Single-step synthesis of a new series of \textit{meso} \textit{di}-Mannich bases from the cyclic aminal (2S,7R,11S,16R)-1,8,10,17-tetraazapentacyclo [8.8.1.1.8,17.0.2,7.0.11,16]icosane and \textit{p}-substituted phenols

Augusto Rivera\(^1\)*, Diego Quiroga\(^1\), Jaime Ríos-Motta\(^1\), Václav Eigner\(^2,3\) and Michal Dušek\(^3\)

Abstract

**Background:** The results presented herein show that the cyclic aminal (2S,7R,11S,16R)-1,8,10,17-tetraazapentacyclo [8.8.1.1.8,17.0.2,7.0.11,16]icosane (6), derived from \textit{cis-}(meso)-1,2-diaminocyclohexane and formaldehyde, is a suitable substrate for the preparation of a series of \textit{cis-meso} Mannich bases such as 8a-l by reaction with \textit{p}-substituted phenols 7a-l in basic media. These compounds are valuable synthetic products and may find application in asymmetric catalysis.

**Results:** The products were characterized principally by NMR and IR spectroscopy. Both the benzylic and aminalic protons of the perhydrobenzimidazolidine moiety were diastereotopic due to the presence of stereogenic nitrogen centers. The occurrence of intramolecular hydrogen bonding interactions was confirmed by the broad OH stretching vibration band in the IR spectra. Vibrational spectra were calculated using B3LYP at 6-31G(d,p) level, and the calculated frequencies for the vOH vibrations were compared to those of the experimental spectra. Hydrogen bonding interactions in the solid state were observed through the X-ray crystallography of 8j. Additionally, Mulliken charges and Fukui indices for 6 were calculated as theoretical descriptors of electrophilicity.

**Conclusion:** A new series of \textit{meso} Mannich bases called 4,4'-disubstituted-2,2'-\{[(3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1\textit{H}-1,3-benzimidazole-1,3-diyl]bis(methylene)} diphenols (8a-l) which are derived from \textit{cis-}(meso)-1,2-diaminocyclohexane, were obtained from cyclic aminal 6. These results confirmed the behavior of 6 as an electrophilic preformed reagent in Mannich reactions in basic media.

Mannich bases are an interesting family of compounds in organic chemistry, and these compounds have been widely used in diverse chemistry fields due to their biological and pharmacological activities [1-4]. Moreover, the Mannich bases have been used as molecular models for studies of intramolecular proton transference processes [5,6] due to their interesting thermodynamic stability. Our interest in Mannich bases is focused on their application as model systems for studying inter and intramolecular hydrogen bond interactions between the phenolic OH atoms and the amine N atoms in phenolic derivatives [7-9]. Mannich bases can be obtained by multi-component Mannich condensation reactions between an amine, formaldehyde and \textit{active hydrogen compounds} in acidic media in low to moderate yields [10].

The main subject of research is the reactivity of cyclic aminals toward nucleophiles and electrophiles. Our results using phenols as nucleophiles have led to the synthesis of \textit{di}-Mannich bases, demonstrating that cyclic aminals behave as preformed electrophilic reagents.

One example of the application of cyclic aminals as Mannich base precursors is the chemical reactivity of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD, 1), which by reaction with \textit{p}-substituted phenols in basic...
media, leads to the synthesis of 2,2′-(imidazolidine-1,3-diyldi(methylene))bis(4-substitutedphenols) (2) (Figure 1), an interesting family of di-Mannich bases that show a stability due to the presence of two OH--N intramolecular hydrogen bonds [11-15].

We believe that the electrophilic behavior of cyclic aminals is determined by their structural features, especially the presence of 1,1- and 1,2-diamine functionalities. The interactions of the nonbonding electron pairs of nitrogen atoms and the presence or absence of stereoelectronic effects play an important role in the relative stability and chemical reactivity of this type of cyclic aminal [16]. Our hypothesis was supported by experiments using a cyclic aminal 6H,13H-5:12,7:14-dimethanedibenzo[d,l][1,3,6,8]tetraazecine DMDBTA (3) (Figure 1), a cyclic aminal analog similar to TATD 1. All the efforts to synthesize type (2) di-Mannich bases were unsuccessful, and N-substituted benzimidazoles were obtained using electron-rich phenols [17], due to spontaneous reaction under air oxidative conditions and thermodynamically driving by aromatisation. To obtain cyclic aminals with molecular structures that do not involve electron delocalization of the nonbonding pairs, we employed aliphatic 1,2-diamines such as 1,2-diaminocyclohexane (4).

