Synthetic Route to an Aromatic Analogue of Strigol

Peter M. Kendall, Julius V. Johnson, and C. E. Cook*

Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709

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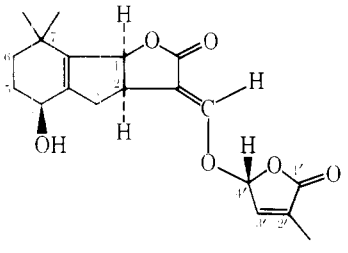
An aromatic analogue which contains all but one of the carbon atoms of the witchweed seed germination stimulant strigol has been prepared. 6-Methyldihydrocoumarin was converted to a phenolic indanone (**4**) which was alkylated by reaction of its dianion with lithium bromoacetate. Reduction and acid treatment yielded a lactone (**7**) which (as its *tert*-butyldimethylsilyl derivative) was converted to the hydroxymethylene compound **9**. The sodium salt of **9** underwent O-alkylation with bromolactone **10** to yield the protected strigol and epistrigol analogues **11**. Removal of the silyl ether was effected with aqueous fluoride at pH 5.

Strigol (**1**), a highly potent stimulant for the germination of the seeds of the parasite witchweed (*Striga lutea* Lour.), was isolated from the root exudates of cotton (*Gossypium hirsutum* L.) in 1966,[1] and its structure was determined in 1972 to be **1**.[2] Witchweed is a chlorophyll-bearing parasite



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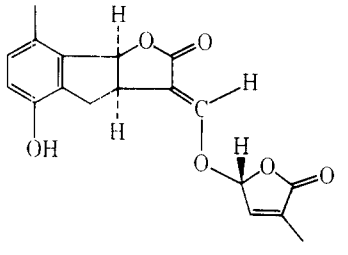


2

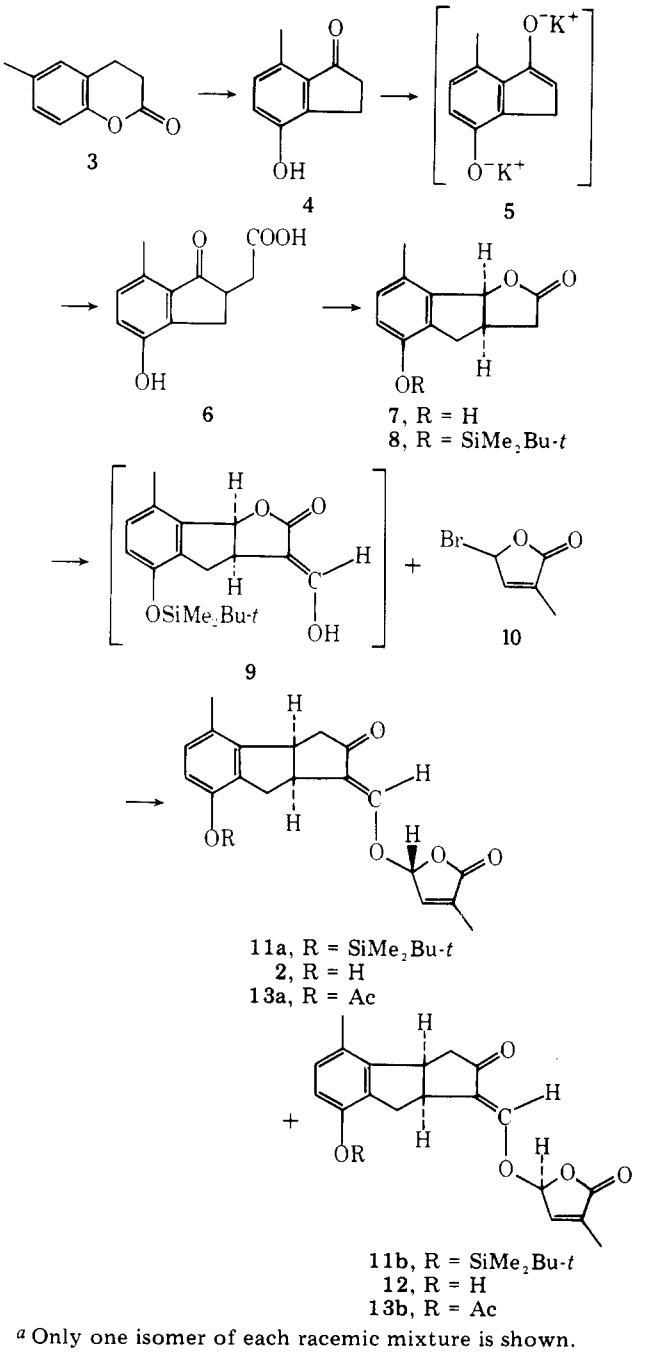
which attaches to roots of corn and numerous other grain crops. It was discovered in the United States in 1956 and has been the object of a costly control program.[3] In the absence of exogenous stimulant, the seeds of witchweed do not germinate, but application of 10^{-11} M solutions of strigol is reported to result in over 50% germination.[2] Total syntheses of strigol were reported in 1974,[4] and various analogues have been reported to have seed germination and cytotoxic activity.[5]

