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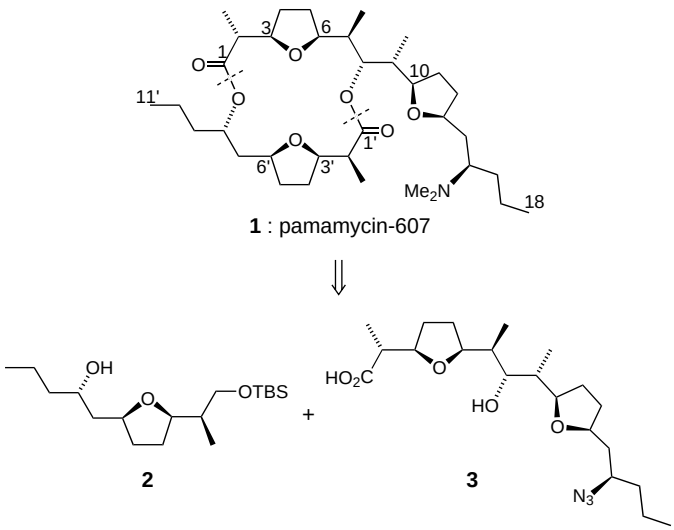


Scheme 1.

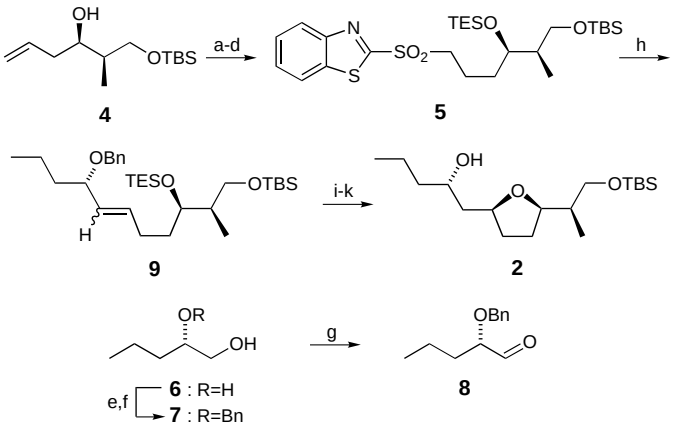
Total Synthesis of (+)-Pamamycin-607**

Sung Ho Kang,* Joon Won Jeong, Yu Sang Hwang, and Sung Bae Lee

The pamamycins are a novel family of naturally occurring homologous macrodiolides, which are found in *Streptomyces sp*.[1–9] They induce the aerial mycelium formation in *S. alboniger* to display autoregulatory activity.[1–3]. They also exhibit antibiotic activity against Gram-positive bacteria and pathogenic fungi,[1,2] inhibit myosin light chain kinase,[5] and mediate hydrophilic ion transport through lipophilic phases.[6] In addition, they show vasodilating,[7] anionophoric,[2–7] protonophoric,[8] and autolytic properties.[9] A major component of the family is pamamycin-607 (**1**), which has a molecular weight of 607. While the structure and relative stereochemistry of pamamycin-607 were elucidated by NMR spectroscopy, its absolute stereochemistry was later determined by a correlation study.[10] The remarkable biological activity of pamamycin-607 and its unique structural features led us to choose **1** as a synthetic target.[11] Herein we report an asymmetric total synthesis of **1**.

