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Photo-Arbuzov rearrangements of cyclic phosphite systems

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Abstract

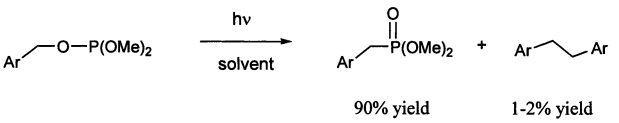
The direct UV irradiation of cyclic phosphites **1**–**4** was carried out in argon-saturated solvents. In all cases examined, the rearranged, ring-contracted Photo-Arbuzov phosphonate was the major product formed with isolated yields ranging from 40 to 50%. These phosphonate photoproducts, **5**–**8**, represent novel, bicyclic, aromatic phosphonate systems never before described in the literature of heterocyclic phosphorus chemistry. These compounds are of interest based on their potential application as ring-constrained, non-hydrolyzable mimics of phosphorylated tyrosine.

Keywords: Photo-Arbuzov; Phosphorylated tyrosine; Cyclic phosphite systems

1. Introduction

The Photo-Arbuzov rearrangement of acyclic allyl, benzyl and 1-naphthylmethyl phosphites has been studied extensively since first introduced by Bentrude, et al. in 1988 [1]. The representative photorearrangement reaction for both the benzyl and naphthyl systems is detailed in Scheme 1. The rearrangement transforms the starting phosphite into the corresponding phosphonate cleanly and in moderate to high yields (70–90% when Ar = Ph). This process has been shown to occur with predominant retention of stereochemical integrity at the migratory alpha carbon [2] and the phosphorus center [3] upon direct irradiation. The influence of such factors as triplet sensitization [4] and presence of acetyl substitution on the aromatic ring [5] on the mechanism and multiplicity of the radical pair intermediates through which these reactions appear to proceed, has been found in product [6], CIDNP [7] and CIDEP studies [8]. The manifold through which the reaction proceeds also determines to what extent radical dimerization photoproduct (Scheme 1, bibenzyl when Ar = Ph) is formed. The origin of this product and the theory of the proximate radical pair intermediates involved are thoroughly detailed elsewhere [9]. For direct irradiation of the unsubstituted systems, the major photoproduct is the rearranged 'Photo-Arbuzov' phosphonate product, in which a new phosphorus carbon bond is formed. The Photo-Arbuzov reaction has proven to be a useful synthetic tool in the facile preparation of acyclic nucleoside-based phosphonates [10] which have been identified as potential prodrug forms of nucleoside antivirals.

As a class, arylphosphonate derivatives have been shown to act as protein tyrosine kinase (PTK) inhibitors or more specifically, non-hydrolyzable mimics of phosphorylated tyrosine residues [11]. PTK are of ubiquitous importance in the regulation of many vital cellular processes, including cellular signal transduction, growth factor signaling and glucose uptake and metabolism [12].



Scheme 1. The Photo-Arbuzov rearrangement.

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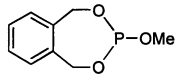
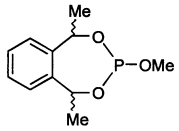
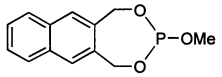


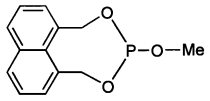
1,5-dihydro-3-methoxy-2,4,3-benzodioxaphosphepin (**1**)



1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepin (**2**)



1,5-dihydro-3-methoxy-naphtho [2,3–e] [1,3,2] dioxaphosphepin (**3**)



3-methoxy-1*H*, 5*H*–naphtho [1,8-*ef*] [1,3,2] dioxaphosphocine (**4**)

Fig. 1. Cyclic phosphite systems studied.

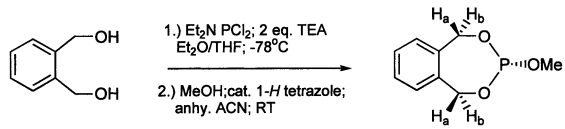
In an effort to obtain information on phosphorus-carbon biradical systems, and to extend the synthetic scope of the Photo-Arbuzov rearrangement to prepare bicyclic aromatic phosphonate systems not otherwise synthetically accessible, the Photo-Arbuzov reactions of the cyclic phosphites **1**–**4** were investigated.

The majority of these proposed cyclic phosphite systems have not been prepared or utilized previously in past literature. Only the conformational aspects of the 1,5-dihydro-3-methoxy-2,3,4-benzodioxaphosphepin system (**1**) have been studied previously [13,14] (Fig. 1).

2. Results and discussion

2.1. Preparations of cyclic phosphites

All cyclic phosphite systems were prepared from their corresponding benzyl and naphthylmethyl diols in a two step sequence. The diols are either commercially available (1,2 benzene dimethanol) or readily acquired by one-step reactions from commercially available starting materials (see Section 4). The preparation of 1,3,2-benzodioxaphosphepin is detailed in Scheme 2 and is representative of the conditions used to prepare both the benzyl and naphthylmethyl 1,3,2-dioxaphosphepine systems studies. This route of preparation incorporates the freedom to install various structural features in the exocyclic substituent. Alternative one-step preparations for these types of cyclic phosphite systems are known [15] for the preparation of strictly methyl substituted systems. Reaction of the diols with



Scheme 2. Preparation of 1,5-dihydro-3-methoxy-2,4,3-benzodioxaphosphepin as a representative synthetic scheme for preparation of cyclic benzo- and naphtho-phosphite systems **1**–**4**.

