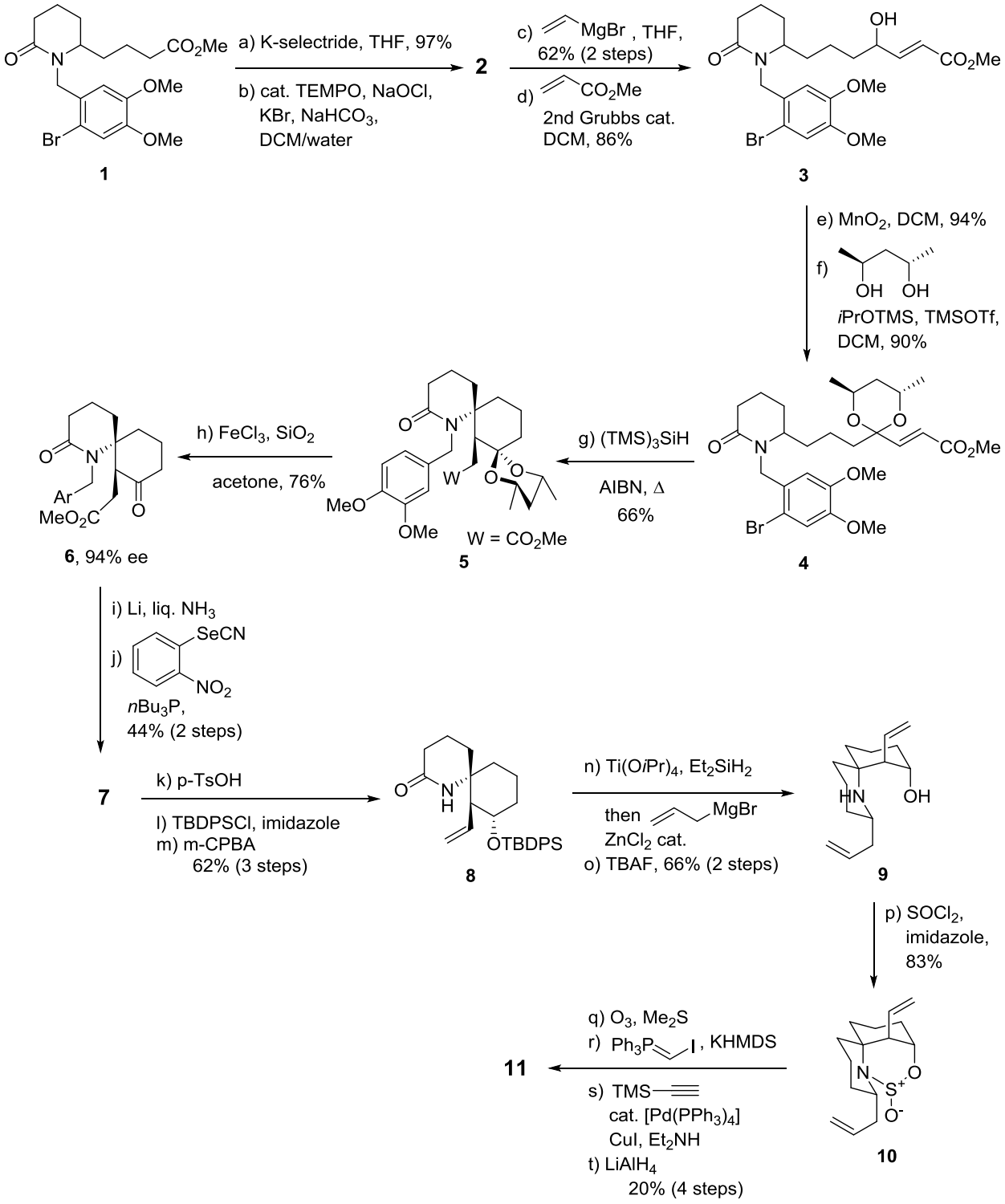
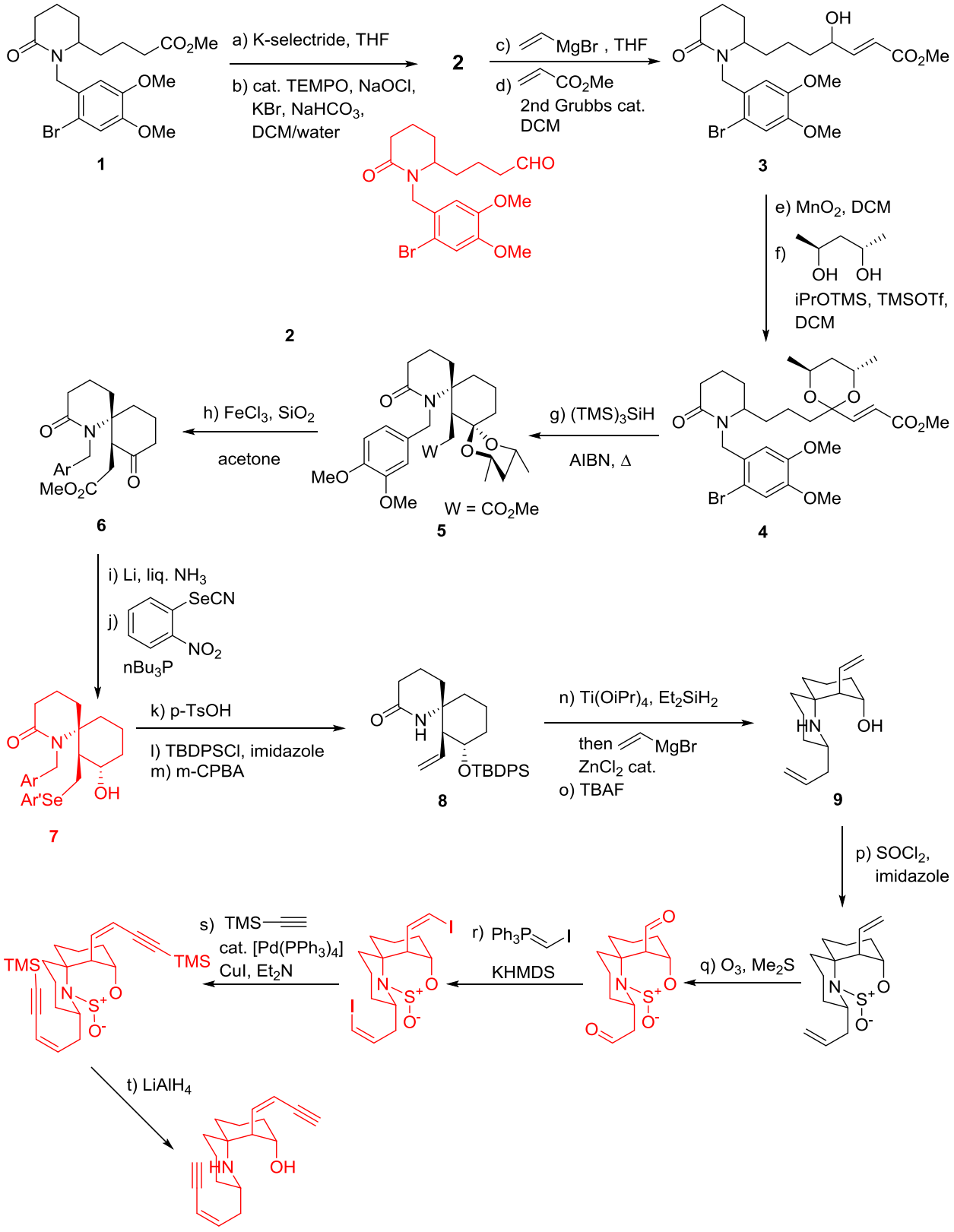
Total Synthesis of (–)-Histrionicotoxin



