

Synthesis and characterization of dimeric steroids based on 5-oxo-4,5-seco-yne units linked by a diyne spacer

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Dedicated to Professor Gordon W. Gribble on the occasion of his retirement from Dartmouth College

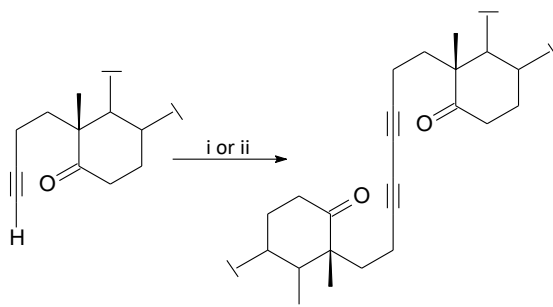
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Abstract

New dimeric steroids in which two 5-oxo-4,5-seco-3-yne steroids units are linked by a flexible diyne spacer, were prepared by both Eglinton and Pd-catalyzed coupling of the corresponding monomers. X-Ray crystallography shows that one of the obtained dimers displays a novel supramolecular network in which the facial hydrophobicity of the steroidal skeleton plays an important role. The crystal packing is dominated by interactions that accommodate the steroid cores in a highly crowded packed columnar self-assembly. Unambiguous NMR characterization of the obtained compounds is also provided.



i) **Method A** $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}/\text{pyr}/\text{CH}_3\text{OH}$ reflux
ii) **Method B** $\text{Pd}(\text{PPh}_3)_4$, O_2 , CuI , Et_3N , RT

Keywords: 5-Oxo-4,5-seco-3-yne steroids, Eglinton alkyne coupling, palladium catalyzed alkyne coupling, bis-4,4-(5-oxo-4,5-seco-3-yne steroids), NMR, X-ray diffraction

Introduction

Steroids are a family of lipophilic compounds that are widespread in nature. Their intrinsic biological activity has kept this kind of compound in the focus of attention for more than a century. The subfamily of steroid dimers added its first members when a few compounds were isolated from nature¹ or occurred as by-products of various reactions.² The interesting chemical, biological and physical properties of the rising number of steroid dimers isolated from living organisms or obtained by synthesis³⁻⁷ has prompted intensive activity in this developing field.

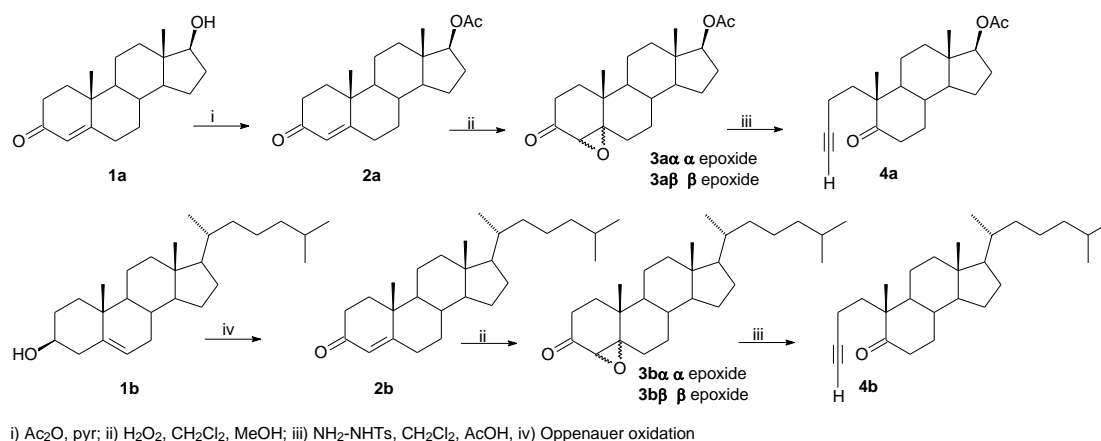
Although dimeric steroids are known to form well-defined crystals, reports on the crystal structure of this type of compound are rather scarce, compared to those of monomeric steroids. As part of a program on the development of steroid-based crystalline systems, we have become interested in the preparation of compounds with flexible structural arrangements. In a previous publication we described the synthesis of dimeric terephthalates derived from epimeric 4,5-*seco*-cholest-3-yn-5-ols that display novel supramolecular networks in the solid state in which the facial hydrophobicity of the steroidal skeletons plays an important role.⁸ This prompted us to set up procedures to prepare dimeric steroids in which the steroid cores are joined by a diyne moiety that acts as a flexible spacer.

