Diethoxyphosphoryl as a Protecting-Activating Group in the Synthesis of Polyazacyclophanes

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The fully diethoxyphosphoryl(Dep)-protected polyamines **1b**–**3b** were prepared from the corresponding polyamines with 'diethyl phosphite' (=diethyl phosphonate) and CCl_4 in a solid base/organic liquid two-phase system in the presence of Bu_4NBr as phase-transfer catalyst. Subsequent phase-transfer-catalyzed alkylation of phosphoramidates **1b**–**3b** with bis(chloromethyl)arenes **5**–**8** in the presence of $Bu_4N(HSO_4)$ followed by deprotection gave good yields of polyazacyclophanes **9a**–**16a**.

Introduction. – Polyazacyclophanes represent one of the most useful macrocyclic multidentate compounds for a variety of applications ranging from molecular recognition (host molecules for inclusion of neutral organic molecules) to coordination chemistry [1]. Furthermore, the reasons for the interest in polyazacyclophanes are twofold: *i*) to modulate lipophilicity and to modify biodistribution of metal-complex-based drugs, *ii*) to create molecules exhibiting new photophysical and photochemical properties (*i.e.*, the presence of a suitable chromophore is required in luminescent lanthanide complexes) [2]. Many cyclization methods have been developed to synthesize azamacrocycles under excellent control of the formed ring size, while minimizing the extent of competing side reactions (*i.e.*, linear oligomer formation and reagent decomposition). The most efficient ring construction is based on the ring closure involving the formation of two C–N bonds by reaction of α,ω-bis(electrophiles) and the dianion formed from a suitably protected α,ω-diamine (*Richman-Atkins* procedure) [3][4]. *p*-Toluenesulfonamides have been used more frequently than any other protective groups (PGs) for primary amines, because of the powerful electron-withdrawing effect of the sulfonyl group, their ease of formation, and their stability under a wide range of reaction conditions. Their removal is accomplished by many different procedures, such as by refluxing in strong acids (H_2SO_4 or HBr), by sodium naphthalenide, lithium aluminum hydride, or *Red-Al*®, by dissolving-metal methods, as well as by photochemical and electrochemical cleavage [5]. Recently, new cleavage methods have been developed, which include the reagents SmI_2 [6], Mg in

MeOH [7], Bu_4NF [8], and Me_3SiI [9]. Furthermore, many other PGs (*e.g.*, nosylamides [9], 2,4-dinitrobenzenesulfonamides [10], naphthalene-2-sulfonamides [11], *tert*-butylsulfonamides [12], trifluoroacetamides, carbamates) have already been proposed for the protection of primary amines, keeping in view the sensitivity of the molecule towards the acidic or basic conditions. All these PGs suffer from one or more disadvantages, such as operationally difficult reaction conditions, long reaction times, expensive precursors, low yields, or contamination of the final product with hardly separable impurities.

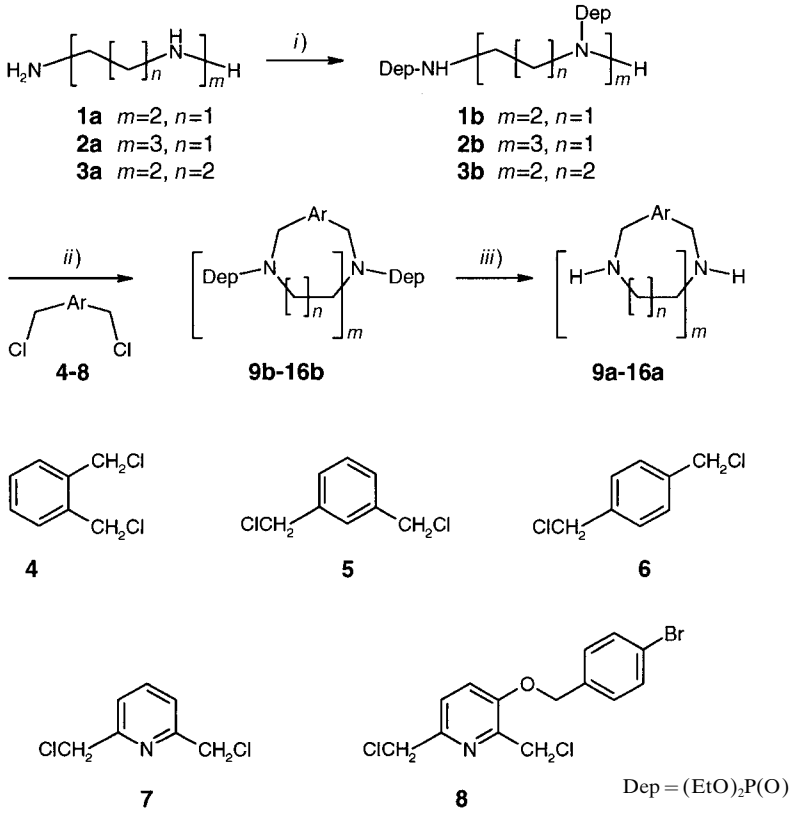
In connection with our project designed to prepare new contrast agents with enhanced relaxivity aimed at magnetic-resonance imaging (MRI), we synthesized a series of azamacrocycles. Some of these have previously been prepared by the *Richman-Atkins* method applied to the nosylamides [9] or tosylamides [1b][13]. While good yields were reported, the reaction conditions were not favorable for an application of the method to prepare other azacyclophanes embodying different subunits. On this background, it appears that diethyl phosphoramidates of primary amines would provide an interesting alternative to the arenesulfonamides in terms of the planned alkylation-deprotection strategy for the synthesis of polyazacyclophanes. If successful, advantages would arise from the easy removal of this PG.

