Synthesis of Ethynylcyclopropanes from Epoxides

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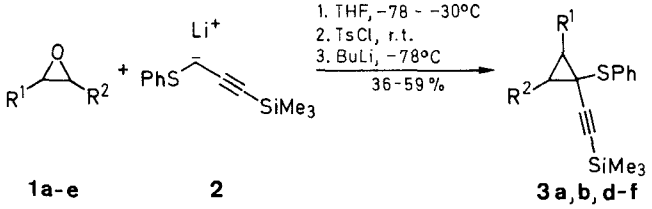
Dedicated to Prof. Hans-Jürgen Bestmann in recognition of his contribution as Executive Editor of Synthesis

The title compounds are prepared by an efficient one-pot reaction involving ring-opening of an epoxide with lithium 3-trimethylsilyl-1-phenylthio-2-propyn-1-ide, tosylation of the intermediate alkoxide, and finally deprotonation. In an alternative approach, intramolecular epoxide ring opening by a β anion is succesfully applied.

Alkynylcyclopropanes are emerging as very useful synthetic intermediates.[2] Traditionally, these compounds are prepared by elimination reactions from appropriately substituted cyclopropanes[3] or by [2 + 1]cycloaddition reactions involving either an alkynyl carbene and an alkene[4] or a simple carbene and an enyne.[5] Recently, the successful application of a 1,3 cycloelimination in 5-bromoalkynes was reported.[6] For 1-hydroxy substituted derivates, a cyclopropanone-based method is available.[7]

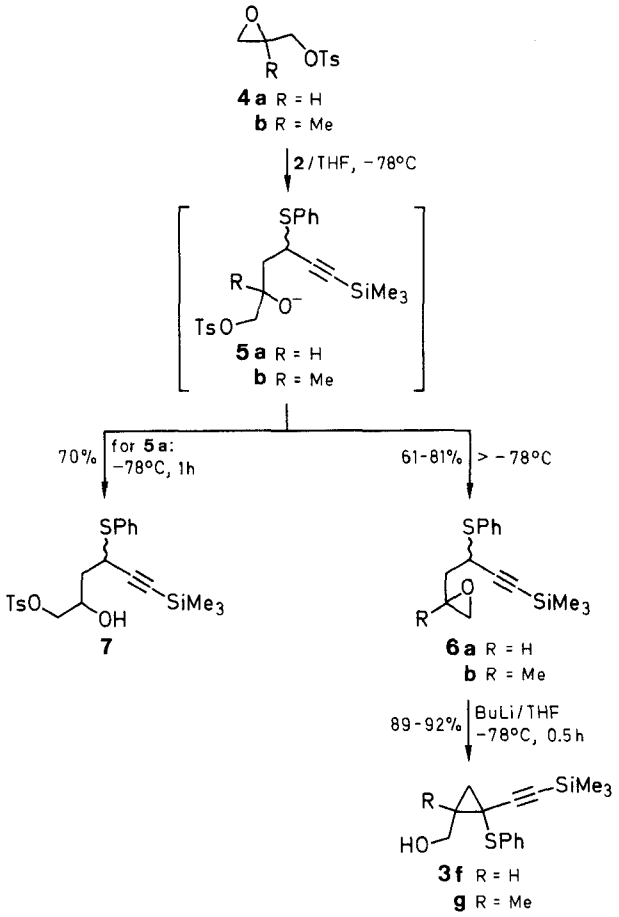
Very recently, we reported an efficient synthesis of vinylcyclopropanes using epoxide ring opening by allyl anions and subsequent cyclization of the tosylated intermediates.[8] In an obvious extension, we investigated the analogous reaction employing a propargyl anion. Here, anion **2** appeared to be a useful candidate as the substitution pattern would allow subsequent elaboration of the products. In fact, ring opening of oxiranes **1a–e** by anion **2** is a smooth reaction at low temperature. For synthetic convenience, the resulting alkoxide (cf. **5**) is not isolated, but tosylated and the resulting tosylate deprotonated by butyllithium in a one-pot reaction. This sequence provides ethynylcyclopropanes **3a,b,d,e** in good yields, while the protecting group in derivative **3c** is cleaved during work-up giving cyclopropylmethanol **3f**. The reaction is highly stereoselective giving preferentially or exclusively one isomer (Tables 1 and 2).



