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Efforts toward Distorted Spiropentanes[†,‡]

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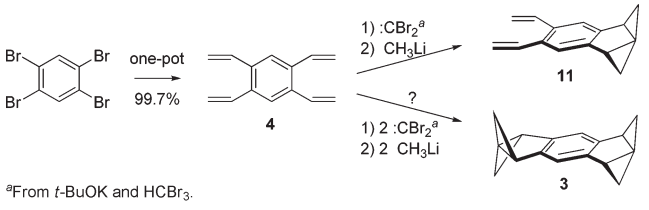

Tetravinylbenzene **4** was prepared in nearly quantitative yield from commercially available tetrabromobenzene; the improved, one-step procedure now employs Suzuki−Miyaura cross-coupling conditions. Intermolecular cyclopropanation of **4** with dibromocarbene gave a series of *gem*-dibromide adducts. Intramolecular cyclopropanation of monoadduct **5**, putatively by its methyllithium-generated cyclopropylidene(oid), produced compound **11**, which features a highly distorted spiropentane having a C−C−C bond angle of 163.5°. The stability of the reported spiropentanes was investigated using DFT calculations.

Tricyclo[4.1.0.0^{1,3}]hept-4-ene (**1**),[1] like other small bridged alicyclic molecules,[2] has aesthetic appeal (Figure 1), but its alluring beauty has eluded synthesis due to its high strain energy.[1] Regardless, tricyclo[4.1.0.0^{1,3}]heptane has been prepared by Skattebøl,[3] who reported the first intramolecular addition of a cyclopropylidene(oid)[4] to a double bond.[5] Thus, we were encouraged by this strategic milestone, which generates the corresponding carbenoid intermediate[6] by reaction of its *gem*-dibromocyclopropane precursor with methyllithium. Besides its elegance, another incentive for studying olefin **1** resides in its nearly collinear arrangement of three carbon atoms,[7] which includes the spiro atom of the distorted spiropentane segment.[8] Furthermore, various rearrangements of unstable **1** to lower-energy isomers were observed.[1] However, as noted, all experimental attempts to isolate **1** have failed,[1] as corroborated by computational evidence.[9] Nevertheless, Brinker and Streu did successfully prepare 4,5-benzotricyclo[4.1.0.0^{1,3}]hept-4-ene (**2**),[10] which retains the two sp^2 carbon centers of the double bond of **1** (Figure 1). Delocalization of the juxtaposing alkene function within the aromatic ring stabilizes the tricycloheptene moiety. Hence, **2** is isolable at room temperature, although it quantitatively isomerizes at 30 °C with a measurable rate constant.[11]

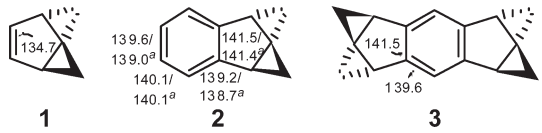

FIGURE 1. Calculated bond lengths in picometers (B3LYP/6-31G(d)) of **1**, **2**, and **3** ([a]X-ray data[12]).

In order to study the influence of the spiropentane moiety on the bond lengths of the attached benzene ring, a single crystal X-ray structure determination of **2** was performed.[12] The annulated bond of the benzene ring was found to be elongated to 1.414 Å, and the distances of the other C−C bonds tended toward one Kekulé structure, i.e., **2** (Figure 1).

We wanted to determine the consequences of placing a second spiropentane moiety on the opposite side of the benzene ring of **2**. In addition, we set out to investigate the influence of the geometry on the stability and bonding characteristics of this molecule and possibly its rearrangement behavior. Therefore, we first embarked on the synthesis of the aesthetically appealing bisspiropentane **3**, which can exhibit *meso*, *d*, and *l* forms (Figure 1).[13] We also explored theoretical aspects of **3**, using computations correlated with experimental results.

[†] Dedicated to my distinguished colleague, Professor John J. Eisch, Department of Chemistry, SUNY-Binghamton, USA, on the occasion of his 80th birthday (UHB).

[‡] Carbene Rearrangements 81. For part 80, see: Mieusset, J.−L.; Brinker, U. H. In Molecular Encapsulation: Organic Reactions in Constrained Systems; Brinker, U. H., Mieusset, J.−L., Eds.; Wiley: Chichester, 2010; pp 269−308.

