syn/anti Diastereoselectivity in the Aldol Reaction of Aldehydes with the C(3) Carbanion of 1,3-Dihydro-2*H*-1,4-benzodiazepin-2-one

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The aldol reaction of the C(3) carbanion of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**2**) with a series of aromatic and aliphatic aldehydes at −78° afforded *threo*/*erythro* diastereoisomers **3**–**16** of 7-chloro-1,3-dihydro-3-(hydroxymethyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepinones, substituted at the C(3) side chain, in a ratio from 55 : 45 to 94 : 6 (*Scheme 1*). *Lewis* acids exhibited limited effect on the *syn*/*anti* diastereoselectivity of this reaction, and kinetic control of the reaction was confirmed. ^{1}H-NMR Data suggested the assignment of the *threo* relative configuration to the first-eluted diastereoisomers **3**, **5**, **7**, and **9** on reversed-phase HPLC, and the *erythro* configuration to the second-eluted counterparts **4**, **6**, **8**, and **10**, respectively. The structures and relative configurations *threo* and *erythro* of the diastereoisomers **5** and **6**, respectively, were established by single-crystal X-ray analysis, confirming the assignment based on the ^{1}H-NMR data. A tentative mechanistic explanation of the diastereoselectivity invokes the enolate anion of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one as the reactive species (*Scheme 2*). Acid-catalyzed hydrolytic ring opening of **3** afforded *threo*-β-hydroxy-phenylalanine **17**, whereas from **4**, the *N*-(benzyloxy)carbonyl derivative **18** of *erythro*-β-hydroxy-phenylalanine was obtained (*Scheme 3*); in both cases, neither elimination of H_2O from the C(3)–CHOH moiety nor epimerization at C(3) were observed. This result opens a new pathway to various configurationally uniform α-amino-β-hydroxy carboxylic acids and their congeners of biological importance.

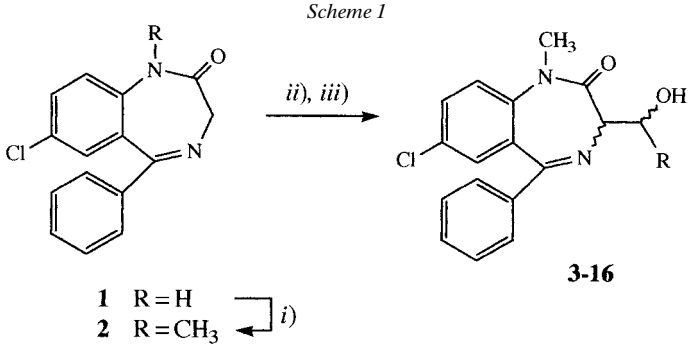
1. Introduction. – The aldol reaction is a useful method for preparing β-hydroxy-substituted carbonyl compounds, optionally with an additional substituent at the α-position, and has, therefore, attracted a great deal of attention from synthetic organic chemists. The generality, versatility, and selectivity associated with this reaction has been the subject of authoritative summaries [1]. The aldol reaction of nitriles [2], glycine derivatives [3], and many other C–H acidic compounds is a useful method for the simultaneous construction of two stereogenic centers and the installation of latent functionalities. In continuation of our project aiming at the use of 3-substituted 2*H*-1,4-benzodiazepin-2-ones as templates for the preparation of optically pure α-amino acids and their congeners [4], we studied the diastereoselectivity of the aldol reaction between aldehydes and the C(3) carbanion of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **2**. Compound **2** comprises a glycine moiety in the conformationally rigid seven-membered ring, and offers a specific stereoelectronic surrounding for carbanions generated at a methylene C-atom. Exploration of such a carbanion in the aldol reaction seems to be a synthetically worthwhile goal, and here, we report on the *syn*/*anti* diastereoselectivity[1]) of this reaction, on the determination of the relative configuration of the separated diastereoisomeric racemates, and on an example of trans-

[1]) The descriptors *syn*/*anti* refer to the relative position of the aldehyde to the 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one anion in the transition state (see below, *Scheme 2*), and *erythro*/*threo* are used in the traditional (carbohydrate) sense to describe the relative configuration at the two stereogenic (N- and OH-substituted) centers (see below, *Footnote 3*).

formation of diastereoisomerically pure products into *threo*- and *erythro*-α-amino-β-hydroxycarboxylic acid derivatives[1]).

2. Results and Discussion. – 2.1. syn/anti *Diastereoselectivity of the Aldol Reaction*. The carbanion at C(3) of **2** was generated *in situ* by treatment with BuLi and diisopropylamine and then exposed to some representative aromatic and aliphatic aldehydes (*Scheme 1* and *Table 1*). In all cases, a mixture of racemic *threo*/*erythro* diastereoisomers[1]) (see **3**–**16**) was formed. The yield of the condensation with aromatic aldehydes varied between 75 and 83%, and the *threo*/*erythro* ratio varied from 30:70 for **3**/**4** to 55:45 for **9**/**10**, as determined by HPLC. With three representative aliphatic aldehydes, a notably higher diastereoselectivity was obtained, ranging from 11:89 for **13**/**4** to 6:94 for **11**/**12**.

Scheme 1



i) MeONa, MeOH, Me_2SO_4, +5°. *ii*) Lithium diisopropylamide (LDA), −78°. *iii*) R-CHO, −78°.

Table 1. *Aldol Reaction of 1,3-Dihydro-2*H*-1,4-benzodiazepin-2-one* **2** *with Aldehydes RCHO: Diastereoisomer Ratio and Yields of the Products*

	R	HPLC Ratio[a])	Yield [%]
3/**4**	Ph	30:70	75
5/**6**	4-Cl−C_6H_4	37:63	77
7/**8**	4-NO_2−C_6H_4	45:55	77
9/**10**	4-MeO−C_6H_4	55:45	83
11/**12**	Et	6:94	65
13/**14**	Pr	11:89	78
15/**16**	Me_2CHCH_2	8:92	71

[a]) First-eluted *threo*-isomer/second-eluted *erythro*-isomer.

As seen from *Table 1*, the second-eluted diastereoisomer on reversed-phase HPLC was regularly formed as the prevailing product. All diastereoisomers were separated on preparative scale by chromatography and then crystallized. Interestingly, the first-eluted diastereoisomers regularly formed slightly yellow crystals, whereas crystals of the second-eluted diastereoisomers were colorless.

With these results in hand, we attempted to improve the diastereoselectivity of the aldol reaction, in particular, in the case of aromatic aldehydes. Thus, various auxiliary agents were examined in the reaction of **2** with benzaldehyde (*Table 2*). Generally,

Table 2. *Effect of the Base and Auxiliary Agents on the Diastereoselectivity of the Formation of* **3**/**4**. Reaction temperature $-70°$.

