One-Pot Three-Component Solvent-Free Syntheses of *n*-Alkyl-Bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines and *N,N*-bis(2-hydroxybenzyl) amines

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Received June 23, 2009: Revised February 23, 2010: Accepted February 24, 2010

Abstract: A simple solvent-free method to prepare four *N,N,N',N'*-tetra(2-hydroxy-3,5-dimethylbenzyl)diaminoalkanes and four *N,N,N',N'*-tetra(2-hydroxy-5-*t*-butyl-3-methylbenzyl)-diaminoalkanes containing a long *n*-alkyl-bridge (5-8 CH_2 groups between N-atoms) is described. In addition, preparations of four dihydrochlorides of prepared *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines are described. This method was also tested in the preparation of eight previously reported *N,N*-bis(2-hydroxybenzyl)amine derivatives.

Keywords: Aminobisphenols, condensation reactions, diaminotetraphenols, solvent free synthesis, X-ray diffraction.

INTRODUCTION

Aminobisphenols are important ligands in catalytic chemistry [1]. Their preparation is generally performed by the Mannich condensation reaction using phenol, formaldehyde and amine as starting materials [2]. Usually these reactions are carried out in polar solvents such as methanol, ethanol or acetonitrile with or without water. The reactions can be carried out over a wide temperature range from RT to the boiling point of the solvent. These methods usually require a long reaction time from a few days up to many weeks. Recently Collins *et al.* [3a] performed some Mannich condensation reactions in pure water. Later Kerton *et al.* [3b] did the reactions "on water" or in polyethyleneglycol (PEG) assisted with microwaves, which reduced reaction times to as short as 10 minutes. Some Mannich reactions have also been shown to proceed without solvent at 80-85 °C, but slowly [4].

We have used amino 2,4-substituted bisphenols for uranyl ion complexation and extraction studies [5] and for tungsten(VI) and molybdenum(VI) complexation [6]. In our previous investigations the length of alkyl amine tail had an influence on uranyl ion extraction from water to dichloromethane in a two phase system [5b].

Now our further focus is on studies of long *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines, which formally are alkylaminobisphenols, where another amino-bisphenol group is situated at the end of an alkyl chain. The alkyl-bridged diaminotetraphenols are interesting difunctional ligands, which have the potential to form homo- and heteronuclear metal complexes with interesting magnetic and catalytic properties, and they can also be effective metal ion extractors. Such ligands have been prepared from 1,2-ethylenediamine using 2,4-disubstituted phenols [4] and a phenol [7]. Also 2-naphthol readily forms a tetra naphtol derivative from 1,7-diaminoheptane [8].

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As earlier used methods produced *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines slowly and in a low yield, we now report a one-pot, three-component preparation method for these compounds *via* a condensation reaction without solvents or radiation devices in open air reaction vessels. This reduces the amount of organic waste in the synthesis and makes the synthesis safer to carry out and easier to monitor. The usefulness of the method is demonstrated by preparing eight new *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines (diaminotetraphenols) from 1,n-diamines (n = 5-8) (two of them were isolated only as dihydrochlorides). The reaction path is shown in Scheme **1**. Also eight known aminobisphenols are synthesized using this new method and the yields obtained are compared to those obtained earlier.

RESULTS AND DISCUSSION

Preparation of *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines

Generally the yield of the Mannich condensation reaction depends on the phenol and amine. For example in the synthesis of aminobisphenols from 2,4-substituted phenols the smaller the substituent at positions 2 and 4, the lower is the yield [3b]. The role of the phenol is also shown by the fact that 2-naphthol reacts so easily [2,8]. To avoid low yields and long reaction times with slowly reacting starting materials we performed the reactions at elevated temperatures without solvent using paraformaldehyde as the aldehyde. In order to demonstrate the usefulness of this synthetic procedure, we have used 2,4-dimethylphenol and 4-*t*-butyl-2-methylphenol as phenolic starting materials, which generally produce low yields in this type of condensation reactions. Diamines ($H_2N(CH_2)_nNH_2$, n = 5-8) were used as amines in these Mannich condensations. The codes and the yields of the prepared *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)di-amines **1**-**8** are shown in Table **1**.

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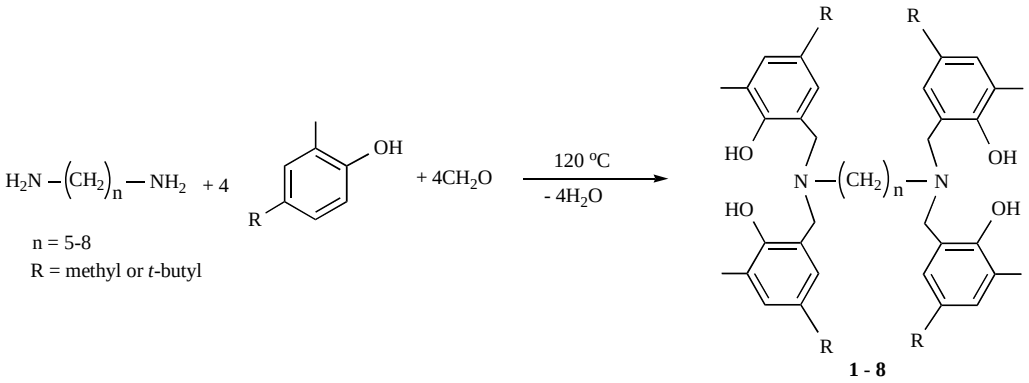


Scheme 1. The reaction path for *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines.

