PRACTICAL SYNTHESIS OF (*S*)-1-OCTYN-3-OL: A KEY INTERMEDIATE FOR THE PROSTAGLANDIN SYNTHESIS

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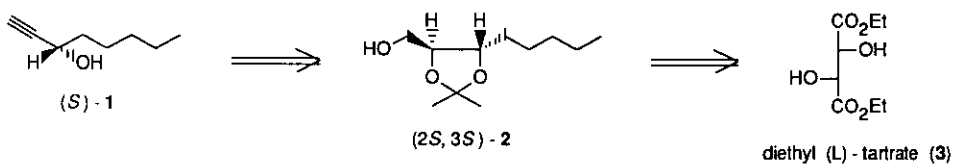
Abstract —— Practical synthesis of (*S*)-octyn-3-ol is devised starting from (2*S*,3*S*)-2,3-*O*-isopropylidenedioxyoctanol readily accessible from diethyl (L)-tartrate.

(*S*)-1-Octyn-3-ol (**1**) is a key intermediate for the construction of the medicinally important prostaglandins[1] as the C_{13}-C_{20} segment. Development of an efficient chiral method leading to the production of optically pure **1** other than resolution[1b] is, therefore, the most important. Although there have been reported some enantioselective methods producing optically active **1** by chiral reduction[1d,2] or by Sharpless epoxidation,[3,4] optical purities introduced were less satisfactory from the medicinal point of view or the procedures employed were not straightforward even though satisfactory optical yield could be obtained.

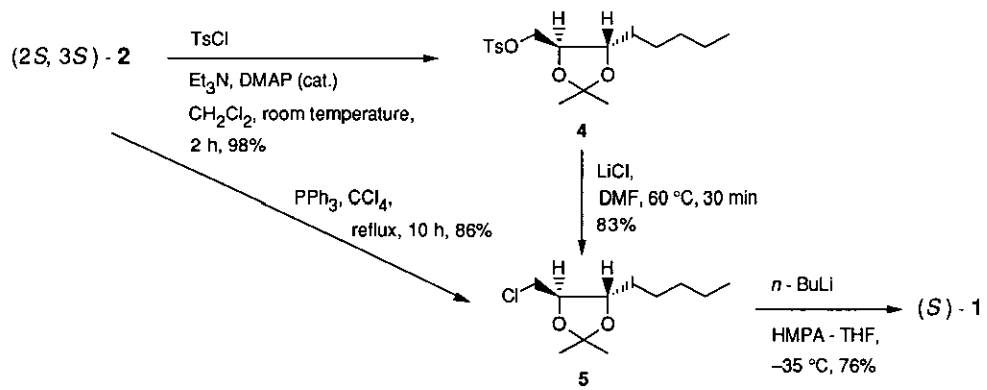
We report herein a practical synthesis of optically pure (*S*)-**1** starting from (2*S*,3*S*)-2,3-*O*-isopropylidenedioxyoctanol[5] (**2**) which may be accessible without difficulties from diethyl (L)-tartrate (**3**) (Scheme 1).



Scheme 1

Treatment of (2*S*,3*S*)-(**2**), $[\alpha]_D^{29}$ –29.34° (*c* 0.81, $CHCl_3$) [reported[5]: $[\alpha]_D^{28}$ –25.36° (*c* 2.32, $CHCl_3$)], prepared from diethyl (L)-tartrate (**3**) in a three or a four step sequence of reactions in about 70% overall yield according to Sakai and co-workers,[5] with *p*-toluenesulfonyl chloride in the presence of triethylamine and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) gave the tosylate (**4**) in an excellent yield. Stirring of **4** with lithium chloride dissolved in warm *N*,*N*-dimethylformamide (DMF) brought about facile exchange reaction to yield the primary chloride (**5**). Overall yield of **5** from the starting alcohol (**2**) was 81%. The chloride (**5**) could also be obtained directly from **2** in 86% yield upon refluxing **2** with triphenylphosphine in carbon tetrachloride.[6]

Transformation of the chloride (**5**) into the target acetylene alcohol [(*S*)-**1**] was carried out in one step by application of the same conditions established for the α-chloromethylepoxides.[4,7,8] Thus, upon exposure to *n*-butyllithium in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA) at –35 °C, **5** furnished the expected acetylene alcohol [(*S*)-**1**] in 76% yield after purification (Scheme 2).



Scheme 2

Since the present method allows direct incorporation of one of the chiral centers of the tartrate ester (**3**) intact, optically pure acetylene alcohol (**1**) can be readily accessible from optically pure tartrate (**3**).

EXPERIMENTAL SECTION

Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Mass spectra were recorded with a JEOL JMS-DX303 instrument, ir spectra with a JASCO A102 spectrophotometer, and ^{1}H Nmr spectra on JEOL-JNM-FX90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Reactions were carried out under argon.

