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An asymmetric synthesis of the pentacyclic core of stemofoline

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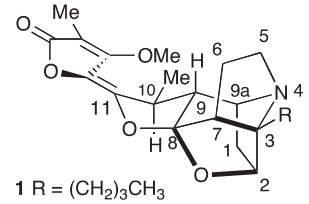
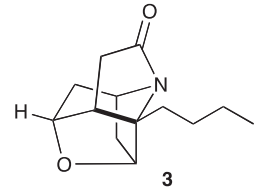
ABSTRACT

On treatment with acid, an open-chain 5-acylamino-3,8-diketo-ester, methyl (4*R*,5*S*,7*S*)-7-benzyloxy-4-[(*S*)-1-benzyloxyprop-2-yl]-5-methoxycarbonylamino-3,8-dioxododecanoate, cyclised via a stereoselective Mannich reaction to give an 8-azabicyclo[3.2.1]octanone. Hydrogenolysis of this with in situ acetal formation, reduction of the ester and a further cyclisation gave a lactam, (4*R*,5*R*,8*S*,9*R*,10*S*,12*S*,13*S*)-13-butyl-8-methyl-1-aza-6,14-dioxapentacyclo[8.3.0.0^{4,13}0^{5,9}.1^{5,12}]tetradecan-2-one, that corresponds to the pentacyclic core of stemofoline.

Stemofoline **1** is the parent member of the Stemona alkaloids that have been isolated from extracts of the roots and leaves of Stemonaceae used in traditional medicine in China, Japan and Thailand.[1] Additional members of this family of interesting natural products continue to be isolated[2] and a biogenetic route has been proposed.[3] Many approaches to the synthesis of these alkaloids have been described[4] and total syntheses of the (*E*)-isomer of (±)-stemofoline[5] and of (±)-asparagamine **2** together with its (*E*)-isomer,[6] have been reported.



1 R = $(CH_2)_3CH_3$
2 R = $CH{=}CHCH_2CH_3$



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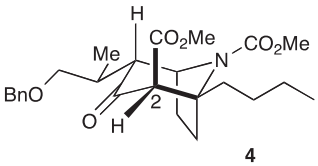

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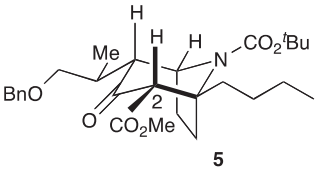

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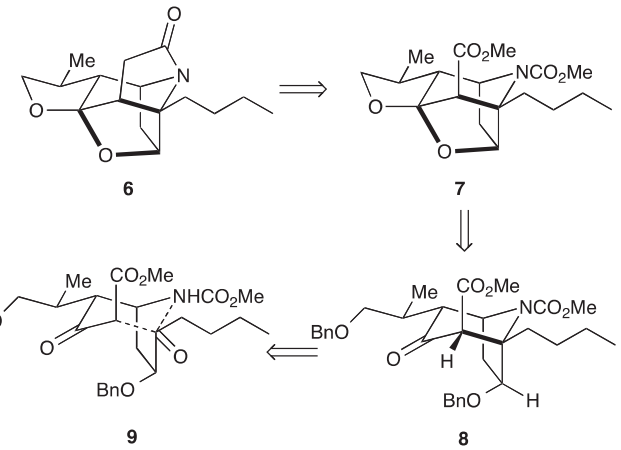
In early work on a synthetic approach to stemofoline, an intramolecular Mannich reaction and a regioselective oxidation were used to prepare the tetracyclic lactam **3** that has the tetracyclic core structure of stemofoline.[7] However, it proved difficult to incorporate the C(9) side-chain and the remaining five-membered ring of stemofoline into this synthesis. More recently, 8-azabicyclo[3.2.]octanes **4** and **5** were prepared using Mannich chemistry albeit slightly different conditions led to different configurations at C(2) in these compounds.[8]

We now report an asymmetric synthesis of the pentacyclic core **6** of stemofoline using this chemistry in which the 3,7-bond (stemofoline numbering) was to be introduced by an intramolecular



6 **7** **9** **8**

Figure 1. Outline of the proposed synthesis.