In general the crude product was obtained by placing all starting materials in the same vessel and heating the vessel at 120 °C in the thermal oven for one hour (in the synthesis of **4** the heating time was 8 h). All syntheses proceed in a similar way; the progress of the reactions was monitored by HPLC measurements.

Table 1. The Codes and the Yields of the Prepared *n*-Alkyl-Bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines 1-8

Compound	n	R in Scheme 1	Isolated Yield
1	5	methyl	81 % / 40 %[a]
2·2HCl	5	*t*-butyl	40 %
3	6	methyl	35 % / 20 %[a]
4	6	*t*-butyl	47 % / 38 %[b]
5	7	methyl	33 %
6·2HCl	7	*t*-butyl	35 %
7	8	methyl	56 %
8	8	*t*-butyl	34 % / 30 %[b]

[a]yield using the solution method, [b]yield isolated as a dihydrochloride.

It is essential that the reactions are performed at higher temperatures than 100°C (optimum is around 120°C). This ensures that water produced in the reaction is evaporated from the system. Lower temperatures lead to very low yields and a poor predictability of the system.

Reactions should be performed in the open reaction vessel covered by a glass plate. Covering the reaction vessel may slow down the evaporation of formaldehyde and amine (if volatile) at the beginning of the reaction processes. Totally open reaction vessel gives slightly lower yields than the covered one, but the tightly closed one produces several side products and considerably lower yields.

In the syntheses of **2**, **6**, **7**, **8** a longer reaction time (up to 8 hours) increased the yield only marginally, but the amount of side products increased, which made isolation of the desired product more difficult. According to these studies only the synthesis of **4** seems to benefit from a longer (8 h) reaction time.

In the case of compounds **4** and **7** experiments were done to find out the influence of a higher temperature (140 °C and 160 °C) on the yields. The lower yields obtained at these temperatures for **4** and **7** supported that temperature of 120 °C was near the optimal one. An excess of paraformaldehyde and phenol (25 %) seems to increase the yields of *n*-alkyl-bridged *N,N,N',N'*-tetra(2-hydroxybenzyl)diamines, but it can cause purification problems later. A large excess of paraformaldehyde can increase the formation of dibenzoxazines [4]. In the syntheses of **2** and **6** the isolation of the product was much easier when the crude product was transformed to a dihydrochloride. This is generally not a desirable step, as one has later to remove the HCl in order to get an actual diaminotetraphenol, but for **2** and **6** it was necessary. In the syntheses of **2**•2HCl, **4**•2HCl and **5** overcritical solutions were easily formed, and mixing of these solutions before cooling significantly reduced the precipitation time.

Generally the yields of diaminotetraphenols were moderate to good (30-56 %), but compound **1** gave a very good 81 % yield. Similar yields (30-92 %) were obtained for diaminoalkylbisphenols using microwave heating [3b]. The yield for *N,N,N',N'*-tetra(2-hydroxy-3,5-dimethylbenzyl)-1,2-diaminoethane was 27 % [4]. Preparation of **1** and **3** was also done in solution, which gave 40 % yield for **1** and 20 % yield for **3** (reaction time **6 days**). Reactions at 120 °C in one hour by solventless method gave 81 % and 35 % yields for **1** and **3** respectively. These two tests show that solventless reactions at 120 °C give much better yields in a short time.

The reported new *n*-alkyl-bridged diaminotetraphenols can be useful compounds for metal ion complexation. Their conformations and crystal packing system in solid state are interesting as such. Thus single crystals were grown for **4**•2HCl and **5** and their structures were solved from X-ray data. The Ortep view of **4**•2HCl•2MeOH is presented in Fig. (**1**), which shows a centrosymmetric structure with an intensive H-bond system.

A crystal structure determination of **5** (Fig. **2**) revealed the cyclic H-bonded arrangement in the molecule.

This intramolecular H-bond system causes a cup like conformation for the molecule. This arrangement is similar to the structure formed by two alkylaminobisphenols [9].

Preparation of *N,N*-bis(2-hydroxybenzyl)amine Derivatives

We also tested the suitability of this one-pot three-component method for the preparation of known

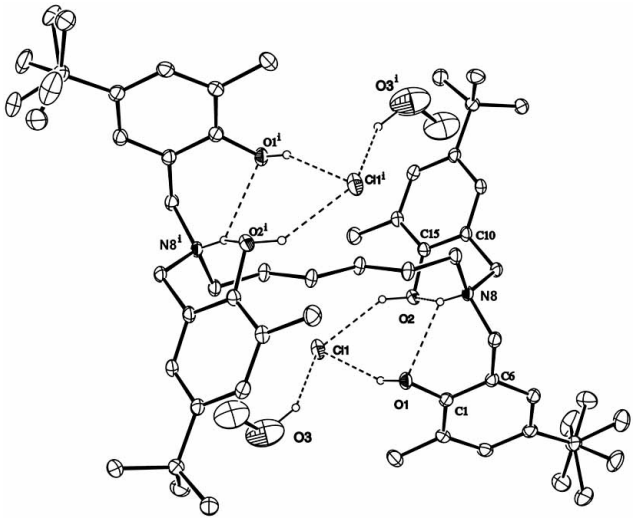


Fig. (1). The ORTEP plot of the solid state structure of **4**•2HCl•2MeOH. (CH hydrogens are omitted for clarity). The *t*-butyl groups at C4 are disordered over two positions.

