Synthesis of C–C bonded dimeric steroids by olefin metathesis

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ABSTRACT

Five new C–C bonded steroidal homodimers derived from deoxycholic acid, pregnenolone, and progesterone were synthesized by an olefin metathesis reaction assisted by microwave heating. Microwave improved the yield and accelerated the reaction allowing the use of less catalyst with good results (2.5 mol %). Due to the bulky nature of the steroidal skeleton the more favorable *E*-dimers were formed as the sole or major products depending on the linker length.

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1. Introduction

Synthesis of symmetric molecules derived from joining two identical moieties has gained importance in recent years. These molecules may act as ligands for proteins and as such, activate cellular processes,[1,2] or increase the affinity of ligands to their binding sites by providing an extra anchoring to the active site of certain domains.[3] In particular dimeric steroids represent a class of compounds that have attracted attention for their rigid and inherently asymmetric architecture.[4] Many dimeric steroids exhibit miscellar, detergent, and liquid crystal behavior.[5] Also, some dimeric steroids are pharmaceutically important exhibiting various biological activities as cytotoxicity and anticancer potential,[6] antimalarial,[7] serum cholesterol lowering effect,[8] and insect molting alteration.[9] They have been also used as molecular umbrellas,[10] building blocks for artificial receptors,[11] and catalysts for some organic reactions.[12] The first reports of dimeric derivatives with various inter-steroid linkages resulted from by-product formation, and only in recent years preparation of these compounds has been sought.

Dimeric steroids may be linear or cyclic and may be connected via rings in the steroid nucleus (A–A, B–B, etc.) or through the side chains, the latter being commonly used to form bile acids dimers. The individual moieties may be linked by direct connection or through spacer groups.[4] In most examples found in the literature,

the connection between the units involves a labile bond such as an ether, amide, amine, hydrazone or ester moiety. Carbon–carbon bonded dimeric steroids should be more stable to biological or harsh chemical media, however they are less common and only a few examples are found in the literature, most of them involving a direct connection between rings.[13,14] To the best of our knowledge the only report of dimeric steroids linked through carbon–carbon spacers is that by Morzycki et al.,[15] who synthesized a series of dimeric pregnane steroids linked via C-20 with long chain hydrocarbon spacers. The C–C dimerization step was performed by a Wurtz reaction and Wicha–Bal alkylation–reduction procedure with very low yields.

During our work directed toward the preparation of structurally diverse analogues of bioactive steroids, capable of invoking a broad spectrum of biological activities,[16,17] we devised a simple route to prepare C–C linked dimeric steroids by means of a metathesis coupling reaction process. Despite being a very mild reaction that tolerates the presence of a wide variety of functional groups,[18] its use in steroid chemistry is limited. Poirier et al.[19] prepared some hybrid inhibitors of type 1 17β-hydroxysteroid dehydrogenase of estradiol and an adenosine mimic through a step that involves a cross-metathesis reaction with a linear terminal olefin that elongates the side chain at C-16 with moderate but not optimized yield. The recent synthesis of 6*E*-hydroxyiminosteroid dimers, bonded through a linker with an ether functionality at C-3, is the only example of steroid homodimerization by metathesis.[20] As the steric and spatial orientation requirements of the catalysts for metathesis are critical, predicting the feasibility of such reaction on the proximity of the rigid and highly asymmetric bulky steroidal

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skeleton is not obvious, even using the most reactive terminal olefins.[21] We report here the synthesis of dimers at C-20 (ring D), C-19 and C-6 (ring B) of the steroid skeleton via an olefin metathesis coupling process using Grubbs catalyst (2nd generation) on terminal olefins, with hydrocarbon linkers of different lengths. The effect of microwave (MW) irradiation on the reaction is also presented.

2. Results and discussion

2.1. Homodimerization at the side chain through C-20

Several bile acid related dimers have been synthesized by connecting the C-20 side chains through a spacer group using ester or amide moieties. The unique characteristics of these steroidal acids in relation to their chiral, rigid, and curved framework, as well as their chemically diverse hydroxyl groups have made them important in tailoring supramolecular hosts. With this in mind we started our work studying the dimerization metathesis reaction at that position. We first prepared 20-methylidene pregnanolone **1** from pregnanolone acetate by a salt-free Wittig reaction (Scheme 1). Compound **1**, a sterically hindered 1,1-disubstituted olefin, did not dimerize in the presence of Grubbs catalysts (1st and 2nd generation) even under MW heating conditions that have proved to effectively accelerate cross-metathesis reaction between deactivated and terminal olefins.[22]

The homodimerization reaction at the C-20 side chain was then attempted on steroid **3**, a terminal olefin with a longer chain easily prepared from deoxycholic acid diacetate **2** (Scheme 1). The degradation of the side chain of **2** was achieved by an oxidative decarboxylation using the methodology developed by Suarez et al.[23] as an alternative to the classical method with Pb(AcO)$_4$ applied to bile acids.[24] The homodimerization of **3** with 2nd generation Grubbs catalyst in dichloromethane under conventional heating conditions gave a single product but did not proceed to completion (Table 1, entries 1–3). The product was characterized as the symmetric *E*-dimer **4**, the dimeric nature of the product was confirmed by electrospray (ESI) exact mass spectrometry with a pseudomolecular ion $(M+Na)^+$ at 855.5729 corresponding to the molecular formula $C_{52}H_{80}O_8Na$. The ^{13}C NMR spectrum showed 26 signals with a single olefinic carbon resonance at 134.2 ppm in accordance with a symmetric dimeric structure. The ^1H NMR spectrum was also consistent with a symmetric dimer and showed the H-22 olefin multiplet at 5.11 ppm. Analysis of ^1H NMR data for compound **4** was in agreement with the expected *E* double bond geometry (see

Table 1
Dimerization reaction of steroid **3** with Grubbs 2nd generation catalyst[a]

Entry	Heating	Catalyst (mol %)	Temp (°C)	Time (h)	Yield[c] (%)
1	Conventional	20	40	6.5	52
2	Conventional	10	40	6	20
3	Conventional	5	25	24	7
4	Microwave[b]	10	100	1.7	97
5	Microwave[b]	5	100	1.7	78
6	Microwave[b]	2.5	100	2	71

[a] Reactions were carried out in 0.3 M solutions of **3** in dichloromethane.
[b] Performed in a CEM Discover reactor at 300 W, closed vessel method.
[c] Yields calculated over isolated product after column chromatography.

below for double bond geometry analysis). Formation of the sterically less favored *Z*-isomer was not observed.

When dimerization of **3** was carried out under microwave heating conditions, an important increase in the reaction rate was observed. Using 10 mol % 2nd generation catalyst, dimer **4** was obtained in 97% yield (Table 1, entry 4). In addition to the increased yield and reaction rate the MW reaction could be carried out with a significantly lower catalyst load (5–2.5 mol %), still with good yields (Table 1, entries 5 and 6). Grubbs 1st generation catalyst was unable to dimerize **3**, even under MW conditions; in this case, the unreacted starting material was recovered intact after chromatography.

Using the optimized conditions found for **3**, the microwave assisted dimerization reaction was then performed at C-20 with two spacer groups of different length and a different functionalization of the steroid nucleus. The terminal olefins were prepared from commercial deoxycholic acid and 3-oxo-4-pregnen-20β-carboxyaldehyde (**8**) (Scheme 2). Deoxycholic acid methyl ester (**5**) was reduced with LiAlH$_4$ to the 3α,12α,24-cholanetriol that was oxidized with PCC to give diketoaldehyde **6**. A regioselective Wittig reaction with salt-free methylidenetriphenylphosphorane was a direct way to selectively olefinate the aldehyde **6** to the terminal olefin **7**. The salt-free ylide was prepared from the corresponding phosphonium salt by a methodology previously developed by our group using sodium amide, ultrasound, and a non-polar solvent with very good results.[26] Monomer **9**, with an α,β-unsaturated carbonyl system on ring A, was prepared from commercial 3-oxo-4-pregnen-20β-carboxyaldehyde using the same Wittig reaction conditions mentioned above with excellent yield (Scheme 2).

