(50 mg, 1.3 mmol) in anhydrous ether (50 mL) and heated at reflux for 48 h. Workup of the reaction mixture followed the procedure described for **9** → **10**. Evaporation of the solvent at room temperature afforded 42 mg (81% yield) of **21** as a colorless liquid. Analysis of the crude reaction mixture by GLC (10 ft × 0.25 in DC-550 column; 175 °C) indicated only a single component. Purification by GLC (above conditions) provided pure **21** as an oil: NMR δ (CCl_4) 4.18–3.93 (br s, 1 H, –CH–O–), 2.34–1.43 (br m, 13 H), and 1.25 (s, 6 H, gem dimethyls); IR ν (CCl_4) 2975, 2905, 2850, 1460, 1440, 1385, 1360, 1255, 1215, 1145, 1120, 1095, 1070, and 1050 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.02; H, 11.08.

Acknowledgment. This work was supported by grants from the Research Corporation and the University of Delaware Research Foundation.

Registry No.—**1**, 21898-84-0; **7**, 21932-99-0; **8**, 66483-52-1; **9**, 66483-53-2; **10**, 21898-86-2; **13**, 66483-54-3; **14**, 66537-45-9; **17**, 66483-55-4; **17** semicarbazone, 66483-56-5; **18**, 28644-53-3; **19**, 66483-57-6; **20**, 66483-58-7; **21**, 66483-59-8; 3-*endo*-carboxybicyclo[3.3.1]non-6-ene, 21932-98-9.

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(9) The chemical shift of the $-CH_2-O-$ protons in **10** has been reported as being δ 3.08[3a] and 3.87.[8a]
(10) The carbon magnetic resonance spectrum was recorded at an operating frequency of 22.63 Hz on a Brüker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data acquisition system and is referenced to an internal standard of tetramethylsilane.
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Insect Antifeedants. 1. Diels–Alder Approach to the Synthesis of Ajugarin I

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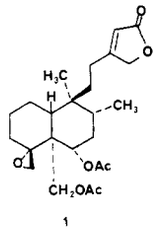
An approach to the synthesis of the antifeedant ajugarin I (**7**) employing a Diels–Alder reaction for the preparation of the decalin position of the molecule is described. Cycloaddition of 2,4-pentadien-1-ol (**5**) and carbomethoxy-*p*-benzoquinone (**6**) affords a mixture of hemiacetals **8** and **9** having the same gross regio- and stereochemistry. The structures of the adducts are determined by spectroscopic means and X-ray crystallography of their reduced transformation products **10** and **11**. Conversion of the initial adduct mixture to a potentially synthetically useful intermediate **31** is accomplished by reductive cleavage of a γ-keto unsaturated acetal, **29**.

Ajugarin I (**1**) isolated from *Ajuga remota* (Labitae) exhibits significant antifeeding activity against African army worms.[1] It is a member of the clerodane class[2] of rearranged diterpenes, many of which have also been shown to act as in-

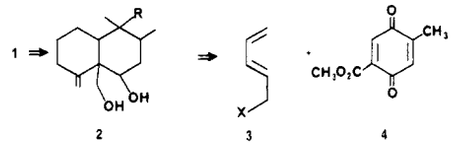


1

sect antifeedants.[3] The structure and activity of ajugarin I were recently described by Nakanishi and associates.

We are presently embarked on a project directed toward the synthesis of ajugarin I and its congeners. In this paper, we report some of the results of a Diels–Alder approach to the construction of the decalin portion of the structure of the natural product.

The placement and the nature of the groups about the periphery of the bicyclic unit of **1** suggested to us the retrosynthetic plan illustrated in brief form in the scheme **1** → **2** → **3** + **4**. As shown, we visualized a rapid and efficient construction of the decalin system by a cycloaddition reaction of suitably substituted diene–dienophile partners. In terms of the specific structural requirements of the Diels–Alder combination, the choice of a 1-heteroalkyl-substituted butadiene **3** and a carboalkoxy-*p*-quinone[4] seemed most appropriate.



2 **3** **4**

Our initial efforts in an experimental realization of this synthetic plan have been focused on the addition of several substituted butadienes to the unsubstituted carbomethoxy-*p*-benzoquinone (**6**).[4] The discussion to follow is concerned with the structural and stereochemical outcome of two of these cycloadditions and with the results of several transformations carried out with the initial Diels–Alder adducts.

The first problem to be faced in the Diels–Alder approach to ajugarin I was the question of orientation in the proposed cycloaddition reaction. Dienes substituted at the 1 position are generally assumed to follow an "ortho" rule in Diels–Alder

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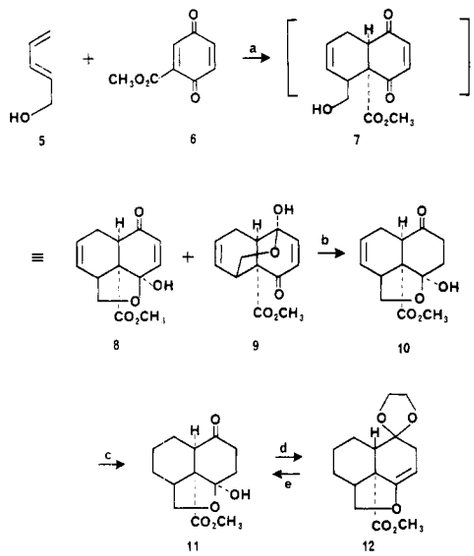
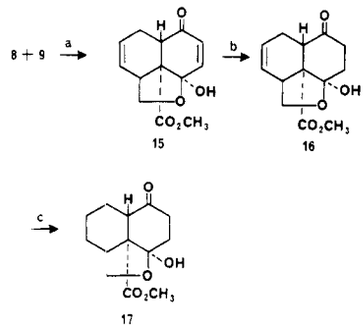
Scheme I



[a] C_6H_6, 25 °C; [b] Zn, HOAc; [c] H_2, Pd; [d] $HOCH_2CH_2OH$, *p*-TSOH; [e] H_3O^+.