Compound **2**, an analogue of strigol possessing an aromatic A ring, contains all of the features of strigol with the exception of one of the *gem*-dimethyl groups and the introduction of formal double bonds in the 4,5 and 6,7 positions. It appeared to us that this compound might therefore form the basis for construction of strigol analogues. The opportunity for rapid construction of the tricyclic lactone system would make compounds of this type readily accessible. We therefore set out to prepare **2** by the route shown in Scheme I.

The starting material for this synthesis was the known 6-methyldihydrocoumarin (**3**).[6] A modified Fries rearrangement[7] using aluminum chloride in refluxing *o*-dichlorobenzene yielded ketone **4**, which had been previously obtained in low yield by a lengthy route involving initial cycloalkylation of 2-methylfuran.[8]

The problem of introduction of the required carboxymethyl side chain was solved in the syntheses of strigol by introduction of a carbethoxy[4a] or ethoxalyl[4b] substituent, which served the dual purpose of activating the position to be alkylated and protecting against dialkylation. In the present case it appeared that the desired result could be achieved by formation and reaction of the dianion of ketone **4**. The utility and selectivity of carbon–carbon bond formation by alkylation of dianions

Scheme I[a]



3 **4** **5** **6** **7**, R = H; **8**, R = $SiMe_2Bu$-*t* **9** **10**

11a, R = $SiMe_2Bu$-*t*; **2**, R = H; **13a**, R = Ac

11b, R = $SiMe_2Bu$-*t*; **12**, R = H; **13b**, R = Ac

[a] Only one isomer of each racemic mixture is shown.

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such as those derived from β-dicarbonyl compounds have been demonstrated many times.[9] The dianion of ketone **4** is similar to the dianion of a β-diketone, and thus it should be possible to alkylate it directly at the desired position.

The obvious choice as the alkylating agent, methyl bromoacetate, was deemed unsuitable in this instance. The dianion of **4** would be a strong base, whereas the α protons of methyl bromoacetate are relatively acidic. Thus, the anticipated result of interaction would be abstraction of a proton from the ester by the ketone dianion. The difficulty could be resolved by using a salt of bromoacetic acid in which the acidity of the α protons is markedly reduced by the adjacent negative charge. This would have a further benefit in that the resulting alkylated product would itself be a dianion which would be resistant to further ion formation and alkylation at carbon.

In the event it was found (after trial of sodium, potassium, and lithium amide) that formation of the dianion of **4** by reaction with 2 mol of potassium amide in liquid ammonia followed by alkylation with lithium bromoacetate smoothly (although slowly) yielded the desired 2-(carboxymethyl)-indanone **6**, attempts to accelerate the reaction by use of a cosolvent such as hexamethylphosphoramide led to products which appeared to derive from alkylation of the phenolic group as well. The alkylated product **6** could be readily separated from starting material **4** by simple manipulation of the pH of the solution. Thus, although the reaction did not go to completion, starting material was readily recovered for recycling and the crude product **6** was sufficiently pure for further steps.

