Synthesis of Spiroacetal Pheromones via Metalated Hydrazones

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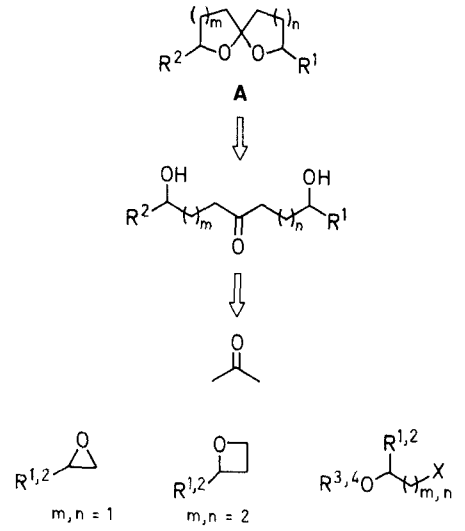
Dedicated to Professor H.J. Bestmann on the occasion of his 65th birthday

The synthesis of simple alkyl substituted spiroacetals by α,α'-alkylation of metalated acetone dimethylhydrazone with appropriate electrophiles and subsequent acid catalyzed cleavage and ring closure of the products is described.

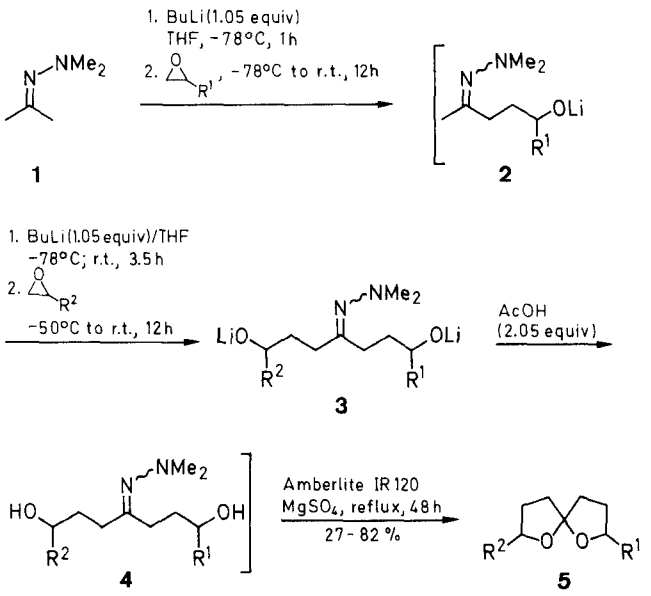
The spiroacetal moiety **A** is part of many natural products with a broad spectrum of biological activities. Among them are for instance, antiparasitic agents (avermectins[1,2,3] and milbemycins[4]), antibiotics (calcimycin[5]) and many volatile spiroacetals with simple substituents used by insects as pheromones[6-8] (e.g. chalcogran[9,10]).

Spiroacetals can retrosynthetically be traced to simple building blocks like ketones, oxiranes, oxetanes and other hydroxyalkylating agents (Scheme **A**). Instead of ketones it is advantageous to use dimethylhydrazones as their equivalents and to deprotonate with strong bases.[11-14] Cleavage and spirocyclization of the obtained alkylation products is then effected under acidic conditions. Examples of the applicability of this technique are the syntheses of calcimycin (A 23187) by Evans et al.,[15] chalcogran **(5b)** by Enders et al.[16] and 1,7-dioxaspiro[5.5]undecane **(8g)** by Mitra et al.[17] We now wish to report the application of this method to the synthesis of alkyl substituted spiroacetals with various ring sizes, which can be found naturally as insect pheromones.



Scheme **A**

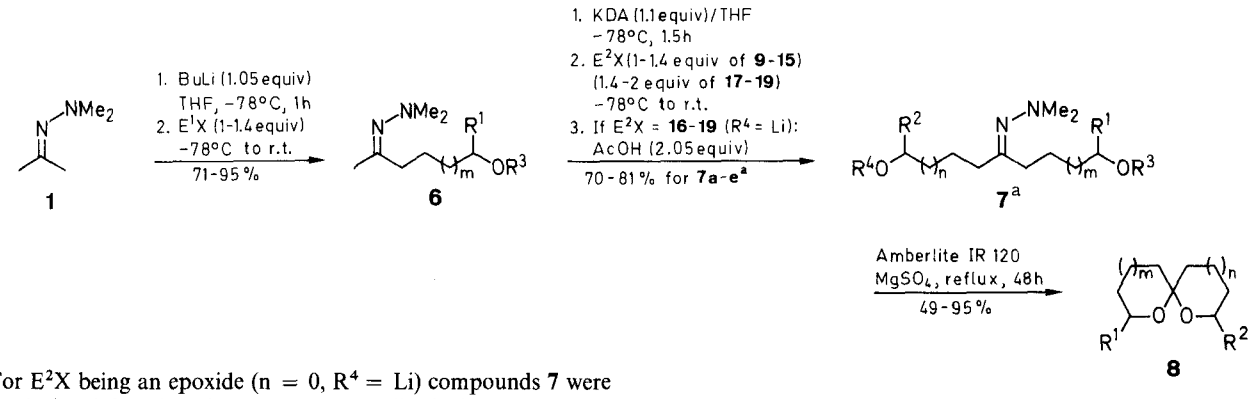
The 1,6-dioxaspiro[4.4]nonanes **5** were synthesized in a one-pot procedure starting from acetone dimethylhydrazone **(1)** and appropriate oxiranes in 27 to 82% overall yield according to Scheme **B** (Table 1). Both metalations were carried out in tetrahydrofuran at −78 °C with butyllithium (1.05 equiv), followed by treatment of the metalated hydrazone with the epoxide. After addition of acetic acid (2.05 equiv) the hydrazone diols **4** were treated with an acidic ion-exchange resin (Amberlite IR120) to effect their cleavage and ring closure.



