155. Preparative Resolution of Heterocyclic Acetals Derived from Glycine, Mercapto-acetic Acid, β-Alanine, and Formyl- or Acetylacetic Acid by Recycling Chromatography on *Chiraspher* and Temperature Dependence of Separation Factors

by **Joachim N. Kinkel**

E. Merck, Sparte Reagenzien, Forschung Chromatographie, Frankfurter Strasse 250, D–6100 Darmstadt

and **Urs Gysel**[1]), **Denis Blaser**[1]), and **Dieter Seebach***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH–8092 Zürich

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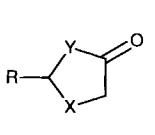
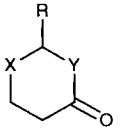
Chiraspher, a polymer of ethyl *N*-acryloylphenylalanine on spherical silica gel, is used for the preparative separation by recycling chromatography of the enantiomers of oxazolidinones *rac*-**5**, thioxolanone *rac*-**6**, perhydropyrimidinone *rac*-**7**, and dioxinones *rac*-**9** and **10** derived from the acids listed in the title (*Figs. 1–5*). The oxazolidinones *rac*-**1a**, **-2**, and **-4** show a peculiar peak of the separation efficiences upon lowering the *Chiraspher*-column temperature to 15° (*Fig. 6*). In some cases, multigram amounts of enantiomerically pure heterocycles could thus be prepared. The absolute configurations of most enantiomers are assigned. First applications of the *tert*-butyl 5-oxo-2-phenyloxazolidine-3-carboxylate (**5**) as a nucleophilic chiral glycine building block are described (products **13–16**, *Scheme 2*). A list of enantiomerically pure 1,3-dioxinones is presented (*Table 1*), showing a correlation between their absolute configuration, sense of optical rotation, and elution behavior on *Chiraspher*.

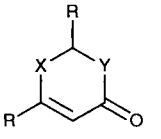
Introduction. – Chiral non-racemic cyclic acetals of type **A–C** have turned out to be useful starting materials for the preparation of α- and β-amino- and α- and β-hydroxy carboxylic acids **A**[1], **B**[1], and **B**[2] (X = OH or NH_2) [1–11]. In some cases, the derivatives **A–C**



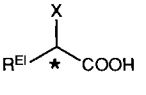
A



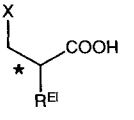
B



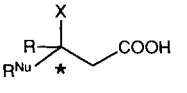
C



A[1]



B[1]

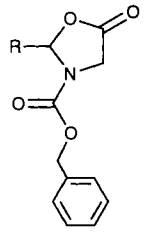


B[2]

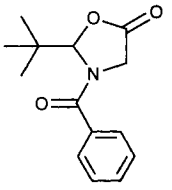
[1]) Parts of the Ph. D. theses of *U.G.* (Diss. No. 9473) and *D.B.* (Diss. No. 9527), ETH Zürich, 1991.

(see **1**–**10**) of achiral carboxylic acids could be synthesized from chiral starting materials [1] [2] [6] [7], in others they were obtained by crystallizing [4] or chromatographic [6] [9] resolution.

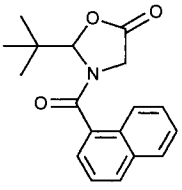
The chiral stationary phase *Chiraspher* turned out to be especially effective for the chromatographic resolution of the oxazolidinones *rac*-**1**–**4** (separation factors α = 1.5–2.4, synthetic applications, see [11] and *Exper. Part* for **1b**). On the other hand, the phenyldioxinones *rac*-**9** and *rac*-**10** were already separated on cellulose triacetate with α values between 2.2 and 4.5 [9]. With compounds *rac*-**5**–**7**, **9**, and **10** for which the α values were smaller than 1.5 (on *Chiraspher*), we have now applied recycling chromatography on *Chiraspher*, and we have tried to increase the α-values by doing single-column elution mode, separations at temperatures below room temperature. The earliest resolutions using the recycling technique on cellulose triacetate were reported by *Schlögl* and *Widhalm* [12], while the first examples of the method as such have been described as early as 1962 [13][2]).



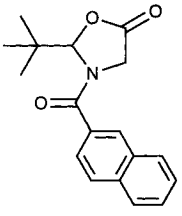
rac-**1a** R = *t*-Bu
rac-**1b** R = i-Pr



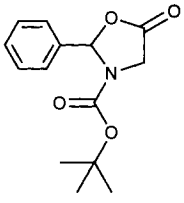
rac-**2**



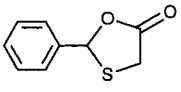
rac-**3**



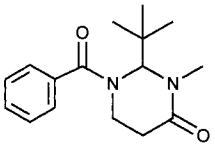
rac-**4**



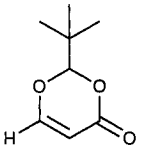
rac-**5**



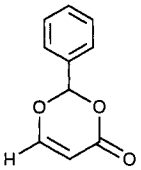
rac-**6**



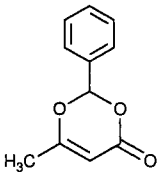
rac-**7**



rac-**8**



rac-**9**

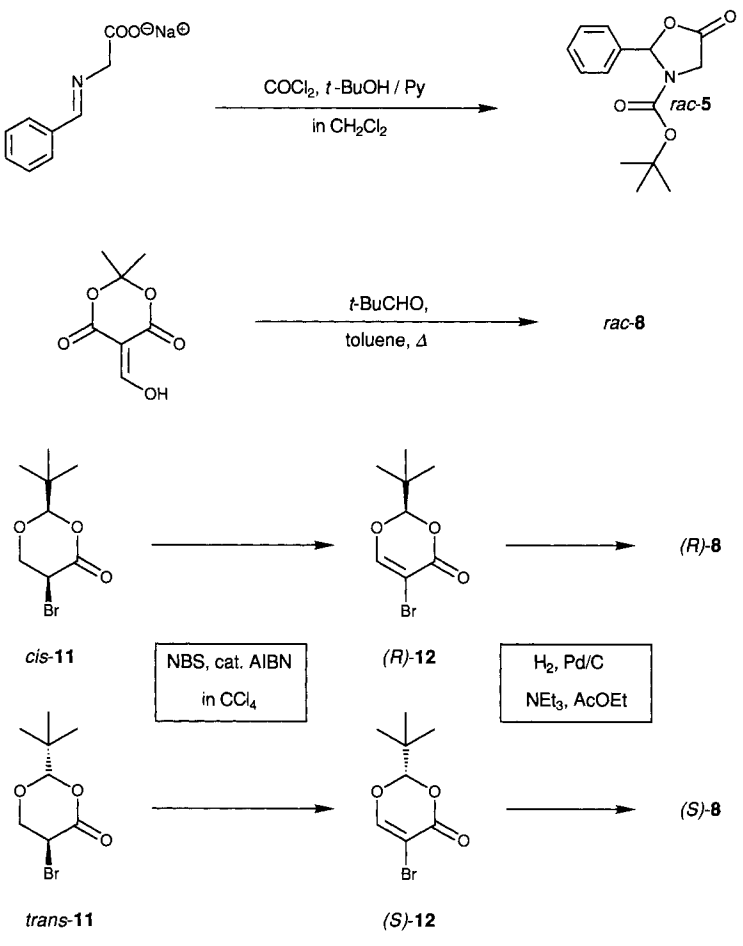


rac-**10**

Preparation of the Racemic Heterocycles. – The heterocycles **1**–**10** were obtained in the following way: treatment of the sodium salts of the imine obtained from glycine and pivalaldehyde with acyl chlorides gave *rac*-**1**–**4** [6]. Similarly, *rac*-**5** was prepared using phosgene and *t*-BuOH for the introduction of the Boc group [16] (*Scheme 1*). Thioxolanone *rac*-**6** was obtained following an old procedure [6] [17]. For the conversion of β-alanine to the perhydropyrimidinone *rac*-**7**, we have just recently given a detailed procedure [10]. The monosubstituted dioxinones *rac*-**8** and -**9** are formed upon heating

[2]) For leading references on theoretical and practical aspects of the method, see [14] [15].

