New Efficient Synthetic Pathways to Tetrakis{*p*-[(diethylphosphono)methyl]}calix[4]arene

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Various operating conditions have been applied on tetrakis[*p*-(halogenomethyl)]- and tetrakis[*p*-(aminomethyl)]calix[4]arene derivatives to improve the synthesis of the 5,11,17,23-tetrakis[(diethylphosphono)methyl]-25,26,27,28-tetrahydroxycalix[4]arene. Two new, high yield, synthetic pathways have been selected, involving, for the first one, the 25,26,27,28-tetrahydroxy-5,11,17,23-tetrakis[(trimethylamino)methyl]calix[4]arene, tetraiodide, DMF, and 10 equiv. of triethyl phosphite ($(EtO)_3P$), and, for the other one, the 5,11,17,23-tetra(bromomethyl)-25,26,27,28-tetrahydroxycalix[4]arene, CH_2Cl_2, and only 4 equiv. of $(EtO)_2P$.

Introduction. – As recently reviewed by *Cherenok* and *Kalchenko* [1], calixarene species bearing phosphor(II) or phosphor(V) at the upper or at the lower rim have been involved in the complexation of metal ions, notably for extraction or catalysis purposes, in the complexation of organic molecules such as amino acids, proteins, nucleic bases derivatives, and some herbicides, and as biologically active substances, for example, as phosphatase inhibitors or calcium pump effectors.

In these domains, our contributions were related to the synthesis of H_2O-soluble *para*-phosphonomethyl derivatives of calixarene-based bipyridyl chelators able to complex and stabilize Cu^I in H_2O, even in the presence of seric proteins, suggesting an interesting role as cation carrier for biological applications [2], or derivatives of calixarene-based bithiazolyl podands evaluated, among other anionic species, as anti-infective agents [3], more precisely as anti-HIV agents on various HIV strains and cells of the lymphocytic lineage.

The need of these derivatives in readily accessible quantities allowing the development of our studies led us to seek a convenient synthetic pathway for the key compound, *i.e.*, the 5,11,17,23-tetrakis[(diethylphosphono)methyl]-25,26,27,28-tetrahydroxycalix[4]arene.

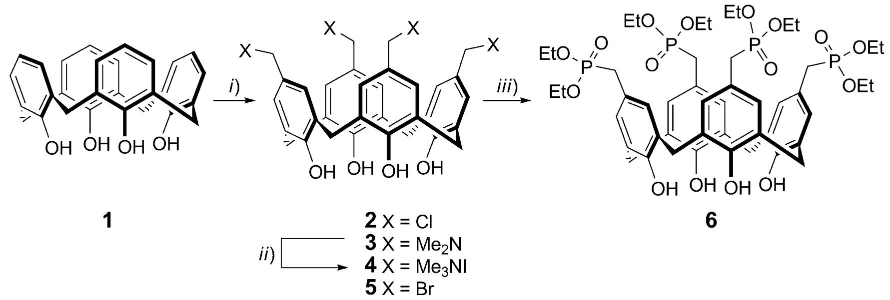
The phosphonomethylation at the upper rim of unprotected calix[*n*]arene platforms has been described by *Ungaro* and co-workers [4]; it involves a preliminary chloromethylation by reaction of chloromethyl octyl ether and $SnCl_4$, followed by reaction of triethyl phosphite ($(EtO)_3P$) under the conditions of *Arbuzov* reaction to give the tetrakis{*p*-[(diethylphosphono)methyl]}calix[4]arene. At the same time, *Shinkai* and co-workers described a similar protocol [5] applied on calix[6]arene hexamethyl ether, using $ClCH_2OMe$ and $ZnCl_2$ to obtain the hexakis(*p*-chloromethyl) derivative, which was then reacted with $(EtO)_3P$ as described above to afford the hexakis{*p*-[(diethylphosphono)methyl]} analog. Similar methods were developed with *O*-alkyl derivatives of *p*-(chloromethyl)calix[6]arenes or calix[4]arenes, involving here a reaction with $(^iPrO)_3P$ to give the corresponding *p*-[(diisopropylphosphono)methyl] analog [6][7].

