Pergamon

Tetrahedron Vol. 51, No. 42, pp. 11431-11444, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00707-5

Stereoselective Free Radical Cycloaddition-Macrocyclization in Facile Synthesis of *trans*-Cyclohexano-fused 12-Membered Crown Thioethers

Emmanuil I. Troyansky[a]*, Rustem F. Ismagilov[a], Vyacheslav V. Samoshin[b], Yury A. Strelenko[a], Dmitry V. Demchuk[a], Gennady I. Nikishin[a], Sergey V. Lindeman[c], Viktor N. Khrustalyov[c]†, and Yury T. Struchkov[c]

[a]N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, Moscow B-334, Russia

[b]M.V.Lomonosov Moscow State Academy of Fine Chemical Technology, Vernadsky Prospect 86, Moscow 117571, Russia

[c]A.N.Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova St. 28, Moscow B-334, Russia

Dedicated to Professor Nikolay S. Zefirov on the occasion of his 60th birthday.

Abstract: *Homolytic cycloaddition of dithiols* ***1,2*** *derived from trans- and cis-1,2-cyclohexanediols to alkynes, induced by Pr_3B-O_2, offers an extremely simple approach to trans- and cis-cyclohexano-fused 12-membered crown thialactones* ***4a-c-7a-c****. The reaction of trans-1 proceeds with pronounced remote 1,6-asymmetric induction to give predominantly (1S*, 6R*, 12S*)-****4a-c****, while cis-2 reacts nonstereoselectively. Basing on molecular mechanics calculations the stereoselectivity is rationalized as a result of entropy favored pathway of macrocyclization.*

Widespread introduction of free radical processes in stereoselective organic synthesis in the last few years might be referred to as one of the most remarkable features of contemporaneous organic chemistry.[1]

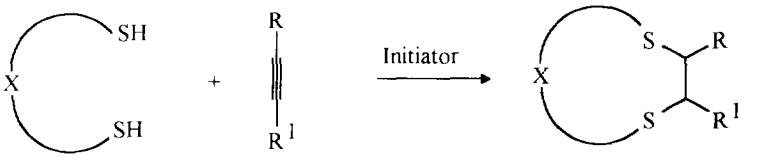
Among numerous free radical reactions widely employed in organic synthesis (addition to multiple bond, cyclization, oxidation, *etc.*) the cyclization, *i.e.* intramolecular homolytic addition to multiple bond, is probably of the most importance due to unique perspective it provides in construction of cyclic and polycyclic systems.[2]

Radical-mediated macrocyclization, pionereed by Porter,[3] has further developed synthetic potential of free radical reactions which was realized with outstanding success in the synthesis of lophotoxin,[4a] taxane ring system,[4b] ring-fused bicycles,[4c] steroid skeleton,[4d] brefeldin ring system,[5a] lysergic acid derivatives.[5b]

However, homolytic cyclization and macrocyclization in particular requires the preliminary multistep synthesis of precursors with precisely located radical centers and multiple bond, and this obviously limits the application of free radical cyclization.

In attempt to overcome such a limitation, we have developed recently a new universal strategy in the design of sulfur-containing cyclic systems based on one-step homolytic cycloaddition of α,ω-dithiols to alkynes, which enabled us to synthesize 6- and 7-membered dithiacyclanes.[6] Application of this strategy to long-chain dithiols offered a general approach to assembling of various crown thioethers from alkynes and dithiols[7] (Scheme 1). Crown thioethers thus prepared differ in their ring size (9-, 12-, 14-, 16-, 18-, 21- and 24-membered), number and type of heteroatoms (sulfur, oxygen) and their mutual location, as well as in substituents.

†Author to whom inquiries regarding the X-ray crystallographic analysis of **4c** should be addressed.



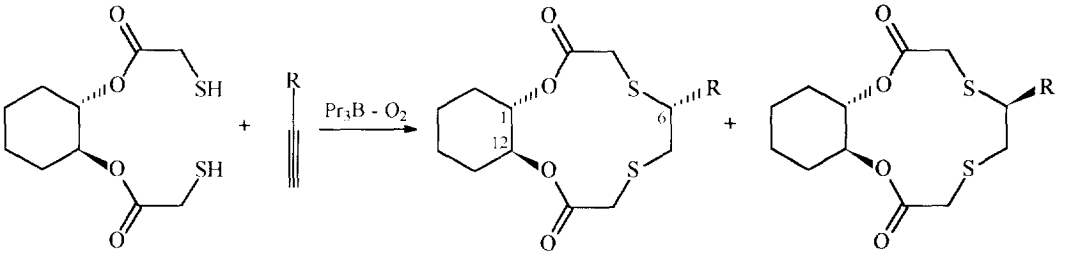
X= $(CH_2)_n$, $(CH_2)_mQ(CH_2)_{n-m}$, where Q = S, O

Initiator: Pr_3B-O_2-MeOH or AIBN.

Scheme 1.

According to our permanent interest in stereochemical aspects of free radical and oxidative processes, *e.g.* remote lactonization of alkanoic acids, [8a] direct γ-cyanation of methylcyclohexanones, [8b] homolytic cycloaddition of 1,2-dithiols to disubstituted alkynes, [6b] in this communication we report our studies on stereochemistry of homolytic cycloaddition - macrocyclization of *trans*- and *cis*-1,2-bis(mercaptoacetoxy)cyclohexanes (**1**, **2**) with alkynes (**3a-c**) induced by the system tripropylborane-oxygen. [9]

It was found that for *trans*-dithiol **1** cycloaddition proceeded with unexpected high diastereoselectivity to afford the mixtures of stereoisomeric (1*S**, 6*R**, 12*S**)- and (1*S**, 6*S**, 12*S**)-*trans*-cyclohexane-fused 12-membered crown thialactones **4a-c**, **5a-c** with significant predominance of the former one (Scheme 2).



1 **3** (1*S**, 6*R**, 12*S**)-**4** (1*S**, 6*S**, 12*S**)-**5**

R	Ratio **4** : **5**	Overall yield of **4** + **5**
Me (**a**)	2.1 : 1	30 %
Bu (**b**)	2.4 : 1	23 %
CH_2OMe (**c**)	3 : 1 : 1*	28 %

Scheme 2.

The major stereoisomers of **4a-c** crystallized spontaneously from their mixtures with **5a-c** on keeping. (1*S**, 6*R**, 12*S**)-configuration of **4c** has been established from X-ray crystallographic data (Fig. 1). Due to close similarity of ^1H and ^{13}C NMR spectra of the mixture **4c**,**5c** and the mixtures **4a**,**5a** and **4b**,**5b**, as well as of **4c** (m.p. 112-112.5 °C) and major crystalline stereoisomers, formed in the reactions of **1** with **3a,b,** the same (1*S**, 6*R**, 12*S**)-configuration has been assigned also to the major stereoisomers **4a** (m.p. 171 °C) and **4b** (m.p. 72-73 °C). The most common characteristic feature of ^1H NMR spectra of individual **4a-c** is the signal of one of CH_2S protons in the range 2.3-2.8 ppm (δ 2.36, 2.40, 2.81 ppm in **4a-c**, respectively) split as doublet of doublets with J_{HH} about 10 and 14 Hz.