1,2-Diaminocyclohexane 4 is an organic compound with a 1,2-disubstituted cyclohexane type structure and two primary amino groups attached to two stereogenic centers (Figure 1). For this compound exists the (R, R)-, (S, S)-, and (S, R) stereoisomers. Both (R, R)- and (S, S)-4 have trans isomerism while (S, R)-4 has cis isomerism. Trans-(R, R)- and trans-(S, S)-4, which presents C2 symmetry, have been widely used in asymmetric synthesis because their two primary amino groups possess nonbonding orbitals allowing their use as a ligand for transition metals [18-20]. Although cis-1,2-diaminocyclohexane stereoisomer with average C2v symmetry is less stable than trans stereoisomers, cis stereoisomer has also been studied for the preparation of metal complexes that can be employed in a variety of applications, including the synthesis and pharmacological activity of inorganic complexes of platinum (II), cobalt (II), nickel (II) and copper (II) [21-25]. Both trans and cis isomers have been used to obtain cyclic aminals (2R,7R,11S,16S)-1,8,10,17-tetrazapentacyclo[8.8.1.18,17.02,7.011,16]icosane (5) and (2S,7R,11S,16R)-1,8,10,17-tetrazapentacyclo[8.8.1.18,17.02,7.011,16]icosane (6) (Figure 1), respectively [26,27].

Moreover, X-ray analysis suggested that compound 6 could be a reactive precursor, considering the presence of strained cyclohexane rings; the geometry of which is nearly planar and presented internal bond angles between 113.9(7)° and 124.6(8)° [27]. The bond angles confirmed that the aminal groups displayed a distorted tetrahedral geometry of 119.9(9)° to 120.4(7)° due to the cis configuration in the diamine moiety [27]. To obtain new Mannich bases involving fused rings in central chiral-based structures and to understand the stereoelectronic effect of nonbonding pairs in cyclic

Figure 1 Structures of 1-6.
aminals, we studied Mannich type reactions with cyclic aminals derived from chiral diamines. We opened the study with new cyclic aminal 6 and various nucleophiles, beginning with the reaction between 6 and \(p\)-substituted phenols 7a-l to afford 4,4\(^{\prime}\)-disubstituted-2,2\(^{\prime}\)-[[3a\(R\),7a\(S\)]-2,3,3a,4,5,6,7,7a-octahydro-1\(H\)-1,3-benzimidazole-1,3-diyl] bis(methylene)]di phenols (8a-l), a new family of Mannich bases (Scheme 1). In this article, we discuss the synthetic methodology and characterization of these compounds using FT-IR and NMR analysis, as well as X-ray diffraction.

Results and discussion

Cyclic aminal 6 was prepared in high yield (90%) by the condensation of \(\text{cis-}(\text{meso})\)-1,2-diaminocyclohexane with paraformaldehyde in \(N\),\(N\)-DMF, according to the previously reported procedure [27].

The overall procedure for the synthesis of Mannich bases (8a-l) is depicted in Scheme 1. The isolated products were characterized by FT-IR and uni- and bi-dimensional NMR experiments. All of the compounds were identified as 4,4\(^{\prime}\)-disubstituted-2,2\(^{\prime}\)-[[3a \(R\),7a\(S\)]-2,3,3a,4,5,6,7,7a-octahydro-1\(H\)-1,3-benzimidazole-1,3-diyl] bis(methylene)]di phenols (8a-l). Reactions between 6 and \(p\)-substituted phenols 7a-l were carried out at 40°C in 1,4-dioxane: water at a volumetric ratio of 3:2

Table 1. Apparently, water is necessary for such reactions because attempts to obtain compounds 8a-l under aprotic conditions were unsuccessful. The reactions showed ortho-regioselective aminomethylation of the aromatic ring of the phenols. The formation of compounds 8a-l can be easily explained by analogy with the mechanism proposed for the reaction of cyclic aminal 1 with phenols [11,12].

