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Total Synthesis of Stemoamide, 9a-*epi*-Stemoamide, and 9a,10-*epi*-Stemoamide: Divergent Stereochemistry of the Final Methylation Steps

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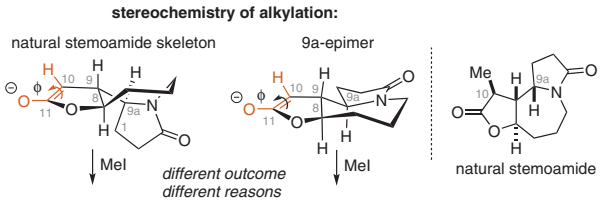

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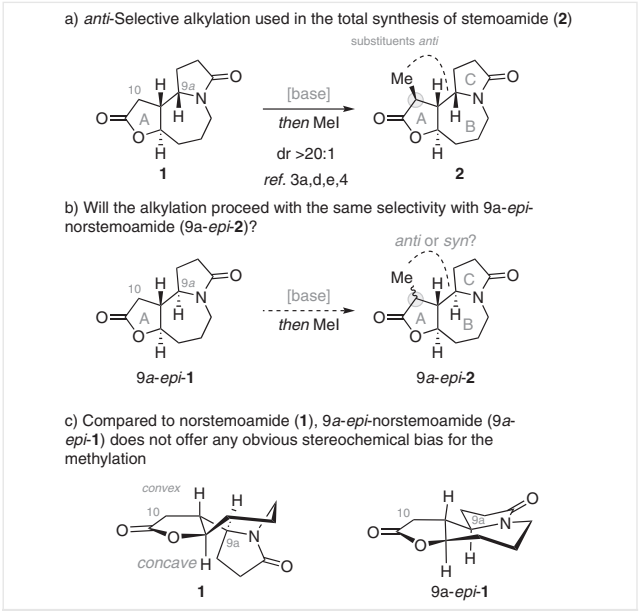
Abstract Total syntheses of stemoamide, 9a-*epi*-stemoamide, and 9a,10-*epi*-stemoamide by a convergent A + B ring-forming strategy is reported. The synthesis required a diastereoselective late-stage methylation of the ABC stemoamide core that successfully enabled access to three of the four possible diastereomeric structures. For the natural stemoamide series, the diastereoselectivity can be rationalized both by kinetic and thermodynamic arguments, whereas for the natural 9a-*epi*-stemoamide series, the kinetic selectivity is explained by the prepyramidalization of the relevant enolate.

Key words total synthesis, *Stemona* alkaloids, cyclic stereocontrol, Mukaiyama–Michael reaction, DFT calculation

Traditional Chinese medicine uses *Stemona* plants to treat various diseases and illnesses. Many structurally diverse alkaloids have been isolated from these *Stemona* plants, with the alkaloid stemoamide (**2**) being the key representative members of the natural product family.[2,3] Several total and formal syntheses of stemoamide (**2**) have been disclosed in the literature.[4] Many of these syntheses rely on a late-stage stereoselective C_{10} methylation of the ring A of norstemoamide (**1**). This methylation is experimentally known to yield natural stemoamide (**2**) in a stereoselective fashion with the C_{10} methyl group disposed *anti* to the adjacent B ring system (Scheme 1, a).[4a,d,e,5] A literature precedent also suggests that methylation of 9a-*epi*-norstemoamide (9a-*epi*-**1**) should proceed with the same sense of selectivity (*anti*, Scheme 1, b).[6] The observed stereoselectivity is somewhat surprising since the stemoamide nucleus does not possess any obvious bias, especially in the case of the 9a-*epi*-norstemoamide (Scheme 1 c).[7] Herein, we report the



Scheme 1 Methylation of different stemoamide scaffolds at C_{10}. a) Methylation of norstemoamide skeleton (**1**) at C_{10} gives the *anti*-alkylation product, stemoamide (**2**).[3,4a,d,e] b) and c) The selectivity of the methylation of 9a-*epi*-norstemoamide is less predictable as no steric bias is obvious.

total syntheses of stemoamide (**2**), 9a-*epi*-stemoamide (9a-*epi*-**2**), and 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**), and provide a rationalization for the sense of diastereoselection.

