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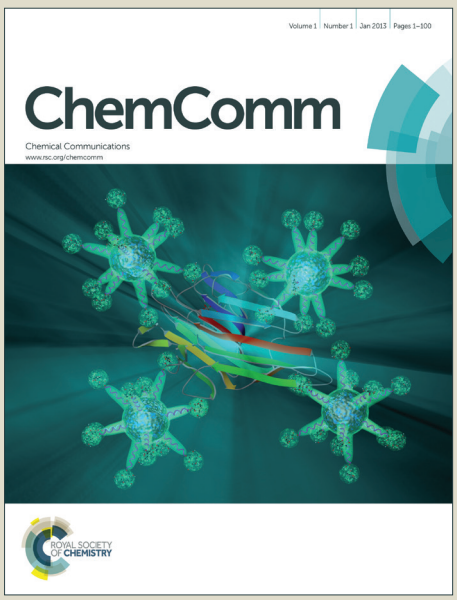

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ARTICLE TYPE

Enantioselective Total Synthesis of (+)-Methoxystemofoline and (+)-Isomethoxystemofoline

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The first enantioselective total synthesis of (+)-methoxystemofoline (2) and (+)-isomethoxystemofoline (3) is reported. The synthesis employed the halide-assisted bromotropanonation method that we developed recently to construct the core structure, and Overman's strategy for the implementation of the butenolide moiety. Through this work, the structure of methoxystemofoline was revised as 2 with an *E*-alkene, and its absolute configuration was established.

Stemofoline alkaloids[1-2] (Figure 1) is a subclass of structurally complex *Stemona* alkaloids.[3,4] Since the isolation of stemofoline (**1**), the first member of this subclass in 1970,[1] considerable efforts have been devoted to their chemical synthesis.[5-9] The three seminal total syntheses are Kende's total synthesis of (±)-isostemofoline in 1999,[6] Overman's total syntheses of (±)-didehydrostemofoline and (±)-isodidehydrostemofoline in 2003,[7] and Martin's enantioselective formal total syntheses of didehydrostemofoline and isodidehydrostemofoline in 2012.[8]

Methoxystemofoline (**2**) was isolated in 1991 by Xu and co-workers from the roots of *S. parviflora* Wright, C. H.[2] The structure of methoxystemofoline (**2**) was elucidated by MS and spectroscopic analyses,[2] while its absolute configuration remains unknown. Recently, Pyne and co-workers disclosed the semisyntheses of several stemofoline alkaloids[9] including isomethoxystemofoline (**3**)[9a] starting from (11*Z*)-1'2'-didehydrostemofoline. The achievement allowed them ready access to several stemofoline alkaloids and analogues, and to reveal acetylcholinesterase inhibitory activity of those alkaloids. Herein, in continuation of our work in the synthesis of alkaloids,[4i,10,11] we report the first enantioselective total synthesis of methoxystemofoline (**2**) and isomethoxystemofoline (**3**).

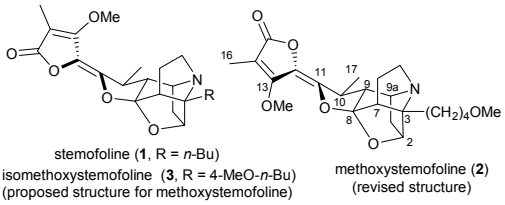
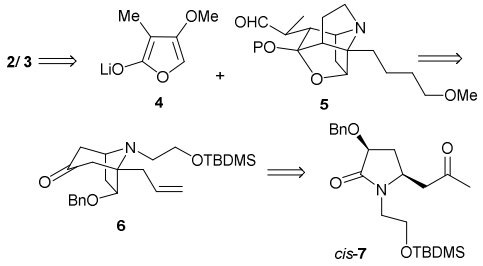


Figure 1. Structures of selected stemofoline alkaloids

Our retrosynthetic analysis of methoxystemofoline (**2**/ **3**) is delineated in Scheme 1. The retro-vinylogous aldol disconnection,[6,7] resulted in vinylogous lithium enolate **4** and the core structure **5**. The latter could be synthesized from **6** by a cross-metathesis (CM) reaction.[12] The tropan-3-one derivative **6** could be prepared from keto-lactam **7** by the method that we developed recently.[11]



Scheme 1. Retrosynthetic analysis of methoxystemofoline.

