Photocycloaddition Reaction of Some Conjugated Hexatriynes with 2,3-Dimethyl-2-butene

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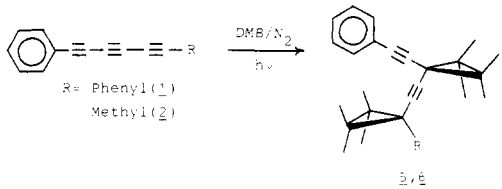
Photolysis of 1-phenyl-1,3,5-hexatriyne and 1-phenyl-6-(*tert*-butyldimethylsilyl)-1,3,5-hexatriyne in deaerated 2,3-dimethyl-2-butene gave dicyclopropyl photoadducts **7–9**, while 1,6-diphenyl-1,3,5-hexatriyne in a deaerated 2,3-dimethyl-2-butene/acrylonitrile (1:1 molar ratio) cosolvent system yielded the photoadducts **5** and **10**. A plausible mechanism for the reaction is proposed.

Introduction

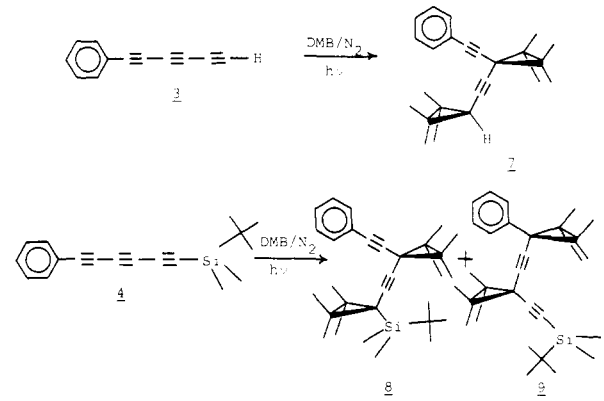
1-Phenyl-1,3,5-heptatriyne (PHT), a conjugated polyacetylene occurring in high concentration in the leaves of the tropical weeds *Bidens pilosa* L., *Coreopsis lanceolate*, *Bidens radiata*, *and Bidens ferulaefolia*, has been reported to be phototoxic to a variety of microorganisms having membranes.[1-6] Recently, some attempts to elucidate the specificity and the mechanism of phototoxicity of PHT have been carried out.[2] We have previously reported the photoreaction of PHT and 1,6-diphenyl-1,3,5-hexatriyne (DPH, **1**) with 2,3-dimethyl-2-butene (DMB) as a model reaction for PHT phototoxicity.[7,8] On the basis of the structure of photoadducts, we suggested a plausible reaction mechanism involving the cumulene type triplet state and carbene formation. In general, [2 + 2] type photocycloaddition of acetylenes to form a cyclobutene ring is well understood, while just a few cases are reported on the cyclopropane ring formation.[9] Furthermore, the examples obtained from simple monoacetylenes are not sufficient to explain the results obtained from the irradiation of phenyl-substituted 1,3,5-hexatriynes with DMB because simple monoacetylenes have just two reactive sites while there are six reactive sites in conjugated hexatriynes. We, therefore, investigated the photoreaction of various 1-phenyl-1,3,5-hexatriynes with some olefins to clarify the photoaddition reaction mechanism of PHT-like compounds with olefins.

Results and Discussion

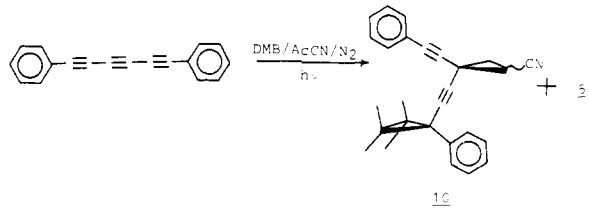
Photocycloaddition Reaction of 1,3,5-Hexatriynes with DMB. The photoaddition reaction of DPH (**1**) and PHT (**2**) with DMB yields only one photoadduct.[7,8]



Irradiation of compounds **3** and **4** in degassed DMB at 350 nm yields 1:2 adducts, 1-(2,2,3,3-tetramethylcyclopropyl)-2-[1-(phenylethynyl)-2,2,3,3-tetramethylcyclopropyl]acetylene (**7**), 1-[1-(*tert*-butyldimethylsilyl)-2,2,3,3-tetramethylcyclopropyl]-2-[1-phenylethynyl)-2,2,3,3-tetramethylcyclopropyl]acetylene (**8**), and 1-(1-phenyl-2,2,3,3-tetramethylcyclopropyl)-2-[1-[(*tert*-butyldimethylsilyl)ethynyl]-2,2,3,3-tetramethylcyclopropyl]-acetylene (**9**). In all these reactions, red polymerized product was obtained as a major byproduct.



