Journal of Chromatography, 358 (1986) 159–168
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 18 508

DERIVATIZATION BY THE ACHIRAL REAGENT N-TRIFLUOROACETYLGLYCINE

ENANTIOMER RESOLUTION OF DIOLS BY GAS CHROMATOGRAPHY ON CHIRASIL-VAL

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(Received January 14th, 1986)

SUMMARY

Achiral amino acids may be incorporated into suitable substrates to improve the chiral recognition of enantiomers by gas chromatography on a chiral diamide stationary phase. The well known drawbacks of the formation of diastereomers with chiral amino acids are thereby avoided. Thus 1,2- and 1,3-diols are converted into the monoesters by reaction with N-trifluoroacetylglycyl chloride. The resolution of the enantiomers on deactivated glass capillaries coated with Chirasil-Val is governed by the location of the free hydroxyl group. The resolution factor, α, and the order of peak elution are closely related to the chemical structures of the solutes, thus indicating the significance of hydrogen-bonding of both the hydroxyl group and the amino acid part to the diamide moieties of the polymeric solvent.

INTRODUCTION

Several techniques[1,2] have been developed in order to determine the enantiomeric purity of a chiral sample originating from chemical or enzymic synthesis. As outlined previously[3–8], the direct resolution of enantiomers by gas chromatography (GC) on a chiral stationary phase is the most accurate and most sensitive method, providing the solutes are sufficiently volatile and have favourable chromatographic properties (retention time, separation factor, peak shape). Though enantiomer resolutions without resorting to derivatization are reported for an increasing number of compounds, using either metal complexes[2,9,10] or diamide stationary phases[7,8,11,12], suitable derivatization is still necessary for many polar compounds.

1,2-Diols are important building blocks in the chemical synthesis of chiral compounds[2,11,13–21]. They are also prepared by biotransformation using baker's yeast[11,22–25], electromicrobial reduction using *Clostridium klyuveri* and *Candida util-*

0021-9673/86/$03.50

is[26–28] and by microsomal epoxide hydratase[29]. 1,3-Diols are versatile synthons[30] and chiral auxiliaries for asymmetric synthesis[31,32].

Unfortunately, up to now only *trans*-1,2-cyclohexanediol has been separated directly into enantiomers[7], using well deactivated glass capillaries coated with either L-[33] or D-Chirasil-Val[34] (fused-silica columns are available from Chrompack, Middelburg, The Netherlands) as the chiral stationary phase. Other examples tested so far gave only one peak distorted by considerable tailing. Symmetrical peaks were obtained after acylation by acetic anhydride or by perfluoropropanoic anhydride. Yet due to the molecular flexibility, enantiomer resolution was observed only in arylglycol diesters[4,7,11], not in simple alkyl derivatives[11]. The flexibility is reduced after derivatization with phosgene to give cyclic carbonates of 1,2-diols or 1,3-diols that are fairly well resolved[35] on modified chiral polysiloxanes[35,36]. Obviously, chiral recognition is rather low if only one carbonyl group of the solute can enter into hydrogen-bonding to the chiral diamide solvent.

In complexation GC, cyclic boronates and acetals of aliphatic diols have been quantitatively separated into enantiomers[37]. Apart from their reduced polarity, again the rigidity of conformation is a useful feature of these derivatives.

However, on diamide stationary phases, enantiomer resolution is crucially dependent on hydrogen-bonding to suitable groups of the solute (N–H, O–H, C=O)[8]. On the other hand, the flexibility of open-chain solutes may be reduced significantly during complexation to the stationary phase, as indicated by a considerable entropy of interaction, at the expense of the enthalpy of interaction[38]. Taking into account the high potential of single hydroxyl groups to enter into rather specific interactions to Chirasil-Val[7], we considered the monofunctionalization of diols by an "amplifier for chiral recognition", *i.e.*, a second group capable of specific bonding to the diamide core of the chiral polysiloxane. Monoacylated phenylglycols originating from yeast fermentation of the corresponding ketoesters[11] are only fairly well resolved on Chirasil-Val[39], but monourethanes (from reaction of the diols with alkyl isocyanates) are well suited for arylglycols[39] that are not resolved as their diperfluoropropionates, *i.e.*, *o*-bromophenyl-1,2-ethanediol[11]. However, it has been shown that the formation of urethanes[40,41] is catalyzed by traces of basic impurities, giving rise to racemization and side-reactions[42]. Under acidic derivatization conditions, racemization appeared to be negligible in many examples, *e.g.*, esterification of carboxylic groups by dry hydrochloric acid in alcohol[43] and acylation of hydroxy or amino groups by perfluoroacyl anhydrides[11]. From this point of view, the introduction of N–H groups into a substrate originally lacking nitrogen, *cf.*, the conversion of ketones into oximes[44] and of carboxylic acids into amides[42,45], may become a useful approach, providing the derivatization reaction can be performed under neutral or acidic conditions.

