Two freeze-pump-thaw-sonicate degassed 2.5-mL methanol solutions each 1.39×10^{-4} M in **1**, 2.75×10^{-4} M in **3**, and 2.0×10^{-3} M in Trizma buffer (1:1 Tris/Tris-HCl) at ambient temperature for 24 h yielded $(6.7 \pm 0.1) \times 10^{-7}$ mol (100%) of **7**, $(7.0 \pm 0.3) \times 10^{-7}$ mol (100%) of **6**, and $(3.6 \pm 0.1) \times 10^{-7}$ mol (100%) of recovered **1**. Yields for **6** and **7** were determined by GLC with a 10% SE-30 on 100/120-mesh Chromasorb W column at 150 °C and for **1** by HPLC with a RSIL-phenyl column eluting with 40% THF 60% aqueous buffer (0.1% ammonium formate adjusted to pH 4.0 with formic acid)[8] and detecting at 480 nm. ^{1}H NMR analysis of the reaction mixture confirmed the chromatographic results and showed that no other products were formed. A similar solution with 5 times higher concentration of **3** gave the visible spectral changes shown in Figure 1 as a function of time. The spectrum of the reaction solution was observed every 2 min. During the period 0-18 min, the absorption of **1** at 480 nm dropped and the absorption at 420 nm assigned to the hydroquinone **5** rose. Over a subsequent time period 18-240 min, the band at 420 nm dropped and the band at 480 nm rose. Subtraction of the absorption at 420 nm predicted to result from residual **1** at 18 min gave an extinction coefficient for **5** at 420 nm of 12 000. Fisher and co-workers have assigned a band at 407 nm to enzyme-bound **5** at pH 7.0 from sodium dithionite reduction of enzyme-bound 2 in sodium phosphate buffer.[9]

The semiquinone of **1** (**8**) was never present at high enough concentration in these reaction solutions to appear significantly in the visible spectrum. An EPR signal for **8** was observed for a degassed methanol solution of **1** and **3** at -20 °C; however signal strength and anisotropic effects precluded an assignment of the splittings. In Me_2SO at 40 °C the signal for **8** was stronger because a higher concentration of **1** could be achieved, and the spectrum was characterized by the following parameters: g = 2.0037, splittings 5.80 (1:1), 3.06 (1:1), 2.32 (1:1), 1.18 (1:1), 0.59 (1:3:3:1).

The rate of decay of the absorption at 420 nm at 25 ± 0.1 °C was studied in methanol solutions 2.04×10^{-4} M in **1** and **3** and 8.0×10^{-3} M in Trizma buffer. The decay after 10 half-lives of **3** (2040 s) followed clean second-order kinetics, first order in both **5** and **6**. A nonlinear least-squares fitting of the data to the integrated rate law, correcting for absorption by **1**, gave a rate constant of 2.06 ± 0.02 M^{-1} s^{-1} for reduction of **6** by **5** and an extinction coefficient for **5** at 420 nm of 12 700 ± 400. The same experiment in methanol-*d* solvent gave a rate constant of 0.69 ± 0.01 M^{-1} s^{-1}. The deuterium kinetic isotope effect is 3.0, consistent with breakage of a bond to hydrogen in the transition state. Reaction of **5** with **6** was further established by the observation of a complete suppression of spectral changes at 420 nm by inclusion of 220 mol equiv of **6** in the original reaction mixture.

A control experiment showed that the rate of disproportionation of **4** to **6** and **7** in methanol in the absence of **1** is very slow. A solution 5.56×10^{-2} M in **3** in methanol-d_4 solvent showed no disproportionation after 135 h at 35.0 ± 0.1 °C by ^{1}H NMR spectroscopy. The deuterium kinetic isotope effect of deuterated solvent on bond homolysis of **3** and on disproportionation of **4** in the absence of a catalyst is small.[3,7]

On the basis of these data and previous work on the mechanism of reduction of daunomycin by **3**,[3] we conclude that the 7-deoxydaunomycinone-catalyzed disproportionation of **3** occurs via reduction of **1** in single-electron steps to give hydroquinone **5** followed by transfer of a hydride from **5** to **6**. Thus, catalysis occurs because a one-electron reducing agent creates a two-electron reducing agent. The hydride transfer appears to be mechanistically related to some quinone-substrate dehydrogenation reactions.[10] The intracellular function of free or DNA-bound **5** as a two-electron reducing agent is unknown; however, it may be expressed in the interior of a tumor that is hypoxic. The two-electron-two-proton reduction potential of **1** is sufficiently negative, -0.66 V vs. SCE,[11] that **5** is thermodynamically capable of reducing many cellular constituents.

