A Synthetic Approach to the *Stemona* Alkaloids

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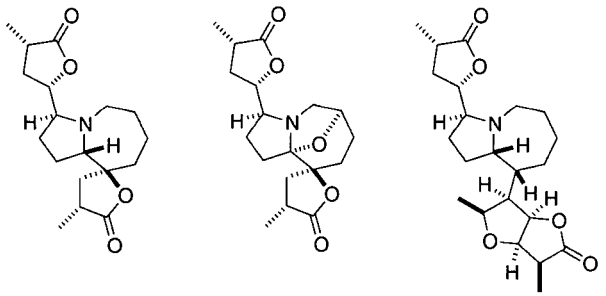
This paper describes our work developing a strategy for the construction of the typical core structure of the *Stemona* alkaloids. The approach is to control the relative stereochemistry of the groups on the core 1-azabicyclo[5.3.0]decane ring system by a [3,3] sigmatropic rearrangement of an acylimmonium ion followed by selective reduction. After optimization, this reaction sequence afforded the desired diastereomer in 62% yield. Further efforts were directed toward elaboration of the characteristic butyrolactone substituent.

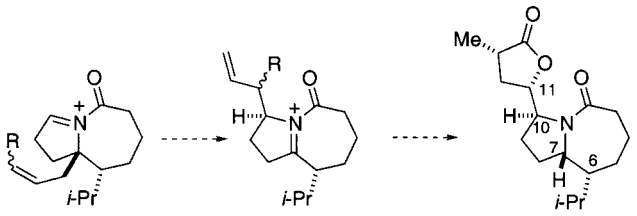
The *Stemona* alkaloids have generated considerable interest in recent years. They are from the *Stemonaceae* family, which has two genera, *Stemona* and *Croomia*. Several alkaloids have been isolated from the roots of these plants; representative examples are croomine (**1**),[1] stemotinine (**2**),[2] and parvistemonine (**3**).[3] Common to all of the *Stemona* alkaloids is the central 1-azabicyclo[5.3.0]-decane ring system. Another common feature is the α-methyl-γ-lactone, although the stereochemistry at the methyl position varies. Their unusual structures have intrigued chemists and inspired several total syntheses of *Stemona* alkaloids.[4−7]



1 **2** **3**

In this article, we report the results of a study to develop a strategy for construction of the typical core structure of this family of alkaloids. Our approach is outlined for a model compound in Scheme 1. An intermediate such as immonium ion **4** might undergo stereocontrolled aza-Cope rearrangement to provide immonium ion **5**, which should undergo stereoselective reduction from the less hindered face to effectuate control of three stereocenters on the 1-azabicyclo[5.3.0]decane skeleton (C6, C7, and C10). Furthermore, if the angular allyl group in **4** is suitably substituted at the terminal position, we might be able to control the configuration at C11.

Scheme 1



4 **5** **6**

We began our investigation with a very simple model system to explore the feasibility of the aza-Cope strategy. Since we planned to install the nitrogen by a Beckmann rearrangement, the synthesis of ketone **9** was our initial goal. Use of Stork's method[8] allowed the cyclohexylimine of cyclohexanone to be deprotonated and alkylated with bromoacetal **7** to give ketone **8** in 65% yield (Scheme 2). Ketone **8** was converted once again into its cyclohexylimine, which was metalated by *sec*-butyllithium and the resulting metalloenamine alkylated with allyl bromide to obtain ketone **9** in 80% yield.[9] Unfortunately, it was not possible to combine these two alkylations and avoid cleavage of the first imine. Nonetheless, this reaction sequence provided a convenient synthesis of ketone **9**.

