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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of 3-(ω-hydroxyalkyl)-2-pyrrolidinones from α-alkylidenelactones and nitromethane

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Abstract

Enantiopure 3-(ω-hydroxyalkyl)-2-pyrrolidinones **7** and **9** were synthesised by Michael-addition of nitromethane to chiral α-alkylidenelactones **1** followed by reduction of the resulting 3-(β-nitroalkyl)-lactones and ring transformation of the intermediate 3-(β-aminoalkyl)-lactones. In an analogous manner the naturally occurring costuslactone **10** was transformed into the butyrolactam **12**.

1. Introduction

Recently we reported on the synthesis of optically active 3-amino-3-(ω-hydroxyalkyl)-2-pyrrolidinones by stereoselective cycloaddition of diazomethane to enantiopure α-alkylidenelactones followed by hydrogenolytic N–N bond cleavage and ring transformation.[1] The products were lactams of α,γ-diaminoacids which are interesting as unnatural peptide building blocks. We now report on the stereoselective synthesis of 3-(ω-hydroxyalkyl)-2-pyrrolidinones **7** and **9** which do not possess an amino group at position 3 and hence are analogues of naturally occurring ornithine (Scheme 1). Again enantiopure α-alkylidene lactones **1** were used as starting materials which now, however, were reacted with nitromethane as a C–N-building block. The synthetic sequence started with DBU-assisted Michael-addition of nitromethane giving 2-(β-nitroalkyl)-lactones **2**, **3** and **4.** As by-products 2:1-Michael-adducts **5** were observed, which fortunately could be circumvented by using a larger excess of nitromethane. After chromatographic separation of the diastereomers the nitro groups of 2-(β-nitroalkyl)-lactones **2** and **3** were hydrogenated in the presence of Raney-Ni. Prior to isolation the expected 2-(β-aminoalkyl)-lactones **6** and **8** underwent ring transformation by nucleophilic attack of the new amino group at the carbonyl group of the lactone ring which was opened to generate the ω-hydroxyalkyl side chain while the lactam ring was formed (principle of ring chain transformation).

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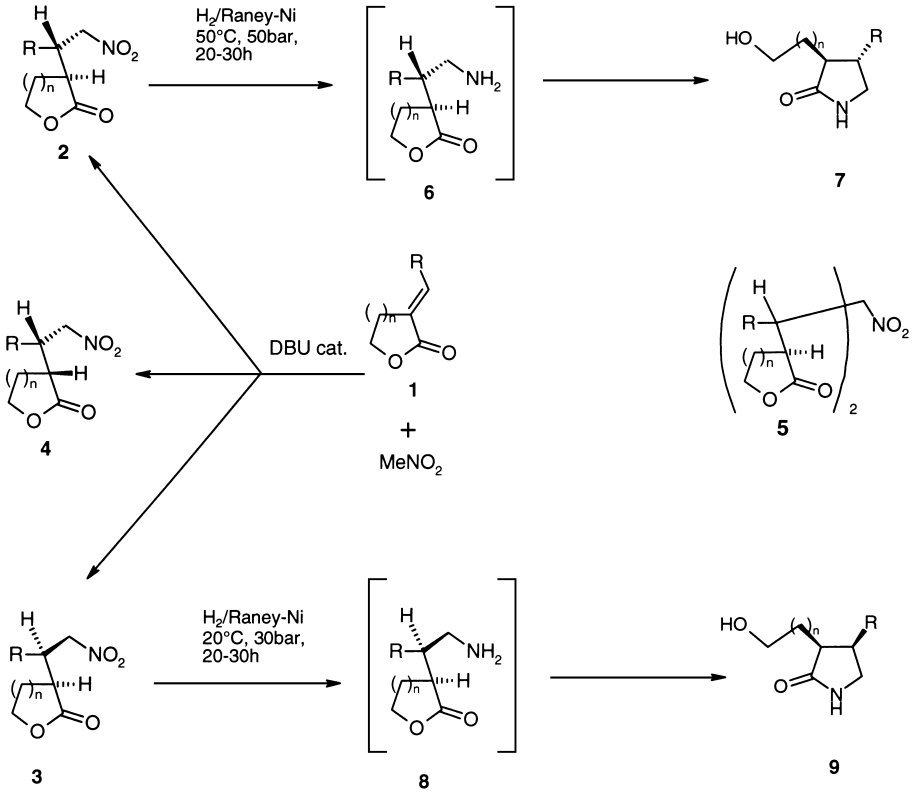
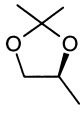
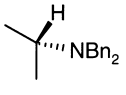


1	2	3	4	5	7	9	R	n
a	**a**		**a**	**a**	**a**		H	1
b	**b**	**b**	**b**		**b**			1
c	**c**	**c**	**c**		**c**			2
d	**d**	**d**				**d**		1

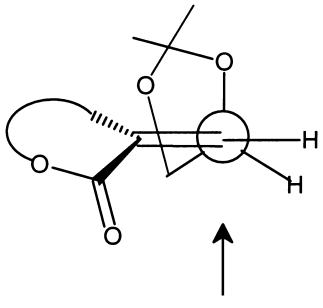
Scheme 1.

