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Practical Method for the Absolute Configuration Assignment of *tert*/*tert* 1,2-Diols Using Their Complexes with $Mo_2(OAc)_4$

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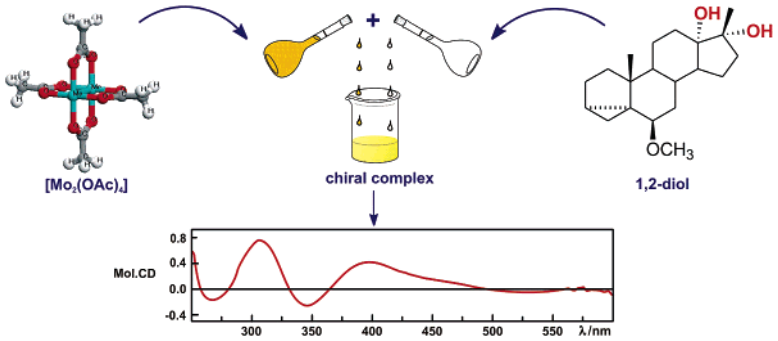

We describe here an application of the practical, simple, and reliable approach for the determination of the absolute configuration of sterically demanding *tert*/*tert vic*-diols. According to this method, it is only necessary to mix dimolybdenum tetraacteate and a chiral diol in DMSO and record the CD spectra in the 250−650 nm spectral range. From the sign of the CD bands occurring at around 310, 350, and 400 nm, it is possible to establish the chirality of the diol unit expressed by the sign of the O−C−C−O torsion angle. Because the preferred conformation of the diol in the formed complex is known, we are able to determine the absolute configuration of the carbon atoms in the diol subunit even in flexible *tert*/*tert vic*-diols.

Introduction

Chiral *vic*-diols represent an important group of organic compounds due to their common occurrence in nature both in a free form and as their respective esters. Many of them are bioactive natural products, which display very interesting and in many cases important biological activity. Moreover, *vic*-diols play a key role in organic chemistry being widely used as chiral building blocks[1] and controllers in asymmetric processes.[2] In general, *vic*-diol moiety is present in carbohydrates, many antibiotics, vitamins, steroids, and other bioactive natural products. Among these products are brassinolides, very active plant growth promoters,[3,4] a variety of antibiotics, for example, erythromycin A,[5] oligomycin A,[6] and olivomycin A,[7] or steroidal hormones.[8]

Because the biological activity is closely related to the stereostructure of bioactive compounds, the access to the methods allowing simple and unequivocal determination of their absolute configuration is of great importance. Circular dichroism

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spectroscopy (CD) seems to be a method of choice for this purpose, especially useful in solution. This approach requires that the compounds under study exhibit measurable absorption in an accessible frequency range. Because *vic*-diols absorb below the range generally available to commercial instruments (<190 nm), a suitable chromophoric system should be introduced into the molecule prior to recording the spectra.

The exciton-coupled circular dichroism (ECCD), based on the quantum mechanical theory of coupled oscillators,[9] belongs to the methods most frequently applied to the absolute stereochemical assignment to *vic*-diols. The "dibenzoate chirality rule", introduced by Harada and Nakanishi,[10,11] was originally formulated to assign the stereochemistry of glycols. A modification made by Wiesler and Nakanishi[12] utilizes two different chromophoric systems added at two hydroxy moieties. Several suitable red-shifted chromophores have been proposed to convert hydroxyl groups of diols into derivatives that absorb light in the visible spectral region.[13,14] The ECCD method has been applied successfully also to the absolute stereochemical assignment of *vic*-diols in the form of their macrocyclic host−guest complexes with a host porphyrin tweezer.[15,16] Recently, new chromophoric systems applicable in the ECCD configurational analysis of various classes of compounds, including *vic*-diols, were reviewed.[17]

The broad applicability of the exciton chirality method is due to the very characteristic shape of the CD bands, the large CD effects in most cases, and its nonempirical character. There are, however, some limitations for cases undergoing conformational changes and for applications to acyclic compounds. The perfect solution to circumvent the problem of conformational mobility of flexible diols could be their transformation into conformationally defined derivatives. Although attempts have been made to obtain such derivatives,[16,18,19] a correct application of the exciton chirality method becomes difficult in some cases,[20,21] or the methods proposed do not have general applicability.[19,22]

In the course of our study on the application of dinuclear transition metal complexes as auxiliary chromophores in the determination of the absolute configuration of transparent molecules by means of circular dichroism spectroscopy, it was demonstrated that, until now, only dimolybdenum tetraacetate is able to form chiral complexes with diols.[23] An empirically based rule correlating a positive/negative helicity expressed by the O−C−C−O torsion angle with the sign of Cotton effects occurring in the 400−260 nm spectral range has been formulated for 1,2-diols.[23] Recently, the successful applicability of the method was further corroborated by Italian authors[24] who confirmed the dimolybdenum method to be "a very reliable, versatile, and elastic procedure for the assignment of the absolute configuration of that fundamental class of molecules, no exceptions being known to the empirical rule."

Up until now, however, the methodology was applied to sterically nonhindered *prim*/*sec*, *sec*/*sec*, and *prim*/*tert* 1,2-diols only. We decided therefore to fill in the gap. In our very recent study, the method was successfully used on *sec*/*tert vic*-diols.[25] In this paper, we decided to check the applicability of the methodology to the sterically most demanding *tert*/*tert vic*-diols. This study is undertaken for two main reasons. First, such a 1,2-diol subunit is present in many bioactive natural products. Among these products, hepatotoxic alkaloid monocrotaline, a representative of pyrrolizidine alkaloids,[26,27] or the peptide-polyketide antibiotic aurantimycin, displaying strong activity against Gram-positive bacteria,[28] can be mentioned. Second, to the best of our knowledge, a method for the determination of the absolute configuration of *tert*/*tert* 1,2-diols based on CD spectroscopy is lacking in the literature. This is most probably due to the fact that derivatization of these diols is very difficult. It is well known that esterification reactions of tertiary alcohols, in contrast to primary and secondary ones, are relatively slow and particularly susceptible to steric factors. Although some esters of tertiary alcohols such as nitrates,[29] trifluoroacetates,[30] or methanesulfonates[31] may be easily obtained, in general, esterification reaction of tertiary alcohols requires application of proper catalysts.[32,33] In many cases, however, esterification reactions of tertiary alcohols may not be successful. Sometimes they lead to a partial or complete epimerization at the chiral center.

Results

Synthesis. To achieve our goal, we have undertaken the chiroptical studies on a variety of *tert*/*tert* diols **1**−**14**, most of them specially synthesized for this purpose (Figure 1). The only exception constitutes monocrotaline (**1**), which is commercially available. In the case of synthesis of compounds **2**−**9**, the crucial step was dihydroxylation of a tetrasubstituted double bond with osmium tetraoxide. It was usually the final step of synthesis, except for compounds **3** and **7**.

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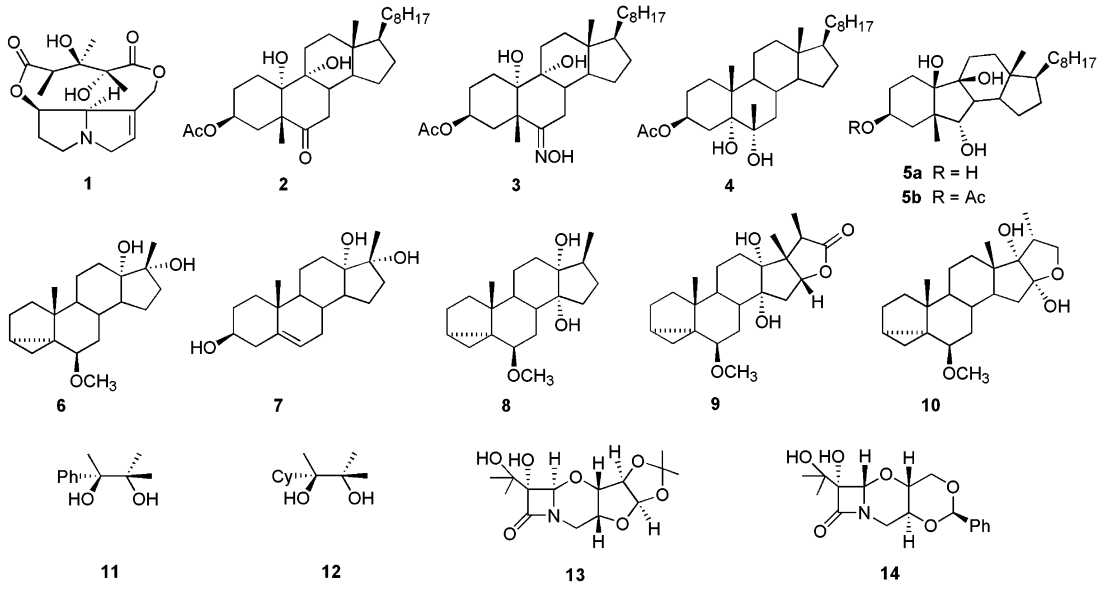
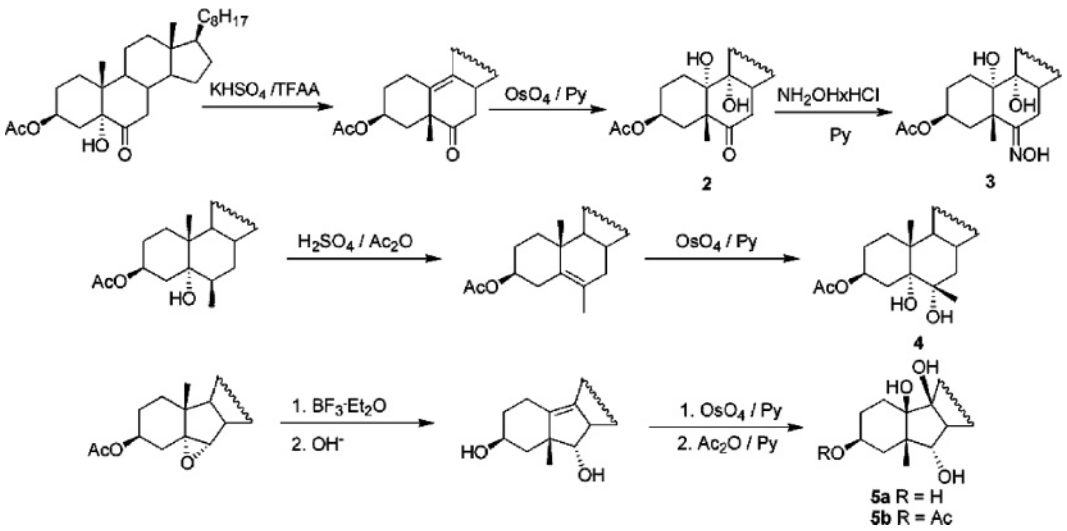


