Direct Synthesis of Polycyclic Tropinones via Condensation-(4+3) Cycloaddition Cascade Reaction

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Synthetic Method

A concise method of constructing polycyclic tropinone frameworks was developed. The single-step synthesis of polycyclic tropinone consists of an intramolecular (4+3) cycloaddition reaction of *N*-nosyl-pyrrole with oxyallyl cation that was generated in situ by an intermolecular condensation reaction of the nucleophilic functional groups on a tethered pyrrole with the aldehyde of 2-(silyloxy)-acrolein. This cascade reaction afforded various polycyclic tropinones including tri-, tetra-, and pentacyclic systems in high yields as single diastereomers.

· Main text

Tropane alkaloids have received a great deal of attention by virtue of their potent biological activities,[1] and some of them, such as atropine, cocaine, and scopolamine, have been used as efficient pharmaceuticals.[2] In addition to these simple tropane alkaloids, polycyclic tropanes have also recently received a lot of attention as not only challenging synthetic targets, but also novel lead compounds for pharmaceuticals, because most polycyclic alkaloids that have a tropane framework exhibit particular and interesting biological activities.[3] Thus, the development of an exhaustive and concise method of constructing novel polycyclic tropane frameworks is expected to lead to the discovery of new lead compounds and biofunctional molecules.[4]

One of the most powerful synthetic approaches to tropane frameworks is a (4+3) cycloaddition reaction of pyrroles with oxyallyl cations, giving rise to tropinones.[5] Furthermore, an application of the (4+3) cycloaddition reaction to an intramolecular reaction is expected to afford polycyclic tropanes most efficiently. However, although there have been several examples of the intramolecular (4+3) cycloaddition reaction of furanes with oxyallyl cations,[5] reaction with pyrroles was not reported until very recently. Because, the use of pyrroles as four-carbon units is generally difficult due to competition with the Friedel-Crafts type reaction.[6] Furthermore, the high reactivity of pyrrole and instability of oxyallyl cation also cause a problem in the preparation of precursor for the intramolecular cycloaddition reaction. Very recently, Chiu *et al* have just reported first intramolecular (4+3) cycloaddition reaction of pyrroles by using epoxy enolsilanes as a source of the oxyallyl cation.[7] On the other hand, we have recently found that *N*-nosyl pyrrole is an efficient four-carbon unit for [4+3] cycloaddition reaction,[8] and the reaction with 2-(silyloxy)-acrolein **2a** as a three-carbon unit is smoothly catalyzed by $Cu(OTf)_2$ or $Sc(OTf)_3$.[9-10] Therefore, we expected that an intramolecular (4+3) cycloaddition would be possible by the generation of an oxyallyl cation from some precursor possessing both *N*-nosyl pyrrole and 2-(silyloxy)-acrolein units as shown by **A** in Scheme 1. Furthermore, since the preparation of such a precursor might be troublesome due to the high reactivity of pyrroles, we planned to generate an oxyallyl cation in situ by the condensation of the aldehyde of 2-(silyloxy)-acrolein with nucleophiles such as hydroxyl, amino, and thiol groups that are tethered by the *N*-nosyl pyrrole. This method would provide easier

access to a cycloaddition precursor, which is expected to be amenable to a wide range of substrates. Herein, we report a direct and concise method for the construction of polycyclic tropinones by the intramolecular (4+3) cycloaddition reaction of pyrroles with an oxyallyl cation.

