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 NK₁ receptor antagonists.

INTRODUCTION

Selective and potent NK₁ receptor antagonists with a variety of distinct chemical structures have been disclosed.¹ Most prominent 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 synthesis⁵ 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.

![Structures](L-733060.png L-742311.png)
SYNTHESIS

The Sharpless AD reaction provides a versatile approach to oxy-substituted heterocycles such as lactones and lactams. Our approach to 1 is based on the AD reaction of the silyl enol ether (3), which is readily available from the ω-azidovalerophenone (2) by the method of Ireland with LDA-HMPA and TBDMS. For practical reasons the enol ether (3) can also be made simply by stirring the ketone (2) in CH₃CN in the presence of triethylamine and TBDMS 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 (S)-enantiomer in 69 % chemical yield and 83 % ee (¹H-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 to yield (2S, 3S)-1a in 83% ee (GC). The absolute configuration of 1a, and consequently also of 4, was assigned by comparison of the optical rotation and the X-Ray analysis 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 NK₁ 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.
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-butyldimethylchlorosilane (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 CH₂Cl₂ (300 mL) and H₂O (200 mL) were added, the layers were separated and the aqueous phase was washed twice with CH₂Cl₂ (200 mL). The combined organic layers were dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash chromatography (SiO₂, 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). ¹H-NMR (CDCl₃): 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=), 1649 (C=C), 1257 (Si(CH₃)₂), 840 (Si(CH₃)₂); MS (El): 289 (M-N₂)⁺, 232 (100, M-(N₂-C₄H₉)⁺); Anal. Calcd for C₇H₇N₃O₆: 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 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 H₂O/t-BuOH (150 mL, 1:1) AD-mix α (21 g) and MeSO₃NH₂ (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 CH₂Cl₂, the layers were separated, the aqueous phase extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄), 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). ¹H-NMR
(CDCl₃): 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 (C=O); MS (El): 219 (M⁺), 105 (100, C₇H₅O⁻); [α]²⁰ₒ = -10.3° (c = 0.99, MeOH). Anal. Calcd for C₇H₇N₂O₂: 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 [α]²⁰ₒ = +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) ([α]²⁰ₒ = -10.4° (c = 0.99, MeOH)) in CH₂Cl₂ (4 mL) N,N'-dicyclohexylcarbodiimide (52 mg, 0.251 mmol), 4-dimethylaminopyridine (0.3 mg, 0.0022 mmol) and (R)-(−)-methoxy-α-trifluoromethylphenylacetic acid (234 mg, 0.228 mmol) were added. After stirring for 6 h, the reaction mixture was filtered, diluted with CH₂Cl₂ (10 mL) and washed with 1N HCl, sat. NaHCO₃ and brine. The organic layer was dried (Na₂SO₄), filtered and evaporated. ¹H-NMR-Analysis (CD₂O-Signal: δ 3.58 vs. δ 3.66) indicated an ee of 88%

(2S,3S)-(−)-2-Phenylpiperidin-3-ol (1)

A mixture of (S)-(−)-5-azido-2-hydroxy-1-phenylpentan-1-one ([α]²⁰ₒ = -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%). ¹H-NMR and anal. GC (dimethylpolysilicon) indicated a cis to trans ratio of 4:1. The cis-isomer was isolated via the tosylate as described⁶ to give (−)-(2S,3S)-2-phenylpiperidin-3-ol (0.94 g, 67 %) as colorless crystals, mp 92-93.5°. ¹H-NMR (CDCl₃): 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 (dd, J = 12, 12 and 3, 1 H), 2.09 (dm, J = 12, 1 H), 1.87 (ddddd, J = 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 (El): 177 (M⁺), 132, 120, 104 (100). [α]²⁰ₒ = +81.5° (c = 0.68, MeOH). (lit.,⁵ ([α]²⁰ₒ = +98.5° (c =1, MeOH)). Anal. GC on a chiral Phase (BGB-176) indicated an ee of 83 %. Anal. Calcd for C₁₁H₁₅NO: 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 \( ([\alpha]_D^{0} = +12.7^\circ \text{ (c } = 0.4, \text{ MeOH}) ) \) yielded a product with \( ([\alpha]_D^{0} = -93^\circ \text{ (c } = 0.4, \text{ MeOH}) ) \) (lit. \( ^5 \) : \( [\alpha]_D^{0} = -97.2^\circ \text{ (c } = 1, \text{ MeOH}) ) \). Anal.GC on a chiral phase (BGB-176) indicated an ee of 95.3%.

REFERENCES AND NOTES

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Received, 18th January, 1999