FIGURE 1. Investigated compounds.

SCHEME 1



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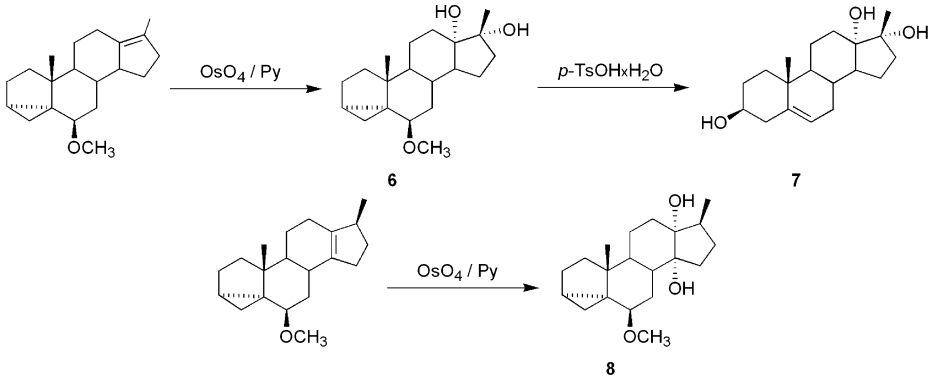

Compound **3** was obtained from diol **2** by oximation reaction of the C-6 ketone **2** with hydroxylamine in pyridine (Scheme 1), and compound **7** was obtained by cycloreversion of the *i*-steroid ether **6** (Scheme 2).

The vicinal *cis*-diol **2** was obtained by dihydroxylation of the known 3β-acetoxy-5-methyl-19-nor-5β-cholest-9(10)-en-6-one[34] with OsO_4 and careful reductive decomposition of the formed osmate with sodium bisulfite. On the basis of the literature data on dihydroxylation of the analogous 3,6-diketone,[35] the configuration of hydroxyl groups at C-9 and C-10

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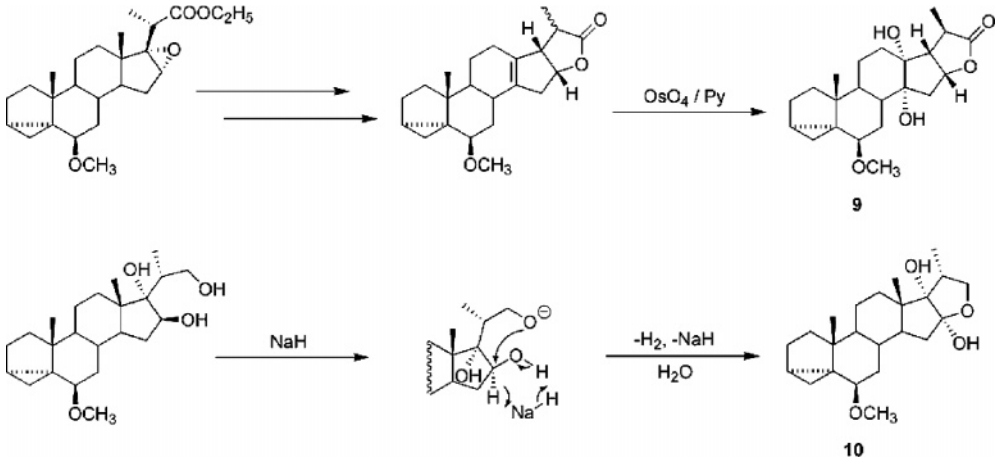
SCHEME 3



was assumed to be α, and this fact was additionally proved by the X-ray analysis (see Supporting Information). Further reaction of the diol **2** with hydroxylamine hydrochloride in pyridine afforded (*E*)-oxime **3** as the only product.

Compound **4** was also synthesized by treatment of the corresponding olefin with OsO_4 (Scheme 1). The tetra-substituted 5(6)-olefin, 3*β*-acetoxy-6-methylcholest-5-ene, was obtained according to the well-known procedure described by Fieser and co-workers.[36] The configuration of hydroxyl groups at C-5 and C-6 in the isolated product **4** was determined on the basis of its ^{1}H NMR spectrum. The presence of a characteristic septet of an axial proton corresponding to the 3α-H signal proved the α configuration of hydroxyl group at C-5 and, consequently, α configuration of hydroxyl group at C-6.

Cis-hydroxylation of 5-methyl-B,19-dinor-5*β*-cholest-9(10)-ene-3*β*,6α-diol, synthesized according to Šorm and co-workers,[37] with OsO_4 gave diol **5a** as the main product (Scheme 1). Its ^{1}H NMR spectrum showed a characteristic septet of an axial proton, which corresponds to the 3α-H signal. Conformational analysis by molecular mechanics calculations[38] made for both potential 9α,10α- and 9*β*,10*β*-dihydroxylated products allowed one to establish the 9*β*,10*β*-configuration of the isolated diol **5a**, because only in this product 3α-proton adopts an axial orientation. It seems that the determining factor of the stereochemical outcome of the dihydroxylation reaction is the presence of 6α-hydroxyl group, which hinders an approach of osmium tetraoxide from the α-side of the starting 9(10)-olefin. To confirm the stereostructure of compound **5a**, it was converted into its crystalline monoacetate **5b**. The X-ray analysis unequivocally proved 9*β*,10*β*-diol configuration and a chair conformation of ring A with axial hydrogen atom at C-3 as a consequence of equatorial orientation of the 3*β*-acetoxyl substituent (see Supporting Information).

Compounds **6** and **8** were obtained by dihydroxylation of the mixture of 13(17)- and 13(14)-olefins with OsO_4 (Scheme 2). The mixture of olefins was obtained by Wagner−Meerwein rearrangement of 17*β*-tosyloxy-androst-5-en-3*β*-ol promoted by ethylmagnesium chloride. According to the original paper by Madaeva,[39] the reaction proceeds selectively to the 13(17)-olefin. However, careful analysis of the crude product by ^{1}H NMR proved the presence of a minor product, the 13(14)-olefin. Because the rearrangement involves formation of a carbocation at C-13, it is not surprising that both tetra-substituted olefins were formed as the reaction products. Before reaction with OsO_4, the C(5)−C(6) double bond had to be protected against oxidation. For this reason, the olefin mixture was converted into 6*β*-methoxy-3α,5α-cyclosteroids (so-called *i*-steroid derivatives). The reaction with OsO_4 proceeded smoothly, affording the corresponding vicinal *cis*-diols **6** and **8**, which were separated by silica gel chromatography. Because the *i*-steroid ethers are usually oily compounds, compound **6** was subjected to cycloreversion in a routine manner to the crystalline triol **7**. The configuration of the C-13 and C-17 hydroxyl groups as well as the conformation of rings C and D was established by an X-ray analysis (see Supporting Information).

Compound **9** was also obtained by reaction of the corresponding olefin with OsO_4 (Scheme 3). The tetra-substituted 13(14)-olefin was obtained by rearrangement of 16α,17α-epoxide that was described a few years ago.[40] However, during the acid-catalyzed rearrangement, cycloreversion took place. Therefore, *i*-steroid protection for the ring B double bond and the 3*β*-OH group was reintroduced. Also, partial isomerization at C-20 took place (the epimeric ratio 20*R*:20*S* was 2:3 as established by integration of H-16*β* signals in the ^{1}H NMR spectrum of the mixture) under the reaction conditions. The 20*R*/20*S* epimeric mixture was subjected to dihydroxylation, and the isomeric vicinal *cis*-diols were separated.

