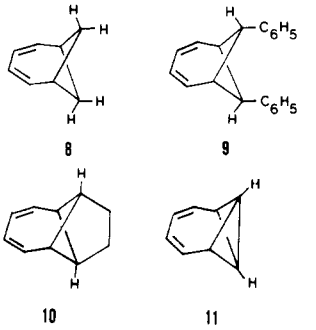
predicted to be shorter for 2 and 4 compared with 1 and 3. This is in line with the larger resonance integral as discussed in the previous section.

The agreement between calculated orbital energies (MINDO/3) and PE data is not satisfactory. Usually the high energy bands are predicted at too low energies, furthermore in case of 4 the MINDO/3 model predicts $9a_1$ at too low energies. It seems to be a general shortcoming of MINDO/3 to give too low binding energies for σ orbitals with a large p character (ribbon orbitals). However, the qualitative orderings are the same.

Discussion

Our PE spectroscopic investigations on 1–4 together with the ZDO treatment reveal a stronger interaction between the π-system and the bicyclobutane unit as compared to the cyclobutane fragment. The increase of interaction is exemplified in the different resonance integrals (2.3 eV vs. 1.9 eV) and it shows up in the lower ionization energy for 2 and 4 compared with 1 and 3.

In line with these findings is the marked difference in reactivity toward dienophiles encountered for 3 and 4[4] as well as 5 and 6[2]. The comparison of the PE results of 3 and 4 shows that the electronic contribution amounts to only 5 kcal/mol. The larger difference in reactivity in case of 5–6[2] we ascribe to steric effects as indicated in the introduction. Note, however, that in some cases[26] methyl groups show remarkable effects on ionization potentials. The syn hydrogen atoms at positions 5 and 6 of 3 are placed closer to the π-system than the corresponding hydrogens in 4. This shielding effect is expected to be seriously stronger for the methyl groups in 5 compared to 6. In line with these arguments is the observation that systems like 8[14,27] or 9[28] do not react or react slowly with *N*-phenyltriazolinedione, whereas 10[29] and octvalene (11)[30] react smoothly.



Experimental Section

The preparation of 1,[31] 3,[3] and 4[4] has been described in the literature. For our PE spectroscopic investigations we used analytically pure material. The PE spectra have been recorded on a Perkin-Elmer PS 18 photoelectron spectrometer. The spectra were recorded at room temperature and were calibrated with argon and xenon. A resolution of 0.03 eV was achieved for the single bands and 0.1 eV for the shoulders.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the A. von Humboldt Foundation, and the BASF Aktiengesellschaft in Ludwigshafen for financial support.

Registry No. 1, 822-41-3; 2, 659-85-8; 3, 50682-99-0; 4, 55678-69-8; 5, 55955-16-3; 6, 50590-86-8.

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Novel Photoinduced Functionalized C-Alkylations in Purine Systems[1]

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The photoinduced reactions of metal enolates with 6-halopurine derivatives result in the formation, in high yields, of a variety of novel functionalized 6-alkylated purines that exist preferentially in the hydrogen-bonded enolic form in nonpolar solvents. High-field ^1H and ^{13}C NMR data provide unambiguous support for the structures proposed. An $S_{RN}1$ mechanism is implicated in these photochemical transformations. The synthetic versatility of the photoproducts is illustrated by their conversion to other functionalized 6-substituted purines such as those bearing alkenyl, epoxy, and diol groups. Extension of the photochemical functionalized C-alkylation to purine nucleosides is described.

Carbon–carbon bond forming reactions are potentially very effective approaches to the synthesis of a wide variety of interesting functionalized nucleosides. However, this methodology has been of limited synthetic utility in the chemistry of purine nucleosides. For example, direct displacement of leaving groups such as methyl sulfone and halide by nucleophiles is limited to nucleophiles derived from carbons bearing one or two strong electron-withdrawing groups.[2] Purines can be converted to nucleophiles by a metal–halogen exchange reaction, and the resulting intermediate may participate in alkylation reactions.[3] However, these reactions must be conducted at very low temperatues (−130 °C) to avoid nucleophilic attack by the butyllithium in the first step and to minimize the relocation of the carbanion to the C-8 position in the lithiopurine intermediate. Although metal-catalyzed reactions have been used to synthesize C-6-alkylated purines, these re-

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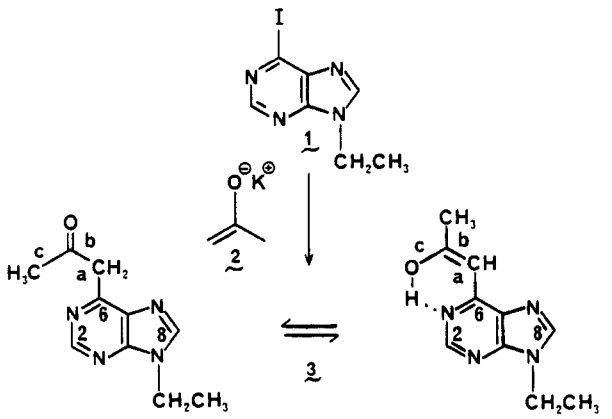
Scheme I



actions have been restricted to some nonfunctionalized alkylpurines.[4]

The Eschenmoser sulfide contraction has been used for C-6 alkylation of purine nucleosides.[5] However, this procedure gives variable results for functionalized C-alkylation.[6] The ylide reaction of 6-chloropurines has been used for the synthesis of some aralkenylpurines,[7] although the application to nucleoside synthesis remains largely unexplored.

Recognition of the potential biological activity of C-6-alkylated purine nucleosides is slowly emerging. The reported antitumor activity of some of these compounds,[6,8-13] and the limitations in generalized synthetic methodology available to attain them, prompted us to consider alternate synthetic approaches to this class of compounds. This paper[14] reports on the successful development of a new, synthetically useful method of carbon–carbon bond formation in purines through a photochemical $S_{RN}1$ reaction (substitution, radical, nucleophilic, unimolecular).[15,16] The synthetic approach has wide applicability. In addition, the products of these photoinduced reactions have remarkable versatility in terms of conversion to other biologically interesting purine systems, and this is exemplified.

