Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Shun-Ichi Hashimoto, Satoshi Kase, Atsushi Suzuki, Yuki Yanagiya & Shiro Ikegami (1991) A Practical Access to Optically Pure (S)-1-Octyn-3-ol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:6, 833-839, DOI: 10.1080/00397919108019765

To link to this article: http://dx.doi.org/10.1080/00397919108019765

SYNTHETIC COMMUNICATIONS, 21(6), 833-839 (1991)

A PRACTICAL ACCESS TO OPTICALLY PURE (*S*)-1-OCTYN-3-OL

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ABSTRACT: A highly efficient resolution of (±)-1-octyn-3-ol through recrytallization of the diastereomeric esters has been achieved by using *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanyl chloride as resolving reagent. The method provides a facile and economical entry to (*S*)-1-octyn-3-ol, a valuable building block for the synthesis of arachidonic acid metabolites.

(*S*)-1-Octyn-3-ol ((*S*)-**1**) is a fundamental source[1] of (*S*)-(*E*)-3-[(tert-butyldimethylsilyl)oxy]-1-(tributylstannyl)-1-octene and (*S*)-(*E*)-1-bromo or iodo-3-[(tert-butyldimethylsilyl)oxy]-1-octene, which are not only ω side-chain units for prostaglandin syntheses[2] but also are now being recognized as valuable segments for the syntheses of the other arachidonic acid metabolites such as levuglandins,[3] diHETE's,[4] and lipoxin A_4.[5] In connection with our studies on the convergent synthesis of (+)-isocarbacyclin and its analogues,[6] we required a large quantity of optically pure (*S*)-**1**. Although there have been reported a number of methods for the access to (*S*)-**1** including a) optical resolution of the racemate *via* the crystalline

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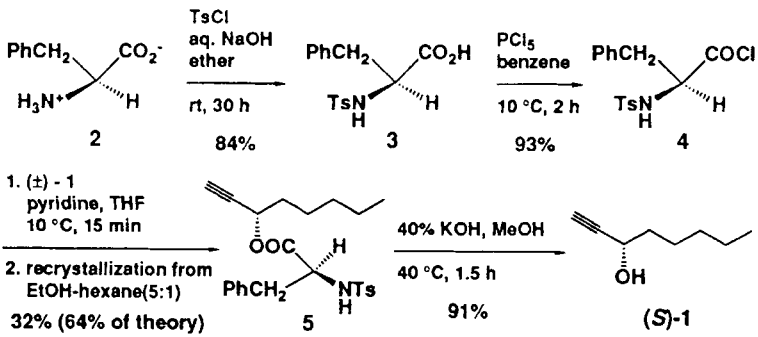
(*S*)-α-methylbenzylamine salt of the hydrogen phthalate[7] or the crystalline 3β-acetoxy-5,16-etiadienate,[8] b) enzymic resolution of the racemic acetate,[9] c) highly enantioselective reduction of 1-octyn-3-one with BINAL-H,[10] Alpine-Borane,[11] or NB-Enantrane,[11] d) Lewis acid catalyzed coupling of a chiral acetal derived from hexanal and (2*S*,4*S*)-2,4-pentanediol with trimethylsilylacetylene,[12] e) enantioselective addition of dipentylzinc to 3-trimethylsilyl-2-propynal using a chiral amino alcohol as catalyst,[13] f) kinetic resolution of (±)-(*E*)-1-iodo-1-octen-3-ol by the Sharpless asymmetric epoxidation followed by 1,2-dehydrohalogenation reaction,[14] g) double elimination of chiral 1-chloro-2,3-epoxyoctane prepared *via* the Sharpless epoxidation,[15] and h) multi-step preparation starting with (*R*)-*O*-tetrahydropyranylglycidol,[16] there still remains a need for the more economical and operationally simple procedure enabling the large-scale preparation of optically pure (*S*)-**1**. Herein we wish to report that a highly efficient resolution of (±)-**1** into (*S*)-**1** can be effected through recrystallization of the diastereomeric esters prepared from (±)-**1** and *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanyl chloride (**4**)[17] as resolving reagent.[18]

The acid chloride **4** was readily prepared from (*S*)-phenylalanine (**2**) by tosylation and subsequent chlorination with PCl_5. Condensation of (±)-**1** with **4** led to the formation of a crystalline mixture of the diastereomeric esters, which was cleanly separated by recrystallization four times from ethanol-hexane (5:1) to give the ester **5** as a single diastereomer in 32% yield (64% of theory). The homo-



chirality of **5** was rigorously established by comparison of ^{1}H NMR (400 MHz) spectrum with a mixture of the diastereomeric esters. Concentration of the mother liquor followed by alkaline hydrolysis recovered *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanine (**3**) without loss of optical purity and optically active (*R*)-**1**, $[\alpha]_D^{22}$ +10.0° (*c* 1.27, ether). The latter could be transformed into (±)-**1** for reuse by Jones oxidation and subsequent sodium borohydride reduction. Alkaline hydrolysis of **5** furnished the desired (*S*)-**1**, $[\alpha]_D^{22}$ -22.2° (*c* 1.16, ether) [lit.[19] $[\alpha]_D$ -21° (*c* 1.0, ether)], the homochirality of which was further confirmed by adopting the Mosher ester technique.[20]

In conclusion, the present method has advantages in providing a facile entry to optically pure (*S*)-**1**, and including practical value as well as operational simplicity.

