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Total Synthesis of (±)-8-Oxo-erythrinine, (±)-8-Oxo-erythraline, and (±)-Clivonine

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Total syntheses of the erythrina alkaloids (±)-8-oxo-erythrinine and (±)-8-oxo-erythraline have been developed, based on a substrate-controlled intramolecular 6-*exo-trig* selective radical spirocyclization that establishes the quaternary center of the B-rings. An improved total synthesis of (±)-clivonine has also been reported, based on an intramolecular 6-*endo-trig* free-radical cyclization of a highly functionalized enamide, and a biomimetic ring-switch of a lycorine-type intermediate. These *endo*/*exo*-selective sequences enabled us to rapidly assemble two different complex alkaloids from a common building block in an economical fashion.

Introduction

Alkaloids featuring the hydroindole skeleton,[1] form a large class of structurally diverse compounds that are widely found in nature. This class of compounds is exemplified by the structures shown in Figure 1, members of the aspidosperma (**1**),[2] strychnos (**2**),[3] erythrina (**3a**),[4] and amaryllidaceae (**4**)[5] families. Such compounds show diverse biological activities, including antitumor, antiviral, sedative, and hypotensive activities, and activities as acetylcholinesterase (AChE) inhibitors and neuromuscular blockers.[6–9] Efficient approaches to the synthesis of *cis*-fused hydroindoles or related frameworks would allow the synthesis not only of other related natural products, but also of related nonnatural products with a variety of biological activities.[7]

Two erythrina alkaloids, 8-oxo-erythrinine (**3a**)[10] and 8-oxo-erythraline (**3b**)[11] were isolated by two different groups in 1984. To date, there is only one report dealing with the total synthesis of these compounds.[12] Clivonine (**4**), a lycorenine-type amaryllidaceae alkaloid, was first isolated from *Clivia miniata* Regel,[13] and was studied for its biological properties long before a biosynthetic route to the compound was proposed.[14] Spivey's group reported the synthesis of clivonine (**4**) through a biomimetic ring-switch from a lycorine-type precursor.[15] Several syntheses of lycorane and erythrina skeletons have also been reported,

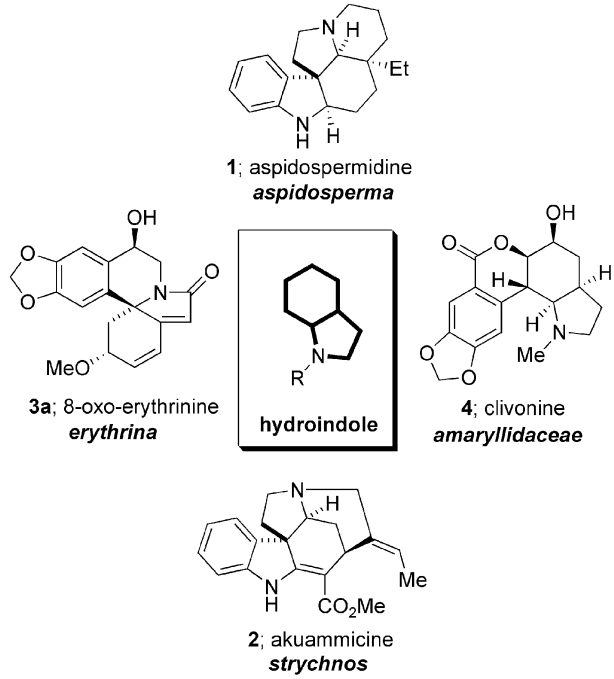

Figure 1. Representative alkaloids containing the hydroindole skeleton.

through synthetic routes involving Heck coupling,[16] or an NBS (*N*-bromosuccinimide) induced [17] or Lewis-acid-induced[18] Pictet–Spengler reaction of tetrahydroindolinones bearing tethered heteroaromatic rings to construct the key rings. Inspired by Padwa's work using an intramolecular 6-*endo-trig* radical cyclization to access *epi*-zephyranthine,[17] we set out to develop a highly efficient route for the synthesis of 8-oxo-erythrinine (**3a**), 8-oxo-erythraline (**3b**), and clivonine (**4**) from a common intermediate. We report the re-

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sults of our investigations in this paper. To the best of our knowledge, no radical cyclization protocols have previously been used in the total synthesis of 8-oxo-erythrinine (**3a**), 8-oxo-erythraline (**3b**), and clivonine (**4**).

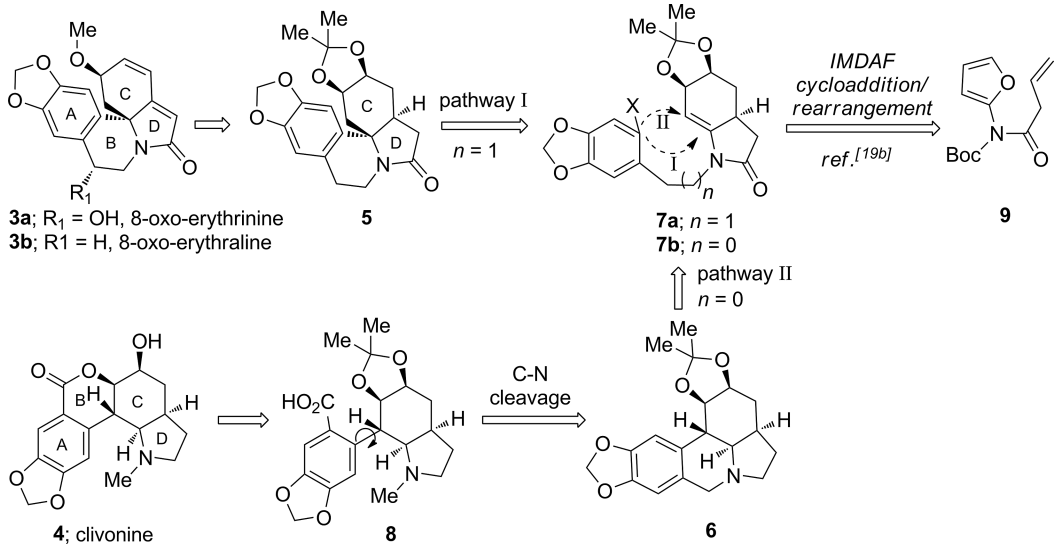
Results and Discussion

Synthetic Plan

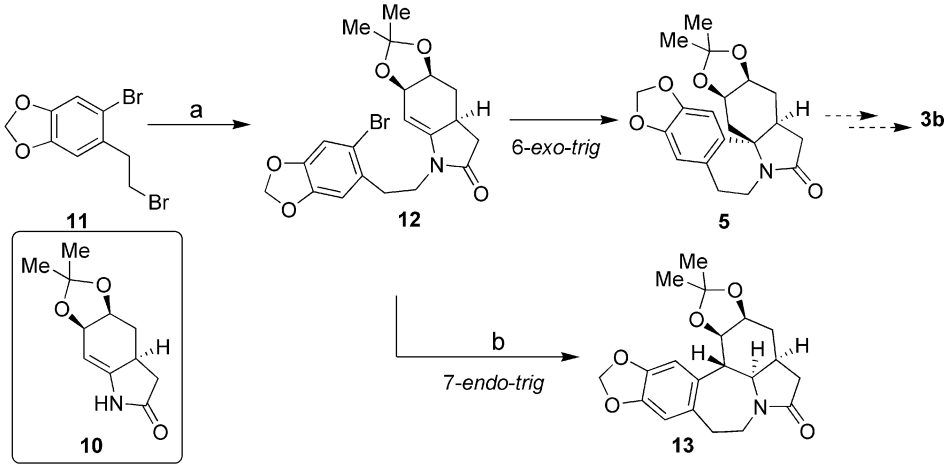
Our initial retrosynthetic analysis of (±)-8-oxo-erythrinine (**3a**), (±)-8-oxo-erythraline (**3b**), and (±)-clivonine (**4**) is shown in Scheme 1. We envision that compounds **5**, which is the core skeleton of (±)-8-oxo-erythrinine (**3a**) and (±)-8-oxo-erythraline (**3b**), and **6**, the core skeleton of (±)-clivonine (**4**), could be assembled from intermediates **7a** and **7b**, respectively, by controlling the *endo*/*exo* selectivity of an intramolecular free-radical cyclization process (pathways I and II). (±)-8-Oxo-erythrinine (**3a**) and (±)-8-oxo-erythraline (**3b**), could be reached from *spiro*-compound **5** in a few steps. (±)-Clivonine could be accessed through a one-pot deprotection/esterification of acid **8**, which is expected to be formed from amine **6** through the biomimetic cleavage of a C–N bond. Intermediates **7a** and **7b** could be assembled from substituted amidofuran **9**.

