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SEDUM ALKALOIDS. X. STRUCTURE AND SYNTHESIS OF NEW 3- AND 5-HYDROXYPIPERIDINE ALKALOIDS .

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Abstract. The structure and absolute configuration of (-)-3-hydroxynorallosedamine 1, (-)-3-hydroxyallosedamine 2 and (-)-5-hydroxysedamine 3, three new minor alkaloids isolated from Sedum acre, are reported. A nitrone-based synthesis of the new bases is described.

Sedum acre contains a variety of piperidine alkaloids most of which appear, at least formally, as derivatives of sedamine[1] and, to a lesser extent, of allosedamine. Until now, three of them were known to accomodate a hydroxyl group in the piperidine ring: sedacryptine[2] and the recently isolated bases 4-hydroxysedamine and 4-hydroxyallosedamine[3]. Our continuing investigations on the alkaloids of Sedum acre have resulted in the isolation, after repetitive countercurrent distribution and column chromatography, of three new hydroxypiperidine derivatives: (-)-3-hydroxynorallosedamine 1, (-)-3-hydroxyallosedamine 2 and (-)-5-hydroxysedamine 3. The structure determination and the synthesis of these bases are reported in the present communication.

Structure of the new bases.

The mass spectrum of 1 revealed a molecular ion at m/z 221 ($C_{13}H_{19}NO_2$ by high resolution mass spectrometry) and a base peak at m/z 100 ($C_5H_{10}NO$; α-cleavage with loss of the side-chain; Fig. 1) indicative of the presence of a hydroxypiperidine ring[3]. In the virtually identical mass spectra of 2 and 3, the corresponding ions appeared respectively at m/z 235 and 114.

+Research Associate of the National Fund for Scientific Research (Belgium).

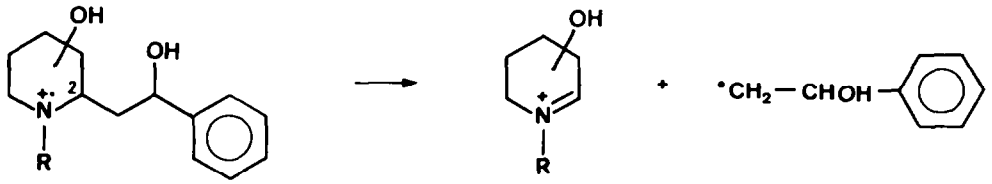
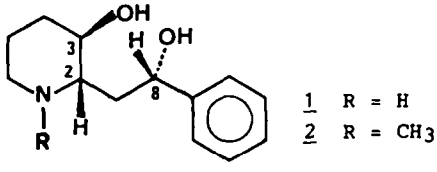
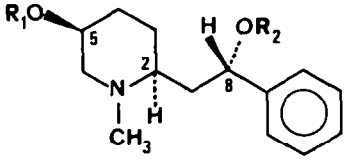


Figure 1.

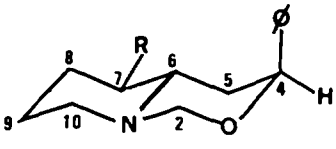
3-Hydroxynorallosedamine 1, m.p. 155-156°, $[\alpha]_D^{22}$ -66° (c=1.3, MeOH) yielded the tetrahydro 1,3-oxazine 5a ($M^{+\cdot}$ at m/z 233) after treatment with aqueous formaldehyde in the presence of KOH. The proton NMR spectrum of 5a established the presence of an equatorial hydroxyl group at C7 (C7-H: 3.50 ppm; ddd, J = 4 (H8e), 8 (H6a) and 10 Hz (H8a)) and an axial phenyl group at C4: C4-H appeared at 5.22 ppm (dd enlarged by coupling with aromatic protons), a value characteristic for an equatorial proton in this series (an axial C4-H should have appeared at ca. 4.5 ppm)[3]. The value of the geminal coupling constant observed for C2-H_2 (-8.5 Hz) and the presence of Bohlmann bands[4] between 2700 and 2800 cm^{-1} in the IR spectrum indicate that the tetrahydro 1,3-oxazine 5a exists predominantly in a trans-fused ring conformation[5]. The ^{13}C NMR data of 5a are also in agreement with the assigned structure; when the ^{13}C signals of 5a were compared with those of 5b[3], α-, β- and γ-effect shifts of 41.6, 9.2 and -2.4 respectively were found to be produced by the C7-OH group, consistent with its equatorial orientation[6]. The relative configuration of 1 is therefore established.



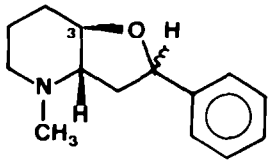
1 R = H
2 R = CH_3



3 $R_1 = R_2 = H$
4 $R_1 = R_2 = Ac$



5a R = OH
5b R = H



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3-Hydroxyallosedamine 2 (perchlorate: m.p. 162-163°, $[\alpha]_D^{22}$ -40° (c=2.4, MeOH) only differs from 1 by the presence of a N-CH_3 group (s at 2.4 ppm in the ^1H NMR spectrum): $LiAlH_4$ reduction of the tetrahydro 1,3-oxazine 5a in refluxing tetrahydrofuran leads to 2 (90% yield from 1) identical in all respects with the natural base. A chemical proof for the 3- position of the hydroxyl group on the piperidine ring in 2 (and therefore also in 1) is provided by the facile conversion of 2 in to

the tetrahydrofuran derivative 6 ($M^{+\cdot}$ at m/z 217) by treatment with TsCl in chloroform and then in strongly basic medium. In this reaction the initial N-tosylammonium chloride leads by internal substitution to a benzylic tosylate whose leaving group is substituted by the oxygen atom at C3.

The absolute configuration of the new bases 1 and 2 as depicted in the formula (2S, 3R, 8S) rests on the isolation of dextrorotatory α-phenylbutyric acid by application of Horeau's method[7] on the tetrahydro 1,3-oxazine 5a.

