# COMMUNICATIONS

Soc. 1994, 116, 6130-6141; c) B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, R. A. J. Smith, J. Am. Chem. Soc. 1990, 112, 4404-4410;
B. H. Lipshutz, C. Hackmann, J. Org. Chem. 1994, 59, 7437-7444;
D. E. Stack, W. R. Klein, R. D. Rieke, Tetrahedron Lett. 1993, 34, 3063-3066.

- [8] TaCl<sub>5</sub> has scarcely been used in organic synthesis. a) J. Howarth, K. Gillespie, *Tetrahedron Lett.* **1996**, *37*, 6011–6012; b) H. Maeta, T. Nagasawa, Y. Handa, T. Takei, Y. Osamura, K. Suzuki, *Tetrahedron Lett.* **1995**, *36*, 899–902; c) K. Suzuki, T. Hashimoto, H. Maeta, T. Matsumoto, *Synlett* **1992**, 125–128; d) T. Hashimoto, H. Maeta, T. Matsumoto, M. Morooka, S. Ohba, K. Suzuki, *Synlett* **1992**, 340–342.
- [9] There is a possibility that low-valent tantalum species are involved in the reaction; however, the reaction mixture did not display significant color.
- [10] There are few examples of the conjugate prenylsilylation of enones with TiCl<sub>4</sub>: ref. [2a] and R. L. Danheiser, D. M. Fink, *Tetrahedron Lett.* 1985, 26, 2509-2512.
- [11] Although we have no further information as yet, this order of reactivity strongly indicates an electron transfer mechanism. J. Otera, Y. Fujita, N. Sakuta, M. Fujita, S. Fukuzumi, J. Org. Chem. 1996, 61, 2951–2962.

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

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The pamamycins are a novel family of naturally occurring homologous macrodiolides, which are found in Streptomyces sp.<sup>[1-9]</sup> They induce the aerial mycelium formation in S. alboniger to display autoregulatory activity.<sup>[1-3]</sup>. They also exhibit antibiotic activity against Gram-positive bacteria and pathogenic fungi,<sup>[1,2]</sup> inhibit myosin light chain kinase,<sup>[5]</sup> and mediate hydrophilic ion transport through lipophilic phases.<sup>[6]</sup> In addition, they show vasodilating.<sup>[7]</sup> anionophoric.<sup>[2–7]</sup> protonophoric,<sup>[8]</sup> and autolytic properties.<sup>[9]</sup> 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.<sup>[10]</sup> The remarkable biological activity of pamamycin-607 and its unique structural features led us to choose 1 as a synthetic target.<sup>[11]</sup> 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<sup>[12]</sup> by iodoetherification of  $\gamma$ -triethylsilyloxyalkenes,<sup>[13]</sup> **9** (see Scheme 2) and **21** (see Scheme 3) were

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Scheme 1.

proposed as the intermediates. Construction of the double bonds in **9** and **21** was planned by means of a sulfone olefination<sup>[14]</sup> 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),<sup>[15]</sup> those of **21** would be transformed by a Paterson<sup>[16]</sup> aldol reaction and Evans *anti* reduction.<sup>[17]</sup>

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,<sup>[19]</sup> 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 $\rightarrow$ RT, 87%; d) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, RT, 90%; e) TsOH, PhCHO, PhMe, reflux ( $-H_2O$ ), 94%; f) DIBAH, PhMe, 0°C, 88% for **7**; g) Swern oxidation; h) LiHMDS, THF,  $-78^{\circ}$ C, then **8**, RT, 80%; i) I<sub>2</sub>, Ag<sub>2</sub>CO<sub>3</sub>, Et<sub>2</sub>O, RT, 92%; j) Ph<sub>3</sub>SnH, Et<sub>3</sub>B, THF, 0°C, 90%; k) H<sub>2</sub>, 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(trimethyl-silyl)amide.

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oxidation.<sup>[20]</sup> 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  $\gamma$ -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 cisalkenes 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<sup>[21]</sup> 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**<sup>[22]</sup> 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  $\alpha$ -alcohol 15, along with a small amount of the isomeric  $\beta$ -alcohol (>60:1). Alcohol 15 was chemoselectively oxidized<sup>[24]</sup> to a six-membered lactone, which was subjected to Weinreb-amide formation<sup>[25]</sup> and regioselective monosilylation to yield the Weinreb amide 16.