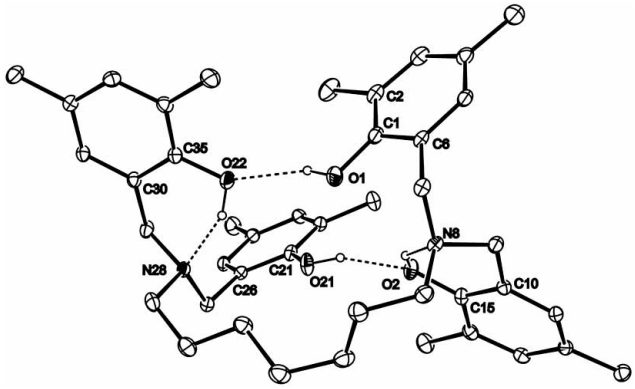
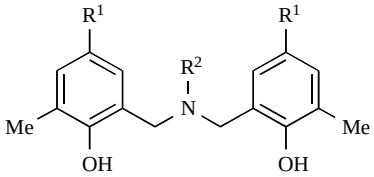


Fig. (2). The ORTEP plot of the solid state structure of **5**. (CH hydrogens are omitted for clarity).

aminobisphenols [5b-5d] and thus several reactions with phenols, paraformaldehyde and amines (aminoalcohols and alkylamines) were carried out at 120 °C. The synthetic procedure for **9**-**16** is similar to that for **1**-**8** in Scheme **1**: the *n*-alkyldiamine is replaced with a primary amine. The compounds prepared are shown in Scheme **2**.

Most of **9**-**16** were isolated as hydrochlorides because for these compounds the isolation as a free base is difficult. The compounds were identified by ^{1}H NMR measurements by comparing their spectra with those reported earlier [5b-5d]. These syntheses were carried out either by refluxing the starting materials in methanol or keeping the reaction mixture in a water bath (50 °C) using 37 % formaldehyde (in water) as aldehyde. The results of the syntheses of compounds **9**-**16** are presented in Table **2**.

The results shows that the isolated yields increased in all cases and the reaction times are much shorter in the solvent-free method. This method provides an easy route for synthesizing these types of compounds.



Compound	R^1	R^2
9	methyl	ethyl-2-ol
10	methyl	propyl-3-ol
11	methyl	butyl-4-ol
12	methyl	pentyl-5-ol
13	*t*-butyl	ethyl-2-ol
14	*t*-butyl	propyl-3-ol
15	*t*-butyl	hexyl
16	*t*-butyl	cyclohexyl

Scheme 2. The synthesized *N*,*N*-bis(2-hydroxybenzyl)amines (isolated as hydrochlorides).

HPLC provided great assistance in monitoring the reaction process. Reaction times longer than five hours did not improve the yield. On the contrary, longer reaction times increased the amount of side products. In particular a methylenebisphenol product was formed. This isolated compound was always observed in chromatograms at longer reaction times.

The actual yields of *N*,*N*-bis(2-hydroxybenzyl)amino alcohols were improved in all cases, some even from very low to moderately good. For compound **10** two experiments *E1* and *E2* were performed. In both experiments the starting materials were heated in the thermal oven in the same way for 4.7 h. Compound **10** was isolated in experiment *E1* by crystallization from cold toluene, as was also done earlier [5c]. The yield was now 38 %, which is much higher than earlier (5.2 %) [5c]. When **10** was isolated from experiment *E2* as hydrochloride, the yield of the hydrochloride was 60 %. This gives some evidence, in particular with compound **10**, that improvements in yield depend on both the reaction and the purification method used.

The final conclusion from this work is that the one-pot three-component synthetic method for the preparation of *N*,*N*-bis(2-hydroxybenzyl)amines and *n*-alkyl-bridged *N*,*N*,*N*,*'N'*-tetra(2-hydroxybenzyl)diamines works very well for the purpose. Isolation of the products can be a problem in some cases. The treatment of the crude product with hydrochloric acid provided an easy and universal method for the purification of the product, especially for the aminobisphenols. This can significantly save time during the purification process.

EXPERIMENTAL

General

The starting materials for all syntheses were purchased from commercial sources and were used as purchased. The solvents were of HPLC grade. All syntheses and extraction

Table 2. The Yields and Reaction Times of 9-16

Compound	Old Method [5b-5d]		New Method	
	Yield [%]	(Time [h])	yield [%]	(Time [h])
9	43*	(24)	66	(2.5)
10	5.2*	(24)	38* / 60	(4.7)
11	13	(118)	48	(2.2)
12	18	(25)	63	(2.3)
13	44*	(30)	89	(4)
14	17	(9)	63	(5)
15	44	(74)	79	(2.5)
16	29	(74)	81	(3.3)

*Isolated as a free aminoalcoholbisphenol.

experiments were performed under ambient laboratory atmosphere. The NMR spectra were recorded on a Bruker AVANCE DRX 500 FT-NMR or on a Bruker AVANCE DPX 250 FT-NMR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, MeOD or d_6-DMSO at 30 °C. The chemical shifts are reported in ppm and referenced internally using the residual polar solvent resonances relative to tetramethylsilane ($CDCl_3$ δ = 7.26, ^{1}H NMR; δ = 77.0, ^{13}C NMR; MeOD δ = 3.30, ^{1}H NMR; δ = 49.15, ^{13}C NMR; DMSO-d_6 δ = 2.50, ^{1}H NMR; δ = 39.50, ^{13}C NMR). Elemental analyses were performed using a VarioEl III elemental analyzer and found figures are averages of two measurements. TOF accurate mass spectra were measured by a Micromass LCT ESI-TOF instrument using leucine encephalin (Sigma, 99 %) as the internal standard. The single crystal X-ray measurement was performed with an Enraf Nonius Kappa CCD area-detector diffractometer. For liquid chromatography measurements a Perkin Elmer series 200 equipment was used (Column: Phenomenex Luna 5u C18 250x4.60 mm, solvent: methanol-tris-buffer (97.5 % methanol, 2 % water and 0.5 % tris(hydroxymethyl) aminomethane) 100-90 % and water 0-10 %, flow rate 2 mL/min for 1-8 and 1 mL/min for 9-16, λ = 254 nm).