1,3-Diynes are considered important building blocks for organic synthesis and material science. This has prompted the development of a large collection of synthetic methods for the preparation of such compounds.^{10,11} In particular, the synthesis of symmetric conjugated diynes can be obtained by several methods that include the different modifications of the Glaser-Eglinton-Hay oxidative coupling.

Herein we report the synthesis and NMR characterization of bis-4,4-(5-oxo-4,5-*seco*-3-yne-steroids) by coupling the corresponding 5-oxo-4,5-*seco*-3-yne steroid units. An X-ray diffraction analysis of compound **5b** confirmed the proposed structure and provided detailed information about the bond lengths, bond angles and the conformation that the molecules adopt in the crystal state.

Results and Discussion

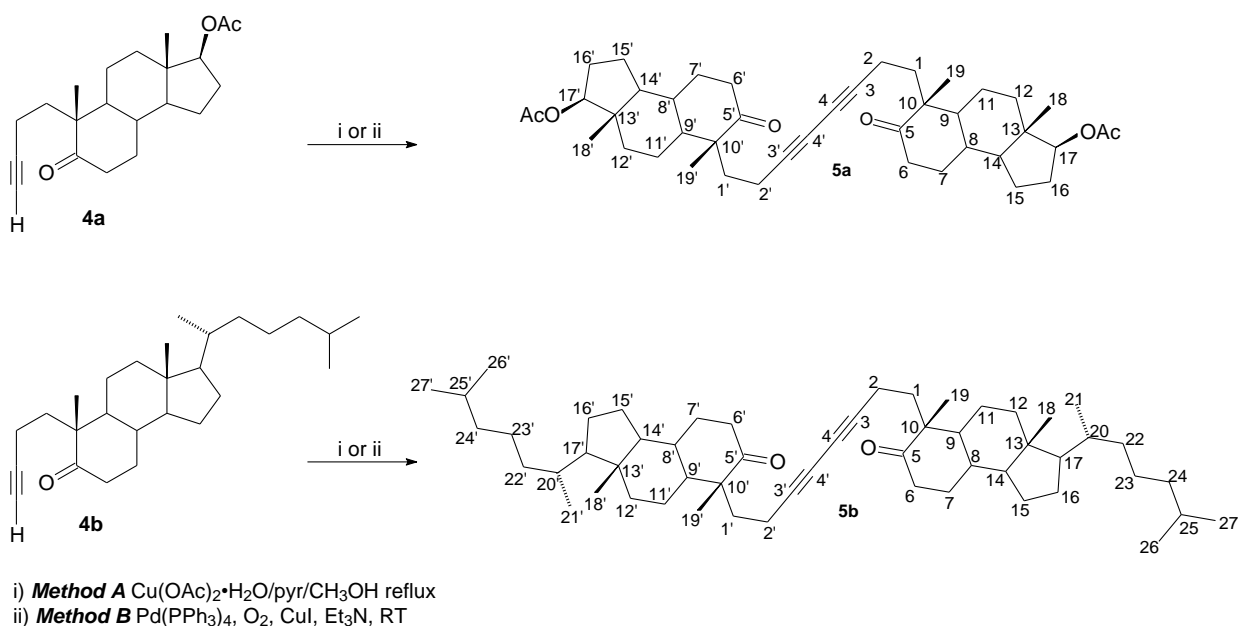
The starting alkynones **4a,b** were obtained following our previously described sequences that include, as key steps, the epoxidation of α,β -unsaturated ketones and the Eschenmoser-Tanabe fragmentation of a mixture of diastereomeric epoxides (Scheme 1).^{8,9,12}



