ORGANIC LETTERS

2001
Vol. 3, No. 16
2505−2508

First Total Synthesis of (±)-Stemonamide and (±)-Isostemonamide

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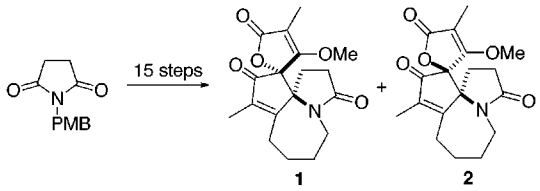
Received May 21, 2001

ABSTRACT



The total synthesis of the tetracyclic alkaloids stemonamide (1) and isostemonamide (2) is presented. The key step is the reaction between a silyloxyfuran and an *N*-acyliminium ion. The second quaternary center is created by an intramolecular aldol spirocyclization. After 1,4-addition of an appropriate side chain, the methyl and double bond are installed by Mannich reaction. The seven-membered ring is closed by intramolecular nucleophilic displacement.

The tetracyclic alkaloids stemonamide (**1**) and isostemonamide (**2**) were isolated from the roots of *Stemona japonica* by Xu et al. in 1994.[1] The highly compact spirocyclic structures of these compounds were elucidated through extensive NMR analyses and by comparison with data for stemonamine **3**, for which an X-ray structure had been obtained[2] (Figure 1).

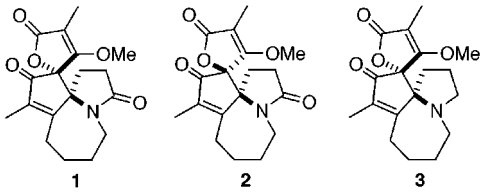
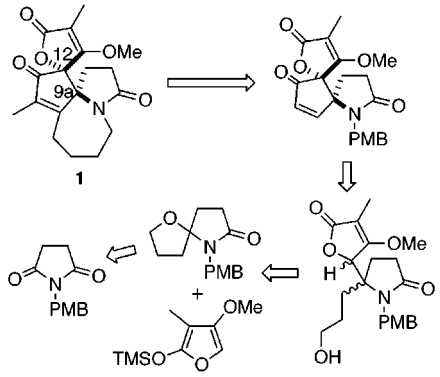


Figure 1.

Extensive synthetic work toward *Stemona* alkaloids, culminating in a number of elegant total syntheses, has been summarized,[3] but no total synthesis of alkaloids having the spirocyclic stemonamide nucleus has been reported.[4] We now report the first total synthesis of (±)-stemonamide (**1**) and (±)-isostemonamide (**2**).

Our approach, retrosynthetically presented in Scheme 1, envisioned the use of acyliminium chemistry[5] to form the C(9a) quaternary center, followed by aldol spirocyclization to obtain the contiguous C(12) quaternary center. The four-

Scheme 1. Retrosynthetic Analysis



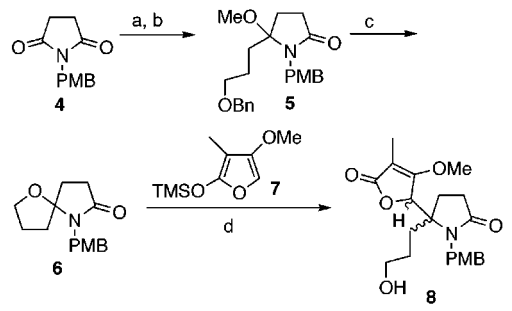
(1) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, *57*, 665.
(2) Iizuka, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1973**, 125.

10.1021/ol010106e CCC: $20.00
Published on Web 07/12/2001

carbon alkyl chain required to build the final azepine ring was to be introduced by conjugate Grignard addition to a tricyclic enone intermediate.

As depicted in Scheme 2, the synthesis began with Grignard addition of (3-benzyloxypropyl)magnesium bromide to succinimide **4**. The resulting unstable hemiaminal was protected as the methoxy derivative **5**, which upon hydrogenolytic debenzylation afforded the spiro compound **6** in 66% overall yield from **4**.