It was also possible to protect the phenolic group of ketone **4** by formation of a *tert*-butyldimethylsilyl ether, generation of a monoanion, and alkylation with ethyl bromoacetate, but this led to substantial amounts of dialkylated product. For example, when ketone **4** was converted to its *tert*-butyldimethylsilyl ether and alkylated using lithium hexamethyldisilazide and ethyl bromoacetate, GLC indicated a ratio of ~1:4.4:0.7 starting material/monoalkylated product/dialkylated product. Better results were obtained by using lithium diisopropylamide as the base, with the ratio being ~1:6.2:0.5, but chromatographic purification was required to obtain the pure monoalkyl compound. The dialkylation is apparently due to rapid deprotonation of the monalkylated product under the reaction conditions used.

Reduction of the sodium salt of keto acid **6** with sodium borohydride, followed by treatment of the reaction mixture with acid, afforded a single lactone **7**. Only a small amount of lactone could be obtained immediately upon acidification of the reaction mixture, the remainder being the hydroxy acid. If, however, the reaction mixture was stirred overnight with dilute aqueous acid, a good yield of lactone was obtained. This is in agreement with the results of House and co-workers,[10] who found that the reduction of 1-keto-2-indanylacetic acid with sodium borohydride led to 79% of a hydroxy acid (assigned trans stereochemistry) which formed a lactone on refluxing with *p*-toluenesulfonic acid in benzene. Catalytic hydrogenation (palladium on charcoal catalyst) of keto acid **6** led also to a mixture of hydroxy acid and lactone, again in agreement with the catalytic reduction of 1-keto-2-indanylacetic acid.[10] Cis stereochemistry is assumed for the lactone **7** based on the steric constraints which apply to fused five–five ring systems[11] and its formation under equilibrating-type conditions.

Phenolic lactone **7** was protected as its *tert*-butyldimethylsilyl ether **8**[12] and then formylated with ethyl formate and sodium hydride. Although the intermediate hydroxymethylene lactone **9** could be isolated by acidification of the mixture, it proved more convenient to react the crude sodium salt of **9** directly with the known[4] bromobutenolide **10** in acetonitrile. It has been shown[4,13] that alkylation of enolates such as **9** in polar solvents favors formation of the enol ether with *E* stereochemistry. In the present case the products isolated exhibited an enol ether proton resonance in the NMR at δ 7.47 and 7.48. This is essentially the same as that in strigol (δ 7.42[2]) and different from that of analogues having the *Z* configuration (δ 6.6–6.8[4b,5a]), thus supporting the *E* stereochemistry of **11**. Isomers **11a** and **11b** (ratio 3:2) were conveniently separated by chromatography at this stage. Inasmuch as the spectral characteristics of these isomers were essentially identical (as is the case with strigol and epistrigol[4a]), the relative stereochemistry was assigned mainly on the basis of TLC mobilities as compared with strigol and its epimer.[4a]

An attempt to cleave the silyl ether protecting groups of **11** using the customary reagent, tetra-*n*-butylammonium fluoride,[12] led to a mixture of products. However, a mixture of aqueous fluoride buffer (pH 5) and tetrahydrofuran effected clean deprotection. We regard this as a useful alternative for base-sensitive systems. It appears that specific fluoride ion catalysis is involved since an acetate buffer of comparable pH was ineffectual.

Phenols **2** and **12** were converted to their corresponding acetates **13** using acetic anhydride and pyridine, and the ability of the compounds to stimulate witchweed seed germination was examined as a check on the stereochemical assignments. The seed germination stimulating ability of **2** was about 2% as great as authentic strigol and 100 times greater than that of its isomer **12**; this difference in activity between the isomers tends to confirm the stereochemical assignment given.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were determined with Perkin-Elmer Model 267 or 467 spectrophotometers. Nuclear magnetic resonance spectra were determined at 100 MHz with a Varian HA-100 spectrometer; chemical shifts are expressed in δ values relative to internal tetramethylsilane. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Dry solvents (where indicated) were prepared as follows: diethyl ether and tetrahydrofuran were distilled from lithium aluminum hydride; *N,N*-dimethylformamide was distilled from barium oxide; and acetonitrile was distilled from phosphorus pentoxide. $MgSO_4$ was used as a drying agent for organic solutions. Dry-column silica gel (where indicated) refers to Woelm Silica Gel for Dry-column Chromatography, Activity III (obtained from ICN Nutritional Biochemicals).

