atoms and the anisotropic temperature factors are given in Table 3. The coordinates of the H atoms found from the electron-density difference synthesis are given in Table 4.

CONCLUSION

The spatial structure of the diterpene alkaloid dictysine has been determined by x-ray structural analysis. Dictysine has a denudatine skeleton.

LITERATURE CITED

1. B. T. Salimov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, Khim. Prir. Soedin., 235 (1978).
2. B. T. Salimov, M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, Khim. Prir. Soedin., 812 (1979).
3. B. T. Salimov, B. Tashkhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, Khim. Prir. Soedin., 86 (1981).
4. D. Brisse, Tetrahedron Lett., 4373 (1969).
5. L. H. Wright, M. G. Newton, S. W. Pelletier, and N. Singh, Chem. Commun., 6, 359 (1970).
6. International Tables for X-Ray Crystallography, Vol. 5, Kynoch Press, Birmingham (1962).
7. V. I. Andrianov, Z. Sh. Safina, and B. L. Tarnopol'skii, Zh. Strukt. Khim., 15, 911 (1974).

ANALOGS OF D(+)-PANTOTHENIC ACID.

VI. SYNTHESIS OF D-, L-, AND DL-4'-AMINO-4'-DEOXYPANTOTHENIC ACID

V. M. Kopelevich, L. N. Bulanova, and V. I. Gunar

UDC 547.164.14.074

A new analog of pantothenic acid, DL-4-amino-2-hydroxy-3,3-dimethylbutanoic acid, has been synthesized and it has been separated into stereoisomer. D-, L-, and DL-N-(4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanines — amino analogs of pantothenic acid — have been synthesized by the condensation of the N-hydroxysuccinimide esters of N-BOC-D-, -L-, and -DL-4-amino-2-hydroxy-3,3-dimethylbutanoic acids with β-alanine, followed by the elimination of the protective groups.

The importance of D-pantothenic acid as a component of coenzyme A and acyl carriers protein has led to the synthesis of a considerable number of its analogs and derivatives. However, the structure of the natural vitamin has proved to be so unusual that even slight modifications of its molecule have resulted in a decrease or in the complete loss of its specific biological activity and, in a number of cases, to the formation of antagonists [1]. At the same time, the study of synthetic analogs of pantothenic acid is giving valuable information on the role of its various groupings in the manifestation of biological activity, which is determined by the conversion of pantothenic acid into coenzyme A. Since the first stage of this process is the phosphorylation of the 4'-hydroxy group of pantothenic acid under the action of pantothenate kinase [2], analogs in which the primary hydroxyl have been modified may be of great interest for studying the specificity of pantothenate kinase. Continuing investigations on the synthesis of pantothenic acid derivatives and their biological activity [2], we have obtained an analog containing an amino group in place of the hydroxy group in position 4' of the pantothenic acid, 4'-amino-4'-deoxypantothenic acid.

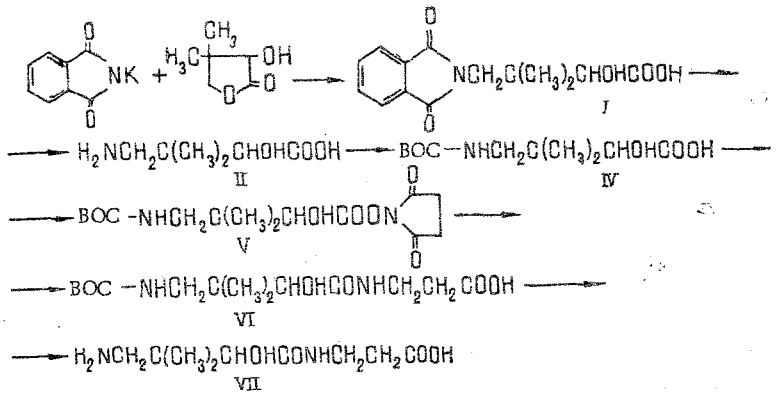
The conversion of a hydroxy group into an amino group usually requires several stages [4]. To introduce an amino group into position 4' of pantothenic acid we alkylated potassium phthalimide with D-pantolactone, as a result of which the optically inactive 2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid (I) was formed. We obtained the stereoisomers of aminopantothenic acid by resolving (I) through its conversion into a salt with L(+)-threo-2-

"Vitaminy" Scientific-Production Amalgamation, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 235-239, March-April, 1982. Original article submitted June 18, 1981.

