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Stereoselective Synthesis of (3S, 4R)-5-Phenylpentane-1, 3, 4-Triol

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Abstract

We describe an efficient synthesis of (3S, 4R)-5-Phenylpentane-1, 3, 4-triol (1) from commercially available 3-phenylpropanal for the first time. The key reactions involved in this synthesis are proline catalyzed hydroxylation, followed by (Z)-selective Wittig olefination, and Sharpless asymmetric epoxidation (Figure 1).

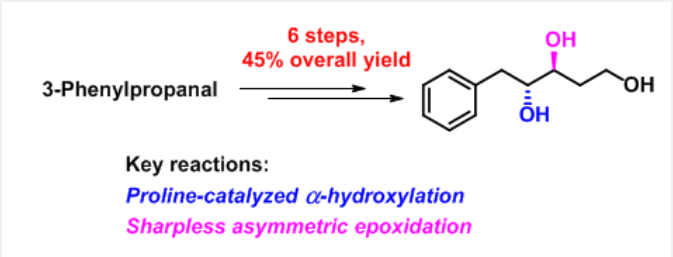
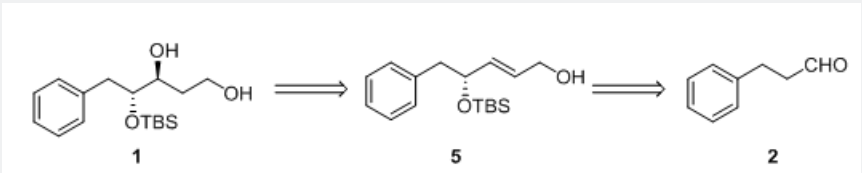


Figure 1.

Keywords: Natural product; Triol; Wittig olefination; Total synthesis; Alzheimers; Parkinsons

Introduction

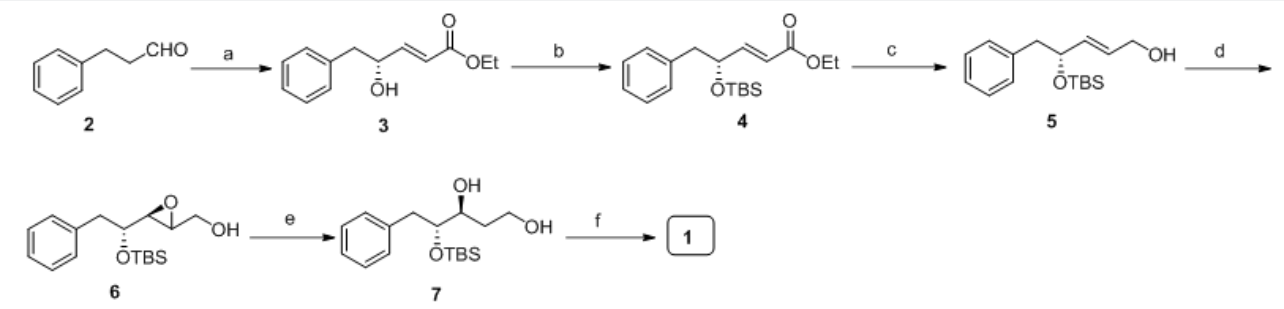
Polyhydroxylated compounds are ubiquitous structural motifs found in a multitude of naturally occurring compounds, pharmaceuticals and material interest [1-5]. In addition to this their synthetic analogues are important as lead structures or drug candidates for the discovery of novel drugs [6-9]. These compounds have explicitly exhibited a broad spectrum of biological activities including antibacterial, antitumoral, antimicrobial, antifeedant, herbicidal, plant growth inhibition and the inhibition of cholesterol biosynthesis properties [10-14]. Recently Hirokazu Kawagishi et al. isolated the triol compound named (3S,4R)-5-Phenylpentane-1,3,4-triol (1, Scheme 1) from the EtOH extract of edible mushroom *Mycoleptodonoides aitchisonii* [15]. It exhibits protective activity against endoplasmic reticulum (ER) stress-dependent cell death. ER stress is caused by abnormalities in cell function such as changes in calcium channel functioning or accumulation of misfolded protein and this may be responsible for Parkinson's, Alzheimer's and prion type of human neuronal diseases, and also other diseases (diabetes, atherosclerosis, and heart & liver disease) [16,17]. Therefore, development of efficient strategies for the preparation of natural and unnatural products, which exhibits protective activity against endoplasmic reticulum stress-dependent cell death, is of great significance. Due to its interesting structural features and evident pharmacological potential, the synthesis of 1 has attracted much attention for the synthetic and medicinal chemists. In continuation of our research on the synthesis of biologically significant natural products from simple starting materials [18,19]. We herein, report a first total synthesis of 1, starting from 3-phenylpropanal (2) in a six steps with 45% overall yield.



Scheme 1: Retrosynthetic plan of (3S, 4R)-5-Phenylpentane-1, 3, 4-triol (1).

