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SYNTHESIS OF (+)-STRIGOL, (+)-4'-EPI-STRIGOL, AND THEIR ENANTIOMERS

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Abstract - A short synthesis of the title compounds amenable to large-scale preparation is reported. Key feature is a simple resolution step.

Strigol (**8a**) was isolated from the root exudates of cotton (Gossypium hirsutum L.). It is a highly potent seed germination stimulant for harmful semi-parasitic Striga species (witchweed) which damage numerous gramineous crops, including millet, sorghum, rice, maize, sugarcane.[1] Inducing Striga germination by strigol or an analogue in the absence of the host plants results in starvation of the seedlings. This could form the basis of a novel method for parasitic weed control.[2] Although the structure of strigol has been known for almost 20 years[3] very little seems to be known on the mode of its biological action and on detailed structure-activity relations.[4] Even the question whether strigol is produced by host plants (cotton is a nonhost) has yet to be answered.[5] Part of this deficiency in knowledge may stem from the fact that synthesizing strigol is still quite difficult. Furthermore, no synthetic scheme seems to be available which allows for the preparation of structurally closely related analogues of **8a** that could be used to study some of the questions mentioned above.

Recently, we disclosed a (formal) EPC synthesis of **8a** in which optical activity was introduced via the chiral pool approach.[6] Although the advantage of this scheme as compared to previous work[7] consists of a number of highly selective steps it is still too complicated to be of use for the preparation of a greater variety of strigol-like structures. We wish to report now on a simple synthesis of the title compounds based on a paper by Dolby and Hanson[8] which improves previous achievements and contains as main feature an efficient resolution step.

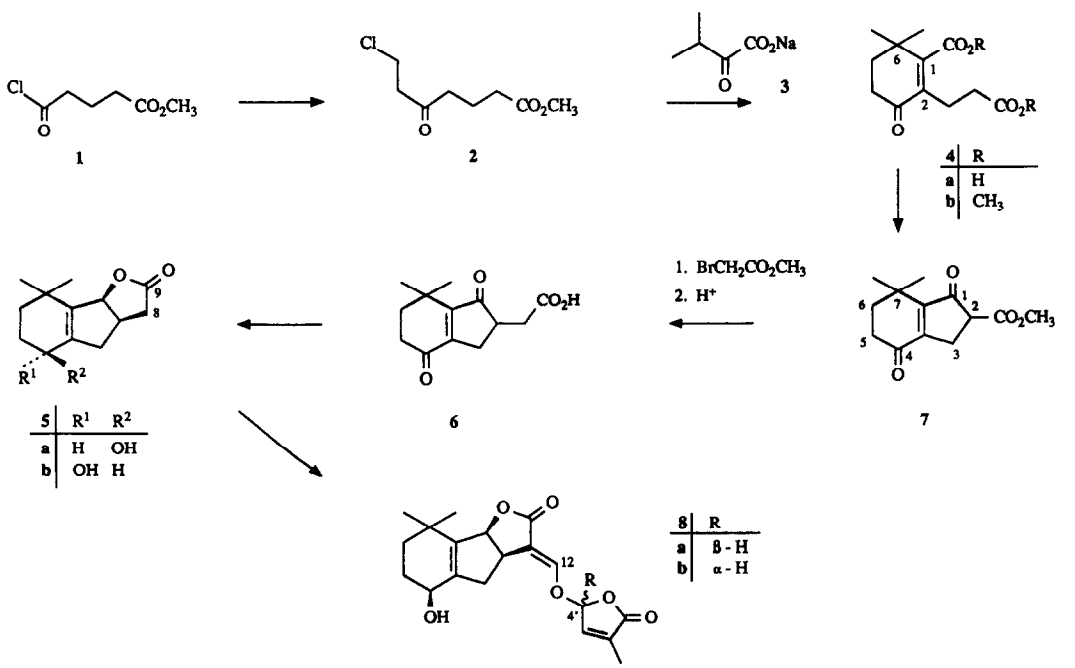
Methyl 7-chloro-5-oxoheptanoate (**2**) was prepared from **1**, essentially as described by Barkley et al.[9] Condensing crude **2** with sodium 3-methyl-2-oxobutanoate[10] in aqueous base provided cyclization product **4a** in 53% yield (based on **1**). Formation of diester **4b** from **4a** with diazomethane[8] is

