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ENANTIOSELECTIVE SYNTHESIS OF (+)-(2S,3S)-3-ETHYNYLTYROSINE

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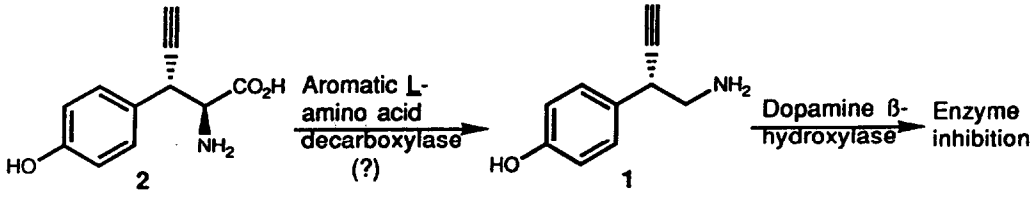
Summary: Homochiral ethynyl tyrosine 2, designed as a potential dopamine ß-hydroxylase irreversible inhibitor prodrug, has been synthesised asymmetrically in 15-steps, using the alkylation and azidation of acylated oxazolidones to establish relative and absolute stereochemistry.

2S-Ethynyltyramine 1 is a high affinity mechanism-based inhibitor of dopamine ß-hydroxylase (DBH).[2] As a means of enhancing the *in vivo* pharmacological profile of 1, ethynyltyrosine 2 was designed as a potential dual enzyme-activated irreversible inhibitor[3] of DBH. Active amino acid transport of 2 into cells and the subsequent action of aromatic L-amino acid decarboxylase (AADC)[4] was envisaged to deliver 1 to target organelles.[2] In this Letter we describe the enantioselective synthesis of (+)-2. The stereocenters at C(3) and C(2) are introduced via asymmetric alkylation and azidation reactions, using Evans' chiral oxazolidones as stereocontrollers.[5,6]

