Convenient Entry to α-Amino-β-hydroxy-γ-methyl Carboxylic Acids. Diastereoselective Formation and Directed Homogeneous Hydrogenation of 3-(3-Aryl-1-hydroxy-2-methylprop-2-enyl)-1,4-benzodiazepin-2-ones

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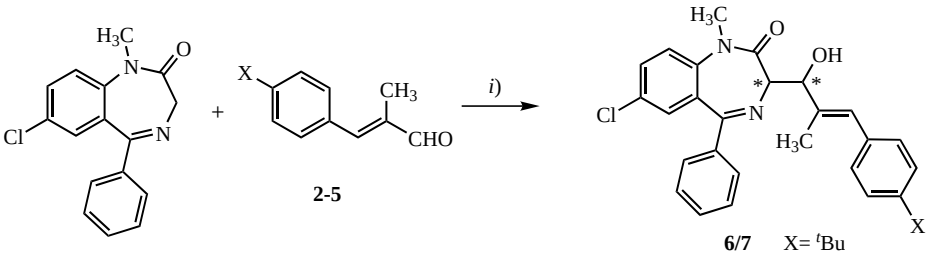
Aldol reaction of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1**) with 4-substituted α-methylcinnamaldehydes **2**–**5** afforded a mixture of *threo*- and *erythro*-3-(3-aryl-1-hydroxy-2-methylprop-2-enyl)-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-ones **6**–**13**. The chromatographically separated *threo* diastereoisomers **6**, **8**, **10**, and **12** and *erythro* diastereoisomers **7**, **9**, **11**, and **13** were submitted to 'directed' homogeneous hydrogenation catalyzed by $[Rh^{I}(cod)(diphos\text{-}4)]ClO_4$ (cod = cyclooctа-1,5-diene, diphos-4 = butane-1,4-diylbis[diphenylphosphine]. From the *erythro*-racemates **9**, **11**, and **13**, the *erythro,erythro*/*erythro,threo*-diastereoisomer mixtures **16**/**17**, **20**/**21**, and **24**/**25** were obtained in ratios of 20:80 to 28:72 (HPLC), which were separated by chromatography. From the *threo* racemates **8**, **10**, and **12**, the *threo,threo*/*threo,erythro*-diastereoisomer mixtures were obtained in a ratio of *ca.* 25:75 (^{1}H-NMR). The relative configurations were assigned by means of ^{1}H-NMR data and X-ray crystal-structure determination of **21**. Hydrolysis of **21** afforded the diastereoisomerically pure *N*-(benzyloxy)carbonyl derivative **27** of α-amino-β-hydroxy-γ-methylpentanoic acid **26**, representative of the novel group of polysubstituted α-amino-β-hydroxycarboxylic acids.

1. Introduction. – α-Amino-β-hydroxycarboxylic acids and their derivatives are present in numerous natural and biologically active compounds. Some of them are incorporated as intermediates in β-lactams [1a] or bound to sugars [1b]. D-Allothreonine is present in the antibiotics catanozin and acuminate [2], β-hydroxytyrosine and β-phenylserine are constituents of the antibiotics vancomycin, chloramphenicol, and catanozin [3a] and of some cyclic peptides [3b]. β-Hydroxyglutamine is found in the antibiotics neopeptin and acitulin [4], β-hydroxyleucine is present in lysobactin, hepaptin, and leuconostatin [5], whereas β-hydroxyproline and β-hydroxyaspartic acid are isolated from empedopeptin [6].

Continuing the project on the use of 1,4-benzodiazepin-2-one derivatives that comprise a glycine moiety in the conformationally rigid 7-membered ring as templates in stereoselective [7][8], catalytic [9], and biocatalytic [10–12] reactions, we entered the study of the aldol reaction with α,β-unsaturated aldehydes and diastereoselective, 'directed' homogeneous hydrogenation of the C=C bond in the diastereoisomeric aldol products. This tandem reactions, followed by hydrolytic ring opening and isolation of *N*-protected acids, opens the route to novel α-amino-β-hydroxy-γ-methylcarboxylic acids that we needed for the preparation of specific biologically active compounds.

2. Results and Discussion. – 2.1. *Diastereoselectivity of the Tandem Aldol/Hydrogenation Reaction*. The α-methylcinnamaldehydes **2**–**5** were prepared according to the reported protocol [13] and treated with the carbanion of **1** under conditions recently reported [8] (*Scheme 1*). The *threo*/*erythro* ratios[1]) of the product mixtures **6**/**7**, **8**/**9**, **10**/**11**, and **12**/**13**, respectively, were determined by reversed-phase HPLC (*Nucleosil C RP18*); under kinetic control, the second-eluted diastereoisomer was regularly formed as the prevailing product, while, on equilibration (thermodynamic control), the first-eluted diastereoisomer could be accumulated [8]. Thus, depending on the reaction conditions, the diastereoisomeric *erythro* or *threo* racemate could be produced as the major product. The ^{1}H-NMR spectra of the first-eluted diastereoisomers **6**, **8**, **10**, and **12** regularly reveal smaller J values (*ca.* 3–3.5 Hz), while, for the second-eluted diastereoisomers **7**, **9**, **11**, and **13**, much larger J values (> 9 Hz) are observed (*Table 1*).

Scheme 1



i) Lithium diisopropylamide, THF, –78°.

Table 1. *^{1}H-NMR Data for Diastereoisomeric Aldol Products* **6**–**13**. a = H–C(3), b = H–C(12)[2]).

