Notes

Ruthenium-Catalyzed C–H Bond Activation. Oxyfunctionalization of Nonactivated C–H Bonds in the Cedrane Series with RuO_4 Generated in Situ

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Saturated hydrocarbons possess neither unbonded electron pairs nor low-lying empty orbitals. As a consequence, the activation and selective functionalization of nonactivated C–H bonds in these hydrocarbons, under homogeneous and mild conditions, is recognized as an important and challenging objective.[1] This is presently a rapidly expanding field because the tailoring of good catalysts would allow for selective hydroxylation of tertiary C–H bonds or oxidation of methylene groups into ketones. Recent studies in this area involve dry ozonation,[2] peroxy acids,[3] ozone in superacid media,[4] and dioxirane.[5] Homogeneous catalysis with transition-metal species has also been used.[1a] For instance, the Gif or related systems[6] are especially interesting because they use dioxygen. Microorganisms have proven their efficiency even through the yields are not very impressive. Enzymes frequently involve a high-valent metal–oxo species such as cytochrome P-450[7] along with metalloporphyrins[8] which constitutes a major area of research. Metallic clusters[9] and elemental fluorine[10] have appeared recently as new fields of investigation.

The understanding of the mechanisms occurring in the above-mentioned processes would allow better control for the oxidation reactions involved and a complete mastering of the overall functionalization process. In view of our interest in oxidation and the use of transition-metal catalysts,[11] we oriented our research toward the use of appropriate metallic species.

Since Chatt observed the first clear-cut example of a simple oxidative addition of a ruthenium center on a C–H bond,[12] it was established that many other metals activate the strong arene C–H bond (110 kcal mol^{-1}) but not the weaker C–H alkane bond (96–102 kcal mol^{-1}).[13] It has been shown that the product bond strength (and not the reactant C–H bond strength) in the [M]–C species controls the hydrocarbon activation equilibria.[14]

One way to overcome this difficulty might be to achieve a H–[M]–O–C species resulting from an oxometal insertion into the C–H bond to be functionalized. Oxometal species (considered as a source of "oxenes"[15]) are good candidates but generally require polydentate ligands for stabilization as in iron or manganese porphyrins.[8] The high-valent RuO_4 is very reactive, stable without additional ligand, and highly electrophilic.[16] It can be generated in situ from hydrated ruthenium trichloride. Once reduced after the oxidation of an alkane, it can be regenerated by a wide variety of reoxidizing reagents;[17] therefore, it can be used also in catalytic amounts.[18] The Sharpless multicomponent solvent mixture renders the regeneration of catalyst particularly efficient.[19]

In order to test the regio- and/or chemoselectivity of such a reagent, particular substrates are required. We have chosen hydrocarbons in the cedrane series because they feature several secondary and tertiary hydrogens which could transform respectively into carbonyl groups or tertiary alcohols. For instance, epicedrane 1 possesses a rigid tricyclic skeleton containing four tertiary hydrogen atoms (among them one bridgehead and one ring junction) and five methylene groups. Thus, the competition between these sites as well as the stereochemistry of the reaction can be studied. It is known that the order of reactivity for RuO_4 is as follows: $CH > CH_2 > CH_3$.[16c,d] Furthermore, oxidation involving microorganisms[20] or mammals,[21] the Gif IV system,[22] dry ozonation,[23] and *m*-chloroperbenzoic

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acid[24] of such derivatives already has been reported so that it is possible to compare the efficiency of the various oxidation procedures. Finally, these derivatives have already been studied extensively in our laboratories both from the reactive and structural point of view.[25] Following our preliminary paper on this topic,[26] we now report the full experimental details on the oxidation of cedrane derivatives with RuO_4 generated in situ.

