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Synthesis and Characterization of New 4-Alkyl-2-Arylmorpholin-2-ol Hydrochlorides

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Synthesis and Characterization of New 4-Alkyl-2-Arylmorpholin-2-ol Hydrochlorides

Teresa Mancilla, Luis S. Zamudio-Rivera, Hiram I. Beltrán, Lourdes Carrillo, and Norberto Farfán

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Abstract: The synthesis of 4-alkyl-2-arylmorpholin-2-ol hydrochlorides by diastereoselective reaction of 2-bromoacetophenones with β -aminoalcohols has been accomplished.

Keywords: Arylmorpholine, hydrochlorides, morpholinol, hemiacetal, hydroxyalkylamino ketones, NMR, X-ray structure, theoretical calculations

4-Alkyl-2-arylmorpholin-2-ol hydrochlorides are biologically important compounds that exhibit hypocholesterolemic, hypolipidemic, antioxidant, and analgesic activity^[1-7] Various 4-alkyl-2-arylmorpholin-2-ol hydrochlorides have been prepared in yields between 34 and $87\%^{[1,6,8]}$ by stirring a mixture of a β -aminoalcohol for 16 to 24 h with a variety of 2-bromoaceto-phenones at room temperature.

Our current interest in 4-alkyl-2-arylmorpholin-2-ol hydrochlorides prompted us to develop better reaction conditions to synthesize these compounds in good yield. Thus, we describe herein the synthesis and characterization of nine new 4-alkyl-2-arylmorpholin-2-ol hydrochlorides (**1a**-**1c**,

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Scheme 1.

2a-2c, 3a-3c) (Scheme 1). The structure of compound 2b was further established by a single-crystal X-ray diffraction study.

RESULTS AND DISCUSSION

4-Alkyl-2-arylmorpholin-2-ol hydrochlorides 1a-1c, 2a-2c, and 3a-3c were prepared in yields between 84-93% by reaction of 2-bromoacetophenones $\mathbf{a}-\mathbf{c}$ with N-benzylamino ethanol (1), (1S,2S)-(+)-pseudoephedrine (2), and (1R,2R)-(-)-pseudoephedrine (3). ¹H NMR spectra evidenced formation of a single diastereoisomer with the OH group axial due to the anomeric effect. In all cases the proton spectra showed a broad signal for the N⁺H⁻Cl proton in the range between 10.38 to 10.85 ppm and AB systems for diastereotopic protons at position 3 (3.00-3.65 ppm) and the benzylic protons (4.33–4.47 ppm). Tables 1 and 2 summarize the ¹H NMR spectra data for compounds 1a, 1c and 2a-2c, 3a-3c, respectively. The ¹³C NMR chemical shift for C-2 (93.50 to 94.80 ppm) remains fairly constant. Since the signals for C3, and C6, and C15 in 1a, 1b, and 1c; C3-C5 in 2a-2c and 3a-3c and the signals for the aromatic protons, have similar chemical shifts, unambiguous assignment was established using HETCOR spectra. Moreover the signals for C7, C10, and C11 in 1c; C7, C10, C11, and C17 in 2c and 3c were assigned using ${}^{1}H{}-({}^{2}J_{CH}){}^{13}C$ COLOC spectra. Tables 3 and 4 summarize the ¹³C NMR data for the compounds studied. The IR spectra show the ν_{OH} band (3406 and 3422 cm⁻¹), ν_{NH} (2362 to

