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Design, Synthesis, and Monoamine Oxidase Inhibitory Activity of (+)-Cinchonaminone and Its Simplified Derivatives

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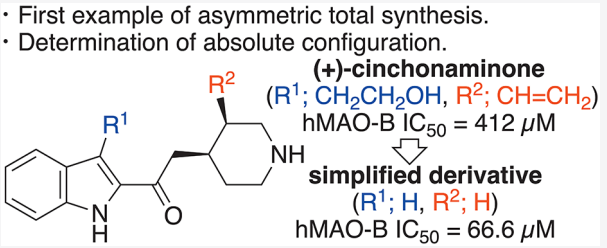
ABSTRACT: The absolute structure of an indole alkaloid (+)-cinchonaminone by total synthesis of both (+)-cinchonaminone and its enantiomer was determined. The main focus of the study was the enantioselective synthesis of both enantiomers of a chiral *cis*-3,4-disubstituted piperidine. We also evaluated monoamine oxidase (MAO) inhibitory activities of these enantiomers. Furthermore, its structurally simplified derivatives were synthesized that did not have any chiral center. Two of these derivatives showed stronger MAO inhibitory activities than that of (+)-cinchonaminone.

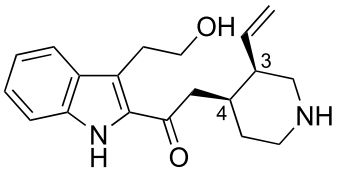


KEYWORDS: *Total synthesis, indole alkaloid, absolute structure determination, monoamine oxidase (MAO) inhibitory activity, structurally simplified derivatives*

Monoamine oxidase (MAO)[1] is an oxidase present in the outer mitochondrial membrane and plays a role in inactivating neurotransmitters in vivo, metabolizing monoamines ingested as drugs and those included in food. Two subtypes of MAO, MAO-A and MAO-B, inhibitors have been applied to the drug therapy of central nervous system diseases because they inactivate neurotransmitters in the central nervous system. MAO-A inhibitors are mainly used in the treatment of depression. On the other hand, MAO-B inhibitors are used to treat Parkinson's disease and attention deficit hyperactivity disorder (ADHD). In this way, MAO is an attractive target for drug discovery.

(+)-Cinchonaminone (**1**, Scheme 1) is an indole alkaloid isolated from Cinchonae Cortex in 1989 and has been reported to have inhibitory activity against bovine plasma-derived MAO (IC_{50} = 31.7 μM);[2] the structural feature of (+)-cinchonaminone ((+)-**1**) is that it has an indole ring and a *cis*-3,4-disubstituted piperidine ring at the indole 2-position. The piperidine rings C3 and C4 are asymmetric carbons, and the configuration of (+)-cinchonaminone ((+)-**1**) in the piperidine ring was estimated (3*R*, 4*S*) by Noro et al. (1989) based on the biosynthetic pathway of cinchona alkaloids and the structure of other cinchona alkaloids.[3] However, as for the reported cases of total synthesis, there is only one case of racemic synthesis,[4] and there is no report of total asymmetric synthesis; the absolute configuration of the compound itself has not been clarified. Here in the background research, we describe the determination of the absolute configuration of (+)-cinchonaminone ((+)-**1**) and design, synthesis, and MAO inhibition activities of structurally simplified derivatives of (+)-cinchonaminone ((+)-**1**).

Scheme 1. Proposed Absolute Structure of (+)-Cinchonaminone (1)



Based on the previously reported racemic synthetic method, we decided to synthesize the chiral piperidine units (+)-**2** and (−)-**2** and the indole unit **3**, which will be subjected to a cross-coupling reaction to give (+)-**1** and (−)-**1** (Scheme 2). Therefore, we first worked on synthesizing optically pure piperidine units (+)-**2** and (−)-**2**. Our retrosynthetic analysis for (+)-**2** and (−)-**2** is shown in Scheme 3.

