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Circular Dichroism of Steroidal and Related Cisoid α,ß-Unsaturated Ketones. Part I.

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Dedicated to the memory of **Professor Günther Snatzke**,
our great teacher and dearest friend, who's inspiration contributed to our research and this paper.

Abstract - Some steroidal and related cisoid conjugated enones have been synthesized and their circular dichroism (CD) has been investigated. The relation between structure and observed Cotton effects (CE's) is discussed in terms of previously published rules. It is shown that CD spectra of these compounds are influenced by substituents located in the allylic axial or equatorial as well as α'-axial or equatorial position(s).

Studies of the relationship between the structure and chiroptical properties of cisoid conjugated enones have been a matter of many papers over the past 35 years. The empirical analysis of data for $n\pi^*$and $\pi\pi^*$ transitions based both on ORD [1-8] and CD [8-25] measurements. However, most studies of the optical activity properties of cisoid enones have been concerned with compounds unsubsituted in the vicinity of the chromophore and only a few examples of γ- or α'-substituted cisoid enones (the nomenclature of positions according to Gawronski [25]) are known in the literature (jervine [2,4,12], isonardosinon and nardofuran [7], 3ß-acetoxy-9α-hydroxy-5α-cholest-8(14)-en-15-one [25]). The available data of this class enones (thirteen compounds) were collected and discussed by Gawronski [25]. However, generalizations useful for structural investigations (such as for transoid conjugated enones [25,26]) could not be made.

Therefore we have paid particular attention to cisoid enones, mainly these with functional groups in the vicinity of the chromophore. The synthesized model compounds were:

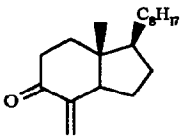
a.) unsubstituted enones (Fig.1: compounds **1, 9, 15-19** and **22**)

b.) enones substituted in γ-transoid allylic position (Fig.1: compounds **2-7** and **10-13**)

c.) enones substituted in γ-cisoid allylic position (Fig.1: compounds **21** and **23**)

d.) enones substituted in α'-axial or equatorial position, with or without allylic substituent (Fig.1: compounds **8, 14** and **20**).

Fig. 1



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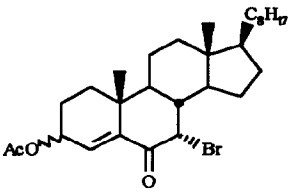
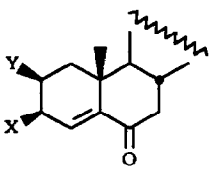
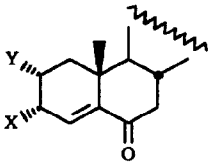


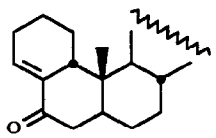
8 3β
14 3α



2 X=Y=OAc
3 X=Cl ; Y=H
4 X=OAc ; Y=H
5 X=OH ; Y=H
6 X,Y= -OCH_2O-
7 X,Y= -$OC(CH_3)_2O$-



9 X=Y=H
10 X=OH ; Y=H
11 X=Y=OH
12 X=Y=OAc
13 X=OAc ; Y=H



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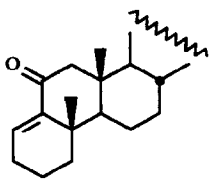

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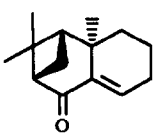
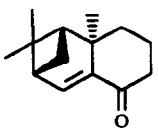


17



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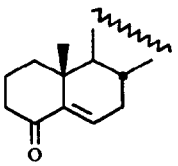

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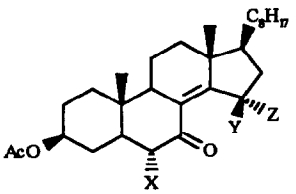


20 X=OAc ; Y=Z=H
21 X=Z=H ; Y=OAc
22 X=Y=Z=H
23 X=Y=H ; Z=OAc

Chiroptical Properties

The CD data of the cisoid enones **1-23** and their UV data for both nπ* and ππ* (band I) transitions are collected in Table 1. For CD spectra we have described the observed CE´s as follow:

a.) in the region from 296 to 385 nm as nπ* CE.

b.) CE between 222 and 272 nm corresponding to ππ* transition in the UV spectrum as band I.

c.) CE in the spectral range from 197 to 218 nm, which has no corresponding UV maximum, as band II.

d.) CE ca. 200 nm, which is assigned to nσ* transition [25] as band III.

According to the known postulate that the CE's for the nπ* and ππ* (band I) transitions should be of opposite signs [27] we apply in our considerations the helicity rule for cisoid α,β-unsaturated ketones or orbital helicity rule [28] . Thus the nπ* CE's should directly correlate with the sign of the enone skew angle.

The exomethylene enone **1** has a bisignate CD curve within the nπ* transition. The negative sign of the band at the long-wavelength side of the bisignate curve (λ_{max}=352 nm) agrees with that predicted by the rules for a negative C=C–C=O torsion angle, which is due to the chair conformation of the six-membered ring. The observed bisignate curve in this region may be caused by the participation of a boat conformer in which the torsional angle of the enone system is changed to a positive value. CD of different sign of various vibrational progressions [27] can also explain the shape of this band.

Compound **15** shows a CD spectrum similar to **1**. The CD curve is also bisignate in the nπ* region. Contrary to **1**, the ring A in **15** can exclusively adopt boat conformation and the inspection of Dreiding models shows only the negative helicity of the enone moiety. Thus the negative sign of the nπ* CE at the long-wavelength side (λ_{max}=332 nm) of the bisignate curve agrees with the predicted one. Moreover, the CD spectrum of **15** shows negative band I CE and positive band II CE. The abnormal behaviour of this compound concerning the negative sign of band I CE and bisignate type of nπ* CE resembles that of enone **1**. Therefore it is necessary to make further investigations on both compounds, e.g. low temperature CD and solvent dependence.

Componds **2-14** possess the same 4-en-6-oxo unit, however, differ in substitution at C-2, C-3 or C-7 position. The Dreiding models of these compounds show negative C=C-C=O torsional angle, thus the expected signs of the nπ* and band I CE's should be negative and positive, respectively. Unsubstituted enone **9** as well as 3α-substituted enones **10-13** obey this rule. In the case of enones **10-13** a strong increase of the magnitude of positive band I CE´s is observed. This can be explained by the influence of γ-allylic oxygen substituent, which has, according to Beecham´s rule [29], a positive contribution (3α-substituent causes positive helicity of the substituent-C3-C4=C5 system) to the band I CE. Two compounds from this series, namely enones **9** and **11**, show weak negative additional band near 260 nm at the long-wavelength side of the band I.

The 3ß-substituted 4-en-6-ones **2-7** demonstrate a diverse behaviour. The nπ* CE remains negative, whereas the band I CE is negative, regardless of the kind of substituent at C-3. According to Beecham's rule [29], the inversion of the sign of band I is caused by γ-transoid equatorial substituents (here: 3ß-OAc, 3ß-OH, 3ß-O-alkyl) because of their negative contributions (negative helicity of the substituent-C3-C4=C5 system). The 3β-Cl substituent (enone **3**) shows the same effect, which has not been reported by Beecham.