Table I. ¹]	H NMR data for compou	inds 1a-1c				
		r^{R} $a: R^{I} = r^{Q}$	15 14 13 12 $1c: R$	$1 = 19 \underbrace{138 \ 17}_{10}$	15 14 13 5 12 12	
	N H ^N R ² 1a-1c	2] 1b: R ¹ =	Cl ¹⁵ 13 13 1a-16	$R^2 = 11$	⁹ / ₂ ⁷ / ₂ - CH ₂ -	
Compound	H-3	R ¹	\mathbb{R}^{2}	H-5	9-H	⁺ NHCl ⁻
la	H_A : 3.22 (d) $J = 12.1$ H_B : 3.00 (d) $J = 12.1$	H_{13} : 7.50 (d) $J = 7.5$ $H_{14,15}$: 7.35–7.43 (m)	H_{7A} : 4.44 (d) J = 12.7 H_{7B} : 7.61 (d) J = 7.3 $H_{10,11}$: 7.35-7.43 (m)	3.37–3.46 (m)	H_{6A} : 4.41 (td) J = 1.8, 12.4 H_{6B} : 4.01 (dd) J = 2.6, 12.4	10.80 (br)
lb	H_A : 3.25 (d) $J = 12.1$ H_B : 3.04 (d) $J = 12.1$	H_{13} : 7.57 (d) $J = 8.6$ H_{14} : 7.45 (d) $J = 8.6$	H_{7B} : 4.46 (d) J = 12.0 H_{7B} : 4.33 (d) J = 12.0 H_9 : 7.61 (dd) J = 2.5, 7.3 H_{10} : 7.40–7.44 (m)	3.36–3.45 (m)	H_{6A} : 4.38 (td) J = 1.8, 12.0 H_{6B} : 4.01 (dd) J = 2.5, 12.0	10.85 (br)
lc	H_A : 3.26 (d) J = 12.1 H_B : 3.05 (d) J = 12.1	$ \begin{array}{l} H_{13}; \ 7.69 \ (d) \ J = 8.4 \\ H_{14}; \ 7.60 \ (d) \ J = 8.4 \\ H_{17,18}; \ 7.40 - 7.51 \ (m) \\ H_{19}; \ 7.37 \ (t) \ J = 7.2 \end{array} $	H_{7A} : 4.47 (d) J = 11.7 H_{7B} : 4.35 (d) J = 11.7 H_9 : 7.66 (dd) J = 7.2 $H_{10,11}$: 7.40–7.51 (m)	3.35–3.46 (m)	H _{6AB} : 4.37–4.50 (m)	10.82 (br)

 $\delta(\text{ppm}), \, |J|$ Hz, solvent DMSO-d6.

	11 11 10 9/1,6	0 2 0H 12 0	Ó	2 . R ¹ 2a, 3a:]	$R^{I} = 16 \underbrace{15}_{15} \underbrace{14}_{14}$	εı
	⁸ CH ₃	$\left(\begin{array}{c} + \\ - \\ + \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\$		J ₃ OLL H ℃l 2b,3b: R	$C^{1} = C^{16} \int_{-15}^{15} \frac{14}{16} \int_{-15}^{14} \frac{15}{16} \frac{14}{16} \int_{-15}^{14} \frac{14}$	ΞŢ
	7. 2a	СН ₃ 1-2с	7 ⁷ CF 3a-3	H_3 c 2c,3c: $R^1 = 0$		14 13
Compound	H-3	R ¹	Н-7	Н-5, Н-8	9-H	H-10 to H-12
2a	H _A : 3.60 (d) J = 12.3 H ₂ : 3.51 (d) I = 12.3	H ₁₄ : 7.66 (d) J = 7.1 H \cdot 7.38 - 7.40 (m)	2.87 (s)	H_5 : 3.72 (m) J = 6.2, 10.1 H_2 : 1.12 (d) $I - 6.2$	5.07 (d) J = 10.1	H ₁₀ : 7.56 (d) $J = 7.0$
2b	H_A : 3.59 (d) J = 12.5	H_{14} : 7.65 (d) $J = 8.7$	2.86 (s)	H ₅ : 3.69 (m) J = $6.2, 9.9$	5.04 (d) J = 9.9	H_{10} : 7.54 (d) $J = 7.3$
26	H _B : 3.48 (d) J = 12.5 H. \cdot 3.65 (d) I = 12.6	H_{15} : 7.51 (d) $J = 8.7$ H 766 (d) $I = 7.9$	2 86 (s)	H ₈ : 1.09 (d) J = 6.2 H ₂ : 3.63 (m) I = 6.2 9.5	5.07 (d) $I = 9.5$	H _{11,12} : 7.41–7.47 (m) H 7 58 (d) $I = 7.4$
1	$H_{\rm B}$: 3.51 (d) $J = 12.6$	H ₉ : 7.47 (d) $J = 7.9$	(a) 00.2	H ₈ : 1.12 (d) $J = 6.2$		H _{11,12} : 7.36–7.51 (m)
		H ₁₈₋₂₀ : 7.36-7.51 (m)				
δ(ppm), J ^a Compour 10.56 (2c), 1	Hz, solvent DMSO-dt nds 3a - 3c show the san 0.60 (3a), 10.52 (3b), a	6. me chemical shifts as their and 10.50 (3c).	enantiome	srs 2a-2c. The chemical shi	ifts for ⁺ NH ⁻ Cl are	10.38 (2a), 10.49 (2b),

