Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives. 9.[1] Hydroquinazolines Possessing the Carbon Skeleton of Tetrodotoxin

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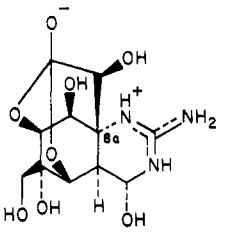
A Diels–Alder reaction between 1-acetoxy-3-methylbutadiene (7) and 2-(acylamino)-6-acetyl-4(1*H*)-pyrimidinones 2 and 3 has led to hydroquinazolines 8–11, potential intermediates for the synthesis of tetrodotoxin and derivatives. X-ray crystallographic analysis of minor pivalate isomer 11 confirmed that 11 possesses a cis-fused hydroquinazoline ring system in which the C-8 acetoxy group is trans to the angular acetyl group at C-9. Major adduct 8 was converted into 2-acetamido-6α-methyl-6β-hydroxy-7β,8β-diacetoxy-9β-acetyl-3,4,5,6,7,8,9,10β-octahydroquinazolin-4-one (14), the structure of which was established by X-ray analysis. The relative stereochemistry at C-7, C-8, and C-9 in 14 corresponds to that of tetrodotoxin.

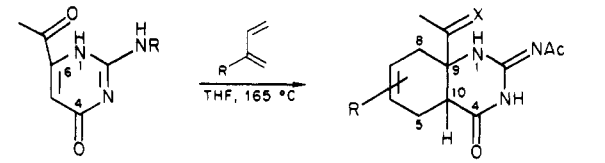
As part of our program directed toward the synthesis[2] of the potent neuropoison tetrodotoxin (TTX, 1) and derivatives, we have recently described the synthesis of a versatile series of functionalized pyrimidinones which possess an oxygenated two-carbon substituent at the 6-position.[1] We now report the utilization of several of these heterocycles as dienophiles in a Diels–Alder reaction.[3] Hydroquinazolines are produced which bear the requisite two-carbon appendage at the 9-position, potentially convertible into the hydroxy acetic acid side chain attached to C-8a of the toxin. Subsequent elaboration of the carbocyclic ring through hydroxylation followed by selective acylation is also described.



1 (TTX)

Results and Discussion

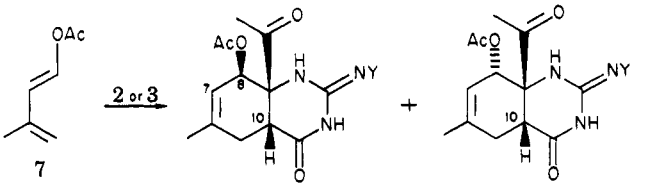
A Diels–Alder reaction between 6-acetylpyrimidinone 2[4] and 1,3-butadiene[5] in tetrahydrofuran (THF) at 165 °C gave hydroquinazoline 4[4] as a partial hydrate in low yield. A similar reaction with isoprene[5] afforded a mixture of regioisomers 5 as a foam from which a pure hydrate 6 eventually could be isolated.



2, R = Ac
3, R = $COC(CH_3)_3$

4, R = H, X = O
5, R = CH_3; X = O
6, R = CH_3; X = OH, OH

1-Acetoxy-3-methylbutadiene (7)[3] appeared to offer several advantages over either butadiene or isoprene, namely, the possibility of greater reactivity and regioselectivity and the presence of additional functionality at the position destined to become C-8 of the hydroquinazoline. After a series of unproductive preliminary experiments involving temperatures below 160 °C and attempts to catalyze the reaction with Lewis acids, nearly optimal conditions were found which involved heating 2 with a two-fold excess of 7 in THF at 165 °C for 48–60 h. The homogeneous reaction mixture contained starting 2 (43%), diene polymer, and two crystalline Diels–Alder adducts (50%, based on recovered 2), separable after chromatography by fractional crystallization: major adduct 8 (23%) and minor adduct 10 (6%).



7

8, Y = Ac
9, Y = $COC(CH_3)_3$

10, Y = Ac
11, Y = $COC(CH_3)_3$
12, Y = Ac; 10 αH

The NMR spectrum of the major isomer 8 displayed a doublet of doublets (J = 7, 11 Hz) at δ 3.20 due to H-10 and a doublet at δ 5.49 (J = 6 Hz) due to H-8. The minor

(1) Part 8: Keana, J. F. W.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Richman, J. E.; Roman, R. B.; Wah, R. M. *J. Org. Chem.*, previous paper in this issue.

(2) An elegant total synthesis TTX has been reported: Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219. Other recent approaches toward TTX and derivatives include: Pavelka, L. A.; Fuhrman, F. A.; Mosher, H. S. *Heterocycles* **1982**, *17*, 225. Nachman, R. J. *Diss. Abstr. Int. B.* **1981**, *42*, 1895. Nimitz, J. S. *Ibid.* **1981**, *42*, 637. Balerna, M.; Lombet, A.; Chicheportiche, R.; Romey, G.; Lazdunski, M. *Biochim. Biophys. Acta* **1981**, *644*, 219. Pavelka, L. A. *Diss. Abstr. Int. B* **1981**, *41*, 4127. Angelides, K. J. *Biochemistry* **1981**, *20*, 4107. Funabashi, M.; Wakai, H.; Sato, K.; Yoshimura, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 14. Chicheportiche, R.; Balerna, M.; Lombet, A.; Romey, G.; Lazdunski, M. *Eur. J. Biochem.* **1980**, *104*, 617.