The two ester linkages of **1** were disconnected by retrosynthetic analysis to provide alcohol **2** and carboxylic acid **3** as the precursors of the C1′ – C11′ and C1 – C18 subunits, respectively (Scheme 1). As we envisaged that the three *cis*-2,5-disubstituted tetrahydrofurans comprising **2** and **3** could be formed[12] by iodoetherification of γ-triethylsilyloxyalkenes,[13] **9** (see Scheme 2) and **21** (see Scheme 3) were proposed as the intermediates. Construction of the double bonds in **9** and **21** was planned by means of a sulfone olefination[14] and the Horner – Emmons reaction. The C2 methyl group could be installed by the cuprate epoxide opening of **23** (see Scheme 4), in which the regioselectivity was assumed to be dictated by the bulky substituent. In addition, while the adjacent hydroxyl and methyl functional groups of **9** were expected to be delivered from the known alcohol **4** (Scheme 2),[15] those of **21** would be transformed by a Paterson[16] aldol reaction and Evans *anti* reduction.[17]

To prepare the bottom subunit **2**, alcohol **4** (78 % *de*) was consecutively subjected to silylation, hydroboration, Mitsunobu reaction, and *m*CPBA oxidation to afford sulfone **5** (Scheme 2). The requisite aldehyde **8** (the coupling partner of **5**) was obtained from the known diol **6**[18] by a sequence of benzylidene formation, DIBAH reduction,[19] and Swern



Scheme 2. a) TESCl, imidazole, DMF, RT, 83 % of desired diastereomer; b) $H_3B \cdot SMe_2$, THF, RT, then aqueous NaOH, H_2O_2, RT, 85 % ; c) Ph_3P, 2-mercaptobenzothiazole, DEAD, THF, 0 °C → RT, 87 %; d) *m*CPBA, CH_2Cl_2, RT, 90 %; e) TsOH, PhCHO, PhMe, reflux ($-H_2O$), 94 %; f) DIBAH, PhMe, 0 °C, 88 % for **7**; g) Swern oxidation; h) LiHMDS, THF, −78 °C, then **8**, RT, 80 %; i) I_2, Ag_2CO_3, Et_2O, RT, 92 %; j) Ph_3SnH, Et_3B, THF, 0 °C, 90 %; k) H_2, 10 % Pd/C, MeOH, RT, 99 %. TES = triethylsilyl, DMF = N,N-dimethylformamide, DEAD = diethyl azodicarboxylate, *m*CPBA = 3-chloroperoxybenzoic acid, Ts = toluenesulfonyl, DIBAH = diisobutylaluminum hydride, LiHMDS = lithium bis(trimethylsilyl)amide.

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oxidation.[20] Addition of **8** to the lithium anion obtained from **5** provided a 1.2:1 mixture of *trans*- and *cis*-alkenes **9**. After several strategic model studies we chose the iodoetherification of γ-triethylsilyloxyalkenes, because our total synthesis required the development of reliable methodology to form *cis*-2,5-disubstituted tetrahydrofurans. Experimental optimization revealed that the most efficient outcome could be attained by exposing **9** to iodine in the presence of silver carbonate in diethyl ether. The iodocyclization of both the *cis* and *trans* isomers proceeded with similar efficiency (since the isomers were inseparable, the 1.2:1 mixture of *trans*- and *cis*-alkenes **9** was subjected to iodoetherification to provide a 1.2:1 mixture of iodides in 92% yield). It is of note that the addition of silver carbonate was unprecedented, to our knowledge, and indispensable for the consistency, stereoselectivity, and completion of the iodocyclization. Remarkably, reductive deiodination[21] and debenzylation of the cyclized products gave rise to **2** as the only stereoisomer.

