Optically Active α-Spirocyclopropyllactones and 3-Aminopyrrolidones via Stereoselective Diazoalkane Cycloaddition at α-Alkylidenelactones

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Abstract: 1,3-Dipolar cycloaddition of diazoalkanes **2** to optically active α-alkylidenelactones **1** gives high yields of pyrazolines **3** and **4** in a stereoselective manner. These pyrazolines can further be transformed into α-spirocyclopropyllactones **5** and **6** by irradiation and into α-amino-α-(ω-hydroxyalkyl)-γ-butyrolactams **7** and **8** by reductive N–N bond cleavage.

Key words: diazoalkanes, cycloaddition, spirocyclopropanes, lactones, α-amino acids, lactams

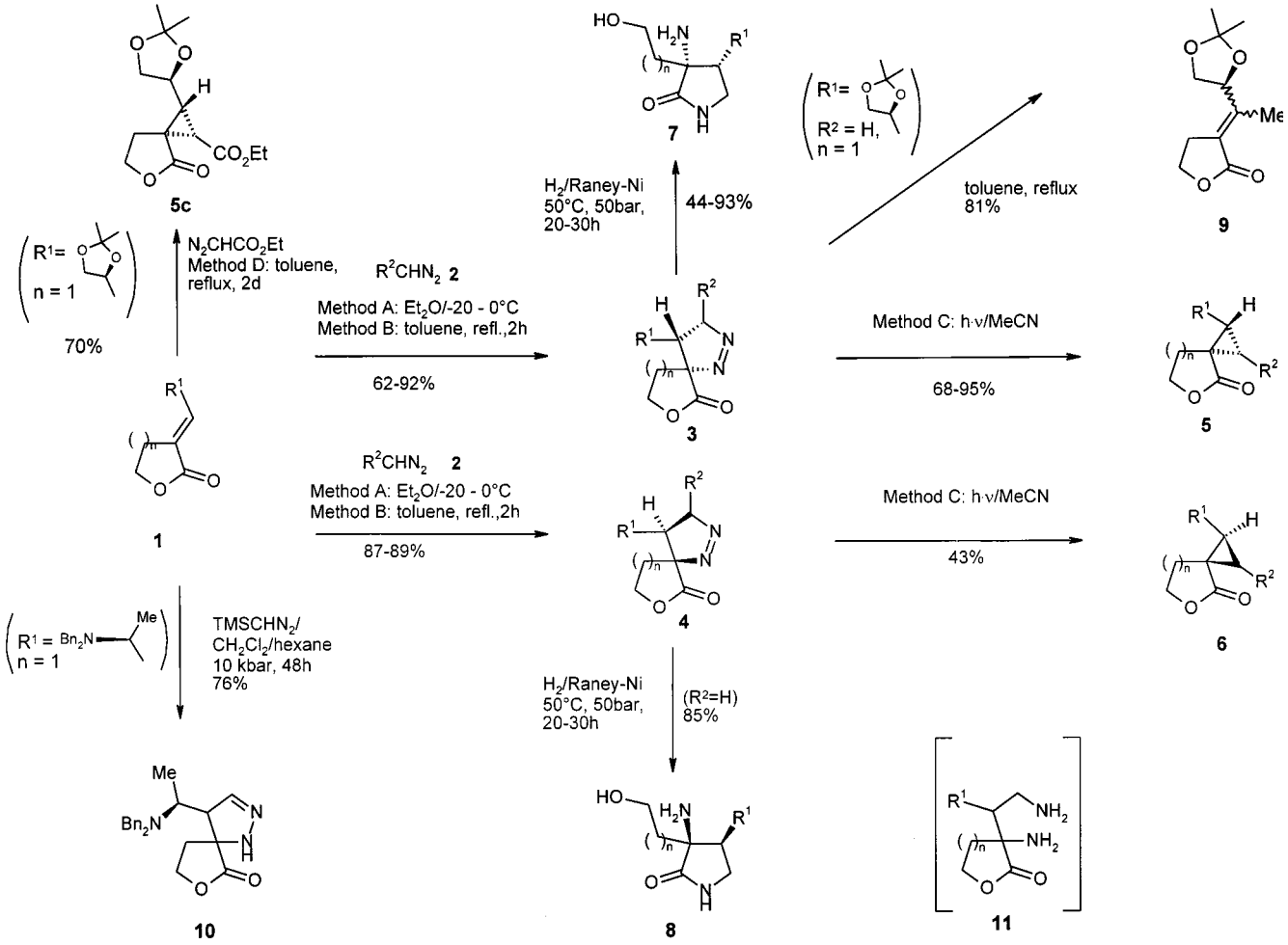
1,3-Dipolar cycloaddition of diazomethane to α-alkylidene or δ-lactones was repeatedly used as the first step in the synthesis of α-spirocyclopropyl-γ-butyrolactones in particular in the naturally occurring α-methylidenelactone series.[1,2] The transformation of the 1-pyrazolines primarily formed into the spirocyclopropyllactones by the loss of nitrogen was achieved by irradiation with UV-light, which is a general method for the synthesis of cyclopropanes.[2] Some of such spirocyclopropyl compounds are interesting as constraint derivatives of anticonvulsant and convulsant α,α-dialkyl-γ-butyrolactones.[3] If additional substituents were attached to a noncondensed α-alkylidenelactone ring a stereoselective *anti*-addition of diazomethane was observed.[4,5]

We became interested if chiral substituents attached to the exocyclic position of the C–C double bond of α-alkylidene-γ-lactones and δ-lactones can also exert a stereodirecting effect onto the cycloaddition of diazoalkanes. The expected optically active pyrazolines were promising candidates for new α-spirocyclopropyllactones by N_2-elimination and for a novel access to α-amino-α-(ω-hydroxyalkyl)-γ-butyrolactams by reductive N–N bond cleavage.

