Concise Enantio- and Stereo-controlled Synthesis of (+)-Equilenin using Chiral Cyclopentadienone Synthon

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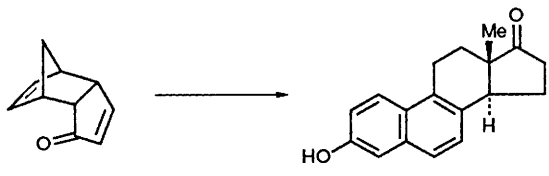
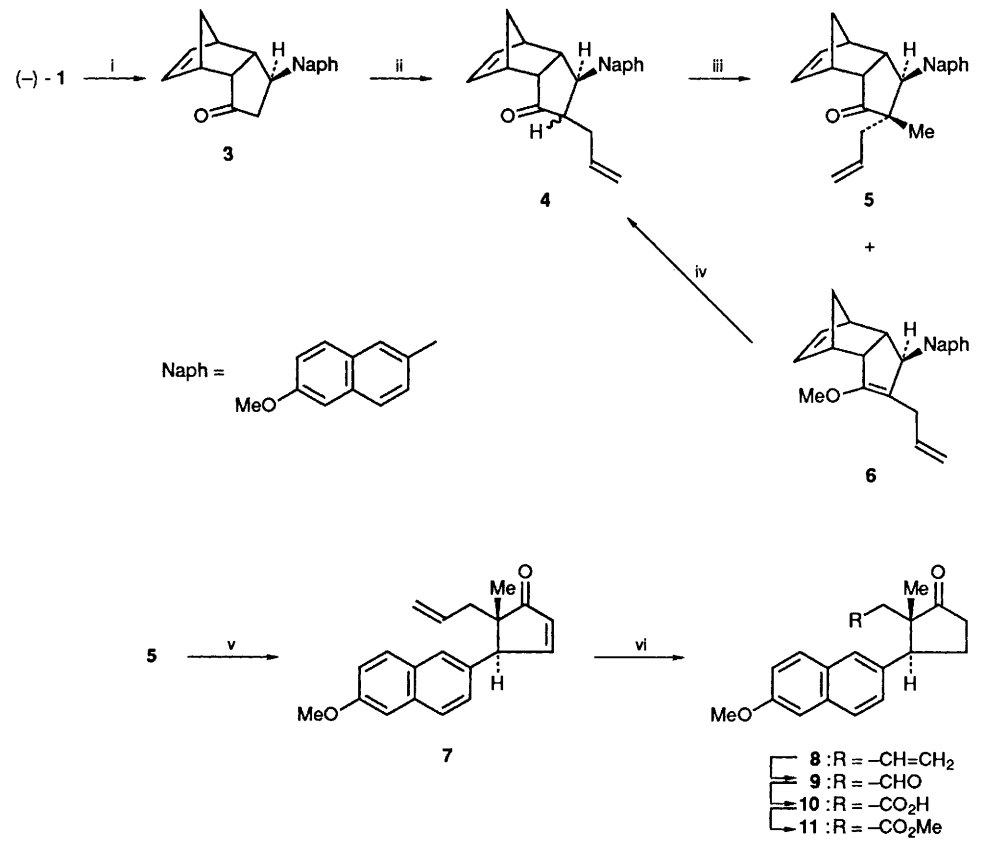
A concise enantio- and stereo-controlled synthesis of the estrogenic steroid (+)-equilenin has been established using the chiral cyclopentadienone synthon.

We have recently reported an efficient construction of the chiral tricyclic dienone **1** in both enantiomeric forms from dicyclopentadiene employing kinetic resolution by lipase in the key stage.[1] Owing to its biased structure, **1** allowed stereospecific introduction of nucleophiles at the β-carbon of the enone system from the convex face of the molecule, which has been successfully applied to the enantiocontrolled synthesis of some naturally occurring compounds bearing a quaternary carbon centre[1,2] as a cyclopentadienone equivalent.



