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Total Synthesis of (−)-Tuberostemonine

Peter Wipf,* Stacey R. Rector, and Hidenori Takahashi

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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Since the first report on the isolation of a pure *Stemona* alkaloid in 1936, >40 congeners have been isolated from genus *Stemona* (family Stemonaceae, order Dioscoreales) and, to a lesser extent, from genus *Croomia* plants.[1] The structure of the complex polycyclic tuberostemonine **(1)**, the major *Stemona* alkaloid, was elucidated in the 1960s by a combination of crystallographic, spectroscopic, and degradative techniques.[2] The biological activity of *Stemona* alkaloids covers an unusually broad range, and applications in Eastern folk medicine against pulmonary tuberculosis and bronchitis as well as insecticides are well documented.[3] Tuberostemonine was also found to function as a glutamate antagonist at the crayfish neuromuscular junction.[3b] Several syntheses of other *Stemona* alkaloids have been completed,[4] and we now report the first total synthesis of tuberostemonine.

Key steps of our retrosynthetic analysis are a ring-closing metathesis reaction to form the azepane followed by the addition of a lithiated ortho ester to introduce the right-side butyrolactone (Figure 1). Bicycle **2**, which is obtained in three steps from Cbz-L-tyrosine and has already provided the lynchpin for our stenine synthesis,[4b,5] serves as a scaffold for installation of nine of the ten stereogenic carbons of tuberostemonine, including the fused left-side butyrolactone which is obtained by a Claisen rearrangement and halolactonization.[4a,b]

Our approach began with an improvement to the π-allyl palladium reaction on compound **2** (Scheme 1).[4b,5] Previously, we had reported this reduction in the presence of triethylammonium formate using PBu_3 as the Pd ligand.[4b] Although excellent yields (>90%) could be attained, the reaction required scrupulously oxygen-free techniques and >99% pure PBu_3. We were delighted to discover that the crystalline and more air-stable PBn_3 also works well as a ligand for the π-allyl palladium complex. The reduction can now be performed on scales as large as 47 g with yields reproducibly exceeding 80%. Silylation of the secondary alcohol was followed by carbamate deprotection and cinnamylation of the resulting amine **5**. Fluoride-induced deprotection of the silyl ether gave alcohol **7** in 80% yield from **3**. After oxidation to the enone, a stereoselective (>95% dr) axial dienolate alkylation was accomplished with KHMDSA and allyl iodide.[6]

To effect the key metathesis reaction, a solution of **8** in CH_2Cl_2 was heated at reflux in the presence of 2−5 mol % of the ruthenium catalyst **9**[7] (Scheme 2). The resulting double bond in azepine **10** was removed via a high-yielding, three-step sequence to give tricycle **11** after transient protection of the enone double bond by conjugate addition−β-elimination of thiophenol. Ester **12** was obtained as a single diastereomer after Luche reduction and TBDMS protection.

In preparation for the introduction of the right-side butyrolactone, we added Weinreb amide **13**, obtained in 94% yield from ester **12**,[8] to a solution of the lithium anion formed from bromo ortho ester **14** and LiDBB in THF (Scheme 3).[9,10] This process resulted in an excellent yield of ketone **15**. The carbonyl group was subsequently reduced with L-Selectride to give a 7:1 ratio of diastereomeric alcohols favoring the Felkin−Anh product. Exposure of this mixture of alcohols to TsOH in methanol removed both the ortho ester and the silyl ether protecting groups and also catalyzed the cyclization, affording the desired lactone **16** as a single diastereomer in 70% yield.

