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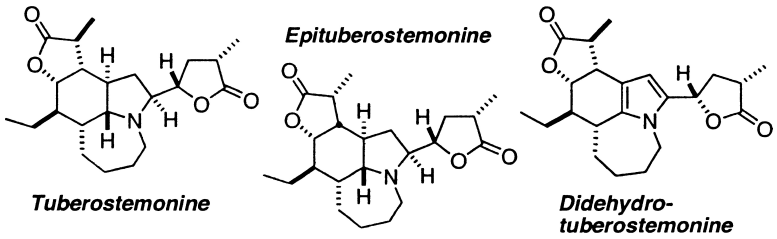

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Asymmetric Total Syntheses of Tuberostemonine, Didehydrotuberostemonine, and 13-Epituberostemonine

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Abstract: Detailed experimental approaches toward the pentacyclic *Stemona* alkaloids tuberostemonine and didehydrotuberostemonine and the close analogue 13-epituberostemonine are described. The syntheses originate with a hydroindolinone derivative that can be obtained on a large scale in a single step from carbobenzoxy-protected L-tyrosine. Highlights of the conversion of this hydroindolinone to the target structures are the three-fold use of ruthenium catalysts, first in azepine ring-closing metathesis and then in alkene isomerization and cross-metathesis propenyl−vinyl exchange, as well as the stereoselective attachment of a γ-butyrolactone ring to a tetracycle core structure by use of a lithiated asymmetric bicyclo-[3.2.1]octane (ABO) ortho ester. Structural analysis by density functional theory (DFT) methods revealed that the ease of oxidation of the natural product is likely due to the conformational preferences of the pyrrolidine and the fused cyclohexane rings.

Introduction

Natural products from *Stemona* and *Croomia* plants have served as inspiration for chemical, biological, and synthetic studies since at least the 1930s, when the first derivatives were described in the western literature.[1−7] Extracts from these plants have been used for centuries in eastern cultures for the treatment of various respiratory problems, such as pertussis, bronchitis, and tuberculosis (Figure 1). However, there is little validated evidence for any beneficial human health effects of the pure compounds, with the exception of insecticidal activities.[6−10] In particular, tuberostemonine was found to have a level of activity as a feeding deterrent that rivaled that of azadirachtin.[11] Since the pioneering total synthesis of croomine in 1989 by Williams et al.,[12] a large number of synthetic studies have showcased contemporary strategies and methodologies in innovative approaches toward these alkaloids.[13−20] Recent noteworthy examples include the total syntheses of stenine,[21−25] stemoamide,[26−30] and stemofoline.[31,32]

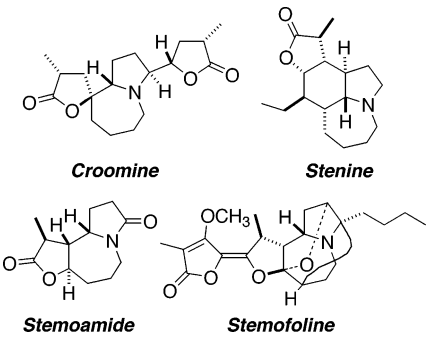

Figure 1. Selected examples of *Stemona* and *Croomia* alkaloids.

In 1934 and in 1936, tuberostemonine was first isolated from *Stemona tuberosa* and *Stemona sessifolia* roots by two separate groups.[33−35] Bond connectivities were determined by Götz's and

(1) Lee, H. M.; Chen, K. K. *J. Am. Pharm. Assoc.* **1940**, *29*, 391.
(2) Edwards, O. E.; Feniak, G.; Handa, K. L. *Can. J. Chem.* **1962**, *40*, 455.
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(17) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587.
(18) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505.
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(22) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.
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(24) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.
(25) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316.
(26) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417.
(27) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356.
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(31) Kende, A. S.; Smalley, T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431.
(32) Brueggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284.

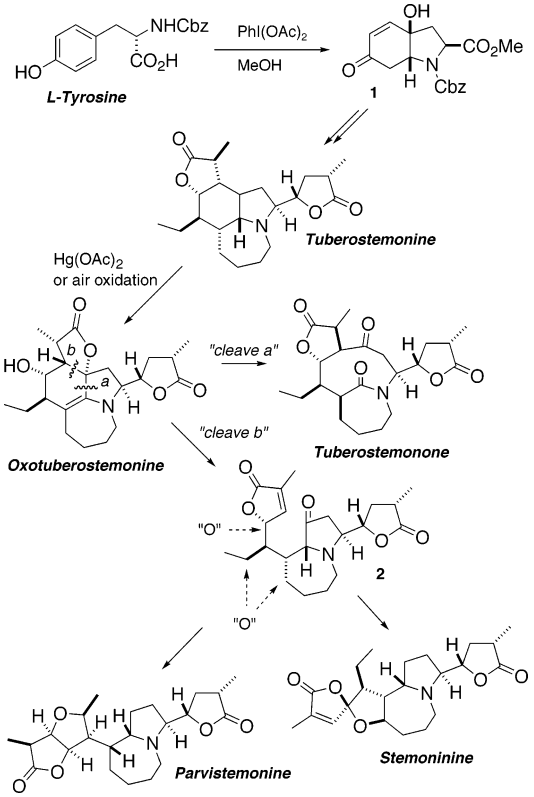

Figure 2. Unified retrosynthetic strategy toward *Stemona* alkaloids.

Feniak's groups in the 1960s,[2,36,37] and the final stereochemical assignment was completed by Uyeo and co-workers in 1967,[38] based on the X-ray structure of tuberostemonine's methobromide salt. In consideration of the years since this structural work has been published, it is not surprising that reliable high-resolution spectroscopic data for tuberostemonine are absent from the literature. A few chemical shifts were reported from a 60 MHz ^{1}H NMR taken in the 1960s.[39] An optical rotation and mass spectral data have been published more recently,[4] but no ^{13}C NMR spectrum nor a complete listing of the ^{1}H NMR chemical shifts has been reported.[2] This dearth of spectroscopic data added to the challenge of the total synthesis of tuberostemonine in that it necessitated a rigorous proof of the connectivity and stereochemistry of the, at least in small quantities, unusually labile final product.

In our studies toward the *Stemona* alkaloids, we envisioned a unified approach toward the major structural classes represented by tuberostemonine, tuberostemonone, and parvistemonine from the readily available amino acid L-tyrosine by a series of oxidative cyclizations and bond cleavage reactions (Figure 2). Specifically, hypervalent iodine oxidation of L-tyrosine led to the bicyclic *cis*-indolinone **1**,[40−43] which provided the core

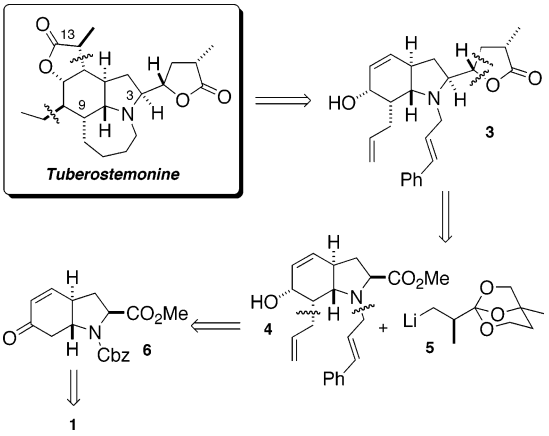

Figure 3. Retrosynthetic approach toward (−)-tuberostemonine.

skeleton of the target molecule. Upon air or Hg(II) oxidation of tuberostemonine, oxotuberostemonine can be isolated,[2] and hypothetical but straightforward further C−C bond cleavage reactions provide access to tuberostemonone as well as the key intermediate **2**. Strategic oxygenations of **2** followed by intramolecular condensation reactions are envisioned to result in the polycyclic scaffolds of stemoninine and parvistemonine.

We have recently completed the first total synthesis of (−)-tuberostemonine.[44] In contrast to our earlier approach toward (−)-stenine,[22] we planned for improved C(9)-chain extension and azepine ring formation steps by the use of allylic electrophiles for C- and N-alkylation, followed by a ring-closing metathesis (RCM) reaction. Since the C(3)-butyrolactone is not present in stenine, we also needed to devise an efficient protocol for the installment of this moiety, which we decided to accomplish with our fully protected homoenolate reagent **5** (Figure 3). The plan for the introduction of the remaining fused butyrolactone and the ethyl side chain was to follow the stenine precedence, i.e., use an amide acetal Claisen rearrangement of the allylic alcohol in **3**, followed by iodolactonization and Keck allylation. Since the tyrosine carboxylate provides an ideal handle for the introduction of the C(3)-butyrolactone and the RCM was well precedented for azepine formation,[45] we expected a successful realization of this retrosynthetic strategy toward (−)-tuberostemonine in about the same number of steps (26) that were necessary for (−)-stenine.