Table 2. ¹H NMR data for compounds 2a-2c and $3a-3c^a$

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Table 3. ¹³ C	NMR data for	compounds 1a-1	$ \mathbf{c}^{a} $						
		$0 \xrightarrow{2} R^{1}$ $N \xrightarrow{+}{3} OH$ R^{2} R^{2} R^{2} R^{2} R^{2}	1a: R ¹ = 1b: R ¹ =	$CI \xrightarrow{14 \ 13} CI \xrightarrow{14 \ 13} CI$	1c: R	$I = 19 \underbrace{19}_{13} \underbrace{13}_{17}$	$\int_{16}^{16} \frac{13}{16} \int_{12}^{14} \frac{13}{12}$		
Compound	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11
la	93.78	57.06	50.43	56.71	59.17	129.04	131.62	128.83	129.69
1b	93.50	57.7	50.23	56.77	59.18	129.01	131.62	128.80	129.71
$1c^b$	93.78	56.93	50.40	56.74	62.42	129.10	131.68	128.84	129.68
δ (ppm). DN ^{<i>a</i>} The chemic 139.54 (1 c).	ASO-d6. al shifts for C-	-12 to C-15 are 14	1.24, 125.77	, 128.17, 128.83	3 (1 a); 140.27	7, 127.90, 128.2	20, 133.64 (1b)	; 140.39, 126.	19, 126.78,
b The chemic	al shifts for C-	-16 to C-19 are 14	40.66, 128.68	, 129.01, 127.7	4.				

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	11 10 9 11		H 12 10.02	60	R ¹	2a, 3a	$R^{1} = 16\sqrt{12}$	13 13	
	⁸ CH ₃	$\int_{-1}^{+} H^{-3}$	CH		°OH CI	2b,3b:]	$R^{1} = C_{1}^{16}$	5 14 13	
		[,] СН ₃ 2а-2с		′СН ₃ 3а-3с	7	c,3c: R ¹ =		15 14	
Compound	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11
$2a^b$	94.05	60.21	61.81	74.63	40.80	11.65	137.56	128.15	128.15
$2\mathbf{b}^c$	93.80	59.92	61.83	74.73	40.91	11.66	137.37	128.78	128.23
$2c^d$	94.04	60.29	61.88	74.72	40.35	11.48	137.35	128.69	128.19
δ (ppm). DN ^a Compounds ^b The chemic	ASO-d6. s 3a-3c show t tal shifts for C-	the same chemi- 12 to C-16 are	ical shifts as th 129.00, 140.97	eir enantiomer 7, 125.92, 128.	s 2a–2c . 75, 128.90.				
^c The chemic ^d The chemic	cal shifts for C- cal shifts for C-	-12 to C-16 are -12 to C-16 are	129.11, 139.94 128.97, 140.16	H, 128.01, 128. 5, 126.44, 126.	23, 134.00. 52, 139.55, 1	40.63, 126.75,	128.97. 127.70.		

Table 4. ¹³C NMR data for compounds 2a-2c and $3a-3c^a$

T. Mancilla et al.

New 4-Alkyl-2-Arylmorpholin-2-ol Hydrochlorides

 2702 cm^{-1}), $\nu_{\text{CHarom.}}$ (3004 to 3062 cm⁻¹), and ν_{CO} in the range between 1062 to 1094 cm⁻¹.

The 70 eV EI mass spectra did not show the ion molecular in any of the cases. The ion fragments at m/z = 91 and m/z = 58 correspond to the base peak for compounds 1a-1c and 2a-2c, 3a-3c, respectively.

The structure of **2b** was established by a single-crystal X-ray diffraction analysis (Fig. 1). In general, all bond distances are within the expected values, and the torsion angles indicate that the methyl and phenyl groups are in equatorial positions and the hydroxyl group in axial ones due to anomeric effect. The configuration of new stereogenic center (C-1) is R while that of nitrogen is S. The crystal structure shows O-H and Cl-H intermolecular, as well as O-H and N-H intramolecular contacts, which are significantly shorter than the sum of their van der Waals radii.^[9] Selected geometrical parameters are given in Table 5.

