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Note

Gas chromatographic separation of enantiomers: determination of the optical purity of the chiral auxiliaries (*R*)- and (*S*)-1-amino-2-methoxymethylpyrrolidine

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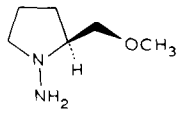
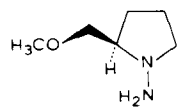
Enantiomers often have different biological activities. Thus, the synthesis of pharmaceuticals, pesticides, food additives, pheromones, etc. of high enantiomeric purity is of considerable significance and a challenge in synthetic organic chemistry. An elegant and economic solution to this problem is of course asymmetric synthesis. Asymmetric C–C bond formation is of great importance. Enders[1] developed a practical asymmetric synthesis using stoichiometric amounts of the chiral auxiliary (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP). SAMP is obtained routinely on a molar scale in four steps from the commercially available amino acid (*S*)-proline[2].



SAMP



RAMP

The other enantiomer of the chiral auxiliary, (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP), may be prepared from synthetic (*R*)-proline. However, due to the high cost of (*R*)-proline a synthesis of RAMP starting from (*R*)-glutamic acid was developed[1]. Both RAMP and SAMP are commercially available now (Merck, Darmstadt, F.R.G.). Routinely, the optical purity of SAMP and RAMP is controlled by measurement of the optical rotation.

By use of SAMP/RAMP hydrazones, the asymmetric synthesis of aldehydes, cycloalkanones, cyclohexenones, acyclic ketones, β-ketoles, β-ketoesters and also a number of natural products was possible[1,3]. Thus, these chiral auxiliaries are widely used in synthetic organic chemistry and a method for the determination of their enantiomeric composition is highly desirable. In addition, the method should be readily accessible and allow the detection of impurities. In order to separate the

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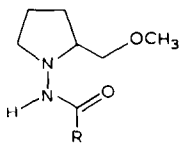
enantiomeric compounds by means of gas chromatography (GC), an optically active stationary phase should be used[4–8]. We have attempted such a separation of SAMP and RAMP as their urea derivatives (I) on a capillary column coated with Chirasil-Val. This phase was developed by Bayer and co-workers[9–11] and is a copolymeric organosiloxane, bound to L-valine *tert.*-butylamide (Applied Science, State College, PA, U.S.A.).



I a R = *iso*-C_3H_7-NH-
b R = *tert.*-C_4H_9-NH-

MATERIALS AND METHODS

SAMP and RAMP were kindly supplied by D. Enders, Universität Bonn. Isopropyl isocyanate and *tert.*-butyl isocyanate were obtained from Fluka (Buchs, Switzerland).

Urea derivatives (I) were prepared by the following procedure. Two milligrams of 1-amino-2-methoxymethylpyrrolidine (SAMP and RAMP) were placed in a screw-cap vial and dissolved in 200 μl methylene chloride and 5 μl pyridine. This solution was treated with either 200 μl isopropyl or *tert.*-butyl isocyanate and kept at room temperature for 1 h. Excess of reagent and solvent were removed with a gentle stream of nitrogen at ambient temperature. The dry residue was dissolved in 50 μl methylene chloride and injected for GC.

The GC analyses were carried out on a Dani Model 3900 gas chromatograph. Separation of the enantiomers of urea derivatives I was accomplished on a 25 m × 0.25 mm glass capillary coated with Chirasil-Val (Applied Science). Carrier gas: helium at 1.2 bar. Temperature programme: 70°C isothermal for 1 min, then raise at 3°C/min to 200°C. Peak integration was effected with the Laboratory Automation System 3357.

TABLE I

GAS CHROMATOGRAPHIC SEPARATION OF UREA DERIVATIVES (I) OF SAMP AND RAMP

Chiral auxiliary	*Urea derivative I*	*Retention time (min)*		$\alpha_{(R)/(S)}$
		*(R)**	*(S)**	
SAMP	R = *iso*-C_3H_7-NH-	38.74	38.53	1.005
	tert.-C_4H_9-NH-	37.48	37.20	1.008
RAMP	*iso*-C_3H_7-NH-	38.76	38.59	1.004
	tert.-C_4H_9-NH-	37.46	37.17	1.008

* (*R*) corresponds to the D configuration and (*S*) to the L configuration.

RESULTS AND CONCLUSIONS

The results of the GC separation are given in Table I. The SAMP sample provided by D. Enders[1] was found to contain less than 0.1% RAMP. On the other hand, the RAMP contained 0.14% of SAMP. Thus, both chiral auxiliaries were found to be of high optical purity.

The method of GC separation of enantiomers on a chiral stationary phase, as described in this paper, is by far the most sensitive analytical method known for the determination of the optical purity of SAMP and RAMP.

REFERENCES

1 D. Enders, in J. D. Morrison (Editor), *Asymmetric Synthesis*, Vol. 3, Academic Press, New York, 1983, Ch. 4.
2 L.-F. Tietze and Th. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum*, Georg Thieme, Stuttgart, New York, 1981, p. 391.
3 D. Enders, *Chemtech.*, (1981) 504.
4 G. Blaschke, *Angew. Chem.*, 92 (1980) 14; *Angew. Chem., Int. Ed. Engl.*, 19 (1980) 13.
5 C. H. Lochmüller and R. W. Souter, *J. Chromatogr.*, 113 (1975) 283.
6 S.-C. Chang, R. Charles and E. Gil-Av, *J. Chromatogr.*, 235 (1982) 87.
7 N. Ôi, T. Doi, H. Kitahara and Y. Inda, *J. Chromatogr.*, 208 (1981) 404.
8 W. A. Koenig, W. Parr, H. A. Lichtenstein, E. Bayer and J. Oró, *J. Chromatogr. Sci.*, 8 (1970) 183.
9 H. Frank, G. J. Nicholson and E. Bayer, *J. Chromatogr. Sci.*, 15 (1977) 174.
10 G. J. Nicholson, H. Frank and E. Bayer, *J. High Resolut. Chromatogr. Chromatogr. Commun.*, 2 (1979) 411.
11 H. Frank, W. Woiwode, G. J. Nicholson and E. Bayer, *Justus Liebigs Ann. Chem.*, (1981) 354.