Reactivity Trends in the Reaction of Alkynes with 3-Oxo-camphorsulfonylimine

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Camphor Alkyne, Nucleophilic Addition, Ring Opening

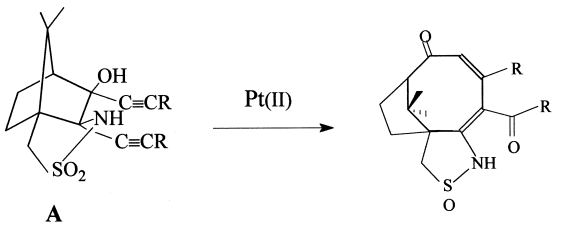
The regioselective addition of deprotonated alkynes (phenyl-1-propyne, propargyl ether or tetrahydropyran-protected 3-butyn-1-ol) to the imine group was identified as a competitive process to the nucleophilic addition to the keto group of (1*S*)-3-oxo-camphorsulfonylimine. The selectivity of the process depends on the characteristics of the nucleophile and the reaction conditions. In the case of propargyl ether it was possible to render the imine addition the main process.

The structural characterization of compounds **1**, **2**, **6** by X-ray diffraction analysis show that the C2–C3 bond becomes longer upon nucleophilic addition to the imine group of (1*S*)-3-oxo-camphorsulfonylimine. This trend is believed to favour the ring opening process that undergoes the formation of the spiro type compound **7**.

Introduction

Combined ring opening/ring closure leading to ring enlargement to more than six members has high relevance for organic synthesis, in particular that of analogues to natural products with pharmaceutical relevance [1]. We have already found that camphor-derived di-alkynes are suitable precursors for the synthesis of compounds with an eight-membered ring of the taxol type. During the reaction a six-membered ring is cleaved and an eight-membered one is formed (Scheme 1), in a cascade process catalysed by Pt(II) [2, 3].

Within our interest in the syntheses of camphor-alkyne derived species able to act as precursors for ring expansion we tried to extend to alkynes such as 3-phenyl-1-propyne, 3-butyne-1-ol or propargyl ether the syntheses of di-alkyne derivatives. The results of this study are now reported.



A

Scheme 1. Six to eight members conversion promoted by platinum in camphor di-alkyne derived species.

Results and Discussion

In the experimental conditions used for the synthesis of the phenyl di-alkyne camphor derivative (1a*S*,3a*S*,7*R*)-7-hydroxy-8,8-dimethyl-1a,7-bis-(phenylethynyl)-1,1a,4,5,6,7,-hexahydro-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (**A**, R = Ph) [4], the reaction of (1*S*)-3-oxo-camphorsulfonylimine (**B**) with 3-phenyl-1-propyne afforded the corresponding di-alkyne product **1**, the mono-alkyne species **2** and a novel type product **3**, Scheme 2 (a).

The diversity of products obtained is indicative of the high reactivity but low selectivity of 3-phenyl-1-propyne compared to phenylacetylene. For the reaction of **B** with 1-hexyne it was reported that the mono addition product (analogous to **2**) was also formed [2].

To our knowledge the propargyl to allenyl conversion (**3** in Scheme 2a) has not been identified in the reaction of **B** with other alkynes. The selectivity of the process is driven by the reaction conditions, *i.e.* longer overall reaction times favour the formation of the di-alkyne species **1**, whether, as expected, shorter reaction times lead to the formation of species **2**. The alkyne to allenyl rearrangement seems to be favoured by an excess of the deprotonated alkyne, conceivably due to its basicity that promotes the abstraction of a proton from the acidic methylene group.

