Chinese Journal of Chemistry, **2004**, *22*, 365—370 **Article**

Synthesis of (2*R*,3a*R*,8a*R*)-6-Chloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic Acid Methyl Ester by Reductive Cyclization

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A synthesis of (2*R*,3a*R*,8a*R*)-6-chloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (**1**) was achieved. An aldol reaction with Garner aldehyde, a hydroxyl introduction by Davis reagent, and a reductive intramolecular ring-closure reaction were served as the key steps. This piece of work provides a new way to synthesize the analogues of hexahydropyrrolo[2,3-*b*]indole, starting from readily available chemical substrates and inexpensive reagents.

Keywords aldol reaction, Davis oxidation, reductive ring-closure reaction, indole derivative, anticancer activity

Introduction

Pyrroloindole derivatives exist in the natural products extensively.[1-2] They have been found to exhibit various activities including antiviral, antitoxic and antibiotic ones. Much attention was paid by synthetic chemists for these challenging structural features and biological interests. Most of existing methods[3b-d] for generating the compounds with core structure of (2*R*, 3a*R*,8a*R*)-6-chloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*] indole-2-carboxylic acid methyl ester (**1**) have suffered from problems with poor yields and lack of stereo-controls. One notable exception was developed by Danishefsky and coworker,[3a] using dimethyldioxirane (DMDO) oxidation of tryptophan derivatives to give both *anti-cis* and *syn-cis* isomers of [2,3-*b*]pyrroloindole derivatives. More recently, a novel entrance was reported by Ley and coworkers,[3e] using selenocyclization and oxidative deselenation of the protected tryptophan derivative to afford the *syn-cis* pyrroloindole derivatives. Herein, we report our recent elaboration on the synthesis of (2*R*,3a*R*, 8a*R*)-6-chloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]idole-2-carboxylic acid methyl ester (**1**). The presented strategy and synthetic route provide the chemical com-

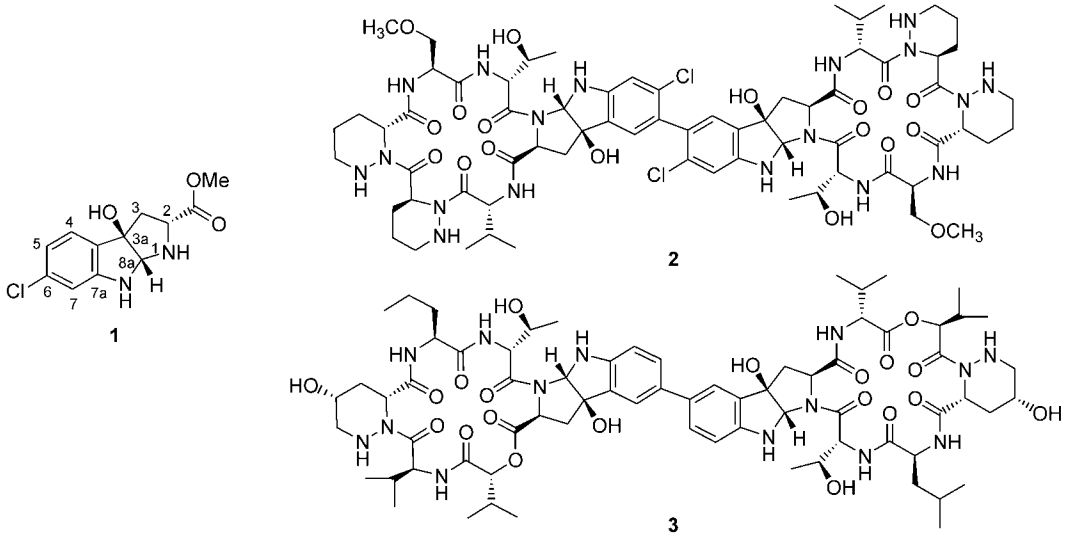

Figure 1 Chemical structures of (2*R*,3a*R*,8a*R*)-6-chloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (**1**), chloptosin (**2**) and himastatin (**3**).

