Dienone–Phenol Type Rearrangements. Part 5.[1] Confirmation of a Rearrangement Pathway using Carbon-13 Labelling

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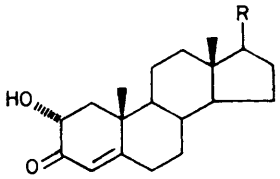
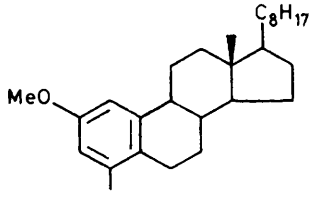
Previous work had shown that 2α-hydroxycholest-4-en-3-one (1a) rearranged in acid solution to give the aromatic 2-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene (2). Labelling of the hydroxy-enone with carbon-13 at C-4 and use of ^{13}C n.m.r. supports previous mechanistic proposals.

In a previous paper [1] we described how, under a variety of acidic conditions, 2α-hydroxycholest-4-en-3-ones gave,



(1) a; R = C_8H_{17}
b; R = OAc



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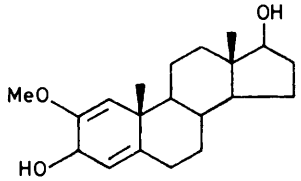


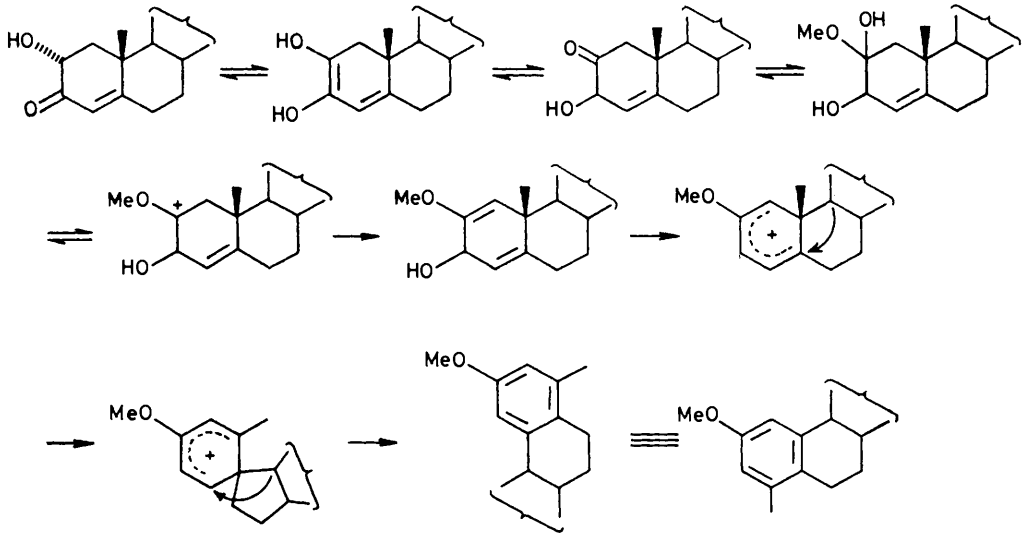
(3)

in general, non-aromatic products with functionality at C-6 while C-2 became saturated. As hydroxy-enones are at the same level of oxidation as dienones they might aromatize by a dienone–phenol type pathway,[2] but only one example of such an aromatization was observed. Reaction of 2α-hydroxycholest-4-en-3-one (1a) with toluene-*p*-sulphonic acid in refluxing methanol gave, as one of the products, 2-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene (2), a result in agreement with the findings of Clarke for the rearrangement of the analogue 2α-hydroxytestosterone acetate (1b).[3]

The intermediacy of 1,4-dien-3-ones was ruled out by Clarke, who proposed instead that the rearrangement involved a 2-methoxy-1,4-dien-3-ol, a postulate that was supported by the ready aromatization of the dienol (3).[3]

In view of its complexity, we decided to test the postulated mechanism (Scheme 1) with carbon-13 labelling, using ^{13}C n.m.r. spectroscopy. 2α-Hydroxy-[4-^{13}C]cholest-4-en-3-one (1a) (25% ^{13}C) was synthesized as shown in Scheme 2. The mechanism of the final step (7) ⟶ (1a) is uncertain but it is necessary to have an aqueous medium. Rearrangement of the hydroxy-enone (1a) gave the expected aryl ether (2) in 37% yield, together with the additional products shown in Scheme 3.

