1-Thiacyclooct-4-yne (= 5,6-Didehydro-3,4,7,8-tetrahydro-2*H*-thiocin), and Its Sulfoxide and Its Sulfone

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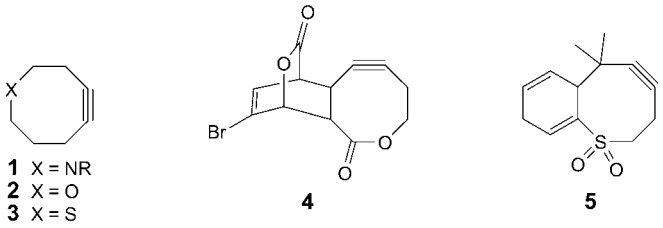
1-Thiacyclooct-4-yne (= 5,6-didehydro-3,4,7,8-tetrahydro-2*H*-thiocin; **9**) can be prepared from thiocan-5-one (**6**) in three steps by applying the so-called selenadiazole method. The heterocyclic alkyne can be oxidized to the corresponding sulfoxide **16** and sulfone **17**. Due to their geometrical strain, all three cyclic alkynes show high reactivities in *Diels–Alder* and 1,3-dipolar cycloadditions. Moreover, tetrathiafulvalenes can be prepared from **9** and **16** by the reaction with CS_2.

Introduction. – Due to their high reactivity in addition and cycloaddition reactions, strained cycloalkynes have a high actuality in click processes and bioorthogonal reactions [1–14]. In the previous five years, many studies of azacyclooct-5-ynes (**1**) appeared [8][11][15–42].

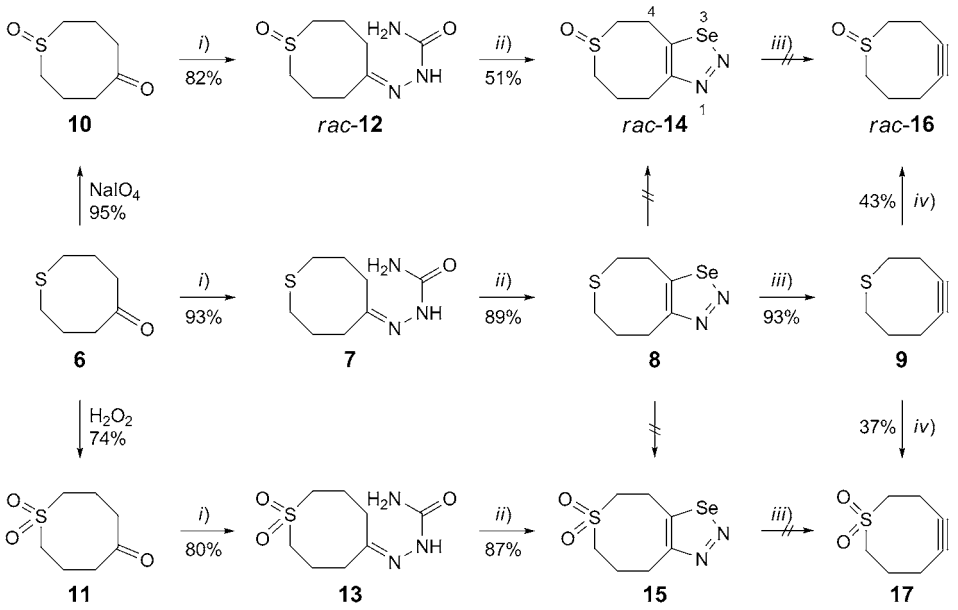
To the best of our knowledge, only one example exists for 1-oxacyclooct-4-ynes (**2**) and one for 1-thiacyclooct-4-ynes **3**, namely the tricyclic lactone **4** [42] and the bicyclic sulfone **5** [43], respectively. This prompted us to report our results on the parent compound **3**.



Results and Discussion. – A convenient and high-yield preparation of strained cyclic alkynes is based on the fragmentation of 1,2,3-selenadiazoles [44]. We used the conversion of thiocanone **6** to the 1,2,3-selenadiazole **8** *via* the semicarbazone **7** [45]. Thermolysis of **8** on Cu powder gave the desired 1-thiacyclooct-4-yne (= 5,6-didehydro-3,4,7,8-tetrahydro-2*H*-thiocin; **9**) in almost quantitative yields (*Scheme 1*).

The 1,2,3-selenadiazole ring is sensitive towards oxidation. Therefore, we tried to oxidize its precursor, the thiocanone **6** with $NaIO_4$ to the sulfoxide **10** and with H_2O_2 to the sulfone **11**. The corresponding 1,2,3-selenadiazoles **14** and **15** were then obtained *via* the semicarbazones **12** and **13**, respectively. However, the thermal fragmentation of **14** and **15** failed. The volatility of the desired products is not high enough, so that decompositions occurred in the hot zone.

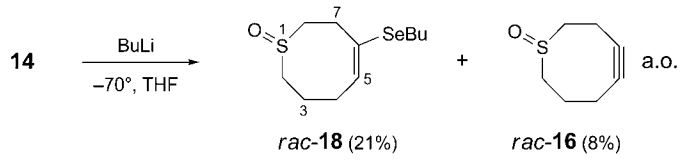
Scheme 1. *Preparation of 5-Thiacyclooctyne* (**9**), and *Its Sulfoxide* (**16**) *and Its Sulfone* (**17**)



i) $H_2NNHCONH_2$, EtOH, AcONa. *ii*) SeO_2, aqueous dioxane. *iii*) Cu, 165–175°, 100 Pa. *iv*) $NaIO_4$, 0°.

Therefore, we tried the alkaline fragmentation of the 1,2,3-selenadiazole **14** with BuLi. The reaction led to a mixture of several Se-containing products. Selenio sulfoxide **18** was the major component, and the desired alkyne **16** was a minor product, in an unsatisfying yield (*Scheme 2*).

Scheme 2



Finally, we realized that the stability of 1-thiacyclooct-4-yne (**9**) is sufficient for the oxidation to its sulfoxide **16** and its sulfone **17**. A fourfold excess of $NaIO_4$ yielded 80% of the oxidation-productmixture **16**/**17** in a 43 : 37 ratio (*Scheme 1*). A higher excess of $NaIO_4$ increased the portion of the sulfone **17**, but reduced the overall yield.

One- and two-dimensional NMR experiments were performed for the characterization of the new alkynes. A ^1H,^1H-shift-correlated NMR spectrum of *rac*-**16** is depicted in the *Figure*. The COSY 45 technique is suitable to distinguish between the geminal and vicinal couplings [46]. A control for the assignment of geminal H-atoms was achieved by a HSQC measurement.

