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REDUCTIVE TRANSFORMATIONS OF 3-ALKYL- AND 3-ARYL-5-(4-PYRIDYL)-2-ISOXAZOLINES

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The reactions of 3-R-(4-pyridyl)-2-isoxazolines and the products of their hydrogenolysis over Raney Ni/$AlCl_3$ with $NaBH_4$ and $KBH(s\text{-}Bu)_3$ as the reducing agents were studied. New polyhydroxyprostanoids were synthesized.

We have already described the synthesis of 13,15-isoxazolinylprostanoids with 15-hetaryl fragments as active pharmacophores, including the synthesis of prostanoid Ia [1]. However, an attempt to modify this compound by a method standard for similar isoxazoloprostanoids proved unsuccessful since 1,3-cycloreversion of the isoxazoline heterocycle was observed upon the action of $KBH(s\text{-}Bu)_3$, $NaCH_2S(O)CH_3$, and BuLi, leading to destruction of the prostanoid ω-chain [2]. Thus reductive transformations are probably the only suitable methods for modifying 15-pyridyl-13,15-isoxazolinylprostanoids in the preparation of prostaglandin heteroanalogs. In the present work, results are given for a study of such transformations of isoxazolinoprostanoids Ia, Ib, and model 3-veratryl-5-(4-pyridyl)-2-isoxazoline (Ic).

The starting 2-isoxazolidines Ia-c were obtained by the 1,3-dipolar addition of nitrile oxides, generated from the corresponding nitro compounds or oximes, to 4-vinylpyridine.

In accord with our isoxazoline strategy for constructing the prostanoid ω-chain [3], the selective transformation of $C_{(9)}$-keto-13,15-isoxazolinoprostanoids to their $C_{(9)}$-α-hydroxy derivatives in order to go from E- to F-prostanoids should be carried out prior to opening of the isoxazoline ring.* In order to avoid destruction of the isoxazoline ring, $NaBH_4$ was used instead of K selectride for reduction of the carbonyl group in isoxazolinoprostanoids Ia-Ic. The reaction in the case of ketones Ia and Ib proceeded to give hydroxy derivatives IIa and IIb in 80% yield as a 1:2 mixture of the 9α- and 9β-diastereomers. Under these conditions, ketone Ic is not reduced and the starting compound was recovered. In light of the lack of stereoselectivity in the reduction of the $C_{(9)}$=O group described above, we tested the feasibility of selective reduction of the carbonyl group to give products of the reductive splitting of the heterocycle in isoxazolinoprostanoids Ia-Ic. The hydrogenolysis of these compounds was carried out in the presence of skeleton catalyst, Raney nickel, in the $AlCl_3$—MeOH—H_2O system; hydrogen *in situ* being the active reducing agent in this system [5]. Under these conditions, Ia-c are converted to β-hydroxyketones IIIa-c in 54-65% yield, which corresponds to the typical scheme for splitting of 2-isoxazolines by the action of such reducing agents [5]. Ketone IVc was isolated in 20% yield in the reductive opening of isoxazoline Ic along with hydroxyketone IIIc obtained in 54% yield; ketones IVa and IVb were detected in trace amounts. The reductive splitting of 9-hydroxy-13,15-isoxazolinoprostanoids IIa and IIb leads to ketodiols Va and Vb in 65-70% yield.

*Prostaglandins with a C=O group in the prostane skeleton belong to the E series, while such derivatives with a $C_{(9)}$—α-OH group belong to the F series. The nomenclature for derivatives a and b has been adopted for prostaglandins [4].

