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Asymmetric Formal Synthesis of (+)-Catharanthine via Desymmetrization of Isoquinuclidine

Masato Kono,[†] Shingo Harada,*[,†] Tomoyuki Nozaki,[†] Yoshinori Hashimoto,[†] Shun-ichi Murata,[†] Harald Gröger,[‡] Yusuke Kuroda,[§] Ken-ichi Yamada,[∥] Kiyosei Takasu,[§] Yasumasa Hamada,[†] and Tetsuhiro Nemoto*[,†,⊥]

[†]Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8675, Japan

[‡]Chair of Organic Chemistry I, Faculty of Chemistry, Bielefeld University, Universitätsstraße 25, 33615 Bielefeld, Germany

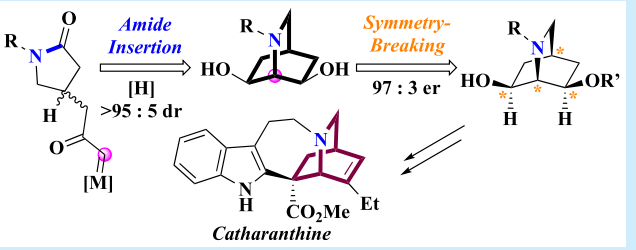
[§]Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

[∥]Graduate School of Pharmaceutical Sciences, Tokushima University, Shomachi, Tokushima 770-8505, Japan

[⊥]Molecular Chirality Research Center, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Supporting Information

ABSTRACT: Although (+)-catharanthine is an attractive alkaloid for both clinical research and organic synthetic chemistry, only a limited number of approaches for its catalytic asymmetric synthesis exist. Herein, we describe a novel strategy for synthesizing a chiral intermediate of (+)-catharanthine via phosphoric acid-catalyzed asymmetric desymmetrization of a *meso*-isoquinuclidine possessing a 1,3-diol unit that was synthesized by a formal amide insertion reaction.



The two-azabicyclo[2.2.2]octane ring system, isoquinuclidine, is a privileged chemical structure found in bioactive alkaloids and pharmaceuticals (Figure 1).[1,2] Novel natural products with an isoquinuclidine core, notably a family of monoterpenoid indoles, continue to be isolated.[3] The molecular architecture is an advantageous scaffold for synthesizing other natural products through functionalization of the framework.[4] The development of synthetic methods, especially asymmetric syntheses, for isoquinuclidine, is therefore in high demand.[5,6]

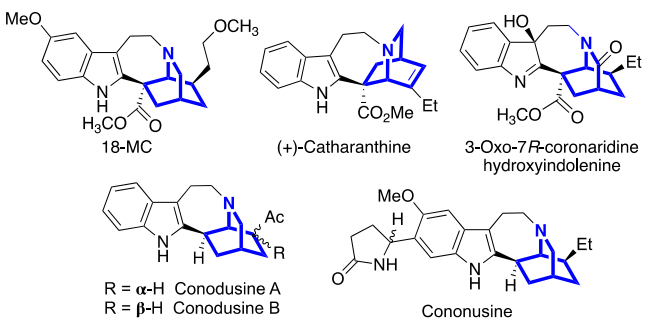


Figure 1. Indole alkaloids possessing an isoquinuclidine framework.

