Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 177–180

TETRAHEDRON: *ASYMMETRY*

An efficient synthetic approach to optically active β-carboline derivatives via Pictet–Spengler reaction promoted by trimethylchlorosilane

Riichiro Tsuji, Masako Nakagawa and Atsushi Nishida*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Chiba 263-8522, Japan

Received 1 November 2002; accepted 21 November 2002

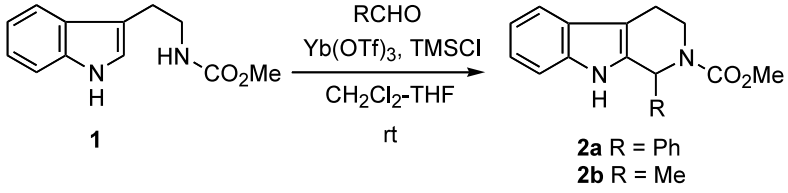
Abstract—A highly diastereoselective Pictet–Spengler reaction using chiral tryptamine carbamates has been developed. The reaction proceeds using aromatic and aliphatic aldehydes in the presence of trimethylchlorosilane.

1. Introduction

β-Carboline alkaloids are an important class of natural products, and many have various biological activities. The Pictet–Spengler reaction is a useful method for the synthesis of tetrahydro-β-carboline derivatives and is also a key reaction for the synthesis of natural products.[1] For example, we achieved the total synthesis of Fumitremorgin[2] and Eudistomins[3] using the Pictet–Spengler reaction to construct the C-1 stereogenic center in the tetrahydro-β-carboline moiety. Recently, we reported the first example of a highly enantioselective Pictet–Spengler reaction using enantiopure diisopinocampheylchloroborane as a chiral Lewis acid,[4] although the substrates were limited to the use of nitrones. The diastereoselective Pictet–Spengler reaction using tryptophan or tryptamine derivatives has also been widely studied. We also found that a combination of $Yb(OTf)_3$ and TMSCl promoted the Pictet–Spengler reaction of imine itself to give tetrahydro-β-carbolines in excellent yields under mild conditions.[5] However, the application of this reaction to enantioselective synthesis has not been successful. Diastereoselective Pictet–Spengler reactions using chiral tryptamine derivatives with a chiral auxiliary on the nitrogen atom have also been intensively studied.[6] Koomen and co-workers reported a diastereoselective Pictet–Spengler reaction using a chiral *N*-sulfinyl group as a removable chiral auxiliary, which induced up to 76% diastereoselectivity (ds).[6f] We describe herein an efficient diastereoselective Pictet–Spengler reaction using chiral tryptamine carbamate promoted by trimethylchlorosilane.

2. Results

First, the Pictet–Spengler reaction of tryptamine methylcarbamate **1** with benzaldehyde was examined to determine suitable reaction conditions (Scheme 1). Based upon our previous observations from Pictet–Spengler reactions using imines,[5] the reaction using a combination of $Yb(OTf)_3$ (0.1 equiv.) and TMSCl (1.0 equiv.) in CH_2Cl_2–THF was tested and the desired product **2a** was obtained in 89% yield (Table 1, entry



1

2a R = Ph
2b R = Me

Scheme 1.

* Corresponding author. Fax: 81-43-290-2909; e-mail: nishida@p.chiba-u.ac.jp

0957-4166/03/$ - see front matter
PII: S0957-4166(02)00793-0

1). In the reaction with acetaldehyde, which is more reactive than benzaldehyde, **2b** was obtained under similar conditions but in 46% yield (entry 2). Surprisingly, this reaction proceeded faster in the presence of TMSCl alone and was complete within 30 min in 86% yield (entry 3). Other acidic promoters such as $BF_3{\cdot}OEt_2$, $ZnCl_2$, $Yb(OTf)_3$, TFA, CSA and TMSOTf gave unsuccessful results.[7]

Comins and co-workers reported the diastereoselective Pictet–Spengler reaction using a chiral carbamate obtained from 3,4-dimethoxyphenethylamine and (−)-8-phenylmenthyl chloroformate.[8] Therefore, (−)-menthyl carbamate was used in our reaction to obtain optically active tetrahydro-β-carbolines. Although the diastereoselective Pictet–Spengler reaction of menthyl carbamate **3a**, prepared from tryptamine and (−)-menthyl chloroformate proceeded smoothly even at −30°C to give the desired **4a** in 86% yield, its d.e. was only 7% (Table 2, entry 1). However, we were pleased to find that the diastereoselectivity increased dramatically (89% yield, 80% d.e.) when a (−)-8-phenylmenthyl group (**3b**) was used as the chiral auxiliary instead of the (−)-menthyl group (entry 2). *N*-Protected derivatives such as **3c** and **3d** exhibited higher reactivity and enabled the reaction to proceed at lower temperature to give **4b** (81% d.e. at −40°C)[9] and **4c** (90% d.e. at −60°C) (entries 3 and 4), although these reactions required longer reaction times.