First-eluted (*threo*)	δ_a [ppm]	δ_b [ppm]	J(a,b) [Hz]	Second-eluted (*erythro*)	δ_a [ppm]	δ_b [ppm]	J(a,b) [Hz]
6	3.71	5.04	3.3	**7**	3.67	5.25	9.1
8	3.73	5.06	3.6	**9**	3.69	5.28	9.3
10	3.70	5.02	3.6	**11**	3.68	5.26	9.3
12	3.72	5.04	3.3	**13**	3.68	5.26	9.3

According to our earlier assignment of ^{1}H-NMR spectra of diastereoisomeric aldol products obtained with benzaldehyde derivatives [8], coupling constants reveal *threo* configuration for the faster-eluting and *erythro* configuration for the slower-eluting diastereoisomers. Importantly, no *cis*/*trans* isomerization of the C=C bond is observed under these conditions. *trans* Configuration at the ArCH=C(Me)R bond in the starting α-methylcinnamaldehydes is maintained in the aldol products, as confirmed by the

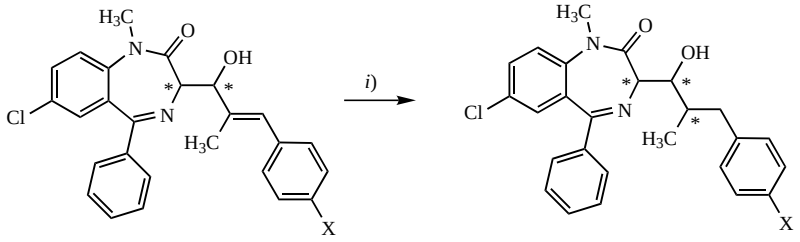
[1]) The descriptors *erythro*/*threo* are used in the traditional (carbohydrate) sense to describe the relative configurations at the two stereogenic N- and OH-substituted centers or at the two stereogenic OH- and Me-substituted centers.

[2]) Arbitrary numbering according to *Fig. 1* (see also *Scheme 3*).

NOESY spectra. All diastereoisomeric racemates were separated on the preparative scale by chromatography (silica gel) and then crystallized.

Hydrogenation of the C=C bond of the aldol products represents a reaction prone to being 'directed' by resident substrate functionalities, a property exceedingly valuable in stereoselective synthesis [14]. Since the Rh complex of the didentate bis[phosphine] ligand diphos-4 (= butane-1,4-diylbis[diphenylphosphine]) was repeatedly cited as specific catalyst for hydrogenation of a sterically hindered, internal allylic bond ($R(R^1)C=C(R^2)CH(R^3)OH$ [15–17], we attempted hydrogenation of **6**–**13** in the presence of $[(Rh(cod)(diphos\text{-}4)]ClO_4$ (cod = cycloocta-1,5-diene) (*Scheme 2*). In these substrates, coordination of Rh^I to the OH group (anchoring effect) is expected [18][19]. Completely regioselective reduction of the C=C bond in **6**–**13** was observed. Interestingly, diastereoisomers **6** and **7** proved resistant to hydrogenation, presumably by reason of the combined steric and electronic effects of the ^{t}Bu group. For the products from the *erythro* substrates **9**, **11**, and **13**, the diastereomer ratios ranged from 20:80 to 28:72 as determined by HPLC (*Table 2*). This method failed for the products of hydrogenation from the *threo* substrates **8**, **10**, and **12**, but the ^{1}H-NMR spectra revealed a *ca.* 75:25 diastereomer ratio for all hydrogenation products in this series (*Table 2*).

Scheme 2



8-13

14/15 X = H
16/17 X = H
18/19 X = Cl
20/21 X = Cl
22/23 X = MeO
24/25 X = MeO

i) $[Rh(cod)(diphos\text{-}4)]ClO_4$, H_2, CH_2Cl_2.

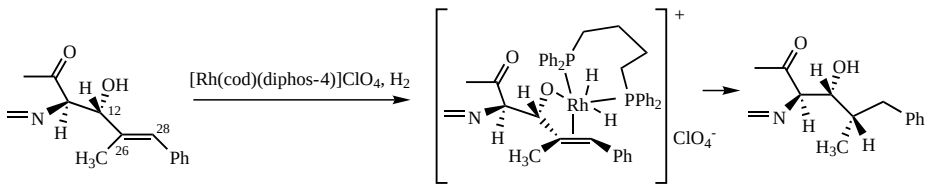
Table 2. *Diastereoselectivity in Hydrogenation of* **8**–**13** *by* $[Rh^I(cod)(diphos\text{-}4)]ClO_4$

Substrate	Products	Product ratio	Yield [%]
8	**14/15**	25:75[a])	68
9	**16/17**	20:80[b])	76
10	**18/19**	25:75[a])	26
11	**20/21**	23:77[b])	75
12	**22/23**	25:75[a])	50
13	**24/25**	28:72[b])	67

[a]) Determined by NMR. [b]) Determined by HPLC.

To determine the direction of diastereoselection in the hydrogenation, the relative *threo* or *erythro* configuration at the stereogenic OH-substituted C(12) and Me-substituted C(26) of the prevailing diastereoisomers was assigned. To predict the outcome of diastereoselection, the unsaturated starting diastereoisomeric compounds **8** and **9** were chosen for conformational analysis. The observation of *Dreiding* models and analysis based on MM2 calculations led to the following conclusion: *erythro* diastereoisomer **8**, with torsion angles ϕ of $-165°$ around the bond N(4)–C(3)–C(12)–OH and of $-146°$ around the bond H–C(12)–C(26)=C(28)[2]), should rotate on complexation to Rh^I by *ca.* $+45°$ to adopt a reactive conformation with *erythro*-eclipsed H–C(12) and C=C, and OH–C(12) coordinated to Rh^I [14]. For the *threo* diastereoisomer **9**, with torsion angles ϕ of $-40°$ for N(4)–C(3)–C(12)–OH and of $+147°$ for H–C(12)–C(26)=C(28)[2]), rotation by *ca.* $-45°$ is required to adopt an analogous reactive conformation in the complex. In such a complex, a H-atom is delivered to the C=C bond forming the third stereogenic center with the Me group *cis* to OH–C(12) (see *Scheme 3*). For the *erythro* (3*R*,12*R*) isomer, such a '*syn*' H-atom delivery should lead to (26*S*) configuration, *i.e.*, to 12,26-*threo* relative configuration of the OH and Me groups[2]). For the *threo* (3*R*,12*S*) isomer, '*syn*' H-transfer should lead to (26*R*) configuration, *i.e.*, to 12,26-*erythro* relative configuration of OH and Me groups[2]). This prediction for the outcome of the hydrogenation is confirmed by the X-ray crystal-structure analysis of the major diastereoisomer **21** obtained on hydrogenation of the *erythro* compound **11** (see below).

