105. The Chiral Glycine Enolate Derivative from 1-Benzoyl-2-(*tert*-butyl)-3-methyl-1,3-imidazolidin-4-one is Alkylated in the 5-Position with Relative Topicity *lk*

Preliminary Communication

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An overall enantioselective substitution of the R-group of an α-hydroxy- or α-amino acid **1** [R–CH(XH)COOH] by another R-group is possible through heterocycles **2** obtained from **1** with pivalaldehyde (**1**→**7**). The *rac*- and the (*S*)-(+)-heterocycles **8** (title compounds of type **5**) are prepared from glycine and *O*-benzyl-(*S*)-serine, respectively. Their enolates (*cf.* **9**, type **6**) are alkylated with iodomethane, iodobutane, 2-iodopropane, benzyl bromide, and acetone to give the *trans*-disubstituted imidazolidinones **10** with ≥95% diastereoselectivity. The configuration of the products is established by chemical correlation with alanine, phenylalanine, and valine.

Through enantiomerically pure heterocycles **2**[4]) of *cis*- or *trans*-configuration and their respective enantiomeric enolates **3**, amino-, hydroxy-, and mercapto-carboxylic acids **1** have been alkylated without racemization to give derivatives **4** with a tetrasubstituted α-C-atom. An aldehyde[4]) [1–6] such as pivalaldehyde, but no chiral auxiliary is required to achieve the overall process. A self-reproduction of the center of chirality takes place (see our most recent papers [2–5] of this series, and ref. cit. therein). Following the same principle, it should also be possible to prepare non-branched, *unnatural* hydroxy and amino acids from the readily available ones[5]). This requires the replacement of the R-group in an optically active heterocycle **2**, first by an H-atom to give a monosubstituted heterocycle **5**, which contains only one asymmetric C-atom, the acetal center[4]). Subsequent alkylation through the enolate **6** with substitution of a proton by an electrophilic moiety, and hydrolysis should give products of type **7**. In this communication, we present an example of such an overall carbon-by-carbon substitution (**1**→**7**) through a chiral glycine enolate.

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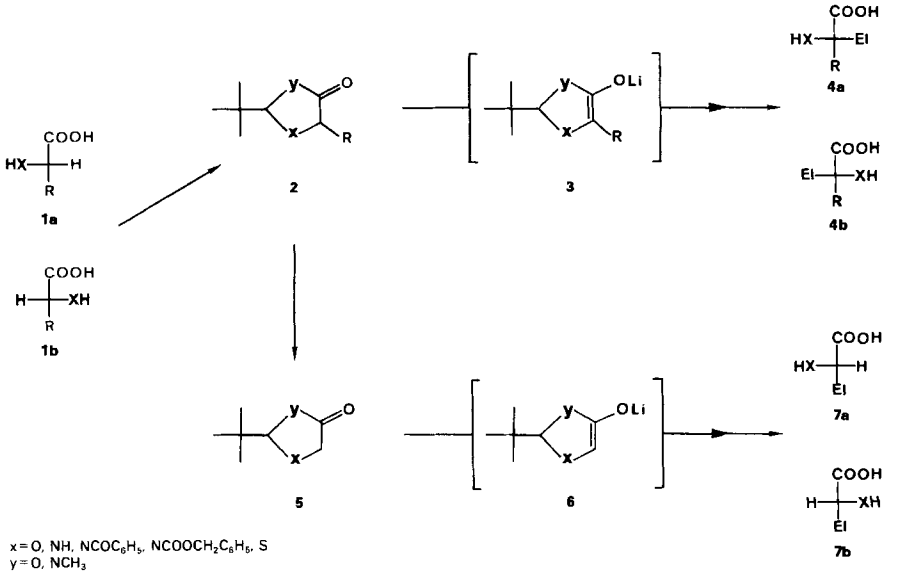
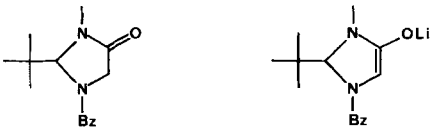
[4]) It is possible to use such acetals (**2**, **5**) for asymmetric synthesis with attack of C-nucleophiles on the acetal center, as recently demonstrated by S. H. Mashraqui and R. M. Kellogg [*J. Org. Chem.* **1984**, *49*, 2513]. For other types of acetals, see *Johnson et al.* [7] and *Yamamoto* and his coworkers [8].

[5]) This will also further extend the 'chiral pool' (pool of chiral building blocks for synthesis) [9] [10].