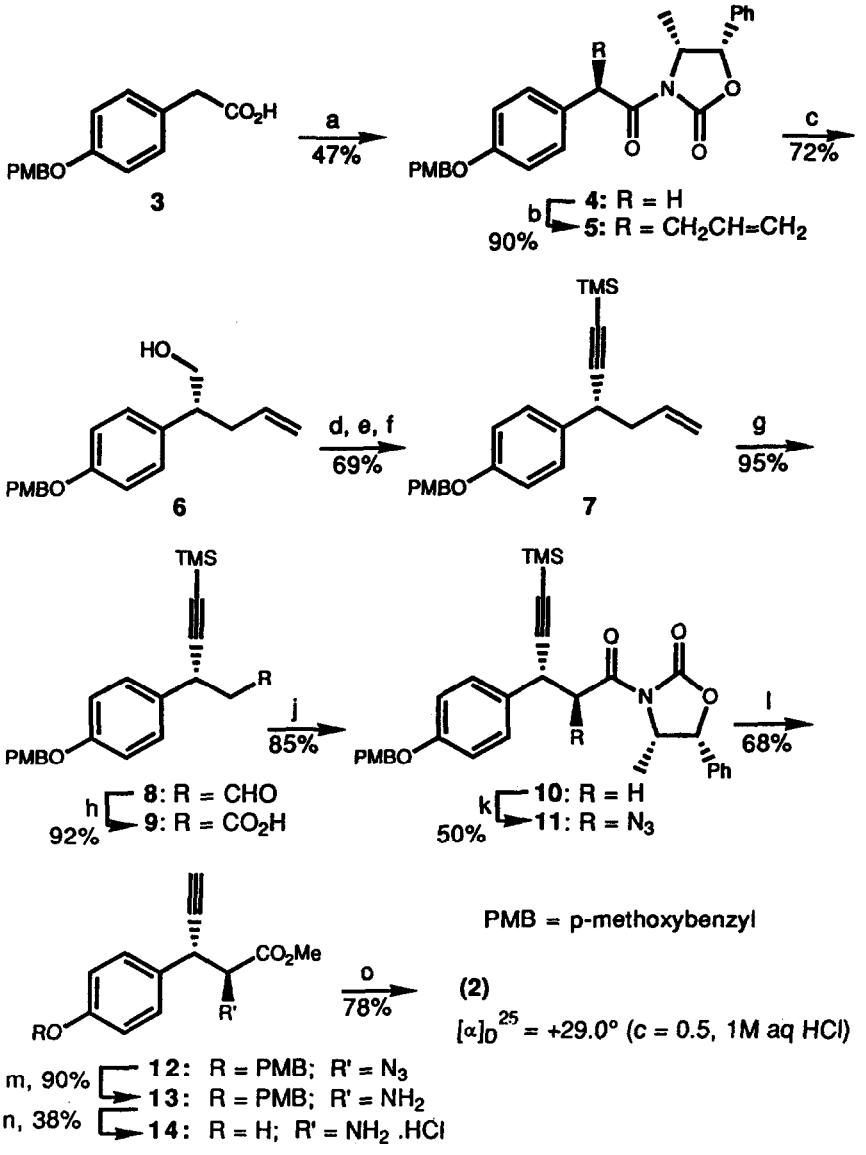


The synthesis of (+)-2 was initiated upon coupling aryl acetic acid 3[7] with (+)-(4R,5S)-4-methyl-5-phenyloxazolidone to give the N-acylated derivative 4[5a,8] (Scheme 1). Alkylation of the sodium enolate of 4 with freshly distilled allyl

bromide (1.1 equiv. NaHMDS, -78 °C, 15 min; 5 equiv. CH_2=$CHCH_2Br$, -50 °C, 1h) furnished oxazolidone 5 in 90% yield.[5b] The alkylated product contained ca. 8% (200 MHz ^{1}H NMR analysis) of the unwanted diastereomer which was inseparable by chromatography and was conveniently removed later in the synthesis. Subsequent removal of the chiral auxiliary (LAH, THF, 0 °C, 30 min) gave alcohol 6 which was converted to the enyne 7 using Corey's procedure:[9] 1) Swern oxidation, 2) Wittig condensation with Ph_3P=CBr_2 (2 equiv.) and 3) treatment with t-BuLi (2 equiv.) and Me_3SiCl (1.5 equiv., 69% overall). Selective ozonolysis of 7 in CH_2Cl_2 (-78 °C) using Sudan 7B as an indicator[10] and reductive work up with Ph_3P produced aldehyde 8. Further oxidation of 8 with $NaClO_2$ in aqueous t-BuOH[11] gave the known acid 9 ($[\alpha]_D^{25}$= -16.2° (c 1.5, DMF) (lit.[2] $[\alpha]_D^{25}$= -19.4° (c 1.5, DMF)). The magnitude of $[\alpha]_D^{25}$ for synthetic 9 implied an ee of 84% indicating that ca. 5% racemization at C(3) occurred during the 6→7 transformation while the (-) sign of $[\alpha]_D^{25}$ confirmed the stereochemistry at C(3) as S.[2]

Introduction of the amine functionality present in 2 was accomplished via an azidation/reduction sequence. Accordingly, oxazolidone 10 derived from 9 and (-)-(4S,5R)-4-methyl-5-phenyloxazolidone was subjected to electrophilic azidation as described by Evans.[5c] Thus a solution of 10 (0.25 M in THF) was cooled to -100 °C and treated with KHMDS (1.1 equiv., 30 min) followed by the addition of a precooled (-78 °C) solution of 2,4,6-triisopropylbenzenesulfonyl azide (3 equiv. THF). The reaction was stirred at -78 °C for 5 min and then quenched with AcOH (5 equiv., -78 °C → 30 °C, 1 h). Extractive workup and chromatography afforded azide 11 in 50% yield (80% de). The use of alternative bases or sulfonyl azides did not improve the yield. Following conversion of 11 to azido ester 12 (three steps: 1) peroxide mediated hydrolysis of the acyl oxazolidone,[5c,d] 2) removal of the Me_3Si protecting group and 3) esterification), azide reduction was accomplished efficiently using Ph_3P (2 equiv. in aqueous THF, reflux, 3 h),[12] procuring amine 13. Tyrosine ester 14 ($[\alpha]_D^{25}$= +30.4° (c 1.1, H_2O)) was obtained as a single diastereomer in 30% yield upon removal of the PMB protecting group from 13 (1 M methanolic HCl, 25 °C, 12 h) and two recrystallizations of the phenol from MeOH--Et_2O (1:1).[13] Final hydrolysis of 14 (3 M aqueous HCl at 60°C, 24 h) completed the preparation of enantiomerically pure (+)-2, $[\alpha]_D^{25}$= +29.0° (c 0.5, 1 M aq HCl).