Synthesis of *n*-alkyl-bridged N,N,N',N'-tetra(2-hydroxybenzyl)diamines

N,N,N',N'-tetra(2-hydroxy-3,5-dimethylbenzyl)-1,5-diaminopentane (1)

The crude product of **1**: 1,5-diaminopentane (0.613 g, 6 mmol), 2,4-dimethylphenol (3.66 g, 30 mmol (24 mmol equiv.)) and paraformaldehyde (0.900 g, 30 mmol (24 mmol equiv.)) were placed in a 50 mL decanter and covered with a glass plate. The vessel was then kept at 120 °C for one hour in a thermal oven and the product was allowed to cool to RT. Purification: The yellowish product was dissolved in hot dichloromethane (10 mL) and *n*-pentane (20 mL) was added. The solution was kept in a refrigerator (7 °C) overnight. The formed milky mixture was centrifuged. The white precipitate obtained was dried and dissolved in boiling acetonitrile (30 mL). The solution was placed in a refrigerator for three hours and precipitated **1** was separated by filtration as a white powder. The filtrate was kept in a refrigerator overnight and a small amount of extra precipitate was filtered and added to the product. Yield 3.1 g (81 %).

^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ = 7.79 (s, 4H, aryl-O*H*), 6.85 (d, *J* = 2 Hz, 4H, aryl *H*), 6.71 (s, 4H, aryl *H*), 3.62 (s, 8H, N-CH_2-aryl), 2.47 (t, *J* = 7 Hz, 4H, N-CH_2-alkyl), 2.25 (s, 12H, aryl-CH_3), 2.20 (s, 12H, aryl-CH_3), 1.53 (m, *J* = 7 Hz, 4H, alkyl CH_2) and 1.25 (m, *J* = 7 Hz, 2H, alkyl CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz, ppm): 152, 131, 129, 128, 124, 122 (aryl *C*), 56.0 (N-*C*H_2-aryl), 53.0 (N-*C*H_2-alkyl), 25.8 and 24.8 (alkyl *C*), 20.4 and 15.9 (aryl-*C*H_3).

ESI-TOF MS 639.4146 $[M+H]^+$. The calculated value 639.4162 $[M+H]^+$.

Elemental anal. for **1**. Calc. for $C_{41}H_{54}N_2O_4$: C, 77.0; H, 8.84; N, 4.38. Found: C, 77.6; H, 8.73; N, 4.14.

N,N,N',N'-tetra(2-hydroxy-5-t-butyl-3-methylbenzyl)-1,5-diaminopentane•2HCl (2•2HCl)

Crude product of **2**: 1,5-diaminopentane (0.307 g, 3 mmol), 4-*t*-butyl-2-methylphenol (2.46 g, 15 mmol (12 mmol equiv.)) and paraformaldehyde (0.450 g, 15 mmol (12 mmol equiv.)) were placed in a 50 mL decanter and covered with a glass plate. The vessel was then kept at 120 °C for one hour in a thermal oven. Purification: The warm solid was dissolved in 10 mL boiling acetonitrile and 6 M HCl (2.0 mL, double amount) and water (500 µL) was added. The solution was cooled down to RT (10 minutes) after which it was vigorously stirred for 10 min with a magnetic stirrer and allowed to settle down at RT for three hours. The filtered solid was purified twice by dissolving it into hot methanol (4 mL) and acetonitrile (40 mL) was added. The vessel was kept in the refrigerator (6 °C) for 4 hours after which **2**•2HCl was collected by filtration as white powder. Yield 1.0 g, 40 %.

^{1}H NMR for **2**•2HCl (MeOD, 500 MHz, ppm): 7.24 (d, *J* = 2 Hz, 4H, aryl *H*), 7.15 (d, *J* = 2 Hz, 4H, aryl *H*), 4.37 (s, 8H, N-CH_2-aryl), 3.12 (t, *J* = 8 Hz, 4H, N-CH_2-alkyl), 2.25 (s, 12H, aryl-CH_3), 1.79 (m, *J* = 8 Hz, 4H, alkyl CH_2), 1.27 (m, 38H, aryl-*t*-butyl, alkyl CH_2 (overlapping)).

^{13}C NMR (MeOD, 126 MHz, ppm): 153, 145, 131, 127, 126, 118 (aryl *C*), 57.1 (N-*C*H_2-aryl), 54.2 (N-*C*H_2-alkyl),

35.0 and 32.0 (*t*-butyl *C*), 24.7 and 24.5 (alkyl *C*), 16.9 (aryl-*C*H_3).

ESI-TOF MS 807.6058 $[M+H]^+$. The calculated value 807.6040 $[M+H]^+$.

Elemental anal. for **2**•2HCl. Calc. for $C_{53}H_{80}N_2O_4Cl_2$: C, 72.3; H, 9.16; N, 3.18. Found: C, 72.0; H, 9.16; N, 2.99.