With ketone **9** in hand, our next task was to install the nitrogen and attempt the aza-Cope reaction. Treatment of ketone **9** with hydroxylamine hydrochloride and sodium acetate in methanol for 20 h at room temperature provided the corresponding oxime in 99% yield. The oxime was treated with *p*-toluenesulfonyl chloride (TsCl) and catalytic *N*,*N*-(dimethylamino)pyridine (DMAP) in

(1) Noro, T.; Fukushima, S.; Ueno, A.; Litaka, Y.; Saiki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1495−97.
(2) Xu, R.; Liu, Yiwei; Yao, J.; Mak, T. C. W. *Jiegou Huaxue* **1986**, *5*, 97−100.
(3) Lin, W.; Yin, B.; Tang, Z.; Xu, R.; Zhong, Q. *Huaxue Xuebao* **1990**, *48*, 811−14.
(4) Stenine: Chen, C.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236−40; **1993**, *58*, 3840−49.
(5) Stemoamide: (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417−20. (b) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063−70. (c) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356−57. (d) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287−89. (e) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409−10.
(6) Croomine: (a)Williams, D. R.; Brown, D. L.; Benbow, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.
(7) For a recent review, see: Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117−27.
(8) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178−80.
(9) Hosomi, A.; Araki, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1982**, *104*, 2081−83.

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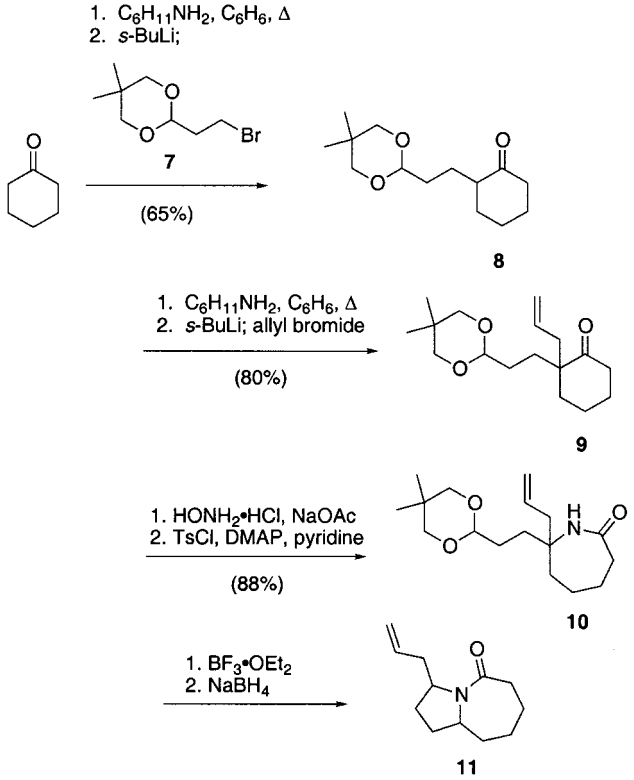
Scheme 2

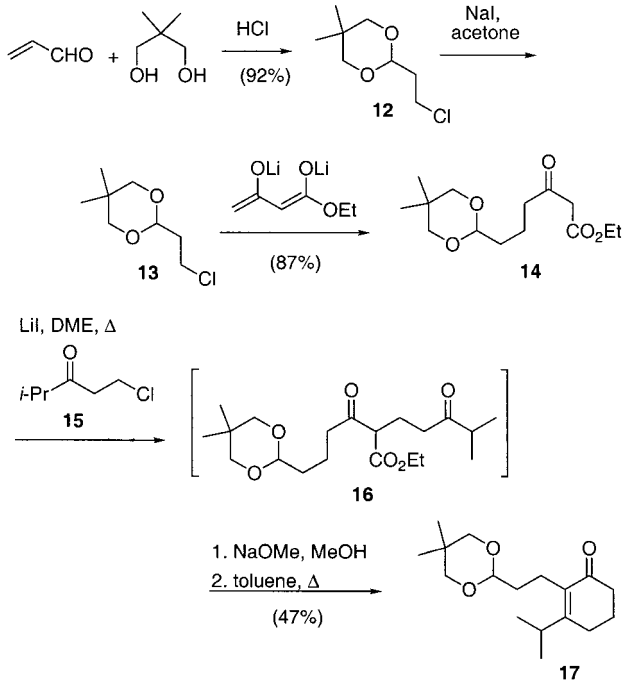


pyridine, followed by an acidic aqueous workup to obtain lactam **10** in 89% yield. Reaction of model lactam **10** with boron trifluoride etherate (BF_3•OEt_2) in d_2-dichloromethane in an NMR tube afforded a new product, presumably the rearranged immonium ion. Treatment with $NaBH_4$ gave a clean conversion to a product tentatively assigned structure **11**.