The postulated pathway requires that the initial C-4 becomes C-10 in the aromatic product; such a shift was observed in the present case with the labelled carbon being identified as follows. The enhanced peak in the ^{13}C n.m.r. spectrum remained a singlet in the off-resonance decoupled spectrum, and the one-bond ^{13}C–^{13}C coupling in the noise-decoupled spectrum showed that the labelled carbon atom was adjacent to a protonated



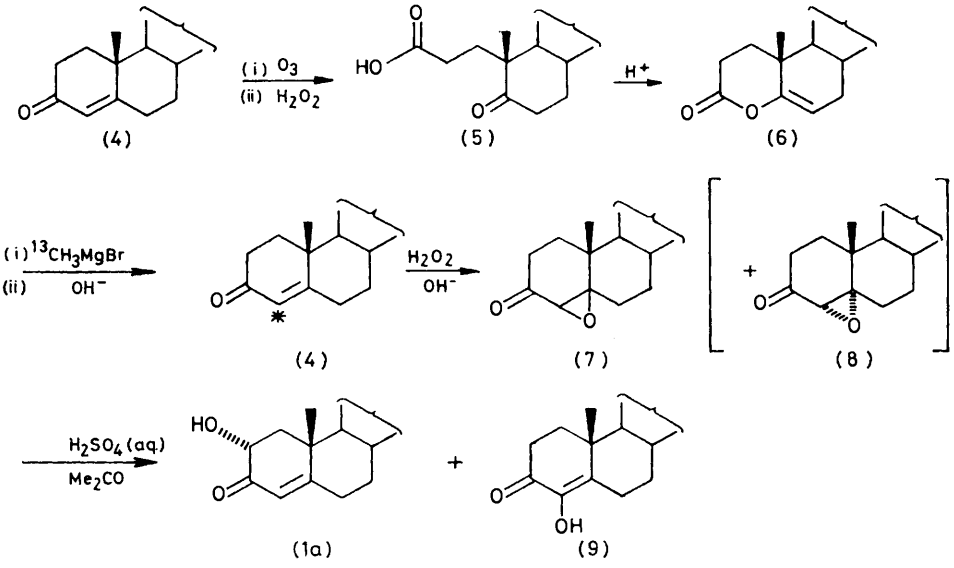
SCHEME 1

[1] K. M. Baker and B. R. Davis *J. Chem. Soc.* (*C*), 1968, 2743.
[2] A. J. Waring, *Adv. Alicyclic Chem.*, 1966, **1**, 131; N. L. Wendler in ' Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1964.
[3] R. L. Clarke, *J. Amer. Chem. Soc.*, 1962, **84**, 467.

aromatic carbon (C-1), a non-protonated aromatic carbon (C-5), and a monoprotonated aliphatic carbon atom (C-9). Coupling was also observed with the protonated C-3 (*para*) but no coupling was observed with the two *meta*-carbon atoms (C-2 and -4).

signals in the ^1H n.m.r. spectrum (see Experimental section).

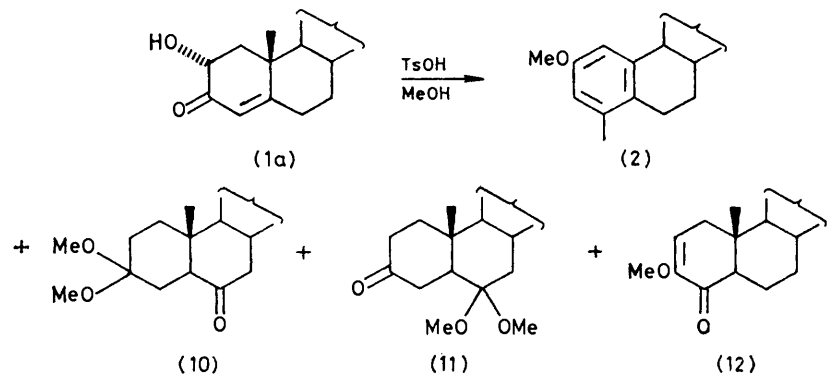
Since functionalization at C-6 is the major reaction course in all cases where aromatization does not occur, it appears that there is competition between the two



SCHEME 2

The chemical shift assignments for the aromatic ring were confirmed by comparing the observed values with those calculated by combining the empirical substituent shifts of Levy and Nelson for the methoxy group [4] with the measured shifts for the unsubstituted 4-methyl-19-norcholesta-1,3,5(10)-triene (13) (see Table). The

possible directions of enolization of the hydroxyenone.[1,3] Since enolization occurs preferentially by abstraction of an axial proton,[6] enolization towards C-2 will not take place readily when a 2β-substituent is present, and enolization towards C-6 is even more favoured with a 6α-alkyl substituent because of charge