Scheme 1. Our previously reported synthesis of the 5-oxo-4,5-*seco*-3-yne steroids **4a** and **4b**.^{8,9,12}

The first attempts at dimerization included the conditions of the Hay coupling¹³ that employs TMEDA as base and a catalytic amount of CuCl in acetone under an oxygen atmosphere. Although this procedure produced the desired dimerization, TLC analysis indicated that after 16 hours the amount of starting material was significant. The more drastic conditions of the Eglinton version¹⁴ in which the alkyne and an excess of cupric acetate are refluxed in methanolic pyridine produced the desired dimers in moderate yields after chromatographic purification (Scheme 2, and Table 1, Method A).

During the course of a parallel investigation⁹ we observed that Sonogashira coupling of the alkyne **4a** with *o*-iodobenzyl alcohol employing Pd(PPh₃)₄ and CuI in triethylamine produced a significant amount of the dimer **5a** as side product. Exclusion of the oxygen by consecutive purging cycles with Ar under sonication solved this problem. This prompted us to drive the reaction to the desired dimers by removal of the iodinated derivative and saturation with oxygen. We were happy to find that treatment of the alkynes **4a,b** in such conditions afforded good yields of the desired dimers **5a,b** in reactions with a clean, fast and easy work-up, followed by chromatographic purification (Scheme 2, and Table 1, Method B).



Scheme 2. Synthesis of dimeric steroids **5a,b**.

Table 1. Yields of the coupling reactions

	5a	5b
Method A (Eglinton)	222 mg, 67 %	259 mg, 68 %
Method B (Pd catalyzed)	303 mg, 92 %	312 mg, 81 %

NMR study allowed unambiguous characterization of the obtained compounds. With the exception of the ¹³C signals of C-2, C-3 and C-4, the dimerization does not induce significant changes in the NMR signals of the neighboring nuclei compared with those of the starting monomer **4** (See Tables 2 and 3). This suggests that in solution the dimeric compounds adopt a linear conformation in which each steroid core is placed well away from the other, resembling the conformation observed in solid state (*vide infra*).

Table 2. Selected ^1H NMR signals of the starting alkynones **4a,b** and the obtained dimers **5a,b*** (δ , ppm)

	4a ¹²	4b ⁸	\bar{X}_4	5a	5b	\bar{X}_5	$\Delta\bar{X}_5-\bar{X}_4$
H-2	2.12	2.12	2.12	2.15	2.16	2.16	+0.04
H-4	1.92	1.92	1.92	-	-	-	-
H-6 ax	2.51	2.51	2.51	2.50	2.50	2.50	-0.01
H-6 eq.	2.25	2.25	2.25	2.27	2.25	2.26	+0.01
H-19	1.08	1.08	1.08	1.07	1.07	1.07	-0.01

\bar{X} = mean value, * Since the dimers **5a,b** are C_2 symmetrical, the chemical shifts of protons are identical for both halves

Table 3. Selected ^{13}C NMR signals of the starting alkynones **4a,b** and the obtained dimers **5a,b*** (δ , ppm)

	4a ¹²	4b ⁸	\bar{X}_4	5a	5b	\bar{X}_5	$\Delta\bar{X}_5-\bar{X}_4$
C-1	33.5	33.6	33.6	33.3	33.3	33.3	-0.3
C-2	13.7	13.7	13.7	14.5	14.6	14.6	+0.9
C-3	84.9	85.1	85.0	77.8	77.9	77.9	-7.2
C-4	68.1	67.9	68.0	65.3	65.3	65.3	-2.7
C-5	214.1	214.7	214.4	214.1	214.7	214.4	0.0
C-6	37.9	38.2	38.1	37.9	38.2	38.1	-0.1
C-7	30.5	31.2	30.9	30.5	31.2	30.9	0.0
C-8	34.6	34.8	34.7	34.6	34.9	34.8	0.0
C-9	47.3	47.4	47.4	47.4	47.5	47.5	+0.1
C-10	50.7	50.7	50.7	50.7	50.7	50.7	0.0
C-19	20.5	20.6	20.6	20.5	20.5	20.5	-0.1

