112. Synthesis of a Glyoxalase I Inhibitor from *Streptomyces griseosporeus* NIIDA *et* OGASAWARA

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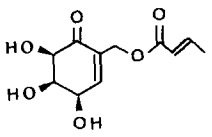
The pseudolactones **6** and **12** were prepared in a straightforward way from methyl α-D-glucopyranoside and methyl α-D-mannopyranoside, respectively. The pseudolactone **6** reacted with *tert*-butyl lithioacetate to give the protected, trihydroxylated cyclohexenone carboxylate **7** (51%). The sterically hindered, L-*ribo*-configurated pseudolactone **12** reacted with diethyl ethylphosphonate and dimethyl methylphosphonate to give the protected trihydroxycyclohexenones **17** (49%) and **18** (62%), respectively. The hydroxymethylated cyclohexenone **21** was obtained from **18** by treatment with Me_2AlSPh and then formaldehyde, oxidation of the product **19**, and elimination. Deprotection of **21** gave **2**, identical with KD16-U1. Esterification of **2** gave **1**, identical with the title compound. Alternatively, **1** was obtained in higher yields by esterification of **21**, followed by deprotection of the hydroxy groups. This synthesis gave **1** and **2** from methyl α-D-mannopyranoside in an overall yield of 18 and 20%, respectively, confirming their absolute configuration.

Introduction. – Two enzymes, glyoxalase I ((*S*)-lactoylglutathione-methylglyoxal-lyase, EC4.4.1.5) and glyoxalase II (2-hydroxyacylglutathione hydrolase, EC3.1.2.6), and reduced glutathione (GSH) as cofactor form the glyoxalase system which catalyses the conversion of α-ketoaldehydes into α-hydroxy acids. The mechanistic details of this conversion are not fully known, but inhibitors of glyoxalase I have been studied as cytotoxic and potentially cancerostatic agents as detailed in a recent review article [1].

In 1975, *Umezawa* and coworkers isolated a glyoxalase-I inhibitor from the culture broth of *Streptomyces griseosporeus* NIIDA *et* OGASAWARA [2][1]) to which, based on chemical studies and the X-ray analysis of a bromo derivative, structure **1** (including the absolute configuration) has been assigned [4]. The alcohol **2**, obtained from **1** upon acidic hydrolysis, was found to be identical with KD16-U1, a metabolite of *Streptomyces filipensis* [5], which has been transformed into **1** by $BF_3 \cdot Et_2O$-catalyzed esterification with crotonic acid [6]. The cancerostatic activity of **1** [2], the unknown details of its mechanism of inhibition[2]) (*cf.* [4]) and its structure as *C*-acyloxymethylated, polyoxygenated cyclohexenone (*C*-alkylated deoxyinositol derivative) justify its synthesis.



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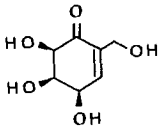

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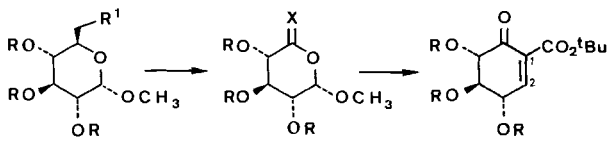
[1]) The same compound has since been isolated from cultures of soil *Streptomycetes* and shown to inhibit alkaline phosphodiesterase and DNA polymerase α [3].

[2]) The inhibitor **1** may be a specific equivalent of bromomethyl acrylate.

Synthesis. – Several methods for the transformation of carbohydrates into polyhydroxycyclohexanes (inositols) are known [7–18]. Particularly noteworthy are the nitromethane synthesis and its modifications leading to deoxynitroinositols [8] and *Ferrier*'s transformation of hex-5-enopyranosides into 3-hydroxycyclohexanones using $HgCl_2$ [9]. *C*-Alkylated polyhydroxycyclohexanes have been prepared from monosaccharides by the cyclization of deoxynitro derivatives [15] [16], by aldolisations [12], and intramolecular olefinations [17] [18]. Applications of these methods for the synthesis of enantiomerically pure, *C*-alkylated hydroxycyclohexanones from carbohydrates would require several steps to introduce an alkyl group and to form the carbocycle.

It appears advantageous to combine the alkylation with the formation of a precursor for an intramolecular *in situ* condensation. This goal might be reached by applying the principles of the *Fujimoto-Belleau* reaction [19] [20] where the addition of a *Grignard* reagent to an enol-lactone is followed by an acid- or base-catalyzed cyclization[3]). To check if the enol-lactone can be replaced by a pseudolactone and the *Grignard* reagent by a stabilized carbanion, we prepared the pseudolactone **6** from the easily available methyl 6-deoxy-6-iodo-α-D-glucopyranoside **3** [22] *via* the intermediates **4** and **5** in an overall yield of 76% *(Scheme 1)*. Treatment of this pseudolactone with the lithium salt of *tert*-butyl acetate[4]) first at −78° and then at room temperature gave the silylated *tert*-butyl trihydroxy-oxo-cyclohexene-carboxylate **7** in a yield of 51%.

Scheme 1



3 R=H; R^1=I **5** R=H; X=CH_2 **7** R=SiEt₃

4 R=Ac; R^1=I **6** R=SiEt₃; X=O

The IR spectrum of **6** is characterized by a carbonyl band at 1765 cm^{-1} and its ^{1}H-NMR spectrum ($CDCl_3$) by $J(2,3) = 3.9$, $J(3,4) = 4.2$, and $J(4,5) = 1.1$ Hz, coupling constants that are notably different from those of triacetoxy-D-xylono-1,5-lactone (C_6D_6), for which a half-chair conformation was proposed [27].