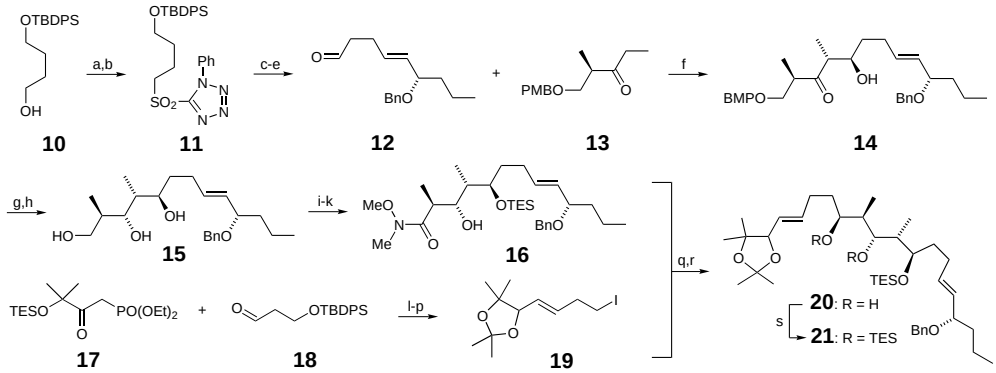
Once the assembly of the C1′–C11′ subunit was complete, the synthesis of the upper subunit **3** began with the formation of sulfone **11**, derived from alcohol **10**[22] by Mitsunobu reaction and *m*CPBA oxidation (Scheme 3). The coupling of **11** with **8** using KHMDS, and the ensuing desilylation, produced a 7:1 separable mixture of *trans*- and *cis*-alkenes. Although the mixture could be employed for the next synthetic sequence, the *trans* and *cis* isomers were separated for the purposes of spectroscopic interpretation in the following steps, and then the *trans*-olefinic alcohol was oxidized to aldehyde **12**.

Aldol condensation of the known ethylketone **13**[23] with **12** occurred via an *E*-boron enolate to provide a 31:1 mixture of the desired *anti*-aldol product **14** and the corresponding diastereomers. Stereoselective *anti* reduction of the keto group of **14** and the subsequent deprotection gave predominantly the desired α-alcohol **15**, along with a small amount of the isomeric β-alcohol (>60:1). Alcohol **15** was chemoselectively oxidized[24] to a six-membered lactone, which was subjected to Weinreb-amide formation[25] and regioselective monosilylation to yield the Weinreb amide **16**.

With access to the right part of **21** secure, it was necessary to prepare its left part as alkyl iodide. Accordingly, the known phosphonate **17**[26] was olefinated with aldehyde **18** to furnish exclusively the *trans*-alkene. The conjugated ketone was reduced,[27] desilylated, protected as the acetonide, and iodinated to give the racemic iodide **19**. Transmetallation of **19** followed by the addition of amide **16** yielded the β-hydroxyketone. Diastereoselective *anti* reduction of the ketone gave a 20:1 mixture of the desired stereoisomeric alcohols **20** and their corresponding diastereomers. After disilylation of **20**, double iodoetherification of the generated silyl ethers **21** was performed under the aforementioned cyclization conditions to supply tetrahydrofurans **22** with complete *cis* stereoselectivity. Derivatization of **22** to form epoxide **23** was achieved by successive acidic deprotection, cyclization, reductive deiodination, and silylation (Scheme 4). Methylation of **23** with lithium dimethylcuprate yielded only the desired regioisomeric alcohols, with partially desilylated secondary silyloxy groups. Hydrogenation of the mixture removed the benzyl and triethylsilyl groups concurrently. The produced tetraols **24** were subjected to Mitsunobu conditions,[28] to convert the least hindered hydroxyl group into an azido group chemoselectively. The resulting vicinal diols were oxidized to give carboxylic acid **3**.

With the synthesis of the two key subunits **2** and **3** completed, these units were coupled under Yamaguchi's conditions,[29] and the coupled ester **25** was desilylated, and subsequently oxidized chemoselectively to carboxylic acid **26**.[30] Lactonization of **26** via the thiopyridyl ester, in the presence of cupric bromide,[31] gave macrodiolide **27**. The azido group of **27** was reduced and the in situ addition of formaldehyde to the generated amine under the hydrogenation conditions produced pamamycin-607 (**1**). The synthetic **1** and its CF_3COOD salt were identical to the natural pamamycin-607 and its CF_3COOD salt in all aspects.[10a, 32]

