

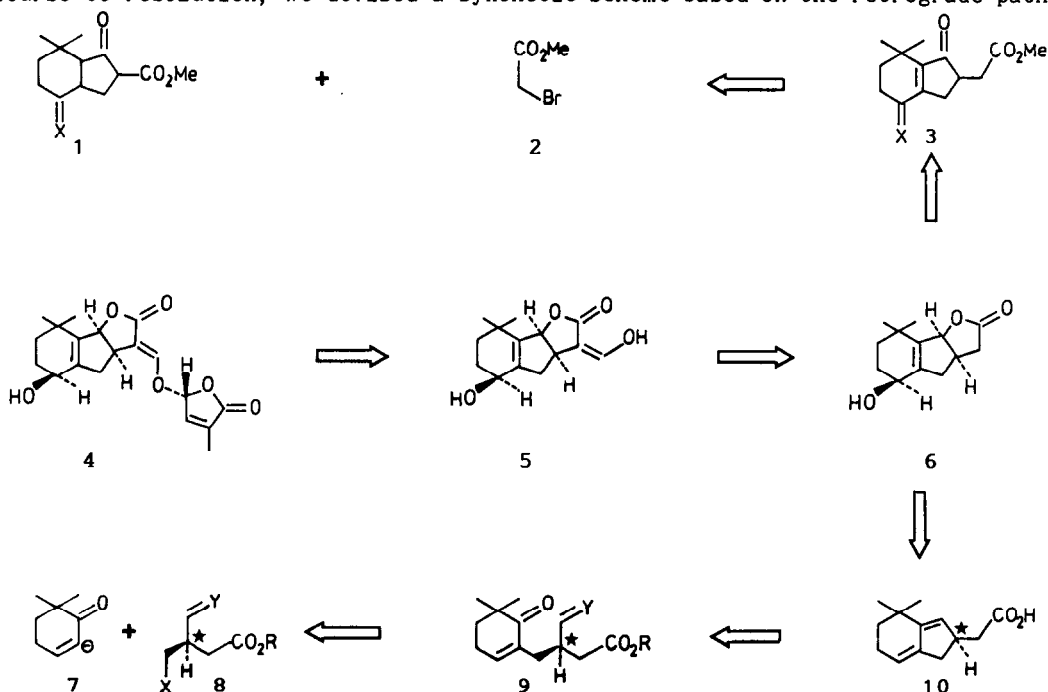
A FORMAL TOTAL SYNTHESIS OF (\pm)-STRIGOL

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Abstract - A novel route to the tricyclic compound (\pm)-6, a known precursor to (\pm)-strigol is disclosed.

Strigol (**4**) is a highly potent seed germination stimulant for witchweed (*Striga lutea* Lour., Scrophulariaceae), a harmful semi-parasitic plant which damages numerous gramineous crops, including corn, sorghum, sugarcane, and rice.¹ Introduction of strigol or an analogue into the soil to germinate the parasite before planting the host could possibly form the basis of a novel method for parasitic weed control. The total syntheses of **4** reported until now all rest on the disconnection sequence **4**→**5**→**6**→**3**→**1** + **2** (Scheme 1).² Alkylation of **1** (X=O or H,H) with **2**, followed by hydrolysis and decarboxylation necessarily led to racemic **3** and thence to racemic **6**. Consequently, until now synthetic (+)-strigol is accessible only at the expense of a resolution step.^{1,3} With the aim of developing an approach to homochiral **4** without recourse to resolution, we devised a synthetic scheme based on the retrograde pathway



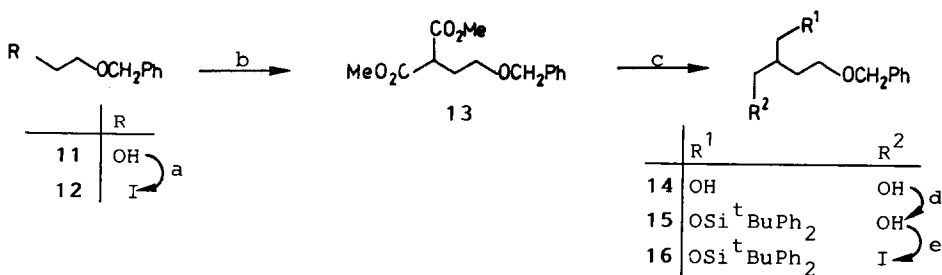
Scheme 1.