| Entry | Compound | R    | Product | m.p. (°C) | \(\alpha\)\(^{20}\) | Yield (%) |
|-------|----------|------|---------|-----------|----------------|-----------|
| 1     | 7a       | F    | 8a      | 168-169   | +5.2           | 20        |
| 2     | 7b       | Cl   | 8b      | 189-190   | +5.7           | 34        |
| 3     | 7c       | Br   | 8c      | 183-184   | +6.0           | 41        |
| 4     | 7d       | I    | 8d      | 175-177   | +7.1           | 20        |
| 5     | 7e       | COOMe| 8e      | 128-130   | +6.3           | 17        |
| 6     | 7f       | COOEt| 8f      | 151-153   | +6.8           | 19        |
| 7     | 7g       | COOPr| 8g      | 118-119   | +5.5           | 18        |
| 8     | 7h       | COOBu| 8h      | 127-129   | +4.9           | 19        |
| 9     | 7i       | H    | 8i      | 146-148   | +6.8           | 20        |
| 10    | 7j       | Me   | 8j      | 162-163   | +7.2           | 46        |
| 11    | 7k       | t-Bu | 8k      | 141-143   | +6.3           | 49        |
| 12    | 7l       | OMe  | 8l      | 132-134   | +5.9           | 45        |

Table 1 shows melting points and yield for each new compound, indicating the \(p\)-substituent in aromatic rings in both phenols and compounds 8a-l.
The experimental FT-IR spectra of the Mannich bases (8a-l) (Table 2) showed a broad absorption band between 3300–2350 cm\(^{-1}\), which was assigned to the O–H stretching vibration of the phenolic moiety and is a result of OH•••N hydrogen bonding interactions, suggesting that the proton remains covalently bonded to the hydroxyl group and that proton transfer to the amino group did not occur. To understand the effect of hydrogen bonding interactions on the molecular structure of these compounds, we performed theoretical calculations. Thus, geometry optimizations and vibrational frequencies of the products were performed in Gaussian 1998 using DFT B3LYP methods at the 6-31G (d,p) level [28].

The computational calculations showed that the calculated frequencies of the \(\nu OH\) vibrations of compounds 8a-l (3335 and 3345 cm\(^{-1}\)) were higher than that of the experimental spectra, where these vibrations appeared as very broad and weak absorptions. As described by several authors who studied similar compounds [29,30], these differences can be attributed to the strong anharmonicity of this type of vibration, which was not included in the calculation process. The calculated frequencies of the aromatic and fused rings of the perhydrobenzimidazolidine moiety were located in the expected ranges. For the calculated C–O stretching frequencies of the phenol precursors (7a-l) we noted that the calculated values are systematically lower than the experimental results of respective product (8a-l), suggesting that the C–O bond length was shortened due to intramolecular hydrogen bonding (Table 2).

However, the use of this band to understand the effects of hydrogen bonding in the structures of 8a-l is limited due to its low intensity and the presence of aromatic ring deformation vibrations in this region, which prevented assignment. The \(^{13}\)C NMR spectra of all of the synthesized compounds 8a-l (Table 3) showed two signals between 21.0 and 25.0 ppm, which were assigned to the methylene carbon atoms of the cyclohexane ring. The signal at 61.0 ppm was assigned to the methine chiral carbon atoms. Using HMQC and HMBC bidimensional experiments, the signal at 73.5 ppm was assigned to the aminal carbon atom (N–CH\(_2\)–N). Moreover, the benzyl carbon atoms showed a signal at 55.0 ppm. The carbon atoms of the aromatic rings appeared as six signals between 115 and 158 ppm. The \(^1\)H NMR spectra of the products obtained from \(p\)-substituted phenols, signals as singlets and doublets with \(meta\) coupling (around 2.0 Hz) in an ABX system were observed and were assigned to hydrogen atoms in the \(ortho\) position with respect to the methylene group and the \(meta\) position with respect to the hydroxyl group. In addition, signals as doublets and doublets of