Results and Discussion

Synthesis of the Hydroindole Core of Tuberostemonine. One of the key transformations in our synthetic strategy toward the *Stemona* alkaloids is the oxidative spirocyclization of L-tyrosine.[43b] In the past, the scalability of this reaction has been limited when methanol was used as both the solvent and the nucleophile to open up the intermediate spirocycle generated by the phenolic oxidation of **7** with iodobenzene diacetate. Because the phenolic oxidation is an intramolecular cyclization, it works best under dilute conditions. The highest yield (54%) of **1** was obtained on a 500 mg scale with an optimum concentration of 0.08 M (Scheme 1). A screen of polar solvents (CF_3CH_2OH, CH_2Cl_2, $MeNO_2$, etc.) revealed that nitromethane was best suited for larger scale reactions (100 g) at higher

(33) Suzuki, K. *J. Pharm. Soc. Jpn.* **1934**, *54*, 573.
(34) Kondo, H.; Suzuki, K.; Satomi, M. *J. Pharm. Soc. Jpn.***1939**, *59*, 443.
(35) Schild, H. *Ber. Dtsch. Chem. Ges.* **1936**, *69B*, 74.
(36) Goetz, M.; Boegri, T.; Gray, A. H.; Strunz, G. M. *Tetrahedron* **1968**, *24*, 2631.
(37) Edwards, O. E.; Feniak, G. *Can. J. Chem.* **1962**, *40*, 2416.
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(40) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.
(41) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.
(42) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.
(43) (a) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (b) For a review on oxidative spirocyclizations, see Rodriguez, S.; Wipf, P. *Synthesis* **2004**, 2767.
(44) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848.
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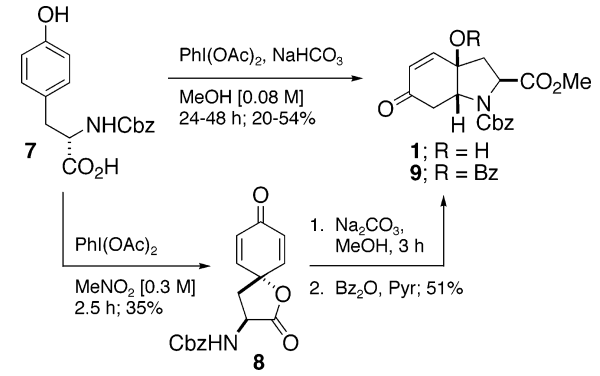
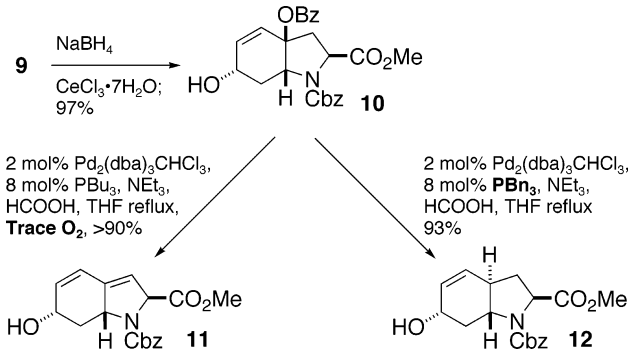
Scheme 1. Optimization of the Oxidative Spirocyclization of l-Tyrosine



Scheme 2. Optimization of the π-Allylpalladium Reduction Sequence

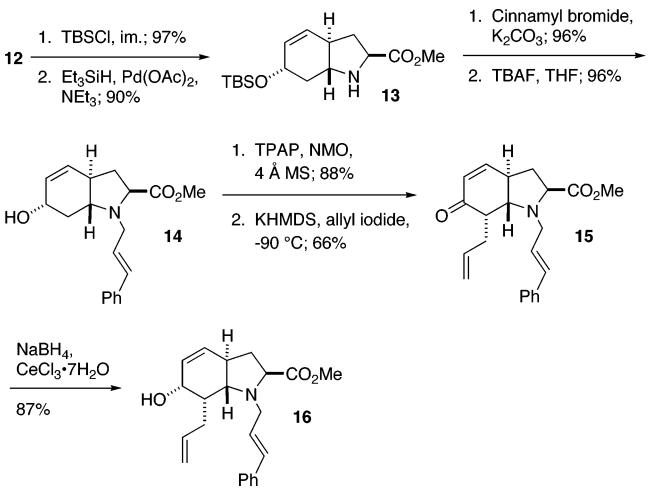


concentrations (0.3 M). The O-benzoylated bicycle **9** was obtained in 51% yield from the intermediate spirocycle **8**.

Ketone **9** was reduced to the equatorial alcohol **10** under Luche conditions.[46] Due to the extraordinary air sensitivity of the palladium-catalyzed allylic reduction[47] of the benzoate, freeze−pump−thawing of the solvent and highest quality tributylphosphine were necessary to avoid quantitative formation of the undesired elimination side product **11** (Scheme 2). A surprisingly simple solution to this experimental problem was identified by replacing tributylphosphine with the more stable, crystalline tribenzylphosphine. The reaction no longer required vigorous degassing and has successfully been performed on batches as large as 47 g with no noticeable decrease in yield.

First-Generation Approach toward Tuberostemonine. The optimized sequence shown in Schemes 1 and 2 provided access to large quantities of bicycle **12**. The allylic alcohol was protected as the silyl ether, and the benzyl carbamate was removed under catalytic palladium(II) acetate/triethylsilane hydrogenolysis conditions.[48] This method allowed selective cleavage of the carbobenzoxy (Cbz) group in the presence of the alkene and provided amine **13** in 87% yield over two steps (Scheme 3). The cinnamyl group was installed on the secondary nitrogen by use of K_2CO_3 in toluene, and the silyl ether was removed with tetrabutylammonium fluoride. A cinnamyl group was chosen instead of an unsubstituted allyl group in order to direct the initial ruthenium attack in the metathesis reaction toward the C-allyl group. It was reasoned that this strategy would allow a greater number and faster frequency of turnover in the catalytic

Scheme 3. Double Allylation of Bicycle **12**



cycle of the ruthenium carbene reagent and also protect the amine from being deallylated under the reaction conditions. Grubbs catalyst has been shown to remove allyl groups from tertiary amines if the ring-closing metathesis reaction is comparatively slow.[49]

The resulting alcohol **14** was oxidized under catalytic tetrapropylammonium perruthenate/4-methylmorpholine *N*-oxide (TPAP/NMO) conditions[50] to give the enone in 88% yield (Scheme 3). On large scale, the Parikh−Doering protocol[51] with sulfur trioxide−pyridine complex in the presence of triethylamine and dimethyl sulfoxide (DMSO) was slightly superior for the oxidation of this alcohol. The enone was allylated under low-temperature potassium bis(trimethylsilyl)amide (KHMDS) conditions (−90 °C) in the presence of excess allyl iodide to give **15** as the only detectable diastereomer in 66% yield. The enone carbonyl group was subsequently reduced under Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) to generate allylic alcohol **16** in good yield.

In preparation for the introduction of the C(3)-butyrolactone, alcohol **16** was converted into the rearranged dimethylamide under standard Eschenmoser−Claisen conditions.[52] The methyl ester was converted into the Weinreb amide derivative **17** by use of dimethylaluminum chloride and *N*,*O*-hydroxylamine hydrochloride.[53] In contrast to the usual reactivity pattern,[54] the dimethylamide proved to be more reactive to nucleophilic addition than the Weinreb hydroxamate (Scheme 4). Bromide **18** was readily prepared in high overall yield from the commercially available methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate and converted to the alkyllithium derivative with lithium naphthalenide.[55,56] Upon in situ addition of the amide **17**, the undesired ketone **19** was formed as the major product.

After a series of related nucleophilic additions, it became clear that the dimethylamide in **17** was a generally more reactive electrophile than the hydroxamate carbonyl function, and therefore the synthetic plan was modified and the sequence of

(46) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
(47) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326.
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(50) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.
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(52) Wipf, P. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 827−74.
(53) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
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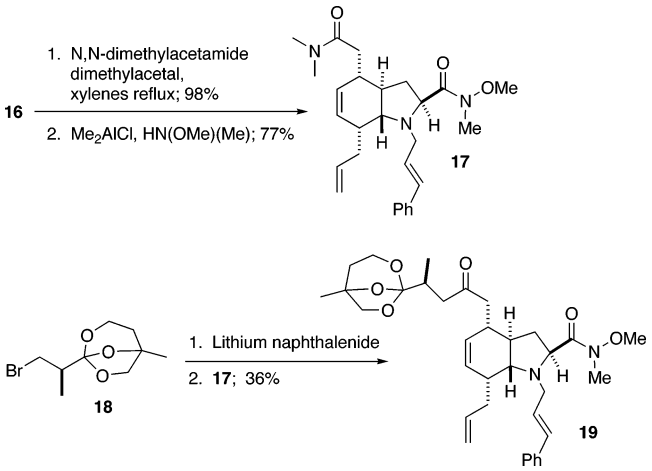
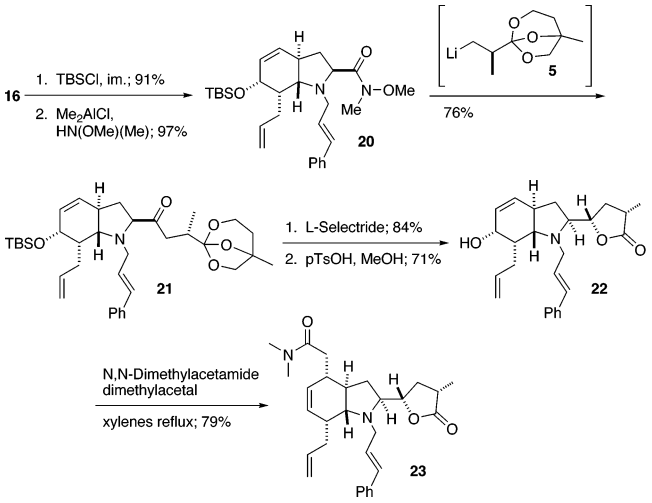
(55) Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575.
(56) Wipf, P.; Tsuchimoto, T.; Takahashi, H. *Pure Appl. Chem.* **1999**, *71*, 415.

