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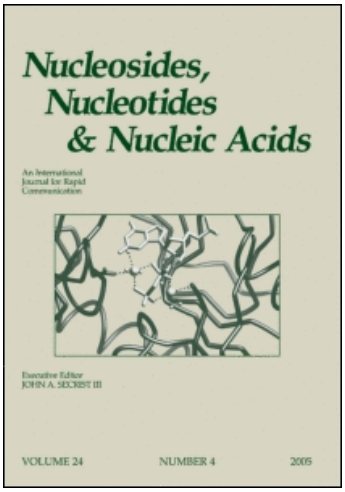

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Potential Antiviral Agents. Synthesis and Properties of Glutarimide-Nucleosides

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NUCLEOSIDES & NUCLEOTIDES, 7(4), 511-517 (1988)

POTENTIAL ANTIVIRAL AGENTS. SYNTHESIS AND PROPERTIES OF GLUTARIMIDE-NUCLEOSIDES.

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ABSTRACT. *The synthesis of 3- and 4-substituted glutarimide-ribosides via different approaches involving Wittig-reactions is described. Oxydation to 1-deazauridine failed, due to instability of the product. One of the compounds obtained exhibited slight activity against Varicella zoster virus.*

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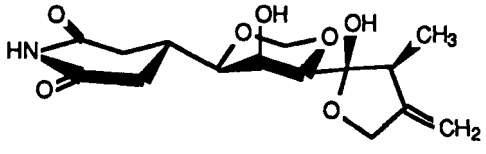
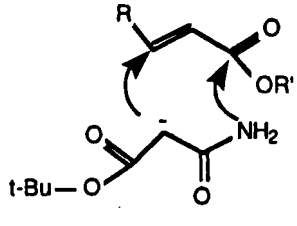
The glutarimide ring is a moiety which is present in a variety of natural products [1,2]. In many cases, the biological activity of these alkaloids is determined by the glutarimide residue.

The glutarimide entity is structurally related to the pyrimidine nucleobases. Although the ring is obviously less planar, it has comparable properties with respect to hydrogen bonding and should in principle be capable of showing nucleic acid type base-base interaction [3]. We assume that this could constitute the basis of the biological activity of glutarimide derivatives, since these type of interactions could lead to complex formation with a macro-molecular receptor.

Recently we published the first stereospecific total synthesis of sesbanimide [4], a highly cytotoxic glutarimide-alkaloid, isolated from the seeds of several Sesbania species [5]. In this total synthesis the glutarimide ring was constructed via a Wittig reaction, followed by a Michael addition to the resulting unsaturated ester and cyclisation (Scheme I). For the reasons, outlined above we decided to apply this synthetic scheme to the preparation of glutarimide nucleosides.



Sesbanimide



Scheme I

The synthesis of the symmetrically 4-substituted glutarimide riboside is depicted in Scheme II. The aldehyde 1 (β-anomer) was obtained from 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose via the corresponding cyanide according to literature procedures [6]. Reduction of the cyanide was carried out in the presence of N,N'-diphenylethylenediamine to trap the aldehyde and to prevent overreduction. In this way, 1 was obtained as its imidazolidine derivative [6].

A Wittig reaction with carbomethoxymethylene- triphenylphosphorane in methylene chloride produced the E-acrylic ester 2 in 94 % yield [7]. Michael addition of malonic ester derivative 3 [4] and cyclisation occurred in one step, leading to 4.

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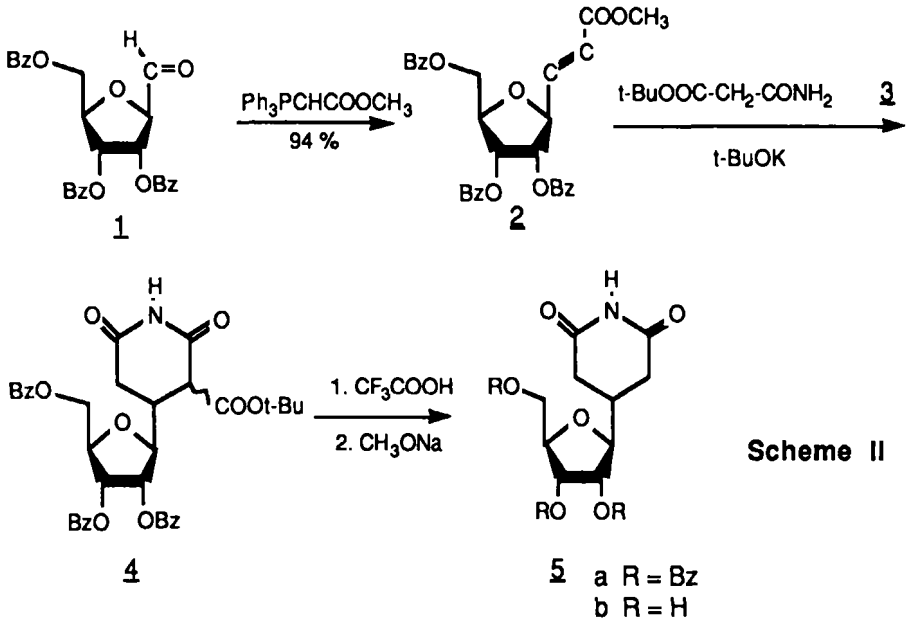

