Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 857–865

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of novel C_2-symmetric bimorpholines

Tõnis Kanger,[a,*] Kadri Kriis,[b] Tõnis Pehk,[c] Aleksander-Mati Müürisepp[a] and Margus Lopp[b]

[a]*Institute of Chemistry at Tallinn Technical University, Akadeemia tee 15, Tallinn 12618, Estonia*
[b]*Faculty of Chemistry, Tallinn Technical University, Ehitajate tee 5, Tallinn 19086, Estonia*
[c]*National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, Tallinn 12618, Estonia*

Received 15 March 2002; accepted 18 April 2002

Abstract—Novel heterocycles—(2*S*,2′*S*)-bimorpholine **1** and (3*S*,3′*S*)-bimorpholine **2**—were synthesised in >98% e.e. starting from tartaric acid ester.

1. Introduction

Chiral heterocycles have become of great importance in recent years because of their increasing use as essential fragments of pharmaceuticals and because of their frequent application as chiral ligands in asymmetric catalysis. Nitrogen-containing compounds have several advantageous properties over other analogous heteroatom-containing compounds, including good chelating ability, strong interaction with metals that usually results in stable catalytic systems, easy separation from non-basic products and the possibility of recycling in chemical processes.[1]

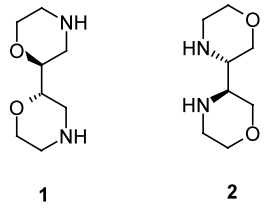


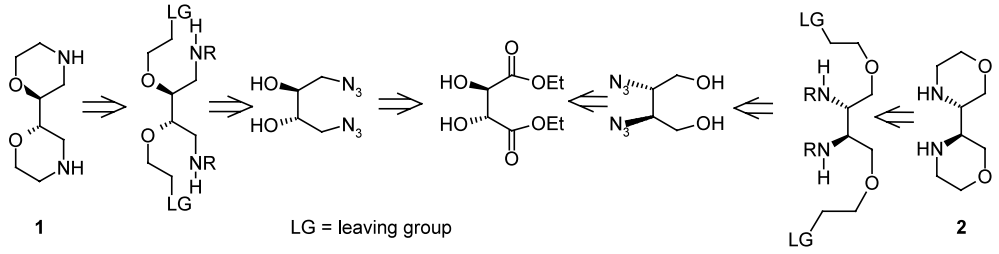
Figure 1.

We have now designed and synthesised two new chiral bimorpholines **1** and **2** (Fig. 1) that combine the positive properties of the nitrogen atom with the positive contribution of the oxygen chelating site. Additionally, these compounds have the advantages of C_2-molecular symmetry.

Although the synthesis of other asymmetric bridged heterocycles like bipyrrolidines,[2–4] bipiperidines[5] and bisaziridines[6] have been reported, no data regarding the preparation of bimorpholines could be found in the literature (except our preliminary communication on the synthesis of 2,2′-bimorpholine **1**[7]).

2. Results and discussion

Retrosynthetic analysis of the target compounds is outlined on Scheme 1. The synthesis of both new compounds is accomplished according to the same general scheme starting from a tartaric acid ester and involving the following key steps: introduction of the nitrogen-containing functionality into the tartaric acid deriva-



Scheme 1.

* Corresponding author. Fax: +372 6547524; e-mail: kanger@chemnet.ee

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00188-X

tive, *O*-alkylation of hydroxyl groups with a functionalised C2 unit, and subsequent intramolecular cyclisation. Substitution of either the primary or secondary hydroxyl group by azide to give the intermediates **20** and **3**, respectively, determines the position of the bridging bond between the heterocyclic rings. Tartaric acid ester is transformed with either retention or inversion of configuration at the stereogenic centres to lead to compound **1** and compound **2**, respectively.

2.1. Synthesis of (2*S*,2′*S*)-bimorpholine

In our previous communication we outlined a route to bimorpholine **1**[7] based on the alkylation of diazido diol **3** followed by reductive cyclisation of compound **4** (Scheme 2). The problems of using this route are connected with the separation and purification of highly hydrophilic target compound **1** from side product **1a** (formed in 10% yield). The complications with separation prompted us to search for a more practical synthetic sequence.

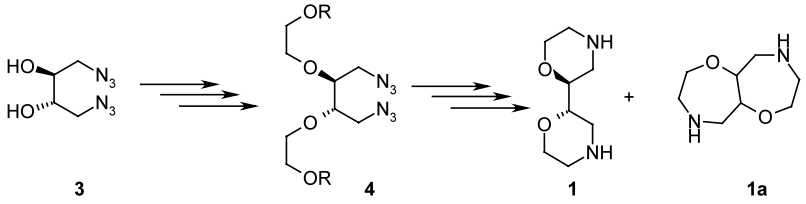
A number of methods have been used for intramolecular heterocyclisation. Among them the Mitsunobu reaction of amino alcohols is the most straightforward way to obtain the target compounds.[8] In this reaction, not only acidic N-compounds (like Ns- and Ts-amides)[9] but also alkyl[10] or arylamines[11] and even primary amines[12] form heterocycles. Our attempts to use the Mitsunobu reaction in constructing the bimorpholine skeleton under various reaction conditions were unsuccessful. Therefore, we turned to another possible alternative (Scheme 3). It is known that lactams can be synthesised from corresponding esters via intramolecular attack of an amino group[13,14] or via reductive cyclisation of azido esters.[15] In our case the corresponding azides in the course of reduction of azido group in compound **5** should give the desired bimorpholine **1**. However, we found that the in situ cyclisation of the diamine **6** results in a mixture of the six-membered ring compound **7** and seven-membered ring compound **8** in approximately a 1:1 ratio.

These negative results forced us to return to the general synthetic Scheme 2[7] as the most reasonable approach for obtaining the target compound. In order to overcome the above complications we modified the cyclisation step using *N*-Boc derivative **13** as a synthon for the cyclisation that reduces the hydrophilicity of the heterocycle **14** and allows easily its isolation from water solution.