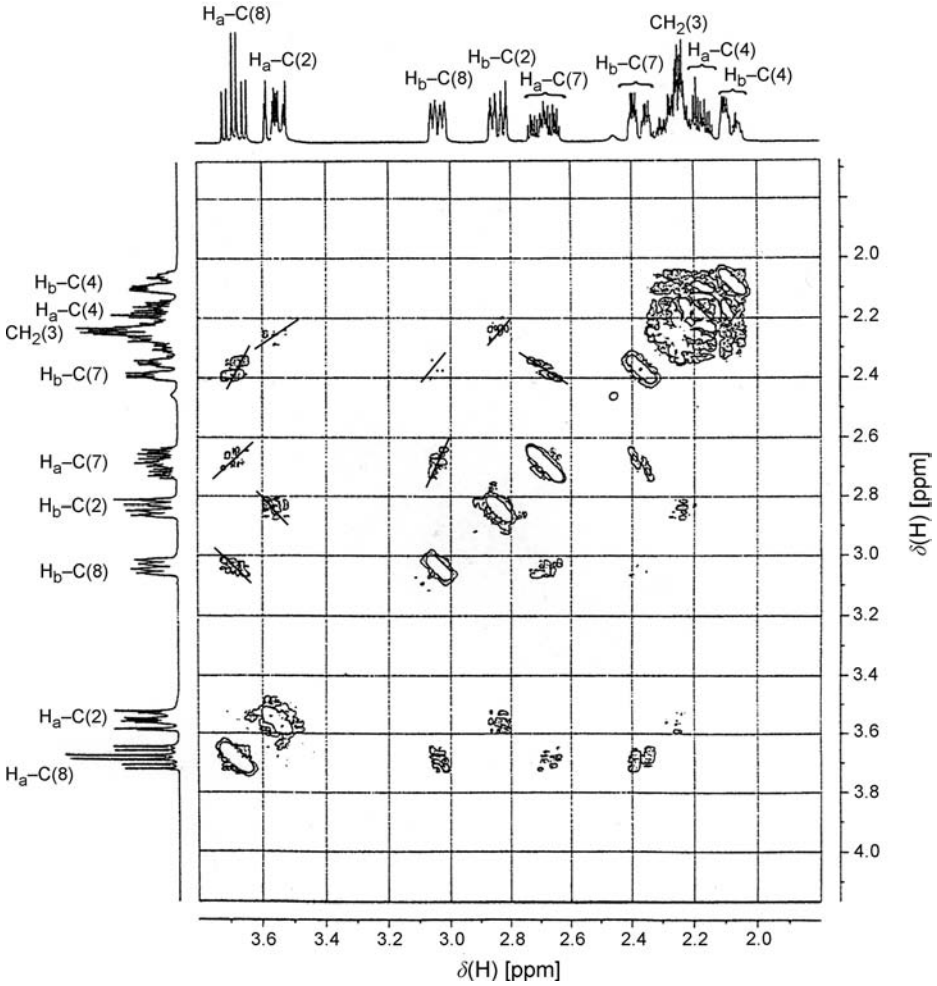


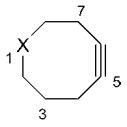
Figure. *^{1}H,^{1}H-COSY-45-NMR Spectrum of* rac-**16**. The cross-peaks, which are characterized by a positive slope, correspond to vicinal couplings, the cross-peaks marked with a negative slope correspond to geminal couplings.

The ^{1}H and ^{13}C chemical shifts ofthe alkynes **9**, **16**, and **17** are compiled in the *Table*.

An easy anchor point for the interpretation of the NMR spectra is always $CH_2(3)$ with two adjacent CH_2 groups, $CH_2(2)$ and $CH_2(4)$. Due to the geometrical strain, the sp-atoms C(5) and C(6) exhibit signals with relatively high δ values. Their difference $\Delta\delta$ is small, which is in accordance with the small polarization of the C≡C bonds and the small regioselectivity of certain cycloadditions shown below.

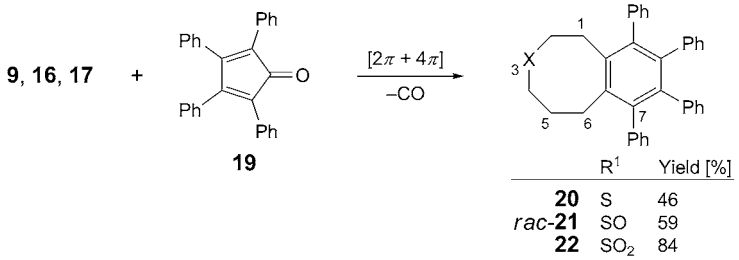
The strain energies of the eight-membered rings of **9**, **16**, and **17** should be comparable to that of cyclooctyne [44]. Hence, a high reactivity of **9**, **16**, and **17** in cycloaddition reactions can be expected. We studied first the reactions with 2,3,4,5-tetraphenylcyclopenta-2,4-dienone (**19**) at room temperature (*Scheme 3*). The *Diels–*

Table. *^{1}H- and ^{13}C-NMR* ($CDCl_3$) *Data of the Heterocyclic Alkynes* **9**, **16**, *and* **17**. δ in ppm relative to Me_4Si as internal standard, *J* in Hz. The atom numbering corresponds to the 2*H*-thiocin nomenclature.



Compound	X	NMR	CH_2(2)	CH_2(3)	CH_2(4)	C(5,6)	CH_2(7)	CH_2(8)
9	S	δ(H)	2.76–2.72	2.19–2.12	2.24–2.19		2.35–2.29	2.97–2.93
		δ(C)	35.5	35.9	19.6	94.1, 92.2	23.6	41.9
rac-**16**	SO	δ(H)	3.59–3.50	2.23–2.30	2.22–2.14		2.74–2.65	3.72–3.65
			2.88–2.80	2.23–2.30	2.12–2.04		2.42–2.32	3.06–3.02
		δ(C)	62.0	25.8	18.5	92.1, 88.7	15.6	60.8
17	SO_2	δ(H)	3.37–3.33	2.36–2.28	2.26–2.20		2.61–2.55	3.55–3.51
		δ(C)	61.9	25.3	18.7	92.1, 88.9	16.0	59.9

Scheme 3



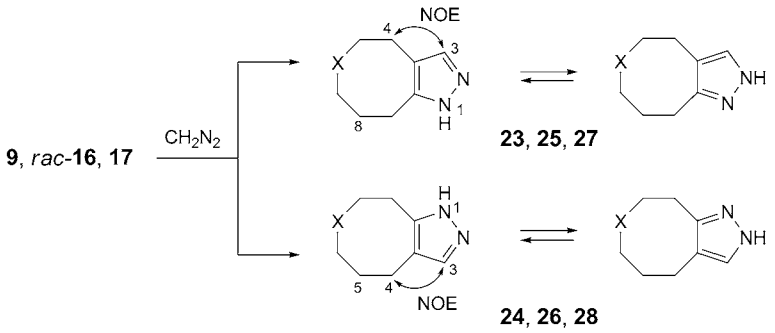
	R^1	Yield [%]
20	S	46
rac-**21**	SO	59
22	SO_2	84

Alder reactions with subsequent aromatization according to the *Alder–Rickert* rule furnished the cycloadducts **20**, **21**, and **22**, respectively, in reasonable-to-good yields.

