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PAPER

A concise stereoselective synthesis of (–)-erycibelline†

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(–)-Erycibelline, the dihydroxynortropane alkaloid isolated from *Erycibe elliptilimba* Merr. et Chun., was synthesized using a cyclic nitrone as advanced intermediate, wherein the key step was the SmI_2-induced intramolecular reductive coupling of cyclic nitrone with aldehyde which resulted in good yield and stereoselectivity.

Introduction

Tropane alkaloids,[1] which possess the 8-azabicyclo[3.2.1]octane framework, are a large family of alkaloids with more than 200 members. Due to their unique structures and promising pharmaceutical applications,[2] tropane alkaloids continue to draw the attention of both synthetic and medicinal chemists since their first discovery in the mid 19th century.[3] (–)-Erycibelline **4** (Fig. 1) is the first naturally occurring dihydroxynortropane alkaloid isolated from the Chinese herb medicine *Erycibe elliptilimba* Merr. et Chun., which has been used for the treatment of rheumatic disease and as a pain-killer.[4] There are a number of hydroxylated nortropane alkaloids which are structurally related to (–)-erycibelline **4**, for example, bao gong teng C **2** and bao gong teng A **3**, isolated from the same species of Chinese herb *Erycibe obtusifolia* benth,[5] the latter of which has hypotensive and miotic activity and has been used for the treatment of glaucoma.[6] Other related compounds include mono-hydroxylated nortropanes, such as nor-ψ-tropine **1**,[7] and tri-hydroxylated nortropanes, such as **5**, **6**[7,8] and calystegines **7** to **9**,[9] which are potent glycosidase inhibitors and have great potential in the treatment of viral infection,[10] cancer,[11] diabetes,[12] and lysosomal storage disorders.[13]

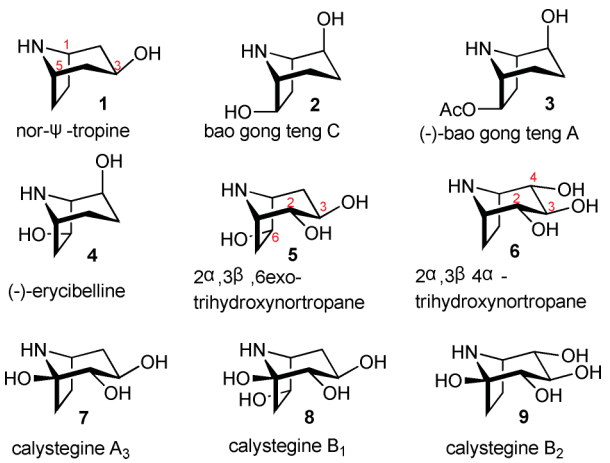
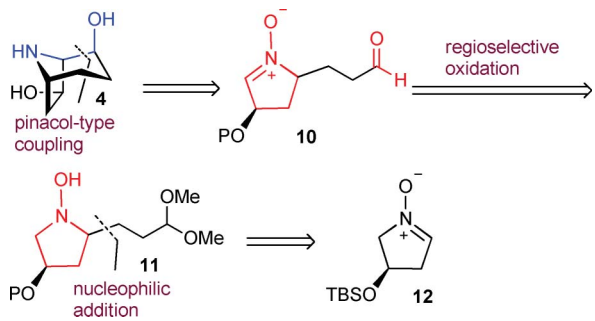


Fig. 1 Natural hydroxylated nortropane alkaloids.

In view of their intriguing structures and biological activities, it is significant to develop efficient methods for the syntheses of this class of nortropanes. There are only a few reports on the syntheses of compounds possessing the 2,6-dihydroxylated nortropane framework. Bao gong teng A **3**, has been synthesized *via* 1,3-dipolar cycloaddition of acrylonitrile or acrylate of methyl (*S*)-lactate to 3-hydroxypyridinium salt,[14] molybdenum-mediated [5 + 2] cycloaddition,[15] and intramolecular reductive coupling of *N*-acyl *N*,*O*-acetal with aldehyde.[16]

In the context of our continuing interest in iminosugars[17] and their derivatives,[18] we wish to develop an efficient and general strategy for the synthesis of the hydroxylated nortropane skeleton. (–)-Erycibelline **4** was chosen as the target compound because it might be a valuable compound in the structure–activity study of the hydroxylated nortropanes and the synthesis will help to fully determine the structure of this compound.[19]

Our retrosynthetic analysis of (–)-erycibelline **4** is outlined in Scheme 1. The *cis* vicinal amino alcohol in the piperidine ring



Scheme 1 Retrosynthetic analysis of (–)-erycibelline (**4**).

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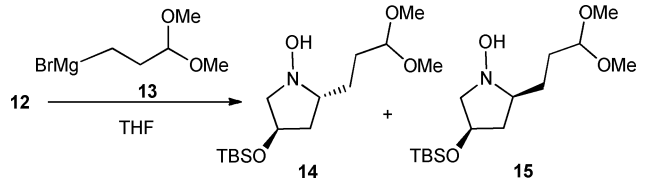
† Electronic supplementary information (ESI) available: Characterization data (^1H, ^{13}C and 2D NMR spectra) of the intermediates and final products. See DOI: 10.1039/c1ob06244a

Table 1 Grignard addition to cyclic nitrone (**12**)



Entry	T/°C	Lewis acid	**14** : **15**[a]	Yield[b] (%)
1	−78	None	67 : 33	96
2	0	None	56 : 44	97
3	0	ZnI_2	62 : 38	93
4	0	$MgBr_2$	66 : 34	89
5	30	None	65 : 35	79
6	60	None	62 : 38	81

[a] Determined by ^{1}H NMR. [b] Isolated yield.

can be constructed by an intramolecular pinacol-type coupling of cyclic nitrone **10** which possesses both nitrone and aldehyde functional groups. Nitrone **10** can be derived from the oxidation of hydroxylamine **11** which can be readily obtained by nucleophilic addition to cyclic nitrone **12**.

