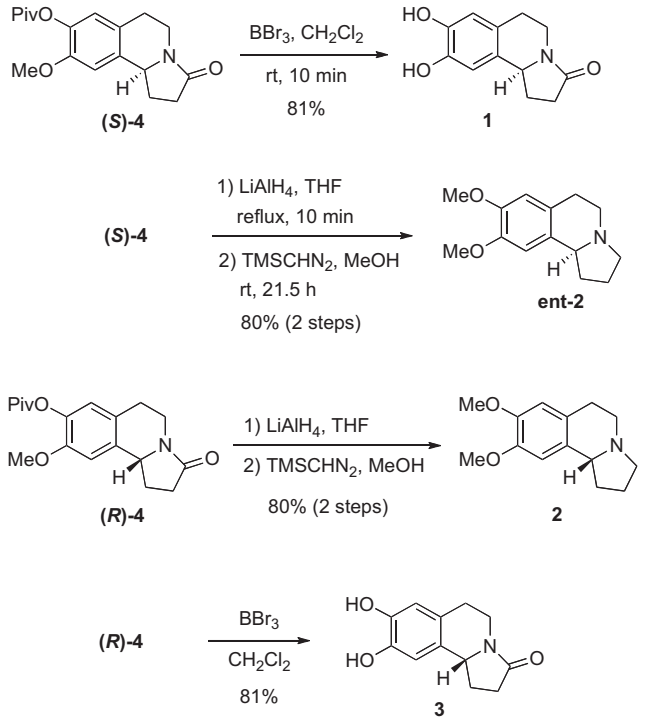
afford the desired product. The use of other catalysts, such as Hoveyda–Grubbs and Schrock catalysts resulted in a non-improvement.

Transformation of the propenyl unit in (*S*)-**5** to the propionate unit, followed by the formation of lactam (*S*)-**4** was subsequently explored, as shown in Scheme 5. Oxidative cleavage of the alkenyl bond of (*S*)-**5** with ozone followed by Wittig reaction of the resulting aldehyde with phosphorane, and hydrogenation gave the saturated ester (*S*)-**15** in 87% yield in two steps. Deprotection of the Boc group by TMSOTf followed by treatment with Et_3N gave lactam (*S*)-**4** in 82% yield. Meanwhile, lactam (*R*)-**4** was obtained from (*R*)-**5** in the same three steps.



Scheme 5. Lactam formation.

Finally, deprotection of the pivaroly and methyl groups of (*S*)-**4** by the treatment with BBr_3 in CH_2Cl_2 was achieved to afford (*S*)-(−)-trolline (**1**) in 81% yield as shown in Scheme 6. On the other hand, reduction of (*S*)-**4** with $LiAlH_4$ in THF followed by the methylation of the resulting catechol with $TMSCHN_2$ provided the antipode of natural isomer of (*R*)-(+)-crispine A, *ent*-**2**, in 80% yield in two steps. The synthesis of (*R*)-(+)-crispine A (**2**), and (*R*)-(+)-oleracein E (**3**) have been accomplished by the same sequences from (*R*)-**4**.



Scheme 6. Completion of the synthesis of alkaloids **1**, **2**, **3**, and *ent*-**2**.

The spectra of synthetic **1** and **2** were in accordance with those of natural (*S*)-(−)-trolline[2] and (*R*)-(+)-crispine A[3], respectively. The specific rotations of synthetic **1** ($[\alpha]_D^{25}$ −204.1 (*c* 0.4, MeOH)) and **2** ($[\alpha]_D^{25}$ +92.7 (*c* 0.8, $CHCl_3$)) were in agreement with the data of natural (−)-trolline ($[\alpha]_D^{25}$ −197 (*c* 0.8, MeOH))[2] and (+)-crispine A ($[\alpha]_D^{25}$ +100.4 (*c* 1.0, $CHCl_3$)),[6a] respectively.