000903130/82/1802-0215$07.50

amino-1-(p-nitrophenyl)propane-1,3-diol (threomine). Fractional crystallization of the salt obtained from ethanol and hydrolysis of the optically pure salts isolated with 10% hydrochloric acid led to the stereoisomers of (I) with opposite signs of rotation. When the isomers of (I) were boiled with hydrazine hydrate, the phthaloyl groups were eliminated with the formation of (+)- and (−)-4-amino-2-hydroxy-3,3-dimethylbutanoic acids (II) in high yield. To determine the configuration of the α-carbon atom in compound (+)-(II), we obtained the γ-lactam (III) from it by heating it in dimethyl sulfoxide at 150°C. On the basis of a comparison of IR, PMR, and mass spectra and the values and signs of rotation with literature information we assigned the D and L configurations to the compound (+)- and (−)-(II), respectively [5, 6].

Attempts to obtain aminopantothenic acid from the N-phthaloyl derivative (I) by various methods were unsuccessful. We synthesized the N-benzyloxycarbonyl (BOC) derivative (IV) from amino acid (II) by a method described in the literature [7]. The treatment of compound (IV) by a method described in the literature [7]. The treatment of compound (IV) with N-hydroxysuccinimide in the presence of N,N'-dicyclohexylcarbodiimide led to the N-hydroxysuccinimide ester of N-BOC-4-amino-2-hydroxy-3,3-dimethylbutanoic acid (V). The condensation of the ester (V) with the sodium salt of β-alanine yielded N-BOC-aminopantothenic acid (VI). The elimination of the N-BOC-group in compound (VI) by hydrogenolysis over 5% Pd/C led to the formation of N-(4-amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine (VII).



In the IR spectrum of substance (VII), strong absorption bands of an amide group stood out about 1660 cm^{-1} (amide I) and 1540 cm^{-1} (amide II), and also bands characteristic for the stretching vibrations (2700 and 2150 cm^{-1}) and deformation vibrations (1570 and 1530 cm^{-1}) of NH_3^+ groups, while a strong band with a maximum at about 1615 cm^{-1} can be assigned to the vibrations of an ionized carboxy group. In the infrared spectrum of pantothenic acid, the terminal group of which is not ionized, there is an absorption band at about 1740 cm^{-1} [3]; it was absent from the spectrum of the amino analog in this region. The PMR spectrum of this substance shows, like that of D-pantothenic acid [5], the presence of two strong signals of the protons of gem-methyl groups with δ 1.04 and 1.10 ppm. In contrast to pantothenic acid, the geminal protons of the 4-CH_2 group give a singlet with δ 3.03 ppm; the signal of the protons of the 4-CH_2 group is shifted upfield in comparison with the case of pantothenic acid by 0.4 ppm. These facts show some difference in the conformations of pantothenic acid and its analog (VII) in aqueous solution.

D(+)-, L(−), and DL-Aminopantothenic acids were obtained by the method given. A study of the specific biological actions of D(+)- and L(−)-aminopantothenic acids in relation to the yeast organism *Saccharomycodes ludwigii*, which is used as a test culture for D-pantothenic acid, show that they possessed neither vitamin nor antivitamin activity. Apparently, aminopantothenic acid does not add to yeast pantothenic kinase, which once more confirms the high specificity of the pantothenic acid molecule in relation to the enzymes of its metabolism.