Results and Discussion

Photochemically generated transient purinyl radicals or their equivalent provide an excellent approach to a variety of specific arylated or heteroarylated purines.[17,18] However, the approach used in the aforementioned studies of arylations by us is not directly applicable to the synthesis of functionalized C-alkylated purine nucleosides. It was envisaged that functionalized carbon–carbon bond formation could be possible through a reaction involving an excited metal enolate and a 9-substituted 6-iodopurine. Thus, when the potassium enolate of acetone was photolyzed in an ammonia solution in the presence of 6-iodo-9-ethylpurine (1) in a Rayonet photochemical reactor for $^1/_2$ h, 6-acetonyl-9-ethylpurine (3) was isolated in 70% yield after chromatographic separation (Scheme I). Its UV data in ethanol showed a bathochromically shifted spectrum [λ_{max} 362 nm (ϵ 23 300), 345 (18 450), 330 (13 650), 266 (3600)] compared to the starting material [λ_{max} 276.5 nm (ϵ 12 000)]. This was taken as evidence that the acetonyl product could exist in the enol form. The 360-MHz ^{1}H NMR spectrum (in $CDCl_3$) at 25 °C provided substantiating evidence for a keto–enol equilibrium with preponderance of the enol isomer probably because of added stabilization from increased conjugation and hydrogen bonding. The keto and enol forms could be discerned, not only by the marked difference in the chemical shifts of H_a but also from the downfield shift of H_2 in each case for the keto form. Solvent and variable-temperature ^{1}H NMR studies showed the expected direction of shift in the keto–enol equilibrium. The keto to enol ratio in $CDCl_3$ for 3 at 25 °C is 20:80, but in D_2O this ratio is close to 50:50. Variable-temperature ^{1}H NMR data of 3 in Me_2SO-d_6 shows an increase in the keto form from 18% at 15 °C to 46% at 100 °C. Further support for the structures for 3 came from the 90.6-MHz ^{13}C NMR data in $CDCl_3$ that showed two resonances for each of the carbons in 3. As expected, there was a major difference in the chemical shift for C_a in the keto form (48.1 ppm) compared to the enolic form (88.6 ppm). The carbonyl carbon appeared at δ 203.2, and this carbon in the enolic form was at δ 185.9. The mass spectrum showed a parent ion peak at m/z 204 and major fragmentation peaks at m/z 189 (loss of methyl) and 162 (loss of CH_3CHO).

The acetonylation of 1 probably occurs via an $S_{RN}1$ (substitution, radical, nucleophilic, unimolecular) mechanism.[19] Support for the $S_{RN}1$ mechanism came from several observations. Although the molecularity of this reaction is identical with that of an S_NAr reaction, if a photostimulative effect can be demonstrated along with an inhibitory effect by a radical scavenger, an $S_{RN}1$ mechanism is implied. When 6-iodo-9-ethylpurine (1) was treated with acetone enolate anion in the dark for $^1/_2$ h, the yield of the reaction dropped to 22%. Longer reaction times resulted in higher yields of 3 but with an abundance of side products. When the photostimulated reaction was carried out in the presence of *p*-dinitrobenzene (DNB),[20] product 3 was isolated in 6% yield while 65% of the starting material was recovered. Additional support for the involvement of an $S_{RN}1$ mechanism can be inferred from the mild conditions and the very short reaction times necessary for our reactions. The normal nucleophilic displacement of groups from the 6-position of purines requires elevated temperatures and extended reaction times.[2] It should also be mentioned that the much slower dark reaction of acetone enolate with 6-iodo-9-ethylpurine (1) in liquid ammonia appears to be of the $S_{RN}1$ type as evidenced by the almost complete quenching of this reaction by DNB. The mechanistic implication is that, in

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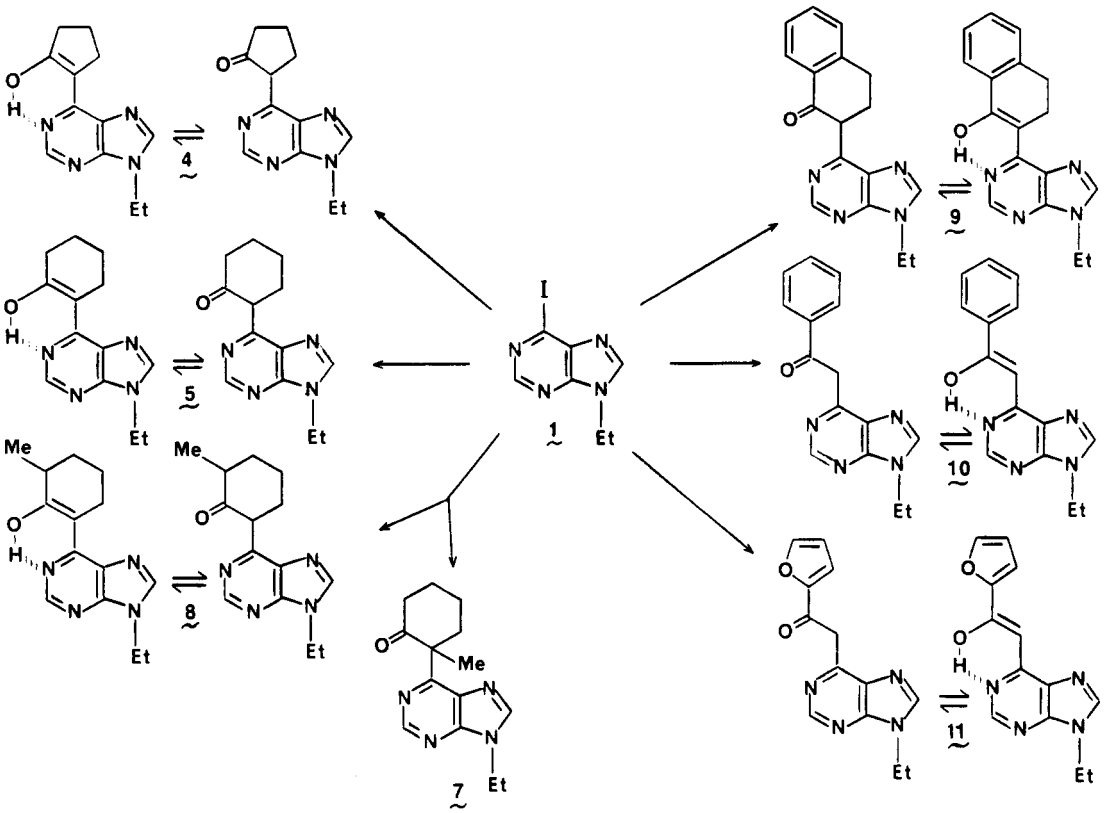
Scheme II



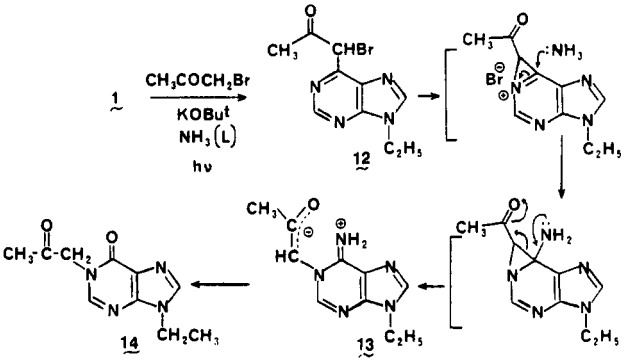
the photostimulated reaction, although photoinduced carbon–iodine bond homolysis may be possible, a much more facile redox initiation pathway may be preferred as the entry point to the $S_{RN}1$ mechanism. It is this redox initiation step that is perhaps stimulated by light,[21] resulting in the highly efficient transformation observed.

