Synthesis of the Germination Stimulant (±)-Strigol

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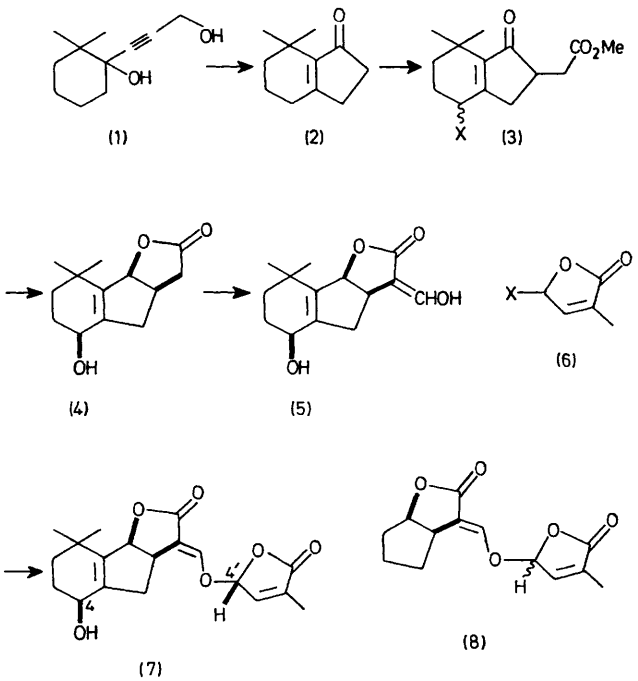
Summary Two synthetic routes to strigol, a germination stimulant of witchweed seeds, are described.

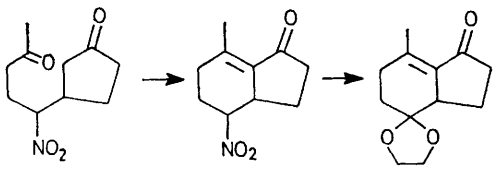
IT has long been known that the germination of the seeds of the semi-parasitic plant *Striga lutea Lour.* (witchweed) is triggered by a stimulant exuding from the rootlets of the growing 'victim' plant. The structure of a crystalline isolate with potent stimulant activity, termed strigol,[1] has been determined by *X*-ray crystallography as (**7**; relative configuration) and very recently a synthesis of the racemic substance was reported.[2] We now describe two novel routes to this intensively active germination stimulant.

Condensation of 2,2-dimethylcyclohexanone with the Grignard derivative of tetrahydropyranyloxypropyne gave, after acid hydrolysis, the diol† (**1**), m.p. 92°. Treatment of (**1**) with a solution of P_2O_5 in methanesulphonic acid[3] for 5 min at room temperature gave[4] the bicyclic unsaturated ketone (**2**), m.p. 45° (53%). Reaction of (**2**) with NaH and diethyl oxalate followed by methyl bromoacetate, and subsequent removal of the oxalyl group, produced the ester (**3**; X = H), m.p. 64—65°, which by sequential treatment with *N*-bromosuccinimide and AgOAc–AcOH gave a mixture of the two epimeric acetoxy-esters (**3**; X = OAc). Reduction of the corresponding hydroxyacids [$Zn(BH_4)_2$ or $Bu^i_2AlH_2$] and acidification gave a liquid and a solid epimer (**4**), m.p. 146—147°, readily separable by preparative t.l.c.

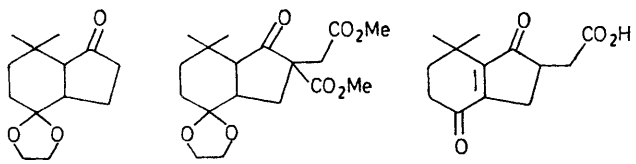


† Spectroscopic and analytical data were consistent with all the assigned structures; racemates are shown by one enantiomer.

Condensation of (**4**) with methyl formate gave the corresponding hydroxymethylene compound (**5**), the potassium salt of which was alkylated with the bromolactone (**6**; X = Br; readily prepared by *N*-bromosuccinimide treatment of the lactone **6**; X = H) to give a mixture of (±)-strigol, m.p. 202—205° (decomp.) and (±) 4′-epistrigol, m.p. 178—180°, separated by t.l.c.[2] That the alkylation of (**5**) to (**7**) would produce the required *E*-stereochemistry about the double bond was initially precedented by the



(9) (10) (11)



(12) (13) (14)

reaction of the bromolactone (**6**; X = Br) with the hydroxymethylene derivative of an analogous model lactone to give the two separable epimers (**8**), m.p.s 86—87° and 116—117°. Both these epimers possessed the required *E*-stereochemistry as shown by n.m.r. spectra (exocyclic vinylic proton at τ 2·62, d, J 2·4 Hz; *cf.* the comparable proton of strigol at τ 2·58, d, J 2·5 Hz). To underpin this assignment each epimer was stereomutated by u.v. light to give the corresponding *Z*-isomer, m.p.s 160—161° and 149—150°; as expected from its removal from the deshielding zone of the lactone carbonyl, the corresponding proton now appeared in both *Z*-isomers at τ 3·16, d, J 1·8 Hz.

The second new synthetic route had the advantage that the required functionality at C-4 was built in from the start. Michael addition of 5-nitropentan-2-one to cyclopentenone gave the expected adduct (**9**) which underwent acid-catalysed cyclisation to the nitroketone (**10**). This was transformed by $TiCl_3$[5] to the corresponding diketone which was selectively converted into the mono-acetal (**11**), m.p. 100—103°, by acid-catalysed interaction with ethylene glycol. Conjugate addition to this mono-acetal with $LiMe_2Cu$ produced the saturated ketone (**12**), m.p. 90—93°. Reaction of (**12**) with methoxymethyl-magnesium carbonate esterification with diazomethane, and consequent base-induced alkylation with methyl bromoacetate gave (**13**) which, without purification, was subjected to acid hydrolysis in an atmosphere of oxygen[6] to yield the unsaturated diketo-acid (**14**), m.p. 135—137°, readily reducible[2] to the key tricyclic lactone (**4**).

We thank Mr. K. Nostadt for valuable preparative help, the Royal Society, the S.R.C., and the N.R.C. Canada for support, and Firmenich et Cie for a generous supply of starting material.

(*Received, 5th August* 1974; *Com.* 997.)

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