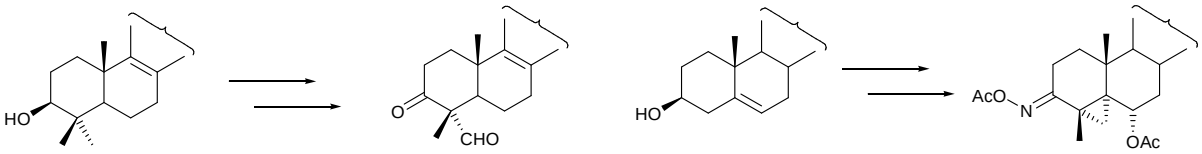
The final published version of this article can be found at
http://dx.doi.org/10.1016/j.tet.2007.10.016.

Graphical Abstract



Functionalization of Terpenoids at C-4 via Organopalladium Dimers: Cyclopropane Formation During Oxidation of Homoallylic σ-Organopalladium Intermediates with Lead Tetraacetate

Susana S. Ramos,[a] Paulo Almeida,[b] Lina Santos,[a] William B. Motherwell,[c] Tom D. Sheppard,[c*] and Maria do Céu Costa,[a]

[a] *INETI – Instituto Nacional de Engenharia, Tecnologia e Inovação, I.P., Estrada Paço do Lumiar, 1649-038 Lisboa, Portugal*

[b] *UBI – Universidade da Beira Interior, Departamento de Química and Unidade de Materiais Têxteis e Papeleiros, Rua Marquês d' Ávila e Bolama, 6200-001, Covilhã, Portugal*

[c] UCL – University College London, Department of Chemistry, 20 Gordon Street, London, WC1H OJA, UK

Abstract— The synthesis of new potential adjuvant saponin aglycons was investigated by selective palladium mediated C-H functionalisation of appropriately functionalized derivatives of lanosterol, cholesterol, and friedelin. The desired equatorial aldehyde functionality was successfully introduced into the lanosterol skeleton as expected. Cyclopalladation of a cholesterol derivative proceeded as expected, but during oxidation of the organopalladium intermediate, participation of the adjacent alkene functionality led to stereoselective formation of a cyclopropane and introduction of an acetate group into the steroid backbone at C-6. Further investigation of this unusual cyclopropane formation on a model decalin system confirmed the result, but C-H activation on a related open chain system was prevented by complexation of the alkene functionality to the palladium.

1. Introduction

The presence of an equatorial aldehyde substituent at the C-4 position of the triterpene unit seems essential to the adjuvant activity shown by saponins[1] such as QS21 which contain quillaic acid as the aglycon portion.[2-5]

We envisaged that the cyclopalladation reaction first reported by Shaw[6] and subsequently studied by Baldwin[7] and others[8-10] would enable us to introduce the aldehyde functionality selectively into a range of rigid steroidal and tritepenoid backbones, as it allows the activation of a C-H bond on an equatorial methyl group adjacent to an oxime, via σ-organopalladium intermediates.

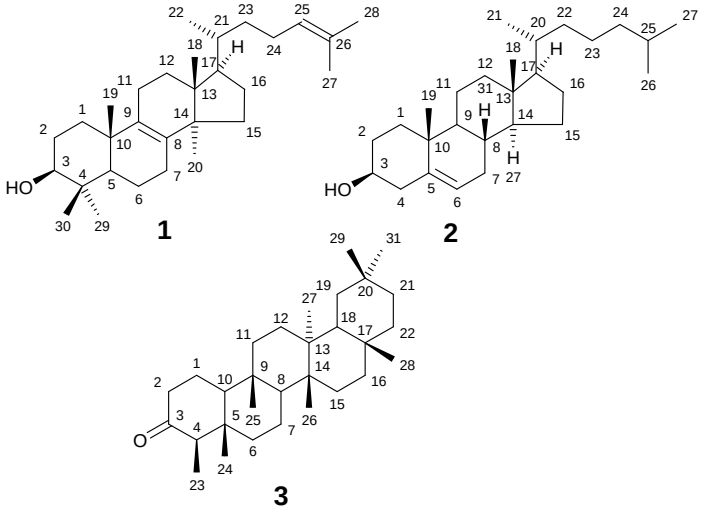


Figure 1

The cyclopalladation reaction takes place regioselectively and the stereochemistry of the complex formed between the oxime function and the palladium was deduced by nOe studies by Baldwin *et al.*[7] The exclusive functionalization of the equatorial methyl group linked to the C-4 carbon is explained by the fact that the cyclopalladation is facilitated by a coplanar arrangement of the oxime and the "target" methyl group.

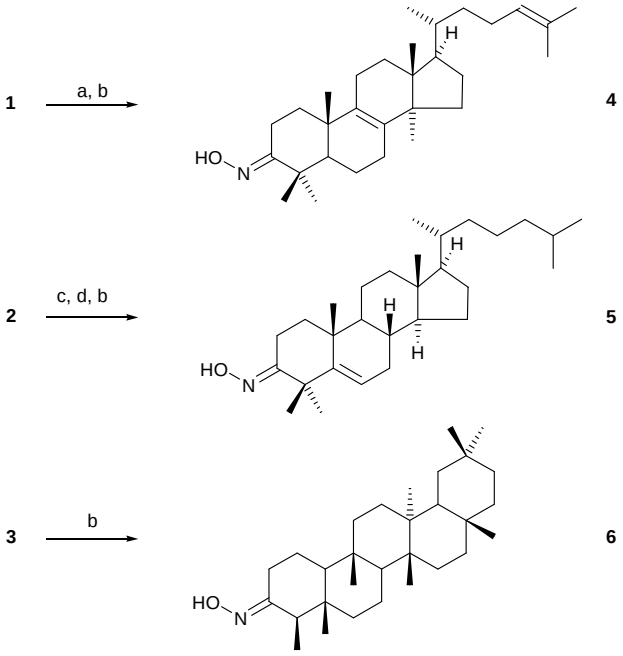
* Corresponding author. Tel.: +44 20 7679 1503; fax: +44 20 7679 7524; e-mail: tom.sheppard@ucl.ac.uk.

The cyclopalladation of appropriately functionalized derivatives of lanosterol (**1**), cholesterol (**2**), and friedelin (**3**) (Figure 1) was therefore investigated with a view to exploring the potential of the Shaw reaction for selectively introducing an equatorial aldehyde group and hence synthesising potential aglycons for new adjuvant saponins.

2. Results and discussion

2.1. Preparation of Oximes

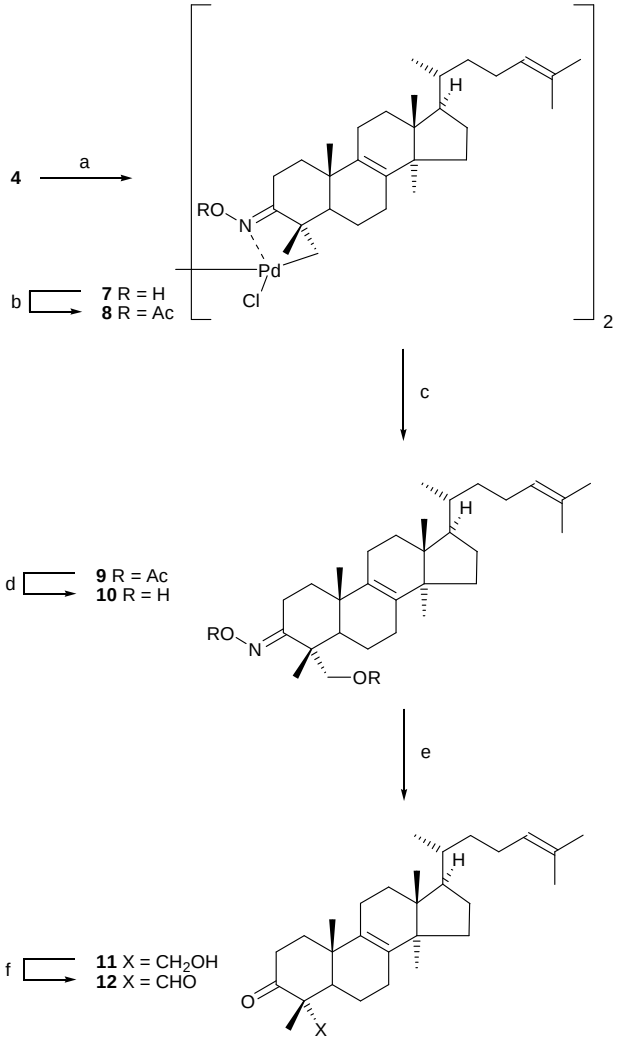
Lanosta-8,24-dien-3-one oxime (**4**),[11] 4,4-Dimethylcholest-5-en-3-one oxime (**5**)[12-13] and friedelan-3-one oxime (**6**) were prepared according to literature methods (Scheme 1).



