

Total Synthesis, Relay Synthesis, and Structural Confirmation of the C18-Norditerpenoid Alkaloid Neofinaconitine

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1. Introduction

1-1. Neofinaconitine as a Norditerpenoid Alkaloids

- Many norditerpenoid alkaloids have been used for centuries as traditional Chinese and Japanese folk medicines.¹
- The isolation and identification of these alkaloids enabled pharmacological studies that have revealed their roles as ion-channel modulators.
- Only a few norditerpenoid alkaloids were total synthesized to date.²

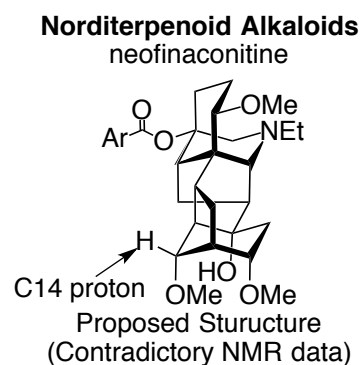


Figure 1. Structure of neofinaconitine

1-2. Author's Motivation

- Biological studies of neofinaconitine have not been reported because of its scarcity.
→ need for chemical synthesis
- Two groups previously reported the isolation of neofinaconitine but the reported spectral data revealed a discrepancy in the chemical shift of the C14 proton (neofinaconitine vs. delphicrispuline).³

2. Results and Discussion

2-1. Synthesis Challenges

- Structural challenges (Fig.1): poly-cyclic fused core structure densely functionalized.
- Synthetic strategy (Fig. 1): two D.A. reactions, a Mannich-type C11-C17 bond formation, and radical C7-C8 bond formation.

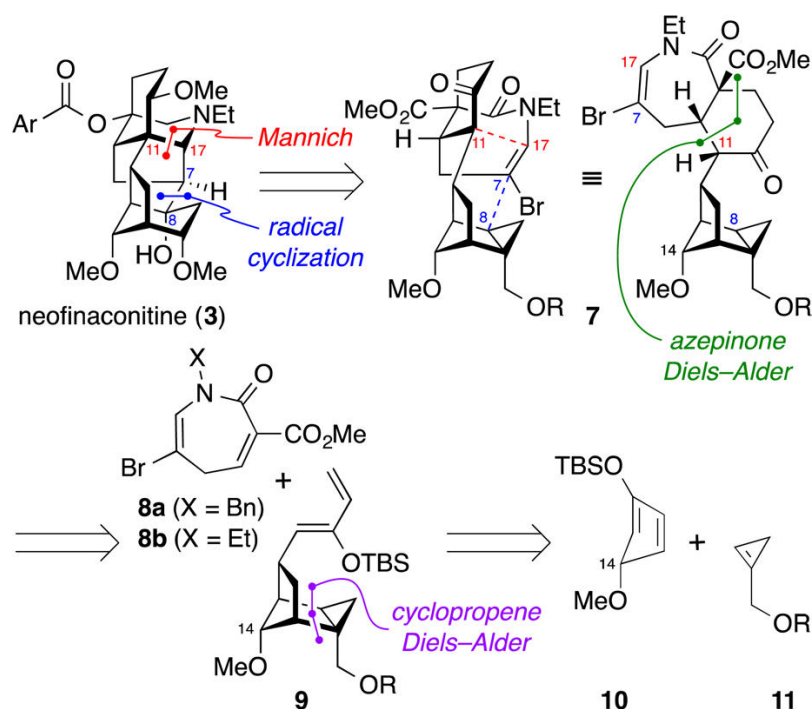
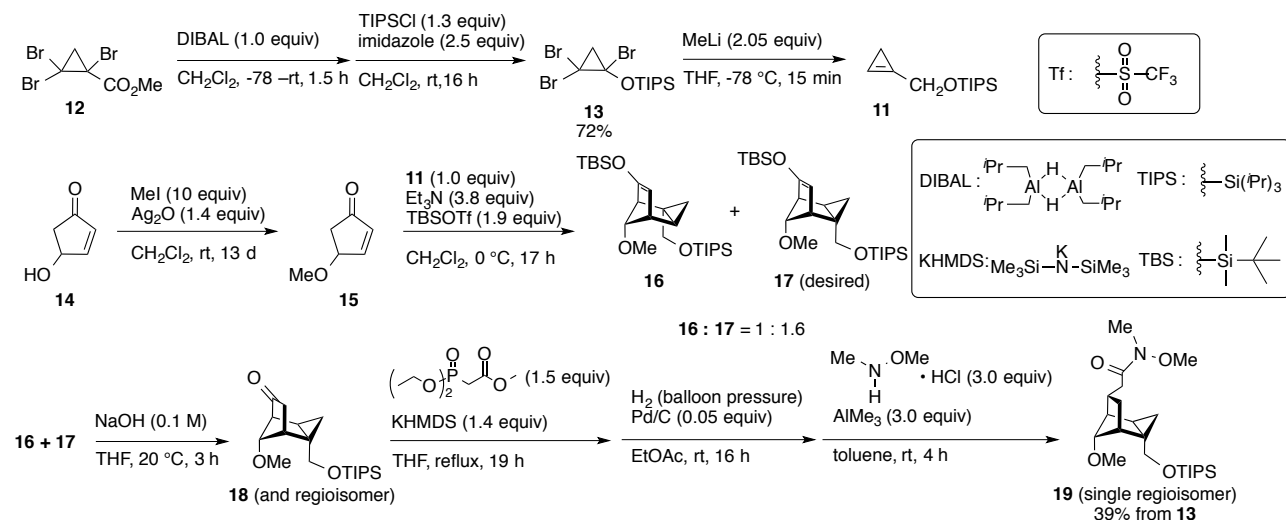