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munity another choice to synthesize the *anti-syn* 3a-hydroxy-pyrroloindole derivatives. It is worthy noting here that, this kind of structures are also key subunits of some biologically important natural cyclic peptides, including chloptosin (**2**)[4] and himastatin (**3**)[3a] (Figure 1).

Results and discussion

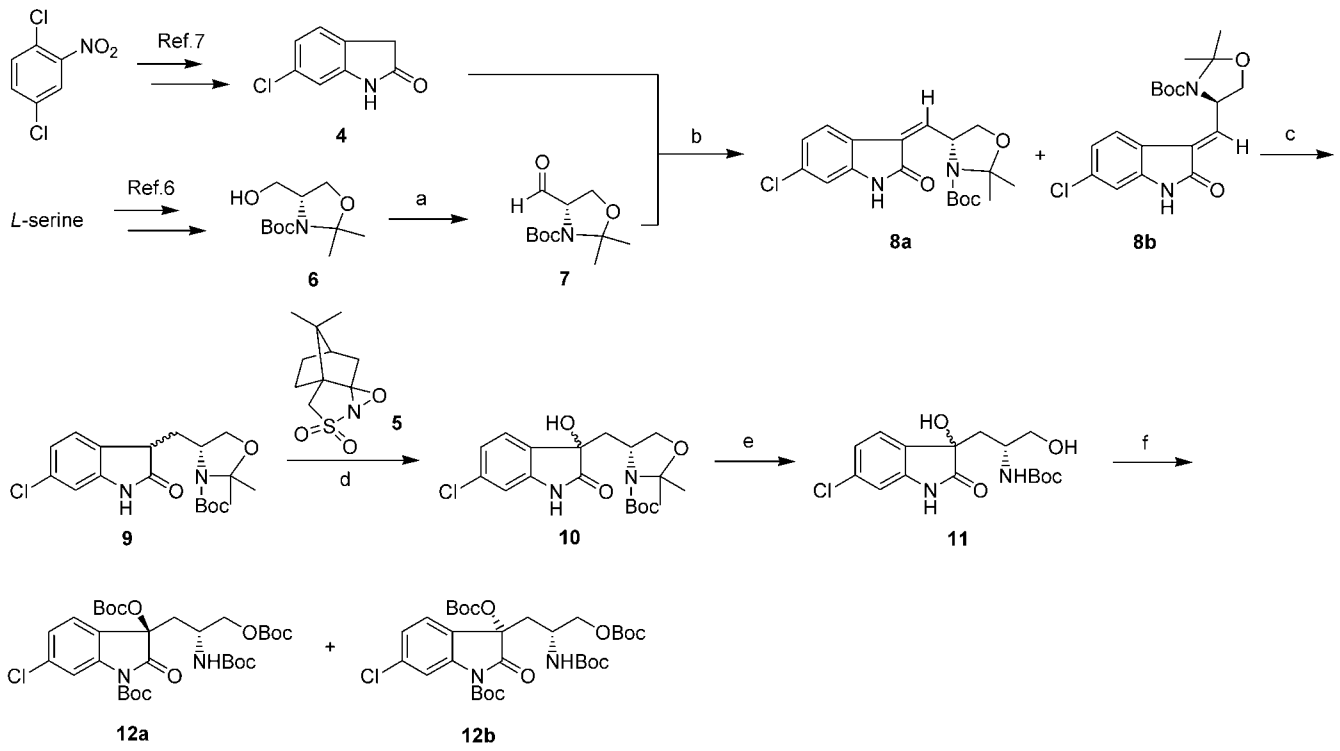
The synthesis started from *L*-serine, which was converted into the protected amino alcohol **6** as the reference procedures.[5] The other segment, 6-chloro-oxindole (**4**) could also be accessed by a direct method from 2,5-dichloronitrobenzene,[6] in which the chlorine atom was pre-introduced in starting material to avoid the complexity in chlorination in later stage. Treatment of **4** with LDA and HMPA followed by addition of freshly prepared Garner's aldehyde **7** at −78 ℃ gave the aldol adducts, which were immediately subjected to MsCl and Et_3N in the same pot to afford the isomeric olefins **8** (E ∶ Z=3.5 ∶ 1).[7] The C=C double bonds of **8a** and **8b** were then reduced by $NaBH_4$ in EtOH at 0 ℃, providing the diastereomeric mixture **9** (ratio 1 ∶ 1.6, measured by HPLC), which could not be separated by chromatography (Scheme 1). At this stage, we did not do any more endeavor to improve the diastereoselectivity because both of them will be enolated in the next step. On the other hand, we also attempted to alkylate compound **4** with fully protected 3-iodo-2-aminopropanol derivatives directly under basic conditions. Unfortunately, all these efforts failed to grant the desired intermediates.

