Enantioselective Synthesis of 2-Alkyl-2-cyanocycloalkanones with a Quaternary Stereogenic Center

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Received 4 January 1993

2-Alkyl-2-cyanocycloalkanones **4** bearing a quaternary stereogenic center are synthesized in good overall yields and high enantiomeric excesses (ee = 90–95%) employing the SAMP-/RAMP-hydrazone method. The absolute configuration is confirmed by NMR-spectroscopic investigations on SAMP-hydrazone **3a** and an X-ray structure analysis of SAMP-hydrazone **3f**.

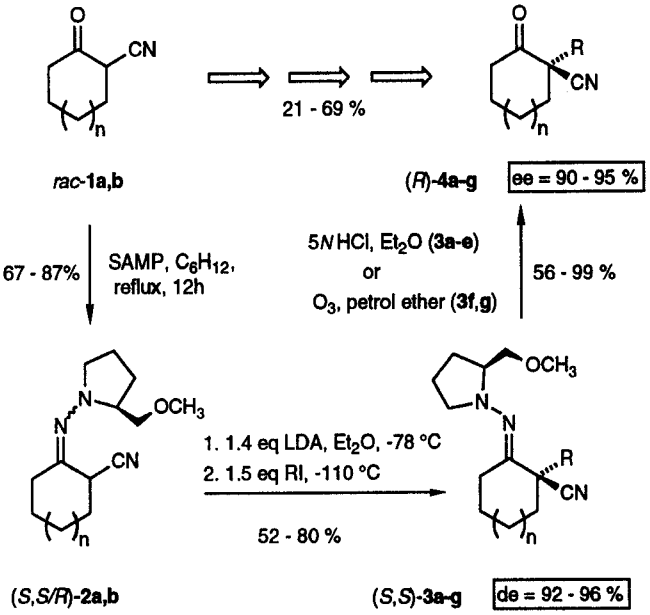
The development of synthetic methods to create quaternary stereogenic centers has been studied extensively in the last two decades.[1] Of special interest are bi- and polyfunctional molecules, which can be used as starting materials to synthesize more complex bioactive products. For the latter purpose efficient asymmetric syntheses are needed and a few methods have been developed in recent years.[2-6]

Recently, we reported a highly enantioselective synthesis of 3-oxo esters and carboxylic acids bearing a quaternary stereogenic center[7] employing the SAMP-/RAMP-hydrazone method.[8] We now wish to describe the asymmetric synthesis of 2-substituted 2-cyanocycloalkanones of type **4**, useful chiral building blocks for the synthesis of natural products and bioactive compounds.[9] Although racemic cyanoketones similar to **4** have been prepared by alkylation of lithium enolates of β-oxo nitriles[10] and lithiated dimethyl hydrazone derivatives[11] in moderate to good diastereoselectivities, overall enantioselective routes have not been available so far.

The 2-cyanocycloalkanone SAMP-hydrazones **2**, easily prepared from the corresponding ketones *rac*-**1** and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP), exist mainly in the ene hydrazine tautomeric form.[12] They were converted diastereoselectively (de = 92–96%) into the 2-alkyl-2-cyanocycloalkanone SAMP-hydrazones **3** in good yields by metalation with lithium diisopropylamide in diethyl ether at −78 °C and subsequent reaction with alkyl iodides at −110 °C. After hydrazone cleavage (**3a–e**: acidic hydrolysis in a two phase system; **3f,g**: ozonolysis) the 2-alkyl-2-cyanocycloalkanones **4** were obtained in good overall yields (21–69%) and high enantiomeric excesses (ee = 90–95%, Scheme).

In contrast to the high asymmetric inductions in the case of the 6- and 8-membered cycloalkanones, the alkylation of cycloheptanone derivatives (n = 2) proceeded only in moderate diastereoselectivity (de = 77%). Attempts to achieve the alkylation of the 2-cyanocyclopentanone (n = 0) in the same manner gave a mixture of regio- and stereoisomers.