3. Conclusions

In summary, the total synthesis of (*S*)-(−)-trolline (**1**), (*R*)-(+)-crispine A (**2**), and (*R*)-(+)-oleracein E (**3**) was achieved from **9** in ten and eleven steps, respectively. The $Bi(OTf)_3$-catalyzed cyclizations via 1,3-chirality transfer have been shown to be potentially useful for the stereoselective synthesis of C-1 substituted tetrahydroisoquinoline alkaloids. Synthesis of additional analogs of alkaloids and their biological tests are currently underway.

4. Experimental section

4.1. General methods

All melting points were measured on a Yanaco MP-J3 and are uncorrected. The infrared spectra were recorded on a JASCO FT/IR-400. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL 500, or Varian Inova Unity XL-400, or JEOL JNM-AL 300 spectrometer in parts per million downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. Optical rotations were measured on a JASCO P-2200. Chiral HPLC analysis was performed on a JASCO PU-2080 and UV-2075 or Shimazu 6A. Mass spectrometric was recorded on a JEOL JMS-GC MATE, or JEOL JMS-SSX 102A QQ. Elemental analyses was recorded on a Perkin–Elmer 2400 (N241-03) CHN analyzer. All reactions were carried out under an N_2 atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates ($60F_{254}$) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. Nacalai silica gel 60 (0.040–0.063 cm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm with Wakogel B-5F. THF was distilled from sodium/benzophenone ketyl. MeCN (acetonitrile), DCM (CH_2Cl_2) were distilled from calcium hydride. Pyridine and DMSO were distilled from CaH_2 under reduced pressure. All reagents were purchased from Aldrich, TCI, Nacalai, Wako, Kishida, or Kanto Chemical Co. Ltd.

*4.1.1. 2-Bromo-5-hydroxy-4-methoxyphenyl-acetonitrile (**10**)*[15]. To the stirred solution of NaCN (866 mg, 17.7 mmol) in DMSO (25 ml) was added the solution of **9** (4.75 g, 16.1 mmol) in DMSO (20 ml) at room temperature, and the resultant mixture was stirred at the same temperature for 5 min. The reaction mixture was poured into H_2O and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (15% EtOAc in hexane) to give **10** (3.2 g, 82%) as a colorless solid. R_f=0.50 (50% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (s, 1H), 7.04 (s, 1H), 5.63 (s, 1H), 3.90 (s, 3H), 3.73 (s, 2H).

*4.1.2. 2-Bromo-5-(2,2-dimethylpropanoyloxy)-4-methoxy-phenyl-acetonitrile (**11**).* To the stirred solution of **10** (4.57 g, 18.9 mmol) in DCM (25 ml) were added pyridine (5.5 ml, 68.0 mmol), DMAP (230 mg, 1.89 mmol), and pivaloyl chloride (2.8 ml, 22.7 mmol) at 0 °C, and the resultant mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with satd NH_4Cl aq and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The

residue was purified by silica gel column chromatography (20% EtOAc in hexane) to give **11** (4.93 g, 80%) as a colorless solid. R_f=0.75 (50% EtOAc in hexane); mp 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.15 (s, 1H), 3.81 (s, 3H), 3.76 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 151.8, 139.9, 123.8, 121.8, 120.1, 116.9, 116.9, 56.3, 39.1, 27.1, 24.0; IR ($CHCl_3$, cm^{-1}) 3022, 2253, 2976, 1753; EI-MS *m*/*z* 325 (M^+); EI-HRMS calcd for $C_{14}H_{16}BrNO_3$ *m*/*z* 325.0313, found: 325.0309; Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; N, 4.29. Found: C, 51.74; H, 5.12; N, 4.24.