1) Give the missing compound **2** and the mechanisms for the transformations b) and d).
2) What is the mechanism for the key-step to form **5**.
3) Give the structure of **7** and the mechanisms of the two steps yielding to it.
4) Give the final product **11** and the intermediates after steps q), r) and s).

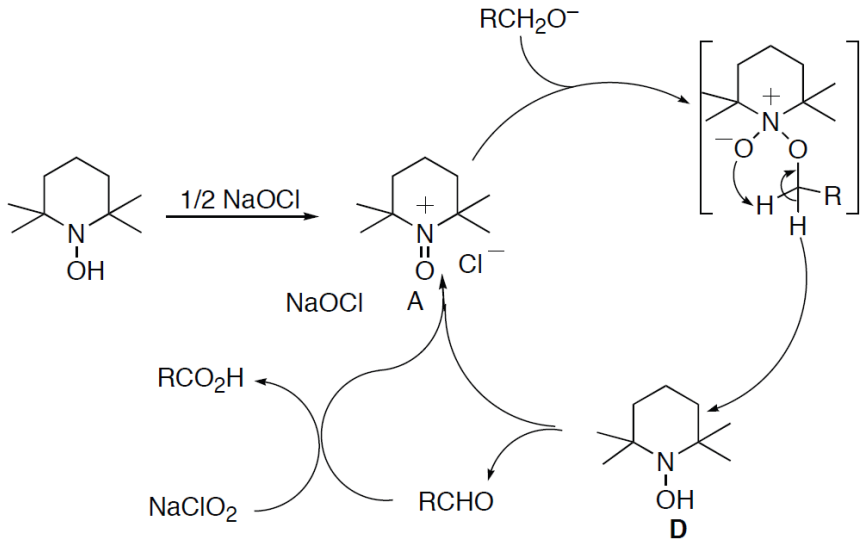
Submitted by Daniel

Total Synthesis of (−)-Histrionicotoxin