Cl_2PNEt_2 produced the intermediate benzyl and naphthylmethyl 3-dimethylamino-1,3,2-dioxaphosphepines which were not isolated. Immediate 1-*H*-tetrazole-catalyzed coupling of these intermediates with one equivalent of MeOH in dry acetonitrile at room temperature produced the desired benzo- and naphtho-2-methoxy-1,3,2-dioxaphosphepines. The phosphites were purified by in vacuo Kugelrohr distillation and characterized using ^1H and ^{31}P nuclear magnetic resonance spectroscopy.

Benzodioxaphosphepin (**1**) was obtained in 40% isolated yield. GC–MS analysis of the distillate shows that the material is $>95\%$ pure ($m/z = 198$). ^{31}P-NMR analysis confirms the structural assignment of the three coordinate symmetric cyclic phosphite system with a characteristic chemical shift of 140.2 ppm. ^1H-NMR spectroscopy confirms the cyclic phosphite structural assignment by revealing characteristic chemical shifts and several diagnostic $^1H-^{31}P$ couplings. The methoxy protons signal at 3.5 ppm show a typical through bond coupling to the phosphorus nuclei of 12 Hz (typical values 10–12 Hz) [16]. The diastereotopic benzylic protons reveal chemical shifts at 4.3 and 5.6 ppm, a geminal coupling of 13.1 Hz, and couplings to phosphorus of 9.8 and 10.2 Hz, respectively.

Following the previously detailed two-step preparation from the racemic diol, benzodioxaphosphepin (**2**) was obtained in 45% isolated yield. The Kugelrohr distillate of **2** was 90% (GC) pure as a 6.6:1.1:1 mixture of three diastereomers, as determined by ^{31}P-NMR spectroscopy, with $m/z = 226$ (GC–MS). From the racemic diol starting material, three diastereomers are expected: one set containing an enantiomeric pair of cyclic phosphites with a *trans* orientation of the benzylic methyl groups and two different phosphorus lone pair orientations (Fig. 2: **2c** *trans* + enantiomer); and two different *meso* systems (Fig. 2: **2a** and **2b** *cis-meso* and *trans-meso*). ^1P-NMR spectroscopy confirms the presence of three diastereomeric phosphites with characteristic chemical shifts of 142.3, 134.0 and 128.0 ppm. ^1H-NMR spectroscopy also supports the cyclic phosphite structure. The methoxy protons, three doublets centered at 3.7 ppm, show an average coupling to the phosphorus nuclei of 10.8 Hz. Three sets benzylic protons are present as multiplets centered at 5.6 ppm.

Resonances for the exocyclic methyl groups are displayed at about 1.5 ppm.

Naphthodioxaphosphepin **3**, isolated in 45% overall isolated yield following Kugelrohr distillation, was > 90% pure (GC–MS, $m/z = 248$). ^{31}P-NMR spectroscopy confirms the symmetric cyclic phosphite structure system with a characteristic chemical shift of 147.3 ppm. The ^{1}H-NMR spectrum displays expected resonances at 3.6 ppm (MeO, $J = 11$ Hz), 4.8 and 6.18 ppm (diastereotopic 1-naphthylmethyl protons). These protons also show a geminal coupling of 14 Hz and couplings to phosphorus ($J = 13.8$ and 14.7 Hz).

Naphthodioxaphosphocin **4** was obtained in 45% overall isolated yield (> 90% purity) following Kugelrohr distillation (GC–MS, $m/z = 248$). ^{31}P-NMR spectroscopy is in accord with the symmetric cyclic phosphite structure with a single resonance at 140.2 ppm. ^{1}H-NMR spectroscopy confirms the structural assignment: methoxy doublet at 3.6 ppm ($J = 11.5$ Hz); diastereotopic CH_2 protons (6.3 and 4.75 ppm.; 7 and 9 Hz proton phosphorus couplings, 13 Hz geminal coupling).

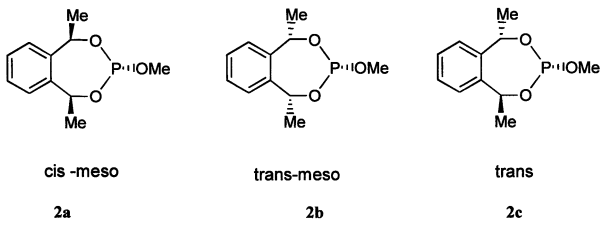
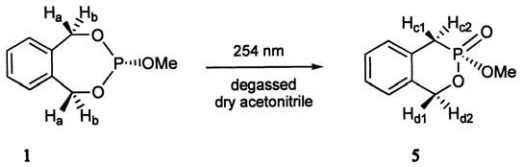


Fig. 2. Diastereomers present from synthesis of racemic 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepin.



Scheme 3. Photolysis of 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepin (**1**).