As far as the stereochemistry is concerned the first step, the Michael-addition, is crucial and the stereoselectivities of formation of **2**, **3** and **4** were modest (see Table 1). The dominating stereofacial mode of the C–C bond formation can be interpreted by applying the concept of the antiperiplanar effect in Houk's outside crowded model (Scheme 2).[2–4] While in the case of a *si* attack (see Scheme 2) just one stereoisomer was formed, a *re* attack of nitromethane to dioxolane derivatives **1b** and **1c** was followed by a non-stereospecific protonation of the ring position affording epimers **2** and **4** (see Table 1). The assignment of the structures of products is based on X-ray crystal analyses of the adduct **2b** (Fig. 1) and the ring transformed aminoethylpyrrolidinone **9d** (Fig. 2). In addition, ring transformed pyrrolidinones **7b** and **7c** gave almost identical CD-spectra thus proving that the corresponding precursors **2b** and **2c** are homochiral. Corresponding stereoisomers **2**, **3** and **4** reveal the same sequence of r_f values in the

chromatographic separation. After separation **4b** could be partially transformed into **2b** by treatment with K_2CO_3 in EtOH at rt for 16 h, thus proving the epimeric relationship of **2b** and **4b**. Only some Michael-adducts could be fully separated from the other stereoisomers and were submitted to reductive transformation affording enantiopure pyrrolidinones **7** and **9**.

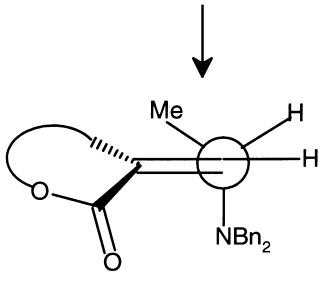
Table 1
Yields and stereoselectivity of the Michael-addition of nitromethane to α-alkylidenelactones **1** and dehydrocostuslactone **10**

Reactant	reaction conditions	yield/%	d. r.
1a	1. 0°C, 16h	76	**2a : 4a** = 1:1
	2. -25°- 20 °C, 21h	86	**2a : 4a** = 1:1
1b	45°C, 18h	85	**2b**:**3b**:**4b** = 41:44:15
1c	20°C, 72h	96	**2c**:**3c**:**4c** = 56:27:17
1d	80°C, 24h	75	**2d**:**3d** = 39:61
10	-25 - 20 °C, 42h	90	**11** >95:5



re-attack

stereochemical mode of attack
interpreted by the anti-periplanar effect



si-attack

Scheme 2.

Dehydrocostuslactone **10** is readily available by isolation from the roots of the African plant *Echinops kebericho M*. The α-methylidenebutyrolactone moiety of this natural product does not bear a chiral substituent attached to the exocyclic position of the C=C double bond but is incorporated in a chiral