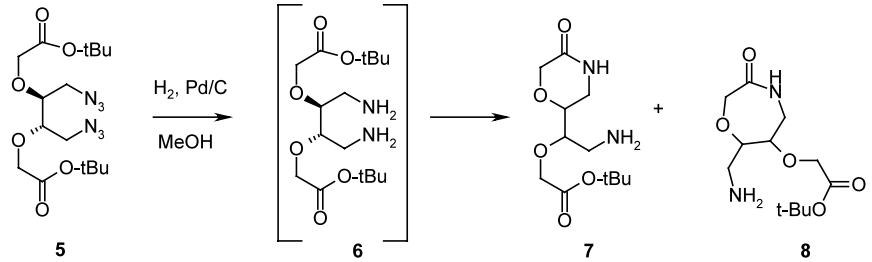
The synthesis started with alkylation of diazido diol **3** with 2-benzyloxyethyl methanesulfonate (Scheme 4). For the subsequent transformations of the benzyl and azido groups a two-step procedure is needed.[16] First, the benzyl groups were cleaved with BBr_3 followed by catalytic hydrogenation of the azido groups, affording diamino diol **11**. The following standard transformations (protection with Boc_2O and mesylation with MsCl) led to the key intermediate **13**. Although the nucleophilicity of the amino groups of compound **13** is reduced by the Boc-protection, the nucleophilicity is still sufficient to enable sodium hydride induced cyclisation. The product **14** was easily worked-up and purified and was also obtained in good yield (40% from **3**). Furthermore, no cross-coupling product analogous to **1a** was formed. Deprotection of **14** with trifluoroacetic acid gave the salt of the target compound, which was isolated under basic conditions as the free amine.

2.2. Synthesis of (3*S*,3′*S*)-bimorpholine

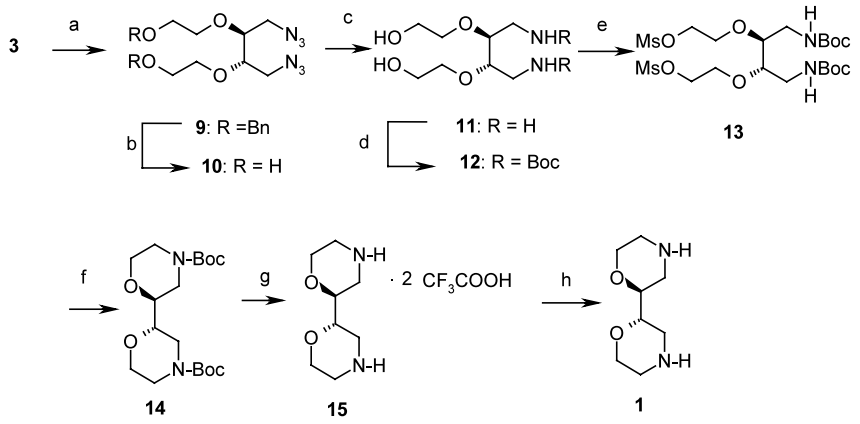
The synthesis of the bimorpholine **2** followed the same general scheme as for the previous compound **1**, involving inversion of the configuration of the stereogenic centres in the synthesis of diazide **20** (Scheme 5). The following steps are basic functional group or protective group transformations (cleavage of benzyl group, cata-



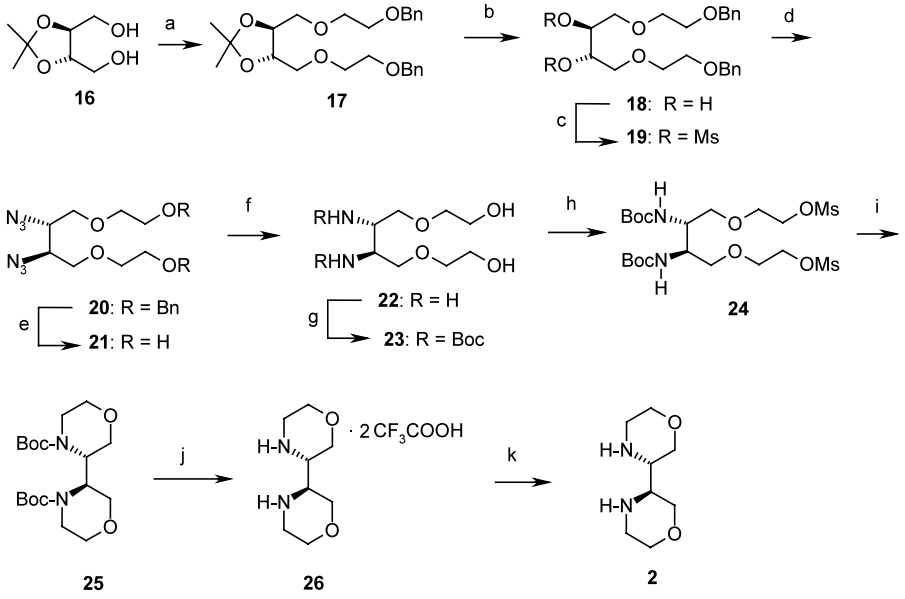
Scheme 2.



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) $BnOCH_2CH_2OMs$, Bu_4NI, *cis*-dicyclohexano-18-crown-6, dioxane, $NaOH/H_2O$, 80°C, 86%; (b) BBr_3, CH_2Cl_2, −78°C, 71%; (c) H_2, Pd/C, MeOH, 100% (crude); (d) Boc_2O, dioxane/H_2O/KOH, 0°C to rt, 88%; (e) MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 76%; (f) NaH, THF, 0°C to rt, 99%; (g) CF_3COOH, CH_2Cl_2; (h) 3.0 M NaOH, Et_2O, 29% (for two steps).



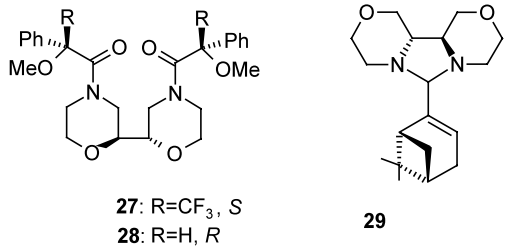
Scheme 5. *Reagents and conditions*: (a) $BnOCH_2CH_2OMs$, Bu_4NI, *cis*-dicyclohexano-18-crown-6, dioxane, $NaOH/H_2O$, 80°C, 69%; (b): 0.5N HCl, MeOH, 86%; (c) MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 100% (crude); (d) NaN_3, DMF, 80°C, 77%; (e) BBr_3, CH_2Cl_2, −78°C, 70%; (f) H_2, Pd/C, MeOH, 99%; (g) Boc_2O, dioxane/H_2O/KOH, 0°C to rt, 84%; (h) MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 90%; (i) NaH, THF, 0°C to rt, 91%; (j) CF_3COOH, CH_2Cl_2, 94%; (k) 3.0 M NaOH, Et_2O, 50%.

lytic hydrogenation of azide, protection of amino group and mesylation), which usually proceed in high yield.