The absolute configuration of the newly formed stereogenic center in **4a** was determined to be *S* by HPLC analysis[10] in comparison with enantiomerically pure **4a** prepared from L-tryptophan methyl ester in seven steps by diastereoselective Pictet–Spengler reaction (33% d.e.) (Scheme 2).[11]

We then studied the effects of aldehyde substitution (entries 5–9): The substrate **3b** was found to be quite reactive with various aldehydes. For example, sterically hindered aldehyde (R = *c*-Hex, entry 8) and linear primary aldehydes (R = Et, *n*-Bu, entries 6 and 7) were smoothly converted to the corresponding products **4f–g** with good d.e. On the other hand, the less encumbered acetaldehyde gave **4d** in 22% d.e. We assume that the diastereoselectivity of this reaction might depend on the bulkiness of the R group, which would affect the stereochemistry of the C=N bond in the iminium cation intermediate (see below). With the less reactive benzaldehyde, the reaction proceeded at higher temperature in the presence of $Yb(OTf)_3$ and occurred with lower selectivity (53% yield, 53% d.e., entry 9).

We found that the Pictet–Spengler reaction using (−)-8-phenoxyphenylmenthyl carbamate **6**[12] with isobutyraldehyde gave the opposite absolute configuration of

Table 1. Pictet–Spengler reaction of tryptamine carbamate

Entry	Aldehyde R	$Yb(OTf)_3$ (equiv.)	TMSCl (equiv.)	Time (h)	Product (%)
1	Ph	0.1	1.0	5	**2a** (89)
2	Me	0.1	1.0	3	**2b** (46)
3	Me	None	1.0	0.5	**2b** (86)

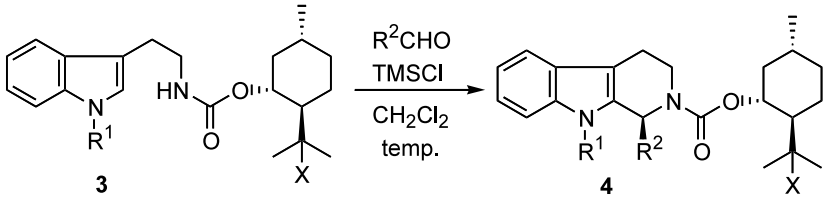
Table 2. Diastereoselective Pictet–Spengler reactions of chiral tryptamine carbamates with aldehydes

Entry	Substrate	R^1	X	Aldehyde R^2	Temp. (°C)	Time (h)	Product	Yield (%)	d.e.%[a] (config.)
1	**3a**	H	H	*i*-Pr	−30	21	**4a**	86	7[b]
2	**3b**	H	Ph	*i*-Pr	−30	24	**4b**	89	80 (*S*)
3	**3c**	TBS	Ph	*i*-Pr	−40	26	**4b**	97	81 (*S*)
4	**3d**	Bn	Ph	*i*-Pr	−60	115	**4c**	83	90 (*S*)
5	**3b**	H	Ph	Me	−30	9	**4d**	86	22[b]
6	**3b**	H	Ph	Et	−30	21	**4e**	72	71[b]
7	**3b**	H	Ph	*n*-Bu	−30	17	**4f**	72	70[b]
8	**3b**	H	Ph	*c*-Hex	−30	21	**4g**	73	69[b]
9[c]	**3b**	H	Ph	Ph	0	10	**4h**	53	53[b]

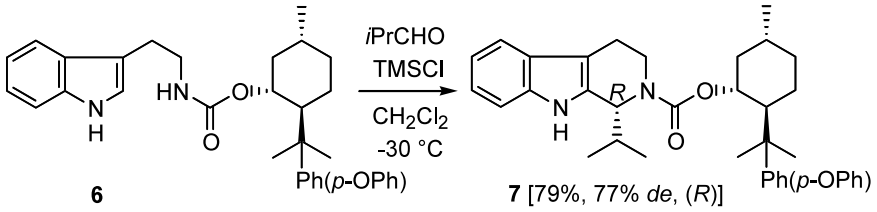
[a] Diastereomeric excesses were determined by HPLC.[10]

[b] The absolute configuration was not determined.

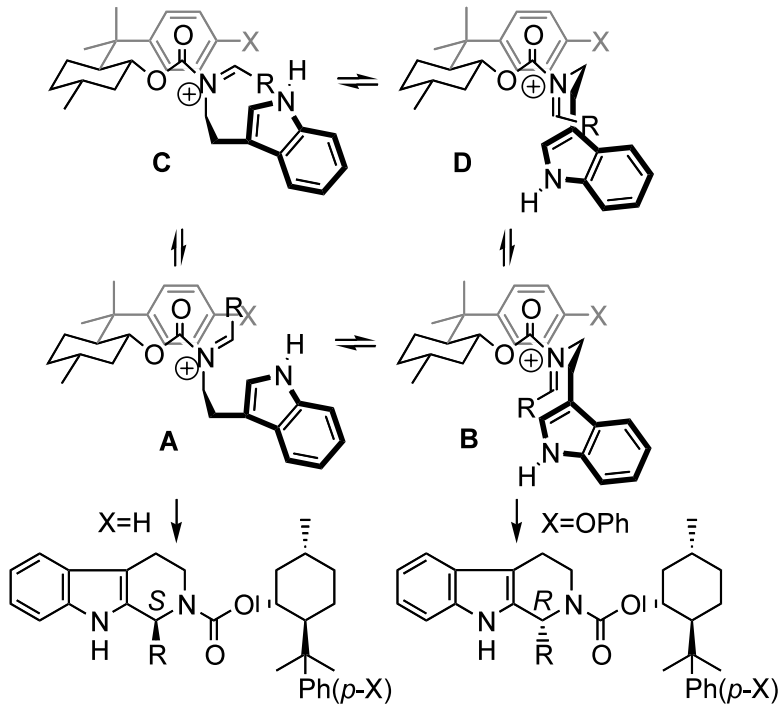
[c] Reaction was carried out in the presence of $Yb(OTf)_3$ (0.1 equiv.) as a co-promoter in CH_2Cl_2–THF (4:1).