Scheme II



[a] Dabco, 25 °C; [b] Zn, HOAc; [c] H_2, Pd.

additions,[5] and a number of theoretical–calculational reports[6] have appeared recently to support the empirical generalization. Specific additions of 1-aryl-substituted butadienes to carbomethoxyquinone **6** have also been studied by Ansell and co-workers.[7] Based on this work as well as on a study we have made of the addition of *trans*-piperylene to **6**,[8] the interaction of 1-hydroxymethylbutadiene (**5**) with **6** was expected to yield predominantly a product with the regiochemistry and stereochemistry shown in Scheme I for structure **7**.

In practice, the reaction of **5** and **6** occurs rapidly at room temperature[9] to yield a solid, mp 108–114 °C, which proved to be a mixture of two adducts. Although these products could not be separated and individually examined, the spectral and chemical evidence to be outlined below leaves little doubt that they are the isomeric hemiketals **8** and **9**, both having been formed with the anticipated geometry and molecular organization.

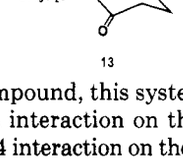
Treatment of the adduct mixture with diazabicyclononane afforded a new substance **15**, mp 142–145 °C (Scheme II), spectrally distinct from either component of the original product. That **15** is the trans-fused isomer of **8** was apparent from a comparison of the proton spectra of **15** and the mixture of **8** and **9**. In the spectrum of **15** a singlet at 3.62 ppm is observed corresponding to the ester methyl group. In contrast the ^1H NMR spectrum of the mixture shows two singlets at lower field, 3.69 and 3.71 ppm, respectively. An upfield shift of approximately 7–8 Hz in going from cis- to trans-fused aryl-substituted esters similar to **8**, **9**, and **15** has been noted by Ansell[10] for the resonance position of the carbomethoxy protons. Although the shift which we have observed is smaller than that found by Ansell, our results parallel his. We have found, moreover, that the same effect occurs in the saturated analogues of these compounds and is not limited to the Diels–Alder adducts and their epimers only. The finding here that both components of the adduct mixture are converted to a common trans isomer **15** (the epimer of **9** being of course sterically unattainable) removes both compound **15** and any substance stereoisomeric at the ring-A oxymethyl group from consideration as one of the components of the product from the cycloaddition.

Examination of the proton spectrum of **15** also helped to establish the regiochemical outcome of the Diels–Alder reaction. This spectrum displays a doublet of doublets centered at 2.81 ppm for the junction proton with coupling constants of 4 and 7 Hz. Such a pattern is consistent only with the regio- and stereochemistry of **15**. The compound must be trans fused with coupling of an axial angular proton to adjacent equatorial and axial neighbors.

The last aspect of the structure of the Diels–Alder product, the presence of a hemiketal group, was apparent first from the ^{13}C spectra of the adduct mixture and of the isomerized compound **15**. In the ^{13}C NMR spectrum of **8** and **9** each of the expected 13 peaks is doubled. More important, however, is the fact that both substances in the mixture show only two carbonyl carbons each. The "missing" carbonyl carbons appear instead as a pair of peaks at 95.1 and 100.6 ppm, indicative of hemiketal carbons.[11] In a similar fashion the isomerized trans compound **15** shows two carbonyl carbons at 196.6 and 169.9 ppm and a hemiketal carbon at 101.5 ppm.

Further evidence that the products of the Diels–Alder reaction are interconvertible hemiketals was provided by the result of zinc–acetic acid reduction of the adduct mixture. This reaction carried out at room temperature for 10 min afforded a single crystalline product **10**, mp 140–142 °C, in 93% yield. Despite the acidic conditions of this reduction, no change other than saturation of the enone double bond and formation of only a five-membered hemiketal ring occurs. The assignment of ring-junction stereochemistry is made again on the basis of the position of the carbomethoxy methyl group in the proton spectrum of **10** relative to the equivalent absorption in the spectrum of the corresponding trans isomer **16** (Scheme II). The latter material was prepared both by isomerization of **10** on silica gel and by zinc reduction of **15**.

Formulation of the hemiketal ring of **10** as five rather than six membered was made originally on conformational grounds. Saturation of the enone double bond of **9** would lead to the 3,3,1 bicyclic system **13**. Depending upon the specific con-



13

formation of the compound, this system would suffer either a severe nonbonded interaction on the concave side of the molecule or a boat 1,4 interaction on the top face of the ketone ring. As a consequence, **13** should be conformationally unfavorable compared to the considerably less hindered five-membered hemiketal **10**. Verification of this conclusion was provided by the result of an X-ray structure determination. As shown in Figure 1, the dihydro material is indeed the five-membered hemiketal isomer.

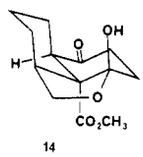
As shown in Scheme I, the next step in the transformation of the Diels–Alder product to an appropriate ajugarin I precursor is saturation of the ring-A double bond. Catalytic hydrogenation of **10** over palladium proceeded smoothly to afford the tetrahydro compound **11**, mp 142–145 °C, in 96%

Table I. X-ray Structure Determination of Compounds 10 and 11[a]

crystal data	10	11
unit-cell parameters		
a	14.08866 (6) Å	14.18523 (7) Å
b	7.09289 (6) Å	21.14905 (11) Å
c	13.19149 (10) Å	8.08458 (6) Å
	90.0222°	90.03551° (6)
	116.0957°	90.09968° (6)
	90.0400°	89.89425° (3)
volume	1184.5 Å^3	2425.4 Å^3
d_{calcd}	1.41	1.39
d_{dis}	1.43	1.41
formula wt.	252	254
Z	4	8
crystal system	monoclinic	orthorhombic
space group	$P2_1/C$	P_{bca}
data collection		
radiation	Mo Kα^- = 0.71069 Å	
mode	θ–2θ scan	
scan rate	5.85–29.3° min^{-1}	7.20–29.3° min^{-1}
scan range	$[2\theta(K\alpha_1) - 1.0]° \rightarrow [2\theta(K\alpha_1) + 1.2]°$	
scan width	2°	2°
check reflect.	measured every 100 reflect.	
2θ range	up to 50°	
reflect. measured	2199	2158
reflect. accepted for refinement		
with $I_o \geq 3.0\ \sigma(I_o)$	1989	1982
R	0.049	0.053
R_w	0.070	0.066

