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Enantiopure tetrahydroisoquinolines via *N*-sulfinyl Pictet–Spengler reactions

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Abstract—Asymmetric Pictet–Spengler reactions with (*R*)-*N*-*p*-tolylsulfinyl-3,4-dimethoxyphenylethyl amine proceeded with high diastereoselectivity. Starting from the commercially available (*R*)- and (*S*)-Andersen reagents a highly efficient route to (+)- and (−)-salsolidine and related tetrahydroisoquinolines was developed.

Tetrahydroisoquinoline ring systems with alkoxy substituents are found in many alkaloids.[1] The biological activities of these compounds and their analogs are interesting and in most cases related to pathogenic processes in the central nervous system. Mono amine oxidase inhibition and prevention of the effects of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were found for the simple tetrahydroisoquinoline **1** (Fig. 1).[2] Because of their structural resemblance the natural products (+)-salsolidine (**2**) and (+)-carnegine (**3**),[3] are of pharmacological interest. Racemic isoquinoline **4**, a synthetic analog, has in vivo activity on human β-adrenoceptors.[4]

The lack of an efficient enantioselective synthetic route to tetrahydroisoquinoline ring systems is one of the main reasons that biological studies are usually carried out with mixtures of enantiomers. A simple and efficient route towards enantiopure tetrahydroisoquinoline ring systems is of importance to prevent possible undesirable effects of one of the enantiomers on the biological activity. The so-called Bischler–Napieralski/reduction pathway is a well-known approach to the synthesis of tetrahydroisoquinoline ring systems both in racemic and enantiopure form. The best results with respect to enantiomeric purity of the products and efficiency of the reaction were obtained by catalytic reduction of the resulting dihydroisoquinolines, either in the presence of chiral ruthenium catalysts,[5] or with chiral auxiliary groups attached to the isoquinoline nitrogen atom (Scheme 1).[6]

The Pictet–Spengler reaction is another tool for the construction of racemic tetrahydroisoquinoline ring systems,[7] but it is only scarcely referred to in asymmetric synthesis of these compounds. This is in contrast to the asymmetric synthesis of tetrahydro-β-carbolines, which relies heavily on asymmetric Pictet–Spengler reactions.[8] In general, the phenyl ring in phenylethyl amines is much less nucleophilic in the ring-closing step than the indole ring in tryptamine derivatives. Elevated temperatures and strong acidic conditions are usually reported in the case of phenylethyl amines and these conditions are often not compatible with asymmetric approaches.

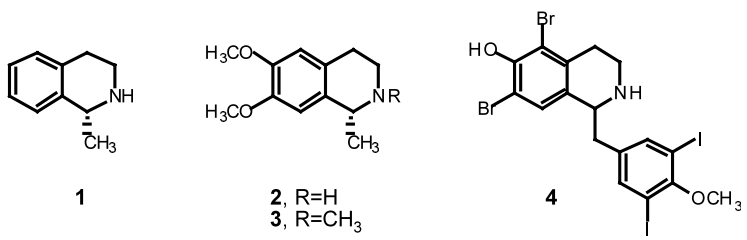

Figure 1. Biologically active tetrahydroisoquinolines.

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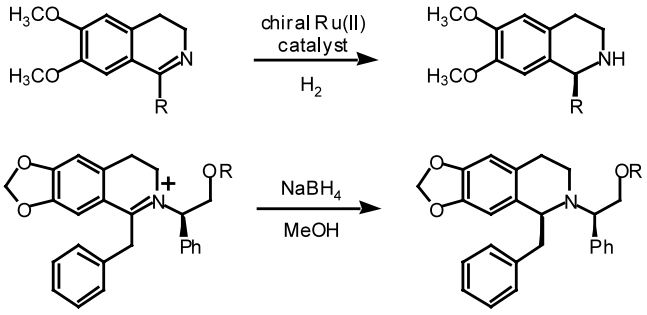
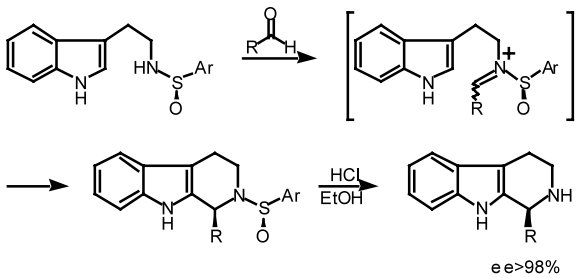


Scheme 1.