<< **Scheme 1**>>

We first attempted the reaction of *N*-nosyl-2-hydroxypropyl pyrrole **1a** to investigate whether the hydroxypropyl group could serve as the tether for the proposed cascade reaction (Table 1). Thus, we initially applied the conditions of the intermolecular (4+3) cycloaddition reaction of *N*-nosyl pyrroles to **1a**, i.e., **1a** was treated with **2a** in the presence of a catalytic amount of $Cu(OTf)_2$ in nitromethane at 0 °C.[9] As we expected, the use of 20 mol % of $Cu(OTf)_2$ afforded the desired tricyclic tropinone **3a** in 58% yield as a single diastereomer (entry 1). The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis (see Supporting Information).[11] Although the yield of **3a** was modest, the result obtained with **3a** encouraged us to further optimize the reaction conditions. Whereas the use of $Sc(OTf)_3$ as the catalyst slightly decreased the yield (entry 2), a similar reaction in hexafluoroisopropanol (HFIP) proceeded smoothly and increased the yield substantially even when 10 mol% of $Sc(OTf)_3$ was used (entry 3). Thus, subsequent optimization was conducted with 10 mol% of catalyst in HFIP. The reaction using hard Lewis acids such as BF_3•OEt_2, Et_2AlCl, and TMSOTf also proceeded smoothly to give **3a** in 78%, 52%, and 81% yields, respectively (entries 4-6). In addition, the use of protic acids further increased yields, and **3a** was obtained in high yields (ca. 90%) in all cases (entries 7-9). As a bis(trifluoromethanesulfonyl)imide (Tf_2NH) catalyzed the reaction at the fastest rate among the protic acids (entry 9), we adopted Tf_2NH as the catalyst. A lower catalyst loading (4 mol %) showed a decline in yield, and **3a** was obtained in 69% yield (entry 10). Similar reactions in other solvents, such as dichloromethane and nitromethane, barely proceeded, giving **3a** in 5% and 18% yields, respectively, and most of the starting material **1a** was recovered. Thus, it was found that the combination of Tf_2NH as the catalyst and HFIP as the solvent is essential for the cascade reaction that leads to polycyclic tropinones.[12-13] In addition, the silyl enol ether moiety and aldehyde group of **2a** were also necessary for the reaction.[14]

<<Table 1>>

We proposed a reaction mechanism based on the density functional theory (DFT) calculation as shown in Scheme 2. The reaction is likely to be initiated by a condensation reaction of the hydroxyl group of **1a** with the protonated aldehyde moiety of **2a-H$^+$** to afford the oxonium cation **B** through the hemiacetal **A**. The oxonium cation **B** is an equivalent of oxygen-stabilized oxyallyl cation **TS**, which is the transition state of the intramolecular (4+3) cycloaddition reaction. The (4+3) cycloaddition reaction with oxyallyl cation is generally accepted to proceed through stepwise mechanism,[15] and the cycloaddition reaction of **B** is also calclated to proceed through a stepwise mechanism, i.e., the Friedel-Crafts type addition of pyrrole to the oxyallyl cation initially occurred through an *endo*-type transition state, and the subsequent addition of the resulting silyl enol ether of **Int$_{C1\text{-}C2}$** was latter induced to afford **C** (vide infra).

<<Scheme 2>>

A two-dimensional (2D) relaxed potential energy surface (PES) scan for the intramolecular addition of pyrrole to the oxyallyl cation showed two low-energy pathways from the endo-type oxonium cation **B** along the edges of the 2D energy scan profile (Figure S3, Supporting Information). In both of the pathways, the transition states indicated a stepwise rather than concerted mechanism. The concerted pathway lies along the diagonal axis of the energy profile, showing a higher energy barrier compared to the stepwise mechanism. In order to explain the feasibility and order of the stepwise formation of two bonds in the intramolecular cycloaddition reaction, we calculated the energy profiles for both pathways. These calculations revealed that the addition of pyrrole moiety to the oxyallyl cation preferably occurs through the pathway involving the formation of a terminal C-C bond (C1-C2) at first (Scheme 3, path 'a') to afford the intermediate **Int$_{C1\text{-}C2}$**, resulting in a ten-membered ring followed by the formation of a C3-C4 bond. It seems more likely that the initial cyclization of **B** favored a six-membered ring formation (**Int$_{C3\text{-}C4}$**) through **TS$_{C3\text{-}C4}$** (4.4 kcal/mol vs 6.0 kcal/mol) over a ten-membered ring (**Int$_{C1\text{-}C2}$**). This is because the transition states for the formation of a six-membered ring (**TS$_{C3\text{-}C4}$**) in the first step showed two short attractive oxygen-hydrogen (O-H) interactions between oxygens at the Ns group and hydrogens

