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Semi-syntheses of new stemofoline derivatives

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Dedicated to Professor Wolfgang Steglich on the occasion of his 70th birthday

Abstract—Semi-syntheses of several new stemofoline derivatives are described. Acidic hydrolysis of the tetronate moiety of stemofoline, followed by re-esterification gave homologues of stemofoline and isostemofoline. Hydrazinolysis resulted in new pyridazinones. Oxidative cleavage of stemofoline afforded the pentacyclic cage lactone, recently prepared by total synthesis.

The structurally intricate alkaloid stemofoline (**1**, Fig. 1) was isolated from stems and leaves of the Asian tree *Stemona japonica* by Irie et al.[1] in 1970. Single crystal X-ray analysis of the hydrobromide[1] revealed a pentacyclic cage system with a pendant conjugated tetronate. Stemofoline (**1**) is reported to exhibit insecticidal properties.[2] More recently, its mode of action was determined as a potent agonist of the insect nicotinic acetylcholine receptor ($EC_{50}=1.7$ nM).[3] The complex hexacyclic framework of this *Stemona* alkaloid has attracted considerable synthetic interest. This has led to the first total synthesis of the (*Z*)-stereomer of **1**, isostemofoline (**2**), by Kende et al.[4] in 1999, as well as to the preparation of various structural fragments by other groups.[5] To explore potentially useful structural modifications of stemofoline (**1**), we initiated a study of its chemical reaction behaviour.

Hydrogenation of the conjugated tetronate moiety of stemofoline (**1**) in ethanol over Pd/C at 1 atm gave the 11(*S*),12(*S*)-dihydro derivative **3** and an unexpected ring-opened derivative **4** in a 3:2 ratio (Scheme 1). The configuration at C-11 of **3** was determined to be as shown by NOE experiments (cross-peaks between 9-H, 11-H and 17-H). Hydrogenation of the 11(*S*),12(*S*)-dihydro derivative **3** in ethyl acetate with Rh/alumina as catalyst at 10 atm afforded the 11(*S*),12(*S*)-13,14-tetrahydro derivative **5** as a diastereomeric mixture. Acylation of **4** (Ac_2O, pyridine, DMAP) gave the *O*-acetyl derivative **6**. Alkylation of stemofoline (**1**) with an excess of alkyl halide in acetonitrile led to the quaternary ammonium salt **7** (Scheme 2).[3] Stemofoline *N*-oxide (**8**) was obtained by the use of MCPBA in CH_2Cl_2.

Oxidative cleavage of the conjugated tetronate moiety of stemofoline (**1**) with lead tetraacetate in benzene afforded the pentacyclic cage lactone **9**, albeit in low yield (Scheme 3). Lactone **9** had been already described in Kende's[4] total synthesis of isostemofoline (**2**). The ^1H

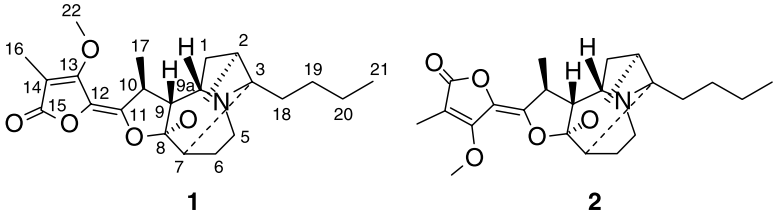

Figure 1.

