TOTAL SYNTHESIS AND PROPERTIES OF PROSTAGLANDINS 34.* SYNTHESIS AND X-RAY STRUCTURAL ANALYSIS OF (+)4-(CARBOXYMETHYLOXYIMINOMETHYL)-2-OXABICYCLO-[3.3.0]-6-OCTEN-3-ONE

K. I. Dikovskaya, T. V. Mazur, A. F. Mishnev, I. V. Turovskii, and Ya. F. Freimanis

The reaction of α-formyl-γ-lactones with O-substituted hydroxylamines has been investigated. An x-ray structural investigation has been carried out on (+)4-(carboxymethyloxyiminomethyl)-2-oxabicyclo[3.3.0]-6-octen-3-one.

When continuing investigations on the modification of the α-carbon atom of the bicyclic γ-lactones (I) and (VII), which are precursors of prostaglandins [2, 3], we carried out the reaction of the α-formyl derivatives of these lactones (II) and (VIII) with O-methyl-, O-allyl-, and O-carboxymethylhydroxylamines (Scheme 1). Synthesis of the formyl derivatives was carried out by ester condensation of the lactones with ethyl formate in the presence of NaH [2]. As shown by NMR spectra, the formyl derivatives (II) and (VIII) obtained were present in chloroform solution in both the enolic (δ 1′-H 7.10 ppm) and the ketonic forms (δ 1′-H 9.76 ppm). Reaction of the formyllactones with the O-substituted hydroxylamines was carried out in methanol in the presence of K_2CO_3. The oximes (III) and (IV) were oily substances, the results of the analysis of which by high performance liquid chromatography (HPLC) and PMR showed that each of them was a mixture of four isomers (relative elution times for each isomer on HPLC are given in Table 1). The signals for the 1′-H protons in the PMR spectra, observed as a doublet of doublets in the range δ 6.72-7.44 ppm, indicate the presence of four isomers (Table 2). However, attempts to separate the oximes obtained preparatively were unsuccessful (see Scheme 1, top of following page).

The oxime acid (V), initially purified by column chromatography and then by recrystallization from a hexane–isopropanol mixture, was isolated in 80% yield and was a single compound with mp 110-111°C. The same applies to its methyl ester (VI) (mp 118-119°C) obtained by reaction with diazomethane. In the PMR spectra of both the acid and the ester a doublet was observed for the 1′-H proton at 6.99 ppm (Tables 1 and 2). However, the PMR spectra of the oxime acid (V), obtained directly after chromatographic purification but without recrystallization, showed the presence of all four theoretically possible isomers (doublets of the CH=N proton at δ 7.59, 7.46, 6.99, and 6.92 ppm). Recrystallization leads to the formation of the single oxime acid (V) in high yield (92%). Transition was observed of three of the isomeric forms into the fourth, which is the most stable and energetically favorable.

Compounds (V) and (VI) may be regarded as endo isomers from the PMR spectral data since the 4-H and 5-H protons have a cis orientation as indicated by the size of the coupling constant $J_{4,5}$ = 8.5 Hz. The high field shift of the 1′-H proton and the low field shift of the 4-H and 5-H protons relative to the corresponding protons of the other isomeric forms may indicate the anti form of the oxime fragment (see Table 2). An x-ray structural investigation of the oxime acid (V) was carried out to confirm its structure (Fig. 1, Table 3).

The results of the analysis showed that the molecule has a folded conformation characterized by a rotatable side chain on the side of the bicyclic octene. The dihedral angle between the mean planes of the five-membered rings was 109.8°. Both

*For Communication 33 see [1].