The enantiomeric excesses of the final products were assigned by gas chromatography employing cyclodextrin phases (Table 2, **4a–e**). The ee-values of the ketones **4f,g** are based on the determination of the corresponding de-values of the hydrazones **3f,g** by ^{13}C NMR spectroscopy. This is permissable, because an epimerization or a racemization during oxidative cleavage by ozonolysis is not possible.[8]



Scheme

The absolute configuration of the cyclooctanone compounds was determined by X-ray structure analysis of (*S,S*)-**3f** (Figure). The relative and absolute configuration of the cyclohexanone derivatives could be assigned by extensive NMR spectroscopic investigations (2D, NOE) on SAMP-hydrazone (*S,S*)-**3a** (correlation of the relative orientation of the 2-methyl and 6-methylene group of the cyclohexane ring with the groups in 2- and 5-position of the pyrrolidine moiety). The *S*-configuration found at the new formed stereogenic center is in agreement with that predicted by the postulated mechanism for electrophilic substitutions via SAMP-/RAMP-hydrazones.[8,13]

Table 1. 2-Alkyl-2-cyanocycloalkanone SAMP-Hydrazones **3** Prepared

Product	n	R	Yield (%)	$[\alpha]_D^{25}$ (*c*, benzene)	de[a] (%)
(*S,S*)-**3a**	1	Me	68	+407.1 (1.02)	92
(*S,S*)-**3b**	1	Et	80	+389.3 (0.98)	95
(*R,R*)-**3b**[b]	1	Et	52	−387.0 (1.16)	94
(*S,S*)-**3c**	1	Pr	59	+341.2 (1.13)	96
(*S,S*)-**3d**	1	Bu	59	+332.6 (1.03)	95
(*S,S*)-**3e**	1	n-C_6H_{13}	73	+301.6 (1.06)	93
(*S,S*)-**3f**	3	Et	66	+194.4 (1.09)	94
(*S,S*)-**3g**	3	Pr	49	+160.9 (0.96)	94

[a] Determined by ^{13}C NMR spectroscopy.
[b] RAMP was used instead of SAMP as auxiliary.

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Table 2. 2-Alkyl-2-cyanocycloalkanones **4** Prepared

Product	n	R	Yield (%)	Overall Yield[a] (%)	$[\alpha]_D^{25}$ (*c*, benzene)	ee[b] (%)
(*R*)-**4a**	1	Me	67	40	+232.2 (1.04)	90
(*R*)-**4b**	1	Et	99	69	+184.2 (0.83)	95
(*S*)-**4b**[c]	1	Et	82	31	−184.7 (1.08)	95
(*R*)-**4c**	1	Pr	85	44	+159.3 (1.07)	94
(*R*)-**4d**	1	Bu	99	51	+147.3 (1.11)	94
(*R*)-**4e**	1	*n*-C_6H_{13}	99	63	+125.8 (1.06)	93[d]
(*R*)-**4f**	3	Et	56	25	−12.7[e] (1.32)	94[d]
(*R*)-**4g**	3	Pr	63	21	−11.1[e] (1.00)	95[d]

[a] Yield of product **4** based on cycloalkanone **1**.
[b] Determined by gas chromatography: 50 m, H_2, 200 °C, heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin.
[c] RAMP was used instead of SAMP as auxiliary.
[d] Indirectly determined by ^{13}C NMR spectroscopy on the de-values of the hydrazones **3**.
[e] The optical rotation value was measured at 21 °C.

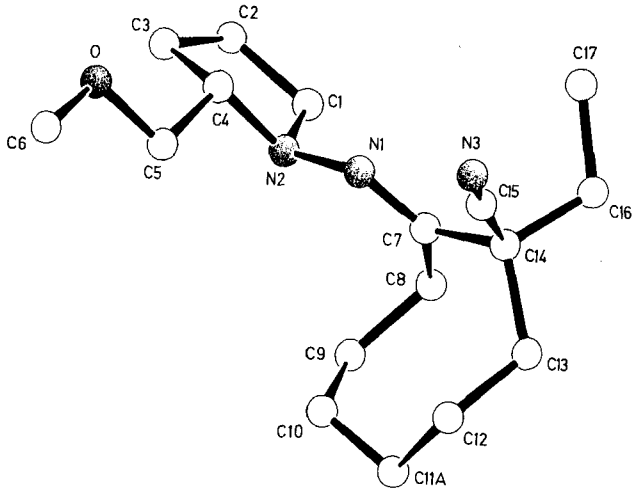

Figure. Molecular structure of (*S,S*)-**3f** in the solid state. Only one component of the disordered carbon atom C11 is shown (SCHAKAL[14] plot).