| Table 2 Assignment of vibrational modes of compounds 8a-l |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Product | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  |
| 8a | 3050 | 2848 | 1630 | 1448 | 1387 | 1194 | 1289 | 1063 | 772 |
|    |     |     | 1495 |     | 1124 |     | 737  |     |     |
| 8b | 3053 | 2922 | 1605 | 1444 | 1385 | 1170 | 1272 | 1069 | 764 |
|    | 2850 | 1480 |     |     | 1069 |     | 680  |     |     |
| 8c | 3054 | 2933 | 1636 | 1444 | 1384 | 1169 | 1283 | 1071 | 761 |
|    | 2849 | 1476 |     |     | 1112 |     | 673  |     |     |
| 8d | 3070 | 2931 | 1603 | 1440 | 1367 | 1179 | 1262 | 1039 | 764 |
|    | 2854 | 1476 |     |     | 1129 |     |     |     |     |
| 8e | 3042 | 2928 | 1609 | 1449 | 1384 | 1190 | 1293 | 1097 | 791 |
|    | 2854 | 1497 |     |     | 1110 |     | 771  |     |     |
| 8f | 3040 | 2980 | 1612 | 1452 | 1384 | 1178 | 1285 | 1098 | 840 |
|    | 2931 | 1495 |     |     | 1124 |     | 1058 | 770  |     |
|    | 2857 |     |     |     |     |     |     |     |     |
| 8g | 3049 | 2932 | 1613 | 1448 | 1384 | 1178 | 1270 | 1037 | 840 |
|    | 2875 | 1497 |     |     | 1127 |     | 771  |     |     |
| 8h | 3056 | 2961 | 1613 | 1449 | 1383 | 1177 | 1258 | 1059 | 874 |
|    | 2931 | 1497 |     |     | 1127 |     | 770  |     |     |
|    | 2858 |     |     |     |     |     |     |     |     |
| 8i | 3037 | 2946 | 1618 | 1469 | 1393 | 1096 | 1243 | 1070 | 742 |
|    | 2913 | 1486 |     |     | 2874 |     |     |     |     |
| 8j | 3060 | 2962 | 1613 | 1449 | 1394 | 1117 | 1259 | 1067 | 817 |
|    | 2934 |     |     |     | 773  |     |     |     |     |
| 8k | 3060 | 2962 | 1613 | 1449 | 1394 | 1122 | 1252 | 1068 | 857 |
|    | 2934 | 1502 |     |     | 824  |     |     |     |     |
| 8l | 3051 | 2962 | 1617 | 1465 | 1384 | 1068 | 1289 | 1039 | 820 |
|    | 2923 | 1497 |     |     | 2850 |     |     |     | 775  |

Vibrational modes: 1) Stretching frequency of O–H bonds, 2) Stretching frequency of the C=O bonds, 3) symmetric and asymmetric stretching frequency of the C–C bond, 4) flexion frequency of the C–H bond in aromatic rings, 5) out of plane flexion frequency of methylene groups, 6) Stretching frequency of the C–N bonds, 7) Stretching frequency of the C–O bonds, 8) in the plane deformation of the C–H bonds in aromatic rings, 9) out of plane deformation of the C–H bonds in aromatic rings.
Table 3 Assignment of the $^{13}$C NMR spectra of the compounds 8a-l