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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<sup>[26]</sup> was olefinated with aldehyde 18 to furnish exclusively the trans-alkene. The conjugated ketone was reduced.<sup>[27]</sup> desilvlated, protected as the acetonide, and iodinated to give the racemic iodide 19. Transmetallation of **19** followed by the addition of amide **16** yielded the  $\beta$ 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 silvlation (Scheme 4). Methylation of 23 with lithium dimethylcuprate yielded only the desired regioisomeric alcohols, with partially desilylated secondary silvloxy groups. Hydrogenation of the mixture removed the benzyl and triethylsilyl groups concurrently. The produced tetraols 24 were subjected to Mitsunobu conditions,<sup>[28]</sup> 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,<sup>[29]</sup> and the coupled ester 25 was desilylated, and subsequently oxidized chemoselectively to carboxylic acid 26.<sup>[30]</sup> Lactonization of 26 via the thiopyridyl ester, in the presence of cupric bromide,<sup>[31]</sup> 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<sub>3</sub>COOD salt were identical to the natural pamamycin-607 and its CF<sub>3</sub>COOD salt in all aspects.<sup>[10a, 32]</sup>

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<sub>3</sub>P, DEAD, THF, RT, 86%; b) *m*CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, RT, 93%; c) KHMDS, **8**, DME,  $-78 \circ C \rightarrow RT$ ; d) *n*Bu<sub>4</sub>NF, THF, RT, 72% for *trans* isomer and 2 steps; e) Swern oxidation; f) **13**, *c*Hx<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, 0°C, then **12**,  $-78 \rightarrow -20°C$ , 85%; g) Me<sub>4</sub>NBH(OAc)<sub>3</sub>, AcOH, MeCN,  $-30 \rightarrow -20°C$ , 88%; h) (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub>, H<sub>2</sub>O, MeCN, 0°C, 88%; i) TEMPO, NCS, *n*Bu<sub>4</sub>NCl, aq. NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> (pH 8.6), CH<sub>2</sub>Cl<sub>2</sub>, RT, 97%; j) MeONHMe · HCl, Me<sub>3</sub>Al, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 92%; k) TESCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, -40°C, 99%; l) *i*Pr<sub>2</sub>NEt, LiCl, MeCN, RT, 88%; m) NaBH<sub>4</sub>, CeCl<sub>3</sub>· 7H<sub>2</sub>O, MeOH, 0°C, 96%; n) *n*Bu<sub>4</sub>NF, THF, RT, 99%; o) *p*-TsOH, acetone, RT, 92%; p) I<sub>2</sub>, Ph<sub>3</sub>P, imidazole, THF, 0°C  $\rightarrow$  RT, 96%; q) *t*BuLi, Et<sub>2</sub>O,  $-78 \rightarrow -20°C$ , then **16**,  $-50 \rightarrow -20°C$ , 82%; r) Me<sub>4</sub>NBH(OAc)<sub>3</sub>, AcOH, MeCN, -20°C, 92%; s) TESOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 98%. KHMDS = potassium bis(trimethylsilyl)amide, DME = 1,2-dimethoxyethane, *c*Hx = cyclohexyl, Ac = acetyl, TEMPO = 2,2,6,6,-tetramethyl-1-piperidinyl-oxy, 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,  $0^{\circ}C$ , 96%; d) TESOTF,  $Et_3N$ ,  $CH_2CI_2$ ,  $-20^{\circ}C$ , 89%; e)  $Me_2CuLi$ ,  $Et_2O$ ,  $5^{\circ}C$ ; f)  $H_2$ ,  $Pd(OH)_2/C$ , EtOH, RT, 88% for 2 steps; g)  $HN_3$ ,  $Ph_3P$ , DEAD, PhH,  $0^{\circ}C$ , 97%; h)  $NaIO_4$ , tBuOH,  $H_2O$ , RT, then 1.25 M Na $H_2PO_4$ , 1M KMnO<sub>4</sub>, 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)<sub>2</sub>,  $Ph_3P$ , 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)<sub>2</sub> = 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<sub>2</sub>O (15 mL) at room temperature for 5 min. The heterogeneous solution was cooled to  $0^{\circ}C$  and then 21 (390 mg, 0.438 mmol) dissolved in Et<sub>2</sub>O (4 mL) was added. The resulting solution was warmed to room temperature immediately and stirred for 15 h. After quenching with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 %, 30 mL), the mixture was extracted with Et<sub>2</sub>O (3  $\times$ 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<sub>2</sub>, EtOAc:hexane 1:30) to give 22 (323 mg, 81%). 1: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 4.88$  (1 H, dd, J = 10.8, 0.6 Hz), 4.82 (1 H, dddd, J = 11.4, 6.6, 4.8, 4.0 Hz), 4.15 (1 H, ddd, J = 8.6, 5.5, 2.2 Hz), 4.01 (1 H, td, J = 9.5, 5.0 Hz), 3.95 (1 H, ddd, J = 9.0, 6.9, 2.2 Hz), 3.86 (1 H, br t, J=8.5 Hz), 3.77-3.71 (1 H, m), 3.60 (1 H, td, J=10.2, 3.9 Hz), 3.34 (1 H, dt, J = 10.0, 6.7 Hz), 3.12 (3 H, d, J = 5.2 Hz), 2.82 (3 H, d, J = 5.0 Hz), 2.58 (1 H, qd, J = 6.9, 2.2 Hz), 2.24 – 1.12 (27 H, m), 1.05 (3 H, d, J = 7.0 Hz), 1.04 (3 H, d, J = 6.8 Hz), 0.97 (3 H, t, J = 7.1 Hz), 0.86 (3 H, t, J = 7.3 Hz), 0.77 (3 H, d, J = 6.6 Hz), 0.77 (3 H, d, J = 6.9 Hz); the protons adjacent to that at 4.82 ppm appear at 2.24 - 1.12 ppm (27 H, m), the other J = 11.4 Hz coupling is buried in this region. