# Chapter 35

# Overview of Synthetic Approaches to Strigol and Its Analogs

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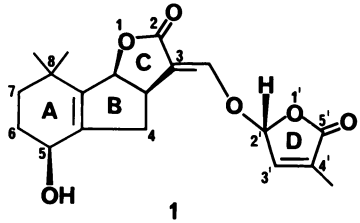
Strigol is a very effective germination stimulant for parasitic weeds in the genus Striga (witchweed). This compound is available only in minute quantities from natural sources. An attractive method of control of witchweed and other parasitic weeds such as Orobanche (broomrape) would involve treatment of an infected field with a biosynthetic product (such as strigol) or synthetic analog to induce suicidal germination of the weed seed in the absence of a host plant. The need exists to prepare sufficient quantities of strigol and its analogs to permit extensive laboratory testing and to determine their utility as control agents when applied to infested fields. The total syntheses of strigol developed by Sih, Raphael, and Brooks are discussed. In addition, a number of partial syntheses, representing alternative approaches to intermediates in Sih's preparation, are presented. A new synthetic route to strigol, utilizing the inexpensive starting materials mesityl oxide and ethyl acetoacetate, has been developed. Finally, a number of simplified two-, three-, and four-ring analogs of strigol have been prepared, several of which have shown activity as Striga and Orobanche germination stimulants.

(+)-Strigol is a very effective germination stimulant for the parasitic weeds in the genus Striga (witchweed) (1). Recently the absolute structure of natural (+)-strigol has been established as shown in 1 (2). Natural (+)-strigol induces greater than 50% germination of witchweed [Striga asiatica (L.) Kuntze] seeds at a concentration of $10^{-11}$ M (1). Synthetic (±)-strigol effects comparable germination in the concentration range of $10^{-10}$ to $10^{-12}$ M (3,4). In one study (5), synthetic (±)-strigol showed activity at $10^{-16}$ M, but these results have not been reproduced.

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The parasitic weeds of Striga species are thought to germinate primarily in response to a chemical signal of the host plant. Corn, rice, sugarcane, and Sorghum are the major crop plants affected by Striga. Recently, the first characterization of a germination stimulant for Striga derived from a natural host (Sorghum) was reported (6). The compound, a hydroquinone derivative, is highly unstable and consequently would have no practical utility. Strigol was originally isolated in small quantities from the root exudates of cotton (a nonhost plant) (1). It has not been identified in exudates of any host plant nor does it appear to be available from any natural source in the quantities required for field testing.

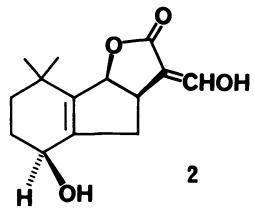
Striga asiatica (L.) Kuntze, one of several species of Striga found commonly in the Eastern Hemisphere, was found in North and South Carolina in 1956 (7). The seed has the capability to remain dormant and viable in the ground for fifteen to twenty years until stimulated by a chemical or chemicals released by the young roots of certain plants. The germinated seed rapidly develops a radicle, which receives a second chemical signal from the host (the haustorial initiation factor) upon contact with the host root. Thereupon, the tip of the radicle is transformed into a haustorium which attaches itself to the host root. The Striga derives carbohydrates, water, minerals, and some photosynthates from the infected parasitized plant which generally appears drought-stricken and often dies if the parasitic plant is not removed. Crop losses approaching 100% occur in heavily infested fields (7-9). In 1957, federal and state quarantines were invoked to prevent the spread of witchweed. Although the quarantine program has been effective, and the control and eradication program has permitted considerable acreage to be removed from quarantine, the problem still exists and further research is needed (10).

Because of the lengthy periods of viability of the seeds of Striga and Orobanche (broomrape) in the soil, effective control of these parasitic weeds is extremely difficult. An attractive method of control would involve treatment of an infected field with a biosynthetic product (such as strigol) or synthetic analog to induce suicidal germination of the weed seed in the absence of a host plant. The results of field tests with ethylene (11) and synthetic strigol analogs (12) offer evidence of the utility of this method of control.

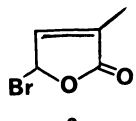
To date, probably less than ten grams of (±)-strigol has been synthesized. For extensive field studies and basic biological studies a large quantity (in excess of 100 g) is required. Although several syntheses of strigol have been reported, the need for an economic synthesis adaptable to large scale preparation still exists.

## Syntheses of Strigol

Four total syntheses of strigol have been reported in the literature (13-15). In each case, (±)-strigol was prepared by a convergent synthesis in which the final step was the alkylation of the tricyclic hydroxymethylene lactone **2** with the bromobutenolide **3**.



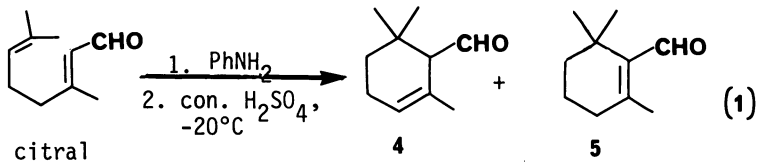

**2**




**3**

Shortly after the structure of strigol was established, its total synthesis was reported by Sih and co-workers (13) and by Raphael et al. (14). Sih's synthetic approach will be presented in its entirety as it provides a useful framework for discussion of other total and partial syntheses of strigol.

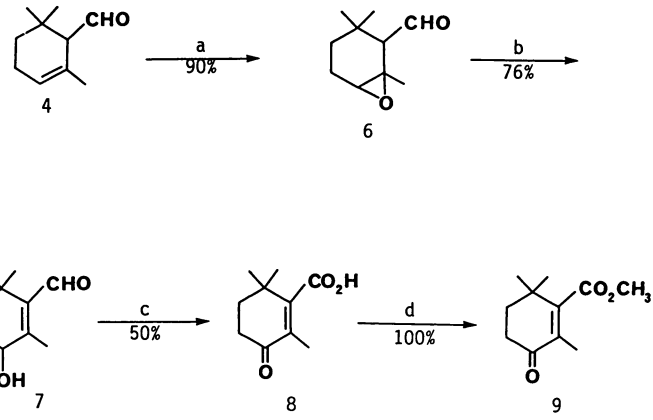
Sih's Synthesis of Strigol. Sih and co-workers utilized citral as starting material for the preparation of **2**, representing the A, B, and C rings of strigol. The anil of citral was converted to a mixture of α-cyclocitral (**4**), and β-cyclocitral (**5**) (Equation 1).




citral **4** **5** (1)

Depending upon the conditions employed, either **4** or **5** could be obtained in good yield, and both were converted to the enone **9** by separate routes. As shown in Scheme I, **9** could be prepared from α-cyclocitral (**4**) in four steps in 34% overall yield. The best route developed for the transformation of β-cyclocitral (**5**) to **9** is outlined in Scheme II. Enone **9** could be obtained in five steps in 47% overall yield as follows: reaction of **5** with oxygen in heptane at 0-5°C in the presence of 5% platinum on carbon furnished the crude acid **10** in 70% yield; methylation afforded the pure ester **11** in 84% yield; treatment with bromine at 0-10°C provided the crude bromo ester **12** in quantitative yield; hydrolysis of **12** gave the hydroxy ester **13** in 81% yield following column chromatography; finally, Jones oxidation furnished **9** in 98% yield.