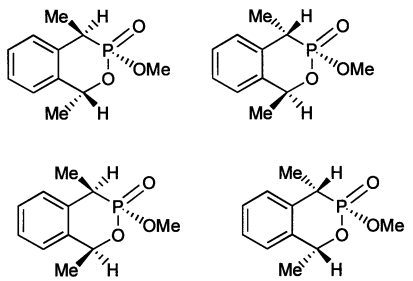


Fig. 3. Predicted diastereomers expected from photolysis of the diastereomeric mixture of 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepins **2a**–**c**.

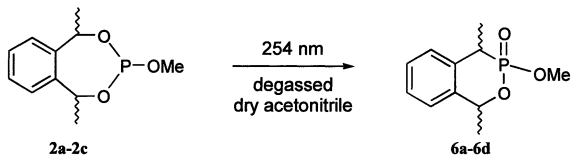
Preparation of the naphthodioxaphosphepin (**3**) and naphthodioxaphosphocin (**4**) systems was desired to allow eventual investigations of triplet energy transfer and use of longer wavelength on direct irradiation. The naphthodioxaphosphocin system (**4**) represents the largest cyclic ring system (8-membered) of the series.

2.2. Photochemistry of Cyclic phosphites *1*–*4*

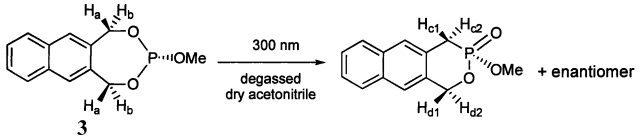
Direct irradiation of 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepin (**1**) in argon-saturated acetonitrile at 254 nm (Rayonet reactor) to 80% conversion of the phosphite leads to the formation of the ring-contracted product 3,4-dihydro-3-methoxy-1*H*-2,3-benzoxaphosphorin-3-oxide (**5**) as shown in Scheme 3. Photoconversion to the single photoproduct of m/z of 198 was determined by GC–MS analysis. The single photoproduct (GC) was purified by column chromatography for an isolated yield of 40%, based on starting **1**. ^{31}P-NMR spectroscopy shows a single resonance at 25.2 ppm, typical of the phosphonate functionality. ^{1}H-NMR confirms the cyclic phosphonate structural assignment: methoxy group signal at 3.8 ppm ($J = 11$ Hz); diasterotopic benzylic protons ($CH_2P(O)$) at 3.2 ppm (H_{c1} and H_{c2}) as a strongly coupled, second order multiplet (small $\Delta v/J$ ratio). The diastereotopic, benzylic, CH_2OP protons (H_{d1} and H_{d2}) appear at 5.3 ppm multiplet (small $\Delta v/J$ ratio) with geminal and phosphorus couplings. ^{13}C-NMR spectroscopy supports the structural with the appearance of a resonance at 26.4 ppm with a large one-bond coupling to phosphorus (129.9 Hz); a methoxy doublet at 52.2 ppm ($J = 6.6$ Hz) and a benzylic ring carbon attached to oxygen at 69.9 ppm ($J = 7.1$ Hz).

The photochemical quantum yield for the conversion of 1,5-dihydro-3-methoxy-2,4,3-benzodioxaphosphepin (**1**) to 3,4-dihydro-3-methoxy-1-*H*-2,3-benzoxaphosphorin-3-oxide (**5**) was determined by actinometry [17] to be 0.27, a value consistent with the quantum yields obtained for acyclic Photo-Arbuzov rearrangements previously [5].

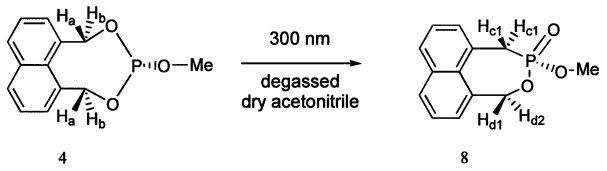
Direct irradiation of the diastereomeric mixture of racemic 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepins, **2a**–**2c**, in argon-saturated acetonitrile at 254 nm (Rayonet reactor) to 80% conversion (GC) of the phosphite leads to the formation of a mixture of new photoproducts, purified together by column chromatography in isolated yield of 50%, purity > 95% (GC). Based upon the photochemistry of **1**, photolysis of **2a**–**2c** was expected to undergo ring contraction to the Photo-Arbuzov product, a mixture of the four, isomeric, ring-contracted photoproducts, **6a**–**d**, shown in Fig. 3. These four phosphonate isomers elute in three bands using the described GC analysis (Scheme 4).



Scheme 4. Photolysis of racemic 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,-benzodioxaphosphepin.



Scheme 5. Direct irradiation of 1,5-dihydro-3-methoxy-naphtho[2,3-*e*][1,3,2] dioxaphosphepin.



Scheme 6. Direct photolysis of 3-methoxy-1*H*,5*H*–naphtho [1,8-*ef*] [1,3,2] dioxaphosphocine.

