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Functional Chimeras: New Bingel–Hirsch-Type Steroid–Fullerene Hybrids

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Cyclopropanations between C_{60} and readily available malonates bearing different steroid moieties (**4**–**6**) by the Bingel–Hirsch protocol has allowed the synthesis of a new series of hybrid functionalized chimeras (**7**–**9**). Whereas cycloadducts **7** and **8** showed the expected chemical structures, the presence of the diene moiety in the ergosterol unit of malonate **6** resulted in the production of the corresponding cycloadduct with an additional oxygen molecule. A thorough spectroscopical study (^{1}H and ^{13}C NMR, COSY, DEPT, HMQC, and HMBC) allowed the structure of monocycloadduct **9** to be unambiguously unraveled as that of an endoperoxide, as a result of the sensitizing effect of the C_{60} unit, which efficiently promotes the addition of excited singlet oxygen to the diene moiety of the steroid. Cyclic voltammetry of hybrids **7**–**9**, as well as their electronic spectra, support the exclusive formation of the corresponding monoadducts.

Introduction

Because of their wide occurrence, particularly in mammalian tissues, their rigid frameworks with varying levels of functionalization, their broad biological activity profiles, and their ability to penetrate cell membranes and to bind to specific hormonal receptors, steroids have found favor as building platforms for hybrid systems.

The roles of sterols in diverse biological systems have been widely studied.[1,2] Cholesterol, β-sitosterol, and ergosterol constitute the main eukaryotic sterols representing the three eukaryotic kingdoms: animals, plants, and fungi, respectively.[3] Cholesterol is considered the main animal sterol, an essential metabolite with an important function for normal cell growth in humans.[4] At the cellular level, it is employed for the biosynthesis of bile and bile acid salts, and its presence also has significant implications for cell-membrane structure.[5] β-Sitosterol, on the other hand, is widely distributed in the plant kingdom and has been reported by several authors as the major phytosterol.[6] It has been successfully used to reduce plasma cholesterol levels[7] and also in the treatment of benign prostatic hyperplasia (BPH).[8] Alternatively, ergosterol is the principal sterol of fungi, and its concentration has several times been employed as an indicator of fungal growth in foods and soils.[9,10] However, ergosterol is best known as the biological precursor of vitamin D_2, and so it is also called provitamin D_2.[11]

The conjugation of steroids to other chemically or biologically relevant molecules is a common approach in the pursuit of interesting biomedical and chemical applications.[12]

Like natural steroid-containing hybrid compounds such as saponins,[13] many synthetic steroidal conjugates have proven to possess physicochemical and biological properties different from those of the separate building blocks. Several drug–steroid hybrids have been developed to achieve specific drug targeting, for example, or to improve intestinal absorption of poorly absorbed drugs.[14] Linkage of steroids to biomolecules has also been a very successful methodology. Synthetic oligosaccharide–steroid conjugates have been produced as analogues of natural antitumoral saponins[15] and to provide novel amphiphilic scaffolds capable of interacting with phospholipid membranes.[16] Oligopeptide–steroid conjugates have been used as synthetic receptors of bioactive peptide sequences,[17] as artificial proteolytic enzymes,[18] and – combined with cyclization – as scaffolds to force peptide chains into folded structures.[19] Designed peptide–steroidal hybrids have also proven to behave as mimics of the natural cationic peptide antibiotics[20] and as RGD-based integrin antagonists.[21]

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Indeed, hybridization of steroids with other molecules not only enables the biological activity of the selected moiety to be modulated, but also allows chimeric molecular entities with completely new properties and functions to be produced.[16–18,22] The success previously achieved in this field confirms that complex molecular hybrids incorporating steroidal scaffolds can be designed to carry out specific actions in natural or artificial systems, thus acting as novel functional chimeras that combine the properties of steroids with those of other materials.

Since the discovery of [60]fullerene[23] and its large-scale preparation,[24] more and more attention has come to be paid to the introduction of biologically active groups onto fullerenes because of their interesting physical and biological properties.[25] Among the various potential applications of fullerene derivatives, their use in medicinal chemistry is probably one of the most promising. It has been shown that they exhibit several types of biological activities, both in vitro and in vivo, that can be exploited for medicinal purposes.[26,27] The ability of C_{60} and its derivatives to scavenge a large number of radicals per molecule[28,29] makes them potentially useful drugs in the prevention or treatment of pathologies in which oxidative damage is involved: namely cardiovascular[30,31] and neurodegenerative diseases.[32,33] Fullerenes have also been used as inhibitors of HIV-1 protease,[34] or in the photodynamic therapy of neoplastic tissues.[35]

Despite these exciting findings, much work remains to be done in developing new methods to produce suitable fullerene derivatives for biological investigations. In this regard, because steroids are the main components of biomembranes, coupling of fullerene units with these molecules may change the physicochemical properties of the fullerenes, improve their solubility and biocompatibility, or facilitate further studies on membrane–drug interactions and membrane-related processes such as, for instance, signal transduction and solute transport.

To the best of our knowledge, out of the multitude of fullerene derivatives that have so far been published, only a very few examples of fullerenes bearing steroid moieties have been reported.[36] One of the first reports in this area involved the synthesis of chiral [60]fullerene–steroid bisadducts by use of steroid templates.[37]

Bjelakovic et al.,[38] for example, synthesized derivatives from starting fulleropyrrolidines incorporating γ-aminobutyric acid (GABA) and the corresponding sterols. In vitro antioxidant studies showed antioxidant activity two to three times higher than that of the parent fullerene. On the other hand, the effect of steroid–fullerene adducts prepared through Diels–Alder reactions were evaluated on sarcoplasmic reticulum (SR) Ca^{2+}-ATPase and survival of human lung adenocarcinoma cancer A549 cells.[39]

The synthesis of steroidal derivatives of fullerenes in which cholesterol, or a cholesterol derivative, is attached through an ester, amide, or ether bond to one of a variety of linkers connected to fullerene through a pyrrolidine ring has very recently been described.[40] The steroid moiety can confer useful solubility in components of biological fluids and/or pharmacologically acceptable carriers and can also affect the biodistribution of the fullerenes, which makes these derivatives useful in imaging, diagnosis, and the treatment or management of disease.