Results. – The required fully diethoxyphosphoryl(Dep)-protected polyamines **1b**–**3b** were efficiently prepared by reacting the corresponding polyamines **1a**–**3a** with diethyl phosphite (=diethyl phosphonate)/CCl_4 in a solid base/organic liquid two-phase system (mixture of solid K_2CO_3 and $NaHCO_3/CH_2Cl_2$) in the presence of Bu_4NBr as phase-transfer catalyst at room temperature (*Scheme*). This procedure (*Atherton-Openshaw-Todd* reaction [14]) was found to be far superior to the use of diethyl phosphorochloridate $(EtO)_2POCl$ in pyridine as phosphorylating agent.

Although phosphoramidates have been alkylated in a number of cases [15], a single report deals with the use of this PG during the synthesis of multidentate macrocyclic compounds [16]. These successful syntheses by *Mertes* and co-workers [16] have relied on the use of NaH in DMSO as base; however, in our cases, we were unable to force the reaction to completion under the reported conditions and variations thereof; messy reactions were uniformly observed. Thus, alternative conditions for macrocyclization involving phosphoramidates under phase-transfer conditions had to be found.

In principle, the success of the alkylation of **1b**–**3b** mainly depends on the efficient generation of anions and their presence in the organic phase to undergo the subsequent reaction with the bis(chloromethyl) derivatives **5**–**8**. Thus, we investigated the effect of different phase-transfer catalysts, bases, and phase systems on the reaction. Tetrabutylphosphonium bromide (Bu_4PBr) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) did not catalyze the reaction at all, while tetrabutylammonium hydrogen sulfate ($Bu_4N(HSO_4)$) was superior to triethyl(benzyl)ammonium chloride and *Aliquat*®-*336*. For example, in the liquid-liquid two-phase system, aqueous NaOH solution/toluene, **2b** reacted with **7** under reflux for 4 h in the presence of $Bu_4N(HSO_4)$ (10 mol-%), providing the Dep-protected cyclophane **16b** in modest to excellent isolated yield. Variations in the concentration of NaOH significantly affected the yield of the procedure. The reaction proceeded most satisfactorily (80%) with a 50% aqueous

Scheme



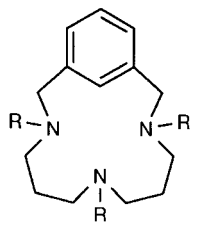
i) $(EtO)_2P(O)H$, CCl_4, $NaHCO_3$, Bu_4NBr, r.t. *ii*) 50% NaOH/PhMe, $Bu_4N(HSO_4)$. *iii*) $HCl_{(g)}$ in dioxane, r.t., then NaOH.

solution (see *Table 1*), whereas the yields fell to only 25% when a 30% aqueous solution was employed. Different phase systems (*e.g.*, liquid/liquid or solid/liquid) and different bases did not much influence the results. When the same reaction was

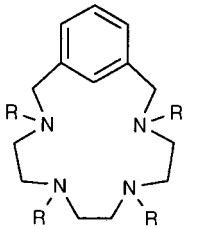
Table 1. *Yields of the Macrocyclization of* **1b**–**3b** *with* **5**–**8** *in the Two-Phase System 50% Aqueous NaOH Solution/Toluene in the Presence of* $Bu_4N(HSO_4)$

$(Dep)_{m+1}$-Polyamine	*m*, *n*	α,ω-Dihalide	$(Dep)_{m+1}$-Cyclophane	Yield [%][a])
3b	2, 2	**5**	**9**	78 (–)
2b	3, 1	**5**	**10b**	73 (–)
2b	3, 1	**6**	**11b**	52 (77) [1b]
3b	2, 2	**6**	**12b**	56 (74) [1b]
1b	2, 1	**7**	**13b**	82 (70) [19]
1b	2, 1	**8**	**14b**	79 (85) [19]
3b	2, 2	**7**	**15b**	68 (–)
2b	3, 1	**7**	**16b**	80 (63) [19]

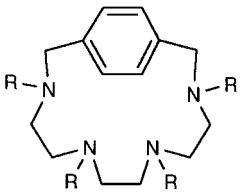
[a]) In parentheses, reported yields for cyclizations employing PGs other than Dep.