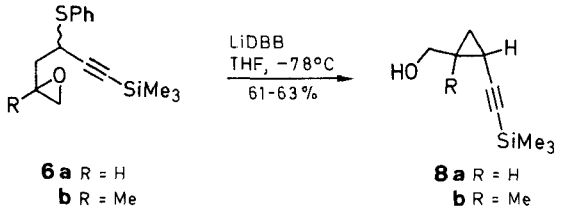
1a-e **2** **3a,b,d-f**

Compound	R^1	R^2	Compound	R^1	R^2
1a, 3a	Me	H	**1d, 3d**	$-(CH_2)_3-$	
1b, 3b	CH_2OBn	H	**1e, 3e**	$-(CH_2)_4-$	
1c	CH_2OTHP	H	**3f**	CH_2OH	H

In an alternative approach, we tried to replace tosyloxy as the leaving-group in the cyclopropane forming step by an epoxide moiety. This requires use of epoxytosylates **4** allowing isolation of a epoxide-containing product in the reaction with **2**. In fact, a clean formation of (3-alkynyl)oxiranes **6a,b** is observed on addition of anion **2** to oxiranes **4a,b**. This reaction may involve either the substitution of the tosyloxy group in **4** or formation of another oxirane ring via intermediate **5**. The latter mechanism was confirmed by isolation of **7** on quenching the reaction mixture as formed from **4a** and **2** at −78 °C.



Intramolecular ring-opening of γ,δ-unsaturated oxiranes had been used before in vinylcyclopropane synthesis, though competition with oxirane isomerization giving allyl alcohols interfered.[9] In the present case, the neighboring triple bond allowed deprotonation of **6a,b** and



LiDBB = lithium 4,4'-di-*tert*-butylbiphenylide

ring closure to **3f,g** without complications. Moreover, compounds **6a,b** could be reductively lithiated[10] with lithium 4,4'-di-*tert*-butylbiphenylide[11] (LiDBB) leading again to cyclopropane formation, here **8**, via intramolecular epoxide opening (Table 1). Based on the ^{13}C-

Table 1. Synthesis of Ethynylcyclopropanes **3** and **8**

Oxirane	Product	Yield (%)[a]	bp[b] (°C)/Torr	Isomer Ratio[c]	Molecular Formula[d]	IR (neat)[e] ν (cm^{-1})	MS (70 eV) m/z (%)
1a	**3a**	59	80/0.2	7	$C_{15}H_{20}SSi$ (260.5)	2154, 1263, 845	260 (100)
1b	**3b**	36	125/0.05	5	$C_{22}H_{26}OSSi$ (366.6)	2158, 1250, 843	245 (45), 91 (100)
1c	**3f**	48[f]	110/0.05	7	$C_{15}H_{20}OSSi$ (276.5)	3351, 2156, 1250, 844	276 (15), 73 (100)
1d	**3d**	53	90/0.1	>10	$C_{17}H_{22}SSi$ (286.5)	2155, 1250, 844	286 (70), 73 (100)
1e	**3e**	59	95/0.1	>10	$C_{18}H_{24}SSi$ (300.5)	2154, 1249, 844	300 (35), 73 (100)
6a	**3f**	92	[g]	1.1	$C_{15}H_{20}OSSi$ (276.5)	3351, 2156, 1250, 844	276 (15), 73 (100)
6a	**8a**	63	20/20	3	$C_9H_{16}OSi$ (168.3)	3317, 2165, 1250, 843	168 (1), 75 (100)
6b	**3g**	89	[g]	6	$C_{16}H_{22}OSSi$ (290.5)	3369, 2163, 1250, 845	290 (8), 73 (100)
6b	**8b**	61	20/20	>9	$C_{10}H_{18}OSi$ (182.3)	3351, 2164, 1250, 844	167 (3), 73 (100)

[a] Yield of pure, isolated product.
[b] Uncorrected, oven temperatures.
[c] Determined by ^{1}H-NMR after chromatographic purification.
[d] Satisfactory microanalyses obtained: C ±0.29, H ±0.17, S ±0.12, except for **3b** (C −0.52).
[e] Recorded on a Perkin Elmer FT 1720 X.
[f] Yield obtained after deprotection.
[g] The compound was purified by column chromatography (petroleum ether/EtOAc 4:1 for **3f** and 6:1 for **3g**).