N-Acylamino acid derivatives have a high potential for chiral recognition by imitating the principles of protein structure[3,8], and these favourable properties are also shown by representatives bearing additional chiral sulphur[12] or phosphorus[4]. However, their utility as derivatization agents still awaits full exploitation. Some years ago, diastereomeric derivatives of alcohols, amines and carboxylic acids were investigated in detail[46]. N-Trifluoroacetylprolyl chloride[47] and N-trifluoroacetylalanyl chloride[48] were the most popular derivatization agents. Unfortunately, both compounds undergo fast racemization[49], *e.g.*, 5–15% during distillation[48]. A serious

source of error may result from this enantiomeric impurity. The enantiomers *RR*/*SS* (and similarly *SR*/*RS*) cannot be separated on achiral stationary phases. All stereoisomers may be completely separated on a chiral stationary phase[48]. However, there is a second source of error: the kinetic resolution of the enantiomers of the original sample according to the different rates of derivatization with the chiral agent is only cancelled after complete conversion into the derivative.

Obviously, these pitfalls are circumvented by using achiral amino acids as derivatization agents for enantiomers to be resolved on a chiral stationary phase. In the present paper we demonstrate the utility of N-trifluoroacetylglycyl chloride as an achiral agent, by its application to the enantiomer resolution of 1,2-diols and 1,3-diols on Chirasil-Val.

EXPERIMENTAL

Reference compounds

Racemic 1,2-propanediol, 1,2-hexanediol, *trans*-1,2-cyclohexanediol and 2-methyl-2,4-pentanediol were obtained from Aldrich, and 1,2-butanediol from Fluka. A mixture of 2,3-butanediol (three stereoisomers) was purchased from Fluka. 2*S*,3*S*-2,3-Butanediol of high e.e. (enantiomeric excess) was synthesized in six steps from 2*R*,3*R*-tartaric acid[11,15], and *S*-1,2-propanediol by lithium aluminium hydride reduction of *S*-ethyl lactate[11,14]. A mixture of 2,4-pentanediol (three stereoisomers) and a sample enriched in the 2*S*,4*S*-isomer were purchased from Aldrich.

N-Trifluoroacetylglycyl chloride

This compound was synthesized following the directions of Weygand *et al.*[50–53]. Glycine (10.0 g, 133 mmol) was dried *in vacuo* (0.5 Torr) and placed in a dry 250-ml round-bottom flask, fitted with a reflux condenser and a drying tube filled with calcium chloride. After dissolution in the minimum amount of trifluoroacetic acid (*ca.* 30 ml), the mixture was cooled efficiently by using a bath of ice and sodium chloride. Precooled trifluoroacetyl anhydride (31.3 g, 21.0 ml, 149 mmol) was added with vigorous stirring using a magnetic stirrer. After the vigorous reaction had ceased, the ice-bath was removed and the mixture heated slowly to 80°C to give a clear liquid. The reaction was left to stand overnight at ambient temperature. Thereby a white precipitate was formed. Trifluoroacetic acid was removed *in vacuo*. The residue was rinsed with small portions of benzene, transferred into a 50-ml flask and recrystallized from benzene to give 21.0 g (92%) of N-trifluoroacetylglycine, m.p. 118°C. This was sublimed *in vacuo* (0.1 Torr, 90°C) to give 17.0 g of white crystals, m.p. 120°C. The first crop, which is waxy and impure, should be discarded.