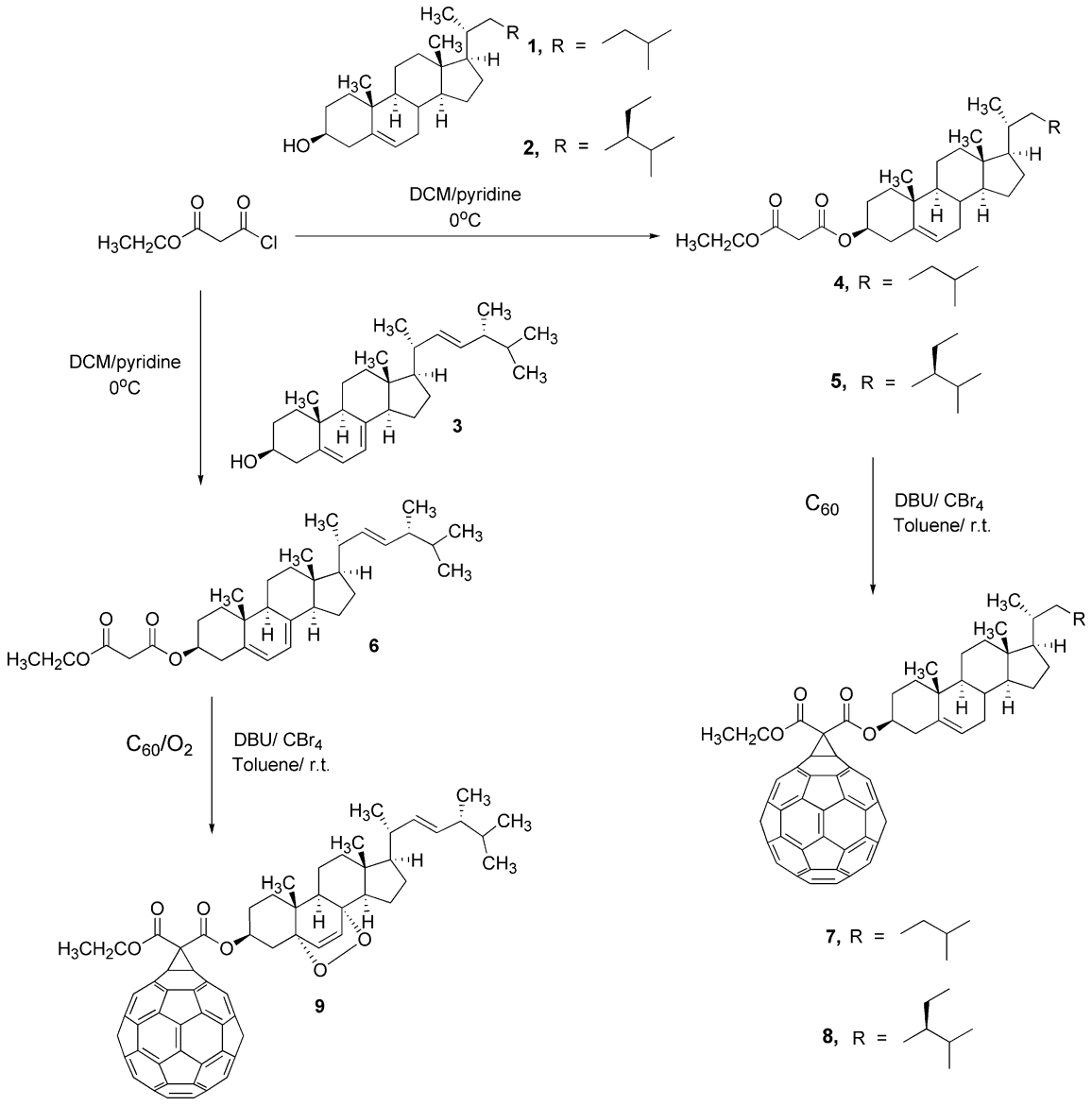
As a part of our studies directed towards the synthesis of new molecular hybrids based on fullerenes, we recently reported the synthesis of new fulleropyrrolidines bearing 1,4-dihydropyridine (1,4-DHP) moieties as biologically active substituents related to the well-known nifedipine [3,5-bis(methoxycarbonyl)-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine]. The fullerene derivatives were synthesized through 1,3-dipolar cycloadditions between azomethine ylides (generated in situ) and C_{60}, or by treatment of the corresponding formyl-substituted 1,4-DHPs with sarcosine and [60]fullerene by Prato's protocol.[41]

In continuation of our interest in the chemistry of fullerene hybrids, here we report on the design of a new type of molecular chimeras produced by conjugation of naturally occurring steroids to fullerene by the so-called Bingel–Hirsch reaction, with the objective of designing membrane anchors or membrane translocators.