It is important to notice that the ¹H and ¹³C NMR spectra of the reaction mixture in CDCl₃, before acidification, showed the presence of a mixture of 4-alkyl-2-arylmorpholin-2-ols and 2-[(2 hydroxyethyl)alkylamino]-1-aryl-ethanones in a 95 : 5 ratio approximately. However, the mixture of compounds could not be separated using different solvents and chromatographic procedures, probably due to the existence of a tautomeric equilibrium between hemiacetal and hydroxyalkylamino ketones forms^[8] (Scheme 2).

In general the chemical shifts of the morpholinols are very similar to their corresponding hydrochlorides. The N-benzyl derivatives show four bond couplings between H3a and H5a. Unambiguous identification of the diastereotopic H5 and H6 protons was established from their coupling constant values and (${}^{1}\text{H}{-}{}^{1}\text{H}$) NOESY techniques, which allowed to assign H5_B and



Figure 1. Molecular structure of 2b showing the crystallograpic numbering.

Bond distances			
C ₁ -O ₁	1.411 (7)	C_2-N_1	1.488 (7)
C ₁ -O ₂	1.405 (7)	C_3-N_1	1.512 (8)
C ₄ -O ₁	1.418 (6)		
Torison angles			
C ₁₂ -C ₃ -N ₁ -C ₁₁	70.39	H _{2c} -C ₂ -N ₁ -C ₁₁	48.29
C_{12} - C_3 - C_4 - C_{13}	-68.33	O_2 - C_1 - C_2 - H_{2b}	53.39
H _{2b} -C ₂ -N ₁ -C ₁₁	-69.41	O_2 - C_1 - C_2 - H_{2c}	-171.39
Intermolecular cont	acts		
O ₁ -H _{11b}	2.562	Cl ₁ -H _{2a}	2.339
Intramolecular cont	acts		
O ₁ -H _{2a}	2.464	N_1 - H_{11a}	2.024
O ₁ -H _{2a}	1.958	N_1 - H_{1b}	2.034
O ₂ -H _{4a}	2.471	N_1 - H_{11c}	2.036
O ₂ -H _{2b}	2.493	N ₁ -H _{12a}	2.640
O ₂ -H _{6a}	2.442	N_1 - H_{12c}	2.650
Cl ₂ -H _{9a}	2.777		

Table 5. Select bond distances (Å), torsion angles (deg), intermolecular and intramolecular contacts (Å) for 2b

 $H6_A$ to the axial position while $H5_A$ and $H6_A$ are equatorial. The compounds derived from pseudoephedrines exhibit a doublet for H6 in the range between 4.69–4.70 ppm with an average coupling constant of 9.5 Hz, which indicates that the methyl (R^3) and phenyl groups (R^6) are equatorial. This was confirmed using ($^{1}H^{-1}H$) NOESY spectra which showed a correlation between H8 and H6.

The ¹³C NMR data for morpholinols shows C-2 is in the range between 94.71 to 94.91 ppm, characteristic of a hemiacetal carbon. Since the signals of C-3, C-6, and C-7 for compounds derived from 2-benzylaminoethanol, and C-3 and C-5 for compounds derived from pseudoephedrines have



Hemiacetal

Hydroxyalkylamino ketones

Scheme 2.



Figure 2. Conformation calculated for the intermediate α -(N-benzyl-ethanolamino)-acetophone.

similar chemical shifts, unambiguous identification was established using HETCOR spectra and aromatic carbons with similar chemical shifts using ¹³C-¹H COLOC spectra.

In order to investigate if the formation of 4-benzyl-2-phenylmorpholin-2ol is thermodynamically favored, a theoretical calculation (AMI) was performed providing a Δ Hreac = 0.596 Kcal/mol at 298 K for the formation of the intermediate α -(N-benzyl ethanolamino)-acetophenone. This value is indicative of a thermodynamic process for the transformation to 4-benzyl-2phenylmorpholin-2-ol, which should proceed through a prefered conformation, which was also calculated. Figure 2 depicts this particular conformation where there is an intramolecular interaction between the OH group and the carbonyl group, which increases the nucleophilicity of this O group an favors formation to the morpholinol.

