Synthesis of 4β-Acetoxyscirpene-3α,15-diol

William R. Roush*[1] and Sandra Russo-Rodriguez

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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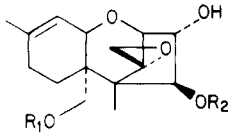
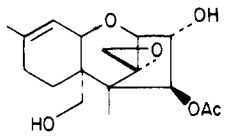
In connection with recent studies on the metabolism of anguidine (diacetoxyscirpenol (1)) we required an authentic sample of 4β-acetoxyscirpene-3α, 15-diol (**2**).[2] This compound, a natural product isolated from *Fusarium roseum*[3a] and *F. sulphureum*,[3b] has previously been prepared by treatment of anguidine with resting cells of *Streptomyces griseus*[4] and by hydrolysis with 40% sulfuric acid.[5] In our hands, however, the latter procedure afforded an apotrichothecene and not **2**. Hydrolysis of anguidine under basic conditions (e.g., K_2CO_3–MeOH, NH_4OH–MeOH,[5] NaOAc–MeOH[6]) is highly regioselective but affords the 15-monoacetate 3 with no more than a trace of **2**. In addition, acylation of scirpenetriol (4) with various carboxylic acid derivatives is not selective and gives complicated product mixtures.[7a] Consequently, we have developed and report herein two unambiguous syntheses of the title compound.



1, $R_1 = R_2 = Ac$
3, $R_1 = Ac$, $R_2 = H$
4, $R_1 = R_2 = H$

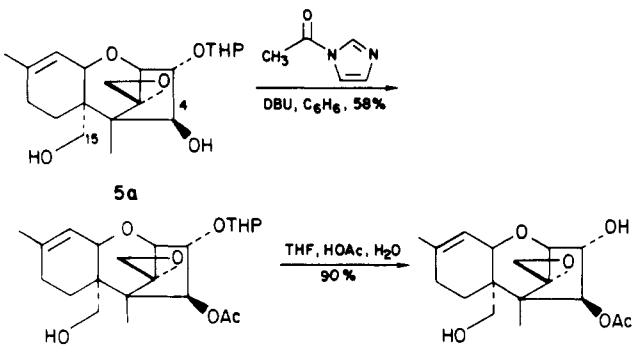


2

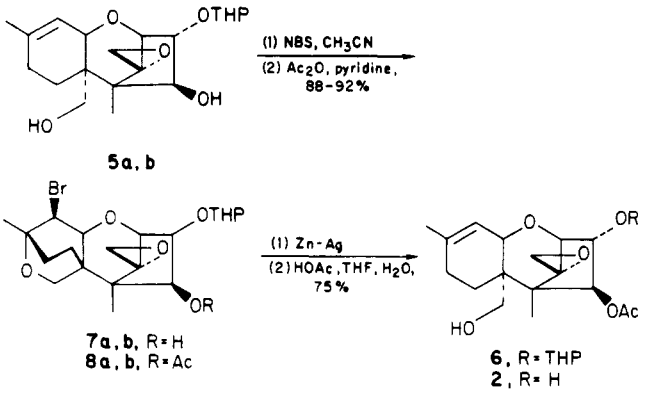
The first synthesis involves the selective acylation of THP derivative **5** (Scheme I). Whereas acylations of **5** with acid chlorides, anhydrides, or carboxylic acids and DCC are selective for C(15)-OH,[7] we suspected by analogy to work in the verrucarol series[8] that selectivity for C(4)-OH could be achieved by reaction of **5** with 1-acetylimidazole. Indeed, treatment of diastereomer **5a**[9] with 1.2 equiv of 1-acetylimidazole and 0.2 equiv of DBU in benzene afforded monoacetate **6a** in 58% yield along with 19% of the corresponding diacetate. Hydrolysis of **6a** in 2:1:1 THF–HOAc–H_2O at room temperature then afforded 4-acetoxyscirpenediol (**2**, 90%), the spectroscopic properties of which were in complete agreement with literature values.[3,4]