The key intermediate **24** was obtained from tartaric acid derivative **16** in the multistep procedure in 24% yield. Similarly to the previous scheme the cyclisation reaction was also effective and led to protected bimorpholine **25** in 91% yield. Deprotection of **25** with trifluoroacetic acid gave the corresponding salt **26**. The target compound **2** was obtained after basic treatment of **26** in 32% yield starting from compound **22**.

2.3. Determination of the enantiomeric excess of bimorpholines

For the determination of the enantiomeric purity of bimorpholine **1**, it was converted into diastereomeric amides **27** and **28** with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) and (*R*)-(−)-α-methoxyphenylacetic acid (MPA) (Fig. 2). The use of MTPA or MPA for the derivatisation of the unsymmetrical secondary amines at room temperature results in



27: R=CF_3, *S*
28: R=H, *R*

29

Figure 2.

NMR spectra with different signals from the (*E*)- and (*Z*)-conformers of the amides. Usually, more profound differences are observed for MTPA derivatives, and that was also observed in the present case. Two secondary amino groups in the bimorpholine structure result, in the case of enantiomerically pure compounds, four sets of signals, from (*EE*)-, (*ZZ*)- and (*EZ*)-isomers correspondingly, with the (*EZ*)-isomer giving separate signals from the (*E*)- and (*Z*)-rings. Thus, an enantiomeric impurity in such compounds should result in additional sets of signals from the diastereoisomers. We have found that both **27** and **28** gave only four sets of signals, which are most clearly seen from the ^{13}C NMR spectra (Table 1). A detailed analysis of the spectra was carried out in the case of diastereoisomers from compound **27**, where larger differences in chemical shifts and in their relative concentrations of isomers were observed. The isomers had the relative concentrations 51:37:12 (the first of them being the (*EZ*)-isomer). The ratio of two minor isomers corresponds to 0.666 kcal/mol difference in ΔG and from that the conformational energy for the (*EZ*)-isomer (0.333 kcal/mol) may be calculated from simple additivity. The calculated value of relative concentrations of three isomers (taking into account that (*EZ*)-isomer can be formed in two ways) is 46:41:13, which is quite close to the observed ratio for the isomers of compound **27**. The assignment of the (*EE*)- and the (*ZZ*)-isomers (and (*E*)- and (*Z*)-rings of the (*EZ*)-isomer) was made on the basis of comparison of ^{1}H differential shielding effects in these isomers with the published data on the conformers of (*R*)-MTPA amides of (*R*)-3-methylpiperidine.[17]

Table 1. ^{1}H and ^{13}C NMR chemical shifts of bimorpholines and their derivatives[a]

Compound	Atoms									
	2		**3**		**5**		**6**		**Other**	
Isomer	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	3.42	77.57	2.76	47.11	2.86	45.69	3.58	68.21		
					2.76		3.92			
2	3.30	69.66	2.68	55.71	2.89	45.59	3.47	67.79		
	3.75				2.91		3.76			
(*EE*)-**14**[b]	3.30	75.18	2.83	43.42	2.90	43.44	3.42	66.39	1.37	154.57, 80.04, 28.18
			3.80		3.75		3.84			
(*ZZ*)-**14**[b]	3.29	74.90	2.88	44.82	2.80	42.12[c]	3.44	66.61[c]	1.37	154.46, 80.05[c], 28.18
			3.67		3.82[c]		3.89[c]			
(*EZ*,*E*)-**14**[b]	3.31	75.28	2.82	43.49	2.92	43.54	2.92	66.45	1.37	154.41, 79.99[c], 28.18
			3.83		3.75		3.75			
(*EZ*,*Z*)-**14**[b]	3.34	74.69	3.03	44.87	2.81	42.01[c]	3.43	66.52[c]	1.37	154.46, 79.93[c], 28.18
			3.69		3.82[c]		3.88[c]			
(*EE*)-**25**[b]	3.65	66.66	4.60	46.90	3.43	40.10	3.78	66.81	1.43	154.26, 79.73, 28.16
	3.98				3.63		3.82			
(*ZZ*)-**25**[b]	3.60	67.36	4.39	48.80	3.30	38.45	3.55	67.39	1.44	153.86, 80.49, 28.19
					3.95		3.89			
(*EZ*,*E*)-**25**[b]	3.58	66.81	4.60	46.60	3.44	40.08	3.43	66.87	1.40	153.97, 80.08, 28.06
	4.00				3.69		3.82			
(*EZ*,*Z*)-**25**[b]	3.49	66.99	4.38	48.60	3.55	38.68	3.52	67.22	1.47	153.78, 80.14, 28.25
	3.83				3.83		3.84			
26	3.76	65.87	3.72	54.44	3.30	44.59	3.83	64.95		
	4.11				3.43		3.98			
(*EE*)-**27**	2.04	73.75	2.05	45.63	2.68	41.88	3.32	66.26	3.69	164.02, 134.04, 126.61, 128.43, 129.59
			3.25		4.51		3.86			
(*ZZ*)-**27**	3.48	75.83	2.30	45.76	2.87	43.30	3.49	66.46	3.72	164.47, 133.31, 126.43, 128.50, 129.43
			3.74		4.46		3.76			
(*EZ*,*E*)-**27**	2.33	74.48	3.06	46.39	2.86	42.14	3.44	66.64	3.69	164.25, 134.14, 126.71, 128.51, 129.80
			3.82		4.58		3.95			
(*EZ*,*Z*)-**27**	2.82	75.12	2.13	45.54	2.16	42.90	3.31	66.17	3.71	164.44, 133.18, 126.35, 128.54, 129.48
			3.65		3.95		3.65			
29 ring A[d]	3.39	69.25	2.40	61.72	2.41	48.33	3.48	66.64		
	3.86				2.68		3.82			
29 ring B	3.41	67.01	2.89	59.09	2.75	45.19	3.63	65.66		
	3.79				2.78		3.76			

[a] In $CDCl_3$, for **26** in CD_3OD.

