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# Stereoselective Carbenoid Cyclization Reactions

**Hans Christian Stiasny, Volker P. W. Böhm, and Reinhard W. Hoffmann***

Fachbereich Chemie, Philipps-Universität Marburg,
Hans-Meerwein-Straße, D-35032 Marburg, Germany

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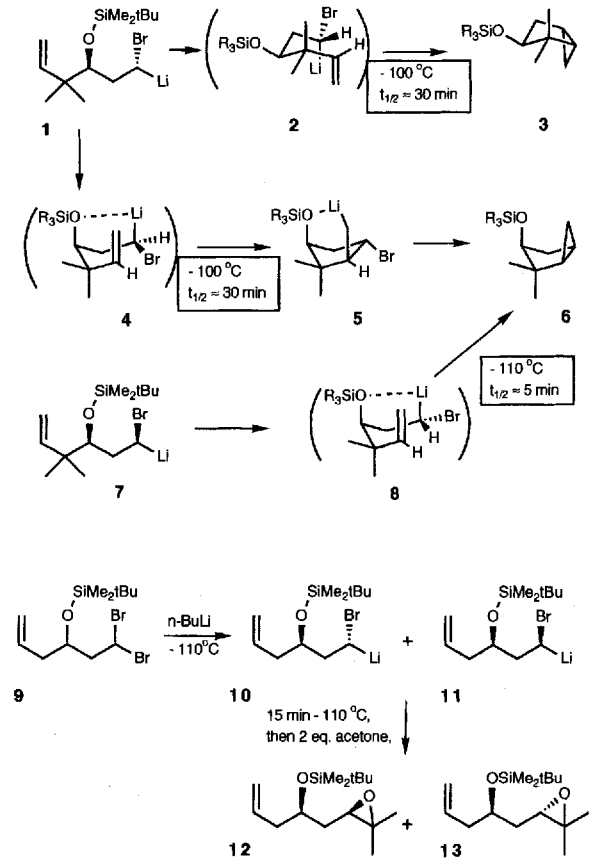
The dichotomy between concerted cyclopropanation and carbolithiation pathways on intramolecular carbenoid cyclopropanation reactions has been studied. These studies have been extended to the intramolecular carbenoid/aldehyde addition reaction.

The cyclopropanation of alkenes by α-halogeno-alkylmetallic species is a widely used reaction[2] in preparative chemistry. In a preceding study[3] we addressed the stereochemistry of this process, which gave hints as to the mechanistic pathways of the cyclopropanation reaction. Starting from the two diastereomeric α-bromoalkyllithium compounds **1** and **7** we discovered that three distinct mechanistic pathways are followed. Thus, it was found that at −100 °C **1** undergoes both a concerted intramolecular carbenoid cyclopropanation via the arrangement **2** to give the bicyclohexane **3**, and a Lewis base assisted[4] intramolecular carbolithiation via the arrangement **4** to give a presumed intermediate **5**, which eventually closes the ring to the stereoisomeric bicyclohexane **6**. In the case of the diastereomeric carbenoid **7**, no reaction via a carbolithiation pathway could be detected, since a very rapid ($t_{1/2}$ = 5 min at −110 °C) Lewis base-assisted carbenoid cyclopropanation via an arrangement **8** occurred to give the bicyclohexane **6**. These findings reflect a delicate balance of reaction rates between carbenoid cyclopropanation and carbolithiation processes on the one hand and Lewis base assisted and unassisted processes on the other. It is anticipated that structural variations will markedly affect the partitioning between these various reaction pathways. For this reason we studied the intramolecular cyclopropanation reactions of structural analogs of **1** and **7**.




### Conformational Preorganization to Cyclization

We surmised that the geminal dimethyl group present in the carbenoids **1** and **7** is critical to facilitate the cyclization reactions due to the well-known geminal dimethyl effect[5]. In order to see to what extent the geminal dimethyl substitution is essential to the intramolecular cyclopropanation reaction, we tested the behavior of the carbenoids **10** and **11**, which lack the geminal disubstitution.

The carbenoids **10** and **11** were generated by treatment of the dibromo compound **9** with *n*-butyllithium at −110 °C, and could be trapped after 15 min at −110 °C by addition of acetone to give the diastereomeric epoxides **12** and **13** in a 70:30 ratio. Thus, in contrast to the carbenoids **1** and **7**, neither of the carbenoids **10** and **11** cyclized to bicyclohexanes at that temperature. In a further experiment the carbenoids **10** and **11** were kept for 1 h at −90 °C before acetone was added.

Under these conditions, adduct **13** was no longer obtained. The formation of the bicyclohexane **14** suggests that a Lewis base assisted concerted cyclopropanation of the carbenoid **11** had occurred. The diastereomeric carbenoid **10** persisted even at −90 °C and was trapped to give the epoxide **12** in 40% yield. Thus the presence or absence of the geminal dimethyl group has a strong effect on the tendency to undergo intramolecular cyclopropanation reactions.