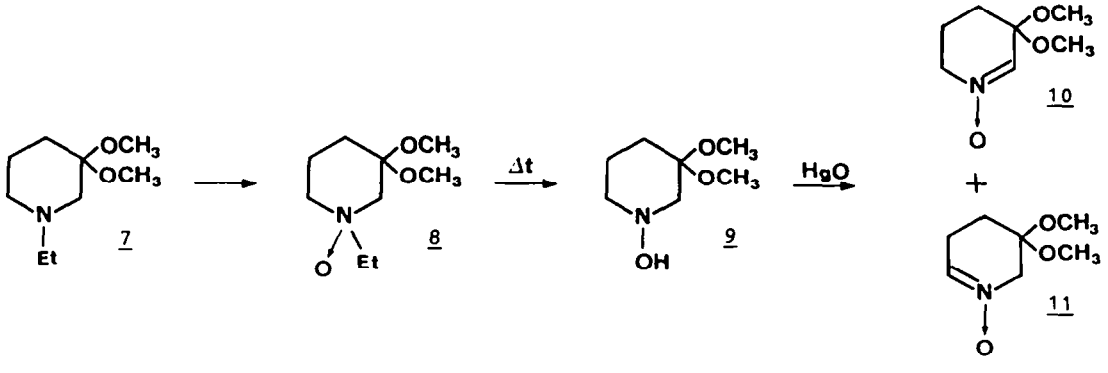
5-Hydroxysedamine 3 was isolated as a noncrystalline base $[\alpha]_D^{22}$ -50° (c=0.3, MeOH). The proton NMR spectrum of the corresponding diacetylderivative 4 supported the presence of a N-CH_3 group, a CH_2-CHOAc-C_6H_5 side chain and indicated that the second acetyl group was axial and located at C5: the C6 protons appeared as double doublets at 2.84 (J = 13 and 5 Hz) and 2.43 ppm (J = 13 and 3 Hz) implying the presence of only one proton equatorially oriented at C5. The position of the C8-H signal in the ^{1}H NMR spectrum of the diol 3 (4.87 ppm) suggested a sedamine-type rather than an allosedamine-type relative configuration. The comparison of a number of compounds has revealed that the H8 chemical shift is of diagnostic value: H8 appears shielded for sedamine- (ca 4.9 ppm) relative to allosedamine-type derivatives (ca. 5.1 ppm); in this last series, as far as the conformation of allosedamine itself is preserved (cis-fused ring conformation with an equatorial phenyl group[8]), the axial C8-H is deshielded by the axial C3-H.

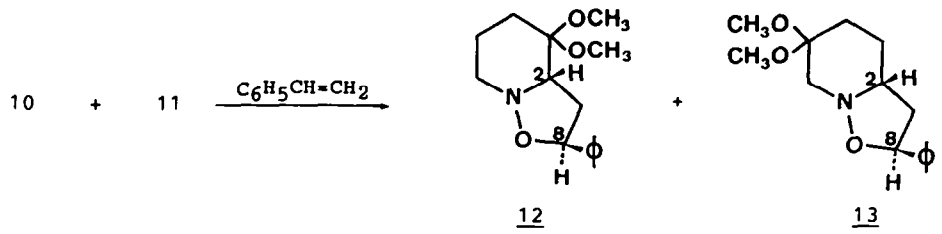
Definite evidence for structure 3 -which also represents the absolute configuration of the new base (2S, 5S, 8S)- rests on the synthetic results described below.

Synthesis of the new bases.

Our synthesis of the new alkaloids 1, 2 and 3 rests on the cycloaddition reaction between styrene and the regioisomeric nitrones 10 and 11, obtained by oxidation of the hydroxylamine 9. The resulting adducts rac-12 and rac-13 led respectively to the 3-hydroxypiperidines rac-1 and rac-2 and to 5-hydroxysedamine after the required functional transformations.

The hydroxylamine 9 was prepared from the amine oxide 8 by Cope elimination. The mercuric oxide induced oxidation of 9 in chloroform at ca. -10° yielded the regioisomeric nitrones 10 and 11 as a mixture in which 10 appeared as the major compound (ca. 3:1 by ^{1}H NMR) in accord with the results of a previous report[9]; when the reaction was carried out above 0°, a 1:1 mixture of 10 and 11 was obtained. The cyclization of styrene with either mixture of the nitrones 10 and 11 in refluxing chloroform afforded a 1:1 mixture of the isoxazolidines rac-12 and rac-13 which were isolated in the pure state (90% overall yield from 9) after separation by flash chromatography.





12 13

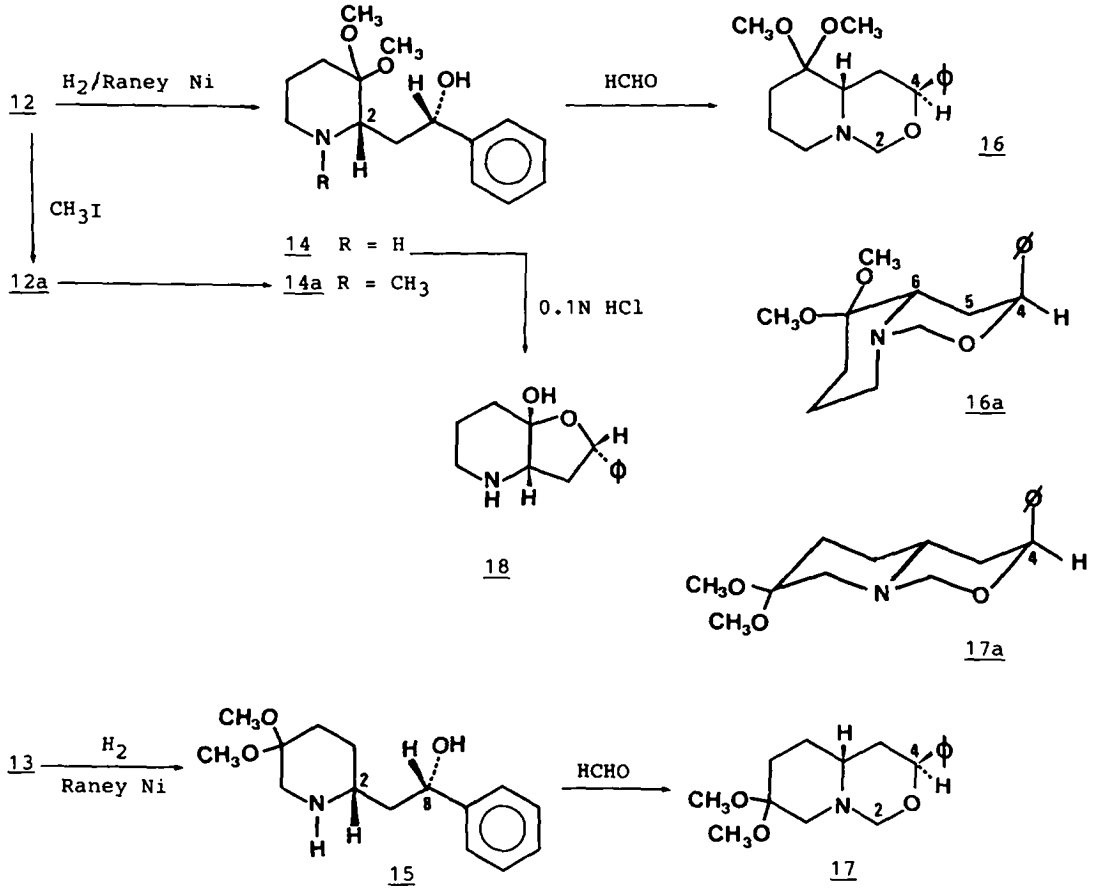
As expected from the results published on related cycloadditions[9,10], the reaction of styrene with both rac-10 and rac-11 takes place with a very high regioselectivity (a regioisomer of rac-13 was isolated in trace amounts) and is highly stereoselective if not stereospecific. Only the adducts arising from the passage through an exo transition state were isolated: the relative configuration at C2 and C8 is of the allosedamine-type. This was proved by the conversion of rac-12 and rac-13 in the tetrahydro 1,3-oxazines rac-16 and rac-17 respectively, whose configuration was established by NMR spectroscopy (v. infra). The appearance of the ^{1}H and ^{13}C NMR spectra of the isoxazolidines rac-12 and rac-13 indicates a "slow" inversion process which may be ascribed to the nitrogen inversion, as already described for related compounds[11]. In $CDCl_3$ at 30° most of the signals appeared as broad absorptions. On the other hand, at 0° the ^{13}C spectrum showed the signals attributable to the trans conformation (rac-12: 30%; rac-13: 70%) and those attributable to the cis pair (2 conformations in rapid equilibrium[11]) for both compounds.

