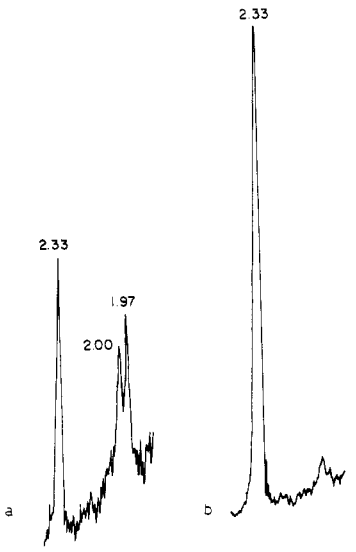

Figure 1. Proton NMR δ values shown of unseparated products from the acetylation of 3α- and 3β-aminocholestane (a) and their pentane-soluble fraction (b).

tography[2] was treated with phosgene (moderate bubbling) in boiling *o*-dichlorobenzene for 2 h. The workup yielded a solid residue which was recrystallized from ether–acetonitrile to give **2d**: 250 mg; mp 70–72 °C; mass spectral mol wt 413; IR showed the absence of NH_2 and a strong absorption at 2270 cm^{-1} (NCO). A 150-mg sample of this material (**2d**) was refluxed with 3 mL of acetic anhydride for 19 h (175 °C). Benzene followed by chloroform elution chromatography on 30 g of silica gel yielded 25 mg of a material identical with **2b** (see above) by melting point, TLC, and ^1H NMR. Starting material (15 mg) was also isolated in procedures known to yield imide if present.

Preparation and Acylation of 3β-Isocyanatocholestane. A 300-mg sample of 3β-aminocholestane was treated as above to yield 250 mg of **2e**: mp 81–83 °C; mass spectral mol wt 413; IR NH_2 absent, strong absorption at 2250 cm^{-1} (NCO). A 200-mg sample of **2e** was acylated as above to yield a brown residue which was purified by chromatography (as above) to give 15 mg of a material identical by melting point and ^1H NMR with **2a** and 5 mg of a material similarly identical with the amide **2c**.

Equilibration of 3β-(Diacetylamido)cholestane(2a). A 50-mg sample of **2a** was refluxed for 1 h in 1 mL of acetic anhydride with 3 drops of pyridine. The acetic anhydride showed a weak infrared absorption at near 3 μm. Solvent was removed under vacuum, and the ^1H NMR of the residue showed the characteristic singlets for **2a** and **2c** in a ratio of ca. 4:1 favoring the imide (**2a**).

Trituration Procedure for Separation of Isomers. A 1-g sample of the mixture of 3-aminocholestane isomers was acetylated as described above. This yielded a crude solid weighing 940 mg. The ^1H NMR in the region from ca. δ 2 to 2.5 is reproduced in Figure 1a. The singlet at low field is due to the imide **2a** while the doublet near δ 2.0 is due to the mixture of amides **2b** and **2c**. Pentane at room temperature was triturated (3 × 25 mL) with this solid and filtered by suction. Evaporation yielded 350 mg of a solid (**2a**) with a ^1H NMR in the same region, as exhibited in Figure 1b. Thin-layer chromatography on silica gel with chloroform showed only traces of amide in this sample. The insoluble residue weighed 580 mg and was subjected again to acetylation as above. The crude solid yield was again triturated with pentane as above to give another 200 mg of the soluble imide **2a**. The insoluble residue weighed 220 mg and was identified as the amide **2b** only slightly contaminated with the epimer **2c**. One crystallization gave pure **2b** as judged by its melting point, 215–216 °C.[2]

Acknowledgment. We are very grateful to the National Institutes of Health, Division of General Medical Sciences, and the Petroleum Research Fund, administered by the American Chemical Society, for the financial support for this work.

Registry No. 1a, 79483-38-8; **1b**, 79499-33-5; **1c**, 79483-39-9; **2a**, 79483-40-2; **2b**, 40937-16-4; **2c**, 1912-64-7; **2d**, 24281-86-5; **2e**, 24281-87-6; **3a**, 79483-41-3; **3b**, 31023-35-5; **3c**, 31023-36-6; 3α-aminocholestane, 2206-20-4; 3β-aminocholestane, 2206-21-5; 3-oxocholane, 19443-04-0; 3-oxocholane oxime, 79483-42-4.