Scheme II

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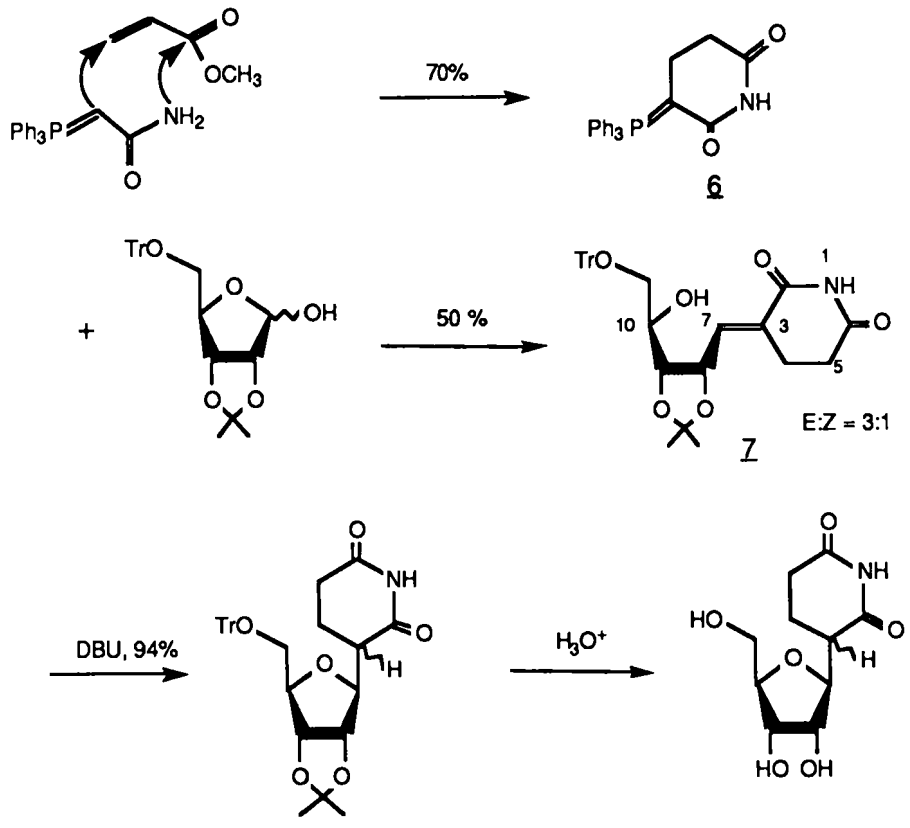
Without isolation, the t-butyl ester was hydrolyzed. The resulting carboxylic acid was decarboxylated (5a) and the protecting benzoyl groups were removed by treatment with sodium methoxide. Riboside 5b (m.p. 145,5-146,5°) was obtained from 2 in 35% overall yield.

For the synthesis of 3-substituted glutarimides a different approach was necessary. The condensation reaction was carried out with the preformed glutarimide phosphorane 6. Although several Wittig reactions with ribose derivatives have been carried out [8-10] and the corresponding succinimide ylid recently has been applied in the synthesis of showdomycin [11], Wittig reagents of type 6 have not been described. The approach appeared to be an extremely convenient way to prepare various substituted glutarimide derivatives. The scope and limitations of these novel type of Wittig reagents will be published elsewhere.

Addition of carbomethoxymethylenetriphenylphosphorane to acrylic amide was not effective, due to the extremely low reactivity of the Wittig reagent. Thus the addition was reversed, as depicted in Scheme III.

