Synthesis of Chiral 4-(ω-Hydroxyalkyl)pyrazolidin-3-ones by Ring-Chain Transformation of α-Alkylidenelactones with Hydrazines

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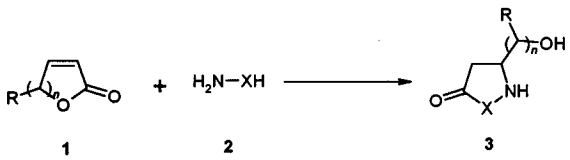
Enantiopure α-alkylidenelactones **7** were prepared by a Wittig reaction from α-bromolactones **4** and chiral aldehydes **6**. Compounds **7** react with hydrazines **9** by stereoselective Michael-like addition and ring–chain transformation affording optically active 4-(ω-hydroxyalkyl)pyrazolidin-3-ones **11**.

Ring−chain transformations of heterocycles are defined as ring transformations of reactants composed of a heterocyclic ring and a side chain resulting in analogous products where the two moieties are exchanged, i.e. the starting heterocyclic ring becomes a side chain and vice versa. This concept is a powerful tool for the synthesis of ω-functionalised alkylheterocycles.[1] As an asymmetric version, butenolides **1** ($n = 1$)[2][3][4] and higher homologous pentenolides **1** ($n = 2$)[2][4][5][6] were transformed into pyrazolidin-3-ones **3** (X = NR′), 1,2-oxazolidinones **3** (X = O), and 6-membered heterocycles with hydrazines, hydroxylamines, and 1,3-nucleophiles, respectively. In these cases, the chiral information was located in the ring next to the oxygen atom of the starting Michael system **1**. Due to the rigidity of the ring, high asymmetric induction was observed in these reactions.

Scheme 1



1 2 3

We were interested to investigate whether α-alkylidenelactones **7** with a chiral substituent R in the side chain could undergo analogous ring−chain transformation with hydrazines. The envisaged ring transformation products **11** are close structural analogues of potent 5-lipoxygenase inhibitors.[7] Since the chiral information of the α-alkylidenelactones **7** is not fixed in the ring but at a substituent capable of rotation, the extent of asymmetric induction to be achieved was uncertain. Hitherto, only one reaction of an α-methylidenebutyrolactone with phenylhydrazine has been reported, where no ring−chain transformation was achieved. In this example, however, the chiral information inducing the high asymmetric induction was found in the ring rather than in the side chain.[8] Secondary amines were also reported to undergo 1,4-additions to α-methylidenelactones[9][10] or to more complex natural products possessing an α-methylidenebutyrolactone ring (for some examples see references[11][12][13]).

Optically active α-alkylidenelactones **7** were recently synthesised by aldol-type reactions of lactams with chiral aldehydes.[14] Since no detailed procedures were given, we synthesised such α,ß-unsaturated lactones **7** by a Wittig reaction,[15] a well-established method for the synthesis of α-alkylidenelactones.[16][17] The products **7** were formed with high preference for the (*E*)-isomers (Table 1) and could be obtained in configurationally pure form by chromatographic separation or recrystallisation (**7d**). In order to prove the (*E*)-configuration at the C−C double bond, compound **7a** was transformed into a Diels-Alder adduct **8** with cyclopentadiene, and was investigated by X-ray crystal analysis (see Figure 1). For **7d**, the minor isomer could only be obtained in trace amounts and was assigned as the (*Z*)-product by a NOE-difference effect of the vinylic hydrogen atom and the allylic ring hydrogen atoms. Thus the major isomer of **7d** possesses the (*E*)-configuration.

In reactions of α-alkylidenelactones **7** with hydrazine, methylhydrazine, or 1,2-dimethylhydrazine, long reaction times and elevated temperatures were necessary to achieve complete conversions. The 6-membered lactone **7f** was more reactive than the 5-membered systems. The products obtained were already the envisaged ring-transformed 4-(ω-hydroxyalkyl)pyrazolidin-3-ones **11**.

In the case of the reaction of α-methylidenelactone **7e** with Boc-hydrazine, however, the Michael-like addition product **10a** ($n = 1$, $R = R^1 = H$, R^2 = Boc) could be obtained (Table 2). Since such hydrazinoalkyllactones **10** can generally be expected as intermediates in the ring transformation of **7** to **11**, an attempt was made to convert compound **10a** into the corresponding 4-(3-hydroxypropyl)pyrazolidin-3-one **11** ($n = 1$, $R = R^1 = R^2 = H$) by acid re-

  1434−193X/98/1111−2667 $ 17.50+.50/0

Scheme 2

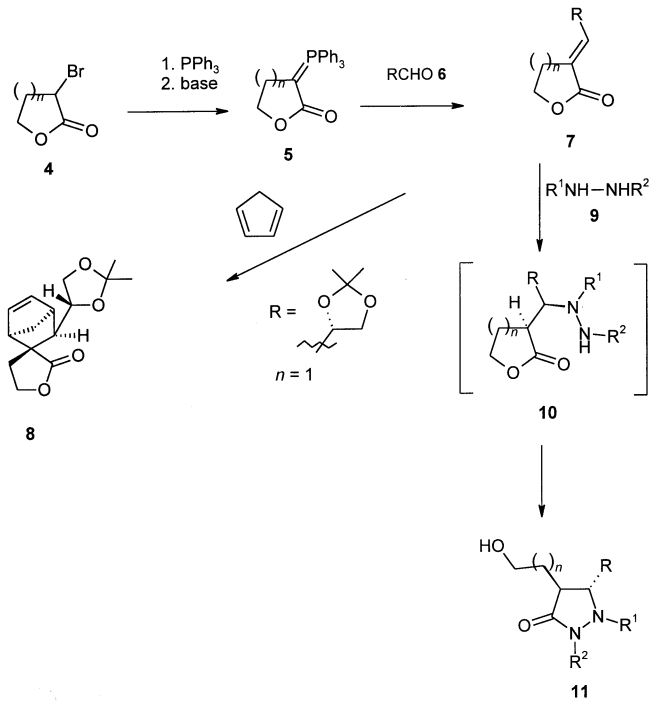
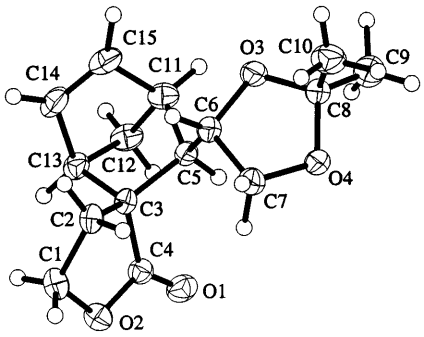