Spirocyclic Ring Construction of Oxo-erythrinine through Intramolecular Radical Cyclization

As shown in Scheme 2, we began a program of research based on the intramolecular [4+2]-cycloaddition/rearrangement cascade of 2-amidofurans (IMDAF), which was developed by Padwa's group and used intensively for the preparation of complex oxygenated polycyclic compounds.[17,19] This concise process provided tetrahydro-1*H*-indol-2(3*H*)-one derivative **10** as a readily accessible starting material (38% overall yield prepared from 2-furoic acid in a four-step procedure).[19b] The coupling reaction of bromide **11**[20] and enamide **10** gave tetrahydroindolinone **12** in 82% yield. We expected that compound **5** would be formed under radical cyclization conditions. However, only 7-*endo*-*trig* adduct



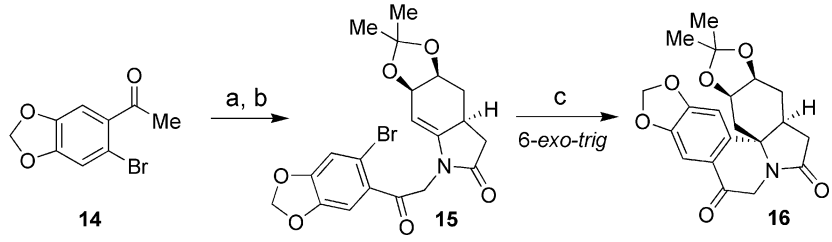
Scheme 1. Retrosynthetic analysis of 8-oxo-erythirinine, 8-oxo-erythraline, and clivonine; Boc = *tert*-butoxycarbonyl.



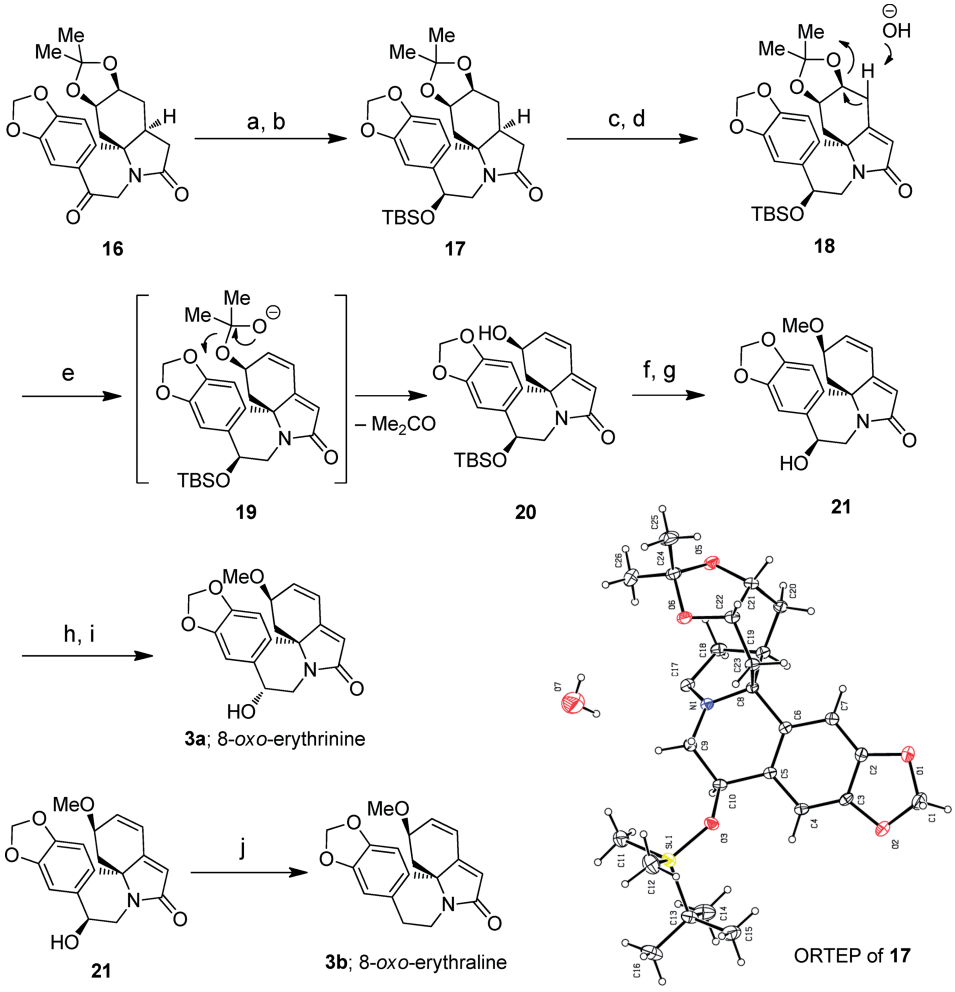
Scheme 2. Attempted synthesis of *spiro* adduct **5**. a) NaH, **10**, DMF, 0 °C to r.t., 82%; b) Bu_3SnH, AIBN, benzene, reflux, 3 h, 68%.

13, which contains the core of hexahydroapoerysopine, was obtained in 68% yield. None of *spiro* adduct **5** was observed under a variety of reaction conditions,[21] including Ph_3SnH/AIBN (azobisisobutyronitrile)/benzene, nBu_3SiH/MeCN/nBu_3SnF/toluene, and Ph_3SnH/nBu_3SnOAc/AIBN/xylene. We hypothesized that this outcome may be attributed to the smaller torsional stress of the benzyl methylene group.

Calculations have indicated[22] that the 2-oxo group has a great influence on the *endo*/*exo* selectivity of radical cyclization reactions. To overcome this unfavorable substrate control, a more torsionally strained sp^2 carbonyl group was introduced into compound **12**, which we expected would favor a 6-*exo*-*trig* free-radical cyclization. As shown in Scheme 3, α-bromination[23] of aryl ketone **14** followed by coupling with enamide **10** gave highly functionalized en-



Scheme 3. Synthesis of key intermediate **16**. a) NBS, TsOH, CH_3CN, reflux, 81%; b) NaH, **10**, DMF, 0 °C, 92.6%; c) Bu_3SnH, AIBN, benzene, reflux, 3 h, 72%.



Scheme 4. Complete total syntheses of (±)-8-oxo-erythraline and (±)-8-oxo-erythrinine. a) $NaBH_4$, MeOH, 0 °C, 30 min; b) TBSOTf, Et_3N, r.t., 30 min, 80% over two steps; c) BuLi, PhSeCl, THF, –78 °C; d) $NaIO_4$, MeOH/H_2O (3:1), r.t., 30 min, 85% over two steps; e) LiOH (0.5 M), THF, r.t., 48 h, 93%; f) TBAB (tetrabutylammonium bromide), MeI, KOH, THF, r.t., 36 h, 91%; g) TBAF (tetrabutylammonium fluoride), THF, r.t., 95%; h) *p*-NO_2PhCO_2H, PPh_3, DIAD (diisopropyl azodicarboxylate), THF, r.t., 5 h; i) LiOH (1 M), THF, r.t., 1 h, 90% over two steps; j) TFA, Et_3SiH, CH_2Cl_2, 0 °C, 85%.

amide **15** in 75% yield over two steps. Fortunately, radical cyclization of compound **15** under the conditions used above gave 6-*exo*-*trig* product **16** in 72% yield; this compound contains the core structure of the erythrina alkaloids. The difference between compounds **13** and **16** was further confirmed by DEPT-135 analysis (see Supporting Information page 40). This efficient substrate control in the radical cyclization gives us the possibility to prepare related amaryllidaceae and erythrina natural products from the same starting point.

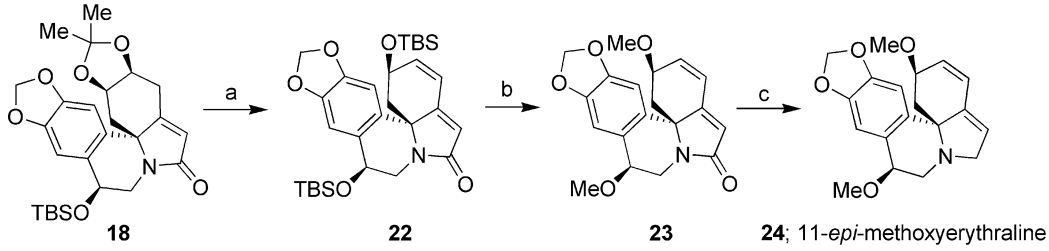
Total Syntheses of (±)-8-Oxo-erythraline, (±)-8-Oxo-erythrinine and (±)-11-*epi*-Methoxyerythraline

With the crucial carbocyclic framework **16** established, we turned our focus onto the final stage of the synthesis of (±)-8-oxo-erythrinine (**3a**) and (±)-8-oxo-erythraline (**3b**), as shown in Scheme 4. Reduction of the ketone in **16** using $NaBH_4$ followed by protection of the secondary alcohol gave silyl ether **17** as a single diastereomer in 80% overall yield. The configuration of **17** was determined by X-ray crystallographic analysis. The double bond of the ^{d}-ring was introduced by phenylselenylation/oxidative elimination,[24] which resulted in the formation of α,β-unsaturated ketone **18** in 85% yield. Then, a unique base-promoted one-pot elimination/ring-opening sequence produced α,β,γ-unsaturated in ketone **20** in 93% yield (Scheme 4).[25] The reaction possibly proceeded through a base-induced elimination to generate intermediate **19**, followed by loss of acetone. Subsequent methylation and TBS (*tert*-butyldimethylsilyl) deprotection gave rise to secondary alcohol **21** in 86% yield over two steps. Finally, inversion of configuration of the secondary alcohol center in **21** using the Mitsunobu procedure[26] led to the desired (±)-8-oxo-erythrinine (**3a**) in 90% yield. The overall yield was 26.5% for the 12-step sequence starting from ketone **14**. Additionally, the total synthesis of (±)-8-oxo-erythraline (**3b**) was accomplished by reduction of benzyl alcohol **21** using Et_3SiH in TFA (trifluoroacetic acid)[27] in 85% yield. The overall yield for (±)-8-oxo-erythraline (**3b**) was 25% from ketone **14** (11 steps).