(3) Keana, J. F. W.; Bland, J. S.; Eckler, P. E.; Nelson, V.; Gougoutas, J. *Z. Org. Chem.* **1976**, *41*, 2124.

(4) The preferred tautomeric form in the pyrimidone and hydroquinazoline series has not been determined, with the exception of the two adducts studied by X-ray crystallography (see text).

(5) Early experiments were performed by Dr. F. P. Mason.

0022-3263/83/1948-3627$01.50/0

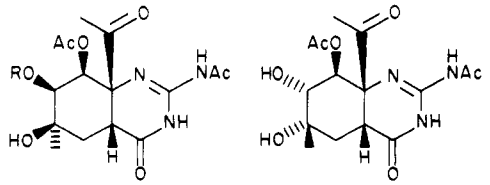
isomer **10** showed a similar pattern of absorptions for H-10 (δ 3.02, dd, J = 7, 8 Hz) and H-8 (δ 5.75, d, J = 6 Hz), indicating that the regioorientation of both isomers was that shown in **8** and **10**. The opposite mode of addition would have given a doublet for H-10 and a doublet of doublets for H-8.

The adducts were shown to be isomeric at C-8 and not C-10 by a series of NMR experiments in hot acetic acid. After 20 min at 100 °C in CD_3CO_2D, H-10 had undergone complete exchange in the major isomer and partial exchange in the minor isomer. Heating the minor isomer for an additional 25 min caused complete exchange. The samples were then heated in CH_3CO_2H, the mixture was evaporated, and the NMR spectra were recorded in $CDCl_3$. In the case of the major adduct the NMR spectrum was identical with that of starting **8**, indicating that the cis ring juncture (see below) is the more stable one thermodynamically. The NMR spectrum derived from the minor adduct, however, indicated the presence of both starting **10** and a new isomer, **12**, isomeric with **10** at H-10 (δ 3.28, t, J = 8 Hz). Formation of **8** was not observed.

A parallel pair of crystalline adducts could be prepared by a Diels–Alder reaction between pivalamide **3** and diene **7**: major isomer **9** (18%) and minor isomer **11** (7%).

While the NMR spectra did not permit an unambiguous stereochemical assignment at C-8, C-9, and C-10 in adducts **8–11**, crystals of minor pivalate adduct **11** fortunately proved suitable for X-ray crystallographic analysis (figure 1). The main conclusion from the X-ray analysis is that a cis-fused hydroquinazoline ring has been obtained from the Diels–Alder reaction, and the C-8 acetoxy group in this minor adduct is trans to the angular acetyl group attached to C-9. In **11**, the cyclohexene ring C(5)–C(10) has a C(10) envelope conformation in which C(10) is 0.61 Å from the C(5)–C(9) plane. The diaza ring defined by N(1)–C(2)–N(3)–C(4)–C(10)–C(9) has a twisted conformation in which C(9) and C(10) are 0.33 Å and −0.31 Å, respectively, from the N(1)–C(2)–N(3)–C(4) plane. The relative magnitude of the three C(2)–N bond lengths, the location of hydrogen atoms on N(1) and N(3), and the involvement of those hydrogens in intramolecular [N(1)–H···O(13), where the N–O distance is 2.62 Å] and intermolecular [N(3)–H···O-(13′), where the N–O distance is 3.01 Å] hydrogen bonds are all consistent with the exocyclic C=N formulation. Other molecular dimensions for **11** (supplementary material) are in accord with accepted values. Tautomerization in solution likely occurs, leading to other C=N locations (cf. **14** below).

Major adduct **8** was confirmed to be regiochemically and stereochemically comparable to TTX by an X-ray analysis of **14**, a derivative further down the synthetic pathway.



13, R = H
14, R = Ac

15

The X-ray analysis of **14** additionally served to establish the stereochemistry of the key hydroxylation step. In the event, **8** was treated with a slight excess of osmium tetraoxide in pyridine at −15 °C, leading to a 1:1 mixture (by $CDCl_3$ NMR) of the corresponding α and β osmate esters in high yield. A reaction run at 25 °C gave the osmate esters in a 37:63 ratio. Separation of the two esters was achieved by preparative chromatography over silica gel with 2-propanol–1% pyridine as the eluant. The major and minor osmate esters were thus obtained complexed with two pyridine molecules in 46% and 23% yields, respectively. Either osmate could be cleaved with H_2S to the corresponding diol **13** or **15** in good yield. Selective acetylation of the major diol **13** gave acetate **14**.

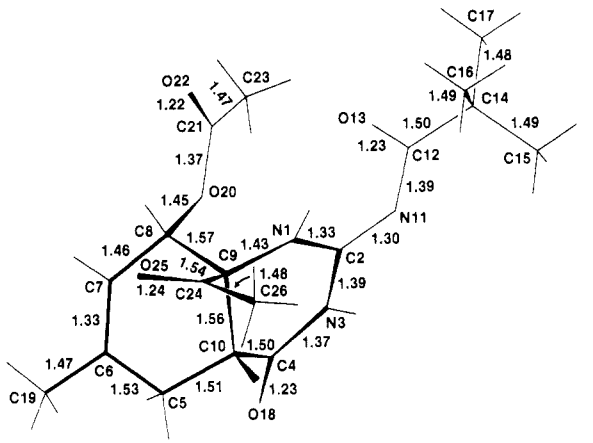


Figure 1. Perspective view of **11**, showing the number scheme and bond lengths. The esd's are 0.01 Å.