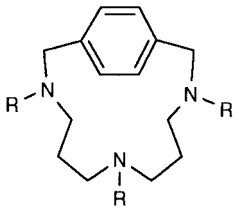
9a R = H
b R = $(EtO)_2P(O)$



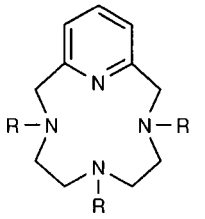
10a R = H
b R = $(EtO)_2P(O)$



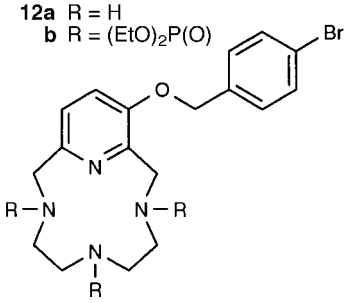
11a R = H
b R = $(EtO)_2P(O)$



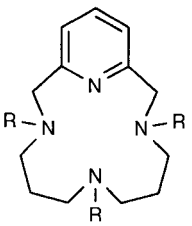
12a R = H
b R = $(EtO)_2P(O)$



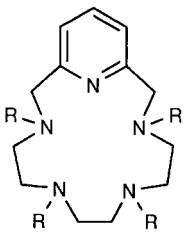
13a R = H
b R = $(EtO)_2P(O)$



14a R = H
b R = $(EtO)_2P(O)$



15a R = H
b R = $(EtO)_2P(O)$



16a R = H
b R = $(EtO)_2P(O)$

conducted in the absence of a phase-transfer catalyst, the starting reagents were recovered unconverted.

We have explored the scope of this phase-transfer-catalyzed reaction and established that for the fully Dep-protected amines **1b**–**3b** and bis(chloromethyl) derivatives **5**–**8** the alkylation proceeded uneventfully, yielding **9b**–**16b** (see *Table 1*). The failure to obtain the corresponding cyclophane with **4** illustrates the practical limit of chemical stability that can be accommodated in this reaction. Moreover, the

efficiency of the phase-transfer catalyst allowed the use of a solvent (toluene) of lower polarity than DMSO, which simplified the workup procedure substantially.

Finally, removal of the Dep groups could be easily accomplished by stirring the crude protected macrocycles **9b**–**16b** in 1,4-dioxane saturated with gaseous HCl [17] at room temperature for 12–24 h. The corresponding hydrochlorides of **9a**–**16a** precipitated from the reaction mixtures and were recovered by filtration. Neutralization, basification, and extraction with CH_2Cl_2 gave the expected free bases **9a**–**16a** in excellent yields (*Table 2*).

Table 2. *Yields of the Deprotection of the Dep-Cyclophanes*

$(Dep)_{m+1}$-Cyclophane	**9b**	**10b**	**11b**	**12b**	**13b**	**14b**	**15b**	**16b**
Cyclophane	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**
Yield [%][a])	92 (–)	90 (–)	87 (53) [1b]	78 (43 [1b]	75 (67) [19]	95 (80) [20]	90 (–)	86 (78) [19]

[a]) In parentheses, reported yields for procedures employing PGs other than Dep.

Conclusion. – Phase-transfer-catalyzed alkylation of phosphoramidates **1b**–**3b** and subsequent deprotection give good yields of polyazacyclophanes **9a**–**16a** that are comparable to or slightly higher than those obtained in the alkylation of sulfonamides. Furthermore, the solubility of the Dep-protected polyamines **1b**–**3b** in a wide range of solvents, excellent product recovery, as well as the easy deprotection after the alkylation step extend their potential synthetic usefulness as valuable intermediates in the synthesis of polyazacyclophanes.

Experimental Part

1. *General*. All amines and phase-transfer catalysts, 'diethyl phosphite' (=diethyl phosphonate), CCl_4 (*Caution*!; when working with CCl_4, the use of standard safety precautions is strongly recommended [18]) were purchased from *Aldrich* and used without purification. Anal. TLC: silica gel *60F$_{254}$* (*Macherey-Nagel*); detection by spraying with alkaline $KMnO_4$ soln., followed by heating to 120°. M.p.: uncorrected; *Büchi-510* apparatus. IR Spectra: *Perkin-Elmer-1420* spectrophotometer; film, unless stated otherwise; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: at 200 and 50.3 MHz, resp.; *Bruker-AC200* spectrometer; $CDCl_3$ soln., unless stated otherwise, chemical shifts δ in ppm downfield from internal $SiMe_4$ (=0.00 ppm; J in Hz). Mass spectra: Cl mode (isobutane); *VG7070EQ* spectrometer. Elemental analyses were carried out on a *Perkin Elmer 240* instrument.