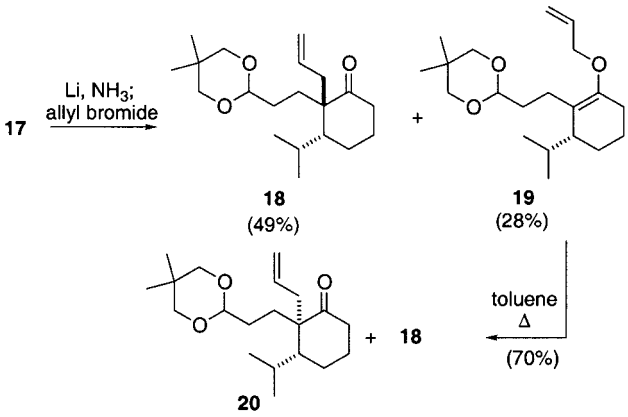
This study provided a promising prognosis for the success of our basic approach, and we turned to the synthesis of a more relevant system. Chloro acetal **12** was prepared in 92% yield by reaction of acrolein with 2,2-dimethylpropane-1,3-diol and gaseous HCl. Chloride **12** was converted into iodide **13** by standard Finklestein conditions.[10] Alkylation of the dianion of acetoacetic ester with iodoacetal **13** gave β-keto ester **14** in an overall yield of greater than 80%. Compound **14** was condensed with the known[11] chloro ketone **15** by stirring a mixture of the two reactants with sodium methoxide in methanol at room temperature. After several hours, sufficient 1 N HCl was added to bring the pH to 1. Workup provided enone **17** in a quite respectable overall yield, given the remarkable sequence of reactions that occurs in this one-pot transformation (β-elimination, Michael addition, aldol condensation, ester hydrolysis, and decarboxylation).

The next task was the installation of the allyl group with stereochemical control. We chose to accomplish this goal by Stork reductive alkylation of enone **17**.[12] Reduction of **17** with lithium in ammonia, followed by addition of allyl bromide, provided the desired ketone **18** in 49%

Scheme 3



Scheme 4



yield, along with 28% of the corresponding O-allylated isomer **19**. We initially believed that this enol ether might be converted into the desired C-allylated isomer through a Claisen rearrangement.[13] However, although this transformation could be effected, it did not provide a solution to the problem because the Claisen rearrangement proceeds with no facial selectivity, giving a 1:1 mixture of **18** and its diastereomer **20** (Scheme 4). We reasoned that a softer electrophile would favor C-alkylation over O-alkylation.[14] To this end, we carried out the Stork reductive alkylation with allyl iodide and obtained the desired C-allylated product **18** in 63% yield, accompanied by none of the O-allylated material. Unfortunately, this procedure also provided 14% of the reduced but not alkylated ketone **21** (Scheme 5). This is probably the result of adventitious water, but the reaction was not further optimized. To execute the Beckmann rearrangement, we needed first to make the oxime of ketone **18**. We first employed the same conditions that had worked exceptionally well with ketone **9**. However, these condi-

(10) Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528−32.

(11) (a) Baisted, D. J.; Whitehurst, J. S. *J. Chem. Soc.* **1965**, 2340−49. (b) Nakahira, H.; Ryu, I.; Ikebe, M.; Oku, Y.; Ogawa, A.; Kambe, N.; Sonoda, N.; Marai, S. *J. Org. Chem.* **1992**, *57*, 17−28. (c) McMahon, E. M.; Roper, J. N., Jr.; Utermohlen, W. P., Jr.; Hasek, R. H.; Harris, R. C.; Brant, J. H. *J. Am. Chem. Soc.* **1948**, *70*, 2971−77.