The photoproduct's phosphonate structure and presence of four isomers was confirmed using ^{31}P-, ^{13}C- and ^{1}H-NMR spectroscopy. ^{31}P-NMR spectroscopy confirms the presence of four phosphorus nuclei in a phosphonate setting with signals at 26.2, 24.3, 21.8 and 21.0 ppm. ^{1}H nuclear magnetic resonance spectroscopy confirms the cyclic phosphonate structural assignments: methoxy group signals centered at 3.7 ppm as a set of multiplets resulting from the diastereomeric mixture; benzylic protons on the carbons of the phosphonate (C–P) moiety as a multiplet centered at 3.2 ppm; a multiplet centered at 5.3 ppm for the benzylic protons next to oxygen. ^{13}C nuclear magnetic resonance spectroscopy supports the structural with the appearance of four phosphonate–carbon resonances at 31.4, 31.5, 31.6 and 32.6 ppm with large one-bond couplings to phosphorus ($J = 129.8$, 131.7, 129.6 and 128.4 Hz, respectively) a set of doublets (J ca. 6.6 Hz) for the methoxy signals at 52.2 ppm; and signals for benzylic ring carbons attached to oxygen centered at 69.9 ppm with coupling values of about 7.1 Hz. The four photoproducts were formed in a diastereomeric product ratio of $\sim$1:2:2:4 as determined by ^{13}C nuclear magnetic resonance spectroscopy.

Direct irradiation of 1,5-dihydro-3-methoxy-naphtho [2,3-*e*] [1,3,2] dioxaphosphepin, **3,** in argon-saturated acetonitrile at 300 nm (Rayonet reactor) to $\sim$80% consumption (GC) of the phosphite leads to the formation of the ring-contracted product, 3,4-dihydro-3-methoxy-1*H*-naphth [2,3-*d*] [1,2] oxaphosphorin-3–oxide, as shown in Scheme 5. The reaction gave a single photoproduct (GC–MS $m/z = 248$) which was purified by column chromatography in 35% isolated yield (based on total **3**), $>$95% purity. Product structures were confirmed by ^{31}P-, ^{13}C- and ^{1}H-NMR spectroscopy. ^{31}P-NMR spectroscopy confirms the presence of a phosphonate chemical shift at 6.4 ppm. ^{1}H-NMR spectroscopy affirms the cyclic phosphonate structural assignment: methoxy proton signal at 3.8 ppm ($J = 11$ Hz); diastereotopic, benzylic phosphonate protons (H_{c1} and H_{c2}) at 3.4 ppm with geminal proton and phosphorus-proton splittings (strongly coupled multiplet resulting from small $\Delta v/J$ ratio). The benzylic protons on the carbon adjacent to ring oxygen (H_{d1} and H_{d2}), centered at 5.3 ppm, are also diastereoptopic and show a strongly coupled second-order pattern because of the small $\Delta v/J$ ratio. ^{13}C-NMR spectroscopy is in accord with the structural assignment as seen in the appearance of a resonance at 27.5 ppm with a large one-bond coupling to phosphorus of 126.9 Hz. Additional diagnostic peaks include the methoxy signal at 52.5 ppm ($J = 6.5$ Hz) and that for the benzylic ring carbon bonded to oxygen at 70.0 ppm ($J = 6.0$ Hz).

Direct irradiation 3-methoxy-1*H*, 5*H* –naphtho [1,8-*ef*] [1,3,2] dioxaphosphocine (**4**) in argon-saturated acetonitrile at 300 nm (Rayonet reactor) to $\sim$80% conversion of the phosphite leads to the formation of the seven-membered ring-contracted product, 3,4-dihydro-3-methoxy-1*H*-naphth [1,8-*de*] [1,2] oxaphosphepin-3-oxide, **8**, as shown in Scheme 6. Conversion to a single photoproduct ($m/z = 248$) was followed by GC–MS analysis and purified by column chromatography, isolated yield 45% (based on total **4**), $>$95% purity.

The structure of **8** was determined by NMR spectroscopy. ^{31}P-NMR spectroscopy shows the presence of a phosphonate moiety at 34.6 ppm. ^{1}H-NMR spectroscopy confirms the cyclic phosphonate structural assignment: methoxy signal at 3.7 ppm ($J = 10.9$ Hz); diastereotopic benzylic protons on the carbon bonded to phosphorus (H_{c1} and H_{c2}) at 3.28; diastereotopic benzylic protons on the carbon bonded to ring oxygen (H_{d1} and H_{d2}) at 5.5 ppm. Both sets of benzylic protons show a strongly coupled second order pattern because of the small $\Delta v/J$ ratio. ^{13}C-NMR spectroscopy affirms the structural assignment: peak at 32.7 ppm ($J = 127.9$), benzylic carbon bonded to phosphorus; benzylic C–O carbon at 70.4 ppm ($J = 4.5$ Hz); methoxy signal at 52.9 ppm ($J = 7.1$ Hz).

3. Conclusions

It has been shown previously that the Photo-Arbuzov rearrangement of acyclic benzyl and 1-naphthylmethyl phosphites is a useful and facile synthetic procedure to produce biologically interesting acyclic benzylphosphonates not easily accessible through traditional thermal

synthetic routes. In this report, it is shown that this straightforward synthetic photochemical protocol can also be applied to readily available cyclic benzyl and naphthylmethyl phosphites to produce novel bicyclic phosphonate heterocycles. This hitherto unstudied variation of the Photo-Arbuzov rearrangement involves a 1,2-migration of carbon from oxygen to phosphorus that results in a ring contraction. Further work is underway to determine if these novel bicyclic phosphonates exhibit favorable activity as PTK inhibitors. These cyclic systems have potentially different biological activities and binding abilities from their acyclic counterparts due to the constrained geometries of the ring atoms and fixed orientation of the phophonate moiety, a difference previously reported in comparisons of cyclic and acyclic analogs [18].