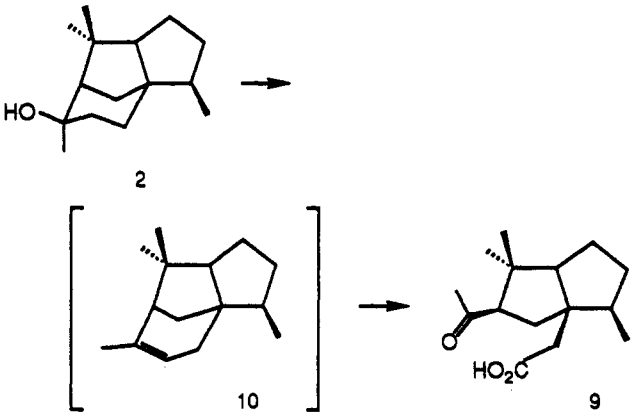
Results and Discussion

All results reported thereafter have been obtained using RuO_4 generated in situ by the oxidation of catalytic amounts (2–4 mol %) of ruthenium chloride hydrate with sodium periodate as the stoichiometric oxidizing agent, in a ternary mixture of solvents $CH_3CN/CCl_4/H_2O$ in a (2/2/3) ratio. These conditions reported by Sharpless[19] have become a standard procedure for the oxidation of a wide range of organic functions[18] and were shown to be the most efficient for the oxidation of saturated hydrocarbons.[27] The presence of acetonitrile is necessary to prevent inactivation of the catalyst and to achieve good conversions, but the role of carbon tetrachloride is not clear[28] since it can be replaced by acetic acid without a decrease in the reaction rate and yield.[29] Water is necessary to dissolve both the ruthenium trichloride hydrate and sodium metaperiodate; anhydrous ruthenium trichloride is ineffective. In all these reactions, the pH remains mildly acidic[29,30] which renders RuO_4 sufficiently stable.

Although a wide variety of reoxidizing reagents can be used, $NaIO_4$ gave the best yields in hydrocarbon functionalization[29] as in the oxidation of epoxynorbornane.[31] Sodium or calcium hypochlorite are fairly efficient and give a satisfactory conversion, but the yields are decreased due to the presence of undesirable chlorinated derivatives.[27,31] Sodium periodate (at least 4 equiv with respect the substrate) is used generally; in some cases, a larger amount is necessary in order to achieve a significant yield (Table I, entries 4, 5) and/or subsequent oxidation reaction (cleavage of the C–C bond; Table I, entry 8).

The functionalization reaction is observed under mild conditions in a temperature range between room temperature and 70 °C.[32] In some cases, hydroxylation does not occur at room temperature or occurs sluggishly. Depending on the nature of the substrate, the oxidation reaction requires between 1 and 5 days. For instance, the conversion of epicedrane 1 into epicedrol 1a (Table I, entry 1) requires 30 h at room temperature, whereas 5 days at 55 °C are needed to hydroxylate neoisocedranol acetate 4 in the 2-position. Hydroxylation yields range from 29% (33% based on recovered starting material) to 80%. The reaction is generally univocal (no significant side products are formed or detected) except in cases where further oxidative cleavage is likely to occur[33] (Table I, entry 6).

It is interesting to compare the hydroxylation yields obtained by the RuO_4 oxidation on various cedrane derivatives with those obtained using other reagents or techniques known to hydroxylate nonactivated C–H bonds. Epicedrane 1 is hydroxylated regioselectively with retention of configuration on the 8α-position with 69% yield (Table I, entry 1). No product with inversion of configuration (i.e. cedrol) is obtained. This result is interesting to compare with the biohydroxylation using *Beauveria sulfurescens*[20] which is inefficient in this case, probably because the substrate has no polar group to be anchored on the active site of the enzymatic(s) system(s). Dry ozonation[23a] is much less efficient (18% yield) and definitely less regioselective as hydroxylation occurs both on the C(2) and C(8) carbon atoms. Inspection of molecular models in the light of reflect effect[34] and proximity effect theories[35] shows that the 8α-H is the less hindered hydrogen atom on a tertiary carbon in isocedrane 1. Accordingly RuO_4 reacts preferentially with unhindered tertiary C–H bonds. When no hydrogen is available on this position as in cedrol 2 or cedryl acetate 3, hydroxylation now occurs on C(2) and requires a higher temperature. The yield is improved significantly starting from cedryl acetate 3 instead of cedrol 2. In the latter case, we have obtained further oxidized products, among which the keto–acid 9 has been identified as main product. This product probably arises from dehydration of cedrol to α-cedrene 10 under these forcing conditions and subsequent cleavage of the double bond by RuO_4.



Neoisocedranol acetate 4 and carbonate 5 are interesting substrates because they can be hydroxylated on both C(2) and C(8). From our previous results, it is clear that the C(8)–H bond is now hindered by the bulky equatorial 9α substituent. Since RuO_4 is sensitive to steric hindrance, it was expected that hydroxylation should occur on C(2), which is indeed the case (Table I, entries 4, 5). In neoisocedranol oxide 6,[25a] the tetrahydrofuran oxygen substituent is 9β, therefore there is no steric interaction with the axial reactive C(8)–H bond. As a consequence the first major product obtained, as shown by TLC monitoring of the reaction, is alcohol 6a, but methyl ketolactone 6b is also formed as a secondary product (Table I, entry 6). When the isolated alcohol 6a was submitted to the same