Condensation of 6 with a suitably protected ribose derivative [12] in refluxing 1,2-dichloroethane produced 7 in 50 % yield. According to NMR-data 7 consisted of a mixture of isomers (E:Z = 3:1), which could be separated by chromatography. Structural assignments were based on the chemical shift of the vinylic proton. In the Z-isomer the absorption was found at $\delta = 6.15$ ppm, whereas in the E-isomer it appeared at lower field ($\delta = 6.89$), due to the influence of the carbonyl group.

Cyclisation of 7 was carried out with a catalytic amount of base (diazabicycloundecene, total yield: 94 %). Although in principle upon cyclisation a complex mixture of α and β anomers could result, formation of the kinetically controlled β–anomers was expected [10,12]. Indeed, after chromatographic separation, 8a and 8b were the only products, isolated as oils in equal amounts. The ratio of 8a / 8b was independent of the geometry of the double bond in 7. The β–configuration was established from NMR data (both ^{1}H and ^{13}C) obtained for the corresponding isopropylidene derivatives [10].



Scheme III

Several attempts were undertaken to oxidise 8 and 9 to 1-deazauridine 11. This compound is reported to be unstable [15] and very sensitive to oxydation, which leads to coloured self- condensationproducts cf. [13,14].

Starting from 7, we attempted to prepare 11 according to Scheme IV, where the oxidation step could be carried out at very low temperature.

The addition of PhSeCl to the double bond of 7 [9,11] was followed immediately by cyclisation and loss of the protective trityl group to give 10 as one isomer, (β-form).

Oxidation with ozone at -76° or H_2O_2 at 0° resulted in the formation of blue coloured condensation products of 11. Since even under these mild conditions 11 seems to be unstable, the synthesis will be repeated with methyl-substituted 6, thus resulting in 1-deazathymidine, from which more stability may be expected.

Compounds 5b and 9a,b were tested against Herpes simplex virus type 1 (SC 16) in human fibroblast (MRC-5) cells and against Influenza A (HK/1/68) and Parainfluenza virus type 1 (Sendai) in Madin Darby canine kidney cells. No activity was found at compound concentrations up to 100 μg/ml. Slight activity was found for 5b against Varicella zoster virus (Ellen) in MRC-5 cells, the MIC_{50} being 100 μg/ml.

Additional tests will be carried out against Herpes simplex virus type 2 (MS) in MRC-5 cells.

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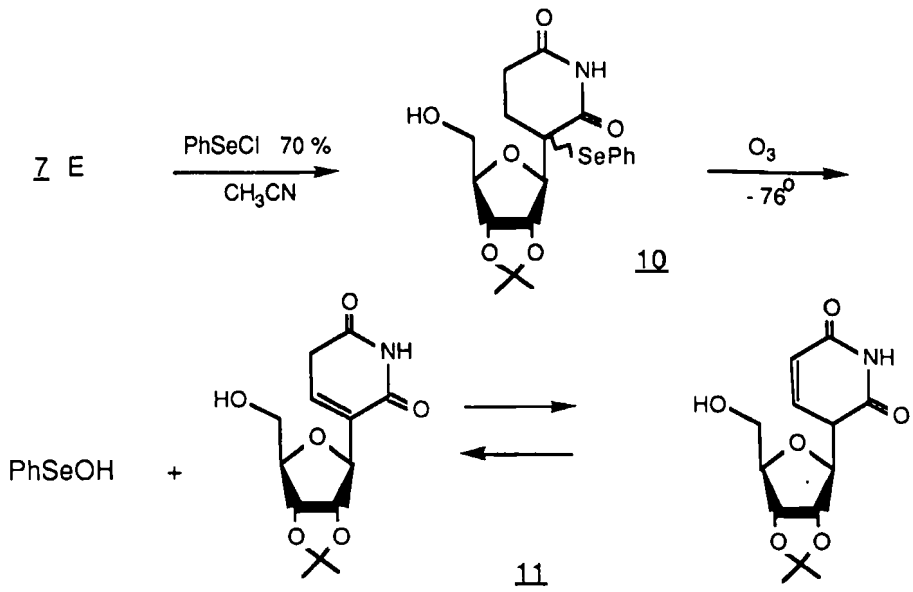

Scheme IV

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EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer. The absorptions are given in cm^{-1}. NMR spectra were run on Bruker WM 250 and AC 200 instruments. Unless stated otherwise, IR and NMR spectra were taken in $CHCl_3$ and $CDCl_3$, respectively. Mass spectra were obtained with a Varian Matt-711 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Flash chromatography was performed on silicagel 60 (230 - 400 mesh). Thin-layer chromatography was carried out with F 254 plates.