around the bond-forming carbons (2.75 Å and 2.30 Å) (Figure S4, Supporting Information), which is shorter compared to those in the ten-membered ring ($\mathbf{TS_{C1\text{-}C2}}$, 2.71 Å and 3.12 Å). However, the significant differences between the energy barrier for the formation of the next six-membered ring in the final step caused path 'a' to be preferable to path 'b'. The corresponding transition states $\mathbf{TS_{C3\text{-}C4}}$ (path 'a') is well stabilized by two attractive short oxygen-hydrogen (O-H) interactions (3.05 Å and 2.21 Å, Figure 1). On the other hand, the similar interaction in the alternative pathway ($\mathbf{TS_{C1\text{-}C2}}$) is weak (Scheme 3, path 'b'). As a result, ring closure occurs through $\mathbf{TS_{C3\text{-}C4}}$ (1.9 kcal/mol), resulting cationic cycloadduct **C**, which leads to tricyclic product **3a**. In addition, the another similar pathway involving *exo*-type **B** and corresponding *exo*-transition states are relatively unstable requiring high energy demand compared to *endo*-route (Figure S5, Supporting information). Moreover, we were unable to locate the transtion state for the conversion of $\mathbf{Int_{C3\text{-}C4}}$ to $\mathbf{Int_{C1\text{-}C2}}$. So, we cannot avoid the alternative mechanism in which, C3-C4 bond is formed in the first step followed by aza cope rearrangement and the ring closure in the final step leading to **3a.** In either case, the calculation study revealed that the nosyl group plays a significant role in the stabilization of the transition state. Indeed, the corresponding polycyclic tropinones were not obtained by the reaction of an *N*-substituent other than the Ns group, such as Boc, Cbz, Ac, and free NH groups.[16-17]

<<Scheme 3>> <<Figure 1>>

Having established a method for the single-step construction of tricyclic tropinones, we next examined the cascade reactions with other pyrroles leading to various tricyclic tropinones (Table 2). The similar reaction of pyrrole **1b** possessing *cis*-allyl alcohol at the 2-position afforded a desired tricyclic tropinone **3b** in quantitative yield (entry 1). We next examined *N*-nosyl-2-hydroxyethylpyrrole **1c** as a one-carbon dehomologated analog, and the desired tricyclic tropinone including the tetrahydrofuran ring **3c** was obtained in 51% yield (entry 2). The lower yield of **3c** was probably due to the strained transition state for forming a 5,7-fused ring system, and a dilute condition (0.01 M) was needed to avoid the intermolecular (4+3) cycloaddition reaction prior to the condensation. On the other hand, in the case of one-carbon homologated analog **1d**, the reaction proceeded smoothly to give tricyclic tropinone including oxepane ring **3c** in 76% yield as a single

diastereomer (entry 3). Surprisingly, even the reaction of further homologated analog **1e**, leading to an eight-membered oxocane ring, also proceeded to give corresponding tropinone **3e** in 44% yield as a single diastereomer under dilute conditions (entry 4). Next, enantiomerically enriched alcohol **1f** (87% *ee*), obtained by the CBS reduction of corresponding ketone was examined,[18] and **3f** was obtained in 50% yield as a single diastereomer in 85% *ee*, suggesting that the chirality of alcohol transfers to the tropane skeleton (entry 5). It is noteworthy that the cycloaddition reaction proceeded without losing the stereochemical integrity of the alcohol, although such benzylic alcohols are easily racemized under acidic conditions.[19] Furthermore, functional groups other than hydroxy groups, such as amines and thiols, were investigated to determine whether they could serve as a tether. Interestingly, the reaction of *N*-nosyl-2-mercaptopropyl pyrrole **1g** as a thiol tether proceeded similarly to afford the thiopyran **3g** in 93% yield as a single diastereomer (entry 6). In clear contrast, the reaction of an amine-tethered analog such as *N*-nosyl-2-benzylaminopropyl pyrrole did not give tropinone, unfortunately, even when a stoichiometric amount of Tf_2NH was used, and only the starting material was recovered.[20] Therefore, the cascade reaction was found to be applicable to the synthesis of various tricyclic tropinones possessing ether and thioether rings.