α-Alkylidenelactones **1**[6] derived from D- or L-glyceraldehyde or from L-alanine, i. e. with heteroatoms connected to the stereogenic centre of R^1, were used as enantiopure starting materials. Reaction of **1** with diazomethane **2** (R^2 = H) or trimethylsilyldiazomethane **2** (R^2 = TMS) at room temperature or at 0°C gave smooth 1,3-cycloaddition affording high yields of 1-pyrazolines **3** and **4** (Methods A and B). The dibenzylaminopropylidenebutyrolactone **1f** however required high pressure conditions to undergo a successful cycloaddition with trimethylsilyldiazomethane. The TMS group was lost and a corresponding 2-pyrazoline **10** was obtained. Silylpyrazolines are known to lose the TMS group during chromatography on silica gel.[7] All cycloadditions of **2** to **1** were stereoselective (for diastereomeric ratios see Table). With the exception of **3b** the major diastereomer of **3** and **4** could be separated in pure form by column chromatography. Ethyl diazoacetate **2** (R^2 = COOEt) was not reactive enough to undergo cycloadditions with α-alkylidenelactones **1** at room temperatures but was found to react in refluxing toluene after two days (Method D). These drastic conditions caused elimination of N_2 from the expected pyrazoline **3** (R^2 = COOEt) giving rise to the formation of the corresponding cyclopropane **5c**. Remarkably, thermal conditions were not appropriate for the N_2-elimination from the other pyrazolines **3** and **4** derived from diazomethane (R^2 = H) in order to synthesize corresponding cyclopropanes **5** and **6** (R^2 = H) since corresponding alkenes such as **9** were formed instead. On the other side UV-irradiation of **3** or **4** gave corresponding α-spirocyclopropyllactones **5** or **6** (R^2 = H), respectively, in high yields (see Table). These products were obtained as single stereoisomers if pure precursors **3** or **4** were used (*v.i.*). A mixture of diastereomeric pyrazolines **3b** gave diastereomeric cyclopropanes **5b** (separable by flash chromatography) in the same ratio as started with (see Table).

Reductive N–N-bond cleavage of pyrazolines represents a convenient pathway to 1,3-diamines.[8,9] If an ester moiety is attached to the pyrazoline ring the resulting diamines can cyclize to corresponding lactams.[10,11] Hydrogenation of the α-spiropyrazolinyllactones **3** or **4** in the presence of Raney Ni gave rise to the formation of α-amino-α-(ω-hydroxyalkyl)-γ-butyrolactams **7** or **8**, respectively (see Table). Obviously the 1,3-diamines **11** formed by reductive N–N bond cleavage undergo a ring transformation reaction by attack of the terminal amino group at the carbonyl carbon. The N-benzyl groups of **8f** survived the hydrogenolytic conditions. The transformation of **1** to **7** or **8** represents a novel comparatively short access to α-amino-α-(ω-hydroxyalkyl)-γ-butyrolactams. Hitherto such lactams and corresponding open-chained α-amino-α-(ω-hydroxyalkyl)carboxylic acid derivatives were only accessible by multistep syntheses.[12,13] These compounds are of interest in the synthesis of dipeptide bioisosteres[12] or as pharmacologically active lactam-conformationally restricted amino acids,[13] respectively.

All products **3**, **4**, **5**, **6**, **7**, **8**, **9** and **10** are new. Their structure was elucidated by X-ray crystal analyses (see Figures 1, 2, 3, 4) and spectroscopic data (see Table). As could be seen from the X-ray crystal analysis of pyrazolines **3a** and **4f** (see Figures 1 and 2) the face selectivity of the cycload-



n	R^1	R^2	1	3	4	5	6	7	8
1		H	**a**	**a**		**a**		**a**	
1		TMS		**b**		**b**			
1		CO_2Et				**c**			
1		H	**d**	**d**					

n	R^1	R^2	1	3	4	5	6	7	8
1		H	**e**		**e**				
1		H	**f**		**f**		**f**		**f**
2		H	**g**	**g**		**g**		**g**	

Scheme 1

dition is governed by the configuration at the substituent R^1. The same mode of asymmetric induction was observed in the stereoselective transformation of α-alkylidenelactones **1** into ω-hydroxyalkylpyrazolidones with hydrazines[6] and in the 1,3-dipolar addition of diazoalkanes to acrylates[14] with the same chiral substitutents R^1 attached to the ß-position as found in the lactones **1**.This effect could be explained by Houks outside-crowded

Table 1 Pyrazolines **3** and **4** and **10**, α-Spirocyclopropyllactones **5** und **6,** α-Amino-α-(ω-hydroxyalkyl)-γ-butyrolactams **7** and **8**, and α-Akylidenelactone **9**