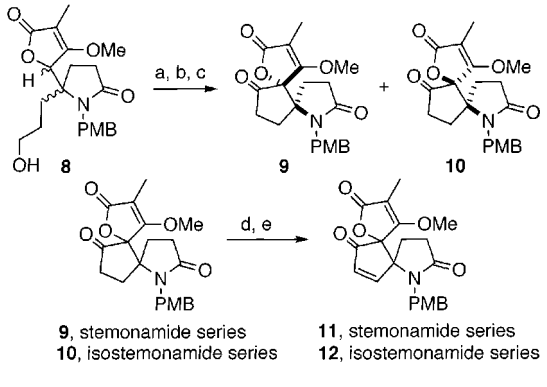
Scheme 2[a]



[a] (a) $BnO(CH_2)_3MgBr$, Et_2O, reflux, 30 min; (b) PPTS, MeOH, rt, 30 min, 90% (2 steps); (c) H_2, 5% Pd/C, 3 h, 90%; (d) BF_3 Et_2O, CH_2Cl_2, rt, 40 min, 82%.

The first quaternary center was created by addition of silyloxyfuran **7**[6] to the *N*-acyliminium ion generated from **6** with BF_3·Et_2O at room temperature.[7,8] Under these conditions a 1:2 mixture of diastereomeric alcohols **8** was produced in 82% yield (Scheme 2). Swern oxidation of alcohols **8** produced the corresponding aldehydes which were cyclized directly using DBU to yield tricyclic aldol products, converted by Swern oxidation to a 1:1 mixture of tricyclic ketones **9** and **10** (Scheme 3). These ketones were readily separated by column chromatography; the faster eluting isomer **9** was subsequently assigned the relative stereochemistry of stemonamide, whereas the more polar isomer **10** corresponded to the isostemonamide series as a result of the individual X-ray analyses of their respective derived targets **1** and **2**.

Scheme 3[a]

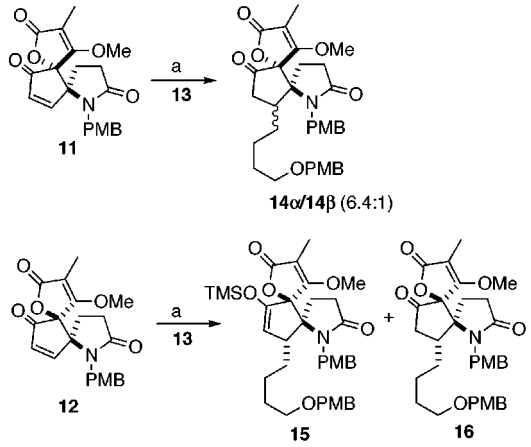


[a] (a) $(COCl)_2$, DMSO, TEA, CH_2Cl_2; (b) DBU, CH_2Cl_2, overnight, rt; (c) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, 70% (3 steps); (d) TBDMSOTf, collidine, toluene, 7 h, 0 °C to room temperature, 80% (stem. series) and 68% (isostem. series); (e) $Pd(OAc)_2$, O_2, DMSO, 80 °C, 24−48h, 93% (**11**) and 89% (**12**).

To effect the desired conjugate addition of the azepine ring carbons, conversion of these saturated ketones to the corresponding conjugated enones was required. Our initial attempts to dehydrogenate ketones **9** and **10** using selenium chemistry failed. Deprotonation of **9** with LDA and reaction with PhSeCl[9] or reaction of its silyl enol ether with PhSeCl[10] gave the corresponding α-phenylselen derivatives in very low yield. The desired enones **11** and **12** were ultimately synthesized by treating the *tert*-butyldimethylsilyl enol ethers[11] with $Pd(OAc)_2$[12] to produce the enones in 76% and 61% yields, respectively (Scheme 3).