SCHEME 3

peaks due to the aromatic carbon atoms of the cholestatriene were assigned using the data of Hanson and Siverns for the analogous estratriene.[5] Having assigned the aromatic carbon resonances we were able to use single-frequency proton-decoupled ^{13}C n.m.r. spectroscopy to assign unequivocally the two aromatic proton

stabilization. With a substituent at C-4 aromatization is not possible by this mechanism regardless of the direction of enolization, because the substituent prevents migration of C-10 to position 4 in the collapse of the spiran intermediate in the rearrangement.[2] Thus the aromatization of 2α-hydroxycholest-4-en-3-one (1a) ap-

[4] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972, p. 81.

[5] J. R. Hanson and M. Siverns, *J.C.S. Perkin I*, 1975, 1110.

[6] E. J. Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175; E. J. Corey and R. A. Sneen, *ibid.*, 1956, **78**, 6269.

pears to involve enolization towards C-2 and subsequent rearrangement as shown in Scheme 1.

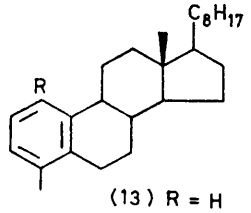
The facility with which rearrangements may be studied by the use of carbon-13 labelling and ^{13}C n.m.r. spectroscopy of the intact product contrasts markedly with the degradative techniques needed in earlier work with carbon-14 labelling. Thus the availability of suitably labelled substrate allowed us to investigate the pathway of the rearrangement of [4-^{13}C]cholesta-1,4-dien-3-one (14) to 4-methyl-19-norcholesta-1,3,5(10)-trien-1-yl acetate (15). As before ^{13}C–^{13}C coupling to C-1, C-5, and C-9 readily identified the labelled carbon atom as C-10. The chemical shift assignments were confirmed by comparison with those calculated using the empirical substituent shift of the acetoxy group [7]

^{13}C N.m.r. chemical shifts in ring A aromatic steroids

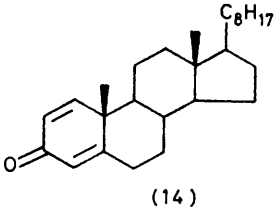
	Carbon atom					
Compound	1	2	3	4	5	10
(13)	123.0	125.2	127.2	135.1	136.2	140.7
(2) (calc.*)	108.6	156.6	112.8	136.1	128.5	141.7
(2) (obs.)	108.7	157.1	112.7	137.3	127.3	141.8
(15) (calc.*)	146.0	118.8	128.5	132.8	137.5	134.3
(15) (obs.)	148.0	119.7	127.7	132.3	138.6	134.3

* Calculated using substituent shifts for OMe: C-1, +31.4; *ortho*, −14.4; +1.0; *para*, −7.7; and for OAc: C-1, +23.0; *ortho*, −6.4; *meta*, +1.3; *para*, −2.3 p.p.m. downfield relative to benzene (128.7).

(see Table). Single-frequency proton-decoupled ^{13}C n.m.r. spectroscopy was again used to make unequivocal assignments of the aromatic proton resonances in the ^{1}H n.m.r. spectrum; the result was the opposite of that reported.[8]



(13) R = H
(15) R = OAc



(14)

EXPERIMENTAL

M.p.s were determined with a Reichert Kofler hot-stage apparatus. I.r. spectra were measured with a Perkin-Elmer 237 spectrometer for solutions in carbon tetrachloride. ^{1}H N.m.r. spectra were measured with a Varian T60 spectrometer (solvent $CDCl_3$ or CCl_4) and ^{13}C n.m.r. spectra with a JEOL JNM-FX60 Fourier transform spectrometer; assignments were confirmed using single frequency off-resonance decoupling (s.f.o.r.d.). Low resolution mass spectra were obtained with a Varian MAT CH-7 spectrometer operating at (nominal) 70 eV.

Ozonolysis of Cholest-4-en-3-one (4).—Cholest-4-en-3-one (4) dissolved in ethyl acetate–acetic anhydride was ozonized and oxidized with hydrogen peroxide by the method of Turner [9] to give the oxo-acid (5), m.p. 151—152° (hexane) (lit.,[10] 154—154.5°), $\nu_{max.}$ 3 600—2 400 (OH) and 1 705 cm^{-1} (C=O), δ_H 0.77 (s, 18-H_3), 1.17 (s, 19-H_3), and 9.20br (s, exchangeable on deuteriation, OH).