4-Hydroxy-7-methyl-1-indanone (4). A mixture of 6-methyldihydrocoumarin (**3**; 96.8 g, 0.6 mol), anhydrous $AlCl_3$ (240 g), and *o*-dichlorobenzene (200 mL) was heated to 180 °C for 1.5 h, allowed to cool slightly, and poured into a mixture of ice (2000 g) and concentrated hydrochloric acid (250 mL). The mixture was diluted with ethyl acetate (1000 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 1000 mL). The combined organic extracts were washed with saturated brine and extracted with 1 N NaOH (1000 mL, then 3 × 500 mL). The combined basic extracts were acidified to pH 8 by addition of dry ice, yielding a tan precipitate which was filtered, washed with water, and dried under reduced pressure, yield 56.9 g (59%). Recrystallization from methanol gave material of mp 194–195 °C (lit.[8] mp 194–195 °C).

(4-Hydroxy-7-methyl-1-indanon-2-yl)acetic Acid (6). A. A suspension of KNH_2 in liquid ammonia (600 mL) was prepared from 17.2 g (0.46 g-atom) of potassium metal. To this was added portionwise with vigorous stirring 32.4 g (0.20 mol) of ketone **4**. The resulting lime-green suspension was stirred at reflux for 1 h; then 37.7 g (0.26 mol) of lithium bromoacetate was added portionwise. The mixture was refluxed with stirring for 32 h, after which time the ammonia was allowed to evaporate. The residue was hydrolyzed with water (700 mL) and acidified to pH 8 by addition of dry ice; it was then extracted with ethyl acetate (3 × 500 mL, then 2 × 250 mL). The combined organic extracts were dried and evaporated to yield 16.8 g of unreacted starting ketone **4**. The aqueous layer from the ethyl acetate extraction was filtered to remove a small amount of suspended material and acidified to pH 2 with concentrated hydrochloric acid. The tan precipitate was filtered, washed with water, and dried under reduced

pressure to yield 17.4 g (82% of **6** based on unrecovered starting material); for preparative purposes this was used without further purification. An analytical sample of mp 208–211 °C was obtained by recrystallization from acetone: IR (KBr pellet) 2500–3500 (broad), 1670–1720 (broad) cm^{-1}; NMR (acetone-d_6) δ 2.48 (s, 3), 2.5–3.1 (m, 4), 3.38 (m, 1, H-2), 6.98 (s, 2), 7.2–8.0 (broad s, D_2O exchangeable, 2).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.10; H, 5.36.

B. 4-Hydroxy-7-methylindanone (5.00 g, 30.9 mmol) and imidazole (4.50 g, 66.1 mmol) were dissolved in 10 mL of dry *N,N*-dimethylformamide and treated with 5.09 g (34 mmol) of *tert*-butyldimethylchlorosilane. The mixture was stirred at 35–45 °C until it solidified (1 h). After another 0.5 h, the reaction mixture was treated with 100 mL of 5% aqueous $NaHCO_3$ and extracted with hexane. Residue from the hexane extract was recrystallized from 10 mL of hexane to yield 8.04 g (94% of theory). This material was used without further purification.