Scheme 1



5-formyl-substituted *Meldrum*'s acid with pival- or benzaldehyde, as shown for *rac*-**8** in *Scheme 1* [6] [9] [18][3]). Finally, *rac*-**10** is the product from diketene and benzaldehyde [6] [9] [19]. For comparison, the dioxinones (*R*)- and (*S*)-**8** were prepared from L-serine *via* the bromodioxanones *cis*- and *trans*-**11** [2] and the bromodioxinones (*R*)- and (*S*)-**12**, respectively (*cf.* [2]).

Separations and Comparisons. – For the chromatographic enantiomer separations, we used the closed-loop recycling mode schematically shown in *Fig. 1* [14] [15]. Standard commercial HPLC equipment was employed (see *Exper. Part*). For maximum amounts of injected materials, we applied *peak shaving* and *overloading of the columns*, either by

[3]) To check whether the cuprate addition ot 2-(*tert*-butyl)dioxinone **8** (lacking substitution at C(6)) is stereoselective, we added Me_2CuLi to it to find a single diastereoisomer (*trans*-2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one), identified by comparison of its NMR spectra with literature data [20].

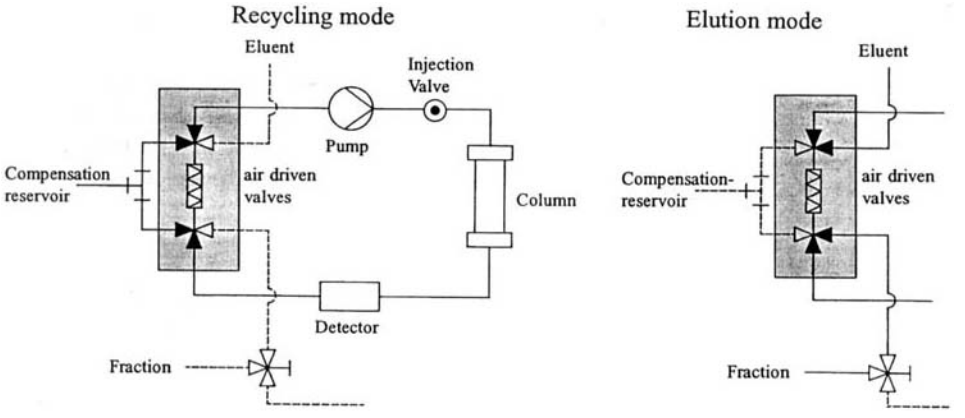


Fig. 1. *Schematic presentation of the closed-loop recycling mode used for the separations described and comparison with the elution mode.* For further details, see *Exper. Part.*

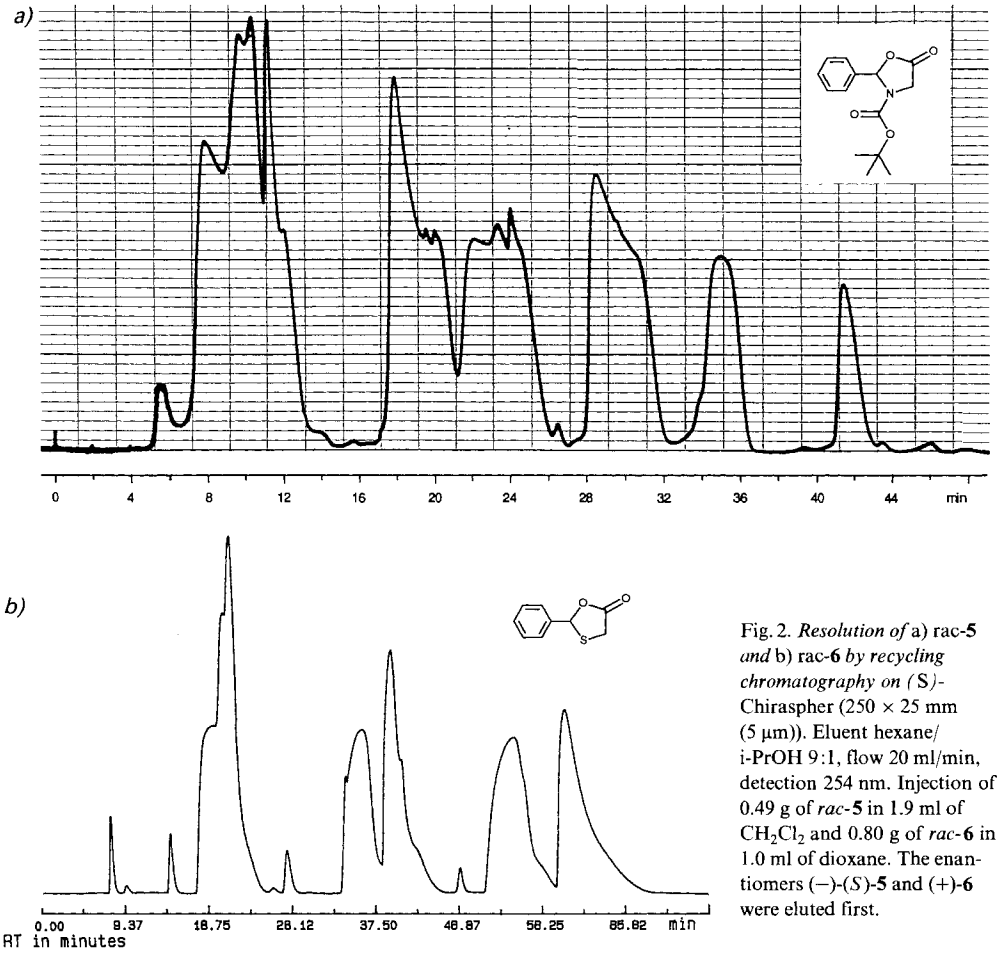


Fig. 2. *Resolution of* a) rac-**5** *and* b) rac-**6** *by recycling chromatography on (*S*)-*Chiraspher (250 × 25 mm (5 µm)). Eluent hexane/i-PrOH 9:1, flow 20 ml/min, detection 254 nm. Injection of 0.49 g of *rac*-**5** in 1.9 ml of CH_2Cl_2 and 0.80 g of *rac*-**6** in 1.0 ml of dioxane. The enantiomers (−)-(*S*)-**5** and (+)-**6** were eluted first.

volume or by concentration. Thus, concentrated solutions of the oxazolidinone *rac*-**5** in CH_2Cl_2 or of the thioxolanone *rac*-**6** in dioxane were injected into the rather apolar mobile phase hexane/i-PrOH 9:1 (*Fig. 2*). If not stated otherwise, *Chiraspher* of 5-μm particle size, containing ethyl (*S*)-phenylalaninate, was used; only in one case (*rac*-**7**, see *Fig. 3*) was the separation factor so small that columns of (*R*)- *and* (*S*)-chirality had to be used in order to prepare samples of *both* enantiomers in high enantiomeric purity. The