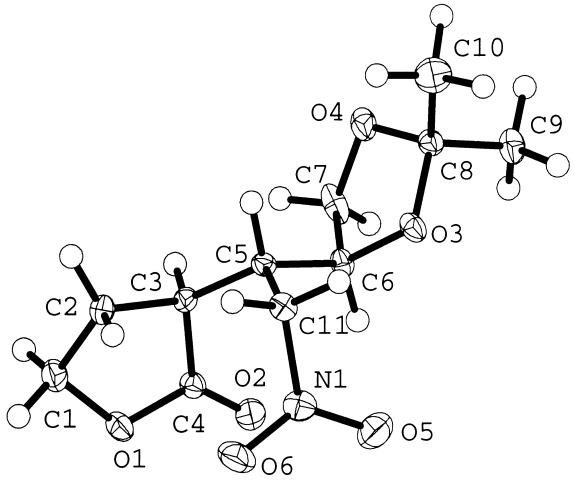


Figure 1. X-Ray crystal analysis of 2-(β-nitroalkyl)-butyrolactone **2b**

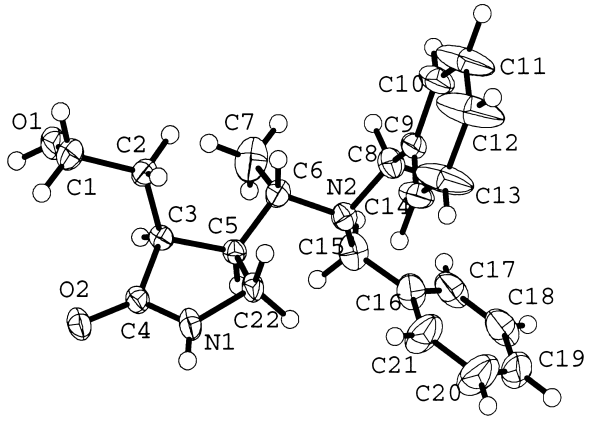
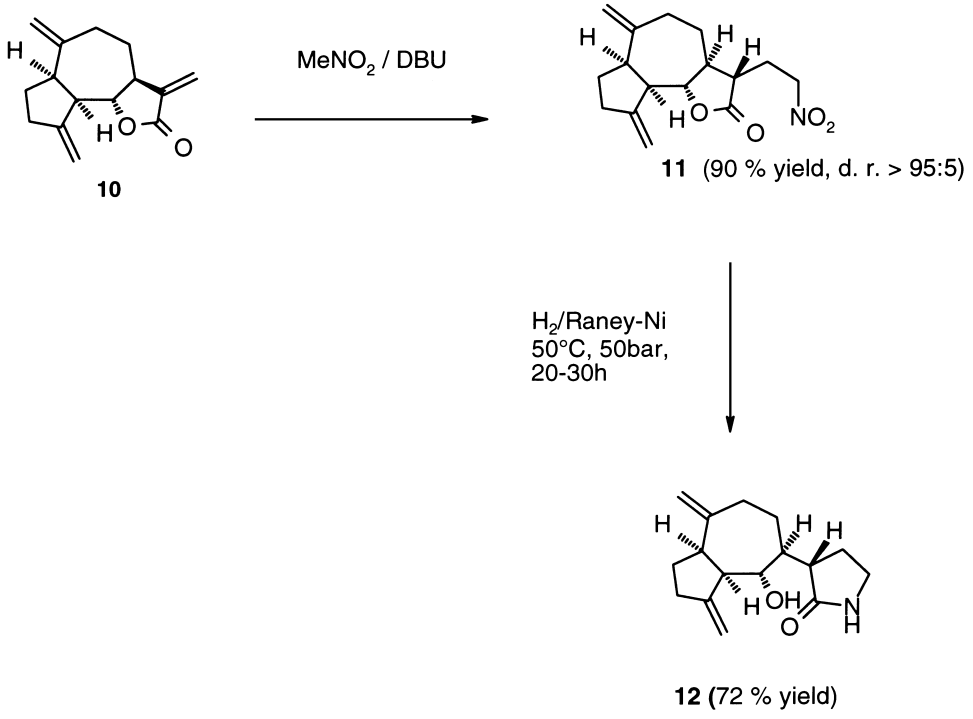


Figure 2. X-Ray crystal analysis of 3-(ω-hydroxyethyl)-butyrolactam **9d**

tricyclic rigid system. This compound gave a smooth and highly stereoselective Michael-addition to **11** if large excesses of nitromethane were used as both reagent and solvent (Scheme 3). Smaller amounts of nitromethane, i.e. higher concentrations of the adduct **10** in the reaction mixture, gave rise to the formation of some 1:2 adducts similar to **5**. Hydrogenation of the nitroethyl derivative **11** again caused subsequent ring transformation affording the interesting pyrrolidinone **12** in good yield. X-Ray crystal analysis of **12** (see Fig. 3) revealed that the protonation occurred from the α-face, obviously governed by a 1,2-induction where the axial H-atom on the seven-membered ring directs the incoming proton to the opposite side.

In summary, a new route to previously unknown optically active 3-(ω-hydroxyalkyl)-2-pyrrolidinones based on the synthetic sequence of diastereoselective Michael-addition, reduction of the nitro group and ring transformation of the resulting α-(ω-aminoalkyl)-lactones was established. So far, syntheses of optically active α-(ω-nitroalkyl)-lactones have been reported by reaction of chiral α-(2-nitrovinyl)-lactones with Grignard reagents,[5,6] (L)-ascorbic acid[7] or $NaBH_4$.[8] Optically active α-(2-aminoalkyl)-lactones were obtained from corresponding α-(2-phthalimidoethyl)[9] or α-(2-nitroethyl)-lactones[7] and underwent ring transformations to corresponding 2-pyrrolidinones before they could be isolated.



Scheme 3.