Base[a])	Base/**2** [mol/l]	*Lewis* acid	*threo*/*erythro* (HPLC)
LDA[b])	0.60 : 0.14	–	30 : 70
LDA	0.03 : 0.03	–	no reaction
LDA[c])	0.25 : 0.05	–	28 : 72
LDA[c])	0.60 : 0.14	–	21 : 79
LDA[c])	0.60 : 0.14	$ZnCl_2$	25 : 75
LDA	0.60 : 0.14	$ZnBr_2$	23 : 77
LDA	0.60 : 0.14	$MgBr_2$	27 : 73
LDA	0.60 : 0.14	BF_3Et_2O	21 : 79
$Ti(OPr)_4$	0.60 : 0.14	$TiCl_4$	no reaction
NaH	0.60 : 0.14	–	40 : 60

[a]) LDA = Lithium diisopropylamide. [b]) Reference experiment.[c]) Reaction temperature $-100°$.

diastereoselectivity can be influenced by temperature, solvent, and dilution [5], and, particularly, by *Lewis* acids [6]. Although *Lewis* acids were repeatedly reported to improve the diastereoselectivity of the aldol reaction, no significant effect was observed in the case of the carbanion of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **2** (*Table 2*). We assume that other binding sites within the heterocyclic enolate anion, in particular the N(4) atom, compete with the carbonyl O-atom of the aldehyde for coordination to the *Lewis* acid.

The notably higher diastereoselectivity with aliphatic aldehydes can tentatively be explained by a generally higher steric demand of the alkyl group attached to the carbonyl function; similarly, high diastereoisomeric excesses (de) were observed for aliphatic aldehydes in the aldol reaction with other enolate anions [7].

2.2. *^{1}H-NMR Study of the Relative Configuration and Conformation in Solution.* The ^{1}H-NMR spectra of the first-eluted diastereoisomers regularly reveal smaller *J* values (*ca.* 5 Hz), while for the second-eluted diastereoisomers, nearly doubled values for *J* (*ca.* 9 Hz) are observed (*Table 3*). Besides, the H-atom of OH–C(12)[2]) of the second-eluted diastereoisomers **4**, **6**, and **8** shows coupling with H–C(12) ($J \approx 2.5$–3.0 Hz), which is not observed for the first-eluted diastereoisomers. Inspection of *Dreiding* models for the diastereoisomeric compounds, combined with ^{1}H-NMR data, indicate that the second-eluted diastereoisomers should possess *erythro*-configuration, since on H-bonding C(12)–OH···O=C(2), they could adopt a low-energy six-membered chelate-ring conformation **I** with the larger groups at C(3) and C(12) in pseudoequatorial position. *threo*-Diastereoisomers, instead, would possess larger phenyl (or alkyl) groups in pseudoaxial position if a H-bond C(12)–OH···O=C(2) was formed. This H-bonded chelate should, therefore, be energetically unfavorable for *threo*-diastereoisomers; H-bonding to N(4) (see **II**), instead, is much weaker and, according to our MM2 calculations [4c], its contribution to conformational stabilization much lower. Consequently, *threo*-configuration is ascribed to the first-eluted diastereoisomers [8a].

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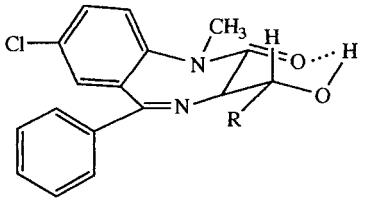
[2]) Arbitrary atom numbering according to the X-ray crystal-structure representations (see *Figs. 1* and *2*).

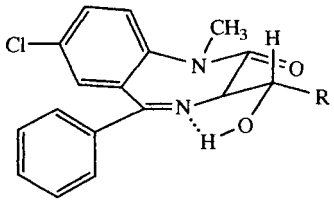
Table 3. *^{1}H-NMR Data for Diastereoisomeric Aldol Products* **3**–**16** (H_a–C(3)–CH_b(12)–OH_c[2]))

First-eluted (*threo*)	δ(a) [ppm]	δ(b) [ppm]	*J*(a,b) [Hz]	*J*(b,c) [Hz]	Second-eluted (*erythro*)	δ(a) [ppm]	δ(b) [ppm]	*J*(a,b) [Hz]	*J*(b,c) [Hz]
3	3.69	5.60	4.9	–	**4**	3.64	5.69	9.0	2.8
5	3.62	5.56	5.1	–	**6**	3.56	5.67	9.2	3.1
7	3.66	5.68	4.6	–	**8**	3.58	5.79	9.0	2.4
9	3.66	5.55	5.4	–	**10**	3.62	5.67	8.7	–
11[a])	–	–	–	–	**12**	3.37	4.53	9.0	–
13	3.42	4.42	–	–	**14**	3.35	4.62	8.5	–
15	3.38	4.50	–	–	**16**	3.34	4.67	–	–

[a]) Formed in minor amounts, not isolated.



I *erythro*



II *threo*

^{1}H,^{1}H-Coupling between H–C(12) and HO–C(12) would be expected for a chelated *erythro*-diastereoisomer, not for the unchelated OH group in the *threo*-diastereoisomers. The smaller *J* values (*ca.* 5 Hz) for the ^{1}H,^{1}H-coupling of H–C(3) and H–C(12) in the first-eluted diastereoisomers are consistent with a *ca.* 160° dihedral angle in the chelated conformer of this diastereoisomer.

To unequivocally establish the *threo*/*erythro* assignment, however, single-crystal X-ray structure analysis was performed for the diastereoisomeric racemates **5** and **6**[3]).

2.3. *Crystal Structures of* **5** *and* **6**. The structures of **5** and **6** with the atom numbering are shown in *Figs. 1* and *2*. Characteristic bond lengths and angles of **5** and **6** are listed in *Table 4*, and the conformations of the seven-membered 1,4-benzodiazepine rings are described by the selected torsional angles given in *Table 5*. H-Bonds are listed in *Table 6* and their patterns shown in the crystal packings (*Figs. 3* and *4*).

Both crystal structures are racemic mixtures: (*R*,*S*)- and (*S*,*R*)-enantiomers were encountered in **5**, whereas (*R*,*R*)- and (*S*,*S*)-enantiomers were found in **6**. Two crystallographically independent molecules **A** and **B** in the crystal of **6** are related by an approximate inversion operation. These two conformers reveal significant conformational difference about the bond N(4)–C(5)–C(20)–C(21)[2]); the corresponding torsion angle is 30.0(6)° in **A** and −147.9(5)° in **B** (*Table 5*). In both molecules, the seven-membered ring adopts a boat conformation with an approximate C_s symmetry.

