HIGHLY ENANTIOSELECTIVE SYNTHESIS OF 3-HYDROXY-2-PHENYLPIPERIDINE *VIA* THE SHARPLESS AD-REACTION

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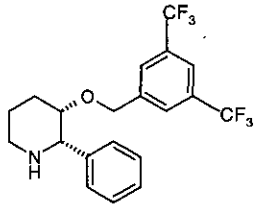
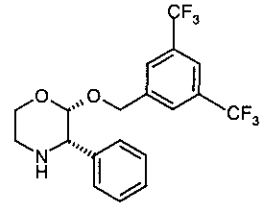
Abstract-Asymmetric dihydroxylation (AD) of the silyl enol ether **(3)** provided after hydrolysis the hydroxy ketone **(4)**. Subsequent hydrogenation yielded the title compound **(1)** as a diastereomeric mixture. The *cis*-isomer is an important building block for the synthesis of potent NK_1 receptor antagonists.

INTRODUCTION

Selective and potent NK_1 receptor antagonists with a variety of distinct chemical structures have been disclosed.[1] Most prominents among these are 2-phenyl-3-benzyloxypiperidines (e.g. L-733060)[2] and 2-phenyl-3-benzyloxymorpholines (e.g. L-742311)[3]. While for the latter an efficient synthesis of the enantiomerically pure compound starting from phenylglycine has been described,[4] the piperidine derivatives are only accessible *via* resolution of the racemic mixture. In addition, the published synthesis[5] of the racemic heterocycle **(1)** provided in our laboratories the product in low yield. This report describes a synthetic protocol for **1** *via* the *Sharpless* AD reaction in high chemical and optical yield.



L-733060

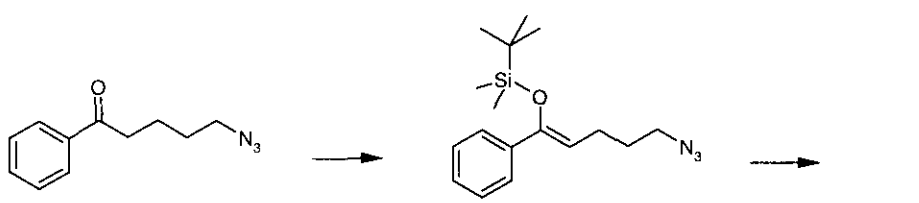


L-742311

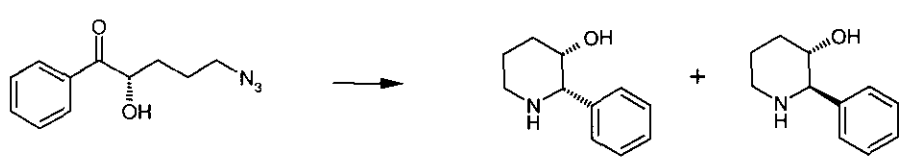
SYNTHESIS

The *Sharpless* AD reaction provides a versatile approach to oxy-substituted heterocycles such as lactones and lactams.[6] Our approach to **1** is based on the AD reaction[7] of the silyl enol ether **(3)**, which is readily available from the ω-azidovalerophenone **(2)**[8] by the method of *Ireland* with LDA-HMPA and TBDMS.[9] For practical reasons the enol ether **(3)** can also be made simply by stirring the ketone **(2)** in CH_3CN in the presence of triethylamine and TBDMS[10] yielding a Z/E ratio of 9/1. Dihydroxylation of this mixture with AD-Mix α gave the chiral hydroxy ketone **(4)** as the expected[7] (*S*)-enantiomer in 69 % chemical yield and 83 % ee (^{1}H-NMR of *Mosher*-Ester). Reaction of **6** under hydrogenolytic conditions led to a mixture (4:1) of *cis*-**1a** and *trans*-**1b** in 96 % yield, which was separated by crystallisation[5] to yield *(2S, 3S)*-**1**a in 83% ee (GC). The absolute configuration of **1a**, and consequently also of **4**, was assigned by comparison of the optical rotation[5] and the X-Ray analysis[2] published by the Merck Group. Applying the same sequence to the pure (Z)-Isomer **(3)** with AD-Mix β gave rise to *(2R, 3R)*-**1a** in 95 % ee. The *cis*-isomer **(1a)** represents an important building block for the synthesis of potent and selective NK_1 receptor antagonists.