Figure 1. X-ray crystal analysis of the Diels-Alder adduct **8**



moval of the Boc group to afford a more nucleophilic NH_2 group. Unfortunately, no definite products could be isolated after this deprotection.

The stereoselectivity of the ring−chain transformation of lactones **7** to pyrazolidinones **11** was moderate to good (60:40 to 88:12) although unfavourably harsh reaction conditions had to be applied. In half of the cases, the major diastereomers could be obtained in a pure state after chromatography (Table 2). *N*-Unsubstituted ($R^1 = R^2 = H$) 4-(ω-hydroxyalkyl)pyrazolidin-3-ones **11a**, **11h**, and **11j** could be further protected as the tosyl derivative at position 1 to afford **11d**, **11i**, and **11k**, respectively.[18]

The constitution of the 4-(ω-hydroxyalkyl)pyrazolidin-3-ones **11** was elucidated from spectroscopic data (see Experimental Section). Thus the ω-hydroxyalkyl chain shows the CH_2−O protons at higher field in the ^{1}H-NMR spectra when compared to lactone moieties such as in **7** and **10**. The orientation of the NH-group of the asymmetrically substituted methylhydrazine could be determined by the lack of CONH protons (δ = 10.8−8.6) in the ^{1}H-NMR spectra of the products **11b**, **11f**, **11g**, i.e. the methylhydrazine NH_2 moiety attacks the exocyclic position of the C−C double bond. This regioselectivity is in contrast to the ring−chain transformation of butenolides with methylhydrazine which occurs in the reverse manner.[4]

The configuration of the products **11** was determined by X-ray crystal analysis of the *N*-tosyl derivative **11d** (Figure 2) and the dibenzylaminoethylpyrazoline **11h** (Figure 3) and by comparative CD investigations of the 4-(2-hydroxyethyl)-pyrazolidin-3-one **11a** and its homologue **11j** (Figure 4). The stereochemical outcome of the ring−chain transformation of the lactones **7** to the 4-(ω-hydroxyalkyl)-pyrazolidin-3-ones **11** can be explained by Houks outside-crowded model[19] and the anti-periplanar effect[20][21] (see Figure 5 for alkoxy-substituted **7** with R = CHR″OR′). Thus the chiral substituent of **7** is oriented mainly in such a way that the small hydrogen atom occupies the crowded outside position. At this conformation the attack of the hydrazine occurs anti-periplanar to the alkoxy group. This 1,4-addition is followed by protonation which obviously occurs from the same face. Similar orientations were found in the conjugate addition of nucleophiles to enones and enoates with a chiral alkoxyalkyl substituent at the β-position.[21]

Figure 2. X-ray crystal analysis of the 4-(2-hydroxyethyl)pyrazolidin-3-one **11d**

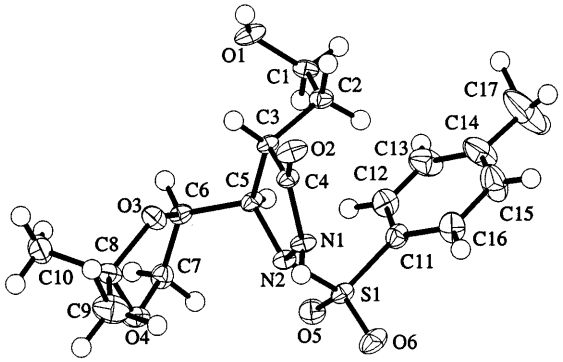
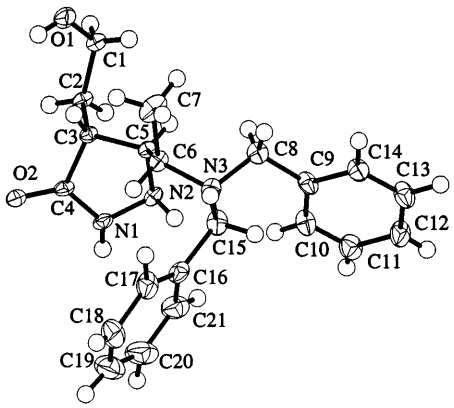


Figure 3. X-ray crystal analysis of the 4-(2-hydroxyethyl)pyrazolidin-3-one **11h**



Our results demonstrate that the concept of ring−chain transformation of α,β-unsaturated lactones can be successfully applied to the synthesis of optically active 4-(ω-hydroxyalkyl)pyrazolidin-3-ones with α-alkylidenelactones

Figure 4. CD spectra of the 4-(2-hydroxyethyl)pyrazolidin-3-one **11d** and its homologue **11k** (in MeCN / mol·l^{-1})