We recognized butenolide aldehyde **3**, accessible *via* an enantioselective Mukaiyama–Michael reaction previously developed in our group (Scheme 2), as a suitable A-ring building block from which the stemoamide (**2**) structure would emerge by installation of the C ring in a second Mukaiyama–Michael reaction with a silyloxypyrrole, followed by cyclization of the B ring.[8]

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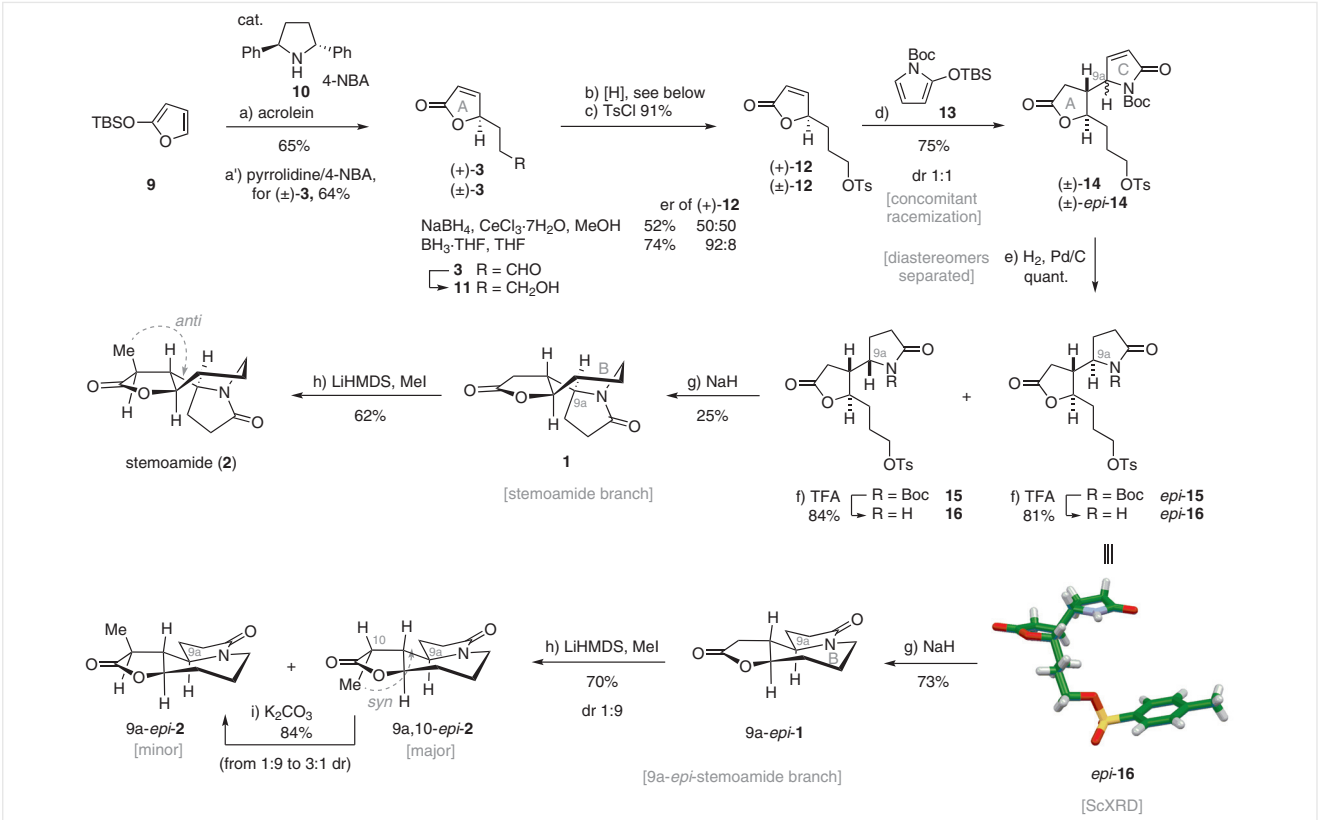
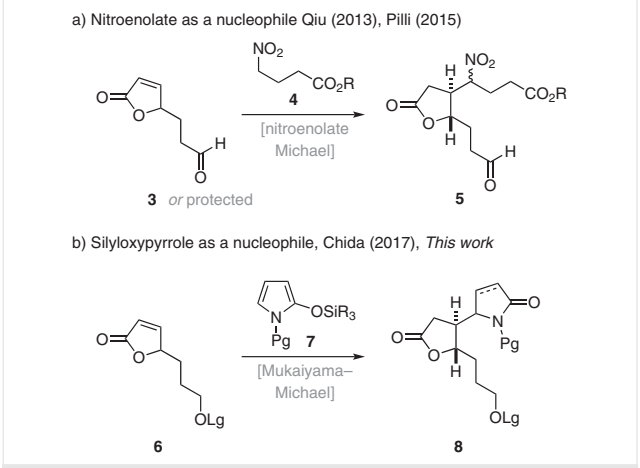