EXPERIMENTAL

IR spectra were taken on a UR-10 spectrophotometer in thin films and in paraffin oil. PMR spectra were recorded on a Hitachi R-20A instrument with a working frequency of 60 MHz in D_2O (internal standard DSS).

Thin-layer chromatography was performed on Silufol UV-254 standard plates (Czechoslovakia) in the following solvent systems: 1) butan-1-ol—98% acetic acid—water (5:2:3); 2) pro-

panol–2 5% NH_4OH–water (6:3:1); and 3) isopropanol–water (2:1). Specific rotations were measured on a A-1-EPL instrument.

The results of elementary analysis corresponded to the calculated figures.

DL-2-Hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic Acid (I). With vigorous stirring, 16.7 g of potassium phthalimide was added in portions to molten D(–)-pantolactone (35.1 g) heated to 140°C. The temperature of the reaction mixture was raised to 120°C and was kept there for 30 min, and the resulting homogeneous melt was cooled and diluted with 80 ml of water. The crystalline precipitate that formed was filtered off, washed with water, and dried in vacuum at 40-60°C. The yield of the compound was 19.2 g (77%), mp 163-165°C (from aqueous ethanol); R_f 0.70 (system 1), 0.59 (system 2), 0.84 (system 3). IR spectrum (ν, cm^{-1}): 3400 (OH), 1760, 1720 (C=O) (in paraffin oil). PMR spectrum (δ, ppm): 1.48 [$(CH_3)_2$, singlet], 4.25 (CH_2, singlet), 4.55 (CHOH, singlet), 7.05-8.75 (ring protons, multiplet) (in D_2O).

Resolution of DL-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic Acid into Optical Isomers. To a solution of 4.14 g of compound (I) in 21 ml of absolute ethanol was added 3.27 g of L(+)-threo-2-amino-1-(p-nitrophenyl)propane-1,3-diol. The solution was left at 20°C for 24 h and the resulting precipitate was filtered off and dried. This fraction (I) amounted to 3.77 g. The filtrate was evaporated and the residue was dried in vacuum. This fraction (II) consisted of 3.20 g of the salt of D(–)-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid with the L(+)-threomine. Fraction (I) was recrystallized from aqueous ethanol (35 ml of absolute ethanol and 3.2 ml of water). This gave 2.86 g of the salt of L(+)-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid with L(+)-threomine. The salt of fraction II (3.20 g) was dissolved in 10 ml of water, and then 10 ml of 10% hydrochloric acid was added and the resulting precipitate was filtered off and dried in vacuum. It consisted of 1.65 g (79.7%) of D(–)-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid with $[\alpha]_D^{20}$ –9.27° (c 1.2; ethanol). The sale of fraction (II) (2.86 g) gave 1.45 g (70%) of L(+)-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid with $[\alpha]_D^{20}$ +10.9 (c 1.2; ethanol).

L-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [L-(II)]. A boiling solution of 6.9 g of L-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid in 50 ml of absolute ethanol was treated with 1.7 ml of 85% ethanolic hydrazine hydrate. The reaction mixture was stirred at the boil for 3 h and was then cooled, and 70 ml of 70% aqueous acetic acid was added. The resulting precipitate was separated off, and the filtrate was concentrated almost to dryness and was diluted with 100 ml of acetone. The new precipitate was filtered off, washed with acetone, and dried in vacuum at 40°C. This gave 3.13 g (85%) of a compound with mp 172-173°C $[\alpha]_D^{20}$ –14.5° (c 1; water); R_f 0.26 (system 1), 0.41 (system 2), 0.53 (system 3). IR spectrum (ν, cm^{-1}): 1600 (NH^+), 1640 (C=O) (in paraffin oil).

D-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [D(II)]. This was obtained from D-2-hydroxy-3-dimethyl-4-phthaloylaminobutanoic acid in a similar manner to L-(II) with a yield of 2.67 mg (73%); $[\alpha]_D^{20}$ +14.0° (c 1; water).