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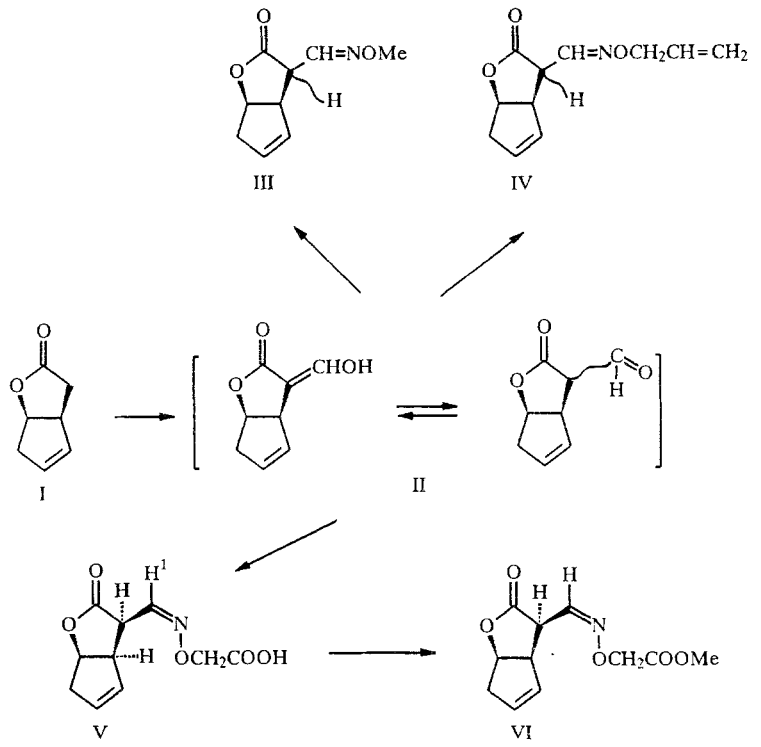
TABLE 1. Mass Spectra and Mobility of the Compounds Synthesized

Compound	R_f (system)*	K (system)*	m/e (I, %)
III	0,74; 0,60 (A)	1,42; 1,85; 2,64; 3,20 (B)	181 (5) $[M]^{+\cdot}$, 151 (5) $[M-OCH_2]^+$, 137 (75) $[M-NOCH_2]^+$, 136 (43) $[M-NOCH_3]^+$, 124 (100) $[M-CH=NOCH_2]^{+\cdot}$, 122 (39)
IV	0,47; 0.36; (B)	1,46; 1,64; 2,51; 3,10 (F)	207 (58) $[M]^{+\cdot}$, 190 (30) $[M-OH]^+$, 163 (100) $[M-CO_2]^{+\cdot}$, 162 (69), 151 (60), 150 (20) $[M-OCH_2CH=CH_2]^+$, 146 (100), 136 (34) $[M-NOCH_2CH=CH_2]^+$, 133 (64), 124 (>100) $[C_7H_8O_2]^{+\cdot}$, 123 (>100) $[M-CH=NOCH_2CH=CH_2]^+$
V	0,25 (A)	—	207 (11) $[M-H_2O]^{+\cdot}$, 180 (5) $[M-COOH]^+$, 151 (100) $[M-OCHCOOH]^+$, 123 (>100) $[M-CH=NOCH_2COOH]^+$
VIII	0,50 (D)	1,10; 1,30 (G)	365 (3) $[M-C_4H_7O]^+$, 348 (10) $[M-C_4H_8O_2]^{+\cdot}$, 279 (36), 278 (94) $[M-C_4H_7O-C_4H_7O_2]^+$, 261 (16) $[M-C_4H_8O_2-C_4H_7O_2]^+$, 260 (29) $[M-2C_4H_8O_2]^{+\cdot}$, 234 (100) $[M-CO-2C_4H_7O_2]^+$
X	0,39 (E)	—	454 (2) $[(M+1)-C_4H_6O]^+$, 436 (10) $[(M+1)-C_4H_8O_2]^{+\cdot}$, 366 (100) $[(M+1)-C_4H_6O-C_4H_8O_2]^+$, 348 (44) $[(M+1)-2C_4H_8O_2]^{+\cdot}$
XI	0,47; 0,41 (H)	2,66; 3,66; 4,66 (H)	384 (60) $[M+1]^{+\cdot}$, 366 (100) $[(M+1)-H_2O]^{+\cdot}$, 348 (65) $[(M+1)-2H_2O]^{+\cdot}$, 296 (65) $[(M+1)-H_2O-C_5H_{10}]^+$