Scheme 2 Total synthesis of (±)-stemoamide (**2**), (±)-9a,10-*epi*-stemoamide (9a,10-*epi*-**2**), and (±)-9a-*epi*-stemoamide (9a-*epi*-**2**). *Reagents and conditions*: a) acrolein (5.0 equiv), (2*S*,5*S*)-diphenylpyrrolidine (**10**, 0.1 equiv), 4-nitrobenzoic acid (0.1 equiv), water (2.0 equiv), DCM, 0 °C, 5 h, 65%. For the racemic series: a′) acrolein (3.0 equiv), pyrrolidine (0.1 equiv), 4-nitrobenzoic acid (0.1 equiv), water (2.0 equiv), DCM, –50 °C, 5 h, 64%; b) BH_3·THF (1.1 equiv), THF, –60 °C, 30 min, 74%; c) TsCl (1.5 equiv), $MeNH_2$·HCl (0.1 equiv), Et_3N (1.5 equiv), DCM, 0 °C to rt, 10 min, 91%; d) **7** (2.0 equiv), TBSOTf (0.1 equiv), HFIP (1.0 equiv), DCM, –25 °C, 8 h, 75%, dr *ca.* 1:1; e) H_2, Pd/C, THF, rt, overnight, quant.; f) TFA (2.0 equiv), DCM, rt, 4 h, 84% for **15**, 81% for *epi*-**15**; g) NaH (5.0 equiv), THF, 0 °C to rt, 17 h, 25% for **16**, 6 h, 73% for *epi*-**16**; h) LiHMDS (1.1 equiv) then MeI (5.0 equiv), THF, –78 °C, 3 h, 62% for **1**, 70% for 9a-*epi*-**1**; g) K_2CO_3 (1.0 equiv), MeOH, rt, 48 h, 84% recovery.

This approach was also supported by very informative previous syntheses utilizing similar Michael–additions to butenolide A ring starting materials such as **3** and **6** (Scheme 3).[4g,h] We should also add that during the course of this study, the group of Chida published an elegant and comprehensive total synthesis of various *Stemona* alkaloids with a similar strategy to ours.[4a]

We first set out to convert the aldehyde functionality of **3** into a leaving group to serve as a handle for the construction of the azepane B ring later in the synthesis. Towards this end, aldehyde **3** was reduced with borane and tosylated using the Tanabe tosylation protocol to give butenolide tosylate **12** in 67% yield over two steps (*er* 92:8, Scheme 2).[9] Attempts at using a Luche reduction instead of borane led to full racemization of the material.[8a] We then installed the C-ring lactam unit onto the butenolide tosylate **12** using a TBSOTf-catalyzed Mukaiyama–Michael reaction with silyloxypyrrole **13**. Unfortunately, again the stereochemical lability of 5*H*-furanones such as **12** presented a serious problem: all attempts at using enantioenriched **12** yielded race-



Scheme 3 Previous synthetic approaches to Stemona alkaloid core relying on conjugate additions to a butenolide[4a,e,h]

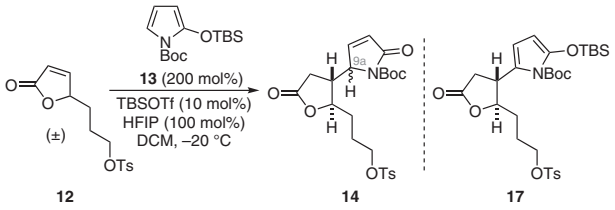
mic Mukaiyama–Michael adduct *rac*-**14**.[10] The racemization is likely taking place *via* a reversible silylation–desilylation of the butenolide. With this setback, we opted to complete the synthesis with racemic butenolide tosylate *rac*-**12** to demonstrate the viability of the route. It is also worth noting that attempts at using alternative leaving groups, such as the corresponding bromide or mesylate, led to low yields of the desired Michael adduct and multiple undesired side reactions.

The TBSOTf/HFIP system used in the key A–C ring coupling to form *rac*-**14** was identified after extensive screening of conditions. Most Lewis acids such as $SnCl_4$, $BF_3{\cdot}OEt_2$, and $Sc(OTf)_3$ in various solvents, temperatures, and addition rates merely decomposed the *N*-Boc-silyloxypyrrole **13** or led to complex mixtures. The decomposition of the *N*-Boc-protected silyloxypyrrole **13** with traditional Lewis acids was also noted in the related total synthesis of *Stemona* alkaloids by Chida and co-workers, who elegantly solved this issue by changing the *N*-protecting group on the silyloxypyrrole nucleophile.[4a,11] The TBSOTf/HFIP-catalyzed Mukaiyama–Michael reaction between A-ring butenolide **12** and *N*-Boc silyloxypyrrole **13** yields a mixture of the desired AC ring adduct **14** and the corresponding silyloxypyrrole **17** (Table 1). To improve the yield of **14**, silyloxypyrrole side product **17** was hydrolyzed to the desired product **14** with a prolonged aqueous quench. The thus obtained AB ring fragment **14** formed as a close to 1:1 mixture of 9a-epimers, with slight variation between batches, in 70–75% yields, allowing for access to both stemoamide (**2**) and its 9a-epimer (9a-*epi*-**2**).