When these hexatriynes were photolyzed in deaerated solutions of several electron deficient olefins such as dimethyl fumarate, methyl crotonate, dimethyl maleate, trans-1,2-dichloroethylene, and acrylonitrile (AcCN), no photoadduct was obtained. But irradiation of the solution of **1** in 1:1 DMB/acrylonitrile cosolvent yielded two photoadducts **5** and 1-(1-phenyl-2,2,3,3-tetramethylcyclopropyl)-2-(1-(phenylethynyl)-2-cyanocyclopropyl)acetylene (**10**) in about a 1:3 ratio along with white polymerized products.



The structures of these photoadducts were determined by various physical methods, including ^{13}C NMR spectroscopy, which is vital for the determination of the reaction sites. Photoadducts **7–10** do not show the general vibrational fine structure of conjugated polyacetylenes in UV absorption spectra (Figure 1), and absorption maxima are similar to those of **5** and **6** because the UV-absorbing chromophore is the phenylethynyl moiety except for **9**. IR spectra show a medium $\nu_{C\equiv C}$ band, and mass spectra of

(1) McLachlan, D.; Arnason, T.; Lam, J. *Biochem. Syst. Ecol.* **1986**, *14*(1), 17.
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(9) Owsley, D. C.; Bloomfield, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 782.

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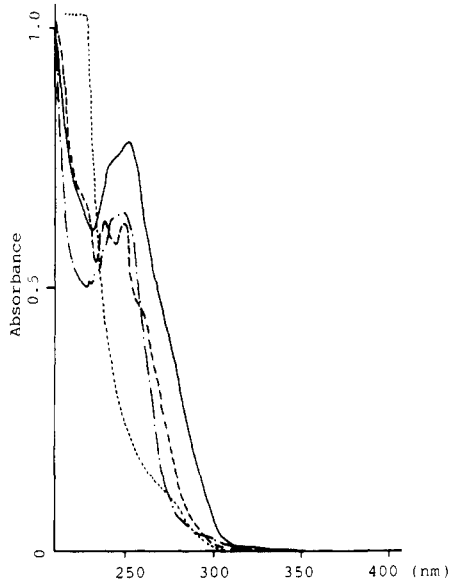


Figure 1. UV spectra of **7** (—), **8** (– – –), **9** (···), and **10** (–·–) in MeOH.

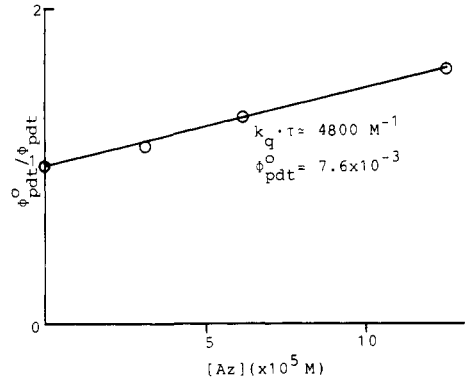


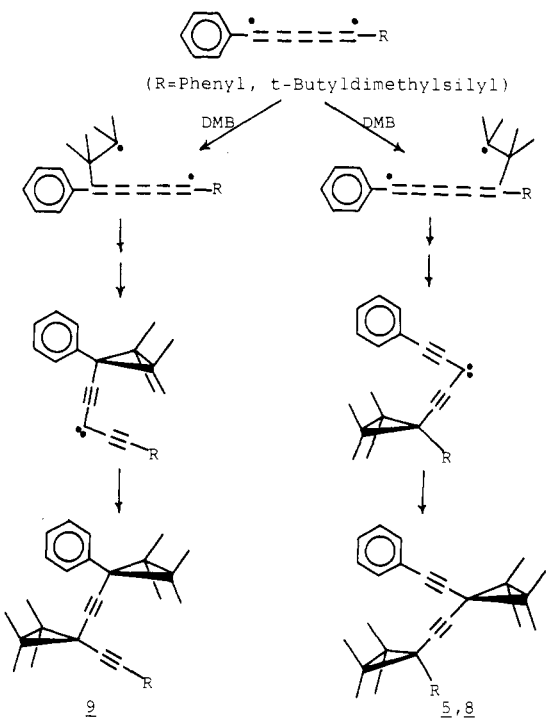
Figure 2. Azulene effect on photocycloaddition reaction of **1** with DMB at 366 nm.