*4.1.3. N-Boc-N-[2-(2-bromo-5-(2,2-dimethylpropanoyloxy)-4-methoxyphenyl)ethyl]amine (**7**).* To the stirred solution of **11** (120 mg, 0.37 mmol) in MeOH (6.0 ml) were added Boc_2O (104 mg, 0.48 mmol), $NiCl_2\cdot 6H_2O$ (4.4 mg, 0.018 mmol), and $NaBH_4$ (95 mg, 2.58 mmol) at 0 °C, and the resultant mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with satd $NaHCO_3$ aq and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (5% Et_2O in benzene) to give **7** (89.8 mg, 57%) as a colorless solid. R_f=0.43 (10% Et_2O in benzene); mp 125–126 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (s, 1H), 6.78 (s, 1H), 4.56 (br s, 1H), 3.68 (s, 3H), 3.24 (td, *J*=6.6, 6.6 Hz, 2H), 2.77 (t, *J*=6.6 Hz, 2H), 1.34 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 155.8, 150.3, 139.4, 130.6, 124.6, 120.7, 116.8, 79.1, 56.2, 40.2, 39.0, 35.4, 28.3, 27.1; IR ($CHCl_3$, cm^{-1}) 3018, 2978, 2935, 1753, 1706; EI-MS *m*/*z* 429 (M^+); EI-HRMS calcd for $C_{19}H_{28}BrNO_5$ *m*/*z* 429.1150, found: 429.1155; Anal. Calcd for $C_{19}H_{28}BrNO_5$: C, 53.03; H, 6.56; N, 3.25. Found: C, 53.11; H, 6.29; N, 3.45.

*4.1.4. (3S)-(E)-N-Boc-N-[2-[5-(2,2-dimethyl-propanoyl-oxy)-2-(3-hydroxybut-1-enyl)-4-methoxy-phenyl]ethyl]amine ((S)-**6**).* To a stirred solution of **7** (24 mg, 0.056 mmol) in 1,4-dioxane (1.0 ml) were added boronate (*S*)-**8** (23 mg, 0.07 mmol), $NaHCO_3$ (14 mg, 0.167 mmol), and H_2O (0.5 ml). After the addition of $PdCl_2$(dppf) (2.3 mg, 2.79 μmol), the mixture was stirred at 80 °C for 2 h. The reaction mixture was poured into H_2O and the aqueous layer was extracted with EtOAc. The organic extracts was washed with brine and dried over $MgSO_4$, filtered, and evaporated. The residue was purified by preparative thin-layer chromatography (5% EtOAc in hexane) to give (3*S*)-(*E*)-*N*-Boc-*N*-[2-[5-(2,2-dimethyl-propanoyl-oxy)-2-(3-*tert*-butyl dimethylsilyloxy-but-1-enyl)-4-methoxy-phenyl]ethyl]-amine (26 mg, 87%) as a colorless oil. R_f=0.63 (20% EtOAc in hexane); $[\alpha]_D^{20}$ −23.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.99 (s, 1H), 6.77 (s, 1H), 6.73 (d, *J*=15.5 Hz, 1H), 6.06 (dd, *J*=15.5, 5.5 Hz, 1H), 4.55 (br s, 1H), 4.49 (qd, *J*=5.5, 5.5 Hz, 1H), 3.81 (s, 3H), 3.31–3.21 (m, 2H), 2.83–2.72 (m, 2H), 1.43 (s, 9H), 1.35 (s, 9H), 1.31 (d, *J*=6.4 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 155.8, 149.8, 139.4, 136.5, 134.5, 128.9, 124.8, 124.1, 110.2, 79.1, 69.3, 56.0, 41.2, 39.0, 32.5, 28.4, 27.2, 25.9, 24.7, 18.3, −4.6, −4.7; IR (neat, cm^{-1}) 3399, 2959, 1754, 1714; EI-MS *m*/*z* 535 (M^+); EI-HRMS calcd for $C_{29}H_{49}NO_6Si$ *m*/*z* 535.3329, found: 535.3334. To a stirred solution of (3*S*)-(*E*)-*N*-Boc-*N*-[2-[5-(2,2-dimethyl-propanoyl-oxy)-2-(3-*tert*-butyldimethylsilyloxy-but-1-enyl)-4-methoxy-phenyl]ethyl]amine (26 mg, 0.048 mmol) in THF (2.6 ml) was added TBAF (0.073 ml, 1.0 M) at 0 °C, and the resultant mixture was stirred at 4 °C for 4 h. The reaction mixture was quenched with satd NH_4Cl aq and the aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (40% EtOAc in hexane) to give (*S*)-**6** (19 mg, 94%) as a colorless oil. R_f=0.48 (50% EtOAc in hexane); $[\alpha]_D^{20}$ +6.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.97 (s, 1H), 6.87 (d, *J*=15.7 Hz, 1H), 6.76 (s, 1H), 6.09 (dd, *J*=15.7, 5.4 Hz, 1H), 4.77 (br s, 1H), 4.51 (m, 1H), 3.80 (s, 3H), 3.33–3.16 (m, 2H), 3.02 (br s, 1H), 2.79–2.72 (m, 2H), 1.43 (s, 9H), 1.37 (d, *J*=6.4 Hz, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 156.0, 149.9, 139.4, 136.3, 134.7, 128.9, 126.1, 123.9, 110.4, 79.5, 68.4, 56.0, 41.3, 39.0, 33.5, 28.4, 27.2, 23.2; IR ($CHCl_3$, cm^{-1}) 3019, 2979, 1747, 1703; EI-MS *m*/*z* 421 (M^+); EI-HRMS calcd for $C_{23}H_{35}NO_6$ *m*/*z* 421.2464, found: 421.2467.

