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Symmetrical and Asymmetrical Bisphosphonate Esters. Synthesis, Selective Hydrolysis, and Isomerization

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Summary. Two simple and efficient one-pot procedures for the synthesis of a series of α-branched N-heterocycle-substituted methane-1,1-bisphosphonates are outlined. In the first method, the parent halosubstrates were reacted with cyanomethylphosphonate followed by reaction with dialkyl phosphonates to give asymmetrical or symmetrical bisphosphonates (*BP*s). In the second approach, the same halocompounds were reacted with tetraethyl methyl-1,1-bisphosphonate to give the requisite *BP*s. Partial and complete hydrolysis of the prepared *BP*s were also investigated. The products contain functional groups advantageous for further synthetic modification as structural units for coupling with the drug.

Keywords. Drug research; Carbanions; Methyl-1,1-bisphosphonates; Bone mineral affinity.

Introduction

Over the past few years, methyl-1,1-bisphosphonates (*BP*s) of type **A** (Formula 1) have been receiving increased attention as a new class of pharmacological active compounds [1]. Following the recent FDA approval of Pamidronate (Aredia®, $H_2NH_2CH_2C–C(OH)[P(O)(OH)_2]_2$) in 1995 [2], for multiple myeloma and breast cancer bone disease, *BP*s have rapidly become the standard treatment for cancer-linked hypercalcemia of malignancy and osteolytis bone disease, all over the world.

Notwithstanding, significant progress has been made in this area over the past two decades, it is likely that realization of the full medicinal potential of both *BP*s and their relevant bisphosphonic acids remains in the future pending on further advances in drug design.

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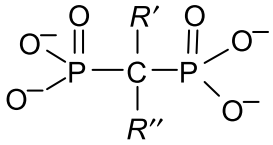
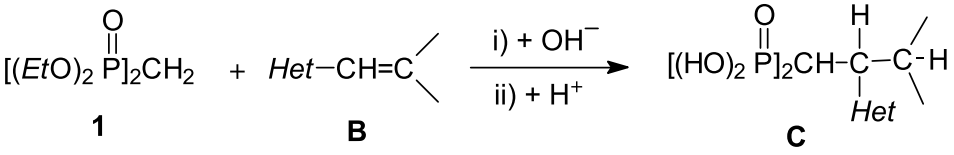


A

Formula 1



1 **B** **C**

Scheme 1

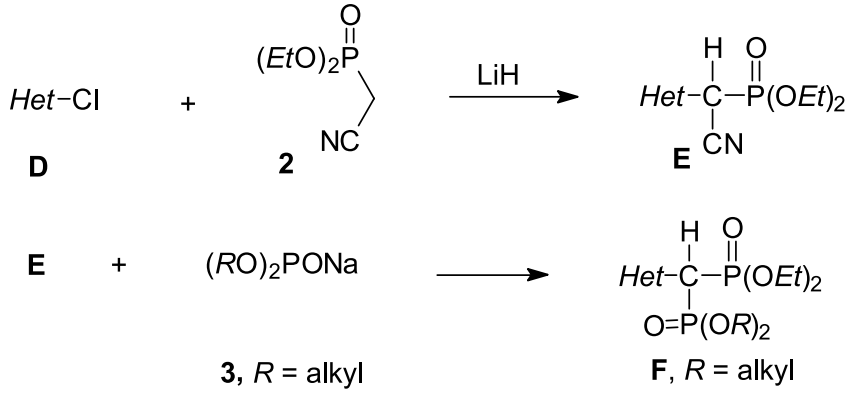
The marked structure-activity relationships observed among several *BP*s of type **A** indicate that the pharmacophore required for maximal activity depends not only upon the bisphosphonate moiety but also on key additional features, especially nitrogen substitution in alkyl or heterocyclic side chains (R' and R'' in **A**). For the reasons already mentioned, in a recent study [3] for developing better drugs suitable for bone diseases, we described a facile and general method for synthesis of several examples of N-heterocycle-substituted methyl-1,1-bisphosphonic acids **C** derived from the *Michael* addition reaction of the parent alkylidene compounds **B** with tetraethyl methyl-1,1-bisphosphonate (**1**), followed by acid hydrolysis (Scheme 1). Screening of some selected products has shown that these compounds have potent cardiovascular and inflammatory activities, and are potentially useful in the treatment of vascularhypertension.

As a sequel, we report herein two different one-pot procedures for the synthesis of a series of symmetrical and asymmetrical α-branched methyl-1,1-bisphosphonates, bearing N-containing heterocycle species. Hydrolysis or partial hydrolysis of the relevant phosphonate esters was also undertaken.

Results and Discussion

The first method involves a coupling reaction between halocompound **D** with the lithium salt of diethyl cyanomethylphosphonate **2** to give the monophosphonate **E**. Further displacement of the nitrile group by the phosphite moiety affords the required bisphosphonate **F** (Scheme 2).

Accordingly, the general experimental procedure is as follows: the methylene activated diethyl cyanomethylphosphonate **2** was treated with two equivalents LiH in *DMF* at room temperature leading to the corresponding lithium salt. This in turn was treated directly with the halogenated species in the presence of a further equivalent LiH. The reaction mixture was refluxed for a proper time (TLC), poured on water, and acidified. The product mixture was easily separated by solvent extraction and purified. The phosphoryl carbanion of **2** was used in threefold excess based on the corresponding halo compounds; otherwise the yields of the resulting products decreased drastically.

