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Efficient Stereoselective Synthesis of Novel Steroid–Polyquinane Hybrids†

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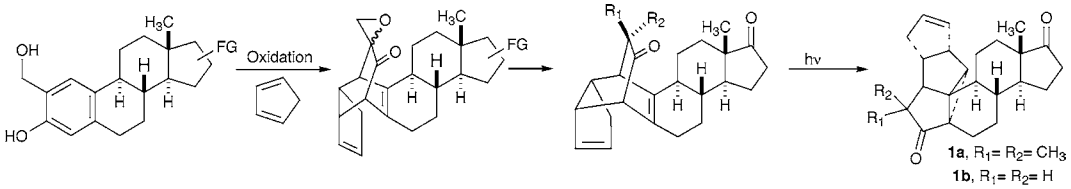
ABSTRACT



A synthesis of steroid–polyquinane hybrids, a new class of molecular entities, is described.

There is growing interest in design and synthesis of hybrid molecules that combine features of two structurally different classes of compounds.[1−5] Such hybrids comprise structures that could possess interesting physical, chemical, and most importantly, biological properties. Many of these hybrids, for example, estrone−talaromycin,[1] estrone−enediyne,[2a] steroid−baccatin,[2c] estrogen−antharancenedione,[3b] and steroid−anthraquinone hybrids, are based on natural products.[3c] Steroids constitute an important subunit in the design of hybrids on account of their established biological importance.[6]

A key step in our synthesis of hybrids **1** is the conversion of the hexacyclic intermediates **3** (Figure 1) via the known oxa-di-π-methane rearrangement.[8] Compounds **3a**,**b** are prepared by standard modification of **4** (see Scheme 2) and **5** (see Scheme 3), respectively, which in turn were derived from $NaIO_4$ oxidation of a suitable estrone derivative to spiroepoxydienone **6** (see Scheme 1), **7** (Scheme 3), and subsequent in situ trapping with cyclopentadiene.

We report here our initial results on the synthesis of novel steroid−polyquinane hybrids of type **1** from estrone **2** (Figure

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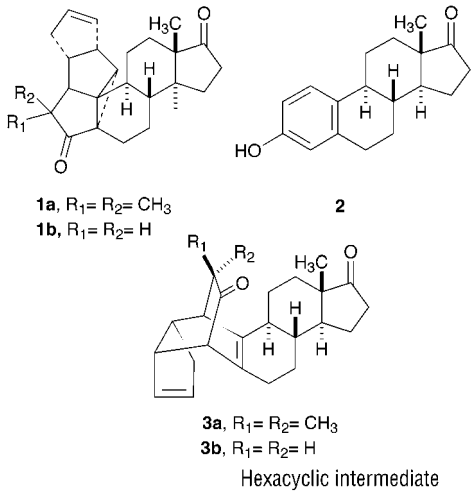
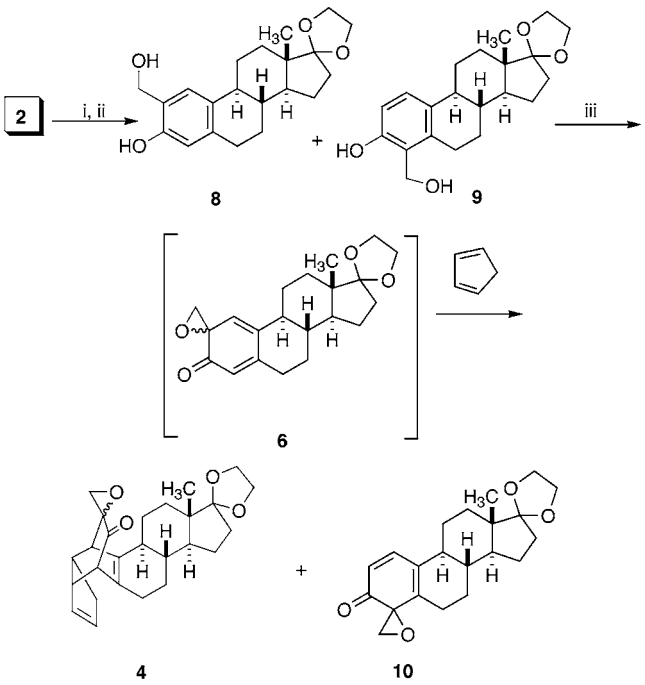


Figure 1.

1). This is the first report on steroid−polyquinane hybrids. Our choice of polyquinane stems from its promising biological activity[7] as a potential anticancer or contraceptive agent. A synthesis of these hybrids would allow future access to various analogues for evaluation of their biological potential.