The second synthesis has its origin in studies directed toward the synthesis of ^{14}C-anguidine.[10] In the latter work bromo ether derivatives (e.g., **7**) were prepared in order to protect the trichothecene C(9),C(10)–olefin from ozonolysis. These derivatives also nicely differentiate the C(4) and C(15) hydroxyl groups of **5**, a property used to advantage in the synthesis outlined in Scheme II. In practice, treatment of **5a** or **5b**[9] with NBS in acetonitrile afforded bromo ether **7a,b** in excellent yield.[11] Best results were obtained when the reaction was carefully monitored and worked up promptly after **5a,b** had been consumed (typically 1–3-h reaction times). On several occasions when these experiments were allowed to proceed overnight, extensive anomerization and THP–ether cleavage was observed. Acylation of **7a,b** afforded **8a,b** in 88–92% yield from **5a,b**. Unmasking of the C(15) and C(3) hydroxyl groups was then smoothly accomplished by treatment with Zn–Ag couple[12] (90%) to effect reductive cleavage of the bromo ether unit followed by THP ether hydrolysis as described in Scheme I. The overall yield of **2** from this four-step sequence was 65–70%.

Scheme I



Scheme II



In summary, two syntheses of 4-acetoxyscripenediol (**2**) have been accomplished. We have shown that this compound is a metabolite of anguidine in in vitro studies and have presented evidence that a glucuronic acid conjugate of **2** is excreted in urine by mice.[2] Additional studies on the chemistry and synthesis of metabolites of anguidine are in progress and will be reported in due course.

Experimental Section

Proton (^1H) NMR spectra were measured at 250 or 270 MHz on Bruker WM250 and 270 instruments. Chemical shifts are reported in δ units, using tetramethylsilane or the 7.24 ppm resonance of residual chloroform as internal reference. Infrared spectra were measured on a Perkin-Elmer Model 283B infrared spectrophotometer calibrated with the 1601-cm^{-1} absorption of

(1) Holder of the Roger and Georges Firmenich Career Development Chair in Natural Products Chemistry, 1981–84; Fellow of the Alfred P. Sloan Foundation, 1982–86.

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polystyrene. IR spectra are reported in wave numbers (cm^{-1}). Optical rotations were measured on a Rudolph Autopol III automatic polarimeter, using a 1 cm^3 capacity quartz cell (10-cm path length). Mass spectra (low and high resolution) were measured on a Finnegan Mat 8200 instrument. Elemental analyses were performed by Robertson Laboratory, Inc. of Florham Park, NJ. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and are uncorrected.

All reactions were conducted in flame- or oven-dried glassware under atmospheres of dry argon or nitrogen. The following solvents were purified before use: ether, THF, and benzene were distilled from sodium benzophenone ketyl; methylene chloride (CH_2Cl_2) and pyridine were distilled from CaH_2; methanol and ethanol were distilled from Mg metal. In addition, acetic anhydride, DBU, and dihydropyran (from CaH_2) were also distilled before use.

Analytical thin layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm layer of silica gel containing PF 254 indicator (Analtech.) Preparative thin layer chromatography (PTLC) was performed by using 20 cm × 20 cm plates coated with 0.25- or 0.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by staining with iodine vapor or by charring with ethanolic H_2SO_4. Compounds were eluted from the adsorbents by using 15% MeOH in CH_2Cl_2. Flash column chromatography was performed by the method of Still[13] using Merck 230–400-mesh silica gel. All chromatography solvents were distilled prior to use.

Tetrahydropyranyl Esters 5a and 5b.[7a] A solution of anguidine (551 mg, 1.50 mmol) in 10 mL of CH_2Cl_2 was treated with dihydropyran (0.30 mL, 3.3 mmol) and pyridinium *p*-toluenesulfonate[14] (48.8 mg, 0.19 mmol) over a 4-day period. After standard workup, the crude product (814 mg) was hydrolyzed with aqueous NaOH in THF–MeOH as described by Kaneko et al.[7a] to afford 695 mg of **5** as a mixture of diastereomers. This material was separated by careful flash chromatography (50 mm × 20 cm column) using 3% MeOH in CH_2Cl_2 as eluant to give 236 mg (44%) of diastereomer **5a** (R_f 0.30, 3% MeOH–CH_2Cl_2), 187 mg (35%) of **5b** (R_f 0.27), and 101 mg (19%) of mixed fractions which were combined with material from a subsequent run.