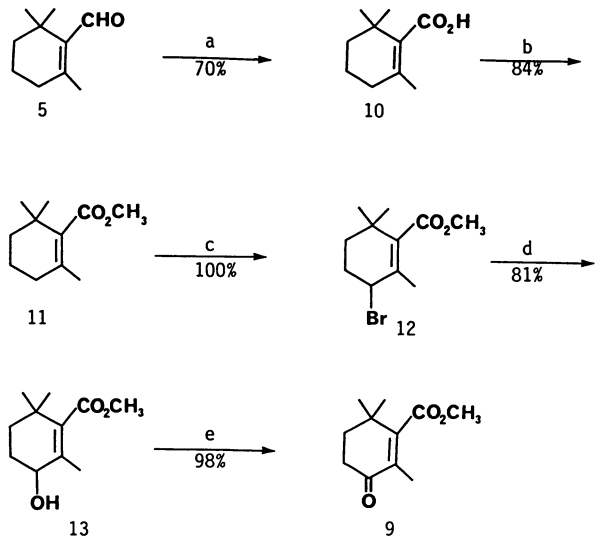
The elaboration of the tricyclic hydroxymethylene lactone **2** is summarized in Scheme III. Treatment of enone **9** with a 20% excess of N-bromosuccinimide (NBS) in refluxing carbon tetrachloride under the




4 6 7 8 9

[a]MCPBA. [b]Pyrrolidine, ether. [c]$CrO_3/H_2SO_4$. [d]$CH_3I$, $K_2CO_3$.

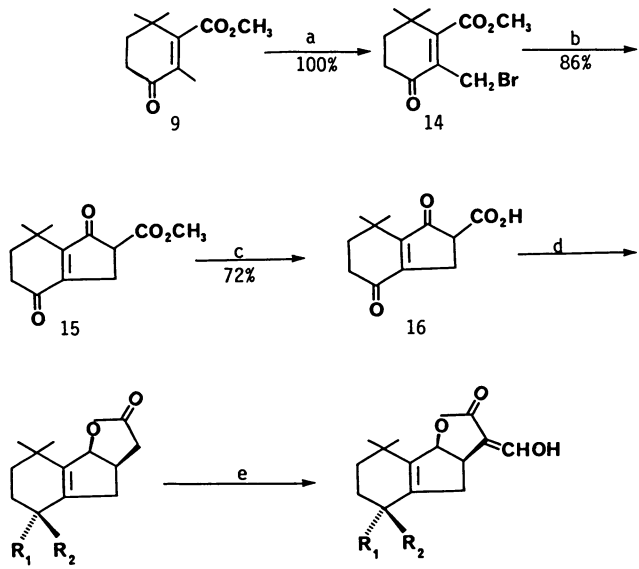
Scheme I. Sih's conversion of α-cyclocitral to enone 9.




5 10 11 12 13 9

[a]$O_2$, 5%Pt/C, heptane. [b]$CH_3I$, $K_2CO_3$, acetone.
[c]$Br_2$, $CHCl_3$, hν, $N_2$, 0-10 °C. [d]$H_2O$,Δ. [e]$CrO_3/H_2SO_4$.

Scheme II. Sih's conversion of β-cyclocitral to enone 9.




17, $R_1$ = H; $R_2$ = OH 26%

18, $R_1$ = OH; $R_2$ = H

2, $R_1$ = H; $R_2$ = OH 78%

[a] NBS, $CCl_4$, hν,Δ. [b] (1) $NaCH(CO_2CH_3)_2$; (2) HOAc.
[c] (1) $BrCH_2CO_2CH_3$, $K_2CO_3$, acetone; (2) HOAc, 6 N HCl,Δ.
[d] (1) DIBAH, $CH_2Cl_2$, -70 °C; (2) 20% $H_2SO_4$. [e] $HCO_2CH_3$, NaH, ether.

Scheme III. Synthesis of the tricyclic hydroxymethylene lactone 2.

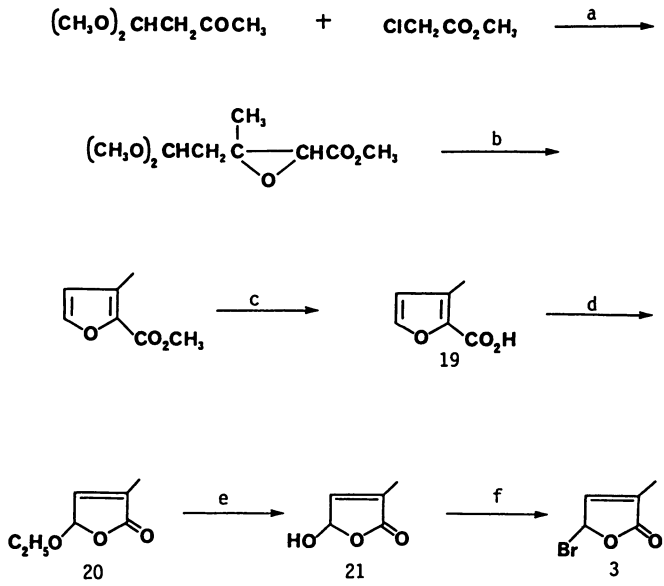
illumination of an incandescent lamp afforded a quantitative yield of crude bromo ester **14**. Reaction of **14** with the sodium salt of dimethyl malonate and subsequent neutralization with acetic acid furnished the bicyclic diketone **15** in 86% yield. Alkylation with methyl bromoacetate and subsequent acid hydrolysis gave the diketo acid **16** in 72% yield. Treatment of **16** with 3.5 equivalents of diisobutylaluminum hydride (DIBAH) afforded a mixture of hydroxy lactones **17** and **18**. Column chromatography and crystallization of the purified mixture afforded the desired isomer **17** in 26% yield. Formylation of **17** provided the hydroxymethylene lactone **2** in 78% yield.

The synthetic route followed for the preparation of the bromobutenolide **3** is presented in Scheme IV. 3-Methyl-2-furoic acid **19** was prepared in three steps by the literature method (16). Three additional steps produced **3**: photooxygenation of **19** in ethanol with subsequent stannous chloride reduction of epoxides to give the alkoxybutenolide **20** (17); hydrolysis in boiling water to the hydroxybutenolide **21** (18); treatment of **21** with carbon tetrabromide and triphenylphosphine (19).

Finally, alkylation of **2** with excess **3** in the presence of anhydrous $K_2CO_3$ in hexamethylphosphoric triamide (HMPA) afforded a diastereomeric mixture of (±)-strigol **1** and (±) -2'-epistrigol (**22**, Equation 2). Column chromatography and crystallization of the isolated components furnished **1** in 27% yield and **22** in 18% yield. Using citral as starting material, the overall yield of **1** was 0.6% *via* α-cyclocitral **(4)** or 0.9% *via* β-cyclocitral **(5)**.

