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Practical synthesis of Schöllkopf's bis-lactim ether chiral auxiliary: (3*S*)-3,6-dihydro-2,5-dimethoxy-3-isopropyl-pyrazine

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Abstract

Practical methodology for the bis-O-methylation of (3*S*)-isopropyl-piperazine-2,5-dione **4** on a 45 g scale to generate Schöllkopf's bis-lactim ether chiral auxiliary (3*S*)-3,6-dihydro-2,5-dimethoxy-3-isopropyl-pyrazine **1** has been developed. Monomethylated intermediates **5** and **6** are reported for the first time. The gelling effects of **4** in a range of common solvents are also described.

1. Introduction

A large number of methods have been developed for the asymmetric synthesis of non-proteinogenic α-amino acids.[1] Many of these approaches are based on stoicheiometric chiral auxiliaries where diastereoselective alkylation of a masked glycine enolate is controlled by an attached homochiral fragment. Schöllkopf's bis-lactim ether methodology was first reported in 1981[2] and this class of auxiliary **1** has proven to be particularly successful for the synthesis of small quantities of novel homochiral α-amino acids.[3] We have found that the greatest problem in using this methodology for synthesis is the difficulty in preparing sufficient quantities of the parent auxiliary **1**.[4] We now report on a thorough investigation that enables **1** to be reliably prepared on a 45 g scale.

The original report of the preparation of **1** lacks experimental detail.[2] Although the synthetic protocol appears straightforward, it is often problematical and we have encountered difficulty in obtaining reproducible yields whilst following this procedure.[5] The synthesis of **1** is conveniently divided into the preparation of parent piperazine-2,5-dione **4** (diketopiperazine, DKP) followed by bis-O-methylation to afford the bis-lactim ether **1** (Scheme 1).

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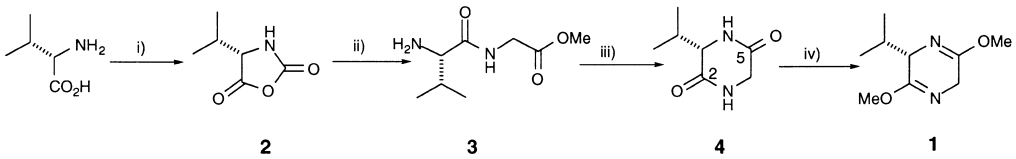


Scheme 1. (i) $COCl_2$; (ii) glycine methyl ester·HCl, 2.1 eq. triethylamine, THF/$CHCl_3$, −78°C; (iii) toluene, Δ; (iv) $Me_3O\cdot BF_4$, CH_2Cl_2

2. Results and discussion

A suspension of homochiral L-valine was stirred with a 1.97 M solution of phosgene in toluene and THF at 50°C to give the desired *N*-carboxy-Leuch's anhydride **2**, as a white crystalline solid in 90–95% yield. Careful control of dilution, reaction temperature and time were necessary for good yields of **2** to be obtained otherwise significant quantities of polymeric material began to accumulate.

Formation of dipeptide H_2N-L-Val-Gly-OMe **3** was best carried out at relatively high concentration and at low temperature in order to minimise competing polymerisation. Two equivalents of triethylamine were added to a solution of glycine methyl ester hydrochloride in chloroform at −78°C followed by the addition of a solution of **2** in THF. It was essential that the reaction was stirred efficiently during this addition since triethylamine hydrochloride forms a gelatinous precipitate which can result in inefficient mixing of reagents and decreased yields of **3**. After stirring for 4 hours at −78°C the reaction mixture was stored overnight at −20°C before removal of the triethylamine hydrochloride by filtration and evaporation of the solvent to afford the thermally unstable dipeptide **3** as a crude oil. Subsequent cyclisation to DKP **4** was achieved by heating crude **3** in toluene at reflux for 24 hours. DKP **4** was purified by refluxing with charcoal in boiling water and after evaporation of solvent the resulting powder was dried for 24 hours at 90°C under vacuum to give an overall yield of 70–80% from L-valine.