4-(2,3,5-tribenzoyl-β-D-ribofuranosyl)-glutarimide 5a.

To a solution of malonamide 3 [4] (0.143 g, 0.9 mmol) in tetrahydrofuran (10 ml, distilled over lithiumaluminiumhydride) at 0° was added potassium t-butoxide (0.095 g, 0.85 mmol). After 15 min, acrylic ester 2 [7] (0.42 g, 0.79 mmol) was added and the reaction mixture was stirred for 1 h at 0°. Addition of water and ether-extraction gave t-butylester 4 as an oil, which was hydrolyzed with trifluoroacetic acid (3 ml) during 1 h at room temperature. The solvent was evaporated and the residu refluxed in dimethylformamide (3 ml) for 5 min. After evaporation the residue was purified by flash chromatography (eluens ethyl acetate/hexanes 1/1), yielding 5a (0.285 g, 64%); mp 147 - 149° (MeOH); IR: 3380, 1700 - 1730 cm^{-1}; ^{1}H-NMR: δ 2.5 - 2.8 (m, 5 H, glutarimide); 4.18 (dd, 1 H, J = 6 Hz, J = 3 Hz, H_7); 4.4 - 4.8 (m, 3 H, H_{10}, H_{11}); 5.45 (dd, 1 H, J = 6 Hz, H_9); 5.63 (dd, 1 H, J = 6 Hz, J = 4 Hz, H_8); 7.3 - 7.6 (m, 9 H, Ar); 7.85 - 8.15 (m, 6 H, Ar); 8.40 (s, 1 H, N-H).

4-(β-D-ribofuranosyl)-glutarimide 5b.

Tri ester 5a (0.162 g, 0.3 mmol) was added to a solution of sodium methoxide (0.5 mmol) in a mixture of methanol (2 ml) and chloroform (2 ml) at -18°. The reaction mixture was

kept at 0° for 2 h, and neutralized with acetic acid (0.5 mmol). Evaporation of the solvents and chromatography (ethyl acetate/methanol) gave 5b (0.041 g, 55%); mp 145.5 - 146.5° (methanol/ether); IR (KBr): 3470, 3430, 3330, 3180, 3080, 1710, 1690 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.2 (m, 1 H, H_4); 2.3 - 2.7 (m, 4 H, H_3, H_5); 3.3 (m, 2 H); 3.6 (m, 1 H); 3.75 (m, 2 H); 4.65 (dd, 1 H, J = 5.6); 4.8 (m, 2 H); 10.69 (s, 1 H, N-H); $[\alpha]_D$ -19.2° (c 1.0, methanol).

3-triphenylphosphoranylidene glutarimide 6.

Methyl acrylate (4.93 ml, 55 mmol) was added to a suspension of triphenylphosphoranylidene acetamide[16] (15.95 g, 50 mmol) in absolute methanol (120 ml). The mixture was stirred at room temperature and after 20 h the product was isolated by filtration, washed with methanol and ether, and air-dried; yield 13.05 g (70%), mp 262-263°. IR: 3400, 1685, 1600 cm^{-1}; ^{1}H-NMR: δ 2.0-2.6 (m, 4 H); 7.6 (m, 15 H); Anal. Calc. for $C_{23}H_{20}NO_2P$: C, 73.98; H, 5.40; N, 3.75. Found: C, 73.84; H, 5.35; N, 3.83.

Wittig reaction of 6 with 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose.