Scheme 3[2])



2.2. *Crystal Structure of* **21**. The crystal structure of **21** with the atom numbering is shown in *Fig. 1*. Characteristic bond lengths and angles are listed in *Table 3*, and the conformation of the seven-membered 1,4-benzodiazepine ring is described by the selected torsion angles given in *Table 4*. H-Bonds and weak interactions are listed in *Table 5*, and their pattern is shown in the crystal packing in *Fig. 2*.

The crystal structure of **21** is the racemic mixture of (*R*,*R*,*S*) and (*S*,*S*,*R*) enantiomers. The bonds C(3)–C(12) and C(12)–C(26) connect three sterogenic centers, and their relative configuration is *erythro*,*threo*; the corresponding torsion angle N(4)–C(3)–C(12)–O(19) is $-174.4(2)°$. The seven-membered ring adopts a boat conformation. The hydroxy group H–O(19) is oriented towards the carbonyl O(11) atom, and H–C(26) is in the vicinity of the N(4) atom. Thus, the molecule is conformationally stabilized by the intramolecular H-bond O(19)–H···O(11) and weak interaction C(26)–H···N(4). In the structure of **21**, the centrosymmetric dimers

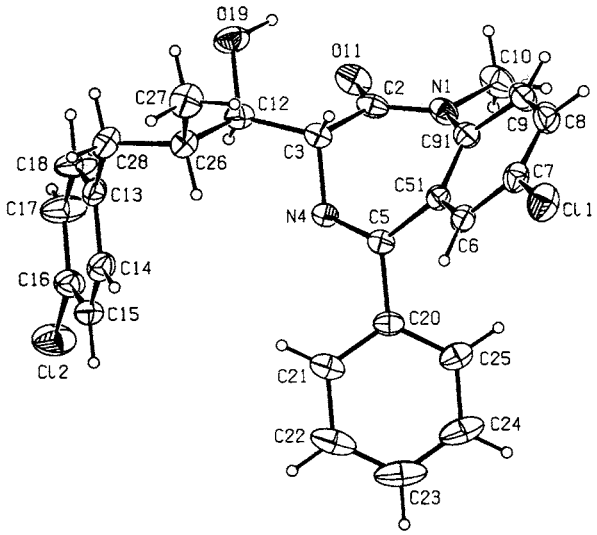


Fig. 1. *ORTEP View of* **21**. Arbitrary numbering; the thermal ellipsoids are scaled at the 30% level.

Table 3. *Geometry of the 1,4-Benzodiazepine Ring in* **21**: *Bond Lengths* [Å] *and Angles* [°]. For numbering, see *Fig. 1*.

N(1)–C(2)	1.365(3)	O(11)–C(2)	1.227(3)
N(1)–C(91)	1.414(3)	C(2)–C(3)	1.523(4)
N(4)–C(5)	1.279(3)	C(5)–C(51)	1.483(3)
N(4)–C(3)	1.465(3)	C(51)–C(91)	1.396(3)
C(2)–N(1)–C(91)	122.9(2)	N(4)–C(3)–C(12)	108.4(2)
C(5)–N(4)–C(3)	117.5(2)	N(4)–C(5)–C(51)	123.9(2)
N(1)–C(2)–C(3)	116.0(2)	C(91)–C(51)–C(5)	121.4(2)
N(4)–C(3)–C(2)	107.0(2)	C(51)–C(91)–N(1)	122.2(2)

Table 4. *Selected Torsion Angles* [°] *of* **21**. For numbering, see *Fig. 1*.

C(91)–N(1)–C(2)–C(3)	– 7.2(4)	C(5)–N(4)–C(3)–C(2)	73.8(3)
C(2)–N(1)–C(91)–C(51)	48.2(4)	N(1)–C(2)–C(3)–N(4)	– 70.0(3)
C(5)–C(51)–C(91)–N(1)	– 1.5(4)	N(4)–C(3)–C(12)–O(19)	– 174.4(2)
N(4)–C(5)–C(51)–C(91)	– 44.9(2)	N(4)–C(3)–C(12)–C(26)	63.6(3)
C(3)–N(4)–C(5)–C(51)	0.3(4)	N(4)–C(5)–C(20)–C(21)	– 32.7(4)

are formed by means of two weak interactions: the first one, C(17)–H···O(19)^{i}, completes the $R^2_2(16)$ ring, while the other, C(9)–H···O(11)^{ii}, connects the dimers into a three-dimensional network where the equivalent positions are denoted as $i = -1/2 - x, 1/2 + y, 1/2 - z$ and $ii = -1/2 - x, 1/2 - y, 1 - z$.

2.3. *Synthetic Utility of the Sequence Aldol Reaction/Directed Hydrogenation/Hydrolysis.* To complete this study, we selected racemic **21** for hydrolysis under optimized conditions; the intermediate **26** was transformed without isolation into *N*-(benzyloxy)carbonyl (*N*–Z) derivative **27** (*Scheme 4*).

Table 5. *H-Bonds and Weak Interactions of* **21**. For numbering, see *Fig. 1*.

