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Stereoselective synthesis of 2-hydroxymorpholines and aminodiols via a three-component boro-Mannich reaction

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Abstract—The three-component coupling of an 1,2-aminoalcohol, a 1,2-dicarbonyl compound and a boronic acid was investigated. The reaction is supposed to proceed through the formation of a heterocyclic iminium species followed by the addition of the organoboron derivative. The diastereoselectivity of this process is discussed. Best results were observed when the probable intermediate was generated from a preformed 3-phenylthiomorpholin-2-ol. Products of this three-component boro-Mannich could be readily converted to the corresponding aminodiols by reduction with lithium aluminium hydride.

1. Introduction

The 2-hydroxymorpholine structural core is found as a basic skeleton in a wide range of biologically active compounds.[1] For example, Aprepitant **1**, an orally active NK_1 receptor antagonist, shows potent and promising activities for the treatment of chemotherapy-induced emesis and depression.[2] (3,5-Difluorophenyl)morpholinol **2** selectively inhibits norepinephrine uptake with antidepressant properties (Fig. 1).[3]

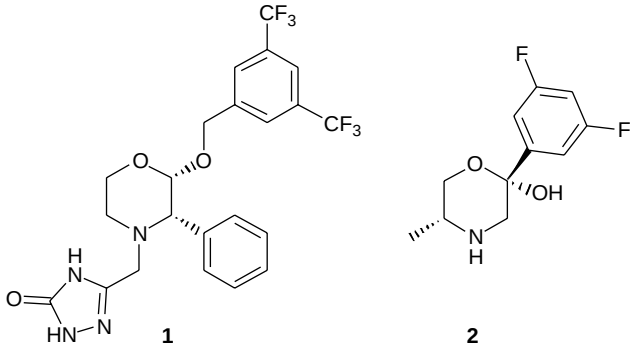

Figure 1.

Based on the NMR structure of the complex between the antibiotic paromomycin and the A-site ribosomal RNA, a set of analogs **3** possessing a morpholino moiety was designed and synthesized.[4] In addition to their antioxidant activities, nitric esters **4** appeared to release NO that can be exploited for the inhibition of artherogenic mechanism (Fig. 2).[5]

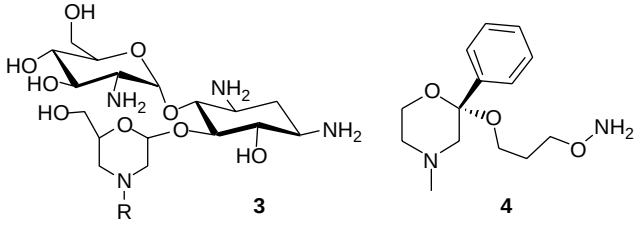

Figure 2.

Besides these remarkable pharmacological properties, 2-hydroxymorpholines are also direct precursors of morpholine-2-ones, their oxidation products. These heterocycles have proven to be versatile intermediates in asymmetric synthesis, as it was amply demonstrated in the stereocontrolled access to α-aminoacids.[6]

Few stereoselective preparations of 2-hydroxymorpholines and derivatives have been hitherto reported. Main procedures include the condensation of an 1,2-aminoalcohol with α-halogeno-ketone,[7] the reaction of an amine with an epoxide [8] and the reduction of morpholin-2-ones.[9] Addition of organometallic reagents to *N*-cyanomethyl-1,3-oxazolidines[10]

Keywords: 2-Hydroxymorpholine; Multicomponent reaction; Boro-Mannich condensation; Boronic acid; Chiral aminodiol.
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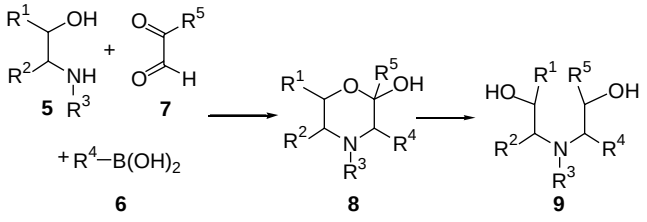
or 2-hydroxy-3-phenylthiomorpholines[11] have been also successfully used in non-racemic series. However, these previous approaches are limited in versatility and restrict the number of accessible structures.

Multicomponent methodologies are still attracting considerable interest due to their high flexibility, selectivity and convergence.[12] Among them, the boro-Mannich reaction, widely developed by Petasis and co-workers, has drawn a lot of attention for the construction of nitrogen-containing systems.[13] With this in mind, we decided to study the three-component condensation of a 1,2-aminoalcool **5**, a boronic acid **6** and a 1,2-dicarbonyl compound **7** (Scheme 1).[14] The use of organoboron compounds is especially valued due to their easily accessibility or commercial availability, their tolerance for a broad range of functional groups, and their air and water stability compared with usual organometallics reagents. We here present a detailed study of the scope and limitations of this reaction, as well as its stereochemical course in the case of chiral *C*-substituted aminoalcohols. Further reduction of the resulting product **8** led to the corresponding aminodiols **9**, some useful ligands in asymmetric catalysis.[15] During the course of our work, Pye and co-workers, from Merck Laboratories, reported an asymmetric version based on the use of a chiral group at the nitrogen atom of the starting aminoalcohol and its application to the synthesis of Aprepitant **1**.[16]



Scheme 1.

2. Results and discussion

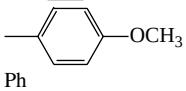
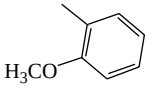
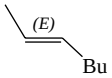
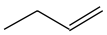
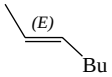
2.1. Synthesis of 2-hydroxymorpholines from achiral 1,2-aminoalcohols

Using *N*-methylaminoethanol ($R^1=R^2=H$, $R^3=Me$), phenylboronic acid ($R^4=Ph$) and glyoxal ($R^5=H$) as models reagents, we first screened several solvents including ethanol, acetonitrile, toluene, tetrahydrofuran and methylene chloride. Of these, ethanol gave best results in terms of yields and reproducibility. The subsequent reactions were therefore carried out by simple mixing equimolar amounts of the aminoalcohol, 1,2-dicarbonyl compound and boronic acid in ethanol for 12 h at room temperature. With aryl and alkenyl boronic acids, the formation of the expected 2-hydroxymorpholines **8** proceeded readily with satisfactory yields and was compatible with the presence of various substituents in different positions of the morpholine core (Table 1). Owing to ring-chain tautomerism, all these compounds were obtained as mixtures of diastereoisomers with a ratio depending on R^3–R^5. In the case of $MeB(OH)_2$, glyoxal and *N*-benzylaminoethanol, the only identified product was the tricyclic compound **10** (see Scheme 3) as previously reported when the reaction was conducted in the absence of the methyl boronic acid.[17] We were also unable to isolate any 2-hydroxy-1,4-oxazepane from *N*-methylaminopropanol instead of *N*-methylaminoethanol.

2.2. Mechanistic hypothesis

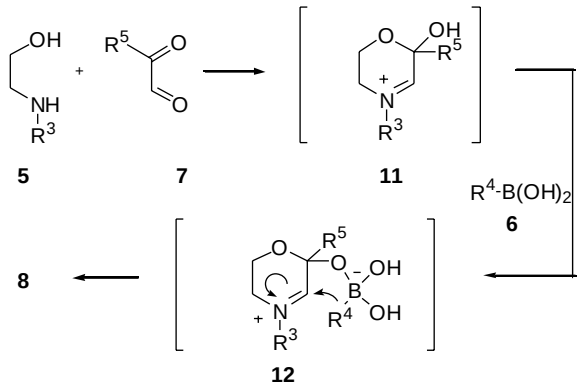
With regard to mechanism, the most plausible hypothesis involves the initial reaction of the amino group of the 1,2-aminoalcohol **5** with the aldehyde function of **7** to give the key intermediate **11**. The coordination between the hydroxyl function of this cyclic iminium species and the boron atom of **6** leads to the formation of a tetracoordinate boron

Table 1. One-pot three-component boro-Mannich reaction with achiral 1,2-aminoalcohols ($R^1=R^2=H$)

Entry	Product	R^3	R^4	R^5	Yield (%)[a]	dr[b]
1	**8a**	Me	Ph	H	62	95/5
2	**8b**	Me		H	65	70/30
3	**8c**	Me		H	80	90/10
4	**8d**	$PhCH_2$	Ph	H	70	85/15
5	**8e**	$PhCH_2$		H	50	80/20
6	**8f**	$PhCH_2$		H	65	75/25
7	**8g**	$PhCH_2$		H	67	60/40
8	**8h**		Ph	H	75	75/25
9	**8i**	$PhCH_2$	Ph	Me	57	85/15
10	**8j**	$PhCH_2$		Me	59	55/45
11	**8k**	$PhCH_2$	Ph	Ph	58	90/10

[a] Yield of isolated product after purification by column chromatography.
[b] Determined by ^1H NMR in $CDCl_3$ solution.

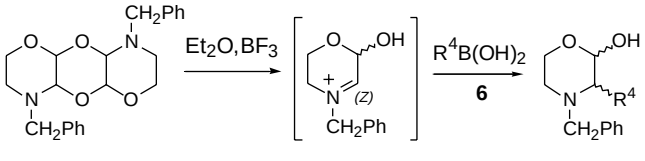
derivative **12** that evolves via an irreversible transfer of the R^4 group to afford the 2-hydroxymorpholine **8** (Scheme 2). Similar intramolecular migrations have been already suggested in the case of 3-hydroxypyrrolidines or salicylaldehyde.[18]



Scheme 2.

