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Total Synthesis of (±)-Didehydrostemofoline (Asparagamine A) and (±)-Isodidehydrostemofoline

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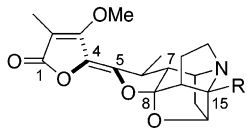
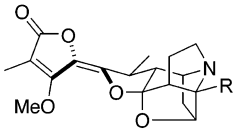
The roots and leaves of various Stemonacea species have found use in traditional Chinese, Japanese, and Thai medicine to treat respiratory disease, parasitic infestation and as insecticides.[2] Stemofoline (**2**), the first member of the hexacyclic family of *Stemona* alkaloids exemplified by **1**−**4**, was first reported by Irie and coworkers in 1970.[3] The 16,17-didehydro analogue **1** of stemofoline was described 25 years later[4,5] and most recently was isolated, together with its 4-*E* stereoisomer **3**, from *Stemona collinsae*.[6] Powerful insecticidal activity, recently associated with antagonism of insect nicotinic acetylcholine receptors,[7b] is seen in *Stemona* alkaloids of this family with didehydrostemofoline (**1**) being particularly potent.[7] Although these structurally intricate *Stemona* alkaloids have attracted considerable synthetic interest,[2] only the pioneering total synthesis of (±)-isostemofoline (**4**) by Kende et al. has been registered.[8] We report herein the first total syntheses of (±)-didehydrostemofoline (**1**) and (±)-isodidehydrostemofoline (**3**).



1: R = (*E*)-CH=CHEt didehydrostemofoline
2: R = *n*-Bu, stemofoline

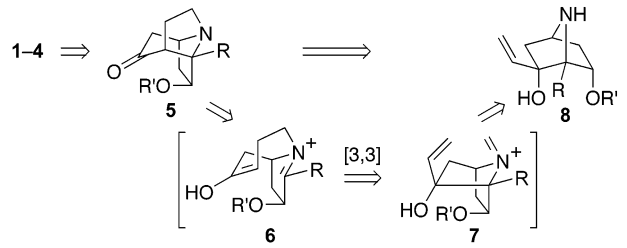


3: R = (*E*)-CH=CHEt isodidehydrostemofoline
4: R = *n*-Bu, isostemofoline

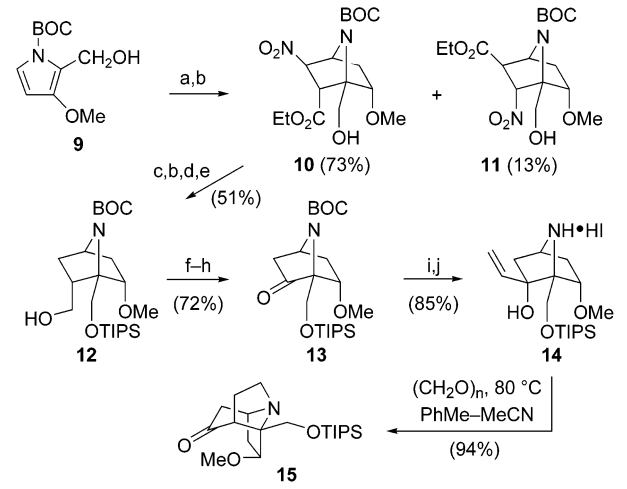
Two structural features of didehydrostemofoline (**1**) and congeners **2**−**4** are found only in *Stemona* alkaloids and present particular challenges for total synthesis: the 1-azatricyclo[5.3.0.0^{4,10}]decane and 4-methoxy-3-methyl-5-tetrahydrofuran-2-ylidene-2(5H)furanone subunits.[2,7c] Our retrosynthetic analysis proceeds by initial disconnection of the C8 acetal and the side chain α to the resulting C8 ketone to azatricyclodecanone **5** (Scheme 1). We saw intermediate **5** arising from 7-azabicyclo[2.2.1]heptanol **8** by aza-Cope−Mannich rearrangement of formaldiminium ion derivative **7**.[9] Whether overlap between the termini of the vinyl and iminium ion functionalities of **7** would be sufficient to allow sigmatropic reorganization to generate **6** was seen as a central issue to be explored in this total synthesis endeavor.