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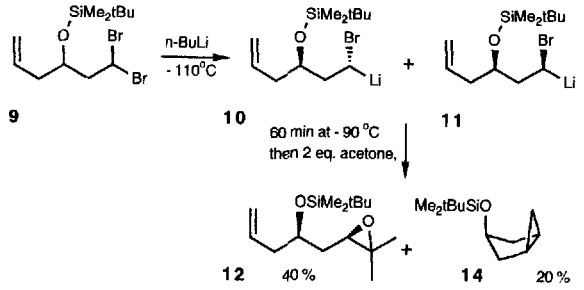
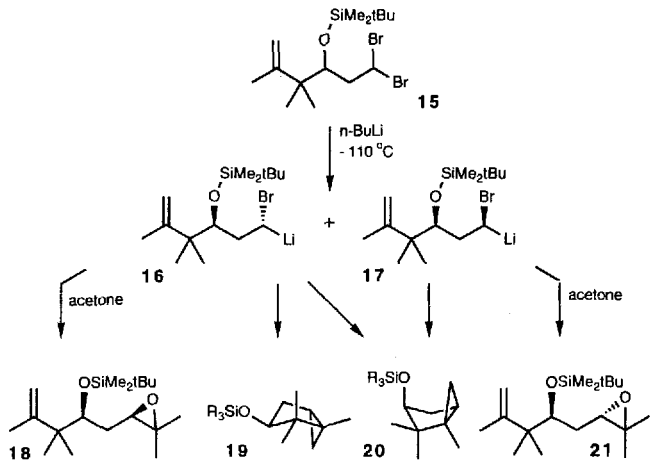



For example, for the carbenoid **7** the reaction occurs at a temperature 20 °C lower than for carbenoid **11**.

### Substituents at the Double Bond

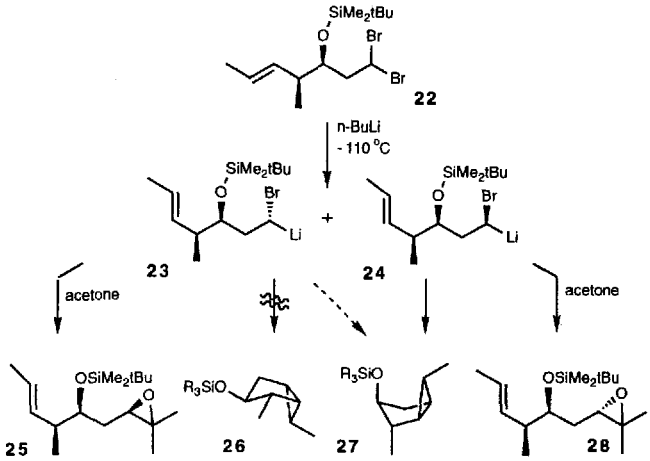
If the concerted cyclopropanation reaction of carbenoids is triggered by interaction of the π-HOMO orbital of the double bond with the σ*-orbital of the C–Br bond of the carbenoid[6], we would expect that a more nucleophilic, i.e. more highly substituted, double bond should undergo the cyclization more readily. To test this prediction, we generated the carbenoids **16** and **17** from the dibromo compound **15**[7]. In situ trapping with acetone led to the epoxides **18** and **21** in a 91:9 ratio[7]. The results of several cyclization experiments of the carbenoids **16** and **17** are summarized below.




| | | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|
| −110 °C | acetone in situ | 71% | – | – | 7% |
| −110 °C | acetone after 60 min | 27% | 5% | 26% | – |
| −120 °C | acetone after 15 min | 69% | – | 22% | – |
| −110 to −90 °C | " | – | 22% | 58% | – |

It was found that the Lewis base assisted concerted cyclization of **17** to **20** proceeds already at −120 °C whereas the cyclization of **7** required a minimum temperature of −110 °C. Likewise, the concerted cyclization of **16** proceeded at a lower temperature (−110 °C) than that of **1** to give **3** (−100 °C). Finally, also the carbolithiation reaction leading from **16** to **19** occurred at a lower temperature (−110 °C) than that of **1** to **4** (−100 °C). Thus, 1-methyl substitution in the alkene moiety accelerates both the carbolithiation and the concerted cyclopropanation processes.

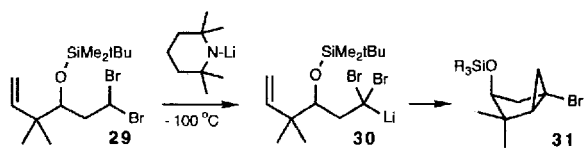
Placement of a methyl group at the terminal position of the double bond should likewise accelerate the concerted cyclopropanation reaction, but could, in turn, retard a carbolithiation process[8]. In order to evaluate this prediction, we examined briefly the behavior of the carbenoids **23** and **24**.




The latter were generated from the dibromo compound **22** at −110 °C in the presence of acetone, resulting in the formation of the epoxides **25** and **28** (84% yield) in a ratio of 82:18. When the carbenoids **23** and **24** were generated first at −110 °C followed by addition of acetone after 15 min, the stereochemically pure epoxide **25** derived from the carbenoid **23** was obtained (38%) as well as the stereochemically pure bicyclohexane **27** (31%). This is in line with a rapid cyclization of **24** to give **27** and a retarded cyclization of **23**. When the carbenoids **23** and **24** were left for 2 h at −90 °C before acetone was added, no epoxide was obtained; the sole product was the bicyclohexane **27** in 62% yield. The absence of the other bicyclohexane **26** was certainly unexpected. This result leaves the question open, of whether the carbenoid **23** cyclizes to **27** via a carbolithiation pathway or whether **23** is slowly epimerized[9] to the epimeric carbenoid **24**, which then cyclizes rapidly to the bicyclohexane **27**.

### Changes of the Carbenoid Moiety

Carbenoid reactivity may be altered by substituents at the carbenoid center. Such a modification can be realized by a change to the dibromo carbenoid **30**. The latter was generated by deprotonation of the dibromo compound **29** with lithium tetramethylpiperidide[10] at −110 °C.