Data for 5a: ^1H NMR (250 MHz, $CDCl_3$) δ 5.45 (br d, 1 H, J = 5.3 Hz, H_{10}), 4.65 (br dd, 1 H, J = 2.2, 5.0 Hz, THP), 4.42 (d, 1 H, J = 3.1 Hz, H_4), 4.05 (dd, 1 H, J = 3.2, 4.7 Hz, H_3), 3.95 (m, slightly overlapping with H_{11}, 1 H, THP), 3.88 (br d, 1 H, J = 5.50 Hz, H_{11}), 3.78 and 3.49 (AB, 2 H, J = 11.9 Hz, H_{15a}, H_{15b}), 3.66 (d, 1 H, J = 4.8 Hz, H_2), 5.50 (m, overlaps with H_{15b}, 1 H, THP), 2.99 and 2.74 (AB, 2 H, J = 4.1 Hz, H_{13}), 2.1–1.5 (m, 4 H), 1.70 (br s, 3 H, H_{16}), 0.90 (s, 3 H, H_{14}); mass spectrum m/e 281 (M^+–C_5H_9O).

Data for 5b: $[\alpha]_D^{22}$ −54° (c 1.02, CH_2Cl_2); mp 75 → 87 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 5.47 (br d, 1 H, J = 5.3 Hz, H_{10}), 4.92 (t, 1 H, J = 2.8 Hz, THP), 4.43 (br s, 1 H, H_4), 4.04 (br dd, 1 H, J = 3.1, 4.8 Hz, H_3), 3.95 (m, 2 H, H_{10} and THP), 3.76 (d, 1 H, J = 11.8 Hz, H_{15a}), 3.69 (d, 1 H, J = 4.8 Hz, H_2), 3.51 (br d, 2 H, J = 11.8 Hz, H_{15b} and THP), 2.99, 2.72 (AB, 2 H, J = 4.0 Hz, H_{13}), 2.1–1.5 (m, 4 H), 1.73 (br, s, 3 H, H_{16}), 0.86 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3620, 3600–3300 (br), 2950, 1440, 1380, 1200, 1120, 1070, 1030, 970, 900, 790 cm^{-1}; mass spectrum m/e 365 (M^+ − H), 281 (M^+ − C_5H_9O); high resolution mass spectrum, calcd, for $C_{20}H_{30}O_6$ − C_5H_9O (M^+ − C_5H_9O) 281.1389, found 281.1398 ± 0.0008.

Monoacetate 6a. To a solution of 1-acetylimidazole (34 mg, 0.31 mmol) in 1 mL of dry benzene was added a solution of THP ether **5a** (96 mg, 0.26 mmol) in 1.0 mL of benzene containing DBU (9 μL, 0.06 mmol). The reaction was stirred at ambient temperature for 6 h and then the solvent was removed in vacuo. The crude product was chromatographed on a 30 mm × 15 cm silica gel column using 2:1 hexane-EtOAc as eluant to give 24 mg (19%) of diacetate and 62 mg (58%) of **6a**: mp 66–68 °C; $[\alpha]_D^{22}$ +89.9° (c 0.93, $CHCl_3$); R_f 0.47 (1:1 hexane–EtOAc); H NMR (250 MHz, $CDCl_3$) δ 5.95 (d, 1 H, J = 3.4 Hz, H_4), 5.55 (br dd, 1 H, J = 1.1, 5.6 Hz, H_{10}), 4.73 (t, 1 H, J = 3.4 Hz, THP), 4.36 (br d, 1 H, J = 5.7 Hz, H_{11}), 4.32 (dd, 1 H, J = 3.4, 4.6 Hz, H_3), 3.82 (m, 2 H, H_{15a} and THP), 3.74 (d, 1 H, J = 4.7 Hz, H_2), 3.66 (br dd, 1 H, J = 3.8, 12.7 Hz, H_{15b}), 3.47 (m, 1 H, THP), 3.02 (br d, J = 3.8 Hz, H_{13a} and OH), 2.74 (d, 1 H, J = 3.8 Hz, H_{13b}), 2.12 (s, 3 H, OAc), 1.70 (s, 3 H, H_{16}), 0.75 (s, 3 H, H_{14}); IR 3620, 3550–3340 (br), 3000, 2940, 1715, 1430, 1415, 1360, 1210 (br), 1120, 1070, 1030, 970 cm^{-1}.