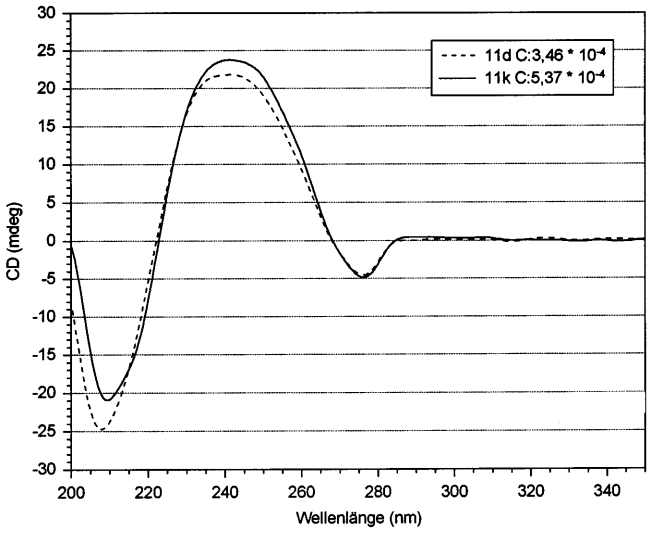
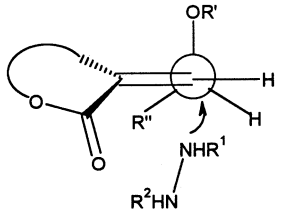


Figure 5. Stereochemical mode of attack of hydrazines **9** at α-alkylidenelactones **7** [R = CH(OR′)R″] governed by the anti-periplanar effect



7 and hydrazines **9** as reactants. Although the chiral information in the starting material is situated in a non-fixed side chain, reasonable asymmetric induction can be achieved. This is the first access to optically active 4-(ω-hydroxyalkyl)pyrazolidin-3-ones. Hitherto, only racemic 4-(hydroxyalkyl)pyrazolidin-3-ones with other substituents could be obtained, and mostly by hydroxyalkylation of corresponding 4-unsubstituted pyrazolidin-3-ones.[7]

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Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75.5 MHz, respectively, with a Bruker AC-300 with TMS as internal standard. − Optical rotations were determined with a Perkin Elmer polarimeter 241. − Circular dichroism was measured on a JASCO J710 spectrometer (minimum wave length 200 nm). The spectral bandwith was 0.5 nm, the time constant 0.5 s and the temperature 24°C. − Mass spectra (HP 5995 A) and high-resolution mass spectra (MAT 711, Varian) were measured at 70eV. − Some of the highly polar products did not give satisfactory microanalyses but showed corresponding NMR spectra and satisfactory high resolution mass spectra. − Silica gel (0.04−0.063 mm, Merck) was used for preparative column chromatography. Unless otherwise mentioned, chemicals were purchased from Aldrich.

Starting Materials: The α-bromovalerolactone **4** was synthesised starting from valerolactone by bromination using a known procedure,[22] via the corresponding silylketene acetal.[23] The optically active aldehydes **6** were prepared according to known procedures.[24][25][26][27][28][29] The phosphaneylides **5** were obtained with triphenylphosphane by a known procedure (n = 1)[30] or adopting this known procedure (n = 2, yield in two steps 57%, m.p. 245−246°C).

General Procedure for the Synthesis of α-Alkylidenelactones **7** *by Wittig Reaction (see Table 1):* A solution of the triphenylphosphanylide **5** (25 mmol) and the chiral aldehyde **6** (24 mmol) in THF (800 ml) was stirred or refluxed for 24−48 h (Table 1). After evaporation of the solvent, diethyl ether (2 × 10 ml) was added, causing precipitation of triphenylphosphane oxide, which was filtered off. The solvent was evaporated and the residue purified by flash chromatography with *n*-hexane/EtOAc.

Table 1. Optically active α-alkylidenelactones **7**

Compound	n	R	Yield [%][a]	d.r. (*E*/*Z*)	time/temp.[°C]
7a[b]	1		81	96:4	24 h/20
7b	1		69	>95:5	24 h/reflux
7c	1		55	89:11	24 h/40
7d	1		70	79:21	48 h/reflux
7e	1	H			
7f[b]	2		79	>95:5	20 h/20

[a] Pure (*E*)-isomers were obtained after flash chromatography. − [b] Spectroscopic data were identical to those reported for the product obtained by aldol reaction[14].

(4′S,E)-3-(1′,4′-Dioxa-spiro[4,5]dec-2′-ylmethylene)dihydrofuran-2-one (**7b**): Colourless oil.− R_f = 0.32 (*n*-hexane/EtOAc, 1:1). − $[\alpha]_D^{20}$ = +8.1(*c* = 1, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14−1.65 (m, 10 H, cyclohex.), 2.89−3.01 (m, 2 H, CH_2C=), 3.63 (dd, *J* = 6.9, 8.1 Hz, 1 H, OCH_2CH), 4.12 (dd, *J* = 6.9, 8.1 Hz, 1 H, OCH_2CH), 4.32 (m, 2 H, OCH_2), 4,67 (m, 1 H, OCH), 6.61 (dt, *J* = 2.9, 7.0 Hz, 1 H, =CH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.4 (CH_2), 23.8, 23.9, 25.0, 25.2, 36.0 (CH_2−cyclohex.), 65.6 (OCH_2), 68.1 (OCH_2), 73.4 (OCH), 110.9 (C), 127.7 (C=), 136.1 (=CH), 170.9 (C=O). − $C_{13}H_{18}O_4$ (238.2): calcd. C 65.51, H 7.62; found: C 64.98, H 7.74.