<<Table 2>>

Having synthesized various tricyclic tropinones, we next attempted to construct more complex polycyclic tropinones, i.e., we investigated the reaction with various pyrroles possessing cyclic alcohols (Table 3). We first examined pyrrole **1h**, which has *trans*-cyclohexanol as a tether. Since the secondary hydroxyl group of **1h** was protected by a TBS group, both the removal of the TBS group and the cascade reaction were conducted in one pot. Initial treatment of **1h** with 20 mol % of Tf_2NH in HFIP afforded deprotected secondary alcohol, and three-carbon unit **2a** was then added to afford tetracyclic tropinone **3h** in 92% yield as a sole product (entry 1). In addition, the similar reaction of *cis*-cyclohexanol derivative **1i** also proceeded smoothly to give desired **3i** in 73% yield as a single diastereomer (entry 2). The five-membered ring analog **1j** was also converted into **3j** in 88% yield, and no other stereoisomers were detected (entry 3). The reaction was applicable to the tetrahydronaphthalene ring system, and the pentacyclic

tropinone **3k** was obtained from **1k** in 67% yield (entry 4). The reaction of more a complicated pyrrole, **1l**, which was expected to be applicable to the natural product synthesis, proceeded smoothly. That is, direct treatment of the mixture of TBS-protected **1l** and 2-(silyloxy)-acrolein **2a** with only 10 mol% of Tf_2NH afforded the tetracyclic tropinone **3l** in 91% yield as a single diastereomer (entry 5). The structure of **3l** was unambiguously confirmed by X-ray crystallographic analysis (see Supporting Information).[21] Thus, the reaction was proven to be useful for the construction of various complex polycyclic tropinones. On the other hand, the phenolic hydroxyl group was unusable as a tether, and only intermolecular (4+3) cycloadduct was obtained.[22]

<<Table 3>>

Finally, we examined the application of 3-substituted-2-(silyloxy)-acrolein to construct the α-substituted tropinones (Scheme 4). The reaction of an *E*/*Z* mixture of 2-(silyloxy)-3-methyl-acrolein **2b** with *N*-nosyl-2-hydroxylpropyl-pyrrole **1a** afforded α-methyl-tricyclic tropinone **3n** as a sole product in 92% yield. The stereochemical outcome of this reaction from the *E*/Z mixture of **2b** suggested that the *E*-isomer was isomerized to form the most stable configuration. Furthermore, the reaction of 3,3-dimethyl analog **2c** also proceeded smoothly to give α,α-dimethyl tricyclic tropinone **3o** in excellent yield. This is a useful reaction for constructing both the quarternary carbon center and the tetra-substituted carbon center bearing nitrogen. We expect it be applied to the synthesis of complex biologically active compounds and natural products.

<<Scheme 4>>

In conclusion, a concise method of constructing a polycyclic tropinone framework was developed. Various tropinones, including tri-, tetra-, and pentacyclic systems, were synthesized in a single step by the reaction of hydroxyl-tethered *N*-nosyl-pyrroles with 2-(silyloxy)-acroleins. The reaction proceeded smoothly via condensation of acrolein with a tethered-hydroxyl group followed by the intramolecular (4+3) cycloaddition reaction of pyrroles and resulting oxyallyl cation. The polycyclic tropinones were

obtained in high yields as single diastereomers, and thus the optically active starting materials afford asymmetric tropinones. The computational studies suggested that the intramolecular cycloadditon reaction proceeds through an unexpected stepwise mechanism. Since the cascade reaction readily provides various complex frameworks in three dimensions, development of novel biologically active compounds would be expected. An application of this cascade reaction to the total synthesis of complex natural products is under way in our laboratory.