Bromo Ethers 7a and 7b. To a solution of THP diastereomer **5b** (141 mg, 0.38 mmol) in 10 mL of reagent grade MeCN was added *N*-bromosuccinimide (71 mg, 0.40 mmol, recrystallized before use). The reaction was stirred at ambient temperature for 2 h and then was concentrated under reduced pressure. The resulting mixture was then purified by flash chromatography (30 × 24 cm column) using 3% MeOH in CH_2Cl_2 as eluant to yield 171 mg (93%) of a 2.5:1 mixture of **7b** and succinimide. This mixture was used directly in the next experiment without additional purification. Bromo ether **7a** was prepared from **5a** in comparable yield. Repeated chromatography (0.25-mm preparative TLC plate, 2.5% MeOH–CH_2Cl_2) of a small sample of **7a** afforded pure material which was fully characterized.

Data for 7a: R_f 0.23 (2.5% MeOH–CH_2Cl_2); mp 70–72 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 4.64 (m, 1 H, THP), 4.24 (m, 2 H, H_{11} and H_4) (dd, 1 H, J = 2.1, 8.7 Hz, H_{10}), 4.03 (dd, 1 H, J = 3.2, 4.7 Hz, H_3), 3.96 (m, 1 H, THP), 3.80 (d, 1 H, J = 4.9 Hz, H_2), 3.73 (br s, 2 H, H_{15a}, H_{15b}), 3.57 (m, 1 H, THP), 3.01 and 2.80 (AB, 2 H, J = 3.2 Hz, H_{13a}, H_{13b}), 2.3–1.8 (m, 4 H), 1.28 (s, 3 H, H_{16}), 0.67 (s, 3 H, H_{14}); IR ($CHCl_3$) 3020, 2980, 2940, 2880, 1540, 1450, 1440, 1215 (br), 1130, 1070 cm^{-1}; mass spectrum, m/e 365 (M^+–Br).

Data for 7b (sample containing succinimide): R_f 0.20 (2.5% MeOH–CH_2–CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 4.96 (br t, 1 H, J = 3 Hz, THP), 4.23 (br dd, 2 H, J = 1.7, 8.7 Hz, H_{11} and buried H_4), 4.12 (m, 2 H, H_3, H_{10}), 3.95 (m, 1 H, THP), 3.83 (d, 1 H, J = 4.9 Hz, H_2), 3.73 (br s, 2 H, H_{15a}, H_{15b}), 3.02, 2.70 (AB, 2 H, J = 3.9 Hz, H_{13}), 2.74 (s, succinimide), 2.3–2.0 and 1.8–1.5 (m, 4 H), 1.25 (s, 3 H, H_{16}), 0.63 (s, 3 H, H_{14}).

Acetates 8a and 8b. A portion of bromo ether **7b** prepared in the preceding experiment (135 mg of a 2.5:1 mixture containing succinimide, thus 0.28 mmol) was dissolved in 3.5 mL of pyridine and treated with acetic anhydride (73 μL, 0.70 mmol) and 4-(dimethylamino)pyridine (9 mg, 0.07 mmol) overnight at room temperature. The reaction was diluted with 50 mL of heptane and concentrated in vacuo to remove pyridine (azeotrope). Repetition of this step afforeded the crude product which was filtered through a $^1/_4$ in. pad of silica gel (1:1 EtOAc–hexane) to give 130 mg (95%; 88% from **5b**) of pure **8b** as a white solid. The yield of **8a** from **5a** was comparable.