A suspension of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose [12] (4.32 g, 10 mmol) and 3-triphenylphosphoranylidene glutarimide 6 (4.1 g, 11 mmol) in 1,2-dichloroethane (50 ml) was stirred and refluxed for 120 h in a nitrogen atmosphere. The dark blue reaction mixture was cooled and filtered to remove some starting material 6. Evaporation of the solvent and chromatography (ethyl acetate/hexanes) gave resp. 7 (Z-isomeer, 0.63 g, 12 %) as a glass and 7 (E-isomeer, 2.0 g, 38 %) as a solid; mp 183 -185°.
7-Z: IR: 3360, 1730, 1710, 1655 cm^{-1}; ^{1}H-NMR: δ 1.34 (s, 3 H, CH_3); 1.39 (s, 3 H, (CH_3); 2.4 - 2.6 (m, 4 H, glutarimide protons); 3.26 (m, 2 H, H_{11}); 3.7 (m, 1 H, H_{10}); 4.42 (m, 1 H, H_9); 5.56 (dd, 1 H, J = 6.9 Hz, J = 7.8 Hz, H_8); 6.15 (d, J = 6.9 Hz, H_7); 7.2 - 7.5 (m, 15 H); 8.02 (s, 1 H, N-H).
7-E: IR: 3380, 1725, 1705, 1650 cm^{-1}; ^{1}H-NMR: δ 1.38 (s, 3 H, CH_3); 1.45 (s, 3 H, CH_3); 2.40 (d, 1 H, J = 4.9 Hz, O-H); 2.6 - 2.7 (m, 4 H, glutarimide protons); 3.34 (m, 2 H, H_{11}); 3.65 (m, 1 H, H_{10}); 4.25 (dd, 1 H, J = 9.3 Hz, J = 6.1 Hz, H_9); 5.01 (dd, 1 H, J = 9.3 Hz, J = 6.1 Hz, H_8); 6.89 (d, 1 H, J = 9.3 Hz, H_7); 7.2 - 7.5 (m, 15 H); 7.45 (s, 1 H, N-H); Anal. Calc. for $C_{32}H_{33}NO_6$: C, 72.85; H, 6.30; N, 2.65. Found: C, 72.35; H, 6.20; N, 2.61.

3-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-glutarimides 8.

Diazabicycloundecene (20 µl) was added to a solution of 7 (1.32 g, 2.5 mmol, E/Z-mixture) in dichloromethane (20 ml, alcohol-free) at room temperature. After 30 min the reaction mixture was applied to a silica column. Elution with respectively 10, 15 and 20% ethyl acetate in dichloromethane yielded two isomeric ribosides 8. 8a (Faster moving component, TLC): yield 0.6 g (45.5%, glass); IR: 3370, 1725, 1710 cm^{-1}; ^{1}H-NMR: δ 1.32 (s, 3 H, CH_3); 1.52 (s, 3 H, CH_3); 2.1 (m, 2 H, H_4); 2.5 (m, 1 H, H_{5a}); 2.7 (m, 1 H, H_{5b}); 2.9 (m, 1 H, H_3); 3.12 (dd, 1 H, J = 10.2 Hz, J = 5.4 Hz, H_{11a}); 3.26 (dd, 1 H, J = 10.2 Hz, J = 3.1 Hz, H_{11b}); 4.05 (m, 1 H, H_{10}); 4.20 (dd, 1 H, J = 4.0 Hz, J = 2.8 Hz, H_7); 4.58 (dd, 1 H, J = 6.6 Hz, J = 5.4 Hz, H_9); 4.98 (dd, 1 H, J = 6.6 Hz, J = 4.3 Hz, H_8); 7.2 - 7.5 (m, 15 H); 7.08 (s, 1 H, N-H); nOe: Irradiating at H_7 gave signals for H_3, H_{4a} and H_{10} (weak). ^{13}C-NMR: δ 22.80 (C-4); 25.56 (CH_3); 27.55 (CH_3); 30.44 (C-5); 43.27 (C-3); 60.30 (C-10); 81.04, 83.01, 84.18, 85.41 (C-6, C-7, C-8, C-9); 86.46 (C-11); 114.46 (C-isopropylidene); 126.94, 127.73, 128.65, 143.79 (C-Ar); 171.92, 172.48 (C-2, C-6).
8b (isomer): yield 0.64 g (48.5%, glass); IR: 3370, 1725, 1710 cm^{-1}; ^{1}H-NMR: δ 1.35 (s, 3 H, CH_3); 1.53 (s, 3 H, CH_3); 2.05 (m, 2 H, H_4); 2.42 (m, 1 H, H_{5a}); 2.72 (m, 2

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H, H_3, H_{5b}); 3.24 (m, 2 H, H_{11}); 4.15 (m, 1 H, H_{10}); 4.35 (dd, 1 H, J = 6.1 Hz, J = 4.7 Hz, H_7); 4.66 (dd, 2 H, J = 6.6 Hz, J = 4.7 Hz, H_9); 4.77 (dd, 1 H, J = 6.6 Hz, J = 4.5 Hz, H_8); 7.2 - 7.5 (m, 15 H); 7.90 (s, 1 H, N-H); nOe: irradiating at H_7 gave signals for H_{5a} and H_{10} (weak). ^{13}C-NMR: δ 19.15 (C-4); 25.53 (CH_3); 27.39 (CH_3); 30.30 (C-5); 43.88 (C-3); 63.89 (C-10), 81.82, 82.31, 82.68, 83.56 (C-6, C-7, C-8, C-9); 114.36, (C-isopropylidene); 127.11, 127.79, 128.59, 143.58 (C-Ar); 127.20, 127.22 (C-2, C-6);

3-(β–D-ribofuranosyl)-glutarimides 9.