all the photoadducts show M^+, M^+ – DMB, and M^+ – 2DMB peaks, indicating that the photoadducts are formed by addition of two DMB molecules to 1,6-disubstituted 1,3,5-hexatriyne. The UV and IR spectral data for the photoadduct **10** were similar to those of other photoadducts, **7** and **8**. The mass spectrum reveals M^+, M^+ – AcCN, and M^+ – AcCN – DMB peaks, supporting the formation of a 1:1:1 (DPH:AcCN:DMB) photoadduct. Typically, ethynyl substituted phenyl carbons are shown at the 120–125-ppm region while cyclopropyl substituted phenyl carbons appear near 140 ppm by the additive rule of ^{13}C chemical shift.[10] ^{13}C NMR spectra of the photoadducts show the substituted aromatic center carbon peaks at the 120–125-ppm region except for **9**, supporting the existence of the phenylethynyl moiety, and also, substituted aromatic center carbon peaks of 140.25 ppm (**9**) and 139.59 ppm (**10**) support the existence of the cyclopropylbenzene moiety. For **9**, a strong downfield-shifted sp-hybridized carbon peak of 106.21 ppm indicates the ethynyl group attached to the silyl group. In the ^{13}C NMR spectrum of **10**, the cyano group carbon peak of 118.14 ppm and 19 other carbon peaks support the structure.

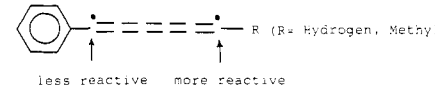
Reaction Mechanism. The photocycloaddition reaction of **1** with DMB is efficiently quenched by azulene as

(10) Pretsch, E.; Seible, J.; Clerc, T.; Simon, W. *Table of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1983.

Scheme I



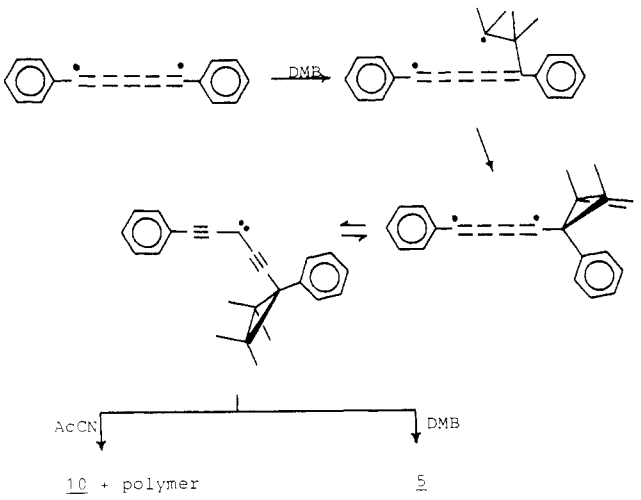
the quantum yields decrease linearly with increasing azulene concentration yielding a large $k_q \cdot \tau$ of 4800 M^{-1} (Figure 2) indicating that the reaction proceeds from the triplet excited state. When oxygen was present (aerated DMB), no photoadduct was observed, supporting the triplet reaction mechanism. A plausible reaction mechanism involving a cumulene type triplet excited state has been proposed for the photocycloaddition reaction of **1** and **2** with DMB based on the structure of photoadducts. To investigate the formation of cumulene type diradical species (electron-delocalized excited state), we varied the R group in PhC≡CC≡CC≡CR from hydrogen to the *tert*-butyldimethylsilyl group. Hydrogen and methyl have no or little radical-stabilizing ability at C-6, while phenyl and *tert*-butyldimethylsilyl can stabilize the radical at C-6 by delocalization of the unpaired electron over the phenyl ring and empty d orbital of the silyl group, respectively. Consequently, the radical at C-6 in 1-phenyl-1,3,5-hexatriyne (**3**) and in **2** is more reactive than the C-1 radical.