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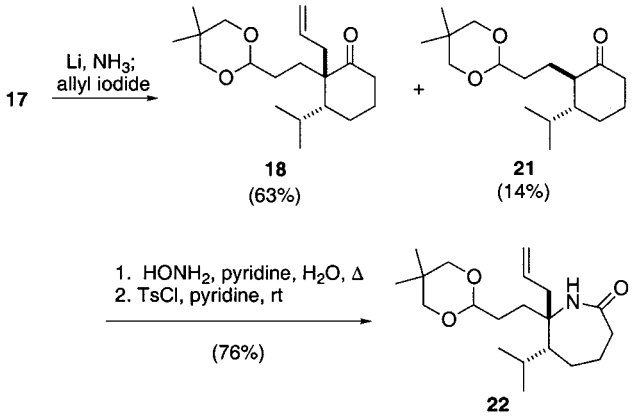
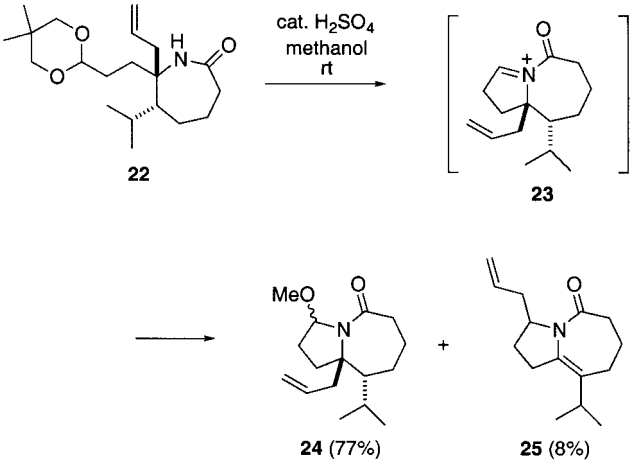
(13) Ziegler, E. E. *Acc. Chem. Res.* **1977**, *10*, 227−32.

(14) Pearson, R. J. *J. Chem. Educ.* **1968**, *45*, 581−86, 643−48. (b) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827−36.

Scheme 5



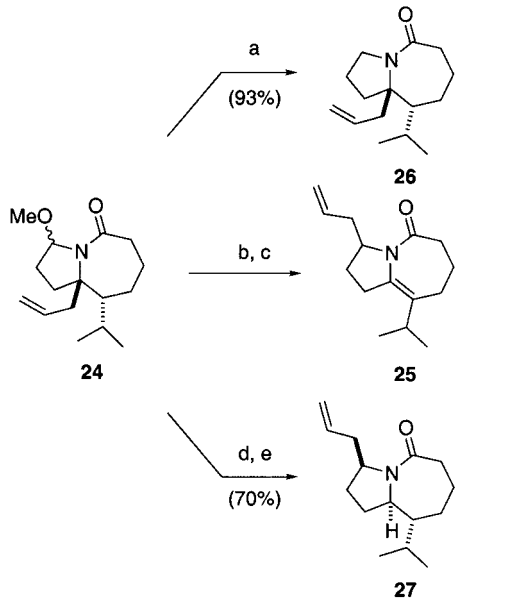
Scheme 6



tions (hydroxylamine hydrochloride in methanol with sodium acetate at room temperature for 24 h) resulted in no reaction. Heating this reaction mixture at reflux for 24 h gave the oxime in 53% yield, along with 46% of recovered starting material. Introduction of the isopropyl group has obviously added significant steric hindrance, requiring more forcing conditions for oxime formation. Success was finally achieved by refluxing ketone **18** with hydroxylamine hydrochloride in a 5:1 mixture of pyridine and water for 16 h; under these conditions, the desired oxime was isolated in 83% yield. Beckmann rearrangement was induced by treatment of the oxime with *p*-toluenesulfonyl chloride in pyridine at room temperature; lactam **22** was obtained in an overall yield of 76% for the two steps.

