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Abstract

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Keywords

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Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Semisynthesis and Acetylcholinesterase Inhibitory Activity of Stemofoline Alkaloids and Analogues

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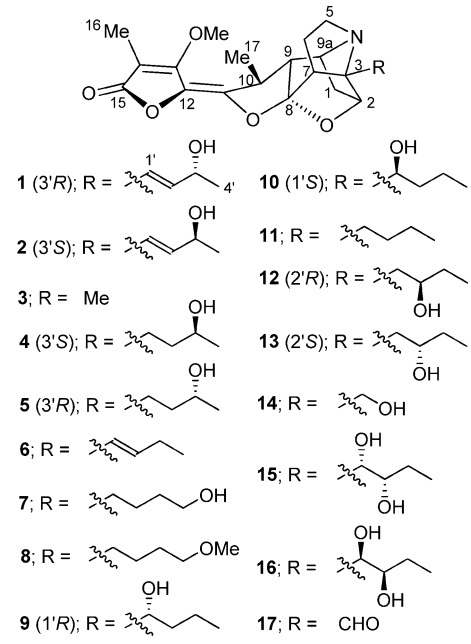
Semisynthesis of the known *Stemona* alkaloids oxystemofoline (**7**) and methoxystemofoline (**8**) has been achieved starting from (11*Z*)-1′,2′-didehydrostemofoline (**6**), which confirmed their structures and absolute configurations. The synthesis of (1′*R*)-hydroxystemofoline (**9**) helped establish this compound as a natural product from *Stemona aphylla*. (1′*S*)-Hydroxystemofoline (**10**) and a number of related analogues were also prepared. In a TLC bioautographic assay, **9** was found to be the most active acetylcholinesterase inhibitor, but it was not as active as galanthamine.

The *Stemona* family of more than 80 alkaloids has been classified by Pilli into eight different structural groups.[1] The pyrrolo[1,2-*a*]azepine (5,7-bicyclic A,B ring system) nucleus is common to all compounds in six of these groups, while a pyrido[1,2-*a*]azepine A,B ring system (6,7-bicyclic A,B ring system) is found in the more recently discovered stemocurtisine group of *Stemona* alkaloids.[1,2] A miscellaneous group comprising five alkaloids has also been identified.[1] Greger has classified the *Stemona* alkaloids into three skeletal types based on their proposed biosynthetic origins.[3] We recently reported the semisynthesis of (3′*R*)-stemofolenol (**1**), (3′*S*)-stemofolenol (**2**), methylstemofoline (**3**), and (3′*S*)-hydroxystemofoline (**4**) and the unnatural analogue (3′*R*)-hydroxystemofoline (**5**) from (11*Z*)-1′,2′-didehydrostemofoline (**6**). This study allowed for the first access to diastereomerically enriched samples of these compounds in quantities sufficient to allow testing of their acetylcholinesterase (AChE) inhibitory activities.[4] This paper reports the semisynthesis of the known *Stemona* alkaloids oxystemofoline (**7**)[5] and methoxystemofline (**8**),[5] which confirmed their structures and resolved the controversy about their absolute configurations.[5,6] We also disclose the synthesis of (1′*R*)-hydroxystemofoline (**9**), which we have now discovered is a natural product, (1′*S*)-hydroxystemofoline (**10**), and a number of related analogues. The inhibitory activities of these compounds against AChE is also reported.

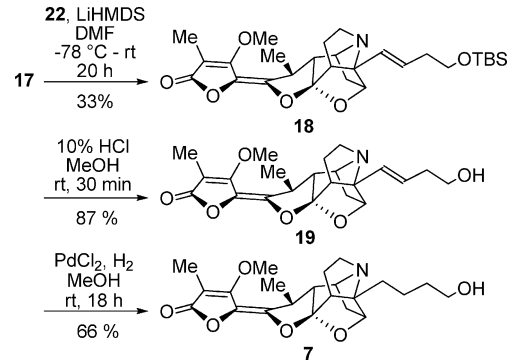


Results and Discussion

For the synthesis of oxystemofoline (**7**) (Scheme 1), (11*Z*)-1′,2′-didehydrostemofoline (**6**) was converted to the known aldehyde **17** as we described previously.[4] In order to form the *trans*-alkene **18**, a modified Julia olefination reaction[7] was employed using the sulfone **22** (Scheme 2). However, while the *E*-selectivity was high (*E*/*Z* = >99:<1) the yield of **18** was low (33%) due to the high sensitivity of aldehyde **17** to the strongly basic conditions. TBS-deprotection of compound **18** gave the homoallylic alcohol **19**, which was then regioselectively hydrogenated to give **7**. The specific rotation of **7** ($[\alpha]_D^{22}$ +297.8 (*c* 0.52, CH_3OH); lit.[5] $[\alpha]_D^{20}$ +106.0 (*c* 0.1, CH_3OH)) was of the same sign but larger in magnitude than that reported for the natural product. The ^1H and ^{13}C NMR data of **7** proved to be identical to the natural product,[5] except for the ^{13}C NMR signals for C-6 and C-1′, which were originally incorrectly assigned. Thus, this synthesis confirmed the proposed structure of the natural product and established its absolute configuration since that of the stemofoline·HBr salt has been established by X-ray crystallographic analysis.[8] A *Stemona* alkaloid named parvistemoninol, which had the same specific rotation as oxystemofoline, was reported to have the structure enantiomeric to **7**.[6] It is now clear that parvistemoninol and oxystemofoline are the same, and we suggest that the name parvistemoninol no longer be used.

Synthesis of methoxystemofoline (**8**) (Scheme 3) was achieved using a method similar to that used for synthesis of **7** except that the sulfone **25** (Scheme 2) was used for the first step. The yield of the *E*-alkene **26** was very low (*E*/*Z* = >99:<1).

Scheme 1. Synthesis of Oxystemofoline (**7**)



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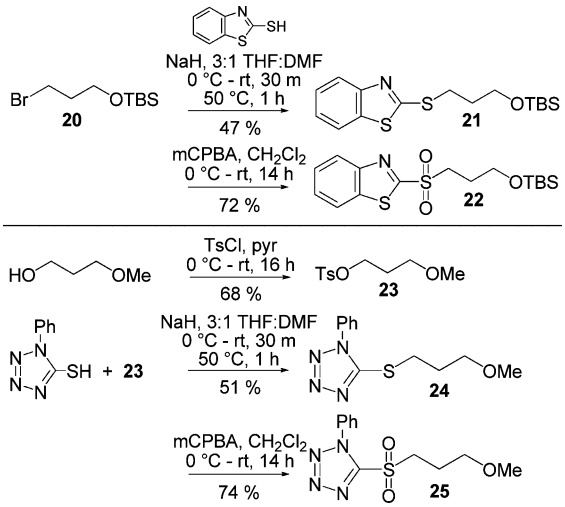
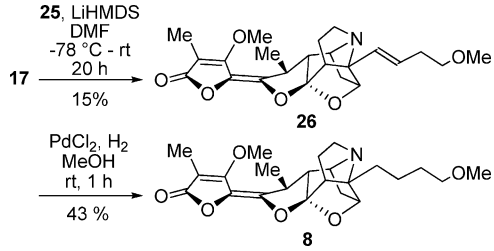
Scheme 2. Synthesis of Sulfones **22** and **25**



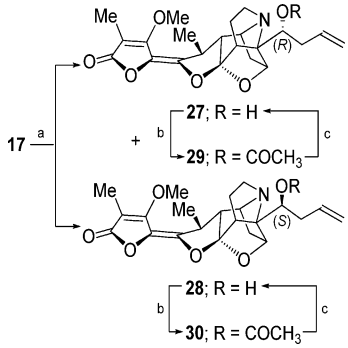
Scheme 3. Synthesis of Methoxystemofoline (**8**)



Hydrogenation of **26** gave methoxystemofoline (**8**) (Scheme 3). The specific rotation of **8** ($[\alpha]_D^{25}$ +247 (*c* 0.29, CH_3OH); lit.[5] $[\alpha]_D^{21.6}$ +75.6 (*c* 0.037, CH_3OH)) was of the same sign but much larger in magnitude compared to that reported for the natural product. Such alkaloids typically have specific rotations around 200.[1] The ^1H and ^{13}C NMR data of **8** agreed with those of the natural product methoxystemofoline[5] except for the incorrect assignment of the ^{13}C NMR signals for C-6 and C-1′.