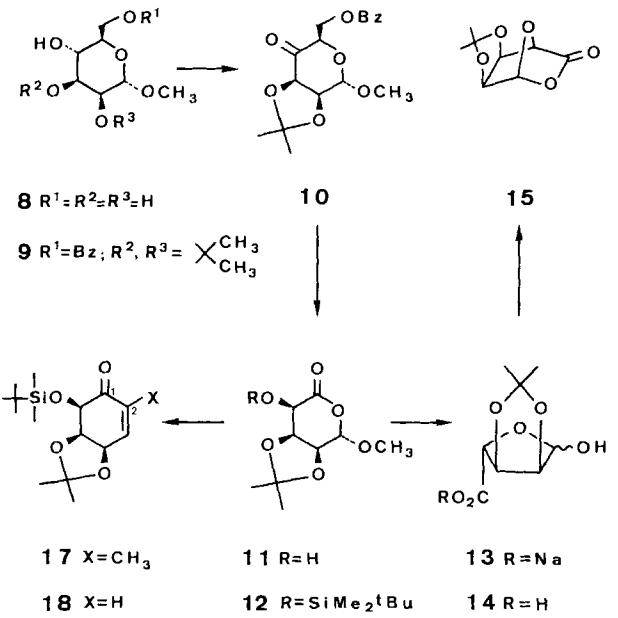
The IR spectrum of **7** shows strong bands at 1740 and 1715 cm^{-1} and a weak one at 1632 cm^{-1}. In the ^{1}H-NMR spectrum, $J(4,5) = 9.9$ and $J(3,4) = 7.2$ Hz evidence the *trans, trans*-configuration at C(3), C(4), and C(5). The signal of the vinylic H appears at 7.21 ppm ($J(2,3) = 2.2$ Hz).

The synthesis of **1** by this method requires a protected L-*ribo*-configurated pseudolactone such as **12** *(Scheme 2)*, which may be obtained in a similar way as **6** by ozonolysis of an enol ether, available in its turn from a D-talose derivative. The preparation of D-talose derivatives by inversion at C(4) of a suitably protected D-mannoside is well-precedented [28]. The 6-benzoate **9** was obtained (78%) from methyl α-D-mannopyranoside (**8**) [28] and oxidized (pyridinium chlorochromate in the presence of molecular sieves [29]) to the ketone **10** (92%). Sequential treatment of **10** with NEt_3 to effect β-elimination, then with $NaBH_4$, and finally with ozone gave the alcohol **11** which was protected by silylation

[3]) Recently, such a sequence has been described for the preparation of cyclopentenones from carbohydrates [21].

[4]) Nucleophiles that either did not give the desired product or else proved unreactive include the anions derived from diethyl cyanomethylphosphonate [23] or ethyl acetate [23], the dianions of acetic acid [24] or trimethylsilyl acetic acid [25], and the *Reformatzky* reagent obtained from ethyl bromoacetate [26].

Scheme 2



with (*t*-Bu)Me_2SiCl. The protected pseudolactone **12** was isolated in an overall yield of 72% from the benzoate **9**, without isolation of the (unstable) intermediates *(Scheme 2)*.

The IR spectrum of **12** shows the carbonyl band at 1780 cm^{-1} and the ^{1}H-NMR spectrum is characterized by $J(1,2) = 0.7$, $J(2,3) = 7.2$, $J(3,4) = 3$, and $J(1,3) = 0.8$ Hz.

The pseudolactone **12** proved unreactive towards the Li anions of *t*-butyl acetate, (*t*-butyl)dimethylsilyl acetate [30] and trimethylsilyl diethylphosphonoacetate, respectively, at temperatures up to −20°. At higher temperatures, **12** partially reacted to give decomposition products. The low reactivity of **12** may be traced back to the severe steric hindrance of the carbonyl group[5]).

The bridged pseudolactone **15** is an equivalent of **12** and possesses a less crowded carbonyl group. It was prepared from **11** by saponification to give the carboxylate **13**, followed by acidification to **14** and lactonization. As reported in the preparation of the enantiomer of **15** [33], the latter two steps were unsatisfactory and **15** was obtained in only 12% yield from the benzoate **9**. The bridged pseudolactone **15** shows a carbonyl group absorption at 1820 cm^{-1}, indicating high reactivity. It did not react with the above mentioned nucleophiles at −100°, and it decomposed upon being warmed to −78°.

The more easily available pseudolactone **12** did, however, react with the anions derived from diethyl ethylphosphonate and dimethyl methylphosphonate to give the cyclohexenones **17** (49%) and **18** (62%), respectively.

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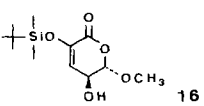
[5]) Treatment of **12** with the more reactive dianion of diethyl (2-hydroxyethyl)phosphonate [31] gave the α,β-unsaturated pseudolactone **16** (the dianion formation was evident from quenching experiments with D_2O). 2-Diethylphosphonomethyl-1,3-dioxane [32] underwent instaneous β-elimination at −78°.



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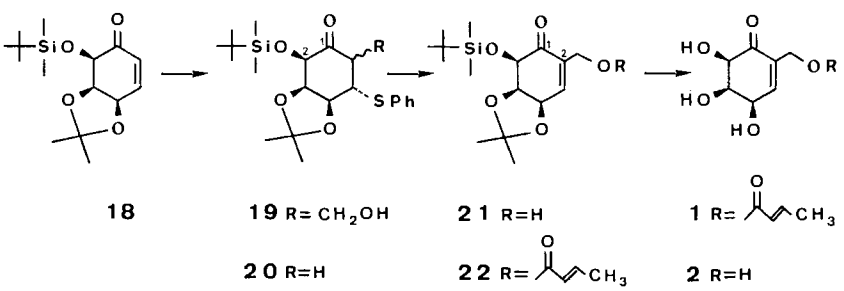
Ketones **17** and **18** showed IR bands at 1703 and 1712 cm^{-1}, respectively. In the ^{1}H-NMR spectrum of **17**, the signals of the (vinylic) H–C(3) appear at 6.29 ppm. The *cis,cis*-configuration is in agreement with $J(5,6) = 2.9$ and $J(4,5) = 5$ Hz. In the ^{1}H-NMR spectrum of **18**, the corresponding values are 6.55 ppm (H–C(3)), 5.99 ppm (H–C(2)), $J(5,6) = 3$ Hz and $J(4,5) = 5$Hz.

Since the functionalization of the allylic CH_3 group of **17** by reaction with *N*-bromosuccinimide [34], or with SeO_2 [35] failed, we circumvent the problem by treating **18** with Me_2AlSPh [36] and then with gaseous formaldehyde *(Scheme 3)*. The hydroxymethylated thioether **19** was obtained (66%) as a mixture of diastereoisomers, whilst the β-(phenylthio)ketone **20**, obtained from **18** and Me_2AlSPh was isolated (51%) as a single, presumably 4,5-*trans*-configurated isomer. The sulfoxides derived by oxidation of **19** with *m*-chloroperbenzoic acid underwent β-elimination during chromatography on silica gel to give the desired hydroxymethylated cyclohexenone **21** (91% from **19**). It showed characteristic IR bands at 3605, 1700, and 1601 cm^{-1}, whilst **19** and **20** showed carbonyl bands at 1729 and 1739 cm^{-1}, respectively. The ^{1}H-NMR spectrum of **21** was very similar to that of **17**.