(4′S,E)-3-(2-Benzyloxy-3-hydroxypropylidene)dihydrofuran-2-one (**7c**): Colourless oil. − R_f = 0.22 (*n*-hexane/EtOAc, 3:7). − $[\alpha]_D^{20}$ = −38.7 (*c* = 1, [D_6]DMSO). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85−2.91 (m, 2 H, OCH_2CH_2), 3.55 (m, 2 H, OCH_2CH), 4.31 (m, 2 H, OCH_2CH$_2$), 4.45 (d, *J* = 12 Hz, 1 H, OCH_2−Ph), 4.52 (d, *J* = 12 Hz, 1 H, OCH_2−Ph), 4.94 (m, 1 H, OCH), 6.46 (dt, *J* = 7.1, 3.0 Hz, 1 H, =CH), 7.26−7.34 (m, 5 H, arom.). − ^{13}C NMR (75.5 MHz, [D_6]DMSO): 25.1 (CH_2), 62.9 (OCH_2), 63.7 (OCH_2), 70.4 (OCH_2), 127.5, 127.7, 128.3 (CH−arom.), 129.3 (C=), 136.6 (=CH), 138.4 (C−arom.), 170.6 (C=O). − $C_{14}H_{16}O_4$ (248.2): calcd. C 67.71, H 6.50; found: C 68.02, H 6.33.

(4′R,E)-3-[2-(Dibenzylamino)propylidene]dihydrofuran-2-one (**7d**): Colourless needles (after chromatographic separation from the minor isomer). – M.p. 119–121°C, R_f = 0.17 (*n*-hexane/EtOAc, 8:2). – $[\alpha]_D^{20}$ = +6.5 (*c* = 1, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.57 (m, 2 H, CH_2CH_2O), 3.51 (d, *J* = 13.7 Hz, 2 H, CH_2N), 3.80 (d, *J* = 13.7 Hz, 2 H, CH_2N), 4.31 (m, 2 H, OCH_2), 4.34 (m, 1 H, CH_3CH), 6.78 (dt, *J* = 3.0, 9.3 Hz, 1 H, =CH), 7.26–7.35 (m, 10 H, CH, arom.). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.3 (CH_3), 25.1 (CH_2), 53.0 (CH), 54.0 (NCH_2), 65.5 (OCH_2), 126.8 (C=), 127.0, 128.3, 128.4 (CH–arom.) 139.7 (=CH), 140.6 (C–arom.), 171.2 (C=O). – $C_{21}H_{23}NO_2$ (321.42): calcd. C 78.47, H 7.21, N 4.36; found C 78.29, H 7.39, N 4.36.

Formation of Cycloadduct **8** *by Diels-Alder Reaction of Cyclopentadiene with α-Alkylidenelactone* **7a**: A mixture of freshly distilled cyclopentadiene (1.00 g, 10.5 mmol) and the α-alkylidenelactone **7a** (240 mg, 1.2 mmol) was heated in an autoclave, with stirring, at 100°C for 5 h. Excess cyclopentadiene was distilled and the residue was purified by flash chromatography with *n*-hexane/EtOAc (7:3). R_f = 0.16 (d.r.: 60.1:34.7:3.7:1.4). Total yield after chromatography: 209 mg (66%) (major isomer 133 mg, next abundant isomer 76 mg). Major isomer: colourless crystals. – M.p. = 123–125°C – $[\alpha]_D^{20}$ = –58.6 (*c* = 1, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.37 (d, *J* = 8.8 Hz, 1 H, $CHCH_2CH$), 1.77 (m, 2 H, CH_2C), 1.91 (d, *J* = 8.8 Hz, 1 H, $CHCH_2CH$), 2.63 (dd, *J* = 3.3, 6.9 Hz, 1 H, $CHCHCH_2$), 2.94 (m, 1 H, C–CH), 3.14 (m, 1 H, $OCHCH$), 3.41 (m, 1 H, OCH), 3.43 (dd, J = 6.8, 8.2 Hz, 1 H, OCH_2CH), 3.94 (dd, J = 6.8, 8.2 Hz, 1 H, OCH_2CH), 4.22 (m, 2 H, CH_2OCO), 6.18 (dd, *J* = 3.0, 5.6 Hz, 1 H, CH=CH), 6.39 (dd, *J* = 3.0, 5.6 Hz, 1 H, CH=CH). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.3 (CH_3), 26.8 (CH_3), 30.6 (CH_2), 45.2 (CH_2), 46.1 (CH), 50.3 (CH), 51.2 (CH), 65.4 (CH_2), 69.0 (CH_2), 108.6 (OCO), 134.6 (=CH), 139.3 (=CH), 180.9 (C=O). – $C_{15}H_{20}O_4$ (264.3): calcd. C 68.16, H 7.63; found: C 67.76, H 7.73.

Procedure for the Synthesis of tert-Butyl N′-(2-Oxotetrahydrofuran-3-ylmethyl)hydrazinecarboxylate **10a**: A solution of the α-alkylidenelactone **7e** (196 mg, 2 mmol) and the $BocNHNH_2$ (1.32 g, 10 mmol) in MeOH (5 ml) was stirred at room temp. for 40 h. The solvent was evaporated, and the residue purified by chromatography with *n*-hexane/EtOAc (4:6), R_f = 0.27. Yield 375 mg (82%), colourless crystals. – M.p. = 85–87°C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, CH_3), 2.11 (m, 1 H, $CHCH_2$), 2.51 (m, 1 H, $CHCH_2$), 2.74 (m, 1 H, CH), 2.97 (dd, *J* = 7.4, 12.3 Hz, 1 H, CH_2N), 3.21 (dd, *J* = 5.4, 12.3 Hz, 1 H, CH_2N), 4.18 (m, 1 H, OCH_2), 4.29 (m, 1 H, OCH_2), 6.22 (s, 1 H, NHC=O). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.5 (CH_2), 28.7 (3 × CH_3), 39.0 (CH), 52.4 (CH_2), 67.2 (CH_2O), 157.2 (C=O), 178.6 (C=O). – $C_{10}H_{18}N_2O_4$ (230.2): calcd. C 52.16, H 7.88, N 12.17: found: C 51.61, H 8.39, N 11.68.