Treatment of rac-12 and rac-13 by hydrogen in the presence of W2 Raney nickel in methanol yielded respectively the aminoalcohols rac-14 and rac-15 (75% yield after crystallization) and their corresponding C2 epimers (ca. 10% yield in both cases). Such a partial epimerization was also observed during the hydrogenolysis of related isoxazolidine derivatives and may originate from the reduction of a Δ^{1}-piperideine formed by an elimination reaction in competition with the single N-O cleavage[11]. Treatment of rac-14 and rac-15 by aqueous formaldehyde in methanol yielded quantitatively the tetrahydro 1,3-oxazines rac-16 and rac-17. In both compounds, the phenyl group is axial as indicated by the chemical shift and the multiplicity of the C4 proton (rac-16: 5.24 ppm, d, J = 6 Hz; rac-17: 5.06 ppm, tr, J = 4.4 Hz) and by the small chemical shift difference between the C2 protons (rac-16: 0.29 ppm; rac-17: 0.28 ppm)[3,5]. The tetrahydro 1,3-oxazine rac-17 exists predominantly in the trans-fused ring conformation rac-17a as evidenced by the value of the geminal coupling constant between the C2 protons (-8.5 Hz)[5]. On the other hand, the C2 protons of rac-16 exhibited a J_{gem} of -10.5 Hz, characteristic of a cis-fused ring conformation[5]. For this last compound, double irradiation experiments allowed the assigment of the signal at 2.56 ppm to H5a; the coupling constants of 14 Hz (J_{gem}), 13 Hz (H5a-H6a) and 6 Hz (H5a-H4e) are only compatible with the relative configuration and the conformation depicted in 16a. The allosedamine-type configuration of rac-16, rac-17 and their precursors is therefore demonstrated.

Cleavage of the acetal group of rac-14 with 0.1N HCl yielded the hemiacetal rac-18 whose treatment with $NaBH_4$ in methanol at -10° furnished the diol rac-1 as the major isomer (77% yield from rac-14), identical (except of course for the rotation) with the natural base. Optically pure 3-hydroxynorallosedamine was obtained by resolution of the racemic synthetic base with 10-camphorsulfonic acid. With

(+)-10-camphorsulfonic acid the salt of (+)-3-hydroxynorallosedamine separated first from acetone; one crystallization of the base from chloroform gave pure ent-1, $[\alpha]_D^{22}$ +66° (c=1.5, MeOH).

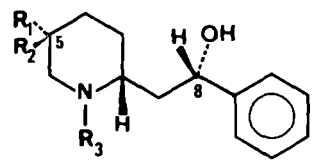
3-Hydroxyallosedamine rac-2 is easily obtained from rac-1 by the procedure described for the correlation of the natural compounds (reduction with $LiAlH_4$ of the tetrahydro 1,3-oxazine derived from rac-1) or from the isoxazolidine rac-12. In this latter case, the quaternary ammonium iodide rac-12a, prepared by iodomethylation of rac-12, was treated with Raney nickel and hydrogen in methanol to give rac-14a whose deprotection followed by reduction with $NaBH_4$ at 0° yielded a mixture of alcohols from which rac-2 was easily isolated by countercurrent distribution (55% yield from rac-12).



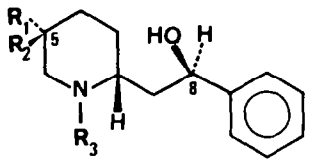
While the relative C_2-C_5 configuration of the naturally occurring 5-hydroxy base 3 was established, the C_2-C_8 configuration was only tentatively assigned on the basis of the chemical shift (v. supra) of C8-H; the two C8 epimers were therefore prepared starting from rac-15.

The 5-hydroxyallosedamine rac-20 was easily obtained. Hydrolysis of the acetal function of rac-15 and reduction of the resulting ketone with potassium trisiamylborohydride in tetrahydrofuran yielded a 92:8 mixture of the alcohols rac-19 and rac-21 respectively. On the other hand, the alcohol rac-21 was the sole product when the reduction of the ketone was performed with $NaBH_4$ in methanol at -10°.

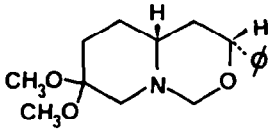
N-Methylation of rac-19 and rac-21 yielded respectively the alcohols rac-20 and rac-22. In the ^1H NMR spectra of the allosedamine derivatives rac-20 and rac-22, which are different from the natural 5-hydroxy base, the C8-H signals appeared at 5.07 and 5.05 ppm respectively.



