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Synthesis of Unusual Cholestane Analogs by Diels-Alder Reaction (A+CD ⟶ ABCD)

Francesco De Riccardis*, Irene Izzo, Consiglia Tedesco, and Guido Sodano*

Dipartimento di Chimica, University of Salerno, 84081 Baronissi (SA) - Italy

Abstract: *Unprecedented cholestane analogs have been synthesized by Diels-Alder reactions between a diene generated in high yields from vitamin D_3 and appropriate dienophiles. This strategy is useful for the scarcely utilized A+CD ⟶ ABCD approach to the tetracyclic steroid nucleus*
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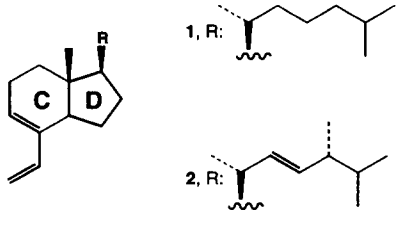
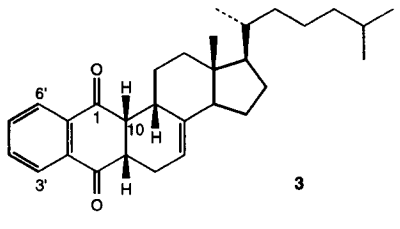
The Diels-Alder reaction has been widely used for the synthesis of steroids.[1] By this approach, various preformed rings are connected to afford the tetracyclic steroid nucleus. In the most common strategy (AB+D ⟶ ABCD), an AB ring diene is reacted with a D ring dienophile, as in the first attempt by Dane in the synthesis of estrone.[2] We report here a strategy for the synthesis of cholestane analogs in which a CD diene (e.g. **1**) is used for an A+CD ⟶ ABCD approach to the tetracyclic steroid nuclues, which to the best of our knoweledge is practically unexploited.[1,3]

Diene **1** is readily available from vitamin D_3 in four steps and in 55% overall yield by using a route recently exploited for the synthesis of the analog **2**.[4] The reaction of **1** with various dienophiles affords an array of cholestane analogs in which the A ring could be varied at will.

In order to preliminarly assess the stereochemistry of the Diels-Alder adducts, the structure of the crystalline benzosteroid **3**,[5] obtained from the reaction of **1** with naphthoquinone (toluene, 90 °C, 5h, 98% yield), was investigated by X-rays.[6]





3

The X-ray analysis showed that the α-*endo* adduct was formed, as with similar compounds,[7] leading to cholestane analogs having the unnatural 9β-*H* configuration. An ORTEP-plot of **3** is reported in fig. 1. The stereochemistry at the newly formed stereogenic centres of the other adducts was established to be the same as in **3** by comparison of the ^{13}C NMR chemical shifts of the relevant carbons.

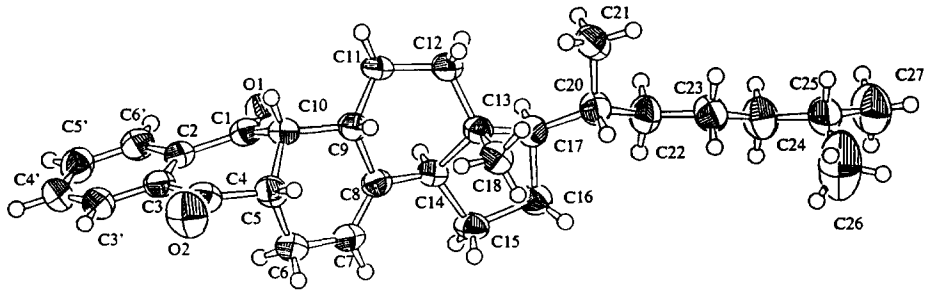
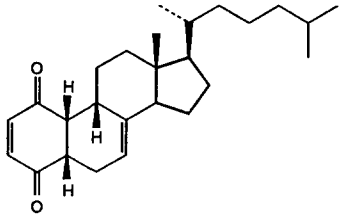
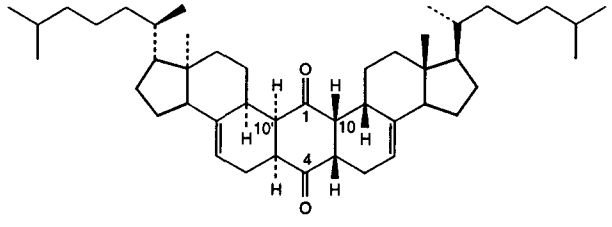


Fig. 1

Reaction of **1** with an excess of *p*-benzoquinone (toluene, 75 °C, 16h) afforded the mono-adduct **4**[8] (56% yield), while either reaction of a 2:1 molar ratio of **1** with *p*-benzoquinone (toluene, 90 °C, 16h) or reaction of **4** with **1** (toluene, 90 °C, 20h), afforded the *bis*-cholestane derivative **5**[9] in 59% and 61% yield, respectively. The structure of **5** was selected among other possibilities on the observation that in the ^{13}C NMR spectrum the two halves of the molecule show single resonances for all the symmetric carbons, while two distinct resonances were observed only for the carbonyl carbons (212.5 and 210.1 ppm). Of the two possible structures having a C_2 symmetry, only **5** is in accordance with this observation. Compound **5** is unique among the cholestane analogs for obvious reasons, including the fact that two cholestane frameworks share the ring A leading to a C_2 symmetric molecule.

