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THE STEREOCHEMISTRY OF PIPITZOLS AND PEREZOLS†

P. JOSEPH-NATHAN,* L. U. ROMÁN and J. D. HERNANDEZ
Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, P.O. Box 14-740, México 14, D.F., México

and

Z. TAIRA and W. H. WATSON*
FASTBIOS Laboratory, Department of Chemistry, Texas Christian University, Fort Worth, TX 76129, U.S.A.

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Abstract—The stereochemistry of α-pipitzol (**1a**) has been established by transformation to cedrene (**4**) and by single crystal X-ray diffraction of α-pipitzol benzoate (**1b**). The stereochemistries of the related cedranolides β-pipitzol (**2a**), α-(**1c**), β-(**2c**) and γ-perezol (**1d**) are assigned from their respective ORD curves.

Although the structures of the naturally occurring α-(**1a**) and β-pipitzol (**2a**) were elucidated more than a decade ago,[1] the stereochemistry of these molecules remained tentative[2] due to the lack of adequate models for ORD and CD comparison. This situation arises from the fact that in the pipitzols (**1a** and **2a**) the three O atoms are arranged in such a way that several types[3] of chromophores could be considered for the interpretation of the chiroptical data. Since the chiral center of perezone (**3**) has been established as *R* by chemical degradation[4] and by ORD measurements,[5] it follows from the reaction mechanism of the perezone (**3**)-pipitzol (**1a** + **2a**) transformation[6] that one of the pipitzols must have the same stereochemistry as cedrene (**4**), a related natural product of known[7] chirality. Our original studies suggested that this should be the case of the α-isomer.

In order to test this assumption, it is necessary to correlate the two molecules, or, alternatively to establish the relative stereochemistry of α-pipitzol (**1a**) using single crystal X-ray diffraction, since the chiral center that arises from perezone (**3**) is known. The present work describes both the chemical transformation of α-pipitzol (**1a**) to cedrene (**4**) and the X-ray crystallographic study of α-pipitzol benzoate (**1b**), which shows that our original stereochemical assignments are indeed correct.

The transformation of a given pipitzol to cedrene (**4**) simply requires the removal of the three O atoms. Many direct and indirect sequences of reactions were explored to achieve the overall transformation, until it was found that two successive formations of dithioethylene-ketals followed in each case by a desulfurization provide a satisfactory route.

Treatment of α-pipitzol benzoate (**1b**) with ethanedithiol in the presence of boron trifluoride etherate gave the dithioketal **5a**. The formation of the heterocyclic ring was deduced from the disappearance of the CO band at 1690 cm^{-1} in the IR spectrum and the presence of the dithioethylene protons as a complex signal in the 3.1–3.5 ppm region of the NMR spectrum.

The sulfur containing ring was eliminated by treatment with absolutely neutral Raney nickel, in order to preserve the enol benzoate. This yielded 4-desoxo-α-pipitzol benzoate (**5b**) which showed only one broad CO band at 1740 cm^{-1} due to the cyclopentanone and benzoate in the IR spectrum, while in the NMR spectrum the benzoate protons are present at 8.12 (2H) and 7.52 (3H), a new broad band at 2.59 (2H) corresponds to the C-4 methylene protons and the vinylic Me group is found as a triplet (J = 1.6 Hz) at 1.64 ppm.

Similary, treatment of β-pipitzol benzoate (**2b**) with ethanedithiol gave the ketal **6a** which after desulfurization provided 4-desoxo-β-pipitzol benzoate (**6b**). Its IR spectrum showed the two CO groups at 1740 cm^{-1} while in the PMR spectrum the benzoate signals appear at 8.08 (2H) and at 7.56 (3H), the C-4 methylene protons are found at 2.95(1H) and at 2.42(1H) representing the AB portion (J_{AB} = 16 Hz) of an ABX_3 system formed with the vinylic Me group which appears as a triplet ($J_{AX_3} = J_{BX_3}$ = 1.6 Hz) at 1.64 ppm.