19 R_1 = OH, R_2 = R_3 = H
20 R_1 = OH, R_2 = H, R_3 = CH_3
21 R_1 = H, R_2 = OH, R_3 = H
22 R_1 = H, R_2 = OH, R_3 = CH_3



23 R_1 = R_2 = OCH_3, R_3 = H
23a R_1 = R_2 = OCH_3, R_3 = CH_3
25 R_1 = OH, R_2 = H, R_3 = CH_3



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For the synthesis of 5-hydroxysedamine, the racemic acetal rac-15 was first resolved with (-)-dibenzoyltartaric acid in acetone. Several crystallizations (cyclohexane) of the free base liberated from the less soluble salt yielded the optically pure laevorotatory aminoalcohol 15 whose absolute configuration rests on the application of Horeau's method on the corresponding N-methyl derivative 15a. In order to obtain a sedamine derivative inversion of the C8-OH of 15 was realized by the method of Mitsunobu[13]: treatment in benzene/ether of the alcohol 15 with triphenylphosphine and benzoic acid in the presence of diethylazodicarboxylate yielded, after $LiAlH_4$ reduction, a 1:6 mixture of the alcohols 15 (unchanged) and 23. The mixture of 15 and 23 was treated with formaldehyde in methanol to give the corresponding tetrahydro 1,3-oxazines 24 and 17 which were separated by column chromatography. Reduction of 24 with $LiAlH_4$ furnished the N-methylderivative 23a whose acetal group was hydrolyzed. Reduction of the resulting ketone with potassium trisiamylborohydride yielded a 2:1 mixture of alcohols which were separated by TLC on alumina. The major isomer ent-3 appeared identical (TLC, ^1H NMR, ^{13}C NMR) with the natural base. Its optical rotation was equivalent in magnitude but opposite in sign to that of the naturally occurring alkaloid which has therefore the structure and the absolute configuration depicted in 3 (2S, 5S, 8S). The second alcohol is the corresponding C5 epimer 25 as indicated by its spectral properties.

EXPERIMENTAL.

Melting points were determined on a Kofler microscope and are uncorrected.
IR spectra were determined on a Perkin-Elmer 237 spectrometer.
Mass spectral data were obtained on a Micromass 7070 spectrometer.
Unless otherwise stated NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker WM 250 spectrometer.
Optical rotations were measured on a Perkin-Elmer 141 polarimeter.
The countercurrent distributions were analyzed by measuring the optical density (420 nm) of the $CHCl_3$ phase of each tube after basification (aq. NaOH), drying and addition of a $CHCl_3$ solution of picric acid.

Isolation of the alkaloids of Sedum acre.

Fresh whole plants (23 kg) of Sedum acre (collected in December near Brussels) were frozen by liquid nitrogen, crushed and poured in 2% aqueous HCl (50 L). After three days at room temperature, the suspension was filtered, basified with NH_4OH and extracted with $CHCl_3$. Evaporation of the organic solvent yielded fraction A. The aqueous phase was rendered strongly alkaline by addition of 2N NaOH and extracted again with $CHCl_3$. The chloroform solution was concentrated to a volume of 150 mL and extracted four times with a borax-HCl buffer pH 8.3 (4 x 200 mL). The aqueous phase was basified by addition of 2N NaOH (200 mL) and extracted with $CHCl_3$ (2 x 1 L). Evaporation of the organic solvent yielded fraction B (1 g).

Isolation of (-)-3-hydroxyallosedamine 2 and (-)-5-hydroxysedamine 3.

Fraction A was subjected to two successive countercurrent distributions ($CHCl_3$/borax-HCl buffer pH 8.7; 50 transfers). From tubes 10-42, diacetyl-5-hydroxysedamine 4 (35 mg) was isolated after acetylation and separation from other new minor derivatives as described earlier[3]; $[\alpha]_D^{20}$ -66° (c=0.6, MeOH); MS: 319 ($M^{+\cdot}$); PMR: δ 5.85 (dd, J=4.6 and 9.4 Hz, C8-H), 4.91 (m, C5-H), 2.32 (s), 2.07 (2s); CMR: δ 73.6 (C8), 68.6 (C5), 58.4 (C2), 57.1 (C6), 47.2 (N-CH_3), 37.6 (C7), 27.3 (C4), 25.8 (C3), 21.4 (CH_3CO), 21.2 (CH_3CO). Hydrolysis of 4 (5 mg) with 2N NaOH in MeOH yielded 3 (3 mg), $[\alpha]_D^{22}$ -40° (c=0.3, MeOH); MS: 235 ($M^{+\cdot}$; 10%), 114 (100); PMR: δ 7.3 (m), 4.87 (dd, J=2.8 and 10.4 Hz, C8-H), 3.88 (trtr, J=3.6 and 7.3 Hz, C5-H), 2.89 (dd, J=7.3 and 12.9 Hz, C6-Ha), 2.69 (m, C2-H), 2.58 (dd, J=3.6 and 12.9 Hz, C6-He), 2.17 (ddd, J=7.8, 10.4 and 14.3 Hz, C7-Ha), 1.50 (ddd, J=2.8, 5.7 and 14.3 Hz, C7-He); CMR: δ 73.7 (C8), 64.0 (C5), 59.8 (C2), 58.0 (C6), 42.8 (N-CH_3), 40.0 (C7), 30.5 (C4), 24.5 (C3). Tubes 0-9 were fractionated again by two successive countercurrent distributions ($CHCl_3$/borax-HCl buffer pH 8.0; 23 transfers): tubes 3-11 gave a colorless residue whose perchlorate was crystallyzed in butanone-ether to give 3-hydroxyallosedamine perchlorate (200 mg), mp. 162-163°, $[\alpha]_D^{22}$ -40° (c=2.4, MeOH). The free amorphous base 2 had $[\alpha]_D^{22}$ -17° (c=1.3, MeOH); SM: 235 ($M^{+\cdot}$, 10%), 114 (100); PMR: δ 7.3 (m), 5.06 (dd, J=3.2 and 10.2 Hz, C8-H), 3.79 (m, J=4.4, 8.4 and 10.3 Hz, C3-H), 2.4 (s); CMR: δ 72.3 (C8), 68.9 (C2 and C3), 56.0 (C6), 43.5 (N-CH_3), 36.1 (C7), 33.3 (C4), 22.6 (C5).

Isolation of (-)-3-hydroxynorallosedamine 1.