Scheme 3



Hydrolysis of **21** with aqueous CF_3COOH gave the hydroxymethyl-trihydroxycyclohexenone **2** in over 95% yield. This compound had the same m.p., $[\alpha]_D$, and UV-, IR-[4], H-NMR, and mass spectrum as KD16-U1 [5]. Treatment of **2** with crotonic acid in the presence of $BF_3 \cdot Et_2O$ [6] gave an ester **1** (48%) which, by the same criteria as mentioned above, was identical with the glyoxalase inhibitor confirming its absolute configuration. The inhibitor **1** was also obtained by first esterifying **21** with crotonic acid in the presence of DCC and catalytic amounts of 4-(dimethylamino)pyridine (85%) and then deprotecting the resulting ester **22** by treating it with aqueous CF_3COOH (quant.). The overall yields of **1** and **2** from methyl α-D-mannopyranoside were 18 and 20%, respectively.

Experimental Part

General. See [37]. UV spectra (λ_{max} in nm (ε)) were measured on a *Perkin-Elmer-599* spectrometer (1-cm cell). ^{1}H- and ^{13}C-NMR spectra were recorded with a *Varian-XL-200* (^{1}H(200 MHz), ^{13}C(50 MHz)) or with a *Varian XL-100-12 FT* (^{13}C(25.2 MHz)) spectrometer. For chromatography, the following mixtures were used: A = AcOEt/hexane 1:9; B = AcOEt/hexane 1:4; C = AcOEt/hexane 1:3; D = AcOEt/hexane 2:3; E = AcOEt/MeOH 9:1; F = AcOEt/MeOH 4:1. TLC: substances were detected by spraying the plates with 0.025M I_2 in 10% aq. H_2SO_4, followed by heating at about 200°.

Methyl 2,3,4-O-Triacetyl-6-deoxy-6-iodo-α-D-glucopyranoside (**4**). A mixture containing **3** (2 g, 6.5 mmol) [22], Ac_2O (10 ml) and Py (15 ml) was stirred at r.t. for 3 h. Evaporation gave a residue, which was crystallized from EtOH to afford 2.74 g (97%) of **4** as white needles, identical with an authentic sample [38].

Methyl 6-Deoxy-α-D-xylo-hex-5-enopyranoside (**5**). To a solution of **4** (10 g, 2.3 mmol) in dry THF (100 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 20.8 ml, 13.8 mmol) was added and the mixture was refluxed for 12 h. Removal of the solvent gave an oil, which was thoroughly dried, taken up in MeOH (100 ml), and shaken with a soln. of NaOMe in MeOH (0.1M, 10 ml). Neutralization with AcOH, concentration *in vacuo*, and chromatography (Et_2O/CH_2Cl_2/EtOH 6:3:1) furnished 3.59 g (88%) of **5** as a colourless oil, identical with an authentic sample [39].

(Methyl 2,3,4-O-Triethylsilyl-α-D-xylopyranosid)urono-5,1-lactone (**6**). A mixture containing **5** (373 mg, 2.1 mmol), Et_3N (2.95 ml, 21 mmol), and Et_3SiCl (2.13 ml, 12.6 mmol) in dry CH_2Cl_2 (5 ml) was refluxed for 10 h, and cooled to 0°. Upon addition of Et_3N (2.95 ml, 21 mmol) and Et_3SiCl (2.13 ml, 12.6 mmol) the mixture was refluxed for further 48 h and diluted with CH_2Cl_2 (100 ml) and H_2O (50 ml). The org. phase was separated, washed with brine, concentrated to 80 ml and treated with O_3 at −78° for 15 min. After adding Me_2S (187 μl), the mixture was allowed to warm to r.t. and poured into 10% aq. $NaHSO_3$. Normal workup with CH_2Cl_2 and chromatography (Et_2O/hexane 1:9, containing 1% Et_3N) gave 981 mg (89%) of **6** as a colourless oil. R_f (Et_2O/hexane 1:9) 0.28, $[\alpha]_D^{25} = +46.3°$ ($c = 1.1$, $CHCl_3$). IR: 2950*s*, 2910*s*, 2875*s*, 1765*s*, 1458*m*, 1410*m*, 1380*m*, 1320*w*, 1140*s*, 1035*s*, 1004*s*, 971*m*, 945*m*, 895*m*, 837*m*. ^{1}H-NMR: 0.51–0.80 (*m*, 18H); 0.86–1.06 (*m*, 27H); 3.55 (*s*, 3H); 3.76 (*dd*, $J = 3.9, 1.1$, H–C(2)); 3.82 (*dd*, $J = 4.2, 3.9$, H–C(3)); 4.04 (*d*, $J = 4.2$, H–C(4)); 5.14 (*d*, $J = 1.1$, H–C(1)). ^{13}C-NMR: 4.85 (*t*); 4.94 (*t*); 5.02 (*t*); 6.02 (*q*); 6.56 (*q*); 6.75 (*q*); 6.85 (*q*); 56.67 (*q*); 72.53 (*d*); 75.72 (*d*); 76.78 (*d*); 100.72 (*d*); 170.27 (*s*). MS: 491 (2), 463 (2), 433 (6), 359 (13), 303 (16), 288 (13), 259 (14), 159 (13), 117 (37), 115 (78), 89 (16), 87 (100), 59 (41). Anal. calc. for $C_{24}H_{52}O_6Si_3$ (520.95): C 55.34, H 10.06; found: C 55.44, H 10.11.

