Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 3, pp. 801-806, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00076-3

An Enantioselective Synthesis of the Williams Glycine Template

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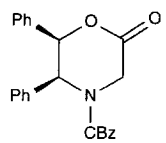
Abstract: The Williams glycine template for amino acid synthesis, benzyl *(2R,3S)*-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (**1**), was prepared in enantiomerically pure form in six steps from benzaldehyde in 48% overall yield. The initial chirality of the molecule was derived from oxynitrilase catalysed addition of HCN to benzaldehyde. A simple procedure for preparation of the biocatalyst is described.

INTRODUCTION

In 1986 Robert M. Williams and coworkers introduced a set of four chiral compounds (**1**, **2** and their enantiomers) as starting materials for the synthesis of α-substituted amino acids with high enantiomeric purity[1]. Since then these chiral templates have proven their utility in the synthesis of rare amino acids[2]. From **1** and **2** *(S)*-amino acids are obtained, whereas *(R)*-amino acids can be derived from their enantiomers.



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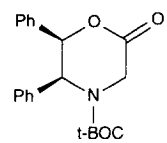

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Williams' synthesis of these chiral templates started from benzoin, which was converted into its oxime. Catalytic hydrogenation then afforded a racemic mixture of *erythro*-1,2-diphenylaminoethanols. Separation of the optical antipodes was accomplished via the diastereomeric L-glutamic acid salts. This rather cumbersome procedure provided both enantiomers in circa 20% yield. The enantiomerically pure *erythro*-1,2-diphenylaminoethanols were protected on nitrogen with either a benzyloxycarbonyl (CBz)- or a t-butyloxycarbonyl (t-BOC) group and cyclised in refluxing benzene in the presence of a catalytic amount of p-toluenesulfonic acid (p-TsOH). The final product **1** was thus obtained in 13% overall yield after a seven step synthesis[1].

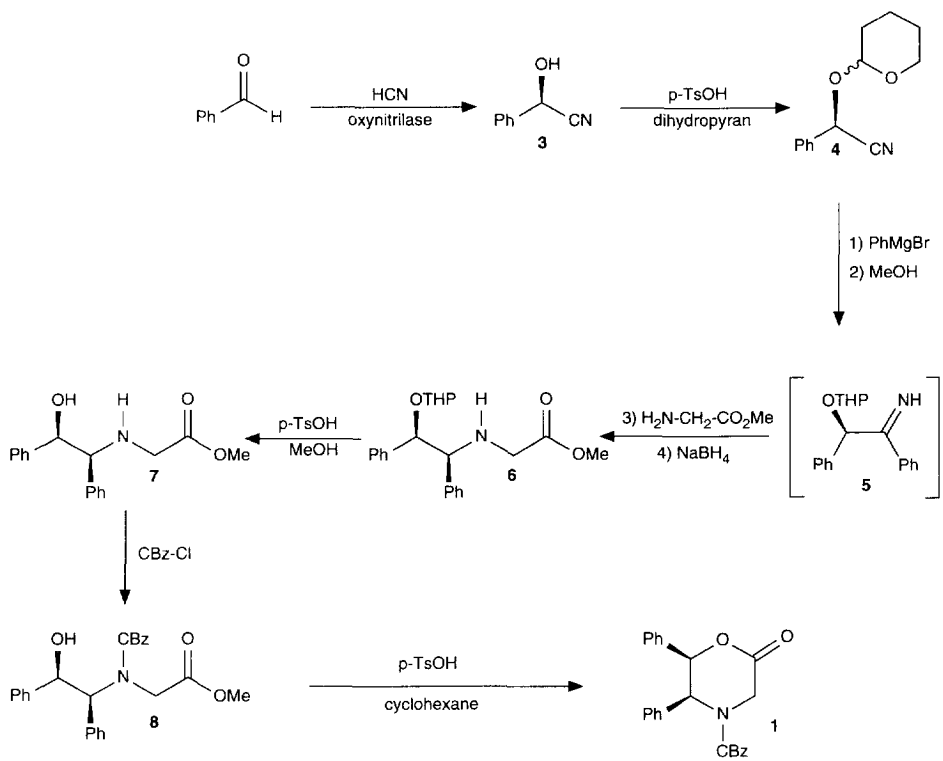
The Williams glycine templates can be alkylated at the position α to the carbonyl function with high diastereoselectivity and in fair yields[3]. Reduction of the alkylated derivatives yields amino acids of high

enantiomeric purity. By choosing either the CBz- or the t-BOC-protected starting material, unprotected as well as N-t-BOC-protected amino acids are accessible[1-3].