| Product | R         | C1, C1’ | C2, C2’ | C3, C3’ | C4, C4’ | C5, C5’ | C6, C6’ | C7, C7’ | ArCH$_2$N | C3a, C7a | C4, C5, C6, C7 |
|---------|-----------|---------|---------|---------|---------|---------|---------|---------|-----------|---------|----------------|
| 8a      | F         | 153.4 d | 122.0 d | 114.7 d | 156.0 d | 115.4 d | 117.0 d | 73.4    | 55.0      | 61.1    | 21.5          |
| 8b      | Cl        | 156.2   | 122.5   | 128.0   | 123.9   | 129.0   | 117.6   | 73.4    | 55.0      | 61.1    | 21.5          |
| 8c      | Br        | 156.9   | 123.2   | 131.0   | 111.2   | 132.1   | 118.3   | 73.6    | 55.0      | 61.2    | 21.6          |
| 8f      | (C = O)OEt | 145.5   | 60.8    | 166.5   | 162.1   | 120.9   | 130.3   | 121.8   | 131.4     | 116.3   | 73.7   55.4 61.2 21.6 |
| 8g      | (C = O)OPr | 10.7    | 22.3    | 66.4    | 166.5   | 162.0   | 121.8   | 130.5   | 121.8     | 131.5   | 116.5   73.4 56.3 61.2 21.6 |
| 8h      | (C = O)OBu | 13.9    | 19.4    | 31.0    | 64.6    | 166.6   | 162.2   | 121.0   | 130.2     | 121.8   | 131.4   116.3 73.7 55.5 61.2 21.7 |
| 8i      | H         | 157.6   | 121.3   | 128.2   | 119.3   | 129.1   | 116.1   | 73.4    | 55.4      | 61.0    | 21.6          |
| 8j      | Me (20.4) | 155.2   | 121.0   | 128.8   | 128.4   | 129.5   | 115.9   | 73.4    | 55.3      | 61.0    | 20.4          |
| 8k      | t-Bu (31.6, 33.9) | 155.2 | 120.4   | 125.0   | 142.0   | 125.8   | 115.5   | 73.5    | 55.9      | 61.0    | 21.7          |
| 8l      | OMe (55.7) | 152.6   | 121.9   | 114.1   | 151.3   | 114.1   | 116.6   | 73.4    | 55.4      | 61.1    | 21.6          |

Table 3 represents all the measured signals for carbon atoms in compounds 8a-l in the $^{13}$C NMR spectra and their assignation in the molecular structure.

doublets with typical ortho and meta coupling constants (8.4 Hz and 2.4 Hz, respectively), were also detected. The $^1$H NMR spectrum of compound (8i) showed an ABCD coupling system with a triplet of doublets around 6.77 ppm with a meta coupling constant of $4J = 1.1$ Hz and an ortho coupling constant of $3J = 7.4$ Hz with the signal at 6.96 ppm, which appeared as a doublet and was assigned to the $R = H$ atoms and the hydrogen atom in the ortho position with respect to the methylene group attached to the aromatic ring. However, the signal at 6.82 ppm appeared as a doublet of doublets with a meta coupling constant $4J = 0.9$ Hz and an ortho coupling constant of $3J = 8.4$ Hz with the signal at 7.17 ppm, which appeared as a multiplet and was assigned to the hydrogen in the ortho position and the hydrogen atoms in the meta position with respect to the hydroxyl group, respectively. The hydrogen atoms of the hydroxyl groups were shifted to a low field (above 10.6 ppm), confirming the existence of intramolecular hydrogen bonding interactions.

The cyclohexane ring can be identified in the $^1$H NMR spectra as four multiplet signals between 1.39 and 3.11 ppm. These hydrogen atoms are diastereotopic due to the presence of chiral carbon atoms and stereogenic nitrogen centers. For the signal at 3.11 ppm, which presented a vicinal $^1$H/$^1$H coupling constant of 4.0 Hz, we calculated the torsional angles between the amine hydrogens and methylene hydrogens using MestReN software, which employs the modified Karplus relation and the dependence of the coupling constant on the torsion angle [31]. The averages over all of the structures (8a-l) were 120° ($\alpha_{eq}$, $\beta_{eq}$) and 52° ($\alpha_{eq}$, $\alpha_{ax}$), respectively. The signals that appeared as doublets at 3.39 and 3.85 ppm with a coupling constant of 6.5 Hz were assigned as the aminal hydrogens. This experimental evidence is in good agreement with the proposed molecular structures of compounds 8a-l, which belong to the $C_1$ symmetric chiral point group and presents the lowest degree of symmetry. Because the aminal protons have a distinct chemical environment due to their spatial orientation (axial and equatorial dispositions in the imidazolidine ring, respectively), the deprotection of the equatorial proton, which was shifted to higher frequencies is evidenced in the doublet signals separated by 0.42 ppm. These results can be explained considering a hyperconjugation effect, which can be attributed to the interaction between nitrogen lone pairs and antibonding orbital $\sigma^*_{C-Hax}$ (n$_N$ $\rightarrow$ $\sigma^*_{C-Hax}$), the latter of which was synperiplanar to the nitrogen lone pairs (Figure 2) [32]. A consequence of this effect is the