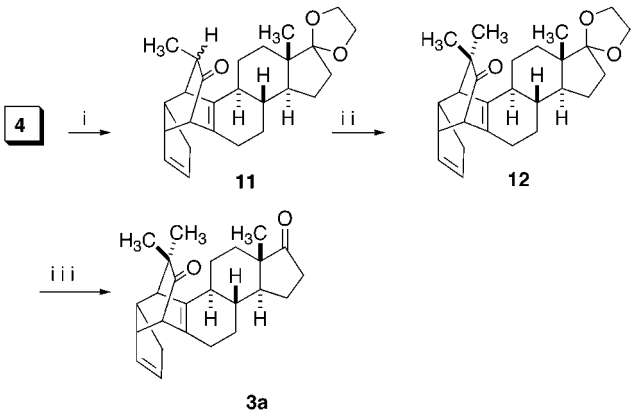
Estrone (**2**) was protected as a ketal and then subjected to hydroxymethylation, which gave an inseparable mixture of 2- and 4-hydroxymethyl derivatives **8** and **9**, respectively, in a 5:1 ratio (300 MHz ^{1}H NMR).[9] Oxidation of this mixture with $NaIO_4$ in $CHCl_3-H_2O$ containing cetyltrimethylammonium bromide (CTAB) and cyclopentadiene gave adduct **4** as a 70:30 mixture of stereoisomers (600 MHz ^{1}H NMR) presumably via in situ generation of **6** and subsequent interception with cyclopentadiene (Scheme 1). The spirocyclohexadienone **10** generated by oxidation of **9** did not undergo cycloaddition under the reaction conditions but allowed clean separation of **4** and **10**.[10] We could fully assign the ^{13}C and ^{1}H (600 MHz) NMR spectra for **4** and **10** and hence confirm these structures. However, no suitable crystals of **4** and **10** could be obtained for an X-ray diffraction measurement.

Scheme 1[a]



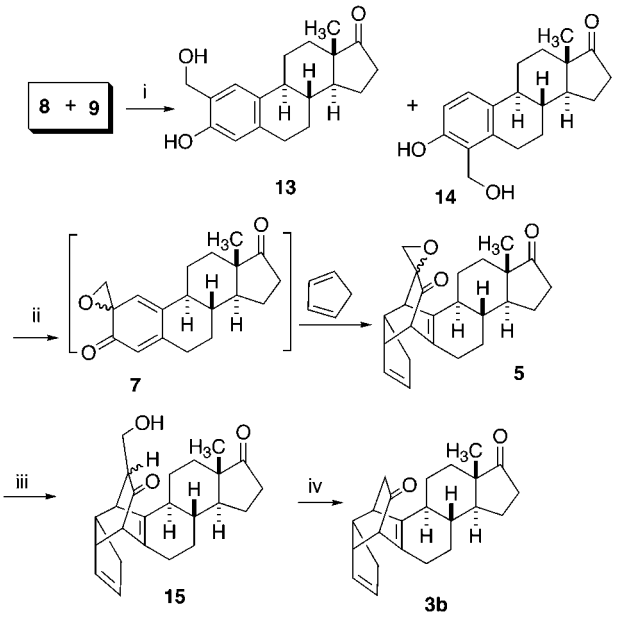
[a] Reagents and conditions: (i) ethyleneglycol, *p*-TsOH, C_6H_6, Δ, 78%. (ii) KOH, HCHO, dioxane−H_2O, 34%. (iii) $CHCl_3-H_2O$, CTAB, $NaIO_4$, cyclopentadiene, **4**:**10** = 45:15%.

Scheme 2[a]



[a] Reagents and conditions: (i) Zn, NH_4Cl, dry dioxane, Δ, 45%. (ii) NaH, CH_3I, THF, Δ, 71%. (iii) HCl, acetone, 84%.

Scheme 3[a]



[a] Reagents and conditions: (i) HCl, THF, 90%. (ii) $CHCl_3$, CTAB, $NaIO_4$, cyclopentadiene, rt, 42%. (iii) Zn, NH_4Cl, CH_3OH-H_2O, 42%. (iv) (a) $CrO_3-H_2SO_4$. (b) THF−H_2O, Δ, 30%.