Scheme 4. Unexpected Reactivity of Dimethylamide **17**



Scheme 5. Modified Synthetic Approach to the C(3)-Butyrolactone



Claisen rearrangement and nucleophilic ortho ester addition was reversed. After silylation of **16**, the corresponding Weinreb amide **20** indeed underwent anionic ortho ester addition in 76% yield (Scheme 5). Reduction of ketone **21** with L-Selectride led to a chelation-controlled 6−7:1 diastereomeric ratio of alcohols that were subjected to ortho ester hydrolysis with TsOH in MeOH. Under these conditions, the alcohol spontaneously cyclized to form the lactone. TsOH also removed the silyl ether protecting group from the allylic alcohol in preparation for the Eschenmoser−Claisen rearrangement. Heating of substrate **22** in xylenes in the presence of *N*,*N*-dimethylacetamide dimethylacetal provided the desired dimethylamide **23** in 79% yield.

With the tricyclic dimethylamide **23** in hand, the stage was set for the formation of the remaining two rings in tuberostemonine. However, amide **23** was found to decompose upon exposure to a diverse set of lactonization conditions, including iodolactonization with buffered I_2 or NIS, bromolactonization, and selenolactonization. The decomposition products showed the loss of some of the ^{1}H NMR alkene signals, but the spectra also showed that the dimethylamide moiety was still present and presumably had not participated in the reaction. We speculated that the failed lactonization might be due to the presence of three reactive double bonds in the substrate. Therefore, the ring-closing metathesis reaction[57] was performed

(57) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

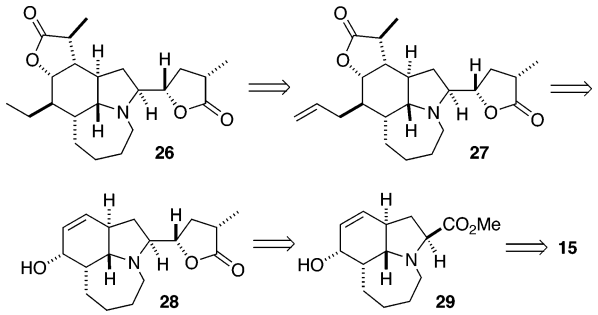
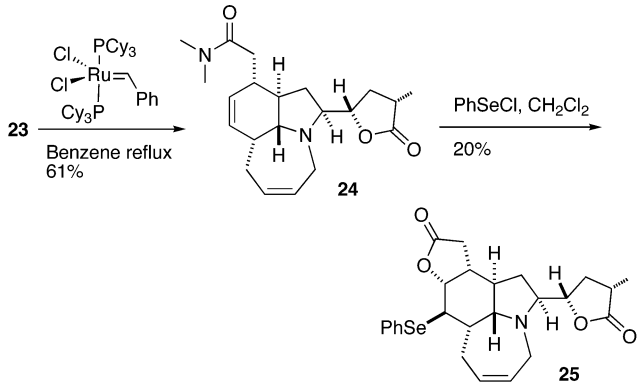


Figure 4. Second-generation retrosynthetic analysis of (−)-tuberostemonine.

Scheme 6. Low-Yielding Selenolactonization of a Tetracyclic Intermediate



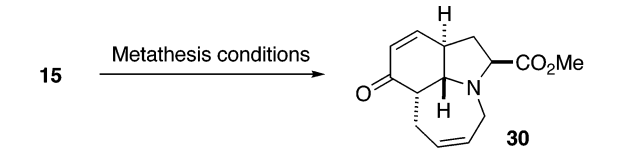
prior to the lactonization step to give tetracycle **24** in moderate yield, but lactonizations failed on this substrate as well (Scheme 6). Only the less oxidizing conditions of a selenolactonization[58] provided an identifiable product, but the yield could not be improved above 20%.

Second-Generation Approach toward Tuberostemonine. The remaining double bond in the azepine ring of **24** provided a likely reason for the lack of success in the lactonization studies, but since a regioselective hydrogenation of **24** failed, a modified retrosynthetic approach was pursued next (Figure 4). The end game still envisioned conversion of an allyl group to the ethyl group and preparation of the allyl lactone from a halolactone. However, the halolactonization would now be performed on a dimethylamide intermediate resulting from **28**, with only one alkene remaining in the substrate. Ortho ester addition was staged on an activated ester derived from tricycle **29**, which could originate from the earlier intermediate **15** by means of an RCM reaction.

The ring-closing metathesis reaction of **15** initially utilized Grubbs' first-generation catalyst.[59] While the reaction proceeded in the presence of high loadings of this catalyst, it stopped at about 50% completion. With the second-generation, dihydroimidazole-containing catalyst **32**,[60] in contrast, the reaction proceeded very smoothly in 2−2.5 h with as little as 2 mol % catalyst loading (Figure 5).

Differentiation of the two alkene moieties in **30** was surprisingly difficult. The usual selective hydrogenation conditions, that is, Wilkinson's catalyst, diimide reductions, hydroborations, etc.,[61] failed to achieve differentiation. Even though the enone

(58) Petragnani, N.; Stefani, H. A.; Valduega, C. J. *Tetrahedron* **2001**, *57*, 1411.
(59) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.
(60) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.



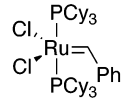
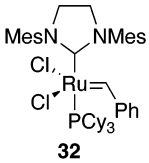
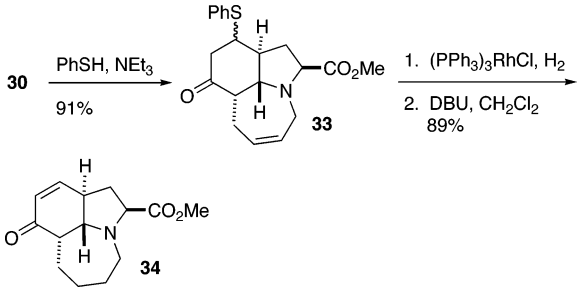
Catalyst	Loading	Time	Yield
 **31**	5 x 4 mol% 20 mol% total	52 h	46% +20% **15**
 **32**	5 mol%	2 h	92%
32	2 mol%	2.5 h	87%

Figure 5. Catalyst dependency of the metathesis of **15**.

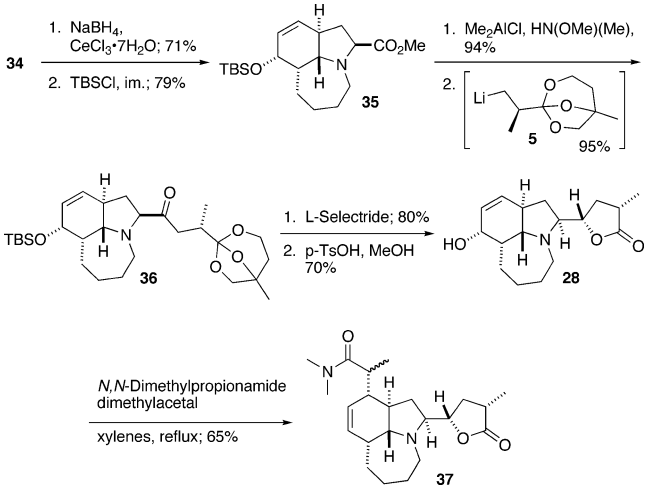
Scheme 7. Selective Alkene Reduction Strategy



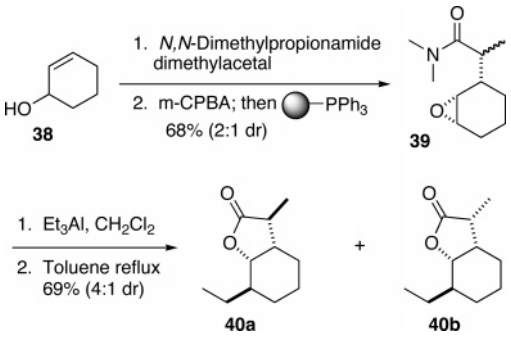
was much less electron-rich than the azepine alkene, the former was sterically very accessible even to bulky hydrogen sources. In general, mixtures of starting material, monohydrogenation at each site, and dihydrogenation products were all observed in the crude reaction mixtures. Finally, a method that proceeded with excellent selectivity and 81% yield over three steps was identified (Scheme 7). Protection of the enone as the thiophenol adduct,[62] hydrogenation of the azepine olefin by homogeneous catalysis, and then elimination of thiophenol with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to regenerate the enone[63] provided an overall yield comparable to or higher than what could have been expected from a one-step procedure.

Most of the steps in the conversion of **34** to the tetracycle **37** proceeded analogously to the first-generation approach (Scheme 8). Luche reduction of the ketone and protection of the equatorial alcohol as the TBS ether provided **35** as a single isomer. The ester functionality was then converted into the Weinreb amide in 94% yield, followed by the addition of the lithiated ortho ester. With this substrate, it was beneficial to use lithium di-*tert*-butylbiphenylide[64] as the radical anion source for the lithium−halogen exchange, resulting in a 95% yield of ketone **36**. Under the standard lithium naphthalenide conditions, only low yields (ca. 25%) of this ketone were obtained, along with

Scheme 8. Conversion of Enone **34** into Tetracyclic Amide **37**



Scheme 9. Model Epoxidation−Ethylation Sequence



a significant amount of product that appeared to result from naphthalene addition to the substrate.

