Total Synthesis of (±)-Stemoamide

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Stemoamide (**1**) is a member of the *stemona* class of alkaloids that was isolated in 1992 from the roots of *Stemona tuberosa* (Figure 1).[1a] Alkaloids of this genus typically incorporate a perhydroazaazulene ring (*cf.* **3**), a structural feature that is present in nearly all compounds isolated thus far [see also stenine (**2**)]. Most members also contain an α-methyl-γ-butyrolactone functionality. Extracts of the *Stemonaceae* species have been used for many years in Chinese traditional medicine for treating a variety of respiratory ailments, including bronchitis, pertussis, and tuberculosis.[1b] In addition, certain *stemona* alkaloids have potent insecticidal activity.
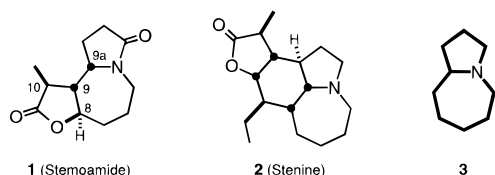

Figure 1.

Recently, members of this class have attracted considerable synthetic attention, in particular with respect to developing new ring-forming reactions.[2] Noteworthy accomplishments include the synthesis in 1995 of (−)-stenine (**2**) by Wipf *et al.*[2a] and an earlier synthesis of (±)-**2** by Hart and Chen.[2c,d] In 1994, Williams *et al.* described the first total synthesis of (−)-stemoamide (**1**), beginning with (R)-(−)-methyl 3-hydroxy-2-methyl-propionate.[2e] Very recently, a second synthesis of (−)-**1** has appeared which made use of a novel Ru-catalyzed enyne metathesis reaction.[2l] In this paper we describe a concise synthesis of (±)-**1** which can be utilized for preparing this important compound on 0.5 g scales and larger. In addition, it should be readily adaptable to the preparation of naturally occurring (−)-**1**.

The key intermediate for our synthesis of **1** was the butenolide derivative **5** (Figure 2), which we expected would be an ideal precursor for establishing the *trans* relative stereochemistry at C_8 and C_{9a} under thermodynamic control.[2n] Thus, with the C_{9a} configuration set, models clearly indicate that the alternative *cis* arrangement found in **4** suffers from severe steric crowding. This is a consequence of the fact that the C_{10} methyl group is forced into close proximity to the C_1 methylene hydrogens. Viewed from a different perspective, the C_{10} methyl bond and

the C_1−C_{9a} pyrrolidinone bond have a dihedral angle close to 0° (pseudoeclipsed). Assuming free equilibration, epimerization at C_8 has the effect of increasing this dihedral angle to ∼60° (pseudostaggered), thereby greatly reducing steric interactions.[3] This relationship, which is qualitatively apparent with models, was verified with molecular mechanics calculations (MM2* strain energy difference for **4** and **5**: $\Delta H_{4,5} = 3.9$ kcal/mol).[4] Once in hand, we expected that *cis* reduction of **5** from the least hindered β-face would afford the methyl lactone **6**, which again suffers from van der Waal's repulsion between Me_{10} and C_1. However, epimerization at C_{10} would relieve this interaction and provide (±)-stemoamide (**1**) as the thermodynamically most stable product ($\Delta H_{6,1} = 4.6$ kcal/mol).
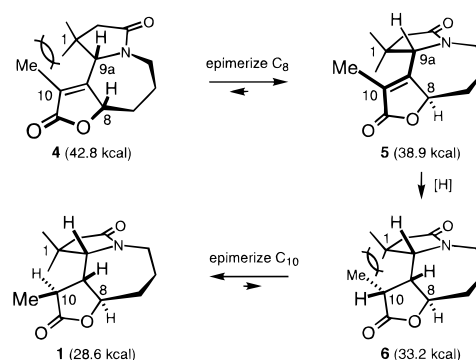

Figure 2.