When both **5b** and **6b** are treated again with ethanedithiol in the presence of boron trifluoride etherate, ketalization at the bridge CO position occurs, which yields the corresponding dithio derivatives **7a** and **8a**. Desulfurization of these compounds with neutrally washed Raney nickel in absolute ethanol, gave the enol-benzoates **7b** and **8b** respectively. Their IR spectra show the enol ester CO at 1740 cm^{-1}. In the PMR spectra the benzoate hydrogens appear in the low field region and the vinylic Me group of each compound appears as a triplet (J = 1.6 Hz) around 1.60 ppm.

At this point it was decided to establish the identity of either **7b** or **8b** with a compound derived from cedrene(**4**). Epoxidation of the double bond of the hydrocarbon followed by boron trifluoride rearrangement gave the known[8] cedranone. This ketone was treated with benzoic anhydride in the presence of perchloric acid to yield the corresponding enol benzoate which was identified as **7b** by mixed m.p. and spectral comparison. It is interesting to mention that both the UV and IR spectra of **8b** and of samples of **7b** derived from either α-pipitzol (**1a**) or cedrene (**4**) are quite similar, thus precluding a definitive identification. However the high

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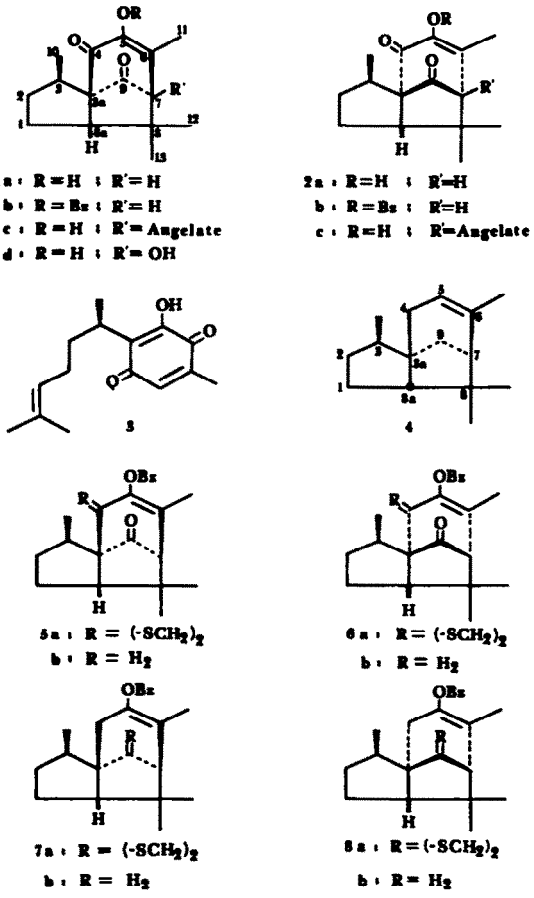

Scheme 1.

field, region of the PMR spectra clearly allowed correlation, since in the α-isomer (**7b**) the *gem*-dimethyl signals appear at 1.15 and 1.01 and the secondary Me group is found at 0.89, while in the β-isomer (**8b**) the secondary Me appears at 0.97 and the *gem*-dimethyl signals at 1.17 and 0.98 ppm. A more objective differentiation of **7b** and **8b** and therefore a better criterion for identification of the samples arising from α-pipitzol (**1a**) and from cedrene(**4**) is obtained by comparison of ^{13}C NMR spectra which are more sensitive to stereochemical changes. The most significant differences are found at the C-3 chiral center. In the case of the α-isomer the secondary Me group is found at 15.4, the C-3 signal at 41.2 and the C-2 methylene at 36.0 ppm while the same signals for the β-isomer appear at 13.6, 34.4 and also 34.4 ppm respectively. The remaining signals show small chemical shift differences for the two isomers.

If the secondary Me group of either pipitzol would have the opposite configuration, the two molecules (**7a** and **8a**) would be enantiomeric and their ^{13}C NMR spectra in achiral media would be identical. However the difference in stereochemistry of all centers except one, produces significant changes in the spectra. This observation suggests that ^{13}C NMR spectroscopy provides a more adequate criterion to establish the identity of organic molecules arising from different sources than the widely used IR comparison. ^{13}C NMR provides other advantages since one is more concerned with chemical shifts and solutions of different concentrations can be compared and even sample purity is not as critical as in IR spectroscopy.