Fraction B was subjected to a countercurrent distribution at pH 8.5 ($CHCl_3$/borax-HCl buffer; 37 transfers). Sublimation under vacuum of the mixture from tubes 32-37 (250 mg) yielded sedridine (90 mg). Crystallyzation from $CHCl_3$ of the residue from the sublimation furnished 3-hydroxynorallosedamine (23 mg), mp. 155-156°, $[\alpha]_D^{22}$ -66° (c=1.6, MeOH); MS: 221 ($M^{+\cdot}$, 28%, $C_{13}H_{19}NO_2$, found: 221.1415, calc.: 221.1415), 114 (31%, $C_6H_{12}NO$, found: 114.0917, calc.: 114.0918), 100 (100%, $C_5H_{10}NO$, found: 100.0762, calc.: 100.0762); PMR: δ 7.35 (m), 5.08 (dd, J=4.2 and 6.8 Hz, C8-H), 3.44 (ddd, J=4.4, 8.8 and 10.3 Hz, C3-H), 3.0 (dddd, J=1.5, 2.6, 4.2 and 12.5 Hz, C6-He), 2.60 (ddd, J= 4.4, 6.3 and 8.8 Hz, C2-Ha), 2.51 (ddd, J= 2.9, 12.5 and 12.5 Hz, C6-Ha); CMR: δ 72.2 (C3), 71.3 (C8), 61.0 (C2), 45.6 (C6), 41.0 (C7), 34.0 (C4), 25.9 (C5). The mother liquors were evaporated to dryness and the residue was acetylated with acetic anhydride-pyridine. Fractionation by column chromatogrphy on aluminum oxide (benzene-ethyl acetate as eluent) yielded diacetylsedridine (25 mg), triacetyl-3-hydroxynorallosedamine (10 mg) and the pentaacetyl derivative of lobelanidine glycoside (5 mg) whose hydrochloride was crystallyzed from acetone-ether, mp. 233-236° (dec.), $[\alpha]_D^{22}$ -28° (c=1, MeOH).

Preparation of the tetrahydro 1,3-oxazine 5a.

3-hydroxynorallosedamine 1 (25 mg) was dissolved in water (1.5 mL) and KOH (100 mg) and 37% aqueous formaldehyde (0.75 mL) were added. After 20 hr, the solution was diluted with water and extracted with $CHCl_3$. Evaporation of the solvent yielded, after filtration through a short column of alumina, the tetrahydo 1,3-oxazine 5a (28 mg); MS: 223 ($M^{+\cdot}$, 57%), 215 (29), 128 (75), 104 (100); PMR: δ 7.40 (m), 5.22 (m, C4-H), 4.18 (d, J=8.3 Hz, C2-Ha), 3.87 (d, J=8.3 Hz, C2-He), 3.5 (ddd, J=4.2, 7.4 and 9.9 Hz, C7-Ha); CMR: δ 79.8 (C2), 73.2 (C7), 71.0 (C4), 61.3 (C6), 48.0 (C10), 32.9 (C8), 28.6 (C5), 22.4 (C9).

9 mg of 5a were allowed to react with α-phenylbutyric anhydride (25 mg) in pyridine (0.5 mL) for 20 hr at room temperature. Som drops of water were added and the mixture was basified with 0.1N NaOH and extracted with $CHCl_3$. The basic aqueous phase was acidified with 0.1N HCl and extracted again with $CHCl_3$. Evaporation of the solvent yielded α-phenylbutyric acid (18.8 mg), $[\alpha]_D^{22}$+6.8° (benzene); optical yield: 21%.

Preparation of 3-hydroxyallosedamine 2 from 5a.

The tetrahydro 1,3-oxazine 5a (95 mg) was treated with $LiAlH_4$ (150 mg) in refluxing THF (25 mL) for 24 hr. After addition of some drops of ethyl acetate, then water the mixture was filtered through celite to give after acid-base extraction (-)-3-hydroxyallosedamine 2 (88 mg) identical ([α], TLC, PMR, CMR) with the natural compound.

Preparation of the tetrahydrofuran derivative 6.

To a solution of 3-hydroxyallosedamine 2 (19 mg) in dry chloroform (2 mL), p-toluenesufonyl chloride (20 mg) was added and the solution was allowed to stand at room temperature for 24 hr. After addition of 2 mL of 2N NaOH and stirring, the organic phase was evaporated. Filtration of the residue through alumina ($CHCl_3$) furnished homogeneous 6 (13 mg); MS: 217 ($M^{+\cdot}$); PMR: δ 7.3 (m), 5.15 (dd, J=3 and 10 Hz, C8-H); CMR: δ 81.2 (C3 or C8), 78.7 (C8 or C3), 69.1 (C2), 57.0 (C6), 43.9 ($N-CH_3$), 38.5 (C7), 29.4 (C4), 23.8 (C5).

Preparation of the hydroxylamine 9.

A solution of m-chloroperbenzoic acid (4.5 g) in $CHCl_3$ (200 mL) was added dropwise to a solution (0°) of the amine 7 (4.33 g) in the same solvent (200 mL). After the addition, the solution was allowed to equilibrate to room temperature and the solvent was evaporated. The residue was chromatographed on alumina according to the usual procedure[12] to give the pure, very hygroscopic N-oxide 8. The solid N-oxide was pyrolyzed under reduced pressure in a sublimator. The hydroxylamine 9 was obtained as white crystals after two sublimation and one crystallyzation from cyclohexane; mp. 98-100°, yield from 7: 73%; MS: 161 ($M^{+\cdot}$); CMR (0°): 99.3 (C3), 62.0 (C2), 58.2 (C6), 47.9 and 47.3 (OCH_3), 30.0 (C4), 20.7 (C5).

Preparation of the isoxazolidines rac-12 and rac-13.

To a solution of the hydroxylamine 9 (3.35 g) in alcohol-free and freshly distilled $CHCl_3$ (70 mL) at 0°, HgO (13.6 g) was added under stirring. After 20 min the mixture is filtered through celite and concentrated to a volume of 70 mL. Styrene was added and the solution was refluxed for three hr. After evaporation of the solvent, the residue was fractionated by flash chromatography on silicagel (AcOEt/hexane 2:3) to yield rac-12 (2.4 g), rac-13 (2.5 g) and a third isomer (9 mg).

rac-12: mp. 90-92° (petroleum ether); MS: 263 ($M^{+\cdot}$, 9%), 248 (7), 232 (16), 142 (43), 126 (13), 115 (11), 105 (18), 101 (100); PMR (0°): major conformer, δ 7.36 (m), 5.44 (dd, J=3.9 and 9.9 Hz, C8-H), 3.95 (dd, J=7.6 and 11.6 Hz, C2-H), 3.26 and 3.22 (2 s, OCH_3); minor conf., δ 5.04 (dd, J=4.9 and 9.5 Hz, C8-H), 3.28 and 3.25 (2 s, OCH_3); CMR (0°): maj. conf., δ 100.9 (C3), 78.2 (C8), 65.6 (C2), 49.4 (C6), 37.2 (C7), 25.8 (C4), 19.8 (C5); min. conf., 99.6 (C3), 78.0 (C8), 72.1 (C2), 53.7 (C6), 38.7 (C7), 30.6 (C4), 20.6 (C5).

rac-13: oil; MS: 263 ($M^{+\cdot}$, 26%), 232 (21), 162 (10), 129 (100), 128 (15); PMR (0°): maj. conf., δ 7.3 (m), 5.17 (dd, J=4.3 and 9.1 Hz, C8-H), 3.83 (dd, J=1.8 and 9.5 Hz, C6-H), 3.27 (s, OCH_3); min. conf., δ 5.37 (dd, J=3.7 and 9.6 Hz, C8-H), 3.29 (s, OCH_3); CMR (0°): maj. conf., δ 100.1 (C5), 78.6 (C8), 66.7 (C2), 59.3 (C6), 42.0 (C7), 31.0 (C4), 24.1 (C3); min. conf., δ 98.9 (C5), 78.6 (C8), 59.1 (C2), 52.9 (C6), 38.4 (C7), 25.8 (C4), 20.9 (C3).