Table 3. Spectroscopic Data of the Cycloalkanone SAMP-Hydrazones **3** Prepared

3[a]	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS)[b] δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS)[b] δ	MS (70 eV) *m/z* (%)
3a	2970, 2935, 2865, 2830, 2240, 1640, 1450, 1195, 1120, 1100, 1060, 920, 735	1.51 (s, 3H, CH_3), 1.48–2.20 (m, 10H, $4CH_{2pyr}$, $6CH_2$), 2.34–2.46 (m, 1H, $N{=}CCH_{2ax}$), 2.46 (m, 1H, CH_2N), 2.77 (m, 1H, $N{=}CCH_{2eq}$), 3.12–3.23 (m, 1H, CH_2N), 3.27–3.45 (m, 3H, CH_2O, CHN), 3.36 (s, 3H, OCH_3)	22.3 (C*^{c}CH_2CH_2), 22.4 (NCH_2CH_2), 23.3 (CH_3), 26.3 [C*$(CH_2)_2CH_2$], 26.5 [$N(CH_2)_2CH_2$], 27.0 ($CH_2C{=}N$), 39.9 (C*CH_2), 41.5 (C*), 55.4 (NCH_2), 59.2 (OCH_3), 66.7 (NCH), 75.1 (CH_2O), 122.9 (CN), 160.6 (C=N)	249 (M^+·, 7), 205 (13), 204 (100), 135 (14), 108 (14), 81 (13), 70 (42), 45 (12), 41 (26), 32 (15)
3b	2960, 2930, 2860, 2820, 2240, 1635, 1450, 1200, 1190, 1115, 1055	1.07 (t, J = 7.4, 3H, CH_3), 1.56–2.18 (m, 12H, $4CH_{2pyr}$, $8CH_2$), 2.34–2.44 (m, 1H, $N{=}CCH_{2ax}$), 2.44 (m, 1H, CH_2N), 2.67 (m, 1H, $N{=}CCH_{2eq}$), 3.13 (m, 1H, CH_2N), 3.27–3.46 (m, 3H, CH_2O, CHN), 3.36 (s, 3H, OCH_3)	9.4 (CH_3), 21.5 (C*CH_2CH_2), 22.3 (NCH_2CH_2), 26.1 (CH_3CH_2), 26.3 [C*$(CH_2)_2CH_2$], 26.5 [$N(CH_2)_2CH_2$], 28.3 ($CH_2C{=}N$), 37.3 (C*CH_2), 47.1 (C*), 55.2 (NCH_2), 59.2 (OCH_3), 66.6 (NCH), 75.1 (CH_2O), 121.8 (CN), 160.8 (C=N)	263 (M^+·, 6), 219 (16), 218 (100), 70 (43), 41 (17)
3c	2950, 2860, 2820, 2235, 1635, 1450, 1200, 1190, 1120, 1100, 970, 920	0.97 (t, J = 7.3, 3H, CH_3), 1.42–2.14 (m, 14H, $4CH_{2pyr}$, $10CH_2$), 2.33–2.41 (m, 1H, $N{=}CCH_{2ax}$), 2.45 (m, 1H, CH_2N), 2.69 (m, 1H, $N{=}CCH_{2eq}$), 3.11–3.18 (m, 1H, CH_2N), 3.27–3.50 (m, 3H, CH_2O, CHN), 3.36 (s, 3H, OCH_3)	14.2 (CH_3), 18.4, 21.5 ($2CH_2$), 22.4 (NCH_2CH_2), 26.1 (CH_2), 26.3 [C*$(CH_2)_2CH_2$], 26.5 [$N(CH_2)_2CH_2$], 37.4, 37.7 ($2CH_2$), 46.5 (C*), 55.2 (NCH_2), 59.2 (OCH_3), 66.6 (NCH), 75.1 (CH_2O), 122.1 (CN), 161.0 (C=N)	277 (M^+·, 6), 233 (17), 232 (100), 70 (25), 41 (12)