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 173.7$ , 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): v2966, 2875, 1737, 1466, 1385, 1265, 1189, 1127, 1112, 1071, 1054 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>35</sub>H<sub>61</sub>NO<sub>7</sub>: 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<sup>+</sup>CF<sub>3</sub>COO<sup>-</sup>: The synthetic **1** (7 mg, 0.0115 mmol) was dissolved in  $[D_6]$ acetone (0.5 mL) in the presence of CF<sub>3</sub>COOD (5 µL, 0.0649 mmol) in a glove box. This solution was sampled for NMR spectral analysis. <sup>1</sup>H NMR (400 MHz,  $[D_6]$ acetone):  $\delta = 4.99$  (1H, dd, J = 11.0, 0.8 Hz), 4.92 (1H, ddd, 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 (25 H, 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); <sup>13</sup>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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- a) P. A. McCann, B. M. Pogell, J. Antibiot. 1979, 32, 673-678; b) W.-G. Chou, B. M. Pogell, Biochem. Biophys. Res. Commun. 1981, 100, 344-350; c) W.-G. Chou, B. M. Pogell, Antimicrob. Agents Chemother. 1981, 20, 443-454.
- [2] S. Kondo, K. Yasui, M. Natsume, M. Katayama, S. Marumo, J. Antibiot. 1988, 41, 1196–1204; b) M. Natsume, J. Tazawa, K. Yagi, H. Abe, S. Kondo, S. Marumo, J. Antibiot. 1995, 48, 1159–1164.
- [3] M. Natsume, J. Antibiot. 1992, 45, 1026–1028.
- [4] M. Natsume, K. Yasui, S. Kondo, S. Marumo, *Tetrahedron Lett.* 1991, 32, 3087–3090.
- [5] S. Nakanishi, K. Kita, Y. Uosaki, M. Yoshida, Y. Saitoh, A. Mikara, J. Kawamoto, Y. Matsuda, J. Antibiot. 1994, 47, 855–861.
- [6] a) C. Stengel, G. Reinhardt, U. Gräfe, J. Basic Microbiol. 1992, 32, 339–345; b) U. Gräfe, R. Schlegel, K. Dornberger, W. Ihn, M. Ritzau, C. Stengel, M. Beran, W. Günther, Nat. Prod. Lett. 1993, 265–271; c) U. Gräfe, C. Schlegel, U. Möllmann, L. Heinisch, Pharmazie 1994, 49, 343–346.
- [7] K. Fujii, O. Hara, S. Marumo, Y. Sakagami, *Bioorg. Med. Chem. Lett.* 1995, 5, 843–846.
- [8] P. A. Grigoriev, A. Berg, R. Schlegel, U. Gräfe, *Bioelectrochem. Bioenerg.* 1996, 39, 295–298.
- [9] A. Hartl, A. Stelzner, R. Schlegel, S. Heinze, H. Hülsmann, W. Fleck, U. Gräfe, J. Antibiot. 1998, 51, 1040-1046.
- [10] a) S. Kondo, K. Yasui, M. Katayama, S. Marumo, T. Kondo, H. Hattori, *Tetrahedron Lett.* **1987**, *28*, 5861–5864; b) M. Natsume, S. Kondo, S. Marumo, J. Chem. Soc. Chem. Commun. **1989**, 1911–1913.
- [11] For a total synthesis of 1 see : a) O. Germany, N. Kumar, E. J. Thomas, *Tetrahedron Lett.* 2001, 42, 4969–4974; b) E. Lee, E. J. Jeong, E. J. Kang, L. T. Sung, S. K. Hong, J. Am. Chem. Soc. 2001, 123, 10131– 10132; c) Y. Wang, H. Bernsmann, M. Gruner, P. Metz, *Tetrahedron Lett.* 2001, 42, 7801–7804. For synthetic approaches to 1 see : a) R. D. Walkup, S. W. Kim, S. D. Wagy, J. Org. Chem. 1993, 58, 6486–6490; b) R. D. Walkup, S. W. Kim, J. Org. Chem. 1993, 58, 6486–6490; c) R. D. Walkup, S. W. Kim, *J. Org. Chem.* 1994, 59, 3433–3441; c) R. D. Walkup, S. W. Kim, *Tetrahedron Lett.* 1995, 36, 3091–3094; d) I. Mavropoulos, P. Perlmutter, *Tetrahedron Lett.* 1996, 37, 3751– 3754; e) G. Mandville, C. Girard, R. Bloch, *Tetrahedron Asymmetry* 1997, 8, 3665–3673; f) G. Mandville, R. Bloch, *Eur. J. Org. Chem.* 1999, 2303–2307; g) G. Solladié, X. J. Salom-Roig, G. Hanquet, *Tetrahedron Lett.* 2000, 41, 551–554; h) M. A. Calter, F. C. Bi, Org. Lett. 2000, 2, 1529–1531; i) G. Solladié, X. J. Salom-Roig, G. Hanquet, *Tetrahedron Lett.* 2000, 41, 2737–2740.
- [12] a) S. D. Rychnovsky, P. A. Bartlett, J. Am. Chem. Soc. 1981, 103, 3963-3964; b) T. L. B. Boivin, Tetrahedron 1987, 43, 3309-3362; c) G. Cardillo, M. Orena, Tetrahedron 1990, 46, 3321-3408; d) J.-C. Harmange, B. Figadere, Tetrahedron Asymmetry 1993, 4, 1711-1754.
- [13] S. H. Kang, S. B. Lee, *Tetrahedron Lett.* **1993**, *34*, 7579–7582.
- [14] a) J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878; b) P. R. Blakemore, W. J. Cole, P. J. Kociénski, A. Morley, *Synlett.* **1998**, 26–28.