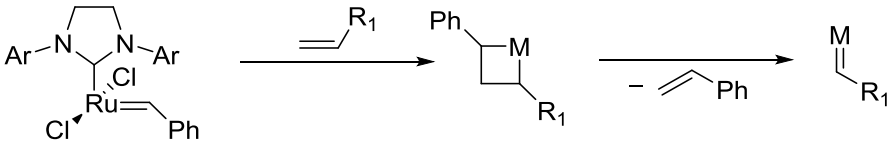
Submitted by Daniel

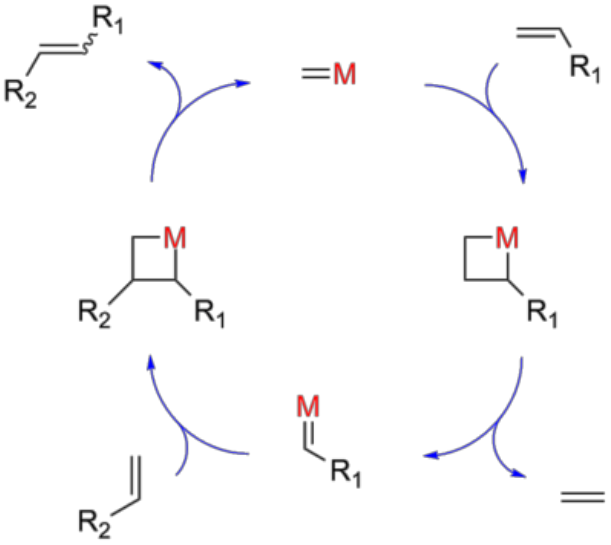
Mechanism TEMPO oxidation



Mechanism metathesis

Initiation





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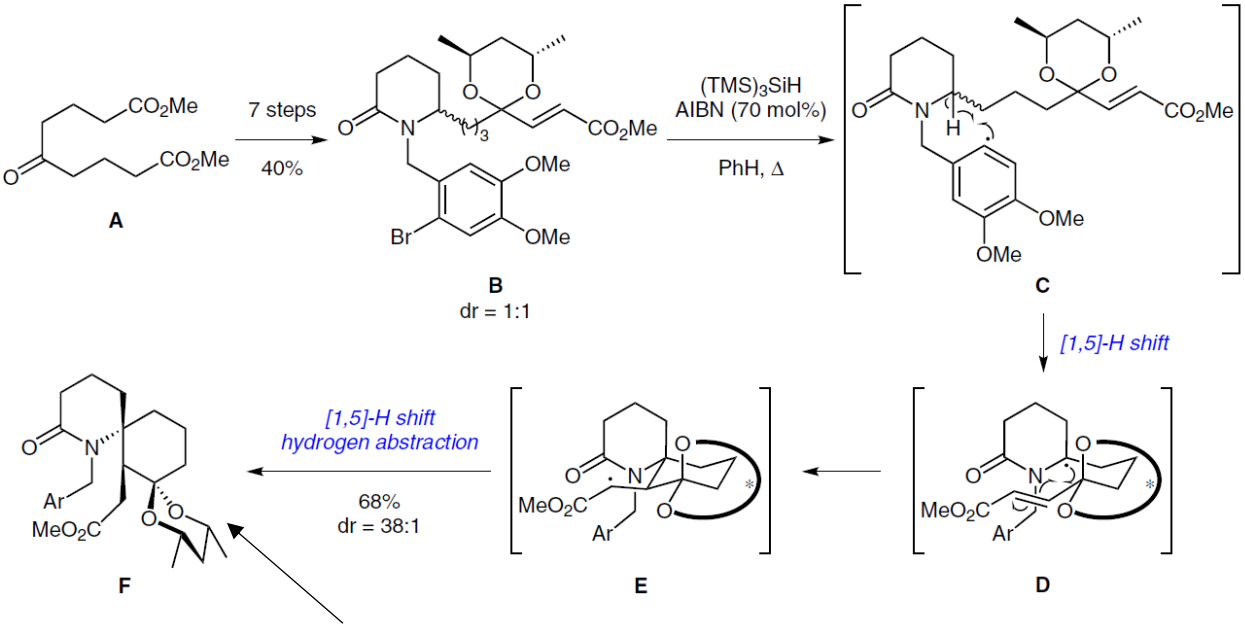
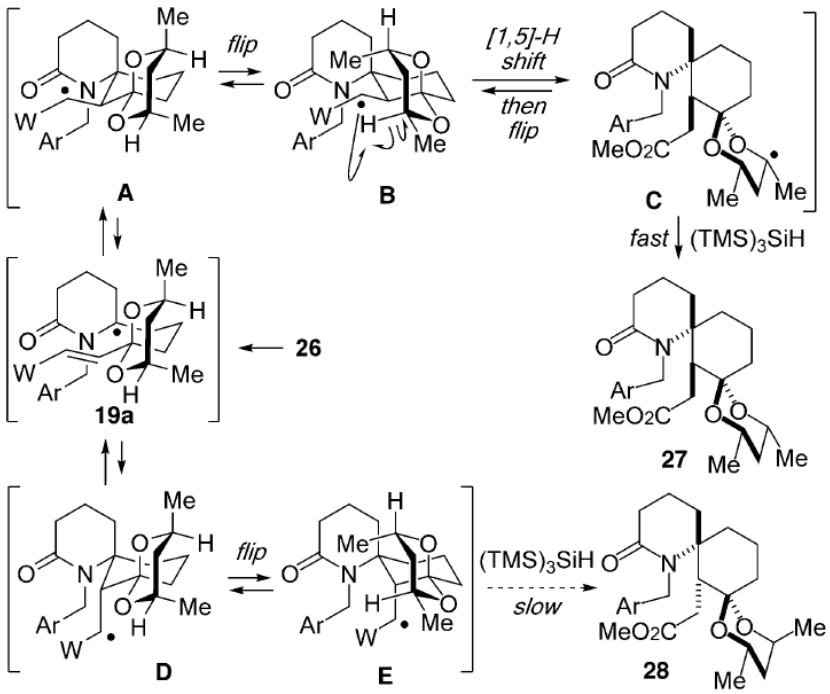
Stereoselective Radical Translocation-Cyclization Reaction



Inversion of methyl-group of acetal!