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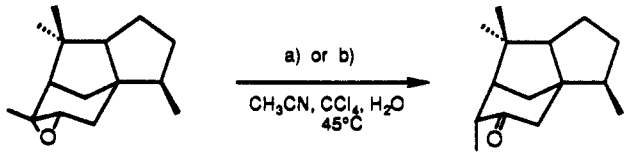
(32) RuO_4 is less thermally stable than the homologue OsO_4. It decomposes explosively at temperatures above 100 °C giving dioxygen and RuO_2. See: Seddon, E. A.; Seddon, K. R. *The Chemistry of Ruthenium*; Elsevier: New York, 1984; p 57.
(33) Tenaglia, A.; Terranova, E.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1344.
(34) Wojnarowski, W.; Ourisson, G. *Bull. Chem. Soc. Fr.* **1967**, 219.
(35) Houk, K. N.; Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* **1990**, *23*, 107.

oxidation conditions (Table I, entry 7), the methyl ketolactone **6b** was the only product. The latter can also be obtained directly from neoisocedranol oxide **6** when a large excess of sodium periodate is used (Table I, entry 8).

With an acid-sensitive substrate, there is obviously a Lewis acid role of the ruthenium species[36] as shown by the clean isomerization of 8α,9-epoxycedrane (7) into cedran-9-one (8) with or without $NaIO_4$.



7 8

a) $RuCl_3$ (5mol%), $NaIO_4$ (400 mol%) 72%
b) $RuCl_3$ (5mol%) 80%

At this stage, general observations concerning this oxidation on cedrane derivatives can be summarized as follows: (1) Hydroxylation occurs exclusively on tertiary carbon atoms with retention of configuration. No bridgehead hydroxylations are observed. The reaction is sensitive to steric hindrance so that it occurs preferentially on C(8) (provided this position is not hindered by a 9α substituent) comparatively to C(2). (2) The hydroxylation reaction with RuO_4 is more regioselective than the one involving *m*-CPBA[24] and is generally more efficient (better yields) than the other techniques known to oxidize hydrocarbons (enzymes in microorganisms[20] or mammals,[21] Gif(IV) system,[22] and dry ozonisation[23]). (3) When hydroxylation can occur on a trisubstituted carbon atom next to a tertiary alcohol, cleavage of a C–C bond is observed.[33]

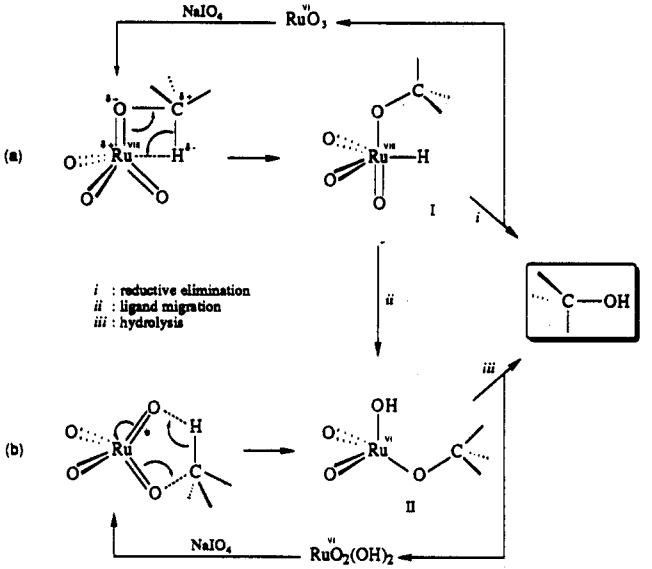
Reaction Mechanism

It is known that the interaction of $RuCl_3 \cdot 3H_2O$ with $NaIO_4$ yields RuO_4.[17a-c] This is the way we prepared ruthenium tetraoxide in a carbon tetrachloride solution in order to show that it was the active species in the hydroxylation of epicedrane 1 which under such stoichiometric conditions yields epicedrol 1a with the same yield as under catalytic conditions. RuO_4 is a highly electrophilic reagent because ruthenium is in its d° state which corresponds to its highest oxidation state.

The oxoruthenium species are most likely to be solvated by CH_3CN ligands[19,38] which would explain the important role of this component in the solvent mixture. As a consequence the whole reactive system is probably fairly bulky, but it is nevertheless able to interact easily with a sterically unencumbered although weakly polarized C–H bond.[39] Due to the strongly electrophilic nature of ruthenium tetraoxide, one would be inclined to favor a ionic mechanism as postulated by Bakke and Lundquist.[16c] This is not in agreement with the stereoselectivity and enantioselectivity observed in our reactions. Epicedrane 1 did not give the epimerization product, and we did not observe any Wagner–Meerwein rearrangements during the hydroxylation reactions on the norbornane skeleton.[26]