N,N,N',N'-tetra(2-hydroxy-3,5-dimethylbenzyl)-1,6-diaminohexane (3)

The crude product of **3** was prepared as that of **1** using 1,6-diaminohexane (0.698 g, 6 mmol) in place of 1,5-diaminopentane. Purification started by dissolving the yellowish product in hot THF (40 mL). A small amount of undissolved solid was filtered and discarded. To the THF solution were added acetone (20 mL) and H_2O (16 mL). The mixture was kept in a refrigerator (7 °C) overnight and **3** was obtained as white powder after filtration. The product was recrystallized from a THF-acetone-water-mixture (10:5:4) as described for the crude product. Both crystallization solutions produced a small amount of substance when stored in a refrigerator for another day. These products were added to the main product. Yield 1.4 g (35 %) (white powder).

^{1}H NMR (DMSO-d_6, 500 MHz, ppm): 9.47 (s, 4H, aryl-O*H*), 6.75 (s, 4H, aryl *H*), 6.69 (d, *J* = 1 Hz, 4H, aryl *H*), 3.57 (s, 8H, N-CH_2-aryl), 2.33 (t, *J* = 7 Hz, 4H, N-CH_2-alkyl), 2.13 (s, 12H, aryl-CH_3), 2.09 (s, 12H, aryl-CH_3), 1.42, (m, *J* = 7 Hz, 4H, alkyl CH_2) and 1.03 (m, *J* = 3 Hz, 4H alkyl CH_2).

^{13}C NMR (DMSO-d_6, 126 MHz, ppm): 152, 130, 128, 127, 124, 123 (aryl *C*), 54.5 (N-*C*H_2-aryl), 52.3 (N-*C*H_2-alkyl), 26.3 and 25.0 (alkyl *C*), 20.0 and 16.0 (aryl-*C*H_3).

ESI-TOF MS 653.4305 $[M+H]^+$. The calculated value 653.4318 $[M+H]^+$.

Elemental anal. for **3**: Calc. for $C_{42}H_{56}N_2O_4$: C, 77.2; H, 8.65; N, 4.29. Found: C, 77.4; H, 8.45; N, 3.90.

N,N,N',N'-tetra(2-hydroxy-5-t-butyl-3-methylbenzyl)-1,6-diaminohexane (4)

The crude product of **4** was obtained like for **2** using 1,6-diaminohexane (0.349 g, 3 mmol) and heating the mixture for 8 h in a thermal oven (120 °C). Purification: The yellow product was dissolved in boiling CH_2Cl_2 (10 mL) and acetonitrile (20 mL) was added. The vessel was vigorously stirred for 5 minutes and then kept at RT for 2.5 hours. The formed solid was separated by filtration. The product was dissolved in warm THF (4.0 mL) and acetonitrile (8.0 mL) was added. The solution was stored at RT for 3 hours after which the precipitate was separated and the filtrate was discarded. The solid was purified once more in THF-acetonitrile (1:2) mixture as previously described. Finally **4**•2MeCN was collected as pale yellow solid after filtration and dried in open air. Yield 1.2 g, 47 %. Acetonitrile-free product was prepared by heating the adduct overnight at 100 °C in open air in a thermal oven.

^{1}H NMR ($CDCl_3$, 500 MHz, ppm): ca. 7.7 (s, 4H, aryl-O*H*), 7.05 (d, *J* = 2 Hz, 4H, aryl *H*), 6.92 (d, *J* = 2 Hz, 4H, aryl *H*), 3.70 (s, 8H, N-CH_2-aryl), 2.49 (t, *J* = 7 Hz, 4H, N-CH_2-alkyl), 2.22 (s, 12H, aryl-CH_3), 1.58 (m, *J* = 7 Hz, 4H, alkyl CH_2), 1.28 (s, 36H, aryl-*t*-butyl) and 1.20 (m, *J* = 3 Hz, 4H alkyl CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz, ppm): 152, 142, 127, 124, 123, 121 (aryl *C*), 56.1 (N-*C*H_2-aryl), 53.2 (N-*C*H_2-alkyl), 33.9 and 31.6 (*t*-butyl *C*), 27.1 and 25.9 (alkyl *C*), 16.2 (aryl-*C*H_3).

ESI-TOF MS 821.6193 $[M+H]^+$. The calculated value 821.6196 $[M+H]^+$.

Elemental anal. for **4**•Calc. for $C_{54}H_{80}N_2O_4$: C, 79.0; H, 9.82; N, 3.41. Found: C, 79.4; H, 9.91; N, 3.34.

From compound **4**•2MeCN an ethyl acetate adduct was prepared by dissolving it in boiling ethyl acetate. In the freezer (-17 °C) colourless crystals with the formula **4**·ethyl acetate were obtained.

Dihydrochloride of **4** was also prepared. The synthesis of **4**•2HCl•2MeOH started as for **4**. After the thermal oven treatment the yellow solid was dissolved in hot chloroform (10 mL) and 6 M HCl (2.0 mL, double amount) was added. The solution was vigorously stirred for 10 minutes and then kept in a refrigerator (6 °C) for two hours. The formed precipitate was separated by filtration. The isolated solid was dissolved in hot methanol (20 mL). The vessel was kept at RT overnight and the solid was filtered out. The solid was dissolved in MeOH (50 mL) and acetonitrile (40 mL) was added. The solution was concentrated into 30 mL using a rotavapor (300 mbar, 50 °C). The white solid begun to form in a few minutes, and the solid was let to form for 5 hours in a refrigerator. The white powder was filtered out and it had the formula of **4**•2HCl•2MeOH. Yield 1.1 g (38 %). **4**•2HCl•2MeOH was dried in vacuum overnight before elemental analysis.