Figure 2. Retrosynthetic analysis of neofinaconitine

2-2. Cyclopropene/Cyclopentadiene Diels-Alder Cycloaddition and separation of regioisomer

Scheme 1. Synthesis of tricyclic **19** from cyclopropane **12** and cyclopentanone **14**



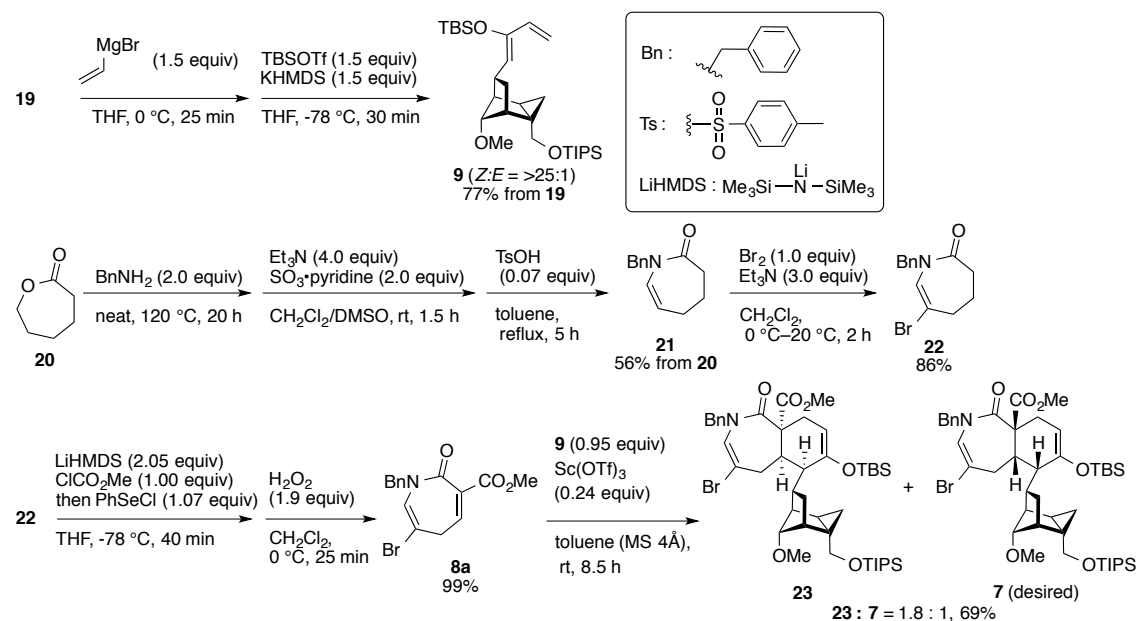
- The D.A. reaction favored the contra-steric approach of the cyclopropene dienophile **11** to the cyclopentadiene.
- 19** could be separated from the regioisomeric mixture by column chromatography.

2-3. Azepinone/Silocydiene Diels-Alder Cycloaddition

- First time to use dihydroazepine as a dienophile. Investigation and improvement of regio-, *endo/exo*-, and facial selectivity of the transformation were conducted.

2-3-1. First Approach

Scheme 2. Synthesis of cycloadduct **7** from Weinreb amide **19** and ϵ -caprolactone **20**



- The D.A. cycloaddition provided complete regioselectivity and *endo* selectivity, but low diastereoselectivity.

• **2-3-2. Author's Strategy**

- To improve the diastereofacial selectivity of the D.A. reaction, the authors envisioned an alternative siloxydiene **36**.

