SYNTHESIS OF β-LACTAMS FROM α,β-UNSATURATED SUGAR δ-LACTONES

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Abstract - Adduct 8 easily available by 1,3-dipolar cycloaddition of nitrone 1 and lactone 6 was transformed into β-lactams having a carbohydrate side chain at the position C-3 of the azetidinone ring. Basic chemical transformations of the 4-oxotetrahydropyrano(3,4-d)isoxazolidine skeleton have been described.

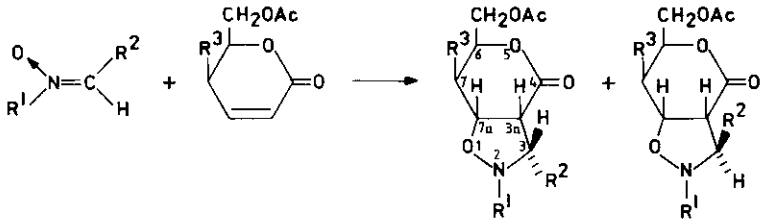
Recently considerable attention has been given to the 1,3-dipolar cycloaddition of nitrones to olefins. Substituted isoxazolidines obtained in these reactions are attractive intermediates for the synthesis of numerous natural products.[1] Due to defined stereochemical pathway of the 1,3-dipolar cycloaddition the relative configuration of substituents within the 5-membered isoxazolidine ring depends mainly on configuration of a nitrone and dipolarophile used. In a previous paper we have reported that 1,3-cycloaddition of nitrones to α,β-unsaturated lactones (Scheme 1) proceeded regiospecifically to afford a mixture of stereoisomers.[2] The nitrone approaches the lactone molecule *anti* to the terminal CH_2OAc group existing in the substrate, and the *exo* addition is favoured over the *endo* one. Adducts described by us represent a class of multifunctional bicyclic compounds which can be opened either on the lactone or on the isoxazolidine side. It was of interest to us the exploration of chemistry of these adducts with the aim of further their utilization in synthesis of selected compounds.

Recently the application of 1,3-dipolar cycloaddition of nitrones to crotonates as the method for construction of β-lactams have been reported.[3] This prompted us to investigate cycloaddition of nitrones to α,β-unsaturated sugar lactones as a source of enantiomerically pure β-amino acid derivatives, and subsequently their transformation into a new type of β-lactams.

Cycloaddition of 1 and 4-deoxylactone 6[4] showed the highest stereodifferentiation and led to a single product 8 in a good yield.[2] Therefore, as the model substrate for our studies 6, easily available in racemic form,[5] was selected.

The cycloaddition reaction of 6 with four other nitrones 2 - 5 gave similar results. The ratios of diastereoisomers obtained were determined approximately after separation of a crude product into pure components. Configurations of cycloadducts 11 - 17 were assigned by analogy to data found pre-

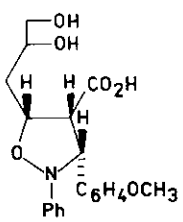
Scheme 1.



R^1=Ph , R^2=p-$MeOC_6H_4$:	1	6 : R^3=H	8	
	1	7 : R^3=OAc	9	10
R^1=CH_3, R^2=Ph :	2	6	11	12
R^1=CH_3, R^2=CO_2Bu:	3	6		13
R^1=CH_2Ph , R^2=CO_2Bu :	4	6	14	15
R^1=CH_2Ph, R^2=p-$MeOC_6H_4$:	5	6	16	17

viously.[2] It is worth noting, that in contrast to 1, 2 and 5, nitrones 3 and 4 afford predominantly cycloadducts (13 and 15) having the relative S* configuration at the C-3 carbon atom of the isoxazolidine ring. This stereochemical results is a consequence of the fact that 3 and 4 exist as mixtures of E and Z isomers with the E isomer predominating.[6]

For the further model investigations we chose the adduct 8 obtained in a good yield and relatively stable. Moreover the C-N bond of the p-methoxybenzyl position should be relatively resistant to hydrogenolysis,[7] and thus should allow the regioselective cleavage of the isoxazolidine O-N bond. Hydrolysis of the terminal acetate group in 8 was accomplished in boiling aqueous saturated sodium



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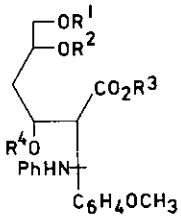
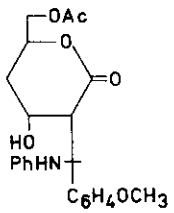