Table 2. NMR Spectral Data of Cyclopropanes **3** and **8**[a]

Product	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ
3a	0.16[a], 0.20 (s, 9H each, $Si(CH_3)_3$), 0.91[a], 1.10 (dd, 1H, J = 4.7[a], 7.2[a], 4.6, 6.6, CH_2), 1.35[a], 1.38 (d, 3H, J = 6.4[a], 6.2, CH_3), 1.42 (m, 1H, CH_2), 1.55, 1.76[a] (m, 1H, $CHCH_3$), 7.21–7.60 (m, $5H_{arom}$)	−0.07[a], −0.04 ($Si(CH_3)_3$), 14.1[a], 15.4 (CH_3), 21.2, 21.3[a] (CSPh), 25.5 ($CHCH_3$), 25.8[a], 27.0 (CH_2), 81.6[a], 106.4, 110.0[a] (C≡C), 125.8[a], 125.9, 128.5[a], 128.51, 128.6, 128.7[a] (CH_{arom}), 136.1[a], 136.4 ($C-S_{arom}$)
3b	0.11[a], 0.14 (s, 9H each, $Si(CH_3)_3$), 1.01[a], 1.26 (dd, 1H, J = 5.1[a], 7.2[a], 5.2, 7.0, CH_2), 1.47, 1.63[a] (dd, 1H, J = 5.2, 8.8, 5.1[a], 9.0[a], CH_2), 1.89, 2.06[a] (m, 1H, $CHCH_2O$), 3.64 (dd, 1H, J = 8.2, 10.6, CH_2OBn), 3.65–3.80[a] (m, 2H, CH_2OBn), 3.84 (dd, 1H, J = 5.4, 10.6, CH_2OBn), 4.55, 4.60 (d, each 1H, J = 11.8, $PhCH_2$), 4.51[a] (s, 2H, $PhCH_2$), 7.17–7.60 (m, $5H_{arom}$)	−0.04, 0.0 ($Si(CH_3)_3$), 21.0, 21.6[a] (CSPh), 22.6[a], 23.3 (CH_2), 30.2[a], 30.6 (CH), 69.7[a], 70.9, 73.0 (CH_2O), 82.6[a], 85.3, 105.8, 108.6[a] (C≡C), 126.2[a], 126.3, 127.6, 127.7, 127.9[a], 128.4, 128.6, 128.7, 129.2, 129.4 (CH_{arom}), 135.6, 138.0[a], 138.4 (q, C_{arom})
3d	0.04 (s, 9H, $Si(CH_3)_3$), 1.55–2.05 (m, $8H_{cyclopentyl}$), 7.05–7.50 (m, $5H_{arom}$)	0.04 ($Si(CH_3)_3$), 24.7, 26.8 (CH_2), 25.1 (q, $C_{cyclopropyl}$), 38.6 (CH), 88.4, 104.1 (C≡C), 125.6, 128.1, 128.6, 136.5 ($C-S_{arom}$) (CH_{arom})
3e	0.07 (s, 9H, $Si(CH_3)_3$), 1.10, 1.40, 1.52, 1.75, 1.90 (m, $2H_{cyclohexyl}$), 7.10–7.45 (m, $5H_{arom}$)	0.07 ($Si(CH_3)_3$), 20.5, 20.8 (CH_2), 24.8 (CSPh), 27.8 (CH), 90.2, 105.9 (C≡C), 125.5, 127.8, 128.5 (CH_{arom}), 137.0 ($C-S_{arom}$)
