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A Concise Synthesis of Tetrabenazine: An Intramolecular Aza-Prins-Type Cyclization via Oxidative C–H Activation[||]

Young Wook Son,[†] Tae Hui Kwon,[†] Jae Kyun Lee,[‡] Ae Nim Pae,[‡,§] Jae Yeol Lee,[†] Yong Seo Cho,[*,‡,§] and Sun-Joon Min[*,‡,§]

Department of Chemistry, College of Sciences, Kyung Hee University, 1 Hoegi-Dong, Seoul 130-701, Republic of Korea, Center for Neuro-Medicine, Korea Institute of Science and Technology (KIST), Seoul, 136-791, Republic of Korea, and School of Science, University of Science and Technology (UST), Daejeon, 305-333, Republic of Korea

ys4049@kist.re.kr; sjmin@kist.re.kr

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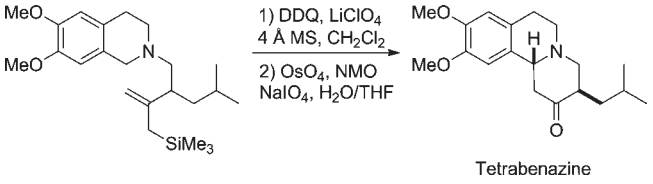
ABSTRACT

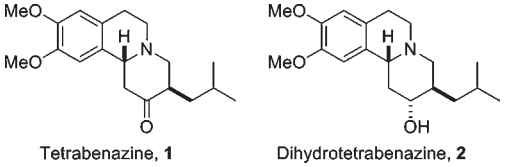


Tetrabenazine

A concise synthesis of tetrabenazine and dihydrotetrabenazine is described. The key feature of this synthesis is the intramolecular aza-Prins-type cyclization of an amino allylsilane via oxidative C–H activation.

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric interruption.[1] Recent studies suggest that the dopamine signaling pathway plays an important role in HD neuropathology. In fact, it has been reported that a high concentration of dopamine causes toxic effects on striatal neurons in mouse models.[2] Therefore, regulation of dopaminergic neurotransmission in HD constitutes a potential therapeutic target for treatment of HD.

Tetrabenazine (TBZ, xenazine, **1**), first introduced as an antipsychotic in the 1950s,[3] was approved by the FDA for treatment of chorea associated with HD (Figure 1).[4] TBZ and its metabolite dihydrotetrabenazine (DTBZ, **2**) reversibly inhibit the vesicular monoamine transporter-2 (VMAT2).[5] Because this transporter is responsible for translocation of dopamine from the cytoplasm into the synaptic vesicle for reuptake, TBZ can decrease the dopamine level in the brain by blocking VMAT2, which exerts antichorea effects in HD patients.[6]



Tetrabenazine, **1** Dihydrotetrabenazine, **2**

Figure 1. Structures of tetrabenazine and dihydrotetrabenazine.

The resolution and biological evaluation studies of the DTBZ enantiomers indicated that the (+)-enantiomer of

[†] Kyung Hee University.
[‡] Korea Institute of Science and Technology.
[§] University of Science and Technology.
[||] Dedicated to Professor Michael E. Jung on the occasion of his 65th birthday.

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(6) Kenney, C.; Jankovic, J. *Expert Rev. Neurother.* **2006**, *6*, 7.

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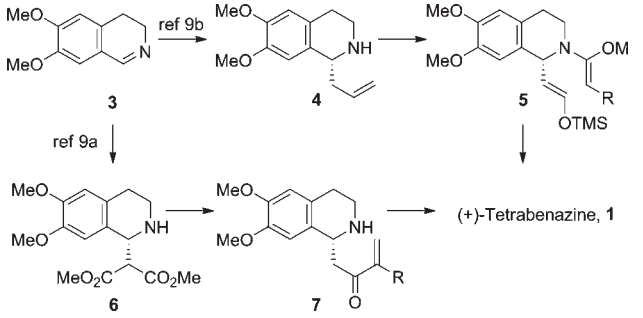
2 showed high affinity with $K_i = 0.97 \pm 0.48$ nM for VMAT2 in rat brains, whereas the (−)-enantiomer was much less effective with $K_i = 2.2 \pm 0.3\,\mu$M.[7] Furthermore, radioactive (+)-DTBZ was specifically distributed in regions of the striatum in mice. These results indicated that the binding of TBZ as well as that of DTBZ to VMAT2 is stereospecific.