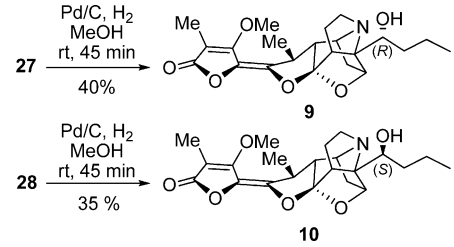
Allylation of **17**[4] using indium powder and allyl bromide, with sonication,[9] gave an inseparable mixture of the diastereomeric alcohols **27** and **28** in a ratio of 65:35 (Scheme 4). Their acetate derivatives (**29** and **30**), however, were readily separated. When the acetate groups were removed under transesterification conditions using $MeOH/Na_2CO_3$, methanol Michael addition products at C-11−C-12 were also formed. Hydrolysis using LiOH in aqueous THF was more successful in providing the desired alcohols **27** and **28** (Scheme 4). The configuration of **27** at C-1′ was assigned from its synthesis from **17** using the chiral borane reagent ^{l}Ipc$_2$Ball, which is generally stereoselective for the (*R*)-homoallylic alcohol product.[10] This reaction gave a mixture of **27** and **28** in a ratio of 9:1, in a yield of 77%. When ^{d}Ipc$_2$Ball was employed, a mixture of **27** and **28** was obtained in a ratio of 14:86, in a yield of 69%. The pure alcohols **27** and **28** were hydrogenated to give (1′*R*)-hydroxystemofoline (**9**) and (1′*S*)-hydroxystemofoline (**10**) in relatively low yields (36−42%) due to the formation of side products arising from reduction of the C-11−C-12 double bond (Scheme 5). Surprisingly, (1′*R*)-hydroxystemofoline (**9**) was identical by NMR spectroscopy to the alkaloid that we had isolated previously from the root extracts of *Stemona aphylla* and which we had incorrectly reported as (2′*S*)-hydroxystemofoline.[11] Thus, (1′*R*)-hydroxystemofoline is also a natural product.

Scheme 4. [a]



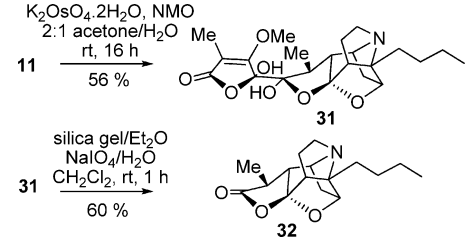
[a] Reagents and conditions: (a) (i) indium, allyl bromide, THF/aq NH_4Cl (5:2), sonication, 2−3 h, **27**:**28** = 65:35; (ii) ^{l}Ipc$_2$Ball, THF, 0 °C, 2 h, **27**:**28** = 9:1, 77% yield; (iii) ^{d}Ipc$_2$Ball, THF, 0 °C, 2 h, **27**:**28** = 14:86, 69% yield; (b) Ac_2O, pyridine, rt, 4 h, **29**: 44% yield (2 steps), **30**: 28% yield (2 steps); (c) LiOH, THF/H_2O (2:1), rt, 16 h, **27**: 61% yield, **28**: 73% yield.

Scheme 5. Synthesis of (1′*R*)-Hydroxystemofoline (**9**) and (1′*S*)-Hydroxystemofoline (**10**)



Dihydroxylation of stemofoline (**11**),[4] using catalytic $K_2OsO_4 \cdot 2H_2O$ and stoichiometric NMO, gave the diol **31**, which was a single diastereomer by NMR analysis. Oxidative cleavage of diol **31** with freshly prepared $NaIO_4$ on silica gel[4] gave the A,B,C ring core structure **32** (Scheme 6).

Scheme 6. Synthesis of the A,B,C Ring Core Structure **32**



The Wittig reaction was utilized for synthesis of enal **33a** from **17** using (triphenylphosphoranylidene)acetaldehyde.[12] This reaction also gave dienal **33b** and trienal **33c** as a result of consecutive Wittig reactions. These aldehydes were difficult to separate from each other and the triphenylphosphine oxide byproduct. Thus, the mixture was reduced with $NaBH_4$/MeOH to give a mixture of alcohols **34a**−**c**, which was separated by PTLC to give pure samples for biological testing (Scheme 7).

Scheme 7. Synthesis of Alcohols **34a**, **34b**, and **34c**

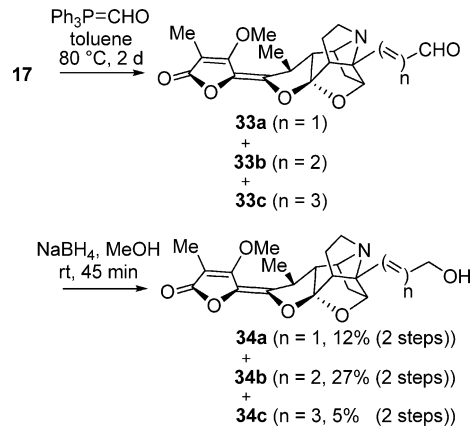
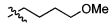
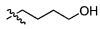


Table 1. Minimum Amount of Sample Found to Inhibit AChE as Indicated by a White Zone of Inhibition

compound	Side chain	minimum inhibitory requirement	
		ng	nmol
galanthamine		1	0.003
9		5	0.012
6[4,16]		5	0.013
34c		10	0.023
34b		10	0.024
15		10	0.024
4[4]		10	0.025
10		10	0.025
12[16]		10	0.025
13[17]		10	0.025
27		10	0.025
11[18]		10	0.026
14[4]		10	0.028
29		50	0.113
30		50	0.113
16		50	0.119
8		50	0.120
7		50	0.124
19		50	0.125
28		50	0.125
34a		50	0.129
26		100	0.241
5[4]		100	0.248
2[4]		100	0.249
3[4]	Me	100	0.290
32	-	100	0.361
31	-	500	1.188
1[4]		500	1.247

The insecticidal activity shown by the root extracts of *Stemona* plants has been associated with the acetylcholinesterase (AChE) inhibitory activities of their alkaloid components.[13,14] Compounds **7**−**16**, **19**, **26**−**32**, and **34a**−**c** were therefore screened by TLC bioautography for their AChE inhibitory activities using the qualitative method of Hostettmann et al.[15] and galanthamine as a positive control. The results are shown in Table 1. The inhibitory activities of the previously tested compounds **1**−**6**[4] are included.

In our earlier study (11*Z*)-1′,2′-didehydrostemofoline (**6**) was the most active inhibitor, with a minimum inhibitory requirement of 5 ng (0.013 nmol).[4] In this study (1′*R*)-hydroxystemofoline (**9**) showed a slightly higher inhibitory activity at 5 ng (0.012 nmol), while its 3′,4′-didehydro deriviative (**27**) and its (1′*S*)-epimer (**10**) were less active (minimum inhibitory requirements of 10 ng, Table 1). Compound **9** was the most active of the compounds reported here. Stemofoline (**11**) was slightly less active than **6** and **9**, while its 11,12-dihydroxy derivative (**31**) and the tricyclic derivative (**32**), which is missing the γ-butyrolactone ring found in **11**, were 50 and 10 times less active, with minimum inhibitory requirements of 500 and 100 ng, respectively. Other compounds with activity similar to that of **11** (which all had a minimum inhibitory requirement of 10 ng) included the trien-ol **34c**, the dien-ol **34b**, the C-1′ and C-2′ alcohols **12**, **13**, **14**, and **27**, and the 1′,2′-diol **15**. The C-3′ hydroxy analogues, (3′*S*)-**4** and its 3′-epimer, (3′*R*)-**5**, showed a 10-fold difference in activities with minimum inhibitory requirements of 10 and 100 ng, respectively. The C-4′ hydroxy- and methoxy-substituted stemofoline derivatives **7**, **8**, **19**, and **26** showed relatively weak activities. Of the truncated side-chain derivatives, the hydroxymethyl derivative **14** showed relatively high activity (10 ng), while the methyl derivative **3** and the 3′-hydroxy-1-propenyl derivative **34a** had much reduced activities (100 and 50 ng, respectively).

In summary, semisynthesis of the known *Stemona* alkaloids oxystemofoline (**7**) and methoxystemofline (**8**) has been achieved starting from (11*Z*)-1′,2′-didehydrostemofoline (**6**), which confirmed their structures and absolute configurations. The synthesis of (1′*R*)-hydroxystemofoline (**9**) helped to establish this compound as a natural product from *S. aphylla*. (1′*S*)-Hydroxystemofoline (**10**) and a number of related analogues were also prepared. In an assay as AChE inhibitors, **9** was the most active. In general, analogues with an OH at C-1′ or C-2′ were more active than analogues with an OH at C-3′ or C-4′, although the C-3′ hydroxy compound **4** was an exception. The configuration of the carbinol center was also important for activity, except for the C-2′ epimeric pair of compounds, **12** and **13**, which were equipotent. Studies are continuing on the insecticidal activity of these alkaloids on insects of importance to the agricultural industry.