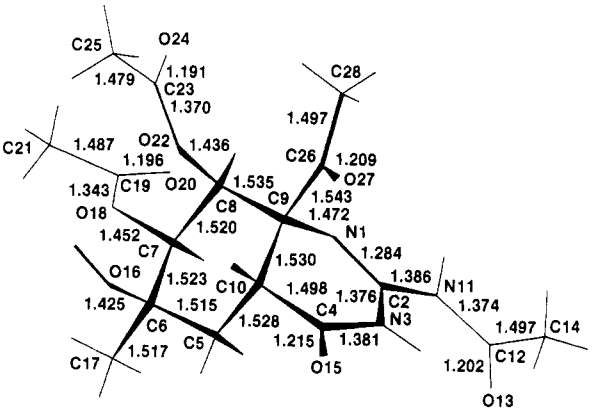
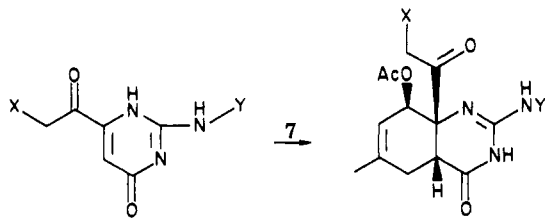


Figure 2. Perspective view of **14** in crystals of **14**·H_2O, with the numbering scheme and bond lengths. The average esd is 0.005 Å.

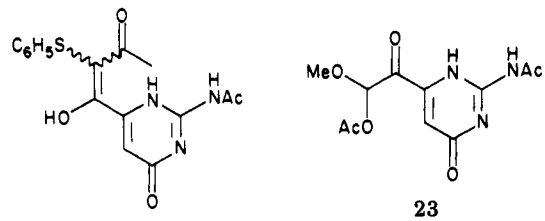
The structure of **14** was determined by X-ray crystallographic analysis of the monohydrate (Figure 2). It is seen that the C-7 and C-8 acetoxy groups are both cis to the angular acetyl substituent at C-9 in this major adduct series, corresponding to the arrangement found in tetrodotoxin. The cyclohexane ring has a chair conformation while the diaza ring has a C(10) envelope conformation in which C(10) is 0.53 Å from the plane of the other five atoms. The C=N bond in crystals of **14** is unequivocally located in the ring at N(1)–C(2) of this derivative, in contrast to what was found in **11** (see above). Also, hydrogens were located at N(3) and N(11), and both take part in N–H···O hydrogen bonds, one intramolecular [N(3)–H···O(13), 2.692 Å] and the other intermolecular [N-(11)–H)···O(water), 2.861 Å]. Intermolecular hydrogen bonds between the hydroxyl O(16) and the carbonyl O(15) (O–H···O, 2.770 Å), between water and the acetoxy carbonyl O(20) (O–H···O, 2.911 Å), and between water and N(1) (O–H···N, 2.892 Å) link molecules in the solid. Other dimensions are in accord with accepted values and have been deposited.

Hydroquinazolines bearing more highly oxygenated side chains at the 9-position could also be prepared by the Diels–Alder reaction, albeit in low (unoptimized) yield in the some cases. Thus phenyl thioether **16**[1] reacted with diene **7**, affording hydroquinazoline **19**. The NMR



16, X = SC_6H_5; Y = Ac
17, X = OAc; Y = Ac
18, X = OAc; Y = $COC(CH_3)_3$
19, X = SC_6H_5; Y = Ac
20, X = OAc; Y = Ac
21, X = OAc; Y = $COC(CH_3)_3$

spectrum of **19** showed the characteristic doublet of doublets at δ 3.24 (H-10) as well as a slightly broadened doublet at δ 5.37 (H-8) and a broadened multiplet at δ 5.64 (H-7). The protons on the carbon bearing the sulfur atom appeared at δ 3.60 and 4.07 (J = 16 Hz). A crystalline byproduct, **22**, was also isolated in 28% yield. Elemental



22

23

analysis indicated that the substance was $C_{16}H_{15}N_3O_4S$, likely formed by addition of an acetyl group to **16** from diene **7**. The NMR spectrum of **22** showed, in addition to the aromatic protons, a singlet at δ 6.02 characteristic of the pyrimidinone ring vinyl proton and two acetyl singlets at δ 2.22 and 2.30. The absence of the characteristic methylene singlet at δ 5.02 present in **16** led to the tentative structure **22** for this byproduct.

While no adduct could be detected between the more highly oxygenated pyrimidinone **23** and diene **7**, probably owing to steric factors, dienophiles **17** and **18** reacted with diene **7** in THF at elevated temperatures, giving the crystalline hydroquinazolines **20** and **21**, respectively. In addition to the characteristic doublet of doublet pattern due to H-10 at about δ 3.2, the NMR spectra also showed a highly characteristic AB pattern centered about δ 4.9 due to the diastereotopic protons on the carbon bearing the acetoxy group.