(+)-Catharanthine is an important member of the Iboga class of alkaloids.[7] It is a representative indole alkaloid and has attracted the attention of clinical researchers because it can be converted into some (pseudo)natural products[4b] and vinblastine in one step,[8] which has strong anticancer activity and is used in the treatment of several human cancers.[9] The supply of (+)-catharanthine, however, has long relied on its extraction from the leaves of Madagascan periwinkle (*Catharanthus roseus* L. Don).[10] The low natural abundance (approximately 0.0003% of dried leaf mass) and unique functionalized isoquinuclidine with a seven-membered ring-fused indole ring system has motivated the development of a new synthetic route to catharanthine. Although syntheses of (±)-catharanthine in a racemic format have been investigated well,[11] only one asymmetric total synthesis was achieved by Oguri,[12] using a chiral auxiliary. Asymmetric formal synthesis of catharanthine based on a chiral pool method,[13] catalytic enantioselective Diels−Alder reaction using chiral amines[5b,14] or a chiral Brønsted acid,[6] and an enantioselective Pictet−Spengler-type reaction[15] have been reported to date. Given its biological importance and limited synthetic methodology, new synthetic approaches to the catalytic asymmetric construction of isoquinuclidines for synthesizing (+)-catharanthine are in high demand.

We recently developed a formal amide insertion of metal-carbene[16] followed by a diastereoselective reduction sequence for the synthesis of *meso*-isoquinuclidine **5** with a 1,3-diol unit from easily available diazo compounds **3** (Scheme 1).[17] This *meso* compound could be a versatile synthetic scaffold for a chiral 2-azabicyclo[2.2.2]octane ring system with four chiral stereocenters if an asymmetric desymmetrization of **5** is

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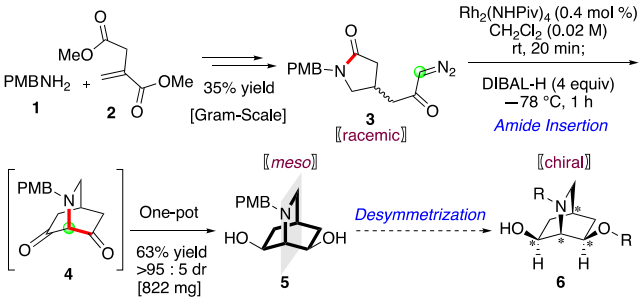
Scheme 1. Synthetic Strategy for Chiral Isoquinuclidine Based on an Amide Insertion-Asymmetric Desymmetrization Sequence[a]



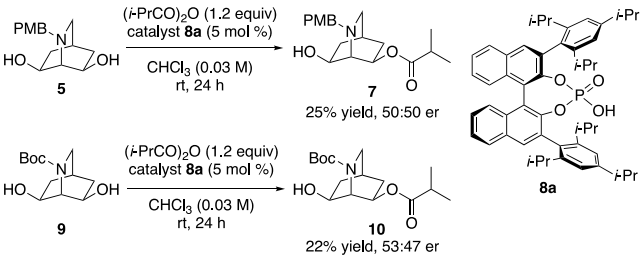
[a]PMB is *p*-methoxybenzyl.

achieved. Methods for the desymmetrization of *meso*-1,3-diol, however, are quite limited[18] compared with that of *meso*-1,2-diol,[19] for which reactions using structurally simple 1,3-diols were developed. Takasu and Yamada developed an asymmetric acylation of cyclic secondary alcohols[20] to separate the enantiomeric constituents from a racemic mixture[21] using a chiral phosphoric acid.[22] The acid catalyst enhanced the electrophilicity of an acylation reagent and activated one enantiomer of the secondary alcohol under a chiral environment. This background led us to hypothesize that desymmetrization of **5** would be realized using a chiral phosphoric acid under the appropriate conditions. The application allowed us to overcome the fundamental limitations of the yield (≤50%) in our previous method based on kinetic resolution and enantioselective synthesis of the isoquinuclidine architecture.

Herein, we report an amide insertion-asymmetric desymmetrization strategy for the synthesis chiral isoquinuclidine, leading to the formal asymmetric synthesis of (+)-catharanthine.