H-Bond	D–HA [Å]	D–H [Å]	H–A [Å]	D–H–A [°]	Symmetry operations on A
O(19)–H(19)···O(11)	2.829(3)	1.121(2)	2.028(2)	125.4(1)	
C(26)–H(26)···N(4)	2.968(3)	0.980(3)	2.536(2)	106.6(2)	
C(9)–H(9)···O(11)	3.289(4)	0.930(3)	2.463(2)	148.0(2)	$-1/2-x$, $1/2+y$, $1/2-z$
C(17)–H(17)···O(19)	3.306(5)	0.930(4)	2.586(2)	134.6(3)	$-1/2-x$, $1/2-y$, $1/2-z$

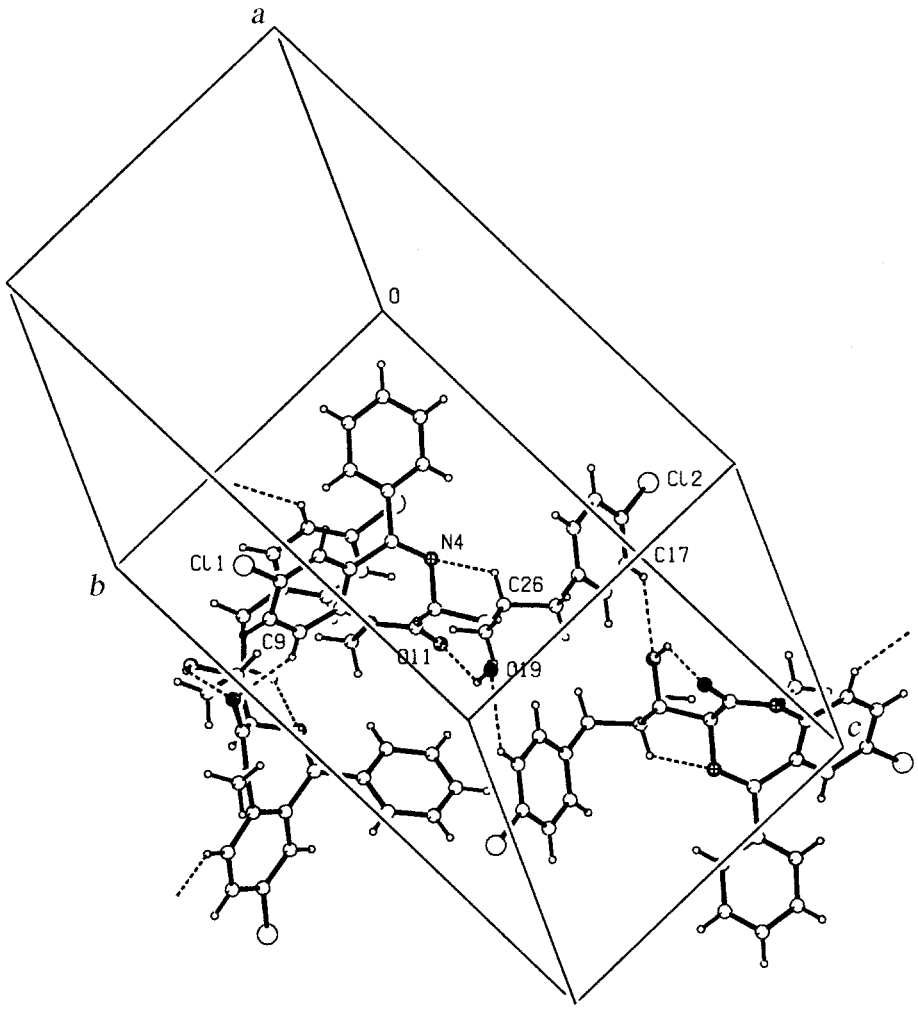
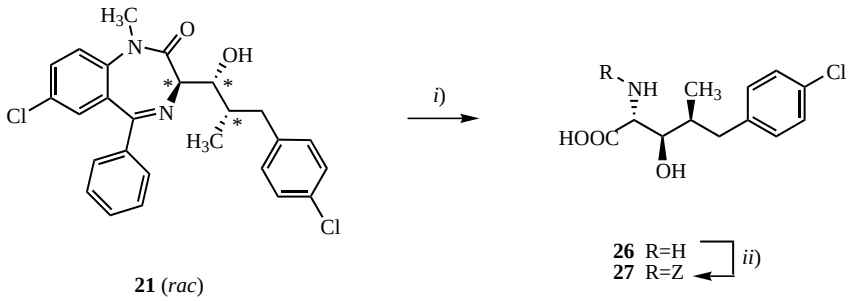


Fig. 2. *Crystal packing of* **21** *with centrosymmetric dimers formed through O(19)–H···O(11) and C(26)–H···N(4) H-bonds*

Simple recovery and recycling of 2-amino-5-chloro-1,4-benzophenone into 1,4-benzodiazepine derivative **1** contributes to the utility of the overall synthetic entry to the title compounds.

Scheme 4



i) Conc. HCl soln., AcOH, Δ. *ii*) Z-Cl, aq. NaOH soln.

3. Conclusions. – We have demonstrated the convenience of a diastereoselective approach to novel α-amino-β-hydroxy-γ-methylcarboxylic acids starting from the 1,4-benzodiazepine derivative **1** as an 'anchoring' template for the aldol reaction with α,β-unsaturated aldehydes. The obtained allylic alcohol intermediates undergo diastereoselective hydrogenation by an achiral Rh^I complex. The final products can be obtained by the one-pot hydrolysis of the heterocyclic precursors and Z protection of the amino acid formed. Such *N*-protected amino acids are envisaged as key intermediates in the preparation of a novel group of enantiomerically pure compounds with specific biological activity.

Experimental Part

General. All commercial reagents were used as received. Compounds **2**–**5** were prepared as reported [13]. HPLC: *HP-1050* chromatograph, *Nucleosil C18-RP* column, *HP-1050 UV* detector set up at 254 nm and connected to a *HP-3396A* integrator CC = Column chromatography. M.p.'s: *Electrothermal* melting-point apparatus; not corrected. IR Spectra: *Perkin-Elmer 297* spectrometer; KBr pellets; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian Gemini-XL-300* spectrometer; δ in ppm rel. to $SiMe_4$ as internal reference, *J* in Hz. Elemental analyses: they were determined by the combustion method in the Laboratory for Microanalysis, Karl Franzens University, Graz (Austria); HPLC purity of anal. samples, 99.5%.