3d	2930, 2860, 2820, 2240, 1630, 1450, 1195, 1120, 1060, 970	0.93 (t, J = 7.1, 3H, CH_3), 1.25–2.18 (m, 16H, $4CH_{2pyr}$, $12CH_2$), 2.33–2.43 (m, 1H, $N{=}CCH_{2ax}$), 2.45 (m, 1H, CH_2N), 2.68 (m, 1H, $N{=}CCH_{2eq}$), 3.13 (m, 1H, CH_2N), 3.27–3.51 (m, 3H, CH_2O, CHN), 3.36 (s, 3H, OCH_3)	13.9 (CH_3), 21.5 (CH_2), 22.3 (NCH_2CH_2), 22.8, 26.1 ($2CH_2$), 26.3 [C*$(CH_2)_2CH_2$], 26.5 [$N(CH_2)_2CH_2$], 27.1, 34.9, 37.7 ($3CH_2$), 46.4 (C*), 55.2 (NCH_2), 59.2 (OCH_3), 66.5 (NCH), 75.2 (CH_2O), 122.1 (CN), 161.0 (C=N)	291 (M^+·, 6), 247 (17), 246 (100), 70 (42), 41 (16)
3e	2930, 2860, 2825, 2230, 1635, 1470, 1450, 1200, 1125, 1050, 970, 910	0.89 (t, J = 7.1, 3H, CH_3), 1.20–2.20 (m, 20H, $4CH_{2pyr}$, $16CH_2$), 2.32–2.41 (m, 1H, $N{=}CCH_{2ax}$), 2.44 (m, 1H, CH_2N), 2.68 (m, 1H, $N{=}CCH_{2eq}$), 3.13 (m, 1H, CH_2N), 3.26–3.50 (m, 3H, CH_2O, CHN), 3.36 (s, 3H, OCH_3)	14.0 (CH_3), 21.5 (CH_2), 22.3 (NCH_2CH_2), 22.6, 24.9, 26.1 ($3CH_2$), 26.3 [C*$(CH_2)_2CH_2$], 26.5 [$N(CH_2)_2CH_2$], 29.3, 31.6, 35.2, 37.7 ($4CH_2$), 46.5 (C*), 55.2 (NCH_2), 59.2 (OCH_3), 66.5 (NCH), 75.2 (CH_2O), 122.1 (CN), 161.0 (C=N)	319 (M^+·, 5), 275 (20), 274 (100), 70 (25), 41 (13)
3f	[d]2975, 2925, 2880, 2850, 1475, 1460, 1450, 1195, 1135, 1000, 960	1.00 (t, J = 7.5, 3H, CH_3), 1.20–2.15 (m, 17H, $4CH_{2pyr}$, $N{=}CCH_{2ax}$, $12CH_2$), 2.45 (m, 1H, CH_2N), 2.48–2.54 (m, 1H, $N{=}CCH_{2eq}$), 3.25–3.52 (m, 4H, CH_2O, CHN, CH_2N), 3.34 (s, 3H, OCH_3)	9.6 (CH_3), 22.7, 24.0, 24.4, 25.5, 25.8, 26.2, 26.3, 31.9, 33.6 ($9CH_2$), 51.8 (C*), 53.2 (NCH_2), 58.9 (OCH_3), 66.4 (NCH), 75.5 (CH_2OCH_3), 122.1 (CN), 161.4 (C=N)	291 (M^+·, 6), 247 (17), 246 (100), 70 (14), 41 (11)
3g	2960, 2930, 2870, 2220, 1625, 1465, 1450, 1200, 1180, 1165, 1150	0.93 (t, J = 7.1, 3H, CH_3), 1.24–2.15 (m, 19H, $4CH_{2pyr}$, $N{=}CCH_{2ax}$, $14CH_2$), 2.44 (m, 1H, CH_2N), 2.45–2.56 (m, 1H, $N{=}CCH_{2eq}$), 3.25–3.53 (m, 4H, CH_2O, CHN, CH_2N), 3.34 (s, 3H, OCH_3)	14.0 (CH_3), 18.5, 22.7, 23.9, 24.4, 25.4, 25.8, 26.2, 26.3, 33.9, 41.0 ($10CH_2$), 51.2 (C*), 53.0 (NCH_2), 58.9 (OCH_3), 66.3 (NCH), 75.4 (CH_2O), 121.3 (CN), 161.3 (C=N)	305 (M^+·, 5), 261 (18), 260 (100), 70 (53), 55 (29), 45 (23), 41 (49)

[a] New compounds, satisfactory microanalyses obtained: C ± 0.41, H ± 0.24, N ± 0.46.
[b] Data of the major diastereomer.
[c] C* = quaternary carbon atom.
[d] IR (KBr), mp 60–61 °C.