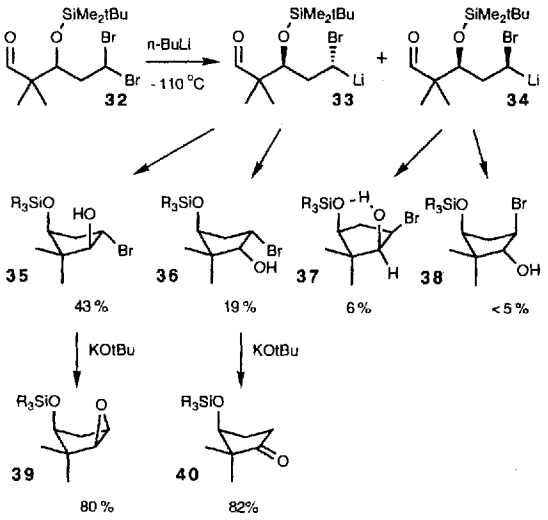

When $CH_3OD$ was added after 3 h at −100 °C, ca. 20% of the bicyclohexane **31** was obtained. The rest of the

material was recovered **29**, formed in part by deuteration of unreacted **30**. Complete conversion of **30** into the bicyclohexane **31** could be achieved by letting the solution of the carbenoid **30** warm to −50°C. In this way the bicyclohexane **31** could be isolated in 78% yield after addition of methanol. The bicyclohexane **31** was formed as a single diastereomer, with the trimethylsilyloxy group in the *endo* position. This indicates that the bicyclohexane is formed in a Lewis base-assisted process, but it does not reveal whether this is a Lewis base-assisted carbolithiation reaction, cf. **1** → **6** or a Lewis base assisted intramolecular carbenoid cyclopropanation, cf. **7** → **6**.

### Intramolecular Carbenoid Aldehyde Additions

In the examples discussed so far the lithium carbenoid was added to a C=C bond. An intramolecular carbenoid addition to an aldehyde function, although mechanistically different, would at least be topologically equivalent to the cyclization of the carbenoid **1** to the lithium compound **5**.

The dibromoaldehyde **32** was obtained by ozonolysis of **29**. Reaction of the dibromoaldehyde **32** in a Trapp solvent mixture at −100°C with *n*-butyllithium generated the carbenoids **33** and **34**, which underwent intramolecular addition during 15 min at −110°C to give all four possible diastereomeric products **35**–**38** in 71% yield.




The structure of the major product **35** is suggested by its conversion to an epoxide **39**, which showed very similar coupling constants to those of the bicyclohexane **6**. The second isomer, **36**, underwent smooth base-induced dehydrobromination to the ketone **40**, involving a 1,2-hydride shift[11]. This establishes a *cis* arrangement of the hydroxy and bromo substituents in **36**. The relative configuration regarding the center with the silyloxy group is only tentative and assumes that the carbenoid **33** is formed in large predominance over **34**, as for similar substrates under in situ trapping conditions[7]. The diastereomer **37** finally displayed an unusual 10.1 Hz H−C−O−H coupling constant, indicative of an intramolecular hydrogen bond as depicted. Since the structure of the other *cis*-dioxy isomer **35** had already been assigned, the structure of **37** follows by exclusion.

GC determination of the product ratio (**35**/**36**/**37**/**38** = 60:27:8:<5) suggests that bromine−lithium exchange on **32** to form the carbenoids **33** and **34** falls within the usual range[7] of such diastereoselectivities (ca. 90:10). Subsequent reactions of the carbenoids **33** and **34**, however, proceeded with low (ca. 2:1) stereoselectivity to furnish all possible bromohydrins **35**–**38**.

The rather nondiscriminate stereochemistry in the cyclization of **33** and **34** differentiates this reaction from the carbenoid cyclopropanation reactions discussed before. The question remains open, as to what extent an intramolecular coordination of the alkyllithium moiety to the aldehyde group is the reason for the different stereochemical preferences.

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## Experimental Section

*General:* All temperatures quoted are uncorrected. Low temperatures (−100°C) were determined with a GTH 215 precision digital thermometer of Fa. Greisinger, Regenstauf, Germany. Reactions with the carbenoids were carried out in a two-chamber low-temperature reaction vessel[3] under nitrogen or argon. – $^1$H and $^{13}$C-NMR: Bruker AC-300. – Boiling range of petroleum ether: 40–60°C. – pH 7 Buffer: 56.2 g $NaH_2PO_4 \cdot 2\,H_2O$ + 213.2 g $Na_2HPO_4 \cdot 2\,H_2O$ in 1.0 l of water. – Flash chromatography: Silica gel Si 60 E. Merck AG, Darmstadt, 40–63 μm. – MPLC: 30 × 2.5 cm column with LiChroprep Si 60, E. Merck AG, Darmstadt, 15–25 μm, 8 bar. – Analytical gas chromatography: Siemens Sichromat 3 with a 30 m × 0.3 mm quartz capillary column with SE 52, 1 bar He, temperature program 5 min at 100°C, subsequent increase with 10°C/min to 230°C.

(1) *1,1-Dibromo-3-(tert-butyldimethylsilyloxy)-5-hexene* (**9**): To a solution of 1.31 g (5.1 mmol) of 1,1-dibromo-5-hexen-3-ol[7] and 1.04 g (15.3 mmol) of imidazole in 5 ml of dimethylformamide was added 1.15 g (7.6 mmol) of *tert*-butyldimethylchlorosilane. After stirring for 4 h, 1 ml of ethanol was added and stirring was continued for 5 min. 10 ml of water was added, the phases were separated, and the aqueous phase was extracted with petroleum ether (4 × 5 ml). The combined organic phases were washed with 10 ml of brine and concentrated in vacuo. Flash chromatography (petroleum ether) of the residue afforded 1.78 g (94%) of dibromide **9** as a colorless oil. – $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 2.24–2.28 (m, 2H), 2.40–2.54 (m, 2H), 3.87–3.95 (m, 1H), 5.03–5.10 (m, 2H), 5.69 (dd, *J* = 9.2 and 4.6 Hz, 1H), 5.71–5.83 (m, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.1, 18.0, 25.9 (3 C), 41.7, 43.4, 52.4, 70.2, 118.1, 133.3. – $C_{12}H_{24}Br_2OSi$ (372.2): calcd. C 38.72, H 6.50; found C 38.90, H 6.42.