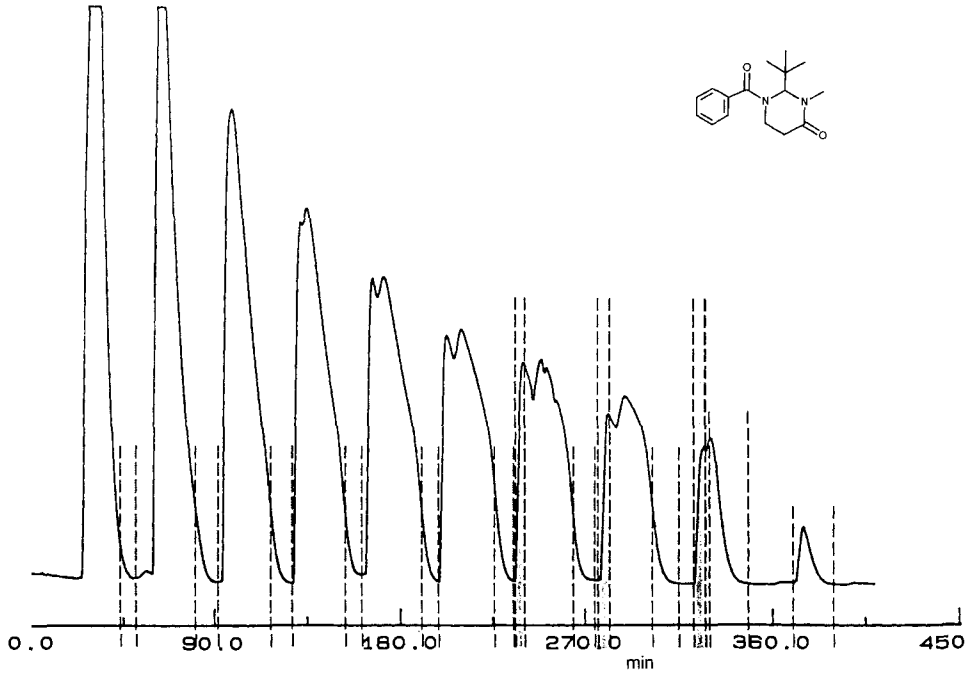


Fig. 3. *Resolution of* rac-**7** *by recycling chromatography on* (R)-Chiraspher (250 × 50 mm (5 μm)). Eluent hexane/i-PrOH 97:3, flow 80 ml/min, detection 254 nm. Injection of 1.0 g of *rac*-**7** in 2 ml of i-PrOH. The (+)-form was eluted first. The peak shaving was done by automatic separation of the fronts and/or tails. Only the faster-moving enantiomer could be obtained in high enantiomeric purity. Thus, the two enantiomers were actually isolated by using columns of enantiomeric stationary phases.

advantages of the recycling mode, even in favorable cases which might allow for single-column operation, are evident from *Fig. 4* for the resolution of the dioxinone *rac*-**9**: improvement of yield and throughput, dramatic reduction of solvent consumption and of sorbent amount. A demonstration of the rather small peak broadening occurring with the *NovaPrep 5000* system, used for some of the separations, is given for dioxinone *rac*-**10** in *Fig. 5* (see also *Exper. Part*).

Except for the compounds **6** and **7**, the absolute configuration of all products separated in this investigation were assigned. For the dioxinones, the following rule emerges (see *Table 1*): with two exceptions so far[4]), the (+)-(*S*)-form of the enantiomers sepa-

[4]) The first-eluted enantiomers of **8** and of 5-bromo-2-(*tert*-butyl)-6-methyl-2*H*,4*H*-1,3-dioxin-4-one are the (−)-(*R*)-forms.

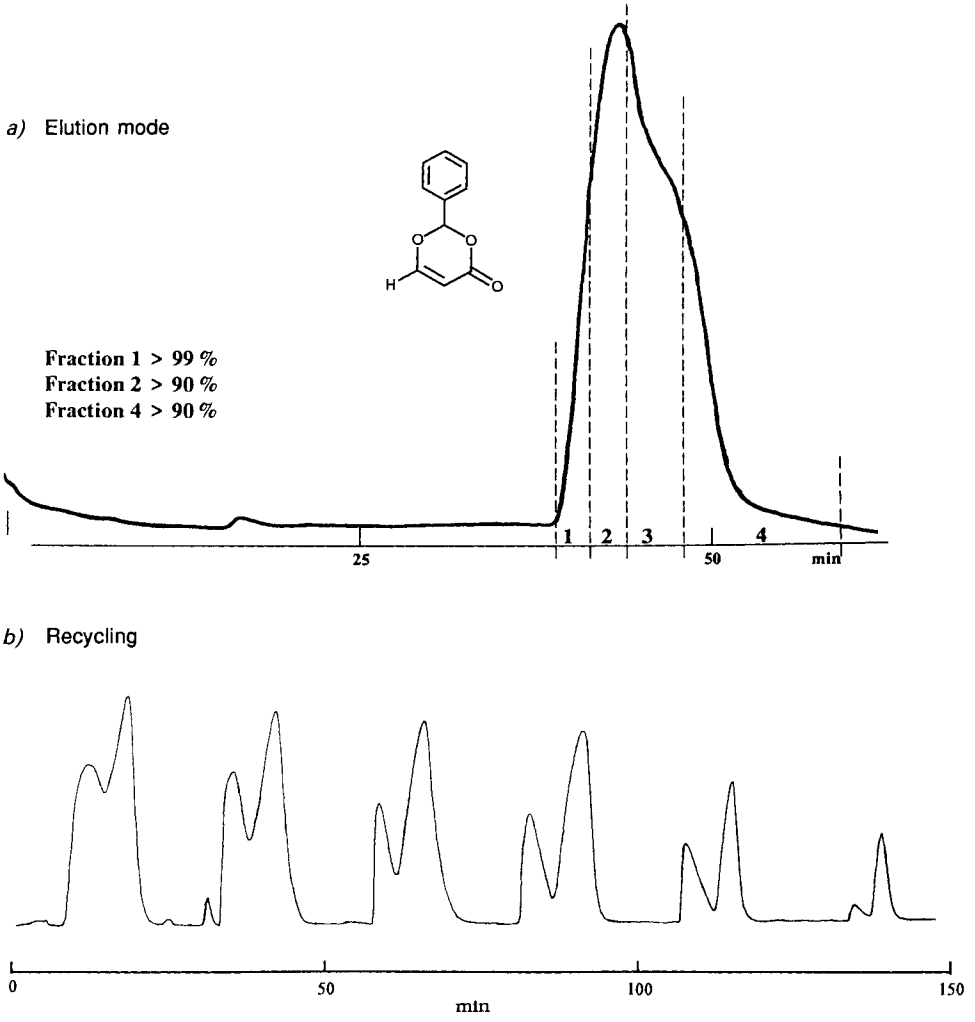


Fig. 4. *Comparison of* a) *the elution mode* (single-column operation) *and* b) *the recycling mode in the preparative resolution of* rac-**9** *on* Chiraspher. Eluent: Hexane/dioxane 95:5.

	Elution mode	Recycling
Sample amount (in dioxane)	5 g	1.25 g
Column dimension	400 × 100 mm	250 × 25 mm
Amount of stationary phase	1700 g	80 g
Flow	50 ml/min	39 ml/min
Particle size	25 μm	5 μm
Solvent consumption	3800 ml	1000 ml
Yield 1. enantiomer (ee > 99%)	0.6 g	0.6 g
Yield 2. enantiomer	0.2 g	0.6 g
Recovery	not determined	> 95%
Cycle time	75 min	120 min

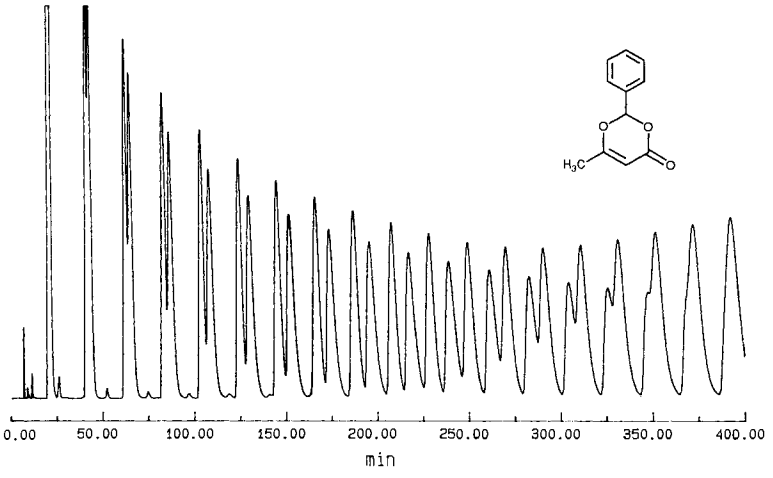
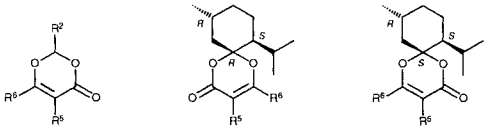