[a] The structures were solved by direct methods. Normalized structure factors (E values) were calculated using overall scale factors and isotopic thermal parameters obtained from Wilson plots. The 350 strongest peaks (E values >1.33 for **10** and E values >1.35 for **11**) were used as input for the program MULTAN. An E map based on the phase set showing the highest figure of merit revealed the positions of all nonhydrogen atoms. Hydrogen positions were obtained from a difference map made after several isotropic refinement cycles, and they were refined using a fixed isotropic thermal parameter of 5.0. They were then held fixed for further isotropic and also during subsequent anisotropic refinement. During the last least-square cycle, no parameter shifted more than 0.001σ and a final difference map showed no peaks greater than 0.27 e/Å^3 for **10** and 0.35 e/Å^3 for **11**.

yield. That the stereochemistry of **11** should be as shown is by no means obvious from simple considerations of possible strain in the tricyclic ring system. The inference drawn from molecular models is that the isomeric structure **14**, in which the hemiketal hydroxyl group has a β configuration, should be of lower energy than **11**. In contrast, the stereochemistry shown for **11** dictates that one of the carbocyclic rings be a



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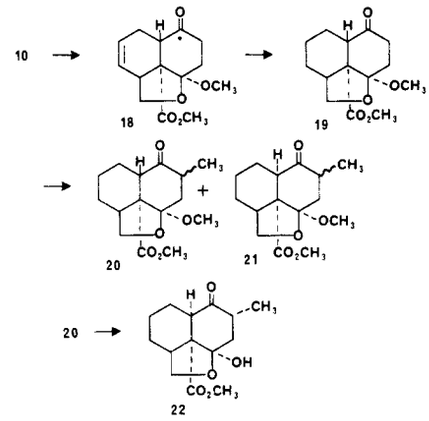
boat. Despite this, the molecule does in fact have the latter geometry at least in the crystalline form. Figure 2 illustrates the structure obtained from X-ray analysis and shows that it is the carbonyl-containing ring which has a twist-boat conformation. Remarkably, the cis-fused isomer **11** also appears to be of lower energy than its trans-fused epimer **17**, mp 153–155 °C (Scheme II). When either of these isomers is absorbed on silica gel to effect ring-junction isomerization, the predominant component of the resulting eluent is the cis compound **11**.[12]

Following the establishment of the regio- and stereochemical course of the Diels–Alder reaction of **5** and **6** and of the isomerizations and reductive transformations already discussed, we focused our attention on two critical problems. Both of these synthetic concerns arise from the particular choice of the original Diels–Alder components. The initial dienophile **6**, although readily available, lacks the eventual C-8 methyl group of ajugarin I. The first problem to be faced then was the practicality of introducing this methyl by al-



kylation of an intermediate along the synthetic trail. Should this step prove particularly inefficient or unachievable it would be necessary to return to the initial cycloaddition reaction and use the appropriate methyl-substituted quinone **4**, a compound requiring a considerable lengthier preparation than **6**. Methylation was achieved in the following way. The *cis*-dihydro material **10** was converted to the *trans*-methyl ketal **18**, mp 91–92.5 °C, by the action of methanol and acid. Hydrogenation of the latter gave the saturated ketal **19**, mp 70–73 °C. Methylation was then effected in 50% yield by means of enolate formation with lithium diisopropylamide and alkylation with methyl iodide. After chromatography, two methylated products **20**, mp 76–80 °C, and **21** were obtained in a ratio of 4:1.[13] Hydrolysis of **20** in acidic medium afforded the methylated hemiketal **22**.

The second and more critical problem arising from the specific Diels–Alder approach discussed so far is that of the

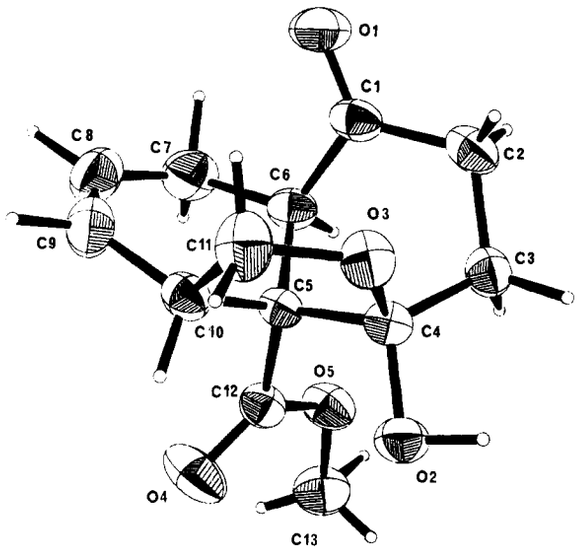


Figure 1. A perspective drawing of **10.**

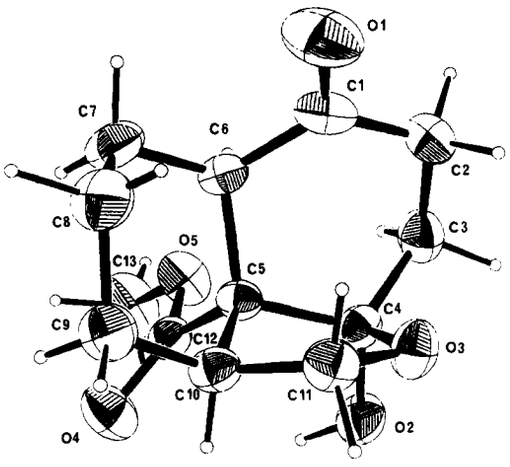


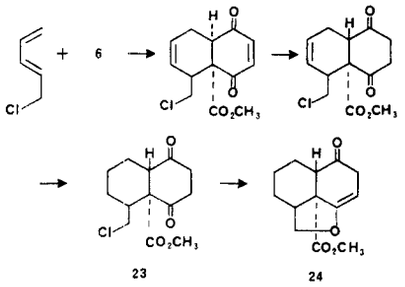
Figure 2. A perspective drawing of **11.**