Scheme 6. Rationale for the observed diastereoselectivity and stereochemical inversion.

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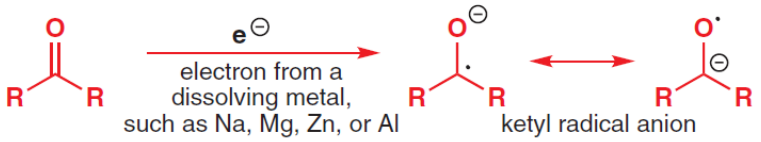
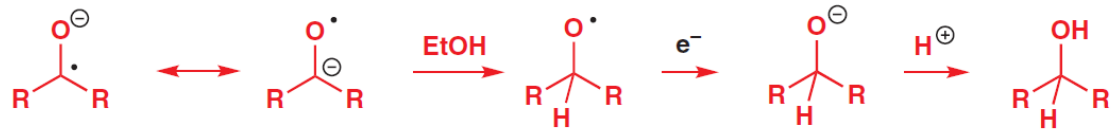
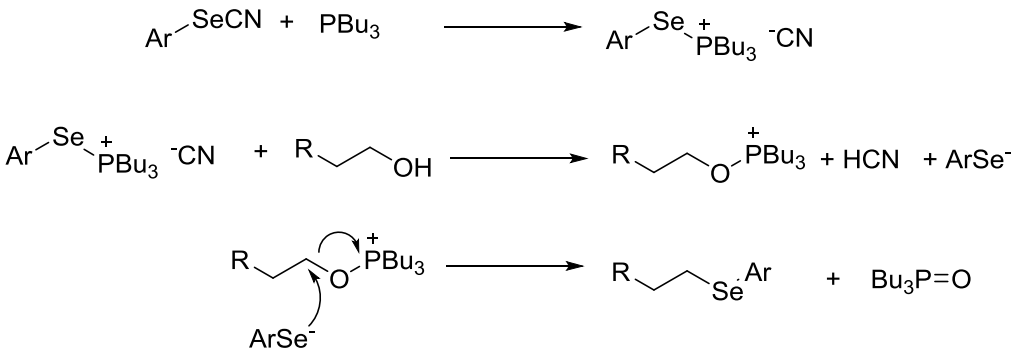
Bouveault–Blanc reduction



reaction of the ketyl radical anion in protic solvents



Conversion into selenide



Ref.: *J. Org. Chem.* **1976**, *41*, 1485–1486.

Natural Products Synthesis

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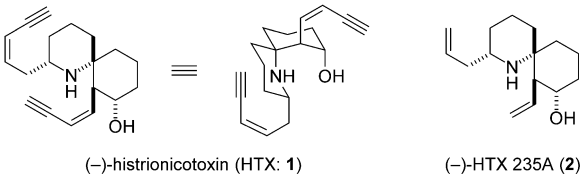
Total Synthesis of (−)-Histrionicotoxin through a Stereoselective Radical Translocation–Cyclization Reaction

*Manabu Sato[+], Hiroki Azuma[+], Akihiro Daigaku[+], Sota Sato, Kiyosei Takasu, Kentaro Okano, and Hidetoshi Tokuyama**

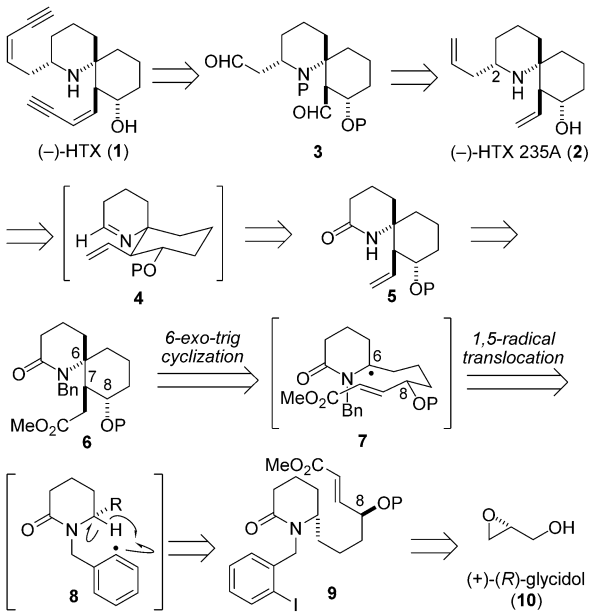
Abstract: *Stereoselective total syntheses of (−)-histrionicotoxin and (−)-histrionicotoxin 235A are described. The 1-azaspiro[5.5]undecane skeleton was constructed diastereoselectively by a radical translocation–cyclization reaction involving a chiral cyclic acetal; the use of tris(trimethylsilyl)silane was crucial for the high diastereoselectivity. The cyclization product was converted into (−)-histrionicotoxin 235A through a one-pot partial-reduction–allylation reaction of a derivative containing an unprotected lactam. Finally, two terminal alkenes were transformed into enynes with the 1,3-amino alcohol protected as an oxathiazolidine oxide to complete the total synthesis of (−)-histrionicotoxin.*