Experimental Section

General Experimental Procedures. These were as described previously.[16] All ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were determined in $CDCl_3$ solution unless otherwise indicated. ^{1}H NMR assignments were achieved with the aid of gCOSY and, in some cases, NOESY experiments. ^{13}C NMR assignments were based upon DEPT, gHSQC, and gHMBC experiments. All compounds were homogeneous by TLC analysis and judged to be of >95% purity based upon ^{1}H NMR analysis.

Plant Material. The known starting material (11*Z*)-1′,2′-didehydrostemofoline (**6**) was isolated from the unidentified *Stemona* species that we reported earlier.[16] Roots of this *Stemona* species were collected at Amphur Mae Moh, Lampang, Thailand, in November 2007. The plant material was identified by Mr. James Maxwell (Department of Biology, Chiang Mai University) as the same species that we had studied previously.[16] Voucher specimen number 25375 was deposited at the Herbarium of the Department of Biology, Chiang Mai University.

Extraction and Isolation. The dry, ground root of the *Stemona* species (935 g) was extracted with 95% EtOH (4 × 3000 mL) over 4 days at rt. The ethanolic solution was evaporated to give a dark brown residue (148 g). The extract was partitioned between MeOH/H_2O (1:1) and CH_2Cl_2. The organic extract was dried over $MgSO_4$ and concentrated in vacuo to give a dark brown residue (20 g). A portion of this material (2.50 g) was chromatographed on silica gel (100 mL) with gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (95:5) to give (11*Z*)-1′,2′-didehydrostemofoline (**6**)[16] as a yellow-brown gum (1.48 g, 59% w/w).

(11*Z*)-1′$_\alpha$,2′$_\alpha$- and (11*Z*)-1′$_\beta$,2′$_\beta$-Dihydroxystemofoline (15 and 16). Compound **16** was a minor component from the synthesis of the known diol **15**[4] using AD-mix-α (4.55 g, Aldrich), methanesulfonamide (617 mg, 6.49 mmol), and **6** (1.25 g, 3.25 mmol). The crude product was purified by column chromatography (CC) with gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (9:1) to give **15**[4] (889 mg, 2.12 mmol, 65% yield) as a white solid and **16** (28 mg, 0.07 mmol, 2% yield). These compounds were also prepared from a similar method using AD-mix-β (474 mg, Aldrich), methanesulfonamide (64 mg, 0.68 mmol), and **6** (130 g, 0.339 mmol) to give **15** (9.9 mg, 0.024 mmol, 7% yield) and **16** (68.9 mg, 0.164 mmol, 48% yield). The ^{1}H and ^{13}C NMR spectra of **15** from both methods agreed with those previously reported.[4] **16**: colorless gum, $[\alpha]_D^{23}$ +251 (*c* 1.0, $CHCl_3$); IR ν_{max} 3380, 2960, 2919, 2873, 1741, 1680 cm^{-1}; ^{1}H NMR δ 4.68 (s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.75 (t, J = 7.5 Hz, 1H, H-2′α), 3.52 (s, 1H, H-1′α), 3.49 (br s, 1H, H-9a), 3.10 (d, J = 6.5 Hz, 1H, H-7), 3.12−3.07 (m, 1H, H-10), 3.03−2.94 (m, 2H, H-5), 2.05 (s, 3H, H-16), 2.02−1.95 (m, 1H, H-6a), 1.93 (d, J = 12.5 Hz, 1H, H-1a), 1.88−1.84 (m, 1H, H-6b), 1.82 (dd, J 9.5 Hz, 2.5 Hz, 1H, H-9), 1.78 (d, J = 12.5 Hz, 1H, H-1b), 1.67−1.50 (m, 2H, H-3′), 1.36 (d, J = 6.5 Hz, 3H, H-17), 0.95 (t, J = 7.5 Hz, 3H, H-4′); ^{13}C NMR δ 170.1 (C-15), 163.1 (C-13), 148.8 (C-11), 128.0 (C-12), 112.5 (C-8), 98.6 (C-14), 85.8 (C-3), 76.4 (C-2), 72.3 (C-1′), 69.9 (C-2′), 61.5 (C-9a), 59.0 (O-C$\underline{H}_3$), 48.9 (C-7), 48.7 (C-5), 47.8

(C-9), 34.7 (C-10), 33.0 (C-1), 28.2 (C-3′), 26.9 (C-6), 18.4 (C-17), 10.4 (C-4′), 9.2 (C-16); ESIMS *m/z* 420.0 (100%) $[M + H]^+$, 421.2 (15%), 422.1 (5%); HRESIMS *m/z* 420.2008 $[M + H]^+$, calcd for $C_{22}H_{30}NO_7$ 420.2022.

1′,2′-Didehydro-4′-(*tert*-butyldimethylsiloxyl)stemofoline (18). A mixture of sulfone **22** (157 mg, 0.424 mmol) in dry DMF (10 mL) under a N_2 atmosphere was cooled to −60 °C, LiHMDS (0.39 mL of 1 M in THF) was added dropwise, and the solution was stirred at −60 °C for 2 h. The mixture was transferred via a cannula to a flask containing a solution of the aldehyde **17**[4] (127 mg, 0.353 mmol) in dry DMF (10 mL) at −60 °C under N_2. The reaction warmed to rt over 20 h before addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was extracted with diethyl ether (3 × 20 mL), and the extract was washed with brine and dried ($MgSO_4$). The concentrated residue was purified by CC using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (98:2) to give the *trans*-alkene product **18** (61 mg, 0.117 mmol, 33% yield): R_f = 0.50 in MeOH/EtOAc (1:4); $[\alpha]_D^{22}$ +179.6 (*c* 1.0, $CHCl_3$); IR ν_{max} 2955, 2924, 2883, 2852, 1746, 1621 cm^{-1}; ^1H NMR δ 5.74 (dt, *J* = 15.5 Hz, 7.0 Hz, 1H, H-2′), 5.58 (d, *J* = 15.5 Hz, 1H, H-1′), 4.21 (br s, 1H, H-2), 4.14 (s, 3H, O−C$\underline{H}_3$), 3.64 (t, *J* = 7.0 Hz, 2H, H-4′), 3.50 (br s, 1H, H-9a), 3.13−3.07 (m, 2H, H-5a, H-10), 3.00−2.95 (m, 1H, H-5b), 2.86 (d, *J* = 6.0 Hz, 1H, H-7), 2.28 (q, *J* 7.0 Hz, 2H, H-3′), 2.07 (s, 3H, H-16), 1.95 (d, *J* 12.5 Hz, 1H, H-1a), 1.88−1.84 (m, 2H, H-6a, H-9), 1.84−1.76 (m, 2H, H-1b, H-6b), 1.38 (d, *J* = 6.5 Hz, 3H, H-17), 0.88 (s, 9H, O-Si$(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (s, 6H, O-Si $(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.5 (C-11), 129.7 (C-1′), 128.4 (C-2′), 128.0 (C-12), 112.9 (C-8), 98.7 (C-14), 83.2 (C-3), 80.8 (C-2), 62.8 (C-4′), 61.0 (C-9a), 59.0 (O-$\underline{C}H_3$), 51.4 (C-7), 48.2 (C-5), 47.8 (C-9), 36.1 (C-3′), 34.7 (C-10), 33.0 (C-1), 27.1 (C-6), 26.1 (O-Si$(CH_3)_2C(\underline{C}H_3)_3$), 18.5 (C-17, O-Si$(CH_3)_2\underline{C}(CH_3)_3$), 9.3 (C-16), −5.1 (O-Si $(\underline{C}H_3)_2C(CH_3)_3$); ESIMS *m/z* 516.3 (100%) $[M + H]^+$, 517.3 (30%), 518.3 (10%); HRESIMS *m/z* 516.2768 $[M + H]^+$, calcd for $C_{28}H_{42}NO_6Si$ 516.2781.