Table 1 details the effects of modifying the optimized Mukaiyama–Michael reaction conditions. These screens revealed that the reaction required both HFIP as well as silyl triflate (Table 1). Without HFIP, or with reduced HFIP loading (10 mol%), the reaction gave low 10% and 12% isolated yields of **14**, respectively (Table 1, entries 2 and 6). The yield of **14** was also lower when a large excess of HFIP was used (Table 1, entry 5). When TBSOTf was replaced with triflic acid, a comparable 61% yield of **14** was obtained (Table 1, entry 7), but without HFIP, the yield dropped to 13% (Table 1, entry 8). These observations suggested that the combination of TBSOTf–HFIP promotes the reaction presumably by forming catalytic amounts of triflic acid *in situ*. HFIP is also crucial for the reaction.[11d,12]

With secured access to key intermediate **14**, we proceeded to construct the final B (azepane) ring. The α,β-unsaturated lactam C ring of **14** was hydrogenated to give two separable epimeric butanolides **15** and *epi*-**15**.[13] Relative configurations of the diastereomers could not be reliably established from NMR data at this stage. Thankfully, after *N*-deprotection of *epi*-**15** with trifluoroacetic acid, the product lactam *epi*-**16** was crystalline, and its relative stereochemistry could be reliably established from a single-crystal X-ray structure (see Scheme 2 inset). The deprotected *epi*-**16** was cyclized with NaH in 4 h to give a 73% yield of 9a-*epi*-**1**.

Table 1 Modifications to the Optimized Mukaiyama–Michael Reaction between Butenolide **12** and Silyloxypyrrole **13**



Entry	Modification to standard protocol	Conversion (%)[a]	Yield (%)[b]
1	–	98	75
2	no HFIP	13	10
3	4 Å MS (50 wt%)	82	65
4	**7** (110 mol%)	68	61
5	HFIP (500 mol%)	63	48
6	HFIP (10 mol%)	15	12
7	TfOH (10 mol%) no TBSOTf	77	61
8	TfOH (10 mol%), no TBSOTf, no HFIP	18	13
9	quenched with Et_3N	–	23 (**17**)

[a] Based on crude ^{1}H NMR spectrum.
[b] Isolated yield after flash column chromatography of both diastereomers. The diastereomeric ratio in all cases was *ca.* 1:1 and varied slightly based on quenching.

The natural 9a-epimer **15** was similarly *N*-deprotected with trifluoroacetic acid and then cyclized to norstemoamide (**1**) with NaH. In marked contrast to the *epi*-**16**, the cyclization of the natural **16** resulted in a lower 25% yield of **1**, taking 17 h to consume tosylate **16**. The different cyclization rates and yields of the natural and 9a-epimeric tosylates **16** are in agreement with the work of Cossy and coworkers, where cyclization of a 1:1 C_{9a}-epimeric mixture of the bromo analogues of tosylates **16** afforded a product mixture enriched in the unnatural 9a-*epi*-norstemoamide (dr 3:1).[14]

With both norstemoamide (**1**) and 9a-*epi*-**1** prepared, the final C_{10} methylation was explored. With LiHMDS and MeI alkylation, norstemoamide (**1**) gave (±)-stemoamide (**2**) as a single diastereomer.[4e] The ^{1}H NMR, ^{13}C NMR, and scXRD data for stemoamide (**2**) were in full agreement with the previously reported data (Figure 1, a).[3,4]

Under the same methylation conditions 9a-*epi*-**1** afforded a 9:1 mixture of C_{10} epimers, with the *syn*-methylated 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**) being the major product. The relative C_{10} *syn* configuration was assigned based on a NOE between H_8 and C_{10} methyl protons, as well as the vicinal coupling constant $^3J_{HH}$ of 7.7 Hz between H_{10} and H_9,