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| Product | R        | Ar-OH | H-5, H-3, H-4, H-5, H-3' H-6' | H-2' ArCH₂N | H-3a, H-7a | H-4, H-5, H-6, H-7 |
|---------|----------|-------|-----------------------------|-------------|------------|------------------|
| 8a      | F        | 10.34 | 6.87, dd, J = 8.0 Hz, J = 8.2 Hz, J = 3.1 Hz | 6.70, dd, J = 8.0 Hz, J = 2.8 Hz | 6.76, dd, J = 8.0 Hz, J = 4.8 Hz | 3.39, d, 3.84, d, J = 6.4 Hz | 3.63, d, 4.03, d, J = 14.0 Hz | 3.11, t, J = 4.0 Hz | 1.30-1.80 m |
| 8b      | Cl       | 10.63 | 7.15, dd, J = 8.6 Hz, J = 2.6 Hz | 6.97, d, J = 2.5 Hz | 6.78, d, J = 8.6 Hz | 3.39, d, 3.85, d, J = 6.6 Hz | 3.64, d, 4.04, d, J = 14.0 Hz | 3.11, t, J = 4.1 Hz | 1.30-1.80 m |
| 8c      | Br       | 10.55 | 7.26, dd, J = 8.6 Hz, J = 2.4 Hz | 7.09, d, J = 2.4 Hz | 6.72, d, J = 8.6 Hz | 3.36, d, 3.84, d, J = 6.6 Hz | 3.62, d, 4.02, d, J = 13.9 Hz | 3.09, t, J = 4.0 Hz | 1.30-1.80 m |
| 8d      | I        | —     | 7.45, d, J = 8.8 Hz | 7.27, s | 6.62, d, J = 8.5 Hz | 3.62, d, 3.85, d, J = 8.0 Hz | 3.62, d, 4.01, d, J = 13.9 Hz | 3.11, t, J = 4.0 Hz | 1.30-1.80 m |
| 8e      | (C = O)OMe (3.87, s) | 10.79 | 7.96, dd, J = 8.4 Hz, J = 2.1 Hz | 7.74, d, J = 2.1 Hz | 6.87, d, J = 8.8 Hz | 3.42, d, 3.85, d, J = 8.0 Hz | 3.67, d, 4.06, d, J = 14.0 Hz | 3.11, t, J = 4.0 Hz | 1.30-1.80 m |
| 8f      | (C = O)OEt (1.35, t; 4.31, q) | —     | 7.88, dd, J = 8.5 Hz, J = 2.1 Hz | 7.70, d, J = 2.0 Hz | 6.83, d, J = 8.5 Hz | 3.37, d, 3.86, d, J = 6.6 Hz | 3.72, d, 4.09, d, J = 13.9 Hz | 3.11, t, J = 4.0 Hz | 1.30-1.80 m |
| 8g      | (C = O)OPr (1.01, t; 1.75, m; 4.22, t) | —     | 7.89, dd, J = 8.5 Hz, J = 2.1 Hz | 7.71, d, J = 1.9 Hz | 6.86, d, J = 8.5 Hz | 3.44, d, 3.91, d, J = 6.2 Hz | 3.75, d, 4.10, d, J = 13.8 Hz | 3.15, t, J = 4.0 Hz | 1.30-1.80 m |
| 8h      | (C = O)OBu (0.96, m; 1.44, m; 1.71, qn; 4.26, t) | —     | 7.88, dd, J = 8.5 Hz, J = 2.1 Hz | 7.69, d, J = 2.1 Hz | 6.83, d, J = 8.5 Hz | 3.36, d, 3.85, d, J = 6.6 Hz | 3.72, d, 4.09, d, J = 13.9 Hz | 3.10, t, J = 4.0 Hz | 1.30-1.80 m |
| 8i      | H (6.77, td) | 10.60 | 7.17, dd, J = 8.0 Hz, J = 1.2 Hz | 6.96, d, J = 7.2 Hz | 6.82, dd, J = 8.1 Hz, J = 1.0 Hz | 3.42, d, 3.84, d, J = 6.6 Hz | 3.67, d, 4.06, d, J = 13.8 Hz | 3.11, t, J = 4.0 Hz | 1.30-1.80 m |
| 8j      | Me (2.24, s) | 10.62 | 6.99, d, J = 8.2 Hz | 6.79, s | 6.74, d, J = 8.2 Hz | 3.44, d, 3.83, d, J = 6.5 Hz | 3.64, d, 4.04, d, J = 13.7 Hz | 3.12, t, J = 4.1 Hz | 1.30-1.80 m |
| 8k      | t-Bu (1.27, s) | 10.62 | 7.19, dd, J = 8.5 Hz, J = 2.4 Hz | 6.96, d, J = 2.4 Hz | 6.75, d, J = 8.5 Hz | 3.47, d, 3.86, d, J = 6.6 Hz | 3.67, d, 4.07, d, J = 13.8 Hz | 3.11, t, J = 4.3 Hz | 1.30-1.80 m |
| 8l      | OMe (3.71, s) | 10.15 | 6.73, d, J = 8.8 Hz | 6.53, d, J = 2.0 Hz | 6.75, d, J = 8.8 Hz | 3.42, d, 3.83, d, J = 6.5 Hz | 3.62, d, 4.02, d, J = 13.7 Hz | 3.11, t, J = 4.1 Hz | 1.30-1.80 m |