A highly enantioselective total synthesis of pamamycin-607 has been attained from the readily available alcohol **10** through 27 steps (5.4% overall yield). The synthetic sequence culminated in a stereoselective double cyclization in the



Scheme 3. a) 1-Phenyl-1H-tetrazole-5-thiol, Ph_3P, DEAD, THF, RT, 86%; b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, RT, 93%; c) KHMDS, **8**, DME, $-78\,^{\circ}C \rightarrow$RT; d) nBu_4NF, THF, RT, 72% for *trans* isomer and 2 steps; e) Swern oxidation; f) **13**, *c*Hx_2BCl, Et_3N, Et_2O, $0\,^{\circ}C$, then **12**, $-78 \rightarrow -20\,^{\circ}C$, 85%; g) $Me_4NBH(OAc)_3$, AcOH, MeCN, $-30 \rightarrow -20\,^{\circ}C$, 88%; h) $(NH_4)_2Ce(NO_3)_6$, H_2O, MeCN, $0\,^{\circ}C$, 88%; i) TEMPO, NCS, nBu_4NCl, aq. $NaHCO_3$, K_2CO_3 (pH 8.6), CH_2Cl_2, RT, 97%; j) $MeONHMe \cdot HCl$, Me_3Al, CH_2Cl_2, $-78\,^{\circ}C$, 92%; k) TESCl, imidazole, CH_2Cl_2, $-40\,^{\circ}C$, 99%; l) iPr_2NEt, LiCl, MeCN, RT, 88%; m) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, $0\,^{\circ}C$, 96%; n) nBu_4NF, THF, RT, 99%; o) *p*-TsOH, acetone, RT, 92%; p) I_2, Ph_3P, imidazole, THF, $0\,^{\circ}C \rightarrow$RT, 96%; q) *t*BuLi, Et_2O, $-78 \rightarrow -20^{0}C$, then **16**, $-50 \rightarrow -20\,^{\circ}C$, 82%; r) $Me_4NBH(OAc)_3$, AcOH, MeCN, $-20\,^{\circ}C$, 92%; s) TESOTf, Et_3N, CH_2Cl_2, $0\,^{\circ}C$, 98%. KHMDS = potassium bis(trimethylsilyl)amide, DME = 1,2-dimethoxyethane, *c*Hx = cyclohexyl, Ac = acetyl, TEMPO = 2,2,6,6,-tetramethyl-1-piperidinyloxy, NCS = N-chlorosuccinimide, OTf = trifuloromethanesulfonate.

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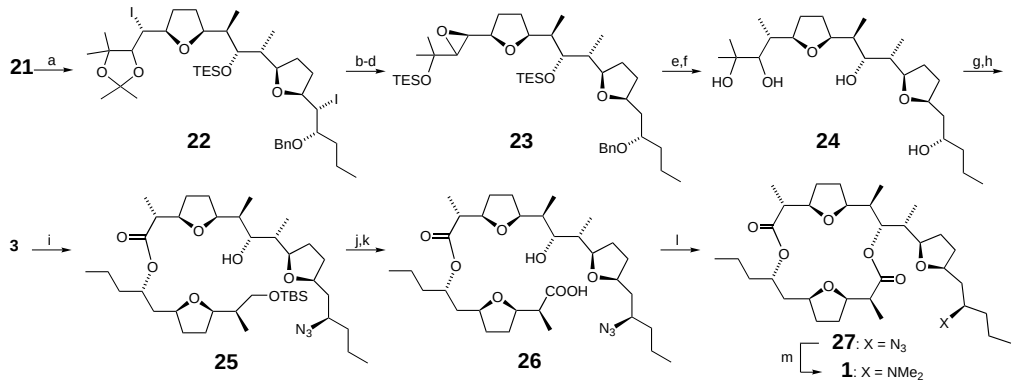

