Total Synthesis of (±)-Isostemofoline

Andrew S. Kende,* Terrence L. Smalley, Jr., and He Huang

Department of Chemistry, University of Rochester
Rochester, New York 14627

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The structurally intricate alkaloid stemofoline (**1**) (Figure 1) was isolated from stems and leaves of the Asian tree *Stemona japonica* by Irie et al. in 1970.[1] Single crystal X-ray analysis of the hydrobromide salt[1] revealed a rigid pentacyclic core with a pendant conjugated butenolide. The complex hexacyclic framework of this alkaloid, which is reported to exhibit insecticidal properties,[2] has attracted considerable synthetic interest.[3] Very recently the *E*-alkene isomer of **1**, isostemofoline (**2**), has been isolated from various *Stemona* species in the laboratories of Professor Yang Ye.[4]

We now report the first total synthesis of (±)-isostemofoline. Our retrosynthetic analysis (Scheme 1) proceeds by initial disconnection of the butenolide and opening of the pentacyclic core to aldehyde **3**. Appropriate functional group interconversions suggest that **3** could arise from α,*β*-unsaturated ketone **4**. The latter would result from sequential, stereocontrolled enolate chemistry starting from the substituted nortropinone **5**, which in turn could be assembled by a formal [4 + 3] cycloaddition reaction upon the alkoxypyrrole **6**.

Selective oxidation[5] of 1,2-hexanediol followed by protection of the primary hydroxyl as the MOM ether provided ketone **7** in 50% yield (Scheme 2). Regiospecific condensation of ketone **7** with the mono-*N*,*N*-dimethylhydrazone of glyoxal[6] provided the dienone **8** in 80% yield. Reductive cyclization of dienone **8** with sodium hydrosulfite in refluxing aqueous ethanol[6] and protection of the resulting unstable pyrrole as the tert-butyl carbamate provided the desired pyrrole **9**.[7]

Assembly of the requisite nortropinone **12** was best accomplished[8] by the elegant Davies equivalent of the conventional [4 + 3] cycloaddition. Reaction of pyrrole **9** with vinyl diazoester **10**[8] and $Rh_2(OCO(CH_2)_6CH_3)_4$ provided bicyclic adduct **11** in 90% yield (Scheme 3).[9] Cleavage of the enol silane with *n*-Bu_4NF and exo-specific hydrogenation, followed by nucleophilic decarbomethoxylation[10] gave **12**[11] in 60% yield. Numerous variants of enolate chemistry[12] were explored to create the α-axial-α′-equatorial substitution pattern exemplified by aldehyde **3**. We found that NaOMe catalyzed condensation of **12** with furfural gave the α,*β*-unsaturated ketone **13** in 90% yield. Its olefin geometry was determined to be as shown by nOe enhancement

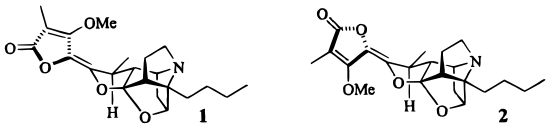
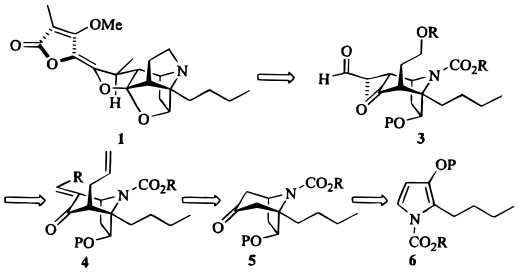
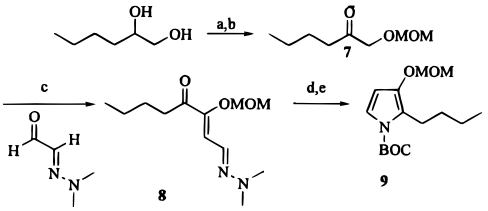


Figure 1.