\bar{X} = mean value, * Since the dimers **5a,b** are C_2 symmetrical, the chemical shifts of carbon atoms are identical for both halves

Crystal structure discussion

While all attempts at production of monocrystals of compounds **5a** suitable for X-ray diffraction were unsuccessful, crystallization of compound **5b** from ethyl acetate-acetone afforded monocrystals suitable for such studies.

The molecular structure of 4,4'-bis(4,5-secocholest-3-yn-5,5'-dione) (**5b**) was solved in the monoclinic space group $C2$ and $Z = 2$. The asymmetric unit contains only half of the dimeric molecule and the other half is generated by a 2-fold rotation axis perpendicular to the alkyne moiety which deviates slightly from linearity (175.6°), in accordance with similar steroidal dimeric structures^{15,16} as shown in Figure 1. Additionally, the planes of both steroidal cores adopt an orthogonal position with respect to the dialkyne axis.

The dimeric molecules of compound **5b** are packed in parallel layers propagated by $C(2)-H(2)\cdots O_{\text{carbonyl}}$ [2.63Å] and $C(19)-H(19)\cdots O_{\text{carbonyl}}$ [2.64Å] interactions between neighboring molecules along the crystallographic bc plane. This particular arrangement favors the interaction between the hydrophobic faces of adjacent steroidal dimers generating a multidimensional highly crowded packed columnar self-assembly (see Figure 2).

The absolute configuration of compound **5b** can be assumed without risk, as that known for the starting material considering that the synthetic transformations carried out do not affect the absolute configuration of

the chiral centres in the naturally occurring steroid framework. Crystal data and experimental details of the structure determination of compound **5b** are listed in Table 4.¹⁷

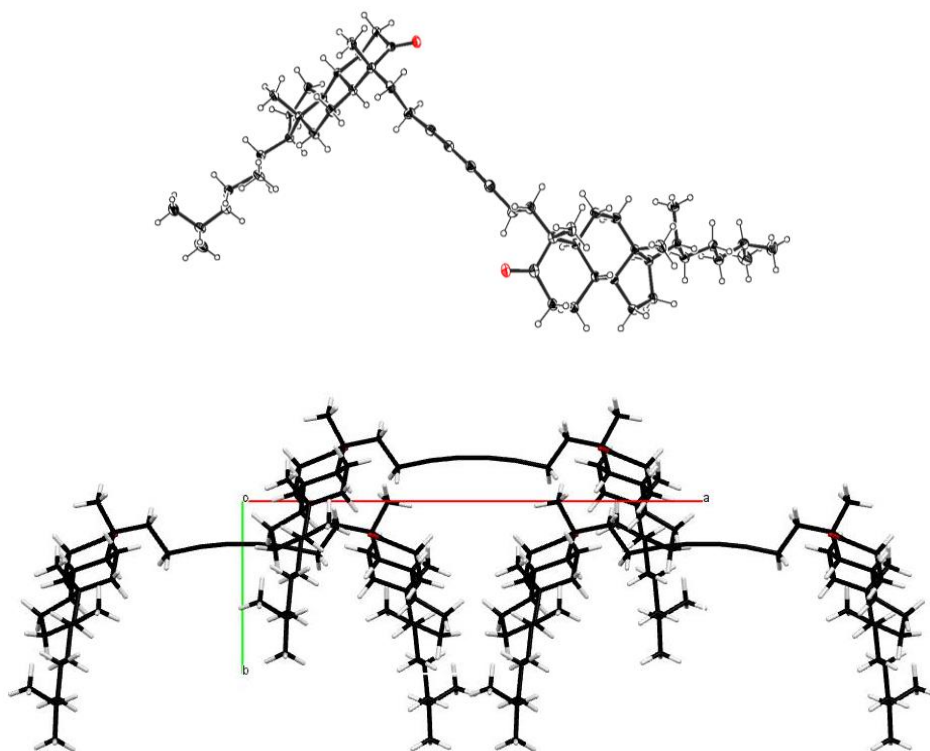


Figure 1. ORTEP perspective of compound **5b** with thermal ellipsoids drawn at 50% probability level for all atoms other than hydrogen, with their corresponding unit cell viewed along the crystallographic c axis.