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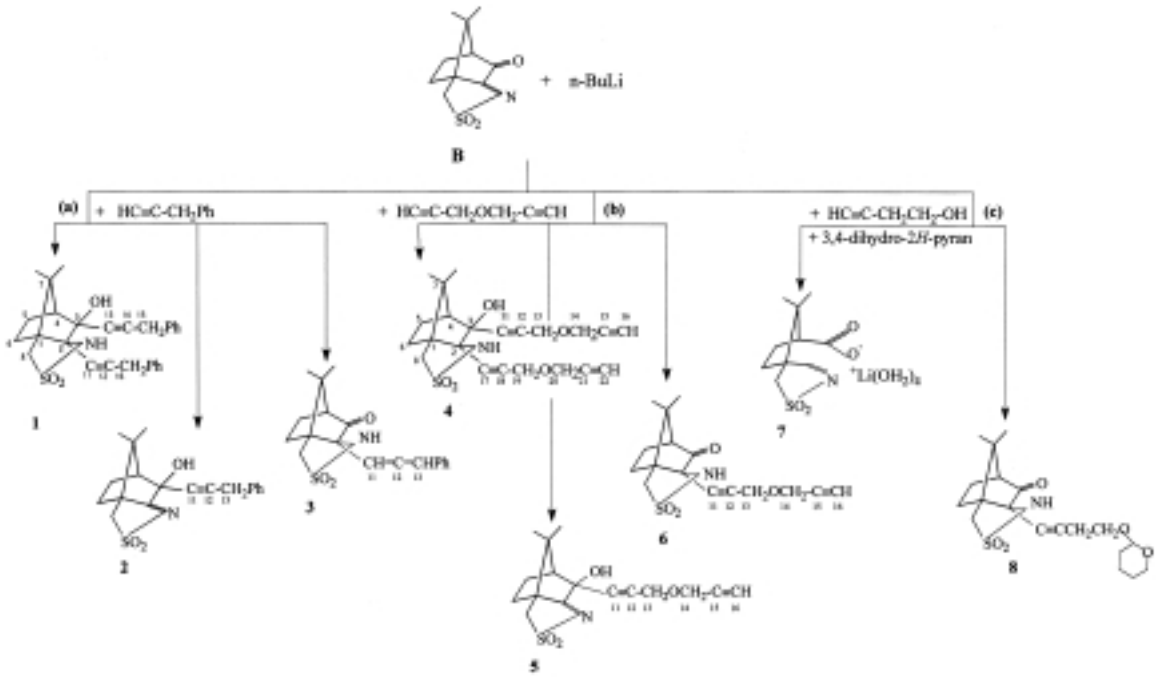

Scheme 2.

In addition to the unusual alkyne to allenyl conversion in systems involving camphor alkyne species, the formation of compound **3** was further unexpected in view of the fact that, in related systems, the nucleophilic attack by the deprotonated alkyne was always observed [2] to occur at the keto rather than at the imino group. However, the regioselective nucleophilic addition to the imine group was conceptually possible, due to its activation by the sulfonyl group. The characteristics of the nucleophiles conceivably play an important role in the reactivity trend.

The characterization of **3** relies mostly on NMR, since no suitable crystals for X-ray analysis could be obtained, in contrast with **1** and **2** whose molecular structures (Figs 1 and 2) have been obtained by X-ray diffraction, although the quality of crystals in the case of compound **2** was just good enough for comparative purposes.

The details on the crystallographic analysis are displayed on Table 1 and selected bond lengths and angles are given in Table 2.

The short carbon-nitrogen bond length (1.310 Å) in compound **2** sustains its double bond character.

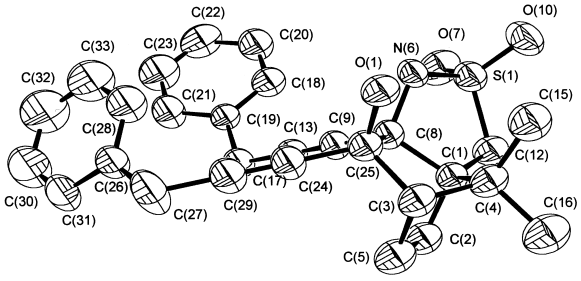

Fig. 1. Molecular structure of compound **1** in the solid state.

The homonuclear five-membered ring of the camphor skeleton displays a considerably strain compared to compound **1**, as evidenced by the smaller angles in the camphor skeleton (Table 2). Moreover, a long C2–C3 bond length in compound **1** suggests some activation towards bond breaking.