1′,2′-Didehydro-4′-hydroxystemofoline (19). To a solution of **18** (32.7 mg, 0.064 mmol) in MeOH (2.0 mL) at rt was added 10% aqueous HCl (1.0 mL), and the solution was left to stir for 30 min. The reaction mixture was evaporated to a white residue, which was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with brine and dried ($MgSO_4$). The concentrated residue was purified by CC using gradient elution from EtOAc to EtOAc/MeOH (90:10) to give the alcohol **19** (22.2 mg, 0.055 mmol, 87% yield): R_f = 0.11 in MeOH/EtOAc (1:4); $[\alpha]_D^{23}$ +240.8 (*c* 1.0, $CHCl_3$); IR ν_{max} 3740, 2960, 2919, 2847, 1743, 1683, 1618 cm^{-1}; ^1H NMR (300 MHz) δ 5.73 (dt, *J* = 15.3 Hz, 6.6 Hz, 1H, H-2′), 5.62 (d, *J* = 15.9 Hz, 1H, H-1′), 4.21 (br s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.64 (t, *J* = 6.6 Hz, 2H, H-4′), 3.49 (br s, 1H, H-9a), 3.10−3.03 (m, 2H, H-5a, H-10), 3.02−2.97 (m, 1H, H-5b), 2.84 (d, *J* = 5.7 Hz, 1H, H-7), 2.32 (q, *J* = 6.3 Hz, 2H, H-3′), 2.05 (s, 3H, H-16), 1.94 (d, *J* = 12.0 Hz, 1H, H-1b), 1.88−1.84 (m, 2H, H-6a, H-6b), 1.83−1.79 (m, 1H, H-9), 1.79−1.74 (m, 1H, H-1a), 1.36 (d, *J* = 6.3 Hz, 3H, H-17); ^{13}C NMR (75 MHz) δ 169.9 (C-15), 162.9 (C-13), 148.4 (C-11), 130.6 (C-1′), 128.0 (C-12), 127.9 (C-2′), 112.8 (C-8), 98.7 (C-14), 83.2 (C-3), 80.6 (C-2), 61.9 (C-4′), 61.0 (C-9a), 59.0 (O-$\underline{C}H_3$), 51.4 (C-7), 48.1 (C-5), 47.7 (C-9), 35.9 (C-3′), 34.7 (C-10), 33.0 (C-1), 27.0 (C-6), 9.2 (C-16); ESIMS *m/z* 402.2 (100%) $[M + H]^+$, 403.2 (20%), 404.2 (10%); HRESIMS *m/z* 402.1898 $[M + H]^+$, calcd for $C_{22}H_{28}NO_6$ 402.1917.

Oxystemofoline (7). To a solution of alcohol **19** (10.9 mg, 0.027 mmol) in dry MeOH (2 mL) at rt was added $PdCl_2$ (2.2 mg, 20% w/w), and the flask was flushed with N_2 for 10 min before left to stir under a H_2 atmosphere (balloon) for 18 h. The flask was flushed with N_2, and the solution was filtered through Celite and then washed with MeOH. The filtrate was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by CC eluting with EtOAc to give oxystemofoline **7** (7.3 mg, 0.018 mmol, 66% yield): R_f = 0.39 in MeOH/CH_2Cl_2 (1:9); $[\alpha]_D^{22}$ +297 (*c* 0.52, CH_3OH); lit.[8] $[\alpha]_D^{20}$ +106.0 (*c* 0.1, CH_3OH). The NMR data agree with those of the natural product[5] except the assignment of the ^{13}C NMR signals for C-6 and C-1′, which were incorrectly assigned. ESIMS *m/z* 403.8 (100%) $[M + H]^+$, 404.9 (20%), 405.8 (13%); HRESIMS *m/z* 404.1977 $[M + H]^+$, calcd for $C_{22}H_{30}NO_6$ 404.2073.

1′,2′-Didehydro-4′-methoxystemofoline (26). Compound **26** was prepared using a method similar to the synthesis of **18**, from aldehyde **17**[4] (54 mg, 0.150 mmol), LiHMDS (0.16 mL of 1 M in THF), and sulfone **25** (51 mg, 0.180 mmol) to give **26** (9 mg, 0.022 mmol, 15% yield) as a yellow gum after purification by CC elution with EtOAc: R_f = 0.23 in MeOH/EtOAc (1:4); $[\alpha]_D^{25}$ +206.2 (*c* 0.71, $CHCl_3$); IR ν_{max} 2957, 2929, 2868, 1745, 1621, 1117 cm^{-1}; ^1H NMR δ 5.75 (dt, *J* = 15.5 Hz, 7.0 Hz, 1H, H-2′), 5.60 (d, *J* = 16.0 Hz, 1H, H-1′), 4.22 (br s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.51 (br s, 1H, H-9a), 3.41 (t, *J* = 6.5 Hz, 2H, H-4′), 3.33 (s, 3H, 4′-O-C$\underline{H}_3$), 3.12−3.06 (m, 2H, H-5a, H-10), 3.00−2.95 (m, 1H, H-5b), 2.86 (d, *J* = 6.0 Hz, 1H, H-7), 2.34 (q, *J* = 7.0 Hz, 2H, H-3′), 2.07 (s, 3H, H-16), 1.95 (d, *J* = 12.0 Hz, 1H, H-1a), 1.83−1.77 (m, 4H, H-1b, H-6, H-9), 1.37 (d, *J* = 6.5 Hz, 3H, H-17); ^{13}C NMR δ 169.8 (C-15), 163.0 (C-13), 148.5 (C-11), 129.6 (C-1′), 128.2 (C-2′), 128.1 (C-12), 112.9 (C-8), 98.8 (C-14), 83.3 (C-3), 80.7 (C-2), 72.2 (C-4′), 61.0 (C-9a), 59.0 (O-$\underline{C}H_3$), 58.7 (4′-O-$\underline{C}H_3$), 51.4 (C-7), 48.2 (C-5), 47.8 (C-9), 32.8 (C-3′), 34.7 (C-10), 33.0 (C-1), 27.0 (C-6); ESIMS *m/z* 415.8 (100%) $[M + H]^+$, 416.9 (20%), 417.9 (5%); HRESIMS *m/z* 416.2089 $[M + H]^+$, calcd for $C_{23}H_{30}NO_6$ 416.2073.

Methoxystemofoline (8). Compound **8** was prepared using a method similar to the synthesis of **7**, from compound **26** (10 mg, 0.025 mmol) and $PdCl_2$ (3 mg, 30% w/w) over a 1 h period. The crude product was purified by CC with gradient elution from EtOAc to EtOAc/MeOH (95:5) to give **8** (4.4 mg, 0.010 mmol, 43% yield) as a yellow gum: R_f = 0.16 in MeOH/EtOAc (1:4); $[\alpha]_D^{25}$ +247.4 (*c* 0.29, CH_3OH); lit.[5] $[\alpha]_D^{21.6}$ +75.6 (*c* 0.037, CH_3OH). The NMR data agree with those of the natural product[5] except for the assignment of the ^{13}C NMR signals for C-6 and C-1′, which were incorrectly assigned. ESIMS *m/z* 417.9 (100%) $[M + H]^+$, 418.9 (25%), 419.9 (10%); HRESIMS *m/z* 418.2233 $[M + H]^+$, calcd for $C_{23}H_{32}NO_6$ 418.2230.

(1′*R*)- and (1′*S*)-Hydroxy-3′,4′-didehydrostemofoline (27 and 28). To a solution of aldehyde **17**[4] (94 mg, 0.261 mmol) in THF/saturated aqueous NH_4Cl (5:2, 6 mL) was added indium powder (60 mg, 0.52 mmol) and allyl bromide (135 μL, 1.56 mmol). The reaction flask was sealed and sonicated for 3 h. The THF was evaporated to give a white residue, which then was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 was washed with brine and dried ($MgSO_4$). The crude mixture of **27** and **28** (81 mg) was put through the next step without purification.

(1′*R*)- and (1′*S*)-Hydroxy-3′,4′-didehydrostemofoline (27 and 28). To a solution of aldehyde **17**[4] (35 mg, 0.099 mmol) in dry THF (3 mL) at 0 °C under a N_2 atmosphere was added $^{l}Ipc_2Ball$ (0.49 mL of 1 M in pentane, 0.49 mmol) and was left to stir at 0 °C for 2 h. The reaction mixture was quenched with MeOH (5 mL), and 10% aqueous HCl (5 mL) was added. The aqueous solution was washed with CH_2Cl_2 (3 × 10 mL). The aqueous phase was basified with aqueous NaOH and then extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with brine and dried ($MgSO_4$). The concentrated residue was purified by CC with gradient elution, EtOAc to EtOAc/MeOH (95:5), to give a mixture of **27** and **28** (dr = 9:1, 31 mg, 0.076 mmol, 77% yield) as a white gum.