•Experimental Section

Experimental details, full data, ^{1}H and ^{13}C NMR spectra of each intermediate, and data of X-ray analysis are available in Supporting Information.

•Acknowledgements

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[11] CCDC No.1826702

[12] Although 30 mg (0.097 mmol) of **1a** was used for the investigation of experimental condition, the optimized condition was applicable to the gram scale synthesis. The reaction using 1.0 g (3.2 mmol) of **1a** proceeded smoothly to afford **3a** in 86% yield.

[13] The nosyl group of **3a** was readily removed by treatment with thiophenol to give secondary amine **4a** in 72% yield.

<Equation here>

[14] The similar reaction of **1a** with **2d** afforded no cycloadducts, whereas the reaction with **2e** gave the desired **3a** in 25% NMR yield.

<<structures of **2d** and **2e** here>>

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[16] The reactions of free pyrrole and Boc-protected pyrrole showed rapid decomposition of starting materials. In the cases of Cbz- and Ac-protected pyrroles, the reaction afforded inseparable multi products, in which trace amount of desired tricyclic tropinones were detected.

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[19] Although the similar reaction afforded **3f** in 76% yield in 0.4 M HFIP solution, *ee* decreased to 64%.

[20] *N*-nosyl-2-benzylaminopropyl pyrrole was treated with 2.0 equiv of **2a** and 10 ~ 110 mol% of Tf_2NH in HFIP (0.2M) at 0 °C.

<<equation here>>

[21] CCDC No.1825405

[22] The reaction of **1m** possessing phenol group instead of alcohols afforded intermolecular cycloadduct **3m** in 48% yield. Since the reaction of **1m** afforded the mixture of **3m** and TBS ether of **3m**, the yield of **3m** was figured out after treatment of the mixture with TBAF to converge into **3m**.

<<Equation here>>

Scheme and Figure legends

Scheme 1. Plan for the intramolecular [4+3] cycloaddition reaction of pyrroles.

Scheme 2. Proposed mechanism.

Scheme 3. Energy profile diagram of cycloaddition reaction of 1a with 2a

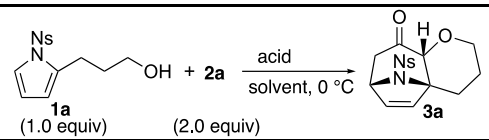
Scheme 4. Direct [4+3] cycloaddition reaction of 1a with 2-(silyloxy)-3-substituted-acrolein 2b and 2c.

Figure 1. Optimized transition states for stepwise mechanism (path ‘a’). Bond lengths in Å.

Table 1

Table 1. Condensation-intramolecular [4+3] cycloaddition cascade reaction leading

to tricyclic tropinone **3c**.

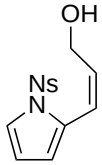
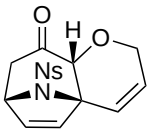
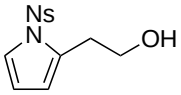
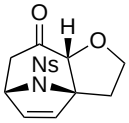
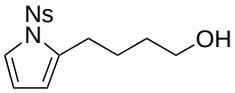
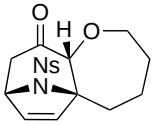
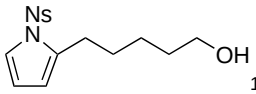
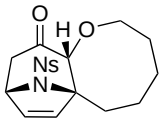
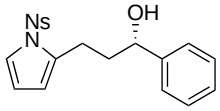
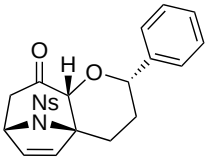
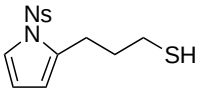
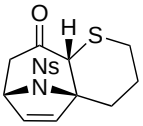