4-Oxacholest-5-en-3-one (6).—A solution of perchloric acid (72%; 0.5 ml) and acetic anhydride (48 ml, 0.52 mol) in ethyl acetate [10] (total volume 500 ml) was added to the oxo-acid (5) (11 g, 2.7 × 10^{-2} mol) in ethyl acetate (500 ml). The solution was kept at room temperature for 1 h before being washed with water. The solvent was removed, the residue was poured into ice–water, and the mixture was stirred overnight. Extraction with ether gave an oil which was chromatographed on silica gel (benzene) to give 4-oxacholest-5-en-3-one (6) (7.38 g, 70%), m.p. 91—92° (aqueous acetone) (lit.,[10] 92—93.5°), $\nu_{max.}$ 1 760 (C=O), 1 690 (C=C), and 1 260 cm^{-1} (C–O), δ_H 0.72 (s, 18-H_3), 1.13 (s, 19-H_3), 2.57 (4 H, m, 2-H_2 and 7-H_2), and 5.27 (1 H, m, 6-H).

[4-^{13}C]*Cholest-4-en-3-one* (4).—A solution of 4-oxacholest-5-en-3-one (6) (5.49 g, 14.1 mmol) in ether (20 ml) was added slowly with stirring to an ethereal solution (10 ml) of [^{13}C]methylmagnesium iodide (14.1 mmol, 25% ^{13}C) under nitrogen at 0 °C and the solution was stirred at room temperature overnight.[11] Methanol (425 ml), water (70 ml), and sodium hydroxide (14 g) were added, and the mixture was heated under reflux for 5 h. After cooling the solution was acidified with dilute hydrochloric acid and extracted with ether to yield a product which was chromatographed on alumina (benzene) to give [4-^{13}C]cholest-4-en-3-one (4) (3.30 g, 61%), m.p. 80—84° (EtOH) (lit.,[12] 81—82°), *m/e* 384 ($M^{+\cdot}$, $C_{27}H_{44}O$) and 385 ($M^{+\cdot}$, $^{12}C_{26}{}^{13}CH_{44}O$, 56%), $\nu_{max.}$ 1 680 (C=O) and 1 610 cm^{-1} (C=C), δ_H 0.70 (s, 18-H_3), 1.20 (s, 19-H_3), and 5.53 [s, $^{12}C(4)H$, and d, J 160 Hz, $^{13}C(4)H$], δ_C 38.9 (C-2), 123.6 (enriched, C-4), 171.0 (C-5), and 199.0 (C-3), and additional peaks due to ^{13}C–^{13}C coupling between C-2 and -4 (12 Hz), C-3 and -4 (51 Hz), and C-4 and -5 (65 Hz).

Epoxidation of [4-^{13}C]*Cholest-4-en-3-one* (4).—A solution of [4-^{13}C]cholest-4-en-3-one (4) (2.5 g, 6.5 mmol) in ether (50 ml) and methanol (100 ml) was cooled to 0 °C and treated successively with hydrogen peroxide (30%; 15 ml) and aqueous sodium hydroxide (4 mol l^{-1}; 5 ml). The mixture was allowed to warm to room temperature and was stirred for 5 h. Work-up gave 4β,5β-epoxy[4-^{13}C]cholestan-3-one (7) (1.5 g) as needles, m.p. 115—117° (MeOH–$CHCl_3$) (lit.,[13] 116—117°), $\nu_{max.}$ 1 705 (C=O) and 1 240 and 1 260 cm^{-1} (C–O), δ_H 0.70 (s, 18-H_3), 1.15 (s, 19-H_3), and 2.80 [s, $^{12}C(4)H$, and d, J 180 Hz, $^{13}C(4)H$], δ_C 32.5 (C-2), 62.6 (enriched, C-4), 70.1 (C-5), and 206.2 (C-3), and peaks due to ^{13}C–^{13}C coupling between C-2 and -4 (12 Hz), C-3 and -4 (53 Hz), and C-4 and -5 (25 Hz). Preparative t.l.c. of the mother liquors (hexane–ether, 8 : 2) gave: (i) cholestenone (4) (0.03 g, 2.5%); (ii) 4α,5α-epoxy[4-^{13}C]cholestan-3-one (8) (0.31 g, 12%) as needles, m.p. 124—125.5° (MeOH–$CHCl_3$) (lit.,[14] 123—124.5°), $\nu_{max.}$ 1 705 (C=O) and 1 260 and 1 240 cm^{-1} (C–O), δ_H 0.70 (s, 18-H_3), 1.07 (s, 19-H_3), and 2.90 [s, $^{12}C(4)H$, and d, J 180 Hz, $^{13}C(4)H$]; and (iii) the epoxy-ketone (7) (0.20 g, total yield 1.70 g, 65%), m.p. 117—118° (MeOH–$CHCl_3$).