From a synthetic point of view, the 1,3-dipolar cycloaddition, another [2π + 4π] cycloaddition, of **8**, **16**, and **17** with CH_2N_2 is more attractive. The tautomeric pyrazoles **23**–**28** were obtained (*Scheme 4*). The regioselectivities **23**/**24**, **25**/**26**, and **27**/**28** change from 3:2 for the reaction of **9** to 1:3 for the reaction of the sulfone **17**. NOE Experiments served for the distinction between the isomeric pyrazoles. Irradiation into the signal of H–C(3) led to a positive NOE for CH_2(4), which is a part of the ethylene 'chain' in **23**, **25**, and **27**, whereas it is a part of the trimethylene 'chain' in **24**, **26**, and **28**.

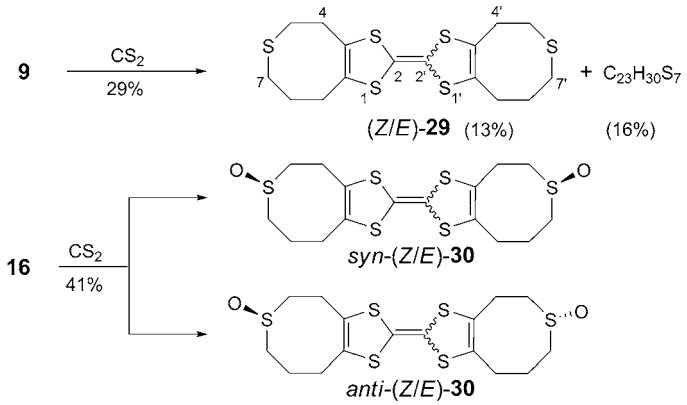
Finally, we studied the behavior of the alkynes toward CS_2 (*Scheme 5*). Alkyne **9** furnished, after 12 d in boiling CS_2, tetrathiafulvalene **29** in low yield. This reaction type is restricted to strained cycloalkynes and to electron-deficient linear alkynes [47][48]. A second reaction product of **9** (obtained in a yield of 16%) had the formula $C_{23}H_{30}S_7$, which corresponds to a 3:2-adduct of **9** and CS_2. Sulfoxide **16** gave 41% of the tetrathiafulvalene **30**. (*Z*/*E*)-Isomers have to be considered for **29** and **30**. It is known that the separation of (*Z*/*E*)-isomeric tetrathiafulvalenes is extremely difficult – even a spectroscopic identification of these isomers is challenging [49]. We found a single set of ^{13}C-NMR signals among which the broad signal at δ(C) 108.2 looked like two superimposed signals for C(2) of **29**. All other ^{13}C-NMR signals of **29** did not show a

Scheme 4



	23	24	rac-25	rac-26	27	28
X	S	S	SO	SO	SO_2	SO_2
Total yield [%]	58		49		38	
Ratio	60 :	40	50 :	50	25 :	75

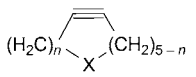
Scheme 5



splitting. Apart from the (*Z*/*E*)-isomerism, **30** exhibits a stereoisomerism owing to the sulfoxide functionalities. Compounds *syn*-(*E*)-**30** and *anti*-(*Z*)-**30** are chiral, and *anti*-(*E*)-**30** and *syn*-(*Z*)-**30** are *meso*-forms. Chiral tetrathiafulvalenes have recently gained a high actuality [50][51]. Most of the ^{13}C-NMR signals of **30** are split into pairs of equal intensity. This corresponds to a *syn*-**30**/*anti*-**30** ratio of 1:1. The resonance region at δ(C) 47.3–47.7 for one of the C-atoms neighboring to the SO group is even split into four signals (*syn*-(*Z*), *anti*-(*Z*), *syn*-(*E*), and *anti*-(*E*); see *Exper. Part*). The other C-atom neighboring to the SO group gives two signals of 52.6 ppm. Sulfone **17** did not show an addition of CS_2 with subsequent tetrathiafulvalene generation.

Conclusions. – In principle, three isomeric thiacyclooctynes (=didehydrotetrahydro-2*H*-thiocins), and their sulfoxides and sulfones should exist. 1-Thiacyclooct-2-yne and -3-yne were synthesized much earlier; here we report the preparation of 1-

thiacyclooct-4-yne (**9**) by applying the selenadiazole method for the formation of the C≡C bond. Oxidation of **9** with $NaIO_4$ generated the sulfoxide **16** and the sulfone **17**.



n \ X	S	SO	SO_2
0	[52]	–	–
1	[52][53]	–	–
2	**9**	*rac*-**16**	**17**

Other sulfoxides or sulfones ($n = 0, 1$) of thiacyclooctynes are not known. All three heterocyclic alkynes, **9**, **16**, and **17**, have high reactivities as 2π components toward 4π components in *Diels–Alder* reactions and 1,3-dipolar cycloadditions. Moreover, the tetrathiafulvalenes **29** and **30** could be obtained from **9** and **16** by the reaction with CS_2. The new cyclic alkynes **9**, **16**, and **17** are stimulating candidates for click reactions and should be also interesting species for applications in bioorthogonal processes.

We are grateful to the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* for financial support.

Experimental Part

*General. 4,7,8,9-Tetrahydro-5*H*-thiocino[5,4-*d*][1,2,3]selenadiazole* (**8**) was prepared as described in [45] from *5-thiocanone* (**6**) *via* semicarbazone **7**. M.p.: *Büchi* melting-point apparatus. IR: *Beckman Acculab 4*; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *AM-400* spectrometer from *Bruker*; $CDCl_3$ as solvent and Me_4Si as internal standard; δ in ppm and J in Hz. EI-MS: *Finnigan-MAT-95* spectrometer, 70-eV ionization energy; in *m*/*z* (rel. %).

Thermal Fragmentation of 1,2,3-Selenadiazole **8**. To 2.0 g (31.5 mmol) of Cu powder, 467 mg (2.0 mmol) of **8** dissolved in 2 ml of CH_2Cl_2 was added. The solvent was removed, and the residue was heated under reduced pressure of 100 Pa to 170 ± 5°. *5-Thiacyclooctyne* (*5,6-didehydro-3,4,7,8-tetrahydro-2*H*-thiocin;* **9**) distilled off as a colorless oil. Yield 235 mg (93%). IR ($CDCl_3$): 2240 (C≡C). NMR: see the *Table*. EI-MS: 126 (62, M^+), 111 (51), 98 (52), 97 (100). According to the NMR spectra, the product was pure, but, due to the volatility, a correct combustion analysis could not be conducted.

Thiocan-5-one 1-Oxide (=*1-Oxo-1*λ^4*-thiocan-5-one*) (**10**). The preparation was performed according to a modified procedure described by *Leonard* and *Johnson* [54]. Thiocanone **8** (1.00 g, 6.93 mmol) was dissolved in 10 ml of MeOH and added at 0° within 20 min to a soln. of 1.58 g (7.39 mmol) of $NaIO_4$ in 10 ml of H_2O. The product was isolated by extraction with $CHCl_3$. The hygroscopic compound melted at 105° (m.p. 91–92° [54]) and was analytically pure. Yield 1.05 g (95%). IR ($CDCl_3$): 1030 (S=O), 1695 (C=O). ^{1}H-NMR ($CDCl_3$): 3.17–3.08 (*ddd*, ^2J = 14.4, ^3J = 8.8, ^3J = 2.6, 1 H each, CH_2(2,8)); 2.73–2.57 (*m*, 1 H each, CH_2(2,4,6,8)); 2.43–2.28 (*m*, 1 H each, CH_2(3,4,6,7)); 2.15–2.04 (*m*, 1 H each, CH_2(3,7)). ^{13}C-NMR ($CDCl_3$): 213.4 (C(5)); 51.1 (C(2,8)), 40.5 (C(4,6)); 18.1 (C(3,7)). EI-MS: 160 (7, M^+), 118 (24), 90 (100). Anal. calc. for $C_7H_{12}O_2S$ (160.2): C 52.47, H 7.55; found: C 52.58, H 7.57.