* Erroneous ratio 2.1:1 was given in [9] due to misprinting.

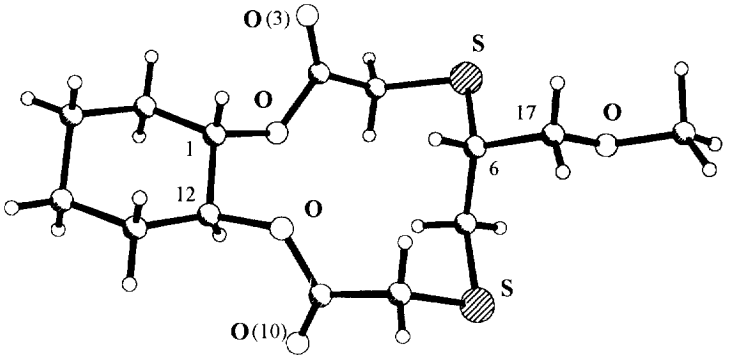
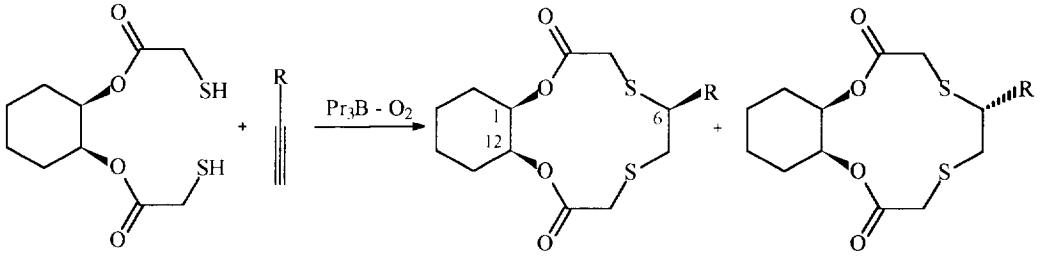


Figure 1. Molecular structure of (1*S**, 6*R**, 12*S**)-**4c**.

In contrast to reactions of *trans*-**1** no remarkable stereoselectivity has been observed in cycloaddition of *cis*-dithiol **2** to alkynes **3a-c** which gave mixtures of stereoisomeric **6a-c** and **7a-c** in the ratios close to 1:1 (Scheme 3).



2	**3**	(1*R**, 6*S**, 12*S**)-**6**	(1*R**, 6*R**, 12*S**)-**7**
R		Ratio **6** :**7** (or **7** : **6**)	Overall yield of **6** + **7**
Me (**a**)		1.20 : 1	18 %
Bu (**b**)		1.15 : 1	30 %
CH_2OMe (**c**)		1.05 : 1	21 %

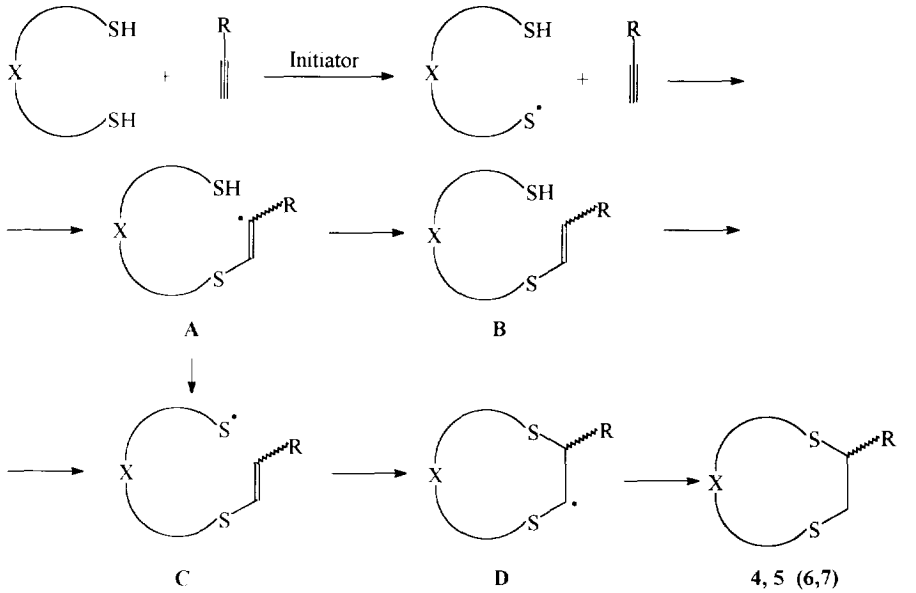
Scheme 3.

In all experiments the ratio of stereoisomers **4** and **5** or **6** and **7** was determined from the integral intensity of highly characteristic SCHR signals in ^{13}C NMR spectra of mixtures of stereoisomers purified from other components by column chromatography. It was proved by special test experiments that under mild conditions of Pr_3B-O_2 system neither individual **4c** nor a mixture of **4c** and **5c** changed their stereochemistry or the ratio of stereoisomers (see Experimental Section).

The studied homolytic cycloaddition of *trans*-dithiol **1** to alkynes **3a-c** is, therefore, genuine stereoselective process in its origin while the level of stereoselectivity is rather high despite of substantial distance between chiral centers of the precursor **1** and newly developed C-6 chiral centers of **4a-c**.

Macrocyclization of **1** with **3** can be formally referred to as remote 1,6-asymmetric induction. Numerous examples of acyclic diastereofacial selection in intermolecular free radical processes are known.[10] However, the major part of them are the reactions with 1,2- and 1,4-asymmetric induction, and only a few examples of remote asymmetric induction of high order in free radical chemistry were published.[11]

In account of the fact that diastereomers **4** and **5** proved to be not interconvertible under the conditions employed (*vide supra*), it is possible to rationalize the observed stereoselectivity in terms of the kinetic control of the reaction, which includes reversible intermolecular free radical addition of thiyl radicals to triple bonds [12] and subsequent intramolecular cyclization of the intermediate β-thiovinyl radicals. [6b,7,13] The relative energy of intermediates **A-D** (Scheme 4) could be used for a rough comparison of energy barriers leading to products **4** and **5**.



Scheme 4.

We have calculated the relative energies of nearest molecular forms by molecular mechanics (MMX, PCMODEL program) and used them for a rough estimation of relative energies of corresponding free radicals, *i.e.* **4** or **5** instead of **D**, and **B** instead of **A** and **C**. Therefore, we had to calculate and compare the energies of **4** *vs.* **5** and **B-4** *vs.* **B-5**

To achieve the complete screening of all possible conformers of **4** and **5** we started calculations from the known conformers of cyclododecane [14] and placed sulfur and oxygen atoms, carbonyl group and cyclohexane fragment in all of the 12 possible positions within the cycle and then minimized the energy of molecule. Alternative route was also used when the macrocycle geometry was optimized separately, then cyclohexane moiety was added with subsequent full optimization of geometry (only in a very few cases these two approaches led to different results). The first 20 most stable conformers of cyclododecane [14] within 5.5 kcal/mol from the global energy-minimum were used as starting points.* Thus the number of calculated conformers of unsubstituted *trans*-cyclohexane-fused 12-membered crown thialactones 2,11-dioxa-5,8-dithiabicyclo[10.4.0]hexadecane-3,10-diones exceeded 240, while some of them were equivalent. The most

* Several new conformers of cyclododecane within these energy limits were generated during this search and also used in further calculations. They differed very slightly in geometry from conformers described by Goto. [14] This kind of 'isomerism' has been yet discussed in detail [14] and very likely arises from the peculiarities of the force field used in PCMODEL.

stable forms were generated several times independently starting from various cyclododecane conformations. The structures **4a** and **5a** were obtained by adjustment of methyl group to appropriate position of S-C-C-S fragment and subsequent optimization of molecular geometry.