tert-*Butyl 3D-(3,5/4)-3,4,5-O-triethylsilyl-3,4,5-trihydroxy-6-oxocyclohex-1-enecarboxylate* (**7**). BuLi (*Fluka*, 1.6M in hexane, 3.13 ml, 5 mmol) was added dropwise to a stirred soln. of $(i\text{-Pr})_2NH$ (605 mg, 6 mmol) in dry THF (2 ml) at 0° unter Ar. After 15 min, a soln. of AcO*t*Bu (804 μl, 6 mmol) in dry THF (2 ml) was introduced dropwise at −78° and stirred for 1 h. An aliquot (1.89 ml, 1.2 mmol) was removed and added dropwise to a soln. of **6** (300 mg, 0.57 mmol) at −78° under Ar. The mixture was allowed to warm to 0°, stirred for 1 h, and poured into sat. aq. NH_4Cl. Usual workup and chromatography (Et_2O/hexane 1:25) afforded 172 mg (51%) of **7** as a colourless oil. R_f (Et_2O/hexane 1:15) 0.35, $[\alpha]_D^{25} = +68.6°$ ($c = 1.1$, $CHCl_3$). UV (EtOH): 237 (5062), 256 (2531). IR: 2975*s*, 2910*s*, 2880*s*, 1740*s*, 1715*s*, 1632*w*, 1458*m*, 1412*m*, 1392*m*, 1370*s*, 1350*m*, 1294*m*, 1240*s*, 1155*s*, 1132*s*, 1090*s*, 1005*s*, 977*s*, 902*m*, 888*m*, 856*m*, 808*m*. ^{1}H-NMR: 0.63–0.77 (*m*, 18H); 0.91–1.06 (*m*, 27H); 1.50 (*s*, 9H); 3.76 (*dd*, $J = 9.9, 7.2$, H–C(4)); 4.01 (*d*, $J = 9.9$, H–C(5)); 4.39 (*dd*, $J = 7.2, 2.2$, H–C(3)); 7.21 (*d*, $J = 2.2$, H–C(2)). ^{13}C-NMR: 5.16 (*t*); 5.33 (*t*); 5.57 (*t*); 6.51 (*q*); 6.91 (*q*); 7.00 (*q*); 28.08 (*q*); 73.34 (*d*); 78.72 (*d*); 79.69 (*d*); 82.10 (*s*); 131.03 (*s*); 152.43 (*d*); 162.38 (*s*); 193.30 (*s*). MS: 503 (4), 483 (10), 369 (40), 288 (68), 87 (100), 75 (52), 59 (60). Anal. calc. for $C_{29}H_{58}O_6Si_3$ (587.04): C 59.34, H 9.96; found: C 59.05, H 9.02.

Methyl 6-O-Benzoyl-2,3-O-isopropylidene-α-D-mannopyranoside (**9**) was prepared according to [28] from methyl α-D-mannopyranoside in an overall yield of 78%.

(Methyl 4-O-[(tert-Butyl)dimethylsilyl]-2,3-O-isopropylidene-β-L-ribopyranosid)urono-5,1-lactone (**12**). Compound **9** (22 g, 65.0 mmol) was added to a suspension of pyridinium chlorochromate (29 g, 134.5 mmol) and powdered 3 Å molecular sieve (40 g, activated at 300° for 8 h) in CH_2Cl_2 (240 ml). The mixture was well stirred for 2 h, diluted with Et_2O and filtered through silica gel containing $CaSO_4$ (10%). Evaporation and chromatography (**B**) of the residue afforded an oil, which was dissolved in CH_2Cl_2 (200 ml) and treated with Et_3N (58.1 g, 80 ml, 0.57 mol) for 10 min at r.t. The mixture was evaported *in vacuo*, diluted with i-PrOH (450 ml), and cooled to 0°. $NaBH_4$ (8.2 g, 217.0 mmol) was added in portions over 30 min and the mixture was stirred for 2 h at 0°. Upon removal of the solvent, the residue was partitioned between CH_2Cl_2 and H_2O. The org. phase was separated, concentrated to 300 ml, and ozonized at −78°. The mixture was allowed to warm to r.t., concentrated *in vacuo* to give a residue, which was thoroughly dried (high vacuum) and taken up in DMF (30 ml). After addition of (*t*-Bu)Me_2SiCl (16.6 g, 110.1 mmol) and imidazol (15 g, 220.3 mmol), the mixture was stirred overnight at r.t. Normal workup with AcOEt and chromatography (**A**) furnished 15.6 g (72%) of **12** as a white crystalline solid. Recrystallization from hexane at −5° gave an anal. sample. M.p. 74–75°, R_f (**B**) 0.3, $[\alpha]_D^{25} = +6.2°$ ($c = 1.0$, $CHCl_3$). IR: 2950*m*, 2932*m*, 2900*w*, 2858*m*, 1780*s*, 1463*w*, 1385*m*, 1376*m*, 1362*w*, 1279*w*, 1250*m*, 1153*m*, 1142*s*, 1095*s*, 1068*m*, 1021*s*, 990*w*, 972*m*, 932*m*, 900*w*, 860*w*, 835*s*. ^{1}H-NMR: 0.13 (*s*, 3H); 0.22 (*s*, 3H); 0.94 (*s*, 9H); 1.35 (*s*, 3H); 1.47 (*s*, 3H); 3.50 (*s*, CH_3O); 4.39 (*dd*, $J = 7.2, 0.7$, H–C(2)); 4.65 (*ddd*, $J = 7.2, 3.0, 0.8$, H–C(3)); 4.80 (*d*, $J = 3.0$, H–C(4)); 5.05 (*dd*, *t*-like, $J = 0.8, 0.7$, H–C(1)). ^{13}C-NMR: −5.44 (*q*); −4.44 (*q*); 18.59 (*s*); 24.63 (*q*); 25.85 (*q*); 26.25 (*q*); 57.01 (*q*); 68.79 (*d*); 75.06 (*d*); 76.46 (*d*); 102.75 (*d*); 111.42 (*s*); 169.11 (*s*). MS: 317 (5), 217 (22), 173 (42), 129 (32), 115 (69), 89 (89), 75 (100), 59 (48), 45 (69), 43 (85). Anal. calc. for $C_{15}H_{28}O_6Si$ (332.52): C 54.18, H 8.50; found: C 54.20, H 8.34.

Sodium 2,3-O-Isopropylidene-α-L-ribofuranuronate (**13**). Manipulation of **9** (1.40 g, 4.14 mmol) as described above gave 900 mg (*ca.* 100%) of crude **11**, which was taken up in H_2O (18 ml) and treated with 0.25M NaOH (18 ml) at 0° for 2 h. The mixture was extracted with Et_2O and the aq. phase lyophilized to afford 765 mg (82%) of **13** as a pale yellow solid. ^{1}H-NMR (D_2O): 1.39 (*s*, 3H); 1.54 (*s*, 3H); 4.43 (*s*, H–C(4)); 4.64 (*dd*, *J* = 6, 1.8, H–C(2)); 5.05 (*d*, *J* = 6, H–C(3)); 5.48 (*d*, *J* = 1.8, H–C(1)).