Aldol Reaction: General Procedure. To the soln. of $^iPr_2NH$ (1.65 ml, 12 mmol) in dry THF (20.0 ml), 2.5M BuLi in hexane (4.7 ml, 12 mmol) was added under Ar at 0°. After 15 min stirring, the mixture was cooled to −78°, and a soln. of **1** (3.0 g, 9.1 mmol) in THF (20.0 ml) was slowly added, followed after 30 min by the soln. of an α-methylcinnamaldehyde **2**–**5** (20.0 mmol in 10 ml of THF). To achieve a high ratio of *erythro* isomer, the reaction was quenched after 10–15 min at −78° by addition of dil. aq. H_3PO_4 soln., adjusting the pH to 3.5; to achieve a high ratio of the *threo* isomer, the reaction was prolonged for *ca.* 1 h, allowing the mixture to reach r.t. Then the mixture was extracted with CH_2Cl_2 (3 × 50 ml) and the extract dried (Na_2SO_4) and evaporated. Diastereoisomer ratios were determined by HPLC (*Nucleosil C18*, 50 → 100% MeOH gradient within 20 min, flow rate 0.8 ml/min). The crude diastereoisomer mixtures were obtained in 70–80% yield. The diastereoisomers were separated by CC (silica gel, CH_2Cl_2/AcOEt 9:1).

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-1-hydroxy-3-[4-(*tert*-butyl)phenyl]-2-methylprop-2-enyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**6**; *threo*). M.p. 178.0–178.5°. IR (KBr): 3430, 1690, 1600, 1480, 1400, 1365, 1320, 1110, 945, 825, 700. ^{1}H-NMR ($CDCl_3$): 1.28 (*s*, 9 H); 1.92 (*s*, 3 H); 3.45 (*s*, 3 H); 3.71 (*d*, *J* = 3.3, 1 H); 5.03 (*d*, *J* = 3.3, 1 H); 6.79 (*s*, 1 H); 7.28–7.55 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 15.06; 31.14; 34.30; 35.11; 65.24; 74.50; 122.82; 124.77; 127.03; 128.30; 128.61; 129.5; 129.73; 130.04; 130.80; 131.67; 134.66; 136.07; 137.58; 141.78; 149.05; 168.05; 169.87. Anal. calc. for $C_{30}H_{31}ClN_2O_2$ (487.04): C 73.98, H 6.41, N 5.75; found: C 73.59, H 6.50, N 5.84.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-1-hydroxy-3-[4-(*tert*-butyl)phenyl]-2-methylprop-2-enyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**7**; *erythro*): M.p. 98.0–98.5°. IR (KBr): 3446, 1670, 1610, 1480, 1400, 1365, 1325, 1115, 945, 825, 700. ^{1}H-NMR ($CDCl_3$): 1.34 (*s*, 9 H); 1.86 (*s*, 3 H); 3.45 (*s*, 3 H); 3.67 (*d*, *J* = 9.1, 1 H); 5.25 (*d*, *J* = 9.3, 1 H); 6.78 (*s*, 1 H); 7.30–7.57 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 13.82; 31.21; 34.38; 35.1; 66.06; 77.51; 122.83; 124.89; 128.34; 128.66; 129.05; 129.48; 129.60; 130.04; 130.70; 131.57; 134.66; 135.25; 137.63; 141.71; 149.24; 166.81; 170.65. Anal. calc. for $C_{30}H_{31}ClN_2O_2$ (487.04): C 73.98, H 6.41, N 5.75; found: C 73.96, H 6.59, N 5.77.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-1-hydroxy-2-methyl-3-phenylprop-2-enyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**8**; *threo*): M.p. 154.0–155.0°. IR (KBr): 3440, 1680, 1610, 1480, 1400, 1325, 1110, 920, 830, 695. ^{1}H-NMR ($CDCl_3$): 1.89 (*s*, 3 H); 3.45 (*s*, 3 H); 3.75 (*d*, *J* = 3.6, 1 H); 5.06 (*d*, *J* = 3.0, 1 H); 6.82 (*s*, 1 H); 7.21–7.64 (*m*, 13 H). ^{13}C-NMR ($CDCl_3$): 14.99; 35.19; 65.07; 74.38; 122.88; 126.19; 127.39; 127.88; 128.37; 128.93; 129.59; 129.87; 130.99; 131.84; 136.68; 137.43; 137.60; 141.85; 168.25; 169.83. Anal. calc. for $C_{26}H_{23}ClN_2O_2$ (430.93): C 72.47, H 5.38, N 6.50; found: C 72.56, H 5.30, N 6.48.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-1-hydroxy-2-methyl-3-phenylprop-2-enyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**9**; *erythro*): M.p. 172.5–174.0°. IR (KBr): 3460, 1660, 1610, 1480, 1405, 1325, 1125, 900, 830, 700. ^{1}H-NMR ($CDCl_3$): 1.87 (*s*, 3 H); 3.47 (*s*, 3 H); 3.7 (*d*, *J* = 9.3, 1 H); 5.28 (*d*, *J* = 9.1, 1 H); 6.84 (*s*, 1 H); 7.24–7.58 (*m*, 13 H). ^{13}C-NMR ($CDCl_3$): 13.72; 35.11; 66.04; 77.43; 122.85; 126.35; 127.96; 128.34; 128.93; 129.26; 129.44; 129.53; 129.63; 130.02; 130.72; 131.60; 135.92; 137.55; 137.65; 141.73; 166.86; 170.62. Anal. calc. for $C_{26}H_{23}ClN_2O_2$ (430.93): C 72.47, H 5.38, N 6.50; found: C 72.20, H 5.26, N 6.41.