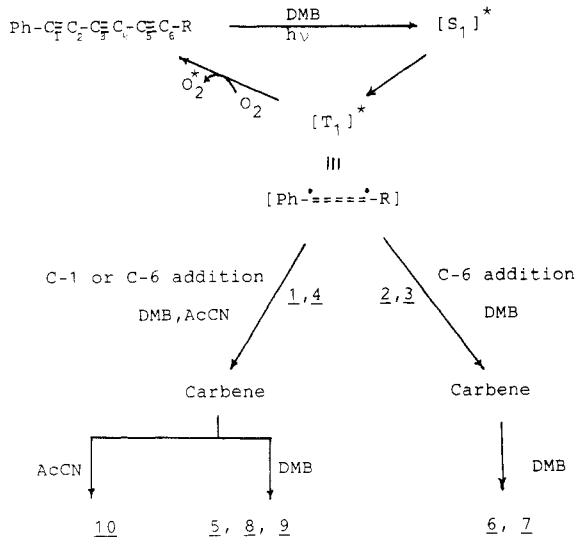
However, when the R group is phenyl or *tert*-butyldimethylsilyl, the radicals at C-1 and C-6 will have similar reactivity due to the stabilization discussed (or effect of R). When R was phenyl, only one photoadduct was obtained due to the symmetry, while two photoadducts, **8** and **9**, were obtained when R was *tert*-butyldimethylsilyl because both of the stabilized radicals at C-1 and C-6 can attack DMB competitively. These two photoadducts obtained strongly support the delocalized electron density through the conjugated triyne system in the excited state (like cumulene type diradical) and the carbene formation. The reaction pathways are shown in Scheme I.

In order to provide the carbene formation, we carried out the photoreaction of **1** in the 1:1 DMB/AcCN mixed solvent. The carbene was formed at the C-3 position, and the electron-rich olefin such as DMB is necessary in the initiation step of the reaction as shown in Scheme II because the photoaddition reaction of **1** with AcCN does not

Scheme II



Scheme III



occur, but the reaction with DMB/AcCN occurs.

The formation of two photoadducts **5** and **10** implies that the carbene generated can add to various olefins. The overall reaction mechanism involving a cumulene type diradical triplet state and carbene formation is shown in Scheme III.

Conclusion

Radical-stabilizing groups such as aryl or *tert*-butyldimethylsilyl groups on terminal carbons of conjugated hexatriynes control the photoaddition reactions of the compounds. In compound **4**, the radicals formed at C-1 and C-6 are about equally stabilized, and consequently, the initial addition of DMB to the C-1 or C-6 carbon is competitive and two photoadducts **8** and **9** are obtained. The electronic nature of the olefins also affects the initiation of the reaction. The electron-rich olefins are required for the initial step as shown by the photocycloaddition reaction of hexatriynes in a DMB/AcCN mixed solvent system. The triyne first adds to DMB and reacts with AcCN while no reaction occurs with AcCN alone. Azulene and oxygen effects on the reactions support the triplet reaction mechanism involving the carbene intermediate.

Experimental Section

Instruments. ^{1}H nuclear magnetic resonance spectra were run in $CDCl_3$ on Varian FT-80A and Bruker AM-200-SY spectrophotometers. Infrared spectra were obtained on a Perkin-Elmer 283B spectrophotometer in KBr pellets and NaCl cell. UV-vis spectra were recorded on a Cary-17 spectrophotometer. Mass spectra were determined at 70 eV with a Hewlett-Packard 5985A GC/MS system by the electron-impact method. Elemental analyses were carried out on a F&M Scientific Cooperation C,H,N analyzer Model 180. High-performance liquid chromatography was performed on a Waters Associates Model 244 liquid chromatograph equipped with a Model 6000A solvent delivery system, Model 440 UV absorbance detector fixed at 254 nm and 280 nm, and Model U6K universal injector.