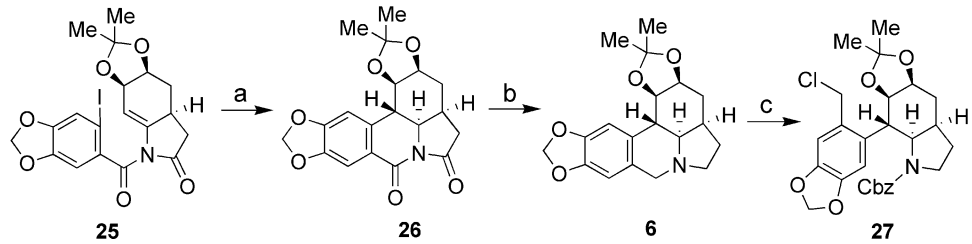
Significantly, exposure of α,β-unsaturated ketone **18** to TBSCl in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) at reflux directly gave silyl protected diene **22** in 73% yield. One-pot deprotection/methylation of **22** provided dimethyl product **23** in 89% yield. In this process, TBAF acted as both the desilylation agent and the phase-transfer reagent. Finally, compound **23** was converted into (±)-11-*epi*-methoxyerythraline (**24**) by treatment with AlH_3 (Scheme 5).

Total Synthesis of (±)-Clivonine

Having successfully completed the synthesis of (±)-8-oxo-erythrinine (**3a**) and (±)-8-oxo-erythraline (**3b**), next we moved onto the synthesis of the structurally related amaryllidaceae alkaloid (±)-clivonine (Scheme 6). Imide **25**[19b] was converted into its 6-*endo*-*trig* tetracyclic product **26** through an intramolecular free-radical cyclization. Compound **26** was then reduced by BH_3 to give amine **6** in high yield. At this stage, the proposed bioinspired strategy was applied to construct the ring-opened skeleton. Unfortunately, efforts to effect the chemoselective benzyl C–N bond cleavage were unfruitful. Various reaction conditions were tested (including using CAN [cerium(IV) ammonium nitrate],[28] BrCN,[29] and Ac_2O/NaOAc[30]), but these led either to the recovery of the starting material or to the formation of a mixture of unidentified products. However, amine **6** was converted into the ring-opened product in a relatively low yield (30%; 70% based on recovered starting material) when it was exposed to $PhOCOCl/CH_2Cl_2$[31,32] at



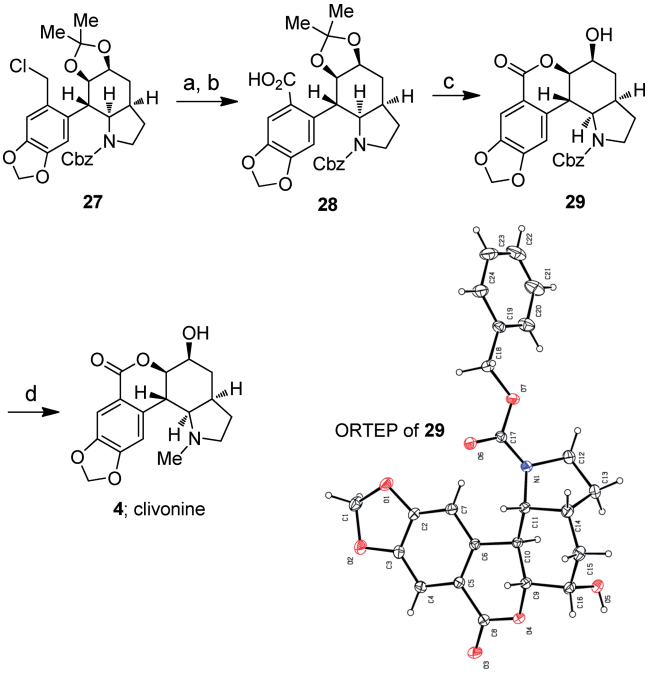
Scheme 5. Synthesis of (±)-11-*epi*-methoxyerythraline. a) DBU, TBSCl, benzene, reflux, 73%; b) MeI, TBAF, KOH, THF, r.t., 89%; c) $AlCl_3$, $LiAlH_4$, THF, –10 °C, 68%.



Scheme 6. Construction of key intermediate **27**. a) nBu_3SnH, AIBN, benzene, 90 °C, 78%; b) BH_3, THF, reflux, 88%; c) CbzCl, $CHCl_3$/THF (1:1), microwave, 55 °C, 82%.

room temperature. The resulting NMR spectroscopic data were consistent with those reported in the literature. Encouraged by this promising result, other reagents of general structure RCOCl were screened, and we were pleased to find out that the reagents $ClCO_2Me$, EtCOCl, AcCl, PhCOCl, and CbzCl (benzyloxycarbonyl chloride) all worked under the general reaction conditions. We elected to use CbzCl as the ring-opening reagent based on the fact that the Cbz group could be transformed into a methyl group in a one-pot linear protocol under $Pd/C/H_2/HCHO$ conditions at a later stage. The optimum reaction conditions for the chemoselective benzyl C–N bond cleavage were thus to use CbzCl (2 equiv.) in $THF/CHCl_3$ (1:1 v/v) in a microwave synthesis reactor (Anton Paar W300) for 2 h. This gave Cbz-protected product **27** in 82% yield.

To complete the total synthesis of (±)-clivonine (Scheme 7), intermediate **27** was treated with anhydrous $NaHCO_3$/DMSO in a Kornblum-type oxidation,[33] followed by standard Pinnick oxidation[34] to produce benzoic acid **28** in 65% yield over two steps. One-pot deprotection/esterification of acid **28** in THF/HCl (1 N) (3:1, v/v) resulted in the formation of ester **29** in 92% yield. At this point, crystals of **29** suitable for X-ray crystallographic analysis were obtained (see ORTEP structure, Scheme 7), which confirmed our stereochemical assignment of the tricyclic core. Finally, direct subjection of ester **29** to Pd/C (10%) and formaldehyde (37% aq.) under a hydrogen atmosphere[35] successfully accomplished the total synthesis of (±)-clivonine (**4**) in 50% yield (75% based on recovered starting material). This linear sequence gave (±)-clivonine (**4**) in 26% overall yield from intermediate **6** (five steps), and so is more efficient than Spivey's synthesis (5%, six steps). A two-step protocol, involving removal of *N*-Cbz group of compound **29** by Pd/C (10%) reduction under a hydrogen atmosphere, and subsequent chemoselective installation of the *N*-Me group through reductive amination[36] also gave the final product (i.e., **4**) in 67% yield over two steps. The synthetic (±)-clivonine was identical in all respects to the reported compound (i.e., ^1H and ^{13}C NMR spectroscopic data, HRMS parent ion).[15,37]



Scheme 7. Total synthesis of (±)-clivonine. a) $NaHCO_3$, DMSO, microwave, 85 °C, 20 min; b) $NaClO_2/NaH_2PO_4$, 2-methyl-2-butene, *t*BuOH/THF, r.t., 5 h, 69% over two steps; c) THF/HCl (1 N) (3:1), 50 °C, 6 h, 92%; d) HCHO (37% aq.), Pd/C, H_2 (20 atm), MeOH, r.t., 48 h, 75% based on recovered starting material.

Conclusions

An efficient strategy for the synthesis of both aromatic-type erythrina alkaloids and a clivonine-type amaryllidaceae alkaloid has been developed. The total syntheses of (±)-8-oxo-erythrinine and (±)-8-oxo-erythraline were accomplished in 26.5% overall yield (12 steps) and 25% overall yield (11 steps), respectively, from ketone **14**. The critical steps in the synthetic strategy include: 1) the substrate-controlled intramolecular 6-*exo*-*trig* selective radical spirocyclization that serves to establish the quaternary center of the B-rings; 2) a regioselective base-promoted elimination/ring-opening sequence to generate the desired α,β,γ-unsaturated ketone. Additionally, an improved total synthesis of (±)-clivonine has also been described (26% overall yield, five steps from intermediate **6**) based on an intramolecular 6-*endo*-*trig* free-radical cyclization of a highly functionalized enamide and a biomimetic ring-switch of a lycorine-type intermediate. The application of this approach to other natural product targets is currently under investigation, and the results of this research will be reported in due course.