Thiocan-5-one 1,1-Dioxide (=*1,1-Dioxo-1*λ^6*-thiocan-5-one*) (**11**). The preparation was conducted according to a modified procedure described by *Leonard et al.* [54][55]. Thiocanone **8** (1.00 g, 6.93 mmol) dissolved in 20 ml of acetone was treated with H_2O_2 (30%, 1.40 g, 73.6 mmol) at r.t. The reaction was monitored by TLC (SiO_2, CH_2Cl_2). At the end, the volatile parts were removed and the residue was recrystallized from EtOH. Yield 904 mg (74%). M.p. 106° ([55]: 124–127°). IR (KBr): 1690 (C=O), 1325 (SO_2), 1125 (SO_2). ^{1}H-NMR ($CDCl_3$): 3.15–3.08 (*m*, 4 H, CH_2(2,8)); 2.66–2.60 (*m*, 4 H, CH_2(4,6)); 2.33–2.24 (*m*, 4 H, CH_2(3,7)). ^{13}C-NMR ($CDCl_3$): 212.8 (C(5)); 54.8 (C(2,8)); 39.8 (C(4,6)); 19.9 (C(3,7)). EI-MS: 176 (8, M^+), 70 (56), 55 42), 42 (100). The compound was identical with an authentic sample [54][55].

rac-*2-(1-Oxidothiocan-5-ylidene)hydrazinecarboxamide* (*rac*-**12**). Semicarbazide hydrochloride (950 mg, 8.5 mmol) and AcONa (1.08 g, 13.2 mmol) were briefly refluxed in 20 ml of dry EtOH. The hot filtrate was added to **10** (1.12 g, 7.0 mmol) dissolved in 5 ml of dry EtOH. After 2 h, the mixture was cooled to 0°. A crystalline precipitate was formed which was recrystallized from MeOH. Yield: 1.25 g (82%). Colorless, fine crystals. M.p. 138°. IR (KBr): 1660 (C=O), 1010 (S=O). ^{1}H-NMR ((D$_6$)DMSO): 9.12 (*s*, NH); 6.26 (*s*, NH$_2$); 3.10–3.01 (*m*, 1 H); 2.95–2.83 (*m*, 2 H); 2.63–2.52 (*m*, 2 H); 2.35–2.27 (*m*, 1 H); 2.27–2.08 (*m*, 3 H); 2.06–1.95 (*m*, 2 H); 1.92–1.81 (*m*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 157.1 (CO); 150.2 (C(5)); 51.3, 50.6 (C(2,8)); 35.6 (C(6)); 26.4 (C(4)); 18.9, 16.4 (C(3,7)). EI-MS: 217 (91, M^+), 166 (56), 160 (100). Anal. calc. for C$_8$H$_{15}$N$_3$O$_2$S (217.3): S 44.22, H 6.69, N 19.34; found: C 44.16, H 6.98, N 19.29.

2-(1,1-Dioxidothiocan-5-ylidene)hydrazinecarboxamide (**13**). The preparation was performed as described for **12**. Ketone **11** (2.33 g, 13.2 mmol) yielded 2.46 g (80%) of **13**. Colorless crystals. M.p. 184° (MeOH). IR (KBr): 1680 (C=O), 1110 (SO$_2$). ^{1}H-NMR ((D$_6$)DMSO): 9.10 (*s*, NH); 6.30 (*s*, NH$_2$); 3.22–3.14 (*m*, 2 H); 3.05–2.96 (*m*, 2 H); 2.54–2.45 (*m*, 2 H); 2.38–2.29 (*m*, 2 H); 2.08–1.95 (*m*, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 157.2 (CO); 149.7 (C(5)); 53.6, 53.1 (C(2,8)); 35.5, 25.8 (C(4,6)); 20.8, 17.6 (C(3,7)). EI-MS: 233 (8, M^+), 97 (24), 83 (37), 67 (30), 44 (43), 41 (100). Anal. calc. for C$_8$H$_{15}$N$_3$O$_3$S (233.3): C 41.19, H 6.48, N 18.01; found: C 41.08, H 6.49, N 17.97.

rac-*4,7,8,9-Tetrahydro-5*H-*thiocino[5,4-*d*][1,2,3]selenadiazole 6-Oxide* (*rac*-**14**). To semicarbazone **12** (870 mg, 4.0 mmol) in 55 ml of dioxane, SeO$_2$ (0.89 g, 8.0 mmol) and 0.25 ml of H$_2$O were added. The reaction in the dark was monitored by TLC (SiO$_2$, toluene). After *ca.* 2 d, when the formation of gas (CO$_2$, NH$_3$) was completed, the mixture was filtered and concentrated to *ca.* 3 ml. The remaining red oil was purified by column chromatography CC (SiO$_2$ (2 × 50 cm); toluene/AcOEt 10:1). Yield: 510 mg (51%). Beige crystals. M.p. 107–108° (dec.). IR (KBr): 1300, 1275, 1025 (S=O), 1000, 990, 780. ^{1}H-NMR (CDCl$_3$): 3.78–3.69 (*m*, 1 H of CH$_2$(4)); 3.43–3.35 (*m*, 1 H, CH$_2$(4)); 3.35–3.29 (*m*, 1 H, CH$_2$(9)); 3.29–3.25 (*m*, 1 H, CH$_2$(9)); 3.25–3.20 (*m*, 1 H of CH$_2$(5)); 3.09–3.03 (*m*, 1 H of CH$_2$(7)); 3.03–2.96 (*m*, 1 H, CH$_2$(5)); 2.50–2.41 (*m*, 1 H, CH$_2$(7)); 2.41–2.31 (*m*, 1 H, CH$_2$(8)); 2.31–2.20 (*m*, 1 H, CH$_2$(8)). ^{13}C-NMR (CDCl$_3$): 159.3 (C(9a)); 157.0 (C(3a)); 53.6, 48.1 (C(5,7)); 25.2, 23.6, 17.7 (C(4,8,9)). EI-MS: 205 (100, [M – C$_3$H$_8$]$^+$), 166 (38), 143 (11, [M – N$_2$ – Se]$^+$), 124 (72), 91 (52). Anal. calc. for C$_7$H$_{10}$N$_2$OSSe (249.2): C 33.74, H 4.04, N 11.24; found: C 33.66, H 4.00, N 11.27.