*Solvent systems were A) hexane–ethyl acetate, 1.5:1; B) 4:1; C) 70:30; D) 1:1.5; E) 1:1; F) hexane–ethyl acetate–acetic acid, 79:20:1; G) hexane–dioxan–isopropyl alcohol, 87:5:8; H) hexane–ethyl acetate–dioxan, 15:80:5.



five-membered rings have an envelope conformation with strictly planar fragments of $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$ and $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, $C_{(4)}$.

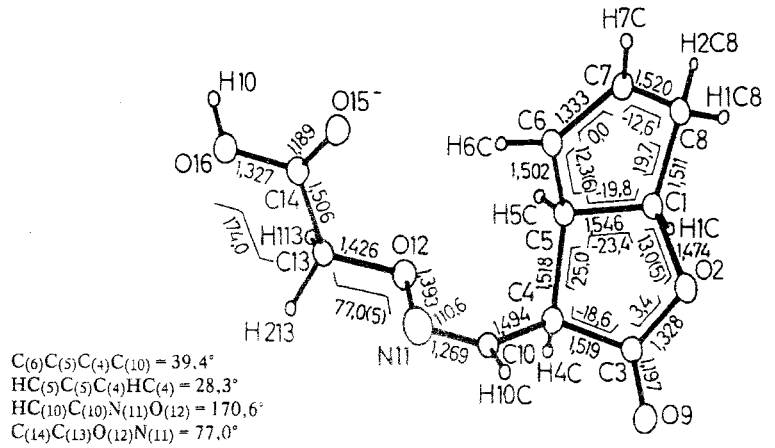


Fig. 1. Bond lengths and torsion angles of (+)4-(carboxymethyloxyiminomethyl)-2-oxabicyclo[3.3.0]-6-octen-3-one (V).

TABLE 2. PMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm
III (4 isomers)	7,40; 7,26; 6,78; 6,72 (1H, d.d. CH=N); 5,32...5,82 (2H, м, 7-H, 6-H); 4,92...5,21 (1H, m 1-H); 3,83; 3,85; 3,90; 3,91 (3H, s, OCH_3); 3,20...3,80 (2H, m, 4-H, 5-H); 2,70 (2H, m 8-H)
IV (4 isomers)	7,44; 7,31; 6,82; 6,78 (1H, d.d. CH=N); 4,92...6,12 (6H, m 7-H, 6-H, 1-H, $CH=CH_2$); 4,40...4,82 (2H, m, OCH_2); 3,20...3,95 (2Hm, 4-H, 5-H); 2,85 (2H, m, 8-H)
V (4 isomers)	10,39 (1H, м, COOH); 7,59; 7,46; 6,99; 6,92 (1H, d, CH=N); 5,50...5,90 (2H, 7-H, 6-H); 5,09 (1H, m, 1-H); 4,68; 4,69 4,85 (2H, s, OCH_2); 4,04; 3,95; 3,70; 3,37 (2H, m, 4-H, 5-H); 2,70 (2H, m, 8-H)
V	6,98 (1H, d, CH=N); 5,86 (1H, m, 7-H); 5,68 (1H, m, 6-H); 5,17 (1H, m, 1-H); 4,80 (2H, s, OCH_2); 4,08 (1H, d.d. 4-H); 4,00 (1H, m, 5-H); 2,77 (2H, m 8-H)
VI	6,99 (1H, d, CH=N); 5,84 (1H, m, 7-H); 5,68 (1H, m, 6-H); 5,14 (1H, m, 1-H); 4,75 4,68 (2H, d, OCH_2); 4,03 (2H, m, 4-H, 5-H); 3,77 (3H, s, $COOCH_3$); 2,76 (2H, м, 8-H)
XI (1st fraction)	7,60; 6,92 (1H, d, CH=N); 5,55 (2H, м, 1'-H, 2'-H); 4,95 (1H, s, 1-H); 4,68 4,53 (2H, s, OCH_2); 4,00 (2H, m, 7-H, 3'-H); 3,72 3,68 (3H, s, $COOCH_3$); 3,81 3,42 (1H, m, 4-H); 2,88 (1H, m, 5-H); 0,90 (3H, t, CH_3)
XI (2nd fraction)	6,97 (1H, d, CH=N); 5,60 (2H, m, 1'-H, 2'-H); 4,95 (1H, m 1-H); 4,62 (2H, c, OCH_2); 3,90...4,20 (3H, m, 7-H, 3'-H, 4-H); 3,80 (3H, s, $COOCH_3$); 3,12 (1H, м, 5-H); 0,90 (3H, s, CH_3)
XI (3rd fraction)	7,48 (1H, d, CH=N); 5,60 (2H, m, 1'-H, 2'-H); 4,90 (1H, m, 1-H); 4,59 4,49 (2H, d, OCH_2); 3,73...4,20 (3H, m, 7-H, 3'-H, 4-H); 3,76 (3H, s, $COOCH_3$); 2,68...3,00 (1H, m, 5-H); 0,90 (3H, t, CH_3)

