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Carbohydrate based formal synthesis of stemoamide using ring-closing metathesis

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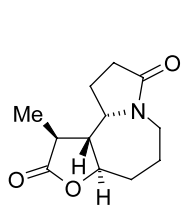
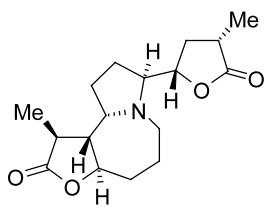
Abstract—A synthesis of stemoamide has been achieved from D-glucose. The stereocontrolled allylation under Barbier reaction conditions led to the installation of the 2-pyrrolidinone ring at C-3 followed by a ring-closing metathesis approach to construct the azepine ring system.

Stemoamide **1**, a member of the *Stemona* class of alkaloids, was isolated in 1992 from *Stemona tuberosa* by Lin et al.[1] The structures of stemoamide (**1**) and the related alkaloids such as stemonine (**2**), croomine (**3**), stenine (**4**) and tuberstemonone (**5**) were elucidated by an extensive series of 2D NMR experiments together with IR spectral studies. The extracts of this plant species (both *Stemona* and the closely related *Croominaceae* species) have long been employed as anthelmintics and as anti-tussives in the traditional folk medicine of China and Japan.[2] Several of these polycyclic alkaloids, because of their powerful insecticidal activity have attracted considerable attention of synthetic chemists, which have resulted in several partial[3] and total syntheses[4] in the past few years. Herein, we report the carbohydrate based synthesis of stemoamide **1** from D-glucose. The basic strategy is founded on the stereocontrolled synthesis of the 2-pyrrolidinone derivative at the C-3 position of D-glucose followed by installation of the azepine ring structure using a ring-closing metathesis approach. Our retrosynthesis of stemoamide is presented in Scheme 1.

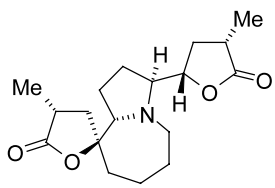
3-Deoxy-3-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **11** obtainable[5] from D-glucose diacetonide (**10**) in three steps was chosen as a starting material. Subsequent oxidation of **11** under Swern reaction conditions afforded a rather unstable aldehyde **12**, which was treated, without delay, with allyl bromide in the presence of activated zinc, in THF-saturated NH_4Cl



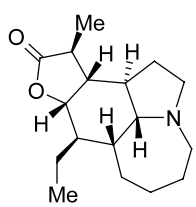
stemoamide (1)



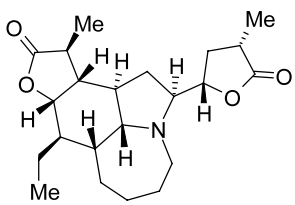
stemonine (2)



croomine (3)



stenine (4)



tuberstemonine (5)

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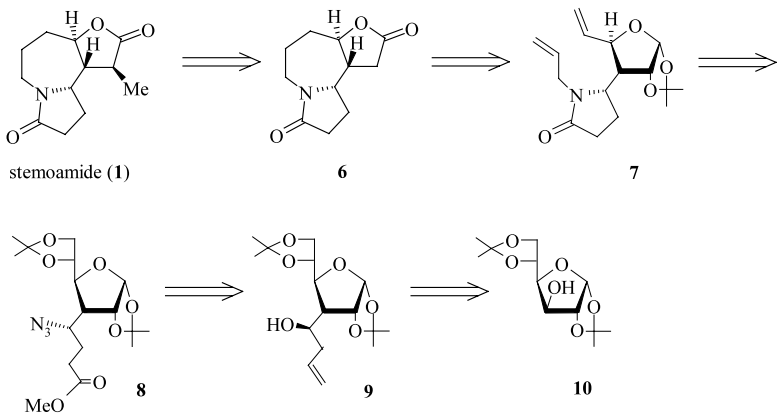


Scheme 1.

solution at 0°C, under Barbier reaction conditions[6] to give **9**, in 81% yield. The optical purity as indicated in **9** was confirmed by the ^{19}F spectral studies of the Mosher ester.[7] A further study to provide the absolute stereochemistry at the newly generated center was confirmed by the Mosher ester method.[8] The formation of **9** was also found when the aldehyde **12** was treated with allylmagnesium bromide–zinc bromide in THF at −78°C. However, the Grignard reaction of **12** with allylmagnesium bromide furnished a chromatographically inseparable 3:1 mixture of diastereomers in which **9** was the major product.