Ketone **36** was reduced with L-Selectride to give two diastereomeric alcohols in a 7:1 ratio that were cyclized with TsOH in methanol. The desired lactone **28** derived from the major alcohol diastereomer was obtained in 57% yield over the two steps. A small amount (10%) of the lactone derived from the minor alcohol diastereomer was also isolated after methanolysis. To avoid a late-stage regioselective α-methylation of the fused butyrolactone, *N*,*N*-dimethylpropionamide dimethylacetal was employed in the subsequent Eschenmoser−Claisen rearrangement. This transformation succeeded but, as expected, gave almost no diastereoselectivity (ca. 1.2:1) at the methylated carbon. Moreover, separation of these epimers was not yet possible at this stage in the synthesis.

Monoalkene **37** provided us with the opportunity to investigate an alternative strategy for the formation of the fused butyrolactone ring and the introduction of the characteristic ethyl side chain of *Stemona* alkaloids. The iodolactonization−allylation approach pioneered by Hart and Chen[21] in their synthesis of (±)-stenine was very effective in the stereoselective formation of the desired C−C and C−O bonds but suffered from the need to remove an extra methylene group at the end of the synthesis. An alternative epoxidation−nucleophilic ring-opening process could reduce the number of steps and streamline the end game. This modification in the route was tested on model system **38** (Scheme 9). Epoxidation with 3-chloroperoxybenzoic acid (*m*-CPBA) was directed to the α-face of the cyclohexene ring by the dimethylamide. In the workup of this reaction, a polymer-supported triphenylphosphine was used in

(61) (a) Tucker, C. E.; Rao, S. A.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 5446. (b) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684. (c) Dirat, O.; Kouklovsky, C.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 6634.
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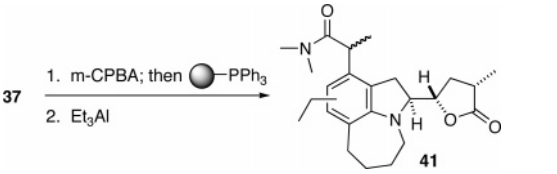
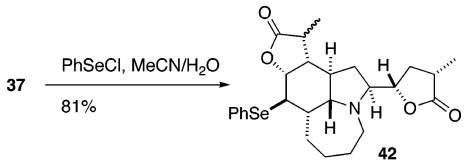
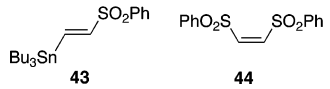
(63) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757.
(64) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

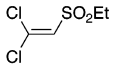
Scheme 10. Attempted Epoxide-Based Butyrolactone Annulation of **37**



Scheme 11. Selenolactonization of **37** and Selected Two-Carbon Radical Trapping Agents





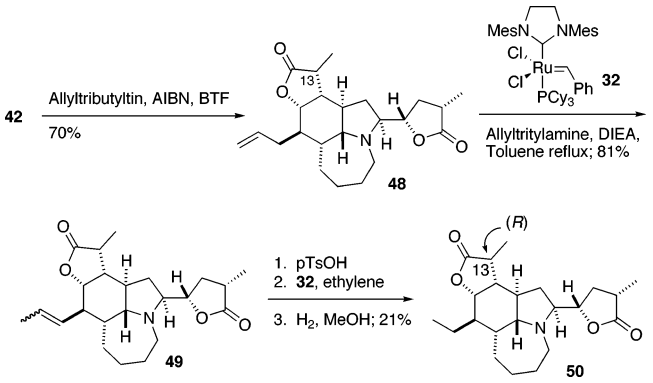


order to test the feasibility of avoiding the use of thiosulfate with the tuberostemonine precursors. The 2:1 diastereomeric mixture of epoxides was subsequently opened with 2 equiv of triethylaluminum.[65] The crude reaction mixture was heated overnight at reflux in toluene, and a 69% yield of the diasteromeric lactones **40a** and **40b** was recovered. The improved diastereoselectivity (4:1) revealed that the α-methyl isomer either closed more slowly or was epimerized to the *β*-isomer under these reaction conditions.

Encouraged by the success of this model study, we attempted an analogous conversion of alkene **37** (Scheme 10). However, sequential exposure of **37** to *m*-CPBA, triphenylphosphine workup, and then triethylaluminum led to the aromatized compound **41** as the only identifiable product. The exact regiochemistry of the ethyl substituent was not determined.

The sensitivity of **37** toward oxidation became fully apparent when conditions for halolactonization were examined. A range of conditions that had been successful on less substituted intermediates led to decomposition similar to what had been observed with **24**. Fortunately, however, the milder PhSeCl in a mixture of acetonitrile and water provided a good yield of the selenolactone product **42** (Scheme 11). To avoid the anticipated major decomposition in the oxidative conversion of the allyl side chain to the ethyl group,[21,22] we explored a number of two-carbon radical trapping agents known in the literature.[66] Attention was focused on reagents that would lead to vinyl sulfones, which could be cleaved with Raney nickel, or vinyl halides or triple bonds, which could be reduced to the desired ethyl substituent. However, only trace amounts of desired product were identified in the presence of **43**−**47**. The major

Scheme 12. Keck Allylation of **42** and Metathesis Strategy for Allyl−Ethyl Side-Chain Conversion



isolated products from these reactions were either recovered starting material or the products resulting from elimination of phenylselenide.

Since a two-carbon chain extension protocol remained elusive, allylation presented the sole viable alternative. Allylstannanes are much more reactive radical trapping agents than the vinyl or acetylenic compounds **43**−**47**,[67] but the lack of reactivity of selenide **42** and the apparent ease of the resulting radical to undergo a 1,2-acyloxy rearrangement[68] required the use of a large excess of the stannane. AIBN and a 1:1 mixture of allyltributyltin and trifluorotoluene (BTF) as the solvent provided the desired alkene **48** in 70% yield as a mixture of C(13)-epimers (Scheme 12). The cosolvent BTF was necessary because the polar tertiary amine was not soluble in neat allyltributyltin, and the more common solvents toluene and CCl_4 gave even lower conversions.

Tetracyclic amide **37** was formed as an approximately 1.2:1 mixture of methyl isomers. As the synthesis progressed, the minor isomer was slowly consumed. After the selenolactonization, the ratio changed to approximately 2−3:1. The isomers were separable after the Keck allylation, but the minor isomer could never be isolated cleanly and proved to be quite unstable. The major, more polar, isomer was isolated in 43% yield after Keck allylation, and so this compound was carried on through the rest of the sequence. The remaining task was to convert the allyl side chain of **48** into the ethyl group of tuberostemonine. Oxidative methods (osmium tetroxide/sodium periodate or osmium tetroxide/NMO or ozonolysis) led to extensive decomposition of **48**. It became clear that a nonoxidative protocol for the cleavage of the C−C bond and the conversion of the allyl into the ethyl substituent had to be identified. We speculated that this could be accomplished by selective isomerization of the terminal to the internal alkene followed by a cross-metathesis reaction with ethylene gas. This would generate a vinyl group that could be hydrogenated to give the desired ethyl chain. Test reactions on a simplified model system revealed that $RhCl_3$[69] was the only catalyst that isomerized the olefin fairly well at room temperature, but only Wilkinson's catalyst[70] and conditions with Grubbs' catalyst **32** that had been reported for the

(65) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999.
(66) (a) Keck, G. E.; Byers, J. H.; Tafesh, A. M. *J. Org. Chem.* **1988**, *53*, 1127. (b) Cossu, S.; DeLucchi, O.; Durr, R.; Fabris, F. *Synth. Commun.* **1996**, *26*, 211. (c) Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741. (d) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943. (e) Xiang, J.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 8597.
(67) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
(68) Crich, D.; Huang, X.; Beckwith, A. L. J. *J. Org. Chem.* **1999**, *64*, 1762.
(69) Nakamura, H.; Arata, K.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2435.
(70) Warmerdam, E.; Tranoy, I.; Renoux, B.; Gesson, J.-P. *Tetrahedron Lett.* **1998**, *39*, 8077.

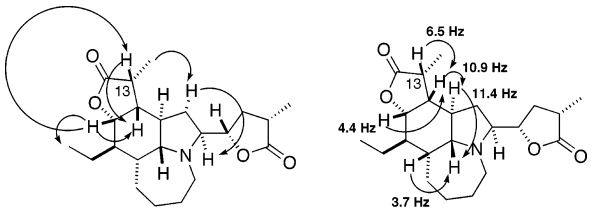


Figure 6. NOESY and coupling constant analysis support the assignment of the (*R*)-stereochemistry at C(13) of **50**.

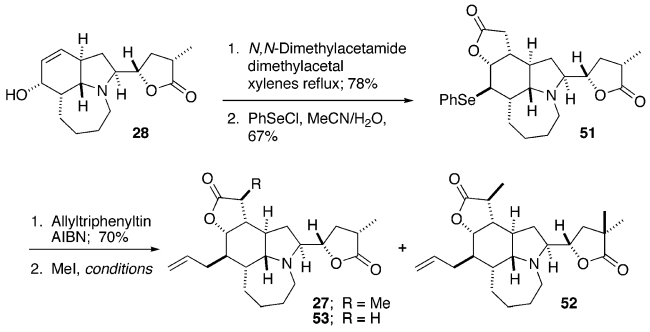
isomerization of allyl ethers[71] worked well in the presence of a tertiary amine. Since **32** was found to be compatible with the advanced intermediate **24**, we selected this catalyst for both isomerization of **48** and subsequent in situ cross metathesis/hydrogenation.[72] Internal alkene **49** was obtained in 81% yield (Scheme 12).