4. Experimental

4.1. General

Anhydrous tetrahydrofuran (Aldrich) dichloromethane (Aldrich), diethyl ether (Fisher), methanol (Aldrich), and benzene (Aldrich) were used as received. Prior to use in photochemical experiments, acetonitrile (Fisher spectrophotometric grade) was distilled from calcium hydride. 1,8-Naphthalic anhydride (Acros), 1, 2-benzene dimethanol (Aldrich), 1,2-benzene dicarboxaldehyde (Aldrich), phosphorus trichloride (Aldrich gold label), triethylamine (Aldrich), 1-*H*-tetrazole, 2,3-naphthalene dicarboxylic acid and azoxybene (Lancaster) were used as received. ^{1}H, ^{13}C, and ^{31}P-NMR spectra were obtained in $CDCl_3$, C_6D_6, DMSO-d_6 and CD_3CN on a Varian VXR-200 or Unity 300 instrument. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane. ^{31}P chemical shifts are referenced to external 85% phosphoric acid. *J* values listed refer to proton-proton couplings unless otherwise indicated. The purity of starting materials, synthetic intermediates, products and the progress of photolytic experiments were assayed using a Hewlett–Packard 5890 gas chromatograph equipped with a HP-1 cross-linked methyl siloxane column ($25 \times 0.2 \times 0.33$ μm) and a flame ionization detector. GC–MS data was obtained on a Hewlett–Packard 5890 series II-Plus gas chromatograph equipped with a Hewlett–Packard 5972 series mass selective detector, HP-5 cross-linked 5% PhMe silicone column, and a thermal conductivity detector.

4.2. Actinometry

Actinometry was done using the azoxybenzene/2-hydroxy-azobenzene chemical actinometer system described by Bunce et al. [17]. The quantum yield for the formation of 3,4-dihydro-3-methoxy-1*H*-2,3-benzoxaphosphorin-3-oxide from 1,5-dihydro-3-methoxy-2,4,3-benzodioxaphosphepin was determined at 254 nm with argon saturated acetonitrile solutions of ca. 0.3 M. Sets of 18 mm diameter quartz tubes, each containing a concentric 8 mm diameter quartz test tube, were irradiated in a Rayonet apparatus equipped with a Merry-go-round system. Prior to quantum yield determinations, it was shown that the actinometer system exhibited a linear response in the time range and light intensities utilized for described photolytic experiments.

4.3. General procedure for photolysis of benzylic phosphites

An argon-saturated acetonitrile solution of the phosphite (ca. 0.1 M) was irradiated at 254 through septum-sealed quartz test tube (~ 8 ml $\times$ 4 tubes) in a Rayonet photochemical apparatus. Agitation of the quartz test tubes was accomplished using a turning mechanism derived from a Kughelrohr system. Irradiations were run until ca. 80% of phosphite was consumed (GC). The photolysate was concentrated on a rotary evaporator and pre-purified by column chromatography on neutral alumina–florisil–silica gel layered column (1:1:8) using 2% methanol in dichloromethane as eluent. The compound was then subjected to HPLC purification as outlined below.

4.4. General procedure for photolysis of naphthyl phosphites

The phosphites (ca. 0.1 M in argon saturated acetonitrile) were irradiated at 300 nm in a sealed Pyrex test tube in a Rayonet photochemical apparatus. Solutions were magnetically stirred. Irradiation time and work-up procedures are similar to the procedure above. The compound was then subjected to HPLC purification as outlined below.

4.5. HPLC purification of phosphonates

The crude compound was dissolved in 1–2 ml of the intended HPLC solvent system. The solution was filtered through a Millex®-HV_{13} (0.45 μm, 13 mm diameter) filter unit. Eluent (isocratic conditions) was 1.2% methanol in chloroform (HPLC grade, Mallinckrodt or EM Science) on a 21.4 mm ID preparative Dynamax® HPLC column (100 Å spherical Microsorb packings, 5 μm particle size) equipped with UV detector. Optimum flow rates were 10–16 ml min^{-1}.

4.6. Et_2NPCl_2

Et_2NPCl_2 was prepared routinely from diethylamine (11.73 g, 16.6 ml, 160.5 mmol) and PCl_3 (11.02g, 7 ml,

80.2 mmol) in 76% yield. Spectroscopic data was consistent with that reported in the literature [19]. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.3 (dq, $J_{PH} = 13.2$, $J = 7$ Hz, 4 H), 1.18 (t, $J = 7$ Hz, 6 H); ^{31}P-NMR (121 MHz, C_6D_6): δ 163.8.