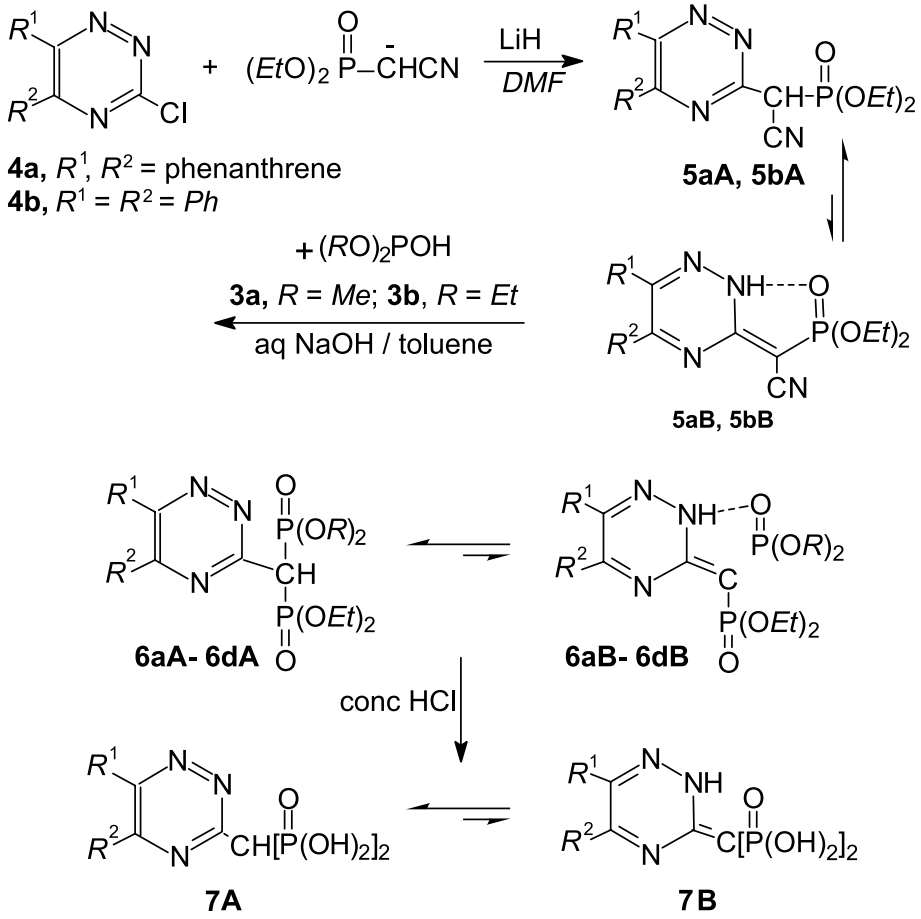


Scheme 2

Following this procedure, 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine (**4a**) (or 3-chloro-5,6-diphenyl-1,2,4-triazine (**4b**)) was treated with **2** (three equivalents) in refluxing *DMF* containing excess of LiH (twice equivalents of **2**) to give the corresponding diethyl 3-cyanomethylphosphonates **5a** (74%) or **5b** (71%) as the sole reaction product (Scheme 3). A similar behavior was observed when **4a** and **4b** were allowed to react with alkylidenephosphoranes [4a]. Furthermore, reactions of **4a** and **4b** with cyclic and acyclic trialkyl phosphites, as well as dialkyl phosphonates have been previously studied by us [4b].

Structure **5** was found to be present in two tautomeric isomers **5A** $\leftrightharpoons$ **5B** as indicated by the NMR spectra. The ^{31}P NMR spectrum of **5a** showed two resonances at $\delta = 32.83$ and 33.94 ppm (3:1 ratio). The ^{1}H NMR spectrum of **5a** (*DMSO*-d_6) showed the exocyclic methine proton of **5aA** as a doublet ($^{2}J_{PH} = 22.2$ Hz) at 4.43 ppm. The presence of an exocyclic methine proton was also attested to a doublet ($^{1}J_{PC} = 144$ Hz) at 51.6 (H*C*-P) in the ^{13}C NMR spectrum of **5a**, a value that coincides with an expected shift for a deshielded methane-carbon due to the electron withdrawing cyano and phosphonate groups. Furthermore, the doublet ($^{1}J_{PC} = 203$ Hz) at 73.4 ppm was assigned for $=$C-P (**5aB**). However, the weak signals for the NH in the ^{1}H NMR ($\delta = 12.34$ ppm) and IR spectra ($\bar{\nu} = 3453\ \mathrm{cm}^{-1}$) indicate that **5aA** is the predominant tautomer.

When the phosphonate **5a** was treated with one equivalent of dimethyl phosphonate (**3a**), the reaction was completed by boiling the reactants in toluene containing 10 cm^3 of a NaOH solution (0.5 *M*) for 24 h. The reaction yielded a colorless crystalline material of diethyl dimethyl phenanthro[9,10-*e*]-1,2,4-triazine-3-methane-1,1-bisphosphonate (**6a**, 62% based on **5a**), *via* elimination of HCN [7a], according to Scheme 3. A similar treatment of **5a** with diethyl phosphonate (**3b**) led to the tetraethyl derivative **6b** (74%). The ^{1}H and ^{13}C NMR spectra of **6b** are similar to those of **6a** except for the ester group, which displays characteristic resonances. Parallel compounds **6c** (68%) and **6d** (72%) were likewise obtained by treating **5b** with dialkyl phosphonates **3a** and **3b** under the same reaction conditions (Scheme 3). The bisphosphonate tautomerism **6aA**–**6dA** $\leftrightharpoons$ **6aB**–**6dB** (3:1 ratio as being indicated from the ^{31}P NMR spectra) is unambiguously supported by the spectral data. The IR spectra of compounds

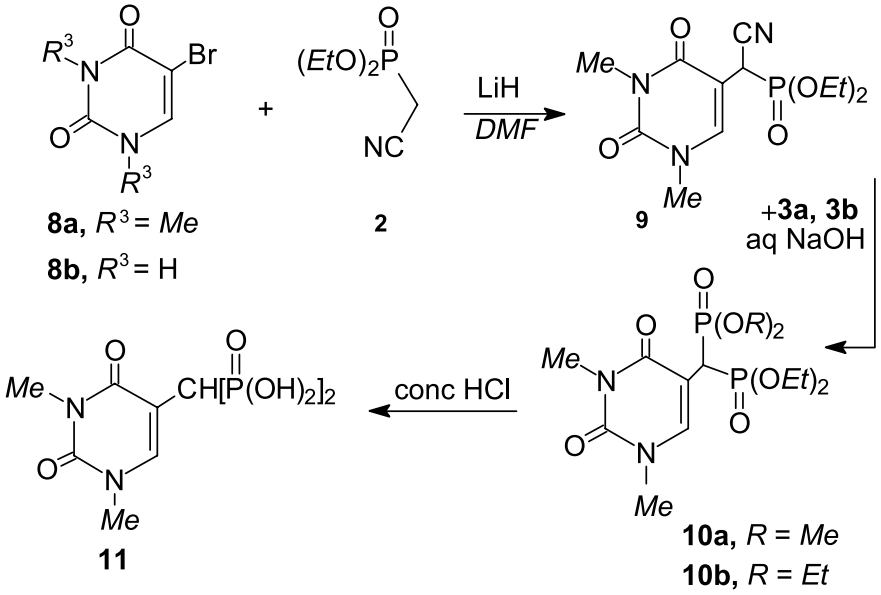


Cpd.	R^1, R^2	R	Cpd.	R^1, R^2	R
6a	phenanthrene	*Me*	**6d**	*Ph*	*Et*
6b	phenanthrene	*Et*	**7**	phenanthrene	-
6c	*Ph*	*Me*			

Scheme 3

6a–**6d** exhibited the presence of NH stretching vibration bands (≈3420 cm^{-1}). The distinguishing features in the ^{13}C NMR spectra of **6a** and **6b** were the presence of signals at $\delta \approx 36$ (t, $J_{PC} = \approx 140$ Hz, α-*C*HP, **6A**) and ≈54 (t, $J_{PC} \approx 200$ Hz, $= C$-P, **6B**) ppm [7]. Furthermore, the ^{31}P NMR spectra of *BP*s **6a**–**6d** showed two doublets ($J_{PP} = 6$ Hz) for P–C–P around $\delta \approx 22$ and 24 ppm [8].