The conversion of α-pipitzol (**1a**) to cedrene (**4**) was completed by hydrolysis of the enol ester of **7b** to the corresponding ketone identified as isocedranone.[8] Reduction of the CO group with $NaBH_4$ gave neoisocedranol[8] which was treated with $POCl_3$ in pyridine to yield cedrene (**4**), identical in all respects with an authentic sample.

Although the above reactions define the stereochemistry of α-pipitzol (**1a**), independent evidence was obtained by a single crystal X-ray diffraction investigation[9] of α-pipitzol benzoate (**1b**). The results are summarized in Fig. 1, which shows that the 5-membered ring containing the ketone function exists in a distorted half-chair conformation while the other 5-membered ring exhibits a normal half-chair conformation. The conjugated portion of the molecule (**3a, 4, 5, 6, 7**) is planar, which forces the 6-membered ring into a 1,2-diplanar conformation with the 7-membered ring having atoms 8 and 8a folded

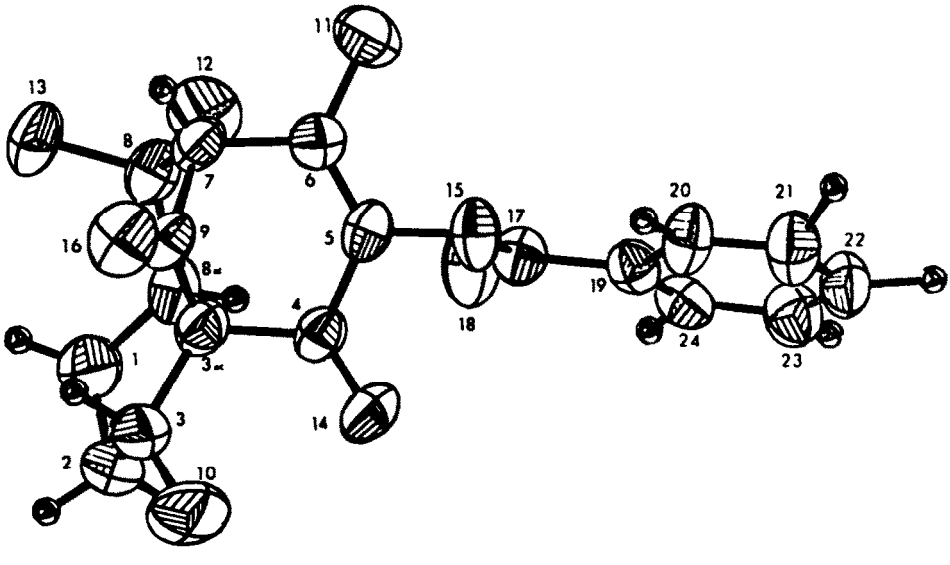

Fig. 1. Perspective view of the molecular structure of α-pipitzol benzoate (**1b**).

sharply out of the plane. The bond lengths and angles are normal and the relative stereochemistry is that shown in (IIb).

Once the stereochemistry of α-pipitzol (1a) is unambiguously proven, that of β-pipitzol (2a) follows from the reaction mechanism of the perezone-pipitzol transformation.[6] Furthermore the ORD curve of α-pipitzol (1a) shows a positive Cotton effect in the 310 nm region while that of β-pipitzol (2a) shows a negative one. Since both α-(1c)[10] and γ-perezol (1d)[11] show positive Cotton effects, they possess the same stereochemistry as α-pipitzol (1a) while β-perezol (2c) with a negative effect[10] has the stereochemistry of β-pipitzol (2a).

EXPERIMENTAL

M.ps are uncorrected. IR spectra in $CHCl_3$ were obtained on a Perkin–Elmer 421 and UV spectra in 95% EtOH on a Unicam SP–800. ^1H NMR spectra in $CDCl_3$ or CCl_4 with internal TMS were recorded on Varian Associates A-60 and XL-100A-12 Spectrometers in the CW mode. ^{13}C NMR spectra were recorded on an XL-100A-12-FT-16K in $CDCl_3$ using deuterium pulse lock. Rotations at 589 nm in 95% EtOH and ORD in dioxane were obtained on a Perkin–Elmer 141M. Chromatographic separations were made on Alcoa F–20 alumina and microanalyses were performed by the Alfred Bernhard Laboratories (West Germany).