DL-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [DL-(II)]. This was obtained from DL-2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid with a yield of 4.27 g (92.6%).

Lactam of L-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [L-(III)]. L-4-Amino-2-hydroxy-3,3-dimethylbutanoic acid (1.14 g) was heated in 30 ml of dimethyl sulfoxide at 150°C for 6 h. The solvent was distilled off in vacuum and the residue was crystallized from a mixture of ethanol and petroleum ether. The yield of lactam was 0.69 g (69%); mp 155-156°C, $[\alpha]_D^{20}$ –20° (c 1; methanol); R_f 0.43 (system 1), 0.57 (system 2), 0.65 (system 3). IR spectrum (ν, cm^{-1}): 3200-3400 (OH and NH), 1700 (C=O) (in paraffin oil). PMR spectrum (δ, ppm): 0.95 and 1.13 [6 H, $(CH_3)_2$, two singlets]; 3.03 (2 H, CH_2, singlet), 4.03 (1 H CH, singlet) (D_2O).

Lactam of D-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [D-(III)]. This was obtained from D-4-amino-2-hydroxy-3,3-dimethylbutanoic acid in a similar manner to compound L-(III). Yield 0.67 g (68%), $[\alpha]_D^{20}$ +30° (c 1; methanol).

Lactam of DL-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [DL-(III)]. This was obtained similarly to compound L-(III) with a yield of 0.85 g (69.1%).

L-N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [L-(IV)]. Over 1 h, 3.76 g of benzyloxyformyl chloride was added dropwise to a solution of compound L-(II) and 1.74 g of caustic soda in 15 ml of water cooled to 0-5°C. The reaction mixture was stirred at 0-5°C for 3 h and was then extracted with ether (3 × 20 ml), the aqueous layer was acidified to pH 1 and extracted with chloroform (3 × 30 ml), and the chloroform extracts were dried and

evaporated in vacuum. This gave 3.72 g (67%) of the oily L-N-BOC-4-amino-2-hydroxy-3,3-dimethylbutanoic acid; $[\alpha]_D^{20}$ +11.0° (c 2; ethanol); R_f 0.58 (system 1); 0.60 (system 2); 0.84 (system 3). IR spectrum (ν, cm^{-1}): 3300-3400 (NH), 1760, 1700 (C=O), 1660 (amide I), 1540 (amide II) (thin film), PMR spectrum (δ, ppm): 1.05 and 1.10 [$(CH_3)_2$, two singlets]; 3.05-3.55 (CH_2O, multiplet); 3.63 (NCH_2, singlet); 3.94 (CHOH, singlet); 7.15-7.88 (5 H, C_6H_5, multiplet) (CD_3OD).

D-N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [D-(IV)]. This was obtained in a similar manner to compound L-(IV) from D-4-amino-2-hydroxy-3,3-dimethylbutanoic acid with a yield of 3.34 g (72.5%), $[\alpha]_D^{20}$ −10.0° (c 2; ethanol).

DL-N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [DL-(IV)]. This was obtained from compound DL-(II) by the method for L-N-BOC-4-amino-2-hydroxy-3,3-dimethylbutanoic acid, with a yield of 5.43 g (97%).

N-Hydroxysuccinimide Ester of L-N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [L-(V)]. At 0-5°C, 3.0 g of dicyclohexylcarbodiimide was added to a solution of 3.72 g of compound L-(IV) and 1.52 g of N-hydroxysuccinimide in 30 ml of methylene chloride, and the mixture was stirred for 3 h. The precipitate was separated off, the filtrate was evaporated, and the residue was dried in vacuum. The yield of oily product was 5.27 g (9%), $[\alpha]_D^{20}$ +15.5° (c 2; ethanol); R_f 0.70 (system 1), 0.1 (system 2), 0.92 (system 3). IR spectrum (ν, cm^{-2}); 3400 (NH); 1780, 1740, 1545 (C=O) (in chloroform).