The tertiary amine/metal incompatibility also became an issue during the optimization of the cross-metathesis reaction on compound **49**. At first, use of a variety of different metathesis catalysts, long reaction times, and continuous bubbling of ethylene gas in methylene chloride and/or toluene at various temperatures failed to give any of the desired vinyl compound. Finally, upon protecting the basic amine as the tosylate salt and using the second-generation Grubbs' catalyst **32**, a modest amount of cross-metathesis product was obtained. The reaction was quite sluggish (78 h), and it worked best if fresh catalyst was added approximately every 12 h during the course of the reaction. The ethylene gas was replaced by a hydrogen atmosphere and the vinyl compound was hydrogenated to give the final product **50** in a modest 21% overall yield. While this sequence completed the assembly of the carbon and heteroatom scaffold of tuberostemonine, ^{1}H−^{1}H correlation spectroscopy (COSY), ^{1}H−^{13}C heteronuclear multiple quantum coherence spectroscopy (HMQC), heteronuclear multiple bond correlation (HMBC), nuclear Overhauser effect spectroscopy (NOESY), and *J*-data revealed that the configuration at C(13) was (*R*), i.e., epimeric to the natural product (Figure 6).

It should be noted that attempts were made to develop conditions for a sequential one-pot isomerization, cross-metathesis, and hydrogenation, but these were not successful. Treating **48** with Grubbs' catalyst **32** in the presence of ethylene gas led to isolation of the isomerized compound **49** and some dimerized compound resulting from cross-metathesis of the starting material **48**. Ethylene was never incorporated in the product(s). The allyltritylamine additive, which was necessary for high conversion to the isomerized compound, inhibited not only the dimerization cross-metathesis pathway but also any cross-metathesis with ethylene when used in one-pot reaction trials.

Completion of the Total Synthesis of Tuberostemonine. The formation of 13-epituberosteminine **50** raised serious concerns about the feasibility of our route, since the diastereomer of intermediate **37** with the natural configuration at C(13) was gradually lost due to instability in the subsequent conversions. Accordingly, we decided to introduce the C(13) stereocenter after the Claisen rearrangement−lactonization sequence (Scheme 13). Allylic alcohol **28** was subjected to the standard Eschenmoser−Claisen rearrangement with the acetamide acetal, and selenolactonization of the resulting dimethylamide provided the fused lactone **51**. Keck allylation of this substrate proved once again to be cumbersome. Under the conditions used earlier (allyltributyltin, BTF, AIBN), a 1:1 mixture of the desired product and some unidentified, less-polar compound was obtained. We suspected that the latter compound contained a six-membered bridged lactone that arose from a radical shift or rearrangement,[73] a side reaction that should be diminished by maximizing the concentration of the radical-trapping agent. Poor results resulted when the reaction was performed in neat allyltributyltin, but reasonable yields (70%) were obtained with neat allyltriphenyltin.

Scheme 13. Stereo- and Regioselective Lactone Methylation



Conditions	**27**	**52**	**53**
LDA/HMPA (excess)	0%	76%	0%
LDA/HMPA (1.3 eq)	51%	38%	0%
LDA/HMPA (1.1 eq)	59%	11%	22%
LDA/HMPA (1.0 eq)	48%	<10%	35%
LiTMP (2 eq)	41%	20%	0%
LiHMDS (1.5 eq)	<10%	58%	0%
LDA (1.2 eq)	37%	0%	40%

At this stage, the introduction of the methyl substituent by use of lithium diisopropylamide (LDA)/hexamethylphosphoramide (HMPA) conditions was envisioned to lead to the desired stereoisomer by preferential exo-attack of methyl iodide. In the presence of excess LDA/HMPA, a 76% yield of the dimethylated compound **52** was isolated. The use of bulkier (LiTMP) or less reactive bases (LiHMDS or LDA without HMPA) did not provide good yields of the desired monomethylated product **27**. Dimethylation was still a major side reaction if excess base was used. In the presence of 1.1 equiv of the LDA/HMPA complex, however, a 59% yield of **27** along with 11% of the dimethylated product **52** and 22% of recovered starting material **53** were isolated.

When **27** was exposed to alkene isomerization conditions in toluene at reflux, a moderate yield (40−50%) of the desired isomerized compound **54** was obtained. This yield could be significantly improved (85%) by lowering the reaction temperature and using methylene chloride instead of toluene (Scheme 14). Due to the instability of this isomer observed in the C(13)-epituberostemonine synthesis, it is likely that the higher reaction temperature was causing decomposition at a much faster rate.

The conditions used previously in the cross-metathesis reaction were also successful in this case, but it was found that

(71) Hu, Y.-J.; Dominique, R.; Das, K. S.; Roy, R. *Can. J. Chem.* **2000**, *78*, 838.
(72) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.
(73) (a) Crich, D.; Beckwith, A. L.; Filzen, G. F.; Longmore, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 7422. (b) Crich, D.; Huang, X.; Beckwith, A. L. J. *J. Org. Chem.* **1999**, *64*, 1762.

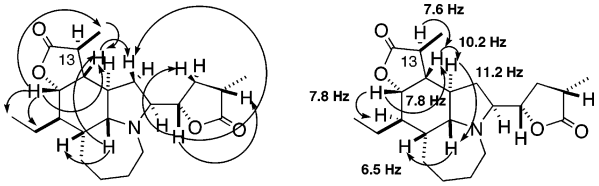
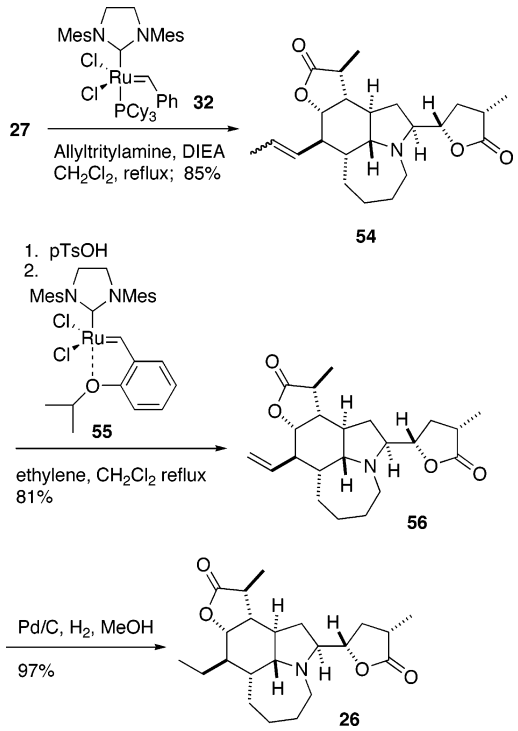


Figure 7. NOESY and coupling constant analysis support the assignment of the natural (*S*)-stereochemistry at C(13) of **26**.

Scheme 14. Completion of the Total Synthesis of (−)-Tuberostemonine



catalyst **55**, reported by both Blechert and Hoveyda,[74] gave a slightly better yield. More importantly, the use of this catalyst allowed isolation of the terminal alkene intermediate without multiple chromatographic purifications. Use of the tricyclohexylphosphine-containing catalyst **32** caused significant decomposition during the extensive purifications needed to remove all of the ruthenium and phosphine oxide side products either at this stage or after the final hydrogenation. Catalyst **55** helped to avoid this serious obstacle by facilitating workup. Because of the consistently observed chromatography problems with these late-stage intermediates, a separate hydrogenation step was selected. Catalytic palladium on carbon in the presence of 1 atm of hydrogen allowed for the isolation and characterization of tuberostemonine (**26**) without the need for any additional chromatographic purifications. The methanol solution from the hydrogenation step was simply filtered through Celite, and NMR data were obtained immediately upon concentration. Attempts to further purify this compound by silica gel chromatography or recrystallization resulted in substantial contamination of the sample with decomposed (mostly oxidized) impurities.

Extensive 2D NMR analyses, including NOESY and *J*-determinations, confirmed the assignment of the synthetic material (Figure 7). Significantly, the C(13) methyl group showed strong correlations to the C-11 and C-12 β-hydrogens.

