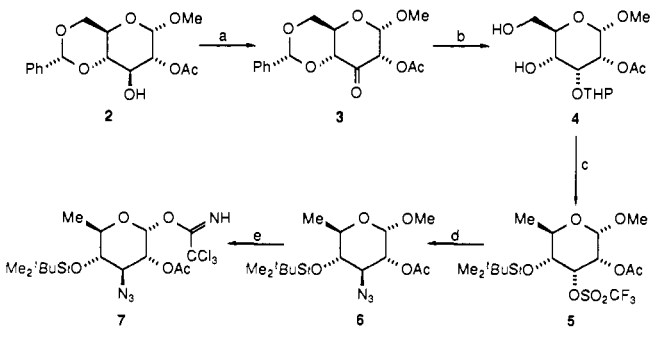
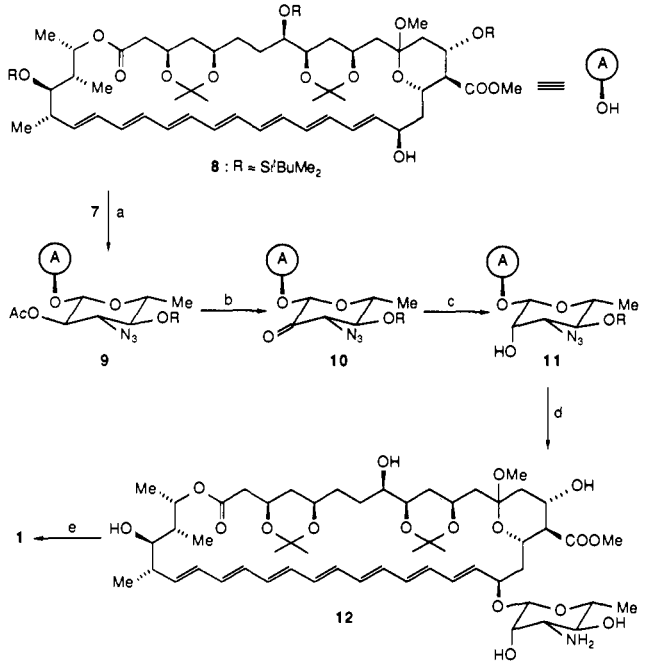
Scheme II[a]



[a] (a) 5.0 equiv of PDC, 4-Å MS, CH_2Cl_2, 25 °C, 16 h, 98%; (b) (i) 1.0 equiv of $NaBH_4$, THF:MeOH (9:1), −10 °C, 1 min, 96%, (ii) 1.2 equiv of dihydropyran, TsOH catalyst, CH_2Cl_2, 0 °C, 0.5 h, 91%, (iii) $Pd(OH)_2$ catalyst, H_2, EtOAc, 25 °C, 16 h, 90%; (c) (i) 3.0 equiv of PPh_3, 3.0 equiv of imidazole, 2.0 equiv of I_2, benzene, 45 °C, 4 h, 89%, (ii) 1.1 equiv of t-$BuMe_2SiOSO_2CF_3$, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 94%, (iii) 2.0 equiv of n-Bu_3SnH, AIBN catalyst, toluene, Δ, 2 h, 99%, (iv) 0.1 equiv of PPTS, MeOH, 50 °C, 3 h, 86%, (v) 1.1 equiv of $(CF_3SO_2)_2O$, 1.5 equiv of pyridine, CH_2Cl_2, 25 °C, 2 h, 100%; (d) 1.1 equiv of NaN_3, 1.1 equiv of 15-crown-5, DMF, 25 °C, 0.5 h, 83%; (e) (i) Ac_2O, H_2SO_4 catalyst, 0–25 °C, 2 h, 90%, (ii) 10 equiv of Cl_2CHOMe, $ZnCl_2$ catalyst, CH_2Cl_2, 25 °C, 2 h, 80%, (iii) 1.0 equiv of $HgBr_2$, MeCN:H_2O (9:1), $CaCO_3$, 25 °C, 0.5 h, and then silica gel, 100% (α:β ca. 9:1), (iv) 1.1 equiv of NaH, 10 equiv Cl_3CCN, CH_2Cl_2, 0 °C, 0.5 h, 90%.