2. *Dep-Polyamines: General Procedure.* To a soln. of polyamine **1a**–**3a** (20 mmol) and CCl_4 (200 mmol; *Caution*!) in CH_2Cl_2 (50 ml), anh. K_2CO_3 (100 mmol for **1a** and **3a**; 120 mmol for **2a**), $NaHCO_3$ (100 mmol for **1a** and **3a**; 120 mmol for **2a**) and Bu_4NBr (2 mmol) are sequentially added. 'Diethyl phosphite' (=diethyl phosphonate; 65 mmol for **1a** and **3a**; 85 mmol for **2a**) is slowly added to the vigorously stirred suspension. The temp. of the mixture (exothermic reaction) is kept at 0–5° by ice-bath cooling. After the addition, the mixture is allowed to reach r.t. and stirred overnight. H_2O (100 ml) is added to the suspension and the mixture stirred until the inorg. salts are completely dissolved. The aq. phase is extracted with CH_2Cl_2 (2 × 10 ml) and the combined org. phase washed with 1M HCl (2 × 20 ml), 10% K_2CO_3 (20 ml), and H_2O (20 ml), dried (Na_2SO_4), and evaporated. Compound **2b** solidifies quickly and is crystallized from diisopropyl ether; pure **1b** and **3b** are obtained as colorless oils after prolonged standing under vacuum to eliminate residual traces of diethyl phosphite.

3. *Cyclization: General Procedure.* Dep-Polyamine **1b**–**3b** (3 mmol), bis(chloromethyl)arene **5**–**8** (3 mmol) and $Bu_4N(HSO_4)$ (0.3 mmol) are dissolved in toluene (10 ml). Aq. 50% NaOH soln. (10 ml) is added, and the vigorously stirred soln. is refluxed for 2–8 h, until TLC (CH_2Cl_2/MeOH 9:1) shows complete disappearance of the starting materials. The two-phase system is then cooled, diluted with H_2O (50 ml) and thoroughly extracted with CH_2Cl_2 (4 × 15 ml). The collected org. extracts are dried (Na_2SO_4), filtered, and

evaporated. The semisolid residue is crystallized from iPr_2O/hexane or submitted to flash chromatography (CH_2Cl_2/MeOH 95:5): pure **9b**–**16b**.

4. *Dep Deprotection: General Procedure.* Dep-polyazacyclophane **9b**–**16b** (1 mmol) is dissolved in dioxane saturated with gaseous HCl (10 ml), the resulting soln. is stirred overnight at r.t. Polyazacyclophane hydrochlorides precipitate, either spontaneously or after addition of Et_2O, and are isolated by filtration and washed with Et_2O. The free polyazacyclophanes are obtained by partitioning the hydrochlorides between 6M NaOH and CH_2Cl_2. The org. extracts are dried (Na_2SO_4/K_2CO_3) and evaporated: pure **9a**–**16a**.

5. *Data. 1,4,7-Tris(diethoxyphosphoryl)-1,4,7-triazaheptane* (= *Diethyl Bis[2-[(diethoxyphosphoryl)amino]ethyl]phosphoramidate*; **1b**). Colorless viscous oil. IR: 3435, 3246, 2981, 2936, 2907, 2874, 1641, 1445, 1234, 1029, 967, 798. ^{1}H-NMR: 3.85–4.06 (*m*, 12 H); 3.43 (*m*, 2 H); 2.98 (*m*, 8 H); 1.61 (*t*, *J* = 6.6, 4 H); 1.24 (*t*, *J* = 7.04, 18 H). ^{13}C-NMR: 62.2 (*J*(C,P) = 5.6, C); 42.2 (CH_2); 38.1 (CH_2); 29.7 (CH_2); 16.1 (*J*(C,P) = 6.4, CH_2). MS: 512 (MH^+). Anal. calc. for $C_{16}H_{40}N_3O_9P_3$ (511.42): C 37.58, H 7.88, N 8.22; found: C 37.45, H 8.01, N 8.20.

1,4,7,10-Tetrakis(diethoxyphosphoryl)-1,4,7,10-tetraazadecane (= *Tetraethyl* N,N′-*Ethan-1,2-diylbis([2-[(diethoxyphosphoryl)amino]ethyl]phosphoramidate)*; **2b**): White solid. M.p. 77° (i-Pr_2O). ^{1}H-NMR: 3.91–4.05 (*m*, 16 H); 3.30 (*m*, 2 H); 3.01–3.12 (*m*, 12 H); 1.27 (*t*, 24 H). ^{13}C-NMR: 62.5 (*d*, *J*(C,P) = 5.3, Me); 62.2 (*d*, CH_2); 47.7 (CH_2); 45.3 (CH_2); 39.9 (CH_2); 16.1 (*d*, *J*(C,P) = 5.3, Me). MS: 691 (MH^+). Anal. calc. for $C_{22}H_{54}N_4O_{12}P_4$ (690.58): C 38.26, H 7.88, N 8.11; found: C 38.07, H 8.01, N 8.09.