19 : R^1=R^2=R^3=R^4=H

21 : R^1=Ac , R^2=R^4=H , R^3=Me

22 : R^1=Ac , R^2=Si⟨+, R^3=Me , R^4=H

23 : R^1=Ac , R^2=R^4=Si⟨+, R^3=Me



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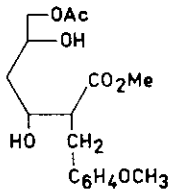

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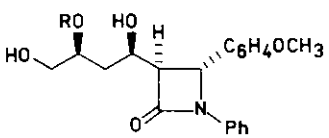


25 : R=Si⟨+

26 : R=H

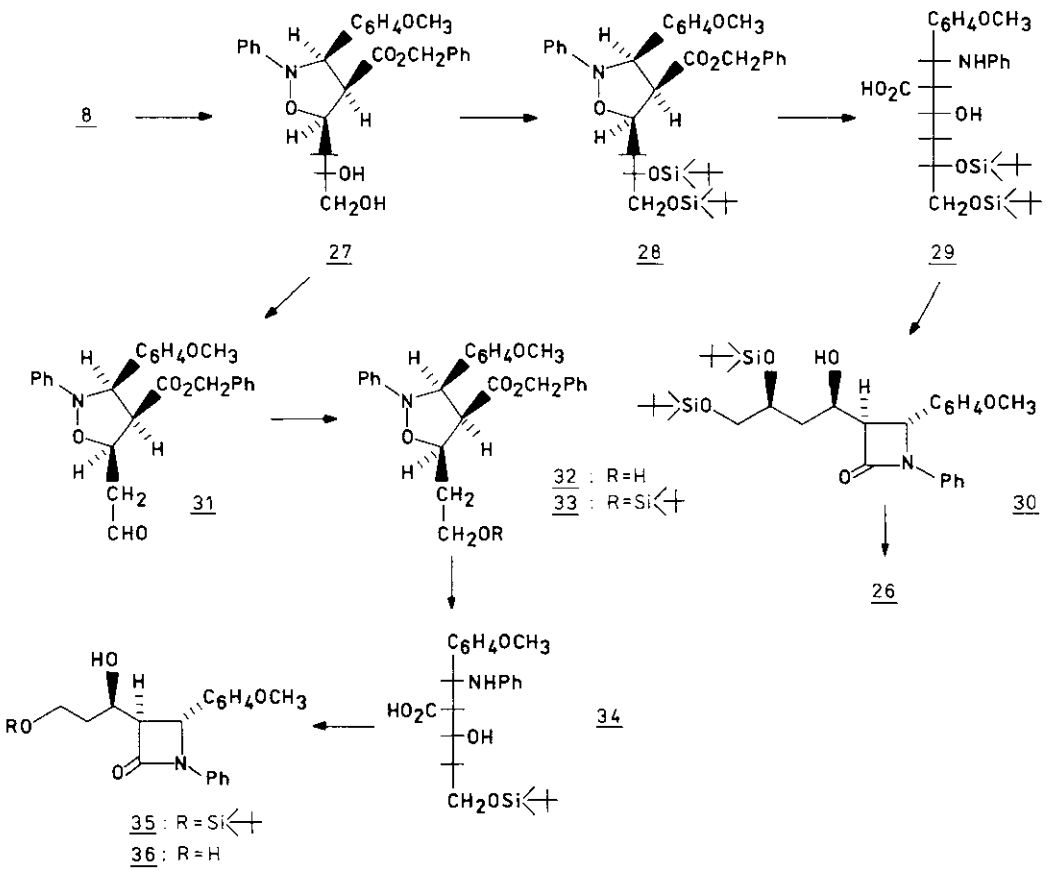
bicarbonate to give the corresponding acid 18. Hydrogenolysis of 18 over palladium catalyst in methanol solution after 1.5 h resulted in selective splitting of the N-O bond, affording the acid 19. The acetate 8 under the same conditions provided after 1.5 h a mixture of the lactone 20 and the open-chain methyl ester 21, whereas after 7 h only 21 was obtained in 90% yield.

It should be mentioned that attempts to cleave only the N-O and N-benzyl bond of isoxazolidine 16 were unsuccessful. Hydrogenolysis resulted in removal of the nitrogen atom from the molecule and formation of 24 as the only product.

The ester 21 was silylated with dimethyl-*tert*-butylsilyl chloride in a standard manner yielding a mixture of mono 22 and disubstituted compound 23. Compound 22 was in turn treated with a Grignard reagent to give respective β-lactam 25 in 35% yield. Removal of the silyl groups with fluoride anion furnished the trihydroxy compound 26.