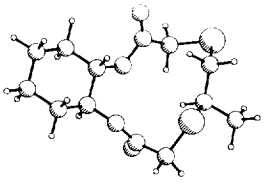
Eleven most stable conformers for both **4a** and **5a** are depicted in Scheme 5 with corresponding energy values in kcal/mol relative to global energy-minimum (within 2.4 kcal/mol from the last one). All other conformers could be neglected because of their high steric energy: *e.g.* the twelfth conformer with (1*S**,6*R**,12*S**) configuration is by 0.7 kcal/mol more strained than the eleventh one, and its population equals only about 1/30 of the population of lowest-energy form of this configuration. One can use these data to reveal general regularities since a lengthening of substituent does not change significantly the relative energy of conformers.

The conformer related to X-ray determined structure of **4c** is placed in a box. After completion of the search and consideration of possible conformers of **4c,** it is important to note that this form is not the most stable one as would be expected. Probably **4c** is preferred in the crystal state due to higher level of the macrocycle's symmetry. The ^{1}H NMR spectra for **4a-c** exhibit a rather large spin-spin coupling value between two vicinal hydrogens in the $SCHRCH_2S$ fragment [$^3J_{HH}$ = 10.3 (**4a**), 8.0 (**4b**), 9.4 Hz (**4c**)] indicating their predominantly *antiperiplanar* conformation (*cf.* [15]). According to Scheme 5 the major part of stable conformers possesses this internal arrangement and therefore it is not possible to determine the preferred conformer in solution based on the available NMR data.

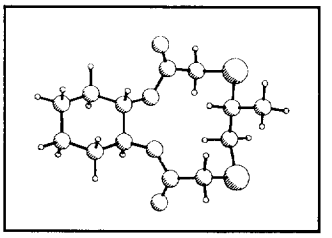
To calculate the geometry and the energy of intermediates **B** we used the results presented above. Starting from the most stable conformers of **4a** and **5a** (Scheme 5) we deleted the S-C(R) bond and replaced the appropriate C-C single bond by a double bond, and then optimized the geometry of the molecule. Hydrogen bonds S-H.. O/S were not taken into account because the structures **B** were the models for macrocyclization intermediate free radicals **C**. The relative energy values thus obtained were the following (within 2.5 kcal/mol from the global energy-minimum): 0.13, 0.80, 1.04, 2.06 and 2.07 kcal/mol for **B-4a**, and 0.00, 1.07 and 2.52 kcal/mol for **B-5a**. The most stable conformers for each diastereomer are depicted in Scheme 6. A distance between S and C atoms to be linked in further cyclization equals to 3.57 Å (**B-4a**) and 3.73 Å (**B-5a**) (compare with the sum of van der Waals radii: 1.85 (S) + 1.7 (C) = 3.55 Å [16]).

Examination of the MMX data revealed the following. The minor diastereomer **5** proved to be more stable than the major one, **4**. (This result is in agreement with the absence of thermodynamic control of macrocyclization.) Therefore, it is quite reasonable to expect the intermediate **D-5** to be less strained than **D-4**. At the same time the intermediate **B-5** (analog of **C-5**) is of lower energy than **B-4** (analog of **C-4**). Thus the cyclization into isomer **5** could pass *via* the intermediates with slightly lower energy than into isomer **4**. However, this advantage is not significant in the view of the uncertainties of molecular mechanics calculation. The steric energy difference between **4a** and **5a** equals only 0.4 kcal/mol and is even less pronounced for **4c** and **5c** (0.2 kcal/mol), **B-4a** and **B-5a** (0.13 kcal/mol), **B-4c** and **B-5c** (0.3 kcal/mol). Thus we consider the energy barriers leading to diastereomers **4** and **5** as to be of approximately equal height. In other words, these two directions of macrocyclization have approximately equal ***enthalpies*** of activation. At the same time they certainly differ in ***entropy*** of activation. Indeed, comparing the number of low-energy intermediates leading to isomer **4** and to isomer **5** (*vide supra*), we have to conclude that the ways to **4** are essentially more numerous than the ways to **5**. Consequently the formation of (1*S**,6*R**,12*S**)-stereoisomers **4** is ***entropy favored***. It is reasonable to assume that in the case of conformationally more flexible *cis*-dithiol **2** system (Scheme 3) this stereochemical discrimination is less pronounced causing almost negligible stereoselectivity of macrocyclization.

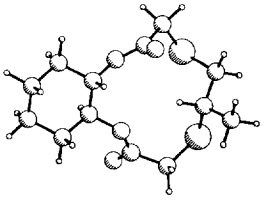
4a (1*S**,6*R**,12*S**) **5a** (1*S**,6*S**,12*S**)



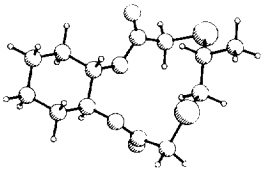
0.41



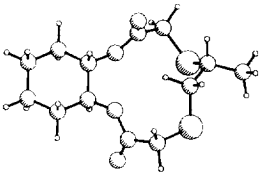
0.80



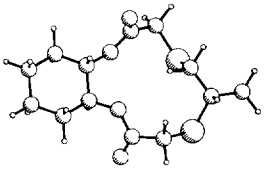
0.00



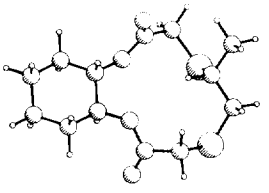
0.89



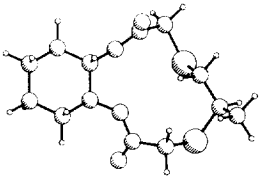
0.95



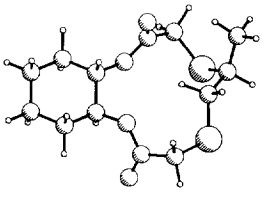
1.32



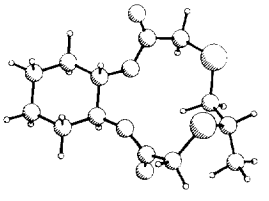
1.03



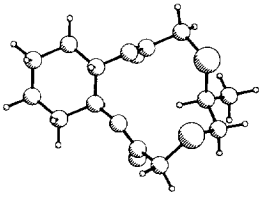
1.24



1.41

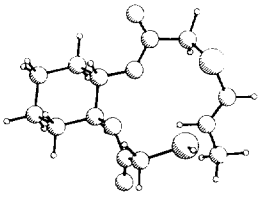


1.42

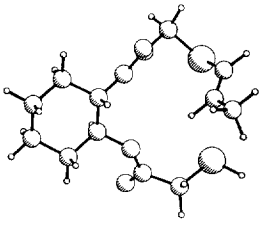


1.69

Scheme 5.