Similar to **6**, this synthesis was extended to tetraalkyl 1,3-dimethyluracil-5-methane-1,1-bisphosphonates **10a** and **10b** in 61% and 65% yields. Thus, application of **2** to 5-bromo-1,3-dimethyluracil (**8a**) afforded the expected diethyl 1,3-dimethyluracil-5-cyanomethylphosphonate (**9**) in 69% yield (Scheme 4). The structure of **9** was substantiated from elemental analysis and spectral properties.



Scheme 4

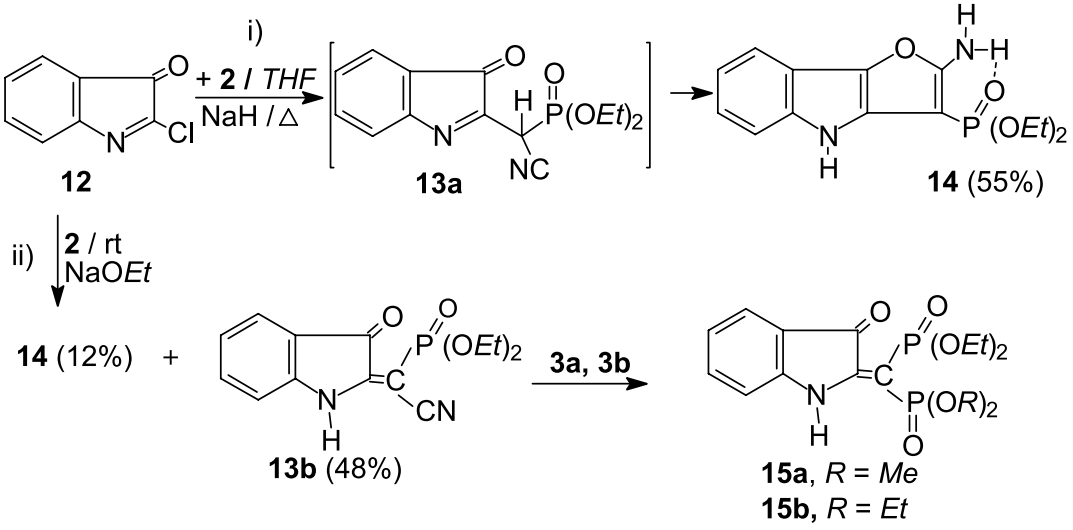
No reaction was observed, as stated before [5], when 5-bromouracil (**8b**) was treated with the same reagent **2** in boiling *DMF* containing LiH, even after 3 days. The reactions of uracils with different ter- and pentavalent phosphorus reagents have been previously studied [5, 6].

When **9** was reacted with dialkyl phosphonates **3a** or **3b** in toluene containing 0.5 *M* sodium hydroxide solution it afforded the required bisphosphonates **10a** or **10b** (Scheme 4). The ^{31}P NMR spectrum of **10b** revealed only one signal at $\delta = 20.67$ ppm [9].

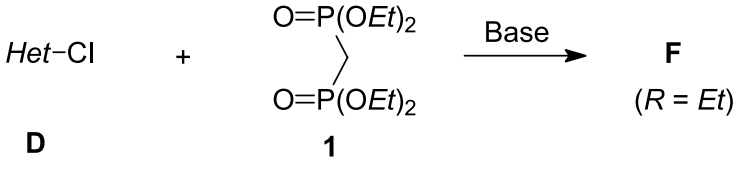
Furthermore, **6a**–**6d**, **10a**, and **10b** could be obtained in better yields when the sodium salt of **3a** or **3b** was added directly to the crude product mixture resulting from the reaction of **4a**, **4b**, or **8a** with **2**.

In one of our previous studies [5], we reported that treatment of 2-chloroisatin (**12**) with phosphonate **2** (4 mol equivalents) in the presence of NaH (twice equivalents of **2**) in boiling *THF* for 14 h led to the formation of the phosphono-substituted furan **14** (55%) *via* the nonisolable intermediate **13a** (Scheme 5, pathway i). In the present investigation, an experiment to slow down the above reaction for isolating the intermediate was undertaken. Thus, **13b** could be isolated in 48% yield along with **14** in 12% yield by allowing **12** to react with **2** in the presence of *Et*ONa at room temperature for 48 h. On the same ground, when **13b** was treated with **3a** or **3b** in a way analogous to the one described for **5**, tetraalkyl isatin-2-methane-1,1-bisphosphonates **15a** and **15b** were obtained (Scheme 5, pathway ii). Notably, in contrast to **5** and **6**, the products **13b** and **15** were present exclusively in one isomeric form as there was no indication for the presence of an exocyclic methine proton in the ^{1}H or ^{13}C NMR spectra of these species (see Experimental).

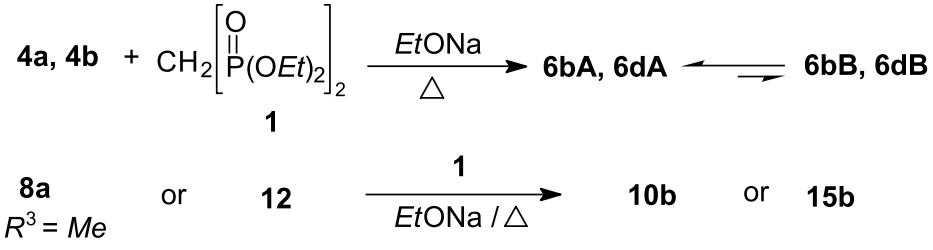
In the second method, we have applied another *Horner-Wittig* reagent, tetraethyl methyl-1,1-bisphosphonate (**1**) to the same halosubstrates **D** whereupon the *BP*s **F** ($R = Et$) were produced (Scheme 6).



Scheme 5



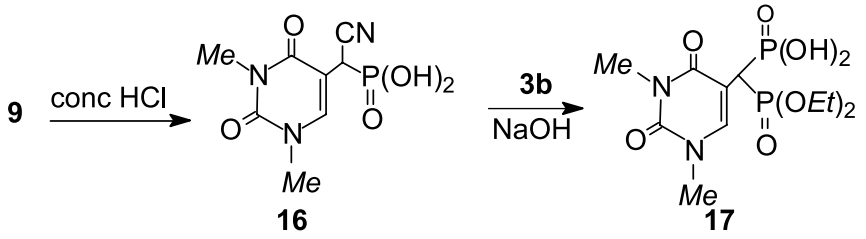
Scheme 6



Scheme 7

The *BP*s **6b** (60%), **6d** (63%), **10b** (66%), and **15b** (67%) were available, unequivocally, by one step synthesis from the reaction of the proper halo substrate **4a**, **4b**, **8a**, or **12** with **1**. The reactions were carried out in alcoholic sodium ethoxide solution at reflux temperature (~15 h, TLC) (Scheme 7). The products were found to be identical in all aspects with compounds described above.