Product	Reaction conditions	Yield (%)	d. r.	mp (°C)[a] (Solvent)	$[\alpha]_D^{20a}$ (c=1, $CHCl_3$)	^{1}H NMR[a] ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR[a] ($CDCl_3$) δ, *J* (Hz)
3a[b]	16 h, 0 °C, Et_2O, 5 eq. **2**	91	85:15	117–118 (MeOH/ Et_2O, 3:1)	–455.6	1.19 (s, 3 H, Me); 1.28 (s, 3 H, Me); 2.49 (ddd, 1 H, C*H*-CH_2N, *J* = 8.6, 3.8, 2.1); 2.61 (m, 2 H, CH_2C); 3.49 (dd, 1 H, CHC*H*$_2$O, *J* = 6.7, 4.6); 3.97 (dd, 1 H, CHC*H*$_2$O, *J* = 6.7, 4.6); 4.02 (m, 1 H, CHO); 4.82 (m, 2 H, CH_2N); 4.86 (m, 2 H, CH_2O)	24.6 (Me); 26.0 (Me); 29.4 (*C*H_2C); 38.5 (*C*HCH$_2$N); 67.4 (CH_2O); 67.7 (CH*C*H$_2$O); 72.7 (CHO); 78.8 (CH_2N); 95.8 (*C*N); 109.7 (Me$_2$*C*); 173.4 (C=O)
3b	4 d, r. t., MePh, 1.5 eq. **2**	74	88:12[c]	yellowish oil		0.00 (s, 9 H, Me_3Si); 1.06 (s, 3 H, Me); 1.15 (s, 3 H, Me); 228 (m, 2 H, C*H*$_2$C); 2.34 (m, 1 H, C*H*CHSi); 3.23 (m, 1 H, CHC*H*$_2$-O); 3.80 (m, 1 H, CHC*H*$_2$O); 4.37 (m, 1 H, CHO); 4.61 (m, 2 H, CH_2O); 4.67 (m, 1 H, CHSi)	0.00 (Me_3Si); 27.0 (Me); 27.5 (Me); 33.3 (CH_2C); 42.5 (*C*HCHSi); 69.4 (CH_2O); 69.8 (CH*C*H$_2$O); 74.4 (CHO); 90.8 (CHSi); 98.1 (C_q-N); 111.4 (C_q Me$_2$*C*); 176.0 (C=O)
3d	2 d, 0 °C, Et_2O, 3 eq. **2**	92	84:16	124–125 (MeOH/ Et_2O, 3:1))	–354.8	1.38–1.51 (m, 10 H, 5x CH_2); 2.49 (m, 1 H, C*H*CH$_2$N), 2.62 (m, 2 H, CH_2C); 3.48 (m, 1 H, CHC*H*$_2$O); 3.98 (m, 1 H, CHC*H*$_2$O); 4.00 (m, 1 H, CHO); 4.55 (m, 2 H, CH_2O); 4.62 (m, 2 H, CH_2N); 4.81 (m, 1 H, CH_2O); 4.86 (m, 1 H, CH_2N)	24.1, 24.2, 25.3, 34.5, 36.1 (5x CH_2); 30.0 (*C*H_2C); 38.7 (*C*HCH$_2$N); 67.7 (CH_2O); 67.8 (CH*C*H$_2$O); 72.7 (CHO); 79.3 (CH_2N); 96.3 (*C*$_q$-N); 110.7 (C_q); 173.9 (C=O)
3g	16 h, 0 °C, Et_2O, 5 eq. **2**	62	82:18	125–126 (MeOH/ Et_2O, 3:1)	–424.2	1.21 (s, 3 H, Me); 1.29 (s, 3 H, Me), 2.09 (m, 2 H, CH_2C); 2.24 (m, 1 H, C*H*$_2$CH$_2$C); 2.65 (m, 1 H, C*H*$_2$CH$_2$C); 2.74 (m, 1 H, C*H*CH$_2$N); 3.48 (m, 1 H, CHC*H*$_2$O); 4.01 (m, 1 H, CHC*H*$_2$O); 4.06 (m, 1 H, CHO); 4.45 (m, 1 H, CH_2O); 4.63 (dd, 1 H, *J* = 17.6, 8.4, CH_2N); 4.79 (m, 1 H, CH_2O); 4.89 (m, 1 H, CH_2N)	21.4 (*C*H$_2$C); 25.3 (Me); 26.0 (Me); 26.6 (*C*H$_2$CH$_2$C); 41.1 (*C*HCH$_2$N); 68.5 (CH*C*H$_2$O); 70.6 (CH_2O); 72.8 (CHO); 79.5 (CH_2N); 96.4 (C_q-N); 110.2 (C_q); 168.6 (C=O)
4c	2 d ,-18 °C - r. t., Et_2O, 3 eq. **2**	89	86:14	102–103 (MeOH)	+304.1	2.22 (s, 1 H, OH); 2.37 (m, 2 H, CH_2-C); 2.63 (m, 1 H, C*H*CH$_2$N); 3.39 (m, 1 H, CH-O); 3.62 (m, 2 H, C*H*$_2$OH); 4.31 (d, 1 H, *J* = 11.8, O-CH_2-arom.); 4.48 (m, 1 H, CH_2-O); 4.59 (d, 1 H, *J* = 11.8, O-CH_2-arom.); 4.72 (m, 1 H, CH_2N); 4.80 (m, 1 H, CH_2O); 4.89 (m, 1 H, CH_2N); 7.11–7.27 (m, 5 H, CH-arom.);	29.4 (*C*H$_2$C); 38.9 (*C*HCH$_2$N); 62.6 (CH$_2$OH); 67.9 (CH_2O); 71.6 (OCH$_2$-arom.); 77.2 (CHO); 79.8 (CH_2N); 96.3 (CN); 127.4, 127.8, 128.3, 128.9, 129.0 (CH-arom.); 138.1 (C_q-arom.); 174.7 (C=O)
4f	20 h, 0 °C, Et_2O, 5 eq. **2**	87	82:18	164–165 (MeOH/ Et_2O, 1:2)	+152.3	0.94 (d, 3 H, J = 6.4, Me); 1.56 (m, 1 H, CH_2C); 1.99 (m, 1 H, CH_2C); 2.43 (1H,C*H*CH$_3$); 2.59 (m, 1 H, C*H*CH$_2$N); 3.21 (d, 2 H, *J* = 13.6, PhC*H*$_2$N); 3.73 (d, 2 H, *J* = 13.6, PhC*H*$_2$N); 4.00 (dd, 1 H, *J* = 18.3, 10.2, NC*H*$_2$CH); 4.38 (m, 1 H, CH_2O); 4.59 (m, 1 H, CH_2O); 5.07 (dd, 1 H, *J* = 18.3, 8.5, NCH_2CH); 7.13–7.28 (m, 10 H, CH-arom.)	11.5 (Me); 27.9 (*C*H$_2$C); 41.6 (*C*HCH$_2$N); 52.5 (*C*HMe); 53.8 (2x PhCH$_2$N); 66.9 (CH_2O); 82.3 (N*C*H$_2$CH); 92.9 (C_qN); 127.4, 128.9, 129.1 (CH-arom.); 139.6 (C_q-arom.); 174.8 (C=O)
5a[d]	1 h, r. t., MeCN, hν Method C	95	>95:5	105–106 (MePh)	–74.1	1.01 (m, 1 H, CHC*H*$_2$-C); 1.21 (s, 3 H, Me); 1.24 (m, 1 H, CHC*H*$_2$C); 1.28 (s, 3 H, Me); 1.53 (m, 1 H, C*H*C); 2.10 (m, 1 H, CH_2C); 2.25 (m, 1 H, CH_2C); 3.59 (dd, 1 H, *J* = 7.8, 6.2, CHC*H*$_2$O); 3.76 (dd, 1 H, *J* = 13.1, 6.1, CHO); 4.02 59 (dd, 1 H, *J* = 7.8, 6.2, CHC*H*$_2$O); 4.29 (m. 2 H, CH_2O)	18.5 (CH*C*H$_2$C); 23.4 (*C*$_q$); 25.6 (*C*HC); 26.12 (Me); 26.8 (Me); 27.1 (*C*H$_2$C); 66.5 (CH_2O); 69.6 (CHC*H*$_2$-O), 75.1 (CHO); 109.8 (C_q); 179.7 (C=O)