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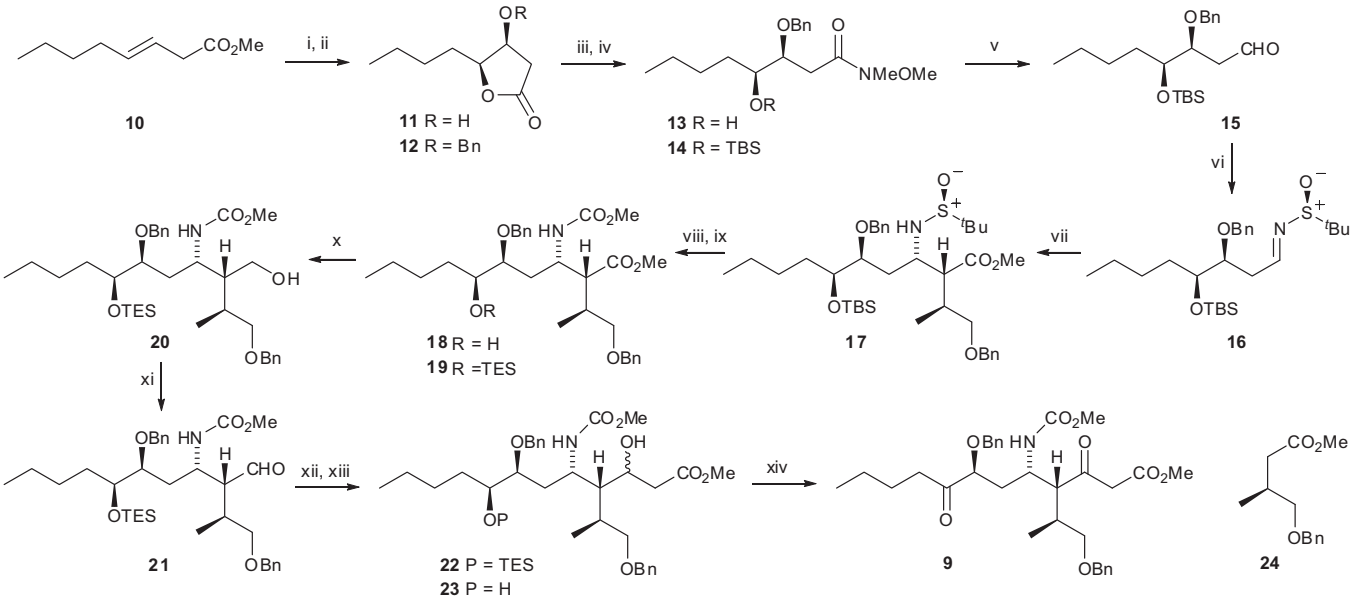