1,5,9-Tris(diethoxyphosphoryl)-1,5,9-triazanonane (= *Diethyl Bis[3-[(diethoxyphosphoryl)amino]propyl]-phosphoramidate*; **3b**): Colorless viscous oil. IR: 3435, 3246, 2982, 2937, 2907, 2874, 1641, 1446, 1393, 1234, 1029, 967, 798. ^{1}H-NMR: 3.96 (*m*, 12 H); 3.43 (*m*, 2 H); 2.98 (*m*, 8 H); 1.61 (*t*, 4 H, *J* = 6.6); 1.24 (*t*, *J* = 7.0, 18 H). ^{13}C-NMR: 62.2 (*J*(C,P) = 5.6, CH_2); 62.0 (*J*(C,P) = 5.2, CH_2); 42.2 (CH_2); 38.1 (CH_2); 29.8 (CH_2); 16.1 (*J*(C,P) = 6.4, CH_2). MS: 540 (MH^+). Anal. calc. for $C_{18}H_{44}N_3O_9P_3$ (539.48): C 40.08, H 8.22, N 7.79; found: C 39.99, H 8.37, N 7.82.

3,7,11-Tris(diethoxyphosphoryl)-3,7,11-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**9b**): Colorless oil. IR: 3468, 2981, 2932, 1636, 1446, 1392, 1367, 1240, 1029, 964, 801. ^{1}H-NMR: 7.40 (*s*, 1 H); 7.26 (*s*, 3 H); 4.17 (*d*, *J*(C,P) = 8.2, 4 H); 4.05 (*m*, 8 H); 3.83 (*m*, 4 H); 2.92 (*dt*, *J* = 10.4, 7.1, 4 H); 2.69 (*dt*, *J* = 10.4, 7.8, 4 H); 1.34 (*quint.*, *J* = 7.2, 4 H); 1.31 (*t*, *J* = 7.1, 12 H); 1.17 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 139.2 (*J*(C,P) = 5.0, C); 129.2 (CH); 128.9 (CH); 127.9 (CH); 62.2 (*d*, *J*(C,P) = 5.4, CH_2); 61.7 (*d*, *J*(C,P) = 5.4, CH_2); 52.2 (CH_2); 45.7 (CH_2); 44.1 (CH_2); 27.9 (CH_2); 16.1 (*d*, *J*(C,P) = 6.7, Me); 15.9 (*d*, *J*(C,P) = 6.7, Me). MS: 642 (MH^+). Anal. calc. for $C_{26}H_{50}N_3O_9P_3$ (641.61): C 48.67, H 7.85, N 6.55; found: C 48.61, H 8.02, N 6.50.

3,6,9,12-Tetrakis(diethoxyphosphoryl)-3,6,9,12-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-triene (**10b**): Thick colorless oil. IR: 3468, 2983, 2933, 2907, 1660, 1462, 1364, 1240, 1029, 962, 795. ^{1}H-NMR: 7.38 (*s*, 3 H); 7.05 (*s*, 1 H); 4.20 (*d*, *J* = 8.2, 4 H); 4.14–3.82 (*m*, 16 H); 2.85 (*m*, 8 H); 2.65 (*m*, 4 H); 1.31 (*t*, 6 H); 1.22 (*t*, 6 H). ^{13}C-NMR: 137.8 (*d*, *J*(C,P) = 4.7, C); 129.7 (CH); 129.2 (CH); 128.1 (CH); 62.5 (*J*(C,P) = 5.7, CH_2); 62.2 (*J*(C,P) = 5.6, CH_2); 50.6 (*J*(C,P) = 4.4, CH_2); 45.9 (CH_2); 44.8 (CH_2); 43.7 (CH_2); 16.1 (*J*(C,P) = 5.7, Me); 16.0 (*J*(C,P) = 5.6, Me). MS: 793 (MH^+). Anal. calc. for $C_{30}H_{60}N_4O_{12}P_4$ (792.72): C 45.45, H 7.63, N 7.07; found: C 45.31, H 7.70, N 6.98.

3,6,9,12-Tetrakis(diethoxyphosphoryl)-3,6,9,12-tetraazabicyclo[12.2.2]octadeca-14,16,17-triene (**11b**): Colorless wax. IR: 3468, 2982, 1664, 1450, 1362, 1244, 1028, 964, 800. ^{1}H-NMR: 7.27 (*s*, 4 H); 4.09 (*d*, *J* = 6.07, 4 H); 3.94–4.08 (*m*, 8 H); 3.72–3.94 (*m*, 8 H); 2.82 (*m*, 4 H); 2.52 (*m*, 4 H); 2.34 (*m*, 4 H); 1.25 (*t*, *J* = 7.05, 12 H); 1.14 (*t*, *J* = 6.07, 12 H). ^{13}C-NMR: 137.5 (*J*(C,P) = 6.8, C); 129.3 (CH); 62.5 (*J*(C,P) = 5.5, CH_2); 62.2 (*J*(C,P) = 5.4, CH_2); 52.3 (*J*(C,P) = 4.4, CH_2); 45.8 (CH_2); 45.1 (CH_2); 44.7 (*J*(C,P) = 4.36, CH_2); 16.1 (*J*(C,P) = 7.1, Me); 15.9 (*J*(C,P) = 7.1, Me). MS: 793 (MH^+). Anal. calc. for $C_{30}H_{60}N_4O_{12}P_4$ (792.72): C 45.45, H 7.63, N 7.07; found: C 45.24, H 7.72, N 6.95.