[b] At 243 K.

[c] Unambiguous assignment of isomers within the columns.

[d] Substituent on five-membered ring *trans* to the C(3)H of **2**. ^{13}C and ^{1}H chemical shifts in **28** from 6,6-dimethyl bicyclo[3.3.1]-2-heptene part of molecule, from atoms 1 to 7: 42.47 (2.32), 147.42, 123.98 (5.57), 31.39 (2.28), 40.82 (2.09), 37.96, 32.25 (1.01 and 2.42). Methyl groups at 21.62 (0.86) and 26.29 (1.30) and CHN(N) at 85.93 (3.74) ppm.

Although, the 3-methylpiperidine MTPA amides are a very rough model for the investigated bimorpholine **1** (having an anomeric effect from the connection of two rings), the observed regularities in differential shieldings of ^{1}H nuclei show that the (*EE*)-isomer should be more stable than the (*ZZ*)-isomer and the compound **1** has (*S*,*S*)-configuration.

For determination of the enantiomeric excess of bimorpholine **2**, the compound was converted into diastereomeric aminal derivative **29** with (1*R*)-(−)-myrtenal[18] (Fig. 2). Only one set of ^{1}H and ^{13}C chemical shifts was observed with different chemical shifts for the two morpholine rings (Table 1). Mutual assignment of the two rings is based on the *gauche* interactions of the substituent with carbons C(3), C(3′), C(5) and C(5′) of **2**.

The above results show that the enantiomeric excess of both of the synthesised bimorpholines **1** and **2** is very high (e.e. >98%).

3. Conclusion

In summary, novel heterocyclic C_2-symmetric bimorpholines with high e.e. were synthesised. These compounds may be used as ligands for chiral metal catalysts. It is assumed that unique structure of the obtained bridged compounds may result in more rigid chelates with metals increasing the conformational influence of the stereodifferentiation in various reactions. The synthesis of different chiral catalysts based on the ligands obtained in this study is currently under investigation.

4. Experimental

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker AMX500 instrument. Solvent peaks (C**H**Cl$_3$ $\delta=7.27$, CD$_2$**H**OD $\delta=3.30$, **C**DCl$_3$ $\delta=77.00$, **C**D$_3$OD $\delta=49.00$) were used as chemical shift references. The mass spectra were recorded on a Hitachi M80B spectrometer using electron ionisation (EI) at 70 eV or chemical ionisation (CI) with isobutane. IR spectra were recorded on Hitachi 270-30 infrared spectrophotometer. Optical rotations were measured using a Krüss Optronic GmbH automatic digital polarimeter P 3002. Elemental analyses were performed on a Perkin–Elmer C, H, N, S–Analyzer 2400.

4.1. (2*S*,3*S*)-2,3-Bis[(2′-benzyloxy)ethoxy]-1,4-diazidobutane 9

To a solution of diazido diol **3** (1.2 g, 6.97 mmol) in dioxane (15 mL) and a 50% NaOH aqueous solution (15 mL), Bu_4NI (268 mg, 0.73 mmol), *cis*-dicyclohexano-18-crown-6 (63 mg, 0.17 mmol) and 2-benzyloxyethyl methanesulfonate (4.0 g, 17.4 mmol) were added. After stirring for 42 h at 80°C, the reaction mixture was cooled to room temperature and a saturated solution of NH_4Cl was added. The aqueous layer was extracted with EtOAc (3×20 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by chromatography on silica gel (petroleum ether/EtOAc, 10:0.5 to 10:2) afforded **9** as a colourless liquid (2.6 g, 86%); $[\alpha]_D^{21}$ +7.6 (*c* 2.73, CH_2Cl_2). IR (film): 3010, 2955, 2920, 2085, 1590, 1445, 1275, 1195. MS (CI) *m*/*z*: 441 [M+H]$^+$, 413, 385, 356, 91. ^{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, CH_2OCH_2Ph), 3.71 (m, 2H, CHO), 3.75 and 3.82 (m, 4H, CH_2OCH), 4.53 (s, 4H, OCH_2Ph), 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 (CH_2OCH_2Ph), 70.82 (CH_2OCH), 73.25 (OCH_2Ph), 79.21 (CHO), 127.63 (*p*-Ph), 127.70 (*o*-Ph), 128.35 (*m*-Ph), 138.06 (*s*-Ph).

4.2. (4*S*,5*S*)-4,5-Diazidomethyl-3,6-dioxa-1,8-octanediol 10

To a solution of dibenzyl ether **9** (1.13 g, 2.58 mmol) in anhydrous CH_2Cl_2 (20 mL) BBr_3 (500 μL, 5.29 mmol) was added dropwise at −78°C under an Ar atmosphere. The mixture was stirred at −65 to −40°C until the reaction was complete (6 h). The reaction was quenched with a saturated solution of $NaHCO_3$ and was extracted several times with CH_2Cl_2. After drying over $MgSO_4$ the filtrate was concentrated affording a crude diazido diol **10** as a brown liquid. The crude product was chromatographed on silica gel (petroleum ether/EtOAc, 1:1 to 0:1) affording the target compound as a yellow oil (475 mg, 71%). MS (EI) *m*/*z*: 259 [M−H]$^+$, 231, 201, 142. ^{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, CH_2OCH), 3.75 and 3.77 (m, 4H, CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.57 (CH_2N), 61.92 (CH_2OH), 72.80 (CH_2OCH), 79.36 (CHO).

4.3. (4*S*,5*S*)-4,5-Diaminomethyl-3,6-dioxa-1,8-octanediol 11

To a solution of diazido diol **10** (440 mg, 1.69 mmol) in MeOH (15 mL) was added 10% Pd/C (90 mg, 0.085 mmol). The mixture was hydrogenated under a hydrogen atmosphere for 4 h. The catalyst was removed by filtration through Celite® and the filtrate was evaporated affording a crude product (350 mg, 100%) which was used in the next step without purification. $[\alpha]_D^{19}$ −35.3, (*c* 1.89, MeOH). IR (film): 3360, 2936, 1596, 1458, 1348, 1110, 1032. MS (CI) *m*/*z*: 209 [M+H]$^+$, 192, 148, 130, 101. HRMS M/2 104.0716 (calcd for $C_4H_{10}NO_2$ 104.0712) ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD) δ 2.44 (dd, 2H, $J=6.7$ and 12.9 Hz, CH_2N), 2.63 (dd, 2H, $J=2.9$ and 12.9 Hz, CH_2N), 3.25 (m, 2H, CHO), 3.38–3.45 (m, 8H, CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD) δ 40.42 (CH_2N), 61.09 (CH_2OH), 72.06 (CH_2OCH), 80.43 (CHO).