The configuration at C-20 in the 20*R*-diol (compound **9**) was unequivocally established by a series of ^{1}H difference NOE experiments (Scheme 4). The irradiation of 17*β*-methyl protons in the less polar 20*R* diol **9** caused a 3% NOE enhancement of the H-16*β* signal at *δ* 4.60. There was also a weak NOE effect (1%) for the H-20 signal at 2.54 upon irradiation of H-16*β*. The more polar 20*S* epimer of diol **9** (compound **9a**) showed a 5% enhancement of the H-20 signal at 2.38 and 1.6% of the H-16*β* signal at 4.46 upon irradiation of 17*β*-methyl protons. However, the 20*S*-diol appeared to be unstable and was lost during final purification by silica gel column chromatography.

Compound **10** was obtained from the triol containing the hydroxyl groups in the positions 16*β*, 17α, and in the side chain

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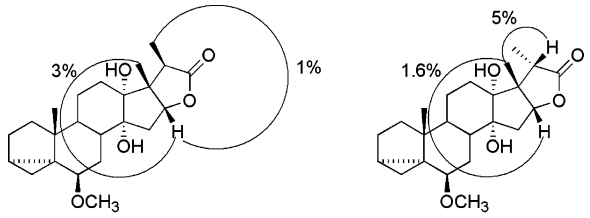
SCHEME 4



(Scheme 3).[41] The reaction with sodium hydride unexpectedly led to dehydrogenation of a secondary alcohol to the corresponding 16-ketone. The product was formed, most likely, via a cyclic mechanism outlined in Scheme 3, assuming participation of the side-chain OH group. Compound **10** exists in a hemiketal form, which is presumably in equilibrium with a hydroxy-ketone form. However, the cyclic form (the one with hydroxyl groups at C-16 and C-17 configured cis) seems to be by far more thermodynamically stable.

Chiroptical Studies. As mentioned in the Introduction, the helicity rule correlates a stereostructure of a *vic*-diol and the sign of the Cotton effects occurring between 300 and 400 nm in its CD spectra recorded in the presence of dimolybdenum tetraacetate. Until now, the rule was successfully applied to all classes of *vic*-diols, except the sterically more demanding *tert*/*tert* diols.[25] To fill in the gap, the chiroptical investigations on *tert*/*tert vic*-diols **1**−**14** were undertaken. According to the X-ray diffraction analysis,[42] the O−C−C−O torsion angle of the diol unit in monocrotaline in the solid state is positive and equals +46.9°. According to this and in agreement with the helicity rule developed before,[23] a positive sign of the Cotton effect at around 310 and 400 nm should be present in the CD spectrum of monocrotaline recorded in the presence of $Mo_2(OAc)_4$. This is indeed the case, as can be seen in Figure 2, additionally presenting the CD spectrum of the Mo-complex of 5β-cholestane-3β,5,6β-triol, a representative of *sec*/*tert vic*-diols, for comparison. In the case of the latter diol (5β-cholestane-3β,5,6β-triol) with a negative sign of the O−C−C−O torsion angle of the diol unit, the Cotton effect at 313 nm is visible as a positive minimum only.[43] Nevertheless, the tendency to form a minimum by this band is clearly visible. The shapes of CD spectra of both compounds are similar, indicating that the complexation modes for both the *sec*/*tert* and the *tert*/*tert* diols are similar.

The stability of the chiral Mo-complex of monocrotaline in solution was also investigated. In general, the signs and the relative intensities of the bands are not time-dependent. However, the intensity of all CD bands does change with time. A significant increase in intensity of all bands is observed in the first 3−5 h, whereas a very small intensity change is evident within the following hours. The time-dependent measurements at $\lambda = 350$ nm showed that the CD band intensity of chiral Mo-complex of monocrotaline becomes stabile in solution after approximately 5 h. This result demonstrates that the formation

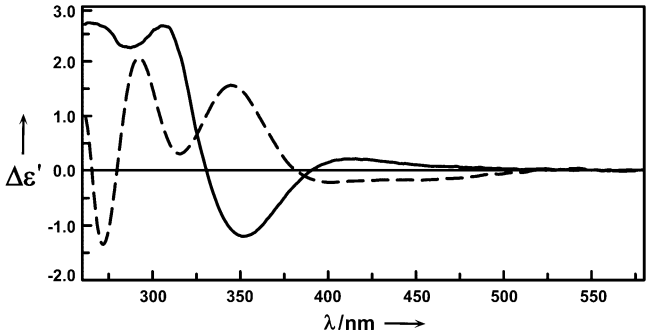


FIGURE 2. CD spectra of in situ formed Mo-complexes of monocrotaline (**1**) (−) and 5β-cholestane-3β,5,6β-triol (− − −). CD curve of 5β-cholestane-3β,5,6β-triol is 1.5 times enhanced.

of chiral Mo-complexes of *tert*/*tert vic*-diols is much slower than that of other *vic*-diols (even in comparison with *sec*/*tert vic*-diols (Figure 3)).

The replacement of carboxylate ligands of the stock complex by the chiral 1,2-diol ligand produces no significant differences in the absorption curve (Figure 4). In general, the shape and position of particular bands remain unchanged. This indicates that no considerable change of the chromophoric system of Mo_2O_8 results from such a ligand exchange and additionally may indicate that only one acetate group of the Mo_2-core is replaced by a diol ligand. However, the presence of two types of complexes, chelating (α-form) and bridging (β-form), cannot be excluded.[23,25] Their existence in solution might explain the observed time-dependence of the spectra.

To establish whether the shape of CD curves depends on the concentration ratio, the CD spectra of monocrotaline (**1**) with the Mo_2-core in 1:1, 3:1, 5:1, and 10:1 ligand-to-metal ratios were recorded. The increase of the ligand concentration resulted in an increase of the band intensity (Figure 5). CD bands at around 300 (band IV), 350 (band III), and 415 (band II) nm are well developed and clearly visible even in the ligand-to-metal ratio of 1:1. On the basis of the above-mentioned results, we decided to measure the CD spectra of other *tert*/*tert vic*-diols with the Mo_2-core in DMSO solution with a ligand-to-metal ratio of 1:1 and after approximately 3 h after mixing the components.

According to the X-ray data and conformational analysis by molecular mechanics calculations,[38] the torsion angle of the diol unit in *cis*-diol **2** is positive and amounts to +20.6°. Therefore, on the basis of the helicity rule, a positive sign of Cotton effects at around 310 and 400 nm accompanied by a negative one between both are expected in its CD spectrum with $Mo_2(OAc)_4$. As can be seen in Figure 6, the signs of CEs at 350 and 405 nm are in agreement with the predicted ones, whereas CE at 298 nm is negative, in contradiction to the expectation. This is due to the presence of the oxo group at C-6, which contributes oppositely to the overall CD spectrum in the same spectral region. After subtraction of the contributions from the oxo group, the CD band at around 300 nm becomes positive (Figure 6). After transformation of the oxo group in diol **2** into its oxime derivative **3**, all three diagnostic CD bands behave as predicted, that is, follow the helicity rule (Figure 6).

As mentioned before, the configuration of the hydroxyl groups in compound **4** is 5α,6α. Thus, the O−C−C−O torsion angle of the diol subunit is negative, and accordingly a negative sign of the CD bands at around 310 and 400 nm should be present in its CD spectrum with dimolybdenum tetraacetate. This is

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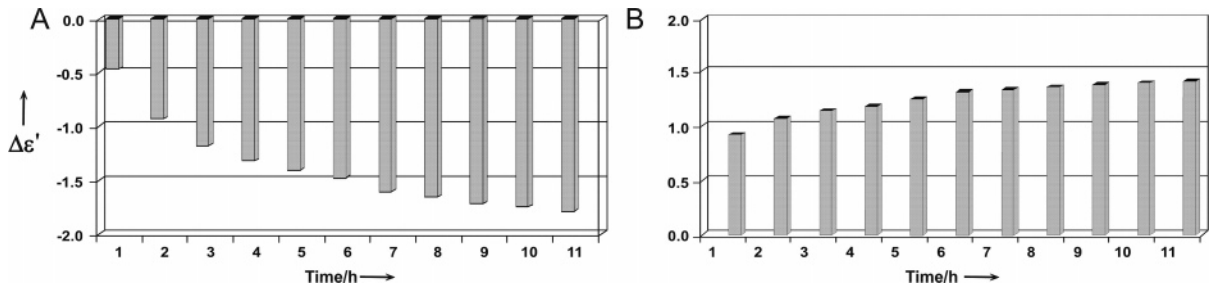

FIGURE 3. (A) Time-dependent measurements at 350 nm of in situ formed Mo-complex of monocrotaline (**1**) recorded in DMSO every 30′; (B) time-dependent measurements at 350 nm of in situ formed Mo-complex of 5β-cholestane-3β,5,6β-triol recorded every 30′.

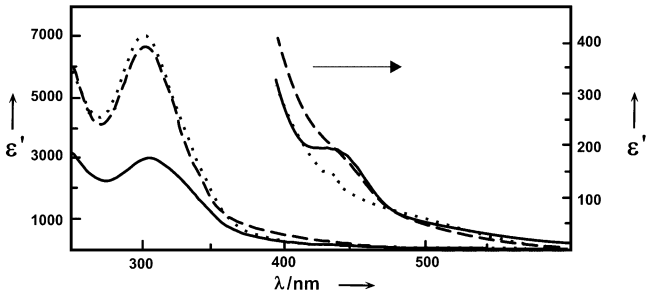

FIGURE 4. UV−vis spectra of dimolybdenum tetraacetate (−) and its in situ formed chiral complexes with monocrotaline (**1**) (− − −) and 5β-cholestane-3β,5,6β-triol (· · ·), recorded in DMSO 3 h after dissolving the components.