In the ^{1}H NMR spectrum of **3** (Table 3) the evidence for the protons of the allenyl group is based on the detection of a pair of doublets (δ = 6.47, 5.92, J_{HH} = 6.2 Hz). In solution, another set of doublets with lower intensity (*ca.* 20%) suggests

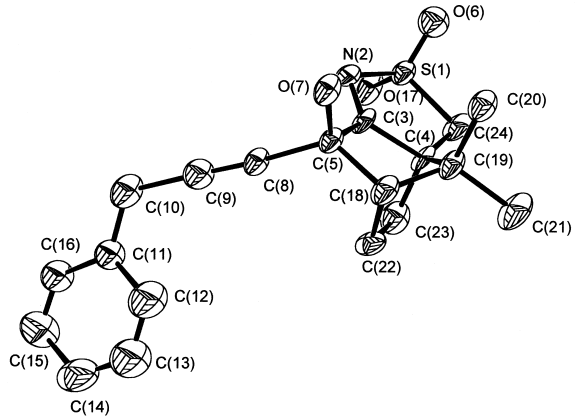

Fig. 2. Molecular structure of compound **2** in the solid state.

the presence of an isomeric species. The chemical shifts of the less abundant compound appear between those of the main species. They do not interconvert by raising the temperature up to 50 °C as verified by ^{1}H NMR and could not be separated by recrystallization.

Some preliminary semi-empirical calculations [5] show that there is a small energy difference between the *M* (ΔH_f = −21.33 kcal mol^{-1}) and *P* (ΔH_f = −25.76 kcal mol^{-1}) diasteromers (*M* and *P* refer to the chirality of the allene moiety, see Fig. 3). Since no conversion between these diastereomers is detected, a kinetic barrier between them must exist.

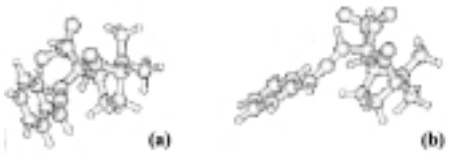

Fig. 3. Optimized structures of the diasteromers *M* (a) and *P* (b) of compound **3**.

In the ^{13}C NMR spectrum of **3** the allenyl pattern is identified by the low field signal (δ = 204.9) attributed to the C=*C*=C in addition to the signals at 94.0 and 99.5 (Table 4).

The reaction of the oxoimine **B** with deprotonated propargyl ether in a 1:2 molar ratio follows a similar trend to that observed in the reaction with phenylacetylene, since both the nucleophilic additions to the keto and the imine groups occur thus affording the di-alkyne species **4** (Scheme 2b). However, when a 1:1 ratio is used, the main product is that resulting from the addition to the imine carbon atom, compound **6**. In the latter case compound **5** is also formed as a minor product.

The compounds can be easily identified by IR spectroscopy since the di-substituted compound **4** displays intense bands in the regions of the OH, NH and C≡C stretching vibrations. In the IR spectrum of compound **5** a band at 1654 cm^{-1} is attributed to ν(C=N) while in the IR spectrum of **6** the band at 1761 cm^{-1} is assigned to ν(C=O) (Table 5).

Table 1. Crystallographic data for camphor derived compounds.

	1	**2**	**6**	**7**
Formula	$C_{28}H_{29}O_3NS$	$C_{19}H_{21}NO_3S$	$C_{16}H_{19}O_4NS$	$C_{10}H_{22}O_8NSLi$
M	459.6	343.5	321.5	323.3
Crystal system	orthorhombic	monoclinic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	9.2163(5)	7.028(8)	7.1460(7)	6.311(2)
b [Å]	12.597(1)	10.196(3)	12.519(2)	8.163(2)
c [Å]	20.717(1)	12.190(1)	17.991(3)	30.163(2)
β [°]	–	91.66(7)	–	–
U [Å^3]	2405	873	1610	1554
Z	4	2	4	4
D_c [g·cm^{-3}]	1.27	1.30	1.35	1.27
μ [mm^{-1}]	0.12 (Mo)	1.67 (Cu)	1.83 (Cu)	1.80 (Cu)
F(000)	976	362	704	624
No. refl. measured	2437	1748	1673	2946
No. uni. refl. (R_{int})	1356	1025 (0.38)	941	2850 (0.07)
*R*1 ($I > 2\sigma(I)$)	0.06	0.15	0.12	0.05
w*R*2	0.11	0.34	0.29	0.14

Table 2. Selected bond lengths and angles (numbering as in Scheme 2).