4.7. 1,2-Bis-(1-hydroxyethyl)-benzene

1,2-Benzene dicarboxaldehyde (1.3 g, 9.7 mmol) was dissolved in THF (100 ml), flushed with argon, sealed with a rubber septum and cooled to 0 °C. Methyl magnesium bromide (2.2 equivalents, 7.1 ml of 3 M solution in THF) was added slowly dropwise to the cooled, stirred solution. The reaction was allowed to warm to room temperature (r.t.) and stirred at r.t. for 2 h. The reaction was added to dilute aqueous acid, and the aqueous layer was extracted with chloroform (5 × 25 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated on a rotary evaporator. The residue was purified via silica gel chromatography using 50:50 ethyl actetate:hexanes. The diol was isolated (1.1 g) as a clear thick oil in 70% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.45 (m, 2 H), 7.25 (m, 2 H), 5.2 (q, $J = 6.4$ Hz, 2 H), 2.75 (s, 2 H), 1.5 (d, $J = 6.4$ Hz, 6 H).

4.8. 2,3-Naphthalene dimethanol

2,3-Naphthalene Dimethanol was prepared from 2,3-naphthalenedicarboxylic according to the procedure of Altman et al. [20].

4.9. 1,8-Naphthalenedimethanol

1,8-Naphthalenedimethanol was prepared according to the procedure of Boekelhiede [21].

4.10. General procedure for preparation of cyclic phosphites from diol precursors

A 0.01–0.05 M solution of the requisite diol and two molar equivalents of anhydrous triethylamine in anhydrous ether/THF was added dropwise over a 1 h period to a solution of the diethylamino-phosphorus dichloride in diethyl ether or diethyl ether/THF (0.01–0.05 M) at −78 °C under a dry, argon atmosphere. A white precipitate of triethylamine hydrochloride was formed. The reaction was allowed to warm to r.t. over a period of 1–2 h. The reaction mixture was filtered through a coarse sintered glass funnel under an argon atmosphere, and the resulting ether solution was concentrated under high vacuum. The resulting oily residue was taken up in enough anhydrous acetonitrile to prepare a 0.2 M solution of the phosphoramidite. A catalytic amount (ca. 0.1 equivalent) of 1*H*-tetrazole and one molar equivalent of anhydrous methanol were added, and the solution was stirred at r.t. overnight. The reaction was typically followed by GC. Upon completion, the acetonitrile solvent was removed in vacuo, and the crude material was purified by bulb to bulb distillation.

4.11. 1,5-Dihydro-3-methoxy-2,4,3-benzodioxaphosphepin (**1**)

Bulb to bulb vacuum distillation afforded the title compound in 40% yield. ^{1}H-NMR (200 MHz, C_6D_6) δ 6.7–7.0 (m, 4 H), 5.6 (dd, $J = 13.1$ Hz $J_{PH} = 10.2$ Hz, 2 H), 4.3 (dd, $J = 13.1$ Hz $J_{PH} = 9.8$ Hz, 2 H), 3.46 (d, $J_{PH} = 12$ Hz, 3 H); ^{13}C-NMR (75 MHz, C_6D_6): δ 129.59, 129.08, 118.26, 64.50, 42.65; ^{31}P-NMR (121 MHz, C_6D_6) 140.2 ppm; GC–MS (EI) m/z (relative intensity) 198 $[M]^+$ (35), 183 (3), 168 (6), 153 (9), 104 (100), 91 (16), 78 (26), 65 (9), 63 (7), 51(6).

4.12. 3,4-Dihydro-3-methoxy-1H-2,3-benzoxaphosphorin-3-oxide (**5**)

The benzoxaphosphorin 3-oxide **5** was obtained from after photolysis of **1** under standard conditions in argon-saturated acetonitrile (ca. 0.1 M) at 254 nm. The pholysate was concentrated on a rotary evaporator and purified. The phosphonate, a thick yellow oil, was obtained by column chromatography on neutral alumina–florisil–silica gel layered column (1:1:8) using 2% methanol in methylene chloride as eluent in 40% yield. Recrystallization from dichloromethane–pentane resulted in off-white crystals, melting point (m.p.) 53–55 °C. ^{31}P-NMR (121 MHz, $CDCl_3$, $\{^1H\}$) δ 25.24; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.12–3.34 (m, 2 H), 3.78 (d, 3 H, $^3J_{PH} = 11.0$ Hz), 5.21–5.40 (m, 2 H), 7.10–7.29 (m, 4 H); ^{13}C-NMR (75 MHz, $CDCl_3$, $\{^1H\}$) δ 26.36 (d, $^1J_{PC} = 129.9$ Hz), 52.24 (d, $^2J_{PC} = 6.6$ Hz), 69.96 (d, $^2J_{PC} = 7.1$ Hz), 125.36 (d, $J_{PC} = 1.5$ Hz), 127.28, 128.28 (d, $J_{PC} = 2.0$ Hz), 129.61 (d, $J_{PC} = 8.1$ Hz), 130.65 (d, $J_{PC} = 14.6$ Hz), 132.48 (d, $J_{PC} = 11.1$ Hz); IR (neat, cm^{-1}) 3400 (br.), 1240, 1250, 1060; GC–EIMS (70eV) m/z (relative intensity) 198 $[M]^+$ (96), 183 (26), 120 (100), 119 (62), 104 (74), 91 (32), 77 (15); HRMS (EI) m/z $[M]^+$ Calc. for $C_9H_{11}O_3P$: 198.0446. Found: 198.0440. Anal. Calc. for $C_9H_{11}O_3P$: C, 54.55; H, 5.60. Found: C, 54.26; H, 5.65%.