rather inconvenient for large-scale experiments. Under Fischer esterification conditions **4a** decomposes. **4b** is, however, nicely available from **4a** (83% yield) using the CH_3I-DBU method of Gundu Rao.[11] Dieckmann condensation converted **4b** into **7** (a 1.3 : 1 mixture of the keto and enol form, according to ^1H NMR ($CDCl_3$ solution)). Alkylation with methyl bromoacetate, ester hydrolysis, and decarboxylation provided **6** which on reduction furnished the two diastereomeric hydroxy lactones **5a** and **5b** in racemic form.

With regard to the synthesis of structural analogues of **8a** with different substituents in the 4-position, it is of interest that the configuration at C-4 in **5a** / **5b** is easily discernible from the signals of the 3- and 4-protons, respectively (see Table 1).

Table 1. ^1H NMR signals of CH_2-3 and 4-H in **5a** and **5b** (in $CDCl_3$ solution)

	3-H	3-H'	4-H
5a	2.43 - 2.51	2.54 - 2.65	4.06 - 4.13 (m)
5b	2.11 - 2.19	2.53 - 2.65	4.15 (t, $J_{4,5}$ = 5.5 Hz)



Base-line separation of **5a** ($[\alpha]_D$ = + 8.1) and ent-**5a** ($[\alpha]_D$ = - 8.6) was achieved upon cellulose triacetate chromatography.[12] The optical purity of the two enantiomers was confirmed by capillary column GLC with heptakis (2,6-di-O-methyl-3-O-trifluoroacetyl)-ß-cyclodextrin as stationary phase.[13] **5a** was converted to naturally occurring (+)-strigol (**8a**) and (+)-4'-epistrigol (**8b**) by condensation with methyl formate and alkylation of the intermediate hydroxymethylene derivative with 4-bromo-2-methyl-but-2-en-4-olide,[14] whereas from ent-**5a** (-)-strigol (ent-**8a**) and (-)-4'-epistrigol (ent-**8b**) were obtained. These compounds are now being compared with respect to their biological activity. Extension of these results towards the synthesis of strigol analogues is actively pursued in our laboratory.

E X P E R I M E N T A L[15]

3-(1-Carboxy-6,6-dimethyl-3-oxo-cyclohex-2-enyl)-propanoic acid (**4a**).

Ethylene was bubbled for 3.5 h through a well-stirred solution of aluminium trichloride (109.58 g, 821.06 mmol) and **1** (67.51 g, 410.17 mmol) in CH_2Cl_2 (1.4 l). The dark red reaction mixture was then treated with aq. sat. NaCl (2.5 l) and extracted three times with CH_2Cl_2. The combined extracts were washed with brine and dried. Solvent evaporation gave **2** (79.50 g, about 412.70 mmol), as a brown gum, that was used without further purification.
A mixture of **3** (52.81 g, 328.41 mmol) and crude **2** (72.13 g, about 374.40 mmol) in 1.5 N aq. KOH (1.4 l) was stirred at 100°C for 3h. After cooling to 20°C, 5% aq. HCl was slowly added to give a white precipitate. The mixture was extracted several times with ethyl acetate. During this operation the pH of the aqueous phase was kept at about 5. After drying (Na_2SO_4), solvent evaporation furnished a yellow crystalline material, which was crystallized from ethyl acetate to give **4a** (yield: 46.44 g, 52% from **1**).- IR (KBr): 1710, 1705, 1630 cm^{-1}.- ^1H NMR (80 MHz, pyridine-d_5): δ = 1.44 (s, two CH_3 at C-6), 1.70 - 1.92 (CH_2-5), 2.45 - 2.75 (CH_2-4), 2.90 - 3.30 (-CH_2-CH_2-CO_2H).- $C_{12}H_{16}O_5$ (240.26), MS: m/z (%) = 240 (M^+; 50), 194 (79), 179 (80), 149 (60), 91 (76), 77 (83), 55 (91), 41 (100).