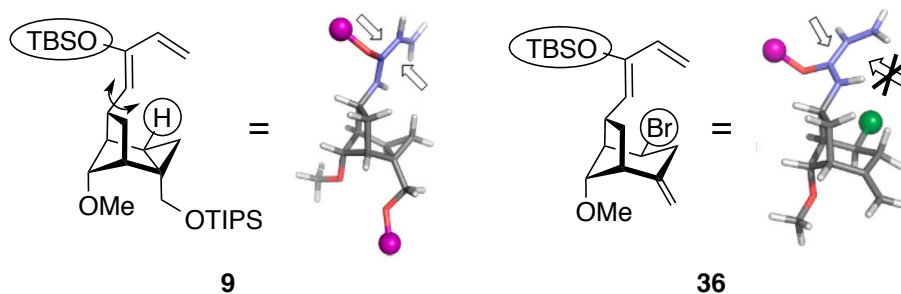
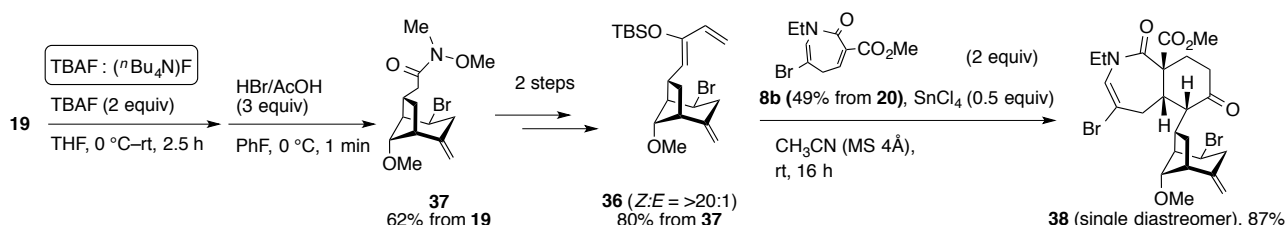


Figure 3. Second generation of the diene **36**

- The authors hypothesized that a sterically demanding **bromine atom would restrict rotation and block the “back” face of the diene**, which favor the desired facial approach of the dienophile from the “front” face.

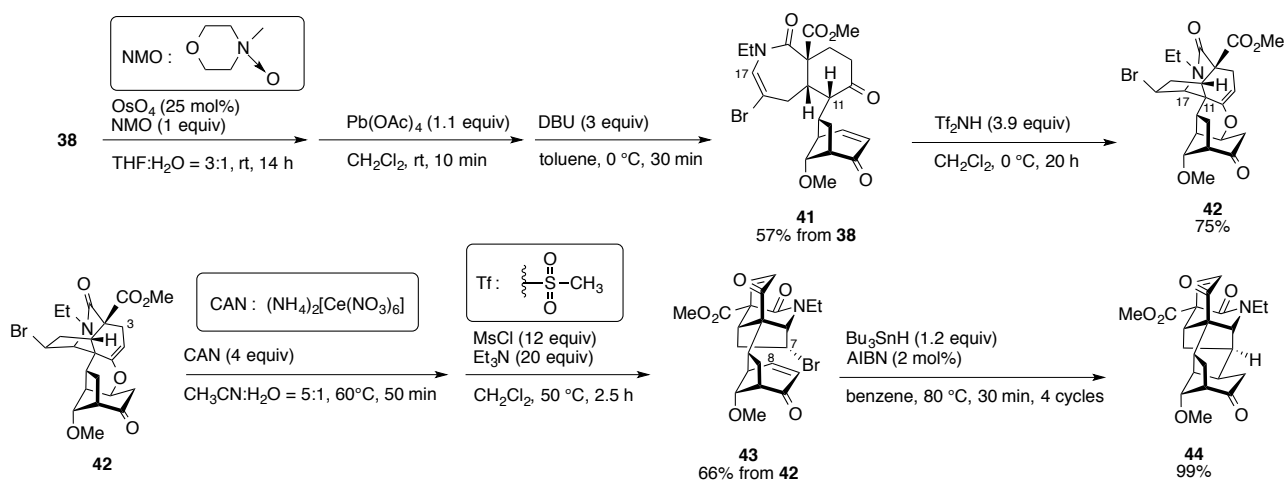
Scheme 3. Improved synthesis of the D.A. cycloadduct



- By optimizing the reaction conditions (the Lewis acids and the solvent), a single isomer with the desired stereochemical configuration was obtained.