Dimerization of compounds **7** and **9** was carried out under MW irradiation with 2.5 mol % of Grubbs 2nd generation catalyst
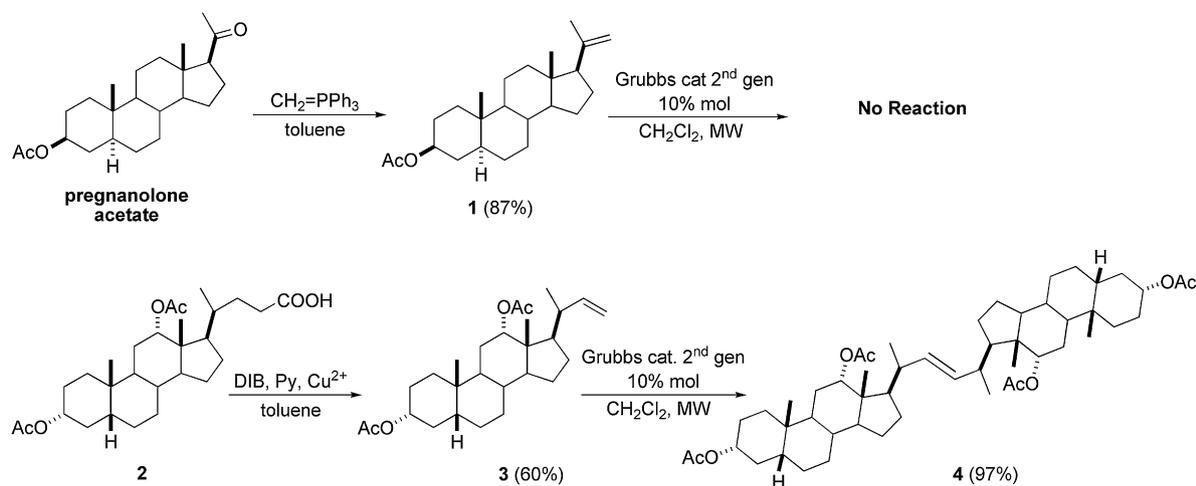
Scheme 1.
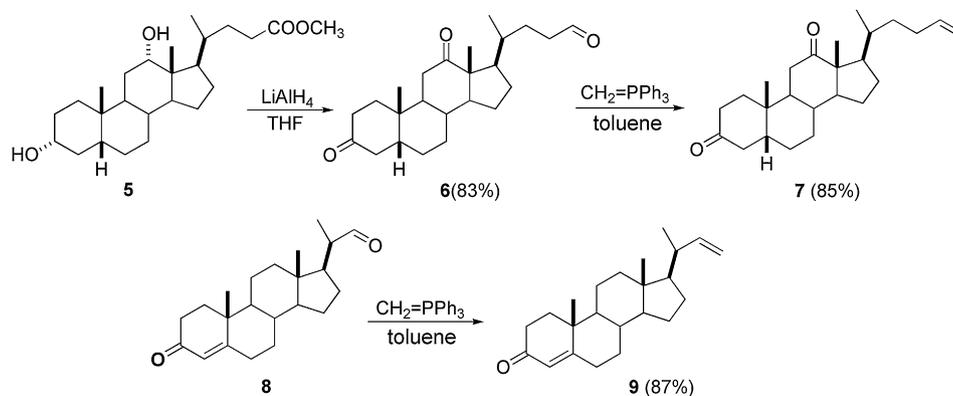
Scheme 2.
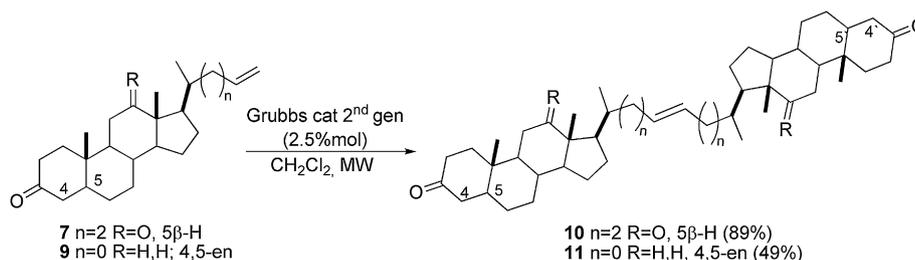
Scheme 3.

(Scheme 3). Steroid **9** gave one dimeric product in 49% yield; only 10% of unreacted material was recovered indicating some decomposition of the product and/or starting material under the reaction conditions. Spectroscopic data of **11** was consistent with the symmetric *E*-dimer structure as described previously for dimer **4**. In the case of monomer **7** with the longer spacer group, dimerization proceeded with very good yield to give a mixture of *E/Z* isomers (9:1 ratio) as observed by ^{1}H NMR. The small amount of the less favored *Z*-isomer (not observed with compounds **4** and **11**) probably arises due to reduced steric hindrance from the steroid nucleus, which is further away from the double bond. As with compound **3**, the dimerization of **7** and **9** did not proceed with 1st generation Grubbs catalyst in dichloromethane, even under MW heating.

2.2. Homodimerization at ring B through C-6

Functionalization of the pregnane skeleton at C-6 starting from steroid **12** is shown in Scheme 4; compound **12** can be easily prepared from pregnenolone acetate.[27] In order to avoid any interference in the metathesis reaction the C-2 double bond was hydrogenated in the presence of 10% Pd/C to give 6-ketosteroid **13**. Addition of allylmagnesium chloride to the 6-ketone in **13** gave a mixture of 6α and 6β allyl steroids (**14** and **15**) that could not be separated. As expected the major product was the 6α-allyl steroid generated by attack to the less hindered alpha face; deacetylation at C-20 was also observed. The mixture of 6-allyl steroids was oxidized with PCC to give after column chromatography the corresponding 20-ketones **16** (72%) and **17** (9%). Steroid **13** was also
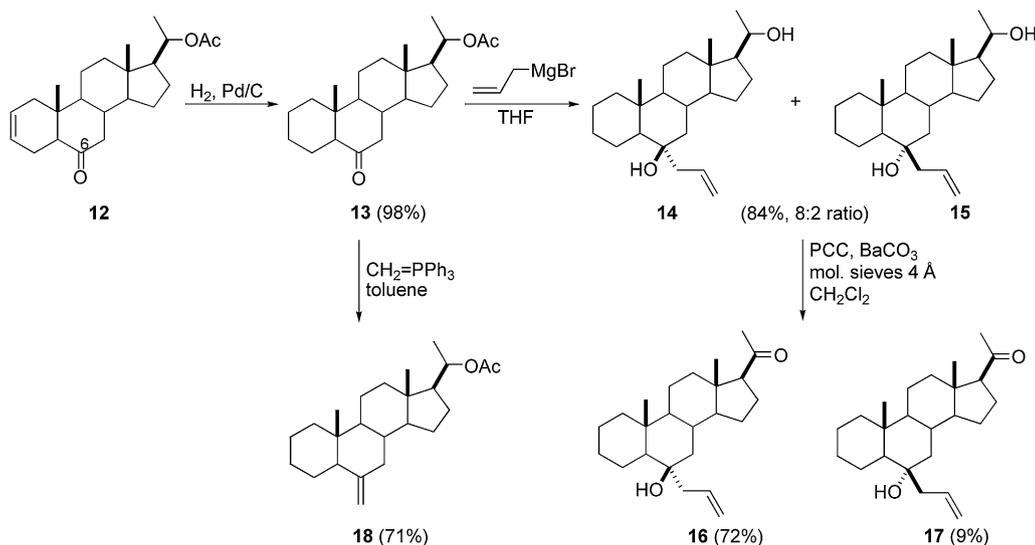
Scheme 4.