3f	0, 0.11[a], 0.1 (s, 9H each, $Si(CH_3)_3$), 1.04[a] (dd, 1H, 5, J = 5.2, 7.2, CH_2), 1.32, 1.41 (dd, 1H each, J = 5.2, 6.8, 5.2, 8.8, CH_2), 1.58[a] (m, 2H, CH_2, OH), 1.73 (br, 1H, OH), 1.81, 1.97[a] (m, 1H, CH), 3.62, 3.93 (br dd, 1H each, J = 9.2, 11.6, 5.6, 11.6, CH_2OH), 3.72[a], 3.85[a] (m, 1H each, CH_2OH), 7.20–7.60 (m, $5H_{arom}$)	−1.3 ($Si(CH_3)_3$), 21.0[a], 23.8 (CH_2), 22.4 (CSPh), 62.3[a], 63.4 (CH_2OH), 81.3[a], 85.6, 105.9, 108.7[a] (C≡C), 126.6[a], 126.9, 128.8, 128.9[a], 129.1[a], 130.1 (CH_{arom}), 135.4 ($C-S_{arom}$)
3g	0.08[a], 0.14 (s, 9H each, $Si(CH_3)_3$), 1.07[a], 1.22, 1.29, 1.48[a] (d, 1H each, J = 5.2, CH_2), 1.49[a], 1.52 (s, 3H each, CH_3), 3.72[a], 3.77, 3.85, 3.91[a] (d, 1H each, J = 12.0, CH_2OH), 7.10–7.50 (m, $5H_{arom}$)	−0.1[a], 0.0 ($Si(CH_3)_3$), 17.0[a], 19.0 (CH_3), 26.1[a], 26.8 (CCH_3), 28.9, 29.1[a] (CH_2), 33.8, 34.9[a] (CSPh), 66.8, 68.7[a] (CH_2OH), 85.5, 106.8, 107.2[a] (C≡C), 126.4, 126.5[a], 128.7, 128.8[a], 128.9, 128.94[a] (CH_{arom}), 135.5[a], 135.8 ($C-S_{arom}$)
8a	0.11 (s, 9H, $Si(CH_3)_3$), 0.66[a] (m, 1H, CH), 0.73 (ddd, 1H, J = 4.6, 6.0, 8.4, CH), 0.92, 0.98[a] (dt, 1H each, J = 4.8, 8.4, 4.4[a], 8.4[a], CH_2), 1.19[a] (dt, 1H, J = 4.6, 8.4, CH_2), 1.33–1.51 (m, 1H, $CHCH_2OH$, CH_2[a]), 1.99, 2.07[a] (br, 1H, OH), 3.45, 3.59[a] (m, 2H, CH_2OH)	−0.06[a], 0.0 ($Si(CH_3)_3$), 5.3[a], 5.8 (CH), 13.2 (CH_2), 20.8[a], 24.4 ($CHCH_2OH$), 63.7[a], 65.1 (CH_2OH), 80.6, 82.6[a], 106.7[a], 108.6 (C≡C)
8b	0.13 (s, 9H, $Si(CH_3)_3$), 0.60 (dd, 1H, J = 4.4, 5.4, CH), 0.91 (dd, 1H, J = 4.4, 9.0, CH_2), 1.28 (s, 3H, CH_3), 1.34 (dd, 1H, J = 5.4, 9.0, CH_2), 1.44 (br s, 1H, OH), 3.37, 3.41 (d, 1H each, J = 11.2, CH_2OH)	0.0, −0.1[a] ($Si(CH_3)_3$), 11.8, 12.8[a] (CH), 16.4, 20.4[a] (CH_3), 19.8, 21.0[a] (CH_2), 25.2 (CCH_3), 67.7[a], 69.5 (CH_2OH), 81.9[a], 82.7, 104.8[a], 106.8 (C≡C)

[a] Signals of the minor diastereomer are designated by[a].