Table 1 (continued)

Product	Reaction conditions	Yield (%)	d. r.	mp (°C)[a] (Solvent)	$[\alpha]_D^{20a}$ (c=1, $CHCl_3$)	^1H NMR[a] ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR[a] ($CDCl_3$) δ, *J* (Hz)
5b[e]	2 h, r. t., MeCN, hν Method C	68	88:12	92–93 (MeOH/ Et_2O, 1:3)	–43.9	0.00 (s, 9 H, MeSi); 0.36 (d, 1 H, *J* = 8.7, CHSi); 1.25 (s, 3 H, Me); 1.29 (s, 3 H, Me); 1.59 (dd, 1 H, *J* = 8.7, 5.5, C*H*CHSi); 2.00 (m, 1 H, CH_2C); 2.39 (m, 1 H, CH_2C); 3.60 (dd, 1 H, *J* = 8.0, 6.8, CHC*H*$_2$O); 3.86 (q, 1 H, *J* = 6.1, CHO); 4.06 (dd, 1 H, *J* = 8.0, 6.1, CHC*H*$_2$O); 4.29 (m, 2 H, CH_2O);	0.0 (Me_3Si); 22.0 (CH-Si); 26.9 (Me); 27.6 (Me); 29.2 (C_qCH_2); 30.3 (CH_2C); 32.5 (*C*HCHSi); 67.3 (CH_2O); 70.7 (CHCH_2O); 76.5 (CHO); 110.5 (C_q); 180.0 (C=O)
5c	2 d, reflux, MePh, 1.5 eq. **2** Method D	70	88:12	yellowish oil	–56.5	1.19 (t, 3 H, *J* = 3.5, *Me*CH); 1.30 (s, 3 H, Me); 1.36 (s, 3 H, Me); 2.18 (m, 1 H, CHC=O); 2.28 (m, 1 H, CH_2C); 2.31 (m, 1 H, C*H*CHC=O); 2.47 (m, 1 H, CH_2C); 3.60 (m, 1 H, CHC*H*$_2$O); 3.71(m, 1 H, MeC*H*$_2$O); 4.08 (m, 2 H, CH_2O); 4.72 (m, 1 H, CHO); 4.19 (m, 1 H, MeC*H*$_2$O); 4.39 (m, 1 H, CHC*H*$_2$O)	14.4 (*Me*CH_2); 26.0 (Me); 26.7 (Me); 28.3 (*C*H_2C); 30.4 (*C*HC=O); 30.6 (C_q-CH_2) 31.8 (*C*HCHC=O); 61.8 (CH_2O); 66.5 (CH*C*H_2O); 69.7 (Me*C*H_2O); 72.3 (CHO); 110.2 (C_q); 167.7 (C=O); 175.3 (C=O)
5g	2 h, r. t., MeCN, hν Method C	89	>95:5	112–113 (MeOH/ Et_2O, 1:2)	–49.7	1.02 (m, 2 H, CHC*H*$_2$C); 1.12 (s, 3 H, Me); 1.19 (s, 3 H, Me); 1.37 (dd, 1 H, *J* = 9.2, 4.0, CHC*H*C); 1.52 (m, 1 H, CH_2CH_2C); 1.67 (m, 2 H, C*H*$_2$CH$_2$C); 1.80 (m, 1 H, CH_2CH_2C); 3.54 (m, 1 H, CHC*H*$_2$O); 3.66 (dd, 1 H, *J* = 12.9, 6.3, CHO); 3.92 (m, 1 H, CHC*H*$_2$O); 4.22 (m, 2 H, CH_2O)	22.7 (CH*C*H_2C); 23.3 (CH_2CH_2C); 23.7 (CH*C*$_q$); 26.2 (Me), 27.2 (Me); 30.3 (CH*C*HC); 69.5 (CH*C*H_2O); 70.4 (CH_2O); 109.7 (C_q); 174.0 (C=O)
6f	1.3 h, r. t., MeCN, hν Method C	43	>95:5	149–150 (MePh)	–44.8	0.78 (m, 1 H, CHC*H*$_2$C); 1.09 (d, 3 H, *J* = 6.6, Me); 1.39 (m, 2 H, CHC*H*$_2$C); 1.57 (m, 1 H, C*H*CH_2); 1.72 (m, 1 H, CH_2C*H*$_2$C); 1.91 (m, 1 H, CH_2C*H*$_2$C); 2.11 (m, 1 H, C*H*Me); 3.48 (d, 2 H, *J* = 13.7, CH_2N); 3.71 (d, 2 H, *J* = 13.7, CH_2N); 4.22 (m, 2 H, CH_2O) 7.11-7.29 (m, 10 H, CH-arom.)	15.2 (Me); 21.3 (CH*C*H_2C); 24.1 (CH_2C_q); 26.1 (*C*H_2C); 29.1 *C*HCH_2); 53.3 (*C*HMe); 54.1 (2x CH_2N); 66.4 (CH_2O); 127.2, 128.6, 129.0, (CH-arom.); 140.5 (C_q-arom.); 180.1 (C=O)
7a[f]	30 h, 50°C, 50 bar, MeOH, Raney Ni	93	>95:5	123–124 (MeOH)	–19.0	1.29 (s, 3 H, Me); 1.36 (s, 3 H, Me); 1.62 (m, 1 H, CH_2C); 1.90 (m, 1 H, CH_2C); 2.43 (dt, 1 H, *J* = 7.7, 4.4, C*H*CH_2N); 2.58 (s, 2 H, NH_2); 3.43 (m, 2 H, CHC*H*$_2$N); 3.59 (dd, 1 H, *J* = 8.3, 6.8; CH_2O); 3.76 (m, 1 H, C*H*$_2$OH); 3.88 (m, 1 H, C*H*$_2$OH); 4.12 (dd, 1 H, *J* = 8.3, 6.8; CH_2O); 2 (CHO); 6.62 (s, 1 H, NH)	24.9 (Me); 26.2 (Me); 39.3 (*C*H_2C); 39.7 (CH_2N); 45.1 (*C*HCH_2N); 58.8 CH_2OH); 59.7 (C_qNH_2); 67.8 (CH_2O); 73.4 (CHO); 109.2 (C_q); 180.7 (C=O)
7g	20 h, 50°C, 50 bar, MeOH, Raney Ni	44	>95:5	129–130 (MeOH)	–23.9	1.25 (s, 3 H, Me); 1.32 (s, 3 H, Me); 1.59 (m, 2 H, C*H*$_2$CH$_2$OH); 1.61 (m, 2 H, CH_2C); 2.34 (m, 1 H, C*H*CH_2N); 2.65 (s, 2 H, NH_2); 3.35 (m, 2 H, CH_2N); 3.56 (m, 2 H, CH_2OH); 3.63 (dd, 1 H, *J* = 13.9, 7.0, CH_2O); 4.08 (dd, 1 H, *J* =8.3, 7.0, CH_2O); 4.36 (m, 1 H, CHO); 6.6 (s, 1 H, NHC=O)	25.2 (Me), 26.6 (Me), 27.8 (*C*H_2CH$_2$OH); 36.4 (*C*H$_2$C); 40.2 (CH_2N); 44.2 (*C*HCH_2N); 59.7 (CH_2OH); 68.2 (CH*C*H_2O); 74.1 (CHO); 109.5 (C_q); 181.4 (C=O)