In oven-dried, nitrogen-filled apparatus, lithium diisopropylamide (2.21 g, 20.6 mmol) in 100 mL of dry tetrahydrofuran at −70 °C was treated with 5.13 g (18.5 mmol) of the above silyl ether ketone. The ketone was added over a 10–15-min period. After an additional 15 min of stirring, ethyl bromoacetate (2.28 mL, 20.6 mmol) was added by syringe rapidly. The mixture was stirred and allowed to come to room temperature. After 16 h, 5% $NaHCO_3$ (600 mL) was added and the mixture was extracted with hexane (3 × 75 mL). The combined organic layers were washed with saturated sodium chloride solution, filtered (Whatman 1-PS filter paper), and evaporated, leaving an oil (6.16 g). A 1.1-g sample of this was chromatographed on dry-column silica gel (300 g) in a 3-cm diameter dry nylon column with methylene chloride as developing solvent. The developed column was cut into bands after visualization by ultraviolet light. The major fraction contained 356 mg (30% yield) of ethyl 4-(*tert*-butyldimethylsilyloxy)-7-methyl-1-ketoindan-2-acetate. An analytical sample was prepared by preparative thin-layer chromatography (colorless oil): NMR ($CDCl_3$) δ 0.20 (s, 6), 0.98 (s, 9), 1.2 (t, J = 7 Hz, 3), 2.52 (s, 3), 2.55–3.45 (m, 5, aliphatic CH), 4.14 (q, J = 7 Hz, 2), 6.89 (q, J = 8 Hz, 2, H-5 and H-6); IR (CH_2Cl_2) 1735, 1710 cm^{-1}.

Anal. required for $C_{20}H_{30}SiO_4$, *m/e* 362.1913; found, *m/e* 362.1916.

When the above ester was refluxed for 1.5 h with a mixture of dioxane/concentrated HCl in water (22:1:6) and the reaction mixture was diluted with $NaHCO_3$ solution, extracted with ethyl acetate, acidified to pH 1, and reextracted with ethyl acetate, evaporation of the acidic ethyl acetate extract left an almost quantitative yield of (4-hydroxy-7-methyl-1-indanon-2-yl)acetic acid, mp 202–207 °C.

(*cis*-1,4-Dihydroxy-7-methylindan-2-yl)acetic Acid γ-Lactone (7). The crude keto acid **6** (17.4 g, 79 mmol) was dissolved in cold 1 N NaOH (300 mL) and treated with $NaBH_4$ (2.98 g, 79 mmol). The solution was stirred for 2 days, cooled in ice, and acidified to pH 2 with concentrated hydrochloric acid. After being stirred overnight, the acidified solution was extracted with chloroform (2 × 300 mL, then 2 × 100 mL). The combined organic extracts were dried, concentrated to 40 mL, and allowed to cool. White crystals were deposited; a small second crop was obtained by further concentrating the mother liquors: yield 10.9 g (68%); mp 145–146 °C; IR (CH_2Cl_2) 3560 (OH), 1760 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.32 (s, 3), 2.50–3.60 (m, 5), 5.30 (s, 1, OH), 5.95 (d, J = 7.5 Hz, 1, H-1), 6.70 and 6.96 (AB quartet, 2, H-5 and H-6).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found: C, 70.46; H, 5.79.

[*cis*-4-(Dimethyl-*tert*-butylsilyloxy)-1-hydroxy-7-methylindan-2-yl]acetic Acid γ-Lactone (8). Imidazole (9.95 g, 146 mmol) was added to a solution of lactone **7** (11.71 g, 59 mmol) and *tert*-butyldimethylchlorosilane (10.57 g, 70 mmol) in dry *N,N*-dimethylformamide (50 mL). The mixture was stirred for 3 h, diluted with 5% aqueous $NaHCO_3$ (250 mL), and extracted four times with hexane. The combined hexane extracts were washed with water, dried, and evaporated to yield 17.8 g (96%) of a white crystalline solid. Recrystallization from heptane gave an analytical sample of mp 92–93 °C: IR (CH_2Cl_2) 1760 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.20 (s, 6), 0.98 (s, 9), 2.34 (s, 3), 2.50–3.60 (m, 5), 5.91 (d, J = 7.5 Hz, 1, H-1), 6.68 and 6.94 (AB quartet, 2, H-5 and H-6).

Anal. Calcd for $C_{18}H_{26}O_3Si$: C, 67.88; H, 8.23. Found: C, 67.58; H, 8.25.