Scheme 1



Reagents and conditions: a) i) t-BuCOCl, Et_3N,THF, 0°C; ii) Li salt of (4R,5S)-4-methyl-5-phenyl-oxazolidone, 0°C; b) i) 1.1 equiv. NaHMDS, 30 min, THF,-78°C; ii) 5 equiv. allyl bromide, -50°C; c) LAH, THF, 0°C; d) i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C ii) Et_3N; e) 2 equiv. CBr_4, 4 equiv. PPh_3, CH_2Cl_2,; f) i) 2.1 equiv. t-BuLi, -78°C, 30min, to 20°C, 1h, ii) 1.2 equiv. TMSCl; g) i) O_3, sudan red 7B, CH_2Cl_2, -78°C, ii) 2 equiv. PPh_3; h) 9 equiv. $NaClO_2$, NaH_2PO_4, aq t-BuOH, 2-methyl-2-butene; j) i) t-BuCOCl, Et_3N, THF, 0°C, ii) Li salt of (4S,5R)-4-methyl-5-phenyloxazolidone, 0°C; k) i)1.05 equiv. KHMDS, -100°C, THF, 30 min, ii) 3 equiv. 2,4,6-tri-isopropylbenzenesulphonyl azide, -78°C, 5 min; iii) 5 equiv. AcOH, -78°C to 30°C; l) i) 2 equiv. LiOH, 4 equiv. H_2O_2, aq THF, 0°C; ii) K_2CO_3, aq MeOH; iii) 1.2 equiv. K_2CO_3, 1.2 equiv. MeI, DMF; m) 2 equiv. PPh_3, aq THF, reflux; n) HCl, MeOH, then recrystallisation (MeOH: Et_2O); o) 25% aq HCl, 60°C, then pyridine.

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8. All new compounds exhibited physical and spectroscopic properties consistent with their structure. 7: ^{1}H NMR δ ($CDCl_3$, 200 MHz) 7.37-7.23 (m, 4H), 6.94-6.89 (m, 4H), 5.84 (m, 1H, C<u>H</u>=CH_2), 5.07-4.99 (m, 2H, CH=C<u>H_2</u>), 4.97 (s, 2H, p-$MeOC_6H_4C\underline{H_2}$), 3.81 (s, 3H, p-<u>Me</u>OC_6H_4), 3.66 (t, 1H, C<u>H</u>C=CTMS, J=7.0 Hz), 2.45 (m, 2H, C<u>H_2</u>CH=C<u>H_2</u>), 0.17 (s, 9H, TMS). 13: ^{1}H NMR δ ($CDCl_3$, 200 MHz) 7.37-7.21 (m, 4H), 6.95-6.89 (m, 4H), 4.97 (s, 2H, p-$MeOC_6H_4C\underline{H_2}$), 4.08 (dd, 1H, C<u>H</u>C=CH, J=5.3, 2.5 Hz), 3.83 (d, 1H, C<u>H</u>CO_2Me, J=5.3 Hz), 3.82 (s, 3H, p-<u>Me</u>OC_6H_4), 3.69 (s, 3H, CO_2<u>Me</u>), 2.36 (d, 1H, C=C<u>H</u>, J=2.5 Hz). 2: ^{1}H NMR (D_2O, 250 MHz) 7.38-7.35 (m, 2H), 6.94-6.90 (m, 2H), 4.59 (dd, 1H, C<u>H</u>C=CH, J=4.3, 2.6 Hz), 4.40 (d, 1H, C<u>H</u>CO_2H, J=4.3 Hz), 2.96 (d, 1H, C=C<u>H</u>, J=2.6 Hz).

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13. Direct inspection of ester 14 and the corresponding bis-Mosher's acid derivative by 250 MHz ^{1}H NMR revealed 14 to be stereochemically homogeneous.

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