*4,7,8,9-Tetrahydro-5*H-*thiocino[5,4-*d*][1,2,3]selenadiazole 6,6-Dioxide* (**15**). The preparation was performed as described for **14**. Semicarbazone **13** (0.93 g, 4.0 mmol) yielded 920 mg (87%) of **15**. Yellow crystals. M.p. 163°. IR (KBr): 1270 (SO$_2$), 1165, 1110 (SO$_2$), 795, 680. ^{1}H-NMR (CDCl$_3$): 3.60–3.54 (*m*, CH$_2$(4)); 3.47–3.42 (*m*, CH$_2$(9)); 3.33–3.27 (*m*, CH$_2$(5)); 2.89–2.83 (*m*, CH$_2$(7)); 2.19–2.27 (*m*, CH$_2$(8)). ^{13}C-NMR (CDCl$_3$): 159.2, 156.1 (C(3a,9a)); 58.6, 53.3 (C(5,7)); 23.9, 22.9, 21.0 (C(4,8,9)). EI-MS: 186 (1, [M – Se]$^+$), 119 (39), 92 (39), 91 (100). Anal. calc. for C$_7$H$_{10}$N$_2$O$_2$SSe: C 31.70, H 3.80, N 10.56; found: C 31.78, H 3.61, N 10.58.

*Oxidation of 4,5-Didehydro-3,6,7,8-tetrahydro-2*H-*thiocine* (**9**). Alkyne **9** (100 mg, 0.79 mmol) was dissolved in 4 ml of MeOH and cooled to 0°. NaIO$_4$ (712 mg, 3.32 mmol) in 4 ml of H$_2$O was added, and the mixture was stirred overnight at 0°. Further 6 ml of MeOH were added, and the mixture was cooled to –20°. The inorg. salts precipitated and were filtered off. The soln. was dried (MgSO$_4$), concentrated, and subjected to CC (SiO$_2$ (1 × 20 cm); AcOEt/EtOH 2:1). The first fraction consisted of 46 mg (37%) of *4,5-didehydro-3,6,7,8-tetrahydro-2*H-*thiocine 1,1-dioxide* (**17**). Colorless crystals. M.p. 113°. The second fraction consisted of 48 mg (43%) of *4,5-didehydro-3,6,7,8-tetrahydro-2*H-*thiocine 1-oxide* (*rac*-**16**). Colorless crystals. M.p. 56°.

Data of rac-**16**. IR (KBr): 1010 (S=O), 2240 (C≡C). ^{1}H- and ^{13}C-NMR: see the *Table*. EI-MS: 142 (54, M^+), 91 (48), 79 (75), 77 (100). Anal. calc. for C$_{17}$H$_{10}$OS (142.2): C 59,12, H 7.09, S 22.54; found: C 59.23, H 7.11, S 22.50.

Data of **17**. IR (KBr): 1110 (SO$_2$), 1275, 1310 (SO$_2$), 2260 (C≡C). ^{1}H- and ^{13}C-NMR: see the *Table*. EI-MS: 158 (100, M^+), 117 (57), 83 (100). Anal. calc. for C$_7$H$_{10}$O$_2$S (158.2): C 53.14, H 6.37; found: C 53.03, H 6.28.

Alkaline Fragmentation of rac-**14**). To *rac*-**14** (250 mg, 1.0 mmol) in 10 ml of dry THF, 0.6 ml (1.5 mmol) of a 15% soln. of BuLi in hexane was added at –70°. After 10 min, the reaction was quenched by addition of 1.2 ml of MeOH and 1.2 ml of H$_2$O. Extraction with CHCl$_3$ at r.t. gave a yellow

soln., which was dried ($MgSO_4$), concentrated, and purified by CC (SiO_2 (1 × 20 cm); AcOEt/EtOH 2:1). The first fraction consisted of *rac*-**18** (yield 60 mg (21%), yellow oil), and the second fraction of *rac*-**16** (yield 11.5 mg (8%)).

rac-*(5*E*)-6-(Butylselanyl)-3,4,7,8-tetrahydro-2*H*-thiocine 1-Oxide* (*rac*-**18**). IR (neat): 1025 (S=O). ^{1}H-NMR ($CDCl_3$): 5.62 (*t*, ^3J = 9.0, H–C(5)); 3.34–3.25 (*m*, 1 H, CH_2(8)); 3.25–3.15 (*m*, 1 H, CH_2(2)); 3.00–2.89 (*m*, 1 H each, CH_2(7,8)); 2.80–2.73 (*m*, 1 H, CH_2(2)); 2.67 (*t*, ^3J = 7.5, α-CH_2); 2.60–2.52 (*m*, 1 H, CH_2(7)); 2.44–2.33 (*m*, 1 H of CH_2(4)); 2.20–2.08 (*m*, 1 H, CH_2(4)); 2.02–1.91 (*m*, 1 H, CH_2(3)); 1.62 (*quint.*, ^3J = 7.5, β-CH_2); 1.38 (*sext.*, ^3J = 7.8, γ-CH_2); 0.90 (*t*, ^3J = 7.8, Me). ^{13}C-NMR ($CDCl_3$): 130.9 (C(6)); 128.8 (C(5)); 52.9, 51.4 (C(2,8)); 31.9, 27.2, 25.3, 25.1, 23.0, 23.0 (other CH_2); 13.5 (Me). EI-MS: 280 (3, M^+, Se pattern), 143 (100, $[M - C_4H_9]^+$). Anal. calc. for $C_{11}H_{20}OSSe$ (279.3): C 47.30, H 7.22; found: C 47.43, H 7.12.

Reaction of **9**, *rac*-**16**, *and* **17** *with 2,3,4,5-Tetraphenylcyclopenta-2,4-dien-1-one* (**19**). Alkyne **9**, *rac*-**16** or **17** (0.20 mmol), and **19** (154 mg, 0.40 mmol) were stirred overnight at r.t. in 4 ml of toluene. The violet soln. was concentrated and purified by CC (SiO_2 (1 × 60 cm); toluene for **20**, AcOEt/EtOH 1:1 for **21**, and $CHCl_3$ for **22**).

*1,4,5,6-Tetrahydro-7,8,9,10-tetraphenyl-2*H*-3-benzothiocine* (**20**). Yield: 45 mg (46%). Colorless crystals. M.p. 224°. IR (KBr): 700, 740. ^{1}H-NMR ($CDCl_3$): 7.19–7.00 (*m*, 10 arom. H); 6.80–6.66 (*m*, 10 arom. H); 3.10–2.98 (*m*, CH_2(1,6)); 2.68–2.61, 2.60–2.50 (2*m*, CH_2(2,4)); 1.65–1.56 (*m*, CH_2(5)). ^{13}C-NMR ($CDCl_3$): 141.2, 141.2, 141.1, 141.0, 140.7, 140.6, 139.9, 139.6, 137.7, 137.2 (arom. C_q); 131.1, 130.7, 130.4, 127.4, 127.2, 126.3, 126.1, 126.0, 125.0 (arom. CH, partly superimposed); 35.1, 33.9, 32.5, 31.0, 27.5 (aliph. CH_2). EI-MS: 482 (89, M^+), 440 (100). Anal. calc. for $C_{35}H_{30}S$: C 87.09, H 6.26; found: C 87.21, H 6.52.