Ethylenedithioketal of α-pipitzol benzoate (5a)

A mixture of 1b (15 g) ethanedithiol (60 ml) and $Et_2O:BF_3$ (60 ml) was stored at room temp during 4 days. The mixture was poured on ice and extracted twice with ether. The combined organic layers were washed some 10–12 time with 20% NaOHaq and then with water until neutral. The ethereal soln was dried over an Na_2SO_4, filtered and concentrated. Akktion of hexane gave 13.8 g of the title compound as white crystals m.p. 218–220°. The analytical sample was obtained after recrystallizations from chloroform-hexane and showed m.p. 220–221°; $(\alpha)_D$–156° (*c*, 2); λ_{max} 231 nm, log ε = 4.23; ν_{max} 1740 (cyclopentanone and benzoate carbonyls) and 1270 cm^{-1} (ester O–C); PMR: 8.15 (2H) and 7.55 (3H) benzoate, 3.5 to 3.0 (complex, 4H) dithioethyleneketal, 2.60 (m, 1H) H-3, 2.18 (s, 1H) H-7, 1.62 (s, 3H) Me at C-6, 1.32 (d, *J* = 7 Hz, 3H) Me at C-3 and 1.31 (s 3H) and 0.93 ppm (s, 3H) *gem*-dimethyl. (Found: C, 67.37; H, 6.62; 0, 11.19; S, 14.91. Calc. for $C_{24}H_{28}O_3S_2$: C, 67.26; H, 6.58; 0, 11.20; S, 14.96%).

Ethylenedithioketal of β-pipitzol benzoate (6a)

A mixture of 2b (10 g), ethanedithiol (40 m.) $Et_2O:BF_3$ (40 m.) was treated as in the previous case, yielding 9.4 g of the title compound as white crystals m.p. 195–197°. The analytical sample obtained after recrystallization from chloroform-hexane showed m.p. 198–199°; $(\alpha)_D$ +77.5°(*c*, 2); λ_{max} 231 nm, log ε = 4.23; ν_{max} 1740 (cyclopentanone and benzoate CO's) and 1270 cm^{-1} (ester O–C); PMR: 8.15 (2H) and 7.55 (3H) benzoate; 3.4 to 3.1 (complex, 4H) dithioethyleneketal, 2.55 (m, 1H) H-3, 2.21 (s, 1H) H-7; 1.71 (s, 3H) methyl at C-6; 1.52 (d, J = 7 Hz, 3h) methyl at C-3 and 1.29 (s, 3H) and 0.99 ppm (s, 3H) *gem*-dimethyl. (Found: C, 67.09; H, 6.56; O, 11.36; S, 14.93; Calc. for $C_{24}H_{28}O_3S_2$: C, 67.26; H, 6.58; O, 11.20; S, 14.96%).

4-Desoxo-α-pipitzol benzoate (5b)

A soln of 5a (5 g) in 300 ml abs EtOH was refluxed during 5 hr in the presence of W-7 Raney Ni. After preparing the catalyst[12] it was washed with distilled water until neutral, then with EtOH and finally two times with absolute alcohol. This prevents hydrolysis of the enol benzoate. After completition of the reaction the catalyst was removed by filtration and the solvent evaporated to dryness. The oily residue was chromatographed over 50 g of alumina. The fractions eluted with hexane and hexane-benzene (9:1) crystallized after addition of MeOH. Recrystallization from the same solvent gave white crystals of the title compound showing m.p. 86–87°; $(\alpha)_D$ +2.5°(*c*, 2); λ_{max} 232 nm, log ε = 4.26; ν_{max} broad 1750–1730 (cyclo pentanone and benzoate carbonyls) and 1270 cm^{-1} ester O–C); proton NMR: 8.12 (2H) and 7.52 (3H) benzoate, 2.59 (broad, 2H) C – 4 protons, 2.52 (m, 1H) H-3, 2.05 (s, 1H) H-7, 1.64 (t, J = 1.6 Hz, 3H) Me at C-6, 0.85 (d, J = 7 Hz, 3H) methyl at C-3 and 1.28 (S, 3H)and 0.92 ppm [s, 3H] *gem*-dimethyl; ORD[*c*, 0.5]: $(\phi)_{577}$ + 7°, $(\phi)_{436}$ + 40°, $(\phi)_{405}$ + 61°, $(\Phi)_{365}$ + 200°, $(\Phi)_{313}$ + 1300°, $(\Phi)_{302}$ – 160°, $(\Phi)_{297}$ – 968°, $(\Phi)_{289}$ – 1350°. (Found: C, 77.95; H, 7.71; O, 14.35. Calc. for $C_{22}H_{26}O_3$: C, 78.07: H, 7.74: O, 14.18%).