(−) - **1** (+) - equilenin **2**

Scheme 1



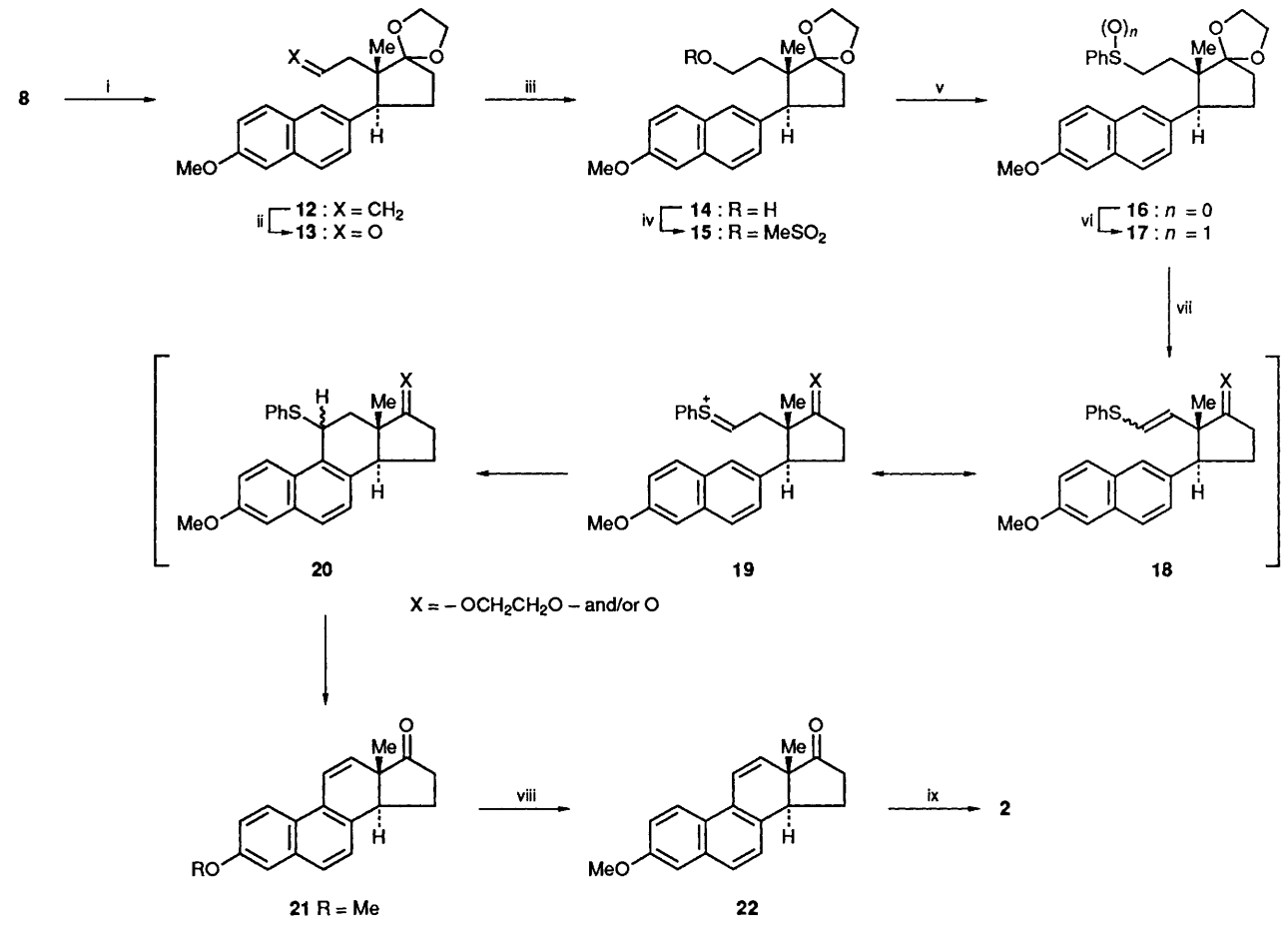
Scheme 2 *Reagents and conditions*: i. 6-methoxy-2-naphthylmagnesium bromide (2.4 equiv.), CuI (1.2 equiv.), THF, −30 °C, 30 min; ii, (*a*) cyclohexylamine (10.0 equiv.), benzene, reflux, 24 h, (*b*) Bu^{n}Li (2.5 equiv.), allyl bromide (5.0 equiv.), THF, −30 °C → room temp., 1.5 h, then AcOH–AcONa–H_2O (1:1:2), reflux, 7 h; iii, Bu^{t}OK (1.2 equiv.), MeI (1.5 equiv.), THF, −30 °C → 0 °C, 1 h; iv, 70% $HClO_4$ aq. (2.0 equiv.), THF, room temp., 5 min; v, *o*-dichlorobenzene, reflux, 24 h; vi, $LiAlH_4$ (1.5 equiv.), CuI (1.5 equiv.), THF–HMPA (4:1), −78 °C, 10 min; vii, OsO_4 (5% mol), $NaIO_4$ (5.0 equiv.), $NaHCO_3$ (25 equiv.), aq. THF, room temp., 12 h; viii, Jones' reagent (2.0 equiv.), acetone, 0 °C → room temp., 1 h; ix, K_2CO_3 (3.0 equiv.), MeI (3.0 equiv.), DMF, room temp., 15 min