As recent structure-activity studies in several pharma laboratories have identified impressively distinct therapeutic characteristics from 1,1-bisphosphonic acid to 1,1-bisphosphonate ester counterparts [10], we also present in this report our preparation of substituted-1,1-bisphosphonic acids. Thus, *e.g.* hydrolysis [7] of the



Scheme 8

bisphosphonates **6a** and **10b** with concentrated HCl gives the corresponding 1,1-bisphosphonic acid **7** (83%) (Scheme 3) and **11** (85%) (Scheme 4).

In another experiment, we applied the acid hydrolysis to the monophosphonate **9**, as a representative example. Cyanomethylphosphonic acid **16** was allowed to react with **3b** using the previous reaction conditions to furnish the partially hydrolyzed bisphosphonate **17** in 55% yield, based on **9** (Scheme 8).

Biological Evaluation

Finally, to predict the effect on bone resorption of these new *BP*s, the examples **6a**, **6b**, **10a**, **10b**, **7**, **11**, and **17** were evaluated *in vitro* [12] and *in vivo* [13]. All tested compounds inhibited *in vitro* osteoclast mediated pit formation for up to 76% at $10^{-8}\,M$. Different side chain substitutions resulted in marked differences in the antiresorptive potency. *In vivo BP*s **6a**, **6b**, and **17** inhibited unstimulated bone resorption at a relatively high dose of $2 \times 200\,\mathrm{mg/kg}$ for up to 60%, whereas the effects with **7**, **10a**, **10b**, and **11** were 10 times stronger. These data indicate that the effects of these new compounds are only moderate when compared to Risedronate. Thus, the results obtained are encouraging for further optimization of the antiresorptive properties of these compounds.

Conclusion

Halo compounds were elaborated as valuable and versatile candidates for the production of α-N-heterocycle – substituted methane-1,1-bisphosphonates. The two reported one-pot procedures for the generation of *BP*s are derived from the treatment of the halo substrates with *Horner-Wittig* reagents. However, despite the first process includes two steps, namely the reaction of the halo compound with cyanomethylphosphonate followed by treatment of the resulting mixture *in situ* with dialkyl phosphonates, this procedure is highly advantageous due to the easily accessible and low cost starting materials. In addition, the two steps of this process allow the possibility of preparing a variety of asymmetrical *BP*s as well as partially hydrolyzed products. On the other hand, the second one-pot procedure for the synthesis of *BP*s, by treatment of the halo species with tetraethyl methyl-1,1-bisphosphonate is a straightforward, simple, and smooth one reaction step, with total avoidance of any further reaction. Moreover, the better yields of the obtainable *BP*s, in question, are the distinct advantage of the latter method. Its major drawback is, however, the high cost of **1**, and the reported methods of preparing such reagents are very long and low yielding [11].

Experimental

All melting points were recorded on an Electrothermal 9100 melting point apparatus. IR spectra (KBr) were recorded on a Jasco FT/IR 300E spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian MERCURY 300 MHz (75 MHz) spectrometer. The ^{31}P NMR spectra were run on a Varian CFT-20 relative to external H_3PO_4 (75%). The mass spectra were recorded on a Finnigan SSQ 7000 (EI 70 eV) spectrometer. The starting halo compounds **4a**, **4b** [14], **8a** [15], and **12** [16] were prepared according to the reported procedures. Satisfactory elemental analyses and molecular weight measurements (MS) were obtained for all new compounds.

*Preparation of the Phosphonates **5a**, **5b**, and **9***

A solution of LiH (9 *M*) in 20 cm^3 *DMF* was treated with 1.6 g **2** (9.0 mmol) followed by 9 *M* LiH in 15 cm^3 *DMF* and 0.8 g (3.0 mmol) triazines **4a**, **4b**, or 0.8 g (3.63 mmol) uracil **8a**. After evolution of H_2 had ceased off, the suspension was stirred at rt for further 30 min and then heated under reflux for the appropriate time (for **4a**, **4b**: 8 h; **8a**: 5 h). The product mixture was concentrated and the excess of LiH was quenched carefully with 50 cm^3 ice/H_2O followed by acidification with conc HCl, solvent extraction ($CHCl_3$), drying, and evaporation. The resulting residue was crystallized from the proper solvent to give **5a**, **5b**, and **9**.

No reaction was observed when 5-bromouracil (**8b**) was reacted with **2** in *DMF* containing LiH using the same procedure as for **8a**.

Diethyl phenanthro[9,10-e]-1,2,4-triazine-3-cyanomethylphosphonate (**5a**, $C_{21}H_{19}N_4O_3P$)

Pale yellow crystals (0.9 g, 74%), mp 252–254°C (*Et*OH); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.05$, 1.11 (2dt, $J_{HH} = 6.8$, $J_{PH} = 2.3$ Hz, 2OCC*H*$_3$), 3.78, 4.01 (2dq, $J_{PH} = 10.8$ Hz, 2OC*H*$_2$), 4.43 (d, $J_{PH} = 22.2$ Hz, α-*H*C-P, **5aA**), 7.44–7.61 (m, 4*H*-Ar), 7.76–7.80 (m, 2*H*-Ph), 8.48–8.62 (m, 1*H*-Ph), 8.88–9.02 (m, 1*H*-Ph), 12.34 (br, N*H*, **5aB**) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 15.4$, 16.1 (2s, 2OCH$_2$*C*H$_3$), 51.6 (d, $J_{PC} = 144$ Hz, α-H*C*-P, **5aA**), 73.4 (d, $J_{PC} = 203$ Hz, =C-P, **5aB**), 62.6, 63.1 (d, $J_{PC} = 5$ Hz, O*C*H$_2$), 117.3 (*C*N), 120.4, 122.3, 123.0, 123.8, 124.8, 128.6, 128.8, 133.3, 133.7 (*C*-Ph) ppm; ^{31}P NMR (*DMSO*-d_6): $\delta = 32.83$, 33.94 (2s, 3:1 ratio) ppm; MS: m/z (%) = 406 (8) [M^+], 404 (14), 380 (31), 269 (22), 243 (100); IR (KBr): $\bar{\upsilon} = 3453$ (NH), 2224 (CN), 1667 (C=C, exocyclic), 1228, 1268 (P=O), 1059 (P–O–C) cm^{-1}.