The final transformations toward tuberostemonine began with a Claisen rearrangement[11,12] using *N*,*N*-dimethylacetamide dimethyl acetal (Scheme 4). All attempts to subject **17** to halolactonization failed or resulted in decomposition, but an alternative selenolactonization[13] followed by a Keck allylation[4b,14] proceeded uneventfully to give tetracycle **20** after selective α-methylation of the fused lactone.[4a,b]

Since previously successful oxidative conditions[4b] to convert the allyl side chain to the desired ethyl group failed, we needed to develop a new method for this chain contraction. Gratifyingly, we

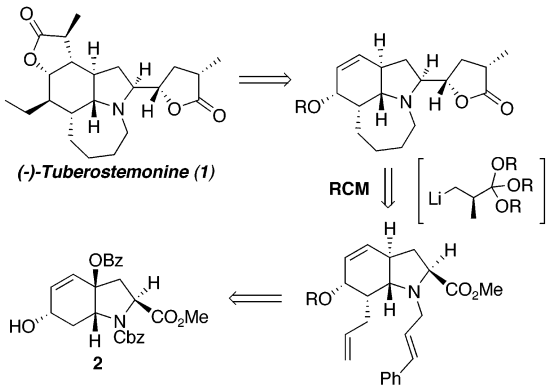
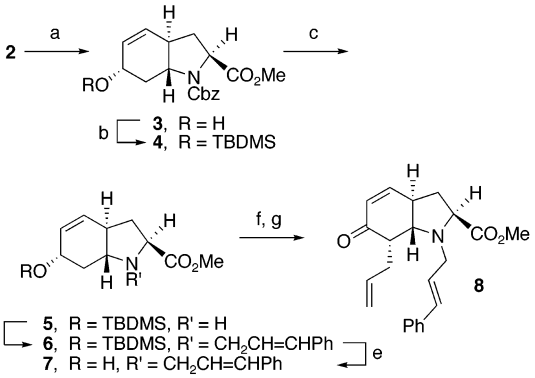


Figure 1. Retrosynthetic analysis.

Scheme 1. Reduction and Double Allylation of Hydroindole Core **2**[a]



[a] (a) $Pd_2(dba)_3CHCl_3$, NEt_3, HCOOH, PBn_3, THF, 65 °C (93%); (b) TBDMS-Cl, imidazole, DMAP, CH_2Cl_2 (97%); (c) Et_3SiH, $Pd(OAc)_2$, NEt_3, CH_2Cl_2, room temperature (90%); (d) cinnamyl bromide, K_2CO_3, toluene, 60 °C (96%); (e) TBAF, THF, room temperature (96%); (f) TPAP, NMO, CH_2Cl_2 (88%); (g) KHMDSA, allyl iodide, −90 °C (66%).

* Corresponding author. E-mail:pwipf@pitt.edu.

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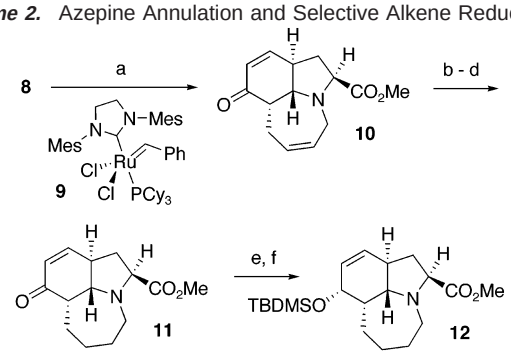
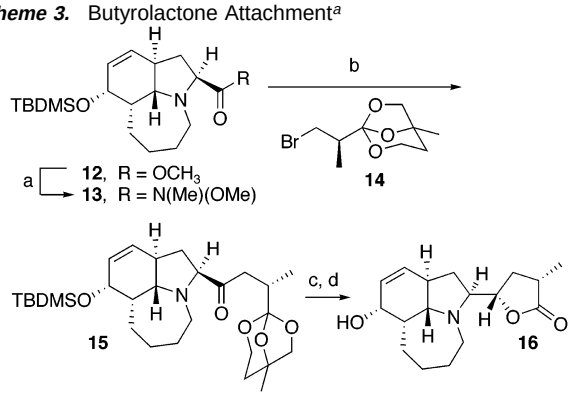
Scheme 2. Azepine Annulation and Selective Alkene Reduction[a]