(1) (a) Brinker, U. H.; Gomann, K.; Zorn, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 869. (b) Brinker, U. H.; Gomann, K.; Zorn, R. *Angew. Chem. Suppl.* **1983**, 1241 and references therein.

(2) (a) Wiberg, K. B. *J. Am. Chem. Soc.* **1983**, *105*, 1227. (b) de Meijere, A. In *Houben-Weyl, Methods of Organic Chemistry*; Thieme: Stuttgart, 1996; Vol. E17a-d, pp 1−3635. (c) Takeuchi, K.; Horiguchi, A.; Inagaki, S. *Tetrahedron* **2005**, *61*, 2601 and references therein. (d) Minyaev, R. M.; Minkin, V. I. *Russ. J. Gen. Chem.* **2008**, *78*, 732. (e) Keese, R. *Chem. Rev.* **2006**, *106*, 4787.

(3) Skattebøl, L. *Chem. Ind.* (*London*) **1962**, 2146.

(4) Azizoglu, A.; Balci, M.; Mieusset, J.−L.; Brinker, U. H. *J. Org. Chem.* **2008**, *73*, 8182.

(5) Backes, J.; Brinker, U. H. In *Houben−Weyl, Methoden der Organischen Chemie*; Regitz, M., Ed.; Thieme: Stuttgart, 1989; Vol. 19b, 391−510.

(6) Jones, M., Jr.; Moss, R. A. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Jr., Eds.; Wiley: Hoboken, 2004; pp 273−328.

(7) Dodziuk, H.; Leszczyński, J.; Nowiński, K. S. *J. Org. Chem.* **1995**, *60*, 6860.

(8) Kuznetsova, T. S.; Eremenko, O. V.; Kokoreva, O. V.; Zatonsky, G. V.; Zefirov, N. S. *Russ. Chem. Bull.* **1996**, *45*, 1662.

(9) Wiberg, K. B.; Snoonian, J. R. *J. Org. Chem.* **1998**, *63*, 1390 and references therein.

(10) Brinker, U. H.; Streu, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 631.

(11) (a) Brinker, U. H.; Wilk, G.; Gomann, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 868. (b) Brinker, U. H.; Wilk, G.; Gomann, K. *Angew. Chem. Suppl.* **1983**, 1228.

(12) Boese, R.; Bläser, D.; Gomann, K.; Brinker, U. H. *J. Am. Chem. Soc.* **1989**, *111*, 1501.

(13) For reasons of simplicity, only one of the possible stereoisomers is shown in the Abstract and Figure 1.

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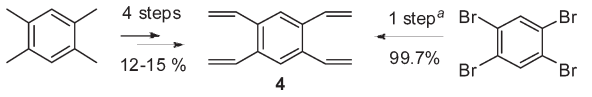
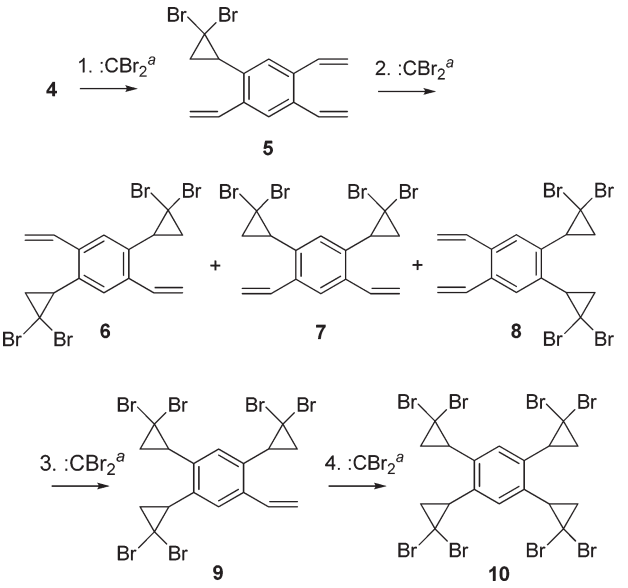
SCHEME 1. Procedures for the Synthesis of 1,2,4,5-Tetravinylbenzene (4)



[a]Trivinylboroxane complex, $Pd(OAc)_2$, PPh_3, K_2CO_3, DME/H_2O, 100 °C, 24 h.