As seen above, the *p*-(chloromethyl)calixarene species are key compounds in the synthesis of phosphono derivatives; they are readily obtained by reaction of the calixarenes with chloromethyl octyl ether or $ClCH_2OMe$ in the presence of *Lewis* acids; *Huang et al.* [8] proposed a cheaper, full or regioselective *para*-chloromethylation of unprotected or partially OH-protected calix[4]arene derivatives, by reaction of gaseous HCl and paraformaldehyde in a $AcOH/H_2SO_4$ mixture.

In our previous works, the key compound tetrakis{*p*-[(diethylphosphono)methyl]}-calix[4]arene tetrol **6** was prepared in a two-step procedure involving first the chloromethylation of 'de-terbutylated' calix[4]arene **1** according to [4], or to the less expensive procedure in [8], to give the compound **2**. The second step was performed *via* a slight modification of the process of *Ungaro* and co-workers [4], consisting in refluxing **2** and a moderate excess (40 equiv.) of $(EtO)_3P$ in CH_2Cl_2 (*Entry 1*); elimination of most of residual phosphite was performed by lyophilization from cyclohexane suspension and chromatography, to give **6** in a good yield, but always polluted by traces of phosphite.

Nevertheless, the adaptation of the chloromethylation process of *Huang et al.* [8] to large quantities gave some irregular results, and the stability of stocks of **2** was found unsatisfactory, even when frozen. These findings and the aim of working without chlorinated reagents led us to explore new approaches leading to **6**, such as shown in the *Scheme* together with the *Table.*

Scheme



i) **1**→**2**: According to [4], $(HCHO)_n$, AcOH, conc. H_2SO_4, HCl gas, r.t.; **1**→**3**: according to [9], $(Me)_2NH$ 40% in H_2O, HCHO 37% in H_2O, AcOH, r.t.; **1**→**5**: according to [11] $(HCHO)_n$, HBr (g), AcOH. *ii)* **3**→**4**: According to [10], MeI, DMSO, r.t. *iii)* From **2**: $CHCl_3$, 40 equiv. of $(EtO)_3P$, reflux; from **3**: *a)* MeI, DMSO, then *b)* 20 equiv. $(EtO)_3P$, 60°, 4 h; from **4**: DMF, 10 equiv. of $(EtO)_3P$, 70°; from **5**: CH_2Cl_2, 4 equiv. of $(EtO)_3P$, reflux.

In this sense, we attempted to use another intermediate with a leaving group attached *via* a CH_2 group to the upper rim of calixarene, and susceptible to react with $(EtO)_3P$. The different conditions employed in this study are compiled in the *Table.*

Table. *Resume of Operating Conditions*

Entry	Substrate	Solvent	$(EtO)_3P$ (equiv.)	*T* [°]	Time [h]	Yield [%]
1	**2**	$(EtO)_3P/CH_2Cl_2$[a])	40	reflux	6	85
2		DMSO[b])	5	80	5	31
3		DMF[c])	5	60	7	n.d.[d])
4		DMF[c])	20	60	4	43
5	**3** → [**4**]	MeCN[e])	5	reflux	7	n.d.
6		MeCN	20	reflux	6	32
7		Sulfolane[f])	5	60	4	37
8		Sulfolane	20	60	24	trace
9		Sulfolane	5	60	24	n.d.
10		Sulfolane	10	70	24	n.d.
11	**4**	$(EtO)_3P$/NMP[g])	50	70	24	n.d.
12		Dimethylacetamide[h])	10	60	24	57
13		DMF	10	70	6	81
14		DMF	5	70	6	75
15	**5**	CH_2Cl_2	5	reflux	6	78
16		CH_2Cl_2	4	reflux	6	89

[a]) CH_2Cl_2 distilled over $CaCl_2$. [b]) DMSO dried over molecular sieves (4 Å). [c]) DMF dried over $CaSO_4$. [d]) n.d.: Not determined. [e]) MeCN distilled over CaH_2. [f]) Sulfolane (99%) was used without purification. [g]) 1-Methylpyrrolidin-2-one. [h]) Dimethylacetamide (99%) was used without purification.