Table 1 (continued)

Product	Reaction conditions	Yield (%)	d. r.	mp (°C)[a] (Solvent)	$[\alpha]_D^{20a}$ (c=1, $CHCl_3$)	^{1}H NMR[a] ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR[a] ($CDCl_3$) δ, *J* (Hz)
8f	20 h, 50 °C, 50 bar, MeOH, Raney Ni	85	>95:5	255–236 (MeOH)	+5.2	1.13 (d, 3 H, *J* = 6.3, Me); 1.63 (m, 1 H, CH_2C); 1.76 (m, 1 H, CH_2C); 2.46 (m, 1 H, C*H*CH_2); 2.80 (m, 1 H, CHC*H*$_2$N); 2.87 (m, 1 H, CHMe); 3.31 (d, 2 H, *J* = 13.7, PhCH_2N); 3.44 (d, 2 H, *J* = 13.7, PhC*H*$_2$N); 3.53 (m, 2 H, CHC*H*$_2$N); 3.68 (d, 2 H, *J* = 13.6, C*H*$_2$OH); 4.47 (s, 1 H, OH); 7.19-7.31 (m, 10 H, CH-arom.); 7.61 (s, 1 H, NH)	10.2 (Me), 40.3 (*C*H_2C); 43.7 (*C*HCH$_2$N); 43.8 (CH*C*H$_2$N); 52.8 (*C*HMe); 53.0 (CH_2OH); 57.4 (2x CH_2N); 58.4 (C_qNH$_2$); 126.7, 128.2, 128.5 (CH-arom.); 140.1 (C_q-arom.); 179.5 (C=O)
9	5 d, reflux, MePh	81	>95:5[g]	colourless oil	+31.5	[g] 1.42 (s, 3 H, MeC); 1.34 (s, 3 H, MeC); 2.16 (t, 3 H, *J* = 2.2, MeC=C); 2.78 (m, 1 H, CH_2C); 2.97 (m, 1 H, CH_2C); 3.58 (t, 1 H, *J* = 8.0, CHC*H*$_2$O); 4.09 (t, 1 H, *J* = 8.0, CHC*H*$_2$O); 4.24 (m, 2 H, CH_2O); 4.68 (t, 1 H, *J* = 7.1, CHO)	12.2 (Me-C=C); 25.33 (Me-C); 25.9 (MeC); 26.9 (*C*H_2C); 64.4 (CH_2O); 67.1 (CH*C*H$_2$O); 77.0 (CHO); 110.3 (C_q); 120.6 (Me-*C*=C); 149.1 (CH_2*C*); 170.1 (C=O)
10	4 d, r. t., 10kbar CH_2Cl_2, 2 eq. **2**	76	74:26	colourless oil	+192.1	0.95 (d, 3 H, *J* = 6.6, Me); 1.76 (m, 1 H, CH_2C); 2.03 (m, 1 H, CH_2C); 2.86 (m, 1 H, C*H*CH_3); 3.30 (d, 1 H, *J* = 13.7, CH_2N); 3.61 (d, 1 H, *J* = 10.85, C*H*C); 3.83 (d, 1 H, *J* = 13.7, CH_2N); 4.14 (m, 2 H, CH_2O); 5.71 (s, 1 H, NH); 7.19 (m, 1 H, CH=N); 7.15–7.26 (m, 10 H, CH-arom.)	11.3 (Me); 30.1 (*C*H_2C); 58.8 (C*H*Me); 54.1 (2 x CH_2N); 56.8 (*C*HC); 65.8 (CH_2O); 69.8 (C_qN); 127.6, 128.8, 129.1 (CH-arom.); 139.5 (C_q-arom.); 147.0 (CH=N); 177.3 (C=O)