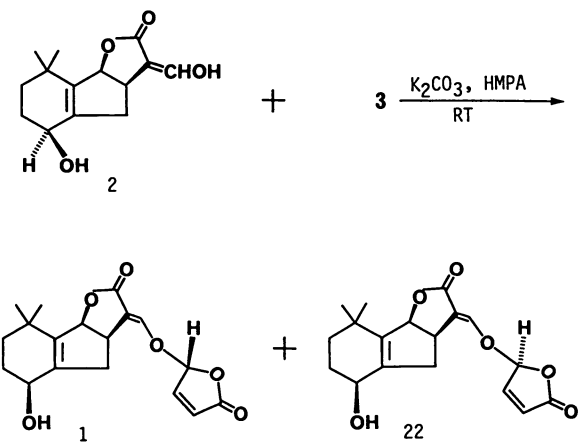
Raphael's Syntheses of Strigol. In 1974, Raphael and co-workers presented two synthetic routes to (±)-strigol (14). These two approaches differ in the steps in the preparation of the hydroxy lactone **17**. The first approach utilizes 2,2-dimethylcyclohexanone **23** as starting material (Scheme V). Treatment of the condensation product **24** with phosphorus pentoxide in methanesulfonic acid at room temperature for 5 minutes produced the bicyclic enone **25** (representing the A and B rings of strigol) in 53% yield. Reaction of **25** with sodium hydride and diethyl oxalate followed by methyl bromoacetate and subsequent removal of the oxalyl grouping by treatment with sodium methoxide in refluxing methanol afforded the methyl ester **26** in 52% yield. In order to introduce the 5-hydroxy group of strigol, **26** was converted to the mixture of acetoxy-esters **27** in 64% yield by sequential treatment with NBS and silver acetate in acetic acid. The hydrolysis products **28** were reduced with DIBAH to afford a mixture of **17** and **18**. Separation by preparative layer chromatography provided the desired alcohol **17** in 22% yield and crude **18** in 23% yield. The overall yield of **17** from **23** was 3.5%; in Sih's synthesis **17** was prepared from citral in 4.2% yield.

The remaining steps of Raphael's synthesis of strigol were the same as Sih's with the exception that bromobutenolide **3** was prepared in a different manner (Equation 3). 2-Methyl-3-butenoic acid was converted to 3-methyl-2(5H)-furanone (**29**) by the method of Frank-Neumann and Berger (reported yield: 75%) (20). Reaction of **29** with NBS in the presence of benzoyl peroxide afforded **3** in 82% yield.

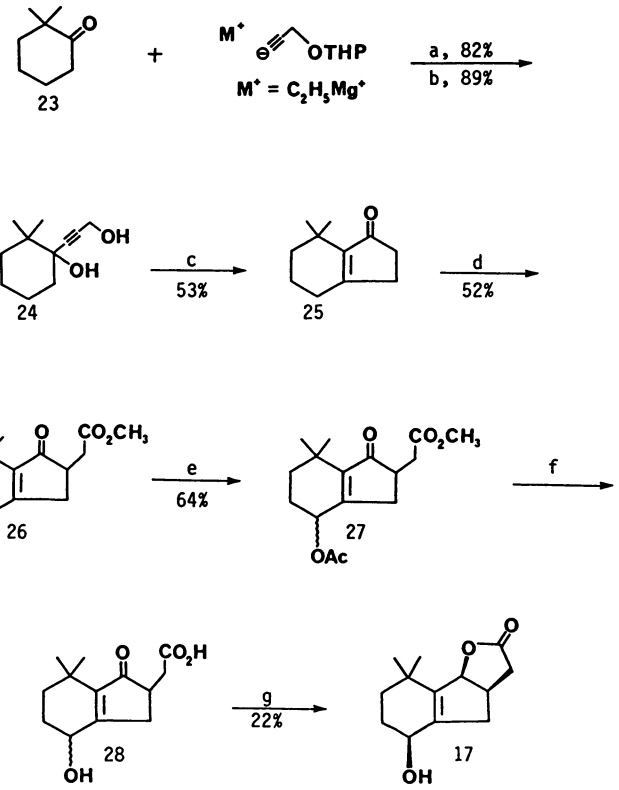



[a] $NaOCH_3$, ether. [b] 150-160 °C. [c] $OH^-$. [d] $O_2$, $C_2H_5OH$, $V_2O_5$, $h\nu$/Sens. [e] $H_2O, \Delta$. [f] $CBr_4$, $Ph_3P$.

Scheme IV. Sih's preparation of the bromobutenolide 3.

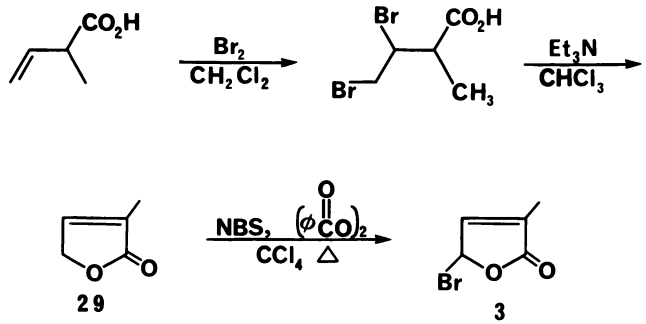



Equation 2. Synthesis of strigol and epistrigol (22).




[a] (1) THF, Δ; (2) $NH_4Cl$. [b] $H_2SO_4$, $CH_3OH$, RT. [c] $P_2O_5$, $CH_3SO_3H$, RT, 5 min. [d] (1) NaH, $(CO_2Et)_2$, PhH, RT; (2) $BrCH_2CO_2CH_3$, Δ, acetone; (3) $NaOCH_3$, $CH_3OH$, Δ; (4) 2 N HCl. [e] NBS, αα'-azobisisobutyronitrile, $CCl_4$, Δ; (2) HOAc, AgOAc, Δ. [f] (1) $CH_3OH$, 6 N NaOH, 0 °C; (2) 10 N HCl. [g] (1) DIBAH, $CH_2Cl_2$, -70 °C; (2) $CH_3OH$; (3) $H_3O^+$; (4) chromatography.

Scheme V. Raphael's first route to strigol. Conversion of 2,2-dimethylcyclohexanone to hydroxy lactone 17.