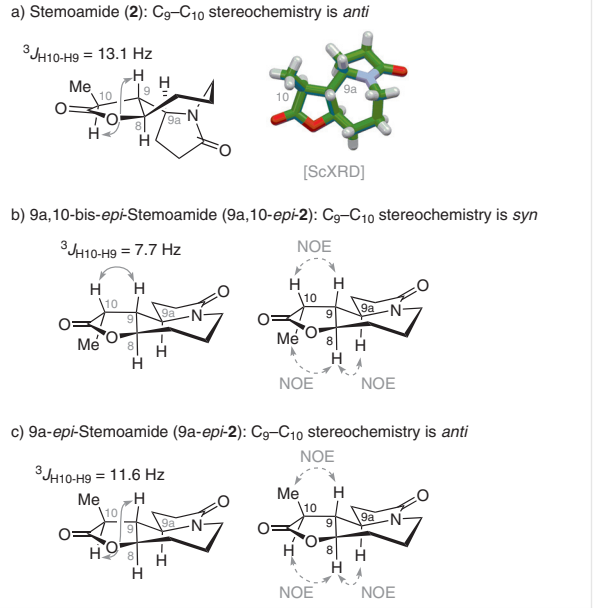


Figure 1 Establishing the C_9–C_{10} configuration of stemoamide diastereomers based on NMR data

a value typical for *syn* configuration. The corresponding $^3J_{HH}$ is 13.1 Hz for natural stemoamide (**2**), where the protons are *anti* to each other (Figure 1, b).

The crude 9:1 mixture of 9a,10-*epi*-**2** and 9a-*epi*-**2** could be equilibrated with K_2CO_3 in methanol to a 1:3 mixture, and the major 9a-*epi*-**2** diastereomer isolated.[15,16] For 9a-*epi*-stemoamide (9a-*epi*-**2**), a diagnostic NOE from H_9 to the C_{10} methyl protons was observed. Additionally, the vicinal coupling constant between H_9 and H_{10} hydrogens $^3J_{H9–H10}$ was 11.6 Hz, indicative of hydrogens disposed *anti* (Figure 1, c). Our ^{1}H NMR and ^{13}C NMR data for 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**) fully match to those previously reported for 9a-*epi*-stemoamide (9a-*epi*-**2**). In addition, our data for 9a-*epi*-stemoamide (9a-*epi*-**2**) was not in agreement with the literature data, suggesting that the previously reported 9a-*epi*-stemoamide (9a-*epi*-**2**) is actually 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**).[6,17]

To rationalize the observed selectivities – the *anti* selectivity for the stemoamide series and the *syn* selectivity for the 9a-*epi* series – the reactions were examined computationally. Using a simple model that includes the enolate derived from 9a-*epi*-**1** and MeI, we identified the alkylation transition states by DFT leading to both the *syn* and *anti* products (see Figure 2, a).[18]

DFT computations predicted the *syn* methylation of C_{10} carbon of the enolate **en** derived from 9a-*epi*-**1** to be clearly favored kinetically (*syn*-**TS** in Figure 2, a).[19] The transition state corresponding to the *anti* attack (*anti*-**TS**) is 1.5 kcal/mol higher than the transition state for *syn* attack, which is in line with the experimentally observed stereoselectivity of kinetic methylation (dr 9:1) to deliver 9a,10-*epi*-

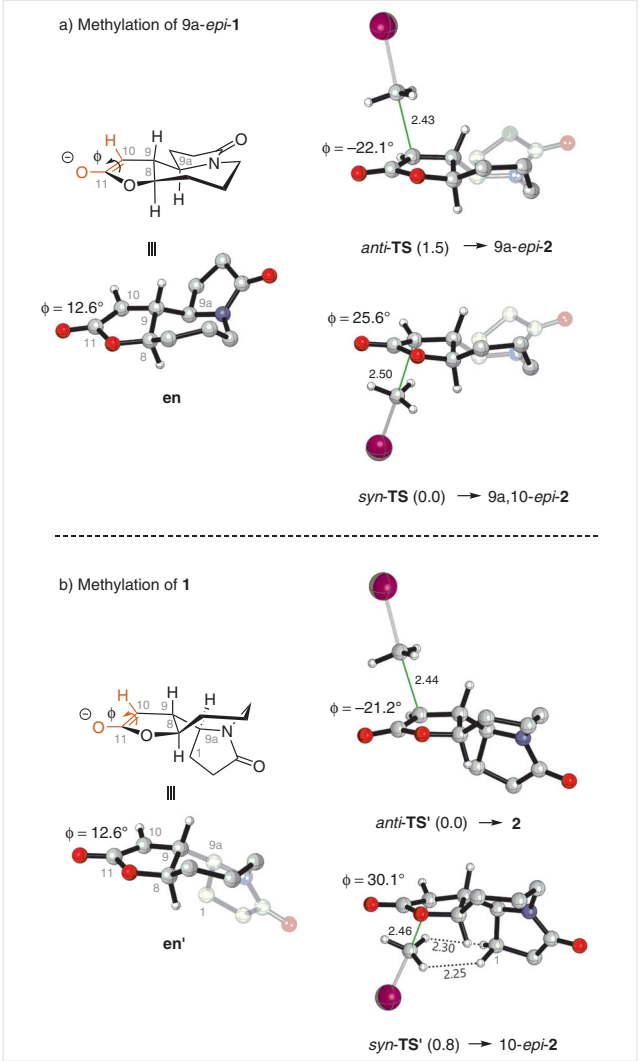


Figure 2 Transition states computed for the methylation of enolates derived from 9a-*epi*-**1** and **1**. The deviation from the planar structure of the enolates is measured via the $O_{11}C_{11}C_{10}H_{10}$ dihedral angle (denoted as ϕ). Relative stabilities are given in kcal/mol (in parenthesis), selected C···C and H···H distances in Å. Most of the hydrogen atoms (except those of the butyrolactone ring) are omitted for clarity.