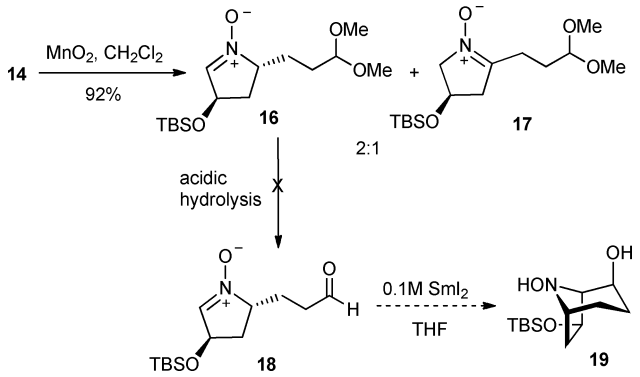
Results and discussion

Synthesis of (−)-erycibelline

The requisite nitrone **12**[20] was prepared through a reported method starting from *trans*-4-hydroxy-L-proline in three steps with a total yield of 40%.

The organometallic addition of (3,3-dimethoxypropyl)-magnesium bromide **13** to nitrone **12** was then attempted (Table 1). Organometallic addition to cyclic nitrones bearing a vicinal alkoxy substituent, such as a benzyloxy group, preferentially gave *trans* adducts,[21] but little attention has been paid to organometallic addition to cyclic nitrones without an α-substituent. It turned out that Grignard addition of **13** to nitrone **12** at 0 °C afforded hydroxylamine **14** and **15** in good yields but with poor diastereoisomeric excess. Optimization of the diastereoselectivity *via* addition of Lewis acid (Table 1, Entry 3 and 4) or lowering the reaction temperature (Table 1, Entry 1) only slightly improved the ratio of the *trans* adduct (dr = 67 : 33 ~ 62 : 38). Fortunately, the two adducts could be easily separated by flash column chromatography. The stereochemistry of the two isomers were determined by NOE experiments.

To transform the hydroxylamine **14** into the desired *aldo* nitrone **16**, compound **14** was treated with activated MnO_2[22] to give a separable mixture of *aldo* nitrone **16** and *keto* nitrone **17** in excellent overall yield with regio-selectivity favouring the formation of *aldo* nitrone **16** (**16** : **17** = 2 : 1, Scheme 2). Previous reports have shown that the regio-selectivity of the oxidation of cyclic hydroxylamine is largely dependent on the structures of the substrates, *i.e.*, 2-substituted 1-hydroxypyrrolidines tending to form *keto* nitrones,[23] whereas a β-alkoxy group has a strong influence on regioselectivity and favors the abstraction of the vicinal *anti* proton.[24] The preferential formation of *aldo* nitrone **16** confirmed that the vicinal alkoxy group was crucial for directing regio-selectivity of the oxidation. Assignment of the *aldo* nitrone **16** was on the basis

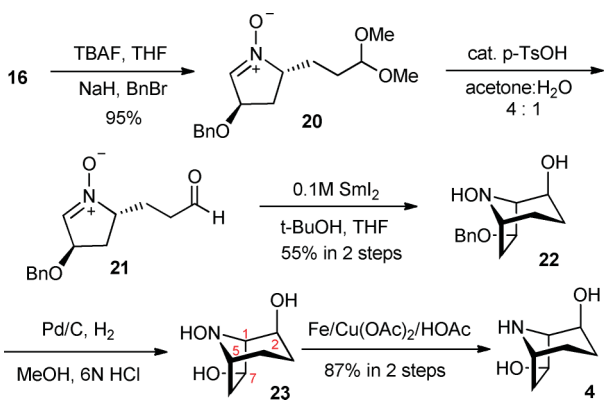


Scheme 2 Initial attempt at the cross-coupling reaction.

of the observation of the signal of the HC=N proton displayed in the ^{1}H NMR spectra (δ 6.74 ppm, triplet, J = 1.5 Hz).

With nitrone **16** in hand, we commenced our attempt on the formation of the nortropane framework by intramolecular reductive pinacol-type coupling of aldehyde and nitrone. Nitrone umpolung mediated by samarium diiodide has attracted much attention in recent years, reactions of nitrones with aldehydes/ketones,[25] imines,[26] and α,β-unsaturated acid derivatives[27] have been well documented in the literature. However, to the best of our knowledge, the construction of the nortropane skeleton by intramolecular coupling of cyclic nitrone with aldehyde has not been reported yet. To liberate the aldehyde group, **16** was subjected to acidic hydrolysis. However, it turned out that the *O*-TBS group was very sensitive toward acidic hydrolysis conditions and liberation of the aldehyde always resulted in *O*-TBS deprotected products. Thus, the approach of constructing the nortropane **19** *via* the intramolecular nitrone-aldehyde coupling of **18** was abandoned (Scheme 2).

An alternative strategy was therefore devised in which TBS was first converted to the non-acid-sensitive benzyl group before hydrolyzing the acetal. TBAF mediated deprotection of the silyl group and subsequent protection of the hydroxyl group with benzyl in a "one-pot" two-step process gave nitrone **20** in 95% yield. In the course of converting the acetal to aldehyde **21**, an unknown byproduct was generated; efforts to purify the aldehyde led to lower yield due to its instability (Scheme 3).