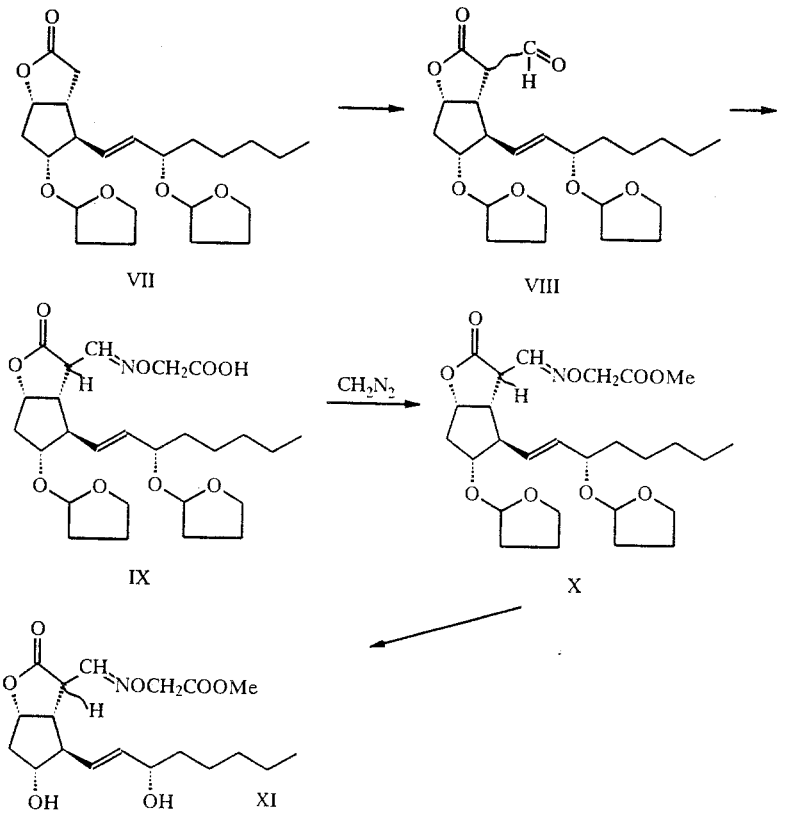
The substituent at the $C_{(4)}$ atom has the endo-orientation. The $C_{(6)}$ and $C_{(10)}$ atoms are inclined to one side of the mean plane of the five-membered heterocycle. The torsion angle $C_{(6)}-C_{(5)}-C_{(4)}-C_{(10)}$ is 39.4°. Correspondingly the protons at the $C_{(4)}$ and $C_{(5)}$ atoms have the cis orientation with a torsion angle about the $C_{(4)}-C_{(5)}$ bond equal to 28.3°.

