Tetrahedron Letters 55 (2014) 7177–7180

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthetic studies on lycopodine: construction of hexahydrojulolidine core by intramolecular Mannich reaction

Takanao Sato, Hirofumi Ueda, Hidetoshi Tokuyama *

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

ARTICLE INFO

Article history:
Received 29 September 2014
Revised 27 October 2014
Accepted 30 October 2014
Available online 5 November 2014

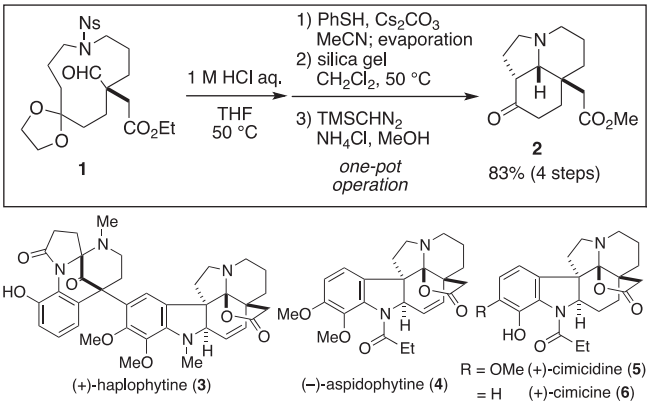
Keywords:
Mannich reaction
Cascade reaction
Oxidation
Lycopodine
Alkaloid

ABSTRACT

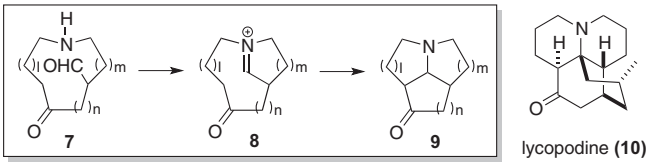
The tricyclic core skeleton of lycopodine was constructed by the intramolecular Mannich reaction of a 12-membered cyclic amine. The concise assembly of the macrocyclic intermediate was executed by the sequential inter- and intramolecular N-alkylation of a linear diol using Ns-amide. The fully functionalized diol was prepared via Michael reaction of enone and malonate. The key Mannich reaction proceeded smoothly in the presence of silica gel to provide the tricyclic core skeleton of lycopodine.

As a number of polycyclic alkaloids possessing attractive bioactivities are found in nature, the development of an efficient synthetic strategy for this class of compounds has become an important topic in synthetic organic chemistry and drug discovery. Polycyclic structures are usually assembled by stepwise cyclizations, however, this conventional synthetic strategy requires lengthy synthetic route. Recently, a cascade reaction has gained much attention[1] for the construction of polycyclic structures. This powerful tool increases the efficiency of multistep synthesis by reducing the reaction steps. In addition, cascade reactions are advantageous with regard to atom economy[2] and green chemistry[3] due to their simplification of experimental operations and generation of less hazardous waste.

Recently, we demonstrated the construction of the tricyclic aminoketone **2** by intramolecular Mannich reaction of a macrocyclic secondary amine bearing two carbonyl groups (Scheme 1).[4] This cascade cyclization proceeded under mild acidic conditions, in the presence of silica gel to give the tricyclic compound **2** as a single diastereomer. The tricyclic aminoketone **2** served as a key intermediate for the synthesis of the aspidosperma class of indole alkaloids, allowing the completed total syntheses of a series of alkaloids including (+)-haplophytine (**3**),[4a] (−)-aspidophytine (**4**),[4b] (+)-cimicidine (**5**),[4b] and (+)-cimicine (**6**).[4b] With the high stereoselectivity and mildness of the reaction conditions, we predicted the general strategy (from **7** to **9**) depicted in Scheme 2