A concerted mechanism (Scheme I) allows a reconciliation of our results and those previously reported,[16] provided we consider a C–H polarization with a partial positive charge on the carbon atom.[40] The question of how the approach really occurs (oxoruthenium double bond parallel, colinear, or perpendicular to the C–H bond) is a problem which still needs to be solved. However, we can assume that as RuO_4 approaches the C–H bond, it modifies the polarity so that a partial positive charge develops on the carbon which favors the insertion of the oxoruthenium group into the C–H bond. This reaction could also result from the interaction of the LUMO[41] of RuO_4 with the HOMO of the C–H bond.[42]

Scheme I. Possible Mechanistic Pathways for RuO_4 Oxidation of C–H Bonds



The alkoxyhydridotrioxoruthenium intermediate I (Scheme I, route a) thus formed can then undergo a reductive elimination [which is known to easily occur with metal hydride[43]] to yield the corresponding alcohol and ruthenium trioxide[44] which can be reoxidized back into RuO_4 by $NaIO_4$. It is interesting to note that if this alkoxyhydridotrioxoruthenium intermediate I forms from a secondary carbon atom, a β-elimination would now be possible and would yield directly the corresponding ketone without the occurrence of an intermediate alcohol. Formation of such ketones has not been observed in the cedrane series but occur in methylcyclohexane,[16c] norbornane,[16c] and brendane.[29]

If instead of reductive elimination, intermediate I undergoes an hydrogen migration to an oxo ligand, a new alkoxyhydroxydioxoruthenium intermediate II is formed. Intermediate II which can also result from the interaction of the two oxo ligands of RuO_4 with the C–H bond as suggested earlier[33] (Scheme I, route b) has to undergo an hydrolysis to release the alcohol and a dihydroxydioxoruthenium(IV) species. The latter is then reoxidized into RuO_4 with $NaIO_4$.

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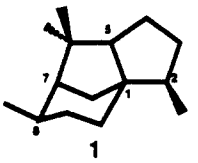
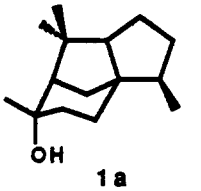
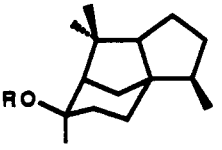
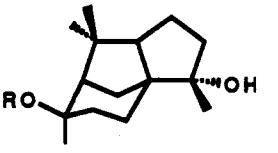
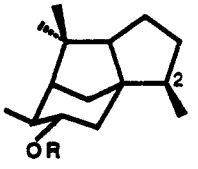
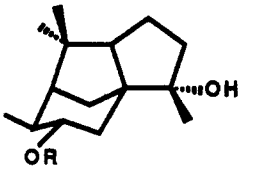
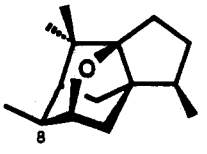
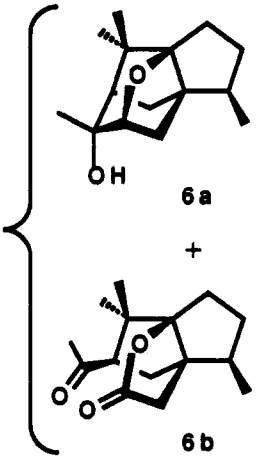
(38) Sharpe, A. G. *The Chemistry of Cyano Complexes of the Transition Metals*; Academic Press: London, 1976.
(39) Coulson, C. A. *Valence*, 2nd ed.; University Press: Oxford, 1965.
(40) Although this is not in agreement with Pauling's electronegativity scale, the C–H bond could be strongly polarized by the approaching, highly electrophilic RuO_4. See the commentary from Allen, L. C. *Acc. Chem. Res.* **1990**, 175.
(41) (a) Rauk, A.; Ziegler, T.; Ellis, D. E. *Theor. Chim. Acta* **1974**, *34*, 49. (b) Foster, S.; Felps, S.; Cusachs, L. C.; Mc Glynn, S. P. *J. Am. Chem. Soc.* **1973**, *95*, 5521.
(42) Although this interaction has not been studied as of yet, the energy of the LUMO of RuO_4 is about −10.16 eV and the energy of the HOMO of a tertiary C–H bond have a average value of −4.13 eV. See also refs 1a and 1f.
(43) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 332.
(44) Although RuO_3 has never been isolated, it was detected at high temperature and postulated as an intermediate in the oxidation of organic compounds by RuO_4. See ref 32, p 71.