We have extended these studies to include other ketone enolates. For example, the photoinduced reaction of the enolate of cyclopentanone with 1 results in the formation of 6-cyclopentanon-2-yl-9-ethylpurine (4), a light yellow solid, in 65% yield. The high-field ^1H NMR data in $CDCl_3$ at 25 °C again showed the existence of a keto–enol equilibrium, with the enol form predominating (90%). Using the enolate of cyclohexanone, 6-cyclohexanon-2-yl-9-ethylpurine (5) was synthesized in 48% yield as a light yellow solid (Scheme II).

The reaction of an unsymmetrical ketone, 2-methylcyclohexanone, capable of forming a kinetic or thermodynamic enolate anion was also examined. The thermodynamic product, 6-(2-methylcyclohexanon-2-yl)-9-ethylpurine (7), was formed in a 30% yield. Compound 7 exists entirely in the keto form as it is not readily enolized. This was confirmed by high-field NMR and UV data. The UV absorption maximum at λ_{max} 266 nm (ethanol) is expected for a nonconjugated C-6-alkylated purine. The kinetic product of this reaction, 8, was obtained in 7% yield and existed in both the keto and enol forms (Scheme II). The relatively low yield of products in this case is the result of a competing side reaction, i.e. the formation of 9-ethylpurine (6) through hydrogen abstraction. Anions generated from ketones with β-hydrogens often lead to substantial amounts of reduction products in $S_{RN}1$ reactions.[16,19]

Enolate anions derived from aryl alkyl ketones are known generally to be poor $S_{RN}1$ nucleophiles.[22] However, the enolate anions derived from acetophenone and α-tetralone reacted readily with 1 to give high yields of 10 and 9, respectively (Scheme II). This may be due to the ease of electron transfer to the electron-deficient 6-iodo-9-ethylpurine (1) system.[23] We were also successful in functionalizing the purine C-6 position with 2-acetylfuran in a reaction that appears to have generality for acylated heteroaromatics. The product of this reaction, 11, has a close structural resemblance to plant growth regulators called cytokinins.[24]

Scheme III



Interestingly, the photoinduced reaction of the enolate of bromoacetone with 1 results in the formation of *N*-1-acetonyl-9-ethylhypoxanthine (14). A plausible mechanism for the formation of 14 involves an initial $S_{RN}1$ reaction of 1 to produce the 6-alkylated purine 12. Intramolecular displacement of bromine, followed by nucleophilic attack on the azirinium system[25] by the solvent and ring opening,

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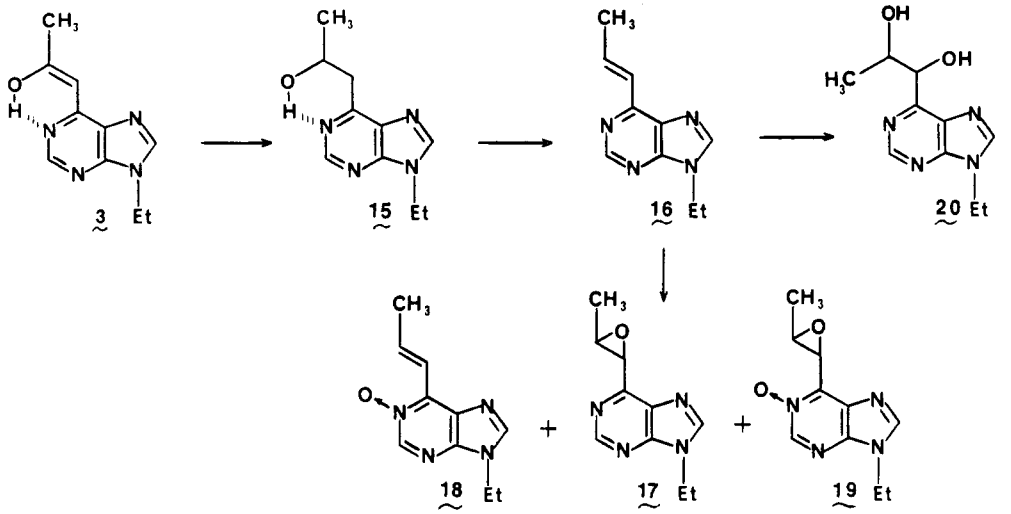
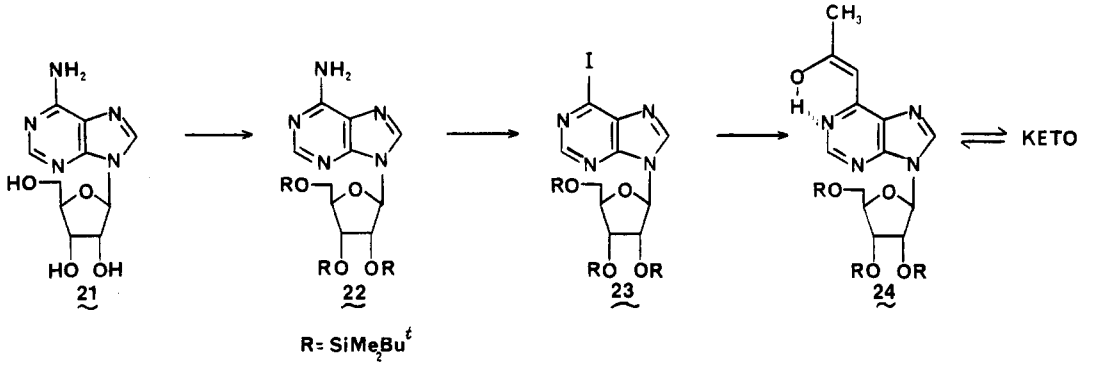
Scheme IV



Scheme V



would give the zwitterion **13**, which undergoes rapid hydrolysis during workup and separation to give **14** (Scheme III).

A major advantage of the C-6-alkylated purines synthesized by this methodology is that the products have versatility in terms of further synthetic elaborations. Thus, when the acetonyl product **3** was reduced with sodium borohydride, 6-(2-hydroxypropyl)-9-ethylpurine (**15**) was isolated as a white solid in 72% purified yield. Dehydration of **15** with potassium bisulfate in toluene results in stereospecific formation of the alkenylpurine **16** in 84% isolated yield. The trans *E* geometry of the double bond could be easily discerned from the vicinal coupling constant (J = 15.7 Hz) of the alkenyl group. Epoxidation of alkene **16** was accomplished with *m*-chloroperbenzoic acid to give the *trans*-epoxide **17** in 16% yield. Several side products including the alkene *N*-1-oxide **18** and the epoxy *N*-1-oxide **19** were also produced. Treatment of the alkene **16** with osmium tetroxide for 24 h followed by workup with sodium bisulfite produced 6-(1,2-dihydroxypropyl)-9-ethylpurine (**20**) in 76% isolated yield (Scheme IV).