B-4a 0.13



B-5a 0.00

Scheme 6.

Potential importance and increased interest in coordination chemistry of crown thioethers as complexing agents in analytical chemistry, medicine, environmental protection stimulated wide studies of their chelating ability in the last few years. [17] However common methods of crown thioether synthesis are usually restricted to traditional 'assembling' from dithiols and α,ω-dihalides under high dilution conditions, [18] or on a solid support. [19] In our opinion, the developed concept of homolytic cycloaddition-macrocyclization markedly expands the synthetic potential of currently existing methodology for preparation of crown thioethers. Considering the availability of optically active *trans*-1,2-cyclohexanediol, [20] the method described in this paper could offer an approach to the synthesis of chiral crown thioethers.

The results of this work also contribute to the problem of stereoselective synthesis of *trans* ring-fused compounds. [21]

EXPERIMENTAL SECTION

trans- and *cis*-1,2-cyclohexanediols were synthesized by oxidation of cyclohexene with H_2O_2 and subsequent hydrolysis or with $KMnO_4$, respectively. On acylation of *trans*- and *cis*-1,2-cyclohexanediols with mercaptoacetic acid (azeotropic esterification catalyzed by TsOH) *trans*- and *cis*-1,2-bis(mercaptoacetoxy)-cyclohexanes **1** and **2** were formed as light-yellow oils, washed with $NaHCO_3$ and purified by column chromatography, yield 98 and 95%.

Typical procedure of homolytic cycloaddition - macrocyclization was as follows. A solution (3 ml, 1 mol dm^{-3}) of tripropylborane (3 mmol) in hexane was added to a solution of 0.79 g (3 mmol) of *trans*-1,2-bis(mercaptomethylcarbonyloxy)cyclohexane **1**, 0.21 g (3 mmol) of methyl propargyl ether **1c** and anhydrous MeOH (0.48 ml, 0.38 g, 12 mmol) in benzene (40 ml) under an argon atmosphere. All experiments were performed under TLC control. After complete consumption of dithiol **1** the reaction mixture was washed with an aqueous solution of KOH (5 ml, 1 mol dm^{-3}) and the benzene layer was separated. The aqueous layer was extracted with ether (3 × 10 ml), the extract was combined with the benzene layer, dried over $MgSO_4$ and evaporated *in vacuo*. A mixture of bicyclic thiacrown ethers **4c, 5c** in the ratio 3.1:1 (0.28 g, yield 28%) was isolated from the residue by chromatography on a column with SiO_2 (100-160 mesh) using a mixture of hexane - ethyl acetate as an eluent.

Spectral data for **4c**+**5c** : ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34-1.37 m (4H), 1.75 m (2H), 2.05 m (2H), 2.70-3.32 m (7H), 3.35 s (3H), 3.57 - 3.69 m (2H), 4.88 m (2H), ^{13}C NMR (250 MHz, $CDCl_3$) δ 23.20, 23.26, 29.91, 30.08, 31.78, 32.28, 33.39, 35.45, 35.76, 41.46, 41.56 (CHS), 42.46, 43.28, 46.15 (CHS), 46.32, 46.58, 58.53 and 58.61 (CH_3O), 72.24 and 74.33 (CH_2O), 74.57, 74.76, 74.92 and 75.02 (CHO), 168.84, 169.78, 169.94 and 170.47 (C=O), MS (electron impact): 71 (100), 302 (66), 103 (48), 81 (46), 45 (32), 149 (27), 334 (M^+, 26), 41 (25), 163 (20), 140 (17). On keeping **4c** crystallized spontaneously, m.p. 112-112.5 °C (hexane-ether), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 m (4H), 1.78 m (2H), 2.10 m (2H), 2.81 dd (1H), 2.91 dd (1H), 3.07 m (1H), 3.15 and 3.27 dd (2H), 3.26 and 3.40 dd (2H), 3.37 s (3H), 3.57 and 3.70 dd (2H), 4.90 m (2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.77 (CH_2, double intensity (d.i.)), 30.49 (CH_2, d.i.), 32.44 (CH_2, d.i.), 32.96 (CH_2), 42.27 (CH), 59.27 (CH_3), 72.83 (CH_2O), 74.96 and 75.40 (CHO), 169.43 (C=O, d.i.); MS (electron impact): 71 (100), 81 (52), 103 (49), 302 (39), 149 (30), 140 (23), 334 (M^+, 20), 41 (25), 163 (19), 173 (15).

Analogously were carried out other cycloaddition reactions of dithiols **1** and **2** with alkynes **3** from which the following bicyclic crown thioethers were isolated:

4a+**5a** (from **1** and **3a**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 d+m (7H), 1.68 m (2H), 2.00 m (2H), 2.27 m (1H), 2.80-3.60 m (6H), 4.80 m (2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17.96 and 19.99 (CH_3), 22.92, 23.29 (d.i),

29.27, 29.57, 29.97, 30.20 (d.i.), 31.42, 31.60, 31.91, 33.46, 34.92 (CHS), 35.67, 40.32, 41.54 (CHS), 74.52, 74.61, 74.81 and 74.87 (CHO), 169.05 (d.i.), 170.32 and 170.45 (C=O); MS (electron impact): 172 (100), 304 (M^+, 95), 81 (95), 133 (74), 119 (50), 41 (43), 114(42), 99 (39), 173 (37), 140 (35). On keeping **4a** crystallized spontaneously, m.p. 171 (hexane-ether), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 d+m (7H), 1.78 m (2H), 2.10 m (2H), 2.36 dd (1H), 3.00 m (1H), 3.08 d (1H), 3.10d (1H), 3.13d (1H), 3.28 d (1H), 3.48 d (1H), 4.90 m (2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.38 (CH_3), 23.70 (CH_2, d.i.), 30.41 (d.i.), 31.94 and 32.07 (CH_2), 35.49 (CHS), 36.21 (CH_2), 75.10 and 75.31 (CHO), 169.47 and 169.49(C=O); MS (electron impact): 304 (M^+, 100), 172 (99), 81 (94), 133 (76), 119 (52), 99 (39), 140 (37), 87 (35), 41 (35), 173 (33), 114(30), 115 (27), 69 (17), 188 (13).

