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SYNTHESIS OF (2*S*,2′*S*)-BIMORPHOLINE

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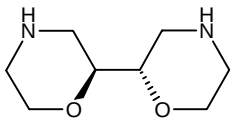
Abstract. (2*S*,2′*S*)-bimorpholine was synthesized starting from 2,3-di-O-isopropylidene-L-threitol derived from (*R*,*R*)-tartaric acid. The key steps were O-alkylation of hydroxyl groups in (2*S*,3*S*)-1,4-diazidobutane-2,3-diol and one-pot reduction and intramolecular cyclization of (2*S*,3*S*)-2,3-di-(2′,2″-bismethanesulphonyl)ethoxy-1,4-diazidobutane.

Key words: chiral diamine, O-alkylation, intramolecular cyclization, bimorpholine.

Chiral nitrogen-containing compounds have been widely used in asymmetric synthesis [1]. Considering their good chelation ability, easy separation from nonbasic products, and recyclability, the nitrogen-containing compounds have special advantages over other compounds. Also, their metal complexes are stable, easily separable, and recyclable catalysts. Therefore, the synthesis of such asymmetric auxiliaries is of great interest and practical value.

This article describes the synthesis of a chiral cyclic C_2-symmetric diamine – (2*S*,2′*S*)-bimorpholine **1**.

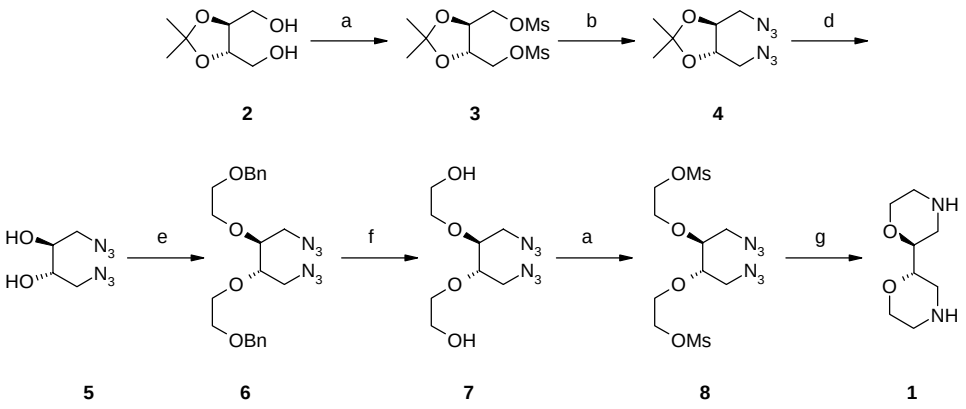


S,*S*-**1**

Chiral diamines with C_2-symmetry belong among the most useful nitrogen-containing auxiliaries [2]. A special property of these compounds is their ability

to form cyclic aminals [3, 4]. Additional conformational influence of the cyclic structure often increases the degree of stereodifferentiation in their reactions. A new proposed bimorpholine derivative **1** is a rigid system, which probably increases the conformational influence on the stereodifferentiation. Also, an extra chelation site on oxygen atom makes it a useful precursor for the synthesis of bidentate ligands [5].