Results and Discussion

Hybrid fullerene–steroid derivatives (**7**–**9**, Scheme 1) were prepared by the Bingel–Hirsch protocol, by treatment of [60]fullerene with malonates bearing the appropriate steroid moieties. Therefore, in the first step, we carried out the preparation of the required starting malonates (**4**–**6**) by treatment of three different sterols – cholesterol (**1**), β-sitosterol (**2**), and ergosterol (**3**) – with commercially available (ethoxycarbonyl)acetyl chloride (Scheme 1). The reactions were carried out under relatively dilute solutions in anhydrous dichloromethane and pyridine at 0 °C. The three new malonates **4**, **5**, and **6** were obtained in 85%, 74%, and 70% yields, respectively. Isolation was achieved by flash chromatography with a hexane/ethyl acetate (8:1) mixture as the eluent, and the new compounds were fully characterized by analytical and spectroscopic techniques (see Experimental Section). In particular, in addition to those signals corresponding to the steroid moieties, the methylene protons of the malonate fragment appear as singlets at $\delta \approx 3.4$ ppm in the ^{1}H NMR spectra. The signal of the H-3 proton of the steroid ring A appears at $\delta = 4.5$ ppm, which is deshielded in relation to the same proton in the unmodified steroids **1**, **2**, and **3**. The chemical structures of the new compounds were further confirmed by MS. Under MALDI conditions, compounds **4** and **5** show pseudomolecular peaks at m/z = 523.37578 and 551.40668 u, each corresponding to the molecular peak plus a sodium atom ($C_{34}H_{56}O_4Na$ and $C_{32}H_{52}O_4Na$, respectively). Similarly, under ESI conditions compound **6** exhibits two pseudomolecular peaks at m/z = 533 $[M + Na]^+$ and 1043 $[2 M + Na]^+$.

The covalent attachment of the obtained malonates **4**–**6** to the fullerene C_{60} was carried out by cyclopropanation under Bingel–Hirsch conditions, by treatment of **4**, **5**, or **6** with C_{60} in the presence of CBr_4 and DBU (see Scheme 1).



Scheme 1. Synthesis of hybrid fullerene–steroid compounds **7**–**9** by Bingel–Hirsch reactions between [60]fullerene and the corresponding steroid-containing malonates **4**–**6**.

The reactions progressed rapidly, and after 2 h, the formation of the expected derivatives was clearly completed. After purification by flash chromatography, initially with carbon disulfide to elute unreacted C_{60}, followed by toluene, compounds **7**, **8**, and **9** were obtained in 56%, 58%, and 50% yields, respectively, as stable brown solids.

The HPLC chromatograms of the reaction mixtures (toluene/acetonitrile 9:1; 1 mL min^{-1}) show peaks at 4.50, 4.52, or 4.38 min, corresponding to **7**, **8**, and **9**, respectively. In each of these chromatograms an additional peak – assigned to the C_{60} starting material – appears at 9.84 min, together with other minor peaks attributed to C_{60} epoxide and the formation of biscycloadducts.

In contrast to those of **4** and **5**, the Bingel–Hirsch reaction between compound **6** and C_{60} afforded adduct **9**, containing two additional oxygen atoms (see Scheme 1). In this case, the 5,6-diene moiety in ring B had undergone a further Diels–Alder cycloaddition reaction with $^1O_2$, similarly to that observed for ergosterol itself.[42] Interestingly, this cycloaddition only occurs when the diene system is in an environment containing oxygen and an efficient triplet sensitizer, such as C_{60}. Thus, molecular oxygen, usually in a triplet ground state, is promoted to the excited singlet state, which behaves as a dienophile, reacting with the diene moiety of the steroid to form an endoperoxide through a Diels–Alder-type cycloaddition reaction.

^{1}H NMR spectroscopy revealed the presence of C_{60}–sterol hybrids. Besides the disappearance of the methylene protons (signals seen at δ = 3.36 ppm) in the malonates **4**, **5**, and **6**, new signals at $\delta \approx$ 1.3 ppm and 4.2 ppm, corresponding to the protons of the ethoxycarbonyl groups, had appeared in **7**, **8**, and **9**. In addition to the expected signals

corresponding to the steroid moiety, the proton on C-3 in ring A of the steroid is observed as a typical signature at δ = 5.07 ppm in the cases of **7** and **8**, whereas in that of **9** it appears at δ = 5.42 ppm. The rest of the signals are in agreement with the data reported for steroids **1**, **2**, and **3** (see Experimental Section).

On the other hand, the number of signals observed in the ^{13}C NMR spectra reveal the lack of symmetry in these compounds. The ^{13}C NMR spectra of **7**, **8**, and **9** each show the presence of the two carbonyl groups at $\delta \approx 167$ and 166 ppm. The positions of the rest of the steroid carbon atoms are relatively insensitive to the presence of the C_{60} cage, the only exception being the C-3 carbon atoms in the steroid A rings, which are each strongly deshielded by ca. 2 ppm, due to the presence of the C_{60} sphere. The signals for the sp^3 carbon atoms of the cyclopropane rings in the **7**, **8**, and **9** hybrids appear at $\delta \approx 72$ and 74 ppm for those at the 6,6-ring junction of the C_{60} cage, whereas the signals of the quaternary carbon atoms are at $\delta \approx 52$ ppm. Because we had achieved unambiguous assignments for the ^1H NMR resonances, the ^{13}C NMR resonances were assigned in a straightforward manner by analysis of the HMQC spectra (Figure 1) for the protonated carbon atoms on the basis of chemical shift theory, substituent effects, and DEPT data. Quaternary carbon atoms were assigned by analysis of the HMBC spectra. It is interesting to note that the compounds showed similar trends in the chemical shifts of the common moiety of the molecular backbone, thus confirming their chemical structures (see Experimental Section).