NMR data (Table 2), the major isomer of **8a,b** exhibits a *trans* relationship of the alkynyl and the hydroxymethyl residues.[12]

THF was distilled from sodium benzophenone ketyl prior to use. All other solvents and reagents were used without further purification. Column chromatography was carried out on Merck silica gel (70–230 mesh). Petroleum ether with boiling range 60–70 °C was used in the separations. Analytical TLC was performed on 0.2 mm silica 60 coated aluminum plates (Merck).

Epoxides **1a,b,d,e** are commercially available, epoxide **1c** was prepared from the corresponding alkene using 3-chloroperoxybenzoic acid[13]. Epoxytosylates **4** were obtained from the corresponding allylic alcohols by conventional methods.[14]

Protonated **2**[15] was prepared in 91% yield by deprotonation of propargyl phenyl sulfide[16] using BuLi in THF and quenching the solution at −78 °C with Me_3SiCl. The mixture was warmed to r.t., treated with aq 2M NH_4Cl, and was extracted with Et_2O. Evapor-

ation of the solvent and distillation of the residue in a Kugelrohr apparatus (bp 70–80 °C/0.1 Torr) gave the desired compound.

Ethynylcyclopropanes 3; General Procedure:
In a dried, nitrogen-filled round-bottom flask, protonated **2** (661 mg, 3 mmol) is dissolved in THF (15 mL) and, after cooling to − 78 °C, the solution is treated with BuLi (2.1 mL, 1.1 equiv) in hexane (1.6 *M*) and stirred at this temperature for 3 h. To the resultant red solution, **1** (3 mmol) is added dropwise and over 2 h allowed to warm to − 30 °C and stirred at this temperature for 3 h (in case of **1d** and **1e**) or left at − 78 °C for 2 h (in case of **1a**, **b**, and **c**). Then a solution of TsCl (629 mg, 3.3 mmol) in THF (5 mL) is added dropwise. The mixture is slowly warmed to r.t. until TLC confirmed consumption of the intermediate alkoxide (petroleum ether/EtOAc 5:1, 3:1 in the case of **1c**). After cooling to − 78 °C, BuLi (2.5 mL, 4.0 mmol, 1.3 equiv) is added slowly. The reaction is complete within 30 min. The mixture is poured into a two-phase system of sat. $NaHCO_3$ (15 mL) and Et_2O (50 mL), and stirred for 0.5 h. After separation of the phases, the organic phase was washed with water (15 mL) and brine (15 mL), and dried ($MgSO_4$). Concentration on the rotary evaporator afforded a red oil, which was chromatographed (petroleum ether/EtOAc 50:1). The first fraction contained the product, contaminated with traces of protonated **2**. Distillation in a Kugelrohr apparatus yielded the pure products (for temperatures see Table 1). An exception was made for product **3c** from **1c**. Here, after filtration over silica gel (15 g) using petroleum ether/EtOAc 50:1, the resulting yellow oil was deprotected in MeOH using TsOH (114 mg, 0.2 equiv). After 1 h, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography (petroleum ether/EtOAc 5:1).

(2-Phenylthio-4-trimethylsilyl-3-butynyl)oxirane (6a):
A solution of **2** (1.76 g, 8 mmol) in THF (25 mL), prepared as described above, is added dropwise to epoxytosylate **4a** (1.83 g, 8 mmol) in THF (50 mL) at − 78 °C. After allowing the mixture to warm to − 20 °C, 2M NH_4Cl (10 mL) is added. Extraction with Et_2O (2 × 50 mL), washing with brine (2 × 20 mL), and drying ($MgSO_4$), affords, after concentration of the solution on the rotary evaporator, a deep yellow oil (2.4 g). Column chromatography (petroleum ether/EtOAc 15:1) yields a pale yellow oil [1.78 g, 81 %, 2 diastereomers (1.1:1*)]

$C_{15}H_{20}OSSi$	calc.	C 65.17	H 7.29	S 11.60
(276.5)	found	65.15	7.12	11.75

^{1}H-NMR ($CDCl_3$, $CHCl_3$ = 7.26) δ = 0.12, 0.13* (s, 9H), 1.85–2.10* (m, 2H), 2.56 (m, 1H9, 2.81 (m, 1H), 3.16, 3.22* (m, 1H), 3.94, 3.98* (dd, J = 6.4, 8.4, 6.4*, 7.2* Hz, 1H), 7.30–7.48 (m, 5H).