A solution of 8a (0.6 g, 1.14 mmol) in a mixture of tetrahydrofuran (12 ml), water (4 ml) and trifluoroacetic acid (1 ml) was stirred and refluxed for 90 min. The solvents were removed and the residue was dissolved in water en extracted three times with dichloromethane. The aqueous layer was concentrated *in vacuo* and the residue was chromatographed (silica gel, 15% methanol in ethylacetate). 9a was isolated as a glass (0.177 g, 63%). ^{1}H-NMR (DMSO-d_6): δ 1.9 (m, 1 H, H_{4a}); 2.1 (m, 1 H, H_{4b}); 2.7 (m, 1 H); 3.3 (AB-system, 2 H); 4.0 (m, 2 H); 10.6 (s, 1 H, N-H); MS(E-I): m/e 227 (M - 18); 196, 172 (100%); 155; 142; 125; 113. $[\alpha]_D$ - 24.1° (c 1.14, methanol). 9b: (Following the same procedure, starting with 0.6 g 8b) glass (0.194 g, 69%). ^{1}H-NMR (DMSO-d_6): δ 1.85 (m, 2 H, H_4); 2.65 (m); 3.4 (AB-system, 2 H); 3.62 (dd, 1 H, J = 4.0 Hz, J = 4.2 Hz); 3.85 (m, 2 H); 4.24 m, 1 H); 10.7 (s, 1 H, N-H). MS(E-I): m/e 227 (M - 18); 209; 196; 172 (100%); 155; 142; 125; 113. $[\alpha]_D$ +5.7° (c 1.64, methanol).

3-(β–D-ribofuranosyl)-3-phenylselenyl-glutarimide 10.

Phenylselenylchloride (0.057 g, 0.3 mmol) was added to a solution of 7-E (0.106 g, 0.2 mmol) in acetonitril (2 ml, distilled over P_2O_5). After 30 min at 55° the reaction mixture was cooled and neutralised with tri-ethylamine. Chromatography with ethylacetate yielded 10 (0.062 g, 70%, 1 isomer) as a glass. IR: 3470, 3370, 1720, 1705 cm^{-1}; ^{1}H-NMR: δ 1.40 (s, 3 H, CH_3); 1.58 (s, 3 H, CH_3); 1.90 (ddd, 1 H, J_{4a-4b} = 14.7, J_{4a-5a} = 2.2, J_{4a-5b} = 5.8, H_{4a}); 2.41 (ddd, 1 H, J_{4a-4b} = 14.7, J_{4b-5a} = 5.1, J_{4b-5b} = 13.6, H_{4b}); 2.66 (ddd,1 H, J_{5a-5b} = 17.9, J_{5a-4b} = 5.1, J_{5a-4a} = 2.2, H_{5a}); 3.02 (ddd, 1 H, J_{5a-5b} = 17.9, J_{5b-4b} = 13.6, J_{5b-4a} = 5.8, H_{5b}); 3.72 (AB-system, 2 H, J_{AB} = 12.2, H_{11}); 4.01 (m, 1 H, H_{10}); 4.50 (d, 1 H, J = 4.6, H_7); 4.67 (dd, 1 H, J = 7.0, J = 5.0 H_9); 4.77 (dd, 1 H, J = 7.0, J = 4.6, H_8); 7.25 - 7.36 (m, 3 H, Ar); 7.68 (d, 2 H, J = 6.8, Ar); 7.93 (s, 1 H, N-H); ^{13}C-NMR: δ 23.51 (C-4); 25.52 (CH_3); 27.40 (CH_3); 28.89 (C-5); 50.84 (C-3); 61.94 (C-11); 80.51, 81.44, 84.49, 85.81 (C-7, C-8, C-9, C-10); 114.71 (C-isopropylidene), 124.65 (C_1-Ar); 129.02, 130.05, 138.32 (C-Ar); 169.48, 171.45 (C-2, C-6).

Oxidation of 10.

Oxidation of 10 with ozone in dichloromethane at -76° followed by neutral or tri-ethylamine work-up gave only instable products. Other oxidations (e.g. hydrogen peroxide in acetonitril at 0°) produced even more complex reaction mixtures.

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