Preparation of Silylated Strigol Analogues (11). A 57% suspension of NaH in mineral oil (1.86 g, 44 mmol) was washed three times with dry hexane (to remove the mineral oil) and suspended in dry ether (250 mL) containing excess methyl formate (4.8 g, 80 mmol) and a catalytic amount (1–2 drops) of methanol. To this was added a solution of the silylated lactone **8** (12.7 g, 40 mmol) in dry ether (100 mL). The mixture was stirred overnight and evaporated to dryness under reduced pressure. The residue was suspended in dry acetonitrile (100 mL) and cooled (0–5 °C); then a solution of butenolide **10** (7.79 g, 44 mmol) in acetonitrile (25 mL) was added dropwise. The mixture was allowed to warm to room temperature with stirring overnight; it was then filtered and washed thoroughly with ether and evaporated to dryness. The crude residue was passed through a short column of 35–70 mesh silica gel (elution with 15% ethyl acetate/benzene) to remove most of the polar materials. The material was then rechromatographed on dry-column silica gel. Elution with 8% ethyl acetate/benzene yielded 3.43 g (19%) of **11b,** mp 189–190 °C, followed by 4.87 g (28%) of **11a,** mp 197–199 °C. The infrared spectra of **11a** and **11b** were virtually superimposeable: IR ($CHCl_3$) 1785 (butenolide), 1740 (lactone), 1680 (enol ether) cm^{-1}.

11a: NMR ($CDCl_3$) δ 0.19 (s, 6), 0.96 (s, 9), 2.03 (s, 3, C-2′ CH_3), 2.37 (s, 3, aromatic CH_3), 2.6–3.6 (m, 2, H-3), 3.94 (m, 1, H-2), 5.99 (d, J = 7.5 Hz, 1, H-1), 6.20 (s, 1, H-4′), 6.68 and 6.94 (AB quartet, 2, H-5 and H-6), 6.99 (s, 1, H-3′), 7.47 (d, J = 2 Hz, 1, enol ether HC=C).

Anal. Calcd for $C_{24}H_{30}O_6Si$: C, 65.13; H, 6.83. Found: C, 65.15; H, 6.83.

11b: NMR ($CDCl_3$) δ 0.18 (s, 6), 0.98 (s, 9), 2.03 (s, 3, C-2′ CH_3), 2.35 (s, 3, aromatic CH_3), 2.6–3.6 (m, 2, H-3), 3.92 (m, 1, H-2), 5.96 (d, J = 7.5 Hz, 1, H-1), 6.18 (s, 1, H-4′), 6.66 and 6.94 (AB quartet, 2, H-5 and H-6), 6.94 (s, 1, H-3′), 7.48 (d, J = 2 Hz, enol ether HC=C).

Anal. Calcd for $C_{24}H_{30}O_6Si$: C, 65.13; H, 6.83. Found: C, 65.06; H, 6.83.

Preparation of Phenol 2. A pH 5 fluoride buffer was prepared by addition of 0.1 M HF (0.84 mL) to 0.1 M NaF (29.16 mL). A solution of silyl ether **11a** (4.87 g) in tetrahydrofuran (80 mL) was added to the buffer, and the resulting mixture was stirred at room temperature for 2 days. The tetrahydrofuran was then evaporated under reduced pressure, and the resulting suspension was extracted with methylene chloride (200 mL, then 4 × 50 mL). The combined organic extracts were washed with water, dried, and evaporated. The residue was recrystallized from ethyl acetate/cyclohexane to yield 2.77 g (77%) of **2**: mp 207–209 °C dec; IR (KBr) 3420 (OH), 1780 (butenolide), 1735 (lactone), 1675 (enol ether) cm^{-1}; NMR (acetone-d_6) δ 2.28 (s, 3, aromatic CH_3), 2.6–3.5 (m, 3, H-3 and OH), 4.0 (m, 1, H-2), 6.0 (d, J = 7.5 Hz, 1, H-1), 6.56 (s, 1, H-4′), 6.70 and 6.90 (AB quartet, 2, H-5 and H-6), 7.30 (s, 1, H-3′), 7.56 (d, J = 2 Hz, enol ether HC=C).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.91; H, 4.65.