2.3. Synthesis of 2-hydroxymorpholines from an activated alkenylboronic ester

No expected 2-hydroxymorpholine was obtained in the one pot procedure from an activated alkenyl boronic acid **5** (R^4=CH=CH–CO_2Me), which may be due to a competitive Michael addition of the amine to the activated double bond. This failure was successfully overcome by using perhydro-4,8-dibenzyl-4,8-diaza-1,5,9,10-tetraoxoanthracene **10** as an iminium precursor in accordance with the suggested mechanism (Scheme 3).[19] By way of comparison with the one pot process, **8d** (R^4=Ph) was obtained from phenylboronic acid in a better yield by this approach.



Compound	R^4	Yd (%)	d.r.
8d	Ph	84	75/25
8l	CO_2Me	76	60/40

Scheme 3.

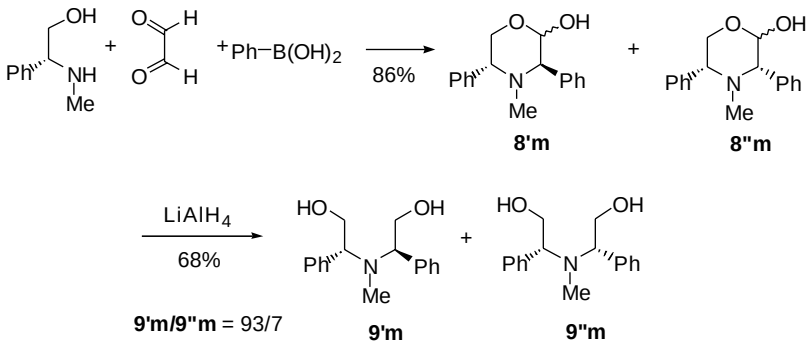
2.4. Synthesis of 2-hydroxymorpholines from chiral 1,2-aminoalcohols

Having developed an efficient method for the preparation of substituted 2-hydroxymorpholines, we then turned our attention to the diastereoselectivity of this process with chiral aminoalcohols. We first chose (1*R*)-*N*-methylphenylglycinol and phenylboronic acid as model reagents. As previously reported, the reaction was carried out in ethanol at room temperature without any special precaution. Compound **8m** was isolated as a mixture of four diastereoisomers (24/69/2/5) in a 86% yield after purification by column chromatography. Stereoselectivity at the new stereocenter C-3 was determined after conversion to the corresponding aminodiols by reduction with $LiAlH_4$. A mixture of two epimers **9′m** and **9″m** was obtained in a 93/7 ratio (Scheme 4).

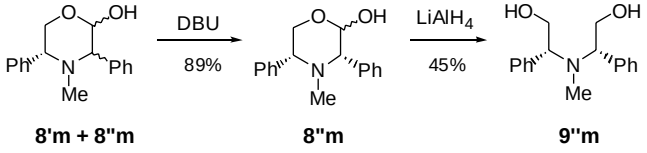
The stereochemistry of the minor isomer **9″m**, and therefore of the major one **9′m**, was determined by treatment of the crude mixture resulting from the boro-Mannich reaction with DBU at 60 °C for 24 h. Under these conditions, epimerisation at C_3 was complete to give the more stable diequatorial compound, that was confirmed after reduction with $LiAlH_4$. Compound **9″m** has indeed an $[\alpha]_D=0$. By comparison, the other epimer **9′m**, which was synthesised from the corresponding thioether **13a** as described further in Scheme 7 (Table 3, entry 1), has an $[\alpha]_D$ +86.5 (*c* 1.35, CH_2Cl_2). (Scheme 5).

To expand the scope and utility of the sequence described in Scheme 4, we envisioned using other boronic acids and 1,2-aminoalcohols. The results of these three-component boro-Mannich reactions followed by the reductive morpholine ring opening are summarized in Table 2 (Scheme 6).

Whatever R^1 and R^2, the control of the configuration at C_3 is definitely more efficient for R^4=Ph than for R^4=alkenyl (entries 1 and 3, 4 and 5, 8 and 9). The replacement of R^2=Ph (entry 1) by R^2=*i*Pr (entry 6) did not induce any significant modification of the diastereoisomeric ratio. Similarly, the same conclusion can be drawn when **5** was substituted at a position α to the oxygen (R^1=Me or Ph, entries 7–9), although it was less significant when the phenyl group is located in α to the oxygen of the starting material. The configuration of the new stereogenic center α to the nitrogen for compounds **9′p**[20] and **9″t**[21] were established from their ^{1}H NMR spectra by comparison



Scheme 4.



Scheme 5.

with literature. For other aminodiols, it was done by analogy with **9′m**, **9′p** or **9′t**. From a stereochemical point of view, the formation of the major compound could be ascribed to a preferred axial attack of the boron derivative that could be favoured by the formation of the tetracoordinate boron complex **12** (Fig. 3).

To improve the stereoselectivity of this reaction, we decided to generate the iminium intermediate from the corresponding 5-phenyl-3-phenylthiomorpholin-2-ols **13**, as previously reported by Agami and co-workers.[19] Compounds **13a** and **13b**, selected as examples, were first prepared by condensation of the aminoalcools **5**, with glyoxal and thiophenol (Scheme 7).

As expected, the addition of a boronic acid in dichloromethane at −78 °C in presence of BF_3–etherate led to the corresponding 2-hydroxymorpholines **8** in good isolated yields (Table 3). Reduction with $LiAlH_4$ in ether gave the corresponding aminoalcohols with good to excellent

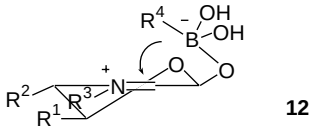
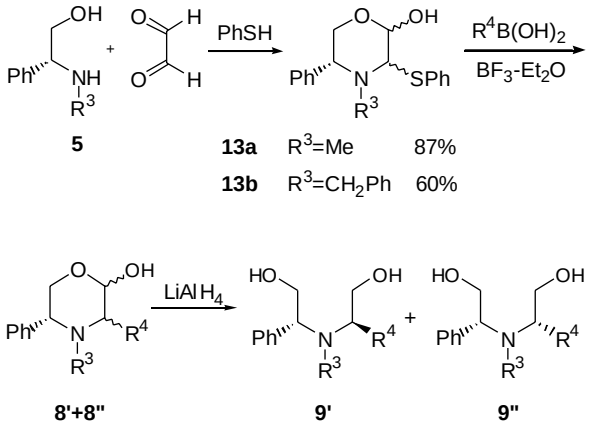
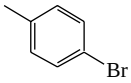
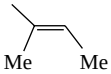


Figure 3.

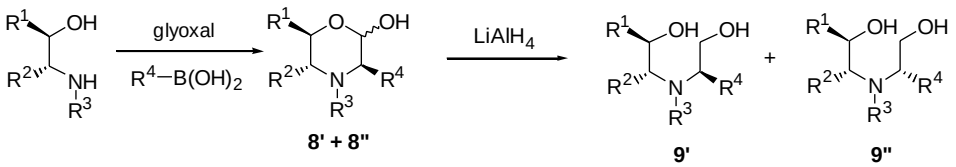


Scheme 7.

Table 2. One-pot three-component boro-Mannich reaction/$LiAlH_4$ reduction

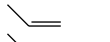
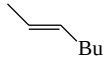
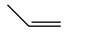
Entry	2-Hydroxy-morpholine	R^1	R^2	R^3	R^4	**8′ + 8″**	**9′ + 9″**	
						Yield (%)[a,b]	Yield (%)[a]	de[c]
1	**8m**	H	Ph	Me	Ph	86	68	86
2	**8n**	H	Ph	Me		47	56	40
3	**8o**	H	Ph	Me		75	78	4
4	**8p**	H	Ph	$PhCH_2$	Ph	76	66	72
5	**8q**	H	Ph	$PhCH_2$		77	63	4
6	**8r**	H	*i*Pr	Me	Ph	74	63	82
7	**8s**	Me	H		Ph	43	76	60
8	**8t**	Ph	H	$PhCH_2$	Ph	66	75	80
9	**8u**	Ph	H	$PhCH_2$		56	72	50
10	**8v**	H	Ph	$PhCH_2$		51	—	—

[a] Yield of isolated product after purification by column chromatography.
[b] All the reactions were performed with optically pure products except **8s**.
[c] Determined by ^1H NMR.



Scheme 6.

Table 3. 2-Hydroxymorpholines **8** and aminodiols **9** from thioethers **13**

Entry	2-Hydroxy-morpholine	R^3	R^4	**8**	**9′+9″**	
				Yield (%)[a]	Yield (%)[a]	de[b]
1	**8m**	Me	Ph	71	96	>98%
2	**8w**	Me		82	92	>98%
3	**8o**	Me		61	72	94
4	**8p**	$PhCH_2$	Ph	65	66	96
5	**8x**	$PhCH_2$		77	72	94

[a] Yield of isolated product after purification by column chromatography.
[b] Determined by ^{1}H NMR.

diastereoisomer excesses from 94 to >98%. This highlights the fact that a modification of the iminium generation can greatly improve the stereoselectivity of the reaction (entries 1, 3 and 4; Tables 2 and 3). The exact origin of this significant amelioration remains unclear for the moment.