Keywords: alkaloid; insecticidal; natural product; stemofoline; Stemona; tetronate.
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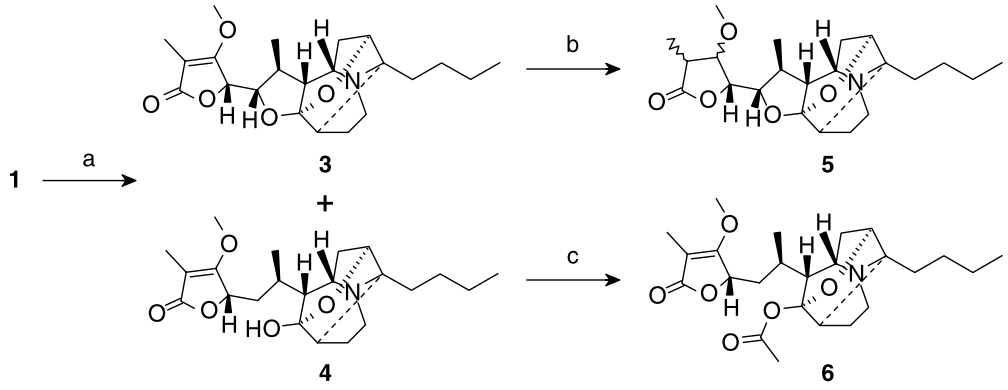
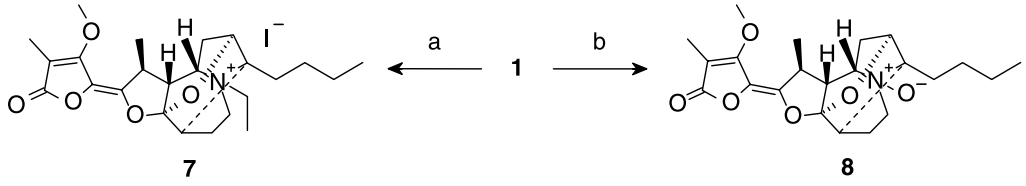
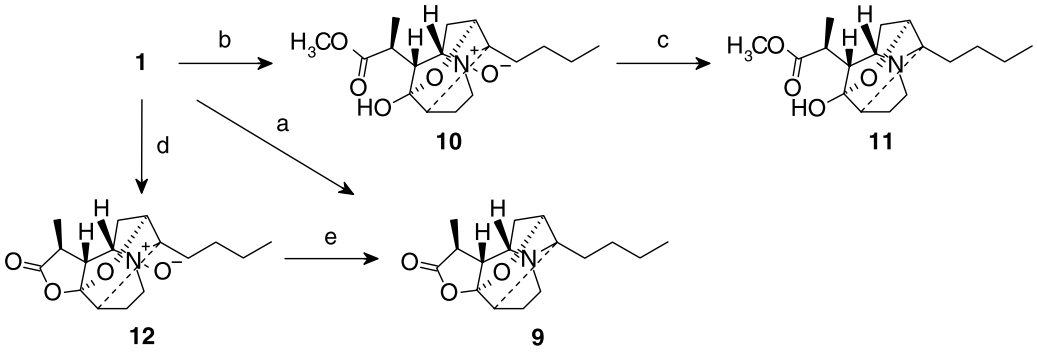


Scheme 1. *Reagents and conditions*: (a) H_2, 10% Pd/C, EtOH, 1 atm, rt, 4 h, **3**: 57%, **4**: 38%; (b) H_2, 5% Rh/Al_2O_3, EtOAc, 10 atm, 20°C, 24 h, **5**: 21%, recovered substrate **3**: 75%; (c) Ac_2O, py, DMAP, rt, 48 h, rt, 34%.



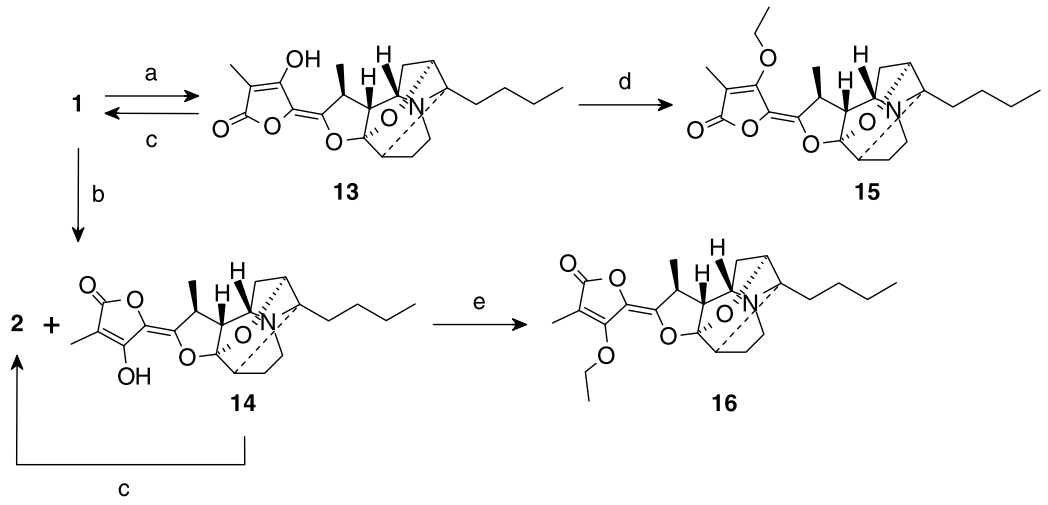
Scheme 2. *Reagents and conditions*: (a) EtI (5 equiv.), MeCN, rt, 48 h, 68%; (b) MCPBA (1.3 equiv.), CH_2Cl_2, rt, 3 h, 98%.