Experimental Section

General Procedures: All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Toluene and tetrahydrofuran (THF) were distilled immediately before use from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2), dimethyl sulfoxide (DMSO), and triethylamine (Et_3N) were distilled from calcium hydride, and stored under an argon atmosphere. Methanol (MeOH) was distilled from magnesium, and stored under an argon atmosphere. Reagents were purchased at the highest commercial quality, and were used without further purification unless otherwise stated. "Brine" refers to a saturated aqueous solution of NaCl. IR spectra were recorded with a Themo Nicolet Nexus 470 FTIR instrument. Melting points (m.p.) were recorded with a YH X-4 apparatus. NMR spectra were recorded with a Bruker AV-400 instrument, and were calibrated using residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.0 ppm) as internal references. Data are reported in the following order: chemical shifts (δ); multiplicities: br. (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants (*J*) [Hz]; integration. High-resolution MS was carried out with a Thermo LTQ XL Orbitrap instrument. Analytical thin-layer chromatography (TLC) was carried out on silica gel aluminum sheets with F-254 indicator. Visualization was accomplished with UV light or with solutions of $K_2CO_3/KMnO_4$ in water. Microwave irradiation was carried out with an Anton Paar monowave 300 mi-

crowave synthesis reactor. Purification by chromatography was carried out using 200–400 mesh SiO_2 with compressed air as a source of positive pressure.

Compound 11: 2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)ethan-1-ol[38] (300 mg, 1.22 mmol), triphenylphosphine (480 mg, 1.5 mmol), and imidazole (208 mg, 2.5 mmol) were dissolved in CH_2Cl_2 (5 mL), and the mixture was cooled to 0 °C. Br_2 (94 μL, 1.5 mmol) was added dropwise to the stirred solution. The reaction mixture was stirred at room temperature for 3 h, then it was cooled to 0 °C, and satd. aqueous $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3× 5 mL), and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (petroleum ether/EtOAc, 5:1) to give **11** (370 mg, 98%) as a white solid, m.p. 48–50 °C. The spectroscopic data matched those reported in the literature.[39] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1 H), 6.75 (s, 1 H), 5.97 (s, 2 H), 3.53 (t, J = 7.5 Hz, 2 H), 3.18 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5, 147.4, 131.1, 114.5, 112.9, 110.6, 101.8, 39.4, 31.2 ppm.

Compound 12: Amide **10**[19b] (200 mg, 0.96 mmol) was dissolved in freshly distilled DMF (3 mL), and the solution was cooled to 0 °C. NaH (60% in mineral oil; 46 mg, 1.15 mmol) was added. The mixture was stirred at 0 °C for 0.5 h, then a solution of **11** (354 mg, 1.15 mmol) in THF (0.5 mL) was added by syringe. The reaction mixture was allowed to warm to room temperature, and was stirred for a further 12 h. After this time, it was quenched with water, and the aqueous layer was extracted with EtOAc (4× 5 mL). The combined organic layers were washed with water and brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1) to give **12** (342 mg, 82%) as a white solid, m.p. 115–118 °C. R_f = 0.5 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1 H), 6.73 (s, 1 H), 5.96 (s, 2 H), 5.16 (s, 1 H), 4.67 (s, 1 H), 4.37–4.16 (m, 1 H), 3.85–3.73 (m, 1 H), 3.55–3.45 (m, 1 H), 3.01–2.82 (m, 2 H), 2.77–2.56 (m, 2 H), 2.35–2.11 (m, 2 H), 1.49 (s, 3 H), 1.44 (d, J = 8.2 Hz, 1 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 147.6, 147.5, 147.3, 130.7, 114.6, 112.8, 110.4, 108.9, 101.7, 93.3, 73.9, 71.4, 39.8, 35.3, 33.4, 32.33, 32.30, 28.4, 25.8 ppm. IR (KBr): $\tilde{\nu}$ = 2939, 2876, 1723, 1674, 1477, 1235, 1174, 1030, 875 cm^{-1}. HRMS (ESI): calcd. for $[(C_{20}H_{22}BrNO_5) + H]^+$ 436.0760; found 436.0761.

Compound 13: A solution of AIBN (30 mg, 0.17 mmol) and Bu_3SnH (183 μL, 0.68 mmol) in benzene (20 mL) was heated to reflux. A solution (0.05 M in benzene) of bromide **12** (150 mg, 0.34 mmol) was added slowly over 30 min. The mixture was heated at reflux for a further 16 h, then KF (1 M aq.; 2 mL) was added. The aqueous layer was extracted with EtOAc (3× 5 mL). The combined organic layers were washed with brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1 to 1:2) to give **13** (82 mg, 68%) as a white solid, m.p. 220–221 °C. R_f = 0.3 (petroleum ether/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 6.67 (s, 1 H), 5.94 (d, J = 1.9 Hz, 2 H), 4.57–4.40 (m, 3 H), 3.29–3.17 (m, 1 H), 3.04–2.86 (m, 2 H), 2.70 (dd, J = 14.7, 5.3 Hz, 1 H), 2.61 (dd, J = 17.3, 9.7 Hz, 1 H), 2.49 (t, J = 12.9 Hz, 1 H), 2.30–2.21 (m, 1 H), 2.14 (d, J = 17.3 Hz, 1 H), 2.09–2.05 (m, 1 H), 1.92–1.81 (m, 1 H), 1.39 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 146.4, 145.8, 134.9, 132.7, 109.7, 108.8, 107.2, 101.0, 73.7, 72.8, 61.5, 44.8, 42.4, 36.4, 34.2, 31.5, 27.4, 24.6 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2864, 1685, 1498, 1372, 1170, 1037, 931, 854 cm^{-1}. HRMS (ESI): calcd. for $[(C_{20}H_{23}NO_5) + H]^+$ 358.1649; found 358.1641.

Compound 15: Compound **14**[40] (4.50 g, 18.50 mmol) and TsOH (4.78 g, 27.75 mmol) were dissolved in freshly distilled CH_3CN (50 mL), and a solution (1 M in CH_3CN) of NBS (3.30 g, 18.50 mmol) was added slowly by syringe over 1 h at room temperature. The mixture was then heated to reflux, and it was stirred at reflux for 3 h. The mixture was then poured into ice-water, and the resulting mixture was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2, 10:1 to CH_2Cl_2) to give 2-bromo-1-(6-bromobenzo[*d*][1,3]-dioxol-5-yl)ethan-1-one (4.80 g, 81%) as a white solid, m.p. 88–90 °C. R_f = 0.2 (petroleum ether/CH_2Cl_2, 3:1). The spectroscopic data matched those reported in the literature.[41] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, J = 2.4 Hz, 1 H), 7.02 (d, J = 1.5 Hz, 1 H), 6.07 (d, J = 0.9 Hz, 2 H), 4.49 (d, J = 1.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 151.0, 147.6, 131.3, 113.8, 112.2, 109.9, 102.6, 33.9 ppm.

Amide **10** (400 mg, 1.91 mmol) was dissolved in freshly distilled DMF (5 mL), and the solution was cooled to 0 °C. NaH (60% in mineral oil; 153 mg, 3.82 mmol) was added. The mixture was stirred at 0 °C for 0.5 h, then a solution of the bromide prepared as described above (740 mg, 2.3 mmol) in THF (1 mL) was added. The mixture was stirred for a further 30 min, then it was quenched with water. The aqueous layer was extracted with EtOAc (3× 5 mL). The combined organic layers were washed with water and brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1) to give **15** (795 mg, 92.6%) as a white solid, m.p. 122–123 °C. R_f = 0.3 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.00 (m, 2 H), 6.07 (d, J = 2.1 Hz, 2 H), 5.02 (dd, J = 17.9, 2.9 Hz, 1 H), 4.96 (d, J = 2.9 Hz, 1 H), 4.66 (dd, J = 3.4, 2.3 Hz, 1 H), 4.61 (d, J = 17.9 Hz, 1 H), 4.29 (ddd, J = 11.2, 7.4, 3.7 Hz, 1 H), 2.91–2.78 (m, 1 H), 2.70 (ddd, J = 16.6, 9.1, 2.0 Hz, 1 H), 2.39–2.27 (m, 1 H), 2.27–2.15 (m, 1 H), 1.59–1.51 (m, 1 H), 1.48 (s, 3 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 174.9, 151.0, 147.5, 147.4, 131.3, 114.0, 112.2, 109.2, 108.9, 102.6, 93.6, 73.8, 71.1, 48.6, 35.0, 32.2, 32.1, 28.3, 25.7 ppm. IR (KBr): $\tilde{\nu}$ = 2984, 2927, 1724, 1681, 1479, 1411, 1244, 1204, 1031, 872 cm^{-1}. HRMS (ESI): calcd. for $[(C_{20}H_{20}BrNO_6) + H]^+$ 450.0552; found 450.0541.