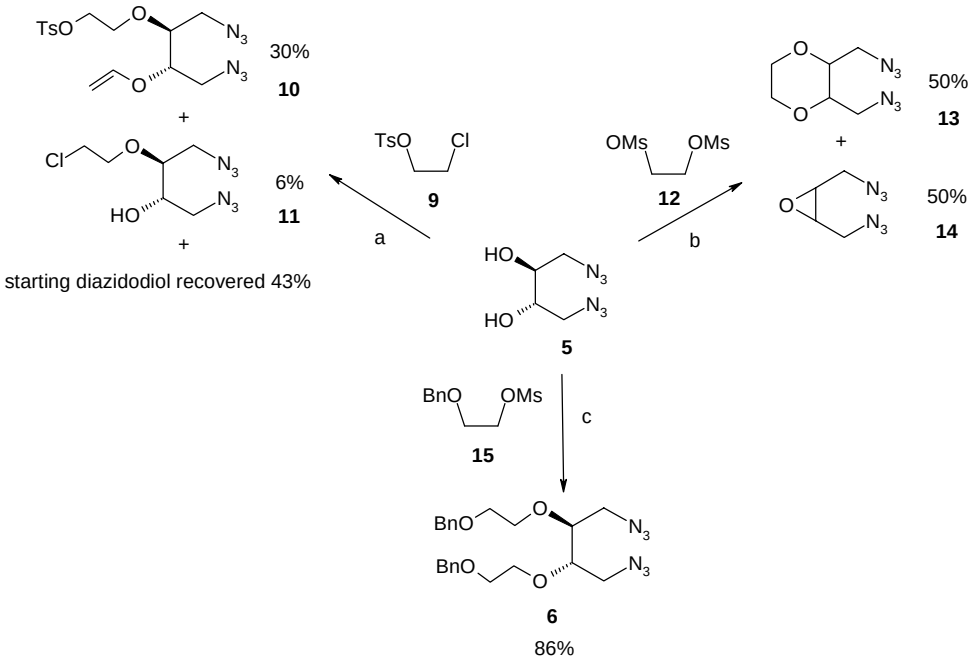
Our general idea for the synthesis of bimorpholine **1** is based on the following key steps: introduction of nitrogen-containing functionality into tartaric acid derivative **3**, O-alkylation of hydroxyl groups in derivative **5**, and one-pot reduction and intramolecular cyclization of compound **8** (Scheme 1). The starting diol **2** derived from (*R*,*R*)-tartaric acid is commercially available (its synthesis is also described in the literature [6]).



Scheme 1. a: MsCl, Et_3N, CH_2Cl_2; b: NaN_3, DMF; d: 0.5N HCl, MeOH; e: $BnOCH_2CH_2OMs$, Bu_4NI, 18-crown-6, dioxane, $NaOH/H_2O$; f: BBr_3, CH_2Cl_2, –78 °C; g: H_2/PtO_2, $MeOH/CH_2Cl_2$.

The transformation into diazide **4** was carried out by standard methods [7] (mesylation of **2** followed by the reaction of the crude bimesylate with sodium azide), resulting in compound **4** in excellent yield (two steps 89%). Diazide **5** was obtained after deprotection of hydroxyl groups and used in the next step without purification. Surprisingly, the alkylation of **5** gave rise to problems (Scheme 2).

First, 2-chloroethyl *p*-toluenesulphonate **9** as an O-alkylating reagent was examined. Unfortunately, this reagent afforded a mixture of different products and half of the starting material was recovered. The competing elimination reaction led to product **10** in 30% yield together with monoalkylated product **11**. Hardly separable cyclic products **13** and **14** in 1:1 ratio were formed when dimesylate **12** was used. The best result was obtained under phase transfer conditions with monoprotected ethylene glycole mesylate. As azido alcohols do not cyclisize under reductive conditions [8], an extra step of adding a leaving group into deprotected azide **7** was needed.



Scheme 2. a: NaH, DMF, **9**; b: Bu_4NI, dioxane, $NaOH/H_2O$, **12**; c: Bu_4NI, 18-crown-6, dioxane, $NaOH/H_2O$, **15**.

The benzyl groups of **6** were removed by boron tribromide in dichloromethane and replaced with mesyl groups resulting in compound **8**. Catalytic hydrogenation of the azido groups using Adams' catalyst [9] under atmospheric pressure with simultaneous cyclization afforded bimorpholine **1** in satisfactory overall yield (44%).

In conclusion, *R,R*-tartaric acid derivative proved to be a suitable starting material for the synthesis of bimorpholine **1**. The enantiomeric purity and use of bimorpholine **1** as a chiral auxiliary in asymmetric synthesis is under investigation.

EXPERIMENTAL

The 1D and 2D FT NMR spectra were obtained on a Bruker AMX500 or a JEOL FX90Q instrument. The mass spectrum was recorded on a Hitachi M80B spectrometer. Optical rotations were measured using A. Krüss Optronic GmbH automatic digital polarimeter P 3002.

(2*S*,3*S*)-2,3-O-isopropylidenebutyl-1,4-dimethanesulphonate 3

Methanesulphonyl chloride (4.6 mL, 59 mmol, 1.2 eq) was slowly added to a cooled solution of diol **2** (3.98 g, 24.6 mmol) and triethylamine (10.3 mL,

74 mmol, 1.5 eq) in anhydrous dichloromethane (100 mL) at 0 °C. After stirring for 2 h at 0 °C the reaction mixture was allowed to warm up to room temperature. After water was added the organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated affording a crude product as a yellow solid. Recrystallization from ethyl acetate/petroleum ether gave dimesylate **3** as white crystals (7.66 g, 98%, m.p. 71–72 °C); $[\alpha]_D^{21} = -10$ (c 2.66, CH_2Cl_2).