The 3-position vinyl group of piperidine unit **2** could be constructed by the dehydration reaction of the primary alcohol **14**. The alcohol **14** could be obtained by diastereoselective reduction of the unsaturated ester **13**, which could be synthesized by oxidation of the secondary alcohol **12** and a subsequent Horner−Wadsworth−Emmons (HWE) reaction. It was also considered that the iodomethylene group at the 4-

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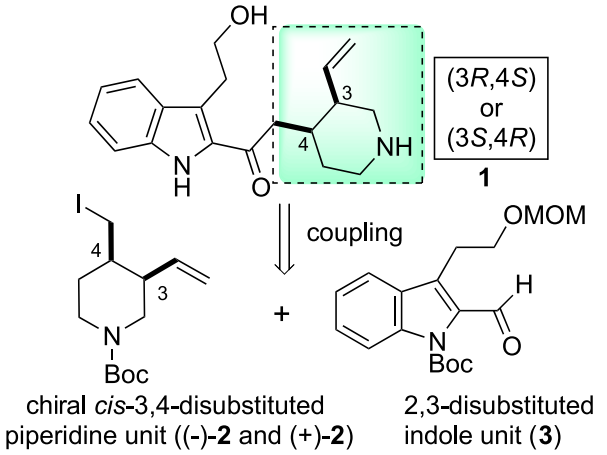
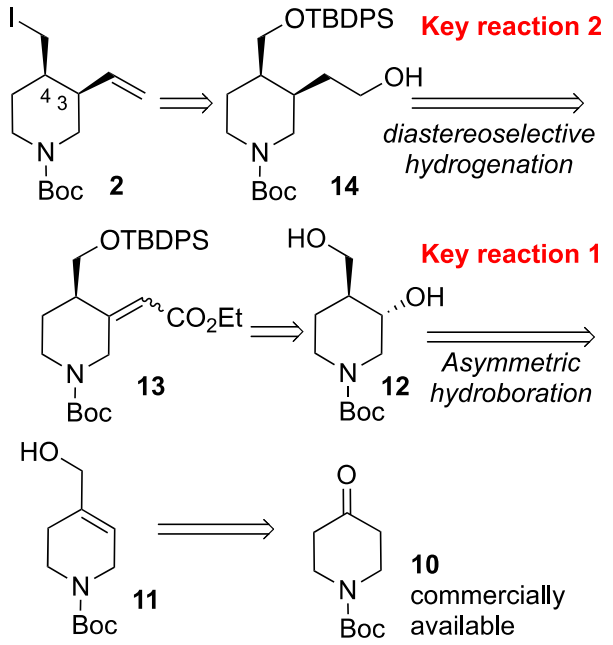
Scheme 2. Our Retrosynthesis Analysis for (+)-1 and (−)-1



Scheme 3. Retrosynthesis of Optically Pure *cis*-3,4-Disubstituted Piperidine Unit 2

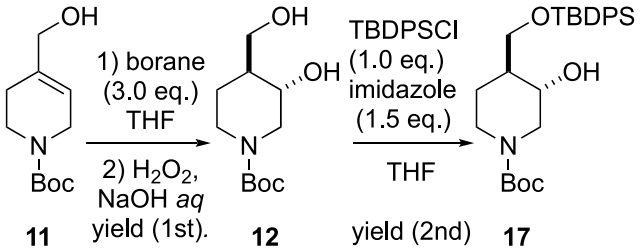


position of compound **2** could be constructed by the Appel reaction of a primary alcohol. It was also considered that the asymmetric carbon center at the 4-position could be constructed by the hydroboration reaction of the allyl alcohol compound **11**. It was thought that **11** could be synthesized from commercially available compound **10** in three steps.

We first investigated the stereoselective synthesis of the piperizine unit **2** by using racemic substrates. Preparation of **11** is summarized in Scheme S1 in the Supporting Information.