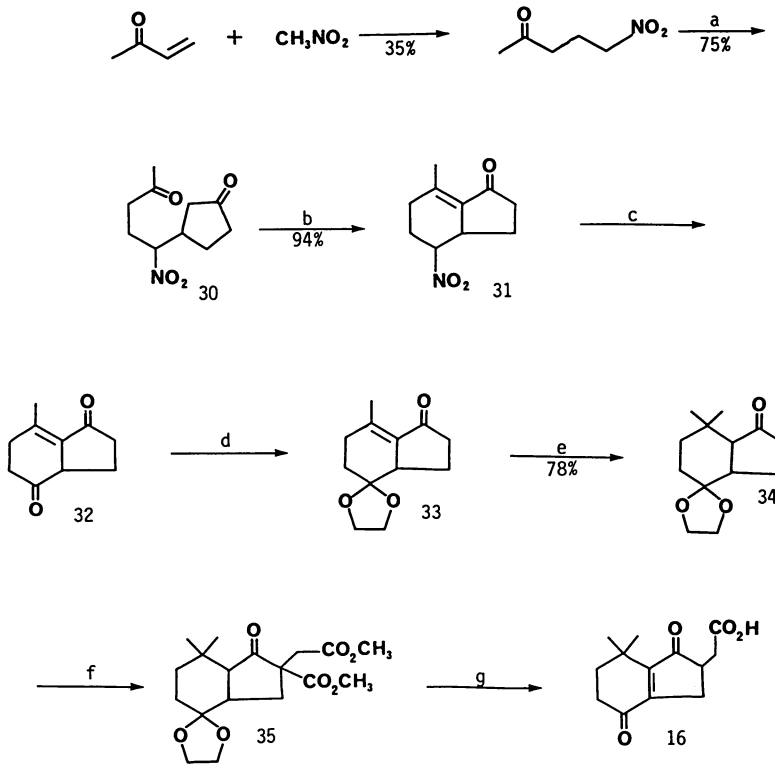

(3)

Raphael's second synthetic route is shown in Scheme VI. In this approach, the bicyclic nitro enone **31**, possessing the proper functionality for elaboration of the A-ring hydroxy of **1**, was prepared by the acid-catalyzed cyclization of nitrodiketone **30**. Attempts to introduce the second A-ring methyl group by treatment of **31** with lithium dimethylcuprate failed. Reaction of **31** with titanium tetrachloride afforded the diketone **32** which was selectively monoketalized to **33**. Reaction with lithium dimethylcuprate furnished the gem-dimethyl compound **34**, which was converted to the diester **35**. Treatment of **35** with acid in an atmosphere of oxygen yielded the unsaturated diketo acid **16** directly, which can be elaborated to strigol as described by Sih. According to Raphael's data, the second route to strigol afforded **16** in 2.4% overall yield.

Brooks' Synthesis of Strigol. In 1982, through a cooperative agreement with the Southern Regional Research Center, D. W. Brooks undertook an improved synthesis of strigol which would be suitable for multigram preparation. The preliminary results of this effort were reported in 1983 with the synthesis of methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate **9** in 48% yield from α-ionone **36** (Scheme VII) (21). Sih's procedure (Scheme II) afforded **9** in 26% yield from citral.

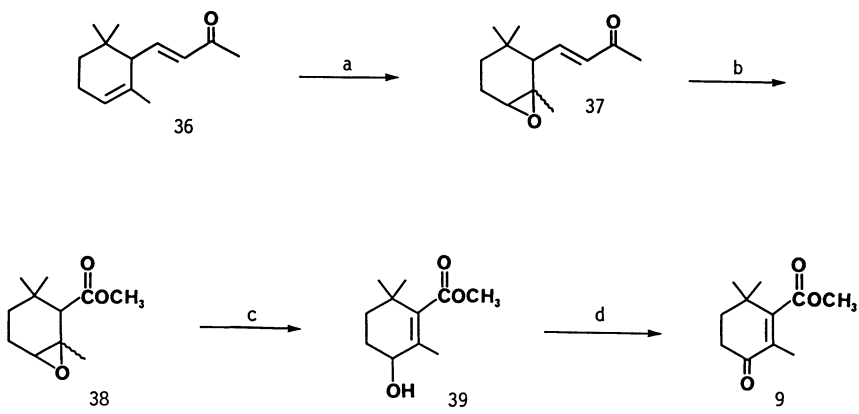
In 1985, Brooks reported an improved total synthesis of (±)-strigol utilizing α-ionone as starting material (Scheme VIII) (15,22). The synthesis is patterned after that of Sih and co-workers (Schemes I and III, Equation 2). There are many common intermediates (**6**,**7**,**14**,**41**,**16**,**17**) but all except **7** are prepared by new or modified methods. The conversion of **17** to strigol was in accordance with Sih's procedure except that N-methylpyrrolidone was used instead of HMPA in the reaction of **2** with **3**. Details of the synthesis are discussed by Brooks et al. in the following chapter.

In summary, Brooks' synthesis provided (±)-strigol in 10 steps and 4.4% overall yield from α-ionone or 12 steps and 6.8% overall yield with the recycling of **18**. The preparation is suitable for scale-up and requires only one chromatographic separation.



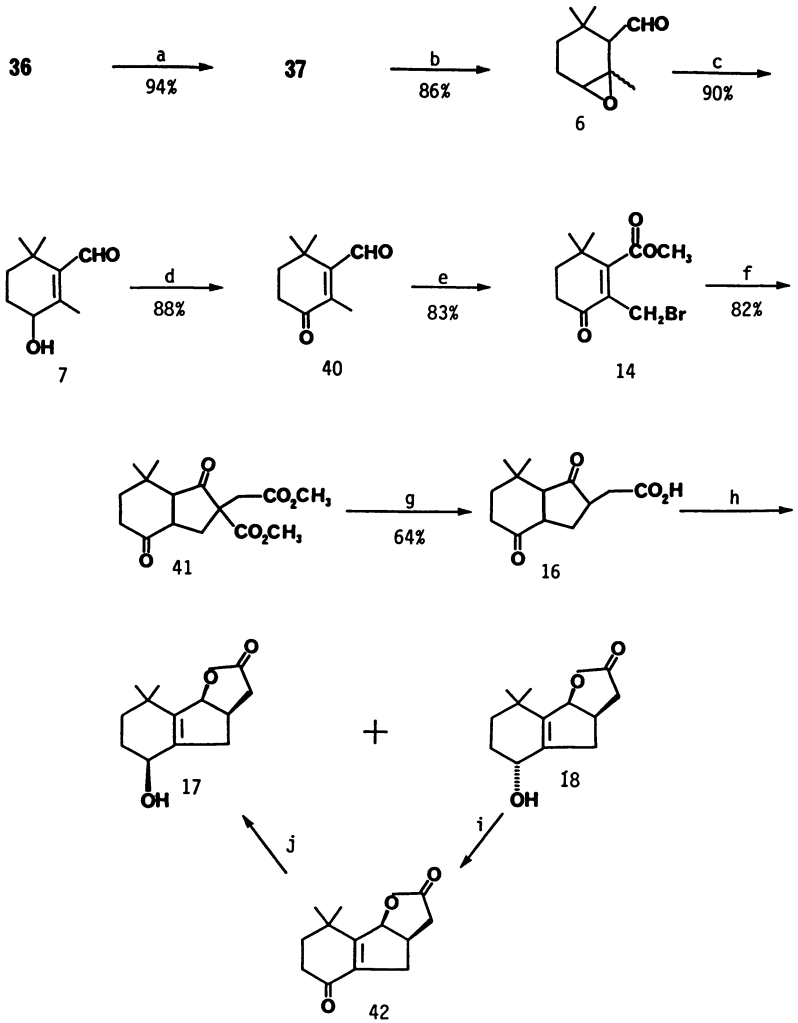

[a] Cyclopentenone, diisopropylamine, $CHCl_3$, 60 °C. [b] TsOH, PhH, △. [c] (1) $CH_3OH$, $NaOCH_3$; (2) $TiCl_4$, $NH_4OAc$ (aq.). [d] $HOCH_2CH_2OH$, TsOH, PhH, △. [e] (1) $LiCuMe_2$, ether, -5 °C, 2 h; (2) satd. $NH_4Cl$ (aq.). [f] (1) Methoxymethylmagnesium carbonate, DMF, 150 °C, $N_2$, 6 h; (2) 1 N HCl; (3)$CH_2N_2$; (4) $BrCH_2CO_2CH_3$, acetone, $K_2CO_3$, △. [g] 5% $H_2SO_4$, $O_2$, $CH_3OCH_2CH_2OCH_3$, △.