An Improved Yield Preparation of 3-Oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylic Acid, an Important Intermediate in the Synthesis of (±)-Strigol[1]

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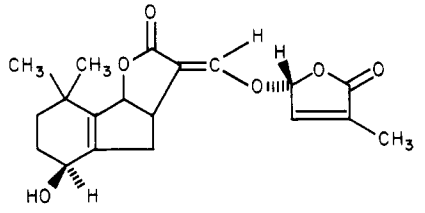
Witchweed [*Striga asiatica* (L.) Kuntze] is a parasitic plant whose seeds will not germinate unless they are stimulated by a chemical exuded from the roots of a host plant or some nonhost plants.[2] The active chemical in the root exudates was isolated in 1966[3] and identified in 1972[4] by Cook and co-workers. The compound 1 was given the trivial name strigol and it has been shown to be a very potent witchweed seed germination stimulant.



1

Total synthesis of (±)-strigol was reported in 1974 by Sih and co-workers,[5] and the details of their sequence and resolution of (±)-strigol was reported in 1976.[6] MacAlpine and co-workers reported the synthesis of strigol by a somewhat different method also in 1974 and 1976.[7]

Cook and co-workers suggested that strigol may be representative of a new class of plant hormones and that other biological effects should be examined.[4] In 1974, C. J. Sih provided the USDA with 4 g of (±)-strigol and 1 g of (±)-epistrigol. The data obtained from some of the experiments conducted with this limited amount of the germination stimulant have been very encouraging and emphasize the need for continuing studies on its biological activity.[8-10]

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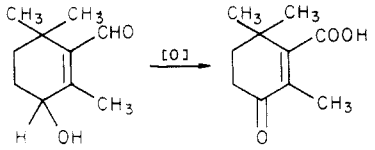
A project was initiated at the Southern Regional Research Center with the goal of preparing sufficient quantities of strigol to permit the broad spectrum of tests necessary to understand strigol's role in the germination, growth, and reproduction of witchweed and its potential as a control agent when applied to infested fields. The first approach was to modify the existing synthetic sequences to give overall better yields of strigol. Sih and co-workers[6] described two routes to strigol, one starting with α-cyclocitral (2,6,6-trimethylcyclohex-2-ene-1-carboxaldehyde) and the other with β-cyclocitral (2,6,6-trimethylcyclohex-1-ene-1-carboxaldehyde). The two routes converged after several steps and the remainder of the synthesis was identical. The α-cyclocitral scheme appeared to us to present fewer experimental problems than the β-cyclocitral scheme. Epoxidation of α-cyclocitral as described proceeded smoothly, but isomerization of the epoxide with pyrrolidine generally produced a lower yield of the hydroxy aldehyde **2** than reported. Several variations in experimental conditions were tried but none made any appreciable difference in yield.

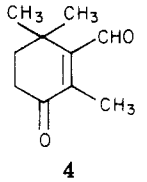
The third step of the sequence involved oxidation of **2** to the keto acid **3**. Sih et al. accomplished this by si-



2 **3**

multaneous oxidation of the allylic alcohol and the α,β-unsaturated aldehyde with the Jones reagent (CrO_3–H_2SO_4).[11] While admitting that there were problems with this reaction, Sih et al. reported yields of 45–55% of crude product. Our results were not as good, with yields only in the range of 10–30%. The 30% yields were obtained only when a double (or triple) distillation of crude **2** was carried out to give hydroxy aldehyde of 95% or greater purity for use in the oxidation step.

The acid formed in the Jones oxidation is readily separated from the nonacidic organic material by extraction of the ether layer with $NaHCO_3$ solution. The material not extracted by $NaHCO_3$ (neutral organics) was shown by NMR spectroscopy to consist of primarily the keto aldehyde **4**.



4

The NMR spectrum of **2** shows the allylic proton on the carbon bearing the hydroxyl group at a chemical shift of δ 4.1 and the hydroxyl proton at δ 3.3. The aldehyde proton resonates at δ 10.1. The NMR spectrum of **4** shows the results of oxidation of the hydroxyl group—loss of both the hydroxyl proton and allylic proton signal and collapse of the *gem*-dimethyl doublet (δ 1.2) in **2** to a singlet (δ 1.35) in **4** due to the loss of the chiral center at the hydroxyl carbon. The aldehyde peak is moved to a lower field (δ 10.34) because of the electron-withdrawing effect of the conjugated ketone.

Table I. Oxidation of Keto Aldehyde 4

method	reagent	% yield of crude acid[a]
1	$KMnO_4$–H_2SO_4	12.5[b]
2	air (bubbled)	37
3	air (thin film)	46
4	Ag_2O	72[c]
5	MnO_2–NaCN	80[d]
6	CrO_3–H_2SO_4 (Jones reagent)	55[b]

[a] Based on the keto aldehyde. [b] Average of two experiments. [c] Average of four experiments. [d] Product is the methyl ester of the acid.