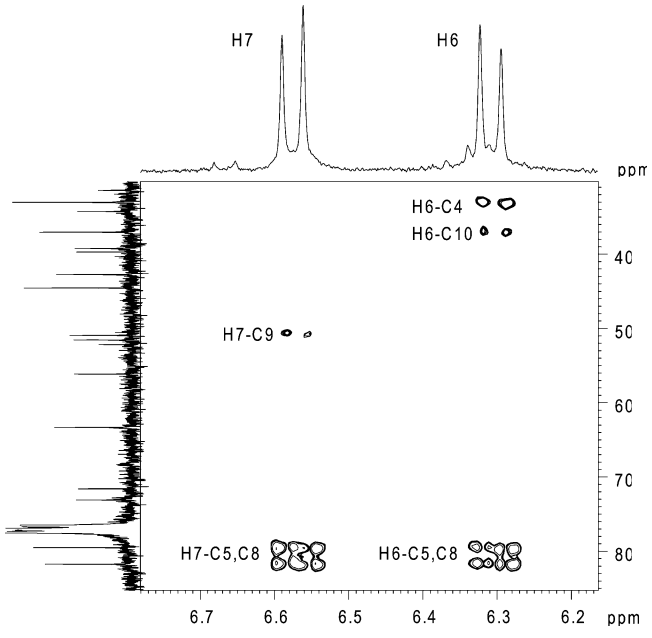


Figure 1. HMQC spectrum of compound **9**.

Determination of the chemical structure of **9** was not an easy task, and a thorough spectroscopic study was necessary to establish the positions of the oxygen atoms in **9** unambiguously. The structure of compound **9** was thus unraveled by combined NMR spectroscopic data from ^1H, ^{13}C, COSY, DEPT, HMQC, and HMBC experiments. Compound **9** has a ^1H NMR spectrum nearly identical to that of precursor **6**. The signals of the olefinic protons H-6 and H-7, however, are changed dramatically. In compound **6** these protons appear at δ = 5.59 (dd) and 5.40 ppm (m), respectively, whereas in compound **9** they appear as an AB system at δ = 6.31 (H-6) and δ = 6.57 ppm (H-7), with J = 8.4 Hz. On the other hand, in compound **6** the ^{13}C NMR spectrum shows the carbon atoms of the diene system in ring B at δ = 141.6 (C-5) and 138.2 ppm (C-8), both quaternary, with the signals of the methyne carbon atoms at δ = 120.3 (C-6) and 116.3 ppm (C-7). In compound **9**, however, the positions of the signals for these carbon atoms are changed to δ = 81.7 (C-5) and 79.5 ppm (C-8) as sp^3 quaternary carbon atoms, and δ = 134.7 (C-6) and 131.19 ppm (C-7) as olefinic carbon atoms. These changes in the positions of the ^1H and ^{13}C NMR signals clearly indicate the chemical transformation of the diene system by the cycloaddition reaction undergone with the O_2 molecule, although intramolecular cycloaddition on the C_{60} sphere could not be ruled out at this stage.

The carbon atoms involved in the Diels–Alder reaction were unambiguously assigned on the basis of HMBC correlations. The olefinic proton signal in the 5α,8α-epidioxy system at δ = 6.31 ppm (H-6) was correlated with C-5, C-8, and C-10. Similarly, the other olefinic proton signal at δ = 6.57 ppm (H-7) correlated with C-5, C-8, and C-9. The methylene proton signals at δ = 2.2 ppm were clearly correlated to two carbon signals at δ = 81.7 (C-5) and 73.1 ppm (C-3). These assignments are in perfect agreement with those reported for related non-fullerene-containing ergosterol peroxide derivatives used as antifungal agents.[43]

MS allowed the proposed structures to be verified. The MALDI spectra for compounds **7** and **8** show peaks at m/z = 1218.37466 and 1246.40222, respectively, which correspond with their molecular ions. For compound **9**, however, the MALDI mass spectrum reveals a peak at m/z = 1260.33116 that corresponds with the molecular formula $C_{93}H_{48}O_6$, thus confirming the addition of two oxygen atoms.

The solution electrochemistry of fullerene steroids **7**, **8**, and **9** was studied by cyclic voltammetry (CV). The results are presented in Figure 2 and the reduction potential data are collected in Table 1. Each methanofullerene shows up to four one-electron reduction steps, which occur at potentials almost identical to those reported for analogous Bingel-type fullerene monoadducts under the same experimental conditions.[44] It is also well known that upon fullerene monoaddition, loss of conjugation leads to a LUMO that is higher in energy, and thus to a decreased electron affinity in the functionalized fullerene. In this sense, the two first reduction waves of **7**, **8** and **9** are ca. 80–100 mV negatively shifted with respect to those of the C_{60} starting material.[45] The stepwise CV study of these compounds in each case shows two quasi-reversible fullerene-based reductions (ΔE = 56–69 mV) and another two reduction processes that are

chemically irreversible, presumably due to the cleavage of one of the cyclopropane bonds connecting the addend to C_{60}. These results are in accordance with the occurrence of a retro-cyclopropanation reaction after the second reduction potential, as has been observed in other Bingel-type adducts.[46] These electrochemical data ruled out the formation of the biscycloadduct resulting from competitive Diels–Alder cycloaddition of the diene moiety of the steroid on the C_{60} sphere, which is known to behave as an efficient dienophile.[47] Furthermore, this result is also supported by the UV/Vis spectra of compounds **7**, **8**, and **9**, which show the typical profiles of fullerene monoadducts, each with a band centered at around 430 nm (Figure 3).