2–5	R^1	R^2	2–5	R^1	R^2
a	H	H	**e**	Et	Et
b	H	Me	**f**	Me	Pr
c	Me	Me	**g**	Pr	Pr
d	H	Et			

Scheme **B**

For the synthesis of 1,6-dioxaspiro[4.5]decanes **8a–e**, 1,6-dioxaspiro[4.6]undecane **(8f)**, 1,7-dioxaspiro-[5.5]undecanes **8g–j** and 1,7-dioxaspiro[5.6]dodecane **(8k)** (Scheme **C**) acetone dimethylhydrazone **(1)** was deprotonated with butyllithium (1.05 equiv) in tetrahydrofuran at −78 °C for 1 h and reacted with the electrophiles E^1X at −78 °C to form the monoalkylated dimethylhydrazones **6** in 71–95% yield (Table 2). Metalations of **6** were carried out with potassium diisopropylamide (1.1 equiv) in tetrahydrofuran at −78 °C for 1.5 h. After addition of E^2X at −78 °C the α,α'-bisalkylated dimethylhydrazones **7** were isolated in 70–81% yield (Table 3). Treatment of **7** with Amberlite IR120 afforded the desired spiroacetals in 49–95% yield (Table 4). When E^2X is an oxirane, the dimethylhydrazones **7** (n = 0) were not isolated, instead the reaction mixtures were neutralized with acetic acid prior to treatment with Amberlite IR120.

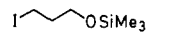
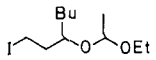
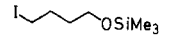
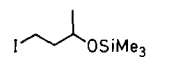
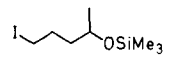
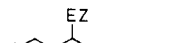
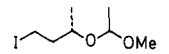
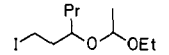


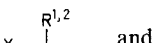
[a] For E^2X being an epoxide (n = 0, R^4 = Li) compounds **7** were not isolated, but the mixtures were neutralized with AcOH (2.05 equiv) prior to treatment with Amberlite to give **8a–f**.

6	m	R^1	R^3
a	1	H	$SiMe_3$
b	1	Me	$SiMe_3$
c	1	Me	CH(Me)OMe
d	1	Et	$SiMe_3$
e	1	Bu	CH(Me)OEt
f	2	Me	$SiMe_3$
g	1	Pr	CH(Me)OEt

7	m	n	R^1	R^2	R^3	R^4
a	1	1	H	H	$SiMe_3$	$SiMe_3$
b	1	1	Me	Me	$SiMe_3$	$SiMe_3$
c	1	1	Pr	H	CH(Me)OEt	$SiMe_3$
d	1	1	Pr	Me	CH(Me)OEt	$SiMe_3$
e	1	2	Me	H	$SiMe_3$	$SiMe_3$

8	m	n	R^1	R^2
a	1	0	H	Me
b	1	0	Me	H
c	1	0	Et	Me
d	1	0	Me	Et
e	1	0	Bu	Me
f	2	0	Me	Me
g	1	1	H	H
h	1	1	Me	Me
i	1	1	Pr	H
j	1	1	Pr	Me
k	1	2	Me	H

Nr.	Electrophiles EX[a]	Nr.	Electrophiles EX[a]
9		**16**	
10		**17**	
11		**18**	
12		(*S*)-**18** (ee 95%)	
13		(*R*)-**18** (ee 95%)	
(*S*)-**14** (ee 89%)		**19**	
15			

[a] Electrophiles EX of the general form  and  .

Scheme C

Table 1. 1,6-Dioxaspiro[4.4]nonanes **5** Prepared

Product	Yield (%)	bp (°C)/ Torr	$[\alpha]_D^{20}$	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ	^{13}C-NMR ($CDCl_3$/TMS)[b,c] δ
5a[d]	27[e]	–	–	$C_7H_{12}O_2$ (128.2)	–	–
5b[d]	60	–	–	$C_8H_{14}O_2$ (142.2)	–	–
5c	65	62/15	–	$C_9H_{16}O_2$ (156.2)	1.14, 1.16, 1.21, 1.24 (4d, 6H, $2CH_3$), 1.35–2.31 (m, 8H, $4CH_2$), 3.81–4.29 (m, 2H, 2CHO)	21.2 (*E*-CH_3), 21.4 (*E*-CH_3), 23.0 (*Z*-CH_3), 32.0, 32.3, 32.7, 32.8, 35.3, 35.7, 36.6, 73.5 (*E*-CHO), 73.7 (*E*-CHO), 75.6 (*Z*-CHO), 114.4, 114.6, 114.8
rac-**5d**[f,g]	70	72/15	–	$C_9H_{16}O_2$ (156.2)	–	–
(2*S*)-**5d**[f,g]	82		−14.9[h] (neat)	$C_9H_{16}O_2$ (156.2)	–	–

