PERKIN 2

Reaction of RuO_4 with carbon–carbon double bonds. Part 8.[1] Reaction of 7,8-didehydrocholesteryl acetate and cholesteryl acetate with RuO_4 and OsO_4. A comparative view

Laura Albarella, Maria Lasalvia, Vincenzo Piccialli * and Donato Sica

Dipartimento de Chimica Organica e Biologica, Università degli Studi di Napoli 'Federico II', Via Mezzocannone 16, 80134 Napoli, Italy

The title reactions have been studied. The first formed compound from the oxidation of 7,8-didehydrocholesteryl acetate with RuO_4 performed in acetone–water (5 : 1), both at room temperature and −70 °C, is the ruthenium(VI) diester 5. In mild acidic conditions compound 5 converts into the isomeric compound 6 that in turn is in equilibrium in the same conditions with a third isomeric ruthenium(VI) diester, 2, a compound previously isolated from the same oxidative process conducted at −70 °C. The structural relationship between the isomeric compounds 2, 5 and 6 has been established by careful spectral analyses and comparison of their NMR properties with those exhibited by the osmium-containing analogues (7 and 8) of the ruthenate esters 2 and 5, synthesized by reaction of 7,8-didehydrocholesteryl acetate with OsO_4 in dioxane. The RuO_4 oxidation of cholesteryl acetate at room temperature also furnishes two ruthenium(VI) diesters (9 and 10) structurally analogous to compounds 2 and 5. NMR evidence is reported that the Ru=O and Os=O groups possess similar magnetic anisotropy. The isomerization process involving the ruthenate esters of 7,8-didehydrocholesteryl acetate has also been studied by ^1H NMR spectroscopy and is briefly discussed.

Introduction

In a previous communication[2] we have reported the isolation and the structure elucidation of the ruthenium(VI) diester **2** (Scheme 1) obtained from the oxidation of 7,8-didehydrocholesteryl acetate (**1**) using an equimolar amount of RuO_4 in acetone–water (1 : 1) at −70 °C. Though the existence of such an intermediate had previously been hypothesized mainly on the basis of kinetic data,[3] compound **2** is the first ruthenate ester ever obtained from the reaction of an olefinic or a dienic substrate with RuO_4.

The structure determination of compound **2** was accomplished on the basis of chemical and NMR evidence and corroborated by the close similarity of its spectral properties to those exhibited by an osmium(VI) diester previously synthesized in our laboratory.[4] The importance of the above finding prompted us to search for further confirmation of the structure of intermediate **2** by X-ray analysis. Such a confirmation also appeared necessary since spectral data did not give definitive proof for the orientation of the Ru=O bond in **2**. Unfortunately, all the attempts to grow crystals of this labile material, suitable for X-ray crystallography, resulted mainly in its hydrolytic decomposition to diol **3**.

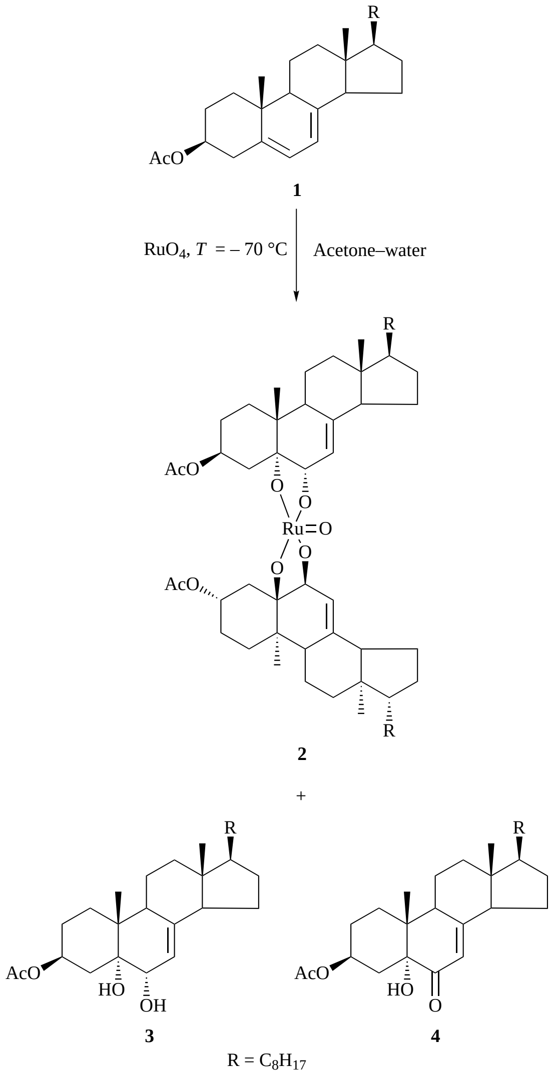
Furthermore, the previous study had evidenced the formation, in the course of the oxidative process, of another brownish and unstable substance (now characterized as diester **6**) whose structure, as evidenced by preliminary ^1H NMR data collected from an impure sample of the compound, had to be very close to that of diester **2**. Therefore, in order to shed further light on the nature of the ruthenium-containing intermediates involved in the RuO_4 oxidation of compound **1**, it appeared essential to undertake a more careful reinvestigation of the process. We reasoned that this study could have also furnished new information on the mechanism of the analogous and more known dihydroxylation process of alkenes with OsO_4. This appeared plausible since, as we[2,5–7] and others[8,9] have proven, RuO_4 affords, like OsO_4, dihydroxylation products in acceptable yields and diester **2** also possesses the very same structure (apart from the nature of the metal involved) as one of the most frequently formed intermediates of the dihydroxylation process involving osmium tetroxide.[10] Note that, in spite of considerable experimental and theoretical efforts so far made,[11–15] the structure of the first formed species in the dihydroxylation of alkenes with OsO_4 has not yet been established with certainty and the mechanism of the reaction is still unclear.

Thus, with the aim of giving a contribution to the aforementioned points we studied the intermediate compounds formed during the RuO_4 oxidation of 7,8-didehydrocholesteryl acetate and report the results in the present paper.