3,7,11-Tris(diethoxyphosphoryl)-3,7,11-triazabicyclo[11.2.2]heptadeca-13,15,16-triene (**12b**): Colorless wax. IR: 3468, 2982, 2933, 2907, 1646, 1446, 1392, 1367, 1240, 1167, 1029, 965. 800. ^{1}H-NMR: 7.36 (*s*, 4 H); 4.15–3.73 (*m*, 6 H); 2.85 (*m*, 4 H); 2.39 (*m*, 6 H); 1.31 (*t*, *J* = 7.0, 12 H); 1.18 (*t*, *J* = 7.0, 6 H); 0.96 (*m*, 4 H). ^{13}C-NMR: 139.3 (*J*(C,P) = 5.5, C); 129.7 (CH); 62.3 (*J*(C,P) = 5.2, CH_2); 61.8 (*J*(C,P) = 4.6, CH_2); 53.4 (CH_2); 46.2 (CH_2); 44.2 (CH_2); 29.7 (CH_2); 16.1 (*J*(C,P) = 5.7, Me); 16.0 (*J*(C,P) = 5.5, Me). MS: 642 (MH^+). Anal. calc. for $C_{26}H_{50}N_3O_9P_3$ (641.61): C 48.67, H 7.85, N 6.55; found: C 48.51, H 8.00, N 6.46.

3,6,9-Tris(diethoxyphosphoryl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**13b**): Colorless oil. ^{1}H-NMR: 7.62 (*t*, *J* = 7.6, 1 H); 7.21 (*d*, *J* = 7.6, 2 H); 4.23 (*d*, 4 H); 3.71–3.97 (*m*, 12 H); 2.82 (*m*, 8 H); 1.14 (*m*, 12 H). ^{13}C-NMR: 156.2 (*d*, *J*(C,P) = 4.8); 138.3 (CH); 122.9 (CH); 62.1 (*d*, *J*(C,P) = 4.7, CH_2); 61.9 (*d*, *J*(C,P) = 5.3, CH_2); 52.8 (CH_2); 43.3 (CH_2); 42.1 (CH_2); 15.9 (*d*, *J*(C,P) = 5.4, Me). MS: 615 (MH^+). Anal. calc. for $C_{23}H_{45}N_4O_9P_3$ (614.55): C 44.95, H 7.38, N 9.12; found: C 44.95, H 7.50, N 9.09.

12-[(4-Bromobenzyl)oxy]-3,6,9-tris(diethoxyphosphoryl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**14b**): Light yellow oil. ^{1}H-NMR: 7.49 (*d*, *J* = 8.4, 2 H); 7.35 (*d*, *J* = 8.4, 2 H); 7.30 (*d*, *J* = 8.4, 1 H); 7.21 (*d*, *J* = 8.4, 1 H); 5.07 (*s*, 2 H); 4.54 (*d*, *J* = 5.6, 2 H); 4.29 (*d*, *J* = 7.8, 2 H); 3.86–4.05 (*m*, 12 H); 2.94–3.15 (*m*, 8 H); 1.16–1.33 (*m*, 12 H). ^{13}C-NMR: 152.6 (C); 148.2 (*d*, *J*(C,P) = 4.5, C); 145.0 (*d*, *J*(C,P) = 7.7, C); 134.7 (C); 131.7 (CH); 128.7 (CH); 124.3 (CH); 122.0 (C); 120.3 (CH); 69.4 (CH_2); 62.1–62.3 (3 CH_2); 52.6 (*d*, *J*(C,P) = 4.6, CH_2); 48.1 (*d*, *J*(C,P) = 4.6, CH_2); 43.9 (CH_2); 42.8 (2*s*, CH_2); 41.9 (CH_2); 15.9–16.1 (3*s*, Me). MS: 799, 801 (MH^+). Anal. calc. for $C_{30}H_{50}BrN_4O_{10}P_3$ (779.57): C 45.07, H 6.30, N 7.01; found: C 44.89, H 6.31, N 6.95.