Scheme 1 a. Jones' reagent, acetone, 0 °C to rt. b. $NH_2OH.HCl$, $NaHCO_3$, EtOH, reflux. c. Br_2, AcOH, NaOAc, Et_2O, rt; $Na_2Cr_2O_7.2H_2O$, AcOH, 90 °C then Zn, AcOH, pyridine, rt. d. K, ^{t}BuOH, MeI.

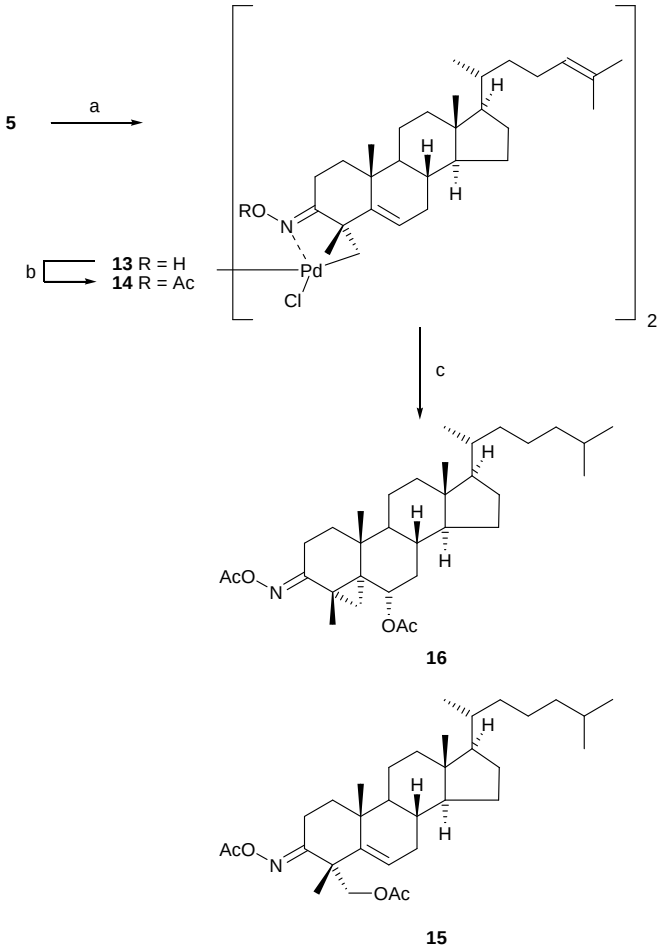
2.2. Cyclopalladation reactions

Dimeric organopalladium complex **7** was obtained as expected from the lanosterol derived oxime **4** by treatment with Na_2PdCl_4 and NaOAc in AcOH (Scheme 2). The formation of the palladium dimer was evidenced by disappearance of the NMR signal corresponding to the equatorial methyl group C-30, and the appearance of a downfield resonance corresponding to the CH_2Pd unit. The ^{13}C resonance for C-30 could not be detected directly but was observed in the 2D HMQC spectrum at approximately 42.5 ppm. The absence of this carbon signal from the ^{13}C spectrum is likely to be due to fluxional behaviour (*vide infra*). Acetylation of **7** with Ac_2O in the presence of Et_3N and DMAP in CH_2Cl_2 gave an unstable acetate **8**, which was immediately oxidized with $Pb(OAc)_4$ and pyridinium acetate in THF, followed by reductive workup with $NaBH_4$ to afford the diacetate **9**. The selective introduction of the acetate at C-30 was confirmed by the presence of an AB methylene resonance at 4.18 ppm. Deacetylation of **9** with Na_2CO_3 in MeOH gave the oxime **10**, which was hydrolysed with $TiCl_3$ in aqueous THF to give the ketone **11**. Transformation of **11** into the target aldehyde **12** was achieved in 52% yield by oxidation with sulphur trioxide pyridine complex and DMSO in the presence of Et_3N. This compares favourably with the preparation of an ursolic acid derivative by Bore *et al*,[9] where a silyl ether at C-23 was converted with RuO_4 into an acid and an aldehyde in 65% and 9% yield respectively.



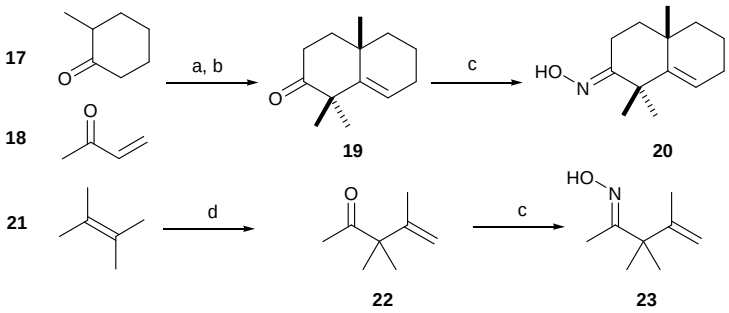
Scheme 2 a. Na_2PdCl_4, NaOAc, AcOH, rt, 88%. b. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt. c. pyridine, $Pb(OAc)_4$, THF, AcOH then $NaBH_4$, NaOH, 0 °C, 83% over two steps. d. Na_2CO_3, MeOH, rt, 95%. e. $TiCl_3$, HCl, NH_4OAc, H_2O, THF, rt, 85%. f. SO_3.py, Et_3N, DMSO, rt, 52%.

As expected, the friedelin derived oxime **6** failed to undergo a successful cyclopalladation reaction, presumably due to the unfavourable orientation of the single methyl group and/or the potential for β-hydride elimination from any resultant σ-organopalladium complex.



Scheme 3 a. Na_2PdCl_4, NaOAc, AcOH, rt, 91%. b. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt. c. pyridine, $Pb(OAc)_4$, THF, AcOH then $NaBH_4$, NaOH, 0 °C, 81% over two steps.

The dimeric organopalladium complex **13** was obtained from the corresponding cholesterol derived oxime **5** using the same procedure described above. Surprisingly, oxidation of the corresponding acetate **14** with $Pb(OAc)_4$ in THF, followed by reductive workup with $NaBH_4$ did not afford the expected diacetate **15**. Instead, the cyclopropane **16** was obtained in excellent yield, where stereoselective acetoxylation has occurred at C-6. The introduction of an equatorial acetate unit at C-6 was evidenced by the appearance of a double doublet at 5.11 ppm with a large diaxial coupling in the ^{1}H NMR, and the corresponding carbon atom at 70.2 ppm in the ^{13}C NMR. Similarly, the formation of the cyclopropane is consistent with the appearance of two signals at 0.81 ppm and 1.30 ppm, correlating to the same carbon atom at 17.5 ppm, together with the low chemical shifts of the resonances corresponding to C-4 and C-5.

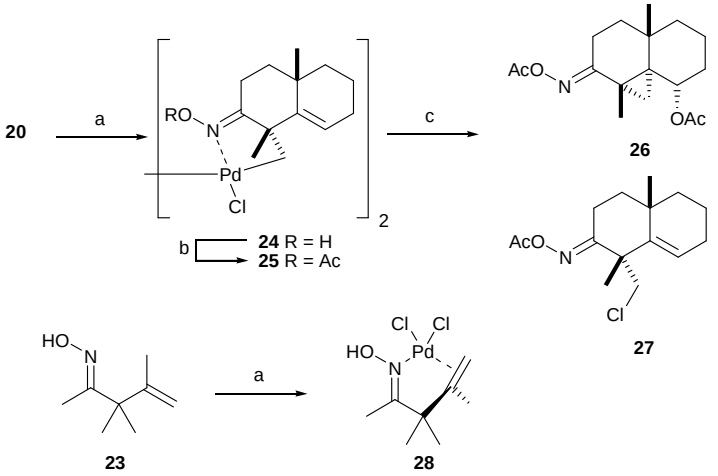


Scheme 4 a. conc. H_2SO_4, reflux. b. KO^{t}Bu, MeI, ^{t}BuOH, reflux. c. $NH_2OH.HCl$, $NaHCO_3$, EtOH, reflux.