4b+**5b** (from **1** and **3b**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.85 t (3H), 1.25-1.45 m (CH_2, 10H), 1.60-1.75 m (2H), 1.90-2.10 m (2H), 2.40 and 2.80 m (2H), 2.90-3.36 m (5H), 4.80 m (2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 13.68 (CH_3, d.i.), 22.19, 23.37 (d.i), 28.03 (d.i), 30.06 (d.i), 30.26, 31.43 (d.i), 31.66 (d.i), 31.95 (d.i), 33.59, 34.14, 34.72 (d.i), 34.82, 38.76 (CH_2 and CH_2S), 41.20 and 47.64 (CHS), 74.57 (d.i), 74.80 and 74.86 (CHO), 169.06, 169.17, 170.26 and 170.55 (C=O); MS (electron impact): 81 (100), 115 (93), 172 (76), 346 (M^+, 66), 173 (62), 140 (48), 41 (45), 55 (44), 83 (41), 161 (39). On keeping **4b** crystallized spontaneously, m.p. 72-73 °C (hexane-ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.85 t (3H), 1.30-1.38 m (CH_2, 10H), 1.65 m (2H), 2.00 m (2H), 2.40 dd (1H), 2.80 m (1H), 2.90-3.36 m (5H), 4.80 m (2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 13.80 (CH_3), 22.30, 23.50 (d.i), 28.15, 30.20 (d.i.), 31.55, 31.80, 32.09, 34.85 (CH_2 and CH_2S), 41.35 (CHS), 74.70 and 74.90 (CHO), 169.20 and 169.32 (C=O); MS (electron impact): 81 (100), 115 (82), 346 (M^+, 78), 172 (70), 173 (62), 161 (48), 41 (48), 140 (44), 55 (43), 83 (41).

6a+**7a** (from **2** and **3a**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 d (3H), 1.35-2.00 m (8H), 2.53 m (1H from $C\underline{H}_2C\underline{H}CH_3$), 2.90-3.40 m (6H, CH_2S+CHS), 5.03 m(2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 19.30 and 19.50 (CH_3), 21.15, 21.27, 27.20, 27.31, 27.35, 27.42, 32.51, 32.90, 33.19, 33.39, 34.17, 35.34 and 38.31 (CH_2), 38.63 (CHS), 38.70(CH_2), 38.97 (CHS), 71.55, 71.74, 74, 72.36 and 72.50 (CHO), 168.57, 168.98, 169.56 and 169.87 (C=O); MS (electron impact): 81 (100),172 (98), 304 (M^+, 96), 133 (77), 119 (57), 41 (48), 99 (41), 87 (39), 140 (35), 74 (29).

6b+**7b** (from **2** and **3b**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.85 t (3H), 1.20-1.90 m (CH_2, 14H), 2.40-3.80 m (7H), 4.60 m and 5.00 m (2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 13.76 (CH_3, d.i.), 20.92, 21.25, 21.44, 21.51, 21.99, 22.29 (d.i), 27.29 (d.i), 27.39 (d.i), 28.32, 28.39, 28.52, 32.76, 33.08, 33.25, 33.50, 33.69, 37.40 (d.i), 44.83 and 45.15 (CHS), 71.73, 71.94, 72.21 and 72.46 (CHO), 169.01 (d.i.), 169.18, 169.70 and 169.78 (C=O); MS (electron impact): 84 (100), 86 (89), 83 (37), 81 (32), 115 (30), 49 (23), 99 (23), 345 (6), 346 (M^+, 20), 347 (4).

6c+**7c** (from **2** and **3c**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20-1.95 m (8H), 2.70-4.00 (9H), 3.25 s (3H), 4.90 and 5.20 m (2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 220.66, 21.35, 21.63, 22.32, 26.86, 27.22, 27.58, 31.25, 32.98, 33.63, 34.03, 34.54, 35.11 and 35.22 (CH_2), 44.53 and 44.89 (CHS), 58.68 and 58.79 (CH_3O), 71.19, 71.76, 71.90 and 72.16 (CHO), 73.37 and 73.76 (CH_2O), 168.46, 169.01, 169.64 and 169.97 (C=O); MS (electron impact): 71 (100), 302 (91), 103 (60), 81 (40), 45 (33), 41 (27), 149 (24), 334 (M^+, 21), 41 (25), 163 (19).

Test experiment. A solution (0.2 ml, 1 mol dm^{-3}) of tripropylborane (0.2 mmol) in hexane was added to a solution of 0.79 g (3 mmol) of *trans*-1,2-bis(mercaptomethylcarbonyloxy)cyclohexane **1**, 0.05 g (0.15 mmol) of (1*S**, 6*R**, 12*S**)-**4c**, isolated from the reaction of **1** with **3c**, and anhydrous MeOH (0.032 g, 1 mmol) in benzene (3 ml) under an argon atmosphere. Mixture was kept during 8 h at ambient temperature. Work-up procedure was the same as described in a typical protocol of homolytic cycloaddition-macrocyclization. 0.047 g (94%) of unreacted (1*S**, 6*R**, 12*S**)-**4c** with no traces of (1*S** ,6*S**, 12*S**)-**5c** (according to ^{13}C NMR data) was isolated.

After analogous treatment of a mixture of **4c**, **5c** (0.10 g, 0.30 mmol) (ratio **4c** : **5c** 3.1:1) **unchanged** mixture of **4c**, **5c** was recovered (0.096 g, 96%).

X-ray study of 4c. To obtain crystals suitable for X-ray determinations, **4c** was dissolved in toluene and precipitated with hexane by vapor diffusion. Crystal data for **4c** were obtained at -120 °C. The structure was solved by direct method and refined by full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were included into the refinement in calculated position (riding model) with fixed isotropic thermal parameters (U_{iso} = 0.05 Å^2) with the exception of the H atoms linked with asymmetric centres (H_1, $H_{1'}$, H_6, $H_{6'}$, H_{12}, $H_{12'}$). The final discrepancy factors were R = 0.063 and R_w = 0.056 for 2124 unique reflections with $I > 3\sigma(I)$ (Table 1).

Crystal structure of **4c** posseses a local non-crystallographic center of symmetry (pseudo-center), which links two crystallographically independent molecules and for this reason both molecules (enantiomers) have the same relative configuration of asymmetric centers. Relevant structural parameters are presented in Tables 2-5. Within the limits of experimental measurements bond lengths and bond angles (Tables 3, 4) of both crystallographically independent molecules are equal. The primed atoms relate to the second crystallographically independent molecule. Coordinates of hydrogen atoms, bonded to the asymmetric centers and located in the difference Fourier map, are presented in Table 5.

Molecules of (1*S**, 6*R**, 12*S**)-**4c** are packed as "puckered" layers oriented along X axis. In and between the layers molecules are connected by weak hydrogen bonds: 1) O(3) (x, y-1, z)...C(9) (x, y, z) 3.26(1) Å, O(3) (x, y-1, z)...H(9A) (x, y, z) 2.4(1) Å, angle O(3)...H(A)-C(9) 144(3)° in the layer; 2) O(3') (1.5+x, -1.5+y, -0.5+z)...C(9) (x, y, z) 3.26(1) Å, O(3') (1.5+x, -1.5+y, -0.5+z)...H(9B) (x, y, z) 2.4(1) Å, angle O(3')...H(9B)-C(9) 156(3)° between the layers (Fig. 2).