After some initial attempts to bring about the aza-Cope rearrangement directly with lactam **22**, we found that it was advantageous to proceed through the intermediate hemiaminal. The lactam could be converted to O-methylhemiaminal **24** by treatment with a catalytic amount of sulfuric acid in methanol. Under optimized conditions, compound **24** was obtained in 77% yield, along with recovered starting material (13%) and byproduct enamide **25** (8%). Both products presumably arise from *N*-acylimmonium ion **23**, which is trapped by methanol to give **24**. Alternatively, intermediate **23** can undergo aza-Cope rearrangement to give an isomeric acylimmonium ion, which deprotonates under the reaction conditions to provide byproduct **25**. We were unable to find conditions that completely eliminated byproduct **25**, but it can be minimized by carrying out the reaction at room temperature. Under these conditions, the reaction requires about 36 h for complete consumption of starting material. At higher temperatures, the amount of byproduct **25** increases, presumably because of reversible formation of acylimmonium ion **23** from aminal **24**.

Scheme 7



a. 1:1:1 CH_2Cl_2-CF_3CO_2H-Et_3SiH, 15 min.
b. 1:1 CH_2Cl_2-CF_3CO_2H, 30 min; c. Et_3SiH, 15 min
d. CH_2Cl_2-$TiCl_4$, −78 °C, 30 min; e. Et_3SiH, 0 °C, 30 min

Our studies were next focused on the aza-Cope reaction itself. There are a number of ways by which other workers have induced aza-Cope reactions.[15] We began with one of the most simple methods. Aminal **24** was dissolved in one portion of dichloromethane, and equal portions of trifluoroacetic acid and triethylsilane were added (Scheme 7). The reaction mixture was worked up after 20 min to afford amide **26** in 93% yield. Amide **26** results from immediate reduction of the initially formed immonium ion, prior to sigmatropic rearrangement. We reasoned that this difficulty could be overcome by allowing aminal **24** to react with trifluoroacetic acid before the reducing agent was added. This analysis was partly correct. Under these conditions (trifluoroacetic acid), the immonium ion formed by the sigmatropic rearrangement apparently deprotonates to give enamide **25** before the reducing agent is added.

Because enamide **25** was relatively easy to obtain by the foregoing method, we briefly explored the possibility of its conversion to the desired target. Treatment of **25** with a 1:1:1 mixture of dichloromethane, trifluoroacetic acid, and triethylsilane for 5 h did afford the desired reduced material in 74% yield, but as a 1:1 mixture of two diastereomers. Although this attempted reduction did not provide a stereocontrolled route to the desired product, it did give us valuable insight. In particular, the experiment showed that reduction of the acylimmonium ion is faster than the aza-Cope rearrangement, since none of lactam **26** was obtained in the reaction.

Partial success was finally achieved by the use of titanium tetrachloride in dichloromethane at −78 °C to

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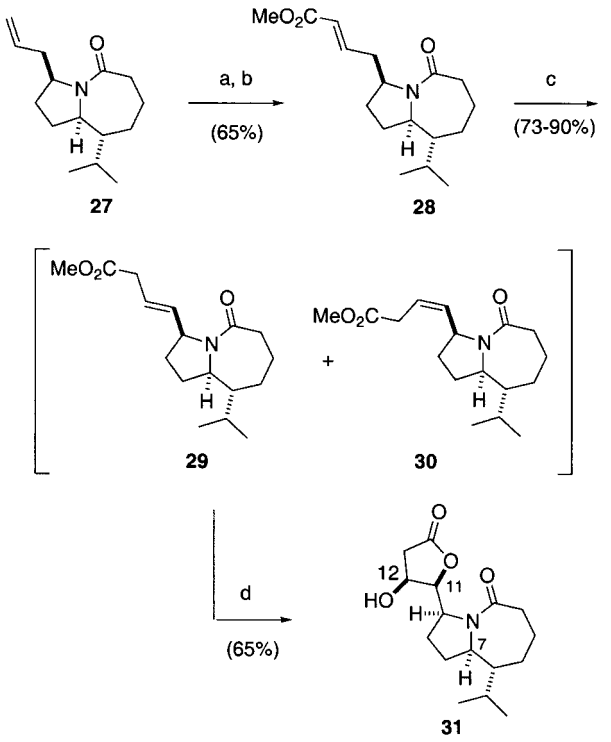
Scheme 8