converted to olefin **18** via a Wittig reaction with methylidene-triphenylphosphorane. The three olefins were then submitted to MW mediated metathesis reaction with 2nd generation Grubbs catalyst. Compound **17**, with the allyl group oriented in an axial position did not dimerize; the same happened when reaction was attempted with the 1,1-disubstituted alkene **18**. On the other hand, steroid **16** reacted to give the *E*-dimer **19** as the major product, with a 5% of the *Z*-isomer detected by NMR (Scheme 5). This mixture could not be separated by chromatography, and compound **19** was purified by recrystallization from 2-propanol. The dimeric nature of **19** was confirmed by exact mass spectrometry (ESI) with a pseudomolecular ion $(M+Na)^+$ at 711.5323 corresponding to the molecular formula $C_{46}H_{72}O_4Na$. The ^{13}C NMR spectrum showed 23 signals with a single olefinic carbon resonance at 129.51 ppm that showed correlation in the HSQC spectrum with the olefinic multiplet at 5.35 ppm in accordance with a symmetric dimeric structure. Complete analysis of the ^1H NMR spectrum (500 MHz) together with 2D spectra (HSQC, HMBC, and COSY) was consistent with a symmetric dimer. The *Z*-isomer could not be separated and was analyzed in the NMR spectra of the mixture, showing also 23 carbon resonances with only one olefinic carbon at 127.38 ppm that correlated with a proton at 5.51 ppm (HSQC). When the mixture of olefins **16** and **17** was submitted to MW metathesis reaction conditions, monomer **16** homodimerized to give **19** while monomer **17** was recovered unreacted after chromatography proving that even the cross-metathesis between the α and β allylic groups is not possible under the conditions used.

2.3. Homodimerization through C-19

Dimerization at C-19 was particularly interesting, since the angular methyl group has an axial orientation on the β face of the steroid. A dimeric steroid connected through C-19 has the possibility to oppose both β faces that, added to the rigidity of the steroid framework may give rise to a cavity, either hydrophobic or hydrophilic depending on the functionalities present on the steroid nucleus. There is only one example of a C-19 dimeric steroid reported in the literature, this was detected as a by-product in the reaction mixture of a Simmons–Smith methylenation and was connected through a linker containing two ether moieties.[25]
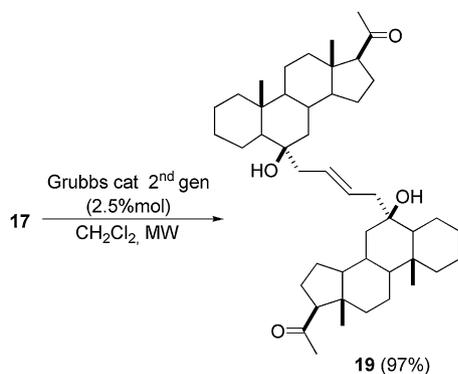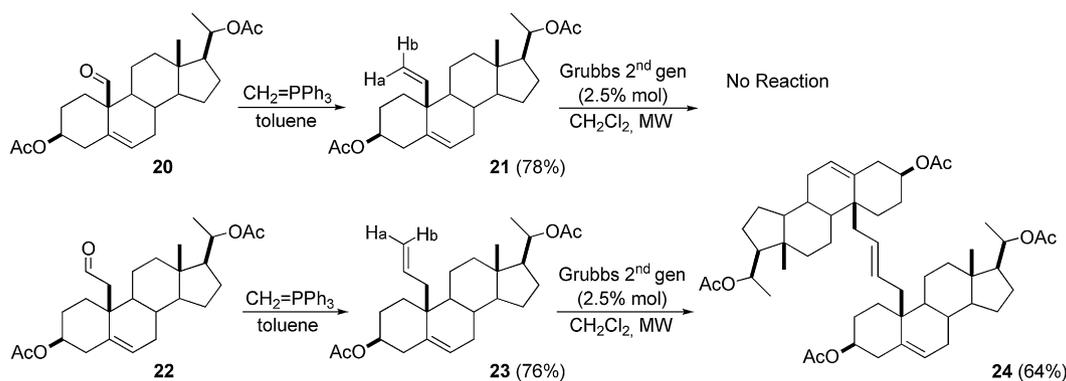
To apply the metathesis reaction to the synthesis of C-19 linked homodimers, we first prepared the C-19 aldehyde steroid **20** and its homologue **22** with one extra methylene group using a methodology previously developed by our group (Scheme 6).[26] The aldehydes were converted to the corresponding terminal olefins **21** and **23** by a salt free Wittig reaction; the olefins were fully characterized by NMR, mass spectrometry, and elemental analysis. Both monomeric olefins were subjected to metathesis under the microwave conditions previously described for preparation of the other dimers. While olefin **21** did not dimerize (the starting material was quantitatively recovered after chromatography) its analogue **23**, with a longer chain, and thus less hindered olefin, gave the *E*-dimer **24** in 64% yield. Only 13% of unreacted monomer was recovered after chromatography, accounting for some side reactions probably due to the presence of the C-5 double bond. Spectroscopic data was in agreement with the dimeric nature of the product. The ^{13}C NMR spectra of **24** showed the presence of 26 carbon atoms consistent with a symmetric structure with only three olefinic carbon resonances at 124.4 (C-6), 137.1 (C-5), and 129.2 (C-22). The latter carbon showed a 1-bond correlation (HSQC) with the hydrogen at 5.42 ppm (H-22) and a long-range correlation (HMBC) with both H-19 at 2.45 and 2.03 ppm. The *E* geometry of the double bond of all dimers was confirmed by a computational and matching procedure of the ^1H NMR resonance as described in the following section.

2.4. ^1H NMR analysis of the symmetric double bond geometry

Geometry assignment of the symmetric double bond present on the dimers was not straightforward. Even though we expected the formation of the less hindered *E*-isomer as the only or major product, chemical equivalence of the olefinic protons due to the symmetric structures precluded using their mutual coupling constant to establish the double bond stereochemistry. However magnetic non-equivalence due to the vicinal hydrogens results in a strongly coupled proton system with irregular splitting and intensity ratios (XAA′X′ or $X_2AA'X_2$ patterns) that contains information on the olefinic protons coupling constant. We solved the problem by using a computational and matching procedure. The simulations (^1H NMR, 500 MHz) were carried out using the experimental chemical shift data taken from the spectra of the dimers; the coupling constants were estimated from the spectra of the corresponding monomers ($^3J_Z \approx 10$–13 Hz and $^3J_E \approx 16$–17 Hz).

Scheme 5.

Scheme 6.
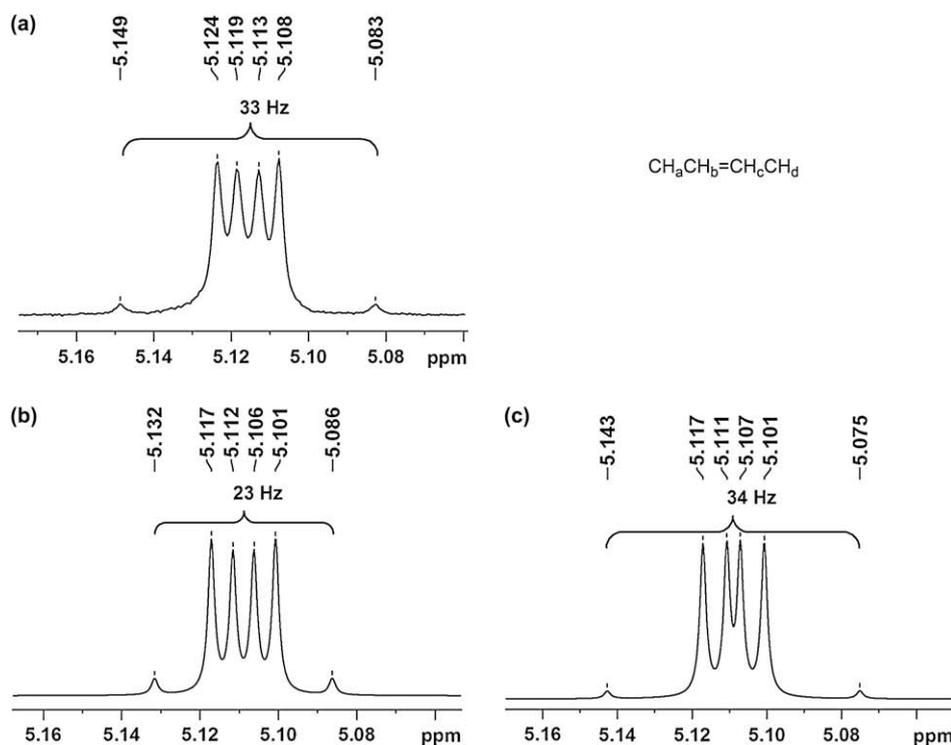
Figure 1. Comparison of the ^{1}H NMR (500 MHz) resonance for the olefinic proton on dimer **11**: (a) experimental resonance at δ_{Hb}=5.11 ppm, (b) simulated resonance for the *Z*-isomer: δ_{Hb}=5.109 ppm, coupling constants (Hz) J_{ab}=8; J_{ac}=0.2; J_{bc}=10; J_{ad}=0, (c) simulated resonance for the *E*-isomer: δ_{Hb}=5.109 ppm, coupling constants (Hz) J_{ab}=8; J_{ac}=0.2; J_{bc}=16; J_{ad}=0 (simulations with NMR-SIM TOPSPIN 2.1).