The most logical precursor to **5** was the corresponding methoxyfuran, which we hoped to prepare using the oxazole Diels−Alder chemistry we have employed in the synthesis of various furanoterpenes (Figure 3; **7 → 8**).[5] Transformations of this type are of considerable synthetic utility, since the appended groups A, B, and C are transposed in an unequivocal fashion to the fused-ring furan **8**. For the case where A = OMe, this approach offered the potential for forming the entire skeleton of **1** in a single step, since hydrolysis of **8** would in principle afford the butenolide **9**.[5]
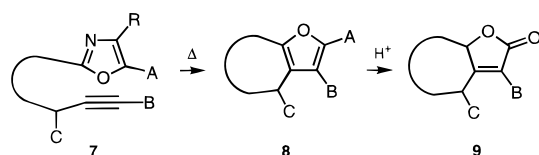

Figure 3.

In order to test this possibility, we have developed a highly efficient synthesis of the acetylenic oxazole **16**, which was prepared in multigram quantities beginning with γ-chlorobutryl chloride (**10**) (Scheme 1). First, acid chloride **10** was readily converted to the methoxyoxazole **12** by initial condensation with methyl alaninate, followed by cyclodehydration of the resultant amide **11** with P_2O_5 (20 g scale; 80%).[5] It proved to be unnecessary to isolate intermediate **11**, which was formed in a high state of purity. Next, N-alkylation of succinimide with **12** proceeded in routine fashion to afford a 97% yield of the oxazole imide **13**. Several possibilities were considered for converting the oxazole imide **13** to the desired acetylenic oxazole

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(1) Isolation: (a) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992,** *55,* 571. (b) Goetz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1976; Vol. IX, pp 545−551 and references cited therein. See, also: (c) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. In *Natural Products Chemistry*; Academic Press: New York, 1975; Vol. 2, pp 292−93.

(2) Recent synthetic efforts: (a) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.*, **1995,** *117,* 11106. (b) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996,** *37,* 739. (c) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993,** *58,* 3840. (d) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990,** *55,* 6236. (e) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994,** *35,* 6417. (f) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993,** *34,* 5773. (g) Martin, S. F.; Corbett, J. W. *Synthesis* **1992,** 55. (h) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992,** 538. (i) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992,** *33,* 5477. (j) Xiang, L. I.; Kozikowski, A. P. *Synlett* **1990,** *2,* 279. (k) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989,** *111,* 1923. (l) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996,** *61,* 8356. See, also: (m) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996,** *69,* 2063. (n) Following the completion of this work, Kinoshita and Mori reported a synthesis of (−)-**1** which also employed butenolide **5**, although the mp for their **5** varies significantly from that reported here (127−29 °C vs 185−86 °C).[2l]

(3) Epimerization at C_{9a} in **4**, while having the same effect, is viewed as less likely due to the lower pK_a of H_8.

(4) (a) Calculations were carried out using MacroModel V5.5, employing the MM2* force field, and using Monte Carlo simulations to locate global minima (>1000 MC steps).[4b] (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989,** *111,* 4379. See, also: (c) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990,** *11,* 440.

(5) Jacobi, P. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; Jai Press Inc.: Greenwich, CT, 1992; Vol. II, pp 251−98, and references cited therein.