a. OsO_4, N-methylmorpholine oxide, $NaIO_4$, THF.
b. $MeO_2CCH_2PO_3Me_2$, $KN(SiMe_3)_2$, THF, 18-crown-6.
c. hν, *i*-Pr_2NH, CH_2Cl_2. d. OsO_4, N-methylmorpholine oxide, THF.

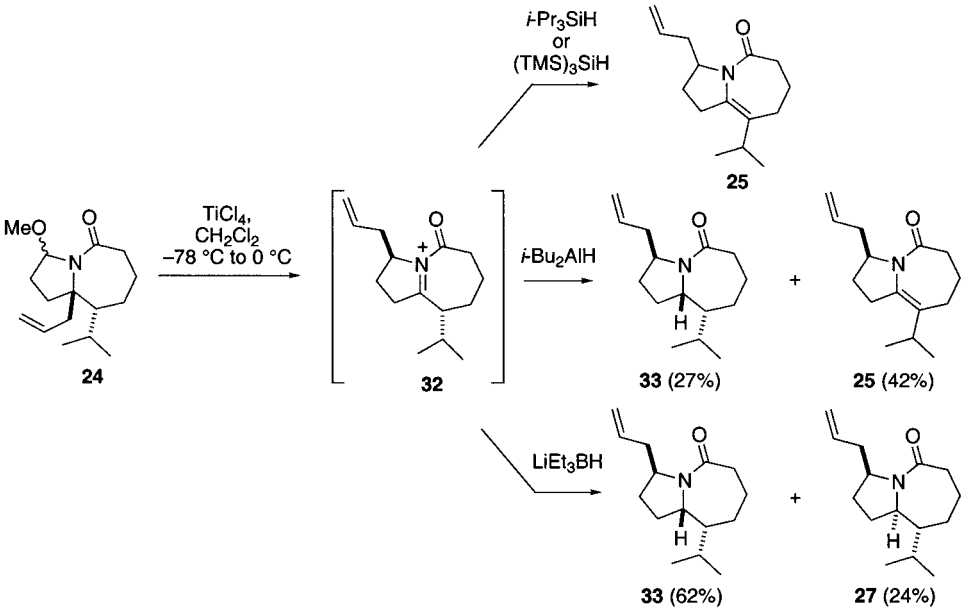
bring about the aza-Cope rearrangement, followed by reduction of the resulting acylimmonium ion with triethylsilane at 0 °C. This process provided a rearranged and reduced product as a single diastereomer in good yield, but later investigations showed that the relative configuration at the ring juncture position is the opposite of what we desired. Surprisingly, reduction of the rearranged acylimmonium ion by triethylsilane in dichloromethane at 0 °C occurred from the face cis to the proximal isopropyl group, providing lactam **27**.

The relative configuration of lactam **27** was only revealed after it had been converted through several additional steps into a later intermediate. Cleavage of the allyl side chain by the Lemeiux−Johnson method[16] gave the corresponding aldehyde, which was condensed with methyl dimethylphosphonoacetate under the conditions of Still and Gennari.[17] This two-step process provided unsaturated ester **28** as a single isomer in 65% yield. Deconjugation of the double bond was accomplished by irradiation in the presence of diisopropylamine.[18] This procedure provided isomers **29** and **30**, somewhat favoring the former isomer. Although, in principle, both isomers could be employed in succeeding reactions, only the major isomer **29** was taken to the next step. Treatment of **29** with catalytic osmium tetroxide in the presence *N*-methylmorpholine oxide gave a diol that spontaneously cyclized to a nicely crystalline hydroxy lactone.[19] Single-crystal X-ray analysis of this material showed it to have structure **31**.