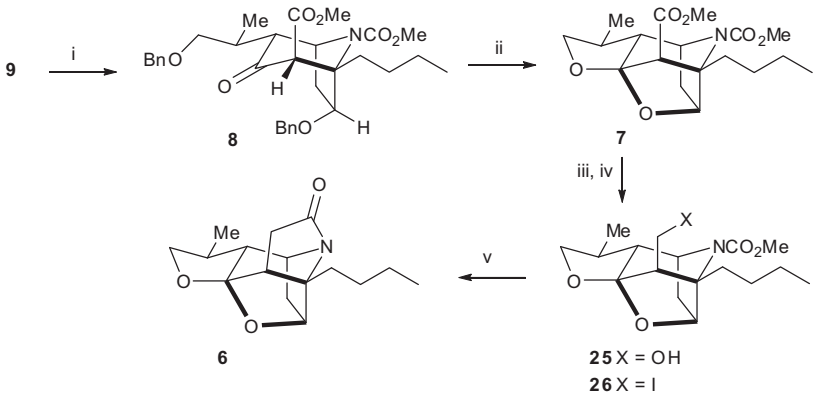
Scheme 1. Synthesis of the open-chain ester **9**; Reagents and conditions: (i) AD-mix-α, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C, 4 d (85%); (ii) $CCl_3C(NH)OBn$, TfOH, DCM, hexane, r.t., 2 h (81%); (iii) NHMeOMe, $MeAlCl_2$, hexane, DCM, r.t., 2 h; (iv) TBSOTf, 2,6-lutidine, DCM, 0 °C, 1 h (56% from **12**); (v) DIBAL-H, DCM, −78 °C, 2 h (58%); (vi) (*S*)-$^tBuS(O)NH_2$, $CuSO_4$, DCM, r.t., 18 h (93%); (vii) ester **24**, LDA, hexanes, THF, −78 °C, 3 h, **16**, −60 °C, 60 h (78%); (viii) aq HCl, dioxane, MeOH, r.t., 1 h, then Et_3N, MeCOCl, 0 °C to r.t., 1 h (84%); (ix) TESCl, imid., DCM, 0 °C, 1 h (84%); (x) $NaBH_4$ $CaCl_2$, THF, 0 °C, 30 min, add **19**, 0 °C, 3 h (76%); (xi) Dess–Martin periodinane, py.,DCM, 0 °C, 3.5 h; (xii) $MeCO_2Me$, LDA, THF, hexanes, −78 °C, 1 h, add **21**, −78 °C, 2 h (74% from **20**; a 1:1.8 mixture of epimers); (xiii) TBAF, DCM, 0 °C, 1 h (89%, two epimers); (xiv) PDC, 4 Å sieves, DCM, r.t., 24 h (86%).

Mannich reaction of the acylaminoketone **9**. Hydrogenolysis of the resulting azabicyclo[3.2.1]octanone **8** with cyclisation in situ was expected to give the tetracyclic acetal **7** and formation of the 5,6-bond would complete the synthesis, see Figure 1.

A synthesis of the open-chain ester **9** is outlined in Scheme 1. Sharpless hydroxylation of the known β,γ-unsaturated ester **10**[9] using AD-mix-α[10] with cyclisation in situ gave the hydroxylactone **11** that was protected as its benzyl ether **12**. Ring-opening using the Weinreb reagent followed by protection of the 4-hydroxyl group gave the *tert*-butyldimethylsilyl ether **14**. Reduction then gave the aldehyde **15** that was condensed with (*S*)-*tert*-butyl sulfinamide to give the sulfinimine **16**. The addition of the enolate of ester **24**[8] mediated by chlorotitanium tris-isopropoxide to this imine gave predominantly one product (78%) identified as the sulfoxamine **17** on the basis of precedent.[11] The minor products from this reaction, <10%, were not identified. As the *tert*-butylsulfinyl group in earlier work had been found to be unstable under the conditions to be used in the next stages of the synthesis,[8] it was removed using acid and the amine protected as its methoxycarbonyl derivative **18**. The *tert*-butyldimethylsilyl group was lost during the acidic step and so the alcohol was now resilylated to give the triethylsilyl ether **19**.

To avoid competing reduction of the methyl carbamate, the reduction of the ester **19** was carried out using calcium borohydride[12] and oxidation of the resulting alcohol **20** using the Dess–Martin periodinane gave the aldehyde **21**. An aldol condensation with methyl acetate gave a mixture of the epimeric hydroxyesters **22** that was desilylated to give the dihydroxy-ester **23** still as a mixture of epimers. Oxidation of this mixture using PDC gave the diketo-ester **9** ready for the Mannich reaction.

The cyclisation was carried out using trifluoroacetic acid (TFA) in dichloromethane at −78 °C. In earlier studies,[8] the use of TFA to effect such a cyclisation, albeit at 0 °C, had given the tropinone **5** in which the methoxycarbonyl group was in the equatorial position, although acylation of initially formed 5-membered cyclic imines had given products with the methoxycarbonyl group axial, for



Scheme 2. Synthesis of the pentacyclic core of stemofoline. Reagents and conditions: (i) TFA, DCM, −78 °C, 12 h (85%); (ii) 10% Pd/C, TFA, EtOAc, rt, 1 h (82%); (iii) DIBAL-H, DCM, −78 °C, 1 h (83%); (iv) Ph_3P, imid., I_2, DCM, 35 °C, 1 h (92%); (v) ^tBuLi, hexanes, THF, −78 to 0 °C, 5 min (86%).