SCHEME 2. Dibromocarbene Addition to 4

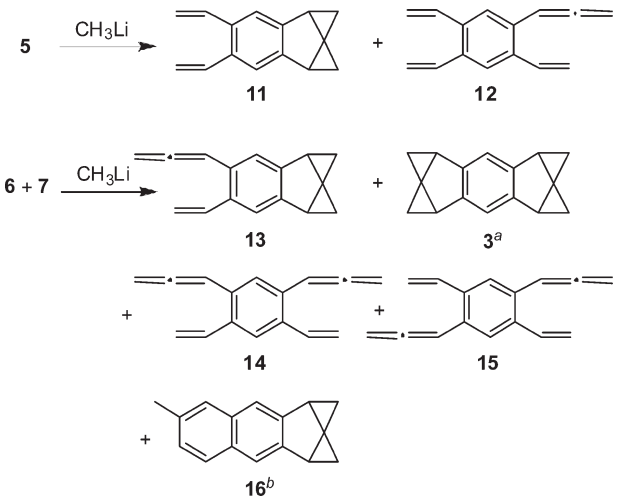


[a]From *t*-BuOk and $HCBr_3$

We surmised that 1,2,4,5-tetravinylbenzene (**4**)[14] would be an appropriate starting material for the construction of two spiropentane subunits (Scheme 1), because the analogous *o*-benzeno-bridged spiropentane **2** was synthesized from *o*-divinylbenzene.[10] We envisioned a 2-fold intramolecular cyclopropylidene(oid) addition to the proximal double bonds of the intermediary bisadduct(s) **6** and/or **7** (Scheme 2) to furnish bisspiropentane **3** (Scheme 3).

The established procedure for **4** begins with 1,2,4,5-tetramethylbenzene and affords the compound in four steps with an overall yield of 12−15%[14a] (Scheme 1). However, we developed a more efficient synthetic route, exploiting Suzuki−Miyaura cross-coupling,[15] that yields a larger supply of **4** in just one step. Substitution of the four bromine atoms in 1,2,4,5-tetrabromobenzene by vinyl groups was readily achieved, and optimization of the reaction conditions led to tetravinylbenzene **4** with an almost quantitative yield.

SCHEME 3



[a]Not observed. [b]When using fresh silica gel.

TABLE 1. Product Distributions[a] from Dibromocarbene Reactions with 1−6 equiv of Bromoform

compound	1 equiv	2 equiv	3 equiv	4 equiv	5 equiv	6 equiv
4	84	39	22	9	17	2
5	11	18	17	18	15	8
6	1	2	3	5	3	4
7	1	1	1	3	1	4
8	2	3	4	6	4	5
9	1	2	5	9	4	8
10	0	35	48	50	56	69

[a]Determined by ^{1}H NMR peak integration of crude mixtures.

The conversion requires heating of the reactants at 100 °C in DME/H_2O for 24 h in an autoclave apparatus.

Regrettably, the subsequent dibromocarbene addition[16] lacks selectivity, and for a series of dienes,[17] indiscriminate additions were reported. Depending on the molar ratio of the generated dibromocarbene, the reaction with **4** (Scheme 2) gave a complex mixture of starting material and mono-, bis-, tris-, and tetrakisadducts (Table 1).

Chromatographic separation of **5**−**10** allowed the hitherto unknown dibromocarbene adducts to be characterized. The separation of isomers **6** and **7**,[18] which have nearly identical retention times, was achieved by repeated chromatography. Single crystals of bisadducts **7** and **8** were obtained and analyzed by X-ray diffraction. Crystals of two stereoisomers of tetrakisadduct **10** were suitable for X-ray analysis as well. In contrast, no crystals suitable for X-ray analysis could be obtained for monoadduct **5** and trisadduct **9**.