*(3*RS*)-7-Chloro-3-[(1*SR*)-3-(4-chlorophenyl)-1-hydroxy-2-methylprop-2-enyl]-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**10**; *threo*): M.p. 86.5–88.0°. IR (KBr): 3460, 1680, 1600, 1480, 1400, 1325, 1115, 700. ^{1}H-NMR ($CDCl_3$): 1.84 (*s*, 3 H); 3.44 (*s*, 3 H); 3.70 (*d*, *J* = 3.6, 1 H); 5.03 (*d*, *J* = 3.3, 1 H); 6.77 (*s*, 1 H); 7.22–7.62 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 14.98; 35.22; 64.90; 74.35; 122.9; 126.35; 128.05; 128.41; 129.58; 129.88; 130.21; 131.04; 131.87; 136.05; 137.34; 137.41; 141.83; 168.34; 169.80. Anal. calc. for $C_{26}H_{22}Cl_2N_2O_2$ (465.38): C 67.10, H 4.76, N 6.01; found: C 67.01, H 4.75, N 5.98.

*(3*RS*)-7-Chloro-3-[(1*RS*)-3-(4-chlorophenyl)-1-hydroxy-2-methylprop-2-enyl]-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**11**; *erythro*): M.p. 197.5–200.0°. IR (KBr): 3450, 1660, 1600, 1480, 1400, 1320, 1120, 700. ^{1}H-NMR ($CDCl_3$): 1.84 (*s*, 3 H); 3.46 (*s*, 3 H); 3.67 (*d*, *J* = 9.3, 1 H); 5.26 (*d*, *J* = 9.1, 1 H); 6.77 (*s*, 1 H); 7.28–7.59 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 13.77; 35.11; 66.06; 77.31; 122.85; 128.02; 128.13; 128.36; 129.39; 129.65; 129.99; 130.21; 130.77; 131.62; 132.03; 135.95; 136.75; 137.60; 141.68; 166.91; 170.55. Anal. calc. for $C_{26}H_{22}Cl_2N_2O_2$ (465.38): C 67.10, H 4.76, N 6.01; found: C 67.11, H 4.59, N 5.93.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*SR*)-1-hydroxy-3-(4-methoxyphenyl)-2-methylprop-2-enyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**12**; *threo*): M.p. 165.0–167.5°. IR (KBr): 3450, 2900, 2850, 1685, 1600, 1510, 1260, 1180, 1010, 830, 730. ^{1}H-NMR ($CDCl_3$): 1.88 (*s*, 3 H); 3.43 (*s*, 3 H); 3.70 (*d*, *J* = 3.5, 1 H); 3.8 (*s*, 3 H); 4.44 (br. *s*, 1 H); 5.03 (*d*, *J* = 3.3, 1 H); 6.73 (*s*, 1 H); 7.24–7.62 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 14.93; 35.15; 55.09; 65.28; 74.64; 113.32; 122.87; 126.91; 128.34; 129.53; 129.78; 130.11; 130.85; 131.70; 135.07; 137.62; 141.85; 157.91; 168.03; 169.89. Anal. calc. for $C_{27}H_{25}ClN_2O_3$ (460.96): C 70.35, H 5.46, N 6.07; found: C 70.58, H 5.46, N 5.98.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*)-1-hydroxy-3-(4-methoxyphenyl)-2-methylprop-2-enyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**13**; *erythro*): M.p. 193.0–194.5°. IR (KBr): 3400, 2360, 1670, 1605, 1510, 1400, 1250, 1110, 830, 700. ^{1}H-NMR ($CDCl_3$): 1.85 (*s*, 3 H); 3.46 (*s*, 3 H); 3.68 (*d*, *J* = 9.3, 1 H); 3.84 (*s*, 3 H); 5.26 (*d*, *J* = 9.1, 1 H); 6.76 (*s*, 1 H); 6.90–7.56 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 13.69; 29.56; 35.08; 55.11; 66.08; 77.53; 113.38; 122.83; 128.32; 128.78; 129.43; 129.61; 130.02; 130.12; 130.68; 131.57; 134.25; 137.68; 141.73; 158.01; 166.81; 170.63. Anal. calc. for $C_{27}H_{25}ClN_2O_3$ (460.96): C 70.35, H 5.46, N 6.07; found: C 70.12, H 5.42, N 6.04.

Hydrogenation: General Procedure. One of the substrates **8**–**13** (0.45 mmol) and [Rh(cod)(diphos-4)]ClO_4 (30.0 mg, 0.041 mmol; prepared according to [20]) were dissolved in CH_2Cl_2 (50 ml) and hydrogenated in a *Parr* autoclave at 50° and 45 bar for 6 h. The crude diastereoisomer mixtures from the *threo* substrates **8**, **10**, and **12** were purified for ^{1}H-NMR analysis by CC (silica gel ^{i}Pr_2O). The diastereoisomer mixtures from the *erythro* substrates **9**, **11**, and **13** were separated as indicated below.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*,2*RS*)-1-hydroxy-2-methyl-3-phenylpropyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**16**; *erythro,erythro*) *and (3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS*,2*SR*)-1-hydroxy-methyl-3-phenylpropyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**17**; *erythro,threo*): Diastereoisomers **16**/**17** (from **9**) were separated by CC (silica gel, CH_2Cl_2/AcOEt 9.5 : 0.5): **16** (19 mg, 10%) followed by **17** (133 mg, 66%).

Data of **16**: M.p. 149.5–151.0°. IR (KBr): 3455, 1670, 1610, 1475, 1320, 1110, 760. ^{1}H-NMR ($CDCl_3$): 1.21 (*d*, *J* = 6.9, 3 H); 2.43 (*dd*, *J* = 13.5, 6.9, 1 H); 2.63 (*dd*, *J* = 13.7, 6.9, 1 H); 2.77 (*dd*, *J* = 13.2, 6.6, 1 H); 3.39 (*s*, 3 H); 3.44 (*d*, *J* = 9.6, 1 H); 4.69 (*d*, *J* = 9.6, 1 H); 7.00–7.59 (*m*, 13 H). ^{13}C-NMR ($CDCl_3$): 11.66; 34.96;

40.52; 65.31; 73.45; 122.80; 125.64; 128.10; 128.34; 129.14; 129.51; 129.95; 130.91; 131.62; 137.37; 141.15; 141.73; 167.34; 170.79. Anal. calc. for $C_{26}H_{25}ClN_2O_2$ (432.94): C 72.13, H 5.82, N 6.47; found: C 71.92, H 6.00, N 6.46.