Due to the low yield of the cyclization induced by Grignard reagents we have attempted the other

Scheme 2.



more convenient approach (Scheme 2). The transformation of the adduct 8 into protected β-amino acid 30 was achieved *via* a three-step process. The adduct 8 was hydrolyzed with 2 equiv. of KOH in water - dioxane solution. Liophilization of the potassium salt followed by benzylation with benzyl bromide in the presence of 18-crown-6 ether provided the ester 27, which was in turn silylated with tert-butyldimethylsilyl chloride, and hydrogenated to β-amino acid 29. Cyclization of 29 using 2-chloro-1-methylpyridinium iodide as a condensing reagent[8] gave the β-lactam 30 in a relatively good yield. Deprotection of hydroxyl groups led to the product 26 identical with that obtained on the other way. We employed the same procedure for the preparation of β-lactam 35 having one carbon atom less in the side chain than that of 30. Transformations leading to 35 are depicted in Scheme 2.

In conclusion, we employed ready available adduct 8 as the model for stereoselective synthesis of β-lactams having polyol side sugar chain. We demonstrated an access to a number of highly functionalized compounds, with defined stereochemistry, which can be used as synthons not only for new type of β-lactams but also for other structures.

EXPERIMENTAL

^{1}H nmr spectra were recorded for solns in $CDCl_3$ on a Jeol-100 and Bruker-500 spectrometers (δ-scale, TMS=0 ppm). Ir spectra were recorded on a Unicam SP-200 spectrophotometer. Mass spectra were recorded with LKB G CMS 2091 mass spectrometer. Tlc was performed with Merck DC Alufolien Kieselgel 60 F-254, preparative tlc was carried out using 20x20 glass plates, coated with 0.5 mm thin layers of silica gel Merck PF-254 and column chromatography with silica gel Merck (230-400 mesh). Mps are uncorrected. Acids 18, 19, 29, and 34 gave inconsistent microanalysis.

Nitrones 1 - 5 were prepared from the respective aldehyde and hydroxylamine according to the standard procedure.[9] Cycloaddition of nitrones 2 - 5 to the lactone 6 were performed according to the procedure described earlier.[2]

(3R*,3aR*,6S*,7aR*) and (3S*,3aR*,6S*,7aR*)-6-Acetoxymetyl-3-phenyl-4-oxo-2-methyltetrahydropyrano[3,4-d]isoxazolidine (11, 12): From 2 and 6 in 60% yield diastereomers 11 and 12 were obtained in the ratio of 5:1 respectively. 11: mp 154-156°C; ir (nujol): 1735, 1230 cm^{-1}; ^{1}H nmr ($CDCl_3$): 1.87 (ddd,1H,J=15.0, 11.9, 3.6 Hz,H-7), 2.13(dt,1H,J=2.2, 1.7 Hz,H-7'), 3.89(t,1H,J=8.8, 8.6 Hz,H-3a), 4.13(d,1H,H-3), 4.14(dd,1H,J=12.1, 5.7 Hz,CH_AH_BOAc), 4.20(dd,1H,J=3.6 Hz,CH_AH_BOAc), 4.76(m,1H,H-7a), 5.10(m,1H,H-6); MS m/z: M^+ 305. 12: colorless oil; ir (film): 1745, 1230 cm^{-1}; ^{1}H nmr ($CDCl_3$): 1.90 (ddd,1H,J=15.2, 11.6, 3.8 Hz,H-7), 2.09(dt,1H,J=1.9, 1.6 Hz,H-7'), 3.50(bs,2H,H-3,3a), 4.25(dd,1H, J=12.0, 5.5 Hz,CH_AH_BOAc), 4.30(dd,1H,J=3.8 Hz,CH_AH_BOAc), 4.69(bs,1H,H-7a), 4.95(m,1H,H-6); MS m/z: M^+, 305.1263 (305.1263 for $C_{16}H_{19}NO_5$); *Anal.* taken for a mixture of 11 and 12 Calc. for $C_{16}H_{19}NO_5$: C,62.9; H,6.2; N,4.6. Found: C,62.2; H,6.2; N,4.4.

