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Diastereoselective reduction of ketimines derived from (*R*)-3,4-dihydroxybutan-2-one: an alternative route to key intermediates for the synthesis of anticancer agent ES-285

Ana C. Allepuz, Ramón Badorrey, María D. Díaz-de-Villegas *, José A. Gálvez *

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Instituto Universitario de Catálisis Homogénea, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Spain

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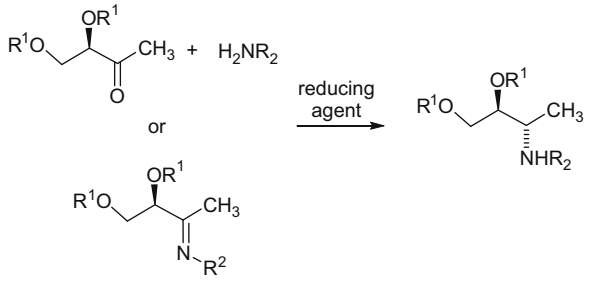
ABSTRACT

A simple and convenient procedure for the diastereoselective reduction of imines derived from (*R*)-3,4-dihydroxybutan-2-one is described. The use of sodium borohydride as a reducing agent in the reactions with pre-synthesised imines gave aminodiol derivatives with the appropriate stereochemistry for use as intermediates in the synthesis of anticancer agent ES-285. The aminodiols were isolated in ca. 62% yield.

1. Introduction

Chiral imines derived from conveniently protected D-glyceraldehyde have proven to be extremely versatile and readily available starting materials for the synthesis of a variety of enantiomerically pure chiral targets such as ABT derivatives, 1,4-dideoxy-1,4-iminohexitols, Selfotel or pipecolic acid-lysine and glutamic acid chimeras among others.[1] We recently described the preparation of 3-amino-1,2-butanediol derivative **5**, a key intermediate in the synthesis of anticancer agent ES-285, by the addition of methyl organometallic reagents to the *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde.[2] The addition of an excess of methylmagnesium bromide to this imine in the presence of $BF_3{\cdot}OEt_2$ gave the required aminodiol derivative of (2*S*,3*S*)-configuration with high diastereoselectivity (96:4), which allowed the isolation of the product in 69% yield. In contrast, the addition of an excess of methylmagnesium bromide to the *N*-benzylimine derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde led to the corresponding aminodiol derivative with total diastereoselectivity,[3] although in this case the diastereoisomer does not have the appropriate configuration for its use as an intermediate in the synthesis of ES-285.

A different approach to obtain 3-amino-1,2-butanediol derivatives of (2*S*,3*S*)-configuration would involve the diastereoselective addition of a hydride to imines derived from conveniently protected (*R*)-3,4-dihydroxybutan-2-one, a process that can be performed by two alternative procedures; (a) reduction of imines obtained in situ in reductive amination processes; and (b) hydride reduction of pre-synthesised imines (Scheme 1).



Scheme 1. Alternative routes to (2*S*,3*S*)-3-amino-1,2-butanediol derivatives by diastereoselective reduction of ketimines derived from (*R*)-3,4-dihydroxybutan-2-one.

Herein we report our results on the asymmetric synthesis of (2*S*,3*S*)-3-amino-1,2-butanediol derivatives starting from conveniently protected (*R*)-3,4-dihydroxybutan-2-one.

2. Results and discussion

The reaction of aldehydes or ketones with amines in the presence of reducing agents to give amines with more substituents, usually known as reductive amination, is among the most useful and important tools in the synthesis of amines.[4,5] This approach has been applied to the asymmetric synthesis of aminodiol derivatives with variable results depending on the substrate and reaction conditions.[6]

Among the different possibilities that exist, the use of metal hydrides that selectively reduce imines in the presence of carbonyl compounds is the method of choice. In this context, acid-stable amine-boranes,[7] sodium or lithium cyanoborohydrides[8] or sodium triacetoxyborohydride[9] are the most commonly used reducing

* Corresponding authors. Tel.: +34 976762274; fax: +34 976761202 (M.D.D); tel.: +34 976762273; fax: +34 976761202 (J.A.G.).
E-mail addresses: loladiaz@unizar.es (M.D. Díaz-de-Villegas), jagl@unizar.es (J.A. Gálvez).