1433-7851/02/4108-1394 \$ 20.00+.50/0 Angew. Chem. Int. Ed. 2002, 41, No. 8

- [15] W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Staub, A. D. Palkowitz, J. Org. Chem. 1990, 55, 4117–4126.
- [16] I. Paterson, J. M. Goodman, M. Isaka, *Tetrahedron Lett.* 1989, 30, 7121-7124.
- [17] D. A. Evans, K. T. Chapman, E. M. Carreira, J. Am. Chem. Soc. 1988, 110, 3560–3578.
- [18] K. Kiegiel, P. Prokopowicz, J. Jurczak, Synth. Commun. 1999, 29, 3999-4005.
- [19] S. Takano, M. Akiyama, S. Sato, K. Ogasawara, Chem. Lett. 1983, 1593–1596.
- [20] A. J. Mancuso, D. Swern, Synthesis 1981, 165-185.
- [21] K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, K. Utimoto, Bull. Chem. Soc. Jpn. 1989, 62, 143 – 147.
- [22] S. Genard, H. Patin, Bull. Soc. Chim. Fr. 1991, 128, 397-406.
- [23] C. J. Forsyth, C. S. Lee, *Tetrahedron Lett.* **1996**, *37*, 6449–6452.
- [24] J. Einhorn, C. Einhorn, F. Ratajczak, J.-L. Pierre, J. Org. Chem. 1996, 61, 7452-7454.
- [25] a) J. L. Levin, E. Turos, S. M. Weinreb, Synth. Commun. 1982, 12, 989–993; b) D. A. Evans, S. L. Bender, J. Morris, J. Am. Chem. Soc. 1988, 110, 2506–2526.
- [26] P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, J. Org. Chem. 1986, 51, 2525-2529.
- [27] J.-L. Luche, J. Am. Chem. Soc. 1978, 100, 2226-2227.
- [28] a) D. L. Hughes, Org. React. 1992, 42, 335-656; b) E. Fabiano, B. T. Golding, M. M. Sadeghi, Synthesis 1987, 190-192.
- [29] J. Inanagana, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, Bull. Chem. Soc. Jpn. 1979, 52, 1989–1993.
- [30] M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, J. Org. Chem. 1999, 64, 2564–2566.
- [31] S. Kim, J. I. Lee, J. Org. Chem. 1984, 49, 1712-1716.
- [32] The physicochemical data of the natural pamamycin-607 and its CF<sub>3</sub>COOD salt were provided by Professor Masahiro Natsume at Tokyo University of Agriculture and Technology.