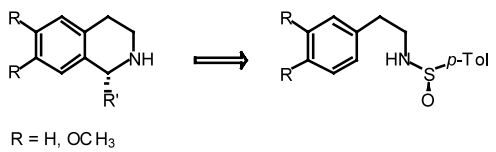
Recently a mild and efficient method for the synthesis of enantiopure tetrahydro-β-carbolines based on a chiral auxiliary mediated Pictet–Spengler reaction has been developed in our laboratory (Scheme 2).[9]

This method involves Pictet–Spengler reactions of *N*-sulfinyl tryptamines and subsequent removal of the chiral auxiliary group under mild acidic conditions. Simple aldehydes were reacted with (*R*)-*N*-*p*-tolyl-sulfinyltryptamine in the presence of camphorsulfonic acid at −78°C, which yielded *N*-sulfinyl tetrahydro-β-carbolines in good yield and selectivity. Removal of the chiral auxiliary group provided the corresponding enantiopure tetrahydro-β-carbolines. In this communication, we report the application of this methodology to the synthesis of enantiopure tetrahydro-isoquinolines (Scheme 3).

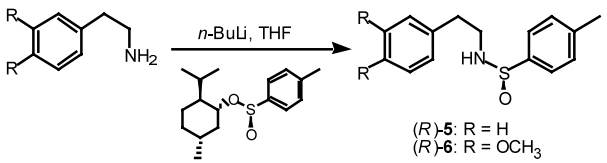
Enantiopure *N*-*p*-tolylsulfinylphenylethyl amines (*R*)-**5** and (*R*)-**6** were obtained by treatment of the corresponding phenylethyl amine with *n*-butyllithium (Scheme 4). Reaction of the anion with the commercially available Andersen reagent (1*R*,2*S*,5*R*)-menthyl-(*S*)-*p*-toluenesulfinate afforded (*R*)-**5** in 76% yield and excellent enantiopurity. The 3,4-dimethoxy analogue (*R*)-**6** was obtained likewise in 86% yield.



Scheme 2.



Scheme 3.



Scheme 4.

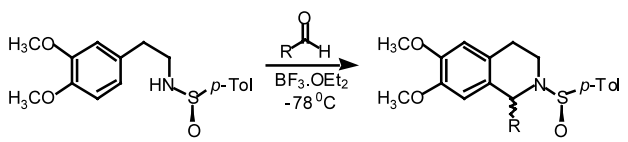
N-*p*-Tolylsulfinylphenylethyl amines (*R*)-**5** and (*R*)-**6** did not give any Pictet–Spengler reactions under protic acidic conditions at −78°C. At temperatures up to 0°C and with higher acid concentrations hydrolysis of the starting material was observed.

In our previous investigations with *N*-*p*-tolylsulfinyl-tryptamine, we attempted to catalyze these *N*-sulfinyl-iminium ion cyclizations with Lewis acids such as $SnCl_4$, $TiCl_4$, $Ti(OiPr)_4$, Et_2AlCl, $Sc(OTf)_3$, $Yb(OTf)_3$ and diisopinocampheylchloroborane. All these Lewis acids led to the formation of reactive enamines and undesirable side products. Application of $BF_3{\cdot}OEt_2$ formed an exception resulting in high yields of the desired products, although the diastereoselectivity was low.

In contrast to the results above, the reaction of (*R*)-**6** with a range of aldehydes in the presence of $BF_3{\cdot}OEt_2$ (2.0 equiv.) resulted in the desired ring-closed products in high yields and good diastereoselectivities (Table 1). Compound (*R*)-**5**, without the electron donating methoxy substituents was unreactive under these reaction conditions.

In Table 1 the Pictet–Spengler reactions of (*R*)-**6** with unbranched, α- and β-branched aliphatic aldehydes and phenylacetaldehyde are summarized. All reactions were performed at −78°C with 5.0 equiv. of the aldehyde and 2.0 equiv. of $BF_3{\cdot}OEt_2$ in a 1:1 mixture of anhydrous methylene chloride and chloroform. The reaction times

Table 1. Pictet–Spengler reactions of (*R*)-**6**



(*R*)-**6** **7-12**

no	diastereomeric ratio[a] (yield, %)	R	yield (%)[b] (+)-**7**-(+)-**12**	$[\alpha]_D$[c]
7	93:7 (89)		81	+193
8	96:4 (84)		78	+65.3
9	91:9 (85)		73	+53.9
10	92:8 (85)		75	+69.5
11	96:4 (43)		38	+46.7
12	77:23 (51)		36	+85.9

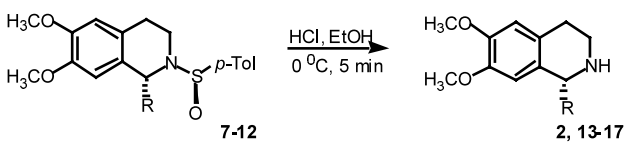
[a] As determined by ^{1}H-NMR. [b] After chromatographic separation of the diastereomers [c] Acetone, c = 0.5-1.0.