Diethyl 5,6-diphenyl-1,2,4-triazine-3-cyanomethylphosphonate (**5b**, $C_{21}H_{21}N_4O_3P$)

Pale yellow crystals (866 mg, 71%); mp 246–248°C (*Et*OH); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.09$, 1.24 (2dt, $J_{HH} = 6.8$, $J_{PH} = 2.5$ Hz, 2OCC*H*$_3$), 3.84, 3.97 (2dq, $J_{PH} = 11$ Hz, 2OC*H*$_2$), 4.28 (d, $J_{PH} = 21.3$ Hz, α-*H*C-P, **5bA**), 7.44–7.61 (m, 4*H*-Ph), 7.76–7.80 (m, 2*H*-Ph), 8.21–8.27 (m, 2*H*-Ph), 8.40–8.78 (m, 2*H*-Ph), 11.88 (br, N*H*, **5bB**) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 15.4$, 16.6 (2s, OCH$_2$*C*H$_3$), 53.6 (d, $J_{PC} = 141$ Hz, α-H*C*-P, **5bA**), 72.5 (d, $J_{PC} = 185$ Hz, =C-P, **5bB**), 61.8, 62.4 (2d, $J_{PC} = 5$ Hz, O*C*H$_2$), 117.7 (*C*N), 118.6, 119.4, 122.5, 123.4, 123.8, 124.3, 124.8, 128.5, 133.6, 134.5 (*C*-Ph) ppm; ^{31}P NMR (*DMSO*-d_6): $\delta = 32.6$, 33.45 (2s, 3:1 ratio) ppm; MS: m/z (%) = 408 (11) [M^+], 406 (18), 382 (28), 271 (36), 245 (100); IR (KBr): $\bar{\upsilon} = 3433$ (NH), 2237 (CN), 1655 (C=C, exocyclic), 1235, 1267 (P=O), 1080 (P–O–C) cm^{-1}.

Diethyl 1,3-dimethyluracil-5-cyanomethylphosphonate (**9**, $C_{12}H_{18}N_3O_5P$)

Yellow leaflets (790 g, 69%); mp 165–167°C ($CHCl_3$); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.16$, 1.27 (2dt, $J_{HH} = 6.8$, $J_{PH} = 1.8$ Hz, 2OCC*H*$_3$), 3.25 (s (br), 2NC*H*$_3$), 3.83 (d, $J_{PH} = 22.2$ Hz, α-*H*C-P), 3.87, 4.11 (2dq, $J_{PH} = 10.4$ Hz, 2OC*H*$_2$), 7.62 (s, 6-C*H*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 15.6$, 15.8 (2s, 2*C*H$_3$CH$_2$O), 33.1, 34.2 (2s, 2N-*C*H$_3$), 52.2 (d, $J_{PC} = 148$ Hz, α-H*C*-P, **9**), 62.3, 62.8 (2O*C*H$_2$), 117.5 (d, $J_{PC} = 7$ Hz, *C*N), 143.1 (6-*C*), 155.4 (5-*C*), 152.5, 163.4 [2d, *C*-2(O), *C*-4(O)] ppm; ^{31}P NMR (*DMSO*-d_6): $\delta = 33.62$ ppm; MS: m/z (%) = 313 (37) [M^+-2], 289 (17), 285 (58), 233 (100), 178 (8); IR (KBr): $\bar{\upsilon} = 2235$ (CN), 1690, 1674 (2C=O), 1235 (P=O), 1083 (P–O–C) cm^{-1}.

*Preparation of the Phosphonates **13b** and **14***

A solution of *Et*ONa in *Et*OH prepared by dissolving 690 mg (30 mmol) sodium in 10 cm^3 abs ethanol was added to a stirred solution of 2.64 g **2** (15 mmol) in 15 cm^3 ethanol. The stirring was continued for 20 min and then a solution of 0.8 g **12** (4.8 mmol) in 10 cm^3 ethanol was added. The reaction mixture was stirred at rt for 48 h. After removing the solvent, 50 cm^3 dist H_2O were added and then extracted with $CHCl_3$, dried, and the solvent was evaporated. The resulting residue was chromatographed on silica gel using *n*-hexane/$CHCl_3$ as the eluent. Fractions up to 2:8 (v/v) afforded **13b**.

Diethyl isatin-2-cyanomethylphosphonate (**13b**, $C_{14}H_{15}N_2O_4P$)

Orange crystals (710 mg, 48%); mp 153–155°C (CH_2Cl_2); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.09$, 1.16 (2dt, $J_{HH} = 6.6$, $J_{PH} = 2.3$ Hz, 2OCC*H*$_3$), 3.85, 4.0 (2dq, $J_{PH} = 10.3$ Hz, 2OC*H*$_2$), 6.92 (d, $J_{HH} = 7.3$ Hz, 1*H*-Ph), 7.62 (d, $J_{HH} = 7.3$ Hz, 2*H*-Ph), 7.88 (d, $J_{HH} = 2.6$ Hz, 1*H*-Ph), 10.58 (br, N*H*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.9$, 15.2 (2s, 2OC*C*H$_3$), 73.5 (d, $J_{PC} = 208$ Hz, =*C*-P), 62.3, 63.1 (2d, $J_{PC} = 5$ Hz, 2O*C*H$_2$), 117.3 (*C*N), 111.3, 121.2, 122.8, 124.2, 127.6, 144.7 (*C*-Ph), 151.7 (N–*C*=C), 165.7 (*C*=O) ppm; ^{31}P NMR (*DMSO*-d_6): $\delta = 31.21$, 33.9 (2s) ppm; MS: m/z (%) = 306 (15) [M^+], 305 (13) [M^+-1], 304 (18) [M^+-2], 280 (71), 278 (26), 252 (100), 169 (21), 143 (35); IR (KBr): $\bar{\upsilon} = 3442$ (NH), 2218 (CN), 1745 (C=O), 1628 (C=C, exocyclic), 1255 (P=O), 1110 (P–O–C) cm^{-1}.

Elution with pure $CHCl_3$ gave in addition yellow crystals, 179 mg (12%), of the known furan **14**; mp 155–157°C (CH_2Cl_2) [Ref [5] 155–157°C (CH_2Cl_2)], identical IR, and MS spectra.

*Preparation of Bisphosphonates **6a–6d**, **10a**, **10b**, **15a**, and **15b***

A mixture of 2.0 mmol **5a**, **5b**, **9**, or **13** and 2.2 mmol **3a** or **3b** in 20 cm^3 toluene and 10 cm^3 NaOH (0.5 *M*), was heated under reflux for 15–20 h (TLC). After evaporation the crude product was crystallized from the appropriate solvent to afford **6a**–**6d**, **10a**, **10b**, **15a**, or **15b**.

