A Highly Stereoselective Synthesis of a New Propargylic Epoxide: (3*R*,4*S*)-1-*tert*-Butyldimethylsilyl-3,4-epoxy-1-pentyne

Tõnis Kanger,*[a], Milana Liiv,[a] Tõnis Pehk,[b] Margus Lopp[a]

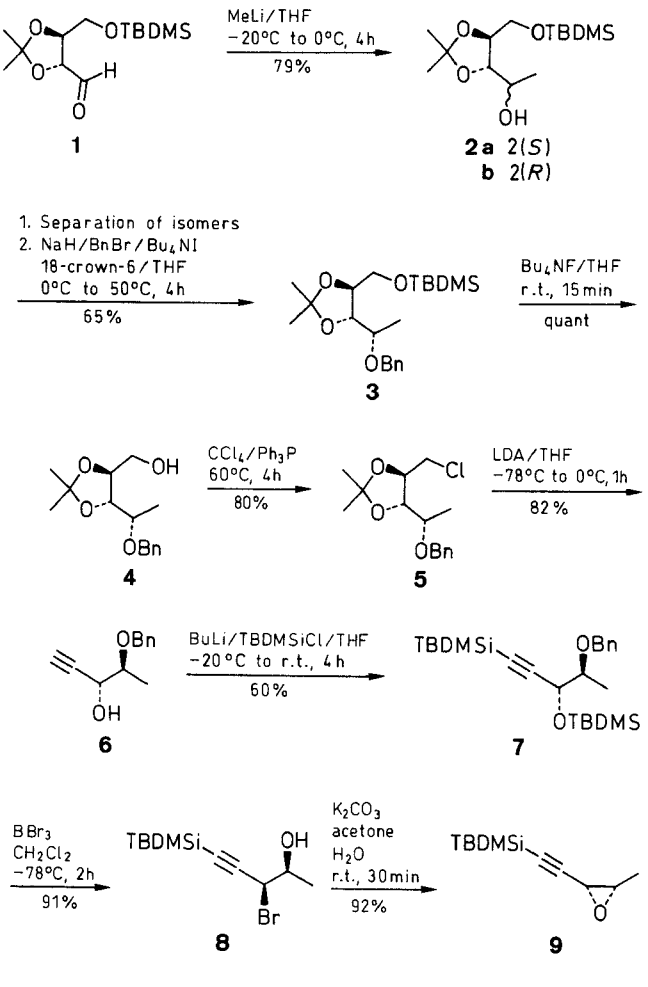
[a] Institute of Chemistry, Estonian Academy of Sciences, Akadeemia tee 15, EE0108, Tallinn, Estonia
[b] Institute of Chemical and Biological Physics, Estonian Academy of Sciences, Rävala pst. 10, EE0001, Tallinn, Estonia

Received 10 July 1992

The synthesis of a novel enantiopure propargylic epoxide, (3*R*, 4*S*)-1-*tert*-butyldimethylsilyl-3,4-epoxy-1-pentyne (**9**), from a readily available tartaric acid derivative, (4*R*,5*S*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxalane-4-carbaldehyde (**1**), is described.

Optically active propargylic compounds are important intermediates in the synthesis of different natural compounds.[1] Their reaction with organocopper reagents[2] is one of the most popular ways of preparing allenes.[3] The use of enantiopure starting material enables the obtention of optically active allenes with high biological activity.[4] Enantiopure propargylic epoxides are easily available via Sharpless epoxidation[5] of an enyne system, but this method only leads to alkynyl epoxy alcohols.[6] The direct epoxidation of a nonallylic enyne system with a chiral manganese complex is also possible and proceeds in high enantioselectivity,[7] but this method yields a mixture of *cis*- and *trans*-epoxides.