opening of the hemiketal ring. Neither the initial Diels–Alder mixture or its isomerized and/or reduced transformation products show any indication of containing the corresponding hydroxymethyl diketone tautomers. Furthermore, attempts to open any of these hemiketals by trapping some small concentration of free primary alcohol have been generally unsuccessful.[14] For example, the treatment of **10** with base (sodium hydride or pyridine) and acylating agents (acetyl chloride, methanesulfonyl chloride, or toluenesulfonyl chloride) yields no recognizable acetate or sulfonate derivatives.

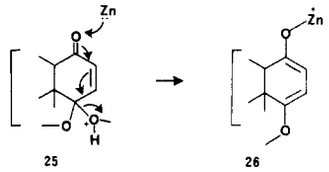
On the basis that the C-9 ketone group in the saturated compounds might be undergoing reaction under the basic conditions used to try to cleave the hemiketal ring, we moved to protect the carbonyl function through ketal formation. However, when **11** was exposed to ethylene glycol and acid, considerably more than simple ketal formation transpired. The intended carbonyl-masking process was accompanied by ring-junction isomerization and dehydration, yielding the cyclic enol ether[15] ketal **12** (Scheme I). The structure of **12** follows from its ^{13}C spectral characteristics as well as from the fact that it is reconverted to **11** upon treatment with aqueous acid.

Our efforts to open the hemiketal ring being thus frustrated, we turned to an alternative approach using a different Diels–Alder adduct; one incapable of forming the adamantine hemiketal unit. To this end, we prepared the chloromethyl diketone **23,** mp 123–125 °C, by the sequence illustrated in Scheme III. Attempted elimination of hydrogen chloride from this molecule to form the exocyclic olefin was unsuccessful. Treatment of **23** with DBN, for example, led only to the keto *enol ether* **24,** which upon acid hydrolysis gave hemiketal **11** again. Clearly, the proximity of the keto group at C-6 to the chloromethyl unit allows the ketone oxygen to participate in the dehydrochlorination process.

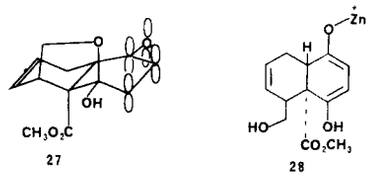
Scheme III



The problem of opening the hemiketal ring was solved finally by recourse to a reaction we had routinely employed in the early stages of this work; zinc in acetic acid reduction of a γ-alkoxyenone.[16] The mechanism for the conversion of **8** and **9** to **10** or of **15** to **16** presumably entails the elimination of one of the γ-oxygen functions as shown in **25** to **26.** The question then arises: can one distinguish between the two groups, or is



either one, alkoxy or hydroxy, eliminated with equal ease? For the cis compounds **8** and **9,** no clear-cut answer is forthcoming from an examination of models. In the case of the trans compound, however, there should be a mechanistic distinction between the two γ-position oxygen groups. As shown in **27,** only the bond linking the ring oxygen to the B-ring lies perpendicular to the plane of the enone system. Only through the cleavage of this bond can overlap between the developing p orbital at C-6 and the rest of the unsaturated unit be achieved. The conversion of the trans compound **15** to **16** should then occur via the intermediacy of the enol–enolate **28.** The ulti-

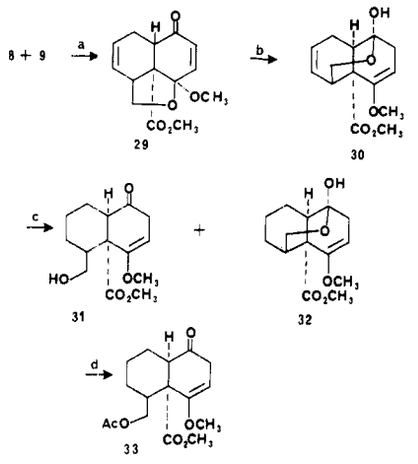


mate production of the keto hemiacetal **16** should result from ketonization of **28** followed by addition of the hydroxyl function to the regenerated C-6 carbonyl.

On the basis of the foregoing argument, a solution to the problem of hemiketal opening seemed readily at hand. Substitution of an alkoxy group for the hydroxy function of **15** should preclude the formation of a ketal product, since the intermediate stage would not be an *enol*–enolate but rather an *enol ether*–enolate.[17] The following sequence was then carried out to test these predictions.

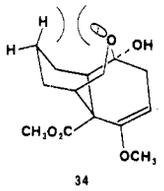
Treatment of the initial Diels–Alder adduct mixture **8** and **9** with methanol and toluenesulfonic acid afforded the trans-fused methyl ketal **29,** mp 106–107 °C (Scheme IV). The latter was then subjected to reduction with zinc in acetic acid. Somewhat surprisingly, the reduction in this case was extremely sluggish in comparison to others reported here. Stirring for 12 h was found necessary to effect saturation of the enone double bond. As anticipated, however, the principal

Scheme IV



[a] CH_3OH, H^+; [b] Zn, HOAc; [c] H_2, Pd; [d] Ac_2O, pyridine.

product was indeed a methyl enol ether[18] but no ketonic carbonyl group appeared in the spectra of the product. Instead, the product was again a hemiketal, in this instance the cis-fused six-membered one **30**, mp 143–145 °C, obtained in 64% yield. Although we had not previously encountered any ring-junction isomerization during short-term zinc reductions, apparently the time required for the reduction of **29** is sufficiently lengthy to allow the epimerization of the initially formed trans product to occur. The Gordian knot of this hemiketal proved simpler to cut than in the case of the five-membered one, however. We anticipated that the stability of the new hemiketal ring ought to be sharply reduced by saturation of the ring A double bond. Such a transformation leads to a 3,3,1-bicyclo system, e.g., **34**, which can relieve conformational interactions by opening of the heterocyclic ring. In the event, catalytic reduction of **30** afforded a product which proved to be a mixture of the keto enol ether **31** and the corresponding hemiketal **32**. Complete opening of the hemiketal ring was then accomplished by treatment of the mixture with acetic anhydride–pyridine to afford the diketo acetate **33**.



