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Enantiopure Tetrahydro-β-carbolines via Pictet–Spengler Reactions with *N*-Sulfinyl Tryptamines

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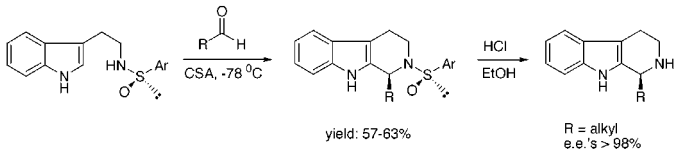
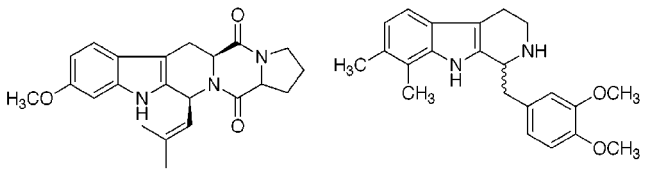
ABSTRACT



The influence of *N*-sulfinyl chiral auxiliaries on the stereochemistry of the Pictet–Spengler reaction has been investigated. From enantiopure (*R*)-*N*-*p*-toluenesulfinyltryptamine a new and efficient route to enantiopure tetrahydro-β-carbolines has been established.

The tetrahydro-β-carboline ring system is an important structural unit that is commonly encountered in naturally occurring indole alkaloids and synthetic analogues with interesting biological activities (Figure 1). Fumitremorgin C



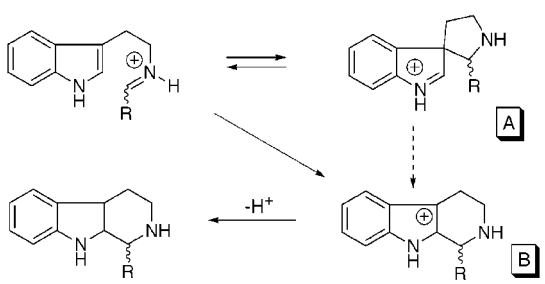
1 2

Figure 1. Biologically active tetrahydro-β-carbolines.

(**1**) is of interest due to its cytostatic activities[1] while compound **2** is an antagonist for the serotonin 2B receptor.[2] A large number of therapeutics are marketed as racemic mixtures. Since it is almost invariably the case that only one enantiomer has the desired effect, the absence of the other enantiomer with possible undesirable effects has a number of clinical advantages including improvement in pharmacological profile and simplified pharmacokinetics.[3] The development of an enantioselective route to tetrahydro-β-carbolines is therefore of interest for both synthetic organic and medicinal chemistry.

The Pictet−Spengler condensation is one of the most powerful methods for the formation of these ring systems.[4] In general, this reaction can be characterized by the formation of an iminium salt after an acid-catalyzed reaction of tryptamine and an aldehyde. This iminium ion is attacked intramolecularly by electrons of the pyrrole ring from either the 2- or 3-position (Scheme 1). The involvement of the *spiro*-indolenine intermediate **A** which is formed after attack from the indole 3-position was proven by isotopic labeling

Scheme 1



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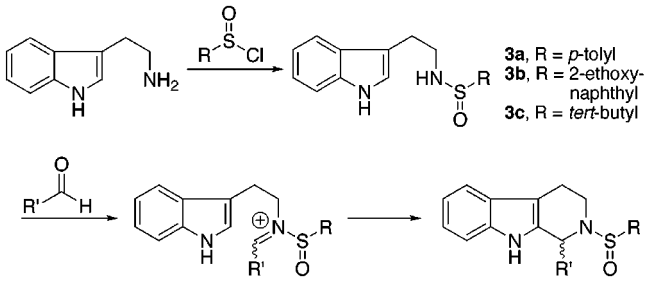
experiments.[5] However, MNDO calculations have indicated that the rearragement from intermediate **A** to **B** is energetically unfavorable.[6] Direct attack from the indole 2-position is therefore believed to be the key step in the Pictet−Spengler condensation.

Over the past decade a number of enantioselective approaches to the Pictet−Spengler reaction have been reported. Many of these approaches rely on the use of enantiopure tryptophan esters.[7] The possibility for enantioselective synthesis of tetrahydro-β-carbolines derived from tryptamine is limited by the absence of the stereodirecting effect of the carboxy group.