Registry No. 1, 32384-98-8; **3**, 53153-53-0; **4**, 57765-64-7; **5**, 86632-73-7; **6**, 53153-46-1; **7**, 86632-74-8; **8**, 86667-95-0; methanol-*d*, 1455-13-6; deuterium, 7782-39-0.

(8) Andrews, P. A.; Brenner, D. E.; Chou, F. E.; Kubo, H.; Bachur, N. *Drug Metab. Dispos.* **1980**, *3*, 152.

(9) Fisher, J.; Ramakrishnan, K.; McLane, K. E. *Biochemistry* **1982**, *21*, 6172.

(10) Becker, H.-D. In "The Chemistry of Quinoid Compounds"; Patai, S., Ed.; Wiley: New York, 1974; pp 335-423.

(11) Rao, G. M.; Lown, J. W.; Plambeck, J. A. *J. Electrochem. Soc.* **1978**, *125*, 534.

Novel Synthesis and Reactivity of 4-Azahomoadamant-3-ene and 4-Aza-4-homobrend-3-enes via Intramolecular Aza-Wittig Reactions

Tadashi Sasaki,* Shoji Eguchi, and Takashi Okano

Institute of Applied Organic Chemistry
Faculty of Engineering, Nagoya University
Furo-cho, Chikusa-ku, Nagoya 464, Japan

Received April 27, 1983

A variety of synthetic methods for preparation of carbocyclic bridgehead olefins have been developed recently,[1,2] whereas only two such methods for bridgehead imines have appeared. These are the photorearrangement of bridgehead azides[3] and lead tetraacetate oxidation of the parent azapolycycles.[4] The former method provides a general route to bridgehead imines but suffers serious disadvantages since unsymmetrical azides generally afford a mixture of bridgehead imines due to nonregioselective ring expansion;[3a,c] moreover the reagents applicable to generated imines are restricted to photostable ones. The latter oxidation method is only useful for limited precursors. In view of the above, the development of regiospecific routes to bridgehead imines is desirable. We would like to report a novel method for generation of bridgehead imines from keto azides and oxoacyl azides, respectively, utilizing the Staudinger reaction followed by an intramolecular aza-Wittig reaction.[5]

When an equimolar mixture of keto azide **1**[6-8] and triphenylphosphine (TPP) in methanol was heated to reflux for 3 h, **1** was converted smoothly into methoxyamine **5a**, which was

(1) (a) For a recent review, see: Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (b) For stability and reactivity, see: Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.

(2) For some of recent leading references, see: (a) Shea, K. J.; Wise, S.; Burke, L. D.; Davis, P. D.; Gilman, J. W.; Greeley, A. C. *J. Am. Chem. Soc.* **1982**, *104*, 5708. (b) Sellers, S. F.; Klebach, T. C.; Hollowood, F.; Jones, M., Jr.; Schleyer, P. v. R. *Ibid.* **1982**, *104*, 5492.

(3) (a) For a review, see: Lwowski, W. In "Reactive Intermediates"; Jones, M., Jr., Moss, R. A., Ed.; Wiley-Interscience: New York, 1978; Vol. 1, p 198. (b) Quast, H.; Eckert, P. *Liebigs* Ann. *Chem.* **1974**, 1727. (c) Quast, H.; Seiferling, B. *Ibid.* **1982**, 1553. (d) Becker, K. B.; Gabutti, C. A. *Tetrahedron Lett.* **1982**, *23*, 1883. (e) Sasaki, T.; Eguchi, S.; Okano, T. *Ibid.* **1982**, *23*, 4969.

(4) (a) Toda, Y.; Hirata, Y.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1597. Toda, Y.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477. (b) Toda, Y.; Niwa, H.; Ienaga, Y.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1972**, 335.

(5) For related reviews, see: (a) Golobov, Y. G.; Zhmurova, I. N.; Kosukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Cadogan, J. I. G.; Mackie, R. K. *Chem. Soc. Rev.* **1974**, *3*, 87. For synthesis of bridgehead olefins via the intramolecular Wittig reaction, see: (c) Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.

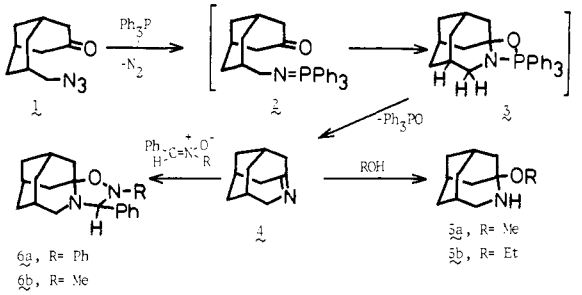
(6) All new isolable compounds were characterized by elemental analysis and by IR, NMR, and mass spectra (see the supplementary material).