Table I. RuO_4-Catalyzed Oxidation of Cedrane and Derivatives

entry	starting compound	reaction conditions: temp (°C)	time (d)	$NaIO_4$ (equiv)	product(s)	yield (%)
1	 1	25	1.25	4	 1a	69
2	 2 R = H	70	1	4	 2a	29
3	3 R = Ac	55	1	4	3a	53
4	 4 R = Ac	55	5	7	 4a	33
5	5 R = CO_2Me	50	3	7.5	5a	35
6	 6	70	2	4	 6a + 6b	48 + 20
7	6a	70	2	4	6b	80
8	6	65	4	14	6b	80

The concerted mechanisms we propose would also be a good rational for the intermediacy of an α cis dioxygenated intermediate to explain oxidative cleavage of neoisocedranol oxide 6 (Scheme II). The occurrence of a key intermediate 11 (see route b in Scheme I), which affords alcohol **6a** in an hydrolysis step, should be responsible for the formation of the tricyclic keto lactone **6b**. Insertion of the oxoruthenium double bond in the C(9)–H bond leads to the dialkoxydihydroxyruthenium(IV) species 12. At this stage hydrolysis is expected to deliver dihydroxylated compound **6c**. To achieve strain release the ring opening of the lactol moiety of **6c** should then give rise to **6d**.

Since no one of these two compounds was detected, we assume a further oxidation of 12 to the dialkoxydioxoruthenium(VI) intermediate 13 which now has a structure similar to the one of the osmate ester formed during the cis dihydroxylation of double bonds.[45] Fragmentation of 13 must occur easily to affords keto lactone **6b** and RuO_2. The occurrence of this process provides an explanation for the need of a large excess of $NaIO_4$. The mechanism of RuO_4 oxidation of secondary alcohols and ethers, known to proceed by hydride abstraction,[46] cannot operate in the oxidation of the tetrahydrofuran ring, i.e. **6**, as it would give rise to a cationic intermediate located on C(9).

The overall hydroxylation (or oxidation) process could also be explained by an insertion of an "oxene",[5] generated from ruthenium tetraoxide, into a C–H bond as does dioxirane. However, at this stage, we do not know to which

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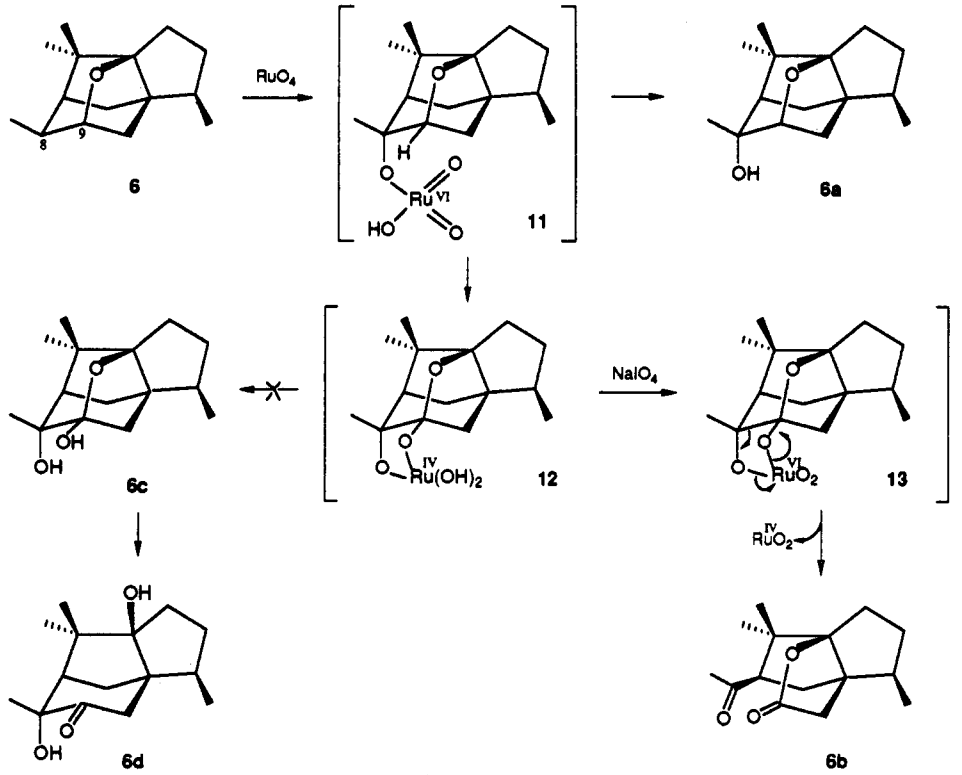
Scheme II. RuO_4 Oxidation of Neoisocedranol Oxide 6



extent RuO_4 can behave as an oxene source. Furthermore, the way the oxene source and the C–H bond would interact remains completely unknown.

If a radical mechanism is considered we must assume that the reaction occurs in a solvent cage in order to explain the complete stereoselectivity and the absence of rearrangement which are observed. There is no evidence for such a mechanism. Furthermore, if we assume the presence of radical intermediates, we would observe dimers and/or chlorinated derivatives due to the presence of CCl_4[47] as a cosolvent. This is not the case.