Conjugate addition of the Grignard reagent **13** in the presence of CuBr−Me_2S occurs mainly *anti* to the C−N bond (Scheme 4). In the stemonamide series, enone **11** gave a 6.4:1 ratio of **14**α and **14**β in 74% yield. In the isostemonamide series, enone **12** gave only products of

Scheme 4[a]



[a] (a) $PMBO(CH_2)_4MgBr$ **13**, 5% CuBr−Me_2S, TMSCl, HMPA, THF, −78 °C, 30 min, 74% of **14**α/**14**β, 57% of **15**, 32% of **16**.

(3) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117.

(4) Narasaka et al. (*Bull Chem. Soc. Jpn.* **1996**, *69*, 2063) have synthesized the tricyclic alkaloid (±)-stemoamide, mistakenly designated as (±)-stemonamide by these authors. For a discussion, see ref 3.

(5) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 4.1, pp 1047−1082. (b) Speckamp, W. N.; Moolenar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(6) Pelter, A.; Al-Bayati, R. H. I.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717.

(7) (a) Arai, Y.; Kontani, T.; Koizumi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 535. (b) Arai, Y.; Kontani, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 15. (c) Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603.

(8) Martin has used a similar addition of a silyloxyfuran to an iminium species in his total synthesis of the *Stemona* alkaloid croomine. Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

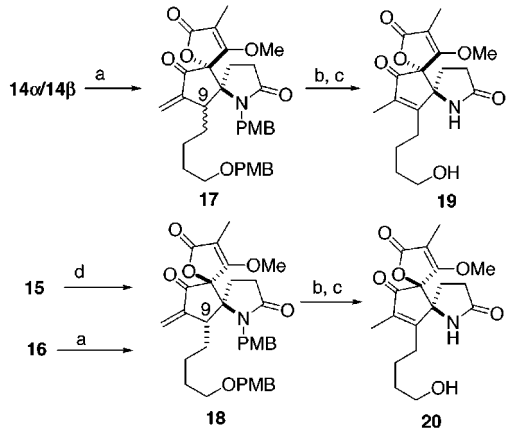
(9) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(10) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460.

α-attack, **15** and **16**, in yields of 57% and 32%, respectively. The use of TMSCl and HMPA as additives was required for any reaction to take place in acceptable yields.[13] In our case, examination of molecular models suggests that the steric hindrance of the N-PMB group is responsible for the observed stereoselectivity in the cuprate addition,[14] although another factor that can contribute to this *anti*-diastereoselectivity is the use of TMSCl as additive.[15]

A Mannich reaction was now used to install the α-methyl group as well as to provide unsaturation (Scheme 5). In the stemonamide series, deprotonation of the **14**α/*β* mixture with KH[16] and treatment with dimethylmethyleneammonium trifluoroacetate[17] gave the α-methylene ketones **17** in 67% yield. Under the same conditions, ketone substrate **16** gave α-methylene compound **18** in 85% yield. The TMS enol ether **15**, also obtained in the 1,4-addition, was converted to **18** in 96% yield by direct treatment with the Mannich reagent in CH_2Cl_2 at room temperature.[18]

Scheme 5[a]