1-Methyl-1-(2-phenylthio-4-trimethylsilyl-3-butynyl)oxirane (6b):
From a similar reaction with **4b** on a 4 mmol scale 2 diastereomers (1.1:1*) are isolated, 61 %:

$C_{16}H_{22}OSSi$	calc.	C 66.15	H 7.63	S 11.04
(290.5)	found	66.39	7.62	11.56

^{1}H-NMR ($CDCl_3$, CH_2Cl_2 = 5.32) δ = 0.12, 0.13* (s, 9H), 1.41, 1.44* (s, 3H), 1.80, 1.94* (dd, J = 10.4, 13.6, 6.4*, 14.4 Hz, 1H), 2.21, 2.30* (ddd, J = 1.2, 5.0, 13.6, 1.1*, 8.2*, 14.4* Hz, 1H), 2.64*, 2.65 (dd, J = 1.1*, 4.8*, 1.2, 4.8 Hz, 1H), 2.79, 2.84* (d, J = 4.8 Hz, 1H), 3.88*, 3.92 (dd, J = 6.4*, 8.2*, 5.0, 10.4 Hz, 1H), 7.30–7.48 (m, 5H).

2-Hydroxy-4-phenylthio-6-trimethylsilyl-5-hexynyl Tosylate (7):
The reaction is carried out as described for **6a**. Instead of warming the solution to − 20 °C after additon of **2**, the mixture is stirred at − 78 °C for 1 h. Then aq NH_4Cl (5 mL) is added. The solution is worked up as described for **6a**. Column chromatography (petroleum ether/EtOAc 5:1) affords a pale yellow oil [2.50 g, 70 %, 2 diastereomers (1.5:1*)]:

$C_{22}H_{28}O_4S_2Si$	calc.	C 58.98	H 6.29	S 14.29
(448.7)	found	59.00	6.40	14.19

^{1}H-NMR ($CDCl_3$, $CHCl_3$ = 7.26) δ = 0.09*, 0.13 (s, 9H), 1.62–1.96 (m, 2H), 2.43 (s, 3H), 2.90 (b, 1H), 3.84–4.08 (m, 3H), 4.12*, 4.21 (m, 1H), 7.21–7.40 (m, 5H), 7.50, 7.78 (m, 2H each).

Ethynylcyclopropanes 3f, g from 6 Using Butyllithium:
Compound **6b** (150 mg, 0.52 mmol) is dissolved in THF (2 mL) and cooled to − 78 °C. BuLi (0.38 mL, 0.6 mmol) is added, and the mixture stirred for 0.5 h. Work-up is performed as described for **6a**. Column chromatography (petroleum ether/EtOAc 5:1) yields **3g** (183 mg, 89 %, Table 1).

The analogous reaction using **6a** (300 mg, 1.09 mmol) yielded, after work-up and chromatography, **3f** (277 mg, 92 %; Table 1).

Ethynylcyclopropanes 8a, b from 6 using LiDBB:
A solution of LiDBB from Li (90 mg, 13 mmol), and di-*tert*-butylbiphenyl (4.04 g, 15.2 mmol) is prepared as described.[11] This solution is cooled to − 78 °C, and a solution of epoxide **6a** (1.0 g, 3.62 mmol) in THF (10 mL) is added dropwise. The reaction is complete within seconds. After addition of water (10 mL), the solution is extracted with Et_2O (2 × 40 mL), washed with NaOH (2*N*, 20 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$) and evaporated to yield a white to yellow solid. Distillation in a Kugelrohr apparatus (bp 120–150 °C/15 Torr) provides the cyclopropane **8a**, which after a second distillation is analytically pure.

A similar reaction with epoxide **6b** (420 mg, 1.44 mmol) provided **8b** (Table 1).

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