EXPERIMENTAL

General

NMR spectra were recorded on JEOL GXS-270, JEOL ECLIPSE-400, and Bruker Avance 300-DPX spectrometers. ¹H and ¹³C chemical shifts are relative to internal SiMe₄ (TMS), ($\delta^{1}H = 0$, $\delta^{13}C = 0$). CDCl₃ and DMSO-d₆ were used as solvents. Mass spectra were obtained with a

Hewlett-Packard 5994-A instrument, and Infrared spectra were recorded as KBr pellets on a Perkin-Elmer 16F PC FT-IR spectrometer. Melting points were taken in open capillary tubes on a Gallemkamp MFB-595 apparatus and are uncorrected. The single-crystal X-ray study was performed on an ENRAF NONIUS CAD4 diffractometer. Compound **2b**, $C_{18}H_{21}Cl_2NO_2$ (MW = 353.82), crystallized in the space group P212121, orthorhombic, from acetone/ethanol as colorless rectangular prisms, size: $0.16 \times 0.12 \times 0.10 \text{ mm}^3$ with a = 6.8560(10), b = 12.097(2), c = 21.849(4) Å, V = 1812.5 (5) Å³. Lattice constants were determined from least-squares refinement on diffractometer angles for 24 automatically centered reflections; ρ 1.172 Mg/m³, Z = 4, μ = 0.217 mm^{-1} , F (000) = 680. Data collection: monitoring of check reflexion showed no signs of decay. A total of 2552 reflections were measured ($2 > \theta > 26^{\circ}$), 2373 were independent, and of these 928 were considered observed [Fo > 4.0σ (Fo)]. Absorption correction was not necessary.

Solution and refinement: direct methods, all nonhydrogen atoms were refined anisotropically, all hydrogens were located by difference Fourier maps and refined with an overall isotropic thermal parameter R = 0.0455, Rw = 0.1194, $w = 1/\sigma^2$, GOOF = 0.966, parameter to data ratio 11.4:1, largest residual electron density peak/hole in the final difference map: $0.514/-0.266 \text{ eÅ}^{-3}$. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.^[10] Data reduction was performed by Jana 98.^[11] All calculations were carried out on a VAX 4000 computer using the SHELX 93 (Sheldrick G. M.) program package.^[12]

The procedure outlined below is general for the preparation of 1a-1c, 2a-2c, 3a-3c.

4-Benzyl-2-phenylmorpholin-2-ol hydrochloride (**1a**). To a solution of 1.32 g (6.61 mmol) of 2-bromoacephenone (**a**) and 1.00 g (6.61 mmol) of 2-benzylaminoethanol (**1**) in 50 mL of acetonitrile was added 0.99 g (9.92 mmol) of potassium bicarbonate at room temperature. The resulting suspension was refluxed and stirred during 7h, cooled to room temperature and filtered. To the filtrate was added 4 mL of a 2.2 M solution of HCl and evaporated in vacuo to get a yellow solid, which was recrystallized from acetone/ethanol to yield 1.74 g (86%) of compound 1a as a white solid, mp 136–139° (decomp). MS: m/z (%) = 270 (2), 161 (12), 134 (13), 105 (9), 91 (100). IR: ν_{OH} 3406, ν_{NH} 2702, 2612, 2358, ν_{CHarom} 3062, 3006, 3036, $\nu_{CHaliph}$. 2948, 2888, $\nu_{C=C}$ 1636, 1496, 1456, ν_{C-O} 1084 cm⁻¹ (KBr). Anal. Calcd. for C₁₇H₂₀ClNO₂ (305.63): C, 66.75; H, 6.59; N, 4.58. Found: C, 66.60; H, 7.00; N, 4.59.

4-Benzyl-2-(4'-chlorophenyl)-morpholin-2-ol hydrochloride (1b). The reaction of 1.54 g (6.61 mmol) of 2-bromo-4'-chloroacetophenone (b), 1.00 g (6.61 mmol) of 2-benzylaminoethanol (1) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/methanol to yield 2.06 g (92%) of compound 1b as a white

New 4-Alkyl-2-Arylmorpholin-2-ol Hydrochlorides

solid, mp 145–146° (decomp). MS: m/z (%) = 164 (26), 139 (5), 91 (100). IR: ν_{OH} 3416, ν_{NH} 2700, 2608, 2362, $\nu_{CHarom.}$ 3068, 3034, $\nu_{CHaliph.}$ 2948, 2884, $\nu_{C=C}$ 1636, 1598, 1490, 1458, $\nu_{C=O}$ 1094 cm⁻¹ (KBr). *Anal.* Calcd. for C₁₇H₁₉Cl₂NO₂ (340.07): C, 59.99; H, 5.63; N, 4.11. Found: C, 59.83; H, 5.78; N, 4.05.