Scheme 4. a) I_2, Ag_2CO_3, Et_2O, RT, 81%; b) 2N HCl, MeOH, reflux, then K_2CO_3, RT, 86%, c) Ph_3SnH, Et_3B, THF, 0°C, 96%; d) TESOTf, Et_3N, CH_2Cl_2, −20°C, 89%; e) Me_2CuLi, Et_2O, 5°C; f) H_2, $Pd(OH)_2$/C, EtOH, RT, 88% for 2 steps; g) HN_3, Ph_3P, DEAD, PhH, 0°C, 97%; h) $NaIO_4$, *t*BuOH, H_2O, RT, then 1.25M NaH_2PO_4, 1M $KMnO_4$, RT, 87%; i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, RT, then **2**, DMAP, PhH, RT, 90%; j) nBu_4NF, THF, RT, 94%; k) TEMPO, $NaClO_2$, NaH_2PO_4 buffer (pH 6.7), NaOCl, MeCN, RT, 91%; l) $(PyS)_2$, Ph_3P, MeCN, then $CuBr_2$, MeCN, RT, 62%; m) H_2, 10% Pd/C, MeOH, RT, then 37% aq. HCHO, AcOH, RT, 89%. DMAP = 4-dimethylaminopyridine, $(PyS)_2$ = 2,2′-dipyridyl disulfide.

presence of the unprecedented additive silver carbonate, and the sterically controlled, regioselective cuprate epoxide opening.

Experimental Section

22: Silver carbonate (970 mg, 3.50 mmol) was stirred with iodine (1.23 g, 8.76 mmol) in Et_2O (15 mL) at room temperature for 5 min. The heterogeneous solution was cooled to 0°C and then **21** (390 mg, 0.438 mmol) dissolved in Et_2O (4 mL) was added. The resulting solution was warmed to room temperature immediately and stirred for 15 h. After quenching with aqueous $Na_2S_2O_3$ (10%, 30 mL), the mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, EtOAc:hexane 1:30) to give **22** (323 mg, 81%).

1: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.88$ (1H, dd, $J = 10.8$, 0.6 Hz), 4.82 (1H, dddd, $J = 11.4$, 6.6, 4.8, 4.0 Hz), 4.15 (1H, ddd, $J = 8.6$, 5.5, 2.2 Hz), 4.01 (1H, td, $J = 9.5$, 5.0 Hz), 3.95 (1H, ddd, $J = 9.0$, 6.9, 2.2 Hz), 3.86 (1H, br t, $J = 8.5$ Hz), 3.77–3.71 (1H, m), 3.60 (1H, td, $J = 10.2$, 3.9 Hz), 3.34 (1H, dt, $J = 10.0$, 6.7 Hz), 3.12 (3H, d, $J = 5.2$ Hz), 2.82 (3H, d, $J = 5.0$ Hz), 2.58 (1H, qd, $J = 6.9$, 2.2 Hz), 2.24–1.12 (27H, m), 1.05 (3H, d, $J = 7.0$ Hz), 1.04 (3H, d, $J = 6.8$ Hz), 0.97 (3H, t, $J = 7.1$ Hz), 0.86 (3H, t, $J = 7.3$ Hz), 0.77 (3H, d, $J = 6.6$ Hz), 0.77 (3H, d, $J = 6.9$ Hz); the protons adjacent to that at 4.82 ppm appear at 2.24–1.12 ppm (27H, m), the other $J = 11.4$ Hz coupling is buried in this region. ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 173.7$, 173.2, 82.2, 80.2, 78.5, 78.3, 76.4, 74.5, 74.4, 71.1, 66.9, 47.2, 43.0, 41.4, 41.0, 38.6, 37.4, 37.0, 36.9, 34.3, 31.5, 31.1, 30.5, 29.6, 29.5, 27.6, 27.3, 19.5, 18.0, 14.1 (2 peaks), 13.8, 10.3, 9.6, 8.7; IR (neat): $\tilde{\nu}$2966, 2875, 1737, 1466, 1385, 1265, 1189, 1127, 1112, 1071, 1054 cm^{-1}; HRMS (EI) calcd for $C_{35}H_{61}NO_7$: 607.4448, found: 607.4447; $([\alpha]_D^{20>} = +10.9$, $c = 0.30$, MeOH), $([\alpha]_D^{32>} = +21.7$, $c = 0.30$, MeOH), $([\alpha]_D^{32>} = +23.0$, c = 0.30, MeOH).