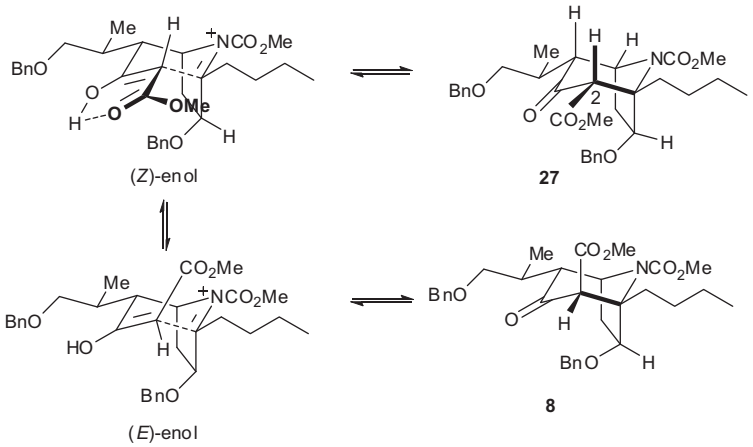


Figure 2. Formation of epimers on cyclisation of keto-ester **9**.

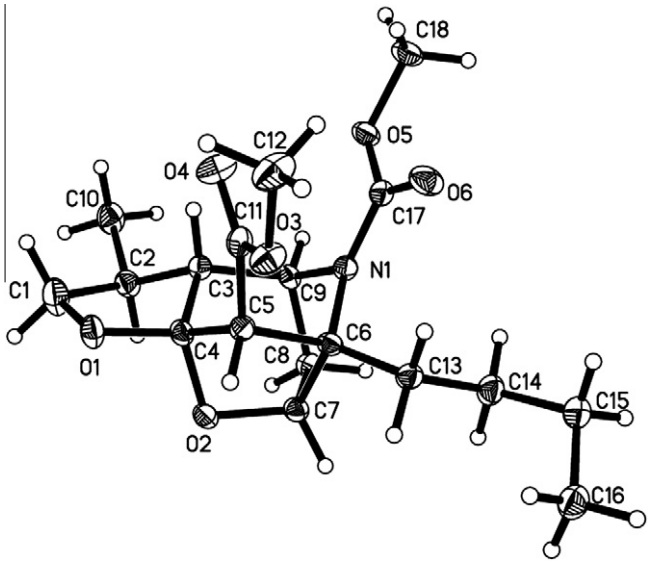


Figure 3. The structure of the acetal **7** as established by X-ray crystallography.

example, **4**.[7] In the present case, the product with the methoxycarbonyl group axial was the only product obtained, see Scheme 2. This stereoselectivity is believed to be due to thermodynamic control. The hydrogen bonded (*Z*)-enol of the keto-ester would be expected to give the equatorial product **27**. However, this isomer is destabilised by a *syn*-gauche interaction with the endo-benzyloxy group so that if the cyclisation is reversible the more stable axial epimer **8** can accumulate, see Figure 2.

By analogy with the structure of stemofoline, it was hoped that the diol formed by hydrogenolysis of the two benzyloxy groups in the tropinone **8** would readily react with the ketone to generate the corresponding acetal. In the event, hydrogenolysis in the presence of trifluoroacetic acid gave the crystalline acetal **7** directly. The structure of this acetal was confirmed by X-ray crystallography that established the structure as shown, see Figure 3.[13] This X-ray structure confirmed all of the stereochemical assignments that had been made earlier in the synthesis, for example, of the sulfinylamine **17**.

To complete a synthesis of the pentacyclic core of stemofoline, it was necessary to form the final five-membered ring. This was carried out by reduction of the ester **7** to give the alcohol **25** that was converted into the iodide **26**. Treatment of this iodide with *tert*-butyllithium effected halogen-lithium exchange and the resulting organolithium reacted with the methoxycarbonyl group of the carbamate with loss of methoxide to give the required pentacyclic lactam **6**, see Scheme 2.[14]

This work constitutes an asymmetric synthesis of the pentacyclic core of stemofoline. It remains to reduce the lactam to the corresponding amine[7] and to attach the tetronic acid fragment to complete a synthesis of stemofoline itself.

