



**Chiral Ligands Derived from *Abrine*. 3.  
Asymmetric Pictet-Spengler Reaction of *Abrine* Methyl Ester and  
Synthesis of Chiral 1,2,3,4-Tetrahydro- $\beta$ -carbolines as Promoters  
in Addition of Diethylzinc toward Aromatic Aldehydes**

Wei-Min Dai,<sup>\*a</sup> Hua Jie Zhu,<sup>a§</sup> and Xiao-Jiang Hao<sup>\*b</sup>

<sup>a</sup>Department of Chemistry, The Hong Kong University of Science and Technology

Clear Water Bay, Kowloon, Hong Kong

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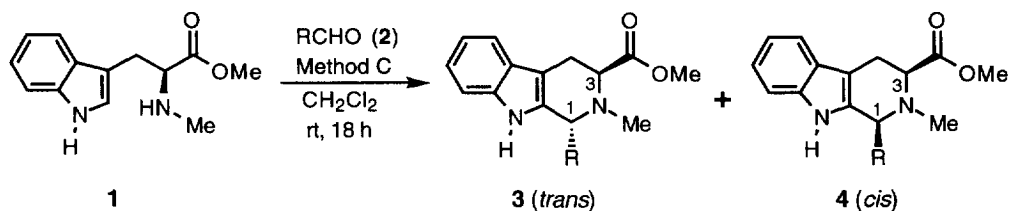
<sup>b</sup>Kunming Institute of Botany, The Academy of Sciences of China,

Heilongtan, Kunming 650204, Yunnan, China

**Abstract:** Asymmetric Pictet-Spengler reaction of a number of aldehydes with *Abrine* methyl ester (1) was performed at room temperature to furnish mainly 3 and high ee was obtained in enantioselective addition of Et<sub>2</sub>Zn with PhCHO catalyzed by chiral 1,2,3,4-tetrahydro- $\beta$ -carboline derivatives 5 synthesized from 3. Copyright © 1996 Elsevier Science Ltd

The Pictet-Spengler reaction<sup>1</sup> has played an important role in the syntheses of isoquinoline<sup>2</sup> and  $\beta$ -carboline<sup>3</sup> alkaloids. Starting from chiral *N*<sub>b</sub>-benzyltryptophan esters, optically active *trans*-1,3-disubstituted-1,2,3,4-tetrahydro- $\beta$ -carboline derivatives could be obtained as the major product through a stereoselective Pictet-Spengler reaction.<sup>4</sup> Steric interaction between the *N*<sub>b</sub>-benzyl and C(3) carboalkoxy groups in the transition state was considered as the cause of the observed stereoselectivity. By changing the *N*<sub>b</sub>-benzyl to *N*<sub>b</sub>-diphenylmethyl analogs, complete *trans* selectivity could be achieved even for acetaldehyde.<sup>4d</sup> Very recently asymmetric Pictet-Spengler reaction using chiral auxiliary groups has also been developed to give diastereomeric excess up to 97%.<sup>5</sup> We have initiated a research program for enantioselective reactions utilizing chiral ligands derived from the alkaloid *Abrine* [(*S*)-*N*-methyltryptophan].<sup>6</sup> A number of indole-containing chiral  $\beta$ -amino alcohols<sup>7a</sup> and oxazolidines<sup>7b</sup> were synthesized and their catalytic potency for the addition of diethylzinc toward aromatic aldehydes was examined. We report here the synthesis of chiral *N*<sub>b</sub>-methyl-1,2,3,4-tetrahydro- $\beta$ -carbolines 3 from *Abrine* methyl ester (1, Scheme 1) and the enantioselective addition of Et<sub>2</sub>Zn with aromatic aldehydes catalyzed by the chiral hydroxy-containing 1,2,3,4-tetrahydro- $\beta$ -carbolines 5.