To investigate the dependence of product distribution on the molar ratio of tetravinylbenzene **4** and the dibromocarbene precursor, e.g., bromoform, a test series was run. Six reaction compositions starting with 1−6 equiv of bromoform were analyzed. The relative product distributions of the samples were determined by peak area integrations of ^{1}H NMR spectra of each crude reaction mixture directly after workup. As expected, six dibromocarbene adducts (and their

(14) (a) Schrievers, T.; Brinker, U. H. *Synthesis* **1988**, 330. (b) Nakamura, Y.; Haashida, Y.; Wada, Y.; Nishimura, J. *Tetrahedron* **1997**, *53*, 4593.

(15) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (e) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (f) Mantel, M. L. H.; Søbjerg, L. S.; Huynh, T. H. V.; Ebran, J. P.; Lindhardt, A. T.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 3570.

(16) (a) Dehmlow, E. V. In *Houben−Weyl, Methoden der Organischen Chemie*; Regitz, M., Ed.; Thieme: Stuttgart, 1989; Vol. 19b, p 1461. (b) Doering, W. v. E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162. (c) Su, K.−J.; Mieusset, J.−L.; Arion, V. B.; Brecker, L.; Brinker, U. H. *Org. Lett.* **2007**, *9*, 113.

(17) (a) Skattebøl, L. *J. Org. Chem.* **1964**, *29*, 2951. (b) Brinker, U. H.; Fleischhauer, I. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 396.

(18) The methine protons of the cyclopropane rings of both isomers are positioned either on the same or on different sides.

stereoisomers), including the 4-fold addition product **10**, were obtained plus some unreacted **4** (Scheme 2). Table 1 shows the dependence of the product ratios in relation to the equivalents of bromoform used. However, it should be taken into consideration that the effective in situ generated dibromocarbene concentration may be lower than the actual bromoform quantity used.

To accumulate monoadduct **5** and bisadducts **6** and **7** in one experiment, the use of 4 equiv of $HCBr_3$ was optimal.

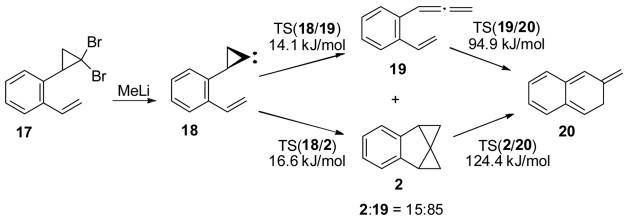
The decisive step in constructing the spiropentane subunit is an intramolecular cyclopropanation of the vinyl group. This was achieved by adding methyllithium to monoadduct **5** at −78 °C and allowing the temperature to rise overnight to 9 °C (Scheme 3).[19] This procedure did indeed yield the expected spiropentane **11** and allene **12** in a ratio of 70:30 after chromatography. Using NMR, the half-lives were determined to be nearly the same ($t_{1/2}$ = ca. 24 h at room temperature). The low isolated yield, i.e., 19%, of the isomeric mixture of **11** and **12** may be due to the known instability of styrenes, which tend to polymerize.

Accordingly, treatment of either bisadduct **6** or **7** with methyllithium, under the same conditions applied for **5**, should lead to a 2-fold intramolecular cyclopropylidene addition giving bisspiropentane **3**. Thus, a mixture of **6** and **7** could be used for further reaction (Scheme 3). The crude product resulting from the cyclopropanation reaction of mixed **6** and **7** showed, however, mostly broad ^{1}H NMR signals that are likely due to polymers. Chromatography on silica gel afforded a 15% isolated yield of an isomeric mixture of spiroallene **13** and bisallenes **14** and **15**. The **13**:**14**:**15** product distribution was determined by ^{1}H peak integration to be 68:23:9, and their structures were determined by 2D NMR techniques. Curiously, no evidence for the desired bisspiropentane **3** was found under the conditions applied. We also noted, when using fresh silica gel, that methylnaphthalene **16** was found in the mixture. It can arise from an electrocyclization of **13** followed by rearomatization via a 1,3-H shift. Alternatively, a retro-Diels–Alder reaction (rDA) of one tricyclo[4.1.0.0^{1,3}]hept-4-ene subunit would also lead to **16** (vide infra).