Data for 8a: R_f 0.64, (1:1 hexane–EtOAc); mp 170–173 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 5.57 (d, 1 H, J = 3.5 Hz, H_4), 4.71 (t, 1 H, J = 3.5 Hz, THP), 4.35 (dd, 1 H, J = 3.8, 5.3 Hz, H_3), 4.28 (m, 2 H, H_{11} and THP), 4.09 (dd, 1 H, J = 3.0, 9.8 Hz, H_{15a}), 3.86 (d, 1 H, J = 4.5 Hz, H_2), 3.75 (br d, 2 H, J = 9.8 Hz, H_{15b} and THP), 3.03 and 2.73 (AB, 2 H, J = 3.9 Hz, H_{13}), 2.3–1.8 (m, 4 H), 2.07 (s, 3 H, OAc), 1.30 (s, 3 H, H_{16}), 0.55 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3050, 2950, 2880, 1735, 1420, 1375, 1250 (br), 1200, 1130, 1080, 1050, 975, 895 cm^{-1}; mass spectrum, m/e 407 (M^+ − Br), 323 (M^+ − Br − C_5H_8O).

Data for 8b: R_f 0.64 (1:1 hexane–EtOAc); $[\alpha]_D^{22}$ −79° (c 0.63, $CHCl_3$); mp 68–73 °C; ^1H NMR ($CDCl_3$, 250 MHz), δ 5.50 (d, 1 H, J = 3.4 Hz, H_4), 4.75 (t, 1 H, J = 2.7 Hz, THP), 4.31 (dd, 1 H, J = 3.6, 4.7 Hz, H_3), 4.26 (br s, 2 H, H_{10}, H_{11}), 4.02 (dd, 1 H, J = 2.6, 9.7 Hz, H_{15a}), 3.94 (m, partially overlapping with H_2, 1 H, THP), 3.87 (d, 1 H, H_2), 3.71 (d, 1 H, J = 9.7 Hz, H_{15b}), 3.5 (m, 1 H, THP), 3.04, 2.72 (AB, 2 H, J = 4.0 Hz, H_{13}), 2.2 (m, 1 H), 2.07 (s, 3 H, OAc), 1.9–1.5 (m, 3 H), 1.27 (s, 3 H, H_{16}), 0.52 (s, 3 H, H_{14}); IR ($CHCl_3$) 2950, 2880, 1730, 1380, 1250, 1125, 1075, 1050, 1040, 975 cm^{-1}; mass spectrum, $m/407$ (M^+ − Br).

Anal. Calcd for $C_{22}H_{31}O_7Br$: C, 54.22; H, 6.41. Found: C, 54.19; H, 6.46.

Monoacetate 6b. To a suspension of Zn–Ag couple (freshly prepared from 21.5 mg of AgOAc, 3.7 g of Zn powder, and 21 mL of glacial HOAc[12]) in 9 mL of dry Et_2O was added a solution of 116 mg (0.23 mmol) of **8b** and 3.5 mL of anhydrous EtOH in 18 mL of dry THF. The mixture was stirred at 55–60 °C (bath temperature) for 15 h and then the solvents were removed in vacuo. The residue was suspended in acetone (50 mL) and filtered through a pad of silica gel overlayered with Celite. The filter pad was rinsed with 50 mL of fresh acetone, and the combined filtrates were concentrated to give 200 mg of a yellow oil. Purification