Although the Williams glycine templates are commercially available, application may be limited by their high cost[4]. We explored an alternative synthetic route to **1**, starting from benzaldehyde and employing a biocatalyst to introduce the first stereogenic centre.

RESULTS and DISCUSSION

Our synthesis, illustrated in scheme 1, proceeds without purification of any intermediates. *(R)*-Mandelonitrile (**3**) was obtained from benzaldehyde using the enzyme *oxynitrilase* (E.C. 4.1.2.10) as present in almond meal[5]. The optical activity of the cyanohydrin was determined by converting an analytical sample into its t-butyldimethylsilyl (TBS) ether[6], followed by HPLC analysis on a Chiralcel OD column. E.e.'s were always 99+%. For the synthesis of **1**, the cyanohydrin was protected as its tetrahydropyranyl (THP) ether. Reaction with dihydropyran afforded the two diastereoisomers of **4** in a 1:1 ratio (NMR). As the enantiomeric purity of compound **4** could not be determined directly by HPLC, proof that the protection step had proceeded without racemization was obtained after acid-catalysed hydrolysis, followed by TBS-protection[6] and HPLC analysis.



Scheme 1: *Enantioselective synthesis of the Williams glycine template* ***1****.*

Conversion of **4** into **6** involved a three step, one pot, ***Grignard addition-transimination-hydride reduction*** procedure, developed earlier in our group[7]. Thus **4** was reacted with phenylmagnesium bromide and the resulting metallo-imine was quenched with methanol to liberate the primary imine **5**. ***Transimination*** with an excess of methyl glycinate gave the more stable secondary imine, which was reduced *in situ* with sodium borohydride at -30 °C. The reduction proceeded with complete diastereoselectivity (NMR) to yield the *erythro* secondary amine **6**. As the THP-ether is still present, the compound remains a 1:1 mixture of two diastereoisomers. Apparently, the induction of the new stereogenic centre is controlled exclusively by the benzylic stereogenic centre and is not influenced by the stereogenic centre of the THP-ether. After removal of the THP-function to give **7** and protection of the amino function, using benzyl chloroformate (CBz-Cl), secondary amine **8** was obtained. Williams treated the ethyl ester analogue of **8** with p-TsOH in refluxing benzene employing a soxhlet apparatus packed with $CaCl_2$. Using the same procedure, we obtained **1** in 37% overall yield based on benzaldehyde. The carcinogenic properties of benzene prompted us to search for an alternative. Application of cyclohexane or toluene as the solvent and using a Dean-Stark apparatus packed with molecular sieves (3Å) for the removal of methanol, proved to be an excellent alternative giving higher yields. With cyclohexane as the solvent **1** was obtained in 48% overall yield, while a reaction in toluene afforded **1** in 47% overall yield. The e.e. of **1** was determined by HPLC analysis and established to be 99+%. The analytical and spectral data were in complete agreement with those from a commercially obtained sample[4].

The enantiomer of **1** can be obtained likewise from *(S)*-mandelonitrile, accessible from its *(R)*-enantiomer by an inversion procedure described earlier[8]. The N-t-BOC protected glycine template **2** can likewise be obtained from the N-t-BOC protected analogue of ethanolamine **8** in comparable yield.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL FX-200 instrument. Samples were measured, unless otherwise stated, in $CDCl_3$, with TMS as an internal standard for ^{1}H NMR, and $CDCl_3$ as internal standard for ^{13}C NMR. The ^{1}H- and ^{13}C-NMR spectra of compound **1** were recorded at 120 °C in DMSO-d_6 with TMS (^{1}H) and DMSO-d_6 (^{13}C) as the internal standard. E.e.'s were determined by HPLC using a CHIRALCEL OD column, using hexane (HEX) 2-propanol (IPA) mixtures as the eluent. Eluents are specified in each case. Optical rotations were measured on a Propol automatic polarimeter. Melting points are uncorrected.

Chemicals

Commercially available chemicals were used as received. Diethyl ether was dried on sodium wire. Methanol was dried on molecular sieves (3Å). All reactions were carried out in an argon atmosphere.