Compound 16: AIBN (182.3 mg, 1.11 mmol) and Bu_3SnH (646.15 mg, 2.22 mmol) were dissolved in benzene (150 mL), and the solution was heated to reflux. A solution (0.1 M in benzene) of aryl bromide **15** (1.0 g, 2.22 mmol) was added slowly over 30 min. The solution was heated at reflux for a further 3 h, then KF (1 M aq.; 10 mL) was added. The aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic layers were washed with brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1 to 1:2) to give **16** (600 mg, 72%) as a white solid, m.p. 232–235 °C. R_f = 0.2 (petroleum ether/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 6.64 (s, 1 H), 6.04 (d, J = 1.2 Hz, 2 H), 4.85 (d, J = 19.1 Hz, 1 H), 4.54 (dt, J = 8.2, 4.1 Hz, 1 H), 4.33 (dt, J = 8.3, 4.2 Hz, 1 H), 3.85 (d, J = 19.1 Hz, 1 H), 2.91 (dd, J = 10.4, 5.6 Hz, 1 H), 2.63 (dd, J = 10.2, 7.6 Hz, 2 H), 2.27 (dd, J = 15.2, 4.3 Hz, 1 H), 2.15 (dd, J = 12.1, 7.5 Hz, 1 H), 2.09–1.99 (m, 1 H), 1.73 (dd, J = 15.2, 4.2 Hz, 1 H), 1.38 (s, 3 H), 1.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 172.4, 152.8, 147.6, 146.3, 125.2, 108.0, 107.0, 103.5, 102.2, 71.2, 70.6, 61.6, 45.8, 37.7, 35.7, 32.9, 30.5, 25.3, 23.1 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2855, 1680, 1477, 1376,

1262, 1033 cm^{-1}. HRMS (ESI): calcd. for $[(C_{20}H_{21}NO_6) + H]^+$ 372.1442; found 372.1434.

Compound 17: $NaBH_4$ (61 mg, 1.61 mmol) was added portionwise to a solution of **16** (500 mg, 1.34 mmol) in MeOH (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then it was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), and poured into a separating funnel containing H_2O (5 mL). The resulting mixture was extracted with CH_2Cl_2 (4× 5 mL), and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo to give a white solid, which was used without further purification.

Freshly distilled CH_2Cl_2 (10 mL) and triethylamine (0.93 mL, 6.7 mmol) were added to the above residue (500 mg), and the mixture was cooled to 0 °C. TBSOTf (1.06 g, 4.02 mmol) was added slowly, and after the addition was complete, the white suspension turned into a clear solution. The reaction mixture was stirred at 0 °C for a further 0.5 h, then it was quenched with brine. The resulting mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to give **17** (523 mg, 80% over two steps) as a white crystalline solid, m.p. 205–208 °C. R_f = 0.2 (petroleum ether/EtOAc, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 1 H), 6.45 (s, 1 H), 5.93 (s, 2 H), 4.72 (dd, J = 9.8, 7.0 Hz, 1 H), 4.52 (dd, J = 8.1, 4.0 Hz, 1 H), 4.41 (dd, J = 8.2, 4.1 Hz, 1 H), 4.33 (dd, J = 12.9, 6.9 Hz, 1 H), 3.01 (dd, J = 12.6, 10.3 Hz, 1 H), 2.73–2.52 (m, 3 H), 2.37 (dd, J = 15.3, 4.3 Hz, 1 H), 2.19–2.08 (m, 1 H), 2.05–1.94 (m, 1 H), 1.82 (dd, J = 15.4, 4.2 Hz, 1 H), 1.42 (s, 3 H), 1.30 (s, 3 H), 0.95 (s, 9 H), 0.21 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 146.94, 146.89, 137.1, 132.0, 107.6, 107.0, 103.9, 101.1, 71.3, 71.2, 65.3, 61.8, 41.8, 37.9, 36.2, 34.8, 30.4, 25.9, 25.6, 23.1, 18.0, –4.1, –4.9 ppm. IR (KBr): $\tilde{\nu}$ = 2932, 2858, 1686, 1481, 1415, 1248, 1204, 1088, 1037, 845, 782 cm^{-1}. HRMS (ESI): calcd. for $[(C_{26}H_{37}NO_6Si) + H]^+$ 488.2463; found 488.2452.

Compound 18: *n*BuLi (1.6 M in hexane; 0.55 mL, 0.88 mmol) was added to a stirred solution of **17** (360 mg, 0.74 mmol) in freshly distilled THF (5 mL) at –78 °C under an argon atmosphere, and the mixture was stirred at –78 °C for 30 min. A solution of PhSeCl (170 mg, 0.88 mmol) in THF (2 mL) was added dropwise over 1 min. The reaction mixture was stirred for 1 h at –78 °C, then the reaction was quenched by the addition of satd. aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc, 2:1) to give a white solid, which was used directly in the next step.

The residue was dissolved in MeOH/H_2O (5:1 v/v; 6 mL), and $NaIO_4$ (1.0 g, 4.5 mmol) was added. The reaction mixture was stirred for 20 min at room temperature, then the solvent was removed in vacuo, and CH_2Cl_2 (10 mL) was added. The organic layer was washed with brine (5 mL), dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to give **18** (305 mg, 85% over two steps) as a white solid, m.p. 180–182 °C. R_f = 0.4 (petroleum ether/EtOAc, 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1 H), 6.62 (s, 1 H), 6.01 (s, 1 H), 5.95 (d, J = 9.8 Hz, 2 H), 4.69 (t, J = 4.6 Hz, 1 H), 4.65–4.56 (m, 2 H), 4.43 (dd, J = 12.7, 6.2 Hz, 1 H), 3.16 (dt, J = 16.2, 9.7 Hz, 2 H), 2.95 (dd, J = 12.5, 10.1 Hz, 1 H), 2.56 (dd, J = 13.6, 5.8 Hz, 1 H), 1.86 (dd, J = 13.6, 8.9 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 0.97 (s, 9 H), 0.24 (s, 3 H), 0.21 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 159.9, 147.2, 146.8, 133.1, 128.7, 123.4, 108.7, 107.6, 104.4, 101.4, 74.4, 72.0, 66.0, 65.9, 42.5, 41.8, 29.6, 27.8, 25.8, 18.1, –4.3, –4.9 ppm. IR (KBr): $\tilde{\nu}$ = 2936, 2890, 1680, 1483, 1376, 1248, 1098, 1043, 864, 780 cm^{-1}. HRMS (ESI): calcd. for $[(C_{26}H_{35}NO_6Si) + H]^+$ 486.2306; found 486.2295.

Compound 20: Lithium hydroxide solution (0.5 M aq.; 3 mL) was added slowly by syringe to a stirred solution of ketone **18** (240 mg, 0.5 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred for 48 h at room temperature. The mixture was then diluted with CH_2Cl_2 (5 mL), and satd. aqueous NH_4Cl (5 mL) was added. The solution was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 3:2) to give **20** (198 mg, 93%) as a white crystalline solid, m.p. 192–195 °C. R_f = 0.2 (petroleum ether/EtOAc, 3:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, J = 1.9 Hz, 2 H), 6.81 (dd, J = 10.2, 2.3 Hz, 1 H), 6.31 (d, J = 10.1 Hz, 1 H), 5.98 (s, 1 H), 5.93 (dd, J = 11.3, 1.2 Hz, 2 H), 4.83 (t, J = 6.3 Hz, 1 H), 4.43 (s, 1 H), 4.32 (dd, J = 13.4, 6.6 Hz, 1 H), 3.37 (dd, J = 13.4, 6.1 Hz, 1 H), 3.23 (dd, J = 11.6, 5.2 Hz, 1 H), 1.66 (m, 1 H), 0.93 (s, 9 H), 0.22 (s, 3 H), 0.14 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 158.2, 147.2, 146.9, 139.7, 130.9, 129.8, 123.8, 119.8, 108.9, 104.7, 101.3, 66.7, 66.3, 66.2, 45.9, 44.4, 25.8, 18.0, –4.4, –4.6 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2952, 2855, 1664, 1478, 1377, 1249, 1102, 1040, 872, 838, 776 cm^{-1}. HRMS (ESI): calcd. for $[(C_{23}H_{29}NO_5Si) + H]^+$ 428.1888; found 428.1878.