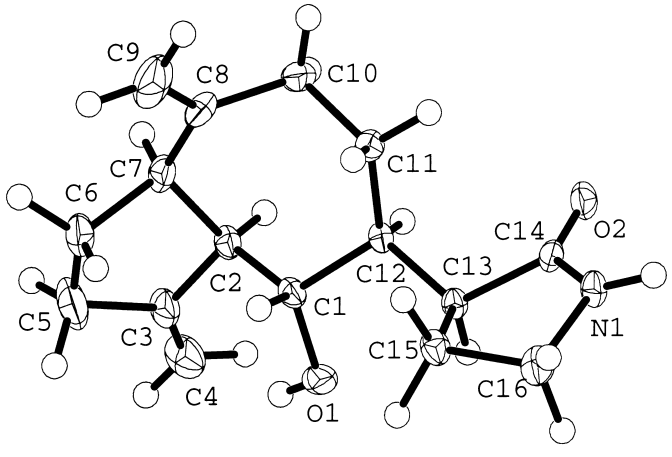


Figure 3. X-Ray crystal analysis of the lactam **12**

2. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC-300 spectrometer with TMS as internal standard. Enantiomeric purity of products was proven by analytical HPLC on cellulose carbamate (Chiralcel OD-R; Daicel). Optical rotation was determined with a Perkin–Elmer polarimeter 241. Starting α-alkylidenlactones **1b**, **1c** and **1d** were prepared as reported before.[10] The lactone **1a** was purchased from Aldrich and the dehydrocustoslactone by extraction from *Echinops kebericho M.* roots with hexane.

2.1. General procedure for the Michael-addition of nitromethane to α-alkylidenelactones **1**

DBU (2 drops) was added to a solution of α-alkylidenelactone **1** (1.5 mmol) in the indicated volume of nitromethane. The mixture was stirred under the conditions given in Table 1. After evaporation of the solvent the remaining material was separated by flash chromatography (see Table 1).

2.2. 3-(2-Nitroethyl)dihydro-2(3H)-furanone **2a**

Light yellow crystals; mp 49–50°C (*n*-hexane:EtOAc, 2:1); R_f=0.34 (*n*-hexane:EtOAc, 1:1); 75 ml nitromethane; ^{1}H NMR (δ/ppm, J/Hz): 1.86 (m, 1H, OCH_2CH_2), 2.09 (m, 1H, $CH_2CH_2NO_2$), 2.26 (m, 1H, $CH_2CH_2NO_2$), 2.32 (m, 1H, OCH_2CH_2), 2.53 (m, 1H, CHC=O), 4.07 (m, 1H, OCH_2), 4.25 (m, 1H, OCH_2), 4.49 (m, 2H, CH_2NO_2); ^{13}C NMR (δ/ppm): 27.8 (CH_2), 28.8, (CH_2), 36.5 (CH), 66.5 (CH_2), 72.9 (CH_2), 177.8 (C=O); Anal. calcd for $C_6H_9NO_4$ (159.13): C, 45.28%; H, 5.70%; N, 8.78%. Found: C, 44.92%; H, 5.76%; 8.77%.

2.3. (3S)-3-{(1S)-1-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-nitroethyl}dihydro-2(3H)-furanone **2b**

Colourless crystals; mp 85–86°C (*n*-hexane:EtOAc, 2:1); R_f=0.28 (acetone:CH_2Cl_2, 2.5:97.5); $[\alpha]_{546}^{20}$ −32.1 (*c* 0.2; $CHCl_3$); 5 ml nitromethane; ^{1}H NMR (δ/ppm, J/Hz): 1.36 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.48 (m, 2H, OCH_2CH_2), 2.88 (m, 1H, CHC=O), 2.96 (m, 1H, $CHCH_2NO_2$), 3.82 (dd, 1H, 5.9/8.7, $CHCH_2O$), 4.21 (dd, 1H, 5.9/8.7, $CHCH_2O$), 4.28 (m, 1H, OCH_2CH_2), 4.31 (m, 1H, OCH), 4.50 (m, 1H, OCH_2CH_2), 4.68 (m, 1H, CH_2NO_2); ^{13}C NMR (δ/ppm): 24.4 (CH_3), 25.6 (CH_2), 25.9 (CH_3), 39.7 (CH), 40.2 (CH), 66.6 (CH), 67.7 (CH_2), 73.7 (CH_2), 74.2 (CH), 109.9 (C_q), 176.9 (C=O); Anal. calcd for $C_{11}H_{17}NO_6$ (259.25): C, 50.96%; H, 6.61%; N, 5.40%. Found: C, 50.92%; H, 6.68%; N, 5.14%.