3. Conclusion

In conclusion, the preparation of 2-hydroxymorpholines was achieved, either in a one-pot process from aminoalcohol, glyoxal and boronic acid or from a preformed 3-phenylthiomorpholin-2-ol. Better results in term of diastereoselectivity were obtained in the last case. Moreover, the corresponding chiral aminodiols were prepared by reduction with lithium aluminium hydride. Further studies focusing on the use of 2-hydroxymorpholines in the synthesis of more elaborated substrates are underway in our laboratory.

4. Experimental

4.1. General comments

^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker AC 300 spectrometer, ^{1}H NMR spectra (200 MHz) and ^{13}C NMR (50 MHz) on a Bruker ARX 200 spectrometer, in $CDCl_3$ solutions with Me_4Si as internal reference. Chemical shifts are given in parts per million and coupling constants *J* in Hertz. Diethylether and tetrahydrofuran were distilled from Na/benzophenone under N_2, dichloromethane from P_2O_5 under N_2. Elemental analyses were performed by the Microanalytical Laboratory of the Centre National de la Recherche Scientifique, Gif sur Yvette. High-resolution mass (HRMS) data spectrum was recorded on a Varian MAT 311 spectrometer from the Centre Regional de Mesures Physiques de l'Ouest. Analytical thin-layer chromatography was performed on Merck Silica Gel 60 F254 plates. Aminoalcohols **5** and boronic acids **6** are commercially available, except the precursor of **8l**, whose preparation is described further. Thioethers **13a** and **13b** were prepared as described by Agami and co-workers.[19]

4.2. 1-Synthesis of 2-hydroxymorpholines 8a–k from achiral 1,2-aminoalcohols

General procedure. A mixture of 1,2-aminoalcohol **5** (1 mmol), boronic acid **6** (1 mmol) and 1,2-dicarbonyl compound **7** (1 mmol) in ethanol (5 mL) was stirred at room temperature for 12 h. The solvent was removed in vacuo to give crude **8**, which was purified by flash chromatography (silica gel, ethyl acetate/heptane).

4.2.1. 4-Methyl-3-phenylmorpholin-2-ol 8a. Yield 62%, mp 115–17 °C (diisopropylether). Major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.42 (td, J=4.1, 11.6 Hz, 1H), 2.71 (d, J=11.7 Hz, 1H), 2.79 (d, J=7.3 Hz, 1H), 3.80–3.94 (m, 2H), 4.51 (br s, 1H), 4.66 (d, J=7.4 Hz, 1H), 7.27–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2, 54.2, 63.9, 74.4, 97.0, 127.7, 128.3, 128.7, 138.3. Minor epimer (characteristic signals): ^{1}H (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 4.93 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 56.1, 58.7, 72.8, 92.9. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 7.78; N, 7.40.

4.2.2. 3-(2-Furyl)-4-methylmorpholin-2-ol 8b. Yield 65%, mp 130–32 °C (diisopropylether). Major epimer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.41 (ddd, J=3.4, 9.0, 12.0 Hz, 1H), 2.78 (dq, J=3.8, 11.8 Hz, 1H), 3.18 (d, J=5.9 Hz, 1H), 3.77 (br s, 1H), 3.87 (ddd, J=2.9, 9.0, 11.8 Hz, 1H), 4.04 (dt, J=3.8, 11.8 Hz, 1H), 4.99 (d, J=5.9 Hz, 1H), 6.39–6.41 (m, 2H), 7.45 (d, J=0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2, 52.8, 63.0, 66.2, 94.4, 109.7, 110.2, 142.3, 150.9. Minor epimer (characteristic signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.45 (ddd, J=3.6, 9.5, 12.9 Hz, 1H), 3.58 (d, J=1.3 Hz, 1H), 3.71 (dt, J=3.8, 11.7 Hz, 1H), 4.22 (ddd, J=3.0, 9.5, 12.1 Hz, 1H), 5.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.4, 53.1, 60.4, 64.8, 92.4, 110.0, 110.3, 142.5, 150.1. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.02; H, 7.29; N, 7.62.

4.2.3. 3-(4-Methoxyphenyl)-4-methylmorpholin-2-ol 8c. Yield 80%, mp 168–170 °C (diethylether/pentane). Major epimer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (br s, 1H), 2.07 (s, 3H), 2.45 (dt, J=3.5, 11.5 Hz, 1H), 2.78 (d, J=7.2 Hz, 1H), 2.81 (d, J=11.7 Hz, 1H), 3.83 (s, 3H), 3.94 (dt, J=1.7, 11.3 Hz, 1H), 4.01 (d, J=11.3 Hz, 1H), 4.71 (d, J=7.2 Hz, 1H), 6.92 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.3, 54.3, 55.2, 64.2, 73.8, 97.4, 113.9, 129.7, 130.3, 159.3. Minor epimer (characteristic signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.51 (dt, J=3.6, 11.8 Hz, 1H), 2.90 (d, J=11.7 Hz, 1H), 3.28 (s, 1H), 3.70 (d, J=8.3 Hz, 1H), 4.32 (dt, J=2.7, 11.7 Hz, 1H), 4.94 (d, J=1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.1, 55.4, 59.0, 72.0, 93.3, 113.8, 130.0. MS (EI) calcd for $C_{12}H_{17}NO_3$ $[M]^+$: 223.1208. Found: 223.1206.

4.2.4. 4-Benzyl-3-phenylmorpholin-2-ol 8d.[22] Yield 70%, mp 148–150 °C. Major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (td, J=4.0, 10.8 Hz, 1H), 2.76 (dt, J=2.0, 11.8 Hz, 1H), 2.98 (d, J=13.4 Hz, 1H), 3.17 (d, J=7.2 Hz, 1H), 3.40–4.24 (m, 4H), 4.78 (d, J=7.2 Hz, 1H), 7.21–7.60 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 58.7, 64.4, 72.8, 97.6, 126.9, 128.2, 128.3, 128.5, 128.7, 128.9, 138.3, 138.7. Minor epimer (characteristic signals): ^{1}H NMR

(300 MHz, $CDCl_3$) δ 2.88 (d, J=11.6 Hz, 1H), 4.16 (t, J=12.6 Hz, 1H), 5.01 (d, J=6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 59.1, 70.9, 93.3. MS (EI) calcd for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416. Found: 269.1418.

4.2.5. 4-Benzyl-3-(2-methoxyphenyl)morpholin-2-ol 8e. Yield 50%, mp 159–160 °C (diisopropylether). Major epimer: ^1H NMR (200 MHz, $CDCl_3$) δ 2.35 (td, J=3.8, 11.5 Hz, 1H), 2.79 (dt, J=1.9, 11.8 Hz, 1H), 2.99 (d, J=13.5 Hz, 1H), 3.48 (d, J=8.9 Hz, 1H), 3.78 (s, 1H), 3.83 (d, J=5.6 Hz, 1H), 3.84–4.00 (m, 2H), 3.93 (s, 3H), 4.66 (dd, J=7.4, 8.8 Hz, 1H), 6.98 (d, J=8.2 Hz, 1H), 7.10 (td, J=1.0, 7.5 Hz, 1H), 7.26–7.38 (m, 6H), 7.80 (dd, J=1.7, 7.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.8, 55.6, 58.5, 63.9, 64.4, 98.6, 110.7, 121.2, 126.8, 127.9, 128.1, 128.4, 128.6, 128.7, 138.4, 158.1. Minor epimer (characteristic signals): ^1H NMR (200 MHz, $CDCl_3$) δ 2.81 (d, J=13.6 Hz, 1H), 4.96 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.2, 55.2, 58.9, 91.8, 120.7, 125.3, 157.2. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.03; H, 7.24; N, 4.43.

4.2.6. 4-Benzyl-3-(2-thienyl)morpholin-2-ol 8f. Yield 65%, mp 100–102 °C (diisopropylether). Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (td, J=3.5, 11.8 Hz, 1H), 2.67 (ddd, J=1.3, 3.0, 11.9 Hz, 1H), 3.05 (d, J=13.4 Hz, 1H), 3.54 (d, J=5.8 Hz, 1H), 3.64–4.02 (m, 4H), 4.76 (d, J=5.8 Hz, 1H), 6.93–7.29 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.2, 58.8, 62.9, 66.4, 96.4, 125.7, 126.5, 127.2, 127.7, 128.3, 128.8, 137.9, 140.2. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (d, J=13.1 Hz, 1H), 5.06 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 64.9, 93.6, 126.3, 126.8, 128.9. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.26; H, 6.26; N, 5.08.