(7) Ethyleneketalization of 7-*endo*-((acetylamino)methyl)bicyclo[3.3.1]-nonan-3-one (ref 8) followed by alkaline hydrolysis gave the corresponding aminomethyl ketal, mp 126-128 °C, which was converted to azidomethyl ketal by the diazo transfer method (NaH-TsN_3-THF). Hydrolysis (1 N HCl-Et_2O) of the azido ketal gave the azido ketone **1** as on oil (54%).

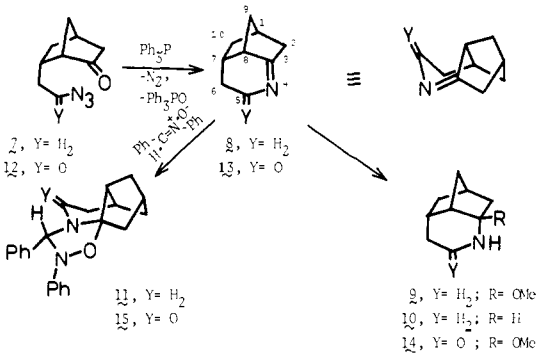
(8) Padegimas, S.; Kovacic, P. *J. Org. Chem.* **1972**, *37*, 2672.

0002-7863/83/1505-5912$01.50/0

Scheme I



Scheme II



isolated after chromatography (neutral alumina) (56%) and identified as the known 3-methoxy-4-azahomoadamantane by comparison of the spectral data to that of an authentic sample.[9a] Treatment of **1** with TPP in refluxing ethanol gave **5b**[9b] in 92% yield. These results strongly suggest that a reactive bridgehead imine, 4-azahomoadamant-3-ene (**4**)[10] is generated from **1** and TPP presumably via **2** and **3** and is trapped with the solvent either methanol or ethanol. The photochemical generation of **4** has already been postulated on the basis of the formation of **5** and the dimer[3b] and is confirmed spectrally at 14 K.[11] The parallel behavior of **4** generated by photochemical and nonphotochemical methods supports clearly the bridgehead imine route. Furthermore, trapping the imine with photolabile nitrones was successful by the present nonphotochemical method. A mixture of **1**, TPP, and *C,N*-diphenylnitrone (2-fold excess) in benzene was heated under reflux for 2 h to give the adduct **6a** (97%), mp 75–78 °C after purification on a neutral alumina column (C_6H_6–AcOEt). Similarly the reaction with *C*-phenyl-*N*-methylnitrone afforded **6b** as an oil, quantitatively (Scheme I). The assigned regiochemistry was corroborated by the chemical shift of the oxadiazolidine ring proton (δ 4.70 for **6a** and 3.95 for **6b**) in the ^{1}H NMR spectra ($CDCl_3$). The observed regioselectivity of the above hetero-1,3-dipolar cycloaddition sequence is in accord with the FMO model as a dipole HOMO controlled reaction.[12,13]

When the above intramolecular aza-Wittig reaction was monitored by NMR spectroscopy, the characteristic signals that indicate the existence of the rarely observed oxazaphosphetane intermediate were seen.[14] In the ^{1}H NMR spectrum of an equimolar mixture of **1** and TPP in $CDCl_3$ at 25 °C, the doublet (J = 7 Hz) that appeared at δ 3.06 due to the CH_2N_3 moiety decreased gradually and was replaced simultaneously by a triplet (J = 3 Hz) located at δ 2.65. The change was nearly complete after 3.5 h; however, this new signal began to decrease with the appearance of another new multiplet at around δ 2.9 after 6 h, and this final conversion was complete after 12 h. In the ^{13}C NMR spectrum (at −25 °C with protons completely decoupled) of a sample prepared by mixing **1** and TPP in $CDCl_3$, which was allowed to stand at 5 °C for 12 h (IR monitored), a characteristic doublet ($J_{^{13}C-^{31}P}$ = 5.9 Hz) at δ 81.9 appeared. Comparison of the chemical shifts with those reported for phosphine imines[15] permitted the assignment of the signal at δ 2.65 to the CH_2N of **3** and the resonance line at δ 81.9 to the quarternary oxazaphosphetane carbon of **3**. These results indicate that the intramolecular addition of ketophosphine imine **2** to **3** occurs rapidly due to entropic assistance, while the elimination of $(C_6H_5)_3PO$ from **3** occurs relatively slowly due to formation of the highly strained imine **4**; this provides a kinetic stability for **3**.