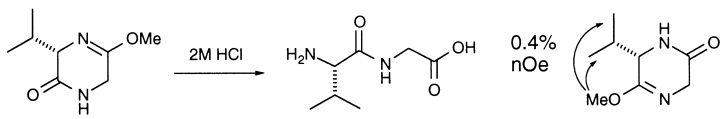
Our initial attempts to methylate DKP **4** with $Me_3O\cdot BF_4$ were unsuccessful affording **1** in poor, non-reproducible yields (<20%). A detailed investigation into this reaction revealed a number of experimental conditions which must be followed if good yields of **1** are to be obtained:

(1) DKP **4** must be totally free of solvent. Any adventitious water results in the premature cleavage of the bis-lactim ether bonds of **1** to afford the methyl esters of valine and glycine. Severe conditions are required to obtain solvent-free DKP **4** as a result of both its hygroscopic nature and its remarkable solvent gelling properties. Our preliminary studies show that as little as 1 mg of DKP **4** can completely gel 1 ml of a wide range of commonly available solvents (acetone, acetonitrile, benzene, chloroform, dichloromethane, dioxane, ethanol, ethyl acetate, nitromethane, tetrahydrofuran and toluene). Many of these gels are stable up to the boiling points of the pure solvents and simple calculations reveal that this gelation process requires a single molecule of DKP **4** to be associated with at least 3000 molecules of solvent.[6] Solvents in which DKP **4** does not gel include butan-2-one, chlorobenzene, cyclohexane, dimethoxyethane, dimethylformamide, di-*n*-butyl ether, diethyl ether, pentane and water.

(2) Good yields of **1** were only obtained when freshly prepared $Me_3O\cdot BF_4$ was used. Commercial samples were of inferior quality and gave poor yields.[7] Fresh $Me_3O\cdot BF_4$ was prepared by modification of the *Organic Synthesis* procedure which involved the dropwise addition of epichlorohydrin to a solution of Me_2O and $BF_3\cdot Et_2O$ in dichloromethane at low temperature.[8] This original procedure was highly wasteful of the gaseous component Me_2O and a protocol was therefore developed where sequential, portionwise additions of epichlorohydrin and $BF_3\cdot Et_2O$ ensure that all of the costly Me_2O is consumed. This modification enables kilogrammes of this valuable oxophilic alkylating agent to be prepared economically in excellent yield.[9]

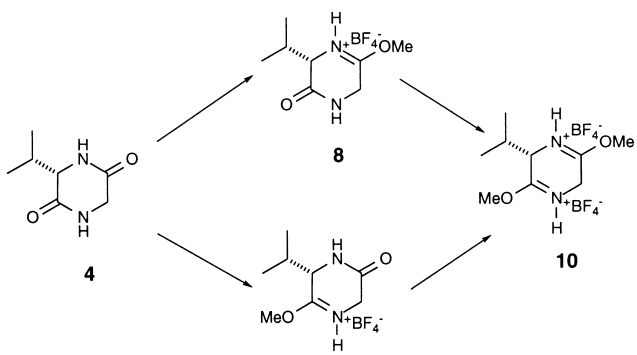
(3) The sampling of aliquots from the reaction mixture revealed that initial methylation of DKP **4**

resulted in the formation of two monomethylated intermediates **5** and **6** in a ratio of 2:1 respectively. These structural isomers could be prepared in good yield by treatment of DKP **4** with one equivalent of $Me_3O{\cdot}BF_4$ followed by chromatographic separation. Structural assignment of these isomers proved difficult due to the similarity and simplicity of their ^1H NMR spectra. Steric arguments suggested that the C_2 carbonyl of DKP **4** was hindered by the C_3 isopropyl group and therefore less available for methylation than the C_5 carbonyl. This reasoning was confirmed by selective hydrolysis of the lactim bond of major isomer **5** into the known dipeptide NH_2-L-Val-Gly-OH **7**.[10] A ^1H NMR NOE experiment was carried out on the more polar minor isomer which revealed a 0.4% enhancement between the OMe resonance at δ 3.74 and the Pr^i methyl substituents at δ 0.82 and δ 1.08 thus confirming the structure of this compound as **6**.



5 **7** **6**

It is clear that the second methylation of the diketopiperazine ring is relatively slow since treatment of DKP **4** with one equivalent of $Me_3O{\cdot}BF_4$ afforded **5** and **6** with only small quantities of **1** being isolated (<2%). This observation reflects both the heterogeneous nature of the reaction and the inherent difficulty in methylating **8** and **9**. This methylation is slow because it requires the introduction of a second positive charge into the ring system to give the highly reactive species **10**. Since this second methylation step is inefficient it is important that a small portion of the crude reaction mixture is always analysed for the presence of monomethylated isomers **5** and **6** before workup. Additional $Me_3O{\cdot}BF_4$ may then be added as required.



4 **8** **9** **10**

(4) The reaction mixture is highly acidic and it is therefore essential that the biphasic reaction mixture is added, as a slurry, to an aqueous bicarbonate solution (pH >7.5) during workup in order to minimise acid catalysed hydrolysis of bis-iminium cation **10**.