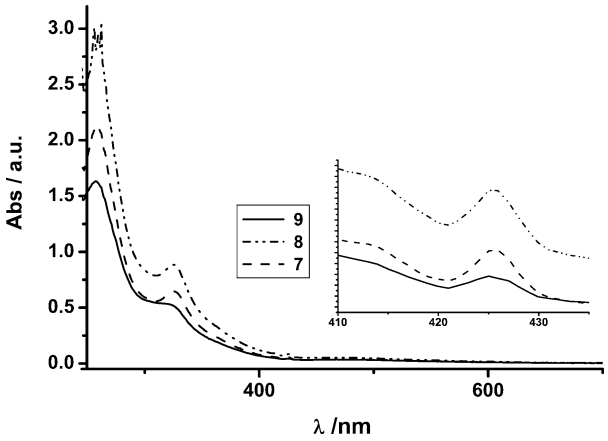


Figure 3. UV/Vis spectra of compounds **7**, **8**, and **9** in $CHCl_3$.

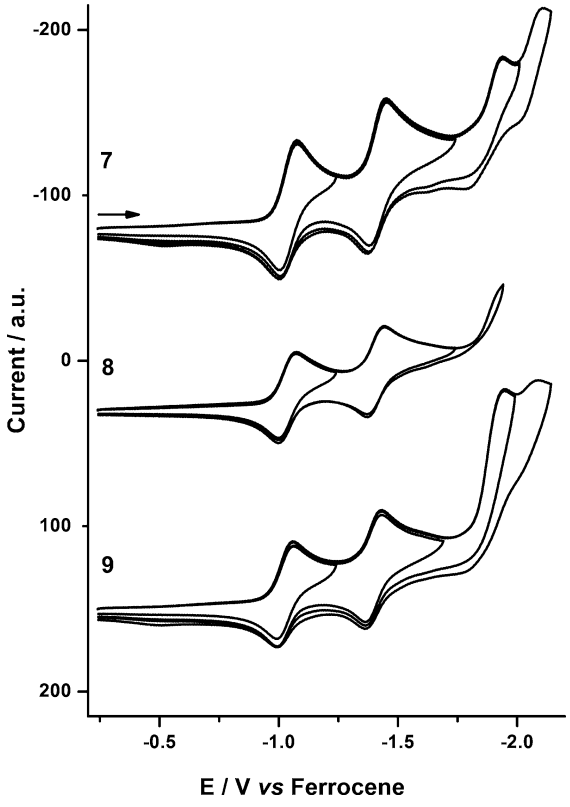


Figure 2. Cyclic voltammograms of the Bingel-type fullerene steroid hybrids **7**–**9** in CH_2Cl_2 at room temperature.

Table 1. Electrochemical data [mV] (vs. Fc/Fc^+) for fullerene derivatives **7**–**9** in CH_2Cl_2.[a]

Compound	$E^1_{½,\,red}$	$E^2_{½,\,red}$	E^3_{red}[b]	E^4_{red}[b]
7	–1025 (ΔE = 69)	–1400 (ΔE = 61)	–1927	–2100
8	–1028 (ΔE = 66)	–1410 (ΔE = 56)	–1894	–2055
9	–1020 (ΔE = 66)	–1401 (ΔE = 66)	–1944	–2065

[a] Experimental conditions: GCE as working electrode, Pt as counter electrode, $Ag/AgNO_3$ as reference electrode, $Bu_4N^+PF_6^-$ (0.1 M) as supporting electrolyte, 100 mV s^{-1} scan rate. [b] Cathodic peak potentials, irreversible processes.

Conclusions

We have carried out the synthesis of new [60]fullerene–steroid hybrids as functional chimeras (**7**, **8**, and **9**) by Bingel–Hirsch cyclopropanation of the corresponding steroid-containing malonates (**4**, **5**, and **6**) with C_{60}. Interestingly, in contrast to cycloadducts **7** and **8**, hybrid **9**, resulting from the reaction between C_{60} and the ergosterol-containing malonate **6**, underwent an additional cycloaddition reaction between excited molecular oxygen and the 1,3-diene moiety, which has been accounted for by the triplet sensitizing effect of the fullerene unit.

A thorough spectroscopic study (^1H and ^{13}C NMR, COSY, DEPT, HMQC, and HMBC) has allowed the chemical structures of the new compounds to be unambiguously determined. The proposed structures are supported by their electronic spectra as well as by cyclic voltammetry, which unequivocally reveal the presence solely of the monoadducts, without observation of any formation of biscycloadducts that would result from the intramolecular Diels–Alder cycloaddition of the steroid diene moiety of ergosterol in **6** to the fullerene double bond.

The new hybrid compounds (**7**, **8**, and **9**), bearing fullerene and steroid units in the same molecule, can be considered promising functional chimeras, the potential biomedical applications of which are under study.

Experimental Section

General: All reagents were of commercial quality and were used as supplied unless otherwise specified. Solvents were dried by standard procedures. Column chromatography was performed on silica gel (60 Å, 32–63 μm). FTIR spectra were recorded with a Bruker Tensor 27 (ATR device) spectrometer in $CHCl_3$. ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR at 75.5 MHz, with a Bruker Avance 300 instrument; the one-bond heteronuclear correlation (HMQC) and the long-range ^1H–^{13}C correlation (HMBC) spectra were obtained by use of the inv4gs and the inv4gslplrnd programs, respectively, with the Bruker software. Mass spectra were obtained with a Hewlett–Packard 5989A spectrometer. Microanalysis was performed with a Perkin–Elmer 2400 CHN instrument.