N-Hydroxysuccinimide Ester of D-N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [D-(V)]. This was obtained from D-(IV) in a similar manner to compound L-(V) with a yield of 7.23 g (99%); $[\alpha]_D^{20}$ −14.0° (c 2; ethanol).

N-Hydroxysuccinimide Ester of DL-N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutanoic Acid [D-(V)]. This was obtained from DL-(IV) by the procedure for L-(V). Yield 0.93 g (99%).

L-N-(N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine [L-(VI)]. A solution of 5.32 g of compound L-(V) in 50 ml of absolute ethanol was added to a solution of 1.25 g of β-alanine and 2.37 g of sodium bicarbonate in 30 ml of water, and the mixture was stirred at 20°C for 18 h. Then it was concentrated to ≈15 ml, 15 ml of water was added, and it was acidified with 5 N hydrochloric acid to pH 2. The precipitate that formed was filtered off, washed with water, and dried in vacuum at 40°C. This gave 3.03 g (61.2%) of L-N-(N-BOC-4-amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine with mp 145-146°C (from ethyl acetate); $[\alpha]_D^{20}$ −22.0° (c 0.4; ethanol); R_f 0.78 (system 1), 0.64 (system 2), 0.90 (system 3). IR spectrum (ν, cm^{-1}): 3400, 3340 (NH, OH); 1735, 1690 (C=O), 1640 (amide I), 1550 (amide II) (in paraffin oil). PMR spectrum (δ, ppm): 1.20 and 1.23 [6 H, $(CH_3)_2$ two singlets]; 2.70 (2 H, CH_2COOH, triplet); 3.15-3.83 (6 H, $NHCH_2$, CH_2(β), CH_2O, multiplet); 4.20 (1 H, CHOH, singlet); 6.79-7.43 (5 H, C_6H_5, triplet).

D-N-(N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine [D-(VI)]. This was obtained from D-(V) by the procedure for compound L-(VI) with a yield of 4.58 g (62.4%); $[\alpha]_D^{20}$ +20.25° (c 0.4; ethanol).

DL-N-(N-BOC-4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine [DL-(VI)]. This was obtained in a similar manner to compound L-(VI) from DL-(V) with a yield of 5.49 g (63%).

L-N-(4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine L-(VII). A solution of 0.48 g of compound L-(IV) in 30 ml of methanol was treated with 0.48 g of 5% Pd on carbon as catalyst and was hydrogenated at 20°C until the absorption of hydrogen ceased (40 min). The catalyst was filtered off, and the filtrate was concentrated in vacuum to ≈5 ml and was left at 5-10°C. The precipitate was filtered off, washed with methanol, and dried in vacuum at 40°C. This yielded 0.2 g (67.3%) of L-N-(4-amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine with mp 174-176°C; $[\alpha]_D^{20}$ −25.3° (c 5.45; water); R_f 0.31 (system 1), 0.47 (system 3). IR spectrum (ν, cm^{-1}): 3340, 3320 (NH, OH); 1660 (amide I); 1615 (NH^+); 1570 (C=O in COO^-); 1540 (amide II) (paraffin oil). PMR spectrum (δ, ppm); 1.04 and 1.10 (6 H, $(CH_3)_2$, two singlets); 2.25-2.55 (2 H, CH_2COOH, triplet); 3.03 (2 H, H_2NCH_2, singlet); 3.26-3.60 [2 H, CH_2(β), triplet] 4.0 (1 H, CHOH, singlet).

D-N-(4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanine [D-(VII)]. This was obtained from compound D-(VI) with a yield of 0.66 g (71%); $[\alpha]_D^{20}$ +22.0° (c 5.45; water).

DL-N-(4-Amino-2-hydroxy-3,3-dimethylbutylyl)-β-alanine [DL-(VII)]. This was obtained from DL-(VI) by the procedure for compound L-(VII) with a yield of 0.58 g (62.4%).