4.2.7. 4-Benzyl-3-[(1*E*)-hex-1-en-1-yl]morpholin-2-ol 8g. Yield 67%, oil. Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=6.6 Hz, 3H), 1.28–1.48 (m, 4H), 2.10–2.17 (m, 2H), 2.28 (dt, J=3.5, 8.2 Hz, 1H), 2.67 (dt, J=3.4, 12.3 Hz, 1H), 2.80 (dd, J=4.6, 8.8 Hz, 1H), 3.28 (d, J=13.3 Hz, 1H), 3.63–3.71 (m, 1H), 3.86 (d, J=13.3 Hz, 1H), 3.94–4.02 (m, 1H), 4.70 (d, J=4.6 Hz, 1H), 5.61 (dd, J=8.8, 15.6 Hz, 1H), 5.75 (dt, J=6.5, 15.5 Hz, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 22.0, 31.1, 32.1, 48.6, 58.4, 62.1, 68.2, 95.0, 125.4, 126.8, 128.0, 128.8, 137.4, 138.2. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) 2.73 (dd, J=3.1, 6.5 Hz, 1H), 3.05 (dd, J=2.0, 9.2 Hz, 1H), 3.16 (d, J=13.4 Hz, 1H), 4.86 (d, J=1.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 32.0, 49.7, 58.6, 60.4, 68.2, 93.7, 126.9, 137.3, 137.6. MS (EI) calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885. Found: 275.1897.

4.2.8. 4-Allyl-3-phenylmorpholin-2-ol 8h. Yield 75%, oil. Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (dt, J=3.3, 11.6 Hz, 1H), 2.58 (dd, J=8.1, 13.8 Hz, 1H), 2.87 (dt, J=1.8, 11.9 Hz, 1H), 3.09 (d, J=7.1 Hz, 2H), 3.85 (dt, J=2.2, 11.4 Hz, 1H), 3.97 (d, J=11.0 Hz, 1H), 4.41 (br s, 1H), 4.72 (d, J=7.1 Hz, 1H), 5.09 (d, J=11.6 Hz, 1H), 5.14 (d, J=4.4 Hz, 1H), 5.68–5.81 (m, 1H), 7.28–7.58 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.2, 57.2, 63.9, 72.0, 97.1, 118.1, 127.6, 128.3, 128.9, 134.0, 138.1. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (dt, J=3.7, 11.8 Hz, 1H), 2.98 (d, J=11.8 Hz, 1H), 3.13 (d, J=4.8 Hz, 2H), 3.27 (dd, J=5.1, 13.8 Hz, 1H), 3.56 (d, J=1.8 Hz, 1H), 3.64 (dd, J=1.8, 12.0 Hz, 1H), 4.28 (dt, J=2.5, 11.8 Hz, 1H), 5.00 (d, J=1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 57.5, 58.6, 70.7, 92.7. MS (EI) calcd for $C_{10}H_{12}NO_2$ $[M-C_3H_5]^+$: 178.0868. Found: 178.0852.

4.2.9. 4-Benzyl-2-methyl-3-phenylmorpholin-2-ol 8i. Yield 57%, mp 178–180 °C (diisopropylether). Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 2.34 (dt, J=4.0, 12.4 Hz, 1H), 2.77–2.83 (m, 1H), 2.84 (d, J=10.1 Hz, 1H), 3.38 (s, 1H), 3.59–3.67 (m, 1H), 3.79 (d, J=13.4 Hz, 1H), 4.08 (dt, J=2.8, 12.4 Hz, 1H), 4.41 (br s, 1H), 7.20–7.56 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 52.3, 59.2, 59.5, 75.7, 95.7, 127.0, 127.8, 127.9, 128.2, 128.4, 128.7, 137.5, 138.1. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 3.19 (d, J=13.6 Hz, 1H), 3.46 (d, J=13.6 Hz, 1H), 5,20 (s, 1H). MS (EI) calcd for $C_{18}H_{21}NO_2$ $[M]^+$: 283.1572. Found: 283.1569.

4.2.10. 4-Benzyl-3-[(1*E*)-hex-1-en-1-yl]-2-methylmorpholin-2-ol 8j. Yield 59%, oil. Major epimer: ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, J=7.0 Hz, 3H), 1.33–1.47 (m, 4H), 1.36 (s, 3H), 2.12–2.24 (m, 2H), 2.81 (d, J=9.4 Hz, 1H), 3.00 (d, J=13.6 Hz, 1H), 3.54 (dd, J=13.1, 22.7 Hz, 2H), 3.93 (dd, J=3.0, 12.1 Hz, 2H), 4.17 (d, J=13.4 Hz, 1H), 4.57 (br s, 1H), 5.41 (ddt, J=1.3, 9.3, 15.4 Hz, 1H), 5.81 (dt, J=5.1, 15.4 Hz, 1H), 7.29–7.41 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.2, 24.7, 31.2, 32.1, 51.4, 58.7, 59.7, 73.8, 95.5, 127.0, 128.2, 128.4, 128.8, 137.5, 138.4. Minor epimer (characteristic signals): ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 3H), 2.45 (dd, J=3.7, 11.8 Hz, 1H), 2.66 (ddd, J=1.2, 3.0, 11.7 Hz, 2H), 2.94 (d, J=10.7 Hz, 1H), 3.72 (dd, J=3.8, 11.8 Hz, 1H), 4.04 (dd, J=3.8, 8.3 Hz, 1H), 4.14 (d, J=11.8 Hz, 1H), 5.22 (s, 1H), 5.61 (dt, J=6.3, 15.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.1, 24.2, 31.4, 32.3, 45.1, 58.7, 59.9, 67.6, 95.2, 121.1, 127.2, 127.4, 128.3, 137.7, 138.9. MS (EI) calcd for $C_{18}H_{27}NO_2$ $[M]^+$: 289.2042. Found: 289.2040.

4.2.11. 4-Benzyl-2,3-diphenylmorpholin-2-ol 8k. Yield 58%, mp 112–114 °C (diethylether/pentane). Major epimer: ^1H NMR (200 MHz, $CDCl_3$) δ 2.51 (td, J=3.8, 12.2 Hz, 1H), 2.85–2.95 (m, 2H), 3.53 (s, 1H), 3.81 (dd, J=3.7, 12.0 Hz, 1H), 3.88 (d, J=13.4 Hz, 1H), 4.31 (td, J=2.8, 12.3 Hz, 1H), 4.58 (br s, 1H), 7.11–7.19 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.4, 59.4, 59.9, 76.8, 97.3, 126.2, 127.1, 127.3, 127.4, 127.5, 127.6, 127.8, 128.3, 128.8, 136.4, 138.0, 141.0. Minor epimer (characteristic signals): ^1H NMR (200 MHz, $CDCl_3$) δ 3.16 (d, J=13.2 Hz, 1H), 4.08 (dd, J=3.7, 11.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.7, 58.9, 60.2, 70.5, 96.4. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.82; H, 6.67; N, 4.35.

4.3. 2-Synthesis of 2-hydroxymorpholine 8l starting from the tetraoxoanthracene 10

4.3.1. Perhydro-4,8-dibenzyl-4,8-diaza-1,5,9,10-tetraoxo anthracene 10.[19] To a solution of glyoxal (22 mmol, 40%

in water) in water (3 mL) was added dropwise *N*-benzylethanolamine (20 mmol) at 0 °C. The solution was stirred at room temperature for 3 h and extracted with dichloromethane (3×20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was washed with diethylether to give **10** as a white solid (yield 70%), mp 190 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (dd, J=1.6, 11.3 Hz, 2H), 2.86 (dt, J=3.6, 11.5 Hz, 2H), 3.71 (dt, J=2.7, 11.45 Hz, 4H), 3.72 (d, J=13.8 Hz, 2H), 3.92 (dd, J=2.8, 11.3 Hz, 4H), 3.95 (d, J=13.8 Hz, 2H), 7.20–7.34 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.8, 57.4, 65.2, 79.0, 94.1, 127.2, 128.3, 128.8, 138.2.

4.3.2. [(1*E*)-3-Methoxy-3-oxoprop-1-en-1-yl]boronic acid. At −10 °C, under N_2, borane–methylsulfide complex (6.6 mL, 66 mmol) was added dropwise to a solution of α-pinene (22.6 mL, 141.2 mmol) in dry THF (20 mL). The mixture was kept at 0 °C for 1 h and then allowed to reach room temperature by removing the cold bath (formation of a white suspension of diisopinocampheylborane). After 2 h, the suspension of $(Ipc)_2BH$ was cooled to −30 °C. A solution of methyl propiolate (6.25 mL, 70 mmol) in dry THF (10 mL) was added dropwise. After 1 h at −30 °C, the reaction mixture was allowed to warm to room temperature (limpid solution). Five hours later, the mixture was cooled to 0 °C and freshly distilled acetaldehyde (43.5 mL, 700 mmol, 10 equiv) was added dropwise. The solution was kept at room temperature for 18 h and then 1 h at 40 °C. The excess of acetaldehyde and about half of the solvent were removed by distillation (15 mmHg). A mixture of THF/water (5 mL/5 mL) was added. The mixture was stirred overnight. After removing most of the solvent under reduced pressure, 30 mL of pentane were added give a solid, which was filtered and washed several times with pentane. Yields varied from 30 to 55%. The boronic acid is only soluble in DMSO that gives an ill-resolved NMR spectrum. It was best characterized as its pinacol derivative, obtained by addition of 1 equiv of pinacol in diethylether in the presence of 2 equiv of methanol during one night. *Pinacol derivative*.[23] Eb=80–85 °C/0.1 mmHg (Kugelrohr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 12H), 3.76 (s, 3H), 6.63 (d, J=18.3 Hz, 1H), 6.76 (d, J=18.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 51.6, 84.3, 134.4, 138.2, 166.4.