The conformation about the bond N(4)–C(3)–C(12)–O(19) of **5**, comprising two chiral centers of different absolute configuration ((3*R*,12*S*) and its enantiomer), is *threo* (torsion angle 56.9(2)°). In **6**, the bond C(3)–C(12) connects two chiral centers of the

[3]) It is important to note that the 'zig-zag' conformation of the C-chain C(2)–C(3)–C(12)–C(13) should be rotated to get a *Fischer*-type projection to assign *threo*/*erythro* relative configurations to the diastereoisomeric racemates [8a]. See also *Footnote 1*.

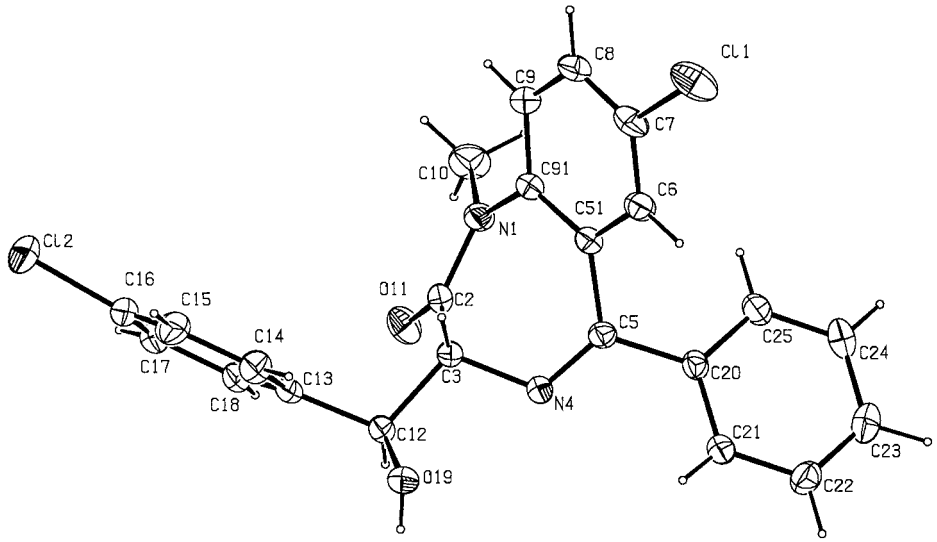


Fig. 1. *ORTEP* [9] *View of* **5**. Arbitrary atom numbering; the thermal ellipsoids are scaled at the 30% level.

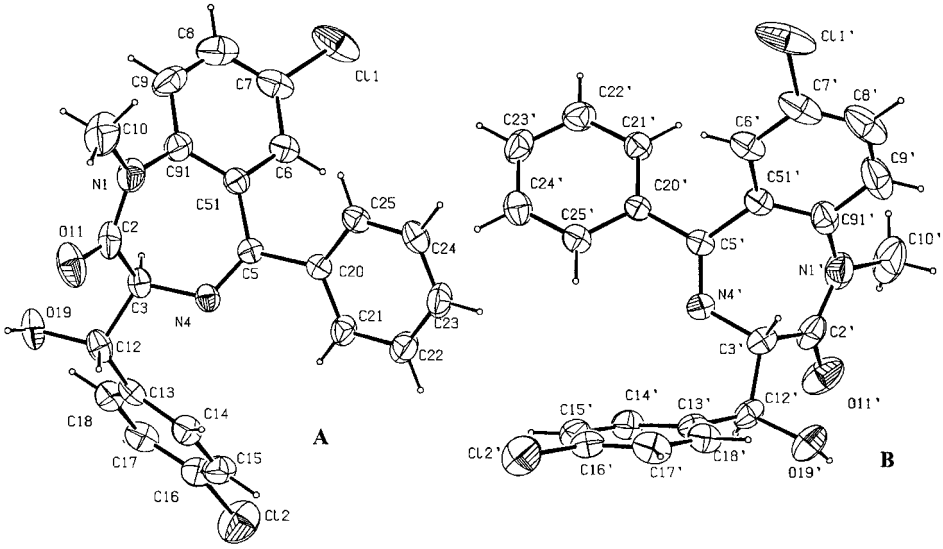


Fig. 2. *ORTEP* [9] *View of* **6** (**A** and **B**). Arbitrary atom numbering; the thermal ellipsoids are scaled at the 30% level.

same relative configuration ((3*R*,12*R*) and its enantiomer), and the conformation is *erythro* (torsion angle 179.7(4)° for **A** and −177.4(4)° for **B**). Thus, the group O(19)–H in **5** is oriented towards N(4), whereas in **6**, it is in the vicinity of the carbonyl O(11)-atom. As a consequence, two chemically distinctive H-bonds are present in **5** and **6** (*Table 6*). In both crystal structures, the centrosymmetric dimers are formed; in **5**,

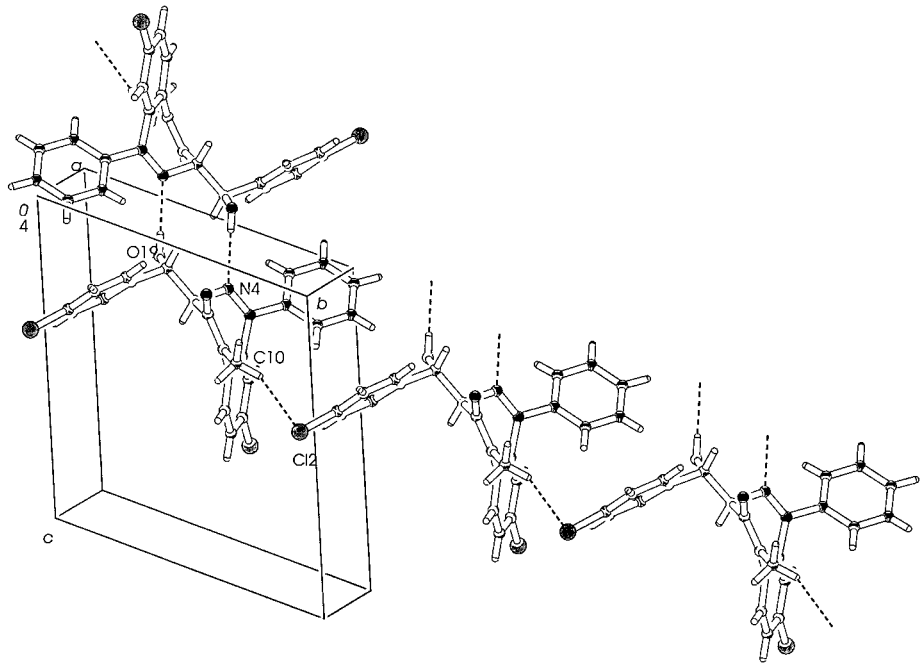


Fig. 3. *Crystal packing of* **5** *with dimers formed through O(19)–H···N(4) H-bonds, connected into an infinite chain* via *C(10)–H···Cl(2) interactions*