Next, the key reaction, the asymmetric hydroboration reaction, was examined (Table 1). The optical purity was determined using compound **17**, in which the primary hydroxy group of diol **12** was protected with a TBDPS group.[5] When a THF solution of optically pure borane (+)-IpcBH$_2$, which has been widely used in asymmetric hydroboration reactions, and compound **11** was stirred at −40 °C, the expected compound **12** was obtained in low yield (6%; run 2). Since the reaction temperature of the optimum conditions for synthesizing *rac*-**12** was 60 °C (run 1), we considered that the reaction rate might

Table 1. Asymmetric Hydroboration of 11 and Subsequent Protection of the Primary Alcohol with the TBDPS Group



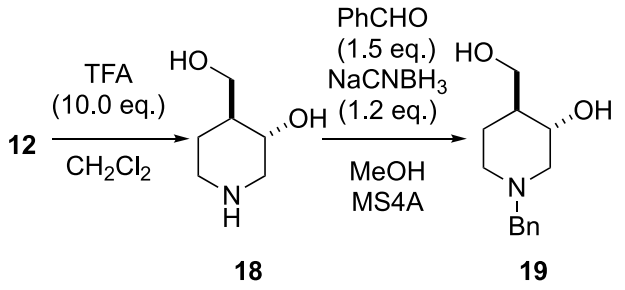
run	borane	temp (°C)	time (h)	yield of **12** (%) first step	yield of **17** (%) second step	ee (%)
1	Cy_2BH	60	3	92	92	
2	(+)-IpcBH$_2$	−40	24	6	89	21[a]
3	(+)-IpcBH$_2$	60	3	90	87	47[a]
4	(+)-IpcBH$_2$	rt	24	81	85	52[a]
5	(+)-IpcBH$_2$	0	24	55	90	62[a]
6	(+)-IpcBH$_2$	0	48	79	89	61[a]
7	(+)-IpcBH$_2$	−25	48	34	88	64[a]
8	(−)-IpcBH$_2$	0	48	77	89	65[b]

[a](3*S*,4*S*)-**17**. [b](3*R*,4*R*)-**17**.

have decreased significantly under the conditions of −40 °C. Therefore, we examined the reaction temperature (runs 3−7) and found that the higher the reaction temperature, the higher the yield of **12**, and the longer the reaction time, the better the yield of **12** (runs 5 and 6). Although the best optical purity of **17** was 62% ee, we increased it to 91% ee by recrystallizing **17** (Scheme S2). From the above results, considering the reaction time and the yield of the reaction from **11** to **17**, including recrystallization, the condition of entry 6 at 0 °C and 48 h was judged the most suitable.

Compound **12** was also converted to known compound **19**[6] to determine its absolute configuration (Scheme 4). The actual

Scheme 4. Synthesis of 19 from 12



experimental results were shown in Scheme S3. As a result of comparing the optical rotation value of the synthesized *N*-Bn protected **19** with the literature value,[6a] we found that (3*R*,4*R*)-**12** and (3*S*,4*S*)-**12** were obtained when (+)-IpcBH$_2$ and (−)-IpcBH$_2$ were used, respectively.

The conversion of compound **17** to unsaturated ester **13** was explained in the Supporting Information.

First, the *Z*-form unsaturated ester *rac*-(*Z*)-**13** was used for examination. No selectivity was found in the production ratio of the *cis*-form and *trans*-form with the Pd catalyst, but the *cis*-form tended to be selectively obtained when the Pt catalyst was used.[7] The structures of the obtained compounds *rac-cis*-**14** and *rac-trans*-**14** were determined by the difference in the

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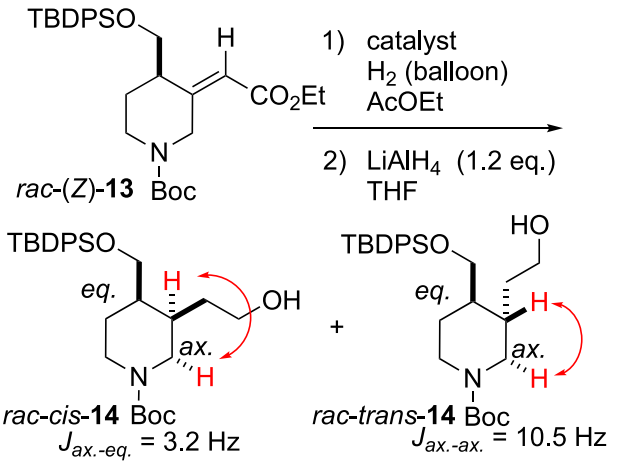
coupling constant between the protons at the 2-axial position and the 3-position of the piperidine ring.