Due to the pharmaceutical significance of TBZ and DTBZ, several reports[8] have been published to date including two recent excellent syntheses achieved by Jonhson and Suh.[9] As depicted in Scheme 1, these syntheses involved initial asymmetric installation at the C-1 position of the dihydroisoquinoline **3**. The enantiomerically enriched **5** and **7** were then subjected to crucial cyclization reactions, such as an intramolecular conjugate addition and an aza-Claisen rearrangement/transannulation, to produce tetrabenazine (**1**) effectively.

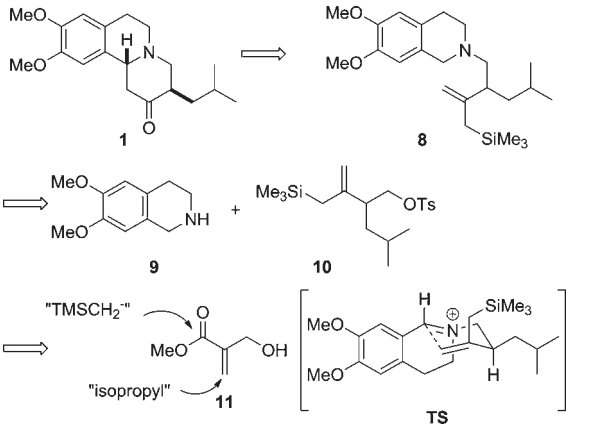
Scheme 1. Reported Syntheses of TBZ



Retrosynthetically, we envisioned the piperidinone ring of TBZ being formed by an aza-Prins-type cyclization of the amino allylsilane **8** followed by oxidative cleavage of exomethylene (Scheme 2). We postulated that direct C−H activation of the tetrahydroisoquinoline derivative **8** by a single-electron oxidative agent would lead to an iminium intermediate, which would undergo Prins-type cyclization to give a benzo[*a*]quinolizidine ring system.[10] In this transformation, we expected a 2,5-*trans* piperidine would be formed via the more favorable chairlike transition state (**TS**) in which the isobutyl substituent is in an equatorial position. On the other hand, the use of allylsilanes in oxidative cyclizations is challenging because termination of Prins cyclization by allylsilane has not been studied intensively.[11] The amino allylsilane **8** could arise from the allylsilane **10**, prepared by radical conjugate addition[12] to α-hydroxymethyl acrylate **11**[13] and a Peterson type olefination.[14]

Herein, we report the total synthesis of the tetrabenazine alkaloids through an intramolecular aza-Prins-type cyclization of an amino allylsilane using an oxidative C−H activation.[15]

Scheme 2. Retrosynthetic Analysis



To examine the viability of our cyclization strategy, we first optimized the reaction conditions using the simple amino allylsilane **13** as the substrate. The allylsilane **13** was prepared from 3-(trimethylsilylmethyl)-but-3-en-1-ol[16] by tosylation and subsequent *N*-alkylation with tetrahydroisoquinoline (Scheme 3). Although several reports have highlighted metal catalyzed C−H activation in benzylic or allylic amine systems,[17] we chose organic oxidizing agents such as phenyliodine diacetate (PIDA), phenyliodine bis(trifluoroacetate) (PIFA), and dichlorodicyanoquinone (DDQ) since they are stable solids that permit more practical as well as mild reaction conditions.[18] To our delight, treatment of the substrate **13** with PIDA in CH_3CN at

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(16) Hydroxy allylsilane **12** was prepared by silylation of the dianion of 3-methyl-3-buten-1-ol followed by desilylation of the silyl ether. For a detailed procedure, see: Trost, B. M.; Chan, D. M. T.; Nanninga, N. *Org. Synth.* **1984**, *62*, 58.