Preparation of the aminoalcohol rac-14 from rac-12.

The isoxazolidine rac-12 (779 mg) dissolved in MeOH (10 mL) was hydrogenated with Raney nickel at room temperature and atmospheric pressure. After the reaction was completed, the catalyst was filtered (celite) and washed with hot methanol. After evaporation of the solvent a 9:1 mixture (771 mg) of rac-14 and its C2 epimer (PMR: δ 4.88, dd, C8-H) was obtained. One crystallization from cyclohexane afforded pure rac-14 (605 mg; 77% yield), mp. 103-105°, MS: 265 ($M^{+\cdot}$, 4%), 250 (44), 164 (21), 144 (100), 112 (69), 107 (31), 101 (49); PMR (C_6D_6): δ 5.26 (tr, J= 4 Hz, C8-H), 2.97 (dtr, J=12.2, 2.2 and 1.2 Hz, C2-H), 2.25 (ddd, J=14.7, 12.2 and 4 Hz, C7-Ha), 1.75 (ddd, J=14.7, 4 and 2.2 Hz, C7-He); CMR: δ 98.2 (C3), 72.7 (C8), 54.0 (C2), 47.7 and 47.1 (OCH_3), 39.0 (C6), 31.1 (C7), 26.5 (C4), 24.3 (C5).

Preparation of the aminoalcohol rac-15 from rac-13.

The isoxazolidine rac-13 (1.22 g) was hydrogenated as described above for rac-12 to give a 9:1 mixture (1.05 g) of rac-15 and its C2 epimer. One crystallization from cyclohexane afforded pure rac-15 (901 mg, 73% yield); preparative TLC on the mother liquors gave the C2 epimer as an homogeneous oil (PMR: δ 4.93 (dd, J=2.4 and 10.6 Hz,C8-H)

CMR: δ 96.5 (C5), 75.6 (C8), 57.8 (C2), 50.0 (C6), 47.9 and 47.6 (OCH_3), 44.2 (C7), 31.7 and 30.7 (C4 and C3).

rac-15: mp. 117-118° (cyclohexane); MS: 265 ($M^{+\cdot}$, 10%), 234 (23), 226 (17), 201 (27), 164 (96), 144 (67), 129 (35), 112 (100); PMR (C_6D_6): δ 5.11 (tr, J=4.6 Hz, C8-H), 2.46 (trtr, J=10 and 3 Hz, C2-H), 2.87 (dd, J=13.8 and 3 Hz, C6-He), 2.22 (d, J=13.8 Hz, C6-Ha), 1.65 (ddd, J=14.4, 10 and 4.6 Hz, C7-Ha), 1.53 (ddd, J=14.4, 4.6 and 3 Hz, C7-He); CMR: δ 96.6 (C5), 72.3 (C8), 53.7 (C2), 50.2 (C6), 47.8 and 47.6 (OCH_3), 42.4 (C7), 30.6 and 30.4 (C4 and C3).

Preparation of the tetrahydro 1,3-oxazines rac-16 and rac-17.

37% aqueous formaldehyde was added to a solution of the aminoalcohol rac-14 or rac-15 (25 mg) in methanol (1 mL). After some minutes, the solvent was evaporated and the residue was filtered ($CHCl_3$) through a short column of alumina. The yield was quantitative.

rac-16: MS: 277 ($M^{+\cdot}$); PMR: δ 5.24 (enl. d, J=5.9 Hz, C8-H), 4.56 and 4.27 (2 d, J=10.7, C2-H_2), 2.56 (ddd, J=14.3, 13.3 and 6 Hz, C5-Ha); CMR: δ 99.5 (C7), 80.0 (C2), 72.9 (C4), 54.0 (C6), 47.7 and 47.6 (OCH_3), 43.8 (C10), 25.7, 21.7 and 20.5 (C7, C8, C9).

rac-17: PMR: δ 5.06 (tr, J=4.4 Hz, C4-H), 4.32 and 4.03 (2 d, J=8.5 Hz, C2-H_2), 3.22 and 3.19 (2 s, OCH_3), 2.60 (trtr, J=4.3 and 8.6 Hz, C6-H); CMR: δ 97.6 (C9), 80.1 (C2), 73.3 (C4), 54.0 (C6), 52.9 (C10), 47.8 and 47.7 (OCH_3), 31.7, 30.2 and 26.9 (C5, C7, C8).

Preparation of 3-hydroxynorallosedamine rac-1 from rac-14.

The acetal rac-14 (1.038 g) was dissolved in 0.1N HCl (400 mL) and the solution was heated for 24 hr at 60°. The solution was basified with diluted NH_4OH and extracted with chloroform. After evaporation of the solvent, the crude hemiacetal rac-18 was dissolved in methanol (50 mL), the solution was cooled to -10° and $NaBH_4$ (1.5 g) was added. After two hr at -10° the solution was allowed to stand overnight at room temperature and then evaporated. The residue was dissolved in 2N NaOH and extracted with chloroform. The solution was concentrated to a small volume to allow the crystallization. 670 mg of pure 3-hydroxynorallosedamine rac-1, mp. 149-150°, were obtained. The base was identical (MS, IR, NMR) with the natural compound.

Resolution of 3-hydroxynorallosedamine rac-1.

Racemic 3-hydroxynorallosedamine (395 mg) and (+)-10-camphorsulfonic acid (416 mg) were dissolved in hot acetone (35 mL). The solution was allowed to stand at room temperature for two days. The crystalline salt was collected and dissolved in 1N NaOH. Extraction with chloroform and evaporation of the organic solvent yielded the free base (145 mg) $[\alpha]_D^{20}$ +62.5° (c=2.1, MeOH). One crystallization from chloroform yielded ent-1 (96 mg) $[\alpha]_D^{20}$ +65.5° (c=1.5, MeOH).