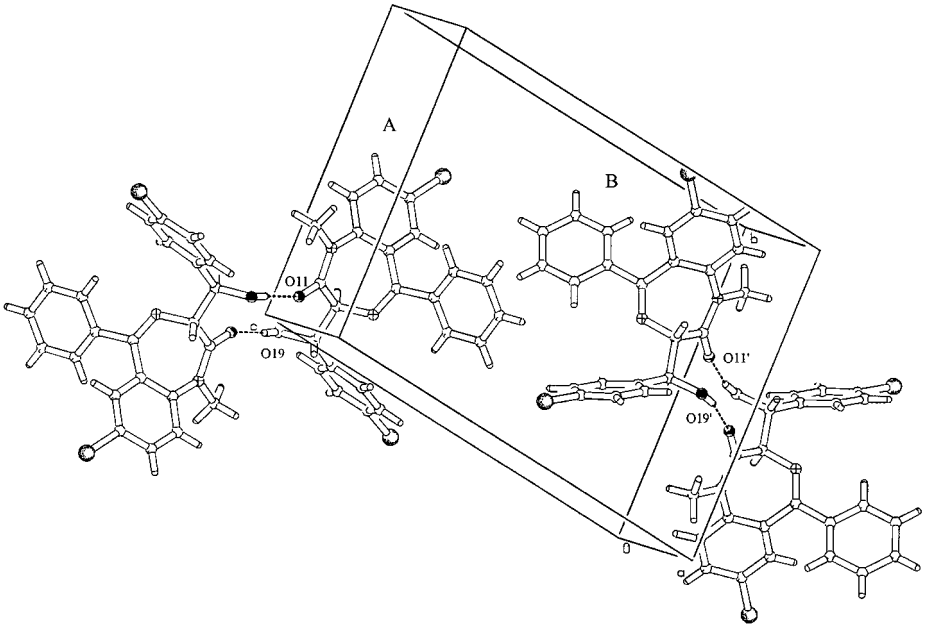


Fig. 4. *Crystal packing of* **6** *with dimers formed of molecules related by inversion symmetry* (**A**···**A**, **B**···**B**) *through O(19)–H···O(11) H-bonds*

Table 4. *Geometry of the 1,4-Benzodiazepine Ring in* **5** *and* **6**: *Bond lengths* [Å] *and Angles* [°]. For numbering, see *Figs. 1* and *2*.

	5	**6**	
		Molecule **A**	Molecule **B**
N(1)–C(2)	1.374(3)	1.37(1)	1.36(1)
C(2)–O(11)	1.209(3)	1.225(7)	1.221(8)
C(2)–C(3)	1.519(4)	1.526(7)	1.514(8)
C(3)–N(4)	1.467(3)	1.461(6)	1.473(7)
N(4)–C(5)	1.286(4)	1.279(6)	1.275(6)
C(5)–C(51)	1.491(3)	1.482(7)	1.497(7)
C(51)–C(91)	1.395(4)	1.392(7)	1.399(8)
C(2)–N(1)–C(91)	124.0(2)	123.5(5)	123.6(5)
C(3)–C(2)–N(1)	115.5(2)	116.9(5)	115.0(5)
C(2)–C(3)–N(4)	104.7(2)	104.7(4)	105.6(5)
C(3)–N(4)–C(5)	116.5(2)	117.7(4)	117.9(4)
N(4)–C(5)–C(51)	124.0(2)	125.1(4)	123.3(4)
C(5)–C(51)–C(91)	122.3(2)	122.0(5)	122.5(5)
C(51)–C(91)–N(1)	121.7(2)	121.9(5)	121.3(5)

Table 5. *Selected Torsional Angles* [°] *of* **5** *and* **6**. For numbering, see *Figs. 1* and *2*.

	5	**6**	
		Molecule **A**	Molecule **B**
C(3)–C(2)–N(1)–C(91)	3.8(4)	– 0.4(7)	1.5(8)
C(2)–N(1)–C(91)–C(51)	40.3(4)	– 43.9(8)	– 47.9(9)
N(1)–C(91)–C(51)–C(5)	0.3(5)	3.1(8)	6.2(9)
C(91)–C(51)–C(5)–N(4)	– 46.7(4)	43.1(7)	40.8(8)
C(51)–C(5)–N(4)–C(3)	2.6(4)	– 0.1(6)	0.2(8)
C(5)–N(4)–C(3)–C(2)	73.3(3)	– 72.7(5)	– 74.5(6)
N(4)–C(3)–C(2)–N(1)	– 78.2(2)	74.5(5)	75.2(6)
N(4)–C(3)–C(12)–O(19)	56.9(2)	179.7(4)	– 177.4(4)
N(4)–C(3)–C(12)–C(13)	178.3(2)	– 57.5(6)	– 55.4(6)
N(4)–C(5)–C(20)–C(21)	– 36.9(4)	30.0(6)	– 147.9(5)

Table 6. *H-Bonds in the Crystals of* **5** *and* **6**. For numbering, see *Figs. 1* and *2*.