UV/Vis spectra were recorded with a Varian Cary 50 spectrophotometer in $CHCl_3$. HRMS-ESI spectra were recorded with an FTMS-Bruker APEX G-IV instrument at 4.7 T, and HRMS-MALDI (dithranol as matrix) in an Applied Biosystem 4700 Reflector machine. An Agilent 1100 high-performance liquid chromatography (HPLC) system was used to determine the purities of the compounds synthesized. A BuckyPrep Waters column (column dimensions, 4.6 × 250 mm; flow rate 1.0 mL min^{-1}, injection volume 15 μL) was employed. The retention times (t_Rs) and the peak areas (PAs) reported were determined at a wavelength of 310 nm. Electrochemical measurements were performed with an Autolab PGStat 30 instrument with a three-electrode configuration system. The measurements were carried out with CH_2Cl_2 solutions [0.1 M in tetrabutylammonium hexafluorophosphate ($TBAPF_6$)]. A glassy carbon electrode (3 mm diameter) was used as the working electrode, and a platinum wire and an $Ag/AgNO_3$ electrode were employed as the counter and the reference electrode, respectively. Ferrocene (Fc) was added as an internal reference, and all the potentials were determined relative to the Fc/Fc^+ couple. Both the counter and the reference electrodes were directly immersed in the electrolyte solution. The surface of the working electrode was polished with commercial alumina prior to use. Solutions were stirred and deaerated by bubbling argon for a few minutes prior to each voltametric measurements. Unless otherwise specified, the scan rate was 100 mV/s.

Synthesis of Malonates 4, 5, and 6: A solution of the appropriate steroid (**1**, **2**, or **3**; 1 mmol) in dichloromethane (60 mL) under argon was prepared. Pyridine (0.08 mL, 1 mmol) was added dropwise to the solution, and the resulting mixture was cooled in an ice bath. (Ethoxycarbonyl)acetyl chloride (0.13 mL, 1 mmol) was added dropwise. The ice bath was removed, after the solution had been stirred for 2 h. The reaction mixture was then stirred at room temperature overnight. Water was added, and the residue was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Purification of products was achieved by column chromatography in silica gel with the eluent specified below for each compound.

(3*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-[(6*R*)-6-methylhept-2-yl]-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl Ethyl Malonate (4): The purification of **4** was performed by column chromatography on silica gel with hexane/ethyl acetate (1:1) as the eluent (420 mg, 85%). White solid. M.p. 68–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.39 (br. d, J = 5.0 Hz, 1 H, H-6), 4.69 (m, 1 H, H-3), 4.22 (q, J = 7.2 Hz, 2 H, CH_2O), 3.36 (s, 2 H, $COCH_2CO$), 2.36 (br. d, J = 7.2 Hz, 2 H), 2.1–1.1 (m, 26 H), 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 1.03 (s, 3 H, CH_3-19), 0.92 (d, J = 6.5 Hz, 3 H, CH_3-21), 0.69 (s, 3 H, CH_3-18), 0.87 (2 × d, J = 6.6 Hz, 6 H, CH_3-26 and CH_3-27) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.71 (C=O), 166.03 (C=O), 139.33 (C-5), 122.89 (C-6), 75.31 (C3), 61.43 (OCH_2), 56.63 (CH), 56.18 (CH), 49.95 (C-9), 42.27 (C-13), 41.96 ($COCH_2CO$), 39.67 (C-22), 39.48 (C-24), 37.84 (C-4), 36.87 (C-1), 36.53 (C-10), 36.14 (CH_2), 35.77 (CH), 31.86 (C-7), 31.80 (CH), 28.20 (CH_2), 27.99 (CH), 27.54 (CH_2), 24.25 (CH_2), 23.79 (CH_2), 22.81 (CH_3), 22.54 (CH_3), 20.99 (CH_2), 19.28 (C-19), 18.68 (C-21), 14.07 (CH_3CH_2), 11.83 (C-18) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2937 1755 (C=O) 1462 1270 cm^{-1}. HRMS-MALDI: calcd. for $C_{32}H_{52}O_4Na$ [M + Na]$^+$ 523.37578; found 523.375778. $C_{32}H_{52}O_4$ (500.39): calcd. C 76.75, H 10.47; found C 3.87, H 10.53.

Ethyl (9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*R*)-5-Ethyl-6-methylhept-2-yl]-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl Malonate (5): The purification of **5** was performed by column chromatography on silica gel with hexane/ethyl acetate (1:1) as the eluent (410 mg, 78%). White solid. M.p. 65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.40 (br. d, J = 5.0 Hz, 1 H, H-6), 4.67 (m, 1 H, H-3), 4.22 (q, J = 7.02 Hz, 2 H, CH_2O), 3.36 (s, 2 H, $COCH_2CO$), 2.36 (br. d, J = 7.2 Hz, 2 H, H4), 2.1–1.1 (m, 27 H), 1.30 (t, J = 7.02 Hz, 3 H, CH_3), 1.03 (s, 3 H, CH_3-19), 0.93 (d, J = 6.5 Hz, 3 H, CH_3-21), 0.88–0.81 (m, 9 H, CH_3-26, CH_3-27, and CH_3-29), 0.69 (s, 3 H, CH_3-18) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.71 (C=O), 166.04 (C=O), 139.33 (C5), 122.90 (C6), 75.21 (C3), 61.44 (OCH_2), 56.64 (CH), 55.99 (CH), 49.95 (C-9), 45.79 (CH), 42.28 (C-13), 41.97 ($COCH_2CO$), 39.67 (CH_2), 37.84 (C-4), 36.88 (C-1), 36.54 (C-10), 36.13 (CH), 33.89 (CH_2), 31.87 (C-7), 31.81 (CH), 29.09 (CH), 28.23 (CH_2), 27.55 (CH_2), 26.00 (CH_2), 24.26 (CH_2), 23.02 (CH_2), 20.99 (CH_2), 19.81 (CH_3), 19.28 (C-19), 19.00 (CH_3), 18.75 (CH_3), 14.07 (CH_3CH_2), 11.96 (CH_3), 11.83 (C-18) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2945, 1752 and 1733 (C=O), 1467, 1270 cm^{-1}. HRMS-MALDI: calcd. for $C_{34}H_{56}O_4Na$ [M + Na]$^+$ 551.40765; found 551.40668. $C_{34}H_{56}O_4$ (528.42): calcd. C 77.22, H 10.67; found C 77.31, H 10.72.