Entry	Acid (mol %)	Solvent	Time (min)	Yield (%)[a]
1	$Cu(OTf)_2$ (20)	CH_3NO_2	300	58
2	$Sc(OTf)_3$ (20)	CH_3NO_2	300	45
3	$Sc(OTf)_3$ (10)	HFIP	85	76
4	$BF_3{\bullet}OEt_2$ (10)	HFIP	50	78
5	Et_2AlCl (10)	HFIP	85	52
6	TMSOTf (10)	HFIP	60	81
7	TFA (10)	HFIP	790	91
8	*p*-TsOH (10)	HFIP	205	91
9	Tf_2NH (10)	HFIP	30	88
10	Tf_2NH (4)	HFIP	80	69
11	Tf_2NH (30)	CH_2Cl_2	240	5[b]
12	Tf_2NH (30)	CH_3NO_2	240	18[b]

[a] isolated yield. [b] ^1H NMR yield using $CHBr_3$ as an internal standard.

Table 2

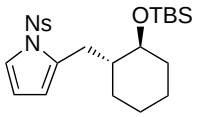
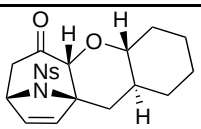
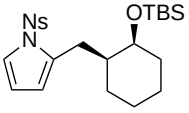
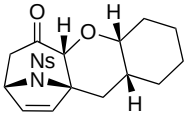
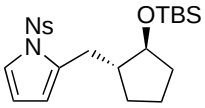
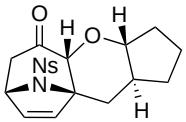
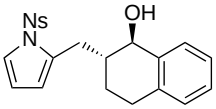
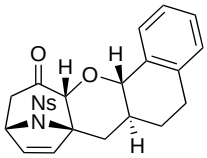
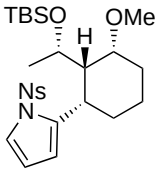
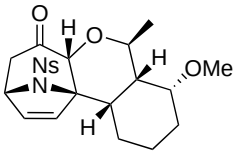
Table 2. Cascade reactions of **2** with pyrroles possessing various tethers in chains.[a]

Entry	Substrate	Tf_2NH (mol%)	Product (yield)[b]
1[c]	 **1b**	10	 **3b** (quant)
2[d]	 **1c**	20	 **3c** (51%)
3	 **1d**	10	 **3d** (76%)
4[d]	 **1e**	10	 **3e** (44%)
5[e]	 87% *ee* **1f**	10	 85% *ee* **3f** (50%)
6[d]	 **1g**	10	 **3g** (93%)

[a] Reaction condition: **1** (1.0 equiv), **2a** (2.0 equiv), HFIP (0.2 M), 0 °C. [b] Isolated yield. [c] 3.0 equiv of **2a** was used. [d] The reaction was conducted under a diluted condition (0.01 M). [e] The reaction was conducted under a concentrated condition (1.0 M).

Table 3

Table 3. Cascade reactions of **2a** with pyrroles possessing various cyclic alcohols as tethers.[a]

Entry	Substrate	Tf_2NH (mol%)	Product (yield)[b]
1	 **1h**	20	 **3h** (92%)
2	 **1i**	20	 **3i** (73%)
3	 **1j**	20	 **3j** (88%)
4	 **1k**	10	 **3k** (67%)
5[c]	 **1l**	10	 **3l** (91%)

[a] Reaction condition: **1** (1.0 equiv), **2a** (2.0 equiv), HFIP (0.2 M), 0 °C. [b] Isolated yield. [c] 3.0 equiv of **2a** was used.