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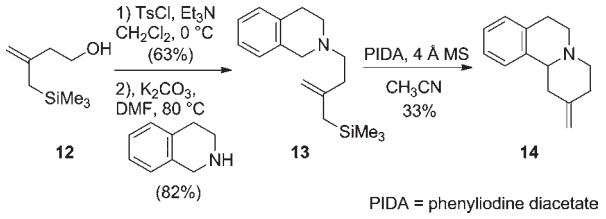
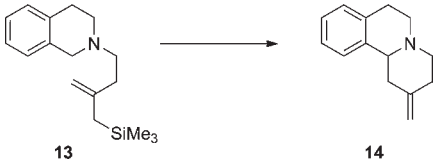
Scheme 3. Initial Attempt of the Aza-Prins-Type Cyclization



room temperature afforded the desired tricyclic ring although the yield was only 33%. Encouraged by this result, we attempted a number of reaction conditions to improve the yield (Table 1). In fact, it turned out that PIDA was a better oxidant than PIFA, which was not effective. When we used DDQ as the oxidant, the reaction proceeded rapidly at ambient temperature to give the corresponding product **14** within 20 min. Moreover, we found that the addition of $LiClO_4$ is crucial for improving the efficiency.[19] Presumably, the counteranion of the intermediate (iminium$^+$−DDQH$^-$ complex) generated by DDQ oxidation is exchanged by ClO_4^- to form a new ion pair (iminium$^+$−ClO_4^-), which serves as a better electrophile. On the basis of these findings, we selected the DDQ/$LiClO_4$/CH_2Cl_2 system as the optimal reaction conditions for our synthesis.

Table 1. Optimization of the Aza-Prins-Type Cyclization of an Amino Allylsilane through Oxidatve C−H Activation[a]

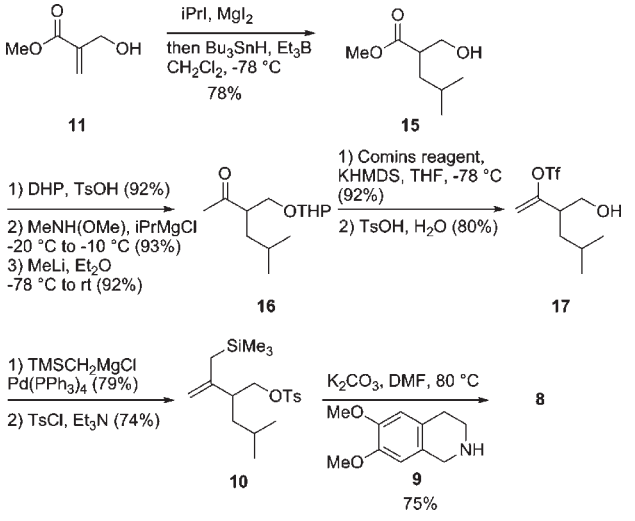


entry	reagent	solvent	t (°C)	time (h)	yield (%)[b]
1	PIDA	CH_3CN	60	24	19
2	PIDA	CH_2Cl_2	rt	6	NR[c]
3	PIDA	THF	rt	6	20
4	PIDA	DMF	rt	6	54
5	PIFA	CH_2Cl_2	rt	24	NR[c]
6	PIFA	CH_3CN	rt	24	12
7	PIFA	DMF	rt	6	–[d]
8	DDQ	CH_3CN	rt	6	39
9	DDQ	CH_2Cl_2	rt	0.25	40
10	DDQ/$LiClO_4$	CH_2Cl_2	rt	0.25	63

[a] All reactions were peformed in the presence of 4 Å molecular sieves. [b] Isolated yield. [c] No reaction. [d] The starting material was decomposed.