The compounds were also prepared from **17**[4] (35 mg, 0.099 mmol) using the above procedure except that $^{d}Ipc_2Ball$ (0.49 mL of 1 M in pentane, 0.493 mmol) was used. This gave a mixture of **27** and **28** (dr = 14:86, 27 mg, 0.068 mmol, 69% yield) as a white gum.

(1′*R*)- and (1′*S*)-Acetyl-3′,4′-didehydrostemofoline (29 and 30). A mixture of **27** and **28** (81 mg) was dissolved in pyridine (2 mL), and acetic anhydride (2 mL) was added at rt. The reaction mixture was left to stir for 4 h before the addition of saturated aqueous $NaHCO_3$ (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by CC using gradient elution (petroleum ether/EtOAc (1:1) to EtOAc) to give **29** (51 mg, 0.115 mmol, 44% yield over 2 steps) as a pale yellow gum as a major product and **30** (32 mg, 0.073 mmol, 28% yield over 2 steps) as a pale yellow gum as a minor product. **29**: R_f = 0.46 in MeOH/EtOAc (1:4); $[\alpha]_D^{24}$ +226.5 (*c* 1.0, $CHCl_3$).; IR ν_{max} 2924, 2858, 1741, 1618, 1372, 1234 cm^{-1}; ^1H NMR δ 5.78−5.70 (m, 1H, H-3′), 5.19 (s, 1H, H-1′), 5.14 (s, 1H, H-(4′*E*)), 5.08 (t, *J* = 12.5 Hz, 1H, H-(4′*Z*)), 4.45 (br s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.46 (br s, 1H, H-9a), 3.26−3.20 (m, 1H, H-5a), 3.09−3.03 (m, 1H, H-10), 3.01−2.96 (m, 1H, H-5b), 2.85 (d, *J* = 6.0 Hz, 1H, H-7), 2.43−2.35 (m, 1H, H-2′), 2.06 (s, 3H, H-16), 2.03 (s, 3H, 1′-OCOC$\underline{H}_3$), 1.93 (d, *J* = 12.5 Hz, 1H, H-1a), 1.89−1.87 (m, 2H, H-6), 1.83 (ddd, *J* = 18.0 Hz, 10.5 Hz, 3.5 Hz, 1H, H-9), 1.63 (d, *J* = 12.0 Hz, 1H, H-1b), 1.36 (d, *J* = 6.5 Hz, 3H, H-17); ^{13}C NMR

δ 170.5 (1′-O$\underline{C}$OCH$_3$), 169.8 (C-15), 162.9 (C-13), 148.2 (C-11), 133.3 (C-3′), 128.1 (C-12), 118.3 (C-4′), 112.7 (C-8), 98.8 (C-14), 85.4 (C-3), 76.6 (C-2), 70.7 (C-1′), 60.9 (C-9a), 59.0 (O-$\underline{C}$H$_3$), 49.4 (C-7), 48.2 (C-5), 47.9 (C-9), 35.6 (C-2′), 34.6 (C-10), 33.2 (C-1), 27.4 (C-6), 21.2 (1′-OCO$\underline{C}$H$_3$), 18.4 (C-17), 9.3 (C-16); ESIMS *m/z* 443.9 (100%) [M + H]$^+$, 444.9 (25%), 446.0 (5%); HRESIMS *m/z* 444.2011 [M + H]$^+$, calcd for $C_{24}H_{30}NO_7$ 444.2022. **30**: R_f = 0.59 in MeOH/EtOAc (1:4); $[\alpha]_D^{24}$ +188.0 (*c* 1.0, CHCl$_3$); IR ν_{max} 2924, 1740, 1629, 1460, 1362, 1234 cm^{-1}; ^{1}H NMR δ 5.76−5.68 (m, 1H, H-3′), 5.10 (s, 1H, H-1′), 5.05 (dd, *J* = 16.5 Hz, 8.0 Hz, 2H, H-4′), 4.48 (br s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.48 (br s, 1H, H-9a), 3.18−3.12 (m, 1H, H-5a), 3.09−3.06 (m, 1H, H-10), 3.04−2.98 (m, 1H, H-5b), 2.71 (d, *J* = 6.0 Hz, 1H, H-7), 2.62 (ddd, *J* = 14.0 Hz, 3.0 Hz, 1.5 Hz, 1H, H-2′a), 2.14−2.09 (m, 1H, H-2′b), 2.08 (s, 3H, 1′-OCOC$\underline{H}_3$), 2.06 (s, 3H, H-16), 2.05−2.01 (m, 1H, H-6b), 1.98 (d, *J* = 12.5 Hz, 1H, H-1a), 1.85−1.80 (m, 1H, H-6a), 1.82 (dd, *J* = 10.5 Hz, 4.5 Hz, 1H, H-9), 1.67 (d, *J* = 12.0 Hz, 1H, H-1b), 1.37 (d, *J* = 7.5 Hz, 3H, H-17); ^{13}C NMR δ 170.9 (1′-O$\underline{C}$OCH$_3$), 169.7 (C-15), 162.8 (C-13), 148.2 (C-11), 134.0 (C-3′), 128.1 (C-12), 117.9 (C-4′), 112.5 (C-8), 98.8 (C-14), 84.9 (C-3), 75.8 (C-2), 69.7 (C-1′), 61.2 (C-9a), 59.0 (O-$\underline{C}$H$_3$), 48.6 (C-7, C-5), 47.8 (C-9), 35.0 (C-2′), 34.6 (C-10), 33.5 (C-1), 26.7 (C-6), 21.0 (1′-OCO$\underline{C}$H$_3$), 18.5 (C-17), 9.3 (C-16); ESIMS *m/z* 443.9 (100%) [M + H]$^+$, 444.9 (25%), 445.9 (5%); HRESIMS *m/z* 444.2015 [M + H]$^+$, calcd for $C_{24}H_{30}NO_7$ 444.2022.

(1′*R*)-Hydroxy-3′,4′-didehydrostemofoline (27). To a solution of acetate derivative **29** (24 mg, 0.053 mmol) in THF/H$_2$O (2:1, 3.0 mL) was added LiOH (21 mg of 53% assay, 0.265 mmol) at rt, and the reaction mixture was left to stir for 16 h. Water was added (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was first washed with saturated aqueous $NaHCO_3$ solution and then brine and dried ($MgSO_4$). The concentrated residue was purified by CC using gradient elution [EtOAc to EtOAc/MeOH (98:2)] to give the alcohol **27** (13 mg, 0.032 mmol, 61% yield) as a pale yellow gum: R_f = 0.23 in MeOH/EtOAc (1:4); $[\alpha]_D^{24}$ +308.0 (*c* 1.0, CHCl$_3$); IR ν_{max} 3446, 2965, 2919, 2847, 1743, 1621 cm^{-1}; ^{1}H NMR δ 5.98−5.88 (m, 1H, H-3′), 5.18 (d, *J* = 18.0 Hz, 1H, H-(4′*Z*)), 5.12 (d, *J* = 10.0 Hz, 1H, H-(4′*E*)), 4.48 (br s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.68 (dd, *J* = 9.5 Hz, 3.5 Hz, 1H, H-1′b), 3.51 (br s, 1H, H-9a), 3.18−3.12 (m, 1H, H-5a), 3.10−3.05 (m, 1H, H-10), 3.05−3.00 (m, 1H, H-5b), 2.82 (d, *J* = 5.0 Hz, 1H, H-7), 2.39−2.34 (m, 1H, H-2′b), 2.32−2.26 (m, 1H, H-1′a), 2.06 (s, 3H, H-16), 1.97 (d, *J* = 12.5 Hz, 1H, H-1a), 1.94−1.89 (m, 2H, H-6), 1.89−1.84 (m, 1H, H-9), 1.64 (d, *J* = 13.0 Hz, 1H, H-1b), 1.37 (d, *J* = 6.0 Hz, 3H, H-17); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.2 (C-11), 135.0 (C-3′), 128.1 (C-12), 117.7 (C-4′), 112.6 (C-8), 98.8 (C-14), 87.0 (C-3), 75.6 (C-2), 67.9 (C-1′), 61.0 (C-9a), 59.0 (O-$\underline{C}$H$_3$), 48.2 (C-7), 48.1 (C-9), 47.6 (C-5), 36.7 (C-2′), 34.5 (C-10), 33.9 (C-1), 27.4 (C-6), 18.4 (C-17), 9.3 (C-16); ESIMS *m/z* 402.2 (100%) [M + H]$^+$, 403.2 (20%); HRESIMS *m/z* 402.1912 [M + H]$^+$, calcd for $C_{22}H_{28}NO_6$ 402.1917.