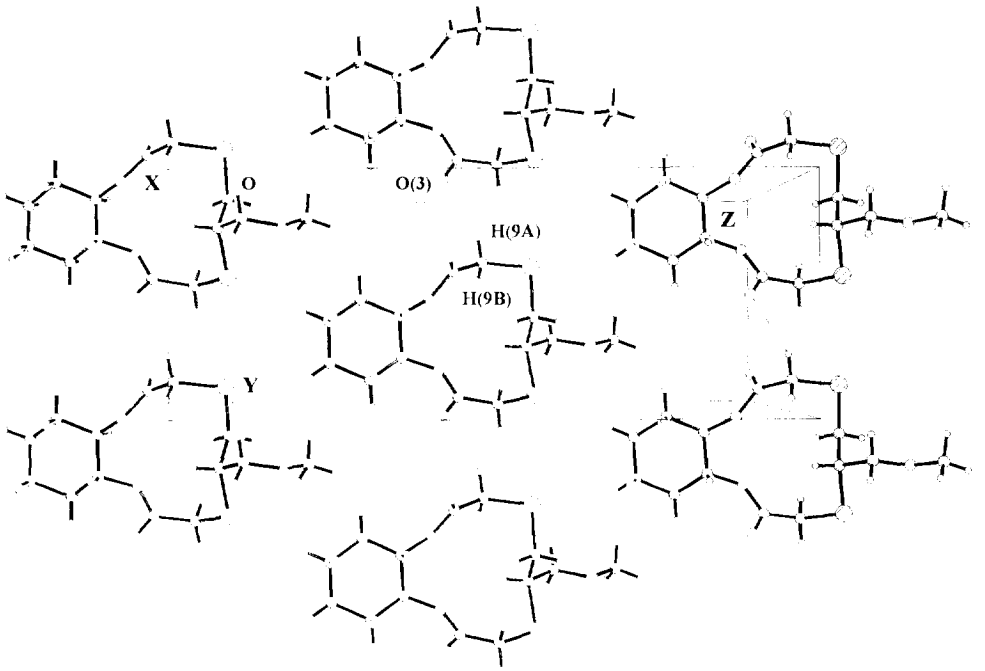


Figure 2. The general view of molecular layer of **4c** along X axis; H-bonds are shown by dotted lines.

Table 1. Experimental data for the crystallographic analysis of (1*S**, 6*R**, 12*S**)-6-methoxymethyl-2,11-dioxa-5,8-dithiabicyclo[10.4.0]hexadecane-3.10-dione **4c.**

Empirical formula	$C_{14}H_{22}O_5S_2$
Color, habit	colorless prizm
Crystal size (mm)	0.2 x 0.3 x 0.4
Crystal system	orthorhombic
Space group	$Pna2_1$
Unit cell dimensions	a = 18.49(1) Å, b = 8.281(5) Å, c = 21.41(2) Å
Volume	3279(4) $Å^3$
Z	8
Formula weight	334.4
Density (calc.)	1.355 Mg/m^3
Absorption coefficient	0.342 mm^{-1}
F(000)	1424
Diffractometer used	Siemens P3/PC
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	153
Monochromator	highly oriented graphite crystal
2q range	2.0 to 54.0 ^{o}
Scan type	ω/2θ
Scan speed	variable, 1.50 to 14.65 ^{o}/min in ω
Scan range (w)	2.20^o
Standard reflections	2 measured every 98 reflections
Index ranges	$0 \le h \le 25$, $0 \le k \le 11$, $-29 \le l \le 0$
Reflections collected	4500
Independent reflections	4500 (R_{int} = 0.00 %)
Observed reflections	2124 ($F > 6.0\ \sigma(F)$)
Absorption correction	N/A
Solution and Refinement	
System used	Siemens SHELXTL PLUS (PC Version) [22]
Solution	Direct Methods
Refinement method	Full-Matrix Least-Squares
Quantity minimized	$Sw(F_o - F_c)^2$
Absolute structure	N/A
Extinction correction	N/A
Hydrogen atoms	riding model, fixed isotropic U_{iso} = 0.05 $Å^2$
Weighting scheme	$w^{-1} = \sigma^2(F) + 0.0001F^2$
Number of parameters refined	378
Final R indices (obs. data)	R = 6.34 %, wR = 5.57 % H
Goodness-of-fit	2.44 H

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients of **4c** ($Å^2 \times 10^3$)

	x	y	z	U(eq)
S(5)	7685(1)	4191(2)	686(2)	34(1)
S(8)	7614(1)	-1222(2)	624(1)	33(1)
O(2)	6998(3)	3056(7)	-875(3)	29(2)
O(3)	7833(3)	4989(7)	-813(3)	40(2)
O(10)	6766(4)	-1615(9)	-690(3)	62(3)
O(11)	7619(3)	91(7)	-1045(3)	31(2)
O(18)	8368(3)	2080(7)	1636(3)	34(2)
C(1)	239(4)	2554(9)	-1484(3)	21(2)
C(3)	7363(5)	4232(10)	-572(3)	21(3)
C(4)	7041(4)	4487(10)	67(4)	25(3)
C(6)	7998(4)	2135(9)	564(4)	24(3)
C(7)	7388(5)	877(8)	660(4)	29(2)
C(9)	7923(5)	-1445(11)	-175(4)	31(3)
C(10)	7340(5)	-1044(10)	-651(4)	31(3)
C(12)	7108(5)	798(10)	-1519(4)	34(3)
C(13)	7302(6)	120(11)	-2156(4)	42(3)
C(14)	6867(7)	1032(13)	-2660(4)	57(4)
C(15)	7038(6)	2776(13)	-2645(4)	48(4)
C(16)	6848(6)	3468(12)	-1992(4)	43(4)
C(17)	8619(4)	1825(10)	1000(4)	29(3)
C(19)	8957(5)	1857(11)	2062(4)	40(3)
S(5')	5149(1)	14501(3)	3471(1)	31(1)
S(8')	5109(2)	9103(3)	3610(1)	35(1)
O(2')	4516(3)	13617(7)	5097(3)	34(2)
O(3')	5469(3)	15171(7)	4903(3)	32(2)
O(10')	4420(4)	8523(8)	5031(3)	47(2)
O(11')	5157(4)	10656(7)	5195(3)	36(2)
O(18')	5836(3)	12387(7)	2539(3)	37(2)
C(1')	4798(5)	13088(10)	5698(4)	33(3)
C(3')	4903(5)	14604(10)	4757(4)	22(3)
C(4')	4534(5)	14848(10)	4120(4)	30(3)
C(6')	5470(4)	12447(9)	3612(4)	28(3)
C(7')	4886(5)	11140(11)	3535(4)	48(3)
C(9')	5470(5)	8914(10)	4383(4)	30(3)
C(10')	4952(4)	9311(12)	4889(4)	29(3)
C(12')	4684(4)	11272(9)	5684(4)	28(3)
C(13')	4884(6)	10529(12)	6323(4)	45(4)
C(14')	4472(7)	11385(10)	6844(4)	50(4)
C(15')	4619(7)	13190(12)	6845(4)	58(4)
C(16')	4427(6)	13911(12)	6223(4)	45(4)
C(17')	6094(5)	12191(11)	3150(4)	33(3)
C(19')	6397(5)	12346(11)	2105(4)	40(3)

* U is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 3. Bond lengths (Å)