This information enabled us to devise the following experimental protocol which enabled the reliable preparation of **1** on a 45 g scale. Anhydrous dichloromethane was added to a mixture of DKP **4** and $Me_3O{\cdot}BF_4$ under an atmosphere of nitrogen and the *heterogeneous* reaction mixture was stirred for 48 hours. The reaction was quenched by slowly pouring the mixture into a rapidly stirred saturated solution of sodium bicarbonate which was maintained at pH >7.5 by portionwise additions of solid sodium bicarbonate. Extraction of the aqueous layer with CH_2Cl_2, and concentration under vacuum, afforded a crude oil which was essentially pure **1** in 70–80% yield.

In conclusion, we have reported on a series of modifications which enable Schöllkopf's auxiliary **1** to

be reliably prepared from valine on a 45 g scale in 60% yield. Bis-lactim auxiliaries which are based on α-amino acids other than valine may also be prepared using this general procedure.[11]

3. Experimental

3.1. General methods

Melting points were measured on a Gallenkamp hot stage apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. ^{1}H NMR spectra were recorded on a Bruker WH 300 and AM 500 and the chemical shifts referenced to $CHCl_3$ (δ 7.27) in $CDCl_3$. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. Mass spectra were recorded using a VG MASSLAB VG 20-250 instrument while HRMS were determined on a VG Autospec. All solvents were purified and dried according to the procedures described in *Purification of Laboratory Chemicals*, D. D. Perrin and W. L. F. Armarego, Pergamon Press, Oxford, 1988. All chemicals used for synthetic procedures were of reagent grade or better. Merck 70–320 mesh silica gel was used for chromatography.

3.2. L-*Valine*-N-*carboxyanhydride [(4*S*)-4-isopropyl-oxazolidin-2,5-dione]* ***2***

Phosgene (243 ml, 20% solution by weight in toluene, 0.47 mol) was added to a suspension of L-valine (50.0 g, 0.43 mol) in THF (500 ml) and the mixture stirred at 50–60°C for 4 hours to afford a homogeneous solution. The solution was cooled and purged of excess phosgene by bubbling N_2 through the reaction mixture and passing the exhaust gases through aqueous sodium hydroxide (2 M). The solvent was removed in vacuum to afford a crude solid which was recrystallised from petrol:ether (2:1, 500 ml) to afford **2** as a white crystalline solid (58.62 g, 96%). M.p. 70°C. $[\alpha]_D^{23}$ −44.2, (*c* 1.0 in THF) [lit.[12] m.p. 62°C, $[\alpha]_D^{23}$ −42.9 (*c* 1.0 in THF)]. ^{1}H NMR ($CDCl_3$) δ: 1.03 (3H, d, *J* 6.8, $CH(C\mathbf{H}_3)_2$), 1.09 (3H, d, *J* 6.8, $CH(C\mathbf{H}_3)_2$), 2.26 (1H, m, *J* 6.8 and 4.0, $C\mathbf{H}(CH_3)_2$), 4.23 (1H, d, *J* 4.0, H_4), 6.99 (1H, s br, NH).

3.3. cyclo-L-*Val-Gly [(3*S*)-isopropyl-piperazine-2,5-dione]* ***4***

Triethylamine (87.55 g, 0.87 mol) was added to a mechanically stirred suspension of glycine methyl ester hydrochloride (54.44 g, 0.43 mol) in chloroform (500 ml) under nitrogen and the reaction mixture cooled to −78°C. A solution of **2** (58.62 g, 0.41 mol) in THF (300 ml) was added dropwise over a period of 4 hours resulting in the precipitation of triethylamine hydrochloride as a gelatinous white solid. After stirring for a further hour at −78°C, the reaction mixture was stored at −20°C for 12 hours. The triethylamine hydrochloride precipitate was removed by filtration through Celite® and the filtrate concentrated in vacuum at room temperature to afford a crude oil which was redissolved in THF (300 ml). Filtration through Celite® and evaporation of the solvent at room temperature afforded a colourless unstable oil **3** which was dissolved in toluene (300 ml) and refluxed for 24 hours. Residual solvent was removed by decantation and the remaining toluene removed under vacuum to afford a crude pink solid which was dissolved in water (300 ml) and refluxed with decolourising charcoal for 1 hour. Charcoal was removed by filtration through Celite®, and ethanol (300 ml) was added to the filtrate in order to facilitate removal of the water in vacuum. The resulting crude solid was powdered and dried for 24 hours at 90°C under high vacuum, to afford DKP **4** as a white powder (53.1 g, 79%). An analytically pure sample was obtained by recrystallisation from ethanol:chloroform (3:1). M.p. 256°C. $[\alpha]_D^{23}$ +23.7 (*c* 1.0 in H_2O),