Table 4 shows all the measured signals for hydrogen atoms in compounds 8a-l in the ¹H NMR spectra and their assignation in the molecular structure.
elongation of the C-Hax bond with respect to the C-Heq bond, which was equal to 0.02 Å, as observed in the optimized molecular structure.

To understand the incidence of cis isomerism in the molecular structure of compounds 8a-l, efforts were made to obtain monocrystals suitable for X-ray diffraction analysis. A monocrystal of compound 8j was obtained via recrystallization from a mixture of chloroform and methanol. Compound 8j exists mainly with the OH groups engaged in an intramolecular hydrogen bond with the N atoms of imidazolidine ring. The molecular structure of compound 8j (Figure 3) is stabilized by two O—H···N intramolecular hydrogen bonds.

The imidazolidine ring adopts an envelope conformation, and the fused six-membered ring adopts a chair conformation. The dihedral angle between the mean planes of these rings, defined by C9-N1-C2 and C5-C4-C8, is 47.84(12)°. The substituents on the N atoms of the five-membered ring are arranged syn with respect to the central ring. The phenyl rings are oriented at angles of 82.15 (14)° (C11-C16) and 83.97 (16)° (C20-C25) with respect to the mean plane of the heterocyclic ring, defined by N1—C2—C9. The two phenyl rings form a dihedral angle of 41.25 (9)°.

To understand the relationship between the molecular structure and observed reactivity of 6, we used two approaches, including: (a) the correlation between the electrophilicity of cyclic aminal 6 with the Fukui function of the methylene bridges and (b) the HOMO-LUMO gap, which was calculated as the difference between the HOMO of the nucleophile (we used phenol 7i, which possessed a calculated HOMO energy of −0.34552 Hartree) and the LUMO of cyclic aminal 6 (Figure 4). In the first approach, the DFT B3LYP method at the 6-31G (d,p) level allowed us to obtain the Mulliken charges of the methylene bridges in aminal 6. However, Mulliken charges are not a good theoretical descriptor of electrophilicity. Thus, we used condensed Fukui functions, which are better theoretical descriptors. We applied the methodology proposed by Yang and Mortimer [33], which is based on a Mulliken population analysis and the following finite difference approximation:

\[ f_1 = q(N) - q(N-1) \]  

For a system of N electrons, independent calculations were made for the corresponding N and (N-1) systems with the same molecular geometry. According to this approach (Table 5), marked differences were observed in the electrophilicity of methylene bridges in aminal 6.

The condensed Fukui function for 6 suggests that the carbon atoms labeled as C19 and C20 are the most reactive sites for the nucleophilic attack of p-substituted phenol 7a-l (Figure 5). The calculated HOMO-LUMO gap between 6 and phenol 7i was 218.2 kCal/mol, which is consistent with the calculated Fukui indices, corroborating the electrophilic character of aminal 6. Furthermore, both the HOMO and LUMO in cyclic aminal 6 was influenced by aminal cis isomerism, such that the calculated HOMO representation for aminal 6 is indicative of a σ type interaction between the nonbonding molecular orbitals of the nitrogen atoms, which is favored by the eclipsed conformation as a result of cis isomerism (Figure 4).
Finally, we propose that the reaction between 6 and p-substituted phenols 7a-l is mediated by the hydrogen bond between any of the four nitrogen atoms in the cyclic aminal and the hydroxyl group of one molecule of phenol, in accordance with the mechanism for the reaction of cyclic aminal 1 previously reported in the literature [11].