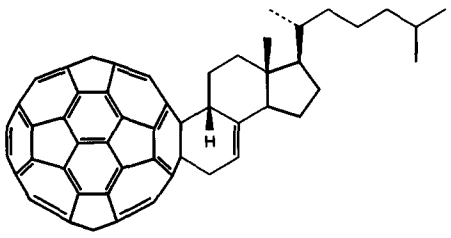


4



5

1 also reacts with buckminsterfullerene (C_{60}) to afford the thermally stable adduct **6**. Addition of one equivalent of **1** to a solution of C_{60} in dry degassed toluene (argon atmosphere, dark, r.t., 2h) afforded **6** in 58% yield. The structure of **6** was secured by NMR and MS spectra.[10] Interestingly, in the proton spectrum of **6** the fullerene ring system exhibits a marked deshielding effect on the C-6, C-7 and C-9 protons of the B ring (steroid numbering) which resonate at 4.06, 6.45 and 3.92 ppm, respectively. Compound **6** adds to a restricted list of steroid-fullerene hybrids which are being synthesized in order to investigate the possible biological applications of fullerene derivatives.[11]



6

Despite the large number of known synthetic methods, there is a continuous demand for strategies which give access to steroids having novel structures. In this respect, dienes **1** and **2** allow a simple construction of cholestane analogs of different types. Work is in progress in our laboratory towards the synthesis of various cholestane hybrids by this approach.

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3. Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*, John Wiley & Sons, New York, 1990.
4. De Riccardis, F.; Spinella, A.; Izzo, I.; Giordano, A.; Sodano G. *Tetrahedron Lett.* **1995**, *36*, 4303.
5. Colorless crystals, m.p. 159-160°C. $[\alpha]_D$ = +190.9 (c = 0.5; $CHCl_3$); ^1H NMR δ ($CDCl_3$, 250 MHz) 0.72 (s, 3H), 0.87 (d, *J*= 6.5 Hz, 6H), 0.92 (d, *J*= 5.8 Hz, 3H), 3.40 (m, 2H), 5.07 (m, 1H), 7.70 (dd, *J*= 5.8 and 3.3 Hz, 2H), 7.90 (dd, *J*= 5.8 and 3.3 Hz, 1H), 8.02 (dd, *J* = 5.8 Hz and 3.3 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 18.4 (C-18), 18.8 (C-21), 22.5 and 22.8 (C-26 and C-27), 22.8 (C-11), 23.9 (C-23), 24.5 (C-15), 27.1 (C-6), 28.0 (C-25), 28.7 (C-16), 35.9 (C-22), 36.1 (C-20), 36.7 (C-9), 37.7 (C-12), 39.4 (C-24), 41.7 (C-13), 49.2 (C-14), 50.7 (C-5), 50.8 (C-10), 57.1 (C-17), 114.3 (C-7), 126.2 and 127.0 (C-3' and C-6'), 132.5 and 135.9 (C-2 and C-3), 133.8 and 134.2 (C-4' and C-5'), 142.0 (C-8), 198.0 (C-1) 199.2 (C-4); UV/Vis (dioxane): λ_{max} (ε) = 210-240 (9600-9200), 257 (6300), 295-307 nm (1400-1200); EIMS (70 eV): *m/z* 432 (M^+), 417, 319.
6. Colorless and flat crystals are monoclinic with space group $P2_1$ and lattice costants *a* = 8.365(6) Å, *b* = 10.423(4) Å, *c* = 14.506(4) Å, β =96.66(4)°,*V* = 1256(1) $Å^3$, Z = 2, d_{calc} = 1.14 g/cm^3. A total of 4330 reflections were collected at 25°C on a Rigaku AFC7S diffractometer, using a graphite

monochromated radiation (λ = 0.71069 Å). The linear absorption coefficient, μ, for MoKα radiation is 0.6 cm^{-1}; because of crystal shape an empirical absortion correction (ψ-scan) was applied, transmission factors range from 0.74 to 1.00. The structure was solved by direct methods (SAPI91) and expanded using Fourier techniques. The final cycle of least square refinement was based on 2296 reflections with I > 3.0 σ_I and 289 variable parametrs. Anisotropic temperature parameters were considered for all non-hydrogen atoms, while hydrogen atoms were included but not refined. Final disagreement indices are R = 0.062 and R_w = 0.046. All calculations were perfomed using the TEXSAN crystallographic software package by Molecular Structure Corporation.