Using these values we simulated the systems as exemplified for dimer **11** (Fig. 1). Simulation of the *E* alkene dimers gave a resonance for the olefinic proton that perfectly matches the experimental result with a splitting between the outer lines of 34–35 Hz (ca. 2×J_E). For the *Z* isomers the splitting was 22–23 Hz (ca. 2×J_Z) (see Supplementary data).

3. Conclusions

Microwave assisted metathesis reaction of terminal steroidal olefins has proven to be a useful methodology for the preparation of homodimeric steroids. In all cases microwave irradiation accelerated the reaction rate and also improved the yield compared with conventional heating allowing to lower the load of catalyst to 2.5 mol% with acceptable yields. Overall five dimeric steroids linked through C-6, C-19, and C-20 were obtained and fully characterized, the homodimers had the *E* geometry although for compounds **10** and **19** a small amount (less than 10%) of *Z*-isomer was detected by NMR.

4. Experimental

4.1. General

Melting points of crystalline solids were measured on a Fisher Johns apparatus and are uncorrected. IR spectra were recorded in thin films using KBr disks on a Nicolet Magna IR 550 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance II 500 (500.13 and 125.72 MHz) NMR spectrometer in deuteriochloroform using TMS as internal standard. The electron impact mass spectra were measured on a Shimadzu QP-5000 mass spectrometer at 70 eV or on a VG-Trio 2 at 20 eV, by direct inlet. Exact mass spectra (ESI) were measured on an Agilent LCTOF, high resolution TOF analyzer with APCI/ESI ionization. Elemental analysis was performed on an EAI Exeter Analytical, Inc. CE-440

apparatus. Microwave assisted reactions were carried out in a CEM Discover reactor. Analytical thin layer chromatography (TLC) was performed on pre-coated silica plates (Merck F$_{254}$, 0.2 mm thickness); compounds were visualized by staining with cerium molybdate (Hannessian's stain). Flash column chromatography was performed on silica gel Merck 9385 (0.0040–0.0063 mm) or Florisil. All solvents used were reagent grade. Solvents were evaporated at 45 °C under vacuum in a rotary evaporator. The homogeneity of all compounds was confirmed by TLC. Products obtained as solids or syrups were dried under high vacuum. 3α,12α-Diacetoxy-5β-cholan-24-oic acid (**2**) was prepared from commercial deoxycholic acid following the procedure described in the literature.[24] 3α,12α-Dihydroxy-5β-cholanic acid methyl ester (**5**) was prepared by esterification of deoxycholic acid with methanol/HCl.[25] 3β,20β-Diacetyloxy-5-pregnen-19-al (**20**) and 3β,20β-diacetyloxy-5-pregnen-19-carboxyaldehyde (**22**) were obtained as described previously.[26]

4.2. Preparation of 'salt-free' methylidenetriphenylphosphorane

To 420 mg (10.7 mmol) of powdered sodium amide in toluene (18.5 mL) under argon was added methyltriphenylphosphonium bromide (2.05 g, 5.7 mmol). The mixture was sonicated in a Cole-Palmer 8852 ultrasound bath (352 W) at room temperature for 1.5 h, degassed under vacuum (0.5 Torr) with stirring for 30 min, and then centrifuged to remove the salts. The resulting ylide solution was used without further treatment in the Wittig olefination reaction.

4.3. Wittig reaction with methilidenetriphenylphosphorane (general procedure)

To a solution of the corresponding aldehyde or ketone (1.5 mmol) in anhydrous toluene (5 mL) under argon was added the

solution of the salt-free ylide (1.5 mmol). The mixture was stirred at room temperature for 1 h and directly applied to a flash chromatography column (silica gel), elution with ethyl acetate/hexanes mixtures of increasing polarity gave the corresponding alkenes.

4.4. Microwave assisted metathesis dimerization (general procedure)

To a solution of the corresponding monomeric alkene in anhydrous dichloromethane (0.3 M) was added Grubbs 2nd generation catalyst (2.5% mol) at room temperature under argon. The reaction tube was sealed and irradiated in a microwave reactor at the indicated temperature for the appropriate time. All microwave irradiations were carried out at 300 W, in a closed vessel, with power max on. The reaction mixture was directly applied to a flash chromatography column on silica gel and eluted with ethyl acetate/hexanes mixtures to give the corresponding dimers.

4.4.1. 3β-Acetyloxy-20-methylidenepregnane (1)

Prepared from pregnanolone acetate (323 mg, 0.9 mmol) following the general methodology for the Wittig reaction compound **1** was obtained as a white solid (281 mg, 87%). Mp 110–112 °C; IR (KBr, cm^{-1}) 2934, 2909, 2843, 1732, 1632, 1266, 1033, 889; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.84 (t, 1H, J=1.4 Hz, 22a-H), 4.69 (m, 2H, 22-Hb and 3-H), 2.02 (m, 3H, acetate), 1.75 (s, 3H, 21-H), 0.82 (s, 3H, 19-H), 0.56 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.7 (COO), 145.8 (C-20), 110.6 (C-22), 73.8 (C-3), 57.3 (C-17), 56.2 (C-14), 54.4 (C-9), 44.7 (C-5), 43.3 (C-13), 38.9 (C-1), 36.8 (C-12), 35.8 (C-8), 35.5 (C-10), 34.0 (C-4), 31.9 (C-7), 28.6 (C-6), 27.5 (C-2), 25.4 (C-21), 24.7 (C-15), 24.2 (C-16), 21.5 (CH$_3$COO), 21.3 (C-11), 12.9 (C-19), 12.3 (C-18). Anal. Calcd for C$_{24}$H$_{38}$O$_2$: C, 80.4; H, 10.7%. Found: C, 80.1; H, 10.8%; MS (EI) m/z 358 (M)$^+$, 298 (M−acetate), 283, 229, 215, 149, 133, 119, 107, 93, 81, 55, 43.

4.4.2. 3α,12α-Diacetoxy-5βH-22-cholene (3)

A solution of **2** (5.4 g, 8.75 mM), Cu(AcO)$_2$ (422 mg, 1.75 mmol), and pyridine (0.66 mL) in anhydrous toluene (53 mL) under argon was stirred at room temperature for 15 min. The mixture was heated under reflux and iodobenzene diacetate was added portionwise every 90 min (5×430 mg, 5 mmol). After the addition was completed heating was continued for 8 h. The reaction mixture was cooled to room temperature and extracted with 5% HCl. The organic layer was washed with water, dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent evaporated. The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate mixtures to give **3** as a white solid (2.8 g, 57%). Further elution gave a second fraction of unreacted **1** (648 mg, 12%). Spectroscopic data of compound **3** (^{1}H NMR, IR) was identical to that found in literature.[23]

4.4.3. (E)-1,2-Bis-(3α,12α-hydroxy-5βH-pregnan-20-yl)-ethene (4)

Method A. Prepared from **3** (25 mg, 0.06 mmol) following the MW assisted metathesis general methodology compound **4** was obtained as a white solid (24 mg, 97%).