**Scheme 1**



The Pictet-Spengler condensation of *N*<sub>b</sub>-benzyltryptophan esters with aldehydes was usually performed in refluxing benzene or toluene<sup>4a-e</sup> with azeotropic removal of water by using a Dean-Stark trap.<sup>4b</sup> For bulky aldehydes, an acid such as trifluoroacetic acid (TFA) was used to facilitate the ring formation.<sup>4d,e</sup> In order to have a simple operational procedure and to avoid decomposition of the materials at higher temperature, we chose to conduct the reaction in CH<sub>2</sub>Cl<sub>2</sub> at rt (Scheme 1). As shown in Table 1,<sup>8</sup> it was found that 4 Å MS alone did not give the desired product from **1** and **2b** (entry 2). TFA promoted the Pictet-Spengler reaction of **1** with PhCHO in excellent yield (entry 10). However, the yields decreased significantly when bulky aldehydes were used (entries 5 and 7). Finally, carrying out the reaction in the presence of a catalytic amount of TFA and MS [Method C] in CH<sub>2</sub>Cl<sub>2</sub> at rt for overnight provided an efficient synthesis of *N*<sub>b</sub>-methyl-1,2,3,4-tetrahydro-β-carbolines **3** and **4**. These results suggest that both acid catalysis and removal of water from the reaction mixture are essential for performing the Pictet-Spengler reaction at rt. It is known<sup>4d</sup> that the bulkiness of the *N*<sub>b</sub>-alkyl group affects the diastereomeric ratio of the product. We expected that in our *N*<sub>b</sub>-methyl series the diastereomeric ratio of **3:4** will be lower compared to the *N*<sub>b</sub>-benzyl series of compounds. However, it was realized that the ratio **3:4** could be increased from 72:28 (**2a**, entry 1) to 90:10 (**2h**, entry 11) with increased size of the R group in **2**. Moreover, it was confirmed that the ratio of **3:4** given in Table 1 is the thermodynamic ratio since no change was noted by treating the isolated product mixture again with TFA at rt.<sup>4e</sup>

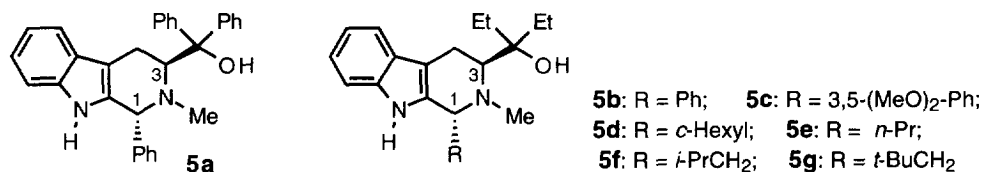
**Table 1.** Asymmetric Pictet-Spengler Reaction of *Abrine* Methyl Ester at rt.

Entry	RCHO ( <b>2</b> ) <sup>a</sup>	Method <sup>b</sup>	Yield (%) <sup>c</sup>	<b>3:4</b> (ratio) <sup>f</sup>
1	<b>2a</b> : R = Et	C [TFA (0.25 eq)+MS]	61.6 <sup>d</sup>	<b>3a:4a</b> (72:28)
2	<b>2b</b> : R = <i>n</i> -Pr	A [MS only, 3 days]	----- <sup>e</sup>	---- <sup>e</sup>
3	<b>2b</b>	C	58.9 <sup>d</sup>	<b>3b:4b</b> (76:24)
4	<b>2c</b> : R = <i>i</i> -Pr	C	72.4	<b>3c:4c</b> (79:21)
5	<b>2d</b> : R = <i>i</i> -PrCH <sub>2</sub>	B [TFA (0.25 eq) only]	51.4	<b>3d:4d</b> (80:20)
6	<b>2d</b>	C	85.5	<b>3d:4d</b> (80:20)
7	<b>2e</b> : R = <i>t</i> -BuCH <sub>2</sub>	B	17.7	<b>3e:4e</b> (87:13)
8	<b>2e</b>	C	87.5	<b>3e:4e</b> (87:13)
9	<b>2f</b> : R = <i>c</i> -Hexyl	C	48.5 <sup>d</sup>	<b>3f:4f</b> (83:17)
10	<b>2g</b> : R = Ph	B	83.4	<b>3g:4g</b> (82:18)
11	<b>2h</b> : R = 3,5-(MeO) <sub>2</sub> -Ph	C	88.2	<b>3h:4h</b> (90:10)
12	<b>2i</b> : R = 1-naphtyl	C	83.3	<b>3i:4i</b> (88:12)

<sup>a</sup>1.5 equivalent of RCHO was used. <sup>b</sup>TFA = trifluoroacetic acid; MS = powdered 4 Å molecular sieves. <sup>c</sup>Yield is calculated based on the isolated homogenous material. <sup>d</sup>Yield is not optimized. <sup>e</sup>A very complex mixture was obtained. <sup>f</sup>Determined by <sup>1</sup>H NMR on a 300 MHz instrument.