S(5)-C(6)	1.818 (8)	S(5')-C(6')	1.826 (8)
S(5)-C(4)	1.798 (8)	S(5')-C(4')	1.817 (9)
S(8)-C(9)	1.813 (8)	S(8')-C(9')	1.791 (8)
S(8)-C(7)	1.789 (7)	S(8')-C(7')	1.744 (9)
O(3)-C(3)	1.19 (1)	O(3')-C(3')	1.19 (1)
O(2)-C(1)	1.44 (1)	O(2')-C(1')	1.46 (1)
O(2)-C(3)	1.35 (1)	O(2')-C(3')	1.31 (1)
O(10)-C(10)	1.17 (1)	O(10')-C(10')	1.22 (1)
O(11)-C(10)	1.36 (1)	O(11')-C(10')	1.35 (1)
O(11)-C(12)	1.51 (1)	O(11')-C(12')	1.46 (1)
O(18)-C(17)	1.45 (1)	O(18')-C(17')	1.40 (1)
O(18)-C(19)	1.43 (1)	O(18')-C(19')	1.39 (1)
C(1)-C(12)	1.48 (1)	C(1')-C(12')	1.52 (1)
C(1)-C(16)	1.51 (1)	C(1')-C(16')	1.48 (1)
C(3)-C(4)	1.51 (1)	C(3')-C(4')	1.54 (1)
C(6)-C(7)	1.55 (1)	C(6')-C(7')	1.54 (1)
C(6)-C(17)	1.50 (1)	C(6')-C(17')	1.53 (1)
C(9)-C(10)	1.52 (1)	C(9')-C(10')	1.48 (1)
C(12)-C(13)	1.52 (1)	C(12')-C(13')	1.55 (1)
C(13)-C(14)	1.54 (1)	C(13')-C(14')	1.53 (1)
C(14)-C(15)	1.48 (1)	C(14')-C(15')	1.52 (1)
C(15)-C(16)	1.55 (1)	C(15')-C(16')	1.50 (1)

Table 4. Bond angles (in degrees)

C(6)-S(5)-C(4)	103.5(4)	C(6')-S(5')-C(4')	103.0(4)
C(9)-S(8)-C(7)	102.3(4)	C(9')-S(8')-C(7')	104.9(4)
C(1)-O(2)-C(3)	119.2(6)	C(1')-O(2')-C(3')	118.9(7)
C(10)-O(11)-C(12)	116.6(7)	C(10')-O(11')-C(12')	118.0(7)
C(17)-O(18)-C(19)	109.5(6)	C(17')-O(18')-C(19')	111.4(7)
O(2)-C(1)-C(16)	111.1(6)	O(2')-C(1')-C(16')	111.4(7)
O(2)-C(1)-C(12)	106.3(6)	O(2')-C(1')-C(12')	103.4(6)
C(16)-C(1)-C(12)	112.3(7)	C(16')-C(1')-C(12')	113.9(7)
O(3)-C(3)-O(2)	122.5(7)	O(3')-C(3')-O(2')	125.7(8)
O(3)-C(3)-C(4)	127.5(8)	O(3')-C(3')-C(4')	124.8(8)
O(2)-C(3)-C(4)	109.8(7)	O(2')-C(3')-C(4')	109.4(7)
S(5)-C(4)-C(3)	112.9(6)	S(5')-C(4')-C(3')	112.3(6)
S(5)-C(6)-C(7)	112.2(5)	S(5')-C(6')-C(7')	114.1(6)
S(5)-C(6)-C(17)	108.3(6)	S(5')-C(6')-C(17')	105.5(6)
C(7)-C(6)-C(17)	111.1(7)	C(7')-C(6')-C(17')	111.2(7)
S(8)-C(7)-C(6)	118.6(6)	S(8')-C(7')-C(6')	120.4(7)
S(8)-C(9)-C(10)	112.8(6)	S(8')-C(9')-C(10')	114.5(6)
O(11)-C(10)-O(10)	125.4(9)	O(11')-C(10')-O(10')	123.3(8)
O(10)-C(10)-C(9)	127.3(8)	O(10')-C(10')-C(9')	125.8(8)
O(11)-C(10)-C(9)	107.3(7)	O(11')-C(10')-C(9')	110.9(7)
O(11)-C(12)-C(1)	104.3(6)	O(11')-C(12')-C(1')	106.0(6)
O(11)-C(12)-C(13)	108.3(7)	O(11')-C(12')-C(13')	110.6(7)
C(1)-C(12)-C(13)	111.8(7)	C(1')-C(12')-C(13')	110.2(7)
C(12)-C(13)-C(14)	108.9(8)	C(12')-C(13')-C(14')	110.0(8)
C(13)-C(14)-C(15)	110.5(9)	C(13')-C(14')-C(15')	111.7(8)
C(14)-C(15)-C(16)	109.3(8)	C(14')-C(15')-C(16')	110.3(8)
C(6)-C(16)-C(15)	110.8(8)	C(6')-C(16')-C(15')	112.3(8)
O(18)-C(17)-C(6)	108.2(6)	O(18')-C(17')-C(6')	109.3(7)

Table 5. H-Atom coordinates ($x10^4$)

	x	y	z		x	y	z
H(1)	7695	2781	-1488	H(1')	5301	13419	5588
H(6)	8171	2084	159	H(6')	5697	12550	4042
H(12)	6571	773	-1412	H(12')	4121	11246	5633

Acknowledgements. We are grateful to Mr. R. Fleming (The University of Nottingham, U.K.) for recording several NMR (400 MHz) spectra. We thank the International Science Foundation (Soros Foundation) (Grant MPL 000) and Russian Foundation of Fundamental Studies (Projects 93-03-18110 and 94-03-09296) for generous financial support. E.I.T. also indebtedly thanks the Royal Society for the Kapitza Fellowship and Professor Gerald Pattenden for very helpful discussion on macrocyclization.