The long-term goal of this investigation is to develop a methodology for the synthesis of biologically active functionalized C-alkylated nucleosides. Therefore, extension of the photoinduced C-alkylation reaction to purine nucleosides was undertaken. To accomplish this, readily available adenosine (**21**) would be iodinated and subsequently subjected to the $S_{RN}1$ reaction. However, protection of hydroxyl groups would be required in both steps. Acetate and related protecting groups would be cleaved in ammonia solution, and so we chose the *tert*-butyldimethylsilyl group. This blocking group could be readily introduced with high yields and selectivity for the ribose hydroxyl groups and not the exocyclic amino group of adenine.[26] However, preliminary experiments with 6-iodo-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (**23**) gave low yields of product due to limited solubility in liquid ammonia and desilylation. To circumvent these problems, we examined other solvents for this reaction. Using the model compound, 6-iodo-9-ethylpurine (**1**), it was discovered that tetrahydrofuran was an excellent solvent for this reaction (yield 87%), when it was conducted at low temperatures (e.g. −44 °C) and with potassium hydride as base. Application of this modified procedure to nucleosides was carried out as follows. Trisilylated adenosine **22** was synthesized by the procedure of Ogilvie and co-workers[26] and purified by flash chromatography on silica gel. The 6-halogenated nucleoside **23** was synthesized from **22** by treatment with trimethylsilyl iodide, diiodomethane, and *n*-pentyl nitrite in hexane at 60 °C, which is a modification of a procedure previously reported by us.[27] Application of the aforementioned photoinduced reaction of **23** with the potassium enolate of acetone in tetrahydrofuran resulted in the formation of **24** in a 51% isolated purified yield (Scheme V).

In summary, novel functionalized 6-alkylated purines can be synthesized from the 6-iodinated purine precursors through an efficient photoinduced reaction with metal enolates. The C-alkylated products may be converted to

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other functionalized purine systems.

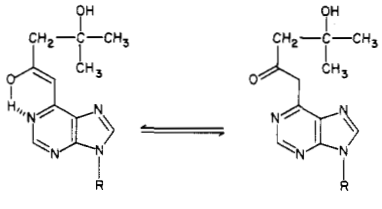
Experimental Section

A Rayonet photochemical reactor, fitted with 3500-Å bulbs, was used in the photolysis experiments. The melting points provided are uncorrected and were taken on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra using tetramethylsilane as an internal standard were recorded on JEOL Model FX90Q and Bruker Model WM360 pulse Fourier transform spectrometers. A Hewlett-Packard 5985 GC/MS system was used for the mass spectra. The ultraviolet spectra were recorded on a Varian Cary Model 219 spectrophotometer. Infrared spectra were recorded on an IBM Model 98 Fourier transform instrument. Microanalytical data were determined on a Perkin-Elmer 240A CHN analyzer. Anhydrous ammonia (Matheson) was used without distillation. Potassium *tert*-butoxide, and potassium hydride (Aldrich) were used directly. Acetone (MCB Omnisolve), cyclopentanone, cyclohexanone, 2-methylcyclohexanone (Aldrich), and tetrahydrofuran (MCB, Omnisolve) were distilled prior to use. Acetophenone, α-tetralone, and acetylfuran (Aldrich) were used without further purification. Preparative layer chromatography employed EM silica gel plates, activated for 3 h at 135 °C.

General Procedure for Photoinduced $S_{RN}1$ Reactions (Procedure A). A 250-mL three-neck RBF fitted with a stir bar, cold finger, and constant-addition funnel was assembled hot and purged with nitrogen. After cooling, potassium *tert*-butoxide (3 equiv) was added and anhydrous ammonia was condensed into the flask with dry ice and acetone in the cold finger. The ketone (3 equiv) was dissolved in freshly distilled tetrahydrofuran (5 mL) and added over 15 min to the ammonia solution. The solution was stirred for 45 min, and 6-iodo-9-ethylpurine (1 equiv) dissolved in a minimum amount of tetrahydrofuran was added. The constant-addition funnel was removed, and the apparatus was placed in the Rayonet photochemical reactor fitted with 3500-Å lamps. Photolysis was carried out for 30 min, with the condensate being washed off the reaction vessel with acetone every 10 min. The reaction mixture was poured into a beaker and quenched with excess ammonium chloride. The ammonia was allowed to evaporate and was replaced with dichloromethane. The solvent was decanted, and the residual salts were washed with more dichloromethane. After drying with anhydrous sodium sulfate, the solution was rotoevaporated and the residue was separated on silica gel plates with 1:15 methanol/dichloromethane. The solid products were crystallized from ether/hexane.

6-Acetonyl-9-ethylpurine (3) by Procedure A. 6-Iodo-9-ethyl-purine (1)[27] (0.500 mmol) was treated with the enolate of acetone (1.600 mmol) as described above. The residue from the workup was eluted twice on silica gel plates using 1:15 methanol/dichloromethane. The major band with R_F 0.32 afforded 0.072 g (0.353 mmol, 70%)[28] of **3** as a light yellow solid: mp 148–149 °C; ^{13}C NMR ($CDCl_3$) δ 15.3, 15.6, 26.3, 30.4, 38.9, 39.0, 48.1, 88.6, 124.8, 133.4, 140.7, 144.1, 145.5, 146.5, 151.0, 151.3, 152.3, 154.8, 185.9, 203.2; ^1H NMR ($CDCl_3$) δ 8.92 (s), 8.27 (s), 8.11 (s), 7.89 (s), 5.98 (s), 4.36 (s), 4.35 (q, J = 7.3 Hz), 4.26 (q, J = 7.3 Hz), 2.34 (s), 2.18 (s), 1.58 (t, J = 7.3 Hz), 1.54 (t, J = 7.3 Hz); UV (EtOH) λ_{max} 362 nm (ε 2.3 × 10^4), 345 (1.8 × 10^4), 330 (1.4 × 10^4), 264 (3.6 × 10^3); FTIR (KBr) 3093, 2983, 1636, 1567, 1557 cm^{-1}; mass spectrum, m/z (relative intensity) (30 eV) 204 (M^+, 50.8), 189 (85.9), 175 (3.4), 162 (100), 147 (9.3), 134 (72.3). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.41; H, 6.18; N, 27.70. Found: C, 58.81; H, 5.92; N, 27.43.