Diethyl dimethyl phenanthro[9,10-e]-1,2,4-triazine-3-methane-1,1-bisphosphonate
(**6a**, $C_{22}H_{25}N_3O_6P_2$)

Colorless needles (670 mg, 62% based on **5a**, 45% based on **4a**); mp 174–175°C (benzene); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.20$, 1.36 (2dt, $J_{HH} = 6.6$, $J_{PH} = 2.5$ Hz, 2OCC*H*$_3$), 3.46 (d, $J_{PH} = 11.6$ Hz, 2OC*H*$_3$), 3.84, 4.08 (2dq, $J_{PH} = 10.3$ Hz, 2OC*H*$_2$), 4.48 (d, $J_{PH} = 21.8$ Hz, *H*C-P, **6aA**), 7.26, 7.76 (2d, $J_{HH} = 5.2$ Hz, 4*H*-Ph), 8.24 (d, $J_{HH} = 5.4$ Hz, 2*H*-Ph), 8.87 (d, $J_{HH} = 5.5$ Hz, 1*H*-Ph), 9.01 (d, $J_{HH} = 5.5$ Hz, 1*H*-Ph), 12.08 (br, N*H*, **6aB**) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 15.6$, 16.3 (2s, 2OCH$_2$*C*H$_3$), 36.6 (t, $J_{PC} = 144$ Hz, α-H*C*-P, **6aA**), 54.2 (d, $J_{PC} = 196$ Hz, =*C*P, **6aB**), 58.3, 58.8 (2m, PO*C*H$_3$), 62.5, 62.8 (2s, 2O*C*H$_2$), 120.2, 121.2, 122.8, 123.8, 124.4, 124.6, 128.5, 128.7, 133.5, 133.8 (*C*-Ph) ppm; ^{31}P NMR (*DMSO*-d_6): $\delta = 23.54$, 26.2 (2d, $J_{PP} = 6$ Hz, 3:1 ratio) ppm; MS: m/z (%) = 487 [M^+-2], 376 (21), 352 (28), 243 (100); IR (KBr): $\bar{\upsilon} = 3442$ (NH), 1655 (C=C), 1233, 1270 (2P=O), 1070, 1038 (2P–O–C) cm^{-1}.

Tetraethyl phenanthro[9,10-e]-1,2,4-triazine-3-methane-1,1-bisphosphonate
(**6b**, $C_{24}H_{29}N_3O_6P_2$)

Colorless crystals (0.8 g, 74% based on **5a**, 51% based on **4a**); mp 168–170°C (*Et*OH); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.21$, 1.36 (2dt, $J_{HH} = 7.4$, $J_{PH} = 2.2$ Hz, 4OCC*H*$_3$), 3.99–4.22 (2q (m), 4OC*H*$_2$), 4.38 (d, $J_{PH} = 22.1$ Hz, α-*H*C-P, **6bA**), 7.45–7.63 (m, 4*H*-Ph), 7.76–7.82 (m, 2*H*-Ph), 8.48–8.62 (m, 1*H*-Ph), 8.88–9.02 (m, 1*H*-Ph), 12.56 (br, N*H*, **6bB**) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 15.8$, 16.6, 17.4 (3s, 4*C*H$_3$CH$_2$O), 36.4 (t, $J_{PC} = 138$ Hz, α-H*C*P, **6bA**), 53.5 (d, $J_{PC} = 208$ Hz, =*C*-P, **6bB**), 62.7, 63.0, 63.4 (3s, 4O*C*H$_2$), 120.3, 121.6, 122.3, 122.8, 123.6, 124.2, 124.6, 128.1, 128.4, 133.6, 134.2 (*C*-Ph) ppm; ^{31}P NMR (*DMSO*-d_6): $\delta = 22.7$, 24.3 (2d, $J_{PP} = 6$ Hz, 3:1 ratio) ppm; MS: m/z (%) = 517 (<5) [M^+], 514 (23) [M^+-3], 380 (100), 243 (48); IR (KBr): $\bar{\upsilon} = 3412$ (NH), 1635 (C=C), 1237, 1262 (2P=O), 1150 (P–O–C) cm^{-1}.

Diethyl dimethyl 5,6-diphenyl-1,2,4-triazine-3-methane-1,1-bisphosphonate (**6c**, $C_{22}H_{27}N_3O_6P_2$)
Colorless crystals (708 mg, 68% based on **5b**, 48% based on **4b**); mp 188–190°C (*Et*OH); ^{1}H NMR ($CDCl_3$): $\delta = 1.13$, 1.25 (2dt, $J_{HH} = 6.8$, $J_{PH} = 3.5$ Hz, 4OCC*H*$_3$), 3.66 (d, $J_{PH} = 11.8$ Hz, 2OC*H*$_3$), 3.89, 3.99 (2dq, $J_{HH} = 6.8$, $J_{PH} = 4.5$ Hz, 2OC*H*$_2$), 4.46 (d, $J_{PH} = 18.86$ Hz, α-*H*C-P, **6cA**), 7.37–7.68 (m, 4*H*-Ph), 7.88–8.18 (m, 2*H*-Ph), 8.21–8.27 (m, 2*H*-Ph), 8.40–8.65 (m, 2*H*-Ph), 11.82 (br, N*H*, **6cB**) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.23$, 16.12 (2s, 2OC*C*H$_3$), 34.1 (t, $J_{PC} = 148$ Hz, α-H*C*-P, **6cA**), 52.3 (d, $J_{PC} = 203$ Hz, =*C*P, **6cB**), 58.2, 58.8 (2m, 2PO*C*H$_3$), 61.8, 63.6 (2s, 2O*C*H$_2$), 118.4, 119.2, 121.7, 122.6, 123.4, 123.8, 124.5, 124.6, 128.5, 128.8, 133.3, 133.9 (*C*-Ph) ppm; ^{31}P NMR ($CDCl_3$): $\delta = 24.36$, 25.94 (2d, $J_{PP} = 6$ Hz, 3:1 ratio) ppm; MS: m/z (%) = 491 (<5) [M$^+$], 489 (13), 378 (38), 370 (27), 354 (100), 352 (88), 245 (40); IR (KBr): $\bar{\upsilon} = 3458$ (NH), 1655 (C=C), 1256, 1262 (2P=O), 1068, 1152 (2P–O–C) cm^{-1}.

Tetraethyl 5,6-diphenyl-1,2,4-triazine-3-methane-1,1-bisphosphonate (**6d**, $C_{24}H_{31}N_3O_6P_2$)
Colorless crystals (793 mg, 72% based on **5b**, 51% based on **4b**); mp 162–164°C (*Et*OH); ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.23$, 1.38 (2dt, $J_{HH} = 7.2$, $J_{PH} = 2.6$ Hz, 4CC*H*$_3$), 3.86–4.04 (2dq (m), 4OC*H*$_2$), 4.35 (d, $J_{PH} = 20.8$ Hz, α-*H*C-P, **6dA**), 7.34-7.61 (m, 4*H*-Ar), 7.86–8.09 (m, 2*H*-Ph), 8.23–8.28 (m, 2*H*-Ph), 8.41–8.63 (m, 2*H*-Ph), 12.69 (br, N*H*, **6dB**) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 14.8$, 15.1, 16.8 (3s, 4*C*H$_3$CH$_2$O), 33.7 (t, $J_{CP} = 138$ Hz, α-H*C*P, **6dA**), 51.8 (d, $J_{PC} = 200$ Hz, =*C*-P, **6dB**), 62.2, 62.8, 63.4 (3s, 4O*C*H$_2$), 118.6, 119.0, 120.8, 121.6, 122.4, 123.5, 123.7, 124.3, 124.7, 128.5, 129.1, 133.3, 134.2 (*C*-Ph) ppm; ^{31}P NMR (*DMSO*-d$_6$): $\delta = 20.55$, 23.32 (2d, $J_{PP} = 6$ Hz, 3:1 ratio) ppm; MS: m/z (%) = 519 (8) [M$^+$], 518 (6), 517 (13), 382 (25), 380 (22), 245 (100); IR (KBr): $\bar{\upsilon} = 3408$ (NH), 1652 (C=C), 1234, 1256 (2P=O), 1156, 1085 (2P–O–C) cm^{-1}.