Acknowledgments

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13. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 100 K using graphite monochromated MoK_α radiation ($\lambda = 0.7107$ Å). The data were reduced by SAINTPLUS; XPREP was used to determine the space group. The crystal structure was solved by direct methods using SHELXS97 and refined by the full-matrix least-squares method on F^2 using SHELXL97. Crystal data: $C_{18}H_{27}NO_6$, $M = 353.41$, orthorhombic, $P2_12_12_1$, $a = 7.0191(12)$, $b = 9.9784(17)$, $c = 25.739(4)$ Å, $V = 1802.7(5)$ Å^3, $Z = 4$, 14522 reflections measured, 2163 unique ($R_{int} = 0.0410$), 2096 reflections > $2\sigma(I)$ ($R_1 = 0.0326$ and $wR_2 = 0.0800$), CCDC 916509.
14. *(1S,2R,4R,5S,7S)-7-Benzyloxy-4-[(S)-1-benzyloxyprop-2-yl]-1-butyl-2,8-dimethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one* **8**: Trifluoroacetic acid (10 μL, 0.13 mol) was added to the diketo-ester **9** (40 mg, 70 μmol) in DCM (3 mL) at −78 °C and the solution was stirred for 16 h. Saturated aqueous sodium hydrogen carbonate (0.3 mL) was added. The aqueous phase was extracted with DCM (2 × 1 mL) and the organic extracts were washed with water (1 mL)