4-Benzyl-2-(4'-biphenyl)morpholin-2-ol hydrochloride (**1c**). The reaction of 1.82 g (6.61 mmol) of 2-bromo-4'-phenylacetophenone (**c**), 100 g 6.61 mmol) of 2-benzylaminoethanol (**1**) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol to yield 2.21/g (88%) of compound 1c as a white solid, mp 166–169° (decomp.). MS: m/z (%) = 327 (13), 236 (29), 164 (73), 152 (23), 91 (100), 65 (8). IR: $\nu_{OH}3424$, ν_{NH} 2770, 2636, 2364, $\nu_{CHarom.}$ 3030, 3006, $\nu_{CHaliph.}$ 2948, 2832, $\nu_{C=C}$ 1636, 1560, 1486, 1456, ν_{C-O} 1084 cm⁻¹ (KBr). *Anal.* Calcd. for C₂₃H₂₄ClNO₂ (381.67): C; 72.31; H, 6.33; N, 3.66. Found: C, 71.90; H, 6.31; N, 3.72.

(2R,4S,5S,6S)-2,6-Diphenyl-4,5-dimethylmorpholin-2-ol hydrochloride (**2a**). The reaction of 1.32 g (6.61 mmol) of 2-bromoacephenone (**a**), 1.09 g (6.61 mmol) of (1S,2S)-(+)-pseudoephedrine (**2**) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol and to yield 1.87 g (89%) of compound 2a as a white solid, mp 158–160° (decomp.). MS: m/z (%) = 265 (5), 176 (67), 132 (12), 118 (36), 117 (31), 105 (27), 91 (21), 77 (36), 58 (100), 44 (25). IR: ν_{OH} 3422, ν_{NH} 2658, 2362, $\nu_{\text{CHarom.}}$ 3060, 3034, $\nu_{\text{CHaliph.}}$ 2992, 2950, 2832, $\nu_{\text{C=C}}$ 1636, 1558, 1496, 1454, $\nu_{\text{C=O}}$ 1082 cm⁻¹ (KBr). *Anal.* Calcd. for C₁₈H₂₂ClNO₂ (319.65): C, 67.57; H, 6.93; N, 4.38. Found: C, 67.62; H, 7.07; N, 4.40.

(2R,4S,5S,6S)-2-(4'-Chlorophenyl)-4,5-dimethylmorpholin-2-ol hydrochloride (**2b**). The reaction 1.54 g (6.61 mmol) of 2-bromo-4'-chloroacetophenone (**b**), 1.09 g (6.61 mmol) of (1S,2S)-(+)-pseudoephedrine (**2**) and 0.99 g (9.91 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol and yield 2.18 g (93%) of compound 2b as a white solid, mp 182–184° (decomp.). MS: m/z (%) = 318 (1), 300 (1), 210 (31), 178 (7), 154 (7), 148 (6), 139 (12), 131 (11), 118 (17), 91 (10), 77 (14), 58 ('00), 44 (20), 42 (16). IR: ν_{OH} 3416, ν_{NH} 2656, 2364, $\nu_{CHarom.}$ 3062, 3032, 3004, $\nu_{CHaliph.}$ 2990, 2960, 2904, 2864, $\nu_{C=}$ 1636, 1598, 1492, 1456, ν_{C-O} 1092 cm⁻¹ (KBr). *Anal.* Calcd. for C₁₈H₂₁Cl₂NO₂ (354.09): C, 61.00; H, 5.97; N, 3.95. Found: C, 60.70; H, 5.89; N, 4.05.

(2R,4S,5S,6S)-2-Phenyl(4'-biphenyl)-4,5-dimethylmorpholin-2-ol hydrochloride (**2c**). The reaction 1.54 g (6.61 mmol) of 2-bromo-4'-phenylacetophenone (**c**), 1.09 g (6.61 mmol) of (1S,2S)-(+)-pseudoephedrine (**2**) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol and to yield 2.18 g (84%) of compound 2c as a white solid, mp 169–171° (decomp.). MS: m/z (%) = 360 (1), 342 (6), 181 (19), 178 (6), 176 (5), 120 (1), 58 (100). IR: ν_{OH} 3412, ν_{NH} 2636, 2362, $\nu_{CHarom.}$ 3056, 3032, $\nu_{CHaliph.}$ 2994, 2946, 2832, $\nu_{C=C}$ 1636, 1614, 1486, 1456, ν_{C-O} 1062 cm⁻¹ (KBr). *Anal.* Calcd. for C₂₄H₂₆ClNO₂ (395.68): C, 72.79; H, 6.62; N, 3.53. Found: C, 73.21; H, 6.75; N, 3.61.