In our previous communication,[8] we reported an efficient method for the synthesis of an enantiopure propargylic epoxide bearing a terminal epoxy group. In this paper we present a highly stereoselective synthesis of epoxide **9**. The synthesis started from aldehyde **1** which was prepared from the tartaric acid ester according to known procedure.[9] Aldehyde **1** was treated with methyllithium to give a 9:1 mixture of epimeric alcohols **2a** and **2b** which are easily separable by column chromatography on silica gel (Scheme). ^{13}C and ^{1}H NMR spectra of the *R*-Mosher's ester of alcohols refer to the *S*-configuration at C-2 of the main product giving high field shifts for the end methyl group in **2b** and for C-3 and the geminal methyl groups of the dioxolane ring in **2a**. Surprisingly, benzylation of the hydroxy group in **2a** proceeded in a low isolated yield (30%). However, the yield was considerably improved (up to 65%) when a catalytic amount of tetrabutylammonium iodide and 18-crown-6 was added to the reaction mixture.[10] The quantitative desilylation and chlorination under nonacidic conditions[11] afforded chloroalkoxy compound **5** in high yield (80%). The base-induced elimination of **5** with lithium diisopropylamide (LDA) led to propargylic alcohol **6**. It has been previously stated that no epimerization takes place under these conditions.[12] In our experiments we also did not find any trace of the diastereoisomeric alcohol by using HPLC and NMR. The comparison of ^{13}C chemical shifts of the end methyl and benzylic groups with the corresponding atoms in *syn* and *anti* isomers of 4-hydroxy-5-benzyloxy-1-hexenes[13] refers to *anti* configuration of substi-



Downloaded by: Collections and Technical Services Department. Copyrighted material.

Table. ^{13}C and ^{1}H Chemical Shifts of Compounds **2, 5, 6, 8, 9** Prepared

Compound	NMR	Assignments									
		1	2	3	4	5	$SiMe_2$		*t*-Bu	gem-Me	OCO
2a	^{13}C	19.30	68.07	83.86	79.32	64.21	−5.57, −5.63		18.26, 25.80	26.74, 26.90	108.63
	^{1}H	1.23	3.78	3.62	3.88	3.66, 3.86	0.08		– 0.88	1.36, 1.37	–
2b	^{13}C	19.60	67.44	82.68	77.62	63.82	−5.48, −5.64		18.26, 25.82	27.18, 27.25	109.11
	^{1}H	1.20	3.79	3.79	3.93	3.76, 3.78	0.05		– 0.87	1.37, 1.39	–
2a-(*R*)-MPTA	^{13}C	16.37	73.69	79.09	78.17	62.79	−5.41, −5.61		18.33, 25.88	26.91, 26.98	109.57
	^{1}H	1.43	5.20	4.01	3.75	3.27, 3.52	0.02		– 0.88	1.30, 1.35	–
2b-(*R*)-MPTA	^{13}C	16.22	72.84	80.21	77.59	63.76	−5.41, −5.48		18.33, 25.97	26.91, 27.36	109.71
	^{1}H	1.31	5.27	4.01	–[a]	–[a]	0.06, 0.07		– 0.89	1.35, 1.38	–
5	^{13}C	45.73	79.74	81.05	76.05	16.50	–	–	– –	27.09, 27.13	109.83
	^{1}H	3.62, 3.77	4.13	3.77	3.62	1.32	–	–	– –	1.40, 1.45	–
6[b]	^{13}C	74.11	81.71	64.98	76.67	14.58	–	–	– –	– –	–
	^{1}H	2.49	–	4.43	3.70	1.31	–	–	– –	– –	–
8	^{13}C	101.23	93.09	45.49	71.11	19.32	−4.93	–	16.60, 25.98	– –	–
	^{1}H	–	–	4.44	3.94	1.40	0.129	–	– 0.95	– –	–
9	^{13}C	101.05	89.39	45.59	54.11	14.65	−4.77	–	16.42, 26.00	– –	–
	^{1}H	–	–	3.42[c]	3.16[c]	1.44	0.127	–	– 0.945	– –	–

[a] Obscured by signals from major isomer **2a**.
[b] Benzyl group: ^{13}C: 71.06, 137.93(s), 127.70(o), 128.30(m), 127.72(p); ^{1}H: 4.57, 4.68, 7.33–7.38.
[c] Vicinal coupling of $J = 4.0$ Hz refers to *cis* configuration.

tuents in **6**. Propargylic alcohol **6** was disilylated to afford **7** in 60% yield (40% of starting material was recovered as *O*-silylated product). Debenzylation followed by a simultaneous highly stereoselective bromination of **7** with boron tribromide[8] afforded bromohydrin **8**. The diastereomeric purity of this compound was determined by HPLC and also by ^{1}H and ^{13}CNMR, and found to exceed 98%. Under basic conditions bromohydrin **8** was converted into target cis epoxide **9** in 92% yield. *cis*-Configuration at the oxirane ring is confirmed by a 4.0 Hz vicinal coupling constant.[7]

The absolute configuration of target compound **9** was determined by its regioselective reduction to homopropargylic alcohol with lithium aluminum hydride. The optical rotation ($[\alpha]_D - 19.8°$) confirms the 4*S*-configuration in **9** ($[\alpha]_D - 20.0°$ for (*S*)-4-pentyn-2-ol[14]).