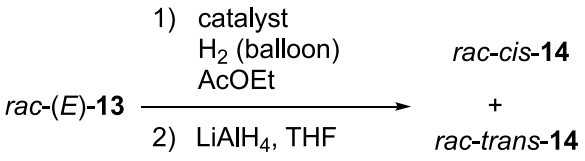
The diastereoselective catalytic reduction of the obtained key intermediate **13** was examined (Tables 2 and 3). The

Table 2. Diastereoselective Catalytic Reduction of *Z*-13



run	catalyst	*rac-cis*-**14** (%)	*rac-trans*-**14** (%)	*rac*-(*Z*)-**13** (%)
1	Pd/C (10 wt %)	41	39	
2	Pd/C (5 wt %)			98
3	$Pd(OH)_2$/C (10 wt %)			97
4	Pt/C (10 wt %)	75	9	
5	PtO_2 (10 mol %)	85		

Table 3. Diastereoselective Catalytic Reduction of *E*-13



run	catalyst	*rac-cis*-**14** (%)	*rac-trans*-**14** (%)	*rac*-(*E*)-**13** (%)
1	Pd/C (10 wt %)	24	65[)]	
2	PtO_2 (10 mol %)	63	27	

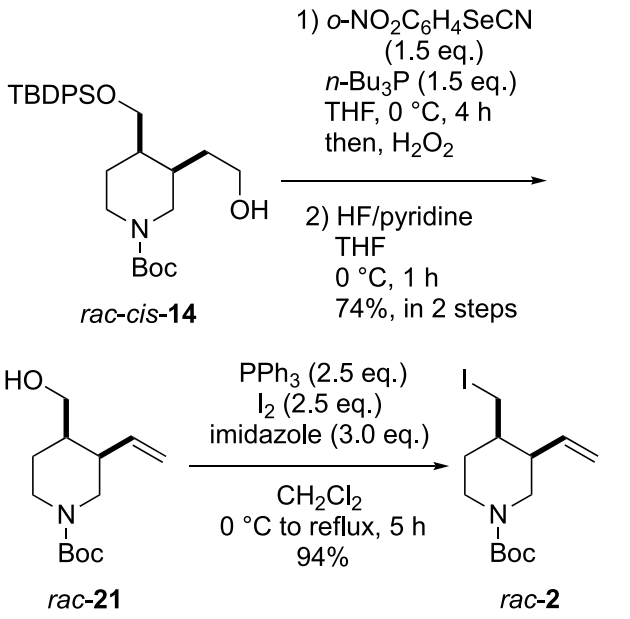
double bond and ester group of the synthesized unsaturated ester **13** were successively reduced using a heterogeneous catalyst and lithium aluminum hydride, respectively, to obtain the corresponding alcohol **14**.

In addition, the reduction of the *E*-form *rac*-(*E*)-**13** was also examined in the same manner, and the same tendency as in the case of the *Z*-form was found for the *cis*/*trans*-selectivity of the products due to the difference in the metal catalyst. However, the *cis*-selectivity of the products was lower than that used in the *Z*-form as the substrate.

In other words, from the results obtained by the present study and the discussions reported in the literature,[8] it became clear that catalytic reduction of the Z-form unsaturated ester **13** using platinum oxide selectively produced the *cis*-form.

Next, we moved to the synthesis of piperidine unit **2** from *cis*-alcohol **14** (Schemes 3 and 5). Alcohol *rac*-**14** was converted to a terminal alkene *rac*-**21** via the corresponding selenoxide to construct a vinyl group at the 3-position. Subsequently, the TBDPS group at the 4-position was removed using HF/pyridine to synthesize *rac*-**21**, and then

Scheme 5. Synthesis of Piperidine Unit *rac*-2



the desired piperidine unit *rac*-**2** was obtained by the Appel reaction. As described, we successfully established a synthetic route for the piperizine unit using the racemic substrates.