The feasibility of the aforementioned spirocyclizations was assessed by ab initio molecular orbital calculations. Electron-correlated single-point energies were computed using the hybrid DFT method B3LYP and a split-valence 6-31G(d) basis set.[20] We first performed computations using 2-(2-ethenylphenyl)cyclopropylidene (**18**) as an unsubstituted model compound and then compared the results with those from experimental data (Scheme 4).[10] Carbene **18** is predicted to form spiropentane **2** by energetically overcoming a low activation barrier of 16.6 kJ/mol, but rearrangement of **18** to allene **19** is expected to be even faster, i.e., E_a = 14.1 kJ/mol. Indeed, these values are compatible with the observed ratio of **2**:**19** at 25 °C, i.e., 15:85.[10]

Statistical considerations reveal that this adverse ratio of spirocycle to allene offers only a small opportunity for the construction of a second spiropentane to form bisspiropentane **3**. Therefore, we presumed the same product distributions from the competitive cyclopropylidene–allene rearrangement

SCHEME 4. Experimental Ratio[10] and Results of DFT Computations for the Synthesis of Spiropentane 2 and Its Rearrangement to 20



and the cyclopropylidene addition to give spiropentane for the methyllithium reaction of bisadducts **6** and **7**. For two consecutive reactions of the aforementioned type, the statistic predicts a product distribution of allenes **14** + **15** to monospiropentane **13** to bisspiropentanes **3** in a ratio of 72:26:2. Combining these assumptions with the experimentally obtained total isolated yield of 15% for the product mixture from the reaction of **6** and **7**, compound **3** would be produced in a low yield of 0.3% (15% × 2% = 0.3%).

However, the synthesis of **3** might be viable using transition-metal catalysis, thereby minimizing the occurrence of competing cyclopropylidene–allene rearrangements. This entails that extrusion of the second bromine nucleofuge should be induced by nucleophilic attack of the nearby vinyl group.

Next, a closer inspection of the effect of benzene ring bifunctionalization by two spiropentylene groups was undertaken.[12] Calculations for bisspiro compound **3** gave essentially the same results as those for monospiro compound **2**. Compared with **3**, only one barrier is slightly lower in energy than in **2**. It involves the decomposition by a rDA that is energetically less favorable for **2** than for **3** [TS(**2**/**20**) 124.4 kJ/mol vs 120.7 kJ/mol]. Consequently, **3** is expected to be kinetically less stable than **2**. An explanation can be found in the bond order[21] of the C–C bonds of the aromatic ring. In contrast to **2**, the alternation of shortened and lengthened C–C bonds in **3** is rather suitable for the generation of the central cyclohexadiene subunit of the rDA product (Figure 1). *exo*-Methylene **20** is thermodynamically unstable and partially rearranges to methylnaphthalene.[11] Finally, in all of the synthesized spiropentanes, the augmentation of the C–C–C bond angle remains similar [**2**, 163.6° (164.0° experimentally[12]); **3**, 163.6°; **11**, 163.5°; **16**, 163.2°].

In conclusion, the highly distorted spiropentane **11** was prepared in only three steps from commercially available 1,2,4,5-tetrabromobenzene. Compound **11** possesses an almost linear arrangement of three C atoms with a C–C–C bond angle of 163.5° about the spiro atom. Thus far, bisspiro compound **3** has not been obtained. Statistical considerations and theoretical calculations provided insight into the difficulties of the formation and instability of **3**. The use of carbenoid reactions induced by transition-metal catalysis may help to prevent the competitive formation of allenes. And finally, an efficient procedure giving **4** in nearly quantitative yield, i.e., 99.7%, is introduced.

Experimental Section

1,2,4,5-Tetravinylbenzene (4). 1,2,4,5-Tetrabromobenzene (776 mg, 2 mmol), $Pd(OAc)_2$ (89 mg, 0.4 mmol), PPh_3 (270 mg,

(19) The intramolecular addition reaction of the generated carbene(oid) intermediate is temperature-dependent and competes with the cyclopropylidene–allene rearrangement; a lower temperature range favors production of the spirocyclic compound.

(20) The energy values given represent E + ZPVE.

(21) Stanger, A. *J. Am. Chem. Soc.* **1998**, *120*, 12034.