16. However, by far the most convenient procedure made use of the methoxylactam **15**, which was readily derived from **13** by selective reduction with $NaBH_4$,[6] followed by treatment with $MeOH/H^+$.[7] Finally, $BF_3 \cdot Et_2O$ catalyzed condensation of **15** with (1-propynyl)tributylstannane gave a 92% yield of the target oxazole **16**.[8]
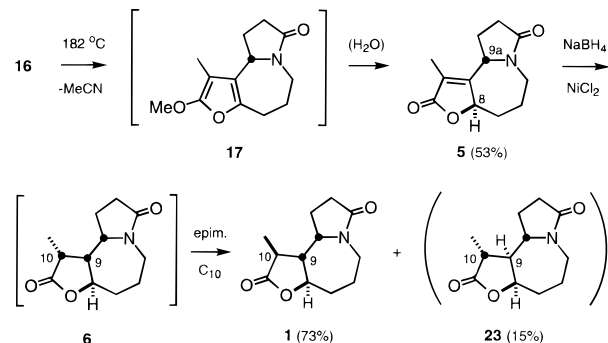
Scheme 1
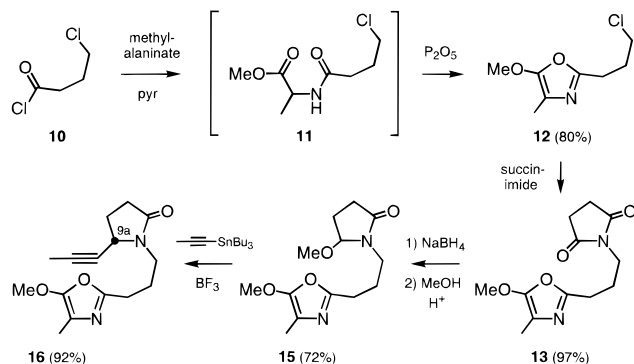
With ample quantities of **16** now in hand, we investigated numerous conditions for carrying out the desired (Diels–Alder)–(*retro*-Diels–Alder) cyclization leading from **16** to the methoxyfuran **17** (Scheme 2). Not surprisingly, **16** was relatively unreactive toward IMDA cyclization, which involves an unactivated alkyne dienophile and produces an entropically disfavored seven-membered ring. At temperatures up to 135 °C (ethylbenzene, reflux), **16** suffered mainly slow decomposition to intractable tars, with at best only trace amounts of **17** detectable by GC. Various efforts at catalyzing this reaction with Lewis acids also failed.[9a] However, at higher temperatures we obtained mixtures of the anticipated methoxyfuran **17** as well as the butenolide **5**, our projected precursor to stemoamide (**1**). In refluxing diethylbenzene (182 °C), this reaction afforded 50–55% of **5** on gram scales and larger, together with only small amounts of byproducts (*vide infra*). Although **17** was the major product by GC-MS analysis, it suffered rapid

(6) Hart, D. J.; Sun, L.-Q.; Kozikowski, A. P. *Tetrahedron Lett.* **1995**, *36*, 7787.

(7) Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.

(8) See, for example: (a) Koot, W.-J.; van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401. (b) Thaning, M.; Wistrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. (c) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949. (d) Keinan, E.; Peretz, M. *J. Org. Chem.* **1983**, *48*, 5302.

(9) (a) Including, for example, $BF_3 \cdot Et_2O$, Et_2AlCl, $TiCl_4$, $SnCl_4$, $AlCl_3$, SiO_2, *p*-TsOH, Bu_3SnOMe, and others. (b) One possible source of oxidant is trace amounts of air in the reaction mixture. Under 1 atm of air **16** undergoes rapid decomposition in refluxing diethylbenzene (182 °C). (c) Oxidation potentials were measured on 7 mM solutions of **16** in MeCN containing 0.1 M Bu_4NPF_6 as electrolyte, employing a Pt working electrode and a $Ag/AgNO_3$ reference electrode. We gratefully acknowledge Mr. John Porter and Professor Albert Fry, of Wesleyan University, for assistance in carrying out these experiments. Helpful discussions with Professor Kevin Moeller, of Washington University, St. Louis, are also acknowledged.

(10) (a) Yueh, W; Bauld, N. L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 871 and references cited therein. (b) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793, and references cited therein.

(11) (a) Satisfactory analytical and spectral data were obtained for all new compounds reported. (b) Upon treatment with $BF_3 \cdot Et_2O$, methyl ester **21** was cleanly converted to butenolide **20**. (c) We are grateful to Dr. Victor G. Young, of The University of Minnesota, for carrying out the X-ray analysis of **18**.