Preparation of Phenol 12. This material was prepared in the same way as its isomer **2**. From 2.85 g of **11b** there was obtained, after recrystallization from ethyl acetate, 1.64 g (78%) of **12**: mp 203–204 °C dec; IR (KBr) 3420 (OH), 1780 (butenolide), 1735 (lactone), 1675 (enol ether) cm^{-1}; NMR (acetone-d_6) δ 2.30 (s, 3, aromatic CH_3), 2.6–3.5 (m, 3, H-3 and OH), 4.0 (m, 1, H-2), 6.0 (d, J = 7.5 Hz, 1, H-1), 6.57 (s, 1, H-4′), 6.72 and 6.92 (AB quartet, 2, H-5 and H-6), 7.33 (s, 1, H-3′), 7.58 (d, J = 2 Hz, 1, enol ether HC=C).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.61; H, 4.97.

Preparation of Acetate 13a. Phenol **2** (100 mg) was acetylated using excess acetic anhydride in pyridine at room temperature. Recrystallization of the crude product from benzene gave beautiful white crystals of **13a** (101 mg, 90%): mp 160–161 °C; IR ($CHCl_3$) 1780 (butenolide), 1745 (acetate), 1740 (lactone), 1675 (enol ether) cm^{-1}; NMR ($CDCl_3$) δ 2.0 (s, 3, C-2′ CH_3), 2.25 (s, 3, CH_3CO_2–), 2.39 (s, 3, aromatic CH_3), 2.6–3.5 (m, 2, H-3), 3.90 (m, 1, H-2), 5.90 (d, J = 7.5 Hz, 1, H-1), 6.10 (s, 1, H-4′), 6.87 (s, 1, H-3′), 6.86 and 7.02 (AB quartet, 2, H-5 and H-6), 7.38 (d, J = 2 Hz, 1, enol ether HC=C).

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 65.06; H, 4.90.

Preparation of Acetate 13b. Acetylation of phenol **12** (200 mg) in the same manner as its isomer **2** gave acetate **13b** (178 mg, 79%), mp 201–202 °C, after recrystallization from benzene: IR ($CHCl_3$) 1780 (butenolide), 1745 (acetate), 1740 (lactone), 1675 (enol ether) cm^{-1}; NMR ($CDCl_3$) δ 2.01 (s, 3, C-2′ CH_3), 2.26 (s, 3, CH_3CO_2–), 2.40 (s, 3, aromatic CH_3), 2.6–3.5 (m, 2, H-3), 3.90 (m, 1, H-2), 5.92 (d, J = 7.5 Hz, 1, H-1), 6.10 (s, 1, H-4′), 6.90 (s, 1, H-3′), 6.87 and 7.03 (AB quartet, 2, H-5 and H-6), 7.40 (d, J = 2 Hz, 1, enol ether HC=C).

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.75; H, 4.95.

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Registry No.—**2**, 69291-96-9; **3**, 92-47-7; **4**, 22242-84-8; **4** *tert*-butyldimethylsilyl ether, 69291-97-0; **5**, 69291-98-1; **6**, 69291-99-2; **7**, 69292-00-8; **8**, 69292-01-9; **9** sodium salt, 69292-03-1; **10**, 59488-94-7; **11a**, 69292-02-0; **11b**, 69350-10-3; **12**, 69350-11-4; **13a**, 69292-04-2; **13b**, 69350-12-5; lithium bromoacetate, 64916-53-6; *tert*-butyldimethylchlorosilane, 18162-48-6; ethyl bromoacetate, 105-36-2; ethyl 4-(*tert*-butyldimethylsilyloxy)-7-methyl-1-ketoindan-2-acetate, 69331-26-6; methyl formate, 107-31-3.