CONCLUSION

1. The synthesis of DL-4-amino-2-hydroxy-3,3-dimethylbutanoic acid has been performed, and it has been resolved into its stereoisomers.

2. D-, L-, and DL-N-(4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanines — amino analogs of pantothenic acid — have been obtained by the condensation of the N-hydroxysuccinimide esters of N-BOC-D-, -L-, and -DL-4-amino-2-hydroxy-3,3-dimethylbutanoic acids with β-alanine followed by the elimination of the protective group.

LITERATURE CITED

1. V. M. Berezovskii, The Chemistry of the Vitamins [in Russian], Moscow (1973), p. 60.
2. Y. Abiko, J. Biochem. (Tokyo), 61, 290 (1967).
3. T. D. Marieva, V. M. Kopelevich, V. V. Mishchenko, et al., Khim. Prir. Soedin., 378 (1979).
4. S. Hanessian, in: Methods in Carbohydrate Chemistry, Vol. 6, R. Whistler and J. BeMiller, eds., Academic Press (1972), p. 208.
5. H. Fritz and W. Lowe, Angew Chem., 74, 751 (1962).
6. T. Konno, H. Megura, and K. Turimura, Tetrahedron Lett., 1305 (1975).
7. J. P. Greenstein and M. Winitz, Chemistry of the Amino Acids, Wiley, New York (1961).

PHEROMONES OF INSECTS AND THEIR ANALOGS. V. A NEW APPROACH TO THE SYNTHESIS OF THE SEX PHEROMONES OF INSECTS OF THE ORDER *Lepidoptera* WHICH IS BASED ON THE SELECTIVE OZONOLYSIS OF 1-METHYLCYCLOOCTA-1Z,5Z-DIENE

G. A. Tolstikov, V. N. Odinokov, R. I. Galeeva, R. S. Bakeeva, and V. R. Akhunova

UDC 547.364+547.996+632.936.2

A new synthesis of 1-acetoxyalk-Z-enes (sex pheromones of insects of the order *Lepidoptera*) has been developed which is based on the selective ozonolysis of 1-methylcycloocta-1Z-5Z-diene — a cooligomer of isoprene and butadiene.

The synthesis of pheromones of *Lepidoptera*, which have the structure of acetates of alk-Z-en-1-ols, is usually performed via acetylene derivatives [1-4]. We have developed a new approach to the synthesis of the sex pheromones of this class which is based on the selective ozonolysis of the readily accessible 1-methylcycloocta-1Z,5Z-diene (I) — a cyclic codimer of isoprene and butadiene [5]. For the selective deoxygenation of the resulting non-4Z-ene-1,8-dione (II) at the keto group, the formyl group must be protected, for example, by reaction with methanol in the presence of ammonium chloride, which leads to 9,9-dimethoxynon-5Z-en-1,2-one (III) [5].

It has been found, however, that under the conditions of reducing the tosylhydrazone of the keto acetal (III) with sodium cyanotrihydroborate — an effective reducing agent for tosyl hydrazones [6] — the acetal protection is not retained, and instead of 1,1-dimethoxynon-4Z-ene a mixture of (3:5) of non-4Z-ene (IV) and nonane — the products of the reduction of both carbonyl groups and of the double bond — is obtained. The acetal group is retained if the tosylhydrazone of the keto acetal (III) is reduced with sodium tetrahydroborate by Caglioti's method [7], but in this case, in addition to the reduction of the keto group, the double bond also undergoes hydrogenation, which leads to a 46% yield of 1,1-dimethoxynonane (V).

The reduction of the keto group to a methylene group leading to the desired non-4Z-en-1-ol (IX) [(X) is the acetate] was successfully achieved by the selective transformation of the keto aldehyde (II) into 9-hydroxynon-5Z-en-2-one (VI) [(VII) is the corresponding acetoxy

Institute of Chemistry of the Bashkir Branch of the Academy of Sciences of the USSR, Ufa.

Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 239-245, March-April, 1982. Original article submitted June 22, 1981.