7. Kolaczkowski, L.; Reusch, W. *J. Org. Chem.* **1985**, *50*, 4766, and references therein.
8. Yellow solid. $[\alpha]_D$ = +237.8 (c = 0.3; $CHCl_3$); ^1H NMR δ ($CDCl_3$, 250 MHz) 0.77 (s, 3H), 0.86 (d, *J*= 6.5 Hz, 6H), 0.90 (d, J= 5.8 Hz, 3H), 3.23 (m, 2H), 5.07 (m, 1H), 6.51 (d, *J*=12.0 Hz, 1H), 6.58 (d, *J*=12.0 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 18.4 (C-18), 18.8 (C-21), 22.5 and 22.8 (C-26 and C-27), 22.7 (C-11), 23.9 (C-23), 24.1 (C-15), 27.1 (C-6), 28.0 (C-25), 28.7 (C-16), 35.8 (C-22), 36.1 (C-20), 36.2 (C-9), 37.5 (C-12), 39.4 (C-24), 41.6 (C-13), 49.0 (C-14), 50.0 (C-5), 50.8 (C-10), 57.1 (C-17), 114.3 (C-7), 141.8 (C-8), 137.0, 141.0, (C-2, C-3), 199.6 (C-1), 201.6 (C-4); UV/Vis (dioxane): λ_{max} (ε) = 214-207 (6500-6600) and 252 nm (1400); EIMS (70eV): *m/z* 382 (M^+), 367, 339, 269.
9. Colorless solid. $[\alpha]_D$ = +86.9 (c = 0.4; $CHCl_3$); ^1H NMR δ ($CDCl_3$, 250 MHz) 0.63 (s, 3H), 0.88 (d, J= 7.0 Hz, 6H), 0.90 (d, J= 5.6 Hz, 3H), 2.81 (dd, J= 5.6 and 4.9 Hz, 1H), 2.99 (m, 1H), 5.16 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 18.4 (C-18, C-18'), 18.6 (C-21, C-21'), 22.5 and 22.8 (C-26, C-26'and C-27, C-27'), 22.5 (C-11, C-11'), 23.9 (C-23, C-23'), 24.5 (C-15, C-15'), 26.1 (C-6, C-6'), 28.0 (C-25, C-25'), 28.7 (C-16, C-16'), 35.8 (C-20, C-20' and C-22, C-22'), 36.1 (C-9, C-9'), 37.3 (C-12, C-12'), 39.4 (C-24, C-24'), 41.8 (C-13, C13'), 47.7 (C-10, C-10'), 48.3 (C-5, C-5'), 49.1 (C-14, C-14'), 56.9 (C-17, C-17'), 114.8 (C-7, C-7'), 142.2, (C-8, C-8'), 210.1 (C-1), 212.5 (C-4); EIMS (70 eV): *m/z* 656 (M^+), 641, 543.
10. Amorphous brown solid, by precipitation with MeOH. ^1H NMR δ ($CDCl_3$, 250 MHz) 0.88 (s, 3H), 0.89 (d, *J*= 6.6 Hz, 3H), 0.90 (d, *J*= 6.6 Hz, 3H), 1.00 (d, *J*= 6.3 Hz, 3H), 2.27 (dt, *J*=14.0 and 5.1 Hz, 1H), 2.63 (m, 2H), 2.87 (m, 1H), 3.92 (m, 1H), 4.01 (dd, *J*= 14.0 and 7.0 Hz, 1H), 4.06 (br dd, 1H), 6.45 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 18.7 (C-18 and C-21), 21.8 (C-11), 22.6 and 22.8 (C-26 and C-27), 23.9 (C-23), 26.5 (C-15), 28.0 (C-25), 29.3 (C-16), 35.9 (C-22), 36.3 (C-20), 36.7 (C-6), 39.5 (C-24), 40.0 (C-12), 43.3 (C-13), 44.1 (C-9), 50.0 (C-14), 56.2 (C-17), 66.7 and 70.1 (C_{60} sp^3 carbons), 119.4 (C-7), 135.0, 135.5, 136.0, 136.5, 138.5, 138.8, 140.2, 141.4, 141.5, 141.7, 141.9, 142.1, 142.3, 142.4, 142.6, 143.1, 143.7, 144.7, 144.7, 144.8, 145.1, 145.4, 145.9, 146.2 146.4, 146.5, 147.0, 147.3, 147.5, 147.6, 147.9, 148.2, 154.5, 155.9, 158.0, 158.9 (C_{60} sp^2 carbons); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 253 (91000), 307 (s; 36000), 348 (s; 16000), 706 (300) nm; FABMS: *m/z* 1011 (MH^++ O)[12], 995 (MH^+), 721.
11. For a review see: Jensen, A. W.; Wilson, S.R.; Schuster, D.I. *Bioorg. Med. Chem.* **1996**, *4*, 767.
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