2.4. Crystal structure determination for compound **2b**[11]

Crystals were obtained by crystallisation from *n*-hexane:EtOAc, 2:1. A colourless crystal of **2b** with the dimensions 0.80×0.47×0.24 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ=0.71073 Å). Crystal data: $C_{11}H_{17}NO_6$, *M*=259.26, orthorhombic space group P 2_1, *a*=5.554(6) Å, *b*=13.64 (3) Å, *c*=16.19(2) Å, *V*=1227 (3) Å^3, *Z*=4, D_c=1.404 g/cm^3, *F*(000)=552, μ (MoK_α)=0.115 mm^{-1}. At 180 (2) K in the range of 1.95°<Θ<26.00° 5362 reflections were measured ($R_{(sig)}$=0.0337) of which 2399 were unique ($R_{(int)}$=0.0292) and 2399, flagged as observed, had intensities larger than 2σ(I). The structure was solved by direct methods and refined by least squares procedure within the SHELX program system. The final residuals were $wR_{2(all)}$=0.0670, $R_{1(all)}$=0.0501 and $R_{1(obs)}$=0.0337. The maximum and minimum peaks in the final difmap were 0.133 and −0.179 e/Å^3, respectively.

2.5. (3S)-3-{(1S)-1-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-nitroethyl}tetrahydro-2H-pyran-2-one **2c**

Colourless crystals; mp 46–47°C (*n*-hexane:EtOAc, 2:1); R_f=0.26 (acetone:CH_2Cl_2, 1:100); $[\alpha]_{546}^{20}$ −52.3 (*c* 0.2; $CHCl_3$); 5 ml nitromethane; ^{1}H NMR (δ/ppm, J/Hz): 1.23 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.78 (m, 1H, CH_2CH_2O), 1.91 (m, 2H, CH_2CH_2CH), 2.10 (m, 1H, CH_2CH_2O), 2.59 (m, 1H, CHC=O), 2.98 (dd, 1H, 4.2/8.3, $CHCH_2NO_2$), 3.68 (m, 1H, OCH_2CH), 4.09 (m, 1H, OCH_2CH), 4.25 (m, 1H, OCH), 4.29 (m 2H, OCH_2CH_2), 4.41 (dd, 1H, 8.6/13.5, CH_2NO_2), 4.57 (dd, 1H, 4.3/13.5, CH_2NO_2); ^{13}C NMR (δ/ppm): 21.4 (CH_2), 22.2 (CH_2), 24.7 (CH_3), 26.1 (CH_3), 40.6 (CH), 41.0 (CH), 68.1 (CH_2),

68.5 (CH_2), 73.6 (CH_2), 74.6 (CH), 109.8 (C_q), 172.3 (C=O); Anal. calcd for $C_{12}H_{19}NO_6$ (273.29): C, 53.50%; H, 7.01%; N, 5.13%. Found: C, 52.97%; H, 7.00%; N, 5.42%.

*2.6. (3*S*)-3-[(1*R*,2*S*)-2-(dibenzylamino)-1-(nitromethyl)propyl]dihydro-2(*3H*)-furanone* ***3d***

Waxy substance; R_f=0.16 (*n*-hexane:EtOAc, 7:3); $[\alpha]_{546}^{20}$ −3.4 (*c* 0.2; $CHCl_3$) 7 ml nitromethane; ^{1}H NMR (δ/ppm, J/Hz): 1.09 (d, 3H, 7.0, CH_3), 1.64 (m, 1H, OCH_2CH_2), 1.95 (m, 1H, OCH_2CH_2), 2.53 (m, 1H, CH_3CH), 2.70 (m, 1H, CHC=O), 3.06 (m, 1H, $CHCH_2NO_2$), 3.17 (d, 2H, 13.1, CH_2NCH), 3.75 (d, 2H, 13.1, CH_2NCH),3.88 (q, 1H, 6.7, CH_2NO_2), 4.03 (m, 1H, OCH_2), 4.22 (m, 1H, OCH_2), 4.65 (dd, 1H, 4.6/13.4, CH_2NO_2), 7.14–7.26 (m, 10H, CH-arom.); ^{13}C NMR (δ/ppm): 9.9 (CH_3), 23.7 (CH_2), 39.1 (CH), 39.8 (CH), 53.6 (2×CH_2), 53.7 (CH), 66.3 (CH_2), 74.9 (CH_2), 127.3, 128.5, 129.2, (10×CH-arom.), 138.8 (C_q), 177.0 (C=O); Anal. calcd for $C_{22}H_{26}N_2O_6$ (382.46): C, 69.09%; H, 6.85%; N, 7.32%. Found: C, 68.97%; H, 7.14%; N, 7.26%.