(28) An additional lower R_f side product is obtained in both procedures A and B. This product has been tentatively assigned the structure:



The yields of this material are as follows: procedure A (R = Et), 15%; procedure B (R = Et), 6%, and (R = protected ribose), 3%.

Dark $S_{RN}1$ Reaction. The procedure for the formation of 6-acetonyl-9-ethylpurine (**3**) (0.500 mmol) was followed except that the reaction flask was protected from light. Workup and chromatography provided 6-acetonyl-9-ethylpurine (**3**) (22%) as the major product together with 6-iodo-9-ethylpurine (**1**) (55%).

Inhibition of Photochemical $S_{RN}1$ Reaction. Following procedure A, 6-iodo-9-ethylpurine (**1**) (0.500 mmol) and acetone enolate (1.600 mmol) were mixed together, and *p*-dinitrobenzene (0.110 mmol) was added to the reaction mixture. Photolysis for 30 min, followed by workup and purification on silica gel plates, produced 6-acetonyl-9-ethylpurine (**3**) (0.006 g, 0.030 mmol, 6%) and recovered starting material (0.091 g, 0.333 mmol, 65%).

Inhibition of Dark $S_{RN}1$ Reaction. The reaction mixture was prepared as described in the foregoing experiment. This solution was stirred in the dark for 30 min. It was quenched, worked up, and purified to give 6-acetonyl-9-ethylpurine (**3**) (3%) and 6-iodo-9-ethylpurine (**1**) (49%).

6-Acetonyl-9-ethylpurine (3) (Procedure B). A low-temperature Hanovia photolysis apparatus with a quartz, vacuum-jacketed inner core and Pyrex filter sleeve was assembled hot and flushed with nitrogen. Dry 6-iodo-9-ethylpurine (**1**) (0.953 mmol) was added directly, followed by the double-tipped needle transfer of freshly distilled tetrahydrofuran (30 mL) that had been purged with nitrogen for 1 h. This solution was cooled to −44 °C in an acetonitrile–dry ice bath. In a separate flask, fitted with a septum, a dispersion of 35% potassium hydride (3.320 mmol) in mineral oil was weighed out and washed twice with dry hexane (5 mL) in a glovebox. Tetrahydrofuran (15 mL) was added via a double-tipped needle. This solution was magnetically stirred at room temperature, and acetone (3.000 mmol) was added directly via a gas-tight syringe. The acetone enolate solution was transferred rapidly to the Hanovia apparatus in the cold bath using a double-tipped needle and washed in with tetrahydrofuran (5 mL). The solution was immediately photolyzed with a 450-W mercury lamp for 20 min. Excess ammonium chloride was added to quench the reaction. The reaction mixture was passed through a short silica gel (60–200 mesh) scrubber column using 1:9 methanol/dichloromethane. The solvent was rotoevaporated to produce a yellow solid that was purified as described in procedure A, providing 6-acetonyl-9-ethylpurine (**3**, 0.169 g, 0.828 mmol, 87%).[28]

6-Cyclopentanon-2-yl-9-ethylpurine (4). A solution of **1** (0.520 mmol) and the enolate of cyclopentanone (1.6 mmol) was prepared and reacted as described in procedure A to give 6-cyclopentanon-2-yl-9-ethylpurine (**4**) (0.078 g, 0.340 mmol, 65%) as a yellow solid: mp 162–164 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 15.7, 20.8, 24.3, 24.4, 35.6, 37.9, 38.6, 38.9, 39.0, 55.4, 98.9, 123.8, 139.7, 140.1, 143.5, 143.9, 146.1, 147.2, 151.8, 152.3, 159.3, 175.9, 216.2; ^1H NMR ($CDCl_3$) δ 1.52 (t, J = 7.3 Hz), 1.60 (t, J = 7.3 Hz), 1.99 (m), 2.49 (m), 3.09 (m), 4.22 (q, J = 7.3 Hz), 7.82 (s), 7.96 (s), 8.05 (s), 8.89 (s); UV (EtOH) λ_{max} 383 nm (ε 2.1 × 10^4), 366 (1.8 × 10^4), 349 (1.1 × 10^4), 266 (2.5 × 10^3), 235 (3.8 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 230 (M^+, 68.6), 229 (M^+–H, 43.4), 201 (42.8), 187 (26.6), 175 (100), 158 (17.2), 147 (28.8), 119 (15.1). Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33; Found: C, 62.97; H, 6.42; N, 24.42.

6-Cyclohexanon-2-yl-9-ethylpurine (5) was prepared by procedure A in 48% yield: mp 132–134 °C; ^{13}C NMR ($CDCl_3$) δ 15.3, 15.4, 21.4, 22.0, 23.2, 25.6, 25.9, 26.0, 32.5, 38.7, 38.9, 42.1, 53.2, 101.0, 126.9, 140.6, 141.0, 143.6, 144.5, 147.2, 149.7, 152.0, 155.0, 158.8, 176.2, 208.0; ^1H NMR ($CDCl_3$) δ 1.54 (t, J = 7.3 Hz), 1.58 (t, J = 7.3 Hz), 1.79 (m), 2.47 (m), 3.09 (m), 4.29 (q, J = 7.3 Hz), 4.33 (q, J = 7.3 Hz), 7.95 (s), 8.04 (s), 8.47 (s), 8.94 (s); UV (EtOH) λ_{max} 384 nm (ε 1.1 × 10^4), 368 (9.7 × 10^3), 348 (9.9 × 10^3), 266 (2.5 × 10^3), 238 (4.3 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 244 (M^+, 43.3), 243 (M^+–H, 18.6), 215 (29.6), 201 (8.5), 188 (100), 175 (52.5), 162 (29.1), 147 (19.5). Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93. Found: C, 63.97; H, 6.34; N, 22.68.

6-(2-Methylcyclohexanon-2-yl)-9-ethylpurine (7) and 6-(6-Methylcyclohexanon-2-yl)-9-ethylpurine (8). Following procedure A, 6-iodo-9-ethylpurine (**I**) (0.910 mmol) and the enolate of 2-methylcyclohexanone (2.700 mmol) were photolyzed. The residue from the workup was eluted twice on silica gel plates using 1:20 methanol/dichloromethane as the eluting solvent. The major band with R_f 0.43 afforded 0.062 g (0.240 mmol, 26%) of **7** as a white solid: mp 76–78 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 22.6, 24.2,

28.3, 38.9, 41.1, 56.7, 131.6, 143.3, 151.6, 151.9, 163.3, 211.6; ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3 H), 1.59 (t, 3 H, J = 7.3 Hz), 1.50–1.85 (m, 5 H), 2.53 (d, 2 H, J = 5.5 Hz), 3.45 (d, 1 H, J = 11.7 Hz), 4.35 (q, 2 H, J = 7.3 Hz), 8.06 (s, 1 H), 8.91 (s, 1 H); UV (EtOH) λ_{max} 266 nm (ϵ 8.6 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 258 (M$^+$, 8.5), 243 (2.1), 230 (26.9), 215 (100), 201 (27.0), 189 (39.7), 175 (16.9), 162 (20.1), 147 (9.2), 112 (8.9). Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.17; H, 7.11; N, 21.63.