In order to further explore this unusual cyclopropane formation during the oxidation of the σ-organopalladium intermediate, we prepared the simpler oximes **20** and **23** which also contain an alkene unit adjacent to the *gem*-dimethyl unit (Scheme 4). The oxime **20** was obtained from known ketone **19**, which was prepared via literature methods.[14-15] Oxime **23** was prepared by $ZnCl_2$ mediated acylation of tetramethylethylene and subsequent treatment of the ketone **22**[16] with hydroxylamine.

Cyclopalladation of oxime **20** gave dimer **24**, where the AB system corresponding to the CH_2Pd unit can be clearly observed at 2.50 ppm and 2.66 ppm with the corresponding carbon atom appearing in the HMQC spectrum at 42.1 ppm. This confirms that cyclopropane formation does not take place during the cyclopalladation reaction. Upon warming the NMR sample to 60 °C, the carbon resonances from both the oxime carbon and the CH_2PdCl carbon become considerably sharper, indicating that dynamic effects are responsible for the very broad peak observed for the latter carbon atom at room temperature. Acylation of **24** and subsequent oxidation of the acetate **25** gave the cyclopropane diacetate **26**, in a similar manner to the cholesterol derivative **14** above, together with a small quantity of the chloroketone **27**. The stereochemistry of the diacetate **26** is consistent with the ^1H coupling constants and was confirmed by nOe experiments in combination with 2D correlation experiments.

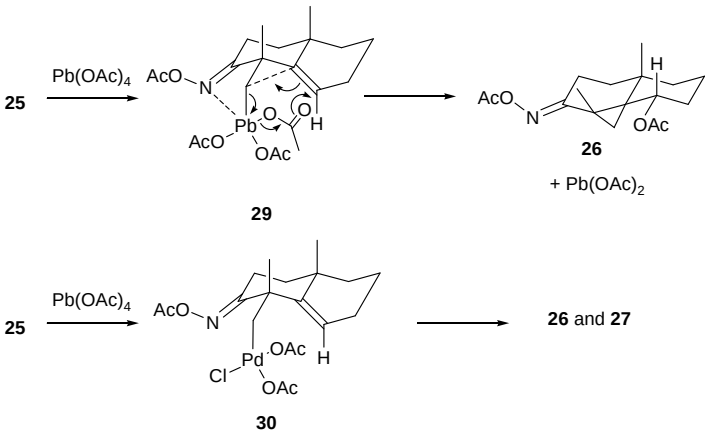
Treatment of oxime **23** with Na_2PdCl_4 led to the formation of a yellow precipitate as for the other systems, but without insertion into any of the methyl C-H bonds. The integrals in the ^1H NMR spectrum indicated the presence of four chemically inequivalent methyl groups, together with an alkene methylene unit. This suggests that complexation of the palladium to the oxime has occurred as expected, but the expected C-H insertion reaction has been prevented by complexation of the adjacent alkene unit to the palladium centre. This holds the methyl groups away from the metal centre, thereby preventing reaction. Such complexation of the palladium by the alkene unit is impossible in oximes **5** and **20** due to the rigid bicyclic ring system. The palladium complex **28** appeared to be exceptionally stable, and attempts to promote decomplexation of the alkene and subsequent C-H insertion by heating the complex to reflux in methanol, ethanol or acetic acid, led only to slow degradation of the complex. In contrast, a related palladium complex of an *O*-allyl oxime readily underwent alkoxypalladation in alcoholic solvent.[17]



Scheme 5 a. Na_2PdCl_4, NaOAc, AcOH, rt, 85% (**24**), 52% (**28**). b. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt. c. pyridine, $Pb(OAc)_4$, THF, AcOH then $NaBH_4$, NaOH, 0 °C, 64% (**26**), 23% (**27**) over two steps.

2.3. Mechanism of Cyclopropane formation

The cyclopropane formation must take place during the oxidation with lead tetraacetate as the cyclopropane is clearly not present in the acetate **25**, from examination of the crude ^1H NMR. A plausible mechanism for the cyclopropane formation is shown in Scheme 6. Transmetallation from palladium to lead gives the organolead intermediate **29**, which can rearrange via acetate transfer to form the cyclopropane **26**. Coordination of the oxime to the lead leads to a trigonal bipyrimidal geometry, which will favour the direct transfer of an apical acetate ligand to the lower face of the alkene, leading to the observed stereochemistry in the product. Alternatively, oxidation of the complex **25** to a Palladium (IV) intermediate **30** would promote a similar rearrangement/reductive elimination of an acetate ligand to yield cyclopropane **26**. Chloride **27** is formally derived from palladium intermediate **25** by reductive elimination, perhaps via a lead-mediated radical mechanism related to that of the Kochi modification of the Hunsdieker decarboxylation or via reductive elimination of the palladium (IV) intermediate **30**.[18] Interestingly, Sutherland *et al* reported the formation of a chloride by oxidation of the palladium complex derived from 2,2,6-trimethylcyclohexanone oxime with *meta*-chlorobenzoic acid, perhaps providing evidence for the latter explanation.[10a]



Scheme 6

3. Conclusions

The selective functionalisation of the hindered C-4 equatorial methyl group in triterpenoids previously reported for ursane, lupane and oleanane skeletons was successfully applied to the functionalisation of the lanostane backbone. The palladium dimer was successfully elaborated to give 3-oxo-4-methyl-lanosta-8,24-diene-4-carbaldehyde (**12**), a potential aglycon unit for the synthesis of novel adjuvant saponins.[19] The presence of the C-5 double bond in the cholestane skeleton interferes in the oxidation of the dimeric palladium complex, leading to stereoselective cyclopropane formation and introduction of an equatorial acetate unit at C-6 (**16**). This unusual transformation was also observed in a simpler decalin system (**26**), however the cyclopalladation of an open chain unsaturated oxime was unsuccessful due to complexation of the alkene group to the palladium and the formation of a novel highly stable palladium complex (**28**).

4. Experimental

4.1. General methods

Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer, and were recorded as thin films (NaCl plate). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker Avance 500 spectrometer in the stated solvent using residual protic solvent $CHCl_3$ (δ = 7.26 ppm, s). Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (*J*) are measured in Hertz. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on a Bruker AMX400 spectrometer or at 125 MHz on a Bruker Avance 500 spectrometer in the stated solvent using the central reference of $CHCl_3$ (δ = 77.0 ppm, t) as the internal standard. All solvents were dried using standard procedures and freshly distilled before use. Lead tetraacetate was recrystallized from acetic acid. Zinc chloride was dried by heating to > 300 °C to fuse the solid and was stored in a glove box. Other reagents were commercially available and used directly without purification. Chromatographic separations were performed with silica gel 60 (230-400 mesh) and thin-layer chromatography and performed on polyester backed sheets coated with silica gel 60 F254, both supplied by Merck.

4.2. General procedure for the synthesis of oximes

A solution of the corresponding ketone (1.0 eq.), hydroxylamine hydrochloride (1.0 eq.), sodium hydrogen carbonate (1.2 eq.) and ethanol (10 mL/mmol) was refluxed for 12-24 hours. After cooling to room temperature, water was added (10 mL/mmol) and the mixture extracted with dichloromethane (3 × 15 mL/mmol). The combined organic phases were dried over $MgSO_4$, filtered and evaporated in vacuum. The resulting product was purified by chromatography on a silica gel column, using petroleum ether/dichloromethane (7:3) as eluent.