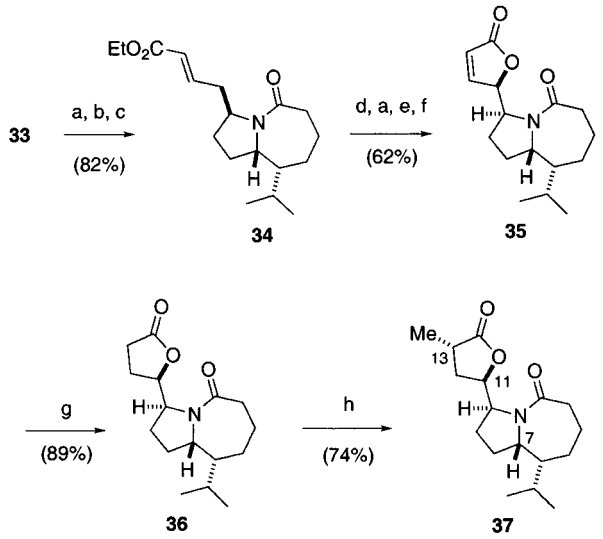
With the full stereostructure of lactone **31** in hand, we could see that two steps in our synthesis had gone completely awry. First, reduction of the *N*-acylimmonium ion resulting from the aza-Cope rearrangement occurred from the face cis to the isopropyl group. Second, osmylation of **29** occurred on the "wrong" face of the double bond. As a result, compound **31** has the incorrect relative configuration at carbons 7 and 11 (the configuration at C12 is irrelevant, as this secondary alcohol was to be dehydrated).

We first turned our attention to the configuration at C7. Methoxylactam **24** was treated with titanium tetrachloride in methylene chloride, first at −78 °C and then at 0 °C. The resulting solution of acylimmonium ion **32** was then treated with various reducing agents. Use of more bulky silanes, triisopropylsilane and tris(trimethylsilyl)silane, gave only the deprotonated enamide **25**. However, diisobutylaluminum hydride gave a mixture consisting of 27% of the desired lactam **33** and 42% of the enamide. Lithium and potassium tri-*sec*-butylborohydrides were also investigated, but both gave mixtures similar to that formed with diisobutylaluminum hydride. Brown and Krishnamurthy have promoted lithium triethylborohydride[20] as a highly nucleophilic reagent.