Fig. 5. *Closed-loop recycling chromatography of 0.20 g of* rac-**10** *in 0.24 ml of dioxane on* Chiraspher (250 × 50 mm (5 μm), eluent hexane/dioxane 9:1, flow 25 ml/min, detection 254 nm). After 11 cycles, a base-line separation is observed, whereupon the two peaks start coalescing again.

rated on *Chiraspher* is eluted first. For comparison, *Table 1* contains not only the monocyclic derivatives **D** prepared by us, but also some bicyclic spiro compounds **E** and **F** prepared from (−)-menthone; the generally smaller specific rotations of the latter ones might be an indication that they exist as mixtures of conformers in solution[5]).

Table 1. *List of the Enantiomerically Pure Dioxinones*



D **E** **F**

	R^2	R^5	R^6		Conf.	$[\alpha]_D$ in $CHCl_3$	Ref.
D	Me	H	Me	[a])	(*R*)	−192.2[d]) (*c* = 1.00)	[6]
	Me	Br	Me	[b])	(*R*)	−185.9[e]) (*c* = 2.52)	[2]
	$(CH_2)_2Ph$	H	Me	[a])	(*R*)	−147.2 (*c* = 1.13)	[9]
	t-Bu	H	H	[a])	(*R*)-**8**	−178.5 (*c* = 1.03)	this work
	t-Bu	H	H	[a])	(*S*)-**8**	+198.4 (*c* = 1.00)	this work
	t-Bu	Br	H	[a])	(*R*)-**12**	−216.9 (*c* = 1.01)	this work
	t-Bu	Br	H	[a])	(*S*)-**12**	+213.4 (*c* = 1.00)	this work
	t-Bu	H	Me	[a])	(*R*)	−217.7 (*c* = 1.00)	[2]
	t-Bu	Br	Me	[a])	(*R*)	−183.9 (*c* = 1.17)	[2]
	t-Bu	N_3	Me	[b])	(*R*)	−218.6 (*c* = 1.34)	[2]
	t-Bu	$NHCOCH_3$	Me	[b])	(*R*)	−177.2 (*c* = 0.45)	[2]
	t-Bu	Me	Me	[c])	(*R*)	−231 (*c* = 0.78)	[7]
	t-Bu	Et	Me	[b])	(*R*)	−222 (*c* = 2.01)	[7]

[5]) In crystal structures (see ref. in *Table 1*), the i-PrCH group of **E** and **F** is in an equatorial position of the dioxinone sofa conformation (*cf.* [5]).

Table 1 (cont.)

	R^2	R^5	R^6		Conf.	$[\alpha]_D$ in $CHCl_3$	Ref.
	t-Bu	C_5H_{11}	Me	b)	(*R*)	−192 (*c* = 1.68)	[7]
	t-Bu	4-$CF_3C_6H_4CH_2$	Me	b)	(*R*)	−133.2 (*c* = 0.60)	[7]
	t-Bu	H	Et	b)	(*R*)	−170.8 (*c* = 1.39)	[2]
	t-Bu	H	$MeCBr_2$	b)	(*R*)	−92.8 (*c* = 0.86)	[2]
	t-Bu	H	$Ph(CH_2)_2$	b)	(*R*)	−119.1 (*c* = 1.24)	[21]
	t-Bu	Br	CH_2N_3	b)	(*R*)	−13.0 (*c* = 0.79)	[22]
	t-Bu	Br	CHO	b)	(*R*)	−12.0 (*c* = 2.32)	[22]
	t-Bu	Br	CH_2Br	b)	(*R*)	−131.6 (*c* = 1.21)	[2]
	t-Bu	H	CCl_2Br	b)	(*S*)	+118.0 (*c* = 1.03)	[23]
	t-Bu	H	$CHCl_2$	b)	(*S*)	+159.9 (*c* = 1.01)	[23]
	t-Bu	Br	$CHCl_2$	b)	(*S*)	+205.6 (*c* = 1.02)	[23]
	t-Bu	H	CF_3	b)	(*R*)	−141.9 (*c* = 1.04)	[24]
	CCl_3	H	Me	a)	(*R*)	−153.7 (*c* = 0.98)	[9]
	Ph	H	H	a)	(*R*)-**9**	−263.5 (*c* = 1.03)	[9]
	Ph	H	H	a)	(*S*)-**9**	+269.0 (*c* = 1.05)	[9]
	Ph	H	Me	a)	(*R*)-**10**	−267.5 (*c* = 0.51)	[9]
	Ph	H	Me	a)	(*S*)-**10**	+265.9 (*c* = 0.51)	[9]
	Ph	Br	Me	c)	(*S*)	+238.0 (*c* = 1.00)	[9]
E	–	H	H	b)	(*R*)	−17.7 (*c* = 1.3)	[25]
	–	H	Me	b)	(*R*)	−22.5 (*c* = 0.4)	[26]
	–	H	CH_2Br	b)	(*R*)	+16.0 (*c* = 1.11)	[27]
	–	H	CHO	b)	(*R*)	+65.1 (*c* = 1.14)	[27]
	–	H	COOMe	b)	(*R*)	+7.0 (*c* = 1.00)	[27]
F	–	H	H	b)	(*S*)	−51.6 (*c* = 1.1)	[25]
	–	H	Me	b)	(*S*)	−27.4 (*c* = 0.48)	[26]
	–	H	CH_2Br	b)	(*S*)	−60.2 (*c* = 1.10)	[27]
	–	H	CHO	b)	(*S*)	−171.8 (*c* = 0.95)	[27]
	–	H	COOMe	b)	(*S*)	−72.0 (*c* = 1.03)	[27]

a) Successfully separated on *Chiraspher*.
b) Separation on *Chiraspher* not investigated.
c) No separation on *Chiraspher*.
d) 72%ee (HPLC).
e) Max. 80%ee.

Change of temperature in chromatographic separations of our cyclic acetals on *Chiraspher* turned out not to be as useful as the application of the recycling technique: the five-ring heterocycles *rac*-**1**, **-2**, and **-4** which separated well at room temperature showed a strong increase of the α values upon cooling, while thioxolanone *rac*-**6** and dioxinones *rac*-**9** and **-10** which started off with meager α values showed only a small effect (see *Fig. 6*). We discovered, however, an interesting maximum of the α values for the first group of compounds at 15° and a distinct bent in the plot of α values against temperature around 0°. A discontinuous temperature dependence had been observed before for other types of stationary phases (*e.g.* for reversed-phase materials *RP-18* [28]; with a liquid crystalline stationary phase covalently bonded to silica gel, a temperature dependence with a minimum of the relative selectivity of polyaromatics had been reported [29]). Such effects are thought to be caused by phase transitions of the coating material.

With the α-naphthoyl derivative *rac*-**3**, a separation of the enantiomers was possible on a 1-g scale with 110 g of 40–63 μm *Chiraspher* using flash-chromatography conditions [30] (see *Exper. Part*).

