CHEMISTRY LETTERS, pp. 213-216, 1993.

Formal Total Synthesis of (-)-Dendrobine Using Zirconium Promoted Cyclization. Determination of the Absolute Configuration of the Intermediary Tricyclic Ketone

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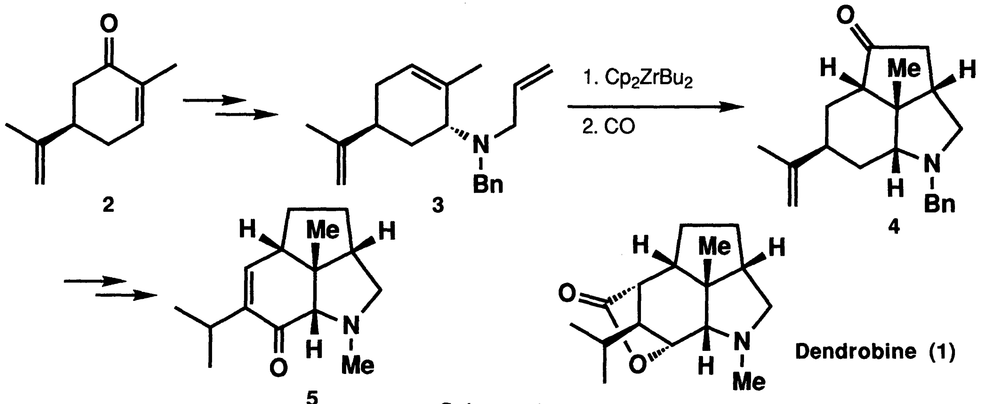
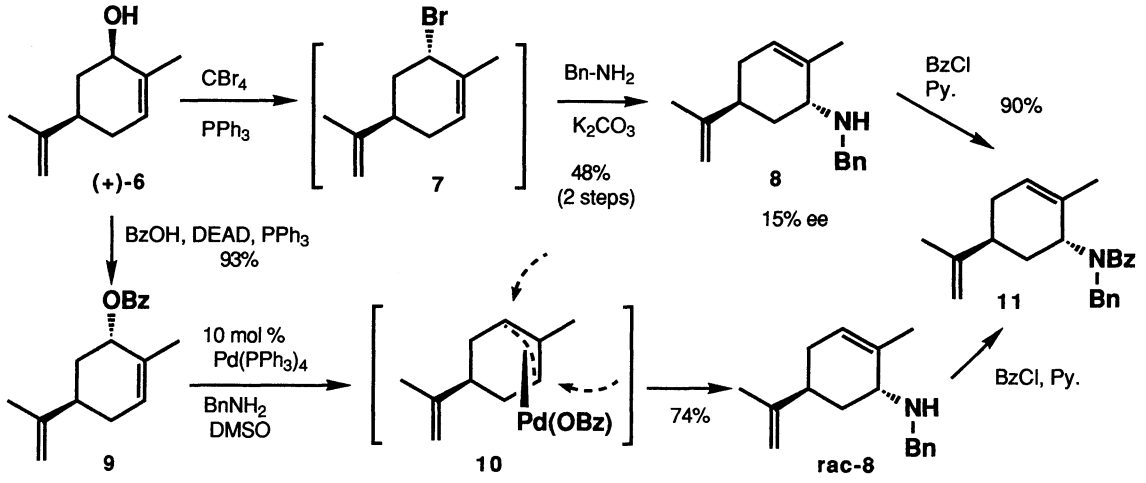
The optical purity of (-)-dendrobine synthesized using zirconium promoted cyclization was improved and the absolute configuration of the intermediary tricyclic ketone was determined using the improved Mosher's method developed by Kusumi.