Table 1. continued

Product	Yield (%)	bp (°C)/ Torr	$[\alpha]_D^{20}$	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ	^{13}C-NMR ($CDCl_3$/TMS)[b,c] δ
5e[i]	65	82/10	–	$C_{11}H_{20}O_2$ (184.3)	0.9 (t, 6H, $2CH_3$), 1.3–2.4 (m, 12H, $6CH_2$), 3.4–4.1 (m, 2H, 2CHO)	9.9, 10.1, 28.5, 29.6, 29.7, 30.1, 30.3, 34.9, 35.3, 36.1, 78.8 (*E*-CHO), 79.0 (*E*-CHO), 80.9 (*Z*-CHO), 81.0 (*Z*-CHO), 113.7, 113.9, 114.2
5f[j]	80[k]	65/12	–	$C_{11}H_{20}O_2$ (184.3)	0.95 (t, 3H, CH_3), 1.26, 1.32 (2d, 3H, CH_3), 1.3–2.3 (m, 12H, $6CH_2$), 3.69–4.41 (m, 2H, 2CHO)	14.20, 19.38, 21.24 (*E*/*Z*-CH_3), 22.93 (*E*/*Z*-CH_3), 30.37, 30.9, 35.31, 35.74, 35.8, 36.8, 38.01, 39.71, 73.49, 74.09, 78.04, 79.83, 114.63
5g[j]	79[k]	102/15	–	$C_{13}H_{24}O_2$ (212.3)	0.9 (t, 6H, $2CH_3$), 1.1–2.3 (m, 16H, $8CH_2$), 3.78–4.29 (m, 2H, 2CHO)	14.33, 19.28, 19.37, 19.49, 30.32, 30.50, 31.08, 35.08, 35.63, 36.24, 36.45, 38.15, 39.94, 40.06, 77.69 (*E*-CH), 78.02 (*E*-CH), 79.81 (*Z*-CH), 79.90 (*Z*-CH), 114.27, 114.64

[a] Satisfactory microanalyses obtained: C ±0.36, H ±0.11, or HRMS gave a mass value for the molecular ion within 0.0013 amu of the calculated value.
[b] Signals of all diastereomers present.
[c] Ratio of diastereomers not determined.
[d] Analytical data are in accordance with those given in the literature.[18]
[e] Low yield because of the products high volatility.
[f] Analytical data are in accordance with those given in the literature.[19]
[g] Chalcogran; Aggregation pheromone of the bark beetle *pityogenes chalcographus*.[9]
[h] Ref.[19]: $[\alpha]_D^{22}$ −15.9° (neat).
[i] Isolated from the bee *andrena wilkella*.[20]
[j] Isolated from the bee *andrena haemorrhoa*.[21]
[k] Isolated by preparative gas chromatography (Apiezon M).

Table 2. Monoalkylated Dimethylhydrazones **6** Prepared

Product	E^1X	Yield (%)	bp (°C)/ Torr	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ	^{13}C-NMR ($CDCl_3$/TMS)[b] δ
6a	**9**	95	56/0.5	$C_{11}H_{26}N_2OSi$ (230.4)	0 (s, 9H, $Si(CH_3)_3$), 1.32–1.55 (m, 4H), 1.78 (s, 3H, CH_3CN), 1.95–2.15 (m, 2H, CH_2CN), 2.21 (s, 6H, $N(CH_3)_2$), 3.37–3.57 (m, 2H, CH_2O)	−0.85, 15.9, 22.07 (*E*/*Z*-$\underline{C}H_3CN$), 22.9, 31.9, 38.2, 46.59, 47.07 (*E*/*Z*-$N(CH_3)_2$), 61.85, 167.04, 168.82 (*E*/*Z*-C=N)
6b	**11**	83	52/0.3	$C_{12}H_{28}N_2OSi$ (244.5)	0 (s, 9H, $Si(CH_3)_3$), 1.05 (d, 3H, CH_3), 1.23–1.49 (m, 4H), 1.8 (s, 3H, CH_3CN), 2.0–2.2 (m, 2H, CH_2CN), 2.3 (s, 6H, $N(CH_3)_2$), 3.7 (m, 1H, CHO)	−0.19, 16.31, 22.49 (*E*/*Z*-$\underline{C}H_3CN$), 23.27, 23.72, 38.87, 38.93, 46.99, 47.45 (*E*/*Z*-$N(CH_3)_2$), 68.19, 167.63
(*S*)-**6c**[c]	(*S*)-**14**	79	71/13	$C_{12}H_{26}N_2O_2$ (230.4)	1.15, 1.25 (2d, 6H, $2CH_3$), 1.2–1.6 (m, 4H), 1.85 (s, 3H, CH_3CN), 2.0–2.2 (m, 2H, CH_2CN), 2.3 (s, 6H, $N(CH_3)_2$), 3.2 (s, 3H, OCH_3), 3.4–3.75 (m, 1H, CHO), 4.5–4.75 (m, 1H, CHO_2)	–
6d	**13**	71	70/0.4	$C_{13}H_{30}N_2OSi$ (258.5)	0 (s, 9H, $Si(CH_3)_3$), 0.78 (t, 3H, CH_3), 1.17–1.5 (m, 8H), 1.72, 1.78 (2s, 3H, *E*/*Z*, CH_3CN), 1.9–2.09 (m, 2H, CH_2CN), 2.20, 2.22 (2s, 6H, *E*/*Z*, $N(CH_3)_2$), 3.31–3.62 (m, 1H, CHO)	–
6e	**16**	85	85/0.1	$C_{16}H_{34}N_2O_2$ (286.5)	0.81–1.69 (m, 21H), 1.93 (s, 3H, CH_3CN), 2.1–2.8 (m, 2H), 2.42 (s, 6H, $N(CH_3)_2$), 3.39–3.79 (m, 1H, CHO), 4.6–4.82 (q, 1H, CHO_2)	14.11, 15.40, 16.43, 20.72, 22.32–39.08 (6), 47.06, 47.50 (*E*/*Z*-$N(CH_3)_2$), 59.89, 60.03, 75.99, 98.71, 167.44, 167.60 (*E*/*Z*-C=N)
6f	**12**	84	60/0.2	$C_{13}H_{30}N_2OSi$ (258.5)	0.03 (s, 9H, $Si(CH_3)_3$), 1.0 (d, 3H, CH_3), 1.20–1.50 (m, 6H), 1.78, 1.80 (2s, 3H, *E*/*Z*, CH_3CN), 2.0–2.22 (m, 2H, CH_2CN), 2.25, 2.30 (2s, 6H, *E*/*Z*, $N(CH_3)_2$), 3.49–3.78 (m, 1H, CHO)	0.07, 16.0, 22.20 (*E*/*Z*-$\underline{C}H_3CN$), 23.57, 25.23, 26.70, 38.65, 31.06, 39.06 (*E*/*Z*-CH_2–CN), 46.63, 47.15 (*E*/*Z*-$N(CH_3)_2$), 68.07, 167.28
6g[d]	**15**	72	78/0.07	$C_{15}H_{32}N_2O_2$ (272.4)	–	–