Finally, both of the optically pure piperidine units (3*R*,4*R*)- and (3*S*,4*S*)-**2** were synthesized using the established pathway from commercially available compound **10** in 12 steps (Scheme S5).

(+)- and (−)-Cinchonaminone were synthesized using the synthesized optically pure piperidine unit (3*R*,4*R*)-**2** or (3*S*,4*S*)-**2** and indole unit **3**[8] (Scheme 6). After Zn was inserted into the carbon−iodine bond of the optically pure piperidine unit **2**, CuCN and 2 equiv of LiCl were added to obtain the corresponding organic copper art reagent. Compound **27** was obtained using a cross-coupling reaction between this reagent and the indole unit **3**. Subsequently, after converting the secondary alcohol to a ketone by Dess-Martin oxidation, the Boc group and the MOM group were removed with hydrochloric acid-methanol to yield (3*R*,4*S*)-cinchonaminone and (3*S*,4*R*)-cinchonaminone in 22 steps.

The optical rotations of the two isomers of synthesized cinchonaminone were measured (Scheme 7). The optical rotations of (3*R*,4*S*)-cinchonaminone and (3*S*,4*R*)-cinchonaminone were $[\alpha]^{24}_{D} = +10.3°$ and $[\alpha]^{24}_{D} = -9.7°$, respectively. Since the optical rotation of the natural (+)-cinchonaminone is $[\alpha]^{22}_{D} = +10.0°$,[2] it turned out that the absolute configuration of the piperidine rings C3 and C4 of the (+)-cinchonaminone is (3*R*,4*S*).

The hMAO-A and hMAO-B inhibitory activity of the synthesized (+)- and (−)-**1** was evaluated (Table 4). Both (+)- and (−)-**1** had similar inhibitory activities for hMAO-B, although they had almost no inhibitory activity for hMAO-A.

Considering the above biological activities results and docking study of (+)- and (−)-**1** with hMAO-A (PDB: 2Z5X,[9] Figure 1a) and hMAO-B (PDB: 2V5Z,[10] Figure 1b),[11] we hypothesized that the vinyl moiety at the C3-position of piperidine was not necessary for hMAO inhibition. Hence, we designed structurally simplified derivatives of **29** without the asymmetric two carbons in the piperizine moiety (Scheme 8). We also noticed that the hydroxyethyl moiety at the C3-position of the indole is surrounded by the hydrophilic region

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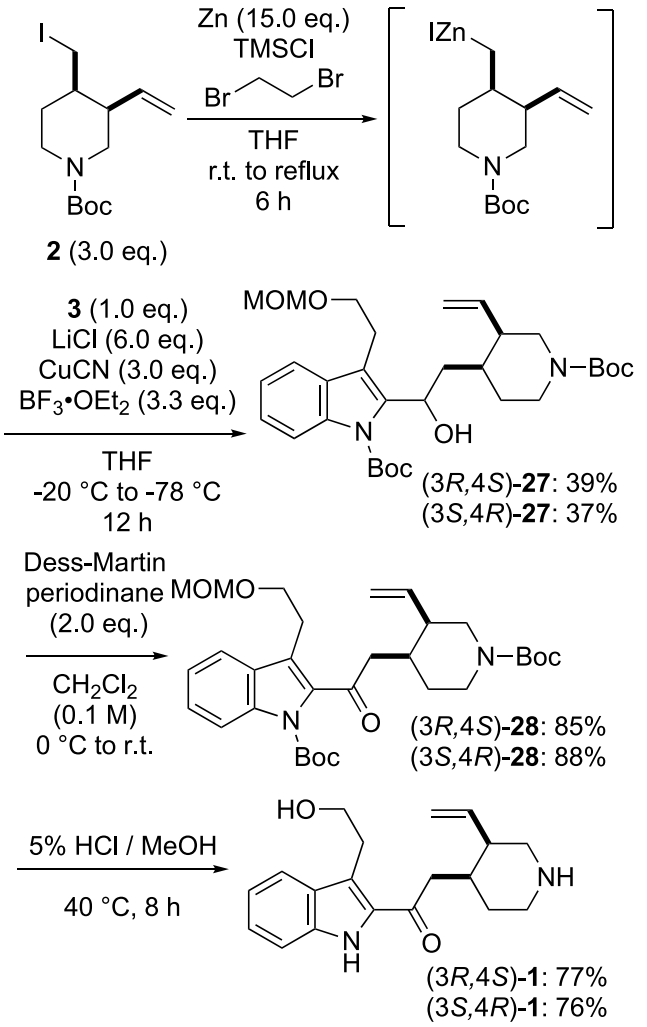
Scheme 6. Synthesis of (3*R*,4*S*)-1 and (3*S*,4*R*)-1