Method B. Alternatively, **4** was prepared by adding Grubbs-type second generation catalyst (20 mol%) to a solution of **3** (128 mg, 0.30 mmol) in anhydrous dichloromethane (0.2 M) at room temperature under argon. The reaction mixture was then stirred for 6.5 h and directly applied to a flash chromatography column (silica gel) to afford **4** (65 mg, 52%) and unreacted **3** (50 mg, 39%). Mp 201–202 °C; IR (KBr, cm^{-1}) ν 2940, 2857, 1729, 1234, 1125; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.08 (m, 1H, 22-H), 5.06 (m, 1H, 12-H), 4.71 (m, 1H, 3-H), 2.11 (s, 3H, acetate), 2.04 (s, 3H, acetate), 0.91 (s, 3H, 19-H), 0.86 (d, J=6.7 Hz, 3H, 21-H), 0.73 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6 (COO), 170.5 (COO), 134.2 (C-22), 75.8 (C-12), 74.2 (C-3), 49.5 (C-14), 47.8 (C-17), 44.9 (C-13), 41.9 (C-5), 39.4 (C-20), 35.7 (C-9), 34.8 (C-10), 34.5 (C-1), 34.1 (C-8), 32.3 (C-4), 27.9 (C-2), 26.9

(C-6), 26.7 (C-7), 25.9 (C-16), 25.7 (C-11), 23.6 (C-15), 23.1 (C-19), 21.5 (CH$_3$COO), 21.4 (CH$_3$COO), 20.4 (C-21), 12.7 (C-18); HRMS (ESI) calcd for C$_{52}$H$_{80}$O$_8$Na (MNa$^+$): 855.5745, found: 855.5729.

4.4.4. 3,20-Dioxo-5βH-cholan-24-al (6)

To a solution of 3α,12α-dihydroxy-5β-cholanic acid methyl ester (**5**, 500 mg, 1.23 mmol) in anhydrous THF (25 mL) was added LiAlH$_4$ (93 mg, 2.46 mmol) at 0 °C under argon. The reaction mixture was stirred for 15 min at room temperature and quenched by successively adding acetone, HCl 10%, and sodium and potassium tartrate saturated solution. The mixture was concentrated in vacuo, the residue was dissolved in dichloromethane, and washed with aqueous sodium bicarbonate, brine, and water. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent evaporated to give 3α,12α,24-5βH-cholanetriol. The crude triol was oxidized without further purification with PCC (1.2 g, 5.54 mmol), barium carbonate (631 mg, 3.20 mmol), and 4 Å molecular sieves in anhydrous dichloromethane (20 mL) at room temperature under a nitrogen atmosphere for 30 min. The reaction was diluted with diethyl ether and the mixture was concentrated in vacuo. The residue was redissolved in diethyl ether and the resulting solution was applied to a flash chromatography column (Florisil) and eluted with diethyl ether to give **6** (368 mg, 83%) as a crystalline solid. Mp 108–110 °C; IR (KBr, cm^{-1}) ν 2967, 1707, 1657, 1460, 1083, 1219, 891; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.78 (t, 1H, J=1.7 Hz, 24-H), 2.59 (dd, J=15.0, 13.2 Hz, 1H, 4α-H), 2.50 (ddd, J=9.5, 5.4, 0.8 Hz, 1H, 23a-H), 2.43 (dt, J=7.7, 1.0 Hz, 1H, 23b-H), 2.33 (dd, J=14.7, 5.4 Hz, 1H, 2a-H), 2.19 (ddd, J=14.7, 6.4, 3.1 Hz, 1H, 2b-H), 1.12 (s, 3H, 19-H), 1.06 (s, 3H, 18-H), 0.86 (d, J=6.6 Hz, 3H, 21-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 214.1 (C-12), 212.1 (C-3), 203.0 (C-24), 58.5 (C-9), 57.6 (C-13), 46.5 (C-17), 44.3 (C-14), 43.7 (C-5), 42.1 (C-4), 41.2 (C-23), 38.4 (C-11), 36.9 (C-2), 36.8 (C-1), 35.6 (C-10), 35.6 (C-20), 35.4 (C-8), 27.6 (C-22), 27.4 and 26.6 (C-7, C-15), 25.5 (C-6), 24.3 (C-16), 22.1 (C-19), 18.7 (C-21), 11.7 (C-18). Anal. Calcd for C$_{24}$H$_{36}$O$_3$: C, 77.4; H, 9.7%. Found: C, 77.3; H, 9.7%; MS (EI) m/z 372 (M)$^+$, 354, 344, 329, 247, 121, 107, 93, 81, 55, 41.

4.4.5. 5βH-24-Cholene-3,12-dione (7)

Prepared from 3,20-dioxo-5βH-cholan-24-al (**6**) (500 mg, 1.35 mmol) following the general Wittig methodology described above compound **7** was obtained as a white crystalline solid (424 mg, 85%). Mp 121–122 °C; IR (KBr, cm^{-1}) ν 2970, 2948, 2906, 2869, 1709, 1507, 1452, 1028; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.79 (ddt, J=17.1, 10.2, 6.7 Hz, 1H, 24-H), 4.98 (ddt, J=17.2, 2.0, 1.7 Hz, 1H, 25a-H), 4.91 (ddt, J=10.1, 2.1, 1.2 Hz, 1H, 25b-H), 2.61 (t, J=12.5 Hz, 1H, 11β-H), 2.59 (dd, J=14.8, 13.6 Hz, 1H, 4α-H), 1.11 (s, 3H, 19-H), 1.05 (s, 3H, 18-H), 0.86 (d, J=6.6 Hz, 3H, 21-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 214.2 (C-12), 212.1 (C-3), 139.5 (C-24), 114.1 (C-25), 58.6 (C-9), 57.6 (C-13), 46.8 (C-17), 44.3 (C-14), 43.7 (C-5), 42.1 (C-4), 38.4 (C-11), 36.9 (C-2), 36.8 (C-1), 35.7 (C-20), 35.6 (C-10), 35.5 (C-8), 34.8 (C-22), 30.9 (C-23), 27.6 and 26.6 (C-7, C-15), 25.5 (C-6), 24.4 (C-16), 22.2 (C-19), 18.8 (C-21), 11.7 (C-18). Anal. Calcd for C$_{25}$H$_{38}$O$_2$: C, 81.0; H, 10.3%. Found: C, 81.0; H, 10.3%; MS (EI) m/z 370 (M)$^+$, 355, 337, 328 (M−ketene), 273, 247, 135, 121, 107, 93, 81, 55, 41.

4.4.6. 20-Ethenyl-4-pregnen-3-one (9)

Prepared from 3-oxo-4-pregnen-20β-carboxyaldehyde (**8**, 500 mg, 1.5 mmol) following the general Wittig methodology described above compound **9** was obtained as a white crystalline solid (426 mg, 87%). Mp 116–117 °C; IR (KBr, cm^{-1}) ν 2951, 2865, 2843, 1671, 1452, 1230, 911, 864; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.72 (s, 1H, 4-H), 5.66 (ddd, J=17.1, 10.2, 8.4 Hz, 1H, 22-H), 4.91 (dd, J=17.1, 2.0 Hz, 1H, 23a-H), 4.82 (dd, J=10.2, 2.0 Hz, 1H, 23b-H), 1.19 (s, 3H, 19-H), 1.04 (d, J=6.6 Hz, 3H, 21-H), 0.74 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.6 (C-3), 171.6 (C-5), 145.1 (C-22), 123.8 (C-4), 111.7 (C-23), 55.9 (C-14), 55.4 (C-17), 53.8 (C-9), 42.4 (C-13), 41.2 (C-20), 39.5 (C-12), 38.6 (C-10), 35.7 (C-1), 35.6 (C-8), 34.0 (C-2), 32.9

(C-6), 32.0 (C-7), 28.3 (C-16), 24.2 (C-15), 21.0 (C-11), 20.1 (C-21), 17.4 (C-19), 12.2 (C-18). Anal. Calcd for $C_{23}H_{34}O$: C, 84.6; H, 10.5%. Found: C, 84.6; H, 10.8%; MS (EI) *m/z* 326 (M)$^+$, 298, 284 (M−ketene), 269, 229, 203, 147, 133, 124, 107, 91, 79, 55, 41.