The sterically hindered aldehyde group was largely untouched by the Jones reagent. The long reaction time (10 h) used by Sih et al. was required to oxidize the aldehyde group since oxidation of the alcohol proceeds readily. However, this long exposure to the Jones reagent caused byproduct formation as was readily apparent from the NMR spectrum of the crude acidic products.

The NMR spectrum of a typical crude product from the Jones oxidation procedure showed impurities in the *gem*-dimethyl region (δ 1.1–1.3) and the ring methylene region (δ 2.3–2.8). The NMR spectrum of recrystallized **3** has a singlet for the *gem*-dimethyl protons and a cleaner pattern for the ring methylenes.

From the results, it appeared that a two-step procedure for the oxidation step, while requiring more laboratory manipulations, would be worthwhile if a substantial improvement of yield could be obtained. Several more suitable methods for aldehyde oxidation were tried on the keto aldehyde **4** isolated from the Jones reagent oxidation, including the following: (1) oxidation with potassium permanganate–sulfuric acid,[12] (2) air oxidation either by bubbling air through an ether solution of **4** or (3) by evaporative thin-film exposure to air, (4) oxidation with alkaline silver(I) oxide,[13,14] (5) oxidation with manganese dioxide in the presence of sodium cyanide,[15] and (6) reoxidation with the Jones reagent for comparison. The results of these experiments are summarized in Table I. Method (1) gave the poorest yield, probably because of byproduct formation from oxidation of the double bond by the permanganate. Air oxidation, methods 2 and 3, gave about 40% conversion to acidic products, but according to their NMR spectra, these were mixtures and the yield of the pure product would be substantially less after recrystallization. Alkaline silver(I) oxide was used in method 4 and gave an excellent conversion of keto aldehyde to the crude acid (72%). The reaction was exothermic and rapid and the crude product has only a small percentage of byproducts shown by NMR. The facility of oxidation of **4** by Ag_2O was unexpected since Thomason and Kubler[14] had obtained yields of only 31% and 40%, respectively, for oxidation of the α,β-unsaturated aldehydes—crotonaldehyde and cinnamaldehyde. Corey et al.[15] observed "little or no oxidation" of cinnamaldehyde with AgO in methanol. Frank[16] observed only a 23% conversion of β-cyclocitral to β-cyclogeranic acid by Ag_2O. The extended conjugation provided by the keto group appears to be the activating influence for the facile oxidation of **4**, since oxidation of β-cyclocitral and the hydroxy aldehyde **2**

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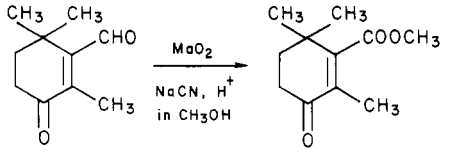
under similar conditions proceeded with 17% and 22% yields, respectively, even after extended reaction times.

The fifth method of oxidation was one developed by Corey[15] for use in natural products synthesis. It worked quite well on a small scale for conversion of 4 to the keto ester 5. Of the methods studied, this procedure gave the



4 5

best conversion of aldehyde to the carboxylic group (80%) and also combined two steps into one, since conversion of the acid to its methyl ester is the next step in the strigol sequence. However, the method has two distinct disadvantages in that a large excess (tenfold by weight) of freshly prepared manganese dioxide is required and hydrogen cyanide is one of the reagents. For these reasons it was considered impracticable to scale-up this oxidation.

The last method of oxidation involved reoxidizing the isolated keto aldehyde with more Jones reagent and gave surprisingly good yields of crude acid, better than those obtained in the initial oxidation of the hydroxy aldehyde. However, this product was not as clean as the Ag_2O product, as evidenced by NMR spectra. The overall crude yield of acid from the double oxidation with the Jones reagent was 50–60% based on hydroxy aldehyde 2, while the two-step oxidation using Jones reagent in the first step and silver(I) oxide in the second step gave 70–85% yields.

Of the several methods studied for oxidation of the keto aldehyde 4, the one which best combined efficiency, practicability, and purity of crude product was the alkaline silver(I) oxide procedure. The one disadvantage of this method is the expense of the reagent. However, this is not as serious a drawback as it first appears, since the colloidal silver recovered from the oxidation can be recycled by dissolving in nitric acid and using this silver nitrate solution in the preparation of fresh silver(I) oxide. The relative purity of the crude product was expected since Ag_2O does not attack carbon–carbon double bonds.