1·D$^+$CF$_3$COO$^-$: The synthetic **1** (7 mg, 0.0115 mmol) was dissolved in [D$_6$]acetone (0.5 mL) in the presence of CF_3COOD (5 μL, 0.0649 mmol) in a glove box. This solution was sampled for NMR spectral analysis. ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 4.99$ (1H, dd, $J = 11.0$, 0.8 Hz), 4.92 (1H, dddd, $J = 11.8$, 6.7, 5.1, 3.8 Hz), 4.28 (1H, ddd, $J = 9.0$, 5.6, 2.3 Hz), 4.09 (1H, ddd, $J = 9.1$, 6.9, 2.2 Hz), 3.92–3.81 (2H, m), 3.71 (1H, ddd, $J = 10.8$, 9.9, 4.0 Hz), 3.66–3.59 (1H, m), 3.41–3.34 (1H, m), 3.23 (3H, s), 2.98 (3H, s), 2.74 (1H, dq, $J = 6.8$, 2.2 Hz), 2.26 (1H, dq, $J = 10.2$, 7.0 Hz), 2.31–2.26 (1H, m), 2.09–1.10 (25H, m), 1.09 (3H, d, $J = 7.0$ Hz), 1.05 (3H, d, $J = 6.8$ Hz), 1.00 (3H, t, $J = 7.2$ Hz), 0.87 (3H, t, $J = 7.3$ Hz), 0.85 (6H, d, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 175.0$, 173.8, 83.2, 81.1, 80.0, 79.3, 77.3, 75.3, 75.2, 71.5, 68.7, 47.9, 43.8, 42.1, 41.6, 39.5, 37.9 (2 peaks), 36.6, 34.3, 32.1, 31.6, 31.2, 30.1, 29.0, 28.1, 28.0, 20.4, 18.8, 14.3, 14.1, 14.0, 10.4, 9.8, 8.7.

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Proton-Coupled Electron Transfer from Phosphorus: A P–H/P–D Kinetic Isotope Effect of 178**

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In the extensive redox chemistry of high oxidation state ruthenium(IV) – oxo,[1] osmium(VI) – nitrido,[2] osmium(IV – VI) – hydrazido,[3] osmium(IV) – cyanoimido,[4] and osmium(IV) – sulfilimido complexes,[5] multiple mechanistic pathways have been uncovered based on multiple electron and atom/group transfers. Examples include O atom,[6] N^- ion,[7] H^- ion,[8] and $NSC_6H_3Me_2^{2-}$ transfer.[9] Kinetic studies have revealed the existence of proton-coupled electron-transfer pathways based on bound oxo/hydroxo/aqua,[1, 10] dialkylhydrazido,[11] and sulfilimido[12] ligands that occur with large H/D kinetic isotope effects. Examples include $k_{O\text{-}H}/k_{O\text{-}D} = 30 \pm 1$[10a] for the oxidation of hydroquinone (H_2Q) to benzoquinone (Q) by *cis*-$[Ru^{IV}(bpy)_2(py)(O)]^{2+}$ (bpy = 2,2′-bipyridine and py = pyridine) [Eq. (1)].

$$cis\text{-}[Ru^{IV}(bpy)_2(py)(O)]^{2+} + H_2Q \rightarrow cis\text{-}[Ru^{II}(bpy)(py)(H_2O)]^{2+} + Q \quad (1)$$