Defatted almond meal

Untreated sweet almonds (2 kg), with brown skin, were cut in a blender[9] into pieces of about 5 mm and then immersed in 2 L of ethyl acetate. After standing at room temperature overnight, the ethyl acetate was decanted and the almond pieces were immersed in fresh ethyl acetate. The decanted ethyl acetate solutions were evaporated *in vacuo* and the residual almond oil was weighed. This procedure was repeated until at least 600 g of almond oil was extracted. The almond pieces were spread out on filter paper in a hood and dried in air.

After drying the pieces were ground to a fine powder in a blender[9] and extracted three more times with ethyl acetate. The total yield of almond oil was approximately 1 kg. The remaining powder was collected on a glass filter and dried in a hood. The yield of almond meal was about 1 kg.
This almond meal can be stored at 4 °C, in the dark for over a year without loosing its oxynitrilase activity.

(*2R*)-Hydroxybezeneacetonitrile ((*R*)-mandelonitrile) (3)

In a three necked 2 L reaction flask equipped with a 1 L pressure equalizing addition funnel and a strong magnetic stirrer, 30 g of almond meal was allowed to swell in 45 mL of 0.02 M sodium citrate buffer (pH = 5.45) for at least 15 minutes. Freshly distilled benzaldehyde (31.8 g, 300 mmol), dissolved in 50 mL of ethyl acetate was added to the almond meal paste. In the meantime 29.4 g (600 mmol) of sodium cyanide was dissolved in 400 mL of water. With careful addition of acetic acid the pH was adjusted to 5.45. (**CAUTION**, at this stage hydrogen cyanide (HCN) may be released from the solution. The procedure should be carried out in a well ventilated hood!) The HCN solution was extracted with 3 x 250 mL of ethyl acetate. The ethyl acetate fractions were combined and placed in the pressure equalizing addition funnel. The equipment was sealed with stoppers and transferred to a room climatised at 5 °C. After one hour the HCN solution was added dropwise (1 hour) to the benzaldehyde mixture and subsequently stirred for 48 hours at 5 °C. It is important that the reaction mixture is well stirred. The mixture was then filtered over a glass filter covered with a layer of Celite. The almond meal was washed twice with ethyl acetate and the filtrate was dried on $MgSO_4$. The solvent was evaporated *in vacuo* (on a water bath of maximal 35 °C) to yield the crude cyanohydrin (41 g).
$[\alpha]^{20}_D$ +40 (c=1, $CHCl_3$); e.e. > 99% (HPLC; determined as TBS-ether[6], HEX:IPA=99.75:0.25, 1 mL/min)
^{1}H NMR δ(ppm) 3.50 (broad s, 1H, OH), 5.53 (s, 1H, PhCH), 7.47 (m, 5H, Ph).
^{13}C NMR δ(ppm) 62.9 (PhCHO); 118.8 (CN); 126.4, 128.8, 129.4, 134.8 (Ph).

(*2R*)-(tetrahydropyranyl)oxybenzeneacetonitril (4)

The crude cyanohydrin ((*R*)-mandelonitrile) (max 300 mmol) and 1.2 g (6 mmol) of p-TsOH were dissolved in 300 mL of dry diethyl ether. At 5 °C, 33.5 g (400 mmol) of 3,4-dihydro-2*H*-pyran was added dropwise. After stirring at room temperature for 3 hours, 50 mL of an aqueous saturated $NaHCO_3$ solution were added. The mixture was stirred vigorously for five minutes. After separation of the layers the ether layer was dried on Na_2SO_4. After evaporation of the solvent *in vacuo*, the crude protected cyanohydrin was obtained as a pale yellow oil that crystallized upon storage at -20 °C (67 g).
$[\alpha]^{20}_D$ +42 (c=1, $CHCl_3$), m.p. 48-53 °C.
Due to the stereogenic centre of the THP-ether **4** was obtained as a 1:1 mixture of diastereoisomers.
^{1}H NMR δ(ppm) *diastereoisomer A:* 1.44-1.98 (m, 6H, THP), 3.77 (m, 2H, OCH_2), 4.74 (broad s, 1H, OCHO), 5.42 (s, 1H, PhCH), 7.48 (m, 5H, Ph). *diastereoisomer B:* 1.44-1.98 (m, 6H, THP), 3.77 (m, 2H, OCH_2), 5.11 (broad s, 1H, OCHO), 5.59 (s, 1H, PhCH), 7.48 (m, 5H, Ph).
^{13}C NMR δ(ppm) *diastereoisomer A:* 18.5, 24.9, 29.6, (THP); 62.2 (OCH_2); 65.6 (OCHO); 96.6 (PhCH); 117.4 (CN); 127.3, 128.8, 129.4, 133.6 (Ph). *diastereoisomer B:* 18.0, 24.8, 29.5 (THP); 61.7 (OCH_2); 66.2 (OCHO); 97.3 (PhCH); 118.1 (CN); 127.1, 128.7, 129.3, 133.4 (Ph).