4.4. (2*S*,3*S*)-Di-*tert*-butyl-2,3-bis[(2′-hydroxy)ethoxy]-1,4-butanedicarbamate 12

To a cooled solution of diamino diol **11** (350 mg, 1.69 mmol) in dioxane:H_2O (15 mL:7 mL) di-*tert*-butyl dicarbonate (810 mg, 3.72 mmol) was added at 0°C. The reaction mixture was allowed to warm up to room temperature and an aqueous solution of KOH (1.2 mmol) was added. The reaction mixture was stirred overnight. After concentration of the reaction mixture, brine was added and the resulting mixture was extracted with EtOAc (4×15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by chromatography on silica gel (hexane/2-propanol, 10:2) afforded compound **12** (608 mg, 88%). $[\alpha]_D^{19}$ −12.1 (*c* 2.22, CH_2Cl_2). IR (film): 3480, 3005, 2960, 1705, 1380, 1265, 1180, 1120. MS (CI) *m*/*z*: 409 $[M+H]^+$, 309, 279, 253. ^1H NMR (500 MHz, $CDCl_3$, exchange broadened spectrum) δ 1.44 (s, 18H, Boc), 3.17 and 3.48 (m, 4H, CH_2N), 3.40 (bs, 2H, OH), 3.53 (m, 2H, CHO), 3.65 and 3.74 (m, 4H, CH_2O), 3.72 (m, 4H, CH_2OH), 5.32 (bs, 2H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.36 (Boc), 40.52 (CH_2N), 62.03 (CH_2OH), 72.74 (CH_2OCH), 79.47 (CHO), 79.60 (Boc), 156.38 (Boc).

4.5. (4*S*,5*S*)-4,5-Bis-(*N*-*tert*-butoxycarbonyl)aminomethyl-3,6-dioxaoctane-1,8-dimethanesulfonate 13

Methanesulfonyl chloride (340 μL, 4.40 mmol) was slowly added to a cooled solution of diol **12** (641 mg, 1.57 mmol) and triethylamine (660 μL, 4.71 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0°C. The mixture was allowed to warm to room temperature during 3 h, water was added, the organic layer was separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on silica gel (hexane/2-propanol, 10:2) affording compound **13** (670 mg, 76%). $[\alpha]_D^{19}$ −8.5 (*c* 2.67, MeOH). MS (CI) *m*/*z*: 565 $[M]^+$, 503, 465, 409, 238. ^1H NMR (500 MHz, $CDCl_3$, exchange broadened spectrum) δ 1.43 (s, 18H, Boc), 3.07 (s, 6H, Ms), 3.18 and 3.45 (m, 4H, CH_2N), 3.53 (m, 2H, CHO), 3.83 and 3.90 (m, 4H, CH_2O), 4.33 and 4.37 (m, 4H, CH_2OMs), 5.12 (bs, 2H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.30 (Boc), 37.62 (Ms), 40.15 (CH_2N), 68.55 (CH_2OCH), 68.88 (CH_2OMs), 79.25 (CHO), 79.48 (Boc), 156.05 (Boc).

4.6. (2*S*,2′*S*)-*N*,*N*′-Di-(*tert*-butoxycarbonyl)bimorpholine 14

To a solution of dimesylate **13** (670 mg, 1.19 mmol) in anhydrous THF (14 mL) was added NaH (285 mg, 7.13 mmol, 60% suspension in mineral oil) portionwise at 0°C. The reaction mixture was stirred overnight at room temperature and quenched with a saturated solution of NH_4Cl at 0°C. The aqueous layer was extracted with EtOAc (3×15 mL) and dried over $MgSO_4$. Concentration in vacuum and purification of the crude product by chromatography on silica gel (hexane/2-propanol, 5:1 to 4:1) afforded compound **14** (443 mg, 99%). $[\alpha]_D^{21}$ +15.3 (*c* 1.78, CH_2Cl_2). MS (CI) *m*/*z*: 373 $[M+H]^+$, 317, 261. The NMR spectrum shows at room temperature exchange broadening. Detailed analysis was performed at 243 K in a $CDCl_3$ solution with the help of data from *tert*-butoxycarbonyl effects on morpholine and sarcosine. ^1H and ^{13}C NMR chemical shifts of individual conformers are given in Table 1. Anal. calcd: C, 58.05; H, 8.66; N, 7.52. Found: C, 58.18; H, 8.61; N, 7.77%.

4.7. (2*S*,2′*S*)-Bimorpholine 1

Compound **14** (443 mg, 1.19 mmol) was dissolved in CH_2Cl_2 (8 mL) and trifluoroacetic acid (3 mL) was added. After stirring for 0.5 h at room temperature reaction was complete. The solution was evaporated and the residue was triturated with Et_2O to give white solid of trifluoroacetate salt **15**. The solid product was isolated by filtration, washed with Et_2O and dried in vacuum to dryness. Salt **15** was dissolved in a 3.0 M NaOH aqueous solution (3 mL) and stirred for 15 min followed by evaporation of water in vacuum. The obtained slurry was triturated with Et_2O several times. Evaporation of Et_2O gave product **1** (59 mg, 29%, mp 115–120°C). An analytical sample was chromatographed on basic aluminium oxide (CH_2Cl_2/MeOH, 90:10) for spectroscopic analysis. $[\alpha]_D^{20}$ +18.0 (*c* 4.89, MeOH). GC–MS (EI) *m*/*z*: 172 $[M]^+$, 116, 86, 57. HRMS *m*/*z* 172.1245 (calcd for $C_8H_{16}N_2O_2$ 172.1211). ^1H and ^{13}C NMR chemical shifts see Table 1.