In summary the *Sharpless* AD reaction has once more been shown to be a valuable method in the field of enantioselective synthesis of heterocyclic compounds.



2 **3**



4 **1a** **1b**

EXPERIMENTAL

(*Z*)- and (*E*)-(5-Azido-1-phenylpent-1-enyloxy)(*tert*-butyldimethyl)silanes (3)

To a mixture of 5-azido-1-phenylpentan-1-one (**2**) (10.6 g, 50 mmol), triethylamine (6.25 g, 62 mmol) and *tert*-butyldimethylchlorsilane (9.18 g, 62 mmol) a solution of NaI (9.25 g, 62 mmol) in acetonitrile (62 mL) was added. After stirring for 60 h CH_2Cl_2 (300 mL) and H_2O (200 mL) were added, the layers were separated and the aqueous phase was washed twice with CH_2Cl_2 (200 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 96 : 4) to give (*Z*)- and (*E*)-(5-azido-1-phenylpent-1-enyloxy)(*tert*-butyldimethyl)silane **A** and **B** (9 : 1) (13.42 g, 84 %) and **2** (1.64 g) each as a colorless oil.

An analytical sample was distilled by Kugelrohr-Distillation (150°/ 0.5 mmHg). ^{1}H-NMR ($CDCl_3$): δ 7.49 -7.41 (m, 2 H, **A** and **B**), 7.38 - 7.27 (m, 3 H, **A** and **B**), 5.10 (t, J = 8, 0.9 H **A**), 5.02 (t, J = 8, 0.1 H **B**), 3.36 (t, J = 8, 1.8 H **A**), 3.29 (t, J = 8, 0.2 H **B**), 2.34 (dt, J = 8 and 8, 1.8 H **A**), 2.22 (dt, J= 8 and 8, 0.2 H **B**), 1.77 (tt, J = 8 and 8, 1.8 H **A**), 1.74 (tt, J = 8 and 8, 0.2 H **B**), 1.03 (s, 8.1 H **A**), 0.96 (s, 0.9 H **B**), 0.05 (s, 0.6 H **B**), 0.00 (s, 5.4 H **A**). Irradiation at δ 5.10: NOE 7.49-7.41 m (16%); IR (Neat): 2096 (N_3), 1649 (C=C), 1257 ($Si(CH_3)_3$), 840 ($Si(CH_3)_3$); MS (EI): 289 $(M\text{-}N_2)^+$, 232 (100, $M\text{-}(N_2\text{-}C_4H_9)^+$); Anal. Calcd for $C_{17}H_{27}N_3O_6$: C 64.31, H 8.57, N 13.24. Found: C 64.15, H 8.62, N 13.16.

The pure (*Z*)-silyl enol ether was prepared by using the method of Ireland[9] with LDA /HMPA in THF.

(*S*)-(-)-5-Azido-2-hydroxy-1-phenylpentan-1-one (4)

To a well-stirred solution of (*Z*)- and (*E*)-(5-azido-1-phenylpent-1-enyloxy)(*tert*-butyldimethyl)-silane (9:1) (4.78 g, 15 mmol) in H_2O/*t*-BuOH (150 mL, 1:1) AD-mix α (21 g) and $MeSO_2NH_2$ (1.425 g, 15 mmol) were added at 0°C. The reaction mixture was stirred for 36 h at 0°C. Solid sodium sulfite (15 g) was added and the mixture stirred for an additional hour. After addition of CH_2Cl_2, the layers were separated, the aqueous phase extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give an oil, which was purified by flash chromatography to give (*S*)-(-)-5-azido-2-hydroxy-1-phenylpentan-1-one (2.3 g, 69%) as a colorless oil. An analytical sample was distilled in a Kugelrohr (150°/ 0.5 mmHg). ^{1}H-NMR

($CDCl_3$): δ 7.92 (d, J = 7, 2 H), 7.63 (dd, J = 7 and 7, 1 H), 7.52 (dd, J = 7 and 7, 2 H), 5.10 (ddd, J = 8, 6 and 3.5, 1 H), 3.75 (d, J = 6, OH), 3.32 (app. t, J = 7, 2 H), 2.09 –1.50 (m, 4 H); IR (Neat): 3469 (OH), 2098 (N_3), 1682 (C=O); MS (EI): 219 (M^+), 105 (100, $C_7H_5O^+$); $[\alpha]^{20}_D$ = -10.3° (c = 0.99, MeOH). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C 60.26, H 5.89, N 19.17. Found: C 60.42, H 5.94, N 19.36.