The following hydroxyl introduction was achieved by a two-step procedure (Scheme 1). Lactam **9** was treated with LDA/HMPA at first, and then the resultant enolate was oxidized by Davis reagent **5**[8,9] *in situ* at –78 °C to give the hydroxylated lactam **10** after aqueous workup. Different Davis reagents and various bases were tested and those results are outlined in Table 1. The configurations of **10** were finally confirmed by NMR analyses of **15** in later stage (see below, Figure 2).

Selective deprotection of acetonide **10** by TsOH in MeOH afforded a mixture of **11** in 91% yield. Reaction of **11** with Boc_2O and DMAP in MeCN at room temperature afforded the compound **12a** and its diastereomer **12b**, which could be separated efficiently by regular flash column chromatography. It is worthy noting that the absolute configurations of **12a** and **12b** could not be identified at this point, and they were finally proved in the later stage by NOESY studies of compound **15** (Figure 2).

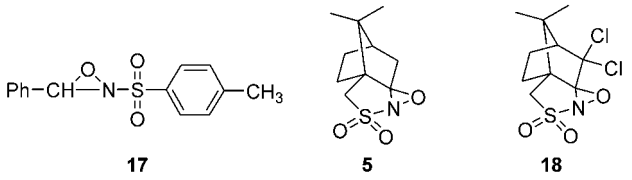
Partial reduction of lactam **12a** by $LiEt_3BH$ in THF at –78 ℃[1a] followed by intramolecular ring-closure reaction with CBr_4-PPh_3 in ether[10] at room temperature gave the desired pyrroloindole **13** in 65% yield (two steps, Scheme 2). Interestingly, of the protecting groups, which were surveyed for hydroxyl we tried, only Boc

Scheme 1



Reaction conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 ℃, 100%. (b) (i) LDA, HMPA, **4**, THF, −78 ℃; (ii) Et_3N, MsCl, CH_2Cl_2, −78 ℃, 90% (20% for **8a**, and 70% for **8b**), two steps. (c) $NaBH_4$, EtOH, 0 ℃, 73%. (d) LDA, HMPA, **5**, THF, 60%, −78 ℃. (e) TsOH, MeOH, 91%. (f) Boc_2O, DMAP, MeCN, 78% (58% for **12a** and 20% for **12b**).