Methyl 3-(1-methoxycarbonyl-6,6-dimethyl-3-oxo-cyclohex-2-enyl)-propanoate (**4b**).

To a well-stirred solution of **4a** (99 mg, 0.41 mmol) in acetonitrile (2 ml) were slowly added DBU (193 µl, 1.29 mmol) and methyl iodide (87 µl, 1.39 mmol). The reaction mixture was stirred for 5h at 20°C. Work-up (CH_2Cl_2) followed by LC (20 g SiO_2, petrol - ethyl acetate 3 : 1) gave pure **4b** (91.6 mg, 83%).- IR ($CHCl_3$): 1730, 1670, 1620 cm^{-1}.- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.22 (s, two CH_3 at C-6), 1.75 - 2.00 (CH_2-5), 2.30 - 2.65 (CH_2-4, -CH_2-CH_2-CO_2CH_3), 3.62 (s, H_3CO), 3.80 (s, H_3CO).- $C_{14}H_{20}O_5$ (268.30), MS: m/z (%) = 268 (M^+; 65), 237 (70), 236 (70), 208 (55), 204 (100), 193 (45), 177 (70), 176 (60), 161 (50), 149 (80).

Methyl 7,7-dimethyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-indene-2-carboxylate (**7**).

4b (19.83 g, 73.90 mmol) was converted to **7** as described in ref.[8] Workup (ether) and LC (300 g SiO_2, petrol - ethyl acetate 5 : 1) afforded pure **7** (16.23 g, 93%).- m.p.: 136 - 138°C.- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.29 (s,

7-CH_3), 1.36 (s, 7-CH_3), 1.73 - 2.06 (CH_2-6), 2.36 - 2.70 (CH_2-5), 2.79 - 2.96 (CH_2-3, keto form), 3.24 (s, CH_2-3, enol form), 3.33 - 3.57 (2-H, keto form), 3.75 (s, H_3CO), 3.79 (s, H_3CO), 10.16 (broad s, -OH). 1.3 : 1 ratio of keto and enol form.- $C_{13}H_{16}O_4$ (236.27), MS: m/z (%) = 236 (M^+; 80), 221 (5), 204 (100), 189 (40), 176 (60), 161 (38).

Hydroxylactones 5a and 5b.

(RS)-(7,7-Dimethyl-1,4-dioxo-2,3,4,5,6,7-hexahydro-inden-2-yl)-acetic acid rac-(6), obtained from 7,[16] was reduced as described previously.[3,16] The mixture of 5a and 5b was separated by MPLC (petrol - ethyl acetate 2 : 3).

(1SR,2RS,4SR)-1,4-Dihydroxy-7,7-dimethyl-2,3,4,5,6,7,-hexahydroinden-2-yl)-9,1-lactone (rac-5a).