Diethyl dimethyl 1,3-dimethyluracil-5-methane-1,1-bisphosphonate (**10a**, $C_{13}H_{24}N_2O_8P_2$)
Pale yellow crystals (608 mg, 61% based on **9**, 42% based on **8a**); mp 130–132°C (cyclohexane); ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.09$, 1.14 (2dt, $J_{HH} = 6.6$, $J_{PH} = 2.4$ Hz, 2OCC*H*$_3$), 3.19, 3.28 (2s, 2NC*H*$_3$), 3.42, 3.45 (2d, $J_{PH} = 10.8$ Hz, 2OC*H*$_3$), 3.85, 3.98 (2dq, $J_{PH} = 11.7$ Hz, 2OC*H*$_2$), 4.32 (d, $J_{PH} = 22.4$ Hz, α-*H*C-P), 7.58 (s, 6-C*H*) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 11.9$, 15.8 (2s, 2OC*C*H$_3$), 33.2, 34.6 (2s, 2NC*H*$_3$), 38.6 (t, $J_{PC} = 155$ Hz, α-H*C*-P), 58.2, 58.8 (2d, 2PO*C*H$_3$), 61.6, 62.5 (2s, 2O*C*H$_2$), 141.4 (6-*C*), 155.1 (5-*C*), 152.8, 163.4 [2d, *C*-2(O), *C*-4(O)] ppm; ^{31}P NMR (*DMSO*-d$_6$): $\delta = 27.62$, 21.59 (2d, $J_{PP} = 6$ Hz) ppm; MS: m/z (%) = 397 (<5) [M$^+$-1], 393 (15), 368 (11), 364 (10), 314 (100), 289 (59), 261 (35), 258 (20), 178 (15); IR (KBr): $\bar{\upsilon} = 1690$, 1668 (2C=O), 1248, 1258 (2P=O), 1085, 1105 (2P–O–C) cm^{-1}.

Tetraethyl 1,3-dimethyluracil-5-methane-1,1-bisphosphonate (**10b**, $C_{15}H_{28}N_2O_8P_2$)
Pale yellow needles (694 mg, 65% based on **9**, 45% based on **8a**); mp 118–120°C (cyclohexane); ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.25$, 1.36 (2dt, $J_{HH} = 6.8$, $J_{PH} = 2.4$ Hz, 4OCC*H*$_3$), 3.13, 3.27 (2s, 2NC*H*$_3$), 3.84, 3.98 (2dq, $J_{PH} = 11.2$ Hz, 4OC*H*$_2$), 4.18 (d, $J_{PH} = 23.3$ Hz, α-*H*C-P), 7.64 (s, 6-C*H*) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 15.2$, 16.2, 16.7 (3s, 4*C*H$_3$CH$_2$O), 32.4, 32.8 (2NC*H*$_3$), 38.4 (t, $J_{PC} = 142$ Hz, α-H*C*-P), 61.8, 62.4, 63.3 (3s, 4O*C*H$_2$), 143.6 (6-*C*), 154.6 (5-*C*), 153.1, 162.6 [2d, *C*-2(O), *C*-4(O)] ppm; ^{31}P NMR (*DMSO*-d$_6$): $\delta = 20.67$, 1.25 (2s) ppm; MS: m/z (%) = 425 (11) [M$^+$-1], 424 (13), 423 (15), 396 (11), 314 (100), 389 (82), 259 (66), 178 (11); IR (KBr): $\bar{\upsilon} = 1701$, 1680 (2C=O), 1254, 1266 (2P=O), 1100 (P–O–C) cm^{-1}.

Diethyl dimethyl isatin-2-methane-1,1-bisphosphonate (**15a**, $C_{15}H_{21}NO_7P_2$)
Straw yellow needles (514 mg, 57% based on **13b**, 27% based on **12**); mp 122–124°C (cyclohexane); ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.2$, 1.23 (2dt, $J_{HH} = 6.6$, $J_{PH} = 2.5$ Hz, 2OCC*H*$_3$), 3.31 (2dt, $J_{PH} = 11.3$ Hz, 2OC*H*$_3$), 4.05 (dq, $J_{PH} = 10.6$ Hz, 2OC*H*$_2$), 6.92 (d, $J_{HH} = 7.3$ Hz, 1*H*-Ph), 7.68 (d, $J_{HH} = 7.3$ Hz, 2*H*-Ph), 7.89 (d, $J_{HH} = 2.6$ Hz, 1*H*-Ph), 10.59 (br, N*H*) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 13.6$, 14.6

(2s, 2OCCH_3), 51.8 (d, $J_{PC}=196$ Hz, *C*-P), 55.6 (d, $J_{PC}=7.2$ Hz, 2O*C*H$_3$), 60.3, 61.4 (d, $J_{PC}=7.2$ Hz, 2O*C*H$_2$), 114, 117, 122.4, 124.5, 127.4, 143.8 (*C*-Ph), 150.2 (N-*C*=C), 165.6 (*C*=O) ppm; ^{31}P NMR (*DMSO*-d$_6$): $\delta=26.35$, 35.12 (2d, $J_{PP}=6.8$ Hz) ppm; MS: m/z (%) = 389 (13) [M$^+$], 388 (13), 333 (27), 305 (100), 280 (44), 143 (28); IR (KBr): $\bar{\upsilon}=3442$ (NH), 1744 (C=O), 1623 (C=C), 1248, 1251 (2P=O), 1024, 1066 (2P–O–C) cm^{-1}.

Tetraethyl isatin-2-methane-1,1-bisphosphonate (**15b**, $C_{17}H_{25}NO_7P_2$)
Straw yellow needles (589 mg, 61% based on **13b**, 29% based on **12**); mp 111–113°C (cyclohexane); ^{1}H NMR (*DMSO*-d$_6$): $\delta=1.11$, 1.16 (2dt, $J_{HH}=7.4$, $J_{PH}=2.4$ Hz, 4OCC*H*$_3$), 3.83, 4.05 (2dq, $J_{PH}=11.2$ Hz, 4OC*H*$_2$), 6.9 (d, $J_{HH}=7.3$ Hz, 1*H*-Ph), 7.62 (d, $J_{HH}=7.3$ Hz, 2*H*-Ph), 7.99 (d, $J_{HH}=2.6$ Hz, 1*H*-Ph), 10.6 (br, N*H*) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta=13.6$, 15.1 (2s, OC*C*H$_3$), 52.6 (d, $J_{PC}=201$ Hz, =*C*-P), 62.6, 63.2 (2d, $J_{PC}=7.2$ Hz, O*C*H$_2$), 115, 117, 121.6, 122.6, 126.8, 144.1 (*C*-Ph), 153.3 (N-*C*=C), 167.1 (*C*=O) ppm; ^{31}P NMR (*DMSO*-d$_6$): $\delta=25.6$, 31.8 (2d, $J_{PP}=6.5$ Hz) ppm; MS: m/z (%) = 417 (<5) [M$^+$], 416 (21), 389 (13), 361 (42), 305 (100), 280 (62), 143 (41); IR (KBr): $\bar{\upsilon}=3424$ (NH), 1730 (C=O), 1623 (C=C), 1248, 1251 (2P=O) 1024, 1086 (2P–O–C) cm^{-1}.