4.3.3. Methyl-(2*E*)-3-(4-benzyl-2-hydroxymorpholin-3-yl)acrylate 8l. To a solution of perhydro-4,8-dibenzyl-4,8-diaza-1,5,9,10-tetraoxoanthracene **10** (1 mmol) and [(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]boronic acid (2 mmol) in dry methylene chloride (20 mL) was added dropwise BF_3–etherate (4.5 mmol) at −78 °C. The solution was stirred at −78 °C for 0.5 h, warmed to room temperature and stirred overnight. After addition of a saturated solution of $NaHCO_3$ (15 mL) at −78 °C, the mixture was extracted with methylene chloride (3×30 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography using 30% ethyl acetate in heptane afforded **8l** as an oil (yield 76%). Major epimer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (td, J=3.3, 8.6 Hz, 1H), 2.66 (td, J=1.5, 4.3 Hz, 1H), 2.94 (dd, J=5.3, 8.8 Hz, 1H), 3.20 (br s, 1H), 3.56–4.04 (m, 4H), 3.75 (s, 3H), 4.68 (d, J=5.4 Hz, 1H), 6.16 (d, J=15.9 Hz, 1H), 7.03 (d, J=1.5, 8.8 Hz, 1H), 7.24–7.33 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 48.6, 51.6, 59.2, 62.4, 67.2, 94.3, 125.9, 127.2, 128.3, 128.8, 137.3, 144.6, 166.1. Minor epimer (characteristic signals): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.72 (td, J=1.2, 4.5 Hz, 1H), 4.90 (d, J=2.3 Hz, 1H), 6.07 (d, J=16.1 Hz, 1H), 7.03 (d, J=1.6, 9.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.2, 59.3, 60.7, 66.7, 93.3, 125.4, 127.3, 128.9, 137.0, 165.9. MS (EI) calcd for $C_{15}H_{19}NO_4$ $[M]^+$: 277.1314. Found: 277.1317.

4.4. 3-One-pot synthesis of 2-hydroxymorpholines 8m–8v from chiral 1,2-aminoalcohols

4.4.1. (3*R*,5*R*)-4-Methyl-3,5-diphenylmorpholin-2-ol 8′m. From thioether **13a**, yield 71%. Major epimer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.84 (s, 3H), 3.66–4.12 (m, 5H), 5.19 (d, J=2.6 Hz, 1H), 7.24–7.56 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.6, 60.7, 65.7, 67.5, 93.9, 127.9, 128.0, 128.2, 128.3, 128.8, 130.3, 135.4, 138.3. Minor epimer (characteristic signals): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81 (s, 3H), 5.27 (d, J=3.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.7, 60.2, 68.0, 71.2, 95.4, 133.6, 138.5. MS (EI) calcd for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416. Found: 269.1415. $[\alpha]_D^{20}$ +78.5 (*c* 0.9, CH_2Cl_2).

4.4.2. (3*S*,5*R*)-4-Methyl-3,5-diphenylmorpholin-2-ol 8″m. From epimerisation, yield 89%, mp 150–52 °C (diethylether/pentane). Major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 3H), 3.07 (d, J=7.5 Hz, 1H), 3.06 (dd, J=3.0, 10.4 Hz, 1H), 3.45 (br s, 1H), 3.68 (dd, J=10.5, 11.8 Hz, 1H), 3.87 (dd, J=3.3, 11.7 Hz, 1H), 4.79 (d, J=7.5 Hz, 1H), 7.24–7.50 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.8, 67.4, 70.8, 74.0, 97.9, 127.8, 127.9, 128.0, 128.4, 128.6, 128.8, 139.1. Minor epimer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 5.03 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.2, 64.6, 69.1, 72.1, 93.3. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.96; H, 7.05; N, 5.12.

4.4.3. (5*R*)-3-(4-Bromophenyl)-4-methyl-5-phenylmorpholin-2-ol 8′n+8″n. Yield 47%. Major diastereoisomer: RMN ^{1}H (300 MHz, $CDCl_3$) δ 1.78 (s, 3H), 3.56 (dd, J=3.7, 8.5 Hz, 1H), 3.69 (d, J=2.7 Hz, 1H), 3.78 (dd, J=3.9, 11.8 Hz, 1H), 3.85 (br s, 1H), 4.05 (dd, J=8.6, 11.8 Hz, 1H), 5.06 (d, J=2.8 Hz, 1H), 7.21–7.44 (m, 9H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 39.6, 60.6, 65.8, 66.7, 93.9, 122.1, 128.0, 128.3, 128.7, 131.2, 132.0, 133.1, 138.0. Minor diastereoisomer (characteristic signals): RMN ^{1}H (300 MHz, $CDCl_3$) δ 1.76 (s, 3H), 5.24 (d, J=3.0 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 39.7, 60.1, 67.2, 71.1, 95.3, 122.5, 138.2. MS (EI) calcd for $C_{17}H_{18}NO_2Br$ $[M]^+$: 347.0521. Found: 347.0526.

4.4.4. (3*R*,5*R*)-3-[(1*E*)-Hex-1-en-1-yl]-4-methyl-5-phenylmorpholin-2-ol 8′o. From thioether **13a**, yield 61%. Major epimer: ^{1}H RMN (300 MHz, $CDCl_3$) δ 0.92 (t, J=7 Hz, 3H), 1.36–1.38 (m, 4H), 2.02 (s, 3H), 2.14 (q, J=7.2 Hz, 2H), 3.27 (dd, J=1.3, 9.3 Hz, 1H), 3.55–4.03 (m, 3H), 4.40 (br s, 1H), 4.67 (d, J=7.6 Hz, 1H), 5.73 (dd, J=8.8, 15.5 Hz, 1H), 5.83 (dt, J=8.7, 15.5 Hz, 1H), 7.29–7.36 (m, 5H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 13.8, 22.1, 31.2, 32.5, 39.5, 61.6, 64.5, 67.3, 93.3, 121.8, 128.4, 128.5, 128.6, 138.7, 141.9. Minor epimer (characteristic signals): RMN (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.18 (q, J=7.3 Hz, 2H),

3.33 (dt, J=2.4, 6.8 Hz, 1H), 5.03 (d, J=2.5 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 22.2, 31.3, 32.3, 39.8, 61.1, 66.6, 71.2, 94.4, 119.4, 138.0, 138.2. MS (EI) calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885. Found: 275.1883.

4.4.5. (3*S*,5*R*)-3-[(1*E*)-Hex-1-en-1-yl]-4-methyl-5-phenylmorpholin-2-ol 8″o. Major epimer: ^{1}H RMN (200 MHz, $CDCl_3$) δ 0.88 (t, J=6.5 Hz, 3H), 1.29–1.39 (m, 4H), 2.04 (s, 3H), 2.07 (q, J=7.2 Hz, 2H), 3.22 (dd, J=3.7, 10.7 Hz, 1H), 3.52 (dd, J=3.8, 12.1 Hz, 1H), 3.79 (dd, J=3.6, 11.8 Hz, 1H), 3.97–4.23 (m, 2H), 4.69 (d, J=7.6 Hz, 1H), 5.36 (dd, J=9.0, 15.5 Hz, 1H), 5.75 (dt, J=6.7, 15.4 Hz, 1H), 7.25–7.36 (m, 5H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 13.9, 22.2, 31.1, 32.1, 40.2, 64.7, 69.2, 70.7, 93.8, 127.6, 127.7, 128.0, 128.6, 135.9, 138.6. Minor epimer (characteristic signals): RMN (200 MHz, $CDCl_3$) δ 1.99 (s, 3H), 4.94 (d, J=1.8 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 14.1, 22.7, 31.2, 32.2, 40.5, 67.6, 70.5, 72.5, 96.3, 137.2, 139.0. MS (EI) calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885. Found: 275.1870.

4.4.6. (3*R*,5*R*)-4-Benzyl-3,5-diphenylmorpholin-2-ol 8′p. From thioether **13b**, yield 65%. Major epimer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (br s, 1H), 3.00 (d, J=14.3 Hz, 1H), 3.59 (d, J=14.3 Hz, 1H), 3.88–4.28 (m, 3H), 5.20 (d, J=2.8 Hz, 1H), 7.28–7.57 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.3, 58.7, 63.1, 66.3, 94.6, 127.1, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 130.5, 138.4, 138.7, 138.9. Minor epimer (characteristic signals): RMN (300 MHz, $CDCl_3$) δ 2.98 (d, J=14.4 Hz, 1H), 5.32 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.9, 59.1, 62.8, 71.8, 95.8. $[\alpha]_D^{20}$ −78.2 (*c* 1.1, CH_2Cl_2).

4.4.7. (3*S*,5*R*)-4-Benzyl-3,5-diphenylmorpholin-2-ol 8″p. Major epimer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J=7.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 51.7, 60.8, 62.9, 72.5, 98.4. Minor epimer (characteristic signals): RMN (300 MHz, $CDCl_3$) δ 5.06 (d, J=2.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.7.

