

Synthesis of a Novel Four-Carbon Chiron - (R)-1-*t*-Butyldimethylsilyl-3,4-Epoxy-but-1-yne

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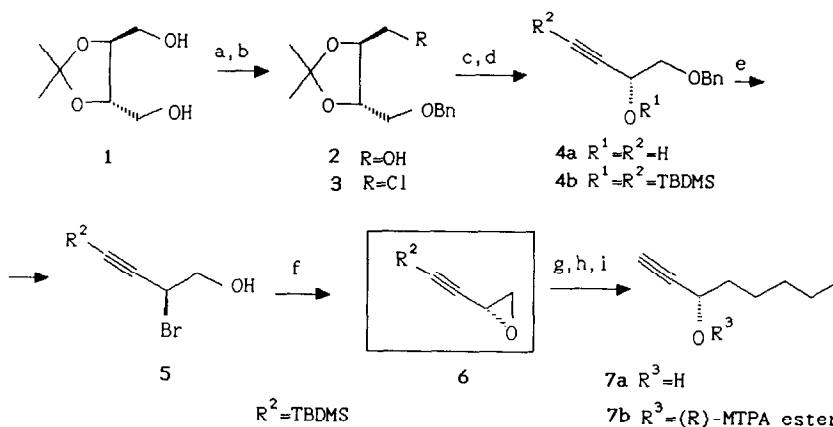
Abstract: A simple and efficient synthesis of the novel chiron-(R)-1-TBDMS-3,4-epoxy-but-1-yne has been developed starting from a derivative of (R,R)-(+)-tartaric acid. A new stereoselective bromination reaction of an O-silyl ether with BBr₃ is also described.

Among the wide variety of chirons,¹ homochiral epoxides have a prominent place as versatile intermediates for the synthesis of different natural products.² Although optically active allylic epoxides can easily be made by the Sharpless oxidation,³ a direct synthesis of epoxides from readily available natural products is still of great importance. As an extension of our synthetic studies⁴ on the use of the least expensive homochiral natural compound (R,R)-(+)-tartaric acid,⁵ we have developed a novel, four-carbon bifunctional chiron (R)-1-*t*-butyldimethylsilyl-3,4-epoxy-but-1-yne **6**.

The synthesis of **6** starts from (S,S)-(+)-2,3-O-isopropylidene-L-threitol **1**, which can easily be obtained from (R,R)-(+)-tartaric acid ester.⁶ While the direct chlorination of **1** gives mainly a disubstituted product, selective monobenylation⁵ was first carried out to afford alcohol **2** which under mild and non-acidic conditions (Ph₃P; CCl₄)⁷ was converted into chloride **3**. The base induced elimination reaction (LiNH₂ in liquid ammonia)⁸ led to propargylic alcohol **4a** in 70% yield. Although it has been stated that no epimerization takes place under these conditions,⁹ we have checked the optical purity of intermediate **4a** prior to subsequent conversions. For that the corresponding Mosher ester¹⁰ was prepared from (R)-(+)- α -methoxy- α -trifluoromethylphenylacetic acid (Aldrich) and the alcohol **4a**. HPLC analysis of the product¹¹ as well as NMR spectra (¹H; ¹³C) did not reveal any trace of the diastereomer corresponding to the (S)-alcohol. Also, in order to verify the absolute configuration, compound **4a** was hydrogenated (H₂/Pd on C) to give (R)-1,2-butanediol with $[\alpha]_D^{20} = +14.8$ (lit.¹² for R-isomer $[\alpha]_D^{20} = +12.6$).

The protection of the triple bond and also the OH group of (R)-4-benzyloxy-3-hydroxy-but-1-yne **4a** with TBDMSCl afforded the disilylated compound **4b**. An unexpected, highly stereoselective bromination together with the simultaneous debenylation of **4b** with BBr₃ as the key step led to the formation of bromohydrin **5**¹³. Under the basic conditions bromohydrin **5** was epoxidized into the target chiron **6**^{14,15}.

The absolute configuration of the chiral centre at C-3 in **6** was determined by the conversion of **6** into the corresponding oct-1-yn-3-ol **7a** with dibutylcuprate. The silyl group was removed with Bu₄NF. The optical rotation of **7a** ($[\alpha]_D^{20} = -21$) confirms its *S* configuration ($[\alpha]_D^{20} = -23$ for (S)-oct-1-yn-3-ol⁹) which corresponds to the R configuration of chiron **6**. The high optical purity of epoxide **6** (e.e. 99%) was determined using the Mosher ester **7b** of octynol **7a** derived from chiron **6** as noted above, by means of HPLC and NMR. This result also demonstrates the high selectivity of the last two steps (**4b** → **5** → **6**) including the new stereoselective bromination reaction of silyl ether **4b**.

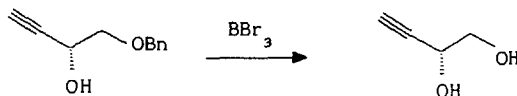


a: NaH, BnCl, DMFA, -20-0°C, 1h r.t. (75%); b: Ph₃P, CCl₄, 70°C, 2h (95%); c: LiNH₂, liq. NH₃, -33°C, 0.5h (70%); d: BuLi, THF, -78°C followed by t-BuMe₂SiCl, -20°C to r.t., 6h (59%); e: BBr₃, CH₂Cl₂, -70°C, 15 min, (85%); f: K₂CO₃, acetone/H₂O, 30 min, r.t. (70%); g: Bu₂LiCu, Et₂O, -60°C, 1h; h: Bu₄NF, THF, 30 min r.t.; i: (R)-MTPA, DCC, DMAP, THF, r.t.

In summary, chiron **6**, which is easily available in both enantiomeric forms from (R,R) or (S,S) tartaric acid, is a promising intermediate for asymmetric synthesis. One of its possible applications, the synthesis of homochiral propargylic alcohols, has already been demonstrated in the present paper. Further applications of this bifunctional chiron are currently under study.

References and Notes:

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11. Column, Zorbax Sil (250 x 4.6 mm); mobile phase, hexane:ethylacetate, 100:4; flow rate, 0.6 ml/min; detection, UV 254 nm.
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13. The debenzoylation of unprotected alcohol **4a** with BBr₃ afforded diol:



14. All the compounds were fully characterized by spectroscopic methods (NMR, IR, MS). ¹³C and ¹H NMR at 500.1 and 125.7 MHz in CDCl₃, chemical shifts δ_{TMS} from C-1 to C-n: **4a**: δ_c = 73.67, 81.67, 61.49, 73.47, 73.37, 137.48, 127.78 (o), 128.47 (m), 127.91 (p); **5**: δ_c = 67.00, 39.53, 100.87, 92.87, -4.90, 16.56, 25.98; **6**: δ_c = 48.95, 39.89, 102.53, 87.55, -4.82, 16.43, 25.98; **7b**: 74.61, 79.72, 66.11, 34.23, 24.49, 31.06, 22.37, 13.83.

15. Optical rotations ([α]_D²⁰) measured in CHCl₃: **1**: +3.8 (c = 10.0); **2**: -9.97 (c = 3.31); **3**: +1.51 (c = 5.29); **4a**: -8.54 (c = 2.68); **4b**: -28.8 (c = 5.63); **5**: -2.66 (c = 4.66); **6**: -72.3 (c = 5.63, in CH₂Cl₂).