General Procedure for the Synthesis of 4-(ω-Hydroxyalkyl)-pyrazolidin-3-ones **11** *by Ring-Chain Transformation of α-Alkylidenelactones* **7** *with Hydrazines (Table 2):* A solution of the α-alkylidenelactone **7** (2 mmol) and the hydrazine **9** (4 mmol) in MeOH (5 ml) was refluxed for 8–36 h or was stirred at 95°C for 4–45 h (dioxan/H_2O, 2:1) (Table 2). The solvent was evaporated and the residue purified by chromatography with $CHCl_3$/MeOH. In case of **11h** a semisolid product was obtained, which was crystallised by heating in acetone.

(4S,5S,4′S)-5-(2,2-Dimethyl[1,3]dioxolan-4-yl)-4-(2-hydroxyethyl)pyrazolidin-3-one (**11a**): Colourless oil. – R_f = 0.44 ($CHCl_3$/MeOH, 8:2). – $[\alpha]_D^{20}$ = –28.4 (*c* = 1, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.68 (m, 2 H, CH_2CH_2CH), 2.66 (m, 1 H, CHC=O), 3.37 (dd, *J* = 3.4, 9.3 Hz, 1 H, CHN), 3.75 (m, 2 H, OCH_2CH_2), 3.81 (m, 1 H, OCH_2CH), 4.04 (m, 1 H, OCH_2CH), 4.24 (m, 1 H, OCH), 8.61 (s, 1 H, NHC=O). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.2 (CH_3), 26.6 (CH_3), 31.2 (CH_2), 43.7 (CH), 61.0 (CH_2), 64.4 (CH), 66.0 (CH_2), 74.1 (CH), 110.0 (C), 178.8 (C=O). – HRMS $C_{10}H_{18}N_2O_4$: calcd. 230.12665; found 230.12666.

(4S,5R,4′S)-5-(2,2-Dimethyl[1,3]dioxolan-4-yl)-4-(2-hydroxyethyl)-2-methylpyrazolidin-3-one (**11b**): Colourless oil. – R_f = 0.26 ($CHCl_3$/MeOH, 9:1). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.76 (m, 2 H, CH_2CH_2CH), 2.49 (m, 1 H, CHC=O), 2.91 (s, 3 H, NCH_3), 3.23 (dd, *J* = 3.3, 9.0 Hz, 1 H, CHN), 3.59 (m, 2 H, CH_2CH_2CH), 3.70 (m, 1 H, OCH_2CH), 3.95 (m, 1 H, OCH_2CH), 4.14 (m, 1 H, OCH). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.5 (CH_3), 25.9 (CH_3), 30.8 (NCH_3), 31.4 (CH_2), 43.3 (CH), 59.7 (CH_2), 60.4, 65.2 (CH_2), 74.3 (CH), 108.9 (C), 172.9 (C=O). – HRMS $C_{11}H_{20}N_2O_4$: calcd. 244.14230; found 244.14231.

(4S,5R,4′S)-5-(2,2-Dimethyl[1,3]dioxolan-4-yl)-4-(2-hydroxyethyl)(1,2-dimethyl)pyrazolidin-3-one (**11c**): Colourless oil. – R_f = 0.31 ($CHCl_3$/MeOH, 9:1). – ^{1}H NMR (300 MHz, MeOD): δ = 1.21 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.73 (m, CH_2CH_2CH), 2.42 (m, 1 H, CHC=O), 2.62 (s, 3 H, $CHNCH_3$), 2.86 (s, 3 H, NCH_3C=O), 3.20 (m, 1 H, CHN), 3.63 (m, 2 H, CH_2CH_2CH), 3.67, (dd,

Table 2. 2-Hydrazinoalkylbutyrolactone **10a** and 4-(ω-hydroxyalkyl)pyrazolidin-3-ones **11**

Compound	*n*	R	R^1	R^2	Yield [%]	d. r. (*E*/*Z*)	time/temp.[°C] solvent
10a	1	H	H	Boc	81	–	40 h/20 MeOH
11a	1		H	H	86	80:20	24 h/95 dioxane/water 2:1
11b	1		H	Me	56	83:17	24 h/reflux MeOH
11c	1		Me	Me	41	68:32[b]	15 h/reflux MeOH
11d	1		Tos	H	57[a]	>95:5	3 d/4 TosCl/pyridine
11e	1		H	H	61	76:24[b]	45 h/95 dioxane/water
11f	1		H	Me	54	60:40[b]	8 h/reflux MeOH
11g	1		H	Me	67	69:31[b]	36 h/reflux MeOH
11h	1		H	H	88	88:12	40 h/95 dioxane/water
11i	1		Tos	H	72[a]	>95:5	3 d/4 TosCl/pyridine
11j	2		H	H	98	84:16	4 h/95 dioxane/water
11k	2		Tos	H	72[a]	>95:5	3 d/4 TosCl/pyridine

[a] Obtained by tosylation of the corresponding **11** (R^1 = H). – [b] Diastereomers could not be separated.