Table 1 The results of Davis oxidation of **9** by different bases and oxidants



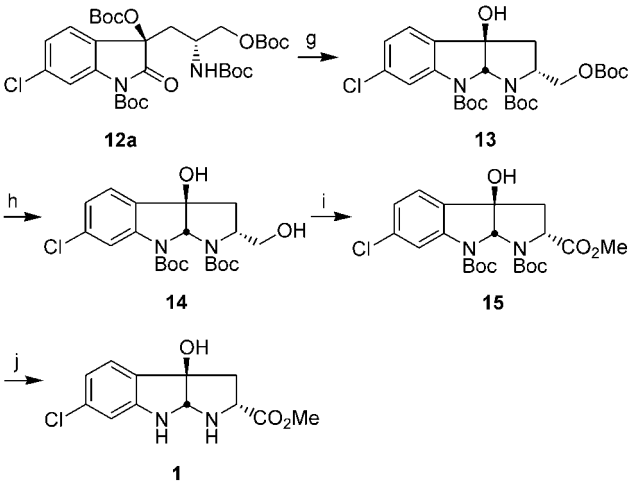
17 **5** **18**

Entry	Base	Davis reagent	*de*[a] of **10**/%	Yield of **10**/%
1	LDA	**17**	15	54
2	LDA	**5**	24	58
3	NaHMDS	**5**	30	60
4	LDA/HMPA	**5**	49	60
5	LDA/HMPA	**18**	55	55

[a] HPLC.

was appropriate for the subsequent reduction and cyclization to the pyrroloindole **13** with $LiEt_3BH$. Other protecting groups (TBS, MOM) and other reduction conditions ($LiAlH_4$, DIBAL-H, $NaBH_4$, BH_3, $BH_3 \cdot SMe_2$) all failed to give the desired products. Selective removal of Boc groups on the hydroxyls with 0.3 mol/L NaOH in MeOH[11] gave compound **14**. Oxidation of **14** with Dess-Martin periodinane followed by $NaClO_2$ and esterification with CH_2N_2 sequentially provided the N,N′-Boc protected methyl ester **15**. The absolute stereochemistries of **15** were finally confirmed by the NOESY experiments (Figure 2). Deprotection of both *N*-Boc groups of **15** with TFA-CH_2Cl_2 (1 ∶ 4) afforded the amino acid methyl ester **1** in quantitative yield.

Scheme 2



12a **13** **14** **15** **1**

Reagents and conditions: (g) (i) $LiBEt_3H$, THF; (ii) CBr_4, PPh_3, ether, 65% in two steps. (h) NaOH, MeOH, 93%. (i) Dess-Martin periodinane CH_2Cl_2; (ii) NaH_2PO_4, 2-methyl-2-butene, $NaClO_2$, *t*-butanol, H_2O; (iii) CH_2N_2, Et_2O, 75% in three steps. (j) TFA, CH_2Cl_2, 100%.

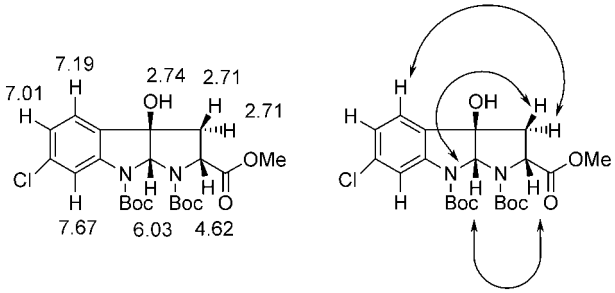


Figure 2 Chemical shifts and NOESY of compound **15**.

Conclusion

In summary, a stereoselective synthesis of (2*R*,3a*R*,8a*R*)-6-chloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (**1**) was described. An aldol reaction with Garner aldehyde, a hydroxyl introduction by Davis reagent, and a reductive intramolecular ring-closure reaction were successfully served as the key steps. It provides a new route to obtain these important pyrroloindole derivatives by chemical synthesis, starting from readily available chemical substrates and inexpensive reagents.

Experimental

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz. Flash column chromatographies were performed on silica gel (10—40 μm) using mixtures of petroleum ether and acetate as eluents.