Both groups of 4-en-6-ones, compounds **2-7** and **9-13**, show also strong positive band II CE around 200 nm which, according to Gawronski [25] , reflects the absolute configuratuon of the Δ^8-octalin-1-one system. Fig. 2 shows the typical CD curves of the enones discussed above.

Table 1: UV and CD data of the conjugated enones in acetonitrile

Comp. No.	ε (λ_{max}/nm) nπ*	ε (λ_{max}/nm) Band I	Δε (λ_{max}/nm) nπ*			Δε (λ_{max}/nm) Band I		Δε (λ_{max}/nm) Band II	Δε (λ_{max}/nm) Band III
1		7,900 (231)	-0.10 (352)	+0.23 (301)		-3.25 (235)		+5.3 (204)	+5.5 (193)
2	43 (319)	4,500 (231)	-1.67 (320)			-6.19 (232)		+11.0 (198)	
3		9,300 (238)	-2.12 (328)			-6.02 (237)		+14.4 (200)	
4	86 (321)	7,100 (232)	-2.33 (326)			-4.80 (237)		+13.2 (197)	
5	94 (321)	6,700 (236)	-2.43 (326)			-2.16 (246)		+16.5 (197)	
6	65 (317)	6,800 (233)	-2.00 (327)			-1.49 (245)		+13.9 (199)	
7	120 (319)	6,700 (235)	-2.00 (326)			-1.00 (251)	-0.86[s] (242)	+15.2 (198)	
8	167 (339)	5,000 (249)	-0.04 (385)	+1.33 (327)		+4.42 (260)	-2.27 (233)	+2.8 (202)	
9	140 (308)	8,400 (240)	-2.37 (325)		-0.30 (261)	+2.23 (232)		+10.5 (198)	
10	76 (320)	8,100 (231)	-2.98 (327)			+7.98 (225)		+11.0 (200)	
11	58 (321)	6,900 (230)	-2.62 (326)		-0.31 (257)	+9.52 (225)		+11.3 (202)	
12	91 (318)	6,100 (227)	-2.07 (325)			+11.30 (225)		+11.1 (200)	
13	94 (321)	10,100 (229)	-3.17 (328)			+14.15 (226)		+14.8 (201)	
14	142 (339)	6,000 (246)	-0.17 (370)	+0.79 (322)		+10.30 (251)	+6.45[s] (229)	+8.7 (202)	+8.8 (192)
15	125 (313)	5,100 (243)	-0.15 (332)	+0.23 (296)		-1.33 (255)		+4.8 (208)	
16	74 (315)	6,800 (236)	+2.64 (325)		+0.15 (265)	-4.33 (234)		-8.0 (197)	
17	63 (313)	8,000 (235)	-0.55 (321)			-4.01 (234)		a)	
18	61 (312)	5,500 (249)	+0.73 (323)		+0.19 (272)	-2.23 (226)		- b)	
19	90 (320)	8,500 (240)	+1.54 (329)		+0.06 (269)	-8.51 (222)		- b)	
20		10,300 (264)	-0.94 (326)			-0.79 (278)		+0.4 (222)	-3.0 (207)
21			-1.05 (332)			-3.24 (248)		+1.5 (218)	+11.3 (193)
22			-1.26 (339)			-4.92 (259)		+5.0 (215)	
23		11,700 (257)	-1.32 (348)			-11.85 (253)		+6.0 (218)	-4.5 (198)

a) not observed b) obscured by broad band I s = shoulder

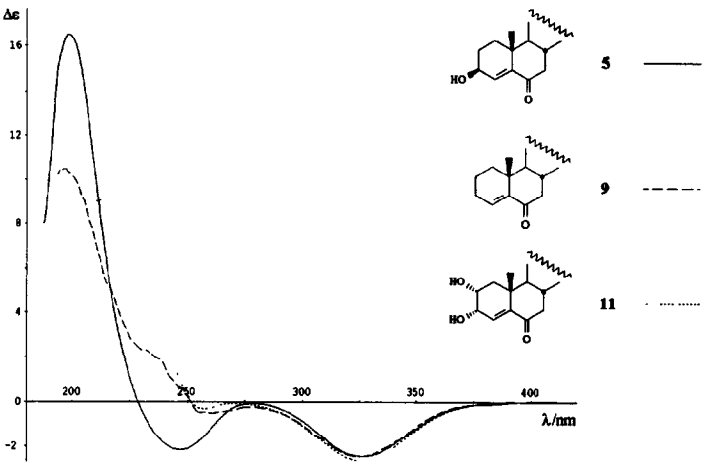


Fig.2: CD spectra of compounds **5**, **9** and **11** in acetonitrile.

Completely different behaviour show two last derivatives of cholest-4-en-6-one bearing 7α-bromo substituent, namely compounds **8** and **14**. The introduced α'-axial substituent strongly influences nπ* , band I and band II CE's. The CD curve in the nπ* transition region becomes bisignate with strongly decreased (compound **14**) or very weak (compound **8**) negative band at longer wavelengths (370 and 385 nm, respectively). Instead, the positive part of the bisignate curve can be seen at about 320-330 nm and shows moderate intensity. It is noteworthy that the sign of this band correlates with the positive helicity of the Br-C7-C6=O system. The band I CE corresponding to the absorption band I (UV) is positive, regardless of the orientation of the acetoxyl substituent at C-3. Only the lower intensity of band I CE for **8** compared to **14** seems to indicate the orientation of substituent at C-3 position. Unexpectedly, in both cases an additional band appears at the short-wavelength side of the band I near 230 nm. Since this bands show different signs, negative for **8** and positive for **14**, we can not assign them as the band II CE. The positive band II CE's of both enones appears at 202 nm and their magnitudes are strongly reduced in comparison with other 4-en-6-ones. Moreover, compound **14** shows positive CE at 192 nm. The CD curves of 7α-bromoenones **8** and **14** and their parent enones **4** and **13** are shown in Fig.3.

The chromophores of the enones **16**, **18** and **19** are quasi-enantiomeric, compared to that of enone **9**. Therefore, their CD curves are essentially of mirror-image type in showing positive nπ* CE and negative band I CE accompanied by a weak positive band around 270 nm. The signs of the nπ* and band I CE's agree with those predicted by the common rules.

The tricyclic enone **17** displays very simple CD curve with two negative CE's corresponding to nπ* and ππ* absorption bands, while the band II CE is not observed. In this case only the negative sign of the nπ* CE can be predicted by the rules (negative C=C-C=O torsional angle).