REFERENCES AND NOTES

1. (a) Porter, N.A.; Giese, B.; Curran, D.P. *Acc. Chem. Res.* **1991**, *24*, 294. (b) Porter, N.A.; Krebs, P.J. *Top. Stereochem.* **1988**, *18*, 27. (c) Curran, D.P. In *Compreh. Org. Synthesis*. Trost, B.M.; Fleming, I.; Eds.; Pergamon Press: Oxford, 1991, vol.4, p. 715. (d) Motherwell, W.B.; Crich, D. *Free Radical Chain Reactions In Organic Synthesis*, Academic Press, 1991. (e) Hart, D.J.; Krishnamurthy, R. *J.Org.Chem.* **1992**, *57*, 4457. (f) Mowbray, C.E.; Pattenden, G. *Tetrahedron. Lett.* **1993**, *34*, 127.
2. (a) Tsai, Y.-M.; Ke, B.-W.; Yang, C.-T.; Lin, C.H. *Tetrahedron Lett.* **1992**, *33*, 7895. (b) Pradhan, S.K.; Sitabkhan, S. *Tetrahedron Lett.* **1993**, *34*, 5615. (c) Bowman, W.R.; Clark, D.N.; Marmon, R.J. *Tetrahedron* **1994**, *50*, 1275 and 1295. (d) Clive, D.L.J.; Magnuson, S.R. *Tetrahedron Lett.* **1995**, *36*, 15. (e) Udding, J.H.; Tuijp, C.J.M.; Hiemstra, H.Speckamp, W.N. *Tetrahedron* **1994**, *50*, 1907 and references cited therein.
3. Porter, N.A.; Chang, V.H.-T.; Magnin, D.R. *J.Amer.Chem.Soc.* **1989**, *111*, 8309.
4. (a) Astley, M.P.; Pattenden, G. *Synthesis* **1992**, 101. (b) Hitchcock, S.A., Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843. (c) Pattenden, G.; Smithies, A.J.; Walter, D.S. *Tetrahedron Lett.* **1994**, *35*, 2413. (d) Chen, L.; Gill, G.B.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 2593.
5. (a) Feldman, K.S.; Berven, H.M.; Romanelli, A.L.; Parvez, M. *J.Org.Chem.* **1993**, *58*, 6851. (b) Özlü, Y., Cladingboel, D.E.; Parsons, P.J. *Tetrahedron* **1994**, *50*, 2183.
6. (a) Demchuk, D.V.; Lutsenko, A.I.; Troyansky, E.I.; Nikishin, G.I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 2801 (*Bull. Acad. Sci USSR, Div. Chem. Sci.* **1990**, *39*, 2542). (b) Troyansky, E.I.; Demchuk, D.V., Samoshin, V.V., Strelenko, Yu.A., Lutsenko, A.I.; Nikishin, G.I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, 1841 (*Bull. Acad. Sci USSR, Div. Chem. Sci.* **1991**, *40*, 1629).
7. (a) Troyansky, E.I. *Phosphorus, Sulfur, and Silicon*, 1994, **95**, 55. (b) Troyansky, E.I.; Ismagilov, R.F.; Korneeva, E.N.; Pogosyan, M.S.; Nikishin, G.I. *Mendeleev Communications* **1995**, 18. (c) Troyansky, E.I., Demchuk, D.V.; Ismagilov, R.F.; Lazareva, M.I.; Strelenko, Yu.A.; Nikishin, G.I. *Mendeleev Commun.* **1993**, 112. (d) Troyansky, E.I.; Lazareva, M.I.; Demchuk, D.V.; Samoshin, V.V.; Strelenko, Yu.A.; Nikishin, G.I. *Synlett.* **1992**, 233. (e) Troyansky, E.I.; Demchuk, D.V.; Lazareva, M.I.; Samoshin, V.V.; Strelenko, Yu.A., Nikishin, G.I. *Mendeleev Commun.* **1992**, 48.

8. (a) Troyansky, E.I., Svitanko, I.V., Nikishin, G.I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 133 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1985**, *34*, 125). (b) Troyansky, E.I.; Mizintsev, V.V.; Samoshin, V.V.; Lutsenko, A.I.; Svyatkin, V.A.; Nikishin, G.I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 344 (*Bull. Acad. Sci. USSR., Div. Chem. Sci.* **1989**, *38*, 294).
9. For a preliminary communication see: Troyansky, E.I.; Ismagilov, R.F.; Demchuk, D.V.; Strelenko, Yu.A., Samoshin, V.V.; Nikishin, G.I.; Lindeman, S.V. , Khrustalyov, V.N.; Struchkov, Yu.T.; *Tetrahedron Lett.* **1995**, *36*, 2293.
10. Smadja, W. *Synlett* **1994**, 1.
11. Leading references for remote asymmetric induction in free radical chemistry: (a) Curran, D.P.; Geib, S.J.; Kuo, L.H. *Tetrahedron Lett.* **1994**, *35*, 6235. (b) Stack, J.G.; Curran, D.P.; Geib, S.V.; Rebek Jr, J.; Ballester, P. *J.Amer.Chem.Soc.* **1992**, *114*, 7007.
12. Two excellent reviews on thiyl radicals and their addition to triple bonds have been published recently: (a) Chatgilialoglu, C., Guerra, M. In *The Chemistry of Sulfur-containing Functional Groups, Supplement S.* Patai, S.; Rappoport, Z., Eds. John Wiley & Sons, Chichester, 1993, p. 363. (b) Chatgilialoglu, C.; Ferreri, C. In *The Chemistry of Triple-bonded Functional Groups, Supplement C2.* Patai, S. Ed. John Wiley & Sons, Chichester, 1994, p. 917.
13. Mechanism of addition of thiyl radicals to acetylenes was considered also in: (a) Benati, L.; Montevecchi, P.C ; Spagnolo, P. *J.Chem.Soc., Perkin Trans. 1* **1991**, 2103. (b) Benati, L.; Capella L.; Montevecchi, P.C ; Spagnolo, P. *J.Org.Chem.* **1994**, *59*, 2103.
14. Goto, H. *Tetrahedron* **1992**, *48*, 7131.
15. Strelenko, Yu.A.; Samoshin, V.V.; Troyansky, E.I.; Demchuk, D.V.; Dmitriev, D.V.; Nikishin, G.I.; Zefirov, N.S. *Tetrahedron* **1994**, *50*, 10107.
16. Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, New York, 1965.
17. (a) Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J.; Sen, D. *Chem. Rev.* **1985**, *85*, 271. (b) Cooper, S.R. *Acc. Chem. Res.* **1988**, *21*, 141. (c) Desper, J.M.; Powell, D.R.; Gellman, S.H. *J. Amer. Chem. Soc.* **1990**, *112*, 4321. (d) Rawle, S.C.; Cooper, S.R. *Structur. Bonding (Berlin)* **1991**, *72*, 1. (e) Blake, A.J.; Holder, A.J.; Reid, G.; Schroeder, M. *J. Chem. Soc., Dalton Trans.* **1994**, 627. (f) Champness, N.R.; Jacob, S.R.; Reid, G.; Frampton, C.S. *Inorg. Chem.* **1995**, *34*, 396.
18. (a) Setzer, W.N.; Tang, Y.; Grant, G.J.; Vanderveer, D.G. *Inorg. Chem.* **1991**, *30*, 3652. (b) Meier, H.; Dai, Y. *Tetrahedron Lett.* **1993**, *34*, 5277. (c) Edema, J.J.H.; Buter, J.; Kellogg, R.M. *Tetrahedron* **1994**, *50*, 2095 See also (d) Singh, H.; Kumar, M.; Singh, P.; Kumar, S. *Indian J. Chem.* **1991**, *30B*, 237.
19. Tan, L.C.; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* **1992**, *33*, 7709.
20. Charette, A.B.; Marcoux, J.-F. *Tetrahedron Lett.* **1993**, *34*, 7151.
21. Clive, D.L.J.; Manning, H.W.; Boivin, T.L.B.; Postema, M.H.D. *J.Org.Chem.* **1993**, *58*, 6857.
22. Robinson, W.; Sheldrick, G.M. SHELX in *Crystallographic Computing Techniques and New Technologies*. Isaaks, N.W.; Taylor, M.R. Eds.; Oxford Univer. Press: Oxford, 1988, p. 366.

(*Received in UK* 27 *June* 1995; *revised* 25 *August* 1995; *accepted* 1 *September* 1995)