#### 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,<sup>[1]</sup> osmium(VI) – nitrido,<sup>[2]</sup> osmium(IV – VI) – hydrazido,<sup>[3]</sup> osmium(IV) – cyanoimido,<sup>[4]</sup> and osmium(IV) –

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sulfilimido complexes,<sup>[5]</sup> multiple mechanistic pathways have been uncovered based on multiple electron and atom/group transfers. Examples include O atom,<sup>[6]</sup> N<sup>-</sup> ion,<sup>[7]</sup> H<sup>-</sup> ion,<sup>[8]</sup> and NSC<sub>6</sub>H<sub>3</sub>Me<sub>2</sub><sup>2-</sup> transfer.<sup>[9]</sup> Kinetic studies have revealed the existence of proton-coupled electron-transfer pathways based on bound oxo/hydroxo/aqua,<sup>[1, 10]</sup> dialkylhydrazido,<sup>[11]</sup> and sulfilimido<sup>[12]</sup> ligands that occur with large H/D kinetic isotope effects. Examples include  $k_{\text{O-H}}/k_{\text{O-D}} = 30 \pm 1^{[10a]}$  for the oxidation of hydroquinone (H<sub>2</sub>Q) to benzoquinone (Q) by *cis*-[Ru<sup>IV</sup>(bpy)<sub>2</sub>(py)(O)]<sup>2+</sup> (bpy=2,2'-bipyridine and py=pyridine) [Eq. (1)].

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

Other examples are  $k_{\text{N-H}}/k_{\text{N-D}} \ge 41.4 \pm 1.3^{[11]}$  for the reduction of Q to H<sub>2</sub>Q by *trans*-[Os<sup>IV</sup>(tpy)(Cl)<sub>2</sub>{N(H)N(CH<sub>2</sub>)<sub>4</sub>O}]<sup>+</sup> [Eq. (2); tpy = 2,2':6',2''-terpyridine], and  $k_{\text{S-H}}/k_{\text{S-D}} \ge 31.1 \pm 0.2^{[12]}$  for the oxidation of *trans*-[Os<sup>IV</sup>(tpy)(Cl)<sub>2</sub>{NS(H)-C<sub>6</sub>H<sub>3</sub>Me<sub>2</sub>}]<sup>+</sup> by Q [Eq. (3)].

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

 $\begin{array}{l} 2 \textit{trans-}[Os^{IV}(tpy)(Cl)_{2}[NS(H)C_{6}H_{3}Me_{2}]]^{+} + Q \rightarrow \\ 2 \textit{trans-}[Os^{V}(tpy)(Cl)_{2}(NSC_{6}H_{3}Me_{2})]^{+} + H_{2}Q \end{array} \tag{3}$ 

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,<sup>[13]</sup> phosphoraniminato complexes,<sup>[14]</sup> and biologically active substances containing P–H acids,<sup>[15]</sup>

A rapid reaction occurs between the osmium(vi)-nitrido complex,  $[Os^{VI}(Tp)(Cl)_2(N)]$  (Tp<sup>-</sup> = tris(pyrazolyl)borate), and diethylphosphane (HPEt<sub>2</sub>) in CH<sub>2</sub>Cl<sub>2</sub> under nitrogen at room temperature to give the osmium(IV)-phosphoraniminato product,  $[Os^{IV}(Tp)(Cl)_2{NP(H)Et_2}]$  (Os<sup>IV</sup>NP(H)Et<sub>2</sub>) [Eq. (4)].

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

The product was isolated (94 % yield) and characterized by elemental analysis,<sup>[16a]</sup> cyclic voltammetry,<sup>[16b]</sup> and UV/Vis,<sup>[16c]</sup> and infrared<sup>[16d]</sup> spectroscopies. Similar to other d<sup>4</sup> Os<sup>IV</sup>– phosphoraniminato complexes,<sup>[17]</sup> Os<sup>IV</sup>-NP(H)Et<sub>2</sub> is paramagnetic as shown by <sup>1</sup>H NMR spectroscopy. Cyclic voltammetric measurements in 1:1 (v/v) CH<sub>3</sub>CN:H<sub>2</sub>O ( $\mu$  = 1.0 m in NH<sub>4</sub>PF<sub>6</sub>) reveal that  $E_{1/2}$  for the osmium(v/v) 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.<sup>[18]</sup> From these data,  $pK_a$ =3.52±0.04 for the acid–base equilibrium shown in Equation (5), and Supporting Information Figure 1.

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

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