[a] Satisfactory microanalyses obtained: C ±0.11, H ±0.19, N ±0.06, or HRMS gave a mass value for the molecular ion within 0.014 amu of the calculated value.
[b] Signals of the *E*- and *Z*-Isomer. Ratio not determined.
[c] $[\alpha]_D^{22}$ +12.4° (neat.), $[\alpha]_D^{22}$ +13.8° (c = 1.14, $CHCl_3$).
[d] NMR spectra were not recorded.
[a] Satisfactory microanalyses obtained: C ±0.11, H ±0.19, N ±0.06, or HRMS gave a mass value for the molecular ion within 0.014 amu of the calculated value.

Table 3. Bisalkylated Dimethylhydrazones **7** Prepared

Product	Substrate	E^2X	Yield (%)	bp (°C)/ Torr	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ	^{13}C-NMR ($CDCl_3$/TMS)[b] δ
7a	**6a**	**9**	70	110/0.4	$C_{17}H_{40}N_2O_2Si_2$ (360.7)	0 (s, 18H, $Si(CH_3)_3$), 1.32–1.58 (m, 8H), 1.98–2.2 (m, 4H, $2CH_2CN$), 2.2 (s, 6H, $N(CH_3)_2$), 3.38–3.58 (m, 4H, $2CH_2O$)	–
7b	**6b**	**11**	81	150/0.2	$C_{19}H_{44}N_2O_2Si_2$ (388.8)	0.1 (s, 18H, $2Si(CH_3)_3$), 1.15 (d, 6H, $2CH_3$), 1.31–1.69 (m, 8H), 2.08–2.39 (m, 4H, $2CH_2CN$), 2.39 (s, 6H, $N(CH_3)_2$), 3.6–4.0 (m, 2H, 2CHO)	0.25, 22.83, 23.59, 23.75, 23.91, 29.55, 35.92, 39.16, 39.58, 47.54, 68.16, 68.32, 172.39
7c[c]	**6g**	**9**	71		$C_{21}H_{46}N_2O_3Si$ (402.7)	–	–
7d[c]	**6g**	**11**	73		$C_{22}H_{48}N_2O_3Si$ (416.7)	–	–
7e	**6b**	**10**	77	103/0.05	$C_{19}H_{44}N_2O_2Si_2$ (388.7)	0 (s, 18H, $2Si(CH_3)_3$), 1.05 (d, 3H, CH_3), 1.15–1.56 (m, 10H), 1.95–2.37 (m, 4H, $2CH_2CN$), 2.22 (s, 6H, $N(CH_3)_2$), 4.47 (t, 2H, CH_2O), 4.52–4.82 (m, 1H, CHO)	0.25, 0.54, 22.98, 24.23, 25.98, 26.49, 26.69, 30.02, 30.22, 32.81, 32.95, 35.98, 39.51, 39.90, 47.76, 62.40, 62.49, 68.17, 68.42, 170

[a] Satisfactory microanalyses obtained: C ±0.03, H ±0.09, N ±0.23, or HRMS gave a mass value for the molecular ion within 0.016 amu of the calculated value.
[b] Signals of all isomers present.
[c] NMR spectra were not recorded.