^{1}H NMR for **4**•2HCl•2MeOH (MeOD, 500 MHz, ppm): 7.24 (d, *J* = 2 Hz, 4H, aryl *H*), 7.16 (s, *J* = 2 Hz, 4H, aryl *H*), 4.36 (s, 8H, N-CH_2-aryl), 3.06 (t, 4H, *J* = 8 Hz, N-CH_2-alkyl), 2.24 (s, 12H, aryl-CH_3), 1.75 (m, *J* = 8 Hz, 4H, alkyl CH_2), 1.28 (s, 36H, aryl *t*-butyl), 1.18 (m, *J* = 3 Hz, 4H, alkyl CH_2).

^{13}C NMR for **4**•2HCl•2MeOH (MeOD, 126 MHz, ppm): 153, 145, 131, 127, 126, 119 (aryl *C*), 57.1 (N-*C*H_2-aryl), 54.0 (N-*C*H_2-alkyl), 49.3 (methanol), 35.0 and 32.0 (*t*-butyl *C*), 26.9 and 24.9 (alkyl *C*), 16.9 (aryl-*C*H_3).

ESI-TOF MS 821.6180 $[M+H]^+$. The calculated value 821.6196 $[M+H]^+$.

Elemental anal. for **4**•2HCl•2MeOH. Calc. for $C_{56}H_{90}N_2O_6Cl_2$: C, 70.2; H, 9.47; N, 2.92. Found: C, 70.4; H, 9.28; N, 2.91.

Colourless single crystals for X-ray studies were obtained by dissolving **4**•2HCl•2MeOH in a methanol-acetonitrile (1:5) solution in a test tube and allowing the solvent to evaporate at RT to near dryness.

N,N,N,'N'-tetra(2-hydroxy-3,5-dimethylbenzyl)-1,7-diaminoheptane (5)

Crude product of **5** was obtained using 1,7-diaminoheptane (0.781 g, 6 mmol). The product from the thermal oven was cooled and dissolved in hot acetonitrile (40 mL). The solution was vigorously stirred at RT for 20 min, which caused precipitation to form. The solution was kept in a refrigerator (7 °C) for two hours after which the solid was filtered off. The filtrate was kept in a freezer (-17

°C) overnight. The formed oil was separated by decantation. The combined products were recrystallized twice from acetonitrile (40 mL). Compound **5** was obtained as white powder. Yield 1.3 g (33 %).

^{1}H NMR ($CDCl_3$, 500 MHz, ppm): 7.1 (s, 4H, aryl-O*H*), 6.85 (s, 4H, aryl *H*), 6.72 (s, 4H, aryl *H*), 3.65 (s, 8H, N-CH_2-aryl), 2.47 (t, *J* = 7 Hz, 4H, N-CH_2-alkyl), 2.22 (s, 12H, aryl-CH_3), 2.17 (s, 12H, aryl-CH_3), 1.57 (m, *J* = 7 Hz, 4H, alkyl CH_2), 1.24 (m, *J* = 7 Hz, 4H, alkyl CH_2) and 1.18 (m, *J* = 7 Hz, 2H, alkyl CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz, ppm): 152, 131, 129, 128, 124, 122 (aryl *C*), 56.1 (N-*C*H_2-aryl), 53.4 (N-*C*H_2-alkyl), 29.1, 27.0 and 26.1 (alkyl *C*), 20.4 and 15.9 (aryl-*C*H_3).

ESI-TOF MS 667.4470 $[M+H]^+$. The calculated value 667.4475 $[M+H]^+$.

Elemental anal. for **5:** Calc. for $C_{43}H_{58}N_2O_4$: C, 77.4; H, 8.77; N, 4.20. Found: C, 77.3; H, 8.85; N, 4.22. Single crystals of **5** were prepared by dissolving 90 mg of white powder product in acetonitrile (10 mL) in a test tube and placing the tube in a freezer (-17 °C) overnight. One colourless single crystal was analyzed by X-ray diffraction.

N,N,N',N'-tetra(2-hydroxy-5-t-butyl-3-methylbenzyl)-1,7-diaminoheptane•2HCl (6•2HCl)

The crude product was obtained similarly to compound **2** using 1,7-diaminoheptane (0.781 g, 6 mmol), 4-*t*-butyl-2-methylphenol (30 mmol, 24 mmol equiv.) and paraformaldehyde (30 mmol, 24 mmol equiv.). After the thermal oven treatment, the product was dissolved in boiling acetonitrile (20 mL) and 6 M HCl (4.0 mL, double amount) and water (1.0 mL) were added. The cooled solution was vigorously stirred for 10 minutes and allowed to settle down at RT for 1.5 hours and the precipitate was filtered off. A small amount of product was separated from the filtrate after 4 hours and was added to main product. Finally the solid was dissolved in hot MeOH (10 mL) and acetonitrile (35 mL) was added. The vessel was kept in a freezer (-17 °C) overnight and **6**•2HCl was collected by filtration. Yield 1.9 g, 35 %.

^{1}H NMR (MeOD, 500 MHz, ppm): 7.24 (d, *J* = 2 Hz, 4H, aryl *H*), 7.17 (d, *J* = 2 Hz, 4H, aryl *H*), 4.38 (s, 8H, N-CH_2-aryl), 3.09 (t, *J* = 8 Hz, 4H, N-CH_2-alkyl), 2.26 (s, 12H, aryl-CH_3), 1.73 (m, *J* = 7 Hz, 4H, alkyl CH_2), 1.28 (m, 36H, aryl *t*-butyl), 1.19 (m, *J* = 7 Hz, 4H, alkyl CH_2), 1.10 (m, *J* = 7 Hz, 2H, alkyl CH_2).