4.4.8. (2*E*,5*R*)-4-Benzyl-3-(2-phenylethylenyl)-2-hydroxy-5-phenylmorpholine 8′q+8″q. Yield 77%. Mixture of four diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90–4.11 (m, 6H), 4.69 (d, J=7.35 Hz, 1H) and 4.93 (d, J=1.7 Hz, 1H) and 4.98 (br s, 1H) and 5.01 (d, J=2.2 Hz, 1H), 5.93 (dd, J=9.3, 16.0 Hz, 1H) and 6.02 (dd, J=8.7, 16.0 Hz, 1H) and 6.63–6.76 (m, 1H+1H), 6.40 (d, J=16.0 Hz, 1H) and 6.55 (d, J=16.0 Hz, 1H) and 6.63 (d, J=16.0 Hz, 1H) and 6.72 (d, J=16.1 Hz, 1H), 7.04–7.47 (m, 15H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 52.9 and 53.7 and 54.3 and 55.1, 60.1 and 60.6 and 61.2 and 62.4, 63.1 and 65.9 and 69.0 and 69.4, 65.0 and 70.8 and 72.1 and 73.2, 93.2 and 93.9 and 95.4 and 96.4, 119.6 and 122.3, 126.4–129.6, 132.9 and 134.7 and 136.8 and 139.5, 136.0 and 136.4 and 136.7 and 138.2. MS (EI) calcd for $C_{24}H_{23}N$ $[M-CH_2O_2]^+$: 325.18305. Found: 325.1844.

4.4.9. (5*R*)-2-Hydroxy-5-isopropyl-4-methyl-3-phenylmorpholine 8′r+8″r. Yield 74%. Major diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, J=7.0 Hz, 3H), 0.87 (d, J=6.9 Hz, 3H), 1.82–1.95 (m, 1H), 2.05 (s, 3H), 2.46–2.52 (m, 1H), 3.58–3.66 (m, 2H), 3.92 (t, J=10.3 Hz, 1H), 4.22 (br s, 1H), 5.17 (d, J=3.0 Hz, 1H), 7.16–7.47 (m, 5H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 16.2, 19.8, 25.9, 38.8, 58.6, 59.5, 67.6, 93.0, 127.8, 130.0, 131.5, 135.7. Second diastereoisomer (characteristic signals): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (d, J=6.8 Hz, 3H), 1.98 (s, 3H), 2.46–2.52 (m, 1H), 3.70 (dd, J=3.0, 11.4 Hz, 1H), 5.25 (br s, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 15.0, 19.6, 25.6, 57.2, 64.5, 68.3, 94.9, 133.9. Third diastereoisomer (characteristic signals): ^{1}H RMN (200 MHz, $CDCl_3$) δ 1.00 (d, J=4.1 Hz, 3H), 1.00 (d, J=4.1 Hz, 3H), 1.03 (d, J=4.0 Hz, 3H), 2.01 (s, 3H), 2.21–2.35 (m, 2H), 2.97 (d, J=7.6 Hz, 1H), 3.68 (t, J=11.5 Hz, 1H), 3.97 (dd, J=3.0, 11.6 Hz, 1H), 4.61 (d, J=7.6 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 15.1, 19.5, 26.2, 38.9, 64.2, 64.9, 74.1, 97.7, 127.6, 128.3, 128.8, 140.2. MS (EI) calcd for $C_{14}H_{21}NO_2$ $[M]^+$: 235.1572. Found: 235.1572.

4.4.10. 4-Allyl-2-hydroxy-6-methyl-3-phenylmorpholine 8′s+8″s. Prepared from racemic 1-(allylamino)propan-2-ol, yield 43%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=6.5 Hz, 3H), 2.43–2.49 (m, 2H), 2.79 (dd, J=6.2, 13.8 Hz, 1H), 3.02 (dd, J=6.3, 13.9 Hz, 1H), 3.65 (d, J=2.3 Hz, 1H), 4.28–4.38 (m, 1H), 5.15–5.22 (m, 3H), 5.76–5.89 (m, 1H), 7.34–7.56 (m, 5H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 18.5, 51.9, 57.3, 65.7, 66.8, 92.9, 118.0, 127.8, 128.0, 130.2, 135.2, 135.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J=7.3 Hz, 3H), 2.67 (dd, J=6.7, 13.4 Hz, 1H), 3.91 (d, J=3.1 Hz, 1H), 3.96–4.06 (m, 1H). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H, 8.16; N, 6.01.

4.4.11. (6*R*)-4-Benzyl-2-hydroxy-3,6-diphenylmorpholine 8′t+8″t. Yield 66%, mp 157–58 °C (diethylether/pentane). Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (t, J=11.2 Hz, 1H), 2.83 (d, J=5.2 Hz, 1H), 2.98 (d, J=13.4 Hz, 2H), 3.23 (d, J=7.4 Hz, 1H), 3.82 (d, J=13.4 Hz, 1H), 4.88 (dd, J=1.8, 10.5 Hz, 1H), 5.00 (dd, J=5.3, 7.0 Hz, 1H), 7.24–7.63 (m, 15H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 57.6, 58.6, 72.1, 76.1, 99.1, 126.3, 127.0, 127.9, 127.95, 128.2, 128.3, 128.6, 128.7, 128.9, 138.0, 138.8, 139.0. Second diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (dd, J=2.8, 11.2 Hz, 1H), 3.04 (t, J=11.0 Hz, 1H), 3.79 (d, J=13.4 Hz, 1H), 4.05 (d, J=13.4 Hz, 1H), 4.39 (br s, 1H), 4.72 (dd, J=2.6, 10.6 Hz, 1H), 5.44 (dd, J=2.4, 9.1 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 59.1, 70.6, 93.6. Third diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 2.57 (dd, J=9.3, 11.8 Hz, 1H), 3.18 (dd, J=2.7, 11.8 Hz, 1H), 3.39 (d, J=13.5 Hz, 1H), 4.25 (d, J=13.4 Hz, 1H), 5.31 (dd, J=5.7, 8.0 Hz, 1H). Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.97; H, 6.97; N, 4.18.

4.4.12. (6*R*)-4-Benzyl-3-hexen-1-yl-2-hydroxy-6-phenylmorpholine 8′u+8″u. Yield 56%. Major diastereoisomer: ^{1}H RMN (300 MHz, $CDCl_3$) δ 0.87 (t, J=6.3 Hz, 3H), 1.18–1.36 (m, 4H), 1.99–2.15 (m, 3H), 2.57 (d, J=11.0 Hz, 1H), 2.61 (d, J=11.9 Hz, 1H), 3.10 (d, J=9.3 Hz, 1H), 3.44 (d, J=10.7 Hz, 1H), 3.50 (d, J=14.8 Hz, 1H), 4.97 (br s, 1H), 5.07 (dd, J=3.9, 10.7 Hz, 1H), 5.62 (dt, J=6.6, 15.5 Hz, 1H), 5.83 (ddt, J=1.2, 9.3, 15.5 Hz, 1H), 7.17–7.32 (m, 10H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 13.8, 22.2, 31.4, 32.5, 52.2, 58.5, 63.3, 70.1, 93.6, 121.6, 126.3, 128.3, 128.4, 128.6, 128.9, 129.0, 137.6, 138.4, 139.8. Second

diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (dd, J=2.6, 9.0 Hz, 1H), 4.73 (dd, J=3.6, 10.3 Hz, 1H), 4.99 (d, J=2.7 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 31.5, 32.6, 52.7, 58.7, 64.2, 76.9, 94.8, 118.7, 126.1, 128.1, 128.2, 138.5, 141.9. Third diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J=10.1 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 31.2, 32.2, 69.1, 94.2, 136.7. Fourth diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 5.01 (d, J=2.6 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 75.9, 96.6, 137.9. MS (EI) calcd for $C_{23}H_{29}NO_2$ $[M]^+$: 351.2198. Found: 351.2177.

4.4.13. (3*E*,5*R*)-4-Benzyl-2-hydroxy-3-(1-methylpropen-1-yl)-5-phenylmorpholine 8′v+8″v. Yield 51%. Major diastereoisomer: ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.67 (d, J= 6.7 Hz, 3H), 1.83 (s, 3H), 3.09 (d, J=14.6 Hz, 1H), 3.28 (d, J=5.8 Hz, 1H), 3.52 (br s, 1H), 3.71 (d, J=14.6 Hz, 2H), 3.82 (t, J=3.7 Hz, 1H), 4.07 (dt, J=3.6, 11.6 Hz, 2H), 5.00 (d, J=5.7 Hz, 1H), 5.58 (q, J=6.6 Hz, 1H), 7.25–7.54 (m, 10H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 13.1, 13.2, 52.4, 57.4, 67.7, 68.2, 95.1, 126.6, 127.4, 127.9, 128.1, 128.2, 128.5, 129.7, 132.6, 138.6, 139.2. Second diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.73 (d, J= 7.0 Hz, 3H), 1.97 (s, 3H), 3.36 (d, J=14.1 Hz, 1H), 3.39 (d, J=3.15 Hz, 1H), 3.69 (d, J=14.4 Hz, 1H), 4.11 (dt, J=4.1, 11.5 Hz, 2H), 5.07 (d, J=6.2 Hz, 1H), 5.40 (q, J=6.5 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 13.2, 17.0, 53.2, 60.0, 65.5, 70.3, 95.1, 126.5, 131.5, 138.8, 139.7. Third diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 4.76 (d, J=7.5 Hz, 1H), 5.78 (q, J= 5.7 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 12.6, 13.3, 53.3, 62.2, 70.7, 72.9, 95.2, 133.2, 139.0. MS (EI) calcd for $C_{21}H_{25}NO_2$ $[M]^+$: 323.1885. Found: 323.1872.