The minor band with R_f 0.32 afforded 0.019 g (0.073 mmol, 8%) of **8** as a golden oil: ^{13}C NMR ($CDCl_3$) δ 14.6, 15.3, 15.4, 18.8, 21.0, 25.2, 26.6, 30.6, 32.3, 36.4, 36.5, 38.8, 38.9, 45.9, 55.1, 100.6, 127.1, 133.3, 140.9, 143.4, 147.2, 152.2, 155.3, 157.5, 158.9, 163.6, 179.9, 209.0; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.8 Hz), 1.28 (d, J = 6.8 Hz), 1.53 (m), 1.84 (m), 2.60 (m), 3.09 (m), 4.24–4.37 (m), 7.95 (s), 8.02 (s), 8.45 (s), 8.94 (s); UV (EtOH) λ_{max} 383 nm (ϵ 3.1 × 10^3), 344 (5.5 × 10^3), 266 (5.4 × 10^3), 248 (5.8 × 10^3); FTIR (neat) 3100, 3060, 2970, 2930, 2830, 1715, 1580, 1570 cm^{-1}; mass spectrum, m/z (relative intensity) (30 eV) 258 (M$^+$, 27.6), 257 (34.0), 243 (6.2), 229 (100), 215 (41.8), 201 (29.7), 189 (60.2), 175 (56.5), 162 (41.7), 147 (22.3). Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.24; H, 7.17; N, 21.48.

6-(1-Tetralon-2-yl)-9-ethylpurine (9) was prepared in 79% yield by procedure A: mp 191–193 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 15.5, 23.0, 28.5, 28.6, 28.9, 38.8, 38.9, 52.6, 100.5, 125.1, 126.5, 126.6, 126.7, 127.2, 127.3, 127.8, 128.7, 130.4, 133.2, 133.6, 140.2, 140.4, 143.7, 144.1, 146.4, 148.9, 151.0, 152.3, 152.8, 159.9, 171.9, 195.9; ^{1}H NMR ($CDCl_3$) δ 1.54 (m), 2.94 (m), 3.53 (m), 4.28 (m), 7.26–7.33 (m), 7.93 (s), 7.98 (s), 8.42 (s), 8.91 (s); UV (EtOH) λ_{max} 403 nm (ϵ 2.0 × 10^4), 250 (9.6 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 292 (M$^+$, 91.9) 291 (100), 263 (67.5), 235 (20.7), 162 (38.6), 149 (28.2), 118 (25.6), 90 (42.0). Anal. Calcd for $C_{17}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.82; H, 5.66; N, 20.31.

6-Acetophenon-2-yl-9-ethylpurine (10) was prepared in 70% yield by procedure A: mp 153–154 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 15.6, 38.9, 43.5, 86.4, 125.9, 126.6, 128.3, 128.6, 130.7, 133.4, 137.4, 141.1, 143.9, 145.9, 147.0, 152.7, 178.4, 194.9; ^{1}H NMR ($CDCl_3$) δ 8.95 (s), 8.39 (s), 8.04–7.94 (m), 7.93 (s), 7.43–7.38 (m), 6.75 (s), 4.89 (s), 4.29 (q, J = 7.3 Hz), 1.56 (t, J = 7.3 Hz); UV (EtOH) λ_{max} 379 nm (ϵ 3.1 × 10^4), 243 (1.0 × 10^4); mass spectrum, m/z (relative intensity) (30 eV) 266 (M$^+$, 39.2), 265 (35.2), 238 (26.2), 189 (31.0), 161 (9.2), 133 (11.4). Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.84; H, 5.37; N, 20.87.

6-[(Furylcarbonyl)methyl]-9-ethylpurine (11) was prepared in 67% yield by procedure A: mp 146–148 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 15.6, 39.1, 43.1, 65.9, 84.6, 111.9, 112.5, 112.7, 118.4, 124.9, 140.6, 144.2, 144.6, 145.7, 146.8, 150.6, 152.3, 152.9, 173.1, 183.7; ^{1}H NMR ($CDCl_3$) δ 1.54 (t, J = 7.3 Hz), 4.26 (q, J = 7.3 Hz), 4.76 (s), 6.51 (m), 6.59 (s), 7.07 (d, J = 3.3 Hz), 7.52 (d, J = 1.5 Hz), 7.88 (s), 8.08 (s), 8.21 (s), 8.93 (s); UV (EtOH) λ_{max} 404 nm (ϵ 3.8 × 10^4), 386 (3.7 × 10^4), 281 (7.1 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 256 (M$^+$, 48.1), 228 (71.9), 202 (76.3), 199 (85.4) 171 (51.6), 160 (35.3), 149 (20.5), 129 (20.1), 111 (14.0), 95 (100). Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.93; H, 4.72; N, 21.61.

Photolysis of 6-Iodo-9-ethylpurine (1) with Bromoacetone. Following procedure A the enolate anion of bromoacetone was photolyzed with **1** for 1 h. Purification on silica gel plates provided *N*-acetonyl-6-oxo-9-ethylpurine (**14**), 50%, R_f 0.25, as a white solid: mp 102–104 °C; ^{13}C NMR ($CDCl_3$) δ 15.1, 25.9, 38.8, 70.1, 120.8, 142.0, 151.0, 152.1, 159.0, 202.6; ^{1}H NMR ($CDCl_3$) δ 1.56 (t, 3 H, J = 7.3 Hz), 2.27 (s, 3 H), 4.32 (q, 2 H, J = 7.3), 5.13 (s, 2 H), 7.97 (s, 1 H), 8.48 (s, 1 H); UV (EtOH) λ_{max} 250 nm (ϵ 1.2 × 10^4); FTIR (KBr) 3100, 2879, 1734, 1607, 1573, 1477 cm^{-1}; mass spectrum (relative intensity) (30 eV) 220 (M$^+$, 7.4), 205 (74.4), 192 (3.2), 177 (100), 165 (6.0), 149 (93.7), 121 (32.2). Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.17; H, 5.58; N, 25.35.