(2*S*,3*S*)-2,3-O-isopropylidene-1,4-diazidobutane 4

A mixture of dimesylate **3** (8.9 g, 28 mmol) and sodium azide (6.4 g, 98 mmol, 1.75 eq) in anhydrous dimethylformamide (80 mL) was stirred for 24 h at 80 °C. After cooling to room temperature the suspension was diluted with water/brine mixture (1:1, 150 mL) and concentrated under reduced pressure. The residue was taken up with water and extracted three times with ethyl acetate and dried over $MgSO_4$. Concentration under vacuum and purification by flash chromatography on silica gel using petroleum ether/ethyl acetate (10:0.5 to 10:1) as eluent afforded diazide **4** as a colourless liquid (5.4 g, 91%).

$[\alpha]_D^{21} = -138$ (c 2.34, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 6H, CH_3), 3.31 and 3.53 (dm, 4H, J_{gem} = 13.1 Hz, CH_2N), 4.03 (m, 2H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.69 (CH_3), 51.38 (CH_2N), 76.73 (CHO), 110.22 (OCO).

(2*S*,3*S*)-1,4-diazidobutane-2,3-diol 5

Diazide **4** (5.4 g, 25.5 mmol) was dissolved in methanol (100 mL), 0.5 N hydrochloric acid (25 mL) was added, and the reaction mixture was refluxed overnight. The mixture was cooled to room temperature and diluted with saturated sodium hydrogen carbonate solution. After evaporation of methanol and acetone, the aqueous layer was extracted three times with ethyl acetate and dried over $MgSO_4$. Filtration and concentration under vacuum to dryness afforded diazidodiol **5** as a colourless syrup which solidified in the fridge (4.3 g, 100%).

$[\alpha]_D^{20} = +19$ (c 1.75, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.70 (s, 2H, OH), 3.47 (d, 4H, J = 5.4 Hz, CH_2N), 3.77 (t, 2H, J = 5.4 Hz, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ 53.83 (CH_2N), 70.52 (CHO).

(2*S*,3*S*)-2,3-di-(2′2″-bisbenzyloxy)ethoxy-1,4-diazidobutane 6

To a solution of diol **5** (1.2 g, 6.95 mmol) in dioxane (15 mL) 50% NaOH aqueous solution (15 mL), Bu_4NI (268 mg, 0.7 mmol), 18-crown-6 (63 mg, 0.17 mmol), and 2-benzyloxyethyl methanesulphonate **9** (4.0 g, 17.4 mmol, 1.25 eq) were added. After stirring for 42 h at 80 °C, the reaction mixture was cooled to room temperature and saturated solution of NH_4Cl was added. The

aqueous layer was extracted three times with ethyl acetate and dried over $MgSO_4$. Concentration under vacuum and purification of the crude product by chromatography on silica gel using petroleum ether/ethyl acetate (10:0.5 to 10:2) as eluent afforded **6** as a colourless liquid (2.6 g, 86%).

$[\alpha]_D^{21} = +7.6$ (c 2.73, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (dd, 2H, J = 6.4 and 12.9 Hz, CH_2N), 3.47 (dd, 2H, J = 2.8 and 12.9 Hz, CH_2N), 3.61 and 3.62 (m, 4H, C**H$_2$**OCH$_2$Ph), 3.71 (m, 2H, CHO), 3.75 and 3.82 (m, 4H, C**H$_2$**OCH), 4.53 (s, 4H, OCH$_2$Ph), 7.30 (m, 2H, *p*-Ph), 7.34 (m, 8H, *o*-,*m*-Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ 50.70 (CH_2N), 69.84 (**C**H$_2$OCH$_2$Ph), 70.82 (**C**H$_2$OCH), 73.25 (OCH$_2$Ph), 79.21 (CHO), 127.63 (*p*-Ph), 127.70 (*o*-Ph), 128.35 (*m*-Ph), 138.06 (*s*-Ph).