4-Desoxo-β-pipitzol benzoate (6b)

Treatment of 6a (2 g) as in the previous case gave 500 mg of the ltitle compound m.p. 102–103°, $(\alpha)_D$ – 27° (*c*, 2); λ_{max} 232 nm, log ε = 4.26; ν_{max} 1740 (cyclopentanone and benzoate CO's) and 1270 cm^{-1} (ester O–C); PMR: 8.08(2H) and 7.56 (3H) benzoate, 2.95 (dq, J_D = 16 Hz, 1H) and 2.42 (d_q, J_d = 16 Hz, J_q = 1.6 Hz, 1H) C–4 protons, 2.49 (m, 1H) H-3, 1.98 (s, 1H) H-7, 1.64 (t, J = 1.6 Hz, 3H) Me at C-6, 1.29 (d, J = 7 Hz, 3H) Me at C-3 and 1.26 (s, 3H) and 0.95 ppm (s, 3H) *gem*-dimethyl; ORD (*c*, 0.125): $(\Phi)_{577}$ – 135°, $(\Phi)_{436}$ – 433°, $(\Phi)_{405}$ – 510°, $(\Phi)_{365}$ – 920°, $(\Phi)_{313}$ – 2000°, $(\Phi)_{302}$ + 1270°, $(\Phi)_{289}$ + 2680°, $(\Phi)_{280}$ – 920°. (Found: C, 78.00; H, 7.71; O, 14.04; Calc. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74; O, 14.18%).

Ethylenedithiodetal (7a) *derived from α-pipitzol* (1a)

A mixture of 5b (750 mg), 3 ml ethanedithiol (3 ml) and $Et_2O:BF_3$ (3 ml) was stored at room temp during 5 hr Workup as in the previous cases gave, after chromatography and recrystallization from MeOH, the title compound, m.p. 77–78°; $(\alpha)_D$ + 20° (*c*, 2); λ_{max} 289 nm, log ε = 3.52; ν_{max} 1730 and 1270 cm^{-1} (ester); PMR: 8.15 (2H) and 7.60 (3H) benzoate, 3.4 to 3.1 (complex, 4H) dithioethyleneketal, 2.32 (s, 1H) H-7, 1.59 (T, J = 1.6 Hz, 3H) methyl at C-6, 1.25 (s, 6H) *gem*-dimethyl and 0.89 ppm (d, J = 7 Hz, 3H) Me at C-3. (Found: C, 69.35;H, 7.29; O, 7.71; Calc. for $C_{24}H_{30}O_2S_2$: C, 69.53; H, 7.30; O, 7.71%).

Ethylenedithioketal (8a) *derived from β-pipitzol* (2a)

A mixture of 6b (1 g), ethanedithiol (4 ml) and $Et_2O:BF_3$ (4 ml) was treated as in the previous case. The crystalline fractions from the chromatography were combined and recrystallized from chloroform-hexane to yield the title compound, m.p. 162–163°; $(\alpha)_D$ + 76° (*c*, 2); λ_{max} 289 nm, log ε = 3.56; ν_{max} 1730 and 1270 cm^{-1} (ester); proton NMR: 8.11 (2H) and 7.51 (3H) benzoate, 3.4–3.0 (complex, 4H) dithioethyleneketal, 2.07 (s, 1H) H-7, 1.54 (T, J = 1.6 Hz, 3H) Me at C-6, 1.41 (s, 3H) and 1.29 (s, 3H) *gem*-dimethyl and 1.23 ppm (d, J = 7 Hz, 3H) methyl at C-3. (Found: C, 69.47; H, 7.25; O, 7.85; S, 15.45; Calc. for $C_{24}H_{30}O_2S_2$: C, 69.53; H, 7.30; O, 7.71; S, 15.46%).