6-(2-Hydroxypropyl)-9-ethylpurine (15). To a solution of 6-acetonyl-9-ethylpurine (**3**) (0.101 g, 0.495 mmol) in absolute ethanol (10 mL) was added sodium borohydride (0.113 g, 3.040 mmol). The solution was stirred for 3 h at room temperature. Acidification of the cooled reaction mixture with 3 N HCl (4 equiv) was followed by neutralization with saturated aqueous sodium bicarbonate. The ethanol was removed by rotoevaporation, and the remaining aqueous solution was extracted with dichloromethane (3 × 30 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed. The residue was purified on silica gel with 1:9 methanol/dichloromethane as the eluting solvent. The major band at R_f 0.5 was extracted to produce 0.073 g (0.355 mmol, 72%) of a white solid: mp 81–83 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 23.2, 39.0, 41.2, 66.3, 132.6, 143.5, 150.6, 151.8, 160.5; ^{1}H NMR ($CDCl_3$) δ 1.37, (d, 3 H, J = 6.2 Hz), 1.59 (t, 3 H, J = 7.3 Hz), 3.08–3.59 (m, 2 H), 4.04–4.47 (m, 3 H), 4.0–5.0 (br s, 1 H), 8.08 (s, 1 H), 8.89 (s, 1 H); UV (EtOH) λ_{max} 263.5 nm (ϵ 9.4 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 206 (M$^+$, 0.7), 205 (M$^+$–H, 0.6), 191 (5.7), 189 (1.1), 162 (100), 134 (48.3), 107 (12.1). Anal. Calcd for $C_{10}H_{14}N_4O$: C, 58.23; H, 6.84; N, 27.16. Found: C, 57.74; H, 7.16; N, 27.34.

6-Prop-1-enyl-9-ethylpurine (16). To a solution of 6-(2-hydroxypropyl)-9-ethylpurine (**15**) (1.14 mmol) in toluene (20 mL) was added acetic anhydride (1.1 equiv) and excess potassium bisulfate. The solution was stirred at 80 °C for 12 h and cooled in an ice bath. Saturated sodium bicarbonate (5 mL) and water (5 mL) were used to wash the toluene phase. The combined aqueous solutions were washed with toluene (2 × 15 mL). After the toluene solutions were dried (Na_2SO_4) and the solvent was removed, the residue was purified on silica gel plates using 1:9 methanol/dichloromethane. The main band at R_f 0.52 provided 0.180 g (0.960 mmol, 84%) of **16** as a white solid: mp 51–53 °C; ^{13}C NMR ($CDCl_3$) δ 15.4, 19.2, 38.8, 126.7, 130.6, 140.0, 143.3, 151.5, 152.2. 154.1; ^{1}H NMR ($CDCl_3$) δ 1.57 (t, 3 H, J = 7.3 Hz), 2.08 (dd, 3 H, J = 6.6 Hz, J = 1.47 Hz), 4.33 (q, 2 H, J = 7.3 Hz), 7.01 (dd, 1 H, J = 15.8 Hz, J = 1.47 Hz), 7.66 (d of quartets, 1 H, J = 15.8 Hz, J = 6.6 Hz), 8.04 (s, 1 H), 8.86 (s, 1 H); UV (EtOH) λ_{max} 287.5 nm (ϵ 1.4 × 10^4); FTIR (KBr) 3095, 3058, 2918, 1653, 1577 cm^{-1}; mass spectrum, m/z (relative intensity) (30 eV) 189 (M$^+$ + H, 11.8), 188 (M$^+$, 94.1), 187 (77.0), 173 (5.7), 162 (6.8), 159 (91.4). Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.76. Found: C, 63.57; H, 6.42; N, 29.53.

6-[(*E*)-1,2-Oxiranylpropyl]-9-ethylpurine (17). To a solution of 6-prop-1-enyl-9-ethylpurine (**16**) (0.094 g, 0.497 mmol) in dry dichloromethane (10 mL) at 0 °C was added *m*-chloroperbenzoic acid (0.780 mmol) dissolved in dichloromethane (20 mL). The solution was stirred for 12 h at room temperature under N_2. The reaction mixture was subsequently washed with saturated sodium bisulfite (5 mL) and 5% sodium bicarbonate (5 mL). The combined aqueous phases were extracted with dichloromethane (60 mL). The solvent was removed from the combined and dried (Na_2SO_4) extracts under reduced pressure. The residue was purified on silica gel plates developed with 1:20 methanol/dichloromethane. The band at R_f 0.5 provided 0.016 g (0.079 mmol, 16%) of **17** as a clear oil: ^{13}C NMR ($CDCl_3$) δ 15.3, 17.7, 40.0, 56.1, 57.6, 132.5, 144.3, 151.3, 152.4, 156.1; ^{1}H NMR ($CDCl_3$) δ 1.56 (d, 3 H, J = 5.1 Hz), 1.57 (t, 3 H, J = 7.3 Hz), 3.84 (dq, 1 H, J = 5.1 Hz, J = 2.2 Hz), 4.27 (d, 1 H, J = 1.8 Hz), 4.35 (q, 2 H, J = 7.3 Hz), 8.10 (s, 1 H), 8.91 (s, 1 H); UV (EtOH) λ_{max} 268 nm (ϵ 9.5 × 10^3); FTIR (KBr) 3103, 3077, 2963, 1513, 1217, 886 cm^{-1}; mass spectrum, m/z (relative intensity) (30 eV) 204 (M$^+$, 10.5), 189 (28.4), 175 (9.0), 159 (19.4), 148 (60.3), 133 (12.9), 120 (100), 106 (22.5). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.50; H, 6.21; N, 27.14.

6-(1,2-Dihydroxypropyl)-9-ethylpurine (20). To a solution of 6-prop-1-enyl-9-ethylpurine (**16**) 0.433 g (2.300 mmol) in dry pyridine (5 mL) was added osmium tetroxide 0.500 g (1.91 mmol) dissolved in pyridine (5 mL). The solution was stirred for 24 h at room temperature. Sodium bisulfite (0.90 g), pyridine (10 mL), and water (15 mL) were added to the reaction mixture. After stirring for 1.5 h, the solution was extracted with dichloromethane (225 mL). The organic phase was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified on silica gel plates developed with 1:9 methanol/dichloromethane. The band at R_f 0.28 provided 0.333 g (1.50 mmol, 78%) of **20** as a white solid: mp 98–100 °C; ^{13}C NMR ($CDCl_3$) δ 15.3, 19.3, 39.2, 70.0, 74.3, 130.8, 143.9, 151.2, 151.6, 159.3; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 3 H, J = 6.6 Hz), 1.59 (t, 3 H, J = 7.3 Hz), 3.40 (d, 1 H, J = 5.8 Hz), 4.37 (q, 3 H, J = 7.3 Hz), 4.78 (d, 1 H, J = 5.9 Hz), 5.11 (m, 1 H), 8.09 (s, 1 H), 8.94 (s, 1 H); UV (EtOH) λ_{max} 265 nm (ϵ 9.9 × 10^3); mass spectrum, m/z (relative intensity) 223 (M$^+$ + H, 2.3), 179 (12.0), 178 (95.8), 149 (100), 121 (58.8). Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.77; H, 6.55; N, 25.16.