Cisoid enones **20-23** belong to the second series of compounds possessing the same enone unit but differing in substitution pattern. All of them show negative nπ* CE's because the enone chirality is the same as for cholest-4-en-6-ones **2-14**. Also the band II CE's have the same (positive) sign. However, the observed sign of the band I CE's is negative and can not be predicted by the applied rules. The magnitudes of these CE's (Fig.4)

strongly depend both on substitution at C-15 (γ-cisoid allylic position) and at C-6 (α'-position). At present it is not possible to discuss in more detail the CD curves of enones **20-23** because of the forward-projecting five-membered steroid ring D.

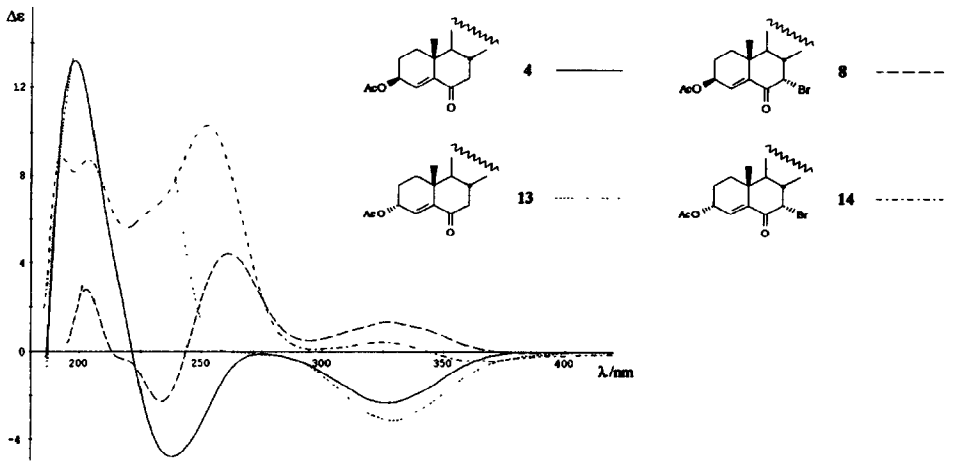


Fig.3: CD spectra of compounds **4**, **8**, **13** and **14** in acetonitrile.

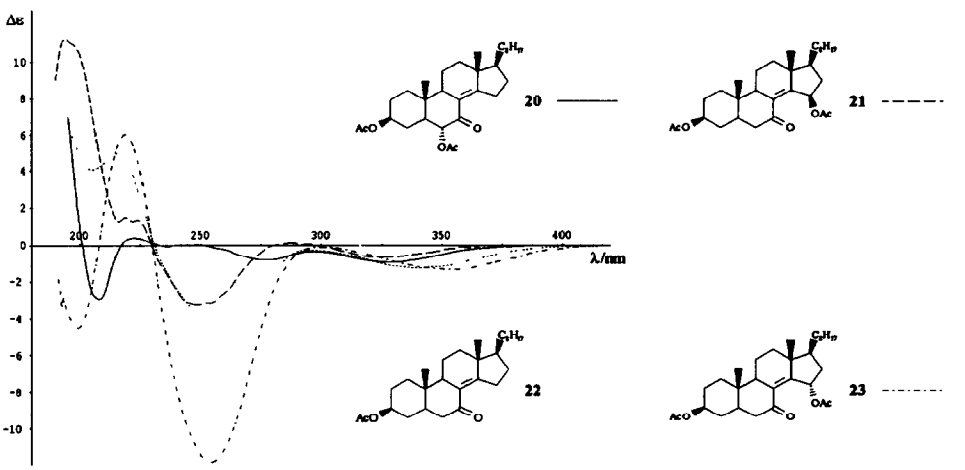


Fig.4: CD spectra of compounds **20**, **21**, **22** and **23** in acetonitrile.

Conclusions

(i) The nπ* CE's of cisoid enones correlate with the enone torsion angle and their sign can be predicted by cisoid enone helicity or orbital helicity rules [28] as well as by the rule proposed for R band of cisoid enones [11,12].

The appearance of the bisignate CD curve in the nπ* region may be explained as a result of overlapping of two vibrational progressions with CD's of different signs [27] or by participation of other conformers (enone **1**).

(ii) The sign of the band I CE's of cisoid enones is governed by earlier mentioned helicity rules [28] in the case of unsubstituted compounds or by the Beecham's rule [29] for γ–substituted ones. The data of 3ß-chloro-enone **3** unequivocally show that the Beecham's rule can be extended on other polar substituents. However, unsubstituted enones **1**, **15**, **17** and **22** have opposite signs to those predicted by the rules. The behaviour of enones **8**, **14**, **20**, **21** and **23** requires additional investigations on model compounds of very similar structure bearing other kind of substituents. Axial and equatorial substituents in the γ–transoid position strongly affect band I CE. Their contributions to this band shows Table 2. Unexpectedly large values, compared to those for 6α-substituted transoid cholest-4-en-3-ones [25], one can observe for equatorial substituents. Furthermore, remarkable influence show substituents in the γ–cisoid position (see Table.1, enones **21** and **23**).

(iii) The band II CE's always are of opposite signs to those of nπ* CE's.

(iv) More information dealing with bisignate curve in the nπ* region and appearance of additional bands could be find after the cisoid enones examination by ACD (CD of partially oriented molecules) method.

Table 2: Contributions of γ-transoid substituents to the band I CE of steroidal 4-en-6-ones

Substituent	δΔε	
	axial	equatorial
Cl	-	-8.2
OAc	+11.9	-7.0
OH	+5.8	-4.4
O-alkyl	-	ca. -3.5

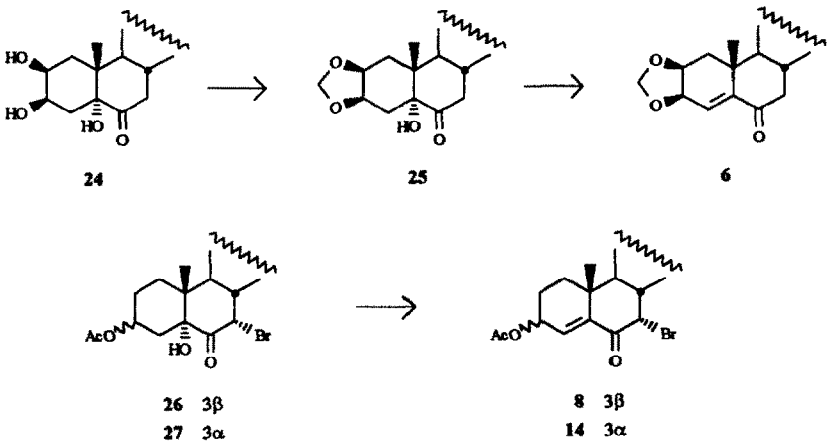
Synthesis

All investigated cisoid conjugated enones, except compounds **17** and **18**, were obtained by multi-step transformation of cholesterol. The enones **1**, **2**, **4**, **5**, 7, **9-13** and **19-23** were synthesized according to the well known procedures.

Functionalized cholest-4-en-6-ones **6**, **8** and **14** (Fig.5) were prepared by $SOCl_2$ dehydratation of the corresponding 5α-hydroxy-6-oxocholestanes **25**, **26** and **27**.