4.4.7. 1,4-Bis-(3,12-dioxo-5βH-pregnan-20-yl)-2E-butene (10)

Prepared from **7** (20 mg, 0.05 mmol) following the general MW assisted metathesis methodology compound **10** was obtained as a white solid (16 mg, 89%). Mp 246–249 °C; IR (KBr, cm^{-1}) *ν* 2926, 2862, 2249, 1705, 1646, 1460, 1383, 1272, 919; ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 5.38 (m, 1H, 24-H), 2.62 (2H, m, 4α-H and 11-Hβ), 1.12 (s, 3H, 19-H), 1.06 (s, 3H, 18-H), 0.86 (d, *J*=6.6 Hz, 3H, 21-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 214.3 (C-12), 212.2 (C-3), 130.5 (C-24), 58.6 (C-9), 57.6 (C-13), 46.8 (C-17), 44.3 (C-14), 43.7 (C-5), 42.2 (C-4), 38.4 (C-11), 36.9 (C-2), 36.8 (C-1), 35.8 (C-20), 35.6 (C-10), 35.5 (C-8), 35.5 (C-22), 29.7 (C-23), 27.6 and 26.6 (C-7, C15), 25.5 (C-6), 24.4 (C-16), 22.2 (C-19), 18.9 (C-21), 11.8 (C-18). Anal. Calcd for $C_{48}H_{72}O_4$: C, 80.9; H, 10.2%. Found: C, 81.0; H, 10.3%; MS (EI) *m/z* 671 (M−ketene), 626, 591, 491, 336, 312, 284, 269, 243, 215, 145, 105, 91, 79, 55, 40.

4.4.8. (E)-1,2-Bis-(3-oxo-4-pregnen-20-yl)-ethene (11)

Prepared from **9** (82 mg, 0.25 mmol) following the general MW assisted metathesis methodology, after chromatography (silica gel, ethyl acetate/hexanes) compound **11** was obtained as a white solid (38 mg, 49%). Mp 250–254 °C (dec); IR (KBr, cm^{-1}) *ν* 2968, 2937, 2865, 1635, 1458, 1269, 1227; ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 5.73 (s, 1H, 4-H), 5.11 (m, 1H, 22-H), 1.19 (s, 3H, 19-H), 0.98 (d, *J*=6.6 Hz, 3H, 21-H), 0.72 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 199.7 (C-3), 171.7 (C-5), 134.3 (C-22), 123.8 (C-4), 56.0 (C-14, C-17), 53.8 (C-9), 42.3 (C-13), 40.1 (C-20), 39.5 (C-12), 38.6 (C-10), 35.7 (C-1), 35.6 (C-8), 34.0 (C-2), 33.0 (C-6), 32.0 (C-7), 28.8 (C-16), 24.3 (C-15), 21.0 (C-11), 20.9 (C-21), 17.4 (C-19), 12.1 (C-18). Anal. Calcd for $C_{44}H_{64}O_2$: C, 84.6; H, 10.3%. Found: C, 84.4; H, 10.4%; MS (EI) *m/z* 624 (M)$^+$, 609, 582 (M−ketene), 269, 147, 131, 119, 107, 95, 81, 55, 41. Further elution rendered a fraction of unreacted **9** (8 mg, 10%).

4.4.9. 20β-Acetyloxy-5αH-2-pregnen-6-one (12)

Prepared from pregnenolone acetate (200 mg, 0.56 mmol) using the method described by Mori et al.[28] compound **12** was obtained as an amorphous solid (164 mg, 82%). IR (KBr, cm^{-1}) *ν* 2942, 2906, 1730, 1708, 1433, 1373, 1075, 1024; ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 5.69 (m, 1H, 3-H), 5.56 (m, 1H, 2-H), 4.85 (br s, 1H, 20-H), 2.02 (s, 3H, acetate), 1.16 (d, *J*=5.8 Hz, 3H, 21-H), 0.71 (s, 3H, 19-H), 0.65 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 211.6 (C-6), 170.3 (COO), 125.0 (C-2), 124.5 (C-3), 72.7 (C-20), 56.1 (C-14), 54.9 (C-17), 53.9 (C-9), 53.5 (C-5), 46.9 (C-7), 42.6 (C-13), 40.0 (C-10), 39.4 (C-1), 39.0 (C-12), 37.5 (C-8), 25.2 (C-16), 24.0 (C-15), 21.6 (C-4), 21.5 (CH$_3$COO), 21.0 (C-11), 19.9 (C-21), 13.5 (C19), 12.5 (C-18); MS (ESI) *m/z* 381 (M+Na)$^+$, 359 (M+H)$^+$, 298, 105, 93, 81, 55, 43. Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6%. Found: C, 76.6; H, 9.3%.

4.4.10. 20β-Acetyloxy-5αH-pregnan-6-one (13)

20β-Acetyloxy-5αH-2-pregnen-6-one (**12**, 150 mg, 0.42 mmol) was dissolved in ethyl acetate (15 mL), 10% Pd/C (15 mg) added and the mixture hydrogenated at 3 bar for 8 h. The catalyst was filtered and the residue purified by column chromatography (silica gel, ethyl acetate/hexanes) to give **13** as a white solid (148 mg, 98%). Mp 163–165 °C; IR (KBr, cm^{-1}) *ν* 2981, 2937, 2873, 1732, 1646, 1372, 1244, 1075, 1019, 877; ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 4.83 (dq, *J*=6.0, 10.6 Hz, 1H, 20-H), 2.28 (dd, *J*=4.5, 13.1 Hz, 1H, 7a-H), 2.13 (dd, *J*=3.2, 12.3 Hz, 1H, 5-H), 2.02 (s, 3H, acetate), 1.15 (d, *J*=6.1 Hz, 3H, 21-H), 0.72 (s, 3H, 19-H), 0.62 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 212.5 (C-6), 170.4 (COO), 72.7 (C-20), 58.9 (C-5), 56.2 (C-14), 54.9 (C-17), 54.4 (C-9), 46.8 (C-7), 42.8 (C-13), 41.8 (C-10), 39.0 (C-12), 38.2 (C-1), 37.8 (C-8), 25.3 (C-16), 25.2 (C-15), 24.0 (C-3), 21.5 (CH$_3$COO), 21.4 (C-2), 21.1 (C-11), 20.5 (C-4), 19.9 (C-21), 13.1 (C-19),

12.5 (C-18); MS (EI) *m/z* 360 (M)$^+$, 300, 285, 124, 107, 95, 81, 55, 43. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1%. Found: C, 76.8; H, 10.1%.

4.4.11. 6β-Hydroxy-6α-(1-propenyl)-5αH-pregnan-20-one (16) and 6α-hydroxy-6β-(1-propenyl)-5αH-pregnan-20-one (17)