The synthesis of azatricyclodecanone **15** began with Diels−Alder condensation of readily available pyrrole **9**[10] and ethyl (*E*)-3-nitroacrylate,[11] the latter serving in this sequence as a regioinverted equivalent of ketene (Scheme 2).[12] Allowing the reaction of these components to proceed for 5 h at room temperature provided largely two cycloadducts, which reverted to the cycloaddends upon attempted purification on silica gel. As a result, this mixture of adducts was directly hydrogenated over Pd/C to give azabicycloheptanes **10** (73%)[13a] and **11** (13%).[13b] The nitro group, which was essential for the cycloaddition, was removed by sequential treatment of **10** with DBU and H_2 (Pd/C), the primary alcohol was protected and the ester was reduced to provide alcohol **12**. Cleavage of the

Scheme 1



Scheme 2 [a]



[a] Reagents: (a) (*E*)-$O_2NCH{=}CHCO_2Et$, rt; (b) H_2, Pd/C, EtOAc, rt; (c) DBU, CH_2Cl_2, rt; (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; (e) DIBALH, MePh, −78 °C; (f) DMP oxid., CH_2Cl_2, rt; (g) TIPSOTf, Et_3N, CH_2Cl_2, −78 °C; (h) O_3, MeOH−CH_2Cl_2, −78 °C; (i) $H_2C{=}CHMgBr$, $CeCl_3$, THF, −78 °C; (j) TMSI, 2,6-lutidine, 0 °C → rt, MeOH.

enoxysilane derivative of the corresponding aldehyde with ozone delivered azabicycloheptanone **13** in 37% overall yield from **10**.[14] Stereoselective vinylation of this ketone, followed by treatment of the product with TMSI provided hydroiodide salt **14** in 85% yield. Finally, heating of this salt with excess paraformaldehyde at 80 °C delivered azatricyclo[5.3.0.0^{4,10}]decanone **15** in nearly quantitative yield.[13c]

The butenyl side chain and additional carbons of the fused tetrahydrofuran rings of **1** and **3** next were incorporated as summarized in Scheme 3. Cleavage of the TIPS group of **15**, oxidation of the resulting alcohol, and Julia−Kocienski olefination[15] provided isomerically pure **16** in 70% overall yield. Alkylation of the lithium salt of **16** with ethyl iodoacetate,[16] followed by DBU-catalyzed epimerization, gave rise to **17**. Selective cleavage of the methyl ether of **17** with BBr_3, silylation of the resulting lactol, and methylation of the lithium ester enolate then provided **18** in 54% overall yield.[16] That this intermediate had the incorrect configuration

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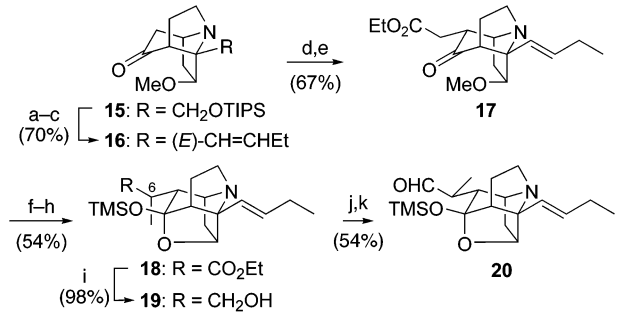
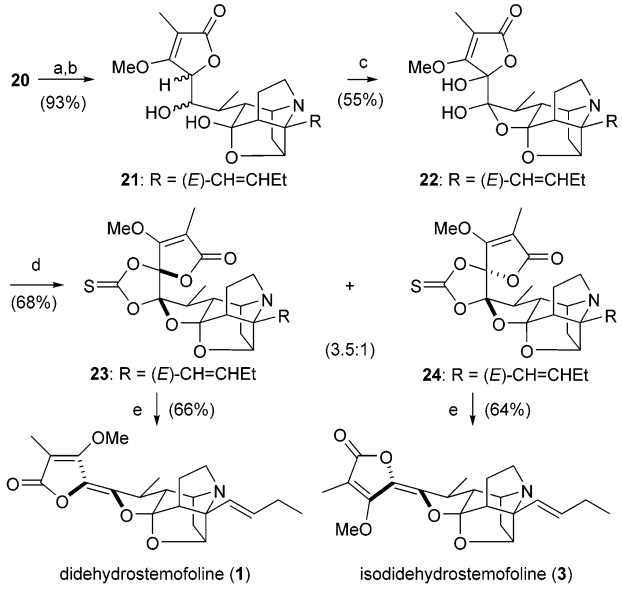
Scheme 3 [a]