Scheme VI. Raphael's second route to strigol. Elaboration of the diketo acid 16.




[a] MCPBA, $CH_2Cl_2$. [b] (1) $NaIO_4$, $KMnO_4$ (cat.), t-BuOH; (2) $CH_3I$, $K_2CO_3$, $(CH_3)_2CO$. [c] $NaOCH_3$, $CH_3OH$. [d] PCC, $CH_2Cl_2$.

Scheme VII. Brooks' conversion of α-ionone to enone 9.




[a] 30% $CH_3CO_3H$, HOAc, NaOAc, 0 °C. [b] (1) $O_3$, $CH_3OH$, -78 °C; (2) Zn, HOAc. [c] Pyrrolidine, ether, 25 °C. [d] Jones reagent. [e] (1) NBS, $CCl_4$, hν, 70 °C; (2) $CH_3OH$, 0 °C. [f] (1) NaH, $CH_2(CO_2CH_3)_2$; (2) $BrCH_2CO_2CH_3$. [g] 6 N HCl, HOAc, 100 °C. [h] $CeCl_3(H_2O)_7$, $NaBH_4$, 0 °C. [i] PCC, $CH_2Cl_2$, 25 °C. [j] $NaBH_4$.

Scheme VIII. Brooks' improved route to strigol. Conversion of α-ionone to hydroxy lactone 17.

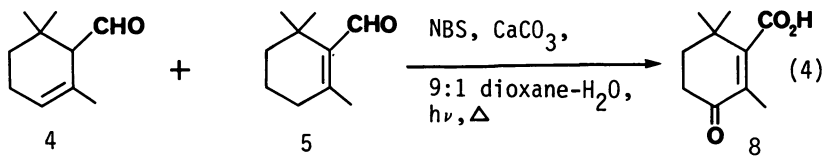
## Partial Syntheses of Strigol

A number of partial syntheses of strigol have been reported in the literature (23-27). These syntheses represent alternative approaches to intermediates in Sih's synthesis.

In 1976, Dolby reported the preparation of the hydrindan **15** (Scheme IX) (23). Dimethylpyruvic acid **45** was prepared according to the procedure of Ramage and Simonsen (28). The condensation of hippuric acid (**43**) and acetone yields the oxazolone **44**, which affords **45** upon treatment with concentrated hydrochloric acid. The Friedel-Crafts acylation of ethylene with glutaric anhydride afforded 5-oxo-6-heptenoic acid **46** in low yield (14-45%). Base-catalyzed condensation of **45** with **46** gave the crude dibasic acid **47** in 79% yield. Treatment of **47** with excess diazomethane provided the diester **48** in quantitative yield. The esterification also can be accomplished in 90% yield with DBU and iodomethane (L. J. Dolby, University of Oregon, personal communication, 1979). Base-catalyzed cyclization of **48** afforded **15** in 98% yield.

In 1979, Cooper and Dolby (24) reported a new synthesis of 3-methyl-5-hydroxy-2(5H)-furanone, **21**, precursor to bromobutenolide **3**. Compound **21** was prepared in five steps in 34% overall yield from 3-(p-toluenesulfonyl)butanal.

In 1983, a one-step synthesis of the acid **8** from a mixture of α- and β-cyclocitrals **4** and **5** (Equation 4) was reported (26). A mixture of 45% **4** and 55% **5** in dioxane - water (9:1) was treated with calcium carbonate and freshly crystallized NBS (5.1 equivalents total) to

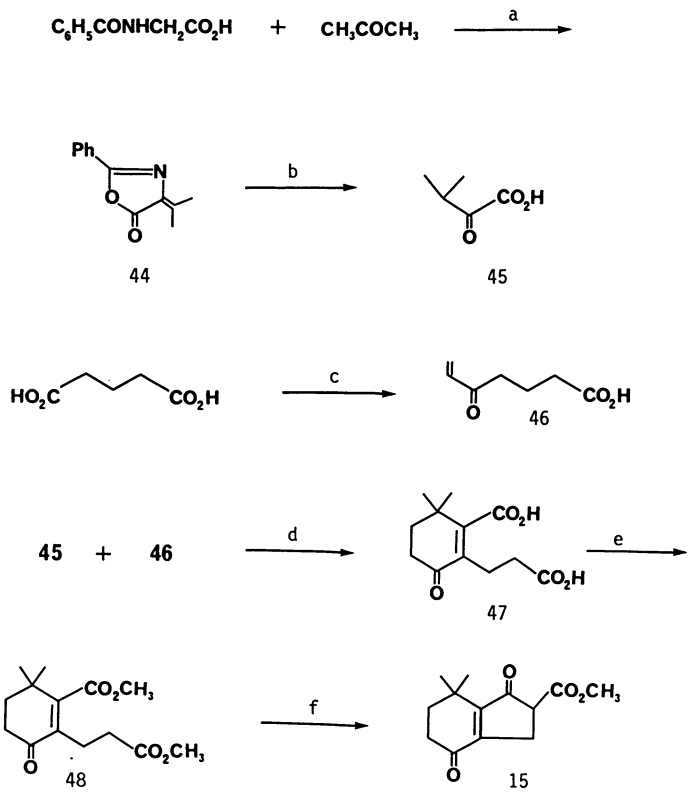



4 5 8 (4)

afford **8** in 40% yield (72% yield from **5**). This represents a significant improvement over Sih's process (Scheme I). However, subsequent attempts to reproduce the procedure were unsuccessful (D. W. Brooks, Purdue University, personal communication, 1984).