4.8. (4*S*,5*S*)-4,5-Bis-[(2′-benzyloxy)ethoxymethyl]l-2,2-dimethyl-1,3-dioxolane 17

To a solution of diol **16** (1.15 g, 7.09 mmol) in dioxane (15 mL) and a 50% NaOH aqueous solution (15 mL), Bu_4NI (262 mg, 0.71 mmol), *cis*-dicyclohexano-18-crown-6 (66 mg, 0.18 mmol) and 2-benzyloxyethyl methanesulfonate (4.07 g, 17.7 mmol) were added. The mixture was stirred for 42 h at 80°C, was cooled to room temperature and a saturated solution of NH_4Cl was added. The aqueous layer was extracted with EtOAc (3×20 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by chromatography on silica gel (petroleum ether/EtOAc, 10:1 to 10:4) afforded **17** as a colourless liquid (2.1 g, 69%). $[\alpha]_D^{19}$ −3.7 (*c* 6.33, CH_2Cl_2). IR (film): 3035, 2985, 2870, 1495, 1455, 1215, 1140, 1095, 735. MS (CI) *m*/*z*: 415 $[M-CH_3]^+$, 339, 263, 91. ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 6H, CH_3), 3.64 (m, 4H, CH_2OBn), 3.65 (m, 4H, CH_2CHO), 3.70 (m, 4H, CH_2O), 4.02 (m, 2H, CHO), 4.56 and 4.57 (both d, 4H, J=12.1 Hz, CH_2Ph), 7.29 (m, 2H, *p*-Ph), 7.35 (m, 8H, *o*-,*m*-Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.95 (Me), 69.34 (CH_2OBn), 70.99 (CH_2O), 71.96 (OCH_2CH), 73.19 (OCH_2Ph), 77.32 (CHO), 109.63 (OCO), 127.54 (*p*-Ph), 127.65 (*o*-Ph), 128.30 (*m*-Ph), 138.15 (*s*-Ph). Anal. calcd: C, 69.74; H, 7.96. Found: C, 69.39; H, 7.86%.

4.9. (2*S*,3*S*)-1,4-Bis-[(2′-benzyloxy)ethoxy]butane-2,3-diol 18

To solution of dibenzyl ether **17** (1.93 g, 4.5 mmol) in methanol (25 mL) 0.5N HCl (5 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with a saturated $NaHCO_3$ solution. After evaporation of methanol and acetone, the aqueous layer was extracted with EtOAc (3×30 mL) and dried over $MgSO_4$. Filtration and concentration to dryness in vacuum afforded the crude product. Purification of the crude product by chromatography on silica gel (petroleum ether/2-propanol, 10:1 to 10:5) afforded diol **18** (1.51 g, 86%). $[\alpha]_D^{18}$ −2.0 (*c* 9.78, CH_2Cl_2). IR (film): 3444, 3036, 2868, 1606, 1496, 1454, 1096, 738. MS (CI) *m*/*z*: 391[M+H]$^+$, 299, 239, 149, 91. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.15 (d, 2H, J=4.6 Hz, OH), 3.63 (m, 4H, CH_2OBn), 3.64 (m, 4H, CH_2CHO), 3.69 (m, 4H, CH_2O), 3.86 (m, 2H, CHO), 4.57 (s, 4H, CH_2Ph), 7.30 (m, 2H, *p*-Ph), 7.34–7.35 (m, 8H, *o*-,*m*-Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.16 (CH_2OBn), 70.37 (CHO), 70.76 (CH_2O), 73.03 (OCH_2CH), 73.18 (OCH_2Ph), 127.64 (*p*-Ph), 127.71 (*o*-Ph), 128.35 (*m*-Ph), 137.92 (*s*-Ph). Anal. calcd: C, 67.67; H, 7.74. Found: C, 67.90; H, 7.89%.

4.10. (1*S*,2*S*)-1,2-Bis-[(2′-benzyloxy)ethoxymethyl]-ethane 1,2-dimethanesulfonate 19

Methanesulfonyl chloride (0.75 mL, 9.36 mmol) was slowly added to a solution of diol **18** (1.51 g, 3.89 mmol) and triethylamine (1.65 mL, 11.86 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0°C. Temperature was allowed to rise to room temperature during 3 h, water was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration in vacuum afforded crude dimesylate **19** (2.12 g, 100%). $[\alpha]_D^{18}$ −14.6 (*c* 9.56, CH_2Cl_2). IR (film): 3032, 2872, 1604, 1496, 1454, 1362, 1174, 1102, 914, 740. MS (CI) *m*/*z*: 546 [M]$^+$, 454, 366, 91. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (s, 6H, Ms), 3.63–3.65 (m, 4H, CH_2OBn), 3.67–3.69 (m, 4H, CH_2O), 3.77 (dd, 2H, J=3.5 and 11.0 Hz, CH_2CHO), 3.82 (dd, 2H, J=6.9 and 11.0 Hz, CH_2CHO), 4.52 (s, 4H, CH_2Ph), 4.96 (m, 2H, CHO), 7.29–7.36 (m, 10H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.65 (Ms), 69.12 (CH_2OBn), 69.82 (OCH_2CH), 70.72 (CH_2O), 73.16 (OCH_2Ph), 79.03 (CHO), 127.74 (*p*-Ph), 127.76 (*o*-Ph), 128.40 (*m*-Ph), 137.82 (*s*-Ph). Anal. calcd: C, 52.73; H, 6.23. Found: C, 52.39; H, 6.37%.

4.11. (1*S*,2*S*)-1,2-Diazido-1,2-bis-[(2′-benzyloxy)ethoxymethyl]ethane 20

A mixture of dimesylate **19** (2.12 g, 3.88 mmol) and sodium azide (0.89 g, 13.65 mmol) in anhydrous DMF (12 mL) was stirred for 48 h at 80°C. After cooling to room temperature the suspension was diluted with a water/brine mixture, was extracted with EtOAc (3×50 mL) and dried over $MgSO_4$. Concentration in vacuum and purification of the crude product by chromatography on silica gel (petroleum ether/EtOAc, 10:1 to 10:4) afforded diazide **20** (1.305 g, 77%). $[\alpha]_D^{19}$ −26.0 (*c* 5.67, CH_2Cl_2). IR (film): 3035, 2868, 2104, 1496, 1454, 1270, 1104, 738. MS (CI) *m*/*z*: 441 [M+H]$^+$, 413, 385, 261, 91. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (m, 4H, CH_2OBn), 3.69 (m, 4H, CH_2O), 3.74 (m, 4H, CH_2CHN_3), 3.75 (m, 2H, CHN_3), 4.58 (s, 4H, CH_2Ph), 7.30 (m, 2H, *p*-Ph), 7.36 (m, 8H, *o*-,*m*-Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.74 (CHN_3), 69.37 (CH_2OBn), 70.87 (OCH_2CH), 70.93 (CH_2O), 73.27 (OCH_2Ph), 127.64 (*p*-Ph), 127.69 (*o*-Ph), 128.37 (*m*-Ph), 138.05 (*s*-Ph). Anal. calcd: C, 59.99; H, 6.41; N, 19.08. Found: C, 59.47; H, 6.51; N, 18.63%.