Finally, a concerted mechanism is the most reasonable and consistent with all our data and those recently reported.[16] We favor a concerted mechanism where the C–H bond is polarized by the electrophilic ruthenium tetraoxide so as to form a partial positive charge on the carbon atom. Our proposals parallel those involving ozone[48] or dioxirane.[5] From the synthetic point of view, the oxidation yields (rates of oxidation) of cedrane derivatives with "RuO_4" generated in situ compete efficiently with other techniques,[20-24] especially if the selectivities observed as well as the mild reaction conditions are taken into consideration.

Experimental Section

All solvents and reagents were purchased from commercial sources and used without further purification unless otherwise indicated. Cedrol was a generous gift from Roure Co. (Grasse, F). 8β-H-cedrane,[37a] cedryl acetate,[37a] 8α-H-9α-acetoxycedrane,[37a] 8α-H-9α,5α-oxycedrane[25a] and 8α,9-epoxycedrane[37a] were prepared according to literature procedures. Infrared spectra were obtained on a Philips PU 9706 infrared spectrophotometer as neat films or in chloroform solution. Frequencies are reported in cm^{-1}. NMR spectra were recorded on a Bruker AC 200 or a Varian XL 200 instrument, with $CDCl_3$ as solvent. Chemical shifts (δ) were reported with Me_4Si (δ 0.00 ppm) or $CHCl_3$ (δ 7.26 ppm) and $CDCl_3$ (77.0 ppm) as internal standards, for ^1H and ^{13}C (50.3 MHz), respectively. The following abbreviations are used: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Melting point were taken on a Reichert apparatus and are uncorrected. Silica gel (Merck, 70–230 or 230–400 mesh for flash chromatography) was used for column chromatography. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254 (0.25 mm, precoated on glass). Elemental analyses were performed by the Service de Microanalyse de la Faculté des Sciences, St-Jêrôme, Marseille, France.

8α-H-9α-[(Methoxycarbonyl)oxy]cedrane (5) was prepared and isolated in 68% yield by chromatography on silica gel (5:95 ether–pentane) according to the procedure described by Tsuji[49] in 68% yield: ^1H NMR ($CDCl_3$) δ 0.83 (d, 3 H, J = 9 Hz), 0.95 (s, 3 H), 1.09 (d, 3 H, J = 6.9 Hz), 1.18 (s, 3 H), 1.20–1.97 (m, 11 H), 2.07 (dq, 1 H, J = 2.3, 6.5 Hz), 3.77 (s, 3 H), 4.88 (ddd, 1 H, J = 6.5, 9.9, 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 155.8 (s), 80.2 (d), 58.1 (d), 55.1 (q), 54.6 (s), 54.4 (d), 46.5 (t), 43.8 (s), 42.7 (d), 41.8 (d), 39.7 (t), 36.7 (t), 28.7 (q), 27.9 (q), 25.7 (t), 17.5 (q),15.4 (q); IR (neat) 2940, 2860, 1735, 1435, 1370, 1360, 1310, 1260, 990, 950 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.06. Found: C, 71.12; H, 10.04.

Oxidation: General Procedure. In a typical reaction, carbon tetrachloride (2 mL), acetonitrile (2 mL), water (3 mL), substrate (1 mmol), sodium metaperiodate (877 mg, 4.1 mmol), and ruthenium chloride hydrate (5 mg, 0.022 mmol) were placed in a 25-mL round-bottom flask and stirred vigorously at the temperature for a length of time indicated for each case (see Table I). The reaction mixture was cooled to 0 °C with an ice bath, and 2-propanol (5 mL) was added (a black color appeared) with vigorous stirring for 1 h. Insoluble materials were filtered through a short pad column of Celite and rinsed with ether (3 × 20 mL). The filtrate was concentrated, and the residue was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

8α-Cedranol (1a) was isolated as a white, crystalline solid by flash chromatography on silica gel (1:1 ether–pentane): mp 34

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(48) Giamalva, D. H.; Church, D. F.; Pryor, W. A. *J. Org. Chem.* 1988, *53*, 3429.

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°C (lit.[37a] mp 35–39 °C); ^{1}H NMR δ 0.78 (d, 3 H, J = 7.0 Hz), 0.94 (s, 3 H), 1.06 (s, 3 H), 1.15–1.95 (m, 14 H), 1.25 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 73.3 (s), 61.5 (d), 56.3 (d), 53.4 (s), 41.9 (s), 41.8 (d), 39.9 (t), 36.9 (t), 34.3 (t), 30.6 (q), 30.5 (t), 29.1 (q), 28.2 (q), 25.4 (t), 15.5 (q); IR ($CHCl_3$) 3600, 3450, 2940, 1455, 1375, 1305, 1085, 990, 965, 890, 855 cm^{-1}.