Next, the inseparable mixture of **3:4** (except for **3e** which was isolated in diastereomeric pure form) was treated with excess amount of PhMgCl or EtMgBr at rt to form the tertiary alcohol **5a-g**<sup>8</sup> in 50-70% yield. Fortunately, the minor product generated from **4** was separated by flash column chromatographic purification

over silica gel. With compounds **5a-g** in hand, enantioselective addition of  $\text{Et}_2\text{Zn}$  toward aromatic aldehydes<sup>9</sup> was investigated by using 5 or 10% of **5a-g** as the catalyst. Table 2 shows these results. It is interesting to note that **5a** bearing a diphenylhydroxymethyl group induced lower enantiomeric excess (ee) than the corresponding diethylhydroxymethyl analog **5b** (24.1% vs. 47.9%, entries 1 and 2).<sup>7a</sup> In general, the catalysts **5b,c** having an aromatic group at C(1) are poor catalysts (<60% ee) compared with **5d** possessing a cyclohexyl group at C(1) (82.4% ee, entry 5). It was further demonstrated that a bulky alkyl side chain attached at C(1) of the catalyst is critical for achieving high enantioselectivity (up to 97.6% ee, entries 6-8) of the ethylation reaction.



**Table 2.** Enantioselective Addition of  $\text{Et}_2\text{Zn}$  toward Aromatic Aldehydes in PhMe at rt.

Entry	ArCHO	Cat <sup>a</sup>	Reaction Time	ArC <sup>*</sup> H(OH)Et <sup>c</sup>	ee% <sup>d</sup>	Configuration <sup>e</sup>
1	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	<b>5a</b> <sup>b</sup>	24 h	71.3%	24.1	<i>R</i>
2	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	<b>5b</b> <sup>b</sup>	46 h	92.7%	47.9	<i>R</i>
3	C <sub>6</sub> H <sub>5</sub> CHO	<b>5b</b>	46 h	86.9%	52.9	<i>R</i>
4	C <sub>6</sub> H <sub>5</sub> CHO	<b>5c</b>	46 h	93.7%	51.9	<i>R</i>
5	C <sub>6</sub> H <sub>5</sub> CHO	<b>5d</b>	46 h	86.6%	82.4	<i>R</i>
6	C <sub>6</sub> H <sub>5</sub> CHO	<b>5e</b>	46 h	88.4%	69.3	<i>R</i>
7	C <sub>6</sub> H <sub>5</sub> CHO	<b>5f</b>	46 h	88.4%	85.2	<i>R</i>
8	C <sub>6</sub> H <sub>5</sub> CHO	<b>5g</b>	46 h	92.5%	97.6	<i>R</i>

<sup>a</sup>5% Cat<sup>\*</sup> was used. <sup>b</sup>10% Cat<sup>\*</sup> was used. <sup>c</sup>Yield is based on the isolated homogenous material.

<sup>d</sup>Determined by HPLC on CHIRALCEL OB column. <sup>e</sup>Based on the positive rotation sign. See ref. 10.

In summary, an efficient asymmetric Pictet-Spengler reaction of *Abrine* methyl ester (**1**) with a number of aldehydes has been performed at rt in  $\text{CH}_2\text{Cl}_2$  in the presence of a catalytic amount of trifluoroacetic acid and 4 Å powdered molecular sieves. The diastereomeric ratio of the products **3:4** could be improved by using a bulky aldehyde. The chiral hydroxy-containing *trans*-1,3-disubstituted-1,2,3,4-tetrahydro- $\beta$ -carbolines **5** could be synthesized from the asymmetric Pictet-Spengler reaction products **3** by reacting with the Grignard reagents. Moreover, compounds **5** exhibit promising catalytic capability for the enantioselective ethylation of aromatic aldehydes with  $\text{Et}_2\text{Zn}$ . This work provides a novel class of 1,2,3,4-tetrahydro- $\beta$ -carboline-based chiral ligands for this exciting catalytic enantioselective reaction.<sup>11</sup> Further investigation is under way in our laboratories.

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