Histrionicotoxin (**1**, HTX), isolated by Daly, Witkop, and co-workers from the poison-arrow frog *Dendrobates histrionicus*, possesses activity as a noncompetitive blocker of nicotinic acetylcholine receptors (Scheme 1).[1,2] The structure of **1**, consisting of a 1-azaspiro[5.5]undecane core with two acid-labile *Z* enyne side chains, has attracted considerable interest from the synthetic community as a platform to demonstrate synthetic strategies for the construction of an azaspirobicyclic system.[3] Three total syntheses of optically active HTX (**1**)[4] and two total syntheses of racemic **1**[5] have been reported previously on the basis of a variety of strategies for the construction of the azaspirobicyclic system. However, no strategy based on radical cyclization[6,7] has been reported so far for the stereocontrolled construction of the spirocyclic system in an optically active form. Herein we report the total synthesis of (−)-HTX (**1**) and (−)-HTX 235A (**2**) through the stereoselective construction of the 1-azaspiro[5.5]undecane core by a diastereoselective radical translocation–cyclization cascade.



Scheme 1. Structures of HTX (**1**) and HTX 235A (**2**).

We planned to synthesize (−)-HTX (**1**) from (−)-HTX 235A (**2**)[4a,b] by conversion of the two terminal olefins into the enyne side chains (Scheme 2).[4] We decided to introduce the allyl group diastereoselectively onto the δ-lactam **5** by developing a one-pot partial-reduction–allylation protocol via imine **4**. For the construction of the 1-azaspiro-[5.5]undecane core, we planned to apply the radical translocation–cyclization reaction developed in our group[8] to δ-lactam **9** bearing an α,β-unsaturated ester side chain. Thus, sp^2 radical **8**, generated from iodide **9** under radical conditions, should undergo 1,5-radical translocation to provide a more stable sp^3 radical **7**.[8] Then, 6-*exo*-trig cyclization via a chair-like conformation **7** bearing an equatorial OP group should proceed to furnish an azaspirobicyclic compound **6** possessing



Scheme 2. Retrosynthetic analysis of HTX (**1**) and HTX 235A (**2**). Bn = benzyl.

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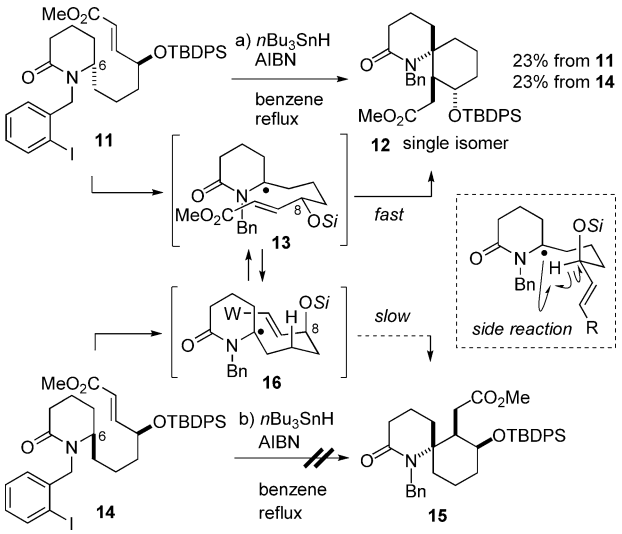
the desired stereostructure, including the C6 spiro center, the substituent at the C7 position, and the hydroxy group at the C8 position. Substrate **9** for the radical reaction would be readily assembled by conventional reactions starting from (+)-(*R*)-glycidol (**10**).

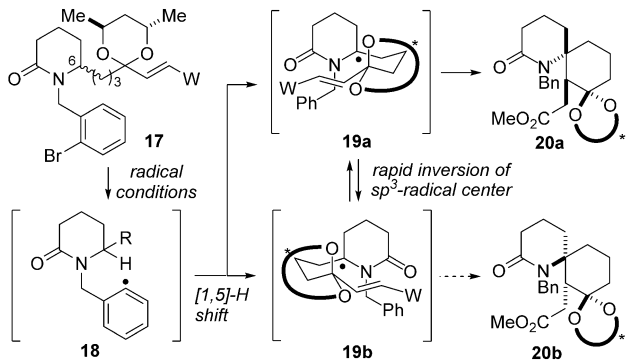
We initiated the project by the stereoselective preparation of substrate **11** from (+)-(*R*)-glycidol (**10**)[9] and subjected **11** to radical cyclization conditions (Scheme 3). Although the expected product **12** of cyclization by the 6-*exo*-trig mode was obtained as a single diastereomer,[10] the yield was just 23%.



Scheme 3. Initial attempts at the radical translocation–cyclization reaction. AIBN = azobisisobutyronitrile, TBDPS = *tert*-butyldiphenylsilyl.

We also examined the reaction of **14**, which is the C6 epimer of **11**. Interestingly, the reaction of **14** also afforded product **12** as a single diastereomer, thus indicating that inversion of configuration occurred after 1,5-radical translocation, and subsequent 6-*exo*-trig cyclization proceeded via **13** to avoid 1,3-diaxial interactions in **16**. It can be concluded that the configuration of the spiro center and the C7 center bearing the side chain was only controlled by the stereogenic C8 center and did not depend on the configuration of the C6 position of the substrates. We reasoned that the low yield was due to an undesired second 1,5-radical translocation to provide an O-stabilized allyl radical, which would decompose during the reaction.