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of this material by flash silica gel chromatography (20 mm × 16 cm column using 2:1 hexane–EtOAc as eluant) afforded 88 mg of pure **6b** (90%): R_f 0.44 (1:1 hexane–EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.87 (d, 1 H, J = 3.6 Hz, H_4), 5.55 (br dd, 1 H, J = 1.2, 5.9 Hz, H_{10}), 4.76 (t, 1 H, J = 2.9 Hz, THP), 4.30 (br d, 1 H, J = 5.9 Hz, H_{11}), 4.25 (dd, 1 H, J = 3.6, 4.7 Hz, H_3), 4.00 (m, 1 H, THP), 3.83 and 3.64 (AB, 2 H, J = 12.6 Hz, H_{15a}, H_{15b}), 3.75 (d, 1 H, J = 4.8, H_2), 3.01 and 2.74 (AB, 2 H, J = 3.9 Hz, H_{13}), 2.02 (s, 3 H, OAc), 1.70 (s, 3 H, H_{16}), 0.75 (s, 3 H, H_{14}); IR ($CHCl_3$) 3620, 3480 (br), 2940, 1720, 1435, 1370, 1210 (br), 1120, 1070, 1020, 970 cm^{-1}.

4β-Acetoxyscirpene-3α,15-diol (2). To a solution of THP ether **6a** (57 mg, 0.14 mmol) in 0.25 mL of THF was added 0.25 mL of H_2O and 0.5 mL of glacial HOAc. The reaction was stirred for 5 days at ambient temperature. The reaction was coevaporated with heptane (3 × 50 mL) to remove HOAc and H_2O. The resulting crude product (67 mg) was purified by flash silica gel chromatography (using a 10 mm × 14 cm column, 1:1 hexane–EtOAc as eluant) to afford 42 mg of **2** (90% yield). The yield of **2** from **6b** was comparable (75% of **2** plus 15% of recovered **6b** after a 3 day reaction period). Attempts to crystallize **2** were unsuccessful: $[\alpha]_D^{22}$ +10.0° (*c* 1.2, 99.7%, acetone), lit.[4] $[\alpha]_D^{22}$ +10.3° (*c* 1, acetone); R_f 0.20 (1:1 hexane–EtOAc), 0.48 (2:1 benzene–acetone); NMR (250 MHz, $CDCl_3$) δ 5.56 (br d, 1 H, J = 5.7 Hz, H_{10}), 5.50 (d, 1 H, J = 3.4 Hz, H_4), 4.24 (dd, 1 H, J = 4.6, 8.1 Hz, H_3), 4.18 (d, 1 H, J = 4.8 Hz, H_{11}), 3.8 (br d, 1 H, J = 10.7 Hz, H_{15a}), 3.65 (d, 1 H, J = 4.9 Hz, H_2), 3.61 (br d, 1 H, J = 10 Hz, H_{15b}), 3.05 and 2.76 (AB, 2 H, J = 4.0 Hz, H_{13}), 2.82 (br d, 1 H, J = 3.9 Hz, OH), 2.18 (s, 3 H, OAc), 1.72 (br s, 3 H, H_{16}), 0.65 (s, 3 H, H_{14}); IR ($CHCl_3$) 3600–3300 (br), 2940, 1720, 1370, 1250, 1070, 950 cm^{-1}; mass spectrum m/e 306 ($M^+ - H_2O$); CI mass spectrum of the bis(trimethylsilyl) derivative, m/e 469 (MH^+), 453 ($M^+ - CH_3$), 409 (M^+ - OAc); high resolution mass spectrum, calcd for $C_{17}H_{22}O_5$ ($M^+ - H_2O$) 306.1467), found 306.1492 ± 0.0007.

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Cyanoketenes. Cycloadditions of Chlorocyanoketene to Alkynes. Generation of Vinylogous Cyanoketenes