Results and Discussion. – *First approach.* We first developed a strategy based on the well explored '*Mannich*' derivative tetrakis{*p*-[(dimethylamino)methyl]}calix[4]arene **3**, involved in many functionalizations at the upper rim of calixarene backbones, through conversion to the corresponding quaternary ammonium salt and replacement of the ammonium moiety with an appropriate nucleophile [9].

The calixarene **3** was thus prepared according to the procedure of *Gutsche* and *Nam* [10], by treatment of a THF/AcOH solution of **1**, 37% aqueous HCHO, and 40% aqueous Me_2NH at room temperature. Compound **3** was then treated with MeI in DMSO to give the quaternary ammonium salt **4**.

In first assays, **4** was not isolated and was reacted directly with 5 equiv. of $(EtO)_3P$ (*Entry 2* of the *Table*) to afford the expected product **6** in low yield (31%) after a laborious workup. The addition of H_2O, commonly employed as counter-solvent for DMSO solutions, did not give a precipitate. This solution, enriched in H_2O to retain DMSO, was finally extracted with CH_2Cl_2. The resulting yellow-brown organic solution was evaporated, and the raw material was chromatographed to give **6** as a yellow oil. This color that could result of the presence of iodine complexed with **6** disappeared partially, when the crude material was washed by aqueous $NaHSO_3$.

The same experiment was performed in dry DMF at 60° (*Entries 3* and *4*) during 7 or 4 h, with 5 or 20 equiv. of $(EtO)_3P$, respectively. Only the excess conditions gave the desired compound in 43% yield. Similar results were obtained in dry MeCN at reflux (*Entries 5* and *6*) with 5 and 20 equiv. of $(EtO)_3P$, respectively; the phosphonocalix[4]arene **6** was isolated with 32% under excess conditions. When the sulfolane (=2,3,4,5-tetrahydrothiophene 1,1-dioxide) was used as solvent (*Entries 7* and *8*), **6** was isolated in 37% yield, but only in the stoichiometric conditions. Most of experiments that provided **6** as an isolated compound, gave good TLC control plates, but unsatisfactory NMR analyses.

Gutsche and co-workers found that the isolation of the tetrakis(ammonium) salt **4** increase the flexibility of the next transformation processes [9]. For this purpose, **3** was treated with MeI for *ca.* 4 h, and the addition of an excess of acetone resulted in the precipitation of **4**, which was recovered by filtration.

The first phosphonation assays were carried out with **4** in sulfolane at 60 and 70° (*Entries 9* and *10*) with moderate excess of $(EtO)_3P$, or in 1-methylpyrrolidin-2-one with an excess of the latter (*Entry 11*). Here also, precipitation of **6** by addition of H_2O failed. The oily materials thus obtained were recovered by extraction with CH_2Cl_2, followed by a lyophilization from CH_2Cl_2/cyclohexane to remove $(EtO)_3P$ and pyrrolidinone (*Entry 11*), and by a final column chromatography that was, however, unable to remove residual traces of solvent from **6**.

Treating **4** by a moderate excess (10 equiv.) of $(EtO)_3P$ in *N,N'*-dimethylacetamide (*Entry 12*) gave interesting results. Evaporation of *N,N'*-dimethylacetamide, followed by lyophilization of the residue from CH_2Cl_2/cyclohexane, gave a raw material that was chromatographed (SiO_2) to give **6** in a yield of 57%. However, a similar procedure performed in dry DMF (*Entry 13*) gave much better results. Thus, the tetrakis(ammonium) salt **4** was treated in DMF by a moderate excess of $(EtO)_3P$ (10 equiv. with respect to **4**) at 70° during 6 h. Compound **6** was isolated as a solid material, in a yield of 81%, after evaporation of DMF, followed by lyophilization cycles from a cyclohexane suspension to remove residual $(EtO)_3P$, and by a final chromatography.