Experimental Section[6]

2-Acetamido-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one (4). A 50-mL glass liner was charged with acetylpyrimidinone **2**[1] (1.17 g, 6.00 mmol), THF (40 mL), 1,3-butadiene (7.5 mL, 41 mmol), and 2,6-di-*tert*-butylphenol (60 mg), placed in a Parr pressure reactor, flushed with N_2, sealed, and heated at 165 °C for 2 days. The resulting clear brown solution was concentrated, and the resulting oil was triturated with MeOH (2 × 40 mL). Removal of the MeOH extract gave a foam which was dissolved in 9 mL of warm EtOAc and allowed to cool, affording starting **2** (0.61 g, 52%). The mother liquor was deposited on silica gel (1 g) which was then placed on a silica gel (10 g) column packed in benzene. Elution with benzene–EtOAc (95:15) gave a white semisolid (400 mg) which still contained some **1** by NMR analysis. This was combined with similar material from another run, and the resulting mixture (610 mg) was rechromatographed over basic alumina (8.5 g). Elution with benzene–EtOAc (9:1) gave crude adduct **4** (310 mg, 11%) which crystallized from EtOAc–benzene–hexane to give crystalline **4**: 80 mg (3%); mp 118–137 °C. Three recrystallizations from EtOAc gave the analytical specimen as radial hemispheres: mp 203.5–204 °C; NMR δ 1.68 (s, 3), 2.18 (s, 3), 1.7–3.2 (m, 6), 6.0 (br s, 2); MS, m/e 249 (M^+), 234, 221, 220. Anal. Calcd for $C_{12}H_{15}N_3O_3 \cdot 0.1\ H_2O$: C, 57.38; H, 6.11. Found: C, 57.15; H, 5.88.

2-Acetamido-6-methyl-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one/2-Acetamido-7-methyl-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one Mixture (5) and 2-Acetamido-6(or 7)-methyl-9β-(1,1-dihydroxyethyl)-3,4,5,8,9,10β-hexahydroquinazolin-4-one (6). By use of the above procedure, pyrimidinone **2** (1.30 g), isoprene (7 mL), and THF (40 mL) were combined and heated at 165 °C for 45 h. After the MeOH extraction and silica gel chromatography there was obtained a white foam (600 mg; elution with benzene–EtOAc, 85:15) which was taken up in EtOAc–hexane (10 mL). When the mixture was cooled, 130 mg of an unidentified solid separated. The mother liquor was filtered through basic alumina (4 g), giving a white foam (310 mg) which consisted (by NMR) mainly or methyl isomers **5**. This was dissolved in EtOAc (1 mL) and allowed to stand for several days with concurrent separation of hydrate mixture **6** [54 mg; mp 153–165 °C] as a powder. Crystallization from CH_3CN–EtOAc gave the analytical specimen as white needles: mp 167–169 °C; NMR δ 1.51 (s, 3), 1.73 (br s, 3), 2.16 (s, 3), 2.1–3.2 (m, 5), 5.2–5.6 (br s, 1), 8.1–8.4 (br s, 1); MS, m/e 263 (M^+), 248, 220, 178. Anal. Calcd for $C_{13}H_{17}N_3O_3 \cdot H_2O$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.52; H, 7.02; N, 14.77.

2-Acetamido-6-methyl-8β-acetoxy-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one (8) and 2-Acetamido-6-methyl-8α-acetoxy-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one (10). A mixture of pyrimidinone **2** (2.14 g, 11.0 mmol) and diene **7** (3.02 g, 24.0 mmol) in dry THF (50 mL) was placed in a Parr pressure reactor, flushed with N_2, sealed, and heated at 165 °C for 60 h. The resulting amber solution was concentrated to a foam which was triturated with $CHCl_3$ (15 mL) and filtered, affording unreacted dienophile **2** (925 mg) which was suitable for reuse after one recrystallization from CH_3CN. The filtrate was chromatographed over silica gel (reflux–recycle). Benzene was recycled through the column for 2 h followed by a 3-h elution with EtOAc–benzene (5:95), affording a yellow mixture, of starting **7** and polymer (587 mg). Continued elution with EtOAc–benzene (1:9) for 10 h gave a pale yellow solid: 552 mg, mp 205–209 °C. Recrystallization from aqueous 2-propranol gave pure major isomer **8** as dense colorless cubes: 460 mg, (23% based on recovered **2**); mp 215–216 °C; TLC (silica gel, EtOAc) R_f 0.39; MS, m/e 321.133 (calcd for $C_{15}H_{19}N_3O_5$, 321.132); NMR δ 1.78 (br s, 1), 1.98 (s, 3), 2.14 (s, 3), 2.16 (s, 3), 2.28–2.60 (m, 2), 3.20 (d of d, J = 7, 11, 1), 5.49 (d, J =6), 5.65 (m, 1). Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 55.90; H, 6.15; N, 12.90.