Reductive deoxygenation of adduct **4** with zinc in dry dioxane containing ammonium chloride gave **11** (as a syn−anti mixture), which was alkylated to **12** with methyl iodide/NaH/THF. Hydrolysis of the ketal unit in **12** with HCl in acetone gave crystalline **3a** (Scheme 2). The structure of **3a** was confirmed by X-ray diffraction (Figure 2).[11−15] In this

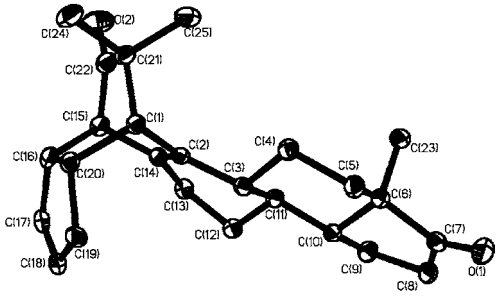


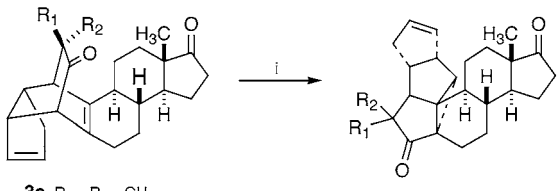
Figure 2. Diagram of compound **3a** thermal ellipsoids depicted at the 50% probability level (hydrogen atoms omitted for clarity).

way the structure of **4** was also confirmed. It also clearly showed π-facial selectivity in the Diels−Alder cyloaddition of cyclopentadiene and spiroepoxycyclohexadienone in **6**.[16]

Analogue **3b**, which lacks the gem-dimethyl group, was prepared as shown in Scheme 3. Upon hydrolysis of the ketal group, the mixture of **8** and **9** gave an easily separable mixture of **13** and **14**. Oxidation of **13** with $NaIO_4$ in the presence of cyclopentadiene gave adduct **5** (via intermediate **7**).[10] Reduction of the oxirane ring with zinc-NH_4Cl in methanol−H_2O gave the β-hydroxy ketone **15**, oxidation of which with Jones' reagent followed by decarboxylation afforded the desired diketone **3b** (Scheme 3).

With substantial amounts of hexacyclic β,γ-enones **3a** and **3b** in hand, we were now ready to explore the crucial photochemical reactions, being mindful that the structural and functional complexity of our substrates, especially the presence of a carbonyl group and a double bond in five-membered rings, could undergo other known photoreactions. First a solution of compound **3a** in dry acetone (solvent as well as a sensitizer) was irradiated for 45 min, under nitrogen, and gave a clean reaction.[17] Careful chromatography of the photolysate gave, in good yield, the product **1a** as the result of a 1,2-acyl shift.[8,18] Similarly, irradiation of **3b** in dry acetone for 35 min gave photoproduct **1b** (Scheme 4). The

Scheme 4[a]



3a, $R_1 = R_2 = CH_3$
3b, $R_1 = R_2 = H$

1a, $R_1 = R_2 = CH_3$
1b, $R_1 = R_2 = H$

[a] Reagents and conditions: (i) acetone, *hν*, **3a** to **1a**, 55%; **3b** to **1b**, 45%.

structures of the photoproducts were clearly deduced from their spectral data.

In summary, the synthesis of novel steroid−polyquinane hybrids, a new class of molecular framework, has been presented. The methodology involves transformation of the