2,3-O-Isopropylidene-α/β-L-ribofuranuronic Acid (**14**). *A*) A soln. of **13** (200 mg, 0.88 mmol) in H_2O (2 ml) at 0° was acidified to pH 3 with 2N HCl. Extraction with AcOEt (10 × 20 ml) and evaporation gave 86 mg (48%) of **14** as a white solid. ^{1}H-NMR (CD_3OD): 1.31 (*s*, 2.55H, α-L-anomer); 1.36 (*s*, 0.45H, β-L-anomer); 1.43 (*s*, 2.55H, α-L-anomer); 1.50 (*s*, 0.45H, β-L-anomer); 4.51 (*s*, 1H, H–C(4)); 4.53 (*d*, *J* = 5.6, 0.85H, H–C(2), α-L-anomer; 0.15H, H–C(2), β-L-anomer); 5.16 (*d*, *J* = 5.6, 1H, H–C(3)); 5.36 (*s*, 0.85H, H–C(1), α-L-anomer); 5.39 (*d*, *J* = 4, 0.15H, H–C(1), β-L-anomer). MS (70 eV): 189 (14), 129 (11), 100 (11), 85 (14), 59 (34), 44 (100).

B) The salt **13** (200 mg, 0.88 mmol) was dissolved in AcOH (2 ml), concentrated (high vacuum), and purified by chromatography on silica gel (AcOEt, containing 1% AcOH) to furnish 70 mg (39%) of **14**, identical with the sample prepared above.

2,3-O-Isopropylidene-α-L-ribofuranurono-5,1-lactone (**15**) [33]. A mixture containing **14** (86 mg, 0.42 mmol), DCC (90 mg, 0.44 mmol), and dry Et_2O (3 ml) was stirred at r.t. for 7 days. After filtration through *Celite*, the mixture was concentrated to dryness and purified by chromatography (B) to give 25 mg (32%) of **15** as a crystalline solid. R_f (B) 0.23. IR: 3032*w*, 2988*m*, 2958*w*, 2941*w*, 1821*s*, 1782*m*, 1458*w*, 1384*s*, 1376*s*, 1343*m*, 1327*w*, 1279*s*, 1265*m*, 1178*m*, 1152*m*, 1091*s*, 1052*m*, 1020*m*, 980*s*, 968*m*, 909*s*, 853*s*, 840*m*, 820*m*. ^{1}H-NMR: 1.34 (*s*, 3H); 1.47 (*s*, 3H); 4.66 (*s*, 3H); 5.93 (*s*, 1H). MS (70 eV): 171 (48), 129 (57), 100 (81), 85 (91), 59 (76), 44 (100).

(Methyl 4-O-[(tert-Butyl)dimethylsilyl]-β-L-glycero-pent-3-enopyranosid)urono-5,1-lactone (**16**). BuLi (*ca.* 1.5M in hexane, 0.4 ml, 0.60 mmol) was added dropwise to a soln. of diethyl (2-hydroxy)ethylphosphonate (55 mg, 0.30 mmol) in dry THF (0.5 ml) under Ar at −78°. After 30 min, a soln. of **12** (50 mg, 0.15 mmol) in dry THF (0.5 ml) was added and the mixture stirred for 1 h. Addition of EtOH (0.1 ml) followed by sat. aq. NH_4Cl (2 ml), workup, and chromatography (D) furnished 21 mg (51%) of **16** as an oil. R_f (D) 0.4. IR: 3647*w*, 3600*w*, 3340 (br.), 3210 (br.), 2960*s*, 2930*s*, 2894*s*, 2854*m*, 2810*m*, 1743*s*, 1650*m*, 1602*w*, 1482*w*, 1462*m*, 1390*w*, 1362*w*, 1297*m*, 1252*s*, 1160*s*, 1147*s*, 1110*m*, 1080*s*, 1068*s*, 981*s*, 834*m*. ^{1}H-NMR: 0.29 (*s*, 3H); 0.30 (*s*, 3H); 1.04 (*s*, 9H); 3.30 (br., OH); 3.67 (*s*, CH_3O); 5.47 (*m*, H–C(2)); 5.20 (*dd*, *J* = 3.4, 1, H–C(1)); 5.96 (*dd*, *J* = 5, 1, H–C(3)). MS: 227, 217, 185, 113, 75.

4L-(4,5,6/0)-6-O-[(tert-Butyl)dimethylsilyl]-4,5,6-trihydroxy-4,5-O-isopropylidene-2-methylcyclohex-2-enone (**17**). Treatment of **12** (100 mg, 0.30 mmol) with diethyl ethylphosphonate (100 mg, 0.60 mmol) and BuLi (1.5M in hexane, 0.4 ml, 0.60 mmol) as described above gave 46 mg (49%) of **17** as a crystalline solid. An anal. sample was obtained by recrystallization from hexane at −5°. M.p. 58°, R_f (B) 0.4, $[\alpha]_D^{25} = -32.8°$ (*c* = 1.4, $CHCl_3$). UV (EtOH): 224 (10138), 268 (3262). IR: 2988*w*, 2955*m*, 2930*m*, 2895*m*, 2858*m*, 1703*s*, 1461*w*, 1448*w*, 1435*w*, 1381*m*, 1370*m*, 1360*w*, 1349*w*, 1300*w*, 1250*m*, 1218*m*, 1165*m*, 1120*m*, 1090*w*, 1049*s*, 1037*s*, 1007*m*, 969*w*, 935*m*, 914*w*, 901*m*, 887*w*, 834*s*. ^{1}H-NMR: 0.09 (*s*, 3H); 0.24 (*s*, 3H); 0.94 (*s*, 9H); 1.33 (*s*, 3H); 1.38 (*s*, 3H); 1.83 (*dd*, *t*-like, *J* = 1.5, CH_3–C(2)); 4.43 (*d*, *J* = 2.9, H–C(6)); 4.65 (*ddd*, *J* = 5.0, 2.9, 2.0, H–C(5)); 4.74 (*ddd*, *J* = 5.0, 3.0, 1.5, H–C(4)); 6.29 (*m*, H–C(3)). ^{13}C-NMR: −5.55 (*q*); −4.30 (*q*); 15.47 (*q*); 18.51 (*s*); 25.76 (*q*); 26.71 (*q*); 27.72 (*q*); 72.64 (*d*); 74.16 (*d*); 79.24 (*d*); 110.94 (*s*); 133.81 (*s*); 138.56 (*d*); 195.85 (*s*). MS: 297 (1), 255 (20), 197 (64), 169 (92), 95 (30), 75 (100), 43 (74). Anal. calc. for $C_{16}H_{28}O_4Si$ (312.53): C 61.48, H 9.05; found: C 61.39, H 8.95.