The relative orientation of the hydrogen atoms on $C_{(4)}$ and $C_{(10)}$ may be regarded as trans since the corresponding torsion angle is 123.6°. In this orientation the H at $C_{(10)}$ is close to $O_{(9)}$ of the lactone carbonyl group.

The oxime fragment has the trans conformation, the torsion angle $HC_{(10)}-C_{(10)}-N_{(11)}-O_{(12)}$ is 170.6°. The plane portions of the carboxyl and oxime groups are turned relative to one another about the $C_{(12)}-C_{(13)}$ bond at an angle of 77.0°. The bond lengths in the molecule are in good agreement with their standard values in similar compounds [4].

The packing of the molecules in the crystal is characterized by the presence of an intermolecular hydrogen bond at $O_{(16)}-H...O_{(9)}$ ($O_{(16)}...O_{(9)}$ = 2.267 Å, $HO_{(16)}...O_{(9)}$ = 2.05 Å, angle $O_{(16)}-H...O_{(9)}$ = 164°).

It is therefore established that the oxime acid (V) has a conformation characterized by an endo orientation of the substituent at the $C_{(4)}$ atom and the anti form of the aldoxime fragment.



Compound (IX), which is also a mixture of isomers, was obtained by the reaction of the α-formyllactone (VIII) with aminooxyacetic acid in methanol in the presence of K_2CO_3. Signals of the 1′-H protons were observed in the PMR spectrum in the 6.83-7.56 ppm region. In order to simplify the analysis, the product (IX) was converted into the methyl ester (X), and then into the deprotected product (XI) [Scheme 2 (see top of following page), Table 1].

The dihydroxylactone (XI) is an oily substance consisting of four isomeric compounds difficult to separate by chromatography. However, three fractions were isolated by HPLC, one of which contained two compounds. Two doublets for the CH=N proton at δ 6.92 and 7.60 ppm were observed in the PMR spectrum of this fraction. The size of the coupling constant $J_{4,5}$ = 4 Hz indicates the trans orientation of the 4-H and 5-H protons. Probably this pair of compounds are the exo isomers differing in conformation at the aldoxime fragment.

The second and third fractions contained individual compounds with relative elution times of 3.66 and 4.66, respectively (see Table 1).

Comparison of the results of x-ray analysis and PMR spectra of compound (V) with the PMR spectra of the isomers (XI) in the second (δ of CH=N proton 6.97 ppm) and third (δ of CH=N proton 7.48 ppm) fractions suggest an endo orientation for the substituent at the 4-C atom in both isomers and anti and syn orientations for the aldoxime portion, respectively (see Table 2).

EXPERIMENTAL

The PMR spectra were obtained on a Bruker WH-90 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were taken on a Kratos MS-50 mass spectrometer, the energy of the ionizing electrons was 70 eV. The FAB mass spectra were taken on the same Kratos instrument fitted with an FAB 11 NF source (Ion Tech Ltd), ionizing gas was argon, matrix was thioglycerol. The IR spectra were recorded on a Perkin Elmer 580B spectrometer in $CHCl_3$ solution.