*4.1.5. (1S)-(E)-N-Boc-6-(2,2-dimethyl-propanoyl-oxy)-7-meth oxy-1-(prop-1-enyl)-1,2,3,4-tetrahydro-isoquinoline ((S)-**5**).* To the mixture of $Bi(OTf)_3$ (2.4 mg, 3.73 μmol) and MS-4 Å (31 mg) in DCM (0.4 ml) was added the solution of (*S*)-**6** (15.7 mg, 0.037 mmol) in DCM (0.4 ml) at −15 °C, and the resultant mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with satd $NaHCO_3$ aq and filtered, the aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by preparative thin-layer chromatography (20% EtOAc in hexane) to give (*S*)-**5** (11.8 mg, 79%) as a colorless solid. Mp <30 °C; R_f=0.50 (20% EtOAc in hexane); $[\alpha]_D^{20}$ +109.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.75 (s, 1H), 6.64 (s, 1H), 5.58 (dd, *J*=15.5, 5.5 Hz, 1H), 5.52–5.47 (m, 2H), 4.10 (m, 1H), 3.74 (s, 3H), 3.11 (m, 1H), 2.79 (m, 1H), 2.60 (m, 1H), 1.67 (d, *J*=6.0 Hz, 3H), 1.47 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 154.4, 149.7, 138.7, 133.6, 130.6, 127.4, 126.9, 122.5, 111.7, 79.5, 56.3, 55.9, 38.9, 37.0, 28.4, 27.7, 27.1, 17.5; Enantiometric excess: 88%, determined by HPLC (Daicel Chiralcel OD-H, hexane/isopropanol=98.75/1.25, flow rate 0.3 ml/min, *T*=20 °C, 254 nm): t_S=20.8 min ((*S*)-**5**), t_R=26.1 min ((*R*)-**5**); IR ($CHCl_3$, cm^{-1}) 3019, 2978, 1748, 1683, 1216; EI-MS *m*/*z* 403 (M^+); EI-HRMS calcd for $C_{23}H_{33}NO_5$ *m*/*z* 403.2358, found: 403.2367; Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.49; H, 8.28; N, 3.51. (*R*)-**5**: $[\alpha]_D^{20}$ −100.0 (*c* 1.00, $CHCl_3$).