Scheme III[a]



[a] (a) **7** (3.0 equiv), PPTS catalyst, hexane (0.007 M), 25 °C, 4 h, 40% (based on aglycon, 50% conversion); (b) (i) 1.5 equiv of K_2CO_3, MeOH–THF (3:2), 25 °C, 6 h, 90%, (ii) 2.5 equiv of $(CF_3CO)_2O$, 5.0 equiv of Me_2SO, 5.0 equiv of tetramethylurea, 5.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 2 h; (c) 1.5 equiv of $NaBH_4$, MeOH–THF (3:2), 25 °C, 5 min, 80% overall from **9**; (d) (i) excess HF·pyr, MeOH, 50 °C, 48 h, 50%; (ii) 10.0 equiv of $HS(CH_2)_3SH$, 10.0 equiv of Et_3N, MeOH, 25 °C, 24 h, 90%; (e) (i) 1.2 equiv of CSA, MeOH, 25 °C, 2 h, and then H_2O, 25 °C, 4 h, 60%, (ii) 10 equiv of LiOH, THF–H_2O (1:1), 25 °C, 1 h, 80%.

90%), to produce the pentakis(*tert*-butyldimethylsilyl)-*N*-acetyl derivative of compound **12**, which was identical (^1H NMR, IR, UV–vis, MS, TLC, HPLC, optical rotation) with an authentic sample, prepared[6] from natural amphotericin B (**1**). The total synthesis of amphotericin B (**1**) from intermediate **11** was then completed by (a) desilylation (HF·pyr, MeOH, 50% based on ca. 50% recovery)[18] followed by reduction of the azido group as described above (90%) leading to compound **12** and (b) sequential deprotection to amphotericin B (**1**) methyl ester (CSA, MeOH, and then H_2O, 55% based on ca. 50% conversion) and finally to amphotericin B (**1**) itself (LiOH, THF–H_2O, 80%). Synthetic amphotericin B (**1**) and its methyl ester were proven to be identical with authentic samples by the usual criteria [^1H NMR, IR, UV–vis, MS, TLC, HPLC, optical rotation]. Thus, the total synthesis of amphotericin B (**1**) was accomplished.

The total synthesis of amphotericin B (**1**) demonstrates the power of modern organic synthesis. With the described strategy and synthetic technology available, attention may now focus on other members of the polyene macrolide class.[19] Accelerated advances in further total syntheses and structural elucidations in this field should be forthcoming.[20]

Acknowledgment. We express our many thanks to Dr. C. Cimarusti, the Squibb Institute for Medical Research for generous samples of amphotericin B, and Dr. M. Weigele, Hoffmann-La Roche, for high-resolution FAB mass spectra. Our thanks are also due to Drs. George Furst, Patrick Carroll, and John Dykins of this department for their superb NMR, X-ray crystallographic, and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp & Dohme, and Hoffmann-La Roche, USA.

Supplementary Material Available: Listing of R_f, $[\alpha]_D$, IR, UV, and ^1H NMR data for compounds **7–9**, **11**, pentakis(*tert*-butyldimethylsilyl)-*N*-acetyl derivative of **12**, and methyl ester of amphotericin B (**1**) (4 pages). Ordering information is given on any current masthead page.

(18) Optimum results were obtained when this reaction was allowed to proceed to a mixture of the fully desilylated product and a monosilyl derivative (as yet unassigned isomeric structure, ca. 1:1 ratio). This monosilyl ether could be recycled to the fully desilylated material.

(19) For reviews on this subject see: (a) Omura, S., Ed. *Macrolide Antibiotics Chemistry, Biology and Practice*; Academic: New York, 1984. (b) Ryley, J. F.; Wilson, R. G.; Gravestock, M. B.; Poyser, J. P. *Adv. Pharmacol. Chemother.* **1981**, *18*, 49. (c) Hammond, S. M. *Prog. Med. Chem.* **1977**, *14*, 105. (d) Tereshin, I. M. *Polyene Antibiotics-Present and Future*; University of Tokyo: Tokyo, Japan, 1976. (e) Hamilton-Miller, J. M. T. *Bactiriol. Rev.* **1973**, *37*, 166.

(20) New compounds exhibited satisfactory spectral and analytical and/or exact mass spectral data. Yields refer to spectroscopically and chromatographically homogenous materials.