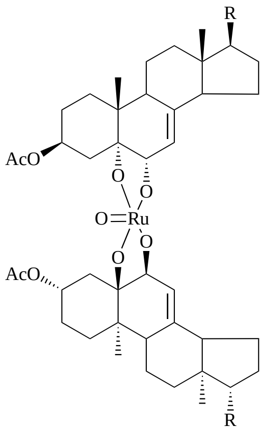
Results and discussion

The RuO_4 oxidation of 7,8-didehydrocholesteryl acetate was performed either at −70 °C or at room temperature. In both cases a brownish precipitate formed almost immediately after mixing the oxidant with the steroidal substrate. This solid was immediately collected by suction filtration, desiccated and analysed by ^1H NMR spectroscopy ($CDCl_3$) which unexpectedly showed it to be composed of an almost pure product structurally similar to the previously isolated diester **2**, that was characterized as **5**, as detailed below. Compound **5** was obtained in 5% yield while diol **3** and α-hydroxy ketone **4** were obtained in 26 and 51% yields, respectively, from the reaction performed at room temperature; similar yields (**3**: 22%; **4**: 50%; **5**: 4%) were obtained from the process conducted at −70 °C. In both cases compound **5** was only contaminated by a 3–5% amount of diesters **2** and of the aforementioned unknown substance closely related to it (compound **6**).

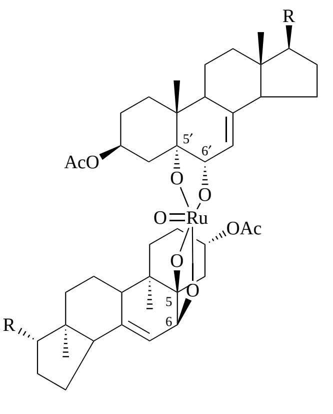
When trying to further purify on silica gel compound **5** obtained as above, we observed its partial conversion into a mixture of the products **2** and **6**. Furthermore, compound **5** was also observed to convert slowly into a mixture of **2** and **6** when left to stand in $CHCl_3$ solution.[16] This evidence suggested to us that compounds **2**, **5** and **6** could be closely related ruthenium-containing species, possibly isomeric ruthenium(VI) diesters, that in mild acidic conditions convert from one to another and that the previously isolated compounds **2** and **6** could mostly derive from **5** during the work-up stage of the reaction.



Scheme 1



5



6

R = C_8H_{17}

Diester **5**, as previously observed for compound **2**, proved to be reasonably stable in hexane–EtOAc mixtures, where it can be left for a long time without appreciable decomposition, and in $CDCl_3$ solutions. Therefore, NMR studies were performed on samples of **5**, freshly obtained by the oxidation of **1**, by simply filtering the reaction mixture, desiccating the solid and dissolving it in $CDCl_3$. All the NMR data obtained following this procedure were satisfactory and gave unambiguous structural information. However, a further HPLC purification of **5** was prevented by the fact that its passage on a silica gel column, also using hexane–EtOAc mixtures as eluent, transformed the substance into a mixture of diesters **2** and **6**.

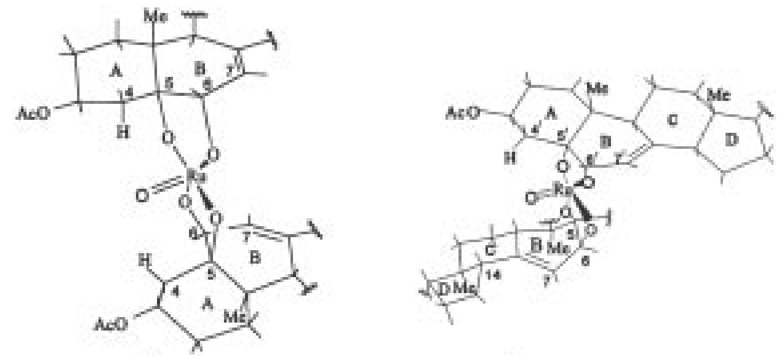
Further corroboration of the isomeric nature of the above products was obtained by treatment of the freshly prepared **2**, **5** and **6** (pure samples of **2** and **6** were obtained by HPLC as previously described for **2**[2]) with aqueous $NaHSO_3$ in dioxane that gave diol **3** as the sole product. This result reinforced our hypothesis that all three substances could be ruthenium(VI) diesters in which the alcoholic portion was constituted of the same steroidal diol **3** thus indicating that the difference between them was confined to the ruthenium-containing portion of the molecule.

The FABMS spectrum of **5** failed to give the molecular ion cluster expected for this compound. However, it contained significant ion clusters at *m*/*z* 919–923 and 941–946, probably originating from the $(M + H)^+$ and $(M + Na)^+$ ions, respectively, by loss of the side-chain of one of the two steroidal moieties belonging to the molecule. The less invasive technique of electrospray ionization mass spectrometry (ESIMS) indicated a molecular mass of *m*/*z* 3104.8 attributable to a trimer of **5**. Correspondingly, the ESIMS spectrum also showed the $(M + H)^+$ ion peak at *m*/*z* 1035.9 (20% of the base peak) accompanied by other surrounding peaks due to the isotopic pattern of the ruthenium atom, and an intense peak at *m*/*z* 921.9 (base peak) corresponding to the triply charged ion of the trimeric species of **5** in which three side-chains had been lost. In this case, the isotopic pattern could not be detected due to the low resolution of the quadrupole instrument used.

^1H and ^{13}C NMR spectra of **5** were very similar to those of **2**. The proton spectrum of **5** contained singlet resonances for the Me-18 and Me-19 of the two steroidal units at δ 0.54 and 1.26, respectively (in **2** Me-18 and Me-19 resonated at δ 0.57 and 1.24, respectively), a broad singlet signal at δ 5.33 attributable to the H-7, olefinic, protons (**2**: δ 5.44) and a broad doublet at δ 5.08 ($J = 2.2$ Hz) for the H-6 protons (**2**: δ 4.99). The H_{eq}-4 protons resonated at δ 2.67 (dd, $J = 13.7$ and 4.4 Hz), strongly downshifted in comparison with their chemical shift value observed in the proton spectrum of **2**, where they resonated at δ 1.77. The broad seven-line multiplet at δ 4.81 indicated that in the intact molecule the two steroidal moieties possessed the A/B *trans* junction[17] as in the product of hydrolysis (**3**) that, therefore, does not affect the configuration of the C-5 and C-6 chiral centres. The ^{13}C NMR spectrum of **5** showed 29 well-resolved resonances thus indicating that this compound could possess a two-fold axis like compound **2**. It confirmed that compound **5** was a ruthenate ester showing signals due to the carbons geminal to ruthenium at δ 95.63 (s, C-5) and 94.30 (d, C-6)[18] and included the resonances pertinent to the two Δ^7 carbon–carbon double bonds at δ 118.38 (d) and 142.14 (s).