[a] Spectra of major isomers. If not otherwise mentioned major isomers could be obtained in d.r. >95:5 by flash chromatography
[b] IR (KBr) ν = 1760 cm^{-1}; MS / *m*/*z* (rel. intensity) 241 (M+1, 0.33), 101 (14), 43 (100).
[c] Diastereomers not separable by flash chromatography.
[d] IR (KBr) ν = 1754 cm^{-1}, MS / *m*/*z* (rel. intensity) 213 (M+1, 0.15), 197 (33), 155 (11), 137 (11), 126 (13), 91 (29), 43 (100).
[e] R^1 and R^2 trans according to ^{1}H NMR[20,21].
[f] IR (KBr) ν = 1685 cm^{-1}, MS / *m*/*z* (rel. intensity) 245 (M-15, 0.98), 142 (9), 115 (22), 100 (28), 82 (21), 70 (26), 43 (100).
[g] Compound suffers partial epimerization after standing in solution and also as a solid.

model [15] and the antiperiplanar effect. [16,17] But these models were developed for 1,2-disubstituted alkenes. Thus we determined the optimized structures of **1a** (Figure 5) and **1f** (Figure 6) by PM3-calculations. They allow to conclude the same preferred facial selectivity (see Figures 5 and 6) as found in the experiment. The ring contraction of pyrazolines **3** and **4** to cyclopropanes **5** and **6** by N_2-elimination maintains the configuration as can be seen from X-ray crystal analysis of **3a** and **5a** (see Figures 1 and 3).

Our results demonstrate that the 1,3-dipolar cycloaddition of diazoalkanes **2** to α-alkylidenelactones **1** is stereoselective and opens an easy access to optically active spirocyclopropyllactones **5** and **6** and α-amino-α-(ω-hydroxyalkyl)-γ-butyrolactams **7** and **8** by N_2-elimination or hydrogenation, respectively.

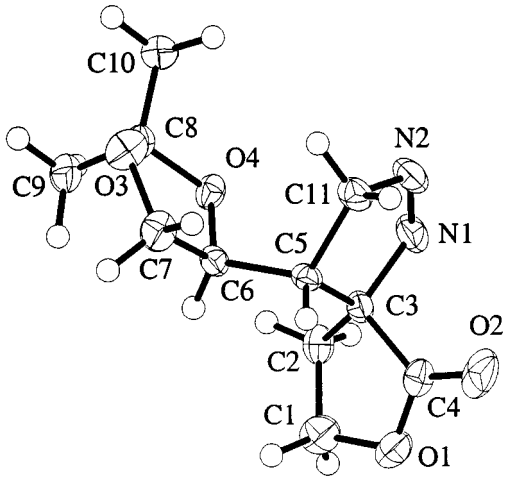


Figure 1. X-ray crystal analysis of pyrazoline **3a**

^{1}H NMR 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. Mass spectra (HP 5995 A) were measured at 70eV. An immersion reactor with Hg high-pressure lamp from HERAEUS Noblelight (150 W) was used for photochemical elimination of N_2. Silica gel (0.04–0.063 mm, MERCK) was used for preparative column chromatography. If not otherwise mentioned, chemicals were purchased from ALDRICH. α-Alkylidenelatones **1** were prepared as reported.[6]