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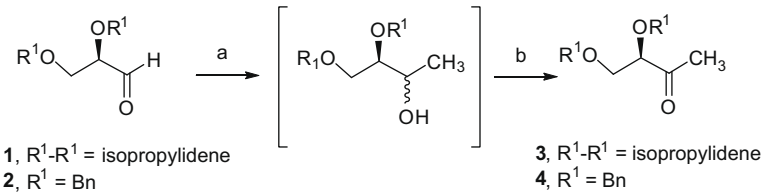
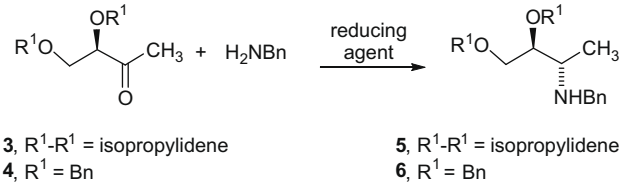


Scheme 2. Synthesis of the starting ketones **3** and **4**. Reagents and conditions: (a) CH_3MgBr, Et_2O, −20 °C; (b) *n*-Pr_4NRuO_4, NMO, CH_2Cl_2, rt (R_1–R_1 = isopropylidene 43% two steps Ref.[10], R_1 = Bn 55% two steps).

reagents. We first examined the reductive amination of conveniently protected (*R*)-3,4-dihydroxybutan-2-one with benzylamine using these reducing agents. (*R*)-3,4-Dihydroxybutan-2-ones **3** and **4** were obtained from the corresponding D-glyceraldehyde derivatives **1** and **2** according to the procedure described by Leyes and Poulter[10] for the synthesis of ketone **3**, with minor modifications required when applied to ketone **4**. The reaction of the D-glyceraldehyde derivatives **1** and **2** with methylmagnesium bromide followed by oxidation of the resulting diastereomeric mixture of glycerol derivatives with tetra-*n*-propylammonium perruthenate[11] afforded ketones **3** and **4** in 43% and 55% yield, respectively (Scheme 2).

The results of the reductive amination of (*R*)-3,4-dihydroxybutan-2-ones **3** and **4** (Scheme 3) are summarised in Table 1. It can be seen that various conditions failed to give the desired aminodiols in preparatively useful yields and/or with high diastereose-

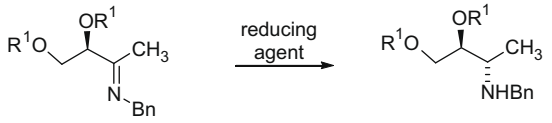


Scheme 3. Diastereoselective reductive amination of ketones **3** and **4**.

lectivities. The best results in the first screen were obtained in the reductive amination of ketone **4** with benzylamine using sodium triacetoxyborohydride/acetic acid (1 mmol) in 1,2-dichloroethane (DCE) at room temperature (entry 6). Under these conditions the corresponding amines[12] were obtained in 46% yield and with a 74/26 diastereomeric ratio. A decrease in the reaction temperature led to an increase in the diastereoselectivity of the reaction (entry 7), but below 0 °C this was accompanied by a decrease in the reaction yield (entry 8).

The reduction of the preformed ketimines, obtained by the literature procedures,[13] with metal hydrides is a useful synthetic alternative to the synthesis of amines from ketones.[14,15] This approach was examined next and the results are summarised in Table 2.

The reduction of imine **7** with lithium triethyl borohydride in THF at −20 °C for 24 h gave amine **5** as an 83/17 mixture of *anti*/*syn* diastereoisomers in 45% yield (entry 1). The use of imine **8** as the substrate under the same reaction conditions led to a significant decrease in the yield (entry 4) and the by-products derived from the elimination of the terminal benzyloxy moiety (Fig. 1) were identified. The formation of such by-products has been observed previously in the addition of certain nucleophiles to imines derived from aldehyde **2**.[16]



Scheme 4. Diastereoselective reduction of ketimines **7** and **8**.

A decrease in the reaction temperature improved the diastereoselectivity, which was total in the reduction of ketimine **8** at −78 °C, but was detrimental in terms of amine yield; only 16% of amine **6** of *anti* configuration was obtained (entry 5).