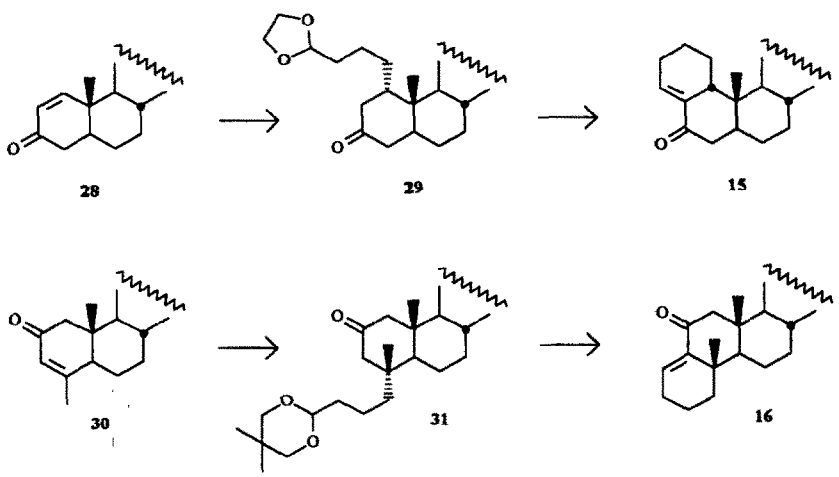
Analysis of the observed coupling constants of olefinic proton (4-H) for C-3 substituted cholest-4-en-6-ones and their comparison with those for 7-substituted cholest-5-enes [30] show that 3ß-substituents are oriented quasi-equatorially ($J_{4H,3\alpha H}$ = 1.9-2.8 Hz and exceptionally 3.2 Hz for acetals **6** and **7**) and 3α–substituents - quasi-axially ($J_{4H,3\beta H}$ = 4.3-5.4 Hz).

Fig.5



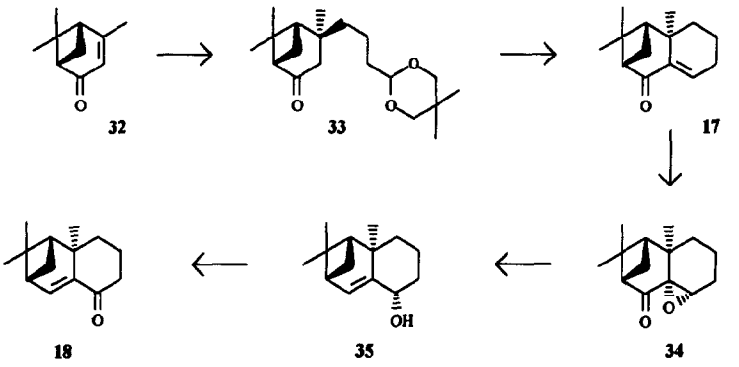
Pentacyclic enones **15** and **16** were obtained from transoid conjugated enones **28** and **30**, respectively (Fig.6). Stereospecific 1,4-addition of the suitable organocuprous reagent to the transoid enones **28** and **30** afforded ketones **29** and **31**.. Hydrolysis of the acetal groups and subsequent condensation of the corresponding keto-aldehydes gave the expected compounds **15** and **16** (Fig.6).

Fig.6



The same procedure was applied in synthesis of the cisoiod enone **17** from (-)-verbenone (**32**) (Fig.7). Epoxidation of **17** gave the epoxy-ketone **34** which was then transformed to the allylic alcohol **35**. Oxidation of this alcohol led to the cisoid enone **18** with inversed enone moiety in comparison to that of **17**.

Fig.7



Acknowledgements

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Experimental

Melting points were determined on a Boetius micro-melting point apparatus and are uncorrected. IR spectra were recorded on an UR-20 spectrometer in KBr or on a Perkin-Elmer PE 1310 spectrometer in CCl_4 solution. ^1H NMR spectra were taken on a Bruker AM-500, Bruker AM-400 or Bruker WP-80 spectrometer in $CDCl_3$. Mass spectra were measured on a Varian MAT CH-5 and a VG AutoSpec (high resolution) spectrometer. UV measurements were made on a Philips PU 8740 apparatus in acetonitrile. CD spectra were recorded in acetonitrile with a modified ISA-Jobin-Yvon Dichrograph Mark III or Mark VI. Solutions with concentrations in the range 0.2 - 0.5 mg/ml were examined in the cells with pathlength 0.05 to 2 cm. Column chromatography was performed on Kieselgel 60, (63-200 μm), Merck.

8-Methylene-des-A,B-cholestan-9-one (**1**) was prepared immediately before measurement according to the published procedure [31].

2β,3β-Diacetoxycholest-4-en-6-one (**2**), 2α,3α-dihydroxycholest-4-en-6-one (**11**) and 2α,3α-diacetoxycholest-4-en-6-one (**12**) were obtained according to Akhrem et al.[32].

***Enone* 2**, m.p. 125-127°C (MeOH); ^1H NMR (400 MHz): 0.67 (3H, s, 18-H), 1.12 (3H, s, 19-H), 2.03 and 2.04 (3H, s and 3H, s, 2xOAc), 5.32 (1H, m, 2α-H), 5.43 (1H, dd, J=4.1, 2.8 Hz, 3α-H), 5.86 (1H, dd, J=2.8, 1 Hz, 4-H); MS (m/z): 500 (M^+), 458, 440, 425, 398 (100%).

***Enone* 11**, m.p. 174-176°C (MeOH); ^1H NMR (400 MHz): 0.68 (3H, s, 18-H), 1.01 (3H, s, 19-H), 1.94 (1H, dd, J=15.8, 12.3 Hz, 7α-H), 2.55 (1H, dd, J=15.8, 4.1 Hz, 7β-H), 3.88 (1H, m, 2β-H), 4.20 (1H, dd, J=9.2, 4.3 Hz, 3β-H), 6.24 (1H, d, J=4.3 Hz, 4-H); MS (m/z): 416 (M^+), 401, 388, 387, 372, 357, 43 (100%).

***Enone* 12**, m.p. 121°C (MeOH); ^1H NMR (400 MHz): 0.68 (3H, s, 18-H), 1.06 (3H, s, 19-H), 2.00 and 2.07 (3H, s and 3H, s, 2xOAc), 2.56 (1H, dd, J=15.8, 4.2 Hz, 7β-H), 5.10 (1H, dd, J=12.2, 4.4 Hz, 2β-H), 5.52 (1H, dd, J=5.4, 4.4 Hz, 3β-H), 6.07 (1H, d, J=5.4 Hz, 4-H); MS (m/z): 500 (M^+), 482, 458, 440, 425, 398 (100%).

3ß-Chlorocholest-4-en-6-one **(3)**, m.p. 165°C (Hexane); ^{1}H NMR (80 MHz): 0.71 (3H, s, 18-H), 1.04 (3H, s, 19-H), 4.53 (1H, dt, J ca. 2.4, 6.6 Hz, 3α-H), 6.21 (1H, dd, J ca. 2.4, 1.4 Hz, 4-H) was synthesized according to Shoppee et al.[33].