(2) *4-(tert-Butyldimethylsilyloxy)-6,7-epoxy-7-methyl-1-octene* (**12** and **13**): 0.65 ml (1.09 mmol) of a 1.67 M solution of *n*-butyllithium in hexane and 1 ml of a Trapp solvent mixture[12] were precooled to −110°C in a two-chamber low-temperature reaction vessel[3]. This solution was added dropwise to a precooled solution of 270 mg (0.73 mmol) of the dibromo compound **9** in 5 ml of the Trapp solvent mixture. After stirring for 15 min a precooled solu-

tion of 0.20 ml (2.7 mmol) of acetone in 2 ml of Trapp solvent mixture was added. Stirring was continued for a further 15 min. The mixture was allowed to warm to 20°C and after stirring for 1 h 10 ml of a pH 7 buffer was added. The phases were separated and the aqueous phase was extracted with petroleum ether (4 × 10 ml). The combined organic phases were washed with 15 ml of brine and concentrated in vacuo. The diastereomer ratio **12/13** was determined by $^1$H or $^{13}$C NMR to be 70:30 in the crude product. Flash chromatography with *tert*-butyl methyl ether/petroleum ether (1:20) yielded 168 mg (86%) of the diastereomeric epoxides as a colorless oil. – $C_{15}H_{30}O_2Si$ (270.5): calcd. C 66.61, H 11.18; found C 66.91, H 11.07. – **12**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.23 (s, 3H), 1.29 (s, 3H), 1.56–1.76 (m, 2H), 2.20–2.29 (m, 2H), 2.86 (t, 6.0 Hz, 1H), 3.85 (quint, 5.9 Hz, 1H), 4.65–5.22 (m, 2H), 5.68–5.89 (m, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −4.9, −4.7, 18.0, 18.9, 24.8, 25.8 (3 C), 35.9, 41.9, 57.6, 61.2, 70.3, 117.2, 134.8. – **13**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.23 (s, 3H), 1.29 (s, 3H), 1.56–1.76 (m, 2H), 2.20–2.29 (m, 2H), 2.82 (dd, *J* = 6.6 and 5.2 Hz, 1H), 3.85–3.92 (m, 1H), 4.65–5.22 (m, 2H), 5.68–5.89 (m, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): −4.9, −4.7, 18.0, 19.0, 24.9, 25.8 (3 C), 36.0, 42.5, 58.3, 61.7, 69.9, 117.2, 134.5.

(3) *endo-3-(tert-Butyldimethylsilyloxy)bicyclo[3.1.0]hexane* (**14**): To a solution of 276 mg (0.74 mmol) of the dibromocompound **9** in 30 ml of a Trapp solvent mixture[12] in a two-chamber low-temperature reaction vessel were added at −110°C 0.65 ml (1.09 mmol) of a precooled 1.67 M solution of *n*-butyllithium in hexane and 2 ml of solvent mixture at −110°C. After stirring for 30 min the mixture was kept for 1 h at −90°C. Then a precooled solution of 0.20 ml (2.7 mmol) of acetone in 2 ml of solvent mixture was added at −110°C. Further treatment and workup was carried out as described under 2. Neither **3** nor **13** could be detected by GC, $^1$H or $^{13}$C NMR. Repeated flash chromatography (*tert*-butyl methyl ether/petroleum ether, 1:20, then petroleum ether) yielded 80 mg (0.30 mmol, 40%) of epoxide **12**, 10 mg (0.03 mmol, 5%) of 1-bromo-3-(*tert*-butyldimethylsiloxy)-5-hexene, and 31 mg (0.14 mmol, 20%) of the bicyclohexane **14** as colorless oils. – **14**: $^1$H NMR (300 MHz, $CDCl_3$): δ = −0.03 (s, 6H), 0.37 (tdt, *J* = 8.2, 4.1, and 1.3 Hz, 1H), 0.61 (q, *J* = 4.0 Hz, 1H), 0.83 (s, 9H), 1.17–1.21 (m, 2H), 1.65 (d, *J* = 13.4 Hz, 2H), 1.97 (dddd, *J* = 13.4, 6.3, 4.3 and 1.3 Hz, 2H), 4.24 (t, *J* = 6.3 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −4.8 (2 C), 10.9 (2 C), 16.7, 17.9, 25.8 (3 C), 38.6 (2 C), 73.7. – $C_{12}H_{24}OSi$ (212.4): calcd. C 67.86, H 11.39; found C 67.69, H 11.50. – 1-Bromo-3-(*tert*-butyldimethylsiloxy)-5-hexene: $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.84–2.09 (m, 2H), 2.2–2.26 (m, 2H), 3.41–3.46 (m, 2H), 3.89 (quint, *J* = 5.8 Hz, 1H), 5.00–5.07 (m, 2H), 5.70–5.84 (m, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.3, 18.1, 25.8 (3 C), 30.5, 39.6, 41.9, 69.7, 117.5, 134.2.