Zirconium promoted reductive cyclization was very attractive for the formation of the C-C bond because the intermediary zirconacycle was very reactive towards various reagents and thus regio- and stereo-controlled products were obtained.[1] Recently, we reported the novel synthesis of nitrogen heterocycles using this procedure and have succeeded in the formal total synthesis of (-)-dendrobine[2] with application of this method (Scheme 1). However, it is regrettable that the optical purity of the synthesized dendrobine was low (15% ee). Now, we want to report the improved synthesis of (-)-dendrobine using zirconium promoted reductive cyclization.



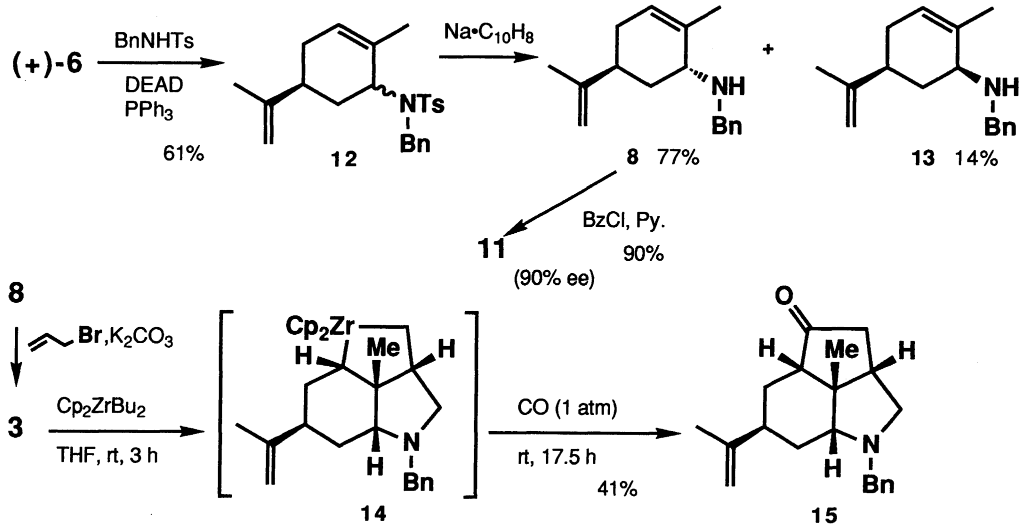
Scheme 1.

In the previous synthesis, (-)-carveol (**6**) was treated with CBr_4 and PPh_3 to produce the bromide **7**, which reacted with benzylamine to give the cyclohexenylamine **8**. In these processes, it was considered that the first step should proceed *via* a S_N2 reaction and the second should proceed *via* a *syn*-S_N2' process.[3] Thus, (-)-carveol would afford the *trans* cyclohexenyl-benzylamine **8**. Since there is a possibility for the formation of the allyl cation intermediate in each process, it was required to determine the optical purity of the amine **8**. Thus, the racemic benzylamine **8** was prepared. (-)-Carveol was converted to the cyclohexenylbenzoate **9** using Mitsunobu procedure,[4] which reacted with benzylamine in the presence of $Pd(PPh_3)_4$ in DMSO to afford the racemic benylamine **8** *via* the π-allyl palladium complex **10**.[5] The benzylamine was converted to **11**, whose optical purity was determined by HPLC using a chiral stationary phase column (CHIRALPAK AD, hexane/*i*-PrOH=9/1, 15% ee). This means that the optical purity of (-)-dendrobine synthesized by us should be 15% ee.



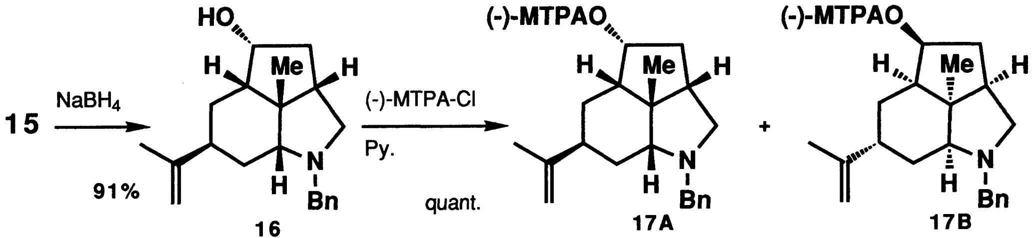
Scheme 2.