Table 4. Spiroacetals **8** Prepared

Product	Substrate	E^2X	Yield (%)	$[\alpha]_D^{20}$	ee (%)	bp (°C)/ Torr	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ	^{13}C-NMR ($CDCl_3$/TMS)[b] δ
8a[c,d]	**6a**	**18**	68	–	–	100/80	$C_9H_{16}O_2$ (156.2)	1.20, 1.28 (2d, 3H, CH_3), 1.37–2.27 (m, 10H, CH_2), 3.40–4.02 (m, 2H, CH_2O), 4.22 (q, 1H, CHO)	20.35, 21.29 (CH_3), 23.20 (CH_3), 25.40, 31.49, 31.78, 34.14, 34.28, 37.86 (C-4), 39.09 (C-4), 61.42 (C-7), 61.54 (C-7), 74.00 (C-2), 76.75 (C-2), 105.62 (C-5), 105.83 (C-5)
(2*S*,5*RS*)-**8a**[c,e]	**6a**	(*S*)-**18**	62	−12.48 (neat) −10.68 (*c* = 3.29, MeOH)[f]	95[g]	–			
(2*R*,5*RS*)-**8a**[c,e]	**6a**	(*R*)-**18**	68	+8.7 (*c* = 1.06, $CDCl_3$)	95[g]	–			
(*E*)-**8b**[c]	**6b**	**17**	61	–	–	130/80	$C_9H_{16}O_2$ (156.2)	1.15 (d, 3H, CH_3), 1.28–2.30 (m, 10H, CH_2), 3.67–4.10 (m, 3H, CH_2O, CHO)	20.42, 22.04 (CH_3), 23.77, 32.62, 32.85 (C-4), 37.99 (C-10), 66.45 (C-2), 67.77 (C-7), 106.03 (C-5)
(*E*)-(5*S*,7*S*)-**8b**[c,h]	(*S*)-**6c**	**17**	60	−71.4 (neat) −63.2 (*c* = 2.7, MeOH)[i]	89.5[j]	–			
8c[c,d,k]	**6d**	**18**	67	–	–	140/80	$C_{11}H_{20}O_2$ (184.3) 140/80	0.9 (t, 3H, CH_3), 1.13 (d, 3H, *E*/*E*-CH_3), 1.23 (d, 3H, *E*/*Z*-CH_3), 1.32–2.21 (m, 12H, CH_2), 3.39–3.79 (m, 1H, CHO, 6-ring), 3.89–4.22 (m, 1H, CHO, 5-ring)	10.06, 10.26, 20.42, 21.26, 23.30, 29.16, 29.32, 30.55, 30.81, 31.39, 31.84, 33.62, 38.03 (*E*-C-10), 39.48 (*E*-C-10), 71.17, 71.53, 73.53 (*E*-C-2), 76.64 (*Z*-C-2), 105.84, 106.06
8d[c,d,k,l]	**6b**	**19**	71	–	–	120/13	$C_{11}H_{20}O_2$ (184.3) 120/13	0.92 (t, 3H, CH_3), 1.15 (2d, 3H, CH_3), 1.20–2.20 (m, 12H, CH_2), 3.59–4.03 (m, 2H, CHO)	10.16, 10.48, 20.42, 20.55, 22.10, 28.48, 29.13, 29.45, 30.71, 32.75, 33.27, 33.43, 37.96 (*E*-C-10), 39.03 (*Z*-C-10), 66.16, 66.25, 79.07 (*E*-C-2), 82.08 (*Z*-C-2), 105.68, 105.90

Table 4. (Continued)