TABLE 2. Compositions for Dibromocarbene Reactions

equiv of $HCBr_3$	A	B	C
1	195 mg	90 mg (0.75 equiv)	0.93 mL (1 equiv)
2	319 mg	294 mg (1.5 equiv)	3.03 mL (2 equiv)
3	338 mg	468 mg (2.25 equiv)	4.82 mL (3 equiv)
4	331 mg	611 mg (3 equiv)	6.29 mL (4 equiv)
5	203 mg	468 mg (3.75 equiv)	4.82 mL (5 equiv)
6	328 mg	908 mg (4.5 equiv)	9.35 mL (6 equiv)

1 mmol), K_2CO_3 (1100 mg, 8 mmol), and 2,4,6-trivinylcyclotriboroxane pyridine complex (1.465 g, 6 mmol) were added to an autoclave apparatus with 1,2-dimethoxyethane (ethylene glycol dimethyl ether) (35 mL) and H_2O (10 mL) as solvents. The closed autoclave apparatus was heated to 95−100 °C for 24 h and then cooled to room temperature. The crude reaction mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. Bulb-to-bulb distillation of the crude product *in vacuo* (0.01 mmHg) at 75 °C afforded the title compound as a white solid (during distillation cooled by dry ice), which melts to a clear colorless liquid (361 mg, 99.7%). Data for **4**: see the Supporting Information.

Dibromocarbene Addition to 1,2,4,5-Tetravinylbenzene (4). To a mixture of A mg of 1,2,4,5-tetravinylbenzene and B mg of potassium *tert*-butoxide in ca. 150 mL of dichloromethane, C mL of a dichloromethane/bromoform (1:9) solution was added dropwise while cooling with an ice−salt bath (see Table 2). Stirring was continued overnight, while the reaction mixture was allowed to warm to room temperature. Next, ca. 200 mL of water was added, the organic phase was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water and dried over $MgSO_4$. The solvent was evaporated, and the compounds contained in the crude mixture of **4**−**10** were separated by column chromatography with hexane as an eluant. Data for **5**−**10**: see the Supporting Information.

Reaction of 1-(2,2-Dibromocyclopropyl)-2,4,5-trivinylbenzene (5) with Methyllithium. 1-(2,2-Dibromocyclopropyl)-2,4,5-trivinylbenzene (**5**, 282 mg, 0.8 mmol) was dissolved with 50 mL of dry ether and cooled in a dry ice−acetone bath at −78 °C. A fresh ethereal solution of methyllithium (∼1.6 M, 1.13 mL, 2.25 equiv) was added by syringe with stirring. The reaction mixture was further stirred overnight (from −78 to 9 °C) and then quenched with water. The reaction mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. By using column chromatography with hexane as eluant, a mixture of spiro compound **11** and allene **12** was obtained (30 mg, 19% of **11** and **12**). Ratio as determined by ^{1}H NMR peak integration: **11**:**12** = 70%:30%. NMR signal allocation for **11** and **12** was verified by 2D NMR techniques. Data for **11** and **12**: see the Supporting Information.

Reaction of Bisadducts 6 and 7 with Methyllithium. Bisadducts **6** and **7** (258 mg, 0.49 mmol) were dissolved with 100 mL of dry ether and cooled in a dry ice−acetone bath at −78 °C. A fresh ethereal solution of methyllithium (∼1.6 M, 1.55 mL, 5 equiv) was added by syringe with stirring. The reaction mixture was further stirred overnight (from −78 to 9 °C) and then quenched with water. The reaction mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. Column chromatographic separation with hexane as eluant gave a mixture of the spiro compound **13** and the corresponding allene isomers **14** and **15** (15 mg, 15% of **13**, **14**, and **15**). Ratio determined by ^{1}H NMR peak integration: **13**:**14**:**15** = 68:23:9. When using fresh, untreated silica gel for chromatography, the rearranged product **16** was also obtained. NMR signal allocation for **13**−**16** was verified by 2D NMR techniques. Data of **13**−**16**: see the Supporting Information.

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Supporting Information Available: Spectral data of all new compounds and crystallographic data in CIF format for **7**, **8** and two stereoisomers of **10** and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.