Herewith, we demonstrate stereoselective introduction of electrophiles at the α-carbon of the saturated system, derived from the enone precursor **1** by the stereoselective nucleophilic 1,4-addition, which leads to a concise enantio- and stereocontrolled total synthesis of the estrogenic steroid (+)-equilenin[3] **2**.

Reaction of (−)-dienone **1** with the Grignard reagent, prepared from 6-methoxy-2-bromonaphthalene, in the presence of copper(I) iodide gave exclusively the *exo*-adduct† **3**, m.p. 116–118 °C, $[\alpha]_D^{27}$ −49.1° (*c* 1.14, $CHCl_3$), in 73% yield. On sequential metallo-enamine formation[4] and alkylation **3** afforded the allyl ketone **4** in 56% yield (82% based on recovered **3**) as a mixture of two epimers after acid work-up. The second alkylation of **4** with an excess of methyl iodide in the presence of potassium t-butoxide proceeded stereoselectively to give the *exo*-methyl ketone **5**, $[\alpha]_D^{27}$ +58.8° (*c* 1.098, $CHCl_3$), in 62% yield, although it was accompanied by a 30% yield of *O*-alkylation product **6**, m.p. 76–77 °C, $[\alpha]_D^{27}$ +267.0° (*c* 1.08, $CHCl_3$). The latter product could be reverted to the starting ketone **4** in 85% yield and recycled (corrected yield of **5** based on recovered **4** was 82%). Refluxing **5** in *o*-dichlorobenzene brought about facile retrograde Diels–Alder reaction[1,2] to give rise to the cyclopentenone **7**, m.p. 82–83 °C, $[\alpha]_D^{27}$ −307.4° (*c* 1.30, $CHCl_3$), in 90% yield. Compound **7** was next treated with a complex,[5] generated from lithium aluminium hydride and copper(I) iodide, in a mixture of tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) (4:1) at −78 °C to afford the cyclopentanone **8**, m.p. 72.5–74 °C, $[\alpha]_D^{31}$ +48.9° (*c* 1.064, $CHCl_3$), in 80% yield by specific hydrogenation of the enone double bond. Oxidative cleavage of the vinyl bond of **8** gave the aldehyde **9**, m.p. 144–146 °C, $[\alpha]_D^{27}$ +62.3° (*c* 0.258, $CHCl_3$), which was transformed to the known ester **11**, m.p. 121–123 °C, $[\alpha]_D^{27}$ +5.0° (*c* 1.07, $CHCl_3$); $[\alpha]_{405}^{22}$ +71.8° (*c* 0.58, $CHCl_3$) [lit.[6]: m.p. 116–118°, $[\alpha]_{365}^{27}$ +168° (*c* 0.36, $CHCl_3$)], in 72% overall yield *via* the carboxylic acid **10**, $[\alpha]_D^{28}$ +22.3° (*c* 0.478, $CHCl_3$). Since racemic syntheses of equilenin **2** from either the racemic alkene[7] **8** or the racemic ester[8] **11** *via* the racemic acid **10** as well as the chiral preparation of the ester[6] **11** by asymmetric reaction have been reported, the present synthesis constitutes an enantioselective synthesis of the hormone in a formal sense at this stage (Scheme 2).