Scheme 3 Synthesis of (−)-erycibelline (**4**).

The subsequent intramolecular reductive coupling reaction of **21** was then attempted without further purification of the

crude aldehyde. It was found that the coupling reaction did not commence in the absence of additives such as proton sources (MeOH, H_2O or *t*-BuOH)[28] or HMPA.[29] The reaction resulted in the formation of only the single diastereoisomer **22**, the desired nortropane derivative, in 55% yield within two steps, by addition of *t*-BuOH as promoter. The excellent diastereoselectivity can be deduced as arising from coordination of a samarium(III) ketyl radical to the oxygen atom of nitrone with the C═O group which preferentially gives *cis* amino alcohol (Fig. 2).

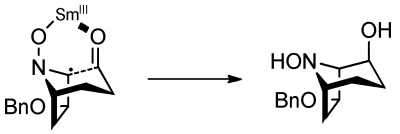


Fig. 2 Proposed coordinated transition state for reductive coupling.

Deprotection of **22** *via* Pd-catalysed hydrogenolysis in acidic methanol solution resulted in the formation of fully deprotected hydroxylamine **23**, which was treated with Fe–Cu(OAc)$_2$/HOAc to afford the amine **4** in 87% yield within two steps. The hydroxylamine **23** was isolated and fully characterized by ESI-MS analysis and NMR experiment. The NOESY spectrum (D_2O) of **23** further supported the *cis* stereochemistry based on the strong NOE effect between H-2 and H-7. The ^{13}C NMR experiment of the synthetic (−)-erycibelline **4** was carried out in various solvents such as D_2O, MeOD, DMSO-d_6, pyridine-d_5 and $CDCl_3$ (see supporting information). To our delight, the chemical shift of synthetic (−)-erycibelline **4** in MeOD was identical to those of the natural product reported by Lu[4] *et al.* Furthermore, the optical rotation of compound **4** {$[\alpha]_D^{20}$ −11.6 (*c* 0.5 in EtOH)} matched well with that of the natural product {$[\alpha]_D^{10}$ −12.5 (*c* 0.57 in EtOH)}.

Synthesis of 7-*epi*-(+)-erycibelline

The synthetic sequence for the synthesis of **4** was then applied to the synthesis of 7-*epi*-(+)-erycibelline **29**. Oxidation of **15** afforded *aldo* nitrone **24** as the main regio-isomer, which was subjected to a three step sequence transformation to provide the benzyl protected aldehyde **26**. The aldehyde **26** underwent intramolecular coupling reaction promoted by SmI_2 in the presence of H_2O to afford **27** as a single diastereoisomer. The *cis* configuration of the new stereo-center in **27** was unambiguously established through 2D NOESY experiment which exhibited strong correlation between H-2 and CH_2Ph. Subsequent hydrogenation and reduction furnished 7-*epi*-(+)-erycibelline **29** in excellent yield (Scheme 4).

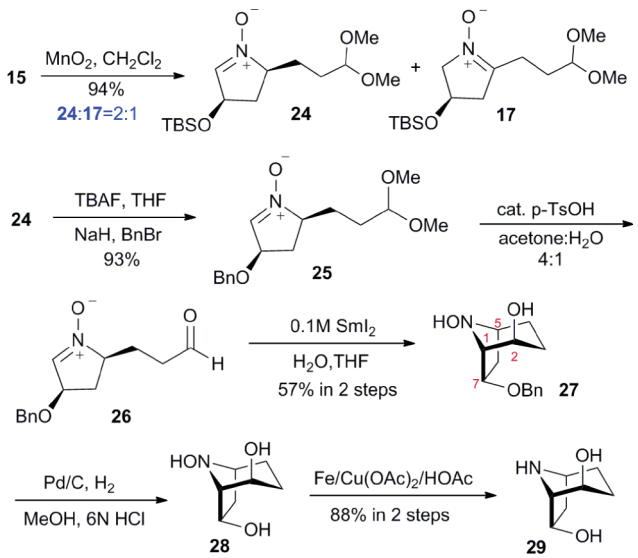
Evaluation of glycosidase inhibition towards various enzymes

(−)-Erycibelline **4** and 7-*epi*-(+)-erycibelline **29** can be seen as the dehydroxylated derivatives of the calystegines which are potent inhibitors of glycosidases. Therefore, these two compounds were assayed as potential glycosidase inhibitors of a range of enzymes, but neither showed any inhibition toward the tested enzymes (Table 2).

Table 2 Concentration of iminosugar giving 50% inhibition of various glycosidases

	IC_{50} (μM)	
Enzyme	**4**	**29**
α-glucosidase		
yeast	NI[a] (0%)[b]	NI (0%)
rice	NI (18.2%)	NI (13.5%)
rat intestinal maltase	NI (20.2%)	NI (8.6%)
β-glucosidase		
almond	NI (0%)	NI (0%)
bovine liver	NI (11.2%)	NI (9.7%)
α-galactosidase		
coffee beans	NI (21.2%)	NI (9.0%)
β-galactosidase		
bovine liver	NI (17.3%)	NI (15.6%)
α-mannosidase		
jack beans	NI (0%)	NI (0%)
β-mannosidase		
snail	NI (0%)	NI (0%)
α-L-fucosidase		
bovine kidney	NI (0%)	NI (0%)
α,α-trehalase		
porcine kidney	NI (9.3%)	NI (0%)
amyloglucosidase		
Aspergillus niger	NI (0%)	NI (0%)
α-L-rhammosidase		
Penicillium decumbens	NI (0%)	NI (0%)

[a] NI: No inhibition (less than 50% inhibition at 1000 μM. [b] (): inhibition% at 1000 μM.