Synthesis and Electrocyclic Ring Opening of 1,3,2λ³,4λ⁵-Diazadiphosphetines

Jurgen Böske,[†] Edgar Ocando-Mavarez,[‡] Edgar Niecke,*[†] Jean-Pierre Majoral,*[‡] and Guy Bertrand*[§]

Fakultät für Chemie, Universität Bielefeld D-4800 Bielefeld, FRG
Laboratoire de Snythèse Structure et Réactivité de Molécules Phosphorées and Laboratoire des Organométalliques Université Paul Sabatier, 31062 Toulouse cedex, France

Received November 5, 1986

Of the three possible types of N–P–N–P four-membered rings, the saturated diazadiphosphetidines A have been widely studied,[1] an example of the fully unsaturated 1,3,2λ⁵,4λ⁵-diazadiphosphete B has been recently isolated,[2] but there is a lack of information

[†] Universität Bielefeld.

[‡] Laboratoire de Synthèse, Structure et Reactivité de Molécules Phosphorées.

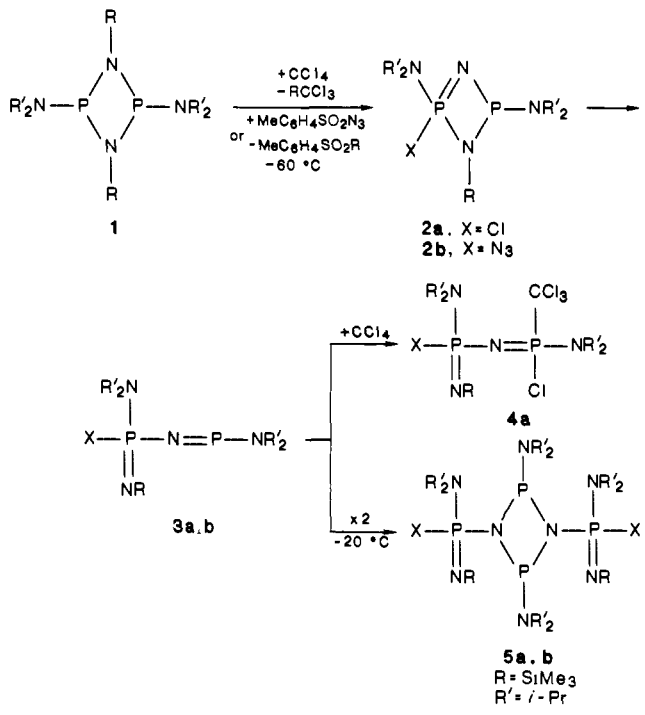
[§] Laboratoire des Organométalliques.

(1) Grapov, A. F.; Razvodovskaya, L. V.; Mel'nikov, N. N. *Russ. Chem. Rev. (Engl. Tranl.)* **1981**, *50*, 324. Chen, H. J.; Haltiwanger, R. C.; Hill, T. G.; Thompson, M. L.; Coons, D. E.; Norman, A. D. *Inorg. Chem.* **1985**, *24*, 4725 and references therein.

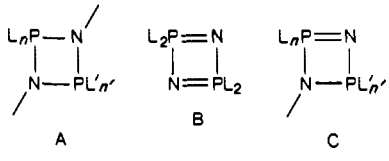
(2) Baceiredo, A.; Bertrand, G.; Majoral, J. P.; Sicard, G.; Jaud, J.; Galy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6088. Baceiredo, A.; Bertrand, G.; Majoral, J. P.; El Anba, F.; Manuel, G. *J. Am. Chem. Soc.* **1985**, *107*, 3945.