The choice of the couple DMF/**4** (*Entry 13*) gave the best results in this first approach, with a high yield of ester **6**. Nevertheless, the relatively difficult workup prompted us to search for an easier procedure.

Second Approach. Here, the tetrakis[*p*-(bromomethyl)]calixarene **5** was chosen as substrate of the phosphonation reaction. Contrary to its chloro analog **2**, this intermediate is easier to obtain and seems to be less unstable. According to the procedure of *Guo et al.* [11], **5** was prepared in high yield from calix[4]arene **1** by bubbling dry HBr gas in the presence of paraformaldehyde and glacial AcOH at room temperature, and was recovered by a very simple workup.

The first phosphonation assay was carried out in dry DMF with **5** and only 5 equiv. of $(EtO)_3P$, at 70° during 6 h (*Entry 14*). Contrary to the $ClCH_2$ analog **2** under the same conditions, this procedure resulted in the rapid and easy conversion of **5** to **6** in a yield of 75% after evaporation of DMF, rapid column chromatography, and crystallization from pentane.

With the aim of relieving the workup, in particular, the time-consuming and delicate high-vacuum evaporation of DMF, we performed the reaction in refluxing CH_2Cl_2, first with 5, then with 4 equiv. of $(EtO)_3P$, at reflux during 6 h (*Entries 15* and *16*, resp.).

It turned out that this new procedure, even with a stoichiometric amount of $(EtO)_3P$ (4 equiv.), provided very good results in terms of reaction yields (78 and 89%, resp.) and, more particularly, in the ease of product recovery. The tetrakis{*p*-[(diethylphosphono)methyl]}calix[4]arene **6** is obtained as a pure, white powder after evaporation of the solvent, and a simple crystallization of the raw material from pentane.

The compound **6** thus obtained was fully characterized, and gave satisfactory NMR and electrospray (ESI) MS data, and elemental analyses. According to *de Mendoza* and co-workers [12][13], who have shown that the resonance of the CH_2 bridge C-atom is near to 31 ppm, when the attached phenol groups are in the *syn*-orientation, and near 37 ppm, when they are in *anti*-orientation, we found that the cone conformation of the calixarene subunit was conserved, as assessed by ^{13}C-NMR resonance signals of Ar–CH_2–Ar, observed between 31 and 33 ppm. An analytically pure sample of **6** was obtained by chromatography (SiO_2; CH_2Cl_2/MeOH 97:3).

Conclusions. – In conclusion, we have developed two new, high-yield synthetic pathways leading to the tetrakis{*p*-[(diethylphosphono)methyl]}calix[4]arene **6**. Various aprotic solvents and stoichiometric conditions have been evaluated for an easiest introduction of the diethylphosphono group in active tetrakis{*p*-[(X)methyl]}calix[4]arene species, in which X is a halogen (Cl, Br), or a quaternary ammonium used pure or generated *in situ*. For ammonium derivative, the results were satisfactory only when used pure, in DMF; for halogeno derivatives, we found that the bromide was the best candidate, first, due to its easy preparation, and second, for its excellent reactivity with *ca.* stoechiometric amounts of $(EtO)_3P$, in DMF or in CH_2Cl_2. The more convenient procedure involved CH_2Cl_2 as solvent and 4 equiv. of $(EtO)_3P$, to give the tetrakis-phosphono ester in 89% yield with a very simple workup.