In order to improve the optical purity of the synthesized dendrobine, we prepared the benzylamine **8** using the Mitsunobu reaction.4) Conversion of (+)-carveol **6** to the sulfonamide **12** followed by treatment with sodium naphthalenide gave the desired benzyl amine **8** in 77% yield along with **13**6) (14% yield). The optical purity of **11** derived from **8** is 90% ee. Reaction of the N-benzyl allylamine **3**, which was converted from **8** (90% ee), with zirconocene prepared from Cp_2ZrCl_2 and BuLi proceeded smoothly to give zirconacycle **14**, which further reacted with carbon monoxide (1 atm) to afford the desired tricyclic ketone **15** in 41% yield.



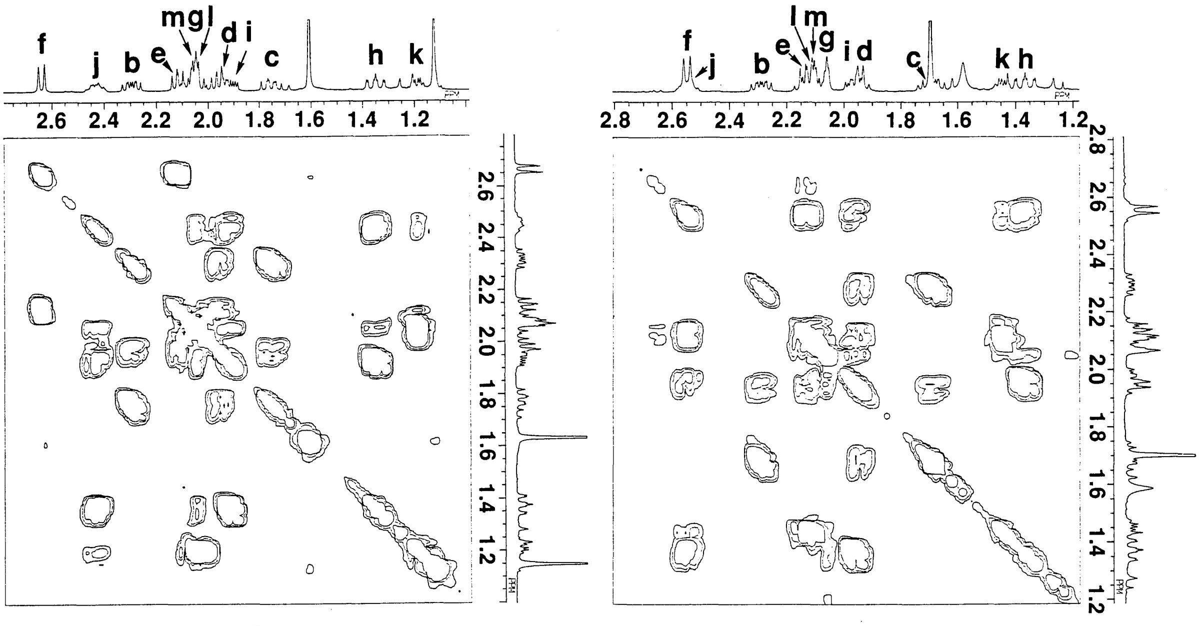
Scheme 3.