N-Trifluoroacetylglycine (7.2 g, 42 mmol) was placed in a 100-ml round-bottom flask fitted with a reflux condenser and a drying tube filled with calcium chloride. Freshly purified thionyl chloride (99.3 g, 60 ml, 835 mmol) was added, along with catalytic amounts of dimethylformamide (0.1 ml). The mixture was gently boiled for 30 min. Prolonged reaction should be avoided. The reflux condenser was replaced by a Vigreux distillation apparatus. The excess of thionyl chloride was removed via a calcium chloride-containing vessel by a water aspirator, under reduced pressure (controlled by a needle valve). Thereafter, the still-head was cleaned and dried carefully, and the reaction product distilled in reduced vacuum (avoid moisture!), b.p.

56°C (7 Torr, bath temperature 90°C), to give 4.0 g (50%) of a slightly yellow oil. In our hands, this compound was stable for 1 year, but small amounts of by-products formed during this period may cause additional chromatographic peaks. Therefore we recommend that the precursor be stored and the acid chloride prepared only in limited amounts. The reaction is also conveniently carried out in a Reactivial (Macherey-Nagel), removing the excess of thionyl chloride as far as possible in a gentle stream of dry nitrogen.

Derivatization

The direct formation of esters of N-trifluoroacetylamino acids with alcohols mediated by dicyclohexylcarbodiimide has been described on a micro-scale[48]. Alternatively, the corresponding acid chloride can be used. Thus, N-trifluoroacetylglycyl chloride (30 μl) was added to a solution containing minute amounts of sample (in the mg range or less) in 0.2 ml of dry dichloromethane, placed in a 1-ml Reactivial. After 1 h at 110°C, the reaction mixture was concentrated in a stream of nitrogen. In order to increase the lifetime of well deactivated capillary columns, the removal of acidic by-products is recommended. Therefore, the residue was dissolved in dichloromethane and washed with portions of sodium hydrogencarbonate solution and water (the aqueous layers were reextracted with the solvent), dried over anhydrous sodium sulphate and concentrated to dryness in a stream of nitrogen. After addition of dichloromethane (50 μl), the sample is ready for chromatography. The whole work-up can be performed on a scale of 1–2 ml, using Pasteur pipettes for transferring the organic phase into appropriate vials. In our hands, the derivatives were stable for more than 1 year.

Gas chromatography

A Duran glass capillary column (20 m × 0.3 mm) was deactivated with diphenyltetramethyldisilazane and coated[54] with L-Chirasil-Val[33] (copolymer Co-MM-2, CDI-No. 2, containing branched chiral side-chains in the ratio of 1:5, referred to unsubstituted dimethylsiloxane units; 0.40% solution in pentane) to give column M110, $n_{eff} = 0.9 \cdot 10^5$. Typically, hydrogen was used as the carrier gas (0.5 bar), with a splitting ratio of 1:50, a flame ionization detector and a Carlo-Erba Model 2001 AC gas chromatograph. Mass spectrometry (MS) was carried out using a Carlo-Erba Model 2960 gas chromatograph coupled to a MAT 112S mass spectrometer, with hydrogen as the carrier gas. Retention data and peak areas were recorded by a Trivector Sci. Model Trilab II computer.

RESULTS AND DISCUSSION

The derivatization of 1,2- and 1,3-diols with the *achiral* reagent N-trifluoroacetylglycyl chloride was performed in dichloromethane according to the usual procedure. Notably, the reagent is rather stable, as compared to the acid halides of homologous trifluoroacetylamino acids[50–53]. After careful work-up, the derivative of racemic 1,2-butanediol was subjected to GC on L-Chirasil-Val. The result is depicted in Fig. 1.