All of the above mother liquors were combined and concentrated. The foamy residue was recrystallized from aqueous 2-propranol to give minor isomer **10** as dense white cubes: 112 mg (6% based on starting **2**); mp 214–215 °C; TLC (silica gel, EtOAc) R_f 0.28; NMR δ 1.76 (br s, 3), 2.10 (s, 3), 2.15 (s, 3), 2.20 (s, 3), 2.54 (d, J = 8, 2), 3.02 (d of d, J = 7, 8, 1), 5.62 (br d, J = 6, 1), 5.75 (d, J = 6, 1). Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.36; H, 6.19; N, 12.73.

2-Pivalamido-6-methyl-8β-acetoxy-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one (9) and 2-Pivalamido-6-methyl-8α-acetoxy-9β-acetyl-3,4,5,8,9,10β-hexahydroquinazolin-4-one (11). Pyrimidinone **3**[1] (2.0 g, 8.5 mmol) and diene **7** (2.46 g, 19.5 mmol) were dissolved in THF (55 mL), 2,6-di-*tert*-butyl-4-methylphenol (20 mg) was added, and the solution (N_2) was heated in a Parr pressure reactor at 165 °C for 64 h. The light tan solution was concentrated, hot CCl_4 (200 mL) was added, and the mixture was then cooled to 4 °C and filtered. The filtrate was concentrated, dissolved in CH_2Cl_2, and chromatographed (reflux–recycle) over silica gel. After continuous elution with CH_2Cl_2 for 13 h, a 5-h elution with $CHCl_3$ gave 1.3 g of a material which was rechromatographed. Elution with hexane–EtOAc (3:2) gave crystalline major isomer **9** (550 mg, 18%). Recrystallization from 2-propanol gave pure **9** as white crystals: mp 187–188 °C; NMR δ 1.25 (s, 9), 1.78 (br s, 3), 1.97 (s, 3), 2.13 (s, 3), 2.26–2.68 (br d of d, 2), 3.03–3.28 (d of d, 1), 5.46

(6) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-100 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed in δ units with Me_4Si as an internal standard. J values are in hertz. Only characteristic absorptions are reported. Elemental analyses were determined at the University of Oregon by Dr. R. Wielesek. All reactions were routinely run under a N_2 atmosphere. Solvents were routinely distilled prior to use.

(br d, 1), 5.66 (br d, 1, vinyl). Anal. Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.03; H, 6.56; N, 11.51.

Continued elution gave crystalline minor isomer **11** (292 mg, 10%) which was recrystallized from 2-propanol to give pure **11** as white crystals: 210 mg; mp 164–166 °C; NMR δ 1.26 (s, 9), 1.60 (s, 3), 2.01 (s, 3), 2.28 (s, 3), 2.29–2.75 (br m, 2), 3.18–3.34 (d of d, 1), 5.35 (br d, 1), 5.46 (br d, 1, vinyl). Anal. Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.49; H, 6.76; N, 11.69.

X-ray Analysis of 11. Crystal data: $C_{18}H_{25}N_3O_5$, M_r = 363.4, monoclinic, a = 11.529 (4) Å, b = 13.068 (3) Å, c = 12.901 (3) Å, β = 92.08 (3)°, U = 1942.4 Å^3, Z = 4, d_c = 1.24 g cm^{-3}, $F(000)$ = 776, Mo Kα (λ = 0.71069 Å), μ = 0.56 cm^{-1}, space group $P2_1/c$ (C_{2h}^5, No. 14) from systematic absences $h0l$, $l = 2n + 1$, and $0k0$, $k = 2n + 1$.

The crystals were of poor quality and did not diffract well. Accurate cell parameters were obtained by a least-squares refinement of the setting angles of 25 reflections (with θ in the range 10–15°) measured on an Enraf-Nonius CAD4 diffractometer. Intensity data were collected by the $\omega/2\theta$ method to a maximum θ of 20°, and 1811 unique data were obtained. After corrections for Lorentz and polarization effects, the data with $I > 3\sigma I$ (972) were labeled "observed" and used in structure solution and refinement.

The structure was solved by using MULTAN-80[7,8] with the 304 E's greater than 1.4; all nonhydrogen atoms were located in the first E map. Six cycles of full-matrix isotropic refinement reduced R to 0.14, and a subsequent difference map revealed positions for all 25 protons. These were then allowed for in idealized positions (C–H, N–H, 0.95 Å), and overall isotropic temperature factors were refined for different types of protons in subsequent refinements. After six further rounds of full-matrix calculations, with the nonhydrogen atoms allowed anisotropic vibration, the refinement converged with R = 0.084 and $R_w = (\sum w\Delta^2/\sum wF_o^2)^{1/2}$ = 0.090. In the refinement cycles, weights were derived from the counting statistics, $w = 1/(\sigma^2 F + 0.0146\,F^2)$, and scattering factors were taken from ref 9 and 10. A final difference map was featureless. Final fractional coordinates are given in Table I, and dimensions not in Figure 1 are in Table II. Table III contains thermal parameters, and Table IV is a listing of observed and calculated structure amplitudes. Tables I–IV are given as supplementary material.