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Table 4. Spectroscopic Data of the Cycloalkanones **4** Prepared

4[a]	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
4a	2935, 2860, 2220, 1730, 1450, 1430, 1380, 1310, 1230, 1160, 1125, 1090, 980	1.44 (s, 3H, CH_3), 1.63–1.81 (m, 2H, C^*CH_{2ax}, $COCH_2CH_{ax}$), 1.82–1.95 (m, 1H, $C^*CH_2CH_{2eq}$), 1.99–2.10 (m, 1H, $C^*CH_2CH_{2ax}$), 2.10–2.21 (m, 1H, $COCH_2CH_{2eq}$), 2.32–2.40 (m, 1H, C^*CH_{2eq}), 2.45–2.54 (m, 1H, $COCH_{2eq}$), 2.77–2.90 (m, 1H, $COCH_{2ax}$)	20.5 (CH_3), 22.4 ($C^{*b}CH_2CH_2$), 27.4 ($COCH_2CH_2$), 38.9 ($COCH_2$), 40.4 (C^*CH_2), 46.4 (C^*), 120.7 (CN), 202.9 (CO)	137 ($M^+\cdot$, 39), 94 (20), 82 (56), 81 (12), 79 (18), 68 (100), 67 (28), 55 (76), 53 (15), 42 (94), 41 (65), 39 (37)
4b	2940, 2860, 2220, 1725, 1460, 1450, 1310, 1220, 1125, 1110, 845	1.07 (t, J = 7.4, 3H, CH_3), 1.63 (dq, J_d = 14, J_q = 7.4, 1H, CH_3CH_2), 1.71–2.11 [m, 5H, C^*CH_{2ax}, $COCH_2(CH_2)_2$], 2.05 (dq, J_d = 14, J_q = 7.4, 1H, CH_3CH_2), 2.28–2.38 (m, 1H, C^*CH_{2eq}), 2.42–2.52 (m, 1H, $COCH_{2eq}$), 2.75 (m, 1H, $COCH_{2ax}$)	9.2 (CH_3), 21.9 ($C^*CH_2CH_2$), 26.8 (CH_3CH_2), 27.8 ($COCH_2CH_2$), 37.9 (C^*CH_2), 39.1 ($COCH_2$), 52.4 (C^*), 119.8 (CN), 203.3 (CO)	151 ($M^+\cdot$, 29), 123 (35), 122 (17), 108 (36), 96 (76), 93 (26), 82 (90), 67 (56), 55 (100), 53 (22), 42 (77), 41 (50), 39 (42)
4c	2960, 2880, 2220, 1730, 1470, 1450, 1220, 1130	0.93 (t, J = 7.3, 3H, CH_3), 1.36–1.61 (m, 3H, CH_2), 1.73–2.13 (m, 6H, CH_2), 2.27–2.38 (m, 1H, C^*CH_2), 2.41–2.53 (m, 1H, $COCH_{2eq}$), 2.74 (m, 1H, $COCH_{2ax}$)	14.1 (CH_3), 18.2, 21.8 ($2CH_2$), 27.8 ($COCH_2CH_2$), 35.6, 38.3 ($2CH_2$), 39.0 ($COCH_2$), 51.8 (C^*), 120.0 (CN), 203.4 (CO)	165 ($M^+\cdot$, 13), 123 (100), 110 (31), 96 (33), 81 (21), 67 (33), 55 (41), 53 (15), 42 (37), 41 (43)