Product	Substrate	E^2X	Yield (%)	$[\alpha]_D^{20}$	ee (%)	bp (°C)/ Torr	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ	^{13}C-NMR ($CDCl_3$/TMS)[b] δ
8e[d,k]	**6e**	**18**	76	–	–	–	$C_{13}H_{24}O_2$ (212.3)	0.90 (t, 3H, CH_3), 1.30 (d, 3H, CH_3), 1.10–2.21 (m, 16H, CH_2), 3.50–4.0 (m, 1H, CHO, 6-ring), 4.0–4.40 (m, 1H, CHO, 5-ring)	14.09, 20.56, 21.35, 22.88, 23.33, 28.04, 31.15, 31.36, 31.52, 32.00, 33.69, 33.77, 36.15, 36.34, 38.11, 39.51, 69.81, 70.09, 73.63 (*E*-C-2), 76.67 (*Z*-C-2), 105.85
(*E,E*)-**8f**[k,m]	**6f**	**18**	80 (both isomers)	–	–	–	$C_{11}H_{20}O_2$ (184.3)	1.05, 1.15 (2d, 6H, $2CH_3$), 1.20–2.20 (m, 12H, CH_2), 3.70–4.30 (m, 2H, 2CHO)	21.07, 23.23, 23.70, 29.54, 32.50, 37.62, 38.72, 39.69, 67.87 (C-7), 73.54 (C-2), 109.93 (C-5)
(*Z,E*)-**8f**[d,k,m]	**6f**	**18**	–	–	–	–	$C_{11}H_{20}O_2$ (184.3)	1.03, 1.25 (2d, 6H, $2CH_3$), 1.30–2.35 (m, 12H, CH_2), 3.70–4.40 (m, 2H, 2CHO)	21.08, 23.25, 23.31, 23.37, 23.50, 23.71, 29.54, 32.50, 32.89, 37.63, 37.75, 38.72, 39.66, 67.44 (*Z*-C-7), 67.90 (*E*-C-7), 75.87 (*E*-C-2), 77.29 (*Z*-C-2), 109.7, 109.71
8g[n,o]	**7a**	–	95	–	–	–	$C_9H_{16}O_2$ (156.2)	1.12–2.09 (m, 12H, CH_2), 3.28–3.79 (m, 4H, $2CH_2O$)	18.73, 25.58, 35.94, 60.26 (C-2), 94.90 (C-6)
(*E,E*)-**8h**[l,p,q]	**7b**	–	92 (both isomers)	–	–	130/15	$C_{11}H_{20}O_2$ (184.3)	1.03 (d, 6H, $2CH_3$), 1.15–2.20 (m, 12H, CH_2), 3.35–3.82 (m, 2H, 2CHO)	19.03 (C-4), 21.94 (CH_3), 32.95 (C-3), 35.31 (C-5), 65.00 (C-2), 96.09 (C-6)
(*E,Z*)-**8h**[l,p,q]	**7b**	–	–	–	–	130/15	$C_{11}H_{20}O_2$ (184.3)	1.02, 1.12 (2d, 6H, $2CH_3$), 1.20–2.10 (m, 12H, CH_2), 3.38–3.77 (m, 1H, CHO), 3.37–4.15 (m, 1H, CHO)	18.46, 19.55, 21.87, 22.13, 29.21, 32.44, 33.26, 36.28, 66.09 (*E*-C-2), 68.89 (*Z*-C-2) (C-6 not found, too small)
8i[k,p]	**7c**	–	61	–	–	–	$C_{12}H_{22}O_2$ (198.3)	0.93 (t, 3H, CH_3), 1.01–2.18 (m, 16H, CH_2), 3.39–3.87 (m, 3H, CH_2O, CHO)	14.33, 18.73, 18.99, 19.20, 25.59, 31.39, 35.58, 36.06, 38.87, 60.32 (C-8), 68.90 (C-2), 95.42 (C-6)
(*E,E*)-**8j**[k,p,r]	**7d**	–	49 (both isomers)	–	–	–	$C_{13}H_{24}O_2$ (212.3)	0.91 (t, 3H, CH_3), 1.10 (d, 3H, CH_3), 1.12–2.05 (m, 16H, CH_2), 3.31–3.89 (m, 2H, 2CHO)	14.26, 18.99, 19.06, 19.17, 21.86, 31.47, 32.94, 35.41, 35.60, 38.83, 65.10, 68.73, 95.99
(*E,Z*)-**8j**[k,p,r]	**7d**	–	–	–	–	–	$C_{13}H_{24}O_2$ (212.3)	0.99 (t, 3H, CH_3), 1.18 (d, 3H, CH_3), 1.28–2.00 (m, 16H, CH_2), 3.25–3.61 (m, 1H, *E*/*Z*-CHO), 4.01–4.42 (m, 1H, *Z*/*E*-CHO)	14.14, 18.28, 19.20, 20.27, 22.19, 28.06, 31.32, 33.28, 36.53, 38.75, 66.29, 72.36, 97.57
(*E*)-**8k**[k]	**7e**	–	85	–	–	140/13	$C_{11}H_{20}O_2$ (184.3)	1.09 (d, 3H, CH_3), 1.19–2.02 (m, 14H, CH_2), 3.40–4.00 (m, 3H, CH_2O, CHO)	19.33, 22.09, 22.60, 29.98, 30.71, 33.05, 35.11, 41.95, 61.21 (C-8), 65.93 (C-2), 100.42 (C-6)

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.12, or HRMS gave a mass value for the molecular ion within 0.006 amu of the calculated value.
[b] ^{13}C-NMR assignment according to spiroacetal nomenclature.
[c] Isolated from the common wasp *paravespula vulgaris*.[22]
[d] Mixture of *E*/*Z*-isomers is formed. ^{13}C-NMR signals of all isomers present are given.
[e] Analytical data are in accordance with those of compound **8a**.
[f] Ref. [24]: $[\alpha]_D$ −10.2° (*c* = 3, MeOH).
[g] Determined by complexation gas chromatography on chiral metal complexes.[23]
[h] Analytical data are in accordance with those of compound **8b**.
[i] Ref. [24]: $[\alpha]_D$ −67.0° (*c* = 3, MeOH), ee = 95%.
[j] Determined from the optical rotation value.
[k] Isolated from the bee *andrena haemorrhoa*.[20,21]
[l] Isolated from the bee *andrena wilkella*.[20]
[m] *Z,E*/*E,E*-**8f** = 1 : 1 from GC; separable by column chromatography (silica gel; Et_2O/pentane, 1 : 4).
[n] Sex pheromone of the olive fruit fly *dacus oleae*.[25]
[o] Only the C_2-symmetrical isomer with axial C—O bonds is formed.
[p] Isolated from the fruit fly *dacus dorsalis*.[26]
[q] *Z,E*/*E,E*-**8h** = 1 : 1, 17 from GC; separable by column chromatography (silica gel; Et_2O/pentane, 1 : 4).
[r] Ratio of diastereomers not determined.