## Synthetic Studies at the Southern Regional Research Center

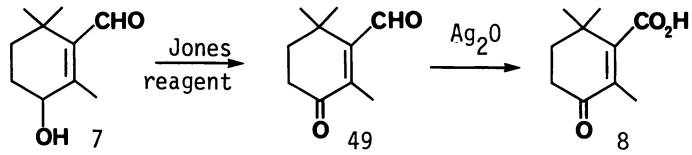
In 1978, a project was undertaken at the Southern Regional Research Center with the goal of preparing sufficient quantities of strigol and its analogs to permit the broad spectrum of tests necessary to understand the role of these compounds in the germination, growth, and reproduction of witchweed and others parasitic weeds, and to determine their utility as control agents when applied to infested fields. We decided to initiate our investigations in the large-scale preparation of strigol through the modification and improvement of one of the existing synthetic sequences. We selected Sih's synthesis of strigol through α-cyclocitral because it appeared to present fewer experimental problems (29). In several cases the literature yields




[a] $Ac_2O$, NaOAc, 110 °C. [b] con. HCl. [c] $AlCl_3$, $CH_2{=}CH_2$, $CH_2Cl_2$.
[d] (1) 1.5 N KOH (aq.), Δ, 2 h; (2) con. HCl. [e] $CH_2N_2$ or $CH_3I$, DBU.
[f] (1) 0.78 N $NaOCH_3$, $CH_3OH$, Δ, $N_2$, 2 h; (2) HOAc, 1% HCl.

Scheme IX. Dolby's partial strigol synthesis. Preparation of the hydrindan 15.

could not be duplicated; preparations of **7**, **8**, **15**, **16**, and **17** gave considerably lower yields. Whereas Sih reported that oxidation of **7**




(5)

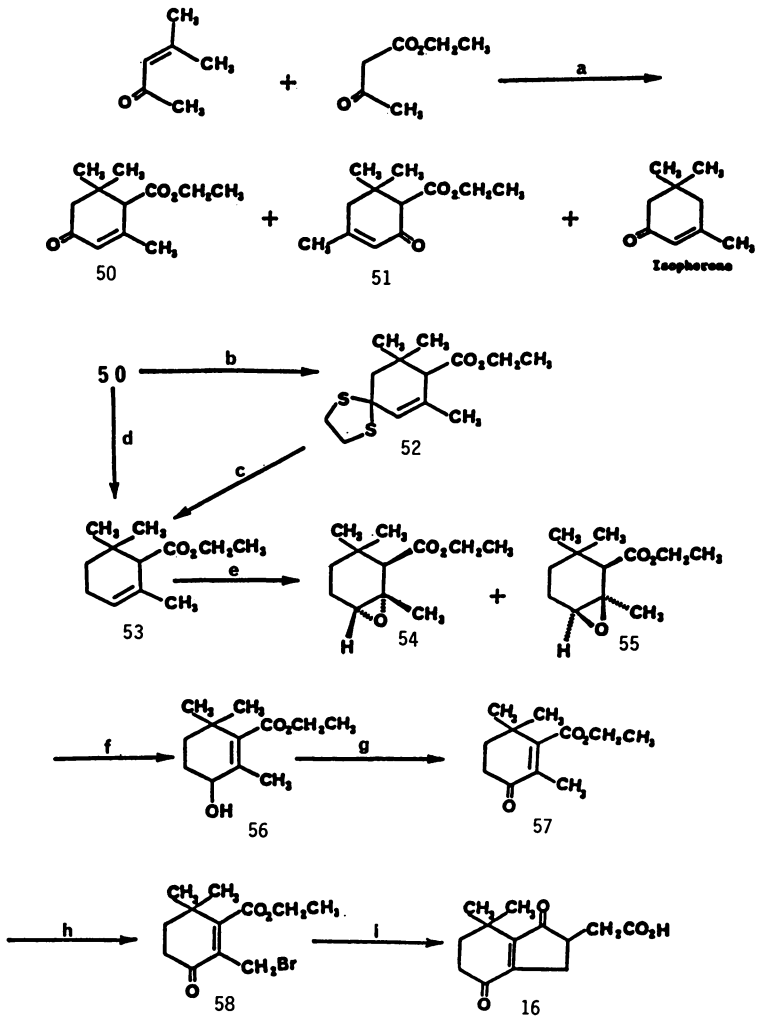
with excess Jones reagent provided keto acid **8** in 45-55% yield, yields of only 30% were obtainable in our laboratory. We developed a two-step procedure (25) that provided for a substantial improvement in the yield of **8** (Equation 5). In this procedure **7** was treated with Jones reagent over a shorter reaction time to afford the keto aldehyde **49** which was oxidized with alkaline silver(I) oxide to **8** in 70-85% overall yield.

Recently, we developed a new synthetic route to strigol (27; Dailey, Jr., O. D. J. Org. Chem., in press). This approach utilizes ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate **50** as starting material (Scheme X). The primary synthetic target was the diketo acid **16**, an intermediate in the latter stages of both the Sih and Brooks strigol syntheses (Schemes III and VIII).

Enone **50** was prepared in molar quantities by the zinc chloride catalyzed condensation of mesityl oxide with ethyl acetoacetate using a modification of the procedure of Surmatis, et al. (30). Distillation of the crude product mixture afforded material consisting of **50** and the isomeric **51** in ratios ranging from 7:1 to better than 10:1 (NMR analysis) in yields in the 27-37% range. The distilled material was sufficiently pure for use in the subsequent reaction.

Enone **50** could be converted to olefin **53** by two different procedures. Treatment of a 8:1 mixture of **50** and **51** with 1,2-ethanedithiol and boron trifluoride etherate (31) and subsequent distillation of the crude product afforded pure dithioketal **54** in 81% yield. Compound **51** did not react under the conditions employed. Raney nickel desulfurization of the dithioketal **52** to **53** was accomplished in high yield (>80%) on a 10-30 g scale; however, the yields decreased substantially (24-29%) when the reaction was done on a larger scale (>100 g).

In the event, a new method was developed for the direct conversion of **50** to **53**. Compound **50** is cleanly reduced to **53** in one to two hours upon treatment with a 2.5-4.0 molar excess of triethylsilane and boron trifluoride etherate at 80-95°C. Compound **51** does not react under these conditions. The reaction proceeded in good yield over a wide range of substrate quantity. Olefin **53** was obtained in 72% yield from 100 g of a 9:1 mixture of **50** and **51**. There are examples in the literature of the reduction of simple aliphatic ketones to the corresponding hydrocarbons using gaseous boron trifluoride and triethylsilane in dichloromethane (32). However, we know of no report of the reduction of a ketone to a methylene compound using boron trifluoride etherate and triethylsilane.

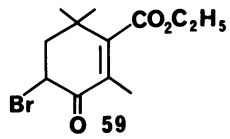



[a] $ZnCl_2$, toluene, heptane, △. [b] $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, 0 °C→RT. [c] W-2 Raney nickel, EtOH, RT. [d] $BF_3{\cdot}Et_2O$, $Et_3SiH$, 80-95 °C. [e] $CH_3CO_3H$, NaOAc, $CH_2Cl_2$, RT. [f] NaOEt, EtOH. [g] Jones reagent. [h] NBS, $CCl_4$, hν. [i] (1) $CH_2(CO_2CH_3)_2$, NaH, THF, 0 °C; (2) $BrCH_2CO_2Et$, 0 °C→RT; (3) HOAc, 6 N HCl, 66-100 °C.

Scheme X. Dailey's synthesis of the diketo acid 16.