Compound 21: KOH (202 mg, 3.6 mmol) and TBAB (290 mg, 0.9 mmol) were added to a mixture of alcohol **20** (130 mg, 0.3 mmol), THF (2 mL), and methyl iodide (1 mL). The reaction mixture was stirred for 12 h at 25 °C. The solution was poured into ice-water, and the resulting mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to give the *O*-methylation product 9-[(*tert*-butyldimethylsilyl)-oxy]-2-methoxy-1,2,8,9-tetrahydro-6*H*-[1,3]dioxolo[4,5-*g*]indolo-[7a,1-*a*]isoquinolin-6-one (120 mg, 91%) as a white solid, m.p. 175–178 °C. R_f = 0.2 (petroleum ether/EtOAc, 1:1). 400 MHz, $CDCl_3$ ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, J = 4.6 Hz, 2 H), 6.82 (d, J = 2.2 Hz, 1 H), 6.32 (d, J = 10.2 Hz, 1 H), 5.98 (s, 1 H), 5.94 (dd, J = 14.9, 1.3 Hz, 2 H), 4.85 (t, J = 6.2 Hz, 1 H), 4.34 (dd, J = 13.4, 6.6 Hz, 1 H), 4.01–3.89 (m, 1 H), 3.45–3.37 (m, 1 H), 3.36 (s, 3 H), 3.26 (dd, J = 11.5, 5.1 Hz, 1 H), 1.66 (dd, J = 11.5, 10.3 Hz, 1 H), 0.93 (s, 9 H), 0.23 (s, 3 H), 0.15 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 158.2, 147.2, 146.8, 137.2, 130.9, 130.1, 124.2, 119.7, 109.0, 104.6, 101.3, 74.7, 66.7, 66.0, 56.7, 44.5, 42.2, 25.8, 18.0, –4.4, –4.6 ppm. IR (KBr): $\tilde{\nu}$ = 2945, 2857, 1680, 1477, 1380, 1248, 1246, 1092, 1038, 841, 779 cm^{-1}. HRMS (ESI): calcd. for $[(C_{24}H_{31}NO_5Si) + H]^+$ 442.2044; found 442.2028.

The *O*-methylation product obtained above (100 mg, 0.23 mmol) was dissolved in THF (2 mL), and TBAF·$3H_2O$ (89 mg, 0.34 mmol) was added. The reaction mixture was stirred at 25 °C for 1 h, and then the reaction was quenched with water. The aqueous layer was extracted with EtOAc (3× 2 mL). The combined organic layers were dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc) to give **21** (70 mg, 95%) as a white crystalline solid, m.p. 215–220 °C; R_f = 0.1 (petroleum ether/EtOAc, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 1 H), 6.86 (s, 1 H), 6.86–6.81 (s, 1 H), 6.36 (d, J = 10.2 Hz, 1 H), 5.97 (s, 1 H), 5.93 (dd, J = 12.3, 1.3 Hz, 2 H), 4.90 (t, J = 6.8 Hz, 1 H), 4.47 (dd, J

= 13.7, 7.0 Hz, 1 H), 4.07–3.96 (m, 1 H), 3.40 (dd, *J* = 12.0, 5.0 Hz, 1 H), 3.37 (s, 3 H), 3.16 (dd, *J* = 11.7, 5.2 Hz, 1 H), 1.70 (dd, *J* = 11.5, 10.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 158.4, 147.5, 147.0, 137.2, 130.5, 129.9, 124.3, 119.6, 109.1, 104.6, 101.3, 74.5, 66.0, 65.5, 56.5, 43.3, 42.1 ppm. IR (KBr): $\tilde{\nu}$ = 3312, 2952, 2844, 1660, 1489, 1408, 1243, 1098, 1038, 864 cm^{-1}. HRMS (ESI): calcd. for $[(C_{18}H_{17}NO_5) + H]^+$ 328.1185; found 328.1180.

(±)-8-Oxo-erythrinine (3a): Diethyl azodicarboxylate (210 mg, 1.0 mmol) was added dropwise to a stirred mixture of **21** (60 mg, 0.18 mmol), triphenylphosphine (240 mg, 0.9 mmol), and 4-nitrobenzoic acid (100 mg, 0.55 mmol) in THF (2 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was then cooled to 0 °C, and satd. aqueous $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3× 3 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was passed through a short column of silica gel (petroleum ether/EtOAc, 1:1) to give the crude *p*-nitrobenzoate of **21** (80 mg) as a colorless oil.

The *p*-nitrobenzoate was dissolved in THF (1 mL), and the solution was cooled to 0 °C. LiOH (1 M aq.; 1 mL) was added, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2, and extracted with CH_2Cl_2 (3× 3 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by preparative TLC (petroleum ether/EtOAc, 1:2) to give (±)-8-oxo-erythrinine (**3a**) (58 mg, 90% over two steps) as a colorless oil. R_f = 0.1 (petroleum ether/EtOAc, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 1 H), 6.86 (dd, *J* = 10.2, 2.2 Hz, 1 H), 6.80 (s, 1 H), 6.34 (d, *J* = 10.2 Hz, 1 H), 6.01 (s, 1 H), 5.95 (d, *J* = 1.1 Hz, 1 H), 5.91 (d, *J* = 1.1 Hz, 1 H), 4.88 (s, 1 H), 4.15 (dd, *J* = 13.7, 4.3 Hz, 1 H), 4.00–3.88 (m, 1 H), 3.67 (dd, *J* = 13.7, 4.8 Hz, 1 H), 3.36 (s, 3 H), 2.68 (dd, *J* = 11.6, 5.1 Hz, 1 H), 1.72–1.57 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 157.1, 147.4, 147.1, 136.7, 130.3, 128.5, 124.3, 120.0, 109.0, 104.3, 101.3, 74.5, 66.3, 66.0, 56.6, 44.0, 41.4 ppm. IR (KBr): $\tilde{\nu}$ = 3352, 2926, 2825, 1667, 1483, 1369, 1259, 1101, 1038, 930, 864, 733 cm^{-1}. HRMS (ESI): calcd. for $[(C_{18}H_{17}NO_5) + H]^+$ 328.1185; found 328.1186.

(±)-8-Oxo-erythraline (3b): Triethylsilane (17.4 mg, 0.15 mmol) was added dropwise to a solution of **21** (30 mg, 0.1 mmol) in CH_2Cl_2/TFA (1:2; 0.6 mL) at 0 °C, and the mixture was stirred at that temperature for 30 min. The reaction was then quenched by the careful addition of satd. aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3× 2 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was passed through a short column of silica gel (petroleum ether/EtOAc, 1:2) to give (±)-8-oxo-erythraline (**3b**) (26 mg, 85%) as a white solid, m.p. 170–172 °C. R_f = 0.2 (petroleum ether/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 10.2 Hz, 1 H), 6.72 (d, *J* = 7.7 Hz, 2 H), 6.30 (d, *J* = 10.3 Hz, 1 H), 6.02 (s, 1 H), 5.91 (d, *J* = 13.7 Hz, 2 H), 3.95–3.83 (m, 1 H), 3.76 (d, *J* = 2.1 Hz, 1 H), 3.68–3.58 (m, 1 H), 3.34 (s, 3 H), 3.20–3.06 (m, 1 H), 2.96 (ddd, *J* = 15.8, 6.5, 4.0 Hz, 1 H), 2.79 (dd, *J* = 11.5, 5.0 Hz, 1 H), 1.69 (t, *J* = 10.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 157.0, 147.0, 146.0, 136.3, 129.9, 127.8, 123.8, 120.3, 109.4, 104.9, 101.1, 74.8, 66.8, 56.4, 41.2, 37.8, 27.3 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2883, 2818, 1679, 1487, 1374, 1245, 1105, 1032, 925, 849 cm^{-1}. HRMS (ESI): calcd. for $[(C_{18}H_{17}NO_4) + H]^+$ 312.1230; found 312.1225.

Compound 22: TBSCl (66 mg, 0.44 mmol) and DBU (91 mg, 0.6 mmol) were added to a solution of **18** (200 mg, 0.4 mmol) in benzene (5 mL). The mixture was stirred at room temperature for 10 min, and then heated to reflux for 36 h. The reaction mixture was cooled to room temperature, and diluted with diethyl ether. The organic layer was washed with water (5 mL), HCl (0.1 N aq.; 2× 5 mL), satd. aqueous $NaHCO_3$, and brine. The solution was dried with Na_2SO_4, and concentrated in vacuo. The residue was passed through a short column of silica gel (petroleum ether/EtOAc, 2:1) to give **22** (150 mg, 73%) as a colorless oil. R_f = 0.4 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 7.4 Hz, 2 H), 6.77 (dd, *J* = 10.1, 2.1 Hz, 1 H), 6.18 (d, *J* = 10.1 Hz, 1 H), 5.97 (d, *J* = 1.3 Hz, 1 H), 5.96 (s, 1 H), 5.92 (d, *J* = 1.2 Hz, 1 H), 4.83 (t, *J* = 6.4 Hz, 1 H), 4.41 (d, *J* = 7.3 Hz, 1 H), 4.36 (dd, *J* = 13.4, 6.7 Hz, 1 H), 3.34 (dd, *J* = 13.4, 6.2 Hz, 1 H), 3.01 (dd, *J* = 11.8, 5.4 Hz, 1 H), 1.75 (dd, *J* = 11.8, 9.8 Hz, 1 H), 0.95 (s, 9 H), 0.86 (s, 9 H), 0.23 (s, 3 H), 0.17 (s, 3 H), 0.06 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 158.3, 147.2, 146.8, 140.3, 131.0, 130.3, 123.2, 119.5, 108.9, 104.5, 101.3, 66.6, 66.2, 46.0, 44.3, 25.9, 25.7, 18.1, 17.9, –4.3, –4.5, –4.6 ppm. IR (film): $\tilde{\nu}$ = 2954, 2927, 2856, 1692, 1484, 1377, 1254, 1095, 1041, 1037, 837, 777 cm^{-1}. HRMS (ESI): calcd. for $[(C_{29}H_{43}NO_5Si_2) + H]^+$ 542.2758; found 542.2758.