J = 7.1, 8.0 Hz, 1 H, OCH_2CH), 3.90 (dd, 1 H, J = 7.1, 8.0 Hz, OCH_2CH), 4.05 (m, 1 H, OCH). − ^{13}C NMR (75.5 MHz, MeOD): δ = 24.5 (CH_3), 26.0 (CH_3), 29.0 (NCH_3), 35.7 (CH_2), 42.6 (CH), 44.7 (NCH_3), 59.7 (CH_2), 65.5 (CH_2), 67.9 (CH), 78.0 (CH), 109.4 (C), 172.7 (C=O). − HRMS $C_{12}H_{22}N_2O_4$: calcd. 258.1579; found 258.1576.

(4S,5R,4′S)-5-(1,4-Dioxaspiro[4.5]dec-2-yl)-4-(2-hydroxyethyl)pyrazolidin-3-one (**11e**). Colourless oil. − R_f = 0.34 ($CHCl_3$/MeOH, 8:2); spectra were obtained from the diasteromeric mixture, ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.21−1.62 (m, 10 H, CH_2), 1.84 (m, 2 H, CH_2CH_2CH), 2.68 (m, 1 H, CHC=O), 3.34 (m, 1 H, CHN), 3.66 (m, 1 H, OCH_2CH), 3.80 (m, 2 H, OCH_2CH$_2$), 3.99 (m, 1 H, OCH_2CH), 4.19 (m, 1 H, OCH), 8.71 (s, 1 H, NHC=O). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 23.7 (CH_2), 24.0 (CH_2), 25.1 (CH_2), 32.0 (CH_2), 34.3 (CH_2), 36.1 (CH_2), 44.8 (CH), 61.6 (CH_2), 62.0 (CH), 65.8 (CH_2), 73.1 (CH), 109.6 (C), 181.2 (C=O). − HRMS $C_{13}H_{22}N_2O_4$: calcd. 270.15795; found 270.15790.

(4S,5R,4′S)-5-(1,4-Dioxaspiro[4.5]dec-2-yl)-4-(2-hydroxyethyl)-2-methylpyrazolidin-3-one (**11f**): Colourless oil. − R_f = 0.36 ($CHCl_3$/MeOH, 9:1); spectra were obtained from the diasteromeric mixture, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31−1.58 (m, 10 H, CH_2), 1.74 (m, 2 H, CH_2CH_2CH), 2.73 (m, 1 H, CHC=O), 2.98 (s, 3 H, NCH_3), 3.26 (m, 1 H, CHN), 3.66 (dd, J = 6.8, 8.2 Hz, 1 H, OCH_2CH), 3.76 (m, 2 H, OCH_2CH$_2$), 4.00 (dd, J = 6.8, 8.2 Hz, 1 H, OCH_2CH) 4.22 (dd, J = 3.4, 6.8 Hz, 1 H, OCH). − (75.5 MHz, $CDCl_3$): δ = 23.6 (CH_2), 23.9 (CH_2), 25.0 (CH_2), 31.5 (CH_3), 31.5 (CH_2), 34.16(CH_2), 35.95 (CH_2), 44.90 (CH), 61.35 (CH_2), 61.56 (CH), 65.28 (CH_2), 72.92 (CH), 110.4 (C), 174.2 (C=O). − HRMS $C_{14}H_{24}N_2O_4$: calcd. 284.17360; found 284.17361.

(4S,5R,4′S)-5-(1-Benzyloxy-2-hydroxymethyl)-4-(2-hydroxyethyl)pyrazolidin-3-one (**11g**): Colourless oil. − R_f = 0.42 ($CHCl_3$/MeOH, 9:1); spectra were obtained from the diasteromeric mixture, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (m, 2 H, CH_2CH_2CH), 2.62 (m, 1 H, CHC=O), 2.91 (s, 3 H, NCH_3), 3.23 (m, 1 H, CHN), 3.51 (m, 2 H, OCH), 3.63 (m, 2 H, HOCH_2), 3.74 (m, 2 H, OCH_2), 4.47 (d, 1 H, J = 11.4 Hz, OCH_2−arom.), 4.69 (d, 1 H, J = 11.4 Hz, OCH_2−arom.), 7.21−7.31 (m, 5 H, CH−arom.) − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.2 (CH_2), 31.4 (CH_3), 44.1 (CH), 61.2 (CH_2), 61.6 (CH_2) 62.5 (CH), 72.6 (CH_2), 75.0 (CH), 128.0−128.7 (3 × CH−arom.), 137.3 (C), 174.1 (C=O). − HRMS $C_{15}H_{22}N_2O_4$: calcd. 294.1579; found 294.1581.

(4R,5S,1′S)-5-(1-Dibenzylaminoethyl)-4-(2-hydroxyethyl)-pyrazolidin-3-one (adduct with one molecule of acetone) (**11h**): Colourless crystals. − M.p. = 123−124°C (the crystals decompose after standing at room temp. exposed to air for one day, but can be kept in a suspension in acetone in a refrigerator for more than one week). − R_f = 0.21 ($CHCl_3$/MeOH, 9:1). − $[\alpha]_D^{20}$ = +46.4 (c = 1, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.6 Hz, 3 H, CH_3), 1.63 (m, 1 H, CH_2CH_2CH), 1.75 (m, 1 H, CH_2CH_2CH), 2.16 (s, 6 H, acetone), 2.29 (m, 1 H, CHC=O), 2.68 (m, 1 H, CHN), 3.22 (d, J = 13.3 Hz, 2 H, CH_2N), 3.30 (m, 1 H, CH_3CH), 3.63 (m, 2 H, OCH_2), 3.73 (d, J = 13.3 Hz, 2 H, CH_2N), 7.16−7.28 (m, 10 H, CH−arom.) − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.5 (CH_3), 31.3 (acetone) 33.6 (CH_2), 46.0 (CH), 54.0 (CH_2), 56.3 (CH), 61.6 (CH_2), 65.6 (CH), 127.7, 128.9, 129.4 (CH−arom.), 139.7 (C), 177.8 (C=O), 207.5 (acetone).