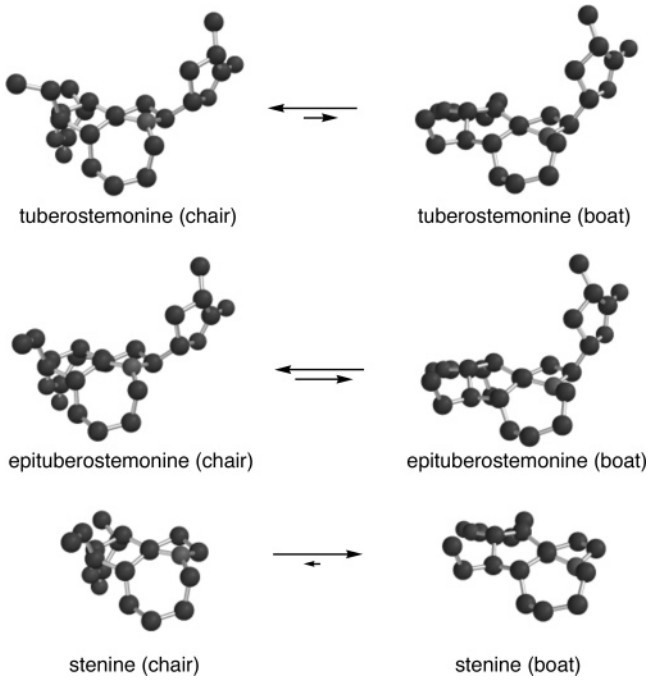


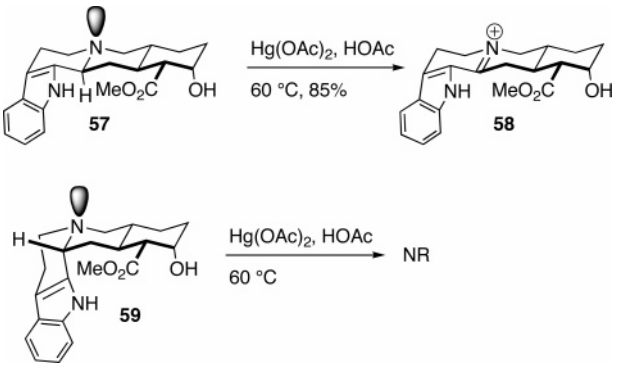
Figure 8. DFT [B3LYP6-31+g(d), MacGaussian] minimized low-energy conformations.

It is interesting to consider possible reasons for the unusually high rate of decomposition of tuberostemonine **26** vs the less labile C(13)-epimer **50** and, in particular, the closely related alkaloid stenine. Synthetic stenine that was obtained in 1995[22] and stored neat under air for 8 years did not show any signs of decomposition, whereas tuberostemonine decayed within hours. Epituberostemonine **50** decomposed more slowly than tuberostemonine, with a half-life of days vs hours, and was considerably more resistant to chromatography on silica gel. We hypothesize that these dramatically different chemical properties derive from different spatial dispositions of the nitrogen lone pair in these alkaloids. The chairlike six-membered ring of tuberostemonine forces an anti orientation of the nitrogen lone pair and the methine hydrogen at C(3) (Figure 8). The preference for the chairlike conformation of **26** is confirmed by the solid-state structure of this compound.[38] For 13-epituberostemonine **50**, the energy difference between the six-membered ring chair and twist-boat conformations is small (<2 kcal/mol), based on density functional theory (DFT) calculations. The twist-boat conformation of the cyclohexane moiety results in a syn orientation of lone pair and C(3) methine hydrogen. Stenine has a less oxidation-prone methylene group at this position and a very significant preference (>4 kcal/mol, DFT) for the twist-boat cyclohexane conformation. The strong influence of conformational properties on the rate of oxidation α to a tertiary nitrogen atom is nicely precedented in the chemistry of Rauwolfia alkaloids (Scheme 15). Oxidation of the anti isomer **57** to iminium ion **58** proceeded in 85% yield, whereas exposure of the syn isomer **59** yielded no reaction.[75,76] It is possible that the high reactivity of natural tuberostemonine toward oxidation

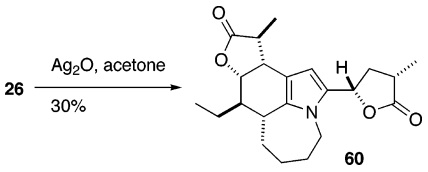
(74) (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(75) Weisenborn, F. L.; Diassi, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 2022.
(76) For conformational effects in alkaloid oxidations, see also Suau, R.; Silva, M. V.; Valpuesta, M. *Tetrahedron* **1991**, *47*, 5841.

Scheme 15. Conformation-Dependent Oxidation of Tertiary Amines Observed in the Conversion of Isoreserpine to Reserpine



Scheme 16. Conversion of Tuberostemonine (**26**) to Didehydrotuberostemonine (**60**)



at the pyrrolidine ring is important for the biological function of this compound.

Conversion of Tuberostemonine (26) to Didehydrotuberostemonine (60). Natural tuberostemonine was converted to its pyrrole derivative, didehydrotuberostemonine, through oxidation of the natural product with silver(I) oxide.[4] This compound has also been isolated from *Stemona tuberosa*,[77,78] and high-field NMR data have recently been reported.[77] Since very little spectral data had been published on natural tuberostemonine, a small amount of the synthetic material was converted to didehydrotuberostemonine to allow spectral comparisons. Synthetic **26**, which unfortunately had already become strongly contaminated with decomposition products, was subjected to silver(I) oxide and provided ca. 30% of a pyrrole product with NMR signals consistent with didehydrotuberostemonine (**60**). This conversion established the first total synthesis of this pyrrole and provided a chemical confirmation of the assignment of the synthetic material as (−)-tuberostemonine (Scheme 16).

Conclusions

The first total synthesis of the *Stemona* alkaloid tuberostemonine has been achieved in 27 steps and ca. 1% overall yield from Cbz-L-tyrosine. Highlights of the synthesis include the use of a ruthenium carbene catalyst for three different key transformations: a ring-closing metathesis reaction, a double-bond isomerization, and a cross-metathesis reaction. The power of the ABO ortho ester chemistry as a homoenolate equivalent to install a chiral γ-butyrolactone moiety on a structurally complex substrate has been showcased. The utility of the oxidative cyclization reaction of Cbz-L-tyrosine has again been demonstrated to provide a rapid entry into the complex bicyclic core of the *Stemona* alkaloids. In the context of this synthetic study, we have discovered a conformation-dependent lability of the natural product toward oxidation of the pyrrolidine ring; a process that is most likely of biological relevance and results in the formation of the pyrrole didehydrotuberostemonine. Further developments of these strategies toward the unified synthesis of other polycyclic *Stemona* alkaloids are currently in progress.

Experimental Section

General Methods. All moisture-sensitive reactions were performed under an atmosphere of N_2, and glassware was dried in an oven at 140 °C prior to use. Tetrahydrofuran (THF) and ether were dried by distillation over sodium benzophenone, and dry CH_2Cl_2 and toluene were obtained by distillation from CaH_2. Unless otherwise stated, solvents or reagents were used as received without further purification. Abbreviations: ABO, asymmetric bicyclo[3.2.1]octane; AIBN, 2,2′-azobis(isobutyronitrile); BTF, benzotrifluoride; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; l-Selectride, tri-*sec*-butylborohydride.

8-Des-ethyl-8(*S*)-allyl-(−)-13-epituberostemonine (48). To a solution of **42** (27 mg, 0.054 mmol) and AIBN (2.7 mg, 0.016 mmol) in α,α,α-trifluorotoluene (0.25 μL) was added allyltributyltin (0.25 μL). The reaction mixture was heated at 95 °C and concentrated in vacuo, and the residue was dissolved in MeCN (50 mL). The MeCN layer was washed with hexanes (3 × 25 mL), concentrated in vacuo, and purified by chromatography on SiO_2 that had been pretreated with 9:1 hexanes/EtOAc containing 0.5% NEt_3 (hexanes/EtOAc, 9:1 to 1:1 to 0:1) to give 5.6 mg (27%) of the minor diastereomer **27** and 9.1 mg (43%) of the major diastereomer **48** as white foams. **48**: $[\alpha]_D$ −14.1 (*c* 0.79, $CHCl_3$, 21 °C); IR (neat) 2922, 1771, 1172 cm^{-1}; ^{1}H NMR δ 5.78−5.69 (m, 1 H), 5.05−5.00 (m, 2 H), 4.22−4.14 (m, 1 H), 4.20 (d, 1 H, J = 3.4 Hz), 3.32 (dd, 1 H, J = 15.2, 6.0 Hz), 3.25−3.17 (m, 1 H), 3.16 (dd, 1 H, J = 7.4, 4.0 Hz), 2.85−2.73 (m, 2 H), 2.66−2.54 (m, 1 H), 2.40−2.09 (m, 6 H), 2.00 (br d, 1 H, J = 10.7 Hz), 1.82−1.67 (m, 3 H), 1.61−1.23 (m, 4 H), 1.22 (d, 6 H, J = 7.0 Hz), 1.11−1.02 (m, 2 H); ^{13}C NMR δ 179.3, 178.5, 136.2, 117.1, 83.3, 80.7, 65.0, 64.0, 50.3, 44.8, 44.1, 41.2, 40.3, 37.1, 35.0 (2C), 34.0, 33.4, 32.6, 29.5, 26.7, 14.8, 11.7; MS (EI) *m*/*z* (rel intensity) 387 (M^+, 4), 344 (14), 288 (100), 246 (8), 134 (4), 91 (6), 81 (8); HRMS *m*/*z* calculated for $C_{23}H_{33}NO_4$ 387.2410, found 387.2394.