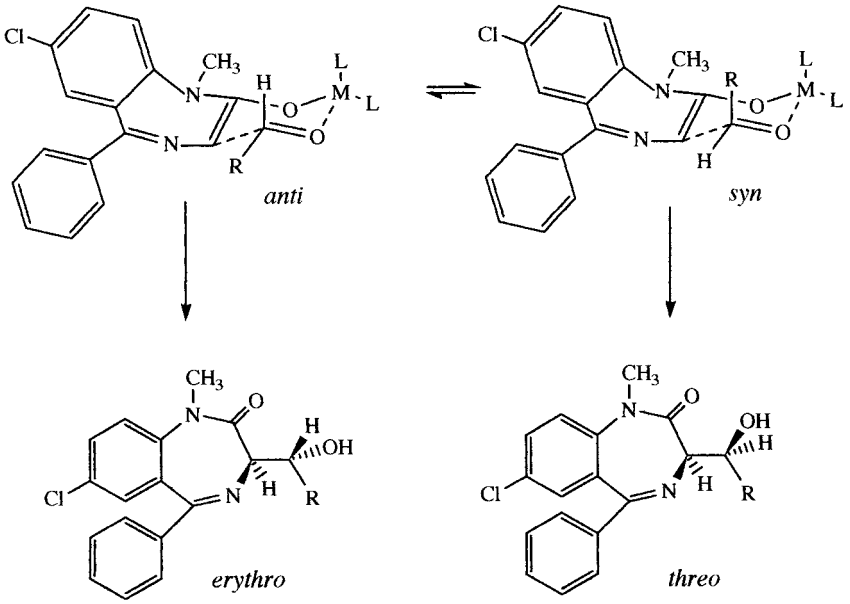
H-Bond	*D*-H*A* [Å]	*D*-H [Å]	H-*A* [Å]	*D*-H*A* [°]	Symmetry operations on *A*
5: O(19)–H(19)···N(4)	2.934(2)	0.801	2.134	175	$1-x, 1-y, -z$
6: O(19)–H(19)···O(11)	2.770(5)	0.820	1.951	177	$-x, -y, 2-z$
O(19A)–H(19A)···O(11A)	2.723(6)	0.820	1.916	168	$1-x, 1-y, -z$

O(19)–H···N(4) completes a $R^2_2(10)$ ring (*Fig. 3*), whereas in **6** the $R^2_2(12)$ motif is generated *via* the O(19)–H···O(11) H-bond (*Fig. 4*) [10]. In the crystal packing of **5**, a weak interaction C(10)–H···Cl connects dimers to an infinite chain (*Fig. 3*).

The H-bonding patterns in the crystal and in solution are completely different. Whereas in the crystal, both diastereoisomers **5** and **6** exhibit intermolecular H-bonding, in solution, only the *erythro*-diastereoisomer is conformationally stabilized by intramolecular H-bonding.

2.4. *Mechanism of the Aldol Reaction*. The aldol reaction is reversible, but may be controlled, according to conditions and the nature of partners, either kinetically or thermodynamically. The *syn*/*anti* stereochemistry of addition under kinetic control can be successfully rationalized by considering the geometry of the transition state. In the majority of cases, a cyclic transition state is the most probable [11][12]. We assumed that the C(3) carbanion of **2** is delocalized, forming a cyclic (*E*)-enolate anion (*Scheme 2*). According to the repeatedly proposed mechanism [13][8b], this enolate anion coordinates the carbonyl electrophile *via* the lithium cation. It seems that specific steric requirements around the C(3) carbanion of the 1,3-dihydro-2*H*-1,4-benzodiazepine-2-one, in particular the effects of ring puckering and the proximity of the annellated aromatic ring and 5-phenyl group, preclude an optimal approach of bulky aldehydes and diminish the enthalpy difference of the two transition states due to complex steric interactions within both transition states (*Scheme 2*).

Scheme 2

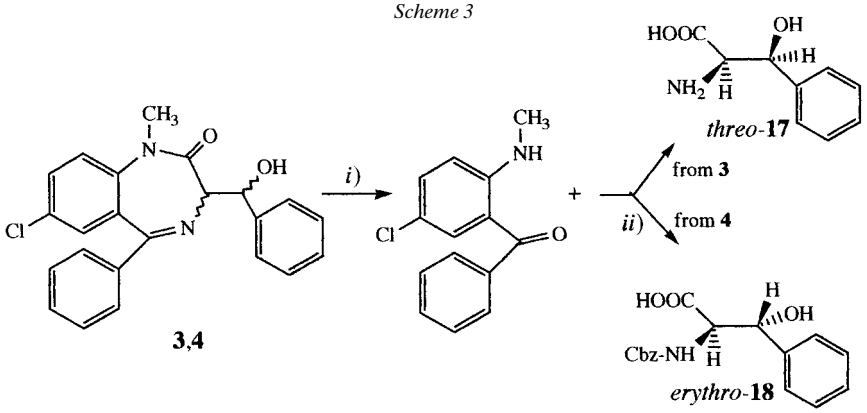


In a recent paper [14], we have reported that, under similar reaction conditions, 2 mol of formaldehyde can react with the C(3) carbanion of **2**, *i.e.* formation of a tertiary carbanion occurs. Such a carbanion derived from **3**–**16**, if not attacked by the second mol of the sterically bulky aldehyde, can epimerize. To examine the influence of epimerization at C(3) on the diastereoselectivity of the aldol reaction, pure **4** was treated with an excess of base at −78°. HPLC Control of the reaction revealed a very slow epimerization; after 8 h, a 40:60 ratio of **3**/**4** was reached. Since no traces of **2** were observed by HPLC, epimerization *via retro*-aldol reaction can be excluded. However, HPLC monitoring of the aldol reaction, which is usually completed within 30 min, revealed that the product ratio does not vary with time; thus, epimerization at C(3) can have only a minor influence on the product ratio. The most acceptable

explanation seems to be that the carbanion formed by the attack of the base is very similar to the transition state shown in *Scheme 2*, leading thus to a constant ratio of diastereoisomers.

2.5. *Synthetic Utility of the Aldol Reaction*. To establish the feasibility of the investigated aldol reaction as a new approach to α-amino-β-hydroxycarboxylic acids, diastereoisomer **3** was subjected to acid-catalyzed hydrolytic ring opening, affording *erythro*-β-hydroxy-phenylalanine **18** (*Scheme 3*), which was isolated as ammonium salt. Similarly, **4** afforded *threo*-β-hydroxy-phenylalanine, which was isolated in 45% yield as the *N*-(benzyloxy)carbonyl derivative **18**. In both cases, neither epimerization nor elimination of H_2O, to form a C(3)=C(12)[2]) bond, was observed.

Scheme 3



i) conc. HCl soln./H_2O/MeOH 3:1:3. *ii*) CbzCl/aq. NaOH

In summary, we have described the first examples of a diastereoselective aldol condensation of the C(3) carbanion of a 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one. The condensation proceeds with good yield and, in the case of aliphatic aldehydes, also with high diastereoselectivity. Diastereoisomeric products can be separated and hydrolyzed to *rac*-α-amino-β-hydroxycarboxylic acids. Our future work will be focused on the understanding of the nuances of diastereoselectivity of this process and on its enantioselective version.