(3S*,3aR*,6S*,7aR*)-6-Acetoxymethyl-3-butoxycarbonyl-4-oxo-2-methyltetrahydropyrano[3,4-d]isoxazolidine (13): From 3 and 6, yield 70%; mp 58-60°C; ir (film): 1745, 1235 cm^{-1}; ^1H nmr ($CDCl_3$): 1.98 (ddd,1H,J=15.2, 11.2, 3.6 Hz,H-7), 2.09(dt,1H,J=3.2, 2.2 Hz,H-7'), 3.85(t,1H,J=7.0, 7.0 Hz,H-3a), 4.24(m,2H,H-3,CH_AH_BOAc), 4.29(dd,1H,J=12.0, 3.5 Hz,CH_AH_BOAc), 4.59(m,1H,H-7a), 4.86(m,1H,H-6); MS m/z: M^+, 329.1474 (329.1474 for $C_{15}H_{23}NO_7$); *Anal.* Calc. for $C_{15}H_{23}NO_7$: C,54.7; H,7.0; N,4.2. Found: C,54.2; H,7.1; N,4.1.

(3R*,3aR*,6S*,7aR*) and (3S*,3aR*,6S*,7aR*)-6-Acetoxymethyl-3-butoxycarbonyl-4-oxo-2-benzyltetrahydropyrano[3,4-d]isoxazolidine (14, 15): From 4 and 6 in 90% yield diastereomers 14 and 15 were obtained in the ratio of 1:5 respectively. 14: colorless oil; ir (nujol): 1745, 1230 cm^{-1}; ^1H nmr ($CDCl_3$): 3.89(t,1H,J=9.0, 8.0 Hz,H-3), 4.0 - 4.4(m,3H,H-3,CH_2OAc), 4.72(m,1H,H-7a), 5.15(m,1H,H-6); MS m/z: M^+, 405. 15: mp 77-80°C; ir (nujol): 1740, 1235 cm^{-1}; ^1H nmr ($CDCl_3$): 3.71(t,1H,J=7.0, 6.8 Hz,H-3a), 3.91(d,1H,H-3), 4.60(m,1H,H-7a), 4.76(m,1H,H-6); MS m/z: M^+, 405.1787 (405.1787 for $C_{21}H_{27}NO_7$; *Anal.* taken for a mixture of 14 and 15, Calc. for $C_{21}H_{27}NO_7$: C,62.2; H,6.7; N,3.4. Found: C, 62.0; H,6.7; N,3.3.

(3R*,3aR*,6S*,7aR*) and (3S*,3aR*,6S*,7aR*)-6-Acetoxymethyl-3-p-methoxyphenyl-4-oxo-2-benzyltetrahydropyrano[3,4-d]isoxazolidine (16, 17): From 5 and 6 in 70% yield diastereomers 16 and 17 were obtained in the ratio of 5:3 respectively. 16: mp 148-150°C; ir (nujol): 1745, 1730, 1240, 1230 cm^{-1}; ^1H nmr ($CDCl_3$): 3.47(t,1H,J=9.0, 8.0 Hz,H-3a), 4.68(m,1H,H-7a), 4.86(m,1H,H-6); MS m/z: M^+, 411. 17: colorless oil; ir (film): 1740, 1725, 1245 cm^{-1}; ^1H nmr ($CDCl_3$): 4.75(m,1H,H-7a), 5.02(m,1H,H-6); MS m/z: M^+, 411.1682 (411.1682 for $C_{23}H_{25}NO_6$); *Anal.* taken for a mixture of 16 and 17, Calc. for $C_{23}H_{25}NO_6$: C,67.1; H,6.1; N,3.4. Found: C,66.2; H,6.1; N,3.3.

(3R*,4R*,5R*,2'S*)-5-(2',3'-Dihydroxypropyl)-3-p-methoxyphenyl-2-phenylisoxazolidine-4-carboxylic Acid (18): Adduct 8 was suspended in a saturated solution of sodium bicarbonate. The mixture was kept under reflux for 3 h, neutralized with diluted hydrochloric acid and extracted with chloroform. The extract was dried, evaporated and the residue was purified by chromatography to give 18 (70%); mp 110-112°C; ir (nujol): 3400, 1700 cm^{-1}; ^1H nmr ($CDCl_3$): 1.83(m,1H,H-1'a), 1.88(m,1H,H-1'b), 3.34 (m,2H,CH_2OH), 3.59(m,1H,H-2'), 3.80(dd,1H,J=7.6, 4.6 Hz,H-4), 4.37(bq,1H,H-5), 5.03(d,1H,H-3).