Rearrangement of 4β,5β-*Epoxy*[4-^{13}C]*cholestan-3-one* (7).—

[7] J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972, p. 197.
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[11] A. Murray, III, and D. L. Williams, 'Organic Synthesis with Isotopes,' Interscience, New York, 1958, Part 1.
[12] L. F. Fieser *Org. Synth.*, 1955, **35**, 43.
[13] M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Toga, M. Inuzuka, and T. Furata, *Tetrahedron*, 1965, **21**, 733.
[14] D. J. Collins, *J. Chem. Soc.*, 1959, 3919.

The epoxy-ketone (7) (1.70 g, 4.2 mmol) was heated under reflux with acetone (70 ml), water (3 ml), and conc. sulphuric acid (1 ml) for 5 h, and the mixture was then poured into water.[13] Preparative t.l.c. (hexane–ether, 7 : 3) gave: (i) 2α-hydroxy[4-^{13}C]cholest-4-en-3-one (1a) (1.19 g, 70%), m.p. 143—145° (lit.,[13] 143—146°), $\nu_{max.}$ 3 490 (OH), 1 680 (C=O), 1 605 (C=C), and 1 115 cm^{-1} (C–O), δ_H 0.70 (s, 18-H_3), 1.30 (s, 19-H_3), 2.25 (m, 6-H_2), 3.27br (s, exchangeable on deuteriation, OH), 2.40 (dd, *J* 14 Hz, 6 Hz, 2β-H), and 5.70 [s, ^{12}C(4)H, and d, *J* 160 Hz, ^{13}C(4)H], δ_C 69.5 (C-2), 120.1 (C-4), 172.8 (C-5), and 199.5 (C-3); and (ii) 4-hydroxy-[4-^{13}C]cholest-4-en-3-one (9) (0.20 g, 12%), m.p. 146—147° (lit.,[15] 146—147°), $\nu_{max.}$ 3 450 (OH), 1 668 (C=O), 1 640 (C=O), and 1 380 cm^{-1} (C–O), δ_H 0.70 (s, 18-H_3), 1.18 (s, 19-H_3), 2.43 (m, 6-H_2), 3.17 (m, 2-H_2), and 5.97br (s, exchangeable on deuteriation, OH), δ_C 34.7 (C-2), 140.3 (C-5), 141.0 (C-4), and 193.5 (C-3).

Rearrangement of 2α-*Hydroxy*[4-^{13}C]*cholest-4-en-3-one* (1a).—A solution of the hydroxy-cholestenone (1a) (1.0 g, 2.5 mmol) and toluene-*p*-sulphonic acid monohydrate (0.20 g) in methanol (25 ml) was heated under reflux for 4 days. Work-up gave an oil (1.10 g) which was separated by preparative t.l.c. (hexane–ether, 9 : 1) to give: (i) 2-methoxy-4-methyl-19-nor[10-^{13}C]cholesta-1,3,5(10)-triene (2) (0.37 g, 37%),[16] $\nu_{max.}$ 1 605 (C=C) and 1 145 and 1 060 cm^{-1} (C–O), δ_H 0.70 (s, 18-H_3), 2.14 (s, aromatic Me), 3.67 (s, OMe), 6.45 (d, *J* 2.5 Hz, 3-H), and 6.58 (d, *J* 2.5 Hz, 1-H), δ_C 20.0 (4-Me), 44.5 (C-9), 55.1 (OMe), 108.7 (C-1), 112.7 (C-3), 127.3 (C-5), 137.3 (C-4), 141.8 (enriched, C-10), and 157.1 (C-2), and peaks due to ^{13}C–^{13}C coupling between C-9 and -10 (41 Hz), C-1 and -10 (61 Hz), C-3 and -10 (51 Hz), and C-5 and -10 (59 Hz); irradiation at 47.67 kHz caused collapse of the signals at δ 108.7 in the s.f.o.r.d. ^{13}C n.m.r. spectrum and at δ 6.45 in the ^{1}H n.m.r. spectrum; (ii) a mixture of two compounds (0.33 g, 30%) the major component of which was identified as 3,3-dimethoxy-5α-[4-^{13}C]cholestan-6-one (10),[1,15] $\nu_{max.}$ 1 710 (C=O) and and 1 102 and 1 057 cm^{-1} (C–O), δ_H 0.68 (s, 18-H_3), 0.72 (s, 19-H_3), and 3.03 and 3.13 [2s, $(OMe)_2$]; the minor component showed ^{1}H n.m.r. peaks at 3.09 and 3.23 and was tentatively identified as 6,6-dimethoxy-5α-cholestan-3-one (11); hydrolysis of this mixture gave 5α-cholestane-3,6-dione, m.p. 170—172° (MeOH) (lit.,[15] 174—176°); and (iii) a mixture (0.25 g, 24%), the major component of which was identified as 3-methoxy-5α-[4-^{13}C]cholest-2-en-4-one (12),[1,17] $\nu_{max.}$ 1 695 (C=O), 1 642 (C=C), and 1 108 cm^{-1} (C–O), δ_H 0.70 (s, 18-H_3), 0.83 (s, 19-H_3), 3.55 (s, OMe), and 5.56 (m, 2-H); peaks due to other components were seen at δ 0.65, 3.57, 5.23, and 5.88.