Introduction of chiral auxiliaries on the nitrogen atom of the ethylamino side chain of tryptamine induced diastereoselectivity in several cases. The use of chiral α-methylbenzyl groups showed diastereoslectivity only with specific aldehydes.[8] Acylation of imines from tryptamine with *N*,*N*-phthaloyl amino acid chlorides gave good diastereoselectivity in Lewis acid-catalyzed Pictet−Spengler reactions.[9] Chiral Lewis acids were used in enantioselective Pictet−Spengler reactions of *N*-hydroxytryptamines but gave only satisfactory results with aromatic aldehydes.[10] A general drawback of these procedures is the fact that removal of the chiral auxiliaries is often difficult and causes racemization due to the harsh conditions required for cleavage.

The use of chiral sulfoxides in organic synthesis has found ample precedent in the literature.[11] *N*-Sulfinylimines have proven to be excellent starting materials for the enantioselective synthesis of α- and β-amino acids,[12] α-aminophosphonic acids,[13] and aziridines.[14] We realized that reaction of the tryptamine-derived sulfinamines **3a**−**c** (Scheme 2) with an aldehyde would in principle lead to the in situ formation of an *N*-sulfinyl iminium ion that could undergo Pictet−Spengler cyclization.

Scheme 2



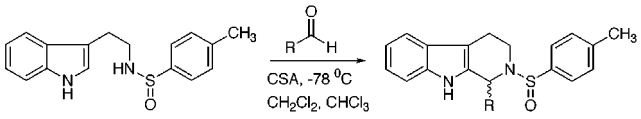
The main objective of our reserach was to investigate the effect of several sulfinyl groups on the reactivity and diastereoselectivity of the Pictet−Spengler condensation. After optimization of the reaction conditions with racemic substrates, optically active sulfinamines should then provide a synthetic route to enantiopure tetrahydro-β-carbolines.

We focused on the *p*-tolyl, the 2-ethoxynaphthyl, and the *tert*-butyl substituents since these moieties gave high diastereomeric ratios in nucleophilic additions to *N*-sulfinyl imines as previously described.[10−12] The sulfinamines **3a**−**c** were easily obtained by reaction of the corresponding sulfinyl chlorides[15,16] with tryptamine. Pictet−Spengler reactions of these sulfinamines were studied under a range of conditions.

The nitrogen−sulfur bond of the sulfinamines turned out to be vulnerable to hydrolysis under acidic conditions. To improve the diastereoselectivity of the reaction and to overcome the problem of hydrolysis, we performed the reactions at low temperature and studied the effect of a variety of protic acids such as acetic acid, trifluoroacetic acid, and *p*-toluenesulfonic acid on the reaction. In general, application of these acid catalysts resulted in hydrolysis of starting material or low diastereoselectivity. The use of Lewis acids such as $TiCl_4$, Et_2AlCl, diisopinocampheylchloroborane, $Sc(OTf)_3$, $Yb(OTf)_3$, and $BF_3{\cdot}OEt_2$ led to the formation of unstable enamines after the initial formation of the *N*-sulfinyliminium ions. The best results for the Pictet−Spengler reaction were obtained with 10-camphorsulfonic acid (CSA) as the acid catalyst in a 1:1 mixture of dry methylene chloride and chloroform at −78 °C.[17,18]

In Table 1 the results of the Pictet−Spengler reactions of *p*-tolylsulfinamine **3a** with several aliphatic and otherwise functionalized aldehydes are summarized. The reactions were slower with branched aldehydes and required higher concentrations of the acid−catalyst. Further increases in concentration of the acid−catalyst led to hydrolysis of the starting material. The steric bulk of the alkyl substituent caused a decrease in rate of the reaction, but only a slight effect on the diastereoselectivity was observed.

Table 1. Pictet−Spengler Reactions of Racemic Sulfinamine **3a**



no.	R	time (h)	CSA (equiv)	yield[a](%)	ratio[b]
4	methyl	4	0.2	75	76:24
5	ethyl	4	0.2	82	73:27
6	propyl	4	0.2	80	78:22
7	butyl	4.5	0.2	84	81:19
8	pentyl	4.5	0.2	69	83:17
9	isobutyl	8	0.6	71	81:19
10	isopropyl	20	0.6	78	86:14
11	cyclohexyl	20	0.6	73	88:12
12	4,4-diethoxybutyl	5	0.2	84	82:18

[a] After chromatography. [b] Diastereomeric ratio as determined by ^{1}H NMR.