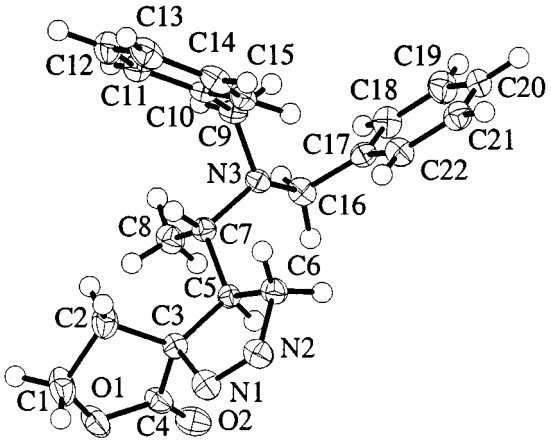


Figure 2. X-ray crystal analysis of pyrazoline **4f**

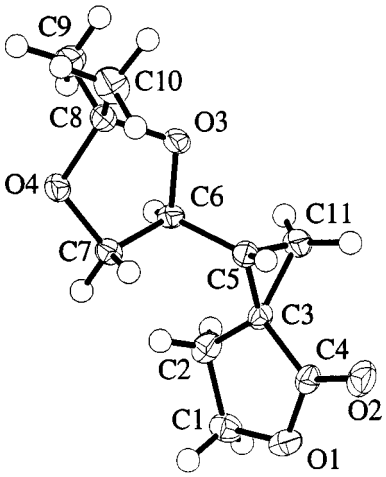


Figure 3. X-ray crystal analysis of α-spirocyclopropyllactone **5a**

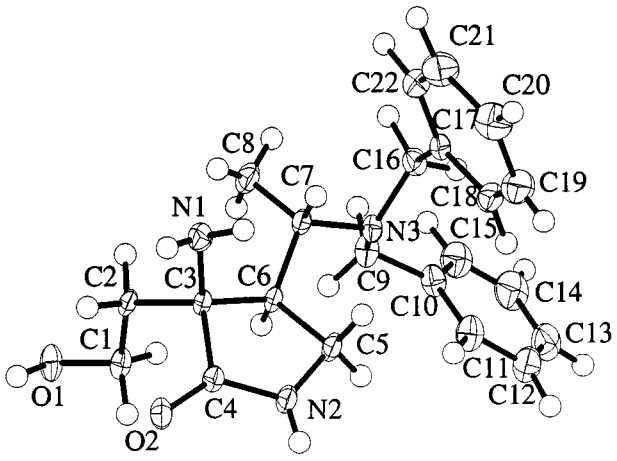


Figure 4. X-ray crystal analysis of α-amino-α-(3-hydroxypropyl)butyrolactam **8f**

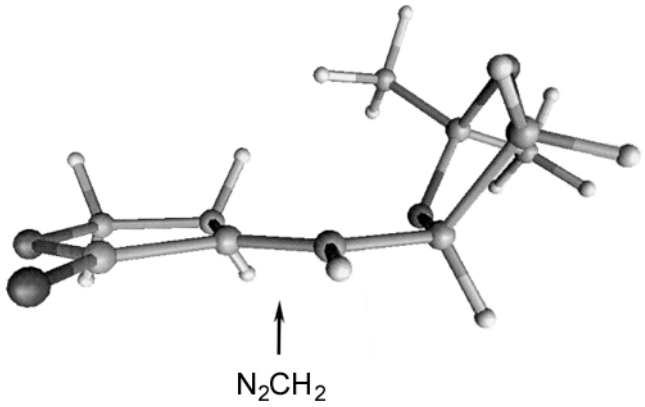


Figure 5. Stereochemical mode of attack of diazomethane at α-alkylidenelactone **1a** (geometry of **1a** optimized by PM3)

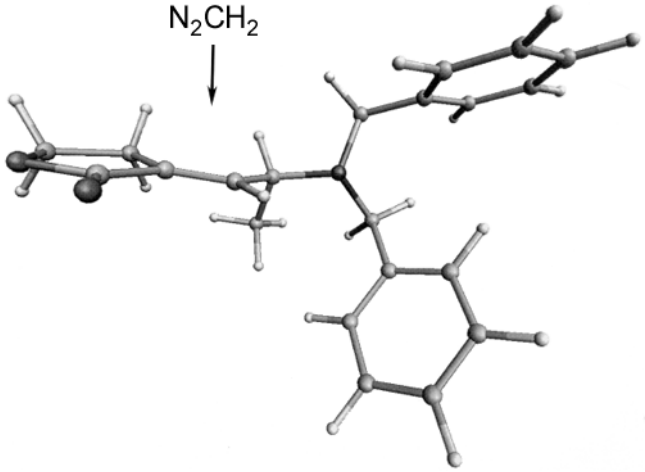


Figure 6. Stereochemical mode of attack of diazomethane at α-alkylidenelactone **1f** (geometry of **1f** optimized by PM3)

Spiropyrazolines 3 and 4 by Addition of Diazoalkanes 2 to α−Alkylidenelactones 1; General Procedures Diazomethane[18]

1M solution of diazomethane in Et_2O was produced from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (DIAZALD^R) in the distillation set "DIAZALD-Kit" (ALDRICH). The safety instructions should be followed.[18]

Cycloaddition

Method A

The freshly prepared solution of diazomethane in Et_2O (1M, for quantities see Table) was added to a solution of the α-alkylidenelactone **1** (1 mmol) in Et_2O (5 mL) at –20 to 0°C under stirring. After further stirring (for temperatures and times see Table) the solution was concentrated with a rotatory evaporator and the residue was purified by flash chromatography (hexane/EtOAc for **3a**, **3h, 4f**, 1:1, for **3d** 6:4, for **4e** 3:7) and eventually by recrystallisation (**3a**, **3d**, **3d**, **3g, 4f**).

Method B

A solution of trimethylsilyldiazomethane in hexane (0.75 mL, 1.5 mmol, 2M) was added to a solution of α-alkylidenelactone **1** (1 mmol) in toluene (5 mL). After stirring at r.t. for 4 d the solvent was removed under vacuum and the remaining crude product was purified by flash chromatography (hexane/EtOAc 7:3)

2-Pyrazoline 10
A solution trimethylsilyldiazomethane in hexane (0.5 ml, ~1 mmol, 2M) was combined with a solution of α-alkylidenelactone **1f** (160 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) and put into a Teflon tube. After sealing the tube was kept at 10 kbar at r.t. for 48 h. The solution was concentrated under vacuum and the remaining material was purified by flash chromatography (hexane/EtOAc 6:4).

α-Alkylidenebutyrolactone 9
A solution of **1a** (120 mg, 0.5 mmol) in toluene (5 mL) was refluxed for 5 days. The solvent was removed under vacuum and the remainder was purified by flash chromatography (hexane/EtOAc 6:4).

α-Spirocyclopropyllactones 5 and 6
Method C; General Procedure
A solution of the spiropyrazoline **3** or **4** (1 mmol) in degassed MeCN (110 mL) was irradiated with broad band-UV (250–400 nm, the major absorption band of **3a** was at 330 nm) for 1–2 h (TLC-control, see Table). After the reaction was complete, the solvent was removed under vacuum. The remaining products **5** or **6** were purified by flash chromatography (hexane/EtOAc).