*4.1.6. (1S)-(E)-6-(2,2-Dimethylpropanoyl)-7-methoxy-1-(prop-1-enyl)-1,2,3,4-tetrahydro-isoquinoline ((S)-**12**).* To a stirred solution of (*S*)-**5** (113 mg, 0.28 mmol) in MeCN (5 ml) were added NaI (84 mg, 0.56 mmol) and TMSCl (70 μL, 0.56 mmol) at room temperature, and the resultant mixture was stirred at the same temperature for 2 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by preparative thin-layer chromatography (10% MeOH in $CHCl_3$) to give (*S*)-**12** (77.0 mg, 91%) as a yellow oil. R_f=0.36 (10% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ +13.0 (*c* 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.61 (s, 1H), 5.80 (dq, *J*=15.3, 6.4 Hz, 1H), 5.65 (ddd, *J*=15.3, 7.5, 1.5 Hz, 1H), 4.68 (d, *J*=7.5 Hz, 1H), 4.51 (br s, 1H), 3.73 (s, 3H), 3.32 (m, 1H), 3.17 (m, 1H), 2.93–2.78 (m, 2H), 1.76 (d, *J*=6.4 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 149.6, 139.4, 132.7, 132.2, 129.7, 125.5, 122.9, 111.4, 58.1, 56.0, 40.0, 39.0, 27.2, 26.6, 17.8; IR (neat, cm^{-1}) 2969, 1750, 1620, 1509, 1271, 1122; EI-MS *m*/*z* 303 (M^+); EI-HRMS calcd for $C_{18}H_{25}NO_3$ *m*/*z* 303.1834, found: 303.1826.

*4.1.7. 5,6-Dihydro-8-(2,2-dimethylpropanoyloxy)-9-methoxy pyrrolo [2,1-a]isoquinoline (**14**)*[16]. To a stirred solution of (*S*)-**12** (13.4 mg, 0.044 mmol) in MeCN (0.5 ml) were added NaH (1.8 mg, 0.044 mmol, 60% in oil) and 3-bromopropene (4.2 μL, 0.049 mmol) at room temperature, and the resultant mixture was stirred at 40 °C for 35 min. The reaction mixture was quenched with satd NH_4Cl aq and the aqueous layer was extracted with the solution (10% MeOH in EtOAc). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by preparative thin-layer chromatography (10% EtOAc in hexane) to give (1*S*)-(*E*)-2-allyl-6-(2,2-dimethylpropanoyl)-7-methoxy-1-(prop-1-enyl)-1,2,3,4-tetrahydro-isoquinoline (12.4 mg, 82%) as a yellow oil. R_f=0.36 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.63 (s, 1H), 5.91 (dddd, *J*=17.1, 10.0, 7.2, 5.5 Hz, 1H), 5.65 (dq, *J*=15.3, 6.3 Hz, 1H), 5.47 (ddq, *J*=15.3, 8.1, 1.5 Hz, 1H), 5.25–5.11 (m, 2H), 3.97 (d, *J*=8.1 Hz, 1H), 3.73 (s, 3H), 3.45 (m, 1H), 3.14–2.96 (m, 2H), 2.88–2.71 (m, 2H), 2.53 (m, 1H), 1.76 (dd, *J*=6.3, 1.5 Hz, 3H),

1.35 (s, 9H). To a stirred solution of (1*S*)-(*E*)-2-allyl-6-(2,2-dimethylpropan-oyl)-7-methoxy-1-(prop-1-enyl)-1,2,3,4-tetrahydro-isoquinoline (12.4 mg, 0.0361 mmol) in DCM (2 ml) was added Grubbs catalyst second generation (9.2 mg, 0.011 mmol) at room temperature, the resultant mixture was stirred at the same temperature for 22 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by preparative thin-layer chromatography (10% EtOAc in hexane) to give **14** (3.3 mg, 31%) as a blue oil. R_f=0.80 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.83 (s, 1H), 6.67 (dd, *J*=2.6, 1.7 Hz, 1H), 6.46 (dd, *J*=3.7, 1.5 Hz, 1H), 6.21 (dd, *J*=3.7, 2.6 Hz, 1H), 4.05 (t, *J*=6.4 Hz, 2H), 3.64 (s, 3H), 2.98 (t, *J*=6.4 Hz, 2H), 0.37 (s, 9H); IR (neat, cm^{-1}) 2972, 1748, 1711, 1505, 1127; EI-MS *m*/*z* 299 (M^+); EI-HRMS calcd for $C_{18}H_{21}NO_3$ *m*/*z* 299.1521, found: 299.1515.