2-Acetamido-6α-methyl-6β,7β-dihydroxy-8β-acetoxy-9β-acetyl-3,4,5,6,7,8,9,10β-octahydroquinazolin-4-one (13). Major adduct **8** (200 mg, 0.62 mmol) was dissolved in dry pyridine (4 mL) and cooled to −15 °C. To the stirred solution was added a solution of OsO_4 (198 mg, 0.78 mmol) in pyridine (0.5 mL). After 5 days at −15 °C, the solution was concentrated in vacuo, and the residue was dissolved in THF (15 mL). H_2S was bubbled through the solution with vigorous stirring. The mixture was centrifuged and the supernatant was concentrated, affording 291 mg of a clear brown oil. This was dissolved in MeOH and filtered through silica gel (1 g). The eluent was concentrated, and the residue (127 mg) was triturated with MeOH (5 mL), affording 32 as white crystals: 44 mg; mp 225–226 °C; NMR (acetone-d_6) δ 1.18 (s, 3), 4.40 (br d, J = 3, H-7), 4.90 (d, J = 3, H-8). The mother liquor was purified by preparative TLC ($CHCl_3$–MeOH, 9:1), giving 16 mg of crude **13**. Crystallization from MeOH gave an additional 7.6 mg of pure **13**: mp 225–226 °C; total yield 23%; MS, m/e 355.139 (calcd for $C_{15}H_{21}N_3O_7$, 355.138).

2-Acetamido-6α-methyl-6β,7β-dihdyroxy-8β-acetoxy-9β-acetyl-3,4,5,6,7,8,9,10β-octahydroquinazolin-4-one 6β,7β-Cyclic Osmate Ester and 2-Acetamido-6β-methyl-6α,7α-dihydroxy-8β-acetoxy-9β-acetyl-3,4,5,6,7,8,9,10β-octahydroquinazolin-4-one 6α,7α-Cyclic Osmate Ester (Not Shown). Major adduct **8** (40 mg, 0.12 mmol) was dissolved in dry pyridine (0.8 mL) and cooled to −15 °C. A solution of OsO_4 (32 mg, 0.12 mmol) in dry pyridine (0.1 mL) was then added. After 10 min at −15 °C the solution was allowed to stand at 25 °C for 12 h. The dark brown solution was concentrated in vacuo, and the brown solid residue was dissolved in $CDCl_3$ (0.3 mL) and again concentrated to give 102 mg of a brown solid. The $CDCl_3$ NMR spectrum showed the crude product to be a 2:1 mixture of two osmate ester–2-pyridine adducts. The mixture was separated by preparative TLC over silica gel (2-propanol–pyridine, 99:1). Besides a black band at the origin, two closely running bands at R_f 0.13 and 0.19 were observed. Extraction of the lower band with $CHCl_3$–MeOH (9:1) gave the cyclic osmate ester of the diol **13**: 42 mg (46%); NMR δ 1.69 (s, 3), 2.04 (s, 3), 2.17 (s, 3), 2.20 (s, 3), 3.34 (d of d, J = 5, 14, 1), 4.37 (d, J = 3, H-7), 4.99 (d, J = 3, H-8), 7.4–9.0 (pyridine absorptions).

Extraction of the upper band as above gave 21 mg (23%) of the minor osmate ester–2-pyridine adduct as a brown solid: NMR δ 1.62 (s, 3), 2.14 (s, 3), 2.21 (s, 3), 2.45 (s, 3), 3.74 (t, J = 5, 1), 4.38 (d, J = 2, H-7), 4.73 (d, J = 2, H-8), 7.4–9.0 (pyridine absorptions). Both osmate esters were used immediately in the next experiments.

2-Acetamido-6β-methyl-6α,7α-dihydroxy-8β-acetoxy-9β-acetyl-3,4,5,6,7,8,9,10β-octahydroquinazolin-4-one (15). Through a stirred solution of the minor cyclic osmate ester (129 mg, R_f 0.19) from the above experiment in THF (70 mL) containing saturated NH_4Cl (3 drops) was bubbled H_2S for 10 min. The resulting black mixture was stirred for 30 min and then centrifuged. The supernate was concentrated, dissolved in MeOH (10 mL), and centrifuged again. The supernate was concentrated, affording diol **15** (59 mg, 95%) as a pale yellow solid. Crystallization from MeOH afforded the analytical specimen as a white powder: mp 211–212 °C; NMR (acetone-d_6) δ 1.20 (s, 3), 3.72 (d, J = 3), 5.59 (d, J = 3). Anal. Calcd for $C_{15}H_{21}N_3O_7$: C, 50.70; H, 5.96; N, 11.82. Found: C, 50.58; H, 6.13; N, 11.79.

The major cyclic osmate ester from the above experiment could be converted into diol **13** under similar conditions.

2-Acetamido-6α-methyl-6β-hydroxy-7β,8β-diacetoxy-9β-acetyl-3,4,5,6,7,8,9,10β-octahydroquinazolin-4-one (14). A solution of diol **13** (10 mg) in dry pyridine (0.4 mL) containing Ac_2O (0.2 mL) was stirred at 25 °C for 12 h and then concentrated in vacuo. The residue was dissolved in $CDCl_3$ and concentrated, leaving a clear glass: NMR (acetone-d_6) δ 1.14 (s, 3), 3.33 (d of d, J = 5, 13, H-10), 4.97 (d, J = 3), 5.69 (d, J = 3). Crystallization from $CHCl_3$–hexane afforded the analytical specimen of **14** as white needles: mp 159–160 °C; MS, m/e 397.150 (calcd for $C_{17}H_{23}N_3O_8$, 397.148).