4d	2960, 2870, 2230, 1730, 1450, 1130	0.93 (t, J = 7.3, 3H, CH_3), 1.31–1.64 (m, 5H, CH_2), 1.72–2.13 (m, 6H, CH_2), 2.27–2.38 (m, 1H, C^*CH_2), 2.41–2.52 (m, 1H, $COCH_{2eq}$), 2.74 (m, 1H, $COCH_{2ax}$)	13.8 (CH_3), 21.9, 22.7, 26.9 ($3CH_2$), 27.8 ($COCH_2CH_2$), 33.3, 38.3 ($2CH_2$), 39.0 ($COCH_2$), 51.8 (C^*), 120.0 (CN), 203.3 (CO)	179 ($M^+\cdot$, 3), 124 (40), 123 (100), 82 (24), 67 (21), 55 (32), 42 (26), 41 (35)
4e	2950, 2930, 2860, 2230, 1730, 1450, 1310, 1220, 1125, 1110	0.89 (t, J = 6.6, 3H, CH_3), 1.24–1.62 (m, 9H, CH_2), 1.71–2.13 (m, 6H, CH_2), 2.27–2.37 (m, 1H, C^*CH_2), 2.41–2.51 (m, 1H, $COCH_{2eq}$), 2.74 (m, 1H, $COCH_{2ax}$)	14.0 (CH_3), 21.8, 22.5, 24.7 ($3CH_2$), 27.8 ($COCH_2CH_2$), 29.2, 31.5, 33.6, 38.3 ($4CH_2$), 39.0 ($COCH_2$), 51.8 (C^*), 120.0 (CN), 203.4 (CO)	207 ($M^+\cdot$, 1), 124 (38), 123 (100), 95 (16), 82 (15), 67 (18), 55 (20), 41 (26)
4f	2970, 2940, 2880, 2860, 2220, 1710, 1470, 1450, 1115, 1085, 1075	1.02 (t, J = 7.4, 3H, CH_3), 1.14–1.44 (m, 2H, CH_2), 1.56–1.98 (m, 8H, CH_2), 2.01–2.12 (m, 1H, CH_2), 2.15–2.28 (m, 1H, CH_2), 2.41 (m, 1H, $COCH_{2eq}$), 2.63 (m, 1H, $COCH_{2ax}$)	9.6 (CH_3), 24.2, 24.9, 25.8, 29.0, 30.1, 33.8, 37.1 ($8CH_2$), 56.7 (C^*), 119.1 (CN), 209.0 (CO)	179 ($M^+\cdot$, 30), 108 (22), 98 (46), 97 (34), 94 (20), 82 (75), 70 (29), 55 (100), 42 (46), 41 (53), 39 (26)
4g	2960, 2935, 2875, 2860, 2240, 1715, 1470, 1450, 1120, 1080	0.95 (t, J = 7.3, 3H, CH_3), 1.13–1.44 (m, 3H, CH_2), 1.47–1.98 (m, 9H, CH_2), 2.01–2.10 (m, 1H, CH_2), 2.15–2.28 (m, 1H, CH_2), 2.42 (m, 1H, $COCH_{2eq}$), 2.58–2.70 (m, 1H, $COCH_{2ax}$)	13.9 (CH_3), 18.6, 24.2, 24.8, 25.9, 29.0, 34.1, 37.1, 38.9 ($8CH_2$), 56.0 (C^*), 119.3 (CN), 209.1 (CO)	193 ($M^+\cdot$, 36), 136 (44), 98 (77), 96 (83), 94 (31), 70 (38), 69 (73), 67 (31), 55 (100), 42 (69), 41 (99), 39 (36)