*2.7. (3a*R*,6a*S*,9a*S*,9b*R*)-6,9-Dimethylene-3-(2-nitroethyl)decahydroazuleno[4,5-b]furan-2(3*H*)-one* ***11***

Colourless crystals; mp 90–92°C (*n*-hexane:EtOAc, 2:1); R_f=0.39 (CH_2Cl_2); $[\alpha]_{546}^{20}$ −13.4 (*c* 0.2; $CHCl_3$); 75 ml nitromethane; ^{1}H NMR (δ/ppm, J/Hz): 1.54 (m, 1H, $CHCH_2CH_2$), 2.11 (m, 2H, CH_2CHC_q), 2.23 (m, 1H, C_qCH_2), 2.25 (m, 1H, OCHCH), 2.29 (m, 1H, $CHCH_2CH_2$), 2.43 (m, 1H, CHC=O), 2.51 (m, 2H, $CH_2CH_2NO_2$), 2.74 (m, 1H, C_qCH_2), 2.76 (m, 2H, CH_2C_q), 3.00 (m, 1H, C_qCH), 3.08 (m, 1H,C_qCH), 4.15 (t, 1H, 9.2, CHO), 4.92 (m, 2H, CH_2NO_2), 4.99, 5.07 (d, 2H, 29.2, CH_2=CH), 5.22, 5.34 (d, 2H, 33.8, CH_2=CH); ^{13}C NMR (δ/ppm): 26.2 (CH_2), 30.1 (CH_2), 32.2 (CH_2), 32.4 (CH_2), 37.2 (CH_2), 43.7 (CH), 47.1 (CH), 47.8 (CH), 51.8 (CH), 72.3 (CH_2), 85.5 (CH), 109.4 (CH_2=), 112.3 (CH_2=), 149.3 (C=), 151.4 (C=), 176.9 (C=O); Anal. calcd for $C_{16}H_{21}NO_4$ (291.34): C, 65.96%; H, 7.27%; N, 4.81%. Found: C, 65.69%; H, 7.40%; N, 4.74%.

2.8. Synthesis of 3-(ω-hydroxyalkyl)-lactams ***7****,* ***9*** *and* ***12*** *by hydrogenation and ring transformation of 3-(β-nitroalkyl)-lactones* ***2****,* ***3*** *and* ***10***

Raney-Ni (about 100 mg) was added to a solution of the 2-(β-nitroalkyl)-lactone (0.5 mmol) in dry EtOH (15 mL) in an autoclave. The mixture was pressurised for the given time. After filtration through Celite the solvent was removed and the remaining material was purified by flash chromatography.

2.9. 3-(2-Hydroxyethyl)-2-pyrrolidinone ***7a***

Yield: 64 mg (99%) of colourless crystals; mp 39–40°C (EtOAc); R_f=0.13 ($CHCl_3$:MeOH, 9:1); 50 atm; 50°C; 21 h; ^{1}H NMR (δ/ppm, J/Hz): 1.63 (m, 1H, $HOCH_2CH_2$), 1.76 (m, 1H, CH_2CH_2N), 1.88 (m, 1H, $HOCH_2CH_2$), 2.27 (m, 1H, CH_2CH_2N), 2.49 (m, 1H, CHC=O), 3.31 (m, 2H, CH_2N), 3.66 (m, 2H, $HOCH_2$), 4.57 (dd, 1H, 3.8/6.9, OH), 7.37 (s, 1H, NH); ^{13}C NMR (δ/ppm): 28.3 (CH_2), 33.9 (CH_2), 40.6 (CH), 41.1 (CH_2), 61.3 (CH_2), 181.6 (C=O). Anal. calcd for $C_6H_{11}NO_2$ (129.15): C, 55.80%; H, 8.58%; N, 10.84%. Found: C, 55.54%; H, 8.71%; N, 10.70%.

*2.10. (3*S*,4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(2-hydroxyethyl)-2-pyrrolidinone* ***7b***

Yield: 71 mg (62%) of waxy substance; R_f=0.26 ($CHCl_3$:MeOH, 9:1); $[\alpha]_{546}^{20}$ −38.5 (*c* 0.2; $CHCl_3$); 50 atm; 50°C; 17 h; ^{1}H NMR (δ/ppm, J/Hz): 1.28 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.76 (m, 2H,