Scheme 4 Synthesis of 7-*epi*-(+)-erycibelline (**29**).

Conclusion

In summary, the first stereoselective synthesis of (−)-erycibelline **4** together with its diastereomer, 7-*epi*-(+)-erycibelline **29**, has been accomplished using a cyclic nitrone as advanced intermediate, wherein the key step was the SmI_2-induced intramolecular reductive coupling of cyclic nitrone with aldehyde which resulted in good yield and stereoselectivity. This synthetic approach is versatile and gives general access to hydroxylated nortropane alkaloids and their analogues. The glycosidase-inhibiting results observed herein may be valuable for further structure–activity studies on hydroxylated nortropane alkaloids.

Experimental

Material and methods

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Tetrahydrofuran was distilled from sodium and benzophenone immediately before use. Reactions were stirred using Teflon-coated magnetic stirring bars. Analytical TLC was performed with 0.20 mm silica gel 60 F plates with 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O} or a solution 0.5% ninhydrin in acetone. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230–400 mesh). Acidic ion exchange chromatography was performed on Amberlite IR-120 (H^+) or Dowex 50WX8-400, H^+ form. Melting points were determined using an electrothermal melting point apparatus. Both melting points and boiling points are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-480 plus Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or D_2O on a Bruker AV300 (^1H at 300 MHz, ^{13}C at 75 MHz) or a Bruker AV400 (^1H at 400 MHz, ^{13}C at 100 MHz) or a Bruker AV600 (^1H at 600 MHz, ^{13}C at 150 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ/FT mass spectrometer or a GCT mass spectrometer. Polarimetry was carried out using an Optical ActivityAA-10R polarimeter and the measurements were made at the sodium D-line with a 0.5 dm path length cell. Concentrations (c) are given in gram per 100 mL.

(2*R*,4*R*)-1-Hydroxy-2-(3,3-dimethoxypropyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (14) and (2*S*,4*R*)-1-hydroxy-2-(3,3-dimethoxypropyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (15)

To a well stirred solution of cyclic nitrone **12** (10 g, 0.046 mol) in anhydrous THF (50 mL) was added a solution of Grignard reagent in THF (1 M, 115 mL) [prepared by stirring Mg turnings (2.88 g, 0.12 mol) and bromide (15.7 mL, 0.115 mol) in THF (115 mL)] at –78 °C. The reaction mixture was stirred for 30 min, quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried and the solvents were removed *in vacuo*. The residue was purified by flash chromatography (silica gel, petroleum ether/AcOEt = 5/1–1/1) to afford **14** and **15** (14.12 g, 96%) as a colorless oil.

14: $[\alpha]_D^{20}$ –17.9 (c 0.67 in CH_2Cl_2); ν_{max}/cm^{-1} 3229m, 2953vs, 2931vs, 2857s, 1469m, 1383m, 1255m, 1195m, 1129s, 1075s, 1007m, 905m, 837s, 778s; δ_H(300 MHz; $CDCl_3$) 4.37–4.33 (2 H, m, 8-H, 4-H), 3.52 (1 H, dd, J 6.0 and 11.1, 5-H), 3.27 (6 H, s, 2×OCH_3), 3.04–3.01 (1 H, m, 2-H), 2.78 (1 H, dd, J 5.7 and 11.1, 5-H), 1.84–1.70 (2 H, m, 3-H and 6-H), 1.64–1.54 (3 H, m, 3-H and 7-H), 1.38–1.36 (1 H, m, 6-H), 0.83 (9 H, s), 0.00 (6 H, s); δ_C(75 MHz; $CDCl_3$) 104.42 (C8), 67.16 (C4), 66.74 (C2 and C5), 52.62 (OCH_3), 38.87 (C3), 29.67 (C7), 27.35 (C6), 25.78, 17.99, –4.86; δ_C(Dept-135; 75 MHz; $CDCl_3$) positive, 104.42, 67.15, 66.74, 52.62, 25.78, –4.86; negative, 38.87, 29.67; HRMS (ESI) calcd for $C_{15}H_{33}NO_4SiH^+$ $[M + H]^+$ 320.2252, found 320.2252.

15: $[\alpha]_D^{20}$ +31.7 (c 0.63 in CH_2Cl_2); ν_{max}/cm^{-1} 3231m, 2953vs, 2931vs, 2857s, 1471m, 1462m, 1384m, 1363m, 1255s, 1195m, 1129s, 1050s, 912m, 837s, 776s; δ_H(300 MHz; $CDCl_3$) 4.36–4.31 (2 H, m, 8-H, 4-H), 3.28 (6 H, s, 2×OCH_3), 3.14 (1 H, dd, J 1.8 and 11.1, 5-H), 2.94 (1 H, dd, J 6.6 and 11.1, 5-H), 2.77–2.67 (1H, m, 2-H), 2.36–2.26 (1 H, m, 3-H), 1.89–1.78 (1 H, m, 6-H), 1.64–1.57 (2 H, m, 7-H), 1.49–1.30 (2 H, m, 6-H and 3-H), 0.83 (9 H, s), 0.00 (6 H, s); δ_C(75 MHz; $CDCl_3$) 104.49 (C8), 68.65 (C4), 67.82 (C2), 66.68 (C5), 52.66, 52.53 (OCH_3), 39.32 (C3), 29.59 (C7), 28.41 (C6), 25.79, 17.99, –4.79, –4.87; δ_C(Dept-135; 75 MHz; $CDCl_3$) positive, 104.49, 68.64, 67.82, 52.66, 52.53, 25.79, –4.79, –4.87; negative, 66.68, 39.33, 29.60, 28.41; HRMS (ESI) calcd for $C_{15}H_{33}NO_4SiH^+$ $[M + H]^+$ 320.2252, found 320.2252.