In summary, the one-step literature oxidation procedure for preparation of the keto acid, 3, from the hydroxy aldehyde, 2, consistently gave poor yields and significantly retarded the effort to prepare strigol on a practical scale. A two-step procedure was developed which requires initial oxidation of the allylic alcohol by the Jones reagent followed by alkaline silver oxide oxidation of the conjugated aldehyde. This procedure was successful on a large scale, giving yields of 70–85% of crude acid 3, thus clearing the way for preparation of gram quantities of the important compound, strigol, for additional biological studies.

Experimental Section

General Procedures. Melting points are uncorrected and were determined with a Thomas-Hoover capillary apparatus;[17] IR spectra were measured on a Perkin-Elmer 137 spectrometer; ^1H NMR spectra were recorded on a Varian EM 360L spectrometer.

The first step of the oxidation followed Sih's procedure except that shorter reaction times were used. The hydroxy aldehyde 2 (0.55 mol) was dissolved in 600 mL of acetone and the mixture cooled to 0–5 °C with an ice–salt bath. Dropwise addition of 150 mL of freshly prepared Jones reagent was carried out over a 4-h period, maintaining the temperature below 5 °C. After the mixture was stirred in the cold for an additional 1 h, excess oxidant was destroyed by adding 2-propanol. Water (500 mL) was added with stirring to dissolve the chromium salts and most of the acetone was removed under vacuum. Another 500 mL of water was added and the mixture extracted with four 150-mL portions of ether. The combined ether extracts were washed once with water and twice with 10% aqueous $NaHCO_3$ solution. The aqueous basic extract was acidified with 6 N HCl and extracted with ether. The ether layer was washed with water, saturated NaCl, and dried over Na_2SO_4. Removal of ether under vacuum gave 18.9 g (19% yield) of acid 3.

The nonacidic organic material was recovered from ether layers that had been extracted with $NaHCO_3$. This ether layer was washed with water, saturated NaCl, and dried over Na_2SO_4. Concentration under reduced pressure gave 62.0 g of yellow oil that was identified as the keto aldehyde 4 by NMR and IR spectra and elemental analysis. Distillation to remove impurities afforded the analytical sample: bp 108 °C (1 mm); IR (neat) ν 2960, 2940, 2880 (CH), 1725 (CH=O), 1690 (>C=O); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.35 (s, 6 H, $(CH_3)_2C$), 1.56–2.02 (m, 2 H, $CH_2C(CH_3)_2$), 2.07 (s, 3 H, CH_3C=C), 2.3–2.8 (m, 2 H, CH_2C=O), 10.34 (s, 1 H, CH=O). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; mol wt, 166.2. Found: C, 72.04; H, 8.66; mol wt, 156.

Silver Oxide Oxidation. A suspension of silver oxide (0.36 mol) and 10% NaOH (180 mL) in 300 mL of water was vigorously stirred by magnetic stirrer. To this was added the keto aldehyde 4 (0.36 mol) in small portions over a 30-min period, keeping the temperature below 30 °C. The mixture was stirred for 1 h more. The colloidal silver was filtered and washed with water. The filtrate was acidified with concentrated HCl and the precipitate was collected and washed with water to give 56.5 g of crude acid 3, an 86% yield based on keto aldehyde and a 56% yield based on hydroxy aldehyde, giving a total yield of crude acid of 75%.

Acknowledgment. I acknowledge the technical assistance of Jacequeline M. Simoneaux and Margaret M. Soltis.

Registry No. (±)-2, 60078-92-4; 3, 51823-74-6; 4, 18378-66-0; (±)-strigol, 51820-11-2.

(17) Names of companies or commercial products are given solely for the purpose of providing specific information; their mention does not imply recommendation or endorsement by the U.S. Department of Agriculture over others not mentioned.

Highly Selective and Convenient Method for the Synthesis of 1,5-Enynes and 1,5-Dienes by the Reaction of 1,3-Dilithiopropargyl Phenyl Sulfide with Allylic Halides[1]

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We describe a selective and efficient propargyl–allyl coupling reaction between 1,3-dilithiopropargyl phenyl sulfide (1) and allylic halides to produce lithiated, 1,5-enynes 2, which can be directly treated with Li in liquid ammonia in the presence of $NaNH_2$ (~1 equiv) to produce cleanly 1,5-enynes in 70–80% overall yields (eq 1).

Stereo- and regioselective synthesis of 1,5-dienes of terpenoid origin via cross-coupling has been achieved most commonly by the procedure of Biellmann and related allyl–allyl couplings.[2] While these methods are satisfac-

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