Preparation of 3-hydroxyallosedamine rac-2 from the isoxazolidine rac-12.

The isoxazolidine rac-12 (1.21 g) in anhydrous ether (25 mL) was treated with methyl iodide (2 mL); the mixture was left overnight at room temperature and then filtered. The methiodide was obtained quantitatively; it was dissolved in methanol (30 mL) and hydrogenated over Raney nickel at room temperature and atmospheric pressure. After the reaction was completed (3 hr) the mixture was filtered through celite and the catalyst was washed with hot methanol. After evaporation of the solvent, diluted NH_4OH and chloroform were added to the residue. The organic phase was evaporated to yield rac-14a (oil): SM: 279 ($M^{+\cdot}$); PMR: δ 7.31 (m), 5.05 (tr, J=4.3 Hz, C8-H), 3.09 and 2.82 (2 s, OCH_3), 2.99 (dtr, J=2.9 and 13.4 Hz, C6-Ha), 2.80 (m, C2-H), 2.57 (m, C6-He), 2.53 (s, NCH_3), 2.33 (ddd, J=4.3, 10.5 and 14.8 Hz, C7-Ha), 1.66 (ddd, J= 2.8, 4.3 and 14.8 Hz, C7-He); CMR: δ 99.7 (C3), 73.3 (C8), 60.0 (C2), 47.3 and 47.0 (OCH_3), 46.0 (C6), 42.0 (NCH_3), 32.0 (C7), 27.0 (C4), 18.4 (C5). The acetal rac-14a was hydrolyzed in 0.2N HCl (250 mL) at 60° for 20 hr. After the usual workup, the product was reduced with $NaBH_4$ (500 mg) in methanol (70 mL) at 0°. After one hr at 0° and two hr at room temperature, the solution was evaporated to dryness. Chloroform and diluted NH_4OH were added to the residue. The organic phase was evaporated and the residue was fractionated in two successive countercurrent distributions (chloroform/borax-HCl buffer pH 8.0; 23 transfers. 628 mg of homogeneous rac-2 were obtained from the tubes 5 - 15; perchlorate: mp. 131-132° (butanone-ether)

Preparation of the alcohols rac-19 and rac-21 from rac-15.

The acetal rac-15 (100 mg) was dissolved in 0.1N HCl (38 mL) and the solution was heated for 24 hr at 60°. After cooling, the solution was basified with diluted NH_4OH and extracted with chloroform; the solvent was evaporated and the ketone was reduced immediately:

-Reduction of the ketone with sodium borohydride: the crude ketone (52 mg) was dissolved in methanol (5 mL) and the solution was cooled to -10°; $NaBH_4$ (75 mg) was added. After two hr, the solution was evaporated and 2N NaOH and chloroform were added to the residue. Evaporation of the chloroform solution yielded quantitatively homogeneous rac-21: PMR: δ 5.0 (dd, J=4.4 and 6.8 Hz, C8-H), 3.76 (trtr, J=5 and 10 Hz, C5-H), 3.2 (ddd, J=2.1, 4.5 and 11.8 Hz, C6-H), 2.39 (dd, J= 10 and 11.8 Hz, C6-H)

-Reduction of the ketone with potassium trisiamylborohydride: the crude ketone obtained from rac-15 was dissolved in THF and the solution was cooled to -78° under nitrogen; a 0.5M solution (4 mL) of potassium trisiamylborohydride in THF was added. After two hr at -78° the solution was allowed to reach the room temperature. Water was added and the mixture was evaporated. The residue was dissolved in 2N HCl and extracted with chloroform. The organic phase was discarded ; the aqueous phase was rendered alkaline with 2N NaOH and extracted again with chloroform. Evaporation of the solvent yielded a 92:8 mixture (77 mg) of the alcohols rac-19 and rac-21. rac-19: PMR: δ 5.01 (dd, J=4.4 and 6 Hz, C8-H), 3.79 (m, C5-H), 2.99 and 2.71 (2 dd, C6-H_2); CMR: δ 71.8 (C8), 67.9 (C5), 53.2 (C2 and C6), 43.2 (C7), 33.7 (C4), 30.8 (C3).

Preparation of the alcohols rac-20 and rac-22.

rac-20: The alcohol rac-19 (77 mg; contaminated by ca. 8% of rac-21) was dissolved in methanol (2 mL) and aqueous formaldehyde was added. After five minutes, the solvent was evaporated to yield the corresponding tetrahydro 1,3-oxazine whose reduction with $LiAlH_4$ (50 mg) in refluxing THF for 17 hr yielded, after the usual workup, the crude N-methylderivative rac-20 (76 mg; 93% yield from rac-19): SM: 235 ($M^{+\cdot}$); PMR: δ 5.07 (dd, J=4.2 and 9.3 Hz, C8-H), 3.88 (m, C5-H), 2.38 (s, NCH_3); CMR: δ 72.0 (C8), 64.8 (C5), 61.2 (C2 and C6), 43.6 (NCH_3), 39.3 (C7), 30.4 (C4), 24.0 (C3).

rac-22: The alcohol rac-21 was treated as described above for rac-19 to yield quantitatively the N-methylderivative rac-22: SM: 235 ($M^{+\cdot}$), PMR: δ 5.05 (dd, J=3.5 and 10.3 Hz, C8-H), 3.71 (trtr, J=4.3 and 10.3 Hz, C5-H), 2.42 (s, NCH_3); CMR: δ 71.8 (C8), 67.0 (C5), 63.8 (C6), 61.8 (C2), 43.8 (NCH_3), 38.9 (C7), 33.4 (C4), 27.5 (C3).

Resolution of the acetal rac-15.

The acetal rac-15 (2.188 g) and (-)-dibenzoyltartaric acid (3.102 g) were dissolved in hot acetone (40 mL) and the solution was allowed to stand overnight. The precipitate was filtered and crystallized again in acetone. Dissolution of the crystals in water, basification with diluted NH_4OH and extraction with chloroform yielded the free base which was crystallized four times from cyclohexane to yield optically pure 15 (459 mg, 42% yield) $[\alpha]_D^{20}$ -12.6° (c=3, MeOH), mp. 119.5-120°.

To 25 mg of the N-methyl derivative 15a (prepared from 15 by $LiAlH_4$ reduction of the corresponding tetrahydro 1,3-oxazine) in pyridine (1 mL) α-phenylbutyric anhydride (56.2 mg) was added. After 20 hr at room temperature, the usual workup yielded α-phenylbutyric acid $[\alpha]_D^{22}$ -12.6° (benzene); optical yield: 15%.

