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.



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Scheme 2 Reagents and conditions: i. 6-methoxy-2-naphthylmagnesium bromide (2.4 equiv.), CuI (1.2 equiv.), THF, $-30 \,^{\circ}$ C, 30 min; ii, (a) cyclohexylamine (10.0 equiv.), benzene, reflux, 24 h, (b) BuⁿLi (2.5 equiv.), allyl bromide (5.0 equiv.), THF, $-30 \,^{\circ}$ C \rightarrow room temp., 1.5 h, then AcOH-AcONa-H₂O (1:1:2), reflux, 7 h; iii, Bu^tOK (1.2 equiv.), MeI (1.5 equiv.), THF, $-30 \,^{\circ}$ C $\rightarrow 0 \,^{\circ}$ C, 1 h; iv, 70% HClO₄ aq. (2.0 equiv.), THF, room temp., 5 min; v, o-dichlorobenzene, reflux, 24 h; vi, LiAlH₄ (1.5 equiv.), CuI (1.5 equiv.), THF-HMPA (4:1), $-78 \,^{\circ}$ C, 10 min; vii, OsO₄ (5% mol), NaIO₄ (5.0 equiv.), NaHCO₃ (25 equiv.), aq. THF, room temp., 12 h; viii, Jones' reagent (2.0 equiv.), acetone, $0 \,^{\circ}$ C \rightarrow room temp., 1 h; ix, K₂CO₃ (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 stereo-controlled total synthesis of the estrogenic steroid (+)-equilenin³ 2.

Reaction of (-)-dienone 1 with the Grignard reagent, prepared from 6-methoxy-2-bromonaphthalene, in the presence of copper(1) iodide gave exclusively the exo-adduct[†] **3**, m.p. 116–118 °C, $[\alpha]_D^{27}$ –49.1° (c 1.14, CHCl₃), in 73% yield. On sequential metallo-enamine formation⁴ 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 reacion^{1,2} to give rise to the cyclopentenone 7, m.p. 82–83 °C, $\alpha]_{D^{27}} - 307.4^{\circ}$ (c 1.30, CHCl₃), in 90% yield. Compound 7 vas next treated with a complex,5 generated from lithium duminium hydride and copper(1) 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, CHCl₃), 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, CHCl₃), which was transformed to the known ester 11, m.p. 121–123 °C, $[\alpha]_D^{27}$ +5.0° (*c* 1.07, CHCl₃); $[\alpha]_{405}^{22}$ +71.8° (*c* 0.58, CHCl₃) [lit.6: m.p. 116–118°, $[\alpha]_{365}^{27}$ +168° (*c* 0.36, CHCl₃)], in 72% overall yield *via* the carboxylic acid 10, $[\alpha]_D^{28}$ +22.3° (*c* 0.478, CHCl₃). Since racemic syntheses of equilenin 2 from either the racemic alkene⁷ 8 or the racemic ester⁸ 11 *via* the racemic acid 10 as well as the chiral preparation of the ester⁶ 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. $101-103 \,^{\circ}$ C, $[\alpha]_D^{25} - 53.9^{\circ}$ (*c* 1.084, CHCl₃), which was then transformed into the primary alcohol **14**, m.p. $132.5-134 \,^{\circ}$ C, $[\alpha]_D^{27} - 22.8^{\circ}$ (*c* 1.18, CHCl₃), in 62% overall yield *via* the aldehyde **13**, m.p. $140.5-141.5 \,^{\circ}$ C, $[\alpha]_D^{29} - 59.1^{\circ}$ (*c* 1.104, CHCl₃), 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**, $[\alpha]_D^{31} - 110.3^{\circ}$ (*c* 0.718, CHCl₃), 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. $188-192 \,^{\circ}$ C,

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



Scheme 3 Reagents and conditions: i, ethylene glycol (5.0 equiv.), p-toluenesulphonic acid (3% mol), toluene, reflux, 12 h; ii, OsO₄ (5% mol), NaIO₄ (5.0 equiv.), NaHCO₃ (25 equiv.), aq. THF, room temp., 12 h; iii, NaBH₄ (2.5 equiv.), NaHCO₃ (5.0 equiv.), methanol, 0 °C, 15 min; iv, MeSO₂Cl (1.5 equiv.), Et₃N (1.5 equiv.), CH₂Cl₂, 0 °C \rightarrow room temp., 20 min; v, PhSH (3.0 equiv.), K₂CO₃ (5.0 equiv.), DMF, room temp., 3 h; vi, mCPBA (1.1 equiv.), NaHCO₃ (5.0 equiv.), CH₂Cl₂, -30 °C, 10 min; vii, TFAA (3.0 equiv.), TFA (6.0 equiv.), toluene, 140 °C, 1 h then H₂O, reflux, 1 h; viii, Pd–C (catalyst), H₂, THF–MeOH (1:1), room temp., 12 h; ix, BBr₃ (1.5 equiv.), CH₂Cl₂, -30 °C \rightarrow 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) {natural¹⁰: m.p. 250–252 °C (decomp.), $[\alpha]_D$

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