Data of **17**: M.p. 94.5–96.0°. IR (KBr): 3450, 1670, 1610, 1480, 1325, 1120, 750, 700. ^{1}H-NMR ($CDCl_3$): 0.74 (*d*, *J* = 6.6, 3 H); 2.48 (*dd*, *J* = 13.5, 6.9, 1 H); 2.78 (*dd*, *J* = 13.2, 8.5, 1 H); 3.0 (*dd*, *J* = 13.5, 6.6, 1 H); 3.42 (*s*, 3 H); 3.59 (*d*, *J* = 9.6, 1 H); 4.72 (*d*, *J* = 9.3, 1 H); 7.20–7.59 (*m*, 13 H). ^{13}C-NMR ($CDCl_3$): 11.66; 34.96; 40.52; 65.26; 72.75; 122.79; 125.62; 128.10; 128.34; 129.14; 129.48; 129.95; 130.85; 131.62; 137.34; 141.15; 141.73; 167.29; 170.79. Anal. calc. for $C_{26}H_{25}ClN_2O_2$ (432.94): C 72.13, H 5.82, N 6.47; found: C 72.43, H 5.75, N 6.29.

*(3*RS*)-7-Chloro-3-[(1*RS,*2*RS*)-3-(4-chlorophenyl)-1-hydroxy-2-methylpropyl]-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**20**; *erythro,erythro*) *and (3*RS*)-7-Chloro-3-[(1*RS,*2*SR*)-3-(4-chlorophenyl)-1-hydroxy-2-methylpropyl]-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**21**; *erythro,threo*): Diastereoisomers **20**/**21** (from **11**) were separated by CC (silica gel, CH_2Cl_2/AcOEt 9:1): **20** (15 mg, 7%) followed by **21** (125 mg, 62%).

Data of **20**: M.p. 221.0–222.5°. IR (KBr): 3450, 1680, 1610, 1490, 1460, 1325, 1115, 700. ^{1}H-NMR ($CDCl_3$): 1.15 (*d*, *J* = 6.9, 3 H); 2.39 (*dd*, *J* = 13.2, 7.7, 1 H); 2.54–2.56 (*m*, 1 H); 2.72 (*dd*, *J* = 13.5, 5.8, 1 H); 3.40 (*s*, 3 H); 3.45 (*d*, *J* = 10.0, 1 H); 4.68 (*d*, *J* = 9.3, 1 H); 6.99–7.59 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 18.34; 35.13; 35.39; 65.08; 74.74; 122.66; 128.02; 128.44; 129.54; 129.75; 130.17; 131.01; 131.19; 131.86; 137.29; 139.98; 141.56; 167.49; 170.58. Anal. calc. for $C_{26}H_{24}Cl_2N_2O_2$ (467.39): C 66.81, H 5.18, N 5.99; found: C 66.84, H 5.16, N 6.91.

Data of **21**: M.p. 157.5–160.0°. IR (KBr): 3520, 1660, 1610, 1480, 1450, 1325, 1115, 700. ^{1}H-NMR ($CDCl_3$): 0.73 (*d*, *J* = 6.6, 3 H); 2.42 (*dd*, *J* = 13.7, 6.9, 1 H); 2.74 (*dd*, *J* = 13.5, 8.2, 1 H); 2.94 (*dd*, *J* = 13.7, 7.1, 1 H); 3.41 (*s*, 3 H); 3.56 (*d*, *J* = 9.6, 1 H); 4.64 (*d*, *J* = 9.6, 1 H); 6.99–7.59 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 11.75; 34.91; 35.01; 39.80; 65.26; 72.53; 122.79; 128.24; 128.36; 129.38; 129.48; 130.04; 130.46; 130.82; 131.35; 131.58; 137.48; 139.62; 141.69; 167.24; 170.87. Anal. calc. for $C_{26}H_{24}Cl_2N_2O_2$ (467.39): C 66.81, H 5.18, N 5.99; found: C 66.70, H 5.21, N 6.01.

*(3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS,*2*RS*)-1-hydroxy-3-(4-methoxyphenyl)-2-methylpropyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**24**; *erythro,erythro*) *and (3*RS*)-7-Chloro-1,3-dihydro-3-[(1*RS,*2*SR*)-1-hydroxy-3-(4-methoxyphenyl)-2-methylpropyl]-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one* (**25**; *erythro,threo*): Diastereoisomers **24**/**25** (from **13**) were separated by CC (silica gel, CH_2Cl_2/AcOEt 9:1): **24** (18 mg, 10%) followed by **25** (107 mg, 53%).

Data of **24**: M.p. 198.0–199.0°. ^{1}H-NMR ($CDCl_3$): 1.16 (*d*, *J* = 6.9, 3 H); 2.36 (*dd*, *J* = 13.5, 7.7, 1 H); 2.56–2.59 (*m*, 1 H); 2.69 (*dd*, *J* = 13.5, 6.0, 1 H); 3.40 (*s*, 3 H); 3.49 (*d*, *J* = 9.6, 1 H); 3.71 (*s*, 3 H); 4.68 (*d*, *J* = 7.7, 1 H); 6.98–7.59 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 18.46; 34.98; 35.11; 35.34; 39.60; 65.12; 74.89; 113.27; 122.58; 128.39; 129.56; 129.65; 129.86; 130.85; 131.57; 133.42; 137.51; 141.58; 157.39; 167.35; 170.77. Anal. calc. for $C_{27}H_{27}ClN_2O_3$ (462.97): C 70.05, H 5.88, N 6.05; found: C 70.03, H 6.09, N 6.27.