Scheme 1

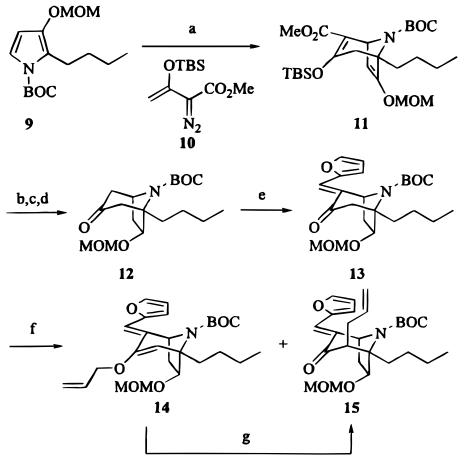


Scheme 2[a]



[a] Reagents: (a) 13% aqueous NaOCl, HOAc, 65%; (b) MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0° → RT, 93%; (c) KOEt, 80%; (d) $Na_2S_2O_4$, EtOH, H_2O, 90 °C, 35%; (e) BOC_2O, 4-DMAP, CH_3CN, 72%.

Scheme 3[a]



[a] Reagents: (a) rhodium octanoate dimer, pentane, reflux, 90%; (b) Bu_4NF, THF, 65%; (c) H_2, 5% Pd/C, MeOH, 90%; (d) H_2O, DMSO, 150 °C, 90%; (e) furfural, NaOH, MeOH, H_2O, reflux, 90%; (f) LiHMDS, 1.1 equiv DMPU, THF, 0 °C, then allyl iodide, rt, 91%; (g) toluene, reflux, 86%.

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(3) (a) Kercher, T.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 4200−4201. (b) Thomas, E. J. *Spec. Publ.- R. Chem. Soc.* **1994**, *147*, 223−237. (c) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538−540. (d) Thompson, W. J.; Buhr, C. A. *J. Org. Chem.* **1983**, *48*, 2769−2772. (e) Buhr, C. A. *Diss. Abstr. Int. B* **1986**, *47*, 1551. (f) Coates, H. M. *Diss. Abstr. Int. B* **1991**, *51*, 4342.

(4) We would like to express deep gratitude to Prof. Yang Ye, Shanghai Institute of Materia Medica, Chinese Academy of Sciences for providing authentic samples of stemofoline and isostemofoline and their corresponding 400 MHz ^{1}H NMR spectra.

(5) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, 4647−4650.

(6) (a) Severin, T.; Supp, W.; Manninger, G. *Chem. Ber.* **1979**, *112*, 3013−3022. (b) Severin, T.; Poehlmann, H. *Chem Ber.* **1977**, *110*, 491−499.

(7) **9**: yellow oil; LRMS (EI) calcd for $C_{15}H_{25}NO_4$: m/z = 283. Found: m/z = 283.

(8) An alternate procedure was developed using the chemistry described by Mann: (a) de Almeida Barbosa, L. C.; Mann, J. *Synthesis* **1996**, 31−33. (b) Mann, J.; de Almeida Barbosa, L. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787−790.

(9) (a) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774−10782. (b) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936−2940.

(10) Krapcho, A. P. *Synthesis* **1982**, 893−914.

(11) **12**: colorless oil; HRMS (FAB) calcd for $C_{18}H_{31}NO_5$: m/z = 341.2273. Found: m/z = 342.2272 (MH^+).

(12) Alkylation of **12** was attempted with LiHMDS, LDA, and KHMDS with allyl iodide. The only products isolated were axial and equatorial C-allylation products at the methylene distal to the *n*-butyl group.

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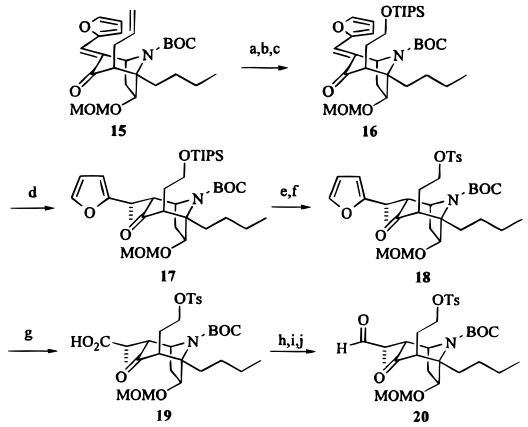
Scheme 4[a]