Experimental Part

General. TLC: Precoated silica-gel thin-layer sheets *60 F 254* from *Merck*. Prep. column chromatography (CC): silica gel (*Baker*, 63–200 μm). Ion-exchange chromatography: *Amberlite XAD-16* (*Rohm & Haas*, 20–50 mesh). HPLC: *Hewlett-Packard-1050* instrument, *HP-3396A* integrator; detection at 254 nm; *RP 18* column (*Nucleosil* 200 × 4 mm, 7 μm); flow rate 0.8 ml/min; gradient elution from 100% *A* to 100% *B* within 20 min (*A* = 50% aq. MeOH, *B* = MeOH). M.p.: *Electrothermal-9100-MP* aparatus; no correction. IR: *Perkin-Elmer 297*; KBr pellets; in cm^{-1}. NMR: *Varian XL-Gem 300*; $CDCl_3$ solns., if not stated otherwise; δ in ppm rel. to $SiMe_4$, *J* in Hz.

Aldol Reaction: General Procedure. A soln. of 2.5M BuLi in hexane (4.93 ml, 11.2 mmol) was added at 0° to a soln. of $(i\text{-Pr})_2NH$ (1.17 ml, 8.4 mmol) in THF (20 ml) under Ar. After 30 min, the stirred mixture was cooled to −78° (dry ice/acetone), and a soln. of **2** (0.8 g, 2.8 mmol) in THF (12.5 ml) was added *via* syringe. After 30 min stirring, the soln. of the aldehyde in dry THF (5.6 mmol in 12.5 ml) was added dropwise. The reaction was followed by TLC (CH_2Cl_2/AcOEt 9:1) and the final diastereomer composition determined by HPLC. The diastereoisomer mixtures were obtained in 65–83% yield, and the diastereoisomers were separated by CC (silica gel, CH_2Cl_2/AcOEt 9:1).

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-hydroxy(phenyl)methyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**3**; *threo*): M.p. 215–217°. IR: 3450, 1670, 1605, 1480, 1400, 1320, 1110, 700. ^{1}H-NMR: 3.38 (*s*, 3 H); 3.69 (*d*, *J* = 5.1, 1 H); 4.34 (*s*, 1 H); 5.60 (*d*, *J* = 4.9, 1 H); 7.26–7.59 (*m*, 13 H). ^{13}C-NMR: 35.0; 68.1; 72.4; 123.0; 127.5; 127.6; 128.1; 128.4; 129.6; 129.9; 130.2; 130.9; 131.7; 137.8; 141.1; 141.8; 168.5; 169.7. Anal. calc. for $C_{23}H_{19}ClN_2O_2$ (390.87): C 70.68, H 4.90, N 7.17; found: C 70.64, H 5.16, N 7.18.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-hydroxy(phenyl)methyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**4**; *erythro*): M.p. 173–174°. IR: 3450, 1660, 1605, 1480, 1400, 1320, 1110, 695. ^{1}H-NMR: 3.44 (*s*, 3 H); 3.64 (*d*, *J* = 9.0, 1 H); 3.90 (*d*, *J* = 2.8, 1 H); 5.69 (*d*, *J* = 9.0, 1 H); 7.12–7.53 (*m*, 13 H). ^{13}C-NMR: 35.0; 69.1; 74.0; 122.9; 127.4; 127.6; 128.0; 128.3; 129.5; 129.8; 130.1; 130.7; 131.6; 131.8; 140.6; 141.6; 167.0; 170.9. Anal. calc. for $C_{23}H_{19}ClN_2O_2$ (390.87): C 70.68, H 4.90, N 7.17; found: C 70.97, H 4.99, N 7.06.

*(3*RS*)-7-Chloro-3-[(1*SR*)-(4-chlorophenyl)hydroxymethyl]-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**5**; *threo*): M.p. 183–184°. IR: 3450, 1670, 1605, 1480, 1400, 1320, 1110, 700. ^{1}H-NMR: 3.38 (*s*, 3 H); 3.62 (*d*, *J* = 5.1, 1 H); 4.36 (*s*, 1 H); 5.56 (*d*, *J* = 4.9, 1 H); 7.12–7.53 (*m*, 12 H). ^{13}C-NMR: 35.0; 68.0; 71.9; 123.0; 128.2; 128.5; 128.9; 129.6; 129.7; 129.9; 130.1; 131.0; 133.8; 133.3; 137.7; 139.6; 141.7; 168.7; 169.6. Anal. calc. for $C_{23}H_{18}Cl_2N_2O_2$ (425.36): C 64.95, H 4.27, N 6.59; found: C 64.86, H 4.22, N 6.63.