Data of **25**: M.p. 178.5–181.0°. IR: 3450, 1670, 1610, 1480, 1325, 1250, 1120, 700. ^{1}H-NMR ($CDCl_3$): 0.73 (*d*, *J* = 6.6, 3 H); 2.40–2.45 (*m*, 1 H); 2.71 (*dd*, *J* = 13.5, 8.5, 1 H); 2.92 (*dd*, *J* = 13.5, 6.9, 1 H); 3.41 (*s*, 3 H); 3.58 (*d*, *J* = 9.3, 1 H); 3.81 (*s*, 3 H); 4.69 (*d*, *J* = 7.9, 1 H); 6.86–7.59 (*m*, 13 H). ^{13}C-NMR ($CDCl_3$): 11.71; 35.01; 35.11; 39.58; 55.09; 65.26; 72.63; 113.5; 122.82; 128.34; 129.51; 129.99; 130.89; 131.64; 133.19; 137.33; 141.76; 157.58; 167.34; 170.79. Anal. calc. for $C_{27}H_{27}ClN_2O_3$ (462.97): C 70.05, H 5.88, N 6.05; found: C 70.17, H 6.00, N 5.89.

Hydrolysis of erythro,threo *Compound* **21**: *(2*RS*,3*RS*,4*SR*)-2-{[(Benzyloxy)carbonyl]amino}-5-(4-chlorophenyl)-3-hydroxy-4-methylpentanoic Acid* (**27**). The soln. of **21** (350 mg, 0.75 mmol) in AcOH (8 ml) and conc. HCl soln. (6 ml) was refluxed for 24 h. The mixture was evaporated almost to dryness, H_2O (30 ml) was added, and the pH was adjusted to 11 by addition of 2M NaOH. The soln. was extracted with CH_2Cl_2 (3 × 20 ml). To the vigorously stirred aq. phase, benzyl carbonochloridate (Z-Cl; 0.15 ml, 0.1 mmol) was added in portions during 6 h at 5°, maintaining the pH at *ca.* 10. Then the pH was raised to 11–12 and the mixture extracted with Et_2O (3 × 10 ml). The aq. phase was adjusted to pH 3 by addition of 1M HCl and extracted with AcOEt (4 × 10 ml). Upon drying and evaporation, 130 mg (45%) of **27** was obtained. M.p. 180° (dec.) IR (KBr): 3389, 2930, 1750, 1689, 1515, 1459, 1064, 1046, 753, 702. ^{1}H-NMR (MeOD): 0.93 (*d*, *J* = 6.5, 3 H); 2.06–2.12 (*m*, 1 H); 2.54 (*dd*, *J* = 13.2, 9.0, 1 H); 2.91 (*dd*, *J* = 13.2, 5.8, 1 H); 3.77 (*dd*, *J* = 7.8, 3.8, 1 H); 4.43 (*d*, *J* = 7.8, 1 H); 5.15 (*d*, *J* = 12.3, 1 H); 5.21 (*d*, *J* = 12.3, 1 H); 7.22–7.52 (*m*, 9 H). ^{13}C-NMR (MeOD): 13.48; 38.17; 40.48; 58.08; 60.91; 75.11; 128.97; 129.17; 129.42; 129.61; 131.97; 132.77; 138.31; 141.08; 158.35; 174.86. Anal. calc. for $C_{20}H_{22}ClNO_5$ (391.12): C 61.30, H 5.66, N 3.57; found: C 70.17, H 5.87, N 3.79.

X-Ray Crystal-Structure Determination of **21**. Compound **21** was crystallized from MeOH. *Table 6* summarizes the crystal data and experimental details of the data collection, refinement, and software used.

The intensities were collected at r.t. on a *Philips PW1100* diffractometer updated by *Stoe* & *Cie* by using MoK_α radiation (0.71073 Å) at 20° with the ω-scan mode and corrected only for *Lorentz* and polarization

Table 6. *Crystallographic Data, Structure Solution, and Refinement of* **21**

Formula	$C_{26}H_{24}Cl_2N_2O_2$
Solvent	MeOH
M_r	467.37
Crystal system	monoclinic
Space group	*C*2/*c*
a [Å]	23.018(3)
b [Å]	10.927(2)
c [Å]	19.432(2)
β [°]	93.78(1)
V [Å^3]	4877(1)
Z	8
F [000]	1952
D_x [Mgm^{-3}]	1.273
Radiation	MoK_α
Wavelength [Å]	0.71073
Range [°]	5.1 – 12.5
μ [mm^{-1}]	0.291
Temp. [K]	293(2)
Crystal form	prismatic
Crystal size [mm]	0.675 × 0.285 × 0.255 mm
Crystal color	colorless
Data-collection method	ω scans
Absorption correction	no correction
Number of measured and total data	12733; 6072
Unique data	5766
Observed data (criterion)	2157 ($I > 2\sigma(I)$)
R_{int}	0.0182
θ_{max} [°]	≤ 34.88
Range of *h*,*k*,*l*	$-26 \le h \le 25$, $0 \le k \le 14$, $0 \le l \le 31$
No. of standard reflections	4
Frequency of standard reflections (min.)	120
Intensity decay [%]	3.2
Refinement on	F^2
$R_1(F_o > \sigma(F_o))$	0.0547
wR_2 (F^2), all data	0.1700
S	0.99
Parameters	291
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0778P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho$(max, min)[eÅ^{-3}]	0.24, −0.26
Data-reduction program	STADI4,X-RED [21][22]
Structure-solution program	SHELXS86 [23]
Structure-refinement program	SHELXL97 [24]
Preparation of material for publication (program)	WINGX [25]

factors. Unit-cell dimensions were refined by using 37 reflections in the range $5.1° \le \theta \le 12.5°$. During the data collection, 3.2% of crystal decomposition was observed. The crystal structure was solved by direct methods and refined by full-matrix least-squares calculations based on F^2 with atomic scattering factors and anomalous dispersion values as defined in SHELXL97 [24]. The H-atom of the OH group was located in a difference *Fourier* map and included in the refinement with the positional parameters fixed. All other H-atoms were treated by using appropriate riding models. The final difference map contained no significant features. The weighting scheme (see *Table 6*) was assumed for all observations.

Crystallographic data (excluding structure factors) for **21** have been deposited with the *Cambridge Crystallographic Date Centre* as deposition No. CCDC-197604. 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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