4.4.14. 4-Epimerisation of 8. To a solution of **8′m** and **8″m** (0.5 mmol) in toluene (2 mL), was added diaza(1,3)bicyclo-[5.4.0]undecane (1 mmol). The solution was stirred for 24 h at 60 °C. The mixture was concentrated in vacuo. Flash chromatography using 30% ethyl acetate in heptane afforded **8″m** (yield 89%) (see above for the NMR data).

4.5. 5-Synthesis of 2-hydroxymorpholines 8 from thioethers 13a and 13b

To a mixture of **13a** or **13b** (1 mmol) and boronic acid **6** (1 mmol) in dry dichloromethane (15 mL) was added BF_3–etherate (567 μL, 4.5 mmol) at −78 °C. The solution was stirred at −78 °C for 0.5 h, warmed to room temperature and stirred overnight. At −78 °C, the mixture was quenched with saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography using 30% ethyl acetate in heptane afforded **8**.

4.5.1. (3*R*,5*R*)-3-Vinyl 4-methyl-5-phenylmorpholin-2-ol 8′w. Yield 82%. Two epimers (56/44): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H) and 2.10 (s, 3H), 3.25–4.20 (m, 5H+ 5H), 5.00 (d, J=1.2 Hz, 1H) and 5.05 (d, J=2.6 Hz, 1H), 5.25–5.70 (m, 2H+2H), 6.10–6.41 (m, 1H+1H), 7.21–7.58 (m, 5H+5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.7 and 40.1, 61.0 and 61.4, 64.8 and 71.6, 67.5 and 68.3, 93.0 and 94.5, 121.5 and 124.4, 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 129.2 and 131.2, 138.5. MS (EI) calcd for $C_{13}H_{17}NO_2$ $[M]^+$: 219.1259. Found: 219.1244. $[\alpha]_D^{20}$ +41.9 (*c* 1.01, CH_3OH).

4.5.2. (5*R*)-4-Benzyl-2-hydroxy-5-phenyl-3-vinylmorpholine 8′x. Yield 77%. Two epimers (50/50): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.91 (d, J=11.6 Hz, 1H) and 3.19 (d, J=11.6 Hz, 1H), 3.27 (d, J=13.4 Hz, 1H) and 3.32 (d, J=13.4 Hz, 1H), 3.60–3.74 (m, 2H+2H), 3.96–4.11 (m, 2H+2H), 4.49 (d, J=10.3 Hz, 1H), 4.94 (d, J=9.5 Hz, 1H) and 4.98 (dd, J=2.5, 11.5 Hz, 1H), 5.21 (dd, J=1.7, 17.3 Hz, 1H) and 5.23 (dd, J=1.9, 17.3 Hz, 1H), 5.53 (dd, J=1.8, 10.4 Hz, 1H) and 5.70 (dd, J=7.9, 10.4 Hz, 1H), 6.25–6.40 (m, 1H+1H), 7.26–7.52 (m, 10H+10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.7 and 53.5, 58.8 and 60.0, 60.5 and 61.8, 62.9 and 63.4, 65.0 and 72.1, 93.1 and 94.8, 122.2 and 125.2, 126.9 and 127.2, 128.0, 128.1, 128.2, 128.5, 128.6, 128.65, 128.7, 128.9, 131.0, 137.8 and 138.1, 138.9 and 139.0. MS (EI) calcd for $C_{19}H_{21}NO_2$ $[M]^+$: 295.1572. Found: 295.1567. $[\alpha]_D^{20}$ +37.2 (*c* 1.04, CH_2Cl_2).

4.6. 6-Synthesis of aminodiols 9 from 2-hydroxymorpholines 8

General procedure. A solution of 2-hydroxymorpholine **8** (1 mmol) in dry diethylether (4 mL) was added dropwise to a suspension of $LiAlH_4$ (3.3 mmol) in dry diethylether (4 mL) at 0 °C. The mixture was stirred at room temperature for 5 h, cooled to 0 °C, and quenched by carefully addition of water (2.5 mL) and a solution of 15% NaOH (2.5 mL). Aqueous phase was extracted with diethylether (2×10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to give crude aminodiol **9**, which was purified by flash chromatography using 5% methanol in dichloromethane.

4.6.1. (1*R*,1′*R*)-2,2′-Dihydroxy-1,1′-diphenyl-*N*-methyldiethanamine 9′m. Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.52 (dd, J=5.4, 10.4 Hz, 2H), 3.66 (dd, J=5.4, 6.9 Hz, 2H), 3.77 (dd, J=6.9, 10.4 Hz, 2H), 4.76 (br s, 2H), 7.10–7.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5, 62.4, 65.8, 127.6, 128.3, 128.8, 137.6. MS (EI) calcd for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572. Found: 271.1584. $[\alpha]_D^{20}$ +86.5 (*c* 1.35, CH_2Cl_2).

4.6.2. (1*S*,1′*R*)-2,2′-Dihydroxy-1,1′-diphenyl-*N*-methyldiethanamine 9″m. Yield 45%.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 2.96 (br s, 2H), 3.89 (dd, J=4.7, 10.3 Hz, 2H), 4.03 (dd, J=7.8, 10.3 Hz, 2H), 4.09 (dd, J= 4.7, 7.8 Hz, 2H), 7.23–7.35 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 62.2, 66.5, 127.6, 128.4, 128.5, 138.4. MS (EI) calcd for $C_{16}H_{18}NO$ $[M-CH_2OH]^+$: 240.1388. Found: 240.1376. $[\alpha]_D^{20}$=0 (*c* 1, CH_2Cl_2).

4.6.3. 2-(4-Bromophenyl)-2-[((1*R*)-2-hydroxy-1-phenylethyl)-*N*-methylamino]ethanol 9′n+9″n. Yield 56%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 0.97 (br s, 2H), 3.57–3.70 (m, 4H), 3.78–3.88 (m, 2H), 7.04 (d, J=8.4 Hz, 1H), 7.13–7.20 (m, 3H), 7.26–7.31 (m, 4H), 7.43 (d, J=8.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.6, 62.6, 65.6, 121.8, 128.0, 128.6, 128.9, 130.5,

131.6, 136.7, 137.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.9, 62.4, 64.9. MS (EI) calcd for $C_{17}H_{20}NO_2Br$ $[M]^{+\cdot}$: 240.13884. Found: 240.1379.

4.6.4. (2*R*,3*E*)-2-[((1*R*)-2-Hydroxy-1-phenylethyl)-*N*-methylamino]oct-3-en-1-ol 9′o. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–0.85 (m, 3H), 1.18–1.28 (m, 4H), 2.02 (q, J=6.3 Hz, 2H), 2.25 (s, 3H), 2.35 (br s, 2H), 3.18 (dt, J=5.5, 8.6 Hz, 1H), 3.31 (dd, J=5.5, 10.6 Hz, 1H), 3.50 (dd, J=9.1, 10.6 Hz, 1H), 3.69–3.91 (m, 3H), 5.17 (dd, J=8.4, 15.5 Hz, 1H), 5.39 (dt, J=6.4, 15.5 Hz, 1H), 7.18–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.0, 31.2, 32.2, 32.7, 61.6, 62.4, 62.9, 66.7, 124.4, 127.5, 128.3, 128.6, 136.2, 138.8. MS (EI) calcd for $C_{17}H_{27}NO_2$ $[M]^{+\cdot}$: 277.2042. Found: 277.2041. $[\alpha]_D^{20}$ −80.2 (*c* 1.15, CH_2Cl_2).

4.6.5. (2*S*,3*E*)-2-[((1*R*)-2-Hydroxy-1-phenylethyl)-*N*-methylamino]oct-3-en-1-ol 9″o. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.83 (m, 3H), 1.16–1.25 (m, 4H), 1.91 (dt, J=6.8, 5.8 Hz, 2H), 2.05 (s, 3H), 2.53 (br s, 2H), 3.44–3.52 (m, 3H), 3.74–3.94 (m, 3H), 5.23 (dd, J=15.3, 6.4 Hz, 1H), 5.53 (dt, J=15.5, 6.7 Hz, 1H), 7.20–7.27 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 21.1, 30.1, 30.2, 31.3, 60.9, 61.5, 63.5, 67.5, 123.4, 126.8, 127.4, 127.8, 135.1, 138.5.

4.6.6. (1*R*,1′*R*)-*N*-Benzyl-2,2′-dihydroxy-1,1′-diphenyldiethanamine 9′p. Mp 138–39 °C (ethylacetate) [lit.[22] 137.5–39 °C (ethylacetate)]. ^{1}H NMR (300 MHz, CD_3OD) δ 2.07 (br s, 2H), 3.51 (d, J=14.9 Hz, 1H), 3.73 (dd, J=4.1, 10.2 Hz, 2H), 4.02 (d, J=9.1 Hz, 1H), 4.04–4.12 (m, 3H), 4.14 (d, J=15.0 Hz, 1H), 7.07–7.49 (m, 15H). ^{13}C NMR (75 MHz, CD_3OD) δ 50.0, 60.9, 61.6, 124.9, 125.2, 126.2, 126.4, 126.7, 127.0, 138.3, 140.1. MS (EI) calcd for $C_{22}H_{22}NO$ $[M-CH_2OH]^+$: 316.17014. Found: 316.1698. $[\alpha]_D^{20}$ −162 (*c* 1.2, $CHCl_3$) [lit.[22] −165.6 (*c* 1.01, $CHCl_3$)].