Since there has been no report of the total synthesis of optically active dendrobine,7) an attemptt was made to determine the absolute configuration of the tricyclic ketone **15**. For this purpose, the improved Mosher's method developed by Kusumi8) was applied. This procedure should be used for the determination of the absolute configuration of the one diastereomer of MTPA esters derived from the racemic products.9) Tricyclic ketone **15** was treated with $NaBH_4$ to give the single isomer of the alcohol **16**, which was treated with (-)-MTPA [(2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid] chloride in the presence of pyridine in CH_2Cl_2 to give two diastereomers **17A** and **17B** of the (-)-MTPA ester. From the NOESY result of the major product **17A**, the configuration of the hydroxy group was *trans* to the angular methyl group (α-configuration). On the basis of the data of these H,H COSY (Fig. 1), NOESY, HSQC and HMBC spectra,10) the chemical shifts of each isomer were determined, respectively, and the values of $\Delta\delta = |\delta_{major}| - |\delta_{minor}|$ were calculated and are shown in Fig.2. Since all assigned protons with positive and negative $\Delta\delta$ values are actually found on the left and right sides of the MTPA plane, respectively, it indicates that the improved Mosher's method can be used for the determination of the absolute configuration of the major enantiomer of the tricyclic ketone **15**. From the data, we decided that the optical purity of the tricyclic ketone **15** was 90% ee and the absolute configuration of the secondary alcohol of **16** has the *R*-configuration as shown in Fig. 2.



two diastereomers (**17A** : **17B** = 95 : 5)

Scheme 4.



17A **17B**

Fig. 1. H, H, COSY spectra (400 MHz) of the (-)-MTPA esters, **17A** and **17B**.

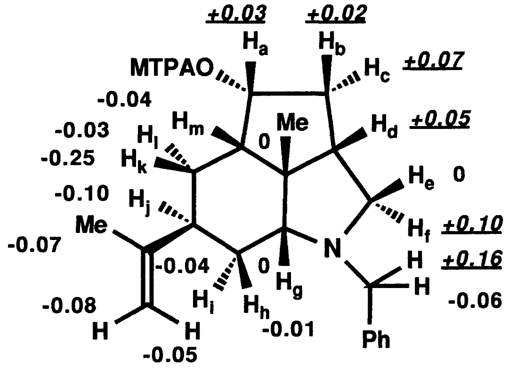


Fig. 2. $\Delta\delta$ values obtained from the MTPA esters, **17A** and **17B**.

This means that the improved Mosher's method was not only effective in determining the optical purity of the synthesized products, but also in determining the absolute configuration of the major diastereomer. Thus, we succeeded in the formal total synthesis of (-)-dendrobine using zirconium promoted cyclization.

The authors are grateful to Prof. Takenori Kusumi (Tokushima University) for his helpful discussion.

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5) It was known that the formation of the π-allyl palladium complex should proceed through a S_N2 reaction and the soft nucleophiles attack from the back side of the complex. On the other hand, since two positions of the π-allylpalladium complex can be attacked by the nucleophiles, the benzyl amine **8**, which was obtained by this process, should be a racemic product and have a *trans* configuration toward the isopropenyl group.
6) The reaction mechanism for the formation of compound **13** was not clear. Probably, the S_N2' reaction would partially occur during the formation of compound **12**.
7) Recently, Trost reported the synthesis of (-)-dendrobine, but the detailed spectral data were not described. B. M. Trost, A. S. Tasker, G. Ruther and A. Brandes, *J. Am. Chem. Soc.*, **113**, 670 (1991).
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9) Since (-)-MTPA chloride was used in our case, two diastereomers, (-)-MTPA-(*R*)-**16** and (-)-MTPA-(*S*)-**16** were obtained. If the absolute configuration of the optically pure natural product is determined by the improved Mosher's method, (-)-MTPA-(*R*)- and (+)-MTPA-(*R*)-esters [or (-)-MTPA-(*S*)- and (+)-MTPA-(*S*)-esters)] were prepared. Since the (-)-MTPA-(*S*)-**16** was an enantiomer of (+)-MTPA-(*R*)-**16**, the NMR spectrum of (-)-MTPA-(*S*)-**16** was same as that of (+)-MTPA-(*R*)-**16**. Thus, the absolute configuration of one diastereomer derived from the racemic compound can be determined.
10) The NMR spectra were recorded on JEOL EX400.

(Received September 28, 1992)