(1) Rabindran, S. K.; He, H.; Singh, M.; Brown, E.; Collins, K. I.; Annable, T.; Greenberger, L. M. *Cancer Res.* **1998**, *58*, 5850.
(2) Audia, J. E.; Evrard, D. A.; Murdoch, G. R.; Droste, J. J.; Nissen, J. S.; Schenck, K. W.; Fludzinski, P.; Lucaites, V. L.; Nelson, D. L.; Cohen, M. L. *J. Med. Chem.* **1996**, *39*, 2773.
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(4) Tatsui, G. J. *J. Pharm. Soc. Jpn.* **1928**, *48*, 92.
(5) Bailey, P. D. *J. Chem. Res.* **1987**, 202.
(6) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L. *Tetrahedron* **1995**, *51*, 2737.
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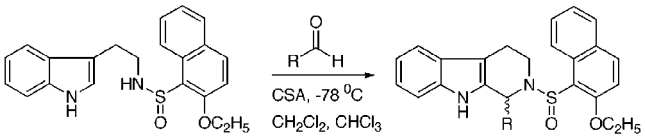
As shown in Table 2 the reactions of 2-ethoxynaphthyl sulfinamine **3b** gave comparable diastereoselectivity. The

Table 2. Pictet−Spengler Reactions of Racemic Sulfinamine **3b**



no.	R	time (h)	CSA (equiv)	yield[a](%)	ratio[b]
13	methyl	6	0.2	68	76:24
14	ethyl	6	0.2	67	76:24
15	propyl	6	0.2	62	77:23
16	butyl	8	0.2	71	82:18
17	pentyl	8	0.2	60	81:19

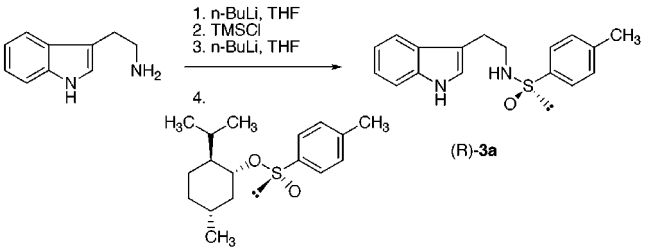
[a] After chromatography. [b] Diastereomeric ratio as determined by ^{1}H NMR.

presence of the sterically demanding 2-ethoxynaphthyl substituent seemed to have an effect only on the rate of the reaction. The *tert*-butylsulfinamines **3c** gave no product formation under these reaction conditions. At elevated temperatures the reaction is characterized by loss of starting material due to cleavage of the nitrogen−sulfur bond.

Separation of the diastereomers was possible by laborious column chromatography. However, from the reaction mixtures containing the *p*-tolylsulfinyl substituent (**4**−**12**) the major diastereomers were all obtained in pure form by simple crystallization. These encouraging results prompted us to develop a synthesis for (*R*)-**3a**.

The *p*-tolylsulfinamine (*R*)-**3a** was prepared using the commercially available Andersen reagent (1*R*,2*S*,5*R*)-(*S*)-menthyl *p*-toluenesulfinate (Scheme 3).[19] Treatment of tryptamine with *n*-butyllithium and chlorotrimethylsilane in

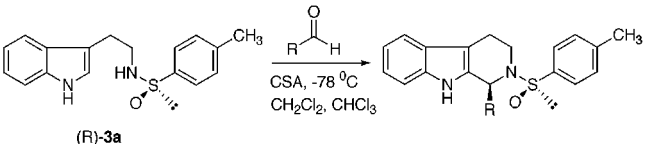
Scheme 3. Synthesis of (*R*)-**3a**



THF and reaction with the Andersen reagent gave sulfinamine (*R*)-**3a** in a satisfying yield (73%).[20] Likewise, the enantiomer (*S*)-**3a** was obtained starting from (1*S*,2*R*,5*S*)-(*R*)-menthyl *p*-toluenesulfinate (68%).

Pictet−Spengler condensations of (*R*)-**3a** were executed under conditions the same as those mentioned in Table 1. The results of these reactions were comparable to the results that were obtained from reactions with racemic **3a**. The major diastereomers were obtained after a single crystallization (Table 3).

Table 3. Pictet−Spengler Reactions of (*R*)-**3a**



no.	R	yield (%)[a]	$[\alpha]_D$[b]	mp (°C)
(+)-**4**	methyl	57	+212	205−207
(+)-**5**	ethyl	61	+196	229−233
(+)-**6**	propyl	58	+190	204−206
(+)-**7**	butyl	60	+167	208−211
(+)-**8**	pentyl	57	+158	179−182
(+)-**9**	isobutyl	59	+190	190−193
(+)-**10**	isopropyl	63	+215	222−224
(+)-**11**	cyclohexyl	57	+196	240−241

[a] After crystallization. [b] Acetone, $c = 0.5-1.0$.