Method D
A solution of α-alkylidenelactone **1a** (198 mg, 1 mmol) and ethyl diazoacetate (150 mg, 1.5 mmol) in toluene (5 mL) was refluxed for 2 d. After removing the solvent under vacuum the crude product **5c** was purified by column chromatography (hexane/EtOAc 1:1).

α-Amino-α-(ω-hydroxyalkyl)-γ-butyrolactams 7 and 8 by Hydrogenation of 3 or 4, General Procedure
NaOH (1.1 g) was added in small portions to a suspension of Ni/Al alloy (0.7 g) in water (7 mL). The mixture was heated to 70°C for 30 min. After cooling to r.t. the Raney Ni was filtered off and washed with H_2O (3x10 mL) and anhyd MeOH (20 mL). This freshly prepared Raney Ni (about 100 mg), anhyd MeOH (10 mL) and the pyrazoline **3** or **4** (1 mmol) was brought into an autoclave and was stirred at 50°C at 50 bar for 20–30 h (see Table). After filtering the resulting mixture through Celite and concentrating the filtrate with a rotatory evaporator the remaining material was purified by flash chromatography ($CHCl_3$/MeOH 9:1).

Crystal Structure Determination for 3a (see Figure 1)[19]
Crystals were obtained by crystallisation from hot toluene. A colourless crystal of **3a** with the dimensions 0.80 x 0.80 x 0.28 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ = 0.71073 Å). Crystal data: $C_{11}H_{16}N_2O_4$, M = 240.3, monoclinic space group P 2_1, a = 9.054 (2) Å, b = 6.4622 (9) Å, c = 10.272 (2) Å, β = 99.08 (2)° V = 593.5 (2) $Å^3$, Z = 2, D_c = 1.345 g/cm^3, F(000) = 256, μ (MoK_α) = 0.064 mm^{-1}. At 295(2) K in the range of 2.3° < Θ < 24.2° 4377 reflections were measured ($R_{(sig)}$ = 0.0321) of which 1802 were unique ($R_{(int)}$ = 0.0709) and 1706, 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 $wR_{2\ (all)}$ = 0.0788, $R_{1\ all)}$ = 0.0323 and $R_{1\ (obs)}$ = 0.0296. The maximum and minimum peaks in the final difmap were 0.129 and –0.129 e/$Å^3$, respectively.

Crystal structure determination for 4f (see Figure 2)[19]
Crystals were obtained by crystallisation from hot toluene. A colourless crystal of **5f** with the dimensions 0.56 x 0.48 x 0.32 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ = 0.71073 Å). Crystal data: $C_{22}H_{25}N_3O_2$, M = 363.45, orthorhombic space group P 2_1, a = 10.7649 (14) Å, b = 12.577 (2) Å, c = 14.273 (2) Å, V = 967.6 (4) $Å^3$, Z = 4, D_c = 1.249 g/cm^3, F(000) = 776, μ (MoK_α) = 0.202 mm^{-1}. At 295 (2) K in the range of 2.2° < Θ < 26.2° 11902 reflections were measured ($R_{(sig)}$ = 0.031) of which 3798 were unique ($R_{(int)}$ = 0.0361) and 3455, 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 $wR_{2\ (all)}$ = 0.0753, $R_{1\ all)}$ = 0.0357 and $R_{1\ (obs)}$ = 0.0311. The maximum and minimum peaks in the final difmap were 0.126 and –0.162 e/$Å^3$, respectively.

Crystal Structure Determination for 5a (see Figure 3)[19]
Crystals were obtained by crystallisation from hot toluene. A colourless crystal of **5a** with the dimensions 0.64 x 0.40 x 0.40 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ = 0.71073 Å). Crystal data: $C_{11}H_{16}O_4$, M = 212.24, orthorhombic space group P 2_1, a = 8.5844 (9) Å, b = 10.8689 (13) Å, c = 10.272 (2) Å, V = 1069.7 (2) $Å^3$, Z = 4, D_c = 1.318 g/cm^3, F(000) = 456, μ (MoK_α) = 0.100 mm^{-1}. At 180 (2) K in the range of 2.6° < Θ < 26.0° 6298 reflections were measured ($R_{(sig)}$ = 0.0463) of which 2106 were unique ($R_{(int)}$ = 0.0777) and 1915, 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 $wR_{2\ (all)}$ = 0.0864, $R_{1\ all)}$ = 0.0376 and $R_{1\ (obs)}$ = 0.0340. The maximum and minimum peaks in the final difmap were 0.159 and –0.176 e/$Å^3$, respectively.

Crystal Structure Determination for 8f (see Figure 4)[19]
Crystals were obtained by crystallisation from hot toluene. A colourless crystal of **8f** with the dimensions 1.52 x 1.14 x 0.38 mm^3 was measured on a STOE Ipds diffractometer using MoK_α radiation (λ = 0.71073 Å). Crystal data: $C_{22}H_{29}N_3O_2$, M = 367.48, monoclinic space group P 2_1, a = 9.6670 (7) Å, b = 8.0517 (4) Å, c = 13.1515 (13) Å, β = 92.172 (7)°, V = 1022.92 (14) $Å^3$, Z = 2, D_c = 1.193 g/cm^3, F(000) = 396, μ (MoK_α) = 0.077 mm^{-1}. At 180 (2) K in the range of 1.55° < Θ < 26.02° 4616 reflections were measured ($R_{(sig)}$ = 0.0457) of which 3986 were unique ($R_{(int)}$ = 0.0241) and 3986, 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 $wR_{2\ (all)}$ = 0.1220, $R_{1\ all)}$ = 0.0468 and $R_{1\ (obs)}$ = 0.0457. The maximum and minimum peaks in the final difmap were 0.285 and –0.264 e/$Å^3$, respectively.

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