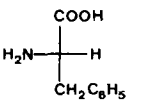


Although we are aware of the fact that a racemic lithium enolate does not necessarily react with the same selectivity as an enantiomerically pure one [11], due to aggregate formation[6]), we first sought information about the reactivity of the glycine derived enolate *rac*-**9** from the racemic 1-benzoyl-2-(*tert*-butyl)-1,3-imidazolidin-4-one (*rac*-**8**). The latter was prepared [2] and deprotonated to the enolate [3] exactly as described previously for imidazolidinones from higher amino acids.

The products **10a–d** of alkylation (**8**, lithium diisopropylamide (LDA) in THF, −75°, RX addition, slow warming to *ca.* 0°) and **10e** of hydroxyalkylation (no warming above −75°) are formed with at least a 95:5 preference for the *trans*-isomers, according to ^{13}C-NMR integration and by comparison with the previously prepared optically active samples (**10a, b, d**) [2]. For reaction conditions, yields, selectivities, and some characteristic physical data of the products, see *Experimental*.



10	El
a	CH_3
b	$CH_2C_6H_5$
c	C_4H_7
d	$CH(CH_3)_2$
e	$C(OH)(CH_3)_2$



Bz = COC_6H_5

[6]) Thus, a dimeric aggregate can be formed from two homochiral units [12] or from a pair of enantiomers. If the resulting diastereoisomers are involved in product-forming steps, they give rise to different ratios of isomeric products! [11] [13].

For the preparation of optically active **8**, a degradation with removal of the R-group from one of the readily available *trans*-imidazolidinones **2** [2] [14] was considered[7]). As candidates, the serine-, cysteine- [14], threonine-, phenylglycine- [2] [3], methionine- [2] [3], aspartic-acid and glutamic-acid-derived [15] imidazolidinones of type **11** (*cf.* **2**) are being pursued. Thus, commercial (*S*)-*O*-benzylserine was converted to the *trans*-heterocycle **11a**, following the procedures described for other amino acids [2]. Hydrogenolytic debenzylation (→**11b**), oxidation to the acid **11c**, and decarboxylation produced the crystalline glycine derivative (*S*)-**8** of $[\alpha]_D^{25} = +133°$.

Methylation and benzylation of (*S*)-**8** under the conditions as specified above for the racemic compound **8**, gave (2*S*,5*S*)-**10a** and (2*S*,5*S*)-**10b** in 95 and > 95% ds, respectively. The product (2*S*,5*S*)-**10a** was identified by comparison (NMR and $[\alpha]_D$) with an authentic sample prepared from (*S*)-alanine [2]. The phenylalanine derivative (2*S*,5S)-**10b** has the relative configuration opposite to the known [2] *u*-isomer. Hydrolysis of (2*S*,5*S*)-**10b** to the (*S*)-amino acid **12** completes the correlation between (*S*)-serine and (*S*)-phenylalanine. Thus, a conversion with overall enantioselective substitution of the R-group of an (*S*)-amino acid by another R-group (*cf.* **1a**→**7a**) has been accomplished.

Improved access to and more reactions of the optically active imidazolidinone **8** as well as of other glycine and glycolic-acid derivatives (**5**, X = O) are currently under investigation[8]).

Experimental. – *Preparation of the Products* **8** *and* **10–12**. The ratios of diastereoisomers (% ds) were determined from the ^{13}C-NMR spectra (*Varian CFT 20*) of the crude products, > 95% indicates that no *cis*-isomer was detected. Unless otherwise stated, the glycine derivative **8** was deprotonated at −75° (LDA; *ca.* 12 ml THF/mmol **9**; 45 min), electrophile (neat) was added, and the temp. allowed to rise to *ca.* 0° overnight. The assignment of the *l*-configuration of the products **10** was achieved by NMR comparison with samples made from optically active amino acids (**a**, **b**, **d**) [2] and by analogy (**c**, **e**). The relative and absolute configuration of **11** followed from its conversion to the known compounds **10** and **12** [2]. All optical rotations were measured in $CHCl_3$, c *ca.* 1. ^{1}H-NMR spectra (300 MHz) were recorded in $CDCl_3$ soln., chemical shifts in δ [ppm], coupling in Hz, peak broadening due to coalescence behaviour was often observed. – Elemental analyses were in accordance with the structures shown.

rac-**8**: from non-benzoylated heterocycle [2] and benzoyl chloride (Et_3N, in CH_2Cl_2). Yield 90%, m.p. 104–105° (from EtOAc/hexane). ^{1}H-NMR: 1.09 (*s*, *t*-Bu); 3.05 (*s*, CH_3N); 3.83 (*d*, *J* = 15.5, H–C(5)); 4.11 (*dd*, *J* = 15.5, 1, H–C(5)); 5.60 (*d*, *J* = 1, H–C(2)).