M.p.: 146°C.- IR ($CHCl_3$): 3500 - 3200, 1760, 1660 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$, NOE irradiation at δ = 4.06 - 4.13): δ = 1.05 (s, 7-CH_3), 1.15 (s, 7-CH_3), 1.38 - 1.45 (ddd, 6β-H, $J_{6,6}$ = 13.5 Hz; $J_{6,5\beta}$ = 3 Hz; $J_{6,5\alpha}$ = 11 Hz), 1.49 - 1.59 (ddd, 6α-H, $J_{6,6}$ = 13.5 Hz; $J_{6,5\alpha}$ = 3 Hz; $J_{6,5\beta}$ = 7 Hz), 1.61 - 1.77 (OH and 5α-H), 1.90 - 2.00 (5β-H), 2.28 - 2.38 (dd, 8-H, $J_{8,8}$ = 18 Hz; $J_{8,2}$ = 5.5 Hz), 2.43 - 2.51 (3α-H, $J_{3,3}$ = 17 Hz), 2.54 - 2.65 (3β-H, $J_{3,3}$ = 17 Hz), 2.73 - 2.84 (dd, 8-H, $J_{8,8}$ = 18 Hz; $J_{8,2}$ = 10 Hz), 2.99 - 3.10 (2-H), 4.06 - 4.13 (4-H), 5.40 - 5.48 (1-H, $J_{1,2}$ = 7.5 Hz).- $C_{13}H_{18}O_3$ (222.28), MS: m/z (%) = 222 (M^+;28), 204 (34), 189 (35), 166 (100), 119 (64), 107 (59), 91 (56), 79 (49), 55 (59), 41 (77).

(1SR,2RS,4RS)-1,4-Dihydroxy-7,7-dimethyl-2,3,4,5,6,7,-hexahydroinden-2-yl)-9,1-lactone (rac-5b).

Oil.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 7-CH_3), 1.11 (s, 7-CH_3), 1.40 - 1.48 (ddd, 6-H, $J_{6,6}$ = 13.5 Hz; $J_{6,5}$ = 8 Hz and 3 Hz), 1.53 - 1.61 (ddd, 6-H, $J_{6,6}$ = 13.5 Hz; $J_{6,5}$ = 10 Hz and 3 Hz), 1.63 - 1.72 (5-H), 1.73 - 1.87 (broad s, -OH), 1.91 - 2.00 (5-H), 2.11 - 2.19 (3-H, $J_{3,3}$ = 16 Hz), 2.30 - 2.35 (dd, 8-H, $J_{8,8}$ = 18 Hz; $J_{8,2}$ = 5 Hz), 2.75 - 2.84 (dd, 8-H, $J_{8,8}$ = 18 Hz; $J_{8,2}$ = 10 Hz), 2.93 - 3.01 (dd, 3-H, $J_{3,3}$ = 16 Hz; $J_{3,2}$ = 8.5 Hz), 3.02 - 3.18 (2-H), 4.15 (t, 4-H, $J_{4,5}$ = 5.5 Hz), 5.43 - 5.47 (1-H, $J_{1,2}$ = 7.5 Hz).

Resolution of rac-5a.

A mixture of (±)-5a (458.8 mg, 2.06 mmol) was separated by HPLC (triacetyl cellulose, Chiral Triacel HPLC-Column 250-1"-20 mm, Macherey u. Nagel, ethanol - water 96 : 4; 3 ml / min) to give ent-5a (184.1 mg, 40.1%) and 5a (138.6 mg, 30.2%). The ent-5a fraction was further purified by LC (20 g SiO_2, petrol - $CHCl_3$ - ethanol 1 : 1 : 0.1) to give pure ent-5a (101.5 mg). These products were recrystallized from benzene - pentane: ent-5a: $[\alpha]_D^{20}$ - 8.58° (c 0.71, $CHCl_3$), 5a: $[\alpha]_D^{20}$ + 8.10° (c 0.39, $CHCl_3$).
Instrumentation used for the resolution:
Waters Associates Chromatography Pump LC-8A, Shimadzu; detection: Perkin-Elmer 241 polarimeter at 365 nm and Du pont Instruments U.V.-Spektrophotometer at 220 nm.
Analytical e.e. determination:
1. HPLC: Cellulose triacetate (CEL-AC-40XF, Macherey u. Nagel), ethanol - water 96 : 4; 0.5 ml/min; UV detection; LC3, PYE UNICAM at 220 nm, Pump: Water Associates Chromatography.
2. GC: Sichromat 3, Siemens, 13.5 m * 0.28 mm glass capillary column (heptakis(2,6-di-O-methyl-3-O-trifluoroacetyl)-β-cyclodextrin), 160°C, carrier gas: H_2.