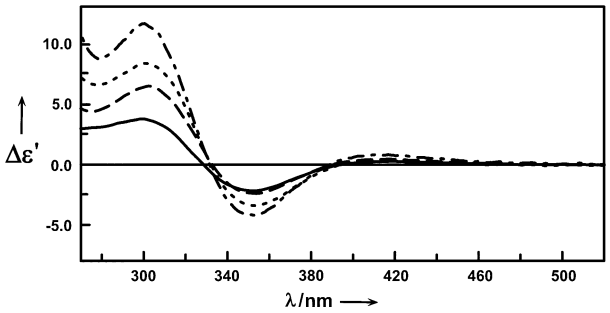

FIGURE 5. CD spectra of in situ formed Mo-complexes of monocrotaline (**1**) at ligand-to metal ratios of 1:1 (−), 3:1 (− − −), 5:1 (· · ·), and 10:1 (− · − · −).

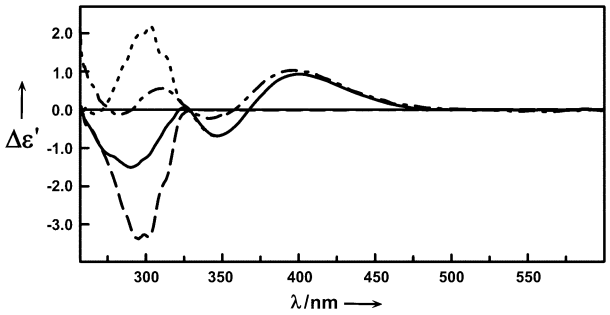

FIGURE 6. CD spectra of in situ formed Mo-complexes of *vic*-diols **2** (−) and **3** (− · − · −). CD spectrum of diol **2** without $Mo_2(OAc)_4$ (− − −) and differential curve of Mo-complex of **2** minus CD spectrum of diol **2** in DMSO (· · ·).

indeed the case, as can be seen from Figure 7. The third decisive CE at around 350 nm is predicted to be positive. In this case, however, this CD band is not well developed to a maximum, most likely due to the presence of strong minima at both its

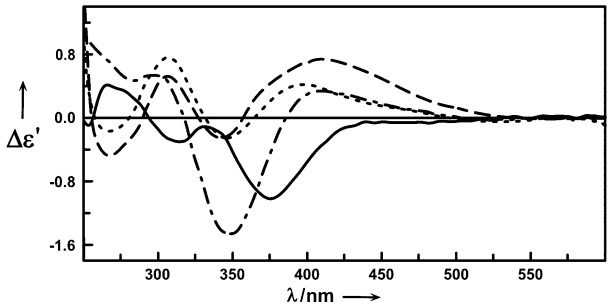

FIGURE 7. CD spectra of in situ formed Mo-complexes of *vic*-diols **4** (−), **5a** (− · − · −), **6** (· · ·), and **7** (− − −) recorded in DMSO.

sides. Nevertheless, the tendency to form a maximum is clearly visible.

An opposite situation is found in the case of diols **5a** and **5b** in which the O−C−C−O torsion angle of the 9β,10β-diol subunit is computed to be positive for **5a**. The X-ray analysis for compound **5b** also showed a positive torsion angle of the diol subunit (+17.2°) (see Supporting Information). In such cases, the helicity rule predicts the presence of positive CEs at around 310 and 400 nm and a negative one between both. The experimental curves, which consist of positive CEs for bands II and IV and of the negative band III, corroborate perfectly with the above prediction (Figure 7).

Compounds **6** and **7** possess the same 1,2-diol subunit in very similar surroundings, and therefore the shapes of their CD curves recorded in the presence of $Mo_2(OAc)_4$ are analogous (Figure 7). The positive signs of CEs at around 310 and 400 nm undeniably indicate a positive sign of the O−C−C−O torsion angle. The X-ray analysis showed the 13α,17α-configuration of hydroxyl groups in compound **7**, and consequently in compound **6**, because compound **7** was prepared from **6**. This assignment is consistent with the mechanism of cis-hydroxylation reaction, which predicts an approach of osmium tetraoxide from the less crowded α-side of the molecule, that is, from the side opposite to the existing 6β- and 10β-substituents. The molecular mechanics calculations indicated positive O−C−C−O torsion angles for compound **7** (+32.3°) and compound **6** (+29.3°), while a negative one for its local stereoisomer **8** (−26.4°).[38] Moreover, the molecular mechanics calculations revealed a boat conformation of ring C for **7** being slightly lower in energy as compared to its chair conformer. Unexpectedly, the O−C−C−O torsion angle in the X-ray structure appeared to be negative and amounted to −37.8° (see Supporting Information). The conformation of ring C in the solid state was also a boat, like for the computed structure, but the difference was for the ring D conformation. The molecular mechanics

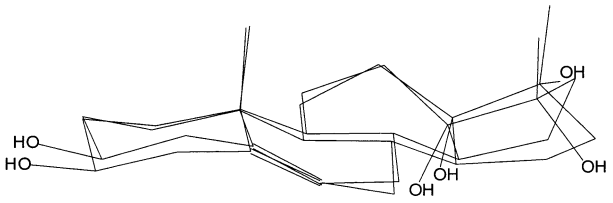

FIGURE 8. Root-mean-square fit for the X-ray structure and the calculated optimal conformation of compound **7** and overlay.

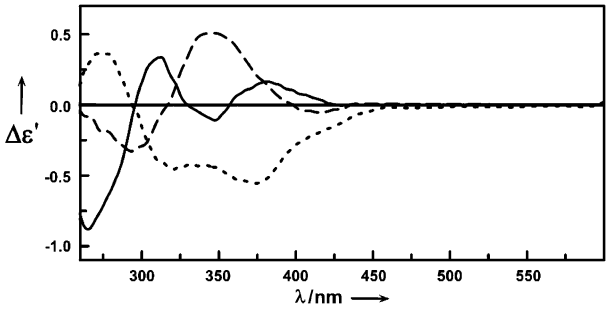

FIGURE 9. CD spectra of in situ formed Mo-complexes of *vic*-diols **8** (· · ·), **9** (− − −), and **10** (−) recorded in DMSO.

calculations show preference for an envelope conformation of the five-membered ring D with carbon atoms C-17, C-13, C-14, and C-15 in one plane and the remaining C-16 carbon atom above the plane. In the X-ray structure, ring D also assumed slightly distorted envelope conformation with C-16 out of the plane, but this time below the plane (Figure 8). Such conformation with pseudo-equatorial methyl and pseudo-axial hydroxyl groups is advantageous for intermolecular hydrogen bonding, but MM+ calculations show that it is less favored in the case of isolated molecule by about 1.2 kcal/mol. The X-ray structure is stabilized by three intermolecular hydrogen bonds: between 3β-OH and oxygen atom at C-17, between 17α-OH and oxygen atom at C-13 of the second molecule, and between 13α-OH and oxygen atom of the solvating water molecule. The CD measurements were made in diluted DMSO (anhydrous) solutions, and the positive signs of CEs at around 310 and 400 nm unequivocally indicate that the conformation in solution is different from that in solid state in agreement with the MM+ calculations.

According to the conformational analysis and molecular mechanics calculations,[38] the O−C−C−O torsion angle of the diol unit in compounds **8** and **9** is negative and equals −26.4° and −32.1°, respectively. Thus, a negative sign of the CD bands at around 310 and 400 nm is expected in the CD spectra of their Mo-complexes. The experimental CD curves agree with this expectation, although band III is not developed to a maximum for compound **8** (Figure 9). This can be explained by the presence of relatively strong minima at both sides of this band. Also, in the case of diol **10**, the signs of the CD bands in experimental curve fit the requirements of the helicity rule. In the last case, the signs of the CEs at around 310, 350, and 380 nm are positive, negative, and positive, respectively, in accordance with the calculated positive sign of the O−C−C−O torsion angle (Figure 9).