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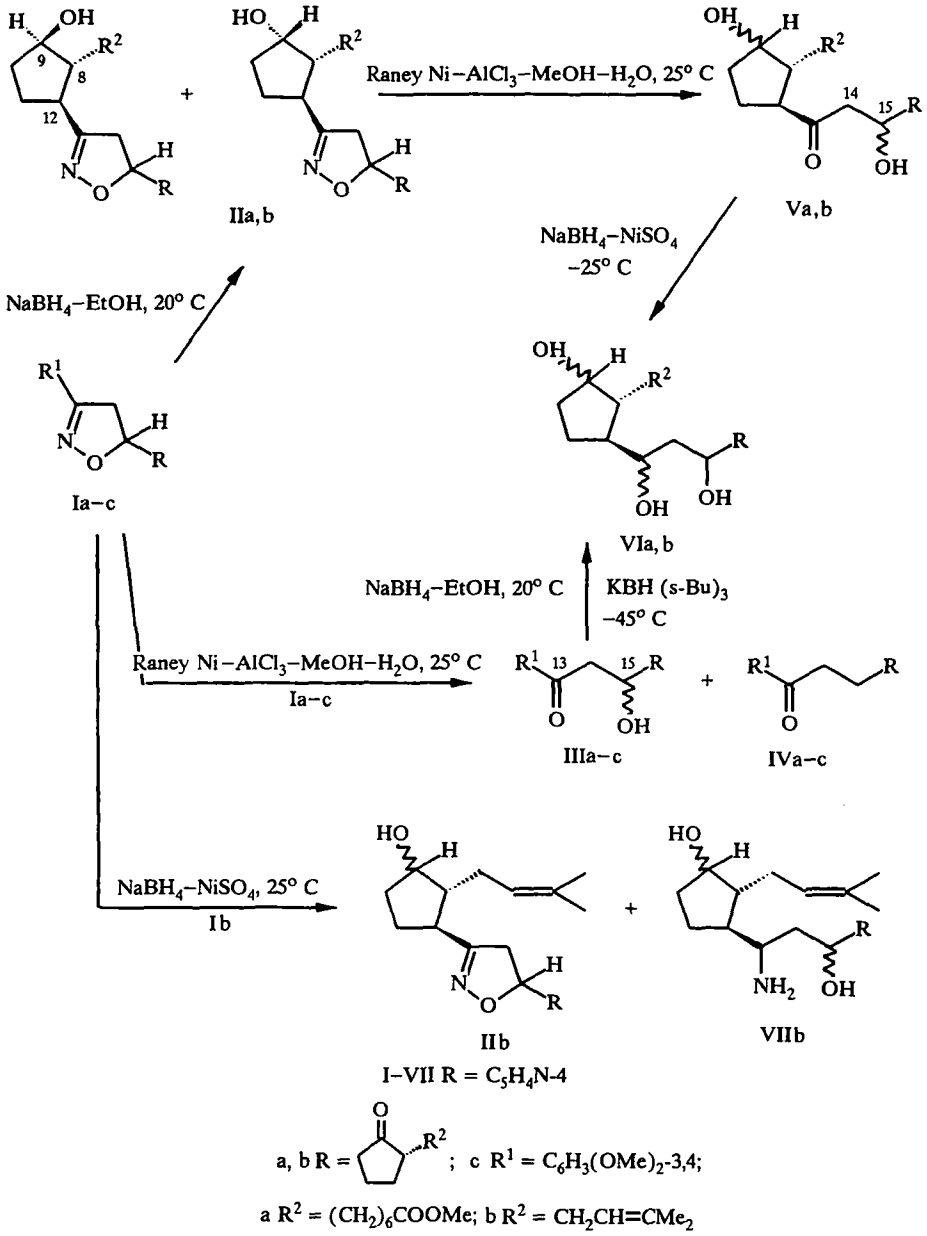

The structure of the obtained products was indicated by their physicochemical characteristics given in Table 1. The IR spectra of III show characteristic hydroxy group stretching bands at 3380-3450 cm^{-1}, while the spectra of IIIa-Va have C=O stretching bands at 1710-1720 cm^{-1}. The characteristic bands for the ring and ester carbonyl groups, also found in starting isoxazolinoprostanoid Ia, are seen at 1735-1745 cm^{-1}. The IR spectrum of diol Vb has a band for the ω-chain C=O group at 1720 cm^{-1} but lacks the characteristic ring C=O group band at 1745 cm^{-1}. In comparison with the starting isoxazolines, the PMR spectra of III and V lack the characteristic multiplets for the isoxazoline ring protons at 5.2-5.3 ppm but show a signal for 15-H at 5.18-5.20 ppm. The shift of this signal indicates that 15-H is close to the aromatic pyridine ring. The signals for the methylene protons 14-H in the hydroxyketone fragment in III appear as two doublets at 2.76-2.88 and 2.88-3.03 ppm. The pyridine ring protons appear as two doublets at 7.25-7.35 and 8.45-8.65 ppm (J = 5 Hz).