2 as the major product. Inspection of the located transition states revealed no steric hindrance between the enolate **en** and the approaching methyl group. We anticipate that the *syn* facial selectivity of methylation of 9a-*epi*-**1** could be associated with the nonplanar structure of the ground state enolate **en**. This enolate features a notably pyramidalized C_{10} atom (ϕ = 12.6° in **en**), predisposing the enolate **en** towards *syn* attack. In the *syn*-**TS**, the degree of pyramidalization is enhanced (ϕ = 25.6°). The *anti* attack is found to be less favored as it requires inversion of the pyramidality at the enolate a carbon (C_{10}, ϕ = –22.1° in *anti*-**TS**). In addition, DFT calculations predict the *anti* product 9a-*epi*-**2** to be 0.7 kcal/mol more stable than the *syn* isomer 9a,10-*epi*-**2**,

which is in good agreement with the isomeric ratio obtained via equilibration (dr 3:1).

In contrast, computational analysis of the methylation of enolate **en′** derived from norstemoamide (**1**) points to a preferential *anti* attack (Figure 2, b). While the *anti* pathway (via *anti*-**TS′**) requires inversion of the pyramidality at the enolate **en′** α (C_{10}) carbon compared to the ground state enolate, the resulting energy penalty is less than that of the steric clashes observed in the diastereomeric *syn* transition state: the methyl hydrogens are in close contact with the C_1 hydrogens of the lactam C ring (see Figure 2, b, *syn*-**TS′**). The computed free energy difference for the two diastereomeric transition states is only 0.8 kcal/mol, implying that experimentally observed high *anti* stereoselectivity (dr >20:1) for stemoamide might be a result of thermodynamically driven equilibration rather than kinetic alkylation. Indeed, computations predict the *anti* product stemoamide (**2**) to be 5.1 kcal/mol more stable than 10-*epi*-stemoamide (10-*epi*-**2**). This result is in line with experimental evidence.[20]

In summary, we have reported total syntheses of stemoamide (**2**), 9a-*epi*-stemoamide (9a-*epi*-**2**), and 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**).[21–24] Our synthetic and computational work demonstrates how the stereocontrol at the late-stage methylation of norstemoamides cannot readily be accounted for by steric effects. Instead, for the 9*a*-epistemoamide series, enolate pyramidalization[25] appears to control the stereochemistry, whereas for the natural stemoamide series the stereochemistry is likely to be under thermodynamic control.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707201.

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(16) For the C_{10} epimers in the 9a-*epi* series, DFT calculations predicted that the anti diastereomer 9a-*epi*-**2** is 0.7 kcal/mol more stable than the *syn* isomer 9a,10-*epi*-**2**, which is in good agreement with the isomeric ratio obtained *via* equilibration (dr 1:3), see the Supporting Information.

(17) See the Supporting Information for $\{^1H\}^{13}C$ shift comparisons.

(18) For the relevance of using the simple molecular model that does not involve the Li^+ ion in the calculations, see the Supporting Information.

(19) The DFT calculations were carried out using the ωB97X-D functional along with the Def2SVP and Def2TZVPP basis sets. The reported relative stabilities were obtained from solution-phase Gibbs free energies. For details, see the Supporting Information.

(20) (a) For an experimental evidence for the epimerization at C10, see: Jacobi, P. A.; Lee, K. J. *J. Am. Chem. Soc.* **1997**, *199*, 3409. (b) In our hands, rapid quench and extraction of the norstemoamide (**1**) methylation reaction gave a mixture of diastereomers that was characterized without further purification.