3ß-Acetoxycholest-4-en-6-one **(4)**, cholest-4-en-6-one **(9)**, 3α-acetoxycholest-4-en-6-one **(13)** and cholest-5-en-4-one **(19)** were obtained by $SOCl_2$ dehydratation of the known corresponding 5α-hydroxyketones.

Enone **4**, m.p. 105-106°C (Me_2CO); ^{1}H NMR (400 MHz): 0.67 (3H, s, 18-H), 0.99 (3H, s, 19-H), 1.88 (1H, dd, J=15.5, 12.4 Hz, 7α-H), 2.04 (3H, s, OAc), 2.53 (1H, dd, J=15.5, 3.4 Hz, 7ß-H), 5.30 (1H, m, 3α-H), 6.03 (1H, J ca. 1.9 Hz, 4-H); MS (m/z): 442 (M^+), 400 (100%), 385. {lit.: m.p. 109-110°C [34]}.

Enone **9**, m.p. 108°C (MeOH); ^{1}H NMR (400 MHz): 0.66 (3H, s, 18-H), 0.92 (3H, s, 19-H), 2.49 (1H, dd, J=10.8, 3.3 Hz, 7ß-H), 6.34 (1H, dd, J=5.0, 2.7 Hz, 4-H); MS (m/z): 384 (M^+), 369, 366, 356, 271, 243, 229, 43 (100%). {lit.: m.p. 106-107°C [36]}.

Enone **13**, m.p. 86-88°C (MeOH); ^{1}H NMR (400 MHz): 0.68 (3H, s, 18-H), 0.93 (3H, s, 19-H), 1.93 (1H, dd, J=15.8, 12.3 Hz, 7α-H), 2.03 (3H, s, OAc), 2.56 (1H, dd, J=15.8, 4.3 Hz, 7ß-H), 5.26 (1H, m, 3ß-H), 6.19 (1H, d, J=4.8 Hz, 4-H); MS (m/z): 442 (M^+), 400 (100%), 385. {lit.: m.p. 86-88°C [35]}.

Enone **19**, m.p. 108°C (MeOH); ^{1}H NMR (400 MHz): 0.67 (3H, s, 18-H), 0.94 (3H, s, 19-H), 2.24 (1H, m, 3ß-H), 2.51 (1H, m, 3α-H), 6.40 (1H, dd, J=5.1, 2.7 Hz, 6-H); MS (m/z): 382 (M^+), 369, 279, 271, 247,229,167, 149 (100%). {lit.: m.p. 111°C [37]}.

3ß-Hydroxycholest-4-en-6-one **(5)** and 3α-hydroxycholest-4-en-6-one **(10)** were obtained by mild hydrolysis of the parent acetoxyenones **4** and **13**, respectively.

Enone **5**, m.p. 150-151°C (MeOH); ^{1}H NMR (400 MHz): 0.67 (3H, s, 18-H), 0.94 (3H, s, 19-H), 1.98 (1H, dd, J=15.8, 12.5 Hz, 7α-H), 2.62 (1H, dd, J= 15.8, 3.9 Hz, 7ß-H), 4.20 (1H, br m, 3α-H), 6.11 (1H, dd, J=2.1, 0.8 Hz, 4-H); MS (m/z): 400 (100%, M^+), 385, 247. {lit.: m.p. 150-152°C [35]}.

Enone ***10***, m.p. 128°C (MeOH); ^{1}H NMR (400 MHz): 0.68 (3H, s, 18-H), 0.93 (3H, s, 19-H), 1.92 (1H, dd, J=15.8, 12.3 Hz, 7α-H), 2.54 (1H, dd, J=15.8, 4.1 Hz, 7ß-H), 4.22 (1H, n m, 3ß-H), 6.28 (1H, d, J=4.7 Hz, 4-H); MS (m/z): 400 (100%, M^+), 385, 247. {lit.: m.p. 124-125°C [34]}.

2ß,3ß-Isopropylidenedioxycholest-4-en-6-one **(7)**, m.p. 161°C (MeOH); ^{1}H NMR (400 MHz): 0.67 (3H, s, 18-H), 1.16 (3H, s, 19-H), 1.32 and 1.38 (3H, s and 3H, s, isopropylidene methyls), 4.42 (1H, m, 2α-H), 4.52 (1H, dd, J=5.7, 3.2 Hz, 3α-H), 6.07 (1H, dd, J=3.2, 1.2 Hz, 4-H); MS (m/z): 456 (M^+), 441, 381, 363, 43 (100%) was synthesized according to Hora et al. [38].

3ß,6α-Diacetoxy-5α-cholest-8(14)-en-7-one **(20)**, 3ß,15ß-diacetoxy-5α-cholest-8(14)-en-7-one **(21)**, 3ß-acetoxy-5α-cholest-8(14)-en-7-one **(22)** and 3ß,15α-diacetoxy-5α-cholest-8(14)-en-7-one **(23)** were synthesized according to Anastasia et al. [39].

Enone **20**, m.p. 99-101°C (MeOH); ^{1}H NMR (500 MHz): 0.87 (3H, s, 18-H), 0.98 (3H, s, 19-H), 2.01 (3H, s, 3ß-OAc), 2.14 (3H, s, 6α-OAc), 4.68 (1H, br m, 3α-H), 4.89 (1H, d, J=12.4 Hz, 6ß-H). {lit.: m.p. 132-133°C, ^{1}H NMR: 0.91 (18-H), 1.01 (19-H), 2.02 (3ß-OAc), 2.15 (6α-OAc), 4.92 (6ß-H) [39]}.

Enone **21**, glassy oil; ^{1}H NMR (500 MHz): 0.88 (3H, s, 19-H), 1.01 (3H, s, 18-H), 1.92 (3H, s, 15ß-OAc), 2.00 (3H, s, 3ß-OAc), 4.67 (1H, br m, 3α-H), 6.06 (1H, m, 15α-H). {lit.: m.p. 112-114°C; ^{1}H NMR: 0.91 (19-H), 1.03 (18-H), 1.91 (15ß-OAc), 2.00 (3ß-OAc), 6.06 (15α-H) [39]}.

Enone **22**, m.p. 140-141°C (MeOH); ^{1}H NMR (500 MHz): 0.84 (3H, s, 18-H), 0.91 (3H, s, 19-H), 2.03 (3H, s, OAc), 2.29 (1H, dd, J=17.9, 5.3 Hz, 6α-H), 2.53 (1H, m, 15ξ-H), 3.10 (1H, m, 15ξ-H), 4.72 (1H, br m, 3α-H). {lit.: m.p. 141-142°C [39]}.

Enone **23**, m.p. 170-173°C (MeOH); ^{1}H NMR (500 MHz): 0.82 (3H, s, 18-H), 0.88 (3H, s, 19-H), 1.95 (3H, s, 15α-OAc), 2.00 (3H, s, 3ß-OAc), 4.68 (1H, br m, 3α-H), 5.80 (1H, n m, 15ß-H). {lit.: m.p. 170-171°C [39]}.