In an alternative, 0.8 g **4a**, **4b** (3.0 mmol) or 0.8 g **8a** (3.63 mmol) were treated with a solution of 1.6 g **2** (9.0 mmol) in *DMF* containing 144 mg (18.0 mmol) of a slurry of LiH dispersion (60% in paraffin oil) and the mixture was refluxed for ≈8 h (TLC). The reaction procedure and workup were as mentioned above. The crude residue of **5a**, **5b**, or **9** produced was treated, *in situ*, with 2.2 mmol **3a** or **3b** in 20 cm^3 toluene containing 10 cm^3 NaOH (0.5 *M*). The reaction mixture was heated under reflux for 20 h (TLC). After evaporation of the volatile materials, the crude product was crystallized from the appropriate solvent to afford **6a** (720 mg, 49%), **6b** (880 mg, 57%), **6c** (750 mg, 51%), **6d** (825 mg, 53%), **10a** (697 mg, 48%), or **10b** (790 mg, 51%); yields based on the halo compounds. They were proved to be identical with the above isolated compounds.

*Preparation of **6b**, **6d**, **10b**, and* **15b**
A solution of 1.4 g **1** (5.0 mmol) in 10 cm^3 absolute ethanol was added at 0°C to a stirred solution of 20 cm^3 *Et*OH containing 230 mg Na (10.0 mmol). After the addition was completed (1 h), a solution of 2.5 mmol **4a**, **4b**, **8a**, or **12** in 5 cm^3 *Et*OH was added and the resulting mixture was heated under reflux for ~15 h (TLC). The mixture was worked up as described for the reaction of **2** with **12**. The residue was crystallized from the appropriate solvent to give **6b** (60%), **6d** (63%), **10b** (66%), and **15b** (67%), which were identical with the products previously obtained.

Preparation of Bisphosphonic Acids *7 and 11*
The phosphonates **6a** (0.5 g, 1.02 mmol) or **10b** (0.5 g, 1.17 mmol) were dissolved in 15 cm^3 conc HCl and the mixture was heated under reflux for 12 h. Then the solution was decolorized with activated C, then filtered, and evaporated to dryness under reduced pressure. After addition of 5 cm^3 *Et*OH the solid was filtered off and washed twice with ether to yield the phosphonic acids **7** or **11**.

Phenanthro[9,10-e]-1,2-4-triazine-2-methane-1,1-bisphosphonic acid (**7**, $C_{16}H_{13}N_3O_6P_2$)
White material (340 mg, 83%), mp >300°C (*Et*OH/H$_2$O, 1/1, *v*/*v*); ^{1}H NMR (D$_2$O): $\delta=4.41$ (d, $J_{PH}=22.1$ Hz, *H*C-P), 7.26–8.96 (m, 8*H*-Ph) ppm; ^{31}P NMR (D$_2$O): $\delta=22.4$, 24.1 ppm; MS (EI): m/z (%) = 404 (8) [M$^+$-1], 401 (44) [M$^+$-4]; IR (KBr): $\bar{\upsilon}=3350$ br (OH), 1658 (N=N), 1200 (P=O) cm^{-1}.

1,3-Dimethyluracil-5-methanephosphonic acid (**11**, $C_7H_{12}N_2O_8P_2$)
White material (310 mg, 85%), mp 293–295°C (acetone/H$_2$O, 1/1, *v*/*v*); ^{1}H NMR (D$_2$O): $\delta=2.99$, 3.17 (2s, 2NC*H*$_3$), 7.42 (s, 6-C*H*) ppm; ^{13}P NMR (D$_2$O): $\delta=22.8$, 23.6 ppm; MS (EI): m/z (%) = 314 (<5) [M$^+$], 310 (53) [M$^+$-4]; IR (KBr): $\bar{\upsilon}=3200$ br (OH), 1690 (C=O), 1210 (P=O) cm^{-1}.

Preparation of ***16*** and the Partially Hydrolyzed Bisphosphonate ***17***
A solution of 630 mg **9** (2 mmol) in 20 cm^3 conc HCl was heated under reflux for 20 h, followed by the above-described workup to give **16**.

1,3-Dimethyluracil-5-cyanomethylphosphonic acid (**16**, $C_8H_{10}N_3O_5P$)
Pale yellow crystals (426 mg, 82%), mp >300°C (*Et*OH/H_2O, 1/1, *v*/*v*); ^{1}H NMR (D_2O): $\delta = 3.41$ (s (br), 2N-C*H*$_3$), 3.87 (d, $J_{HP} = 21.2$ Hz, α-*H*C-P), 7.59 (s, 6-C*H*) ppm; ^{31}P NMR (D_2O): $\delta = 32.41$ ppm; MS (EI): m/z (%) = 259 (59) [M^+]; IR (KBr): $\bar{\upsilon} = 3190$ w, 2950 (P-OH), 2230 (CN), 1690 (C=O), 1230 (P=O) cm^{-1}.

1,3-Dimethyluracil-5-methane-1-diethoxyphosphono-1-phosphonic acid (**17**, $C_{11}H_{20}N_2O_8P_2$)
Compound **16** (518 mg, 2.0 mmol) was allowed to react with 2.2 mmol **3b** under the same conditions described for **9**. After refluxing for 20 h, usual workup and crystallization afforded **17**. Yellow leaflets (481 mg, 65% based on **9**), mp 287–289°C (acetone); ^{1}H NMR (D_2O): $\delta = 1.36$ (2dt, $J_{HH} = 6.6$, $J_{PH} = 3.8$ Hz, 2OCC*H*$_3$), 3.24 (s.br, 2NC*H*$_3$), 3.85 (d, $J_{PH} = 21.5$ Hz, *H*C-P), 4.09, 4.13 (2dq, $J_{HH} = 6.6$, $J_{PH} = 4.2$ Hz, 2,OC*H*$_2$), 7.59 (s, 6-C*H*) ppm; ^{31}P NMR (D_2O): $\delta = 32.17$, 33.45 (2d, each $J_{pp} = 6$ Hz, *P*–C–*P*) ppm; MS (EI): m/z (%) = 370 (48) [M^+]; IR (KBr): $\bar{\upsilon} = 3190$, 2910 (P-OH), 2228 (CN), 1690 (C=O), 1232 (P=O), 1100 (P–O–C) cm^{-1}.

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