Having established the reaction condtions for aza-Prins-type cyclizations using DDQ oxidation, we commenced with the synthesis of tetrabenazine as illustrated in Scheme 4. Following the protocol developed by Sibi, we were able to incorporate the isopropyl group into the acrylate **11** to provide **15** in 78% yield. After THP protection, we attempted the direct conversion of the correponding ester to the allylsilane using $TMSCH_2MgCl$ (Peterson type olefination)[20] suggested in Scheme 2; however, it was unsuccessful presumably because of steric hindrance due to the isopropyl group. Alternatively, we transformed **15** to the methyl ketone **16** through the Weinreb amide intermediate.[21] The ketone **16** was then treated with the Comins reagent[22] and KHMDS at −78 °C to afford the vinyl triflate, which was subjected to hydrolysis to give the alcohol **17** in 74% yield (2 steps). At this point, we could effectively introduce the trimethylsilyl methyl group into **17** using a palladium-catalyzed coupling reaction[23] to obtain the desired allylsilane, which was easily converted to the correspoding tosylate **10**. Finally, the amino allylsilane **8** was prepared according to the same reaction conditions as those for the synthesis of **13**.

Scheme 4. Synthesis of **8**



With precursor **8** in hand, we applied the aza-Prins-type cyclization for the construction of the piperidinone ring of tetrabenazine (Scheme 5). Indeed, the amino allylsilane **8** was stereoselectively converted to the desired benzoisoquinolizidine **18** under the best conditions identified in Table 1. The relative stereochemistry of **18** was tentatively assigned by analysis of the spectral data resulting from the NMR experiments including ^1H, ^{13}C, ^1H COSY and HMQC.

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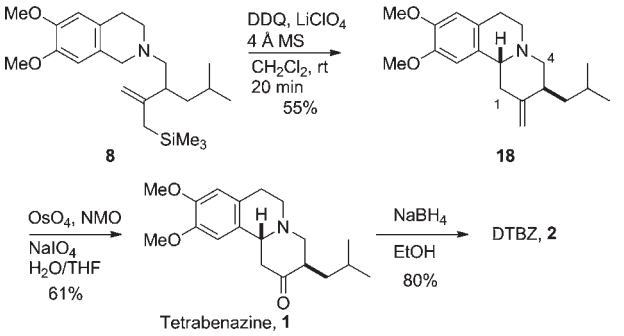
Scheme 5. Complete Syntheis of TBZ and DTBZ



Most importantly, the coupling constants of the axial C_1-proton (2.21 ppm, dd, J = 12.2, 12.2 Hz) and the axial C_4-proton (1.97 ppm, dd, J = 11.1, 11.1 Hz) indicated that the major isomer had the 2,5-*trans* stereochemistry in the piperidine ring system. Final oxidative cleavage of **18** using OsO_4, NMO, and $NaIO_4$ cleanly yielded tetrabenazine **1** in 61% yield. Additionally, treatment of **1** with $NaBH_4$ in EtOH afforded the alcohol **2**, which was shown to be dihydrotetrabenazine **2** since its spectroscopic data were identical to those reported in the literature.[9]

In summary, this study describes the concise syntheses of TBZ (**1**) and DTBZ (**2**) using an intramolecular aza-Prins-type cyclization of an amino allylsilane. In particular, we have shown that a single electron oxidant such as DDQ could generate an iminium intermediate and that subsequent nucleophilic addition of an allylsilane moiety could efficiently construct the benzoisoquinolizidine ring system. Furthermore, this transformation is highly stereoselective, which allowed us to access a TBZ alkaloid with high diastereomeric purity. Currently, an asymmetric synthesis of TBZ and DTBZ and their application for neurological disorders are under investigation.

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Supporting Information Available. Experimental details and NMR spectra of all intermediates. These materials are available free of charge via the Internet at http://pubs.acs.org.