(3*S*,9*S*,10*R*,13*R*,14*R*,17*R*)-10,13-Dimethyl-17-[(2*R*,3*E*,5*R*)-5,6-dimethylhept-3-en-2-yl]-2,3,4,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3-yl Ethyl Malonate (6): The purification of **6** was performed by column chromatography on silica gel with hexane/ethyl acetate (8:1) as the eluent (355 mg, 70%). White solid. M.p. 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.58 (dd, J = 2.2, J = 5.8 Hz, 1 H, H-7), 5.40 (m, 1 H, H-6), 5.21 (m, 2 H, H-22, H-23), 4.77 (m, 1 H, H-3), 4.23 (q, J = 7.02 Hz, 2 H, CH_2O), 3.37 (s, 2 H, $COCH_2CO$), 1.32 (t, J = 7.02 Hz, 3 H, CH_3), 2.6–1.2 (m, 20 H), 1.05 (d, J = 6.6 Hz, 3 H, CH_3-21), 0.96 (s, 3 H, CH_3-19), 0.93 (d, J = 6.6 Hz, 3 H, CH_3-28), 0.85 (d, J = 6.6 Hz, 3 H, CH_3-27), 0.84 (s, 3 H, CH_3-18), 0.83 (d, J = 6.6 Hz, 3 H, CH_3-26) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.70 (C=O), 166.06 (C=O), 141.62 (C-5), 138.16 (C-8), 135.54 (C-22), 131.96 (C-23), 120.38 (C-6), 116.26 (C-7), 74.06 (C-3), 61.47 (OCH_2), 55.67 (CH), 54.50 (CH), 45.98 (CH), 42.79 (C-20), 41.95 ($COCH_2CO$), 40.44 (C-24), 38.98 (C-12), 37.80 (C-10), 37.05 (C-10), 36.38 (C-1), 33.07 (C-25), 28.28 (CH_2), 27.90 (CH_2), 22.97 (CH_2), 21.09 (C-21), 21.00 (CH_2), 19.95 (CH_3), 19.64 (CH_3), 17.59 (CH_3), 16.15 (CH_3), 14.08 (CH_3CH_2), 12.05 (C-18) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2953, 1760 (C=O), 1458, 1269 cm^{-1}. MS-ESI: m/z = 533 [M + Na]$^+$, 1043 [2 M + Na]$^+$. $C_{33}H_{50}O_4$ (510.37): calcd. C 77.60, H 9.87; found C 77.69, H 9.96.

Synthesis of Bingel–Hirsch Adducts 7, 8, and 9: A solution of C_{60} (50 mg, 0.069 mmol) in toluene (50 mL) was prepared. The corresponding malonate (**4**, **5**, or **6**; 0.090 mmol), CBr_4 (0.090 mmol), and diazabicyclo[4.2.0]undec-7-ene (DBU; 0.17 mL, 1.13 mmol) were added in that order. The reaction mixture was then stirred at room temperature for 2 h. Water was added, and the residue was extracted with toluene. The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Purification of the products was achieved by column chromatography on silica gel, first with CS_2 to elute unreacted C_{60} and finally with the eluent specified below for each compound (**7**, **8**, or **9**).

Compound 7: HPLC: BuckyPrep Waters, toluene/acetonitrile (9:1), flow rate 1 mL min^{-1}, t_R = 4.50 min. The purification of **7** was performed by column chromatography on silica gel with CS_2 and toluene as the eluents. Yield 38 mg (56%). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.51 (br. d, J = 3.7 Hz, 1 H, H-6), 5.03 (m, 1 H, H-3), 4.57 (q, J = 7.1 Hz, 2 H, CH_2O), 1.52 (t, J = 7.1 Hz, 3 H, CH_3), 2.56 (2 × d, J = 7.9 Hz, 2 H, CH_2-4), 2.1–1.2 (m, 24 H), 1.01 (s, 3 H, CH_3-19), 0.94 (d, J = 6.4 Hz, 3 H, CH_3-

21), 0.70 (s, 3 H, CH_3-18), 0.88 (d, J = 6.6 Hz, 6 H, CH_3-26 and CH_3-27) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.62 (C=O), 162.93 (C=O), 145.99, 145.44, 145.22, 145.16, 145.14, 144.83, 144.65, 144.56, 143.85, 143.04, 142.97, 142.92, 142.18, 141.87, 140.89, 139.17 (C-5), 138.99, 138.85, 123.47 (C-6), 77.46 (C-3), 74.70 (Csp^3 cyclopropane ring), 71.65 (Csp^3 cyclopropane ring), 63.33 (OCH_2), 56.63 (CH), 56.10 (CH), 52.30 (Csp^3 cyclopropane ring), 49.96 (CH-9), 42.27 (C-13), 39.67 (C-22), 39.48 (C-24), 37.89 (CH_2-4), 36.92 (C-1), 36.63 (C-10), 36.15 (CH_2), 35.77 (CH), 31.92 (CH_2), 31.82 (CH), 28.22 (CH_2), 27.99 (CH), 27.69 (CH_2), 24.28 (CH_2), 23.81 (CH_2), 22.82 (CH_3), 22.55 (CH_3), 21.04 (CH_2), 19.38 (C-19), 18.70 (CH_3), 14.30 (CH_3CH_2), 11.86 (C-18) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 1743 (C=O), 1467, 1235 cm^{-1}. UV/Vis: λ_{max} ($\log\varepsilon$) = 425 (3.70), 325 (4.31), 258 (4.52) nm. HRMS-MALDI: calcd. for $C_{92}H_{50}O_4$ $[M]^{\cdot-}$ 1218.370336; found 1218.37463.