Compound 23: KOH (24 mg, 0.4 mmol) and TBAF·3H_2O (24 mg, 0.09 mmol) were added to a mixture of **22** (20 mg, 0.036 mmol), THF (1 mL), and methyl iodide (0.1 mL). The reaction mixture was stirred for 6 h at 25 °C. The solution was poured into ice-water, and the resulting mixture was extracted with CH_2Cl_2 (3× 1 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether/EtOAc, 2:1) to give **23** (11 mg, 89%) as a colorless oil . R_f = 0.6 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 4.5 Hz, 2 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.34 (d, *J* = 10.2 Hz, 1 H), 6.00 (s, 1 H), 5.96 (dd, *J* = 11.5, 1.3 Hz, 2 H), 4.45 (dd, *J* = 6.6, 3.1 Hz, 1 H), 4.35 (dd, *J* = 13.9, 6.6 Hz, 1 H), 3.91–3.81 (m, 1 H), 3.63 (dd, *J* = 13.9, 3.1 Hz, 1 H), 3.41 (s, 3 H), 3.34 (s, 3 H), 3.31 (dd, *J* = 11.9, 5.1 Hz, 1 H), 1.72–1.62 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 157.9, 147.4, 147.0, 137.5, 131.5, 127.1, 123.9, 119.8, 110.6, 105.3, 101.4, 75.4, 74.8, 66.3, 56.3, 56.2, 42.5, 42.1 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 2852, 1684, 1485, 1378, 1255, 1103, 1038, 870 cm^{-1}. HRMS (ESI): calcd. for $[(C_{19}H_{19}NO_5) + H]^+$ 342.1336; found 342.1330.

Compound 24: $LiAlH_4$ (1 M solution in ether; 0.18 mL, 0.18 mmol) was added to a solution of $AlCl_3$ (8 mg, 0.06 mmol) in freshly distilled THF (2 mL) at –10 °C, and the mixture was stirred at the same temperature for 30 min. Then a solution of **23** (10 mg, 0.03 mmol) in THF (0.5 mL) was added. The mixture was stirred for 0.5 h at –10 °C, then the reaction was quenched by the addition of NH_4OH (5% aq.). The aqueous layer was extracted with CH_2Cl_2 (3× 2 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (petroleum ether/EtOAc, 1:1) to give (±)-11-*epi*-methoxyerythraline (**24**) (6 mg, 68%) as a colorless oil. R_f = 0.2 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 6.81 (s, 1 H), 6.52 (d, *J* = 9.9 Hz, 1 H), 6.00 (d, *J* = 10.2 Hz, 1 H), 5.91 (d, *J* = 6.8 Hz, 2 H), 5.70 (s, 1 H), 4.51 (t, *J* = 7.3 Hz, 1 H), 4.07 (s, 1 H), 3.74 (d, *J* = 12.5 Hz, 1 H), 3.55 (d, *J* = 14.4 Hz, 1 H), 3.45 (s, 3 H), 3.40–3.35 (m, 2 H), 3.33 (s, 3 H), 2.74 (dd, *J* = 11.6, 5.5 Hz, 1 H), 1.80 (t, *J* = 11.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 146.6, 143.3, 133.3, 132.1, 127.8, 125.2, 122.9, 108.3, 105.9, 100.9, 75.8, 71.4, 66.4, 57.1, 56.2, 56.1, 46.6, 40.6 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2821, 1686, 1503, 1482, 1380, 1239, 1102, 1038, 930, 872, 811 cm^{-1}. HRMS (ESI): calcd. for $[(C_{19}H_{21}NO_4) + H]^+$ 328.1549; found 328.1549.

Compound 6: AIBN (25 mg, 0.15 mmol) and Bu_3SnH (162 μL, 0.6 mmol) were dissolved in benzene (100 mL), and the mixture was heated to reflux. A solution (0.05 M in benzene) of iodide **25**[17] (150 mg, 0.3 mmol) was added slowly over 30 min. The mixture was heated at reflux for a further 2 h, then KF (1 M aq.; 2 mL) was added. The aqueous layer was extracted with EtOAc (3× 5 mL). The combined organic layers were washed with brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1 to 1:2) to give cyclization product **26** (83 mg, 78%) as a white solid. The spectroscopic data matched those reported in the literature.[17]

The cyclization product (80 mg, 0.22 mmol) was dissolved in freshly distilled THF (1 mL), and the solution was cooled to 0 °C. BH_3 (1.0 M in THF; 1.1 mL, 1.1 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h, then it was heated to reflux for 12 h, and then quenched with MeOH (3 mL). The solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography (basified with 5% Et_3N; petroleum ether/EtOAc/Et_3N, 4:1:0.2) to give aminodioxolane **6** (65 mg, 89%) as a white solid. The spectroscopic data matched those reported in the literature.[17]

Compound 27: Aminodioxolane **6** (300 mg, 0.91 mmol) was dissolved in THF/$CHCl_3$ (1:1; 10 mL), and CbzCl (250 μL, 1.82 mmol) was added. The reaction mixture was heated to 55 °C in a sealed tube in a microwave reactor (Anton Paar W300). After 2 h, the mixture was cooled to room temperature, and the reaction was quenched by the addition of satd. aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were washed with brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to give **27** (375 mg, 82%) as a colorless oil. R_f = 0.3 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 7.2 Hz, 3 H), 7.18–7.08 (m, 3 H), 6.71 (s, 1 H), 5.87 (br. s, 2 H), 5.01 (d, J = 12.5 Hz, 2 H), 4.66 (d, J = 11.5 Hz, 1 H), 4.41 (d, J = 11.4 Hz, 1 H), 4.31 (ddd, J = 24.3, 12.3, 8.2 Hz, 3 H), 3.75 (t, J = 6.4 Hz, 1 H), 3.44–3.37 (m, 1 H), 3.21 (m, 1 H), 2.43 (dd, J = 16.9, 7.2 Hz, 1 H), 2.16 (ddd, J = 26.5, 12.4, 6.5 Hz, 2 H), 1.85 (dd, J = 6.4, 3.9 Hz, 2 H), 1.45 (s, 3 H), 1.27 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 148.0, 145.9, 141.0, 129.9, 128.4, 128.3, 128.2, 127.7, 127.6, 127.4, 126.9, 109.8, 108.6, 101.1, 81.1, 73.0, 66.5, 65.1, 53.5, 45.2, 42.2, 31.0, 27.4, 24.4 ppm. IR (KBr): $\tilde{\nu}$ = 2926, 1697, 1487, 1359, 1267, 1211, 1040, 937, 869 cm^{-1}. HRMS (ESI): calcd. for $[(C_{27}H_{30}ClNO_6) - Cl]^+$ 464.2068; found 464.2061.

Compound 28: Flame-dried $NaHCO_3$ (97 mg, 1.16 mmol)was added to a solution of **27** (115 mg, 0.23 mmol) in dry DMSO (2 mL). The reaction mixture was heated to 85 °C in a sealed tube. After 30 min, the mixture was cooled down, and water (5 mL) was added. The aqueous layer was extracted with EtOAc (4× 5 mL). The combined organic extracts were washed with water and brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1) to give the aldehyde benzyl 4-(6-formylbenzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyloctahydro-5*H*-[1,3]-dioxolo[4,5-*f*]indole-5-carboxylate (82 mg, 75%) as a colorless oil. R_f = 0.2 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 7.30 (q, J = 5.4 Hz, 3 H), 7.11 (s, 4 H), 5.94 (br. s, 2 H), 4.89 (d, J = 12.5 Hz, 1 H), 4.44 (br. s, 1 H), 4.36 (dd, J = 13.7, 6.2 Hz, 1 H), 4.14 (br. s, 1 H), 4.06–3.96 (m, 1 H), 3.74 (t, J = 6.4 Hz, 1 H), 3.59 (br. s, 1 H), 3.44–3.31 (m, 1 H), 2.40 (dd, J = 14.7, 7.2 Hz, 1 H), 2.25–2.15 (m, 1 H), 2.11 (dd, J = 12.8, 5.4 Hz, 1 H), 2.02 (dd, J = 19.2, 8.7 Hz, 1 H), 1.89–1.80 (m, 1 H), 1.42 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 154.8, 152.3, 146.8, 139.7, 136.6, 130.3, 128.3, 127.7, 127.5, 110.0, 108.9, 108.1, 101.8, 77.6, 73.1, 67.9, 66.6, 60.4, 45.5, 39.7, 27.6, 25.6, 24.9 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2936, 2895, 2731, 1697, 1614, 1485, 1412, 1358, 1250, 1040, 933, 872, 699 cm^{-1}. HRMS (ESI): calcd. for $[(C_{27}H_{29}NO_7) + H]^+$ 480.2017; found 480.2014.