(3R*,4R*,6S*)-6-Acetoxymethyl-4-hydroxy-3-(R*-p-methoxyphenyl-N-phenylaminomethyl)-tetrahydro-2H-pyron (20) and Methyl (2R*,3R*,5S*)-6-Acetoxy-3,5-dihydroxy-2-(R*-p-methoxyphenyl-N-phenylaminomethyl)-hexanoate (21): A solution of 8 (1.0 g, 2.5 mmol) in methanol was shaken at 40°C in the presence of 10% Pd/C under hydrogen (2 atm) for 1.5 h, subsequently methanol was evaporated and the residue was separated on a silica gel column to give two following fractions: 20 (0.6 g, 60%); mp 154-155°C; ir (nujol): 3500, 3400, 1740 cm^{-1}; ^1H nmr ($CDCl_3$): 1.91(ddd,1H,J=13.9, 11.9, 1.9 Hz,H-5), 2.10(dt,1H, J=4.5, 3.8 Hz,H-5'), 2.90(t,1H,J=2.7, 2.5 Hz,H-3), 4.15(dd,1H,J=12.2, 5.0 Hz,CH_AH_BOAc), 4.28(dd,1H,

J=3.2 Hz,CH_AH_BOAc), 4.59(m,1H,H-4), 4.83(d,1H,>CHN-), 4.98(m,1H,H-6); MS m/z: $M^+-C_6H_5NH_2$, 306.1089 (306.1103 for $C_{16}H_{18}O_6$). 21 (0.4 g, 37%); mp 90-92°C; ir (film): 3400, 1730 cm^{-1}; ^1H nmr (DMSO-d_6): 1.48(m,2H,H-4,4'), 2.84(dd,1H, J=8.8, 5.1 Hz,H-3), 3.58(m,1H,H-5'), 3.80(m,3H,H-3,6,6'), 4.84(d,1H, >CHN-); MS m/z: M^+, 431.1944 (431.1943 for $C_{23}H_{29}NO_7$); *Anal.* Calc. for $C_{23}H_{29}NO_7$: C,64.0; H,6.7; N, 3.2. Found: C,64.2; H,6.8; N,3.1. The triacetate obtained by acetylation of 21 was identical with that described in the previous paper.[2] Hydrogenolysis of 8 at 50°C and 5 atm for 7 h gave 21 only in 90% yield.

(2R*,3R*,5S*)-3,5,6-Trihydroxy-2-(R*-p-methoxyphenyl-N-phenylaminomethyl)-hexanoic Acid (19): Hydrogenolysis of 18 was performed according to the procedure described above, 90%; mp 128-132°C; ir (nujol): 3330, 1700 cm^{-1}; ^1H nmr (DMSO-d_6): 1.4 - 1.8(m,2H,H-4,4'), ~2.7(m,1H,H-2), 4.76(d,1H,J=8.0 Hz,>CHN-); MS m/z: M^+-H_2O, 339.1468 (339.1470 for $C_{20}H_{21}NO_4$).

Methyl (2R*,3R*,5S*)-6-Acetoxy-3-hydroxy-5-*tert*-butyldimethylsilyloxy-2-(R*-p-methoxyphenyl-N-phenylaminomethyl)-hexanoate (22) and Methyl (2R*,3R*,5S*)-6-Acetoxy-3,5-di(*tert*-butyldimethylsilyloxy)-2-(R*-p-methoxyphenyl-N-phenylaminomethyl)-hexanoate (23): To a solution of 21 (0.4 mmol) in DMF (1 ml) *tert*-butyldimethylsilyl chloride (1.0 mmol) and imidazole (1.0 mmol) were added at 0°C. The mixture was stirred for 4 h at room temperature, allowed to stand overnight, then 2 ml of water were added and the solution was extracted with ether. The extract was dried, evaporated and separated on a silica gel column using hexane - ether (7:3) as an eluent to afford two fractions: 23 (13.1%): colorless oil : ir (film): 3420, 1750, 1260 cm^{-1}; ^1H nmr ($CDCl_3$): 1.7 - 2.1(m,2H,H-4,4'), 2.78(m,1H, H-2), 4.60(d,1H,J=4.5 Hz,>CHN-); MS m/z: M^+, 659.3673 (659.3672 for $C_{35}H_{57}NO_7Si_2$); *Anal.* Calc. for $C_{35}H_{57}NO_7Si_2$: C,63.7; H,8.6; N,2.1. Found: C,63.2; H,9.1; N,1.9. 22 (63.5%); mp 74-75°C; ir (film): 3520, 3410, 1720, 1260 cm^{-1}; ^1H nmr ($CDCl_3$): 1.65(ddd,1H,J=14.2, 9.4, 5.9 Hz,H-4), 1.71(ddd,1H,J=6.1, 3.7 Hz,H-4'), 2.74(dd,1H,J=7.9, 4.7 Hz,H-2), 3.92(m,1H,H-3), 4.00(m,2H,H-6,6'), 4.04(m,1H,H-5), 4.83 (d,1H,>CHN-); MS m/z: M^+, 545.2809 (545.2808 for $C_{29}H_{43}NO_7Si$); *Anal.* Calc. for $C_{29}H_{43}NO_7Si$: C,63.8; H,7.9; N,2.6. Found: C,63.5; H,7.9; N,2.2.