*(3*RS*)-7-Chloro-3-[(1*RS*)-(4-chlorophenyl)hydroxymethyl]-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**6**; *erythro*): M.p. 189–190°. IR: 3500, 1660, 1605, 1480, 1400, 1320, 1120, 700. ^{1}H-NMR: 3.45 (*s*, 3 H); 3.56 (*d*, *J* = 9.2, 1 H); 3.90 (*d*, *J* = 3.1, 1 H); 5.67 (*dd*, *J* = 9.0, 3.1, 1 H); 7.19–7.60 (*m*, 12 H). ^{13}C-NMR: 35.0; 69.0; 73.4; 122.8; 128.1; 128.4; 128.7; 129.4; 129.8; 130.1; 130.8; 131.6; 133.3; 137.6; 139.1; 141.5; 155.1; 167.2; 170.8. Anal. calc. for $C_{23}H_{18}Cl_2N_2O_2$ (425.36): C 64.95, H 4.27, N 6.59; found: C 64.77, H 4.51, N 6.53.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-hydroxy(4-nitrophenyl)methyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**7**; *threo*): M.p. 95° (dec.). IR: 3450, 1670, 1600, 1520, 1400, 1350, 1110, 700. ^{1}H-NMR: 3.42 (*s*, 3 H); 3.66 (*d*, *J* = 4.6, 1 H); 4.58 (*s*, 1 H); 5.68 (*d*, *J* = 4.1, 1 H); 7.25–8.20 (*m*, 12 H). ^{13}C-NMR: 35.1; 67.6; 71.9; 123.0; 123.3; 128.3; 128.5; 129.5; 129.8; 130.0; 131.2; 132.0; 137.5; 141.5; 147.4; 148.4; 153.0; 169.0; 169.6. Anal. calc. for $C_{23}H_{18}ClN_3O_4$ (435.87): C 63.38, H 4.16, N 9.64; found: C 63.56, H 4.44, N 9.61.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-hydroxy(4-nitrophenyl)methyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**8**; *erythro*): M.p. 224–225°. IR: 3500, 1660, 1605, 1520, 1350, 840, 690. ^{1}H-NMR: 3.47 (*s*, 3 H); 3.58 (*d*, *J* = 9.0, 1 H); 4.02 (*d*, *J* = 2.4, 1 H); 5.79 (*d*, *J* = 9.0, 1 H); 7.17–8.23 (*m*, 12 H). ^{13}C-NMR: 35.1; 69.0; 73.2; 122.9; 123.1; 128.3; 128.5; 129.4; 129.9; 130.0; 131.0; 131.8; 137.5; 141.4; 147.5; 148.1; 153.2; 167.2; 170.5. Anal. calc. for $C_{23}H_{18}ClN_3O_4$ (435.87): C 63.38, H 4.16; N 9.64; found: C 63.52, H 4.42, N 9.56.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-hydroxy(4-methoxyphenyl)methyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**9**; *threo*): M.p. 188–189°. IR: 3300, 1680, 1600, 1510, 1400, 1240, 1100, 830, 700. ^{1}H-NMR: 3.37 (*s*, 3 H); 3.66 (*d*, *J* = 5.4, 1 H); 3.79 (*s*, 3 H); 4.22 (*s*, 1 H); 5.55 (*d*, *J* = 4.9, 1 H); 6.88 (*d*, *J* = 8.7, 2 H); 7.25–7.60 (*m*, 10 H). ^{13}C-NMR: 34.9; 55.0; 68.2; 72.0; 113.4; 122.9; 128.4; 128.6; 129.6; 129.9; 130.2; 131.7; 133.2; 137.7; 139.5; 141.8; 159.0; 168.4; 169.6. Anal. calc. for $C_{24}H_{21}ClN_2O_3$ (420.90): C 68.49, H 5.03, N 6.66; found: C 68.26, H 5.17, N 6.51.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-hydroxy(4-methoxyphenyl)methyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**10**; *erythro*): M.p. 171–172°. IR: 3400, 1660, 1510, 1400, 1240, 1030, 820. ^{1}H-NMR: 3.45 (*s*, 3 H); 3.62 (*d*, *J* = 8.7, 1 H); 3.81 (*s*, 3 H); 5.67 (*d*, *J* = 9.0, 1 H); 6.91 (*m*, 2 H); 7.30–7.53 (*m*, 10 H). ^{13}C-NMR: 35.0; 55.0; 69.2; 73.5; 113.4; 122.8; 128.3; 128.5; 129.5; 129.8; 130.1; 130.7; 131.6; 132.8; 137.8; 141.7; 159.0; 167.0; 171.0. Anal. calc. for $C_{24}H_{21}ClN_2O_3$ (420.90): C 68.49, H 5.03, N 6.66; found: C 68.54, H 5.05, N 6.71.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-1-hydroxypropyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**12**; *erythro*): M.p. 167–168°. IR: 3500, 1670, 1605, 1480, 1400, 1110, 690. ^{1}H-NMR: 1.09 (*t*, *J* = 7.4, 3 H); 1.36–1.46 (*m*, 1 H); 1.94–2.01 (*m*, 1 H); 3.37 (*d*, *J* = 9.0, 1 H); 3.42 (*s*, 3 H); 4.51–4.57 (*m*, 1 H); 7.26–7.59 (*m*, 8 H). ^{13}C-NMR: 9.7; 25.4; 29.5; 34.9; 67.7; 72.8; 122.8; 128.4; 129.4; 129.7; 130.4; 130.8; 131.6; 137.8; 141.8; 167.4; 171.0. Anal. calc. for $C_{19}H_{19}ClN_2O_2$ (342.83): C 66.57, H 5.59, N 8.17; found: C 66.49, H 5.62, N 8.16.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-1-hydroxybutyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**13**; *threo*): M.p. 158–159°. IR: 3450, 1670, 1620, 1480, 1400, 1325, 1110, 695. ^{1}H-NMR: 0.95 (*t*, *J* = 6.9, 3 H); 1.40–1.72 (*m*, 4 H); 3.40 (*s*, 3 H); 3.42 (*s*, 1 H); 3.80 (*s*, 1 H); 4.42 (*s*, 1 H); 7.26–7.67 (*m*, 8 H). ^{13}C-NMR: 13.9; 18.7; 34.8; 35.5; 66.2; 70.1; 122.8; 128.4; 129.6; 129.8; 130.4; 130.9; 131.6; 137.8; 142.0; 168.4; 170.5.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-1-hydroxybutyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**14**; *erythro*): M.p. 157–158°. IR: 3500, 1675, 1610, 1480, 1400, 1120, 825, 690. ^{1}H-NMR: 1.00 (*t*, *J* = 7.4, 3 H); 1.31–1.90 (*m*, 4 H); 3.35 (*d*, *J* = 8.46, 1 H); 3.37 (*s*, 1 H); 3.41 (*s*, 3 H); 4.62 (*m*, 1 H); 7.26-7.56 (*m*, 8 H). ^{13}C-NMR: 14.0; 18.5; 34.9; 34.9; 68.0; 71.4; 122.8; 128.4; 129.5; 129.7; 130.4; 130.8; 131.6; 137.8; 141.9; 167.4; 171.0. Anal. calc. for $C_{20}H_{21}ClN_2O_2$ (356.85): C 67.32, H 5.93, N 7.85; found: C 67.15, H 5.66, N 7.75.

Table 7. *Crystallographic Data, Structure Solutions, and Refinement of* **5** *and* **6**