Scheme 7. Optical Rotation of (3*R*,4*S*)-1 and (3*S*,4*R*)-1

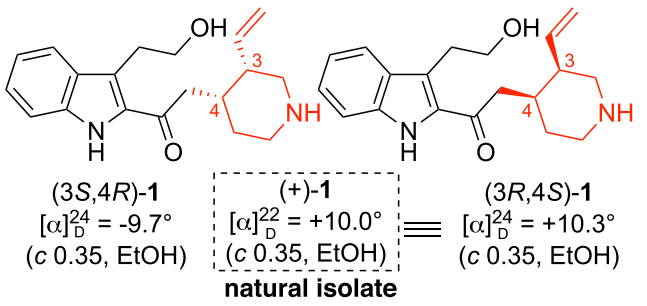


Table 4. hMAO-A and hMAO-B Inhibitory Activities of the Synthesized (+)- and (−)-1[a]

	IC_{50} (μM)	
	(+)-1	(−)-1
hMAO-A	>1000	>1000
hMAO-B	412 ± 108	488 ± 137

[a]Mean ± SD (n = 3).

of the hMAO-B, and we designed compound **30** without the hydroxyethyl substituent at the indole 3-position. We further considered the substituent at the indole 3-position may be

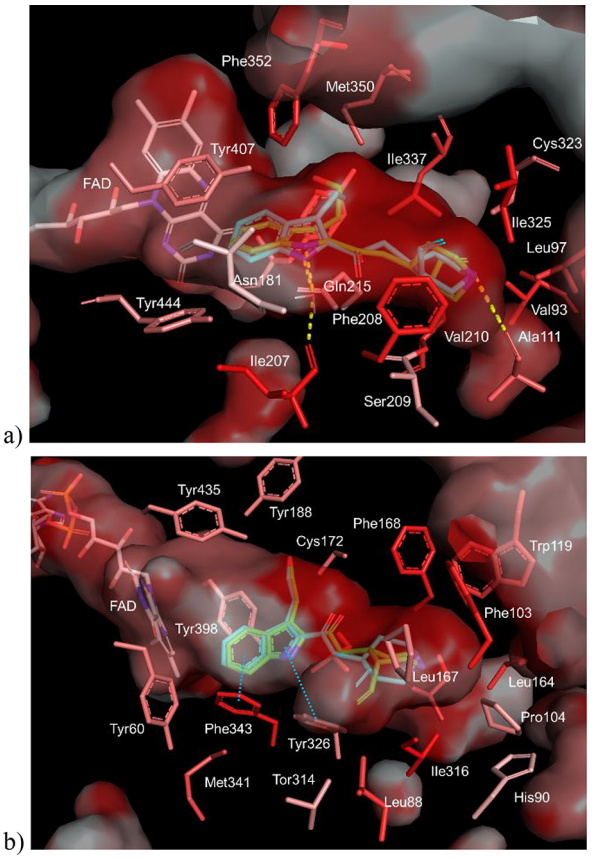
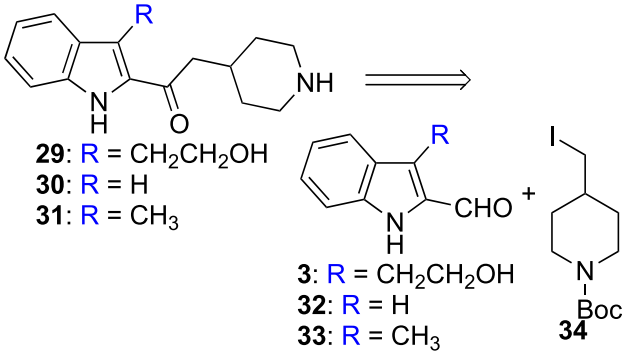