Compounds 8a and 8b To a solution of oxalyl chloride (2.83 mL, 32.4 mmol) in dry CH_2Cl_2 (40 mL) at −75 ℃ was added DMSO (3.7 mL, 52 mmol) in dry CH_2Cl_2 (5 mL) in 15 min. After being stirred at −75 ℃ for an additional 15 min, alcohol **6** (5.0 g, 21.6 mmol) in dry CH_2Cl_2 (40 mL) was added over 5 min. After the reaction was stirred at −75 ℃ for 2 h, dry Et_3N (8.2 mL, 58.4 mmol) was added and the mixture was slowly warmed to room temperature. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (50 mL). The combined Et_2O layers were washed with brine, dried over Na_2SO_4 and concentrated to yield a yellow oil **7**, which was used directly for the next step.

To a solution of diisopropylamine (4.2 mL, 30 mmol) in dry THF (100 mL) at −75 ℃ was added dropwise *n*-BuLi (2.5 mol/L in hexane, 10 mL, 25 mmol). After 30 min, HMPA (3.5 mL, 20 mmol) was added dropwise and the mixture was stirred for an additional 30 min. Indole derivative **4** (1.67 g, 10 mmol) in dry THF (40 mL) was added over 5 min. After 30 min, the above aldehyde **7** in dry THF (40 mL) was added dropwise and the reaction was stirred for 1.5 h. Saturated NH_4Cl

was added at −78 ℃ to quench the reaction. The mixture was warmed to room temperature and extracted with EtOAc (50 mL×3). The combined organic layers were washed with water (50 mL×2) and brine (50 mL), dried over Na_2SO_4 and concentrated to give a red oil, which was used directly for the next step.

To a solution of the above intermediate in CH_2Cl_2 (30 mL) at −78 ℃ was added Et_3N (4.1 mL, 30 mmol) and MsCl (1.2 mL, 15 mmol), and the solution was stirred for 2 h. Saturated NH_4Cl was added at −78 ℃ and the mixture was warmed to r.t. and extracted with CH_2Cl_2 (50 mL×3). The combined organic layers were washed with water (50 mL×3) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **8a** and **8b** as yellow solids (760 mg of **8a** and 2.64 g of **8b**, in 90% yield totally). Data for **8a**: m.p. 208—210 ℃; $[\alpha]_D^{25}$ −51.9 (*c* 0.856, CH_3Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.96 (brs, 1H), 7.34—6.72 (m, 4H), 5.86 (brs, 1H), 4.39 (brs, 1H), 3.84 (d, *J*=8.2 Hz, 1H), 1.73—1.33 (m, 15H); IR (KBr) *v*: 3240, 2976, 1708 cm^{-1}; MS (EI) *m/z*: 322 (M^++1−57). Anal. calcd for $C_{19}H_{23}ClN_2O_4$: C 60.23, H 6.12, N 7.39; found C 60.12, H 6.29, N 6.97. Data for **8b**: m.p. 152—153 ℃; $[\alpha]_D^{25}$ +9.8 (*c* 1.377, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.89 (brs, 1H), 7.36 (d, *J*=8.1 Hz, 1H), 7.01—6.83 (m, 3H), 5.17 (brs, 1H), 4.30 (dd, *J*=9.3, 6.9 Hz, 1H), 3.88 (dd, *J*=9.0, 3.0 Hz, 1H), 1.70—1.28 (m, 15H); IR (KBr) *v*: 2982, 1716, 1613, 1392 cm^{-1}; MS (EI) *m/z*: 379 (M^++1). Anal. calcd for $C_{19}H_{23}ClN_2O_4$: C 60.23, H 6.12, N 7.39; found C 60.63, H 6.38, N 6.99.

Compound 9 To a solution of $NaBH_4$ (860 mg, 22.6 mmol) in absolute EtOH (150 mL) at 0 ℃ was added a solution of **8a** and **8b** (4.3 g, 11.3 mmol) in absolute EtOH (10 mL) and the mixture was stirred for 2 h at 0 ℃. The reaction was quenched by addition of saturated $NaHCO_3$ at 0 ℃ and EtOH was evaporated *in vacuo*. The mixture was extracted by EtOAc (50 mL×3) and the combined EtOAc layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **9** as a white solid (3.14 g, 73%, 23% *de* by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.64 (brs, 1H), 7.37—6.99 (m, 3H), 4.38—4.35 (m, 1H), 4.05—3.89 (m, 2H), 3.50—3.40 (m, 1H), 2.16—2.06 (m, 2H), 1.55—1.45 (m, 15H); MS (EI) *m/z*: 380 (M^+); HRMS (EI) calcd for $C_{19}H_{25}ClN_2O_4$ [M^+] 380.1503, found 380.1455.