	Compound			
	1	**2**	**6**	**7**
Bond lengths (Å)				
S–N	1.655(6)	1.693(13)	1.646(12)	1.672(3)
S–C	1.785(7)	1.781(18)	1.783(12)	1.7787(24)
N–C	1.487(8)	1.310(21)	1.423(18)	1.277(3)
C2–C3	1.615(9)	1.520(23)	1.589(21)	
C–O	1.421(9)	1.448(18)	1.163(21)	1.252(3)
C–C≡	1.466(8)	1.528(21)	1.484(19)	
	1.479(10)			
C≡C	1.188(8)	1.17(24)	1.191(20)	
	1.155(11)			
Bond angles (°)				
C–C≡C	178.3(9)	175.5(11)	171.9(8)	
	176.6(6)		177.3(13)	
S–C8–C1	106.2(3)	105.3(9)	107.7(7)	104.79(11)
C1–C7–C4	91.9(3)	95.3(10)	94.5(8)	99.3(7)
C2–C1–C7	103.6(4)	94.2(8)	99.4(8)	102.89(15)

By ^{1}H NMR the imine addition product **6** displays a characteristic collapse of the signals of the CH_2 group attached to the sulfonylimine group (generally observed as a doublet or a pair of doublets). The tendency of the signals to collapse was already observed in compound **3** in which the signals become separate just by 1.8 Hz (Table 3).

In contrast with compound **3**, the signals of the methyl groups in compounds **2** and **5** coincide in agreement with a trend also found in the related compound derived from 1-hexyne which was previously obtained [2]. From the data in Table 3 it seems that the chemical shift and coupling of the methylenic groups attached to the sulfonylimine are affected by addition to the imine group while those of the methyl groups in the five membered ring of the camphor skeleton are influenced by addition to the keto group. This tendency needs, however, to be corroborated by future studies.

The X-ray diffraction analysis showed that **6** shows crystallised in space group $P2_12_12_1$. The molecular structure (Fig. 4) of **6** displays a long C2–C3 bond (1.589 Å) in addition to a relatively short C–N (1.423 Å) bond length (Table 2). The elongation of the C2–C3 bond distance is also verified in compound **1**, suggesting that in both cases there is some activation towards bond rupture.

The reactivity of the deprotonated form of the tetrahydropyranyl-protected 3-butyn-1-ol, $HC{\equiv}C(CH_2)_2OC_5H_9O$, with **B** resembles that of the above-mentioned alkynes in what concerns the promotion of nucleophilic addition to the sulfonylimine group. In the reaction compound **8** was isolated, although in a very low yield (Scheme 1c).

Table 3. ^{1}H NMR data[a] of the camphor derived species **1–8** (numbering as in Scheme 2).

Compound	4-H (d)	5,6-H (m, 2*H* each)	8-H (d)	9,10-H (2s, 3*H* each)	Other C*H* or CH_2	Ph	Other N*H* or O*H*
1	2.09 (5.1)	1.7–2.3	3.29 (2.4)	0.99, 1.44	3.57, 3.50 (s, 2H each, 15-H, 16-H	7.3–7.2 (m, 10H)	5.07 (s, 1H) 2.89 (s, 1H)
2	2.27 (3.3)	1.7–2.4	3.23, 3.12 (13.5)	1.09, 1.08	3.68 (s, 2H 13-H)	7.3–7.2 (m, 5H)	3.15
3	2.32 (5.7)	1.3–2.4	3.40[c]	1.08, 1.29	6.47, 5.92 (2d, 2H, 6.2)[b]	7.3–7.2 (m, 5H)	4.88 (s, 1H)
4	2.06 (3.4)	1.6–2.0	3.26[c]	0.95, 1.41	4.26, 4.23 (d, 2.4, 2H each, 14-H, 20-H) 2.46, 2.44 (t, 2.4, 1H, 16-H, 22-H)	5.4 (s, 1H) 3.9 (s, 1H)	
5	2.29 (3.6)	1.7–2.2	3.23, 3.12 (13.5)	1.09[d]	4.33 (s, 2H 13-H) 4.22 (d, 2.1, 2H, 14-H) 2.45 (t, 2.1, 1H, 16-H)		
6	2.42 (4.5)	1.7–2.4	3.37[c]	1.04, 1.21	4.29 (s, 2H, 13-H) 4.20 (d, 2.1, 2H, 14-H) 2.45 (t, 2.1, 1H)	5.54 (s, 1H)	
7[e]	2.82[f] (9.3)	2.0–2.7	3.52, 3.24 (13.8)	1.28, 1.30	5.68 (s, 1H)[g]	9.00 (s, 1H)	
8[h]	2.30 (5.0)	1.6–2.5[i]	5.03, 4.87 (11.2)	1.30, 1.00	3.2–4.2 (OCH_2)		