^{13}C NMR (MeOD, 126 MHz, ppm): 153, 145, 131, 128, 126, 119 (aryl *C*), 57.2 (N-*C*H_2-aryl), 54.2 (N-*C*H_2-alkyl), 35.0 and 32.0 (*t*-butyl *C*), 29.3, 27.1 and 25.0 (alkyl *C*), 16.9 (aryl-*C*H_3).

ESI-TOF MS 835.6313 $[M+H]^+$. The calculated value 835.6353 $[M+H]^+$.

Elemental anal. for **6**•2HCl. Calc. for $C_{55}H_{84}N_2O_4Cl_2$: C, 72.7; H, 9.32; N, 3.08. Found: C, 72.0; H, 9.39; N, 3.25.

N,N,N'N'-tetra(2-hydroxy-3,5-dimethylbenzyl)-1,8-diamino-octane (7)

The crude material of **7** was prepared as that of **1** using 1,8-diamino-octane (0.866 g, 6 mmol). After reaction in a thermal oven at 120 °C the yellowish product was dissolved in hot acetonitrile (40 mL) and the solution was stored in a refrigerator (7 °C) overnight. The formed solid was decantated and recrystallized twice from acetonitrile (40 mL) in a refrigerator. Compound **7** was obtained as white powder. Yield 2.3 g (56 %).

^{1}H NMR ($CDCl_3$, 500 MHz, ppm): 8.3 (s, 4H, aryl-O*H*), 6.83 (s, 4H, aryl *H*), 6.73 (d, *J* = 2 Hz, 4H, aryl *H*), 3.64 (s, 8H, N-CH_2-aryl), 2.52 (t, *J* = 7 Hz, 4H, N-CH_2-alkyl), 2.22 (s, 12H, aryl-CH_3), 2.07 (s, 12H, aryl-CH_3), 1.60 (m, *J* = 7 Hz, 4H, alkyl CH_2), 1.46 (m, *J* = 7 Hz, 4H, alkyl CH_2) and 1.26 (m, *J* = 7 Hz, 4H, alkyl CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz, ppm): 152, 131, 129, 128, 124, 122 (aryl *C*), 55.9 (N-*C*H_2-aryl), 54.1 (N-*C*H_2-alkyl), 30.0, 26.9 and 26.8 (alkyl *C*), 20.3 and 16.1 (aryl-*C*H_3).

ESI-TOF MS 681.4644 $[M+H]^+$. The calculated value 653.4631 $[M+H]^+$.

Elemental anal. for **7:** Calc. for $C_{44}H_{60}N_2O_4$: C, 77.5; H, 8.88; N, 4.11. Found: C, 77.3; H, 8.87; N, 4.24.

N,N,N'N'-tetra(2-hydroxy-5-t-butyl-3-methylbenzyl)-1,8-diamino-octane (8)

The crude material of **8** was prepared as that of **2** using 1,8-diamino-octane (0.433 g, 3 mmol). After reaction in a thermal oven at 120 °C the yellowish product was dissolved in hot acetonitrile (15 mL) and water was dropwise added (500 μL). The solution was left to stand in a refrigerator (7 °C) for 3 hours after which the top layer of the cold solution was separated by decantation. The top layer was discarded, and the yellow bottom layer was dissolved in dichloromethane (5 mL) and acetonitrile (15 mL) was added. The solution was placed in a freezer (-20 °C) and filtered after 7 hours. The product was recrystallized in a CH_2Cl_2-MeCN (1:3) mixture as previously described. Compound **8** was allowed to dry in open air and obtained as a white powder. Yield 0.86 g, 34 %.

^{1}H NMR (DMSO-d_6, 500 MHz, ppm): 9.52 (s, 4H, aryl-O*H*), 6.97 (d, *J* = 2 Hz, 4H, aryl *H*), 6.92 (d, *J* = 2 Hz, 4H, aryl *H*), 3.62 (s, 8H, N-CH_2-aryl), 2.36 (t, *J* = 7 Hz, 4H, N-CH_2-alkyl), 2.12 (s, 12H, aryl-CH_3), 1.44 (m, *J* = 7 Hz, 4H, alkyl CH_2), 1.20 (s, 36H, aryl *t*-butyl), 1.03 (m, *J* = 7 Hz, 8H, alkyl CH_2).

^{13}C NMR (DMSO-d_6, 126 MHz, ppm): 152, 141, 126, 124, 123, 122 (aryl *C*), 54.6 (N-*C*H_2-aryl), 52.4 (N-*C*H_2-alkyl), 33.4 and 31.3 (*t*-butyl *C*), 28.5, 26.5 and 25.1 (alkyl *C*), 16.3 (aryl-*C*H_3).

ESI-TOF MS 849.6473 $[M+H]^+$. The calculated value 849.6509 $[M+H]^+$.

Compound **8** was crystallized twice from a CH_2Cl_2-MeCN (1:3) mixture and heated at 90 °C in a thermal oven before elemental analysis. Elemental anal. for **8**: Calc. for $C_{56}H_{84}N_2O_4$: C, 79.2; H, 9.97; N, 3.30. Found: C, 78.9; H, 9.93; N, 3.19.

In the synthesis of compound **8**•2HCl the amounts of starting materials and heating in a thermal oven were the same as those for the HCl free compound. The yellow solid from the thermal oven was dissolved in boiling acetonitrile (10 mL) and 6 M HCl (2 mL, double amount) was added.

The solution was stored at RT for 45 min after which the solid was separated by filtration. The filtrate was kept in a refrigerator (7 °C) overnight during which a small amount of the product separated. The combined solid was dissolved in methanol (10 mL) and acetonitrile (30 mL) was added. The vessel was kept in a freezer (-17 °C) overnight. The separated (by filtration) **8**•2HCl was once more crystallized from a methanol – acetonitrile mixture (36 mL, 1:5) in a freezer (-17 °C). Yield 0.84 g, 30 %.