4.2.1. Lanosta-8,24-dien-3-one oxime (4)

η = 82%; mp 169-172 ºC; IR (KBr) 3272, 2949, 2868, 1652, 1559, 1458, 1373, 949 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (s, 3H, H-18), 0.80-0.95 (m, 2H, H-16), 0.86 (s, 3H, H-19), 0.91 (d, *J* = 6.0 Hz, 3H, H-21), 1.00-1.50 (m, 9H, H-1, H-5, H-12, H-15, H-17, H-20, H-22), 1.09 (s, 3H, H-28), 1.10 (s, 3H, H-29), 1.16 (s, 3H, H-30), 1.60 (s, 3H, H-27), 1.65-1.75 (m, 2H, H-6), 1.68 (s, 3H, H-26), 1.80-2.05 (m, 8H, H-1, H-7, H-11, H-12, H-23), 2.10-2.30 (m, 1H, H-2), 3.125 (dt, *J* = 4,0 *J* = 15,3 Hz, 1H, H-2), 5.10 (t, *J* = 5,7 Hz, 1H, H-24); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.78 (C-18), 17.62 (C-27), 17.62 (C-30), 18.61 (C-2), 18.73 (C-21), 18.73 (C-28), 18.92 (C-6), 21.06 (C-11), 23.01 (C-29), 24.09 (C-16), 24.23 (C-19), 24.90 (C-23), 25.71 (C-26), 26.35 (C-7), 28.15

(C-12), 35.63 (C-22), 36.13 (C-10), 36.23 (C-20), 36.32 (C-15), 36.46 (C-1), 40.38 (C-4), 44.43 (C-13), 49.82 (C-14), 50.35 (C-5), 50.47 (C-17), 125.21 (C-24), 130.90 (C-25), 133.76 (C-8)[a], 134.83 (C-9)[a], 167.11 (C-3); *m/z* (FAB^+) 441 ($M+H^+$, 89.4), 145 (12.9), 95 (32.4), 69 (100.0); Anal. Calcd for $C_{30}H_{49}NO$ (439.72): C, 81.94; H, 11.23; N, 3.19. Found: C, 81.55; H, 11.17; N, 3.62.

4.2.2. 4,4-Dimethylcholest-5-en-3-one oxime (5).
η = 60%; mp 224-226 ºC; IR (KBr) 3315, 2948, 2869, 1652, 1543, 1459, 1380, 950 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.61 (s, 3H, H-18), 0.77 (s, 3H, H-19), 0.796 (d, *J* = 6.5 Hz, 3H, H-26)[a], 0.799 (d, *J* = 6.5 Hz, 3H, H-27)[a], 0.80-2.20 (m, 20H, H-8, H-9, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24, H-25), 0.85 (d, *J* = 6.5 Hz, 3H, H-21), 1.19 (s, 3H, H-28)[b], 1.20-1.40 (m. 1H, H-1), 1.27 (s, 3H, H-29)[b], 1.40-1.60 (m, 1H, H-7), 1.70-1.90 (m, 1H, H-1), 1.90-2.10 (m, 1H, H-7), 2.31 (dd, *J* = 7.1, 19.0 Hz, 1H, H-2), 2.88 (ddd, *J* = 8.5, 12.0, 19.0 Hz, 1H, H-2), 5.50 (dd, *J* = 2.2, 5.0 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3 (C-18), 19.1 (C-21), 19.3 (C-19), 19.7 (C-2), 21.8 (C-11), 22.9 (C-26)[a], 23.2 (C-27)[a], 24.3 (C-23), 24.6 (C-15), 28.4 (C-16), 28.6 (C-28), 28.7 (C-29), 30.9 (C-1), 31.2 (C-25), 32.2 (C-7), 33.9 (C-8), 36.2 (C-20), 36.6 (C-22), 37.6 (C-10), 39.9 (C-24), 40.3 (C-12), 41.6 (C-4), 42.8 (C-13), 49.5 (C-9), 56.6 (C-17), 57.4 (C-14), 119.3 (C-6), 150.3 (C-5), 166.5 (C-3); *m/z* (FAB^+) 428 ($M+H^+$, 65.2), 107 (90.1), 69 (100.0), 55 (68.1); Anal. Calcd for $C_{29}H_{49}NO$ (427.71): C, 81.44; H, 11.55; N, 3.27. Found: C, 81.66; H, 11.43; N, 3.16.

4.2.3. Friedelan-3-one oxime (6)
η = 68%; mp 290-294 ºC; ^1H NMR (500 MHz, $CDCl_3$): δ 0.74 (s, 3H, H-24), 0.84 (s, 3H, H-25), 0.85-0.90 (m, 1H, H-22), 0.94 (d, *J* = 6.6 Hz, 3H, H-23), 0.95 (s, 3H, H-29), 1.00 (s, 6H, H-26 and H-30), 1.03 (s, 3H, H-27), 1.17 (s, 3H, H-28), 1.15-1.65 (m, 24H, H-1, H-2, H-4, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-15, H-16, H-18, H-19, H-21, H-22), 1.77 (d, *J* = 13.0 Hz, 1H, H-2), 2.02 (q, *J* = 6.6 Hz, 1H, H-4), 3.43 (ddd, *J* = 1.5, 4.2, 13.0 Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.36 (C-23), 14.21 (C-24), 17.96 (C-25), 18.34 (C-7), 18.66 (C-27), 20.24 (C-26), 20.53 (C-2), 24.42 (C-1), 28.17 (C-20), 30.01 (C-17), 30.54 (C-12), 31.78 (C-30), 32.09 (C-28), 32.40 (C-15), 32.78 (C-21), 35.03 (C-29), 35.33 (C-19), 35.56 (C-11), 36.03 (C-16), 37.29 (C-9), 38.30 (C-14), 39.26 (C-22), 39.66 (C-13), 40.29 (C-5), 41.15 (C-6), 42.78 (C-18), 50.96 (C-4), 53.09 (C-8), 59.99 (C-10), 162.36 (C-3).

4.2.4. (E)-1,1,4a-Trimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1H)-one oxime (20)
η = 83%; mp 65-66 ºC; IR (film) 3281, 2972, 2930, 2866, 1456, 1435, 1383, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, Me), 1.26 (s, 3H, Me), 1.28-1.35 (m, 4H, Me and C*H*H), 1.47 (br dt, *J* = 12.7, 3.3 Hz, 1H, CH*H*), 1.53-1.72 (m, 4H, 2 × CH_2), 1.96-2.12 (m, 2H, CH_2CH=C), 2.39 (ddd, *J* = 18.8, 6.2, 2.9 Hz, 1H, C*H*HC=NOH), 3.01 (ddd, *J* = 18.8, 11.2, 9.0 Hz, 1H, CH*H*C=NOH), 5.57 (dd, *J* = 4.1, 3.2 Hz, 1H, C*H*=C), 9.75 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2 (CH_2), 19.4 (CH_2), 23.8 (Me), 25.6 (CH_2), 28.0 (Me), 32.7 (Me), 34.07 (CH_2*C*Me), 34.10 (CH_2), 38.9 (CH_2), 41.2 (*C*C=NOH), 119.5 (*C*H=C), 148.9 (CH=*C*), 165.8 (*C*=NOH); *m/z* (EI) 208 ($[M+H]^+$, 100), 179 (26); HRMS: $[M+H]^+$, found 208.17052, $C_{13}H_{21}NO$ requires 208.17014; Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.36; H, 10.37; N, 6.84.