To a solution of allylmagnesium chloride (2.0 M in THF, 1.2 mL) at 0 °C was added a solution of 20β-acetyloxy-6-methylidene-5αH-pregnane (**13**, 200 mg, 0.56 mmol) in THF (0.8 mL). The mixture was stirred at room temperature for 30 min and quenched with saturated aqueous NH$_4$Cl (1 mL). The solvent was evaporated and the residue was dissolved in dichloromethane (5 mL). The organic layer was washed with water (5 mL) and dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent evaporated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate) to give the mixture of 6α-OH and 6β-OH isomers of 5α-H-20β,6-dihydroxy-6-(1-propenyl) (8:2 ratio, 170 mg, 84%). An analytical sample of 6β-OH isomer **14**: ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 5.76 (ddt, 1H, *J*=17.1, 7.5, 10.0 Hz, 1H, 23-H), 5.07 (dd, *J*=9.9, 2.2 Hz, 1H, 24b-H), 5.05 (dd, *J*=16.8, 2.5 Hz, 1H, 24a-H), 2.22 (dd, *J*=14.0, 7.9 Hz, 1H, 22a-H), 2.17 (dd, *J*=13.7, 7.7 Hz, 1H, 22b-H), 1.14 (d, *J*=6.1 Hz, 3H, 21-H), 1.02 (s, 3H, 19-H), 0.77 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 134.4 (C-23), 118.0 (C-24), 73.7 (C-6), 70.6 (C-20), 58.6 (C-17), 55.7 (C-14), 54.3 (C-9), 50.9 (C-5), 46.9 (C-22), 43.1 (C-7), 42.5 (C-13), 40.8 (C-1), 40.2 (C-12), 36.7 (C-10), 30.8 (C-8), 26.9 (C-3), 25.6 (C-15), 24.4 (C-16), 23.6 (C-21), 21.8 (C-2), 20.5 (C-11), 20.4 (C-4), 15.5 (C-19), 12.6 (C-18). Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.9; H, 11.2%. Found: C, 79.9; H, 11.1%. An analytical sample of 6α-OH isomer **15**: ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 5.86 (dddd, *J*=17.4, 9.9, 6.9, 8.1 Hz, 1H, 23-H), 5.19 (dd, *J*=10.2, 2.3 Hz, 1H, 24b-H), 5.14 (dd, *J*=17.1, 2.3 Hz, 1H, 24a-H), 3.74 (m, 1H, 20-H), 2.29 (dd, *J*=13.7, 6.7 Hz, 1H, 22a-H), 1.97 (dd, *J*=13.7, 8.1 Hz, 1H, 22b-H), 1.13 (d, *J*=6.1 Hz, 3H, 21-H), 1.12 (s, 3H, 19-H), 0.76 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 133.4 (C-23), 119.4 (C-24), 75.0 (C-6), 70.6 (C-20), 58.7 (C-17), 55.8 (C-14), 52.2 (C-5), 46.4 (C-22), 42.7 (C-13), 41.1 (C-9), 40.3 (C-12), 39.7 (C-7), 38.8 (C-1), 36.3 (C-10), 32.0 (C-8), 27.7 (C-19), 26.9 (C-3), 25.7 (C-15), 25.0 (C-4), 24.5 (C-16), 23.6 (C-21), 20.9 (C-2), 20.5 (C-11), 12.6 (C-18). Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.9; H, 11.2%. Found: C, 79.8; H, 11.2%.

The mixture of 6α and 6β isomers obtained above (170 mg, 0.47 mmol) was oxidized with PCC (253 mg, 0.94 mmol), barium carbonate (172 mg, 0.71 mmol), and 4 Å molecular sieves in anhydrous dichloromethane (15 mL) at room temperature under a nitrogen atmosphere for 45 min. The reaction was diluted with diethyl ether, concentrated in vacuo, and the residue purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to give in order of elution: 6α-hydroxy-6β-(1-propenyl)-5αH-pregnan-20-one (**17**, 15 mg, 9%), a mixed fraction (**16**+**17**, 8 mg) and 6β-hydroxy-6α-(1-propenyl)-5αH-pregnan-20-one (**16**, 121 mg, 72%). 6β-Hydroxy-6α-(1-propenyl)-5αH-pregnan-20-one (**16**): mp 105–107 °C; IR (KBr, cm^{-1}) *ν* 3406, 2920, 2848, 1716, 1457, 1261, 1096; ^{1}H NMR (500 MHz, CDCl$_3$) *δ* 5.75 (ddt, *J*=17.0, 10.0, 7.5 Hz, 1H, 23-H), 5.08 (d, *J*=10.0 Hz, 1H, 24b-H), 5.04 (d, *J*=17.0 Hz, 1H, 24a-H), 2.12 (s, 3H, 21-H), 1.01 (s, 3H, 19-H), 0.63 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) *δ* 209.6 (C-20), 134.3 (C-23), 118.1 (C-24), 73.6 (C-6), 63.9 (C-17), 56.5 (C-14), 54.2 (C-9), 50.9 (C-5), 46.9 (C-22), 44.2 (C-13), 43.0 (C-7), 40.8 (C-1), 39.1 (C-12), 36.7 (C-10), 31.5 (C-21), 31.0 (C-8), 26.9 (C-2), 24.4 (C-15), 22.8 (C-16), 21,8 (C-11), 20.7 and 20.4 (C-4, C-3), 15.5 (C-19), 13.5 (C-18); MS (EI) *m/z* 358 (M$^+$), 340 (M-H$_2$O), 317 (M-C$_3$H$_5$), 299, 281, 189, 161, 107, 81, 55, 43. Anal. Calcd for $C_{24}H_{38}O_2 \cdot 1/2H_2O$: C, 78.1; H, 10.8%. Found: C, 77.9; H, 10.5%.[†] 6α-Hydroxy-6β-(1-propenyl)-5αH-pregnan-20-one (**17**): amorphous solid; IR (KBr, cm^{-1}) *ν* 3406, 2920, 2848, 1716, 1457,

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† Attempts to further dry these compounds failed; the content of water was determined based on found and calculated elemental analysis data.

1261, 1096; ^{1}H NMR (500 MHz, CDCl$_3$) [1]H δ 5.88 (dddd, J=17.3, 9.9, 7.7, 5.5 Hz, 1H, 23-H), 5.22 (dd, J=10.2, 2.1 Hz, 1H, 24b-H), 5.17 (dd, J=17.1, 2.0 Hz, 1H, 24a-H), 2.56 (t, J=8.9 Hz, 1H, 17-H), 2.14 (s, 3H, 21H), 1.14 (s, 3H, 19-H), 0.65 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 209.9 (C-20), 133.2 (C-23), 119.6 (C-24), 74.9 (C-6), 63.9 (C-17), 56.6 (C-14), 52.1 (C-9), 46.4 (C-5), 44.5 (C-22), 41.1 (C-13), 39.6 (C-7), 39.2 (C-1), 38.8 (C-12), 36.3 (C-10), 31.5 (C-21), 30.9 (C-8), 27.6 (C-19), 26.9 (C-2), 25.0 (C-15), 24.5 (C-16), 22.9 (C-11), 20.9 (C-3), 20.6 (C-4), 13.5 (C-18); MS (EI) m/z 358 (M$^+$), 340 (M−H$_2$O), 317 (M−C$_3$H$_5$), 299, 281, 189, 161, 107, 81, 55, 43. Anal. Calcd for C$_{24}$H$_{38}$O$_2$·1/2H$_2$O: C, 78.1; H, 10.8%. Found: C, 77.8; H, 10.4%.[†]

4.4.12. 20β-Acetyloxy-6-methylidene-5αH-pregnane (18)

Prepared from 20β-acetyloxy-5αH-pregnan-6-one (13, 250 mg, 0.69 mmol) using the general Wittig methodology compound 18 was obtained as a white solid (178 mg, 71%). Mp 156–157 °C; IR (KBr, cm^{-1}) ν 2981, 2937, 2873, 2862, 2845, 2826, 1732, 1646, 1372, 1244, 1075, 1019, 877; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.84 (m, 1H, 20-H), 4.67 (d, J=1.1 Hz, 1H, 22a-H), 4.42 (d, J=1.1 Hz, 1H, 22b-H), 2.01 (s, 3H, acetate), 1.15 (d, J=5.8 Hz, 3H, 21-H), 0.66 (s, 3H, 18-H), 0.61 (s, 3H, 19-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.4 (COO), 150.8 (C-6), 105.6 (C-22), 72.9 (C-20), 55.9 (C-14), 55.2 (C-9), 55.1 (C-17), 51.4 (C-5), 42.5 (C-13), 42.2 (C-7), 39.3 (C-12), 38.5 (C-10), 38.3 (C-1), 37.4 (C-8), 26.4 (C-3), 25.5 (C-16), 24.3 (C-2), 24.1 (C-15), 22.0 (C-4), 21.5 (CH$_3$COO), 21.0 (C-11), 19.9 (C-21), 12.6 (C-19), 12.4 (C-18); MS (EI) m/z 358 (M)$^+$, 298, 229, 161, 147, 133, 122, 105, 93, 81, 55, 43. Anal. Calcd for C$_{24}$H$_{38}$O$_2$: C, 80.4; H, 10.7%. Found: C, 80.2; H, 10.8%.