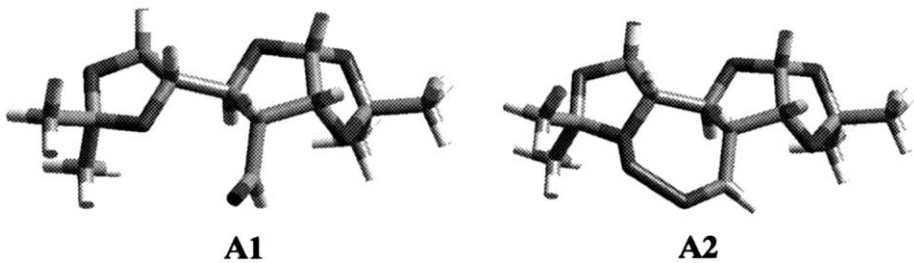
The mechanistic implications of the formation of **9** can now be discussed. Zinc has a profound affinity to complex with oxygen atoms. With substrate **12**, this complexation can occur between the carbonyl oxygen and the C-2 oxygen leading to six-membered chelated complex. However, due to steric factors induced by the methyl group of 1,2-*O*-isopropylidene (**A1**), zinc seems to prefer to complex with the C-5 oxygen to produce the seven-membered complex **A2**. Therefore, the attack of the nucleophile $(CH_2{=}CH{-}CH_2)^-$ from the preferred β-face, predominantly, gave **9**.

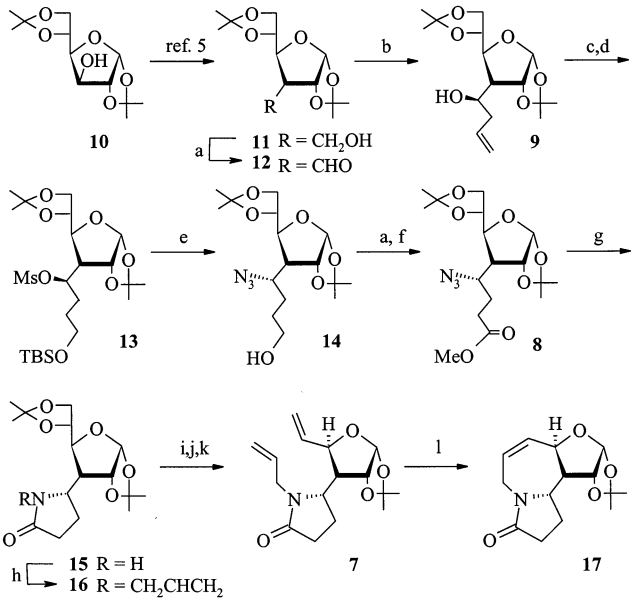
Having secured the stereochemistry of **9**, we then focused our attention on the construction of the 2-pyrrolidinone ring system. Hydroboration–oxidation of **9** followed by a protection–deprotection sequence furnished the mesylate (**13**), which with NaN_3 in DMF at 85°C gave the azido alcohol (**14**). It was interesting to observe that during the displacement reaction, deprotection of the TBS group also occurred. Oxidation of **14** in the presence of $RuCl_3$, $NaIO_4$ in a mixture of H_2O–CH_3CN–CCl_4 was not satisfactory and therefore a two-step sequence was adopted. For example, **14** was oxidized under Swern conditions and the resulting aldehyde was treated with $NaClO_2$ to give the azido acid isolated after esterification as its methyl ester (**8**). Hydrogenation of **8** over 10% Pd/C in MeOH at normal pressure and temperature took place with concomitant cyclization to give the 2-pyrrolidinone derivative **15**. The structure of **15** was supported by spectral and analytical data.

The installation of the seven-membered azepine ring system through a ring-closing metathesis approach[9] necessitated the construction of the diene system **7**. The phase transfer *N*-allylation of **15** in a biphasic system of 50% solution of KOH–benzene with tetra-*n*-butyl ammonium iodide gave **16** (Scheme 2). The formation of the 5,6-ene derivative **7** was straightforward involving selective deprotection of the 5,6-acetonide moiety with 0.8% H_2SO_4 in methanol, dimesylation of the resulting diol with MsCl and Et_3N in CH_2Cl_2, and elimination with NaI in ethyl methyl ketone.[10]

The ring-closing metathesis reaction of **7** was successfully accomplished with Grubbs' catalyst in refluxing CH_2Cl_2 to afford **17**. The ^1H NMR spectrum of **17** showed characteristic olefinic protons at δ 5.75, while H_{7a} and H_{7b} were located at δ 3.39 and 4.67 as a broad doublet and a double-doublet, respectively. The rest of the protons had the expected chemical shifts. Furthermore, the NOE studies of **17** revealed the interactions as shown in Fig. 1, which clearly confirmed the assigned structure.