Since tartaric acid is available in both enantiomeric forms, the enantiomeric epoxide of **9** may also be prepared by applying the present method.

IR spectra were measured with a Specord IR-75 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-500 spectrometer in $CDCl_3$ solution. The chemical shifts are reported in relative to TMS from solvent ($CDCl_3$) signal ($\delta_H = 7.27$, $\delta_C = 77.0$) and are presented in the Table. Optical rotations were obtained at 20°C using a Polamat A polarimeter. Microanalyses were obtained using a Hewlett-Packard 178 element analyser. Mass spectra were recorded on a Hitachi M80B spectrometer at an ionizing potential 70 eV. HPLC analyses were performed using a LKB liquid chromatograph equipped with a UV spectrophotometric detector (206 nm, 254 nm; column Separon SGX 3 × 300 mm). Merck silica gel 60 (230–400 mesh) was used for column chromatography. THF was distilled from $LiAlH_4$ before use.
Compound **1** was prepared according to Ref. 9. Due to its instability it was used in the next step without purification.

(3*S*,4*S*)-5-*tert*-Butyldimethylsiloxy-3,4-isopropylidenedioxy-2-pentanol 2a and 2b (Mixture of 2*S* and 2*R* Isomers):
To a stirred −20°C solution of aldehyde **1** (3.70 g, 13.5 mmol) in THF (40 mL) at −20°C was added dropwise MeLi (12 mL, 1.44 M in Et_2O, 17.3 mmol) under Ar. The mixture was allowed to warm to 0°C and was stirred at this temperature for 4 h. After addition of brine (20 mL) the layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated on a rotatory evaporator. Isomers **2a** and **2b** were separated by column chromatography on silica gel using hexane/EtOAc (100:4) as eluent to give 2.78 g of **2a** and 0.31 g of **2b**; total yield: 79%; $[\alpha]_D - 8.9°$ ($c = 8.0$, MeOH).

$C_{14}H_{30}O_4Si$ (290.5) calc. C 57.89 H 10.41
found 57.76 10.45

IR (film): ν = 3360, 2980, 1380, 1260, 1150, 1090, 840 cm^{-1}.

MS: *m/z* (%) = 275 ($M^+ - CH_3$ 22), 233 (12), 175 (63), 131 (100), 117 (72), 75 (93).

(2*S*,3*S*,4*S*)-4-Benzyloxy-1-*tert*-butyldimethylsiloxy-2,3-isopropylidenedioxypentane (3):
To a stirred suspension of NaH (55% dispersion in oil, 57 mg, 1.3 mmol) in THF (10 mL) at 0°C was added dropwise alcohol **3** (379 mg, 1.3 mmol) in THF (3 mL). Stirring was continued for 1 h allowing the mixture to warm up to r.t. The mixture was cooled to 0°C and Bu_4NI (48 mg, 0.13 mmol) and 18-crown-6 (3.4 mg, 0.01 mmol) were added in one portion. To this mixture benzyl bromide (223 mg, 1.3 mmol) was added, the resulting mixture was heated to 50°C and stirred at this temperature for 4 h. The reaction was quenched with brine (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with aqueous $Na_2S_2O_3$ (30 mL), dried ($MgSO_4$) and the solvent was evaporated on a rotatory evaporator. The reaction product was purified by column chromatography on silica gel (hexane/EtOAc, 100:2) affording **3**; yield: 321 mg (65%); $[\alpha]_D^{20} + 9.4°$ ($c = 7.15$, CH_2Cl_2).

$C_{21}H_{36}O_4Si$ (380.6) calc. C 66.27 H 9.53
found 66.17 9.51

IR (film): ν = 3030, 2870, 1550, 1490, 1260, 1090, 840 cm^{-1}.

MS: *m/z* (%) = 365 ($M^+ - CH_3$, 1), 235 (3), 187 (3), 135 (16), 91 (100), 75 (5).