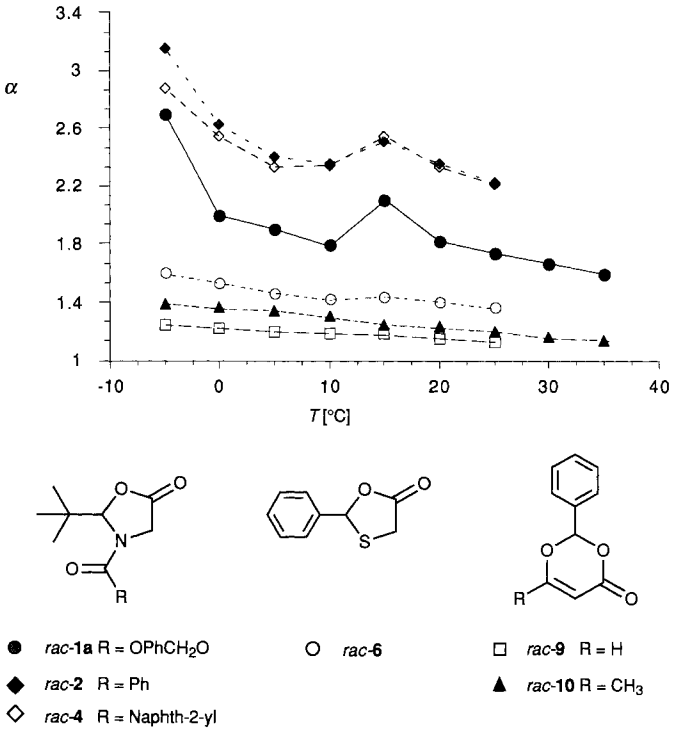


Fig. 6. *Temperature dependence of the separation factors α for the resolution of* rac-**1a**, **-2**, **-4**, **-6**, **-9**, *and* **-10** *on* Chiraspher (250 × 4 mm (5 μm), eluent: hexane/i-PrOH 95:5, flow 1,0 ml/min, injection 20 μl, detection 254 nm).

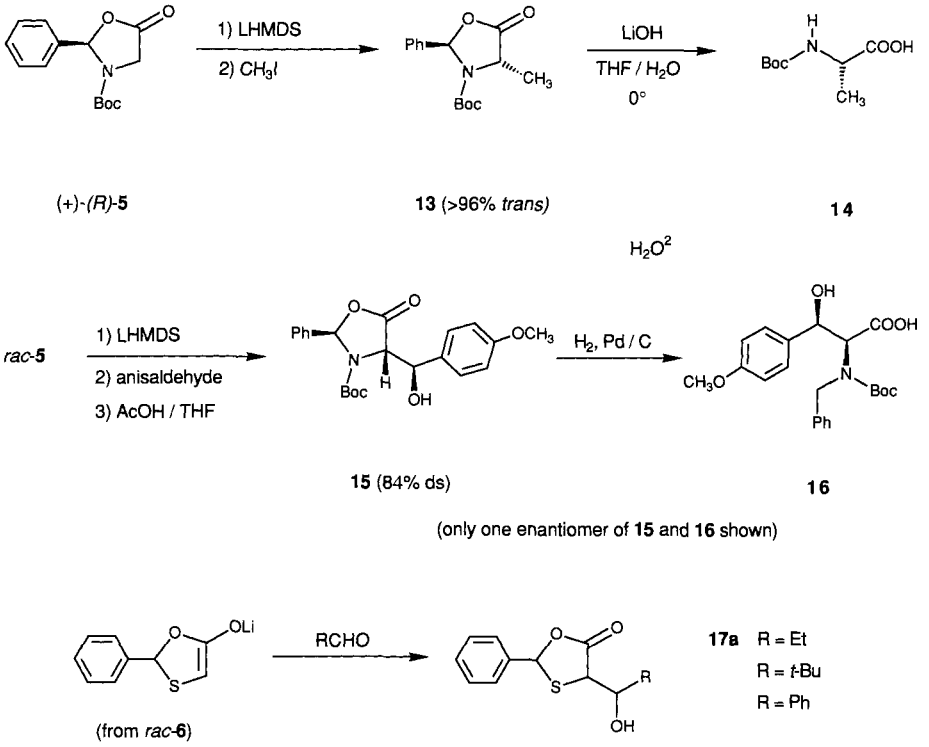
Some Reactions of 5 and 6. – The absolute configurations of the enantiomerically heterocycles **1**–**4** [6] and **9**, **10** [9] were assigned previously. Dioxinone **8** was separated only on an analytical *Chiraspher* column, and the enantiomers (*R*)- and (*S*)-**8** were identified by comparison with independently prepared samples (*Scheme 1* and *Table 1*). Of the three remaining compounds *rac*-**5**–**7**, we have studied the reactions of the β-alanine derivative *rac*-**7** [10], but not yet determined the sense of chirality of its enantiomers.

The enantiomers *of rac*-**5** were assigned (+)-(*R*) and (−)-(*S*) on the basis of the following transformations (see *Scheme 2a*): a dextrorotatory sample was deprotonated and methylated to give a single diastereoisomer **13**. The *trans*-configuration of **13** was established by NOE measurements and by comparison of its NMR spectrum and sign of specific rotation (both are dextrorotatory) with those of the analogous *trans*-4-methyl-5-oxo-2-phenyloxazolidin-3-yl benzoate [31][6]). Cleavage of the heterocyclic ring of **13** led to the known *N*-Boc-protected (−)-L-alanine **14** in essentially optically pure form [32].

The availability of enantiomerically pure **5** by chromatography on *Chiraspher* makes this chiral glycine derivative a highly welcome new reagent for the preparation of amino acids: *i*) the very mild conditions of hydrolysis (LiOH in aqueous THF at 0°) contrast most favorably to those required for the hydrolysis of the corresponding imidazolidi-

[6]) We have noticed previously [8] that the sign of rotation does not change on going from 1-benzoyl- to 1-(*tert*-butoxycarbonyl)imidazolidin-4-ones.

Scheme 2



nones (*cf.* [8] [33] with [31] [34] [35]); *ii*) the Boc-protected amino acid, which can directly be used in peptide synthesis, is obtained, rather than the free amino acid, which is difficult to purify and to isolate in pure form; *iii*) the benzylic C–O bond of the 2-phenyloxazolidinone system present in **5** and **13** may also be cleaved by catalytic hydrogenation (*Scheme 2b*). Thus, the aldol adduct **15** of *rac*-**5** and anisaldehyde, formed with a diastereoselectivity of *ca.* 6:1 (configuration by analogy [3] [8] [34])[7]) was converted to the *N*-benzyl-*N*-Boc-protected 3-(4-methoxyphenyl)serine **16** in a H_2 atmosphere of normal pressure and in the presence of Pd/C.

The thioxolanone **6** was a disappointing experience altogether. *i*) It is extremely sensitive to hydrolysis. *ii*) It has such a large tendency to racemize, even in the solid state, that several dispatches of enantiomerically pure samples of **6** put in the mail in Darmstadt had racemized upon arrival in Zürich! *iii*) Also, the Li enolate of **6** was rather unstable[8]), so that we allowed it to react only with the 'fastest' electrophiles, *i.e.* aldehydes. *iv*) We found that the products **17** were formed (60–80% yield) in poor diastereoselectivity (2:1 to 6:1) even at −100°; these hydroxyalkylated compounds **17a–c** (*Scheme 2c*) were

[7]) It appears that aldol additions of Boc-protected imidazolidinones and oxazolidinones are generally less selective than those of the benzyloxycarbonyl- or benzoyl-protected analogues ([8] [11] [34] [36] and ref. cit. therein).

[8]) For reactions of other thioxolanone enolates, see [37] [38].

mainly spectroscopically[9]) characterized. The properties of the thioxolanone **6** prevented its use as a chiral acetic-acid enolate (*via Raney*-Ni desulfurization of products such as **17**, diastereoselectively formed with electrophiles), the purpose for which we had originally designed it.