Diols **11**−**14** belong to a conformationally flexible group of compounds. Therefore, the determination of their absolute configuration requires knowledge of their conformation in the complexed form. It is well known that after ligation to the Mo_2-core an internal conformational mobility of the flexible diol

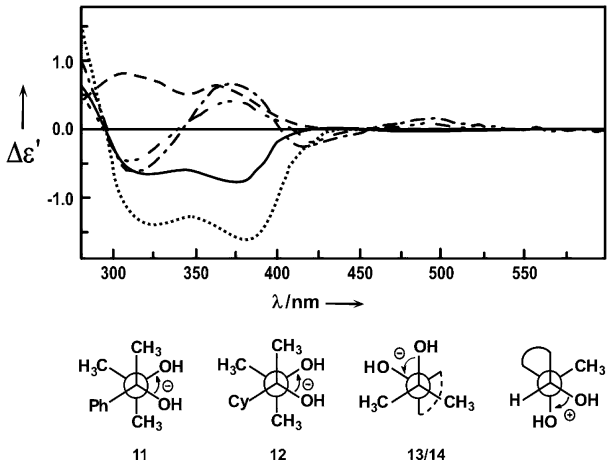

FIGURE 10. CD spectra of in situ formed Mo-complexes of *vic*-diols **11** (−), **12** (· · ·), **13** (− · − · −), **14** (− ·· − ·· −) and of (1*R*,2*S*)-1-methylcyclohexane-1,2-diol (− − −) recorded in DMSO (top) and preferred conformation of the diols in the chiral Mo-complexes (bottom). CD curves of diols **13** and **14** are 2-fold enhanced.

molecule becomes substantially reduced due to the steric requirements of the stock complex.[44,45] As a result, the molecule appears to exist only as a single conformer, in most cases. The energetically preferred conformation of a *vic*-diol molecule in the chiral Mo-complexes is the one with an antiperiplanar orientation of both O−C−C−R units. This is very reasonable, because only in such a conformation the bulky R-groups point away from the rest of the complex and do avoid the close interaction with the remaining acetate ligands in the stock complex. Additional evidence in support of such preferred conformation is given by quantum-mechanical calculations.[46] These calculations made for the model systems of *vic*-diols indicate that the best gauche conformer (O−C−C−O ≈ 60°) is ca. 8 kJ mol^{-1} lower in energy than the best trans conformer (O−C−C−O ≈ 180°). Thus, the relative configuration of *vic*-diol after ligation to the Mo_2-core is established to be gauche with an antiperiplanar orientation of each O−C−C−R group.

In the CD spectra of diols **11** and **12**, two negative CD bands at around 310 and 370 nm can be seen (Figure 10). The negative sign of these CD bands corresponds to a negative torsion angle of the O−C−C−O moiety in its preferred antiperiplanar conformation, as presented in the bottom of Figure 10. The shape of the CD curves of **11** and **12** resembles the one for *sec*/*tert* 1,2-diols, for example, for (1*R*,2*S*)-1-methylcyclohexane-1,2-diol shown also in Figure 10. (1*R*,2*S*)-1-Methylcyclohexane-1,2-diol exhibits positive CEs at around 310 and 370 nm corresponding to the positive sign of the O−C−C−O torsion angle in its complexed form.

A preferred conformation of the diol unit in compound **13** in its complexed form depends on the configuration at the C-7 carbon atom. So, for a (7*S*) configuration, the O−C−C−O torsion angle is positive, while for its local enatiomer, that is, a (7*R*) isomer, it is negative. Consequently, in the CD spectrum of its Mo-complex, the CEs with a positive or a negative sign at around 310 and 400 nm should be present, respectively. Because the sign of the relevant CEs is negative (Figure 10),

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(45) Frelek, J.; Majer, Z.; Perkowska, A.; Snatzke, G.; Vlahov, I.; Wagner, U. *Pure Appl. Chem.* **1985**, *57*, 441−451.
(46) Brock, C. P. *Acta Crystallogr.* **2002**, *B58*, 1025−1031.

TABLE 1. CD Data of in Situ Formed Mo-Complexes of *vic*-Diols 1−12[a]

comp.	A[b]	B[c]	CD band V	CD band IV	CD band III	CD band II	CD band I
1	+[d]	+		+5.95 (299.0)	−2.65 (353.0)	+0.44 (414.0)	
2	+	+	−2.05 (294.5)	+0.10 (323.5)	−0.50 (344.5)	+1.32 (396.0)	
3	+	+	−0.08 (275.5)	+0.56 (305.0)	−0.18 (337.0)	+1.02 (393.0)	
4	−	−	+0.41 (266.0)	−0.30 (316.5)	a[e] (331.5)	−1.02 (375.5)	−0.07 (482.0)
5a	+	+		+0.69 (300.0)	−1.43 (350.5)	+0.36 (417.0)	
5b	+	+	−0.43 (276.0)	+0.39 (310.0)	−0.21 (353.0)	+0.21 (399.5)	
6	+	+	−0.11 (268.5)	+0.37 (306.5)	−0.03 (344.0)	+0.18 (389.0)	+0.14 (433.0)
7	+	+	−0.85 (264.2)	+0.71 (313.0)	+0.93 (358.2)	+0.14 (424.2)	
8	−	−	−0.40 (274.5)	−0.41 (321.0)	a[e] (342.5)	−0.53 (376.0)	−0.11 (436.0)
9	−	−		−0.31 (293.5)	+0.52 (348.5)	−0.03 (414.5)	+0.07 (512.0)
10	+	+	−1.28 (262.0)	+0.28 (307.0)	−0.05 (342.5)	+0.23 (380.5)	
11	−	−		−0.76 (318.5)	a[e] (349.0)	−0.88 (379.5)	
12	−	−	+2.07 (272.2)	−1.48 (324.5)	a[e] (350.5)	−1.51 (381.5)	
13	−	−	+0.41 (269.0)	−0.32 (307.8)	+0.38 (368.0)	−0.15 (417.0)	+0.10 (486.2)
14	−	−		−0.17 (298.5)	+0.28 (369.0)	−0.11 (420.5)	+0.07 (478.0)

[a] Values are given as $\Delta\epsilon'$(nm). For explanation of term $\Delta\epsilon'$, see text. [b] A, calculated sign of the O−C−C−O torsion angle. [c] B, sign of the O−C−C−O torsion angle from CD. [d] X-ray data. [e] a, negative inflection point.

thus we are able to assign the absolute configuration at C-7 in **13** to be (*R*). This assignment was additionally proven to be correct by the X-ray analysis.[47]

Cis-hydroxylation reaction of the respective oxacepham bearing an exo isopropylene group at C-7 gave an inseparable mixture of diols in a ratio of 4.5:1. The absolute configuration at the bridgehead carbon atom in the major product **14** was established to be (6*S*) by NMR and CD spectroscopies.[48] However, the absolute configuration at C-7 could not be ascribed unequivocally by these methods. Thus, we decided to apply the CD dimolybdenum methodology for this purpose. As can be seen from Figure 10, CD spectrum of the Mo-complex of **14** is very similar to that of compound **13** in both signs of particular CEs and in the shape of the CD curve. This points definitely to the same (7*R*) absolute configuration in both compounds.

The results discussed above perfectly reflect the stereochemical situation in chiral Mo-complexes of flexible *vic*-diols and the relationship with their CD spectra. On these grounds, we came to the conclusion that flexible *tert*/*tert vic*-diols **11**−**14** also fall under our empirical helicity rule established previously for other classes of glycols.

Discussion and Conclusions

The chiroptical data for *vic*-diols **1**−**14** collected in Table 1 demonstrate that the sign of the O−C−C−O torsion angle predicted by the helicity rule is in excellent agreement with the one resulting from their stereostructure. This statement holds equally for rigid (compounds **1**−**10**) as well as for flexible *tert*/*tert* 1,2-diols (compounds **11**−**14**). Thus, the results obtained validate profitable applicability of the dimolybdenum methodology to *tert*/*tert* 1,2-diols too. In other words, the empirical rule finds application for determining the 3D molecular structure of this class of *vic*-diols with confidence.

On the other hand, the nature of the equilibrium formed in solution and the complexes involved still remains unknown. It means that by using the in situ dimolybdenum CD method one does not obtain quantitative values because the real complex structure as well as the concentration of the chiral complex formed in solution are not known. Therefore, the CD data are presented as the $\Delta\epsilon'$ values. These $\Delta\epsilon'$ values are calculated in the usual way as $\Delta\epsilon' = \Delta A/c \times d$, where c is the molar concentration of the chiral ligand, assuming 100% complexation (ΔA = the difference in absorption of left and right circularly polarized light; d = path length of the cell). This, however, creates no disadvantage for the method because, for the purpose of absolute configuration determination, only the sign of the appropriate Cotton effects is important and the magnitude of $\Delta\epsilon$ is irrelevant. In addition, provided that the appropriate complexation takes place, CD spectra of chiral Mo-complexes allow one to match both pattern and sign with absolute configuration of diol ligand. On account of this, it is recommended to measure the CD spectra for one class of compounds always at similar concentration ratios.

The present study demonstrates that: (1) the scope of the dimolybdenum CD method can be extended to *tert*/*tert* 1,2-diols; (2) the absolute configuration can be determined unequivocally by means of the empirical helicity rule relating the sign of the CEs arising in the 300−400 nm spectral region with the helicity of the O−C−C−O subunit; (3) the method also allows one to establish the preferred conformation of compound in solution, if its absolute configuration is known; (4) no exception to the helicity rule has as yet been found; and (5) despite its empirical character, this simple methodology allows easy, fast, and effective determination of the absolute configuration of a variety of classes of *vic*-diols, including even sterically demanding *tert*/*tert* diols, in a reliable and versatile manner.