The signals of 9-H, which is adjacent to the hydroxy group, in the PMR spectra of 9-hydroxy derivatives IIa and IIb and diols Va and Vb appear at 3.94-4.30 ppm as two multiplets, corresponding to the α- and β-oriented proton. A significant difference is found for the chemical shifts of the signals for 9-H and 15-H in diols V, which permits us to determine the selectivity of the hydroxylation using PMR spectroscopy and assign the stereochemistry of the OH group at $C_{(9)}$. Thus, the doublet of doublets at 4.20-4.28 ppm was assigned to 9β-H. The

TABLE 1. Major Physicochemical Characteristics of Synthesized Isoxazolinoprostanoids and Products of Their Reductive Transformations

Compound	Empirical formula	Found, % / Calculated, %			IR spectrum, cm^{-1}	M^+	PMR spectrum, δ, ppm (*J*, Hz)					
		C	H	N			8-H*	9-H*[2]	12-H*	13-H*[2]	14-H*	15-H
Ia	$C_{21}H_{28}N_2O_4$	68,05 67,72	7,46 7,58	7,66 7,52	1610, 1740	372	—	—	2,98 m	—	2,92 dd (18,0; 7,0) 3,50 dd (18,0; 10,0)	5,63 dd (10,0; 7,0)
Ib	$C_{18}H_{22}N_2O_2$	71,10 72,45	7,39 7,43	9,55 9,39	1595, 1730	298	1,80 m	—	2,98 m	—	2,88 dd (17,0; 7,0) 3,52 dd 17,0; 5,0)	5,60 dd (7,0; 5,0)
IIa	$C_{21}H_{30}N_2O_4$	67,97 67,35	8,00 8,08	7,12 7,48	1605, 1640, 1735, 3380	374	—	4,30 t (4,0) 3,98 dd (4,5)	2,64 dd	—	2,90 dd (17,0; 6,5) 3,48 dd (17,0; 11,0)	5,58 dd (11,0; 6,5)
IIb	$C_{18}H_{24}N_2O_2$	71,37 71,91	8,05 8,05	8,99 9,33	1600, 3380	300	—	4,28 dd (3,5) 3,98 dd (5,0)	2,64 m*[2]	—	2,86 dd (17,0; 7,0) 3,46 dd (17,0; 5,0)	5,56 dd (7,0; 5,0)
IIIa	$C_{21}H_{29}NO_5$	66,66 67,18	7,84 7,79	3,89 3,73	1605, 1710, 1735, 3450	375	2,58 m	—	2,92 m	—	2,83 dd (18,0; 3,0) 3,03 dd (18,0; 8,5)	5,28 dd (8,0; 3,0)
IIIb	$C_{18}H_{23}NO_3$	71,86 71,73	7,77 7,69	4,77 4,65	1610, 1720, 1745, 3380	301	—	—	2,96 m	—	2,76 dd (17,0; 3,5) 2,88 dd (17,0; 8,0)	5,21 dd (8,0; 3,5)
Va	$C_{21}H_{31}NO_5$	66,79 66,82	8,27 8,28	3,69 3,71	1610, 1740, 3450	377	2,18 m	4,28 t (3,0) 3,94 dd (4,0)	2,64 dd	—	2,90 d	5,20 t (5,5)
Vb	$C_{18}H_{25}NO_3$	70,99 71,25	8,25 8,31	4,62 4,69	1610, 1720, 3400	303	2,18 m	4,28 m 3,94 q (4,0)	2,60 dd	—	2,84 dd (5,5)	5,18 t
VIa	$C_{21}H_{33}NO_5$	66,46 66,46	8,89 8,77	3,79 3,69	1610, 1735, 3450	379	—	4,24 m 3,94 m	—	3,88 m 4,12 m	—	5,06 m*[2] 4,96 m
VIb	$C_{18}H_{27}NO_3$	70,37 70,79	8,79 8,91	4,44 4,59	1605, 3400	305	—	4,24 m 3,98 m	—	3,90 m 3,68 m	—	5,06 m*[2] 4,92 m
VIIb	$C_{18}H_{28}N_2O_2$	70,88 71,01	9,23 9,27	9,07 9,20	1610, 3400 3440	304	—	4,24 m	—	3,80 m	2,90 m	5,55 m

* Signals in the region for acyclic methylene protons 1.05-2.20 ppm not indicated.