(3R*,4R*)-3-[(1'R*,3'S*)-1',4'-Dihydroxy-3'-*tert*-butyldimethylsilyloxybutyl]-4-p-methoxyphenyl-1-phenylazetidinone-2 (25): Ester 22 (1.0 mmol) was dissolved in THF (3 ml), cooled to -10°C and treated with *tert*-butylmagnesium chloride (3.0 mmol) in THF (3 ml). The mixture was stirred and kept at room temperature overnight. Subsequently 10 ml of water were added and the resulting solution was extracted with dichloromethane. Removal of solvent under reduced pressure and chromatography of the residue afforded 25 (35%); mp 102-104°C; ir (film): 3440, 1740 cm^{-1}; ^1H nmr ($CDCl_3$): 1.88(ddd,1H,J=15.1, 6.1, 2.3 Hz,H-2'a), 2.07(ddd,1H,J=9.8, 5.2 Hz,H-2'b), 3.15(dd,1H,J=5.0, 2.5 Hz,H-3), 3.64(m,2H,H-4'a, 4'b), 4.07(m,1H,H-3'), 4.30(m,1H,H-1'), 4.94(d,1H,H-4); MS m/z: M^+, 471.2441 (471.2440 for $C_{26}H_{37}NO_5Si$); *Anal.* Calc. for $C_{26}H_{37}NO_5Si$: C,66.2; H,7.8; N,3.0. Found: C,66.1; H,7.9; N,2.8.

(3R*,4R*)-3-(1'R*,3'S*)-1',3',4'-Trihydroxybutyl-4-p-methoxyphenyl-1-phenylazetidinone-2 (26): Compound 25 (1.0 mmol) was desilylated in THF (3 ml) with tetrabutylammonium fluoride (1.5 mmol) at room temperature in 30 min. The solvent was evaporated and the residue was purified by chromatography to give 26 (90%); mp 132-133°C; ir (film): 3500, 3440, 1730 cm^{-1}; ^1H nmr (DMSO-d_6): 1.74(dt,1H, J=15.7, 7.8, 7.8 Hz,H-2'a), 1.79(dt,1H,J=5.6, 5.6 Hz,H-2'b), 3.23(t,1H,J=4.0, 2.4 Hz,H-3), 3.65(m, 1H,H-3'), 3.76(s,2H,H-4'a,4'b), 4.12(m,1H,H-1'), 5.06(d,1H,H-4); MS m/z: M^+, 357.1576 (357.1576 for $C_{20}H_{23}NO_5$); *Anal.* Calc. for $C_{20}H_{23}NO_5$: C,67.2; H,6.4; N,3.9. Found: C,66.4; H,6.4; N,3.8.

Benzyl (3R*,4R*,5R*,2'S*)-5-(2',3'-Dihydroxypropyl)-3-p-methoxyphenyl-2-phenylisoxazolidine-4-carboxylate (27): The lactone 8 (2.0 mmol) in aqueous dioxane (1:1; 4 ml) was treated with KOH (4 mmol) in water (2 ml) and left at room temperature overnight. After lyophilization the potassium salt was directly treated with benzyl bromide (2 ml) in DMF (2 ml) in the presence of a catalytic amount of 18-crown-6. Removal of solvents under reduced pressure and chromatographical purification of the crude product provided 27 in 60% yield; mp 139-141°C; ir (nujol): 3400, 3300, 1738 cm^{-1}; ^1H nmr ($CDCl_3$): 1.90(ddd,1H,J=14.7, 4.6, 3.9 Hz,H-1'a), 2.03(dt,1H,J=8.7, 8.0 Hz,H-1'b), 3.49(dd,1H,J=11.0, 6.6 Hz,H-3'a), 3.58(dd,1H,J=3.9 Hz,H-3'b), 3.85(dd,1H,J=7.8, 4.9 Hz,H-4), 3.88(m,1H,H-5), 5.01(d, 1H,H-3); MS m/z: M^+, 463.1995 (463.1994 for $C_{27}H_{29}NO_6$); *Anal.* Calc. for $C_{27}H_{29}NO_6$: C,69.9; H,6.3; N,3.0. Found: C,69.2; H,6.3; N,2.9.