4L-(4,5,6/0)-6-O-[(tert-Butyl)dimethylsilyl]-4,5,6-trihydroxy-4,5-O-isopropylidene-cyclohex-2-enone (**18**). BuLi (*Merck;* 1.62M in hexane, 1.11 ml, 1.80 mmol) was added dropwise to a stirred soln. of dimethyl methylphosphonate (223 mg, 0.19 ml, 1.80 mmol) in dry THF (6 ml), at −78° under Ar. After 30 min, a soln. of **12** (200 mg, 0.60 mmol) in dry THF (2 ml) was added dropwise and the mixture stirred for 3 h at −78°. EtOH (0.1 ml) was added, followed by sat. aq. NH_4Cl (5 ml). The mixture was allowed to warm to r.t. Usual workup and chromatography (A) afforded 111 mg (62%) of **18** as a colourless solid. M.p. 62.5–64°, R_f (B) 0.28, $[\alpha]_D^{25} = -88.6°$ (*c* = 1.1, $CHCl_3$). UV (EtOH): 208 (13990), 268 (2886). IR: 2995*m*, 2958*s*, 2932*s*, 2900*m*, 2860*s*, 1712*s*, 1625*w*, 1470*m*, 1462*m*, 1382*s*, 1371*s*, 1361*w*, 1350*w*, 1332*w*, 1300*w*, 1279*w*, 1251*s*, 1220*s*, 1166*s*, 1151*s*, 1092*s*, 1045*s*, 1006*w*, 991*w*, 969*w*, 939*w*, 911*s*, 895*s*, 838*s*, 823*s*. ^{1}H-NMR: 0.11 (*s*, 3H); 0.25 (*s*, 3H); 0.95 (*s*, 9H); 1.37 (*s*, 3H); 1.39 (*s*, 3H); 4.48 (*d*, *J* = 3.0, H–C(6)); 4.73 (*ddd*, *J* = 5.0, 3.0, 2.0, H–C(5)); 4.82 (*ddd*, *J* = 5.0, 3.0, 1.2, H–C(4)); 5.99 (*dd*, *J* = 10.2, 1.2, H–C(2)); 6.55 (*ddd*, *J* = 10.2, 3.0, 2.0, H–C(3)). ^{13}C-NMR: −5.38 (*q*); −4.12 (*q*); 18.65 (*s*); 25.89 (*q*); 26.75 (*q*); 27.72 (*q*); 73.25 (*d*); 74.17 (*d*); 79.38 (*d*); 111.27 (*s*); 126.95 (*d*); 143.68 (*d*); 194.93 (*s*). MS: 283 (2), 241 (10), 183 (88), 155 (100), 123 (12), 111 (20), 81 (52), 75 (67), 43 (47). Anal. calc. for $C_{15}H_{26}O_4Si$ (298.50): C 60.35, H 8.80; found: C 60.56, H 9.02.

*2D-(2,3,4/5,6)- and 2D-(2,3,4,6/5)-2-O-[(*tert*-Butyl)dimethylsilyl]-2,3,4-trihydroxy-6-hydroxymethyl-3,4-O-isopropylidene-5-phenylthio-1-cyclohexanone* (**19**). Me_3Al (1.9M in hexane, 2.2 ml, 4.0 mmol) was added under Ar to a soln. of thiophenol (440 mg, 0.4 ml, 4.0 mmol) at 0°, and the mixture was stirred for 20 min. To this, a soln. of **18** (1.0 g, 3.35 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise at −78°, and after 1 h, the mixture was diluted with dry THF (20 ml). Gaseous formaldehyde (excess) was bubbled through the mixture at −50°, followed by addition of sat. aq. NH_4Cl (10 ml). The mixture was allowed to warm to r.t. Normal workup and chromatography (C) furnished 0.97 g (66%) of **19** as a mixture of diastereoisomers. R_f (D) 0.40, $[\alpha]_D^{25} = -48.3°$ (c = 1.4, $CHCl_3$). IR: 3535 (br.), 2995*m*, 2954*s*, 2932*s*, 2900*m*, 2886*m*, 2860*m*, 1729*s*, 1582*w*, 1470*m*, 1462*m*, 1440*m*, 1406*w*, 1384*m*, 1377*m*, 1361*w*, 1252*s*, 1162*s*, 1107*m*, 1088*s*, 1042*s*, 1025*m*, 1002*m*, 970*m*, 940*w*, 890*m*, 837*s*. ^{1}H-NMR: 0.13 (*s*, 3H); 0.23 (*s*, 3H); 0.94, 0.96 (2*s*, 9H); 1.33 (*s*, 3H); 1.48 (*s*, 3H); 2.19 (br., OH); 3.20 (*m*, H–C(6)); 3.64 (*d*, J = 4.5, H–C(5)); 3.74 (*dd*, J = 11.3, 5.9, C*H*OH); 4.24 (*dd*, J = 11.3, 7.3, C*H*OH); 4.69 (*m*, 2H, H–C(3), H–C(4)); 4.94 (*d*, J = 2.6, H–C(2)); 7.26–7.58 (*m*, C_6H_5S). ^{13}C-NMR: −5.28 (*q*); −4.22 (*q*); 18.67 (*s*); 23.98 (*q*); 25.94 (*q*); 46.37 (*d*, minor); 47.77 (*d*); 48.70 (*d*); 53.04 (*d*, minor); 61.49 (*t*); 63.18 (*t*, minor); 74.90 (*d*); 76.21 (*d*); 76.82 (*d*); 109.65 (*s*); 127.68 (*d*); 128.17 (*d*, minor); 129.37 (*d*); 131.19 (*d*); 132.39 (*d*, minor); 133.49 (*s*); 207.17 (*s*). MS: 423 (0.5), 323 (18), 195 (33), 183 (39), 167 (24), 156 (24), 110 (40), 75 (100), 73 (74), 43 (43). Anal. calc. for $C_{22}H_{34}O_5SSi$ (438.71): C 60.23, H 7.83, S 7.31; found: C 60.25, H 7.82, S 7.25.