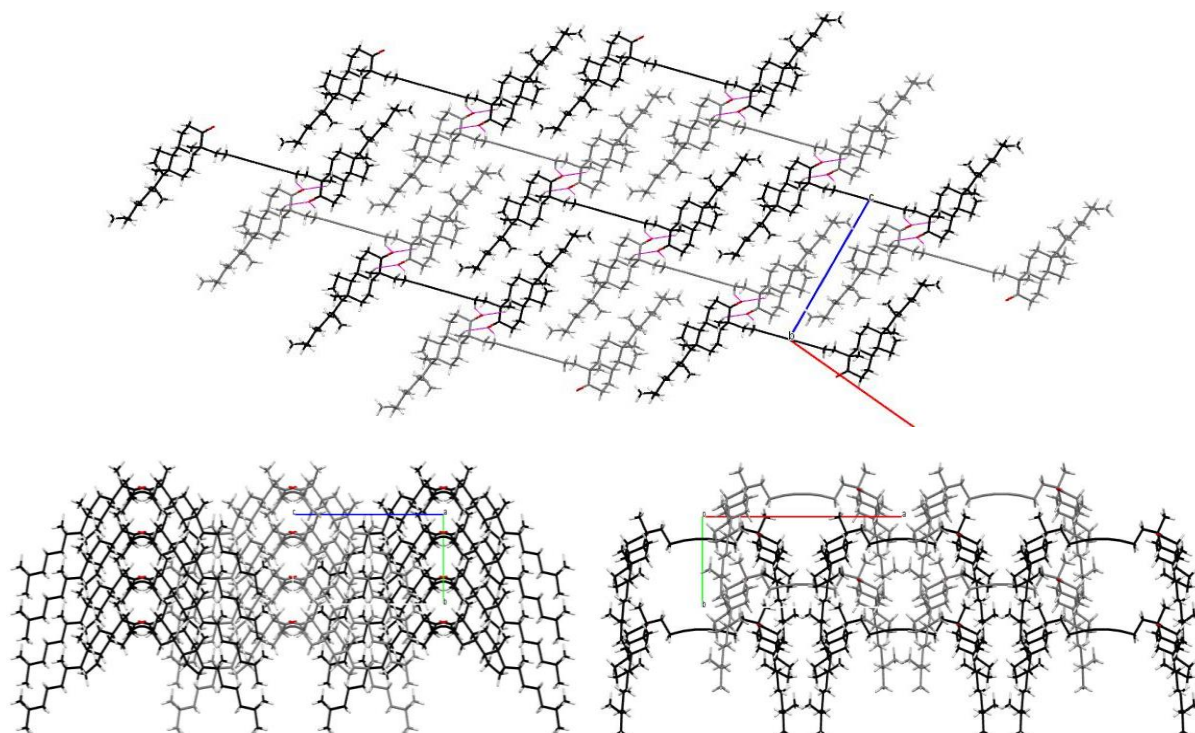


Figure 2. Crystal packing of compound **5b**.