	5	**6**
Formula	$C_{23}H_{18}Cl_2N_2O_2$	$C_{23}H_{18}Cl_2N_2O_2$
Solvent	–	–
M_r	425.31	425.31
Crystal system	triclinic	triclinic
Space group	*P*-1	*P*-1
a [Å]	8.490(2)	10.25(1)
b [Å]	10.410(2)	12.32(1)
c [Å]	12.462(4)	17.59(1)
α [°]	70.39(2)	81.05(7)
β [°]	75.26(3)	76.16(7)
γ [°]	87.31(3)	87.8(1)
V[Å^3]	1002.5(5)	2130(3)
Z	2	4
F(000)	440	880
D_x [Mgm^{-3}]	1.4(4)	1.34(2)
Radiation	MoK_α	MoK_α
Wavelength [Å]	0.71069	0.71069
Range [°]	3.81 – 19.91	4.68 – 10.70
μ [mm^{-1}]	0.35	0.33
Temp. [K]	295(5)	295(5)
Crystal form	plate	plate
Crystal size [mm]	$0.12 \times 0.08 \times 0.13$	$0.16 \times 0.08 \times 0.22$
Crystal color	Colorless	Colorless
Data-collection method	θ scans	2θ scans
Absorption correction	no correction	no correction
Total data collected	4311	9129
Unique data	4075	8624
Observed data (criterion)	2456 ($I > 2(I)$)	2985 ($I > 2(I)$)
R_{int}	0.0332	0.0361
θ_{max} [°]	≤ 26.32	≤ 26.32
Range of *h*, *k*, *l*	$-10 \leq h \geq 10$	$-12 \leq h \geq 0$
	$0 \leq k \geq 13$	$-15 \leq k \geq 15$
	$-15 \leq l \geq 15$	$-21 \leq l \geq 21$
No. of standard reflections	3	3
Frequency of standard reflections [min]	120	180
Intensity decay [%]	2.9	0.6
Refinement on	F^2	F^2
R_1 ($F_o > \sigma(F_o)$)	0.041	0.050
$wR2$ (F^2), all data	0.1215	0.1021
S	0.82	0.77
Parameters	324	544
Weighting scheme	$w = 1/[2(F_o^2) + (0.0401P)^2 + 0.46P]$ where $P = (F_o^2 + 2F_c^2)/3$	
$\Delta\rho$ (max; min) [eÅ^{-3}]	0.22, −0.25	0.23, −0.26
Data-reduction programme	HELENA [15]	HELENA
Structure-solution programme	SIR97 [16]	SIR97
Structure-refinement programme	SHELXL97 [17]	SHELXL97
Preparation of material for publication (programme)	PLATON98 [18]	PLATON98

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-1-hydroxy-3-methylbutyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**16**; *erythro*): M.p. 189–191°. IR: 3520, 1670, 1610, 1480, 1400, 1120, 695. ^{1}H-NMR: 0.99 (*d*, *J* = 6.7, 3 H); 1.05 (*d*, *J* = 6.4, 3 H); 1.25–1.37 (*m*, 1 H); 1.56–1.64 (*m*, 1 H); 1.96–2.08 (*m*, 1 H); 3.31–3.36 (*m*, 2 H); 3.41 (*s*, 3 H); 4.62–4.69 (*m*, 1 H); 7.71–7.64 (*m*, 8 H). ^{13}C-NMR: 21.6; 23.9; 24.2; 34.8; 42.1; 68.5; 69.9; 122.8; 128.4; 129.5; 129.7; 130.4; 130.8; 131.5; 137.8; 141.9; 167.2; 171.1. Anal. calc. for $C_{21}H_{23}ClN_2O_2$ (370.87): C 68.01, H 6.25, N 7.55; found: C 67.87, H 6.15, N 7.68.

*(α*RS*,β*SR*)-β-Hydroxy-phenylalanine Ammonium Salt* (**17** · NH_3; *threo*). A soln. of **3** (300 mg, 0.76 mmol) in a mixture of conc. HCl soln. (3.0 ml), H_2O (1.0 ml), and MeOH (3.0 ml) was refluxed for 18 h. The mixture was neutralized to pH 10 with 10% Na_2CO_3 soln. and was washed with CH_2Cl_2 (3 × 5 ml) to remove 5-chloro-2-(methylamino)benzophenone. Upon adjustment of the pH to 2.5 with 10% H_3PO_4 soln., the aq. soln. was purified by ion-exchange chromatography (*Amberlite XAD-16* (5 g), H_2O (50 ml), followed by 1% NH_3 soln. (50 ml)). Evaporation of the NH_3 eluate afforded 73 mg (44%) of **17** · NH_3, 99% pure by HPLC. M.p. 350°. IR: 3620, 3150, 1645, 1490, 1400, 1010, 705. ^{1}H-NMR (D_2O): 3.80 (*d*, *J* = 4.3, 1 H); 5.19 (*d*, *J* = 4.2, 1 H); 7.29–7.38 (*m*, 5 H). ^{13}C-NMR (D_2O): 61.7; 72.1; 126.8; 129.5; 129.9; 140.1; 173.0.

*(α*RS*,β*RS*)*-N-*[(Benzyloxy)carbonyl]-β-hydroxy-phenylalanine* (**18**; *erythro*). As described for **17** · NH_3, with **4** (1.0 g, 2.5 mmol), conc. HCl (9.0 ml), H_2O (3.0 ml), and MeOH (9.0 ml). After washing with CH_2Cl_2 (3 × 10 ml) the aq. soln. was treated at r.t. with benzyl carbonochloridate (0.7 ml, 5.1 mmol), in portions within 6 h. The mixture was stirred for additional 10 h and then extracted with Et_2O (2 × 10 ml). Upon adjustment of the pH to 3 with 5% HCl soln., the precipitated product was filtered and dried: 347 mg (45%) of **18**; 99% pure by HPLC. M.p. 350°. IR: 3400, 3330, 1695, 1540, 1250, 1020, 700. ^{1}H-NMR ((D$_6$)DMSO): 4.16 (*t*, *J* = 8.7, 1 H); 4.76 (*d*, *J* = 8.4, 1 H); 4.92 (*s*, 2 H); 7.13–7.55 (*m*, 10 H). ^{13}C-NMR ((D$_6$)DMSO): 60.6; 65.4; 72.6; 127.2; 127.6; 127.7; 127.9; 128.0; 128.6; 137.2; 142.5; 155.9; 172.7.

X-Ray Structure Determination of **5** *and* **6**. Compound **5** was crystallized from MeOH/CH_2Cl_2 3:1, and **6** from i-PrOH with a few drops of CH_2Cl_2. *Table 7* summarizes crystal data and experimental details of data collection, refinement, and software used. Intensities were measured on an *Enraf-Nonius-CAD4* diffractometer with graphite-monochromated MoK_α radiation using ω/θ (**5**) and $\omega/2\theta$ (**6**) scans. During measurements, there were no variations in intensities for three standard reflections. The data were corrected for *Lorentz* and polarization effects [15]. The crystal-structure determination of **6** revealed two molecules (**A** and **B**) in the asymmetric unit. The free rotation about the bonds C(12)–C(13)[1]) resulted in two slightly different conformers in the asymmetric unit. These two molecules are related by a pseudo inversion centre; a hypercentric distribution of the normalized structure factors was observed.

H-Atom coordinates of **5** were determined from the subsequent difference *Fourier* maps with exception of a Me group C(10); its H-atom positions were calculated on the basis of stereochemical considerations. For **6**, all H-atom positions were calculated on the basis of stereochemical considerations. Atomic scattering factors and anamalous dispersion values for the Cl-atoms were those included in SHELXL97 [17].

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-136204 and CCDC-136242. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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