*2D-(2,3,4/5)-2-O-[(*tert*-Butyl)dimethylsilyl]-2,3,4-trihydroxy-3,4-O-isopropylidene-5-phenylthio-1-cyclohexanone* (**20**). Compound **18** (100 mg, 0.34 mmol) was treated with Me_3Al (1.9M in hexane, 0.22 ml, 0.40 mmol) and thiophenol (44 mg, 40 µl, 0.40 mmol) in the manner described above. Usual workup and chromatography (A) afforded 73 mg (53%) of **20** as crystalline material. Recrystallization from hexane/Et_2O at −5° gave an anal. sample. M.p. 61–62°, R_f (B) 0.40, $[\alpha]_D^{25} = -27.4°$ (c = 1.2, $CHCl_3$). IR: 2995*w*, 2955*w*, 2930*m*, 2860*m*, 1739*s*, 1583*w*, 1470*w*, 1462*w*, 1440*w*, 1384*m*, 1374*m*, 1361*w*, 1255*m*, 1162*s*, 1127*m*, 1081*s*, 1042*m*, 1022*m*, 1005*w*, 970*w*, 961*w*, 937*w*, 899*s*, 865*w*, 839*s*, 824*m*. ^{1}H-NMR: 0.15 (*s*, 3H); 0.25 (*s*, 3H); 0.97 (*s*, 9H); 1.36 (*s*, 3H); 1.47 (*s*, 3H); 2.55 (*ddd*, J = 19.1, 1.7, 1.2, H–C(6)); 2.97 (*dd*, J = 19.1, 5.4, H–C(6')); 3.70 (*m*, H–C(5)); 4.59 (*ddd*, *dt*-like, J = 7.1, 1.7, H–C(4)); 4.68 (*ddd*, J = 7.1, 2.9, 0.7, H–C(3)); 5.15 (*d*, J = 2.9, H–C(2)); 7.21–7.59 (*m*, C_6H_5S). ^{13}C-NMR: −5.41 (*q*); −4.39 (*q*); 18.60 (*s*); 23.95 (*q*); 25.88 (*q*); 26.17 (*q*); 38.77 (*t*); 44.46 (*d*); 74.55 (*d*); 75.92 (*d*); 77.59 (*d*); 109.57 (*s*); 127.86 (*d*); 129.35 (*d*); 131.77 (*d*); 133.02 (*s*); 203.94 (*s*). MS: 393 (0.6), 351 (4), 293 (62), 183 (100), 155 (37), 149 (73), 129 (55), 73 (99), 43 (48). Anal. calc. for $C_{21}H_{32}O_4SSi$ (408.68): C 61.71, H 7.91, S 7.84; found: C 61.53, H 7.93, S 7.75.

*4L-(4,5,6/0)-6-O-[(*tert*-Butyl)dimethylsilyl]-4,5,6-trihydroxy-2-hydroxymethyl-4,5-O-isopropylidenecyclohex-2-enone* (**21**). A soln. of *m*-chloroperbenzoic acid (90%; 177 mg, 0.92 mmol) in CH_2Cl_2 (3 ml) was added dropwise over 10 min to a stirred soln. of **19** (355 mg, 0.81 mmol) in CH_2Cl_2 (8 ml) at 0°. After 1 h, the mixture was diluted with CH_2Cl_2. The org. phase was separated, washed successively with sat. aq. Na_2CO_3 and H_2O, and concentrated to *ca.* 10 ml. Silica gel (5 g) was added, and the mixture was stirred overnight. Filtration, evaporation *in vacuo*, and chromatography of the residue furnished 241 mg (91%) of **21** as a solid. An anal. sample was prepared by recrystallization from hexane/CH_2Cl_2 at −5°. M.p. 88°, R_f (D) 0.19, $[\alpha]_D^{25} = -39°$ (c = 1.0, $CHCl_3$). UV (EtOH): 220 (7661), 266 (1843). IR: 3605 (br.), 3034*w*, 2995*m*, 2956*m*, 2932*m*, 2900*m*, 2860*m*, 1700*s*, 1601*w*, 1470*w*, 1462*w*, 1382*m*, 1372*m*, 1360*m*, 1300*w*, 1251*m*, 1166*s*, 1120*m*, 1081*w*, 1048*s*, 1009*m*, 988*m*, 970*w*, 939*m*, 919*m*, 900*m*, 887*w*, 835*s*. ^{1}H-NMR: 0.11 (*s*, 3H); 0.24 (*s*, 3H); 0.96 (*s*, 9H); 1.36 (*s*, 3H); 1.40 (*s*, 3H); 2.28 (*t*, J = 6.3, OH); 4.32 (*ddd*, *dt*-like, J = 6.3, 1.2, C*H*$_2$OH); 4.49 (*d*, J = 3.0, H–C(6)); 4.71 (*ddd*, J = 5.0, 3.0, 2.1, H–C(5)); 4.84 (*ddd*, J = 5.0, 2.6, 1.2, H–C(4)); 6.52 (*m*, H–C(3)). ^{13}C-NMR: −5.35 (*q*); −4.20 (*q*); 18.52 (*s*); 25.79 (*q*); 26.67 (*q*); 27.78 (*q*); 60.05 (*t*); 72.53 (*d*); 74.23 (*d*); 79.14 (*d*); 111.09 (*s*); 136.07 (*s*); 138.54 (*d*); 195.87 (*s*). MS: 313 (2), 271 (19), 213 (23), 183 (23), 167 (26), 75 (100), 43 (82). Anal. calc. for $C_{16}H_{28}O_5Si$ (328.53): C 58.49, H 8.61; found: C 58.36, H 8.50.