Large scale epoxidation of **53** (50-100 g) with peracetic acid (33) consistently furnished the epoxides **54** and **55** in essentially quantitative yield. Treatment of the epoxides (40-100 g) with sodium ethoxide in refluxing ethanol provided allylic alcohol **56**. Oxidation of **56** (0.50 mmol-0.50 mol) with the Jones reagent (13,34) consistently afforded enone **57** in yields of 95% or better. In large scale conversions of **53** to **57**, the crude intermediate compounds **54**, **55**, and **56** were used directly in the subsequent reaction without further purification. Typically, for the three-step process, **57** is obtained in 95% yield, sufficiently pure for the next reaction.

The conversion of **57** to bromoketone **58** was not as straightforward as expected. The literature procedure (13) for the bromination of the methyl ester **9** (light initiation, 20% excess NBS, refluxing carbon tetrachloride) gave highly variable results. In all instances, a significant amount of bromoketone **59** was formed as



**59**

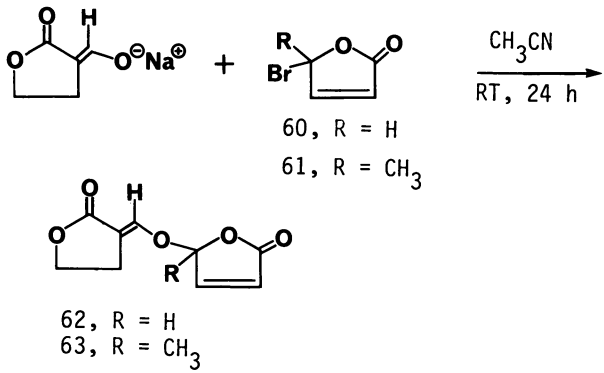
side-product. When less than one gram of **57** was brominated, the product mixture consisted of 85-90% **58** and 10-15% **59**. On a larger scale (using 15 to 45 g of **57**) the percentage of **59** increased to 25-42%. It was established that heating the reaction mixture at reflux increased the amount of **59** formed. The amount of **59** formed could be kept at an acceptably low level (0-15%) by using the light as the sole source of heat and maintaining the temperature of the reaction mixture at or below 50°C. In a modification of Brooks' procedure (15, Scheme VIII), bromoketone **58** could be converted directly to diketo acid **16** in 60% yield. The two literature methods for conversion of **16** to the hydroxy lactone **17** were investigated: reduction with diisobutylaluminum hydride (13) and treatment with ceric chloride followed by excess sodium borohydride (15). The latter method was found to give superior results. The synthesis of strigol may be completed as described in the literature (13,15).

Sih's synthesis (13) using citral as starting material affords diketo acid **16** in 16% yield in eight steps. Brooks' procedure (15) using α-ionone as starting material provides **16** in 28% yield in seven steps. With ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate **50** as starting material, **16** can be produced in 38% yield in six steps. The relative low cost of mesityl oxide and ethyl acetoacetate more than offsets the low yield of the condensation reaction producing **50**. Each step of the new synthetic route to **16** is suitable for large-scale production, being based upon inexpensive starting materials and reagents and requiring no chromatographic purification.

## Syntheses of Strigol Analogs

Since 1974, the syntheses of a large number of simplified analogs of strigol have been reported. The vast majority of these analogs retain the structure of the C and D rings of strigol.

In 1974, Cassady and Howie reported (35) the preparation of the dilactones **62** and **63** (Equation 6). Compound **63** showed antitumor activity. Results of testing for seed germination activity have not been reported.



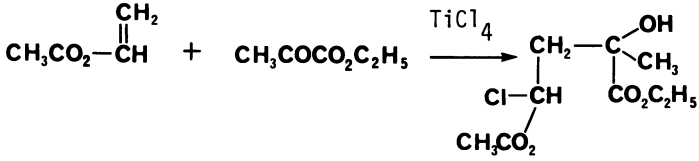

60, R = H
61, R = $CH_3$

(6)

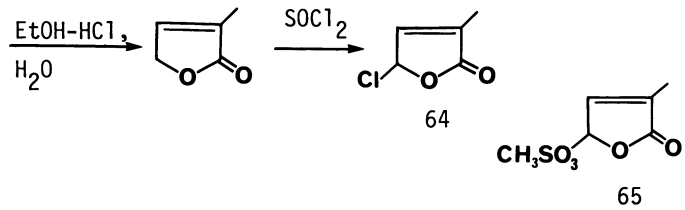
62, R = H
63, R = $CH_3$

Johnson's Syntheses of Strigol Analogs. The greatest volume of work in the preparation of synthetically simpler analogs of strigol has been performed by Johnson and coworkers (12,36-39) who have prepared two-, three-, and four-ring analogs.

Whereas the bromobutenolide **3** was invariably utilized in the syntheses of strigol, Johnson employed the chloride **64** (38) or the sulfonate **65** (37). Compound **64** could be prepared as shown in Equation 7.



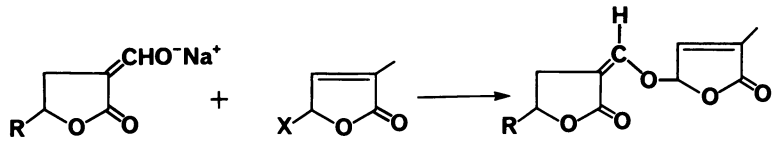

(7)




64

65

Johnson's syntheses of two- and three-ring analogs of strigol were first reported in the form of patents (37,38). Of the two-ring analogs prepared, compound **66** (Equation 8), labeled GR5 (36), showed low-level activity in promoting the germination of both Striga and Orobanche spp. The methyl derivative **67** showed increased activity, especially for Striga spp.

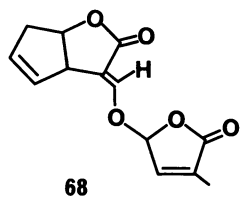



(8)

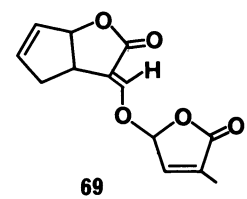
64, X = Cl
65, X = $CH_3SO_3$

66, R = H
67, R = $CH_3$

The three-ring analogs of strigol were prepared from **64** or **65** and the sodium salt of the appropriate bicyclic oxymethylenelactone (36,39). Of the compounds prepared, the isomeric GR-7 (**68**) and GR-28 (**69**), were highly effective in promoting germination of the seeds

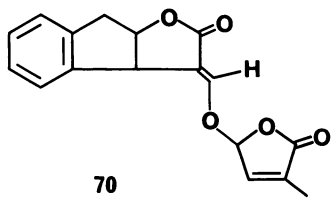



**68**

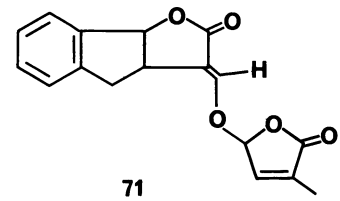



**69**

of Striga and Orobanche spp. Both **68** and **69** incorporate the B, C, and D rings of strigol and **69** contains the double bond in the same relative position as in strigol. Unfortunately, extensive field studies established that GR-7 exhibited low soil stability, particularly in alkaline media (36). Compound **69** proved to be considerably less stable than **68** towards light, heat, and alkali (39). Of the four-ring analogs of strigol, GR-18 (**70**) and GR-24 (**71**) (36, 39) have received the most attention. Compound **71**, which possesses the greatest structural similarity to strigol, proved to be the most active and most stable of all three- and four-ring analogs in both the laboratory and limited field trials.