A Laboratorni pristroje (Prague) liquid chromatograph was used for the chromatographic investigations, the detector was a differential refractometer. For normal phase HPLC a column (3.0 × 150 mm) packed with Separon TM SGX sorbent of particle size 5 μm was used. For the preparative separation of the (XI) mixture a column (10 × 250 mm) was used packed

TABLE 3. Coordinates ($\times 10^4$) of Atoms Other Than Hydrogen in the Crystal of Compound (V)

Atom	x	y	z	Atom	x	y	z
$C_{(1)}$	-139(12)	1989(5)	-1940(3)	$O_{(9)}$	-4738(11)	3546(5)	-3003(2)
$O_{(2)}$	-2292(9)	2164(4)	-2515(2)	$C_{(10)}$	-2655 (10)	4907(4)	-1825(3)
$C_{(3)}$	-2951(13)	3217(5)	-2592(2)	$N_{(11)}$	-1764(10)	5619(3)	-1371(2)
$C_{(4)}$	-1117(10)	3910(4)	-2087(2)	$O_{(12)}$	963(8)	5361(3)	-1136(2)
$C_{(5)}$	-12(11)	3095(4)	-1525(3)	$C_{(13)}$	1880(12)	6184(4)	-632(3)
$C_{(6)}$	-1971(14)	2898(5)	-888(2)	$C_{(14)}$	573(11)	6045(4)	118(3)
$C_{(7)}$	-2636(19)	1840(5)	-819(3)	$O_{(15)}$	-1219(10)	5401(4)	274(2)
$C_{(8)}$	-1219(21)	1139(5)	-1404(5)	$O_{(16)}$	1712(10)	6765(4)	579(2)

with Silasorb 600 (10 μm). The relative elution times of compounds were calculated from the formula $K = (t_R - t_0)/t_0$, where t_R is the retention time of the sorbate and t_0 the retention time of hexane. The solvent systems used are given in Table 1.

The crystals of composition $C_{10}H_{11}NO_5$ obtained from compound (VIb) were rhombic: $a = 4.724(1)$, $b = 12.188(4)$, $c = 18.180(5)$ Å; $V = 1046.7(5)$ Å^3, $M = 224.2$, $d_{calc} = 1.42$ g·cm^{-3}, $Z = 4$, $\mu(MoK\alpha) = 0.8$ cm^{-1}, space group $P2_12_12_1$.

The intensities of 1360 independent nonzero reflections were measured on a Syntex $P2_1$ diffractometer ($\theta/2\theta$ scanning, Mo radiation, graphite monochromator, $2\theta_{max} = 52°$). The structure was solved by the direct method using the SHELXS86 set of programs [5] and refined using the SHELX76 program [6] by the method of least squares in an anisotropic approach. The final R factor was 0.074. Atomic coordinates in the crystal cell are given in Table 3.

(+)4-(Carboxymethyloxyiminomethyl)-2-oxabicyclo[3.3.0]-6-octen-3-one (V, $C_{10}H_{11}NO_5$). The α-formyllactone (II) (0.2 g: 1.5 mmole) in methanol (2 ml) was added to a solution of aminooxyacetic acid hemichloride (0.30 g: 1.4 mmole) and potassium carbonate (0.2 g: 1.5 mmole) in methanol (4 ml). The mixture was stirred for 4 h, diluted with water, and extracted with ethyl acetate. The organic solution was dried over Na_2SO_4, evaporated under reduced pressure, and purified by column chromatography on Silasorb 600, eluting with solvent systems A and E. The oxime acid (V) was obtained (0.26 g: 88%), which was recrystallized from a mixture of hexane and isopropyl alcohol. The endo-, anti-oxime acid (V) (0.23 g: 92%) was obtained having mp 110-111°C, $[\alpha]_D^{20}$ +228 ($CHCl_3$, c = 1.0). IR spectrum ($CHCl_3$): 1775, 1740 cm^{-1}.

Compounds (III) (77%) and (IV) (62%) were obtained analogously.

(+)4-Methoxycarbonylmethyloxyiminomethyl)-2-oxabicyclo[3.3.0]-6-octen-3-one (VI, $C_{11}H_{13}NO_5$). A solution of diazomethane in ether (4 ml) was added dropwise to a solution of the oxime acid (V) (0.14 g: 0.64 mmole) in diethyl ether (3 ml). The product (VI) precipitated directly as white crystals. The ester (VI) (0.15 g: 98%) was obtained having mp 118-119°C, R_f 0.44 (Silufol UV-254, A), K = 3.92 (B), $[\alpha]_D^{20}$ +236 ($CHCl_3$, c = 1.0).