(3*R*,5*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(3,3-dimethoxypropyl)pyrroline *N*-oxide (16) and (4*R*)-2-(3,3-dimethoxypropyl)-4-(*tert*-butyldimethylsilyloxy)pyrroline *N*-oxide (17)

Activated manganese dioxide (0.65 g, 7.52 mmol) was added portionwise to a cooled (0 °C) solution of *N*-hydroxypyrrolidine **14** (1.2 g, 3.76 mmol) in CH_2Cl_2 (30 mL). The suspension was stirred at room temperature overnight. The resultant mixture was filtrated with celite, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, petroleum ether/AcOEt = 2/1) to afford *aldo* nitrone **16** and *keto* nitrone **17** as a yellow oil (1.09 g, 92%). **16** : **17** = 2 : 1.

16: $[\alpha]_D^{20}$ +27.7 (c 0.65 in CH_2Cl_2); ν_{max}/cm^{-1} 2952s, 2932s, 2895m, 2857m, 1573m, 1467m, 1365m, 1256m, 1127s, 1064s, 1007w; δ_H(300 MHz; $CDCl_3$) 6.74 (1 H, t, J 1.5), 4.82–4.79 (m, 1H), 4.30 (1 H, t, J 5.4), 4.18–4.04 (1 H, m), 3.25 (6 H, s), 2.17–2.13 (2 H, m), 2.07–2.00 (1 H, m), 1.62–1.49 (3 H, m), 0.80 (9 H, s), 0.00 (6 H, s); δ_C(75 MHz; $CDCl_3$) 134.50 (C2), 104.31, 71.13, 69.98, 53.23, 53.18, 36.82, 28.04, 27.27, 25.66, 18.01, –4.68, –4.81; HRMS (ESI) calcd for $C_{15}H_{31}NO_4SiH^+$ $[M + H]^+$ 318.2095, found 318.2098.

17: $[\alpha]_D^{20}$ –7.5 (c 0.80 in CH_2Cl_2); ν_{max}/cm^{-1} 2952s, 2932s, 2896m, 2857m, 2831m, 1600m, 1469m, 1441m, 1375m, 1253m, 1205m, 1162m, 1125s, 1082s, 997m, 919m; δ_H(300 MHz; $CDCl_3$) 4.43 (1 H, td, J 4.2 and 6.3), 4.30 (1 H, t, J 5.4), 4.11 (1 H, dd, J 6.0 and 14.1), 3.81–3.73 (1 H, m), 3.27 (6 H, s), 2.99 (1 H, dd, J 6.6 and 18.1), 2.58–2.45 (3 H, m), 1.82–1.75 (2 H, m), 0.80 (9 H, s), 0.00 (6 H, s); δ_C(75 MHz; $CDCl_3$) 146.18, 104.19, 70.74, 64.07, 53.55, 53.38, 42.53, 27.99, 25.63, 21.87, 17.89, –4.88; HRMS (ESI) calcd for $C_{15}H_{31}NO_4SiH^+$ $[M + H]^+$ 318.2095, found 318.2093.

(3*R*,5*R*)-3-(Benzyloxy)-5-(3,3-dimethoxypropyl)pyrroline *N*-oxide (20)

To a solution of nitrone **16** (1.27 g, 4.0 mmol) dissolved in anhydrous THF (20 mL) was added TBAF (1.05 g, 4.0 mmol), after stirring for 5 min, NaH (60%, 0.19 g, 4.8 mmol) and BnBr (0.57 mL, 4.8 mmol) were added to the above mixture successively, the reaction was continued for another 30 min, then quenched by adding saturated aqueous NH_4Cl (5 mL), concentrated, then dissolved in ethyl acetate (10 mL), the organic layer was separated

and aqueous layer was extracted by ethyl acetate (3 × 5 mL), the organic phases combined, dried, concentrated. The aqueous layer which contained TBS deprotected nitrone was concentrated and extracted with THF, the crude nitrone was subjected to NaH and BnBr again, repeating the procedure twice. The crude oil **20** was purified by flash chromatography (silica gel, petroleum ether/AcOEt = 1/1) to afford nitrone **20** as light yellow oil (1.11 g, 95%); $[\alpha]_D^{20}$ +34.1 (*c* 1.35 in CH_2Cl_2); ν_{max}/cm^{-1} 2936m, 2832m, 1571m, 1454m, 1360m, 1280m, 1261m, 1195m, 1127s, 1065s; δ_H(300 MHz; $CDCl_3$) 7.31–7.21 (5 H, m, *Ph*CH_2O), 6.87 (1 H, s, 2-H), 4.58–4.55 (1 H, m, 3-H), 4.51–4.42 (2 H, m, PhC*H*$_2$O), 4.31–4.28 (1 H, m, 8-H), 4.13–4.10 (1 H, m, 5-H), 3.25 (6 H, s, 2×OC*H*$_3$), 2.36–2.28 (1 H, m, 4-H), 2.17–2.02 (2 H, m, 4-H and 6-H), 1.62–1.49 (3 H, m, 6-H and 2 × 7-H); δ_C(75 MHz; $CDCl_3$) 136.33, 131.47 (C2), 127.62, 127.38, 127.13, 126.83, 103.27 (C8), 74.99 (C3), 70.38 (Ph*C*H$_2$O), 70.12 (C5), 52.21, 52.18 (O*C*H$_3$), 32.56 (C4), 26.95 (C7), 26.27 (C6); δ_C(Dept-135; 75 MHz; $CDCl_3$) positive, 131.48, 127.62, 127.13, 126.83, 103.26, 74.99, 70.12, 52.21, 52.18; negative, 70.38, 32.56, 26.95, 26.28; HRMS (ESI) calcd for $C_{16}H_{23}NO_4H^+$ $[M + H]^+$ 294.1700, found 294.1702.