6-Amino-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (22).[26] Adenosine (**21**) (0.259 g, 0.972 mmol) and imidazole (0.536 g, 7.89 mmol) were dissolved in dry dimethylformamide (1 mL), followed by *tert*-butyldimethylsilyl chloride (0.638 g, 4.2 mmol). The solution was stirred under N_2 for 2 h until homogeneous and then allowed to sit for 24 h. The solution was pumped to dryness, taken up in ethyl acetate, and eluted through a short silica gel scrubber column with 1:1 hexane/ethyl ether. Final purification by flash chromatography on silica gel (1:1 hexane/ethyl ether) provided 0.444 g (0.728 mmol, 75%) of a white solid: mp 142–144 °C (lit.[26] mp 142–144 °C); ^{1}H NMR ($CDCl_3$) δ −0.04 (s), 0.11 (s), 0.13 (s), 0.80 (s), 0.94 (s), 0.96 (s), 3.72–4.04 (m, 2 H), 4.14 (m, 1 H), 4.37 (m, 1 H), 4.75 (m, 1 H), 5.90 (br s, 1 H), 6.06 (d, 1 H, J = 5.1 Hz), 8.18 (s, 1 H), 8.37 (s, 1 H).

6-Iodo-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (23). To a solution of 6-amino-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (**22**) (0.316 g, 0.519 mmol) in dry nitrogen purged hexane (30 mL) was added trimethylsilyl iodide (0.125 mL, 0.880 mmol) followed by diiodomethane (0.90 mL, 11.2 mmol) and *n*-pentyl nitrite (1.50 mL, 11.1 mmol). The mixture was stirred at 60 °C for 24 h under N_2. Upon cooling, hexane (20 mL) was added and the reaction mixture was extracted with saturated sodium sulfite (5 mL) and water (5 mL). The combined aqueous phases were extracted with ethyl ether (60 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified on silica gel plates developed with 1:1 hexane/ethyl ether. The band at R_f 0.80 provided 0.261 g (0.363 mmol, 70%) of **23** as a clear oil: ^{1}H NMR ($CDCl_3$) δ −0.04 (s), 0.10 (s), 0.13 (s), 0.78 (s), 0.93 (s), 0.95 (s), 3.71–4.19 (m, 3 H), 4.31 (t, 1 H, J = 3.8 Hz), 4.63 (t, 1 H, J = 4.6 Hz), 6.08 (d, 1 H, J = 5.1 Hz), 8.48 (s, 1 H), 8.61 (s, 1 H); UV (EtOH) λ_{max} 276 nm (ε 1.1 × 10^4); mass spectrum m/z (relative intensity) (30 eV) 705 (M^+–CH_3, 0.4), 663 (M^+–C_4H_9, 12.6), 417 (2.3), 403 (5.7), 261 (6.7), 231 (4.5), 149 (4.9), 147 (10.5), 133 (3.9). Anal. Calcd for $C_{28}H_{53}N_4IO_4Si_3$: C, 46.65; H, 7.41; N, 7.77. Found: C, 46.30; H, 7.38; M, 7.64.

6-Acetonyl-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (24). Following procedure B the enolate anion of acetone was photolyzed with 6-iodo-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (**23**) (0.551 mmol). Purification on silica gel plates using 1:1 hexane/ethyl ether as the developer produced **24**, 0.183 g (0.281 mmol, 51%),[28] R_f 0.53, as a yellow solid: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ −0.04 (s), 0.11 (s), 0.14 (s), 0.79 (s), 0.94 (s), 0.96 (s), 2.17 (s), 2.29 (s), 3.72–4.75 (m), 5.81–6.14 (m), 8.22 (s), 8.26 (s), 8.41 (s), 8.89 (s); UV (EtOH) λ_{max} 362 nm (ε 3.0 × 10^4), 345 (2.5 × 10^4), 330 sh (1.8 × 10^4), 264 (3.8 × 10^3); mass spectrum, m/z (relative intensity) (30 eV) 650 (M^+, 0.8), 635 (M^+–CH_3, 4.1), 593 (M^+–C_6H_9, 100), 447 (13.2), 417 (12.5), 343 (18.0), 333 (83.0), 301 (17.7), 285 (18.0), 275 (16.0), 261 (44.1), 231 (35.9), 211 (30.1), 177 (31.0), 147 (66.3), 133 (9.6), 115 (32.5). Anal. Calcd for $C_{31}H_{58}N_4O_5Si_3$: C, 57.19; H, 8.98; N, 8.60. Found: C, 57.09; H, 8.60; N, 8.45.

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Total Synthesis and Absolute Configuration of Zeylena

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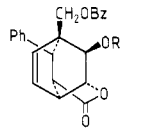
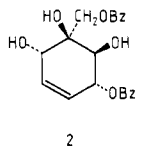
Zeylena (**1a**), isolated from the methanol extract of the roots of *Uvaria zeylanica* (Annonaceae), has been totally synthesized by an intramolecular Diels–Alder reaction of (2*R*)-*trans*-3-[(*E*)-cinnamoyloxy]-2-hyxroxy-1-[(benzoyloxy)methyl]cyclohexa-4,6-diene (**3c**). The absolute configuration of **1a** formerly proposed has been established by the present synthesis.

Zeylena (**1a**) and zeylenol (**2**) were isolated from the methanol extract of the roots of *Uvaria zeylanica* L. (Annonaceae) during the extensive work on tumor inhibitory constituents of these species.[1] Although both



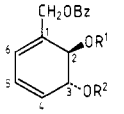
1a R = H
1b R = Ac
1c R = COCH=CHPh



2

compounds were found to be inactive in the P-338 lymphocytic leukemia test system, their biogenetic relationship[2] to other *Uvaria* constituents has stimulated much interest.[1,3] The structure of **1a** was established by the ^{1}H NMR spectra of **1a** and derivatives, and the absolute configuration has been postulated on the basis of the CD curve of the octahydro ketone derived by a catalytic hydrogenation of **1a**, followed by oxidation.[1]

In continuation of our study of highly oxygenated cyclohexane compounds,[4] we now describe a total synthesis of **1a** starting from (2*R*)-*trans*-2,3-dihydroxy-1-[(benzoyloxy)methyl]cyclohexa-4,6-diene[4] (**3a**) via an intramolecular cycloaddition reaction of the hypothetical diene intermediate **3c** proposed for the biosynthesis of **1a**.[1] The



	R^1	R^2
3a	H	H
3b	COCH=CHPh	H
3c	H	COCH=CHPh
3d	COCH=CHPh	COCH=CHPh
3e	Ac	H
3f	Ac	COCH=CHPh

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