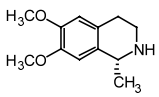
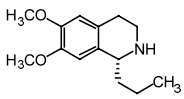
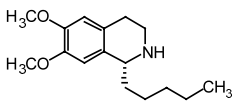
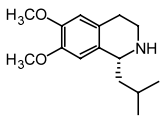
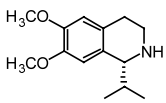
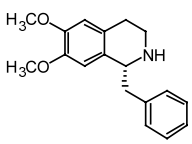
are short and the yields generally high when the steric bulk of the aldehyde is low.

Reactions with isobutyraldehyde and phenylacetaldehyde did not go to completion, even with higher concentrations of $BF_3{\cdot}OEt_2$ and additional equivalents of the aldehyde. In these cases, the starting material could be recovered. The diastereomeric mixtures mentioned in Table 1 were separated by flash chromatography, furnishing the diastereomerically pure *N*-*p*-tolylsulfinyltetrahydroisoquinolines (+)-**7**–**12**.

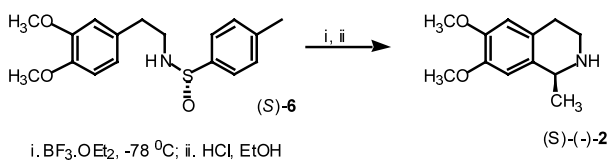
Removal of the chiral auxiliary proceeded without racemization upon treatment with HCl in ethanol at 0°C. The alkyl- and benzyl-substituted tetrahydroisoquinolines (+)-**2** and (+)-**13**–**17** were obtained in good yield and excellent enantiopurity (Table 2).

Table 2. Removal of the chiral auxiliary



no	compound	yield[a] (ee[b])	$[\alpha]_D$[c]
(+)-2		92 (>98)	+56.0[d]
(+)-13		89 (>98)	+22.4
(+)-14		86 (>98)	+10.2
(+)-15		94 (>98)	+16.9
(+)-16		92 (>98)	+81.1
(+)-17		90 (>98)	+15.0

[a] After chromatography. [b] As determined by ^{1}H-NMR using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol. [c] Acetone, *c* 0.5-1.0. [d] Lit. (*R*)-**2**: $[\alpha]_D$ = +54.0 (*c* 0.63, EtOH).



Scheme 5.

The absolute configuration of these isoquinolines was related to (+)-salsolidine **2** (R = Me) and to the stereochemistry of isopropyl and benzyl substituted tetrahydroisoquinolines **16** and **17** as reported in the literature.[10]

Enantioselective approaches to the synthesis of both (*R*)-(+)- and (*S*)-(−)-salsolidine (**2**) have found ample precedent in the recent literature. This can in part be accounted by the general interest in the enantiopure tetrahydroisoquinoline systems. Another factor that can explain the large number of reported enantioselective approaches to this simple compound is its use in biological studies that are mostly related to the pathogenesis of Parkinson's disease. Other biological applications of **2** were reported in the field of enzyme inhibition of catechol-*O*-methyl transferase[11] and inhibitory effects on testicular endocrine function.[12]

Enantioselective approaches to **2** are well-documented but usually characterized by multistep pathways or low to moderate enantioselectivity.[13] Using the method that was described above we were able to prepare enantiopure salsolidine (*R*)-(+)-**2** via *N*-sulfinyl Pictet–Spengler cyclization of (*R*)-6 in 75% yield. Application of (*S*)-**6**, which was obtained from the commercially available (*R*)-Andersen reagent, furnished the enantiomeric salsolidine (*S*)-(−)-**2** in 70% yield (Scheme 5).

As a typical example of the methodology described in this paper the experimental details of the three-step synthesis of (*R*)-(+)-salsolidine **2** are outlined below:

Synthesis of (*R*)-6: To a solution of 3,4-dimethoxyphenylethyl amine (20.0 mmol) in THF (200 mL) at −78°C was added a solution of *n*-BuLi (22 mmol) in hexanes. The reaction mixture was allowed to warm to ambient temperature and 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 (100 mL, 1 M). Extractive workup and recrystallization (ethyl acetate) yielded (*R*)-**6** (86%), $[\alpha]_D$ = +66.9 (acetone, *c* = 0.5).