The Diels–Alder approach to the synthesis of ajugarin I discussed above has at present accomplished our initial goal; rapid construction of the decalin ring system with functionality strategically located for introduction of the remaining structural features of the natural product. Further transformations and alternative strategies will be discussed in forthcoming publications.

Experimental Section

Melting points were determined on an Arthur A. Thomas uni-melt apparatus. All melting and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating infrared spectrometer, and Nuclear Magnetic Resonance (NMR) spectra were recorded using a Varian EM-360 spectrometer. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.0 ppm) as an internal standard. ^{13}C spectra were recorded on a Varian Associates CFT-20 instrument. Mass spectra were determined either with a Varian Associates M-66 cycloidal mass spectrometer or a Finnigan Model 4000 GC–MS instrument. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Ga., and precise mass measurements were obtained with the M-66 mass spectrometer.

Diels–Alder Reaction of Carbomethoxy-*p*-benzoquinone and 1-Hydroxymethylbutadiene. Preparation of 8 and 9. To a stirred solution of 1.28 g (7.6 mmol) of carbomethoxy-*p*-benzoquinone in 6 mL of dry benzene at 0 °C was added dropwise, via a syringe, 0.68 g (8.1 mmol) of 2,4-pentadien-1-ol.[19] The reaction mixture was allowed to warm to room temperature and stirred under nitrogen for 2 h, during which a solid was precipitated. The solid was filtered and washed with cold benzene. Recrystallization from benzene afforded a white crystalline solid: 1.44 g (74.3%), mp 108–114 °C; IR ($CHCl_3$) 1740, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.78–4.43 (m, 7 H), 3.69, 3.71 (2 s, 3 H), 5.76 (m, 2 H), 6.01–6.72 (m, 2 H).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.45; H, 5.66.

Preparation of the Dihydro Cis Adduct 10. To a stirred solution of 5.05 g (20.2 mmol) of **8** and **9** in 50 mL of glacial acetic acid was added 10.0 g of zinc dust in small portions. The reaction mixture was allowed to stir at room temperature for 10 min. The mixture was poured into 200 mL of ice water. The zinc was removed by filtration and the filtrate was washed with chloroform. The aqueous layer was extracted four times with chloroform, and the combined chloroform extracts were washed with 10% aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent gave 4.70 g (93%) of a white solid, mp 140–142 °C. An analytical sample was prepared by recrystallization from benzene: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.49–2.92 (m, 6 H), 3.12–3.62 (m, 4 H), 4.08–4.48 (m, 2 H), 5.67 (m, 2 H), 3.78 (s, 3 H); ^{13}C NMR δ 210.2, 171.9, 125.3, 123.0, 106.0, 72.4, 60.4, 53.1, 45.5, 38.5, 35.3, 31.2, 20.3.

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.84; H, 6.39.

Catalytic Reduction of 10. Preparation of the Cis Hemiacetal 11. A solution of 3.0 g (11.9 mmol) of **10** in 25 mL of ethanol was hydrogenated under atmospheric pressure using 10% palladium on charcoal as catalyst. Hydrogen uptake ceased after 1 h. The catalyst was filtered through a Celite cake, and the solvent was removed on the rotory evaporator to give a white solid, 2.9 g (96%), mp 142–144.5 °C. An analytical sample was prepared by crystallization from benzene: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.79–1.71 (m, 5 H), 1.91–2.86 (m, 5 H), 3.19–3.52 (m, 3 H), 3.65 (s, 1 H), 3.78 (s, 3 H), 3.88–4.18 (m, 1 H); ^{13}C NMR δ 211.5, 172.5, 105.9, 69.6, 60.5, 52.8, 45.9, 36.9, 35.7, 30.4, 21.5, 16.1.

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.15. Found: C, 61.24; H, 7.20.

Formation of Enol Ether Ketal 12. A mixture of **11** [2.0 g (7.8 mmol) in 25 mL of dry benzene], 0.438 mL (7.8 mmol) of ethylene glycol, and a catalytic amount of *p*-toluenesulfonic acid monohydrate was refluxed in a nitrogen atmosphere under a Dean–Stark trap. Separation of the water began immediately. Refluxing was continued for 4 h. The mixture was cooled, washed with 10% aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil: 2.1 g (95%); IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.75–2.0 (m, 6 H), 2.11–2.72 (m, 3 H), 2.30 (dd, 1 H, J = 4, 8 Hz), 3.77–4.16 (m, 2 H), 3.67 (s, 3 H), 3.84 (m, 4 H), 4.76 (t, 1 H); ^{13}C NMR 175.6, 151.7, 110.0, 91.9, 73.6, 64.3, 64.0, 54.5, 52.4, 42.6, 41.3, 31.7, 27.8, 23.7, 22.6; MS *m/e* 280.

Anal. Calcd for $C_{15}H_{20}O_5$: 280.13098. Found: *m/e* 280.13056.