The synthesis started with (*S*)-α-hydroxy-γ-lactone **8**. *O*-benzylation and aminolysis gave hydroxy amide **9** in 81% overall yield (Scheme 2). Oxidation of **9** with Dess-Martin periodinane[13] afforded a tautomeric mixture of aldehyde-amide and hemiaminal. The mixture was refluxed in MeOH in the presence of silica gel to convert the former to the latter that was acetylation to yield acetate **10** as a 1.3: 1 diastereomeric mixture in 74% yield over three steps. Treatment of **10** with silyl enol ether of acetone and TMSOTf in CH_2Cl_2 yielded the α-amidoalkylation[14] products. The *tert*-butyldimethylsilyl (TBDMS) group did not survive in these conditions and resilylation of the primary alcohol was required to afford the desired *cis*-lactam **7** in 72% yield, along with a small amount of the *trans* isomer. The stereochemistry of the minor diastereomer of **7** was determined by NOESY experiments. Formation of the requisite tropanone structure **11** was accomplished smoothly using the method that we

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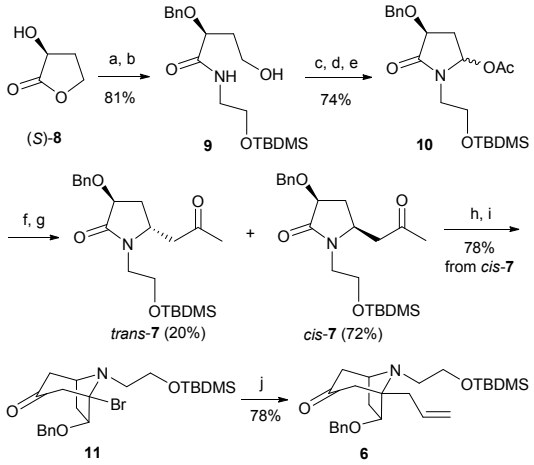
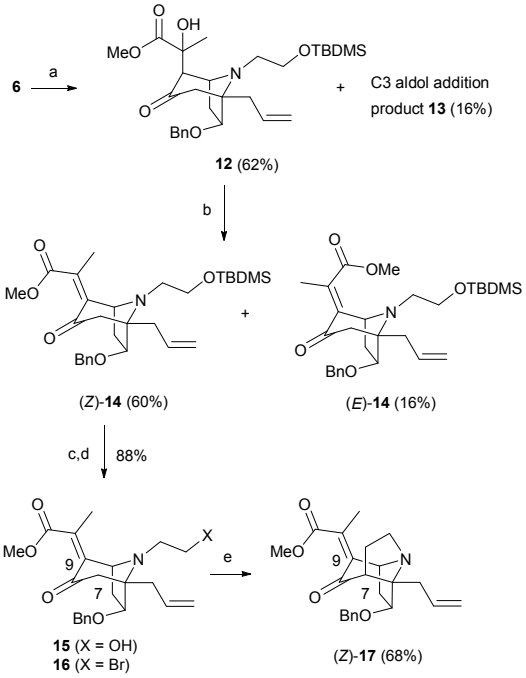
developed recently.[11] Hence, *cis*-**7** was treated with TMSOTf in the presence of Et_3N to get a silyl enol ether. Intramolecular addition of the silyl enol ether onto the *in situ* activated lactam afforded 1-bromotropan-3-one **11** in 78% yield. Heating a mixture of **11**, 1,1'-azobis(cyclohexanecarbonitrile) (ACCN),[15] and allyltributylstannane[16] in toluene at 85 ºC for 18 h led to the desired cross-coupling product **6** in 78% yield.