On the basis of these results, we revised the strategy for the construction of the 1-azaspiro[5.5]undecane core (Scheme 4). To prevent the undesired 1,5-radical translocation while maintaining the chiral environment, we designed a substrate of type **17** bearing a chiral cyclic acetal[11] in the side chain. We hoped that radical cyclization of a substrate containing a chiral cyclic acetal derived from (+)-(2*S*,4*S*)-pentanediol or its enantiomer would proceed via a stable chair-like conformation **19a** to furnish the desired azaspirobicyclic product **20a**. According to the results with substrates **11** and **14** (Scheme 3), we expected that a 1:1 mixture of diastereomers with respect to the C6 position would provide one product through rapid inversion of the sp^3 radical center

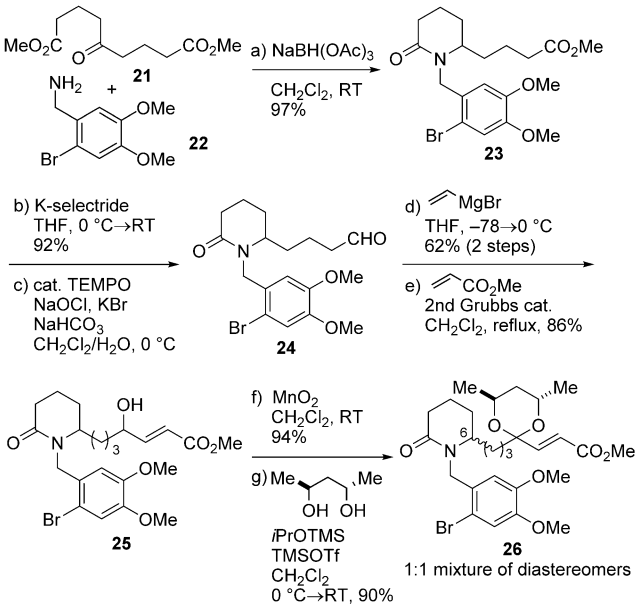


Scheme 4. Working hypothesis for the radical reaction of a substrate containing a chiral acetal.

and 6-*exo*-trig cyclization via the sterically favorable conformation.

With this idea in mind, we developed a facile and scalable assembly of substrate **26** bearing a chiral cyclic acetal (Scheme 5). Reductive amination[12] of the readily available ketodiester **21** and benzylamine **22**[13] gave δ-lactam **23**, which was then converted into aldehyde **24** through reduction and oxidation of the resultant primary alcohol. Subsequent 1,2-addition of a vinyl Grignard reagent, followed by cross-metathesis with methyl acrylate afforded the unsaturated ester **25**. Finally, oxidation with MnO_2 and acetal formation of the resultant enone with (+)-(2*S*,4*S*)-pentanediol by the Noyori protocol[14] provided **26** as a 1:1 diastereomeric mixture at the C6 position.

Having synthesized the requisite substrate **26** bearing a chiral cyclic acetal, we tested the radical cyclization. Treatment with nBu_3SnH in benzene at reflux afforded the



Scheme 5. Preparation of chiral acetal **26** for the key reaction. K-selectride = potassium tri-*sec*-butylborohydride, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

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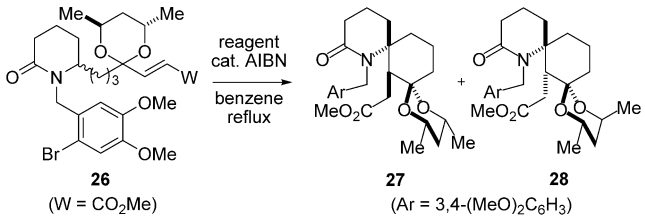
Table 1: Diastereoselectivity of the radical translocation–cyclization reaction of substrate **26** containing a chiral acetal.



Entry	Reagent	Yield [%]	**27**/**28**[a]
1	nBu$_3$SnH	79	3:1
2	Ph$_3$SnH	84	1.7:1
3	(TMS)$_3$SiH	68 (66[b])	38:1

[a] The ratio was determined on the basis of ^{1}H NMR spectroscopy. [b] The reaction was carried out on a 13 g scale.

cyclization product **27** in good yield with moderate diastereoselectivity (Table 1, entry 1). The structure of product **27** was determined unambiguously after conversion into the bromide **29**. X-ray crystallographic analysis revealed that **29** possessed the desired absolute and relative configuration for the synthesis of natural **1** and **2** (Figure 1). The configuration of one acetal methyl group of the major product was inverted in the reaction,[15] whereas that of the minor diastereomer was retained (see below). Furthermore, we observed significant effects of the H-atom source on the diastereoselectivity. Thus, a reaction with Ph$_3$SnH gave a mixture of **27** and **28** in a lower diastereomeric ratio (Table 1, entry 2). Surprisingly, the ratio was dramatically improved when using bulky (TMS)$_3$SiH (entry 3). Eventually, we found that we could carry out the reaction on more than a 10 g scale with (TMS)$_3$SiH.