(2*S*,3*S*,4*S*)-4-Benzyloxy-2,3-isopropylidenedioxy-1-pentanol (4):
To a solution of **3** (250 mg, 0.66 mmol) in THF (10 mL) was added Bu_4NF (1 M in THF, 0.66 mL, 0.66 mmol) and the mixture was stirred at r.t. for 15 min. The mixture was poured into water (10 mL) and extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$) and evapora-

Downloaded by: Collections and Technical Services Department. Copyrighted material.

ted to give **4**; yield: 175 mg (quant.). It was further used without purification. An analytical sample was obtained by chromatography on silica gel (hexane/EtOAc, 10:1); $[\alpha]_D$ + 39.8° (*c* = 2.86, CH_2Cl_2).

$C_{15}H_{22}O_4$ calc. C 67.65 H 8.33
(266.3) found 67.74 8.31

IR (film): *v* = 3300, 2980, 1560, 1480, 1390, 1220, 1090 cm^{-1}.

MS: *m/z* (%) = 251 ($M^+ - CH_3$, 4), 208 (3), 131 (23), 91 (100), 59 (60).

(2*R*,3*S*,4*S*)-4-Benzyloxy-1-chloro-2,3-isopropylidendioxypentane (5):
A solution of **4** (175 mg, 0.66 mmol) and Ph_3P (260 mg, 1 mmol) in anhydr. CCl_4 (0.38 mL) was stirred at 60 °C for 4 h. The mixture was allowed to cool to r.t. and was triturated with hexane (5 × 2 mL). The insoluble residue was filtered and the crude product and passed through a short column of silica gel eluting with hexane/EtOAc (100:4) to give **5** (150 mg, 80%); $[\alpha]_D$ + 30.7° (*c* = 2.72, CH_2Cl_2).

$C_{15}H_{21}ClO_3$ calc. C 63.26 H 7.43
(284.8) found 63.17 7.40

IR (film): *v* = 3030, 2890, 1570, 1490, 1260, 1120, 1090 cm^{-1}.

MS: *m/z* (%) = 269/271 (6), 226/228 (2), 149/151 (28), 135 (16), 91 (100), 59 (28)

(3*R*,4*S*)-4-Benzyloxy-1-pentyn-3-ol (6):
To a stirred solution of diisopropylamine (227 mg, 2.25 mmol) in THF (5 mL) was added dropwise BuLi (1.6 M in hexane, 1.41 mL, 2.25 mmol) at − 30 °C under Ar and the mixture was stirred for 30 min. The solution was cooled to − 78 °C, chloride **5** (128 mg, 0.45 mmol) was added in THF (1 mL) and the mixture was stirred at this temperature for 30 min. The mixture was allowed to warm up to 0 °C during 30 min and quenched with sat. aq NH_4Cl (2 mL). The solution was extracted with Et_2O (4 × 20 mL), dried ($MgSO_4$) and the solvents evaporated in vacuo. Flash chromatography on silica gel (hexane/EtOAc, 10:1) afforded propargylic alcohol **6**, yield: 70 mg (82%); mp 46–47 °C. $[\alpha]_D$ + 7.0° (*c* = 3.21, CH_2Cl_2).

$C_{12}H_{14}O_2$ calc. C 75.76 H 7.42
(190.2) found 75.84 7.46

IR (film): *v* = 3360, 2890, 1560, 1490, 1160, 1090 cm^{-1}.

MS: *m/z* (%) = 160 (2), 135 (41), 91 (100).

(3*R*,4*S*)-1-*tert*-Butyldimethylsilyl-3-*tert*-butyldimethylsiloxy-4-benzyloxy-1-pentyne (7):
To a solution of alcohol **6** (58 mg, 0.31 mmol) in THF (5 mL) was added BuLi (1.6 M in hexane, 0.38 mL, 0.61 mmol) at − 78 °C. The mixture was allowed to warm to − 20 °C and *t*-$BuSiMe_2Cl$ (138 mg, 0.92 mmol) in THF (1 mL) was added. The mixture was stirred for 4 h while warming up to r.t., and quenched with sat. aq NH_4Cl (2 mL). The mixture was extracted with hexane (3 × 20 mL), washed with brine, dried ($MgSO_4$) and the solvents were evaporated. Column chromatography on silica gel eluting with hexane afforded disilylated compound **7**; yield: 78 mg (60%); $[\alpha]_D$ − 42.4° (*c* = 3.64, CH_2Cl_2).