Materials. 2,3-Dimethyl-2-butene (DMB) and acrylonitrile (AcCN) were purchased from Aldrich Chemical Co. and were used as received. Azulene and purchased from Aldrich and was used after vacuum sublimation. Compounds **1** and **2** were prepared according to the literature procedure.[11] Extra pure solvents were used as received or after purification by distillation or by the standard methods.[12] Column chromatography was performed by using Kieselgel 60 (Merck, 70–230 mesh and 230–400 mesh). Preparative thin-layer chromatography was conducted by using Kieselgel 60 GF_{254} (Merck) containing a fluorescent indicator.

1-Phenyl-6-(*tert*-butyldimethylsilyl)-1,3,5-hexatriyne (4) was prepared by the Cadiot–Chodkiewicz coupling method between bromophenylacetylene and (*tert*-butyldimethylsilyl)-1,3-butadiyne at room temperature in >90% yield.[13] (*tert*-Butyldimethylsilyl)-1,3-butadiyne was prepared by the same procedure used for the preparation of (trimethylsilyl)-1,3-butadiyne in 50% yield. **4**: ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 1.0 (s, 9 H), 0.2 (s, 6 H); IR (KBr) 3080, 2980, 2950, 2900, 2880, 2190, 2090, 1610, 1590, 1505, 1488, 1480, 1460, 1425, 1410, 1380, 1350, 1265, 850, 828, 810, 780, 758, 690 cm^{-1}; UV (methanol) λ_{max} 342, 318, 299, 282, 257, 245 nm; MS, *m/e* 264 (M^+, 12.4), 207 (M^+ – *tert*-butyl, 100). Anal. Calcd for $C_{18}H_{20}Si$: C, 81.76; H, 7.62. Found: C, 81.69; H, 7.70.

1-Phenyl-1,3,5-hexatriyne (3). A solution of 0.264 g of **4** (1 mmol) in MeOH (1.5 mL) was treated with 1 N NaOH, 1.5 mL, at 10 °C. The reaction mixture was stirred for 1 h at 20 °C, acidified with 0.4 mL of methanolic 5 N HCl, and extracted with *n*-pentane/H_2O to obtain **3**, quantitatively. Compound **3** was not isolated because it was very unstable when concentrated. The formation of **3** was identified by UV spectroscopy and thin-layer chromatography.

Irradiation of 3 with DMB. A fresh DMB solution of **3** was prepared by the extraction of the desilylating reaction mixture with DMB. The concentration of **3** was determined from the quantity of **4** and the volume of DMB used. An about 4 mM DMB solution of **3** was deaerated by three freeze–pump–thaw cycles and irradiated with 350-nm UV light in a Rayonet photochemical reactor Model RPR-208 equipped with RUL-3500 Å lamps. After the irradiation for 48 h, the resulting photoreaction mixture was concentrated in vacuo. The photoadduct **7** was isolated by preparative thin-layer chromatography followed by column chromatography using *n*-pentane as an eluent in 7% yield. **7**: ^{1}H NMR ($CDCl_3$) δ 7.1 (m, 5 H), 1.03 (s, 6 H), 1.0 (s, 6 H), 0.9 (s, 12 H), 0.73 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 131.69, 128.06, 127.35, 124.19, 89.65, 80.31, 80.24, 78.03, 32.35, 25.56, 25.48, 22.47, 20.52, 19.42, 19.34, 18.61; IR (KBr) 3080, 3020, 2970, 2950, 2900, 2240, 1620, 1510, 1460, 1395, 1190, 1120, 940, 920, 760, 695 cm^{-1}; UV (methanol) λ_{max} 250 nm; MS, *m/e* 318 (M^+, 13.0), 234 (M^+ – DMB, 52.1), 150 (M^+ = 2DMB, 54.3), 84 (DMB^+, 100). Anal. Calcd for $C_{24}H_{30}$: C, 90.51; H, 9.49. Found: C, 90.60; H, 9.54.