Conclusions
In summary, we synthesized a series of new meso Mannich bases called 4,4′-disubstituted-2,2′-[((3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3-benzimidazole-1,3-diyl] bis(methylene)] diphenols (8a-l) by reacting preformed Mannich reagent (6) with p-substituted phenols 7a-l. The presence of hydrogen bonding interactions in the molecular structure was demonstrated using X-ray diffraction, theorectical calculations and experimental spectroscopy. We demonstrated the synthetic potential of cyclic aminal 6 as a Mannich base precursor.

Experimental
General and instrumentation
Melting points were determined with an Electrothermal apparatus and are uncorrected. Diastereomerically pure cis-(meso)-1,2-diaminocyclohexane was purchased from Aldrich. (2S,7R,11S,16R)-1,8,10,17-tetraazapentacyclo[8.8.1.1.8,17.0.2,7.11,16]icosane (6) was prepared according to the procedure described in the literature [27]. p-Substituted phenols (7a-l) were purchased from Merck and were used without further purification.

General procedure for the synthesis of compounds 8a-l
To a stirred solution of (2S,7R,11S,16R)-1,8,10,17-tetraazapentacyclo[8.8.1.1.8,17.0.2,7.11,16]icosane (6) (276 mg, 1.00 mmol) in dioxane (3 mL), the respective p-substituted phenol (2.00 mmol) in dioxane (3 mL) was added dropwise. After stirring for 15 min at room temperature, water (4 mL) was added and the mixture was heated to 40°C for 30 h. After cooling to room temperature, the solvent was removed in vacuo, and the crude product was purified by chromatography on a silica column and subjected to gradient elution with light petroleum ether and ethyl acetate.

Single crystal X-ray measurements
Crystal data for compound 8j, C23H30N2O2, were collected using an Xcalibur Atlas Gemini ultra diffractometer using the following parameters: Oxford Diffraction at 120 K, M_r = 366.5, triclinic, P1, a = 6.0346(4) Å, b = 12.4793(8) Å, c = 14.2169(10) Å, α = 67.847(7)°, β = 85.183(6)°, γ = 85.605(5)°, V = 986.93(12) Å³, Z = 2, Dx = 1.233 Mg m⁻³, CuKα X-ray source (radiation), λ = 1.5418 Å and F(000) = 396 colorless crystals 0.17 × 0.06 × 0.03 mm. All non-hydrogen atoms were refined with anisotropic thermal parameters using full-matrix least squares procedures on F² to give R = 0.036, wR = 0.086 for 2546 independently observed reflections and 251 parameters. Crystallographic data (excluding structural factors) for the given structure in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 929464. Copies of these data can be obtained, free of charge, upon request to the CCDC at 12 Union Road, Cambridge. CB2 1EZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk. Program used to refine structure: JANA2006 [34].
**Competition interests**  
The authors declare that they have no competing interests.

**Authors’ contributions**  
AR conceived the study, participated in its design and coordination and helped draft the manuscript. DQ synthesized the compounds, performed the analysis, elucidated the structures and drafted the manuscript. JR-M participated in the development of theoretical models and computational analysis. EV collected the X-ray data and solved the crystal structure under the guidance of MD. All authors read and approved the final manuscript.

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**Author details**  

1 Departamento de Química, Facultad de Ciencias, Universidad Nacional de Colombia, Ciudad Universitaria, Carrera 30 No 45-03, Bogotá, D.C., Colombia.  
2 Department of Solid State Chemistry, Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic.  
3 Institute of Physics AS CR, v.v.i., Na Slovance 2, Prague 8 182 21, Czech Republic.  
4 Institute of Physics AS CR, v.v.i., Na Slovance 2, Prague 8 182 21, Czech Republic.

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Figure 5 Atom labeling of compound 6.

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