(4) *3-(tert-Butyldimethylsilyloxy)-1,2,2-trimethylbicyclo[3.1.0]-hexanes* (**19** and **20**): 112 mg (0.27 mmol) of the dibromo compound **15**[7], 0.25 ml (0.40 mmol) of a 1.59 M solution of *n*-butyllithium, and finally, after 1 h at −110°C, 0.10 ml (1.4 mmol) of acetone were allowed to react as described under 2. This resulted in a mixture of **18**, **19**, **20** and of 1-bromo-3-(*tert*-butyldimethylsilyloxy)-4,4,5-trimethyl-5-hexene in a 41:7:40:12 ratio determined by GC, $^1$H or $^{13}$C NMR of the crude reaction mixture; no **21** could be detected. Flash chromatography (*tert*-butyl methyl ether/petroleum ether, 1:20) yielded 23 mg (27%) of epoxide **18**, 21 mg (31%) of the bicycles **19** and **20**, and 7 mg (8%) of 1-bromo-3-(*tert*-butyldimethylsilyloxy)-4,4,5-trimethyl-5-hexene as colorless oils. – **19**: $^1$H NMR (300 MHz, $CDCl_3$): δ = −0.03 (s, 3H), −0.02 (s, 3H), 0.00–0.06 (m, 1H), 0.31 (dd, *J* = 4.8 and 3.8 Hz, 1H), 0.84 (s, 3H), 0.86 (s, 9H), 0.89 (s, 3H), 0.90 (s, 3H), 0.91–0.97 (m, 1H), 1.61 (ddd, *J* = 12.0, 9.2, and 4.4 Hz, 1H), 1.81 (dd, *J* = 12.0 and 7.0 Hz, 1H), 3.33 (dd, *J* = 9.2 and 7.0 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.5, 15.0, 18.0, 18.9, 20.7, 22.2, 25.8 (3 C), 26.3, 29.2, 34.3, 42.3, 77.8. – **20**: $^1$H NMR (300 MHz, $CDCl_3$): δ = −0.04 (s, 3H), −0.03 (s, 3H), 0.01–0.08 (m, 1H), 0.85 (s, 9H), 0.90 (s, 3H), 0.91 (s, 3H), 0.88–0.99 (m, 2H), 1.10 (s, 3H), 1.53 (d, *J* = 13.5 Hz, 1H), 2.12 (dddd, *J* = 13.5, 5.9, 4.4 and 1.3 Hz, 1H), 3.58 (d, *J* = 6.0 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −5.2, −4.7, 16.8, 17.5, 18.0, 19.1, 23.3, 25.9 (3 C), 26.6, 31.1, 36.4, 45.8, 81.3. – $C_{15}H_{30}OSi$ (254.5): calcd. C 70.79, H 11.88; found C 70.61, H 11.65.

*1-Bromo-3-(tert-butyldimethylsiloxy)-4,4,5-trimethyl-5-hexene:* $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.01 (s, 3H), 1.03 (s, 3H), 1.74 (d, *J* = 0.5 Hz, 3H), 1.83 (dddd, *J* = 14.8, 8.0, 6.6 and 4.7 Hz, 1H), 1.94 (dddd, *J* = 14.8, 9.3, 7.0 and 2.6 Hz, 1H), 3.37 (td, *J* = 9.6 and 6.5 Hz, 1H), 3.50 (ddd, *J* = 9.8, 7.1 and 4.7 Hz, 1H), 3.77 (dd, *J* = 7.9 and 2.6 Hz, 1H), 4.77 (br. s, 2H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = −3.8, −3.6, 18.5, 20.1, 20.7, 26.2 (3 C), 32.2, 36.8, 44.3, 75.4, 111.0, 151.0. – 149 mg (0.36 mmol) of the dibromo compound **15**[7], 0.32 ml (0.53 mmol) of a 1.67 M solution of *n*-butyllithium in hexane and, after 15 min, 0.05 ml (0.7 mmol) of acetone were allowed to react at −120°C as described under 2. The product ratio **18/20** was determined from the crude reaction mixture to be 82:18. Neither **19** nor **21** could be detected by gas chromatography, $^1$H- or $^{13}$C-NMR spectroscopy. Flash chromatography with *tert*-butyl methyl ether/petroleum ether (0:1–1:10) furnished 77 mg (69%) of the epoxide **18** and 20 mg (22%) of the bicycle **20**. – 320 mg (0.77 mmol) of the dibromo compound **15**[7] and 0.69 ml (1.15 mmol) of a 1.67 M solution of *n*-butyllithium in hexane were allowed to react at −110°C as described under 2. The mixture was held for 2 h at −90°C and was recooled to −110°C before 0.10 ml (1.4 mmol) of acetone was added followed by workup as described under 2. The ratio of **19/20** was determined in the crude product to be 72:28; no epoxides could be detected. Flash chromatography with petroleum ether yielded 157 mg (80%) of the bicyclohexanes **19** and **20**, which could be separated by repeated flash chromatography.

(5) *(3R*,4R*,5E)-1,1-Dibromo-4-methyl-5-heptene-3-ol:* 1.90 g (9.7 mmol) of 4,4,5,5-tetramethyl-2-[(2*Z*)-1-methyl-2-butenyl]-1,3,2-dioxaborolane[13] was added at 0°C to a solution of 2.20 g (10.2 mmol) of 3,3-dibromopropionaldehyde[14] in 25 ml of petroleum ether. After stirring for 3 h the solution was kept for 12 h at 20°C. 10 ml of a pH 7 buffer was added, the phases were separated and the aqueous phase was extracted with petroleum ether (3 × 10 ml). The combined organic phases were washed with 10 ml of brine and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:6) and MPLC, cf. ref.[3], to give 1.66 g (60%) of the product as a colorless oil. – $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.8 Hz, 3H), 1.69 (dd, *J* = 6.3 and 1.0 Hz, 3H), 2.25 (sext, *J* = 6.8 Hz, 1H), 2.39 (ddd, *J* = 14.7, 9.9 and 3.1 Hz, 1H), 2.51 (ddd, *J* = 14.7, 10.3 and 2.4 Hz, 1H), 3.65 (ddd, *J* = 9.9, 5.6 and 2.4 Hz, 1H), 5.30 (ddq, *J* = 15.3, 8.0 and 0.8 Hz, 1H), 5.54 (dqd, *J* = 15.3, 6.3 and 0.8 Hz, 1H), 5.87 (dd, *J* = 10.5 and 3.1 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 15.4, 18.0, 42.6, 43.9, 49.7, 73.2, 127.5, 131.9. – $C_8H_{14}Br_2O$ (286.0): calcd. C 33.59, H 4.93; found C 33.76, H 4.82.