**70**

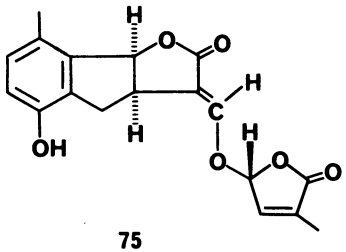



**71**

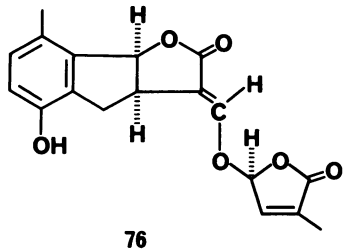
The synthesis of the ABC-ring portion of **71** is shown in Scheme XI (39). Indan-1-one was converted to 1-oxo-indan-2-ylacetic acid **72** by the method of Groves and Swan (40). Reduction of **72** with sodium borohydride produced the alcohol **73** which was treated with p-toluenesulfonic acid to provide the tricyclic lactone **74** (41). Subsequent formylation and condensation with either butenolide **3** or **65** affords **71**. Larger quantities of **71** are required for adequate evaluation, and optimization of its synthesis is required for its manufacture to be economically feasible (36).

The strigol analogs prepared by Johnson and co-workers are normally obtained almost exclusively as the natural E-isomers. Each geometric isomer can exist as two diastereomers (39). Compounds **68** and **70** have been separated into their diastereoisomeric forms. In each case, the two diastereomers were almost equally active as germination stimulants (36).

Other Syntheses of Strigol Analogs. In 1979, Cook and Co-workers reported the synthesis of the aromatic analog **75** (42), which contains all but one of the carbon atoms of strigol. It was about 2% as active as strigol as a seed germination stimulant. The diastereomeric compound **76** exhibited one-hundredth of the activity of **75**.

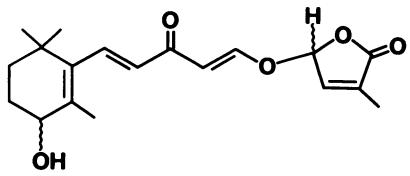


**75**

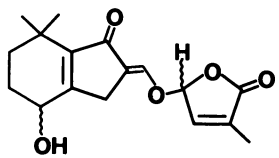


**76**

Finally, Brooks (22) has reported the syntheses of the AD-ring analog **77** and the ABD-ring analog **78**. His syntheses of additional analogs are reported in the following chapter of this volume.

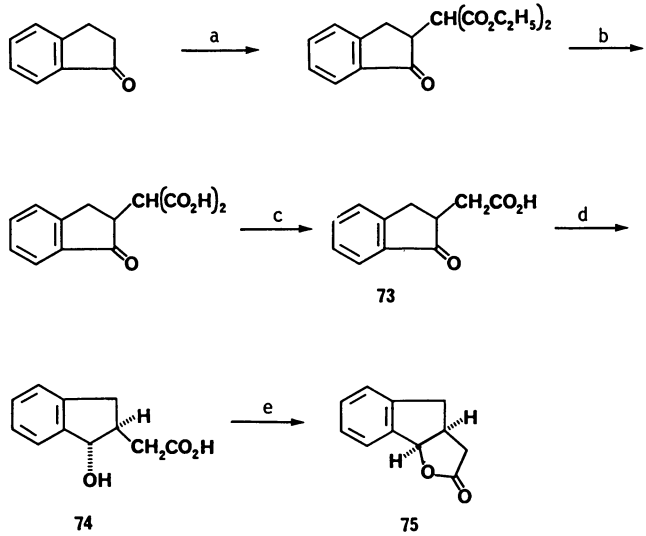


**77**



**78**

Strigol has been evaluated as a germination stimulant for several parasitic weeds in addition to witchweed. It has also been tested as a germination regulator for non-parasitic weed species. A large number of precursors and analogs of strigol have been evaluated as germination stimulants, germination inhibitors, growth inhibitors,




[a] (1) $Br_2$; (2) $NaCH(CO_2Et)_2$, benzene, △. [b] KOH, EtOH, △.
[c] 170 °C. [d] $NaBH_4$. [e] TsOH, benzene, △.

Scheme XI. Preparation of the ABC-ring portion of GR-24.

fungicides, insecticides, and herbicides. These topics, as well as structure-activity correlations, are discussed in detail in our companion paper "Biological Activity of Strigol, its Precursors, and Analogs" found elsewhere in this book.

## Conclusion

Strigol, a potent weed seed germination stimulant, is available only in minute quantities from natural sources. This compound is a potential control agent for parasitic weeds of the genera *Striga* and *Orobanche*. Multigram quantities are required for extensive laboratory testing and field studies. In response to this need, a number of synthetic studies have been undertaken. Total syntheses of strigol have been reported by Sih, Raphael (two routes), and Brooks. A practical economically feasible synthesis, suitable for large-scale production, would utilize inexpensive starting materials and require a minimum of chromatographic purification. The final step of all the reported total syntheses of strigol is the alkylation of the tricyclic hydroxymethylene lactone **2** with the bromobutenolide **3**. Sih's synthetic approach provides **2** in slightly higher yield than either of Raphael's routes and appears to be more adaptable to large-scale preparation. Compound **3** can be prepared from 2-methyl-3-butenoic acid in high yield in three steps as reported by Raphael. Sih's synthesis of **3**, although lengthier, requires considerably less expensive starting materials. In 1985, Brooks reported the conversion of α-ionone to (±)-strigol in ten steps in 4.4% overall yield. The preparation is suitable for scale-up and requires only one chromatographic separation. Sih's synthesis afforded strigol in less than 1% yield. Recently, Dailey reported the conversion of ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate **50** to the diketo acid **16**, an intermediate in the latter stages of both the Sih and Brooks syntheses, in six steps in 38% yield. This process is quite suitable for large-scale production, being based upon inexpensive starting materials and reagents and requiring no chromatographic purification.

A large number of simplified analogs of strigol have been prepared. Such compounds, requiring shorter and less expensive syntheses, may have utility even if their activities are less than that of strigol. Upon consideration of such factors as stability, ease of synthesis, and expense of synthesis, none of the analogs prepared to date are superior or equivalent to strigol. The four-ring analog GR-24, **(71)**, appears to be the most promising analog presently available. However, larger quantities are required for evaluation, and optimization of its synthesis is required for its manufacture to be economically feasible.

Interest in utilizing strigol as a germination stimulant for *Striga* continues, particularly in Africa and Asia. The strigol syntheses of Sih and Raphael and the improvements and modifications introduced by Brooks and Dailey should serve as the foundation of any practical preparation.



In Synthesis and Chemistry of Agrochemicals; Baker, Don R., et al.;
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