(2*S*,3*S*)-2,3-di-(2′,2″-bishydroxy)ethoxy-1,4-diazidobutane 7

To a solution of dibenzyl ether **6** (1.13 mg, 2.58 mmol) in anhydrous CH_2Cl_2 (20 mL) BBr_3 (500 μL, 5.28 mmol, 1.025 eq) was added dropwise at −78 °C under argon atmosphere. The mixture was stirred at −65 °C to −40 °C until reaction was complete (6 h). The reaction was quenched with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted four times with CH_2Cl_2. After drying over $MgSO_4$ the filtrate was concentrated affording a crude diazidodiol **7** as a brown liquid. This crude product was chromatographed on silica gel with petroleum ether/ethyl acetate (1:1 to only ethyl acetate) to give target compound as a yellow oil (475 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (s, 2H, OH), 3.33 (dd, 2H, J = 5.5 and 12.9 Hz, CH_2N), 3.52 (dd, 2H, J = 3.4 and 12.9 Hz, CH_2N), 3.67 (m, 2H, CHO), 3.70 and 3.80 (m, 4H, C**H$_2$**OCH), 3.75 and 3.77 (m, 4H, C**H$_2$**OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 50.57 (CH_2N), 61.92 (CH_2OH), 72.80 (**C**H$_2$OCH), 79.36 (CHO).

(2*S*,3*S*)-2,3-di-(2′,2″-bismethanesulphonyl)ethoxy-1,4-diazidobutane 8

Dimesylate **8** was prepared according to the procedure of synthesis of compound **3**. Purification of the crude product by chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent afforded **8** as a colourless liquid (978 mg, 91%).

^{1}H NMR (90 MHz, $CDCl_3$): δ 3.051 (s, 6H), 3.357–3.478 (m, 4H), 3.633–3.704 (m, 2H), 3.867–3.971 (m, 4H), 4.313–4.411 (m, 4H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ 37.660, 50.799, 68.608, 69.319, 79.536.

(2*S*,2′*S*)-bimorpholine 1

To a solution of diazidodimesylate **8** (710 mg, 1.71 mmol) in CH_2Cl_2:MeOH (1.5:15 mL) PtO_2 (Adams' catalyst, 25.5 mg, 0.11 mmol) was added. The mixture was hydrogenated under atmospheric pressure overnight. The catalyst was removed by filtration through Celite and the filtrate was evaporated under vacuum affording a crude product (610 mg). This crude product was purified by

acid–base treatment affording bimorpholine **1** as pale yellow crystals (265 mg, 91%). An analytical sample was chromatographed on basic aluminium oxide (CH_2Cl_2:MeOH 90:10) for spectroscopic analysis. GC-MS (70 eV, EI) *m/*z (%): 172 (7) [M^+], 116 (62), 88 (43), 57 (100).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.00 (bs, 2H, NH), 2.76–2.82 (m, 6H, CHC**H$_2$**NH, OCH$_2$**CH$_2$**(*eq*)NH), 2.89 (dt, 2H, J_{ae} = 3.3 Hz, $J_{aa} = J_{gem}$ = 12 Hz, OCH$_2$**CH$_2$**(*ax*)NH), 3.42 (m, 2H, OCH(*ax*)), 3.58 (dt, 2H, J_{ae} = 2.8 Hz, $J_{aa} = J_{gem}$ = 12 Hz, OC**H$_2$**CH$_2$(*ax*)NH), 3.92 (ddd, 2H, J_{ee} = 1 Hz, J_{ea} = 3.3 Hz, J_{gem} = 11.5 Hz, OC**H$_2$**CH$_2$(*eq*)).

^{13}C NMR (125 MHz, $CDCl_3$): δ 45.69 (OCH$_2$**CH$_2$**N), 47.11 (CH**C**H$_2$NH), 68.21 (CH_2O), 77.57 (CHO).

$[\alpha]_D^{19}$ = +49 (c 0.45, MeOH).

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(2*S*,2′*S*)-BIMORFOLIINI SÜNTEES

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(2*S*,2′*S*)-bimorfoliin sünteesiti lähtudes (*R*,*R*)-viinhappe derivaadist, 2,3-di-O-isopropülideen-L-treitoolist**.** Võtmeetappideks olid (2*S*,3*S*)-1,4-diasiidobutaan-2,3-diooli O-alküleerimine ja asiidrühmade taandamine ning sisemolekulaarne tsükliseerimine ühes etapis.