Compound 10 To a solution of diisopropylamine (16 mg, 0.158 mmol) in dry THF (1 mL) was added *n*-BuLi (1.6 mol/L in hexane, 100 μL, 0.16 mmol) at −78 ℃. After 30 min, HMPA (29 mg, 0.16 mmol) was added and the mixture was stirred for an additional 30 min. Compound **9** (50 mg, 0.13 mmol) in dry THF (1 mL) was added dropwise. After the reaction was stirred for 30 min, Davis reagent **5** (60 mg, 0.26 mmol) in dried THF (1 mL) was added. The reaction was continued to stir for 2 h at −78 ℃. The reaction was quenched by addition of saturated NH_4Cl and then warmed to r.t. The mixture was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **10** as a white solid (32 mg, 60%, 49% *de* by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75 (brs, 1H), 7.33—6.77 (m, 3H), 4.58—4.37 (m, 1H), 4.09—3.68 (m, 2H), 2.43—1.93 (m, 2H), 1.54—1.34 (m, 15H) (one of the active protons was not observed in the spectrum); MS (EI) *m/z*: 381 (M^+−15); HRMS (EI) calcd for $C_{18}H_{23}ClN_2O_5$ [M^++1−15] 382.1260, found 382.1310.

Compound 11 To a solution of diastereomeric mixture **10** (453 mg, 1.14 mmol) in MeOH (10 mL) was added TsOH hydrate (12 mg, 0.063 mmol), and the mixture was stirred at r.t. overnight. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography to give **11** as a white solid (413 mg, 91%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.35 (brs, 1H), 7.25—7.18 (m, 1H), 6.98—6.96 (m, 1H), 6.74—6.70 (m, 1H), 5.92—5.89 (m, 1H), 4.63—4.61 (m, 1H), 3.25 (brs, 1H), 3.13 (brs, 2H), 2.17—2.10 (m, 2H), 1.33—1.19 (m, 9H) (one of the active protons was not observed in the spectrum); MS (ESI) *m/z*: 357 (M^++1). Anal. calcd for $C_{16}H_{21}ClN_2O_5$: C 53.86, H 5.93, N 7.85; found C 53.56, H 6.00, N 7.49.

Compound 12 To a solution of compound **11** (1.0 g, 2.8 mmol) in MeCN (10 mL) was added DMAP (40 mg, 0.3 mmol) and Boc_2O (1.83 g, 8.4 mmol) at r.t. The reaction was stirred overnight and quenched with sat. NH_4Cl. The mixture was diluted with EtOAc (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (30 mL×3) and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification on silica gel provided **12** as a white solid (1.64 g of **12a**, 0.41 g of **12b**, 78% yield totally). Data for **12a**: m.p. 143—145 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (s, 1H), 7.40 (d, *J*=8.1 Hz, 1H), 7.19 (dd, *J*=8.1, 1.2 Hz, 1H), 4.57 (d, *J*=8.4 Hz, 1H), 4.04 (d, *J*=8.1 Hz, 2H), 3.94—3.90 (m, 1H), 2.32—2.28 (m, 1H), 2.07 (d, *J*=11.4 Hz, 1H), 1.65 (s, 9H), 1.46 (s, 9H), 1.39 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.0, 154.5, 153.0, 150.5, 148.4, 140.6, 135.8, 124.8, 124.7, 123.8, 116.4, 85.0, 84.0, 82.5, 69.2, 45.0, 38.5, 28.2, 27.9, 27.6, 27.4; IR (KBr) *v*: 3381, 2981, 1770, 1745, 1613, 1526, 1283 cm^{-1}; MS (ESI) *m/z*: 674 ($M+NH_4^+$); HRMS (ESI) calcd for $C_{31}H_{45}ClN_2NaO_{11}$ [M^++Na] 679.2604, found 679.2611.