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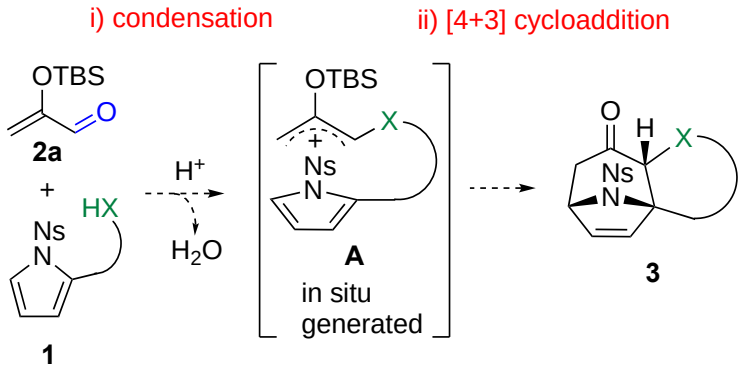
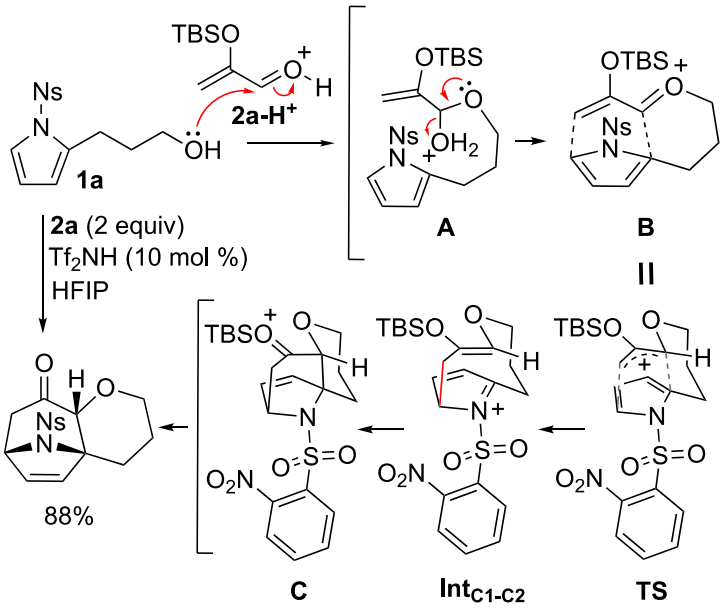
A concise method of constructing polycyclic tropinone frameworks was developed. The single-step synthesis of polycyclic tropinone was accomplished by the cascade reaction of condensation and (4+3) cycloaddition reaction of *N*-nosyl-pyrrole with an oxyallyl cation generated in situ, and this cascade reaction afforded various polycyclic tropinones including tri-, tetra-, and pentacyclic systems in high yields as single diastereomers.

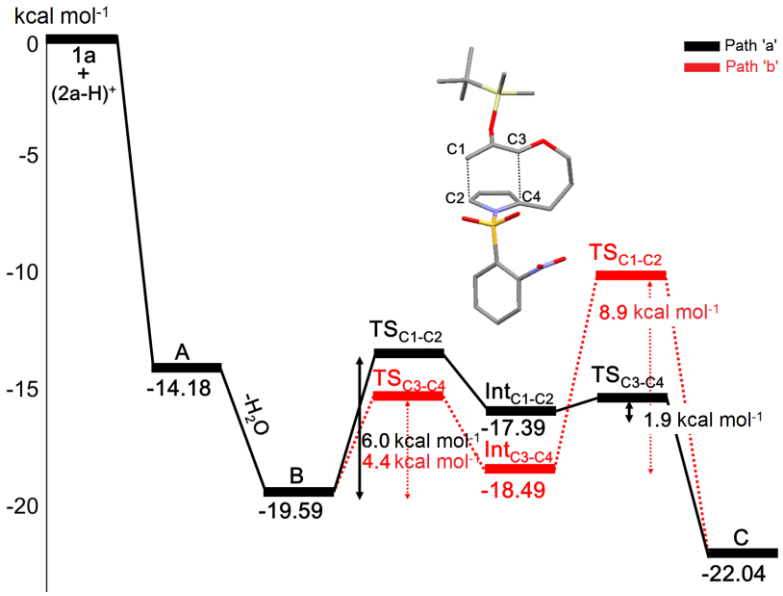
Keywords: synthetic method • cycloaddition • tropane alkaloid • pyrrole • oxyallyl cation