The data detailed above pointed to structure **5** for the compound under investigation. Compound **5** differs from **2** only in the orientation of the Ru=O group that in the former protrudes towards, and is located between, the A rings of the two steroidal units. Such a choice for the orientation of the Ru=O group in **5** (the alternative possibility is the one in structure **2**) was suggested by the unusually high chemical shift value (δ 2.67) observed for the H_{eq}-4 protons that can be explained by their vicinity to the Ru=O group (Fig. 1 shows a tridimensional view of **5** in which only the A/B ring portion of the two steroidal moieties is depicted).

Confirmation of the correctness of stereostructure **5** came from the structure elucidation of the third ruthenium(VI) diester **6** mostly achieved by NMR studies, taking into account the striking similarity of ^1H and ^{13}C NMR spectra of this compound with those of either **2** or **5**. Both the ^1H and ^{13}C NMR spectra of **6** showed a doubling of all signals, a fact that indicated that **6** did not possess the symmetry properties of compounds **2** and **5**. This immediately suggested to us that **6** could be a ruthenium(VI) diester, isomeric with **2** and **5**, in which the central RuO_5 portion of the molecule is pyramidally arranged



5

6

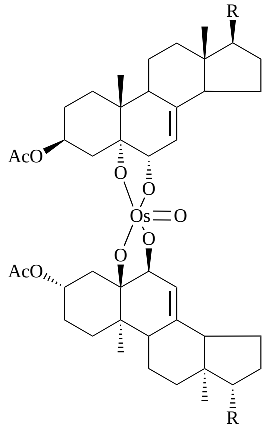
Fig. 1 Stereochemical view of ruthenium(VI) diesters **5** and **6**. For compound **5** only the A/B ring portion of the two steroidal moieties is shown. The A ring of the lower steroidal moiety in **6** and the side chains are omitted for clarity.

and connects two A/B *trans* steroidal units that are spatially oriented in such a way that the B/C/D ring portion of one of them and the A ring of the other one are approximately situated on the same side of the basal plane of the pyramid, as shown in Fig. 1. FABMS and ESIMS spectra for **6** were virtually identical to those of **5** (see Experimental section).

The proton spectrum of **6** included two singlet signals at δ 0.56 and 0.50 for the two Me-18 groups and two other singlets at δ 1.23 and 1.22 for the two Me-19. The two acetate singlets were seen at δ 1.99 and 2.02 while the H-6, H-7 and H-3 protons resonated as signals at δ 5.44 and 5.33 (both broad singlets, $w_{\frac{1}{2}} = 5.4$ Hz), 5.00 and 4.96 (both doublets with $J = 2.0$ Hz) and 4.79 and 4.67 (both seven-line multiplets characteristic of A/B *trans* steroids[17]), respectively. In addition, the proton spectrum of **6** also included two one-proton resonances at δ 2.59 (dd, $J = 13.7$ and 4.9 Hz) and 2.29 (br dd, $J = 9.0$ and 9.0 Hz) attributed to the H_{eq}-4 of one steroidal unit and to the H-14 of the other unit on the basis of decoupling work. Examination of a molecular model of **6** revealed that these two protons were in spatial proximity with the Ru=O group that, as hypothesized to explain the deshielding observed for the H_{eq}-4 protons in **5**, could be responsible for the somewhat high chemical shift value of their ^1H NMR resonances.

At this stage, to further support the above formulated structures for the ruthenium(VI) diesters **2**, **5** and **6**, we decided to synthesize their osmium-containing analogues. The synthesis and the NMR analysis of the osmium(VI) diester of α-pinene had previously been an important step in the structure elucidation of the ruthenium(VI) diester intermediate in the oxidative scission of this compound with RuO_4.[19] In fact, through this study it was possible to prove for the first time that a striking structural analogy exists between ruthenate and osmate esters. However, a careful comparison of the spectral properties of the osmium(VI) and ruthenium(VI) diesters formed by α-pinene could not be achieved because the latter compound was not stable enough to be isolated and the spectral data pertinent to it (mainly ^1H NMR data) were extracted from the proton spectrum of the reaction mixture, by conducting the oxidation in an NMR tube. The synthesis of the osmate esters of 7,8-didehydrocholesteryl acetate gave us the opportunity to compare more closely the spectral properties of these two materials. Thus, reaction of 7,8-didehydrocholesteryl acetate with OsO_4 in dioxane gave the two osmium(VI) diesters **7** and **8**, structurally analogous to the ruthenium(VI) diesters **2** and **6**, respectively, which were separated by HPLC. Compounds **7** and **8** on silica gel had the same chromatographic mobility showed by the corresponding ruthenate esters **2** and **6** (**5** has an R_f value identical to that of **2**) and, interestingly, unlike **2** and **6**, they showed no natural tendency to convert from one to another. No trace of the osmate ester analogue to **5** was detected in the reaction mixture.

The proton spectrum of the osmate ester **7** was very similar to that of its ruthenium-containing analogue **2** with only slight differences observed in the chemical shift of H-6 and H-7 protons (**2**: H-6, δ 4.99; H-7, δ 5.44. **7**: H-6, δ 4.87; H-7, δ 4.99). The ^{13}C NMR spectra of **2** and **7** were astonishingly similar to each other as well. In particular, the carbons geminal to osmium in **7** resonated at δ 98.71 and 88.07 while in **2** these carbons resonated at δ 101.03 and 88.95. The similarity in the NMR spectra noticed between compounds **2** and **7** was also observed between the asymmetric ruthenate ester **6** and its osmium-containing analogue **8** (see Experimental section); this was a confirmation of the structural similarities of the analogous compounds **2** and **7**, and **6** and **8**.



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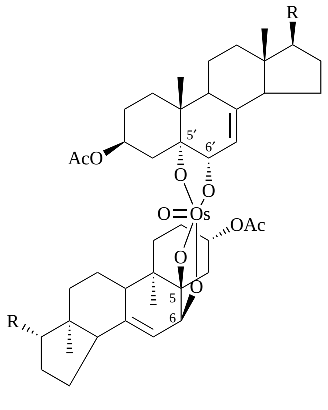


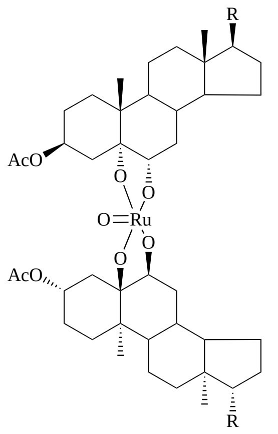
8

$R = C_8H_{17}$

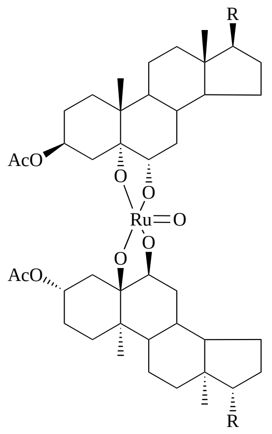
Further evidence for the structure of osmate esters **7** and **8** came from FAB mass spectrometry. These compounds, unlike their ruthenium-containing analogues, showed FABMS spectra that included abundant ion clusters for the quasi-molecular ions at *m/z* 1120–1125, compatible with the expected molecular formula of $C_{58}H_{92}OsO_9$ for both.