Isomerization of the Diels–Alder Adduct. Formation of 15. To a stirred solution of 0.48 g (1.92 mmol) of **8** and **9** in 10 mL of methanol was added a few milligrams of diazabicyclononane (DABCO). The reaction mixture was allowed to stir at room temperature for 48 h. The solvent was concentrated on the rotory evaporator and the residual brownish oil was taken up in 50 mL of methylene chloride, washed with 3 N HCl, 10% aqueous sodium bicarbonate, and finally with brine solution. It was then dried over anhydrous magnesium sulfate. Removal of the solvent gave 0.40 g of a light-yellow semisolid, which was recrystallized from benzene to give a white crystalline material: 0.295 g (61.5%); mp 142–145 °C; IR ($CHCl_3$) 1730, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.83–2.37 (m, 2 H), 2.81 (dd, 1 H, J = 4, 7 Hz), 3.63 (s, 3 H), 3.82 (m, 2 H), 4.45 (m, 2 H), 5.74 (m, 2 H), 6.28 (AB q, 2 H, J = 10 Hz); ^{13}C NMR δ 196.6, 169.9, 141.6, 129.2, 127.1, 124.5, 101.5, 73.5, 62.2, 52.7, 43.7, 40.6, 21.7.

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.29; H, 5.64.

Zinc Reduction of 15. Preparation of 16. A solution of 0.180 g (0.42 mmol) of **15** in 4 mL of glacial acetic acid was reduced with 0.36 g of zinc dust as previously described for the reduction of **8** and **9**. Evaporation of the solvent gave a clear oil which solidified upon standing: 0.173 g (95%); mp 116–118 °C; IR ($CHCl_3$) 1728 cm^{-1}; NMR ($CDCl_3$) δ 1.73–2.79 (m, 4 H), 2.42 (s, 4 H), 3.58–3.76 (m, 2 H), 3.62 (s, 3 H), 3.94–4.77 (m, 2 H), 5.67 (m, 2 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.85; H, 6.43.

Catalytic Reduction of 16. Preparation of Trans Hemiketal 17. A solution of 82 mg (0.32 mmol) of **16** in 4 mL of ethyl acetate was

hydrogenated with 10% palladium/charcoal as previously described for the hydrogenation of **10**. Removal of the solvent gave 80 mL (97%) of a white solid: mp 153–155 °C; IR ($CHCl_3$); NMR ($CDCl_3$) 0.80–2.32 (m, 7 H), 2.42 (br s, 4 H), 3.09–3.55 (m, 1 H), 3.68 (s, 3 H), 3.78–4.38 (m, 2 H).

Anal. Calcd for $C_{13}H_{18}O_5$: 254.11621. Found: *m/e* 254.11538.

Diels–Alder Reaction of Carbomethoxy-*p*-benzoquinone with 1-Chloromethylbutadiene. To a stirred solution of 1.2 g (7.14 mmol) of carbomethoxy-*p*-benzoquinone in 8 mL of benzene was added dropwise 1.0 g (9.8 mmol) of 2,4-pentadienyl chloride.[20] The reaction mixture was stirred at room temperature overnight, during which time the color of the solution changed from orange to yellow. Removal of the solvent and the excess diene gave a yellow oil which solidified upon standing. The solid was recrystallized from an ether–hexane mixture to give a light-yellow crystalline solid: 1.51 g (79%); mp 99.5–101 °C; IR ($CHCl_3$) 1700, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (m, 2 H), 2.97 (m, 1 H), 3.74 (s, 3 H), 3.45–4.07 (m, 3 H), 5.76 (m, 2 H), 6.60 (d, 2 H, J = 3 Hz); ^{13}C NMR δ 197.3, 194.1, 170.3, 140.4, 137.8, 125.9, 124.5, 62.5, 53.6, 50.1, 44.8, 43.6, 25.3.

Anal. Calcd for $C_{13}H_{13}O_4Cl$: C, 58.11; H, 4.88. Found: C, 58.15; H, 4.91.

Zinc Reduction of the Chloromethyl Adduct. A solution of 0.53 g (1.79 mmol) of the chloromethyl adduct in 8 mL of glacial acetic acid was reduced with 1.0 g of zinc dust as previously described for the reduction of **8** and **9**. Removal of the solvent gave a white solid: 0.48 g (91%); mp 121–124 °C. An analytical sample was prepared by recrystallization from ether–hexane: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.02–3.07 (m, 2 H), 3.17–4.16 (m, 3 H), 3.79 (s, 3 H), 5.74 (m, 2 H).

Anal. Calcd for $C_{13}H_{15}O_4Cl$: C, 57.68; H, 5.58. Found: C, 57.64; H, 5.60.

Preparation of 23. A solution of 0.177 g (0.66 mmol) of the above zinc reduction product in 8 mL of ethyl acetate was hydrogenated with 10% palladium/charcoal as previously reported for the hydrogenation of **10**. Removal of the solvent gave a white solid, 0.178 g (97%). An analytical sample was prepared by crystallization from chloroform–hexane: mp 123–125 °C; IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.19–2.28 (m, 7 H), 2.44–3.11 (m, 5 H), 3.77 (s, 3 H), 3.40–4.23 (m, 2 H).

Anal. Calcd for $C_{13}H_{17}O_4Cl$: C, 57.25; H, 6.28. Found: C, 57.15; H, 6.29.

Formation of Keto Enol Ether 24. Ketone **23** [0.150 g (0.55 mmol)] was dissolved in 6 mL of dry benzene in a 10-mL round-bottom three-neck flask equipped with septum, nitrogen inlet, and a refluxing condenser. Diazabicyclononene (0.1 g) was added via syringe. The solution became brown. The reaction mixture was heated in an oil bath to 50–60 °C for 4 h. It was then cooled to room temperature, poured into ice, and neutralized with cold dilute sulfuric acid. The neutral solution was extracted twice with benzene. The combined yellow benzene extracts were washed with water and 10% sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow-brown oil which was kugelrohr distilled to give a light-yellow oil: IR ($CHCl_3$) 1730, 1700, 1640 cm^{-1}; NMR ($CDCl_3$) 0.94–2.15 (m, 6 H), 2.46–2.84 (m, 2 H), 2.88 (d, 2 H, J = 4 Hz), 3.62 (s, 3 H), 4.26 (dd, 1 H, J = 4 Hz), 4.97 (t, 1 H); MS *m/e* 236 (M^+).

The above oil was dissolved in 3 mL of a THF–H_2O–HCl mixture and allowed to stir overnight. Workup afforded hemiketal **11**.