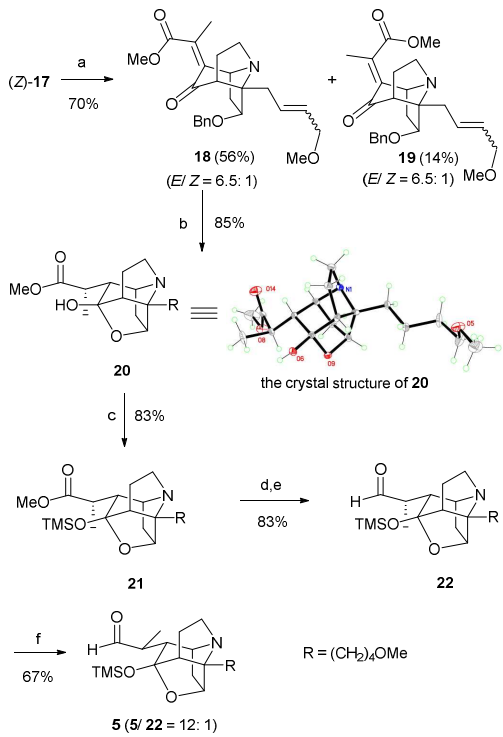
Scheme 2. Synthesis of tropan-3-one derivative **6**. Reagents and conditions: (a) Ag_2O, BnBr, rt; (b) $TBDMSOCH_2CH_2NH_2$, MeOH, rt; (c) Dess-Martin periodinane, CH_2Cl_2, rt; (d) MeOH, silica gel, reflux; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (f) silyl enol ether of acetone, TMSOTf, CH_2Cl_2, –78 °C ~ rt; (g) imidazole, TBDMSCl, rt; (h) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (i) Tf_2O, DTBMP, $ZnBr_2$, CH_2Cl_2, –78 °C ~ rt; (j) ACCN, allyl(*n*-Bu)$_3$Sn, toluene, 85 °C.

We next investigated the regioselective C-C bond formations at α and α' positions of the ketone of tropanone **6** (Scheme 3). Successive treatment of **6** with LDA and methyl pyruvate yielded the desired product **12** in 62% along with a small amount of undesired regioisomer **13** (16%) and some recovered starting material (17%). Dehydration of **12** with $POCl_3$ in the presence of pyridine produced the desired *Z*-isomer (*Z*)-**14** as a major product in 60% yield. Desilylation of (*Z*)-**14** under acidic conditions (*p*-TsOH, acetone, 50 ºC) followed by bromination with Ph_3P and CBr_4 afforded bromide **16**. **16** cyclized easily when treated with NaOMe in THF at 0°C to give the tricyclic product (*Z*)-**17** in 68% yield.

For the side chain elongation, the hydrochloride salt of (*Z*)-**17** was heated with (*Z*)-1,4-dimethoxybut-2-ene in the presence of Grubbs' 2nd generation catalyst[12] in toluene at 60 ºC (Scheme 4) to afford the desired cross-coupling product **18** in 56% yield (*E*/*Z* = 6.5:1). Isomerization of tetrasubstituted double bond occurred under the reaction conditions and a small amount of **19** (14%) was also obtained. Hydrogenation of **18** proceeded smoothly to give compound **20** in 85% yield. The structure of **20** was confirmed by single crystal X-ray analysis.[17] Silylation of **20** with TMS-imid. at 130 ºC[7] led to ester **21** in 83% yield. DIBAL-H reduction of the ester group of **21** followed by Swern oxidation produced aldehyde **22** in 83% yield. The stereochemistry α to the aldehyde group is wrong for the natural product. Hence, aldehyde **22** was epimerized by treating it with DBU in toluene[7] at 100 ºC to afford the desired diastereomer **5** (**5**/ **22** = 12:1).



Scheme 3. Construction of the functionalized tricyclic core (*Z*)-**17**. Reagents and conditions: (a) LDA, methyl pyruvate, THF, –78 °C; (b) $POCl_3$, pyridine, 0 °C ~ rt; (c) *p*-TsOH, acetone, 50 °C; (d) Ph_3P, CBr_4, CH_2Cl_2, 0 °C; (e) NaOMe, THF, 0 °C.