Paul L. Fishbein and Harold W. Moore*

Department of Chemistry, University of California, Irvine, California 92717

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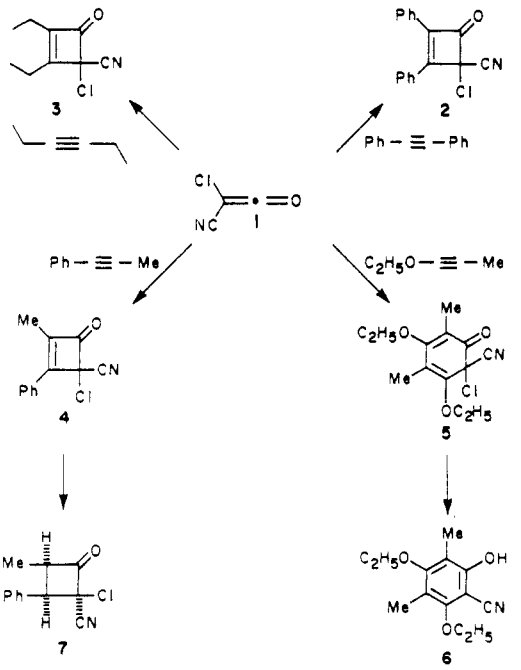
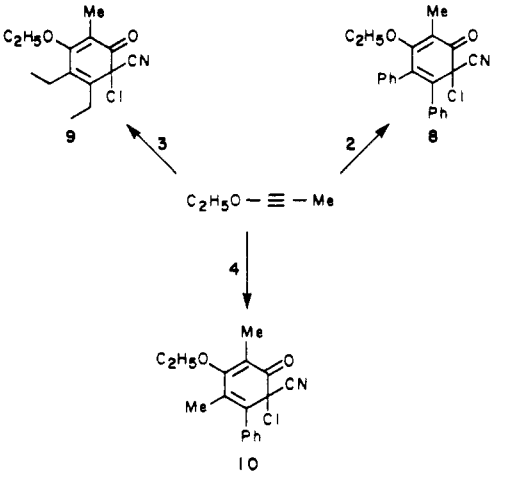
Chlorocyanoketene (CCK), an exceptionally reactive electrophilic ketene, has previously been shown to undergo facile cycloadditions to imines,[1] formimidates,[2] aryl aldehydes,[3] sulfurdimides,[4] and alkenes.[5] Its ability to cycloadd to selected alkynes is reported in this manuscript. Also reported is the observation that the resulting cyclobutenones function as precursors to vinylketenes. Indeed, the 4-chloro-4-cyanocyclobutenones arising from the initial cycloadditions are in equilibrium with their respective vinylketenes at ambient temperature, and these reactive intermediates can be intercepted by other ketenophiles. The details of these results are given below.

Scheme I



Scheme II



The cycloadditions were carried out in toluene (103 °C) by generating approximately 3 equiv of CCK in the presence of 1 equiv of the aklyne. The alkynes employed were 1-hexyne, phenylacetylene, diphenylacetylene, 3-hexyne, 1-phenylpropyne, and 1-ethoxypropyne. The reactions of the terminal alkynes with CCK gave complex mixtures from which no pure product was obtained. On the other hand, the internal alkynes, diphenylacetylene, 3-hexyne, and 1-phenylpropyne gave, respectively the cyclobutenones **2** (77%), **3** (61%), and **4** (84%) (Scheme I). The formation of **4** deserves further comment since only the indicated regioisomer was observed. Its structure was shown to be 4-chloro-4-cyano-2-methyl-3-phenylcyclobutenone as established by its conversion (H_2, Pd–C, 40%) to the corresponding cyclobutanone, **7**, which was independently prepared from the cycloaddition of CCK to (*Z*)-1-phenylpropene.[5]

A most interesting transformation took place when 1-ethoxypropyne was treated with CCK under the above reaction conditions. No cyclobutenone was observed. Rather, the cyclohexadienone, **5**, was obtained as a yellow crystalline solid in 56% yield. The structure of **5** is based upon its spectral properties, as well as upon the observation that it undergoes facile reductive elimination (Zn,

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(2) Moore, H. W.; Hernandez, L.; Chambers, R. *J. Am. Chem. Soc.* **1978**, *100*, 2245.
(3) Moore, H. W.; Kunert, D.; Mercer, F; Albaugh, P. *J. Am. Chem. Soc.* **1979**, *101*, 5435.
(4) Moore, H. W.; Axon, B. X.; Goldish, D. M. *Heterocycles* **1983**, *20*, 187.
(5) The cycloaddition of CCK to alkenes has previously been reported. See: Fishbein, P. L.; Moore, H. W. *J. Org. Chem.* **1984**, *49*, 2190.

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