X-ray Analysis of 14·H$_2$O. Crystal data: $C_{17}H_{23}N_3O_8 \cdot H_2O$, M_r = 415.4, monoclinic, a = 8.952 (3) Å, b = 22.548 (5) Å, c = 9.927 (5) Å, β = 93.73 (4)°, U = 1999.5 Å^3, Z = 4, d_c = 1.38 g cm^{-3}, $F(000)$ = 840, Mo Kα (λ = 0.71069 Å), μ = 0.67 cm^{-1}, space group $P2_1/n$ (alternative setting of C_{2h}^5, No. 14) from systematic absences $h0l$, $h + l = 2n + 1$ and $0k0$, $k = 2n + 1$.

Accurate cell parameters were obtained by a least-squares refinement of the setting angles of 25 reflections (with θ in the range 10–15°) measured on an Enraf-Nonius CAD4 diffractometer. The intensities of 2742 reflections with $2 < \theta < 22°$ were measured by the $\omega/2\theta$ scan technique. The 1312 reflections with $I > 3\sigma(I)$ were labeled "observed" and used, after correction for Lorentz and polarization factors, in the determination and refinement of the structure.

The structure was solved by using MULTAN-80[7,8] and refined in a manner similar to that described for **11** above. At the conclusion of anisotropic refinement (with isotropic hydrogen atoms) R = 0.036 and R_w = 0.037, and a final difference map was featureless.

Table V contains the final fractional coordinates, and Table VI has molecular dimensions not given in Figure 2. Tables VII and VIII contain thermal parameters and structure factor listings, respectively. These Tables V–VIII are given as supplementary material.

Equilibration of Adducts 8 and 10 at C-10. Major adduct **8** (5 mg) was dissolved in CD_3CO_2D (0.3 mL) in an NMR tube, and its NMR spectrum was measured, showing H-10 as a doublet of doublets (J = 7, 11) at δ 3.31. After 3 h at 25 °C no change was observed. After 20 min at 100 °C, the H-10 absorption had disappeared. Continued heating at 100 °C overnight caused the disappearance of the two acetyl peaks. The sample was concentrated to dryness and treated with HOAc (1 mL). After a

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heating period, the sample was concentrated to dryness. The NMR ($CDCl_3$) spectrum was identical with that reported above for **8**.

A 8-mg sample of minor adduct **10** was heated in CD_3CO_2D at 100 °C for 20 min. The NMR spectrum showed partial exchange at C-10 had occurred (d of d at δ 3.22). An additional 25 min at 100 °C caused complete exchange at C-10. The sample was evaporated to dryness, redissolved in HOAc, heated for 25 min at 100 °C, and the reevaporated to dryness. The NMR spectrum in $CDCl_3$ of the residue showed a mixture of starting **10** and a new isomer **12**, with characteristic signals at δ 3.28 (t, J = 8), 5.25 (br s), 5.57 (d, J = 6), and 5.69 (br s).

2-Acetamido-6-methyl-8β-acetoxy-9β-[(phenylthio)-acetyl]-3,4,5,8,9,10β-hexahydroquinazolin-4-one (19) and 2-Acetamido-6-[1-hydroxy-2-(phenylthio)-2-acetylvinyl]-4-(1*H*)-pyrimidinone (22, Tentative Assignment). A mixture of diene **7** (1.56 g, 12.4 mmol), pyrimidinone **16**[1] (1.50 g, 4.96 mmol) as a yellow foam, and THF (20 mL) was placed in a Parr pressure reactor and heated at 150 °C for 46 h. The resulting dark brown solution was concentrated, and the residue was triturated with pentane (discarded). Then the residue was dissolved in EtOAc and filtered through silica gel (1.5 g), giving 1.99 g of a brown semisolid. This was dissolved in benzene and placed on a reflux–recycle column of silica gel. Continuous elution with benzene for 2.5 h, benzene–EtOAc (97:3) for 2.5 h, and then benzene–EtOAc (95:5) for 2.5 h gave a total of 556 mg of R_f 0.66 (EtOAc) materials as a yellow oil which was discarded. Elution with benzene–EtOAc (9:1) for 1.6 h gave **19** (221 mg, R_f 0.56) as a yellow foam. Crystallization from EtOAc–hexanes gave **19** (121 mg) as pale yellow crystals, mp 212–214 °C. The analytical specimen was obtained by recrystallization from the same solvent: mp 217 °C; NMR (acetone-d_6) δ 1.79 (br s, 3), 1.86 (s, 3), 2.10 (s, 3), 2.2–2.5 (m, 2), 3.24 (d of d, 1), 3.60 (d, 1), 4.07 (d, 1), 5.40 (br d, 1), 5.56 (m, 1, vinyl), 7.2–7.3 (m, 5). Anal. Calcd for $C_{21}H_{32}N_3O_5S$: C, 58.73; H, 5.40; N, 9.78. Found: C, 58.98; H, 5.20; N, 9.46.