[a] Reagents: (a) TBAF, THF, rt; (b) SO_3·Py, NEt_3, DMSO, rt; (c) $C_7H_5N_4SO_2$*n*-Pr, KHMDS, DME, −55 °C; (d) LDA, THF; ICH_2CO_2Et, −10 °C; (e) DBU, MePh, 130 °C; (f) BBr_3, CH_2Cl_2, −78 → −10 °C; aq NaOH; (g) TMS-imid., 130 °C; (h) LDA, MeI, THF−DMPU, −45 °C; (i) DIBALH, CH_2Cl_2, −78 °C; (j) DMP oxid., rt; (k) SiO_2, $CHCl_3$, rt.

Scheme 4 [a]



[a] Reagents: (a) **25**, *n*-BuLi, THF, −78 °C; (b) aq HCl, $CHCl_3$−MeOH, rt; (c) IBX, DMSO, 55 °C; (d) $CSCl_2$, DMAP, CH_2Cl_2, −50 °C; (e) $(MeO)_3P$, 120 °C.

at C6 was established by single-crystal X-ray analysis of the corresponding alcohol **19**.[13d] Fortunately, equilibration of the derived aldehyde in the presence of silica gel (or DBU) provided a 94:6 separable mixture of methyl epimers from which the major epimer **20** was isolated in 68% yield.

To circumvent problems with retroaldolization, we developed an approach to elaborate the remaining tetrahydrofuranylidene butenolide units of **1** and **3** that avoided the need to dehydrate a hexacyclic lactol intermediate.[17] This sequence began by adding the lithium anion of 4-methoxy-3-methyl-2(5H)furanone (**25**)[18] to **20**, followed by acidic cleavage of the silyl protecting group to provide **21** (Scheme 4). This intermediate was oxidized with excess *o*-iodoxybenzoic acid (IBX) in DMSO to yield **22**, which was largely one of the four possible stereoisomers.[19] Condensation of this product with thiophosgene provided a separable mixture of two cyclic thionocarbonates, **23** and **24**, whose ratio varied with reaction temperature (**23**:**24**: 3.5:1 at −50 °C, 1:2 at 0 °C).[20] Finally, upon heating with excess trimethyl phosphite at 120 °C, **23** and **24** fragmented to deliver (±)-didehydrostemofoline (**1**) and (±)-isodidehydrostemofoline (**3**) in respective 66 and 64% yields[21].

The total synthesis of (±)-didehydrostemofoline (**1**) recorded herein is the first preparation of a member of stemofoline family of *Stemona* alkaloids having the apparently more bioactive[4,7] *Z* configuration of the tetrahydrofuranylidene butenolide functionality. Notable steps include use of ethyl (*E*)-3-nitroacrylate as a regioinverted[11b] equivalent of ketene in a Diels−Alder reaction, aza-Cope−Mannich reaction[9] to form the 1-azatricyclo[5.3.0.0^{4,10}]-decane moiety, and Corey−Winter reaction[20] to elaborate the 1,2-dialkoxy alkene units.