Alkaline borohydrides were next tested as reducing agents. The reduction of an ethanolic solution of imine **7** with sodium borohydride at room temperature gave amine **5** as a 75/25 mixture of *anti*/*syn* diastereoisomers in 90% yield (entry 6). The use of lithium or potassium borohydride did not improve the diastereoselectivity of the reduction process and was detrimental in terms of yield (entries 7 and 8). The reaction yield and the level of diastereoselectivity in the reduction of ketimine **7** with sodium borohydride were shown to be almost independent of the reaction temperature; a change in the temperature from room temperature to −78 °C led only to slight changes in the *anti*/*syn* ratio (compare entry 6 with entries 9 and 10).

Table 1
Diastereoselective reductive amination of ketones **3** and **4** according to Scheme 3

Entry	Ketone	Conditions	Molar ratio	Time (h)	Yield[c] (%)	*anti*:*syn*[d]
1	**3**	$NaBH_3CN$, MeOH, rt	1/1.4[a]	22	28	53/47
2	**4**	$NaBH_3CN$, MeOH, rt	1/1.4[a]	40	24	50/50
3	**3**	$PicBH_3$, MeOH/HOAc (10:1), rt	1/1[a]	6	52	54/46
4	**4**	$PicBH_3$, MeOH/HOAc (10:1), rt	1/1[a]	6	46	58/42
5	**3**	$NaBH(OAc)_3$/HOAc, DCE, rt	1/1.4/1[b]	48	22	81/19
6	**4**	$NaBH(OAc)_3$/HOAc, DCE, rt	1/1.4/1[b]	24	43	74/26
7	**4**	$NaBH(OAc)_3$/HOAc, DCE, 0 °C	1/1.4/1[b]	30	46	81/19
8	**4**	$NaBH(OAc)_3$/HOAc, DCE, −20 °C	1/1.4/1[b]	96	32	79/21

[a] Moles of substrate/moles of reducing agent.
[b] Moles of substrate/moles of reducing agent/moles of acetic acid.
[c] Mixture of diastereoisomers. Determined by ^1H NMR from crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.
[d] Determined by ^1H NMR in $CDCl_3$ (**5**) or C_6D_6 (**6**) from crude reaction mixtures.

Table 2
Diastereoselective reduction of ketimines **7** and **8** according to Scheme 4

Entry	Ketimine	Conditions	Molar ratio[a]	Time (h)	Yield[b] (%)	*anti*:*syn*[c]
1	**7**	$LiEt_3BH$, THF, −20 °C	1/1.5	24	45	83/17
2	**7**	$LiEt_3BH$, THF, −40 °C	1/1.5	30	38	88/12
3	**7**	$LiEt_3BH$, THF, −78 °C	1/1.5	72	25	91/9
4	**8**	$LiEt_3BH$, THF, −20 °C	1/1.5	48	38	91/9
5	**8**	$LiEt_3BH$, THF, −78 °C	1/3	84	16	>98/2
6	**7**	$NaBH_4$, EtOH, rt	1/2	1.5	90	75/25
7	**7**	$LiBH_4$, EtOH, rt	1/2	1.5	51	74/26
8	**7**	KBH_4, EtOH, rt	1/2	1.5	79	74/26
9	**7**	$NaBH_4$, EtOH, −20 °C	1/2	1.5	91	74/26
10	**7**	$NaBH_4$, EtOH, −78 °C	1/2	1.5	90	72/28
11	**8**	$NaBH_4$, EtOH, rt	1/1.2	1	50	76/24
12	**8**	$NaBH_4$, EtOH, −20 °C	1/1.2	2	60	79/21
13	**8**	$NaBH_4$, EtOH, −78 °C	1/1.2	2	72	85/15

[a] Moles of substrate/moles of reducing agent.
[b] Mixture of diastereoisomers. Determined by ^{1}H NMR on crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.
[c] Determined by ^{1}H NMR in $CDCl_3$ (**5**) or C_6D_6 (**6**) from crude reaction mixtures.

by-product **A** by-product **B**

Figure 1. By-products identified in the reduction of imine **8** with lithium triethyl borohydride.