The aryl aldehyde obtained above (30 mg, 0.063 mmol) was dissolved in a mixture of THF and *t*BuOH (1:1; 1 mL), and then 2-methyl-2-butene (157 mg, 3.15 mmol) was added. In a separate flask, $NaClO_2$ (57 mg, 0.63 mmol) and NaH_2PO_4 (53 mg, 0.38 mmol) were dissolved in water (0.5 mL). Once fully dissolved, the aqueous solution was poured into the stirred organic solution, and the mixture was stirred vigorously. When TLC indicated that the reaction was complete (2 h), the solvent was evaporated, and water (2 mL) was added. The aqueous layer was extracted with EtOAc (4× 2 mL). The combined organic layers were washed with brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/MeOH, 10:1) to give **28** (29 mg, 92%) as a white solid, m.p. 172–175 °C. R_f = 0.2 (petroleum ether/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 1 H), 7.28 (t, J = 7.1 Hz, 3 H), 7.12 (d, J = 5.8 Hz, 3 H), 5.90 (br. s, 2 H), 4.94 (d, J = 12.5 Hz, 1 H), 4.46 (d, J = 23.4 Hz, 2 H), 4.41–4.24 (m, 2 H), 3.97 (br. s, 1 H), 3.52 (br. s, 1 H), 3.43 (d, J = 5.3 Hz, 1 H), 2.35 (dd, J = 14.9, 7.5 Hz, 1 H), 2.24–2.12 (m, 1 H), 2.05 (t, J = 5.9 Hz, 3 H), 1.46 (s, 3 H), 1.31 (s, 3 H) ppm. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.53 (br. s, 1 H), 7.54–7.16 (m, 5 H), 7.04 (s, 2 H), 5.92 (br. t, J = 71.7 Hz, 2 H), 4.83 (br. s, 1 H), 4.47 (br. s, 1 H), 4.30 (dd, J = 24.6, 14.0 Hz, 2 H), 4.00 (dd, J = 11.0, 7.4 Hz, 1 H), 3.45–3.38 (m, 1 H), 2.29 (br. s, 1 H), 2.09 (dt, J = 9.0, 5.6 Hz, 1 H), 2.06–1.87 (m, 2 H), 1.76 (br. s, 1 H), 1.32 (s, 3 H), 1.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 155.0, 151.2, 145.9, 138.6, 136.7, 128.2, 127.6, 127.4, 124.0, 110.7, 108.9, 108.4, 101.7, 78.2, 73.2, 66.6, 60.6, 45.6, 40.7, 29.3, 27.4, 25.1 ppm. IR (KBr): $\tilde{\nu}$ = 2958, 2923, 1662, 1439, 1260, 1111, 1041, 919, 879, 805, 699 cm^{-1}. HRMS (ESI): calcd. for $[(C_{27}H_{29}NO_8) + H]^+$ 496.1966; found 496.1951.

Compound 29: A magnetically stirred solution of acid **28** (37.1 mg, 0.075 mmol) in a mixture of THF and HCl (1 N aq.) (3:1 v/v; 2 mL) was heated at 50 °C for 5 h. Then the mixture was cooled to room temperature, and quenched with satd. aqueous $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (3× 2 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1) to give **29** (30 mg, 92%) as a white solid, m.p. 147–149 °C. R_f = 0.5 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.28 (m, 7 H), 6.04 (s, 2 H), 5.22 (d, J = 10.8 Hz, 2 H), 4.46 (br. s, 1 H), 4.31–4.20 (m, 2 H), 3.89 (br. s, 1 H), 3.49–3.38 (m, 2 H), 2.66 (br. s, 1 H), 2.50 (s, 1 H), 2.28–2.19 (m, 2 H), 2.12–2.02 (m, 1 H), 1.92–1.80 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 156.7, 152.8, 146.8, 137.9, 128.5, 128.1, 127.9, 118.5, 109.4, 106.7, 101.9, 81.0, 67.5, 66.9, 65.8, 60.3, 44.5, 42.6, 37.3, 33.5, 27.6 ppm. IR (KBr): $\tilde{\nu}$ = 3420, 2925, 2853, 1696, 1483, 1405, 1280, 1120, 1033, 930, 870, 772 cm^{-1}. HRMS (ESI): calcd. for $[(C_{24}H_{23}NO_7) + H]^+$ 438.1547; found 438.1534.

(±)-Clivonine (4)

Method A: Pd/C (5 mg) was added to a solution of ester **29** (18 mg, 0.04 mmol) in methanol (1 mL) at room temperature. The mixture was stirred under a hydrogen atmosphere (20 atm) at room temperature for 6 h, and then it was filtered through a pad of Celite.

The solid was washed carefully with methanol (10 mL), and the combined filtrates were concentrated to give the crude amine.

Methanol (1 mL) was then added to the free amine, and then formaldehyde solution (37% HCHO aq.; 10 μL) and $NaBH_3CN$ (5 mg, 0.08 mmol) were added sequentially at room temperature. Then $ZnCl_2$ (2.2 mg, 0.016 mmol) was added. The mixture was stirred at room temperature for 0.5 h. Then it was cooled to 0 °C, and NaOH (0.1 M aq.; 0.5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine, and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by preparative TLC (petroleum ether/EtOAc, 1:4) to give (±)-clivonine (**4**) (8 mg, 67% over two steps) as a white solid.

Method B: Formaldehyde solution (37% HCHO aq.; 10 μL) and Pd/C (5 mg) were added to a solution of ester **29** (15 mg, 0.034 mmol) in methanol (1 mL) at room temperature. The mixture was stirred under a hydrogen atmosphere (20 atm) at room temperature for 48 h, and then it was filtered through a pad of Celite. The solid was washed carefully with methanol (10 mL), and the combined filtrates were concentrated. The residue was purified by preparative TLC (petroleum ether/EtOAc, 1:4) to give (±)-clivonine (**4**) (5 mg, 50%; 75% based on recovered starting material) as a white solid, m.p. 197–200 °C (ref.[15] 199–200 °C). R_f = 0.2 (EtOAc/MeOH, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.48 (s, 1 H), 6.04 (d, J = 5.0 Hz, 2 H), 4.26 (d, J = 3.1 Hz, 1 H), 4.11 (dd, J = 12.4, 2.5 Hz, 1 H), 3.38–3.17 (m, 2 H), 2.91 (dd, J = 9.7, 6.5 Hz, 1 H), 2.63–2.48 (m, 5 H), 2.35–2.25 (m, 2 H), 2.18–2.10 (m, 1 H), 1.82 (ddd, J = 15.3, 6.5, 3.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 152.7, 146.7, 140.8, 118.7, 109.3, 107.2, 101.8, 81.8, 69.5, 67.4, 53.0, 45.2, 33.5, 33.2, 30.8, 28.8 ppm. IR (KBr): $\tilde{\nu}$ = 3456, 2921, 1701, 1470, 1262, 1032 cm^{-1}. HRMS (ESI): calcd. for $[(C_{17}H_{19}NO_5) + H]^+$ 318.1341; found 318.1338.

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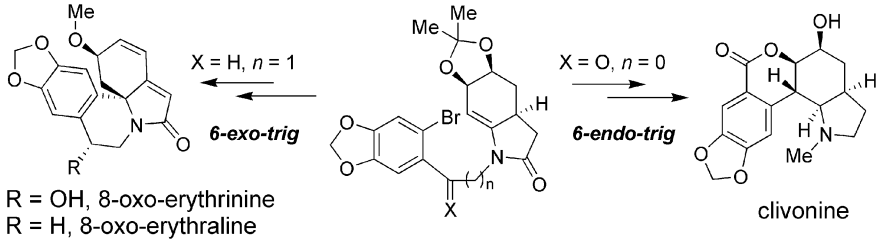
Total Synthesis



Total syntheses of the erythrina alkaloids (±)-8-oxo-erythrinine and (±)-8-oxo-erythraline have been developed, based on an intramolecular 6-*exo-trig* radical cyclization of a highly functionalized enamide (X = O, *n* = 1). An improved linear total synthesis of the amaryllidaceae alkaloid (±)-clivonine through a 6-*endo-trig* cyclization of a similar intermediate (X = O, *n* = 0) is also reported.

Keywords: Total synthesis / Alkaloids / Polycycles / Radical reactions / Cyclization