Frustratingly, once more the desired definitive confirmation of the structure of the ruthenate esters **2**, **5** and **6** by X-ray analysis could not be obtained because neither of these compounds gave crystals suitable for crystallographic analysis; nor could the osmate esters **7** and **8** be induced to crystallize.

At this stage, we decided to test whether also cholesteryl acetate, a molecule closely related to 7,8-didehydrocholesteryl acetate, could give ruthenium(VI) diesters structurally similar to compounds **2**, **5** and **6** on oxidation with RuO_4. Indeed, when cholesteryl acetate was mixed with equimolar amounts of RuO_4 at room temperature, a brownish precipitate was immediately formed. However, the amount of the solid recovered after suction filtration of the reaction mixture was consistently less than that derived from the reaction of 7,8-didehydrocholesteryl acetate with RuO_4. ^1H and ^{13}C NMR analysis of this solid showed that it was mainly composed of a 4:1 mixture of the ruthenium(VI) diesters of cholesteryl acetate **9** and **10** contaminated by 5% of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one.[20] HPLC



9



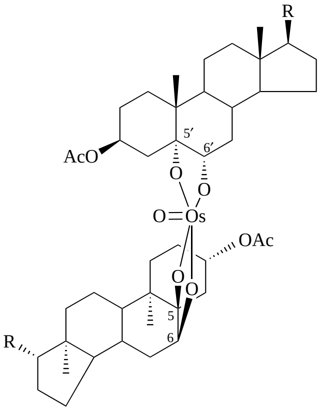
10

R = C_8H_{17}

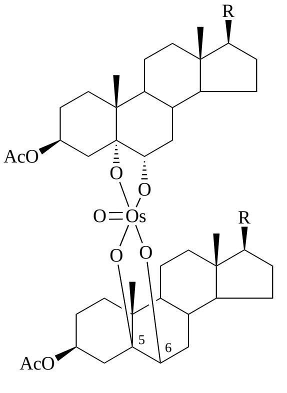
separation (hexane–EtOAc, 88:12) of the above mixture gave pure **9** (1.5 mg, 1% yield) while compound **10** could not be recovered after the HPLC run due to its decomposition. The small amount of **9** available and its instability prevented the acquisition of a ^{13}C NMR spectrum of the pure substance. However, the ^{13}C NMR spectrum of the crude solid recovered from the reaction mixture contained, *inter alia*, four signals in the range 85–105 ppm that strongly suggested the presence of both the ruthenium(VI) diesters of cholesteryl acetate **9** and **10** in the mixture. In particular, the signals resonating at δ 102.51 and 87.82 were attributed to compound **10** because they were reminiscent of the C-5 and C-6 carbons of the ruthenium(VI) diester **2** (in **2** C-5 and C-6 resonated at δ 101.03 and 88.95, respectively) while those at δ 95.59 and 93.64 were reminiscent of the same carbons in diester **5** (**5**: C-5, δ 95.64; C-6, δ 94.30) thus indicating that they belong to compound **9**. Further corroboration for the above deduction came from the analysis of the ^{1}H NMR spectrum of the same mixture. It contained pairs of signals pertinent to compounds **9** and **10** in the approximate ratio of 4:1. In particular, the H-6 protons for **9** and **10** resonated as double doublets at δ 5.14 and 5.22 (J = 10.2 and 7.3 Hz), respectively, while the H_{ax}-3 protons were seen at δ 4.78 and 4.88, respectively, and had the normal appearance for A/B *trans* steroidal units.[17] The double doublet signal resonating at δ 2.53 (J = 13.2 and 4.9 Hz) was easily attributed to the H_{eq}-4 proton of **9** while the Me-19 and Me-18 protons of **9** resonated at δ 1.21 and 0.65 and at δ 1.20 and 0.67 for **10**. In addition, the proton spectrum of the mixture also included two one-proton signals resonating at δ 2.28 (m) and −0.06 (ddd, J = 11.7, 11.7 and 10.2 Hz) that were attributed respectively to the H_{eq}-7 and H_{ax}-7 protons of **9** by decoupling experiments. ^{1}H NMR analysis of pure **9** confirmed the correctness of the above attributions. The rather high chemical shift value for the H_{eq}-4 protons in **9** was not surprising since it was similar to that observed for this proton in **5** and in **6**. However, the upfield position of the H_{ax}-7 proton initially appeared rather strange. Inspection of the molecular model of **9** revealed that this proton is situated in the region of space opposite the oxygen atom of the Ru=O group, near ruthenium. It seems reasonable to hypothesize that the vicinity of the H_{ax}-7 to the metal could be responsible for the upfield position of this proton.

Interestingly, the FABMS spectrum of **9**, unlike that of **5**, included an abundant ion cluster for the quasi-molecular ion at 1036–1044 and, as observed for **5**, it contained another ion cluster at *m*/*z* 921–928 probably derived from the $(M + Na)^+$ ion by loss of a side-chain. The ESIMS spectrum of **9** was similar to that of **5**. It indicated a molecular mass of 3115.3 corresponding to a trimeric species of **9** and included an ion cluster centred at *m*/*z* 1039.8 $(M + H)^+$ and a large peak at *m*/*z* 925.8 corresponding, as for **5**, to the triply charged ion of the trimeric species in which three side-chains have been lost. Also in this case, the isotopic patterns could not be detected due to the low resolution of the instrument.

Reaction of cholesteryl acetate with OsO_4 in dioxane afforded two main products. One of them, **11**, possesses an asymmetric structure analogous to that of ruthenium(VI) diesters **6** and its osmium containing analogue **8**. Like these compounds, **11** showed a doubling of all the NMR resonances. Furthermore, as for compound **9**, the proton spectrum of **11** included a double double doublet signal at a chemical shift value near to zero (δ −0.27; J = 12.4, 12.4 and 10.2 Hz) and a double doublet signal at δ 2.31 (dd, J = 13.5 and 5.1 Hz). These protons were attributed, respectively, to the H_{ax}-7 and H_{eq}-4 protons of the upper steroidal subunits of **11** by examination of the molecular model of this compound which revealed the position of the protons in question relative to the Os=O group to be the same as that observed for these protons relative to the Ru=O group in diester **9**. This suggested that the Os=O group possesses a magnetic anisotropy similar to that exhibited by the Ru=O group. As a confirmation of the above conclusion, the proton spectrum of the second reaction product, **12**, in which one of the two steroidal moieties possesses an A/B *cis* junction, included a singlet methyl resonance at δ 0.24, a very upfield position for an angular methyl in the steroid nucleus. Inspection of the molecular model of **12** showed that the above resonance must be attributed to Me-19 of the A/B *cis* steroidal unit that is located, like the H_{ax}-7 protons in **9** and **11**, in the region of space opposite the oxygen atom of the Os=O group, near the metal.