Irradiation of 4 with DMB. A 4 mM DMB solution of **4** was deaerated by three freeze–pump–thaw cycles and irradiated for 48 h as described. The resulting photoreaction mixture was concentrated in vacuo, and the photoadducts **8** and **9** were isolated by preparative thin-layer chromatography followed by column chromatography using *n*-pentane as an eluent in 11% and 10% yields, respectively. Highly pure photoadduct **8** was obtained from the reverse-phase HPLC using a μBondapak C_{18} column and a MeOH/H_2O/THF (10:1:1, v/v/v) solvent system. **8**: ^{1}H NMR δ 7.3 (m, 5 H), 1.44 (s, 12 H), 1.26 (s, 6 H), 1.21 (s, 6 H), 1.00 (s,

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(12) Perrin, D. D.; Armarego, W. L. F.; Perrin, B. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.
(13) (a) Schulte, K. E.; Reisch, J.; Hörner, L. *Chem. Ber.* **1962**, *95*, 1943. (b) Eastmond, R.; Walton, D. R. *Tetrahedron* **1972**, *28*, 4591.

9 H), 0.17 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 129.12, 128.16, 127.24, 124.60, 92.62, 89.94, 89.21, 82.00, 34.68, 30.87, 29.48, 26.16, 25.96, 22.57, 22.20, 20.14, 16.84, 14.01, −4.52; IR (KBr) 3080, 2980, 2950, 2880, 2160, 1615, 1510, 1485, 1480, 1460, 1380, 1260, 900, 840, 830, 820, 780, 700 cm^{-1}; UV (methanol) λ_{max} 248 nm; MS, *m/e* 432 (M^+, 1.4), 375 (M^+ − *tert*-butyl, 3.5), 348 (M^+ − DMB, 2.4), 291 (M^+ − *tert*-butyl − DMB, 13.5), 207 (M^+ − *tert*-butyl − 2DMB, 7.2), 73 ($C_3H_9Si^+$, 100). Anal. Calcd for $C_{28}H_{44}Si$: C, 83.26; H, 10.26. Found: C, 83.19; H, 10.22. **9**: ^{1}H NMR ($CDCl_3$) δ 7.19 (s, 5 H), 1.36 (s, 6 H), 1.14 (s, 6 H), 1.02 (s, 6 H), 1.00 (s, 6 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 140.25, 131.06, 127.90, 125.84, 106.21, 84.13, 82.00, 78.62, 32.97, 31.90, 28.67, 26.14, 23.78, 20.55, 19.19, 19.04, 16.65, −4.37; IR (KBr) 3080, 3030, 2980, 2960, 2880, 2170, 1620, 1510, 1490, 1480, 1460, 1390, 1375, 1260, 1120, 845, 830, 820, 780, 770, 730, 710, 680 cm^{-1}; UV (methanol) λ_{max} 250 nm (sh); MS, *m/e* 432 (M^+, 2.1), 375 (M^+ − *tert*-butyl, 20.9), 348 (M^+ − DMB, 33.0), 291 (M^+ − *tert*-butyl − DMB, 81.1), 207 (M^+ − *tert*-butyl − 2DMB, 100), 73 ($C_3H_9Si^+$, 90.9). Anal. Calcd for $C_{28}H_{44}Si$: C, 83.26; H, 10.26. Found: C, 83.29; H, 10.17.

Irradiation of 1 with DMB/AcCN. Deaerated 4 mM DMB/AcCN (1:1 molar ratio) solution of 1 was irradiated with 350-nm UV light in a Rayonet photochemical reactor Model RPR-208. A 20-mL Pyrex ampule was used as a reaction vessel for three freeze–pump–thaw degassing cycles. After the irradiation, the solvent was evaporated in vacuo and the photoadducts **5** and **10** were isolated in 4% and 14% yields, respectively, by preparative thin-layer chromatography using *n*-hexane/diethyl ether (2:1, v/v) followed by column chromatography using *n*-hexane/diethyl ether (20:1, v/v) as eluents. Highly pure photoadduct **10** was obtained from reverse-phase HPLC using a μ-Bondpak C_{18} column and a MeOH/H_2O/THF (10:1:1, v/v/v) solvent system. **10**: ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 7.32 (s, 5 H), 1.9–1.4 (m, 3 H), 1.41 (s, 6 H), 1.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 139.59, 132.55, 132.08, 129.27, 128.97, 128.85, 127.08, 122.99, 118.14, 88.10, 86.23, 78.99, 76.41, 30.38, 26.70, 21.32, 21.18, 21.08, 17.89, 13.57; IR (KBr) 3060, 3010, 2930, 2240, 1600, 1490, 1380, 1360, 1110, 755, 700, 690 cm^{-1}; UV (methanol) λ_{max} 248 nm; MS, *m/e* 363 (M^+, 21.9), 279 (M^+ − DMB, 16.4), 226 (M^+ − DMB − AcCN, 97.3). Anal. Calcd for $C_{27}H_{25}N$: C, 89.22; H, 6.93; N, 3.82. Found: C, 89.17; H, 7.11; N, 3.71.