From steric considerations, the predominant formation of monoesters is expected, favouring the attack of the acid halide on the less hindered hydroxyl group

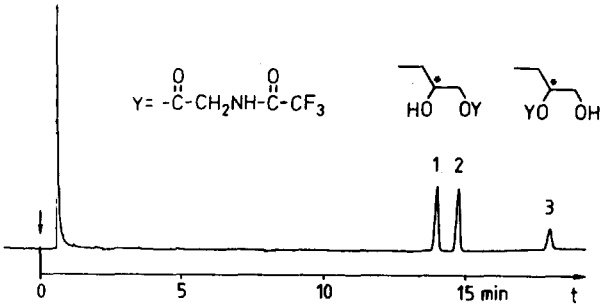


Fig. 1. Enantiomer resolution of 1,2-butanediol (after derivatization with N-TFA-Gly-Cl) on a glass capillary (20 m × 0.3 mm, deactivated with diphenyltetramethyldisilazane, coated with L-Chirasil-Val; $n_{eff} = 0.9 \cdot 10^5$). Temperature: 100°C, isothermal. Carrier gas: hydrogen, 0.5 bar. Flame ionization detection. Splitting ratio: 1:50.

of the 1,2-diol. In fact, the main product of the reaction was 2-hydroxy-1-(trifluoroacetylglycyloxy)butane. The enantiomers of this regioisomer are separated completely within a reasonable analysis time. No sophisticated optimization of chromatography using highly efficient columns is required (peak resolution, $R > 2$; resolution factor, $\alpha = 1.057$ at 100°C; $n_{eff} = 0.9 \cdot 10^5$ theoretical plates). Enantiomer resolution is indicated by equal peak areas and confirmed by GC–MS. The by-product, 1-hydroxy-2-(trifluoroacetylglycyloxy)butane, though chiral, is not resolved into enantiomers on Chirasil-Val. Obviously the chiral recognition of the regioisomers by the stationary phase is strongly dependent on their structures (see below).

The regioselectivity of this reaction, as measured by the peak area ratio (1 + 2)/3, *i.e.*, the ratio of attack on the primary hydroxyl group to that on the secondary hydroxyl group, is pronounced (5.3:1). This value is very similar to that previously determined (5:1) for the attack by the reagent triphenylphosphane–diethyl azodicarboxylate on *S*-1,2-propanediol[15]. Even more pronounced is the exclusive formation of mono derivatives with 1,2-butanediol. This observation has been confirmed also for other vicinal diols, as summarized in Table I. Diesters are formed only with the less hindered 1,3-diols. These by-products are hard to detect, and only after heating to 180°C for a considerable period. Using diols of high enantiomeric purity, *e.g.*, *S*-1,2-propanediol[11,14] or 2*S*,3*S*-butanediol (synthesized in six steps from *R*,*R*-tartaric acid)[11,15], there is no indication of detectable racemization within the uncertainty of the enantiomeric impurity of the diol samples (less than 1%).

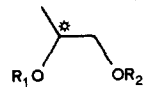
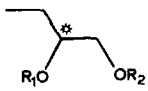
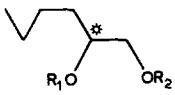
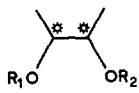
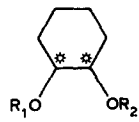
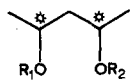
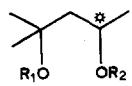
From our experience, the reaction is quite useful for the determination of the enantiomeric purity of diols on Chirasil-Val. For instance, considerable amounts of the 2*R*,4*R*-enantiomer and of the 2*S*,4*R*-diastereomer have been detected in a commercial sample of 2*S*,4*S*-pentanediol. The enantiomeric yield from an asymmetric synthesis using this compound as a chiral auxiliary[31,32] cannot exceed its own enantiomeric purity. Hence a careful check of the enantiomeric purity of any chiral precursor or auxiliary is warranted.

A mixture of stereoisomers of 2,4-pentanediol (2*S*, 4*R* = 2*R*, 4*S*/*meso* with unlike configurations[55]; 2*S*, 4*S* and 2*R*, 4*R*/*chiro* with like configurations[55]), after derivatization with N-trifluoroacetylglycyl chloride, gave four peaks of monoesters on Chirasil-Val (see Fig. 2). The monoesters of unlike configuration are no longer

TABLE I

ENANTIOMER RESOLUTION OF N-TRIFLUOROACETYLGLYCYL ESTERS (Y = –CO–CH_2NH–TFA) OF 1,2- AND 1,3-DIOLS ON L-CHIRASIL-VAL AT 100°C

The resolution factor, α, is increased at lower temperatures.