4.13. 1,5-Dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepin (**2a**–**2c**)

The phosphite was obtained after bulb to bulb vacuum distillation of the crude phosphite from the procedure stated above to yield the title compound in 45% yield. ^{1}H-NMR (200 MHz, $CHCl_3$) δ 7.4 (m, 4 H), 5.6 (m, 1 H), 3.7 (m, 3 H), 3.2 (m, 1 H), 1.5 (m, 6 H); ^{31}P-NMR (121 MHz, C_6D_6): δ 142.34 134.0, 128.0 (6.6:1.1:1 mixture of diastereomers); GC–MS (EI) m/z

(relative intensity): 226 $[M]^+$ (16), 211 (9), 182 (12), 152 (5), 131 (25), 117 (100), 103 (10), 91(21), 77 (16), 65 (5), 51(6).

4.14. 3,4-Dihydro-3-methoxy-1,4-dimethyl-1H-2,3-benzoxaphosphorin-3-oxide (**6a**–**6d**)

3,4-Dihydro-3-methoxy-1,4-dimethyl-1*H*-2,3-benzoxaphosphorin-3-oxide, a thick slightly yellow oil, was obtained by irradiation of 1,5-dihydro-3-methoxy-1,5-dimethyl-2,4,3-benzodioxaphosphepin in argon saturated acetonitrile (ca. 0.1 M) at 254 nm in a quartz cell in a Rayonet apparatus by the standard procedure. Column chromatography on neutral alumina–florisil–silica gel layered column (1:1:8) using 2% methanol in methylene chloride as eluent afforded **6a**–**6d** in an average yield of ca. 50%. Further purification by HPLC yielded a colorless oil as a mixture of isomers. ^{31}P-NMR (121 MHz) C_6D_6, $\{^1H\}$) δ 21.0, 21.8, 24.3, 26.2; ^{1}H-NMR (200 MHz, C_6D_6) δ 1.6 (m, 6 H), 3.2 (m, 1 H), 3.7 (m, 3 H), 5.6 (m, 1 H), 7.0–7.4 (m, 4 H); ^{13}C-NMR (75 MHz, $CDCl_3$, $\{^1H\}$) δ 12.8, 12.9, 14.4, 14.5, 14.7, 16.2, 16.3, 18.0, 18.1, 21.6, 21.8, 22.8, 22.9, 24.3, 26.0, 31.4 (d, $^1J_{PC} = 129.8$ Hz), 31.5 (d, $^1J_{PC} = 131.7$ Hz), 31.6 (d, $^1J_{PC} = 129.6$ Hz), 32.6 (d, $^1J_{PC} = 128.4$ Hz), 51.7, 51.8, 52.0, 52.1, 52.2, 52.6, 75.3, 75.4, 76.9, 77.1, 77.5, 77.6, 78.3, 78.4, 125.0, 125.5, 125.7, 126.2, 126.4, 126.6, 127.0, 127.1, 127.3, 127.5, 127.6, 129.1, 129.4, 129.6, 130.2, 130.3, 135.3, 135.4, 136.6, 136.7, 136.9, 137.0, 137.3, 137.5; IR (neat, cm^{-1}) 3400 (br.), 1240, 1250, 1060; GC–EIMS (70 eV) *m*/*z* (relative intensity) 226 $[M]^+$ (63), 211 (89), 148 (33), 133 (100), 117 (55), 91 (10); HRMS (EI) *m*/*z* $[M]^+$ Calc. for $C_{11}H_{15}O_3P$: 226.0759. Found: 226.0733. Anal. Calc. for $C_{11}H_{15}O_3P$: C, 58.37; H, 6.67. Found: C, 58.41; H, 6.68%.

4.15. 1,5-Dihydro-3-methoxy-naphtho[2,5–e][1,3,2]-dioxaphosphepin (**3**)

The crude phosphite, ~90% pure, was obtained in 45% yield. ^{1}H-NMR (200 MHz, C_6D_6) δ 7.6-8.1 (m, 6H), 6.18 (dd, $J = 13.94$ Hz, $J_{PH} = 13.8$ Hz, 1H), 4.75 (dd, $J = 14$ Hz, $J_{PH} = 14.7$ Hz, 1H), 3.6 (d, $J_{PH} = 11$ Hz, 3H); ^{31}P-NMR (121 MHz, C_6D_6): δ 147.3; GC–MS (EI) *m*/*z* (relative intensity) 248 $[M]^+$ (19), 233 (6), 170 (32), 154 (100), 139 (17), 115 (22), 76 (20), 63 (7), 51 (3).

