Tetrahedron Letters, Vol.32, No.26, pp 2995-2996, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

# Asymmetric Pictet-Spengler Synthesis of Tetrahydroisoquinolines. An Enantioselective Synthesis of (-)-Laudanosine.

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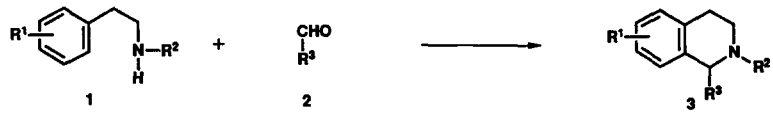
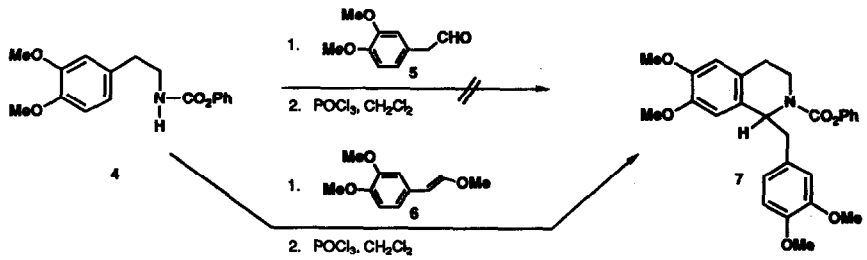
***Summary:*** *A chiral auxiliary mediated Pictet-Spengler reaction was utilized in a synthesis of the tetrahydroisoquinoline alkaloid, (-)-laudanosine.*

Although the Pictet-Spengler reaction has been extensively used in the synthesis of isoquinoline alkaloids[1], there have been no examples reported where the stereochemical outcome has been controlled by a recoverable chiral auxiliary.[2] In general, the Pictet-Spengler synthesis involves the condensation of an arylethylamine **1** with an aldehyde **2** to give tetrahydroisoquinolines **3**. This reaction, when $R^2$ is an acyl group



containing a chiral auxiliary, appeared to have potential for the enantioselective preparation of tetrahydroisoquinolines. To determine if the Pictet-Spengler synthesis could be carried out with an N-acyl group on the arylethylamine **1**, we prepared carbamate **4** from 3,4-dimethoxyphenethylamine (PhOCOCl, 1N NaOH, $CH_2Cl_2$) and attempted a condensation with 3,4-dimethoxyphenylacetaldehyde (**5**). The reaction failed, apparently because the sensitive aldehyde **5** was unstable to the reaction conditions ($POCl_3$, $CH_2Cl_2$, RT). The use of "protected" aldehyde **6** was investigated next, based on the premise that a low concentration of aldehyde may be released in situ as the reaction proceeds. Acetals[3], enol ethers[3], and chloromethyl methyl ethers[4] have been used as chemical equivalents of carbonyl compounds in modified Pictet-Spengler reactions. Vinyl ethers, i.e. **6**, are easily prepared from the aryl aldehyde and methoxymethyldiphenylphosphine oxide[5]. The reaction of **4** and **6** ($POCl_3$, $CH_2Cl_2$, RT, 3h) gave a 69% yield of tetrahydroisoquinoline **7**.



Prompted by this success, enantiopure carbamate **8** was prepared from 3,4-dimethoxyphenethylamine and (-)-8-phenylmenthyl chloroformate[6]. Condensation of **8** and vinyl ether **6** gave a 68% yield of diastereomers **9** and **10** in a ratio of 83:17. A 50:50 mixture of **9** and **10** was prepared by treatment of carbamate **7** with the potassium salt of (-)-8-phenylmenthol (*t*-BuOK, THF, RT, 3h). The absolute configuration of the major diastereomer (**9**) was determined in the following manner. The mixture of **9** and **10** was treated with lithium aluminum hydride to give (-)-laudanosine (**11**)[7] (73%) [ $[\alpha]_D^{23}$ - 63° (c 1, EtOH) ] and recovered (-)-8-phenylmenthol (76%). The isolated alkaloid (**11**) had an enantiomeric excess of 63% as determined by comparison to reported optical rotation values.[2] The observed stereochemical outcome is consistent with the rationalization depicted in Fig. 1.

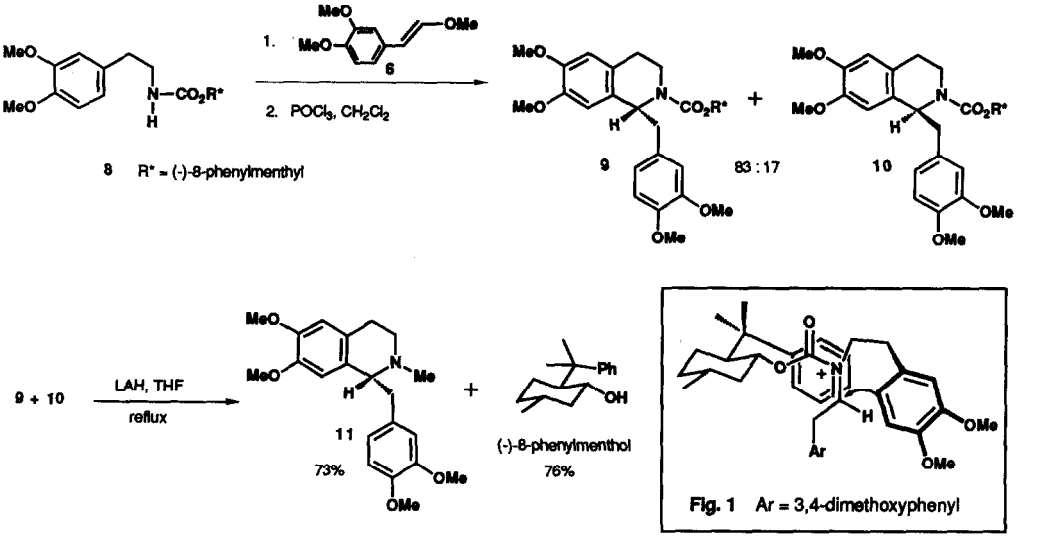



Fig. 1 Ar = 3,4-dimethoxyphenyl

Our results show that the chiral auxiliary mediated Pictet-Spengler reaction has considerable potential for the enantioselective synthesis of tetrahydroisoquinolines. We are currently trying to improve the diastereoselectivity through the use of more efficient chiral auxiliaries. Additional studies on the mechanism and scope of this asymmetric reaction are also in progress.

## References and Notes


1. "Isoquinolines", in "The Chemistry of Heterocyclic Compounds", Grethe, G., Ed.; Wiley: New York, 1981; Part 1, Vol. 38.
2. Pictet-Spengler condensations using enantiopure aldehydes or amino acids as components have been reported. Czarnocki, Z.; Maclean, D.B.; Szarek, W.A., Can. J. Chem., **1986**, 64, 2205 and references therein.
3. Yamato, E., Chem. Pharm. Bull., **1970**, 18, 2038.
4. Jaques, B.; Deeks, R.H.L.; Shah, P.K.J., J. Chem. Soc. D., **1969**, 1283.
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6. Comins, D.L.; Goehring, R.R.; Joseph, S.P.; O'Connor, S., J. Org. Chem., **1990**, 55, 2574.
7. This is the unatural form (R) of the alkaloid, see Yamada, S.; Konda, M.; Shiori, T., Tetrahedron Lett., **1972**, 2215 and references therein.


(Received in USA 13 March 1991)