0002-7863/87/1509-2822$01.50/0

Scheme I

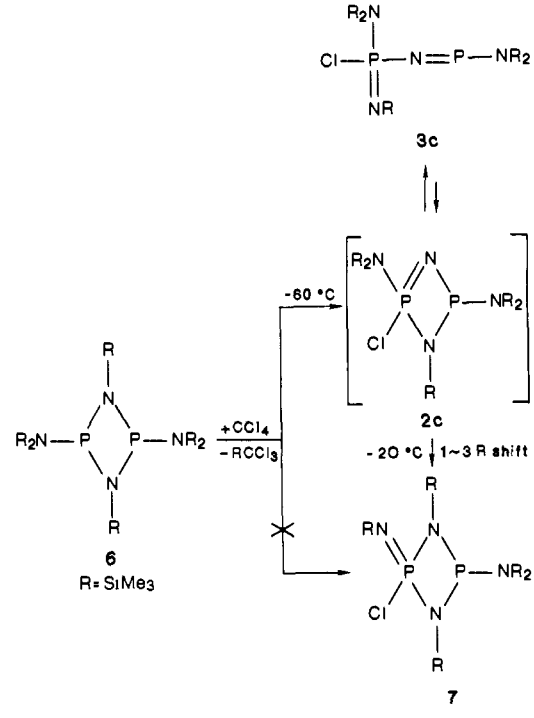


concerning the analogous monounsaturated derivatives C. Here we wish to report a facile synthesis of transient or relatively stable, depending on the nature of the substituents, 1,3,2λ³,4λ⁵-diazadiphosphetines and their electrocyclic ring opening.



Treatment of the easily available 1,3-bis(trimethylsilyl)-2,4-bis(diisopropylamino)-1,3,2λ³,4λ³-diazadiphosphetidine (**1**) (cis isomer)[3] by a stoichiometric amount of CCl_4 at −60 °C led, after loss of Me_3SiCCl_3, to iminophosphane–iminophosphorane **3a**. This compound, containing a dicoordinated phosphorus atom, was characterized by its typical ^{31}P NMR spectrum (+303.7 and −8.5 ppm, $J(PP)$ = 103.5 Hz) and by preparation of its carbon tetrachloride adduct **4a**.[4,5] Above −40 °C, it dimerized to give diazadiphosphetidine **5a** (cis isomer) as two diastereoisomers[5] (Scheme I). Since addition of CCl_4 on silylated aminophosphines followed by Me_3SiCCl_3 elimination is a well-known method for obtaining iminophosphoranes,[6] it seems quite reasonable to rationalize the formation of **3a** by postulating the electrocyclic ring opening of a transient 4-chlorodiazadiphosphetine **2a** (Scheme I). Conclusive proof for this hypothesis was obtained by reacting **1** with an equimolar amount of tosyl azide. Indeed, 4-azidodiazadiphosphetine **2b** (one isomer) was found stable enough to be characterized by NMR at −60 °C: ^{31}P NMR δ +83.2, +25.1, $J(PP)$ = 38.1 Hz; ^1H NMR δ 0.02 (d, $J(PH)$ = 1.6 Hz, CH_3Si); ^{13}C NMR δ 1.19 (dd, $J(PC)$ = 4.43, 2.04 Hz, CH_3Si); ^{29}Si NMR δ 6.42 (d, $J(PSi)$ = 0.4Hz); IR (pentane) 2135 cm^{-1} (P–N3). Electrocyclic ring opening of **2b** occurred at ca. −20 °C, affording the corresponding iminophosphane–iminophosphorane **3b** (^{31}P NMR δ +306.0, −7.4, (δ ^{31}P +306.0 and −7.4 pm, $J(PP)$ = 85.6 Hz), which in turn quickly dimerized to **5b** (cis isomer) as two diastereoisomers[5] (Scheme I).

Scheme II



Finally, when the aminosilylated diazadiphosphetidine **6** (trans isomer)[7] was treated with a stoichiometric amount of CCl_4 at −60 °C, we first observed the quantitative formation of iminophosphane **3c** (δ ^{31}P +341.1 and −10.6 ppm, $J(PP)$ = 79.9 Hz), but instead of dimerizing upon warmup, **3c** rearranged into 1,3,2λ³,4λ⁵-diazadiphosphetidine **7** (cis isomer).[5] It is noteworthy that **7** does not result from a direct Me_3SiCCl_3 exocyclic elimination because of the primary observation of **3c**. Moreover, although a direct pathway from **3c** to **7** cannot be totally excluded, this would be a very strange mechanism. It seems therefore very probable that there is an equilibrium between the open form **3c** and the diazadiphosphetine **2c**, which then undergoes a classical 1~3 trimethylsilyl migration leading to **7** (Scheme II).