Experimental Part

General. THF was distilled under Ar over K/benzophenone ketyl prior to use and transferred with a syringe. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithium reagents were dried for *ca.* 12 h at 120°. All reactions involving air- or moisture-sensitive compounds were performed under dry Ar. The side arm of the reaction flask was stoppered with a serum cap, and the flask was connected to an Ar line by three-way taps. A positive Ar pressure was established by following the operation 'flask evacuation/Ar introduction' several times. Hexamethyldisilazane (HMDS) was distilled from CaH_2 and stored over 4-Å molecular sieves. BuLi was purchased from the *Metallgesellschaft*, Frankfurt/Main, Germany, as a 1.56M soln. in hexane. All other commercial reagents were used as received. TLC: precoated silica gel *60* F_{254} plates (*Merck*); detection by UV_{254} light, phosphomolybdic acid soln. (25 g of phosphomolybdic acid, 10 g of $Ce(SO_4)_2 \cdot 4H_2O$, 60 ml of conc. H_2SO_4 and 940 ml of H_2O), ninhydrin soln. (600 mg of ninhydrin, 2 ml of AcOH and 285 ml of BuOH), or an anisaldehyde soln. (10 ml anisaldehyde, 10 ml of conc. H_2SO_4, 5 ml of AcOH and 275 ml of EtOH). Column chromatography (flash chromatography (FC)): silica gel *60* (230–400 mesh, 0.04–0.063 mm; *Fluka*). Anal. HPLC: *Kontron* instrument (2 pumps, UV dectector *Uvikon-LCD-75*, programmer *200*), coupled with an integrator (*Shimadzu-C-R-1B-Chromatopak*) using a steel column from *Merck*, *Chiraspher* (250 × 4 mm). Prep. HPLC: *Knauer* equipment (type *64* with prep. head, programmer *50*, UV detector 'Variable-Wavelength Monitor'), using a steel column from *Merck Chiraspher* (250 × 25 mm). M.p.: open glass capillaries; *Büchi 510* apparatus, uncorrected. $[\alpha]_D$: at r.t. (20°), with a *Perkin-Elmer 241* polarimeter; in $CHCl_3$ (stabilized 1% EtOH; *Fluka*) unless stated otherwise. IR spectra: $CHCl_3$ solns. or KBr discs. *Perkin-Elmer 283* instrument; $\tilde{\nu}$ in cm^{-1}. NMR spectra: for ^1H, *Bruker WM-300* (300 MHz) or *Varian Gemini* (200 MHz) spectrometer; for ^{13}C *Bruker WM-300* or *Varian XL-300* spectrometer at 75 MHz, *Varian Gemini* at 50 MHz and *Bruker AM-400* at 100 MHz; δ in ppm downfield of TMS ($\delta = 0$), J in Hz; unless stated otherwise, $CDCl_3$ solns. MS: *Hitachi-Perkin-Elmer RMU-6M* spectrometer; fragment ions in m/z with relative intensities (%) in parentheses.

Benzyl rac-*(2RS)-5-Oxo-2-(isopropyl)oxazolidine-3-carboxylate* (*rac*-**1b**) was prepared according to the procedure in [6]. The crude oil contained mainly two compounds (TLC: SiO_2; hexane/CH_2Cl_2/AcOEt 3:1:1): R_f 0.40 (oxazolidinone); R_f 0.22 (benzyl alcohol). The desired compound crystallized at −30° from hexane/Et_2O 1:1. Recrystallization from Et_2O/pentane yielded colorless crystals (31.6 g, 54%). M.p. 45.8–46.8°. IR ($CHCl_3$): 3020*w*, 2970*w*, 2940*w*, 2880*w*, 1800*s*, 1715*s*, 1500*w*, 1470*w*, 1450*w*, 1415*m*, 1350*m*, 1300*m*, 1250*m*, 1220 (br.), 1175*m*, 1120*m*, 1115*m*. ^1H-NMR (90 MHz): 0.90 (*d*, J = 7.2, 3 H, $(CH_3)_2CH$); 1.02 (*d*, J = 7.2, 3 H, $(CH_3)_2CH$); 2.20 (*m*, $(CH_3)_2CH$); 4.07 (*AB*, J = 17.4, $CH_2(4)$); 5.17 (*s*, $PhCH_2O$); 5.65 (*d*, H–C(2)); 7.30 (*m*, Ph). Anal. calc. for $C_{14}H_{17}NO_4$ (263.29): C 63.87, H 6.51, N 5.32; found: C 63.93, H 6.69, N 5.29.

tert-*Butyl (2RS)-5-Oxo-2-phenyloxazolidine-3-carboxylate* (*rac*-**5**). According to a procedure of *Woodward* [16], a suspension of sodium *N*-benzylideneglycinate (3.7 g, 20 mmol), dry pyridine (1.58 g, 1.6 ml, 20 mmol) and *t*-BuOH (1.48 g, 1.88 ml, 20 mmol) in 50 ml of CH_2Cl_2 was cooled to −78° and treated dropwise within 30 min with a *ca.* 1.93M phosgene soln. in toluene (10.4 ml, 20 mmol). The resulting pale yellow suspension was stirred for additional 3 h at −78° and warmed up to *ca.* −15°. Stirring was continued for 4 d at −15°. Finally, the mixture was filtered and the filtrate directly hydrolyzed in a phosphate buffer pH 7 (100 ml). The org. phase was separated and the aq. phase extracted with 50 ml of CH_2Cl_2. The combined org. extracts were dried (Na_2SO_4), filtered, and evaporated to yield a partially crystallized brown solid (4.0 g). According to ^1H-NMR, the crude product contained *ca.* 60% of the desired compound. Purification by FC (hexane/CH_2Cl_2/Et_2O 30:25:5): *rac*-**5** as white powder, contaminated with traces of benzaldehyde (1.55 g, 29%). Recrystallization from Et_2O/pentane afforded fine colorless crystals (1.27 g, 25%). R_f (hexane/CH_2Cl_2/Et_2O 30:25:5) 0.27. M.p. 126.0–126.5°. IR (KBr): 3090*w*, 3060*w*, 3040*w*, 3000*w*, 2880*m*, 2830*w*, 1805*s*, 1795*s*, 1695*s*, 1655*w*, 1535*w*, 1495*w*, 1480*w*, 1455*m*, 1400*s*, 1370*s*, 1330*w*, 1310*m*, 1255*s*, 1200*m*, 1170*s*, 1125*w*, 1080*w*, 1040*m*, 1030*m*. ^1H-NMR (300 MHz): 1.40 (br. *s*, *t*-BuO); 4.07

[9]) We thank *Claudio Cescato* for carrying out these reactions as part of his course work done under the supervision of one of the authors (*D.B.*).

(*A* of *AB*, J = 17.5, H–C(4)); 4.33 (*B* of *AB*, J = 17.5, H–C(4)); 6.62 (br. *s*, H–C(2)); 7.40 (*s*, Ph). ^{13}C-NMR (100 MHz): 28.15; 44.97; 82.33; 90.00; 126.12; 128.78; 129.82; 136.89; 152.06; 169.66. MS: 264 ($[M+1]^+$), 206 (52), 190 (36), 164 (43), 118 (49), 105 (52), 91 (47), 77 (52), 65 (14), 57 (100), 41 (67). Anal. calc. for $C_{14}H_{17}NO_4$ (263.29): C 63.87; H 6.51; N 5.32; found: C 63.71, H 6.49, N 5.24.

rac-*2-(*tert-*Butyl)-2*H,*4*H-*1,3-dioxin-4-one* (*rac*-**8**). According to the procedure in [18] by using toluene as solvent, *rac*-**8** was obtained in 29% yield. B.p. 30°/0.04 Torr. IR ($CHCl_3$): 3010*w*, 2980*m*, 2960*m*, 2880*w*, 1745*s*, 1730*s*, 1610*s*, 1480*m*, 1405*m*, 1395*s*, 1370*m*, 1280*s*, 1265*s*, 1080*s*, 1040*m*, 925*m*, 810*s*. ^{1}H-NMR: 1.06 (*s*, *t*-Bu); 5.10 (*s*, H–C(2)); 5.47 (*d*, J = 5.6, H–C(5)); 7.36 (*d*, J = 5.6, H–C(6)). ^{13}C-NMR: 23.94; 34.44; 99.42; 106.69; 160.73; 161.94. MS: 86 (18), 70 (15), 69 (5), 57 (81), 55 (7), 44 (6), 43 (19), 42 (8), 41 (100), 40 (5), 39 (42), 38 (6), 29 (42), 27 (22). Anal. calc. for $C_8H_{12}O_3$ (156.18): C 61.52, H 7.64; found: C 61.39, H 7.64.