(−)-13-Epituberostemonine (50). To a solution of **48** (21 mg, 0.054 mmol) in toluene (0.85 mL) were added allyltritylamine (34 mg, 0.11 mmol), ruthenium catalyst **32** (10 mg, 0.011 mmol), and *N*,*N*-diisopropylethylamine (9.4 μL, 0.054 mmol). The reaction mixture was heated at reflux for 15 h, concentrated in vacuo, and purified by chromatography on SiO_2 prewashed with a solution of 0.5% NEt_3 in hexanes/EtOAc (9:1) (hexanes/EtOAc gradient elution from 9:1 to 2:1 to 1:1 to 0:1) to give 17 mg (81%) of an (*E*,*Z*) mixture (ca. 2:1) of **49** as a yellow oil. A solution of this mixture of double-bond isomers (20 mg, 0.052 mmol) in CH_2Cl_2 (2.3 mL) was treated with *p*-toluenesulfonic acid monohydrate (9.9 mg, 0.052 mmol) and stirred at room temperature for 30 min. After addition of catalyst **32** (0.88 mg, 1.0 μmol), the solution was heated at reflux while ethylene gas was bubbled through it with additional portions of catalyst **32** (0.88 mg, 1.0 mmol) added approximately every 12 h. After 78 h, the mixture was concentrated slightly by bubbling ethylene through it without a condenser until ca. 1 mL of CH_2Cl_2 remained. Methanol (2 mL) was added, and the mixture was hydrogenated for 17 h at room temperature, concentrated in vacuo, and dissolved in EtOAc (25 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), concentrated in vacuo, and purified by preparative TLC on SiO_2 (EtOAc with 0.5% NEt_3) to give 4.0 mg (21%) of **50** as a white foam: $[\alpha]_D$ −22.0 (*c* 0.061, acetone, 21 °C); IR (neat) 2923, 1764, 1178 cm^{-1}; ^{1}H NMR (500 MHz) δ 4.23−4.18 (m, 2 H), 3.33 (dd, 1 H, J = 15.2, 6.1 Hz), 3.22 (dt, 1 H, J = 9.9, 7.0 Hz), 3.14 (dd, 1 H, J = 11.4, 3.7 Hz), 2.85−2.78 (m, 2 H), 2.64 (dddd, 1 H, J = 19.5, 10.3, 7.7, 7.1 Hz), 2.37 (ddd, 1 H, J = 12.4, 8.5, 5.4 Hz), 2.27 (ddd, 1 H, J = 10.9, 6.5, 4.4 Hz), 2.21 (dt, 1 H, J = 11.9, 6.0 Hz), 2.04−1.98 (m, 2 H), 1.82−1.73 (m, 3 H), 1.63−1.35 (m, 6 H), 1.28 (d, 6 H, J = 6.8 Hz), 1.26 (br s, 1 H), 1.10 (q, 1 H, J = 11.3 Hz), 1.01 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (125 MHz) δ 179.5, 178.8, 83.4, 81.8, 65.4, 64.3, 50.8, 47.0, 45.3, 41.6, 40.2, 35.3, 34.3,

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33.8, 32.9, 29.9, 29.8, 26.9, 25.9, 15.0, 13.2, 12.0; MS (EI) *m*/*z* (rel intensity) 375 (M^+, 0.6), 374 (1.4), 344 (1), 276 (100), 119 (5), 111 (8); HRMS *m*/*z* calculated for $C_{22}H_{32}NO_4$ (M − H) 374.2331, found 374.2322.

N,*N*-Dimethyl-2*R*,*S*-[2*S*-(4*S*-methyl-5-oxotetrahydrofuran-2-yl)-1,2*S*,4,5,6,7,7a*S*,10,10a*R*,10b*S*-decahydroazepino[3,2,1-*hi*]indol-10-yl)-propionamide. To a solution of **28** (105 mg, 0.36 mmol) in xylenes (10 mL) was added *N*,*N*-dimethylacetamide dimethylacetal (0.44 mL, 2.9 mmol). The reaction mixture was heated at 130−140 °C for 16 h, concentrated in vacuo, and purified by chromatography on SiO_2 (pretreated with 1:1 hexanes/EtOAc with 0.5% NEt_3) (hexanes/EtOAc, 1:1 to 0:1 with 5% MeOH) to give 102 mg (78%) of the dimethylamide as a yellow foam: $[\alpha]_D$ −26.6 (*c* 0.42, $CHCl_3$, 21 °C); IR (neat) 2916, 1772, 1642, 1153 cm^{-1}; ^1H NMR δ 5.55 (ddd, 1 H, J = 9.5, 4.9, 2.2 Hz), 5.39 (br d, 1 H, J = 9.8 Hz), 4.23 (ddd, 1 H, J = 10.9, 7.5, 5.6 Hz), 3.45 (br d, 1 H, J = 13.6 Hz), 3.34 (dd, 1 H, J = 14.7, 8.0 Hz), 3.14 (dd, 1 H, J = 10.6, 5.8 Hz), 2.96 (s, 3 H), 2.90 (s, 3 H), 2.70 (dd, 1 H, J = 14.6, 11.5 Hz), 2.58−2.43 (m, 2 H), 2.37−2.28 (m, 3 H), 2.16 (dd, 1 H, J = 15.2, 8.7 Hz), 2.00 (dt, 1 H, J = 12.2, 6.5 Hz), 1.73 (br d, 2 H, J = 12.0 Hz), 1.55−1.35 (m, 6 H), 1.19 (d, 3 H, J = 6.9 Hz), 1.16−1.05 (m, 1 H); ^{13}C NMR δ 179.6, 171.5, 131.9, 129.8, 82.5, 65.7, 63.7, 47.2, 42.0, 41.3, 39.0, 37.3, 35.3, 34.7, 34.3, 31.2, 30.8, 29.9, 28.2, 14.7; MS (EI) *m*/*z* (rel intensity) 360 (M^+, 1.5), 274 (6), 261 (100), 172 (17), 149 (11), 130 (8), 105 (6), 91 (7), 72 (19); HRMS *m*/*z* calculated for $C_{21}H_{32}N_2O_3$ 360.2413, found 360.2405.

8-Des-ethyl-8*S*-phenylseleno-(−)-tuberostemonine (51). To a 0 °C solution of the above dimethylamide (99 mg, 0.27 mmol) in a 5:1 mixture of MeCN/water (3.8 mL) was added phenylselenyl chloride (83 mg, 0.45 mmol). The reaction mixture was stirred at 0 °C for 20 h, quenched with a saturated $NaHCO_3$ solution, and extracted into EtOAc (3 × 30 mL) and CH_2Cl_2 (1 × 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 1:1) to give 87 mg (67%) of **51** as a white foam: $[\alpha]_D$ −16.4 (*c* 0.61, $CHCl_3$, 21 °C); IR (neat) 2921, 1770, 1165, 916 cm^{-1}; ^1H NMR δ 7.53 (dd, 2 H, J = 4.6, 2.0 Hz), 7.31−7.28 (m, 3 H), 4.54 (dd, 1 H, J = 3.8, 2.5 Hz), 4.22 (ddd, 1 H, J = 10.8, 7.6, 5.4 Hz), 3.72 (s, 1 H), 3.43−3.22 (m, 3 H), 2.78 (dd, 1 H, J = 15.4, 10.1 Hz), 2.69−2.53 (m, 4 H), 2.39 (d, 1 H, J = 16.3 Hz), 2.39−2.31 (m, 1 H), 2.10 (dt, 1 H, J = 11.8, 6.1 Hz), 1.81−1.70 (m, 4 H), 1.56−1.33 (m, 3 H), 1.25 (d, 3 H, J = 7.0 Hz), 1.19−1.08 (m, 1 H); ^{13}C NMR δ 179.3, 175.7, 133.6, 129.5, 129.4, 128.0, 83.4, 82.5, 64.6, 64.3, 49.5, 47.9, 43.6, 38.8, 38.4, 35.9, 34.9, 34.1, 32.7, 31.4, 29.7, 26.9, 14.8; MS (EI) *m*/*z* (rel intensity) 488 (M^+, 1), 390 (100), 332 (8), 230 (34), 199 (8), 184 (42), 174 (21), 158 (17), 134 (6), 91 (12), 78 (44), 67 (9); HRMS *m*/*z* calculated for $C_{25}H_{30}NO_4Se$ 488.1340, found 488.1317.