To conclude, it appears that 1,3,2λ³,4λ⁵-diazadiphosphetines are intrinsically unstable because of the extensively displaced equilibrium in favor of the corresponding open form isomer but play an essentiel role as intermediates in the oxidation reaction of 1,3,2λ³,4λ³-diazadiphosphetidines.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (E.N.) as well as the Centre National de la Recherche Scientifique (J.P.M., G.B.) for financial support.

(3) Scherer, O. J.; Glässel, W. *Chem. Ber.* **1977**, *110*, 3874. Zeiss, W.; Feldt, C.; Weis, J.; Dunkel, G. *Chem. Ber.* **1978**, *111*, 1180.

(4) Niecke, E.; Bitter, W. *Chem. Ber.* **1976**, *109*, 415.

(5) Compounds **4a**, **5a**, **5b**, and **7** afforded satisfactory elemental analysis. Typical spectroscopic data are the following. **4a** (60% yield), two diastereoisomers 80/20: ^{31}P NMR δ −5.78 (d, $J(PP)$ = 33.0 Hz), −25.38 (d, $J(PP)$ = 33.0 Hz)/−5.32 (d, $J(PP)$ = 35.6 Hz), −23.98 (d, $J(PP)$ = 35.6 Hz); ^1H NMR δ 0.35 (s)/0.34 (s, Me_3Si); ^{13}C NMR δ 3.99 (d, $J(PC)$ = 5.04 Hz)/4.20 (d, $J(PC)$ = 5.6 Hz, Me_3Si); mass spectrum, *m/e* 550 (M+). **5a** (64% yield), two diastereoisomers 50/50 according to ^{31}P NMR at 121.5 MHz but not differentiated in ^1H and ^{13}C NMR: ^{31}P NMR δ 104.2 (t, $J(PP)$ = 39.7 Hz), −20.1 (t, $J(PP)$ = 39.7 Hz), 104.1 (t, $J(PP)$ = 39.7 Hz), −20.1 (t, $J(PP)$ = 39.7 Hz); ^1H NMR δ 0.54 (s, Me_3Si); mass spectrum, *m/e* 796 (M+). **5b** (82% yield), two isomers 50/50 according to ^{13}C NMR but not differentiated in ^1H and ^{31}P NMR: ^{31}P NMR δ +99.02 (t, $J(PP)$ = 34.4 Hz), −22.24 (t, $J(PP)$ = 34.4 Hz); ^1H NMR δ 0.36 (s, Me_3Si); ^{13}C NMR δ 4.90 (d, $J(PC)$ = 1.20 Hz)/4.93 (d, $J(PC)$ = 1.20 Hz, Me_3Si); IR 2140 cm^{-1} (N_3); mass spectrum, *m/e* 810 (M+). **7** (42% yield), one isomer: ^{31}P NMR δ +102.5 (d, $J(PP)$ = 46.5 Hz), −28.9 (d, $J(PP)$ = 46.5 Hz); ^1H NMR (−35 °C) δ 0.02 (d, $J(PH)$ = 0.6 Hz, =N–$SiMe_3$), 0.20 (t, $J(PH)$ <0.2 Hz, ⟨N–$SiMe_3$), 0.26 (d, $J(PH)$ = 4.4 Hz, $NSiMe_3$), 0.38 (s, $NSiMe_3$); ^{13}C NMR (−40 °C) δ 0.06 (t, $J(CP)$ = 3.0 Hz, ⟨N–$SiMe_3$), 2.52 (d, $J(PC)$ = 5.3 Hz, =N–$SiMe_3$), 4.97 (d, $J(PC)$ = 21.6 Hz, $NSiMe_3$), 4.83 (s, $NSiMe_3$); ^{29}Si NMR (room temperature) δ −10.3 (d, $J(SiP)$ = 20.7 Hz, =N–Si), 6.4 (d, $J(SiP)$ = 13.1 Hz, $N(SiMe_3)_2$), 8.4 (br s, ⟨N–$SiMe_3$); mass spectrum, *m/e* 503 ($M^+ - CH_3$).

(6) Li, B. L.; Engenito, J. S.; Neilson, R. H.; Wisian-Neilson, P. *Inorg. Chem.* **1983**, *22*, 575, Scherer, O. J.; Schieder, G. *Chem. Ber.* **1968**, *101*, 4184.

(7) Niecke, E.; Flick, W.; Pohl, S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 309.