4, 9-*Bisdesoxo-α-pipitzol benzoate* (7b)

A soln of 7a (100 mg) in 60 ml abs alcohol was refluxed in the presence of 2 g Raney Ni for 5 hr Workup as usual followed by chromatography of the oily residue and recrystallization of the crystalline fractions from MeOH gave the title compound, m.p. 50–51°; $(\alpha)_D$ – 65°, λ_{max} 231, log ε = 4.23, ν_{max} 1730 and 1270 cm^{-1} (benzoate), PMR: 8.06 (2H) and 7.51 (3H) benzoate, 1.60 (t, J = 1.6 Hz, 3H) methyl at C-6, 1.15 (s, 3H) and 1.01 (s, 3H *gem*-dimethyl and 0.89 ppm d, J = 7 Hz, 3H) Me at C-3. (Found: C, 81.37; H, 8.59; O, 10.04; Calc. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70; O, 9.86%).

4, 9-*Bisdesoxo-β-pipitzol benzoate* (8b)

A soln of 8a (350 mg) in 100 ml abs alcohol was refluxed in the presence of 7 g Raney Ni as in the previous case. This yielded the title compound, m.p. 109–110°; $(\alpha)_D$ + 46° (*c*, 2); λ_{max} 231 nm, log ε = 4.22; ν_{max} 1730 and 1270 cm^{-1} (benzoate); PMR: 8.09 (2H) and 7.53 (3H) benzoate, 1.59 (t, J = 1.6 Hz, 3H) Me at C-6, 1.17 (s, 3H) and 0.98 (s, 3H) *gem*-dimethyl and 0.97 ppm (d, J = 7 Hz, 3H) methyl at C-3. (Found: C, 81.29; H, 8.71; O, 9.87; Calc. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70; O, 9.86%).

Cedranone enol benzoate (7b)

A soln of 4 ml cedranone,[8] (4 ml) benzoic angydride (8 g), 65% $HClO_4$ (3 drops) and CH_2Cl_2 (25 ml) was stirred under a N_2 at room temp during 24 hr. The mixture was poured on ice water and extracted with ether. The organic layer was washed with water dried over Na_2SO_4, filtered and evaporated to dryness. The

brown residue was chromatographed over 50 g of alumina. The fractions eluted with hexane were rechromatographed. The crystalline fractions eluted with pentane and hexane were combined and recrystallized from MeOH yielding 2 g of crystals, m.p. 49–50°. A final recrystallization gave the title compound, m.p. 50–51°. This specimen was identical to the sample obtained from α-pipitzol by mized m.p. and comparison of their proton and ^{13}C NMR spectra.

Transformation of 4, 9-*bisdesoxo-α-pipitzol benzoate* (7b) *to cedrene* (4)

A soln of 700 mg of 7b in 250 ml MeOH was refluxed for 3 hr in the presence of 1 g $NaHCO_3$ in 1 ml water. The soln was concentrated to a small volume, diluted with water and extracted with ether. The organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated. The residue was chromatographed over 25 g of alumina. The fractions eluted with pentane gave 125 mg of the starting material. Those eluted with hexane afforded 400 mg of the starting material. Those eluted with hexane afforded 400 mg of isocedranone[8] as a colorless liquid, $(\alpha)_D$ −16° (lit[8] −15°); ν_{max} 1710 (cyclohexanone); proton NMR singlets at 57 and 55 and doublets at 64 and 52 Hz (at 60 MHz) due to[8] four Me groups.

A soln of 400 mg of the above isocedranone and 400 mg $NaBH_4$ in 10 ml MeOH was stored at room temp for 3 hr Workup as usual followed by chromatography over 15 g of alumina gave 150 mg of a colorless oil identified as neoisocedranol. It showed $(\alpha)_D$ −32° (lit[8] −33.4°); ν_{max} 3605 cm^{-1} (OH); PMR 3.96 (m, 1H) H–C–O, 1.26 and 0.93 (two singlets) and 0.98 and 0.83 ppm (two doublets) from Me groups.

A soln of 100 mg of the above alcohol in 10 ml pyridine was treated at 0° with 10 drops $POCl_3$. The mixture was stored at 0° during 19 hr and worked up as usual. This yielded 60 mg of cedrene (4) identical in all respects with an authentic sample.

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