Compound 8: HPLC: BuckyPrep Waters, toluene/acetonitrile (9:1), flow rate 1 mL min^{-1}, t_R = 4.52 min. The purification of **8** was performed by column chromatography on silica gel with CS_2 and hexane/ethyl acetate (9.5:0.5) as the eluents. Yield 40 mg (58%). Brown solid. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.50 (br. d, J = 4.0 Hz, 1 H, H-6), 5.03 (m, 1 H, H-3), 4.57 (q, J = 7.2 Hz, 2 H, CH_2O), 1.51 (t, J = 7.2 Hz, 3 H, CH_3), 2.56 (2 × d, J = 7.8 Hz, 2 H, CH_2-4), 2.1–1.2 (m, 27 H), 1.09 (s, 3 H, CH_3-19), 0.92 (d, J = 6.4 Hz, 3 H, CH_3-21), 0.70 (s, 3 H, CH_3-18), 0.88–0.81 (m, 9 H, CH_3-26, CH_3-27, and CH_3-29) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.64 (C=O), 162.96 (C=O), 145.50, 145.46, 145.24, 145.18, 145.15, 144.84, 144.67, 144.58, 143.87, 143.06, 142.99, 142.94, 142.29, 141.89, 140.91, 139.18, 139.15, 138.86, 123.48 (C-6), 77.41 (C-3), 73.81 (Csp^3 cyclopropane ring), 71.66 (Csp^3 cyclopropane ring), 63.34 O (CH_2), 56.64 (CH), 56.01 (CH), 52.32 (Csp^3 cyclopropane ring), 49.98 (CH), 45.79 (CH), 42.30 (C-13), 39.68 (CH_2), 37.90 (CH_2), 36.94 (CH_2), 36.65 (C-10), 36.15 (CH), 33.91 (CH_2), 31.92 (C-7), 31.84 (CH), 29.69 (CH_2), 29.10 (CH), 28.24 (CH_2), 27.70 (CH_2), 26.03 (CH), 24.29 (CH_2), 23.03 (CH_2), 21.04 (CH_2), 19.82 (CH_3), 19.38 (C-19), 19.01 (CH_3), 18.77 (CH_3), 14.30 (CH_3CH_2), 11.97 (CH_3), 11.86 (C-18) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2948, 1745 (C=O), 1464, 1235 cm^{-1}. UV/Vis: λ_{max} ($\log\varepsilon$) = 425 (3.70), 325 (4.31), 258 (4.50) nm. HRMS-MALDI: calcd. for $C_{94}H_{54}O_4$ $[M]^{\cdot-}$ 1246.40222; found 1246.40166.

Compound 9: HPLC BuckyPrep Waters, toluene/acetonitrile (9:1), flow rate 1 mL min^{-1}, t_R = 4.38 min. The purification of **9** was performed by column chromatography on silica gel with CS_2 and toluene as the eluents. Yield 34 mg (50%). Brown solid. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.57 (d, J = 8.4 Hz, 1 H, H-7), 6.31 (d, J = 8.4 Hz, 1 H, H-6), 5.42 (m, 1 H, H-3), 5.21 (m, 2 H, H-22, H-23), 4.57 (q, J = 7.1 Hz, 2 H, CH_2O), 1.51 (t, J = 7.1 Hz, 3 H, CH_3), 2.4–1.5 (m, 20 H), 1.02 (d, J = 6.6 Hz, 3 H, CH_3-21), 0.98 (s, 3 H, CH_3-19), 0.93 (d, J = 6.6 Hz, 3 H, CH_3-28), 0.85 (m, 9 H, CH_3-18, CH_3-26, and CH_3-27) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.69 (C=O), 162.54 (C=O), 145.23, 145.16, 145.02, 144.85, 144.69, 144.64, 144.58, 143.87, 143.07, 142.89, 142.93, 142.20, 141.91, 141.86, 140.92, 139.40, 138.65, 135.14 (C-22), 134.75 (C-6), 132.33 (C-23), 131.19 (C-7), 81.74 (C-5), 79.51 (C-8), 73.08 (C-3), 72.79 (Csp^3 cyclopropane ring), 71.58 (Csp^3 cyclopropane ring), 63.35 (OCH_2), 56.16 (C-17), 52.18 (Csp^3 cyclopropane ring), 51.56 (C-14), 50.94 (C-9), 44.56 (C-13), 42.75 (C-20), 39.73 (C-24), 39.25 (C-12), 37.05 (C-10), 34.27 (C-1), 33.04 (C-25), 29.70 (CH_2), 28.63 (CH_2), 26.22 (CH_2), 23.39 (CH_2), 20.87 (C-21), 20.59 (CH_2), 19.94 (CH_3), 19.62 (CH_3), 18.16 (C-19), 17.56 (CH_3), 14.27 (CH_3CH_2), 12.81 (C-18) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2956, 1745 (C=O), 1461, 1236 cm^{-1}. UV/Vis: λ_{max} ($\log\varepsilon$) = 425 (3.70), 323 (4.20), 257 (4.50) nm. HRMS-ESI: calcd. for $C_{93}H_{48}O_4$ $[M]^{\cdot-}$ 1260.34509; found 1260.33116.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **4**–**8**, ^1H, ^{13}C NMR, and DEPT spectra of **9**, mass spectra (MS-ESI or HRMS-MALDI) of compounds **4**–**9**, FTIR spectra of compounds **4**–**9**, and HPLC chromatograms of the crude reaction products to obtain hybrids **7**–**9**.

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