The new intramolecular aza-Wittig method was applied to the synthesis of novel tricyclic bridgehead imines 4-aza-4-homobrend-3-ene (4-azatricyclo[5.2.1.$0^{3,8}$]dec-3-ene) (**8**) and its 5-oxo derivative **13** (Scheme II). Thus, an equimolar mixture of ketoazide **7**[16] and TPP in methanol was heated at reflux for 3 h to give a mixture, whose ^{1}H NMR reveals characteristic peaks as the methoxyamine **9**: δ 3.25 (s, OCH_3) and 3.0–2.7 (m, CH_2N). Unfortunately, however, further purification on a neutral alumina column gave only an intractable tar. Treatment of the mixture with excess sodium borohydride at 25 °C afforded cleanly (87%) 4-aza-4-homobrendane (**10**), HCl salt: mp 178–181 °C dec. From Wiseman's postulate[17] and the OS stability criterion,[1b] the (*E*)-1-azacyclooctene subunit of **8** should be less strained and should survive at room temperature. However, neither the imine **8** nor the corresponding oxazaphosphetane could be detected by ^{1}H NMR and IR monitoring analyses at 25 °C.[18] On the other hand, the reaction of ketoacyl azide **12** with TPP in MeOH at reflux produced the stable methoxyamine **14**, mp 76–79 °C, in 75% overall yield based on the starting keto acid.[16] The methoxyamine **14** was transformed into the amine **10** (53%) ($LiAlH_4$, reflux in THF). In contrast, with $NaBH_4$ in refluxing EtOH, **14** was recovered unchanged indicating that regeneration of 5-oxoimine **13** from **14** was unlikely. Fortunately, bridgehead imines **8** and **13** were successfully trapped with diphenylnitrone in refluxing benzene to yield oxadiazolidines **11** and **15** in 84% and 46% yields, respectively. The structural elucidation of **15** was based on its unusually lower chemical shift of the oxadiazolidine proton at δ 6.65 due to a negative anisotropic effect of the C=O group. A simple explanation for the observed stereoselective approach of the nitrone to **13** is suggested by examination of molecular models. Thus, the other possible approach causes a severe steric repulsion between *N*-phenyl and $C_{2exo}H$. The structure **11** follows the similar arguments.[19]

Supplementary Material Available: Tables of physical data, methods of purification, microanalytical data, and spectral data[6] (3 pages). Ordering information is given on any current masthead page.

(9) (a) Kovacic, P.; Liu, J.-H.; Levi, E. M.; Roskos, P. D. *J. Am. Chem. Soc.* **1971**, *93*, 5801. (b) Starewicz, P. M.; Breitwieser, G. E.; Hill, E. A.; Kovacic, P. *Tetrahedron* **1979**, *35*, 819.

(10) The OS (olefinic strain) value of homoadamant-3-ene has been evaluated as 20.2 kcal/mol (ref 1b), which suggests that 4-aza analogue **4** may be also a considerably strained bridgehead imine. Cf. also ref 11.

(11) Michl, J.; Radziszewski, G. J.; Downing, J. W.; Wiberg, K. B.; Walker, F. H.; Miller, R. D.; Kovacic, P.; Jawdosiuk, M.; B.-Koutecký, V. *Pure Appl. Chem.* **1983**, *55*, 315.

(12) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976; pp 148–161.

(13) For a successful trapping of highly strained bridgehead olefin with *C,N*-diphenylnitrone, see: Chan, T. H.; Massuda, D. *J. Am. Chem. Soc.* **1977**, *99*, 936.

(14) For exceptionally stable oxazaphosphetanes, see: (a) Schmidpeter, A.; von Criegern, T. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 55. (b) For extensive studies on oxaphosphetanes in the Wittig reactions, see: Vedejs, E.; Meier, G. P.; Snoble, K. A. *J. Am. Chem. Soc.* **1981**, *103*, 2823 and references cited therein.

(15) Smuszkovicz, J.; Kane, M. P.; Laurian, L. G.; Chidester, C. G.; Scahill, T. A. *J. Org. Chem.* **1981**, *46*, 3564.

(16) The azidoketone **7** was prepared from the known ketoalcohol via the tosylate: Naemura, K.; Nakazaki, M. *Bull Chem. Soc. Jpn.* **1973**, *46*, 888.

(17) Wiseman, J. R.; Pletcher, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 956.

(18) The strong IR ($CDCl_3$) bands of **7** at 2100 and 1735 cm^{-1} changed finally to weak bands at 1738 and 1680 cm^{-1}; the ^{1}H NMR triplet (δ 3.32, J = 7 Hz) of **7** collapsed to a complex multiplet (δ 3.6–2.9) in $CDCl_3$. Similar IR and NMR data have been reported for decomposition products of 1-azido-4-methylbicyclo[2.2.2]octane (ref 3c).

(19) This work has been supported by the Ministry of Education, Japanese Government (Grant-In Aid 57118006 and 58110005 to S.E.). We thank Professor Hisashi Yamamoto for helpful discussions.