Our next objective was to deoxygenate the C-2 hydroxyl of **17** using Barton's radical deoxygenation reaction.[11] Hydrogenation of the double bond in the presence of 10% Pd/C was carried out to give **18**. Treatment of **18** with methanol and Amberlyst-15 under reflux gave an α,β-mixture of methyl glycoside





Scheme 2. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, −78°C, 1 h, 80%; (b) allyl bromide, Zn, satd NH_4Cl, THF, 30 min or $(CH_2CHCH_2)_2Zn$, THF–Et_2O, −78°C, 30 min, 81%; (c) $BH_3{\cdot}(CH_3)_2S$, THF, 0°C–rt, 1 h, then NaOAc, H_2O_2, 30 min, 65%; (d) i. TBSCl, imidazole, CH_2Cl_2, rt, 1 h, 90%, ii. MsCl, Et_3N, CH_2Cl_2, 0°C–rt, 30 min, 85%; (e) NaN_3, DMF, 75–85°C, 32 h, 77%; (f) i. $NaClO_2$, DMSO, NaH_2PO_4, H_2O, 0°C–rt, 1 h, 95%, ii. CH_2N_2, 50% KOH soln, Et_2O, −20°C, 5 min, 94%; (g) 10% Pd/C, H_2, MeOH, rt, 6 h, 87%; (h) allyl bromide, 50% KOH soln, C_6H_6, TBAI, rt, 2 h, 74%; (i) 0.8% H_2SO_4, MeOH, rt, 8 h, 84%; (j) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min, 70%; (k) NaI, ethyl methyl ketone, reflux, 4 h, 66%; (l) Grubbs' catalyst, CH_2Cl_2, reflux, 12 h, 83%.

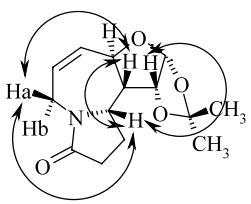


Figure 1. NOE studies on **17**.

with β-isomer **19** being isolated in 90% yield after silica gel chromatography. Conversion of **19** into the corresponding imidazolyl xanthate derivative was accomplished by using thiocarbonyl diimidazole in refluxing toluene, then by in situ addition of $^nBu_3SnH$ and catalytic AIBN gave the 2-deoxy product **20** (Scheme 3).

Finally, transformation of **20** into the corresponding γ-lactone derivative **6** was successfully achieved by using Grieco's procedure,[12] according to which **20** was treated with $BF_3{\cdot}Et_2O$, *m*CPBA in CH_2Cl_2 to give the requisite compound **6**. The ^1H and ^{13}C NMR spectra of **6** were compatible with the reported data.[4h] Since **6** has already been transformed[4h] into the stemoamide **1** in one step the present synthesis constitutes a formal total synthesis of stemoamide **1** (Scheme 3).[13]

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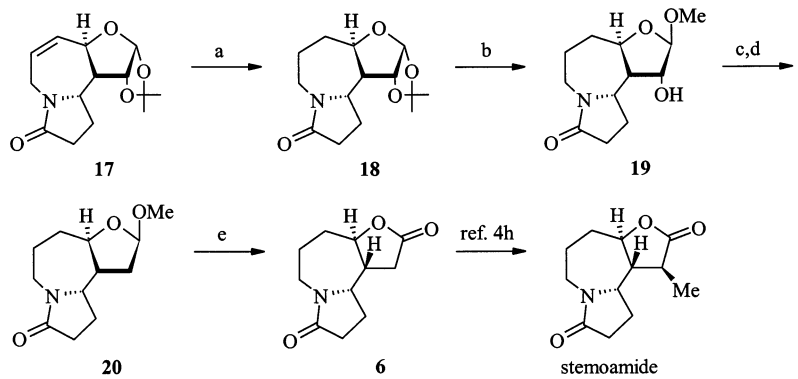

Scheme 3. *Reagents and conditions*: (a) 10% Pd/C, H_2, MeOH, rt, 6 h, 85%; (b) Amberlyst-15, MeOH, reflux, 3 h, 70%; (c) Im–CS–Im, toluene, reflux, 6 h; (d) $^nBu_3SnH$, AIBN, toluene, reflux, 12 h, 45% (two steps); (e) *m*CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C–rt, 12 h, 30%.