(6) *(3R*,4R*,5E)-1,1-Dibromo-3-(tert-butyldimethylsilyloxy)-4-methyl-5-heptene* (**22**): 0.40 ml (1.8 mmol) of *tert*-butyldimethylsilyl triflate was added to a solution of 334 mg (1.17 mmol) of (3*R**, 4*R**,5*E*)-1,1-dibromo-4-methyl-5-heptene-3-ol[7] and 0.30 ml (2.6

mmol) of 2,6-dimethylpyridine in 10 ml of dichloromethane. After stirring for 2 h, 1 ml of ethanol was added and stirring was continued for 5 min. 10 ml of water was added, the phases were separated, and the aqueous phase was extracted with petroleum ether (4 × 5 ml). The combined organic phases were washed with 10 ml of brine and concentrated in vacuo. Flash chromatography (petroleum ether) afforded 450 mg (1.12 mmol, 96%) of dibromide **22** as a colorless oil. – $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 1.61 (dd, *J* = 5.0 and 1.1 Hz, 3H), 2.29 (m, 1H), 2.31–2.49 (m, 2H), 3.69–3.75 (m, 1H), 5.38–5.51 (m, 2H), 5.66 (dd, *J* = 9.5 and 4.3 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.6, –4.3, 15.0, 17.9, 18.0, 25.7 (3 C), 41.3, 43.9, 49.2, 74.7, 125.5, 131.6. – $C_{14}H_{28}Br_2OSi$ (400.3): calcd. C 42.01, H 7.05; found C 42.08, H 7.11.

(7) *(5R*,6R*,7E)-5-(tert-Butyldimethylsilyloxy)-2,3-epoxy-2,6-dimethyl-7-nonene* (**25** and **28**): Into a solution of 117 mg (0.29 mmol) of the dibromo compound **22** and 45 µl (0.6 mmol) of acetone in 3 ml of a Trapp solvent mixture[12] in a two-chamber low-temperature reaction vessel at –110°C were added 0.26 ml (0.48 mmol) of a precooled 1.85 M solution of *n*-butyllithium in hexane and 1 ml of solvent mixture. After stirring for 15 min the mixture was warmed to 20°C, stirred for 1 h and worked up as described under 2. The diastereomer ratio **25/28** was determined from the crude product by $^1$H or $^{13}$C NMR to be 82:18. Flash chromatography (*tert*-butyl methyl ether/petroleum ether, 1:50) yielded 73 mg (0.24 mmol, 84%) of the diastereomeric epoxides **25** and **28** as a colorless oil. – $C_{17}H_{34}O_2Si$ (298.6): calcd. C 68.39, H 11.48; found C 68.04, H 11.80. – **25**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 3H), 1.28 (s, 3H), 1.53–1.76 (m, 2H), 1.63 (d, *J* = 5.0 Hz, 3H), 2.19–2.34 (m, 1H), 2.86 (t, *J* = 6.1 Hz, 1H), 3.61 (q, *J* = 5.5 Hz, 1H), 5.34–5.47 (m, 2H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.5, –4.4, 15.5, 18.1, 18.9, 24.8, 25.9 (4 C), 33.5, 42.0, 57.8, 61.6, 74.6, 125.0, 133.6. – **28**: $^1$H NMR (300 MHz, $CDCl_3$), characteristic signals: δ = 0,04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.28 (s, 3H). – $^{13}$C NMR (75 MHz, $CDCl_3$), characteristic signals: δ = 15.1, 18.1, 19.1, 24.9, 25.9 (3 C), 32.9, 42.2, 58.4, 61.9, 74.3, 124.6, 133.5. – $C_{17}H_{34}O_2Si$ (298.6): calcd. C 68.39, H 11.48; found C 68.34, H 11.60.

(8) *endo-3-(tert-Butyldimethylsilyloxy)-2-exo,6-exo-dimethylbicyclo[3.1.0]hexane* (**27**): 294 mg (0.73 mmol) of the dibromo compound **22**, 0.62 ml (1.12 mmol) of a 1.81 M solution of *n*-butyllithium, and, after 15 min at –110°C, 0.20 ml (2.7 mmol) of acetone were allowed to react at –110°C as described under 2. The product ratio of **25/27** was determined in the crude mixture to be 50:50, whereas neither **26** nor **28** could be detected by GC, $^1$H- or $^{13}$C-NMR spectroscopy. Flash chromatography (*tert*-butyl ethyl ether/petroleum ether, 1:30) yielded 83 mg (0.28 mmol, 38%) of the epoxide **25** and 54 mg (0.23 mmol, 31%) of bicycle **27** as colorless oils. – **27**: $^1$H NMR (300 MHz, $CDCl_3$): δ = –0.03 (s, 3H), –0.02 (s, 3H), 0.67 (dd, *J* = 6.1 and 3.1 Hz, 1H), 0.84 (s, 9H), 0.85 (d, *J* = 3.9 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.80–0.98 (buried, 1H), 0.98–1.04 (m, 1H), 1.53 (d, *J* = 13.7 Hz, 1H), 1.85 (q, *J* = 7.2 Hz, 1H), 1.95–2.04 (m, 1H), 3.74 (d, *J* = 6.3 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.7 (2C), 18.1 (2 C), 19.8, 25.0, 25.9 (4 C), 32.7, 36.5, 45.0, 81.1. – $C_{14}H_{28}OSi$ (240.5): calcd. C 69.93, H 11.74; found C 69.98, H 11.68.