Experimental Section

3*β*-Acetoxy-9α,10-dihydroxy-5-methyl-19-nor-5*β*,10α-cholestan-6-one (2). To a solution of 3*β*-acetoxy-5-methyl-19-nor-5*β*-cholest-9(10)-en-6-one[34] (1.0 g; 2.26 mmol) in pyridine (25 mL) was added OsO_4 (500 mg; 1.97 mmol), and the mixture was left standing at room temperature for 2 weeks. The mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in ethanol (30 mL). The obtained solution was treated with a saturated aqueous solution of $NaHSO_3$ at 50 °C for 5 h. Next, it was diluted with water (75 mL) and extracted with chloroform (2 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (30 g). The column was washed with hexane−dichloromethane (50:50 and 25:75) mixtures, dichloromethane, and dichloromethane−ethyl acetate (90:10, 80:20, 70:30, and 60:40) mixtures. Fractions containing the main product were combined and evaporated to dryness. The residue was crystallized twice from

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methanol to give 262 mg (28%) of the title compound; mp 217−219 °C. IR (KBr): 3428, 3388, 1706, 1280, 1024, 962 cm^{-1}. ^1H NMR (500 MHz): 0.73 (3H, s, 18-H), 1.43 (3H, s, 5β-Me), 2.03 (3H, s, OAc), 5.15 (1H, narrow m, 3α-H equatorial). ^{13}C NMR (125.758 MHz): 214.5 (C, C═O ketone), 170.1 (C, C═O acetate), 75.5 (C), 74.3 (C), 69.5 (CH_3/CH), 55.8 (CH_3/CH), 50.2 (C), 46.3 (CH_3/CH), 43.5 (C), 39.4 (CH_2), 36.9 (CH_2), 36.4 (CH_3/CH), 36.2 (CH_2), 36.0 (CH_2), 35.7 (CH_3/CH), 35.6 (CH_2), 31.7 (CH_2), 28.3 (CH_2), 28.0 (CH_3/CH), 25.4 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 22.8 (CH_3/CH), 22.5 (CH_3/CH), 22.4 (CH_3/CH), 21.6 (CH_3/CH), 18.5 (CH_3/CH), 12.0 (CH_3/CH). EI MS (70 eV): 476 (M^+, 1.4%), 458 (3.2%), 430 (5.8%), 416 (15.2%), 388 (45.0%), 370 (21.0%), 305 (17.9%), 264 (19.0%), 193 (36.8%), 150 (100%). EI HRMS: calcd for $C_{29}H_{48}O_5$, 476.35017; found, 476.35166.

(6*E*)-6-Hydroxyimino-5-methyl-19-nor-5β,10α-cholestanetriol-3β,9α,10 3-Acetate (3). 3β-Acetoxy-9α,10-dihydroxy-5-methyl-19-nor-5β,10α-cholestan-6-one (**2**; 262 mg; 0.55 mmol) and $NH_2OH.HCl$ (267 mg; 3.84 mmol) were dissolved in pyridine (15 mL), and the obtained solution was left standing at room temperature for 1 week. The reaction mixture was diluted with water (100 mL) and extracted with chloroform (2 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (15 g). The column was washed with dichloromethane and dichloromethane−ethyl acetate (95:5, 90:10, 85:15, 80:20, and 70:30) mixtures. Fractions containing the substrate were combined and evaporated to dryness to give 129 mg (49%) of the solid. Fractions containing the product were combined and evaporated to dryness. The residue was crystallized from methanol to give 118 mg (44%) of the title compound; mp 184−185 °C. IR (KBr): 3530, 3419, 3361, 1715, 1648, 1278, 908 cm^{-1}. ^1H NMR (500 MHz): 0.71 (3H, s, 18-H), 1.51 (3H, s, 5β-Me), 2.03 (3H, s, OAc), 3.48 (1H, s, −OH), 5.13 (1H, narrow m, 3α-H equatorial), 7.96 (1H, narrow m, −OH). ^{13}C NMR (125.758 MHz): 170.2 (C, C═O acetate), 165.6 (C, C═N), 75.5 (C), 74.4 (C), 69.3 (CH_3/CH), 55.8 (CH_3/CH), 46.8 (CH_3/CH), 43.7 (C), 43.5 (C), 39.5 (CH_2), 37.8 (CH_2), 36.2 (CH_2), 36.1 (CH_2), 35.8 (CH_3/CH), 35.3 (CH_3/CH), 31.9 (CH_2), 28.4 (CH_2), 28.0 (CH_3/CH), 25.5 (CH_2), 25.3 (CH_3/CH), 24.2 (CH_2), 23.8 (CH_2), 23.2 (CH_2), 22.8 (CH_3/CH), 22.5 (CH_3/CH), 22.4 (CH_2), 21.6 (CH_3/CH), 18.5 (CH_3/CH), 12.0 (CH_3/CH). EI MS (70 eV): 491 (M^+, 3.7%), 474 (43.1%), 456 (10.6%), 431 (8.3%), 414 (27.9%), 397 (47.0%), 386 (22.6%), 357 (10.1%), 227 (10.7%), 150 (16.0%), 110 (100%). EI HRMS: calcd for $C_{29}H_{49}NO_5$, 491.36107; found, 491.36277.

3β-Acetoxy-6β-methyl-5α-cholestan-5,6α-diol (4). To a solution of 3β-acetoxy-6-methylcholest-5-ene[36] (0.411 g; 0.93 mmol) in pyridine (30 mL) was added OsO_4 (250 mg; 0.98 mmol), and the mixture was left standing at room temperature for 1 week. The mixture was then evaporated to dryness under reduced pressure, and the residue was dissolved in ethanol (30 mL). The obtained solution was treated with a saturated aqueous solution of $NaHSO_3$ at 50 °C for 2 h and then extracted with chloroform (4 × 15 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (13 g). The column was washed with dichloromethane and dichloromethane−ethyl acetate (97.5:2.5, 95:5, 92.5:7.5, 90:10, and 80:20) mixtures. Fractions containing the main product were combined and evaporated to dryness to give 154 mg (35%) of the title compound as a glassy oil. IR (KBr): 3504, 1736, 1717, 1268, 1245, 1036 cm^{-1}. ^1H NMR (500 MHz): 0.66 (3H, s, 18-H), 1.06 (3H, s, 19-H), 1.27 (3H, s, 6β-Me), 2.02 (3H, s, OAc), 2.56 (1H, s, −OH), 5.17 (1H, septet, $J_1 \approx J_2 \approx 11.0$ Hz and $J_3 \approx J_4 \approx 5.5$ Hz, 3α-H axial). ^{13}C NMR (125.758 MHz): 170.6 (C, C═O acetate), 78.8 (C), 74.1 (C), 71.7 (CH_3/CH), 56.2 (CH_3/CH), 55.5 (CH_3/CH), 45.1 (CH_3/CH), 42.7 (C), 42.0 (CH_2), 39.8 (CH_2), 39.5 (CH_2), 39.4 (C), 36.1 (CH_2), 35.8 (CH_3/CH), 33.4 (CH_2), 33.2 (CH_3/CH), 32.1 (CH_2), 28.2 (CH_2), 28.0 (CH_3/CH), 26.6 (CH_2), 25.0 (CH_3/CH), 24.3 (CH_2), 23.9 (CH_2), 22.8 (CH_3/CH), 22.5 (CH_3/CH), 21.5 (CH_3/CH), 21.1 (CH_2), 19.1 (CH_3/CH), 18.6 (CH_3/CH), 12.1 (CH_3/CH). EI MS (70 eV): 476 (M^+, 9.7%), 461 (9.7%), 440 (13.1%), 416 (7.4%), 398 (62.2%), 380 (52.2%), 365 (10.4%), 355 (12.6%), 329 (15.2%), 285 (15.3%), 263 (100%). EI HRMS: calcd for $C_{30}H_{52}O_4$, 476.38656; found, 476.38579. Anal. Calcd for $C_{30}H_{52}O_4$: C, 75.58%; H, 10.99%. Found: C, 75.37% and 75.34%; H, 10.99% and 11.15%.

5-Methyl-B,19-dinor-5β,10α-cholestane-3β,6α,9α,10-tetraol (5a). To a solution of 5-methyl-B,19-dinor-5β-cholest-9(10)-ene-3β,6α-diol[37] (806 mg; 2.07 mmol) in pyridine (25 mL) was added OsO_4 (500 mg; 1.97 mmol), and the mixture was left standing at room temperature for 1 week. The mixture was then evaporated to dryness under reduced pressure, and the residue was dissolved in ethanol (50 mL). The obtained solution was treated with a saturated aqueous solution of $NaHSO_3$ at 50 °C for 3 h. Next, it was diluted with water (75 mL) and extracted with chloroform (2 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (24 g). The column was washed with dichloromethane−ethyl acetate (60:40, 50:50, 30:70, 20:80, and 10:90) mixtures and ethyl acetate. Fractions containing the main product were combined and evaporated to dryness to give 349 mg (42%) of the title compound as a glassy oil. IR (KBr): 3430, 1067, 1021 cm^{-1}. ^1H NMR (500 MHz): 0.90 (3H, s, 18-H), 1.05 (3H, s, 5β-Me), 2.08 (1H, ddd, $J = 13.6$, 5.2, and 1.9 Hz), 2.20 (1H, dd, $J = 12.6$ and 6.3 Hz), 2.28 (1H, s, −OH), 2.66 (1H, d, $J = 0.9$ Hz, −OH), 3.79 (1H, dd, $J = 6.3$ and 3.5 Hz, 6β-H), 4.08 (1H, septet, $J_1 \approx J_2 \approx 10.9$ Hz and $J_3 \approx J_4 \approx 5.5$ Hz, 3α-H axial). ^{13}C NMR (125.758 MHz): 80.7 (C), 80.3 (CH_3/CH), 79.5 (C), 68.1 (CH_3/CH), 56.1 (CH_3/CH), 51.0 (CH_3/CH), 49.9 (C), 43.5 (CH_3/CH), 43.0 (CH_2), 41.3 (C), 39.5 (CH_2), 36.03 (CH_3/CH), 35.97 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.0 (CH_3/CH), 25.0 (CH_2), 24.1 (CH_3/CH), 23.8 (CH_2), 22.8 (CH_3/CH), 22.5 (CH_3/CH), 18.5 (CH_3/CH), 16.3 (CH_3/CH). EI MS (70 eV): 404 ($M^+ - H_2O$, 5.2%), 386 (63.1%), 371 (6.7%), 345 (8.5%), 318 (9.5%), 293 (100%), 263 (94.9%), 193 (9.6%), 163 (21.8%), 141 (20.4%), 128 (32.3%). EI HRMS: calcd for $C_{26}H_{46}O_4$, 422.33961; found, 422.34099.