$HOCH_2CH_2$), 2.29 (m, 1H, $CHCH_2N$), 2.36 (m, 1H, CHC=O), 3.28 (t, 1H, 9.9, CH_2N), 3.40 (m, 1H, CH_2N), 3.53 (dd, 1H, 7.0/8.1, OCH_2), 3.72 (m, 2H, $HOCH_2$), 4.00 (dd, 1H,6.3/8.1, OCH_2), 4.12 (m, 1H, CHO), 4.39 (q, 1H, 3.7, OH), 6.97 (s, 1H, NH); ^{13}C NMR (δ/ppm): 25.2 (CH_3), 26.4 (CH_3), 33.1 (CH_2), 42.5 (CH_2), 43.4 (CH), 43.5 (CH), 61.5 (CH_2), 67.0 (CH_2), 75.6 (CH), 109.2 (C_q), 180.4 (C=O); Anal. calcd for $C_{11}H_{19}NO_4$ (229.26): C, 57.63%; H, 8.35%; N, 6.11%. Found: C, 57.11%; H, 8.42%; N, 6.28%.

2.11. (3S,4S)-4-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(3-hydroxypropyl)-2-pyrrolidinone ***7c***

Yield: 74 mg (61%) of waxy substance; R_f=0.17 ($CHCl_3$:MeOH, 9:1); $[\alpha]_{546}^{20}$ −32.8 (*c* 0.2; $CHCl_3$); 40 atm; 50°C; 22 h; ^{1}H NMR (δ/ppm, J/Hz): 1.28 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.60 (m, 2H, $HOCH_2CH_2$), 1.63 (m, 2H, CH_2CHC=O), 2.19 (m, 1H, CH_2CHC=O), 2.26 (m, 1H, $CHCH_2N$), 3.12 (s, 1H, OH), 3.25 (m, 1H, CH_2N), 3.37 (m, 1H, CH_2N), 3.52 (m, 1H, OCH_2), 3.57 (m, 2H, $HOCH_2$), 3.99 (m, 1H, OCH_2), 4.06 (m, 1H, CHO), 6.87 (s, 1H, NH); ^{13}C NMR (δ/ppm): 25.3 (CH_3), 25.9 (CH_2), 26.6 (CH_3), 29.6 (CH_2), 42.3 (CH_2), 42.7 (CH), 43.1 (CH), 61.9 (CH_2), 67.3 (CH_2), 76.6 (CH), 109.1 (C_q), 179.9 (C=O); Anal. calcd for $C_{12}H_{21}NO_4$ (243.29): C, 59.24%; H, 8.70%; N, 5.76%. Found: C, 58.92%; H, 8.63%; N, 5.39%.

2.12. (3S,4R)-4-[(1S)-1-(Dibenzylamino)ethyl]-3-(2-hydroxyethyl)-2-pyrrolidinone ***9d***

Yield: 108 mg (61%) of colourless crystals; mp 168–169°C (EtOAc); R_f=0.17 ($CHCl_3$:MeOH, 95:5); $[\alpha]_{546}^{20}$ −12.1 (*c* 0.2; $CHCl_3$); 30 atm; 20°C; 17 h; ^{1}H NMR (δ/ppm, J/Hz): 0.95 (d, 3H, 6.3, CH_3), 1.12 (m, 1H, $HOCH_2CH_2$), 1.44 (m, 1H, $HOCH_2CH_2$), 2.30 (m, 1H, CHC=O), 2.56 (dd, 1H, 7.6/17.9, $CHCH_2N$), 2.71 (m, 1H, CH_3CH), 2.95 (t, 1H, 10.3, CH_2N), 3.22 (d, 2H, 13.6, CH_2NCH), 3.47 (m, 1H, CH_2N), 3.58 (m, 2H, $HOCH_2$), 3.65 (d, 2H, 13.6, CH_2NCH), 6.89 (s, 1H, NH), 7.11–7.23 (m, 10H, CH-arom.); ^{13}C NMR (δ/ppm): 9.9 (CH_3), 26.9 (CH_2), 41.6 (CH), 43.8 (CH), 45.7 (CH_2), 51.0 (CH), 53.4 (2×CH_2), 60.8 (CH_2), 127.1, 128.4, 128.6, (CH-arom.), 139.6 (C_q), 181.8 (C=O); Anal. calcd for $C_{22}H_{28}N_2O_2$ (352.47): C, 74.97%; H, 8.01%; N, 7.95%. Found: C, 74.76%; H, 7.81%; N, 7.72%.