2ß,3ß-Methanediyldioxy-5-hydroxy-5α-cholestan-6-one **(25)**. To a solution of 2ß,3ß,5-trihydroxy-5α-cholestan-6-one [40] (**24**, 20 mg) in 5 ml of toluene 0.1 ml of chlorodimethylether and 10 mg of p-TsOH were added. After stirring at 50°C for 2 h the

solvent was removed and the product **25** was separated by column chromatography. Yield 11 mg (54%), m.p. 143-144°C (MeOH); IR (CCl_4): 3520, 1715 cm^{-1} ; ^1H NMR (400 MHz): 0.63 (3H, s, 18-H), 0.92 (3H, s, 19-H), 1.78 (1H, dd, J=14.9, 10.2 Hz, 4ß-H), 1.89 (1H, dd, J=14.9, 7.1 Hz, 4α-H), 1.94 (1H, dd, J=15.3, 4.8 Hz, 1α-H), 2.12 (1H, dd, J=13.1, 4.5 Hz, 7ß-H), 2.14 (1H, dd, J=15.3, 1.3 Hz, 1ß-H), 2.64 (1H, dd, J=13.1, 12.6 Hz, 7α-H), 4.01 (1H, m, 2α-H), 4.32 (1H, m, 3α-H), 4.83 (1H, s, 28 exo-H), 5.09 (1H, s, 28 endo-H); MS (m/z): 446 (M^+), 428, 413, 400, 383, 43 (100%); HRMS for $C_{28}H_{46}O_4$ (M^+) found 446.3391, calcd. 446.3396.

2ß,3ß-Methanediyldioxycholest-4-en-6-one **(6).** The hydroxyketone **25** (11 mg) was dissolved in 2 ml of pyridine and then 2 drops of thionyl chloride were added at 0°C. After stirring for 30 min. the mixture was diluted with saturated sodium bicarbonate solution and the precipitate was filtered, washed with water and crystallized. Yield 10 mg (90%), m.p. 104°C (EtOH); IR (CCl_4): 2960, 2870, 1700, 1640 cm^{-1} ; ^1H NMR (400 MHz): 0.68 (3H, s, 18-H), 1.14 (3H, s, 19-H), 2.36 (1H, dd, J=15.1, 3.0 Hz, 1ß-H), 4.24 (1H, m, 2α-H), 4.59 (1H, dd, J=6.0, 3.2 Hz, 3α-H), 4.89 (1H, s, 28 exo-H), 5.01 (1H, s, 28 endo-H), 6.06 (1H, dd, J=3.2, 1.0 Hz, 4-H); MS (m/z): 428 (M^+), 413, 398, 383, 370, 43 (100%); HRMS for $C_{28}H_{44}O_3$ (M^+) found 428.3279, calcd. 428.3290.

3ß-Acetoxy-7α-bromocholest-4-en-6-one **(8).** To a solution of hydroxybromoketone **26** [41] (4.52 g) in pyridine (30 ml) a mixture of thionyl chloride (6.4 ml) and pyridine (9 ml) was added at r.t. After 1 h the resulting mixture was poured onto ice and then extracted with ether. Chromatography of the crude product afforded enone **8**. Yield 3.62 g (80%), m.p. 111-113°C (MeOH); IR (KBr): 1745, 1700, 1650, 1240, 1050 cm^{-1}; ^1H NMR (400 MHz): 0.69 (3H, s, 18-H), 1.00 (3H, s, 19-H), 2.04 (3H, s, OAc), 4.30 (1H, d, J=2.9 Hz, 7ß-H), 5.40 (1H, ddd, J=9.7, 6.3, 2.2 Hz, 3α-H), 6.12 (1H, t, J ca. 1.9 Hz, 4-H); Anal. found C 66.8; H 8.8: $C_{29}H_{45}O_3Br$ requires C 66.8; H 8.7.

3α-Acetoxy-7α-bromo-5-hydroxy-5α-cholestan-6-one **(27).** 3α-Acetoxy-5-hydroxy-5α-cholestan-6-one [42] (3.75 g) was dissolved in chloroform (60 ml) and a solution of bromine (0.5 ml) and hydrobromic acid (40%, 4 drops) in chloroform-acetic acid (4:1, 25 ml) was added. The resulting mixture was occasionally heated to 40°C and the reaction was monitored by TLC. After 4 h the reaction mixture was diluted with water and extracted with chloroform. The organic layer was washed successively with aqueous sodium bisulphite, water and aqueous sodium bicarbonate. After evaporation to dryness the crude product was purified by column chromatography. Yield 3.68 g (84%), m.p. 100-101°C (MeOH); IR (KBr): 3560, 1725, 1245, 1040 cm^{-1} ; ^1H NMR (80 MHz): 0.69 (3H, s, 18-H), 0.78 (3H, s, 19-H), 2.05 (3H, s, OAc), 3.53 (1H, s, OH), 4.21 (1H, d, J ca. 4.5 Hz, 7ß-H), 5.29 (1H, m, 3ß-H); Anal. found C 64.6; H 8.9: $C_{29}H_{47}O_4Br$ requires C 64.6; H 8.8.

3α-Acetoxy-7α-bromocholest-4-en-6-one **(14).** Hydroxybromoketone **27** (2.93 g) was dehydrated according to the published procedure [35]. The crude product was chromatographed to give enone **14**. Yield 2.68 g (92%), m.p. 172-174°C (Et_2O); IR (KBr): 1745, 1700, 1645, 1230, 1020 cm^{-1}; ^1H NMR (500 MHz): 0.73 (3H, s, 18-H), 0.96 (3H, s, 19-H), 2.06 (3H, s, OAc), 4.35 (1H, d, J=2.6 Hz, 7ß-H), 5.27 (1H, dt, J=4.8, 3.3 Hz, 3ß-H), 6.30 (1H, d, J=4.8 Hz, 4-H); Anal. found C 66.9; H 8.7: $C_{29}H_{45}O_3Br$ requires C 66.8; H 8.7.