Scheme 9

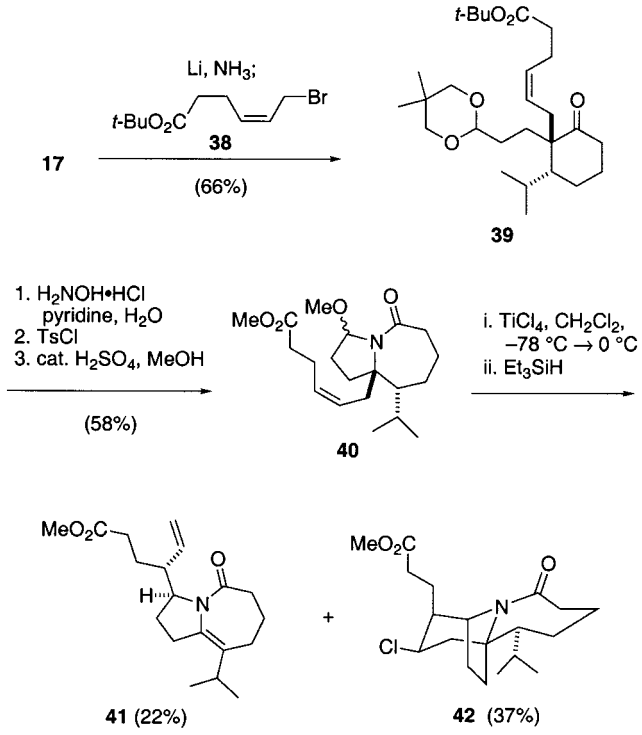


Scheme 10



a. OsO_4, N-methylmorpholine oxide. b. $NaIO_4$, THF. c. $Ph_3P{=}CHCO_2Et$. d. hν, *i*-Pr_2NH, CH_2Cl_2. e. *p*-TsOH, benzene, reflux. f. CH_3SO_2Cl, Et_3N. g. $NiCl_2$, $NaBH_4$. h. LDA, THF, CH_3I.

Scheme 11



Indeed, use of this reducing agent provided the desired stereoisomer **33** in 62% yield, accompanied by 24% of diastereomer **27** and none of enamide **25**. Although this reducing agent still gives a mixture of stereoisomers at C7, isomers **33** and **27** are readily separated by column chromatography.

Compound **33** was elaborated by the route previously developed for isomer **27** (Scheme 10). Cleavage of the double bond by osmium tetroxide dihydroxylation and cleavage of the resulting diol with sodium periodate gave the corresponding aldehyde, which was condensed with ethyl (triphenylphosphoranylidine)acetate to obtain unsaturated ester **34** in good overall yield. Photochemical deconjugation of the double bond gave a mixture of cis and trans β,γ-unsaturated isomers, as before. The mixture was treated successively with osmium tetroxide and then *p*-toluenesulfonic acid in refluxing benzene to cause ring closure to the γ-lactone. Because we had employed both double-bond isomers in the cis-hydroxylation reaction, the hydroxy lactone obtained at this point was a mixture of two diastereomers. However, when this mixture was treated with methanesulfonyl chloride and triethylamine, butenolide **35** was obtained in an overall yield of 62% for the four-step sequence, accompanied by about 8% of another isomer. Reduction of the butenolide double bond was accomplished by treatment with nickel dichloride and sodium borohydride. The resulting saturated γ-lactone was methylated by successive treatment with lithium diisopropylamide and methyl iodide to give crystalline lactone **37** in 74% yield. The structure of **37** was elucidated by single-crystal X-ray analysis.

We carried out a brief exploration of the possibility of carrying out the foregoing process with a more elaborated allyl group to facilitate construction of the butyrolactone ring. To this end, cyclohexenone **17** was subjected to Stork reductive alkylation using allylic bromide **38** to obtain keto ester **39** in 66% yield. This substance was converted into the oxime, which was subjected to Beckmann rearrangement. Treatment of the derived lactam with acidic methanol provided methoxylactam **40** as a mixture of diastereomers. When methoxylactam **40** was treated under the conditions that worked best for rearrangement and subsequent reduction of methoxylactam **24**, we obtained a mixture of two products. The minor product, obtained in 22% yield, was enamide **41**, resulting from rearrangement and subsequent deprotonation of the resulting acylimmonium ion. The major product was a chlorine-containing compound lacking a double bond. Although this unwanted product was not completely characterized, we have tentatively assigned it stucture **42**, the result of cyclization of the initial acylimmonium ion. Because of this discouraging result, we abandoned further work toward using a more highly substituted side chain in the rearrangement.

The work reported herein describes a novel approach to the typical core structure of the *Stemona* alkaloids. As typified in the synthesis of model compound **37**, the approach delivers a material in which four of five stereocenters are properly configured. The configuration at C11 is opposite that found in the *Stemona* alkaloids because of the intrinsic facial selectivity in the cis-dihydroxylation step. However, because the configuration at C11 is *R**, the methylation step (**36** → **37**) delivers the desired configuration at C13, relative to the centers in the 1-azabicyclo[5.3.0]decane moiety. This result offers the possibilities that the route might be employed with

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a suitably constructed analogue of ketone **18** and that the configuration at C11 could be inverted after construction and methylation of the γ-lactone ring.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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