and brine (1 mL) then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using ether/light petroleum (85:15) gave the title compound **8** (34 mg, 85%) as an oil, R_f 0.82 (ether) (found: M^++Na, 574.2796. $C_{32}H_{41}NO_7Na$ requires *M*, 574.2781); υ_{max} (film) 1730, 1710, 1446, 1368, 1320, 1235, 1198, 1173, 1100, 741 and 697 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.23 (10H, m, ArH), 4.54 (1H, dd, *J* 4, 8, 5-H), 4.32, 4.29 and 4.19 (each 1H, d, *J* 12, HC*H*Ph), 4.20 (1H, s, 2-H), 3.99 (1H, d, *J* 12, HC*H*Ph), 3.76 (1H, dd, *J* 4, 10, 7-H), 3.63 (1H, dd, *J* 4, 9, 1′-H), 3.52 (1H, dd, *J* 4, 8.5, 4-H), 3.46 (1H, dd, *J* 6,9, 1′-H′), 3.40 and 3.22 (each 3H, s, OCH_3), 2.36 (2H, m, 2′-H and 1″-H), 2.06 (1H, td, *J* 4.5, 12, 1″-H′), 1.74 (1H, m, 6-H), 1.36-1.20 (4H, m), 1.18 (1H, m, 6-H′), 0.97 (3H, d, *J* 7.5, 3′-H_3) and 0.79 (3H, t, *J* 7, 4″-H_3); *m*/*z* (ES^+) 574 (M^++23, 100%). *(1S,3S,4R,5S,8R,10S,11R)-1-Butyl-2,11-dimethoxycarbonyl-5-methyl-7,9-dioxa-2-azatetracyclo[6.2.1.0*^{4,8}*.1*^{3,10}*]dodecane* **7**: Palladium (10% on carbon, 2 mg, 1.76 μmol) was added to the tropinone **8** (10 mg, 17.6 μmol) in ethyl acetate (0.5 mL) at room temperature. Trifluoroacetic acid (2 μL, 26 μmol) was added and the suspension stirred under an atmosphere of hydrogen at room temperature for 1 h. The mixture was filtered through silica and the silica was washed with ethyl acetate (5 mL). The organic extracts were concentrated under reduced pressure and chromatography of the residue using ether/light petroleum (50:50) gave the title compound **7** (5 mg, 82%) as a solid that was recrystallised from DCM/hexane, R_f 0.62 (50:50 ether/light petroleum) $[\alpha]_D^{26}$ −21 (*c* 3.6, $CHCl_3$); (found: M^+ +H, 354.1925. $C_{18}H_{28}NO_6$ requires *M*, 354.1917); υ_{max} (film) 1740, 1446, 1378, 1241, 1185, 1163, 1132, 1099, 1080 and 836 cm^{-1}; δ_H (400 MHz, C_6D_6) 4.73 (1H, m, 3-H), 4.29 (1H, t, *J* 8, 6-H), 4.14 (1H, t, *J* 3, 10-H), 3.59 (3H, s, OCH_3), 3.54 (1H, t, *J* 8, 6-H′), 3.26 (1H, s, 11-H), 3.20 (1H, dd, *J* 3.5, 12, 4-H), 2.30 (1H, m, 5-H), 1.88 (1H, m 1′-H), 1.82 (1H, d, *J* 11.5, 12-H), 1.43-1.36 (4H, m), 1.33 (1H, ddd, *J* 2, 6, 9, 12-H′), 1.20 (1H, m, 3′-H′), 0.97 (3H, t, *J* 7, 4′-H_3), 0.89 (3H, d, *J* 7, 6-CH_3); δ_H (125 MHz, C_6D_6) 156.13, 130.16, 102.44, 98.75, 78.42, 76.78, 57.69, 51.66, 48.64, 46.59, 43.13, 40.35, 31.81, 27.12, 23.04, 19.63, 14.58 and 11.83; *m*/*z* (ES^+) 354 (M^++1, 100%). *(4R,5R,8S,9R,10S,12S,13S)-13-Butyl-8-methyl-1-aza-6,14-dioxapentacyclo[8.3.0.0*^{4,13}*.0*^{5,9}*.1*^{5,12}*]tetra-decan-2-one* **6**: *tert*-Butyllithium (1.6 M in hexanes, 14 μL, 22 μmol) was added to the iodide **26** (5 mg, 11 μmol) in THF (100 μL) at −78 °C and the cooling bath was removed. After stirring for 5 min, saturated aqueous ammonium chloride (0.5 mL) was added and the organic phase diluted with ether (1 mL) then washed with water (0.5 mL). The aqueous phase was washed with ethyl acetate (3 × 2 mL) and the organic extracts were washed with brine (0.5 mL) and dried (Na_2SO_4). After concentration under reduced pressure, chromatography of the residue using ether/light petroleum gave the title compound **6** (2.5 mg, 9.4 μmol, 86%) as a clear colourless oil, R_f = 0.63 (50:50 ether/light petroleum) (Found: M^++H, 278.1744. $C_{16}H_{24}NO_3$ requires *M*, 278.1751) $[\alpha]_D^{26}$ −17.5 (*c* 4.2 in $CHCl_3$); υ_{max} 1748, 1734, 1201, 1158, 1091, 1021, 999, 942, 866 and 714 cm^{-1}; δ_H (500 MHz, C_6D_6) 4.02 (1H, t, *J* 8, 7-H), 3.94 (1H, br s, 10-H), 3.81 (1H, br s, 12-H), 3.10 (1H, t, *J* 8, 7-H′), 2.42 (1H, d *J* 5.5, 4-H), 2.27 (1H, dd *J* 5.5, 18.5, 3-H), 2.12 (1H, d, *J* 18.5, 3-H′), 2.10 (1H, m, 8-H), 1.72 (1H, dd, *J* 4, 11, 9-H), 1.58 (1H, d, *J* 12, 11-H), 1.26–0.70 (7H, m, 11-H′, 1′-H_2, 2′-H_2 and 3′-H_2), 0.66 (3H, t, *J* 7.5, 4′-H_3) and 0.38 (3H, d, *J* 6.5, 8-CH_3); δ_C (125 MHz, C_6D_6) 153.46, 73.74, 70.62, 66.53, 50.89, 48.17, 46.98, 31.89, 28.32, 25.06, 18.57, 14.10 and 13.05. *m*/*z* (ES^+) 278 (M^++1, 100).