*1,4,5,6-Tetrahydro-7,8,9,10-tetraphenyl-2*H*-3-benzothiocine 3-Oxide* (**21**). Yield 59 mg (59%). Colorless crystals. M.p. 227°. IR (KBr): 700, 740, 1025 (S=O). ^{1}H-NMR ($CDCl_3$): 7.34–6.97 (*m*, 10 arom. H); 6.82–6.66 (*m*, 10 arom. H); 3.31–3.15, 3.08–2.85, 2.81–2.63 (3*m*, CH_2(1,2,4,6)); 1.97–1.79 (*m*, CH_2(5)). ^{13}C-NMR ($CDCl_3$): 141.5, 141.4, 140.8, 140.4, 140.3, 140.2, 140.1, 140.1, 135.7, 135.4 (arom. C_q); 130.9, 130.3, 130.2, 130.1, 127.7, 127.5, 127.3, 126.5, 126.4, 126.3, 125.2 (arom. CH, partly superimposed); 58.3, 55.3 (C(2,4)); 28.5, 23.5, 22.8 (C(1,5,6)). EI-MS: 498 (97, M^+), 407 (100). Anal. calc. for $C_{35}H_{30}OS$ (498.7): C 84.30, H 6.06; found: C 84.05, H 6.05.

*1,4,5,6-Tetrahydro-7,8,9,10-tetraphenyl-2*H*-3-benzothiocine 3,3-Dioxide* (**22**). Yield: 87 mg (84%). Colorless crystals. M.p. 255°. IR (KBr): 700, 740, 1120 (SO_2), 1280 (SO_2). ^{1}H-NMR ($CDCl_3$): 7.21–7.00 (*m*, 10 arom. H); 6.83–6.68 (*m*, 10 arom. H); 3.15–2.97 (*m*, CH_2(1,2,4,6)); 1.71–1.67 (*m*, CH_2(5)). ^{13}C-NMR ($CDCl_3$): 141.6, 141.5, 141.0, 140.4, 140.2, 140.1, 140.0, 139.9, 135.5, 135.2 (arom. C_q); 130.8, 130.2, 129.9, 127.8, 127.5, 126.7, 126.5, 125.3 (arom. CH, partly superimposed); 58.7, 52.5 (C(2,4)); 27.1, 24.6, 22.6 (C(1,5,6)). EI-MS: 514 (43, M^+), 349 (56), 348 (50), 347 (100). Anal. calc. for $C_{35}H_{30}O_2S$ (514.7): C 81.68, H 5.87; found: C 81.51, H 5.68.

Reaction of **9**, *rac*-**16**, *and* **17** *with* CH_2N_2. To 0.50 mmol of the **9**, *rac*-**16**, or **17**, dissolved in 10 ml of dry Et_2O, a 0.1 M soln. of CH_2N_2 in Et_2O (*ca.* 10 ml, *ca.* 1.0 mmol) was added. The yellow soln. was stirred for 24 h, and then the excess CH_2N_2 was removed by passing compressed air through the flask (the air is then introduced to a trap with aq. HCl). The remaining soln. was concentrated, and the product was purified by CC (SiO_2 (2 × 38 cm); Et_2O/petroleum ether (b.p. 40–70°) 3:1). The separation of the regioisomeric cycloadducts **23**/**24**, *rac*-**25**/*rac*-**26**, and **27**/**28** by CC was not successful. The correlation of the NMR signals was based on NOE experiments and ^{1}H,^{1}H-COSY 45 spectra.

*1,4,5,7,8,9-Hexahydrothiocino[5,4-*c*]pyrazole* (**23**)/*1,4,5,6,8,9-Hexahydrothiocino[4,5-*c*]pyrazole* (**24**). Yield: 49 mg (58%). Colorless crystals. M.p. 96°. Ratio **23**/**24** according to the ^{1}H-NMR signals 60:40. ^{1}H-NMR ($CDCl_3$) of **23**: 7.25 (*s*, H–C(3)); 3.04–2.99 (*m*, CH_2(9)); 2.88–2.85 (*m*, CH_2(4)); 2.67–2.63 (*m*, CH_2(5)); 2.47–2.43 (*m*, CH_2(7)); 1.89–1.81 (*m*, CH_2(8)). ^{1}H-NMR ($CDCl_3$) of **24**: 7.28 (*s*, H–C(3)); 3.07–3.03 (*m*, CH_2(9)); 2.76–2.81 (*m*, CH_2(4)); 2.71–2.67 (*m*, CH_2(8)); 2.43–2.39 (*m*, CH_2(6)); 1.78–1.70 (*m*, CH_2(5)). ^{13}C-NMR ($CDCl_3$) of **23**: 144.8 (C(9a)); 133.4 (C(3a)); 118.1 (C(3)); 37.3, 31.4, 31.2, 28.0, 21.3 (C(4,5,7,8,9)). ^{13}C-NMR ($CDCl_3$) of **24**: 146.4 (C(9a)); 132.4 (C(3a)); 116.9 (C(3)); 35.4, 32.4, 31.5, 30.1, 19.2 (C(4,5,6,8,9)). EI-MS: 168 (100, M^+), 121 (39), 107 (50), 94 (84). Anal. calc. for $C_8H_{12}N_2S$ (168.3): C 57.11, H 7.19, N 16.65; found: C 57.00, H 7.18, N 16.68.

rac-*1,4,5,7,8,9-Hexahydrothiocino[5,4-*c*]pyrazole 6-Oxide* (**25**)/rac-*1,4,5,6,8,9-Hexahydrothiocino[4,5-*c*]pyrazole 7-Oxide* (**26**). Yield: 45 mg (49%). Viscous oil. Ratio **25**/**26** according to the ^{1}H-NMR signals 50:50. IR (neat): 1010 (S=O). ^{1}H-NMR ($CDCl_3$): 7.35 (*s*, H–C(3)) and 7.25 (*s*, H–C(3)); 3.32–2.95 (*m*, 9 H), 2.92–2.78 (*m*, 2 H), 2.73–2.62 (*m*, 4 H), 2.52–2.42 (*m*, 1 H), 2.21–2.05 (*m*, 3 H), 2.04–1.93 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 145.3, 144.6 (C(9a)); 132.5, 130.9 (C(3a)); 115.6, 115.5 (C(3)); 55.8, 54.0, 51.5, 51.2 (C(5,7) of **25** and C(6,8) of **26**); 25.0, 23.6, 23.2, 21.1, 18.2, 16.0 (C(4,8,9) of **25** and C(4,5,9) of **26**). EI-MS: 184 (22, M^+), 108 (12), 85 (66), 84 (21), 83 (100). Anal. calc. for $C_8H_{12}N_2OS$ (184.3): C 52.15, H 6.56, N 15.20; found: C 52.40, H 6.85, N 15.17.