To a solution of 302 mg (0.75 mmol) of the dibromo compound **22** in 7.5 ml of a Trapp solvent mixture[12] in a two-chamber low-temperature reaction vessel at –110°C was added 0.62 ml (1.12 mmol) of a precooled 1.81 M solution of *n*-butyllithium in hexanes and 1 ml of solvent mixture. The mixture was allowed to warm to –90°C within 2 h, and a precooled solution of 0.20 ml (2.7 mmol) of acetone in 1 ml of solvent mixture was added at –110°C. Stirring was continued for 15 min, the mixture was warmed to 20°C and stirred for 1 h. 10 ml of pH 7 buffer was added, the phases were separated, and the aqueous phase was extracted with petroleum ether (3 × 10 ml). The combined organic phases were washed with 10 ml of brine and concentrated in vacuo. In the crude product neither **26** nor the epoxides **25**, **28** could be detected. Flash chromatography (petroleum ether) yielded 112 mg (0.47 mmol, 62%) of bicyclic compound **27** as a colorless oil.

(9) *5-Bromo-3-(tert-butyldimethylsilyloxy)-2,2-dimethylbicyclo[3.1.0]hexane* (**31**): To a solution of 206 mg (1.46 mmol) of 2,2,6,6-tetramethylpiperidine in 20 ml of THF was added 0.75 ml (1.34 mmol) of a 1.78 M solution of *n*-butyllithium in hexane over 2 min at 20°C. After stirring for 10 min the solution was cooled to –110°C in a two-chamber reaction vessel. A solution of 200 mg (0.50 mmol) of the dibromo compound **29**[3] in 2 ml of THF was added dropwise and the solution was kept at –105 to –100°C for 3 h. First 0.2 ml of [$D_4$]methanol and then 10 ml of pH 7 buffer were added. The phases were separated and the aqueous phase was extracted with petroleum ether (3 × 10 ml). The combined organic phases were washed with 5 ml of brine and concentrated in vacuo. The product ratio of **29/31** was determined by $^1$H and $^{13}$C NMR to be 77:23, **29** being monodeuterated to about 40%. – [$D_1$]-**29**: characteristic signals in the $^1$H-NMR spectrum (300 MHz, $CDCl_3$): δ = 2.40 (dd, 14.9 and 8.2 Hz, 1H). – Flash chromatography (petroleum ether) yielded 166 mg (tot. 0.44 mmol, 87%) of a product mixture as a colorless oil. – **31**: $^1$H NMR (300 MHz, $CDCl_3$): δ = –0.03 (s, 3H), –0.01 (s, 3H), 0.86 (s, 9H), 0.94 (s, 3H), 0.95–1.01 (m, 1H), 1.08 (s, 3H), 1.41–1.51 (m, 2H), 2.18 (d, *J* = 13.6 Hz, 1H), 2.60 (ddd, *J* = 13.6, 6.1 and 1.9 Hz, 1H), 3.55 (d, *J* = 6.1 Hz, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = –5.2, –4.7, 17.9, 19.8, 20.7, 25.8 (3 C), 28.5, 34.1, 38.7, 44.8, 47.1, 79.9. – $C_{14}H_{27}BrOSi$ (319.4): calcd. C 52.65, H 8.52; found C 52.51, H 8.72.

291 mg (2.06 mmol) of 2,2,6,6-tetramethylpiperidine, 1.15 ml (1.92 mmol) of a 1.67 M solution of *n*-butyllithium in hexane, and 299 mg (0.75 mmol) of the dibromo compound **29** were allowed to react at –110°C as described above and allowed to warm to –50°C over 6 h. After quenching and workup as described above, no starting material could be detected by gas chromatography. Flash chromatography of the crude product with petroleum ether furnished 179 mg (75%) of the bicyclohexane **31**.

(10) *5,5-Dibromo-3-(tert-butyldimethylsilyloxy)-2,2-dimethylpentanal* (**32**): Into a solution of 400 mg (1.00 mmol) of the dibromo compound **29**[3] in 10 ml of dichloromethane was introduced at –78°C a stream of ozone in oxygen until the blue color persisted. The excess ozone was removed by blowing further oxygen through the solution. 289 mg (1.10 mmol) of triphenylphosphane was added, the mixture was stirred for 1 h at 20°C and 0.08 ml (0.4 mmol) of a 5 M solution of *tert*-butyl hydroperoxide in octane was added. After stirring for 30 min 1 g of silica gel was added and the solvents were removed in vacuo. The residual silica gel was added on the top of a flash chromatography column and eluted with *tert*-butyl methyl ether/petroleum ether (1:15) to furnish 332 mg (83%) of the aldehyde **32** as a colorless oil. – $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.16 (s, 3H), 0.86 (s, 9H), 1.02 (s, 3H), 1.09 (s, 3H), 2.47–2.59 (m, 2H), 3.94–4.03 (m, 1H), 5.63–5.69 (m, 1H), 9.53 (s, 1H). – $^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.1, –3.8, 17.3, 18.4, 19.2, 26.0 (3 C), 43.0, 49.7, 50.8, 74.7, 204.8. – $C_{13}H_{26}Br_2O_2Si$ (402.3): calcd. C 38.82, H 6.53; found C 38.64, H 6.50.