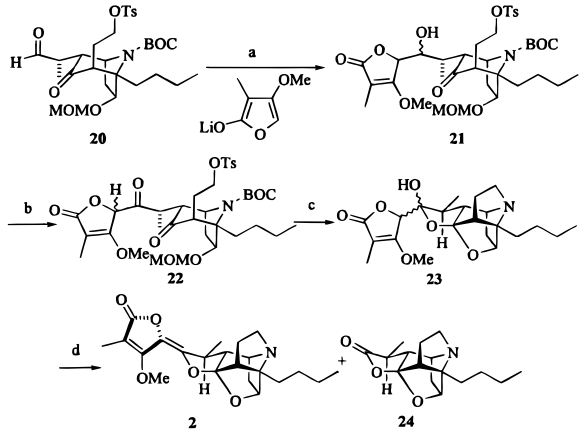
[a] Reagents: (a) K_2OsO_4, $NaIO_4$, Et_2O, H_2O, rt; (b) $Zn(BH_4)_2$, THF, −10 °C, 52%; (c) TIPSCl, imidazole, DMF, 93%; (d) 2.2 MeLi, 1.1 DMPU, Et_2O, −40 °C, 85%; (e) Bu_4NF, THF, 90%; (f) TsCl, pyridine, $CHCl_3$, 90%; (g) O_3, CH_2Cl_2; Me_2S, 65%; (h) *i*-BuOCOCl, *N*-methylmorpholine, THF, 0 °C; (i) $NaBH_4$, MeOH; (j) Dess−Martin periodinane, CH_2Cl_2, 30% overall.

of the furan protons upon irradiation of the proximal bridgehead proton. Alkylation of **13** using LiHMDS, DMPU, and allyl iodide occurred in 91% yield to give a 2.4:1 mixture of **14**:**15**. Stereoselective Claisen rearrangement[13] of enol ether **14** afforded desired α,β-unsaturated ketone **15** in 86% yield.

Oxidative cleavage of the terminal alkene in **15** with potassium osmate/$NaIO_4$,[14] followed by selective $Zn(BH_4)_2$ reduction[15] of the aldehyde gave a hemiketal intermediate which was converted by TIPSCl/imidazole[16] to the TIPS-protected keto alcohol **16** in 50% overall yield (Scheme 4). We could introduce the missing C-methyl group by reaction of **16** with methyllithium/DMPU in ether[17] at −40 °C to provide 1,4 adduct **17** as all single compound having the desired methyl stereochemistry.[18,19] At this point O-desilylation and tosylation of the primary alcohol gave **18**,[20] and subsequent ozonolysis gave acid **19** in 56% overall yield. The delicate conversion of acid **19** to the aldehyde was achieved through the mixed anhydride,[21] selective sodium borohydride reduction[22] and Dess−Martin oxidation[23] to give aldehyde **20** in 30% overall yield.

Installation of the butenolide was carried out by addition of the lithium anion of 4-methoxy-3-methyl-2(5H)-furanone[24] (Scheme 5) to the aldehyde (**20**) to provide a 2:1 mixture of separable diastereomeric alcohols (**21**) which with Dess−Martin oxidation each gave the same 2:1 mixture of diastereomeric ketones **22** in 36% overall yield. Ketones **22** were stirred with trifluoroacetic

Scheme 5[a]



[a] Reagents: (a) THF, −78 °C, 56%; (b) Dess−Martin periodinane, CH_2Cl_2, 61%; (c) (1) CF_3CO_2H; (2) saturated aqueous $NaHCO_3$, 67%; (d) Tf_2O, CH_2Cl_2, **2**: 12%, **24**: 14%.

acid, followed by adjustment of the pH to 10 resulting in a *tandem triple cyclization* to give a 67% yield of stemofoline hydrates **23** showing only 1765 cm^{-1} butenolide carbonyl IR absorption and four separate butenolide carbonyl ^{13}C-resonances, suggesting that all four possible diastereomers of **23** were present in approximately equal amounts.