4.2.5. (E)-3,3,4-Trimethylpent-4-en-2-one oxime (23)
Anhydrous zinc chloride (4 g, 29.3 mmol) was added portionwise to a mixture of tetramethylethylene (7 mL, 58.9 mmol) and acetic anhydride (56 mL, 589 mmol) under nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. Saturated sodium carbonate (100 mL) was then added slowly and the mixture stirred for 20 min then extracted with hexane (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated to give 3,3,4-trimethylpent-4-en-2-one as a brown liquid. Sodium bicarbonate (17.98 g, 214 mmol) and hydroxylamine hydrochloride (12.41 g, 176.7 mmol) were added to a solution of the crude ketone in ethanol (140 mL) which was heated to reflux for 20 h. After cooling, water (100 mL) was added and the mixture extracted with dichloromethane (3 × 100 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography (10:1 Petrol:Ether) to give the oxime as a low-melting point white solid (3.83 g, 46% over two steps).
η = 46%; mp 27-28 ºC; IR (film) 3300, 2974, 1699, 1639, 1456, 1379, 1134, 1024, 999, 935 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (6H, s, 2 × Me), 1.64 (3H, s, Me), 1.76 (3H, s, Me), 4.88-4.89 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.7, 19.7, 24.5, 46.3, 111.0, 149.4, 162.3; *m/z* (CI) 142 ($[M+H]^+$, 80), 126 ($[M-CH_3]^+$, 100), 109 (40), 83 (62); HRMS: $[M+H]^+$, found 142.12266, $C_8H_{15}NO$ requires 142.12318.

4.3. General procedure for the synthesis of dimers

Sodium acetate (1.1 eq.) and Na_2PdCl_4 (1.12 eq.) were added to a solution of the oxime (1.0 eq.) in acetic acid (40 mL/mmol). The solution was allowed to stir at room temperature under nitrogen atmosphere for 72 h. Ice cold water (45 mL/mmol) was added to give a yellow precipitate which was filtered and dried in vacuum, at 60 ºC over P_2O_5, for 24 h. The corresponding dimer was obtained as an amorphous solid which was directly used in the following step without any additional purification.

4.3.1. Chloro-bis(lanost-8,24-dien-3-one-C^{30},N) oxime dipalladium (II) complex (7)

η = 88%; mp > 300 ºC; IR (KBr) 3375, 2951, 1652, 1559, 1458, 1373, 952 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.68 (s, 3H, H-18), 0.87 (s, 3H, H-19), 0.89 (br d, *J* = 7.5 Hz, 3H, H-21), 1.00-1.50 (m, 5H, H-1, H-15 and H-20), 1.05 (br s, 3H, H-28), 1.25-1.50 (m, 5H, H-5, H-12, H-16 and H-17), 1.28 (br s, 3H, H-29), 1.50-1.75 (m, 3H, H-6 and H-23), 1.60 (s, 3H, H-27), 1.68 (br s, 3H, H-26), 1.75-2.20 (m, 9H, H-2, H-6, H-7, H-11, H-12 and H-22), 2.25-2.75 (m, 2H, H-30), 2.90-3.10 (m, 1H, H-2), 5.09 (br s, 1H, H-24), 8.10 (br s, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8 (C-18), 18.00 (C-6), 18.00 (C-27), 18.70 (C-21), 18.70 (C-28), 20.5 (C-2), 21.3 (C-11), 23.3 (C-29), 24.1 (C-16), 24.2 (C-19), 24.9 (C-23), 25.7 (C-26), 26.0 (C-7), 28.1 (C-12), 35.3 (C-22), 36.2 (C-20), 36.40 (C-1), 36.40 (C-15), 37.4 (C-10), 44.4 (C-13), 49.9 (C-14), 50.3 (C-5), 50.4 (C-17), 51.8 (C-4), 125.2 (C-24), 130.9 (C-25), 132.8 (C-8)[a], 135.5 (C-9)[a], 177.7 (C-3); Anal. Calcd for $C_{60}H_{96}N_2O_2Pd_2Cl_2$ (1161.18): C, 61.26; H, 8.51; N, 2.46. Found: C, 61.10; H, 8.54; N, 2.20.

4.3.2. Chloro-bis(4,4-dimethylcolest-5-en-3-one-C^{29},N) oxime dipalladium (II) complex (13)

η = 91%; mp > 300 ºC; IR (KBr) 3402, 2950, 1651, 1543, 1458, 1380, 954 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (s, 3H, H-18), 1.00-2.00 (m, 22H, H-1, H-8, H-9, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24, H-25), 1.02 (s, 3H, H-19), 1.07 (d, *J* = 6.6 Hz, 6H, H-26 and H-27), 1.11 (d, *J* = 6.3 Hz, 3H, H-21), 1.72 (s, 3H, H-28), 2.00-3.00 (m, 6H, H-2, H-7, H-29), 5.64-5.66 (m, 1H, H-6), 8.36 (br s, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4 (C-18), 19.10 (C-19), 19.10 (C-21), 21.5 (C-11), 22.1 (C-2), 22.9 (C-26)[a], 23.2 (C-27)[a], 24.2 (C-23), 25.5 (C-15), 28.4 (C-29β), 28.6 (C-16), 29.9 (C-1), 31.7 (C-25), 31.9 (C-7), 34.3 (C-8), 36.2 (C-20), 36.6 (C-22), 38.4 (C-10), 39.9 (C-24), 40.2 (C-12), 42.7 (C-13), 48.5 (C-9), 52.9 (C-4), 56.6 (C-17), 57.2 (C-14), 120.4 (C-6), 149.2 (C-5), 177.1 (C-3); Anal. Calcd for $C_{58}H_{96}N_2O_2Pd_2Cl_2$ (1137.15): C, 61.26; H, 8.51; N, 2.46. Found: C, 61.10; H, 8.54; N, 2.20.

4.3.3. Chloro-bis(1,1-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-one-C^{2},N) oxime dipalladium (II) complex (24)

η = 85%; mp 115-117 ºC (dec); IR (film) 3373, 2959, 2928, 2866, 1558, 1423, 1400, 1379, 1364, 1288, 1097, 999 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (s, 3H, Me), 1.29 (td, *J* = 12.9, 4.3 Hz, 1H, C*H*HCMe), 1.46-1.55 (m, 6H, Me, CH*H*CMe and CH_2CMe), 1.59-1.68 (m, 2H, CH_2CH$_2$CMe), 1.92-1.97 (m, 2H, CH_2CH=C), 2.36 (ddd, *J* = 20.2, 6.1, 2.7 Hz, 1H, C*H*HC=NOH), 2.47-2.53 (br m, 1H, C*H*HPd), 2.66 (d, *J* = 8.0 Hz, 1H, CH*H*Pd), 2.81 (ddd, *J* = 20.2, 11.4, 8.9 Hz, 1H, CH*H*C=NOH)), 5.45 (dd, *J* = 4.3, 3.1 Hz, 1H, C*H*=C), 8.17 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1 (*C*H$_2$CH$_2$CMe), 21.2 (*C*H$_2$C=NOH), 23.0 (CH$_2$C*Me*), 25.4 (*C*H$_2$CH=C), 32.8 (*C*H$_2$CH$_2$C=NOH), 33.6 (*Me*CCH$_2$Pd), 34.8 (CH$_2$*C*Me), 37.4 (*C*H$_2$CMe), (42.1, *C*H$_2$Pd), 52.5 (*C*CH$_2$Pd), 120.6 (*C*H=C), 147.7 (CH=*C*), 176.7 (*C*=NOH); *m/z* (FAB) 660 (MH$^+$-Cl).

4.3.4. (3,3,4-Trimethylpent-4-en-2-one oxime-C^{4},C^{5},N) palladium dichloride (28)

η = 52%; mp 122-127 ºC (dec.); IR (film) 3260, 1558, 1427, 1375, 1055, 993 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 3H, Me), 1.61 (s, 3H, Me), 2.05 (s, 3H, Me), 2.14 (s, 3H, Me), 4.90 (s, 1H, C*H*H), 5.43 (s, 1H, CH*H*), 9.88 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.9, 25.1, 25.9, 52.3, 84.2, 138.3, 174.2. *m/z* (CI) 317 (10, M$^+$), 142 (98, M+H- Cl_2Pd), 126 (100, M-CH_3Cl_2Pd); HRMS: [M]$^+$, found 316.95716, $C_8H_{15}ClNOPd$ requires 316.98655.

4.4. General procedures for the synthesis of *O*-acetate of oximes

Triethylamine (5.72 eq.), DMAP (0.12 eq.), and acetic anhydride (5.72 eq.) were added to a stirred solution of the dimer (1.0 eq.) in dry dichloromethane (54 mL/mmol), under nitrogen atmosphere. The mixture was stirred at room temperature for 45 min, then washed with water (2 × 50 mL), dried over magnesium sulfate, filtered and evaporated in vacuum to afford the acetate as a colourless oil which was used immediately in the following step.