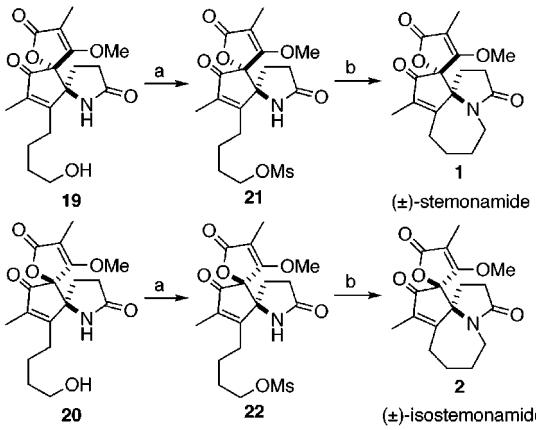


[a] (a) KH, $Me_2N{=}CH_2{}^+CF_3COO^-$, THF, overnight, 67% (**17**) and 85% (**18**); (b) CAN, CH_3CN-H_2O, 2 h, 80% (stem.) and 75% (isostem.); (c) $RhCl_3{\cdot}xH_2O$, EtOH−H_2O (10:1), reflux, 36h, 66% (**19**) and 69% (**20**); (d) $Me_2N{=}CH_2{}^+CF_3COO^-$, CH_2Cl_2, rt, 3 h, 96%

Our first attempts to isomerize the exocyclic double bond of **17** and **18** into the ring using $RhCl_3$[19] were largely unsuccessful, giving mainly products derived from deprotection of the O-PMB group and addition of the solvent to the methylene group. In the case of ketones **17**, $RhCl_3$ isomerization did produce ca. 10% the desired enone system of **19**. This observation suggested the hypothesis that steric hindrance by the large N-PMB substituent interfered with the formation of the hypothetical *σ*-alkyl intermediate.[20] The isomerization requires the metal and the endocyclic hydrogen H-9 to be *syn*. This hypothesis was confirmed by experiments with pure **17**α and **17***β*. While treatment with $RhCl_3$ of the α-isomer (**17**α) gave a complex mixture of products without traces of isomerization, the *β*-isomer (**17***β*) afforded the expected endocyclic alkene with partial loss of the O-PMB group in ca. 60% yield under the same conditions. This obstacle was cleanly overcome by initial removal of the N-PMB (and O-PMB) groups in the **17**α/*β* mixture and in **18**, using cerium(IV) ammonium nitrate.[21] The resulting unprotected lactams then underwent facile $RhCl_3$-mediated isomerization to yield the desired enones **19** and **20** in acceptable yields.

Azepine ring closure was then achieved by intramolecular nucleophilic displacement of the mesylates **21** and **22** (Scheme 6).[22] Reaction of the mesylate **21** with NaH in tetrahydrofuran produced racemic stemonamide **(1)** in 33% yield, along with 10% of unreacted **21**. In a similar way, isostemonamide **(2)** was prepared in 58% yield.

Scheme 6[a]



[a] (a) MsCl, DMAP, py, CH_2Cl_2 0 °C, 1 h (stem.), 4 h (isostem.); (b) NaH, THF, rt, 30 h (stem.), 5 h (isostem.).

The structures of our synthetic stemonamide[23] and isostemonamide[24] were corroborated by single-crystal X-ray determinations[25] of each compound and by their elemental analyses and NMR, IR and mass spectra. Their ^{1}H NMR

(11) Arseniyadis, S.; Rico Ferreira, M. R.; Quilez del Moral, J.; Martin Hernando, J. I.; Potier, P.; Toupet, L. *Tetrahedron: Asymmetry* **1998**, *9*, 4055.

(12) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zeng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.

(13) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

(14) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(15) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186.

(16) Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621.

(17) Ahond, A.; Cave, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J.; Potier, P. *J. Am. Chem. Soc.* **1968**, *90*, 5622.

(18) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.

(19) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem Soc., Perkin Trans. 1* **1977**, 359.

(20) Yamamoto, A. In *Organotransition Metal Chemistry*; Wiley-Interscience: New York, 1986; pp 372−374. A mechanism through a *π*-allyl intermediate also requires a hydrogen abstraction from the α-face of the molecule.

(21) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C.-G. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.

(22) (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. (b) Kohno, Y.; Narasaka, K. *Bull Chem. Soc. Jpn.* **1996**, *69*, 2063.

and ^{13}C NMR spectra were indistinguishable from spectra kindly provided to us by Prof. Y. Ye.[26] Our route comprises the first total syntheses of (±)-stemonamide and (±)-isostemonamide in 4% and 7% yields from succinimide **4**, respectively.