The enantiomeric excesses (ee) of (2*S*,5*RS*)- and (2*R*,5*RS*)-**8a** formed by using (*S*)- and (*R*)-1,2-epoxypropane [(*S*)-**18** and (*R*)-**18**] (each with ee = 95%) as electrophiles E^2X were shown to be also 95% enantiomerically pure by complexation gas chromatography on chiral metal complexes[23] (Figure). The ee of ((*E*)-5*S*,7*S*)-**8b** synthesized by using (*S*)-**14** (ee = 89%) as E^1X was determined to be 89% by its optical rotation value.[24]

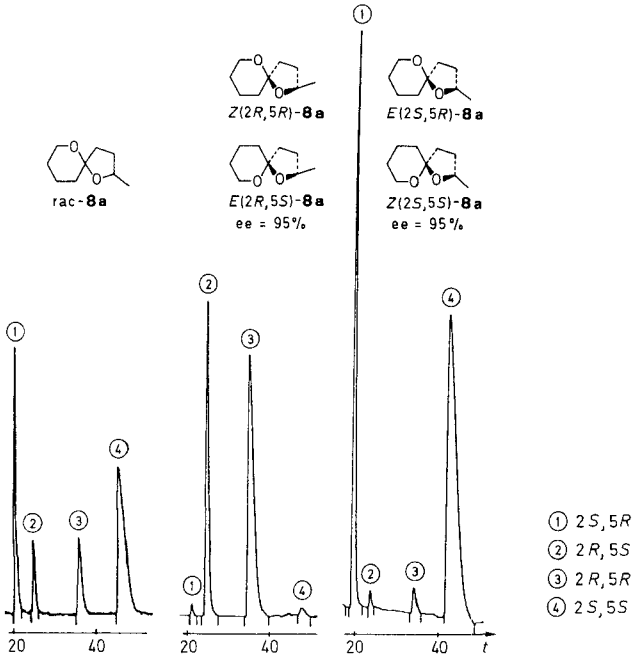
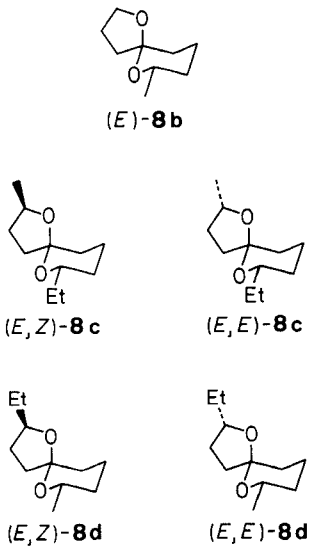


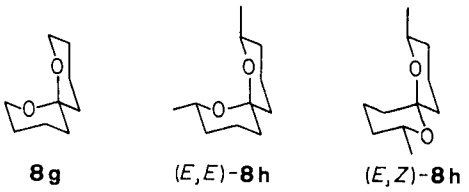
Figure. Enantiomeric excesses (ee) of (2*S*,5*RS*)- and (2*R*,5*RS*)-**8a** shown by complexation gas chromatography on chiral metal complexes.

According to the ^{13}C-NMR spectra,[27] 1,6-dioxaspiro[4.5]decanes **8c** and **8d** were formed as mixtures of *E*/*Z*-isomers and **8b** as *E*-isomer exclusively, with alkyl substituents of C_6-rings occupying equatorial positions.



2,7-Dimethyl-1,6-dioxaspiro[4.6]undecane **(8f)** isolated from the pheromone bouquets of the bee *andrena haemorrhoa*[20,21] and the common wasp *paravespula vulgaris*[22] was synthesized as a 1:1 mixture of the *Z,E*- and *E,E*-isomers, which were separable by chromatography (silica gel, diethyl ether/pentane 1:4).

The four 1,7-dioxaspiro[5.5]undecanes **8g–j** were obtained in 49–95% yield from the corresponding bisalkylated dimethylhydrazones **7a–d** (Table 4). With the exception of **8g** they were all isolated as mixtures of *E,Z*-isomers. Due to the anomeric effect[28] **8g**, the female produced sex pheromone of the olive fruit fly *dacus oleae*,[25] was synthesized as a C_2 symmetrical molecule with axial C–O bonds exclusively, thus showing just five signals in its ^{13}C-NMR spectrum. The spiroacetal **8h**, isolated from the bee *andrena wilkella*,[20] was formed as a 1:1.17 mixture of the *E,Z*- and *E,E*-isomers, which could be separated by chromatography (silica gel, diethyl ether/pentane, 1:4).



A 1,7-dioxa[5.6]dodecane we synthesized was **8k**, isolated from the bee *andrena haemorrhoa*.[20,21] The yield of the isolated *E*-isomer was 85%.

Using (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) as a chiral hydrazine, we showed that it is possible by a similar reaction path to prepare diastereo- and enantioselectively α,α′-disubstituted spiroacetals with respect to the central spiro carbon atom.[29]

In summary, the hydrazone method gives an efficient and flexible entry to a great variety of spiroacetal structures.

Solvents were dried and purified according to known procedures. All reagents were destilled prior to use or were of commercial quality from freshly opened containers. Optical rotation values were measured using a Perkin–Elmer P241 polarimeter. Microanalyses were obtained using a Heraeus Micro U/D. IR-spectra were recorded on a Beckman Acculab 4 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian EM 360 and EM 390 and ^{13}C-NMR spectra using Bruker WH 90 and Varian CFT 20 spectrometers. MS spectra were recorded on a Kratos MS 50 and MS 30.