4.12. (5*S*,6*S*)-5,6-Diazido-3,8-dioxadecane-1,10-diol 21

To a solution of compound **20** (169 mg, 0.38 mmol) in anhydrous CH_2Cl_2 (3 mL), BBr_3 (1.0 M in CH_2Cl_2, 780 μL, 0.78 mmol) was added dropwise at −78°C under an argon atmosphere. The mixture was stirred at −65 to −45°C until reaction was complete (5 h). Purification of the crude product by chromatography on silica gel (petroleum ether/2-propanol, 10:2 to 10:5) afforded diazido diol **21** (69 mg, 70%). $[\alpha]_D^{20}$ −38.4 (*c* 4.44, CH_2Cl_2). IR (film): 3388, 2872, 2100, 1264, 1052, 736. MS (CI) *m*/*z*: 261 [M+H]$^+$, 233, 205, 115. Anal. calcd: C, 36.92; H, 6.20; N, 32.29. Found: C, 36.41; H, 6.02; N, 31.97%.

4.13. (5*S*,6*S*)-5,6-Diamino-3,8-dioxadecane-1,10-diol 22

To a solution of diazido diol **21** (514 mg, 1.98 mmol) in MeOH (15 mL) 10% Pd/C (105 mg, 0.10 mmol) was added. The mixture was hydrogenated overnight under a hydrogen atmosphere. The catalyst was removed by filtration through Celite® and the filtrate was evaporated under vacuum affording a crude diamino diol **22** (410 mg, 99%). $[\alpha]_D^{20}$ +11.6 (*c* 3.78, MeOH). IR (film): 3356, 2872, 1598, 1458, 1358, 1122, 1072, 892. MS (CI) *m*/*z*: 209 [M+H]$^+$, 104. HRMS M/2 104.0714 (calcd for $C_4H_{10}NO_2$ 104.0712). ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD) δ 2.89 (m, 2H, $CHNH_2$), 3.37 (dd, 2H, J=5.8 and 9.6 Hz, CH_2CHN), 3.44 (dd, 2H, J=4.0 and 9.6 Hz, CH_2CHN), 3.46 (m, 2H, CH_2O), 3.60 (m, 2H, CH_2O), 3.60 (m, 4H, CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD) δ 52.38 ($CHNH_2$), 61.01 (CH_2OH), 72.50 (CH_2O), 73.45 (OCH_2CH).

4.14. (1*S*,2*S*)-Di-*tert*-butyl-1,2-bis[(2′-hydroxyethoxy)-methyl-1,2-ethanedicarbamate 23

To a cooled solution of diamino diol **22** (410 mg, 1.97 mmol) in dioxane:H_2O (15 mL:5 mL) di-*tert*-butyl dicarbonate (945 mg, 4.34 mmol) was added at 0°C. The reaction mixture was allowed to warm up to room temperature and an aqueous solution of KOH (1.2 mmol) was added. The reaction mixture was stirred overnight. After concentration of the reaction mixture, brine was added and the resulting mixture was extracted with EtOAc (4×30 mL). Combined organic layers were dried over $MgSO_4$ and concentrated. Purification by chromatography on silica gel (hexane/2-propanol, 10:2) afforded compound **23** (675 mg, 84%). MS (CI) *m*/*z*: 409 [M+H]$^+$, 353, 309, 279, 253. ^{1}H

NMR (500 MHz, $CDCl_3$, exchange broadened spectrum) δ 3.36 (bs, 2H, OH), 3.51 (dd, 2H, $J=4.1$ and 9.3 Hz, CH_2CHN), 3.56 (t, 4H, $J=4.3$ Hz, CH_2O), 3.59 (dd, 2H, $J=3.0$ and 9.3 Hz, CH_2CHN), 3.71 (dt, 4H, $J=3.6$ and 5.3 Hz, CH_2OH), 4.01 (m, 2H, CHN), 5.30 (bs, 2H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.35 (Boc), 51.27 (CHN), 61.48 (CH_2OH), 71.17 (OCH_2CH), 72.81 (CH_2O), 79.80 (Boc), 156.39 (Boc).

4.15. (5*S*,6*S*)-5,6-Bis-(*N*-*tert*-butoxycarbonyl)amino-3,6-dioxadecane 1,10-dimethanesulfonate 24

Methanesulfonyl chloride (50 μL, 0.65 mmol) was slowly added to a solution of diol **22** (90 mg, 0.22 mmol) and triethylamine (95 μL, 0.68 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0°C. The crude product was purified by chromatography on silica gel (hexane/2-propanol, 10:3 to 10:5) affording compound **24** as a colourless syrup which solidifies in the fridge (110 mg, 90%). $[\alpha]_D^{21}$ −7.7 (*c* 3.78, CH_2Cl_2). IR (film): 3384, 2980, 2940, 1708, 1352, 1248, 1172. MS (CI) *m*/*z*: 565 $[M+H]^+$, 509, 465, 409. ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 18H, Boc), 3.06 (s, 6H, Ms), 3.55 (dd, 2H, $J=3.5$ and 9.7, CH_2CHN), 3.64 (dd, 2H, $J=2.2$ and 9.7 Hz, CH_2CHN), 3.73–3.74 (m, 4H, CH_2O), 3.92 (m, 2H, CHN), 4.34–4.37 (m, 4H, CH_2OMs), 5.20 (d, 2H, $J=$ 5.7, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.32 (Boc), 37.63 (Ms), 51.39 (CHN), 68.69 (CH_2OMs), 68.96 (CH_2O), 70.98 (OCH_2CH), 79.56 (Boc), 156.18 (Boc). Anal. calcd: C, 42.55; H, 7.14; N, 4.96. Found: C, 42.52; H, 7.23; N, 4.88%.