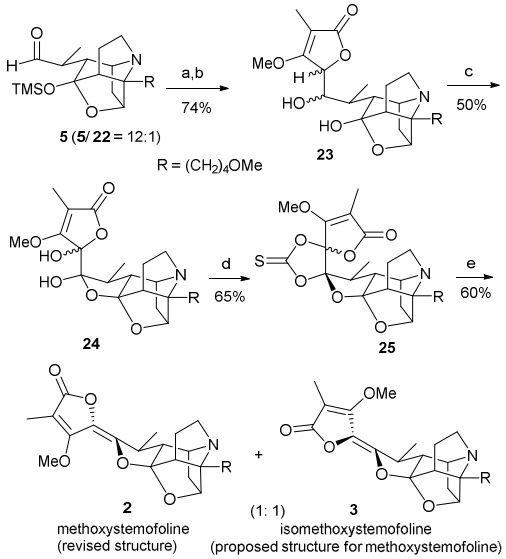


Scheme 4. Synthesis of the advanced tetracyclic core **5**. Reagents and conditions: (a) 2 *N* HCl, MeOH; then (*Z*)-1,4-dimethoxybut-2-ene, Grubbs catalyst, 2nd generation, toluene, 60 °C; (b) Pd/C, H_2, MeOH, rt, 24 h; then 2 *N* HCl, 48 h; (c) TMS-imid., 130 °C; (d) DIBAL-H, CH_2Cl_2, –78 °C; (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, –78 °C; (f) DBU, toluene, 100 °C.

With compound **5** in hand, Overman's strategy[7] was adopted for the installation of the butenolide moiety.[18] Thus,

aldehydes **5** was reacted with vinylogous lithium enolate **4** at −78 ºC and the resulting adducts were treated with HCl in MeOH/$CHCl_3$ to give the vinylogous aldol adduct **23** as a mixture of stereoisomers (Scheme 5). Oxidation of **23** with IBX in DMSO[7,19] at rt yielded a diastereomeric mixture **24**, which was treated with thiophosgene in the presence of DMAP[7,20] to afford **25** in 65% yield. Finally, heating **25** and $P(OMe)_3$ at 120 ºC provided methoxystemofoline (**2**) in 30% yield, along with isomethoxystemofoline (**3**) in 30% yield. The specific rotation {**2**: $[\alpha]_D^{20}$ +71~85 (*c* 0.1, CH_3OH); lit.[2] $[\alpha]_D^{21.6}$ +75.6 (*c* 0.037, CH_3OH); **3**: $[\alpha]_D^{20}$ +220~226 (*c* 0.1, CH_3OH); lit.[9a] $[\alpha]_D^{25}$ +249 (*c* 0.29, CH_3OH)} and spectral data of our synthetic compounds **2** and **3** are consistent with those reported by Xu[2] and Pyne,[9a] respectively. Since Pyne and co-workers employed (11*Z*)-1'2'-didehydrostemofoline as the sarting material for the semisynthesis, their product should have a 11*Z* stereochemistry (**3**). Accordingly, the structure of the natural methoxystemofoline suggested by Xu should be revised as **2**, with a 11*E* stereochemistry, and Pyne's product be named as isomethoxystemofoline (**3**).

In summary, we have accomplished the first enantioselective total synthesis of (+)-methoxystemofoline (**2**) and (+)-isomethoxystemofoline (**3**). The absolute configuration of the natural methoxystemofoline (**2**) was established as (11*E*,13*E*,2*S*,3*S*,7*R*,8*S*,9*R*,9a*S*,10*S*).



Scheme 5. Completion of the total synthesis of methoxystemofoline (**2**) and isomethoxystemofoline (**3**). Reagents and conditions: (a) **4**, THF, −78 °C; (b) HCl, MeOH/ $CHCl_3$; (c) IBX, DMSO, rt; (d) $CSCl_2$, DMAP, CH_2Cl_2, −50 °C; (e) $P(OMe)_3$, 120 °C.

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