Results and Discussion

Our approach to the asymmetric synthesis of (3S, 4R)-5-Phenylpentane-1, 3, 4-triol (1) is shown in scheme 1. We envisioned that the target molecule can be derived from allyl alcohol 5 via Sharpless asymmetric epoxidation protocol. The allylic alcohol 5 from 3-phenylpropanal (2) using proline catalyzed sequential α -aminooxylation and Horner-Wadsworth-Emmons olefination. The synthetic sequence began with the preparation of ester fragment 3 from commercially available 3-phenylpropanal (2, scheme 2). Thus, phenylpropanal (2) was subjected to α –aminooxylation process by using nitrosobenzene as an oxygen source and *L*-proline as a catalyst at -20°C, followed by in situ (Z)-selective Wittig olefination reaction with the triethyl phosphonoacetate, LiCl and DBU to furnish crude α -aminooxy ester [20]. Subsequent reduction of the α -aminooxy compound with 30 mol % $CuSO_4.5H_2O$ in methanol provided the γ –hydroxy unsaturated ester 3 in 69% yield. The enantiomeric purity of the hydroxyl ester 3 was determined as 99% by using chiral HPLC analysis. The protection of the hydroxy group in compound 3 with TBS-Cl, imidazole in THF gave silyl ether compound 4 in 96% yield [21]. The reduction of ester functionality in compound 4 was carried out with Dibal-H in THF at room temperature to afford allylic alcohol 5 in 92% yield [22]. Next, installation of chiral epoxide on intermediate 5, has been achieved using Sharpless asymmetric epoxidation protocol with (-)-di-isopropyl tartrate, tert-butyl hydroperaxide and titanium tetra (isopropaxide) in tert-butanol and water at -20°C for 12h, gave the chiral epoxide 6 in 91% yield [23]. Opening of the epoxide in a compound 6 with Red-Al provided diol 7 in 86% yield [24]. Finally, deprotection of the silyl group in 1, 3-diol 7 with TBAF in THF yielded the title compound, (3S, 4R)-5-Phenylpentane-1, 3, 4-triol (1) in 95% yield.



Scheme 2: Reagents and conditions: a) i) Nitrosobenzene, L-proline, anhydrous DMSO, 0°C, 30min. then, triethyl phosphonoacetate, DBU, LiCl, CH_3CN, 1 h. ii) $CuSO_4$. $5H_2O$, MeOH, rt, overnight. b) TBDMS-Cl, imidazole, anhydrous DCM, 0°C-rt, 6h. c) Dibal-H, THF, 0°C-rt, 2 h. d) Titanium tetraisopropoxide, (-)-di-isopropyl tartrate, MS 4Å, TBHP, DCM, -20°C, 12 h. e) Red-Al, THF, 0°C-rt, 11 h. f) TBAF, THF, 0°C-rt, 5h.

In conclusion, the first asymmetric synthesis of (3S, 4*R*)-5-phenylpentane-1, 3, 4-triol (1) starting from commercially available 2-phenylpropioal has been achieved in a six steps with 45% overall yield. The key reactions include, a proline-catalyzed α -aminooxylation, followed by (Z)-selective Wittig olefination and Sharpless asymmetric epoxidation.

Experimental

Synthesis of ((3S)-3-((R)-1-((tert-butyldimethylsilyl) oxy)-2-phenylethyl)oxiran-2-yl)methanol (6)

To a stirred mixture of powdered molecular sieves (4Å, 4.0g) and titanium tetraisopropoxide (1.37mL, 1.37mmol, 1M solution in CH_2Cl_2, 0.2equiv.) in (20mL) cooled at -20°C was added a (-)-di-isopropyl tartrate in CH_2Cl_2 (0.64g, 2.74mmol, 0.4equiv.). The mixture was stirred at -20°C for 10min, and a solution of allylic alcohol 5(2.00g, 6.84mmol, 1equiv.) in CH_2Cl_2(15mL) and a 5M solution (1,2-dichloroethane) of tert-butylhydroperoxide (2.46g, 5.47mL, 27.40mmol, 4equiv.) were added, successively. The resulting mixture was stirred at -20°C for 12h and quenched with 3mL H_2O and 0.8ml 20% NaOH. After the mixture was stirred at rt for 45min, the organic layer was separated, and filtered the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (2 x 30mL). The organic layer and the extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was purified by column chromatography over silica gel using hexanes/ethyl acetate (80:20) to give 6(1.92g, 91%) as a colorless oil.

Synthesis of target molecule 1

To an ice cold solution of silyl ether 7 (0.50 g, 1.61 mmol, 1 equiv.) in THF (20mL) was added TBAF (2.41 mL, 1.0 M solution in THF, 2.41 mmol, 1.5 equiv.). The solution was stirred at room temperature for 5 h and diluted with saturated NH_4Cl (20 mL) and ethyl acetate (20mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 30mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain an oily residue, which was purified by chromatography over silica gel using hexanes/ethyl acetate (70:30) to afford 1 (300mg, 95% yield); [α]D20 +63.9 (c 0.12, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.32 (m, 2H), 7.19-7.24 (m, 3H), 3.77-3.87 (m, 4H), 2.83 (dd, J = 14.0, 3.7 Hz, 1H), 2.69 (dd, J = 13.9, 9.0 Hz, 1H), 1.75-1.81 (m, 2H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 138.3, 129.3, 128.5, 126.4, 75.3, 73.4, 60.7, 38.4, 33.0; IR (KBr): vmax = 3351, 2924, 1464, 1224,

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1171, 725 cm^{-1}; MS (ESI): m/z 219 $(M+Na)^+$; HRMS (ESI):m/z calcd for $C_{11}H_{16}NaO_3$ $(M+Na)^+$: 219.0992, found: 219.0995.

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