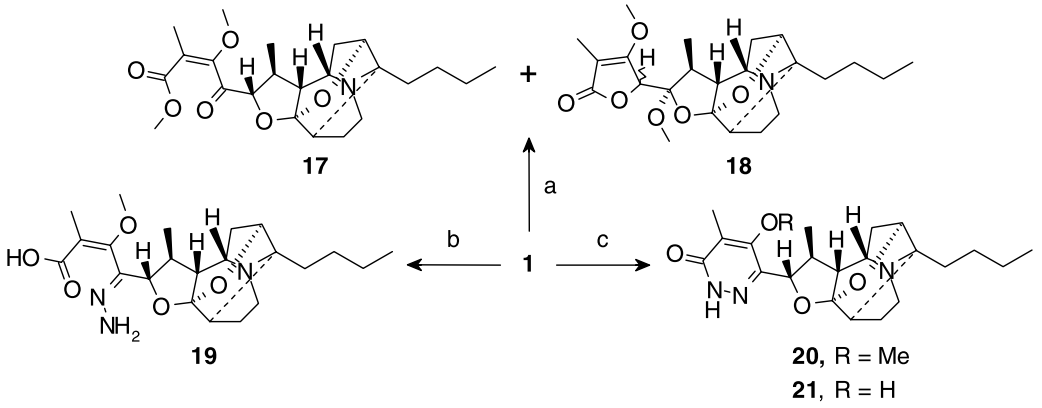
Scheme 3. *Reagents and conditions*: (a) $Pb(OAc)_4$ (5 equiv.), benzene, 50°C, 20 h, 16%; (b) O_3, MeOH, −78°C, 10 min; Me_2S, 91%; (c) NaHTe, $NaBH_4$, EtOH, −15°C to rt, 1 h, 76%; (d) O_3, CH_2Cl_2, −78°C, 10 min; Me_2S; (e) NaHTe, $NaBH_4$, EtOH, −15°C to rt, 1 h, 40% for two steps.

NMR data of our semi-synthetic product are identical to those reported by Kende. However, ozonolysis of stemofoline (**1**) in methanol, followed by a reductive workup (DMS), led to the tetracyclic *N*-oxide **10**. Selective reduction of the *N*-oxide **10** with sodium hydrogen telluride[6] gave the corresponding amine **11**. On the other hand, in the case of the ozonolysis of stemofoline (**1**) in CH_2Cl_2, the reaction cleanly furnished the pentacyclic cage *N*-oxide **12**, which was further reduced to the cage lactone **9** in satisfactory overall yield (40%).

Hydrolysis of the tetronate moiety in **1** under mild acidic conditions (2N HCl, 50°C) yielded stemofolinic acid (**13**, Scheme 4). More vigorous acidic conditions (48% HBr, rt) resulted in the formation of the (*E*)-stereomer of **13**, isostemofolinic acid (**14**), and isostemofoline (**2**). The configuration of the 11,12-double bond of compounds **13** and **14** was determined by derivatization. The tetronic acids **13** and **14** were esterified with diazomethane in order to obtain the corresponding methyl tetronates stemofoline (**1**) and isostemofoline (**2**), respectively. Furthermore, alkylation of **13** and **14** by *N*,*N*-dimethylformamide acetals proceeded cleanly to give homologues of stemofoline (**1**) and isostemofoline (**2**) (e.g. ethyl tetronates **15** and **16**, respectively). Treatment of stemofoline (**1**) with sodium methoxide yielded the ring-opened keto ester **17** and the methanol addition product **18** (Scheme 5). Reaction of stemofoline (**1**) with hydrazine monohydrate in methanol at room temperature provided the ring-opened hydrazone **19**. More vigorous conditions (hydrazine monohydrate, EtOH, reflux) gave the pyridazinones **20** and **21**. The configuration at C-11 of derivatives **17**–**21** was determined to be as shown by NOE experiments.



Scheme 4. *Reagents and conditions*: (a) 2N HCl, 50°C, 5 h, **13**: 50%, recovered substrate **1**: 30%; (b) 48% HBr, rt, 24 h, **14**: 62%; **2**: 32%; (c) CH_2N_2, Et_2O, rt; (d) $Me_2NCH(OEt)_2$, benzene, reflux, 24 h, 33%; (e) $Me_2NCH(OEt)_2$, benzene, reflux, 1 h, 98%.



Scheme 5. *Reagents and conditions*: (a) NaOMe, MeOH, rt, 16 h, **17**: 16%; **18**: 3%; (b) $N_2H_4{\cdot}H_2O$, MeOH, rt, 16 h, 50%; (c) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 16 h, **20**: 20%; **21**: 13%.

The above described chemical reactions provide a basis for the identification of structure–activity relationships of stemofoline (**1**). They could give hints for the design of structurally-simplified synthetic compounds based on stemofoline (**1**).

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