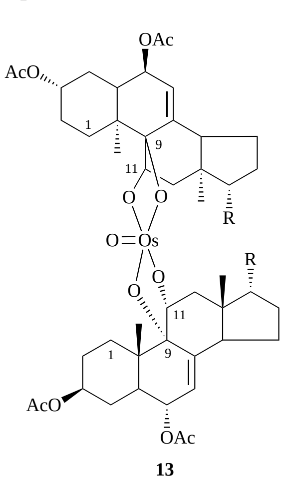
11



12

R = C_8H_{17}

We had previously noticed, but not rationalized, a similar strong shielding effect for the H_{ax}-1 protons in the C-9–C-11 steroidal osmium(VI) diester **13**.[4] Examination of the molecular model of this compound showed once again that the H_{ax}-1 protons are located in the hypothesized shielding region of the Os=O group, near the osmium atom.



13

R = C_8H_{17}

As far as we know this is the only comparative study carried out so far involving ruthenate and osmate esters.

^{1}H NMR evidence for the isomerization of ruthenium(VI) diesters 2, 5 and 6

^{1}H NMR spectroscopy was used to study the above described isomerization process involving the ruthenium(VI) diesters **2**, **5** and **6**. Pure samples of **2**, **5** and **6** (2 mg each) were dissolved in $CDCl_3$, to the solutions was added silica gel and the suspensions were stirred at room temperature. At regular intervals the brownish solutions were recovered and checked by ^{1}H NMR spectroscopy. The relative height of the Me-18 resonances of the isomeric ruthenium(VI) diesters was taken as a probe to follow the conversion. Thus, ^{1}H NMR analysis revealed that compound **5** had completely transformed into a 6 : 1 mixture of diesters **6** and **2** within a 30 min period. Interestingly, in the course of the above conversion no formation of the hydrolysis product, the diol **3**, or of the α-hydroxy ketone **4**, was noticed. Diester **6**, in turn, only transformed to the isomer **2**, not **5**, and the isomerization was rather slow and incomplete. In particular, when the amount of **2** reached about 20% of the mixture of **2** and **6**, signals from diol **3** began to be detectable in the proton spectrum of the mixture. From this time on no appreciable variation of the ratio **6** : **2** was noticed while the amount of diol **3** increased with time. After about 6 h, the complete disappearance of both diesters **2** and **6** occurred, in favour of **3**. This result seems to suggest that the little amount of **2** present in the mixture of **6** and **2** obtained from the isomerization of **5** could derive from **5** *via* **6** though the direct conversion **5**→**2** cannot be *a priori* ruled out. Analogously, diester **2**, under the same conditions initially converted into **6** to a 10% extent (*ca.* 1 h) but completely transformed to **3** in 16 h; during this period the amount of **6** remained approximately constant. No formation of diester **5** was noticed in this case either.

The above data indicated that diester **5**, the first formed product of 7,8-didehydrocholesteryl acetate with RuO_4, is the least stable of the three isomers **2**, **5** and **6** and that it converts irreversibly to the isomer **6**. The latter, in turn, seems to be in equilibrium with the third isomer **2**; this equilibrium favours compound **6**, the more stable of the three isomers. Finally, though in the isomerization process involving **6** the accumulation of **2** before the appearance of the hydrolysis product **3** seems to suggest that **2** alone hydrolytically cleaves to **3**, the hydrolysis of **6** itself cannot be ruled out provided that the interconversion of **2** and **6** is reasonably fast relative to their hydrolysis rate. All the above can be summarized as shown below.

$$\begin{tikzcd}
\mathbf{5} \arrow[r] & \mathbf{6} \arrow[rr, shift left] \arrow[dr] & & \mathbf{2} \arrow[ll, shift left] \arrow[dl] \\
 & & \mathbf{3} &
\end{tikzcd}$$

The isomerization sequence **5**→**6**→**2** that is deduced from the above experiments indicates that during this process the sequential rearrangement of the two steroidal subunits belonging to **5** does occur. In fact, the examination of the molecular model of **5** reveals that the transformation of **5** to **6** requires only the rearrangement of one of the two steroidal subunits implying its rotation of about 180° around an axis perpendicular to the ring system of the steroidal skeleton in such a way that the B/C/D ring portion of the moving steroid and the A ring of the other one are approximately found on the same side of the basal plane of the pyramid. The result of this movement is that the Ru–O(C-5) bond exchanges with the Ru–O(C-6) bond. Similarly, another movement of the same type should occur to the other steroidal portion of the molecule to obtain **2** from **6**. If a mechanism of this kind works it seems improbable that a direct conversion of **5** to **2** (without passing through **6**) could occur.

Conclusions

In conclusion, a detailed study concerning the reaction of 7,8-didehydrocholesteryl acetate and cholesteryl acetate with RuO_4 and OsO_4 has been carried out. The results presented demonstrate that both the oxidative processes involving these oxides proceed through ruthenium(VI) and osmium(VI) diester intermediates having analogous structures. A careful spectral comparison of the two materials has been conducted which conclusively demonstrates a strong similarity between their NMR properties.

The rigid skeleton of the steroidal nucleus has given us the opportunity of observing the magnetic influence of the Os=O and Ru=O groupings on the chemical shift values of some near-in-space protons. The data collected clearly indicate that the Ru=O and Os=O groups act in a very similar fashion and thus that they must possess very similar magnetic anisotropy properties.

In addition, the ability of the isomeric ruthenium(VI) diesters of 7,8-didehydrocholesteryl acetate to interconvert to one another in mild acidic conditions has been observed and spectroscopically studied, a phenomenon not observed for their osmium-containing analogues.