[a] In $CDCl_3$, unless stated otherwise. δ values in ppm *versus* TMS. Multiplicity, integration and coupling constants (Hz) in parentheses; [b] 11-H, 13-H. Another set of doublets at δ = 6.35, 5.98 (J = 6.6 Hz) (*ca.* 20%) is observed; [c] coincide as a singlet. In the case of **3** two singlet signals separated by 1.8 Hz can be detected; [d] integrates to six protons; [e] in MeOD; [f] triplet; [g] 2-H; [h] in CD_2Cl_2; [i] overlapped with CH_2 in tetrahydropyran.

Table 4. ^{13}C NMR data[a] of the camphor derived species **1–8** (numbering as in Scheme 2).

	Camphor skeleton									Others		
Compound	C-1	C-2	C-3	C-4	C-5,6	C-7	C-8	C-9,10	*C*≡*C* or *C*=*C*=*C*	*C*H$_2$	Ph(ipso)	Ph(CH)
1	62.3	72.5	81.9	56.4	28.3 23.9	48.8	51.2	24.0 23.5	88.4, 86.5, 82.7, 80.6	25.0 25.2	136.3 136.0	128.5, 128.4, 127.9, 127.8, 126.7, 126.5
2	64.1	194.1	73.8	55.9	27.9 23.9	47.5	50.2	21.1 21.0	88.2, 79.3	25.2	135.4	128.7, 127.8, 126.9
3	56.5	70.1	207.7	58.7	28.1 20.9	45.7	49.8	22.6 19.7	99.5, 94.0 204.9[b]		132.6	128.7, 127.8, 127.1
4	61.5	71.9	81.3	55.9	28.0 23.6	49.0	50.9	23.3 23.7	87.2, 85.4, 85.1, 83.1 79.0, 78.8 75.4[d], 75.2[d]	56.7[c] 56.5[c]		
5	64.1	193.5	73.0	55.7	27.8 23.8	47.5	50.1	21.1 20.9	84.7, 83.6 78.5, 75.6	57.0 56.7		
6	64.7	56.8	205.0	58.2	28.8 21.5	45.1	49.5	22.4 19.6	85.3, 82.0, 78.6, 75.4[d]	56.5[c]		
7[e]	68.6	180.4	181.1	59.3	36.3 26.9	[f]	51.5	27.2 21.1				
8[g]	69.4	69.6	205.6	58.3	29.4 20.1	45.4	51.6	22.0 21.3	91.0, 81.4	68.3[h], 63.7[h], 25.8, 25.3, 24.5, 23.7		

[a] In $CDCl_3$ unless stated otherwise (δ values). The signals were attributed on the basis DEPT and HETCOR in the cases of compounds **1**, **3**, **5**, **6**; [b] corresponds to C-12; [c] assigned to two carbon atoms; [d] attributed to C≡*C*H; [e] in MeOD; [f] covered by solvent signal; [g] in CD_2Cl_2; [h] attributed to oxygen bonded carbon atoms.

The main product was compound **7**, formed upon C2–C3 bond breaking of the six-membered ring of the oxoimine. In the literature there are some examples of ring opening of camphor derivatives [6–8] but there is only scarce evidence for related processes in camphorsulfonic acid derivatives. Ring rupture of an oxidized derivative of **A** with formation of a spiro type compound was reported before [9].

The characterization of **7** by X-ray diffraction analysis (Fig. 5) indicates hydrogen bridging between the carboxylate group and the lithium tetrahydrate moiety (O–O, 2,86 Å), which is possibly responsible for the stability of the compound. In the ^1H NMR spectrum the signal at δ = 9.0 is attributed to the bridging hydrogen.

The results herein show that nucleophilic addition to the imine group of 3-oxo-camphorsulfonylimine is a process with high probability that can occur in a number of cases. Moreover, depending on the nucleophile, it can even become the main process, competing favourably with the well established nucleophilic addition to the vicinal carbonyl group.