The reduction of imine **8** with sodium borohydride at room temperature led to a 76/24 mixture of *anti*/*syn* diastereoisomers of amine **6** but only 50% yield was obtained (entry 11). In this case a decrease in the reaction temperature increased both the diastereoselection and the reaction yield (compare entry 11 with entries 12 and 13). Working at −78 °C amine **6** with the (2*S*,3*S*)-configuration could be isolated in 61% yield.

3. Conclusion

It can be concluded from this study that the best way to obtain (2*S*,3*S*)-3-amino-1,2-butanediol derivatives from imines derived from (*R*)-3,4-dihydroxybutan-2-one is to perform the metal hydride reduction of pre-synthesised imines using sodium borohydride as the reducing agent. Reduction of imines **7** or **8** under the appropriate reaction conditions allowed the isolation of aminodiol derivatives **5** or **6** with the required *anti* configuration in 64% or 61% yield, respectively. This constitutes as a new approach to the asymmetric synthesis of the useful intermediates for the anticancer agent ES-285.

4. Experimental

4.1. General experimental

All the reagents for the reactions were of analytical grade and were used as obtained from commercial sources. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Anhydrous solvents were used with the exception of methanol. Wherever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and the products were visualised using UV light (254 nm) and ninhydrin or phosphomolybdic acid as visualising agents followed by heating. Column chromatography was performed using silica gel (60 Å, 35–70 μm). (*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl methyl ketone **3** was prepared by the reaction of 1,2-*O*-isopropylidene-D-glyceraldehyde with methylmagnesium bromide followed by oxidation of the resulting diastereomeric mixture of glycerol derivatives, as previously described in the literature.[10] (*S*)-*N*-(1-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylidene)-1-phenylmethanamine **7** was prepared from (*R*)-2,2-dimethyl-1,3-dioxolan-4-yl methyl ketone according to a literature procedure.[13]

FT-IR spectra of oils were recorded as thin films on NaCl plates and FT-IR spectra of solids were recorded as KBr pellets, using a Thermo Nicolet Avatar 360 FT-IR spectrophotometer; ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a Jasco P-1020 polarimeter at λ 589 nm and 25 °C in a cell with 10 cm path length, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 mL. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AV-400 instrument operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR using a 5-mm probe. The chemical shifts (δ) are reported in parts per million and are referenced to the residual solvent peak. Coupling constants (J) are quoted in Hertz. The following abbreviations are used: s, singlet; d, doublet; m, multiplet; dd, doublet of doublets; qd, quartet of doublets, br s, broad signal. High resolution mass spectra were recorded using a Bruker Daltonics MicroToF-Q instrument from methanolic solutions using the positive electrospray ionisation mode (ESI+).

4.2. (*R*)-3,4-Bis(benzyloxy)butan-2-one 4

A solution of (*R*)-2,3-di-*O*-benzylglyceraldehyde (3.98 g, 14.7 mmol) in dry diethyl ether (15 mL) was added under argon to a cooled (−20 °C) 3 M ethereal solution of methylmagnesium bromide (14.8 mL, 44.3 mmol) in dry diethyl ether (150 mL). The cooling bath was removed and the mixture was stirred for 12 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (15 mL) and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford a diastereomeric mixture of alcohols, which was used in the next step without further purification.

A solution of *N*-methylmorpholine oxide (NMO) (9.1 g, 77.7 mmol) in dichloromethane (100 mL) was treated with $MgSO_4$ (6.0 g, 49.9 mmol) and the mixture was stirred for 20 min at room temperature. The drying agent was removed by filtration and 4 Å molecular sieves and a solution of the obtained diastereomeric mixture of alcohols (3.7 g, 12.94 mmol) in dichloromethane (20 mL) were added. The solution was stirred for 10 min and tetra-*n*-propylammonium perruthenate (149 mg, 0.42 mmol) was added. The mixture was stirred for 1 h at room temperature, fil-

tered through Celite® and evaporated in vacuo. Purification of the crude product by silica gel column chromatography (eluent: EtOAc/hexanes 1:8) afforded 2.21 g (55%) of compound **4** as a pale yellow oil. $[\alpha]_D^{25} = +32.2$ (*c* 0.91, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 1716, 1105; ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.75 (d, *J* = 4.0 Hz, 2H), 3.98 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 7.16–7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 70.1, 72.5, 73.4, 83.9, 127.6, 127.6, 127.8, 127.9, 128.3, 128.4, 137.3, 137.6, 209.2.; HRMS (ESI+): *m*/*z* [M+Na^+] calcd for $C_{18}H_{20}NaO_3$ (MNa^+) 307.1305, found 307.1318.