In principle the 10-camphorsulfonate counterion of the iminium salt could influence the diastereoselectivity of the Pictet−Spengler reaction. Since no change in the diastereomeric ratio was observed using (+)-CSA instead of the

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(17) **General procedure:** A solution of the sulfinamide (0.2 mmol) and the aldehyde (1.0 mmol) in dry methylene chloride/chloroform (2 mL) was cooled to −78 °C. The indicated quantity of CSA was added, and the reaction mixture was stirred at −78 °C for the indicated time. The reaction was quenched with triethylamine, and the solvents were removed in vacuo. Purification using column chromatography (silica gel, 1:1 light petroleum/ethyl acetate) yielded the mixture of diastereomers.

(18) Pure chloroform solidifies at −78 °C, and the solubility of **3a**−**c** in pure methylene chloride is low.

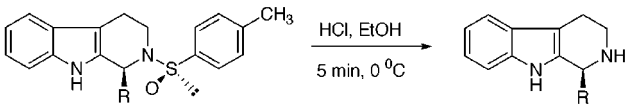
(19) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, *8*, 173.

(20) **General procedure:** To a solution of tryptamine (20 mmol) in THF (200 mL) at −78 °C was added a solution of *n*-BuLi (41 mmol) in hexanes. The reaction mixture was allowed to warm to ambient temperature, and chlorotrimethylsilane (21 mmol) was added. After stirring for 30 min *n*-BuLi (21 mmol) in hexanes was added and the reaction mixture was stirred for an additional 45 min. The reaction mixture was added to a solution of (1*S*,2*R*,5*S*)-(*S*)-menthyl *p*-toluenesulfinate (10 mmol) in THF. The reaction was quenched after 1 h by the addition of an aqueous solution of Na_2HPO_4 (200 mL, 0.1 M). Extractive workup and recrystallization (ethyl actetate) yielded (*R*)-**3a** (73%).

racemic catalyst, this possibility was excluded. Removal of the *p*-tolylsulfinyl chiral auxiliary was accomplished in high yield and without racemization using hydrochloric acid in ethanol at 0 °C which yielded the tetrahydro-β-carboline and the ethyl ester of *p*-toluenesulfinic acid.[21,22]

As shown in Table 4 the resulting tetrahydro-β-carbolines were obtained in enantiopure form and good yield.

Table 4. Removal of the Chiral Auxiliary



no.	R	yield (%)[a]	ee[b]	$[\alpha]_D$
(−)-**18**	methyl	89	>98%	−44.0[c]
(−)-**19**	ethyl	93	>98%	−62.6
(−)-**20**	propyl	91	>98%	−30.0
(−)-**21**	butyl	93	>98%	−65.8
(−)-**22**	pentyl	82	>98%	−40.0
(−)-**23**	isobutyl[23]	90	>98%	−47.1
(−)-**24**	isopropyl	93	>98%	−58.3
(−)-**25**	cyclohexyl	86	>98%	−68.5

[a] After chromatography. [b] As determined with ^{1}H NMR using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol. [c] Lit. (*S*)-**18**: $[\alpha]_D = -41$.[24]

In summary, the application of *N*-sulfinyl iminium ion chemistry to the Pictet−Spengler reaction of tryptamine provided a synthesis of enantiopure tetrahydro-β-carbolines. The use of the chiral *p*-tolylsulfinyl group was characterized by good yields and diastereoselectivity. Efficient separation of the diastereomers by crystallization and cleavage of the chiral auxiliary without racemization furnished the tetrahydro-β-carbolines in excellent enantiopurity. We are currently conducting further investigations on the scope and limitations of this procedure by the introduction of substituents on the phenyl ring of the *p*-tolylsulfinyl group.

Supporting Information Available: Experimental details and characterization for all new compounds (^{1}H NMR and mass spectral data). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) In principle, regeneration of the Andersen reagent is possible when the chiral auxiliary is removed in the presence of (−)-menthol.

(22) **General procedure:** To a solution of the *N*-sulfinyl tetrahydro-β-carboline (0.5 mmol) in ethanol (2 mL) at 0 °C was added concentrated hydrochloric acid (100 μL). After stirring for 5 min a saturated solution of K_2CO_3 (2 mL) was added. Extractive workup (ethyl acetate) and flash chromatography yielded the corresponding tetrahydro-β-carboline.

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