[lit.[2] m.p. 254°C, $[\alpha]_D^{23}$ +20.2 (*c* 0.9 in H_2O)]. ^{1}H NMR (D_2O) δ: 0.90 (3H, d, *J* 7.0, CH(C**H**$_3$)$_2$), 0.99 (3H, d, *J* 7.0, CH(C**H**$_3$)$_2$), 2.24 (1H, m, *J* 3.8 and 7.0, C**H**(CH$_3$)$_2$), 3.89 (1H, d, *J* 3.8, H_3), 3.94 (1H, d, *J* 19.2, H_6), 4.12 (1H, dd, *J* 19.2 and 1.2, H_6). ^{13}C NMR (D_2O) δ: 16.6 (CH(**C**H$_3$)$_2$), 18.8 (CH(**C**H$_3$)$_2$), 33.7 (**C**H(CH$_3$)$_2$), 44.6 (C_6), 60.7 (C_3), 169.7 (C=O), 171.1 (C=O).

3.4. Solvent gelling reactions

DKP **4** (20 mg) was dissolved in refluxing acetone:water (20:1, 2 ml) and cooled to room temperature. A portion of this solution (0.1 ml) was then added to the appropriate solvent (1 ml) at 0°C and the resulting solution allowed to stand for 5 minutes. Those solvents whose gels were stable at room temperature are detailed above.

3.5. Trimethyloxonium tetrafluoroborate

Trimethyloxonium tetrafluoroborate was prepared by modification of the method of Curphey.[8] Dimethyl ether (400 g) was condensed into a three neck flask containing dichloromethane (500 ml) and epichlorohydrin (50 g) at −78°C under an atmosphere of nitrogen. The reaction vessel was fitted with a dry-ice condenser and the mixture allowed to warm to −20°C. $BF_3 \cdot Et_2O$ (50 g) was then added dropwise with cooling and stirring. After addition was complete, more epichlorohydrin (50 g) was added to the reaction vessel and the dropwise addition of another portion of $BF_3 \cdot Et_2O$ (50 g) was repeated. This alternating stepwise addition of epichlorohydrin and $BF_3 \cdot Et_2O$ was repeated until no more dimethyl ether was seen to be refluxing from the cold finger (6–7 additions). The reaction mixture was allowed to warm to room temperature and the white solid filtered off under a stream of nitrogen, washed with chloroform (500 ml), and dried under vacuum to afford $Me_3O \cdot BF_4$ (590 g, 92% yield).

3.6. Formation of monomethylated lactim ether intermediates **5** and **6**

DKP **4** (1 g, 6.10 mmol) and $Me_3O \cdot BF_4$ (0.95 g, 6.44 mmol) were stirred together in dichloromethane (20 ml) under an atmosphere of nitrogen for six hours. The reaction mixture was quenched into phosphate buffer (50 ml) and the aqueous layer extracted with ethyl acetate (2×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under vacuum to give a crude oil (627 mg). ^{1}H NMR analysis revealed a 2:1 mixture of the two monomethylated isomers **5** and **6** and the mixture was separated by flash column chromatography (silica, ethyl acetate).

3.7. (6S)-6-Isopropyl-2-methoxy-5-oxo-3,4,5,6-tetrahydropyrazine **5**

R_f 0.35 (EtOAc). M.p. 134°C (Dec). $[\alpha]_D^{23}$ +9.1 (*c* 1.0 in H_2O). IR (KBr) 3246 (NH), 2969 (CH), 1705 (C=N), 1673 (C=O), 1633 (NH). ^{1}H NMR (CD_3OD) δ: 0.88 (3H, d, *J* 6.8, CH(C**H**$_3$)$_2$), 0.98 (3H, d, *J* 6.8, CH(C**H**$_3$)$_2$), 2.16 (1H, m, C**H**(CH$_3$)$_2$), 3.71 (3H, s, OMe), 3.90 (1H, m, H_6), 4.02 (2H, J_{AB} 21, J_{AX} 2.3, δ_{AB} 0.06, 2×H_3). ^{13}C NMR (CD_3OD) δ: 16.9 (CH(**C**H$_3$)$_2$), 18.6 (CH(**C**H$_3$)$_2$), 34.1 (**C**H(CH$_3$)$_2$), 50.5 (C_3), 53.7 (OMe), 59.4 (C_6), 162.7 (C_2), 171.8 (C_5). HRMS for $C_8H_{15}N_2O_2$ $(M+1)^+$, calcd 171.1139, found 171.1134.