(12) (a) Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420 and references cited therein. (b) Jacobi, P. A.; Frechette, T.; Arrick, B.; Walker, D.; Craig, T. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (c) This same step is reported in ref 2l to give a single product. However, in our hands this reduction consistently produced a ~5:1 mixture of **1** and **23**.

(13) We are grateful to Professor David R. Williams, of Indiana University, for providing us with NMR, IR, and mass spectra of authentic (−)-**1**.

(14) Financial support of this work by NSF Grant No. CHE-9424476 is gratefully acknowledged.

hydrolysis to **5** upon attempted isolation. As expected on the basis of the arguments outlined in Figure 2, we could detect none of the epimeric *cis*-substituted butenolide **4**. If formed at all, **4** underwent spontaneous isomerization to **5**.

Scheme 2

The mechanism for the cyclization of oxazole **16** to methoxyfuran **17** is of some interest. On large scales this transformation is facilitated by electron acceptors such as benzoquinone, an effect that suggests a stepwise process. In fact we have isolated and characterized several byproducts from this reaction whose formation is consistent with an electron transfer pathway (Figure 4) (*cf.* Supporting Information). These range from lactones **18** and **19**, the products of apparent methyl migration, to butenolide **20** and methyl ester **21**, which are clearly derived by oxidation. In addition to their spectral and analytical properties,[11a] the identities of **20** and **21** were established by chemical correlation.[11b] The structure of **18** was confirmed by single crystal X-ray analysis.[11c] In any event, the identity of butenolide **5** was unequivocally established by its highly characteristic NMR and IR spectra,[11a] as well as by its subsequent conversion to (±)-stemoamide (**1**).
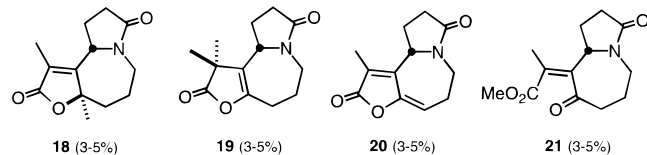

Figure 4.

The remaining steps necessary in order to convert **5** to **1** involved the stereoselective *cis*-reduction of **5** from the β-face, followed by epimerization at C_{10} (Scheme 2, **6** → **1**). Butenolide **5** was completely unreactive to standard hydrogenation conditions (PtO_2, Pd, or Ni/H_2) and was recovered unchanged upon treatment with various hydride reducing reagents. However, we obtained excellent results with the nickel boride catalyst derived from $NiCl_2$ and $NaBH_4$,[12] which we have previously employed in the synthesis of methyllactones.[5,12b] When this reaction was carried out at −30 °C in MeOH we obtained a 73% yield of (±)-stemoamide (**1**) as a colorless crystalline solid, mp 184–85 °C [lit. mp for (−)-**1**: 190–91 °C;[2e] 187–88 °C[2l]]. As in the case with **4** above, we could detect none of the C_{10} epimer **6**, which underwent quantitative isomerization to **1**. The only other compound isolated from this reaction was a small amount of the *cis*-lactone **23** (15%), derived by α-face reduction of **5** followed by epimerization at C_{10}.[12c] (±)-Stemoamide (**1**) thus prepared, in two steps from acetylenic oxazole **16** and seven steps overall, had identical 500 MHz NMR, IR, and mass spectra as an authentic sample.[2e,13,14]

Supporting Information Available: Evidence for a possible electron transfer mechanism for the cyclization of oxazole **16** to methoxyfuran **17** and copies of ^{1}H- and ^{13}C-NMR spectra and experimental procedures for compounds **1**, **5**, **11**–**21**, and **23**; MM2* structures for **1** and **4**–**6**; and crystal structure for **18** (39 pages). See any current masthead page for ordering and Internet access instructions.