Benzyl (3R*,4R*,5R*,2'S*)-5-(2',3'-Di-(*tert*-butyldimethylsilyloxy)propyl)-3-p-methoxyphenyl-2-phenylisoxazolidine-4-carboxylate (28): Compound 27 was silylated according to the procedure described above (90%); colorless oil; ir (film): 1745, 1250 cm^{-1}; ^1H nmr ($CDCl_3$): 2.07(m,2H,H-1'a,1'b), 3.57 (dd,1H,J=10.3, 5.2 Hz,H-3'a), 3.70(dd,1H,J=6.0 Hz,H-3'b), 3.76(dd,1H,J=7.8, 4.8 Hz,H-4), 3.88(m,1H, H-2'), 4.54(dt,1H,J=6.9, 5.6 Hz,H-5), 4.98(d,1H,H-3); MS m/z: M^+, 691.3424 (691.3424 for $C_{39}H_{57}NO_6Si_2$); *Anal.* Calc. for $C_{39}H_{57}NO_6Si_2$: C,67.7; H,8.2; N,2.0. Found: C,67.3; H,8.6; N,1.9.

(2R*,3R*,5S*)-3-Hydroxy-5,6-di-(*tert*-butyldimethylsilyloxy)-2-(R*-p-methoxyphenyl-N-phenylaminomethyl)hexanoic Acid (29): A mixture of compound 28 (2.0 mmol) in 95% ethanol was hydrogenated in the presence of 10% Pd/C at 2 atm for 2 h. The catalyst was filtered off, the filtrate was evaporated to dryness and purified on a silica gel column to give 29 (85%); mp 198-199°C; ir (nujol): 3300, 1575 cm^{-1}; ^1H nmr ($CDCl_3$): 1.6 - 2.1(m,2H,H-4,4'), ~2.7(m,1H,H-2), 3.3 - 3.9(m,4H,H-3,5,6,6'), 4.5(d,1H, J=8.0 Hz,>CHN-); MS m/z: M^+, 603.

(3R*,4R*)-3-((1'R*,3'S*)-1'-Hydroxy-3',4'-di-(*tert*-butyldimethylsilyloxy)-butyl)-4-p-methoxyphenyl-1-phenylazetidinone-2 (30): To a suspension of 29 (0.1 mmol) in dichloromethane (5 ml) 2-chloro-1-methylpyridinium iodide (0.11 mmol) and triethylamine (0.2 ml) were added, and the reaction mixture was stirred for 2 h at room temperature. Evaporation of the solvent followed by purification of the residue by chromatography on preparative plates afforded the corresponding β-lactam 30 in 80% yield;

colorless syrup; ir (film): 3370, 1840 cm^{-1}; ^1H nmr ($CDCl_3$): 1.79(dt,1H,J=14.3, 6.3, 5.3 Hz,H-2'a), 2.10(ddd,1H,J=7.5, 3.6 Hz,H-2'b), 3.50(dd,1H,J=10.3, 7.3 Hz,H-4'a), 3.62(dd,1H,J=6.5, 4.3 Hz,H-3), 3.88(m,1H,H-3'), 4.68(dt,1H,H-1'), 4.76(d,1H,H-4); MS m/z: M^+, 585. Desilylation of 30 with tetrabutylammonium fluoride gave 26.

Benzyl (3R*,4R*,5R*)-5-(2'-Oxoethyl)-3-p-methoxyphenyl-2-phenylisoxazolidine-4-carboxylate (31): A solution of 27 (0.5 mmol) in methanol (7 ml) was treated with sodium metaperiodate (0.65 mmol) in water (3 ml) at room temperature for 2 days. The precipitate of sodium iodide was filtered off, the solvent was removed under diminished pressure, and the remaining solution was extracted with dichloromethane. The extract was dried and evaporated. The crude product was purified by chromatography to give the aldehyde 31 (85%); mp 97-98°C; ir (film): 1760, 1290 cm^{-1}; ^1H nmr ($CDCl_3$): 3.02(ddd,1H, J=18.3, 6.8, 1.5 Hz,H-1'a), 3.13(ddd,1H,J=6.8, 1.5 Hz,H-1'b), 3.96(dd,1H,J=8.3, 5.8 Hz,H-4), 4.78 (q,1H,H-5), 5.06(d,1H,H-3), 9.69(t,1H,H-2'); MS m/z: M^+, 431.1733 (431.1732 for $C_{26}H_{25}NO_5$); *Anal.* Calc. for $C_{26}H_{25}NO_5$: C,72.4; H,5.8; N,3.2. Found: C,72.1; H,5.6; N,3.1.