Dehydration of **23** proved surprisingly difficult, typically leading to a retro-aldol scission giving the pentacyclic lactone **24**.[25] However, $(CF_3SO_2)_2O$ uniquely led to loss of water from **23** and appearance of the characteristic chromophore at 295 nm. Chromatography produced, in addition to **24**, a *single* conjugated butenolide having a UV spectrum and HRMS consistent with stemofoline (**1**) but differing slightly in the high field proton NMR from that published by Irie and also provided by Ye. The richly detailed ^1H NMR spectrum of our product was however indistinguishable from that of isostemofoline (**2**), kindly provided by Professor Ye.[26] TLC analysis (silica gel, 95:5 CH_2Cl_2:MeOH) showed that our product co-eluted with natural isostemofoline with an $R_f = 0.30$, while stemofoline had an $R_f = 0.36$. This route comprises the first total synthesis of (±)-isostemofoline.

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Supporting Information Available: Experimental procedures and spectra for key intermediates (PDF). A crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Seebach, D.; Locher, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 957−958. In contrast, Me_2CuLi failed to react with **16**.

(18) The stereochemistry about the methyl center was determined from the X-ray crystal structure of pentacyclic lactone **24**. The structure revealed the methyl group to be equatorial as in the natural product. Homonuclear decoupling of the methyl group revealed a coupling constant $J = 11.3$ Hz between the bridgehead proton and the methine proton, further confirming the assigned stereochemistry.

(19) Molecular modeling suggested that the α,β-unsaturated ketone should be oriented to preferentially allow attack from the bottom face of the alkene. The steric bulk of the TIPS protecting group may also have helped direct the approach of the nucleophile from the bottom face.

(20) **18**: thick colorless oil; HRMS (FAB) calcd for $C_{33}H_{47}NO_9S$: 633.3940. Found: 656.2870 ($M + Na^+$).

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(25) **24**: colorless crystals (recrystallized from hexane), mp = 110−111 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (br s, 1H), 3.45 (br s, lh), 3.17 (m, 1H), 3.05 (m, 1H), 2.78 (dq, 1H, $J = 7.5$, 19.7 Hz), 2.67 (d, 1H, $J = 6.0$ Hz), 1.98 (m, 3H), 1.83 (m, 2H), 1.59 (m, 2H), 1.43 (m, 1H), 1.35 (qu, 2H, $J =$ 7.2 H), 1.26 (d, 3H, $J = 7.2$ Hz), 1.23 (m, 1H), 0.92 (t, 3H, $J = 7.2$ Hz) ppm; IR ($CDCl_3$) 2956, 2875, 1800, 1457 cm^{-1}. HRMS (FAB) calcd for $C_{16}H_{23}NO_3$; *m/z* = 277.1740. Found: *m/z* = 278.1772 (MH^+). Reaction of **23** with *p*-TsOH, TMSOTf, PhNCO, DCC, $BF_3{\cdot}Et_2O$, HCl, or Martin sulfurane produced **24**; hot $SOCl_2$ or P_2O_5 or Burgess reagent gave no reaction. Direct addition of the lithium enolate of the butenolide to lactone **24** was unsuccessful; the retro-aldol equilibrium favors the lactone **24**.

(26) **2**: off white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (s, 1H), 4.12 (s, 3H), 3.49 (m, 1H), 3.20 (m, 2H), 3.03 (m, 1H), 2.73 (d, 1H, $J = 5.2$ Hz), 2.05 (s, 3H), 2.00 (m, 2H), 1.84 (m, 1H), 1.74 (dd, 2H, $J = 3.6$, 10.8 Hz), 1.58 (m, 3H), 1.46 (d, 3H, $J = 6.4$ Hz), 1.36 (qu, 2H, $J = 6.8$ Hz), 1.28 (m, 1H), 0.92 (t, 3H, $J = 6.8$ Hz) ppm; IR ($CDCl_3$) 2956, 1736, 1691, 1619 cm^{-1}. UV (EtOH) $\lambda_{max} = 295$ nm ($\epsilon = 22500$). HRMS (DEI) calcd for $C_{22}H_{29}NO_5$: *m/z* = 387.2045. Found: *m/z* = 387.2044. In our hands authentic **1** did not isomerize to **2** after 36 h in excess $CF_3CO_2H-CH_2Cl_2$.