5-Methyl-B,19-dinor-5β,10α-cholestane-3β,6α,9α,10-tetraol 3-Acetate (5b). A solution of 5-methyl-B,19-dinor-5β,10α-cholestane-3β,6α,9α,10-tetraol (**5a**; 245 mg) in pyridine (5 mL) was treated with acetic anhydride (3 mL), heated to reflux, and then left standing at room temperature for 2 h 15 min. The reaction mixture was evaporated to dryness under reduced pressure. The residue was treated with water (60 mL) and extracted with chloroform (2 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (10 g). The column was washed with dichloromethane and dichloromethane−ethyl acetate (95:5, 92.5:7.5, 90:10, and 85:15) mixtures. Fractions containing the main product were combined and evaporated to dryness. Crystallization of the residue from hexane−dichloromethane gave 240 mg (89%) of the title compound; mp 192−193 °C. IR (KBr): 3452, 3377, 1711, 1273, 1014 cm^{-1}. ^1H NMR (500 MHz): 0.89 (3H, s, 18-H), 1.03 (3H, s, 5β-Me), 2.01 (3H, s, OAc), 2.10 (1H, ddd, $J = 13.5$, 5.4 and 2.0 Hz), 2.19 (1H, dd, $J \approx 12.7$ and 6.4 Hz), 2.26 (1H, s, −OH), 2.75 (1H, d, $J = 1.3$ Hz, −OH), 3.80 (1H, dd, $J = 6.4$ and 4.1 Hz, 6β-H), 5.16 (1H, septet, $J_1 \approx J_2 \approx 10.9$ Hz and $J_3 \approx J_4 \approx 5.4$ Hz, 3α-H axial). ^{13}C NMR (125.758 MHz): 171.0 (C, C═O acetate), 80.8 (C), 80.0 (CH_3/CH), 79.4 (C), 71.7 (CH_3/CH), 56.1 (CH_3/CH), 50.8 (CH_3/CH), 49.8 (C), 43.5 (CH_3/CH), 41.3 (C), 39.5 (CH_2), 38.6 (CH_2), 36.05 (CH_3/CH), 35.98 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.0 (CH_3/CH), 26.9 (CH_2), 24.9 (CH_2), 23.87 (CH_2), 23.86 (CH_3/CH), 22.8 (CH_3/CH), 22.5 (CH_3/CH), 21.5 (CH_3/CH), 18.5 (CH_3/CH), 16.3 (CH_3/CH). EI MS (70 eV): 446 ($M^+ - H_2O$, 2.2%), 404 (12.0%), 386 (39.7%), 371 (6.3%), 331 (11.3%), 293 (85.0%), 263 (100%), 193 (16.0%), 163 (25.0%), 151 (20.5%), 123 (31.0%), 110 (57.5%). ESI HRMS: calcd for $C_{28}H_{48}O_5Na$, 487.3394; found, 487.3417.

6*β*-Methoxy-3α,5α-cyclo-18-nor-17-methylandrost-13(17)-ene and 6*β*-Methoxy-3α,5α-cyclo-18-nor-17*β*-methylandrost-13-(14)-ene. 17*β*-Tosyloxy-androst-5-en-3*β*-ol (11.80 g, 26.6 mmol) was dissolved in dry ether (150 mL) and gradually added to a solution of ethylmagnesium chloride in ether (100 mL), prepared from 5.5 g of magnesium and ethyl chloride (it is a slightly modified literature procedure[39]). The majority of ether (about 70 mL) was distilled from the stirred solution, and dry benzene (150 mL) was added. The reaction mixture was refluxed for 4 h at 60−62 °C, cooled to room temperature, and quenched with water and 5% H_2SO_4. Organic layer was separated, dried over anhydrous $MgSO_4$, and evaporated in vacuo. A mixture of two olefins ($\Delta^{13(17)}$ and $\Delta^{13(14)}$) was obtained in 96% yield (6.94 g). The ^{1}H NMR spectrum showed that the former olefin prevailed as it was evident from integration of the signals of 17-methyl group (a broadened singlet at 1.61 ppm deriving from 13(17)-olefin and a doublet at 0.98 ppm (J = 6.2 Hz) from 13(14)-olefin).

The mixture of olefins was treated with *p*-toluenesulphonic chloride in pyridine, and the resulting 3*β*-tosylates were subjected to a buffered methanolysis (in the presence of potassium acetate), as previously described.[49] A mixture of 6*β*-methoxy-3α,5α-cyclo-18-nor-17-methylandrost-13(17)-ene and 6*β*-methoxy-3α,5α-cyclo-18-nor-17-methylandrost-13(14)-ene was obtained in 51% yield (3.7 g).

6*β*-Methoxy-3α,5α-cyclo-18-nor-17-methylandrostan-13α,17α-diol (6) and 6*β*-Methoxy-3α,5α-cyclo-18-nor-17*β*-methylandrostan-13α,14α-diol (8). To a stirred solution of the described above olefin mixture (560 mg, 1.96 mmol) in pyridine (30 mL) was added a solution of OsO_4 (648 mg, 2.55 mmol) in pyridine (7 mL) at room temperature. The reaction mixture was stirred for 6 days at 25 °C. Next, an aqueous solution of sodium bisulfite (20 mL of 40% $NaHSO_3$) was added, and the reaction mixture was stirred for 3 days at room temperature, poured into water, and extracted with dichloromethane. The extract was dried with anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The products were separated by silica gel column chromatography. Elution with ethyl acetate−hexane (10:90) mixture afforded consecutively 275 mg (44%) of 6*β*-methoxy-3α,5α-cyclo-18-nor-17-methylandrostan-13α,17α-diol (**6**) and 45 mg (7%) of 6*β*-methoxy-3α,5α-cyclo-18-nor-17*β*-methylandrostan-13α,14α-diol (**8**).

Compound 6. An oil. IR: ν_{max} 3618, 3556, 1092, 1076 cm^{-1}. ^{1}H NMR: δ 0.46 (1H, m, H-4), 0.66 (1H, m, H-3), 0.99 (3H, s, H-19), 1.27 (s, 3H, 17*β*-C**H**$_3$), 2.28 (2H, broad s, **H**O−), 2.78 (1H, m, H-6α), 3.32 (3H, s, C**H**$_3$O−). ^{13}C NMR: δ 82.1 (CH), 81.1 (C), 80.4 (C), 56.5 (CH_3), 51.3 (CH), 44.1 (C), 43.1 (CH), 38.1 (CH_2), 36.5 (CH_2), 36.3 (CH), 35.3 (C), 33.6 (CH_2), 30.9 (CH_2), 26.5 (CH_2), 24.8 (CH_2), 23.9 (CH_3), 22.4 (CH_2), 21.6 (CH), 18.6 (CH_3), 12.9 (CH_2). MS-ESI, *m*/*z* (%) 343 (M + Na$^+$, 100), 663 (2M + Na$^+$, 28). EI HRMS calcd for $C_{20}H_{32}O_3Na$, 343.2249; found, 343.2239.

Compound 8. An oil. IR: ν_{max} 3610, 3532, 1085, 1011 cm^{-1}. ^{1}H NMR: δ 0.48 (1H, m, H-4), 0.66 (1H, m, H-3), 1.02 (3H, s, H-19), 1.08 (3H, d, J = 7.1 Hz, 17*β*-C**H**$_3$), 2.87 (1H, m, H-6α), 3.34 (3H, s, C**H**$_3$O−). ^{13}C NMR: δ 83.8 (C), 82.1 (CH), 79.2 (C), 56.4 (CH_3), 43.7 (C), 43.3 (CH), 42.3 (CH), 38.3 (CH_2), 37.2 (CH), 35.0 (C), 33.8 (CH_2), 30.3 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 21.7 (CH), 19.3 (CH_3), 18.7 (CH_3), 13.2 (CH_2). MS-ESI, *m*/*z* (%) 343 (M + Na$^+$, 100). ESI HRMS: calcd for $C_{20}H_{32}O_3Na$, 343.2249; found, 343.2239.