1-Iodo-3-trimethylsiloxypropane **(9)**,[28] 1-iodo-4-trimethylsiloxybutane **(10)**,[28] 1-iodo-3-trimethylsiloxybutane **(11)**,[28] 1-iodo-4-trimethylsiloxypentane **(12)**,[28] 1-iodo-3-trimethylsiloxypentane **(13)**,[28] (*S*)-1-iodo-3-(1-methoxyethoxy)butane [(*S*)-**14**],[29,30] 1-iodo-3-(1-ethoxyethoxy)hexane **(15)**,[28] 1-iodo-3-(1-ethoxyethoxy)-heptane **(16)**[28] were prepared according to literature procedures.

Acetone Dimethylhydrazone (1):
N,N-dimethylhydrazine (45.7 mL, 0.6 mol, 1.5 equiv) and acetone (29.4 mL, 0.4 mol, 1 equiv) are heated under reflux. Alternatively the reaction can be carried out in cyclohexane while the H_2O formed is removed via a Dean Stark trap. After the reaction is complete (TLC control) the mixture is poured into Et_2O (200 mL

per 40 mmol of hydrazone), washed with little H_2O, dried ($MgSO_4$) and evaporated *in vacuo*. The crude hydrazone is purified by distillation at 93 °C; yield: 33 g (84%). All data are in accordance with those given in the literature.[14]

One-Pot-Synthesis of 1,6-Dioxaspiro[4.4]nonanes 5; General Procedure:

In a dried, argon-filled round-bottomed flask fitted with a septum cap acetone dimethylhydrazone (**1**; 10 mmol) is dissolved in anhydrous THF (20 mL). The solution is cooled to −78 °C and BuLi (10.5 mmol, 1.6 M solution in hexane) is added dropwise. After 1 h further stirring the appropriate epoxide (10.1–20 mmol; when using two different epoxides the most volatile is used first) is added dropwise and the mixture is allowed to warm up to r.t. slowly (about 15 h). Excess epoxide is removed *in vacuo* and the loss of THF compensated. Under Ar the solution is cooled to −78 °C, BuLi (10.5 mmol) is added and stirred at r.t. for 3.5 h. The second epoxide is added at −78 °C. After the mixture has warmed up to r.t. slowly, excess epoxide is again removed and the bis-*O*-lithium compound **3** is quenched with AcOH (2.05 equiv) to form the bis-hydroxyalkylated dimethylhydrazone **4**. After filtration and extraction of the precipitated LiOAc with THF, the filtrates are refluxed together with Amberlite IR120 (1.5 g per mmol) and $MgSO_4$ (1 g per mmol) for 48 h. The acidic ion-exchange resin and $MgSO_4$ are filtered off and extracted with THF several times. THF is then removed under reduced pressure, the residue dissolved in CH_2Cl_2 (20 mL) and washed with sat. aq $NaHCO_3$ (20 mL), pH-7 phosphate buffer (20 mL) and H_2O (20 mL). After drying (Na_2SO_4) and removal of CH_2Cl_2 *in vacuo* the crude product is purified by distillation under reduced pressure (Table 1).

Monoalkylated Acetone Dimethylhydrazones 6; General Procedure:

Under argon acetone dimethylhydrazone (**1**; 10 mmol) is dissolved in THF (20 mL) and at −78 °C BuLi (10.5 mmol, 1.6 M solution in hexane) is added slowly. After stirring for 1 h the alkylating agent E^1X (10–15 mmol) is added at −78 °C and the mixture is allowed to warm up to r.t. slowly. THF is removed *in vacuo* and the residue is dissolved in Et_2O/pentane (1:1). Salts are removed by filtration over basic aluminium oxide. After evaporation of the solvent under reduced pressure the crude product is purified by distillation.

Bisalkylated Acetone Dimethylhydrazones 7; General Procedure:

For the metalation of monoalkylated acetone dimethylhydrazone **6** (10 mmol) freshly sublimed *t*-BuOK (1.23 g, 11 mmol) is dissolved in THF (40 mL) under Ar and at −78 °C are added *i*-Pr_2NH (1.4 mL, 10 mmol) and BuLi (10 mmol, 1.6 M solution in hexane). After stirring for 30 min **6** is added at −78 °C and the mixture is stirred for further 1.5 h at this temperature before the electrophile E^2X is added. When E^2X is an *O*-protected iodo alcohol **9–15** the preceding procedure can be followed from this point. The epoxides **16–19** (14–20 mmol) are added at −78 °C and the reaction mixture is allowed to warm up to r.t. slowly. Excess of epoxide is removed under reduced pressure and the residue is treated with AcOH (2.05 equiv). LiOAc is filtered off and extracted with THF several times. Compounds **7** are not isolated, but cleavage and cyclization is carried out at once.

Formation of Spiroacetals 8 (Cleavage and Spirocyclization); General Procedure:

The bisalkylated acetone dimethylhydrazone **7** (10 mmol) dissolved in THF (approx. 70 mL) is refluxed for 48 h together with Amberlite IR120 (15 g; 1.5 g per mmol) and $MgSO_4$ (10 g; 1 g per mmol). Acidic ion-exchange resin and $MgSO_4$ are filtered off and extracted with THF several times. The solvent is removed *in vacuo*, the residue dissolved in Et_2O (20 mL) and washed with sat. aq $NaHCO_3$ (20 mL), pH-7 phosphate buffer (20 mL) and H_2O (20 mL). After drying (Na_2SO_4) and removal of Et_2O *in vacuo* the crude product is purified by distillation *in vacuo* or chromatography.

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