Compound 13 To a solution of **12a** (36 mg, 0.055 mmol) in dry THF (3 mL) at −78 ℃ was added $LiBEt_3H$ (1 mol/L in THF, 0.12 mL, 0.12 mmol). The reaction mixture was stirred at −78 ℃ for 30 min before it was quenched with sat. $NaHCO_3$ and diluted with EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 mL×2). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and

concentrated *in vacuo*. The residue was directly used in the next step.

To a solution of the above residue in Et_2O (5 mL) was added CBr_4 (40 mg, 0.12 mmol) and PPh_3 (31 mg, 0.12 mmol). The reaction mixture was stirred at r.t. for 30 min before it was diluted with EtOAc (5 mL) and quenched with sat. $NaHCO_3$. The layers were separated and aqueous layer was extracted with EtOAc (5 mL×3). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification on silica gel provided **13** as a waxy solid (19 mg, 65% in two steps). $[\alpha]_D^{25}$ −44.5 (*c* 0.867, CH_3Cl); ^1H NMR (300 MHz, $CDCl_3$) δ:7.75 (s, 1H), 7.30 (d, *J*=8.4 Hz, 1H), 7.06 (dd, *J*=7.8, 1.8 Hz, 1H), 6.08 (s, 1H), 4.36—4.33 (m, 1H), 3.89 (dd, *J*=10.2, 5.1 Hz, 1H), 3.13 (t, *J*=9.9 Hz,1H), 2.56 (dd, *J*=13.8, 9.0 Hz, 1H), 2.43 (dd, *J*=13.5, 1.5 Hz, 1H), 1.59 (s, 9H), 1.49 (s, 9H) 1.40 (s, 9H) (one active proton was not observed in the spectrum); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.0, 152.9, 152.2, 142.9, 136.2, 131.9, 124.1, 123.8, 117.6, 84.9, 83.5, 82.5, 82.2, 81.1, 66.7, 57.2, 39.7, 28.5, 28.3, 28.2, 27.7; IR (film) *v*: 3416, 2925, 1719, 1598 cm^{-1}; MS (ESI) *m/z*: 541 (M^++1); HRMS (ESI) calcd for $C_{26}H_{37}O_8N_2ClNa$ [M^++Na] 563.2131, found 563.2137.

Compound 14 To a solution of **13** (42 mg, 0.078 mmol) in MeOH (10 mL) was added NaOH solution (0.6 mol/L in MeOH, 10 mL, 6.0 mmol). The reaction mixture was stirred for 24 h at r.t., and then diluted with EtOAc and neutralized with aqueous HCl (1 mol/L). MeOH was evaporated under reduced pressure and the residue extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography on silica gel provided **14** (32 mg, 93%) as a waxy solid. $[\alpha]_D^{25}$ −72.7 (*c* 0.787, CH_3Cl); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.65 (s, 1H), 7.30 (d, *J*=7.8 Hz, 1H), 7.07 (dd, *J*=8.4, 1.8 Hz, 1H), 6.10 (s, 1H), 4.30 (d, *J*=6.3 Hz, 1H), 3.07—3.05 (m, 2H), 2.62—2.51 (m, 1H), 2.28 (dd, *J*=13.2, 1.8 Hz, 1H), 1.57 (s, 9H), 1.48 (s, 9H) (two active protons were not observed in the spectrum); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.7, 152.2, 142.6, 135.9, 132.3, 124.0, 117.9, 84.6, 83.5, 82.6, 81.9, 65.6, 60.8, 39.6, 28.4, 28.2; IR (film) *v*: 3399, 2982, 2927, 2847, 1723, 1602, 1477, 1395 cm^{-1}; MS (EI) *m/z*: 440 (M^+); HRMS (MALDI) calcd for $C_{21}H_{29}ClN_2NaO_6$ [M^++Na] 463.1606, found 463.1628.