18-Nor-17-methylandrost-5-ene-3*β*,13α,17α-triol (7). To a stirred solution of 6*β*-methoxy-3α,5α-cyclo-18-nor-17-methylandrostan-13,17-diol (115 mg, 0.36 mmol) in a dioxane−water (4:1) mixture (15 mL) was added *p*-TsOH·H_2O (23 mg, 0.12 mmol). The reaction mixture was stirred at 70 °C for 1.5 h, poured into water, and extracted with ethyl acetate. The extract was washed with water, dried (anhydrous $MgSO_4$), and the solvent was evaporated in vacuo. The product was purified by silica gel column chromatography. With a hexane:ethyl acetate (80:20) mixture, 18-nor-17-methylandrost-5-ene-3*β*,13α,17α-triol (**7**) was eluted (100 mg, 91%) and crystallized from methanol; mp 160−162 °C. IR: ν_{max} 3608, 3524, 1044, 995 cm^{-1}. ^{1}H NMR: δ 0.98 (3H, s, H-19), 1.22 (3H, s, 17*β*-C**H**$_3$), 3.55 (1H, m, H-3α), 5.36 (1H, m, H-6). ^{13}C NMR: δ 141.0 (C), 121.2 (CH), 80.8 (C), 80.5 (C), 71.6 (CH), 51.5 (CH), 45.4 (CH), 41.9 (CH_2), 38.3 (CH_2), 37.8 (C), 36.8 (CH_2), 36.2 (CH), 32.7 (CH_2), 31.3 (CH_2), 29.0 (CH_2), 26.3 (CH_2), 23.5 (CH_3), 19.0 (CH_2), 17.9 (CH_3). MS-EI, *m*/*z* (%) 306 (M$^+$, 67), 288 (45), 270 (24), 255 (54), 230 (100). EI HR: calcd for $C_{19}H_{30}O_3$, 306.2195; found, 306.2203.

(20*R*/*S*)-6*β*-Methoxy-18-nor-17*β*-methyl-3α,5α-cyclopregn-13-ene-20,16α-carbolactone. Ethyl (20*S*)-6*β*-methoxy-16α,17α-oxido-3α,5α-cyclopregnane-20-carboxylate (500 mg, 1.24 mmol) prepared as previously described[40] was subjected to slow column chromatography on silica gel impregnated with 50% H_2SO_4 (7% weight). 3*β*-Hydroxy-18-nor-17*β*-methylpregna-5,13-diene-20,16α-carbolactone (as a mixture of C-20 epimers) was eluted with a hexane:ethyl acetate (80:20) mixture in 64% yield. The epimeric ratio (20*R*:20*S*) 2:3 was established by integration of H-16*β* signals at δ 4.56 and 4.62, respectively, in the NMR spectrum.

The epimeric mixture (203 mg, 0.6 mmol) was dissolved in anhydrous pyridine (10 mL), and *p*-toluenesulphonic chloride (208 mg, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 14 h, poured into iced water, and extracted with benzene:ethyl ether (1:1). The extract was dried (anhydrous $MgSO_4$) and evaporated in vacuo. The crude product (289 mg, 98% yield) was dissolved in methanol (15 mL) containing anhydrous (freshly melted) potassium acetate (548 mg, 5.6 mmol), and the reaction mixture was refluxed for 4 h. After being cooled, the mixture was poured into water, and the product was extracted with chloroform. Evaporation of the solvent from dried (anhydrous $MgSO_4$) extract followed by silica gel column chromatography afforded the title compound as an epimeric mixture at C-20. The product was eluted with a hexane:ethyl acetate (90:10) mixture in 54% yield (113 mg).

(20*R*)-6*β*-Methoxy-18-nor-17*β*-methyl-3α,5α-cyclopregna-13α,14α-diol-20,16α-carbolactone (9). To a stirred solution of mixture (20*R*/*S*)-6*β*-methoxy-3α,5α-cyclo-18-nor-17*β*-methylpregn-13-ene-20,16α-carbolactone (113 mg, 0.32 mmol) in pyridine (15 mL) was added osmium tetraoxide (105 mg, 0.41 mmol) dissolved in pyridine (1 mL) at room temperature. The reaction mixture was stirred for 18 h at 25 °C. The obtained osmate complex was reduced with aqueous solution of sodium hydrogen sulfite (40% $NaHSO_3$). The reaction mixture was stirred for 2 days at room temperature, poured into water, and extracted with benzene:ether (1:1) and then with ethyl acetate. Both extracts were dried with anhydrous $MgSO_4$, and the solvents were evaporated in vacuo. TLC control (chloroform−methanol 9:1) showed two spots (less polar product predominated) in the first extract, while the second one contained the more polar product only. Column chromatography purification of the first extract afforded (20*R*)-6*β*-methoxy-18-nor-17*β*-methyl-3α,5α-cyclopregna-13α,14α-diol-20*β*,16α-carbolactone (18 mg, 15%) eluted with a hexane:ethyl acetate (80:20) mixture. An oil. ^{1}H NMR: δ 0.50 (1H, m, H-4), 0.68 (1H, m, H-3), 0.99 (3H, s, H-19), 1.38 (3H, d, J = 7.3 Hz, H-21), 1.59 (3H, s, 17*β*-CH_3), 2.54 (1H, q, H-20α, J = 7.3 Hz), 2.89 (1H, m, H-6α), 3.34 (3H, s, CH_3O−), 4.60 (1H, dd, J_1 = 8.1 Hz, J_2 = 3.1 Hz, H-16*β*). ^{13}C NMR δ (ppm): 178.8 (C), 86.3 (CH), 85.4 (C), 81.8 (CH), 80.7 (C), 56.6 (CH_3), 55.3 (C), 47.0 (CH), 43.4 (C), 43.0 (CH), 38.7 (CH), 37.4 (CH_2), 34.3 (C), 33.8 (CH_2), 31.7 (CH_2), 30.5 (CH_2), 24.8 (CH_2), 23.1 (CH_3), 21.9 (CH_2), 21.3 (CH), 19.1 (CH_3), 13.4 (CH_2), 8.8 (CH_3). MS-EI, *m*/*z* (%) 390 (M$^+$, 2), 335 (19), 299 (4), 231 (100). EI HR: calcd for $C_{23}H_{34}O_5$, 390.2406; found, 390.2389.

In the ethyl acetate extract, (20*S*)-6*β*-methoxy-18-nor-17*β*-methyl-3α,5α-cyclopregna-13α,14α-diol-20*β*,16α-carbolactone (**9a**) was found as a 1:1 complex with pyridine. ^{1}H NMR: δ 0.47 (1H, m, H-4), 0.66 (1H, m, H-3), 1.02 (3H, s, H-19), 1.36 (3H, d, J = 7.1 Hz, H-21), 1.52 (3H, s, 17*β*-C**H**$_3$), 2.89 (1H, m, H-6α), 3.36

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(3H, s, C**H**$_3$O−), 4.46 (1H, dd, J_1 = 6.2 Hz, J_2 = ∼1 Hz, H-16*β*), 7.49 (2H, m, H-Pyr), 7.86 (2H, m, H-Pyr), 8.8 (1H, d, J = 5.2 Hz, H-Pyr). However, all attempts to remove pyridine (acid extraction or column chromatography) led to the decomposition of the product.

6*β*-Methoxy-3α,5α-cyclo-23,24,25,26,27-pentanorfurostan-16α,17α-diol (10). A stirred solution of (20*R*)-20-hydroxymethyl-6*β*-methoxy-3α,5α-cyclopregnan-16*β*,17α-diol (30 mg, 0.08 mmol) in dry THF was treated with NaH (15.8 mg, 0.4 mmol) at 25 °C. The reaction mixture was refluxed for 24 h, quenched with water, and the product was extracted with dichloromethane. The organic extract was dried (anhydrous $MgSO_4$) and evaporated in vacuo. The product was purified by silica gel column chromatography. 6*β*-Methoxy-3α,5α-cyclo-23,24,25,26,27-pentanorfurostan-16α,-17α-diol (**10**) was eluted with a hexane:ethyl acetate (80:20) mixture (18 mg, 60%). An oil. IR: ν_{max} 3604, 3416, 1090, 1006 cm^{-1}. ^{1}H NMR: δ 0.45 (1H, m, H-4), 0.67 (1H, m, H-3), 0.92 (3H, d, J = 7.1 Hz, H-21), 0.95 (3H, s, H-18), 1.04 (3H, s, H-19), 2.46 (1H, m, H-20), 2.78 (1H, m, H-6α), 3.33 (3H, s, CH_3O−), 3.67 (1H, def. t, J_{gem} = 8.7 Hz, J_{vic} = 9.4 Hz), 4.15 (1H, def. t, J_{gem} = 8.7 Hz, J_{vic} = 8.4 Hz). ^{13}C NMR: δ 112.8 (C), 89.3 (C), 82.1 (CH), 76.6 (CH_2), 56.6 (CH_3), 52.0 (CH), 47.5 (CH), 45.8 (C), 43.5 (C), 39.8 (CH_2), 35.12 (CH_2), 35.08 (C), 34.0 (CH), 33.3 (CH_2), 31.8 (CH_2), 30.2 (CH), 24.9 (CH_2), 21.9 (CH_2), 21.3 (CH), 19.3 (CH_3), 16.5 (CH_3), 13.3 (CH_3), 13.1 (CH_2). MS-EI, *m*/*z* (%) 376 (M^+, 13), 361 (33), 344 (22), 321 (74), 214 (54), 41 (100). EI HR calcd for $C_{23}H_{36}O_4$, 376.2614; found, 376.2598.

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Supporting Information Available: General experimental methods, IR, ^{1}H, ^{13}C, MS spectra for reported compounds, X-ray crystallographic structures (ORTEP) of compounds **2**, **5a**, and **7**, and computational details including hin files. This material is available free of charge via the Internet at http://pubs.acs.org.

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