(*S*)-**8**: by decarboxylation of **11c**, m.p. 142–143° (from CH_2Cl_2/pentane); $[\alpha]_D = +133°$. ^{1}H-NMR as of *rac*-**8**.

l-**10a**: from *rac*-**8** and iodomethane (1.2 equiv.), yield 90%, 95% ds, m.p. 145.6–146.2° (from EtOAc/petroleum ether).

(2*S*,5*S*)-**10a**: from (*S*)-**8** and iodomethane, yield 51%, 95% ds, m.p. 184° (from CH_2Cl_2/pentane); $[\alpha]_D = +45.0°$ ([2]: m.p. 175°; $[\alpha]_D = +44.5°$).

l-**10b**: from *rac*-**8** and benzyl bromide (1.2. equiv.), yield 83%, > 95% ds, m.p. 151.0–151.8° (from EtOAc). ^{1}H-NMR: 0.94 (*s*, *t*-Bu); 2.86 (*s*, CH_3N); 4.66 (*m*, H–C(5)) (*cf.* ^{1}H-NMR of the *u*-isomer [2]).

(2*S*,5*S*)-**10b**: from (*S*)-**8** and benzyl bromide, yield 45%, > 95% ds, m.p. 148° (from CH_2Cl_2/pentane); $[\alpha]_D = +121°$. ^{1}H-NMR as of the racemic compound *l*-**10b**.

l-**10c**: from *rac*-**8** and iodobutane (5 equiv.), yield 89%, > 95% ds, m.p. 118.4–119.0° (from EtOAc/petroleum ether). ^{1}H-NMR (90 MHz): 1.07 (*s*, *t*-Bu), 3.07 (*s*, CH_3N); 4.37 (*m*, H–C(5)); 5.67 (*s*, H–C(2)).

l-**10d**: from *rac*-**8** and 2-iodopropane (5 equiv., 25% *N*,*N*′-dimethylpropyleneurea cosolvent [18], yield 27% (+57% recovered **8**), > 95% ds, m.p. 148.0–148.6° (from Et_2O). ^{1}H-NMR: 0.62 and 0.96 (2 *d*, *J* = 6.7, $(CH_3)_2C$); 1.04 (*s*, *t*-Bu); 3.04 (*s*, CH_3N); 4.22 (*s*, H–C(5)); 5.67 (*s*, H–C(2)) (*cf.* ^{1}H-NMR of the *u*-isomer [2]).

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[7]) Diastereoselective carboxylation of *rac*-**8** (→**10**, El = COOH), resolution of the resulting aminomalonic-acid derivative, and decarboxylation is also a possibility for preparing optically active **8**.

[8]) For previous work on achiral and chiral glycine-enolate derivatives see [16] and [17], respectively.

l-**10e**: from *rac*-**8** and acetone (2 equiv., maintained at –75°), yield 89%, > 95% ds, m.p. 133.2–133.8° (from EtOAc/petroleum ether). ^{1}H-NMR: 0.97 (*s*, *t*-Bu); 1.58 (*s*, CH_3); 1.78 (*s*, CH_3); 2.97 (*s*, CH_3N); 4.17 and 4.27 (1 H each, J = 2, H–C(2) and H–C(5)).

(2*S*,5*S*)-**11a**: from (*S*)-*O*-benzylserine, following the procedure given in [2], intermediates are the methyl ester, *N*-methyl amide, pivalaldehyde imine and the non-benzoylated heterocycle. Overall yield *ca.* 45%, > 95% ds, m.p. 156° (from Et_2O/hexane); $[\alpha]_D$ = +48°. ^{1}H-NMR: 1.1 (*s*, *t*-Bu); 3.1. (*s*, CH_3N); 3.75 (*d*, J = 13.5, CH_2–C(5)); 4.1 (*s*, $C_6H_5CH_2O$); 4.2 (br., H–C(5)); 5.7 (*s*, H–C(2)).

(2*S*,5*S*)-**11b**: from **11a**, H_2/Pd (10% C) in EtOAc, yield 79%, m.p. 164° (from ether/hexane). IR (in KBr): 3360 (OH); 1695, 1655 (2 C=O). ^{1}H-NMR: 2.6 (br., OH); 3.7 (br., CH_2OH); 4.25 (br., H–C(5)).

(2*S*, 5*S*)-**11c**: from **11b**, $RuCl_3/NaIO_4$ in $CCl_4/CH_3CN/H_2O$ 2:2:3 [19], yield: 83%. ^{1}H-NMR: 4.85 (*s*, H–C(5)); 5.7 (*s*, H–C(2)).

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