Compound 15 To a solution of **14** (20 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (28 mg, 0.66 mmol) at r.t. The reaction mixture was stirred for 30 min and quenched with sat. $NaHCO_3$ containing $Na_2S_2O_3$. After being stirred for 20 min, the layers were separated. The aqueous layer was extracted with EtOAc (5 mL×3) and the combined extracts were washed with sat. $NaHCO_3$ (5 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was used directly in the next step.

To a solution of the above aldehyde in *t*-butanol and water (4∶1, *V*/*V*, 10 mL) at 0 ℃ was successively added 2-methyl-2-butene (13 mg, 0.184 mmol), NaH_2PO_4 (6 mg, 0.048 mmol) and $NaClO_2$ (12.5 mg, 0.138 mmol). After being stirred at room temperature for 1 h, the reaction mixture was quenched with NH_4Cl (sat.) and extracted with EtOAc (5 mL×3). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the acid as a white solid, which was used directly in the next step.

To a solution of the above acid in Et_2O (15 mL) at 0 ℃, CH_2N_2 in Et_2O was added until the solution turned to yellow. After being stirred for an additional 20 min, excess CH_2N_2 was destroyed by adding glacial acetic acid. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography to give **15** as a white solid (15 mg, 75% in three steps). m.p. 162—164 ℃; $[\alpha]_D^{25}$ −33.3 (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.27 (s, 1H), 7.19 (d, *J*=8.1 Hz, 1H), 7.01 (dd, *J*=8.1, 1.8 Hz, 1H), 6.03 (s, 1H), 4.62 (t, *J*=5.3 Hz, 1H), 3.24 (s, 3H), 2.75 (s, 1H), 2.71 (d, *J*=5.7 Hz, 2H), 1.57 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 152.2, 144.4, 136.4, 130.4, 124.4, 123.4, 117.6, 84.3, 82.5, 82.1, 82.1, 81.1, 59.4, 52.0, 39.7, 28.3, 28.2; IR (KBr) *v*: 3445, 1729, 1679, 1601, 1478, 1401, 1365, 1239, 1169, 809, 747 cm^{-1}; MS (ESI) *m/z*: 491 (M^++Na); HRMS (ESI) calcd for $C_{22}H_{29}ClN_2NaO_7$ [M^++Na] 491.1556, found 491.1541.

Compound 1 To a solution of **15** (9 mg, 0.019 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL) at 0 ℃. After being stirred at r.t. for 5 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL), neutralized to pH 7—8 by $NaHCO_3$ (sat.) and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **1** as a white solid in quantitative yield. m.p. 163—165 ℃; $[\alpha]_D^{25}$ −57.4 (*c* 0.14, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6) δ: 7.04 (d, *J*=7.5 Hz, 1H), 6.52 (dd, *J*=8.1, 2.4 Hz, 1H), 6.39 (d, *J*=1.5 Hz, 1H), 6.32 (s, 1H), 5.63 (s, 1H), 4.71 (d, *J*=1.8 Hz, 1H), 3.95 (t, *J*=7.2 Hz, 1H), 3.42 (s, 3H), 2.30 (dd, *J*=12.9, 7.2 Hz, 1H), 2.07 (dd, *J*=12.6, 6.9 Hz, 1H) 1.33 (s, 1H); IR (film) *v*: 3270, 2955, 1735, 1486, 1442, 1311, 1230, 1138, 1106, 805 cm^{-1}; MS (ESI) *m/z*: 291 [M^++Na]; HRMS (ESI) calcd for $C_{12}H_{13}ClN_2NaO_3$ [M^++Na] 291.0512, found 291.0507.

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