Preparation of Ketal 18. To a solution of 0.40 g (1.58 mmol) of **10** in 10 mL of methanol was added a few milligrams of *p*-toluenesulfonic acid monohydrate. The reaction was stirred at room temperature for 2 days. Workup was carried out as described for the preparation of **12**. Removal of the solvent gave a white oily solid. Recrystallization from an ether–hexane mixture gave 0.295 g of white crystalline solid: mp 91–92.5 °C (70.2%); IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.68–2.80 (m, 7 H), 3.22 (s, 3 H), 3.62 (s, 3 H), 3.54–4.31 (m, 3 H), 5.71 (m, 2 H); ^{13}C NMR δ 207.2, 169.9, 126.6, 126.0, 106.0, 71.1, 62.5, 52.1, 48.6, 46.0, 40.6, 36.17, 28.3, 21.7.

Anal. Calcd for $C_{14}H_8O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.14.

Preparation of Saturated Ketal 19. A solution of 1.2 g (4.5 mmol) of **18** in 15 mL of ethanol was hydrogenated with 10% palladium/charcoal as previously described for the hydrogenation of **10**. Removal of the solvent gave a white solid: 1.19 g (98%); mp 70–73 °C. An analytical sample was obtained by crystallization from an ether–hexane mixture: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.61–2.08 (m, 7 H), 2.08–2.60 (m, 5 H), 3.16 (s, 3 H), 3.26–4.21 (m, 2 H), 3.59 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.79; H, 7.56.

Methylation of Ketal 19. Following the procedure of House,[21] 0.41 mL (0.926 mmol) of 2.29 M *n*-butyllithium and a few milligrams of triphenylmethane were dissolved in 5 mL of dry 1,2-dimethoxyethane (dried over lithium aluminum hydride) under nitrogen. The reaction mixture was cooled to −20 °C and 0.129 mL (0.926 mmol) of diisopropylamine was added dropwise via syringe. Ketal **19** [0.250 g (0.926 mmol)] in 2.5 mL of 1,2-dimethoxyethane was added dropwise. The resultant pink solution was allowed to warm to room temperature, and then 0.42 mL (7.3 equiv) of methyl iodide was added. The reaction was stirred at room temperature for 15 min, during which a precipitate was formed. Three milliliters of dilute hydrochloric acid was added and the resultant yellow solution was extracted twice with ether. The combined ether extracts were washed with a 10% aqueous sodium bicarbonate solution and then with brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave a thick yellow oil, 0.216 g. The oil was chromatographed on 35 g of silica gel. Elution with an ethyl acetate–hexane mixture gave 33 mg of the cis isomer as a clear oil: IR ($CHCl_3$) 1722 cm^{-1}; NMR ($CDCl_3$) 0.92–3.07 (m, 9 H), 1.19 (d, 3 H, J = 6.5 Hz), 3.20 (s, 3 H), 3.25–4.03 (m, 4 H), 3.77 (s, 3 H).

Further elution gave the trans isomer, 95 mg, as a white solid: mp 76–80 °C; total yield 49.21%; IR ($CHCl_3$) 1722 cm^{-1}; NMR ($CDCl_3$) δ 0.86–3.05 (m, 10 H), 1.19 (d, 3 H, J = 6.5 Hz), 3.24 (s, 3 H), 3.35–4.22 (m, 3 H), 3.65 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_5$: *m/e* 282.14683. Found: *m/e* 282.14511.

Preparation of Ketal 29. To a solution of 2.0 g (8 mmol) of **8** and **9** in 20 mL of absolute methanol was added a few milligrams of *p*-toluenesulfonic acid monohydrate. The reaction was stirred at room temperature for 3.5 h. The solvent was concentrated on the rotory evaporator and the residue was taken up in 30 mL of chloroform, washed with 10% aqueous sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a white oily solid. The solid was recrystallized from a chloroform–hexane mixture to give 0.82 g of white crystalline material: mp 106–107 °C. The mother liquor was concentrated and chromatographed on silica gel. Elution with ethyl acetate–hexane gave an additional 0.43 g (59%): IR ($CHCl_3$) 1685, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.36 (m, 2 H), 2.57 (dd, 1 H, J = 6, 8 Hz), 3.27 (s, 3 H), 3.58 (s, 3 H), 3.45–4.33 (m, 3 H), 5.88 (m, 2 H), 6.43 (AB q, 2 H).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.14.

Formation of Hemiketal Enol Ether 30. To a stirred solution of 1.5 g (5.68 mmol) of **19** in 20 mL of glacial acetic acid was added 3.0 g of zinc dust in small portions. The reaction mixture was stirred at room temperature under nitrogen for 12 h. It was then poured into a solution of 5% aqueous sodium acetate. The zinc was filtered and washed with chloroform. The aqueous layer was extracted three times with chloroform. The combined chloroform extracts were washed with 10% aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oily solid. The solid was recrystallized from a chloroform–hexane mixture to give a white crystalline material: 0.87 g, mp 143–145 °C. The mother liquor was concentrated on the rotory evaporator and yielded, after recrystallization, an additional 95 mg of product (63.8%): IR ($CHCl_3$) 1735, 1670 cm^{-1}; NMR ($CDCl_3$) 2.07–2.84 (m, 6 H), 3.37–4.20 (m, 3 H), 3.45 (s, 3 H), 3.65 (s, 3 H), 4.73 (t, 1 H), 5.72 (m, 2 H).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.07; H, 6.84.

Formation of Ketone–Hemiketal Mixtures 31 and 32. A solution of 1.0 g (3.8 mmol) of **30** in 25 mL of ethanol was hydrogenated with 10% palladium/charcoal as previously reported for the hydrogenation of **10**. Evaporation of the solvent gave a light yellow oil (1.04 g) which partially solidified upon standing: IR ($CHCl_3$) 1730, 1670 cm^{-1}; NMR ($CDCl_3$) 3.41, 3.50 (2 s, 3 H), 3.63, 3.68 (2 s, 3 H), 4.70 (m, 1 H).