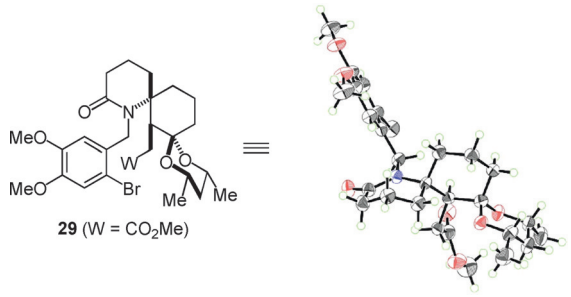
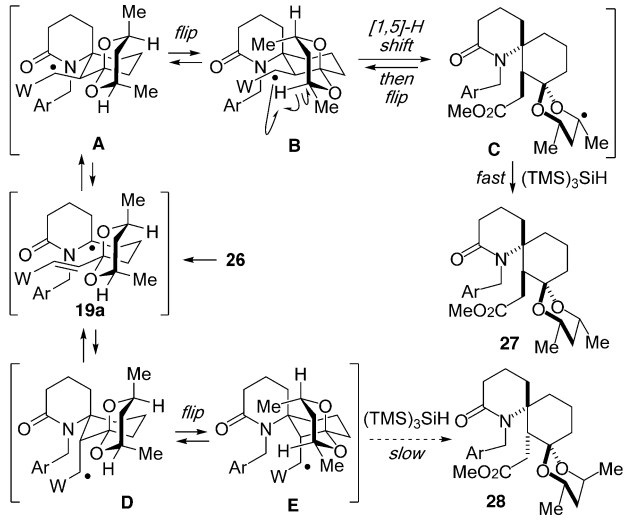


Figure 1. X-ray crystallographic structure of the azaspirocyclic compound **29**, which was prepared from **27** by bromination of the benzene ring.

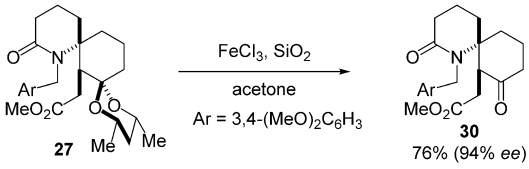
The dependence of the diastereoselectivity on the H-atom source and the stereochemical inversion of the acetal moiety of the major isomer can be rationalized as shown in Scheme 6. The minor isomer **28** would be formed by H abstraction from the relatively hindered radical species **D** or **E**. On the other hand, the major product **27** would be obtained by H abstraction from the readily accessible radical species **C**, which would be formed by conformational flipping of the acetal ring of intermediate **A** to **B** and subsequent 1,5-radical translocation and reflipping of the acetal moiety. We considered that the



Scheme 6. Rationale for the observed diastereoselectivity and stereochemical inversion.

high diastereoselectivity of the reaction with less active[16] and bulky (TMS)$_3$SiH could be due to smooth H-atom transfer to the radical species **C**, which is more readily accessible than other radical species in the equilibrium between **A** and **E**. In contrast, H-atom transfer from active[16] and sterically less hindered H-atom sources would be less selective.

The facial selectivity of the 6-*exo*-trig radical cyclization was determined after removal of the acetal moiety (Scheme 7).[15] Deacetalization was conducted by the treatment of **27** with FeCl$_3$ and silica gel in acetone[17] to provide keto lactam **30**. Surprisingly, compound **30** showed an



Scheme 7. Removal of the acetal moiety to determine facial selectivity.

excellent *ee* value (94% *ee*), which was independent of the H-atom source. Although we currently do not have a clear explanation for this excellent selectivity, it is conceivable that facial selectivity is controlled by the relative rate of the 6-*exo*-trig cyclization step and is independent of the final H-abstraction step for two reasons (Scheme 8). One is that the high *ee* value was independent of the diastereomeric ratio between **27** and **28**. The second is that after configurational inversion of the chiral acetal moiety through the second 1,5-radical translocation (see above) of **d**, the minor product formed by the opposite facial selectivity became the enantiomer of the major product **27**. Therefore, there should be no rate difference for the terminal H-abstraction steps. As for the cyclization step, cyclization via the conformer **a** would be favorable since there would be steric repulsion between one methyl group on the cyclic acetal moiety and a hydrogen atom on the chain in conformer **c**, which leads to *ent*-**27**.

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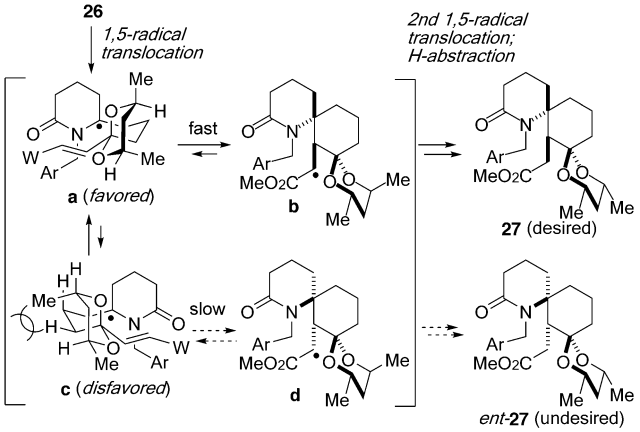
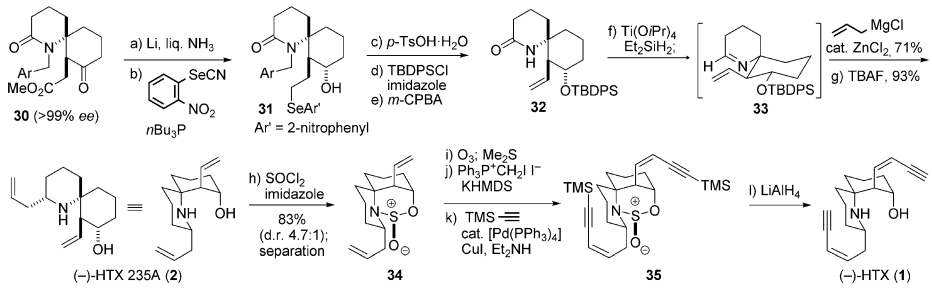