Scheme 2.



Scheme 3.



Scheme 4.

4a with 77% d.e., as shown in Scheme 3. Its absolute configuration was again determined by HPLC analysis in comparison with enantiomerically pure **7** derived from L-tryptophan. These results show that readily available chiral menthyl auxiliaries with the same stereochemistry can induce opposite stereoselectivity at C-1 of the β-carbolines by controlling the transition state. The stereoselectivities using **3b** and **6** can be explained by the transition state models shown in Scheme 4. In the reaction of **3b**, transition state A should be most favorable when considering steric interactions between R and the indole ring leading to (1*S*)-β-carbolines. On the other hand, when the phenyl group in the chiral auxiliary has a phenoxy substituent at the 4-position, transition state B should be the most stable and gives (1*R*)-isomers as the major product.

In conclusion, we have realized the diastereoselective Pictet–Spengler reaction using TMSCl as a promoter. The results described here may lead to further progress in the synthesis of homochiral β-carbolines.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science, and Technology.

References

1. (a) Whaley, W. M.; Govindachari, T. R. *Organic Reactions*; Wiley: New York, 1951; Vol. 6, pp. 151–206; (b) Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797–1842.
2. (a) Nakagawa, M.; Kodato, S.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron Lett*. **1986**, *27*, 6217–6220; (b) Kodato, S.; Nakagawa, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359–377; (c) Hino, T.; Kawate, T.; Nakagawa, M. *Tetrahedron* **1989**, *45*, 1941–1944.

3. (a) Nakagawa, M.; Liu, J.; Hino, T. *J. Am. Chem. Soc.* **1989**, *111*, 2721–2722; (b) Nakagawa, M.; Liu, J.; Hino, T.; Tsuruoka, A.; Harada, N.; Ariga, M.; Asada, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3477–3486; (c) Liu, J.; Hino, T.; Tsuruoka, A.; Harada, N.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3487–3494.
4. (a) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron Asymmetry* **1996**, *7*, 1249–1252; (b) Kawate, T.; Yamada, H.; Matsumizu, M.; Nishida, A.; Nakagawa, M. *Synlett* **1997**, *7*, 761–762; (c) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348–6354.
5. Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428–429.
6. (a) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347–358; (b) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033–1038; (c) Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron Lett.* **1993**, *34*, 5867–5870; (d) Waldmann, H.; Schmidt, G. *Tetrahedron* **1994**, *50*, 11865–11884; (e) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402–2403 and references cited therein; (f) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955–1958.
7. Trimethylchlorosilane may activate aldehydes by behaving as a mild Lewis acid and can also remove water from the reaction mixture to form $(TMS)_2O$. Stronger Lewis acids such as $BF_3{\cdot}OEt_2$-promoted side reactions.
8. (a) Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, *26*, 2995–2996; (b) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327–16339.
9. Deprotection of the TBS group of β-carbolines was observed under these conditions.
10. **Representative procedure** (synthesis of **4b**, Table 2, entry 2): To a solution of carbamate **3b** (105 mg, 0.25 mmol) in dry methylene chloride (2.5 mL) were added isobutanal (54 μL, 0.6 mmol) and TMSCl (63 μL, 0.5 mmol) at −30°C. The reaction mixture was stirred for 24 h at −30°C and quenched with satd $NaHCO_3$. The organic layer was washed with brine and dried over Na_2SO_4. Removal of solvent in vacuo gave a residue which was purified by column chromatography (silica gel, 8:1 *n*-hex/AcOEt) to give **4b** as a mixture of diastereomers (105 mg, 89%, 80% d.e.). Diastereomeric excess was determined by HPLC [DAICEL CHIRALCEL OD, hexane:*i*PrOH = 95:5, flow rate: 2.0 mL/min, retention time: 4.1 min (minor) and 7.2 min (major)].
11. (a) Akimoto, H.; Okamura, K.; Yui, M.; Shioiri, T.; Kuramoto, M.; Kikugawa, Y.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *11*, 2614–2623; (b) Shiqi, P.; Min, G.; Winterfeldt, E. *Liebigs Ann. Chem.* **1993**, 137–140.
12. (a) Potin, D.; Dumas, F. *Synth. Commun.* **1990**, *20*, 2805–2813; (b) Ort, O. *Org. Synth. Coll. VIII* **1993**, 522.