(1′*S*)-Hydroxy-3′,4′-didehydrostemofoline (28). Compound **28** was prepared via a method similar to the synthesis of **27**, using acetate derivative **30** (15 mg, 0.034 mmol) and LiOH (14 mg of 53% assay, 0.170 mmol) to give alcohol **28** (10 mg, 0.025 mmol, 73% yield) as a white gum: R_f = 0.36 in MeOH/EtOAc (1:4); $[\alpha]_D^{24}$ +380.0 (*c* 0.41, CHCl$_3$); IR ν_{max} 3286, 2957, 2924, 2854, 1744, 1615 cm^{-1}; ^{1}H NMR δ 5.90−5.82 (m, 1H, H-3′), 5.19 (d, *J* = 11.5 Hz, 1H, H-(4′*Z*)), 5.16 (s, 1H, H-(4′*E*)), 4.40 (s, 1H, H-2), 4.13 (s, 3H, O-C$\underline{H}_3$), 3.71 (d, *J* = 10.5 Hz, 1H, H-1′a), 3.49 (br s, 1H, H-9a), 3.17−3.13 (m, 1H, H-9), 3.13−3.06 (m, 1H, H-10), 3.03 (d, *J* = 5.5 Hz, 1H, H-5a), 3.04−2.98 (m, 1H, H-7), 2.53 (dd, *J* = 14.0 Hz, 5.5 Hz, 1H, H-2′a), 2.07 (s, 3H, H-16), 2.02 (d, *J* = 14.5 Hz, 1H, H-2′b), 2.00 (d, *J* = 11.5 Hz, 1H, H-6b), 1.97 (d, *J* = 13.0 Hz, 1H, H-1a), 1.90−1.88 (m, 1H, H-6a), 1.85 (d, *J* = 7.5 Hz, 1H, H-5b), 1.69 (d, *J* = 12.5 Hz, 1H, H-1b), 1.37 (d, *J* = 6.0 Hz, 3H, H-17); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.5 (C-11), 135.2 (C-3′), 128.1 (C-12), 118.6 (C-4′), 112.9 (C-8), 98.8 (C-14), 86.0 (C-3), 77.0 (C-2), 69.8 (C-1′), 61.7 (C-9a), 59.0 (O-$\underline{C}$H$_3$), 49.3 (C-7, C-9), 48.0 (C-5), 37.8 (C-2′), 34.6 (C-1, C-10), 27.3 (C-6), 18.4 (C-17), 9.3 (C-16); ESIMS *m/z* 402.2 (100%) [M + H]$^+$, 403.2 (20%), 404.2 (10%); HRESIMS *m/z* 402.1903 [M + H]$^+$, calcd for $C_{22}H_{28}NO_6$ 402.1917.

(1′*R*)-Hydroxystemofoline (9). To a solution of alcohol **27** (12 mg, 0.029 mmol) in dry MeOH (2 mL) at rt was added Pd/C (1.2 mg, 10% w/w), and the flask was flushed with N_2 for 10 min before being left to stir under a H_2 atmosphere (balloon) for 45 min. The flask was flushed with N_2, and the solution was filtered through Celite and washed with MeOH. The filtrate was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by CC [gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (98:2)] to give the alcohol **9** (4.1 mg, 0.010 mmol, 35% yield) as a yellow gum: R_f = 0.19 in MeOH/EtOAc (1:4); $[\alpha]_D^{23}$ +298.7 (*c* 0.34, CHCl$_3$); IR ν_{max} 3462, 2960, 2919, 2868, 1744, 1620 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.47 (br s, 1H, H-2), 4.14 (s, 3H, O-C$\underline{H}_3$), 3.64−3.59 (m, 1H, H-1′b), 3.54 (br s, 1H, H-9a), 3.23−3.15 (m, 1H, H-5a), 3.15−3.07 (m, 1H, H-10), 3.07−2.99 (m, 1H, H-5b), 2.80 (br s, 1H, H-7), 2.07 (s, 3H, H-16), 1.98 (d, *J* = 12.3 Hz, 1H, H-1a), 1.91−1.86 (m, 3H, H-6, H-9), 1.70−1.62 (m, 2H, H-1b, H-3′a), 1.55−1.47 (m, 2H, H-2′), 1.44−1.42 (m, 1H, H-3′b), 1.38 (d, *J* = 6.6 Hz, 3H, H-17), 0.97 (t, *J* = 7.2 Hz, 3H, H-4′); ^{13}C NMR (75 MHz) δ 169.8 (C-15), 162.8 (C-13), 148.2 (C-11), 128.2 (C-12), 112.9 (C-8), 98.8 (C-14), 87.4 (C-3), 75.6 (C-2), 67.9 (C-1′), 61.1 (C-9a), 59.0 (O-$\underline{C}$H$_3$), 48.2 (C-9), 48.1 (C-7), 47.5 (C-5), 34.5 (C-10), 34.2 (C-2′), 34.0 (C-1), 27.4 (C-6), 20.2 (C-3′), 18.5 (C-17), 14.3 (C-4′), 9.3 (C-16); ESIMS *m/z* 404.2 (100%) [M + H]$^+$, 405.2 (18%), 406.2 (10%); HRESIMS *m/z* 404.2069 [M + H]$^+$, calcd for $C_{22}H_{30}NO_6$ 404.2073.

(1′*S*)-Hydroxystemofoline (10). Compound **10** was prepared via a method similar to the synthesis of **9**, using alcohol **28** (17 mg, 0.042 mmol) and Pd/C (1.7 mg, 10% w/w) to give alcohol **10** (7 mg, 0.017 mmol, 40% yield) as a white gum: R_f = 0.28 in MeOH/EtOAc (1:4); $[\alpha]_D^{23}$ +219.0 (*c* 0.58, CHCl$_3$); IR ν_{max} 3183, 2924, 2854, 1744, 1615, 982 cm^{-1}; ^{1}H NMR δ 4.36 (br s, 1H, H-2), 4.14 (s, 3H, O-C$\underline{H}_3$), 3.73 (d, *J* = 9.5 Hz, 1H, H-1′a), 3.58 (br s, 1H, H-9a), 3.23 (br s, 1H, H-5a), 3.12−3.10 (m, 1H, H-10), 3.07−3.03 (m, 1H, H-5b), 3.00 (d, *J* = 6.0 Hz, 1H, H-7), 2.07 (s, 3H, H-16), 2.10−2.02 (m, 1H, H-6a), 1.99 (d, *J* = 12.5 Hz, 1H, H-1a), 1.91−1.87 (m, 2H, H-6b, H-9), 1.78−1.76 (m, 1H, H-1b), 1.65−1.57 (m, 2H, H-2′b, H-3′b), 1.38 (d, *J* = 6.5 Hz, 3H, H-17), 1.41−1.30 (m, 2H, H-2′a, H-3′a), 0.95 (t, *J* = 6.5 Hz, 3H, H-4′); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.2 (C-11), 128.2 (C-12), 112.8 (C-8), 98.8 (C-14), 87.0 (C-3), 77.4 (C-2), 70.9 (C-1′), 62.0 (C-9a), 59.0 (O-$\underline{C}$H$_3$), 49.4 (C-5), 47.9 (C-9), 47.7 (C-7), 34.6 (C-10), 35.2 (C-2′), 33.1 (C-1), 27.2 (C-6), 19.9 (C-3′), 18.4 (C-17), 14.1 (C-4′), 9.3 (C-16); ESIMS *m/z* 404.2 (100%) [M + H]$^+$, 405.2 (20%), 406.2 (5%); HRESIMS *m/z* 404.2064 [M + H]$^+$, calcd for $C_{22}H_{30}NO_6$ 404.2073.