*[2] Chemical shifts given for H_β and H_α.

chemical shift, multiplicity, and coupling constant (J = 4.5 Hz) of this proton, in accord with the empirical rules for the PMR spectra of prostanoids [6], indicate its pseudoequatorial orientation and β-configuration and, thus, α-configuration of the OH group. The triplet at 3.94-4.00 ppm was assigned to the signal for 9α-H in the isomer with a 9β-OH group.

Ketones IV are apparently the products of the dehydration of hydroxyketones III and subsequent reduction of the double bond in the intermediate eneketones. The driving force for the spontaneous *in situ* dehydration of hydroxyketone IIIc is probably the tendency to form a conjugated system. However, since the corresponding eneketone was not detected among the reaction products, we may assume that it readily undergoes further hydrogenation. We note that dehydration of hydroxyketone IIIa under standard conditions (MsCl and Py) proceeds with low yield and requires a prolonged reaction time.

Hydroxydiketones IIIa and IIIb are reduced by K selectride at -45°C, which should provide stereoselective reduction of one or both carbonyl functions [7]. Mixtures of isomeric triols VIa and VIb were obtained in 40-50% yield. The PMR spectra of these triols have multiplets for 9-H, 13-H, and 15-H adjacent to hydroxy groups at 4.24-4.26, 3.68-4.12, and 4.90-5.10 ppm, respectively. The downfield signal is probably related to 15-H, which is most subjected to influence of the pyridine ring. The signal for 9-H is found at 4.24-4.28 ppm. The finding of only one multiplet for this proton indicates that triols VI formed in the reaction are isomers at $C_{(13)}$. The PMR spectrum indicates a 1:1 ratio of these isomers. The signals for 12-H and 14-H are shifted significantly upfield relative to the analogous signals for ketodiols V. In the absence of anisotropic C=O group, these signals, similar to most of the other methylene and methine protons, are found at 1.05-2.20 ppm as overlapping multiplets. The lack of C=O stretching bands in the IR spectrum of triol VIb indicates complete reduction of both C=O functions.

The reduction of hydroxydiketones IIIa and IIIb by sodium borohydride was studied to compare the selectivity of action of various reducing agents. A mixture of triols VI is also formed in this case in 40% yield. Comparison of the PMR spectra of the mixtures of triols obtained in the reactions with K selectride and sodium borohydride and also analysis of the PMR spectra of the triols chromatographically isolated and purified showed that the sodium borohydride reduction proceeds without specificity both at the $C_{(9)}$=O and $C_{(13)}$=O groups. The former is reduced with 65% β-stereoselectivity, while in the latter case isomer mixture is formed with a 1:1 isomer ratio.

The low triol yields using both K selectride and sodium borohydride in the reduction of hydroxyketones III, despite the complete conversion of the latter, are probably related to the large losses at chromatographic separation.

Ketodiols Va and Vb were also reduced by sodium borohydride in the presence of nickel sulfate. Triols VI obtained in up to 70% yield in this case are mixtures of isomers at $C_{(9)}$ and $C_{(13)}$. Thus, none of these methods for synthesis of these products gives high steric selectivity. However, pathway I → III → VI occurs to be the most efficient relative to the total yield of triols VI.

A mixture of diastereomeric aminoalcohols VIIb is formed as expected in 45% yield in the reductive opening of isoxazoline Ib by $NaBH_4$ in the presence of $NiSO_4$ [8]. Isoxazoline IIb was also isolated as a minor reaction product. In this case, the reduction of the carbonyl group occurs with 90% steric selectivity. The IR and PMR spectra of VIIb correspond to the proposed aminoalcohol structure. The multiplets at 3.80, 4.24, and 5.55 ppm (Table 1) were assigned to the methine protons at the carbon atoms attached to the hydroxy and amino groups. However, determination of the relative stereochemistry of the substituents at $C_{(13)}$ and $C_{(15)}$ requires special study.