*(*R*)-5-Bromo-2-(*tert-*butyl)-2*H,*4*H-*1,3-dioxin-4-one* ((*R*)-**12**). The mixture of *cis*-**11** (2.5 g, 10.5 mmol), *N*-bromosuccinimide (NBS; 4.1 g, 23.0 mmol) and 2,2′-dimethyl-2,2′-azobis[propanenitrile] (AIBN; 50 mg) in CCl_4 (50 ml) was refluxed for 1.5 h, then cooled to 0°, filtered, and evaporated. The residue was purified by FC (aluminium oxide basic, act. I, Et_2O). Crude (*R*)-**12** (802 mg, 32%; m.p. 85.5–90.0°, $[\alpha]_D = -183.5$ (c = 1.00)) was recrystallized (Et_2O/pentane): needles (260 mg, 10%). M.p. 91.0–94.0°. $[\alpha]_D = -216.9$ (c = 1.01). IR (KBr): 3060*w*, 2970*m*, 2930*w*, 2870*w*, 1740*s*, 1600*s*, 1485*m*, 1400*m*, 1370*m*, 1350*m*, 1290*m*, 1270*m*, 1140*m*, 1060*s*, 990*m*, 780*w*, 750*w*. ^{1}H-NMR: 1.06 (*s*, *t*-Bu); 5.19 (*s*, H–C(2)); 7.62 (*s*, H–C(6)). ^{13}C-NMR: 23.86; 34.48; 94.04; 107.50; 158.45; 159.24. MS: 237 (69, $[M+2]^+$), 236 (39, $[M+1]^+$), 235 (71, M^+), 234 (34), 193 (7), 191 (7), 151 (30), 150 (17), 149 (31), 148 (17), 122 (5), 120 (5), 87 (43), 86 (45), 71 (21), 69 (23), 57 (100), 43 (28), 41 (31), 39 (10), 29 (15), 27 (6), 18 (10). Anal. calc. for $C_8H_{11}BrO_3$ (235.08): C 40.88, H 4.72, Br 33.99; found: C 40.86, H 4.77, Br 33.84.

*(*S*)-5-Bromo-2-(*tert-*butyl)-2*H,*4*H-*1,3-dioxin-4-one* ((*S*)-**12**). As described above, from *trans*-**11** (2.0 g, 8.44 mmol): crude (*S*)-**12** (655 mg, 33%), $[\alpha]_D = -183.5$ (c = 1.00). Recrystallization (pentane) gave (*S*)-**12** (425 mg, 21%). M.p. 98.2–99.0°. $[\alpha]_D = +213.4$ (c = 1.00).

*(*R*)-2-(*tert-*Butyl)-1,3-dioxin-4-one* ((*R*)-**8**). The mixture of (*R*)-**12** (107 mg, 0.45 mmol), Et_3N (0.07 ml, 0.50 mmol) and Pd/C (4 mg, 10%) in AcOEt (2 ml) was stirred under H_2 for 1 h (TLC: hexane/Et_2O 3:1). More Pd/C (4 mg) was added and stirring continued for 2 h. After filtration and evaporation, the residue was purified by prep. TLC (hexane/Et_2O 3:1): (*R*)-**8** (55 mg, 78%). M.p. 39.0–40.8°. $[\alpha]_D = -178.5$ (c = 1.02).

*(*S*)-2-(*tert-*Butyl)-1,3-dioxin-4-one* ((*S*)-**8**). As described for (*R*)-**8**, from (*S*)-**12** (110 mg, 0.47 mmol), Et_3N (0.07 ml, 0.50 mmol) and Pd/C (4 mg, 10%) in AcOEt (2 ml; 75 min): (*S*)-**8** (48 mg, 67%). M.p. 41.8–45.8°. $[\alpha]_D = +198.4$ (c = 1.00).

Recycling Chromatography. The following systems were used for the separation of enantiomers with the recycling mode: *a*) *Knauer* pump, type *64* with prep. head, injection (loop: 2 ml) and valve from *Rheodyne*; UV detector: *Knauer* with superprep. flow cell, connections: 1/16 inch steel capillars. *b*) *Shimatsu LC-8A* pump, integrator: *Hitachi*; otherwise as for *a*. *c*) *Novaprep 5000* system from *Separations Technology*.

Data of the Separated Compounds. Benzyl Carboxylates **1b**: (–)-(*S*)-**1b**: M.p. 59.6–60.4°. $[\alpha]_D = -17.2$ (c = 1.13). (+)-(*R*)-**1b**: M.p. 55.6–56.6°. $[\alpha]_D = +15.3$ (c = 0.92).

tert-*Butyl Carboxylates* **5**: (–)-(*S*)-**5**: M.p. 140.5–141.6°. $[\alpha]_D = -76.3$ (c = 1.05). (+)-(*R*)-**5**: M.p. 140.4–141.8°. $[\alpha]_D = +76.4$ (c = 1.05). Correlation *via* **13** to **14**, see below.

*2-(*tert-*Butyl)perhydro-3-methyl-4-oxopyrimidin-1-yl Benzoates* **7**: (–)-**7**: Purity ≥ 95% ee. M.p. 93.2–95.2°. $[\alpha]_D = -50.3$ (c = 1.01). (+)-**7**: Purity ≥ 94.5% ee. M.p. 92.0–93.2°. $[\alpha]_D = +49.6$ (c = 1.00).

*Separation of (2*RS*)-2-(*tert-*Butyl)-3-[(naphthalen-1-yl)carbonyl]oxazolidin-5-one* (*rac*-**3**) *by FC.* Conditions: *Chiraspher* (40–63 μm), 110 g; column diameter 3 cm; 1 g of *rac*-**3** in 1 ml of CH_2Cl_2; pressure 0.3 bar; fraction size 20 ml. Results: *Table 2.*

Table 2. *FC Separation of* rac-**3**

Eluent Hexane/ i-PrOH	Temp. [°C]	Total number of fractions	First enantiomer		Second enantiomer	
			Amount [mg]	Purity [%ee][a])	Amount [mg]	Purity [%ee][a])
9:1	0	42	370 mg	95	171	97
11:1	0	60	326 mg	> 99.5	353	83
9:1	–10	80	402 mg	97	378	91

[a]) Determined by HPLC.