The reaction carried out with the pure (*Z*)-Isomer and AD mix β yielded a product with $[\alpha]^{20}_D$ = + 12.7° (c = 0.4, MeOH).

Mosher-Ester preparation and enantiomeric excess determination

To a solution of (*S*)-(-)-5-azido-2-hydroxy-1-phenylpentan-1-one (50 mg, 0.228 mmol) ($[\alpha]^{20}_D$ -10.4° (c = 0.99, MeOH)) in CH_2Cl_2 (4 mL) *N,N'*-dicyclohexylcarbodiimide (52 mg, 0.251 mmol), 4-dimethylaminopyridine (0.3 mg, 0.0022 mmol) and (*R*)-(+)-α-methoxy-α-trifluormethylphenyl-acetic acid (234 mg, 0.228 mmol) were added. After stirring for 6 h, the reaction mixture was filtered, diluted with CH_2Cl_2 (10 mL) and washed with 1N HCl, sat. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated. ^{1}H-NMR-Analysis (CH_3O-Signal: δ 3.58 vs. δ 3.66) indicated an ee of 88 %.

(2*S*,3*S*)-(+)-2-Phenylpiperidin-3-ol (1)

A mixture of (*S*)-(-)-5-azido-2-hydroxy-1-phenylpentan-1-one ($[\alpha]^{20}_D$ = -10.4° (c = 0.99, MeOH) (1.75 g, 7.9 mmol) and Pd on charcoal (100 mg, 5%) in ethanol (20 mL) was hydrogenated for 16 h. The catalyst was filtered off and the solvent evaporated to give a colorless oil (1.35 g, 96%). ^{1}H-NMR and anal. GC (dimethylpolysilicon) indicated a *cis* to *trans* ratio of 4:1. The *cis*-Isomer was isolated *via* the tosylate as described[5] to give (+)-(2*S*,3*S*)-2-phenylpiperidin-3-ol (0.94 g, 67 %) as colorless crystals, mp 92-93.5°. ^{1}H-NMR ($CDCl_3$): δ 7.43 –7.23 (m, 5 H), 3.85 (br s, 1 H), 3.78 (br s, 1 H), 3.20 (dddd, J = 12, 4, 2 and 2, 1 H), 2.80 (ddd, J = 12, 12 and 3, 1 H), 2.09 (dm, J = 12, 1 H), 1.87 (ddddd, J = 12, 12, 12, 4 and 4, 1 H), 1.68 (dddd, J = 12, 12, 4 and 2, 1 H), 1.50 (dm, J = 12, 1 H); IR (Nujol): 3253 (OH), 1603 (Ar), 1499 (Ar), 1062 (OH), 718 (Ar). MS (EI): 177 (M^+), 132, 120, 104 (100). $[\alpha]^{20}_D$ = +81.5° (c = 0.68, MeOH). (lit.,[5] ($[\alpha]^{20}_D$ = + 98.5° (c =1, MeOH)). Anal. GC on a chiral Phase (BGB-176) indicated an ee of 83 %. Anal. Calcd for $C_{11}H_{15}NO$: C 74.54, H 8.53, N 7.90. Found: C 74.25, H 8.60, N 7.87.

The reaction carried out with (*R*)-(-)-5-azido-2-hydroxy-1-phenylpentan-1-one ($[\alpha]^{20}_D$ = +12.7° (c = 0.4, MeOH) yielded a product with ($[\alpha]^{20}_D$ = - 93° (c = 0.4, MeOH)) (lit.,[5] : $[\alpha]^{20}_D$ = - 97.2° (c =1, MeOH)). Anal.GC on a chiral phase (BGB-176) indicated an ee of 95.3 %.

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