EXPERIMENTAL

The IR spectra were taken neat on a UR-20 spectrometer. The PMR spectra were taken on a Bruker AC-200 spectrometer at 200 MHz with TMS as the internal standard. The mass spectra were obtained on a Varian MAT-311 mass spectrometer with ionizing voltage 70 eV. The column chromatography was carried out on silica gel 40/100μ. Thin-layer chromatography was carried out on Silufol UV-254 and Kieselgel 60 F_{254} plates with 85:15 chloroform—methanol as the eluent. The spots were developed with anisaldehyde. Preparative thin-layer

chromatography was carried out on glass plates coated with Kieselgel L5/4μ using 5% methanol in chloroform as the eluent. The characteristics of I-VII are given in Table 1.

3-[2α-(3-Methylbuten-2-yl)-3-oxocyclopent-1β-yl)-5-(4-pyridyl)-2-isoxazoline (Ib). Sample of 3 mmol of phenyl isocyanate and 0.1 ml of triethylamine were added consecutively to 1 mmol of 2-(2-methyl-2-buten-4-yl)-3-nitromethyl-1-oxo-2-cyclopentene and 5-7 mmol of 4-vinylpyridine dissolved in 15 ml of dry benzene in argon atmosphere. The mixture was carefully stirred at 30-35°C until turbidity appeared and then held at this temperature for 4 h and at room temperature for 36 h, and filtered. After evaporation of the filtrate, the residue was placed on an alumina column and separated from diphenylurea using ether—hexane as the eluent. The product was eluted from the column using 20% methanol in ether. When necessary, the product was additionally purified on a silica gel column using ether with methanol gradient as the eluent or by preparative thin-layer chromatography. The yield of Ib was 92%.

3-(3,4-Dimethoxyphenyl)-5-(4-pyridyl)-2-isoxazoline (Ic). Sample of 5.2 mmol of veratraldehyde oxime was added with stirring in one portion to mixture of 5.2 mmol of N-chlorosuccinimide in 30 ml of chloroform containing 0.01 ml of pyridine. After the precipitate fully dissolved, 2.6 mmol of 4-vinylpyridine were added in one portion. After a few minutes, 5.2 mmol of triethylamine in 20 ml of chloroform were added with stirring over 2 h. The mixture obtained was stirred for 48 h at room temperature, evaporated, diluted with water, extracted with ether, dried over Na_2SO_4, and evaporated. The residue was placed on silica gel column. Elution gave 80% Ic. IR spectrum: 1520, 1605, 1645, 2840 cm^{-1}. Mass spectrum: 284 (M^+). PMR spectrum: 3.38 (1H, dd, J = 16.0 and 8.85 Hz, 4-H isox); 3.92 (1H, dd, J = 16.0, 11.0 Hz, 4-H isox); 3.84 and 3.86 (6H, two s, two OMe); 5.64 (1H, dd, J = 11.0, 8.5 Hz, 5-H isox); 6.46 (1H, d, J = 2.0 Hz, 1-H_{Ar}); 6.53 (1H, dd, J = 8.5, 2.0 Hz, 6-H_{Ar}); 7.34 (2H, d, (J = 5.0 Hz, H_{Py}); 7.72 (1H, d, J = 8.5 Hz, 5-H_{Ar}); 8.60 (2H, d, J = 5.0 Hz, H_{Py}). Found, %: C 66.35; H 7.49; N 9.86. $C_{16}H_{22}N_2O_3$. Calculated, %: C 66.16; H 7.46; N 9.65.

3-[1β-cyclopentyl-3β-Hydroxy-2α-(6-methoxycarbonylhexyl)]-5-(4-pyridyl)-2-isoxazoline (IIa) and 3-[1β-cyclopentyl-3α-hydroxy-2α-(6-methoxycarbonylhexyl)]-5-(4-pyridyl)-2-isoxazoline (IIb). Sample of 0.44 mmol of $NaBH_4$ was added in portions to solution of 0.4 mmol of isoxazoline Ia or Ib in 25 ml of methanol at room temperature and stirred for 2 h until the starting isoxazoline disappeared as indicated by thin-layer chromatography. The solvent was removed. When necessary, the product was purified by chromatography on silica gel column with 0:100 → 50:50 ether—hexane as the eluent or by thin-layer chromatography using 2:1 ether—hexane as the eluent. The yield was 90%.