Preparation of the alcohol 23a from 15.

To a solution of the alcohol 15 (303 mg) and triphenylphosphine (449 mg) in benzene:ether (3:1) was added a solution of benzoic acid (293 mg) in benzene (5 mL). After twenty minutes, ethyl diazodicarboxylate (0.18 mL) in benzene (3 mL) was added slowly and the mixture was allowed to stand for 17 hr at room temperature. After evaporation of the solvents, the residue was chromatographed on alumina (hexane/ethyl acetate) to yield a mixture of benzoates (302 mg) which was treated with $LiAlH_4$ (305 mg) in THF (20 mL) at reflux for 16 hr. After the usual workup, a 1:6 mixture of 15 and 23 was obtained (115 mg).

To 91 mg of the mixture of 15 and 23 in methanol (5 mL), a 37% aqueous solution of formaldehyde was added. After standing for 18 hr at room temperature the solution was evaporated to dryness and the mixture was fractionated by chromatography on alumina (hexane/ethyl acetate) to give the homogeneous tetrahydro 1,3-oxazines 17 (4 mg) and 24 (70 mg). The tetrahydro 1,3-oxazine 24 (65 mg) was refluxed for 19 hr in THF (10 mL) in the presence of $LiAlH_4$ (89 mg). After the usual workup, the homogeneous alcohol 23a (65 mg) was isolated: PMR: δ 7.3 (m), 4.84 (dd, J=2.9 and 10.4 Hz, C8-H), 3.19 and 3.18 (2 s, OCH_3), 2.97 (d, J=13.5 Hz, C6-Ha), 2.76 (m, C2-H), 2.52 (s, NCH_3); CMR: δ 97.5 (C5), 74.0 (C8), 59.8 (C2), 54.9 (C6), 47.6 and 47.5 (OCH_3), 42.3 (NCH_3), 28.7 (C4), 24.0 (C3).

Preparation of (+)-5-hydroxysedamine ent-3 from the acetal 23a.

The acetal 23a (64 mg) was dissolved in 0.1N HCl (23 mL) and the solution was heated at 65° for 24 hr. After cooling, the solution was basified with diluted NH_4OH and extracted with chloroform. After evaporation of the solvent, the crude ketone was dissolved in THF (10 mL) and to the solution cooled to -78° a 1M solution (1.2 mL) of potassium trisiamylborohydride in THF was added under nitrogen. After two hr at -78°, the solution was allowed to warm to room temperature then water was added and the mixture was evaporated. The residue was dissolved in 2N HCl and extracted with chloroform. The organic phase was discarded, the aqueous phase was basified with 2N NaOH and extracted again with chloroform. Evaporation of the solvent yielded a 2:1 mixture (41 mg) of alcohols from which ent-3, $[\alpha]_D^{22}$ +41° (c=0.9, MeOH), and the corresponding C5 epimer 25 $[\alpha]_D^{22}$ +51° (c=0.9, MeOH) were isolated by preparative TLC (methanol/$CHCl_3$/NH_4OH); ent-3 had NMR properties identical with those of the natural base.

25: SM: 235 ($M^{+\cdot}$); PMR: δ 7.3 (m), 4.85 (dd, J=3.2 and 10.2 Hz, C8-H), 3.83 (trtr, J=4.1 and 8.3 Hz, C5-H), 3.04 (ddd, J=1.3, 4.1 and 12.3 Hz, C6-He), 2.63 (m, C2-H), 2.44 (s, NCH_3), 2.32 (dd, J=8.4 and 12.3 Hz, C6-Ha), 2.03 (ddd, J=6.6, 10.2 and 14.3 Hz C7-Ha), 1.58 (ddd, J=3.2, 6.3 and 14.3 Hz, C7-He); CMR: δ 73.4 (C8), 65.5 (C5), 60.7 (C6), 60.1 (C2), 41.1 (NCH_3), 39.5 (C7), 32.1 (C4), 25.5 (C3).

Acetylation of ent-3 and 25 with acetic anhydride in the presence of pyridine yielded the corresponding diacetyl derivatives:

ent-4: MS: 319 ($M^{+\cdot}$); $[\alpha]_D^{20}$ +72° (c=0.9, MeOH); the NMR properties of ent-4 were identical with those of 4 described in the isolation procedure.

Diacetyl derivative of 25: MS: 319 ($M^{+\cdot}$); $[\alpha]_D^{20}$ +52° (c=0.7, MeOH); PMR: δ 7.3 (m), 5.84 (dd, J=4.5 and 9.4 Hz, C8-H), 4.83 (trtr, J=4.4 and 9.3 Hz), 2.99 (ddd, J=1.8, 4.2 and 11.3 Hz, C6-He), 2.32 (s, NCH_3), 2.16 (dd, J=9.4 and 11.3 Hz, C6-Ha), 2.07 and 2.02 (2 s, acetyl groups); CMR: δ 73.5 (C8), 69.0 (C5), 59.0 (C6), 58.9 (C2), 42.0 (NCH_3), 38.8 (C7), 29.2 and 27.8 (C3 and C4), 21.2 (CH_3).

REFERENCES.

1. B. Colau and C. Hootelé, Can. J. Chem. 61, 470 (1983).
2. C. Hootelé, B. Colau, F. Halin, J.P. Declercq, G. Germain and M. Van Meerssche, Tetrahedron Letters, 21, 5061 (1980).
3. F. Halin, P. Slosse and C. Hootelé, Tetrahedron, 41, 2891 (1985).
4. F. Bohlmann, Chem. Ber. 91, 2157 (1958).
5. T.A. Crabb and R.F. Newton, Tetrahedron, 24, 4423 (1968).
6. F.W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden, 1976.
7. A. Horeau in "Stereochemistry, Fundamentals and Methods", Ed. by H.B. Kagan, Vol. 3; Georg Thieme Stuttgart (1977).
8. C. Hootelé, F. Halin, S. Thomas and D. Tourwé, Tetrahedron, 41, 5563 (1985).
9. J.J. Tufariello, Acc. of Chem. Research, 12, 396 (1979).
10. C. Hootelé, W. Ibebeke-Bomangwa, F. Driessens and S. Sabil, Bull. Soc. Chim. Belges, 96, 57 (1987)
11. E. Gössinger, Monatshefte für Chemie, 112, 1017 (1981).
12. O. Mitsunobu, Synthesis, 1 (1980).
13. C. Piccinni-Leopardi, B. Tinant, J.P. Declercq, M. Van Meerssche and C. Hootelé, Bull. Soc. Chim. Belges, in press.