6→10→9→7 + 8. Main features are (i) C-C bond formation between synthons 7 and 8 by nucleophilic substitution, (ii) an intramolecular C-C double bond formation (9→10), and (iii) an oxidative cyclization (10→6). It was thought, that the starred chiral centre could be preserved throughout the synthesis and would exercise stereochemical control in the formation of the remaining chiral centres (in step 10→6). The present communication describes a total synthesis of racemic 6 along these lines. In the following note in this issue an attempt to use the new approach for the total synthesis of homochiral 6 is reported.⁴

Reagent 16 was chosen as synthetic equivalent for synthon 8. It was prepared as summarized in Schema 2. 11, obtained by reductive opening⁵ of 2-phenyl-[1,3]dioxolane, was converted into 12 with triphenylphosphine-iodine-imidazole.⁶ With THF as solvent instead of toluene (as recommended by Garegg and Samuelsson⁶) the reaction proceeded cleanly at room temperature and furnished 12 in 94% yield. Alkylation of malonic ester with 12 and reduction of the ester groups of 13 (best accomplished with borane - dimethyl sulfide⁷) gave 14 which was selectively monoprotected using the stannylene acetal method⁸ to afford 15 in 92% yield. For the conversion of 15 into 16 again the Garegg-Samuelsson procedure was employed.⁶

Formation of the lithiated hydrazone anion (the synthetic equivalent of 7) from 17 with LDA, followed by α -alkylation of 9 with 16 and subsequent acid cleavage of the hydrazone group gave the β,γ -unsaturated ketone 18 which on treatment with Et_3N in methanol readily rearranged into the desired conjugated ketone 19.

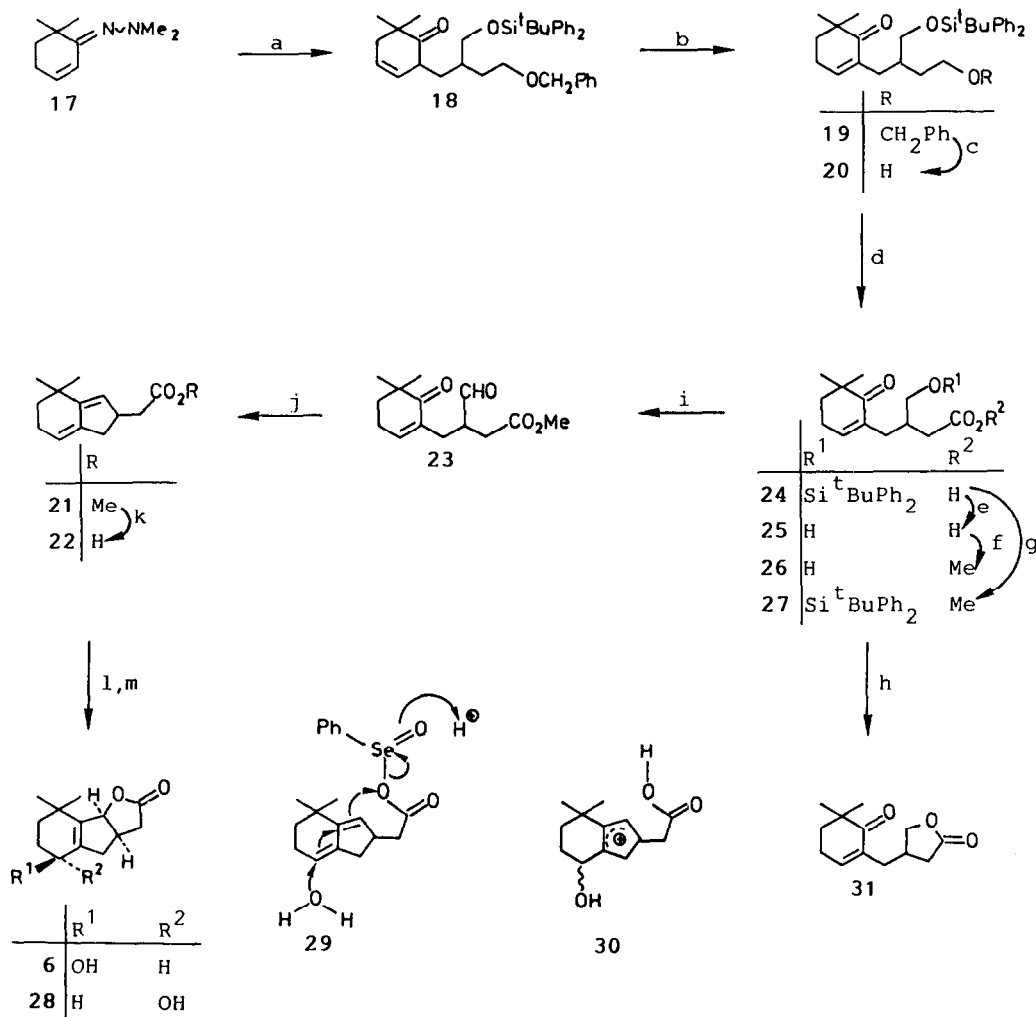
Conversion of 19 to 23 was affected by the following sequence: (1) removal of the benzyl protecting group by brief treatment of 19 with boron tribromide in CH_2Cl_2 at 0°C to give 20 (70%), (2) Jones oxidation of 20 to 24, (3) desilylation of 24 with Bu_4NF in THF, (4) esterification with diazomethane to give 26 (80% from 20), and (5) Swern oxidation (75%). Conditions had to be carefully selected in this seemingly simple phase of the synthesis, since from 25 readily lactone 31 was formed which in attempts to be reopened yielded a octahydrochromene derivative by conjugate addition of the OH group to the enone system. Lactone 31 was also obtained when 27 was treated with Bu_4NF .