Finally, our results are in line with those recently reported by Sharpless and co-workers.[11] They have, in fact, demonstrated that Ru^{VIII} structures calculated by DFT (density functional theory) agree closely with X-ray structures of the corresponding Os complexes and that in theoretical calculations ruthenium can be taken as a good model for osmium.[11]

The reported data also fill in, in part, the almost complete lack of structural data for ruthenium diester compounds.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker WM 270 and 400 spectrometers in $CDCl_3$ solutions. $CDCl_3$ (99.8%) was purchased from Merck. Proton chemical shifts were referenced to the residual $CHCl_3$ signal (7.26 ppm). ^{13}C NMR chemical shifts were referenced to the solvent ($CDCl_3$: 77.0 ppm). J and $w_{\frac{1}{2}}$ values are given in Hz throughout. Electrospray ionization mass spectra (ESIMS) were recorded on a Bio-Q triple quadrupole instrument (Micromass). Fourier transform IR (FTIR) spectra were obtained with a Perkin-Elmer 1760-X FTIR spectrophotometer. UV spectra were recorded on a Perkin-Elmer lambda 7 spectrophotometer. ε Values are given in units of $dm^3\ mol^{-1}\ cm^{-1}$. FAB mass spectra (positive) were determined with a double-focusing mass spectrometer (ZAB 2SE) using 3-nitrobenzyl alcohol as the matrix. High-performance liquid chromatography (HPLC) was carried out using a Varian 2510 pump equipped with a Waters dual cell refractometer using Hibar LiChrosorb Si-60 (250 × 10 mm, and 250 × 4 mm) columns. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter in $CHCl_3$ solutions and are given in units of $10^{-1}\ deg\ cm^2\ g^{-1}$. Column chromatography was carried out on Merck silica gel 40 (70–230 mesh). Thin-layer chromatography (TLC) analyses were performed on precoated silica gel F_{254} plates (0.25 and 0.5 mm thick, Merck).

Synthesis of ruthenium(VI) diesters 5

To a solution of $NaIO_4$ (990 mg, 4.6 mmol) in H_2O (7 ml), $RuO_2\cdot 2H_2O$ (142 mg, 0.84 mmol) was added under stirring. When the black RuO_2 disappeared and the aqueous solution became yellow (10 min), acetone (20 ml) was added to precipitate excess $NaIO_4$. The suspension was centrifuged and the supernatant collected and added at room temperature to a solution of 7,8-didehydrocholesteryl acetate (300 mg, 0.70 mmol) in acetone (15 ml) in one portion. The brownish material that separated almost immediately was recovered by suction filtration and desiccated. The recovered solid (30 mg, 5% yield) was dissolved in $CDCl_3$ and checked by silica gel TLC analysis (hexane–EtOAc, 7 : 3; one spot at R_f 0.4). Immediate ^{1}H NMR

(400 MHz) analysis of a $CDCl_3$ solution of the above material showed it to be composed of almost pure (95%) ruthenate diester **5** contaminated by 3–5% of a mixture of diesters **2** and **6**. The filtrate was concentrated and the resulting aqueous suspension extracted three times with $CHCl_3$ to give 260 mg of a mixture of **3** and **4** that were separated by column chromatography using hexane–EtOAc (7 : 3) as eluent; 84 mg of **3** (26% yield) and 162 mg of **4** (51% yield) were obtained. The same reaction conducted at −70 °C as previously reported[2] gave compounds **3**, **4** and **5** in 22, 50 and 4% yields, respectively.

5: $[\alpha]_D$ 0 (*c* 0.03; $CDCl_3$); ν_{max}(film)/cm^{-1} 1733 (s), 1471 (m), 1451 (w), 1382 (m), 1365 (m), 1245 (s), 1049 (w), 1028 (m), 955 (m), 810 (w), 838 (w), 733 (m); δ_H($CDCl_3$, 400 MHz) 5.33 (1H, br d, *J* 1.5, H-7), 5.08 (1H, br d, *J* 2.4, H-6), 4.81 (1H, m, H_{ax}-3), 2.67 (1H, dd, *J* 13.7, 4.4, H_{eq}-4), 2.41 (1H, br dd, *J* 9.3, 9.3, H-14), 1.99 (3H, s, acetate), 1.26 (3H, s, CH_3-19), 0.91 (3H, d, *J* 6.3, CH_3-21), 0.86 (6H, d, *J* 6.8, CH_3-26 and CH_3-27), 0.54 (3H, s, CH_3-18); δ_C($CDCl_3$, 100.1 MHz) 170.09, 118.38, 95.64, 94.30, 69.64, 56.69, 54.34, 42.22, 41.44, 39.59, 39.37, 39.01, 36.45, 36.18, 35.23, 30.21, 28.12, 28.12, 26.64, 24.61, 23.66, 22.72, 22.60, 21.30, 20.67, 18.68, 17.99, 11.70; *m*/*z* (FAB) significant ion clusters are present at 941–946 $(M + Na - \text{side-chain})^+$ and 919–923 $(M + H - \text{side-chain})^+$; *m*/*z* (ESI) 3104.8 $(3M + H)^+$, 1035.9 $(M + H)^+$, 921.9 $(M + H - \text{side-chain})^+$.

Isomerization of diesters 2, 5 and 6

Isomerization of diesters **2**, **5** and **6** was performed as detailed in the Results and discussion section. Spectral data for compound **2** are reported in ref. 2.

6: $[\alpha]_D$ −23.6 (*c* 0.03; $CDCl_3$); ν_{max}(film)/cm^{-1} 1735 (s), 1470 (m), 1452 (w), 1378 (m), 1365 (m), 1244 (s), 1049 (w), 1027 (m), 957 (w), 911 (w), 805 (m), 792 (m), 767 (m), 725 (s); λ_{max}(hexane)/nm 349 (ε 2570), 550 (ε 675); δ_H($CDCl_3$, 400 MHz) 5.44, 5.33 (each 1H, br s, both $w_{\frac{1}{2}}$ 5.4, H-7), 5.00, 4.96 (each 1H, br d, both *J* 2.0, H-6), 4.79, 4.67 (each 1H, seven-line multiplet, H_{ax}-3), 2.59 (1H, dd, *J* 13.7 and 4.9, H_{eq}-4′), 2.29 (1H, br dd, *J* 9.0 and 9.0, H-14), 2.02, 1.99 (each 3H, s, acetate), 1.23, 1.22 (each 3H, s, CH_3-19), 0.922, 0.917 (each 3H, d, both *J* 5.9, CH_3-21), 0.86, 0.84 (each 6H, d, both *J* 6.3, CH_3-26 and CH_3-27), 0.56, 0.50 (each 3H, s, CH_3-18); δ_C($CDCl_3$, 100.1 MHz) 170.43, 169.97, 144.93, 142.19, 118.02, 117.02, 100.69, 94.65, 94.26, 89.52, 70.60, 70.14, 55.94, 55.83, 54.11, 53.98, 43.43, 43.39, 42.06, 41.80, 40.90, 40.60, 39.52, 39.46, 38.92, 38.54, 37.93, 36.15, 36.11, 36.08, 36.03, 35.90, 34.82, 30.48, 28.03, 28.00, 27.84, 26.73, 26.61, 24.05, 23.73, 22.86, 22.80, 22.76, 22.71, 22.54, 22.51, 21.85, 21.39, 21.27, 21.00, 18.82, 18.78, 18.74, 18.54, 12.06, 11.68; *m*/*z* (FAB) significant ion clusters are present at 941–946 $(M + Na - \text{side-chain})^+$ and 919–923 $(M + H - \text{side-chain})^+$; *m*/*z* (ESI) 3104.7 $(3M + H)^+$, 1035.7 $(M + H)^+$, 921.6 $(M + H - \text{side-chain})^+$.