3,7,11-Tris(diethoxyphosphoryl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**15b**): Colorless viscous oil. IR: 3469, 2981, 2932, 1642, 1576, 1456, 1392, 1368, 1245, 1029, 964, 800. ^{1}H-NMR: 7.60 (*t*, *J* = 7.6, 1 H); 7.35 (*d*, *J* = 7.6, 3 H); 4.24 (*d*, *J* = 9.9, 4 H); 3.99 (*m*, 8 H); 3.80 (*m*, 4 H); 2.91 (*m*, 4 H); 2.73 (*dt*, *J* = 10.2, 7.6, 4 H); 1.44 (*quint.*, *J* = 7.3, 2 H); 1.24 (*t*, *J* = 7.1, 12 H); 1.14 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR: 158.1 (C); 137.2 (CH); 122.4 (CH); 62.1 (*d*, *J*(C,P) = 5.3, CH_2); 61.7 (*d*, *J*(C,P) = 5.3, CH_2); 53.5 (*d*, *J*(C,P) = 4.4, CH_2); 45.7 (CH_2); 45.3 (CH_2); 28.3 (CH_2); 15.9 (*d*, *J*(C,P) = 6.7, Me). MS: 643 (MH^+). Anal. calc. for $C_{25}H_{49}N_4O_9P_3$ (642.60): C 46.73, H 7.69, N 8.72; found: C 46.55, H 7.89, N 8.62.

3,6,9,12-Tetrakis(diethoxyphosphoryl)-3,6,9,12,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-triene (**16b**): Colorless crystals. M.p. 87° (i-Pr_2O). ^{1}H-NMR: 7.74 (*t*, *J* = 7.7, 1 H); 7.47 (*d*, *J* = 7.7, 2 H); 4.38 (*d*, *J* = 10.4, 4 H); 4.04 (*m*, 16 H); 3.01 (*m*, 8 H); 2.85 (*m*, 4 H); 1.35 (*m*, 6 H); 1.29 (*d*, *J* = 7.1, 6 H). ^{13}C-NMR: 157.5 (C); 137.6 (CH); 122.3 (CH); 62.5 (*d*, *J*(C,P) = 19.8, CH_2); 62.3 (*d*, *J*(C,P) = 19.4, CH_2); 52.1 (CH_2); 45.9 (CH_2); 44.5 (CH_2); 43.7 (CH_2); 16.1–15.9 (2 Me). MS: 794 (MH^+). Anal. calc. for $C_{29}H_{59}N_5O_{12}P_4$ (793.70): C 43.88, H 7.49, N 8.82; found: C 43.74, H 7.57, N 8.82.

3,7,11-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**9a**): Colorless wax. ^{1}H-NMR: 7.71 (*s*, 1 H); 7.23 (*t*, *J* = 7.0, 2 H); 7.05 (*d*, *J* = 7.0, 1 H); 3.89 (*s*, 4 H); 2.78 (*t*, *J* = 5.6, 4 H); 2.54 (*t*, *J* = 5.9, 4 H); 1.71 (*quint.*, *J* = 5.7, 4 H); 1.60 (br. *s*, exch. with D_2O, 3 H). ^{13}C-NMR: 140.3 (C); 127.9 (CH); 126.8 (CH); 124.3 (CH); 52.7 (CH_2); 46.3 (CH_2); 43.9 (CH_2); 28.9 (CH_2). MS: 234 (MH^+). Anal. calc. for $C_{14}H_{23}N_3$ (233.36): C 72.06, H 9.93, N 18.01; found: C 71.93, H 10.15, N 18.00.

3,6,9,12-Tetraazabicyclo[12.3.1]octadeca-1(18),14,16-triene (**10a**): Colorless foam. ^{1}H-NMR: 7.72 (*s*, 1 H); 7.40–7.06 (*m*, 3 H); 3.82 (*s*, 4 H); 2.72 (*m*, 8 H); 2.68 (*s*, 4 H); 1.99 (br. *s*, exch. with D_2O, 4 H). ^{13}C-NMR: 141.4 (C); 127.8 (CH); 126.8 (CH); 126.6 (CH); 52.8 (CH_2); 49.1 (CH_2); 48.8 (CH_2); 48.2 (CH_2). MS: 249 (MH^+). Anal. calc. for $C_{14}H_{24}N_4$ (248.37): C 67.70, H 9.74, N 22.56; found: C 67.57, H 9.93, N 22.50.

3,6,9,12-Tetraazabicyclo[12.2.2]octadeca-14,16,17-triene (**11a**): Colorless wax. ^{1}H-NMR: 7.29 (*s*, 4 H); 3.71 (*s*, 4 H); 2.76 (*m*, 4 H); 2.46 (*m*, 4 H); 2.12 (br. *s*, exch. with D_2O, 3 H); 2.03 (*s*, 4 H). ^{13}C-NMR: 141.0 (C); 129.7 (CH); 53.6 (CH_2); 49.1 (CH_2); 48.9 (CH_2); 46.2 (CH_2). MS: 249 (MH^+). Anal. calc. for $C_{14}H_{24}N_4$ (248.37): C 67.70, H 9.74, N 22.56; found: C 67.58, H 9.82, N 22.40.