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Supporting Information Available: Experimental details for key steps; copies of ^{1}H and ^{13}C NMR spectra of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Current addresses: (a) Cytokinetics, 280 E. Grand Ave. South San Francisco, CA 94080. (b) Johnson & Johnson Pharmaceutical Research and Development, 3210 Merryfield Row, San Diego, CA 92121. (c) Aventis, Haan, Germany. (d) Merck, Sharp & Dohme Ltd., Hertford Rd., Hoddeson EN11 9BU, UK.
(2) For a recent review, see: Pilli, R. A.; da Conceição Ferreira de Oliveira, M. *Nat. Prod. Rep.* **2000**, *17*, 117−127.
(3) Irie, H.; Masaki, N.; Ohno, K.; Osaki, K.; Taga, T.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1066.
(4) (a) Sekine, T.; Fukasawa, N.; Kashiwagi, Y.; Ruangrungsi, N.; Murakoshi, I. *Chem. Pharm. Bull.* **1994**, *42*, 1360−1362. (b) Sekine, T.; Ikegami, F.; Fukasawa, N.; Kashiwagi, Y.; Aizawa, T.; Fujii, Y.; Ruangrungsi, N.; Murakoshi, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 391−393.
(5) This alkaloid was named asparagamine A by these authors who believed, likely erroneously,[7a,c] that its plant source was *Asparagus racemosus*.
(6) Jiwajinda, S.; Hirai, N.; Watanabe, K.; Santisopasri, V.; Chuengsamarnyart, N.; Koshimizu, K.; Ohigashi, H. *Phytochemistry* **2001**, *56*, 693−695.
(7) For recent reports, see: (a) Brem, B.; Seger, C.; Pacher, T.; Hofer, O.; Vajrodaya, S.; Greger, H. *J. Agric. Food Chem.* **2002**, *50*, 6383−6388. (b) Godfrey, C.; Benner, J.; Clough, M.; Dunbar, S.; Earley, F.; Russell, A.; Urch, C.; Ware, A. *10th IUPAC International Congress on the Chemistry of Crop Protection* **2002**, *1*, 236. (c) Kaltenegger, E.; Brem, B.; Mereiter, K.; Kalchhauser, H.; Kählig, H.; Hofer, O.; Vajrodaya; S.; Greger, H. *Phytochemistry* **2003**, *63*, 803−816.
(8) Kende, A. S.; Smalley, T.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431−7432.
(9) For brief reviews, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (b) Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107−120.
(10) Prepared in >95% yield by Boc protection and $NaBH_4$ reduction of 3-methoxypyrrole carboxaldehyde: Bellamy, F.; Martz, P.; Streith, J. *Heterocycles* **1975**, *3*, 395−400.
(11) (a) McMurray, J. E.; Musser, J. *Org. Synth.* **1977**, *56*, 65−68. (b) Danishefsky, S.; Prisbylls, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918−2920.
(12) (a) For a review of the synthesis of 7-azabicyclo[2.2.1]heptanes, see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179−1193. (b) Because of their high aromaticity, pyrroles are rarely useful Diels−Alder dienes, cf.: Donnini, C. P.; Just, G. *J. Heterocycl. Chem.* **1997**, *14*, 1423−1425.
(13) Crystallographic data for this compound have been deposited at the Cambridge Crystallographic Data Centre. (a) Methyl ester analogue: CCDC 220604. (b) Methyl ester analogue: CDCC 220605. (c) Silyl-deprotected hydroiodide salt: CCDC 220606. (d) CCDB 220607. (e) CCDB 220608.
(14) Ozonolysis of the ketene silyl acetal derivative of the corresponding ester was complicated by the formation of the α-hydroxy ester.
(15) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178.
(16) Prior to workup, DABCO was added to quench unreacted alkylating agent.
(17) Such a step eroded the efficiency of the Kende total synthesis of **4**.[8]
(18) Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635−640.
(19) Acyl-2(5H)furanones are readily oxidized at C5, see: Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717−742.
(20) (a) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677−2678.
(21) (a) Synthetic **1** showed ^{1}H and ^{13}C NMR and chromatographic properties identical to those of authentic specimens; we are grateful to Professor Suratwadee Jiwajinda (Kasetsart University, Thailand) for a sample of natural **1** and copies of NMR spectra of **3**. (b) The structure of **3** was further confirmed by single-crystal X-ray analysis.[13e]

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