(*1S',2R'*)-Methyl *N*-[1',2'-diphenyl-2'-(tetrahydropyranyl)oxyethyl]glycinate (6)

The THP-protected cyanohydrin **4** (11.2 g, circa 47 mmol) was dissolved in 300 mL of dry diethyl ether. Phenylmagnesium bromide (19 mL of a 3 M solution in diethyl ether, 57 mmol) was diluted with 100 mL of dry diethyl ether and added dropwise. The resulting suspension was stirred for another hour at room

temperature. After cooling to 0 °C, 200 mL of dry methanol was added, followed by 61 g (486 mmol) of glycine methyl ester hydrochloride and 23 g (426 mmol) of anhydrous NaOMe. The suspension was stirred at room temperature for one hour and then cooled to -30 °C. At this temperature 2 x 1.0 g (total 59 mmol) of $NaBH_4$ was added with a five minute interval. After the addition the mixture was stirred for one hour while slowly warming up. Then it was poured into 1000 mL of water and extracted with 3 x 300 mL of diethyl ether. The organic layers were combined, washed with saturated brine and dried on sodium sulphate. After evaporation of the solvent the crude product was obtained as a viscous orange oil (17.8 g).

$[\alpha]^{20}_D$ +13 (c=1.3, $CHCl_3$)

^{1}H NMR δ(ppm) *diastereoisomer A:* 1.25-1.95 (m, 6H, THP), 3.18 (m, 2H, NCH_2), 3.60 (s, 3H, OMe), 3.73 (m, 2H, OCH_2), 3.96 (d, 1H, J = 7.2 Hz, PhCHN), 4.25 (broad s, 1H, OCHO), 4.58 (d, 1H, J = 7.2 Hz, PhCHO), 7.33 (m, 10H, Ph). *diastereoisomer B:* 1.25-1.95 (m, 6H, THP), 3.18 (m, 2H, NCH_2), 3.60 (s, 3H, OMe), 3.73 (m, 2H, OCH_2), 3.97 (d, 1H, J = 7.2 Hz, PhCHN), 4.41 (broad s, 1H, OCHO), 4.71 (d, 1H, J =7.2 Hz, PhCHO), 7.33 (m, 10H, Ph).

^{13}C NMR δ(ppm) *diastereoisomer A:* 18.0, 25.1, 29.8, 47.8 (THP); 51.2 (OMe); 60.1 (NCH_2); 66.6 (OCHO); 80.3 (PhCHN); 93.4 (PhCHO); 126.3, 127.3, 127.6, 127.9, 128.5, 138.5, 139.9 (Ph); 172.5 (CO). *diastereoisomer B:* 18.3, 25.2, 30.1, 48.0 (THP); 51.2 (OMe); 61.1 (NCH_2); 66.9 (OCHO); 83.0 (PhCHN); 98.4 (PhCHO); 127.1, 127.4, 127.7, 128.0, 128.7, 139.6, 140.1 (Ph); 172.5 (CO).

***(1S',2R')*-Methyl *N*-(1',2'-diphenyl-2'-hydroxyethyl)glycinate (7)**

The crude compound **6** was dissolved in 200 mL of methanol. 11.4 g (60 mmol) Of p-TsOH was added and the reaction mixture was stirred at room temperature for 20 hours. Then 600 mL of water was added and the mixture was extracted with 2 x 150 mL of diethyl ether to remove organic side products. The water layer was made basic with 20 g of Na_2CO_3 and extracted with 3 x 150 mL of CH_2Cl_2. These organic layers were combined and dried on Na_2SO_4. After evaporation of the solvent the crude ethanolamine **7** was obtained as pale yellow crystals (9.0 g).

An analytical sample was crystallized from ethanol. $[\alpha]^{20}_D$ +2.1 (c = 0.96, $CHCl_3$); m.p. 115-117 °C.