Synthesis of osmium(VI) diesters 7 and 8

To 7,8-didehydrocholesteryl acetate (50 mg) dissolved in dioxane (5 ml), OsO_4 (100 mg) was added. After 10 min, silica gel TLC analysis revealed the complete disappearance of the starting product and the formation of two brownish products having the very same R_f value of the ruthenium(VI) diesters **2**, **5** and **6**. The reaction mixture was evaporated and subjected to HPLC separation on a Hibar LiChrosorb Si-60 (250 × 10) column using hexane–EtOAc (88 : 12) as eluent to give 9.0 mg (14% yield) and 10.2 mg (16% yield) of diesters **7** and **8**, respectively.

7: $[\alpha]_D$ 0 (*c* 0.04; $CDCl_3$); ν_{max}(film)/cm^{-1} 1737 (s), 1469 (m), 1455 (w), 1378 (m), 1366 (m), 1243 (s), 1049 (w), 1025 (m), 994 (m), 911 (w), 869 (w), 830 (w), 693 (w), 679 (w), 618 (m); λ_{max}(hexane)/nm 278 (ε 4519), 322 (sh, ε 2808), 469 (ε 356), 562 (ε 237); δ_H($CDCl_3$, 400 MHz) 4.99 (1H, br s, $w_{\frac{1}{2}}$ 5.2, H-7), 4.93 (1H, m, H_{ax}-3), 4.87 (1H, br d, *J* 2.2, H-6), 1.91 (3H, s, acetate), 1.26 (3H, s, CH_3-19), 0.91 (3H, d, *J* 5.9, CH_3-21), 0.86 (6H, d, *J* 6.6, CH_3-26 and CH_3-27), 0.55 (3H, s, CH_3-18); δ_C($CDCl_3$, 100.1 MHz) 169.51, 144.75, 117.04, 98.71, 88.08, 69.71, 55.99, 54.17, 43.38, 41.76, 39.49, 39.44, 39.08, 37.17, 36.06, 31.14, 30.88, 28.01, 27.85, 26.91, 23.77, 22.77, 22.77, 22.54, 21.31, 21.14, 19.08, 18.81, 12.01; *m*/*z* (FAB) significant ion clusters are present at 1144–1150 $(M + Na)^+$, 1120–1125 $(M + H)^+$, 1102–1110 $(M + Na - CH_2CO)^+$, 1060–1068 $(M + H - CH_3COOH)^+$.

8: $[\alpha]_D$ −2.3 (*c* 0.03; $CDCl_3$); ν_{max}(film)/cm^{-1} 1743 (s), 1470 (m), 1450 (w), 1383 (m), 1369 (m), 1247 (s), 1028 (m), 1003 (m), 837 (w), 762 (w), 697 (w), 622 (w); λ_{max}(hexane)/nm 280 (ε 5308), 332 (sh, ε 3056), 466 (ε 236), 559 (ε 73); δ_H($CDCl_3$, 400 MHz) 5.05, 5.03 (each 1H, br s, both $w_{\frac{1}{2}}$ 5.4, H-7), 4.95, 4.84 (each 1H, br d, both *J* 1.6, H-6), 4.76, 4.67 (each 1H, seven-line multiplet, H_{ax}-3), 2.32 (1H, dd, *J* 12.4 and 4.1, H_{eq}-4′), 2.01, 1.99 (each 3H, s, acetate), 1.26, 1.24 (each 3H, s, CH_3-19), 0.90 (each 6H, d, *J* 6.6, CH_3-21), 0.86, 0.83 (each 6H, d, CH_3-26 and CH_3-27), 0.54, 0.48 (each 3H, s, CH_3-18); δ_C($CDCl_3$, 100.1 MHz) 170.46, 170.02, 144.80, 142.60, 117.23, 117.12, 98.35, 93.68, 91.50, 88.61, 70.52, 69.85, 55.89, 55.76, 54.02, 53.10, 43.40, 43.33, 41.27, 40.49, 39.63, 39.50, 39.43, 38.88, 38.72, 38.45, 37.47, 36.13, 36.08, 36.01, 34.92, 30.58, 30.43, 29.69, 28.03, 28.00, 27.84, 26.64, 26.50, 24.08, 23.72, 22.78, 22.70, 22.54, 21.88, 21.40, 21.17, 20.94, 19.05, 18.87, 18.80. 18.73, 12.05, 11.64; *m*/*z* (FAB) significant ion clusters are present at 1144–1150 $(M + Na)^+$, 1120–1125 $(M + H)^+$, 1102–1110 $(M + Na - CH_2CO)^+$, 1060–1068 $(M + H - CH_3COOH)^+$.

Synthesis of ruthenium(VI) diesters 9 and 10

A solution of cholesteryl acetate (300 mg, 0.69 mmol) in 15 ml of acetone was treated at room temperature as described above for 7,8-didehydrocholesteryl acetate with 27 ml of an acetone–water (3 : 1, v/v) solution of RuO_4 prepared from 140 mg of $RuO_2{\cdot}2H_2O$ (0.83 mmol). The brownish precipitate was recovered by suction filtration, desiccated and dissolved again in $CDCl_3$. ^1H and ^{13}C NMR analyses revealed that it was composed of a mixture of ruthenium(VI) diesters **9** and **10** in the approximate ratio of 4 : 1 contaminated by a 5% amount of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one.[19] HPLC separation (hexane–EtOAc, 88 : 12) of the crude solid afforded 1.5 mg (1%) of pure **9**.