The X-ray data indicate that the nucleophilic addition to the imino group prompts the conditions

Table 5. IR data[a] of the camphor derived species **1–8**.

	IR (ν/cm^{-1})					
Compound	OH	NH	C≡C or C=C=C	C=O	C=N	SO_2 (asym, sym)
1	3426	3322	2240			1333, 1138
2	3425		2132		1650	1335, 1164
3		3177	1955	1762		1306, 1142
4	3409	3244	2112			1344, 1134
5	3440		2121		1654	1333, 1167
6		3283	2117	1761		1312, 1139
7	3590, 3490			1663, 1606	1545	1316, 1163
8		3294	2119	1766		1312, 1145

[a] In KBr pellets.

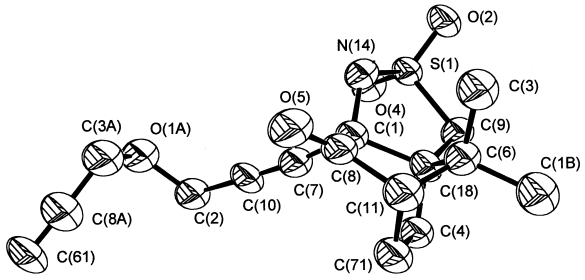

Fig. 4. Molecular structure of compound **6** in the solid state.

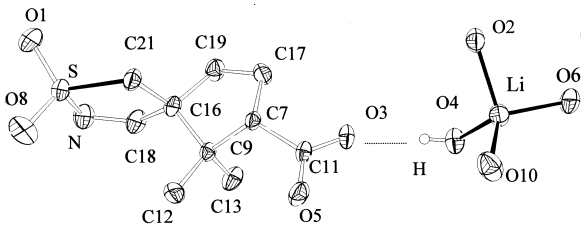

Fig. 5. Molecular structure of compound **7** in the solid state.

that favour C2–C3 bond breaking. Under this hypothesis the formation of compound **7** conceivably involves compound **8** as an intermediate.

Experimental Section

(1*S*)-3-Oxo-camphorsulfonylimine was prepared by literature methods [9, 10]. Diethyl ether was pre-dried under sodium wire and distilled prior to use. The alkynes were purchased from Aldrich.

The NMR spectra were recorded on a Varian UNITY 300 spectrometer. The IR spectra were obtained using a BIO-RAD FTS 3000 MX. FAB mass spectra were measured using a TRIO 2000 FISONS instrument. The optical activity was measured using an automatic Optical Activity ATAGO instrument.

Syntheses

A general procedure was used to synthesise the camphorsulfonyl alkyne derived species **1–8**: (i) deprotonation of the alkyne by *n*-butyl lithium (*ca*. 1:1.1 stoichiometry ratio, using a 1.6 M solution in hexane, previously diluted in 10–15 ml of Et_2O) followed by the addition of oxoimine (*ca*. 2 equivalents relative to alkyne) in dried diethyl ether (50 ml); (ii) addition of H_2O (typically 25 ml), separation of the ether phase (needs drying with $MgSO_4$ followed by filtration of the drying agent) and evaporation of the solvent afforded compounds **1**, **2**, **5** and **8**. Extraction of the aqueous solution with several portions of CH_2Cl_2, drying over $MgSO_4$, filtration and evaporation of the solvent close to dryness afford compounds **1**, **3**, **4,** and **6**. In the case of the reaction with 3-butyn-1-ol, prior to deprotonation of the alkyne the protection of the alcohol function with pyran, to form $HC{\equiv}C(CH_2)_2OC_5H_9O$, was necessary. Compound **7** was obtained from the aqueous phase.