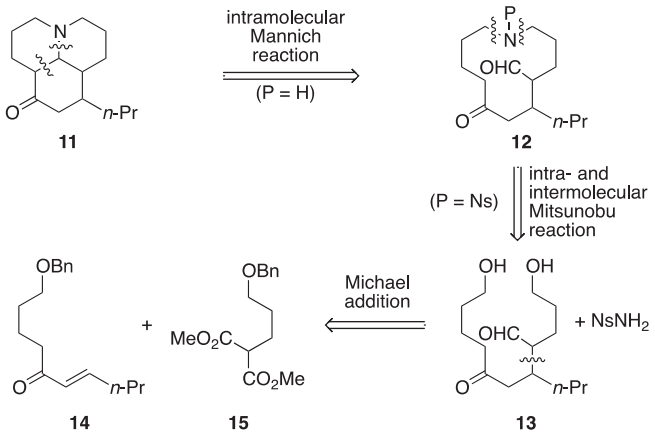
Scheme 1. Intramolecular Mannich reaction and application to the total syntheses of (+)-haplophytine (**3**) and related compounds.



Scheme 2. General strategy and target compound in this study.

* Corresponding author.
E-mail address: tokuyama@mail.pharm.tohoku.ac.jp (H. Tokuyama).

http://dx.doi.org/10.1016/j.tetlet.2014.10.150
0040-4039/

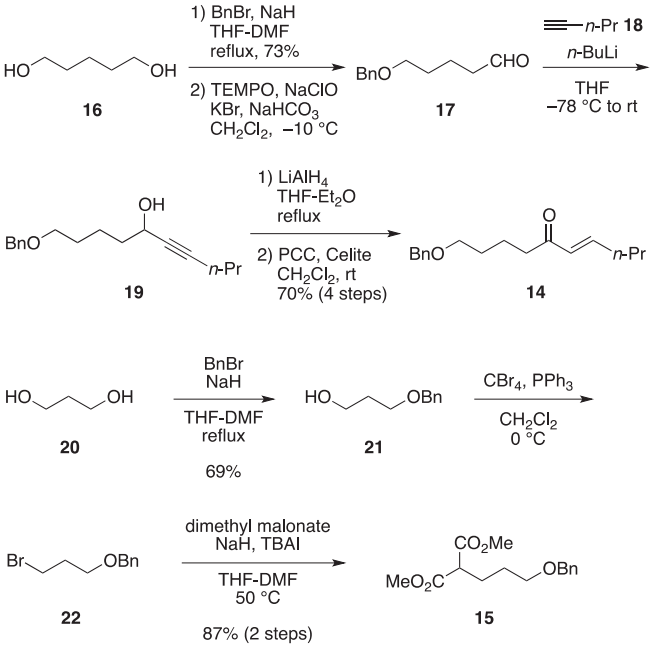


Scheme 3. Synthetic strategy for the tricyclic core of lycopodine (**10**).

to be applicable to the synthesis of a wide variety of polycyclic alkaloids. As such we initiated synthetic studies on lycopodine (**10**) featuring the intramolecular Mannich reaction cascade.

Lycopodine (**10**) is a representative *Lycopodium* alkaloid[5] isolated from *Lycopodium complanatum* by Bödeker.[6] The *Lycopodium* species has been utilized in Chinese folk medicine for the treatment of muscle and skin disorders.[7] In addition, its congeners are expected to be lead compounds for the remedy of Alzheimer's disease.[8] To date numerous synthetic studies and total syntheses of lycopodine (**10**), including many racemic total syntheses,[9a–h] two formal syntheses,[9i,j] and only one asymmetric total synthesis of **10** by Carter and co-workers[10] were reported.

The synthetic strategy for the tricyclic aminoketone **11**, a model compound of a lycopodine synthetic intermediate, is shown in Scheme 3. For construction of the tricyclic skeleton, we planned to apply the intramolecular Mannich reaction to 12-membered cyclic amine **12**. The macrocyclic secondary amine derivative would be then synthesized by sequential inter- and intramolecular Mitsunobu reaction of diol **13** using 2-nitrobenzenesulfonamide (Ns-amide).[11] A concise assembly of **13** could then be executed via Michael addition with enone **14** and aldehyde **15**.