[a] New compounds, satisfactory microanalyses obtained: C ± 0.41, H ± 0.33, N ± 0.20.
[b] C* = quaternary carbon atom.

In conclusion, an efficient, highly enantioselective synthesis of 2-alkyl-2-cyanocycloalkanones **4** has been developed, useful bifunctional building blocks bearing a quaternary stereogenic center. Further applications by conversion of the carbonyl and cyano group into other functionalities, such as hydroxy, aldehyde and amino groups, are now being studied.

All reagents were of commercial quality from freshly opened containers or distilled before use. 2-Cyanocyclohexanone,[15] 2-cyanocyclooctanone[16] and SAMP[8] were prepared according to literature procedures. Et_2O was freshly distilled from Na/benzophenone. Petroleum ether bp 30–50°C. Analytical TLC plates (silica gel 60 F_{254}) and silica gel (230–400 mesh) were purchased from Merck. BuLi (1.6 N in hexane) was purchased from Aldrich. All melting points (Büchi-apparatus, system Dr. Tottoli) are uncorrected. Optical rotation values were measured using a Perkin-Elmer P 241 polarimeter. Microanalyses were obtained with a Heraeus CHN-O-RAPID element analyser; satisfactory microanalyses also obtained for **2a,b**: C ± 0.33, H ± 0.19, N ± 0.27. Mass spectra were recorded on a Varian MAT 212 (70 eV, 1 mA) spectrometer with DEI ionization. IR spectra were obtained using a Perkin-Elmer Infracord 337 spectrophotometer. The ^1H and ^{13}C NMR spectra were measured on a Varian VXR 300 or Unity 500 (300 and 75 MHz or 500 and 125 MHz). GC analyses were obtained using a Siemens Sichromat 2 and 3.

(2*S*)-1-[(2*R*/*S*)-2-Cyanocyclohexylideneamino]-2-methoxymethylpyrrolidine [(*S*,*R*/*S*)-2a]:

2-Cyanocyclohexanone (*rac*-**1a**; 6.15 g, 50 mmol) and SAMP (6.50 g, 50 mmol) were diluted in cyclohexane (80 mL). After adding a few crystals of *p*-TsOH the mixture was refluxed for 12 h. The solution was diluted with Et_2O (100 mL), washed with sat. aq $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$). The product was purified by flash chromatography (silica gel, Et_2O/petroleum ether, 2:1), affording 10.3 g (87%) of a yellow solid; mp 60–62°C; $[\alpha]_D^{28}$ + 40.5° (c = 1.11, benzene).

MS (70 eV): m/z (%) = 235 ($M^+\cdot$, 18), 191 (13), 190 (100), 70 (50), 41 (12).

IR (KBr): ν = 3250 (NH), 2980–2810, 2160 (CN), 1620 (C=C), 1525, 1460, 1445, 1200, 1160, 1130, 1100, 910 cm^{-1}.

^1H NMR[17] ($CDCl_3$): δ = 1.55–2.78 (m, 14H, 12 CH_2, CH_2N, CHCN), 3.15–3.40 (m, 4H, CH_2N, CH_2O, CHN), 3.34 (s, 3H, OCH_3), 5.29 (s, 1H, NH).

^{13}C NMR[17] ($CDCl_3$): δ = 20.8, 21.7, 22.4, 25.2, 25.7, 25.9 (6 CH_2), 57.3 (NCH_2), 59.1 (OCH_3), 66.5 (NCH), 71.2 (C=CCN), 74.0 (CH_2O), 121.1 (CN), 159.2 (C=C–N).

(2*R*)-1-[(2*R*/*S*)-2-Cyanocyclohexylideneamino]-2-methoxymethylpyrrolidine [(*R*,*R*/*S*)-2a]:

Compound (*R*,*R*/*S*)-**2a** was prepared by the same procedure as described for (*S*,*R*/*S*)-**2a** using RAMP instead of SAMP as auxiliary, yielding 0.84 g (72%) of a yellow oil; $[\alpha]_D^{26}$ − 38.9° (c = 0.97, benzene).

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(2*S*)-1-[2*R*/*S*)-2-Cyanocyclooctylideneamino]-2-methoxymethylpyrrolidine [(*S*,*R*/*S*)-2b]:

2-Cyanocyclooctanone (*rac*-**1b**; 5.59 g, 37 mmol) and SAMP (4.81 g, 37 mmol) were diluted in cyclohexane (60 mL). The preparation was as described for **2a**, yielding 6.52 g (67%) of an orange oil; $[\alpha]_D^{26}$ + 36.5° (*c* = 1.03, benzene).

MS (70 eV): *m/z* (%) = 263 (M^+·, 12), 248 (12), 218 (60), 178 (11), 70 (100), 41 (16).

IR (neat): *v* = 3240 (NH), 2970–2830, 2160 (CN), 1610 (C=C), 1130 cm^{-1}.