4.6.7. (1*S*,1′*R*)-*N*-Benzyl-2,2′-dihydroxy-1,1′-diphenyldiethanamine 9″p. Characteristic signals: ^{1}H NMR (300 MHz, CD_3OD) δ 3.26 (d, J=14.0 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 48.6, 59.7, 62.6, 138.9.

4.6.8. (3*E*)-2-[Benzyl((1*R*)-2-hydroxy-1-phenylethyl)-amino]-4-phenylbut-3-en-1-ol 9′q+9″q. Yield 63%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (br s, 2H), 3.51 (d, J=7.1 Hz, 1H), 3.63 (d, J=14.3 Hz, 1H), 3.67–3.81 (m, 2H), 3.75 (d, J=15.2 Hz, 1H), 3.89 (d, J=2.4 Hz, 1H), 4.03 (d, J=14.7 Hz, 1H), 4.07–4.15 (m, 1H), 6.24 (dd, J=7.7, 16.1 Hz, 1H), 6.49 (dd, J=0.7, 16.1 Hz, 1H), 7.26–7.39 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.8, 50.8, 59.2, 60.8, 65.4, 126.3, 126.9, 127.4, 127.8, 128.4, 128.5, 128.6, 128.7, 128.8, 132.3, 133.1, 138.3, 140.0, 140.4. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, J=6.4, 16.3 Hz, 1H), 6.10 (d, J=16.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 61.8, 62.4, 62.5, 63.5, 133.1, 136.2, 139.8. MS (EI) calcd for $C_{24}H_{24}NO$ $[M-CH_2OH]^{+\cdot}$: 342.1858. Found: 342.1854.

4.6.9. 2-[((1*R*)-2-Hydroxy-1-phenylethyl)(methyl)-amino]-3-methylbutan-1-ol 9′r+9″r. Yield 63%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J=6.5 Hz, 3H), 0.87 (d, J=6.7 Hz, 3H), 1.67–1.75 (m, J=6.7 Hz, 1H), 2.44 (s, 3H), 2.62 (dt, J=4.9, 9.3 Hz, 1H), 3.16 (br s, 2H), 3.46–3.58 (m, 2H), 3.69 (dd, J=8.4, 14.4 Hz, 1H), 3.93–4.01 (m, 2H), 7.25–7.37 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 21.7, 28.4, 33.8, 60.3, 63.5, 66.3, 68.0, 127.3, 128.1, 128.3, 140.5. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 60.5, 62.6, 69.8, 70.5, 140.3. MS (EI) calcd for $C_{14}H_{23}NO_2$ $[M]^{+\cdot}$: 237.1728. Found: 237.1725.

4.6.10. 1-[Allyl((1*R*)-2-hydroxy-1-phenylethyl)amino]-propan-2-ol 9′s+9″s. Yield 76%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J=6.2 Hz, 3H), 2.21 (dd, J=2.3, 13.3 Hz, 1H), 2.63 (dd, J=10.2, 13.3 Hz, 1H), 2.99 (dd, J=8.1, 14.3 Hz, 1H), 3.31 (ddt, J=2.2, 4.6, 14.3 Hz, 1H), 3.52 (br s, 2H), 3.73 (dd, J=10.0, 16.0 Hz, 1H), 3.85–3.95 (m, 1H), 4.04 (d, J=3.8 Hz, 1H), 4.06 (d, J=2.5 Hz, 1H), 5.19 (d, J=9.3 Hz, 1H), 5.23 (d, J=16.2 Hz, 1H), 5.81–5.94 (m, 1H), 7.19–7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 54.4, 56.3, 61.3, 63.9, 64.4, 117.3, 127.4, 128.1, 128.5, 136.6, 136.7. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (d, J=9.2 Hz, 1H), 2.50 (d, J=8.6 Hz, 1H), 2.71 (d, J=4.0 Hz, 1H), 5.10 (d, J=3.2 Hz, 1H), 5.12 (d, J=6.7 Hz, 1H). MS (EI) calcd for $C_{13}H_{18}NO$ $[M-CH_2OH]^{+\cdot}$: 204.1388. Found: 204.1386.

4.6.11. (1*R*)-2-[Benzyl(2-hydroxy-1-phenylethyl)amino]-1-phenylethanol 9′t+9″t.[21] Yield 75%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (dd, J=2.6, 13.7 Hz, 1H), 2.95 (dd, J=10.3, 13.7 Hz, 1H), 3.46 (d, J=13.9 Hz, 1H), 3.62 (dd, J=4.4, 10.8 Hz, 1H), 3.85 (d, J=13.9 Hz, 1H), 3.92 (dd, J=4.4, 10.2 Hz, 1H), 4.02 (dd, J=10.5, 21.2 Hz, 1H), 4.59 (dd, J=2.5, 10.3 Hz, 1H), 7.05–7.37 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.1, 57.4, 61.7, 64.5, 71.2, 125.8, 127.3, 127.5, 127.8, 128.4, 128.5, 128.6, 128.8, 129.0, 136.5, 139.1, 142.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (dd, J=7.8, 13.6 Hz, 1H), 2.99 (dd, J=5.0, 13.7 Hz, 1H), 3.39 (d, J=13.9 Hz, 1H), 3.48 (dd, J=6.9, 13.7 Hz, 1H), 3.88 (d, J=13.9 Hz, 1H), 4.41 (dd, J=5.2, 7.9 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 59.4, 61.4, 66.2, 72.8. MS (EI) calcd for $C_{16}H_{18}NO$ $[M-PhCH_2OH]^{+\cdot}$: 240.1388. Found: 240.1376.

4.6.12. (1*R*,3*E*)-2-[Benzyl(2-hydroxy-2-phenylethyl)-amino]oct-3-en-1-ol 9′u+9″u. Yield 72%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7.0 Hz, 3H), 1.21–1.31 (m, 4H), 1.97 (q, J=6.1 Hz, 2H), 2.50 (dd, J=2.7, 13.5 Hz, 1H), 2.70 (dd, J=10.5, 13.5 Hz, 1H), 3.08 (br s, 2H), 3.43 (dd, J=1.6, 7.7 Hz, 1H), 3.53 (d, J=4.0 Hz, 1H), 3.57 (br s, 2H), 3.86 (d, J=13.5 Hz, 1H), 4.57 (dd, J=2.7, 10.3 Hz, 1H), 5.15 (dd, J=9.9, 15.4 Hz, 1H), 5.63 (dt, J=6.7, 15.3 Hz, 1H), 7.17–7.31 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 22.1, 31.4, 32.3, 56.1, 57.3, 62.2, 63.1, 70.9, 122.9, 125.8, 126.0, 127.3, 127.5, 128.4, 128.6, 137.7, 139.2, 142.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, J=5.2, 13.5 Hz, 1H), 3.80 (d, J=13.5 Hz, 1H), 5.28 (dd, J=8.3, 15.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.0, 63.5, 71.8. MS (EI) calcd for $C_{22}H_{28}NO$ $[M-CH_2OH]^{+\cdot}$: 322.2171. Found: 322.2175.

4.6.13. (2*R*)-2-[[(1*R*)-2-Hydroxy-1-phenylethyl](methyl)-amino]but-3-en-1-ol 9′w. Yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.66 (br s, 2H), 3.21–4.08 (m, 6H), 5.05 (dt, $J=0.9$, 17.3 Hz, 1H), 5.26 (dd, $J=1.8$, 10.5 Hz, 1H), 5.58–5.79 (m, 1H), 7.27–7.46 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.2, 61.8, 63.4, 63.5, 67.3, 119.9, 128.2, 129.0, 129.1, 134.2, 139.1. MS (EI) calcd for $C_{12}H_{16}NO$ $[M-CH_2OH]^{+\cdot}$ 190.12319. Found: 190.1231. $[\alpha]_D^{20}$ −32.1 (*c* 0.76, CH_2Cl_2).

4.6.14. (2*R*)-2-{Benzyl[(1*R*)-2-hydroxy-1-phenylethyl]-amino}but-3-en-1-ol 9′x. Mp 98–100 °C (ether/heptane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (br s, 2H), 3.59 (d, $J=14.5$ Hz, 1H), 3.65–3.73 (m, 4H), 3.93–4.00 (m, 2H), 4.10 (dd, $J=10.1$, 10.7 Hz, 1H), 4.88 (dd, $J=10.3$, 17.6 Hz, 1H), 5.01 (d, $J=10.3$ Hz, 1H), 5.30–5.38 (m, 1H), 7.28–7.48 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.7, 59.1, 61.6, 61.7, 62.5, 117.5, 127.2, 127.8, 128.5, 128.6, 128.8, 128.85, 135.0, 138.15, 140.2. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.69; H, 7.79; N, 4.67. $[\alpha]_D^{20}$ −187.8 (*c* 0.74, CH_2Cl_2).

References and notes

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