*1,4,5,7,8,9-Hexahydrothiocino[5,4-*c*]pyrazole 6,6-Dioxide* (**27**)/*1,4,5,6,8,9-hexahydrothiocino[4,5-*c*]pyrazole 7,7-Dioxide* (**28**). Yield 38 mg (38%). Viscous oil. Ratio **27**/**28** according to the ^{1}H-NMR signals 25:75. IR ($CHCl_3$): 1105 (SO_2), 1270 (SO_2). ^{1}H-NMR ($CDCl_3$, **27**): 7.40 (*s*, H–C(3)); 3.21–3.14, 3.02–2.90, 2.03–2.01 (3*m*, CH_2(4,5,7,8,9)). ^{1}H-NMR ($CDCl_3$, **28**): 7.32 (*s*, H–C(3)), 3.28–3.23, 3.21–3.14, 2.96–2.88, 2.83–2.77, 2.01–1.93 (5*m*, CH_2(4,5,6,8,9)). ^{13}C-NMR ($CDCl_3$, **27**): 145.2 (C(9a)); 130.2 (C(3a)); 116.1 (C(3)); 59.7, 52.9 (C(5,7)); 23.1, 21.4, 18.2 (C(4,8,9)). ^{13}C-NMR ($CDCl_3$, **28**): 147.0 (C(9a)); 129.8 (C(3a)); 115.9 (C(3)); 58.2, 52.5 (C(6,8)); 24.5, 20.8, 19.1 (C(4,5,9)). EI-MS: 200 (1, M^+), 84 (93), 66 (100). Anal. calc. for $C_8H_{12}N_2O_2S$ (200.3): C 47.98, H 6.04, N 13.99; found: C 47.88, H 6.30, N 14.02.

Reaction of the **9** *or rac-*__16__ *with* CS_2. Alkyne (1.0 mmol) and CS_2 (4 ml, 5.08 g, 66.7 mmol) were refluxed under N_2 for 12–15 d. The colorless soln. turned orange and then redbrown. The soln. was concentrated, and the products were purified by CC (SiO_2 (3 × 40 cm); toluene/petroleum ether (b.p. 40–70°) 2:1 for **29** and AcOEt/EtOH 1:1 for product **30**).

(*2Z/*E*)-4,7,8,9-Tetrahydro-2-(4,7,8,9-tetrahydro-5*H*-1,3-dithiolo[4,5-*d*]thiocin-2-ylidene)-5*H*-1,3-dithiolo[4,5-*d*]thiocine*; **29**). Yield: 53 mg (13%). Red-orange crystals. M.p. 195°. IR ($CDCl_3$): 1270, 1445. ^{1}H-NMR ($CDCl_3$): 2.75–2.63 (*m*, CH_2(4,5,7,9,4′,5′,7′,9′)); 1.91–1.81 (*m*, CH_2(8,8′)). ^{13}C-NMR ($CDCl_3$): 128.8, 128.7 (C(3a,9a,3a',9a')); 108.2 (C(2,2′)); 34.7, 32.0, 31.4, 31.1, 25.1 (C(4,5,7,8,9,4′,5′,7′,8′,9′)). EI-MS: 404 (100, M^+), 202 (4, M^{2+}). Anal. calc. for $C_{16}H_{20}S_6$ (404.7): C 47.49, H 4.98; found: C 47.39, H 4.89. As second fraction, a dark-red solid $C_{23}H_{30}S_7$ (85 mg, 16%) was obtained. The structure was not determined.

syn-*(2Z/*E*)- and* anti-*(2Z/*E*)-4,7,8,9-Tetrahydro-2-(4,7,8,9-tetrahydro-6-oxido-5*H*-1,3-dithiolo[4,5-*d*]thiocin-2-ylidene)-5*H*-1,3-dithiolo[4,5-*d*]thiocine 6-Oxide*; **30**). Yield: 179 mg (41%). Red-orange solid. M.p. 204°. IR (KBr): 1010, 1445, 1625. ^{1}H-NMR ($CDCl_3$): 3.30–3.19 (*m*, 2 H); 3.19–3.07 (*m*, 4 H); 3.00–2.89 (*m*, 2 H); 2.88–2.73 (*m*, 4 H); 2.55–2.45 (*m*, 2 H); 2.42–2.30 (*m*, 2 H); 2.26–2.20 (*m*, 2 H); 2.20–2.13 (*m*, 2 H) (CH_2 groups). ^{13}C-NMR ($CDCl_3$): 129.0, 129.0, 127.3, 127.2 (C(3a,9a,3a',9a')); 108.3, 108.2 (C(2,2′)); 52.6, 52.6, 47.7, 47.6, 47.4, 47.3 (C(5,7,5′,7′)); 26.5, 26.4, 23.0, 22.8, 18.9, 18.8 (C(4,8,9,4′,8′,9′)). EI-MS: 436 (30, M^+), 142 (100), 97 (56), 85 (49), 72 (58), 71 (84). Anal. calc. for $C_{16}H_{20}O_2S_6$ (436.7): C 44.01, H 4.62, S 44.05; found: C 43.89, H 4.61, S 43.87.

REFERENCES

[1] J. Tummatorn, P. Batsomboon, R. J. Clark, I. V. Alabugin, G. B. Dudly, *J. Org. Chem.* **2012**, *77*, 2093.
[2] W. Chen, D. Wang, C. Dai, D. Hamelberg, B. Wang, *Chem. Commun.* **2012**, *48*, 1736.
[3] K. Banert, O. Plefka, *Angew. Chem.* **2011**, *123*, 6295; *Angew. Chem., Int. Ed.* **2011**, *50*, 6171.
[4] V. A. D'yakonov, R. A. Tuktarova, L. M. Khalilov, U. M. Dzhemilev, *Tetrahedron Lett.* **2011**, *52*, 4602.
[5] M. F. Debets, S. S. van Berkel, J. Dommerholt, A. J. Dirks, F. P. J. T. Rutjes, F. L. van Delft, *Accounts Chem. Res.* **2011**, *44*, 805.
[6] J. Moran, C. S. McKay, J. P. Pezacki, *Can. J. Chem.* **2011**, *89*, 148.
[7] B. C. Sanders, F. Friscourt, P. A. Ledin, N. E. Mbua, S. Arumugam, J. Guo, T. J. Boltje, V. V. Popik, G.-J. Boons, *J. Am. Chem. Soc.* **2011**, *133*, 949.
[8] F. Starke, M. Walther, H.-J. Pietzsch, *Arkivoc* **2010**, Part XI, 350.
[9] E. M. Sletten, H. Nakamura, J. C. Jewett, C. R. Bertozzi, *J. Am. Chem. Soc.* **2010**, *132*, 11799.
[10] J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272.