Experimental Section

General. Melting points were determined on a Yanagimoto micro melting apparatus and are not corrected. Infrared (IR) spectra were recorded on a JASCO A-302 diffraction grating infrared spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-GX 400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane as an internal standard. Optical rotations were recorded on a JASCO DIP-181 polarimeter. Mass spectra (MS) were determined on a JEOL JMS-D 300 mass spectometer, operating with an ionization energy of 70 eV. Bulb-to-bulb distillation was performed using Büchi Kugelrohr apparatus, and the oven temperature is recorded as boiling point.

Commercial grade reagents and solvents were used without further purification except as indicated below. Pyridine was distilled from calcium hydride. Benzene was azeotropically distilled, and tetrahydrofuran was distilled from sodium benzophenone ketyl.

***N*-(*p*-Toluenesulfonyl)-(*S*)-phenylalanine (3).** (*S*)-Phenylalanine (**2**) (180 g, 1.09 mol) was dissolved in a solution of NaOH (61.2 g, 1.53 mol) and Na_2CO_3 (162.2 g, 1.53 mol) in water (1.2 L) at 0 °C. To this solution was added ether (450 mL) and then *p*-toluenesulfonyl chloride (207.8 g, 1.09 mol), and the whole mixture was mechanically stirred at room temperature for 30 h. The reaction

mixture containing a large mass of white precipitates was poured into an ice-cold, two-layer mixture of ether (250 mL) and *c*. HCl (600 mL), and the whole was extracted with ethyl acetate (2 x 1 L). The organic layers were washed with brine (3 x 150 mL), dried over anhydrous Na_2SO_4, filtered, and then evaporated *in vacuo*. The resultant solid (322 g) was recrystallized from chloroform (3 L) to give the product **3** (185 g, 53%) as colorless fine needles. Concentration of the mother liquor followed by recrystallization gave the further crops (108 g, 31%): mp 166~167 °C (lit.[17] mp 163~165 °C); $[\alpha]_D^{22}$ -2.53° (*c* 4.51, acetone); IR (nujol) 3300, 3000~2500, 1730, 1670, 1600, 1497, 1340, 1162 cm^{-1}; ^1H NMR (CD_3OD) δ 2.37 (3H, s), 2.83 (1H, dd, J=8.2, 13.7 Hz), 3.02 (1H, dd, J=5.7, 13.7 Hz), 4.01 (1H, dd, J=5.7, 8.2 Hz), 7.09~7.13 (2H, m), 7.16 ~7.20 (3H, m), 7.21 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz); MS *m/z* 274 (M^+-COOH).

***N*-(*p*-Toluenesulfonyl)-(*S*)-phenylalanyl Chloride (4).** *N*-(*p*-Toluenesulfonyl)-(*S*)-phenylalanine (**3**) (121 g, 0.38 mol) was added to a stirred suspension of PCl_5 (86 g, 0.41 mol) in dry benzene (900 mL) at 10 °C. The whole mixture was stirred at this temperature for 2 h, and then at room temperature for 1 h. After the two third of the benzene was removed *in vacuo*, hexane (500 mL) was added to the concentrated mixture, and then filtered through Celite$_{545}$ with suction to furnish the crude product (119 g, 93%) as white powders. This acid chloride **4** was used without further purification for the next reaction. The analytical sample was obtained by recrystallization from chloroform-hexane (2:1) as colorless prisms: mp 132.5~133.5 °C (decomp.) [lit.[17] mp 128~129 °C (decomp.)]; $[\alpha]_D^{22}$ +9.38° (*c* 2.97, $CHCl_3$); IR (nujol) 3300, 1815, 1600, 1500, 1320, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (3H, s), 3.17 (2H, d, J=6.1 Hz), 4.51 (1H, dt, J=6.1, 9.5 Hz), 5.00 (1H, br d, J=9.5 Hz), 7.08~7.13 (2H, m), 7.23~7.32 (5H, m), 7.59 (2H, d, J=8.6 Hz); MS *m/z* 339, 337 (M^+); Anal. Calcd for $C_{16}H_{16}NO_3SCl$: C, 56.89; H, 4.77; N, 4.14. Found: C, 56.99; H, 4.75; N, 3.91.