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(9) All new compounds have been satisfactorily characterized spectroscopically, and their elemental compositions have been determined by combustion analysis or by HRMS. Data for selected new compounds: **Compound 1b.** Mp: 149−151 °C. IR (film, cm^{-1}): 1739, 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.72 (m, 2H), 3.02 (br m, 1H), 2.96 (d, 1H, J = 9.5 Hz), 2.60−2.24 (cluster of m, 6H), 2.20−1.8 (m, 8H), 1.7−1.20 (cluster of m, 5H), 1.02−0.88 (4H, CH_3 + 1H), 0.78−0.62 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.54, 217.35, 133.74, 131.88, 57.66, 51.75, 50.70, 49.82, 49.12, 48.22, 46.09, 44.90, 42.24, 39.34, 37.38, 35.74, 31.88, 29.74, 28.59, 23.77, 23.12, 21.68, 14.14. HRMS: found, 337.2155 (M + H); calcd for $C_{23}H_{28}O_2$, 337.2162. **Compound 3b.** Mp: 141−143 °C. IR (film, cm^{-1}): 1735, 1715 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.64 (m of d, J = 6 Hz, 1H), 5.40 (m of d, J = 6 Hz, 1H), 3.26−3.18 (m, 1H), 3.0(m, 1H), 2.89 (d, J = 1.5 Hz, 1H), 2.70−2.42 (m, 3H), 2.28−1.10 (cluster of m, 17H), 0.90 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.77, 213.57, 139.80, 138.13, 132.35, 129.84, 57.59, 49.83, 48.76, 48.47, 47.02, 41.81, 39.80, 39.06, 38.68, 37.44, 35.85, 31.71, 29.13, 25.62, 24.95, 21.46, 14.17. HRMS: found, 336.2086; calcd for $C_{23}H_{28}O_2$, 336.2089. **Compound 1a.** Mp: 155−157 °C. IR (film, cm^{-1}): 1739, 1716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74 (m, 2H), 2.80−2.72 (m, 2H), 2.52−2.24 (m, 5H), 2.20−2.00 (m, 3H), 1.98−1.22 (m, 9H), 1.10 (s overlapped with a m, total 4H, CH_3 and 1 other proton), 0.94 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.79−0.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.60, 220.51, 134.05, 131.85, 55.48, 52.67, 51.49, 50.35, 49.79, 49.25, 48.24, 45.19, 44.90, 42.61, 38.73, 37.46, 35.80, 31.93, 29.21, 28.93, 24.14, 23.73, 21.72, 18.42, 14.16. HRMS: found, 365.2479 (M + H); calcd for $C_{25}H_{32}O_2$, 365.2475. **Compound 3a.** Mp: 146−147 °C. IR (film, cm^{-1}): 1739, 1717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.59 (m, 1H), 5.38 (m, 1H), 3.20−3.10 (m, 1H), 3.0−2.90 (m, 1H), 2.80 (br s, 1H), 2.62 (br s, 1H), 2.55−2.40 (m, 2H), 2.30−1.75 (m, 7H), 1.70−1.15 (m, 8H), 1.10 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.32, 216.35, 138.37, 132.42, 130.20, 128.34, 57.56, 50.15, 48.89, 48.48, 48.11, 47.19, 44.56, 38.51, 38.29, 35.65, 31.86, 28.75, 28.06, 26.99, 26.19, 25.20, 24.08, 21.55, 14.03. HRMS: found, 364.2398; calcd for $C_{25}H_{32}O_2$, 364.2402.

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(11) X-ray Measurement of **3a**. All data were collected from shock-cooled crystals on an Bruker Nonius Apex three-circle diffractometer (graphite-monochromated Mo Kα radiation, λ = 71.073 pm) equipped with a low-temperature device at 193(2) K.[14] An empirical absorption correction was employed for structure **3a**.[15] The structure was solved by direct methods (SHELXS-97[16]) and refined by full-matrix least-squares methods against F^2 (SHELXL-97[17]). R values: $R_1 = S||F_o| - |F_c||/S|F_o|$, $wR_2 = [Sw(F_o^2 - F_c^2)^2/Sw(F_o^2)^2]^{0.5}$, $w = [s^2(F_o^2) + (g_1P)^2 + g_2P]^{-1}$, $P = 1/3[\max(F_o^2, 0) + 2F_c^2]$. **3a**: $C_{25}H_{32}O_2$, monoclinic, space group $P2_1$, $Z = 2$, a = 1134.37(7) pm, b = 644.85(4) pm, c = 1377.45(11) pm, a = 90°, b = 97.9340(10)°, g = 90°, V = 9.9796(11) nm^3, r_c = 1.213 Mg/m^3, 6394 reflections measured, 4063 unique, $R_1[I > 2s(I)] = 0.0375$, wR_2(all data) = 0.0945, $g_1 = 0.0570$, $g_2 = 0.1804$ for 248 parameters and 1 restraint. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms of the molecule were assigned ideal positions and refined isotropically using a riding model with U_{iso} constrained to 1.2 times the U_{eq} of the parent atom in the case of $C(sp^2)$- and 1.5 times for $C(sp^3)$-bonded hydrogen atoms. Crystallographic data (excluding structure factors) for structure **3b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-203382. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (international) + 44(1223)336-033. E-mail: deposit@ccdc.cam.ac.uk].

aromatic ring of estrone into a highly reactive spiroepoxycyclohexa-2,4-dienone, cycloaddition with cyclopentadiene and photochemical rearrangement of the adduct. This method in turn also provides a new and efficient route to compounds with a β,γ-enone chromophore. The methodology constitutes an example in which molecular complexity is generated early on in the [2 + 4] cycloaddition, a most desirable criterion in synthesis design and development of methodology.[19]

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Note Added after ASAP Posting. Scheme 1 contained a graphical error and the Scheme 3 footnote was incorrect in the version posted ASAP May 29, 2003. The corrected version was posted June 3, 2003.

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