Acknowledgment. We thank the University of Rochester for partial support of this research.

Supporting Information Available: Data for **9**, **10**, **11**, **12**, **21**, and **22**. ^{1}H and ^{13}C NMR spectra of for **9**, **10**, **11**, **12**, **21**, and **22**. ^{1}H and ^{13}C NMR spectra of synthetic **1** and **2**. ORTEP plots of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) (±)-**1**: colorless crystals, mp 240−241 °C ($EtOAc/CH_2Cl_2$). IR (cm^{-1}): 2925, 1765, 1698, 1661, 1456, 1389, 1326, 1145, 1075, 1006, 858. ^{1}H NMR (400 MHz, $CDCl_3$): 1.22−1.44 (2H, m); 1.81 (1H, bd, $J = 17.0$); 1.84 (3H, s); 1.93 (1H, dt, $J = 8.8, 12.5$); 1.99 (3H, s); 2.05−2.16 (2H, m); 2.27 (1H, dd, $J = 8.8, 16.6$); 2.34 (1H, dd, $J = 7.8, 12.5$); 2.58 (1H, ddd, $J = 7.8, 12.5, 16.6$); 2.82 (1H, bt, $J = 13.0$); 2.97 (1H, bdd, $J = 5.8, 12.8$); 3.97 (3H, s); 4.16 (1H, bd, $J = 14.4$). ^{13}C NMR (100 MHz, $CDCl_3$): 8.4, 9.1, 27.3, 29.8, 30.1, 31.9, 41.2, 59.2, 74.5, 90.1, 99.6, 136.9, 168.6, 170.9, 172.9, 175.8, 196.5. APCI: 663 ($[2MH]^+$, 10), 332 ($[MH]^+$, 100), 207 (9), 125 (12). HRMS (DCI/NH_3): calcd for $C_{18}H_{22}NO_5$ $m/z = 332.1498$, found 332.1507. Anal. Calcd: C, 65.24; H, 6.39. Found: C, 65.53; H, 6.58.

(24) (±)-**2**: colorless crystals, mp 225−227 °C ($EtOAc/CH_2Cl_2$). IR (cm^{-1}): 2926, 2360, 1766, 1698, 1661, 1450, 1393, 1331, 1248, 1165, 1126, 1073, 1036, 1006, 963, 734. ^{1}H NMR (400 MHz, $CDCl_3$): 1.22−1.43 (2H, m); 1.76 (1H, bd, $J = 14.2$); 1.84 (3H, s); 1.90 (1H, dt, $J = 9.1, 13.0$); 2.05 (3H, s); 2.01−2.04 (2H, m); 2.24 (1H, ddd, $J = 7.1, 13.0, 16.5$); 2.33 (1H, dd, $J = 9.1, 16.5$); 2.59 (1H, dd, $J = 7.1, 13.0$); 2.90−2.98 (2H, m); 4.13 (3H, s); 4.14 (1H, bd, $J = 15.0$). ^{13}C NMR (100 MHz, $CDCl_3$): 8.3, 9.2, 26.9, 27.6, 29.4, 29.7, 42.3, 59.8, 73.5, 86.4, 102.7, 136.6, 168.7, 171.7, 172.6, 174.6, 196.9. APCI: 663 ($[2MH]^+$, 16), 332 ($[MH]^+$, 100). HRMS (DCI/NH_3): calcd for $C_{18}H_{22}NO_5$ $m/z = 332.1498$, found 332.1495. Anal. Calcd: C, 65.24; H, 6.39. Found: C, 65.36; H, 6.59.

(25) Huffman, J. C.; Molecular Structure Center, Department of Chemistry, Indiana University.

(26) We thank Prof. Y. Ye (Shanghai Institute of Materia Medica) for sending us copies of ^{1}H and ^{13}C NMR spectra of natural **1** and **2**.