(2S,4R,5R,6R)-2,6-Diphenyl-4,5-dimethylmorpholin-2-ol hydrochloride (**3a**). The reaction 1.32 g (6.61 mmol) of 2-bromoacetophenone (**a**), 1.09 g (6.61 mmol) of (1R,2R)-(-)-pseudoephedrine (**3**) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol and to yield 1.93 g (91%) of compound 3a as a white solid, mp 158–160° (decomp.). MS: m/z (%) = 266 (10), 191 (11), 176 (22), 132 (20), 118 (33), 117 (47), 105 (26), 91 (21), 77 (35), 58 (100), 44 (24). IR: ν_{OH} 3420, ν_{NH} 2656, 2362, ν_{CHarom} 3060, 3034, $\nu_{CHaliph}$ 2992, 2950, 2832, $\nu_{C=C}$ 1636, 1558, 1494, 1456, $\nu_{C=O}$ 1080 cm⁻¹ (KBr). *Anal.* Calcd. for C₁₉H₂₂ClNO₂ (319.65): C, 67.57; H, 6.93; N, 4.38. Found: C, 67.63; H, 7.13; N, 4.38.

(2S,4R,5R,6R)-2-(4'-Chlorophenyl)-4,5-dimethylmorpholin-2-ol hydrochloride (**3b**). The reaction 1.54 g (6.61 mmol) of 2-bromo-4'-chloroacetophenone (**b**), 1.09 g (6.61 mmol) of (1R,2R)-(-)-pseudoephedrine (**3**) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol and to yield 2.04 g (87%) of compound 3b as a white solid, mp 182–184° (decomp.). MS: m/z (%) = 318 (1), 300 (1), 210 (40), 178 (8), 154 (7), 148 (10), 139 (14), 131 (12), 118 (18), 91 (12), 77 (18), 58 (100), 44 (23), 42 (20). IR: ν_{OH} 3418, ν_{NH} 2656, 2366, ν_{CHarom} . 3062, 3032, 3004, $\nu_{CHaliph}$ 2990, 2960, 2864, $\nu_{C=C}$ 1636, 1598, 1492, 1456, ν_{C-O} 1092 cm⁻¹ (KBr). *Anal.* Cald. for C₁₈H₂₁Cl₂NO₂ (354.09): C, 61.00; H, 5.97; N, 3.95. Found: C, 61.35; H, 6.11; N, 3.98.

(2S,4R,5R,6R)-2-(4'-Chlorophenyl)-4,5-dimethylmorpholin-2-ol hydrochloride (**3c**). The reaction 1.54 g (6.61 mmol) of 2-bromo-4'-phenylacetophenone (**c**), 1.09 g (6.61 mmol) of (1R,2R)-(-)-pseudoephedrine (**3**) and 0.99 g (9.92 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from acetone/ethanol and to yield 2.29 g (88%) of compound 3c as a white solid, mp 169–171° (decomp.). MS: m/z (%) = 360 (1), 342 (5), 181 (20), 178 (10), 176 (4), 120 (3), 58 (100) IR: ν_{OH} 3412; ν_{NH} 2368, 2364, $\nu_{CHarom.}$ 3056, 3032, $\nu_{CHaliph.}$ 2994, 2946, 2832, $\nu_{C=C}$ 1636, 1614, 1486, 1456, ν_{C-O} 1064 cm⁻¹ (KBr). *Anal.* Calcd. for C₂₄H₂₆ClNO₂ (395.68): C, 72.79; H, 6.68; N, 3.53. Found: C, 72.90; H, 6.66; N, 3.63.

Supplementary material: Crystallographic data for **2b** has been deposited at the Cambridge Crystallographic Data Center, UK, CCDC as supplementary material No. 236159. e-mail: deposit@ccdc.cam.ac.uk

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