For NMR and elemental analysis, **8**•2HCl was recrystallized twice from 10 mL MeOH – 40 mL ethyl acetate mixture in a freezer, and dried overnight in a thermal oven (90 °C).

^{1}H NMR (MeOD, 500 MHz, ppm): 7.25 (s, 4H, aryl *H*), 7.17 (s, 4H, aryl *H*), 4.38 (s, 8H, N-C*H*$_2$-aryl), 3.09 (t, 4H, alkyl N-C*H*$_2$), 2.25 (s, 12H, aryl-C*H*$_3$), 1.73 (m, 4H, alkyl C*H*$_2$), 1.29 (s, 36H, aryl *t*-butyl), 1.17 (m, 4H, alkyl C*H*$_2$), 1.09 (m, 4H, alkyl C*H*$_2$).

^{13}C NMR (MeOD, 126 MHz, ppm): 153, 145, 131, 128, 126, 119 (aryl), 57.2 (N-CH$_2$-aryl), 54.1 (alkyl N-CH$_2$), 35.0 and 32.0 (*t*-butyl *C*), 29.7, 27.2 and 25.0 (alkyl C), 16.9 (aryl-CH$_3$).

ESI-TOF MS 849.6505 $[M+H]^+$. The calculated value 849.6509 $[M+H]^+$.

Elemental anal. for **8**•2HCl: Calc. for $C_{56}H_{86}N_2O_4Cl_2$: C, 72.9; H, 9.40; N, 3.04. Found: C, 72.2; H, 9.35; N, 2.87.

The compounds **1** and **3** were also prepared using the solution method [5d] by dissolving corresponding diaminoalkane (3 mmol), 2,4-dimethylphenol (12 mmol), aqueous solution of formaldehyde (36.5 %) (15 mmol, 25 % excess), triethylamine (1.4 mmol) and water (2 mL) in methanol (10 mL). The sealed flasks were kept in a 50 °C water bath for 6 days, after which the oily product was separated and purified as mentioned for **1** and **3**. The HPLC analysis showed that after 3 days the amount of product did not increase, whereas the amount of unknown side products did. The yield of this method was lower in both cases: For **1** the yield was 40 % (81 % in the one-pot method) and for **3** 20 % (35 % in the one-pot method).

General Preparation Process of Aminobisphenols (9-16)

The phenol (22 mmol), formaldehyde (22 mmol) and amine (10 mmol) were measured into the reaction vessel and it was placed in the thermal oven (T = 120 °C). The reaction was followed by HPLC to ensure some optimization of the yield. The reaction time was between one and five hours. The resulting yellow syrup was dissolved in diethyl ether and 6 M HCl (2 mL) was added to the solution. After that, in the case of amino alcohols, the best result was obtained by adding water (10 mL) to the HCl-treated ether solution of the crude product and then extracting the non-hydrochloride impurities a few times with diethyl ether. The precipitation occurred then in the water phase. In the case of alkylamines the precipitation occurred readily in the Et_2O-phase after addition of the acid. Crude precipitates were crystallized from a mixture of acetonitrile and methanol. The purity and identity of the products were analysed by ^{1}H NMR in $CDCl_3$ or MeOD.

X-Ray Studies

Suitable colorless single crystals of **4**•2HCl•2MeOH and **5** were obtained as mentioned earlier. Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer using graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å).

The structures were solved by direct methods using the SHELXS-97 program [10] and full-matrix, least-squares refinements on F^2 were performed using the SHELXL-97 program [10]. The CH hydrogen atoms were included at the fixed distances with the fixed displacement parameters from their host atoms (1.2 times that of the host atom). The OH hydrogen atoms were refined isotropically with a thermal displacement of 1.2 times that of the host atom, except that a fixed value of 0.10 for H3 in the refinement of **4**•2HCl•2MeOH was used.

Crystal Data for 4•2HCl•2MeOH

$C_{56}H_{90}Cl_2N_2O_6$, M_r = 958.20, triclinic, space group *P-1* (no. 2), a = 8.7529(3), b = 12.4612(4), c = 13.4645(5) Å, α = 72.397(2), β = 88.404(2), γ = 80.020(2)°, V = 1378.17(8) Å^3, T = 173 K, Z = 1, μ(Mo-K_α) = 0.166 mm^{-1}, 4844 unique reflections (R_{int} = 0.0295), which were used in the calculations. The final *R1* and *wR*(F^2) for all data were 0.1012 (0.0805) and 0.2358 (0.2183), respectively. The values in parentheses are for I > 2σ(I).

Crystal Data for 5

$C_{43}H_{58}N_2O_4$, M_r = 666.91, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 10.1000(2), b = 10.1927(2), c = 37.1338(9) Å, α, β, γ = 90°, V = 3822.79(14) Å^3, T = 173 K, Z = 4, μ(Mo-K_α) = 0.073 mm^{-1}, 4686 unique reflections (R_{int} = 0.0718), which were used in the calculations. The final *R1* and *wR*(F^2) for all data were 0.064 (0.0486) and 0.113 (0.1052), respectively. The values for I > 2σ(I) are in parentheses.

ACKNOWLEDGEMENTS

We are grateful to Matti Nurmia for correcting the language of this paper, to Reijo Kauppinen for doing the NMR measurements, Elina Hautakangas for performing the elemental analysis and to Mirja Lahtiperä for measuring the mass spectra.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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