(1aS,3aS,7R)-7-Hydroxy-1a,7-bis(3-phenyl-1-propynyl)-8,8-dimethyl-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (**1**) *and (3aS,7R)-7-hydroxy-8,8-dimethyl-7-(3-phenyl-1-propynyl)-4,5,6,7-tetrahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide* (**2**)

Butyl lithium (7.9 ml, 12.6 mmol) was slowly added to a solution of 3-phenyl-1-propyne (1.5 ml, 11.7 mmol) and the mixture was stirred for 18 h. Oxoimine (1.06 g, 4.68 mmol) was then added and the pale yellow suspension stirred for 46 h. Upon addition of H_2O and separation of the ether phase the solvent was evaporated close to dryness to obtain the di-alkyne derivative **1** (0.20 g, 0.44 mmol). The main crop of **1** (1.05 g, 2.28 mmol) was obtained upon extraction of the aqueous solution with three different portions of dichloromethane (125, 175, and 150 ml), drying over $MgSO_4$ and evaporation close to dryness. Total yield 58%. Recrystallization of **1** from MeOH gave suitable crystals for X-rays crystal structure analysis. M.p. 183.8 ± 0.1 °C. – FAB-MS (matrix 4-nitrobenzyl alcohol): *m/z* (%) = 460 (8). – $C_{28}H_{29}NO_3S \cdot \frac{1}{2}H_2O$ (468.6): calcd. C 71.8, H 6.5, N 3.0, S 6.8; found C 71.9, H 6.5, N 3.3, S 7.3.

Traces (*ca*. 1%) of compound **2** were obtained from the residual Et_2O phase by evaporation of the solvent and recrystallized from E_2O/*n*-pentane. The yield of **2** increases to *ca*. 10% if the deprotonation of the alkyne (5 h) and reaction with the oxoimine (19 h) are carried out for shorter periods. Reasonable crystals for X-ray analysis of **2** were grown from Et_2O/*n*-pentane. – FAB-MS: *m/z* (%) = 344 (10). – $C_{19}H_{21}NO_3S$ (343.4), calcd. C 66.4, H 6.2, N 4.1, S 9.3; found C 66.5, H 6.3, N 4.0, S 9.2.

(1aS,3aS)-8,8-Dimethyl-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-7-oxo-1a-(3-phenylpropadienyl)-2,1-benzisothiazole 2,2-dioxide (**3**)

A similar procedure to that used for the preparation of compound **1** was followed. The main change was that a 3:1 excess of 3-phenyl-1-propyne (0.50 ml, 3.9 mmol) relatively to the oxoimine (0.296 g, 1.3 mmol) was used. Traces of compounds **1** (5.25 mg, 0.011 mmol) and **2** (19 mg, 0.055 mmol) are detected in the Et_2O phase. Compound **3** was obtained from the CH_2Cl_2 layer (125 ml). Addition of the minimum amount of Et_2O followed by a large excess of *n*-pentane (*ca.* 100 ml) to the oily material formed upon almost complete evaporation of the solvent afforded the yellow compound **3** (89 mg, 0.26 mmol, 20% yield). M.p. 202–4 °C. – FAB-MS (matrix 4-nitrobenzyl alcohol): *m/z* (%) = 344 (21). – $C_{19}H_{21}NO_3S \cdot \frac{1}{5}\ CH_2Cl_2$ (411.4): calcd. C 57.8, H 5.5, N 3.4, S 7.8; found C 57.8, H 5.2, N 3.3, S 7.8.

(1aS,3aS,7R)-7-Hydroxy-1a,7-bis(4-oxa-1,6-heptadiyn-1yl)-8,8-dimethyl-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (**4**)

Butyl lithium (2.8 ml, 4.5 mmol) was slowly added to a mixture of dipropargyl ether (0.46 ml, 4.4 mmol) with the oxoimine (0.50 g, 2.2 mmol) and the mixture was stirred overnight at 20 °C. Following the general procedure mentioned above no compound could be obtained from the ether layer. Upon several extractions of the aqueous layer with 40 cm^3 portions of CH_2Cl_2, drying over $MgSO_4$ and evaporation of the solvent, compound **4** was isolated as a pale yellow powder that was recrystallized from Et_2O/*n*-pentane (0.37 g, 0.88 mmol, yield 40 %). M.p. 73–76 °C. – $C_{22}H_{27}NO_6S \cdot H_2O$ (433.6): calcd. C 60.9, H 6.3, N 3.2, S 7.4; found C 60.5, H 6.6, N 3.5, S 7.3.