In order to establish an alternative chiral route, **8** was first converted into the ketal **12**, m.p. 101–103 °C, $[\alpha]_D^{25}$ −53.9° (*c* 1.084, $CHCl_3$), which was then transformed into the primary alcohol **14**, m.p. 132.5–134 °C, $[\alpha]_D^{27}$ −22.8° (*c* 1.18, $CHCl_3$), in 62% overall yield *via* the aldehyde **13**, m.p. 140.5–141.5 °C, $[\alpha]_D^{29}$ −59.1° (*c* 1.104, $CHCl_3$), by sequential oxidative cleavage and borohydride reduction. Methanesulphonation of **14** gave the methanesulphonate **15** which was transformed to the sulphoxide **17** *via* the sulphide **16**, $[\alpha]_D^{31}$ −110.3° (*c* 0.718, $CHCl_3$), in 81% overall yield. Upon exposure to a 1:2 mixture of trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) in toluene at reflux,[9] **17** underwent smooth cyclization to furnish Δ^{11}-equilenin methyl ether **21**, m.p. 188–192 °C,

All new compounds gave the expected microanalytical, IR, NMR, and mass spectral data.



Scheme 3 *Reagents and conditions*: i, ethylene glycol (5.0 equiv.), *p*-toluenesulphonic acid (3% mol), toluene, reflux, 12 h; ii, OsO_4 (5% mol), $NaIO_4$ (5.0 equiv.), $NaHCO_3$ (25 equiv.), aq. THF, room temp., 12 h; iii, $NaBH_4$ (2.5 equiv.), $NaHCO_3$ (5.0 equiv.), methanol, 0 °C, 15 min; iv, $MeSO_2Cl$ (1.5 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, 0 °C → room temp., 20 min; v, PhSH (3.0 equiv.), K_2CO_3 (5.0 equiv.), DMF, room temp., 3 h; vi, mCPBA (1.1 equiv.), $NaHCO_3$ (5.0 equiv.), CH_2Cl_2, −30 °C, 10 min; vii, TFAA (3.0 equiv.), TFA (6.0 equiv.), toluene, 140 °C, 1 h then H_2O, reflux, 1 h; viii, Pd–C (catalyst), H_2, THF–MeOH (1:1), room temp., 12 h; ix, BBr_3 (1.5 equiv.), CH_2Cl_2, −30 °C → 0 °C, 3 h

$[\alpha]_D^{26}$ +170.3° (*c* 0.40, dioxane), in 60% yield without forming stereo- and regio-isomers. Since the vinyl sulphide (**18**: X = O) was formed with a minor amount of **21** unless TFA was present, the reaction probably proceeded with the intervention of the intermediates, such as **18**, **19** and **20** as shown. Catalytic hydrogenation of **21** yielded (+)-equilenin methyl ether **22**, m.p. 198–200 °C, $[\alpha]_D^{31}$ +81.9° (*c* 0.44, dioxane), in 90% yield, which was verified by direct comparison with an authentic material, m.p. 197–198 °C, $[\alpha]_D^{28}$ +82.8° (*c* 1.04, dioxane), prepared from natural equilenin **2**. Finally, **22** was treated with boron tribromide to give (+)-equilenin **2**, m.p. 249–252 °C (decomp.), $[\alpha]_D^{29}$ +86.9° (*c* 1.06, dioxane) {natural[10]: m.p. 250–252 °C (decomp.), $[\alpha]_D$ +87° (*c* 1.0, dioxane)}, in 83% yield, which was identical in all respects with the naturally occurring compound (Scheme 3).

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