Pictet–Spengler cyclization: A solution of (*R*)-**6** (0.2 mmol) and acetaldehyde (56 μL, 1.0 mmol) in dry methylene chloride/chloroform (2 mL) was cooled to −78°C. $BF_3{\cdot}OEt_2$ (51 μL, 0.4 mmol) was added and the reaction mixture was stirred at −78°C for 1 h. The reaction was quenched with triethylamine, and the solvents were removed in vacuo. Separation of the diastereomers using flash chromatography with gradient elution (silica gel, light petroleum to light petroleum/ethyl acetate 1:1) yielded (+)-**7** (R_f = 0.65, light petroleum/ethyl acetate 1:1) in 81%, $[\alpha]_D$ = +193.

Removal of the chiral auxiliary: To a solution of (+)-**7** (0.1 mmol) in ethanol (0.5 mL) at 0°C was added concentrated hydrochloric acid (30 μL). After stirring for 5 min at 0°C a saturated solution of K_2CO_3 (0.5 mL) was added. Extractive workup (ethyl acetate) and flash chromatography (ethyl acetate/methanol/aqueous

ammonia 85:10:5) yielded (*R*)-(+)-salsolidine **2** in 92% (ee >98%), $[\alpha]_D = +56.0$.

In summary, the use of the *p*-tolylsulfinyl chiral auxiliary provided a practical enantioselective route to tetrahydroisoquinolines with alkyl and benzyl substituents. Separation of the diastereomers and removal of the *N*-sulfinyl group under mild conditions without racemization yielded a range of enantiopure tetrahydro isoquinolines. This procedure allows the efficient synthesis of biologically relevant enantiopure alkaloids such as (*R*)-(+)- and (*S*)-(−)-salsolidine.

References

1. For a review of the recent literature, see: (a) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148; (b) Bentley, K. W. *Nat. Prod. Rep.* **1999**, *16*, 367; (c) Bentley, K. W. *Nat. Prod. Rep.* **1998**, *15*, 341.
2. (a) Yamakawa, T.; Ohta, S. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 676; (b) Thull, U.; Kneubühler, S.; Gallair, D. P.; Carupt, P.-A.; Testa, B.; Altomare, C.; Carotti, A.; Jenner, P.; McNaught, K. S. P. *Biochem. Pharmacol.* **1995**, *50*, 869.
3. Gluszynska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2359.
4. He, Y.; Nikulin, V. I.; Vansal, S. S.; Feller, D. R.; Miller, D. D. *J. Med. Chem.* **2000**, *43*, 591.
5. (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916; (b) Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org. Chem.* **2000**, 2274.
6. (a) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859; (b) Barbier, D.; Marazano, C.; Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1998**, *63*, 1767; (c) Ziólkowski, M.; Czarnocki, Z. *Tetrahedron Lett.* **2000**, *41*, 1963; (d) Cabedo, N.; Andrebu, I.; Ramírez de Arellano, M. C.; Chagraoui, A.; Serrano, A.; Bermejo, A.; Protais, P.; Cortes, D. *J. Med. Chem.* **2001**, *44*, 1794.
7. (a) Cox, E. D.; Cook, J. M. *J. Org. Chem.* **1995**, *60*, 1797; (b) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Tetrahedron Lett.* **1999**, *40*, 4969; (c) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327.
8. (a) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347; (b) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033; (c) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402; (d) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1249; (e) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348.
9. Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955.
10. (a) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859; (b) Rozwadowska, M. D.; Brossi, A. *J. Org. Chem.* **1989**, *54*, 3202.
11. Sanft, K.; Thomas, H. *Z. Naturforsch. C* **1989**, *44*, 173.
12. Stammel, W.; Thomas, H.; Staib, W.; Kuhnvelten, W. N. *Life Sci.* **1991**, *49*, 1392.
13. (a) Burton, A. J.; Graham, J. P.; Simpkins, N. S. *Synlett* **2000**, 1640; (b) Tomioka, K.; Hasegawa, M. J. *Synth. Org. Chem. Jpn.* **2000**, *58*, 848; (c) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533; (d) Gluszynska, H.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2359; (e) Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, *36*, 9105; (f) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086; (g) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 6709.