Quantum Yield Measurements. Samples for quantum yield determination were degassed and sealed in Pyrex ampules. DMB solutions of samples (3 mL) were pipetted into ampules, degassed through three cycles of the freeze–pump–thaw method with cooling in liquid nitrogen, and sealed. Azulene concentrations were 0–2.5 × 10^{-4} M, and the concentration of 1 was 10^{-4} M. The samples were irradiated with a Hanovia 450-W medium-pressure mercury arc lamp (Type 679A36) in a merrgy-go-round apparatus. Mercury emission line of 366 nm was isolated by Corning glass filters 0-52 and 7-37. Ferrioxalate actinometry was used to monitor the intensity of the light absorbed. Quantitative analysis was carried out by HPLC utilizing a Radialpak Si column and *n*-hexane as a solvent.

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Registry No. 1, 20264-56-6; 3, 17814-74-3; 4, 113860-44-9; 5, 106507-59-9; 7, 113860-46-1; 8, 113860-47-2; 9, 113860-48-3; 10, 113860-49-4; DMB, 563-79-1; AcCN, 107-13-1; $C_6H_5C{\equiv}CBr$, 932-87-6; $HC{\equiv}CC{\equiv}CSi(CH_3)_2C_4H_9$-*t*, 113860-45-0.

Synthesis of C-Nucleoside Analogue of (*S*)-9-(2,3-Dihydroxypropyl)adenine and Related Acyclonucleosides

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Synthesis of C-nucleoside analogue of (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA] and related compounds is described. 3-Amino-4-[2,3-(isopropylidenedioxy)-1-propyl]pyrazole (**6**) was prepared in six steps from 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) by routes involving Wittig reaction, sodium borohydride reduction, formylation, and the cyclocondensation with thiosemicarbazide followed by the alkaline hydrolysis of 3-amino-2-thiocarbamoylpyrazole **9**. Cyclization of **6** with *N*-cyanoformimidate, followed by the removal of protecting group yielded 4-amino-8-(2,3-dihydroxy-1-propyl)pyrazolo[1,5-*a*]-1,3,5-triazine (**11**), the C-nucleoside analogue of (*S*)-DHPA. The guanine analogue **15** was synthesized by cyclizing **6** with *N*-(ethoxycarbonyl)-*S*-methylisothiourea followed by the deblocking of isopropylidene group. Analogous sequence of reactions of **6** with ethoxycarbonyl isothiocyanate and the subsequent desulfurization of **21** gave the inosine analogue **23**. Synthesis of 8-(2,3-dihydroxy-1-propyl)-4-thioxo-3,4-dihydropyrazolo[1,5-*a*]-1,3,5-triazine (**17**) from **9** is also reported.

The acyclonucleosides have been the subject of intense research for the past 10 years. Their chemistry and biology has been the subject of a recent review.[1] Acyclovir, the first clinically useful antiherpes (herpes type-2) agent, has inspired continuing research in this area. The usefulness of acyclovir originates from the drug's selective inhibitory activities on several virally induced enzymes such as thymidine kinase and DNA polymerase.[2]

A number of acyclonucleosides have been synthesized as potential antiviral agents.[1] Among them, (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA] (Figure 1) seems to be an interesting compound. It possesses broad-spectrum antiviral activities on DNA and RNA viruses as well as plant viruses.[3] It is interesting to note that only the *S* enantiomer exhibits antiviral activity. Recently, De Clercq, Holy, and co-workers reported selective broad-spectrum antiviral activities of a (*S*)-DHPA analogue, (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine [(*S*)-HPMPA][4] (Figure 1). Again, only the *S* isomer exhibited antiviral activity, whereas the *R* enantiomer is markedly less active. During the toxicological studies of (*S*)-DHPA, it was found that the compound inhibited spermatogenesis in mice. Moreover, the testicular dysfunction generated

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