[11] M. F. Debets, S. S. van Berkel, S. Schoffelen, F. P. J. T. Rutjes, J. C. M. van Hest, F. L. van Delft, *Chem. Commun.* **2010**, *46*, 97.
[12] S. C. Kornmayer, F. Rominger, R. Gleiter, *Synthesis* **2009**, 2547.
[13] F. Schoenebeck, D. H. Ess, G. O. Jones, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 8121.
[14] J. A. Codelli, J. M. Baskin, N. J. Agard, C. R. Bertozzi, *J. Am. Chem. Soc.* **2008**, *130*, 11486.
[15] R. van Geel, G. J. M. Pruijin, F. L. van Delft, W. C. Boelens, *Bioconjugate Chem.* **2012**, *23*, 392.
[16] J.-L. Chaubard, C. Krishnamurthy, W. Yi, D. F. Smith, L. C. Hsieh-Wilson, *J. Am. Chem. Soc.* **2012**, *134*, 4489.
[17] S. Brauch, M. Henze, B. Osswald, K. Naumann, L. A. Wessjohann, S. S. van Berkel, B. Westermann, *Org. Biomol. Chem.* **2012**, *10*, 958.
[18] H. E. Bostic, M. D. Smith, A. A. Poloukhtine, V. V. Popik, M. D. Best, *Chem. Commun.* **2012**, *48*, 1431.
[19] J. Z. Yao, C. Uttamapinant, A. Poloukhtine, J. M. Baskin, J. A. Codelli, E. M. Sletten, C. R. Bertozzi, V. V. Popik, A. Y. Ting, *J. Am. Chem. Soc.* **2012**, *134*, 3720.
[20] M. Simon, U. Zangemeister-Wittke, A. Plückthun, *Bioconjugate Chem.* **2012**, *23*, 279.
[21] S. Arumugam, J. Chin, R. Schirrmacher, V. V. Popik, A. P. Kostikov, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6987.
[22] M. Liong, M. Fernandez-Suarez, D. Issadore, C. Min, C. Tassa, T. Reiner, S. M. Fortune, M. Toner, H. Lee, R. Weissleder, *Bioconjugate Chem.* **2011**, *22*, 2390.
[23] J. C. Jewett, C. R. Bertozzi, *Org. Lett.* **2011**, *13*, 5937.
[24] E. M. Sletten, C. R. Bertozzi, *J. Am. Chem. Soc.* **2011**, *133*, 17570.
[25] R. D. Carpenter, S. H. Hausner, J. L. Sutcliffe, *ACS Med. Chem. Lett.* **2011**, *2*, 885.
[26] V. Bouvet, M. Wuest, F. Wuest, *Org. Biomol. Chem.* **2011**, *9*, 7393.
[27] L. S. Campbell-Verduyn, L. Mirfeizi, A. K. Schoonen, R. A. Dierckx, P. H. Elsinga, B. L. Feringa, *Angew. Chem.* **2011**, *123*, 11313; *Angew. Chem., Int. Ed.* **2011**, *50*, 11117.
[28] Z. Cheng, D. R. Elias, N. P. Kamat, E. D. Johnston, A. Poloukhtine, V. Popik, D. A. Hammer, A. Tsourkas, *Bioconjugate Chem.* **2011**, *22*, 2021.
[29] J. C. M. van Hest, L. A. Canalle, R. P. Brinhkuis, S. A. Meeuwissen, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2011**, *52*, 415.
[30] J. Xu, T. M. Filion, F. Prifti, J. Song, *Chem. Asian J.* **2011**, *6*, 2730.
[31] D. Lisse, V. Wilkens, C. You, K. Busch, J. Piehler, *Angew. Chem.* **2011**, *123*, 9524; *Angew. Chem., Int. Ed.* **2011**, *50*, 9352.
[32] C. Besanceney-Webler, H. Jiang, T. Zheng, L. Feng, D. Soriano del Amo, W. Wang, L. M. Klivansky, F. L. Marlow, Y. Liu, P. Wu, *Angew. Chem.* **2011**, *123*, 8201; *Angew. Chem., Int. Ed.* **2011**, *50*, 8051.
[33] T. Zheng, H. Jiang, M. Gros, D. Soriano del Amo, S. Sundaram, G. Lauvau, F. Marlow, Y. Liu, P. Stanley, P. Wu, *Angew. Chem.* **2011**, *123*, 4199; *Angew. Chem., Int. Ed.* **2011**, *50*, 4113.
[34] Z. Hao, Y. Song, S. Lin, M. Yang, Y. Liang, J. Wang, P. R. Chen, *Chem. Commun.* **2011**, *47*, 4502.
[35] J. Xu, F. Prifti, J. Song, *Macromolecules* **2011**, *44*, 2660.
[36] L. A. Canalle, M. van der Knaap, M. Overhand, J. C. M. van Hest, *Macromol. Rapid Commun.* **2011**, *32*, 203.
[37] A. Kuzmin, A. Poloukhtine, M. A. Wolfert, V. V. Popik, *Bioconjugate Chem.* **2010**, *21*, 2076.
[38] X. Ning, R. P. Temming, J. Dommerholt, J. Guo, D. B. Ania, M. F. Debets, M. A. Wolfert, G.-J. Boons, F. L. van Delft, *Angew. Chem.* **2010**, *122*, 3129; *Angew. Chem., Int. Ed.* **2010**, *49*, 3065.
[39] J. C. Jewett, E. M. Sletten, C. R. Bertozzi, *J. Am. Chem. Soc.* **2010**, *132*, 3688.
[40] K. Chenoweth, D. Chenoweth, W. A. Goddard III, *Org. Biomol. Chem.* **2009**, *7*, 5255.
[41] E. M. Sletten, C. R. Bertozzi, *Org. Lett.* **2008**, *10*, 3097.
[42] J.-T. Shin, S. Shin, C.-G. Cho, *Tetrahedron Lett.* **2004**, *45*, 5857.
[43] J. K. Crandoll, T. A. Ayers, *J. Org. Chem.* **1992**, *57*, 2993.
[44] H. Meier, *Advances in Strain in Organic Chemistry* **1991**, *1*, 215.
[45] H. Schuhmacher, H. Meier, *Z. Naturforsch., B* **1992**, *47*, 563.
[46] H. Meier in M. Hesse, H. Meier, B. Zeeh, (S. Bienz, L. Bigler, T. Fox) 'Spektroskopische Methoden in der organischen Chemie', 8th edn, Thieme Verlag, Stuttgart, 2012, pp. 161 – 163.

[47] R. Csuk, B. I. Glänzer, in 'Comprehensive Heterocyclic Chemistry II', Ed. A. R. Katritzky, C. W. Rees, E. F. V. Scriven, I. Shinkai, Elsevier, Oxford, 1996, Vol. 3, p. 651.
[48] A. Gorgues, P. Hudhomme, M. Sallé, *Chem. Rev.* **2004**, *104*, 5151.
[49] E. Fanghänel, L. Van Hinh, G. Schukat, A. Herrmann, *J. Prakt. Chem.* **1996**, *338*, 523.
[50] N. Avarvari, *Actualité Chimique* **2009**, *333*, 18.
[51] J. L. Segura, N. Martin, *Angew. Chem.* **2001**, *113*,1416; *Angew. Chem., Int. Ed.* **2001**, *40*, 1372.
[52] H. Meier, E. Stavridou, C. Storek, *Angew. Chem.* **1986**, *98*, 838; *Angew. Chem., Int. Ed.* **1986**, *25*, 809.
[53] E. Stavridou, H. Schuhmacher, H. Meier, *Liebigs Ann. Chem.* **1989**, 435.
[54] N. J. Leonard, C. R. Johnson, *J. Am. Chem. Soc.* **1962**, *84*, 3701.
[55] N. J. Leonard, T. W. Milligan, T. L. Brown, *J. Am. Chem. Soc.* **1960**, *82*, 4075.

Received May 16, 2012