Compound	*Composition of esters (%)*			*Resolution factor, α, and later eluting enantiomers*	
	Monoesters		*Diester*		
	$R_1 = H$, $R_2 = Y$	$R_1 = Y$, $R_2 = H$	$R_1 = Y$, $R_2 = Y$	$R_1 = H$, $R_2 = Y$	$R_1 = Y$, $R_2 = H$
	83	17	–	(*S*) 1.052	1*
	84	16	–	1.057	1
	88	12	–	1.048	1
	(no regioisomers) ≈100		–	(2*S*, 3*S*) 1.040	unlike** 1.027
	≈100		–	(*trans*) like 1.108	(*cis*) unlike not determined
	96		4	(2*S*, 4*S*) 1.019	unlike*** 1.054
	82	16	2	1.025	1.051

* Not resolved.
** Diastereoisomer with unlike configuration[55], eluted before like.
*** Unlike eluted after like.

congruent. Reaction of the derivatizing agent at either the *R*- or *S*-carbinol centre leads to the enantiomers 2*R*,4*S*-4-hydroxy-2-(trifluoroacetylglycyloxy)pentane and 2*S*,4*R*-4-hydroxy-2-(trifluoroacetylglycyloxy)pentane, respectively, in equal amounts

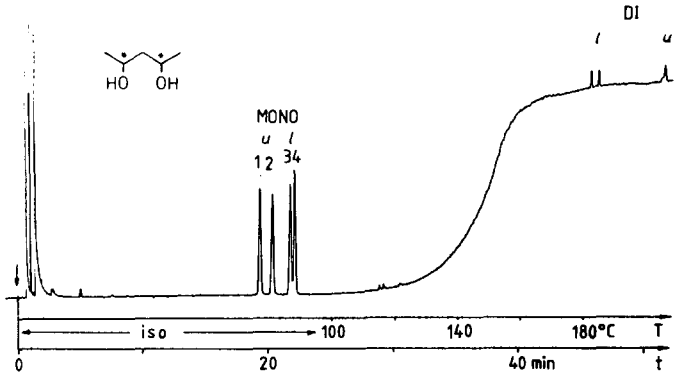
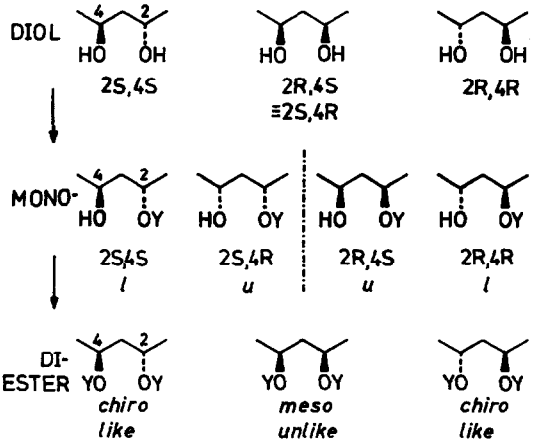


Fig. 2. Resolution of isomers of 2,4-pentanediol (after derivatization with N-TFA-Gly-Cl). Carrier gas: hydrogen, 0.5 bar. Temperature program: 100°C isothermal for 25 min; 4°C/min for 20 min; 180°C isothermal. Mono- and difunctionalization of hydroxyl groups to give esters as follows: u = unlike (1/2: 2*S*, 4*R* and 2*R*, 4*S* not assigned); l = like (3: 2*R*, 4*R*; 4: 2*S*, 4*S*).

(see Scheme I). Both, unlike (u) and like (l) monoesters are split into enantiomers (peaks 1, 2 and 3, 4 in Fig. 2). For the diester, there are only three possible isomers, similar to the situation found in 2,4-pentanediol.



Scheme 1. Possible isomers after esterification of 2,4-pentanediol (Y = $-CO-CH_2NH-COCF_3$).