Scheme 2: Reagents, conditions, yields.

a) 11 + Ph_3P (1 equiv) + imidazole (2 equiv) + I_2 (1 equiv) in THF, 1h at 20°C : 94%; b) dimethyl malonate (1.1 equiv) + NaH (1.1 equiv) + 12 in C_6H_6 -DMF (1:1.8), 14h at 50°C : 89%; c) 13 + $\text{BH}_3\text{-Me}_2\text{S}$ (2 equiv) in THF, 9h at 75°C : 76%; d) (i) 14 + Bu_2SnO (1.2 equiv) in toluene, 10h reflux (water trap), (ii) Bu_4NBr (0.6 equiv) + $\text{tBuPh}_2\text{SiCl}$ (1.2 equiv), 8h reflux: 92%; e) see a: 92%.

The crucial conversion of **23** into diene **21** was nicely accomplished (52% yield) by intramolecular titanium induced dicarbonyl coupling (McMurry reaction¹²). Ester hydrolysis furnished the carboxylic acid **22**. With a number of oxidizing agents



Scheme 3: Reagents, conditions, yields.

a) (i) **17** (1.2 equiv) + LDA (1.4 equiv) in THF, 1h at 0°C, (ii) at -78°C + **16**, -78°C → -20°C (5h), (iii) work-up (ether), (iv) + p-TsOH (1.5 equiv) in wet ether, 5h at 20°C, (v) work-up; b) Et₃N (excess) in MeOH, 12h at 20°C: 57% (from **16**); c) in CH₂Cl₂ + BBr₃ (1 equiv), 15 min at 0°C: 71%; d) in acetone + Jones reagent (2.2 equiv), 1h at 20°C, work-up; e) Bu₄NF (2.2 equiv) in THF, 8h at 20°C, work-up; f) ethereal CH₂N₂ (excess) in ether-methanol (1:1) at 20°C: 80% (from **20**); g) see f: 85%; h) see e: 74%; i) (COCl)₂ (1.2 equiv) + DMSO (2.3 equiv) in CH₂Cl₂ + **26**, 15 min at -55°C: 75%; j) (i) Zn-Cu (2.36g) + TiCl₃ (15.7 mmol=11 equiv) in DME, 1h reflux, (ii) dropwise addition (97h) of **23** in DME at reflux temp.: 52%; k) (i) in THF + 0.15 M aqueous LiOH, 5h at 0°C, (ii) Dowex 50, H⁺ form: 83%; l) MCPBA (2 equiv) in ether, -78°C → -20°C (2h): **6** (38%) + **28** (38%); m) diphenyl diselenide (0.01 equiv) + 30% H₂O₂ (1.9 equiv) in THF, 3.5h at 0°C: 58%.

(*m*-chloroperbenzoic acid, 2-benzenesulfonyl-3-phenyloxaziridine¹⁴, hydrogen peroxide) **22** reacted to give a 1:1-mixture of **6** and **28**.¹⁵ We assume, that first two epimeric diene monoepoxides¹⁷ are formed which rearrange (possibly via **30**) to give **6** and **28**.¹⁸ Delightfully, oxidation of **22** with 30% H₂O₂ and a catalytic amount of diphenyldiselenide in CH₂Cl₂¹⁹ proceeded stereoselectively with the exclusive formation of the desired stereoisomer **6** (isolated in 70% yield, m.p. 144°C) whose identity was ascertained through comparison with a sample prepared by published procedures.¹⁵ It seems obvious that the formation of **6** under these conditions takes another course than the oxidation reactions leading to the 1:1-mixture of **6** and **28** (vide supra). It may be speculated that an anhydride intermediate of type **29**, formed from phenylseleninic acid (the oxidation product of diphenyldiselenide¹⁹) with **22**, reacts as indicated in **29** to yield **6** and phenylselenenic acid which could be reoxidized to phenylseleninic acid. If the peracid version of **29** were the precursor of **6** the oxidative cyclization would directly result in the formation of phenylseleninic acid. By associating our work with that of Sih,³ Raphael² and Brooks² in a formal sense a total synthesis of racemic strigol has been established.

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