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Experimental Part

General. All commercially available products were used without further purification unless otherwise specified. Chloromethyl, (dimethylamino)methyl, and (trimethylamino)methyl iodide derivatives **2** [4], **3** [9], **4** [10], resp., and bromomethyl derivative **5** [11] were synthesized as described in the literature. M.p.: *Electrothermal 9200* in capillary apparatus; uncorrected. TLC: *Merck* plates (SiO_2, ref *1.05554*; Al_2O_3, ref *1.05581*). UV Spectra: *SAFAS UV mc*^{2} apparatus, λ_{max} in nm, ε in mol^{-1} dm^3 cm^{-1}. IR Spectra: *Bruker Vector 22* apparatus (KBr, ν in cm^{-1}). ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX 400* (chemical shifts in ppm). MS (electronic ionisation (EI), and electrospray (ESI)): *Micromass Platform II* apparatus, at the Service Commun de Spectrométrie de Masse Organique, Nancy. Elemental analyses: performed at the Service de Microanalyse, Nancy.

Syntheses. 5,11,17,23-Tetrakis[(diethylphosphono)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (=Octaethyl {[25,26,27,28-Tetrahydroxypentacyclo[19.3.1.1^{3,7}*.1*^{9,13}*.1*^{15,19}*]octacosa-1(25),3(28),4,6,9(27),10,12,15(26),16,18,21,23-dodecaene-5,11,17,23-tetrayl]tetramethanediyl}tetrakis(phosphonate)*; **6**): *from 5,11,17,23-tetra(chloromethyl)-25,26,27,28-tetrahydroxycalix[4]arene (=5,11,17,23-tetrakis(chloromethyl)pentacyclo[19.3.1.1*^{3,7}*.1*^{9,13}*.1*^{15,19}*]octacosa-1(25),3(28),4,6,9(27),10,12,15(26),16,18,21,23-dodecaene-25,26,27,28-tetrol*; **2**). A mixture of **2** (1 g, $1.62 \cdot 10^{-3}$ mol) and $(EtO)_3P$ (11 ml, $64.0 \cdot 10^{-3}$ mol, 40 equiv.) in CH_2Cl_2 (15 ml) was refluxed during 6 h under Ar. The solvent was evaporated, and the residue was concentrated under high vacuum at 50° to remove most of residual phosphite. The resulting oily material was lyophilized from a cyclohexane suspension to remove residual $(EtO)_3P$ (^{1}H-NMR control; 2 or 3 times). The residue was chromatographed (SiO_2; CH_2Cl_2/MeOH 97:3) to give **6** (1.34 g, 85%; pure on the basis of TLC and ^{1}H-NMR analysis).

From 5,11,17,23-Tetrakis[(dimethylamino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (=5,11,17,23-Tetrakis[(dimethylamino)methyl]pentacyclo[19.3.1.1^{3,7}*.1*^{9,13}*.1*^{15,19}*]octacosa-1(25),3(28),4,6,9(27),10,12,15(26),16,18,21,23-dodecaene-25,26,27,28-tetrol*; **3**). To a soln. of **3** (0.2 g, $0.31 \cdot 10^{-3}$ mol) in anh.

DMF (5 ml) was added MeI (0.10 ml, $1.53 \cdot 10^{-3}$ mol). The mixture was stirred at r.t. during 30 min. $(EtO)_3P$ (1.05 ml, $6.13 \cdot 10^{-3}$ mol, 20 equiv.) was added, and the soln. was heated at 60° during 4 h. After cooling to r.t., DMF was evaporated under high vacuum. The crude material was dissolved in CH_2Cl_2 (50 ml), then washed with H_2O (50 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2; CH_2Cl_2/MeOH 97:3) to give **6** (0.14 g, 43%; pure on the basis of TLC and ^{1}H-NMR analysis).