(1*S*,2*S*,5*R*,7*R*)-7-(Benzyloxy)-8-azabicyclo[3.2.1]octane-2,8-diol (22)

To a well stirred solution of nitrone **20** (0.18 g, 0.61 mmol) in acetone : H_2O (30 mL, 4 : 1) was added catalytic *p*-TsOH (12 mg, 0.061 mmol). The reaction mixture was stirred for 1 h at reflux. The acetone was removed *in vacuo*. The aqueous layer was extracted with THF (8 × 2 mL). The combined organic layers were dried, filtered and the solvents were removed under reduced pressure. The crude aldehyde **21** was used directly for the cross-coupling reaction.

To a stirring and carefully deoxygenated solution of aldehyde **21** (directly obtained from the last step, 0.61 mmol) in THF (18 mL) was added *t*-BuOH (0.46 mL, 4.88 mmol) under an Ar atmosphere. The mixture was cooled to −78 °C to which was added freshly prepared SmI_2 in THF (15 mL, 1.22 mmol). The reaction was completed within 10 min, then quenched by successively adding aqueous solutions of $Na_2S_2SO_3$ (5 mL) and $NaHCO_3$ (5 mL), the aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$. Filtration, concentration *in vacuo* and purification by chromatography (silica gel, petroleum ether/AcOEt = 2/1) afforded the *N*-hydroxylamino alcohol **22** (83 mg, 55%) as a colorless oil. $[\alpha]_D^{20}$ +3.7 (*c* 0.53 in CH_2Cl_2); ν_{max}/cm^{-1} 3370s, 2947s, 2866s, 1496m, 1453s, 1400m, 1364m, 1244m, 1195s, 1092s, 1074s, 1007s; δ_H(300 MHz; $CDCl_3$) 7.25–7.19 (5 H, m), 4.50–4.39 (2 H, m), 3.87 (1 H, dd, *J* 2.1 and 6.3), 3.75–3.66 (1 H, m), 3.60–3.56 (1 H, m), 3.42–3.38 (1 H, m), 2.07–1.94 (1 H, m), 1.92–1.70 (2 H, m), 1.53–1.48 (1 H, m), 1.32–1.27 (1 H, m), 1.22–1.13 (1 H, m); δ_C(75 MHz; $CDCl_3$) 137.75, 128.47, 127.84, 127.76, 80.57, 76.08, 71.53, 69.44, 67.11, 33.75, 27.15, 23.77; HRMS (ESI) calcd for $C_{14}H_{19}NO_3H^+$ $[M + H]^+$ 250.1438, found 250.1440.

(−)-Erycibelline (4)

10% Pd/C (10 mg) and 6 N HCl (2 mL) was added to a solution of hydroxylamine **22** (53 mg, 0.21 mmol) in MeOH (10 mL). The resulting suspension was stirred under an atmosphere of H_2 at room temperature for 2 h, the hydroxylamine **22** was judged to diminish by TLC, The flask was bubbled with Ar, and the Pd/C was filtered off. After the solution was concentrated *in vacuo*, the residue dissolved in acetic acid (2 mL) was subjected to pre-activated Fe/$Cu(OAc)_2$ suspended in acetic acid for further reduction of hydroxylamine **23**, the reaction mixture was stirred at r.t. overnight, acetic acid was removed under reduced pressure, the residue was dissolved in MeOH, the Fe powder removed by filtration with Celite, Neutralized with aqueous ammonium solution, concentrated *in vacuo*. The above procedure was repeated three times to ensure complete neutralization. The residue was purified by an acid resin column (DOWEX 50WX8-400, H^+ form) affording **4** (26 mg, 87%) as a brown syrup.

23: $[\alpha]_D^{20}$ +2.5 (*c* 0.8 in EtOH), ν_{max}/cm^{-1} 3340s, 2974s, 1563s, 1422s, 1136m, 1091s, 1048s; δ_H(300 MHz; D_2O) 4.18 (1 H, dd, *J* 3.3 and 7.8, 7-H), 4.04–3.94 (1 H, m, 2-H), 3.90–3.81 (1 H, m, 5-H), 3.59–3.51 (1 H, m, 1-H), 2.24 (1 H, dd, *J* 7.8 and 14.1, 6-H), 2.12–2.05 (1 H, m, 6-H), 1.90–1.80 (1 H, m, 4-H), 1.46–1.41 (1 H, m, 4-H), 1.32–1.29 (2 H, m, 3-H); δ_C(75 MHz; D_2O) 78.05 (C1), 71.52 (C7), 68.08 (C2), 67.25 (C5), 34.95 (C6), 25.50 (C4), 21.79 (C3); δ_C(Dept-135; 75 MHz; D_2O) positive, 78.05, 71.52, 68.07, 67.25; negative, 34.95, 25.49, 21.79; HRMS (ESI): calcd for $C_7H_{13}NO_3H^+$ $[M + H]^+$ 160.0968, found 160.0969.