2α,8β-Dihydroxycedrane (2a) was isolated as a white, crystalline solid by flash chromatography on silica gel (1:1 AcOEt–pentane): mp 134 °C (lit.[23b] mp 135–137 °C, lit.[24b] mp 80–82 °C);[50] ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 3 H), 1.18 (s, 3 H), 1.28 (s, 3 H), 1.30 (s, 3 H), 1.15–1.96 (m, 14 H), ^{13}C NMR ($CDCl_3$) δ 79.6 (s), 74.9 (s), 59.1 (d), 57.6 (s), 53.5 (d), 45.0 (s), 41.3 (t), 36.6 (t), 35.7 (t), 30.4 (q), 30.0 (t), 28.5 (q), 27.5 (q), 24.3 (q), 21.5 (t); IR ($CHCl_3$) 3600, 3460, 2950, 1705, 1455, 1375, 1295, 1170, 1125, 1090, 1010, 975, 945, 920 cm^{-1}.

2α-Hydroxy-8β-acetoxycedrane (3a) was isolated as a white, crystalline solid by flash chromatography on silica gel (1:1 ether–pentane): $[\alpha]^{22}_D$ +20.6° (c 7.29, $CHCl_3$); mp 58 °C (lit.[23a] mp 57–58 °C, lit.[24b] mp 59–60 °C); ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 3 H), 1.04 (d, 3 H, J = 7.1 Hz), 1.17 (s, 6 H), 1.10–2.16 (m, 11 H), 2.05 (s, 3 H), 5.0 (1 H, ddd, J = 11, 11, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 85.9 (s), 79.4 (s), 57.4 (s), 54.9 (d), 53.8 (d), 44.9 (s), 41.3 (t), 35.7 (t), 33.6 (t), 29.6 (t), 28.0 (q), 26.7 (q), 25.9 (q), 24.2 (q), 22.7 (q), 21.5 (t); IR ($CHCl_3$) 3600, 3460, 2950, 1715, 1470, 1450, 1370, 1245, 1025, 1015, 975, 965 cm^{-1}.

2α-Hydroxy-8α-H-9α-acetoxycedrane (4a) was isolated as a clear, colorless oil by flash chromatography on silica gel (1:1 ether–pentane): $[\alpha]^{22}_D$ +46.5° (c 9.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 3 H), 1.05 (d, 3 H, J = 7.1 Hz), 1.1–2.2 (m, 12 H), 1.16 (s, 6 H), 2.05 (s, 3 H), 5.0 (ddd, 1 H, J = 11, 11, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.8 (s), 79.6 (s), 75.4 (d), 57.9 (s), 54.8 (d), 53.1 (d), 45.1 (s), 42.4 (d), 41.1 (t), 40.6 (t), 37.8 (t), 28.1 (q), 27.6 (q), 24.1 (q), 21.7 (t), 21.1 (q), 17.3 (q); IR ($CHCl_3$) 3595, 3480, 2950, 1720, 1460, 1440, 1370, 1245, 1030, 1015, 980, 970 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.06. Found: C, 72.15; H, 10.54.

2α-Hydroxy-8α-H-9α-[(methoxycarbonyl)oxy]cedrane (5a) was isolated as a clear, colorless oil by flash chromatography on silica gel (1:1 AcOEt–pentane): $[\alpha]^{22}_D$ +49.9° (c 7.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.10 (d, 3 H, J = 7.1 Hz), 1.17 (s, 6 H), 1.22–2.15 (m, 12 H), 3.77 (s, 3 H), 4.84 (ddd, 1 H, J = 6.5, 10.7, 10.7 Hz); ^{13}C NMR ($CDCl_3$) δ 155.8 (s), 80.1 (d), 79.7 (s), 58.1 (s), 55.0 (q), 54.5 (d), 53.2 (d), 45.3 (s), 42.5 (d), 41.2 (t), 40.7 (t), 37.9 (t), 28.3 (q), 27.7 (q), 24.3 (q), 21.9 (t), 17.4 (q); IR ($CHCl_3$) 3595, 3460, 2950, 2900, 1730, 1440, 1370, 1360, 1315, 1270, 1140, 945 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52. Found: C, 68.80; H, 9.55.