4.4.13. 1,4-Bis-(6β-hydroxy-20-oxo-5αH-pregnan-6-yl)-2E-butene (19)

Prepared from 16 (60 mg, 0.016 mmol) following the general MW assisted metathesis methodology, after chromatography (silica gel, ethyl acetate/hexanes) homodimer 19 was obtained as a white solid (53 mg, 97%). Mp 240–245 °C (dec); IR (KBr, cm^{-1}) ν 3401, 2931, 2906, 1696, 1197, 1144, 750; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.38 (dd, J=5.1, 3.4 Hz, 1H, 23-H), 2.32 (dd, J=13.5, 4.5 Hz, 1H, 22a-H), 2.14 (s, 3H, 21-H), 1.98 (dd, J=6.3, 13.7 Hz, 1H, 22b-H), 1.05 (s, 3H, 19-H), 0.67 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 209.4 (C-20), 129.5 (C-23), 74.3 (C-6), 64.0 (C-17), 56.8 (C-14), 54.6 (C-9), 50.2 (C-5), 45.6 (C-22), 44.2 (C-13), 42.7 (C-7), 40.9 (C-1), 39.3 (C-12), 36.7 (C-10), 31.5 (C-21), 31.0 (C-8), 27.0 (C-3), 24.4 (C-15), 22.8 (C-16), 21.8 (C-2), 20.7 (C-11), 20.6 (C-4), 15.5 (C-19), 13.5 (C-18); HRMS (ESI) calcd for C$_{46}$H$_{72}$O$_4$Na (M+Na)$^+$: 711.5328, found: 711.5323.

4.4.14. 3β,20β-Diacetyloxy-19-methylidene-5-pregnene (21)

Prepared from 3β,20β-diacetyloxy-5-pregnen-19-al (20, 500 mg, 1.2 mmol) using the general Wittig methodology compound 21 was obtained as a white solid (338 mg, 78%). Mp 87–88 °C; IR (KBr, cm^{-1}) ν 2936, 2905, 2869, 1729, 1370, 1241, 1033; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.65 (dd, J=17.6, 10.6 Hz, 1H, 19-H), 5.63 (dd, J=5.1, 1.9 Hz, 1H, 6-H), 5.29 (dd, J=10.6, 1.8 Hz, 1H, 22b-H), 4.96 (dd, J=17.5, 1.8 Hz, 1H, 22a-H), 4.83 (m, 1H, 3-H), 4.64 (m, 1H, 20-H), 2.03 (s, 3H, acetate), 2.02 (s, 3H, acetate), 0.56 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6 (COO), 170.4 (COO), 142.1 (C-22), 136.1 (C-5), 125.1 (C-6), 117.8 (C-19), 73.9 (C-3), 72.9 (C-20), 55.5 (C-14), 54.9 (C-17), 50.2 (C-9), 44.7 (C-10), 42.2 (C-13), 39.2 (C-12), 38.4 (C-4), 35.6 (C-1), 31.7 (C-7), 31.0 (C-8), 28.3 (C-2), 25.4 (C-16), 24.3 (C-15), 21.5 (CH$_3$COO), 21.4 (CH$_3$COO), 21.2 (C-11), 19.9 (C-21), 12.3 (C-18); MS (EI) m/z 354 (M−AcO)$^+$, 294, 161, 117, 91, 79, 55, 43. Anal. Calcd for C$_{26}$H$_{38}$O$_4$: C, 75.3; H, 9.2%. Found: C, 75.5; H, 9.2%.

4.4.15. 19-Ethenyl-3β,20β-diacetyloxy-5-pregnene (23)

Prepared from 3β,20β-diacetyloxy-5-pregnen-19-carboxy-aldehyde (22, 40 mg, 0.1 mmol) using the general Wittig method-ology compound 23 was obtained as a white solid (30 mg, 76%). Mp 125–127 °C; IR (KBr, cm^{-1}) ν 2956, 2868, 1740, 1727, 1370, 1034, 737;

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.76 (ddt, J=22.0, 10.0, 5.0 Hz, 1H, 22-H), 5.57 (td, J=5.2, 1.8 Hz, 1H, 6-H), 5.05 (ddd, J=17.2, 2.1, 1.5 Hz, 1H, 23b-H), 4.96 (dt, J=10.1, 2.0 Hz, 1H, 23a-H), 4.83 (dq, J=10.9, 6.0 Hz, 1H, 20-H), 4.63 (tt, J=11.5, 5.0 Hz, 1H, 3-H), 2.57 (ddt, J=14.5, 5.0, 1.9 Hz, 1H, 19a-H), 2.09 (dd, J=15.1, 9.8 Hz, 1H, 19b-H), 2.04 (s, 3H, acetate), 2.03 (s, 3H, acetate), 1.15 (d, J=6.1 Hz, 3H, 21-H), 0.62 (s, 3H, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6 (COO), 170.5 (COO), 137.3 (C-22), 136.8 (C-5), 124.7 (C-6), 115.3 (C-23), 73.9 (C-3), 72.9 (C-20), 57.2 (C-14), 54.8 (C-17), 51.4 (C-9), 42.4 (C-13), 39.7 (C-10), 39.5 (C-12), 38.2 (C-4), 37.2 (C-1), 36.5 (C-19), 32.5 (C-8), 31.4 (C-7), 27.7 (C-2), 25.4 (C-16), 24.2 (C-15), 21.6 (CH$_3$COO), 21.4 (CH$_3$COO), 21.2 (C-11), 19.9 (C-21), 12.7 (C-18); MS (EI) m/z 387 (M−allyl), 368 (M−AcOH), 327, 309, 267, 143, 133, 121, 105, 91, 79, 55, 43. Anal. Calcd for C$_{27}$H$_{40}$O$_4$·1/2H$_2$O: C, 74.1; H, 9.4%. Found: C, 74.2; H, 9.1%.[†]

4.4.16. E-1,2-Bis-(3β,20β-diacetoxy-5-pregnen-19-yl)-ethene (24)

Prepared from 23 (22 mg, 0.05 mmol) following the general MW assisted metathesis methodology, after chromatography (silica gel, ethyl acetate/hexanes) compound 24 was obtained as a white solid (12.4 mg, 64%). Mp 195–198 °C; IR (KBr, cm^{-1}) ν 2939, 2873, 2850, 1733, 1367, 1247, 1031, 926; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.48 (d, J=5.0 Hz, 1H, 6-H), 5.40 (m, 1H, 22-H), 4.83 (dq, J=10.4, 6.0 Hz, 1H, 20-H), 4.62 (tt, J=11.7, 5.0 Hz, 1H, 3-H), 2.44 (dd, J=15.7 Hz, 5.2, 1H, 19a-H), 2.05 (3H, s, acetate), 2.04 (3H, s, acetate), 1.16 (d, J=6.1 Hz, 3H, 21-H), 0.65 (3H, s, 18-H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6 (COO), 170.5 (COO), 137.1 (C-5), 129.2 (C-22), 124.4 (C-6), 73.9 (C-3), 72.9 (C-20), 57.1 (C-14), 54.9 (C-17), 51.3 (C-9), 42.3 (C-13), 40.1 (C-10), 39.4 (C-12), 38.4 (C-4), 37.1 (C-1), 35.5 (C-19), 32.7 (C-8), 31.6 (C-7), 27.7 (C-2), 25.6 (C-16), 24.2 (C-15), 21.5 (C-11), 21.5 (CH$_3$COO), 21.5 (CH$_3$COO), 19.9 (C-21), 12.7 (C-18); MS (ESI) m/z 387, 327, 267, 143, 121, 58, 43. Anal. Calcd for C$_{52}$H$_{76}$O$_8$: C, 75.3; H, 9.2%. Found: C, 75.8; H, 9.5%. Further elution rendered a fraction of unreacted 23 (3 mg, 14%).

Acknowledgements

Supplementary data

Supplementary data includes ^{1}H and ^{13}C NMR spectra for all monomers and dimeric steroids with the complete E/Z geometry analysis data of dimers by the ^{1}H NMR simulation-matching method. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.006.

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