6β-(3α-Tetrahydrofuranyloxy-1E-octenyl)-7α-tetrahydrofuranyloxy-4-formyl-2-oxabicyclo[3.3.0]octan-3-one (VIII, $C_{24}H_{36}O_7$). A solution of the lactone (VII) (0.6 g: 1.5 mmole) in ethyl formate (1 ml: 12.3 mmole) was added dropwise with stirring in an argon atmosphere to a suspension of NaH (0.13 g: 3.8 mmole) in hexane (10 ml). The mixture was stirred for 5 h, water and ethyl acetate added, the mixture was cooled to 0-5°C, neutralized with 2 M HCl, and extracted with ethyl acetate. The organic layer was washed with water, with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed on Silasorb eluting with solvent systems A and D. Crystalline product (VIII) (0.55 g: 84%) was obtained with mp 110-111°C.

6β-(3α-Tetrahydrofuranyloxy-1E-octenyl)-7α-tetrahydrofuranyloxy-4-(methoxycarbonylmethyloxyiminomethyl)-2-oxabicyclo[3.3.0]octan-3-one (X, $C_{27}H_{41}NO_9$). The α-formyllactone (VIII) (0.35 g: 0.82 mmole) in methanol (3 ml) was added to a solution of aminooxyacetic acid hemichloride (0.21 g: 0.97 mmole) and K_2CO_3 (0.15 g: 1.1 mmole) in methanol (3 ml) and the mixture stirred for 5 h. After treatment as described above the crude acid (IX) (0.46 g) was obtained with R_f 0.45 (D). The latter was methylated with a solution of diazomethane in diethyl ether. The ester (X) obtained was purified by column chromatography on Silasorb eluting with system E. Compound (X) (0.4 g: 92%) was obtained. IR spectrum ($CHCl_3$): 1770 cm^{-1}.

6β-(3α-Hydroxy-1E-octenyl)-7α-hydroxy-4-(methoxycarbonylmethyloxyiminomethyl)-2-oxabicyclo[3.3.0]octan-3-one (XI, $C_{19}H_{29}NO_7$). The hydroxyl groups of ester (X) (0.1 g: 0.2 mmole) were deprotected by stirring in methanol (3 ml) with Dowex 50W × 2 (H^+) cation exchange resin for 5 h. The resin was filtered off, washed, the solvent evaporated, and the residue

purified by column chromatography on Silasorb eluting with system H. The ester (XI) (0.07 g: 91%) was obtained. IR spectrum ($CHCl_3$): 3610-3400, 1770 cm^{-1}.

REFERENCES

1. K. Dikovskaya, G. Laivins, I. Turovskis, and J. Freimanis, Latv. Kim. J. (in press).
2. K. I. Dikovskaya, T. V. Mazur, I. V. Turovskii, M. P. Gavars, and Ya. F. Freimanis, Khim. Geterotsikl. Soedin., No. 12, 1621 (1991).
3. A. P. Kalnin'sh, K. I. Dikovskaya, A. V. Kuchin, V. V. Kudryashova, V. R. Korits, Ya. F. Freimanis, M. P. Gavars, O. V. Sakhartova, and I. V. Turovskii, Zh. Org. Khim., **24**, 742 (1988).
4. F. H. Allen, O. Kennard, P. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, J. Chem. Soc., Perkin Trans. II, No. 12, S1 (1987).
5. G. M. Sheldrick, SHELX86. Crystallographic Computing 3, G. M. Sheldrick, C. Kruger, and R. Goddard (eds.), Oxford University Press (1985), p. 175.
6. G. M. Sheldrick, SHELX76. Programme for Crystal Structure Determination, University of Cambridge, England (1976).