(21) ***tert*-Butyl (*RS*)-2-oxo-5-{(2*R*,3*R*)-5-oxo-2-[3-(tosyloxy)propyl]tetrahydrofuran-3-yl}-2,5-dihydro-1*H*-pyrrole-1-carboxylate (14, -14)*epi***

To a stirred solution of tosylate **12** (100 mg, 0.34 mmol, 1.0 equiv) at –25 °C in DCM (10 mL) was added TBSOTf (8 µL, 9 mg, 0.1 equiv) and HFIP (35 µL, 57 mg, 1.0 equiv). To this solution was then added silyloxypyrrole 13 (201 mg, 0.67 mmol, 2.0 equiv) in DCM (0.5 mL), and the resulting solution was stirred for 8 h. The reaction was quenched with pH 7.0 buffer (2 mL), and vigorously stirred for 1 h at rt to hydrolyze all silylated product. The resulting mixture was then extracted with EtOAc (5 × 3 mL), the combined organic layers dried with Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by CombiFlash automated chromatography system (10% EtOAc/hexane to 80% EtOAc/hexane) afforded **14** and *epi*-**14** as a white foam (121 mg, 75%, dr ca. 1:1 with slight variation between batches). R_f (60% EtOAc/hexane) = 0.19 (ninhydrin, brown). ^{1}H NMR (500 MHz, $CDCl_3$, diastereomers overlapping, integrals were normalized to 1 H for signal at δ = 6.21 ppm): δ = 7.75–7.82 (m, 2 H), 7.33–7.39 (m, 2 H), 7.07 (dt, *J* = 6.2, 2.1 Hz, 1 H), 6.29–6.25 (m, 1 H), 4.74 (dt, *J* = 4.0, 1.8 Hz, 0.5 H), 4.72 (dt, *J* = 4.0, 1.8 Hz, 0.5 H), 4.42–4.40 (m, 0.5 H), 4.17–4.11 (m, 1 H), 4.08–3.90 (m, 1.5 H), 3.91–3.88 (m, 0.5 H), 3.26–3.22 (m, 0.5 H), 3.22–3.16 (m, 0.5 H), 2.88–2.83 (m, 0.5 H), 2.45 (s, 3 H), 2.43–2.38 (m, 0.5 H), 2.04 (t, *J* = 2.5 Hz, 0.5 H), 1.95–1.62 (m, 4 H), 1.57 (s, 3.5 H), 1.56 (s, 3.5 H). ^{13}C NMR (126 MHz, $CDCl_3$, diastereomers overlapping): δ = 174.8, 168.2, 168.1, 149.9, 149.8, 145.52, 145.49, 145.2, 145.1, 132.9, 130.5, 130.13, 130.10, 129.8, 128.0, 84.5, 84.3, 80.5, 78.7, 69.52, 69.47, 63.1, 62.7, 40.1, 40.0, 31.8, 31.7, 30.8, 28.3, 28.2, 28.0, 25.1, 25.02, 21.83, 21.82 ppm. FTIR (film): ν = 2978 (weak), 2934 (weak), 1769, 1738, 1771, 1353, 1310, 1172, 1153, 816, 662, 553 cm^{-1}. HRMS (ESI$^+$): *m/z* [M + Na] calcd for [$C_{23}H_{29}NO_8SNa^+$]: 502.1506; found: 502.1511, Δ = –0.5 mDa.

(22) **Stemoamide (2)**

To a solution of norstemoamide **1** (5.0 mg, 0.024 mmol, 1.0 equiv) in THF (0.5 mL) LiHMDS (27 µL, 4.4 mg, 0.026 mmol, 1.1 equiv, 1.0 M in THF) was added at –78 °C. After 10 min the reaction mixture was warmed to 0 °C for 10 min and then recooled to –78 °C. To the stirred yellow suspension, methyl iodide (7 µL, 17 mg, 0.12 mmol, 5.0 equiv) was added dropwise. After 3 h the reaction mixture was quenched with sat. aq NH_4Cl (0.5 mL) and extracted with EtOAc (5 × 2 mL). Combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (EtOAc to 5% MeOH/EtOAc) gave (±)-stemoamide (**2**) as a white solid (3.3 mg, 62%). Note: X-ray quality crystals were obtained upon slow evaporation from EtOAc. Spectroscopic data matched those reported previously.[3,4a,b,e] R_f (10% MeOH/EtOAc) = 0.34 ($KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.19 (app. td, *J* = 4.8, 10.7 Hz, 1 H), 4.16 (td partially obstructed, *J* = 3.0, 14.8 Hz, 1 H), 4.02 (td, *J* = 10.7, 6.4 Hz, 1 H), 2.26–2.68 (m, 1 H), 2.60 (dq, *J* = 12.3, 6.9 Hz, 1 H), 2.40–2.46 (m, 4 H), 2.04–2.10 (m, 1 H), 1.87–1.91 (m, 1 H), 1.74 (app. dq, *J* = 12.3, 10.7 Hz, 1 H), 1.51–1.60 (m, 2 H), 1.33 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.5, 174.2, 77.8, 56.0, 52.9, 40.4, 37.5, 35.0, 30.8, 25.8, 22.7, 14.3 ppm. FTIR (film): ν = 3501, 2935, 1764, 1676, 1420, 1190, 1008 cm^{-1}.