tert-Butyl (2R,4S)-4-Methyl-5-oxo-2-phenyloxazolidine-3-carboxylate (**13**). BuLi (0.61 ml, 0.98 mmol) was added dropwise at −78° to a soln. of HMDS (0.2 ml, 0.98 mmol) in THF (5 ml). The resulting soln. was stirred for 30 min at −78° and added '*via* cannula' to a soln. of (+)-**5** (237 mg, 0.9 mmol) in 12 ml of THF, which was precooled to −78°. The resulting pale yellow enolate soln. was stirred for an additional 15–20 min at −78° and treated with MeI (255 mg, 0.11 ml, 1.8 mmol). The mixture was warmed up to r.t. overnight and poured into a mixture of sat. aq. NH_4Cl soln. (20 ml) and Et_2O (20 ml). The org. phase was separated, the aq. phase extracted with another portion of 20 ml of Et_2O. The combined org. extracts were dried (Na_2SO_4), filtered, and concentrated to afford a white-yellow solid (223 mg, 90%), which was purified by FC (hexane/CH_2Cl_2/Et_2O 30:25:2) to yield **13** as a colorless powder (172 mg, 70%). Recrystallization from Et_2O/pentane yielded fine crystals (162 mg, 62%); %ds ⩾ 96 (300-MHz ^{1}H-NMR). R_f (hexane/CH_2Cl_2/Et_2O 30:25:2) 0.24. M.p. 162.0–162.6°. $[\alpha]_D = +116.6$ ($c = 1.02$). IR (KBr): 3090*w*, 3060*w*, 3040*w*, 3000*w*, 2980*m*, 2940*w*, 2880*w*, 1780*s*, 1740*w*, 1690*s*, 1650*w*, 1590*w*, 1540*w*, 1490*w*, 1475*m*, 1460*m*, 1445*w*, 1405*s*, 1370*s*, 1340*w*, 1325*m*, 1300*w*, 1280*w*, 1250*s*, 1200*m*, 1175*s*, 1140*s*, 1070*m*, 1010*s*. ^{1}H-NMR (200 MHz): 1.22 (br. *s*, *t*-BuO); 1.68 (*d*, $J = 6.6$, CH_3–C(4)); 4.51 (*q*, $J = 6.8$, H–C(4)); 6.40 (br. *s*, H–C(2)); 7.31–7.43 (*m*, Ph). NOE: irrad. at 1.68→signal increase at 6.40 (*trans*-arrangement); irrad. at 4.51→signal increase at 7.31–7.43 (*trans*-arrangement). ^{13}C-NMR (100 MHz): 16.89; 27.98; 51.95; 81.80; 89.66; 126.55; 128.73; 129.96; 137.75; 151.28; 172.65. MS: 277 (M^+), 221 (21), 204 (5), 178 (13), 132 (41), 107 (20), 90 (6), 77 (16), 70 (20), 57 (100), 51 (8), 41 (35), 29 (20). Anal. calc. for $C_{15}H_{19}NO_4$ (277.32): C 64.97; H 6.91; N 5.05; found: C 64.94, H 6.93, N 4.95.

Hydrolysis of **13** *to (−)-*N*-[(tert-Butoxy)carbonyl]-*L*-alanine* (**14**). A soln. of **13** (112 mg, 0.4 mmol) in THF/H_2O 3:1 (10 ml) was treated at 0° with LiOH (19.4 mg, 0.8 mmol). After 20 min, no more **13** could be detected by TLC. Benzaldehyde was extracted twice in 20 ml of CH_2Cl_2. The aq. phase was separated and carefully acidified to pH 2–3 at 0° by adding aq. 1N HCl. The product was extracted with AcOEt (2 × 20 ml) and the combined org. phases dried (Na_2SO_4), filtered, and evaporated: **14** (74.1 mg, 97%). Colorless, highly viscous oil. $[\alpha]_D = -24.5$ ($c = 2.25$, AcOH) ([32]: $[\alpha]_D = -22.4$ ($c = 2$, AcOH)). ^{1}H-NMR: identical with that of an authentic sample.

tert-Butyl (2RS,4SR,αRS)-4-(α-Hydroxy-4-methoxybenzyl)-5-oxo-2-phenyloxazolidine-3-carboxylate (*rac*-**15**). As described above for **13**, a soln. of the Li-enolate of *rac*-**5** (789 mg, 3 mmol) was treated dropwise at −100° with anisaldehyde (0.4 ml, 3.3 mmol) (pale yellow→colorless soln.). Stirring was continued for another 30 min at −100° and the reaction was finally quenched by adding 1N AcOH in THF. The mixture was poured into a mixture of 20 ml of sat. aq. NH_4Cl and 20 ml of Et_2O. The org. phase was separated and the aq. phase extracted with another 20 ml of Et_2O. The combined org. extracts were washed with brine, dried (Na_2SO_4), and evaporated: TLC (hexane/CH_2Cl_2/AcOEt 3:3:1) of the oily residue: R_f 0.17 (major) and 0.38 (by-product). 300-MHz ^{1}H-NMR (at 59.4° due to the presence of rotamers at r.t.): two diastereoisomers in a *ca.* 6:1 ratio. FC (hexane/CH_2Cl_2/AcOEt 3:3:1) afforded *rac*-**15** (0.80 g, 67%) and its diastereoisomer (R_f 0.38; 202 mg, 17%) as colorless oils.

15: ^{1}H-NMR (300 MHz): 1.18 (br. *s*, *t*-BuO); 3.25 (br. *s*, OH); 3.82 (*s*, MeO); 4.86 (*dd*, $J = 4.7, 1.1$, H–C(4)); 5.52 (*d*, $J = 4.7$, H–C(α)); 5.61 (br. *s*, H–C(2)); 6.90–7.40 (*m*, Ph, $MeOC_6H_4$); similarity of this spectrum to that of *benzyl (2R,4S,αR)-2-(*tert*-butyl)-4-(α-hydroxy-4-methoxybenzyl)-5-oxooxazolidine-3-carboxylate* [11] suggests the same relative *threo*-configuration for **15**.

Diastereosiomer of **15**: ^{1}H-NMR (300 MHz): $\delta = 1.27$ (*s*, 9 H, *t*-BuO); 3.30 (br. *s*, 1 H, OH); 4.72 (*d*, $J = 4$, 1 H, H–C(4)); 5.28 (br. 1 H, H–C(1′)); 6.29 (br. *s*, 1 H, H–C(2)); 6.90–7.40 (*m*, 9 H, C_6H_5, C_6H_4).

*(2RS,3SR)-*N*-Benzyl-*N*-[(*tert*-butoxy)carbonyl]-3-(4-methoxyphenyl)serine* (**16**). According to the procedure of *Anwer* [39], **15** (200 mg, 0.5 mmol) was treated under *catalytic transfer hydrogenation* with $HCOONH_4$ (126 mg, 2 mmol) and 10% Pd/C (100 mg) in 5 ml of MeOH at r.t. (TLC monitoring). After 60 min, the catalyst was filtered off through a *Celite* pad and the filtrate evaporated. The residue was taken up in 10 ml of AcOEt and washed with brine. The org. phase was dried (Na_2SO_4), filtered, and evaporated to afford a white solid in quant. yield. Recrystallization from AcOEt/hexane: anal. pure **16** (153 mg, 98%). M.p. 144.6–145° (dec.). ^{1}H-NMR (200 MHz): 1.45 (*s*, *t*-Bu); 3.83 (*s*, MeO); 3.95 (*A* of *AB*, $J = 15$, 1 H, $PhCH_2$); 4.09 (*d*, $J = 5$, H–C(2)); 4.22 (*B* of *AB*, $J = 15$, 1 H, $PhCH_2$); 5.43 (br., H–C(3)); 6.82 (*d*, $J = 8.5$, 1 arom. H); 6.91 (br. *s*, OH, COOH); 7.16 (*d*, $J = 8.6$, 2 arom. H); 7.20 (*s*, Ph). ^{13}C-NMR (100 MHz): 28.24; 54.37; 55.28; 67.42; 73.04; 82.17; 113.73; 127.07; 127.36; 127.85; 128.35; 132.74; 136.59; 157.93; 158.98; 172.19. Anal. calc. for $C_{22}H_{27}NO_6$ (401.46): C 65.82; H 6.78; N 3.49; found: C 65.45; H 6.68; N 3.38.

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