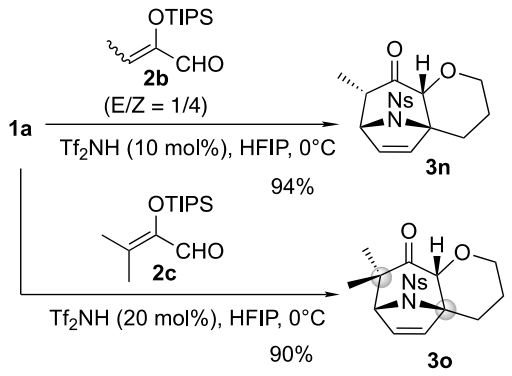
Scheme 1



Scheme 2.



Scheme 3.



Scheme 4.

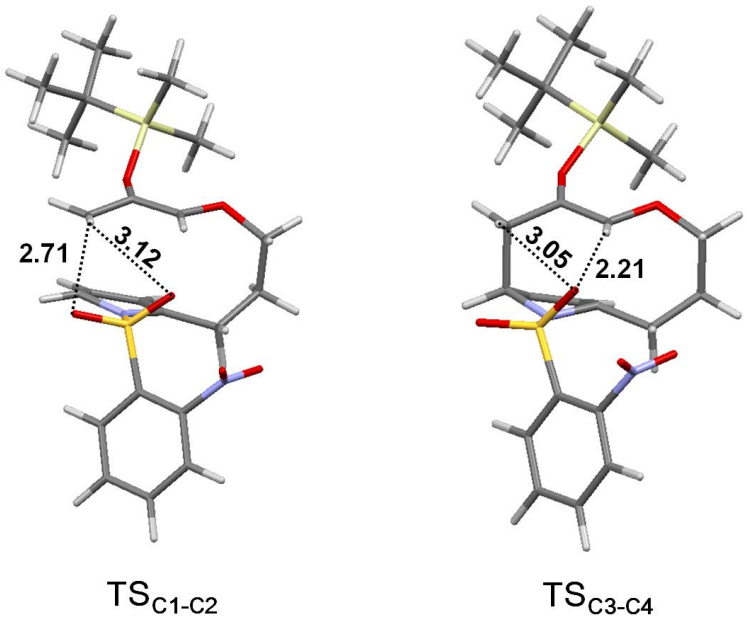
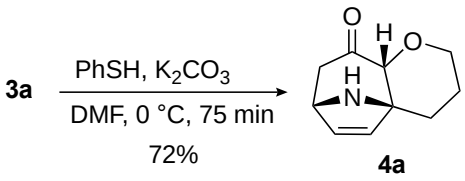
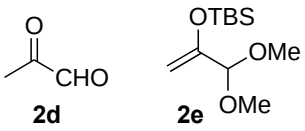


Figure 1.



Reference 13



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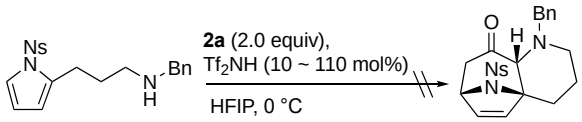
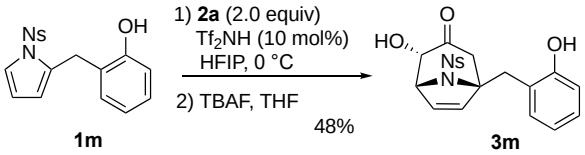


Reference 19



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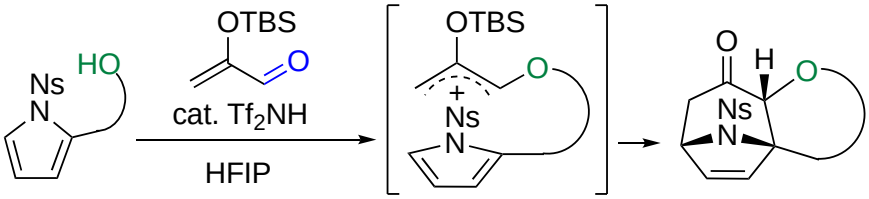

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