(4R,5R,6R)-2-Hydroxymethyl-4,5,6-trihydroxycyclohex-2-enone (**2**) [4] [5]. Ice-cooled 60% aq. CF_3COOH (4 ml) was added to **21** (100 mg, 0.30 mmol), and the mixture was stirred at r.t. for 4 h. Removal of the solvent and concentration with abs. EtOH (2×) gave a reddish solid, which was purified by chromatography (E) to afford 53 mg (100%) of **2** as white crystals. Recrystallization from AcOEt/EtOH gave colourless needles. M.p. 112–113° ([4]: 112–113°, [5]: 113–114°), $[\alpha]_D^{20} = -163°$ (c = 0.5, H_2O) ([5]: −168° (c = 1.0, H_2O)). UV (H_2O): 229 (9228), 312 (88). IR (KBr): 3435*s*, 3380*s*, 3240*s*, 2980*w*, 2942*w*, 2910*w*, 2860*w*, 1688*s*, 1650*w* (sh), 1459*w*, 1441*w*, 1415*m*, 1388*m*, 1360*w*, 1330*m*, 1269*w*, 1224*w*, 1202*m*, 1150*m*, 1130*m*, 1072*m*, 1067*m*, 1057*m*, 1038*m*, 1007*m*, 980*m*, 929*w*, 919*m*, 890*w*, 854*w*, 806*w*, 756*w*, 729*w*, 670*w*, 605*m*. ^{1}H-NMR (D_2O): 4.31 (*m*, C*H*$_2$OH); 4.50 (*m*, 2H); 4.84 (*m*, 1H); 6.80 (*m*, H–C(3)). MS (70 eV): 156.6 (6), 143 (1), 138 (33), 127 (49), 126 (15), 125 (13), 114 (72), 112 (13), 111 (10), 110 (28), 109 (38), 97 (24), 96 (88), 71 (27), 69 (26), 68 (100).

(4R,5R,6R)-2-Crotonyloxymethyl-4,5,6-trihydroxycyclohex-2-enone (= [(3R,4R,5R)-3,4,5-Trihydroxy-6-oxocyclohex-1-enyl]methyl Crotonate; 1) [2] [4]. A) *From* **2**. A mixture containing **2** (48 mg, 0.28 mmol), crotonic acid (72 mg, 0.84 mmol), $BF_3 \cdot OEt_2$ (132 mg, 0.93 mmol) and molecular sieve (4 Å, 50 mg) in CH_3CN (3 ml) was stirred for 24 h at 5°. MeOH (0.2 ml) was added, and the mixture was evaporated *in vacuo*. Chromatography on silica gel (E) and on *Sephadex LH-20* (MeOH) furnished 32 mg (48%) of **1** as a white powder. Recrystallization from $CHCl_3$/MeOH at −5° gave colourless needles. M.p. 179–180° ([4]: 181°); R_f (F) 0.45, $[\alpha]_D^{24} = -106°$ ($c = 0.6$, MeOH) ([4]: − 109° ($c = 1.5$, MeOH)). UV (H_2O): 213 (20455). IR (KBr): 3425*s*, 3340*m*, 3240*m*, 2935*w*, 2860*w*, 1720*s*, 1690*s*, 1658*m*, 1447*m*, 1412*w*, 1386*w*, 1332*m*, 1313*m*, 1300*m*, 1255*w*, 1198*s*, 1152*m*, 1134*m*, 1127*m*, 1109*m*, 1056*s*, 1044*s*, 1010*w*, 1000*w*, 970*w*, 944*w*, 910*w*, 894*w*, 861*w*, 841*w*, 801*w*, 768*w*, 755*w*, 727*w*, 696*w*. ^{1}H-NMR ((D_6) DMSO): 1.86 (*dd*, $J = 6.9$, 1.8, allylic CH_3); 4.17 (*m*, 2H); 4.55 (*m*, 1H); 4.63 (*dt*, $J = 13.5$, 1.5, 1H); 4.75 (*dt*, $J = 13.5$, 1.5, 1H); 5.07 (*d*, $J = 3.3$. OH); 5.19 (*d*, $J = 5.5$, OH); 5.37 (*d*, $J = 7.0$, OH); 5.92 (*dq*, $J = 15.6$, 1.8, 1 olef. H); 6.62 (*m*, H–C(3)); 6.93 (*dq*, $J = 15.6$, 6.9, 1 olef. H). MS (70 eV): 243, 225, 207, 199, 138, 137.

B) *From* **2** via **22**. A soln. of DCC (220 mg, 1.06 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise to a stirred mixture of **21** (152 mg, 0.46 mmol), crotonic acid (132 mg, 1.54 mmol) and 4-(dimethylamino)pyridine (catalytic) in dry CH_2Cl_2 (2 ml). The mixture was stirred for 24 h and filtered through *Celite*. Removal of the solvent and chromatography (A) afforded 155 mg (85%) of *6-(*tert*-butyl)dimethylsilyloxy-2-crotonyloxymethyl-4,5-isopropylidenedioxy-cyclohex-2-enone(= [5-(*tert*-butyl)dimethylsilyloxy-3,4-isopropylidenedioxy-6-oxocyclohex-1-enyl]-methyl crotonate;* (**22**) as a colourless oil. R_f (D) 0.48. IR: 3035*w*, 2995*w*, 2956*m*, 2935*m*, 2900*m*, 2860*m*, 1722*s*, 1660*m*, 1470*w*, 1462*m*, 1443*m*, 1383*m*, 1372*m*, 1361*m*, 1337*m*, 1310*m*, 1297*m*, 1255*s*, 1174*s*, 1121*m*, 1105*m*, 1048*s*, 1008*m*, 970*m*, 955*m*, 937*m*, 920*m*, 903*m*, 890*m*, 836*s*. ^{1}H-NMR: 0.10 (*s*, 3H); 0.25 (*s*, 3H); 0.95 (*s*, 9H); 1.34 (*s*, 3H); 1.39 (*s*, 3H); 1.90 (*dd*, $J = 6.9$, 1.7, allylic CH_3); 4.49 (*d*, $J = 3$, H–C(6)); 4.70 (*m*, H–C(5)); 4.84 (*m*, allylic CH_2, H–C(4)); 5.88 (*dq*, $J = 15.6$, 1.7, 1 olef. H); 6.47 (*m*, H–C(3)); 7.02 (*dq*, $J = 15.6$, 6.9, 1 olef. H). MS: 381 (2), 281 (26), 237 (18), 195 (100), 167 (75), 143 (100), 75 (97), 73 (95), 69 (100), 41 (97).

Compound **22** (28 mg, 0.07 mmol) was treated with 50% aq. CF_3COOH (1 ml) at r.t. for 2 h. Manipulation as before furnished 17 mg (100%) of **1**, identical with the sample prepared above.

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