Pyridine (3.5 eq.) and dry THF (54 mL/mmol) were added to this oil and the solution was stirred at room temperature under nitrogen atmosphere for 15 min. The solution was cooled to 0 °C and a solution of lead tetra-acetate (4.0 eq.) in acetic acid (27 mL/mmol) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature, and stirred for 16 h. A solution of sodium borohydride (4.0 eq.), in 1 N aqueous NaOH solution (50 mL) was added and the mixture stirred for 10-15 min to precipitate palladium salts.

After the mixture was filtered, the filtrate was diluted with dichloromethane (250 mL) and washed with saturated aqueous sodium hydrogen carbonate solution until AcOH was completely removed, dried over magnesium sulfate, filtered and evaporated in vacuum.

The solid residue was purified by flash column chromatography of silica gel using petroleum ether/ethyl acetate (2:1) as eluent, to give *O*-acetate of the corresponding oxime.

4.4.1. 3-Acetoxy-imino-30-acetoxylanost-8,24-diene (9)

η = 83%; mp 119-122 ºC; IR (KBr) 2961, 1773, 1738, 1621, 1468, 1373, 1238, 1204, 935 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.70 (s, 3H, H-18), 0.85-0.95 (m, 2H, H-16), 0.89 (s, 3H, H-19), 0.92 (d, *J* = 6.3 Hz, 3H, H-21), 1.00-1.25 (m, 2H, H-15), 1.06 (s, 3H, H-28), 1.20 (s, 3H, H-29), 1.25-1.50 (m, 3H, H-12, H-17 and H-20), 1.25-1.65 (m, 5H, H-1, H-6 and H-22), 1.50-1.65 (m, 1H, H-5), 1.61 (s, 3H, H-27), 1.65-2.00 (m, 4H, H-1, H-11 and H-12), 1.69 (s, 3H, H-26), 1.90-2.10 (m, 4H, H-7 and H-23), 2.05 (s, 3H, H-2''), 2.18 (s, 3H, H-2'), 2.56 (ddd, *J* = 7.2, 10.5, 16.6 Hz, 1H, H-2), 2.82 (ddd, *J* = 3.7, 7.2 and 16.6 Hz, 1H, H-2), 4.18 (AB system, *J* = 11.4 Hz, 2H, H-30), 5.10 (t, *J* = 7.0 Hz, 1H, H-24); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.86 (C-18), 18.60 (C-21), 18.71 (C-28), 18.90 (C-29), 19.01 (C-27), 19.16 (C-6), 20.61 (C-2), 20.01 (C-2'), 20.93 (C-2''), 21.03 (C-11), 24.07 (C-16), 24.23 (C-19), 24.88 (C-23), 25.69 (C-26), 26.08 (C-7), 28.10 (C-12), 34.10 (C-1), 34.10 (C-22), 36.20 (C-20), 36.29 (C-15), 36.72 (C-10), 44.04 (C-4), 44.40 (C-13), 44.67 (C-5), 49.90 (C-14), 50.34 (C-17), 67.89 (C-30), 124.15 (C-24), 130.92 (C-25), 132.81 (C-8), 135.45 (C-9), 169.75 (C-3), 170.64 (C-1'), 170.93 (C-1''); *m/z* (FAB^+) 540 ($M+H^+$, 6.2), 482 (32.1), 422 (30.9), 198 (14.5), 145 (25.2), 95 (67.1), 69 (100.0); Anal. Calcd for $C_{34}H_{53}NO_4$ (539.80): C, 75.65; H, 9.90; N, 2.59. Found: C, 74.93; H, 9.78; N, 2.62.

4.4.2. 3-Acetoxy-imino-6-acetoxy-4-methyl-5α,29α-cyclo-cholestane (16)

η = 81%; IR (KBr) 2972, 1777, 1739, 1628, 1472, 1381, 1239, 1208, 936 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.67 (s, 3H, H-18), 0.80-1.00 (m, 1H, H-9), 0.81 (d, *J* = 5.9 Hz, 1H, H-29), 0.85 (d, *J* = 5.0 Hz, 3H, H-26)[a], 0.85 (d, *J* = 5.0 Hz, 3H, H-27)[a], 0.87 (d, *J* = 5.0 Hz, 3H, H-21), 0.90-1.10 (m, 1H, H-20), 1.07 (s, 3H, H-19), 1.00-1.20 (m, 4H, H-7, H-14, H-15 and H-17), 1.10-1.25 (m, 3H, H-12 and H-24), 1.20-1.30 (m, 1H, H-16), 1.20-1.40 (m, 8H, H-1, H-11, H-22, H-23 and H-29), 1.40-1.60 (m, 3H, H-1, H-15 and H-25), 1.60-1.80 (m, 1H, H-8), 1.61 (s, 3H, H-28), 1.70-2.00 (m, 1H, H-7), 1.75-1.90 (m 1H, H-16), 1.90-2.00 (m, 1H, H-12), 2.04 (s, 3H, H-2''), 2.19 (s, 3H, H-2'), 2.25-2.35 (m, 1H, H-2), 2.40-2.50 (m, 1H, H-2), 5.51 (dd, *J* = 3.3 and 12.3 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.98 (C-18), 16.27 (C-19), 17.48 (C-29), 18.61 (C-21), 19.91 (C-28), 20.13 (C-2), 21.50 (C-2''), 22.05 (C-11), 22.53 (C-26), 22.53 (C-27), 22.78 (C-2'), 23.74 (C-23), 23.94 (C-15), 26.64 (C-4), 27.26 (C-1), 27.98 (C-25), 28.10 (C-16), 35.37 (C-8), 35.68 (C-20), 36.06 (C-22), 36.37 (C-7), 36.93 (C-10), 39.46 (C-24), 39.61 (C-12), 40.59 (C-5), 42.79 (C-13), 46.27 (C-9), 55.73 (C-14), 56.08 (C-17), 70.19 (C-6), 169.23 (C-3), 169.96 (C-1''), 170.13 (C-1'); *m/z* (FAB^+) 528 ($M+H^+$, 87.7), 470 (25.7), 444 (10.6), 408 (30.1), 154 (100.0); Anal. Calcd for $C_{33}H_{53}NO_4$ (527.79): C, 75.10; H, 10.12; N, 2.65. Found: C, 74.75; H, 10.08; N, 2.33.

4.4.3. (±)-(1aS,4aS,8S,8aR)-1a,4a-Dimethyl-2-(acetoxyimino)-decahydrocyclopropanaphthalen-8-yl acetate (26)

η = 64%; mp 77 ºC; IR (film) 2937, 1771, 1738, 1456, 1367, 1238, 1033, 932 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, *J* = 5.7 Hz, 1H, C*H*HCMeC=N), 1.13 (s, 3H, CH_2CMeCH_2), 1.17-1.22 (m, 1H, C*H*HCMeCH$_2$), 1.26 (ddd, *J* = 14.8, 8.2, 2.0 Hz, 1H, C*H*HCH$_2$C=N), 1.28 (d, *J* = 5.7 Hz, 1H, CH*H*CMeC=N), 1.43 (ddd, *J* = 13.2, 12.9, 4.7 Hz, 1H, CH*H*CMeCH$_2$), 1.45 (ddd, *J* = 14.8, 12.0, 7.6 Hz, 1H, CH*H*CH$_2$C=N), 1.53 (dddd, *J* = 13.2, 12.6, 12.0, 6.9 Hz, 1H, C*H*HCHOAc), 1.62 (s, 3H, *Me*CC=NOAc), 1.75 (ddddd, *J* = 13.2, 7.3, 6.9, 4.7, 2.5 Hz, 1H, C*H*HCH$_2$CHOAc), 1.84 ((qdd, *J* = 13.2, 4.7, 4.4 Hz, 1H, CH*H*CH$_2$CHOAc), 1.91-1.96 (m, 1H, CH*H*CHOAc), 2.05 (s, 3H, Me), 2.18 (s, 3H, Me), 2.44 (ddd, *J* = 19.9, 7.6, 2.0 Hz, 1H, C*H*HC=N), 2.57 (ddd, *J* = 19.9, 12.0, 8.2 Hz, CH*H*C=N), 5.44 (dd, *J* = 12.0, 3.0 Hz, 1H, C*H*=C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (CH_2C*Me*CH_2), 17.8 (*C*H_2CC=N), 19.9 (*Me*CO), 20.2 (*C*H_2C=N), 20.6 (*C*H_2CH_2CHOAc), 21.5 (*Me*CO), 24.4 (*Me*CC=N), 26.7 (*C*C=N), 30.9 (*C*H_2CHOAc), 32.0 (*C*H_2CH_2C=N), 33.4 (*C*H_2CMeCH$_2$), 34.6 (CH_2*C*MeCH$_2$), 39.1 (*C*CHOAc), 70.9 (*CH*OAc), 169.2 (C=N), 170.0 (C=O), 170.3 (C=O); *m/z* (CI) 308 ($[M+H]^+$, 31), 248 (29), 206 (78), 188 (100), 172 (67), 162 (42), 147 (37), 134 (62), 121 (32), 107 (43), 95 (70), 81 (52); HRMS: $[M+H]^+$, found 308.18656, $C_{17}H_{25}NO_4$ requires 308.18617.