4: $[\alpha]_D^{20}$ −11.6 (*c* 0.5 in EtOH), [Lit. $[\alpha]_D^{10}$ −12.5 (*c* 0.57 in EtOH)]; ν_{max}/cm^{-1} 3310vs, 2938vs, 1560s, 1401s, 1113s, 1070s, 1044s, 1004s; δ_H(300 MHz; $CDCl_3$) 4.33–4.19 (3 H, m, NH, 2 × OH), 3.82–3.76 (1 H, m), 3.73 (1 H, d, *J* 6.6), 3.62–3.59 (1 H, m), 3.46–3.39 (1 H, m), 2.24 (1 H, q, *J* 7.2), 1.96–1.92 (1 H, m), 1.84–1.78 (1 H, m), 1.64–1.57 (1 H, m), 1.50–1.38 (1 H, m), 1.29–1.25 (1 H, m); δ_C(75 MHz; MeOD) 71.29, 69.89, 65.78, 56.91, 38.49, 26.34, 25.05, [Lit.[4] δ_C 67.7, 67.5, 62.2, 54.3, 35.5, 22.8, 22.3]; HRMS (ESI) calcd for $C_7H_{13}NO_2H^+$ $[M + H]^+$ 144.1019, found 144.1019.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(3,3-dimethoxypropyl)pyrroline *N*-oxide (24) and (4*R*)-2-(3,3-dimethoxypropyl)-4-(*tert*-butyldimethylsilyloxy)pyrroline *N*-oxide (17)

Activated manganese dioxide (0.70 g, 8.02 mmol) was added portionwise to a cooled (0 °C) solution of *N*-hydroxypyrrolidine **15** (1.28 g, 4.01 mmol) in CH_2Cl_2 (30 mL). The suspension was stirred at room temperature overnight. The resultant mixture was filtrated with celite, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, AcOEt) to afford *aldo* nitrone **24** and *keto* nitrone **17** as a light yellow oil (1.19 g, 94%). **24** : **17** = 2 : 1; **24**: $[\alpha]_D^{20}$ +44.9 (*c* 1.78 in CH_2Cl_2); ν_{max}/cm^{-1} 2952s, 2932s, 1577m, 1469m, 1365m, 1255m, 1192w, 1129s, 1069s, 1008w; δ_H(300 MHz; $CDCl_3$) 6.74 (1 H, s), 4.84 (1 H, d, *J* 5.1), 4.30 (1 H, t, *J* 5.4), 3.84 (1 H, t, *J* 3.9), 3.24 (6 H, s), 2.64–2.54 (1 H, m), 2.14–2.03 (1 H, m), 1.82–1.67 (2 H, m), 1.65–1.53 (2 H, m), 0.8 (9 H, s), 0.00 (6 H, s); δ_C(75 MHz; $CDCl_3$) 135.24, 104.30, 71.92, 70.01, 53.14, 52.88, 36.02, 28.06, 27.76, 25.62, 17.90, –4.75, –4.86; HRMS (ESI) calcd for $C_{15}H_{31}NO_4SiH^+$ $[M + H]^+$ 318.2095, found 318.2096.

(3*R*,5*S*)-3-(Benzyloxy)-5-(3,3-dimethoxypropyl)pyrroline *N*-oxide (25)

To a solution of nitrone **24** (0.47 g, 1.48 mmol) dissolved in anhydrous THF (10 mL) was added TBAF (0.39 g, 1.48 mmol), after

stirring for 5 min, NaH (60%, 71 mg, 1.78 mmol) and BnBr (0.21 mL, 1.78 mmol) were added to the above mixture successively, the reaction was continued for another 30 min, then quenched by adding saturated aqueous NH_4Cl (5 mL), concentrated, then dissolved in ethyl acetate (10 mL), the organic layer was separated and aqueous layer was extracted by ethyl acetate (3 × 5 mL), and the combined organic phase, dried, and concentrated. The aqueous layer which contained TBS deprotected nitrone was concentrated and extracted with THF, the crude nitrone was subjected to NaH and BnBr again, repeating the procedure twice. The crude oil **25** was purified by flash chromatography (silica gel, AcOEt) to afford nitrone **25** as a yellow oil (0.4 g, 93%). $[\alpha]_D^{20}$ +66.7 (*c* 1.5 in CH_2Cl_2); ν_{max}/cm^{-1} 2941m, 2831m, 1574s, 1521w, 1495w, 1454m, 1360m, 1248m, 1194w, 1128s, 1068s; δ_H(300 MHz; $CDCl_3$) 7.31–7.21 (5 H, m, *Ph*CH_2O), 6.83 (1 H, s), 4.61–4.58 (1 H, m, 3-H), 4.53–4.43 (2 H, m, PhCH_2O), 4.33–4.30 (1 H, m, 8-H), 3.87–3.84 (1 H, m, 5-H), 3.25 (6 H, s, 2 × OCH_3), 2.65–2.55 (1 H, m, 4-H), 2.14–2.08 (1 H, m, 6-H), 1.89–1.71 (2 H, m, 4-H and 6-H), 1.70–1.58 (2 H, m, 7-H); δ_C(75 MHz; $CDCl_3$) 137.36, 132.84 (C2), 128.60, 128.11, 127.83, 104.28 (C8), 76.20 (C3), 71.94 (Ph*C*H_2), 71.62 (C5), 53.17, 52.94 (O*C*H_3), 32.85 (C4), 28.13 (C7), 27.92 (C6); δ_C(Dept-135; 75 MHz; $CDCl_3$) positive, 132.84, 128.61, 128.11, 127.83, 104.28, 76.20, 71.94, 53.17, 52.94; negative, 71.62, 32.84, 28.12, 27.92; HRMS (ESI) calcd for $C_{16}H_{23}NO_4H^+$ $[M + H]^+$ 294.1700, found 294.1705.