Table 4. Crystal data and structure refinement for the dimeric steroid **5b**

Parameters	Value
Empirical formula	C ₅₄ H ₈₆ O ₂
Formula weight	767.22
Temperature	130(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	C 2
Unit cell dimensions	a = 20.6034(19) Å, b = 7.4289(6) Å, c = 15.9737(14) Å, β = 101.557(9) °
Volume	2395.4(4) Å ³
Z	2
Density (calculated)	1.064 Mg/m ³
Absorption coefficient	0.461 mm ⁻¹
F(000)	852
Crystal size	0.410 x 0.170 x 0.030 mm ³
Theta range for data collection	4.381 to 74.132°
Index ranges	-24 ≤ h ≤ 25, -9 ≤ k ≤ 5, -19 ≤ l ≤ 19
Reflections collected	8086
Independent reflections	3267 [R(int) = 0.0566]
Completeness to theta = 67.684°	100.0 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3267 / 1 / 258
Goodness-of-fit on F ²	1.066
Final R indices [I > 2σ(I)]	R1 = 0.0505, wR2 = 0.1202
R indices (all data)	R1 = 0.0734, wR2 = 0.1388
Absolute structure parameter	0.1(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.186 and -0.195 e.Å ⁻³

Conclusions

We have developed straightforward procedures that allow the synthesis of dimers constituted of two units of a 5-oxo-4,5-seco-3-yne steroid derived from the naturally occurring compounds testosterone (**1a**), and cholesterol (**1b**). Although both procedures afforded the desired compounds, the palladium-catalyzed homocoupling emerged as more convenient than the Eglinton procedure due to its more environmental friendly conditions, higher yields and easier work-up of the reaction mixture.

Crystallographic studies showed that the flexible diyne spacer of dimer **5b** favors a crystal packing dominated by interactions that are capable of accommodating the steroid cores in a highly crowded packed columnar self-assembly. Further studies to explore the solid-state properties and synthetic applications of dimers derived from the obtained compounds are in development.

Experimental Section

General. Reactions were monitored by TLC on ALUGRAM SIL G/UV254 plates from MACHEREY-NAGEL. TLC plates were sprayed with a 1% solution of vanillin in 50% HClO₄ and heated until color developed. Melting points were measured on a Melt-Temp II apparatus. NMR spectra were recorded in CDCl₃ solutions in a Varian INOVA 400 spectrometer using the solvent signal as reference. NMR signals assignments were carried out with the aid of combined 1D and 2D NMR techniques that included ¹H, ¹³C, COSY, Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Correlation (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). High resolution mass spectra were registered in a Jeol, AccuTOF JMS-T100LC spectrometer. The starting alkynones **4a** and **4b** were obtained following our previously described protocols (*vide supra* Scheme 1).^{8,9,12} Previously obtained physical and NMR data for **4a** and **4b** are provided for comparison purposes.

17β-Acetoxy-4,5-epoxy-5β-androstan-3-one (4a).¹² Mp 140–142 °C (from EtOAc) ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.59 (dd, *J* 9.2, 7.8 Hz, 1H, H-17), 2.51 (ddd, *J* 14.5, 6.3, 6.3 Hz, 1H, H-6 ax.), 2.26 (ddd, *J* 14.7, 4.5, 2.4 Hz, 1H, H-6 eq.), 1.91 (m, 1H, H-4), 2.03 (s, 3H, CH₃ acetyl), 1.07 (s, 3H, H-19), 0.84 (s, 3H, H-18). ¹³C NMR (CDCl₃ 100 MHz) δ ppm: 33.5 C-1, 13.7 C-2, 84.9 C-3, 68.1 C-4, 214.1 C-5, 37.9 C-6, 30.5 C-7, 34.6 C-8, 47.3 C-9, 50.7 C-10, 21.0 C-11, 36.2 C-12, 42.5 C-13, 50.2 C-14, 23.5 C-15, 27.4 C-16, 82.3 C-17, 12.0 C-18, 20.5 C-19, 21.1 CH₃ acetyl, 171.1 C=O acetyl.