3,7,11-Triazabicyclo[11.2.2]heptadeca-13,15,16-triene (**12a**): Colorless wax. ^{1}H-NMR: 7.27 (*s*, 4 H); 3.68 (*s*, 4 H); 2.45 (*m*, 4 H); 2.31 (br. *s*, exch. with D_2O, 3 H); 2.12 (*m*, 4 H); 1.33 (*quint.*, *J* = 7.1, 4 H). ^{13}C-NMR: 140.2 (C); 129.1 (CH); 53.0 (CH_2); 43.3 (CH_2); 41.7 (CH_2); 29.7 (CH_2). MS: 234 (MH^+). Anal. calc. for $C_{14}H_{23}N_3$ (233.36): C 72.06, H 9.93, N 18.01; found: C 71.95, H 10.05, N 17.89.

3,6,9,15-Tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**13a**): White solid. M.p. 75–78° (*t*-BuOMe). ^{1}H-NMR: 7.49 (*t*, *J* = 7.6, 1 H); 6.98 (*d*, *J* = 7.6, 2 H); 3.94 (*s*, 4 H); 2.69 (*m*, 4 H); 2.33 (br. *s*, exch. with D_2O, 3 H); 2.25 (*m*, 4 H). ^{13}C-NMR: 159.5 (C); 136.2 (CH); 119.6 (CH); 53.7 (CH_2); 49.1 (CH_2); 48.9 (CH_2). MS: 207 (MH^+). Anal. calc. for $C_{11}H_{18}N_4$ (206.29): C 64.05, H 8.79, N 27.16; found: C 63.93, H 8.91, N 26.98.

12-[(4-Bromobenzyl)oxy]-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**14a**): Light yellow solid. M.p. 92–95° (i-Pr_2O-hexane). ^{1}H-NMR: 7.54 (*d*, *J* = 7.7, 2 H); 7.30 (*d*, *J* = 7.7, 2 H); 7.08 (*d*, *J* = 8.3, 1 H); 6.96 (*d*, *J* = 8.3, 1 H); 5.04 (*s*, 2 H); 4.06 (*s*, 2 H); 3.95 (*s*, 2 H); 2.75 (*m*, 4 H); 2.41 (*m*, 4 H); 2.29 (br. *s*, exch. with D_2O, 3 H). ^{13}C-NMR: 150.5 (C); 149.8 (C); 148.6 (C); 136.7 (C); 131.6 (CH); 128.8 (CH); 123.0 (CH); 121.9 (C); 120.0 (CH); 69.3 (CH_2); 52.1 (CH_2); 48.6 (CH_2); 47.8 (CH_2); 47.1 (CH_2); 47.0 (CH_2); 46.4 (CH_2). MS: 391, 393 (MH^+). Anal. calc. for $C_{18}H_{23}BrN_4O$ (391.31): C 55.25, H 5.92, N 14.32; found: C 55.02, H 6.02, N 14.21.

3,7,11,17-Tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**15a**): White solid. M.p. 83–85° (*t*-BuOMe). ^{1}H-NMR: 7.54 (*t*, *J* = 7.5, 1 H); 7.01 (*d*, *J* = 7.5, 2 H); 3.88 (*s*, 4 H); 2.76 (*t*, *J* = 6.0, 4 H); 2.63 (*t*, *J* = 6.0, 4 H); 2.36 (br. *s*, exch. with D_2O, 3 H); 1.75 (*quint.*, *J* = 6.0, 4 H). ^{13}C-NMR: 159.0 (C); 136.6 (CH); 120.7 (CH); 54.1 (CH_2); 47.6 (CH_2); 46.4 (CH_2); 28.8 (CH_2). MS: 235 (MH^+). Anal. calc. for $C_{13}H_{22}N_4$ (234.24): C 66.63, H 9.46, N 23.91; found: C 66.43, H 9.63, N 23.79.

3,6,9,12,18-Pentaazabicyclo[12.3.1]octadeca-1(18),14,16-triene (**16a**): White wax. ^{1}H-NMR: 7.54 (*t*, *J* = 7.5, 1 H); 7.04 (*d*, *J* = 7.5, 2 H); 3.90 (*s*, 4 H); 2.84 (*m*, 4 H); 2.77 (*m*, 4 H); 2.75 (*s*, 4 H); 2.33 (br. *s*, exch. with D_2O,

4 H). ^{13}C-NMR: 156.1 (C); 136.6 (CH); 121.3 (CH); 53.9 (CH_2); 48.6 (CH_2); 47.8 (CH_2); 47.1 (CH_2). MS: 250 (MH^+). Anal. calc. for $C_{13}H_{23}N_5$ (249.36): C 62.62, H 9.30, N 28.09; found: C 62.62, H 9.45, N 27.98.

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