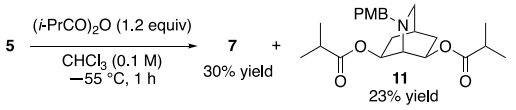
Our synthesis commenced by the synthesis of **5** via a formal amide insertion reaction, and then asymmetric acylation of the *meso*-1,3-diol was examined using chiral phosphoric acid catalyst **8a** (Scheme 2).[23] At first, the asymmetric acylation

Scheme 2. Initial Trial of Desymmetrization



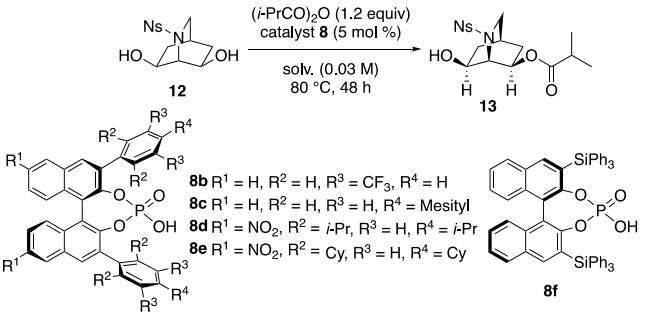
was applied to **5** in $CHCl_3$ at room temperature, but that resulted in low yield with no enantiomeric excess. This is presumably due to a basic nitrogen functionality of the substrate, which would cause a background reaction promoted by intramolecular hydrogen bonding and/or deactivation of the acid catalyst. Actually, the reaction of **5** without a catalyst proceeded even at low temperatures (Scheme 3). To suppress the nonselective reaction, we prepared *N*-Boc-protected substrate **9** and tried desymmetrization, which afforded **10** with a 53:47 er. The reaction of **12** with an *N*-Ns group[24] as a more powerful electron-withdrawing substituent using **8a**

Scheme 3. Acylation Reaction without the Use of a Catalyst



furnished the corresponding monoester **13** in an enantioenriched form, although a prolonged reaction time and a higher temperature were required [89:11 er (entry 1, Table 1)].

Table 1. Optimization of the Reaction Conditions for Asymmetric Desymmetrization



entry	catalyst	solvent	yield (%)	er
1[a]	**8a**	$CHCl_3$	40	89:11
2	**8a**	1,4-dioxane	35	66:34
3	**8a**	benzene	55	86:14
4	**8a**	$PhCF_3$	36	91:9
5	**8a**	toluene	51	92:8
6	**8b**	toluene	68	78:22
7	**8c**	toluene	55	77:23
8	**8f**	toluene	49	80:20
9	**8d**	toluene	60	96:4
10	**8e**	toluene	74	97:3

[a]Reaction was performed under reflux.

Subsequent solvent screening to optimize the reaction conditions revealed that a polar solvent was not suitable for this reaction, giving **13** with decreased enantioselectivity (1,4-dioxane, 66:34 er, entry 2). Nonpolar solvents, such as benzene, $PhCF_3$, and toluene, afforded **13** with good enantioselectivity, although the product yields were still low (36−55% yield, entries 3−5, respectively). Next, electronic tuning and steric tuning of the Brønsted acid catalyst were performed. The use of catalyst **8b**, **8c**, or **8f** possessing a 3,5-$(CF_3)_2$-C_6H_3, 4-Mes-C_6H_3, or Ph_3Si group, respectively, at the 3,3′-positions of the BINOL core was not effective (77:23−80:20 er, entries 6−8). Meanwhile, introduction of a nitro group at the 6,6′-positions of the BINOL backbone was beneficial for improving both the yield and the enantioselectivity (**8d**, 60% yield, 96:4 er, entry 9).[20,25] Isopropyl groups on catalyst **8e** were replaced with cyclohexyl groups to further increase the reaction efficiency, producing **13** in 74% yield and 97:3 er (entry 10).[26,27]

Having successfully constructed chiral isoquinuclidine **13**, we moved on to the formal synthesis of (+)-catharanthine (Scheme 4). First, **13** was converted into **14** via cost-friendly Albright−Goldman oxidation[28] using Ac_2O in DMSO in 89% yield. After recrystallization of **14** to increase the optical purity, triflation using KHMDS and $PhNTf_2$ proceeded in good yield. Triflate **15** was next exposed to reductive conditions with $PdCl_2(PPh_3)_2$/HCOOH, affording disubstituted olefin **16** in