^1HNMR[17] ($CDCl_3$): δ = 1.40–2.79 (m, 18H, 16 CH_2, CH_2N, CHCN), 3.13–3.48 (m, 4H, CH_2N, CH_2O, CHN), 3.33 (s, 3H, OCH_3), 5.36 (s, 1H, NH).

^{13}CNMR[17] ($CDCl_3$): δ = 20.8, 25.8, 26.1, 26.4, 26.6, 28.1, 29.1, 30.3 (8CH_2), 57.7 (NCH_2), 59.0 (OCH_3), 65.4 (NCH), 73.1 (C=CCN), 74.0 (CH_2O), 121.7 (CN), 162.2 (C=C–N).

2-Alkyl-2-cyanocycloalkanone SAMP-Hydrazones 3; General Procedure:

A solution of 2-cyanocycloalkanone SAMP-hydrazone **2** (10 mmol) in Et_2O (20 mL) was added to a solution of LDA (14 mmol) in Et_2O (30 mL) at −78 °C. After allowing to warm up to r.t. overnight the mixture was cooled to −110 °C and treated with an alkyl iodide (15 mmol). After again warming up to r.t. the mixture was diluted in Et_2O (100 mL), washed with H_2O (2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). The product was purified by flash chromatography (silica gel, Et_2O/petroleum ether, 1:1–4).

2-Alkyl-2-cyanocyclohexanones 4a–e; General Procedure:

Compound **3** (1 mmol) was diluted in Et_2O (25 mL) and treated with 5N HCl (10 mL). When the reaction was complete (TLC control) the aqueous layer was extracted Et_2O (3 × 50 mL). The organic layer was neutralized with pH 7-buffer, washed with H_2O (10 mL) and dried ($MgSO_4$). The product was purified by flash chromatography (silica gel, Et_2O/petroleum ether, 1:2–3).

2-Alkyl-2-cyanocyclooctanones 4f,g; General Procedure:

Ozonolysis of compound **3** (1 mmol) in petroleum ether (30 mL) at −78 °C led to the crude product **4**, which was purified by flash chromatography (silica gel, Et_2O/petroleum ether, 1:2–3).

X-ray Structure Determination of (*S*,*S*)-3f:

Crystals of sufficient quality were obtained from Et_2O/petroleum ether (1:2) at 2 °C. The compound crystallizes in orthorhombic spacegroup $P2_12_12_1$ (19), a = 10.380 (1), b = 11.679 (1), c = 14.654 (1) Å. Z = 4, V = 1776.5 Å^3 and M_r = 291.44 result in a calculated density of ϱ_{cal} = 1.090 g cm^{-3}, while the total number of electrons per cell amounts to F(000) = 640. $\sin\theta/\lambda_{max}$ = 0.621 for solution and refinement. The structure has been solved by direct methods as implemented in the Xtal3.0 package of crystallographic programms,[18] employing GENSIN[19] to generate structure invariant relationships and GENTAN[20] for the general tangent phasing procedure. A total number of 3448 reflections has been collected in the range ±h +k +l at 0 °C on an ENRAF-NONIUS CAD4 diffractometer. R_{av} = 0.0145. Graphite-monochromated Cu K_α radiation (λ = 1.54179 Å), μ = 5.045 cm^{-1}, no absorption correction. 1616 reflections with $I > 2\sigma(I)$ were used in the final full-matrix least-squares refinement process of 190 variables terminating at R = 0.071 (R_w = 0.051, $w = 1/\sigma^2(F)$) and a final shift/error smaller than 0.0002. Residual electron density 0.4, Zachariasen parameter r* = 4503. The positions of the hydrogen atoms have been calculated and held fixed during the refinement process (U_H = 0.10 Å^2). The eight-membered ring of the molecule is disordered in that carbon atom C11 occurs in two positions with almost equal site occupation parameters (C11A: 0.445, C11B: 0.555). Both components have been refined isotropically. Another disorder in C1-C2 region of the five-membered ring could not be resolved. Further details of the X-ray structure determination may be obtained through the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, W-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 56943, the authors and the bibliographical data.

This work was supported by the Fonds der Chemischen Industrie. We thank BASF AG, Degussa AG, Bayer AG, Hoechst AG and Wacker Chemie for the donation of chemicals. A.Z. thanks the Konrad-Adenauer-Stiftung for a fellowship.

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