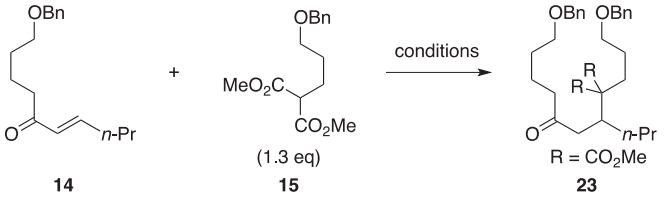
Scheme 4. Preparation of Michael accepter **14** and donor **15**.

Our study was initiated by preparing fragments **14** and **15** for Michael addition (Scheme 4). After mono-benzylation of 1,5-pentanediol **16**, the remaining hydroxyl group was oxidized to aldehyde. 1,2-Addition of lithium acetylide to aldehyde afforded propargyl alcohol **19**, which was then reduced with $LiAlH_4$. Subsequent oxidation with PCC gave Michael acceptor **14**. Michael donor **15**, on the other hand, was obtained by alkylation of dimethyl malonate with alkyl bromide **22**,[12] which was prepared from 1,3-propanediol (**20**) by mono-benzylation and bromination.

With these two fragments in hand, we then examined the Michael addition (Table 1). First, we tested several bases such as DBU and NaH, however, these reaction conditions resulted in only trace amounts of the desired Michael adduct **23** (entries 1–2). Treatment with sodium methoxide slightly improved the Michael adduct yield (entry 3). After further optimization, we found the yield of the Michael adduct strongly depended on the concentration of the reaction mixture. Finally, we obtained the desired adduct **23** in a 57% yield when the reaction was conducted in solvent free conditions (entry 4).

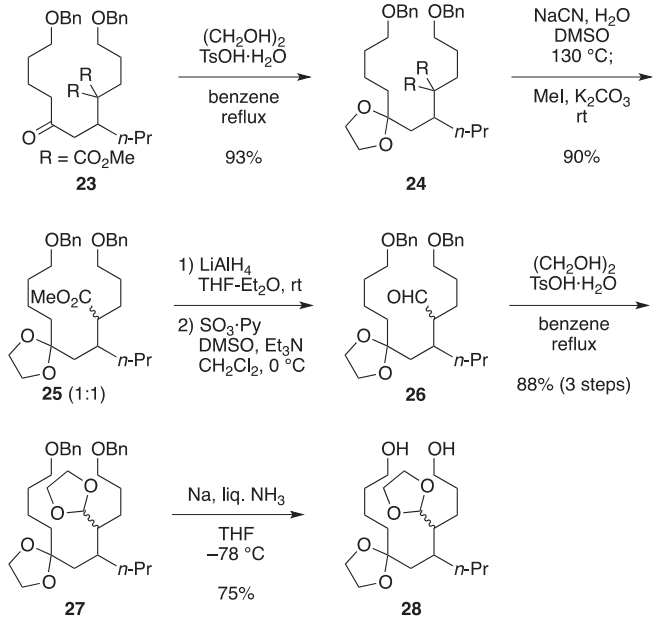
Next, we conducted functional group manipulations of ketoester **23** in preparation for the 12-membered cyclic amine formation by double Mitsunobu reaction (Scheme 5). After protection of the

Table 1
Optimization of the Michael reaction



Entry	Base (equiv)	Solvent	Temp	Time (h)	Yield
1	DBU (4)	THF	rt	12	Trace
2	NaH (4)	DMF	50 °C	1	Trace
3	NaOMe (1.2)	MeOH (1.0 M)	50 °C	1.5	10%
4[a]	NaOMe (0.3)	None	rt	3	57%

[a] Michael donor **15** (1.2 equiv) was used.



Scheme 5. Preparation of diol **28**.