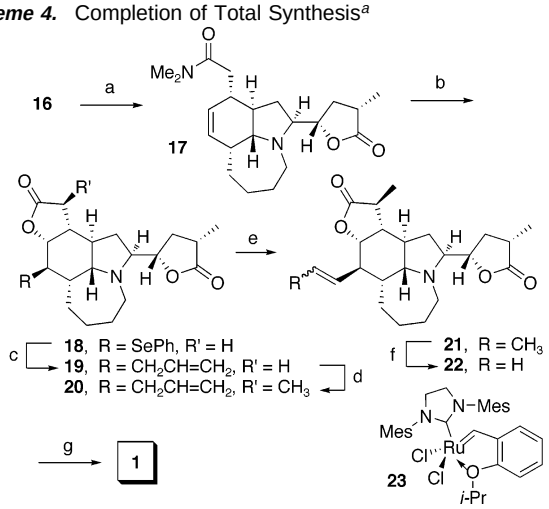
[a] (a) **9**, CH_2Cl_2 reflux (92%); (b) PhSH, NEt_3, CH_2Cl_2 (91%); (c) $(PPh_3)_3RhCl$, H_2, EtOH/CH_2Cl_2, room temperature; (d) DBU, CH_2Cl_2, room temperature (89%); (e) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, THF/MeOH, 0 °C (71%); (f) TBDMS-Cl, imidazole, DMAP, CH_2Cl_2, room temperature (79%).

Scheme 3. Butyrolactone Attachment[a]



[a] (a) (Me)(OMe)NH·HCl, Me_2AlCl, CH_2Cl_2, room temperature (94%); (b) **14**, LiDBB; then **13** (95%); (c) L-Selectride, THF, −78 °C (80%); (c) TsOH, MeOH (70%).

Scheme 4. Completion of Total Synthesis[a]



[a] (a) *N*,*N*-Dimethylacetamide dimethyl acetal, xylenes, 135 °C (78%); (b) PhSeCl, MeCN/H_2O, 0 °C (67%); (c) AIBN, allyltriphenyltin (neat) 95 °C (70%); (d) LDA, HMPA, THF, −78 °C; MeI (76%, based on rec'd sm); (e) **9**, allyltritylamine, DIEA, toluene, 110 °C (85%); (f) TsOH, **23**, CH_2Cl_2 reflux, ethylene (81%); (g) Pd/C, H_2 (1 atm), MeOH, (97%).

were able to accomplish a novel sequence by first isomerizing the allyl group using a modification of a method developed by Roy et al. for allyl ethers,[15] followed by ethylene cross-metathesis on **21** in the presence of Ru catalyst **23**[16] and TsOH[17] to access the desired terminal vinyl group. Phosphine-free conditions were important to avoid extensive chromatographic purification that led to decomposition. The first total synthesis of tuberostemonine was completed by a catalytic hydrogenation over Pd on carbon.[18]

In conclusion, the pentacyclic *Stemona* alkaloid tuberostemonine was prepared in 24 steps and 1.4% overall yield from bicycle **2**, which is readily obtained in three steps from Cbz-L-tyrosine and has served as a key building block for other alkaloid syntheses.[4b,19] Among the highlights of our approach are the 3-fold use of ruthenium catalysts, first in an azepine ring-closing metathesis and then in the alkene isomerization and cross-metathesis propenyl−vinyl exchange, as well as the stereoselective attachment of the γ-butyrolactone to the core tetracycle by use of the lithiated ortho ester **14**.

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Supporting Information Available: Experimental procedures and characterization data for **3**, **16**, and **1** and 1D and 2D NMR spectra for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) This sequence allowed isolation of **1** after filtration of the reaction mixture through a plug of Celite. The natural product readily oxidizes upon chromatography and storage at ambient temperature.[2b] The structure of synthetic **1** was confirmed by 1D and 2D NMR experiments, and its $[\alpha]_D$ −29.4 (*c* 0.10, acetone, 21 °C) compared well to the literature value ($[\alpha]_D$ −25.4 (*c* 0.06, acetone, 21 °C); Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571−576).

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