The relative amounts of isomers formed from the various diols are compiled in Table I. The regioselectivity varies slightly in the series of monoalkyl-1,2-ethanediols from 83:17 (R = methyl) to 88:12 (R = *n*-butyl). With branched side-chains, even higher regioselectivities are expected. The resolution factors, α, are recorded for the temperature of 100°C. For all monoalkyl-1,2-diols, the isomers bearing the hydroxyl group at the asymmetric centre are resolved very well. The resolution factor increases from 1.052 (R = Me) to 1.057 (R = Et; increased difference in size between R and H), but decreases to 1.048 (R = *n*-Bu). Similar trends have been found for

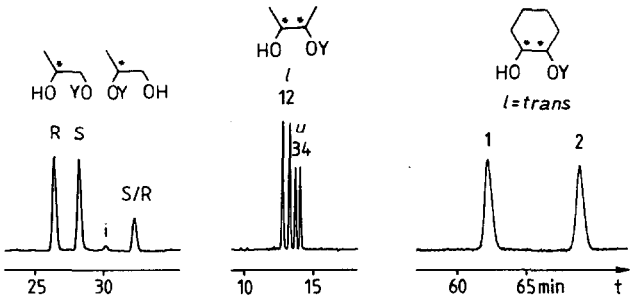
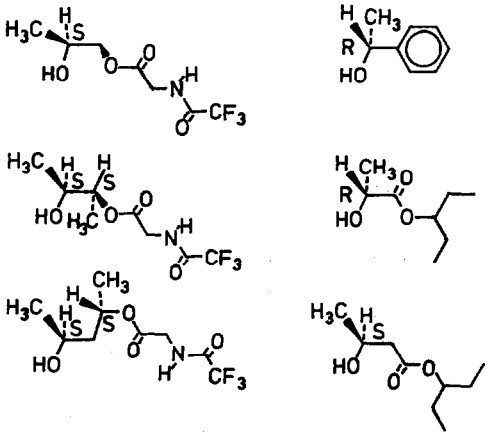


Fig. 3. Resolution of enantiomers of various vicinal diols (after monoderivatization with N-TFA-Gly-Cl). Carrier gas: hydrogen, 0.5 bar. Temperature: isothermal. Left hand: 1,2-propanediol; 80°C (i = impurity). Middle: 2,3-butanediol; 100°C; l = like (1: 2*R*, 3*R*; 2: 2*S*, 3*S*); α = 1.040; u = unlike (3/4: 2*S*, 3*R* and 2*R*, 3*S* not assigned). Right hand: *trans*-1,2-cyclohexanediol; 100°C; 1 = like (1*R*, 2*R* and 1*S*, 2*S*, respectively); α = 1.108.

the series of 2-hydroxy acid alkyl esters[43]. A detailed interpretation of the findings is only valid on the basis of the thermodynamic parameters, $-\Delta\Delta H$, $\Delta\Delta S$ and χ (chiral recognition factor)[8]. Hence it is not surprising that the second chiral centre in 2,3-butanediol gives rise to a decrease in the resolution factor for both combinations (like and unlike) of relative configuration in the monoesters, see Table I and Fig. 3. However, there is strong evidence for the influence of molecular flexibility on chiral recognition, even on the basis of the resolution factor, α. The monoester of *trans*-1,2-cyclohexanediol with a rigid orientation of the two vicinal C–O bonds exhibits a rather high resolution factor of 1.108 (at 100°C), see Fig. 3.

For all examples investigated, the compounds having a primary hydroxyl group are not resolved, but a free hydroxyl group at either a secondary or tertiary (even achiral) carbon centre contributes strongly to enantiomer resolution. On the other hand, the achiral glycyl moiety is also involved in the recognition process. This is evident from the different resolution factors for compounds with two asymmetric



Scheme 2. Absolute configuration of stereoisomers strongly interacting with L-Chirasil-Val (as compared to the antipode). Left hand: this communication; right hand: according to ref. 7.

centres of like and unlike configurations, respectively. It is of interest that molecules obtaining their chirality from the difference between a methyl group and a hydrogen atom are completely resolved (similar to derivatives of chiral amino acids, *e.g.*, alanine), in contrast to simple aliphatic alcohols of the type CH_3–CH(OH)–R[56]. Furthermore, the order of elution is reversed, as compared to suitable alcohols[7], but in parallel with the observations for 3-hydroxy acid alkyl esters[7,56]. Hence it is concluded that hydrogen-bonding of both the hydroxy group and the achiral amino acid part to the chiral diamide moiety of the polysiloxane stationary phase plays an important rôle in chiral recognition (*cf.*, Scheme II).