*4.1.8. (1S)-N-Boc-6-(2,2-dimethylpropanoyloxy)-7-methoxy-1-(3-methoxy-3-oxopropyl)-1,2,3,4-tetrahydro-isoquinoline ((S)-**15**).* The stirred solution of (*S*)-**5** (368 mg, 0.912 mmol) in DCM (15 ml) was bubbled a stream of ozone at −78 °C for 2 min. N_2 gas was bubbled through the reaction mixture for 5 min, and the reaction mixture was stirred for 15 min at 0 °C after the addition of PPh_3 (915 mg, 2.74 mmol). After the addition of methyl (triphenylphosphoranylidene)acetate (957 mg, 3.65 mmol), the resulting mixture was stirred at room temperature for 30 min the reaction mixture was quenched with satd NH_4Cl aq and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was passed through a short column of silica gel. After the removal of solvent, the residue dissolved in MeOH (15 ml) and treated with Pd on carbon (40 mg). The mixture was stirred at room temperature for 12 h under the atmosphere of H_2 gas and diluted with $CHCl_3$, filtrated, then evaporated. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give (*S*)-**15** (355 mg, 87% in two steps) as a colorless solid. Mp 60–66 °C; R_f=0.23 (10% EtOAc in hexane); $[\alpha]_D^{20}$ +76.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); the compound exists as a 1.5:1 mixture of carbamate rotamers; signals corresponding to the major rotamer: δ 6.74 (s, 2H), 5.06 (m, 1H), 4.20 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.05 (m, 1H), 2.82 (m, 1H), 2.61 (m, 1H), 2.54–2.38 (m, 2H), 2.15–1.97 (m, 2H), 1.46 (s, 9H), 1.35 (s, 9H); representative signals corresponding to the minor rotamer: δ 6.74 (s, 2H), 5.17 (m, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.19 (m, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.54–2.38 (m, 2H), 2.15–1.97 (m, 2H), 1.46 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$); signals corresponding to both rotamers: δ 176.8, 173.6, 155.1, 154.6, 149.5, 138.8, 135.6, 135.3, 126.6, 126.3, 122.8, 122.6, 111.2, 111.0, 80.1, 79.7, 56.0, 53.9, 53.3, 51.5, 39.0, 38.1, 36.3, 31.4, 31.0, 30.6, 28.3, 27.6, 27.3, 27.1; IR ($CHCl_3$, cm^{-1}) 2970, 2935, 1753, 1733, 1691; EI-MS *m*/*z* 449 (M^+); EI-HRMS calcd for $C_{24}H_{35}NO_7$ *m*/*z* 449.2413, found: 449.2418; Anal. Calcd for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85; N, 3.12. Found: C, 64.36; H, 7.86; N, 3.09. (*R*)-**15**: $[\alpha]_D^{20}$ −76.9 (*c* 1.00, $CHCl_3$).

*4.1.9. (10bS)-8-(2,2-Dimethylpropanoyloxy)-9-methoxy-1,5,6,10b-tetrahydro-2H-pyrrolo[2,1-a]isoquinolin-3-one ((S)-**4**).* To a stirred solution of **15** (60.9 mg, 0.14 mmol) in DCM (6 ml) were added TMSOTf (75 μL, 0.406 mmol), and after a while, Et_3N (113 μL, 0.81 mmol) at room temperature, the resultant mixture was stirred at the same temperature for 42 h. The reaction mixture was quenched with satd NH_4Cl aq and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to give (*S*)-**4** (35.2 mg, 82%) as a colorless solid. Mp 170–172 °C; R_f=0.57 (10% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ −174 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79 (s, 1H), 6.64 (s, 1H), 4.74 (t, *J*=7.8 Hz, 1H), 4.28 (ddd, *J*=12.6, 6.0, 2.1 Hz, 1H), 3.79 (s, 3H), 3.01 (ddd, *J*=12.6, 12.6, 4.4 Hz, 1H), 2.85 (m, 1H), 2.70–2.44 (m, 4H), 1.87 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 173.1, 150.2, 139.4, 135.4, 125.8, 123.1, 108.7, 56.7, 56.1, 39.0, 36.9, 31.7, 27.6, 27.6, 27.2; IR ($CHCl_3$, cm^{-1}) 3018, 1749, 1680, 1510, 1123; EI-MS *m*/*z* 317 (M^+); EI-HRMS calcd for $C_{18}H_{23}NO_4$ *m*/*z* 317.1627, found: 317.1622; Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.81; H, 7.21; N, 4.20. (*R*)-**4**: $[\alpha]_D^{20}$ +175 (*c* 1.0, $CHCl_3$).