Benzyl (3R*,4R*,5R*)-5-(2'-*tert*-Butyldimethylsilyloxyethyl)-3-p-methoxyphenyl-2-phenylisoxazolidine-4-carboxylate (33): Compound 31 (0.4 mmol) and sodium cyanoborohydride (24 mg) were dissolved in 5 ml of methanol. A trace of methyl orange was added and 2N HCl - methanol - water was added dropwise with stirring to maintain the red color, after 15 min the color changed very slowly. Stirring was continued for additional 45 min and then methanol was evaporated *in vacuo*. The residue was taken up in 5 ml of water and extracted with ether, dried and evaporated at reduced pressure to give 32 (90%); mp 106-108°C; ir (film): 3430, 1730 cm^{-1}; MS m/z: M^+, 433. The crude syrup was silylated according to the procedure described above to afford 33 (90%); mp 45-47°C; ir (film): 1740, 1250 cm^{-1}; ^1H nmr ($CDCl_3$): 1.96(m,1H,H-1'a), 2.07(m,1H,H-1'b), ~4.8(m,3H,H-4,2'a,2'b), 4.51(dt,1H,H-5), 5.04(d,1H,J= 8.0 Hz,H-3); MS m/z: M^+, 547.2754 (547.2753 for $C_{32}H_{41}NO_5Si$); *Anal.* Calc. for $C_{32}H_{41}NO_5Si$: C,70.2; H,7.5; N,2.5. Found: C,69.7; H,7.6; N,2.5.

(2R*,3R*)-3-Hydroxy-5-*tert*-butyldimethylsilyloxy-2-(R*-p-methoxyphenyl-N-phenylaminomethyl)-pentanoic Acid (34): Compound 33 was hydrogenated according to the procedure described for hydrogenolysis of 28 to give 34 (85%); mp 109-111°C; ir (nujol): 3360, 1690 cm^{-1}; ^1H nmr ($CDCl_3$): 1.61(m,1H,H-4), 1.86(m,1H,H-4'), 2.69(dd,1H,J=9.3, 3.0 Hz,H-2), 3.73(m,1H,H-5), 3.85(m,2H,H-3,5'), 4.76(d,1H,>CHN-); MS m/z: M^+, 459.

(3R*,4R*)-3-[(1'R*)-1'-Hydroxy-3'-*tert*-butyldimethylsilyloxypropyl]-4-p-methoxyphenyl-1-phenylazetidinone-2 (35): Compound 35 was obtained according to the procedure described for 30 as a colorless syrup; ir (film): 3400, 1840 cm^{-1}; ^1H nmr ($CDCl_3$): 1.79(m,1H,H-2'a), 2.00(m,1H,H-2'b), 3.67(m, 3H,H-3,3'a,3'b), 4.64(m,1H,H-1'), 4.77(d,1H,J=6.8 Hz,H-4); MS m/z: M^+, 441; *Anal.* Calc. for $C_{25}H_{35}NO_4Si$: C,68.0; H,7.9; N,3.2. Found: C,67.9; H,7.6; N,3.0.

(3R*,4R*)-3-[(1'R*)-1',3'-Dihydroxypropyl]-4-p-methoxyphenyl-1-phenylazetidinone-2 (36): Desilylation of 35 with tetrabutylammonium fluoride according to the procedure described above afforded 36 as a colorless oil; ir (film): 3300, 1730 cm^{-1}; MS m/z: M^+, 327.

Methyl (2R*,3R*,5S*)-6-Acetoxy-3,5-dihydroxy-2-(p-methoxybenzyl)-hexanoate (24): Hydrogenolysis of 16 in the manner described for 28 afforded 24 (70%) as a colorless oil; ir (film): 3440, 1735, 1250 cm^{-1}; ^1H nmr ($CDCl_3$): 1.5 - 1.9(m,2H,H-4,4'), 2.78(dt,1H,J=7.3, 5.5 Hz,H-2), 2.91(d,2H,J=7.3 Hz, benzyl), 3.3 - 4.4(m,4H,H-3,5,6,6'); MS m/z: M^+, 340.1522 (340.1521 for $C_{17}H_{24}O_7$).

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Klaus Bock, The Technical University of Denmark, for the recording of the ^1H nmr spectra. This work was suported by grant No. MR-I.12.1.1.1.

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Received, 7th January, 1986