2-4. C11-C17 Bond Formation by Mannich-Type *N*-Acyliminium Cycloaddition and C7-C8 Bond Formation by Radical Cyclization

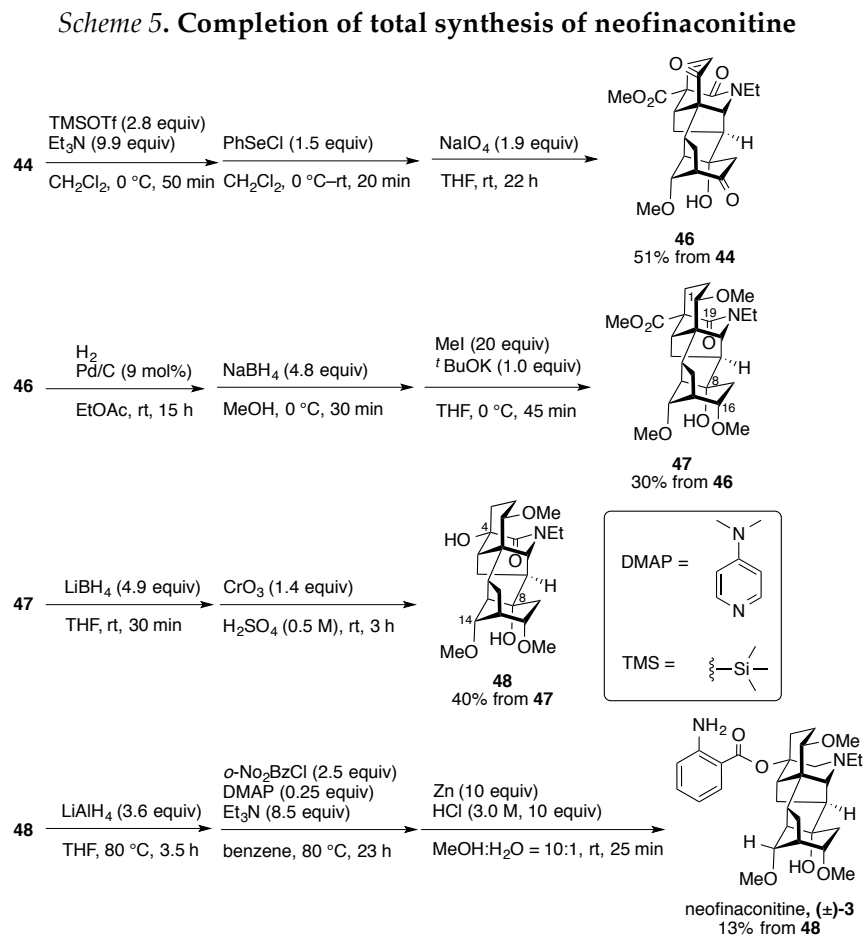
Scheme 4. bond formation of C11-C17 from cycloadduct 38 and C7-C8 from enol ether 42



- The use of the strong acid Tf_2NH not only cleaved the cyclopropane, but also catalyzed the formation of the C11-C17 bond.
- To cleave the enol ether, C3 allylic oxidation using CAN was carried out.

2-5. Completion of the Hexacyclic Skeleton of the Norditerpenoid Alkaloid

- Both C1 and C16 ketones were reduced by NaBH₄ to produce a single diastereomer.
- Methylation reaction (MeI, ^tBuOK) gave C1-O and C16-O monomethylated compounds as byproducts. C8 tertiary alcohol was not methylated.
- Selective acylation of the C4 tertiary alcohol in the presence of C8 tertiary alcohol occurred due to steric shielding of the C8 alcohol by the C14- and C16-methoxy groups.



- The ¹HNMR chemical shift of C14-proton of the synthesized compound was unambiguously assigned. → Neofinaconitine

3. Conclusion

- The authors achieved the total synthesis of neofinaconitine through two D.A. reactions, a Mannich-type *N*-acyliminium cycloaddition and a radical cyclization as key reactions.
- They optimized the diastereofacial selectivity of the second D.A. reaction by introducing steric bias to the diene.
- The total synthesis elucidated the identity of the natural product as neofinaconitine.

4. References

- Amiya, T, et al. *The Alkaloids Chemistry and Pharmacology* **1988**, 34, 95–179.
- (a) Synthesis: Wiesner, K, et al. *J. Am. Chem. Soc.* **1974**, 96, 4990–4992.
(b) Structure determination: Khaimova, M. A, et al. *Tetrahedron* **1971**, 27, 819–822.
- (a) Neofinaconitine: Jiang, S, et al. *Acta Chim. Sin.* **1988**, 46, 26–29.
(b) Delphicrispuline: Ulubelen, A, et al. *W. Phytochemistry* **1999**, 50, 513–516.