3.8. (3S)-3-Isopropyl-2-methoxy-5-oxo-3,4,5,6-tetrahydropyrazine **6**

R_f 0.25 (EtOAc). M.p. 138°C (Dec). $[\alpha]_D^{23}$ +8.5 (*c* 1.0 in H_2O). IR (KBr) 3264 (NH), 2948 (CH), 1699 (C=N), 1680 (C=O), 1649 (NH). ^{1}H NMR (CD_3OD) δ: 0.82 (3H, d, *J* 6.9, CH(C**H**$_3$)$_2$), 1.08 (3H, d, *J* 6.9, CH(C**H**$_3$)$_2$), 2.33 (1H, m, C**H**(CH$_3$)$_2$), 3.74 (3H, s, OMe), 3.88 (1H, m, H_3), 3.92 (2H, J_{AB} 17.4, J_{AX} 2.5, δ_{AB} 0.03, 2×H_6). ^{1}H NMR NOE, 2×0.4% enhancement between δ 3.74 to δ 0.82 and δ 3.74 to δ 1.08. ^{13}C NMR (CD_3OD) δ: 15.6 (CH(**C**H$_3$)$_2$), 17.4 (CH(**C**H$_3$)$_2$), 32.4 (**C**H(CH$_3$)$_2$), 48.8 (OMe), 52.1 (C_6), 57.9 (C_3), 161.8 (C_2), 172.4 (C_5). HRMS for $C_8H_{15}N_2O_2$ $(M+1)^+$, calcd 171.1139, found 171.1133.

3.9. H_2N-L-Val-Gly-OH **7**

Compound **5** was dissolved in 2 M HCl for 12 hours and the solvent removed under vacuum to afford, after treatment with epoxypropane, **7** in quantitative yield. This compound was identical to material obtained from treating dipeptide **3** with 2 M HCl. $[\alpha]_D^{23}$ +94.8 (*c* 2.0 in H_2O), m.p 253°C [lit.[10] m.p 258°C, $[\alpha]_D^{23}$ +101.5 (*c* 2.0 in H_2O)]. This compares with literature data for NH_2-Gly-L-Val-OH [lit.[10] m.p. 248°C, $[\alpha]_D^{23}$ −20.2 (*c* 2.0 in H_2O)].

3.10. (3S)-3,6-Dihydro-2,5-dimethoxy-3-isopropyl-pyrazine **1**

$Me_3O\cdot BF_4$ (135 g, 915 mmol) and DKP **4** (50 g, 320 mmol) were efficiently mixed together, as solids, then covered with dichloromethane (500 ml) under an atmosphere of nitrogen. After 24 hours the heterogeneous reaction mixture was stirred vigorously using a mechanical stirrer. After a further 48 hours a small portion of the lower phase was removed and ^{1}H NMR spectral analysis carried out to determine whether any **5** or **6** was remaining. An extra equivalent of $Me_3O\cdot BF_4$ (35 g) was then added if required and the reaction mixture stirred for a further 24 hours. The biphasic reaction mixture was then poured slowly, with rapid stirring and cooling, into a saturated solution of sodium bicarbonate (750 ml) [caution — effervescence], ensuring that the solution remained above pH 7.5 at all times by the addition of solid bicarbonate. The biphasic solution was extracted with dichloromethane (2×200 ml), filtered through Celite®, the organic layers dried ($MgSO_4$), and concentrated in vacuum to afford **1** (45 g, 245 mmol) as a pale yellow oil. $[\alpha]_D^{23}$ +108.9 (*c* 1.0 in EtOH) [lit.[2] $[\alpha]_D^{23}$ +106.3 (*c* 1.0 in EtOH)]; ^{1}H NMR ($CDCl_3$) δ: 0.77 (3H, d, *J* 6.9, CH(C**H**$_3$)$_2$), 1.04 (3H, d, *J* 6.9, CH(C**H**$_3$)$_2$), 2.23 (1H, m, C**H**(CH$_3$)$_2$), 3.69 (3H, s, OMe), 3.73 (3H, s, OMe), 3.90 (3H, m, H_3 and 2×H_6). ^{13}C NMR ($CDCl_3$) 16.8, 18.9 (2×CH(**C**H$_3$)$_2$), 32.3 (**C**H(CH$_3$)$_2$), 46.4 (C_6), 52.3 (OCH_3), 52.34 (OCH_3), 60.8 (C_3), 162.2, 164.7 (C_2 and C_5). MS: m/z 185 $(M+1)^+$.

Acknowledgements

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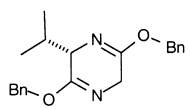

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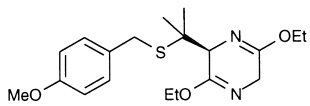

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