Preparation of Strigol and 4'-Epistrigol.

5a (101.3 mg, 0.46 mmol) was converted to a mixture of **8a** and **8b** as described by Sih.[16] LC ($CHCl_3$ - acetone 12 : 1) gave **8b** (77.5 mg, 49%) and **8a** (45.5 mg, 29%). Similarly, ent-**5a** (93.5 mg, 0.42 mmol) was converted to ent-**8b** (56.4 mg, 39%) and ent-**8a** (48.0 mg, 33%).

(+)-Strigol (**8a**).[3,16]

After crystallization of **8a** from ethanol - water: m.p. 183 - 186°C, $[\alpha]_D^{20}$ + 262.7° (c 0.69, $CHCl_3$). After crystallization from CH_2Cl_2 - pentane: m.p. 191 - 192°C, $[\alpha]_D^{20}$ + 244.6° (c 0.40, $CHCl_3$).- IR ($CHCl_3$): 3600 - 3200, 1765, 1730, 1660 cm^{-1}.- ^1H NMR (400 MHz, COSY, $CDCl_3$): δ = 1.06 (s, 7-CH_3), 1.14 (s, 7-CH_3), 1.43 - 1.50 (ddd, 6-H, $J_{6,6}$ = 13.5 Hz; $J_{6,5}$ = 11 Hz and 3 Hz), 1.52 - 1.61 (ddd, 6-H, $J_{6,6}$ = 13.5 Hz; $J_{6,5}$ = 6.5 Hz and 3 Hz), 1.63 - 1.78 (5-H and OH), 1.93 - 1.99 (5-H), 2.01 (t, 2'-CH_3, J = 1.5 Hz), 2.62 - 2.75 (CH_2-3), 3.57 - 3.65 (2-H), 4.06 - 4.14 (4-H), 5.45 - 5.42 (1-H, $J_{1,2}$ = 8 Hz), 6.10 - 6.15 (4'-H), 6.90 - 6.94 (3'-H), 7.45 (d, 12-H, J = 2.5 Hz).- $C_{19}H_{22}O_6$ (346.14), MS: m/z (%) = 328 (0.8), 284 (1.5), 231 (35), 203 (12), 97 (100), 91 (10), 69 (14), 41 (42).

(-)-Strigol (ent-**8a**).[3,16]

After crystallization of ent-**8a** from ethanol - water: m.p. 181 - 184°C, $[\alpha]_D^{20}$ - 249.5° (c 0.51, $CHCl_3$). After crystallization from CH_2Cl_2 - pentane: m.p. 192 - 194°C, $[\alpha]_D^{20}$ -244.3° (c 0.36, $CHCl_3$).

(+)-4'-Epistrigol (**8b**).[16]

8b was obtained as a slightly yellow oil: $[\alpha]_D^{20}$ + 94.0° (c 1.24, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 7-CH_3), 1.15 (s, 7-CH_3), 1.38 - 1.48 (ddd, 6-H, $J_{6,6}$ = 14 Hz; $J_{6,5}$ = 11.5 Hz and 3 Hz), 1.51 - 1.59 (ddd, 6-H, $J_{6,6}$ = 14 Hz; $J_{6,5}$ = 7 Hz and 3 Hz), 1.60 - 1.85 (CH_2-5 and OH (broad s)), 2.00 (s, 2'-CH_3), 2.60 - 2.75 (CH_2-3), 3.59 - 3.66 (2-H), 4.03 - 4.12 (4-H), 5.48 - 5.53 (1-H, $J_{1,2}$ = 8 Hz), 6.13 - 6.15 (4'-H), 6.90 - 6.92 (3'-H), 7.42 - 7.45 (d, J = 2.5 Hz, 12-H).

(-)-4'-Epistrigol (ent-**8b**).[16]

(-)-**8b** was obtained as a slightly yellow oil: $[\alpha]_D^{20}$ - 85.9° (c 1.38, $CHCl_3$).

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