4.16. 3,4-Dihydro-3-methoxy-1H-naphth[2,3-d][1,2]-oxaphosphorin-3-oxide (**7**)

3,4-Dihydro-3-methoxy-1*H*-naphth[2,3-*d*][1,2]oxaphosphorin-3-oxide (**7**) was obtained from photolysis of 1,5-dihydro-3-methoxy-naphtho [2, 3–*e*] [1, 3, 2] dioxaphosphepin in argon-saturated acetonitrile (ca. 0.1 M in concentration) at 300 nm in a sealed Pyrex® test tube in a Rayonet apparatus by the standard procedure. The phosphonate was obtained as a waxy white solid after column chromatography on neutral alumina–florisil–silica gel layered column (1:1:8), using 4% methanol in methylene chloride as eluent, in 35% yield. The compound was further purified by preparatory HPLC as described earlier. Recrystallization from dichloromethane–pentane resulted in off-white crystals, m.p. 90–92 °C. ^{31}P-NMR (121 MHz, $CDCl_3$, $\{^1H\}$) δ 26.41; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.34–3.53 (m, 2 H), 3.76 (d, 3 H, $^3J_{PH} = 11.0$ Hz), 5.30–5.36 (m, 2 H), 7.47–7.54 (m, 2 H), 7.67 (d, 2 H, $J = 11.0$ Hz), 7.78–7.82 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$, $\{^1H\}$) δ 27.46 (d, $^1J_{PC} = 126.9$ Hz), 52.55 (d, $^2J_{PC} = 6.5$ Hz), 70.0 (d, $^2J_{PC} = 6.0$ Hz), 125.1 (d, $J_{PC} = 1.5$ Hz), 126.59, 126.82, 127.31, 127.71, 127.87 (d, $J_{PC} = 8.6$ Hz), 128.99 (d, $J_{PC} = 13.6$ Hz), 130.87, (d, $J_{PC} = 10.1$ Hz), 132.12, 133.13; GC-EIMS (70eV) *m*/*z* (rel intensity) 248 $[M]^+$ (100), 233 (17), 170 (88), 169 (39), 154 (20); HRMS (EI) *m*/*z* $[M]^+$ Calc. for $C_{13}H_{13}O_3P$: 248.0602. Found: 248.0596. Anal. Calc. for $C_{13}H_{13}O_3P$: C, 62.91; H, 5.28. Found: C, 62.77; H, 5.23%.

4.17. 3-Methoxy-1H, 5H–naphtho[1,8-ef][1,3,2]dioxaphosphocine (**4**)

The crude phosphite, obtained by the standard method, was used in the subsequent photoreactions without further purification. The compound was ~90% pure and obtained in 45% yield. ^{1}H-NMR (200 MHz, C_6D_6) δ 7.4–8.0 (m, 6 H), 6.3 (dd, $J = 13$ Hz, $J_{PH} = 9$ Hz, 1 H), 4.75 (dd, $J = 13$ Hz, $J_{PH} = 7$ Hz, 1 H), 3.6 (d, $J_{PH} = 11.5$ Hz, 3 H); ^{31}P-NMR (121 MHz, C_6D_6) δ 140.2; GC–MS (EI) *m*/*z* (relative intensity): 248 $[M]^+$ (32), 233 (20), 203 (4), 187 (8), 169 (12), 153 (100), 141 (20), 116 (16), 76 (12), 63 (8), 51 (3).

4.18. 3-Methoxy-3-oxo-1,4-dihydro-naphth[2,3-d][1,2]-oxaphosphorin (**8**)

The title compound was obtained by irradiation of 3-methoxy-1*H*, 5*H*–naphtho [1,8-*ef*] [1,3,2] dioxaphosphocine (**4**) in argon saturated acetonitrile (ca. 0.1 M) at 300 nm in a sealed pyrex test tube in a Rayonet apparatus by the standard method. The phosphonate was obtained as a waxy solid in 45% yield after column chromatography on neutral alumina–florisil–silica gel layered column (1:1:8) using 2% methanol in methylene chloride eluent. Further purification by HPLC, followed by recrystallization from dichloromethane–pentane, resulted in white needles, m.p. 40–42 °C. ^{31}P-NMR (121 MHz, $CDCl_3$, $\{^1H\}$) δ 34.63; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.74 (d, 3 H, $^3J_{PH} = 10.9$ Hz), 3.77–4.00 (m, 2 H), 5.48 (m, 2 H), 7.37–7.46 (m, 4 H), 7.79–7.88 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$, $\{^1H\}$)

δ 32.74 (d, $^1J_{PC} = 127.9$ Hz), 52.89 (d, $^2J_{PC} = 7.1$ Hz), 70.42 (d, $^2J_{PC} = 4.5$ Hz), 125.10, 126.06 (d, $J_{PC} = 1.5$ Hz), 127.17 (d, $J_{PC} = 7.6$ Hz), 128.54 (d, $J_{PC} = 1.5$ Hz), 129.27 (d, $J_{PC} = 3.0$ Hz), 130.54 (d, $J_{PC} = 2.0$ Hz), 130.56 (d, $J_{PC} = 12.6$ Hz), 132.36, 135.39 (d, $J_{PC} = 2.5$ Hz); GC–EIMS (70 eV) m/z (rel intensity) 248 $[M]^+$ (13), 153 (39), 152 (100); HRMS (EI) m/z $[M]^+$ Calc. for $C_{13}H_{13}O_3P$: 248.0602, Found: 248.0610. Anal. Calc. for $C_{13}H_{13}O_3P$: C, 62.91; H, 5.28. Found: C, 62.78; H, 5.20%.

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