Preparation of Keto Acetate 33. A mixture of 91 mg (0.34 mmol) of **31** and **32** in 0.5 mL of dry pyridine and 0.086 g (0.85 mmol) of acetic anhydride, under nitrogen, was allowed to stir at room temperature for 2 h, during which time the solution became reddish orange. Sodium bicarbonate (2 mL of 10% solution) was added to destroy excess acetic anhydride. The reaction mixture was added into water and extracted twice with 10 mL of ether. The ether extracts were washed with 5% acetic acid, 10% sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 79 mg of an orange oil. The oil was purified by preperative thin-layer chromatography to give a light-yellow oil: IR ($CHCl_3$) 1730, 1670; NMR ($CDCl_3$) 1.19–2.54 (m, 7 H), 2.01 (s, 3 H), 2.80–3.16 (m, 1 H), 2.90 (d, 2 H, J = 4 Hz), 3.56 (s, 3 H), 3.69 (s, 3 H), 4.04 (m, 2 H).

Anal. Calcd for $C_{16}H_{22}O_6$: 310.14152. Found: *m/e* 310.14432.

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aid in obtaining X-ray measurements and Dr. Walter Dean of this department for help in solution of the structures. We also thank the National Science Foundation for a Departmental Instrument Grant in support of the purchase of a Finnigan Model 4000 GC–MS data system.

Registry No.—**1**, 62640-05-5; **5**, 4949-20-6; **6**, 3958-79-0; **8**, 66515-72-8; **9**, 66515-73-9; **10**, 66515-74-0; **11**, 66515-75-1; **12**, 66515-76-2; **15**, 66538-02-1; **16**, 66538-03-2; **17**, 66538-04-3; **18**, 66515-77-3; **19**, 66515-78-4; **20**, 66515-79-5; **21**, 66538-05-4; **23**, 66515-80-8; **24**, 66515-81-9; **29**, 66515-82-0; **30**, 66551-68-6; **31**, 66515-83-1; **32**, 66515-84-2; **33**, 66515-85-3; 2,4-pentadienyl chloride, 40596-30-3; 4a-α-carbomethoxy-5β-chloromethyl-4a,5,8,8a-β-tetrahydronaphthalene-1,4-dione, 66515-86-4; 4a-α-carbomethoxy-5β-chloromethyl-2,3,4a,5,8,8a-β-hexahydronaphthalene-1,4-dione, 66515-87-5.

Supplementary Material Available. Tables listing atom parameters, thermal parameters, bond distances, and bond angles for compounds **10** and **11** (12 pages). Ordering information is given on any current masthead page.

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(8) This Diels–Alder combination yields the "ortho" product exclusively and quantitatively. Unpublished results of this laboratory.

(9) In our experience, Diels–Alder reactions with carbomethoxy-*p*-benzoquinone are best carried out at room temperature. Elevated temperatures lead to lower yields of less pure products.

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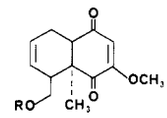
(12) The cis compound **11** is also produced as the major product in the hydrolysis of enol ether ketal **12**, as well as when either **11** or **17** is treated with DABCO.

(13) Our assignment of stereochemistry to the methyl group of **22** is tentative. Since isomerization of the ring junction occurs in the hydrolysis of **20** to **22**, we assume that epimerization also occurs at C-8 to produce the more stable equatorial isomer.

(14) It has been reported recently [J.-L. Gras, *Tetrahedron Lett.*, 4117 (1977)] that 3-methoxy-2,4-toloquinone reacts with **5** to give adduct i (R = H) and that the latter is converted to its tetrahydropyranyl ether ii (R = THP) with dihydropyran at 0 °C. We have also found that the mixture of adducts **8** and **9** also form a THP derivative under these conditions. Unfortunately, this diketo ether has not proven synthetically useful. We would also suggest that Gras' adduct is almost certainly the hemiketal compound equivalent to **8** rather than the free hydroxymethyl material.



i, R = H
ii, R = THP

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(17) Ketalization could of course occur by protonation of the enol ether double bond and addition of the hydroxymethyl oxygen to the resulting cation.

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Synthesis of the New Nucleoside Antibiotic 1-(2-Deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione[1]

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1-(2-Deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione, "DHAdT" (I), a new nucleoside with both antiviral and antibacterial activity, has been synthesized along with its ribosyl analogue via the silyl ether modification of the Hilbert–Johnson reaction. Condensation of the mono- or disilyl-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-diones (V and VI) with 3,5-ditoluoyl-2-deoxy-D-ribofuranosyl chloride (VII) gave the protected nucleosides VIII and IX which, after removal of the protecting groups, afforded "DHAdT" (I) and its α anomer X. Condensation of V with tribenzoylribofuranosyl bromide (XI) or acetate (XII) gave the N_3 riboside. When V was condensed with tetraacetyl ribose (XIII), the N_1 and N_3 isomers were isolated. The ribose analogue was devoid of both antiviral and antibacterial activity.

Bannister and DeBoer recently reported the isolation of a nucleoside antibiotic, 1-(2-deoxy-β-D-ribofuranosyl)-5,6-dihydro-*s*-triazine-2,4(1*H*,3*H*)-dione, I (DHAdT), from the culture *Streptomyces platensis* var. *clarensis*.[2] This same culture produces the nucleoside 1-*N*-methylpseudouridine, a compound whose isolation was reported by Argoudelis and Mizsak[3] and whose synthesis was recently reported by Fox et al.[4]

DHAdT exhibited in vitro activity against a variety of DNA viruses, including herpes simplex type 1, herpes simplex type 2, varicella zoster, and vaccinia, and gram-negative bacteria, although modest activity was observed vs. *Streptococcus hemolyticus* bacteria and poor activity vs. *Diplococcus pneumoniae*.[5] Thymidine and deoxyuridine completely reversed the antiviral activity, while deoxycytidine was partially effective.

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