Reductive Opening of 2-Isoxazolines (General Method). Sample of 0.60 g of Raney nickel, 0.10 g of $AlCl_3$, and 2 ml of water were added to solution of 0.54 mmol of I or II in 10 ml of methanol. The reaction mixture was stirred for 12-24 h until starting I disappeared as indicated by thin-layer chromatography. The mixture was filtered through silica gel layer, evaporated, diluted with water, and extracted with ether. The extract was dried over Na_2SO_4 and the solvent was evaporated. The residue was subjected to chromatography on silica gel column using methanol—chloroform as the eluent. Products III and IV were obtained from I, while products V were obtained from II.

3-Hydroxy-1-(3,4-dimethoxyphenyl)-3-(4-pyridyl)-1-propanone (IIIc) was obtained in 54% yield. IR spectrum: 1610, 1670, 3450 cm^{-1}. Mass spectrum: 287 (M^+). PMR spectrum: 3.26 and 3.44 (2H, dd, J = 9.0, 3.0 Hz, J_{gem} = 16.0 Hz, CH_2); 3.89 and 3.91 (6H, two s, two OMe); 5.28 (1H, dd, J = 9.0, 3.0 Hz, CH_2CH); 6.44 (1H, d, J = 1.5 Hz, 5-H_{Ar}); 6.56 (1H, dd, J = 8.5, 1.5 Hz, 6-H_{Ar}); 7.36 (2H, d, J = 5.0 Hz, H_{Py}); 7.88 (1H, d, J = 8.5 Hz, 5-H_{Ar}); 8.56 (2H, br. d, H_{Py}). Found, %: C 65.32; H 7.67; N 4.69. $C_{16}H_{23}NO_4$. Calculated, %: C 65.51; H 7.90; N 4.78.

1-(3,4-Dimethoxyphenyl)-3-(4-pyridyl)-1-propanone (IVc) was obtained in 20% yield. IR spectrum: 1610, 1670, 2850 cm^{-1}. PMR spectrum: 3.00 and 3.3 (2H, t, J = 8.0 Hz, $CH_2C{=}O$); 3.85 and 3.88 (6H, 2s, two OMe); 6.48 (1H, br. s, 2-H_{Ar}); 6.56 (1H, d, J = 9.0 Hz, 6-H_{Ar}); 7.20 (2H, d, J = 5.0 Hz, H_{Py}); 7.82 (1H, d, J = 9.0 Hz, 5-H_{Ar}); 8.48 (2H, br. d, H_{Py}). Found, %: C 69.01; H 8.24; N 5.12. $C_{16}H_{23}NO_3$. Calculated, %: C 69.28; H 8.36; N 5.05.

Reduction by K Selectride (General Method). Sample of 0.5 mmol of hydroxyketone III in 20 ml of tetrahydrofuran freshly distilled over $LiAlH_4$ was added to a flask heated in an argon stream and cooled to -45°C. Then, 2.5 mmol of K selectride as 1 M solution in hexane (supplied by Aldrich Chemical Co.) was added using a

syringe with stirring. The mixture was stirred for 4 h at -45°C and then 1 ml 30% H_2O_2 and 0.5 ml 5 M KOH were added at -20 to -5°C. The mixture was stirred for 10 min and then, water (5 ml) was added at 0-5°C. Excess hydrogen peroxide was removed by adding a small amount of manganese dioxide. The solvents were evaporated. The aqueous suspension was extracted with ether. The extract was washed with water and dried over Na_2SO_4. The residue was subjected to chromatography on silica gel column or silica gel plates. Triols VI were obtained in yields up to 50%.

2α-(2-Methyl-2-buten-4-yl)-1α,β-hydroxy-3β-[3-hydroxy-3-(4-pyridyl)-1-aminopropyl)]cyclopentane (VIIb). Sample of 2.5 mmol of sodium borohydride was added to solution of 0.5 mmol of Ib and 0.5 mmol of $NiSO_4 \cdot 7H_2O$ in 10 ml of methanol at -25°C. After 15 min, cooling was ceased and the reaction mixture was stirred for 1 h. Then, the mixture was added to 10 ml of 25% aq. ammonia and evaporated. The aqueous residue was extracted with ether. The extract was dried over Na_2SO_4 and the solvent was evaporated. Chromatography of the residue on silica gel plates gave IIb in 15% yield and VIIb in 40% yield. The reduction of ketodiols V to give triols VI was carried out by an analogous procedure.

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