4.3. (*S*)-*N*-[3,4-Bis(benzyloxy)butan-2-ylidene]-1-phenylmethanamine 8

Benzylamine (0.62 mL, 5.1 mmol) and triethylamine (1.2 mL, 8.45 mmol) were successively added dropwise to a solution of ketone **4** (1.2 g, 4.2 mmol) in dry dichoromethane (10 mL) under argon at room temperature. The solution was cooled to −78 °C and a 1 M solution of titanium tetrachloride in dichloromethane (2.1 mL, 2.1 mmol) was carefully added dropwise, while maintaining the temperature below −78 °C. The resulting suspension was warmed to room temperature and stirred for 5 h. The reaction mixture was treated with ice-cold water (15 mL) and filtered through Celite®. The filtrate was cooled to 0 °C and treated with cooled (0 °C) 1 M aqueous NH_4Cl (15 mL). The organic layer was washed with ice-cold water (15 mL), dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford ketimine **8**, which was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 3.69 (dd, *J* = 10.5, 5.4 Hz, 1H), 3.73 (dd, *J* = 10.5, 6.0 Hz, 1H), 4.23 (dd, *J* = 6.0, 5.4 Hz, 1H), 4.45–4.62 (m, 6H), 7.10–7.40 (m, 15H).

4.4. (*S*)-*N*-Benzyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine 5

To a solution of ketimine **7** (233 mg, 1.0 mmol) in ethanol (10 mL) at −78 °C under argon was added sodium borohydride (75.6 mg, 2.0 mmol) and stirring was continued for 1.5 h at the same temperature. The solvent was removed by evaporation in vacuo and water (3 mL) was added to a solution of the resulting residue in diethyl ether (10 mL). The mixture was treated with saturated aqueous NH_4Cl (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give **5** as a 75/25 *anti*/*syn* mixture of diastereoisomers. Purification of the crude product by silica gel column chromatography (first eluent: diethyl ether/hexanes 1:1, second eluent: diethyl ether/hexanes 3:1) afforded 151 mg (64%) of pure compound **5** of *anti* configuration, the physical and spectroscopic data for which fully agree with those previously described.[2]

4.5. (2*S*,3*S*)-*N*-Benzyl-3,4-bis(benzyloxy)butan-2-amine 6

To a solution of ketimine **8** (373 mg, 1.17 mmol) in ethanol (10 mL) at −78 °C under argon was added sodium borohydride (45.4 mg, 1.2 mmol) and stirring was continued for 2 h at the same temperature. The solvent was removed by evaporation in vacuo and water (3 mL) was added to a solution of the resulting residue in diethyl ether (10 mL). The mixture was acidified with 2 M hydrochloric acid, neutralised with saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give **6** as an 85/15 *anti*/*syn* mixture of diastereoisomers. Purification of the crude product by silica gel column chromatography (eluent: diethyl ether/hexanes 1:3) afforded 229 mg (61%) of pure compound **6** of *anti* configuration as a colourless oil. $[\alpha]_D^{25} = -3.5$ (*c* 0.70, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3330, 1069; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.63 (br s, 1H), 2.98–2.90 (m, 1H), 3.58 (d, *J* = 13.2 Hz, 1H), 3.50–3.65 (m, 3H), 3.71 (d, *J* = 13.2 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 7.10–7.40 (m, 15H); ^1H NMR (400 MHz, C_6D_6) δ 1.00 (d, *J* = 6.4 Hz, 3H), 2.87 (qd, *J* = 6.4, 3.6 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.56 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.60–3.70 (m, 2H), 4.30 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 7.05–7.40 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 51.5, 53.2, 71.1, 72.5, 73.3, 80.8, 126.7, 127.4, 127.5, 127.5, 127.7, 128.0, 128.2, 138.3, 138.8, 140.6.; HRMS (ESI+): *m*/*z* [M+H^+] calcd for $C_{25}H_{30}NO_2$ (MH^+) 376.2271, found 376.2281.

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