(11) *1-Bromo-5-(tert-butyldimethylsilyloxy)-2-hydroxy-3,3-dimethylcyclopentanes* (**35–38**): Into a solution of 301 mg (0.75

mmol) of the dibromocompound **32** in 7.5 ml of a Trapp solvent mixture[12] in a two-chamber reaction vessel was added at −110°C a precooled solution of 0.67 ml (1.12 mmol) of a 1.67 M solution of *n*-butyllithium in hexane and 1 ml of petroleum ether. The mixture was stirred for 15 min and hydrolyzed by addition of 5 ml aqueous saturated $NH_4Cl$ solution. The phases were separated and the aqueous phase was extracted with petroleum ether (3 × 10 ml). The combined organic phases were washed with 10 ml of brine and concentrated in vacuo. The residue was purified by flash chromatography with *tert*-butyl methyl ether/petroleum ether (1:10) to furnish 62 mg (25%) of a mixture of the alcohols **36/38** as well as 112 mg (46%) of the alcohols **35/37**. The diastereomer ratio of the alcohols was determined from the crude reaction product by $^1H$ and $^{13}C$ NMR to be **35/36/37/38** = 60:27:8:<5. The following spectral data were recorded: −**35**: $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H, and s, 3H), 1.04 (s, 3H), 2.21−2.32 (m, 2H), 2.66 (d, *J* = 7.1 Hz, OH), 3.80 (t, *J* = 6.5 Hz, 1H), 3.84 (t, *J* = 6.3 Hz, 1H), 4.16 (q, *J* ca. 7.5 Hz, 1H). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = −5.1, −4.7, 15.2, 17.9, 25.1, 25.7 (3 C), 42.6, 45.8, 52.8, 78.4, 86.9. − **36**: $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.89 (s, 3H), 1.07 (s, 3H), 2.12 (d, *J* = 4.5 Hz, OH), 2.21 (ddd, *J* = 14.6, 9.1 and 5.2 Hz, 1H), 2.43 (ddd, *J* = 14.6, 7.9 and 6.6 Hz, 1H), 3.66 (t, *J* = 4.6 Hz, 1H), 4.08 (dd, *J* = 8.0 and 5.2 Hz, 1H), 4.64 (ddd, *J* = 9.0, 6.5 and 4.8 Hz, 1H). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.7, 18.0, 21.5, 21.6, 25.8 (3 C), 42.6, 45.5, 55.2, 78.0, 79.8. − **37**: $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 9H), 0.88 (s, 3H), 1.07 (s, 3H), 2.13 (ddd, *J* = 15.0, 5.9 and 4.5 Hz, 1H), 2.76 (d, *J* = 10.2 Hz, OH), 2.79 (ddd, *J* = 15.1, 9.4 and 6.3 Hz, 1H), 3.46 (dd, *J* = 10.0 and 5.6 Hz, 1H), 3.64 (t, *J* = ca. 5.4 Hz, 1H), 4.45 (dt, *J* = 9.5 and 6.2 Hz, 1H). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 17.5, 25.4, 43.9, 45.7, 52.3, 79.2, 79.7. − **38**: $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.92 (s, 3H), 0.95 (s, 3H), 3.10 (d, *J* = 3.0 Hz, OH), 3.36 (br. d, *J* = ca. 3 Hz, 1H), 3.52 (dd, *J* = ca. 7.7 and 1 Hz, 1H), 3.93 (t, *J* = ca. 5.2 Hz, 1H). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 22.1, 34.2, 35.2, 75.7, 78.7. − $C_{13}H_{27}BrO_2Si$ (325.4): calcd. C 48.29, H 8.42; found **35** + **37**: C 48.50, H 8.65; **36** + **38**: C 48.41, H 8.70.

(12) *3-endo-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-6-oxabicyclo[3.1.0]hexane* (**39**): Into a solution of 55 mg (0.17 mmol) of the alcolhol **35** in 2 ml of THF was added 32 mg (0.2 mmol) of potassium *tert*-butoxide and the mixture was stirred for 2 h. Ca. 50 mg of solid ammonium chloride was added and the mixture was stirred for 30 min and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography with *tert*-butyl methyl ether/petroleum ether (1:10) to furnish 33 mg (80%) of **39** as a colorless oil. − $^1H$ NMR (300 MHz, $CDCl_3$): δ = −0.01 (s, 3H), 0.00 (s, 3H), 0.86 (s, 9H), 0.89 (s, 3H), 1.08 (s, 3H), 1.92 (d, *J* = 15.0 Hz, 1H), 2.11 (ddd, *J* = 15.0, 7.0, and 1.4 Hz, 1H), 3.05 (d, *J* = 2.6 Hz, 1H), 3.39 (br. s, 1H), 3.68 (d, *J* = 6.9 Hz, 1H). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.7, 18.2, 18.9, 24.3, 25.9 (3 C), 37.6, 43.6, 56.0, 65.7, 78.0.

(13) *3-(tert-Butyldimethylsilyloxy)-2,2-dimethylcyclopentanone* (**40**): 23 mg (0.07 mmol) of **36** was treated as described under 12. to give 14 mg (82%) of the ketone **40** as a colorless oil. − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.95 (s, 3H), 0.97 (s, 3H), 1.75−1.86 (m, 1H), 2.03−2.23 (m, 2H), 2.33−2.48 (m, 1H), 3.93 (t, *J* = 5.9 Hz, 1H). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.6, 17.5, 18.0, 22.1, 25.7 (3 C), 28.4, 34.2, 50.3, 78.6, 221.3. − $C_{13}H_{26}O_2Si$ (242.4): calcd. C 64.41, H 10.81; found C 64.57, H 10.82.


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