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

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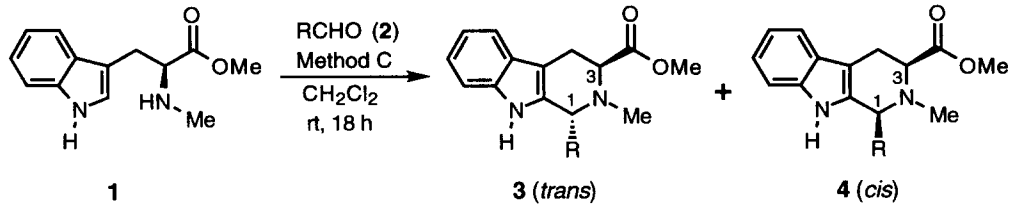
Abstract: Asymmetric Pictet-Spengler reaction of a number of aldehydes with *Abrine* methyl ester (**1**) was performed at room temperature to furnish mainly **3** and high ee was obtained in enantioselective addition of Et_2Zn with PhCHO catalyzed by chiral 1,2,3,4-tetrahydro-β-carboline derivatives **5** synthesized from **3**. Copyright © 1996 Elsevier Science Ltd

The Pictet-Spengler reaction[1] has played an important role in the syntheses of isoquinoline[2] and β-carboline[3] alkaloids. Starting from chiral N_b-benzyltryptophan esters, optically active *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carboline derivatives could be obtained as the major product through a stereoselective Pictet-Spengler reaction.[4] Steric interaction between the N_b-benzyl and C(3) carboalkoxy groups in the transition state was considered as the cause of the observed stereoselectivity. By changing the N_b-benzyl to N_b-diphenylmethyl analogs, complete *trans* selectivity could be achieved even for acetaldehyde.[4d] Very recently asymmetric Pictet-Spengler reaction using chiral auxiliary groups has also been developed to give diastereomeric excess up to 97%.[5] We have initiated a research program for enantioselective reactions utilizing chiral ligands derived from the alkaloid *Abrine* [(*S*)-*N*-methyltryptophan].[6] A number of indole-containing chiral β-amino alcohols[7a] and oxazolidines[7b] were synthesized and their catalytic potency for the addition of diethylzinc toward aromatic aldehydes was examined. We report here the synthesis of chiral N_b-methyl-1,2,3,4-tetrahydro-β-carbolines **3** from *Abrine* methyl ester (**1**, Scheme 1) and the enantioselective addition of Et_2Zn with aromatic aldehydes catalyzed by the chiral hydroxy-containing 1,2,3,4-tetrahydro-β-carbolines **5**.

Scheme 1



1 **3** (*trans*) **4** (*cis*)

The Pictet-Spengler condensation of N_b-benzyltryptophan esters with aldehydes was usually performed in refluxing benzene or toluene[4a-e] with azeotropic removal of water by using a Dean-Stark trap.[4b] For bulky aldehydes, an acid such as trifluoroacetic acid (TFA) was used to facilitate the ring formation.[4d,e] 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_2Cl_2 at rt (Scheme 1). As shown in Table 1,[8] 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_2Cl_2 at rt for overnight provided an efficient synthesis of N_b-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[4d] that the bulkiness of the N_b-alkyl group affects the diastereomeric ratio of the product. We expected that in our N_b-methyl series the diastereomeric ratio of **3**:**4** will be lower compared to the N_b-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.[4e]

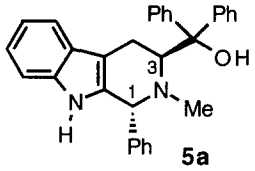
Table 1. Asymmetric Pictet-Spengler Reaction of *Abrine* Methyl Ester at rt.

Entry	RCHO (**2**)[a]	Method[b]	Yield (%)[c]	**3**:**4** (ratio)[f]
1	**2a**: R = Et	C [TFA (0.25 eq)+MS]	61.6[d]	**3a**:**4a** (72:28)
2	**2b**: R = *n*-Pr	A [MS only, 3 days]	-----[e]	----[e]
3	**2b**	C	58.9[d]	**3b**:**4b** (76:24)
4	**2c**: R = *i*-Pr	C	72.4	**3c**:**4c** (79:21)
5	**2d**: R = *i*-PrCH$_2$	B [TFA (0.25 eq) only]	51.4	**3d**:**4d** (80:20)
6	**2d**	C	85.5	**3d**:**4d** (80:20)
7	**2e**: R = *t*-BuCH$_2$	B	17.7	**3e**:**4e** (87:13)
8	**2e**	C	87.5	**3e**:**4e** (87:13)
9	**2f**: R = *c*-Hexyl	C	48.5[d]	**3f**:**4f** (83:17)
10	**2g**: R = Ph	B	83.4	**3g**:**4g** (82:18)
11	**2h**: R = 3,5-(MeO)$_2$-Ph	C	88.2	**3h**:**4h** (90:10)
12	**2i**: R = 1-naphtyl	C	83.3	**3i**:**4i** (88:12)

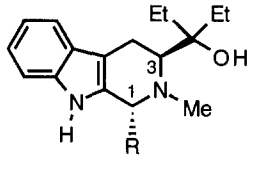
[a]1.5 equivalent of RCHO was used. [b]TFA = trifluoroacetic acid; MS = powdered 4 Å molecular sieves. [c]Yield is calculated based on the isolated homogenous material. [d]Yield is not optimized. [e]A very complex mixture was obtained. [f]Determined by ^{1}H NMR on a 300 MHz instrument.

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**[8] 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 Et_2Zn toward aromatic aldehydes[9] 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).[7a] 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.



5a



5b: R = Ph; **5c**: R = 3,5-$(MeO)_2$-Ph;
5d: R = *c*-Hexyl; **5e**: R = *n*-Pr;
5f: R = *i*-$PrCH_2$; **5g**: R = *t*-$BuCH_2$

Table 2. Enantioselective Addition of Et_2Zn toward Aromatic Aldehydes in PhMe at rt.

Entry	ArCHO	Cat*[a]	Reation Time	ArC*H(OH)Et[c]	ee%[d]	Configuration[e]
1	*p*-ClC_6H_4CHO	**5a**[b]	24 h	71.3%	24.1	*R*
2	*p*-ClC_6H_4CHO	**5b**[b]	46 h	92.7%	47.9	*R*
3	C_6H_5CHO	**5b**	46 h	86.9%	52.9	*R*
4	C_6H_5CHO	**5c**	46 h	93.7%	51.9	*R*
5	C_6H_5CHO	**5d**	46 h	86.6%	82.4	*R*
6	C_6H_5CHO	**5e**	46 h	88.4%	69.3	*R*
7	C_6H_5CHO	**5f**	46 h	88.4%	85.2	*R*
8	C_6H_5CHO	**5g**	46 h	92.5%	97.6	*R*

[a]5% Cat* was used. [b]10% Cat* was used. [c]Yield is based on the isolated homogenous material. [d]Determined by HPLC on CHIRALCEL OB column. [e]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 CH_2Cl_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-β-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 Et_2Zn. This work provides a novel class of 1,2,3,4-tetrahydro-β-carboline-based chiral ligands for this exciting catalytic enantioselective reaction.[11] Further investigation is under way in our laboratories.

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