Figure 1. Docking of (+)- and (−)-**1** in a) hMAO-A (PDB: 2Z5X) and b) hMAO-B (PDB: 2V5Z). Blue compound: (+)-**1**. Green compound: (−)-**1**. The hydrophilic region of the protein is colored red. It is considered that ethyl alcohol does not form hydrogen bonds and has a high affinity because it is located in the highly hydrophilic part of the pocket. In hMAO-A, it was suggested that the nitrogen in the indole moiety and the carbonyl oxygen of Ile325 were hydrogen-bonded via water and that the hydrogen bonded to the nitrogen in the piperidine moiety and the carbonyl oxygen of Ala111 were hydrogen-bonded. In hMAO-B, it was suggested that Phe343 and Tyr326 form a $\pi-\pi$ interaction with the indole moiety.

Scheme 8. Designed Structurally Simplified Derivatives of 1 and 29−31 and Their Retrosynthesis Analysis



essential for the hMAO-A or -B binding to restrict the relative special positioning of the indole and the piperizine moieties due to its rather significant steric repulsion for the eclipsed 2-side chain and therefore designed compound **31** having a methyl substituent at the 3-position.

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Using the same coupling for the synthesis of **1**, **29**−**31** were successfully prepared from indole units **3**, **32**,[12] and **33**[13] and piperidine unit **34** (Scheme S6).[14] Then, hMAO-A and hMAO-B inhibitory activities of the synthesized analogs **29**−**31** were evaluated (Table 5). Although compound **29** did not show any inhibitory activities for hMAO-A and hMAO-B, compounds **30** and **31** were moderately potent. It was interesting that compound **30**, which has a methyl substituent at the 3-position of indole, had some selectivity for hMAO-A probably due to the expected steric repulsion, although compound **31**, which has no substituent at the 3-position of indole had some selectivity for hMAO-B. Among compounds **29**−**31**, compound **30** showed both the highest selectivity as selectivity index (SI) 11 (IC_{50} value of hMAO-A/IC_{50} value of hMAO-B) and the highest hMAO-B inhibitory activity, suggesting some alkyl-substituent effect at the C3-position of the indole in hMAO-B inhibitory activity and selectivity. We have calculated the selectivity index (SI) according to the previous report.[15] On the other hand, the hMAO-A inhibitory activity was changed by modifying the substituent at the C3-position of the indole, but no obvious association between them, such as hMAO-B, was observed. We observed that the subtype selectivity of **30** and **31** was changed just by the methyl substituent at the C3-position of the indole, probably due to preferable conformational difference. We believe these are useful results to further the development of hMAO inhibitors.

Table 5. hMAO-A and hMAO-B Inhibitory Activity of 29−31[a]

	IC_{50} (μM)		
	29	30	31
hMAO-A	>1000	720 ± 87	82.5 ± 14.7
hMAO-B	>1000	66.6 ± 18.9	121 ± 38.2

[a]Mean ± SD (n = 3).

In conclusion, we synthesized (+)-cinchonaminone and its enantiomer, (+)- and (−)-**1**, based on the enantioselective synthesis of both enantiomers of a chiral *cis*-3,4-disubstituted piperidine derivative and determined the absolute structure of (+)-cinchonaminone. Furthermore, we designed and synthesized a simplified (+)-cinchonaminone derivative to obtain compound **30**, which showed both the highest selectivity with selectivity index 11 (IC_{50} value of hMAO-A/IC_{50} value of hMAO-B) and the highest hMAO-B inhibitory activity. We think that the compounds we have synthesized this time are worth assessing whether or not they have the biological activity confirmed by other cinchona alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00310.

Experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

CIF file (CIF)

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Author Contributions

Y.S. and N.O. contributed equally.

Notes

The authors declare no competing financial interest.

Crystallographic data for CCDC 2074803 can be accessed free of charge at www.ccdc.cam.ac.uk/data_request/cif.

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