(1*R*,2*R*,5*S*,7*R*)-7-(Benzyloxy)-8-azabicyclo[3.2.1]octane-2,8-diol (27)

To a well stirred solution of nitrone **25** (50 mg, 0.17 mmol) in acetone : H_2O (10 mL, 4 : 1) was added catalytic *p*-TsOH (3 mg, 0.017 mmol). The reaction mixture was stirred for 1 h at reflux. Acetone was removed *in vacuo*. The residue was extracted with THF (8 × 2 mL). The organic layers were combined, dried, filtered and the solvents were removed under reduced pressure. The crude aldehyde was used directly for the cross-coupling reaction.

To a stirring and carefully deoxygenated solution of aldehyde **26** (directly obtained from the last step, 0.17 mmol) in THF (5 mL) was added H_2O (0.24 mL, 13.6 mmol) under an Ar atmosphere. The mixture was cooled to −78 °C to which was added freshly prepared SmI_2 in THF (4.3 mL, 0.34 mmol). The reaction was completed within 10 min, then quenched by successively adding aqueous solutions of $Na_2S_2SO_3$ (2 mL) and $NaHCO_3$ (2 mL), the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$. Filtration, concentration *in vacuo* and purification by chromatography (petroleum ether/AcOEt = 1/1) afforded the *N*-hydroxylamino alcohol **27** as colorless oil (24 mg, 57%); $[\alpha]_D^{20}$ −14.0 (*c* 1.6 in CH_2Cl_2); ν_{max}/cm^{-1} 3331s, 2950s, 2861s, 1454s, 1359m, 1074s, 1005s; δ_H(300 MHz; $CDCl_3$) 7.35–7.28 (5 H, m, *Ph*CH_2O), 4.91 (2 H, br, OH), 4.65–4.59 (1 H, m, 7-H), 4.55–4.49 (2 H, m, PhCH_2O), 4.20–4.09 (1 H, m, 2-H), 3.79–3.67 (1 H, m, 1-H), 3.56–3.54 (1 H, m, 5-H), 2.61–2.51 (1 H, m, 6-H), 2.11–1.94 (2 H, m, 3-H and 4-H), 1.65–1.47 (3 H, m, 3-H, 4-H and 6-H); δ_C(75 MHz; $CDCl_3$) 138.26, 128.42, 127.66, 127.39, 78.75 (C7), 72.94 (Ph*C*H_2), 71.87 (C1), 68.72 (C2), 65.24 (C5), 31.56 (C6), 28.11, 23.79 (C4 and C3); δ_C(Dept-135; 75 MHz; $CDCl_3$) positive, 128.43, 127.66, 127.39, 78.75, 71.87, 68.72, 65.24; negative, 72.94, 31.57, 28.10, 23.79; HRMS (ESI) calcd for $C_{14}H_{19}NO_3H^+$ $[M + H]^+$ 250.1438, found 250.1441.

7-*epi*-(+)-Erycibelline (29)

10% Pd/C (5 mg) and 6 N HCl (1 mL) were added to a solution of hydroxylamine **27** (24 mg, 0.096 mmol) in MeOH (10 mL). The resulting suspension was stirred under an atmosphere of H_2 at room temperature for 2 h, the hydroxylamine **27** was judged to diminish by TLC, The flask was bubbled with Ar, and the Pd/C was filtered off. After the solution was concentrated *in vacuo*, the residue dissolved in acetic acid (2 mL) was subjected to pre-activated Fe/$Cu(OAc)_2$ suspended in acetic acid for further reduction of hydroxylamine **28**, the reaction mixture was stirred at r.t. overnight, acetic acid was removed under reduced pressure, the residue was dissolved in MeOH, filtered through Celite to remove the Fe powder, neutralized with aqueous ammonium solution and concentrated *in vacuo*. The above procedure was repeated three times to ensure complete neutralization. The residue was purified by an acid resin column (DOWEX 50WX8-400, H^+ form) affording **29** as a brown syrup (12 mg, 88%); $[\alpha]_D^{20}$ + 47.0 (*c* 0.38 in EtOH); ν_{max}/cm^{-1} 3337s, 2971s, 2925s, 1563m, 1412m, 1118s, 1051s; δ_H(300 MHz; D_2O) 4.62–4.55 (1 H, m, 7-H), 4.12–4.05 (1 H, m, 2-H), 3.76–3.74 (1 H, m, 5-H), 3.63–3.54 (1 H, m, 1-H), 2.52–2.41 (1 H, m, 6-H), 2.14–1.90 (2 H, m, 3-H and 4-H), 1.67–1.55 (3 H, m, 3-H, 4-H and 6-H); δ_C(75 MHz; D_2O) 68.38 (C7), 63.84 (C2), 60.74 (C1), 54.34 (C5), 32.94 (C6), 25.23, 22.63 (C3 and C4); δ_C(Dept-135; 75 MHz; D_2O) positive, 68.36, 63.83, 60.73, 54.34; negative, 32.93, 25.22, 22.62; HRMS (ESI) calcd for $C_7H_{13}NO_2H^+$ $[M + H]^+$ 144.1019, found 144.1018.

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