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Intramolecular Thermal Reactions of the Derivatives of 5′-Azido-5′-deoxyuridine. New Feasible Route to the Regio- and Stereospecific Synthesis of Reversed Nucleosides Carrying a Substituted Five-Membered Heterocycle

Tadashi Sasaki,* Katsumaro Minamoto, Toshimichi Suzuki, and Toyoyuki Sugiura

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

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With a view to probing the reactivity of the "naked" 5,6-double bond of uracil nucleosides as a dipolarophile, 1-(5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**1a**) and its 5-deuterated analogue (**1b**), N^3-methylated analogue (**1c**), and 2′,3′-*O*-ethoxymethylene analogue (**1d**) were synthesized and submitted to an intramolecular thermal reaction, which yielded a high yield of N^1,5′-anhydro-N^{ω}-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-allophanoyl-1,2,3-triazole (**3a**), its N^{β}-methyl analogue (**3b**), and its 2′,3′-*O*-ethoxymethylene analogue (**3c**), respectively. 6,5′-Imino-1-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**4a**) and its N^3-methyl analogue (**4b**) were respectively isolated as byproduct in the case of **1a** and **1c**. Intermediacy of the triazoline, **2**, was confirmed for the formation of **3** and **4**. **3a** with methanol, ammonia, and hydrazine gave 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-ureido-1-β-D-ribofuranose (**8a**), its 4-carboxamido analogue (**8b**) and its 4-carboxyhydrazido analogue (**8c**), respectively. Similarly, their 2,3-ethoxymethylene analogues **6a** and **6b** were obtained from **3c**. **6a,b** were deprotected to 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-1-ureido-1-β-D-ribofuranose (**7a**) and its 4-carboxamido analogue **7b**. Diazotization of **8a** yielded 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-β-D-ribofuranose (**11a**) and its 1-*O*-acetate (**12a**). Analogous treatment of **8b** afforded the corresponding 4-carboxamido analogues, **11b** and **12b**. Deacetonation of **11a,b** and/or **12a,b** gave 5-(4-carboxamido-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-1-β-D-ribofuranose (**13a**) and its 4-carboxamido analogue (**13b**). Some synthetic implications are suggested for the formation of **3**.

Much effort has been devoted to the study of photodimerization[1,2] and photocycloaddition of pyrimidines to electron-rich monoolefins[3] as a model for photochemical transformation of natural nucleic acids and for preparative chemistry aiming at direct carbon–carbon bond formation and functionalization. On the other hand, there are only few examples which use the 5,6-double bond of pyrimidines as a dipolarophile: the hitherto known two cases are 1,3-dipolar cycloaddition reactions of an azide with pyrimidine nuclei activated with 5-nitro or 5-bromo substituent.[4,5] In these cases, addition is usually followed by elimination of the activating group to furnish directly aromatized cycloadducts. The possibility of thermal 1,3-dipolar cycloaddition to the "naked" 5,6-double bond of pyrimidine nucleosides was suggested by the known ground state reactivity of these heterocyclic bases. It is well established[6] that the 6 position of pyrimidine nucleosides can accept nucleophiles in the manner of a Michael reaction, while the 5 position is vulnerable to attack by electrophiles. This behavior is explicable on the basis of a simple HOMO–LUMO consideration[7] and is reflected in the synthesis of 6,5′-*O*-,[8] 6,5′-*S*-,[9] and 6,5′-*N*-cyclopyrimidine nucleosides.[10]

Synthetic exploitation of pyrimidines as dipolarophiles or dienophiles is important in view of the great variability of the expected products and the direct use of natural nucleosides with a given stereochemistry involving, among others, that of the anomeric position. From this point of view, 1-(5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**1a**)[11] is a readily accessible, simple model compound for roughly evaluating the reactivity of the "naked" 5,6-double bond with 1,3-dipoles. A preliminary communication[12] has reported the major results of the intramolecular thermal reactions of **1a** and the 5-deuterated analogue **1b**, which lead to a regiospecific synthesis of some 4-substituted triazole reversed nucleosides. This paper describes the details of this work with additional experiments and accompanying observations.

Synthesis of the Substrates 1a–d for 1,3-Dipolar Cycloaddition. **1a** was synthesized nearly as described[11] except that a one-to-one mixture of sodium azide and ammonium chloride or tetraethylammonium chloride was used rather than lithium azide at the azidation step. **1b** was synthesized starting from 5-deuterated uridine[13] essentially in the same way with **1a**, avoiding recrystallization from protic solvents

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