4,5-secocholest-3-yn-5-one (4b).⁸ Transparent oil. ¹H NMR (CDCl₃, 400 MHz): δ ppm: 2.51 (td, *J* 14.5, 6.4 Hz, 1H, H-6 ax.), 2.25 (ddd, *J* 14.5, 4.5, 2.3 Hz, 1H, H-6 eq.), 1.92 (t, *J* 2.4 Hz, 1H, H-4), 2.12 (m, 2H, H-2) 1.08 (s, 3H, H-19), 0.91 (d, *J* 6.5 Hz, 3H, H-21), 0.87 (d, *J* 1.8 Hz, 3H, H-26), 0.85 (d, *J* 1.8 Hz, 3H, H-27), 0.72 (s, 3H, H-18). ¹³C NMR (CDCl₃, 100 MHz) δ ppm: 33.6 C-1, 13.7 C-2, 85.1 C-3, 67.9 C-4, 214.7 C-5, 38.2 C-6, 31.2 C-7, 34.8 C-8, 47.4 C-9, 50.7 C-10, 21.5 C-11, 39.3 C-12, 42.5 C-13, 55.8 C-14, 23.8 C-15, 28.1 C-16, 56.0 C-17, 12.0 C-18, 20.6 C-19, 35.7 C-20, 18.6 C-21, 36.1 C-22, 24.2 C-23, 39.5 C-24, 28.0 C-25, 22.8 C-26, 22.5 C-27.

Method A (Eglinton coupling): A solution of the alkynone **4a**, **4b** (1 mmol) and Cu(OAc)₂•H₂O (280 mg, 1.40 mmol) in CH₃OH/pyridine (10 mL, 1:1) was refluxed for 6 h. The mixture was cooled to 0 °C and poured carefully into chilled concentrated HCl (4 mL) and extracted with EtOAc (2 x 30 mL). The organic layer was washed with H₂O (3 x 20 mL), 10% aq. CuSO₄, H₂O (2 x 30 mL), dried (Na₂SO₄) and evaporated to produce an oil that was purified in a column packed with silica gel (15 g) employing hexane-EtOAc 15/1 as eluent to afford the desired dimeric compound (See Table 1 for yields).

Method B (Pd catalyzed coupling): A mixture of the alkynone (1 mmol), Pd(PPh₃)₄ (9.6 mg, 0.0083 mmol) and CuI (3.2 mg, 0.0166 mmol in Et₃N (3 mL) was stirred at rt for 2 h under an oxygen atmosphere. EtOAc (50 mL) was added and the mixture was washed with H₂O (5 x 20 mL) dried (anh. Na₂SO₄) and evaporated. The residue produced was purified in a chromatographic column packed with silica gel (15 g) that was eluted with hexane/EtOAc mixture (10/0 → 10/3) to afford the desired dimer (See Table 1 for yields).

4,4'-Bis-(4,5-secoandrost-3-yn-5-one) (5a). Oil. NMR ¹H (CDCl₃, 400 MHz) δ (ppm): 4.59 (dd, *J* 9.2, 7.7 Hz, 2H, H-17β, H-17β'), 2.50 (ddd, *J* 15.0, 14.5, 6.3 Hz, 2H, H-6 ax. H-6'ax.), 2.27 (ddd, *J* 15.0, 4.6, 2.4 Hz, 1H, H-6 eq. H-6'eq.), 2.15 (m, 4H, H-2 H-2'), 2.04 (s, 6H 2x CH₃ acetyl), 1.07 (s, 6H, H-19 H-19'), 0.84 (s, 6H, H-18 H-18') ¹³C NMR (CDCl₃, 100.53 MHz) δ (ppm): 33.3 C-1 C-1', 14.5 C-2 C-2', 77.8 C-3 C-3', 65.3 C-4 C-4', 214.1 C-5 C-5', 37.9 C-6 C-6', 30.5 C-7 C-7', 34.6 C-8 C-8', 47.4 C-9 C-9', 50.7 C-10 C-10', 21.1 C-11 C-11', 36.22 C-12 C-12', 42.5 C-13 C-13', 50.1 C-14 C-14', 23.5 C-15 C-15', 27.4 C-16 C-16', 82.4 C-17 C-17', 12.1 C-18 C-18', 20.5 C-19 C-19' 171.0 2 x C=O acetyl, 21.1 2 x CH₃ acetyl. HRMS (FAB) Estimated for C₄₂H₅₉O₆ (MH⁺) 659.4312, observed 659.4312.