^{1}H NMR δ(ppm) 1.75 (broad s, 1H, NH), 2.77 (broad s, 1H, OH), 3.24 (AB q, 2H, J = 17.5 Hz, NCH_2), 3.65 (s, 3H, OMe), 3.95 (d, 1H, J = 5.7 Hz, PhCHN), 4.80 (d, 1H, J = 5.7 Hz, PhCHO), 7.23 (m, 10H, Ph).

^{13}C NMR δ(ppm) 48.1 (NCH_2); 51.6 (OMe); 68.1 (PhCHN); 77.1 (PhCHO); 126.9, 127.5, 127.7, 128.0, 128.2, 128.4, 138.5, 140.2 (Ph); 172.6 (CO).

***(1S',2R')*-Methyl *N*-(benzyloxycarbonyl)-*N*-(1',2'-diphenyl-2'-hydroxyethyl)glycinate (8)**

The crude ethanolamine **7** (9.0 g, 31 mmol) was dissolved in 100 mL of CH_2Cl_2 and subsequently 100 mL of saturated aqueous $NaHCO_3$ solution and 4.7 mL (5.6 g, 33 mmol) of benzyl chloroformate were added. The reaction mixture was stirred vigorously for 18 hours. The layers were separated and the water layer was extracted with 2 x 50 mL of CH_2CL_2. The combined organic layers were washed with water and saturated brine, dried on Na_2SO_4 and concentrated *in vacuo* to yield **8** as a yellow oil (13.9 g).

$[\alpha]^{20}_D$ +12 (c = 0.96, $CHCl_3$).

^{1}H NMR (80 °C) δ(ppm) 3.34 (broad s, 1H, OH), 3.53 (s, 3H, OMe), 3.89 (AB q, 2H, J = 17.5 Hz, NCH_2), 5.12 (AB q, 2H, J = 12.3 Hz, $PhCH_2$), 5.42 (d, 1H, J = 5.2 Hz, PhCHN), 5.51 (broad s, 1H, PhCHO), 7.35 (m, 15H, Ph).

^{13}C NMR (80 °C) δ(ppm) 46.9 (NCH_2); 51.4 (OMe); 65.6 (PhCHN); 67.4 ($PhCH_2$); 74.3 (PhCHO); 126.2, 127.0, 127.3, 127.5, 127.6, 127.7, 127.8, 128.1, 129.8, 135.8, 136.1, 141.3 (Ph); 155.7 (OCN); 170.6 (CO).

Benzyl *(2R,3S)*-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (1)

The crude compound **8** was dissolved in 450 mL of cyclohexane while warming to reflux temperature. After addition of 0.70 g (3.7 mmol) of p-TsOH the reaction was refluxed for 4 hours using a Dean-Stark apparatus packed with molecular sieves (3 Å). During the reaction, **1** started to crystallize. After cooling to 5 °C, filtration, washing with cold cyclohexane and drying *in vacuo*, 9.3 g of **1** was obtained as colourless crystals. The overall yield based on benzaldehyde was 48%.

$[\alpha]^{20}_{D}$ -67 (c = 0.50, CH_2Cl_2, lit[1] -67.4), m.p. 198-199 °C (lit[1] 200 °C), e.e. > 99% (HPLC, HEX:IPA=80:20, 1 mL/min)

^{1}H NMR (DMSO-d_6, 120 °C) δ(ppm) 4.59 (AB q, 2H, J = 17.5 Hz, NCH_2), 5.06 (AB q, 2H, J = 12.9 Hz, $PhCH_2$), 5.28 (d, 1H, J = 3.1 Hz, PhCHN), 6.20 (d, 1H, J = 3.1 Hz, PhCHO), 6.66 (s, 1H, Ph), 6.69 (s, 1H, Ph), 7.15 (m, 13H, Ph).

^{13}C NMR (DMSO-d_6, 120 °C) δ(ppm) 44.8 (NCH_2); 59.0 ($PhCH_2$); 66.3 (PhCHN); 78.9 (PhCHO); 125.6, 126.6, 126.8, 127.0, 127.2, 127.5, 134.1, 135.5, 135.7 (Ph); 153.1 (OCN); 166.0 (CO).

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9. During this procedure the temperature should not rise above 40 °C to prevent loss of enzyme activity.

(*Received in UK* 26 *January* 1995)