1α-[3-(1,3-Dioxolane-2-yl)-propyl]-5α-cholestan-3-one **(29).** In a flask, filled with argon, 0.2 g of magnesium turnings were placed. Then a solution of 2-(3-chloropropyl)-1,3-dioxolane [43] (0.7 g) and 1,2-dibromoethane (0.02 g) in 4 ml of abs. THF was added slowly at r.t. After heating on a steam bath (70°C) for 30 min the solution was cooled to -78°C and 0.17 g of CuBr-Me_2S [44] dissolved in 1.8 ml of dimethylsulfide was added. Then a solution of 5α-cholest-1-en-3-one [45] (1.0 g) in 8 ml of dry diethyl ether was added dropwise. After stirring for 3h at -78°C the reaction mixture was allowed to warm to r.t. Then 5 ml of saturated ammonium chloride solution, adjusted with ammonia to pH 8, were added, and the mixture was stirred for 4 h. The organic layer was separated and washed twice with water and finally with brine. After removal of solvent the residue was purified by column chromatography to give ketone **29**. Yield 0.63 g (62%), m.p. 139-140°C (MeOH); IR (CCl_4): 1715 cm^{-1}; ^1H NMR (400 MHz): 0.64 (3H, s, 18-H), 1.08 (3H, s, 19-H), 2.03 (1H, m, 4α-H), 2.17 (1H, dd, J=14.7, 13.2 Hz, 4ß-H), 2.29 (1H, dt, J=14.9, 2 Hz, 2α-

H), 2.51 (1H, dd, J=14.9, 5.8 Hz, 2ß-H), 3.81 and 3.92 (4H, m and m, 4- and 5-H, dioxolane), 4.80 (1H, t, J=4.6 Hz, 2-H, dioxolane); MS (m/z): 500 (M^+), 482, 457, 385, 73 (100%); HRMS for $C_{33}H_{56}O_3$ (M^+) found 500.4224, calcd. 500.4229.

1ß,4',5',6'-Tetrahydrobenzo[1,2]-5α-cholest-1-en-3-one **(15)**. Acetal **29** (110 mg) and 0.1 g of p-TsOH were dissolved in 20 ml THF and 15 ml of water. The solution was stirred at r.t. for 48 h. After evaporation of the solvent the residue was stirred with 20 ml of toluene at 30°C for 6 h and then it was heated at 55°C for 0.5 h. The organic layer was then washed with saturated sodium bicarbonate solution, water, dried over magnesium sulfate and evaporated. The crude product was chromatographed giving enone **15** as colourless oil. Yield 25 mg (23%); IR (CCl_4): 1685, 1615 cm^{-1}; ^1H NMR (400 MHz): 0.66 (3H, s, 18-H), 0.82 (3H, s, 19-H), 2.06 (1H, dd, J=19.5, 12 Hz, 4ß-H), 2.07 (1H, m, 1ß-H), 2.23 (2H, m, 4'-H), 2.24 (1H, dd, J=19.5, 6.6 Hz, 4α-H), 6.40 (1H, m, 3'-H); MS (m/z): 438 (M^+), 420, 315, 314, 108 (100%); HRMS for $C_{31}H_{50}O$ (M^+) found 438.3853, calcd. 438.3862.

4-Methyl-5α-cholest-3-en-2-one **(30)**. 5α-Cholest-2-en-4-one [46] (1 g) was dissolved in 15 ml of abs. THF and 2 ml of methyllithium (1.6 M solution in ether) were added dropwise at r.t. After stirring for 10 min the reaction mixture was treated with 10 ml of saturated ammonium chloride solution and diluted with 20 ml of ether. The organic layer was separated and washed twice with water. After drying and evaporation of solvent the crude product (4-hydroxy-4-methyl-5α-cholest-2-ene) was dissolved in 25 ml of abs. dichloromethane and treated with 3 g of pyridinium dichromate. The mixture was stirred for 24 h and then diluted with 50 ml of abs. ether. It was passed through a short silica gel column, evaporated and the residue was purified by column chromatography to give enone **30**. Yield 510 mg (51%), m.p. 135-137°C (MeOH); IR (CCl_4): 1670, 1630 cm^{-1}; ^1H NMR (400 MHz): 0.63 (3H, s, 18-H), 0.84 (3H, s, 19-H), 1.87 (3H, t, J=1.4 Hz, 4-Me), 2.02 (1H, d, J=16.2 Hz, 1ß-H), 2.51 (1H, d, J=16.2 Hz, 1α-H), 5.86 (1H, br s, 3-H); MS (m/z): 398 (M^+), 383, 356, 314, 243 (100%); HRMS for $C_{28}H_{46}O$ (M^+) found 398.3546, calcd. 398.3549.

4α-[3-(5,5-Dimethyl-1,3-dioxane-2-yl)-propyl]-4ß-methyl-5α-cholestan-2-one **(31)**. Magnesium turnings (0.10 g) were placed into a nitrogen filled flask and covered with 2 ml of dry THF. 2-(3-Bromopropyl)-5,5-dimethyl-1,3-dioxane (0.71 g, Riedel-de Haën) was added slowly whilst the mixture was smoothly warmed until the Grignard reaction started. After cooling to -78°C a solution of CuBr-Me_2S [44] (62 mg) in dimethyl sulfide (0.5 ml) was added and then keton **30** (0.4 g) dissolved in THF (4 ml) was added dropwise. The resulting mixture was stirred for 3 h at -78°C and worked up as in the case of **29**. Yield 210 mg (52%), oil; IR (CCl_4): 1715 cm^{-1}; ^1H NMR (400 MHz): 0.61 (3H, s, 18-H), 0.70 (3H, s, 5-Me, dioxane), 0.83 (3H, s, 4ß-Me), 0.86 (3H, s, 19-H), 1.16 (3H, s, 5-Me, dioxane), 3.41 and 3.69 (4H, d and d, J=6.9 Hz, 4– and 6–H, dioxane), 4.40 (1H, t, J=3.1 Hz, 2-H, dioxane); MS: 556 (M^+), 452, 399, 115 (100%); HRMS for $C_{37}H_{64}O_3$ (M^+) found 556.4852, calcd. 556.4855.

4ß-Methyl-3',4',5'-trihydrobenzo[3,4]-5α-cholest-3-en-2-one **(16)**. The acetal **31** (260 mg) was dissolved in THF (35 ml) and concd. HCl (5 ml) and water (14 ml) were added. The solution was refluxed for 2 h. Then it was extracted with ether and the organic layer was washed with water, sodium bicarbonate solution and brine. Chromatography of the crude isolated product gave enone **16**. Yield 170 mg (66%), m.p. 115-116°C (MeOH); IR (CCl_4): 1690, 1625 cm^{-1}; ^1H NMR (400 MHz): 0.62 (3H, s, 18-H), 0.97 (6H, s,19-H and 4ß-Me), 2.00 (1H, d, J=14.5 Hz, 1ß-H), 2.53 (1H, d, J=14.5 Hz, 1α-H), 6.20 (t, J=3.8 Hz, 6'-H); MS: 452 (M^+), 314, 122 (100%); HRMS for $C_{32}H_{52}O$ (M^+) found 452.4036, calcd. 452.4018.