CONCLUSIONS

The scope of enantiomer resolution on Chirasil-Val can be extended by new approaches to derivatization. The ability of free hydroxyl groups to enter into rather specific hydrogen bonds to the stationary phase has been demonstrated[7], and exemplified again in the complete resolution of monoesters of diols with trifluoroacetylglycine. Derivatization by achiral amino acid derivatives may become a promising tool for hitherto unsolved tasks. Even the nearly intractable enantiomers of 2-butanol[57] are resolved completely[58] after reaction with the achiral amino acid derivative 2-trifluoromethyl-4,4-dimethyloxazolone (derived from 2-aminoisobutanoic acid, AIB)[59]. Further applications may be expected.

REFERENCES

1 J. D. Morrison (Editor), *Asymmetric Synthesis, Vol. 1, Analytical Methods*, Academic Press, New York, 1983.
2 V. Schurig, *Kontakte (Merck)*, 1 (1985) 54 (and subsequent articles).
3 E. Gil-Av, *J. Mol. Evol.*, 6 (1975) 131.
4 E. Bayer, *Z. Naturforsch., Teil B*, 38 (1983) 1281.
5 W. A. König, *J. High Resolut. Chromatogr. Chromatogr. Commun.*, 5 (1982) 588.
6 V. Schurig, *Angew. Chem.*, 96 (1984) 733; *Angew. Chem., Int. Ed. Engl.*, 23 (1984) 747.
7 B. Koppenhoefer, H. Allmendinger and G. J. Nicholson, *Angew. Chem.*, 97 (1985) 46; *Angew. Chem., Int. Ed. Engl.*, 24 (1985) 48.
8 B. Koppenhoefer and E. Bayer, in F. Bruner (Editor), *The Science of Chromatography*, Elsevier, Amsterdam, 1985, p. 1.
9 V. Schurig and W. Bürkle, *J. Am. Chem. Soc.*, 104 (1982) 7573.
10 V. Schurig, *Angew. Chem.*, 89 (1977) 113; *Angew. Chem., Int. Ed. Engl.*, 16 (1977) 110.
11 B. Koppenhoefer, *Thesis*, University of Tübingen, 1980.
12 E. Bayer, E. Küsters, G. J. Nicholson and H. Frank, *J. Chromatogr.*, 320 (1985) 393.
13 K Mori, M. Sasaki, S. Tamada, T. Suguro and S. Matsuda, *Tetrahedron*, 35 (1979).
14 V. Schurig, B. Koppenhoefer and W. Bürkle, *Angew. Chem.*, 90 (1978) 993; *Angew. Chem., Int. Ed. Engl.*, 17 (1978) 937.
15 V. Schurig, B. Koppenhoefer and W. Bürkle, *J. Org. Chem.*, 45 (1980) 538.
16 J. Barry and H. B. Kagan, *Synthesis*, (1981) 453.
17 M. Asami and T. Mukaiyama, *Chem. Lett.*, (1983) 93.
18 K.-Y. Ko, W. J. Frazee and E. L. Eliel, *Tetrahedron*, 40 (1984) 1333.
19 G. Helmchen and R. Wierzchowski, *Angew. Chem.*, 96 (1984) 59; *Angew. Chem., Int. Ed. Engl.*, 23 (1984) 60.
20 M. K. Ellis and B. T. Golding, *Org. Synth.*, 63 (1985) 140.
21 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem.*, 97 (1985) 1; *Angew. Chem., Int. Ed. Engl.*, 24 (1985) 1.
22 P. A. Levene and A. Walti, *J. Biol. Chem.*, 94 (1931) 361.