8-Des-ethyl-8*S*-allyl-(−)-tuberostemonine (27). To a mixture of **51** (0.20 g, 0.41 mmol) and AIBN (21 mg, 0.082 mmol) was added allyltriphenyltin (2.4 g, 6.1 mmol). The reaction mixture was heated at 100 °C for 14 h (the solid mixture becomes a cloudy solution immediately upon heating), cooled to room temperature, and purified by chromatography on SiO_2 that had been pretreated with 9:1 hexanes/EtOAc containing 0.5% NEt_3 (hexanes/EtOAc, 9:1 to 1:1 to 0:1) to give 0.11 g (70%) of the allyl intermediate as a white foam. A solution of this lactone (150 mg, 0.402 mmol) in THF (4 mL) and HMPA (0.4 mL) was cooled to −78 °C and an LDA/HMPA solution (0.982 mL, 0.442 mmol) [0.45 M LDA solution made from diisopropylamine (0.175 mL, 1.25 mmol) and ^{n}BuLi (1.6 M, 0.781 mL, 1.25 mmol) in THF (1.6 mL) at 0 °C and then treated with HMPA (0.224 mL, 1.29 mmol) at −78 °C] was added. The reaction mixture was stirred at −78 °C for 30 min, and then MeI (75.3 μL, 1.21 mmol) was added. This solution was stirred at −78 °C for 20 min and quenched with saturated $NaHCO_3$. The product was extracted into EtOAc (3 × 15 mL), washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on SiO_2 that had been prewashed with 4:1 hexanes/EtOAc containing 0.5% NEt_3 (hexanes/EtOAc, 2:1 to 1:1) to give 91.4 mg (59%) of **27** as a white foam along with 33.4 mg (22%) of recovered **53** and 17.7 mg (11%) of **52**. **27**: $[\alpha]_D$ −3.3 (*c* 0.17, CD_2Cl_2, 21 °C); IR (neat) 2920, 1771, 1455, 1171, 1013 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 5.91−5.72 (m, 1 H), 5.10−5.05 (m, 2 H), 4.40 (dd, 1 H, J = 9.1, 7.8 Hz), 4.25 (ddd, 1 H, J = 10.8, 7.8, 5.4 Hz), 3.45−3.35 (m, 2 H), 3.00 (dd, 1 H, J = 11.1, 6.8 Hz), 2.68−2.47 (m, 2 H), 2.40−2.10 (m, 5 H), 2.00 (dt, 2 H, J = 10.3, 7.8 Hz), 1.88−1.72 (m, 3 H), 1.69−1.38 (m, 6 H), 1.22 (d, 3 H, J = 7.3 Hz), 1.19 (d, 3 H, J = 6.9 Hz), 1.13−1.01 (m, 1 H); ^{13}C NMR (CD_2Cl_2) δ 179.7, 179.4, 135.9, 117.5, 81.8, 80.1, 65.2, 63.6, 48.0, 47.4, 43.9, 41.9, 41.3, 41.0, 35.9, 35.1, 34.8, 32.3, 30.1, 30.0, 28.9, 15.0, 14.9; MS (EI) *m*/*z* (rel intensity) 388 ($[M + 1]^+$, 3), 360 (5), 344 (16), 288 (100), 274 (22), 246 (14), 172 (8), 134 (8), 91 (19), 81 (15); HRMS *m*/*z* calculated for $C_{23}H_{33}NO_4$ 387.2410, found 387.2395. **52**: $[\alpha]_D$ −27.6 (*c* 0.11, acetone, 21 °C); IR (neat) 2923, 1769, 1448, 1157 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 5.91−5.78 (m, 1 H), 5.09 (d, 1 H, J = 5.8 Hz), 5.06 (s, 1 H), 4.41 (dd, 1 H, J = 9.2, 7.8 Hz), 4.38−4.27 (m, 1 H), 3.46−3.35 (m, 2 H), 3.01 (dd, 1 H, J = 11.0, 6.7 Hz), 2.67−2.59 (m, 1 H), 2.38 (pentet, 1 H, J = 7.4 Hz), 2.26 (dd, 2 H, J = 6.7, 5.8 Hz), 2.15 (dt, 1 H, J = 13.8, 7.0 Hz), 2.05−1.96 (m, 2 H), 1.84−1.74 (m, 3 H), 1.67 (dd, 2 H, J = 12.6, 10.7 Hz), 1.54−1.42 (m, 5 H), 1.23 (d, 3 H, J = 7.3 Hz), 1.21 (s, 3 H), 1.20 (s, 3 H), 1.08−0.98 (m, 1 H); ^{13}C NMR (CD_2Cl_2) δ 182.1, 179.4, 136.0, 117.6, 80.4, 80.2, 65.5, 63.8, 48.1, 47.6, 44.1, 42.0, 41.4, 41.1 (2 C), 39.6, 36.1, 32.5, 30.2 (2 C), 29.0, 24.9, 24.5, 15.0; MS (EI) *m*/*z* (rel intensity) 401 (M^+, 1), 399 (2), 288 (100), 172 (7), 97 (8), 84 (37), 71 (22), 58 (46); HRMS *m*/*z* calculated for $C_{24}H_{35}NO_4$ 401.2566, found 401.2570.

(−)-Tuberostemonine (26). To a solution of **27** (53.1 mg, 0.137 mmol) in CH_2Cl_2 (2.5 mL) were added allyltritylamine (82.0 mg, 0.274 mmol), ruthenium catalyst **32** (25.0 mg, 0.0274 mmol), and *N*,*N*-diisopropylethylamine (23.9 μL, 0.137 mmol). The reaction mixture was heated at reflux for 16 h, concentrated in vacuo, and purified by chromatography on SiO_2 (pretreated with 9:1 hexanes/EtOAc with 0.5% NEt_3) (hexanes/EtOAc gradient elution from 9:1 to 2:1 to 1:1 to 0:1) to give 45.3 mg (85%) of an (*E*,*Z*)-mixture (ca. 2:1) of **54** as a yellow oil. A solution of this mixture of double-bond isomers (47.1 mg, 0.122 mmol) in CH_2Cl_2 (5.2 mL) was treated with *p*-toluenesulfonic acid monohydrate (23.2 mg, 0.122 mmol) and heated at reflux for 30 min. After addition of catalyst **55** (3.81 mg, 0.0061 mmol), the solution was heated at reflux while ethylene gas was bubbled through it with additional portions of catalyst **55** (3.81 mg, 0.0061 mmol) added approximately every 12 h. After 60 h, the mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on SiO_2 prewashed with a solution of 0.5% NEt_3 in hexanes/EtOAc (9:1) (hexanes/EtOAc gradient elution from 9:1 to 2:1 to 1:1 to 1:2) to give 37.1 mg (81%) of **56** as a white foam. A solution of **56** in methanol (4.6 mL) was hydrogenated for 17 h at room temperature in the presence of 10% Pd/C (37.1 mg), filtered through a plug of Celite, and concentrated in vacuo to give 36.0 mg (97%) of **26** as a white foam: $[\alpha]_D$ −29.4 (*c* 0.10, acetone, 21 °C) [lit.[9] $[\alpha]_D$ −25.4 (*c* 0.06, acetone, 21 °C)]; IR (neat) 2925, 1772, 1451, 1163 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 4.41 (t, 1 H, J = 7.8 Hz), 4.25 (ddd, 1 H, J = 10.7, 7.8, 5.4 Hz), 3.42−3.37 (m, 2 H), 3.02 (dd, 1 H, J = 11.2, 6.5 Hz), 2.68−2.51 (m, 2 H), 2.39−2.29 (m, 2 H), 2.15 (dt, 1 H, J = 12.1, 6.7 Hz), 2.00 (dt, 1 H, J = 10.2, 7.6 Hz), 1.83−1.74 (m, 4 H), 1.59−1.39 (m, 8 H), 1.22 (d, 3 H, J = 7.3 Hz), 1.19 (d, 3 H, J = 6.9 Hz), 1.12−1.01 (m, 1 H), 0.94 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (CD_2Cl_2) δ 179.7 (s), 179.5 (s), 82.0 (d), 80.6 (d), 65.2 (d), 63.8 (d), 48.1 (t), 47.5 (d), 45.2 (d), 42.2 (d), 41.2 (d), 41.1 (d), 35.1 (d), 34.8 (t), 32.4 (t), 30.5 (t), 30.3 (t), 28.8 (t), 24.7 (t), 15.0 (q), 14.9 (q), 11.2 (q),; MS (EI) *m*/*z* (rel intensity) 375 (M^+, 1), 374 (4), 373 (5), 344 (14), 304 (15), 290 (26), 276 (100), 260 (11), 200 (6), 134 (6); HRMS *m*/*z* calculated for $C_{22}H_{32}NO_4$ (M − H) 374.2331, found 374.2317.

Didehydrotuberostemonine (60). To a solution of **26** (13 mg, 0.035 mmol) in acetone (2.6 mL) was added freshly prepared (from 10%

aqueous $AgNO_3$ and 10% aqueous NaOH) Ag_2O (13 mg, 0.056 mmol). The reaction mixture was heated at 40 °C for 15 h and filtered through a plug of Florisil (EtOAc containing 0.5% NEt_3). The filtrate was concentrated in vacuo and purified by preparative TLC (hexanes/EtOAc, 1:1) to give 3.9 mg (30%) of a 7:3 mixture of **60** and unidentified impurities. **60**: ^{1}H NMR δ 5.99 (s), 5.38 (dd, 1 H, J = 11.1, 5.1 Hz), 4.62 (dd, 1 H, J = 7.8, 6.6 Hz), 4.27−4.20 (m, 1 H), 3.75−3.63 (m, 1 H), 3.08 (dd, 1 H, J = 7.0, 5.9 Hz), 2.90−2.62 (m, 2 H), 2.59 (t, 1 H, J = 7.3 Hz), 2.27−2.15 (m, 2 H), 2.12−1.83 (m, 5 H), 1.64−1.52 (m, 4 H), 1.40 (d, 3 H, J = 7.3 Hz), 1.37 (d, 3 H, J = 6.8 Hz), 1.02 (t, 3 H, J = 7.5 Hz); ^{1}H NMR (CD_2Cl_2) δ 6.00 (s), 5.36 (dd, 1 H, J = 11.3, 5.2 Hz), 4.61 (dd, 1 H, J = 7.3, 6.4 Hz), 4.24−4.16 (m, 1 H), 3.75−3.62 (m, 1 H), 3.07 (t, 1 H, J = 6.5 Hz), 2.82−2.56 (m, 2 H), 2.55 (pentet, 1 H, J = 7.1 Hz), 2.24−2.11 (m, 2 H), 2.08−1.90 (m, 5 H), 1.60−1.49 (m, 4 H), 1.36 (d, 3 H, J = 7.3 Hz), 1.30 (d, 3 H, J = 6.8 Hz), 1.01 (t, 3 H, J = 7.4 Hz); MS (EI) m/z (rel intensity) 371 (M^+, 100), 327 (66), 298 (32), 272 (97), 228 (21); HRMS m/z calculated for $C_{22}H_{29}NO_4$ 371.2097, found 371.2095.

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Supporting Information Available: Experimental procedures and spectral data for **1**, **9**−**25**, **28**, **30**, **34**−**37**, **39**, **40a**,**b**, and **42**. This information is available free of charge via the Internet at http://pubs.acs.org.

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