(1aS,3aS)-8,8-Dimethyl-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-1a-(4-oxa-1,6-heptadiynyl)-7-oxo-2,1-benzisothiazole 2,2-dioxide (**6**)

The reaction is performed analogously to the one that afforded compound **4** but a 1:1 ratio of propargyl ether (0.35 ml, 3.37 mmol) and oxoimine (0.75 g, 3.30 mmol) is used. Traces of compound **5** were obtained from the ether phase (*ca.* 20 mg, *ca*. 5% yield). FAB-MS (matrix 4-nitrobenzyl alcohol): *m/z* (%) = 322 (23). – $C_{12}H_{19}NO_4S$ (321.4): calcd. C 59.8, H 6.0, N 4.4; found C 59.2, H 5.8, N 4.7.

Compound **6** (0.42 g, 1.31 mmol, yield 40%) was obtained from the dichloromethane phase (5 × 80 ml) upon evaporation of the solvent and was recrystallized from Et_2O/*n*-pentane. M.p. 115–7 °C. – FAB-MS (matrix 4-nitrobenzyl alcohol): *m/z* (%) = 321 (5). – $C_{16}H_{19}NO_4S \cdot H_2O$ (339.4): calcd. C 56.6, H 6.2, N 4.1, S 9.4; found C 56.5, H 6.0, N 4.0, S 10.0.

(S,S)-3-Aza-6,6-dimethyl-4-thia-spiro[4.4]non-2-ene-7-carboxylate (**7**)

3,4-Dihydro-2*H*-pyran (6 ml, 64 mmol) and five drops of HCl (37%) were added to a solution of $HC{\equiv}C(CH_2)_2OH$ (5 ml, 64 mmol) in Et_2O (50 ml) and the mixture stirred for 30 min BuLi (40 ml, 64 mmol) was then slowly added to the deprotonated tetrahydropyran-protected 3-butyn-1-ol. The suspension was stirred for *ca*. 2 h prior to addition of **B** (7.0 g, 31 mmol) and then allowed to react for 12 h. Acidified water (100 cm^3, with a few drops of HCl) was added and the organic phase separated. Traces of **8** (*ca.* 1%) were obtained from the Et_2O layer upon drying over $MgSO_4$ and evaporation of the solvent. – $C_{19}H_{27}NO_5S$ (381.5): calcd. C 59.8, H 7.2, N 3.7, S 8.4; found C 59.8, H 7.2, N 3.6, S 8.3.

The aqueous solution was concentrated (*ca.* 40 ml) and left to stand for 10 days. White crystals of **7** were obtained that were washed with ethanol/diethyl ether (910 mg, 2.94 mmol, yield 10%). $[\alpha]_D^{20} = 78.0$ (*c* = 0.54 in MeOH). – $C_{10}H_{22}NO_8SLi$ (323.3): calcd. C 37.1, H 6.9, N 4.3, S 9.9; found C 37.1, H 6.9, N 4.2, S 9.8.

X-ray crystallographic analyses

X-ray data were collected from white crystals of complexes **1**, **2**, **6** and **7** mounted in thin-walled glass capillaries. Data were collected at room temperature on Enraf-Nonius MACH3 (**1**) or TURBO CAD4 (**2**, **6**, **7**) diffractometers with graphite-monochromatized Mo–K_α (**1**) and Cu–K_α (**2**, **6**, **7**) radiation, using an ω-2θ scan mode. Unit cell dimensions were obtained by least-squares refinement of the setting angles of 25 reflections. The crystal data are summarized in Table 1. The data were corrected[11] for Lorentz-polarization effects, for linear decay and empirically for absorption. The heavy atom positions were located by Patterson methods using SHELXS-86 [12]. The remaining atoms were located in successive Fourier-difference maps and refined by least squares on F^2 using SHELXL-93 [13]. All the non-hydrogen atoms were refined with anisotropic thermal motion parameters. The hydrogen atoms bonded to carbons were included in calculated positions, constrained to ride at fixed

distances of the parent carbon atom. Hydroxyl hydrogen atoms were located and refined. Atomic scattering factors and anomalous dispersion terms were as in SHELXL-93 [13]. The ORTEP drawings were made with ORTEX [14] the ellipsoids displayed with 40% probability.

Crystallographic data for the structure(s) have been deposited with the Cambridge Crystallographic Centre, CCDC-182327–182330. Copies of the data can be obtained free of charge on application to the Director, CCDC-, 12 Union Road, Cambridge CB2 1EZ, UK
(Fax: int. code +(1223) 336-033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk).

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