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13. Data for the selected compounds: **9**: ^{1}H NMR (200 MHz, $CDCl_3$): 1.31, 1.38, 1.47, 1.52 (4s, 12H); 1.91 (m, 1H); 2.33 (dd, 1H, $J=6.0$, 15.1 Hz); 2.60 (m, 1H); 3.9–4.21 (m, 5H); 4.66 (t, 1H, $J=3.0$ Hz); 5.15 (m, 2H); 5.68 (d, 1H, $J=3.0$ Hz); 6.00 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 25.2, 26.1, 26.2, 26.7, 39.1, 55.3, 67.9, 68.1, 77.0, 81.7, 82.4, 104.3, 110.0, 112.0, 116.6, 135.0, EI-MS: 299 (M^+–Me). Anal. calcd C, 61.14; H, 8.28. Found: C, 60.82; H, 8.64; **14**: IR ($CHCl_3$): 2112 cm^{-1} (azide), ^{1}H NMR (200 MHz, $CDCl_3$): 1.35 (s, 6H); 1.44, 1.57 (2s, 6H); 1.85 (m, 5H); 3.70 (m, 3H); 3.8–4.2 (m, 4H); 4.72 (t, 1H, $J=4.6$ Hz); 5.73 (d, 1H, $J=4.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 24.9, 25.9, 26.1, 26.4, 28.6, 29.3, 51.5, 58.4, 61.4, 66.9, 77.1, 78.9, 80.8, 104.4, 109.5, 112.3, EI-MS: 342 (M^+–Me). Anal. calcd C, 53.77; H, 7.61. Found: C, 53.63; H, 7.52; **15**: IR ($CHCl_3$): 1687 cm^{-1} (amide), ^{1}H NMR (200 MHz, $CDCl_3$): 1.31, 1.32, 1.40, 1.52 (4s, 12H); 2.02 (m, 2H); 2.36 (m, 3H); 3.85 (m, 4H); 4.06 (m, 1H); 4.69 (dd, 1H, $J=3.6$ Hz); 5.70 (d, 1H, $J=3.6$ Hz); 6.15 (brs, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): 24.8, 25.8, 25.9, 26.2, 26.7, 29.5, 52.2, 53.5, 66.9, 76.6, 80.5, 81.7, 104.0, 109.0, 111.8, 177.6, EI-MS: 327 (M^+). Anal. calcd C, 58.70; H, 7.70. Found: C, 59.02; H, 7.73; **17**: mp 162°C, ^{1}H NMR (500 MHz, $CDCl_3$): 1.31, 1.52 (2s, 6H); 2.20 (m, 2H); 2.37 (m, 2H); 2.54 (m, 1H); 3.39 (brd, 1H, $J=17.5$ Hz); 4.16 (m, 1H); 4.67 (dd, 1H, $J=7.2$, 17.5 Hz); 4.79 (t, 1H, $J=3.6$ Hz); 4.90 (dd, 1H, $J=1.25$, 9.3 Hz); 5.75 (m, 2H); 5.87 (d, 1H, $J=3.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 24.4, 26.1, 26.6, 31.4, 39.0, 49.2, 56.9, 76.3, 81.1, 105.2, 112.3, 127.4, 130.7, 174.0, EI-MS: 265 (M^+). Anal. calcd C, 63.39; H, 7.17. Found: C, 63.19; H, 7.41; **19**: mp 168–171°C, ^{1}H NMR (200 MHz, $CDCl_3$): 1.41 (m, 2H); 2.25 (m, 5H); 2.64 (m, 3H); 3.38 (s, 3H); 4.1 (m, 3H); 4.31 (d, 1H, $J=5.7$ Hz); 4.74 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 25.1, 26.2, 31.3, 37.3, 40.1, 49.2, 54.1, 56.9, 76.8, 78.6, 110.0, 174.9, EI-MS: 241 (M^+). Anal. calcd C, 59.74; H, 7.88. Found: C, 59.33; H, 7.63; **6**: ^{1}H NMR (500 MHz, $CDCl_3$): 1.50–1.75 (m, 3H); 1.87 (m, 1H); 2.05–2.12 (m, 1H); 2.30–2.45 (m, 4H); 2.52 (dd, 1H, $J=12.5$, 17.1 Hz); 2.65 (dd, 1H, $J=8.9$, 17.1 Hz); 2.80–2.90 (m, 1H); 4.00 (dt, 1H, $J=6.3$, 10.7 Hz); 4.16 (m, 1H); 4.29 (dt, 1H, $J=2.4$, 10.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): 22.7, 25.5, 30.5, 31.0, 34.7, 40.2, 45.0, 56.1, 79.8, 174.0 (2C).