2.13. Crystal structure determination for compound ***9d***[11]

Crystals were obtained by crystallisation from toluene. A colourless crystal of **9d** with the dimensions 0.78×0.60×0.42 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ=0.71073 Å). Crystal data: $C_{22}H_{28}N_2O_2$, *M*=352.46, orthorhombic space group P 2_1, *a*=14.062 (2) Å, *b*=16.5231 (16) Å, *c*=8.415 (2) Å, *V*=1955.2 (6) Å^3, *Z*=4, D_c=1.197 g/cm^3, *F*(000)=760, μ (MoK_α)=0.077 mm^{-1}. At 180 (2) K in the range of 2.72°<Θ<24.04° 1701 reflections were measured ($R_{(sig)}$=0.0642) of which 1701 were unique ($R_{(int)}$=0.0000) and 1701, flagged as observed, had intensities larger than 2σ(I). The structure was solved by direct methods and refined by least squares procedure within the SHELX program system. The final residuals were w$R_{2(all)}$=0.1706, $R_{1(all)}$=0.0841 and $R_{1(obs)}$=0.0642. The maximum and minimum peaks in the final difmap were 0.316 and −0.305 e/Å^3, respectively.

2.14. (3R)-3-[(3aS,4S,5S,8aS)-4-Hydroxy-3,8-dimethylenedecahydro-5-azulenyl]-2-pyrrolidinone ***12***

Yield: 94 mg (72%) of colourless crystals; mp 183–184°C (EtOAc); R_f=0.25 ($CHCl_3$:MeOH, 95:5); $[\alpha]_{546}^{20}$ −17.1 (*c* 0.2; $CHCl_3$); 30 atm; 20°C; 20 h; ^{1}H NMR (δ/ppm, J/Hz): 1.17 (m, 1H, $CHCH_2CH_2$), 1.61 (m, 1H, CH_2C_q), 1.80 (m, 1H, $CH_2CH_2C_q$), 1.84 (m, 1H, $CHCH_2CH_2$), 1.86 (m, 1H, $C_qCH_2CH_2$),

1.93 (m, 1H, C*H*$_2$C$_q$), 1.99 (m, 1H, C$_q$CH), 2.06 (m, 1H, C*H*$_2$CH$_2$C$_q$), 2.29 (m, C$_q$C*H*$_2$CH$_2$), 2.38 (m, 2H, C*H*$_2$CH$_2$N), 2.72 (m 1H, C*H*CHOH), 2.83 (m, 1H, CHO), 3.05 (m, 1H, C*H*OH), 3.16 (m, 1H, C*H*CHC=O), 3.26 (m, 2H, CH$_2$N), 4.64, 4.75 (d, 2H, 33.3, CH$_2$=), 5.01, 5.07 (d, 2H, 16.8, CH$_2$=); ^{13}C NMR (δ/ppm): 22.0 (CH$_2$), 28.6 (CH$_2$), 29.5 (CH$_2$), 30.6 (CH$_2$), 34.7 (CH$_2$), 40.6 (CH$_2$), 42.3 (CH), 46.6 (CH), 47.5 (CH), 55.5 (CH), 67.5 (CH), 110.3 (CH$_2$=), 111.4 (CH$_2$=), 152.5 (C$_q$), 153.4 (C$_q$), 181.2 (C=O) Anal. calcd for $C_{16}H_{23}NO_2$ (261.36): C, 73.52%; H, 8.87%; N, 5.36%. Found: C, 73.30%; H, 8.53%; N, 5.16%.

2.15. Crystal structure determination for compound ***12***[11]

Crystals were obtained by crystallisation from hot toluene. A colourless crystal of **12** with the dimensions 0.88×0.51×0.24 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ=0.71073 Å). Crystal data: $C_{16}H_{23}NO_2$, M=261.35, orthorhombic space group P 2$_1$, a=5.8215 (18) Å, b=13.581 (4) Å, c=18.669 (4) Å, V=1476.0 (7) Å^3, Z=4, D_c=1.176 g/cm^3, F(000)=568, μ (MoK_α)=0.077 mm^{-1}. At 180 (2) K in the range of 2.18°<Θ<26.09° 2736 reflections were measured ($R_{(sig)}$=0.0425) of which 2358 were unique ($R_{(int)}$=0.0273) and 2358, flagged as observed, had intensities larger than 2σ(I). The structure was solved by direct methods and refined by least squares procedure within the SHELX program system. The final residuals were w$R_{2(all)}$=0.1051, $R_{1(all)}$=0.0638 and $R_{1(obs)}$=0.0425. The maximum and minimum peaks in the final difmap were 0.143 and −0.143 e/Å^3, respectively.

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10. Otto, A.; Ziemer, B.; Liebscher, J. *Eur. J. Org. Chem*. **1998**, 2667; erroneous configurations were given for compounds **7c**, **11a**, **11g** in this paper. The correct configurations are for **7c**:1′*R*,*E*; for **11a**: 4*S*, 5*R*, 4′*S*; and for **11g**: 4*R*, 5*S*, 1′*R*.
11. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-133192 (**2b**), CCDC-133190 (**9d**), CCDC-133191 (**12**). 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).