2-(3-{(1S,2S,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-4-on-2-yl}-propyl)-5,5-dimethyl-1,3-dioxane **(33)**. The synthesis was done in the same way as for **31** using 1.5 of (-) verbenone (**32**, Janssen), 0.61 g of magnesium turnings, 4 g of 2-(3-bromopropyl)-5,5-dimethyl-1,3-dioxane and 0.65 g CuBr-Me_2S [44]. After chromatographic separation **33** was obtained as a colourless oil. Yield 1.9 g (62%); IR (CCl_4): 2960, 2880, 1710, 1470, 1130 cm^{-1}; ^1H NMR (400 MHz): 0.66 (3H, s, 5-Me, dioxane), 0.96 (3H, s ,6 endo-Me), 1.09 (3H, s, 2-Me), 1.13 (3H, s, 5-Me, dioxane), 1.30 (1H, s, 6 exo-Me), 1.31 (4H, m, 2-and 3-H, propyl), 1.53 (2H, m, 1-H, propyl), 1.57 (1H, d, J=10.8 Hz, 7 endo-H), 1.94 (1H, dd, J=6.1 and 5.1 Hz, 1-H), 2.22 and 2.32 (2H, ABq, J=19.8 Hz, 3-H), 2.41 (1H, m, 7 exo-H), 2.47 (1H, t, J=5.2 Hz, 5-H), 3.37 and 3.55 (4H, d and d, J=11.0 Hz, 4-and 6-H, dioxane), 4.37 (1H, t, J=7.6 Hz, 2-H, dioxane); MS: 308 (M^+), 293, 266, 115, 69 (100%); HRMS for $C_{19}H_{32}O_3$ (M^+) found 308.2344, calcd. 308.2351.

(1S,8R,9R)-8,10,10-Trimethyltricyclo[7.1.1.0^{3,8}]undec-3-en-2-one (17). A solution of 33 (1.9 g) in THF (50 ml) and 10% HCl (25 ml) was refluxed for 5 days. The reaction mixture was extracted with ether and the organic layer was washed with water, sodium bicarbonate and brine. After drying and evaporation of the solvent the crude product was purified by column chromatography to give enone 17. Yield 0.84 g (67%), m.p. 47-49°C (MeOH); IR (CCl_4): 2960, 2930, 1705, 1630 cm^{-1}; ^{1}H NMR (400 MHz): 1.07 (3H, s, 10 endo-Me), 1.20 (3H, s, 8-Me), 1.25 (1H, m, 7ξ-H), 1.36 (3H, s, 10 exo-Me), 1.39 (1H, m, 7ξ-H), 1.45 (1H, d, J=10.0 Hz, 11 endo-H), 1.69 (1H, m, 6ξ-H), 1.92 (1H, t, J=5.6 Hz, 9-H), 1.96 (1H, m, 6ξ-H), 2.28 (2H, m, 5-H), 2.42 (1H, m, 11 exo-H), 2.46 (1H, t, J=5.5 Hz, 1-H), 6.68 (1H, t, J=4.2 Hz, 4-H); MS (m/z): 204 (M^+), 189 (100%), 161, 147; HRMS for $C_{14}H_{20}O$ (M^+) found 204.1523, calcd. 204.1514.

(1S,3R,4S,8R,9R)-3,4-Epoxy-8,10,10-trimethyltricyclo[7.1.1.0^{3,8}]undecan-2-one (34). To a solution of 17 (0.52 g) in methanol (30 ml) 2.4 ml of 30% H_2O_2 and 1 ml of 10% aqueous sodium hydroxide were added. The mixture was stirred for 2 h at r.t., then diluted with 5% sodium bisulphite solution (10 ml) and extracted with ether. The organic layer was washed with water, brine and then dried and evaporated. Purification by column chromatography gave epoxide 34. Yield 0.47 g (84%), m.p. 42-43°C (MeOH); IR (CCl_4): 2950, 1725, 900 cm^{-1}; ^{1}H NMR (400 MHz): 1.05 (1H, m), 1.06 (3H, s, 10 endo-Me), 1.14 (3H, s, 8-Me), 1.21 (1H, m), 1.36 (3H, s, 10 exo-Me), 1.37 (1H, m), 1.48 (1H, m), 1.69 (1H, m), 1.74 (1H, d, J=11.0 Hz, 11 endo-H), 2.01 (1H, t, J=6.1 Hz, 9-H), 2.12 (1H, m), 2.51 (1H, m, 11 exo-H), 2.61 (1H, m, 1-H), 3.09 (1H, br s, 4-H); MS: 220 (M^+), 205, 177, 149, 137, 84 (100%); HRMS for $C_{14}H_{20}O_2$ found 220.1462, calcd. 220.1463.

(1R,4S,8R,9R)-8,10,10-Trimethyltricyclo[7.1.1.0^{3,8}]undec-2-en-4-ol (35). The epoxide 34 (0.3 g) was refluxed with hydrazine hydrate (10 ml, 80%) for 20 min. The resulting mixture was diluted with water (10 ml) and extracted with ether. The organic layer was washed with water, dried and evaporated. The crude product purified by column chromatography afforded alcohol 35. Yield 0.16 g (57%), m.p. 54-55°C (MeOH); IR (CCl_4): 3620, 3480, 3000, 2940, 1640 cm^{-1}; ^{1}H NMR (400 MHz)· 1.05 (3H, s, 10 endo-Me), 1.22 (1H, m, 7ξ-H), 1.28 (3H, s, 8-Me), 1,32 (1H, d, J=9.0 Hz, 11 endo-H), 1.36 (3H, s, 10 exo-Me), 1.4-1.6 (4H, m), 1.67 (1H, t, J=6.0 Hz, 9-H), 1.93 (1H, m), 2.0-2.1 (2H, m), 2.24 (1H, dt, J=9.0 and 5.6 Hz, 11 exo-H), 4.30 (1H, t, J=2.8 Hz, 4-H), 6.03 (1H, d, J=6.4 Hz, 2-H); MS: 206 (M^+), 191, 188, 173, 163, 145 (100%); HRMS for $C_{14}H_{22}O$ found 206.1659, calcd. 206.1671.

(1R,8R,9R)-8,10,10-Trimethyltricyclo[7.1.1.0^{3,8}]undec-2-en-4-one (18). A solution of alcohol 35 (0.12 g) in dry methylene chloride (20 ml) was stirred with pyridinium dichromate (1 g) for 12 h. The resulting mixture was diluted with ether (30 ml) and passed through a small column. After evaporation the crude product was purified by column chromatography to give enone 18. Yield 91 mg (77%), m.p. 45-46°C (MeOH); IR (CCl_4): 2960, 1680, 1630 cm^{-1}; ^{1}H NMR (400 MHz): 0.99 (3H, s, 10 endo-Me), 1.18 (3H, s, 8-Me), 1.30 (3H, s, 10 exo-Me) 1.36 (1H, m, 7ξ-H), 1.40 (1H, d, J=9.3 Hz, 11 endo-H), 1.81 (2H, br m, 6ξ-and 7ξ-H), 1.92 (1H, t, J=5.7 Hz, 9-H), 2.04 (1H, br m, 6ξ-H), 2.27 (2H, br m, 1-H and 5ξ-H), 2.37 (1H, dt, J=9.4, 5.6 Hz, 11 exo-H), 2.48 (1H, m, 5ξ-H), 6,72 (1H, d, J=6.4 Hz, 2-H); MS (m/z): 204 (M^+), 189, 161, 135 (100%); HRMS for $C_{14}H_{20}O$ found 204.1529, calcd 204.1514.

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