4,4'-Bis-(4,5-secocholest-3-yn-5-one) (5b). Mp. 132-135 °C (from EtOAc-Me₂CO). NMR ¹H (CDCl₃, 400 MHz) δ (ppm): 2.50 (td, *J* 14.4, 6.3 Hz, 2H, H-6 ax. H-6'ax.), 2.25 (m, 2H, H-6eq. H-6'eq.), 2.16 (m, 4H, H-2 H-2'), 1.07 (s, 6H, H-19 H-19'), 0.91 (d, *J* 6.5 Hz, 6H, H-21 H-21'), 0.87 (d, *J* 1.9 Hz, 6H, H-26 H-26'), 0.85 (d, *J* 1.9 Hz, 6H, H-27 H-27'), 0.72 (s, 6H, H-18 H-18') ¹³C NMR (CDCl₃, 100.53 MHz) δ (ppm): 33.3 C-1 C-1', 14.6 C-2 C-2', 77.9 C-3 C-3', 65.3 C-4 C-4', 214.7 C-5 C-5', 38.2 C-6 C-6', 31.2 C-7 C-7', 34.9 C-8 C-8', 47.5 C-9 C-9', 50.7 C-10 C-10', 21.6 C-11 C-11', 39.3 C-12 C-12', 42.5 C-13 C-13', 56.1 C-14 C-14', 23.9 C-15 C-15', 28.1 C-16 C-16', 55.8 C-17 C-17', 12.0 C-18 C-18', 20.5 C-19 C-19', 35.7 C-20 C-20', 18.6 C-21 C-21', 36.1 C-22 C-22', 24.2 C-23 C-23', 39.5 C-24 C-24', 28.0 C-25 C-25', 22.6 C-26 C-26', 22.8 C-27 C-27'. HRMS Estimated for C₅₄H₈₇O₂ (MH⁺) 767.6706, observed 767.6688.

X-ray crystallography. A monocrystal of the dimer **5b** grown by slow evaporation from an EtOAc-Me₂CO solution was mounted on a glass fiber in the goniometer head with a crystal-to-detector distance of 55.00 mm and crystallographic data were collected at 130 K with an Oxford Diffraction Gemini "A" diffractometer ($\lambda_{\text{CuK}\alpha} = 1.54184 \text{ \AA}$, monochromator: graphite) with a CCD area detector. The collected data set consisted of 19 runs of 1126 frames of intensity (1° in ω). The double pass method of scanning was used to exclude any noise. The collected frames were integrated by using an orientation matrix determined from the narrow frame scans. CrysAlisPro and CrysAlis RED software packages¹⁸ were used for data collection and integration. Analysis of the integrated data did not reveal any decay. Final cell parameters were determined by a global refinement of 1699 ($4.318 < \theta < 72.464^\circ$). Collected data were corrected for absorption effects by analytical numeric absorption¹⁹ using a multifaceted crystal model based on expressions upon the Laue symmetry with equivalent reflections. Structure solution and refinement were carried with the programs SHELXS-2014 and SHELXL-2014 respectively.²⁰ WinGX and ORTEP softwares²¹ were used to prepare material for publication. Full-matrix least-squares refinement was carried out by minimizing $(F_o^2 - F_c^2)^2$. All nonhydrogen atoms were anisotropically refined. Hydrogen atoms attached to carbons were placed in geometrically idealized positions and refined as riding on their parent atoms, with C-H = 0.98 – 1.00 Å with Uiso (H) = 1.2Ueq(C) for methylene and methyne groups, and Uiso (H) = 1.5 Ueq(C) for methyl groups.

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Supplementary Material

¹H and ¹³C NMR spectra of the dimeric steroids **5a** and **5b**.

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17. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1450338. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).
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