4.4.4. O-Acetyl-1-(chloromethyl)-1,4a-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1H)-one oxime (27)

η = 23%; IR (film) 2928, 2868, 1771, 1454, 1429, 1366, 1211, 1003, 926 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 3H, Me), 1.21-1.35 (m, 3H, CH_2 and C*H*H), 1.36 (s, 3H, Me), 1.51-1.59 (m, 1H, CH*H*), 1.61-1.68 (m, 1H, C*H*H), 1.73 (ddddd, *J* = 17.0, 11.0, 9.8, 6.6, 3.5 Hz, 1H, CH*H*), 2.06 (dddd, *J* = 18.2, 10.7, 6.9, 2.8 Hz, 1H, C*H*HCH=C), 2.15-2.22 (m, 1H, CH*H*CH=C), 2.24 (s, 3H, MeCO), 2.54 (ddd, *J* = 19.4, 6.5, 2.5 Hz, 1H, C*H*HC=N), 2.93 (ddd, *J* = 19.4, 11.7, 8.3 Hz, 1H, CH*H*C=N)), 3.61 (d, *J* = 10.9 Hz, 1H, C*H*HCl), 4.16 (d, *J* = 10.9 Hz, 1H, CH*H*Cl), 5.62 (dd, *J* = 4.4, 3.2 Hz, 1H, C*H*=C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.9 (CH_2), 20.1 (Me), 21.2 (CH_2), 23.4 (Me), 25.6 (CH_2), 30.6 (Me), 33.4 (CH_2*C*Me), 33.8 (CH_2), 38.8 (CH_2), 47.3 (Me*C*C=N), 49.7 (CH_2Cl), 122.0 (*CH*=C), 143.2 (CH=*C*), 168.6 (*C*=O), 170.1 (*C*=N); *m/z* (ES) 286 (43, MH+), 284 (100 MH^+), 248 (43, M-Cl); HRMS: $[M+H]^+$, found 284.14272, $C_{15}H_{22}ClNO_2$ requires 284.14173.

4.5. 3-Hydroxy-imino-30-hydroxylanost-8,24-diene (10)

A solution of 3-acetoxy-imino-19-acetoxy-8,24-lanostadiene (**7**) (0.29 g, 0.51 mmol, 1.0 eq.) and sodium carbonate (0.24 g, 2.27 mmol, 4.5 eq.) in methanol (40 mL) was stirred under nitrogen atmosphere at room temperature for 24 h. After removal of methanol in vacuum, the resultant solid was dissolved in ethyl ether (20 mL) and a 1 N aqueous HCl solution was added (20 mL). The organic layer was washed three times with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and evaporated in vacuum

to give a solid. The solid was purified by flash column chromatography [petroleum ether-ethyl acetate (2:1)] to give 3-hydroxy-ymino-30-hydroxylanosta-8,24-dieno (**10**) (0.22 g, 95 %), as a white solid.

Mp 182-185 ºC; IR (KBr) 3410, 2948, 2874, 1639, 1464, 1371, 1041, 933 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.71 (s, 3H, H-18), 0.85-0.95 (m, 2H, H-16), 0.87 (s, 3H, H-19), 0.92 (d, *J* = 6.3 Hz, 3H, H-21), 1.00-1.20 (m, 1H, H-1), 1.00-1.50 (m, 6H, H-12, H-15, H-20 and H-22), 1.08 (s, 3H, H-28), 1.14 (s, 3H, H-29), 1.30-1.50 (m, 1H, H-17), 1.40-1.60 (m, 1H, H-5), 1.50-1.80 (m, 4H, H-6 and H-23), 1.61 (s, 3H, H-27), 1.69 (s, 3H, H-26), 1.80-1.95 (m, 3H, H-1 and H-11), 1.85-2.00 (m, 1H, H-12), 1.95-2.15 (m, 3H, H-2 and H-7), 3.20 (ddd, *J* = 2.7, 4.6 and 15.5 Hz, 1H, H-2), 3.59 (AB system, *J* = 11.2 Hz, 2 H, H-30), 5.10 (t, *J* = 6.9 Hz, 1H, H-24), 7.80 (br s, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8 (C-18), 17.6 (C-27), 17.9 (C-2), 18.3 (C-28), 18.6 (C-21), 19.1 (C-29), 18.9 (C-6), 21.2 (C-11), 24.1 (C-16), 24.3 (C-19), 24.9 (C-23), 25.7 (C-26), 26.1 (C-7), 28.2 (C-12), 35.2 (C-22), 35.2 (C-1), 36.3 (C-20), 36.3 (C-15), 36.9 (C-10), 44.9 (C-4), 44.4 (C-13), 45.6 (C-5), 49.9 (C-14), 50.4 (C-17), 67.7 (C-30), 125.2 (C-24), 130.9 (C-25), 133.6 (C-8), 135.1 (C-9), 166.7 (C-3); *m/z* (FAB^+) 456 ($M+H^+$, 73.4), 154 (37.3), 95 (66.9), 69 (100.0); Anal. Calcd for $C_{30}H_{49}NO_2$ (455.72): C, 79.07; H, 10.84; N, 3.07. Found: C, 79.12; H, 10.40; N, 3.31.

4.6. 30-Hydroxylanost-8,24-dien-3-one (11)

A buffered solution of titanium chloride (III) [1.30 mL of 20% aqueous hydrochloric acid solution containing 19% of titanium chloride (III)), ammonium acetate (0.775 g; 10.05 mmol; 27 eq.) and water (28 mL)] was added to a solution of 3-hydroxy-imino-30-hydroxylanost-8,24-diene (**10**) (0.17 g; 0.373 mmol; 1.0 eq.) in THF (27 mL). The mixture was stirred at room temperature for 6 h.

The resulting aqueous solution was extracted three times with ether. The combined organic phases were washed three times with saturated aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate, filtered and evaporated to give a solid that was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 7:3) to give to 30-hydroxylanost-8,24-dien-3-one (**11**) (0.14 g, 85%) as a white solid.