Continued elution of the column with benzene–EtOAc (9:1) for 2 h brought down a yellow foam (290 mg) consisting of 3 spots, R_f 0.56 (**19**), 0.44 (minor isomer), and 0.32 (**22**). Crystallization from EtOAc–hexanes gave 25 mg of major adduct **19** (total yield, 7%) but the minor isomer could not readily be obtained in pure form. A further elution of the column gave side product **22** (412 mg, 28%). Crystallization from EtOAc–hexanes gave the analytical specimen: mp 202–203 °C; NMR δ 2.22 (s, 3), 2.30 (s, 3), 6.02 (s, 1), 7.4 (m, 5). Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17. Found: C, 55.59; H, 4.19; N, 12.27.

2-Acetamido-6-methyl-8β-acetoxy-9β-(acetoxyacetyl)-3,4,5,8,9,10β-hexahydroquinazolin-4-one (20). The pressure reactor was charged with acetoxy dienophile **17**[1] (150 mg, 0.59 mmol), diene **7** (163 mg, 1.29 mmol), and THF (10 mL), sealed, and heated at 155 °C for 48 h. The resulting brown solution was concentrated, leaving a brown oil (315 mg). Preparative TLC over silica gel (EtOAc) gave four bands. The third band from the bottom yielded 17 mg (8%) of crude adduct **20**. Two recrystallizations from EtOAc gave **4** mg of the pure specimen: mp 218.5–219.5 °C; NMR δ 1.76 (br s, 3), 2.04 (s, 3), 2.12 (s, 3), 2.16 (s, 3), 2.2–2.4 (m, 2), 3.21 (d of d, 1), 4.92 (AB system, 2), 5.56 (m, 2, H-8 and vinyl); MS, m/e (relative intensity) 379.139 (1, calcd for $C_{17}H_{21}N_3O_7$, 379.138), 320 (1), 296 (5), 254 (100).

2-Pivalamido-6-methyl-8β-acetoxy-9β-(acetoxyacetyl)-3,4,5,8,9,10β-hexahydroquinazolin-4-one (21). The pressure reactor was charged with acetoxy dienophile **18** (3.25 g, 11.0 mmol), diene **7** (3.02 g, 24.0 mmol), butylated hydroxytoluene (20 mg) and THF (50 mL), sealed, and heated at 170 °C for 90 h. The resulting tan solution was concentrated and triturated with pentane. The insoluble solid was dissolved in $CHCl_3$, and silica gel (6 g, 60–200 mesh) was added. The solvent was removed, and the residue was layered on top of a 2 × 15 cm column of silica gel in a reflux–recycle column. Elution with benzene for 18 h gave 1.5 g of crude material which was chromatographed again as above. Elution with EtOAc–hexanes (1:4) gave fractions which were a single spot (R_f 0.3; EtOAc–hexanes, 1:1). These were combined, affording 148 mg of crude **21** from which 100 mg (2%) of **21** was obtained as white crystals by crystallization from EtOAc-hexanes: mp 162–163 °C; NMR δ 1.26 (s, 9), 1.76 (s, 3), 2.04 (s, 3), 2.12 (s, 3), 2.15–2.60 (m, 2), 3.16 (br d of d, 1), 4.84 and 4.92 (AB, 2), 5.46 (br d, 1, H-9), 5.60 (br d, 1). Anal. Calcd for $C_{20}H_{27}N_3O_7 \cdot 1.5\ H_2O$: C, 57.02; H, 6.24; N, 8.67. Found: C, 56.94; H, 5.98; N, 8.90.

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Registry No. **1**, 4368-28-9; **2**, 86944-21-0; **3**, 86993-48-8; **4**, 87011-53-8; **5** (isomer 1), 86970-97-0; **5** (isomer 2), 86971-08-6; **6** (isomer 1), 86970-98-1; **6** (isomer 2), 86971-09-7; **7**, 17616-47-6; **8**, 86970-99-2; **9**, 86971-00-8; **10**, 87037-51-2; **11**, 87037-52-3; **13**, 86971-01-9; **13** osmate ester, 86971-07-5; **14**, 86971-02-0; **15**, 87067-99-0; **15** osmate ester, 87037-53-4; **16**, 86944-30-1; **17**, 86944-42-5; **18**, 86944-43-6; **19**, 86971-03-1; **20**, 86971-04-2; **21**, 86971-05-3; **22**, 86971-06-4; 1,3-butadiene, 106-99-0; isoprene, 78-79-5.

Supplementary Material Available: Tables I–VI containing final fractional coordinates, molecular dimensions, and anistropic temperature factors for X-ray analysis of **11** and **14**·H_2O (14 pages). Ordering information is given on any current masthead page.

Diastereoselective α Allylation of Secondary and Tertiary Thioamides via Thio-Claisen Rearrangement. A Structural Proof of *Z* Secondary Thioamide Dianions and *Z* Tertiary Thioamide Anions[1a,b]

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Highly diastereoselective α allylation of secondary and tertiary thioamides is achieved by making use of thio-Claisen rearrangement. From the correlation between the diastereoselectivities in products and the structures of allylating agents, the *Z* structures of secondary thioamide dianion (~100% *Z*) and tertiary thioamide anion (>97% *Z*) are concluded.

The studies on the structures of organometallics and the stereochemical outcome of the reactions with these reagents have been the subject of continuing interest. Particularly the methodology based on the enolate chemistry

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