(*S*)-1-Octyn-3-yl *N*-(*p*-Toluenesulfonyl)-(*S*)-phenylalaninate (5). To a vigorously stirred solution of (±)-**1** (36.5 g, 0.29 mol) in dry THF (45 mL) was added rapidly pyridine (117 mL, 1.45 mol) and then a suspension of **4** (152 g, 0.45 mol) in dry THF (240 mL) at 10 °C under argon atmosphere. After 15 min of stirring at this temperature, the mixture was treated with an ice-cold water (5 mL) followed by stirring for 0.5 h. The whole mixture was partitioned between

ethyl acetate-hexane (10:1, 700 mL) and water (200 mL). The separated organic layer was washed with 20% aq. HCl (2 x 150 mL), water (50 mL), and satd. $NaHCO_3$ solution-water (1:1, 2 x 60 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* afforded the crude product (136 g) as a pale yellow solid, which was recrystallized four times from EtOH-hexane (5:1, 42 mL/10 g) to give the diastereomerically pure ester **5** (39.7 g, 64% of theory) as colorless fine needles: mp 124.5~125.5 °C ; $[\alpha]_D^{22}$ -48.4° (*c* 2.21, $CHCl_3$); IR (nujol) 3330, 3300, 1720, 1600, 1497, 1327, 1270, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t , J=7.0 Hz), 1.20~1.34 (6H, m), 1.51~1.64 (2H, m), 2.39 (3H, s), 2.46 (1H, d, J=2.1 Hz), 3.07 (2H, d, J=5.5 Hz), 4.22 (1H, dt, J=5.5, 9.5 Hz), 5.02 (1H, d, J=9.5 Hz), 5.09 (1H, dt, J=2.1, 6.7 Hz), 7.12~7.17 (2H, m), 7.20~7.28 (5H, m), 7.63 (2H, d, J=8.2 Hz) ; MS *m/z* 427.1806 (M^+, calcd for $C_{24}H_{29}NO_4S$ 427.1815); Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.28. Found: C, 67.37; H, 6.85; N, 3.16. The homochirality of this sample was judged by ^1H NMR analysis [diagnostic signals for the diastereomer of **5**: δ 0.88 (3H, t, J=7.0 Hz), 3.04 (2H, d, J=6.2 Hz), 7.08~7.12 (2H, m)].

From the combined mother liquor, the acid **3** (49.4 g), mp 166~167 °C, $[\alpha]_D^{22}$ -2.52° (*c* 4.68, acetone), and optically active (*R*)-**1** (20.2 g), $[\alpha]_D^{22}$ +10.0° (*c* 1.27, ether), were recovered by the usual method (*vide infra*).

(*S*)-1-Octyn-3-ol ((*S*)-1). To the ester **5** (38.5 g, 0.09 mol) was added EtOH (65 mL) and then 40% aq. KOH (37 mL), and the whole was heated at 40°C for 1.5 h. After the solution was concentrated *in vacuo* to one fourth of the original volume, the resultant solution was partitioned between ether-hexane (10:1, 150 mL) and water (50 mL), and the organic layer was separated. The aqueous layer was further extracted with ether-hexane (10:1, 2 x 75 mL), and the combined organic layers were washed with water (10 mL), satd. NH_4Cl solution-brine (1:1, 15 mL), and brine (2 x 15 mL), and then dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (11.2 g), which was purified by column chromatography on silica gel (Wakogel C-200, 80 g) with ether-hexane (10:1~1:1) and subsequent bulb-to-bulb distillation to give (*S*)-**1** (10.3 g, 91%) as a colorless oil: bp 100 °C (20 mmHg); $[\alpha]_D^{22}$ -22.2° (*c* 1.16, ether) [lit.[19] $[\alpha]_D$ -21° (*c* 1.0, ether)]; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J= 7.0 Hz), 1.28~1.40 (4H, m), 1.40~1.54 (2H, m), 1.68~1.78 (2H, m), 1.89 (1H, br s), 2.46 (1H, d, J=2.1 Hz), 4.37 (1H, ddt, J=2.1, 6.4, 6.4 Hz). (*R*)-(+)-MTPA ester of (*S*)-**1**: ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J=7.0 Hz), 1.26~1.37 (4H, m), 1.40~1.57 (2H, m),

1.80~1.92 (2H, m), 2.49 (1H, d, J=2.1 Hz), 3.55 (1H, q, J=1.2 Hz), 5.51 (1H, dt, J=2.1, 6.7 Hz), 7.38~7.45 (3H, m), 7.51~7.58 (2H, m) [diagnostic signals for the ester of (*R*)-**1**: δ 0.85 (3H, t, J=7.0 Hz), 2.54 (1H, d, J=2.1 Hz), 3.60 (1H, q, J=1.0 Hz)].

The alkaline aqueous phase was acidified with *c*. HCl (50 mL), and then extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and then evaporated *in vacuo* to leave a white solid (27.3 g), which was recrystallized from chloroform to give **3** (23.5 g, 82%) as colorless fine needles: mp 166~167 °C; $[\alpha]_D^{22}$ -2.50° (*c* 4.57, acetone).

Acknowledgement. We are grateful to Misses J. Otani, H. Ishido, and F. Taki for spectroscopic measurements. Partial financial support for this research from the Japan Research Foundation for Optically Active Compounds, the Fujisawa Foundation, and the Ministry of Education, Science and Culture of Japan is gratefully acknowledged.

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(Received in USA 5 February, 1991)