23 J. P. Guetté and N. Spassky, *Bull. Soc. Chim. Fr.*, (1972) 4217.
24 D. D. Ridley and M. Stralow, *J. Chem. Soc., Chem. Commun.*, (1975) 400.
25 B. Koppenhoefer, W. Winter and E. Bayer, *Liebigs Ann. Chem.*, (1983) 1986.
26 H. Günther, C. Frank, H.-J. Schuetz, J. Bader and H. Simon, *Angew. Chem.*, 95 (1983) 325; *Angew. Chem., Int. Ed. Engl.*, 22 (1983) 322.
27 H. Simon, J. Bader, H. Günther, S. Neumann and J. Thanos, *Angew. Chem.*, 97 (1985) 541; *Angew. Chem., Int. Ed. Engl.*, 24 (1985) 539.
28 B. Koppenhoefer, G. Laupp, E. Bayer, H. Simon and A. Beer, submitted for publication.
29 V. Schurig and D. Wistuba, *Angew. Chem.*, 96 (1984) 808; *Angew. Chem., Int. Ed. Engl.*, 23 (1984) 796.
30 K. Hintzer, B. Koppenhoefer and V. Schurig, *J. Org. Chem.*, 47 (1982) 3850.
31 W. S. Johnson, R. Elliott and J. D. Elliott, *J. Am. Chem. Soc.*, 105 (1983) 2905.
32 K. Maruoka and H. Yamamoto, *Angew. Chem.*, 97 (1985) 670; *Angew. Chem., Int. Ed. Engl.*, 24 (1985) 668.
33 H. Frank, G. J. Nicholson and E. Bayer, *Angew. Chem.*, 90 (1978) 396; *Angew. Chem., Int. Ed. Engl.*, 17 (1978) 363.
34 E. Bayer, H. Allmendinger, G. Enderle and B. Koppenhoefer, *Fresenius' Z. Anal. Chem.*, 321 (1985) 321.
35 W. A. König, E. Steinbach and K. Ernst, *Angew. Chem.*, 96 (1984) 516; *Angew. Chem., Int. Ed. Engl.*, 23 (1984) 527.
36 D. Thumm, *Thesis*, University of Tübingen, 1980.
37 V. Schurig and D. Wistuba, *Tetrahedron Lett.*, 25 (1984) 5633.
38 B. Koppenhoefer and E. Bayer, *Chromatographia*, 19 (1984) 123.
39 B. Koppenhoefer, unpublished results.
40 I. Benecke and W. A. König, *Angew. Chem.*, 94 (1982) 709; *Angew. Chem. Int., Ed. Engl.*, 21 (1982) 709.
41 W. A. König, I. Benecke, N. Lucht, E. Schmidt, J. Schulze and S. Sievers, *J. Chromatogr.*, 279 (1983) 555.
42 H. Frank, J. Gerhardt, G. J. Nicholson and E. Bayer, *J. Chromatogr.*, 270 (1983) 159.
43 B. Koppenhoefer, H. Allmendinger, G. J. Nicholson and E. Bayer, *J. Chromatogr.*, 260 (1983) 63.
44 W. A. König, I. Benecke and K. Ernst, *J. Chromatogr.*, 253 (1982) 267.
45 E. Koch, G. J. Nicholson and E. Bayer, *J. High Resolut. Chromatogr. Chromatogr. Commun.*, 7 (1984) 398.
46 E. Gil-Av and D. Nurok, *Adv. Chromatogr. (N.Y.)*, 10 (1974) 99.
47 B. Halpern and J. W. Westley, *Tetrahedron Lett.*, 21 (1966) 2283.
48 K. Kruse, W. Francke and W. A. König, *J. Chromatogr.*, 170 (1979) 423.
49 I. W. Wainer and T. D. Doyle, *LC, Liquid Chromatogr. HPLC Mag.*, 2 (1984).
50 F. Weygand and E. Csendes, *Angew. Chem.*, 64 (1952) 136.
51 F. Weygand and E. Leising, *Chem. Ber.*, 87 (1954) 251.
52 F. Weygand and R. Geiger, *Chem. Ber.*, 89 (1956) 647.
53 F. Weygand and U. Glöckler, *Chem. Ber.*, 89 (1956) 653.
54 G. J. Nicholson, personal communication.
55 D. Seebach and V. Prelog, *Angew. Chem.*, 94 (1982) 696.
56 H. Allmendinger, *Thesis*, University of Tübingen, 1986.
57 W. Bürkle, *Thesis*, University of Tübingen, 1980.
58 B. Koppenhoefer, H. Allmendinger and E. Bayer, to be published.
59 H. Allmendinger, *Diplomarbeit*, University of Tübingen, 1982.