11,12-Dihydroxystemofoline (31). To a solution of **11**[18] (40 mg, 0.104 mmol) in 2:1 acetone/H$_2$O (3.0 mL) at rt was added 4-methylmorpholine-*N*-oxide (23 mg, 0.193 mmol) and $K_2OsO_4 \cdot 2H_2O$ (2 mg, 0.005 mmol), respectively. The reaction was left to stir at rt for 16 h, sodium sulfite (50 mg) was added, and stirring was continued for 1 h. The reaction mixture was filtered through a pad of cotton. A saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with brine and dried ($MgSO_4$). The concentrated residue was purified by CC [CH_2Cl_2 to CH_2Cl_2/MeOH (90:10)] to give **31** (25 mg, 0.058 mmol, 56% yield) as a pale yellow gum: R_f = 0.40 in MeOH/CH_2Cl_2 (1:9); $[\alpha]_D^{25}$ −8.4 (*c* 1.55, CHCl$_3$); IR ν_{max} 3282, 2954, 2931, 2871, 1671, 1327, 1022 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$OD) δ 4.25 (br s, 1H, H-2), 4.14 (s, 3H, O-C$\underline{H}_3$), 3.40 (br s, 1H, H-9a), 3.14−3.08 (m, 3H, H-5, H-9), 2.86 (br, 1H, H-10), 2.44 (d, *J* = 5.7 Hz, 1H, H-7), 2.05−1.93 (m, 1H, H-1a), 1.96 (s, 3H, H-16), 1.91−1.78 (m, 2H, H-6), 1.65−1.60 (m, 1H, H-1b), 1.60−1.55 (m, 2H, H-1′), 1.45−1.28 (m, 4H, H-2′, H-3′), 1.08 (d, *J* = 6.9 Hz, 3H, H-17), 0.94 (t, *J* = 11.0 Hz, 3H, H-4′); ^{13}C NMR (75 MHz, CD$_3$OD) δ 175.1 (C-15), 171.4 (C-13), 112.3 (C-8), 109.1 (C-11), 104.1 (C-12), 100.4 (C-14), 84.2 (C-3), 79.2 (C-2), 62.5 (C-9a), 59.8 (O-$\underline{C}$H$_3$), 51.4 (C-7), 48.3 (C-5), 45.3 (C-9), 37.2 (C-10), 33.6 (C-1), 32.4 (C-1′), 28.3 (C-2′), 26.6 (C-6), 24.2 (C-3′), 14.3 (C-4′), 12.7 (C-17), 8.2 (C-16). The NMR spectra were also determined in CDCl$_3$; however, the signal for C-12 could not be observed. ^{1}H NMR (CDCl$_3$) δ 4.25 (br s, 1H, H-2), 4.12 (s, 3H, O-C$\underline{H}_3$), 3.45 (br s, 1H, H-9a), 3.14−3.08 (m, 1H, H-5a), 3.02−2.96 (m, 1H, H-5b), 2.73−2.66 (m, 1H, H-10), 2.51 (d, *J* = 6.0 Hz, 1H, H-7), 2.01 (s, 3H, H-16), 1.98 (d, *J* = 12.5 Hz, 1H, H-1a), 1.91 (d, *J* = 10.0 Hz, 1H, H-9), 1.86−1.81 (m, 1H, H-6a), 1.79−1.73 (m, 1H, H-6b), 1.70 (d, *J* = 12.5 Hz, 1H, H-1b), 1.54 (d, *J* = 9.5 Hz, 2H, H-1′), 1.42−1.36 (m, 1H, H-2′), 1.35−1.31 (m, 2H, H-3′), 1.28−1.20 (m, 1H, H-2′), 1.13 (br s, 2H, 11-O$\underline{H}$, 12-O$\underline{H}$), 1.03 (d, *J* = 6.5 Hz, 3H, H-17); 0.90 (t, *J* = 7.0 Hz, 3H, H-4′); ^{13}C NMR δ 172.7 (C-15), 168.0 (C-13), 111.3 (C-8), 101.9 (C-11), 100.0 (C-14), 83.2 (C-3), 78.7 (C-2), 61.0 (C-9a), 59.1 (O-$\underline{C}$H$_3$), 49.8 (C-7), 47.5 (C-5), 46.0 (C-9), 36.0 (C-10), 32.9 (C-1), 31.5 (C-1′), 27.4 (C-2′), 26.2 (C-6), 23.2 (C-3′), 14.1 (C-4′), 12.6 (C-17), 8.7 (C-16); ESIMS *m/z* 422.0 (100%) [M + H]$^+$, 423.1

(20%), 424.1 (5%); HRESIMS *m/z* 422.2166 $[M + H]^+$, calcd for $C_{22}H_{32}NO_7$ 422.2179.

(2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*)-7b-Butylhexahydro-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)furo[2,3,4-*gh*]pyrrolizin-10-one (32). To a stirred mixture of silica gel (1.67 g) suspended in diethyl ether (1 mL) at rt was added $NaIO_4$ (16 mg, 0.076 mmol) in water (1 mL). Then a solution of **31** (25 mg, 0.058 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was left to stir for 1 h at rt. The reaction mixture was filtered through a pad of cotton, and the filtrate was dried ($MgSO_4$). The crude product was purified by CC [CH_2Cl_2 to CH_2Cl_2/MeOH (95:5)] to give **32** (10 mg, 0.035 mmol, 60% yield) as a clear yellow gum: R_f = 0.37 in MeOH/EtOAc (1:4); $[\alpha]_D^{25}$ +26.3 (*c* 0.21, $CHCl_3$); IR ν_{max} 2945, 2921, 2868, 1797, 970 cm^{-1}; ^1H NMR δ 4.32 (br s, 1H, H-2), 3.41 (br s, 1H, H-9a), 3.19−3.12 (m, 1H, H-5b), 3.05−2.98 (m, 1H, H-5a), 2.77 (dq, *J* = 11.5 Hz, 7.5 Hz, 1H, H-10), 2.65 (d, *J* = 6.0 Hz, 1H, H-7), 1.98 (d, *J* = 12.5 Hz, 1H, H-1a), 1.96−1.92 (m, 1H, H-9), 1.92−1.88 (m, 1H, H-6a), 1.84−1.78 (m, 1H, H-6b), 1.75 (dt, *J* = 12.5 Hz, 3.5 Hz, 1H, H-1b), 1.62−1.50 (m, 2H, H-1′), 1.46−1.38 (m, 1H, H-2′), 1.35 (q, *J* = 7.0 Hz, 2H, H-3′), 1.26 (d, *J* = 7.0 Hz, 3H, 10-C$\underline{H}_3$), 1.28−1.20 (m, 1H, H-2′), 0.92 (t, *J* = 7.0 Hz, 3H, H-4′); ^{13}C NMR δ 178.5 (C-11), 109.26 (C-8), 83.2 (C-3), 78.9 (C-2), 61.2 (C-9a), 50.2 (C-7), 47.7 (C-5), 45.7 (C-9), 35.9 (C-10), 32.9 (C-1), 31.9 (C-1′), 27.3 (C-2′), 26.6 (C-6), 23.2 (C-3′), 14.1 (C-4′), 13.4 (10-C$\underline{H}_3$); ESIMS *m/z* 278.2 (100%) $[M + H]^+$, 279.2 (20%); 280.2 (3%); HRESIMS *m/z* 278.1679 $[M + H]^+$, calcd for $C_{16}H_{24}NO_6$ 278.1756.

(2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*,10*Z*)-Tetrahydro-10-(3-methoxy-4-methyl-5-oxo-2(5*H*)-furanylidene)-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)-furo[2,3,4-gh]pyrrolizine-7b(6*H*)-(2*E*)-2-propenal (33a), (2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*,10*Z*)-Tetrahydro-10-(3-methoxy-4-methyl-5-oxo-2(5*H*)-furanylidene)-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)furo[2,3,4-*gh*]-pyrrolizine-7b(6*H*)-(2*E*,4*E*)-2,4-pentadienal (33b), and (2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*,10*Z*)-Tetrahydro-10-(3-methoxy-4-methyl-5-oxo-2(5*H*)-furanylidene)-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)furo[2,3,4-*gh*]-pyrrolizine-7b(6*H*)-(2*E*,4*E*,6*E*)-2,4,6-septatrienal (33c). To a solution of **17**[4] (56 mg, 0.157 mmol) in dry toluene (3 mL) at rt under a N_2 atmosphere was added (triphenylphosphoranylidene)acetaldehyde (95 mg, 0.314 mmol). Then the reaction mixture was heated to 80 °C under N_2 for 2 days. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with brine and dried over $MgSO_4$. After evaporation the crude product mixture (114 mg) was obtained as a yellow gum. This mixture was taken through the next step without further purification.