Other examples are $k_{N\text{-}H}/k_{N\text{-}D} \geq 41.4 \pm 1.3$[11] for the reduction of Q to H_2Q by *trans*-$[Os^{IV}(tpy)(Cl)_2\{N(H)N(CH_2)_4O\}]^+$ [Eq. (2); tpy = 2,2′:6′,2″-terpyridine], and $k_{S\text{-}H}/k_{S\text{-}D} \geq 31.1 \pm 0.2$[12] for the oxidation of *trans*-$[Os^{IV}(tpy)(Cl)_2\{NS(H)C_6H_3Me_2\}]^+$ by Q [Eq. (3)].

$$2\,trans\text{-}[Os^{IV}(tpy)(Cl)_2\{N(H)N(CH_2)_4O\}]^+ + Q \rightarrow 2\,trans\text{-}[Os^{V}(tpy)(Cl)_2\{NN(CH_2)_4O\}]^+ + H_2Q \quad (2)$$

$$2\,trans\text{-}[Os^{IV}(tpy)(Cl)_2\{NS(H)C_6H_3Me_2\}]^+ + Q \rightarrow 2\,trans\text{-}[Os^{V}(tpy)(Cl)_2(NSC_6H_3Me_2)]^+ + H_2Q \quad (3)$$

We report here the first example of proton-coupled electron transfer based on a phosphorus atom. Its existence may have important implications for the redox reactivity of organophosphorus compounds,[13] phosphoraniminato complexes,[14] and biologically active substances containing P–H acids.[15]

A rapid reaction occurs between the osmium(VI) – nitrido complex, $[Os^{VI}(Tp)(Cl)_2(N)]$ ($Tp^- =$ tris(pyrazolyl)borate), and diethylphosphane ($HPEt_2$) in CH_2Cl_2 under nitrogen at room temperature to give the osmium(IV) – phosphoraniminato product, $[Os^{IV}(Tp)(Cl)_2\{NP(H)Et_2\}]$ ($Os^{IV}NP(H)Et_2$) [Eq. (4)].

$$[Os^{IV}(Tp)(Cl)_2(N)] + HPEt_2 \rightarrow [Os^{IV}(Tp)(Cl)_2\{NP(H)Et_2\}] \quad (4)$$

The product was isolated (94 % yield) and characterized by elemental analysis,[16a] cyclic voltammetry,[16b] and UV/Vis,[16c] and infrared[16d] spectroscopies. Similar to other d^4 Os^{IV} – phosphoraniminato complexes,[17] Os^{IV}-$NP(H)Et_2$ is paramagnetic as shown by ^1H NMR spectroscopy. Cyclic voltammetric measurements in 1:1 (v/v) CH_3CN:H_2O ($\mu = 1.0$ M in NH_4PF_6) reveal that $E_{1/2}$ for the osmium(V/IV) couple decreases by 57 mV/pH unit from pH 0 ($E_{1/2} = 0.560$ V, versus sodium saturated calomel electrode (SSCE)) to 3.5 ($E_{1/2} = 0.360$ V, versus SSCE) and is pH independent above pH 3.5.[18] From these data, $pK_a = 3.52 \pm 0.04$ for the acid – base equilibrium shown in Equation (5), and Supporting Information Figure 1.

$$[Os^{IV}(Tp)(Cl)_2\{NP(H)Et_2\}] \overset{K_a}{\rightleftharpoons} [Os^{IV}(Tp)(Cl)_2(NPEt_2)]^- + H^+ \quad (5)$$

Reminiscent of the $[Os^{V}(tpy)(Cl)_2\{NN(CH_2)_4O\}]^+$/$[Os^{IV}(tpy)(Cl)_2\{N(H)N(CH_2)_4O\}]^+$ and $[Os^{V}(tpy)(Cl)_2(NSC_6H_3Me_2)]^+$/$[Os^{IV}(tpy)(Cl)_2\{NS(H)C_6H_3Me_2\}]^+$ couples,

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