(2*S*,3*S*)-2,3-*O*-Isopropylidenedioxy-1-*p*-toluenesulfonyloxyoctane (4) ----- To a stirred solution of the alcohol,[5] $[\alpha]_D^{29}$ –29.34° (*c* 0.81, $CHCl_3$) [lit.[5] $[\alpha]_D^{28}$ –25.36° (*c* 2.32, $CHCl_3$)], (**2**: 138 mg, 0.68 mmol) in dichloromethane (2.0 ml), triethylamine (0.19 ml, 1.36 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (8.0 mg, 65 μmol), and *p*-toluenesulfonyl chloride (156 mg, 0.82 mmol) were added sequentially at 0 °C and the stirring was continued for 2 h at room temperature. After evaporation of the solvent under reduced pressure, the residue was taken up into ether and the ethereal solution was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave a pale yellow oil. The oil was purified by chromatography on a silica gel column (8.0 g) using a mixture of ether-hexane (1:10 v/v) as eluent to give the pure tosylate (**4**) as a colorless oil; yield: 238 mg (98%); $[\alpha]_D^{29}$ –17.06° (*c* 1.05, $CHCl_3$). Ir (film) ν_{max}: 1455, 1368, 1189, 1177, 666 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 0.68-1.78 (m, 11H), 1.30, 1.36 (each s, each 3H), 2.45 (s, 3H), 3.60-3.92 (m, 2H), 3.92-4.26 (m, 2H), 7.34 (d, *J*=8.3 Hz, 2H), 7.80 (d, *J*=8.3 Hz, 2H); ms (mz): 341 (M^+-15, 100%), 213, 155, 109, 91. *Anal.* Calcd for $C_{17}H_{25}O_5S$: 341.1422. Found: 341.1425.

(a) (2*S*,3*S*)-1-Chloro-2,3-*O*-isopropylidenedioxyoctane (5) from the tosylate (4) —— A mixture of the tosylate (**4**: 492 mg, 1.38 mmol) and lithium chloride (92.0 mg, 2.17 mmol) in *N*,*N*-dimethylformamide (DMF) (6.0 ml) was stirred at 60 °C for 3.5 h. After cooling, the mixture was diluted with ether and was washed with water and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the pale yellow oily residue was purified by chromatography on silica gel column (20 g) using a mixture of ether-hexane (1:50 v/v) as eluent to give the pure chloride (**5**) as a colorless oil; yield: 252 mg (83%); $[\alpha]_D^{28}$ –16.47° (*c* 1.08, $CHCl_3$). Ir (film) ν_{max}: 1458, 1377, 749 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 0.90 (br t, *J*=6.0 Hz, 3H), 1.42 (s,

6H), 1.03-1.85 (m, 8H), 3.46-3.72 (m, 2H), 3.72-4.04 (m, 2H); ms (m/z): 207 (M^+-15), 205 (M^+-15), 171, 149, 43 (100%). *Anal.* Calcd for $C_{11}H_{22}O_2{}^{37}Cl$: 223.1279. Found: 223.1299. Calcd for $C_{11}H_{22}O_2{}^{35}Cl$: 221.1308. Found: 221.1299.

(b) **(2*S*,3*S*)-1-Chloro-2,3-*O*-isopropylidenedioxyoctane (5) from the alcohol (2)** —— A solution of the alcohol (**2**) (83.0 mg, 0.41 mmol) and triphenylphosphine (163 mg, 0.62 mmol) in carbon tetrachloride (3.0 ml) was refluxed for 10 h. After removal of the precipitate by filtration using Celite, the filtrate was diluted with ether and the organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the pale yellow oily residue was purified by chromatography on silica gel column (6.0 g) using a mixture of ether-hexane (1:50 v/v) as eluent to give the pure chloride (**5**) as a colorless oil; yield: 78.0 mg (86%). Physical and spectral data were identical with those of **5** obtained via the tosylate (**4**).

(*S*)-1-Octyn-3-ol (1) —— To a stirred solution of *n*-butyllithium (1.40 M hexane solution, 4.9 ml, 6.86 mmol) and hexamethylphosphoric triamide (HMPA) (1.20 ml, 6.90 mmol) in tetrahydrofuran (THF) (3.0 ml) was added the chloride (**5**: 252 mg, 1.14 mmol) in THF (5.0 ml) dropwise within 5 min at –35 °C. After 8 min at the same temperature, the reaction mixture was treated with saturated aqueous NH_4Cl and was raised to room temperature. The organic layer was separated, washed with brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the pale yellow oily residue was purified by chromatography on silica gel column (15 g) using a mixture of ether-hexane (1:4 v/v) as eluent to give the pure acetylene alcohol (**1**) as a colorless oil; yield: 110 mg (76%); bp 130 °C/760 Torr (Kugelrohr), $[\alpha]_D{}^{31}$ –23.28° (*c* 0.70, Et_2O) [~100% ee by ^1H nmr (500 MHz) of (*R*)- and (*S*)-MTPA esters[9]] [lit. $[\alpha]_D{}^{20}$ –21.0° (*c* 1.0, Et_2O),[1b] $[\alpha]_D{}^{21}$ +22.0° (*c* 1.10, Et_2O)[3b]]. Ir (film) ν_{max}: 3400, 3310, 1466 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.90 (br t, *J*=5.9 Hz, 3H), 0.95-2.10 (m, 9H, 1H exchangeable with D_2O), 2.46 (d, *J*=2.2 Hz, 1H), 4.16-4.52 (m, 1H). Spectral data were identical with those of an authentic material.

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Received, 26th July, 1990