(4S,5R,4′S)-5-(2,2-Dimethyl[1,3]dioxolan-4-yl)-4-(3-hydroxypropyl)pyrazolidin-3-one (**11j**): Colourless oil. − R_f = 0.37 (CH_3Cl/MeOH, 8:2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (m, 1 H, CH_2CH_2CH), 1.14 (m, 1 H, CH_2CH_2CH), 1.28 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.61 (m, 2 H, OCH_2CH_2), 2.40 (m, 1 H, CHC=O), 3.30 (m, 1 H, CHN), 3.59 (m, 2 H, OCH_2CH$_2$), 3.76 (m, 1 H, OCH_2CH), 3.99 (m, 1 H, OCH_2CH), 4.21 (m, 1 H, OCH_2CH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.9 (CH_2), 25.3 (CH_3), 26.7 (CH_3), 30.1 (CH_2), 44.01 (CH_2) 62.0 (CH_2), 64.1 (CH), 67.7 (CH_2), 76.0 (CH), 110.3 (C), 178.6 (C=O) − $C_{11}H_{20}N_2O_4$ (244.3) calcd. C 54.08, H 8.25, N 11.47; found: C 53.77, H 8.60, N 10.95

General Procedure for the Synthesis of 4-(ω-Hydroxyalkyl)-1-tosylpyrazolidin-3-ones **11** *by N-Tosylation: p*-Toluenesulfonyl chloride (190 mg, 1 mmol) was added to a solution of the pyrazolidin-3-one **11** (R^1 = H) (1 mmol) in dry pyridine (4 ml) at 0°C in small portions. After standing at 4°C for 3 d, the reaction was quenched with aqueous phosphate buffer (pH 7) at 0°C and was then allowed to warm up to room temp. for 1 h. The mixture was extracted with Et_2O (2 × 30 ml) and with CH_2Cl_2 (2 × 30 ml). The combined organic phases were dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by flash chromatography with *n*-hexane/EtOAc or $CHCl_3$/MeOH.

(4S,5R,4′S)-5-(2,2-Dimethyl[1,3]dioxolan-4-yl)-4-(2-hydroxyethyl)-1-(toluene-4-sulfonyl)pyrazolidin-3-one (**11d**): Colourless crystals. − M.p. = 138−140°C. − R_f = 0.24 ($CHCl_3$/MeOH, 95:5). − $[\alpha]_D^{20}$ = +33.7 (c = 1, $CHCl_3$). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = −0.06 (m, 1 H, CH_2CH_2CH), 0.89 (m, 1 H, CH_2CH_2CH), 1.24 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 2.33 (m, 1 H, CHC=O), 2.39 (s, 3 H, CH_3−arom.), 3.15 (dd, J = 5.1, 10.0 Hz, 2 H, OCH_2CH$_2$), 3.82 (m, 1 H, CHN), 3.99 (d, J = 6.9 Hz, 2 H, OCH_2CH), 4.13 (m, 1 H, OCH), 4.39 (s, 1 H, OH), 7.47 (d, J = 8.2 Hz, 2 H, CH−arom.) 7.71 (d, J = 8.2 Hz, 2 H, CH−arom.), 10.86 (s, 1 H, NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 21.4 (CH_3), 25.4 (CH_3), 26.3 (CH_3), 32.7 (CH_2), 41.5 (CH), 58.4 (CH_2O), 63.2 (CHN), 64.8 (CH_2O), 77.8 (CHO), 108.9 (C), 129.6 (CH), 130.2 (C), 130.3 (CH), 145.9 (C), 176.2 (C=O). − $C_{17}H_{24}N_2O_6S$ (384.2): calcd. C 53.11, H 6.29, N 7.29; found: C 53.47, H 6.60, N 6.98.

(4R,5S,1′S)-5-(1-Dibenzylaminoethyl)-4-(2-hydroxyethyl)-1-(toluene-4-sulfonyl)pyrazolidin-3-one (**11i**): Colourless crystals. − M.p. = 164−166°C. − R_f = 0.17 (*n*-hexane/EtAcO, 1:1). − $[\alpha]_D^{20}$ = −20.5 (c = 1, DMSO). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = −0.04 (m, 1 H, CH_2CH_2CH), 0.86 (m, 1 H, CH_2CH_2CH), 1.27 (d, J = 6.7 Hz, 3 H, CH_3), 2.28 (m, 1 H, CHC=O), 2.40 (s, 3 H, CH_3−arom.), 2.69 (m, 1 H, CHN), 3.30 (d, J = 13.3 Hz, 2 H, CH_2N), 3.37 (m, 2 H, OCH_2), 3.74 (m, 1 H, CH_3CH), 3.81 (d, J = 13.3 Hz, 2 H, CH_2N), 7.29 (m, 10 H, CH−arom.), 7.48 (d, J = 8.1 Hz, 2 H, CH−arom.), 7.69 (d, J = 8.1 Hz, 2 H, CH−arom.) 10.96 (s, 1 H, NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 10.1 (CH_3), 21.4 (CH_3), 32.5 (CH_2), 42.0 (CH), 55.0 (2 × CH_2), 55.9 (CH_2), 68.1 (CH), 127.2, 128.5, 129.4, 129.9, 130.3 (CH−arom.), 130.3 (C) 140.0 (C), 145.6 (C), 176.0 (C=O). − $C_{28}H_{33}N_3O_4S$ (507.6): calcd. C 66.25, H 6.55, N 8.28; found: C 65.81, H 6.57, N 7.97.