Scheme 8. Rationale for the facial selectivity of the 6-*exo* cyclization.

Having established a highly stereoselective and scalable method for the construction of the azaspirobicyclic skeleton, we focused our attention on the introduction of two enyne side chains (Scheme 9). The optical purity of **30** was increased to > 99 % *ee* by recrystallization. Reduction of ketoester **30**[5a] gave the corresponding diol as a single diastereomer, which was converted into selenide **31**.[18] A sequence comprising the removal of the 3,4-dimethoxybenzyl group under acidic conditions, silylation of the secondary alcohol, and selenoxide elimination[19] then gave spirolactam **32**. At this point, we established a one-pot partial-reduction–allylation protocol for the unprotected lactam. Thus, cyclic imine **33** was obtained by modification of the protocol described by Buchwald and co-workers.[20] For the subsequent allylation in the one-pot process, we found that a Grignard reagent in the presence of catalytic $ZnCl_2$[21] was effective. The desired product was obtained in 71 % yield as a single diastereomer.[22] The configuration of the allylation product was established by conversion into (−)-HTX 235A (**2**).[23]



Scheme 9. One-pot allylation of the δ-lactam and total synthesis of (−)-HTX (**1**) and (−)-HTX 235A (**2**). Reagents and conditions: a) Li, liq. NH_3, *t*BuOH/THF, −78 °C; b) 2-nitrophenyl selenocyanate, nBu_3P, THF, room temperature, 44 % (2 steps); c) *p*-TsOH·H_2O, toluene, reflux; d) TBDPSCl, imidazole, CH_2Cl_2, room temperature, 75 % (2 steps); e) *m*-CPBA, CH_2Cl_2, 0 °C→RT, 83 %; f) $Ti(OiPr)_4$, Et_2SiH_2, THF, reflux; allylmagnesium chloride, cat. $ZnCl_2$, −78 °C→RT, 71 %; g) TBAF, THF, reflux, 93 %; h) $SOCl_2$, imidazole, CH_2Cl_2, 0 °C, 83 % (d.r. 4.7:1); i) O_3; Me_2S, CH_2Cl_2/MeOH, −78 °C, 76 %; j) iodomethyltriphenylphosphonium iodide, KHMDS, THF, −78 °C, 40 %; k) trimethylsilyl acetylene, cat. $[Pd(PPh_3)_4]$, CuI, Et_2NH, room temperature, 77 %; l) $LiAlH_4$, THF, 0 °C→RT, 49 %. *p*-Ts = *p*-toluenesulfonyl, *m*-CPBA = *m*-chloroperoxybenzoic acid, KHMDS = potassium bis(trimethylsilyl)amide, TBAF = tetrabutylammonium fluoride.

Finally, we completed the total synthesis of (−)-HTX (**1**) by conversion of the two terminal alkenes into *Z* enyne chains (Scheme 9).[4] According to the past synthetic studies on (−)-HTX (**1**) and our preliminary studies, protection of the secondary amine of the azaspirobicyclic system was a difficult task, as was the elongation of the two terminal alkenes without protection of the nitrogen atom.[4a] We overcame this problem by using thionyl chloride for the problematic protection of the nitrogen atom. Thus, the treatment of (−)-HTX 235A (**2**) with thionyl chloride afforded oxathiazolidine oxide **34** as a 4.7:1 mixture of diastereomers. The two terminal alkenes were then converted into enyne side chains according to the protocol developed by the research groups of Stork[4a,24] and Holmes.[4b] After separation of the two isomers,[25] the major isomer **34**[26] was ozonized to provide a dialdehyde, which was subjected to *Z*-selective Wittig olefination followed by Sonogashira coupling[4,27] with trimethylsilylacetylene to provide **35** with two *Z* enyne units. Finally, the protecting groups of the amino alcohol and the terminal acetylene were removed with $LiAlH_4$ to complete the total synthesis of (−)-HTX (**1**).[4b,c]

In conclusion, we have completed the total synthesis of (−)-HTX (**1**) and (−)-HTX 235A (**2**) through a strategy featuring a highly stereoselective radical translocation–cyclization cascade for the construction of the 1-azaspiro[5.5]undecane skeleton. For the late-stage construction of the two enyne side chains, we developed a one-pot partial reduction–allylation of an unprotected lactam as well as a unique protecting group for the amino alcohol.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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Keywords: alkaloids · diastereoselectivity · radical cyclization · spiro compounds · total synthesis

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