(5*Z*)-5-[(2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*)-Hexahydro-7b-[(1*E*)-3-hydroxybutenyl]-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)furo[2,3,4-*gh*]-pyrrolizin-10-ylidene]-4-methoxy-3-methyl-2(5*H*)-furanone (34a), (5*Z*)-5-[(2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*)-Hexahydro-7b-[(1*E*,3*E*)-5-hydroxy-1,3-pentadienyl]-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)furo[2,3,4-*gh*]pyrrolizin-10-ylidene]-4-methoxy-3-methyl-2(5*H*)-furanone (34b), and (5*Z*)-5-[(2*S*,2a*R*,6*S*,7a*S*,7b*S*,8*R*,9*S*)-Hexahydro-7b-[(1*E*,3*E*,5*E*)-7-hydroxy-1,3,5-septatrienyl]-9-methyl-4*H*-2,2,6-(epoxy[1]propanyl[3]ylidene)furo[2,3,4-*gh*]pyrrolizin-10-ylidene]-4-methoxy-3-methyl-2(5*H*)-furanone (34c). To a solution of **33a**−**c** (114 mg) in dry MeOH (2 mL) was added $NaBH_4$ (12 mg) at rt. The reaction mixture was left to stir at rt for 45 min. The MeOH was then evaporated to give a white residue. A saturated aqueous solution of $NaHCO_3$ (5. mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with brine and dried ($MgSO_4$). Evaporation gave the crude product as a yellow gum (112 mg). This was purified by PTLC using 10% MeOH/EtOAc to give **34a** (7.1 mg, 0.018 mmol, 12% yield over 2 steps), **34b** (17.5 mg, 0.042 mmol, 27% yield over 2 steps), and **34c** (3.3 mg, 0.008 mmol, 5% yield over 2 steps). **34a**: R_f = 0.06 in MeOH/CH_2Cl_2 (1:9); $[\alpha]_D^{25}$ +280.1 (*c* 1.14, $CHCl_3$); IR ν_{max} 3329, 2933, 2921, 2864, 1752, 1621, 1003 cm^{-1}; ^1H NMR δ 5.94 (dt, *J* = 15.0 Hz, 5.0 Hz, 1H, H-2′), 5.81 (d, *J* = 15.5 Hz, 1H, H-1′), 4.24 (s, 1H, H-2), 4.19 (br s, 2H, H-3′), 4.14 (s, 3H, O-C$\underline{H}_3$), 3.51 (br s, 1H, H-9a), 3.13−3.07 (m, 2H, H-5a, H-10), 3.02−2.97 (m, 1H, H-5b), 2.88 (d, *J* = 5.5 Hz, 1H, H-7), 2.07 (s, 3H, H-16), 1.96 (d, *J* = 12.0 Hz, 1H, H-1a), 1.92−1.86 (m, 2H, H-6), 1.86−1.82 (m, 1H, H-9), 1.78 (d, *J* = 12.0 Hz, 1H, H-1b), 1.70 (br s, 1H, 3′-O$\underline{H}$), 1.38 (d, *J* = 6.5 Hz, 3H, H-17); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.4 (C-11), 130.5 (C-2′), 129.1 (C-1′), 128.1 (C-12), 112.9 (C-8), 98.8 (C-14), 83.1 (C-3), 80.6 (C-2), 63.0 (C-3′), 61.1 (C-9a), 59.0 (O-C$\underline{H}_3$), 51.6 (C-7), 48.3 (C-5), 47.8 (C-9), 34.7 (C-10), 32.9 (C-1), 27.0 (C-6), 18.4 (C-17), 9.3 (C-16); ESIMS *m/z* 388.0 (100%) $[M + H]^+$, 389.1 (20%); HRESIMS *m/z* 388.1762 $[M + H]^+$, calcd for $C_{21}H_{25}NO_6$ 388.1760. **34b**: R_f = 0.13 in MeOH/CH_2Cl_2 (1:9); $[\alpha]_D^{25}$ +229.9 (*c* 0.77, $CHCl_3$); IR ν_{max} 3288, 3007, 2937, 2872, 1726, 1613, 1005 cm^{-1}; ^1H NMR δ 6.34 (dd, *J* = 14.5 Hz, 10.5 Hz, 1H, H-3′), 6.30 (dd, *J* = 15.5 Hz, 10.5 Hz, 1H, H-2′), 5.87 (dt, *J* = 14.5 Hz, 5.5 Hz, 1H, H-4′), 5.76 (d, *J* = 14.5 Hz, 1H, H-1′), 4.23 (s, 1H, H-2), 4.20 (d, *J* = 6.0 Hz, 2H, H-5′), 4.14 (s, 3H, O-C$\underline{H}_3$), 3.52 (br s, 1H, H-9a), 3.14−3.06 (m, 2H, H-5a, H-10), 3.03−2.97 (m, 1H, H-5b), 2.88 (d, *J* = 5.5 Hz, 1H, H-7), 2.08 (s, 3H, H-16), 1.96 (d, *J* = 12.5 Hz, 1H, H-1a), 1.90−1.82 (m, 3H, H-6, H-9), 1.78 (d, *J* = 12.5 Hz, 1H, H-1b), 1.59 (br s, 1H, 5′-O$\underline{H}$), 1.38 (d, *J* 6.5 Hz, 3H, H-17); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.4 (C-11), 132.8 (C-4′), 131.7 (C-1′), 130.6 (C-2′), 130.0 (C-3′), 128.1 (C-12), 112.9 (C-8), 98.8 (C-14), 83.5 (C-3), 80.8 (C-2), 63.4 (C-5′), 61.1 (C-9a), 59.0 (O-C$\underline{H}_3$), 52.1 (C-7), 48.4 (C-5), 47.8 (C-9), 34.7 (C-10), 33.0 (C-1), 27.0 (C-6), 18.5 (C-17), 9.3 (C-16); ESIMS *m/z* 414.0 (100%) $[M + H]^+$, 415.0 (20%); HRESIMS *m/z* 414.1902 $[M + H]^+$, calcd for $C_{23}H_{27}NO_6$ 414.1917. **34c**: R_f = 0.27 in MeOH/CH_2Cl_2 (1:9); $[\alpha]_D^{25}$ +174.2 (*c* 0.15, $CHCl_3$); IR ν_{max} 3378, 2962, 2921, 2851, 1742, 1618 cm^{-1}; ^1H NMR δ 6.38−6.33 (m, 1H, H-2′), 6.31−6.26 (m, 1H, H-5′), 6.26−6.23 (m, 2H, H-3′, H-4′), 5.87 (dt, *J* = 14.5 Hz, 5.5 Hz, 1H, H-6′), 5.77 (d, *J* = 15.0 Hz, 1H, H-1′), 4.24 (br s, 1H, H-2), 4.21 (d, *J* = 5.5 Hz, 2H, H-7′), 4.14 (s, 3H, O-C$\underline{H}_3$), 3.52 (br s, 1H, H-9a), 3.14−3.06 (m, 2H, H-5b, H-10), 3.04−2.88 (m, 1H, H-5a), 2.88 (d, *J* = 5.5 Hz, 1H, H-7), 2.07 (s, 3H, H-16), 1.96 (d, *J* = 12.0 Hz, 1H, H-1a), 1.91−1.86 (m, 1H, H-9), 1.86−1.77 (m, 2H, H-6), 1.78 (d, *J* = 12.5 Hz, 1H, H-1b), 1.75 (br s, 1H, 7′-O$\underline{H}$), 1.38 (d, *J* 6.5 Hz, 3H, H-17); ^{13}C NMR δ 169.8 (C-15), 162.9 (C-13), 148.4 (C-11), 132.9 (C-6′), 132.5 (C-4′), 132.2 (C-3′), 131.8 (C-1′), 131.2 (C-5′), 130.7 (C-2′), 128.1 (C-12), 112.9 (C-8), 98.8 (C-14), 85.6 (C-3), 80.8 (C-2), 63.5 (C-7′), 61.1 (C-9a), 59.0 (O-C$\underline{H}_3$), 52.1 (C-7), 48.4 (C-5), 47.8 (C-9), 34.7 (C-10), 33.0 (C-1), 27.0 (C-6), 18.5 (C-17), 9.3 (C-16); ESIMS *m/z* 440.1 (100%) $[M + H]^+$, 441.2 (5%); HRESIMS *m/z* 440.2049 $[M + H]^+$, calcd for $C_{25}H_{29}NO_6$ 440.2073.

Bioautography Procedure. TLC bioautography was performed using the method described by Hostettmann et al.[15] TLC plates were prepared for bioautography by washing with acetone and then thoroughly dried. Samples were applied to the plates in varying quantities and sprayed with AChE enzyme stock solution (prepared from acetylcholinesterase (EC 3.1.1.7, 906 U/mg) as described in the literature[15]). The plates were incubated at 37 °C for 20 min and then sprayed with freshly prepared indicator solution (from 1-naphthyl acetate and Fast Blue B salt prepared according to the literature[15]) to give the plate a purple coloration after 1−2 min. A white spot indicated inhibition of AChE by the sample.

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Supporting Information Available: Copies of the ^1H NMR and ^{13}C NMR spectra of all compounds and full experimental procedures for Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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