4.16. (3*S*,3′*S*)-*N*,*N*′-Di-(*tert*-butoxycarbonyl)bimorpholine 25

To a solution of dimesylate **24** (778 mg, 1.38 mmol) in anhydrous THF (15 mL) was added NaH (393 mg, 9.83 mmol, 60% suspension in mineral oil) portionwise at 0°C. The reaction mixture was stirred overnight at room temperature and quenched with a saturated solution of NH_4Cl at 0°C. The aqueous layer was extracted with EtOAc (3×30 mL) and dried over $MgSO_4$. Concentration in vacuum and purification of the crude product by chromatography on silica gel (hexane/2-propanol, 10:0.7 to 10:1) afforded compound **25** (465 mg, 91%). $[\alpha]_D^{20}$ +86.2 (*c* 5.33, CH_2Cl_2). IR (film): 3010, 2965, 2890, 1710, 1470, 1435, 1380, 1250, 1185, 1130. MS (CI) *m*/*z*: 373$[M+H]^+$, 317, 261. NMR spectra at room temperature show exchange broadening, but the interconversion barrier is somewhat higher than in **14**. Results of measured spectra (at 243 K) with the assignment of individual conformers are given in Table 1.

4.17. (3*S*,3′*S*)-Bimorpholine 2

To a solution of compound **25** (110 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (1 mL). After stirring for 0.5 h at room temperature, the reaction was complete. The solution was evaporated and the residue was triturated with Et_2O to give the white solid of trifluoroacetate salt **26**. The solid product was isolated by filtration, washed with Et_2O and concentrated in vacuum to dryness. Then trifluoroacetate salt **26** (113 mg, 0.28 mmol, 94%) was dissolved in a 3.0 M NaOH aqueous solution (1 mL) and stirred for 15 min followed by evaporation of water. The obtained slurry was triturated with Et_2O several times. Evaporation of Et_2O afforded product **2** (24 mg, 50%, mp 66–68°C). $[\alpha]_D^{20}$ −29.4 (*c* 2.0, MeOH). MS (EI) *m*/*z*: 172 $[M]^+$, 114, 86, 58. HRMS *m*/*z* 172.1234 (calcd for $C_8H_{16}N_2O_2$ 172.1211). For ^1H and ^{13}C NMR chemical shifts see Table 1.

4.18. Preparation of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid diamide 27 and (*R*)-(−)-α-methoxyphenylacetic acid diamide 28 from (2*S*,2′*S*)-bimorpholine 1

A solution of (*S*)-(−)-MTPA (46 mg, 0.20 mmol) and DCC (42.5 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was stirred 0.5 h at 0°C. Bimorpholine **1** (15 mg, 0.087 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added and stirring was continued overnight. The reaction mixture was filtered, the filtrate was washed with water, brine and dried over Na_2SO_4. After concentration in vacuum the crude product was purified by chromatography affording diamide **27** (26 mg, 50%). Diamide **28** was synthesised from (*R*)-MPA analogously. ^1H and ^{13}C NMR chemical shifts of individual conformers at room temperature are given in Table 1.

4.19. Preparation of aminal 29 with (1*R*)-(−)-myrtenal from (3*S*,3′*S*)-bimorpholine 2

To a solution of bimorpholine **2** (18 mg, 0.10 mmol) and 4 Å MS in anhydrous Et_2O (1*R*)-(−)-myrtenal (32 μL, 0.21 mmol) was added via syringe under an argon atmosphere and the mixture was stirred overnight. The molecular sieves were removed by filtration through Celite® and the filtrate was evaporated under vacuum affording a crude aminal. Purification by chromatography on silica gel (hexane/EtOAc, 10:2, 1% Et_3N) afforded compound **29** (17 mg, 57%). For ^1H and ^{13}C NMR chemical shifts see Table 1.

Acknowledgements

This research was supported by Estonian Science Foundation, Grant Nos. 4976, 5133 and 3781.

References

1. Fache, F.; Schulz, E.; Lorraine Tommasino, M.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231.
2. Oishi, T.; Hirama, M.; Sita, L. R.; Masamune, S. *Synthesis* **1991**, 789–792.
3. Kotsuki, H.; Kuzume, H.; Ghoda, T.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hirama, M.; Shiro, M. *Tetrahedron: Asymmetry* **1995**, *9*, 2227–2236.
4. Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093–4095.

5. Sato, M.; Sato, Y.; Yoshikawa, S. *J. Chem. Soc., Dalton Trans* **1985**, 895–898.
6. Buijsters, P. J. J. A.; van der Reijden, F. P.; Feiters, M. C.; de Gelder, R.; Sommerdijk, N. A. J. M.; Nolte, R. J. M.; Zwanenburg, B. *J. Chem. Crystallogr*. **1999**, *29*, 179–183.
7. Kriis, K.; Kanger, T.; Pehk, T.; Lopp, M. *Proc. Estonian Acad. Sci. Chem*. **2001**, *50*, 173–179.
8. Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp. 1–31.
9. Mao, H.; Joly, G. J.; Peeters, K.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955–6967.
10. Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett*. **1991**, *32*, 161–164.
11. Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Ito, S. *Tetrahedron Lett*. **1999**, *37*, 2463–2466.
12. Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109–117.
13. Miller, H. W.; Newlander, K. A.; Eggleston, D. S.; Haltiwanger, R. C. *Tetrahedron Lett*. **1995**, *36*, 373–376.
14. Wrobel, J.; Dietrich, A.; Gorham, J.; Sestanj, K. *J. Org. Chem*. **1990**, *55*, 2694–2702.
15. Barnett, C. J.; Wilson, T. M.; Wendel, S. R.; Winningham, M. J.; Deeter, J. B. *J. Org. Chem*. **1994**, *59*, 7038–7045.
16. Scheurer, A.; Mosse, P.; Saalfrank, R. W. *Tetrahedron: Asymmetry* **1997**, *8*, 1243–1251.
17. Hoye, T. R.; Renner, M. K. *J. Org. Chem*. **1996**, *61*, 2056–2064.
18. Mangeney, P.; Alexakis, A.; Normant, J. N. *Tetrahedron Lett*. **1988**, *29*, 2677–2680.