4-*Methyl*-19-*norcholesta*-1,3,5(10)-*triene* (13).—This compound was prepared by treatment of cholest-4-en-3-one with acetyl bromide and HBr[18] in glacial acetic acid; δ_C[5] 19.7 (4-Me), 123.0 (C-1), 125.2 (C-2), 127.2 (C-3), 135.1 (C-4), 136.2 (C-5), and 140.7 (C-10).

[4-^{13}C]*Cholesta*-1,4-*dien*-3-*one* (14).—Labelled cholestenone (4) (0.5 g, 1.3 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.44 g, 1.95 mmol) were heated together under reflux in benzene (10 ml) for 20 h.[19] The solvent was removed and the product was chromatographed on alumina (benzene) to give [4-^{13}C]cholesta-1,4-dien-3-one (14) (0.40 g, 80%) as needles, m.p. 111—112° (MeOH) (lit.,[20] 111.5—112.5°), $\nu_{max.}$ 1 660 (C=O) and 1 620 and 1 595 cm^{-1} (C=C), δ_H 0.73 (s, 18-H_3), 1.22 (s, 19-H_3), 5.90 [m, ^{12}C(4)H, and d, *J* 160 Hz, ^{13}C(4)H], 6.13 (m, 2-H), and 6.90 (d, *J* 10 Hz, 1-H), δ_C 123.6 (C-4), 127.3 (C-2), 155.7 (C-1), 169.0 (C-5), and 186.0 (C-3).

Aromatization of [4-^{13}C]*Cholesta*-1,4-*dien*-3-*one* (14).—A solution of conc. sulphuric acid (10 drops) in acetic anhydride (2 ml) was added to the labelled dienone (14a) (0.40 g, 1.1 mmol) in acetic anhydride (8 ml) and the mixture was kept at room temperature overnight before being poured into ice–water. Extraction with ether gave an oil which was chromatographed on silica gel (benzene) to give 1-acetoxy-4-methyl-19-nor[10-^{13}C]cholesta-1,3,5(10)-triene (15) as an oil (0.323 g, 73%), $\nu_{max.}$ 1 758 (C=O) and 1 194 cm^{-1} (C–O), δ_H 0.73 (s, 18-H_3), 2.18 (6 H, s, aromatic Me and AcO), 2.58 (3 H, m, 6-H_2 and 9-H), 6.60 (1 H, d, *J* 8.2 Hz, 2-H), and 6.90 (1 H, d, *J* 8.2 Hz, 3-H), δ_C 19.6 (aromatic Me), 21.3 (acetate Me), 44.8 (C-9), 118.7 (C-2), 128.0 (C-3), 132.3 (C-4), 134.3 (enriched, C-10), 138.6 (C-5), 148.2 (C-1), and 169.2 (acetate C), and peaks due to ^{13}C–^{13}C coupling between C-1 and -10 (70 Hz), C-5 and -10 (37 Hz), and C-9 and -10 (45 Hz); irradiation at 47.68 kHz caused collapse of the doublets at δ 128.0 in the s.f.o.r.d. ^{13}C n.m.r. spectrum and at δ 6.9 in the ^{1}H n.m.r. spectrum.

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