Mp 146-149 ºC; IR (KBr) 3434, 2943, 1699, 1462, 1374, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.72 (s, 3H, H-18), 0.85-0.95 (m, 2H, H-16), 0.89 (s, 3H, H-19), 0.92 (d, *J* = 6.3 Hz, 3H, H-21), 1.05 (s, 3H, H-28), 1.10-1.30 (m, 1H, H-12), 1.20-1.30 (m, 3H, H-15 and H-20), 1.22 (s, 3H, H-29), 1.30-1.50 (m, 1H, H-17), 1.50-1.80 (m, 2H, H-6), 1.61 (s, 3H, H-27), 1.69 (s, 3H, H-26), 1.85-1.95 (m, 1H, H-12), 1.91 (dd, *J* = 2.7 and 12.0 Hz, 1H, H-5), 2.00-2.20 (m, 10H, H-1, H-7, H-11, H-22 and H-23), 2.31 (ddd, *J* = 2.7, 5.1 and 15.9 Hz, 1H, H-2), 2.55 (br s, -OH), 2.67 (ddd, *J* = 6.6, 13.5 and 15.9 Hz, 1H, H-2), 3.55 (AB system, *J* = 11.1 Hz, 2H, H-30), 5.10 (t, *J* = 6.9 Hz, 1H, H-24); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8 (C-18), 16.7 (C-28), 17.6 (C-27), 18.6 (C-21), 19.0 (C-6), 19.1 (C-29), 21.2 (C-11), 24.1 (C-16), 24.3 (C-19), 24.9 (C-23), 25.7 (C-26), 26.0 (C-7), 28.2 (C-12), 35.7 (C-1), 35.9 (C-2), 36.2 (C-20), 36.3 (C-15), 36.5 (C-22), 36.7 (C-10), 44.5 (C-13), 45.1 (C-5), 49.9 (C-14), 50.4 (C-17), 52.3 (C-4), 66.9 (C-30), 125.2 (C-24), 131.0 (C-25), 133.1 (C-8), 135.6 (C-9), 219.4 (C-3); *m/z* (FAB^+) 441 ($M+H^+$, 33.1), 154 (35.4), 95 (61.3), 69 (100.0); Anal. Calcd for $C_{30}H_{48}O_2$ (440.71): C, 81.76; H, 10.98. Found: C, 81.60; H, 11.35.

4.7. 3-Oxo-4-methyl-lanost-8,24-dien-4-carbaldehyde (12)

A solution of sulfur trioxide/pyridine complex (70 mg, 0.44 mmol, 6.5 eq.) in dry dimethylsulfoxide (0.6 mL) was added dropwise to a stirred solution of 30-hydroxylanost-8,24-dien-3-one (**11**) (30.0 mg, 0.068 mmol, 1.0 eq.) and triethylamine (0.19 mL; 1.36 mmol; 20.0 eq.) in dry dimethylsulphoxide (1mL) under nitrogen. After addition, the reaction mixture was stirred under nitrogen atmosphere and at room temperature for about 1.5 h, until total consumption of the starting material was observed by TLC. Ether (5 mL) was added and the phases were separated. The organic phase was washed with 10 % aqueous sodium chloride solution.

A cold 10% aqueous sodium chloride was carefully added to the dimethylsulphoxide phase and the resulting mixture was extracted with ether. The combined aqueous phases were extracted with ether and the combined organic phases were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was distilled under reduced pressure to give 3-oxo-4-methyl-lanost-8,24-dien-4-carbaldehyde (**12**) (15.5 mg, 52.4%) as a yellow oil.

IR (KBr) 2956, 2874, 1737, 1701, 1464, 1374 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.70 (s, 3H, H-18), 0.80-0.90 (m, 2H, H-16), 0.89 (s, 3H, H-19), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 1.18 (s, 3H, H-28), 1.20-1.40 (m, 1H, H-12), 1.29 (s, 3H, H-29), 1.30-1.40 (m, 3H, H-15 and H-20), 1.40-1.50 (m, 1H, H-17), 1.50-1.70 (m, 2H, H-6), 1.59 (s, 3H, H-27), 1.60-1.80 (m, 3H, H-1 and H-22), 1.67 (s, 3H, H-26), 1.80-2.00 (m, 1H, H-12), 2.00-2.10 (m, 7H, H-1, H-7, H-11 and H-23), 2.30 (dd, *J* = 2.4 and 12.9 Hz, 1H, H-5), 2.36 (ddd, *J* = 3.2, 5.9 and 15.9 Hz, 1H, H-2), 2.57-2.65 (m, 1H, H-2), 5,08 (ddt, *J* = 1.4, 2.7 and 4.2 Hz, 1H, H-24), 9.37 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (C-29), 15.8 (C-18), 17.6 (C-27), 18.6 (C-21), 19.0 (C-28), 19.8 (C-6), 21.2 (C-11), 24.1 (C-16), 24.3 (C-19), 24.9 (C-23), 25.6 (C-7), 25.7 (C-26), 28.1 (C-12), 35.4 (C-2), 35.8 (C-10), 35.8 (C-22), 36.0 (C-1), 36.2 (C-15), 36.4 (C-20), 44.0 (C-5), 44.4 (C-13), 49.8 (C-14), 50.3 (C-17), 63.6 (C-4), 125.1 (C-24), 131.0 (C-

25), 132.7 (C-8), 135.9 (C-9), 200.2 (C-30), 212.4 (C-3); *m/z* (FAB$^+$) 439 (M+H$^+$, 45.2), 154 (24.7), 95 (51.9), 69 (100.0); Anal. Calcd for $C_{30}H_{46}O_2$ (440.71): C, 82.14; H, 10.57. Found: C, 81.97; H, 10.72.

Acknowledgments

S. S. Ramos thanks the *Fundação para a Ciência e Tecnologia*, Portugal (SFRH/BD/1237/2000) for granting her a Ph.D scholarship. T. Sheppard would like to thank the EPSRC for providing a postdoctoral fellowship. We would also like to thank Dr Abil Aliev for help with NMR experiments.

References

1. Press, J. B.; Reynolds, R. C.; May, R.D.; Marciani, D., In *Structure/Function Relationships of Immunostimulating Saponins, in: Studies in Natural Products Chemistry*, Atta-or-Rahman (Ed.), Elsevier Science, N. Y., 2000; Vol. 24, pp 131-174.
2. Soltysik, S.; Wu, J.-Y.; Recchia, J.; Wheeler, D. A.; Newman, M. J.; Coughlin, R. T.; Kensil, C. R. *Vaccine* **1995**, *13*, 1403-1410.
3. Barr, I. G.; Sjölander, A.; Cox, J. C. *Adv. Drug Deliv. Rev.* **1998**, *32*, 247-271.
4. Pillion, D. J.; Amsden, J. A.; Kensil, C. R.; Recchia, J.; *J. Pharm. Sci.* **1996**, *85*, 518-524.
5. Marciani, D. J.; Press, J. B.; Reynolds, R. C.; Pathak, A. K.; Pathak, V.; Gundy, L. E.; Farmer, J. T.; Koratich, M. S.; May, R. D. *Vaccine* **2000**, *18*, 3141-3151.
6. Constable, A. G.; McDonald, S. W.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1980**, 1992-2000.
7. Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699-711.
8. White, A.; Horsington, E. J.; Nedjar, N.; Peakman, T. M.; Curiale, J. A. *Tetrahedron Lett.* **1998**, *39*, 3031-3034.
9. Bore, L.; Honda, T.; Gribble, G. W. *J. Org. Chem.* **2000**, *65*, 6278-6282.
10. a. Carr, K.; Sutherland, J. *J. Chem. Soc. Chem. Comm.* **1984**, 1227-1228. b. Carr, K.; Saxton, H. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1599-1601.
11. For the oxidation procedure see: Paranjape, B. V.; Pyle, J. L. *J. Org. Chem.* **1971**, *36*, 1009-1011.
12. For the oxidation of cholesterol see: Fieser, A. L. F. *Organic Syntheses, Collective Volume IV*, John Wiley & Sons: New York, 1963.
13. For dimethylation of cholestenone: Duan, H.-Y.; Wang, J.-X.; Li, T.-S. *Synth. Comm.* **1999**, *29*, 3197-3205.
14. Heathcock, C. H.; Ellis, J. E. *Tetrahedron Lett.* **1971**, *12*, 4995-4996.
15. Kepler, J. A.; Philip, A.; Lee, Y. W.; Musallam, H. A.; Carroll, F. I. *J. Med. Chem.* **1987**, *30*, 1505-1509.
16. Kiefer, E. F.; Carlson, D. A. *Tetrahdron Lett.* **1967**, *8*, 1617-1622.
17. Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc. Dalton Trans.* **1980**, 1992-2000.
18. Kochi, J. K. *J. Org. Chem.* **1965**, *30*, 3265-3271.
19. Marciani, D. J.; Pathak, A. K.; Reynolds, R. C.; Seitz, L.; May, R. D. *Int. Immunopharmacology* **2001**, *1*, 813-818.