From 25,26,27,28-Tetrahydroxy-5,11,17,23-tetrakis[(trimethylamino)methyl]calix[4]arene tetraiodide (= [25,26,27,28-Tetrahydroxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3(28),4,6,9(27),10,12,15(26), 16,18,21,23-dodecaene-5,11,17,23-tetrayl]tetrakis(N,N,N-trimethylmethanaminium) Tetraiodide; **4**). To a soln. of **4** (4.77 g, $3.91 \cdot 10^{-3}$ mol) in anh. DMF (45 ml) was added $(EtO)_3P$ (6.7 ml, $39.11 \cdot 10^{-3}$ mol, 10 equiv.); the mixture was heated at 70° under Ar during 6 h. After cooling, DMF was evaporated under high vacuum, and the residue was lyophilized from a cyclohexane suspension, then chromatographed (SiO_2; CH_2Cl_2/MeOH 97:3) to give **6** (3.21g, 81%; pure on the basis of TLC and ^{1}H-NMR analysis).

From 5,11,17,23-Tetrakis(bromomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (= 5,11,17,23-Tetrakis(bromomethyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3(28),4,6,9(27),10,12,15(26),16,18, 21,23-dodecaene-25,26,27,28-tetrol; **5**). To a soln. of **5** (0.15 g, $0.19 \cdot 10^{-3}$ mol) in CH_2Cl_2 (5 ml) was added $(EtO)_3P$ (0.13 ml, $0.75 \cdot 10^{-3}$ mol, 4 equiv.); the mixture was refluxed during 6 h. After cooling to r.t., the solvent was evaporated, and the residue was dried under vacuum to give an oil. An excess of pentane (50 ml) was then added, and the oily material was triturated and sonicated. After 24 h, the resulting solid that was formed was filtered off, washed with pentane, and dried under vacuum to give **6** (0.17 g, 89%). White solid. M.p.: 139 – 140°. ^{1}H NMR (400 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.1, 8 *Me*CH$_2$O); 2.89 (*d*, *J* = 21.2, 4 C*H*$_2$P); 3.48 – 4.18 (br. '*q*', *AB*, J_{AB} = 13.4, 4 ArC*H*$_2$Ar); 3.79 (*m*, 8 MeC*H*$_2$O); 6.96 (*d*, *J* = 1.5, 8 arom. H); 10.04 (*s*, 4 OH). ^{13}C NMR (100 MHz, $CDCl_3$): 16.8 (*d*, *J* = 5.9, *Me*CH$_2$O); 32.0 (ArCH$_2$Ar); 33.1 (*d*, *J* = 138.4, CH$_2$P); 65.5 (*d*, *J* = 16.6, MeCH$_2$O); 125.4 (*d*, *J* = 8.8, C_p); 128.6 (*d*, *J* = 2.9, C_o); 130.7 (*d*, *J* = 6.6, C_m); 148.2 (*d*, *J* = 3.7, C_{ipso}). ES-MS (pos.): 1047.33 ($[M + Na]^+$), 1025.35 ($[M + H]^+$), 997.32 ($[M - Et + 2\,H]^+$), 969.28 ($[M - 2\,Et + 3\,H]^+$), 941.26 ($[M - 3\,Et + 4\,H]^+$), 913.23 ($[M - 4\,Et + 5\,H]^+$). ES-MS (neg.): 1023.34 ($[M - H]^-$), 885.29 ($[M - (PO(OEt)_2) - 2\,H]^-$), 857.24 ($[M - (PO(OEt)_2) - Et - H]^-$), 811.18 ($[M - (PO(OEt)_2) - Et - EtO - 2\,H]^-$), 783.13 ($[M - (PO(OEt)_2) - 2\,Et - EtO - H]^-$), 747.25 ($[M - 2\,(PO(OEt)_2) - 3\,H]^-$), 719.19 ($[M - 2\,(PO(OEt)_2) - Et - 2\,H]^-$), 673.17 ($[M - 2\,(PO(OEt)_2) - Et - EtO - 3\,H]^-$). Anal calc. for $C_{48}H_{68}O_{16}P_4$ (1024.94): C 56.25, H 6.69; found: C 56.30, H 6.54.

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