*4.1.10. (S)-Trolline (**1**) and (R)-oleracein E (**3**).* To a stirred solution of (*S*)-**4** (31.6 mg, 0.10 mmol) in DCM (2 ml) was added BBr_3 (28 μL, 0.30 mmol), and the resultant mixture was stirred at room temperature for 10 min. The reaction mixture was quenched with H_2O and the aqueous layer was extracted with the solution (25% MeOH in $CHCl_3$). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **1** (17.6 mg, 81%) as a colorless solid: $[\alpha]_D^{20}$ −204 (*c* 0.44, MeOH), lit.,[2] $[\alpha]_D^{20}$ −197 (*c* 0.8, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (br s, 2H), 6.51 (s, 1H), 6.49 (s, 1H), 4.57 (t, *J*=7.8 Hz, 1H), 3.95 (m, 1H), 2.91 (m, 1H), 2.63–2.46 (m, 3H), 2.40 (m, 1H), 2.21 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 144.2, 144.0, 128.4, 123.7, 115.4, 111.7, 55.6, 36.6, 31.3, 27.4, 27.3; IR (MeOH, cm^{-1}) 3121, 2726, 1666, 1278; EI-MS *m*/*z* 219 (M^+); EI-HRMS calcd for $C_{12}H_{13}NO_3$ 219.0895, found: 219.0891. Compound **3**: $[\alpha]_D^{20}$ +187 (*c* 0.44, MeOH), lit.,[4] $[\alpha]_D^{20}$ +61.1 (*c* 0.32, MeOH).

*4.1.11. (R)-Crispine A (**2**) and ent-**2**.* To a stirred solution of **4** (30 mg, 0.095 mmol) in THF (2 ml) was added $LiAlH_4$ (17.9 mg, 0.47 mmol), and the resultant mixture was refluxed for 10 min. The reaction mixture was quenched with satd Na_2SO_4 aq and filtered, the filtrate was evaporated. The residue dissolved in MeOH (2 ml) and treated with $TMSCHN_2$ (2.2 ml, 0.6 M) at room temperature, the resultant mixture was stirred at the same temperature for 21.5 h. After the removal of solvent, the residue was purified by neutral aluminum column chromatography (50% EtOAc in hexane) to give **2** (17.7 mg, 80%) as a colorless solid. Mp 53–55 °C; $[\alpha]_D^{20}$ +92.7 (*c* 0.86, $CHCl_3$), lit.,[6a] $[\alpha]_D^{20}$ +100.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.60 (s, 1H), 6.56 (s, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.42 (t, *J*=8.2 Hz, 1H), 3.18 (m, 1H), 3.10–2.98 (m, 2H), 2.73 (m, 1H), 2.63 (m, 1H), 2.56 (m, 1H), 2.31 (m, 1H), 1.99–1.80 (m, 2H), 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 147.2, 130.9, 126.2, 111.3, 108.8, 62.9, 56.0, 55.9, 53.1, 48.3, 30.5, 28.0, 22.2; IR ($CHCl_3$, cm^{-1}) 3019, 2938, 2400, 1611, 1512, 1254; EI-MS *m*/*z* 234 (M^++H); EI-HRMS (CI^+) calcd for $C_{14}H_{20}NO_2$ *m*/*z* 234.1494, found: 234.1490. *ent*-**2**: $[\alpha]_D^{20}$ −91.9 (*c* 0.58, $CHCl_3$).

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16. The compound **14** in the solution gradually decomposed to several products.