5β,9β-Oxy-8α-hydroxycedrane (6a) was isolated as a white, crystalline solid by flash chromatography on silica gel (3:7 ether–pentane): $[\alpha]^{22}_D$ −5.1° (c 5.83, $CHCl_3$); mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (1 H, d, J = 4.1 Hz), 1.43 (s, 3 H), 1.23 (s, 3 H), 1.0–2.0 (m, 11 H), 0.98 (s, 3 H), 0.92 (d, 3 H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 101.3 (s), 84.7 (d), 72.4 (s), 62.5 (d), 61.1 (s), 44.3 (s), 41.6 (d), 38.7 (t), 37.5 (t), 36.1 (t), 29.3 (q); 28.2 (q), 26.6 (t), 23.6 (q), 14.8 (q); IR ($CHCl_3$) 3590, 3430, 2935, 2855, 1475, 1445, 1365, 1225, 1160, 1115, 1085, 1050, 1005, 985, 965, 940, 915, 895 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.25; H, 10.19.

Keto lactone 6b was isolated as a white, crystalline solid by flash chromatography on silica gel (1:1 ether–pentane): $[\alpha]^{22}_D$ −55.5° (c 8.38, $CHCl_3$); mp 87 °C; ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 1 H), 2.74 (1 H, d, J = 19.3 Hz), 2.33 (1 H, d, J = 19.3 Hz), 2.17 (s, 3 H), 1.05–2.07 (m, 7 H), 1.28 (s, 3 H), 1.02 (d, 3 H, J = 6.6 Hz), 0.83 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.6 (s), 177.7 (s), 107.0 (s), 57.2 (d), 54.1 (s), 46.4 (s), 46.1 (d), 39.4 (t), 37.7 (t), 34.6 (t), 31.8 (t), 31.6 (q), 23.5 (q), 18.5 (q), 14.1 (q); IR ($CHCl_3$) 2960, 2860, 1760, 1705, 1415, 1360, 1215, 995 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. Found: C, 71.93; H, 8.78.

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Registry No. 1, 13567-54-9; **1a**, 19903-73-2; **2**, 77-53-2; **2a**, 67152-03-8; **3**, 77-54-3; **3a**, 65669-75-2; **4**, 19903-81-2; **4a**, 127558-82-1; **5**, 127558-83-2; **5a**, 127558-84-3; **6**, 61234-88-6; **6a**, 142745-21-9; **6b**, 142745-22-0; **7**, 13567-39-0; **8**, 13567-40-3; **9**, 142864-21-9; **10**, 469-61-4; R_4O_4, 20427-56-9.

(50) The melting point reported in ref 24b for 2α,2β-dihydroxycedrane is apparently erroneous.

Tautomerization of 1-(*N*-Methoxyamino)cyclohepta-1,3,5-triene into 3,5-Cycloheptadien-1-one *O*-Methyloxime: A Regiospecific Enamine–Imine Interconversion

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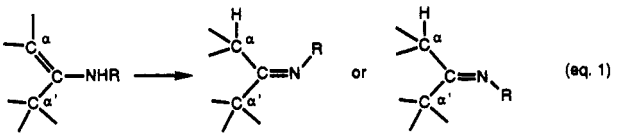
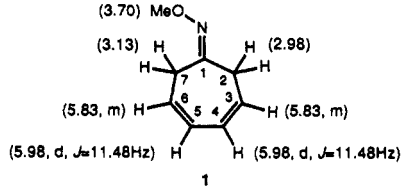
Although there have been many investigations of stereospecificity and regiospecificity in the reactions of enamines,[1] there appears to have been no investigation of the steric course of an enamine–imine interconversion (e.g., eq 1), presumably because imines are normally hydrolyzed much faster than they are formed from the enamines.[2] As shown in eq 1, the R group attached to the nitrogen of the imine product can lie either on the same or the opposite side of the double bond of the original enamine (syn or anti to the group which was protonated).



(eq. 1)

The signals in the ^{1}H NMR spectrum of 3,5-cycloheptadien-1-one *O*-methyloxime in DMSO-d_6 were assigned as shown in **1**. The protons at positions 2 and 7 had different chemical shifts as a result of hindered rotation around the C=N bond, but those at positions 3 and 6 and at positions 4 and 5 were indistinguishable from one another in the 270-MHz spectrum. A nuclear Overhauser effect (NOE) experiment indicated that the low-field methylene group signal at δ 3.13 was that of the protons syn to the methoxyl group whereas the high-field signal at δ 2.98 was due to the protons anti to the methoxyl group. Irradiation of the low-field signal (δ 3.13) gave a 10.4% enhancement of the signal of the methoxyl group (δ 3.70), but irradiation of the high-field signal (δ 2.98) gave no enhancement.



1

The N-deuterated enamine form (**3**) of this *O*-methyloxime was generated by hydrolysis of its *N*-trimethylsilyl derivative **2** in DMSO-d_6–D_2O (95:5 v/v) at 25 °C which

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