(4S,5R,4′S)-5-(2,2-Dimethyl[1,3]dioxolan-4-yl)-4-(3-hydroxypropyl)-1-(toluene-4-sulfonyl)pyrazolidin-3-one (**11k**): Colourless crystals. − M.p. = 75−77°C. − R_f = 0.27 ($CHCl_3$/MeOH, 95:5). − $[\alpha]_D^{20}$ = +14.3 (c = 1, $CHCl_3$). − ^{1}H NMR (300 Mhz, $CDCl_3$): δ = 0.01 (m, 1 H, CH_2CH), 0.85 (m, 1 H, CH_2CH), 1.17 (s, 3 H, CH_3), 1.20 (m, 2 H, OCH_2CH_2), 1.24 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3−arom.), 2.32 (m, 1 H, CHC=O), 3.19 (t, J = 6.3 Hz, 2 H, OCH_2CH$_2$), 3.59 (t, J = 3.2 Hz, 1 H, CHN), 3.92 (m, 2 H, OCH_2CH), 4.12 (m, 1 H, OCH_2CH),), 7.24 (d, J = 8.0 Hz, 2 H, CH−arom.), 7.63 (d, J = 8.0 Hz, 2 H, CH−arom.), 8.9 (s, 1 H, NH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.0 (CH_3), 25.2 (CH_3), 26.4 (CH_3), 30.4 (CH_2), 61.8 (CH_2), 63.9 (CH), 65.4 (CH_2), 76.9 (CH), 110.1 (C), 129.0 (2 × CH), 130.6 (2 × CH), 132.4 (C),

146.5 (C), 176.5 (C=O). – $C_{18}H_{26}N_2O_6S$ (398.4): calcd. C 54.26, H 6.58, N 7.03; found: C 53.89, H 6.75, N 6.77.

Crystal Structure Determination for the Compound **8**:[31] Crystals were obtained by recrystallisation from hot hexane/EtOAc (7:3). A colourless crystal of **8** with the dimensions 1.03 × 0.67 × 0.30 mm^3 was measured on a STOE Stadi4 diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Crystal data: $C_{15}H_{20}O_4$, M = 264.35, monoclinic space group $P2_1$, a = 9.879(5), b = 6.546 (8), c = 10.833(6) Å, β = 96.36(5)°, V = 696.3(10) $Å^3$, Z = 2, D_c = 1.261 $g.cm^{-3}$, $F(000)$ = 284, μ(Mo-K_α) = 0.053 mm^{-1}. At 295(2) K in the range of 1.89° < Θ < 27.04°, 3378 reflections were measured ($R_{(sig)}$ = 0.0724) of which 1663 were unique ($R_{(int)}$ = 0.0718) and 1345, flagged as observed, had intensities larger than 2$\sigma(I)$. The structure was solved by direct methods and refined by a least squares procedure within the SHELX program system. The final residuals were $wR2_{(all)}$ = 0.0694, $R1_{(all)}$ = 0.0465 and $R_{1\,(obs)}$ = 0.0345. The maximum and minimum peaks in the final difmap were 0.149 and −0.126 e/$Å^3$, respectively.

Crystal Structure Determination for the Compound **11d** [31] Crystals were obtained by recrystallisation from hot toluene. A colourless crystal of **11d** with the dimensions 0.56 × 0.56 × 0.32 mm^3 was measured on a STOE Ipds diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Crystal data: $C_{17}H_{24}N_2O_6S$, M = 384.44, monoclinic space group $P2_1$, a = 10.695(3), b = 7.990(2), c = 11.373(3) Å, β = 95.40(3)°, V = 967.6(4) $Å^3$, Z = 2, D_c = 1.320 $g.cm^{-3}$, F(000) = 408, μ(Mo−K_α) = 0.202 mm^{-1}. At 200(2) K in the range of 2.75° < Θ < 26.09°, 7863 reflections were measured ($R_{(sig)}$ = 0.0769) of which 3606 were unique ($R_{(int)}$ = 0.1343) and 3138, flagged as observed, had intensities larger than 2$\sigma(I)$. The structure was solved by direct methods and refined by least-squares procedure within the SHELX program system. The final residuals were $wR2_{(all)}$ = 0.1067, $R1_{(all)}$ = 0.0525 and $R1_{(obs)}$ = 0.0440. The maximum and minimum peaks in the final difmap were 0.261 and −0.335 e/$Å^3$, respectively.

Crystal Structure Determination for the Compound **11h**·**CH_3COCH_3**[31]: Crystals were obtained by recrystallisation from hot acetone. A colourless crystal of **11h** with the dimensions 1.00 × 0.82 × 0.24 mm^3 was measured on a STOE Ipds diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Crystal data: $C_{24}H_{33}N_3O_3$, M = 411.53, monoclinic space group $P2_1$, a = 11.209(3), b = 8.173(2), c = 13.540(3) Å, β = 109.35(3)°, V = 1170.4(5) $Å^3$, Z = 2, D_c = 1.168 $g.cm^{-3}$, $F(000)$ = 444, μ(Mo-K_α) = 0.077 mm^{-1}. At 180(2) K in the range of 2.88° < Θ < 25.25°, 7178 reflections were measured ($R_{(sig)}$ = 0.0494) of which 4045 were unique ($R_{(int)}$ = 0.0404) and 3604, flagged as observed, had intensities larger than 2$\sigma(I)$. The structure was solved by direct methods and refined by least-squares procedure within the SHELX program system. The final residuals were $wR2_{(all)}$ = 0.0723, $R1_{(all)}$ = 0.0356 and $R1_{(obs)}$ = 0.0302. The maximum and minimum peaks in the final difmap were 0.133 and −0.125 e/$Å^3$, respectively.

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[31] Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102542 (**8**), -102543 (**11d**), -102544 (**11h**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

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