(23) **9a,10-*epi*-Stemoamide (9a,10-*epi*-2)**

To a solution of 9a-*epi*-norstemoamide (9a-*epi*-**1**, 16.0 mg, 0.76 mmol, 1.0 equiv) in THF (1 mL) at –78 °C was added LiHMDS (84 µL, 14 mg, 0.84 mmol, 1.1 equiv, 1.0 M in THF). After 10 min the reaction mixture was warmed to 0 °C for 10 min and then recooled to –78 °C. To the stirred yellow suspension methyl iodide (38.8 µL, 54 mg, 0.38 mmol, 5.0 equiv) was added dropwise. After 3 h the reaction mixture was quenched with sat. aq NH_4Cl (0.5 mL) and extracted with EtOAc (5 × 2 mL). Combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography (5% MeOH/EtOAc) gave 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**) as a white solid (12.0 mg, 70%); mp 127.3–127.9 °C. R_f (10% MeOH/EtOAc) = 0.32 ($KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.51 (td, *J* = 10.7, 4.8 Hz, 1 H), 3.90 (ddd, *J* = 14.6, 6.3, 3.6 Hz, 1 H), 3.65 (ddd, *J* = 10.4, 7.3, 6.2 Hz, 1 H), 3.04 (ddd, *J* = 14.3, 10.7, 3.1 Hz, 1 H), 2.81 (app. pent, *J* = 7.7 Hz, 1 H), 2.52–2.41 (3 H, m), 2.37–2.29 (1 H, m), 2.25 (app. td, *J* = 7.8, 10.4 Hz, 1 H), 1.98–1.66 (4 H, m), 1.30 (d, *J* = 7.7 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.2, 174.1, 80.6, 57.9, 52.5, 40.9, 38.6, 30.3, 30.2, 23.3, 21.8, 11.0 ppm. FTIR (film): ν = 2940, 1773, 1681, 1208, 1005 cm^{-1}. HRMS (ESI$^+$): *m/z* [M + H] calcd for [$C_{12}H_{17}NO_3H^+$]: 224.1208; found: 224.1201, Δ = –0.7 mDa.

(24) **9a-*epi*-Stemoamide (9a-*epi*-2)**

To a solution of 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**, 6.0 mg, 2.7 µmol, 1.0 equiv) in methanol (0.5 ml) was added potassium carbonate (3.7 mg, 2.7 µmol, 1.0 equiv). The resulting suspension was stirred at rt for 48 h, concentrated *in vacuo* and acidified with 2 M HCl (0.5 mL). The resulting solution was extracted with DCM (5 × 1 mL) and the combined organic layers dried with Na_2SO_4. The solvent was evaporated *in vacuo* to give a 3:1 mixture of 9a-*epi*-stemoamide (9a-*epi*-**2**) and 9a,10-*epi*-stemoamide (9a,10-*epi*-**2**, 5.0 mg, 84% recovery). A sample of 9a-*epi*-**2** for further NMR analysis was purified by flash column chromatography (5% MeOH/EtOAc to 8% MeOH/EtOAc). R_f (10% MeOH/EtOAc) = 0.32 ($KMnO_4$ stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.30 (ddd, *J* = 10.9, 10.0, 5.2 Hz, 1 H), 3.89 (ddd, *J* = 14.6, 6.4, 3.3 Hz, 1 H), 3.58 (td, *J* = 9.1, 6.6 Hz, 1 H), 3.14 (ddd, *J* = 14.6, 9.3, 3.4 Hz, 1 H), 2.37–2.52 (m, 3 H), 2.28–2.36 (m, 1 H), 2.24 (ddt, *J* = 15.2, 8.0, 3.1 Hz, 1 H), 1.94 (dt, *J* = 11.0 Hz, 10.2 Hz, 1 H), 1.79–1.88 (m, 2 H), 1.73 (ddt, *J* = 13.4, 11.1, 6.7 Hz, 1 H), 1.67–1.61 (m, 1 H), 1.39 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.6, 174.3, 81.2, 62.2, 55.4, 40.4, 40.0, 30.9, 30.5, 25.0, 22.5, 15.5 ppm. FTIR (film): 2924, 2851, 1774, 1683, 1278, 1177, 1010 cm^{-1}. HRMS (ESI$^+$): *m/z* [M + H] calcd for [$C_{12}H_{17}NO_3H^+$]: 224.1286; found: 224.1300, Δ = –1.4 mDa.

(25) For an expanded computational study of the effect of enolate pyramidalization on the stereochemistry of methylation reactions of *trans*-fused butyrolactones, see: Csókás, D.; Siitonen, J. H.; Pihko, P. M.; Pápai, I. *Org. Lett.* **2020**, *22*, 4597.