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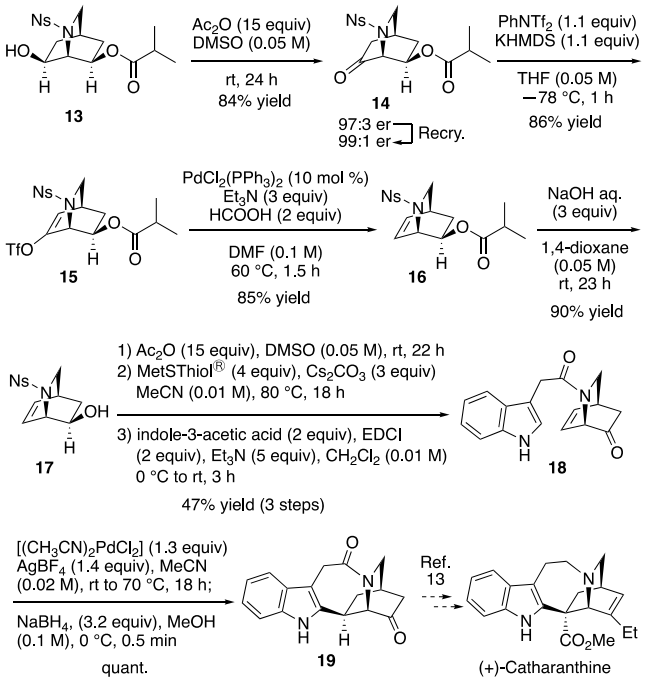
Scheme 4. Asymmetric Formal Synthesis of (+)-Catharanthine[a]



[a]EDCI is 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide.

85% yield. Direct dehydration of **13** to **16** using Burgess reagent or Martin's Sulfurane did not proceed. The ester unit at each side in **16** was cleaved with aqueous NaOH in 1,4-dioxane at 80 °C. The hydroxyl group of **17** was oxidized under Albright−Goldman oxidation conditions, and its crude product was pure enough to be utilized for the next step without further purification. Although deprotection of the Ns group was unsuccessful by common methods such as using PhSH, it could be removed with a solid-supported thiol resin[29] at an elevated temperature for 15 h. After the used MetSthiol had been removed by filtration, the resulting secondary amine was condensed with indole-3-acetic acid using EDCI to afford **18** in 47% yield (three steps). The absolute configuration was determined at this stage by comparing the optical rotation with the known compound.[5b,13] Finally, C−C bond linkage between the indole C-2 position and the isoquinuclidine ring was constructed (**18** → **19**) through the reaction sequence using Pd-mediated seven-membered ring formation followed by hydride reduction.[11c]

In summary, we achieved an asymmetric formal synthesis of (+)-catharanthine via desymmetrization of *meso*-isoquinuclidine using an electronically and sterically tuned Brønsted acid catalyst. The key *meso*-2-amino-1,3-diol was synthesized by an amide insertion reaction followed by protecting-group manipulation. The obtained chiral mono ester was converted into a chiral synthetic intermediate for (+)-catharanthine in eight steps. The late-stage introduction of the indole unit would contribute to the development of a diversity-oriented strategy for the syntheses of other Iboga-class alkaloids with an array of substituents on the indole ring. Studies based on the symmetry-breaking strategy for other ring systems are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01198.

Experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: sharada@chiba-u.jp.
*E-mail: tnemoto@faculty.chiba-u.jp.

ORCID

Harald Gröger: 0000-0001-8582-2107
Kiyosei Takasu: 0000-0002-1798-7919
Tetsuhiro Nemoto: 0000-0001-8858-161X

Notes

The authors declare no competing financial interest.

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