$C_{24}H_{42}O_2Si_2$ calc. C 68.84 H 10.11
(418.8) found 68.91 10.13

IR (film): *v* = 2980, 2890, 2240, 1480, 1120, 850, 840 cm^{-1}.

MS: *m/z* (%) = 361 (1), 171 (3), 131 (16), 91 (100), 75 (7), 73 (53).

(3*S*,4*S*)-3-Bromo-1-*tert*-butyldimethylsilyl-1-pentyn-4-ol (8):
To a stirred solution of **7** (84 mg, 0.20 mmol) in anhydr. CH_2Cl_2 (4 mL) BBr_3 (50 mg, 0.20 mmol) was added at stirring at − 78 °C. After stirring for 2 h at this temperature, aq $NaHCO_3$ (1 mL) was added. The mixture was allowed to warm to r.t., extracted with Et_2O (3 × 20 mL), dried ($MgSO_4$) and the solvents were evaporated; yield: 50 mg (91%). The crude product was used in the next step without purification. An analytical sample was obtained by chromatography on silica gel (hexane/EtOAc, 100:5); $[\alpha]_D$ − 17.3° (*c* = 0.93, CH_2Cl_2).

$C_{11}H_{21}BrOSi$ calc. C 47.65 H 7.63
(277.3) found 47.55 7.59

IR (film): *v* = 3300, 2980, 1260, 1040, 840, 820 cm^{-1}.

MS: *m/z* (%) = 219/221 (1), 196 (1), 180 (7), 139 (44), 123 (100), 75 (37)

(3*R*,4*S*)-1-*tert*-Butyldimethylsilyl-3,4-epoxy-1-pentyne (9):
A solution of **8** (70 mg, 0.25 mmol) and K_2CO_3 (52 mg, 0.38 mmol) in 1:1 mixture of acetone/H_2O (10 mL) was stirred at r.t. for 30 min. Acetone was evaporated in vacuo, the mixture was extracted with Et_2O (3 × 20 mL), washed with brine, dried ($MgSO_4$) and the solvents were evaporated. The residue was passed through as silica gel column eluting with pentane to give **9**; yield: 45 mg (92%); $[\alpha]_D$ − 35.2° (*c* = 2.91, CH_2Cl_2).

$C_{11}H_{20}OSi$ calc. C 67.68 H 10.27
(196.4) found 67.74 10.29

IR (film): *v* = 3060, 2240, 1370, 1260, 860, 840, 820 cm^{-1}.

MS: *m/z* (%) = 196 (M^+, 10), 139 (100), 97 (37), 83 (53), 75 (67).

We thank the Estonian Science Foundation for financial support and Dr. A. Müürissepp for measuring MS.

(1) Midland, M.M. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: 1983; Vol. 2; Part A, p 64.
(2) Alexakis, A; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* **1990**, *112*, 8042
(3) Pasto, D.J. *Tetrahedron* **1984**, *40*, 2805.
(4) Huguet, J.; Carmen Reyes, M. *Tetrahedron Lett.* **1990**, *31*, 4279. Gooding, O.W.; Beard, C.C.; Jackson, D.Y.; Wren, D.L.; Cooper, G.F. *J. Org. Chem.* **1991**, *56*, 1083.
(5) Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(6) Oehlschlager, A.C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587.
(7) Lee, N.H.; Jacobsen, E.N. *Tetrahedron Lett.* **1991**, *32*, 6533.
(8) Lopp, M.; Kanger, T.; Müraus, A.; Pehk, T.; Lille, Ü. *Tetrahedron: Asymmetry* **1991**, *2*, 943.
(9) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.
(10) Nemoto, H.; Takumatsu, S.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 1321.
(11) Gruber, L.; Tömösközi, I.; Radics, L. *Synthesis* **1975**, 708.
(12) Kang, S.K.; Lee, D.H.; Lee, J.M. *Synlett* **1990**, 591.
(13) Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* **1989**, *54*, 1570.
(14) Jacobson, R.; Taylor, R.J.; Williams, H.J.; Smith, L.R. *J. Org. Chem.* **1982**, *47*, 3140.

Downloaded by: Collections and Technical Services Department. Copyrighted material.