9: δ_H($CDCl_3$, 400 MHz) 5.14 (1H, dd, *J* 9.8, 7.3, H-6), 4.78 (1H, seven-line multiplet, H_{ax}-3), 2.53 (1H, dd, *J* 13.2, 4.9, H_{eq}-4), 2.28 (1H, m, H_{eq}-7), 1.99 (3H, s, acetate), 1.21 (3H, s, CH_3-19), 0.89 (3H, d, *J* 6.8, CH_3-21), 0.85 (6H, d, *J* 6.8, CH_3-26 and CH_3-27), 0.65 (3H, s, CH_3-18), −0.06 (*J* 11.7, 11.7, 10.2, H_{ax}-7); δ_C($CDCl_3$, 100.1 MHz) (selected data from the crude reaction mixture) 170.14, 95.59, 93.64, 69.69, 56.83; *m*/*z* (FAB) significant ion clusters are present at 921–928 $(M - \text{side-chain})^+$, 1036–1044 $(M + H)^+$; *m*/*z* (ESI) 3115.3 $(3M + H)^+$, 1039.8 $(M + H)^+$, 925.8 $(M + H - \text{side-chain})^+$.

10: δ_H($CDCl_3$, 400 MHz) (data from the crude reaction mixture) 5.22 (1H, dd, *J* 9.8, 7.3, H-6), 4.88 (1H, seven-line multiplet, H_{ax}-3), 1.92 (3H, s, acetate), 1.20 (3H, s, CH_3-19), 0.68 (3H, s, CH_3-18); δ_C($CDCl_3$, 100.1 MHz) (selected data from the crude reaction mixture) 169.60, 102.51, 87.82, 69.69, 56.61.

Synthesis of osmium(VI) diesters 11 and 12

To cholesteryl acetate (80 mg, 0.19 mmol) dissolved in dioxane (2 ml), OsO_4 (100 mg) dissolved in 3 ml of dioxane was added in one portion. After 12 h silica gel TLC analysis revealed the disappearance of the starting product and the formation of two major products. The reaction mixture was evaporated and subjected to separation on a TLC plate using light petroleum (bp 40–70 °C)–Et_2O (6 : 4) as eluent to give 24 mg (22% yield) and 6.3 mg (6%) of diesters **11** and **12**, respectively.

11: azure crystalline solid; $[\alpha]_D$ −3.1 (*c* = 0.15; $CDCl_3$); ν_{max}(film)/cm^{-1} 1737 (s), 1469 (m), 1448 (m), 1377 (m), 1366 (m), 1244 (s), 1022 (w), 990 (w), 823 (m), 757 (s), 685 (m), 603 (w); λ_{max}(hexane)/nm 281 (ε 4270), 332 (sh, ε 2678), 475 (ε 360); δ_H($CDCl_3$, 400 MHz) 4.87, 4.69 (each 1H, dd, both *J* 10.2, 6.6, H-6), 4.75, 4.65 (each 1H, seven-line multiplet, H_{ax}-3), 2.31 (1H, dd, *J* 13.5 and 5.1, H_{eq}-4′), 2.16 (1H, m, H_{eq}-7), 2.02, 1.94 (each 3H, s, acetate), 1.23, 1.22 (each 3H, s, CH_3-19), 0.91, 0.89 (each 3H, d, both *J* 6.3, CH_3-21), 0.85, 0.83 (each 6H, d, both *J* 6.3, CH_3-26 and CH_3-27), 0.64, 0.61 (each 3H, s, CH_3-18), −0.27 (*J* 12.4, 12.4, 10.2, H_{ax}-7); δ_C($CDCl_3$, 100.1 MHz) 171.51, 170.82, 100.66, 95.27, 90.93, 86.61, 70.41, 69.48, 55.91, 55.53, 55.23, 54.80, 42.80, 42.63, 42.09, 42.03, 39.89, 39.53, 39.08, 39.03, 38.89, 38.65, 37.76, 37.57, 35.73, 35.61, 35.28, 35.20, 33.71, 33.41, 32.45, 31.56, 28.50, 28.42, 27.64, 27.51, 27.45, 25.61, 25.51, 23.46, 23.38, 23.02, 22.16, 22.06, 21.90, 21.15, 20.71, 20.04, 19.97, 17.98, 17.90, 17.76, 17.42, 11.28, 10.92; *m/z* (FAB) significant ion clusters are present at 1145–1153 $(M + Na)^+$, 1123–1131 $(M + H)^+$, 1063–1071 $(M + H - CH_3COOH)^+$.

12: violet crystalline solid; $[\alpha]_D$ +17.7 (*c* 0.08; $CDCl_3$); ν_{max}(film)/cm^{-1} 1736 (s), 1466 (m), 1445 (m), 1377 (m), 1369 (m), 1242 (s), 1023 (m), 991 (m), 826 (w), 756 (w), 685 (w), 666 (w), 606 (w); λ_{max}(hexane)/nm 283 (ε 4044), 337 (sh, ε 1865), 478 (ε 253); δ_H($CDCl_3$, 400 MHz) 5.12 (1H, br s, $w_{\frac{1}{2}}$ 8.8, H_{ax}-3 of the A/B *cis* unit), 4.91 (1H, seven-line multiplet, H_{ax}-3 of the A/B *trans* unit), 4.75 (1H, dd, *J* 9.3, 7.8, H-6 of the A/B *trans* unit), 4.50 (1H, br d, *J* 3.4, H-6 of the A/B *cis* unit), 2.58 (1H, dd, *J* 13.5, H_{eq}-4 of the A/B *trans* unit), 2.11, 1.89 (each 3H, s, acetate), 1.22 (3H, s, CH_3-19 of the A/B *trans* unit), 0.90 (6H, d, *J* 6.3, CH_3-21), 0.86 (12H, d, *J* 6.8, CH_3-26 and CH_3-27), 0.66, 0.65 (each 3H, s, CH_3-18), 0.24 (3H, s, CH_3-19 of the A/B *cis* unit); δ_C($CDCl_3$, 100.1 MHz) 171.32, 169.36, 99.67, 98.58, 95.94, 86.61, 69.40, 68.66, 56.89, 56.38, 56.21, 55.92, 43.46, 43.12, 42.53, 42.44, 40.41, 39.74, 39.52, 39.48, 39.35, 36.65, 36.22, 36.16, 36.08, 35.73, 34.47, 32.32, 30.87, 30.05, 29.82, 29.69, 28.25, 28.13, 28.00, 26.72, 26.40, 24.14, 24.09, 24.06, 23.64, 23.79, 22.78, 22.54, 21.74, 21.04, 20.72, 19.57, 18.69, 18.26, 12.04, 11.63; *m/z* (FAB) significant ion clusters are present at 1145–1153 $(M + Na)^+$, 1123–1131 $(M + H)^+$, 1063–1071 $(M + H - CH_3COOH)^+$.

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